GLYCOGEN PHOSPHORYLASE INHIBITOR COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF

FIELD OF THE INVENTION

The present invention relates to glycogen phosphorylase inhibitor compounds, pharmaceutical compositions of these compounds, the use of these compounds or pharmaceutical compositions containing them in the treatment of diabetes, conditions associated with diabetes, and/or tissue ischemia including myocardial ischemia, and processes for making the compounds.

BACKGROUND OF THE INVENTION

Treatment of diabetes remains less than satisfactory. In addition, recently compiled data from the World Health Organization (WHO) show that approximately 150 million people have diabetes mellitus worldwide, and that this number may well double by the year 2025.

A number of drugs are available for the treatment of diabetes. These include injected insulin and drugs such as sulfonylureas, glipizide, tobutamide, acetohexamide, tolazimide, biguanides, and metformin (glucophage) which are ingested orally. Insulin self-injection is required in diabetic patients in which orally ingested drugs are not effective. Patients having Type 1 diabetes (also referred to as insulin dependent diabetes mellitus) are usually treated by self-injecting insulin. Patients suffering from Type 2 diabetes (also referred to as non-insulin dependent diabetes mellitus) are usually treated with a combination of diet, exercise, and an oral agent. When oral agents fail insulin may be prescribed. When diabetic drugs are taken orally usually multiple daily doses are often required.

Determination of the proper dosage of insulin requires frequent testing of the sugar in urine and/or blood. The administration of an excess dose of insulin generally causes hypoglycemia which has symptoms ranging from mild abnormalities in blood glucose to coma, or even death. Orally ingested drugs are likewise not without undesirable side effects. For example, such drugs can be

ineffective in some patients and cause gastrointestinal disturbances or impair proper liver function in other individuals. There is a continuing need for drugs having fewer side effects and/or ones that succeed where others fail.

In Type 2 or non-insulin dependent diabetes mellitus, hepatic glucose production is an important target. The liver is the major regulator of plasma glucose levels in the fasting state. The rate of hepatic glucose production in Type 2 patients is typically significantly elevated when compared to normal (non-diabetic) individuals. For Type 2 diabetics, in the fed or postprandial state, the liver has a proportionately smaller role in the total plasma glucose supply, and hepatic glucose production is abnormally high.

The liver produces glucose by glycogenolysis (breakdown of the glucose polymer glycogen) and gluconeogenesis (synthesis of glucose from 2- and 3-carbon precursors). Glycogenolysis therefore is an important target for interruption of hepatic glucose production. There is some evidence to suggest that glycogenolysis may contribute to the inappropriate hepatic glucose output in Type 2 diabetic patients. Individuals having liver glycogen storage diseases such as Hers' disease or glycogen phosphorylase deficiency often display episodic hypoglycemia. Further, in normal post-absorptive humans up to about 75% of hepatic glucose production is estimated to result from glycogenolysis.

Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. This enzyme cleaves the glycogen macromolecule to release glucose-1-phosphate and a shortened glycogen macromolecule.

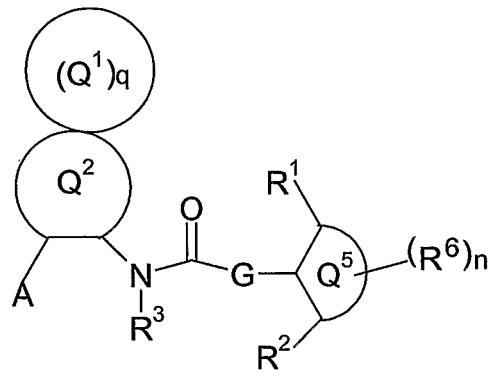
Glycogen phosphorylase inhibitors include glucose and its analogs, caffeine and other purine analogs, cyclic amines with various substitutents, and indole-like compounds. These compounds and glycogen phosphorylase inhibitors in general have been postulated to be of potential use in the treatment of Type 2 diabetes by decreasing hepatic glucose production and lowering glycemia. Furthermore, we believe it maybe desirable that a glycogen phosphorylase inhibitor be sensitive to glucose concentrations in blood. Several different types of glycogen phoshorylase inhibitors have been reported. These include glucose and glucose analogs, caffeine and other purine analogs, indole compounds and acyl ureas.

Accordingly, what is desired is a new compound and pharmaceutical composition thereof for the treatment of diabetes and/or conditions associated with diabetes.

SUMMARY OF THE INVENTION

The present invention provides a novel glycogen phosphorylase inhibitor compound and a pharmaceutical composition thereof that binds to at least one site of the glycogen phosphorylase enzyme. We believe that this novel glycogen phosphorylase inhibitor compound and a pharmaceutical composition thereof bind to the AMP allosteric binding site, and are glucose sensitive.

In one embodiment of the invention there is provided a novel compound of Formula 1 comprising:



Formula 1

a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof

wherein:

A is $C(=O)NQ^3Q^4$ or C(=O)OH;

Q^1 and Q^2 are fused together;

Q^1 is selected from the group consisting of (i) a 5- or 6- membered aromatic ring, (ii) a 5- or 6- membered cycloalkyl ring, (iii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, or sulfur, and (iv) a 4- to 8- membered heterocyclic

ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, or sulfur; and q is 0 or 1;

Q^2 is selected from the group consisting of (i) a 5- or 6- membered aromatic ring and (ii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, or sulfur;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo (Cl, Br, I, and F), alkoxy, monoalkylamino, and dialkylamino;

R^3 is hydrogen or a C_{1-6} alkyl;

Q^3 and Q^4 are each independently selected from the group consisting of (i) hydrogen, (ii) C_{1-6} alkyl, (iii) $-CR^4R^5Z$, where Z is a 5- or 6- membered heteroaryl having at least one heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur, (iv) aryl, and (v) $-CR^4R^5COOH$;

R^4 and R^5 are each independently selected from the group consisting of (i) hydrogen, (ii) a C_{1-6} alkyl, (iii) a 4- to 8- membered cycloalkyl, (iv) a 5- or 6- membered aryl, (v) a 5- or 6- membered heteroaryl, (vi) a 5- or 6- membered aralkyl, (vii) a 5- or 6- membered heteroarakyl, having at least one heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, (viii) a 4- to 8- membered cycloalkylalkyl, and (ix) a 4- to 8- membered heterocyclic ring;

R^4 and R^5 taken together can form a (i) 3-10 membered cycloalkyl or (ii) a 4-8 membered heterocyclic ring;

G is selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

Q^5 is selected from the group consisting of (i) a 5- or 6- membered aromatic ring and (ii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur; and

R^6 is selected from the group consisting of (i) C_{1-6} alkyl, (ii) halogen, (iii) alkoxy, (iv) cyano, (v) hydroxyl, (vi) haloalkyl, (vii) mono- or dialkyl- amino, (viii) 3-5 membered cycloalkyl, (ix) 3-5 membered cycloalkylalkyl, (x) alkenyl, (xi) alkyny, and (xii) acyl; and n is 0 or 1.

Another embodiment of the invention provides a pharmaceutical composition comprising the above-identified compound of Formula 1, a pharmaceutically

acceptable salt, solvate, or physiologically functional derivative thereof and at least one excipient.

In one aspect of the invention there is provided a method of treating a mammal, especially a human, suffering from diabetes, a condition associated with diabetes or both comprising the administration, preferably orally, of a compound of Formula 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. There is further provided a method of treating a mammal, especially a human, suffering from diabetes, a condition associated with diabetes or both comprising the administration, preferably orally, of a pharmaceutical composition comprising a compound of Formula 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal.

There is provided a method of treating a mammal, especially a human suffering from tissue ischemia, particularly myocardial ischemia, comprising administering to said mammal a compound of Formula 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. There is further provided a method of treating a mammal, especially a human, suffering from tissue ischemia, particularly myocardial ischemia, comprising the administration of a pharmaceutical composition containing a compound of Formula 1, a pharmaceutically acceptable salt, solvate, or physiological functional derivative thereof to said mammal.

In another aspect of the invention, there is provided a process for preparing a compound of Formula 1.

In yet another aspect of the invention, the invention provides the use of a compound of Formula 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the preparation or manufacture of a medicine for treating diabetes and/or a condition associated with diabetes in a mammal, including a human.

In still another aspect of the invention, the invention provides the use of a pharmaceutical composition of the compound of Formula 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the

preparation or manufacture of a medicine, such as a medicine for treating diabetes and/or a condition associated with diabetes in a mammal, including a human.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, "a compound of the invention" or "a compound of Formula 1" means a compound of Formula 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. Similarly, with respect to isolatable intermediates the phrase means a compound having the formula and pharmaceutically acceptable salts, solvates, and physiologically functional derivatives thereof.

As used herein, the terms "alkyl" (and "alkylene") refer to straight or branched hydrocarbon chains containing from 1 to 8 carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, and tert-butyl. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, propylene, butylenes, and isobutylene. "Alkyl" also includes substituted alkyl. The alkyl groups may be optionally substituted one or more times with hydroxyl, alkyl, alkoxy, halo, amino, thio, carboxyl, amido, guanidino, and cyano.

As used herein, the term "cycloalkyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless otherwise specified) and no carbon-carbon double bonds. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. "Cycloalkyl" also includes substituted cycloalkyl. The cycloalkyl may be optionally substituted with substituents selected from the group consisting of hydroxyl, cyano, halo, alkoxy, and alkyl.

The term "cycloalkylalkyl" refers to a cycloalkyl group as defined hereinbefore attached to an alkyl group, for example, cyclopropylmethyl, cyclohexylethyl, and the like.

As used herein, unless otherwise specified, the term "alkenyl" refers to straight or branched hydrocarbon chains containing 2 to 8 carbon atoms and at least one and up to three carbon-carbon double bonds. Examples of "alkenyl" as used herein include, but are not limited to, ethenyl and propenyl. "Alkenyl" also

includes substituted alkenyl. The alkenyl groups may be optionally substituted with alkyl, halo, hydroxyl, alkoxy, and cyano.

As used herein, unless otherwise specified, the term "alkynyl" refers to straight or branched hydrocarbon chains containing 2 to 8 carbon atoms and at least on and up to three carbon-carbon triple bonds. Examples of "alkynyl as used herein include, but are not limited to, ethynyl, propynyl and butynyl.

As used herein, unless otherwise specified, the term "cycloalkenyl" refers to a non-aromatic carbocyclic ring having 3 to 8 carbon atoms (unless otherwise specified) and up to 3 carbon-carbon double bonds. "Cycloalkenyl" includes, by way of example, cyclobutenyl, cyclopentenyl, and cyclohexenyl. "Cycloalkenyl" also includes substituted cyclalkenyl. The ring may be optionally substituted with at lease one substituent selected from the group consisting of cyano, halo, hydroxyl, NH_2, $-N_3$, -CN, $-O-C_{1-3}$alkyl, $-NH(C_{1-3}alkyl)$, $-N(C_{1-3}alkyl)_2$, and C_{1-3}alkyl (including haloalkyl).

As used herein, the terms "halo" or "halogen" refer to fluorine, chlorine, bromine, and iodine. Preferred among these are chlorine (or chloro) and fluorine (or fluoro).

The term "alkoxy" includes both branched and straight chain alkyl groups attached to a terminal oxygen atom. Typical alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, trifluoromethoxy, and the like.

The term "monoalkylamino" refers to an alkyl group attached to a nitrogen atom, for example, methylamino, isopropylamino, and the like.

The term "dialkylamino" refers to two alkyl groups, which may be the same or different, attached to a nitrogen atom, for example, dimethylamino, N-ethyl-N-methylamino, and the like.

As used herein, unless otherwise specified, the term "aryl" refers to monocyclic carbocyclic groups and fused bicyclic carbocyclic groups having from 6 to 12 carbon atoms and having at least one aromatic ring. Examples of particular aryl groups include, but are not limited to, phenyl and naphthyl. "Aryl" also includes substituted aryl, especially substituted phenyl. Aryl rings may be optionally substituted with substituents selected from the group consisting of halo, alkyl (including haloalkyl), alkenyl, cycloalkyl, cycloalkenyl, alkoxy, amino, hydroxy,

hydroxyalkyl, aminoalkyl, carboxy, carboxamide, sulfonamide, aryl, heteroaryl (abbreviated as "Het"), amidine, cyano, nitro, and azido. Preferred aryl groups include, but are not limited to, phenyl, substituted phenyl, substituted thienyl, and substituted pyridyl. Preferred substituted phenyl is a phenyl containing one or more halo groups, particularly chloro and fluoro groups. Preferred substituted thienyl is a thienyl containing one or more alkyl groups, particularly methyl. Preferred substituted pyridyl is a pyridyl containing one or more alkyl groups, particularly methyl.

The term "aralkyl" is used to describe a group wherein the alkyl chain can be branched or straight chain with the aryl portion, as defined hereinbefore, forming a terminal portion of the aralkyl moiety. Examples of aralkyl groups include, but are not limited to, optionally substituted benzyl and phenethyl such as 4-chlorobenzyl, 2,4-dibromobenzyl, 2-methylbenzyl, 2-(3-fluorophenyl)ethyl, 2-(4-methylphenyl)ethyl, 2-(4-trifluoromethyl)phenyl)ethyl, 2-(2-methoxyphenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 4-(trifluoromethoxy)benzyl, 4-hydroxybenzyl, and the like.

As used herein, the term "heterocyclic," unless otherwise specified, refers to monocyclic saturated or unsaturated non-aromatic groups and fused bicyclic non-aromatic groups, having the specified number of members (e.g., carbon and heteroatoms N and/or O and/or S) in a single ring and containing 1,2,3, or 4 heteroatoms selected from N, O, and S. Examples of particular heterocyclic groups include, but are not limited to, tetrahydrofuran, dihydropyran, tetrahydropyran, pyran, oxetane, thietane, 1,4-dioxane, 1,3-dioxane, 1,3-dioxalane, piperidine, piperazine, tetrahydropyrimidine, pyrrolidine, morpholine, thiomorpholine, thiazolidine, oxazolidine, tetrahydrothiopyran, hydrotiophene, and the like. "Heterocyclic" also includes substituted heterocyclic. The heterocyclic group may be optionally substituted with substituents selected from the group consisting of halo, alkyl (including haloalkyls), alkenyl, cycloakyl, cycloalkenyl, perfluoroalkyl, alkoxy, amino, hydroxyl, alkylhydroxy, alkylamine, carboxy, carboxamide, sulfonamide, heteroaryl, amidine, cyano, nitro, and azido. Preferred heterocyclic groups according to the invention include, but are not limited to, piperidine and tetrahydropyran.

As used herein, the term "heteroaryl," unless otherwise specified refers to aromatic monocyclic groups and aromatic fused bicyclic groups having the specified number of members (e.g., carbon and heteroatoms N and/or O and/or S) and containing 1, 2, 3, or 4 heteroatoms selected from N, O, and S. Examples of particular heteroaryl groups include, but are not limited to, furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, and indazole. "Heteroaryl" also includes substituted heteroaryl. The heteroaryl group may be optionally substituted with substituents selected from the group consisting of halo, alkyl (including perhalo alkyl, e.g., perfluoroalkyl), aryl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, amino, hydroxy, alkylhydroxy, alkylamine, carboxy, carboxamide, sulfonamide, heteroaryl, amidine, cyano, nitro, and azido. Preferred heteroaryl groups according to the invention include, but are not limited to substituted and unsubstituted pyridine, thiophene, thiazole, imidazole, isoxazole, and indole.

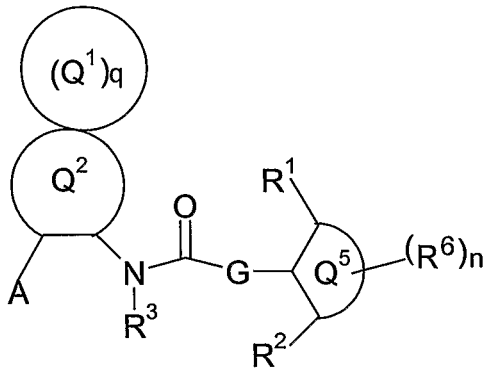
The term "heteroaralkyl" is used to describe a group wherein the alkyl chain can be branched or straight chain with the heteroaryl portion, as defined hereinbefore, forming a terminal portion of the heteraralkyl moiety, for example, 3-furylmethyl, thenyl (thienylmethyl), furfuryl, indolyl, imidazolyl, and the like.

A used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and event(s) that do not occur.

The term "substituted" means that a hydrogen atom on a molecule has been replaced with a different atom or molecule. The atom or molecule replacing the hydrogen atom is denoated as "substituent."

Formula 1 of the invention is set forth in detail as follows.

The invention is a compound of Formula 1 comprising:



Formula 1

a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

A in Formula 1 is selected from the group consisting of $C(=O)NQ^3Q^4$ and C(=O)OH.

In Formula 1, Q^1 and Q^2 are fused together. Q^1 is (i) a substituted or unsubstituted 5- or 6- membered aromatic ring, (ii) a substituted or unsubstituted 5- or 6- membered cycloalkyl ring, (iii) a substituted or unsubstituted 5- or 6- membered heteroaromatic ring having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur, and (iv) a substituted or unsubstituted 4- to 8- membered heterocyclic ring having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur. And, in Formula 1, q is 0 or 1. Preferably, Q^1 is a thienyl, a pyridyl, or a phenyl group. Most preferably, Q^1 is phenyl.

When Q^1 is (i) a 5- or 6- membered aromatic ring, (ii) a 5- or 6- membered cycloalkyl ring, (iii) a heteroaromatic ring having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur, or (iv) a 4- to 8- membered heterocyclic ring having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur, Q^1 can be substituted with a moiety selected from acyl; alkyl; alkenyl; alkynyl; alkylsulfonyl; alkoxy; cyano; halogen; haloalkyl; hydroxyl; $-CO_2H$; CO_2R^a; $-R^aOH$; $-NR^aR^b$; $-CONR^aR^b$; $-NR^aSO_2R^d$, $-NR^aCOR^c$; $-SO_2NR^aCOR^c$; $-SO_2NR^aR^b$; and $-CONR^aSO_2R^d$ wherein each of R^a, R^b, R^c, and R^d independently are selected from the group consisting of hydrogen, alkyl, and cycloalkyl.

Q^2 of Formula 1 is (i) a substituted or unsubstituted 5- or 6- membered aromatic ring or (ii) a 5- or 6- membered substituted or unsubstituted heteroaromatic ring having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur. When Q^2 is substituted, and q is 1, the preferred substituted moiety is alkoxy or halo. Preferably, Q^2 is an unsubstituted aromatic ring, a methoxysubstituted aromatic ring, or a mono- or dihalosubstituted aromatic ring. Preferably, when Q^2 is a heteroaromatic ring, the preferred heteroatom is N or S. Most preferred is an unsubstituted aromatic ring, in which Q^2 is phenyl and q is 1;

When Q^2 is (i) a 5- or 6- membered aromatic ring, or (ii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom (and up to 4 heteratoms) selected from the group consisting of nitrogen, oxygen, and sulfur, it can be substituted with halogen; alkoxy; alkyl; acyl; alkenyl; alkynyl; alkylsulfonyl; cyano; haloalkyl; hydroxyl; cycloalkyl, which may be further substituted with acyl, alkoxy, alkyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxyl; heterocyclyl, which may be further substituted with acyl, alkoxy, alkyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxyl, or nitro; aryl, which may be further substituted with acyl, alkoxy, alkyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxyl, or nitro; heteroaryl which may be further substituted with acyl, alkoxy, alkyl, alkysulfonyl, cyano, halogen, haloalkyl, hydroxyl, or nitro; $-CO_2H$; $-CO_2R^a$; $-R^aOH$; $-NR^aR^b$; $-CONR^aR^b$; $-NR^aSO_2R^d$, $-NR^aCOR^c$; $-SO_2NR^aCOR^c$; $-SO_2NR^aR^b$; and $-CONR^aSO_2R^d$ where each of R^a, R^b, R^c, and R^d independently are selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl.

When Q^2 is (i) a 5- or 6- membered aromatic ring, or (ii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur, and q is 0, Q^2 can be substituted with a moiety selected from acyl; alkyl; alkenyl; alkynyl; aryl; heteroaryl; cycloalkyl, heterocyclic; alkylsulfonyl; alkoxy; cyano; halogen; haloalkyl; hydroxyl; $-CO_2H$; CO_2R^a; $-R^aOH$; $-NR^aR^b$; $-CONR^aR^b$; $-NR^aSO_2R^d$, $-NR^aCOR^c$; $-SO_2NR^aCOR^c$; $-SO_2NR^aR^b$; and $-CONR^aSO_2R^d$ wherein each of R^a, R^b, R^c, and R^d independently are selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and aryloxy. Preferably, when q is 0, Q^2 is an substituted phenyl,

pyridyl, or thienyl containing one or more halo groups, particularly chloro and fluoro groups, or a substituted phenyl, pyridyl, or thienyl containing one or more alkyl groups, particularly methyl, or a substituted phenyl, pyridyl, or thienyl containing one aryl group, particularly a substituted phenyl.

In Formula 1, R^1 and R^2 are each independently selected from the group consisting of (i) hydrogen, (ii) substituted or unsubstituted C_{1-6} alkyl, (iii) halo (Cl, Br, I, and F), (iv) substituted or unsubstituted alkoxy, (v) monoalkylamino, and (vi) dialkylamino. Preferably, R^1 and R^2 are each independently selected from the group consisting of halo and C_{1-6} alkyl. When R^1 or R^2 is a C_{1-6} alkyl or alkoxy, said alkyl or allkoxy may contain a halogen group. A most preferred combination occurs when R^1 is chloro and R^2 is methyl or vice versa, when R^1 and R^2 are both chloro or both methyl. In Formula 1, R^1 and R^2 are each in the ortho position with respect to G.

R^3 of Formula 1 can be (i) hydrogen or (ii) a substituted or unsubstituted C_{1-6} alkyl. Preferably, R^3 is hydrogen.

In Formula 1, Q^3 and Q^4 are each independently selected from the group consisting of (i) hydrogen, (ii) a substituted or unsubstituted C_{1-6} alkyl, (iii) $-CR^4R^5Z$, where Z is a 5- or 6- membered substituted or unsubstituted heteroaryl having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur, (iv) substituted or unsubstituted aryl, and (v) $-CR^4R^5COOH$. Preferably, Q^3 and Q^4 are each independently selected from the group consisting of (i) $-CR^4R^5COOH$ and (ii) hydrogen. Most preferred combinations are when Q^3 is $-CR^4R^5COOH$ and Q^4 is hydrogen in which R^4 and R^5 are as defined herein.

When Q^3 or Q^4 is (ii) a C_{1-6} alkyl, it can be substituted with alkyl; acyl; alkenyl, alkynyl, alkylsulfonyl; alkoxy; cyano; halogen; haloalkyl; hydroxyl; alkylthio; guanidino; cycloalkyl, which may be further substituted with acyl, alkoxy, alkyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxyl; heterocyclyl, which may be further substituted with acyl, alkoxy, alkyl, cyano, halogen, haloalkyl, hydroxyl, or nitro; aryl, which may be further substituted with acyl, alkoxy, alkyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxyl; heteroaryl which may be further substituted with acyl, alkoxy, alkyl, alkysulfonyl, cyano, halogen, haloakyl, hydroxyl, or nitro; -

CO_2H; CO_2R^a, $-R^aOH$; $-NR^aR^b$, $-CONR^aR^b$; $-NR^aSO_2R^d$, $-NR^aCOR^c$; $-SO_2NR^aCOR^c$; $-SO_2NR^aR^b$; and $-CONR^aSO_2R^d$ where each of R^a, R^b, R^c, and R^d independently are selected from the group consisting of hydrogen, or alkyl.

When Q^3 or Q^4 is (iii) $-CR^4R^5Z$, where Z is a 5- or 6- membered heteroaryl having at least one heteroatom (and up to 4 heteroatom) selected from the group consisting of nitrogen, oxygen, and sulfur, or (iv) aryl, said Q^3 and Q^4 can be substituted with alkyl; acyl; alkenyl, alkynyl, alkylsulfonyl; alkoxy; cyano; halogen; haloalkyl; hydroxyl; alkylthio; $-CO_2H$; $-R^aOH$; $-CO_2R^a$; $-NR^aR^b$; $-CONR^aR^b$; $-NR^aSO_2R^d$, $-NR^aCOR^c$; $-SO_2NR^aCOR^c$; $-SO_2NR^aR^b$; $-CONR^aSO_2R^d$ or $-NR^aR^b$ where each of R^a, R^b, R^c, and R^d independently are selected from the group consisting of hydrogen, or alkyl.

In Formula 1, R^4 and R^5 are each independently selected from the group consisting of (i) hydrogen, (ii) a substituted or unsubstituted C_{1-6} alkyl, (iii) a 4- to 8- membered substituted or unsubsituted cycloalkyl, (iv) a 5- or 6- membered substituted or unsubstituted aryl, (v) a 5- or 6- membered substituted or unsubstituted heteroaryl, (vi) a 5- or 6- membered substituted or unsubstituted aralkyl, (vii) a 5- or 6- membered substituted or unsubstituted heteroaralkyl, having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur, (viii) a 4- to 8- membered substituted or unsubstituted cycloalkylalkyl, and (ix) a 4- to 8- membered substituted or unsubstituted heterocyclic ring. Preferably, R^4 and R^5 are selected from the group consisting of (i) hydrogen, (ii) cycloalkyl, (iii) aryl, (iv) substituted or unsubstituted C_{1-6} alkyl, and (v) aralkyl. Most preferably, R^4 and R^5 are selected from the group consisting of hydrogen, aryl, cycloalkyl, and substituted C_{1-6} alkyl, which alkyl is optionally substituted with alkoxy or $-CO_2H$.

When R^4 or R^5 is (ii) a substituted or unsubstituted C_{1-6} alkyl, said R^4 and R^5 can be substituted with alkyl; acyl; alkenyl, alkynyl, alkylsulfonyl; alkoxy; cyano; halogen; haloalkyl; hydroxyl; alkylthio; guanidino; cycloalkyl, which may be further substituted with acyl, alkoxy, alkyl, alkylsolfonyl, cyano, halogen, haloalkyl, hydroxyl; heterocyclyl, which may be further substituted with acyl, alkoxy, alkyl, cyano, halogen, haloalkyl, hydroxyl, or nitro; aryl, which may be further substituted with acyl, alkoxy, alkyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxyl; heteroaryl

which may be further substituted with acyl, alkoxy, alkyl, alkysulfonyl, cyano, halogen, haloakyl, hydroxyl, or nitro; $-CO_2H$; CO_2R^a, $-R^aOH$; $-NR^aR^b$, $-CONR^aR^b$; $-NR^aSO_2R^d$, $-NR^aCOR^c$; $-SO_2NR^aR^b$; $-SO_2NR^aCOR^c$; and $-CONR^aSO_2R^d$ where each of R^a, R^b, R^c, and R^d independently are selected from the group consisting of hydrogen and alkyl.

When R^4 or R^5 is (iii) a 4- to 8- membered cycloalkyl, (iv) a 5- or 6- membered aryl, (v) a 5- or 6- membered heteroaryl, (vi) a 5- or 6- membered aralkyl, (vii) a 5- or 6- membered heteroaralkyl, having at least one heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur, (viii) a 4- to 8- membered cycloalkylalkyl, or (ix) a 4- to 8- membered heterocyclic ring, said R^4 and said R^5 can be substituted with hydroxyl; halogen; alkyl; acyl; alkylsulfonyl; alkoxy; cyano; haloalkyl; alkylthio; $-CO_2H$; CO_2R^a, $-R^aOH$; $-NR^aR^b$, $-CONR^aR^b$; $-NR^aSO_2R^d$, $-NR^aCOR^c$; $-SO_2NR^aCOR^c$; $-SO_2NR^aR^b$; and $-CONR^aSO_2R^d$ where each of R^a, R^b, R^c, and R^d independently are selected from the group consisting of hydrogen and alkyl.

In Formula 1, R^4 and R^5 taken together can form a (i) 3-10 membered cycloalkyl or (ii) a 4-8 membered heterocyclic ring.

When R^4 and R^5 taken together form a (i) 3-10 membered cycloalkyl or (ii) a 4-8 membered heterocyclic ring, said ring can be substituted with hydroxyl; halogen; alkyl; acyl; alkylsulfonyl; alkoxy; cyano; haloalkyl; alkylthio; $-CO_2H$; CO_2R^a, $-R^aOH$; $-NR^aR^b$, $-CONR^aR^b$; $-NR^aSO_2R^d$, $-NR^aCOR^c$; $-SO_2NR^aCOR^c$; $-SO_2NR^aR^b$; and $-CONR^aSO_2R^d$, where each of R^a, R^b, R^c, and R^d independently are selected from the group consisting of hydrogen and alkyl.

G is selected from the group consisting of carbon, nitrogen, oxygen, and sulfur. Preferably in Formula 1, G is carbon or nitrogen.

Q^5 of Formula 1 is (i) a substituted or unsubstituted 5- or 6- membered aromatic ring, or (ii) a 5- or 6- membered substituted or unsubstituted heteroaromatic ring having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur. When Q^5 is (i) a 5- or 6- membered aromatic ring or (ii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom (and up to 4 heteroatoms) selected from the group consisting of nitrogen, oxygen, and sulfur, said Q^5 can be substituted with R^1, R^2

and/or R^6 as defined herein. Preferably Q^5 is a substituted or unsubstituted 6-membered aromatic ring. Most preferably, Q^5 is substituted phenyl.

Optionally, Q5 can have an additional substituent R6 in any of the remaining positions (that is, the non-ortho positions relative to G). This is denoted by (R6)n, where n is 0 or 1. In Formula 1, when R6 is present (that is when n equals 1), R6 is selected from the group consisting of (i) substituted or unsubstituted C1-6 alkyl, (ii) halogen, (iii) alkoxy, (iv) cyano, (v) hydroxyl, (vi) haloalkyl, (vii) mono- or dialkyl-amino, (viii) 3-5 membered cycloalkyl, (ix) 3-5 membered cycloalkylalkyl, (x) alkenyl, (xi) alkynyl, and (xii) acyl;. When R6 is a C1-6 alkyl, it can be substituted with halogen. Preferably, R6 is C1-3 alkyl, trihalomethyl, cycloalkylalkyl, trifluoromethoxy or halo. Most preferably R6 is in the para position with respect to G.

As used herein throughout the present specification, the phrase "optionally substituted" or variations thereof denote an optional substitution, including multiple degrees of substitution, with one or more substituent groups. The phrase should not be interpreted so as to be imprecise or duplicative of substitution patterns herein described or depicted specifically. Rather, those of ordinary skill in the art will appreciate that the phrase is included to provide for obvious modifications, which are encompassed within the scope of the appended claims.

Specific compounds of Formula 1 include but are not limited to those set forth in Table 1 below and/or those prepared in the examples herein.

Preferred compounds according to the invention are

N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]glycine;

Phenyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(2S)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(2S)({[4-chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl] carbonyl}amino)(cyclohexyl) ethanoic acid;

(2S)-Cyclohexyl{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthoyl]amino} ethanoic acid;

(2S)-Cyclohexyl{[3-({[(2-ethyl-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino} ethanoic acid;

(2S)-({3-[({[2-Chloro-6-(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthoyl}amino)(cyclohexyl) ethanoic acid;

(2S)-Cyclohexyl[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-2-naphthoyl) amino]ethanoic acid

(2S)-Cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl) amino]ethanoic acid;

(2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid; and

(2*S*)-({[4-Chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid;

(2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid; and

(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-pyridinyl)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(2-thienyl)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-hydroxy-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,6- dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2S)-Cyclohexyl({[4'-hydroxy-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-({[4'-Amino-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4-{[(methylamino)carbonyl]amino}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclopentyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3',4'-difluoro-4-biphenylyl)carbonyl]amino}ethanoic acid;

(2*S*)-Cyclohexyl({[4'-[(dimethylamino)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-biphenylyl)carbonyl]amino}ethanoic acid;

(2*S*)-Cyclohexyl({[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-(1-pyrrolidinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-cyclohexyl({[4'-(4-morpholinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-(ethyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-norleucine;

1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylic acid;

(2*S*)-Cyclohexyl({[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-({[4-(1,3-Benzodioxol-5-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid;

O-(1,1-Dimethylethyl)-N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine; and

1-({[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid;

(2*S*)-Cyclohexyl({[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-({[3',4'-Bis(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid;

(2*S*)-Cyclohexyl({[4,5-difluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid;

1-({[4'-(Methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid;

N-{[3-{[({2,6-Dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine;

O-(1,1-Dimethylethyl)-N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

(2S)-Cyclohexyl({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

O-(1,1-Dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

O-(1,1-Dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-threonine;

(2S)-Cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

1-({[3'-Fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine;

O-(1,1-dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

5-methyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine;

6,6,6-trifluoro-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine;

O-(1,1-dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-leucine;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-isoleucine;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline;

O-(1,1-dimethylethyl)-N-[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]-L-threonine;

O-butyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-[2-(methyloxy)ethyl]-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-ethyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-(1-methylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-(2,2-dimethylpropyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-(tetrahydro-2H-pyran-4-yl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-(1-methylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

(2S)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid;

1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclodecanecarboxylic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cycloheptanecarboxylic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cyclooctanecarboxylic acid;

1-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid;

2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-2,3-dihydro-1H-indene-2-carboxylic acid;

2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid;

1-({[5-Chloro-3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylic acid;

(2S)-Cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)ethanoic acid;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylic acid;

O-(phenylmethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

(3R)-3-[(phenylmethyl)oxy]-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline;

(2*S*)-(4,4-difluorocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2*S*)-cyclopentyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(cis and trans)-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(cis and trans)-(4-{[(methylamino)carbonyl]amino}cyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid;

N-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-aspartic acid;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-aspartic acid;

(2*S*)-[(1*S*)-3-oxocyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2*S*)-[(1*S*)-3-hydroxycyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2*S*)-{(1*S*)-3-[(trifluoroacetyl)oxy]cyclohexyl}({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid;

(2*S*)-2-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid;

N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartic acid;

N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine;

N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid;

N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparagine;

N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-glutamic acid;

(2S)-cyclohexyl[({3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl({[5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl[({2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thienyl)carbonyl]amino}ethanoic acid;

(2S)-cyclohexyl[({3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoic acid;

N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-valine;

N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-isoleucine;

N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-norleucine;

O-(1,1-dimethylethyl)-N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-serine;

O-(1,1-dimethylethyl)-N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-threonine;

1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-proline;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopentanecarboxylic acid;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cycloheptanecarboxylic acid;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclooctanecarboxylic acid;

(2S)-cyclohexyl({[3-({[(2,6-dichloro-4-fluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl{[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid;

(2S)-cyclohexyl({[3-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid;

(2S)-(trans-4-methylcyclohexyl)({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

2-cyclohexyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine;

2-cyclohexyl-N-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-alanine;

{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[trans-4-(trifluoromethyl)cyclohexyl]acetic acid;

{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[cis-4-(trifluoromethyl)cyclohexyl]acetic acid;

{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(tetrahydro-2H-pyran-4-yl)acetic acid;

tetrahydro-2H-pyran-4-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(2S)-cyclohexyl({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propyn-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl[({3-[({[2,6-dimethyl-4-(propyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl({[2-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl({[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl({[2-({[(2,6-dimethyl-4-pentylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid;

2-cyclohexyl-N-{[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-alanine;

(2S)-({[2-({[(4-butyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoic acid;

O-(1,1-dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-L-threonine;

(2S)-cyclohexyl[({2-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid;

N-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-O-(1,1-dimethylethyl)-L-threonine;

1-({[2-[4-(Methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylic acid;

(2*S*)-(4-hydroxyphenyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2*S*)-(4-hydroxycyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

N^4,N^4-dimethyl-N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparagine;

N-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threonine;

N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid;

O-(Phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

N-{[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(phenylmethyl)-L-serine;

(3*R*)-5-Methyl-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine;

O-cyclobutyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-phenylalanine;

(2S)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid;

5,5-dimethyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine;

O-cyclobutyl-N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

O-(1-methylcyclopentyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

(2S)-cyclohexyl({[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

O-(1,1-Dimethylethyl)-N-{[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

N-{[3',5'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine;

(2S)-Cyclohexyl({[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

O-(1,1-Dimethylethyl)-N-{[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

O-(1,1-Dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

1-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid;

N-{[3-({[(4-Cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine;

(2S)-cyclohexyl({[3-({[(4-cyclopropylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

N-{[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine;

1-({[5-(4-chlorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid; and

1-({[5-(3,4-difluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid.

It will be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt, or solvate, or physiologically functional derivative thereof.

The pharmaceutically acceptable salts of the compounds of Formula 1 include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium salts. More specific examples of suitable acid salts include hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumic, toluenesulfonic, methanesulfonic (mesylate), naphthalene-2-sulfonic, benzenesulfonic, hydroxynaphthoic, hydroidic, malic, steroicc, tannic, and the like. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminium, calcium, zinc, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine salts.

The term "physiologically functional derivative" as used herein refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide of a compound of Formula 1, which upon administration to an animal, particularly a mammal, such as a human, is capable of providing (directly or indirectly) a compound of the present invention or an active

metabolite thereof. See, for example, Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Volume 1: Principles and Practice.

Processes for preparing pharmaceutically acceptable salts, solvates, and physiologically functional derivative of a compound of Formula 1 are conventional in the art. See, for example, Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Volume 1: Principles and Practice.

As will be apparent to those skilled in the art, the processes described herein for the preparation of compounds of Formula 1, certain intermediates, may be in the form of pharmaceutically acceptable salts, solvates, or physiologically functional derivatives of the compound. Those terms as applied to any intermediate employed in a process of preparing compounds of the invention have the same meanings as noted above with respect to compounds of Formula 1. Processes for preparing pharmaceutically acceptable salts, solvates, and physiologically functional derivatives of such intermediates are known in the art and are analogous to the process for preparing pharmaceutically acceptable salts, solvates, and physiologically functional derivatives of the compounds of Formula 1.

Certain compounds of Formula 1 may exist in stereoisomeric forms (e.g., they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers), and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by Formula 1 as mixtures with isomers thereof in which one or more chiral centers are inverted. Certain compounds of Formula 1 may be prepared as a mixture of regioisomers. The present invention covers both the mixture of regioisomers as well as the individual compounds. Likewise, it is understood that compounds of Formula 1 may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

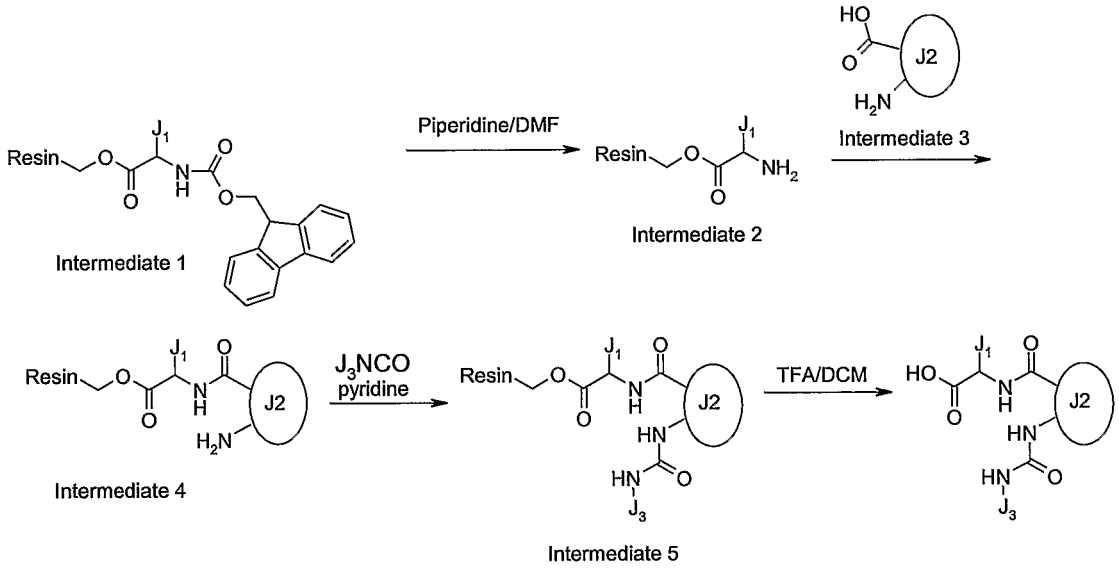
It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove.

Compounds of Formula 1 may be conveniently prepared by the processes outlined below. The order of the foregoing steps is not critical to the practice of the invention and the processes may be practiced by performing the steps in any

suitable order based on the knowledge of those skilled in the art. The compounds of the invention can be prepared using Methods A through F described below.

Method A (Solid-Phase Synthesis of Compounds of Formula 1 using Intermediate 1 and/or 2 and/or 3 and/or 4 and/or 5.)

Schematic 1

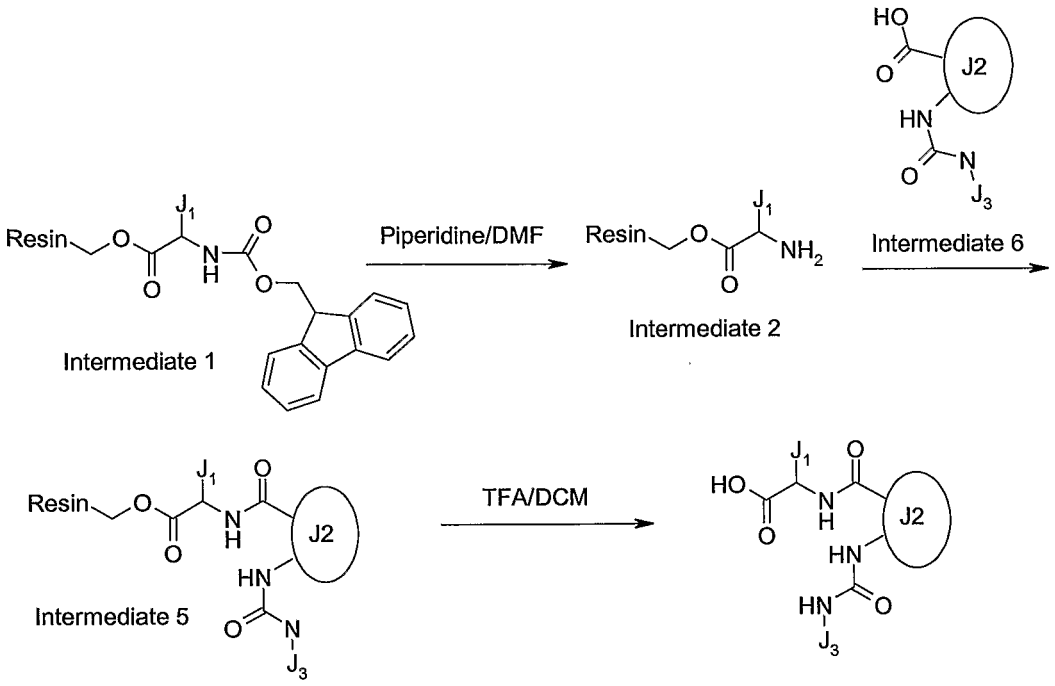


Fmoc (9-fluorenylmethoxycarbonyl) protected resin bound amino acids (e.g., Intermediate 1 in which J_1 represents various amino acid side chains) can be purchased commercially or formed by standard methods. (See, for example, Sieber, P. Tetrahedron Letters 1987, 28, 6147-6150 and references therein; and Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. Tetrahedron Letters 1990, 31, 1701-1704 and references therein.) The reactions to form intermediate 2 are typically run in DMF (N,N-dimethylformamide) as a solvent, in which intermediate 1 is mixed with 20% piperidine at room temperature. Intermediate 3 (with variations at J2) can be purchased commercially or formed by standard methods. Intermediate 4 (with variations at J_1 and J2) can be formed by mixing intermediate 3 and intermediate 2 using standard coupling methods. These methods include the use of DIC (N, N'-diisopropylcarbodiimide), PyBop (Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), PyBrOP (Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate), HATU (2-(1H-9-Azabenzotriazxole-1-yl)-1,1,3,3-

tetramethyluronium hexafluorophosphate, or HOBT (N-hydroxybenzotriaole) at room or elevated temperature. Preferably EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), DIEA (N,N-diisopropylethylamine) and/or HOAT (N-hydroxy-9-azabenzotriaole) are employed at room temperature. Solvents can include DMF, methylene chloride (DCM), or preferably NMP (N-methylpyrrolidinone). Intermediate 4 is then mixed with an isocyanate (e.g., J_3NCO, in which J_3 represents various side chains) in methylene chloride, diisopropylethylamine, triethylamine, or pyridine, preferably with pyridine to form intermediate 5. The reactions can be heated, but are preferably mixed at room temperature. The final product is formed by cleavage of intermediate 5 from the resin using a mixture of TFA (trifluoroacetic acid) in methylene chloride, preferably 50% TFA in DCM.

Method B (Solid-Phase Synthesis of Compounds of Formula 1 using Intermediate 1 and/or 2 and/or 5 and/or 6.)

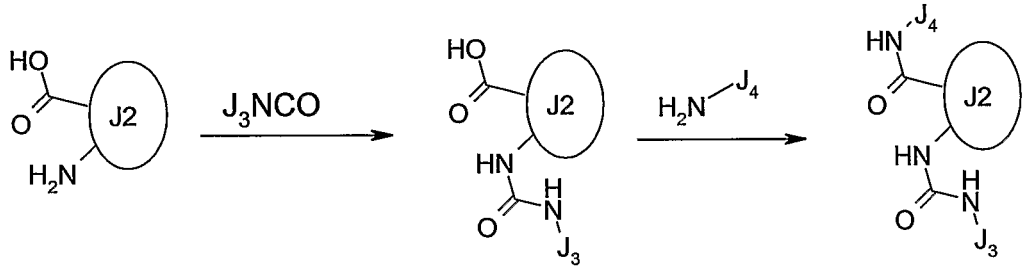
Schematic 2



In Method B, compounds of Formula 1 can be made according to Method A, except that Intermediate 6 is used in place of intermediates 3 and 4 to form intermediate 5. Intermediate 6 can be formed by standard methods from intermediate 3 as described in Method C below.

Method C (Solution-Phase Synthesis of Compounds of Formula 1 from corresponding Intermediates 3 and/or 6.

Schematic 3

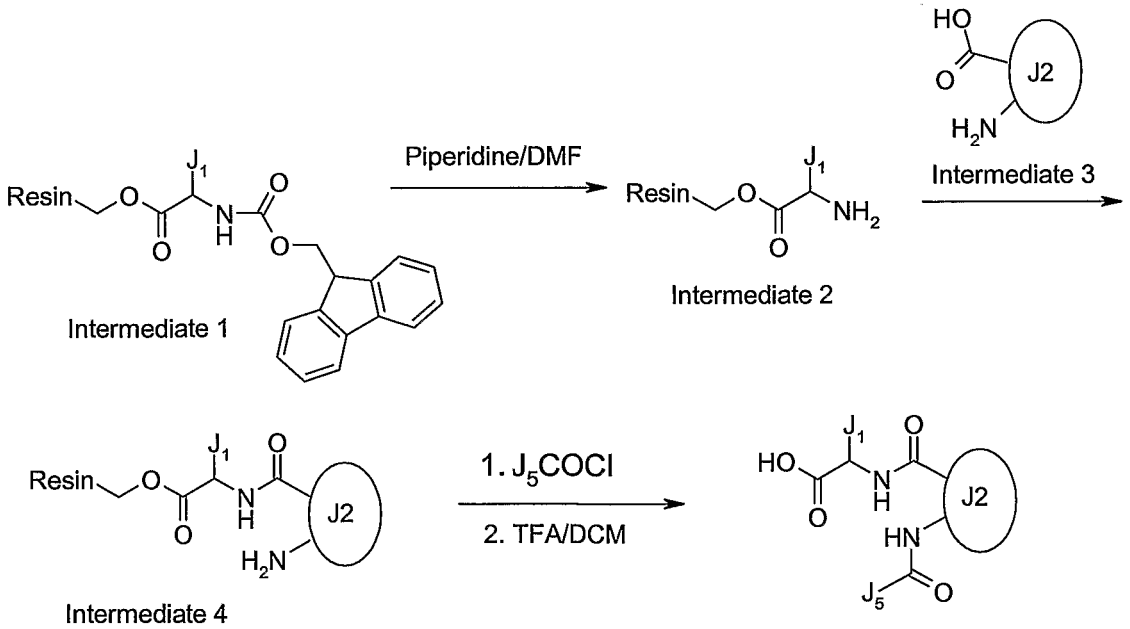


Intermediate 6 is formed by mixing intermediate 3 with an isocyanate (J_3NCO in which J_3 represents various groups) in diisopropylethylamine (DIEA), triethylamine, pyridine, DMF, or preferably DMSO (dimethylsulfoxide). The reaction

is heated or preferably run at room temperature. The final product is formed using standard coupling methods by mixing intermediate 6 with an amine (J_4-NH_2 in which J_4 represents various groups) and a reagent such as EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), PyBop (Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), PyBrOP (Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate), HOBT (N-hydroxybenzotriaole), HOAT (N-hydroxy-9-azabenzotriaole), or preferably HATU (2-(1H-9-Azabenzotriazxole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) or DIC (N, N'-diisopropylcarbodiimide) and DIEA (N,N-diisopropylethylamine) at room temperature. Solvents that can be used include DMF, NMP or preferably DMSO. When J_4-NH_2 contains a methyl ester in the J_4 side chain, the ester can be hydrolysed to the corresponding carboxylic acid by adding lithium hydroxide (LiOH) in solvents which include tetrahydrofuran (THF) and/or methanol (MeOH) and/or water and/or 1,4-dioxane as described in Method E.

Method D (Solid-Phase Synthesis of Compounds of Formula 1 from Intermediates 1 and/or 2 and/or 3 and/or 4). Method D is conducted according to Method A, except that acid chlorides are employed in place of isocyanates.

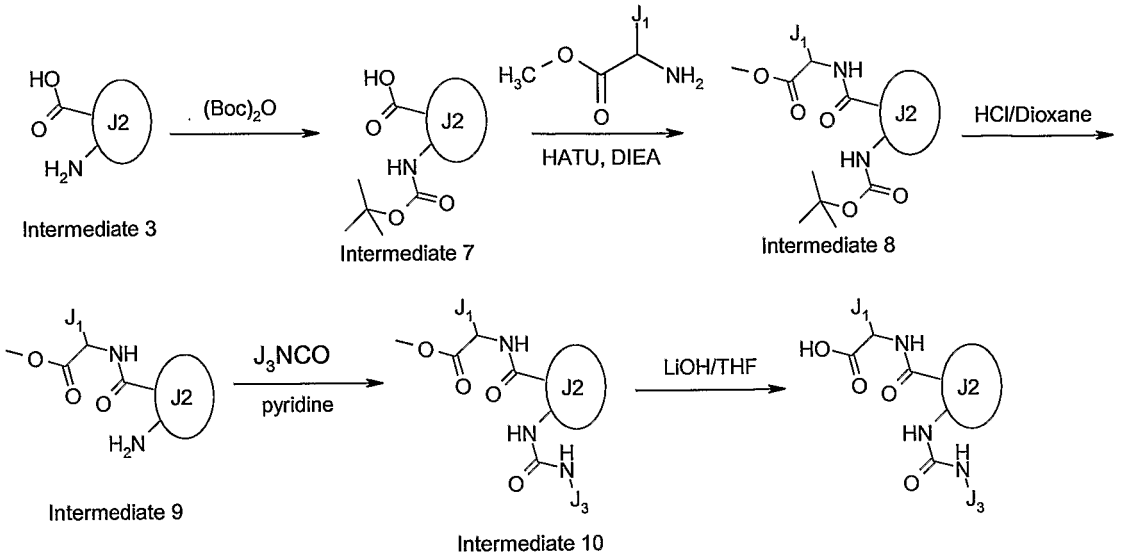
Schematic 4



In Method D, the Fmoc (9-fluorenylmethoxycarbonyl) protected resin-bound amino acids (e.g, Intermediate 1 in which J_1 represents various amino acid side chains) can be purchased commercially or formed by standard methods. (See, for example, Sieber, P. Tetrahedron Letters 1987, 28, 6147-6150 and references therein; and Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. Tetrahedron Letters 1990, 31, 1701-1704 and references therein.) The reactions to form intermediate 2 are typically run in DMF (N,N-dimethylformamide) as a solvent, in which intermediate 1 is mixed with 20% piperidine at room temperature. Intermediate 3 (with variations at J2) can be purchased commercially or formed by standard methods. Intermediate 4 (with variations at J_1 and J2) can be formed by mixing intermediate 3 and intermediate 2 using standard coupling methods. These methods include the use of DIC (N, N'-diisopropylcarbodiimide), PyBop (Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), PyBrOP (Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate), HATU (2-(1H-9-Azabenzotriazxole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), or HOBT (N-hydroxybenzotriaole). Preferably EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), DIEA (N,N-diisopropylethylamine) and), and/or HOAT (N-hydroxy-9-azabenzotriaole) are employed at room temperature. Solvents can include DMF, methylene chloride (DCM), or preferably NMP (N-methylpyrrolidinone). Intermediate 4 is then mixed with an acid chloride (J_5COCl in which J_5 represents various groups) in methylene chloride, diisopropylethylamine, triethylamine, or preferably pyridine in methylene chloride. The reactions can be heated, but are preferably mixed at room temperature. The final product is then isolated by cleavage from the resin using a mixture of TFA (trifluoroacetic acid) in methylene chloride, preferably 50% TFA in DCM.

Method E (Solution-Phase Synthesis of Compounds of Formula 1 from corresponding Intermediates 3 and/or 7 and/or 8 and/or 9 and/or 10).

Schematic 5



Intermediate 7 is formed by mixing Intermediate 3 with di-tert-butyl-dicarbonate ($(Boc)_2O$) or equivalent with an appropriate base which can include potassium hydroxide or preferably sodium hydroxide. Solvents that can be used include diethylether, dioxane, or preferably THF. The reaction is preferably run at room temperature. Intermediate 8 is formed by mixing intermediate 7 with an appropriate amine or its hydrochloride salt ($NH_2CHJ_1CO_2Me$ in which J_1 represents various side chains) using standard coupling conditions. These conditions include the use of EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), PyBop (Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), PyBrOP (Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate), HOBT (N-hydroxybenzotriaole), HOAT (N-hydroxy-9-azabenzotriaole), or DIC (N, N'-diisopropylcarbodiimide), or preferably HATU (2-(1H-9-Azabenzotriazxole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) and DIEA (N,N-diisopropylethylamine) at room temperature. Solvents that can be used include DMSO, NMP or preferably DMF. Intermediate 9 is formed by removal of the tert-butoxycarbonyl protecting group by mixing Intermediate 8 with an appropriate acid which is preferably hydrochloric acid (HCl). Solvents can include dichloromethane, diethylether, tetrahydrofuran, or preferably dioxane. The reaction is preferably mixed at room temperature.

Intermediate 9 can also be prepared directly by the reaction of intermediate 3 with an appropriate amine or its hydrochloride salt ($NH_2CHJ_1CO_2Me$ in which J_1 represents various side chains) using standard coupling conditions. These conditions include the use of EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), PyBop (Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), PyBrOP (Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate), HOBT (N-hydroxybenzotriaole), HOAT (N-hydroxy-9-azabenzotriaole), or DIC (N, N'-diisopropylcarbodiimide), or preferably HATU (2-(1H-9-Azabenzotriazxole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) and DIEA (N,N-diisopropylethylamine) at room temperature. Solvents that can be used include DMSO, NMP or preferably DMF.

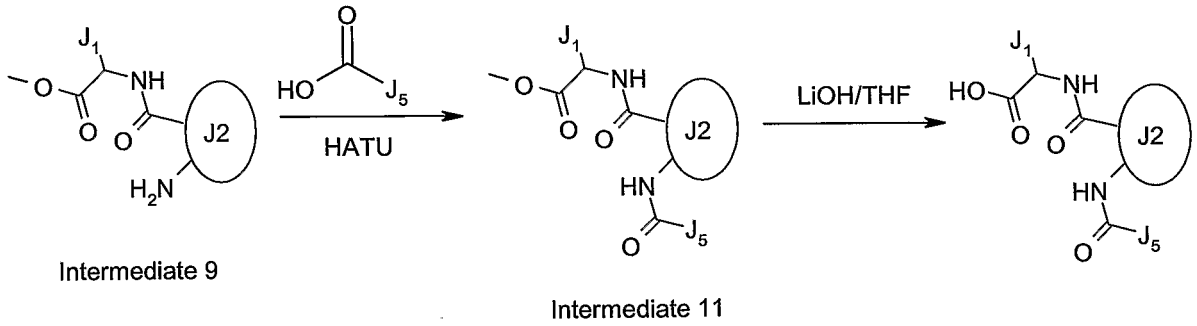
Intermediate 10 is formed by mixing Intermediate 9 with an isocyanate (J_3NCO in which J_3 represents various groups) in diisopropylethylamine (DIEA), triethylamine, DMSO, DMF, or preferably pyridine. The reaction is heated or preferably mixed at room temperature.

The final product is formed by mixing Intermediate 10 with lithium hydroxide (LiOH) in solvents which include tetrahydrofuran (THF) and/or methanol (MeOH) and/or water and/or 1,4-dioxane. The reaction is preferably run at room temperature.

A simple modification of Method E is to prepare intermediate 9 directly from intermediate 3 by coupling with an appropriate amine or its hydrochloride salt ($NH_2CHJ_1CO_2tBu$ in which J_1 represents various side chains) using standard coupling conditions. The resulting intermediate 9 as the t-butyl ester is converted to intermediate 10 (as the t–butyl ester) by treatment with an isocyanate (J_3NCO in which J_3 represents various groups) in diisopropylethylamine (DIEA), triethylamine, DMSO, DMF, or preferably pyridine. The reaction is heated or preferably mixed at room temperature. The final product is obtained by treatment with triflouroacetic acid or hydrogen chloride in solvents which include dichloromethane, tetrahydrofuran, 1,4-dioxane or ether.

Method F (Solution-Phase Synthesis of Compounds of Formula 1 from corresponding Intermediates 9 and/or 11).

Schematic 6



Intermediate 9

Intermediate 11

Intermediate 11 is formed by mixing Intermediate 9 (formed as described in Method E) with a carboxylic acid (J_5CO_2H in which J_5 represents various groups) using standard coupling methods (as described in Method E for the formation of intermediate 8). The carboxylic acid (J_5CO_2H in which J_5 represents various groups) can be converted to the acid chloride under standard conditions and reacted with intermediate 9 to yield intermediate 11. The final product is formed by mixing Intermediate 11 with lithium hydroxide (LiOH) as described in Method E.

In the methods outlined above (methods A-F) examples of group J_1 can be but are not limited to, side chains of natural and unnatural amino acids, modified side chains of natural amino acids such as alkyl serine and threonine, alkyl groups, cycloalkyl such as cyclohexyl and cyclopentyl, aryl groups such as phenyl, heteroaryl, alkylaryl groups such as benzyl, and spirocyclic alkyl groups. Examples of J_2 include but are not limited to aryl groups such as phenyl and substituted phenyl, naphthyl and substituted naphthyl, biphenyl and substituted biphenyl, heteroaryl such as thienyl and pyridyl, and substituted heteroaryl. Examples of J_3 include but are not limited to aryl such as phenyl and substituted phenyl such as 2,6-disubstituted phenyl and 2,4,6-trisubstituted phenyl. Examples J_4-NH_2 (method C, Schematic 3) include but are not limited to natural or unnatural amino acids containing the side chains defined by J_1, and alkyl aminobenzoates. Examples of J_5 include but are not limited to benzyl and substituted benzyl groups such as 2,6-disubstituted benzyl.

While it is possible that, for use in therapy, a therapeutically effective amount of a compound of Formula 1 may be administered as the raw chemical, it is typically presented as the active ingredient of a pharmaceutical composition or

formulation. Accordingly, the invention further provides a pharmaceutical composition comprising a compound of Formula 1. The pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers, diluents, and/or excipients. The carrier(s), diluent(s), and/or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof (that is, the patient). In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition comprising mixing (or admixing) a compound of Formula 1 with one or more pharmaceutically acceptable carriers, diluents, and/or excipients.

Pharmaceutical compositions may be in unit dose form containing a predetermined amount of active ingredient per unit dose. Such a unit may contain a therapeutically effective dose of the compound of Formula 1 or a fraction of a therapeutically effective dose such that multiple unit dosage forms might be administered at a given time to achieve the desired therapeutically effective dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well-known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example, by the oral (including bucccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, or intradermal) routes. Such compositions may be prepared by any method known in the art of pharmacy, for example, by bringing into association the active ingredient with the carrier(s), diluent(s), and/or excipient(s).

When adapted for oral administration, pharmaceutical compositions may be in discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; oil-in-water liquid emulsions or water-in-oil liquid emulsions. The compounds of the invention or pharmaceutical compositions thereof may also be incorporated into a candy, a

wafer, and/or tongue tape formulation for administration as a "quick-dissolve" medicine.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders or granules are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agents can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin or non-gelatinous sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicine when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt, and/or an absorption agent such as bentonite, kaolin or dicalcium

phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar, or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different dosages.

Oral fluids such as solutions, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of active ingredient. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers, such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as, for example, by coating or embedding particulate material in polymers, wax, or the like.

The present invention provides a method of treatment in a mammal, especially a human, suffering from diabetes or a related condition such as obesity, syndrome X, insulin resistance, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, cardiovascular disease, stroke, atherosclerosis, lipoprotein disorders, hypertension, tissue ischemia, myocardial ischemia, and depression.

Such treatment comprises the step of administering a therapeutically effective amount of a compound of Formula 1, including a salt, solvate, or physiologically functional derivative thereof to said mammal. Treatment can also comprise the step of administering a therapeutically effective amount of a pharmaceutical composition containing a compound of Formula 1, including a salt, solvate, or physiologically functional derivative thereof to said mammal. As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, preventing or delaying the onset of a condition, or preventing or delaying the recurrence of the condition in a previously afflicted patient or subject such as a mammal, particularly a human.

As used herein, the term "therapeutically effective amount" means an amount of a compound of Formula 1, including a salt, solvate, or physiologically functional derivative thereof or an amount of a pharmaceutical composition containing said compound of Formula 1 and/or salt, solvate, or physiologically functional derivative thereof, which amount is sufficient, in the subject or patient to which it is administered, to elicit the biological or medical response of a cell, culture, tissue, system, animal (including human), that is being sought, for instance by a researcher or clinician.

The precise therapeutically effective amount of the compounds of the invention will depend on a number of factors, including, but not limited to, the age and weight of the subject being treated, the precise disorder requiring treatment and its severity, the nature of the pharmaceutical formulation/composition, and route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. Typically, a compound of Formula 1 will be given for treatment in the range of 0.1 to 200 mg/kg body weight of recipient (animal) per day and more usually in the range of 1 to 100 mg/kg body weight per day. Acceptable daily dosages may be from about 0.1 to about 200 mg/day, and preferably from about 0.1 to about 100 mg/day.

The administration of a compound of the invention or a pharmaceutical composition containing a compound of the invention to an animal, particularly a mammal such as a human, may be by way of oral (including buccal or sub-lingual), parenteral (including subcutaneous, intramuscular, intravenous or intradermal),

nasal, rectal, vaginal, or transdermal administration. Preferably, oral administration is employed.

A pharmaceutical composition of a compound of the invention may be prepared by any method known in the art of pharmacy, for example, by bringing into association the active ingredient (e.g., a compound of the invention) with one or more carriers, diluents, and/or excipients.

Additionally, the present invention comprises a compound of Formula 1, a salt, solvate, physiologically functional derivative thereof, or a pharmaceutical composition thereof with at least one other diabetic drug. Such diabetic drugs can include, for example, injected insulin and drugs such as sulfonylureas, thiazolidinediones, glipizide, glimepiride, tobutamide, acetohexamide, tolazimide, biguanides, rosiglitazone, and metformin (glucophage) and salts or combinations thereof which are ingested orally. When a compound of the invention is employed in combination with another diabetic drug, it is to be appreciated by those skilled in the art that the dose of each compound or drug of the combination may differ from that when the drug or compound is used alone. Appropriate doses will be readily appreciated and determined by those skilled in the art. The appropriate dose of the compound(s) of Formula 1 and the other therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect, and are within the expertise and discretion of the attendant clinician.

EXPERIMENTAL

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way, the invention being defined by the claims. Unless otherwise noted, reagents are commercially available or are prepared according to procedures in the literature.

Section 1: Preparation of Specific Compounds of the Invention

Chromatographic purifications of final products were carried out using reverse phase high pressure liquid chromatography, or standard silica gel chromatography unless otherwise specified. Chromatographic purification of

intermediates, when necessary, was carried out using standard silica gel chromatography. Reactions were carried out in suitable containers, which can include IRORI vessels, polypropylene or teflon tubes, or glass vessels.

Example 1: Preparation of N-[3-({[(2,6-dimethylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid (Method A, Schematic 1)

a). Preparation of L-ASP-Wang resin

Fmoc-L-Aspartic acid tert-butyl (Asp(tBu))-Wang resin (0.8 mmol/g, obtained from Polymer Lab)(80 mg, 64 umol) in an IRORI minikan was shaken in excess 20% piperdine/DMF solution at room temperature overnight. The resin was drained, washed with DMSO (3X10 mL), DCM (3X10 mL), acetonitrile (3X10 mL), DMSO (1X10 mL), and DCM (3 X10 mL). The resin was then dried in vacuo overnight to obtain L-Asp(tBu)-Wang resin as free amine.

b). Preparation of N-[3-({[(2,6-dimethylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid

Diisopropyl ethyl amine (0.057 ml, 0.32 mmol) was added to the solution of EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.061 g, 0.32 mmol), HOAt (1-hydroxybenzotriazole, 0.043 g, 0.32 mmol) in N-methylpyrrolidinone, followed by the addition of IRORI minikan containing L-Asp(tBu)-Wang Resin (from Example 1a). After the reaction mixture was shaken at room temperature for 10 min, 3-amino-2-naphthalenecarboxylic acid (0.059 g, 0.32 mmol) was added to the reaction solution. The resulting reaction mixture was shaken at room temperature for 24 hours. The resin was drained, washed with DMSO (3X10 mL), DCM (3X10 mL), acetonitrile (3X10 mL), DMSO (3X10 mL), and DCM (6 X10 mL), and dried in vacuo. A small portion of resin was taken out, cleaved by 1:1 TFA: DCM for 30 min. at room temperature. LC-MS showed >90% formation of desired coupling intermediate product.

The resin in the minikan was added to the solution of 2,6-dimethyl phenyl isocyanate (0.094 g, 0.64 mmol) in pyridine (20 mL). The reaction mixture was shaken at room temperature for 24 hours. The resin was drained, washed with DMSO (3X10 mL), DCM (3X10 mL), acetonitrile (3X10 mL), DMSO (3X10 mL), and DCM (6 X10 mL), and dried in vacuo. The resin was then cleaved in 1:1 TFA: DCM

for 30 minutes. The crude product was dried in vacuo over night, taken up by DMSO (0.6 mL), purified by HPLC, and dried in vacuo to give the title compound as a light brown solid. ESMS [M+H]+m/z 450.4.

Example 2: Preparation of (2S)-{[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(cyclohexyl)acetic acid (Method A, Schematic 1).

a). Preparation of Fmoc-L-CHG-Wang resin (Example of Intermediate 1)

Wang resin (loading 1.7 mmol/g obtained from Polymer Lab) (7.8 g, 13.3mmol) was swollen in DMF (85 mL) for 10 minutes. To the above reaction solution, Fmoc-L-cyclohexylglycine(CHG) (10.0 g, 26.35 mmol) was added, followed by the addition of pyridine (3.4 g, 43.5 mmol), 2,6-dichlorophenyl acid chloride (5.5 g, 26.34 mmol). The reaction solution was then shaken at room temperature overnight. The resin was drained, washed with DMSO (3X100 mL), DCM (3X100 mL), acetonitrile (3X100 mL), DMSO (1X100 mL), and DCM (3 X100 mL).). The resin was then dried in vacuo overnight.

b). Preparation of L-CHG-Wang resin (Example of Intermediate 2)

Fmoc-L-CHG-Wang resin from 2a (80 mg, 64 umol) in an IRORI minikan was shaken in excess 20% piperdine/DMF solution at room temperature overnight. The resin was drained, washed with DMSO (3X10 mL), DCM (3X10 mL), acetonitrile (3X10 mL), DMSO (1X10 mL), and DCM (3 X10 mL). The resin was then dried in vacuo overnight to obtain L-CHG-Wang resin as free amine.

c). Preparation of (2S)-{[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(cyclohexyl)acetic acid

The title compound was prepared by the same procedure as example 1b except that L-Asp(tBu)-Wang resin was replaced with L-CHG-Wang resin (obtained from 2b) and 2,6-dimethyl phenyl isocyanate was replaced with 2-chloro-6-methyl phenyl isocyanate to give the title compound. ESMS [M+H]+m/z 494.4.

Example 3: Preparation of N-{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-valine.

a). Preparation of 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (Example of Intermediate 3)

A suspension of ethyl 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (10 g) in 100 mL 2.5 N sodium hydroxide (NaOH) solution (1:1 water/ethanol) was heated at 80 °C overnight. After the mixture was cooled and filtered to remove unreacted starting material, the solution was concentrated in vacuo. The residue was acidified to pH 3 by addition of 6N HCl and then filtered, resulting in a light brown solid (7.43 grams, ESMS $[M+H]^+$m/z 198.3).

b). Preparation of N-{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-valine

The title compound was prepared by the same procedure as in Example 1 except that L-Asp(tBu)-Wang resin was replaced with L-Val-Wang resin (obtained from Polymer Lab, 0.8 mmol/g) and 3-amino-2-naphthalenecarboxylic acid was replaced with 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (obained from 3a). to give the title compound. ESMS [M+H]+m/z 444.6

Example 4: Preparation of (2S)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-1-benzothien-3-yl]carbonyl}amino)acetic acid

a). Prepararation of 2-amino-1-benzothiophene-3-carboxylic acid

Ethyl 2-amino-1-benzothiophene-3-carboxylate (obtained according to procedures described in Hallas, G.; Towns, A.D., Dyes and Pigments (1997), 35, 219-237) (10 g, 40.0 mmol) was suspended in ethanol (100 mL), and heated to reflux. A solution of potassium hydroxide (KOH, 8.4 g) in water (100 mL) was added over the period of 10 minutes. The reaction mixture was refluxed for another 10 minutes, cooled to room temperature, and filtered. The collected solid was washed with water to pH neutral to give the title compound as a brown solid (1.0 g, 13.0 % yield). ESMS [M+H]+m/z 194.2.

b). Preparation of (2S)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-1-benzothien-3-yl]carbonyl}amino)ethanoic acid

The title compound was prepared by the same procedure as in Example 2 except that 3-amino-2-naphthalenecarboxylic acid was replaced by 2-amino-1-benzothiophene-3-carboxylic acid (obtained from 4a) and 2-chloro-6-methyl phenylisocyanate was replaced with 2,6-dimethyl phenylisocyanate to give the title compound. ESMS [M+H]+m/z 480.6.

Example 5: Preparation of {[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(piperidin-3-yl)acetic acid trifluoroacetate (Method B)

a). Preparation of 3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoic acid (Example of Intermediate 6)

3-Amino-2-naphthoic acid (0.56 g, 85% technical grade, 2.5 mmol) was dissolved in 8 mL DMSO and treated with 2-chloro-6-methylphenylisocyanate (440uL, 3.2 mmol) then shaken at room temperature for 20 hours. The reaction mixture was diluted with 25 mL H_2O and the resulting tan solid precipitate filtered, rinsed with H_2O (3 x 10 mL), dioxane (1 x 3 mL), and acetonitrile (1 x 3 mL) and dried in vacuo. Yield = 0.58 g (64%). ESMS $[M+H]^+$m/z 355.2.

b). Preparation of {[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(piperidin-3-yl)acetic acid trifluoroacetate

N-Fmoc-(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin was prepared as described in Example 2a. Fmoc deprotection was achieved as in Example 2b. Approximately 90mg (90 umol) of the resulting (1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin was loaded into an IRORI Minikan and treated with a solution of 5 eq. (0.159 g, 450 umol) 3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoic acid (obtained as in example 5a) and 6 eq. HOAt (1-Hydroxy-7-aza-benzotriazole, 0.073 g, 540 umol) dissolved in 3 mL NMP (N-methylpyrrolidinone). To this mixture was added 7 eq. DIC (1,3-diisopropylcarbodiimide, 100uL, 630 umol) and the resulting reaction mixture shaken at room temperature for 20 hours. The solution was removed and the resin-filled Minikan washed with NMP (1 x 5 mL), CH_2Cl_2 (1 x 5 mL), MeOH (2 x 5 mL), CH_2Cl_2 (1 x 5 mL), MeOH (1 x 5mL), and CH_2Cl_2 (3 x 5 mL). The resin was then cleaved in 1:1 TFA/CH_2Cl_2 (2 mL) for 2 hours. The cleavage solution was removed and the Minikan washed with CH_2Cl_2 (2 x 2 mL). Cleavage solution and washes were combined, dried, taken up in 0.5 mL

DMSO and subjected to HPLC purification to provide the title compound as a tan solid film. ESMS $[M+H]^+$m/z 495.6.

Example 6: Preparation of 3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-N-[(3-methylisoxazol-5-yl)methyl]-2-naphthamide (Method C)

3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoic acid (from Example 5a) (0.044 g, 125 umol) was dissolved in 0.25 mL DMSO and added to a mixture of (3-methyl-isoxazol-5-yl)-methylamine HCl (0.020 g, 134 umol) and DIEA (diisopropylethylamine, 87 uL, 500 umol) dissolved in 0.25 mL DMSO. DIC (1,3-diisopropylcarbodiimide, 60 uL, 375 umol) was added and the reaction mixture shaken at room temperature for 20 hours. The reaction mixture was directly subjected to HPLC purification to provide the title compound as a white solid. Yield = 0.019 g (34%). ESMS $[M+H]^+$m/z 449.2.

Example 7: Preparation of (2S)-cyclohexyl{[(3-{[(2-methylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid (Method D)

a). Preparation of resin bound (2S)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoic acid on Wang resin.

The title compound was prepared by the same procedure as in Example 1b except that L-Asp(tBu)-Wang resin was replaced with L-CHG-Wang resin in a polypropylene tube (resin prepared as in 2b) to give the title compound. The resin was drained and washed with NMP until the yellow color is gone. The resin was then washed with DCM (3X100 mL), methanol (3X100 mL), DCM (3X100 mL), acetonitrile (3 X100 mL), and DCM (3 X100 mL) and dried in vacuo. A small portion of resin was taken out, cleaved by 1:1 TFA: DCM for 30 min at room temperature. LC-MS showed 100% formation of desired coupling intermediate product.

b). Preparation of (2S)-cyclohexyl{[(3-{[(2-methylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid

To the resin from 7a (100 mg) in 1 mL pyridine was added a solution of (2-methylphenyl)acetyl chloride (25 mg, 2 eq) in a minimal amount of DCM for transfer (0.5 mL). After 4 hours at room temperature, the resin was washed and the reaction progress checked by LCMS. The resin was retreated under these

conditions, until the reaction was complete by LCMS. The resin was drained, and then washed with DCM (3X5 mL), acetonitrile (3X5 mL), DCM (3 X5 mL), acetonitrile (3X5 mL), and DCM (3 X5 mL), and then dried in vacuo. The resin was then cleaved in 1:1 TFA: DCM for 30 minutes. The crude product solution was concentrated in vacuo, taken up by DMSO (0.6 mL), purified by HPLC, and dried in vacuo to give the title compound as a white solid (16.4 mg). ESMS [M+H]+m/z 459.6.

By similar methods, the following compounds were prepared as shown, with characterizaton data given in Table 1.

Example 8: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate.

Example 9: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate.

Example 10: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]glycine. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-glycine Wang resin was substituted for Fmoc-L-Aspartic acid(Asp)(tBu)-Wang resin.

Example 11: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]glycine. This compound was prepared as described in Example 1 except Fmoc-glycine Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 12: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]glycine. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-glycine Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 13: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-alanine. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-alanine Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 14: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-threonine. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-threonine(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 15: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-isoleucine. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-isoleucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 16: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-leucine. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-leucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 17: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-asparagine. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-asparagine(Trityl(Trt))-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 18: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-alanine. This compound was prepared as described in Example 1 except that Fmoc-L-alanine Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 19: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-serine. This compound was prepared as described in Example 1 except that Fmoc-L-serine(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 20: 1-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-proline. This compound was prepared as described in Example 1 except that Fmoc-L-proline-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 21: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-valine. This compound was prepared as described in Example 1 except that Fmoc-L-valine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 22: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-threonine. This compound was prepared as described in Example 1 except that Fmoc-L-threonine(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 23: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-isoleucine. This compound was prepared as described in Example 1 except that Fmoc-L-isoleucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 24: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-leucine. This compound was prepared as described in Example 1 except that Fmoc-L-leucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 25: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-asparagine. This compound was prepared as described in Example 1 except that Fmoc- L-asparagine(Trt)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 26: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamine. This compound was prepared as described in Example 1 except that

Fmoc-L-glutamine(Trt)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 27: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-alanine. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-alanine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 28: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-serine. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-serine(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 29: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-threonine. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-threonine(tBu)-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 30: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-isoleucine. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-isoleucine-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 31: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-asparagine. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-asparagine(Trt)-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 32: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamine. This compound was prepared as described in Example 1 except that 2-

chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-glutamine(Trt)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 33: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-alanine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-alanine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 34: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-serine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc- L-serine(tBu)-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 35: 1-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-proline. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-proline-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 36: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-valine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-valine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 37: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-threonine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc- L-threonine(tBu)-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 38: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-isoleucine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc- L-isoleucine-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 39: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-leucine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc- L-leucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 40: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-asparagine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc- L-asparagine(Trt)-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 41: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc- L-glutamine(Trt)-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 42: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamic acid. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-glutamic acid(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 43: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-methionine. This compound was prepared as described in Example 1 except that

2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-methionine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 44: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-histidine trifluoroacetate. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-histidine(Trt)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 45: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-phenylalanine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 46: N-[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-tryptophan. This compound was prepared as described in Example 1 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 47: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-lysine trifluoroacetate. This compound was prepared as described in Example 1 except Fmoc-L-lysine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 48: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamic acid. This compound was prepared as described in Example 1 except Fmoc-L-glutamic acid(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 49: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-methionine. This compound was prepared as described in Example 1 except Fmoc-L-methionine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 50: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-histidine trifluoroacetate. This compound was prepared as described in Example 1 except Fmoc-L-histidine(Trt)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 51: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine. This compound was prepared as described in Example 1 except Fmoc-L-phenylalanine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 52: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-arginine. This compound was prepared as described in Example 1 except Fmoc-L-arginine(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl(Pbf))-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 53: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-tyrosine. This compound was prepared as described in Example 1 except Fmoc-L-tyrosine(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 54: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-tryptophan trifluoroacetate. This compound was prepared as described in Example 1 except Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 55: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamic acid. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and

Fmoc-L-glutamic acid(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 56: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-histidine trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-histidine(Trt)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 57: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-phenylalanine-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 58: N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-tryptophan trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 59: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-lysine trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-lysine(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 60: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-methionine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-methionine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 61: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-histidine trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-histidine(Trt)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 62: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-phenylalanine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 63: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-arginine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-arginine(Pbf)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 64: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-tyrosine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-tyrosine(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 65: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-tryptophan trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 66: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 67: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 68: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-leucine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-leucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 69: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-L-leucine. This compound was prepared as described in Example 1 except that 2-chl oro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-leucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 70: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-isoleucine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-isoleucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 71: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-L-isoleucine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-isoleucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 72: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-phenylalanine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-phenylalanine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 73: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-L-phenylalanine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-phenylalanine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 74: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-tryptophan trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 75: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-L-tryptophan trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was

substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 76: N-[2-({[(2-chlorophenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-tryptophan trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 77: N-[2-({[(2-chlorophenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-L-tryptophan trifluoroacetate. This compound was prepared as described in Example 1 except that 2-chlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 78: N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 79: N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-leucine. This compound was prepared as described in Example 1 except that 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-leucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 80: N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-isoleucine. This compound was prepared as described in Example 1 except that 2-amino-4,5-difluorobenzoic acid was substituted for 3-

amino-2-naphthalenecarboxylic acid, and Fmoc-L-isoleucine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 81: N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-phenylalanine. This compound was prepared as described in Example 1 except that 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-phenylalanine-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 82: N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-L-tryptophan trifluoroacetate. This compound was prepared as described in Example 1 except that 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-tryptophan(Boc)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 83: N-[2-({[(2,6-diethylphenyl)amino]carbonyl}amino)benzoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2,6-diethylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and 2-aminobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 84: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate.

Example 85: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]glycine. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-glycine-Wang resin was substituted for Fmoc-L-Asp(tBu)-Wang resin.

Example 86: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamic acid. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-glutamic acid(tBu)-Wang resin was substituted for Fmoc- L-Asp(tBu)-Wang resin.

Example 87: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)benzoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and 2-aminobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 88: N-[4-chloro-2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)benzoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and 2-amino-4-chlorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 89: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-5-iodobenzoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and 2-amino-5-iodobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 90: N-[3-({[(2-bromophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid. This compound was prepared as described in Example 1 except that 2-bromophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate.

Example 91: 4-bromo-N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine. This compound was prepared as described in Example 2 except that and Fmoc-L-4-bromophenylalanine was substituted for Fmoc –L-cyclohexylglycine.

Example 92: (2S)-cyclohexyl{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}acetic acid. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate.

Example 93: (2S)-cyclohexyl({[3-({[(2,6-diethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid. This compound was prepared as described in Example 2 except that 2,6-diethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate.

Example 94: (2S)-cyclohexyl{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)benzoyl]amino}acetic acid. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and 2-2-aminobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 95: {[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(phenyl)acetic acid. This compound was prepared as described in Example 2 except that 2-methylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 96: N-{[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-(2-thienyl)-L-alanine. This compound was prepared as described in Example 2 except that 2-methylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-2-thienylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 97: {[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(phenyl)acetic acid. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-

chloro-6-methylphenylisocyanate, and Fmoc-L-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 98: N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-(2-thienyl)-L-alanine. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-2-thienylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 99: 3-cyclohexyl-N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-alanine. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-cyclohexylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 100: {[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(phenyl)acetic acid. This compound was prepared as described in Example 2 except that 2-chlorophenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 101: N-{[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-(2-thienyl)-L-alanine. This compound was prepared as described in Example 2 except that 2-chlorophenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-2-thienylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 102: N-{[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-(2-thienyl)-L-alanine. This compound was prepared as described in Example 2 except that Fmoc-L-2-thienylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 103: Phenyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid. This compound was prepared as described in Example 2 except that 2,4,6-trimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-D-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 104: {[3-({[(2-isopropyl-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(phenyl)acetic acid. This compound was prepared as described in Example 2 except that 2-isopropyl-6-methylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-D-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 105: {[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]amino}(phenyl)acetic acid. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-D-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 106: [(2-{[(mesitylamino)carbonyl]amino}-4,5-dimethoxybenzoyl)amino](phenyl)acetic acid. This compound was prepared as described in Example 2 except that 2,4,6-trimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-D-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 107: {[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]amino}(phenyl)acetic acid. This compound was prepared as described in Example 2 except that 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-D-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 108: (2R)-cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl)amino]acetic acid. This compound was prepared as described in Example 2 except that 2,4,6-trimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-D-cyclohexylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 109: (2R)-cyclohexyl{[3-({[(2-isopropyl-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}acetic acid. This compound was prepared as described in Example 2 except that 2-isopropyl-6-methylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-D-cyclohexylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 110: (2R)-cyclohexyl{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}acetic acid. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-D-cyclohexylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 111: (2R)-{[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(cyclohexyl)acetic acid. This compound was prepared as described in Example 2 except that Fmoc-D-cyclohexylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 112: (2S)-{[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]amino}(cyclohexyl)acetic acid. This compound was prepared as described in Example 2 except that 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 113: (2S)-{[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]amino}(cyclohexyl)acetic acid. This compound was prepared as described in Example 2 except that 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 114: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-3-cyclohexyl-L-alanine. This compound was prepared as described in Example 2 except that 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-cyclohexylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 115: N-[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-3-cyclohexyl-L-alanine. This compound was prepared as described in Example 2 except that 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-cyclohexylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 116: (2S)-cyclohexyl{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]amino}acetic acid. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 117: (2S)-cyclohexyl{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]amino}acetic acid. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid.

Example 118: 3-cyclohexyl-N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-alanine. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, 2-amino-4,5-difluorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-cyclohexylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 119: 3-cyclohexyl-N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]-L-alanine. This compound was prepared as described in Example 2 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, 2-amino-4,5-dimethoxybenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-cyclohexylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 120: {[3-({[(2,6-diethylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(phenyl)acetic acid. This compound was prepared as described in Example 2 except that 2,6-diethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 121: N-[4-chloro-2-({[(2,6-diethylphenyl)amino]carbonyl}amino)benzoyl]-2-fluoro-D-phenylalanine. This compound was prepared as described in Example 2 except that 2,6-diethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, 2-amino-4-chlorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-D-2-fluorophenylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 122: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-3-cyclohexyl-L-alanine. This compound was prepared as described in Example 2 except that Fmoc-L-cyclohexylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 123: {[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(phenyl)acetic acid. This compound was prepared as described in Example 2 except that Fmoc-L-phenylglycine was substituted for Fmoc–L-cyclohexylglycine.

Example 124: N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-2-fluoro-D-phenylalanine. This compound was prepared as described in

Example 2 except that Fmoc-D-2-fluorophenylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 125: N-[4-chloro-2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)benzoyl]-3-cyclohexyl-L-alanine. This compound was prepared as described in Example 2 except that 2-amino-4-chlorobenzoic acid was substituted for 3-amino-2-naphthalenecarboxylic acid, and Fmoc-L-cyclohexylalanine was substituted for Fmoc–L-cyclohexylglycine.

Example 126: N-{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-isoleucine. This compound was prepared as described in Example 3 except that Fmoc-L-isoleucine-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 127: N-[(2-{[(mesitylamino)carbonyl]amino}-4,5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-L-isoleucine. This compound was prepared as described in Example 3 except that 2,4,6-trimethylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-isoleucine-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 128: N-{[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-isoleucine. This compound was prepared as described in Example 3 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-isoleucine-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 129: N-{[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-isoleucine. This compound was prepared as described in Example 3 except that 2,6-dichlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-isoleucine-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 130: N-{[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-leucine. This compound was prepared as described in Example 3 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-leucine-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 131: N-{[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-leucine. This compound was prepared as described in Example 3 except that 2,6-dichlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-leucine-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 132: N-{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 3 except that Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 133: N-[(2-{[(mesitylamino)carbonyl]amino}-4,5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-L-aspartic acid. This compound was prepared as described in Example 3 except that 2,4,6-trimethylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 134: N-{[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 3 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 135: N-{[2-({[(2-isopropyl-6-methylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 3 except that 2-isopropyl-6-

methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 136: N-{[2-({[(2,6-diethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 3 except that 2,6-diethylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 137: N-{[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 3 except that 2,6-dichlorophenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–L-valine-Wang resin.

Example 138: (2S)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}amino)acetic acid. This compound was prepared as described in Example 3 except that Fmoc-L-cyclohexylglycine-Wang resin (prepared as in Example 2a) was substituted for Fmoc–L-valine-Wang resin.

Example 139: (2S)-({[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}amino)(cyclohexyl)acetic acid. This compound was prepared as described in Example 3 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-cyclohexylglycine-Wang resin (prepared as in Example 2a) was substituted for Fmoc–L-valine-Wang resin.

Example 140: (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}amino)acetic acid. This compound was prepared as described in Example 3 except that 2,6-dichlorophenylisocyanate

was substituted for 2,6-dimethylphenylisocyanate, and Fmoc-L-cyclohexylglycine-Wang resin (prepared as in Example 2a) was substituted for Fmoc–L-valine-Wang resin.

Example 141: (2S)-cyclohexyl({[2-({[(2-methylphenyl)amino]carbonyl}amino)-1-benzothien-3-yl]carbonyl}amino)acetic acid. This compound was prepared as described in Example 4 except that 2-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate.

Example 142: (2S)-({[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-1-benzothien-3-yl]carbonyl}amino)(cyclohexyl)acetic acid. This compound was prepared as described in Example 4 except that 2-chloro-6-methylphenylisocyanate was substituted for 2,6-dimethylphenylisocyanate.

Example 143: (2S)-cyclohexyl{[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}acetic acid. This compound was prepared as described in Example 5 except that 2-methylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-cyclohexylglycine-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 144: 3-cyclohexyl-N-{[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine. This compound was prepared as described in Example 5 except that 2-methylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-cyclohexylalanine-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 145: 3-cyclohexyl-N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine. This compound was prepared as described in Example 5 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-cyclohexylalanine-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 146: 3-cyclohexyl-N-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine. This compound was prepared as described in Example 5 except that 2,6-dichlorophenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-cyclohexylalanine-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 147: N-{[3-({[(3,5-dimethyl-4-isoxazolyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 5 except that 3,5-dimethylisoxazole-4-isocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 148: N-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 5 except that 2,6-dichlorophenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 149: N-{[3-({[(2,6-difluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 5 except that 2,6-difluorophenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 150: N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 5 except that 2,6-dimethylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 151: N-{[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid. This compound was prepared as described

in Example 5 except that 2,6-chlorophenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 152: N-{[3-({[(2-methylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid. This compound was prepared as described in Example 5 except that 2-methylphenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-Aspartic acid(tBu)-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 153: (2S)-cyclohexyl({[3-({[(2,6-difluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid. This compound was prepared as described in Example 5 except that 2,6-difluorophenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-cyclohexylalanine-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 154: (2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid. This compound was prepared as described in Example 5 except that 2,6-dichlorophenylisocyanate was substituted for 2-chloro-6-methylphenylisocyanate, and Fmoc-L-cyclohexylalanine-Wang resin was substituted for Fmoc–(1-Boc-piperidin-3-yl)-D,L-glycine-Wang resin.

Example 155: (2S)-cyclohexyl{[(3-{[(2,6-dichlorophenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid. This compound was prepared as described in Example 7 except that (2,6-dichlorophenyl)acetyl chloride was substituted for (2-methylphenyl)acetyl chloride.

Example 156. (2S)({[4chloro2({[(2,6dichlorophenyl)amino]carbonyl}amino) phenyl] carbonyl}amino)(cyclohexyl)ethanoic acid.

Step 1. 4-chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)benzoic acid.

2,6-Dichlorophenyl isocyanate (0.60 g, 3.21 mmol) was added to a solution of 4-chloroanthranilic acid (0.50 g, 2.91 mmol) and triethylamine (0.59 g, 5.82 mmol) in 20 mL of DMF. The mixture was heated at 70°C for 2 hours. The cooled reaction mixture was acidified with 10 mL of 1N HCl, and filtered to collect the precipitated white solid. After washing with water and drying under vacuum 0.616 g (59% yield) of desired product was obtained. ES-MS m/z 358

Step 2. Methyl(2S)({[4chloro2({[(2,6dichlorophenyl)amino] carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate.

HATU (0.319 g, 0.84 mmol) was added to a solution of 4-chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)benzoic acid (0.200 g, 0.56 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.115 g, 0.56 mmol) and diisopropylethylamine (0.11 g, 0.84 mmol) in 10 mL of DMF. After stirring at RT (room temperature) overnight, the mixture was diluted with ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate, filtered , the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.195 g of 80% pure product.

Step 3. (2S)({[4chloro2({[(2,6dichlorophenyl)amino]carbonyl}amino) phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide (0.089 g, 3.70 mmol) was added to a solution of methyl(2S)({[4chloro2({[(2,6dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl} amino)(cyclohexyl)ethanoate (0.190 g, 0.37 mmol) in THF: MeOH: water/4:1:1. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and evaporated to dryness. The residue was extracted between dichloromethane and water. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified by chromatography on silica gel with dichloromethane/methanol to give 12 mg (6.5% yield) of pure desired product as a white solid. ES MS m/z 496 (M-H).

Example 157: (2S)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino) phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid.

This compound was synthesized by methods similar to those described as in Example 156 in 1% overall yield using 2,6-dimethylphenyl isocyanate in place of 2,6-dichlorophenyl isocyanate. ES MS m/z 456 (M-H)

Example 158: (2S)-cyclohexyl{[3({[(2,4,6trichlorophenyl)amino]carbonylamino) -2-naphthoyl]amino}ethanoic acid.

Step 1. 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid

Di-tert-butyl-dicarbonate (1.75 g, 8.01 mmol) was added to 3-amino-2-naphthoic acid (1.0 g, 5.34 mmol) in 20 mL of THF and 20 mL of 1N aqueous sodium hydroxide. The mixture was stirred at RT for ca. 20 h. The THF was removed under reduced pressure and the aqueous phase as acidified with 1N aqueous $NaHSO_4$. The resulting solution was extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified by chromatography on silica gel with dichloromethane/methanol to give 1.1 g (71 % yield) of desired product as a off white solid. ES MS m/z 286 (M-H).

Step 2. Methyl (2S)-({3-[(tert-butoxycarbonyl)amino]-2-naphthoyl}amino)(cyclohexyl)ethanoate

HATU (0.595 g, 1.56 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (0.390 g, 1.36 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.325 g, 1.56 mmol) and diisopropylethylamine (0.263 g, 2.04 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 3 h. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.443g of product.

Step 3. Methyl (2S)-[(3-amino-2-naphthoyl)amino](cyclohexyl)ethanoate hydrochloride

Methyl (2S)-({3-[(tert-butoxycarbonyl)amino]-2-naphthoyl}amino)(cyclohexyl)ethanoate (0.44 g, 1.0 mmol) in 10 mL of CH_2Cl_2 was treated with 5 mL of 4 N HCl in dioxane. The mixture as stirred at RT for ca. 1.5 h and the solvents were removed under reduced pressure to give the 0.376 g (100%) of the product.

Step 4. Methyl (2S)-cyclohexyl{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl} amino)-2-naphthoyl]amino}ethanoate

Methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate hydrochloride (0.05 g, 0.133 mmol) in 5 mL of pyridine was treated with 2,4,6-trichlorophenyl isocyanate (0.15 g, 0.67 mmol) for ca. 4h at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.052 g of product.

Step 5. (2S)-cyclohexyl{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthoyl]amino}ethanoic acid

Lithium hydroxide monohydrate (0.0.018 g, 3.70 mmol) was added to a solution of methyl (2S)-cyclohexyl{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthoyl]amino}ethanoate (0.052 g, 0.09 mmol) in THF: MeOH: water/3:1:1. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 42 mg (82 % yield) of desired product as a white solid. ES MS m/z 546 (M-H).

Example 159: (2S)-cyclohexyl{[3-({[(2-ethyl-6-methylphenyl)amino]carbonyl} amino)-2-naphthoyl]amino}ethanoic acid

This compound was synthesized by methods similar to those described as in Example 158 in 65% overall yield using 2-ethyl-6-methylphenyl isocyanate in place of 2,4,6-trichlorophenylisocyanate. ES MS m/z 486 (M-H).

Example 160: (2S)-({3-[({[2-chloro-6-(trifluoromethyl)phenyl]amino}carbonyl) amino]-2-naphthoyl}amino)(cyclohexyl)ethanoic acid.

This compound was synthesized by methods similar to those described as in Example 158 in 70% overall yield using 2-chloro-6-trifluoromethylphenyl isocyanate in place of 2,4,6-trichlorophenylisocyanate. ES MS m/z 546 (M-H).

Example 161: (2S)-cyclohexyl{[3-({[2,6-dichloro-4-(trifluoromethyl) phenyl]acetyl} amino)-2-naphthoyl]amino}ethanoic acid.

Step 1.

Methyl (2S)-cyclohexyl{[3-({[2,6-dichloro-4-(trifluoromethyl)phenyl] acetyl}amino)-2-naphthoyl]amino}ethanoate

HATU (0.058 g, 0.15 mmol) was added to a solution of methyl (2S)-[(3-amino-2-naphthoyl)amino](cyclohexyl)ethanoate hydrochloride (prepared as described in Example 158) (0.0.05 g, 0.133 mmol), [2,6-dichloro-4-(trifluoromethyl) phenyl]acetic acid (0.042 g, 0.15 mmol) and diisopropylethylamine (0.03 g, 0.20 mmol) in 3 mL of DMF. The mixture was stirred at RT for ca. 20 h. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with $NaHCO_3$ and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.042 g of product.

Step 2.

(2S)-cyclohexyl{[3-({[2,6-dichloro-4-(trifluoromethyl)phenyl]acetyl}amino)-2-naphthoyl]amino}ethanoic acid

Lithium hydroxide monohydrate (0.0.009 g, 0.2 mmol) was added to a solution methyl (2S)-cyclohexyl{[3-({[2,6-dichloro-4-(trifluoromethyl)phenyl]acetyl}amino)-2-naphthoyl]amino}ethanoate (0.040 g, 0.07 mmol) in THF: MeOH: water/3:1:1. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 38 mg (97 % yield) of desired product as a white solid. ES MS m/z 579 (M-H).

Example 162: (2S)-cyclohexyl[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-2-naphthoyl)amino]ethanoic acid.

This compound was synthesized by similar methods to those described as in Example 161 in 45% overall yield using (2,4,6-trichlorophenyl)acetic acid in place of [2,6-dichloro-4-(trifluoromethyl)phenyl]acetic acid. ES MS m/z 546 (M-H).

Example 163: N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-beta-alanine.

Step 1. 3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoic acid

To a DMF solution (50 mL) containing 3-amino-2 napthoic acid (2g, 10.68 mmol) was added TEA (3 mL, 21.36 mmol). After stirring for 30 min, 2,6-dimethylphenyl isocyanate (1.72 mL, 11.75mmol) was added and the solution heated at 75 °C for 2h. After cooling to RT the mixture was acidified with 1.0M HCl and extracted with ethyl acetate. A white precipitate was observed in the organic layer and was separated by filtration. The resulting solid was identified as the product by proton NMR and was taken on without further purification. The product was isolated as a white solid in a 94% yield.

Step 2. Methyl N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-beta-alaninate

To a DMF solution (5 mL) of 3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoic acid (0.2g, .597 mmol) was added HATU (0.27g, 0.717mmol) and DIEA

(0.124mL, 0.717 mmol). After stirring for 30 min, beta-alanine methylester hydrochloride (0.1g, 0.717mmol) in DMF (2 mL) was added. After 2 h at RT the reaction was poured in sat. $NaHCO_3$ and extracted with ethyl acetate. The combined organics were then washed with water, dried over $MgSO_4$, filtered and reduced in vacuo to yield a yellow solid. The solid was purified using flash chromotography (EtOAc/Hexanes). The product was isolated as a white solid in a 62% yield.

Step 3. N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-beta-alanine

To a THF soln (5mL) containing methyl N-[3-({[(2,6-dimethylphenyl)amino] carbonyl}amino)-2-naphthoyl]-beta-alaninate (0.15g, 0.357mmol) was added LiOH (0.085g, 3.57mmol) in a 2mL soln of H_2O + 1mL of MeOH. The soln was allowed to stir at RT for 2 h. To the mixture was added 1.0 M HCl and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, filtered and reduced in vacuo to yield a white solid. The solution was triturated with ether and filtered to yield the product as a white solid in a 35% yield. ES MS m/z 404 (M-H).

Example 164: (2S)-cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl)amino]ethanoic acid.

Step 1. 3-{[(mesitylamino)carbonyl]amino}-2-naphthoic acid
The title compound was prepared in 65% yield as described in Example 163, Step 1, except that 2,4,6-trimethylphenylisoycanate was substituted for 2,6-dimethylphenyl isocyanate.

Step 2. Methyl (2S)-cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl)amino]ethanoate
The title compound was prepared in 65% yield as described in Example 163, Step 2, except that 3-{[(mesitylamino)carbonyl]amino}-2-naphthoic acid was substituted for 3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoic acid and methyl

(2S)-amino(cyclohexyl)ethanoate hydrochloride was substituted for beta-alanine methyl ester hydrochloride.

Step 3. (2S)-cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl)amino]ethanoic acid

The title compound was prepared in 40% yield as described in Example 163, Step 3, except that methyl (2S)-cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl)amino]ethanoate was substituted for methyl N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-beta-alaninate and 1,4-dioxane was substituted for THF. ESMS m/z 486 (M-H).

Example 165: 4-Chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)benzoic acid

Triethylamine (0.81 mL, 5.82 mmol) was added to a solution of 2-amino-4-chlorobenzoic acid (0.50 g, 2.91 mmol) in 20 mL of DMF. After stirring at room temperature for 15 minutes, 2,6-dichlorophenylisocyanate (0.60g, 3.21 mmol) was added. The mixture was heated at 75°C for 2 hours. After cooling to room temperature, 1N HCl (10 mL) was added, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under vacuum to give 0.616 g (59% yield) of desired product as a white powder. ES MS m/z 358 (M-H).

Example 166: 2-({[(2,6-Dimethylphenyl)amino]carbonyl}amino)benzoic acid

Triethylamine (1.6 mL, 11.7 mmol) was added to a solution of 2-amino-4-chlorobenzoic acid (1.00 g, 5.83 mmol) in 30 mL of DMF. After stirring at room temperature for 30 minutes, 2,6-dimethylphenylisocyanate (0.94 g, 6.41 mmol) was added. The mixture was heated at 75°C for 1 hour. After cooling to room temperature, 1N HCl (15 mL) was added. The precipitated solid was poorly soluble in ethyl acetate. The solid was collected by filtration, washed with water and dried under vacuum to give 1.58 g (85% yield) of desired product. ES MS m/z 317 (M-H).

Example 167: (2*S*)-({[4-Chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

Step 1. Methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate

HATU (0.179 g, 0.47 mmol) was added to a solution of 2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)benzoic acid (0.100 g, 0.31 mmol), in 5 mL of DMF. After stirring for 30 minutes, methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.064 g, 0.31 mmol) and diisopropylethylamine (0.081 mL, 0.46 mmol) was added. The mixture was stirred at room temperature overnight. The DMF was removed under vacuum and the residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.079 g (54% yield) of desired product as a colorless gum.

Step 2. (2*S*)-({[4-Chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

A solution of lithium hydroxide (0.040 g, 1.70 mmol) in 0.5 mL of water was added to a solution of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.079 g, 0.17 mmol) in THF:methanol/4:1. The mixture was heated at 50°C overnight. The reaction mixture was acidified with 1N aqueous HCl and the solvent was evaporated to dryness. The residue was extracted between water and dichloromethane. The organic phase was dried over sodium sulfate and the solvent was removed under vacuum to give 0.025 g (32% yield) of desired product as a white solid. ES MS m/z 456 (M-H).

Example 168: (2*S*)-({[4-Chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

Step 1. Methyl (2*S*)-({[4-chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate

HATU (0.319 g, 0.84 mmol) was added to a solution of 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)benzoic acid (0.200 g, 0.56 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.115 g, 0.56 mmol) and diisopropylethylamine (0.15 mL, 0.84 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight. The reaction mixture was extracted between ethyl acetate and water. The organic phase was washed with water and brine and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave a mixture containing 80% of desired product. This material was carried on to the next step without additional purification.

Step 2. (2*S*)-({[4-Chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

A solution of lithium hydroxide (0.089 g, 3.70 mmol) in 1 mL of water was added to a solution of methyl (2*S*)-({[4-chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.190 g, 0.37 mmol) in 5 ml of THF:methanol/4:1. The mixture was heated at 50°C for 2 hours. The solvent was evaporated and the residue was treated with aqueous 1N hydrochloric acid and extracted with dichloromethane. The organic phase was dried over sodium sulfate and the the solvent was evaporated. Chromatography on silica gel with dichloromethane/methanol gave 0.012 g (6.5% yield) ES MS m/z 496 (M-H).

Example 169: (2*S*)Cyclohexyl({[2({[(2,6dimethylphenyl)amino]carbonyl}amino)-5-methylphenyl]carbonyl}amino)ethanoic acid

Step 1. 2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-5-methylbenzoic acid

Triethylamine (0.81 mL, 5.82 mmol) and 2,6-dimethylphenylisocyanate (0.47 g, 3.21 mmol) were added to a solution of 2-amino-5-methylbenzoic acid (0.500 g, 3.3 mmol) in anhydrous DMF (15 mL). The mixture was heated at 70°C for one hour. After cooling to room temperature, 2 mL of 6N aqueous HCl was added and the mixture was diluted with water. The precipitated solid was filtered, washed with water and dried under vacuum overnight to give 0.96 g of desired product as a white powder.

Step 2. Methyl (2*S*)-cyclohexyl({[2({[(2,6dimethylphenyl)amino]carbonyl}amino)-5-methylphenyl]carbonyl}amino)ethanoate

HATU (0.191 g, 0.50 mmol) was added to a solution of 2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-5-methylbenzoic acid (0.100 g, 0.33 mmol),

methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.070 g, 0.33 mmol) and diisopropylethylamine (0.087 mL, 0.50 mmol) in 5 mL of DMF. After stirring at room temperature overnight, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate and the solvent was evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.066 g (44% yield) of desired product as a white solid.

Step 3. (2*S*)Cyclohexyl({[2({[(2,6dimethylphenyl)amino]carbonyl}amino)-5-methylphenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.034 g, 1.41 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2({[(2,6dimethylphenyl)amino]carbonyl}amino)-5-methylphenyl]carbonyl}amino)ethanoate (0.064 g, 0.14 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature for 4 hours and acidified with 1N aqueous HCl. The solvents were evaporated and the residue was extracted between dichloromethane and water. An insoluble white solid remained in suspension which was filtered and dried under vacuum to give 0.039 g (64% yield) of desired product. ES MS m/z 436 (M-H).

Example 170:
N{[4chloro2({[(2,6dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}glycine

Step 1. 1,1-Dimethylethyl *N*-{[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}glycinate

HATU (0.177 g, 0.46 mmol) was added to a solution of 2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-chlorobenzoic acid (0.100 g, 0.31 mmol), 1,1-dimethylethyl glycinate (0.061 g, 0.46 mmol) and diisopropylethylamine (0.11 mL, 0.62 mmol) in 5 mL of DMF. After stirring at room temperature for 2 hours, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate and the solvent was evaporated.

Chromatography on silica gel with hexane/ethyl acetate gave 0.076 g (57% yield) of desired product as a white solid.

Step 2. *N*-{[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}glycine

Trifluoroacetic acid (0.040 mL, 0.53 mmol) was added to a solution of 1,1-Dimethylethyl *N*-{[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}glycinate (0.076 g, 0.18 mmol) in 1 mL of dichloromethane. The solution was stirred at room temperature for 60 hours. The crude product was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.037 g (55% yield) of the desired product as a white solid. ES MS m/z 374 (M-H).

Example 171: (2*S*)-({[4-Chloro-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

Step 1. Methyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}-(cyclohexyl)ethanoate

HATU (1.66 g, 4.36 mmol) was added to a solution of 2-amino-4-chlorobenzoic acid (0.50 g, 2.91 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (2.54 g, 12.2 mmol) and diisopropylethylamine (0.76 mL, 4.36 mmol) in 25 mL of DMF. The mixture was stirred at room temperature overnight, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.66 g (70% yield) of a white solid.

Step 2. Methyl (2*S*)-({[4-chloro-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate

2,4,6-Trichlorophenylisocyanate (0.343 g, 1.54 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.100 g, 0.31 mmol) in anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.160 g of desired product.

Step 3. 2*S*)-({[4-Chloro-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

Lithium hydroxide (0.068 g, 2.8 mmol) was added to a solution of methyl (2*S*)-({[4-chloro-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.155 g, 0.28 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.026 g (17% yield) of desired product as a white solid. ES MS m/z 532 (M-H).

Example 172: (2*S*)-({[4-Chloro-2-({[(2-chloro-6-methylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. Methyl (2*S*)-({[4-chloro-2-({[(2-chloro-6-methylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate

2-Chloro-6-methylphenylisocyanate (0.26 g, 1.54 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate

(0.100 g, 0.31 mmol) in anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.158 g of desired product as a clear resin.

Step 2. (2*S*)-({[4-chloro-2-({[(2-chloro-6-methylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide (0.073 g, 3.0 mmol) was added to a solution of methyl (2*S*)-({[4-chloro-2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)phenyl]-carbonyl}amino)(cyclohexyl)ethanoate (0.150 g, 0.30 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.038 g (26% yield) of desired product as a white solid. ES MS m/z 476 (M-H).

Example 173: (2*S*)-({[4-Bromo-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

Step 1. 4-Bromo-2-nitrobenzoic acid

Sodium carbonate (4.53 g, 42 mmol) was added to a suspension of 4-bromo-2-nitrotoluene (2.00 g, 9.26 mmol) in 140 mL of water. The mixture was heated to 80°C. Potassium permanganate (5.85 g, 37 mmol) was added and the temperature was raised to 105°C and heating was continued under a reflux condenser overnight. The reaction mixture was cooled to room temperature and filtered

through Celite. The filtrate was acidified with 6N aqueous HCl and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated to give 0.59 g (26% yield) of desired product as a beige solid.

Step 2. Methyl (2*S*)-{[(4-bromo-2-nitrophenyl)carbonyl]amino}(cyclohexyl)-ethanoate

HATU (1.35 g, 3.55 mmol) was added to a solution of 4-bromo-2-nitrobenzoic acid (0.585 g, 2.37 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.592 g, 2.85 mmol) and diisopropylethylamine (0.62 mL, 3.55 mmol) in 25 mL of DMF. The mixture was stirred at room temperature overnight, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.704 g (74% yield) of desired product as a white solid.

Step 3. Methyl (2*S*)-{[(2-amino-4-bromophenyl)carbonyl]amino}(cyclohexyl)-ethanoate

Tin(IV) chloride dihydrate (3.37 g, 14.9 mmol) was added to a suspension of methyl (2*S*)-{[(4-bromo-2-nitrophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.595 g, 1.49 mmol) in 20 mL of methanol. The mixture was heated at reflux for 5 hours. The solvent was evaporated, the residue was shaken with ethyl acetate and water and filtered through Celite. The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was removed under vacuum to give 0.370g (67% yield) of desired product.

Step 4. Methyl (2*S*)-({[4-bromo-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)ethanoate

2,6-Dimethylphenylisocyanate (0.49 g, 4.92 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-bromophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.363 g, 0.98 mmol) in 15 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.409 g (81% yield) of desired product as a white solid.

Step 5. (2*S*)-({[4-Bromo-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide (0.046 g, 1.90 mmol) was added to a solution of methyl (2*S*)-({[4-bromo-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]-carbonyl}amino)(cyclohexyl)ethanoate (0.100 g, 0.19 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.069 g (72% yield) of desired product as a white solid. ES MS m/z 502, 504 (M, M+2).

Example 174: *N*-{[4-Chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartic acid

Step 1. Dimethyl *N*-{[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}-L-aspartate

HATU (0.268 g, 0.705 mmol) was added to a solution 4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)benzoic acid (0.150 g, 0.47 mmol), dimethyl L-aspartate hydrochloride (0.102 g, 0.52 mmol) and diisopropylethylamine (0.12

mL, 0.705 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.120 g (55% yield) of desired product as a colorless gum.

Step 2. *N*-{[4-Chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartic acid

Lithium hydroxide (0.062 g, 2.60 mmol) was added to a solution of dimethyl *N*-{[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartate (0.120 g, 0.26 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.022 g (20% yield) of desired product as a white solid. ES MS m/z 432 (M-H)

Example 175: (2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-Bromo-2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.185 g, 0.36 mmol), phenylboronic acid (0.044 g, 0.36 mmol), transdichlorobis(triphenylphosphine)-palladium(II) (0.013 g, 0.018 mmol), and 0.70 mL of 1M aqueous sodium carbonate in 1.5 mL of acetonitrile was heated to 150°C in a microwave reactor for 5 minutes. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over anhydrous

sodium sulfate and the solvent was evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.116 g (63% yield) of desired product as a white solid.

Step 2. (2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.054 g, 2.30 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.116 g, 0.23 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.068 g (59% yield) of desired product as a white solid. ES MS m/z 498 (M-H).

Example 176: (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-methylphenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-{[(2-amino-4-methylphenyl)carbonyl]amino}(cyclohexyl)-ethanoate

HATU (1.13 g, 2.98 mmol) was added to a solution 2-amino-4-methylbenzoic acid (0.300 g, 1.99 mmol), methyl (2*S*)-cyclohexyl(methylamino)ethanoate hydrochloride (0.495 g, 2.38 mmol) and diisopropylethylamine (0.52 mL, 2.98 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.270 g (45% yield) of desired product as a colorless gum.

Step 2. Methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4-methylphenyl]carbonyl}amino)ethanoate

2,6-Dimethylphenylisocyanate (0.27 g, 1.87 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-methylphenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.114 g, 0.37 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.153 g (90% yield) of desired product as a white solid.

Step 3. 2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-methylphenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.081 g, 3.40 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-methylphenyl]carbonyl}amino)ethanoate (0.153 g, 0.34 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.092 g (62% yield) of desired product as a white solid. ES MS m/z 436 (M-H).

Example 177: (2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]-carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. 2-Amino-4,5-dichlorobenzoic acid

Azidotrimethylsilane (2.34 g, 20.7 mmol) was added to a suspension of 5,6-dichloro-2-benzofuran-1,3-dione (3.00 g, 13.8 mmol) in 60 mL of toluene. The mixture was heated at 80°C for 3 hours. The temperature was raised to 100°C and heating was continued overnight. Toluene was evaporated under reduced pressure and 30 mL of ethanol was added to the residue, and the solvent again removed under vacuum. The resulting white solid was suspended in 50 mL of concentrated HCl and heated to 100°C for 1 hour. The mixture was cooled to room temperature and evaporated to dryness to give 3.3 g of an off-white powder. This crude product was carried on to the next step without further purification.

Step 2. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

HATU (7.87 g, 20.7 mmol) was added to a solution of 2-amino-4,5-dichlorobenzoic acid (0.300 g, 1.99 mmol), 1,1-dimethylethyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (3.78 g, 15.2 mmol) and diisopropylethylamine (3.6 mL, 20.7 mmol) in 100 mL of DMF. The mixture was stirred at room temperature overnight, then concentrated under vacuum, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 2.06 g (37% yield) of desired product as a yellow solid

Step 3. Methyl (2*S*)-cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

2,6-Dichlorophenylisocyanate (1.17 g, 6.23 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.500 g, 1.25 mmol) in 20 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried

over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.164 g (22% yield) of desired product as a white solid.

Step 4. (2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.164 g, 0.28 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature overnight. The solvent was evaporated to give 0.155 g (100% yield) of desired product as a white solid. ES MS m/z 531 (M-H).

Example 178: (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(trifluoromethyl)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[2-nitro-4-(trifluoromethyl)phenyl]carbonyl}-amino)ethanoate

HATU (0.730 g, 1.92 mmol) was added to a solution 2-nitro-3-trifluoromethylbenzoic acid (0.300 g, 1.28 mmol), (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.265 g, 1.28 mmol) and diisopropylethylamine (0.33 mL, 1.92 mmol) in DMF. The mixture was stirred at room temperature overnight, then diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum to give 0.442 g (88% yield) of desired product as a white solid.

Step 2. Methyl (2*S*)-({[2-amino-4-(trifluoromethyl)phenyl]carbonyl}-amino)(cyclohexyl)ethanoate

A mixture of methyl (2*S*)-cyclohexyl({[2-nitro-4-(trifluoromethyl)phenyl]carbonyl}-amino)ethanoate (0.374 g, 0.96 mmol) and 5% palladium on carbon (0.102 g, 0.048 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.176 g (49% yield) of desired product.

Step 3. (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(trifluoromethyl)phenyl]carbonyl}amino)ethanoic acid

2,6-Methylphenylisocyanate (0.36 g, 2.45 mmol) was added to a solution of methyl (2*S*)-({[2-amino-4-(trifluoromethyl)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate (0.176 g, 0.49 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.265 g of desired product as a white solid.

Step 4. (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(trifluoromethyl)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.123 g, 5.1 mmol) was added to a solution of (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(trifluoromethyl)phenyl]carbonyl}amino)ethanoic acid (0.260 g, 0.51 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum

to give 0.204 g (81% yield) of desired product as a white solid. ES MS m/z 490 (M-H).

Example 179: (2*S*)-({[4-Chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. Methyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate

2,4,6-Trimethylphenylisocyanate (0.587 g, 3.65 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate, (0.237 g, 0.73 mmol) in anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.321 g (90% yield) of desired product as a white solid.

Step 2. (2*S*)-({[4-Chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide (0.155 g, 6.50 mmol) was added to a solution of methyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-amino)(cyclohexyl)ethanoate (0.314 g, 0.65 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.250 g (81% yield) of desired product as a white solid. ES MS m/z 470 (M-H).

Example 180: (2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dimethylphenyl)-amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. 2-Amino-4,5-dichlorobenzoic acid

Azidotrimethylsilane (0.53 g, 6.9 mmol) was added to a suspension of 5,6-dichloro-2-benzofuran-1,3-dione (1.00 g, 4.6 mmol) in 20 mL of toluene. The mixture was heated at 80°C for 3 hours. The temperature was raised to 100°C and heating was continued overnight. Toluene was evaporated under reduced pressure and 10 mL of ethanol was added to the residue, and the solvent was again removed under vacuum. The resulting white solid was suspended in 10 mL of concentrated HCl and heated to 100°C for 1 hour. The mixture was cooled to room temperature and evaporated to dryness to give 0.491 g of an off-white powder. This crude product was carried on to the next step without further purification.

Step 2. Methyl (2*S*)-{[(2-amino-4,5-dichlorophenyl)carbonyl]amino}(cyclohexyl)-ethanoate

HATU (1.33 g, 3.49 mmol) was added to a solution 2-amino-4,5-dichlorobenzoic acid (0.480 g, 2.33 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.531 g, 2.56 mmol) and diisopropylethylamine (0.61 mL, 3.49 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight, then diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.283 g (34% yield) of desired product as a white solid.

Step 3. Methyl (2*S*)-cyclohexyl({[4,5-dichloro-2-({[(2,6-dimethylphenyl)amino]-carbonyl}amino)phenyl]carbonyl}amino)ethanoate

2,6-Dimethylphenylisocyanate (0.34 g, 2.28 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4,5-dichlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate

(0.164 g, 0.46 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.191 g (82% yield) of desired product as a white solid.

Step 4. (2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.084 g, 3.50 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[4,5-dichloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)ethanoate (0.178 g, 0.35 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight, acidified with 1N aqueous HCl, and the solvent was removed under vacuum. The residue was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.141 g (82% yield) of desired product as a white solid. ES MS m/z 490 (M-H).

Example 181: (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-pyridinyl)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)ethanoate

HATU (0.97 g, 2.56 mmol) was added to a solution 4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)benzoic acid (0.546 g, 1.71 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.427 g, 2.06 mmol) and diisopropylethylamine (0.44 mL, 2.56 mmol) in DMF. The mixture was stirred at room temperature overnight, then diluted with ethyl acetate and washed with water

and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.575 g (71% yield) of desired product as a white solid.

Step 2. Methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4-(3-pyridinyl)phenyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate, (0.151 g, 0.32 mmol), 3-pyridinylboronic acid (0.047 g, 0.38 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.012 g, 0.016 mmol), and 2M aqueous sodium carbonate (0.48 mL, 0.96 mmol) in 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The reaction mixture was cooled to room temperature and diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.060 g of a white solid containing 70% desired product.

Step 3. (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-pyridinyl)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.028 g, 1.2 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-pyridinyl)phenyl]carbonyl}amino)ethanoate (0.060 g, 0.12 mmol) in THF:methanol:water/2:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous HCl was added to the residue. Aqueous sodium hydroxide was then added to adjust the pH to 5, and the mixture was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The residue was purified by reverse phase HPLC with acetonitrile/water with 0.1%

formic acid to give 0.007 g (12% yield) of desired product as a white solid. ES MS m/z 499 (M-H).

Example 182: (2*S*)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}-amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl 3-nitro-4-biphenylcarboxylate

Methyl 4-chloro-2-nitrobenzoate (0.50 g, 2.32 mmol), phenylboronic acid (0.31 g, 2.55 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.084 g, 0.115 mmol) and cesium fluoride (1.06 g, 6.95 mmol) were mixed in 13 mL of acetonitrile:water/3:1 in each of two microwave reaction vials and heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixtures were combined and filtered through Celite, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.95 g (80% yield) of desired product as a yellow oil.

Step 2. 3-Nitro-4-biphenycarboxylic acid

Lithium hydroxide (0.259 g, 10.78 mmol) was added to a solution of methyl 3-nitro-4-biphenylcarboxylate (0.924 g, 3.59 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was removed under vacuum to give 0.854 g (98% yield) of the desired acid as a white solid.

Step 3. 1,1-Dimethylethyl (2*S*)-cyclohexyl{[(3-nitro-4-biphenylyl)carbonyl]amino}-ethanoate

HATU (1.97 g, 5.17 mmol) was added to a solution of 3-nitro-4-biphenylcarboxylic acid (0.838 g, 3.45 mmol), 1,1-dimethylethyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.861 g, 3.45 mmol) and diisopropylethylamine (0.90 mL, 5.17 mmol) in 40 mL of DMF. The mixture was stirred at room temperature overnight, then concentrated under vacuum, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.13 g (75% yield) of desired product as a white solid.

Step 4. 1,1-Dimethylethyl (2*S*)-{[(3-amino-4-biphenylyl)carbonyl]amino}-(cyclohexyl)ethanoate

A mixture of 1,1-dimethylethyl (2*S*)-cyclohexyl{[(3-nitro-4-biphenylyl)carbonyl]amino}ethanoate (1.10 g, 2.51 mmol) and 5% palladium on charcoal (0.267 g, 0.125 mmol), in a pressure reaction vessel, was evacuated and flushed with nitrogen three times, then evacuated and filled with hydrogen and stirred at 50 psi for one hour. Filtration through Celite and evaporation of the solvent gave 0.864 g (84% yield) of desired product as an off-white solid.

Step 5. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]-carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.598 g, 3.71 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-{[(3-amino-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.303 g, 0.74 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.300 g (71% yield) of desired product as a white solid.

Step 6. (2*S*)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (1.5 mL) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.300 g, 0.53 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate and triturated with ethyl acetate, to give 0.127 g (47% yield) of desired product as a white solid. ES MS m/z 512 (M-H).

Example 183: (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(2-thienyl)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)-ethanoate

HATU (4.56 g, 12.0 mmol) was added to a solution 2-amino-4-chlorobenzoic acid (1.38 g, 8.0 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (2.00 g, 9.6 mmol) and diisopropylethylamine (2.1 mL, 12.0 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight, then diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 1.50 g (58% yield) of desired product as a white solid.

Step 2. Methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)ethanoate

2,6-Dimethylphenylisocyanate (3.28 g, 22.6 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (1.47 g, 4.53 mmol) in anhydrous pyridine. The mixture was stirred at room temperature

overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 1.80 g (84% yield) of desired product as a white solid

Step 3. Methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4-(2-thienyl)phenyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.42 mmol), 2-thienylboronic acid (0.065 g, 0.51 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.021 mmol), 0.6 mL of 2M aqueous sodium carbonate and 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.133 g (61% yield) of desired product as a white solid.

Step 4. (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(2-thienyl)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.055 g, 2.3 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(2-thienyl)phenyl]carbonyl}amino)ethanoate (0.119 g, 0.23 mmol) in 5 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by

chromatography on silica gel with hexane/ethyl acetate to give 0.045 g (39% yield) of the desired product as a white solid. ES MS m/z 504 (M-H).

Example 184: (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-thienyl)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4-(3-thienyl)phenyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.42 mmol), 3-thienylboronic acid (0.065 g, 0.51 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.021 mmol), 0.6 mL of 2M aqueous sodium carbonate and 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.155 g (71% yield) of desired product as a white solid

Step 2. (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-thienyl)phenyl]carbonyl}amino)ethanoic acid.

Lithium hydroxide (0.065 g, 2.7 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-thienyl)phenyl]carbonyl}amino)ethanoate (0.141 g, 0.27 mmol) in 6 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.066 g (48% yield) of the desired product as a white solid. ES MS m/z 504 (M-H).

Example 185: (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(4-pyridinyl)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4-(4-pyridinyl)phenyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.42 mmol), 4-piridinylboronic acid (0.063 g, 0.51 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.021 mmol), 0.6 mL of 2M aqueous sodium carbonate and 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.081 g of a white solid containing about 75% of desired product. This material was carried further without additional purification.

Step 2. (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(4-pyridinyl)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.035 g, 1.50 mmol) was added to a solution of crude methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(4-pyridinyl)phenyl]carbonyl}amino)ethanoate (0.076 g, approx 0.15 mmol) in 5 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue followed by addition of aqueous sodium hydroxide to a pH of 5. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with dichloromethane/methanol to give 0.010 g (13% yield) of the desired product as a white solid. ES MS m/z 501 (M+H).

Example 186: (2*S*)-Cyclohexyl{[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-4-biphenylyl)carbonyl]amino}ethanoic acid

Step 1. Methyl (2*S*)-{[(4-chloro-2-nitrophenyl)carbonyl]amino}(cyclohexyl)-ethanoate

HATU (1.41 g, 3.72 mmol) was added to a solution of 4-chloro-2-nitrobenzoic acid (0.50 g, 2.48 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.515 g, 2.48 mmol) and diisopropylethylamine (0.65 mL, 3.72 mmol) in 20 mL of DMF. The mixture was stirred at room temperature for 3.5 hours, then diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.656 g (75 % yield) of desired product as a white solid.

Step 2. Methyl (2*S*)-cyclohexyl{[(3-nitro-4-biphenylyl)carbonyl]amino}ethanoate

A mixture of methyl methyl (2*S*)-{[(4-chloro-2-nitrophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.294 g, 0.83 mmol), phenylboronic acid (0.121 g, 0.99 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.031 g, 0.041 mmol),1.25 mL of 2M aqueous sodium carbonate and 3.0 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.126 g (38% yield) of desired product as an off-white solid.

Step 3. Methyl (2*S*)-{[(3-amino-4-biphenylyl)carbonyl]amino}(cyclohexyl)-ethanoate

5% Palladium on charcoal (0.032 g, 0.015 mmol) was added to a solution of methyl (2*S*)-cyclohexyl{[(3-nitro-4-biphenylyl)carbonyl]amino}ethanoate (0.121 g, 0.305 mmol), in absolute ethanol. The mixture was evacuated and flushed with nitrogen three times, then evacuated and flushed with hydrogen three times, and stirred at 50 psi for one hour. The reaction mixture was filtered through Celite and the filtrate was evaporated to give 0.116 g of desired product as a yellow solid.

Step 4. Methyl (2*S*)-cyclohexyl{[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-4-biphenylyl)carbonyl]amino}ethanoate

HATU (0.175 g, 0.46 mmol) was added to a solution of methyl (2*S*)-{[(3-amino-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.112 g, 0.31 mmol), (2,4,6-trichlorophenyl)acetic acid (0.073 g, 0.31 mmol) and diisopropylethylamine (0.081 mL, 0.46 mmol) in 5 mL of DMF. The mixture was stirred at room temperature overnight. An additional 0.050 g (0.21 mmol) of (2,4,6-trichlorophenyl)acetic acid and 0.100g (0.26 mmol) of HATU was added and stirring was continued at room temperature for ca. 18 hours. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.056 g (31% yield) of desired product as a white solid.

Step 5. (2*S*)-Cyclohexyl{[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-4-biphenylyl)carbonyl]amino}ethanoic acid

Lithium hydroxide (0.022 g, 0.94 mmol) was added to a solution of methyl (2*S*)-cyclohexyl{[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-4-biphenylyl)carbonyl]amino}ethanoate (0.055 g, 0.094 mmol) in 1.5 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over

sodium sulfate. The solvent was evaporated to give 0.030 g (56% yield) of the desired product as a white solid. ES MS m/z 573 (M).

Example 187: (2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-hydroxy-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4'-hydroxy-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.42 mmol), 4-hydroxyphenylboronic acid (0.070 g, 0.51 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.021 mmol), 0.6 mL of 2M aqueous sodium carbonate and 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.100 g of a white solid containing about 80% of desired product. This material was carried further without additional purification.

Step 2. (2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-hydroxy-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.045 g, 1.90 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-hydroxy-4-biphenylyl]carbonyl}amino)ethanoate (0.100 g, approx 0.19 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate and by reverse phase

HPLC with methanol/water with 0.1% formic acid to give 0.035 g (36% yield) of the desired product as a white solid. ES MS m/z 516 (M+H).

Example 188: (2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-3',4'-difluoro-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.42 mmol), 3,4-difluorophenylboronic acid (0.081 g, 0.51 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.021 mmol), 0.6 mL of 2M aqueous sodium carbonate and 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.135 g of a white solid containing about 85% of desired product. This material was carried further without additional purification.

Step 2. (2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.059 g, 2.4 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}amino)ethanoate (0.135 g, approx 0.24 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by

reverse phase HPLC with acetonitrile/water with 0.1% formic acid to give 0.037 g (29% yield) of the desired product as a white solid. ES MS m/z 534 (M-H).

Example 189: (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(5-pyrimidinyl)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4-(5-pyrimidinyl)phenyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.211 g, 0.45 mmol), 5-pyrimidinylboronic acid (0.066 g, 0.54 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.017 g, 0.022 mmol), 0.68 mL of 2M aqueous sodium carbonate and 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.051 g of a white solid containing about 80% of desired product. This material was carried further without additional purification.

Step 2. (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(5-pyrimidinyl)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.024 g, 0.99 mmol) was added to a solution methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(5-pyrimidinyl)phenyl]carbonyl}amino)ethanoate (0.051 g, approx 0.099 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue followed by aqueous sodium hydroxide to adjust to pH 5. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by reverse phase HPLC

with acetonitrile/water with 0.1% formic acid to give 0.007 g (14% yield) of the desired product as a white solid. ES MS m/z 500 (M-H).

Example 190: (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl{[(4-fluoro-2nitrophenyl)carbonyl]amino}ethanoate

HATU (1.54 g, 4.05 mmol) was added to a solution 4-fluoro-2-nitrobenzoic acid (0.50 g, 2.70 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.561 g, 2.70 mmol) and diisopropylethylamine (0.70 mL, 4.05 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.795 g (87% yield) of desired product as a white solid.

Step 2. Methyl (2*S*)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclohexyl)-ethanoate

5% Palladium on charcoal (0.249 g, 0.12 mmol) was added to a solution of methyl (2*S*)-cyclohexyl{[(4-fluoro-2nitrophenyl)carbonyl]amino}ethanoate (0.791 g, 2.34 mmol) in 20 mL of absolute ethanol. The mixture was evacuated and flushed with nitrogen three times, then evacuated and flushed with hydrogen three times, and stirred at 50 psi for one hour. The reaction mixture was filtered through Celite and the filtrate was evaporated to give 0.600 g (83% yield) of desired product as an off-white solid.

Step 3. Methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4-fluorophenyl]carbonyl}amino)ethanoate

2,6-Dimethylphenylisocyanate (0.23 g, 1.62 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.100

g, 0.32 mmol) in anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.103 g (71% yield) of desired product as a white solid.

Step 4. (2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.054 g, 2.3 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate (0.103 g, 0.23 mmol) in 5 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated to give 0.070 g (69% yield) of desired product as a white solid. ES MS m/z 440 (M-H).

Example 191: (2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.195 g, 0.41 mmol), 4-methoxyphenylboronic acid (0.075 g, 0.50 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.020 mmol), 0.62 mL of 2M aqueous sodium carbonate and 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted

with ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.077 g (34% yield) of desired product as a white solid.

Step 2. (2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.034 g, 1.42 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoate (0.077 g, 0.142 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.042 g (56% yield) of desired product as a white solid. ES MS m/z 530 (M+H).

Example 192: (2*S*)-Cyclohexyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.528 g, 3.28 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.202 g, 0.65 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.272 g (89% yield) of desired product as a white solid.

Step 2: (2*S*)-Cyclohexyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.135 g, 5.6 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.264 g, 0.56 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated to give 0.181 g (71% yield) of desired product as a white solid. ES MS m/z 456 (M+H).

Example 193: (2*S*)-Cyclohexyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)-ethanoate

HATU (16.6 g, 43.6 mmol) was added to a solution 2-amino-4-chlorobenzoic acid (5.00 g, 29.1 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (6.05 g, 29.1 mmol) and diisopropylethylamine (7.6 mL, 43.6 mmol) in DMF. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 3.31 g (35% yield) of desired product.

Step 2. Methyl (2S)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate

2,4,6-Trimethylphenylisocyanate (8.13 g, 50.5 mmol) was added to a solution of methyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (3.28 g, 10.1 mmol) in anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 3.70 g (75% yield) of desired product as a white solid.

Step 3. Methyl (2S)-cyclohexyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture methyl (2S)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.500 g, 1.03 mmol), 4-methoxyphenylboronic acid (0.172 g, 1.13 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.038 g, 0.051 mmol), cesium fluoride (0.469 g, 3.09 mmol), 3 mL of water and 8 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water, and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.278 g of a white solid containing about 85% desired product.

Step 4. (2*S*)-Cyclohexyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.118 g, 5.0 mmol) was added to a solution of methyl (2S)-cyclohexyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.278 g, 0.50 mmol) in 9 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by

chromatography on silica gel with hexane/ethyl acetate to give 0.143 g (53% yield) of desired product as a white solid. ES MS m/z 542 (M-H).

Example 194: (2S)-Cyclohexyl({[4'-hydroxy-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[4'-hydroxy-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of methyl (2S)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.500 g, 1.03 mmol), 4-hydroxyphenylboronic acid (0.156 g, 1.13 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.038 g, 0.051 mmol), cesium fluoride (0.469 g, 3.09 mmol), 3 mL of water and 8 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water, and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.181 g (32% yield) of desired product as a white solid.

Step 2: Methyl (2S)-cyclohexyl({[4'-hydroxy-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

Lithium hydroxide (0.080 g, 3.3 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[4'-hydroxy-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.181 g, 0.33 mmol) in 6 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated to give 0.130 g (74% yield) of desired product as a white solid. ES MS m/z 530 (M+H).

Example 195: (2*S*)-Cyclohexyl({[4-nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. 4-Nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)benzoic acid

2,4,6-Trimethylphenylisocyanate (0.292 g, 1.81 mmol) was added to a mixture of 2-amino-4-nitrobenzoic acid (0.300 g, 1.65 mmol) and triethylamine (0.46 mL, 3.3 mmol) in 10 mL of anhydrous DMF. The mixture was heated to 75°C for 2 hours. After cooling to room temperature, 2 mL of 6N hydrochloric acid was added and the mixture was diluted with water. The precipitated solid was collected by filtration, washed with water and dried under vacuum to give 0.576 g of a light brown solid containing about 80% of the desired product.

Step 2. Methyl (2*S*)-cyclohexyl({[4-nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

HATU (0.929 g, 2.44 mmol) was added to a mixture of 4-Nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)benzoic acid (0.560 g, approx 1.63 mmol), methyl (2*S*)-amino(cyclohexyl)ethanoate (0.339 g, 1.63 mmol) and diisopropylethylamine (0.42 mL, 2.44 mmol). The mixture was stirred at room temperature for 2.5 hours, diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.546 g (67% yield) of desired product as a yellow solid.

Step 3: (2*S*)-Cyclohexyl({[4-nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.048 g, 2.01 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[4-nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.100 g, 0.201 mmol) in 6 mL of THF:methanol:water/4:1:1. The mixture was stirred at room

temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.056 g (58% yield) of desired product as a yellow solid. ES MS m/z 483 (M+H).

Example 196: (2*S*)-({[4-Amino-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. Methyl (2*S*)-({[4-amino-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}-amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate

5% Palladium on charcoal (0.085 g, 0.040 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[4-nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.399 g, 0.83 mmol) in 20 mL of absolute ethanol in a pressure vessel. The vessel was evacuated and filled with nitrogen three times, then evacuated and filled with hydrogen three times, and the reaction mixture was stirred at 50 psi for one hour. The reaction mixture was filtered through Celite and the filtrate was evaporated to give 0.284 g (76% yield) of desired product as a light yellow solid.

Step 2. (2*S*)-({[4-Amino-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide (0.052 g, 2.1 mmol) was added to a solution of methyl (2*S*)-({[4-amino-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.100 g, 0.21 mmol) in 6 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated, and 1N aqueous HCl was added to the residue. Aqueous sodium hydroxide was added to adjust the pH to 6. The mixture was extracted with ethyl acetate. An insoluble solid remained between the aqueous and organic layer and was collected by filtration. The organic phase was evaporated.

The residue was combined with the solid collected and the mixture was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.033 g (35% yield) of desired product as a yellow solid. ES MS m/z 453 (M+H).

Example 197: (2*S*)-Cyclohexyl({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2S)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate

HATU (11.42 g, 30.06 mmol) was added to a solution of 2-amino-4-chlorobenzoic acid (3.44 g, 20.04 mmol), 1,1-dimethylethyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (5.00 g, 20.04 mmol) and diisopropylethylamine (5.2 mL, 30.06 mmol) in DMF. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and water. The organic phase was washed with water and brine and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 4.26 g (58% yield of desired product as a white solid.

Step 2. 1,1-Dimethylethyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate

2,4,6-Trimethylphenylisocyanate (4.39 g, 27.3 mmol) was added to a solution of 1,1-Dimethylethyl (2S)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (2.00 g, 5.45 mmol) in 30 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 2.72 g (95% yield) of desired product as a white solid.

Step 3. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of 1,1-dimethylethyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.38 mmol), 4-nitrophenylboronic acid (0.076 g, 0.45 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.014 g, 0.019 mmol) and 2M aqueous sodium carbonate (0.6 mL) in 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with water and ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.174 g of a yellow solid containing about 85% of desired product.

Step 4. (2*S*)-Cyclohexyl({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.73 mL, 9.47 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.174 g, 0.28 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature for 48 hours. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.117 g (75% yield) of desired product as a yellow solid. ES MS m/z 559 (M+H).

Example 198: (2*S*)-Cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of 1,1-Dimethylethyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.38 mmol), [4-(hydroxymethyl)phenyl]boronic acid (0.068 g, 0.45 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.014 g, 0.019 mmol) and 2M aqueous sodium carbonate (0.6 mL) in 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with water and ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.166 g (73% yield) of desired product as a yellow solid.

Step 2. (2*S*)-Cyclohexyl({[4'-{[(trifluoroacetyl)oxy]methyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.73 mL) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.166 g, 0.28 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature for 48 hours. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.123 g of a white solid.

Step 3. (2*S*)-Cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.025 g, 1.05 mmol) was added to a solution of (2*S*)-Cyclohexyl({[4'-{[(trifluoroacetyl)oxy]methyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid (0.067 g, 0.105 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature for one hour. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The mixture was extracted with ethyl acetate. The organic phase was evaporated to give 0.050 g (87% yield) of desired product as a white solid. ES MS m/z 542 (M-H).

Example 199: (2*S*)-({[4'-Amino-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. 1-Dimethylethyl (2*S*)-({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate

A mixture of 1,1-Dimethylethyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.38 mmol), 4-nitrophenylboronic acid (0.076 g, 0.45 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.014 g, 0.019 mmol) and 2M aqueous sodium carbonate (0.6 mL) in 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with water and ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.170 g (73% yield) of desired product as a yellow solid.

Step 2. 1,1-Dimethylethyl (2*S*)-({[4'-amino-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate

5% Palladium on charcoal (0.029 g, 0.013 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.166 g, 0.27 mmol) in 10 mL of absolute ethanol in a pressure vessel. The vessel was evacuated and filled with nitrogen three times, then evacuated and filled with hydrogen three times, and stirred at 50 psi for one hour. The reaction mixture was filtered through Celite and the filtrate was evaporated to give 0.108 g (68% yield) of desired product as a white solid.

Step 3. (2*S*)-({[4'-Amino-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.49 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-({[4'-amino-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate (0.105 g, 0.18 mmol) in 4 mL of dichloromethane. The mixture was stirred at room temperature for 18 hours and the solvent was evaporated to give 0.070 g (60% yield) of the trifluoroacetic acid salt of the desired product as a beige solid. ES MS 529 (M+H).

Example 200: (2*S*)-Cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. 3-Nitro-4-biphenylcarboxylic acid

Methyl 4-chloro-2-nitrobenzoate (0.200 g, 0.93 mmol), phenylboronic acid (0.113 g, 0.93 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.034 g, 0.046 mmol) and 2M aqueous sodium carbonate (1.4 mL) were combined in 1 mL of acetonitrile in each of two microwave reaction vials and heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixtures were combined and acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.283 g (63% yield) of desired product as an off-white solid.

Step 2. 1,1-Dimethylethyl (2*S*)-cyclohexyl{[(3-nitro-4-biphenylyl)carbonyl]amino}ethanoate

HATU (0.644 g, 1.69 mmol) was added to a solution 3-nitro-4-biphenylcarboxylic acid (0.276 g, 1.13 mmol), 1,1-dimethylethyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.283 g, 1.13 mmol) and diisopropylethylamine (0.29 mL, 1.69

mmol) in 15 mL of DMF. The mixture was stirred at room temperature overnight. The reaction mixture was extracted between ethyl acetate and water. The organic phase was washed with water and brine and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.355g of a white solid containing about 80% of the desired product.

Step 3. 1,1-Dimethylethyl (2*S*)-{[(3-amino-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate

5% Palladium on charcoal (0.085 g, 0.040 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl{[(3-nitro-4-biphenylyl)carbonyl]amino}ethanoate (0.350 g, 0.80 mmol) in 20 mL of absolute ethanol in a pressure vessel. The vessel was evacuated and filled with nitrogen three times, then evacuated and filled with hydrogen three times, and stirred at 50 psi for one hour. The reaction mixture was filtered through Celite and the filtrate was evaporated to give 0.310 g (68% yield) of a gray solid containing about 85% of desired product.

Step 4. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,4,6-Trichlorophenylisocyanate (0.500 g, 2.25 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-{[(3-amino-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.184 g, 0.45 mmol) in 10 mL anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.216 g (76%) of desired product as a yellow solid.

Step 5. 2*S*)-Cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.210 g, 0.33 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature for ca. 18 hours. The solvent was evaporated and the residue was purified by reverse phase HPLC,on a C18 column with a gradient of acetonitrile/water containing 0.1% formic acid, to give 0.030 g (16% yield) of desired product as a white powder. ES MS m/z 574 (M).

Example 201: 3-Methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valine

Step 1. Methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate

A mixture of methyl 4-chloro-2-nitrobenzoate (0.700 g, 3.25 mmol), 4-methoxyphenylboronic acid (0.494 g, 3.25 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.120 g, 0.16 mmol), 5 mL of 2M aqueous sodium carbonate and 5 mL of acetonitrile, in each of three microwave reaction vials, was heated in a microwave reactor at 150°C for 5 minutes. After cooling to room temperature, the three reaction mixtures were combined, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The crude product (a mixture of desired product and the corresponding carboxylic acid) was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.96 g (34% yield) of desired product as a yellow solid.

Step 2. 4'-(Methyloxy)-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.238 g, 9.93 mmol) was added to a solution of methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate (0.95 g, 3.31 mmol) in 24 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature for 2 hours. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.854 g (91% yield) of desired product as a yellow solid.

Step 3. 3-Methyl-*N*-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-valine

HATU (0.627 g, 1.65 mmol) was added to a solution of 4'-(Methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.300 g, 1.10 mmol), methyl 3-methyl-L-valinate hydrochloride (0.199 g, 1.10 mmol), and diisopropylethylamine (0.29 mL, 1.65 mmol) in 15 mL of DMF. The mixture was stirred at room temperature overnight. The reaction mixture was extracted between ethyl acetate and water. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.356 g (81% yield) of desired product as an off-white solid.

Step 4. Methyl *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-3-methyl-L-valinate

A mixture of 3-Methyl-*N*-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-valine (0.348 g, 0.87 mmol) and 5% palladium on carbon (0.92 g, 0.043 mmol) in 20 mL of ethanol in a pressure reaction vessel was evacuated and filled with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.300 g (81% yield) of desired

Step 5. Methyl 3-methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valinate

2,4,6-Trichlorophenylisocyanate (0.394 g, 1.75 mmol) was added to a solution of methyl *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-3-methyl-L-valinate (0.131 g, 0.35 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.091 g (44%yield) of desired product as a white solid.

Step 6. 3-Methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valine

Lithium hydroxide (0.037 g, 1.5 mmol) was added to a solution of methyl 3-methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valinate (0.091 g, 0.15 mmol) in 3 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.065 g (75% yield) of desired product as a white solid. ES MS m/z 577 (M-H).

Example 202: 3-Methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valine

Step 1. Methyl 3-methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valinate

2,4,6-Trimethylphenylisocyanate (0.344 g, 2.13 mmol) was added to a solution of methyl *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-3-methyl-L-valinate (0.158 g, 0.43 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at

room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.191 g (84%yield) of desired product as a white solid.

Step 2. 3-Methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valine

Lithium hydroxide (0.086 g, 3.60 mmol) was added to a solution of methyl 3-methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valinate (0.191 g, 0.36 mmol) in 5 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.190 g (100% yield) of desired product as a white solid. ES MS m/z 518 (M+H).

Example 203: (2*S*)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,6-Dichlorophenylisocyanate (0.276 g, 1.47 mmol) was added to a solution of 1,1-dimethylethyl (2S)-{[(3-amino-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.120 g, 0.29 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced

pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.135 g (84%yield) of a white solid containing about 85% of desired product.

Step 2. (2*S*)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.130 g, 0.22 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature for 18 hours and the solvent was removed under vacuum. The residue was triturated with methanol to give 0.030 g (25% yield) of desired product as a white solid. ES MS m/z 538 (M-H).

Example 204: (2*S*)-Cyclohexyl({[4'-[(trifluoromethyl)oxy]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate

2,4,6-Trimethylphenylisocyanate (4.19 g, 26.0 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-{[(2-amino-4-chlorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (1.906 g, 5.20 mmol) in 20 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 2.54 g (92% yield) of desired product as a white solid.

Step 2. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4'-[(trifluoromethyl)oxy]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of 1,1-dimethylethyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.150 g, 0.28 mmol), {4-[(trifluoromethyl)oxy]phenyl}boronic acid (0.064 g, 0.31 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.010 g, 0.014 mmol), cesium fluoride (0.128 g, 0.84 mmol), 0.5 mL of water and 1.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.136 g (74% yield) of desired product as a white solid.

Step 3. (2*S*)-Cyclohexyl({[4'-[(trifluoromethyl)oxy]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4'-[(trifluoromethyl)oxy]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.133 g, 0.203 mmol) in 2 mL of dichloromethane. The mixture was stirred at room temperature for 18 hours and the solvent was removed under vacuum. The residue was purified by reverse phase HPLC on a C18 column with a gradient of acetonitrile/water with 0.1% formic acid to give 0.074 g (61% yield) of desired product as a white powder. ES MS m/z 598 (M+H).

Example 205: *N*-[(*S*)-cyclohexyl(1*H*-tetrazol-5-yl)methyl]-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylcarboxamide

Step 1. (*S*)-1-cyclohexyl-1-(1*H*-tetrazol-5-yl)methanamine

Trifluoroacetic acid (1.5 mL, 19.4 mmol) was added to a solution of 1,1-dimethylethyl [(*S*)-cyclohexyl(1*H*-tetrazol-5-yl)methyl]carbamate (0.500 g, 1.78

mmol) in dichloromethane. The mixture was stirred at room temperature for 3 hours and the solvent was removed under vacuum to give a yellow oil. The crude product was taken on to the next step without further purification.

Step 2. *N*-[(*S*)-Cyclohexyl(1*H*-tetrazol-5-yl)methyl]-4'-(methyloxy)-3-nitro-4-biphenylcarboxamide

HATU (0.519 g, 0.47 mmol) was added to a solution of (4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.300, 1.09 mmol), (*S*)-1-cyclohexyl-1-(1*H*-tetrazol-5-yl)methanamine (approx. 1.7 mmol) and diisopropylethylamine (0.24 mL, 1.37 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight. DMF was evaporated under vacuum and the residue was extracted between ethyl acetate and water. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.168 g (35% yield) of desired product as a white solid.

Step 3. 3-Amino-*N*-[(*S*)-cyclohexyl(1*H*-tetrazol-5-yl)methyl]-4'-(methyloxy)-4-biphenylcarboxamide

A mixture of *N*-[(*S*)-cyclohexyl(1*H*-tetrazol-5-yl)methyl]-4'-(methyloxy)-3-nitro-4-biphenylcarboxamide (0.165 g, 0.38 mmol) and 5% palladium on carbon (0.040 g, 0.019 mmol) in 30 mL of ethanol in a pressure reaction vessel was evacuated and filled with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.145 g of a yellow solid containing mainly the desired product.

Step 4. *N*-[(*S*)-cyclohexyl(1*H*-tetrazol-5-yl)methyl]-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylcarboxamide

2,4,6-Trimethylphenylisocyanate (0.287 g, 1.78 mmol) was added to a solution of 3-Amino-*N*-[(*S*)-cyclohexyl(1*H*-tetrazol-5-yl)methyl]-4'-(methyloxy)-4-biphenylcarboxamide (0.145 g, 0.36 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel with hexane/ethyl acetate and reverse phase HPLC on C18 with acetonitrile/water containing 0.1% formic acid to give 0.015 g (7% yield) of desired product as a white solid. . ES MS m/z 566 (M-H).

Example 206: 2*S*)-Cyclohexyl({[4-{[(methylamino)carbonyl]amino}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. 4-Nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)benzoic acid

2,4,6-Trimethylphenylisocyanate (2.92 g, 18.1 mmol) was added to a mixture of 2-amino-4-nitrobenzoic acid (3.00 g, 16.5 mmol) and triethylamine (4.6 mL, 33.0 mmol) in 100 mL of anhydrous DMF. The mixture was heated to 75°C for 2 hours. After cooling to room temperature, 20 mL of 6N hydrochloric acid was added and the mixture was diluted with water. The precipitated solid was collected by filtration, washed with water and dried under vacuum to give 5.97 g of a yellow solid. This crude product was carried further without additional purification.

Step 2. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4-nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

HATU (9.40 g, 24.75 mmol) was added to a solution of 4-Nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)benzoic acid (5.66 g, 16.5 mmol), 1,1-dimethylethyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (4.12 g, 16.5 mmol) and diisopropylethylamine (6.4 mL, 24.75 mmol) in 200 mL of DMF. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with

ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 5.97 g (67% yield) of desired product as a light yellow solid.

Step 3. 1,1-Dimethylethyl (2*S*)-({[4-amino-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate

A mixture of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4-nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (3.00 g, 5.58 mmol) and 5% palladium on carbon (0.59 g, 0.28 mmol) in 150 mL of ethanol in a pressure reaction vessel was evacuated and filled with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 2.49 g (84% yield) of desired product as a light yellow solid

Step 4. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4-{[(methylamino)carbonyl]amino}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

Methylisocyanate (0.084 g, 1.48 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-({[4-amino-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoat e (0.150 g, 0.29 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.134 g (82% yield) of desired product as a white solid.

Step 5. 2*S*)-Cyclohexyl({[4-{[(methylamino)carbonyl]amino}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Trifluoracetic acid (0.5 mL, 6.49 mmol) was added to a solution of 1-dimethylethyl (2*S*)-cyclohexyl({[4-{[(methylamino)carbonyl]amino}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.132 g, 0.23 mmol) in 2 mL of dichloromethane. The mixture was stirred at room temperature overnight and the solvent was evaporated. The residue was purified by reverse phase HPLC on a C18 column with a water/acetonitrile gradient with 0.1% formic acid to give 0.052 g (44% yield) of desired product as a white solid. ES MS m/z 510 (M+H).

Example 207: (2*S*)-Cyclohexyl({[4-(dibutylamino)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2S)-cyclohexyl({[4-(dibutylamino)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

Butyraldehyde (0.021 g, 0.29 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-({[4-amino-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.150 g, 0.29 mmol) in 5 mL of 1,2-dichloroethane. Sodium triacetoxyborohydride (0.154 g, 0.725 mmol) was added after a few minutes and the mixture was stirred at room temperature for ca. 18 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and dried over sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.101 g of product as a white solid.

Step 2. (2*S*)-Cyclohexyl({[4-(dibutylamino)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.49 mmol) was added to a solution of 1,1-dimethylethyl (2S)-cyclohexyl({[4-(dibutylamino)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.101 g, 0.18 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature overnight and the solvent was evaporated. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.077g (63% yield) of the trifluoroacetic acid salt of the desired product as a white solid. ES MS m/z 565 (M+H).

Example 208: (2*S*)-Cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}ethanoic acid

Step 1. Methyl (2S)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}ethanoate

1,3-Dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.177 g, 0.65 mmol) was added to a solution of 1 methyl (2S)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.100 g, 0.325 mmol) in anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.163 g (86% yield) of desired product as a white solid.

Step 2. (2*S*)-Cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}ethanoic acid

Lithium hydroxide (0.065 g, 2.70 mmol) was added to a solution of methyl (2S)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}ethanoate (0.157 g, 0.27 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature for ca. 18 hours. The solvent was evaporated,1N aqueous hydrochloric acid was added, and the resulting suspension was extracted with ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.065 g (45% yield) of desired product as a white solid. ES MS m/z 564 (M-H).

Example 209: (2*S*)-Cyclohexyl({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl 3',4'-difluoro-3-nitro-4-biphenylcarboxylate

In each of two microwave reaction vials, a mixture of methyl 4-chloro-2-nitrobenzoate (0.500 g, 2.62 mmol), 3,4-difluorophenylboronic acid (0.403 g, 2.55 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.086 g, 0.115 mmol), cesium fluoride (1.05 g, 6.95 mmol), 2.5 mL of water and 7.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.916 g (67% yield) of desired product as a white solid.

Step 2. 3',4'-Difluoro-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.219 g, 9.13 mmol) was added to a solution of methyl 3',4'-difluoro-3-nitro-4-biphenylcarboxylate (0.892 g, 3.04 mmol) in THF:methanol:water/3:1:1. The mixture was stirred at room temperature for ca. 18 hours. The solvent was evaporated,1N aqueous hydrochloric acid was added, and the resulting suspension was extracted with ethyl acetate. The organic phase was

dried over sodium sulfate and the solvent evaporated to give 0.810 g (95% yield) of desired product as a white solid.

Step 3. 1,1-Dimethylethyl (2S)-cyclohexyl{[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]amino}ethanoate

HATU (1.12 g, 2.95 mmol) was added to a solution of 3',4'-Difluoro-3-nitro-4-biphenylcarboxylic acid (0.550 g, 1.97 mmol), 1,1-dimethylethyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.541 g, 2.17 mmol) and diisopropylethylamine (0.52 mL, 2.95 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight. The reaction mixture was extracted between ethyl acetate and water. The organic phase was washed with water and brine and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.739 g (79% yield) of desired product as a white solid.

Step 4. 1,1-Dimethylethyl (2S)-{[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate

A mixture of 1,1-dimethylethyl (2S)-cyclohexyl{[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]amino}ethanoate (0.711 g, 1.50 mmol) and 5% palladium on carbon (0.160 g, 0.075 mmol) in 25 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.652 g (97% yield) of desired product as a beige solid.

Step 5. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.362 g, 2.25 mmol) was added to a solution of 1,1-dimethylethyl (2S)-{[(3-amino-3',4'-difluoro-4-

biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.200 g, 0.45 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.249 g of a white solid containing mainly desired product and some unknown impurity. This material was carried on to the next step without further purification.

Step 6. (2*S*)-Cyclohexyl({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.49 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.239 g, 0.39 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.173 g (81% yield) of desired product as a white solid. ES MS m/z 550 (M+H).

Example 210: (2*S*)-Cyclopentyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclopentyl({[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)ethanoate

HATU (0.515 g, 1.36 mmol) was added to a solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.247 g, 0.904 mmol), methyl (2S)-amino(cyclopentyl)ethanoate trifluoroacetate (0.245 g, 0.904 mmol) and diisopropylethylamine (0.24 mL, 1.36 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, then diluted with ethyl acetate and washed

with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.235 g (63% yield) of desired product as a white solid.

Step 2. Methyl (2*S*)-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)(cyclopentyl)ethanoate

A mixture of methyl (2*S*)-cyclopentyl({[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)ethanoate (0.201 g, 0.49 mmol) and 5% palladium on carbon (0.052 g, 0.024 mmol) in 15 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.177 g (94% yield) of desired product as a white solid.

Step 3. Methyl (2*S*)-cyclopentyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.339 g, 2.11mmol) was added to a solution of methyl (2*S*)-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)(cyclopentyl)ethanoate (0.161 g, 0.42 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.116 g of a white solid containing 85-90% desired product. This material was carried on to the next step without further purification.

Step 4: (2*S*)-Cyclopentyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.050 g, 2.08 mmol) was added to a solution of methyl (2*S*)-cyclopentyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.113 g, 0.21 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature for 2 hours and 1N aqueous HCl was added. The solvents were evaporated and the residue was extracted between ethyl acetate and water. The organic phase was dried over sodium sulfate and the solvent was evaporated to give 0.066 g (59% yield) of desired product as a white solid. ES MS m/z 528 (M-H).

Example 211: (2*S*)-Cyclopentyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2S)-cyclopentyl{[(4-fluoro-2-nitrophenyl)carbonyl]amino}ethanoate

HATU (1.54 g, 4.05 mmol) was added to a solution of 4-fluoro-2-nitrobenzoic acid (0.500 g, 2.70 mmol), methyl (2S)-amino(cyclopentyl)ethanoate trifluoroacetate (0.732 g, 2.70 mmol) and diisopropylethylamine (0.70 mL, 4.05 mmol) in DMF. The mixture was stirred at room temperature overnight, then diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.519 g (59% yield) of desired product as a white solid.

Step 2. Methyl (2S)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclopentyl)ethanoate

A mixture of methyl (2S)-cyclopentyl{[(4-fluoro-2-nitrophenyl)carbonyl]amino}ethanoate (0.473 g, 1.46 mmol) and 5% palladium on carbon (0.155 g, 0.073 mmol) in 25 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated

and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.360 g (84% yield) of desired product as a white solid.

Step 3. Methyl (2*S*)-cyclopentyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.548 g, 3.40 mmol) was added to a solution of methyl (2S)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclopentyl)ethanoate (0.200 g, 0.68 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.266 g (85% yield) of desired product as a white solid.

Step 4. (2*S*)-Cyclopentyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.128 g, 5.31 mmol) was added to a solution of methyl (2*S*)-cyclopentyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.242 g, 0.53 mmol) in 6 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature for 2 hours and 1N aqueous HCl was added. The solvents were evaporated and the residue was extracted between ethyl acetate and water. The organic phase was dried over sodium sulfate and the solvent was evaporated to give 0.201 g (86% yield) of desired product as a white solid. ES MS m/z 440 (M-H).

Example 212: (2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3',4'-difluoro-4-biphenylyl)carbonyl]amino}ethanoic acid

Step 1. 1,1-Dimethylethyl (2S)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3',4'-difluoro-4-biphenylyl)carbonyl]amino}ethanoate

1,3-Dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.177 g, 0.65 mmol) was added to a solution of 1,1-dimethylethyl (2S)-{[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.150 g, 0.29 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.229 g (59% yield) of desired product as a white solid.

Step 2. (2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3',4'-difluoro-4-biphenylyl)carbonyl]amino}ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution 1,1-dimethylethyl (2S)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3',4'-difluoro-4-biphenylyl)carbonyl]amino}ethanoate (0.222 g, 0.31 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.155 g (76% yield) of desired product as a white solid. ES MS m/z 658 (M-H).

Example 213: (2*S*)-Cyclohexyl({[4'-[(dimethylamino)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

In each of two microwave reaction vials, a mixture of 1,1-Dimethylethyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.500 g, 0.94 mmol), [4-(hydroxymethyl)phenyl]boronic acid (0.158 g, 1.04 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.035 g, 0.047 mmol), cesium fluoride (0.43 g, 2.83 mmol), 2.5 mL of water and 7.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixtures were combined, filtered through Celite, diluted with ethyl acetate, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.583 g of a white solid containing about 85% of desired product. This product was carried on to the next step without further purification.

Step 2. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4'-formyl-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

Manganese dioxide (1.67 g, 19.3 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.577 g, 0.96 mmol) in 50 mL of dichloromethane. The mixture was stirred at room temperature for 18 hours, filtered through Celite and the solvent evaporated. Chromatography on silica gel gave 0.446 g of a white solid containing 90% desired product.

Step 3. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4'-[(dimethylamino)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

Dimethylamine (0.85 mL of a 2M solution in THF) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4'-formyl-3-({[(2,4,6-

trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.206 g, 0.34 mmol) in 15 mL of 1,2-dichloroethane. Sodium triacetoxyborohydride (0.216 g, 1.02 mmol) was added and the mixture was stirred at room temperature under nitrogen for ca. 18 hours. Ethyl acetate was added and the reaction mixture was washed with saturated aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and the solvent was evaporated. Chromatography on silica gel with dichloromethane/methanol gave 0.111 g (52% yield) of desired product as a white solid.

Step 4. 1-Dimethylethyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4'-[(dimethylamino)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.111 g, 0.18 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel with dichloromethane/methanolic ammonia to give 0.057 g (46% yield) of desired product as the trifluoroacetic acid salt. ES MS m/z 571 (M+H).

Example 214: (2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-biphenylyl)carbonyl]amino}ethanoic acid

Step 1. 1,1-Dimethylethyl (2S)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-biphenylyl)carbonyl]amino}ethanoate

1,3-Dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.266 g, 0.98 mmol) was added to a solution of 1,1-dimethylethyl (2S)-{[(3-amino-4-

biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.200 g, 0.49 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.251 g (75% yield) of desired product as a white solid.

Step 2. (2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-biphenylyl)carbonyl]amino}ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4'-[(dimethylamino)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.238 g, 0.35 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature for 3 hours. The solvent was evaporated and the residue was triturated with methanol to give 0.120 g (55% yield) of desired product as a white solid. ES MS m/z 622 (M-H).

Example 215: (2*S*)-Cyclohexyl({[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate

In each of two microwave reaction vials, a mixture of methyl 4-chloro-2-nitrobenzoate (0.500 g, 2.62 mmol), 4-methoxyphenyl]boronic acid (0.385 g, 2.55 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.084 g, 0.115 mmol), cesium fluoride (1.95 g, 6.95 mmol), 2.5 mL of water and 7.5 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled

reaction mixtures were combined, filtered through Celite, diluted with ethyl acetate, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 1.02 g (76% yield) of an off-white solid.

Step 2. 4'-(Methyloxy)-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.248 g, 10.33 mmol) was added to a solution of methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate (0.988 g, 3.44 mmol) in 30 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight and 1N aqueous HCl was added. The solvents were evaporated and the residue was extracted between ethyl acetate and water. The organic phase was dried over sodium sulfate and the solvent was evaporated to give 0.910 g (97% yield) of desired product as a yellow solid.

Step 3. 1,1-Dimethylethyl (2S)-cyclohexyl({[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)ethanoate

HATU (0.570 g, 1.50 mmol) was added to a solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.300 g, 1.10 mmol), 1,1-dimethylethyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.274 g, 1.10 mmol) and diisopropylethylamine (0.29 mL, 1.65 mmol) in 15 mL of DMF. The mixture was stirred at room temperature overnight. The reaction mixture was extracted between ethyl acetate and water. The organic phase was washed with water and brine and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.467 g of desired product as a yellow solid.

Step 4. 1,1-Dimethylethyl (2S)-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate

A mixture of 1,1-dimethylethyl (2S)-cyclohexyl({[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)ethanoate (0.461 g, 0.98 mmol) and 5% palladium on

carbon (0.105 g, 0.049 mmol) in 25 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.422 g (98% yield) of desired product as a beige solid.

Step 5. 1,1-Dimethylethyl (2S)-cyclohexyl({[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoate

1,3-Dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.266 g, 0.98 mmol) was added to a solution of 1,1-dimethylethyl (2S)-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate (0.220 g, 0.502 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.180 g (50% yield) of desired product as a white solid.

Step 6. (2*S*)-Cyclohexyl({[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of . 1,1-dimethylethyl (2S)-cyclohexyl({[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoate (0.172 g, 0.24 mmol) in dichloromethane. The mixture was stirred at room temperature for overnight. The solvent was evaporated and the residue was triturated with methanol to give 0.040 g (25% yield) of desired product as a white solid. ES MS m/z 652 (M-H).

Example 216: (2S)-Cyclohexyl({[4'-(1-pyrrolidinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2S)-cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of 1,1-dimethylethyl (2S)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.652 g, 1.24 mmol), [4-(hydroxymethyl)phenyl]boronic acid (0.207 g, 1.36 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.046 g, 0.062 mmol), cesium fluoride (0.565 g, 3.72 mmol), 3 mL of water and 8 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.341 g (46% yield) of desired product as a white solid.

Step 2. 1,1-Dimethylethyl (2S)-cyclohexyl({[4'-formyl-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

Manganese dioxide (0.98 g, 11.3 mmol) was added to a solution of 1,1-dimethylethyl (2S)-cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.338 g, 0.56 mmol) in dichloromethane. The mixture was stirred at room temperature for 18 hours, filtered through Celite and the solvent was evaporated. Chromatography on silica gel gave 0.247 g (74% yield) of desired product as a white solid.

Step 3. 1,1-Dimethylethyl (2S)-cyclohexyl({[4'-(1-pyrrolidinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

Sodium triacetoxyborohydride (0.140 g, 0.66 mmol) was added to a solution of 1,1-dimethylethyl (2S)-cyclohexyl({[4'-formyl-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.132 g, 0.22 mmol) and pyrrolidine (0.078 g, 1.10 mmol) in 5 mL of 1,2-dichloroethane. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel with dichloromethane/methanol to give 0.091 g (63% yield) of desired product as a colorless resin.

Step 4. (2*S*)-Cyclohexyl({[4'-(1-pyrrolidinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of 1,1-dimethylethyl (2S)-cyclohexyl({[4'-(1-pyrrolidinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.091 g, 0.14 mmol) in dichloromethane. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel with dichloromethane/methanol to give 0.026 g (31% yield) of desired product as a white solid. ES MS m/z 595 (M-H).

Example 217: (2*S*)-cyclohexyl({[4'-(4-morpholinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2S)-cyclohexyl({[4'-(tetrahydro-2H-pyran-4-ylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

Sodium triacetoxyborohydride (0.114 g, 0.54 mmol) was added to a solution of 1,1-dimethylethyl (2S)-cyclohexyl({[4'-formyl-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

(0.108 g, 0.18 mmol) and morpholine (0.079 g, 0.90 mmol) in 5 mL of 1,2-dichloroethane. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel with dichloromethane/methanol to give 0.127 g desired product as a colorless gum.

Step 2. (2*S*)-cyclohexyl({[4'-(4-morpholinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a solution of 1,1-dimethylethyl (2S)-cyclohexyl({[4'-(tetrahydro-2H-pyran-4-ylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.120 g, 0.18 mmol) in 4 mL of dichloromethane. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel with dichloromethane/methanol to give 0.046 g (35% yield) of desired product as a white solid. ES MS m/z 611 (M-H).

Example 218: (2*S*)-Cyclohexyl({[4'-(ethyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[4'-(ethyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.41 mmol), [4-(ethyloxy)phenyl]boronic acid (0.075 g, 0.45 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.021 mmol), cesium fluoride (0.187 g, 1.23 mmol), 1.5 mL of water and 4 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, washed with water and dried over sodium sulfate.

Chromatography on silica gel with hexane/ethyl acetate gave 0.078 g (33% yield) of a white solid containing 85-90% desired product.

Step 2. (2*S*)-Cyclohexyl({[4'-(ethyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.033 g, 1.37 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[4'-(ethyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.078 g, 0.14 mmol) in 3 mL of THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight and 1N aqueous HCl was added. The solvent was evaporated and the residue was extracted between ethyl acetate and water. The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.041 g (52% yield) of desired productas a white solid. ES MS m/z 556 (M-H).

Example 219: *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-norleucine

Step 1. Methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate

Methyl 4-chloro-2-nitrobenzoate (1.79 g, 8.31 mmol), 4-methoxyphenylboronic acid (1.39 g, 9.14 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.306 g, 0.41 mmol) and cesium fluoride (3.79 g, 24.9 mmol) were mixed in 40 mL of acetonitrile:water/3:1 was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.604 g (25% yield) of desired product.

Step 2. 4'-(Methyloxy)-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.135 g, 5.64 mmol) was added to a solution of methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate (0.540 g, 1.88 mmol) in THF:methanol:water/5:1:1. The mixture was stirred at room temperature overnight.

The solvent was evaporated and 1N aqueous HCl was added to the residue. The resulting suspension was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.328 g (64% yield) of desired product.

Step 3. Methyl N-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-norleucinate

HATU (0.334 g, 0.88 mmol) was added to a solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.162 g, 0.59 mmol), methyl L-norleucinate hydrochloride (0.118 g, 0.65 mmol), and diisopropylamine (0.15 mL, 0.88 mmol) in DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.203 g (86% yield) of desired product as an off-white solid.

Step 4. Methyl N-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-norleucinate

A mixture of methyl N-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-norleucinate (0.203 g, 0.51 mmol) and 5% palladium on carbon (0.054 g, 0.025 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.159 g (84% yield) of desired product.

Step 5. Methyl N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-norleucinate

2,4,6-Trimethylphenylisocyanate (0.198 g, 1.23 mmol) was added to a solution of methyl N-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-norleucinate (0.152 g, 0.41 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.173 g (79% yield) of desired product as a white solid.

Step 6. *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-norleucine

Lithium hydroxide (0.074 g, 3.1 mmol) was added to a solution of methyl N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-norleucinate (0.164 g, 0.31 mmol) in THF:methanol:water/4:1:1. The mixture was stirred at room temperature overnight.

The solvent was evaporated and 1N aqueous HCl was added to the residue. The resulting suspension was extracted between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.124 g (77% yield) of desired product. ES MS m/z 516 (M-H).

Example 220: (2*S*)-Cyclohexyl({[4-(methylsulfonyl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4-(methylsulfonyl)-2-nitrophenyl]carbonyl}amino)ethanoate

HATU (1.16 g, 3.06 mmol) was added to a solution of 4-(methylsulfonyl)-2-nitrobenzoic acid (0.500 g, 2.04 mmol), 1,1-dimethylethyl (2*S*)-

amino(cyclohexyl)ethanoate hydrochloride (0.509 g, 2.04 mmol), and diisopropylamine (0.53 mL, 3.06 mmol) in DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.668 g (74% yield) of desired product as a white solid.

Step 2. 1,1-Dimethylethyl (2*S*)-({[2-amino-4-(methylsulfonyl)phenyl]carbonyl}amino)(cyclohexyl)ethanoate

A mixture of 1,1-dimethylethyl (2*S*)-cyclohexyl({[4-(methylsulfonyl)-2-nitrophenyl]carbonyl}amino)ethanoate (0.641 g, 1.46 mmol) and 5% palladium on carbon (0.155 g, 0.073 mmol) in 120 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.557 g (93% yield) of desired product as a gray solid.

Step 3. 1,1-Dimethylethyl (2*S*)-cyclohexyl({[4-(methylsulfonyl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.353 g, 2.19 mmol) was added to a solution of 1,1-Dimethylethyl (2*S*)-({[2-amino-4-(methylsulfonyl)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.300 g, 0.73 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.274 g (66% yield) of desired product as a white solid.

Step 4. 2*S*)-Cyclohexyl({[4-(methylsulfonyl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Trifluoroacetic acid (0.50 mL, 6.49 mmol) was added to a solution of ,1-dimethylethyl (2*S*)-cyclohexyl({[4-(methylsulfonyl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.270 g, 0.47 mmol) in 10 mL of dichloromethane. The mixture was stirred at room temperature overnight and the solvent was evaporated. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.115 g (48% yield) of desired product as a white solid. ES MS m/z 514 (M-H).

Example 221: 1-({[4-Fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)cycloheptane-carboxylic acid

Step 1. Methyl 1-{[(4-fluoro-2-nitrophenyl)carbonyl]amino}cycloheptanecarboxylate

HATU (1.54 g, 4.05 mmol) was added to a solution of 4-fluoro-2-nitrobenzoic acid (0.500 g, 2.70 mmol), methyl 1-aminocycloheptanecarboxylate hydrochloride (0.560 g, 2.70 mmol), and diisopropyethylamine (0.70 mL, 4.05 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.475 g (52% yield) of desired product as a white solid.

Step 2. Methyl 1-{[(2-amino-4-fluorophenyl)carbonyl]amino}cycloheptanecarboxylate

A mixture of methyl 1-{[(4-fluoro-2-nitrophenyl)carbonyl]amino}cycloheptanecarboxylate (0.468 g, 1.38 mmol) and 5% palladium on carbon (0.147 g, 0.069 mmol) in 30 mL of ethanol in a pressure

reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.400 g (94% yield) of desired product as an off-white solid.

Step 3. Methyl 1-({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)cycloheptane-carboxylate

2,4,6-Trimethylphenylisocyanate (0.624 g, 3.88 mmol) was added to a solution of methyl 1-{[(2-amino-4-fluorophenyl)carbonyl]amino}cycloheptanecarboxylate (0.398 g, 1.29 mmol) in 10 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.439 g (72% yield) of desired product as a white solid.

Step 4. 1-({[4-Fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)cycloheptane-carboxylic acid

Lithium hydroxide (0.226 g, 9.4 mmol) was added to a solution of methyl 1-({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)cycloheptanecarboxylate (0.439 g, 0.94 mmol) in THF:methanol:water/2.5:1:1. The mixture was heated to 50°C for one hour. The solvent was evaporated, and 1N aqueous HCl was added to the residue. The resulting suspension was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. The solvent was removed under vacuum to give 0.401 g (94% yield) of the desired product as a white solid. ES MS m/z 454 (M-H).

Example 222: 1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylic acid

Step 1. Methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate

In each of two microwave reaction vials, a mixture of methyl 4-chloro-2-nitrobenzoate (0.700 g, 3.25 mmol), 4-methoxyphenylboronic acid (0.543 g, 3.57 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.120 g, 0.16 mmol), cesium fluoride (1.48 g, 9.75 mmol), 3 mL of water and 8 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixtures were combined, diluted with ethyl acetate, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 1.44 g (77% yield) of desired product as an off-white solid.

Step 2. 4'-(Methyloxy)-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.36 g, 14.8 mmol) was added to a solution of methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate (1.42 g, 4.94 mmol) in 25 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 1.26 g (93% yield) of desired product as a yellow solid.

Step 3. Methyl 1-({[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylate

HATU (1.04 g, 2.74 mmol) was added to a solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.500 g, 1.83 mmol), methyl 1-aminocycloheptanecarboxylate hydrochloride (0.380 g, 1.83 mmol), and

diisopropylethylamine (0.48 mL, 2.74 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.588 g (75% yield) of desired product as a yellow solid.

Step 4. Methyl 1-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylate

A mixture of methyl 1-({[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylate (0.584 g, 1.37 mmol) and 5% palladium on carbon (0.146 g, 0.069 mmol) in 35 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.516 g (95% yield) of desired product as an off-white solid.

Step 5. Methyl 1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylate

2,4,6-Trimethylphenylisocyanate (0.244 g, 1.51 mmol) was added to a solution of methyl 1-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylate (0.200 g, 0.505 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl , dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.179 g (64% yield) of desired product as a white solid.

Step 6. 1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylic acid

Lithium hydroxide (0.076 g, 3.2 mmol) was added to a solution of methyl 1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylate (0.176 g, 0.32 mmol) in 3 mL of THF: methanol:water/4:1:1. The mixture was heated at 50°C overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.155 g (89% yield) of desired product as a yellow solid. ES MS m/z 542 (M-H).

Example 223: (2*S*)-Cyclohexyl({[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

A mixture of methyl (2S)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.41 mmol), 4-fluorophenylboronic acid (0.063g, 0.45 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.0205 mmol), cesium fluoride (0.187 g, 1.23 mmol), 1 mL of water and 3 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water, and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.165 g of a white solid containing about 85% desired product.

Step 2. (2*S*)-Cyclohexyl({[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.071 g, 2.95 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.161 g, 0.29 mmol) in 3 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.075 g (49% yield) of desired product as a white solid. ES MS m/z 530 (M-H).

Example 224: (2*S*)-({[4-(1,3-Benzodioxol-5-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

Step 1. Methyl (2S)-({[4-(1,3-benzodioxol-5-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoate

A mixture methyl (2S)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.41 mmol), 1,3-benzodioxol-5-ylboronic acid (0.075 g, 0.45 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.0205 mmol), cesium fluoride (0.187 g, 1.23 mmol), 1 mL of water and 3 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water, and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.182 g of a white solid containing about 85% desired product.

Step 2. (2*S*)-({[4-(1,3-Benzodioxol-5-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)-ethanoic acid

Lithium hydroxide (0.069 g, 2.88 mmol) was added to a solution of methyl (2S)-({[4-(1,3-benzodioxol-5-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.165 g, 0.29 mmol) in 3 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.103 g (64% yield) of desired product as a white solid. ES MS m/z 556 (M-H).

Example 225: *O*-(1,1-Dimethylethyl)-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Step 1. Methyl *O*-(1,1-dimethylethyl)-*N*-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate

HATU (0.627 g, 1.65 mmol) was added to a solution of 4'-(Methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.300 g, 1.10 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.248 g, 1.10 mmol), and diisopropylethylamine (0.29 mL, 1.65 mmol) in 15 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.329 g (67% yield) of desired product as a light yellow solid.

Step 2. Methyl *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl *O*-(1,1-dimethylethyl)-*N*-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate (0.324 g, 0.73 mmol) and 5% palladium on carbon (0.078 g, 0.036 mmol) in 20 mL of ethanol in a pressure reaction vessel was

evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.297 g (98% yield) of desired productas an off-white solid.

Step 3. Methyl *O*-(1,1-dimethylethyl)-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate

2,4,6-Trimethylphenylisocyanate (0.334 g, 2.07 mmol) was added to a solution of methyl *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate (0.286 g, 0.69 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.327 g (82% yield) of desired product as a white solid.

Step 4. *O*-(1,1-Dimethylethyl)-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide (0.133 g, 5.5 mmol) was added to a solution of methyl *O*-(1,1-dimethylethyl)-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate (0.319 g, 0.55 mmol) in 6 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.266 g (86% yield) of desired product as a white solid. ES MS m/z 560 (M-H).

Example 226: *O*-(1,1-Dimethylethyl)-*N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-threonine

Step 1. Methyl O-(1,1-dimethylethyl)-N-[(4-fluoro-2-nitrophenyl)carbonyl]-L-threoninate

HATU (1.54 g, 4.05 mmol) was added to a solution of 4-fluoro-2-nitrobenzoic acid (0.500 g, 2.70 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.609 g, 2.70 mmol), and diisopropylethylamine (0.70 mL, 4.05 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.621 g (65% yield) of desired product as a colorless gum.

Step 2. Methyl N-[(2-amino-4-fluorophenyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-[(4-fluoro-2-nitrophenyl)carbonyl]-L-threoninate (0.586 g, 1.65 mmol) and 5% palladium on carbon (0.175 g, 0.0825 mmol) in 35 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.534 g (99% yield) of desired product as a colorless gum.

Step 3. Methyl O-(1,1-dimethylethyl)-N-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-threoninate

2,4,6-Trimethylphenylisocyanate (0.345 g, 2.14 mmol) was added to a solution of methyl N-[(2-amino-4-fluorophenyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate (0.233 g, 0.71 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate

was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.292 g (84% yield) of desired product as a white solid.

Step 4. *O*-(1,1-Dimethylethyl)-*N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-threonine

Lithium hydroxide (0.140 g, 5.85 mmol) was added to a solution of methyl O-(1,1-dimethylethyl)-N-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-threoninate (0.285 g, 0.585 mmol) in 6 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.110 g (40% yield) of desired product as a white solid. APCI MS m/z 472 (M-H).

Example 227: 1-({[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1. Methyl 1-{[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]amino}cyclooctanecarboxylate

HATU (0.467 g, 1.23 mmol) was added to a solution of 3',4'-difluoro-3-nitro-4-biphenylcarboxylic acid (0.230 g, 0.82 mmol), methyl 2-amino-2-ethyloctanoate (0.152 g, 0.82 mmol), and diisopropylethylamine (0.21 mL, 1.23 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum.

Chromatography on silica gel with hexane/ethyl acetate gave 0.248 g (68% yield) of desired product as a white solid.

Step 2. Methyl 1-{[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]amino}cyclooctanecarboxylate

A mixture of methyl 1-{[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]amino}cyclooctanecarboxylate (0.243 g, 0.54 mmol) and 5% palladium on carbon (0.058 g, 0.027 mmol) in 15 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.231g of desired product as a white solid.

Step 3. Methyl 1-({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

2,4,6-Trimethylphenylisocyanate (0.258 g, 1.60 mmol) was added to a solution of methyl 1-{[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]amino}cyclooctanecarboxylate (0.222 g, 0.53 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.235 g (77% yield) of desired product as a white solid.

Step 4. 1-({[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid

Lithium hydroxide (0.096 g, 4.0 mmol) was added to a solution of methyl 1-({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate (0.231 g, 0.40 mmol) in 3 mL of THF: methanol:water/4:1:1. The mixture was heated at 50°C overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.220 g (98% yield) of desired product as a white solid. ES MS m/z 564 (M+H).

Example 228: (2*S*)-Cyclohexyl({[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2S)-cyclohexyl({[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

A mixture of methyl (2S)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.41 mmol), 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (0.0815 g, 0.45 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.0205 mmol), cesium fluoride (0.186 g, 1.23 mmol), 0.5 mL of water and 3 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water, and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.187 g (78% yield) of desired product as a white solid.

Step 2. (2*S*)-Cyclohexyl({[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.077 g, 3.2 mmol) was added to a solution of methyl (2S)-cyclohexyl({[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.187 g, 0.32 mmol) in 3 mL of THF: methanol:water/4:1:1. The mixture was stirred at room

temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.040 g (22% yield) of desired product as a white solid. ES MS m/z 572 (M+H).

Example 229: (2*S*)-({[3',4'-Bis(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. Methyl (2S)-({[3',4'-bis(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate

A mixture of methyl (2S)-({[4-chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.41 mmol), [3,4-bis(methyloxy)phenyl]boronic acid (0.082 g, 0.45 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.015 g, 0.0205 mmol), cesium fluoride (0.186 g, 1.23 mmol), 0.5 mL of water and 3 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water, and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.086 g (36% yield) of desired product as a white solid.

Step 2. (2*S*)-({[3',4'-Bis(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide (0.035 g, 1.5 mmol) was added to a solution of methyl (2S)-({[3',4'-bis(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate (0.086 g, 0.15 mmol) in 2.5 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature

overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.016 g (19% yield) of desired product as a white solid. ES MS m/z 574 (M+H).

Example 230: (2*S*)-Cyclohexyl({[4,5-difluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2S)-cyclohexyl{[(4,5-difluoro-2-nitrophenyl)carbonyl]amino}ethanoate

HATU (1.402 g, 3.69 mmol) was added to a solution of 4,5-difluoro-2-nitrobenzoic acid (0.500 g, 2.46 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride(0.510 g, 2.46 mmol), and diisopropylethylamine (0.64 mL, 3.69 mmol) in 20 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.853 g of crude desired product as a yellow oil. This material was carried on to the next step without further purification.

Step 2. Methyl (2S)-{[(2-amino-4,5-difluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate

A mixture of methyl (2S)-cyclohexyl{[(4,5-difluoro-2-nitrophenyl)carbonyl]amino}ethanoate (0.850 g, 2.39 mmol) and 5% palladium on carbon (0.254 g, 0.119 mmol) in 30 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by chromatography on silica gel with

hexane/ethyl acetate to give 0.333 g (43% yield) of desired product as a white solid.

Step 3. Methyl (2S)-cyclohexyl({[4,5-difluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.148 g, 0.921 mmol) was added to a solution of methyl (2S)-{[(2-amino-4,5-difluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.100 g, 0.307 mmol) in 3 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.152 g of desired product as a white solid.

Step 4. (2*S*)-Cyclohexyl({[4,5-difluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.057 g, 2.4 mmol) was added to a solution of methyl (2S)-cyclohexyl({[4,5-difluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoate (0.116 g, 0.24 mmol) in 3 mL of THF: methanol:water/4:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.095 g (84% yield) of desired product as a white solid. ES MS m/z 474 (M+H).

Example 231: 1-({[4'-(Methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1. Methyl 1-({[3-nitro-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

HATU (0.524 g, 1.38 mmol) was added to a solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.250 g, 0.92 mmol), methyl 2-amino-2-ethyloctanoate (0.169 g, 0.92 mmol), and diisopropylethylamine (0.24 mL, 1.38 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.276 (68% yield) g of desired product as a yellow solid.

Step 2. Methyl 1-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

A mixture of methyl 1-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate (0.274 g, 0.62 mmol) and 5% palladium on carbon (0.066 g, 0.031 mmol) in 15 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.260 g of desired product as an off-white solid.

Step 3. Methyl 1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

2,4,6-Trimethylphenylisocyanate (0.304 g, 1.89 mmol) was added to a solution of methyl 1-({[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate (0.258 g, 0.63 mmol) in 5 mL of

anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.238 g (66% yield) of desired product as a white solid.

Step 4. 1-({[4'-(Methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid

Lithium hydroxide (0.094 g, 3.9 mmol) was added to a solution of methyl 1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate (0.223 g, 0.39 mmol) in 6 mL of THF: methanol:water/4:1:1. The mixture was heated at 50°C overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.088 g (40% yield) of desired product as a white solid. ES MS m/z 558 (M+H).

Example 232: N-{[3-{[({2,6-Dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine

Step 1. Methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate

Methyl 4-chloro-2-nitrobenzoate (1.00 g, 4.64 mmol), 4-methoxyphenylboronic acid (0.77 g, 5.10 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.171 g, 0.23 mmol) and cesium fluoride (2.11 g, 13.9 mmol) were mixed in 13 mL of acetonitrile:water/3:1 in each of four microwave reaction vials and heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixtures were combined and filtered through Celite, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and

the solvent was evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 4.59 g (86% yield) of desired product.

Step 2. 4'-(Methyloxy)-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (3.81 g, 158.8 mmol) was added to a solution of methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate (4.56 g, 15.98 mmol) in 50 ml of THF:methanol:water/3:1:1. The mixture was stirred at room temperature for 2.5 hours.. The solvent was evaporated and the residue was treated with aqueous 1N hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and the the solvent was evaporated to give 4.37 g (100% yield) of desired product as a yellow solid.

Step 3. Methyl O-(1,1-dimethylethyl)-N-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate

HATU (7.07 g, 18.6 mmol) was added to a solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (3.37 g, 12.4 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (2.79 g, 12.4 mmol), and diisopropylethylamine (3.2 mL, 18.6 mmol) in 100 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 3.79 (69% yield) g of desired product as a white solid.

Step 4. Methyl N-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate (3.77 g, 8.49 mmol) and 5% palladium on carbon (0.894 g, 0.42 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen

and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 3.38 g (96% yield) of desired product as an off-white solid.

Step 5. Methyl N-{[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate

1,3-Dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.316 g, 1.21 mmol) was added to a solution of methyl N-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate (0.200 g, 0.48 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.243 g (74% yield) of desired product as a white solid.

Step 6. N-{[3-{[({2,6-Dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine

Lithium hydroxide (0.085 g, 3.4 mmol) was added to a solution of methyl 1 N-{[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate (0.236 g, 0.34 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.222 g (97% yield) of desired product as a white solid. ES MS m/z 672 (M+H).

Example 233: O-(1,1-Dimethylethyl)-N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Step 1. Methyl 3'-fluoro-3-nitro-4-biphenylcarboxylate

A mixture methyl 4-chloro-2-nitrobezoate (0.500 g, 2.32 mmol), 3-fluorophenylboronic acid (0.357 g, 2.55 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.087 g, 0.116 mmol), cesium fluoride (1.06 g, 6.96 mmol), 1 mL of water and 6 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was filtered through Celite, diluted with ethyl acetate, washed with water, and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.525 g (82% yield) of desired product as a white solid.

Step 2. 3'-Fluoro-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.440 g, 18.3 mmol) was added to a solution of methyl 3'-fluoro-3-nitro-4-biphenylcarboxylate (0.504 g, 1.83 mmol) in 10 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.454 g (95% yield) of desired product as a white solid.

Step 3. Methyl O-(1,1-dimethylethyl)-N-[(3'-fluoro-3-nitro-4-biphenylyl)carbonyl]-L-threoninate

HATU (0.483 g, 1.27 mmol) was added to a solution of 3'-Fluoro-3-nitro-4-biphenylcarboxylic acid (0.221 g, 0.85 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.191 g, 0.85 mmol), and diisopropylethylamine (0.22 mL, 1.27 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine.

The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.302 g (82% yield) g of desired product as a white solid.

Step 4. Methyl N-[(3-amino-3'-fluoro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-[(3'-fluoro-3-nitro-4-biphenylyl)carbonyl]-L-threoninate (0.293 g, 0.69 mmol) and 5% palladium on carbon (0.072 g, 0.034 mmol) in 25 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.264 g (95% yield) of desired product as a white solid.

Step 5. Methyl O-(1,1-dimethylethyl)-N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate

2,4,6-Trimethylphenylisocyanate (0.307 g, 1.91 mmol) was added to a solution of methyl N-[(3-amino-3'-fluoro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate (0.256 g, 0.64 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.304 g (84% yield) of desired product as a white solid.

Step 6. O-(1,1-Dimethylethyl)-N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide (0.124 g, 5.2 mmol) was added to a solution of methyl O-(1,1-dimethylethyl)-N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-

biphenylyl]carbonyl}-L-threoninate (0.292 g, 0.52 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.260 g (91% yield) of desired product as a white solid. ES MS m/z 550 (M+H).

Example 234: (2S)-Cyclohexyl({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2S)-cyclohexyl{[(3'-fluoro-3-nitro-4-biphenylyl)carbonyl]amino}ethanoate

HATU (0.471 g, 1.24 mmol) was added to a solution of 3'-Fluoro-3-nitro-4-biphenylcarboxylic acid (0.216 g, 0.83 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.172 g, 0.83 mmol), and diisopropylethylamine (0.22 mL, 1.27 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.216 g (63% yield) of desired product as a white solid.

Step 2. Methyl (2S)-{[(3-amino-3'-fluoro-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate

A mixture of methyl (2S)-cyclohexyl{[(3'-fluoro-3-nitro-4-biphenylyl)carbonyl]amino}ethanoate (0.215 g, 0.52 mmol) and 5% palladium on carbon (0.055 g, 0.026 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated

and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.192 g (96% yield) of desired product as a light tan solid.

Step 3. Methyl (2S)-cyclohexyl({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.241 g, 1.5 mmol) was added to a solution of methyl (2S)-{[(3-amino-3'-fluoro-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.192 g, 0.50 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.213 g (78% yield) of desired product as a white solid.

Step 4. (2S)-Cyclohexyl({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.090 g, 3.8 mmol) was added to a solution of methyl (2S)-cyclohexyl({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.205 g, 0.38 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.136 g (67% yield) of desired product as a white solid. ES MS m/z 532 (M+H).

Example 235: O-(1,1-Dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Step 1. Methyl 3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylcarboxylate

In each of two microwave reaction vials, a mixture of methyl 4-chloro-2-nitrobenzoate (1.00 g, 4.64 mmol), 3-fluoro-4-methoxyphenylboronic acid (0.87 g, 5.10 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.171 g, 0.23 mmol), cesium fluoride (2.11 g, 13.9 mmol), 2 mL of water and 12 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixtures were combined, diluted with ethyl acetate, filtered through Celite, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 2.24 g (79% yield) of desired product as an off-white solid.

Step 2. 3'-Fluoro-4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.53 g, 21.9 mmol) was added to a solution of methyl 3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylcarboxylate (2.23 g, 7.31 mmol) in 50 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 1.87 g (88% yield) of desired product as a white solid.

Step 3. Methyl O-(1,1-dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate

HATU (0.585 g, 1.54 mmol) was added to a solution of 3'-Fluoro-4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.300 g, 1.03 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.232 g, 1.03 mmol), and diisopropylethylamine (0.27 mL, 1.54 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.392 g (82% yield) g of desired product as a white solid.

Step 4. Methyl N-{[3-amino-3'-fluoro-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate (0.388 g, 0.84 mmol) and 5% palladium on carbon (0.089 g, 0.042 mmol) in 25 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.340 g (94% yield) of desired product as an off-white solid.

Step 5. Methyl O-(1,1-dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate

2,4,6-Trimethylphenylisocyanate (0.376 g, 0.78 mmol) was added to a solution of methyl N-{[3-amino-3'-fluoro-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate (0.336 g, 0.78 mmol) in 7 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.359 g (60% yield) of desired product as a white solid.

Step 6. O-(1,1-Dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide (0.144 g, 6.0 mmol) was added to a solution of methyl O-(1,1-dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate (0.357 g, 0.60 mmol) in 10 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous

hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.319 g (92% yield) of desired product as a white solid. ES MS m/z 580 (M+H).

Example 236: O-(1,1-Dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-threonine

Step 1. Methyl O-(1,1-dimethylethyl)-N-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate

HATU (1.06 g, 2.79 mmol) was added to a solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.509 g, 1.86 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.420 g, 1.86 mmol), and diisopropylethylamine (0.48 mL, 2.79 mmol) in 15 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.589 g (71% yield) g of desired product as a white solid.

Step 2. Methyl N-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate (0.581 g, 1.31 mmol) and 5% palladium on carbon (0.139 g, 0.065 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.521 g (96% yield) of desired product as a beige solid.

Step 3. Methyl N-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate

5-bromo-2-isocyanato-1,3-dimethylbenzene (0.205 g, 0.91 mmol) was added to a solution of N-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate (0.150 g, 0.36 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.226 g of desired product as a white solid.

Step 4. Methyl O-(1,1-dimethylethyl)-N-{[3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-threoninate

Tributyl(2-propen-1-yl)stannane (0.138 g, 0.41 mmol) was added to a suspension of methyl N-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate (0.226 g, 0.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.024 g, 0.021 mmol) in 4.5 mL of acetonitrile. The mixture was heated to 150°C in a microwave reactor for 30 minutes. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 0.166 g of a white solid containing about 75% of desired product. This material was carried on to the next step without further purification.

Step 5. Methyl O-(1,1-dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-{[3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-

threoninate (0.164 g, 0.27 mmol) and 5% palladium on carbon (0.058 g, 0.027 mmol) in 10 mL of ethyl acetate in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.153 g of a mixture containing 85% desired product.

Step 6. O-(1,1-Dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide (0.061 g, 2.55 mmol) was added to a solution of methyl O-(1,1-dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-threoninate (0.154 g, 0.255 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.089 g (59% yield) of desired product as a white solid. ES MS m/z 590 (M+H).

Example 237: (2S)-Cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2S)-cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)ethanoate

HATU (0.585 g, 1.54 mmol) was added to a solution of 3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.300 g, 1.03 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.214 g, 1.03 mmol), and diisopropylethylamine (0.27 mL, 1.54 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and

washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.395 g (86% yield) g of desired product as a white solid.

Step 2. Methyl (2S)-({[3-amino-3'-fluoro-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate

A mixture of methyl (2S)-cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)ethanoate (0.391 g, 0.88 mmol) and 5% palladium on carbon (0.094 g, 0.044 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.330 g (90% yield) of desired product as a beige solid.

Step 3. Methyl (2S)-cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.379 g, 2.35 mmol) was added to a solution of methyl (2S)-({[3-amino-3'-fluoro-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate (0.325 g, 0.78 mmol) in 7 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.378 g (84% yield) of desired product as a white solid.

Step 4. (2S)-Cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.156 g, 6.5 mmol) was added to a solution of methyl (2S)-cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.375 g, 0.65 mmol) in 10 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.158 g (43% yield) of desired product as a white solid. APCI MS m/z 562 (M+H).

Example 238: 1-({[3'-Fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1. Methyl 1-({[3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

HATU (0.585 g, 1.54 mmol) was added to a solution of 3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.300 g, 1.03 mmol), methyl 1-aminocyclooctanecarboxylate hydrochloride (0.228 g, 1.03 mmol), and diisopropylethylamine (0.27 mL, 1.54 mmol) in 10 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.243 g (51% yield) g of desired product as an off-white solid.

Step 2. Methyl 1-({[3-amino-3'-fluoro-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

A mixture of methyl 1-({[3'-fluoro-4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate (0.240 g, 0.52 mmol) and 5% palladium on carbon (0.056 g, 0.026 mmol) in 25 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.212 g (95% yield) of desired product as an off-white solid.

Step 3. Methyl 1-({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

2,4,6-Trimethylphenylisocyanate (0.232 g, 1.44 mmol) was added to a solution of methyl 1-({[3-amino-3'-fluoro-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate (0.206 g, 0.48 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.214 g (76% yield) of desired product as a white solid.

Step 4. Methyl 1-({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

Lithium hydroxide (0.082 g, 3.4 mmol) was added to a solution of methyl 1-({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate (0.201 g, 0.34 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was heated at 50°C overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the

residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.170 g (43% yield) of desired product as a white solid. ES MS m/z 574 (M-H).

Example 239: (2*S*)-[({3-[({[2,4-bis(methyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoic acid

Step 1. Methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate

HATU (6.55 g, 17.23 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (5.0 g, 14.35 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (3.53 g, 17 mmol) and diisopropylethylamine (2.22 g, 17.21 mmol) in 100 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 5.01 g of light yellow solid.

Step 2. Methyl (2*S*)-[({3-[({[2,4-bis(methyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoate

Methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate (0.2 g, 0.588 mmol) in 3 mL of DMF was treated with triethylamine (0.16g, 1.58mmol) and 1-isocyanato-2,4-bis(methyloxy)benzene (0.13 g, 0.73 mmol) and was heated to 70°C for ca. 15h overnight. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.035 g of product.

Step 3. (2*S*)-[({3-[({[2,4-bis(methyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoic acid

Lithium hydroxide monohydrate (0.016 g, 0.67 mmol) was added to a solution of Methyl (2*S*)-[({3-[({[2,4-bis(methyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoate (0.035 g, 0.067 mmol) in dioxane:water/10:1(5ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was filtered through Varian chem-elut tubes and concentrated to dryness to give 6.3 mg (18% yield) of desired product as a light orange solid. ES MS m/z 506 (M+H).

Example 240: (2*S*)-[({3-[({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoic acid

Step 1. Methyl (2*S*)-[({3-[({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoate

Methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate (0.2 g, 0.588 mmol) in 3 mL of DMF was treated with triethylamine (0.16g, 1.58mmol) and 1-isocyanato-3,5-bis(trifluoromethyl)benzene (0.18 g, 0.71 mmol) and was heated to 70°C for ca. 15h overnight. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.264 g of product.

Step 2. (2*S*)-[({3-[({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoic acid

Lithium hydroxide monohydrate (0.11 g, 4.43 mmol) was added to a solution of Methyl (2*S*)-[({3-[({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoate (0.264 g, 0.44 mmol) in

dioxane:water/10:1(5ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was filtered through Varian chem-elut tubes and concentrated to dryness to give 103 mg (40% yield) of desired product as a light orange solid. ES MS m/z 582 (M+H).

Example 241: *N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(2-pyridinylmethyl)glycine

Step 1. Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(2-pyridinylmethyl)glycinate

HATU (0.27 g, 0.71 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.2 g, 0.57 mmol), ethyl *N*-(2-pyridinylmethyl)glycinate hydrochloride (0.15 g, 77 mmol) and diisopropylethylamine (0.09 g, 0.70 mmol) in 3 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.311 g of amber oil.

Step 2. Ethyl *N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(2-pyridinylmethyl)glycinate

Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(2-pyridinylmethyl)glycinate (0.15 g, 0.413 mmol) in 3 mL of DMF was treated with triethylamine (0.087g, 0.86mmol) and 2-isocyanato-1,3-dimethylbenzene (0.067 g, 0.455 mmol) and was heated to 70°C for ca. 3h and then stirred at RT for 48 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.05 g of light yellow semi-solid.

Step 3. *N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(2-pyridinylmethyl)glycine

Lithium hydroxide monohydrate (0.023 g, 0.96 mmol) was added to a solution of ethyl *N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(2-pyridinylmethyl)glycinate (0.05 g, 0.098 mmol) in dioxane:water/10:1(5ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was filtered through Varian tubes and concentrated to dryness to give 42 mg (89% yield) of desired product as a light orange solid. ES MS m/z 483 (M+H).

Example 242: *N*-(2-pyridinylmethyl)-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Step 1. ethyl *N*-(2-pyridinylmethyl)-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate

Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(2-pyridinylmethyl)glycinate (0.15 g, 0.413 mmol) in 3 mL of DMF was treated with triethylamine (0.087g, 0.86mmol) and 1,3,5-trichloro-2-isocyanatobenzene (0.100 g, 0.449 mmol) and was heated to 70°C for ca. 3h and then stirred at RT for 48 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.077 g of product.

Step 2. *N*-(2-pyridinylmethyl)-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Lithium hydroxide monohydrate (0.031 g, 1.29 mmol) was added to a solution of ethyl *N*-(2-pyridinylmethyl)-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate (0.077 g, 0.131 mmol) in dioxane:water/10:1(5ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was filtered

through Varian tubes and concentrated to dryness to give 65 mg (89% yield) of desired product as a cream solid. ES MS m/z 557 (M+H).

Example 243: *N*-(cyclohexylmethyl)-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Step 1. Phenylmethyl *N*-(cyclohexylmethyl)glycinate

Triethylamine (5.02g, 49.65mmol) was added to a solution of phenylmethyl glycinate hydrochloride (5.0g, 24.81mmol) in 15 ml of MeOH to which was then added cyclohexanecarbaldehyde (2.79g, 24.93mmol). The reaction was stirred at RT for 2 hours and then sodium borohydride (1.89g, 49.96mmol) was added portionwise, and the reaction was then allowed to stir at RT for 15 hours. The reaction was quenched with 5% sodium bicarbonate solution and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.202g of clear oil.

Step 2. Phenylmethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(cyclohexylmethyl)glycinate

HATU (0.27 g, 0.71 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.2 g, 0.57 mmol), phenylmethyl *N*-(cyclohexylmethyl)glycinate (0.18 g, 0.689 mmol) and diisopropylethylamine (0.089 g, 0.69 mmol) in 3 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.159 g of product.

Step 3. Phenylmethyl *N*-(cyclohexylmethyl)-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate

Phenylmethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(cyclohexylmethyl)glycinate (0.159 g, 0.369 mmol) in 3 mL of DMF was treated with triethylamine (0.074g, 0.73mmol) and 2-isocyanato-1,3-dimethylbenzene (0.59 g, 4.01 mmol) and was heated to 70°C for ca. 15 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.072 g of product.

Step 4. *N*-(cyclohexylmethyl)-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of phenylmethyl *N*-(cyclohexylmethyl)-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate (0.072g, 0.125mmol) in 5ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a pad of Celite and the solvent evaporated to give 0.023g (38% yield) of product as a cream solid ES MS m/z 488 (M+H).

Example 244: *N*-cyclopentyl-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine.

Step 1. Phenylmethyl *N*-cyclopentylglycinate

Triethylamine (5.02g, 49.65mmol) was added to a solution of phenylmethyl glycinate hydrochloride (5.0g, 24.81mmol) in 15 ml of MeOH to which was then added cyclopentanone (2.74g, 32.53mmol). The reaction was stirred at RT for 2 hours and then sodium borohydride (1.89g, 49.96mmol) was added portionwise, and the reaction was then allowed to stir at RT for 15 hours. The reaction was quenched with 5% sodium bicarbonate solution and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent

evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.363g of clear oil.

Step 2. Phenylmethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-cyclopentylglycinate

HATU (0.27 g, 0.71 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.2 g, 0.57 mmol), phenylmethyl *N*-cyclopentylglycinate (0.16 g, 0.686 mmol) and diisopropylethylamine (0.089 g, 0.69 mmol) in 3 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.166 g of product.

Step 3. Phenylmethyl *N*-cyclopentyl-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate

Phenylmethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-cyclopentylglycinate (0.166 g, 0.412 mmol) in 3 mL of DMF was treated with triethylamine (0.074g, 0.73mmol) and 2-isocyanato-1,3-dimethylbenzene (0.59 g, 4.01 mmol) and was heated to 70°C for ca. 15 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.092 g of product.

Step 4. *N*-cyclopentyl-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of phenylmethyl *N*-(cyclohexylmethyl)-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate (0.072g, 0.125mmol) in 5ml of EtOH in a flask under nitrogen. A balloon of H_2 was then

affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a pad of Celite and the solvent evaporated to give 0.021g (27% yield) of product as a cream solid ES MS m/z 460 (M+H).

Example 245: *N*-cyclohexyl-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Step 1. Phenylmethyl *N*-cyclohexylglycinate

Triethylamine (5.02g, 49.65 mmol) was added to a solution of phenylmethyl glycinate hydrochloride (5.0g, 24.81 mmol) in 15 ml of MeOH to which was then added cyclohexanone (2.45g, 24.96 mmol). The reaction was stirred at RT for 2 hours and then sodium borohydride (1.89g, 49.96 mmol) was added portionwise, and the reaction was then allowed to stir at RT for 15 hours. The reaction was quenched with 5% sodium bicarbonate solution and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 3.65g of light amber oil.

Step 2. Phenylmethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-cyclohexylglycinate

HATU (2.28 g, 5.99 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (1.0 g, 5.34 mmol), phenylmethyl *N*-cyclohexylglycinate (1.59 g, 6.43 mmol) and diisopropylethylamine (0.78 g, 6.02 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.240g of product.

Step 3. Phenylmethyl *N*-cyclohexyl-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate

Phenylmethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-cyclohexylglycinate (0.240 g, 0.576 mmol) in 10 mL of DMF was treated with triethylamine (0.12g, 1.15mmol) and 2-isocyanato-1,3-dimethylbenzene (0.09 g, 0.61 mmol) and was heated to 70°C for ca. 48 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.077 g of product.

Step 4. *N*-cyclohexyl-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of Phenylmethyl *N*-cyclohexyl-*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate (0.077g, 0.137mmol) in 5ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a pad of Celite and the solvent evaporated to give 0.011g (17% yield) of product as a cream solid ES MS m/z 474 (M+H).

Example 246: 2,2'-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}imino)diacetic acid

Step 1. Bis(1,1-dimethylethyl) 2,2'-{[(3-amino-2-naphthalenyl)carbonyl]imino}diacetate

HATU (2.44 g, 6.41 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (1.0 g, 5.34 mmol), bis(1,1-dimethylethyl) 2,2'-iminodiacetate (1.57 g, 6.40 mmol) and diisopropylethylamine (0.83 g, 6.42 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 48 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent

evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.66 g of product as a light orange solid.

Step 2. Bis(1,1-dimethylethyl) 2,2'-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}imino)diacetate

Bis(1,1-dimethylethyl) 2,2'-{[(3-amino-2-naphthalenyl)carbonyl]imino}diacetate (1.66 g, 4.00 mmol) in 50 mL of DMF was treated with triethylamine (0.81g, 8.03 mmol) and 2-isocyanato-1,3-dimethylbenzene (0.65 g, 4.42 mmol) and was heated to 70°C for ca. 15 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated to give 1.41 g of crude product. Chromatography on silica gel of 1.0 g of crude product with hexane/ethyl acetate gave 0.44 g of product as a fluffy yellow semi-solid.

Step 3. 2,2'-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}imino)diacetic acid

Bis(1,1-dimethylethyl) 2,2'-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}imino)diacetate (0.44g, 0.78 mmol) was dissolved in 2:1(v/v) of TFA (2ml) and CH_2Cl_2 (1ml) and stirred at RT for 30 minutes. The reaction was concentrated by a nitrogen stream and dried further in vacuo to give 252mg (72% yield) of product as a fluffy amber solid. ES MS m/z 450 (M+H).

Example 247: (2*S*)-({[3-({[(4-butylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. Methyl (2*S*)-({[3-({[(4-butylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.2g, 0.588 mmol) in 3 mL of DMF was treated with triethylamine (0.12g, 1.15 mmol) and

1-butyl-4-isocyanatobenzene (0.12 g, 0.685 mmol) and was heated to 70°C for ca. 3 hours and then allowed to stir at RT for ca. 15 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. The crude material was then triturated with ethyl acetate and then filtered to give 0.135 g of product.

Step 2. (2*S*)-({[3-({[(4-butylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide monohydrate (0.063 g, 2.61 mmol) was added to a solution of methyl (2*S*)-({[3-({[(4-butylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.135 g, 0.262 mmol) in dioxane:water/10:1 (3ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was filtered through Varian Chem-elut tubes and concentrated to dryness and purified by Agilent prep-HPLC to give 11.2 mg (8% yield) of desired product as a cream solid. ES MS m/z 502 (M+H).

Example 248: (2*S*)-cyclohexyl{[(3-{[(2,3-dihydro-1-benzofuran-5-ylamino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid.

Step 1. Methyl (2*S*)-cyclohexyl{[(3-{[(2,3-dihydro-1-benzofuran-5-ylamino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoate

Methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.2g, 0.588 mmol) in 3 mL of DMF was treated with triethylamine (0.12g, 1.15 mmol) and 5-isocyanato-2,3-dihydro-1-benzofuran (0.11 g, 0.682 mmol) and was heated to 70°C for ca. 3 hours and then allowed to stir at RT for ca. 15 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. The crude material was then triturated with ethyl acetate and then filtered to give 0.192 g of product.

Step 2. (2*S*)-cyclohexyl{[(3-{[(2,3-dihydro-1-benzofuran-5-ylamino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid

Lithium hydroxide monohydrate (0.092 g, 3.83 mmol) was added to a solution of methyl (2*S*)-cyclohexyl{[(3-{[(2,3-dihydro-1-benzofuran-5-ylamino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoate (0.192 g, 0.383 mmol) in dioxane:water/10:1 (3ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was filtered through Varian Chem-elut tubes and concentrated to dryness to give 98 mg (53% yield) of desired product as a tan solid. ES MS m/z 488 (M+H).

Example 249: (2*S*)-cyclohexyl({[3-({[(5-methyl-3-phenyl-4-isoxazolyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid.

Step 1. Methyl (2*S*)-cyclohexyl({[3-({[(5-methyl-3-phenyl-4-isoxazolyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

Methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.2g, 0.588 mmol) in 3 mL of DMF was treated with triethylamine (0.12g, 1.15 mmol) and 4-isocyanato-5-methyl-3-phenylisoxazole (0.14 g, 0.699 mmol) and was heated to 70°C for ca. 3 hours and then allowed to stir at RT for ca. 15 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. The crude material was then chromatographed with ethyl acetate/hexanes to give 0.168 g of product.

Step 2. (2*S*)-cyclohexyl({[3-({[(5-methyl-3-phenyl-4-isoxazolyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.075 g, 3.14 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[(5-methyl-3-phenyl-4-isoxazolyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.168 g, 0.311 mmol) in dioxane:water/10:1 (3ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over MgSO4, filtered and concentrated in vacuo to give 66 mg (42% yield) of product. ES MS m/z 527 (M+H).

Example 250: *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)-L-alanine

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(phenylmethyl)-L-alaninate

HATU (0.61 g, 1.60 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.25g g, 1.34 mmol), methyl *N*-(phenylmethyl)-L-alaninate hydrochloride (0.37 g, 1.61 mmol) and diisopropylethylamine (0.21 g, 1.61 mmol) in 3 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.085 g of product.

Step 2. Methyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)-L-alaninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(phenylmethyl)-L-alaninate (0.085g, 0.235 mmol) in 3 mL of DMF was treated with triethylamine (0.047g, 0.466 mmol) and 1,3-dichloro-2-isocyanatobenzene (0.049 g, 0.261 mmol) and was heated to 70°C for ca. 3 hours and then allowed to stir at RT for ca. 48 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate and then filtered

through a Varian Chem-elut tube. Chromatography on silica gel with hexane/ethyl acetate gave 0.077 g of product.

Step 3: *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)-L-alanine

Lithium hydroxide monohydrate (0.034 g, 1.42 mmol) was added to a solution of methyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)-L-alaninate (0.077 g, 0.140 mmol) in dioxane:water/10:1 (3ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over MgSO4, filtered and concentrated in vacuo, followed by purification on Agilent prep-HPLC to give 12.8 mg (16% yield) of product. ES MS m/z 536 (M+H).

Example 251: *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)phenylalanine

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(phenylmethyl)phenylalaninate

HATU (0.61 g, 1.60 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.25g g, 1.34 mmol), methyl *N*-(phenylmethyl)phenylalaninate hydrochloride (0.49 g, 1.60 mmol) and diisopropylethylamine (0.21 g, 1.61 mmol) in 3 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.32 g of product.

Step 2. Methyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)phenylalaninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(phenylmethyl)phenylalaninate (0.32g, 0.730 mmol) in 3 mL of DMF was treated with triethylamine (0.145g, 1.43 mmol) and 1,3-dichloro-2-isocyanatobenzene (0.15 g, 0.798 mmol) and was heated to 70°C for ca. 3 hours and then allowed to stir at RT for ca. 48 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate and then filtered through a Varian Chem-elut tube. Chromatography on silica gel with hexane/ethyl acetate gave 0.030 g of product.

Step 3. *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)phenylalanine

Lithium hydroxide monohydrate (0.011 g, 0.459 mmol) was added to a solution of methyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)phenylalaninate (0.030 g, 0.0479 mmol) in dioxane:water/10:1 (3ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 10.4 mg (32% yield) of product. ES MS m/z 611 (M-H).

Example 252: *N*-butyl-*N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Step 1. Phenylmethyl *N*-butylglycinate

Triethylamine (5.01g, 49.50 mmol) was added to a solution of phenylmethyl glycinate hydrochloride (5.0g, 24.81 mmol) in 100 ml of MeOH to which was then added butanal (1.80g, 24.93 mmol). The reaction was stirred at RT for 2 hours and then sodium borohydride (1.89g, 49.96 mmol) was added portionwise, and the reaction was then allowed to stir at RT for 15 hours. The reaction was quenched with 5% sodium bicarbonate solution and diluted with ethyl acetate. The organic

layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.454g of clear oil.

Step 2. Phenylmethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-butylglycinate

HATU (0.61 g, 1.60 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.25g g, 1.34 mmol), phenylmethyl *N*-butylglycinate (0.35 g, 1.58 mmol) and diisopropylethylamine (0.21 g, 1.61 mmol) in 3 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.155 g of product.

Step 3. Phenylmethyl *N*-butyl-*N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate

Phenylmethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-butylglycinate (0.155g, 0.397 mmol) in 3 mL of DMF was treated with triethylamine (0.080g, 0.789 mmol) and 1,3-dichloro-2-isocyanatobenzene (0.082 g, 0.436 mmol) and was heated to 70°C for ca. 3 hours and then allowed to stir at RT for ca. 48 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate and then filtered through a Varian Chem-elut tube. Chromatography on silica gel with hexane/ethyl acetate gave 0.0725 g of product.

Step 4. *N*-butyl-*N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of phenylmethyl *N*-butyl-*N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycinate (0.0725g, 0.125mmol) in 5ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The

reaction was then filtered through a pad of Celite and the solvent evaporated and then crude material purified by Agilent prep-HPLC to give 0.0235g (38% yield) of product as a cream solid ES MS m/z 488 (M+H).

Example 253: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine

Step 1: Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-norleucinate

HATU (1.14 g, 3.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5g g, 2.67 mmol), methyl L-norleucinate (0.47 g, 3.24 mmol) and diisopropylethylamine (0.38 g, 2.95 mmol) in 15 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.0 g of product as a yellow oil.

Step 2. Methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-norleucinate (1.0 g, 3.18 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (2.6 g, 16.13 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.5 g of product as a white solid.

Step 3. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine

Lithium hydroxide monohydrate (0.25 g, 10.44 mmol) was added to a solution of methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-

naphthalenyl]carbonyl}-L-norleucinate (0.5 g, 1.05 mmol) in dioxane:water/10:1 (20ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.47 g (92% yield) of product. ES MS m/z 462 (M+H).

Example 254: (2*S*)-4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylic acid

Step 1. 1-(1,1-dimethylethyl) 3-methyl (3*S*)-4-[(3-amino-2-naphthalenyl)carbonyl]-1,3-piperazinedicarboxylate

HATU (1.14 g, 3.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5g g, 2.67 mmol), 1-(1,1-dimethylethyl) 3-methyl (3*S*)-1,3-piperazinedicarboxylate (0.78 g, 3.19 mmol) and diisopropylethylamine (0.38 g, 2.95 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.58 g of product as a tan solid.

Step 2. 1-(1,1-dimethylethyl) 3-methyl (3*S*)-4-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-1,3-piperazinedicarboxylate

1-(1,1-dimethylethyl) 3-methyl (3*S*)-4-[(3-amino-2-naphthalenyl)carbonyl]-1,3-piperazinedicarboxylate (0.58 g, 1.40 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.13 g, 7.01 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated.

Chromatography on silica gel with hexane/ethyl acetate gave 0.74 g of product as a light yellow semi-solid.

Step 3. (2*S*)-4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylic acid

Lithium hydroxide monohydrate (0.08 g, 3.34 mmol) was added to a solution of 1-(1,1-dimethylethyl) 3-methyl (3*S*)-4-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-1,3-piperazinedicarboxylate (0.2 g, 0.348 mmol) in dioxane:water/10:1 (4ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.144 g (73% yield) of product. ES MS m/z 561 (M+H).

Example 255: (2*S*)-cyclohexyl({[3-({[5-(2,4-dichlorophenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate

HATU (6.55 g, 17.23 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (5.0 g, 14.35 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (3.53 g, 17 mmol) and diisopropylethylamine (2.22 g, 17.21 mmol) in 100 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 2.82 g of amber oil.

Step 2. Methyl (2*S*)-cyclohexyl({[3-({[5-(2,4-dichlorophenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

To a solution of methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.2g, 0.588 mmol) and 5-(2,4-dichlorophenyl)-2-furancarbonyl chloride (0.16g, 0.581 mmol) was added triethylamine (0.058g, 0.574 mmol). The reaction was allowed to stir for ca. 15 hours and then reaction mixture partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.31 g of light yellow solid.

Step 3. (2*S*)-cyclohexyl({[3-({[5-(2,4-dichlorophenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.13 g, 5.43 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[5-(2,4-dichlorophenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.31 g, 0.535 mmol) in dioxane:water/10:1 (7ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo, triturated with hexanes/ethyl acetate to give 0.120 g (42% yield) of product. ES MS m/z 563 (M-H).

Example 256: (2*S*)-4-(methylsulfonyl)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylic acid

Step 1. Methyl (2*S*)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylate

1-(1,1-dimethylethyl) 3-methyl (3*S*)-4-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-1,3-piperazinedicarboxylate (0.5 g, 0.870 mmol) in 15 mL of CH_2Cl_2:TFA (2:1). The mixture as stirred at RT for ca. 15 h and the solvents were removed under reduced pressure to give the 0.8 g of the product.

Step 2. Methyl (2*S*)-4-(methylsulfonyl)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylate

A solution of methyl (2*S*)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylate (0.1g, 0.211 mmol) in 3 ml of CH_2Cl_2 was cooled in an ice bath and to which was added triethylamine (0.032g, 0.316 mmol) and methanesulfonyl chloride (0.027g, 0.233 mmol). The reaction was allowed to come to room temperature stirring for 15 hours. The reaction was quenched with saturated sodium bicarbonate and the organics were dried over sodium sulfate, filtered and loaded directly onto silica for chromatography. Chromatography on silica gel with 5% MeOH in CH_2Cl_2 gave 0.2 g of product which still contained impurities. Material was further purified on Agilent semi-prep HPLC to give 33 mg of light yellow oil.

Step 3. (2*S*)-4-(methylsulfonyl)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylic acid

Lithium hydroxide monohydrate (0.014 g, 0.585 mmol) was added to a solution of methyl (2*S*)-4-(methylsulfonyl)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylate (0.033 g, 0.060 mmol) in dioxane:water/10:1 (3ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over

magnesium sulfate, filtered and concentrated in vacuo to give 0.012 g (19% yield) of product. ES MS m/z 539 (M+H).

Example 257: (2*S*)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperidinecarboxylic acid

Step 1. Methyl (2*S*)-1-[(3-amino-2-naphthalenyl)carbonyl]-2-piperidinecarboxylate

HATU (1.14 g, 3.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5g g, 2.67 mmol), methyl (2*S*)-2-piperidinecarboxylate hydrochloride (0.58 g, 3.23 mmol) and diisopropylethylamine (0.38 g, 2.95 mmol) in 15 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.49 g of product as yellow oil.

Step 2. Methyl (2*S*)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperidinecarboxylate

Methyl (2*S*)-1-[(3-amino-2-naphthalenyl)carbonyl]-2-piperidinecarboxylate (0.49g, 1.57 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.27 g, 7.86 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.18 g of product as a fluffy yellow foam.

Step 3. (2*S*)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperidinecarboxylic acid

Lithium hydroxide monohydrate (0.091 g, 3.80 mmol) was added to a solution of methyl (2*S*)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-

naphthalenyl]carbonyl}-2-piperidinecarboxylate (0.18 g, 0.380 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.23 g (100% yield) of product. ES MS m/z 460 (M+H).

Example 258: *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-serinate

HATU (1.14 g, 3.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5g g, 2.67 mmol), methyl *O*-(1,1-dimethylethyl)-L-serinate hydrochloride (0.68 g, 3.22 mmol) and diisopropylethylamine (0.38 g, 2.95 mmol) in 15 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.16g of product as yellow solid.

Step 2. Methyl *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-serinate (1.16 g, 3.37 mmol) in 15 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (2.72 g, 16.83 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated to give 1.01 g of product as amber oil.

Step 3. *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Lithium hydroxide monohydrate (0.062 g, 2.59 mmol) was added to a solution of methyl *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate (0.130 g, 0.257 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.037 g (25% yield) of product. ES MS m/z 492 (M+H).

Example 259: 5-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine

Step 1: Methyl (2*E*)-5-methyl-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-hexenoate

To a solution of methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)-oxy]carbonyl}amino)acetate (2.12g, 6.40 mmol) in CH_2Cl_2 was added DBU (0.92g, 6.02 mmol) and the resulting solution was stirred at RT for 10 minutes. To that was then added 3-methylbutanal (0.5g, 5.81 mmol), and the reaction was stirred for 16 hours at RT. The reaction was quenched with 1N HCl and the CH_2Cl_2 layer dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.34g of product as clear oil.

Step 2. Methyl 5-methylnorleucinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl (2*E*)-5-methyl-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-hexenoate (1.34g, 4.60mmol) in 25ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 16 hours at RT. The reaction was then filtered through a pad of Celite and the solvent evaporated to give 0.46g of yellow oil.

Step 3. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-5-methylnorleucinate

HATU (1.10 g, 2.89 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.45g g, 2.40 mmol), methyl 5-methylnorleucinate (0.46 g, 2.89 mmol) and diisopropylethylamine (0.29 g, 2.24 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.44g of product as yellow oil.

Step 4. Methyl 5-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-5-methylnorleucinate (0.44 g, 1.34 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.08 g, 6.68 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.34 g of product as a light tan semi-solid.

Step 5. 5-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine

Lithium hydroxide monohydrate (0.17 g, 7.10 mmol) was added to a solution of methyl 5-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucinate (0.34 g, 0.694 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.34 g (100% yield) of product. ES MS m/z 476 (M+H).

Example 260: 6,6,6-trifluoro-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine.

Step 1: Methyl (2*E*)-6,6,6-trifluoro-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-hexenoate

To a solution of methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)-oxy]carbonyl}amino)acetate (1.44g, 4.35 mmol) in CH_2Cl_2 was added DBU (0.64g, 4.21 mmol) and the resulting solution was stirred at RT for 10 minutes. To that was then added 4,4,4-trifluorobutanal (0.5g, 3.97 mmol), and the reaction was stirred for 16 hours at RT. The reaction was quenched with 1N HCl and the CH_2Cl_2 layer dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.39g of product as a white solid.

Step 2. Methyl 6,6,6-trifluoronorleucinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl (2*E*)-6,6,6-trifluoro-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-hexenoate (0.39g, 1.18mmol) in 25ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 16 hours at RT. The reaction was then filtered through a pad of Celite and the solvent evaporated to give 0.16g of white semi-solid.

Step 3. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-6,6,6-trifluoronorleucinate

HATU (0.30 g, 0.789 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.125g g, 0.668 mmol), methyl 6,6,6-trifluoronorleucinate (0.16 g, 0.803 mmol) and diisopropylethylamine (0.104 g, 0.803 mmol) in 12 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the

solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.13g of product as orange oil.

Step 4. Methyl 6,6,6-trifluoro-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-6,6,6-trifluoronorleucinate (0.13 g, 0.353 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.29 g, 1.79 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.17 g of product as a light yellow solid.

Step 5. 6,6,6-trifluoro-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine

Lithium hydroxide monohydrate (0.038 g, 1.59 mmol) was added to a solution of methyl 6,6,6-trifluoro-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucinate (0.17 g, 0.321 mmol) in dioxane:water/10:1 (5ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.109 g (66% yield) of product. ES MS m/z 516 (M+H).

Example 260: *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate

HATU (1.22 g, 3.21 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5g g, 2.67 mmol), methyl *O*-(1,1-dimethylethyl)-L-

threoninate hydrochloride (0.72 g, 3.19 mmol) and diisopropylethylamine (0.41 g, 3.21 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.72g of product as amber oil.

Step 2. Methyl *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate (0.72 g, 2.01 mmol) in 12 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.62 g, 10.02 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.85 g of product as a yellow fluffy tar.

Step 3. *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Lithium hydroxide monohydrate (0.39 g, 16.28 mmol) was added to a solution of methyl *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate (0.85 g, 1.64 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.523 g (65% yield) of product. ES MS m/z 506 (M+H).

Example 262: 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)heptanoic acid

Step 1. Methyl (2*E*)-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-heptenoate

To a solution of methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)oxy]-carbonyl}amino)acetate (2.12g, 6.40 mmol) in CH_2Cl_2 was added DBU (0.93g, 6.08 mmol) and the resulting solution was stirred at RT for 10 minutes. To that was then added pentanal (0.5g, 5.81 mmol), and the reaction was stirred for 16 hours at RT. The reaction was quenched with 1N HCl and the CH_2Cl_2 layer dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.92g of product as a colorless oil.

Step 2. Methyl 2-aminoheptanoate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl (2*E*)-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-heptenoate (0.92g, 3.16mmol) in 30ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 16 hours at RT. The reaction was then filtered through a pad of Celite and the solvent evaporated to give 0.32g of light yellow oil.

Step 3. Methyl 2-{[(3-amino-2-naphthalenyl)carbonyl]amino}heptanoate

HATU (0.76 g, 2.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.31g g, 1.66 mmol), methyl 2-aminoheptanoate (0.32 g, 2.01 mmol) and diisopropylethylamine (0.26 g, 2.01 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.21g of product as a light amber oil.

Step 4. Methyl 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)heptanoate

Methyl 2-{[(3-amino-2-naphthalenyl)carbonyl]amino}heptanoate (0.21 g, 0.639 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.52 g, 3.22 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.220 g of product as a light orange solid.

Step 5. 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)heptanoic acid

Lithium hydroxide monohydrate (0.11 g, 4.59 mmol) was added to a solution of methyl 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)heptanoate (0.22 g, 0.449 mmol) in dioxane:water/10:1 (20ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.277 g (100% yield) of product. ES MS m/z 476 (M+H).

Example 263: 3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid

3-amino-2-naphthalenecarboxylic acid (5.00 g, 26.71 mmol) in 100 mL of DMF was treated with triethylamine (5.40g, 53.37 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (4.7 g, 29.16 mmol) and was heated to 70°C for ca. 3 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated to give 7.95 g (84%) of product. ES MS m/z 349 (M+H).

Example 264: 5,7,7-trimethyl-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)octanoic acid

Step 1. Methyl (2*E*)-5,7,7-trimethyl-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-octenoate

To a solution of methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)oxy]carbonyl}amino)acetate (1.28g, 3.86 mmol) in CH_2Cl_2 was added DBU (0.57g, 3.74 mmol) and the resulting solution was stirred at RT for 10 minutes. To that was then added 3,5,5-trimethylhexanal (0.5g, 3.52 mmol), and the reaction was stirred for 16 hours at RT. The reaction was quenched with 1N HCl and the CH_2Cl_2 layer dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.36g of product as a colorless oil.

Step 2: methyl 2-amino-5,7,7-trimethyloctanoate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl (2*E*)-5,7,7-trimethyl-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-octenoate (1.36g, 3.91 mmol) in 25ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 16 hours at RT. The reaction was then filtered through a pad of Celite and the solvent evaporated to give 0.85g of light yellow oil.

Step 3. Methyl 2-{[(3-amino-2-naphthalenyl)carbonyl]amino}-5,7,7-trimethyloctanoate

HATU (1.48 g, 3.89 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.62g g, 3.31 mmol), methyl 2-amino-5,7,7-trimethyloctanoate (0.85 g, 3.95 mmol) and diisopropylethylamine (0.50 g, 3.90 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.04g of product as amber oil.

Step 4. Methyl 5,7,7-trimethyl-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)octanoate

Methyl 2-{[(3-amino-2-naphthalenyl)carbonyl]amino}-5,7,7-trimethyloctanoate (1.04 g, 2.70 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (2.19 g, 13.55 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.91 g of product as amber oil.

Step 5. 5,7,7-trimethyl-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)octanoic acid

Lithium hydroxide monohydrate (0.20 g, 8.35 mmol) was added to a solution of methyl 5,7,7-trimethyl-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)octanoate (0.91 g, 1.67 mmol) in dioxane:water/10:1 (20ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.87 g (97% yield) of product. ES MS m/z 532 (M+H).

Example 265: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-leucine

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-leucinate

HATU (1.14 g, 3.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5g g, 2.67 mmol), methyl L-leucinate hydrochloride (0.58 g, 3.19 mmol) and diisopropylethylamine (0.38 g, 2.98 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was

dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.76g of product as yellow oil.

Step 2. Methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-leucinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-leucinate (0.76 g, 2.42 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.96 g, 12.13 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.75 g of product as amber semi-solid.

Step 3. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-leucine

Lithium hydroxide monohydrate (0.38 g, 15.87 mmol) was added to a solution of methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-leucinate (0.75 g, 1.58 mmol) in dioxane:water/10:1 (20ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.35 g (47% yield) of product. ES MS m/z 462 (M+H).

Example 266: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-isoleucine

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-isoleucinate

HATU (1.14 g, 3.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5g g, 2.67 mmol), methyl L-alloisoleucinate

hydrochloride (0.58 g, 3.19 mmol) and diisopropylethylamine (0.38 g, 2.98 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.92g of product as yellow oil.

Step 2. Methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-isoleucinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-isoleucinate (0.92 g, 2.93 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (2.37 g, 14.67 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.63 g of product as amber semi-solid.

Step 3. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-isoleucine

Lithium hydroxide monohydrate (0.32 g, 13.36 mmol) was added to a solution of methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-isoleucinate (0.63 g, 1.32 mmol) in dioxane:water/10:1 (20ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.314 g (52% yield) of product as a light yellow fluffy solid. ES MS m/z 462 (M+H).

Example 267: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-norvalinate

HATU (1.14 g, 3.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5g g, 2.67 mmol), methyl L-norvalinate hydrochloride (0.5 g, 2.98 mmol) and diisopropylethylamine (0.38 g, 2.98 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.72g of product as yellow oil.

Step 2. Methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvalinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-norvalinate (0.72 g, 2.4 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.94 g, 12.00 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.8 g of product as light yellow semi-solid.

Step 3. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline

Lithium hydroxide monohydrate (0.41 g, 17.12 mmol) was added to a solution of methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvalinate (0.8 g, 1.73 mmol) in dioxane:water/10:1 (25ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.77 g (100% yield) of product as a tan fluffy solid. ES MS m/z 448 (M+H).

Example 268: *O*-(1,1-dimethylethyl)-*N*-[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]-L-threonine.

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate

HATU (2.44 g, 6.42 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (1.0g g, 5.34 mmol), methyl *O*-(1,1-dimethylethyl)-L-threoninate hydrochloride (1.44 g, 6.38 mmol) and diisopropylethylamine (0.83 g, 6.42 mmol) in 40 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.3g of product as amber oil.

Step 2. Methyl *O*-(1,1-dimethylethyl)-*N*-[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]-L-threoninate

HATU (0.68 g, 1.79 mmol) was added to a solution of methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate (0.32g g, 0.89 mmol), (2,4,6-trimethylphenyl)acetic acid (0.19 g, 1.07 mmol) and diisopropylethylamine (0.14 g, 1.09 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.41g of product as yellow oil.

Step 3. *O*-(1,1-dimethylethyl)-*N*-[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]-L-threonine

Lithium hydroxide monohydrate (0.19 g, 7.93 mmol) was added to a solution of methyl *O*-(1,1-dimethylethyl)-*N*-[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-

naphthalenyl)carbonyl]-L-threoninate (0.41 g, 0.79 mmol) in dioxane:water/10:1 (20ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. Chromatography on silica gel with CH_2Cl_2/MeOH gave 0.0705 g (18% yield) of product as a cream fluffy solid. ES MS m/z 505 (M+H).

Example 269: 2-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}leucine

Step 1. *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-2-methylleucine

To a solution of 2-methylleucine (0.5g, 3.44 mmol) and triethylamine (1.05g, 10.33 mmol) in CH_2Cl_2 (10ml) cooled to 0°C was added di-tert-butyl dicarbonate (1.65g, 7.59 mmol) portionwise, followed by DMAP (0.51g, 4.18 mmol). The reaction was allowed to warm to RT and stir 16 hours. The reaction was then quenched with 0.1N HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over sodium sulfate, filtered and stripped to give 0.825g of product as a light yellow solid.

Step 2. Methyl *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-2-methylleucinate

To a solution of *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-2-methylleucine (0.8g, 3.26 mmol) in MeOH (25ml) was added TMS-diazomethane (0.74g, 6.5 mmol), and the rection was allowed to stir for 16 hours at RT. The organic phase was concentrated in vacuo to give 1.17 g of product as a dark brown semi-solid.

Step 3: Methyl 2-methylleucinate

Methyl *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-2-methylleucinate was dissolved in 2:1 CH2Cl2:TFA (30ml) and allowed to stir at RT for 1 hour. The organic phase was concentrated in vacuo and then dissolved in EtOAc and washed with 1N NaOH,

dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.43g of product as a brown solid.

Step 4. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-methylleucinate

HATU (0.48 g, 1.26 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.2g g, 1.07 mmol), methyl 2-methylleucinate (0.2 g, 1.26 mmol) and diisopropylethylamine (0.16 g, 1.26 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.078g of product as amber oil.

Step 5. Methyl 2-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}leucinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-methylleucinate (0.078 g, 0.238 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.19 g, 1.18 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.066 g of product as yellow oil.

Step 6. 2-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}leucine

Lithium hydroxide monohydrate (0.032 g, 1.34 mmol) was added to a solution of methyl 2-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}leucinate (0.066 g, 0.135 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. Trituration

with hexanes gave 0.033 g (53% yield) of product as a light yellow solid. ES MS m/z 476 (M+H).

Example 270: (2*S*)-cyclohexyl({[3-({[5-(2,4,6-trimethylphenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-{[(3-{[(5-bromo-2-furanyl)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate

Triethlyamine (0.17g, 1.72 mmol) was added to a solution of methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.57g, 1.67 mmol) and 5-bromo-2-furancarbonyl chloride (0.35g, 1.67 mmol) in CH_2Cl_2 (20ml) and allowed to stir at RT for 16 hours. The reaction was then partiotioned between 1N HCl and EtOAc and the EtOAc layer dried over magnesium sulfate, filtered and concentrated in vacuo to give0.68g of fluffy orange glassy solid.

Step 2. Methyl (2*S*)-cyclohexyl({[3-({[5-(2,4,6-trimethylphenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

To a solution of methyl (2*S*)-{[(3-{[(5-bromo-2-furanyl)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.11g, 0.214 mmol) in DME (3ml) was added tetrakis(triphenylmethyl)palladium (0.007g, 0.006 mmol), (2,4,6-trimethylphenyl)boronic acid (0.053g, 0.323 mmol) and 2M Na2CO3 (0.2ml). The reaction was heated to 110oC for 16 hours and then loaded directly onto silica. Chromatography on silica gel with hexane/ethyl acetate gave 0.07g of product as yellow oil.

Step 3. (2*S*)-cyclohexyl({[3-({[5-(2,4,6-trimethylphenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.030 g, 1.25 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[5-(2,4,6-trimethylphenyl)-2-furanyl]carbonyl}amino)-2-

naphthalenyl]carbonyl}amino)ethanoate (0.07 g, 0.127 mmol) in dioxane:water/10:1 (5ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.033 g (48% yield) of product as a light yellow solid. ES MS m/z 539 (M+H).

Example 271: *O*-butyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Step 1. 2-methyl 1-(phenylmethyl) (2*S*)-1,2-aziridinedicarboxylate

To a solution of methyl (2*S*)-1-(triphenylmethyl)-2-aziridinecarboxylate (5.0g, 14.56 mmol) in $CHCl_3$ (50ml) and MeOH (12ml) cooled to -10°C was added 24ml of TFA and allowed to stir at -10°C for 2 hours. The reaction was then concentrated in vacuo and taken up in another 50ml of $CHCl_3$. The resulting solution was then cooled to 0°C and triethylamine (3.69g, 36.51 mmol) was added followed by benzyl chloroformate (2.49g, 14.6 mmol). After stirring for 2 hours at 0°C, the reaction was diluted with H_2O and the pH was adjusted to 8 with saturated $NaHCO_3$. The organic layer was dried over magnesium sulfate, filtered and loaded onto silica for purification. Chromatography on silica gel with hexane/ethyl acetate gave 2.7g of product as a clear oil.

Step 2. Methyl *O*-butyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate

To a solution of 2-methyl 1-(phenylmethyl) (2*S*)-1,2-aziridinedicarboxylate (0.5g, 2.26 mmol) in $CHCl_3$ (5ml) was added 1-butanol (6.49g, 87.53 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl2. The CH2Cl2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.6g of product as a clear oil.

Step 3. Methyl *O*-butyl-L-serinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-butyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate (0.6g, 1.94 mmol) in 12ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.26g of clear oil.

Step 4. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-butyl-L-serinate

HATU (0.61 g, 1.60 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.24 g, 1.28 mmol), methyl *O*-butyl-L-serinate (0.26 g, 1.61 mmol) and diisopropylethylamine (0.21 g, 1.61 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.2 g of amber oil.

Step 5. Methyl *O*-butyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-butyl-L-serinate (0.2 g, 0.581 mmol) in 8 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.47 g, 2.91 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.3 g of product as a cream solid.

Step 6. *O*-butyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Lithium hydroxide monohydrate (0.14 g, 5.85 mmol) was added to a solution of methyl *O*-butyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate (0.3 g, 0.593 mmol) in dioxane:water/10:1 (5ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.22 g (76% yield) of product as a cream solid. ES MS m/z 492 (M+H).

Example 272: *O*-[2-(methyloxy)ethyl]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Step 1. Methyl *O*-[2-(methyloxy)ethyl]-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate

To a solution of 2-methyl 1-(phenylmethyl) (2*S*)-1,2-aziridinedicarboxylate (0.5g, 2.26 mmol) in $CHCl_3$ (5ml) was added 2-(methyloxy)ethanol (7.72g, 101.45 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.63g of product as a clear oil.

Step 2. Methyl *O*-[2-(methyloxy)ethyl]-L-serinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-[2-(methyloxy)ethyl]-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate (0.63g, 2.02 mmol) in 12ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.27g of clear oil.

Step 3. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-[2-(methyloxy)ethyl]-L-serinate

HATU (0.57 g, 1.49 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.24 g, 1.28 mmol), methyl *O*-[2-(methyloxy)ethyl]-L-serinate (0.27 g, 1.52 mmol) and diisopropylethylamine (0.19 g, 1.49 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.31 g of amber oil.

Step 4. Methyl *O*-[2-(methyloxy)ethyl]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-[2-(methyloxy)ethyl]-L-serinate (0.3 g, 0.87 mmol) in 8 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.7 g, 4.33 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.18 g of product as a tan semi-solid.

Step 5. *O*-[2-(methyloxy)ethyl]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Lithium hydroxide monohydrate (0.085 g, 3.55 mmol) was added to a solution of methyl *O*-[2-(methyloxy)ethyl]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate (0.18 g, 0.355 mmol) in dioxane:water/10:1 (8ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.098 g (58% yield) of product as a cream solid. ES MS m/z 494 (M+H).

Example 273: *O*-ethyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Step 1. 2-methyl 1-(phenylmethyl) (2*S*)-1,2-aziridinedicarboxylate

To a solution of methyl (2*S*)-1-(triphenylmethyl)-2-aziridinecarboxylate (5.0g, 14.56 mmol) in $CHCl_3$ (50ml) and MeOH (12ml) cooled to -10°C was added 24ml of TFA and allowed to stir at -10°C for 2 hours. The reaction was then concentrated in vacuo and taken up in another 50ml of $CHCl_3$. The resulting solution was then cooled to 0°C and triethylamine (3.69g, 36.51 mmol) was added followed by benzyl chloroformate (2.49g, 14.6 mmol). After stirring for 2 hours at 0°C, the reaction was diluted with H_2O and the pH was adjusted to 8 with saturated $NaHCO_3$. The organic layer was dried over magnesium sulfate, filtered and loaded onto silica for purification. Chromatography on silica gel with hexane/ethyl acetate gave 2.53g of product as a clear oil.

Step 2. Methyl *O*-ethyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate

To a solution of 2-methyl 1-(phenylmethyl) (2*S*)-1,2-aziridinedicarboxylate (0.5g, 2.26 mmol) in $CHCl_3$ (5ml) was added ethanol (6.32g, 137.18 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.52g of product as a clear oil.

Step 3 Methyl *O*-ethyl-L-serinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-ethyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate. (0.52g, 1.85 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.16g of clear oil.

Step 4. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-ethyl-L-serinate

HATU (0.34 g, 0.89 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.17 g, 0.91 mmol), methyl *O*-ethyl-L-serinate (0.16 g, 1.09 mmol) and diisopropylethylamine (0.12 g, 0.92 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.18 g of amber oil.

Step 5. Methyl *O*-ethyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-ethyl-L-serinate (0.18 g, 0.57 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.46 g, 2.85 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.16 g of product as a white solid.

Step 6. *O*-ethyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Lithium hydroxide monohydrate (0.080 g, 3.34 mmol) was added to a solution of methyl *O*-ethyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate (0.16 g, 0.335 mmol) in dioxane:water/10:1 (8ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.036 g (23% yield) of product as a fluffy tan solid. ES MS m/z 464 (M+H).

Example 274: *O*-(1-methylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Step 1. Methyl *O*-(1-methylethyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate

To a solution of 2-methyl 1-(phenylmethyl) (2*S*)-1,2-aziridinedicarboxylate (0.5g, 2.26 mmol) in $CHCl_3$ (5ml) was added 2-propanol (6.28g, 104.49 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.6g of product as a clear oil.

Step 2. Methyl *O*-(1-methylethyl)-L-serinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-(1-methylethyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate (0.6g, 2.03 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.27g of clear oil.

Step 3. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1-methylethyl)-L-serinate

HATU (0.53 g, 1.39 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.26 g, 1.39 mmol), methyl *O*-(1-methylethyl)-L-serinate (0.27 g, 1.67 mmol) and diisopropylethylamine (0.18 g, 1.38 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.23 g of amber oil.

Step 4. Methyl *O*-(1-methylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1-methylethyl)-L-serinate (0.23 g, 0.696 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.56 g, 3.47 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.25 g of product as light yellow semi-solid.

Step 5. *O*-(1-methylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Lithium hydroxide monohydrate (0.12 g, 5.01 mmol) was added to a solution of methyl *O*-(1-methylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate (0.25 g, 0.508 mmol) in dioxane:water/10:1 (8ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.088 g (36% yield) of product as a fluffy tan solid. ES MS m/z 478 (M+H).

Example 275: *O*-(2,2-dimethylpropyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Step 1. Methyl *O*-(2,2-dimethylpropyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate

To a solution of 2-methyl 1-(phenylmethyl) (2*S*)-1,2-aziridinedicarboxylate (0.5g, 2.26 mmol) in $CHCl_3$ (5ml) was added 2,2-dimethyl-1-propanol (1.87g, 21.21 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was

dried over magnesium sulfate, filtered and concentrated in vacuo to give 1.0g of product as a clear oil.

Step 2. Methyl *O*-(2,2-dimethylpropyl)-L-serinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-(2,2-dimethylpropyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-serinate (1.0g, 3.09 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.47g of clear oil.

Step 3. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(2,2-dimethylpropyl)-L-serinate

HATU (0.8 g, 2.10 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.39 g, 2.08 mmol), methyl *O*-(2,2-dimethylpropyl)-L-serinate (0.47 g, 2.48 mmol) and diisopropylethylamine (0.27 g, 2.09 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.51 g of orange solid.

Step 4. Methyl *O*-(2,2-dimethylpropyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(2,2-dimethylpropyl)-L-serinate (0.51 g, 1.42 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.15 g, 7.12 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried

over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.47 g of product as a cream solid.

Step 5. *O*-(2,2-dimethylpropyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Lithium hydroxide monohydrate (0.19 g, 7.93 mmol) was added to a solution of methyl *O*-(2,2-dimethylpropyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate (0.47 g, 0.905 mmol) in dioxane:water/10:1 (8ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.173 g (43% yield) of product as a fluffy tan solid. ES MS m/z 506 (M+H).

Example 276: *O*-(tetrahydro-2*H*-pyran-4-yl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Step 1. Methyl *N*-{[(phenylmethyl)oxy]carbonyl}-*O*-(tetrahydro-2*H*-pyran-4-yl)-L-serinate

To a solution of 2-methyl 1-(phenylmethyl) (2*S*)-1,2-aziridinedicarboxylate (0.5g, 2.26 mmol) in $CHCl_3$ (5ml) was added tetrahydro-2*H*-pyran-4-ol (2.30g, 22.55 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 1.01g of product as a clear oil.

Step 2. Methyl *O*-(tetrahydro-2*H*-pyran-4-yl)-L-serinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *N*-{[(phenylmethyl)oxy]carbonyl}-*O*-(tetrahydro-2*H*-pyran-4-yl)-L-

serinate (1.01g, 3.09 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.63g of light yellow oil.

Step 3. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(tetrahydro-2*H*-pyran-4-yl)-L-serinate

HATU (0.99 g, 2.60 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.48 g, 2.56 mmol), methyl *O*-(tetrahydro-2*H*-pyran-4-yl)-L-serinate (0.63 g, 3.10 mmol) and diisopropylethylamine (0.33 g, 2.58 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.06 g of amber oil.

Step 4. Methyl *O*-(tetrahydro-2*H*-pyran-4-yl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(tetrahydro-2*H*-pyran-4-yl)-L-serinate (0.06 g, 0.16 mmol) in 5 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.13 g, 0.804 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.06 g of product as amber oil.

Step 5. *O*-(tetrahydro-2*H*-pyran-4-yl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Lithium hydroxide monohydrate (0.027 g, 1.13 mmol) was added to a solution of methyl *O*-(tetrahydro-2*H*-pyran-4-yl)-*N*-{[3-({[(2,4,6-

trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate (0.06 g, 0.112 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification on Agilent gave 0.012 g (21% yield) of product as a fluffy amber solid. ES MS m/z 520 (M+H).

Example 277: *O*-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Step 1. Methyl *N*-(triphenylmethyl)-L-threoninate

To a cooled (0°C) solution of methyl L-threoninate hydrochloride (5.0g, 29.48 mmol) and triethylamine (5.97g, 58.97 mmol) in chloroform (100ml) was added trityl chloride as a solid (8.22g, 29.49 mmol). The reaction was stirred for 12 hours and allowed to come to RT. The reaction was concentrated in vacuo and then dissolved in ethyl acetate and washed with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$, and saturated sodium chloride. The organic layer was dried over $MgSO_4$, filtered and stripped to give10.16g of product as a fluffy cream solid. ES MS m/z 398 (M+Na).

Step 2. Methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate

To a cooled (0°C) solution of methyl *N*-(triphenylmethyl)-L-threoninate (10.16g, 27.95 mmol) in anhydrous pyridine was added methanesulfonyl chloride (9.61g, 83.85 mmol) and the reaction was allowed to stirfor 12 hours and allowed to come to RT. The solvent was removed in vacuo and the residue dissolved in ethyl acetate. The organic layer was washed with saturated sodium chloride and then dried over $MgSO_4$, filtered and stripped to 12.33g of amber oil which was then dissolved in 80ml of anhydrous THF and to which was added triethylamine (8.50g, 84.01 mmol) and heated to 80°C and allowed to reflux for 48 hours.

The heat was removed and the reaction was concentrated in vacuo and the residue dissolved in ethyl acetate and washed successively with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$ and saturated sodium chloride. The ethyl acetate layer was dried over $MgSO_4$, filtered and stripped to give 9.04g of amber oil. Chromatography on silica gel with hexane/ethyl acetate gave 5.26 g of product fluffy cream solid. ES MS m/z 380 (M+Na).

Step 3. 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate

To a solution of methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate (5.26g, 14.72 mmol) in $CHCl_3$ (12ml) and MeOH (12ml) cooled to 0°C was added 11.6ml of TFA and allowed to stir at 0°C for 2.5 hours. The reaction was then concentrated in vacuo and evaporated with ether newly added several times to remove TFA. The residue was dissolved in ether which was extracted with water three times. To the aqueous extract at 0°C was added $NaHCO_3$ (5.84g, 69.52 mmol), benzyl chloroformate (2.51g, 14.71 mmol) and 50ml of ethyl acetate under vigorous stirring for 1.5 hours. The ethyl acetate layer was separated and the water layer back-extracted. The organics were dried over $MgSO_4$, filtered and concentrated to give 2.96g of light yellow oil. Chromatography on silica gel with hexane/ethyl acetate gave 2.45g of product as a clear oil. ES MS m/z 250 (M+H).

Step 4. Methyl *O*-methyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-allothreoninate

To a solution of 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate (0.5g, 2.06 mmol) in $CHCl_3$ (10ml) was added methanol (0.64g, 20.00 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.68g of product as a clear oil.

Step 5. Methyl *O*-methyl-L-allothreoninate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-methyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-allothreoninate (0.68g, 2.42 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 3 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.21g of clear oil.

Step 6. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-methyl-L-threoninate

HATU (0.53 g, 1.39 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.22 g, 1.18 mmol), methyl *O*-methyl-L-allothreoninate (0.21 g, 1.43 mmol) and diisopropylethylamine (0.18 g, 1.38 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.4 g of amber oil.

Step 7. Methyl *O*-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-methyl-L-threoninate (0.4 g, 1.27 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.02 g, 6.31 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.36 g of product as cream solid.

Step 8. *O*-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Lithium hydroxide monohydrate (0.18 g, 7.52 mmol) was added to a solution of methyl *O*-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-

naphthalenyl]carbonyl}-L-threoninate (0.36 g, 0.754 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.124 g (36% yield) of product as a fluffy cream solid. ES MS m/z 464 (M+H).

Example 278: *O*-(1-methylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Step 1. 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate

To a solution of methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate (5.26g, 14.72 mmol) in $CHCl_3$ (12ml) and MeOH (12ml) cooled to 0°C was added 11.6ml of TFA and allowed to stir at 0°C for 2.5 hours. The reaction was then concentrated in vacuo and evaporated with ether newly added several times to remove TFA. The residue was dissolved in ether which was extracted with water three times. To the aqueous extract at 0°C was added $NaHCO_3$ (5.84g, 69.52 mmol), benzyl chloroformate (2.51g, 14.71 mmol) and 50ml of ethyl acetate under vigorous stirring for 1.5 hours. The ethyl acetate layer was separated and the water layer back-extracted. The organics were dried over $MgSO_4$, filtered and concentrated to give 2.96g of light yellow oil. Chromatography on silica gel with hexane/ethyl acetate gave 2.45g of product as a clear oil. ES MS m/z 250 (M+H).

Step 2. Methyl *O*-(1-methylethyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-allothreoninate

To a solution of 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate (0.5g, 2.06 mmol) in $CHCl_3$ (10ml) was added isopropanol (1.20g, 19.97 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.8g of product as a clear oil.

Step 3. Methyl *O*-(1-methylethyl)-L-allothreoninate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-(1-methylethyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-allothreoninate (0.8g, 2.59 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 3 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.28g of clear oil.

Step 4. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1-methylethyl)-L-threoninate

HATU (0.61 g, 1.60 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.25 g, 1.34 mmol), methyl *O*-(1-methylethyl)-L-allothreoninate (0.28 g, 1.60 mmol) and diisopropylethylamine (0.21 g, 1.61 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.27 g of amber oil.

Step 5. Methyl *O*-(1-methylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1-methylethyl)-L-threoninate (0.27 g, 0.78 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.63 g, 3.90 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.39 g of product as amber semi-solid.

Step 6. *O*-(1-methylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Lithium hydroxide monohydrate (0.185 g, 7.72 mmol) was added to a solution of methyl *O*-(1-methylethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate (0.39 g, 0.771 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.067 g (18% yield) of product as a fluffy cream solid. ES MS m/z 492 (M+H).

Example 279: 1-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclopentanecarboxylate

3-Amino-2-naphthoic acid (0.2 g, 1.0 mmol) and methyl 1-aminocyclopentanecarboxylate hydrochloride (0.21 g, 1.17 mmol) were dissolved in DMF (10 mL) and diisopropylethylamine (0.41 g, 3.20 mmol) and HATU (0.45 g, 1.17 mmol) were added. The solution was heated to 50 °C for 1 h and stirred overnight. The reaction was diluted with water and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.17 g of product as a yellow solid.

Step 2. Methyl 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclopentanecarboxylate (47 mg, 0.15 mmol) was dissolved in DMF (1 mL) and triethylamine (30 mg, 0.30 mmol) and 2,4,6-trichlorophenyl isocyanate (40 mg, 0.18 mmol) were added. The reaction

was heated to 70 °C for 2 h and cooled. The reaction was diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 50 mg of product.

Step 3. 1-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylic acid

Methyl 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylate (50 mg, 0.093 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 1 M NaOH (0.47 mL) was added. The solution was heated to 50 °C for 2 h and cooled. The reaction was diluted with water, acidified with 1 M HCl (0.5 mL), and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 46 mg of product as a tan solid. ES MS m/z 521 (M+H).

Example 280: 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylate

Methyl 1-aminocyclohexanecarboxylate hydrochloride (0.28 g, 1.45 mmol) and 3-amino-2-naphthoic acid (0.3 g, 1.60 mmol) were dissolved in DMF (10 mL) and diisopropylethylamine (0.56 g, 4.33 mmol) and HATU (0.60 g, 1.59 mmol) were added. The reaction was heated to 50 °C for ca. 30 min and cooled. The reaction was diluted with ethyl acetate and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.42 g of product as a yellow solid.

Step 2. 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylic acid

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylate (0.42 g, 1.28 mmol) was dissolved in THF (5 mL) and MeOH (5 mL) and 5 M NaOH (2.6 mL, 13 mmol) and water (2.5 mL) were added. The solution was heated to 55 °C for ca. 3 h and cooled. The solution was acidified with 5 M HCl (3 mL), diluted with water, and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 0.23 g of product as a gold solid.

Step 3. 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

1-{[(3-Amino-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylic acid (0.1 g, 0.32 mmol) was dissolved in DMF (3 mL) and 2,4,6-trimethylphenyl isocyanate (57 mg, 0.35 mmol) and triethylamine (65 mg, 0.64 mmol) were added. The solution was heated to 70 °C for ca. 90 min and cooled. The reaction was diluted with water and 5 M HCl (1 mL) was added. The solution was extracted with ethyl acetate and the extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 97 mg of product as a gold solid. ES MS m/z 474 (M+H).

Example 281: 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1. 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

1-{[(3-Amino-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylic acid (50 mg, 0.16 mmol) was dissolved in DMF (1 mL) and 2,4,6-trichlorophenyl isocyanate (39 mg, 0.17 mmol) and triethylamine (33 mg, 0.32 mmol) were added. The solution was heated to 70 °C for ca. 90 min and stirred overnight. The reaction was diluted with water and 5 M HCl (1 mL) was added. The solution was extracted with ethyl acetate and the extracts were dried ($MgSO_4$) and concentrated onto SiO_2.

Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 45 mg of product as a gold solid. ES MS m/z 534 (M+H).

Example 282: 4-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylic acid

Step 1. Methyl 4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylate

4-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylic acid (0.5 g, 2.03 mmol) was dissolved in MeOH (6 mL) and the solution was cooled to 0 °C. Trimethylsilyldiazomethane (3.5 mL of a 2 M solution) was added dropwise until a yellow color persisted and the reaction was stirred for 60 min and concentrated to afford 0.52 g of product as a viscous oil.

Step 2. Methyl 4-aminotetrahydro-2*H*-pyran-4-carboxylate
Methyl 4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylate (0.52 g, 1.69 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (0.75 mL) was added. The mixture was stirred overnight and concentrated to afford product as a viscous oil which was used without further purification.

Step 3. Methyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}tetrahydro-2*H*-pyran-4-carboxylate

3-Amino-2-napthoic acid (0.18 g, 0.80 mmol) was dissolved in DMF (3 mL) and diisopropylethylamine (0.28 g, 2.2 mmol) and HATU (0.31 g, 0.80 mmol) were added. The solution was stirred 20 min and methyl 4-aminotetrahydro-2*H*-pyran-4-carboxylate (0.20 g, 0.73 mmol) was added. The reaction was heated to 50 °C for 1 h, cooled, diluted with water, and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 0.13 g of product.

Step 4. Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylate

Methyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}tetrahydro-2*H*-pyran-4-carboxylate (76 mg, 0.23 mmol) was dissolved in pyridine (1 mL) and 2,4,6-trimethylphenyl isocyanate (0.19 g, 1.15 mmol) was added. The reaction was stirred 6 h and then diluted with ethyl acetate and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 100 mg of product.

Step 5. 4-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylic acid

Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylate (110 mg, 0.22 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (1.1 mL) was added. The reaction was heated to 50 °C for 1 h, acidified with 1 M HCl (2.2 mL), and extracted with ethyl acetate. The extracts were dried (MgSO4), concentrated, redissolved in diethyl ether, and reconcentrated to afford 100 mg of product as a foam. ES MS m/z 476 (M+H)

Example 283: 4-({[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylic acid

Step 1. Methyl 4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylate
1 (47 mg, 0.14 mmol) was dissolved in pyridine (1 mL) and 2,6-dichlorophenyl isocyanate (0.13 g, 0.71 mmol) was added. The reaction was stirred 90 min and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 46 mg of product.

Step 2. 4-({[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylic acid

Methyl 4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-pyran-4-carboxylate (56 mg, 0.22 mmol) was dissolved in 1:1 THF/MeOH (mL) and 2 M LiOH (0.54 mL) was added. The reaction was heated to 50 °C for 1 h, cooled, diluted with ethyl acetate and acidified with 1 M HCl (2.2 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was taken up in CH_2Cl_2 and a colorless solid formed. The solid was dried under vacuum to provide 36 mg of product. ES MS m/z 502 (M+H)

Example 284: 4-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylic acid

Step 1. Methyl 4-aminotetrahydro-2*H*-thiopyran-4-carboxylate hydrochloride

4-Aminotetrahydro-2*H*-thiopyran-4-carboxylic acid hydrochloride (0.5 g, mmol) was dissolved in MeOH (20 mL) and HCl (g) was bubbled through the solution for 20 min. The solution was heated to reflux for 4 h, cooled, and concentrated afford product as a colorless solid which was used without further purification.

Step 2. Methyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}tetrahydro-2*H*-thiopyran-4-carboxylate

3-Amino-2-naphthoic acid (0.3 g, 1.36 mmol) was dissolved in DMF (5 mL) and diisopropylethylamine (0.53 g, 4.08 mmol) and HATU (0.57 g, 1.50 mmol) were added and stirred for 15 min. Methyl 4-aminotetrahydro-2*H*-thiopyran-4-carboxylate hydrochloride (0.35 g, 1.63 mmol) was added and the mixture was stirred overnight. The reaction was diluted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 92 mg of product.

Step 3. Methyl 4-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylate

Methyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}tetrahydro-2*H*-thiopyran-4-carboxylate (92 mg, 0.26 mmol) was dissolved in DMF (2 mL) and triethylamine (81 mg, 0.11 mL) and 2,4,6-trichlorophenyl isocyanate (0.12 g, 0.53 mmol) was added. The reaction was heated to 60 °C for 4 h and then stirred at RT overnight. The reaction was diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 30 mg of product.

Step 4. 4-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylic acid

Methyl 4-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylate (30 mg, 0.053 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (0.26 mL) was added. The reaction was heated to 60 °C for 4 h, cooled, diluted with water, and acidified with 1 M HCl (0.55 mL). The mixture was extracted with ethyl acetate and the extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH (1 mL) and purifed on the reverse-phase HPLC to afford 20 mg of product. MS m/z 553 (M+H)

Example 285: 4-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide

Step 1. Methyl 4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylate 1,1-dioxide

4-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide (0.5 g) was suspended in MeOH (6 mL) and cooled to 0 °C.

Trimethylsilyldiazomethane (4 mL of a 2 M solution) was added dropwise and stirred 60 min. The reaction was concentrated to afford 0.52 g of product.

Step 2. 4-Aminotetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide trifluoroacetate

Methyl 4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylate 1,1-dioxide (0.52 g, 1.69 mmol) was dissolved in CH_2Cl_2 and TFA (0.75 mL) was added and the reaction was stirred for 15 h. The solution was concentrated to afford product as a solid.

Step 3. Methyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}tetrahydro-2*H*-thiopyran-4-carboxylate 1,1-dioxide

3-Amino-2-naphthoic acid (0.19 g, 0.85 mmol) was dissolved in DMF (3 mL) and diisopropylethylamine (0.30 g, 0.41 mmol) and HATU (0.32 g, 0.85 mmol) were added and stirred for 15 min. 4-Aminotetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide trifluoroacetate (0.25 g, 0.78 mmol) was added and the mixture was heated to 50 °C for 60 min and cooled. Water was added and the mixture was extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 150 mg of product.

Step 4. Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylate 1,1-dioxide

Methyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}tetrahydro-2*H*-thiopyran-4-carboxylate 1,1-dioxide (0.14 g, 0.37 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (0.30 g, 1.86 mmol) was added. The reaction was stirred 6 h, diluted with ethyl acetate, and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.50 g of product as a solid.

Step 5. 4-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide

Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2*H*-thiopyran-4-carboxylate 1,1-dioxide (136 mg, 0.25 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (1.26 mL) was added. The reaction was heated to 50 °C for 1 h and stirred overnight. The reaction was acidified with 1 M HCl (2.5 mL). The mixture was extracted with ethyl acetate and the extracts were dried ($MgSO_4$) and concentrated. The resulting solid was triturated with CH_2Cl_2 to provide 104 mg of product. MS m/z 524 (M+H)

Example 286: 4-({[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1-(phenylmethyl)-4-piperidinecarboxylic acid

Step 1. 8-(Phenylmethyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione

1-(Phenylmethyl)-4-piperidinone (10.2 g, 53.9 mmol) was added to a suspension of NaCN (7.1 g, 144 mmol) and $(NH_4)_2CO_3$ (49.6 g, 518 mmol) in 1:1 EtOH/water (140 mL). The mixture was heated to 60 °C overnight and cooled. The solution was allowed to stand 2 days and the resulting solid was filtered off and dried under vacuum to afford 13.0 g of product.

Step 2. 4-Amino-1-(phenylmethyl)-4-piperidinecarboxylic acid

8-(Phenylmethyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (13.0 g, 50.1 mmol)was suspended in water (160 mL) and LiOH (6.0 g, 250 mmol) was added. The solution was heated to reflux for 48 h and cooled. The solution was filtered and the filtrate was concentrated to a residue and the pH was adjusted to 5 by addition of conc HCl. The resulting solid was filtered, suspended in MeOH, refiltered and dried under vacuum to afford 8 g of product.

Step 3. Ethyl 4-amino-1-(phenylmethyl)-4-piperidinecarboxylate

4-Amino-1-(phenylmethyl)-4-piperidinecarboxylic acid (4 g, 17 mmol) was suspended in EtOH (40 mL) and the solution was cooled to 0 °C and $SOCl_2$ (7.5 mL) was added. The solution was warmed to RT and heated to reflux for 5 h. The solution was concentrated to an oil, which was dissolved in water and neutralized to pH = 7 with 1 M NaOH and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and concentrated to afford 0.78 g of product as an oil.

Step 4. Ethyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}-1-(phenylmethyl)-4-piperidinecarboxylate

3-Amino-2-napthoic acid (0.66 g, 3.01 mmol) was dissolved in DMF (8 mL) and diisopropylethylamine (0.89 g, 6.86 mmol) and HATU (1.14 g, 3.01 mmol) were added and stirred 15 min. Ethyl 4-amino-1-(phenylmethyl)-4-piperidinecarboxylate (0.72 g, 2.74 mmol) was dissolved in DMF (2 mL) and the solution was added to the reaction and heated to 50 °C for 45 min and cooled. The mixture was diluted with ethyl acetate and washed with water. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 1.07 g of product.

Step 5. Ethyl 4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1-(phenylmethyl)-4-piperidinecarboxylate

Ethyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}-1-(phenylmethyl)-4-piperidinecarboxylate (40 mg, 0.092 mmol) was dissolved in pyridine (1.5 mL) and 2,6-dichlorophenylisocyanate (87 mg, 0.46 mmol) was added. The reaction was stirred overnight, diluted with ethyl acetate, and concentrated onto SiO_2. Chromatography on SiO2 eluting with ethyl acetate/hexanes provided 50 mg of product as a solid.

Step 6 4-({[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1-(phenylmethyl)-4-piperidinecarboxylic acid

Ethyl 4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1-(phenylmethyl)-4-piperidinecarboxylate (40 mg, 0.08 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (0.4 mL) was added. The reaction was heated to 60 °C overnight, cooled, acidified with 1 M HCl (0.9 mL) and a solid formed. The solid was filtered off, dissolved in MeOH (1 mL), and purified by reverse-phase HPLC to afford 13 mg of product ES MS m/z 492 (M+H)

Example 287: 1-{[(1,1-Dimethylethyl)oxy]carbonyl}-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid

Step 1. 1-(1,1-Dimethylethyl) 4-methyl 4-({[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}amino)-1,4-piperidinedicarboxylate

1-{[(1,1-Dimethylethyl)oxy]carbonyl}-4-({[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}amino)-4-piperidinecarboxylic acid (1 g, 2.14 mmol) was dissolved in MeOH (9 mL) and the solution was cooled to 0 °C. A solution of $TMSCHN_2$ (6 mL of a 2 M solution) was added dropwise and the reaction was stirred overnight. The solution was concentrated to provide 1.0 g of product.

Step 2. 1-(1,1-Dimethylethyl) 4-methyl 4-amino-1,4-piperidinedicarboxylate

1-(1,1-Dimethylethyl) 4-methyl 4-({[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}amino)-1,4-piperidinedicarboxylate (1.0 g, 2.1 mmol) was dissolved in dioxane and polymer supported piperidine (2.1 g of PL-PPZ (5 mmol/g loading)) was added and stirred 24 h at RT and then heated to 50 °C for an additional 15 h. The solution was cooled, filtered, and concentrated to afford an oil which was used in the next step without purification.

Step 3. 1-(1,1-Dimethylethyl) 4-methyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}-1,4-piperidinedicarboxylate

3-Amino-2-napthoic acid (0.43 g, 2.3 mmol) was dissolved in DMF (8 mL) and diisopropylethylamine (0.89 g, 6.86 mmol) and HATU (1.14 g, 3.01 mmol) were added and stirred 20 min. 1-(1,1-Dimethylethyl) 4-methyl 4-amino-1,4-piperidinedicarboxylate (0.54 g, 2.1 mmol) was dissolved in DMF (2 mL) and the solution was added to the reaction and heated to 50 °C for 60 min and cooled. The mixture was poured onto water and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.75 g of product.

Step 4. 1-(1,1-Dimethylethyl) 4-methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,4-piperidinedicarboxylate

1-(1,1-Dimethylethyl) 4-methyl 4-{[(3-amino-2-naphthalenyl)carbonyl]amino}-1,4-piperidinedicarboxylate (0.4 g, 0.93 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (0.75 g, 4.68 mmol) was added. The reaction was stirred overnight, diluted with ethyl acetate, and concentrated onto SiO_2. Chromatography on SiO2 eluting with ethyl acetate/hexanes provided 0.50 g of product as a solid.

Step 5. 1-{[(1,1-Dimethylethyl)oxy]carbonyl}-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid

1-(1,1-Dimethylethyl) 4-methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,4-piperidinedicarboxylate (50 mg, 0.085 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.42 mL) was added. The reaction was heated to 55 °C for 2 h, cooled, acidified with 1 M HCl (0.84 mL) and extracted with ethyl acetate. The

extracts were dried ($MgSO_4$), concentrated, redissolved in CH_2Cl_2, filtered and concentrated to afford 39 mg of product as a tan foam. ES MS m/z 575 (M+H)

Example 288. 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid trifluoroacetate

Step 1. Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate trifluroroacetate

1-(1,1-Dimethylethyl) 4-methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,4-piperidinedicarboxylate (0.44 g, 0.75 mmol) was dissolved in CH_2Cl_2 (5 mL) and TFA (0.5 mL) was added and stirred overnight. The solution was concentrated to provide product as a solid which was used without further purification.

Step 2. 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid trifluoroacetate

Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate trifluoroacetate (50 mg, 0.083 mmol) was dissolved in 1:1 THF/MeOH (0.8 mL) and 2 M LiOH (0.42 mL) was added. The reaction was heated to 55 °C for 2.5 h, cooled, acidified with 1 M HCl (0.84 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$), concentrated, and redissolved in MeOH. The solution was purified by reverse-phase HPLC to afford 13 mg of product as the trifluoroacetate salt. ES MS m/z 475 (M+H).

Example 289: 1-Butyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid

Step 1. Methyl 1-butyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate

Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate trifluroroacetate (57 mg, 0.095 mmol) was dissolved in DMF (1 mL) and K_2CO_3 (39 mg, 0.28 mmol) and n-butylbromide (19 mg, 0.14 mmol) were added and the reaction was heated to 50 °C overnight and cooled. The reaction was diluted with water and a solid precipitated which was dissolved in ethyl acetate. The aqueous was extracted with ethyl acetate and the combined organics were dried ($MgSO_4$) and concentrated to afford 50 mg of product.

Step 2. 1-Butyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid

Methyl 1-butyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate (50 mg, 0.092 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.46 mL) was added. The reaction was heated to 50 °C for 4 h, cooled, and stirred overnight. The solution was acidified with 1 M HCl (0.9 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 31 mg of product. ES MS m/z 531 (M+H).

Example 290: 1-Butanoyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid

Step 1. Methyl 1-butanoyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate

Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate trifluroroacetate (50 mg, 0.083 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and diisopropylethylamine (10 mg, 0.091 mmol) was added followed by butyryl chloride (10 mg, 0.091 mmol). The solution was stirred 15 h and then concentrated onto SiO_2 and purified by

chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 32 mg of product.

Step 2. 1-Butanoyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid

Methyl 1-butanoyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate (32 mg, 0.057 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.29 mL) was added. The reaction was heated to 50 °C for 30 min, cooled, acidified with 1 M HCl (0.6 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 31 mg of a foam. ES MS m/z 545 (M+H).

Example 291: 1-[(Ethyloxy)carbonyl]-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid

Step 1. 1-Ethyl 4-methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,4-piperidinedicarboxylate

Methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylate trifluroroacetate (50 mg, 0.083 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and diisopropylethylamine (10 mg, 0.091 mmol) was added followed by ethyl chloroformate (10 mg, 0.091 mmol). The solution was stirred 15 h and then concentrated onto SiO_2 and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 31 mg of product.

Step 2. 1-[(Ethyloxy)carbonyl]-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid

1-Ethyl 4-methyl 4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,4-piperidinedicarboxylate (31 mg, 0.055 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.29 mL) was added. The reaction was heated to 50 °C for 30 min, cooled, acidified with 1 M HCl (0.6 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 31 mg of a foam. ES MS m/z 547 (M+H).

Example 292: 1-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-oxocyclohexanecarboxylic acid

Step 1. Methyl 2-({[(phenylmethyl)oxy]carbonyl}amino)-2-propenoate

Methyl *O*-[(4-methylphenyl)sulfonyl]-*N*-{[(phenylmethyl)oxy]carbonyl}serinate (11 g, 27 mmol) was dissolved in $CHCl_3$ (70 mL) and triethylamine (5.46 g, 54 mmol) was added in one portion. The solution was stirred overnight and then concentrated and the residue was resuspended in Et_2O. The solution was cooled to 0 °C and the precipitated solid was filtered off. The filtrate was concentrated, redissolved in $CHCl_3$, washed with 1 M HCl and water, dried ($MgSO_4$), and concentrated to provide product as an oil which was immediately used in the next reaction.

Step 2. Methyl 4-oxo-1-({[(phenylmethyl)oxy]carbonyl}amino)-2-cyclohexene-1-carboxylate

Methyl 2-({[(phenylmethyl)oxy]carbonyl}amino)-2-propenoate (6.3 g, 26.7 mmol) and Danishefsky's diene (9.3 g, 53.5 mmol) were dissolved in toluene (100 mL) and heated to reflux for 5 days. The solution was cooled, concentrated, and redissolved in THF (75 mL). 1 M HCl (25 mL) was added and the mixture was stirred 15 h and concentrated. The residue was redissolved in CH_2Cl_2 and concentrated onto SiO2. Chromatography on SiO2 eluting with ethyl acetate/hexanes afforded 4.4 g of an oil. The oil was dissolved in CH_2Cl_2 (100 mL) and DBU (1.5 g, 9.8 mmol) was added. The reaction was stirred overnight and then washed with saturated $NaHCO_3$

solution, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 3.9 g of product as a clear oil.

Step 3. Methyl 1-amino-4-oxocyclohexanecarboxylate

Methyl 4-oxo-1-({[(phenylmethyl)oxy]carbonyl}amino)-2-cyclohexene-1-carboxylate (3 g, 9.9 mmol) was dissolved in CH_2Cl_2 (30 mL) and 0.5 g of 10% Pd/C was added. A H_2 atmosphere was established and the reaction was stirred overnight, filtered through celite, concentrated, and redissolved in CH_2Cl_2. 10% Pd/C (0.5 g) was added and an H_2 atmosphere was established and stirred overnight. The reaction was then filtered through celite and concentrated to afford 1.62 g of product as an oil.

Step 4. Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}-4-oxocyclohexanecarboxylate

3-Amino-2-napthoic acid (155 mg, 0.69 mmol) was dissolved in DMF (4 mL) and diisopropylethylamine (0.20 g, 1.58 mmol) and HATU (0.26 g, 0.69 mmol) were added and stirred 20 min. Methyl 1-amino-4-oxocyclohexanecarboxylate (108 mg, 0.63 mmol) was dissolved in DMF (1 mL) and the solution was added to the reaction and heated to 50 °C for 60 min, cooled, and stirred 3 d. The mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 148 mg of product.

Step 5. Methyl 1-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-oxocyclohexanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}-4-oxocyclohexanecarboxylate (0.14 g, 0.41 mmol) was dissolved in pyridine (3 mL) and 2,6-dichlorophenylisocyanate (0.39 g, 2.0 mmol) was added. After 30 min an additional 1 mL of pyridine was added and the reaction was diluted with ethyl acetate and

concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 210 mg of product.

Step 6. 1-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-oxocyclohexanecarboxylic acid

Methyl 1-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-oxocyclohexanecarboxylate (0.2 g, 0.37 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (0.95 mL) was added and the reaction was heated to 50 °C for 90 min and cooled. The solution was acidified with 1 M HCl (1.9 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$), concentrated, redissolved in CH_2Cl_2, and reconcentrated to provide a solid. Trituration of the solid with CH_2Cl_2 provided 25 mg of product. ES MS m/z 515 (M+H).

Example 293: 4-Oxo-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1. Methyl 4-oxo-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}-4-oxocyclohexanecarboxylate (0.99 g, 2.9 mmol) was dissolved in pyridine (13 mL) and 2,4,6-trimethylphenylisocyanate (2.34 g, 14.5 mmol mmol) was added. After 4 h, the reaction was concentrated onto SiO_2. Chromatography on SiO_2 eluting with $MeOH/CH_2Cl_2$ afforded 0.84 g of product.

Step 2. 4-Oxo-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

Methyl 4-oxo-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylate (0.5 g, 0.99 mmol) was dissolved in 1:1 THF/MeOH (6 mL) and 2 M LiOH (2.5 mL) was added and the reaction stirred overnight. The solution was acidified with 5 M HCl (1 mL) and extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and concentrated to 0.49 g of solid. 40 mg of the solid was purified by reverse-phase HPLC to provide 11 mg of product. ES MS m/z 488 (M+H).

Example 294 & 295:cis and trans 4-[(phenylmethyl)amino]-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1: 4-[(phenylmethyl)amino]-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

4-Oxo-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid (53 mg, 0.10 mmol) was dissolved in MeOH (1 mL) and polymer bound cyanoborohydride (80 mg, 0.32 mmol) and benzylamine (26 mg, 0.23 mmol) were added. The reaction was stirred overnight, filtered, and the solution was purified by reverse-phase HPLC to afford 5 mg each of the *cis* and *trans* products. Compound 1: ES MS m/z 579 (M+H). Compound 2: ES MS m/z 579 (M+H).

Example 296: 4-(hydroxyimino)-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid

A solution of hydroxylamine hydrochloride (11 mg, 0.15 mmol) and K_2CO_3 (20 mg, 0.18 mmol) in water (0.5 mL) were cooled to 5 °C and a solution of 4-Oxo-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-

naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid (50 mg, 0.10 mmol) dissolved in MeOH (0.5 mL) was added. The solution was stirred 1 h, diluted with water, and extracted with ethyl acetate. The aqueous layer was acidified with 1 M HCl (0.18 mL) and extacted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was redissolved in MeOH and purified by revere-phase HPLC to afford 3 mg of product. ES MS m/z 503 (M+H)

Example 297: (2*S*)-cyclohexyl({[2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-quinolinyl]carbonyl}amino)ethanoic acid

Step 1. Ethyl 2-cyano-3-(2-nitrophenyl)-2-propenoate

2-Nitrobenzaldehyde (5 g, 33.1 mmol) and n-Hexyltrimethylammonium bromide (1.2 g, 33.1 mmol) were suspended in water (290 mL) and stirred for 24 h. The stirring was stopped and the reaction stood for an additional 24 h. The resulting solid ethyl 2-cyano-3-(2-nitrophenyl)-2-propenoate was filtered off and dried under vacuum.

Step 2. Ethyl 2-amino-3-quinolinecarboxylate

Titanium tetrachloride (2.2 mL, 20 mmol) was added slowly to a stirring suspension of zinc (2.6 g, 40 mmol) in THF. When the addition was complete, the solution was refluxed for 2 h and cooled to RT. A solution of ethyl 2-cyano-3-(2-nitrophenyl)-2-propenoate (2.46 g, 10 mmol) in THF (20 mL) was added dropwise to the reaction. After 90 min the reaction was concentrated and the residue was poured onto 10% potassium carbonate and extracted with chloroform. The chloroform layer was filtered through celite, dried (MgSO4) and concentrated. The solids were concentrated onto SiO2 and purified by silica gel chromatography eluting with ethyl acetate/hexanes to afford 0.33 g of ethyl 2-amino-3-quinolinecarboxylate.

Step 3. 2-Amino-3-quinolinecarboxylic acid

Ethyl 2-amino-3-quinolinecarboxylate (0.23 g, 1.0 mmol) was dissolved in 1:1 THF/MeOH (5 mL) and 1 M NaOH (5.3 mL) was added. The reaction was stirred for

90 mins and then 5 M HCl (1 mL) was added. A colorless solid precipitated out of solution and was collected. After drying under vacuum, 0.11 g of 2-amino-3-quinolinecarboxylic acid was obtained.

Step 4. Methyl (2*S*)-{[(2-amino-3-quinolinyl)carbonyl]amino}(cyclohexyl)ethanoate

2-Amino-3-quinolinecarboxylic acid (0.11 g, 0.58 mmol) was dissolved in DMF (5 mL) and diisopropylethylamine (0.13 mL, 0.70 mmol) was added followed by HATU (0.27 g, 0.70 mmol). The reaction was heated to 50 °C for 30 min, the heating was removed and methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.15 g, 0.70 mmol) was added. After ca. 1 h, the reaction was diluted with ethyl acetate and washed water. The organic layer was dried over $MgSO_4$ and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided a yellow oil, which was redissolved in methylene chloride, filtered and concentrated to provide methyl (2*S*)-{[(2-amino-3-quinolinyl)carbonyl]amino}(cyclohexyl)ethanoate (0.12 g) as a yellow oil.

Step 5. Methyl (2*S*)-cyclohexyl({[2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-quinolinyl]carbonyl}amino)ethanoate

Methyl (2*S*)-{[(2-amino-3-quinolinyl)carbonyl]amino}(cyclohexyl)ethanoate (50 mg, 0.14 mmol) was dissolved in DMF (2 mL) and triethylamine (30 mg, 0.29 mmol) was added followed by 2,4,6-trimethylphenyl isocyanate (26 mg, 0.16 mmol). The solution was heated to 75 °C for ca. 90 min and cooled. The reaction was diluted with water and a solid precipitated out of solution. The solid was collected and dried under vacuum to provide 44 mg of product.

Step 6. (2*S*)-Cyclohexyl({[2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-quinolinyl]carbonyl}amino)ethanoic acid

A solution of LiOH (10 mg, 0.43 mmol) in water (0.5 mL) was added to a suspension of methyl (2*S*)-cyclohexyl({[2-({[(2,4,6-

trimethylphenyl)amino]carbonyl}amino)-3-quinolinyl]carbonyl}amino)ethanoate (44 mg, 0.087 mmol) in THF (1 mL) and MeOH (1 mL) and stirred for ca. 3 h. 1 M HCl (0.43 mL) was added and a tan solid formed, which was filtered off and dried under vacuum to afford 23 mg of (2*S*)-cyclohexyl({[2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-quinolinyl]carbonyl}amino)ethanoic acid. ES MS m/z 489 (M+H).

Example 298: (2*S*)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid

Step 1. *N*-[2-cyano-1-(phenylcarbonyl)-1,2-dihydro-3-quinolinyl]benzamide

3-Aminoquinoline (7.56 g, 52.4 mmol) was dissolved in CH_2Cl_2 (100 mL) and a solution of KCN (10.2 g, 157 mmol) in water (40 mL) was added. Benzoyl chloride (14.7 g, 105 mmol) was added dropwise and the solution was stirred for 3 h. The layers were separated and the organic layer was washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated to a foam. The foam was redissolved in CH_2Cl_2 and triturated with hexanes. The resulting solid was collected to afford 14.2 g of product.

Step 2. 3-Amino-2-quinolinecarboxylic acid

A suspension of -[2-cyano-1-(phenylcarbonyl)-1,2-dihydro-3-quinolinyl]benzamide (5 g, 13.2 mmol) in AcOH (10 mL) and 48% HBr (5 mL) was heated to 100 °C for 5 min and cooled. Ice water (10 mL) was added and the solution was cooled in an ice bath for 15 min. The resulting solid was collected by filtration and dried under vacuum. The solid was suspended in EtOH (60 mL) and 5 M NaOH (115 mL) and heated to reflux for ca. 18 h. The solution was cooled and concentrated to ~50 mL and extracted with CH_2Cl_2. The pH of the aqueous phase was adjusted to 4 and the aqueous layer was reextracted with CH_2Cl_2. The extracts were concentrated and the resulting solid was washed with ethyl acetate to provide 0.6 g of product.

Step 3. Methyl (2*S*)-{[(3-amino-2-quinolinyl)carbonyl]amino}(cyclohexyl)ethanoate

Methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.33 g, 1.59 mmol) and 3-amino-2-quinolinecarboxylic acid (0.25 g, 1.32 mmol) were dissolved in DMF (6 mL) and diisopropylethylamine (0.38 g, 2.92 mmol) and HATU (0.60 g, 1.59 mmol) were added. The reaction was stirred for ca. 18 h and diluted with ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.24 g of product.

Step 4. Methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoate

Methyl (2*S*)-{[(3-amino-2-quinolinyl)carbonyl]amino}(cyclohexyl)ethanoate (50 mg, 0.15 mmol) was dissolved in DMF (1 mL) and triethylamine (29 mg, 0.29 mmol) and 2,6-dichlorophenyl isocyanate (33 mg, 0.17 mmol) were added. The reaction was heated to 70 °C for ca. 90 min and cooled. The solution was diluted with ethyl acetate and washed with water. The extracts were dried ($MgSO_4$) and concentrated on SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 61 mg of product as a yellow solid.

Step 5. (2*S*)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid

Methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoate (61 mg, 0.11 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (0.28 ml, 0.57 mmol) was added and the reaction was stirred ca. 18 h. The solution was diluted with water, acidified with 1 M HCl (0.66 mL), and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 60 mg of product as a yellow foam. ES MS m/z 515 (M+H).

Example 299: (2*S*)-Cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoate

Methyl (2*S*)-{[(3-amino-2-quinolinyl)carbonyl]amino}(cyclohexyl)ethanoate (50 mg, 0.15 mmol) was dissolved in DMF (1 mL) and triethylamine (30 mg, 0.29 mmol) and 2,4,6-trichlorophenyl isocyanate (39 mg, 0.17 mmol) were added. The reaction was heated to 70 °C for ca. 3 h, cooled and stirred overnight. The solution was diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated on SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 50 mg of product as a yellow solid.

Step 2. (2*S*)-Cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid

Methyl (2*S*)-cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoate (50 mg, 0.088 mmol) was dissolved in 1:1 THF/MeOH (3 mL) and 2 M LiOH (0.44 mmol, 0.88 mmol) was added and the reaction was stirred 2 h. The solution was diluted with water, acidified with 1 M HCl (0.88 mL), and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 30 mg of product. ES MS m/z 551 (M+H).

Example 300: (2*S*)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2*S*)-cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoate

Methyl (2*S*)-{[(3-amino-2-quinolinyl)carbonyl]amino}(cyclohexyl)ethanoate (0.17g, 0.50 mmol) was dissolved in pyridine (4 mL) and 2,4,6-trimethylphenyl isocyanate

(0.41 g, 2.5 mmol) was added. The reaction was stirred for 3 h and then filtered, diluted with ethyl acetate, and washed with 1 M HCl. The extracts were dried (MgSO4), concentrated onto SiO2, and purified by chromatography on SiO2 eluting with ethyl acetate/hexanes to afford 0.21 g of product.

Step 2. (2*S*)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid

Methyl (2*S*)-cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoate (0.21 g, 0.41 mmol) was dissolved in 1:1 THF/MeOH (3 mL) and 2 M LiOH (1.0 mL) was added. The reaction was heated to 40 °C for 6 h, cooled, acidified with 5 M HCl (0.41 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated and the residue was redissolved in CH_2Cl_2. The organics were concentrated onto SiO_2 and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 130 mg of product. ES MS m/z 489 (M+H).

Example 301: 1-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cycloheptanecarboxylate

3-Amino-2-naphthoic acid (0.2 g, 1.0 mmol) and methyl 1-aminocycloheptanecarboxylate hydrochloride (0.25 g, 1.17 mmol) were dissolved in DMF (10 mL) and diisopropylethylamine (0.41 g, 3.20 mmol) and HATU (0.45 g, 1.17 mmol) were added. The solution was heated to 50 °C for 1 h and stirred overnight. The reaction was diluted with water and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.29 g of product as a yellow solid.

Step 2. Methyl 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cycloheptanecarboxylate (0.1 g, 0.29 mmol) was dissolved in DMF (1 mL) and triethylamine (59 mg, 0.58 mmol) and 2,4,6-trichlorophenyl isocyanate (78 mg, 0.35 mmol) were added. The reaction was heated to 70 °C for 2 h and cooled. The reaction was diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 100 mg of product.

Step 3. 1-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid

Methyl 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate (85 mg, 0.15 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 1 M NaOH (0.76 mL) was added. The solution was heated to 60 °C for 2 h and cooled. The reaction was stirred at RT for 15 h and then 0.8 mL of 1 M NaOH was added and heated to 60 °C for 4 h and cooled. The reaction was diluted with water, acidified with 1 M HCl (1.7 mL), and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 70 mg of product as a solid. ES MS m/z 549 (M+H).

Example 302: 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid

Step 1. Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cycloheptanecarboxylate (40 mg, 0.12 mmol) was dissolved in pyridine (2 mL) and 2,4,6-trimethylphenyl

isocyanate (95 mg, 0.58 mmol) was added. The solution was stirred overnight and then concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 55 mg of product as an oil.

Step 2. Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate

Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate (55 mg, 0.11 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 1 M NaOH (1.1 mL) was added. The solution was heated to 60 °C for 2 h and cooled. The reaction was acidified with 1 M HCl (1.1 mL), and a solid precipitate formed. The solid was collected and dried under vacuum to provide 31 mg of product. ES MS m/z 488 (M+H).

Example 303: 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclooctanecarboxylate

3-Amino-2-naphthoic acid (0.35 g, 1.58 mmol) and methyl 1-aminocyclooctanecarboxylate hydrochloride (0.32 g, 1.74 mmol) were dissolved in DMF (10 mL) and diisopropylethylamine (0.62 g, 4.76 mmol) and HATU (0.66 g, 1.74 mmol) were added. The solution was heated to 50 °C for 1 h and stirred overnight. The reaction was diluted with water and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.29 g of product as a yellow solid.

Step 2. Methyl 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclooctanecarboxylate (40 mg, 0.11 mmol) was dissolved in pyridine (2 mL) and 2,4,6-trichlorophenylisocyanate (125 mg, 0.56 mmol) was added. The reaction was stirred for ca. 15 h and concentrated onto SiO2. Chromatography on SiO2 eluting with ethyl acetate/hexanes provided 65 mg of product.

Step 3. 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid

Methyl 1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylate (65 mg, 0.11 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 1 M NaOH (1.1 mL) was added. The reaction was heated to 90 °C for 6 h, cooled to RT and stirred overnight. 1 M HCl (1.2 mL) was added and the solution was extracted with ethyl acetate. The extracts were concentrated and the residue was dissolved in MeOH and purified by reverse phase HPLC to afford 22 mg of product. ES MS m/z 563 (M+H)

Example 304: 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1. Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclooctanecarboxylate (40 mg, 0.11 mmol) was dissolved in pyridine (2 mL) and 2,4,6-trimethylphenylisocyanate (91 mg, 0.56 mmol) was added. The reaction was stirred for ca. 15 h and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 58 mg of product.

Step 2. 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid

(65 mg, 0.11 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 1 M NaOH (1.1 mL) was added. The reaction was heated to 90 °C for 6 h, cooled to RT and stirred overnight. 1 M HCl (1.2 mL) was added and a solid precipitate formed. The solids were collected and dried under vacuum to provide 28 mg of product. ES MS m/z 502 (M+H)

Example 305: 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclodecanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclodecanecarboxylate

3-Amino-2-naphthoic acid (0.34 g, 1.54 mmol) was dissolved in DMF (10 mL) and diisopropylethylamine (0.45 g, 3.51 mmol) and HATU (0.59 g, 1.54 mmol) were added. The reaction was stirred for 20 min and and methyl 1-aminocyclodecanecarboxylate hydrochloride (0.30 g, 1.40 mmol) was added. The solution was heated to 55 °C for 2 h, cooled, and diluted with ethyl acetate. The mixture was washed with water and the organics were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.34 g of product as a yellow solid.

Step 2. Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclodecanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclodecanecarboxylate (0.34 g, 0.89 mmol) was dissolved in pyridine (6 mL) and 2,4,6-trimethylphenylisocyanate (0.72 g, 4.44 mmol) was added. The reaction was stirred for ca. 15 h and diluted with ethyl acetate. The solution was filtered and the filtrate was washed with 1 M HCl, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with $MeOH/CH_2Cl_2$ provided a brown solid that was triturated with ethyl acetate to provide 0.28 g of product.

Step 3. 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclodecanecarboxylic acid

Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclodecanecarboxylate (0.28 g, 0.51 mmol) was suspended in 1:1 THF/MeOH and 2 M LiOH (1.3 mL) was added. The reaction was heated at 65 °C for 4 days, cooled, and acidified with 1 M HCl (2.6 mL). The solution was extracted with ethyl acetate and the organic layer was concentrated. The residue was suspended in ethyl acetate and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 22 mg of product as a beige solid. ES MS m/z 530 (M+H).

Example 306: 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cycloheptanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-2-quinolinyl)carbonyl]amino}cycloheptanecarboxylate

3-Amino-2-quinolinecarboxylic acid (0.25 g, 1.32 mmol) was dissolved in DMF (5 mL) and diisopropylethylamine (0.51 g, 3.98 mmol) and HATU (0.55 g, 1.46 mmol) were added. The reaction was stirred for 30 min and methyl 1-aminocycloheptanecarboxylate hydrochloride (0.30 g, 1.46 mmol) was added. The reaction was heated to 50 °C for 90 min and cooled. The reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.21 g of product.

Step 2. Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cycloheptanecarboxylate

Methyl 1-{[(3-amino-2-quinolinyl)carbonyl]amino}cycloheptanecarboxylate (0.21 g, 0.61 mmol) was dissolved in pyridine (4 mL) and 2,4,6-trimethylphenylisocyanate (0.49 g, 3.07 mmol) was added. The reaction was stirred for 6 h, diluted with ethyl

acetate and filtered. The filtrate was washed with 1 M HCl, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 198 mg of product.

Step 3. 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cycloheptanecarboxylic acid

Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cycloheptanecarboxylate (190 mg, 0.38 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (1.9 mL) was added. The reaction was heated to 55 °C for 4 h, cooled to RT and acidified with 5 M HCl (0.76 mL). The solution was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated. The residue was redissolved in CH_2Cl_2 and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 140 mg of product. ES MS m/z 489 (M+H)

Example 307: 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-2-quinolinyl)carbonyl]amino}cyclooctanecarboxylate

3-Amino-2-quinolinecarboxylic acid (0.14 g, 0.74 mmol) and methyl 1-aminocyclooctanecarboxylate hydrochloride (0.15 g, 0.81 mmol) were dissolved in DMF (5 mL) and diisopropylethylamine (0.34 g, 2.6 mmol) and HATU (0.31 g, 0.81 mmol) were added. The reaction was stirred for 3 h and diluted with ethyl acetate. The mixture was washed with water, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.19 g of product.

Step 2. Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cyclooctanecarboxylate

Methyl 1-{[(3-amino-2-quinolinyl)carbonyl]amino}cyclooctanecarboxylate (0.18 g, 0.50 mmol) was dissolved in pyridine (4 mL) and 2,4,6-trimethylphenylisocyanate (0.40 g, 2.5 mmol) was added. The reaction was stirred for 5 h, filtered, and the solids were washed with ethyl acetate. The filtrate was washed with 1 M HCl, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.25 g of product.

Step 3. 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cyclooctanecarboxylic acid

Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cyclooctanecarboxylate (230 mg, 0.44 mmol) was dissolved in 1:1 THF/MeOH (3.5 mL) and 2 M LiOH (2.2 mL) was added. The reaction was heated to 55 °C for 3 h, cooled to RT, diluted with water and acidified with 5 M HCl (0.89 mL). The solution was extracted with diethyl ether, dried ($MgSO_4$) and concentrated. The residue was triturated with diethyl ether to afford a solid, which was dried under vacuum to afford 197 mg of product. ES MS m/z 503 (M+H)

Example 308: 1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid

Step 1. Methyl 1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cycloheptanecarboxylate (0.31 g, 0.91 mmol) was dissolved in pyridine (7 mL) and 4-bromo-2,6-dimethylphenyl isocyanate (0.51 g, 2.27 mmol) was added. The solution was stirred overnight and then diluted with ethyl acetate, washed with 1 M HCl, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.48 g of product as a solid.

Step 2. 1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid

Methyl 1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate (83 mg, 0.14 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (0.73 mL) was added. The reaction was heated to 60 °C for 3 h, cooled to RT, acidified with 1 M HCl (1.46 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. The residue was triturated with methanol to afford a solid, which was dried under vacuum to afford 58 mg of product. ES MS m/z 553 (M+H)

Example 309: 1-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid

Step 1. Methyl 1-[({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]cycloheptanecarboxylate

Methyl 1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate (0.2 g, 0.35 mmol) was suspended in CH_3CN (5 mL) and $Pd(PPh_3)_4$ (20 mg, 0.018 mmol) and allyltributylstannane (0.13 g, 0.38 mmol) were added. The reaction was purged with N_2 and heated to 150 °C for 30 min. The solution was cooled and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 149 mg of product.

Step 2. Methyl 1-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate

Methyl 1-[({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]cycloheptanecarboxylate (0.14 g, 0.26 mmol) was dissolved in ethyl acetate (5 mL) and 10% Pd/C (20 mg) was added. A H_2

atmosphere was established and the reaction was stirred overnight. The mixture was filtered through celite and washed with MeOH. The filtrate was concentrated onto SiO_2 and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 118 mg of product.

Step 3. 1-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid

Methyl 1-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate (118 mg, 0.22 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (1.1 mL) was added. The reaction was heated to 60 °C for 3 h, cooled to RT, acidified with 1 M HCl (2.2 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to provide 20 mg of product. ES MS m/z 516 (M+H)

Example 310: 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-2,3-dihydro-1*H*-indene-2-carboxylic acid

Step 1. Methyl 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2,3-dihydro-1*H*-indene-2-carboxylate

2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2,3-dihydro-1*H*-indene-2-carboxylic acid (0.26 g, 0.93 mmol) was dissolved in MeOH (6 mL) and a solution of trimethylsilyldiazomethane (2.5 mL) was added dropwise until a yellow color persisted. The solution was then concentrated to provide product as a solid which was used without further purification.

Step 2. Methyl 2-amino-2,3-dihydro-1*H*-indene-2-carboxylate trifluoroacetate

Methyl 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2,3-dihydro-1*H*-indene-2-carboxylate (0.27 g, 0.93 mmol) was dissolved in CH_2Cl_2 (5 mL) and TFA (0.5 mL)

was added and stirred overnight. The solution was concentrated to provide product as the TFA salt.

Step 3. Methyl 2-{[(3-amino-2-naphthalenyl)carbonyl]amino}-2,3-dihydro-1*H*-indene-2-carboxylate

3-Amino-2-quinolinecarboxylic acid (0.22 g, 1.0 mmol) was dissolved in DMF (6 mL) and diisopropylethylamine (0.41 g, 3.2 mmol) and HATU (0.38 g, 1.0 mmol) were added and stirred 20 min. Methyl 2-amino-2,3-dihydro-1*H*-indene-2-carboxylate trifluoroacetate (0.28 g, 0.92 mmol) was added and the reaction was heated to 55 °C for 1 h and cooled. The mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.30 g of product.

Step 4. Methyl 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-2,3-dihydro-1*H*-indene-2-carboxylate

Methyl 2-{[(3-amino-2-naphthalenyl)carbonyl]amino}-2,3-dihydro-1*H*-indene-2-carboxylate (0.30 g, 0.83 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (0.67 g, 4.1 mmol) was added and stirred overnight. The solution was diluted with ethyl acetate, washed with 1 M HCl, filtered, dried (Na_2SO_4) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 0.35 g of product.

Step 5. 2-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-2,3-dihydro-1*H*-indene-2-carboxylic acid

Methyl 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-2,3-dihydro-1*H*-indene-2-carboxylate (0.35 g, 0.67 mmol) was dissolved in 1:1 THF/MeOH (3 mL) and 2 M LiOH (1.7 mL) was added. The reaction was heated to 55 °C for 2 h, cooled to RT and stirred overnight. The

mixture was acidified with 5 M HCl (0.7 mL) and a solid formed. The solid was collected and dried under vacuum to provide 0.24 g of product. ES MS m/z 508 (M+H).

Example 311: 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid

Step 1. Methyl 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylate

2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (1 g, 3.43 mmol) was dissolved in MeOH (30 mL) and a solution of trimethylsilyldiazomethane was added dropwise until a yellow color persisted and stirred 30 min. The solution was then concentrated to provide product as a solid which was used without further purification.

Step 2. Methyl 2-amino-1,2,3,4-tetrahydro-2-naphthalenecarboxylate trifluoroacetate

Methyl 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (1 g, 3.4 mmol) was dissolved in CH_2Cl_2 and TFA (2 mL) was added and stirred overnight. The solution was concentrated and dried under vacuum to provide product as the TFA salt.

Step 3. Methyl 2-{[(3-amino-2-naphthalenyl)carbonyl]amino}-1,2,3,4-tetrahydro-2-naphthalenecarboxylate

3-Amino-2-quinolinecarboxylic acid (0.22 g, 0.96 mmol) and methyl 2-amino-1,2,3,4-tetrahydro-2-naphthalenecarboxylate trifluoroacetate (0.28 g, 0.88 mmol) were dissolved in DMF (5 mL) and diisopropylethylamine (0.40 g, 3.0 mmol) and HATU (0.37 g, 0.96 mmol) were added. The reaction was heated to 50 °C overnight and cooled. The mixture was diluted with ethyl acetate, washed with water, dried

($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.19 g of product.

Step 4. Methyl 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylate

Methyl 2-{[(3-amino-2-naphthalenyl)carbonyl]amino}-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (0.19 g, 0.50 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (0.42 g, 2.5 mmol) was added and stirred overnight. The solution was diluted with ethyl acetate, filtered, and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 0.24 g of product.

Step 5. 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid

Methyl 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (0.24 g, 0.45 mmol) was dissolved in 1:1 THF/MeOH (4 mL) and 2 M LiOH (2.2 mL) was added. The reaction was heated to 55 °C for 3 h, cooled to RT, acidified with 1 M HCl (4.4 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. The residue was purified by reverse-phase HPLC to provide 136 mg of product. ES MS m/z 522 (M+H)

Example 312: 2-Cyclohexyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-D-alanine

Step 1. Methyl *N*-[(3-amino-2-quinolinyl)carbonyl]-2-cyclohexyl-D-alaninate

3-Amino-2-quinolinecarboxylic acid (0.25 g, 1.32 mmol) was dissolved in DMF (6 mL) and diisopropylethylamine (0.60 g, 4.64 mmol) and HATU (0.55 g, 1.46 mmol)

were added. The reaction was stirred for 20 min and methyl 2-cyclohexyl-D-alaninate hydrochloride (0.32 g, 1.46 mmol) was added. The reaction was heated to 55 °C for 60 min and cooled. The reaction was diluted with ethyl acetate and washed with water and brine, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.32 g of product.

Step 2. Methyl 2-cyclohexyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-D-alaninate

Methyl *N*-[(3-amino-2-quinolinyl)carbonyl]-2-cyclohexyl-D-alaninate (0.32 g, 0.90 mmol) was dissolved in pyridine (2 mL) and 2,4,6-trimethylphenylisocyanate (0.72 g, 4.5 mmol) was added. The reaction was stirred overnight, diluted with ethyl acetate, washed with 1 M HCl, and filtered. The filtrate was concentrated onto SiO_2 and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.28 g of product.

Step 3. 2-Cyclohexyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-D-alanine

Methyl 2-cyclohexyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-D-alaninate (0.28 g, 0.54 mmol) was dissolved in 1:1 THF/MeOH (4 mL) and 2 M LiOH (2.7 mL) was added. The reaction was heated to 50 °C for 1 h, cooled to RT, acidified with 5 M HCl (1 mL) and extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 130 mg of product. ES MS m/z 503 (M+H).

Example 313: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucine

Step 1. Methyl *N*-[(3-amino-2-quinolinyl)carbonyl]-L-norleucinate

3-Amino-2-quinolinecarboxylic acid (0.12 g, 0.66 mmol) was dissolved in DMF (6 mL) and diisopropylethylamine (0.26 g, 1.99 mmol) and HATU (0.28 g, 0.73 mmol) were added. The reaction was stirred for 20 min and methyl L-norleucinate hydrochloride (0.13 g, 0.73 mmol) was added and stirred for 3 days. The reaction was diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.11 g of product.

Step 2. Methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucinate

Methyl *N*-[(3-amino-2-quinolinyl)carbonyl]-L-norleucinate (50 mg, 0.16 mmol) was dissolved in pyridine (3 mL) and 2,4,6-trimethylphenylisocyanate (0.13 g, 0.79 mmol) was added. The reaction was stirred overnight, diluted with ethyl acetate and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 46 mg of product.

Step 3. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucine

Methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucinate (46 mg, 0.096 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.48 mL) was added. After 5 min an additional 1 mL of MeOH was added and the reaction was stirred overnight. The reaction was acidified with 1 M HCl (1 mL) and a precipitate formed. The solid was collected and dried to provide 27 mg of product. ES MS m/z 463 (M+H).

Example 314: *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucine

Step 1. Methyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucinate

Methyl *N*-[(3-amino-2-quinolinyl)carbonyl]-L-norleucinate (56 mg, 0.18 mmol) was dissolved in pyridine (3 mL) and 2,6-dichlorophenylisocyanate (0.17 g, 0.88 mmol) was added. The reaction was stirred overnight, diluted with ethyl acetate and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 90 mg of product.

Step 2. *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucine

Methyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucinate (90 mg, 0.18 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.93 mL) was added and the reaction was stirred overnight. The reaction was acidified with 1 M HCl (1.86 mL) and a precipitate formed. The solid was collected and dried to provide 74 mg of product. ES MS m/z 489 (M+H).

Example 315: 2-Propyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norvaline

Step 1. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-propylnorvalinate

3-Amino-2-napthoic acid (0.27 g, 1.44 mmol) was dissolved in DMF (5 mL) and diisopropylethylamine (0.56 g, 4.32 mmol) and HATU (0.60 g, 1.58 mmol) were added and stirred 15 min. Methyl 2-propylnorvalinate hydrochloride (0.27 g, 1.58 mmol) was added and the reaction was stirred overnight. The mixture was diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.28 g of product.

Step 2. Methyl 2-propyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norvalinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-propylnorvalinate (53 mg, 0.15 mmol) was dissolved in DMF (2 mL) and triethylamine (31 mg, 0.30 mmol) and 2,4,6-trimethylphenyl isocyanate (41 mg,0.25 mmol) were added. The reaction was heated to 70 °C for 3 h and then stirred at RT overnight. The reaction was filtered and the filtrate was diluted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 37 mg of product.

Step 3. 2-Propyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norvaline

Methyl 2-propyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norvalinate (37 mg, 0.073 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.53 mL) was added and the reaction was heated to 60 °C overnight. The reaction was cooled, diluted with water, acidified with 1 M HCl (1.86 mL) and extracted with ethyl acetate. The extracts were concentrated and the residue was dissolved in MeOH (1 mL) and purified by reverse-phase HPLC to afford 27 mg of product. ES MS m/z 490 (M+H).

Exampe 316: *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-propylnorvaline

Step 1. Methyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-propylnorvalinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-propylnorvalinate (53 mg, 0.15 mmol) was dissolved in DMF (2 mL) and triethylamine (31 mg, 0.30 mmol) and 2,6-dichlorophenyl isocyanate (35 mg,0.18 mmol) were added. The reaction was heated to 70 °C for 3 h and then stirred at RT overnight. The reaction was diluted

with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 60 mg of product.

Step 2. *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-propylnorvaline

Methyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-propylnorvalinate (60 mg, 0.11 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.35 mL) was added and the reaction was heated to 60 °C overnight. The reaction was cooled, diluted with water, acidified with 1 M HCl (1.86 mL) and extracted with ethyl acetate. The extracts were concentrated and the residue was dissolved in MeOH (1 mL) and purified by reverse-phase HPLC to afford 15 mg of product. ES MS m/z 516 (M+H).

Example 317: (2*S*)-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. 2-Bromo-5-chloro-3-nitropyridine according to the literature

2-Amino-5-chloro-3-nitropyridine (25.5 g, 147 mmol) was added to a solution of 48% HBr (83 mL) at 0 °C. Bromine (25.1 mL) was added dropwise to the solution, maintaining the reaction temperature below 0 °C. A solution of $NaNO_2$ (35.3 g, 511 mmol) in water (48 mL) was added, again maintaining the reaction temperature below 0 °C. After the addition was complete, the reaction was stirred 45 min and then a solution of NaOH (53.8 g) in water (80 mL) was added, maintaining the reaction temperature below 20 °C. The mixture was stirred an additional 1 h and the resulting product was filtered off and dried to afford 26 g of product.

Step 2. 5-Chloro-3-nitro-2-pyridinecarbonitrile

2-Bromo-5-chloro-3-nitropyridine (1.5 g, 6.31 mmol) and CuCN (1.13 g, 12.63 mmol) were dissolved in NMP (12 mL) and heated to 170 °C for 10 min and cooled.

The solution was poured onto water and ethyl acetate was added. The mixture was filtered through celite and the organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 0.97 go of product. This reaction was repeated to provide additional product.

Step 3. 3-Amino-5-chloro-2-pyridinecarboxamide

5-Chloro-3-nitro-2-pyridinecarbonitrile (0.97 g, 5.28) was dissolved in EtOH (20 mL) and Raney-nickel (100 mg, prewashed with water, 5% AcOH, water and EtOH) was added. The mixture was placed under 50 psi H_2 and shaken for 3 h. The mixture was then filtered through celite and concentrated to afford 0.76 g of product as a brown solid. This reaction was repeated to provide additional product.

Step 4. 3-Amino-5-chloro-2-pyridinecarboxylic acid

3-Amino-5-chloro-2-pyridinecarboxamide (2.5 g, 14.5 mmol) was suspended in concentrated HCl (25 mL) and heated to reflux for 15 h and cooled in an ice bath. Precipitated solid was filtered off to provide1.0 g of the product as the hydrochloride salt and the pH of the filtrate was adjusted to 6 with 5 M NaOH and extracted with ethyl acetate. The extracts were concentrated to afford 1.27 g of the product.

Step 5. Methyl (2*S*)-{[(3-amino-5-chloro-2-pyridinyl)carbonyl]amino}(cyclohexyl)ethanoate

3-Amino-5-chloro-2-pyridinecarboxylic acid hydrochloride (0.21 g, 1.0 mmol) was dissolved in DMF (5 mL) and diisopropylethylamine (0.52 g, 4.01 mmol) and HATU (0.42 g, 1.10 mmol) were added and stirred 20 min. Methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.23 g, 1.10 mmol) was added and the reaction was stirred for 20 min and then diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2.

Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.28 g of product.

Step 6. Methyl (2*S*)-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2*S*)-{[(3-amino-5-chloro-2-pyridinyl)carbonyl]amino}(cyclohexyl)ethanoate (0.28 g, 0.86 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (0.69 g, 4.29 mmol) was added. The reaction was stirred overnight, diluted with ethyl acetate and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided product contaminated with an impurity. The mixture was repurified by reverse-phase HPLC to afford 176 mg of product as a colorless foam.

Step 7. (2*S*)-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Methyl (2*S*)-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)(cyclohexyl)ethanoate (60 mg, 0.1 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 2 M LiOH (0.5 mL) was added and the reaction was stirred 5 min and a solid precipitate formed. The reaction was acidified with 1 M HCl (1.0 mL) and a colorless solid resulted. The solid was collected and dried under vacuum to afford 45 mg of product. ES MS m/z 473 (M+H).

Example 318: *N*-{[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine

Step 1. Methyl *N*-[(3-amino-5-chloro-2-pyridinyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate

3-Amino-5-chloro-2-pyridinecarboxylic acid (0.22 g, 1.27 mmol) and methyl *O*-(1,1-dimethylethyl)-L-threoninate (0.35 g, 1.52 mmol) were dissolved in DMF (4 mL) and

diisopropylethylamine (0.58 g, 4.46 mmol) and HATU (0.58 g, 1.52 mmol) were added and stirred 3 days. The reaction was diluted with ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.28 g of product.

Step 2. Methyl *N*-{[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate

Methyl *N*-[(3-amino-5-chloro-2-pyridinyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.26 g, 0.75 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (0.60 g, 3.78 mmol) was added. The reaction was stirred 5 h, diluted with ethyl acetate, washed with 1 M HCl, and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 170 mg of product.

Step 3. *N*-{[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine

Methyl *N*-{[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate (0.17 g, 0.33 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (0.84 mL) was added and the reaction was stirred 2 h and acidified with 5 M HCl (0.33 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to provide 154 mg of product as a pale yellow foam. ES MS m/z 491 (M+H).

Example 319: 1-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-5-chloro-2-pyridinyl)carbonyl]amino}cycloheptanecarboxylate

3-Amino-5-chloro-2-pyridinecarboxylic acid (0.22 g, 1.27 mmol) was dissolved in DMF (10 mL) and diisopropylethylamine (0.55 g, 4.29 mmol) and HATU (0.51 g, 1.34 mmol) were added and stirred 30 min. Methyl 1-aminocycloheptanecarboxylate hydrochloride (0.28 g, 1.34 mmol) was added and the mixture was heated to 55 °C for 2 h and cooled. The reaction was diluted with ethyl acetate and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.55 g of product.

Step 2. Methyl 1-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylate

Methyl 1-{[(3-amino-5-chloro-2-pyridinyl)carbonyl]amino}cycloheptanecarboxylate (0.55 g, 1.69 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (1.4 g, 8.44 mmol) was added. The reaction was stirred overnight, diluted with ethyl acetate, filtered, washed with 1 M HCl and brine, and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 170 mg of product.

Step 3. 1-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylic acid

Methyl 1-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylate (0.17 g, 0.35 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (1.7 mL) was added. The reaction was heated to 55 °C for 3 h, cooled, acidified with 5 M HCl (0.7 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to provide 130 mg of product. ES MS m/z 473 (M+H).

Example 320: 1-({[5-Chloro-3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-5-chloro-2-pyridinyl)carbonyl]amino}cyclooctanecarboxylate

3-Amino-5-chloro-2-pyridinecarboxylic acid (0.53 g, 2.53 mmol) and methyl 1-aminocycloheptanecarboxylate (0.52 g, 2.78 mmol) were dissolved in DMF (10 mL) and diisopropylethylamine (1.14 g, 8.87 mmol) and HATU (1.06 g, 2.78 mmol) were added and stirred for 3 h. The mixture was diluted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.68 g of product.

Step 2. Methyl 1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-5-chloro-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylate

Methyl 1-{[(3-amino-5-chloro-2-pyridinyl)carbonyl]amino}cyclooctanecarboxylate (0.2 g, 0.59 mmol) was dissolved in pyridine (5 mL) and 4-bromo-2,6-dimethylphenylisocyanate (0.27 g, 1.17 mmol) was added. The reaction was stirred 4 h, diluted with ethyl acetate, washed with 1 M HCl, dried ($MgSO_4$), and concentrated to a solid. The solid was triturated with MeOH to provide 0.27 g of product

Step 3. Methyl 1-[({5-chloro-3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-2-pyridinyl}carbonyl)amino]cyclooctanecarboxylate

Methyl 1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-5-chloro-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylate (143 mg, 0.25 mmol) was suspended in CH_3CN (5 mL) and $Pd(PPh_3)_4$ (15 mg, 0.012 mmol) and allyltributylstannane (0.10 g, 0.30 mmol) were added. The reaction was purged with N_2 and heated to 150 °C for 20 min. The solution was cooled and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 100 mg of product.

Step 4. Methyl 1-({[5-chloro-3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylate

Methyl 1-[({5-chloro-3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-2-pyridinyl}carbonyl)amino]cyclooctanecarboxylate (100 mg, 0.19 mmol) was dissolved in ethyl acetate (3 mL) and 10% Pd/C (20 mg) was added. A H_2 atmosphere was established and the reaction was stirred overnight. The mixture was filtered through celite and concentrated to afford 64 mg of product.

Step 5. 1-({[5-Chloro-3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylic acid

Methyl 1-({[5-chloro-3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylate (0.64 mg, 0.12 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (0.6 mL) was added. The reaction was heated to 60 °C for 4 h, cooled, acidified with 1 M HCl (1.2 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated and the residue was redissolved in MeOH. After standing 2 days, a solid film resulted which was sonicated in MeOH (1 mL) to provide a colorless solid which was dried under vacuum to afford 18 mg of product. ES MS m/z 515 (M+H).

Example 321: (2*S*)-Cyclohexyl({[5-phenyl-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)ethanoic acid

Methyl (2*S*)-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)(cyclohexyl)ethanoate (48 mg, 0.08 mmol), phenyl boronic acid (11 mg, 0.09 mmol), and $PdCl_2(PCy_3)_2$ (3 mg, 0.004 mmol) were dissolved in CH_3CN (1.8 mL) and 2 M Na_2CO_3 (0.16 mL) was added. The mixture was heated to 150 °C for 10 min and cooled. 2 M LiOH (1.0 mL) was added and the mixture

was stirred overnight. 5 M HCl (0.45 ml) was added and the mixture was stirred vigorously until a solid resulted, which was filtered off and dissolved in MeOH. Reverse-phase HPLC purification provided 29 mg of product as the TFA salt. ES MS m/z 515 (M+H).

Example 322: (2*S*)-Cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)ethanoic acid

Methyl (2*S*)-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)(cyclohexyl)ethanoate (48 mg, 0.08 mmol), 4-methoxyphenyl boronic acid (13 mg, 0.09 mmol), and $PdCl_2(PCy_3)_2$ (3 mg, 0.004 mmol) were dissolved in CH_3CN (1.8 mL) and 2 M Na_2CO_3 (0.16 mL) was added. The mixture was heated to 150 °C for 10 min and cooled. 2 M LiOH (1.0 mL) was added and the mixture was heated to 50 °C for 90 min and cooled. 5 M HCl (0.55 ml) was added and the mixture was stirred vigorously until a solid resulted, which was filtered off and triturated with MeOH to provide 20 mg of product. ES MS m/z 545 (M+H).

Example 323: *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-L-threonine

N-{[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine (50 mg, 0.10 mmol), 4-methoxyphenylboronic acid (19 mg, 0.12 mmol), and $PdCl_2(PCy_3)_2$ (4 mg, 0.005 mmol) were dissolved in CH_3CN (2.5 mL) and 2 M Na_2CO_3 (0.15 mL) was added. The reaction was heated to 160 °C for 15 min and cooled. The reaction was diluted with ethyl acetate and water and 1 M HCl (0.30 mL) was added. The organic layer was separated, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 7 mg of product. ES MS m/z 563 (M+H)

Example 324: *N*-{[5-(3,4-Difluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine

N-{[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine (78 mg, 0.16 mmol), 3,4-difluorophenylboronic acid (30 mg, 0.19 mmol), and PdCl2(PCy3)2 (6 mg, 0.008 mmol) were dissolved in CH3CN (3 mL) and 2 M Na2CO3 (0.23 mL) was added. The reaction was heated to 160 °C for 10 min and cooled. The reaction was diluted with water, 1 M HCl (0.48 mL) was added, and the mixture was extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. The residue was redissolved in MeOH (1 mL) and purified by reverse-phase HPLC to afford 18 mg of product. ES MS m/z 569 (M+H).

Example 325: 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylic acid

1-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylic acid (0.11 g, 0.23 mmol), 4-methoxyphenylboronic acid (42 mg, 0.28 mmol), and $PdCl_2(PCy_3)_2$ (9 mg, 0.01 mmol) were dissolved in CH_3CN (4 mL) and 2 M Na_2CO_3 (0.46 mL) was added. The reaction was heated to 150 °C for 15 min and cooled. The reaction was acidified with 5 M HCl (0.18 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided a solid which was triturated with MeOH to afford 18 mg of product. ES MS m/z 545 (M+H).

Example 326: (2*S*)-({[6-Bromo-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. 3-Amino-6-bromo-1-benzofuran-2-carboxylic acid (U22318-11)
Ethyl 3-amino-6-bromo-1-benzofuran-2-carboxylate (1.05 g, 5.11 mmol) was dissolved in 1:1 THF/MeOH (20 mL) and 2 M LiOH (5.1 mL) was added. The reaction was stirred overnight. The reaction was acidified with 1 M HCl (10 mL) and ethyl acetate was added. The organic layer was separated and concentrated to afford 1.0 g of product.

Step 2. Methyl (2*S*)-{[(3-amino-6-bromo-1-benzofuran-2-yl)carbonyl]amino}(cyclohexyl)ethanoate

3-Amino-6-bromo-1-benzofuran-2-carboxylic acid (0.5 g, 1.95 mmol) was dissolved in DMF (10 mL) and diisopropylethylamine (0.55 g, 4.19 mmol) and HATU (0.89 g, 2.34 mmol) were added and stirred for 15 min. Methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride (0.49 g, 2.34 mmol) was added and stirred overnight. Water was added and the mixture was extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 0.58 g of product.

Step 3. Methyl (2*S*)-({[6-bromo-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2*S*)-{[(3-amino-6-bromo-1-benzofuran-2-yl)carbonyl]amino}(cyclohexyl)ethanoate (50 mg, 0.12 mmol) was dissolved in pyridine (1 mL) and 2,4,6-trichlorophenylisocyanate (30 mg, 0.13 mmol) was added. The reaction was heated to 50 °C for 15 h and then an additional 60 mg of 2,4,6-trichlorophenylisocyanate was added and stirred for 15 min at 50 °C and then cooled and stirred for 24 h. The reaction mixture was then concentrated onto SiO_2 and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 77 mg of product as a solid.

Step 4. (2*S*)-({[6-Bromo-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoic acid

Methyl (2*S*)-({[6-bromo-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoate (77 mg, 0.12 mmol) was dissolved in 1:1 THF/MeOH (5 mL) and 2 M LiOH (0.6 mL) was added. The reaction was stirred for 4 h, diluted with water, acidified with 1 M HCl (1.2 mL) and a solid formed. The solid was collected and dried under vacuum to provide 62 mg of product. MS m/z 618 (M+H).

Example 327: (2*S*)-({[6-Bromo-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. Methyl (2*S*)-({[6-bromo-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2*S*)-{[(3-amino-6-bromo-1-benzofuran-2-yl)carbonyl]amino}(cyclohexyl)ethanoate (50 mg, 0.12 mmol) was dissolved in DMF (1 mL) and triethylamine (19 mg, 0.14 mmol) and 2,6-dichlorophenylisocyanate (28 mg, 0.14 mmol) was added. The reaction was heated to 60 °C for 4 h and stirred overnight. The reaction mixture was then diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 40 mg of product.

Step 2. (2*S*)-({[6-Bromo-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoic acid

Methyl (2*S*)-({[6-bromo-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoate (40 mg, 0.066 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (0.33 mL) was added. The reaction was stirred for 4 h, diluted with water, acidified with 1 M HCl (0.7 mL) and

extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to a solid. The solid was triturated with warm MeOH to provide 9 mg of product. MS m/z 584 (M+H).

Example 328: *O*-(phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Step 1. Methyl *N*-(triphenylmethyl)-L-threoninate

To a cooled (0°C) solution of methyl L-threoninate hydrochloride (5.0g, 29.48 mmol) and triethylamine (5.97g, 58.97 mmol) in chloroform (100ml) was added trityl chloride as a solid (8.22g, 29.49 mmol). The reaction was stirred for 12 hours and allowed to come to RT. The reaction was concentrated in vacuo and then dissolved in ethyl acetate and washed with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$, and saturated sodium chloride. The organic layer was dried over $MgSO_4$, filtered and stripped to give10.16g of product as a fluffy cream solid.

Step 2. Methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate

To a cooled (0°C) solution of methyl *N*-(triphenylmethyl)-L-threoninate (10.16g, 27.95 mmol) in anhydrous pyridine was added methanesulfonyl chloride (9.61g, 83.85 mmol) and the reaction was allowed to stirfor 12 hours and allowed to come to RT. The solvent was removed in vacuo and the residue dissolved in ethyl acetate. The organic layer was washed with saturated sodium chloride and then dried over $MgSO_4$, filtered and stripped to 12.33g of amber oil which was then dissolved in 80ml of anhydrous THF and to which was added triethylamine (8.50g, 84.01 mmol) and heated to 80°C and allowed to reflux for 48 hours. The heat was removed and the reaction was concentrated in vacuo and the residue dissolved in ethyl acetate and washed successively with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$ and saturated sodium chloride. The ethyl

acetate layer was dried over $MgSO_4$, filtered and stripped to give 9.04g of amber oil. Chromatography on silica gel with hexane/ethyl acetate gave 5.26 g of product fluffy cream solid.

Step 3. 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate

To a solution of methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate (5.26g, 14.72 mmol) in $CHCl_3$ (12ml) and MeOH (12ml) cooled to 0°C was added 11.6ml of TFA and allowed to stir at 0°C for 2.5 hours. The reaction was then concentrated in vacuo and evaporated with ether newly added several times to remove TFA. The residue was dissolved in ether which was extracted with water three times. To the aqueous extract at 0°C was added $NaHCO_3$ (5.84g, 69.52 mmol), benzyl chloroformate (2.51g, 14.71 mmol) and 50ml of ethyl acetate under vigorous stirring for 1.5 hours. The ethyl acetate layer was separated and the water layer back-extracted. The organics were dried over $MgSO_4$, filtered and concentrated to give 2.96g of light yellow oil. Chromatography on silica gel with hexane/ethyl acetate gave 2.45g of product as a clear oil.

Step 4. Methyl *O*-(phenylmethyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-allothreoninate

To a solution of 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate (0.5g, 2.06 mmol) in $CHCl_3$ (10ml) was added benzyl alcohol (2.16g, 20.00 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 2.66g of product as a clear oil.

Step 5. Methyl *O*-(phenylmethyl)-L-allothreoninate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-(phenylmethyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-allothreoninate (2.66g, 7.44 mmol) in 10ml of EtOH in a flask under nitrogen. A

balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 3 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 1.96g of clear oil.

Step 6. Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(phenylmethyl)-L-threoninate

HATU (0.76 g, 2.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.31 g, 1.66 mmol), methyl *O*-(phenylmethyl)-L-allothreoninate (0.45 g, 2.01 mmol) and diisopropylethylamine (0.26 g, 2.01 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was diluted with ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.476 g of yellow oil.

Step 7. Methyl *O*-(phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(phenylmethyl)-L-threoninate (0.47 g, 1.19 mmol) was dissolved in pyridine (10 mL) and 2,4,6-trimethylphenylisocyanate (0.58 g, 3.59 mmol) was added. The reaction was stirred 4 h, diluted with ethyl acetate, and washed with 1 M HCl. The extracts were dried and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.59 g of product.

Step 8. *O*-(phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Methyl *O*-(phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate (0.59 g, 1.06 mmol) was dissolved in 1:1 THF/MeOH (10 mL) and 2 M LiOH (5.3 mL) was added. The reaction was stirred for 3 h, acidified with 1 M HCl (10.6 mL) and extracted with ethyl acetate. The

extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded an impure solid. Purification of 200 mg of the solid by reverse-phase HPLC afforded 53 mg of product. MS m/z 539 (M+H).

Example 329: (3*R*)-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline

Step 1. (1*R*)-1-[(2*S*,5*R*)-5-(1-methylethyl)-3,6-bis(methyloxy)-2,5-dihydro-2-pyrazinyl]-1-propanol

(2*R*)-2-(1-methylethyl)-3,6-bis(methyloxy)-2,5-dihydropyrazine (1 g, 5.42 mmol) was dissolved in THF (30 mL) and cooled to -78 °C. A solution of n-BuLi (3.6 mL of a 1.6 M solution) was added dropwise and stirred for 30 min. Propionaldehyde (0.35 mL, 5.97 mmol) was added and the reaction was stirred for 4 h and poured onto water and Et_2O. The organic layer was separated, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 0.85 g of product as a clear oil.

Step 2. (2*R*,5*S*)-2-(1-methylethyl)-3,6-bis(methyloxy)-5-{(1*R*)-1-[(phenylmethyl)oxy]propyl}-2,5-dihydropyrazine

(1*R*)-1-[(2*S*,5*R*)-5-(1-methylethyl)-3,6-bis(methyloxy)-2,5-dihydro-2-pyrazinyl]-1-propanol (0.8 g, 3.30 mmol) was dissolved in DMF (20 mL) and the solution was cooled to 0 °C. Sodium hydride (0.15 g, 3.80 mmol) was added and stirred 30 min and then benzyl bromide (0.62 g, 3.63 mmol) was added and stirred overnight. The reaction was diluted with water, extracted with ethyl acetate, and the extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 0.51 g of product.

Step 3. Methyl (3*R*)-3-[(phenylmethyl)oxy]-L-norvalinate

(2*R*,5*S*)-2-(1-Methylethyl)-3,6-bis(methyloxy)-5-{(1*R*)-1-[(phenylmethyl)oxy]propyl}-2,5-dihydropyrazine (0.51 g, 1.53 mmol) was dissolved in CH_3CN (6 mL) and 0.5 N HCl (6.1 mL) was added and the solution was stirred for 4 days. Sodium chloride and Et_2O were added to the solution and the pH was adjusted to 9 with ammonium hydroxide. The mixture was extracted with Et_2O, the extracts were combined and concentrated to afford 0.49 g of oil as a 1:1 mixture of desired product and methyl D-valinate.

Step 4. Methyl (3*R*)-*N*-[(3-amino-2-naphthalenyl)carbonyl]-3-[(phenylmethyl)oxy]-L-norvalinate

A 1:1 mixture of methyl (3*R*)-3-[(phenylmethyl)oxy]-L-norvalinate and methyl D-valinate (0.49 g, 1.32 mmol) and 3-amino-2-naphthalenecarboxylic acid (0.35 g, 1.59 mmol) was dissolved in DMF (10 mL) and diisopropylethylamine (0.51 g, 3.98 mmol) was added followed by HATU (0.60 g, 1.59 mmol). The solution was stirred overnight and then diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$), concentrated onto SiO_2, and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 0.48 g of a 1:1 mixture of product and methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-D-valinate.

Step 5. Methyl (3*R*)-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvalinate

A 1:1 mixture of methyl (3*R*)-*N*-[(3-amino-2-naphthalenyl)carbonyl]-3-[(phenylmethyl)oxy]-L-norvalinate and methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-D-valinate (0.48 g, 0.68 mmol) was dissolved in pyridine (7 mL) and 2,4,6-trimethylphenylisocyanate (0.33 g, 2.03 mmol) was added and stirred for 3 h. The solution was diluted with ethyl acetate, washed with 1 M HCl, dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO2 eluting with ethyl acetate/hexanes afforded 0.48 g of a 1:1 mixture of product and methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-valinate.

Step 6. (3*R*)-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline

A 1:1 mixture of methyl (3*R*)-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvalinate and methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-valinate (0.48 g, 0.46 mmol) was dissolved in 1:1 THF/MeOH (3 mL) and 2 M LiOH (2.3 mL) was added. The reaction was stirred for 3 h, acidified with 1 M HCl (4.6 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. A 100 mg sample of the residue was dissolved in MeOH (1 mL) and purified by reverse-phase HPLC to afford 34 mg of product. MS m/z 554 (M+H).

Example 330: *N*-(cyclohexylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide

Step 1. 3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid

3-amino-2-naphthalenecarboxylic acid (5.00 g, 26.71 mmol) in 100 mL of DMF was treated with triethylamine (5.40g, 53.37 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (4.7 g, 29.16 mmol) and was heated to 70°C for ca. 3 hours. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated to give 7.95 g (84%) of product.

Step 2. *N*-(cyclohexylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide

3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.1 g, 0.29 mmol) and (cyclohexylmethyl)amine (36 mg, 0.31 mmol) were dissolved in DMF (1.5 mL) and diisopropylethylamine (74 mg, 0.1 mL) and HATU (0.12 g, 0.31 mmol) were added and stirred ca. 18 h. The solution was diluted with ethyl acetate and washed with water. The extracts were dried ($MgSO_4$), concentrated onto SiO_2, and purified by chromatography on SiO_2 to afford 34 mg of product. ES MS m/z 444 (M+H).

Example 331: *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)-beta-alanine

Step 1. Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(phenylmethyl)-beta-alaninate

3-Amino-2-naphthoic acid (0.2 g, 1.0 mmol) and ethyl *N*-(phenylmethyl)-beta-alaninate (0.24 g, 1.17 mmol) were dissolved in DMF (5 mL) and HATU (0.44 g, 1.17 mmol) and diisopropylethylamine (0.27 g, 2.13 mmol) were added. The solution was stirred ca. 90 min, diluted with ethyl acetate and washed with water and brine. The organic layer was dried ($MgSO_4$), concentrated onto SiO_2, and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 0.34 g of product as a brown solid.

Step 2. Ethyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)-beta-alaninate

Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(phenylmethyl)-beta-alaninate (0.11 g, 0.30 mmol) was dissolved in DMF (2 mL) and triethylamine (62 mg, 0.61 mmol) was added followed by 2,6-dichlorophenyl isocyanate (69 mg, 0.36 mmol). The reaction was heated to 70 °C for ca. 60 min and cooled. The solution was diluted with ethyl acetate, washed with water, and dried ($MgSO_4$). The extracts were concentrated onto SiO_2 and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 0.11 g of product as an oil.

Step 3. *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)-beta-alanine

Ethyl *N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)-beta-alaninate (0.1 g, 0.17 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 1 M NaOH (0.88 mL) was added. The solution was heated to 50 °C for 90 min and cooled. The reaction was diluted with water, acidified with 1 M HCl (1.1 mL), and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated to afford 45 mg of product as a solid. ES MS m/z 536 (M+H).

Example 332: *N*-(phenylmethyl)-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Step 1. Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(phenylmethyl)glycinate

3-Amino-2-naphthoic acid (0.2 g, 1.0 mmol) and ethyl *N*-(phenylmethyl)glycinate (0.23 g, 1.17 mmol) were dissolved in DMF (5 mL) and diisopropylamine (0.41 g, 3.20 mmol) and HATU (0.45 g, 1.17 mmol) were added. The reaction was heated to 50 °C for 1 hour and then stirred ca. 18 h at RT. The reaction was diluted with ethyl acetate and washed with water and brine. The extracts were dried ($MgSO_4$), concentrated onto SiO_2, and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 0.35 g of product as a gold oil.

Step 2. Ethyl *N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)glycinate

Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*N*-(phenylmethyl)glycinate (0.1 g, 0.27 mmol) was dissolved in DMF (4 mL) and triethylamine (56 mg, 0.55 mmol) and 2,4,6-trichlorophenyl isocyanate (74 mg, 0.33 mmol) were added. The reaction was heated to 70 °C for 2 h and cooled. The reaction was diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated

onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 90 mg of product.

Step 3. *N*-(phenylmethyl)-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine

Ethyl *N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-(phenylmethyl)glycinate (90 mg, 0.15 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 1 M NaOH (0.77 mL) was added. The solution was heated to 50 °C for 2 h and stirred an additional 18 h. The reaction was diluted with water, acidified with 1 M HCl (0.8 mL), and extracted with ethyl acetate. The extracts were dried (MgSO4) and concentrated. The residue was dissolved in MeOH (1 mL) and purified by reverse phase HPLC. The fractions were concentrated to afford 47 mg of product as a tan solid. . ES MS m/z 577 (M+H).

Example 333: 1-{[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-piperidinecarboxylic acid

Step 1. Ethyl 1-[(3-amino-2-naphthalenyl)carbonyl]-3-piperidinecarboxylate

3-Amino-2-naphthoic acid (0.25 g, 1.33 mmol) and ethyl nipecotate (0.22 g, 1.47 mmol) were dissolved in DMF (5 mL) and HATU (0.56 g, 1.47 mmol) and diisopropylethylamine (0.34 g, 2.67 mmol) were added. The solution was stirred 90 min, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried (MgSO4) and concentrated onto SiO2. Chromatography on SiO2 eluting with ethyl acetate/hexanes provided 0.35 g of product as an oil.

Step 2. Ethyl 1-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-piperidinecarboxylate

Ethyl 1-[(3-amino-2-naphthalenyl)carbonyl]-3-piperidinecarboxylate (0.1 g, 0.30 mmol) was dissolved in DMF (2 mL) and triethylamine (62 mg, 0.61 mmol) and 2,6-

dichlorophenyl isocyanate (69 mg, 0.36 mmol) were added. The reaction was heated to 70 °C for 1 h and cooled. The reaction was diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 38 mg of product.

Step 3. 1-{[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-piperidinecarboxylic acid

Ethyl 1-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-piperidinecarboxylate (32 mg, 0.062 mmol) was dissolved in 1:1 THF/MeOH (1 mL) and 1 M NaOH (0.31 mL) was added. The solution was heated to 50 °C for 90 min and cooled. The reaction was diluted with water, acidified with 1 M HCl (0.4 mL), and extracted with ethyl acetate. The extracts were dried (MgSO4) and concentrated to afford 23 mg of product as a colorless solid. ES MS m/z 486 (M+H).

Example 334: 1-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-proline

Step 1. 1,1-dimethylethyl 1-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-prolinate

A solution of HATU (0.37 g, 0.97 mmol) and 3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.29 g, 0.88 mmol) in DMF (5 mL) were stirred at RT for 5 minutes then 1,1-dimethylethyl L-prolinate (0.18 g, 1.06 mmol) was added. After 3h, ethyl acetate and 1N HCl were added. The organic layer was washed with 1N HCl, water, brine solution, dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate over 25 minutes) to give 0.28 g (65%) of desired product.

Step 2. 1-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-proline

TFA (3 mL) was added to a solution of 1,1-dimethylethyl 1-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-prolinate (0.30 g, 0.62 mmol) in DCM (10 mL). The solution was stirred at RT with occasional heating until all the starting material was consumed as evident from TLC. The solution was concentrated to dryness and DCM (5 mL) and MeOH (1 mL) were added, followed by Et_2O (20 mL) and hexanes (5 mL). The resulting precipitate was filtered and dried under vacuum to give 0.026 (10%) of the title product as a white solid. ES MS m/z 430 (M-H).

Example 335: 3-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-valine

Step 1. *N*-[(3-amino-2-naphthalenyl)carbonyl]-3-methyl-L-valine

HATU (0.88 g, 2.33 mmol) was added to a mixture of 3-amino-2-naphthalenecarboxylic acid (0.36 g, 1.94 mmol), methyl 3-methyl-L-valinate hydrochloride (0.40 g, 2.14 mmol) and N,N-diisopropylethylamine (0.68 mL, 3.88 mmol) in DMF (10 mL). The solution was stirred at RT for 16 h then saturated $NaHCO_3$ solution and ethyl acetate were added. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give 0.40 g (66%) of the title compound as a brown oil.

Step 2. 3-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-valine

A solution of *N*-[(3-amino-2-naphthalenyl)carbonyl]-3-methyl-L-valine (0.23 g, 0.74 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.13 g, 0.81 mmol) in dry pyridine (3 mL) was stirred at RT for 16 h, then concentrated to dryness. A 1N HCl solution and ethyl acetate were added. The organic layer was washed with brine solution,

dried over $MgSO_4$, filtered and concentrated. The solid was dissolved in MeOH (2 mL) and THF (2 mL) to which LiOH (0.18 g, 7.40 mmol) in water (5 mL) was added. After 3 h, TLC shows no remaining starting material. A 1N HCl solution and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by reverse-phase HPLC (Gilson: MeCN, 1% TFA/water) to give 0.060 g (18%) of the title compound as a white solid. ES MS m/z 460 (M-H).

Example 336: (3*R*)-3-phenyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoic acid

Step 1. 1,1-dimethylethyl (3*R*)-3-{[(3-amino-2-naphthalenyl)carbonyl]amino}-3-phenylpropanoate

HATU (0.47 g, 1.24 mmol) was added to a mixture of 3-amino-2-naphthalenecarboxylic acid (0.21 g, 1.13 mmol), 1,1-dimethylethyl (3*R*)-3-amino-3-phenylpropanoate (0.30 g, 1.36 mmol) and N,N-diisopropylethylamine (0.40 mL, 2.26 mmol) in DMF (10 mL). The solution was stirred at RT for 2 h then saturated $NaHCO_3$ solution and ethyl acetate were added. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give 0.42 g (94%) of the title compound as a brown oil.

Step 2. (3*R*)-3-phenyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoic acid

A solution of 1,1-dimethylethyl (3*R*)-3-{[(3-amino-2-naphthalenyl)carbonyl]amino}-3-phenylpropanoate (0.38 g, 0.97 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.17 g, 1.07 mmol) in dry pyridine (5 mL) were stirred at RT for 16 h. Water and 1N HCl (3 mL) were added followed by ethyl acetate. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate over 25 minutes) to give an orange solid.

The solid was dissolved in DCM and TFA (2 mL) was added. The solution was heated to reflux until no starting material remained then the solvent was removed via rotary evaporation. The crude material was purified by reverse-phase HPLC (Gilson: MeCN, 1% TFA/water) to give 0.064 g (13% over two steps) of the title compound as a white solid. ES MS m/z 494 (M-H).

Example 337: 1,1-dimethylethyl (3*R*)-3-cyclohexyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoate

Step 1. 1,1-dimethylethyl (3*R*)-3-amino-3-cyclohexylpropanoate

A mixture of 1,1-dimethylethyl (3*R*)-3-amino-3-phenylpropanoate (0.50 g, 2.26 mmol) and Rh/Al_2O_3 (0.10 g) in MeOH (10 mL) under hydrogen (60 psig) was heated to 80 °C for 24 h. The reaction was cooled to RT, carefully vented, and then filtered through Celite. The filtrate was concentrated to give 0.41 g (80%) of the title compound as a yellow oil.

Step 2. 1,1-dimethylethyl (3R)-3-{[(3-amino-2-naphthalenyl)carbonyl]amino}-3-cyclohexylpropanoate

HATU (0.96 g, 2.53 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.34 g, 1.81 mmol), 1,1-dimethylethyl (3*R*)-3-amino-3-cyclohexylpropanoate (0.41 g, 1.81 mmol) and N,N-diisopropylethylamine (0.69 mL, 3.98 mmol) in DMF (10 mL). The solution was stirred at RT for 48 h then saturated $NaHCO_3$ solution and ethyl acetate were added. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate over 25 minutes) to give 0.57 g (80%) of the title compound as a yellow solid.

Step 3. 1,1-dimethylethyl (3*R*)-3-cyclohexyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoate

A solution of 1,1-dimethylethyl (3R)-3-{[(3-amino-2-naphthalenyl)carbonyl]amino}-3-cyclohexylpropanoate (0.17 g, 0.43 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.084 g, 0.52 mmol) in dry pyridine (3 mL) were stirred at RT for 16 h then concentrated to dryness via rotary evaporation. 1N HCl and ethyl acetate were added. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate over 25 minutes) to give 0.13 g (54%) of the title compound as an orange solid. ES MS m/z 556 (M-H).

Example 338: (3*R*)-3-cyclohexyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoic acid

1,1-dimethylethyl (3*R*)-3-cyclohexyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoate (0.11 g, 0.19 mmol) was dissolved in DCM and TFA (1.5 mL) was added. The solution was stirred for 6 h then concentrated to dryness via rotary evaporation. The crude material was dissolved in a minimal amount of DCM then triturated with Et_2O and hexanes. The solid was filtered and dried under vacuum to give 0.077 g (81%) of the title compound as a white powder. ES MS m/z 500 (M-H).

Example 339: (3*R*)-4-methyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)pentanoic acid

Step1. 1,1-dimethylethyl [(1*S*)-1-(iodomethyl)-2-methylpropyl]carbamate

Iodine (8.74 g, 34.7 mmol) was added to a suspension of polystyrene-supported diphenylphosphine (15.8 g, 34.7 mmol) in DCM (300 mL), After 15 min, imidazole (2.7 g, 39.5 mmol) was added and after 15 min a solution of 1,1-dimethylethyl [(1*S*)-1-(hydroxymethyl)-2-methylpropyl]carbamate (3.2 g, 15.8 mmol) in DCM (60 mL)

was added. The mixture was stirred overnight then filtered through Celite. The solution was washed with 0.5M $Na_2S_2O_3$ solution, water, dried over $MgSO_4$, filtered and concentrated to give 2.3 g of the title compound with some unreacted 1,1-dimethylethyl [(1*S*)-1-(hydroxymethyl)-2-methylpropyl]carbamate impurity. The material was used without further purification.

Step 2. 1,1-dimethylethyl [(1*R*)-1-(cyanomethyl)-2-methylpropyl]carbamate

A solution of 1,1-dimethylethyl [(1*S*)-1-(iodomethyl)-2-methylpropyl]carbamate (2.3 g) and tetraethylammonium cyanide (1.26 g, 8.09 mmol) in DCM (100 mL) was heated to reflux for 4 h then concentrated to dryness. The crude material was purified on silica gel using an ISCO chromatography system (100% hexanes to 100% ethyl acetate over 25 min) to give 0.67 g (20% over two steps) of the title compound as a white solid.

Step 3. methyl (3*R*)-3-amino-4-methylpentanoate hydrochloride

HCl gas was bubbled into MeOH (10 mL) at 0 °C until saturated and then 1,1-dimethylethyl [(1*R*)-1-(cyanomethyl)-2-methylpropyl]carbamate (0.60 g, 2.83 mmol) was added. A little more HCl gas was bubbled in then the tube was sealed at stirred at RT for 16 h. The vessel was vented and water (ca. 7 drops) was added. The solution was stirred for 1 h then concentrated. Et_2O and MeOH were added and the solution was concentrated to dryness. Et_2O was again added and the solution concentrated to give 0.63 g of the title compound as a white solid.

Step 4. methyl (3*R*)-3-{[(3-amino-2-naphthalenyl)carbonyl]amino}-4-methylpentanoate

HATU (1.43 g, 3.77 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.59 g, 3.14 mmol), methyl (3*R*)-3-amino-4-methylpentanoate hydrochloride (0.63 g, 3.46 mmol) and N,N-diisopropylethylamine (1.20 mL, 6.91 mmol) in DMF (6 mL). The solution was

stirred at RT for 6 h then ethyl acetate and saturated $NaHCO_3$ solution were added. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate over 25 minutes) to give 0.25 g (25%) of the title compound as a yellow solid.

Step 5. (3*R*)-4-methyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)pentanoic acid

A solution of methyl (3*R*)-3-{[(3-amino-2-naphthalenyl)carbonyl]amino}-4-methylpentanoate (0.19 g, 0.60 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.115 g, 0.71 mmol) in dry pyridine (3 mL) was stirred at RT for 24 h then concentrated to dryness via rotary evaporation. 1N HCl and ethyl acetate were added. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in THF (ca. 2 mL) and MeOH (ca. 2 mL) and a solution of LiOH (0.20 g, 8.33 mmol) in water (5 mL) was added. The mixture was stirred until no starting material remained as evident from TLC then 1N HCl and ethyl acetate were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by reverse-phase HPLC (Gilson: MeCN, 1% TFA/water) to give 0.11 g (40% over two steps) of the title compound as a white solid. ES MS m/z 460 (M-H).

Example 340: *N*-[(1*S*)-2-methyl-1-(1*H*-tetrazol-5-yl)propyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide

Step 1. [(1*S*)-2-methyl-1-(1*H*-tetrazol-5-yl)propyl]amine trifluoroacetate

A mixture of 1,1-dimethylethyl [(1*S*)-1-cyano-2-methylpropyl]carbamate (2.00 g, 10.09 mmol), sodium azide (1.30 g, 20.20 mmol) and $ZnBr_2$ (1.14 g, 5.05 mmol) in water (30 mL) and iPrOH (15 mL) were heated to 80 °C for 16 h then cooled to RT. Ethyl acetate (30 mL) and 3N HCl (5 mL) were added. The aqueous layer was

extracted again with ethyl acetate and the organic layers were combined and concentrated to dryness via rotary evaporation to give a white solid. ^{1}H NMR showed a mixture of the desired product and starting material (nitrile). Therefore this material was re-dissolved in water (30 mL) and iPrOH (15 mL) then sodium azide (1.30 g, 20.20 mmol) and $ZnBr_2$ (1.14 g, 5.05 mmol) were added. The mixture was heated to 100 °C for 6 h then the mixture was cooled to RT. Ethyl acetate (30 mL) and 3N HCl (5 mL) were added. The aqueous layer was extracted again with ethyl acetate and the organic layers were combined and concentrated to dryness via rotary evaporation to give a white solid. The material (ca. 0.50 g) was dissolved in DCM and TFA (1 mL) was added. After 2 h, the solution was concentrated to dryness via rotary evaporation to 0.20 g (8%) the title compound.

Step 2. 3-amino-*N*-[(1*S*)-2-methyl-1-(1*H*-tetrazol-5-yl)propyl]-2-naphthalenecarboxamide

HATU (0.33 g, 0.86 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.15 g, 0.80 mmol), [(1*S*)-2-methyl-1-(1*H*-tetrazol-5-yl)propyl]amine trifluoroacetate (0.20 g, 0.78 mmol) and N,N-diisopropylethylamine (0.4 mL, 2.34 mmol) in DMF (10 mL). The solution was stirred at RT for 2 h then ethyl acetate and brine solution were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude material was stirred with 2-isocyanato-1,3,5-trimethylbenzene (0.15 g, 0.93 mmol) in dry pyridine (3 mL) at RT for 3 h then concentrated to dryness via rotary evaporation. 1N HCl and ethyl acetate were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by reverse-phase HPLC (Gilson: MeCN, 1% TFA/water) to give 0.06 g (16% over two steps) of the title compound as a tan solid. ES MS m/z 470 (M-H).

Example 341: (2*S*)-(4,4-difluorocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

And

Example 342: *N*-[(*S*)-cyano(4,4-difluorocyclohexyl)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide

Step 1. (4,4-difluorocyclohexyl)methanol

A solution of 4,4-difluorocyclohexanecarboxylic acid (2.00 g, 12.20 mmol) in THF (6 mL) was added dropwise to $NaBH_4$ (0.46 g, 12.20 mmol) in THF (10 mL) at 0 °C. After stirring for 1h, neat BF_3-Et_2O (1.54 mL, 12.20 mmol) was added dropwise and the resulting white slurry was stirred at RT overnight. EtOH (12 mL) was added slowly and the mixture was stirred for 0.5h then concentrated via rotary evaporation. DCM (300 mL) and water (300 mL) were added. The aqueous layer was extracted again with DCM and the combined organic layers were dried over $MgSO_4$, filtered and concentrated to give 2.1 g (115%) of the title compound as a clear oil. Note: although some DCM still remained (as evident from ^1H NMR) it was not concentrated excessively due to the potential volatility of the product.

Step 2. 4,4-difluorocyclohexanecarbaldehyde

Dess-Martin periodinane (7.21 g, 17.00 mmol) was added as a solid to a solution of (4,4-difluorocyclohexyl)methanol (1.70 g, 11.30 mmol) in DCM (150 mL) at -78 °C. The mixture was allowed to warm to RT and water (ca. 3 drops) was added. After 3 h at RT, the mixture was poured into a 1:1 mixture of saturated $NaHCO_3$ and $Na_2S_2O_3$ solutions (90 mL each) and then stirred for 0.5 h. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated to give 1.70 g (100%) of the title compound.

Step 3. (S)-*N*-[(1*E*)-(4,4-difluorocyclohexyl)methylidene]-4-methylbenzenesulfinamide

Titanium (IV) ethoxide (12.0 mL, 57.5 mmol) was added to a solution of 4,4-difluorocyclohexanecarbaldehyde (1.7 g, 11.5 mmol) and (S)-4-methylbenzenesulfinamide (1.78 g, 11.5 mmol) in DCM (25 mL). The yellow solution was heated to reflux for 5 h then cooled to RT. Water (15 mL) was added and the thick slurry was stirred with a spatula. DCM was added and the solid was filtered off and washed with DCM. The combined organic layers were washed with water (3x's), brine, dried over $MgSO_4$, filtered and concentrated via rotary evaporation at RT to give 2.44 g (75%) of the title compound.

Step 4. *N*-[(S)-cyano(4,4-difluorocyclohexyl)methyl]-(S)-4-methylbenzenesulfinamide

A 1N solution of diethylaluminum cyanide (12.9 mL, 12.9 mmol) in toluene was added to a solution of iPrOH (0.65 mL, 8.49 mmol) in THF (100 mL) at RT. After 0.5 h, the solution was cooled to -78 °C and (S)-*N*-[(1*E*)-(4,4-difluorocyclohexyl)methylidene]-4-methylbenzenesulfinamide (2.44 g, 8.59 mmol) in THF (200 mL) was added. The reaction was warmed to RT and stirred for 3.5 h, after which saturated NH_4Cl solution (4 mL) was added followed by water (200 mL) and ethyl acetate (200 mL). The mixture was filtered through Celite and the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate over 25 minutes) to give 0.70 g (26%) of the title compound as a white solid. ^1H NMR shows a 13:1 mixture of diastereomers (84% d.e.).

Step 5. Mixture of methyl (2*S*)-amino(4,4-difluorocyclohexyl)ethanoate hydrochloride and (2*S*)-amino(4,4-difluorocyclohexyl)ethanenitrile hydrochloride

HCl gas was bubbled into a solution of *N*-[(S)-cyano(4,4-difluorocyclohexyl)methyl]-(S)-4-methylbenzenesulfinamide (0.70 g, 2.24 mmol) in MeOH (15 mL) and water (0.25 mL) in a sealable tube until saturated. The tube was sealed and heated to 100 °C for 24 h. The vessel was cooled to RT, carefully vented, and the solution

was concentrated. Ethyl acetate and saturated $NaHCO_3$ solution were added. The organic layer was dried over $MgSO_4$, filtered and concentrated The crude material was converted to the HCl salt with 1N HCl in Et_2O and the solid was washed with hexanes/Et_2O and dried under vacuum to give 0.41 g (75%) of a mixture of the title compounds as a white solid.

Step 6. Mixture of methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(4,4-difluorocyclohexyl)ethanoate and 3-amino-*N*-[(*S*)-cyano(4,4-difluorocyclohexyl)methyl]-2-naphthalenecarboxamide

A mixture of methyl (2*S*)-amino(4,4-difluorocyclohexyl)ethanoate hydrochloride and (2*S*)-amino(4,4-difluorocyclohexyl)ethanenitrile hydrochloride (0.35 g, 1.44 mmol) was dissolved in DMF (5 mL). Next, 3-amino-2-naphthalenecarboxylic acid (0.27 g, 1.44 mmol) and N,N-diisopropylethylamine (1.5 mL, 8.6 mmol) were added followed by HATU (0.77 g, 2.02 mmol). The solution was stirred at RT for 24 h then ethyl acetate and saturated $NaHCO_3$ solution were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give 0.66 g of a mixture of the title compounds.

Step 7. Mixture of methyl (2*S*)-(4,4-difluorocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate and *N*-[(*S*)-cyano(4,4-difluorocyclohexyl)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide

A mixture of methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(4,4-difluorocyclohexyl)ethanoate and 3-amino-*N*-[(*S*)-cyano(4,4-difluorocyclohexyl)methyl]-2-naphthalenecarboxamide (0.66 g, 1.76 mmol) was stirred with 2-isocyanato-1,3,5-trimethylbenzene (0.34 g, 2.11 mmol) in dry pyridine (3 mL) at RT for 4 h then concentrated to dryness via rotary evaporation. 1N HCl and ethyl acetate were added. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$, filtered and concentrated to give 0.40 g (42%) of a mixture of the title compounds.

Step 8. (2*S*)-(4,4-difluorocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

and

N-[(*S*)-cyano(4,4-difluorocyclohexyl)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide

A mixture of methyl (2*S*)-(4,4-difluorocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate and *N*-[(*S*)-cyano(4,4-difluorocyclohexyl)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide (0.40 g, 0.74 mmol) was dissolved in THF (ca. 2 mL) and MeOH (ca. 2 mL) and a solution of LiOH (0.10 g, 4.17 mmol) in water (5 mL) was added. The mixture was stirred until no starting material remained as evident from LC/MS (ca. 4 h) then 1N HCl and ethyl acetate were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate to 5% MeOH/ethyl acetate) to give two products:

0.26 g (68%) of (2*S*)-(4,4-difluorocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid. ES MS m/z 522 (M-H).

and

0.15 g (40%) of *N*-[(*S*)-cyano(4,4-difluorocyclohexyl)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide. ES MS m/z 503 (M-H).

Example 343: (2*S*)-cyclopentyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-amino(cyclopentyl)ethanoate trifluoroacetate

The dicyclohexylamine salt of (2*S*)-cyclopentyl({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethanoic acid (2.0 g, 4.72 mmol) was dissolved in ethyl acetate and converted to the free acid with 1N HCl solution. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. This material (1.0 g, 4.1 mmol) was dissolved in ethyl acetate (15 mL) and methanol (15 mL) then a 2M solution of (trimethylsilyl)diazomethane in hexanes (4.11 mL, 8.23 mmol) was added dropwise. After 4 h, the yellow solution was concentrated to dryness. The crude material was dissolved in DCM and TFA (2 mL) was added. After 1.5 h, the solution was concentrated to dryness to give 0.82 (74%) of the title compound as a yellow oil.

Step 2. methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclopentyl)ethanoate

HATU (1.62 g, 4.24 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.57 g, 3.03 mmol), methyl (2*S*)-amino(cyclopentyl)ethanoate trifluoroacetate (0.82 g, 3.03 mmol) and N,N-diisopropylethylamine (2.0 mL, 11.5 mmol) in DMF (10 mL). The solution was stirred at RT for 16 h then ethyl acetate and saturated $NaHCO_3$ solution were added. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 50% ethyl acetate/hexanes) to give 0.60 g (61%) of the title compound as an orange solid.

Step 3. methyl (2*S*)-cyclopentyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

A solution of methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclopentyl)ethanoate (0.21 g, 0.64 mmol) and 1,3,5-trichloro-2-isocyanatobenzene (0.157 g, 0.71 mmol) in dry pyridine (3 mL) were stirred at RT for 16 h then concentrated to dryness via rotary evaporation. 1N HCl

and ethyl acetate were added. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give 0.31 g (89%) of the title compound as a white solid.

Step 3. (2*S*)-cyclopentyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

LiOH (0.30 g, 12.50 mmol) in hot water (10 mL) was added to a solution of methyl (2*S*)-cyclopentyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.26 g, 0.47 mmol) in THF (10 mL) and MeOH (5 mL). The mixture was stirred until no starting material remained as evident from TLC then 1N HCl and ethyl acetate were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in hot EtOH and hexane was added. The solution was allowed to cool to RT overnight then the resulting solid was filtered and dried under vacuum to give 0.23 g (94%) of the title compound as a white solid. ES MS m/z 533 (M-H).

Example 344: (2*S*)-cyclopentyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-amino(cyclopentyl)ethanoate hydrochloride

(2*S*)-cyclopentyl({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethanoic acid dicyclohexylamine (2.9 g, 6.84 mmol) was dissolved in ethyl acetate (400 mL) and washed with 1N HCl (200 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give (2*S*)-cyclopentyl({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethanoic acid as the free acid. The clear oil was dissolved in ethyl acetate (25 mL) and MeOH (25 mL) and a 2M solution of TMS-diazomethane in Et_2O (6.84 mL, 13.68 mmol) was added slowly. (Note: yellow color persists at the end of the addition). The solution was stirred overnight then concentrated to dryness to give a white solid which was dissolved in CH_2Cl_2 (30

mL) and TFA (5 mL). After 3 h the solution was concentrated to give 2.2 g (119%) of the title compound as a yellow oil. Some of the material was converted to the HCl salt in an attempt to solidify the compound.

Step 2. methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclopentyl)ethanoate

HATU (2.57 g, 6.77 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.99 g, 4.51 mmol), methyl (2*S*)-amino(cyclopentyl)ethanoate hydrochloride (0.87 g, 4.51 mmol), and N,N-diisopropylethylamine (3.25 mL, 13.53 mmol) in DMF (15 mL) at RT. After 3 h, saturatued $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 40 min) to give 0.75 g (51%) of the title compound as a yellow solid (ca. 80% pure).

Step 3. methyl (2*S*)-cyclopentyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

A solution of methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclopentyl)ethanoate (0.55 g, 1.69 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.54 g, 3.37 mmol) in pyridine (5 mL) were stirred at RT for 4 h. The solvent was removed under reduced pressure and ethyl acetate (100 mL) and 1N HCl (100 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give a pale yellow solid (ca. 80% pure by ^1H NMR). The crude material was purified on silica gel (ISCO chromatography: 100 % hexanes to 80% ethyl acetate/hexanes) to give 0.48 g (58%) of a yellow solid.

Step 4. (2*S*)-cyclopentyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

LiOH (0.20 g, 8.33 mmol) in hot water (25 mL) was added to a solution of methyl (2*S*)-cyclopentyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.48 g, 0.98 mmol) in MeOH/THF (1:1, 10mL). The reaction was stirred until no starting material remained then 1N HCl and ethyl acetate were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by reverse-phase HPLC (Gilson: MeCN, 1% TFA/water) to give 0.083 g (18%) of the title compound as a white solid. ES MS m/z 472 (M-H).

Example 345: 1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

Step 1. methyl 1,4-dioxaspiro[4.5]dec-8-ylidene({[(phenylmethyl)oxy]carbonyl}amino)acetate

DBU (3.8 mL, 25.4 mmol) was added dropwise to a solution of 1,4-dioxaspiro[4.5]decan-8-one (3.31 g, 21.2 mmol) and methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)oxy]carbonyl}amino)acetate (7.02 g, 21.20 mmol) in DCM (50 mL) at RT. After 3 days, the brown solution was concentrated to dryness and ethyl acetate and water were added. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give 5.6 g (73%) of the title compound as an orange oil.

Step 2. methyl amino(1,4-dioxaspiro[4.5]dec-8-yl)acetate

A mixture of methyl 1,4-dioxaspiro[4.5]dec-8-ylidene({[(phenylmethyl)oxy]carbonyl}amino)acetate (5.2 g, 14.4 mmol) and 10% Pd/C (0.2 g) in MeOH (50 mL) was stirred under H_2 (60 psig) overnight. The next day, the reaction was carefully vented, diluted with ethyl acetate, filtered through

Celite, and concentrated to dryness. The crude material was dissolved in hot EtOH and hexane was added slowly until cloudy. The solution was allowed to cool slowly to RT and the resulting solid was filtered and dried under vacuum to give 2.6 g (79%) of the title compound as an off-white solid. ^{1}H NMR shows material is only ca. 70% pure.

Step 3. methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}(1,4-dioxaspiro[4.5]dec-8-yl)acetate

HATU (1.53 g, 4.01 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.50 g, 2.67 mmol), methyl amino(1,4-dioxaspiro[4.5]dec-8-yl)acetate (0.61 g, 2.67 mmol), and N,N-diisopropylethylamine (1.9 mL, 8.01 mmol) in DMF (15 mL) at RT. After 5 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 40 min) to give 0.37 g (34%) of the title compound as a yellow solid. ^{1}H NMR shows material is only ca. 85% pure.

Step 4. 1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

A solution of methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}(1,4-dioxaspiro[4.5]dec-8-yl)acetate (0.37 g, 0.92 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.18 g, 1.11 mmol) in pyridine (5 mL) were stirred at RT for 5 h. The solvent was removed under reduced pressure and ethyl acetate (100 mL) and 0.1N HCl (100 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give a pale yellow solid. The crude material was dissolved in THF (10 mL) and MeOH (10 mL) then a hot solution of LiOH (0.30 g, 12.50 mmol) in water (25 mL) was added. The yellow solution was stirred until no starting material remained as evident by TLC

(100% ethyl acetate) then ethyl acetate (200 mL) and 1N HCl solution (100 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give 0.46 g of yellow solid (ca. ~85% purity). A portion of the crude material (~0.075 g) was purified by reverse phase HPLC (Gilson: MeCN, 1% TFA/water) to give 0.070 g of the title compound as a pinkish solid. ES MS m/z 544 (M-H).

Example 346: (4-oxocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

Pyridinium p-toluenesulfonate (ca. 100 mg) was added to a solution of 1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid (0.40 g, 0.73 mmol) in acetone (10 mL) and water (10 mL) and the solution was heated at 70 °C. After 24 h, TLC and LCMS show no starting material remaining so 1N HCl (100 mL) and ethyl acetate (100 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give 0.28 g of yellow solid (85% purity by ^1H NMR). Reverse phase HPLC (Gilson: MeCN, 1% TFA/water) gave 0.17 g (46%) of the title compound as a white solid. ES MS m/z 500 (M-H).

Example 347: (cis and trans)-[4-(cyclobutylamino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

Step 1. methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}(1,4-dioxaspiro[4.5]dec-8-yl)acetate

HATU (2.04 g, 5.37 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.67 g, 3.58 mmol), methyl amino(1,4-dioxaspiro[4.5]dec-8-yl)acetate (0.82 g, 3.58 mmol), and N,N-diisopropylethylamine (2.6 mL, 10.7 mmol) in DMF (50 mL) at RT. After 5 h, saturatued $NaHCO_3$ solution (200 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude

product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethylacetate/hexanes over 40 min) to give 1.02 g (71%) of the title compound as a yellow solid.

Step 2. methyl 1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetate

A solution of methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}(1,4-dioxaspiro[4.5]dec-8-yl)acetate (0.95 g, 2.38 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.78 g, 4.77 mmol) in pyridine (20 mL) were stirred at RT for 5 h. The solvent was removed under reduced pressure and ethyl acetate (200 mL) and 0.1N HCl (200 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give 1.17 g (88%) of a pale yellow solid.

Step 3. 1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

LiOH (0.80 g, 33.33 mmol) was dissolved in hot water (25 mL) and added while still hot to a solution of methyl 1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetate (0.69 g, 1.23 mmol) in THF (10 mL) and MeOH (10 mL). The yellow solution was stirred until no starting material remained as evident by TLC (100% ethyl acetate) then ethyl acetate (300 mL) and 1N HCl solution (100 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give 0.66 g (98%) of the title compound as a yellow solid.

Step 4. (4-oxocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

Pyridinium p-toluenesulfonate (ca. 200 mg) was added to a solution of 1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-

naphthalenyl]carbonyl}amino)acetic acid (0.65 g, 1.19 mmol) in acetone (20 mL) and water (20 mL) and the solution was heated at 70 °C for 24 h. 1N HCl (100 mL) and ethyl acetate (200 mL) added. The organic layer was washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated to give 0.56 g (94%) of the title compound as a yellow solid. ES MS m/z 500 (M-H).

Step 5. (cis and trans)-[4-(cyclobutylamino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

$NaB(OAc)_3H$ (0.057 g, 0.27 mmol) was added to a solution of (4-oxocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid (0.092 g, 0.18 mmol) and cyclobutylamine (0.12 g, 1.69 mmol) in DCE (5 mL). The solution was stirred for 16 h then ethyl acetate (100 mL) and water (50 mL) were added and the pH was adjusted to ca. 7 with 1N HCl. The organic layer was separated. The aqueous layer was acidified slightly (to ca. pH 3) with 1N HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 0.015 g (15%) of the title compound as a mixture of cis- and trans-isomers. APCI MS m/z 557 (M+H).

Example 348: (cis and trans)-[4-(4-morpholinyl)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

$NaB(OAc)_3H$ (0.16 g, 0.78 mmol) was added to a solution of (4-oxocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid (0.13 g, 0.26 mmol) and morpholine (0.12 g, 1.38 mmol) in DCE (10 mL). The solution was stirred for 16 h then the solution was concentrated. MeOH (5 mL) and water (2 mL) were added. After stirring for 15 min, the mixture was concentrated to dryness and taken up in 3 mL of MeOH. The compound was purified by reverse phase HPLC (Gilson: MeCN, 1% TFA/water) to give 0.067 g (45%) of the title compound as a racemic mixture of cis- and trans-isomers. ES MS m/z 572 (M-H).

Example 349: (cis and trans)-methyl [4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetate

Step 1. methyl [4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexylidene]({[(phenylmethyl)oxy]carbonyl}amino)acetate

DBU (1.72 mL, 11.26 mmol) was added dropwise to a solution of methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)oxy]carbonyl}amino)acetate (3.11 g, 9.39 mmol) and 1,1-dimethylethyl (4-oxocyclohexyl)carbamate (2.00 g, 9.39 mmol) in DCM (25 mL). The solution was stirred at RT for 16 h then the solvent was removed on a rotary evaporator. Ethyl acetate (200 mL) and water (200 mL) were added followed by 1N HCl until the pH was acidic. The organic phase was separated, washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Et_2O (150 mL) was added to the solid and the mixture was sonicated. The solid was filtered and dried to give 1.12 g (29%) of the title compound as a white powder.

Step 2. (cis and trans)-methyl amino[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]acetate

A mixture of methyl [4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexylidene]({[(phenylmethyl)oxy]carbonyl}amino)acetate (1.10 g, 2.63 mmol) and 10% Pd/C (0.15 g) in MeOH (75 mL) was stirred under hydrogen (60 psig) at RT for 24 h then carefully vented, filtered through Celite, and the solution was concentrated to give 0.80 g (106%) of the title compound as a racemic mixture of cis- and trans-isomers.

Step 3. (cis and trans)-methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]acetate

HATU (1.59 g, 4.19 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.52 g, 2.79 mmol), (cis and trans)-methyl amino[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]acetate (0.80 g, 2.79 mmol), and N,N-diisopropylethylamine (2.01 mL, 8.37 mmol) in DMF (15 mL) at RT. After 16 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 40 min) to give 0.96 g (76%) of the title compound as a yellow solid.

Step 4. (cis and trans)-methyl [4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetate

A solution of (cis and trans)-methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]acetate (0.55 g, 1.21 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.39 g, 2.41 mmol) in pyridine (10 mL) were stirred at RT for 72 h. The solvent was removed under reduced pressure and ethyl acetate (200 mL) and 1N HCl (200 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give 0.71 g (95%) of the title compound as a pale yellow solid. ES MS m/z 615 (M-H).

Example 350: (cis and trans)-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

LiOH (0.12 g, 5.03 mmol) was dissolved in hot water (10 mL) and added while still hot to a solution of (cis and trans)-methyl [4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetate

(0.31 g, 0.50 mmol) in THF (5 mL) and MeOH (5 mL). The yellow solution was stirred for 3 h then ethyl acetate (300 mL) and 1N HCl solution (100 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give 0.30 g (100%) of the title compound as a yellow solid. ES MS m/z 601 (M-H).

Example 351: (cis and trans)-(4-aminocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid trifluoroacetate

TFA (1.5 g, 13.2 mmol) was added to a solution of (cis and trans)-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid (0.26 g, 0.43 mmol) in DCM (10 mL). The yellow solution was stirred for 16 h then concentrated to give a yellow oil (still has TFA remaining). The crude material was dissolved in DCM (5 mL) and Et_2O was added (50 mL). The solid was filtered, washed with Et_2O/hexane and dried under vacuum to give 0.26 g (98%) of the title compound as a white powder. ES MS m/z 501 (M-H).

Example 352: (cis and trans)-(4-{[(methylamino)carbonyl]amino}cyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

Methyl isocyanate (0.02 g, 0.35 mmol) was added to a solution of (cis and trans)-(4-aminocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid trifluoroacetate (0.125 g, 0.20 mmol) in pyridine (2 mL). After 2 h, LC/MS show ca. 1:1 mixture of starting material and product so more methyl isocyanate (0.025 g, 0.44 mmol) was added. The solution was stirred for 24 h then concentrated and ethyl acetate (100 mL) and 1N HCL (50 mL) were added. The organic layer was washed with brine, filtered to remove a terrible emulsion, dried over $MgSO_4$, filtered and concentrated. Reverse phase

chromatography (Gilson: MeCN, 1% TFA/water) gave 0.026 g (23%) of the title compound as a white powder. ES MS m/z 558 (M-H).

Example 353: bis(1,1-dimethylethyl) *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartate

Step 1. bis(1,1-dimethylethyl) *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-aspartate

HATU (3.24 g, 8.54 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (1.06 g, 5.69 mmol), bis(1,1-dimethylethyl) L-aspartate hydrochloride (1.60 g, 5.69 mmol), and N,N-diisopropylethylamine (2.05 mL, 8.54 mmol) in DMF (70 mL) at RT. After 16 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (300 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 20 min) to give 1.8 g (76%) of the title compound as a yellow solid.

Step 2. bis(1,1-dimethylethyl) *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartate

A solution of bis(1,1-dimethylethyl) N-[(3-amino-2-naphthalenyl)carbonyl]-L-aspartate (0.41 g, 0.99 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.32 g, 1.98 mmol) in pyridine (10 mL) were stirred at RT for 72 h. The solvent was removed under reduced pressure and ethyl acetate (200 mL) and water (200 mL) and 1N HCl (50 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The solid was purified on silica gel (ISCO: 10% ethyl acetate/hexanes to 100% ethyl acetate over 30 min) to give 0.55 g (97%) of the title compound as a pale orange solid. ES MS m/z 574 (M-H).

Example 354: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid

TFA (3 mL) was added to a solution of bis(1,1-dimethylethyl) *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartate (0.49 g, 0.85 mmol) in DCM (20 mL). The solution was occasionally heated to reflux with a heat gun then stirred overnight at RT. The solvent was removed under reduced pressure and DCM (5 mL) and Et_2O (60 mL) were added. The white solid was filtered and dried to give 0.26 g (66%) of the title compound as a white powder. ES MS m/z 462 (M-H).

Example 355: *N*-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-aspartic acid

Step 1. bis(1,1-dimethylethyl) *N*-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-aspartate

A solution of bis(1,1-dimethylethyl) *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-aspartate (0.40 g, 0.97 mmol) and 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.52 g, 1.94 mmol) in pyridine (10 mL) was stirred at RT for 16 h. The solvent was removed under reduced pressure and ethyl acetate (100 mL) and water (50 mL) and 1N HCl (50 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The solid was purified on silica gel (ISCO: 10% ethyl acetate/hexanes to 100% ethyl acetate over 30 min) to give 0.43 g (65%) of the title compound as a yellow oil.

Step 2. *N*-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-aspartic acid

TFA (3 mL) was added to a solution of bis(1,1-dimethylethyl) *N*-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-aspartate (0.40 g, 0.58 mmol) in DCM (20 mL). The solution was heated occasionally to reflux with a heat gun then stirred at RT overnight. The solution was concentrated to give 0.33 g (99%) of the title compound as an off-white solid. ES MS m/z 572 (M-H).

Example 356: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-aspartic acid

Step 1. bis(phenylmethyl) *N*-[(3-amino-2-naphthalenyl)carbonyl]-D-aspartate

HATU (1.17 g, 3.09 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.38 g, 2.06 mmol), bis(phenylmethyl) D-aspartate tosylate (1.00 g, 2.06 mmol), and N,N-diisopropylethylamine (2.05 mL, 8.54 mmol) in DMF (40 mL) at RT. After 16 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (300 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 20 min) to give 0.77 g (77%) of the title compound as an orange oil.

Step 2. bis(phenylmethyl) *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-aspartate

A solution of bis(phenylmethyl) *N*-[(3-amino-2-naphthalenyl)carbonyl]-D-aspartate (0.34 g, 0.97 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.23 g, 1.40 mmol) in pyridine (5 mL) were stirred at RT for 5 h. The solvent was removed under reduced pressure and ethyl acetate (100 mL) and water (50 mL) and 1N HCl (50 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The solid was

purified on silica gel (ISCO: 10% ethyl acetate/hexanes to 100% ethyl acetate over 30 min) to give 0.39 g (87%) of the title compound as an orange solid.

Step 3. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-aspartic acid

A solution of bis(phenylmethyl) *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-aspartate (0.38 g, 0.59 mmol) and 10% Pd/C (0.15 g) in MeOH (25 mL) was stirred under hydrogen (60 psig) for 16 h. The reaction was carefully vented, filtered through Celite, and concentrated. The white residue was dissolved in hot ethyl acetate and hexane was added until a white solid formed. The solid was filtered and dried to give 0.071 g (26%) of the title compound as a white powder. ES MS m/z 462 (M-H).

Example 357: 1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-proline

Step 1. 1,1-dimethylethyl 1-[(3-amino-2-naphthalenyl)carbonyl]-D-prolinate

HATU (1.83 g, 4.82 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.60 g, 3.21 mmol), 1,1-dimethylethyl D-prolinate (0.55 g, 3.21 mmol), and N,N-diisopropylethylamine (2.0 mL, 4.82 mmol) in DMF (15 mL) at RT. After 5 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 40 min) to give 0.88 g (81%) of the title compound as a white solid.

Step 2. 1,1-dimethylethyl 1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-prolinate

A solution of 1,1-dimethylethyl 1-[(3-amino-2-naphthalenyl)carbonyl]-D-prolinate (0.40 g, 0.92 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.38 g, 2.35 mmol) in pyridine (10 mL) were stirred at RT for 5 h. The solvent was removed under reduced pressure and ethyl acetate (100 mL) and 0.1N HCl (100 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give a pale yellow oil. The product was purified on silica gel (ISCO: 5% ethyl acetate/hexanes to 100% ethyl acetate over 25 min) to give 0.50 g (85%) of the title compound as a white solid.

Step 3. 1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-proline

TFA (3 mL) was added to a solution of 1,1-dimethylethyl 1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-prolinate (0.48 g, 0.96 mmol) in DCM (20 mL). The solution was stirred overnight at RT then concentrated to give yellow solid. The crude material was dissolved in ethyl acetate (200 mL) and 1N NaOH added. The aqueous layer was separated, made acidic with 1N HCl, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 0.033 g of crude product. Reverse phase HPLC (Gilson: MeCN and 1%TFA/water) gave 0.026 g (6%) of the title compound as a white powder. ES MS m/z 444 (M-H).

Example 358: (2*S*)-[(1*S*)-3-oxocyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. 1,1-dimethylethyl (2*S*)-[(diphenylmethylidene)amino][(1*S*)-3-oxocyclohexyl]ethanoate

A solution of 2-cyclohexen-1-one (1.04 g, 10.83 mmol) in DCM (10 mL) was added dropwise over ca. 10 min to a mixture of 1,1-dimethylethyl *N*-(diphenylmethylidene)glycinate (1.00 g, 3.39 mmol), Cinchonidine alkaloid (0.20 g,

0.34 mmol) and $CsOH\text{-}H_2O$ (5.69 g, 33.9 mmol) in DCM (10 mL) at -78 °C. After 2 h, the cold bath was removed and the solution was warmed to RT upon which the solution turned from yellow to dark brown. Ethyl acetate (200 mL) and water (200 mL) were added. The organic phase was washed with water (200 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give 1.6 g of brown oil (^1H NMR shows product + alkaloid). The crude product was purified on silica gel (ISCO: 100% hexanes to 100% ethyl acetate over 30 min) to give 1.17 g (88%) of the title compound as a ca. 4:1 mixture of diastereomers.

Step 2. 1,1-dimethylethyl (2*S*)-amino[(1*S*)-3-oxocyclohexyl]ethanoate

A mixture of 1,1-dimethylethyl (2*S*)-[(diphenylmethylidene)amino][(1*S*)-3-oxocyclohexyl]ethanoate (1.10 g, 2.81 mmol) and 10% Pd/C (0.15 g) in MeOH (25 mL) was stirred under hydrogen (60 psig) for 16 h, then carefully vented, filtered through Celite and concentrated. ^1H NMR showed a new product but some aromatic protons still remained. Therefore the material was dissolved in MeOH and 10% Pd/C and 2 drops of concentrated HCl were added. The mixture was stirred under hydrogen (60 psig) for 4 h then carefully vented, filtered through Celite and concentrated to give 0.61 g of crude product. The material was used without further purification.

Step 3. 1,1-dimethylethyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}[(1*S*)-3-oxocyclohexyl]ethanoate

HATU (1.52 g, 4.01 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.50 g, 2.67 mmol), 1,1-dimethylethyl (2*S*)-amino[(1*S*)-3-oxocyclohexyl]ethanoate (0.61 g, 2.67 mmol), and N,N-diisopropylethylamine (1.9 mL, 8.01 mmol) in DMF (10 mL) at RT. After 5 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was partially purified on silica gel using an ISCO chromatography system

(increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 40 min) to give 0.37 g (35%) of the title compound as a yellow solid in ca. 60% purity.

Step 4. 1,1-dimethylethyl (2*S*)-[(1*S*)-3-oxocyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

A solution of 1,1-dimethylethyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}[(1*S*)-3-oxocyclohexyl]ethanoate (0.45 g, 1.14 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.22 g, 1.36 mmol) in pyridine (5 mL) were stirred at RT for 5 h. The solvent was removed under reduced pressure and ethyl acetate (100 mL) and 0.1N HCl (100 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (ISCO chromatography: 100% hexanes to 80% ethyl acetate/hexanes) to give 0.18 g (28%) of the title compound as a yellow solid.

Step 5. (2*S*)-[(1*S*)-3-oxocyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

TFA (3 mL) was added to a solution of 1,1-dimethylethyl (2*S*)-[(1*S*)-3-oxocyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.17 g, 0.30 mmol) in DCM (20 mL). The solution was heated occasionally to reflux with a heat gun then stirred at RT overnight. The solution was concentrated to give an off-white solid. The residue was dissolved in a small amount of DCM & MeOH then Et_2O was added followed by hexane. The solid was filtered and dried to give 0.041 g (27%) of the title compound as a white powder. ES MS m/z 500 (M-H).

Example 359: (2*S*)-[(1*S*)-3-hydroxycyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

and

Example 360: (2*S*)-{(1*S*)-3-[(trifluoroacetyl)oxy]cyclohexyl}({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step1. 1,1-dimethylethyl (2*S*)-[(diphenylmethylidene)amino][(1*S*)-3-oxocyclohexyl]ethanoate

A solution of 2-cyclohexen-1-one (2.58 g, 26.84 mmol) in DCM (20 mL) was added dropwise over ca. 10 min to a mixture of 1,1-dimethylethyl *N*-(diphenylmethylidene)glycinate (2.44 g, 8.26 mmol), Cinchonidine alkaloid (0.50 g, 0.82 mmol) and CsOH-H_2O (13.15 g, 78.32 mmol) in DCM (20 mL) at -78 °C. The cold bath was allowed to warm to RT then ethyl acetate (200 mL) and water (200 mL) were added. The organic phase was washed with water (200 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel (ISCO: 100% hexanes to 100% ethyl acetate over 30 min) to give 1.79 g (55%) of the title compound as a clear oil.

Step 2. 1,1-dimethylethyl (2*S*)-[(diphenylmethyl)amino][(1*S*)-3-hydroxycyclohexyl]ethanoate

$NaBH_4$ (0.13 g, 3.54 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-[(diphenylmethylidene)amino][(1*S*)-3-oxocyclohexyl]ethanoate (0.63 g, 1.61 mmol) in MeOH (10 mL) at RT. The solution was stirred overnight then water (100 mL) and ethyl acetate (200 mL) added. Organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated to give 0.63 g (99%) of the title compound as a clear oil.

Step 3. 1,1-dimethylethyl (2*S*)-amino[(1*S*)-3-hydroxycyclohexyl]ethanoate

A mixture of 1,1-dimethylethyl (2*S*)-[(diphenylmethyl)amino][(1*S*)-3-hydroxycyclohexyl]ethanoate (0.63 g, 1.59 mmol) and 10% Pd/C (0.10 g) in MeOH

(25 mL) was stirred under hydrogen (60 psig) at RT for 16 h. The reaction was carefully vented, diluted with ethyl acetate, filtered through Celite and concentrated to give the title compound which was used without further purification.

Step 4. 1,1-dimethylethyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}[(1*S*,3*R*)-3-hydroxycyclohexyl]ethanoate

HATU (1.52 g, 4.01 mmol) was added to a suspension of 3-amino-2-naphthalenecarboxylic acid (0.50 g, 2.67 mmol), 1,1-dimethylethyl (2*S*)-amino[(1*S*)-3-hydroxycyclohexyl]ethanoate (0.61 g, 2.67 mmol), and N,N-diisopropylethylamine (1.9 mL, 8.01 mmol) in DMF (10 mL) at RT. After 5 h, saturatued $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 40 min) to give 0.37 g (34%) of the title compound as a yellow solid.

Step 5. (2*S*)-[(1*S*)-3-hydroxycyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

and

(2*S*)-{(1*S*)-3-[(trifluoroacetyl)oxy]cyclohexyl}({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

A solution of 1,1-dimethylethyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}[(1*S*,3*R*)-3-hydroxycyclohexyl]ethanoate (0.37 g, 0.93 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.15 g, 0.93 mmol) in pyridine (5 mL) were stirred at RT for 16 h, then concentrated to dryness. 1N HCl (50 mL) and ethyl acetate (50 mL) were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in DCM (10 mL) and TFA (3 mL) was added. The yellow solution was occasionally heated

to reflux and stirred until no starting material remained. The solution was concentrated to dryness and dried under vacuum. Reverse-phase HPLC (Gilson: MeCN, 1% TFA/water) gave two products:

0.034 g (7% over two steps) of (2*S*)-[(1*S*)-3-hydroxycyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid. ES MS m/z 502 (M-H).

and

0.060 g (11% over two steps) of. (2*S*)-{(1*S*)-3-[(trifluoroacetyl)oxy]cyclohexyl}({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid. ES MS m/z 598 (M-H).

Example 361: bis(1,1-dimethylethyl) *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate

Step 1. 3-amino-4'-(methyloxy)-4-biphenylcarboxylic acid

A solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.50 g, 1.83 mmol) and 10% Pd/C (100 mg) under H_2 (60 psig) in EtOH (20 mL) was stirred at RT for 16 h (a cloudy suspension formed). The suspension was dissolved in ethyl acetate (50 mL), filtered through Celite, and concentrated to give 0.43 g (98%) of the title compound as an orange solid.

Step 2. bis(1,1-dimethylethyl) *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate

HATU (0.40 g, 1.04 mmol) was added to a solution of 3-amino-4'-(methyloxy)-4-biphenylcarboxylic acid (0.23 g, 0.95 mmol), bis(1,1-dimethylethyl) L-aspartate hydrochloride (0.53 g, 1.89 mmol), and N,N-diisopropylethylamine (2 mL, 8.34 mmol) in DCM (10 mL) at RT. After 3 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated. The crude

oil was purified on silica gel (hexanes to 90% ethylacetate/hexanes over 30 min) to give 0.63 g (71%) of the title compound as a white powder.

Step 3. bis(1,1-dimethylethyl) *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate

A solution of bis(1,1-dimethylethyl) *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate (0.32 g, 0.67 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.54 g, 3.35 mmol) in pyridine (3 mL) were stirred at RT for 4 h then the pyridine was removed in vacuo. The residue was taken up in 1N HCl (50 mL), water (200 mL), and ethyl acetate (200 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel (ISCO: 100% hexanes to 90% ethyl acetate/hexanes over 25 min) to give 0.40 g (94%) of the title compound as a white powder. APCI MS m/z 630 (M-H).

Example 362: *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid

TFA (3 mL) was added to a solution of bis(1,1-dimethylethyl) *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate (0.40 g, 0.63) in DCM (10 mL). The solution was heated occasionally to reflux with a heat gun then stirred at RT for 2 days. The solution was concentrated and the resulting oil was dissolved in DCM (1 mL) and Et_2O (5 mL) then hexanes (5 mL) were added. The white precipitate was filtered and dried to give 0.18 g (55%) of the title compound as a white powder. ES MS m/z 518 (M-H).

Example 363: (2*S*)-4-(ethyloxy)-4-oxo-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid

Step 1. 4-ethyl 1-(phenylmethyl) *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-L-aspartate

DMAP (0.30 g, 2.47 mmol) was added to a solution of (3*S*)-3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-4-oxo-4-[(phenylmethyl)oxy]butanoic acid (4.00 g, 12.37 mmol) and EDC (1.78 g, 9.28 mmol) in EtOH (14.11 g, 37.12 mmol) and DCM (40 mL) at RT. The solution was stirred for 2 days then sat $NaHCO_3$ solution and ethyl acetate were added. The organic layer was washed with sat $NaHCO_3$ solution, water, brine, dried $MgSO_4$, filtered and concentrated to give 4.41 g (101%) of the title compound as a colorless oil.

Step 2. 4-ethyl 1-(phenylmethyl) L-aspartate trifluoroacetate

TFA (10 mL) was added to a solution of 4-ethyl 1-(phenylmethyl) *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-L-aspartate (4.41 g, 12.51 mmol) in DCM (20 mL). The yellow solution was stirred overnight then concentrated to give 5.2 g of the title compound as a yellow oil (note: excess TFA still present).

Step 3. 4-ethyl 1-(phenylmethyl) *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-aspartate

HATU (1.63 g, 4.29 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.54 g, 2.86 mmol), 4-ethyl 1-(phenylmethyl) L-aspartate trifluoroacetate (1.57 g, 4.30 mmol) and N,N-diisopropylethylamine (3.43 mL, 14.3 mmol) in DMF (10 mL) at RT under nitrogen. After 1 h, saturated $NaHCO_3$ soln (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude oil was purified on silica gel (ISCO: 100% hexanes to 90% ethyl acetate/hexanes over 30 minutes) to give 1.11 g (92%) of the title compound as an orange oil.

Step 4. 4-ethyl 1-(phenylmethyl) *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartate

A solution of 4-ethyl 1-(phenylmethyl) *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-aspartate (0.61 g, 1.45 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.70 g,

4.35 mmol) in pyridine (4 mL) were stirred at RT for 2 days. The pyridine was removed in vacuo and ethyl acetate (200 mL) and sat $NaHCO_3$ solution (150 mL) were added. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give 0.41 g (49%) of the title compound as a white powder.

Step 5. (2*S*)-4-(ethyloxy)-4-oxo-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid

A solution of 4-ethyl 1-(phenylmethyl) *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartate (0.20 g, 0.34 mmol) in EtOH (15 mL) and ethyl acetate (2 mL) was purged with nitrogen. Next, 10% Pd/C (0.10 g) was added and the suspension was stirred under one atmosphere of hydrogen (balloon) for 16 h. The next day TLC showed a little starting material remaining so the H_2 balloon was reinserted and stirred for another 3 h. The reaction was carefully vented and filtered through Celite. The solution was concentrated to give 0.14 g (83%) of the title compound as a white solid. ES MS m/z 490 (M-H).

Example 364: *N*-{[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-aspartic acid

Step 1. bis(1,1-dimethylethyl) *N*-[(4-fluoro-2-nitrophenyl)carbonyl]-L-aspartate

HATU (7.71 g, 20.29 mmol) was added to a suspension of 4-fluoro-2-nitrobenzoic acid (2.50 g, 13.51 mmol), bis(1,1-dimethylethyl) L-aspartate hydrochloride (6.08 g, 21.62 mmol), and N,N-diisopropylethylamine (9.7 mL, 40.53 mmol) in DCM (40 mL) at RT. After 2 days, 1N HCl (100 mL), water (100 mL) and ethyl acetate (400 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution (300 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give 3.78 g (68%) of the title compound as an orange oil.

Step 2. bis(1,1-dimethylethyl) *N*-[(2-amino-4-fluorophenyl)carbonyl]aspartate hydrochloride

A mixture of bis(1,1-dimethylethyl) *N*-[(4-fluoro-2-nitrophenyl)carbonyl]-L-aspartate (3.78 g, 9.12 mmol) and 10% Pd/C (0.2 g) in EtOH (10 mL) were stirred under hydrogen (60 psig) for 3 h, then the reaction vessel was carefully vented. Ethyl acetate (50 mL) was added and the mixture was filtered through Celite and concentrated to give 3.31 g of yellow oil. ^{1}H NMR shows that the reduction was not complete. Therefore the material was dissolved in EtOH (10 mL) and 10% Pd/C (0.2 g) was added. The mixture was stirred under hydrogen (60 psig) for 5 h then carefully vented. Ethyl acetate (50 mL) was added and the mixture was filtered through Celite and concentrated. The yellow oil was dissolved in DCM (10 mL) and Et_2O (20 mL) then 1N HCl in Et_2O (10 mL) was added. The solvent was removed by rotary evaporation to give 2.65 g (69%) of the title compound as a pale orange solid.

Step 3. bis(1,1-dimethylethyl) *N*-{[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-aspartate

A solution of bis(1,1-dimethylethyl) *N*-[(2-amino-4-fluorophenyl)carbonyl]aspartate hydrochloride (0.40 g, 0.96 mmol) and 1,3-dichloro-2-isocyanatobenzene (0.75 g, 3.99 mmol) in pyridine (4 mL) were stirred at RT for 16 h then the pyridine was removed in vacuo. The residue was taken up in 1N HCl (50 mL), water (200 mL), and ethyl acetate (200 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel (ISCO: 100% hexanes to 90% ethyl acetate/hexanes) to give 0.37 g (68%) of the title compound as a white powder.

Step 4. *N*-{[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-aspartic acid

TFA (5 mL) was added to a solution of bis(1,1-dimethylethyl) *N*-{[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-aspartate (0.30 g, 0.53) in DCM (10 mL). The solution was heated occasionally to reflux with a heat gun then stirred at RT for 24 h. The solution was concentrated to give 0.20 g (82%) of the title compound as a white powder. ES MS m/z 456 (M-H).

Example 365: *N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartic acid

Step 1. bis(1,1-dimethylethyl) *N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartate

A solution of bis(1,1-dimethylethyl) *N*-[(2-amino-4-fluorophenyl)carbonyl]-L-aspartate hydrochloride (0.40 g, 0.96 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.77 g, 4.78 mmol) in pyridine (4 mL) were stirred at RT for 16 h then the pyridine was removed in vacuo. The residue was taken up in 1N HCl (50 mL), water (200 mL), and ethyl acetate (200 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel (ISCO: 100% hexanes to 90% ethyl acetate/hexanes) to give 0.36 g (69%) of the title compound as a white powder.

Step 2. *N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartic acid

TFA (5 mL) was added to a solution of bis(1,1-dimethylethyl) *N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartate (0.31 g, 0.57 mmol) in DCM (10 mL). The solution was heated occasionally to reflux with a heat gun then stirred at RT overnight. The solution was concentrated to give an oil which was dissolved in DCM (1 mL) and Et_2O (5 mL) then hexanes (5 mL) was added. The white precipitate was filtered and dried to give 0.16 g (55%) of the title compound as a white powder. ES MS m/z 430 (M-H).

Example 366: 4-ethyl 1-(phenylmethyl) *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate

Step 1. methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate

Two microwave reaction vials were each charged with a mixture of methyl 4-chloro-2-nitrobenzoate (1.00 g, 4.64 mmol), [4-(methyloxy)phenyl]boronic acid (0.78 g, 5.10 mmol), cesium fluoride (2.11 g, 13.92 mmol) and $Pd(Cy_3)_2Cl_2$ (0.17 g, 0.23 mmol) in MeCN (10 mL) and water (4 mL). Each vial was heated to 150 °C for 5 min in a microwave reactor then the two reaction mixtures were combined in a separatory funnel, diluted with ethyl acetate (300 mL), washed with water (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified on silica gel (ISCO: eluting with 100% hexanes to 100% ethyl acetate over 50 min) to give 2.21 g (83%) of the title compound as a yellow oil.

Step 2. 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid

A solution of LiOH (0.92 g, 38.33 mmol) in hot water (15 mL) was added to a solution of methyl 4'-(methyloxy)-3-nitro-4-biphenylcarboxylate (2.20 g, 7.67 mmol) in THF (15 mL) and MeOH (5 mL). The yellow solution was stirred at RT for 5 h then 1N HCl (100 mL) and ethyl acetate (250 mL) were added. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated to give 2.02 g (96%) of the title compound as a pale yellow solid.

Step 3. 3-amino-4'-(methyloxy)-4-biphenylcarboxylic acid

A solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.71 g, 2.60 mmol) and 10% Pd/C (0.15 g) under hydrogen (60 psig) in MeOH (20 mL) was stirred at RT for 16 h (a cloudy suspension formed). The suspension was dissolved in ethyl acetate (50 mL), filtered through Celite, and concentrated to give 0.63 g (100%) of the title compound as a yellow solid.

Step 4. 4-ethyl 1-(phenylmethyl) *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate

HATU (1.48 g, 3.89 mmol) was added to a solution of 3-amino-4'-(methyloxy)-4-biphenylcarboxylic acid (0.63 g, 2.59 mmol), 4-ethyl 1-(phenylmethyl) L-aspartate trifluoroacetate (1.89 g, 5.19 mmol) and N,N-diisopropylethylamine (3 mL, 12.5 mmol) in DCM (10 mL) at RT. After 3 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated. The crude oil was purified on silica gel (100% hexanes to 90% ethyl acetate/hexanes over 30 min) to give 0.66 g (53%) of the title compound as a yellow oil.

Step 5. 4-ethyl 1-(phenylmethyl) *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate

A solution of 4-ethyl 1-(phenylmethyl) *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate (0.19 g, 0.40 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.19 g, 1.20 mmol) in pyridine (3 mL) were stirred at RT for 4 h then the pyridine was removed in vacuo. The residue was taken up in 1N HCl (25 mL), water (100 mL), and ethyl acetate (100 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give 0.23 g (90%) of the title compound as a yellow solid. ES MS m/z 638 (M+H).

Example 367: (2S)-4-(ethyloxy)-2-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid

A solution of 4-ethyl 1-(phenylmethyl) *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate (0.21 g, 0.36 mmol) in EtOH (15 mL) and ethyl aceate (15 mL) was purged with nitrogen. Next, 10% Pd/C (0.10 g) was added and the suspension was stirred under one atmosphere of hydrogen (balloon) for 16 h. The next day, TLC showed that a little

starting material still remained so the hydrogen balloon was re-inserted and stirred for another 3 h. The reaction was carefully vented and filtered through Celite. The solvent was removed to give 0.11 g (56%) of the title compound as a white solid. ES MS m/z 546 (M-H).

Example 368: 4-ethyl 1-(phenylmethyl) *N*-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate

A solution of 4-ethyl 1-(phenylmethyl) *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate (0.46 g, 0.97 mmol) and 5-bromo-2-isocyanato-1,3-dimethylbenzene (0.66 g, 2.90 mmol) in pyridine (3 mL) were stirred at RT for 16 h then the pyridine was removed in vacuo. The residue was taken up in 1N HCl (25 mL), water (100 mL), and ethyl acetate (100 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give 0.62 g (91%) of the title compound as a yellow powder. ES MS m/z 703 (M+H).

Example 369: (2*S*)-2-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid

Step 1. 4-ethyl 1-(phenylmethyl) *N*-{[3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate

A mixture of 4-ethyl 1-(phenylmethyl) *N*-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate (0.58 g, 0.83 mmol), tributyl(2-propen-1-yl)stannane (0.30 g, 0.91 mmol) and $Pd(PPh_3)_4$ (0.057 g, 0.05 mmol) in MeCN (10 mL) were heated in a Microwave Reactor at 150 °C for 30 min. The mixture was extracted between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (ISCO: 100% hexanes to 80% ethyl acetate/hexanes) to give 0.39 g (72%) of the title compound as a white solid.

Step 2. (2S)-2-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid

A solution of 4-ethyl 1-(phenylmethyl) N-{[3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate (0.38 g, 0.57 mmol) in EtOH (15 mL) and ethyl acetate (15 mL) was purged with nitrogen. Next, 10% Pd/C (0.10 g) was added and the suspension was stirred under one atmosphere of hydrogen (balloon) for 16 h. TLC showed a little starting material remaining so the hydrogen balloon was re-inserted. After stirring for 16 h, the flask was carefully vented and the mixture was filtered through Celite and concentrated. SFC purification gave 0.16 g (49%) of the title compound as a white powder. APCI m/z 574 (M-H).

Example 370: *N*-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartic acid

LiOH (0.080 g, 3.33 mmol) was dissolved in hot water (5 mL) and added while still warm to a solution of (2S)-2-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid (0.06 g, 0.10 mmol) in THF (5 mL) and MeOH (5 mL). The solution was stirred at RT for 6 h then 1N HCl was added until the pH < 7. Ethyl acetate (100 mL) and water (50 mL) were added and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give 0.045 g (79%) of the title compound as a white powder. APCI MS m/z 547 (M-H).

Example 371: 4-(1,1-dimethylethyl) 1-methyl *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate

Step 1. 4-(1,1-dimethylethyl) 1-methyl *N*-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-aspartate

HATU (0.94 g, 2.47 mmol) was added to a solution of 4'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.45 g, 1.65 mmol) and N,N-diisopropylethylamine (1 mL, 4.17 mmol) in DCM (10 mL) at RT. After 5 min, 4-(1,1-dimethylethyl) 1-methyl L-aspartate hydrochloride (0.48 g, 2.14 mmol) was added. The yellow solution was stirred at RT for 2 h then saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated. The crude solid was purified on silica gel (100% hexanes to 90% ethyl acetate/hexanes over 30 min) to give 0.66 g (87%) of the title compound as a white solid.

Step 2. 4-(1,1-dimethylethyl) 1-methyl *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate

A mixture of 4-(1,1-dimethylethyl) 1-methyl *N*-{[4'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-aspartate (0.66 g, 1.44 mmol) and 10% Pd/C (0.10 g) under hydrogen (60 psig) in MeOH (15 mL) and ethyl acetate (15 mL) was stirred at RT for 16 h. Ethyl acetate (50 mL) was added and the mixture was filtered through Celite. The solution was concentrated to give 0.62 g (100%) of the title compound as a white solid.

Step 3. 4-(1,1-dimethylethyl) 1-methyl *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate

A solution of 4-(1,1-dimethylethyl) 1-methyl *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate (0.62 g, 1.45 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.70 g, 4.35 mmol) in pyridine (3 mL) was stirred at RT for 5 h then the pyridine was removed in vacuo. The residue was taken up in 1N HCl (25 mL), water (200 mL), and ethyl acetate (200 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give 0.81 g (95%) of the title compound as a yellow powder. ES MS m/z 588 (M-H).

Example 372: (3*S*)-4-(methyloxy)-3-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid

A solution of 4-(1,1-dimethylethyl) 1-methyl *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate (0.79 g, 1.34 mmol) and TFA (4 mL) in DCM (5 mL) was stirred at RT for 16 h then concentrated to dryness. The residue was taken up in DCM (ca. 5 mL) and Et_2O (10 mL) and hexanes (30 mL) were added. The solid was filtered and dried under vacuum to give 0.64 g (90%) of the title compound as an off-white solid. ES MS m/z 532 (M-H).

Example 373: *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine

Step 1. methyl 3',4'-difluoro-3-nitro-4-biphenylcarboxylate

Five separate microwave reaction vials were each charged with a mixture of methyl 4-chloro-2-nitrobenzoate (1.00 g, 5.64 mmol), (3,4-difluorophenyl)boronic acid (0.81 g, 5.10 mmol), $Pd(Cy_3)_2Cl_2$ (0.17 g, 0.23 mmol) and CsF (2.11 g, 13.90 mmol) in MeCN (10 mL) and water (5 mL). The vials were sealed then heated to 150 °C for 7 min. The vials were vented, diluted with ethyl acetate and reaction mixtures were combined. The solids were filtered off and the solution was washed with water, dried over Na_2SO_4, filtered and concentrated to give 5.67 g (83%) of the title compound.

Step 2. 3',4'-difluoro-3-nitro-4-biphenylcarboxylic acid

LiOH (1.39 g, 57.95 mmol) was dissolved in hot water (30 mL) and added while still warm to a solution of methyl 3',4'-difluoro-3-nitro-4-biphenylcarboxylate (5.66 g, 19.32 mmol) in THF (100 mL) and MeOH (30 mL). The solution was stirred for 16 h then the reaction was concentrated to dryness. Water (50 mL) was added, followed

by 1N HCl until the pH < 7. The white solid was filtered then dissolved in ethyl acetate (150 mL), dried over $MgSO_4$, filtered and concentrated to give 5.25 g (97%) of the title compound as a white powder.

Step 3. methyl *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate

N,N-diisopropylethylamine (1.0 mL, 4.2 mmol) was added to a suspension of 3',4'-difluoro-3-nitro-4-biphenylcarboxylic acid (0.50 g, 1.79 mmol), methyl *O*-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.49 g, 2.15 mmol) and HATU (1.02 g, 2.69 mmol) in DCM (10 mL) and DMF (2 mL). The yellow solution was stirred for 1 h then sat $NaHCO_3$ solution (150 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with sat $NaHCO_3$ solution (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (ISCO: 100% hexanes to 80% ethyl acetate/hexanes over 20 min) to give 0.79 g (98%) of the title compound as a white solid.

Step 4. methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate

A solution of methyl *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate (0.78 g, 1.73 mmol) and 10% Pd/C (0.10 g) under hydrogen (60 psig) in MeOH (15 mL) and ethyl acetate (15 mL) was stirred at RT for 5 h. The flask was carefully vented and ethyl acetate (50 mL) was added. The mixture was filtered through Celite and concentrated to give 0.71 g (97%) of the title compound as an off-white solid.

Step 5. methyl *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate

A solution of methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate (0.20 g, 0.48 mmol) and 2-isocyanato-1,3,5-

trimethylbenzene (0.09 g, 0.57 mmol) in pyridine (3 mL) were stirred at RT for 16 h. The solvent was removed under reduced pressure and ethyl acetate (100 mL) and 0.1N HCl (100 mL) were added. The organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (ISCO: 100% hexanes to 80% ethyl acetate/hexanes over 30 min) to give 0.25 g (90%) of the title compound as a white solid.

Step 6. *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine

LiOH (0.031 g, 1.29 mmol) was dissolved in hot water (5 mL) and added while still warm to a solution of methyl *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate (0.25 g, 0.43 mmol) in THF (5 mL) and MeOH (5 mL). After 4 h, the reaction was concentrated to dryness and water (5 mL) was added, followed by 1N HCl until the pH < 7. Ethyl acetate (100 mL) was added and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give 0.21 g (86%) of the title compound as a white powder. ES MS m/z 566 (M-H).

Example 374: (2*S*)-2-({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid

Step 1. 4-ethyl 1-(phenylmethyl) *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-L-aspartate

N,N-diisopropylethylamine (1.00 mL, 4.17 mmol) was added to a suspension of 3',4'-difluoro-3-nitro-4-biphenylcarboxylic acid (0.45 g, 1.61 mmol) and HATU (0.92 g, 2.42 mmol) in DCM (10 mL) and DMF (2 mL). After 5 min, 4-ethyl 1-(phenylmethyl) L-aspartate trifluoroacetate (1.18 g, 3.23 mmol) was added and the

yellow solution was stirred for 16 h then sat $NaHCO_3$ solution (150 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with sat $NaHCO_3$ solution (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (ISCO: 100% hexanes to 80% ethyl acetate/hexanes over 20 min) to give 0.47 g (57%) of the title compound as a white solid.

Step 2. 4-ethyl 1-(phenylmethyl) *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-L-aspartate

A mixture of 4-ethyl 1-(phenylmethyl) *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-L-aspartate (0.47 g, 0.92 mmol) and Pt on sulfided carbon (5 wt. %, 0.10 g) in MeOH (15 mL) were stirred under one atmosphere of hydrogen (balloon) at RT. After 4 h, the balloon was removed and ethyl acetate (100 mL) was added. The mixture was filtered through Celite and the solution was concentrated to give a yellow oil which was dissolved in Et_2O (25 mL) then filtered through Celite again. The solution was concentrated to give 0.44 g (99%) of the title compound as a yellow oil.

Step 3. 4-ethyl 1-(phenylmethyl) *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate

A solution of 4-ethyl 1-(phenylmethyl) *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-L-aspartate (0.44 g, 0.91 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.29 g, 1.82 mmol) in pyridine (6 mL) were stirred at RT for 16 h. The solvent was removed under reduced pressure and ethyl acetate (200 mL) and 1N HCl (50 mL) and water (150 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (ISCO: 100% hexanes to 80% ethyl acetate/hexanes over 30 min) to give 0.44 g (75%) of the title compound as a white solid.

Step 4. (2*S*)-2-({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid

A solution of 4-ethyl 1-(phenylmethyl) *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate (0.44 g, 0.68 mmol) in MeOH (15 mL) and ethyl acetate (5 mL) was purged with nitrogen. Next, 10% Pd/C (0.10 g) was added and the suspension was stirred under one atmosphere of hydrogen (balloon) for 16 h then carefully vented and filtered through Celite. The solvent was removed and the resulting orange solid was partially dissolved in hot ethyl acetate (10 mL), sonicated and allowed to cool to RT. The solid was filtered and dried to give 0.21 g (56%) of title compound as a white powder. APCI m/z 554.29 (M+H).

Example 375: *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid

LiOH (0.041 g, 1.70 mmol) was dissolved in hot water (5 mL) and added while still warm to a solution of (2*S*)-2-({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid (0.092 g, 0.17 mmol) in THF (5 mL) and MeOH (5 mL). The solution was stirred at RT for 6 h then 1N HCl was added until the pH < 7. Ethyl acetate (100 mL) and water (50 mL) were added and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give 0.056 g (64%) of the title compound as a white powder. APCI MS m/z 524.33 (M-H).

Example 376: *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-D-aspartic acid

Step 1. bis(phenylmethyl) *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-D-aspartate

Bis(phenylmethyl) D-aspartate 4-methylbenzenesulfonate (0.67 g, 1.38 mmol) was added to a suspension of HATU (0.61 g, 1.59 mmol), 3',4'-difluoro-3-nitro-4-biphenylcarboxylic acid (0.30 g, 1.06 mmol) and N,N-diisopropylethylamine (0.76 mL, 3.17 mmol) in DCM (10 mL) and DMF (5 mL) at RT. After 16 h, saturated $NaHCO_3$ solution (100 mL) and ethyl acetate (200 mL) were added. The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing gradient from 100% hexanes to 90% ethyl acetate/hexanes over 20 min) to give 0.41 g (67%) of the title compound as a yellow solid.

Step 2. bis(phenylmethyl) *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-D-aspartate

A mixture of bis(phenylmethyl) *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-D-aspartate (0.41 g, 0.71 mmol) and Pt on sulfided carbon (5 wt. %, 0.12 g) in MeOH (20 mL) under one atmosphere of hydrogen (balloon) was stirred at RT for 6 h. The balloon was removed, ethyl acetate (100 mL) was added and the mixture was filtered through Celite and concentrated. The brown oil was purified on silica gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate over 25 minutes) to give 0.36 g (94%) of the title compound as a yellow oil.

Step 3. bis(phenylmethyl) *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-D-aspartate

A solution of bis(phenylmethyl) *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-D-aspartate (0.36 g, 0.66 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.21 g, 1.32 mmol) in pyridine (6 mL) were stirred at RT for 72 h. The solvent was removed under reduced pressure and ethyl acetate (200 mL) and 1N HCl (50 mL) and water (150 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in hot ethyl acetate (ca. 5 mL) and

hexanes added until cloudy. The precipitate was filtered and dried to give 0.27 g (58%) of the title compound as a yellow solid.

Step 4. *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-D-aspartic acid

A solution of bis(phenylmethyl) *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-D-aspartate (0.27 g, 0.38 mmol) in MeOH (15 mL) was purged with nitrogen. Next, 10% Pd/C (0.10 g) was added and the suspension was stirred under one atmosphere of hydrogen (balloon) for 16 h then carefully vented and filtered through Celite. The solvent was removed under vacuum and the resulting material was dissolved in hot ethyl acetate (ca. 5 mL) and triturated with Et_2O and hexanes. The resulting solid was filtered and dried to give 0.12 g (60%) of the title compound as a white powder. APCI m/z 524 (M+H).

Example 377: methyl N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparaginate

A 30% aqueous solution of ammonium hydroxide (1 mL) was added to a suspension of (3*S*)-4-(methyloxy)-3-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid (0.13 g, 0.24 mmol) and HATU (0.14 g, 0.37 mmol) in DCM (5 mL). After stirring at RT for 3 h, the reaction was concentrated to dryness. Water (5 mL) was added and the resulting white precipitate was filtered and dried under vacuum to give 0.088 g (68%) of title compound as a white powder. APCI MS m/z 531 (M-H).

Example 378: N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparagine

LiOH (0.10 g, 4.17 mmol) was dissolved in hot water (3 mL) and added while still warm to a solution of methyl N^2-{[4'-(methyloxy)-3-({[(2,4,6-

trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparaginate (0.060 g, 0.11 mmol) in THF (3 mL) and MeOH (3 mL). The solution was stirred at RT for 5 h then 1N HCl was added until the pH < 7. The resulting white powder was filtered and dried. The solid was sonicated with MeOH, filtered, washed with Et_2O and dried under vacuum to give 0.020 g (35%) of the title compound as a white powder. APCI MS m/z 517 (M-H).

Example 379: *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-glutamic acid

Step 1. bis(phenylmethyl) *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-L-glutamate

N,N-diisopropylethylamine (1.00 mL, 4.17 mmol) was added to a suspension of 3',4'-difluoro-3-nitro-4-biphenylcarboxylic acid (0.30 g, 1.08 mmol) and HATU (0.61 g, 1.61 mmol) in DCM (10 mL) and DMF (2 mL). After 5 min, bis(phenylmethyl) L-glutamate 4-methylbenzenesulfonate (0.805 g, 1.61 mmol) was added and the yellow solution was stirred for 16 h at RT then 1N HCl solution (50 mL) and ethyl acetate (100 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (ISCO: 100% hexanes to 80% ethyl acetate/hexanes over 20 min) to give 0.53 g (84%) of the title compound as a clear oil.

Step 2. bis(phenylmethyl) *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-L-glutamate

A mixture of bis(phenylmethyl) *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-L-glutamate (0.50 g, 0.85 mmol) and Pt on sulfided carbon (5 wt. %, 0.12 g) in MeOH (20 mL) was stirred under one atmosphere of hydrogen gas (balloon) at RT. After 4 h, the balloon was removed, ethyl acetate (100 mL) was added and the mixture was filtered through Celite then concentrated. The yellow oil was purified on silica

gel using an ISCO chromatography system (gradient: 100% hexanes to 100% ethyl acetate over 25 minutes) to give a yellow solid that was a mixture of two compounds. The material was dissolved in hot ethyl acetate and hexane was slowly added until a precipitate just began to form, then the solution was allowed to cool overnight. The solid was filtered off and the resulting filtrate was concentrated to give 0.15 g (32%) of the title compound as a yellow solid.

Step 3. bis(phenylmethyl) *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-glutamate

A solution of bis(phenylmethyl) *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-L-glutamate (0.15 g, 0.27 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.086 g, 0.54 mmol) in pyridine (2 mL) were stirred at RT for 16 h. The solvent was removed under reduced pressure and ethyl acetate (150 mL) and 1N HCl (50 mL) and water (100 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in a minimal amount of MeOH/DCM (ca. 1 mL, 2mL), then Et_2O (5 mL) and hexanes (5 mL) were added. The solid was filtered and dried under vacuum to give 0.090 (47%) of the title compound as a yellow solid.

Step 4. *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-glutamic acid

A solution of bis(phenylmethyl) *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-glutamate (0.09 g, 0.13 mmol) in MeOH (15 mL) and ethyl acetate (5 mL) was purged with nitrogen. Next, 10% Pd/C (0.06 g) was added and the suspension was stirred under one atmosphere of hydrogen (balloon) for 16 h then carefully vented and filtered through Celite. The solvent was removed to give 0.058 g (87%) of the title compound as a white powder. APCI m/z 538 (M-H).

Example 380: 4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylcarboxylic acid

A solution of 3-amino-4'-(methyloxy)-4-biphenylcarboxylic acid (0.15 g, 0.62 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.21 g, 0.93 mmol) were stirred in pyridine (5 mL) overnight. The next day, TLC showed some starting material still remaining so more 2-isocyanato-1,3,5-trimethylbenzene (ca. 0.2 g, 1.24 mmol) was added. When the starting material was gone as evident by TLC, 1N HCl was added followed by ethyl acetate (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a white solid. The crude material was purified on silica gel to give 0.015 g (6%) of the title compound. ES m/z 403 (M-H).

Example 381: 3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylcarboxylic acid

A solution of 3-amino-4'-(methyloxy)-4-biphenylcarboxylic acid (0.15 g, 0.62 mmol) and 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.25 g, 0.93 mmol) were stirred in DCM (5 mL) and N,N-diisopropylethylamine (1 mL, 4.17 mmol)) at RT overnight. Next, 1N HCl was added followed by ethyl acetate (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a white solid. Recrystallization from hot ethyl acetate gave 0.030 g (9%) of the title compound. APCI m/z 517 (M+H).

Example 382: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-amino-5-phenyl-3-thiophenecarboxylate

To a mixture of phenylacetaldehyde 4.0 g (0.0333 mole) and 1,1-dimethylethyl cyanoacetate 4.69 g (0.0333 mole) and sulfur 1.17 g (0.0366 mole) in ethanol (50

mL) was added morpholine 3.33 mL (0.038 mole) and the contents heated under nitrogen at 50 °C for 18 h. After filtration, water was added to the reaction to precipitate the desired product. Filtration of the solid followed by washing with 30% aqueous ethanol and drying afforded 6.4 g (70%) of a yellow solid.

Step 2. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thiophenecarboxylate

To 1,1-dimethylethyl 2-amino-5-phenyl-3-thiophenecarboxylate 0.5 g (1.818 mmole) and 1,3-dichloro-2-isocyanatobenzene 0.342 g (1.818 mmole) was added DMF (3.0 mL), triethylamine 0.255 mL (1.818 mmole), and the contents heated at 80 °C for 2 h. The crude reaction was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.53 g (63%) of a white solid.

Step 3. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thiophenecarboxylate 0.1 g (0.216 mmol) was added TFA 0.324 mL (4.32 mmol) and the contents heated at 50 °C for 3 h. Concentration of the reaction under vacuum afforded the desired product. ES MS m/z 407 (M + H).

Example 383: methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thienyl]carbonyl}amino)ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thiophenecarboxylic acid 0.1 g (0.246 mmol) in DMF (3.0 mL) was added HATU 0.094 g (0.246 mmol) and Hunig's base (0.419 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.051 g (0.246 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column

and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.060 g (44 %) of a colorless oil. ES MS m/z 560 (M + H).

Example 384: (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thienyl]carbonyl}amino)ethanoate 0.055 g (0.098 mmol) was added a 1.0 M solution of lithium hydroxide 0.108 mL(0.108 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.030 g (57%) as a yellow soild. ES MS m/z 555 (M + H).

Example 385: 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thiophenecarboxylic acid

Step 1. 3-amino-5-(4-fluorophenyl)-2-thiophenecarboxylic acid

To methyl 3-amino-5-(4-fluorophenyl)-2-thiophenecarboxylate 3.0 g (0.0119 mole) in dioxane (40 mL) was added a 1 M solution of lithium hydroxide 14.3 mL (14.34 mmol) and the contents refluxed for 4 h. Acidification of the reaction mixture with 1N HCl to pH = 4 gave a solid which was filtered and dried under vacuum.

Step 2. 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thiophenecarboxylic acid

To a solution of 3-amino-5-(4-fluorophenyl)-2-thiophenecarboxylic acid 0.5 g (2.10 mmol) in DMF (3 mL) was added 1,3-dichloro-2-isocyanatobenzene 0.395 g (2.10 mmol) and triethylamine and the contents heated to 50 °C for 16 h. After addition of sat. Na_2CO_3 (20 mL), water and EtOAc were added and the layers separated. The aqueous solution was acidified and then extracted with EtOAc and dried over

magnesium sulfate followed by concentration under vacuum to afford the desired product as an off white solid 0.64 g (71%). ES MS m/z 425 (M + H).

Example 386: methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thienyl]carbonyl}amino)ethanoate

To 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thiophenecarboxylic acid 0.090 g (0.212 mmol) in DMF (2.0 mL) was added HATU 0.088 g (0.233 mmol) and Hunig's base 0.075 mL (0.424 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.044 g (0.212 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.100 g (82 %) of a colorless oil. ES MS m/z 578 (M + H).

Example 387: (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thienyl]carbonyl}amino)ethanoate 0.090 g (0.156 mmol) was added a 1.0 M solution of lithium hydroxide 0.187 mL(0.187 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.76 g (87%) as a yellow solid. (U22007-21-2). ES MS m/z 564 (M + H).

Example 388: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-amino-5-methyl-3-thiophenecarboxylate

To a mixture of propanal 2.41 g (0.0333 mole) and 1,1-dimethylethyl cyanoacetate 4.69 g (0.0333 mole) and sulfur 1.17 g (0.0366 mole) in ethanol (50 mL) was added morpholine 3.33 mL (0.038 mole) and the contents heated under nitrogen at 50 °C for 18 h. After filtration, the contents were concentrated and loaded onto an isco column eluting with EtOAc/Hexane (0 – 100%) to afford 2.1 g (24%) of the desired product.

Step 2. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thiophenecarboxylate

To 1,1-dimethylethyl 2-amino-5-methyl-3-thiophenecarboxylate 0.5 g (2.53 mmole) and 1,3-dichloro-2-isocyanatobenzene 0.475 g (2.53 mmole) was added DMF (4.0 mL) and triethylamine 0.354 mL (2.53 mmole) and the contents heated at 80 °C for 2 h. The crude reaction was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.54 g (53%) of a yellow solid.

Step 3. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thiophenecarboxylate 0.150 g (0.375 mmol) was added TFA 0.144 mL (1.87 mmol) and dioxane (3.0 mL) and the contents heated at 50 °C for 3 h. Concentration of the reaction under vacuum afforded the desired product. ES MS m/z 345 (M + H).

Example 389: methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thienyl]carbonyl}amino)ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thiophenecarboxylic acid 0.129 g (0.375 mmol) in DMF (2.0 mL) was added HATU 0.142 g (0.375 mmol) and Hunig's base 0.067 mL (0.375 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.078 g (0.375 mmol) and the contents

stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.11 g (59 %) of a colorless oil. ES MS m/z 498 (M + H).

Example 390: (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thienyl]carbonyl}amino)ethanoate 0.053 g (0.107 mmol) was added a 1.0 M solution of lithium hydroxide 0.127 mL(0.128 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.042 g (%) as a yellow solid. ES MS m/z 484 (M + H).

Example 391: 5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate

To 1,1-dimethylethyl 2-amino-5-phenyl-3-thiophenecarboxylate 0.5 g (1.818 mmole) and 1,3,5-trichloro-2-isocyanatobenzene 0.398 g (1.818 mmole) was added DMF (3.0 mL) and triethylamine 0.255 mL (1.818 mmole) and the contents heated at 80 °C for 2 h. The crude reaction was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.560 g (70%) of a white solid.

Step 2. 5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.150 g (0.301 mmol) was added TFA 0.30 mL (3.92 mmol) and chloroform (1.2 mL), the contents were heated at 50 °C for 4 h. Concentration of the reaction under vacuum afforded the desired product. ES MS m/z 441 (M + H).

Example 392: methyl (2*S*)-cyclohexyl({[5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoate

To 5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid 0.132 g (0.302 mmol) in DMF (3.0 mL) was added HATU 0.114 g (0.302 mmol) and Hunig's base 0.0527 mL (0.132 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.0627 g (0.302 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.070 g (40 %) of a yellow solid. ES MS m/z 594 (M + H).

Example 393: (2*S*)-cyclohexyl({[5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoate 0.049 g (0.083 mmol) was added a 1.0 M solution of lithium hydroxide 0.10 mL (0.10 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.035 g (73%) as a yellow solid. ES MS m/z 580 (M + H).

Example 394: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-amino-5-(1-methylethyl)-3-thiophenecarboxylate

To a mixture of 3-methylbutanal 2.86 g (0.0333 mole) and 1,1-dimethylethyl cyanoacetate 4.69 g (0.0333 mole) and sulfur 1.17 g (0.0366 mole) in ethanol (50 mL) was added morpholine 3.33 mL (0.038 mole) and the contents heated under nitrogen at 50 °C for 18 h. After filtration, water was added to the reaction to precipitate the desired product. Filtration of the solid followed by washing with 30% aqueous ethanol and drying afforded 2.3 g (28%) of a yellow solid.

Step 2. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thiophenecarboxylate

To 1,1-dimethylethyl 2-amino-5-(1-methylethyl)-3-thiophenecarboxylate 0.5 g (2.07 mmole) and 1,3-dichloro-2-isocyanatobenzene 0.429 g (2.27 mmole) was added DMF (3.0 mL) and triethylamine 0.354 mL (2.07 mmole) and the contents heated at 80 °C for 2 h. The crude reaction was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.38 g (43%) of a white solid.

Step 3. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thiophenecarboxylate 0.150 g (0.350 mmol) was added TFA 0.30 mL (3.90 mmol) and chloroform (1.5 mL), the contents were heated at 50 °C for 4 h. Concentration of the reaction under vacuum afforded the desired product. ES MS m/z 373 (M + H).

Example 395: methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thienyl]carbonyl}amino)ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thiophenecarboxylic acid 0.130 g (0.350 mmol) in DMF (3.0 mL) was added HATU 0.133 g (0.350 mmol) and Hunig's base 0.125 mL (0.700 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.073 g (0.350 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-100%) over 35 min to afford 0.110 g (60 %) of a yellow solid. ES MS m/z 526 (M + H).

Example 396: (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thienyl]carbonyl}oxy)ethanoic acid

To methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thienyl]carbonyl}amino)ethanoate 0.095 g (0.181 mmol) was added a 1.0 M solution of lithium hydroxide 0.217 mL(0.217 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.060 g (65%) as a yellow solid. ES MS m/z 580 (M + H).

Example 397: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-amino-5-(phenylmethyl)-3-thiophenecarboxylate

To a mixture of 3-phenylpropanal 2.23 g (0.0166 mole) and 1,1-dimethylethyl cyanoacetate 2.34 g (0.0166 mole) and sulfur 0.585 g (0.018 mole) in ethanol (30 mL) was added morpholine 1.66 mL (0.019 mole) and the contents heated under nitrogen at 50 °C for 18 h. After filtration, water followed by EtOAc was added to the reaction mixture. Separation of the organic layer followed by drying with magnesium sulfate and concentration under vacuum gave the crude product which was columned using an isco column eluting with EtOAc/Hexane (0 – 60%) to afford 2.2 g (46%) a yellow oil.

Step 2. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thiophenecarboxylate

To 1,1-dimethylethyl 2-amino-5-(phenylmethyl)-3-thiophenecarboxylate 0.5 g (1.73 mmol) and 1,3-dichloro-2-isocyanatobenzene 0.357 g (1.90 mmole) was added DMF (3.0 mL) and triethylamine 0.266 mL (1.90 mmole) an the contents heated at 80 °C for 2 h. The crude reaction was loaded onto an isco column and eluted with a gradient of EtOAc/Hex (0-60%) over 35 min to afford 0.41 g (50%) of a white solid.

Step 3. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thiophenecarboxylate 0.150 g (0.315 mmol) was added TFA 0.30 mL (3.90 mmol) and chloroform (1.5 mL), the contents were heated at 50 °C for 3 h. Concentration of the reaction under vacuum afforded the desired product. ES MS m/z 421 (M + H).

Example 398: methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thienyl]carbonyl}amino)ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thiophenecarboxylic acid 0.132 g (0.315 mmol) in DMF (3.0 mL) was added HATU 0.119 g (0.315 mmol) and Hunig's base 0.112 mL (0.630 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.065 g (0.315 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hex (0-60%) over 35 min to afford 0.113 g (63 %) of a white solid. ES MS m/z 575 (M + H).

Example 399: (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thienyl]carbonyl}oxy)ethanoic acid

To methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thienyl]carbonyl}amino)ethanoate 0.075 g (0.130 mmol) was added a 1.0 M solution of lithium hydroxide 0.169 mL(0.169 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.050 g (68%) as a yellow solid. ES MS m/z 561 (M + H).

Example 400: 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thiophenecarboxylic acid

Step 1. (2*E*)-3-chloro-3-(4-pyridinyl)-2-propenenitrile

To DMF (16.4 mL) cooled to 0 °C was added phosphorousoxychloride 9.89 mL (0.106 mole) and the contents stirred for 10 mins. To the cooled reaction was added 1-(4-pyridinyl)ethanone 4.0 g (0.0244 mole). After warming to r.t., the reaction mixture was heated at 50 °C for 10 mins. The reaction was then cooled to 0 °C and hydroxylamine hydrochloride 11.78 g (0.169 mole) was added slowly. After stirring for 5 mins., the contents were heated at 120 °C for 15 mins. On cooling to r.t., EtOAc was added followed by neutralization with satd. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layer was dried, and then concentrated under vacuum to afford a brown oil that was carried on to the next step.

Step 2. methyl 3-amino-5-(4-pyridinyl)-2-thiophenecarboxylate

To methanol (60 mL) was added a 25% solution of sodium methoxide in methanol 6.85 mL (0.0317 mole) and methyl mercaptoacetate 2.19 mL (0.0244 mole) under nitrogen followed by the addition of (2*E*)-3-chloro-3-(4-pyridinyl)-2-propenenitrile 4.0

g (0.0244 mole) in DMF (20 mL) at 0 °C. After stirring for 30 mins., water was added to precipitate the desired product. After filtration and washing with water, the product was dried under vacuum 2.1 g (37%).

Step 3. 3-amino-5-(4-pyridinyl)-2-thiophenecarboxylic acid

To methyl 3-amino-5-(4-pyridinyl)-2-thiophenecarboxylate 1.0 g (4.27 mmol) was added 1.0 M solution of lithium hydroxide 5.46 mL (5.55 mmol) and dioxane 10 mL. After refluxing for 2 h, the reaction was cooled and then acidified with 1N HCl. The precipitated product was filtered, dried and carried on to the next step.

Step 4. 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thiophenecarboxylic acid

To a solution of 3-amino-5-(4-pyridinyl)-2-thiophenecarboxylic acid 0.3 g (1.36 mmol) in DMF (2.0 mL) was added 1,3-dichloro-2-isocyanatobenzene 0.282 g (1.49 mmole) and triethylamine 0.209 mL (1.36 mmol). After heating at 80 °C for 2 h, the reaction mixture was acidified with 1N HCl to pH = 6 and then filtered. The filtered solid was washed with water, ether and EtOAc and then dried under vacuum to afford 0.513 g (100%) of the desired product as a white solid. ES MS m/z 408 (M + H).

Example 401: methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thienyl]carbonyl}amino)ethanoate

To 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thiophenecarboxylic acid 0.150 g (0.368 mmol) in DMF (3.0 mL) was added HATU 0.153 g (0.404 mmol) and Hunig's base 0.079 mL (0.441 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.077 g (0.368 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was

loaded onto an isco column and eluted with a gradient of EtOAc/Hex (0-100%) over 35 min to afford 0.120 g (58 %) of a white solid. ES MS m/z 562 (M + H).

Example 402: (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thienyl]carbonyl}oxy)ethanoic acid

To methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thienyl]carbonyl}amino)ethanoate 0.075 g (0.133 mmol) was added a 1.0 M solution of lithium hydroxide 0.173 mL(0.173 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.051 g (70 %) as a yellow solid. ES MS m/z 548 (M + H).

Example 403: 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thiophenecarboxylic acid

Step 1. (2*E*)-3-chloro-3-(3-pyridinyl)-2-propenenitrile

To DMF (16.4 mL) cooled to 0 °C was added phosphorousoxychloride 9.89 mL (0.106 mole) and the contents stirred for 10 mins. To the cooled reaction was added 1-(3-pyridinyl)ethanone 4.0 g (0.0244 mole). After warming to r.t., the reaction mixture was heated at 50 °C for 10 mins. The reaction was then cooled to 0 °C and hydroxylamine hydrochloride 11.78 g (0.169 mole) was added slowly. After stirring for 5 mins., the contents were heated at 120 °C for 15 mins. On cooling to r.t., EtOAc was added followed by neutralization with satd. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layer was dried, and then concentrated under vacuum to afford a brown oil that was carried on to the next step.

Step 2. methyl 3-amino-5-(3-pyridinyl)-2-thiophenecarboxylate

To methanol (50 mL) was added a 25% solution of sodium methoxide in methanol 6.40 mL (0.0296 mole) and methyl mercaptoacetate 2.04 mL (0.0228 mole) under nitrogen followed by the addition of (2*E*)-3-chloro-3-(3-pyridinyl)-2-propenenitrile 3.74 g (0.0228 mole) in DMF (20 mL) at 0 °C. After stirring for 30 mins., water was added to precipitate the desired product. After filtration and washing with water, the product was dried under vacuum 2.8 g (53%).

Step 3. 3-amino-5-(3-pyridinyl)-2-thiophenecarboxylic acid

To methyl 3-amino-5-(3-pyridinyl)-2-thiophenecarboxylate 1.0 g (4.27 mmol) was added 1.0 M solution of lithium hydroxide 5.46 mL (5.55 mmol) and dioxane 10 mL. After refluxing for 2 h, the reaction was cooled and then acidified with 1N HCl. The precipitated product was filtered, dried and carried on to the next step.

Step 4. 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thiophenecarboxylic acid

To a solution of 3-amino-5-(3-pyridinyl)-2-thiophenecarboxylic acid acid 0.3 g (1.36 mmol) in DMF (2.0 mL) was added 1,3-dichloro-2-isocyanatobenzene 0.282 g (1.49 mmole) and triethylamine 0.209 mL (1.36 mmol). After heating at 80 °C for 2 h, the reaction mixture was acidified with 1N HCl to pH = 6 and then filtered. The filtered solid was washed with water, ether and EtOAc and then dried under vacuum to afford 0.563 g of the desired product as a yellow solid. ES MS m/z 408 (M + H).

Example 404: methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thienyl]carbonyl}amino)ethanoate

To 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thiophenecarboxylic acid 0.150 g (0.368 mmol) in DMF (3.0 mL) was added HATU 0.153 g (0.404 mmol) and Hunig's base 0.079 mL (0.441 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.077 g (0.368

mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-100%) over 35 min to afford 0.090 g (44%) of a white solid. ES MS m/z 562 (M + H).

Example 405: (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thienyl]carbonyl}oxy)ethanoic acid

To methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thienyl]carbonyl}amino)ethanoate 0.075 g (0.133 mmol) was added a 1.0 M solution of lithium hydroxide 0.173 mL(0.173 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.046 g (63 %) as a yellow solid. ES MS m/z 548 (M + H).

Example 406: 5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid

Step 1. 4-[(*E*)-1-chloro-2-cyanoethenyl]benzonitrile

To DMF (16.4 mL) cooled to 0 °C was added phosphorousoxychloride 9.89 mL (0.106 mole) and the contents stirred for 10 mins. To the cooled reaction was added 4-acetylbenzonitrile 6.15 g (0.0424 mole). After warming to r.t., the reaction mixture was heated at 50 °C for 10 mins. The reaction was then cooled to 0 °C and hydroxylamine hydrochloride 11.78 g (0.169 mole) was added slowly. After stirring for 5 mins., the contents were heated at 120 °C for 15 mins. On cooling to r.t., EtOAc was added followed by neutralization with satd. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layer was dried, and then concentrated under vacuum to afford a brown oil that was carried on to the next step.

Step 2. methyl 3-amino-5-(4-cyanophenyl)-2-thiophenecarboxylate

To methanol (60 mL) was added a 25% solution of sodium methoxide in methanol 4.77 mL (0.0222 mole) and methyl mercaptoacetate 1.53 mL (0.0187 mole) under nitrogen followed by the addition of 4-[(*E*)-1-chloro-2-cyanoethenyl]benzonitrile 3.20 g (0.017 mole) in DMF (20 mL) at 0 °C. After stirring for 30 mins., water was added to precipitate the desired product. After filtration and washing with water, the product was dried under vacuum 2.6 g (59%).

Step 3. 3-amino-5-(4-cyanophenyl)-2-thiophenecarboxylic acid

To methyl 3-amino-5-(4-cyanophenyl)-2-thiophenecarboxylate 1.5 g (5.81 mmol) was added 1.0 M solution of lithium hydroxide 6.39 mL (6.39 mmol) and dioxane 10 mL. After refluxing for 2 h, the reaction was cooled and then acidified with 1N HCl. The precipitated product was filtered, dried and carried on to the next step.

Step 4. 5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid

To a solution of 3-amino-5-(4-cyanophenyl)-2-thiophenecarboxylic acid 0.5 g (2.04 mmol) in DMF (3.0 mL) was added 1,3-dichloro-2-isocyanatobenzene 0.385 g (2.04 mmole) and triethylamine 0.314 mL (2.24 mmol). After heating at 80 °C for 2 h, the reaction mixture was acidified with 1N HCl to pH = 6 and then filtered. The filtered solid was washed with water, ether and EtOAC and then dried under vacuum to afford 0.521 g of the desired product as a yellow solid. ES MS m/z 432 (M + H).

Example 407: (2*S*)-({[5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. methyl (2*S*)-({[5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)(cyclohexyl)ethanoate

To 5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.195 g (0.452 mmol) in DMF (3.0 mL) was added HATU 0.189 g (0.497 mmol) and Hunig's base 0.241 mL (1.35 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.094 g (0.452 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-100%) over 35 min to afford 0.171 g (65%) of a yellow solid.

Step 2. (2*S*)-({[5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)(cyclohexyl)ethanoic acid

To methyl (2*S*)-({[5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)(cyclohexyl)ethanoate 0.020 g (0.0342 mmol) was added a 1.0 M solution of lithium hydroxide 0.064 mL(0.064 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.012 g (61 %) as a yellow solid. ES MS m/z 571 (M + H).

Example 408: 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid

Step 1. (2*E*)-3-chloro-3-[4-(methyloxy)phenyl]-2-propenenitrile

To DMF (16.4 mL) cooled to 0 °C was added phosphorousoxychloride 9.89 mL (0.106 mole) and the contents stirred for 10 mins. To the cooled reaction was added 1-[4-(methyloxy)phenyl]ethanone 6.36 g (0.0424 mole). After warming to r.t., the reaction mixture was heated at 50 °C for 10 mins. The reaction was then cooled to 0 °C and hydroxylamine hydrochloride 11.78 g (0.169 mole) was added slowly. After stirring for 5 mins., the contents were heated at 120 °C for 15 mins.

On cooling to r.t., EtOAc was added followed by neutralization with satd. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layer was dried, and then concentrated under vacuum to afford a brown oil that was carried on to the next step.

Step 2. methyl 3-amino-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylate

To methanol (60 mL) was added a 25% solution of sodium methoxide in methanol 9.42 mL (0.0436 mole) and methyl mercaptoacetate 3.02 mL (0.0336 mole) under nitrogen followed by the addition of (2*E*)-3-chloro-3-[4-(methyloxy)phenyl]-2-propenenitrile 6.5 g (0.0336 mole) in DMF (30 mL) at 0 °C. After stirring for 30 mins., water was added to precipitate the desired product. After filtration and washing with water, the product was dried under vacuum 4.8 g (55%).

Step 3. 3-amino-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid

To methyl 3-amino-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylate 1.5 g (5.70 mmol) was added 1.0 M solution of lithium hydroxide 6.84 mL (6.84 mmol) and dioxane 10 mL. After refluxing for 2 h, the reaction was cooled and then acidified with 1N HCl. The precipitated product was filtered, dried and carried on to the next step.

Step 4. 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid

To a solution of 3-amino-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid 0.5 g (2.0 mmol) in DMF (3.0 mL) was added 1,3-dichloro-2-isocyanatobenzene 0.377 g (2.0 mmole) and triethylamine 0.280 mL (2.0 mmol). After heating at 80 °C for 2 h, the reaction mixture was acidified with 1N HCl to pH = 6 and then filtered. The filtered solid was washed with water, ether and EtOAc and then dried under vacuum to afford 0.521 g of the desired product as a yellow solid. ES MS m/z 437 (M + H).

Example 409: (2*S*)-cyclohexyl[({3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl[({3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoate

To 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid 0.167 g (0.383 mmol) in DMF (3.0 mL) was added HATU 0.146 g (0.383 mmol) and Hunig's base 0.068 mL (0.383 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.080 g (0.383 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-100%) over 35 min to afford 0.120 g (53%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl[({3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid

To methyl (2*S*)-cyclohexyl[({3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoate 0.10 g (0.170 mmol) was added a 1.0 M solution of lithium hydroxide 0.338 mL(0.338 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.012 g (61 %) as a yellow solid. ES MS m/z 576 (M + H).

Example 410: 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-2-thiophenecarboxylic acid

To a solution of 3-amino-5-phenyl-2-thiophenecarboxylic acid 0.5 g (2.28 mmol) in DMF (3 mL) was added 1,3-dichloro-2-isocyanatobenzene 0.428 g (2.28 mmol) and triethylamine 0.319 mL (2.28 mmol) and the contents heated to 80 °C for 2 h. After

addition of sat. Na_2CO_3 (20 mL), water and EtOAc were added and the layers separated. The aqueous solution was acidified and then extracted with EtOAc and dried over magnesium sulfate followed by concentration under vacuum to afford the desired product as an off white solid 0.64 g (71%). ES MS m/z 407 (M + H).

Example 411: (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-2-thienyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-2-thienyl]carbonyl}amino)ethanoate

To 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-2-thiophenecarboxylic acid 0.20 g (0.492 mmol) in DMF (3.0 mL) was added HATU 0.187 g (0.492 mmol) and Hunig's base 0.171 mL (0.984 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.102 g (0.492 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-100%) over 35 min to afford 0.145 g (53%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-2-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-2-thienyl]carbonyl}amino)ethanoate 0.10 g (0.178 mmol) was added a 1.0 M solution of lithium hydroxide 0.534 mL(0.534 mmol) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.080 g (82 %) as a yellow solid. ES MS m/z 546 (M + H).

Example 412: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-amino-3-thiophenecarboxylate

To 1,1-dimethylethyl cyanoacetate 19.8 g (140 mmol) and methyl mercaptoacetate 10.66 g (70 mmol) in DMF (100 mL) was added triethylamine 19.72 mL (140 mmol) dropwise over 15 mins and the contents heated at 45 °C for 45 mins. After the addition of water, EtOAc was added. Washing of the organic layer with water followed by drying with magnesium sulfate and concentration under vacuum afforded the crude product. The crude product was purified using an isco column eluting with EtOAc/Hexane (0-60%) to afford 21 g (75%) of a white solid.

Step 2. 1,1-dimethylethyl 2-[(trifluoroacetyl)amino]-3-thiophenecarboxylate

To 1,1-dimethylethyl 2-amino-3-thiophenecarboxylate 9.86 g (0.049 mole) in DCM (100 mL) was added Hunig's base 11.21 mL(0.064 mole). After cooling the contents to 0 °C, TFAA 7.73 mL (0.054 mmol) was added dropwise. After stirring for 2 h, the reaction mixture was washed with water, dried with magnesium sulfate and then concentrated under vacuum to afford the desired product in quantative yield.

Step 3. 1,1-dimethylethyl 5-bromo-2-[(trifluoroacetyl)amino]-3-thiophenecarboxylate

To 1,1-dimethylethyl 2-[(trifluoroacetyl)amino]-3-thiophenecarboxylate 4.0 g (0.005 mole) in dioxane (80 mL) cooled to 0 °C was added, bromine 0.68 mL (0.005 mole) dropwise over 15 mins. After stirring for 15 mins, EtOAc was added (200 mL) followed by the addition of water. The organic layer was washed with brine and then dried with magnesium sulfate. Concentration of the organic layer under vacuum afforded 4.2 g (84 %) of the bromide.

Step 4. 1,1-dimethylethyl 2-amino-5-bromo-3-thiophenecarboxylate

To 1,1-dimethylethyl 5-bromo-2-[(trifluoroacetyl)amino]-3-thiophenecarboxylate 4.2 g (0.01126 mole) was added MeOH (40 mL) and water (20 mL). To the reaction mixture was then added K_2CO_3 4.67 g (0.0337 mole) and the contents stirred under nitrogen for 8 h. After adding EtOAc, the organic layer was separated, dried with magnesium sulfate and concentrated to afford the crude product that was carried to the next step.

Step 5. 1,1-dimethylethyl 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 2-amino-5-bromo-3-thiophenecarboxylate 2.21 g (7.98 mmole) in DMF (15 mL) was added 1,3-dichloro-2-isocyanatobenzene 1.5 g (7.98 mole) and triethylamine 1.23 mL (8.77 mmol) and the contents heated to 80 °C for 2 h. The crude mixture was loaded onto an isco column and eluted with EtOAc/Hexane (0 – 60%) to afford 2.1 g (57%) of a white solid.

Step 6. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.3 g (0.645 mmol) in DME (5 mL) was added [4-(methyloxy)phenyl]boronic acid 0.147 g (0.967 mmol) followed by a solution of 2M Na_2CO_3 1.29 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.05 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-80%) to afford 0.210 g (66%) of a white solid.

Step 7. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylate 0.145 g (0.294 mmol) was added TFA 0.3 mL (3.90 mmol) and chloroform (1.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product. ES MS m/z 437 (M + H).

Example 413: 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid

To a solution of 1,1-dimethylethyl 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.035 g (0.075 mmol) was added TFA 0.3 mL (3.89 mmol) and the contents heated at 60 °C for 2 h. Concentration of the reaction under vacuum gave the desired product. ES MS m/z 410 (M + H).

Example 414: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.3 g (0.645 mmol) in DME (5 mL) was added 3-pyridinylboronic acid 0.118 g (0.967 mmol) followed by a solution of 2M Na_2CO_3 1.29 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.05 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-80%) to afford 0.210 g (43%) of a white solid.

Step 2. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thiophenecarboxylate 0.10 g (0.215 mmol) was added TFA 0.3 mL (3.98 mmol) and chloroform (1.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product. ES MS m/z 408 (M + H).

Example 415: (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thienyl]carbonyl}amino)ethanoic acid

Step1. methyl (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thienyl]carbonyl}amino)ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thiophenecarboxylic acid 0.080 g (0.196 mmol) in DMF (2.0 mL) was added HATU 0.082 g (0.215 mmol) and Hunig's base 0.101 mL (0.588 mmol), followed by the addition of methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride 0.041 g (0.196 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-100%) over 35 min to afford 0.045 g (41%) of a yellow solid.

Step 2. (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thienyl]carbonyl}amino)ethanoate 0.100 g (0. mmol) was added a 1.0 M solution of lithium hydroxide 1.0 mL(1.06 mmol) and THF (1.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.096 g (99 %) as a yellow solid (U22007-80-2). ES MS m/z 546 (M + H).

Example 416: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.4 g (0.860 mmol) in DME (7 mL) was added [3-(methyloxy)phenyl]boronic acid 0.196 g (1.29 mmol) followed by a solution of 2M Na_2CO_3 1.72 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.06 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-80%) to afford 0.210 g (50%) of a white solid.

Step 2. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylate 0.180 g (0.365 mmol) was added TFA 0.5 mL (6.51mmol) and chloroform (2.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product in quantative yield. ES MS m/z 437 (M + H).

Example 417: (2*S*)-cyclohexyl[({2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl[({2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thiophenecarboxylic acid 0.159 g (0.365 mmol) in DMF (3.0 mL) was added HATU 0.138 g (0.365 mmol) and Hunig's base 0.254 mL (1.46 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.076 g (0.365 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hex (0-60%) over 35 min to afford 0.161 g (75%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl[({2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoic acid

To methyl (2*S*)-cyclohexyl[({2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoate 0.100 g (0. mmol) was added a 1.0 M solution of lithium hydroxide 1.96 mL(1.96 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.10 g (64%) as a yellow solid. ES MS m/z 576 (M + H)

Example 418: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.4 g (0.860 mmol) in DME (7 mL) was added (4-fluorophenyl)boronic acid 0.180 g (1.29 mmol) followed by a solution of 2M Na_2CO_3 1.72 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.06 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product

which was loaded onto an isco column and eluted with EtOAc/Hexane (0-80%) to afford 0.230 g (56%) of a white solid.

Step 2. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thiophenecarboxylate 0.207 g (0.431 mmol) was added TFA 0.3 mL (3.91mmol) and chloroform (2.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product in quantative yield. ES MS m/z 425 (M + H).

Example 419: (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thienyl]carbonyl}amino)ethanoic acid

Step1. methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thienyl]carbonyl}amino)ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thiophenecarboxylic acid 0.206 g (0.488 mmol) in DMF (3.0 mL) was added HATU 0.185 g (0.488 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.101 g (0.488 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hex (0-60%) over 35 min to afford 0.20 g (71%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thienyl]carbonyl}amino)ethanoate 0.210 g (0.365 mmol) was added a 1.0 M solution of lithium hydroxide 1.83 mL(1.83 mmol) and THF (2.0 mL) and the

contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.10 g (49%) as a yellow solid. ES MS m/z 564 (M + H).

Example 420: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.4 g (0.860 mmol) in DME (7 mL) was added (4-fluoro-2-methylphenyl)boronic acid 0.198 g (1.29 mmol) followed by a solution of 2M Na_2CO_3 1.72 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.06 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-80%) to afford 0.251 g (59%) of a white solid.

Step 2. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thiophenecarboxylate 0.190 g (0.384 mmol) was added TFA 0.3 mL (3.97 mmol) and chloroform (2.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product in quantative yeild. ES MS m/z 439 (M + H).

Example 421: (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thienyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thienyl]carbonyl}amino)ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thiophenecarboxylic acid 0.168 g (0.384 mmol) in DMF (3.0 mL) was added HATU 0.146 g (0.384 mmol) and Hunig's base 0.201 mL (1.15 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.080 g (0.384 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.20 g (88%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thienyl]carbonyl}amino)ethanoate 0.215 g (0.365 mmol) was added a 1.0 M solution of lithium hydroxide 1.83 mL(1.83 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded to desired product 0.127 g (61%) as a yellow solid. ES MS m/z 564 (M + H)

Example 422: 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.4 g (0.860 mmol) in DME (7 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-

1*H*-pyrazole 0.268 g (1.29 mmol) followed by a solution of 2M Na_2CO_3 1.72 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.06 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-80%) to afford 0.251 g (56%) of a white solid.

Step 2. 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thiophenecarboxylate 0.171 g (0.367 mmol) was added TFA 0.3 mL (3.97 mmol) and chloroform (2.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product in quantative yield. ES MS m/z 411 (M + H).

Example 423: (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thienyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thienyl]carbonyl}amino)ethanoate

To 2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thiophenecarboxylic acid 0.150 g (0.365 mmol) in DMF (3.0 mL) was added HATU 0.138 g (0.365 mmol) and Hunig's base 0.254 mL (1.46 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.076 g (0.365 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.158 g (77%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1*H*-pyrazol-4-yl)-3-thienyl]carbonyl}amino)ethanoate 0.158 g (0.280 mmol) was added a 1.0 M solution of lithium hydroxide 1.4 mL(1.40 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.129 g (84%) as a yellow solid. ES MS m/z 550 (M + H)

Example 424: 5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 5-bromo-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 2-amino-5-bromo-3-thiophenecarboxylate 4.38 g (13.5 mmole) in DMF (20 mL) was added 2-isocyanato-1,3,5-trimethylbenzene 2.82 g (17.55 mmole) and triethylamine 3.78 mL (27 mmol) and the contents heated to 60 °C for 3 h. The crude mixture was loaded onto an isco column and eluted with EtOAc/Hexane (0 – 60%) to afford 6.48 g (88%) of a white solid.

Step 2. 1,1-dimethylethyl 5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylate

1,1-dimethylethyl 5-bromo-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.319 g (0.728 mmol) in DME (5 mL) was added [4-(methyloxy)phenyl]boronic acid 0.143 g (0.946 mmol) followed by a solution of 2M Na_2CO_3 1.46 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.06 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-50%) to afford 0.128 g (38%) of a white solid.

Step 3. 5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.128 g (0.274 mmol) was added TFA 1.0 mL (13 mmol) and chloroform (2.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product in quantative yield. ES MS m/z 411 (M + H).

Example 425: (2*S*)-cyclohexyl({[5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoate

To 5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid 0.112 g (0.274 mmol) in DMF (3.0 mL) was added HATU 0.104 g (0.274 mmol) and Hunig's base 0.141 mL (0.822 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.057 g (0.274 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.120 g (78%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl({[5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoate 0.105 g (0.186 mmol) was added a 1.0 M solution of lithium hydroxide 0.746 mL(0.746 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under

vacuum afforded the desired product 0.129 g (84%) as a yellow solid. ES MS m/z 550 (M + H).

Example 426: 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 5-bromo-2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3-thiophenecarboxylate

To a solution of 1,1-dimethylethyl 2-amino-5-bromo-3-thiophenecarboxylate 2.5 g (8.99 mmole) in DMF (20 mL) was added 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene 4.87 g (18.0 mmole) and triethylamine 2.53 mL (18.0 mmol) and the contents heated to 60 °C for 3 h. The crude mixture was loaded onto an isco column and eluted with EtOAc/Hexane (0 – 60%) to afford 3.1 g (79%) of a white solid.

Step 2. 1,1-dimethylethyl 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylate

To 1,1-dimethylethyl 5-bromo-2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3-thiophenecarboxylate 0.40 g (0.728 mmol) in DME (5 mL) was added [4-(methyloxy)phenyl]boronic acid 0.143 g (0.946 mmol) followed by a solution of 2M Na_2CO_3 1.46 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.06 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-50%) to afford 0.278 g (66%) of a white solid.

Step 3. 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylate 0.278 g (0.482 mmol) was added TFA 1.0 mL (13 mmol) and chloroform (2.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product in quantative yield. ES MS m/z 521 (M + H).

Example 427: (2*S*)-cyclohexyl[({2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl[({2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoate

To 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylic acid 0.250 g (0.482 mmol) in DMF (3.0 mL) was added HATU 0.183 g (0.482 mmol) and Hunig's base 0.251 mL (1.45 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.100 g (0.482 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.189 g (58%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl[({2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoic acid

To methyl (2*S*)-cyclohexyl[({2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-

thienyl}carbonyl)amino]ethanoate 0.189 g (0.186 mmol) was added a 1.0 M solution of lithium hydroxide 1.12 mL(1.12 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.129 g (70%) as a yellow solid. ES MS m/z 660 (M + H).

Example 428: 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thiophenecarboxylate

To 1,1-dimethylethyl 5-bromo-2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3-thiophenecarboxylate 0.40 g (0.728 mmol) in DME (5 mL) was added {4-[(trifluoromethyl)oxy]phenyl}boronic acid 0.194 g (0.946 mmol) followed by a solution of 2M Na_2CO_3 1.46 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.06 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-30%) to afford 0.182 g (40%) of a white solid.

Step 2. 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thiophenecarboxylate 0.182 g (0.288 mmol) was added TFA 1.0 mL (13.3 mmol) and chloroform (2.0 mL) and the contents heated at

50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product in quantative yield. ES MS m/z 575 (M + H).

Example 429: (2*S*)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thienyl)carbonyl]amino}ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thienyl)carbonyl]amino}ethanoate

To 2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thiophenecarboxylic acid 0.165 g (0.288 mmol) in DMF (3.0 mL) was added HATU 0.109 g (0.288 mmol) and Hunig's base 0.150 mL (0.864 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.060 g (0.288 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-40%) over 35 min to afford 0.085 g (41%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thienyl)carbonyl]amino}ethanoic acid

To methyl (2*S*)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thienyl)carbonyl]amino}ethanoate 0.085 g (0.116 mmol) was added a 1.0 M solution of lithium hydroxide 0.467 mL(0.467 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.061 g (73%) as a yellow solid. ES MS m/z 714 (M + H).

Example 430: 5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid

Step 1. 1,1-dimethylethyl 5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylate

1,1-dimethylethyl 5-bromo-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.319 g (0.728 mmol) in DME (5 mL) was added {4-[(trifluoromethyl)oxy]phenyl}boronic acid 0.194 g (0.946 mmol) followed by a solution of 2M Na_2CO_3 1.46 mL and Dichlorobis(triphenylphosphine)palladium(II) 0.06 g (10 mole%) and the contents refluxed under nitrogen for 6 h. Filtration of the reaction mixture through celite followed by washing with EtOAc and concentration afforded the crude product which was loaded onto an isco column and eluted with EtOAc/Hexane (0-30%) to afford 0.086 g (23%) of a white solid.

Step 2. 5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid

To 1,1-dimethylethyl 5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylate 0.080 g (0.153 mmol) was added TFA 1.0 mL (13.42 mmol) and chloroform (2.0 mL) and the contents heated at 50 °C for 2 h. Concentration of the reaction under vacuum afforded the desired product in quantative yield. ES MS m/z 465 (M + H).

Example 431: (2*S*)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoate

To 5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid 0.080 g (0.172 mmol) in DMF (3.0 mL) was added HATU 0.071 g (0.189 mmol) and Hunig's base 0.089 mL (0.516 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.040 g (0.189 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hex (0-60%) over 35 min to afford 0.050 g (75%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoate 0.050 g (0.081 mmol) was added a 1.0 M solution of lithium hydroxide 0.324 mL(0.324 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.042 g (87%) as a yellow solid. ES MS m/z 630 (M + H).

Example 432: 3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid

To a solution of 3-amino-5-(4-methoxyphenyl)-2-thiophenecarboxylic acid 2.52 g (10.15 mmol) in DMF (20 mL) was added 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene 2.75 g (10.15 mmol) and triethylamine 1.85 mL (13.19 mmol) and the contents heated to 70 °C for 1.5 h. After addition of water, the reaction was acidified to pH = 4 and the precipitated product filtered, washed with EtOAc and dried under vacuum to afford a yellow solid 3.1 g (71%). ES MS m/z 521 (M + H).

Example 433: (2*S*)-cyclohexyl[({3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl[({3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoate

To 3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid 0.248 g (0.478 mmol) in DMF (3.0 mL) was added HATU 0.219 g (0.573 mmol) and Hunig's base 0.085 mL (0.478 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.099 g (0.478 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 40 min to afford 0.108 g (34%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl[({3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid

To methyl (2*S*)-cyclohexyl[({3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoate 0.108 g (0.160 mmol) was added a 1.0 M solution of lithium hydroxide 0.480 mL(0.480 mmol) and THF (1.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.091 g (87%) as a yellow solid. ES MS m/z 660 (M + H).

Example 434: 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylic acid

Step 1. (2*E*)-3-chloro-3-{4-[(trifluoromethyl)oxy]phenyl}-2-propenenitrile

To DMF (60 mL) cooled to 0 °C was added phosphorousoxychloride 6.72 mL (72.0 mmole) and the contents stirred for 10 mins. To the cooled reaction was added 1-{4-[(trifluoromethyl)oxy]phenyl}ethanone 5.88 g (72 mmole). After warming to r.t., the reaction mixture was heated at 50 °C for 10 mins. The reaction was then cooled to 0 °C and hydroxylamine hydrochloride 8.0 g (115.2 mole) was added slowly. After stirring for 5 mins., the contents were heated at 120 °C for 15 mins. After cooling to r.t., EtOAc was added followed by neutralization with satd. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layer was dried, and then concentrated under vacuum to afford a brown oil that was carried on to the next step.

Step 2. methyl 3-amino-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylate

To methanol (75 mL) was added a 25% solution of sodium methoxide in methanol 8.06 mL (0.037 mole) and methyl mercaptoacetate 2.58 mL (0.0288 mole) under nitrogen followed by the addition of (2*E*)-3-chloro-3-{4-[(trifluoromethyl)oxy]phenyl}-2-propenenitrile 7.42 g (0.0288 mole) in DMF (30 mL) at 0 °C. After stirring for 30 mins., water was added to precipitate the desired product. After filtration and washing with water, the product was dried under vacuum to afford 6.4 g (67%).

Step 3. 3-amino-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylic acid

To methyl 3-amino-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylate 1.8 g (5.70 mmol) was added 1.0 M solution of lithium hydroxide 6.84 mL (6.84 mmol) and dioxane 10 mL. After refluxing for 2 h, the reaction was cooled and then acidified with 1N HCl. The precipitated product was filtered, dried and carried on to the next step.

Step 4. 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylic acid

To a solution of 3-amino-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylic acid 0.250 g (0.825 mmol) in DMF (3.0 mL) was added 1,3-dichloro-2-isocyanatobenzene 0.186 g (0.99 mmol) and triethylamine 0.150 mL (1.07 mmol) and the contents heated to 70 °C for 1.5 h. After addition of water, the reaction was acidifies to pH = 4 and the precipitated product filtered, washed with EtOAc and dried under vacuum to afford a yellow solid 0.31 g (77%). ES MS m/z 491 (M + H).

Example 435: (2*S*)-cyclohexyl{[(3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thienyl)carbonyl]amino}ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl{[(3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thienyl)carbonyl]amino}ethanoate

To 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylic acid 0.207 g (0.422 mmol) in DMF (3.0 mL) was added HATU 0.176 g (0.464 mmol) and Hunig's base 0.220 mL (1.27 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.096 g (0.464 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hex (0-50%) over 35 min to afford 0.210 g (77%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl{[(3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thienyl)carbonyl]amino}ethanoic acid

To methyl (2*S*)-cyclohexyl{[(3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thienyl)carbonyl]amino}ethanoate 0.210 g (0.326 mmol) was added a 1.0 M solution of lithium hydroxide 0.979 mL(0.979 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the

organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.142 g (69%) as a yellow solid. ES MS m/z 630 (M + H).

Example 436: 5-{4-[(trifluoromethyl)oxy]phenyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid

To a solution of 3-amino-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylic acid 0.250 g (0.825 mmol) in DMF (3.0 mL) was added 2-isocyanato-1,3,5-trimethylbenzene 0.159 g (0.99 mmol) and triethylamine 0.150 mL (1.07 mmol) and the contents heated to 70 °C for 1.5 h. After addition of water, the reaction was acidifies to pH = 4 and the precipitated product filtered, washed with EtOAc and dried under vacuum to afford a yellow solid 0.294 g (77%). ES MS m/z 465 (M + H).

Example 437: (2*S*)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoate

To 5-{4-[(trifluoromethyl)oxy]phenyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.191 g (0.411 mmol) in DMF (3.0 mL) was added HATU 0.171 g (0.452 mmol) and Hunig's base 0.215 mL (1.23 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.093 g (0.452 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.230 g (91%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoate 0.230 g (0.372 mmol) was added a 1.0 M solution of lithium hydroxide 1.11 mL(1.11 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.184 g (82%) as a yellow solid. ES MS m/z 604 (M + H).

Example 438: 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid

To a solution of 3-amino-5-(4-methoxyphenyl)-2-thiophenecarboxylic acid 4.0 g (16.0 mmol) in DMF (40 mL) was added 2-isocyanato-1,3,5-trimethylbenzene 2.84 g (17.6 mmol) and triethylamine 2.71 mL (19.2 mmol) and the contents heated to 70 °C for 2 h. After concentration of the reaction mixture, the contents were loaded onto an isco column eluting with EtOAc/Hexane (0-100%) to afford 1.9 g (29%) of a white solid. ES MS m/z 411 (M + H).

Example 439: (2*S*)-cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoate
To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.150 g (0.344 mmol) in DMF (3.0 mL) was added HATU 0.143 g (0.378 mmol) and Hunig's base 0.179 mL (1.03 mmol), followed by the addition of methyl (2*S*)-amino(cyclohexyl)ethanoate hydrochloride 0.071 g (0.344 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.124 g (64%) of a yellow solid.

Step 2. (2*S*)-cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoic acid

To methyl (2*S*)-cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoate 0.10 g (0.178 mmol) was added a 1.0 M solution of lithium hydroxide 0.532 mL(0.532 mmol) and THF (0.5 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.093 g (96%) as a yellow solid. ES MS m/z 550 (M + H).

Example 440: (2*S*)-3-methyl-2-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}oxy)butanoic acid

Step 1. methyl *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-valinate
To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl L-valinate hydrochloride 0.122 g (0.731 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.20 g (78%) of a yellow solid.

Step 2. (2*S*)-3-methyl-2-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}oxy)butanoic acid

To methyl *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-valinate 0.20 g (0.382 mmol) was added a 1.0 M solution of lithium hydroxide 1.53 mL(1.53 mmol) and THF (3.5 mL) and the contents stirred for 16 h. The reaction was then acidified to

pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.168 g (86%) as a yellow solid. ES MS m/z 510 (M + H).

Example 441: *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-D-valine

Step 1. methyl *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-D-valinate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.10 g (0.243 mmol) in DMF (2.0 mL) was added HATU 0.101 g (0.267 mmol) and Hunig's base 0.084 mL (0.486 mmol), followed by the addition of methyl methyl D-valinate hydrochloride 0.045 g (0.267 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 35 min to afford 0.067 g (53%) of a yellow oil.

Step 2. *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-D-valine

To methyl *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-D-valinate 0.067 g (0.128 mmol) was added a 1.0 M solution of lithium hydroxide 0.512 mL(0.512 mmol) and THF (1.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.051 g (78%) as a yellow solid. ES MS m/z 510 (M + H).

Example 442: *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-isoleucine

Step 1. methyl *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-isoleucinate
To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl L-isoleucinate hydrochloride 0.116g (0.804 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.277 g (71%) of a yellow solid.

Step 2. *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-isoleucine

To methyl *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-isoleucinate 0.277 g (0.515 mmol) was added a 1.0 M solution of lithium hydroxide 2.06 mL(2.06 mmol) and THF (3.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.210 g (78%) as a yellow solid. ES MS m/z 524 (M + H).

Example 443: *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-norleucine

Step 1. methyl *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-norleucinate
To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU

0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl L-norleucinate hydrochloride 0.134g (0.804 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.389 g (99%) of a yellow solid.

Step 2. *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-norleucine

To methyl *N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-norleucinate 0.413 g (0.769 mmol) was added a 1.0 M solution of lithium hydroxide 3.84 mL(3.84 mmol) and THF (4.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.298 g (74%) as a yellow solid. ES MS m/z 524 (M + H).

Example 444: 3-cyclohexyl-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-alanine

Step 1. methyl 3-cyclohexyl-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-alaninate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl 3-cyclohexyl-L-alaninate hydrochloride 0.178 g (0.804 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.350 g (83%) of a yellow solid.

Step 2. 3-cyclohexyl-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-alanine

To methyl 3-cyclohexyl-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-alaninate 0.340 g (0.589 mmol) was added a 1.0 M solution of lithium hydroxide 1.5 mL(1.5 mmol) and THF (3.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.182 g (55%) as a yellow solid. ES MS m/z 564 (M + H).

Example 445: *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-serine

Step 1. methyl *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-serinate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl *O*-(1,1-dimethylethyl)-L-serinate hydrochloride 0.168 g (0.804 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.350 g (85%) of a yellow solid.

Step 2. *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-serine

To methyl *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-serinate 0.350 g (0.617 mmol) was added a 1.0 M solution of lithium hydroxide 2.46 mL(2.4 mmol)

and THF (3.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.298 g (87%) as a yellow solid. ES MS m/z 554 (M + H).

Example 446: *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-threonine

Step 1. methyl *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-threoninate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl *O*-(1,1-dimethylethyl)-L-threoninate hydrochloride 0.180 g (0.804 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.348 g (82%) of a yellow solid.

Step 2. *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-threonine

To methyl *O*-(1,1-dimethylethyl)-*N*-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-threoninate 0.48 g (0.60 mmol) was added a 1.0 M solution of lithium hydroxide 2.40 mL(2.40 mmol) and THF (3.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.258 g (76%) as a yellow solid. ES MS m/z 568 (M + H).

Example 447: 1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-proline

Step 1. 1,1-dimethylethyl 1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-prolinate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of 1,1-dimethylethyl L-prolinate 0.125 g (0.731 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 40 min to afford 0.301 g (73%) of a yellow solid.

Step 2. 1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-proline

To 1,1-dimethylethyl 1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-prolinate 0.301 g (0.534 mmol) was added TFA 1mL (12.96 mmol) and chloroform (3 mL). The reaction mixture was refluxed for 1 h and then concentrated under vacuum to afford the product 0.268 g (99%) as a grey solid. ES MS m/z 508 (M + H).

Example 448: (2*S*)-1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-2-piperidinecarboxylic acid

Step 1. methyl (2*S*)-1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-2-piperidinecarboxylate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU

0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl (2*S*)-2-piperidinecarboxylate hydrochloride 0.131 g (0.731 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 40 min to afford 0.312 g (80%) of a white solid.

Step 2. (2*S*)-1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-2-piperidinecarboxylic acid

To methyl (2*S*)-1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-2-piperidinecarboxylate 0.312 g (0.583 mmol) was added a 1.0 M solution of lithium hydroxide 1.75 mL(1.75 mmol) and THF (2.0 mL) and the contents stirred for 16 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.216 g (71%) as a yellow solid. ES MS m/z 522 (M + H).

Example 449: 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopropanecarboxylic acid

Step 1. methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopropanecarboxylate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl 1-aminocyclopropanecarboxylate hydrochloride 0.110 g (0.731 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was

loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 40 min to afford 0.217 g (59%) of a yellow solid.

Step 2. 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopropanecarboxylic acid

To methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopropanecarboxylate 0.217 g (0.428 mmol) was added a 1.0 M solution of lithium hydroxide 2.14 mL(2.14 mmol) and dioxane (5.0 mL) and the contents refluxed for 2 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.178 g (84%) as a yellow solid. ES MS m/z 494 (M + H).

Example 450: 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclobutanecarboxylic acid

Step 1. methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclobutanecarboxylate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl 1-aminocyclobutanecarboxylate 0.103 g (0.731 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 40 min to afford 0.350 g (92%) of a yellow solid.

Step 2. 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclobutanecarboxylic acid

To methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclobutanecarboxylate 0.349 g (0.671 mmol) was added a 1.0 M solution of lithium hydroxide 3.35 mL(3.35 mmol) and dioxane (5.0 mL) and the contents refluxed for 2 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.281 g (83%) as a yellow solid. ES MS m/z 508 (M + H).

Example 451: 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopentanecarboxylic acid

Step 1. methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopentanecarboxylate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl 1-aminocyclopentanecarboxylate hydrochloride 0.143 g (0.804 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-60%) over 40 min to afford 0.350 g (90%) of a yellow solid.

Step 2. 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopentanecarboxylic acid

To methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopentanecarboxylate 0.350 g (0.654 mmol) was added a 1.0 M solution of lithium hydroxide 3.27 mL(3.27 mmol) and dioxane (5.0 mL) and the contents refluxed for 2 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.294 g (87%) as a yellow solid. ES MS m/z 522 (M + H).

Example 452: 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1. methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl 1-aminocyclohexanecarboxylate 0.143 g (0.913 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.280 g (70%) of a yellow solid.

Step 2. 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

To methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-

thienyl]carbonyl}amino)cyclohexanecarboxylate 0.280 g (0.510 mmol) was added a 1.0 M solution of lithium hydroxide 2.55 mL(2.55 mmol) and dioxane (5.0 mL) and the contents refluxed for 2 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.226 g (83%) as a yellow solid. ES MS m/z 536 (M + H).

Example 453: 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cycloheptanecarboxylic acid

Step 1. methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cycloheptanecarboxylate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl 1-aminocycloheptanecarboxylate 0.155 g (0.913 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 35 min to afford 0.282 g (69%) of a yellow solid.

Step 2. 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cycloheptanecarboxylic acid

To methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cycloheptanecarboxylate 0.280 g (0.497 mmol) was added a 1.0 M solution of lithium hydroxide 2.48 mL(2.48 mmol) and dioxane (5.0 mL) and the contents refluxed for 2 h. The reaction was then acidified to pH = 4.0, the

precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.210 g (77%) as a yellow solid. ES MS m/z 550 (M + H).

Example 454: 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1. methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclooctanecarboxylate

To 5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid 0.30 g (0.731 mmol) in DMF (3.0 mL) was added HATU 0.305 g (0.804 mmol) and Hunig's base 0.255 mL (1.46 mmol), followed by the addition of methyl 1-aminocyclooctanecarboxylate 0.135 g (0.731 mmol) and the contents stirred at r.t. for 16 h. The crude reaction mixture was loaded onto an isco column and eluted with a gradient of EtOAc/Hexane (0-50%) over 40 min to afford 0.310 g (73%) of a yellow solid.

Step 2. 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclooctanecarboxylic acid

To methyl 1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclooctanecarboxylate 0.30 g (0.519 mmol) was added a 1.0 M solution of lithium hydroxide 1.57 mL(1.57 mmol) and dioxane (3.0 mL) and the contents refluxed for 2 h. The reaction was then acidified to pH = 4.0, the precipitated product was then extracted with EtOAc. Drying of the organic layer with magnesium sulfate followed by concentration under vacuum afforded the desired product 0.268 g (92%) as a yellow solid. ES MS m/z 564 (M + H).

Example 455: (2*S*)-cyclohexyl({[3-({[(2,6-dichloro-4-fluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichloro-4-fluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate.

Methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate hydrochloride (0.05 g, 0.133 mmol) in 5 mL of pyridine was treated 1,3-dichloro-5-fluoro-2-isocyanatobenzene (0.139 g, 0.67 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.051 g of product.

Step 2. (2*S*)-cyclohexyl({[3-({[(2,6-dichloro-4-fluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.020 g, 0.48 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[(2,6-dichloro-4-fluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.050 g, 0.09 mmol) in THF: MeOH: water-3:1:1 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 45 mg (92 % yield) of desired product as a white solid. ES MS m/z 530 (M-H).

Example 456: 2-cyclohexyl-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine

Step 1. methyl 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alaninate
To a solution of 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alanine (1.0 g, 2.54 mmol) in 25 mL of dichloromethane was added a dilute solution of

diazomethane in methylene chloride until a yellow color remained. This was stirred for ca. 15 min and then acetic acid was added to remove the yellow color. The mixture was wash with aqueous $NaHCO_3$, dried over sodium sulfate and concentrated to dryness to give 1.1 g (100 % yield) of desired product as a white solid.

Step 2. methyl 2-cyclohexyl-L-alaninate hydrochloride

To methyl 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alaninate (0.65 g, 1.60 mmol) in 20 mL of dioxane was added polymer bound piperizine (Aldrich Chemical catalog number 54,754-9, 5.3 g). The mixture was stirred at RT for 72 h, and then filtered and concentrated to dryness. To the crude product was added HCl in ether (1 M) followed by hexanes to give 0.205 g (57 % yield) of the desired product as a white solid.

Step 3. methyl 2-cyclohexyl-*N*-{[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alaninate

HATU (0.189 g, 0.50 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (0.129 g, 0.45 mmol), methyl 2-cyclohexyl-L-alaninate hydrochloride (0.10 g, 0.45 mmol) and diisopropylethylamine (0.09 g, 0.68 mmol) in 5 mL of DMF. The mixture was stirred at RT for ca. 5 h. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate and water. The organic layer was washed with sodium hydrogen sulfate, sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.147 g (72 % yield) of product.

Step 4. methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-cyclohexyl-L-alaninate hydrochloride

To methyl 2-cyclohexyl-*N*-{[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alaninate (0.145 g, 0.318 mmol) in 10 mL of dichloromethane was added 5 mL of HCl in dioxane (4 N). The reaction was stirred at RT for ca. 3 h, and concentrated to dryness to give 0.139 g of the desire product.

Step 5. methyl 2-cyclohexyl-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alaninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-cyclohexyl-L-alaninate hydrochloride (0.130 g, 0.33 mmol) in 10 mL of pyridine was treated 1,3,5-trichloro - 2-isocyanatobenzene (0.37 g, 1.66 mmol) at RT for 6 h. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.15 g (80 % yield) of product.

Step 6. 2-cyclohexyl-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine

Lithium hydroxide monohydrate (0.095 g, 2.26 mmol) was added to a solution of methyl 2-cyclohexyl-*N*-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alaninate (0.150 g, 0.26 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at 70 C overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave to give 83 mg (55 % yield) of desired product as a white solid. ES MS m/z 560 (M-H).

Example 457: (2*S*)-cyclohexyl{[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl{[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoate

HATU (0.14 g, 0.37 mmol) was added to a solution of methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate hydrochloride (0.12 g, 0.32 mmol), (2,4,6-trimethylphenyl)acetic acid (0.062 g, 0.35 mmol), and diisopropylethylamine (0.062 g, 0.48 mmol) in 5 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 0.072 g (45 % yield) of product.

Step 2. (2*S*)-cyclohexyl{[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid

Lithium hydroxide monohydrate (0.025 g, 0.60 mmol) was added to a solution of methyl (2*S*)-cyclohexyl{[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoate (0.068 g, 0.14 mmol) in THF: MeOH: water-3:1:1 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 57 mg (86 % yield) of desired product as a white solid. ES MS m/z 485 (M-H).

Example 458: (2*S*)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. methyl (2*S*)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoate (u22087/26/1)

Methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate hydrochloride (0.11 g, 0.29 mmol) in 10 mL of pyridine was treated 5-bromo-2-isocyanato-1,3-dimethylbenzene (0.139 g, 0.67 mmol) for 5 h at RT. The pyridine was removed at

reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.115 g (70 % yield) of product.

Step 2. (2*S*)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide monohydrate (0.017 g, 0.40 mmol) was added to a solution of methyl (2*S*)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.020 g, 0.035 mmol) in THF: MeOH: water-3:1:1 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 19 mg (97 % yield) of desired product as a white solid. ES MS m/z 550 (M-H).

Example 459: (2*S*)-cyclohexyl{[(3-{[(2,3,6-trichlorophenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl{[(3-{[(2,3,6-trichlorophenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoate

HATU (0.12 g, 0.31 mmol) was added to a solution of methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate hydrochloride (0.100 g, 0.27 mmol), (2,3,6-trichlorophenyl)acetic acid (0.070 g, 0.29 mmol), and diisopropylethylamine (0.069 g, 0.53 mmol) in 6 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 0.068 g (45 % yield) of product.

Step 2. (2*S*)-cyclohexyl{[(3-{[(2,3,6-trichlorophenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid

Lithium hydroxide monohydrate (0.030 g, 0.71 mmol) was added to a solution of methyl (2*S*)-cyclohexyl{[(3-{[(2,3,6-trichlorophenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoate (0.065 g, 0.12 mmol) in THF: MeOH: water-5:1.5:1.5 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 56 mg (88 % yield) of desired product as a white solid. ES MS m/z 545 (M-H).

Example 460: (2*S*)-cyclohexyl({[3-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1: methyl (2*S*)-cyclohexyl({[3-({[(4-ethenyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

Tetrakis(triphenylphosphine)palladium(0) (0.012 g, 0.01 mmol) was added to methyl (2*S*)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.088 g, 0.16 mmol) and tributyl(ethenyl)stannane (0.056 g, 0.18 mmol) in ca. 4 mL of toluene. The mixture was heated at reflux overnight. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.046 g (56 % yield) of product.

Step 2. methyl (2*S*)-cyclohexyl({[3-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-cyclohexyl({[3-({[(4-ethenyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.046 g, 0.09 mmol) and palladium (10 % on carbon, 0.04 g) in ca. 6 mL of ethyl

acetate was stirred under 1 atm of hydrogen overnight. The mixture was flushed with nitrogen, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.038 g (83 % yield) of product.

Step 3. (2*S*)-cyclohexyl({[3-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.020 g, 0.48 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.032 g, 0.06 mmol) in THF: MeOH: water-3:1:1 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Crystallization from ethyl acetate and hexanes gave 22 mg (71 % yield) of desired product as a white solid. ES MS m/z 500 (M-H).

Example 461: (2*S*)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid

Step 1. Methyl (2S)-({3-[(tert-butoxycarbonyl)amino]-2-naphthoyl}amino)(cyclohexyl)ethanoate

HATU (0.875 g, 2.30 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (0.575 g, 2.00 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.479 g, 2.30 mmol) and diisopropylethylamine (0.387 g, 3.00 mmol) in 20 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarbonate, and brine, dried over sodium sulfate, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.715 g of product.

Step 2. Methyl (2S)-[(3-amino-2-naphthoyl)amino](cyclohexyl)ethanoate hydrochloride

Methyl (2S)-({3-[(tert-butoxycarbonyl)amino]-2-naphthoyl}amino)(cyclohexyl)ethanoate (0.700 g, 1.0 mmol) in 20 mL of CH_2Cl_2 was treated with 20 mL of 4 N HCl in dioxane. The mixture as stirred at RT for ca. 3 h and the solvents were removed under reduced pressure to give the 0.675 g of the product.

Step 3. 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene

2,6-dichloro-4-[(trifluoromethyl)oxy]aniline (0.50 g, 2.03 mmol) in 8 mL of dichloromethane was added to a mixture of phosgene (20 % solution in toluene, 4 g) and PS-DIEA (Argonaut Technologies, 2.1 g, 3.9 mmol/g) in 25 mL of dichloromethane. After stirring at RT overnight the mixture was filtered and concentrated to give 0.52 g (94 % yield) of the product.

Step 4. methyl (2*S*)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoate

Methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate hydrochloride (0.100 g, 0.265 mmol) in 7 mL of pyridine was treated 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.360 g, 0.1.33 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.101 g (62 % yield) of product.

Step 5. (2*S*)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid

Lithium hydroxide monohydrate (0.05 g, 0.1.19 mmol) was added to a solution of methyl (2*S*)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoate (0.095 g, 0.155 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 73 mg (79 % yield) of desired product as a white solid. ES MS m/z 596 (M-H).

Example 462: (2*S*)-(*trans*-4-methylcyclohexyl)({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. (*trans*-4-methylcyclohexyl)methanol

Trans-4-methylcyclohexanecarboxylic acid (1.00 g, 7.03 mmol) in 8 mL of THF was added to an ice cold solution of lithium aluminum hydride (1 N in THF, 7 mL, 7 mmol). The mixture was stirred at RT for 2.5 h and then returned to an ice bath. To this mixture was then added in order dropwise, water (0.28 mL), 15 % NaOH (0.28 mL), and water (0.80 mL). After stirring 10 min, sodium sulfate was added, and the mixture was diluted with ether and filtered. Removal of the solvent gave 0.958 g of the desired product.

Step 2. *trans*-4-methylcyclohexanecarbaldehyde

Dess-Martin periodinane (4.45 g, 10.5 mmol) was added to (*trans*-4-methylcyclohexyl)methanol (7.0 mmol) in 60 mL of dichloromethane in 2 portions. The reaction was stirred at RT for 2.5 h, then was washed with sodium bicarbonate

and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was diluted with ether, filter to remove solids and concentrate to give the product as an oil (0.95 g).

Step 3. (S)- 4-methyl-*N*-[(1*E*)-(*trans*-4-methylcyclohexyl)methylidene]benzenesulfinamide

A mixture of (S)-4-methylbenzenesulfinamide (0.30 g, 1.93 mmol), *trans*-4-methylcyclohexanecarbaldehyde (0.37 g, 2.90 mmol) and titanium (IV) ethoxide (1.32 g, 5.8 mmol) in 20 mL of dichloromethane was refluxed overnight. The reaction was cooled to RT and 15 mL of water was added slowly. The resulting mixture was diluted with dichloromethane and filtered through a pad of celite. The phases were separated and the dichloromethane phase was washed with water and brine, dried over sodium sulfate, filtered, and the solvent evaporated to give 0.475 g (93 % yield) of the product.

Step 4. *N*-[(*S*)-cyano(trans-4-methylcyclohexyl)methyl]-(S)-4-methylbenzenesulfinamide

To diethylaluminum cyanide (1 N in THF, 2.35 mL, 2.35 mmol) in 7 mL of THF at -78 C was added isopropyl alcohol (0.94 g, 1.57 mmol). The mixture was stirred at RT for 30 min. This mixture was then cannulated into a -78 C solution of (S)- 4-methyl-*N*-[(1*E*)-(*trans*-4-methylcyclohexyl)methylidene]benzenesulfinamide (0.42 g, 1.57 mmol) in 20 mL of THF. The mixture was warmed to RT over 2 h and stirred at RT overnight. The mixture was cooled to -78 C and 10 mL of a saturated ammonium chloride solution was added and the mixture was warmed to RT. The mixture was filtered through celite and extract with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.275 g (62 % yield) of product.

Step 5. (2*S*)-amino(trans-4-methylcyclohexyl)ethanenitrile hydrochloride

A mixture of *N*-[(*S*)-cyano(trans-4-methylcyclohexyl)methyl]-(S)-4-methylbenzenesulfinamide (0.20 g, 0.69 mmol), hydrogen chloride (4 N in dioxane, 10 mL, 40 mmol) in 10 mL of methanol was heated at reflux for 6h. The mixture was cooled to RT and the solvent evaporated. To the residue was added 10 mL of water and sodium bicarbonate, and this was extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane and hydrogen chloride (4 N in dioxane, 5 mL) was added and the solvent was removed. The residue was washed with ether to give 0.132 g of the product.

Step 6. methyl (2*S*)-amino(trans-4-methylcyclohexyl)ethanoate hydrochloride

Hydrogen chloride gas was bubbled into a mixture of (2*S*)-amino(trans-4-methylcyclohexyl)ethanenitrile hydrochloride (0.128 g, 0.68 mmol) in 15 mL of methanol until saturated. The mixture was refluxed overnight. The solvent was removed and the residue dissolved in water. Sodium bicarbonate was added and the mixture was extracted with ethyl acetate, dried over sodium sulfate and the solvent removed. The resulting residue was dissolved in methanol (15 mL) and was saturated with hydrogen chloride gas, and the mixture was refluxed for 6 h. Removal of the solvent gave the product.

Step 7. methyl (2*S*)-({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(*trans*-4-methylcyclohexyl)ethanoate

HATU (0.219 g, 0.575 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (0.15 g, 0.523 mmol), (2*S*)-amino(trans-4-methylcyclohexyl)ethanoate hydrochloride (0.116 g, 0.523 mmol) and diisopropylethylamine (0.101 g, 0.784 mmol) in 7 mL of DMF. The mixture was stirred at RT for ca. 4.5 h. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarobnate and brine, dried over sodium sulfate, filtered,

and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.197 g of ca. 60 % pure product.

Step 8. methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(*trans*-4-methylcyclohexyl)ethanoate hydrochloride

Methyl (2*S*)-({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(*trans*-4-methylcyclohexyl)ethanoate (0.195 g, 1.0 mmol) in 6 mL of CH_2Cl_2 was treated with 6 mL of 4 N HCl in dioxane. The mixture as stirred at RT for ca. 2 h and the solvents were removed under reduced pressure to give the 0.190 g of the product.

Step 9. methyl (2*S*)-(*trans*-4-methylcyclohexyl)({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

Methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(*trans*-4-methylcyclohexyl)ethanoate hydrochloride (0.19 g, 0.53 mmol) in 10 mL of pyridine was treated 1,3,5-trichloro-2-isocyanatobenzene (0.49 g, 2.10 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.089 g of product.

Step 10. (2*S*)-(*trans*-4-methylcyclohexyl)({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.050 g, 1.19 mmol) was added to a solution of methyl (2*S*)-(*trans*-4-methylcyclohexyl)({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

(0.084 g, 0.145 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.081 g (99 % yield) of desired product as a white solid. ES MS m/z 560 (M-H).

Example 463: (2*S*)-[*trans*-4-(1,1-dimethylethyl)cyclohexyl]({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. [*trans*-4-(1,1-dimethylethyl)cyclohexyl]methanol

Trans-4-(1,1-dimethylethyl)cyclohexanecarboxylic acid (1.00 g, 5.43 mmol) in 8 mL of THF was added to an ice cold solution of lithium aluminum hydride (1 N in THF, 6 mL, 6 mmol). The mixture was stirred at RT for 2.5 h and then returned to an ice bath. To this mixture was then added in order dropwise, water (0.23 mL), 15 % NaOH (0.23 mL), and water (0.69 mL). After stirring 10 min, sodium sulfate was added, and the mixture was diluted with ether and filtered. Removal of the solvent gave 0.953 g of the desired product.

Step 2. *trans*-4-(1,1-dimethylethyl)cyclohexanecarbaldehyde

Dess-Martin periodinane (3.45 g, 8.14 mmol) was added to [*trans*-4-(1,1-dimethylethyl)cyclohexyl]methanol (5.43 mmol) in 50 mL of dichloromethane in 3 portions. The reaction was stirred at RT for 2 h, then was washed with sodium bicarbonate and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was diluted with ether, filter to remove solids and concentrate to give the product as an oil (0.822 g).

Step 3. (S)- *N*-{(1*E*)-[*trans*-4-(1,1-dimethylethyl)cyclohexyl]methylidene}benzenesulfinamide

A mixture of (S)-4-methylbenzenesulfinamide (0.60 g, 3.87 mmol), *trans*-4-(1,1-dimethylethyl)cyclohexanecarbaldehyde (0.714 g, 4.25 mmol) and titanium (IV) ethoxide (2.65 g, 11.61 mmol) in 40 mL of dichloromethane was refluxed overnight. The reaction was cooled to RT and 50 mL of water was added slowly. The resulting mixture was diluted with dichloromethane and filtered through a pad of celite. The phases were separated and the dichloromethane phase was washed with water and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.49 g (41 % yield) of product.

Step 4. *N*-{(*S*)-cyano[*trans*-4-(1,1-dimethylethyl)cyclohexyl]methyl}benzenesulfinamide

To diethylaluminum cyanide (1 N in THF, 2.37 mL, 2.37 mmol) in 7 mL of THF at -78 C was added isopropyl alcohol (0.95 g, 1.58 mmol). The mixture was stirred at RT for 30 min. This mixture was then cannulated into a -78 C solution of (S)- *N*-{(1*E*)-[*trans*-4-(1,1-dimethylethyl)cyclohexyl]methylidene}benzenesulfinamide (0.485 g, 1.58 mmol) in 20 mL of THF. The mixture was warmed to RT overnight. The mixture was cooled to -78 C and 10 mL of a saturated ammonium chloride solution was added and the mixture was warmed to RT. The mixture was filtered through celite and extract with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.428 g (81 % yield) of product.

Step 5. (2*S*)-amino[*trans*-4-(1,1-dimethylethyl)cyclohexyl]ethanoic acid hydrochloride

Hydrogen chloride gas was bubbled into a solution of *N*-{(*S*)-cyano[*trans*-4-(1,1-dimethylethyl)cyclohexyl]methyl}benzenesulfinamide (0.42 g, 1.26 mmol) in 15 mL of methanol in a high pressure tube until the solution was saturated. The tube was sealed and heated at 100 C for 24 h. The tube was cooled to RT then on ice and

the cap carefully removed. The solvent was removed and water and sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The mixture was concentrated and 15 mL of hydrochloric acid (6 N) was added and the solution refluxed overnight. The mixture was cooled to RT and 30 mL of ether was added. The resulting solid was collect by filtration and dried under reduced pressure to give 0.159 g of the product.

Step 6. methyl (2*S*)-amino[*trans*-4-(1,1-dimethylethyl)cyclohexyl]ethanoate hydrochloride

(2*S*)-amino[*trans*-4-(1,1-dimethylethyl)cyclohexyl]ethanoic acid hydrochloride (0.155 g, 0.72 mmol), concentrated hydrochloric acid (0.8 mL) and 2,2-Dimethoxypropane (10 mL) was stirred at RT overnight. The solvent was removed under reduced pressure and methanol was added. The methanol was removed under reduced pressure, and this was repeated. The resulting solid was triturated with ether to give 0.153 g of the product.

Step 7. methyl (2*S*)-[*trans*-4-(1,1-dimethylethyl)cyclohexyl]({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

HATU (0.259 g, 0.682 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (0.163 g, 0.568 mmol), methyl (2*S*)-amino[*trans*-4-(1,1-dimethylethyl)cyclohexyl]ethanoate hydrochloride (0.150 g, 0.568 mmol) and diisopropylethylamine (0.147 g, 1.14 mmol) in 7 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.139 g (49 % yield) of product.

Step 8. methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}[*trans*-4-(1,1-dimethylethyl)cyclohexyl]ethanoate hydrochloride

Methyl (2*S*)-[*trans*-4-(1,1-dimethylethyl)cyclohexyl]({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.135 g, 0.27 mmol) in 8 mL of CH_2Cl_2 was treated with 8 mL of 4 N HCl in dioxane. The mixture as stirred at RT for ca. 2.5 h and the solvents were removed under reduced pressure to give the 0.132 g (100%) of the product.

Step 9. methyl (2*S*)-[*trans*-4-(1,1-dimethylethyl)cyclohexyl]({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

Methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}[*trans*-4-(1,1-dimethylethyl)cyclohexyl]ethanoate hydrochloride (0.131 g, 0.33 mmol) in 10 mL of pyridine was treated 1,3,5-trichloro-2-isocyanatobenzene (0.30 g, 1.32 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.120 g (59 % yield) of product.

Step 10. (2*S*)-[*trans*-4-(1,1-dimethylethyl)cyclohexyl]({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.075 g, 1.79 mmol) was added to a solution of methyl (2*S*)-[*trans*-4-(1,1-dimethylethyl)cyclohexyl]({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.115 g, 0.186 mmol) in THF: MeOH: water-12:4:4 mL . The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.105 g (93 % yield) of desired product as a white solid. ES MS m/z 602 (M-H).

Example 464: 2-cyclohexyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine

Step 1. methyl 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alaninate

To a solution of 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alanine (1.0 g, 2.54 mmol) in 15 mL of ethyl acetate and 15 mL of methanol was added (trimethylsilyl)diazomethane (2.0 M in hexanes, 3.74 mL). This was stirred for ca. 30 min and concentrated to dryness to give 1.15 g of desired product as a tacky white solid.

Step 2. methyl 2-cyclohexyl-L-alaninate hydrochloride

To methyl 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alaninate (1.1 g, 2.73 mmol) in 25 mL of dioxane was added polymer bound piperizine (Aldrich Chemical catalog number 54,754-9, 5.0 g). The mixture was stirred at RT for 72 h, then at ca. 60 C for 18 h. The mixture was filtered and concentrated to dryness. The residue was dissolved in 20 mL of dichloromethane and 5 mL of hydrogen chloride (4 N in dioxane) was added. Remove solvent and crystallize from dichloromethane and hexanes to give 0.493 g (81 % yield) of the product.

Step 3. methyl 2-cyclohexyl-*N*-{[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alaninate

HATU (0.880 g, 2.32 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (0.606 g, 2.11 mmol), methyl 2-cyclohexyl-L-alaninate hydrochloride (0.468 g, 2.11 mmol) and diisopropylethylamine (0.408 g, 3.16 mmol) in 20 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarbonate and brine and dried over sodium sulfate, filtered, and the solvent

evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.667 g (70 % yield) of product.

Step 4. methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-cyclohexyl-L-alaninate hydrochloride

To methyl 2-cyclohexyl-*N*-{[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alaninate (0.667 g, 1.47 mmol) in 20 mL of methylene chloride was added 10 mL of HCl in dioxane (4 N). The reaction was stirred at RT for ca. 3.5 h, and concentrated to dryness to give 0.575 g of the desire product.

Step 5. methyl 2-cyclohexyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alaninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-cyclohexyl-L-alaninate hydrochloride (0.155 g, 0.397 mmol) in 7 mL of pyridine was treated 2-isocyanato-1,3,5-trimethylbenzene (0.30 g, 1.98 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.171 g (83 % yield) of product.

Step 6. 2-cyclohexyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine

Lithium hydroxide monohydrate (0.150 g, 3.6 mmol) was added to a solution of methyl 2-cyclohexyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alaninate (0.170 g, 0.33 mmol) in THF: MeOH: water-15:5:5 mL . The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 147 mg (88 % yield) of desired product as a white solid. ES MS m/z 500 (M-H).

Example 465: 2-cyclohexyl-*N*-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-alanine

Step 1. 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene

2,6-dichloro-4-[(trifluoromethyl)oxy]aniline (4.00 g, 16.26 mmol) in 20 mL of dichloromethane was added to a mixture of phosgene (20 % solution in toluene, 20.1 g) and PS-DIEA (Argonaut Technologies, 10.4 g, 3.9 mmol/g) in 150 mL of dichloromethane. After stirring at RT overnight the mixture was filtered and concentrated to give 4.8 g of the product (some toluene remaining).

Step 2. methyl 2-cyclohexyl-*N*-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-alaninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-2-cyclohexyl-L-alaninate hydrochloride (0.20 g, 0.512 mmol) in 10 mL of pyridine was treated 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.70 g, 2.56 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.273 g (85 % yield) of product.

Step 3. 2-cyclohexyl-*N*-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-alanine

Lithium hydroxide monohydrate (0.150 g, 3.57 mmol) was added to a solution of methyl 2-cyclohexyl-*N*-[(3-{[({2,6-dichloro-4-

[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-alaninate (0.270 g, 0.431 mmol) in THF: MeOH: water-15:5:5 mL . The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 0.164 g (62 % yield) of product. ES MS m/z 610 (M-H).

Example 466: {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[*trans*-4-(trifluoromethyl)cyclohexyl]acetic acid

Step 1. methyl ({[(phenylmethyl)oxy]carbonyl}amino)[4-(trifluoromethyl)cyclohexylidene]acetate

DBU was added to a mixture of 4-(trifluoromethyl)cyclohexanone (1.00 g, 6.02 mmol), and methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)oxy]carbonyl}amino)acetate (1.99 g, 6.02 mmol) in 25 mL of dichloromethane. The mixture was stirred at RT overnight, diluted with 20 mL of dichloromethane and was washed with 1 N hydrochloric acid, sodium bicarbonate, and brine. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 1.38 g (62 % yield) of product.

Step 2. methyl amino[4-(trifluoromethyl)cyclohexyl]acetate

Methyl ({[(phenylmethyl)oxy]carbonyl}amino)[4-(trifluoromethyl)cyclohexylidene]acetate (1.35 g, 3.64 mmol) and Pd on carbon (10 %, 1.0 g) in 75 mL of methanol was stirred at RT overnight under 40 psi of hydrogen. The mixture was flushed with nitrogen, filtered through celite, and concentrated to dryness to give 0.875 g (100% yield) of the product as a 2:1 mixture of isomers.

Step 3. methyl ({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)[*trans*-4-(trifluoromethyl)cyclohexyl]acetate and methyl ({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)[*cis*-4-(trifluoromethyl)cyclohexyl]acetate

HATU (0.456 g, 1.20 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (0.313 g, 1.09 mmol), methyl amino[4-(trifluoromethyl)cyclohexyl]acetate (0.261 g, 1.09 mmol) and diisopropylethylamine (0.211 g, 1.64 mmol) in 15 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.242 g of methyl ({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)[*trans*-4-(trifluoromethyl)cyclohexyl]acetate and 0.100 g of methyl ({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)[*cis*-4-(trifluoromethyl)cyclohexyl]acetate.

Step 4. methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}[*trans*-4-(trifluoromethyl)cyclohexyl]acetate hydrochloride

Methyl ({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)[*trans*-4-(trifluoromethyl)cyclohexyl]acetate (0.240 g, 0.472 mmol) in 20 mL of CH_2Cl_2 was treated with 15 mL of 4 N HCl in dioxane. The mixture as stirred at RT for ca. 3 h and the solvents were removed under reduced pressure to give the 0.243 g of the product.

Step 5. methyl {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[*trans*-4-(trifluoromethyl)cyclohexyl]acetate

Methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}[*trans*-4-(trifluoromethyl)cyclohexyl]acetate hydrochloride (0.472 mmol) in 10 mL of pyridine was treated 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.385 g, 1.42 mmol) overnight at RT. The pyridine was removed under reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.275 g (86 % yield) of product.

Step 6. {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[*trans*-4-(trifluoromethyl)cyclohexyl]acetic acid

Lithium hydroxide monohydrate (0.15 g, 3.57 mmol) was added to a solution of methyl {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[*trans*-4-(trifluoromethyl)cyclohexyl]acetate (0.270 g, .4 mmol) in THF: MeOH: water-15:5:5 mL . The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.265 g (99 % yield) of desired product as a white solid. ES MS m/z 664 (M-H).

Example 467: {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[*cis*-4-(trifluoromethyl)cyclohexyl]acetic acid

Step 1. methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}[*cis*-4-(trifluoromethyl)cyclohexyl]acetate hydrochloride

Methyl ({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)[*cis*-4-(trifluoromethyl)cyclohexyl]acetate (0.10 g, 0.197 mmol) in 15 mL of CH_2Cl_2 was treated with 10 mL of 4 N HCl in dioxane. The

mixture as stirred at RT for ca. 4 h and the solvents were removed under reduced pressure to give the 0.09 g of the product.

Step 2. methyl {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[*cis*-4-(trifluoromethyl)cyclohexyl]acetate

Methyl {[(3-amino-2-naphthalenyl)carbonyl]amino}[*cis*-4-(trifluoromethyl)cyclohexyl]acetate hydrochloride (0.197 mmol) in 5 mL of pyridine was treated with 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.165 g, 0.727 mmol) overnight at RT. The pyridine was removed under reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.123 g (92 % yield) of product.

Step 3. {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[*cis*-4-(trifluoromethyl)cyclohexyl]acetic acid

Lithium hydroxide monohydrate (0.075 g, 1.79 mmol) was added to a solution of methyl {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[*cis*-4-(trifluoromethyl)cyclohexyl]acetate (0.118 g, 0.173 mmol) in THF: MeOH: water-9:3:3 mL . The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.090 g (78 % yield) of desired product as a white solid. ES MS m/z 664 (M-H).

Example 468: {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(tetrahydro-2*H*-pyran-4-yl)acetic acid

Step 1. methyl ({[(phenylmethyl)oxy]carbonyl}amino)(tetrahydro-4*H*-pyran-4-ylidene)acetate

DBU (0.909 g, 5.98 mmol) was added to a mixture of tetrahydro-4*H*-pyran-4-one (0.498 g, 4.98 mmol), and methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)oxy]carbonyl}amino)acetate (1.647 g, 4.98 mmol) in 20 mL of dichloromethane. The mixture was stirred at RT overnight, diluted with 10 mL of dichloromethane and wash with 1 N hydrochloric acid, sodium bicarbonate, and brine. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 0.855 g (56 % yield) of product.

Step 2. methyl amino(tetrahydro-2*H*-pyran-4-yl)acetate

methyl ({[(phenylmethyl)oxy]carbonyl}amino)(tetrahydro-4*H*-pyran-4-ylidene)acetate (0.430 g, 1.40 mmol) and Pd on carbon (10 %, 0.35 g) in 30 mL of methanol was stirred at RT overnight under 50 psi of hydrogen. The mixture was flushed with nitrogen, filtered through celite and concentrated to dryness to give 0.225 g (92% yield) of the product.

Step 3. ({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(tetrahydro-2*H*-pyran-4-yl)acetic acid

HATU (0.484 g, 1.27 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (0.317 g, 1.11 mmol), methyl amino(tetrahydro-2*H*-pyran-4-yl)acetate (0.220 g, 1.27 mmol) and diisopropylethylamine (0.214 g, 1.66 mmol) in 12 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.412 g (84 % yield) of product.

Step 4. {[(3-amino-2-naphthalenyl)carbonyl]amino}(tetrahydro-2*H*-pyran-4-yl)acetic acid hydrochloride

({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(tetrahydro-2*H*-pyran-4-yl)acetic acid (0.410 g, 0.93 mmol) in 10 mL of CH_2Cl_2 was treated with 10 mL of 4 N HCl in dioxane. The mixture as stirred at RT for ca. 3 h and the solvents were removed under reduced pressure to give the 0.405 g of the product.

Step 5. methyl {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(tetrahydro-2*H*-pyran-4-yl)acetate

{[(3-amino-2-naphthalenyl)carbonyl]amino}(tetrahydro-2*H*-pyran-4-yl)acetic acid hydrochloride (0.200 g, 0.528 mmol) in 12 mL of pyridine was treated 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.431 g, 1.58 mmol) at RT overnight. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.297 g (92 % yield) of product.

Step 6. {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(tetrahydro-2*H*-pyran-4-yl)acetic acid

Lithium hydroxide monohydrate (0.150 g, 3.57 mmol) was added to a solution of methyl {[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(tetrahydro-2*H*-pyran-4-yl)acetate (0.285 g, 0.464 mmol) in THF: MeOH: water-15:5:5 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to

dryness to give 262 mg (90 % yield) of desired product as a white solid. ES MS m/z 558 (M-H).

Example 469: tetrahydro-2*H*-pyran-4-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

Step 1. methyl tetrahydro-2*H*-pyran-4-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetate

{[(3-amino-2-naphthalenyl)carbonyl]amino}(tetrahydro-2*H*-pyran-4-yl)acetic acid hydrochloride (0.200 g, 0.528 mmol) in 12 mL of pyridine was treated 2-isocyanato-1,3,5-trimethylbenzene (0.255 g, 1.58 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.210 g (79 % yield) of product.

Step 2. tetrahydro-2*H*-pyran-4-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid

Lithium hydroxide monohydrate (0.100 g, 2.38 mmol) was added to a solution of methyl tetrahydro-2*H*-pyran-4-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetate (0.205 g, 0.407 mmol) in THF: MeOH: water-12:4:4 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.183 g (92 % yield) of desired product as a white solid. ES MS m/z 488 (M-H).

Example 470: (2*S*)-cyclohexyl({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

HATU (2.287 g, 6.01 mmol) was added to a solution of 3-[(tert-butoxycarbonyl)amino]-2-naphthoic acid (1.50 g, 5.23 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (1.25 g, 1.56 mmol) and diisopropylethylamine (1.01 g, 7.84 mmol) in 50 mL of DMF. The mixture was stirred at RT for ca. 3 h. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.73 g (75 % yield) of product.

Step 2. methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate hydrochloride

Methyl (2*S*)-cyclohexyl({[3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate
(1.725 g, 3.92 mmol) in 50 mL of dichloromethane was treated with 35 mL of 4 N HCl in dioxane. The mixture as stirred at RT for ca. 4 h and the solvents were removed under reduced pressure to give the 1.51 g of the product.

Step 3. methyl (2*S*)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate hydrochloride (0.700 g, 1.86 mmol) in 40 mL of pyridine was treated 5-bromo-2-isocyanato-1,3-dimethylbenzene (1.05 g, 4.65 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.825 g (80 % yield) of product.

Step 4. methyl (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoate

Tetrakis(triphenylphosphine)palladium(0) (0.025 g, 0.022 mmol) was added to methyl (2*S*)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.363 mmol) and tributyl(2-propen-1-yl)stannane (0.132 g, 0.399 mmol) in ca. 10 mL of toluene. The mixture was heated at reflux overnight. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.090 g (46 % yield) of product.

Step 5. methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

A mixture of methyl (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoate (0.090 g, 0.171 mmol) and palladium (10 % on carbon, 0.090 g) in ca. 15 mL of ethyl acetate was stirred under 50 psi of hydrogen for 4 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 0.075 g (83 % yield) of product.

Step 6. (2*S*)-cyclohexyl({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.065 g, 1.55 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.075 g, 0.14 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on

silica gel with hexane/ethyl acetate gave 0.037 g (51 % yield) of desired product as a white solid. ES MS m/z 514 (M-H).

Example 471: (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propyn-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propyn-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoate

Tetrakis(triphenylphosphine)palladium(0) (0.013 g, 0.01 mmol) was added to methyl (2*S*)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.100 g, 0.181 mmol) and tributyl(2-propyn-1-yl)stannane (0.065 g, 0.199 mmol) in ca. 2.5 mL of acetonitrile. The mixture was heated in a microwave reactor at 150 C for 30 min. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.039 g (41 % yield) of product.

Step 2. (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propyn-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid

Lithium hydroxide monohydrate (0.025 g, 0.60 mmol) was added to a solution of methyl (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propyn-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoate (0.038 g, 0.07 mmol) in THF: MeOH: water-3:1:1 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.036 g (98 % yield) of desired product as a white solid. ES MS m/z 510 (M-H).

Example 472: 2-cyclohexyl-*N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-alanine

Step 1. Methyl 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alaninate

To a solution of 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alanine (1.0 g, 2.54 mmol) in 15 mL of ethyl acetate and 15 mL of methanol was added (trimethylsilyl)diazomethane (2.0 M in hexanes, 3.50 mL). This was stirred for ca. 45 min and concentrated to dryness to give 1.15 g of desired product as a tacky white solid.

Step 2. methyl 2-cyclohexyl-L-alaninate hydrochloride

To methyl 2-cyclohexyl-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}-L-alaninate (1.1 g, 2.73 mmol) in 25 mL of dioxane was added polymer bound piperizine (Aldrich Chemical catalog number 54,754-9, 5.0 g). The mixture was heated at 60 C for 36 h. The mixture was filtered and concentrated to dryness. The residue was dissolved in 20 mL of dichloromethane and 5 mL of hydrogen chloride (4 N in dioxane) was added. The solvent was removed and the residue was crystallize from dichloromethane and hexanes. The mother liquors were concentrated to dryness and triturated with ethyl acetate and hexanes. Solids were combined to give 0.545 g (90 % yield) of the product.

Step 3. methyl 2-cyclohexyl-*N*-[(4-fluoro-2-nitrophenyl)carbonyl]-L-alaninate

HATU (0.514 g, 1.35 mmol) was added to a solution of 4-fluoro-2-nitrobenzoic acid (0.208 g, 1.13 mmol), methyl 2-cyclohexyl-L-alaninate hydrochloride (0.250 g, 1.13 mmol) and diisopropylethylamine (0.218 g, 1.69 mmol) in 10 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.308 g (78 % yield) of product.

Step 4. methyl *N*-[(2-amino-4-fluorophenyl)carbonyl]-2-cyclohexyl-L-alaninate

A mixture of methyl 2-cyclohexyl-*N*-[(4-fluoro-2-nitrophenyl)carbonyl]-L-alaninate (0.305 g, 0.866 mmol) and palladium (10 % on carbon, 0.200 g) in ca. 15 mL of ethanol was stirred under 60 psi of hydrogen for 2 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 0.219 g (78 % yield) of product.

Step 5. methyl 2-cyclohexyl-*N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-alaninate

Methyl *N*-[(2-amino-4-fluorophenyl)carbonyl]-2-cyclohexyl-L-alaninate (0.100 g, 0.310 mmol) in 6 mL of pyridine was treated 2-isocyanato-1,3,5-trimethylbenzene (0.151 g, 0.932 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.132 g (88 % yield) of product.

Step 6. 2-cyclohexyl-*N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-alanine

Lithium hydroxide monohydrate (0.075 g, 0.48 mmol) was added to a solution of methyl 2-cyclohexyl-*N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-alaninate (0.130 g, 0.269 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.128 g (100 % yield) of desired product as a white solid. ES MS m/z 468 (M-H).

Example 473: (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(propyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid

Step 1. 3,5-dimethyl-4-nitrophenol

To 3,5-dimethylphenol (9.00 g, 75 mmol) in 10 mL of ether was add a few drops of nitric acid (5 mL of 75 % diluted with 20 mL of water). The reaction was cooled on ice and the remainder of the nitric acid solution was added dropwise. After 2 h the mixture was diluted with ether, washed with water, dried over sodium sulfate and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 3.4 g (27 % yield) of product.

Step 2. 3,5-dimethyl-4-nitrophenyl 2-propyn-1-yl ether

3-bromo-1-propyne (0.375 g, 3.15 mmol) was added dropwise to 3,5-dimethyl-4-nitrophenol (0.50 g, 3.0 mmol) and potassium carbonate (0.517 g, 3.75 mmol) in 20 mL of DMF and the reaction was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was dissolved in ethyl acetate, wash with water and brine, dried over sodium sulfate and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.50 g (81 % yield) of product.

Step 3. 2,6-dimethyl-4-(propyloxy)aniline

A mixture 3,5-dimethyl-4-nitrophenyl 2-propyn-1-yl ether (0.250 g, 1.22 mmol) and palladium (10 % on carbon, 0.200 g) in ca. 12 mL of ethanol was stirred under 60 psi of hydrogen for 20 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 0.185 g (85 % yield) of product.

Step 4. 2-isocyanato-1,3-dimethyl-5-(propyloxy)benzene

Phosgene (20 % solution in toluene, 1.208 g) was added to a mixture of 2,6-dimethyl-4-(propyloxy)aniline (0.175 g, 0.976 mmol) and PS-DIEA (Argonaut Technologies, 0.626 g, 3.9 mmol/g) in 10 mL of dichloromethane. After stirring at RT overnight the mixture was filtered and concentrated to give 0.202 g (99 % yield) of the product.

Step 5. methyl (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(propyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoate

Methyl (2S)-[(3-amino-2-naphthoyl) amino](cyclohexyl)ethanoate hydrochloride (0.184 g, 0.488 mmol) in 7 mL of pyridine was treated 2-isocyanato-1,3-dimethyl-5-(propyloxy)benzene (0.200 g, 0.97 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.125 g (47 % yield) of product.

Step 6. (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(propyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid

Lithium hydroxide monohydrate (0.075 g, 1.79 mmol) was added to a solution of methyl (2*S*)-cyclohexyl[({3-[({[2,6-dimethyl-4-(propyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoate (0.120 g, 0.22 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.105 g (90 % yield) of desired product as a white solid. ES MS m/z 530 (M-H).

Example 474: 2-cyclohexyl-*N*-[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]-L-alanine

Step 1. methyl 2-cyclohexyl-*N*-[(4-fluoro-2-nitrophenyl)carbonyl]-L-alaninate

HATU (0.498 g, 1.31 mmol) was added to a solution of 4-fluoro-2-nitrobenzoic acid (0.202 g, 1.09 mmol), methyl 2-cyclohexyl-L-alaninate hydrochloride (0.290 g, 1.31 mmol) and diisopropylethylamine (0.211 g, 1.63 mmol) in 10 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.390 g (100 % yield) of product.

Step 2. methyl *N*-[(2-amino-4-fluorophenyl)carbonyl]-2-cyclohexyl-L-alaninate

A mixture of methyl 2-cyclohexyl-*N*-[(4-fluoro-2-nitrophenyl)carbonyl]-L-alaninate (0.385 g, 1.09 mmol) and palladium (10 % on carbon, 0.225 g) in ca. 25 mL of ethanol was stirred under 60 psi of hydrogen for 2 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 0.362 g of product.

Step 3. methyl 2-cyclohexyl-*N*-[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]-L-alaninate

Methyl *N*-[(2-amino-4-fluorophenyl)carbonyl]-2-cyclohexyl-L-alaninate (0.155 g, 0.481 mmol) in 8 mL of pyridine was treated 1,3-dichloro-2-isocyanato-5-[(trifluoromethyl)oxy]benzene (0.261 g, 0.961 mmol) at RT overnight. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried

over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.158 g (55 % yield) of product.

Step 4. 2-cyclohexyl-*N*-[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]-L-alanine

Lithium hydroxide monohydrate (0.100 g, 2.38 mmol) was added to a solution of methyl 2-cyclohexyl-*N*-[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]-L-alaninate (0.155 g, 0.26 mmol) in THF: MeOH: water-12:4:4 mL. The mixture was stirred at 60 C overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.136 g (90 % yield) of desired product as a white solid. ES MS m/z 578 (M-H).

Example 475: (2*S*)-cyclohexyl({[2-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl{[(4-fluoro-2-nitrophenyl)carbonyl]amino}ethanoate

HATU (2.37 g, 6.22 mmol) was added to a solution of 4-fluoro-2-nitrobenzoic acid (1.00 g, 5.41 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.1.292 g, 6.22 mmol) and diisopropylethylamine (1.05 g, 8.11 mmol) in 50 mL of DMF. The mixture was stirred at RT overnight. The DMF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with sodium hydrogensulfate, sodium bicarbonate and brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.39 g (76 % yield) of product.

Step 2. methyl (2*S*)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate

A mixture of methyl (2*S*)-cyclohexyl{[(4-fluoro-2-nitrophenyl)carbonyl]amino}ethanoate (1.39 g, 4.11 mmol) and palladium (10 % on carbon, 0.75 g) in ca. 60 mL of ethanol was stirred under 60 psi of hydrogen for 2 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 1.19 g (94 % yield) of product.

Step 3. methyl (2*S*)-({[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2*S*)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.600 g, 1.95 mmol) in 40 mL of pyridine was treated 5-bromo-2-isocyanato-1,3-dimethylbenzene (1.10 g, 4.86 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.958 g (92 % yield) of product.

Step 4. methyl (2*S*)-cyclohexyl({[2-({[(4-ethenyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate

Tetrakis(triphenylphosphine)palladium(0) (0.025 g, 0.022 mmol)was added to methyl (2*S*)-({[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.200 g, 0.374 mmol) and tributyl(ethenyl)stannane (0.130 g, 0.412 mmol) in 4 mL of acetonitrile. The mixture was heated at 150 C for 30 min in a microwave reactor. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.083 g (46 % yield) of product.

Step 5. methyl (2*S*)-cyclohexyl({[2-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate

Methyl (2*S*)-cyclohexyl({[2-({[(4-ethenyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate (0.080 g, 0.166 mmol) and palladium (10 % on carbon, 0.050 g) in ca. 12 mL of ethyl acetate was stirred under 60 psi of hydrogen for 2 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 0.075 g (94 % yield) of product.

Step 6. (2*S*)-cyclohexyl({[2-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.060 g, 1.43 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate (0.075 g, 0.155 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 0.045 g (62 % yield) of product as a white solid. ES MS m/z 468 (M-H).

Example 476: (2*S*)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoate

Tetrakis(triphenylphosphine)palladium(0) (0.032 g, 0.028 mmol) was added to methyl (2*S*)-({[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.250 g, 0.468 mmol) and tributyl(2-propen-1-yl)stannane (0.170 g, 0.515 mmol) in 4.5 mL of acetonitrile. The

mixture was heated at 150 C for 30 min in a microwave reactor. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.178 g (77 % yield) of product.

Step 2. (2*S*)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid

Lithium hydroxide monohydrate (0.060 g, 1.42 mmol) was added to a solution of methyl (2*S*)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoate (0.055 g, 0.11 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.053 g (99 % yield) of desired product as a white solid. ES MS m/z 480 (M-H).

Example 477: (2*S*)-cyclohexyl({[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate

Methyl (2*S*)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoate (0.112 g, 0.226 mmol) and palladium (10 % on carbon, 0.090 g) in ca. 15 mL of ethyl acetate was stirred under 60 psi of hydrogen for 2 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 0.105 g (93 % yield) of product.

Step 2. (2*S*)-cyclohexyl({[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.075 g, 1.79 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate (0.105 g, 0.211 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 0.099 g (97 % yield) of desired product as a white solid. ES MS m/z 482 (M-H).

Example 478: (2*S*)-cyclohexyl({[2-({[(2,6-dimethyl-4-pentylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-cyclohexyl{[(2-{[({2,6-dimethyl-4-[(1*E*)-1-penten-1-yl]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}ethanoate

A mixture of methyl (2*S*)-({[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.100 g, 0.187 mmol), (1*E*)-1-penten-1-ylboronic acid (0.023 g, 0.206 mmol), cesium fluoride (0.085 g, 0.561 mmol) and trans-dichlorobis(tricyclohexylphosphine)palladium (II) (0.007 g, 0.009 mmol) in 3 mL of acetonitrile and 1 mL of water was heated at 150 C for 6 min in a microwave reactor. The reaction was diluted with ethyl acetate and washed with water and brine. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.078 g (80 % yield) of product.

Step 2. methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethyl-4-pentylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate

Methyl (2*S*)-cyclohexyl{[(2-{[({2,6-dimethyl-4-[(1*E*)-1-penten-1-yl]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}ethanoate (0.078 g, 0.149 mmol) and palladium (10 % on carbon, 0.050 g) in ca. 8 mL of ethyl acetate was stirred under 60 psi of hydrogen for 2 h. The mixture was flushed with

nitrogen, filtered, and the solvent evaporated to give 0.069 g (88 % yield) of product.

Step 3. (2*S*)-cyclohexyl({[2-({[(2,6-dimethyl-4-pentylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid

Lithium hydroxide monohydrate (0.060 g, 1.42 mmol) was added to a solution of methyl (2*S*)-cyclohexyl({[2-({[(2,6-dimethyl-4-pentylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoate (0.067 g, 0.127 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT for 7 h. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 0.047 g (72 % yield) of product as a white solid. ES MS m/z 510 (M-H).

Example 479: 2-cyclohexyl-*N*-{[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-alanine

Step 1. methyl *N*-{[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-2-cyclohexyl-L-alaninate

Methyl *N*-[(2-amino-4-fluorophenyl)carbonyl]-2-cyclohexyl-L-alaninate (0.175 g, 0.543 mmol) in 10 mL of pyridine was treated 5-bromo-2-isocyanato-1,3-dimethylbenzene (0.370 g, 1.63 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.245 g (82 % yield) of product.

Step 2. methyl 2-cyclohexyl-*N*-({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)-L-alaninate

Tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.026 mmol)was added to methyl *N*-{[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-2-cyclohexyl-L-alaninate (0.240 g, 0.438 mmol) and tributyl(2-propen-1-yl)stannane (0.166 g, 0.503 mmol) in 5 mL of acetonitrile. The mixture was heated at 150 C for 30 min in a microwave reactor. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.169 g (76 % yield) of product.

Step 3. methyl 2-cyclohexyl-*N*-{[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-alaninate

Methyl 2-cyclohexyl-*N*-({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)-L-alaninate (0.165 g, 0.324 mmol) and palladium (10 % on carbon, 0.115 g) in ca. 15 mL of ethyl acetate was stirred under 60 psi of hydrogen for 2 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 0.160 g (96 % yield) of product.

Step 4. 2-cyclohexyl-*N*-{[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-alanine

Lithium hydroxide monohydrate (0.100 g, 2.38 mmol) was added to a solution of methyl 2-cyclohexyl-*N*-{[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-alaninate (0.160 g, 0.313 mmol) in THF: MeOH: water-12:4:4 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 0.121 g (75 % yield) of product as a white solid. ES MS m/z 496 (M-H).

Example 480: (2*S*)-({[2-({[(4-butyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. 2-[(1*E*)-1-buten-1-yl]-1,3,2-benzodioxaborole

Butyne (ca. 4 g) was condensed into a sealable pressure bottle cooled in a -78 C bath. To this was added catecholborane (1 M in THF, 65 mL). The bottle was capped and after warming to RT was heated at 75 C overnight (blast shield used). The reaction was cooled to -78 C and the cap was removed carefully and the solvent evaporated. Distillation under reduce pressure (ca. 1 torr) gave 7.0 g of the product as a clear liquid.

Step 2. methyl (2*S*)-{[(2-{[({4-[(1*E*)-1-buten-1-yl]-2,6-dimethylphenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate

A mixture of methyl (2*S*)-({[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.135 g, 0.253 mmol), 2-[(1*E*)-1-buten-1-yl]-1,3,2-benzodioxaborole (0.048 g, 0.278 mmol), cesium fluoride (0.115 g, 0.759 mmol) and trans-dichlorobis(tricyclohexylphosphine)palladium (II) (0.009 g, 0.012 mmol) in 3.5 mL of acetonitrile and 1.2 mL of water was heated at 150 C for 7 min in a microwave reactor. The reaction was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate, the solvent was removed under reduced pressure, and chromatography on silica gel with hexane/ethyl acetate gave 0.093 g (72 % yield) of product.

Step 3. methyl (2*S*)-({[2-({[(4-butyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2*S*)-{[(2-{[({4-[(1*E*)-1-buten-1-yl]-2,6-dimethylphenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.090 g, 0.177 mmol) and palladium (10 % on carbon, 0.075 g) in ca. 10 mL of ethyl acetate was stirred under 60 psi of hydrogen for 2 h. The mixture was flushed

with nitrogen, filtered, and the solvent evaporated to give 0.089 g (99 % yield) of product.

Step 4. (2*S*)-({[2-({[(4-butyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoic acid

Lithium hydroxide monohydrate (0.075 g, 1.79 mmol) was added to a solution of methyl (2*S*)-({[2-({[(4-butyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.089 g, 0.174 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate gave 0.051 g (59 % yield) of product as a white solid. ES MS m/z 496 (M-H).

Example 481: *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-L-threonine

Step 1. methyl *N*-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate

Methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate (0.470 g, 1.12 mmol) in 30 mL of pyridine was treated 5-bromo-2-isocyanato-1,3-dimethylbenzene (0.633 g, 2.79 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was diluted with ethyl acetate and filtered. The ethyl acetate phase was washed with aqueous $NaHCO_3$, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.721 g (99 % yield) of product.

Step 2. methyl *O*-(1,1-dimethylethyl)-*N*-({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-L-threoninate

Tetrakis(triphenylphosphine)palladium(0) (0.024 g, 0.021 mmol)was added to methyl *N*-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate (0.225 g, 0.348 mmol) and tributyl(2-propen-1-yl)stannane (0.132 g, 0.40 mmol) in 4.5 mL of acetonitrile. The mixture was heated at 150 C for 30 min in a microwave reactor. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.157 g (74 % yield) of product.

Step 3. methyl *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-L-threoninate

Methyl *O*-(1,1-dimethylethyl)-*N*-({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-L-threoninate (0.155 g, 0.254 mmol) and palladium (10 % on carbon, 0.120 g) in ca. 10 mL of ethyl acetate was stirred under 60 psi of hydrogen for 3 h. The mixture was flushed with nitrogen, filtered, and the solvent evaporated to give 0.0142 g (91 % yield) of product.

Step 4. *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide monohydrate (0.100 g, 2.38 mmol) was added to a solution of methyl *O*-(1,1-dimethylethyl)-*N*-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-L-threoninate (0.140 g, 0.230 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness. Chromatography on silica gel with

hexane/ethyl acetate gave 0.023 g (17 % yield) of product as a white solid. ES MS m/z 594 (M-H).

Example 482: (2*S*)-cyclohexyl[({2-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid

Step 1. methyl (2*S*)-({[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2*S*)-{[(2-amino-4-fluorophenyl)carbonyl]amino}(cyclohexyl)ethanoate (0.300 g, 0.97 mmol) in 20 mL of pyridine was treated 5-bromo-2-isocyanato-1,3-dimethylbenzene (0.552 g, 2.435 mmol) overnight at RT. The pyridine was removed at reduced pressure and the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.481 g (93 % yield) of product.

Step 2. methyl (2*S*)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoate

Tetrakis(triphenylphosphine)palladium(0) (0.062 g, 0.054 mmol)was added to methyl (2*S*)-({[2-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoate (0.480 g, 0.898 mmol) and tributyl(2-propen-1-yl)stannane (0.327 g, 0.988 mmol) in 5 mL of acetonitrile. The mixture was heated at 150 C for 30 min in a microwave reactor. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.309 g (69 % yield) of product.

Step 3. methyl (2*S*)-cyclohexyl[({2-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoate

Diazomethane (1.2 mmol in 10 mL dichloromethane, generated from N-methyl-N-nitrosourea) was added drop-wise to an ice cold solution of methyl (2*S*)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoate (0.100 g, 0.202 mmol) and palladium (II) acetylacetonate (0.003 g, 0.01 mmol) in 10 mL of ether over ca. 20 min. The reaction was stirred on ice for 15 min, then warmed to RT over 30 min. The mixture was flushed with nitrogen, filtered through celite and concentrated to dryness. NMR showed this to be a mixture of product and starting material, so the material was subjected to the reaction procedure again. The resulting material was chromatographed on silica gel with hexane/ethyl acetate to give 0.080 g (78 % yield) of the product.

Step 4. (2*S*)-cyclohexyl[({2-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid

Lithium hydroxide monohydrate (0.075 g, 1.79 mmol) was added to a solution of methyl (2*S*)-cyclohexyl[({2-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoate (0.080 g, 0.157 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to dryness to give 80 mg (100 % yield) of desired product as a white solid. ES MS m/z 494 (M-H).

Example 483: *N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threonine

Step 1. methyl *O*-(1,1-dimethylethyl)-*N*-({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-L-threoninate

Tetrakis(triphenylphosphine)palladium(0) (0.024 g, 0.021 mmol)was added to methyl *N*-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate (0.225 g, 0.348 mmol) and tributyl(2-propen-1-yl)stannane (0.132 g, 0.40 mmol) in 4.5 mL of acetonitrile. The mixture was heated at 150 C for 20 min in a microwave reactor. The solvent was removed under reduced pressure and chromatography on silica gel with hexane/ethyl acetate gave 0.165 g (78 % yield) of product.

Step 2. methyl *N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threoninate

Diazomethane (2.42 mmol in 20 mL dichloromethane, generated from N-methyl-N-nitrosourea) was added drop-wise to an ice cold solution of methyl *O*-(1,1-dimethylethyl)-*N*-({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-L-threoninate (0.125 g, 0.206 mmol) and palladium (II) acetylacetonate (0.003 g, 0.01 mmol) in 12 mL of ether over ca. 30 min. The reaction was stirred on ice for 10 min, then warmed to RT over 30 min. The mixture was flushed with nitrogen, filtered through celite and concentrated to dryness. Chromatography on silica gel with hexane/ethyl acetate to give 0.103 g (80 % yield) of the product.

Step 3. *N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threonine

Lithium hydroxide monohydrate (0.075 g, 1.79 mmol) was added to a solution of methyl *N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threoninate (0.100 g, 0.161 mmol) in THF: MeOH: water-9:3:3 mL. The mixture was stirred at RT for 4 h. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated to

dryness to give 0.091 g (93 % yield) of desired product as a white solid. ES MS m/z 606 (M-H).

Example 484: (2S)-Cyclohexyl({[2-[4-(methyloxy)phenyl]-4-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1,3-thiazol-5-yl]carbonyl}amino)ethanoic acid

Step 1. Methyl 4-methoxybenzenecarbodithioate

Methyl 4-methoxybenzoate (10.15g, 61.08 mmol) and Davy Reagent (17.37g, 61.08 mmol) were combined in 1,2,4-trichlorobenzene. The reaction was heated to 200°C in an oil bath and stirred for 1h. Cooled to rt and poured onto a column of silica and eluted with hex/Ether (15/1). The solvent was stripped off and the residue was placed under vacuum until constant weight was obtained to give 12.08g (61 mmol, 100%) of product as a red oil.

Step 2. Methyl 4-amino-2-(4-methoxyphenyl)-1,3-thiazole-5-carboxylate

Methyl 4-methoxybenzenecarbodithioate (5.43g, 26.88 mmol), cyanamide (1.13g, 26.88 mmol) and potassium methoxide (1.885g, 26.88 mmol) were combined in dry methanol(100 mL) and stirred at rt for 4h. The reaction was concentrated down to give a red solid. The residue was dissolved in dry DMF (100 mL) and MeI (5.723g, 40.32 mmol) was added. The reaction went from dark red to light clear red immediately upon addition. Stirred for 2.5h at RT and then diluted with EtOAc (300 mL), washed with water (3 x 500 mL) dried over $MgSO_4$, filtered and concentrated. The residue was taken up in dry methanol (100 mL) and then ethyl thioglycolate (26.88 mmol, 3.23g) and triethylamine (80.64 mmol, 8.15 g) were added. The reaction was stirred for 1h and precipitate was collected. Mother liquor was allowed to stir over night and a small second crop was collected. Total of 1.7g (6.11 mmol, 23%) of the desired product, as a light yellow solid was collected.

Step 3. 4-Amino-2-[4-(methyloxy)phenyl]-1,3-thiazole-5-carboxylic acid

Methyl 4-amino-2-(4-methoxyphenyl)-1,3-thiazole-5-carboxylate (1.1g, 3.96 mmol) was taken up in dioxane (20 mL). 1M lithium hydroxide (20 mL) was added and the reaction stirred overnight at 80°C. The reaction was cooled to RT and neutralized with 1N HCl. Diluted with water (50 mL). Product was water soluble, so a large excess of sodium chloride was added. Precipitate was collected to give 1.1g (4.4 mmol, 111%) of product as a light yellow solid.

Step 4. Methyl (2*S*)-[({4-amino-2-[4-(methyloxy)phenyl]-1,3-thiazol-5-yl}carbonyl)amino](cyclohexyl)ethanoate

(4-Amino-2-[4-(methyloxy)phenyl]-1,3-thiazole-5-carboxylic acid (0.56g, 0.24 mmol) and methyl (2S)-amino(cyclohexyl)ethanoate (0.556g, 2.69 mmol) were combined in DMF (10 mL). Triethylamine (0.67 mL, 4.93 mmol) was added followed by HATU (1.28g, 3.36 mmol). The reaction was stirred for 2 d. The reaction was then diluted with EtOAc (50 mL) and washed with water (2 x 50 mL). The organics were dried over $MgSO_4$, filtered, concentrated and purified on a chromatatron (1:1 Hex:EtOAc) to afford 0.456g (1.13 mmol, 51%) of the product as a yellow solid.

Step 5. (2*S*)-cyclohexyl({[2-[4-(methyloxy)phenyl]-4-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1,3-thiazol-5-yl]carbonyl}amino)ethanoic acid

Methyl (2S)-[({4-amino-2-[4-(methyloxy)phenyl]-1,3-thiazol-5-yl}carbonyl)amino](cyclohexyl)ethanoate (0.05g, 0.12 mmol) was suspended in toluene (1 mL) and heated to 120°C. 1,3,5-Trichloro-2-isocyanatobenzene (0.03g, 0.14 mmol) was added. The reaction was stirred overnight at 120°C. The reaction was concentrated to dryness and the residue purified on a chromatatron (3:1 Hex:EtOAc). The desired product and the starting thiazole coeluted. The mixture was dissolved in THF (1 mL) and 1M lithium hydroxide was added and the reaction

stirred overnight. Concentrated and purified on a Gilson to separate. Lyophilized to afford 0.009g (12%) of the product. ES MS m/z 611 (M + H).

Example 485: 1-({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1. Methyl 1-({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylate

Methyl (2S)-[({4-amino-2-[4-(methyloxy)phenyl]-1,3-thiazol-5-yl}carbonyl)amino](cyclohexyl)ethanoate (0.099g, 0..25 mmol) was suspended in toluene (1 mL) and heated to 120°C. 2-Isocyanato-1,3,5-trimethylbenzene (0.119g, 0.74 mmol) was added. The reaction was stirred overnight during which the reaction went dry. The residue was taken up in minimal methylene chloride and purified on a chromatatron (1:1 Hex:EtOAc) to give 0.06g of an impure material. The impure material was repurified on a chromatatron (100% CH_2Cl_2) to give 0.04g (0.071 mmol, 29%) of the desired product.

Step 2. 1-({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylic acid

Methyl (2S)-cyclohexyl({[2-[4-(methyloxy)phenyl]-4-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-5-yl]carbonyl}amino)ethanoate (0.04g, 0.07 mmol) was taken up in dioxane (1 mL) and treated with 1M lithium hydroxide (1 mL). The reaction was heated to 100°C and monitored by LCMS, until all of the start material was gone. The reaction was cooled to RT and acidified with 1N HCl. The reaction was diluted with water (20 mL), and extracted with EtOAc (2 x 40 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give

0.028g (0.05 mol, 72%) of the product as a light brown gum. ES MS m/z 551 (M + H).

Example 486: (2S)-cyclohexyl({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)ethanoic acid

Step 1. Methyl (2S)-cyclohexyl({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)ethanoate

Methyl (2S)-[({5-amino-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino](cyclohexyl)ethanoate (0.069g, 0.17 mmol) was suspended in toluene (1 mL) and heated to 120°C. 2-Isocyanato-1-methyl-3-(1-methylethyl)benzene (0.09g, 0.51 mmol) was added. The reaction was stirred overnight during which the reaction went dry. The residue was taken up in minimal methylene chloride and purified on a chromatatron (1:1 Hex:EtOAc) to give 0.06g of an impure material. The impure material was re-purified on a chromatatron (100% CH_2Cl_2) to give 0.019g (0.0032 mmol, 19%) of the desired product.

Step 2. (2S)-cyclohexyl({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)ethanoic acid

Methyl (2S)-cyclohexyl({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)ethanoate (0.019g, 0.03 mmol) was taken up in dioxane (1 mL) and treated with 1M lithium hydroxide (1 mL). The reaction was heated to 100°C and monitored by LCMS, until all of the start material was gone. The reaction was cooled to rt and acidified with 1N HCl. Diluted with water (20 mL), and extracted with EtOAc (2 x 40 mL). Organics were dried over $MgSO_4$, filtered and concentrated to give 0.014g (0.024mmol, 76%) of the desired product as a light brown gum. ES MS m/z 565 (M + H).

Example 487: (2S)-Cyclohexyl[({5-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino]ethanoic acid

Step 1. Methyl (2S)-cyclohexyl[({5-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino]ethanoate

Methyl (2S)-[({5-amino-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino](cyclohexyl)ethanoate (0.089g, 0.22 mmol) was suspended in toluene (1 mL) and heated to 120°C. 1,3-Dichloro-2-isocyanatobenzene (0.124g, 0.66 mmol) was added. The reaction was stirred overnight during which the reaction went dry. The residue was taken up in minimal methylene chloride and purified on a chromatatron (3:1 Hex:EtOAc) to give 0.022g (0.037 mmol, 17%) of the desired product.

Step 2. (2S)-Cyclohexyl[({5-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino]ethanoic acid

Methyl (2S)-[({5-amino-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino](cyclohexyl)ethanoate (0.022g, 0.04 mmol) was taken up in dioxane (1 mL) and treated with 1M lithium hydroxide (1 mL). The reaction was heated to 100°C and monitored by LCMS, until all of the start material was gone. The reaction was cooled to rt and acidified with 1N HCl. Diluted with water (20 mL), and extracted with EtOAc (2 x 40 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 0.019g (0.032mmol, 88%) of the desired product as a light brown solid. ES MS m/z 577 (M + H), 599 (M + Na).

Example 488: 2-[4-(Methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazole-4-carboxylic acid

Step 1. Diethyl ({[4-(methyloxy)phenyl]carbonyl}amino)propanedioate.

4- Diethyl aminopropanedioate (25.32g, 148.42 mmol) and sodium bicarbonate (15.73g, 148.42 mmol) were combined in a biphasic mixture of water (200 mL) and methylene chloride (200 mL). (Methyloxy)benzoyl chloride (27.248, 148.42 mmol) was added and the reaction stirred overnight at rt. The organics were removed and then washed with water (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated to give 42.35g (150 mmol, 100%) of the product as a white solid.

Step 2. Ethyl 5-(ethyloxy)-2-[4-(methyloxy)phenyl]-1,3-oxazole-4-carboxylate

Diethyl ({[4-(methyloxy)phenyl]carbonyl}amino)propanedioate (21.62g, 76.94 mmol) was dissolved in chloroform (200 mL). Phosphorous pentachloride (16.022g, 76.94 mmol) was added and the reaction heated to reflux. The reaction was stirred for 2.5 days. The reaction was concentrated and the residue taken up in Ether (500 mL). The reaction was then poured on to ice and then neutralized with solid Sodium Bicarb. The organics were separated and dried over $MgSO_4$, filtered and concentrated. The residue was divided into several portions and purified on ISCO to give 10.5g of pure product.

Step 3. 5-(ethyloxy)-2-[4-(methyloxy)phenyl]-1,3-oxazole-4-carboxylic acid

Ethyl 5-(ethyloxy)-2-[4-(methyloxy)phenyl]-1,3-oxazole-4-carboxylate (10.50g, 36.08 mmol) was taken up in THF (100 mL). 1M lithium hydroxide (40 mL) was added and heated to 70°C. The reaction was stirred for 2h until complete by TLC. The reaction was cooled and acidified with 1N HCl, white precipitate was formed. The precipitate was collected and dried to give 7.97g (30.30 mmol, 84%) of the product as a white solid.

Step 4. 5-(Ethyloxy)-2-[4-(methyloxy)phenyl]-1,3-oxazole-4-carboxamide

5-[(Ethyloxy)carbonyl]-2-[4-(methyloxy)phenyl]-1,3-oxazole-4-carboxylic acid (1.78g, 6.77 mmol) was suspended in methylene chloride (100 mL) and DMF (0.02

mL) was added. Oxalyl Chloride (2.64 mL, 6.77 mmol) was added dropwise and the reaction stirred overnight at rt. The reaction was concentrated and the excess oxalyl chloride was azetroped off with methylene chloride to give an off white solid. Aqueous ammonia (50 mL) was cooled in an ice bath. The acid chloride was suspended in minimal THF and then added slowly to the ammonia. The reaction was stirred for 6h. The precipitate was collected to give 1.394g (5.32 mmol, 79%) of the desired product as an off white solid.

Step 5. Ethyl 5-amino-2-[4-(methyloxy)phenyl]-1,3-thiazole-4-carboxylate

5-(Ethyloxy)-2-[4-(methyloxy)phenyl]-1,3-oxazole-4-carboxamide (4.37g, 16.68 mmol) and Lawesson's Reagent (13.492g, 33.36 mmol) were taken up in THF (100 mL) and heated to 70°C and stirred overnight. The reaction was cooled to rt and filtered through celite. The reaction was concentrated and then purified on an ISCO (20% EtOAc in Hex) to give 1.6g (5.75 mmol, 35%) of the product as a pink solid.

Step 6. 5-Amino-2-[4-(methyloxy)phenyl]-1,3-thiazole-4-carboxylic acid

Ethyl 5-amino-2-[4-(methyloxy)phenyl]-1,3-thiazole-4-carboxylate (1.08g, 3.89 mmol) was taken up in THF (100 mL) and 1M Lithium hydroxide (10 mL) was added. The reaction was heated to 70°C and was stirred for 3d, until all start material was gone. The reaction was cooled and acidified with 1N HCl. The reaction was then extracted with EtOAc (2 x 200 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 1g (4 mmol, 100%) of the product as an orange solid.

Step 7. 2-[4-(Methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazole-4-carboxylic acid

4-Amino-2-[4-(methyloxy)phenyl]-1,3-thiazole-5-carboxylic acid (0.105g, 0.42 mmol) and 2-Isocyanato-1,3,5-trimethylbenzene (0.203g, 1.26 mmol) were combined in toluene and heated to 120°C. The reaction was stirred overnight and reaction went

dry. The reaction was cooled and the residue was purified on a chromatatron (2.5% methanol in methylene chloride) to afford 0.028g (0.07 mmol, 16%) of the product as a dull yellow solid.

Example 489: 1-({[2-[4-(Methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1. Methyl 1-[({5-amino-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino]cyclohexanecarboxylate.

5-Amino-2-[4-(methyloxy)phenyl]-1,3-thiazole-4-carboxylic acid (0.088g, 0.35 mmol) and methyl 1-aminocyclohexanecarboxylate (0.068g, 0.35 mmol) were combined in DMF (5 mL). Triethylamine (0.105 mL, 0.77 mmol) and HATU (0.201g, 0.53 mmol) were added. The reaction was stirred over night at rt. The reaction was partioned between water (50 mL) and EtOAc (50 mL). The aqueous fraction was removed and the organics were washed with water (2 x 50 mL), brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The residue purified on an ISCO (1:1 Hex:EtOAc) to give 0.050g (0.128 mmol, 37%).

Step 2. Methyl 1-({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylate

Methyl 1-[({5-amino-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino]cyclohexanecarboxylate (0.046g, 0.12 mmol) was taken up in toluene and heated to 120°C. 2-Isocyanato-1,3,5-trimethylbenzene (0.038g, 0.24 mmol) was add and the reaction stirred for 2h. Additional isocyanate (0.057g, 0.36 mmol) was added and the reaction stirred overnight. The reaction was concentrated and the residue purified on a chromatatron (100% CH_2Cl_2) to give 0.040g (0.07 mmol, 62%) of the product as a light brown semisolid.

Step 3. 1-({[2-[4-(Methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylic acid

Methyl 1-({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylate (0.040, 0.08 mmol) was taken up in dioxane (1 mL) and 1M Lithium hydroxide (1 mL) was added. The reaction was heated to 100°C and stirred for 1h. The reaction was cooled and neutralized with 1N HCl. The reaction was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL). The organics were washed with water (2 x 20 mL), brine (1 x 20 mL), dried over $MgSO_4$, filtered and concentrated. The residue was placed under vacuum, until a constant weight was obtained, to give 0.021g (0.039 mmol, 47%) of the product as a light tan solid. ES MS m/z 537 (M + H).

Example 490: (2S)-({[2-(4-Chlorophenyl)-5-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)(cyclohexyl)ethanoic acid

Step 1. Diethyl {[(4-chlorophenyl)carbonyl]amino}propanedioate

4- Diethyl aminopropanedioate (20.72g, 97.90 mmol) and sodium bicarbonate (10.37g, 97.90 mmol) were combined in a biphasic mixture of water (200 mL) and methylene chloride (200 mL). 4-chlorobenzoyl chloride (17.13, 97.90mmol) was added and the reaction stirred overnight at rt. The organics were removed and then washed with water (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated to give 29.38g (195.08 mmol 97%) of the product as a white solid.

Step 2. Ethyl 2-(4-chlorophenyl)-5-(ethyloxy)-1,3-oxazole-4-carboxylate

Diethyl {[(4-chlorophenyl)carbonyl]amino}propanedioate (29.38g, 104.56 mmol) was dissolved in chloroform (200 mL). Phosphorous pentachloride (21.77g, 104.56

mmol) was added and the reaction heated to reflux. The reaction was stirred for 4 days. The reaction was concentrated and the residue taken up in Ether (500 mL). The organics were poured on to ice and then neutralized with solid Sodium Bicarb. The organics were separated and dried over $MgSO_4$, filtered and concentrated to give 28.4g (107 mmol, 100%) of product as a white solid.

Step 3. 2-(4-Chlorophenyl)-5-(ethyloxy)-1,3-oxazole-4-carboxylic acid

Ethyl 2-(4-chlorophenyl)-5-(ethyloxy)-1,3-oxazole-4-carboxylate (28.4g, 96.27 mmol) was taken up in THF (200 mL). 1M Lithium hydroxide (100 mL) was added and heated to 70°C. The reaction was stirred overnight, then cooled and neutralized with 1N HCl. A white precipitate was formed. The reaction was extracted with EtOAc (2 x 200 mL) and the combined organics were washed with water (1 x 200 mL), brine (1 x 200 mL), dried over $MgSO_4$, filtered and concentrated to give 2.56g (8.67mmol, 9%) of starting ester. The aqueous fraction was acidified with 1N HCl and reextracted with EtOAc (2 x 300 mL). The organics were washed with water (1 x 200 mL), brine (1 x 200 mL), dried over $MgSO_4$, filtered and concentrated to give 18.56g (69.51 mmol, 72%) of the desired product as a fluffy white solid.

Step 4. 2-(4-Chlorophenyl)-5-(ethyloxy)-1,3-oxazole-4-carboxamide

2-(4-Chlorophenyl)-5-(ethyloxy)-1,3-oxazole-4-carboxylic acid (4.27g, 15.99 mmol) was suspended in methylene chloride (50 mL) and DMF (0.02 mL) was added. Oxalyl Chloride (1.54 mL, 17.59 mmol) was added dropwise and reaction warmed to 50°C and stirred overnight. The reaction was concentrated and the residue taken up in dioxane (50 mL). Ammonia in dioxane (68 mL of a 0.5M sol) was added via an addition funnel. The reaction was stirred at rt for 3h. The reaction was concentrated and the residue taken up in minimal methylene chloride. The organics were triturated with ether and the precipitate removed. The mother liquor was concentrated to give 4.6g (17.36 mmol, 108%) of product as a tan solid.

Step 5. 2-(4-Chlorophenyl)-5-(ethyloxy)-1,3-oxazole-4-carbothioamide

2-(4-Chlorophenyl)-5-(ethyloxy)-1,3-oxazole-4-carboxamide 2.83g, 10.68 mmol) and Lawesson's Reagent were combined in THF (100 mL), heated to 70°C and stirred for 3h. The reaction was concentrated and charged to a flash column. The product was eluted with 1:1 Hex:EtOAc to obtain contaminated product. The crude material was triturated with hexane to afford 0.176g (0.62 mmol, 6%) of the product.

Step 6. ethyl 5-amino-2-(4-chlorophenyl)-1,3-thiazole-4-carboxylate

2-(4-Chlorophenyl)-5-(ethyloxy)-1,3-oxazole-4-carbothioamide (0.190g, 0.68 mmol) was taken up in toluene (5 mL), heated to 110°C and stirred overnight. The reaction was concentrated to afford 0.19g (0.68 mmol, 100%) of the product as a light tan solid.

Step 7. Methyl (2*S*)-({[5-amino-2-(4-chlorophenyl)-1,3-thiazol-4-yl]carbonyl}amino)(cyclohexyl)ethanoate

5-Amino-2-(4-chlorophenyl)-1,3-thiazole-4-carboxylic acid (0.149g, 0.59 mmol) and methyl (2S)-amino(cyclohexyl)ethanoate (0.121g, 0.59 mmol) were combined in DMF (50 mL). Triethylamine (0.13g, 1.29 mmol) was added followed by HATU (0.334g, 0.88 mmol). The reaction was stirred overnight at rt. The reaction was partioned between EtOAc (50 mL) and with water (50 mL). The organics were washed with water (2 x 50 mL), brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on a chromatatron (5:1 Hex:EtOAc) to afford 0.06g (0.147 mmol, 25%) of the product as a yellow solid.

Step 8. Methyl (2*S*)-({[2-(4-chlorophenyl)-5-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)(cyclohexyl)ethanoate

Methyl (2S)-({[5-amino-2-(4-chlorophenyl)-1,3-thiazol-4-yl]carbonyl}amino)(cyclohexyl)ethanoate (0.056g, 0.14 mmol) and 2-isocyanato-1,3,5-trimethylbenzene (0.092g, 0.41 mmol) were combined in DMF and heated to 120°C. The reaction was stirred for 3h and then concentrated. The residue was purified on a chromatatron (8:1 Hex:EtOAc) to afford a binary mixture. The crude material was repurified on a chromatatron (100% CH_2Cl_2) to give 0.02g (0.032 mmol, 23%) of the desired product.

Step 9. (2*S*)-({[2-(4-Chlorophenyl)-5-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)(cyclohexyl)ethanoic acid

Methyl (2S)-({[2-(4-chlorophenyl)-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)(cyclohexyl)ethanoate (0.02g, 0.03 mmol) was taken up in THF (1 mL) and 1M lithium hydroxide (0.03 mL) was added. The reaction was heated to 70°C and stirred for 1h. The reaction was acidified with 1N HCl and diluted with EtOAc (10 mL). The organics were washed with water (1 x 20 mL), dried over MgSO4, filtered and concentrated. The residue was pllaced under vacuum and pumped to constant weight to afford 0.015g (0.02 mmol, 77%) as an off white solid. ES MS m/z 615 (M + H).

Example 491: *N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-methylglycine

Step 1. methyl *N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-methylglycinate

HATU (0.34 g, 0.90 mmol) and N,N-diisopropylethylamine (0.16 mL, 0.66 mmol) were added to a solution of 3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.20 g, 0.60 mmol) in DMF (5 mL). After stirring for 30 min, a solution of methyl *N*-methylglycinate hydrochloride (0.12 g, 0.90 mmol) in

DMF (2 mL) and N,N-diisopropylamine (0.21 mL, 0.90 mmol) were added. The solution was stirred for 12 h then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The crude solid was triturated with Et_2O, filtered, and dried under vacuum to give 0.17g (68%) of the desired product as a white solid.

Step 2. *N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-methylglycine

A solution of LiOH (0.10 g, 4.17 mmol) in water (2 mL) was added to a solution of methyl *N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-methylglycinate (0.18 g, 0.41 mmol) in 1,4-dioxane (5 mL). After stirring for 30 min at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (hexanes/ethyl acetate) to give 0.03 g (18%) of the title compound as a white solid. ^1H NMR (DMSO) 400 MHz δ 10.75 (s, 1H), 8.65 (d, 1H), 7.8 (d, 1H), 7.78 (d, 2H), 7.4 (t, 1H), 7.35 (t, 1H), 7.1-6.99 (m, 3H), 3.4-3.2 (m, 2H), 2.83 (s, 3H), 2.2 (s, 6H) ppm.

Example 492: 4-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid

Step 1. ethyl 4-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoate

HATU (0.34 g, 0.90 mmol) and N,N-diisopropylethylamine (0.16 mL, 0.67 mmol were added to a solution of 3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.20 g, 0.60 mmol) in DMF (5 mL). After 30 min, a solution of ethyl 4-aminobutanoate hydrochloride (0.15 g, 0.90 mmol) in DMF (2 mL) and N,N-diisopropylethylamine (0.21 mL, 0.90 mmol) were added. The solution was stirred for 12 h then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered

and concentrated. The crude solid was triturated with Et_2O, filtered, and dried under vacuum to give 0.17g (63%) of the title compound as a white solid.

Step 2. 4-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid

A solution of LiOH (0.08 g, 3.33 mmol) in water (2 mL) was added to a solution of ethyl 4-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoate (0.15 g, 0.34 mmol) in 1,4-dioxane (5mL). After stirring for 24 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude solid was triturated with Et_2O, filtered and dried under vacuum to give 0.06 g (44%) of the title compound. ^1H NMR (DMSO) 400 MHz δ 9.85 (s, 1H), 8.9 (s, 1H), 8.6 (s, 1H), 8.2 (s, 1H), 7.8 (d, 1H), 7.7 (d, 1H), 7.45 (t, 1H), 7.39 (t, 1H), 7.1-6.98 (m, 3H), 2.39-2.20 (m, 2H), 2,20-2.0 (m, 8H), 1.8 (s, 2H) ppm.

Example 493. methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-beta-alaninate

Step 1. 3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid

Triethylamine (0.74 mL, 5.34 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.50 g, 2.67 mmol) in DMF (20 mL). After stirring for 30 min, 2-isocyanato-1,3,5-trimethylbenzene (.47g, 2.93mmol) was added and the solution heated to 75 °C for 3 h. The reaction was cooled to RT and then 1.0M HCl and ethyl acetate were added. The organic layer was concentrated and the resulting solid was washed with Et_2O, filtered, and dried under vacuum to give 0.61 g (65% yield) of the title compound as a tan solid.

Step 2. methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-beta-alaninate

HATU (0.33 g, 0.87 mmol) and N,N-diisopropylethylamine (0.15 mL, 0.86 mmol) were added to a solution of 3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.20 g, 0.57 mmol) in DMF (5 mL). After 30 min, a solution of methyl beta-alaninate hydrochloride (0.15 g, 0.90 mmol) in DMF (2 mL) and N,N-diisopropylethylamine (0.16 mL, 0.90 mmol) were added. The solution was stirred for 3 h then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The solid was triturated with Et_2O, filtered and dried under vacuum to give 0.18 g (72%) of the title compound as a white solid. ^1H NMR (DMSO) 400 MHz delta 9.8 (s, 1H), 8.95 (s, 1H), 8.6 (s, 1H), 8.1 (s, 1H), 7.8 (d, 1H), 7.75 (d, 1H), 7.5 (t, 1H), 7.39 (t, 1H), 6.9 (s, 2H), 3.6 (s, 2H), 3.3 (s, 3H), 2.65 (s, 2H), 2.22 (s, 3H), 2.15 (s, 6H) ppm.

Example 494. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-beta-alanine

A solution of LiOH (0.10 g, 3.46 mmol) in water (2 mL) was added to a solution of methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-beta-alaninate (0.15 g, 0.34 mmol) in 1,4-dioxane (5 mL). After stirring for 3 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel (hexanes/ethyl acetate) to give 0.025 g (18%) of the title compound as a white solid. ^1H NMR (DMSO) 400 MHz delta 12.3 (s, 1H), 9.8 (s,m 1H), 8.9 (s, 1H), 8.8 (s, 1H), 8.1 (s, 1H), 7.8 (d, 1H), 7.7 (d, 1H), 7.5 (t, 1H), 7.39 (t, 1H), 6.9 (s,, 2H), 3.5 (s, 2H), 2.6 (s, 2H), 2.2 (s, 3H), 2.19 (s, 6H) ppm.

Example 495. 3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)benzoic acid

Step 1. 1,1-dimethylethyl 3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)benzoate

HATU (0.24 g, 0.64 mmol) and N,N-diisopropylethylamine (0.11 mL, 0.64 mmol) were added to a solution of 3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.15 g, 0.43 mmol) in DMF (5 mL). After 30 min, a solution of 1,1-dimethylethyl 3-aminobenzoate (0.15 g, 0.90 mmol) in DMF (2 mL) was added. The solution was stirred for 4 h at RT then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The solid was triturated with Et_2O, filtered and dried under vacuum to give 0.17 g (75%) of the title compound.

Step 2. 3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)benzoic acid

TFA (2 mL) was added to a solution of1,1-dimethylethyl 3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)benzoate (.17g, .32mmol) in DCM (5mL). After stirring for 12 h at RT, the solution was concentrated to dryness. The resulting solid was triturated with Et_2O, filtered and dried under vacuum to give 0.025 g (18%) of the desired product as a white solid. ^1H NMR (DMSO) 400 MHz delta 12.8 (s, 1H), 10.85 (s, 1H), 9.4 (s, 1H), 8.6 (s, 1H), 8.37 (s, 1H), 7.98 (d, 2H), 7.8 (d, 2H), 7.7 (d, 2H), 7.58-7.4 (m, 3H), 6.9 (s, 2H), 2.2 (s, 3H), 2.15 (s, 6H) ppm.

Example 496. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-valine

Step 1. 3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid

Triethylamine (4.46 mL, 32 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (3.00 g, 16.04 mmol) in DMF (100 mL). After stirring for 30 min, 2-isocyanato-1,3,5-trimethylbenzene (2.83 g, 17.60 mmol) was added and the solution heated to 75 °C for 3 h. The reaction was cooled to RT and then 1.0M

HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting crude residue was washed with Et_2O and the solid was filtered and dried under vacuum to give 4.2 g (75%) of the title compound as a cream solid.

Step 2. methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-valinate

HATU (0.26 g, 0.68 mmol) and N,N-diisopropylethylamine (0.12 mL, 0.68 mmol) were added to a solution of 3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.20 g, 0.57 mmol) in DMF (3 mL). After 30 min, a solution of methyl L-valinate hydrochloride(0.15 g, 0.90 mmol) in DMF (2 mL) and N,N-diisopropylethylamine (0.1 mL, 0.57 mmol) was added. The solution was stirred for 4 h at RT then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (hexanes/ethyl acetate) to give 0.18 g (70%) of thetitle compound.

Step 3. *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-valine

A solution of LiOH (0.1 g, 3.9 mmol) in water (2 mL) was added to a solution of methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-valinate (0.18 g, 0.39 mmol) in 1,4-dioxane (5 mL). After stirring for 3 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 0.010 g (7%) of the title compound. ^1H NMR (DMSO) 400 MHz delta 12.8 (s, 1H), 9.6 (s, 1H), 8.9 (s, 1H), 8.8 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.79 (d, 1H), 7.5 (t, 1H), 7.4 (t, 1H), 6.9 (s, 2H), 4.5 (s, 1H), 2.3-2.0 (m, 10H), 1.0 (s, 6H) ppm.

Example 497. 4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-3-thiophenecarboxylic acid

Step 1. 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid

Triethylamine (4.4 mL, 32.0 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (3.00 g, 16.04 mmol) in DMF (100 mL). After stirring for 30 min, 1,3-dichloro-2-isocyanatobenzene (3.3 g, 17.6 mmol) was added and the solution heated to 75 °C for 3 h. The reaction was cooled to RT and then 1.0M HCl was added. The resulting precipitate was filtered, washed with ethyl acetate and Et_2O then dried under vacuum to give 4.5 g (75%) of the title compound as a cream solid.

Step 2. methyl 4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-3-thiophenecarboxylate

HATU (0.38 g, 1.00 mmol) and N,N-diisopropylethylamine (0.73 mL, 4.20 mmol) were added to a solution of 3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.25 g, 0.67 mmol) in DCM (5 mL) and DMF (1 mL). After 30 min, a solution of methyl 4-amino-3-thiophenecarboxylate (0.17 g, 1.08 mmol) in DMF (3 mL) was added. The solution was stirred for 24 h at RT then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (100% hexanes to 30% ethyl acetate/hexanes over 30 min) to give 0.17g (50%) of the title compound.

Step 3. 4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-3-thiophenecarboxylic acid

A solution of LiOH (0.08 g, 3.33 mmol) in water (2 mL) was added to a solution of methyl 4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-3-thiophenecarboxylate (0.17 g, 0.33 mmol) in 1,4-

dioxane (2 mL) and water (1 mL). After stirring for 3 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 0.06 g (37%) of the desired product as a white solid. ^1H NMR (DMSO) 400 MHz delta 11.25 (2, 1H), 9.8 (s, 1H), 9.4 (s, 1H), 8.67 (s, 1H), 8.4 (d, 2H), 8.0 (s, 1H), 7.97 (d, 1H), 7.8 (d, 1H), 7.6-7.5 (m, 2H), 7.5 (t, 1H), 7.38 (t, 1H) ppm.

Example 498: 5-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,3-benzenedicarboxylic acid

Step 1. dimethyl 5-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,3-benzenedicarboxylate

HATU (0.41g, 1.08 mmol) and N,N-diisopropylethylamine (0.14 mL, 0.81 mmol) were added to a solution of 3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.25 g, 0.72 mmol) in DMF (1 mL). After 30 min, a solution of dimethyl 5-amino-1,3-benzenedicarboxylate (0.22 g, 1.08 mmol) in DCM (4 mL) was added. The solution was stirred for 4 h at RT then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (ethyl acetate/hexanes) to give 0.08 g (21%) of the title compound.

Step 2. 5-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,3-benzenedicarboxylic acid

A solution of LiOH (0.04 g, 1.50 mmol) in water (2 mL) was added to a solution of dimethyl 5-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,3-benzenedicarboxylate (0.08 g, 0.15 mmol) in 1,4-dioxane (2 mL) and water (1 mL). After stirring for 3 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and

concentrated. The crude solid was triturated with Et_2O to give 0.01 g (13%) of the title compound. ES-MS M/Z 512 (M+H).

Example 499: 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopropanecarboxylic acid

Step 1. methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclopropanecarboxylate

HATU (1.5 g, 3.9 mmol) and N,N-diisopropylethylamine (0.68 g, 4.05 mmol) were added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5 g, 2.7 mmol) in DMF (5 mL). After 30 min, a solution of methyl 1-aminocyclopropanecarboxylate (0.22 g, 1.08 mmol) in DCM (2 mL) was added. The solution was stirred for 4 h at RT then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (ethyl acetate/hexanes) to give 0.45 g (60%) of the title compound.

Step 2. methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopropanecarboxylate

To a pyridine solution (5 mL) containing methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclopropanecarboxylate (0.22 g, 0.77 mmol) was added 2-isocyanato-1,3,5-trimethylbenzene (0.37 g, 2.31 mmol). The solution was stirred at RT for approximately 12 h then the pyridine was removed in vacuo. The residue was dissolved in ethyl acetate and the resulting precipitate was removed by filtration. The organic layer was washed with 1.0M HCl, dried over $MgSO_4$, and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (0 – 40% hexane/ethyl acetate) to give 0.17 g (50%) of the title compound as a white solid.

Step 3. 2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopropanecarboxylic acid (u21828/49).

A solution of LiOH (0.09 g, 3.80 mmol) in water (2 mL) was added to a solution of methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopropanecarboxylate (0.17 g, 0.38 mmol) in 1,4-dioxane (2 mL) and water (1 mL). After stirring for 3 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude solid was triturated with Et_2O to give 0.03 g (18%) of the title compound. ^1H NMR (DMSO) 400 MHz delta 12.6 (s, 1H), 10.2 (s, 1H), 9.4 (s, 1H), 8.63 (s, 1H), 8.25 (s, 1H), 7.80 (d, 1H), 7.78 (d, 1H), 7.5 (t, 1H), 7.4 (t, 1H), 6.9 (s, 2H), 2,2 (s, 3H), 2.18 (s, 6H), 1.5 (s, 2H), 1.2 (s, 2H) ppm.

Example 500. 3-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid

Step 1. ethyl 3-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoate

HATU (0.26 g, 0.68 mmol) and N,N-diisopropylethylamine (0.11 mL, 0.67 mmol) were added to a solution of 3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid (0.15 g, 0.45 mmol) in DMF (3 mL). After 30 min, a solution of ethyl 3-aminobutanoate (0.1 g, 0.7 mmol) in DMF (2 mL) was added. The solution was stirred for 4 h at RT then poured into saturated $NaHCO_3$ and extracted into ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (ethyl acetate/hexanes) to give 0.06 g (30%) of the title compound.

Step 2. 3-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid

A solution of LiOH (0.03 g, 1.3 mmol) in water (1 mL) was added to a solution of ethyl 3-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoate (0.06 g, 0.13 mmol) in 1,4-dioxane (2 mL) and water (1 mL). After stirring for 3 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude solid was triturated with Et_2O and $CHCl_3$ to give 0.02 g (37%) of the title compound. ^1H NMR (DMSO) 400 MHz delta 8.5 (d, 1H), 8.0 (s, 1H), 7.74 (d, 1H), 7.52 (d, 1H), 7.36-7.23 (m, 1H), 7.19 (m, 1H), 6.97 (s, 1H), 6.08 (s, 2H), 4.42-4.29 (m, 1H), 4.14-3.95 (m, 2H), 3.38 (s, 3H), 2.5 (s, 6H) ppm.

Example 501: (2*S*)-(4-hydroxyphenyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(4-hydroxyphenyl)ethanoate

HATU (0.76 g, 2.00 mmol) and N,N-diisopropylethylamine (0.34 mL, 1.96 mmol) were added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.25 g, 1.33 mmol) in DMF (1.5 mL) and DCM (1.5 mL). After 30 min, a solution of methyl (2*S*)-amino(4-hydroxyphenyl)ethanoate (0.1 g, 0.7 mmol) in DMF (2 mL) was added. The solution was stirred for 4 h at RT then poured into saturated $NaHCO_3$ and extracted into DCM. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (ethyl acetate/hexanes) to give 0.15 g (32%) of the title compound.

Step 2. methyl (2*S*)-(4-hydroxyphenyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

To a pyridine solution (15 mL) containing methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(4-hydroxyphenyl)ethanoate (0.15 g, 0.43 mmol) was

added 2-isocyanato-1,3,5-trimethylbenzene (0.34 g, 2.11 mmol). The solution was stirred for 12 h at RT then the pyridine was removed in vacuo. The residue was dissolved in ethyl acetate and the resulting precipitate was removed by filtration. The organic layer was washed with 1.0M HCl, dried over $MgSO_4$, and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (0 – 40% hexane/ethyl acetate) to give 0.05 g (23% yield) of the title compound.

Step 3. (2*S*)-(4-hydroxyphenyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

A solution of LiOH (0.02 g, 0.97 mmol) in water (2 mL) was added to a solution of methyl (2*S*)-(4-hydroxyphenyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.05 g, 0.10 mmol) in 1,4-dioxane (5 mL). After stirring for 3 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified on a reverse phase HPLC (Gilson: MeCN, 1%TFA/water) to give 0.001 g (20%) of the title compound. ES-MS M/Z 496 (M-H).

Example 502: (2*S*)-(4-hydroxycyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1. methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(4-hydroxycyclohexyl)ethanoate

HATU (1.21 g, 3.20 mmol) and N,N-diisopropylethylamine (0.56 mL, 3.21 mmol) were added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.50 g, 2.67 mmol) in DMF (2.5 mL) and DCM (2.5 mL). After 30 min, a solution of (2*S*)-amino(4-hydroxycyclohexyl)ethanoic acid (0.6 g, 3.2 mmol) in DCM (2 mL) was added. The solution was stirred for 4 h at RT then poured into saturated $NaHCO_3$ and extracted into DCM. The organic layer was washed with water, dried over

$MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (ethyl acetate/hexanes) to give 0.37 g (41%) of the title compound.

Step 2. methyl (2*S*)-(4-hydroxycyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

To a pyridine solution (5 mL) containing methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(4-hydroxycyclohexyl)ethanoate (0.15 g, 0.42 mmol) was added 2-isocyanato-1,3,5-trimethylbenzene (0.2 g, 1.2 mmol). The solution was stirred for 12 h at RT then the pyridine was removed in vacuo. The residue was dissolved in ethyl acetate and the resulting precipitate was removed by filtration. The organic layer was washed with 1.0M HCl, dried over $MgSO_4$, and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (0-40% ethyl acetate/hexanes) to give 0.065 g (30%) of the title compound.

Step 3. (2*S*)-(4-hydroxycyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

A solution of LiOH (0.03 g, 1.25 mmol) in water (1 mL) was added to a solution of methyl (2*S*)-(4-hydroxycyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.06 g, 0.12 mmol) in THF (5 mL) and MeOH (1 mL). After stirring for 12 h at RT, 1.0 M HCl and ethyl acetate were added. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude solid was triturated with Et_2O and dried to give 0.20 (34%) of the title compound. ES-MS M/Z 502 (M-H).

Example 503: methyl N^4,N^4-dimethyl-N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparaginate

A solution of HATU (0.61 g, 1.60 mmol) and (3*S*)-4-(methyloxy)-3-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid (0.28 g, 0.53 mmol) in DCM (10 mL) were stirred at RT for 5 min then a 2M solution of dimethylamine (1.6 mL, 3.2 mmol) in THF was added. After stirring at RT for 2 h, ethyl acetate (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL) were added. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (100 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified on silica gel (ISCO: eluting with 100% hexanes to 100% ethyl acetate over 40 min) to give 0.23 g (77%) of the title compound as a white powder. APCI m/z 561 (M+H).

Example 504: N^4,N^4-dimethyl-N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparagine

A solution of LiOH (0.058 g, 2.43 mmol) in hot water (3 mL) was added to a solution of methyl N^4,N^4-dimethyl-N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparaginate (0.17 g, 0.30 mmol) in THF (5 mL) and MeOH (3 mL). After stirring at RT for 1 h, the THF was removed via rotary evaporation then 1N HCl (20 mL) was added to the remaining aqueous layer. The resulting white slurry was filtered, washed with water (20 mL), then dissolved in ethyl acetate (50 mL) and dried over $MgSO_4$. The organic layer was filtered, concentrated via rotary evaporation and dried under vacuum. The crude material was dissolved in DCM (2 mL) and Et_2O (5 ml) was added. The white solid was filtered and dried under vacuum to give 0.077 g (46%) of the title compound as a white powder. APCI m/z 547 (M+H).

Example 505: *N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threonine

Step 1: methyl 3'-fluoro-3-nitro-4-biphenylcarboxylate

Five 20ml microwave reaction vials were each charged with methyl 4-chloro-2-nitrobenzoate (1.00 g, 4.64 mmol), (3-fluorophenyl)boronic acid (0.71 g, 5.10 mmol), cesium fluoride (2.12 g, 13.92 mmol) and $Pd(Cy_3)_2Cl_2$ (0.17 g, 0.23 mmol) in MeCN (12 mL) and water (2 mL). The vials were sealed and heated to 150 °C for 5 min in a Microwave Reactor. The vials were carefully vented then combined in a separatory funnel, diluted with ethyl acetate (300 mL), washed with water (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified on silica gel (ISCO: eluting with 100% hexanes to 100% ethyl acetate over 50 min) to give 5.64 g (89%) of the title compound as a yellow oil.

Step 2: 3'-fluoro-3-nitro-4-biphenylcarboxylic acid

A solution of LiOH (1.48 g, 61.48 mmol) in hot water (40 mL) was added to a solution of methyl 3'-fluoro-3-nitro-4-biphenylcarboxylate (5.64 g, 20.49 mmol) in THF (100 mL) and MeOH (30 mL). After stirring at RT for 1 h, the THF was removed via rotary evaporation then 1N HCl (75 mL) was added to the remaining aqueous layer. The resulting white slurry was filtered, washed with water (20 mL) and dried under vacuum to give 4.30 g (80%) of the title compound as a white powder.

Step 3: methyl *O*-(1,1-dimethylethyl)-*N*-[(3'-fluoro-3-nitro-4-biphenylyl)carbonyl]-L-threoninate

HATU (2.91 g, 7.66 mmol) was added to a suspension of 3'-fluoro-3-nitro-4-biphenylcarboxylic acid (1.00 g, 3.83 mmol) in DCM (25 mL). After 5 min, N,N-diisopropylethylamine (1.33 mL, 7.66 mmol) was added, followed by methyl *O*-(1,1-dimethylethyl)-L-threoninate hydrochloride (1.29 g, 5.74 mmol). The solution was stirred at RT for 3 h then saturated aqueous $NaHCO_3$ solution (100 mL) and ethyl acetate (150 mL) were added. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (100 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified on silica gel (ISCO: eluting with 100%

hexanes to 60% ethyl acetate over 40 min) to give 1.58 g (95%) of the title compound as a white gummy powder. APCI m/z 433 (M+H).

Step 4: methyl *N*-[(3-amino-3'-fluoro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl *O*-(1,1-dimethylethyl)-*N*-[(3'-fluoro-3-nitro-4-biphenylyl)carbonyl]-L-threoninate (1.52 g, 3.51 mmol) and 10% Pd/C (0.15 g) in ethyl acetate (30 mL) and MeOH (15 mL) was stirred under hydrogen (60 psig) at RT for 16 h. The next day the reaction was carefully vented, diluted with ethyl acetate, and filtered through Celite to give 1.26 g (83%) of the title compound as a white gummy powder. APCI m/z 403 (M+H).

Step 5: methyl *N*-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate

A solution of methyl *N*-[(3-amino-3'-fluoro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-L-threoninate (0.59 g, 1.47 mmol) and 5-bromo-2-isocyanato-1,3-dimethylbenzene (0.67 g, 2.95 mmol) in pyridine (8 mL) were stirred at RT for 16 h then concentrated to dryness via rotary evaporation. An aqueous 1N HCl solution (50 mL) and ethyl acetate (150 mL) were added. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (100 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated to give 0.92 g (99%) of the title compound as a white solid. APCI m/z 626 (M-H).

Step 6:
methyl *O*-(1,1-dimethylethyl)-*N*-({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-L-threoninate

A mixture of methyl *N*-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate (0.92 g, 1.46 mmol), allyltributylstannane (0.53 g, 1.61 mmol) and

tetrakispalladium(trphenylphosphine) (0.085 g, 0.070 mmol) in MeCN (10 mL) were heated to 150 °C for 30 min in a microwave reactor. Upon cooling to RT, the mixture was poured into a separatory funnel containing water (100 mL) and ethyl acetate (150 mL). The organic layer was washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel using an ISCO chromatography system (increasing solvent gradient from 100% hexanes to 90% ethyl acetate (hexanes over 30 min) to give 0.19 g (22%) of the title compound as a clear oil solid. APCI m/z 590 (M+H).

Step 7: methyl *N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threoninate

N-methyl-*N*-nitrosourea (0.33 g, 3.22 mmol) was added as a solid to a mixture of 30% aqueous KOH (32 mL) and DCM (25 mL) at 0 °C. After stirring for 5 min, the mixture was poured into a smooth separatory funnel (ie no chips, cracks, etc) with a Teflon stopcock. The yellow organic layer was separated and dried over KOH pellets at 0 °C. Half of the solution was added to a smooth addition funnel with a Teflon stopcock and added dropwise to a mixture of methyl *O*-(1,1-dimethylethyl)-*N*-({3-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-L-threoninate (0.19 g, 0.32 mmol) and $Pd(acac)_2$ (0.01 g, 0.03 mmol) in Et_2O at 0 °C. Upon addition, the remaining diazomethane solution was added to the separatory funnel and added dropwise. Upon complete addition, the solution was warmed to RT and stirred for 0.5 h. The pale yellow solution was filtered through Celite and concentrated. The crude yellow oil was purified on silica gel using an ISCO chromatography system (increasing solvent gradient from 100% hexanes to 90% ethyl acetate/hexanes over 30 min) to give 0.153 (79%) of the title compound as a pale yellow oil. APCI m/z 604 (M+H).

Step 8: *N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threonine

A hot solution of LiOH (0.089 g, 3.73 mmol) in water (5 mL) was added to a solution of methyl *N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threoninate (0.15 g, 0.25 mmol) in THF (5 mL) and MeOH (5 mL). After 3 h, the organic solvent was removed under reduced pressure then 1N HCl solution (5 mL) and ethyl acetate (50 mL) were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was dissolved in a minimal amount of hot ethyl acetate (ca. 5 mL) then hexanes (50 mL) was added. The white precipitate was filtered (gummy solid), dissolved in ethyl acetate and DCM, and concentrated to give 0.105 g (72%) of the title compound as a white solid. APCI m/z 588 (M-H).

Example 506: (2*S*)-4-(ethyloxy)-2-({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid

Step 1: 4-ethyl 1-(phenylmethyl) *N*-[(3'-fluoro-3-nitro-4-biphenylyl)carbonyl]-L-aspartate

HATU (1.16 g, 3.06 mmol) was added to a suspension of 3'-fluoro-3-nitro-4-biphenylcarboxylic acid (0.40 g, 1.53 mmol) in DCM (10 mL). After 5 min, N,N-diisopropylethylamine (0.54 mL, 3.06 mmol) was added, followed by 4-ethyl 1-(phenylmethyl) L-aspartate trifluoroacetate (0.84 g, 2.30 mmol). The solution was stirred at RT for 16 h then saturated aqueous $NaHCO_3$ solution (100 mL) and ethyl acetate (150 mL) were added. The organic layer was washed with aqueous 1N HCl solution (2 x's 50 mL), saturated aqueous $NaHCO_3$ solution (100 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified on silica gel (ISCO: eluting with 100% hexanes to 100% ethyl acetate over 40 min) to give 0.227 g (30%) of the title compound as a white powder. APCI m/z 494 (M-H).

Step 2: 4-ethyl 1-(phenylmethyl) *N*-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate

A mixture of 4-ethyl 1-(phenylmethyl) *N*-[(3'-fluoro-3-nitro-4-biphenylyl)carbonyl]-L-aspartate (0.23 g, 0.47 mmol) and Pt(sulfided) (0.10 g) in MeOH (15 mL) was stirred under a balloon of hydrogen (1 atmosphere) at RT for 16 h. The next day the reaction was carefully vented, diluted with ethyl acetate, and filtered through Celite to give the title compound as a white gummy powder. LC/MS shows multiple peaks; used as is in next step. The crude product was dissolved in pyridine (8 mL) and 2-isocyanato-1,3,5-trimethylbenzene (0.15 g, 0.94 mmol) was added. The mixture was stirred for 16 h then concentrated to dryness. An aqueous 1N HCL solution (50 mL) and ethyl acetate (100 mL) were added. The organic layer was washed with saturated $NaHCO_3$ solution (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel using an ISCO chromatography system (increasing solvent gradient from 100% hexanes to 90% ethyl acetate/hexanes over 30 min) to give 0.094 g (32%) of the title compound as a white solid. APCI m/z 626 (M+H).

Step 3:
(2*S*)-4-(ethyloxy)-2-({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid

A mixture of 4-ethyl 1-(phenylmethyl) *N*-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate (0.094 g, 0.15 mmol) and 10% Pd/C (0.060 g) in MeOH (5 mL) and ethyl acetate (5 mL) were stirred at RT under 1 atmosphere of hydrogen (balloon) for 5 h. The mixture was diluted with ethyl acetate (ca. 50 mL), filtered through Celite and concentrated to give 0.070 g (87%) of the title compound as a grey white solid. APCI m/z 536 (M+H).

Example 507: *N*-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid

A hot solution of LiOH (0.034 g, 1.40 mmol) in water (5 mL) was added to a solution of (2*S*)-4-(ethyloxy)-2-({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid (0.05 g, 0.09 mmol) in THF (5 mL) and MeOH (5 mL). After 3 h, the organic solvent was removed under reduced pressure then 1N HCl solution (5 mL) was added. The grey precipitate was filtered then dissolved in ethyl acetate (ca. 25 mL), dried over $MgSO_4$, filtered and concentrated to give 0.035 g (74%) of the title compound as a white solid. APCI m/z 508 (M+H).

Example 508: 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylic acid

Step 1. Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclopentanecarboxylate

3-Amino-2-naphthoic acid (0.25 g, 1.11 mmol) and methyl 1-aminocyclopentanecarboxylate hydrochloride (0.22 g, 1.22 mmol) were dissolved in DMF (10 mL) and diisopropylethylamine (0.50 g, 3.9 mmol) and HATU (0.46 g, 1.22 mmol) were added. The solution was stirred for 2 h. The reaction was diluted with ethyl acetate and washed with water. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.47 g of product as a yellow oil.

Step 2. Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylate

Methyl 1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclopentanecarboxylate (0.41 g, 1.31 mmol) was dissolved in pyridine (10 mL) and 2,4,6-trimethylphenyl isocyanate (0.53 g, 3.28 mmol) was added. The reaction was stirred for 3 h, diluted with ethyl acetate, and washed with water. The organics were dried ($MgSO_4$) and

concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate provided 0.44 g of product as a orange solid.

Step 3. 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylic acid

Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylate (0.24 g, 0.50 mmol) was dissolved in 1:1 THF/MeOH (5 mL) and 2 M LiOH (2.5 mL) was added. The reaction was heated to 50 °C for 4 h and cooled. The solution was acidified with 1 M HCl (5 mL) and extracted with ethyl actetate. The extracts were dried ($MgSO_4$) and concentrated. MeOH was added to the residue and a solid formed. The solid was filtered off and the MeOH filtrate was purified by reverse-phase HPLC to afford 21 mg of product as a beige solid. ES MS m/z 460 (M+H).

Example 509: *O*-(Phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Step 1: *N*-[(3-Amino-2-naphthalenyl)carbonyl]-*O*-(phenylmethyl)-L-serine

3-Amino-2-naphthoic acid (0.29 g, 1.31 mmol) and *O*-(phenylmethyl)-L-serine hydrochloride (0.36 g, 1.45 mmol) were dissolved in DMF (10 mL) and diisopropylethylamine (0.60 g, 4.60 mmol) and HATU (0.55 g, 1.45 mmol) were added. The solution was stirred for 3 h, diluted with water, and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.48 g of product as an orange solid.

Step 2: Methyl *O*-(phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate

N-[(3-Amino-2-naphthalenyl)carbonyl]-*O*-(phenylmethyl)-L-serine (0.2 g, 0.55 mmol) was dissolved in pyridine (10 mL) and 2,4,6-trimethylphenylisocyanate (0.22 g, 1.37 mmol) was added. The reaction was stirred 3 h, diluted with ethyl acetate, and washed with 1 M HCl. The organic layer was dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.13 g of product as a colorless solid.

Step 3: *O*-(Phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine

Methyl *O*-(phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serinate (0.13 g, 0.24 mmol) was dissolved in 1:1 THF/MeOH (2 mL) and 2 M LiOH (1.2 mL) was added. The reaction was heated to 60 °C for 2 h, cooled, and acidified with 1 M HCl (0.5 mL). The solution was extracted with ethyl acetate and the extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH and purified by reverse-phase HPLC. The resulting solid was triturated with MeOH to afford 16 mg of product as a colorless solid. ES MS m/z 526 (M+H).

Example 510: *N*-{[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(phenylmethyl)-L-serine

Step 1: Methyl *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-*O*-(phenylmethyl)-L-serinate

3',4'-Difluoro-3-nitro-4-biphenylcarboxylic acid (0.2 g, 0.72 mmol) and *O*-(phenylmethyl)-L-serine hydrochloride (0.19 g, 0.78 mmol) were dissolved in DMF (5 mL) and diisopropylethylamine (0.32 g, 2.50 mmol) and HATU (0.30 g, 0.78 mmol) were added. The solution was stirred overnight, diluted with ethyl acetate, and washed with water. The organic layer was dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.3 g of product as a colorless solid.

Step 2: Methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-(phenylmethyl)-L-serinate

Methyl *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-*O*-(phenylmethyl)-L-serinate (0.3 g, 0.63 mmol) was dissolved in EtOH (7 mL) and saturated NH_4Cl (3 mL) and indium powder (0.6 g) was added. The reaction was heated to reflux for 5 h, cooled, diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.19 g of product.

Step 3: Methyl *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(phenylmethyl)-L-serinate

Methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-(phenylmethyl)-L-serinate (0.19 g, 0.44 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (0.25 g, 1.54 mmol) was added. The reaction was stirred for 4 h, diluted with ethyl acetate, and washed with 1 M HCl. The organics were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes provided 0.19 g of product.

Step 4: *N*-{[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(phenylmethyl)-L-serine

Methyl *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(phenylmethyl)-L-serinate (0.19 g, 0.31 mmol) was dissolved in 1:1 THF/MeOH (5 mL) and 2 M LiOH (1.6 mL) was added. The reaction was stirred overnight, acidified with 1 M HCl (3.2 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH and a solid formed. The solid was collected to afford 24 mg of product as a colorless solid. ES MS m/z 588 (M+H).

Example 511: (3*R*)-5-Methyl-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine

Step 1: (1*R*)-3-Methyl-1-[(2*S*,5*R*)-5-(1-methylethyl)-3,6-bis(methyloxy)-2,5-dihydro-2-pyrazinyl]-1-butanol

(2*R*)-2-(1-methylethyl)-3,6-bis(methyloxy)-2,5-dihydropyrazine (1 g, 5.42 mmol) was dissolved in THF (40 mL) and cooled to -78 °C. A solution of n-BuLi (3.8 mL of a 1.6 M solution) was added dropwise and stirred for 30 min. 3-Methylbutanal (0.51 mL, 5.97 mmol) was added and the reaction was stirred overnight. The mixture was poured onto water and extracted with ethyl acetate. The extracts were separated, dried ($MgSO_4$), and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 1.13 g of product as a clear oil.

Step 2: (2*R*,5*S*)-2-(1-Methylethyl)-3,6-bis(methyloxy)-5-{(1*R*)-3-methyl-1-[(phenylmethyl)oxy]butyl}-2,5-dihydropyrazine

(1*R*)-3-Methyl-1-[(2*S*,5*R*)-5-(1-methylethyl)-3,6-bis(methyloxy)-2,5-dihydro-2-pyrazinyl]-1-butanol (1.13 g, 4.18 mmol) was dissolved in DMF (20 mL) and the solution was cooled to 0 °C. Sodium hydride (0.20 g, 5.0 mmol) was added and stirred 20 min and then benzyl bromide (0.79 g, 4.59 mmol) was added and stirred 3 days. The reaction was diluted with ethyl acetate, washed with water, and the organics were dried ($MgSO_4$) and concentrated onto SiO_2. Chromatography on SiO_2 eluting with ethyl acetate/hexanes afforded 1.05 g of product as a colorless oil.

Step 3: Methyl (3*R*)-5-methyl-3-[(phenylmethyl)oxy]-L-norleucinate

(2*R*,5*S*)-2-(1-Methylethyl)-3,6-bis(methyloxy)-5-{(1*R*)-3-methyl-1-[(phenylmethyl)oxy]butyl}-2,5-dihydropyrazine (1.05 g, 2.91 mmol) was dissolved in CH_3CN (12 mL) and 0.5 N HCl (11.6 mL) was added and the solution was stirred for 2 days. Sodium chloride and Et_2O were added to the solution and the pH was adjusted to 9 with ammonium hydroxide. The mixture was extracted with Et_2O, the

extracts were combined and concentrated to afford 0.33 g of oil as a 1:1 mixture of desired product and methyl D-valinate.

Step 4: Methyl (3*R*)-*N*-[(3-amino-2-naphthalenyl)carbonyl]-5-methyl-3-[(phenylmethyl)oxy]-L-norleucinate

A 1:1 mixture of Methyl (3*R*)-5-methyl-3-[(phenylmethyl)oxy]-L-norleucinate and methyl D-valinate (0.33 g, 0.83 mmol) and 3-amino-2-naphthalenecarboxylic acid (0.22 g, 1.0 mmol) was dissolved in DMF (5 mL) and diisopropylethylamine (0.32 g, 2.50 mmol) was added followed by HATU (0.38 g, 1.0 mmol). The solution was stirred overnight and then diluted with water and extracted with ethyl acetate. The extracts were dried ($MgSO_4$), concentrated onto SiO_2, and purified by chromatography on SiO_2 eluting with ethyl acetate/hexanes to afford 0.21 g of a 1:1 mixture of product and methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-D-valinate.

Step 5: Methyl (3*R*)-5-methyl-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucinate

A 1:1 mixture of methyl (3*R*)-*N*-[(3-amino-2-naphthalenyl)carbonyl]-5-methyl-3-[(phenylmethyl)oxy]-L-norleucinate and methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-D-valinate (0.21 g, 0.28 mmol) was dissolved in pyridine (5 mL) and 2,4,6-trimethylphenylisocyanate (0.27 g, 1.71 mmol) was added and stirred for 3 h. The solution was diluted with MeOH and filtered. The filtrate was concentrated and the resulting residue was dissolved in ethyl acetate, washed with 1 M HCl, and dried ($MgSO_4$). The solution was concentrated to afford an orange oil weighing 0.50 g, consisting of a 1:1 mixture of product and methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-valinate.

Step 6: (3*R*)-5-Methyl-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine

A 1:1 mixture of methyl (3*R*)-5-methyl-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucinate and methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-valinate (0.50 g, 0.28 mmol) was dissolved in 1:1 THF/MeOH (5 mL) and 2 M LiOH (1.4 mL) was added. The reaction was stirred for 3 h, acidified with 1 M HCl (2.8 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated. A 200 mg sample of the residue was dissolved in MeOH (1 mL) and purified by reverse-phase HPLC to afford 46 mg of product as a brown solid. MS m/z 582 (M+H).

Example 512: *O*-cyclobutyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine.

Step 1: Methyl *N*-(triphenylmethyl)-L-threoninate

To a cooled (0°C) solution of methyl L-threoninate hydrochloride (5.0g, 29.48 mmol) and triethylamine (5.97g, 58.97 mmol) in chloroform (100ml) was added trityl chloride as a solid (8.22g, 29.49 mmol). The reaction was stirred for 12 hours and allowed to come to RT. The reaction was concentrated in vacuo and then dissolved in ethyl acetate and washed with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$, and saturated sodium chloride. The organic layer was dried over $MgSO_4$, filtered and stripped to give10.16g of product as a fluffy cream solid. ES MS m/z 398 (M+Na).

Step 2: Methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate

To a cooled (0°C) solution of methyl *N*-(triphenylmethyl)-L-threoninate (10.16g, 27.95 mmol) in anhydrous pyridine was added methanesulfonyl chloride (9.61g, 83.85 mmol) and the reaction was allowed to stirfor 12 hours and allowed to come to RT. The solvent was removed in vacuo and the residue dissolved in ethyl acetate. The organic layer was washed with saturated sodium chloride and then dried over $MgSO_4$, filtered and stripped to 12.33g of amber oil which was then

dissolved in 80ml of anhydrous THF and to which was added triethylamine (8.50g, 84.01 mmol) and heated to 80°C and allowed to reflux for 48 hours.
The heat was removed and the reaction was concentrated in vacuo and the residue dissolved in ethyl acetate and washed successively with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$ and saturated sodium chloride. The ethyl acetate layer was dried over $MgSO_4$, filtered and stripped to give 9.04g of amber oil. Chromatography on silica gel with hexane/ethyl acetate gave 5.26 g of product fluffy cream solid. ES MS m/z 380 (M+Na).

Step 3: 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate

To a solution of methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate (5.26g, 14.72 mmol) in $CHCl_3$ (12ml) and MeOH (12ml) cooled to 0°C was added 11.6ml of TFA and allowed to stir at 0°C for 2.5 hours. The reaction was then concentrated in vacuo and evaporated with ether newly added several times to remove TFA. The residue was dissolved in ether which was extracted with water three times. To the aqueous extract at 0°C was added $NaHCO_3$ (5.84g, 69.52 mmol), benzyl chloroformate (2.51g, 14.71 mmol) and 50ml of ethyl acetate under vigorous stirring for 1.5 hours. The ethyl acetate layer was separated and the water layer back-extracted. The organics were dried over $MgSO_4$, filtered and concentrated to give 2.96g of light yellow oil. Chromatography on silica gel with hexane/ethyl acetate gave 2.45g of product as a clear oil. ES MS m/z 250 (M+H).

Step 4: Methyl *O*-cyclobutyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-threoninate

To a solution of 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate (0.4g, 1.60 mmol) in $CHCl_3$ (10ml) was added cyclobutanol (1.16g, 16.09 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.76g of product as a rose oil.

Step 5: Methyl *O*-cyclobutyl-L-threoninate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-cyclobutyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-threoninate (0.76g, 2.36 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.37g of clear oil.

Step 6: Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-cyclobutyl-L-threoninate

HATU (0.76 g, 2.00 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.31 g, 1.66 mmol), methyl *O*-cyclobutyl-L-threoninate (0.37 g, 1.98 mmol) and diisopropylethylamine (0.26 g, 2.01 mmol) in 15 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.27 g of yellow oil.

Step 7: Methyl *O*-cyclobutyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-cyclobutyl-L-threoninate (0.27 g, 0.76 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.61 g, 3.77 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.22 g of product as cream solid.

Step 8: *O*-cyclobutyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Lithium hydroxide monohydrate (0.102 g, 4.26 mmol) was added to a solution of methyl *O*-cyclobutyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate (0.22 g, 0.425 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.066 g (30% yield) of product as a fluffy cream solid. ES MS m/z 504 (M+H).

Example 513: 1-{[(3-{[(4-biphenylylamino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylic acid.

Step 1: 1-{[(3-{[(4-biphenylylamino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylic acid

1-{[(3-amino-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylic acid (0.04 g, 0.13 mmol) in 5 mL of pyridine was treated with 4-isocyanatobiphenyl(0.12 g, 0.61 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.038 g of product as cream solid. ES MS m/z 508 (M+H).

Example 514: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-phenylalanine.

Step 1: Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-phenylalaninate

HATU (1.22 g, 3.21 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5 g, 2.67 mmol), ethyl L-phenylalaninate hydrochloride (0.74 g, 3.22 mmol) and diisopropylethylamine (0.41 g, 3.21 mmol) in 15 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The

organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.79 g of yellow oil.

Step 2: Ethyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-phenylalaninate

Ethyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-L-phenylalaninate (0.79g, 2.18 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.76 g, 10.89 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.47 g of product as light pink semi-solid.

Step 3: *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-phenylalanine

Lithium hydroxide monohydrate (0.215 g, 8.98 mmol) was added to a solution of ethyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-phenylalaninate (0.47 g, 0.90 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.072 g (16% yield) of product as a white solid. ES MS m/z 496 (M+H).

Example 515: (2*S*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)butanoic acid.

Step 1: Methyl (2*S*)-2-{[(2-amino-4-fluorophenyl)carbonyl]amino}-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)butanoate

HATU (1.48 g, 3.89 mmol) was added to a solution of 2-amino-4-fluorobenzoic acid (0.5 g, 3.22 mmol), methyl (2*S*)-2-amino-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)butanoate hydrochloride (1.04 g, 3.87 mmol) and diisopropylethylamine (0.50 g, 3.90 mmol) in 25 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated to give 1.6 g of fluffy cream solid.

Step 2: Methyl (2*S*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)butanoate

Methyl (2*S*)-2-{[(2-amino-4-fluorophenyl)carbonyl]amino}-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)butanoate (0.62g, 1.68 mmol) in 20 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.36 g, 8.42 mmol) for ca. 15h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated to give 1.39 g of product as white semi-solid.

Step 3: (2*S*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)butanoic acid

Lithium hydroxide monohydrate (0.27 g, 11.27 mmol) was added to a solution of methyl (2*S*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)butanoate (0.6 g, 1.13 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.077 g (11% yield) of product as a light orange fluffy solid. ES MS m/z 517 (M+H).

Example 516: (2*S*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid.

Step 1: Methyl (2*S*)-2-{[(3-amino-2-naphthalenyl)carbonyl]amino}-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)butanoate

HATU (1.22 g, 3.21 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.5 g, 2.67 mmol), methyl (2*S*)-2-amino-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)butanoate hydrochloride (0.86 g, 3.20 mmol) and diisopropylethylamine (0.41 g, 3.21 mmol) in 20 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.86 g of yellow oil.

Step 2: Methyl (2*S*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoate

Methyl (2*S*)-2-{[(3-amino-2-naphthalenyl)carbonyl]amino}-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)butanoate (0.3g, 0.75 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.6 g, 3.71 mmol) for ca. 3h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.15 g of product as a cream solid.

Step 3: (2*S*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid

Lithium hydroxide monohydrate (0.06 g, 2.50 mmol) was added to a solution of methyl (2*S*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoate (0.15 g, 0.27 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.044 g (30% yield) of product as a fluffy white solid. ES MS m/z 549 (M+H).

Example 517: 5,5-dimethyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine.

Step 1: Methyl (2*E*)-5,5-dimethyl-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-hexenoate

To a solution of methyl [bis(methyloxy)phosphoryl]({[(phenylmethyl)oxy]carbonyl}amino)acetate (1.82g, 5.49mmol) in CH_2Cl_2 was added DBU (0.84g, 5.52 mmol) and the resulting solution was stirred at RT for 10 minutes. To that was then added 3,3-dimethylbutanal (0.5g, 4.99 mmol), and the reaction was stirred for 16 hours at RT. The reaction was quenched with 1N HCl and the CH_2Cl_2 layer dried over sodium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.6g of product as clear oil.

Step 2: Methyl 5,5-dimethylnorleucinate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl (2*E*)-5,5-dimethyl-2-({[(phenylmethyl)oxy]carbonyl}amino)-2-hexenoate (1.6g, 5.24mmol) in 25ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 16 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.50g of clear oil.

Step 3: Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-5,5-dimethylnorleucinate

HATU (1.10 g, 2.89 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.45 g, 2.40 mmol), methyl 5,5-dimethylnorleucinate (0.5 g, 2.89 mmol) and diisopropylethylamine (0.38 g, 2.93 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated Chromatography on silica gel with hexane/ethyl acetate gave 0.74 g of yellow oil.

Step 4: Methyl 5,5-dimethyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucinate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-5,5-dimethylnorleucinate (0.74g, 2.16 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.75 g, 10.83 mmol) for ca. 3h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.69 g of product as a cream solid.

Step 5: 5,5-dimethyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine

Lithium hydroxide monohydrate (0.33 g, 13.78 mmol) was added to a solution of methyl 5,5-dimethyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucinate (0.69 g, 1.37 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.44 g (65% yield) of product as a fluffy amber solid. ES MS m/z 489 (M+H).

Example 518: 1-({[3-({[(3,5-dimethyl-4-biphenylyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid.

Step 1: Methyl 1-({[3-({[(3,5-dimethyl-4-biphenylyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate

To a solution of methyl 1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate (0.17g, 0.30 mmol) in DME (5ml) was added tetrakis(triphenylmethyl)palladium (0.01g, 0.008 mmol), phenylboronic acid (0.055g, 0.45 mmol) and 2M Na2CO3 (0.3ml). The reaction was heated to 110°C for 16 hours and then loaded directly onto silica. Chromatography on silica gel with hexane/ethyl acetate gave 0.36g of product as yellow semi-solid.

Step 2: 1-({[3-({[(3,5-dimethyl-4-biphenylyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid

Lithium hydroxide monohydrate (0.13 g, 5.43 mmol) was added to a solution of methyl 1-({[3-({[(3,5-dimethyl-4-biphenylyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylate (0.31 g, 0.55 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.024 g (8% yield) of product as a cream solid. ES MS m/z 550 (M+H).

Example 519: *O*-cyclobutyl-*N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine.

Step 1: Methyl *N*-(triphenylmethyl)-L-threoninate

To a cooled (0°C) solution of methyl L-threoninate hydrochloride (4.0g, 23.58 mmol) and triethylamine (4.78g, 47.21 mmol) in chloroform (100ml) was added trityl chloride as a solid (6.57g, 23.57mmol). The reaction was stirred for 12 hours and allowed to come to RT. The reaction was concentrated in vacuo and then dissolved in ethyl acetate and washed with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$, and saturated sodium chloride. The organic layer was dried over $MgSO_4$, filtered and stripped to give 9.14g of product as an amber oil.

Step 2: Methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate

To a cooled (0°C) solution of methyl *N*-(triphenylmethyl)-L-threoninate (9.14g, 25.15 mmol) in anhydrous pyridine was added methanesulfonyl chloride (8.64g, 75.45 mmol) and the reaction was allowed to stir for 12 hours and allowed to come to RT. The solvent was removed in vacuo and the residue dissolved in ethyl acetate. The organic layer was washed with saturated sodium chloride and then dried over $MgSO_4$, filtered and stripped to a brown oil which was then dissolved in 80ml of anhydrous THF and to which was added triethylamine (7.59g, 74.97 mmol) and heated to 80°C and allowed to reflux for 16 hours.
The heat was removed and the reaction was concentrated in vacuo and the residue dissolved in ethyl acetate and washed successively with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$ and saturated sodium chloride. The ethyl acetate layer was dried over $MgSO_4$, filtered and stripped. Chromatography on silica gel with hexane/ethyl acetate gave 4.6g of product as a yellow oil.

Step 3: 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate

To a solution of methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate (4.6g, 12.87 mmol) in $CHCl_3$ (12ml) and MeOH (12ml) cooled to 0°C was added 11.6ml of TFA and allowed to stir at 0°C for 2.5 hours. The reaction was then concentrated in vacuo and evaporated with ether newly added several times to remove TFA. The residue was dissolved in ether which was extracted with water three times. To the aqueous extract at 0°C was added $NaHCO_3$ (5.12g, 60.95

mmol), benzyl chloroformate (2.21g, 12.96 mmol) and 50ml of ethyl acetate under vigorous stirring for 1.5 hours. The ethyl acetate layer was separated and the water layer back-extracted. The organics were dried over $MgSO_4$, filtered and concentrated to give 3.45g of light yellow oil. Chromatography on silica gel with hexane/ethyl acetate gave 2.22g of product as a clear oil.

Step 4: Methyl *O*-cyclobutyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-threoninate

To a solution of 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate (0.58g, 2.33 mmol) in $CHCl_3$ (10ml) was added cyclobutanol (1.68g, 23.25 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.89g of product as clear oil.

Step 5: Methyl *O*-cyclobutyl-L-threoninate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-cyclobutyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-threoninate (0.89g, 2.77 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The reaction was then filtered through a filter paper and the solvent evaporated to give 0.33g of clear oil.

Step 6: Methyl *O*-cyclobutyl-*N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-L-threoninate

HATU (0.67g, 1.76 mmol) was added to a solution of 3-amino-3',4'-difluoro-4-biphenylcarboxylic acid (0.41g, 1.47 mmol), methyl *O*-cyclobutyl-L-threoninate (0.33 g, 1.76 mmol) and diisopropylethylamine (0.23 g, 1.78 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was

dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 1.09 g of yellow oil.

Step 7: Methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-cyclobutyl-L-threoninate

To a solution of methyl *O*-cyclobutyl-*N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-L-threoninate (1.90g, 2.43 mmol) in 25 ml of ethanol was added 11 ml of saturated ammonium chloride and indium (2.18g, 18.99 mmol). The reaction was heated to reflux for 16 hours and then diluted with water and ethyl acetate. The organic layer was dried over magnesium sulfate filtered and concentrated. Chromatography on silica gel with hexane/ethyl acetate gave 0.32g of yellow residue.

Step 8: Methyl *O*-cyclobutyl-*N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate

Methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-cyclobutyl-L-threoninate (0.32g, 0.76 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.62 g, 3.84 mmol) for ca. 16h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated to give 0.35 g of product as a light yellow solid.

Step 9: *O*-cyclobutyl-*N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide monohydrate (0.14 g, 5.85 mmol) was added to a solution of methyl *O*-cyclobutyl-*N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate (0.35 g, 0.60 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered

and concentrated in vacuo to give 0.200 g (61% yield) of product as a fluffy orange solid. ES MS m/z 566 (M+H).

Example 520: *O*-(1-methylcyclopentyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine.

Step 1: Methyl *N*-(triphenylmethyl)-L-threoninate

To a cooled (0°C) solution of methyl L-threoninate hydrochloride (4.0g, 23.58 mmol) and triethylamine (4.78g, 47.21 mmol) in chloroform (100ml) was added trityl chloride as a solid (6.57g, 23.57mmol). The reaction was stirred for 12 hours and allowed to come to RT. The reaction was concentrated in vacuo and then dissolved in ethyl acetate and washed with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$, and saturated sodium chloride. The organic layer was dried over $MgSO_4$, filtered and stripped to give 9.14g of product as an amber oil.

Step 2: Methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate

To a cooled (0°C) solution of methyl *N*-(triphenylmethyl)-L-threoninate (9.14g, 25.15 mmol) in anhydrous pyridine was added methanesulfonyl chloride (8.64g, 75.45 mmol) and the reaction was allowed to stir for 12 hours and allowed to come to RT. The solvent was removed in vacuo and the residue dissolved in ethyl acetate. The organic layer was washed with saturated sodium chloride and then dried over $MgSO_4$, filtered and stripped to a brown oil which was then dissolved in 80ml of anhydrous THF and to which was added triethylamine (7.59g, 74.97 mmol) and heated to 80°C and allowed to reflux for 16 hours.
The heat was removed and the reaction was concentrated in vacuo and the residue dissolved in ethyl acetate and washed successively with saturated sodium chloride, 10% citric acid, saturated $NaHCO_3$ and saturated sodium chloride. The ethyl acetate layer was dried over $MgSO_4$, filtered and stripped. Chromatography on silica gel with hexane/ethyl acetate gave 4.6g of product as a yellow oil.

Step 3: 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate

To a solution of methyl (2*R*,3*S*)-3-methyl-1-(triphenylmethyl)-2-aziridinecarboxylate (4.6g, 12.87 mmol) in $CHCl_3$ (12ml) and MeOH (12ml) cooled to 0°C was added 11.6ml of TFA and allowed to stir at 0°C for 2.5 hours. The reaction was then concentrated in vacuo and evaporated with ether newly added several times to remove TFA. The residue was dissolved in ether which was extracted with water three times. To the aqueous extract at 0°C was added $NaHCO_3$ (5.12g, 60.95 mmol), benzyl chloroformate (2.21g, 12.96 mmol) and 50ml of ethyl acetate under vigorous stirring for 1.5 hours. The ethyl acetate layer was separated and the water layer back-extracted. The organics were dried over $MgSO_4$, filtered and concentrated to give 3.45g of light yellow oil. Chromatography on silica gel with hexane/ethyl acetate gave 2.22g of product as a clear oil.

Step 4: Methyl *O*-(1-methylcyclopentyl)-*N*-{[(phenylmethyl)oxy]carbonyl}-L-threoninate

To a solution of 2-methyl 1-(phenylmethyl) (2*R*,3*S*)-3-methyl-1,2-aziridinedicarboxylate (1.00g, 4.01 mmol) in $CHCl_3$ (10ml) was added cyclobutanol (4.02g, 40.14 mmol) and boron trifluoride diethyl etherate (5 drops) and stirred for 16 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give 1.21g of product as grey oil.

Step 5: Methyl *O*-(1-methylcyclopentyl)-L-threoninate

Palladium (10% weight on activated carbon, catalytic amount) was added to a solution of methyl *O*-cyclobutyl-*N*-{[(phenylmethyl)oxy]carbonyl}-L-threoninate (1.21g, 3.46 mmol) in 10ml of EtOH in a flask under nitrogen. A balloon of H_2 was then affixed to the reaction flask and the reaction was stirred for 2 hours at RT. The

reaction was then filtered through a filter paper and the solvent evaporated to give 0.64g of tan oil.

Step 6: Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1-methylcyclopentyl)-L-threoninate

HATU (1.13g, 2.97 mmol) was added to a solution of 3-amino-2-naphthalenecarboxylic acid (0.46g, 2.46 mmol), methyl *O*-(1-methylcyclopentyl)-L-threoninate (0.64 g, 2.97 mmol) and diisopropylethylamine (0.38 g, 2.98 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.30 g of yellow oil.

Step 7: Methyl *O*-(1-methylcyclopentyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate

Methyl *N*-[(3-amino-2-naphthalenyl)carbonyl]-*O*-(1-methylcyclopentyl)-L-threoninate (0.30g, 0.78 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.63 g, 3.90 mmol) for ca. 16h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated to give 0.45 g of product as an amber semi-solid.

Step 8: *O*-(1-methylcyclopentyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine

Lithium hydroxide monohydrate (0.20 g, 8.35 mmol) was added to a solution of methyl *O*-(1-methylcyclopentyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threoninate (0.45 g, 0.824 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT

overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to give 0.084 g (19% yield) of product as a light orange solid. ES MS m/z 532 (M+H).

Example 521: *N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-*O*-(phenylmethyl)-L-threonine.

Step 1: Phenylmethyl *N*-[(2-amino-4-fluorophenyl)carbonyl]-*O*-(phenylmethyl)-L-threoninate

HATU (0.65g, 1.71 mmol) was added to a solution of 2-amino-4-fluorobenzoic acid (0.22g, 1.42 mmol), phenylmethyl *O*-(phenylmethyl)-L-threoninate (0.5 g, 1.67 mmol) and diisopropylethylamine (0.22 g, 1.72 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated to give 1.03 g of amber oil.

Step 2: Phenylmethyl *N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-*O*-(phenylmethyl)-L-threoninate

Phenylmethyl *N*-[(2-amino-4-fluorophenyl)carbonyl]-*O*-(phenylmethyl)-L-threoninate (1.03g, 2.36 mmol) in 10 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (1.91 g, 11.82 mmol) for ca. 16h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated to give 2.04 g of product as a light orange semi-solid.

Step 3: *N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-*O*-(phenylmethyl)-L-threonine

Lithium hydroxide monohydrate (0.82 g, 34.24 mmol) was added to a solution of phenylmethyl *N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-*O*-(phenylmethyl)-L-threoninate (2.04 g, 3.41 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated. Chromatography on silica gel with hexane/ethyl acetate gave 0.166 g of product. (10% yield) ES MS m/z 508 (M+H).

Example 522: *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-D-threonine.

Step 1: Methyl *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-D-threoninate

HATU (0.57g, 1.50 mmol) was added to a solution of 3-amino-3',4'-difluoro-4-biphenylcarboxylic acid (0.35g, 1.25 mmol), methyl *O*-(1,1-dimethylethyl)-D-threoninate hydrochloride (0.34 g, 1.51 mmol) and diisopropylethylamine (0.19 g, 1.49 mmol) in 10 mL of DMF. The mixture was stirred at RT for ca. 15 h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated to give 0.88 g of yellow oil.

Step 2: Methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-D-threoninate

To a solution of methyl *N*-[(3',4'-difluoro-3-nitro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-D-threoninate (0.88g, 1.95 mmol) in 20 ml of ethanol was added 8.8

ml of saturated ammonium chloride and indium (1.76g, 15.33 mmol). The reaction was heated to reflux for 16 hours and then diluted with water and ethyl acetate. The organic layer was dried over magnesium sulfate filtered and concentrated. Chromatography on silica gel with hexane/ethyl acetate gave 0.33g of yellow oil.

Step 3: Methyl *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-D-threoninate

Methyl *N*-[(3-amino-3',4'-difluoro-4-biphenylyl)carbonyl]-*O*-(1,1-dimethylethyl)-D-threoninate (0.33g, 0.78 mmol) in 15 mL of pyridine was treated with 2-isocyanato-1,3,5-trimethylbenzene (0.63 g, 3.90 mmol) for ca. 16h at RT. The reaction was quenched with 1N HCl and extracted with ethyl acetate. The organic layer dried over magnesium sulfate, filtered, and the solvent evaporated. Chromatography on silica gel with hexane/ethyl acetate gave 0.40g of light yellow oil.

Step 4: *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-D-threonine

Lithium hydroxide monohydrate (0.16 g, 6.68 mmol) was added to a solution of methyl *N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-D-threoninate (0.40 g, 0.69 mmol) in dioxane:water/10:1 (10ml). The mixture was stirred at RT overnight. The reaction mixture was acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated to give 0.118 g of fluffy orange solid (30% yield) ES MS m/z 568 (M+H).

Example 523: (2S)-cyclohexyl({[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1: Methyl 2'-(methyloxy)-3-nitro-4-biphenylcarboxylate

A mixture of methyl 4-chloro-2-nitrobenzoate (0.500 g, 2.32 mmol), 2-methoxyphenylboronic acid (0.38 g, 2.55 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.086 g, 0.12 mmol), cesium fluoride (1.05 g, 6.95 mmol), 1 mL of water and 6 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, filtered through Celite, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.571 g (86% yield) of desired product as a colorless oil

Step 2: 2'-(Methyloxy)-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.457 g, 19.0 mmol) was added to a solution of methyl 2'-(methyloxy)-3-nitro-4-biphenylcarboxylate (0.547 g, 1.90 mmol) in 10 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.517 g (99% yield) of desired product as a white solid.

Step 3: Methyl (2S)-cyclohexyl({[2'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)ethanoate

HATU (0.473g, 1.24 mmol) was added to a solution of 2'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.226 g, 0.83 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.142 g, 0.83 mmol), and diisopropylethylamine (0.21 mL, 1.24 mmol) in 5 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.244 g (69% yield) g of desired product as a white solid.

Step 4: Methyl (2S)-({[3-amino-2'-(methyloxy)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate

A mixture of methyl (2S)-cyclohexyl({[2'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}amino)ethanoate (0.242 g, 0.57 mmol) and 5% palladium on carbon (0.060 g, 0.028 mmol) in 20 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.219 g (97% yield) of desired product as an off-white solid.

Step 5: Methyl (2S)-cyclohexyl({[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.261 g, 0.54 mmol) was added to a solution of methyl (2S)-({[3-amino-2'-(methyloxy)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoate (0.214 g, 0.54 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.223 g (74% yield) of desired product as a white solid.

Step 6: (2S)-cyclohexyl({[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.091 g, 3.80 mmol) was added to a solution of methyl (2S)-cyclohexyl({[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.215 g, 0.38 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the

residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.164 g (79% yield) of desired product as a white solid. ES MS m/z 544 (M+H)

Example 524: O-(1,1-Dimethylethyl)-N-{[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Step 1: Methyl O-(1,1-dimethylethyl)-N-{[2'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate

HATU (0.467 g, 1.23 mmol) was added to a solution of 2'-(methyloxy)-3-nitro-4-biphenylcarboxylic acid (0.224 g, 0.82 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.185 g, 0.82 mmol), and diisopropylethylamine (0.21 mL, 1.23 mmol) in 5 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.272 g (75% yield) g of desired product as a white solid.

Step 2: Methyl N-{[3-amino-2'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-{[2'-(methyloxy)-3-nitro-4-biphenylyl]carbonyl}-L-threoninate (0.268 g, 0.60 mmol) and 5% palladium on carbon (0.064 g, 0.030 mmol) in 20 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.178 g (72% yield) of desired product as a white solid.

Step 3: Methyl O-(1,1-dimethylethyl)-N-{[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate

2,4,6-Trimethylphenylisocyanate (0.204 g, 1.27 mmol) was added to a solution of methyl N-{[3-amino-2'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate (0.175 g, 0.42 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.187 g (77% yield) of desired product as a white solid.

Step 4: O-(1,1-Dimethylethyl)-N-{[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide (0.075 g, 3.13 mmol) was added to a solution of methyl O-(1,1-dimethylethyl)-N-{[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate (0.180 g, 0.31 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. The residue was purified by chromatography on silica gel with dichloromethane:methanol to give 0.036 g (21% yield) of desired product. ES MS m/z 562 (M+H)

Example 525: N-{[3',5'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine

Step 1: Methyl 3',5'-difluoro-3-nitro-4-biphenylcarboxylate

A mixture of methyl 4-chloro-2-nitrobenzoate (0.500 g, 2.32 mmol), 3,5-difluorophenylboronic acid (0.403 g, 2.55 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.087 g, 0.12 mmol), cesium

fluoride (1.06 g, 6.96 mmol), 1 mL of water and 6 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, filtered through Celite, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.562 g (83% yield) of desired product as a white solid.

Step 2: 3',5'-Difluoro-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.133 g, 5.53 mmol) was added to a solution of methyl 3',5'-difluoro-3-nitro-4-biphenylcarboxylate (0.540 g, 1.84 mmol) in 10 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.467 g (91% yield) of desired product as a white solid.

Step 3: Methyl N-[(3',5'-difluoro-3-nitro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate

HATU (0.471 g, 1.24 mmol) was added to a solution of 3',5'-difluoro-3-nitro-4-biphenylcarboxylic acid (0.233 g, 0.83 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.188 g, 0.83 mmol), and diisopropylethylamine (0.22 mL, 1.24 mmol) in 5 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.273 g (73% yield) g of desired product as a white solid.

Step 4: Methyl N-[(3-amino-3',5'-difluoro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl N-[(3',5'-difluoro-3-nitro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate (0.267 g, 0.59 mmol) and 5% palladium on carbon (0.063 g, 0.029 mmol) in 15 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.240 g (97% yield) of desired product as an off-white gum.

Step 5: Methyl N-{[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate

2,4,6-Trimethylphenylisocyanate (0.275 g, 1.71 mmol) was added to a solution of methyl N-[(3-amino-3',5'-difluoro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate (0.239 g, 0.57 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.259 g (78% yield) of desired product as a white solid.

Step 6: : N-{[3',5'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine

Lithium hydroxide (0.105 g, 4.37 mmol) was added to a solution of methyl N-{[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate (0.254 g, 0.44 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.252 g (100% yield) of desired product. ES MS m/z 566 (M-H)

Example 526: (2S)-Cyclohexyl({[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Step 1: Methyl (2S)-cyclohexyl{[(3',5'-difluoro-3-nitro-4-biphenylyl)carbonyl]amino}ethanoate

HATU (0.441 g, 1.16 mmol) was added to a solution of 3',5'-difluoro-3-nitro-4-biphenylcarboxylic acid (0.215 g, 0.77 mmol), methyl (2S)-amino(cyclohexyl)ethanoate hydrochloride (0.160 g, 0.77 mmol), and diisopropylethylamine (0.20 mL, 1.16 mmol) in 5 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.287 g (86% yield) g of desired product as a white solid.

Step 2: Methyl (2S)-{[(3-amino-3',5'-difluoro-4-biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate

A mixture of methyl (2S)-cyclohexyl{[(3',5'-difluoro-3-nitro-4-biphenylyl)carbonyl]amino}ethanoate (0.270 g, 0.62 mmol) and 5% palladium on carbon (0.067 g, 0.031 mmol) in 25 mL of ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.224 g (89% yield) of desired product as a beige gum.

Step 3: Methyl (2S)-cyclohexyl({[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate

2,4,6-Trimethylphenylisocyanate (0.274 g, 1.64 mmol) was added to a solution of methyl (2S)-{[(3-amino-3',5'-difluoro-4-

biphenylyl)carbonyl]amino}(cyclohexyl)ethanoate (0.220 g, 0.55 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.278 g (90% yield) of desired product as a white solid.

Step 4: (2S)-Cyclohexyl({[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid

Lithium hydroxide (0.115 g, 4.77 mmol) was added to a solution of methyl (2S)-cyclohexyl({[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoate (0.269 g, 0.48 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.208 g (79% yield) of desired product as an off-white solid. APCI MS m/z 550 (M+H)

Example 527: O-(1,1-Dimethylethyl)-N-{[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Step 1: Methyl 4'-fluoro-3-nitro-4-biphenylcarboxylate

A mixture of methyl 4-chloro-2-nitrobenzoate (0.500 g, 2.32 mmol), 4-fluorophenylboronic acid (0.357 g, 2.55 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.086 g, 0.12 mmol), cesium fluoride (1.06 g, 6.96 mmol), 1 mL of water and 6 mL of acetonitrile was heated in a microwave reactor at 150°C for 5 minutes. The cooled reaction mixture was diluted with ethyl acetate, filtered through Celite, washed with water and dried over sodium

sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.537 g (84% yield) of desired product as a white solid.

Step 2: 4'-Fluoro-3-nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.137 g, 5.73 mmol) was added to a solution of methyl 4'-fluoro-3-nitro-4-biphenylcarboxylate (0.525 g, 1.91 mmol) in 10 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.465 g (93% yield) of desired product as a white solid.

Step 3: Methyl O-(1,1-dimethylethyl)-N-[(4'-fluoro-3-nitro-4-biphenylyl)carbonyl]-L-threoninate

HATU (0.502 g, 1.32 mmol) was added to a solution of 4'-Fluoro-3-nitro-4-biphenylcarboxylic acid (0.229 g, 0.88 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.198 g, 0.88 mmol), and diisopropylethylamine (0.23 mL, 1.32 mmol) in 5 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.300 g (79% yield) g of desired product as a white solid.

Step 4: Methyl N-[(3-amino-4'-fluoro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-[(4'-fluoro-3-nitro-4-biphenylyl)carbonyl]-L-threoninate (0.294 g, 0.68 mmol) and 5% palladium on carbon (0.072 g, 0.034 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50

psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.264 g (96% yield) of desired product as a white solid.

Step 5: Methyl O-(1,1-dimethylethyl)-N-{[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate

2,4,6-Trimethylphenylisocyanate (0.310 g, 1.92 mmol) was added to a solution of methyl N-[(3-amino-4'-fluoro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate (0.258 g, 0.64 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.277 g (77% yield) of desired product as a white solid.

Step 6: O-(1,1-Dimethylethyl)-N-{[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide (0.115 g, 4.81 mmol) was added to a solution of methyl O-(1,1-dimethylethyl)-N-{[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate (0.271 g, 0.48 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.131 g (50% yield) of desired product as a white solid. APCI MS m/z 550 (M+H).

Example 528: O-(1,1-Dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Step 1: Methyl 3-nitro-4-biphenylcarboxylate

A mixture of methyl 4-chloro-2-nitrobenzoate (1.00 g, 4.64 mmol), phenylboronic acid (0.623 g, 5.10 mmol), trans-dichlorobis(tricyclohexylphosphine)palladium(II) (0.171 g, 0.23 mmol), cesium fluoride (2.11 g, 13.9 mmol), 5 mL of water and 10 mL of acetonitrile was heated in a microwave reactor at 150°C for 7 minutes. The cooled reaction mixture was diluted with ethyl acetate, filtered through Celite, washed with water and dried over sodium sulfate. Chromatography on silica gel with hexane/ethyl acetate gave 0.99 g (83% yield) of desired product as a white solid.

Step 2: 3-Nitro-4-biphenylcarboxylic acid

Lithium hydroxide (0.39 g, 16.4 mmol) was added to a solution of methyl 3-nitro-4-biphenylcarboxylate (0.423 g, 1.64 mmol) in 16 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.383 g (96% yield) of desired product as a white solid.

Step 3: Methyl O-(1,1-dimethylethyl)-N-[(3-nitro-4-biphenylyl)carbonyl]-L-threoninate

HATU (0.448 g, 1.18 mmol) was added to a solution of 3-nitro-4-biphenylcarboxylic acid (0.192 g, 0.79 mmol), methyl O-(1,1-dimethylethyl)-L-threoninate hydrochloride (0.178 g, 0.79 mmol), and diisopropylethylamine (0.21 mL, 1.18 mmol) in 5 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give 0.345 g of desired product as a white solid.

Step 4: Methyl N-[(3-amino-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl O-(1,1-dimethylethyl)-N-[(3-nitro-4-biphenylyl)carbonyl]-L-threoninate (0.325 g, 0.78 mmol) and 5% palladium on carbon (0.083 g, 0.039 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.299 g (99% yield) of desired product as a white solid.

Step 5: Methyl O-(1,1-dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate

2,4,6-Trimethylphenylisocyanate (0.368 g, 2.30 mmol) was added to a solution of methyl N-[(3-amino-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate (0.294 g, 0.76 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.292 g (70% yield) of desired product as a white solid.

Step 6: O-(1,1-Dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine

Lithium hydroxide (0.127 g, 0.53 mmol) was added to a solution of methyl O-(1,1-dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threoninate (0.288 g, 0.53 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was stirred at room temperature overnight. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over

anhydrous sodium sulfate and the solvent removed under vacuum to give 0.227 g (81% yield) of desired product as a white solid. APCI MS m/z 532 (M+H).

Example 529: 1-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid

Step 1: Methyl 1-{[(3-nitro-4-biphenylyl)carbonyl]amino}cyclooctanecarboxylate

HATU (0.414 g, 1.09 mmol) was added to a solution of 3-nitro-4-biphenylcarboxylic acid (0.178 g, 0.73 mmol), methyl 1-aminocyclooctanecarboxylate hydrochloride (0.162 g, 0.73 mmol), and diisopropylethylamine (0.19 mL, 1.09 mmol) in 5 mL of DMF. The mixture was stirred at room temperature overnight, and then diluted with ethyl acetate, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave 0.163 g (54% yield) of desired product as a white solid.

Step 2: Methyl 1-{[(3-amino-4-biphenylyl)carbonyl]amino}cyclooctanecarboxylate

A mixture of methyl 1-{[(3-nitro-4-biphenylyl)carbonyl]amino}cyclooctanecarboxylate (0.159 g, 0.39 mmol) and 5% palladium on carbon (0.041 g, 0.019 mmol) in ethanol in a pressure reaction vessel was evacuated and flushed with nitrogen three times, then evacuated and filled with 50 psi of hydrogen and stirred for one hour. The reaction vessel was then evacuated and flushed with nitrogen. The mixture was filtered through Celite and the filtrate was evaporated to give 0.116 g (78% yield) of desired product as a colorless resin.

Step 3: Methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate

2,4,6-Trimethylphenylisocyanate (0.147 g, 0.91 mmol) was added to a solution of methyl 1-{[(3-amino-4-biphenylyl)carbonyl]amino}cyclooctanecarboxylate (0.116 g,

0.305 mmol) in 5 mL of anhydrous pyridine. The mixture was stirred at room temperature overnight. Pyridine was removed under vacuum and ethyl acetate was added to the residue. The insoluble material was filtered off, the filtrate was washed with 1N aqueous HCl, dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Chromatography on silica gel with hexane/ethyl acetate gave 0.129 g (78% yield) of desired product as a white solid.

Step 4: 1-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid

Lithium hydroxide (0.054 g, 2.24 mmol) was added to a solution of methyl 1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylate (0.121 g, 0.22 mmol) in 5 mL of THF: methanol:water/3:1:1. The mixture was heated at 60°C for 6 hours. The solvent was evaporated and 1N aqueous hydrochloric acid was added to the residue. The resulting suspension was extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 0.085 g (73% yield) of desired product as a white solid. APCI MS m/z 528 (M+H).

Example 530: N-{[3-({[(4-Cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine

Step 1: Methyl N-{[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate

A mixture of methyl N-[(3-amino-3'-fluoro-4-biphenylyl)carbonyl]-O-(1,1-dimethylethyl)-L-threoninate (0.216 g, 0.54 mmol), 5-cyclopropyl-2-isocyanato-1,3-dimethylbenzene (0.120 g, 0.64 mmol), and triethylamine (0.15 mL, 1.08 mmol) in 3 mL of DMF was heated at 70°C for 3 hours. An additional 0.100g of isocyanate was added and the mixture was heated for another hour. The reaction mixture was cooled to room temperature and the DMF was removed under vacuum. Chromatography on silica gel with hexane/ethyl acetate gave a mixture containing

65% of the desired product. This mixture was carried on to the next step without further purification.

Step 2: N-{[3-({[(4-Cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine

The product from Step 1 containing ca 65% of methyl N-{[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threoninate (0.165 g, 0.28 mmol) was dissolved in 5 mL of THF:methanol:water/3:1:1 and 0.067 g (2.80 mmol) of lithium hydroxide was added. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was treated with aqueous 1N hydrochloric acid. The resulting suspension was extracted with ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was subjected to chromatography with dichloromethane/methanol, and hexane/ethyl acetate to give 0.052 g of a mixture containing ca 84% of desired product and an amine byproduct. To a solution of this material in 2 mL of tetrahydrofuran was added 0.090 g (0.12 mmol) of MP-isocyanate resin. The mixture was heated at 60°C for 18 hours, cooled to room temperature and filtered. The filtrate was evaporated to dryness to give 0.032 g of desired product as a yellow solid. APCI MS m/z 576 (M+H).

Example 531: (2*S*)-cyclohexyl({[3-({[(4-cyclopropylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

Step 1: *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide

To a solution of 4-bromo-2,6-dimethylaniline (4.0 g, 20.0 mmol) in 50 mL CH_2Cl_2 cooled to 0 °C was added Hunig's base (6.97 mL, 40 mmol) followed by the addition of trifluoroacetic anhydride (0.294 mL, 2.1 mmol). After stirring for an hour, the contents were washed with water, dried (K_2CO_3) and then concentrated under vacuum to afford the crude product (4.5 g, 76% yield).

Step 2: *N*-(4-cyclopropyl-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide

To a solution of *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide (4.5 g, 15.2 mmol) in DME (90 mL) was added 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.06 g, 18.24 mmol) followed by the addition of bistriphenylphosphine Pd (II) dichloride (1.1 g, 10 mol%) and 2M Na_2CO_3 (30 mL). The contents were refluxed for 48 h. Concentration followed by loading of the crude reaction onto an isco column eluting with EtOAc/Hexane (0 – 30%) gave a white solid (3.1 g, 80% yield).

Step 3: (4-cyclopropyl-2,6-dimethylphenyl)amine
4-cyclopropyl-2,6-dimethylaniline

To a solution of *N*-(4-cyclopropyl-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide (1.0 g, 3.89 mmol) in dioxane (20 mL) was added 4N NaOH (5 mL) and then contents refluxed for 6 h. The reaction was cooled and then followed by the addition of EtOAc. Separation of the organic layer followed by drying ($MgSO_4$) and concentration under vacuum gave the amine which was taken crude to the next step.

Step 4: 5-cyclopropyl-2-isocyanato-1,3-dimethylbenzene

To a solution of (4-cyclopropyl-2,6-dimethylphenyl)amine
4-cyclopropyl-2,6-dimethylaniline (0.551 g, 3.42 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added pyridine (0.828 mL, 10.26 mmol) followed by 2.0M solution of phosgene (2.56 mL, 4.78 mmol) in toluene. After warming to rt. The contents were stirred for 16 h. Addition of 1N HCl (30 mL) followed by separation of the organic layer, drying ($MgSO_4$) and concentration under vacuum gave the desired product.

Step 5: methyl (2*S*)-cyclohexyl({[3-({[(4-cyclopropylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate

To a solution of methyl (2*S*)-{[(3-amino-2-naphthalenyl)carbonyl]amino}(cyclohexyl)ethanoate hydrochloride salt (0.187 g, 0.5 mmol) in DMF (3.0 mL) was added 5-cyclopropyl-2-isocyanato-1,3-dimethylbenzene (0.112 g, 0.6 mmol) followed by triethyl amine (0.210 mL, 1.5 mmol) and the contents heated at 70 C for 2 h. The reaction was loaded onto an isco column and leuted with EtOAc/Hexane (0 – 60%) to afford 0.250 g (93%) of the product as a yellow solid.

Step 6: (2*S*)-cyclohexyl({[3-({[(4-cyclopropylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid

To a solution of . methyl (2*S*)-cyclohexyl({[3-({[(4-cyclopropylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoate (0.30 g, 0.569 mmol) in THF (2.0 mL) was added 1.0 M LiOH (1.99 mL, 1.99 mmol) and the contents stirred at rt. For 16 h. The reaction mixture was acidified to pH = 4.0 followed by extraction with EtOAc. Drying with $MgSO_4$ followed by concentration under vacuum gave the product as a yellow solid (0.250 g, 98%). ES m/z 514 (M+H).

Example 532: *N*-{[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine

Step 1: methyl *N*-{[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate

To a solution of methyl *N*-{[3-amino-4'-(methyloxy)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate (0.207 g, 0.5 mmol) in DMF (3.0 mL) was added 5-cyclopropyl-2-isocyanato-1,3-dimethylbenzene (0.112 g, 0.6 mmol) followed by triethyl amine (0.210 mL, 1.5 mmol) and the contents heated at 70 °C for 2 h. The reaction was loaded onto an isco column and leuted with EtOAc/Hexane (0 – 60%) to afford 0.160 g (53%) of the product as a yellow solid.

Step 2: (2*S*)-cyclohexyl({[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid

To a solution of methyl *N*-{[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threoninate (0.110 g, 0.183 mmol) in THF (2.0 mL) was added 1.0 M LiOH (0.640 mL, 0.640 mmol) and the contents stirred at rt. For 16 h. The reaction mixture was acidified to pH = 4.0 followed by extraction with EtOAc. Drying with $MgSO_4$ followed by concentration under vacuum gave the product as a yellow solid (0.096 g, 90%). ES m/z 588 (M+H).

Example 533: 1-({[5-(4-Chlorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1: 3-Amino-5-(4-chlorophenyl)-2-thiophenecarboxylic acid

Methyl 3-amino-5-(4-chlorophenyl)-2-thiophenecarboxylate (3.28g, 12.24 mmol) was dissolved in dioxane (50 mL) and 1M lithium hydroxide was added. The reaction was heated to 100°C and stirred overnight. Cooled to rt and acidified with 1N HCl. Precipitate was collected and triturated with ethyl acetate to afford 2.89g (11.42 mmol, 93%) of product as a yellow solid.

Step 2: Methyl 1-({[3-amino-5-(4-chlorophenyl)-2-thienyl]carbonyl}amino)cyclohexanecarboxylate.

3-Amino-5-(4-chlorophenyl)-2-thiophenecarboxylic acid (2.039g, 8.06 mmol), methyl 1-aminocyclohexanecarboxylate (1.555g, 8.06 mmol) and triethyl amine (4.2 mL, 24.18 mmol) were dissolved in DMF (50 mL). HATU (4.59g, 12.09 mmol) was added and the reaction stirred overnight. Diluted with ethyl acetate (100 mL) and washed with water (2 x 100 mL), brine (1 x 100 mL), dried over $MgSO_4$, filtered

and concentrated. Purified on an ISCO (0-25% EtOAc in Hexane over 20 min) to afford 0.300g (0.765 mmol, 9%) of the product as a yellow foam.

Step 3: 1-({[5-(4-Chlorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

Methyl 1-({[3-amino-5-(4-chlorophenyl)-2-thienyl]carbonyl}amino)cyclohexanecarboxylate (0.30g, 0.76 mmol) was suspended in pyridine. 2-Isocyanato-1,3,5-trimethylbenzene (0.369g, 2.29 mmol) was added. The reaction was stirred overnight at rt. Methanol (10mL) was added and the reaction stirred for 30 min. Reaction was filtered and organics diluted with EtOAc (50 mL) and 1N HCl (25 mL). A precipitate was formed and collected. Purified on a chromatatron (5% MeOH in CH_2Cl_2) to give an impure material. The material was taken up in dioxane (2 mL) and 1M lithium hydroxide (2 mL) was added. Heated to 100°C and stirred for 1h. Cooled to rt and acidified with 1N HCl and diluted with EtOAc (40 mL). Organics were washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated. Attempted to dissolve in methylene chloride, but and insoluble white solid remained. Collected solid to afford 0.123g (0.228 mmol, 30%) of the titled product. ES MS m/z 540 (M + H), 538 (M –H).

Example 534: 1-({[5-(3,4-difluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1: (2Z)-3-chloro-3-(3,4-difluorophenyl)-2-propenenitrile

DMF (30 mL) was cooled to 0°C and phosphorousoxychloride (6.72 mL, 72 mmol) was added. The reaction was stirred at 0°C for 10 min and then 1-(3,4-difluorophenyl)ethanone (6.61g, 42.9 mmol) was added. The reaction was warmed to rt and then heated to 50°C for 10 mins. The reaction was cooled to 0°C and hydroxylamine hydrochloride (11.78g, 170 mmol) was added slowly. After stirring at rt for 5 mins, the reaction was heated to 120°C for 15 mins. The reaction was

cooled to rt and diluted with EtOAc and neutralized with satd. $NaHCO_3$. The organics were removed and the aqueous layer extracted with EtOAc. The combined organics were dried and concentrated. Carried forward without further purification.

Step 2: Methyl 3-amino-5-(3,4-difluorophenyl)-2-thiophenecarboxylate

To methanol (80 mL) was added sodium methoxide (11.71 mL of a 25% sol in MeOH) and methyl mercaptoacetate (3.76 mL, 30 mmol). (2Z)-3-Chloro-3-(3,4-difluorophenyl)-2-propenenitrile (8.3g, 41.7 mmol) in DMF (30 mL) was added. The reaction was stirred at rt for 30 min. Water was added and the precipitate was collected. Solids were dried under vacuum to give 2.747g (10.21 mmol, 24%) of the product as a light brown solid.

Step 3: 3-Amino-5-(3,4-difluorophenyl)-2-thiophenecarboxylic acid

Methyl 3-amino-5-(3,4-difluorophenyl)-2-thiophenecarboxylate (1.126g, 4.19 mmol) was dissolved in dioxane (25 mL) and 1M lithium hydroxide was added. The reaction was heated to 100°C and stirred overnight. Cooled to rt , diluted with EtOAc (100 mL) and acidified with 1N HCl. Organics were washed with water (2 x 100 mL), brine (1 x 100 mL), dried over $MgSO_4$, filtered and concentrated to give 0.9847g (3.86 mmol, 92%) of product as a yellow solid.

Step 4: Methyl 1-({[3-amino-5-(3,4-difluorophenyl)-2-thienyl]carbonyl}amino)cyclohexanecarboxylate

3-Amino-5-(3,4-difluorophenyl)-2-thiophenecarboxylic acid (0.985g, 3.86 mmol), methyl 1-aminocyclohexanecarboxylate (0.745g, 3.86 mmol) and triethyl amine (2 mL, 11.58 mmol) were dissolved in DMF (10 mL). HATU (2.201g, 5.79 mmol) was added and the reaction stirred overnight. Diluted with ethyl acetate (100 mL) and washed with water (2 x 100 mL), brine (1 x 100 mL), dried over $MgSO_4$, filtered

and concentrated. Purified on an ISCO (0-25% EtOAc in Hexane over 20 min) to afford 0.383g (0.97 mmol, 25%) of the product as a white solid.

Step 5: 1-({[5-(3,4-difluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

Methyl 1-({[3-amino-5-(3,4-difluorophenyl)-2-thienyl]carbonyl}amino)cyclohexanecarboxylate (0.383g, 0.97 mmol) was suspended in pyridine. 2-Isocyanato-1,3,5-trimethylbenzene (0.270g, 2.92 mmol) was added. The reaction was stirred overnight at rt. Methanol (10mL) was added and the reaction stirred for 30 min. Reaction was filtered and organics diluted with EtOAc (50 mL) and 1N HCl (25 mL). A precipitate was formed and collected. The crude material was taken up in dioxane (2 mL) and 1M lithium hydroxide (2 mL) was added. Heated to 100°C and stirred for 1h. Cooled to rt and acidified with 1N HCl and diluted with EtOAc (40 mL). Organics were washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated. Purified on a chromatatron (5% MeOH in CH_2Cl_2) to afford 0.163g (0.301 mmol, 31%) of the titled product. ES MS m/z 542 (M + H), 540 (M –H).

Example 535: 1-({[5-(3,4,5-trifluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

Step 1: (2Z)-3-chloro-3-(3,4,5-trifluorophenyl)-2-propenenitrile

DMF (30 mL) was cooled to 0°C and phosphorous oxychloride (9.89 mL, 106 mmol) was added. The reaction was stirred at 0°C for 10 min and then 1-(3,4,5-trifluorophenyl)ethanone (7.37 g, 62.69 mmol) was added.The reaction was warmed to rt and then heated to 50°C for 10 mins. The reaction was cooled to 0°C and hydroxylamine hydrochloride (11.78 g, 170 mmol) was was added slowly. After stirring at rt for 5 mins, the reaction was heated to 120°C for 15 mins. The reaction

was cooled to rt and diluted with EtOAc and neutralized with satd. $NaHCO_3$. The organics were removed and the aqueous layer extracted with EtOAc. The combined organics were dried and concentrated. Carried forward without further purification.

Step 2: Methyl 3-amino-5-(3,4,5-trifluorophenyl)-2-thiophenecarboxylate

To methanol (80 mL) was added sodium methoxide (2,33 g, 43.32 mmol) and methyl mercaptoacetate (3.06 mL, 30 mmol). (2Z)-3-Chloro-3-(3,4-difluorophenyl)-2-propenenitrile (7.45 g, 36.1 mmol) in DMF (30 mL) was added. The reaction was stirred at rt for 30 min. Water was added and the precipitate was collected. Solids were dried under vacuum to give 2.46g (8.571mmol, 14%) of the product as a light brown solid.

Step 3: 3-Amino-5-(3,4,5-trifluorophenyl)-2-thiophenecarboxylic acid

Methyl 3-amino-5-(3,4,5-trifluorophenyl)-2-thiophenecarboxylate (0.45 g, 1.57 mmol) was dissolved in dioxane (25 mL) and 1M lithium hydroxide was added. The reaction was heated to 100°C and stirred overnight. Cooled to rt , diluted with EtOAc (100 mL) and acidified with 1N HCl. Organics were washed with water (2 x 100 mL), brine (1 x 100 mL), dried over MgSO4, filtered and concentrated to give 0.358g (1.31 mmol, 83%) of product as a yellow solid.

Step 4: Methyl 1-({[3-amino-5-(3,4,5-trifluorophenyl)-2-thienyl]carbonyl}amino)cyclohexanecarboxylate

3-Amino-5-(3,4,5-trifluorophenyl)-2-thiophenecarboxylic acid (0.358 g, 1.31mmol), methyl 1-aminocyclohexanecarboxylate (0.253 g, 1.31 mmol) and triethyl amine (0.68 mL, 3.93 mmol) were dissolved in DMF (10 mL). HATU (0.746 g, 1.96 mmol) was added and the reaction stirred overnight. Diluted with ethyl acetate (100 mL) and washed with water (2 x 100 mL), brine (1 x 100 mL), dried over $MgSO_4$,

filtered and concentrated. Purified on an ISCO (0-25% EtOAc in Hexane over 20 min) to afford 0.245g (0.59 mmol, 45%) of the product as a white solid.

Step 5: 1-({[5-(3,4,5-trifluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

Methyl 1-({[3-amino-5-(3,4,5-trifluorophenyl)-2-thienyl]carbonyl}amino)cyclohexanecarboxylate (0.245g, 0.59 mmol) was suspended in pyridine. 2-Isocyanato-1,3,5-trimethylbenzene (0.287g, 1.78 mmol) was added. The reaction was stirred overnight at rt. Methanol (10mL) was added and the reaction stirred for 30 min. Reaction was filtered and organics diluted with EtOAc (50 mL) and 1N HCl (25 mL). A precipitate was formed and collected. The crude material was taken up in dioxane (2 mL) and 1M lithium hydroxide (2 mL) was added. Heated to 100°C and stirred for 1h. Cooled to rt and acidified with 1N HCl and diluted with EtOAc (40 mL). Organics were washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated to afford 0.276g (0.49 mmol, 84%) of the product as a yellow foam. ES MS m/z 560 (M + H), 582 (M + Na) 558 (M –H).

Biological Protocols

The utility of the compounds of Formula 1, a salt, solvate, or physiologically functional derivative thereof, in the treatment or prevention of diseases (such as detailed herein) in animals, particularly mammals (e.g., humans) may be demonstrated by the activity in conventional assays known to one of ordinary skill in the relevant art, including the in vitro assays described below.

The purified glycogen phosphorylase (GP) enzyme, wherein glycogen phosphorylase is in the activated "a" state, referred to as human liver glycogen phosphoarylase a (HLGPa), can be obtained according to the following procedures.

Appropriate Cloning and Expression of Human Liver Glycogen Phosphorylase

Human liver glycogen phosphorylase cDNA was amplified by polymerase chain reaction (PCR) from a commercially available human liver cDNA library (BD

Biosciences). The cDNA was amplified as 2 overlapping fragments using the primers 5'GGCGAAGCCCCTGACAGACCAGGAGAAG3' with 5'CGATGTCTGAGTGGATTTTAGCCACGCC3' and 5'GGATATAGAAGAGTTAGAAGAAATTG3' with 5'GGAAGCTTATCAATTTCCATTGACTTTGTTAGATTCATTGG3'. PCR conditions were 94°C 1 min., 55°C 1 min., 72°C 2 min. for 40 cycles using the enzyme Pfu Turbo (Stratagene), 0.5% DMSO, 250uM each nucleotide triphosphate, and 0.4uM each primer plus the buffer recommended by the polymerase manufacturer. Each PCR fragment was molecularly cloned and the DNA sequence of each insert was determined. The 2 DNA fragments of the glycogen phosphorylase cDNA were then joined together in a bacterial expression plasmid, pTXK1007LTev (GlaxoSmithKline), creating a full-length cDNA fused at the 5' end to codons for methionine-glycine-alanine-histidine-histidine-histidine-histidine-histidine-histidine-glycine-glycine-glutamate-asparagine-leucine-tyrosine-phenylalanine-glutamine-glycine-glycine-. The protein product would have a 6Xhistidine tag followed by a Tev protease cleavage site. The DNA sequence of both strands of the cDNA in pTXK1007LTev was determined.

Purification of Human Liver Glycogen Phosphorylase

The frozen cell paste (100g) was thawed and suspended in 1200ml of 50mM Tris, 100mM NaCl, 15 mM imidazole, pH 8.0. The cells were disrupted gently with a Polytron (Brinkmann, PT10-35), and passed twice through an AVP homogenizer. The E. coli cell lysates were clarified by centrifugation at 27,500 x g for 45 minutes and filtered through a 0.8 micron filter. The solution was applied to a 21ml Ni-NTA Superflow (Qiagen) column (ID 26mm X H 4.0 cm) pre-equilibrated with 50mM Tris, 100mM NaCl, and 15 mM imidazole, pH 8.0. The column was washed with equilibration buffer until the A280 returned to baseline. The weakly bound proteins were eluted from the column with 10 bed column volumes of 50mM imidazole in the same buffer. The glycogen phosphorylase was eluted with steps of 100 mM and 250 mM imidizole. Both the100mM and 250 mM fractions were pooled and then diluted 5 fold with 50mM Tris, pH 8.0 buffer. This solution was loaded on a 21ml Q fast flow column (Amersham Pharmacia Biotech AB, ID 2.6cm X H 4.0 cm) pre-

equilibrated with 50 mM Tris, pH 8.0. Glycogen phosphorylase was eluted with a continuous gradient from 0- 30% of 1M NaCl in 50 mM Tris, pH 8.0 (buffer B). Fractions of purified glycogen phosphorylase between 15% and 20% buffer B were pooled, aliquoted into microfuge tubes, and stored at –80° C. The purified fraction formed a single ~100kd band on a SDS-PAGE gel.

Activation of Human Liver Glycogen Phosphorylase

The activation of human liver glycogen phosphorylase (i.e., conversion of the inactive HLGPb form to the activated HLGPa form) was achieved by phosphorylating HLGPb with immobilized phosphorylase kinase.

10mg of phosphorylase kinase (Sigma, P-2014) was dissolved in 2.5 ml of 100mM HEPES, 80mM CaCl2 (pH 7.4) and gently mixed with 1ml of Affi-Gel (Active Ester Agarose, BioRad # 153-6099) beads previously equilibrated in the same buffer. The mixture was rocked 4 hours at 4° C. The beads were washed once with the same buffer and blocked for 1 hour at room temperature with a solution of 50mM HEPES, 1M glycine methyl ester, pH 8.0. The beads were then washed with 50mM HEPES, 1 mM β-mercaptoethanol, pH 7.4 and stored at 4°C.

Frozen purified glycogen phosphorylase (HLGPb) was thawed in at 4° C then dialyzed overnight into 50 mM HEPES, 100mM NaCl, pH 7.4. 15 mg of the dialyzed HLGPb, 3mM ATP and 5mM MgCl2 was incubated with 500ul of the prepared Affi-Gel immobilized phosphorylase kinase beads equilibrated with 50mM HEPES, 100mM NaCl, pH 7.4. The degree of phosphorylation was monitored by following the increase in activity at 10 minute intervals using a modification of the assay system outlined below. Briefly, the assay contained 0.1 uM human liver glycogen phosphorylase, 50mM HEPES, 100mM KCl, 2.5 mM EGTA, $MgCl_2$, 3.5 mM KH_2PO_4, 0.5mM DTT, 0.4mg/mL glycogen, 7.5 mM Glucose, 0.50 mM β-nicotinamide adenine dinucleotide (β-NAD), 3 U/mL phosphoglucomutase, and 5 U/mL glucose-6-phosphate dehydrogenase, Activity was monitored by following the reduction of NAD^+ at 340 nm. The reaction was stopped by removal of the beads from the mixture when no further increase in activity was observed (30-60 minutes). Phosphorylation was further confirmed by analysis of the sample by

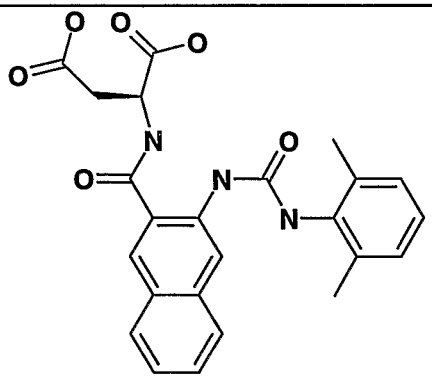
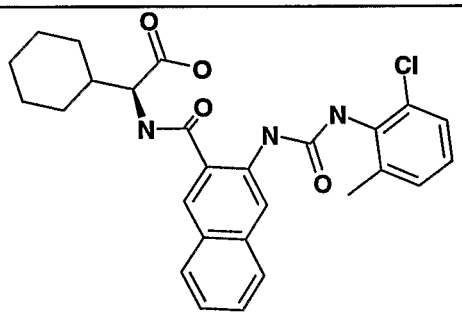
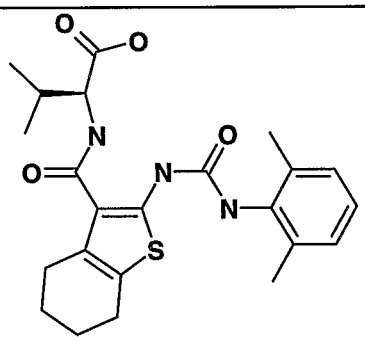
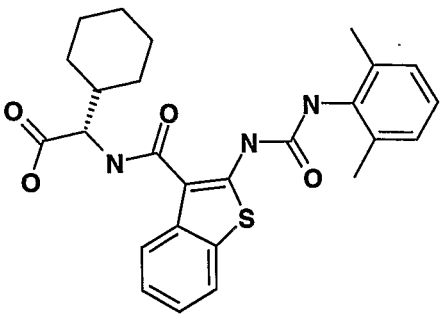
mass spectroscopy. The supernatant containing the activated sample was dialyzed in 50mM HEPES, 100mM NaCl, pH 7.4 overnight. The final sample was mixed with an equal volume of glycerol, aliquoted into microfuge tubes and stored at –20° C.

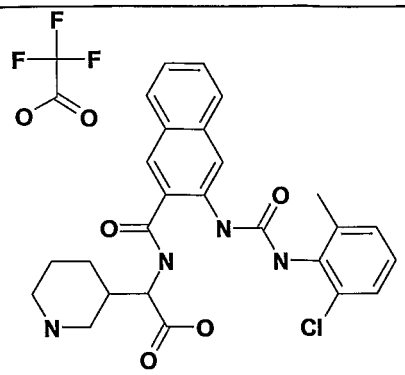
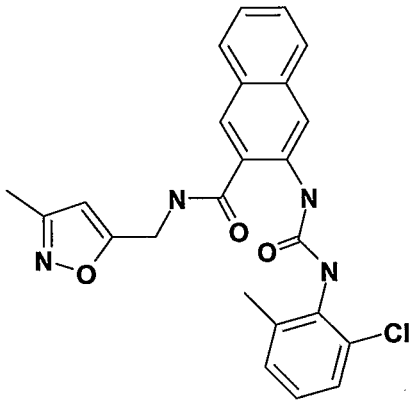
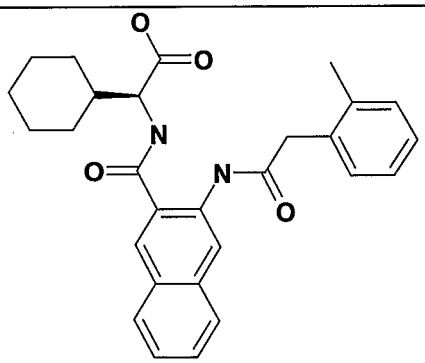
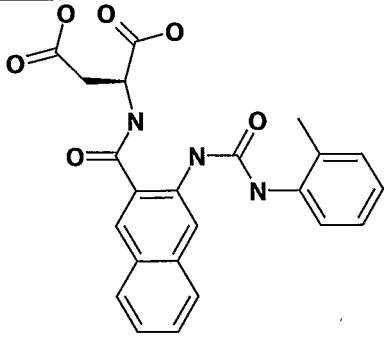
Human Liver Glycogen Phosphorylase a Enzymatic Activity Assay

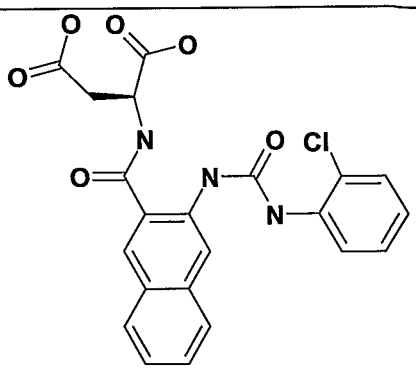
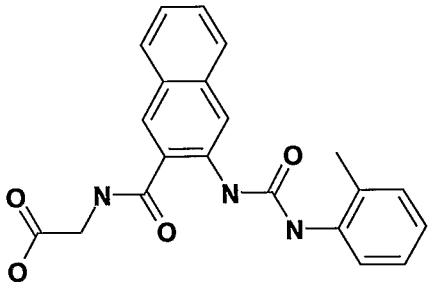
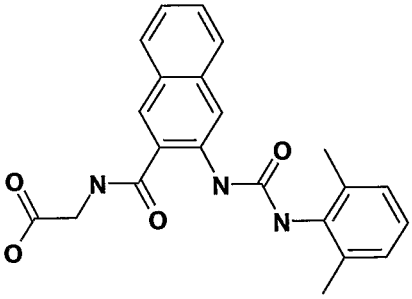
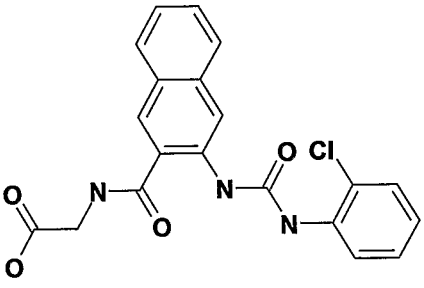
An enzymatic assay was developed to measure the response of the activated form of glycogen phosphorylase (HLGPa) to small molecule (<1000 Da.) compounds. The assay was configured to monitor the pharmacologically relevant glycogenolytic reaction by coupling the production of glucose-1-phosphate from glycogen and inorganic phosphate to phosphoglucomutase, glucose-6-phosphate dehydrogenase, NADH oxidase and horseradish peroxidase to produce the fluorescent product resorufin. The concentrations of the reagent components were as follows: 5-25 nM human liver glycogen phosphorylase a, 1mg/mL glycogen, 5 mM K_2HPO_4, 20 U/mL phosphoglucomutase (Sigma), 20 U/mL glucose-6-phosphate dehydrogenase (Sigma), 200 nM Thermus thermophilus NADH oxidase (prepared as described in Park, H.J.; Kreutzer, R.; Reiser, C.O.A.; Sprinzl, M. Eur. J. Biochem. 1992, 205, 875-879.), 2 U/mL horseradish peroxidase (Sigma), 30 uM FAD, 250 uM NAD^+, +/- 0.05% casein and 0.05% CHAPS as indicated, 100 mM NaCl, 50 uM amplex red, 10 mM glucose. The base assay buffer used was 50 mM HEPES, pH 7.6. To aid in the identification of glucose-sensitive inhibitors of glycogen phosphorylase, the assay was performed with and without 10 mM glucose. In order to scrub the assay of contaminating components that may contribute to non-HLGPa specific resorufin production, the reagents were prepared as two 2x concentrated cocktails. A solution of catalase-coated agarose beads is prepared in the base assay buffer. The first cocktail (cocktail #1) consisted of Thermus thermophilus NADH oxidase, NAD^+, glycogen, phosphoglucomutase, glucose-6-phosphate dehydrogenase, K_2HPO_4, FAD, and 50U/mL catalase-coated agarose beads. Amplex red was added to this solution after incubation at 25 C for 30 minutes and the catalase-coated agarose beads were removed by centrifugation and retention of supernatant. The second cocktail (cocktail #2) contained human

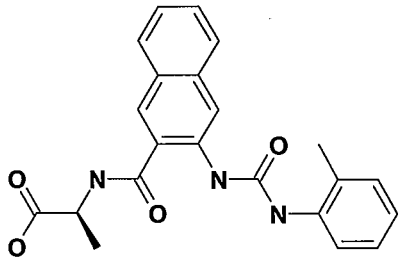
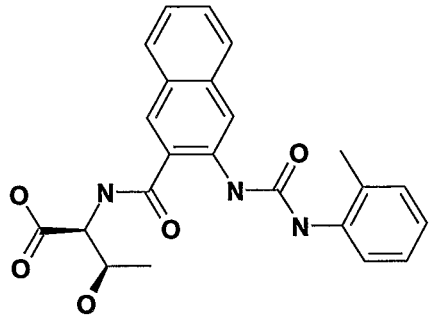
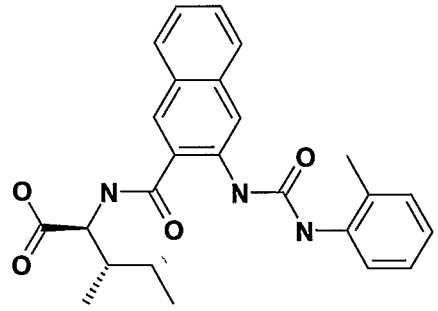
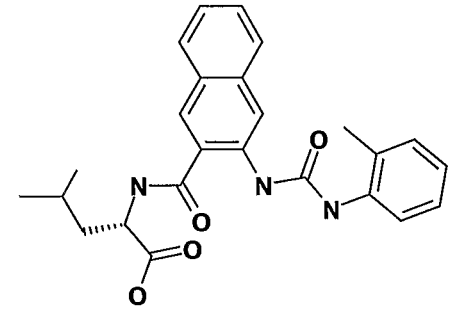
liver glycogen phosphorylase-a and horseradish peroxidase (with and without glucose). The assays were performed with preincubation of compounds of this invention with cocktail #2 for 15 minutes, followed by the addition of cocktail #1 to initiate the reaction. The assays were performed in duplicate in 96 (black ½ volume Costar) or 384-well microtiter plates (small volume black Greiner) and the change in fluorescence due to product formation was measured on a fluorescence plate reader (Viewlux, Perkin Elmer, Molecular Devices) using a 525 nm excitation filter and 595 emission filter (ex560/em590 nm for Molecular devices).

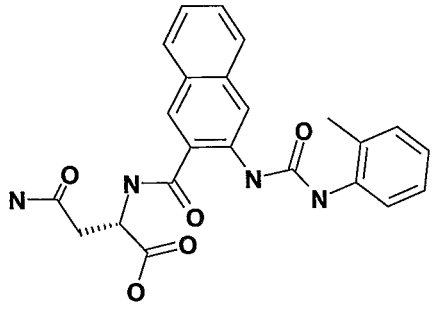
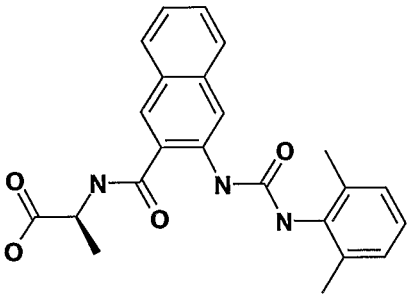
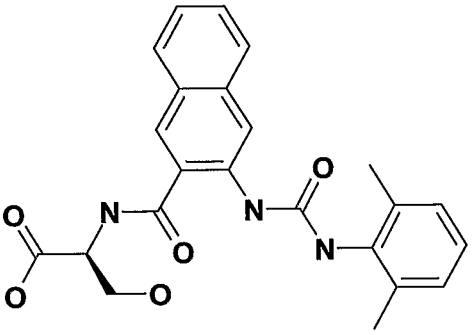
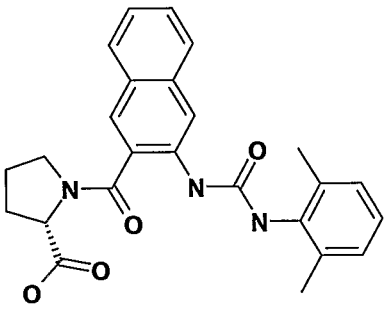
Table 1

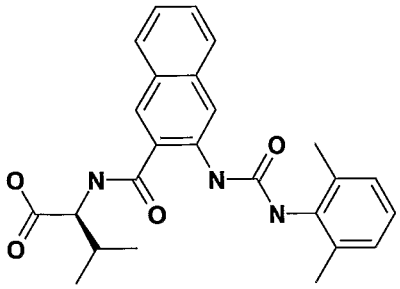
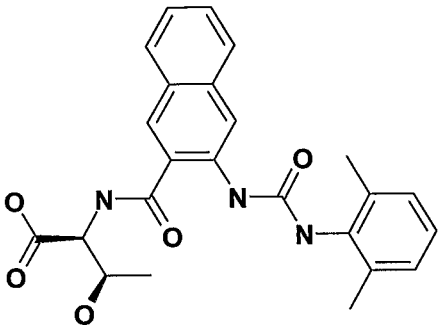
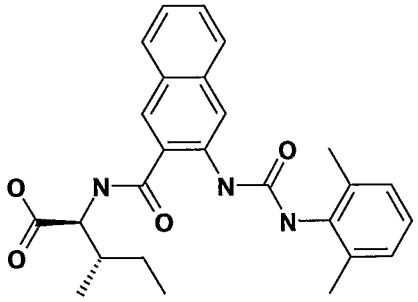
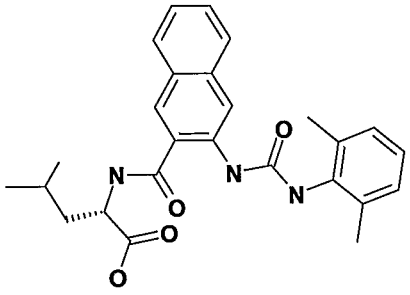
Ex #	Structure	Chemical Name	ESMS +m/z	IC50 (uM)
1		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid	450.4	0.46
2		(2S)-{[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] amino} (cyclohexyl) acetic acid	493.2	0.12
3		N-{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-valine	444.6	32.20
4		(2S)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-1-benzothien-3-yl]carbonyl} amino)acetic acid	480.4	0.73

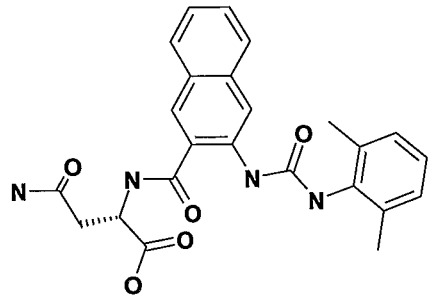
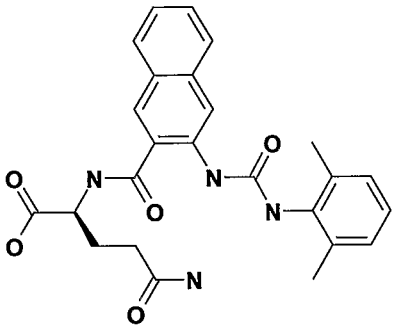
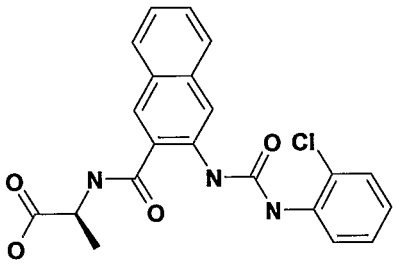
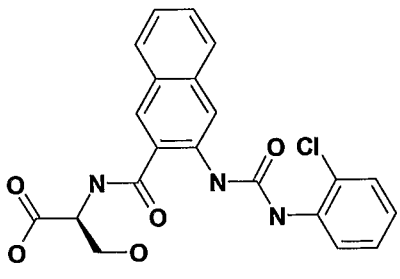
5		{[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] amino} (piperidin-3-yl)acetic acid trifluoroacetate	495.6	20.90
6		3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-N-[(3-methylisoxazol-5-yl)methyl]-2-naphthamide	449.2	35.10
7		(2S)-cyclohexyl{[(3-{[(2-methylphenyl) acetyl]amino}-2-naphthalenyl) carbonyl]amino} ethanoic acid	459.6	17.00
8		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid	436.4	3.91

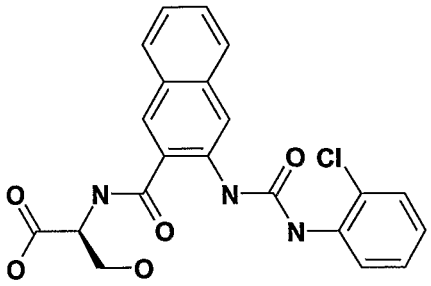
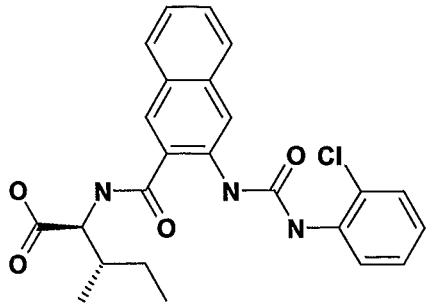
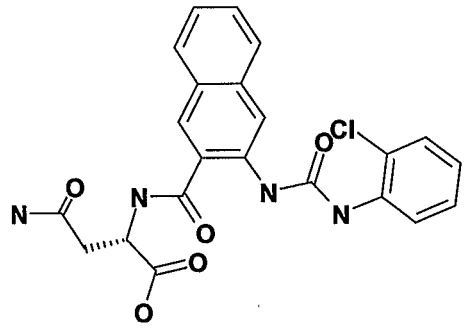
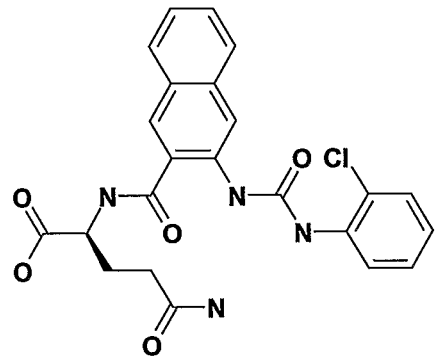
9		N-[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid	456.2	2.78
10		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] glycine	378.2	6.50
11		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl] glycine	392.2	0.09
12		N-[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthoyl] glycine	398.2	2.52

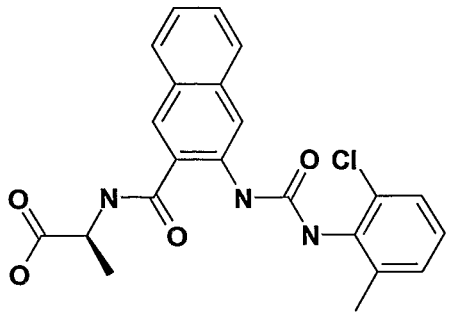
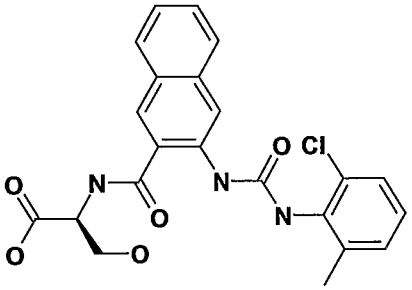
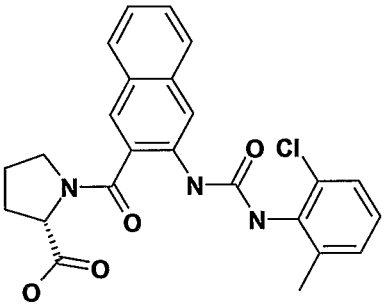
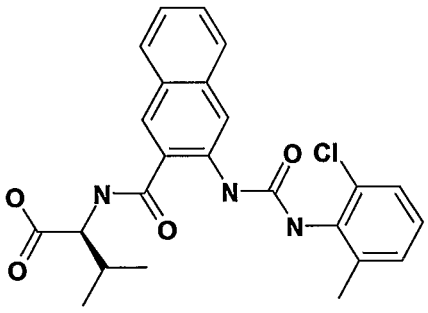
13		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-alanine	392.2	15.50
14		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-threonine	422.2	6.41
15		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-isoleucine	434.4	11.00
16		N-[3-({[(2-methylphenyl) amino]carbonyl} amino)-2-naphthoyl]-L-leucine	434.4	5.10

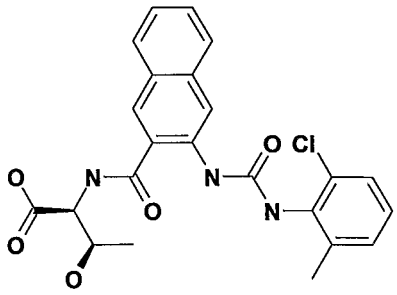
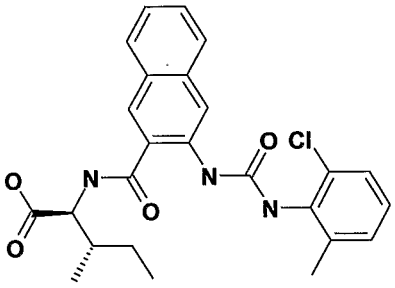
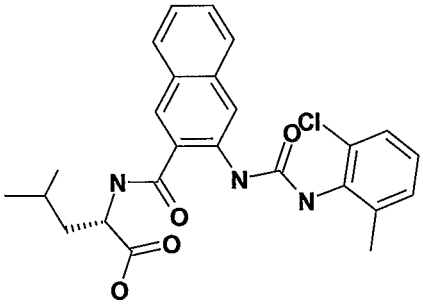
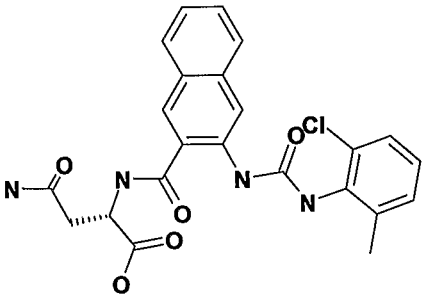
17		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-asparagine	435.4	4.72
18		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-alanine	406.4	1.48
19		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-serine	422.2	2.00
20		1-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-proline	432.4	2.24

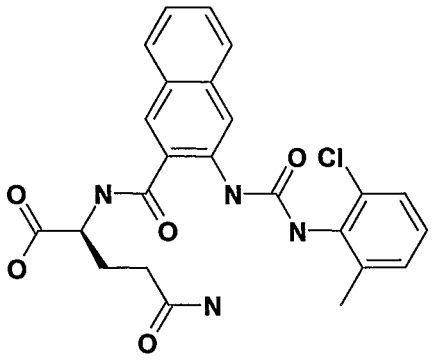
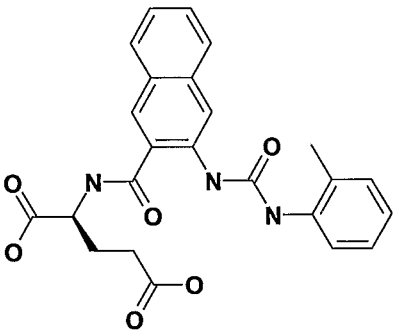
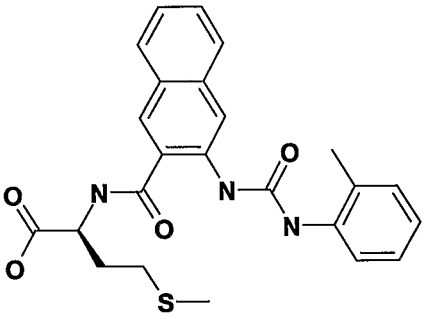
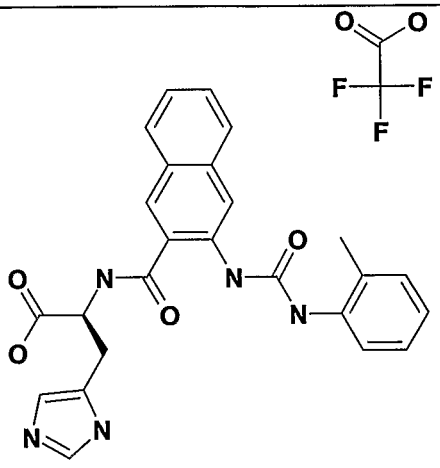
21		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-valine	434.4	1.96
22		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-threonine	436.4	1.08
23		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-isoleucine	448.4	0.89
24		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-leucine	448.4	1.19

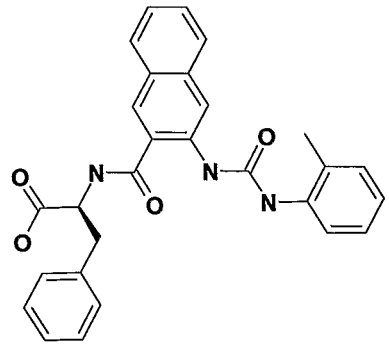
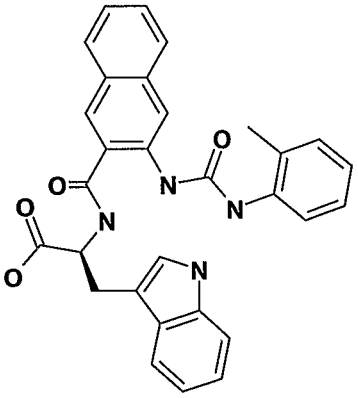
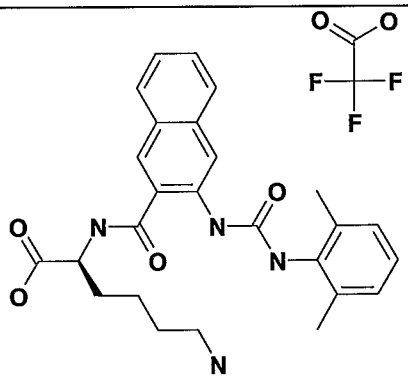
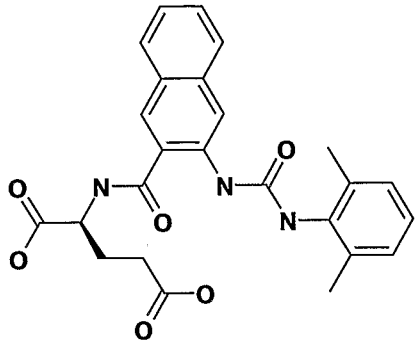
25		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-asparagine	469.2	0.67
26		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamine	463.4	3.01
27		N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-alanine	412.2	13.50
28		N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-serine	428.2	24.10

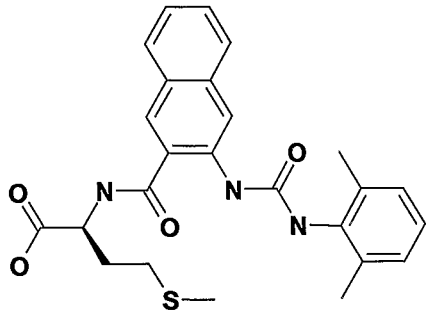
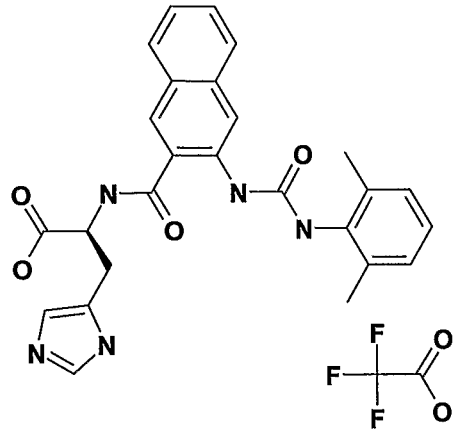
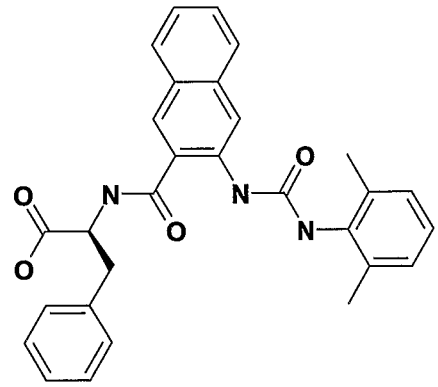
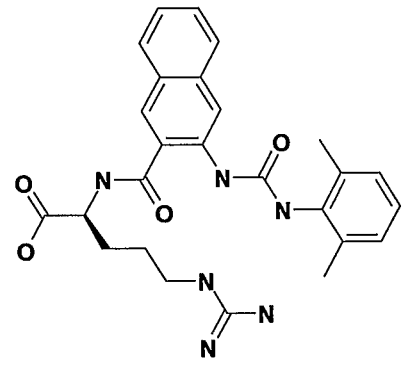
29		N-[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthoyl]-L-threonine	442.2	7.26
30		N-[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthoyl]-L-isoleucine	454.2	22.10
31		N-[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthoyl]-L-asparagine	455.2	11.40
32		N-[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthoyl]-L-glutamine	469.2	41.00

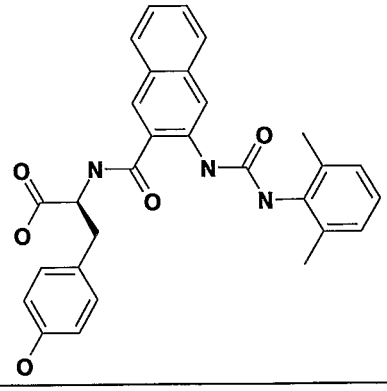
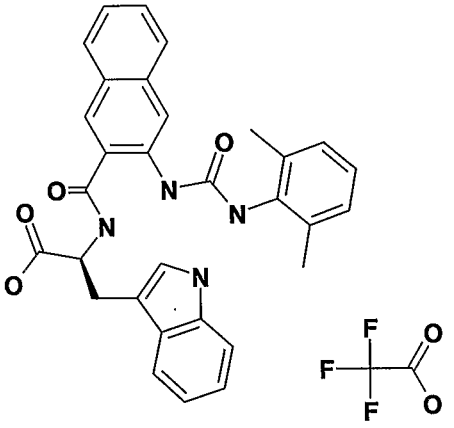
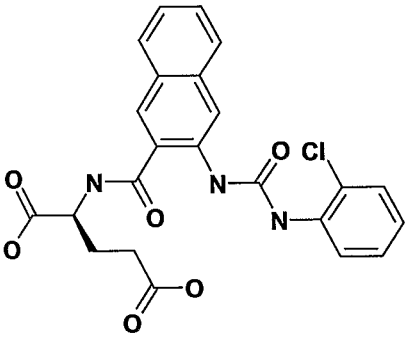
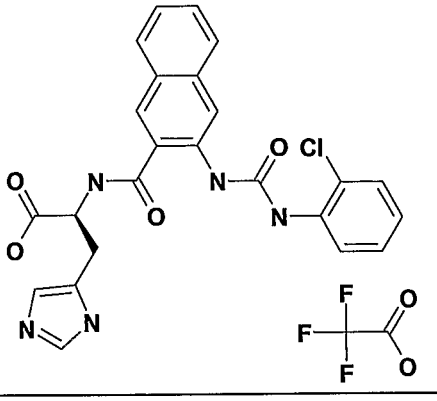
33		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl} amino)-2-naphthoyl]-L-alanine	426.2	0.52
34		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-serine	442.2	0.64
35		1-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-proline	452.2	0.58
36		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-valine	454.2	1.71

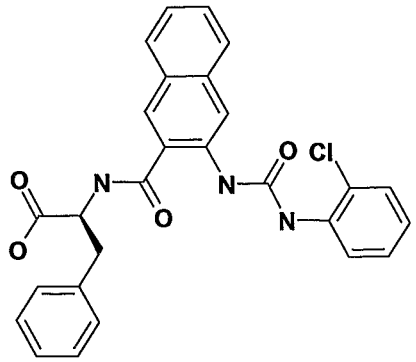
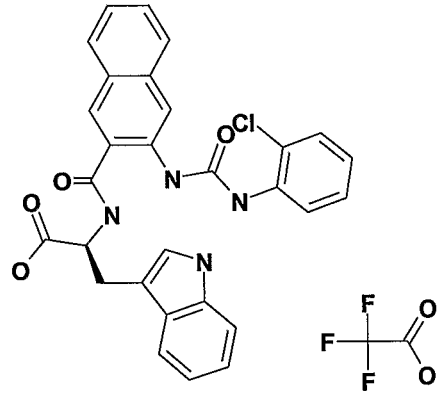
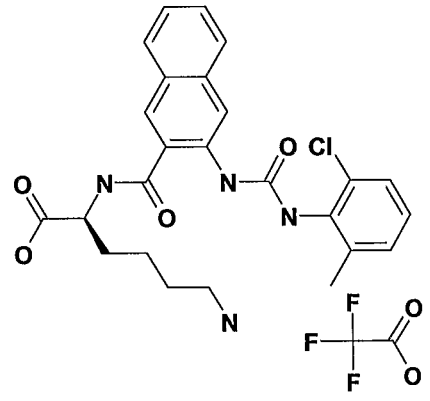
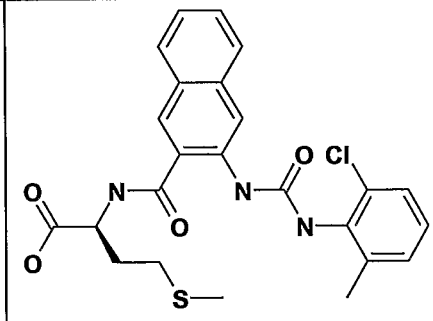
37		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-threonine	456.2	0.43
38		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-isoleucine	468.2	0.28
39		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-leucine	467.2	0.60
40		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-asparagine	469.2	0.42

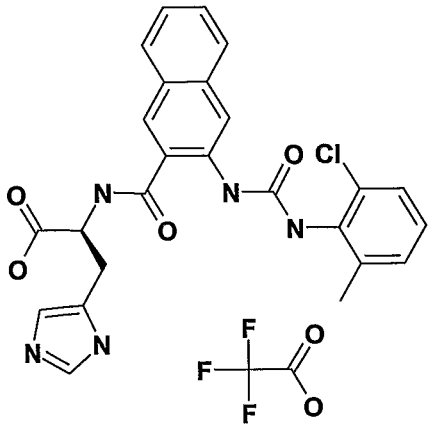
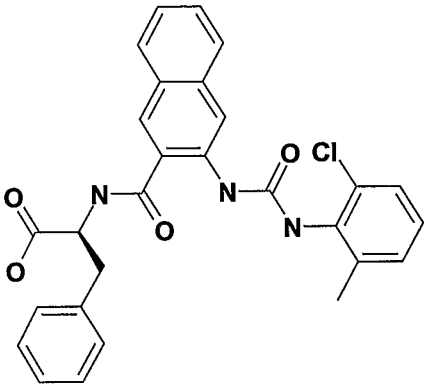
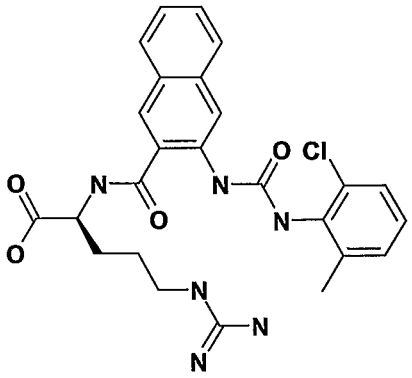
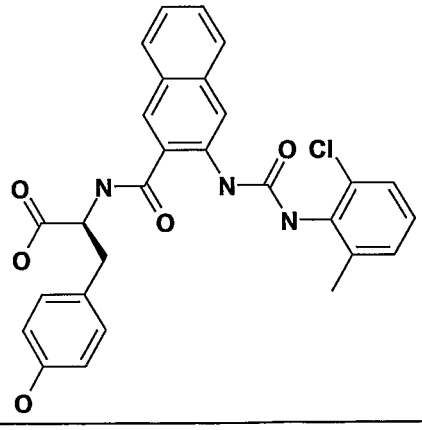
41		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-glutamine	483.2	1.32
42		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-glutamic acid	450.2	28.30
43		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-methionine	452.2	18.90
44		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-histidine trifluoroacetate	458.2	5.18

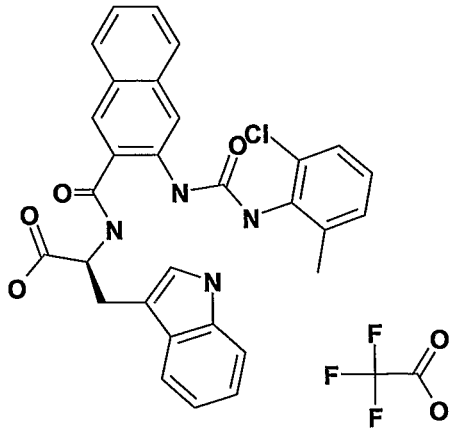
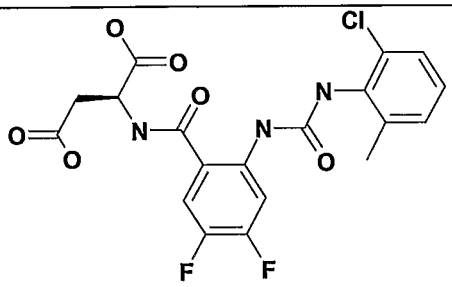
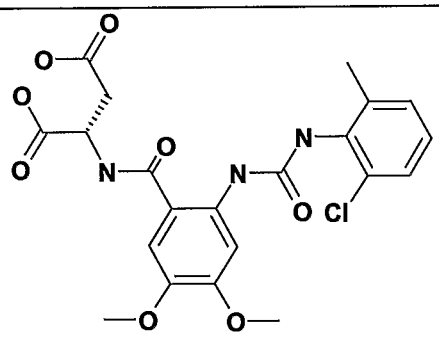
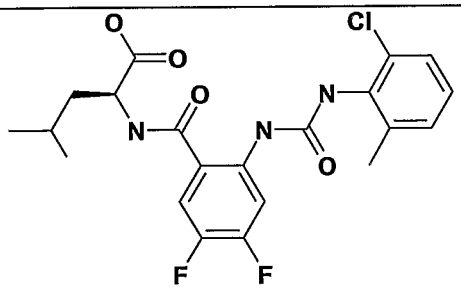
45		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine	468.2	16.90
46		N-[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-tryptophan	507.4	3.73
47		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-lysine trifluoroacetate	463.4	8.06
48		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamic acid	464.2	1.73

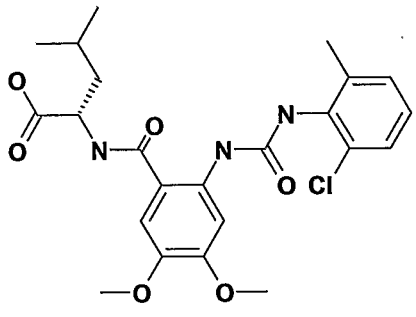
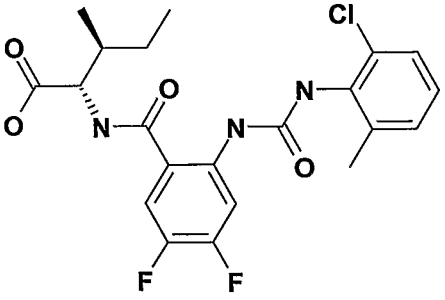
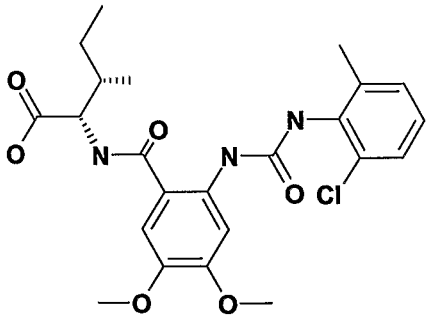
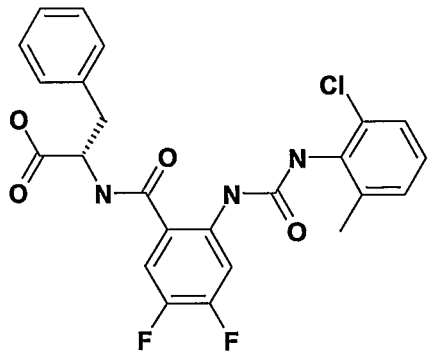
49		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-methionine	466.4	1.67
50		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-histidine trifluoroacetate	472.4	2.30
51		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine	482.4	0.68
52		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-arginine	491.4	4.64

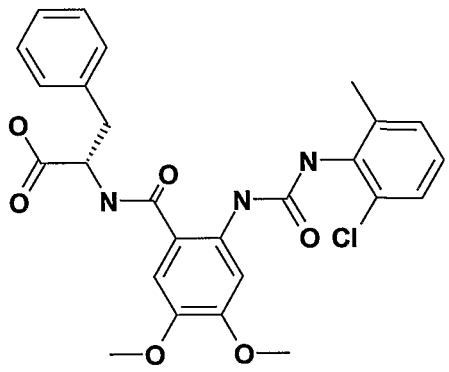
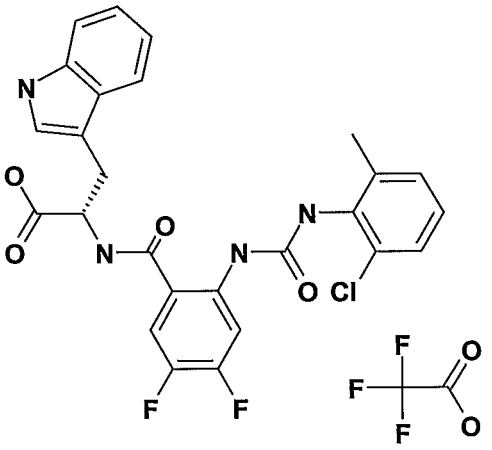
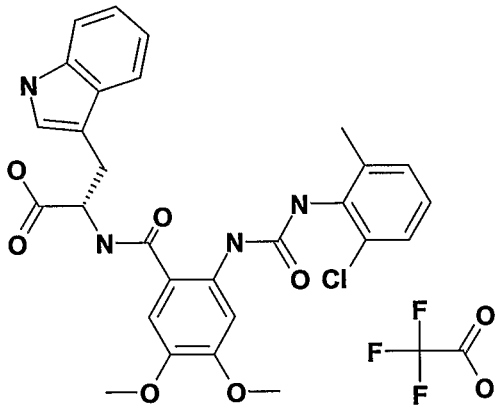
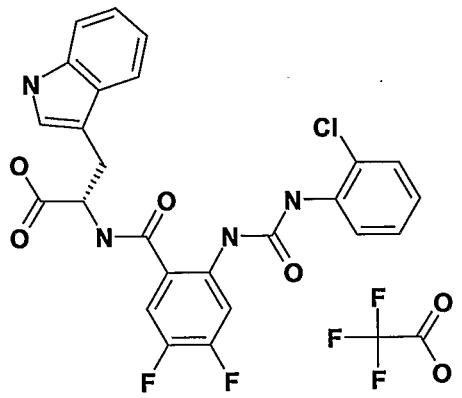
53		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-tyrosine	498.4	0.36
54		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-tryptophan trifluoroacetate	521.4	0.51
55		N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-glutamic acid	470.2	10.40
56		N-[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]-L-histidine trifluoroacetate	478.2	3.08

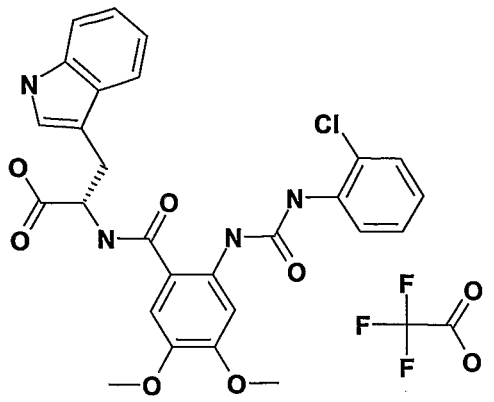
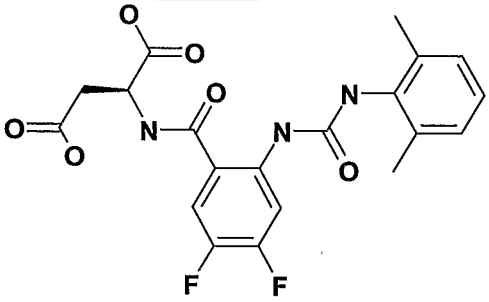
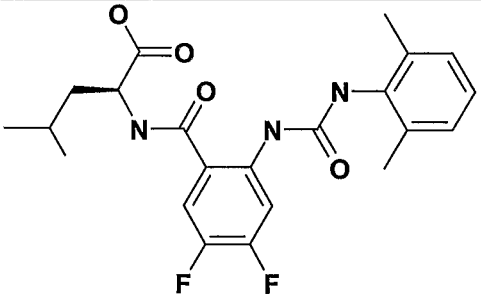
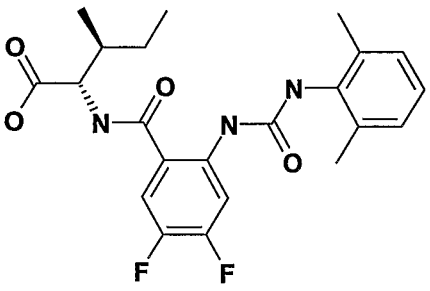
57		N-[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine	488.4	5.21
58		N-[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthoyl]-L-tryptophan trifluoroacetate	527.4	4.70
59		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-lysine trifluoroacetate	483.4	2.99
60		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-methionine	452.2	0.64

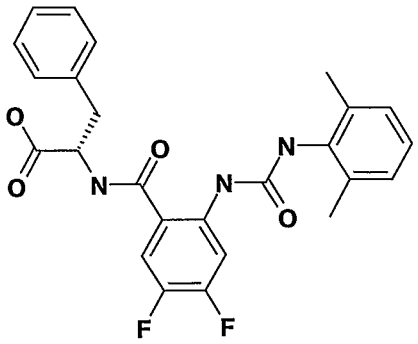
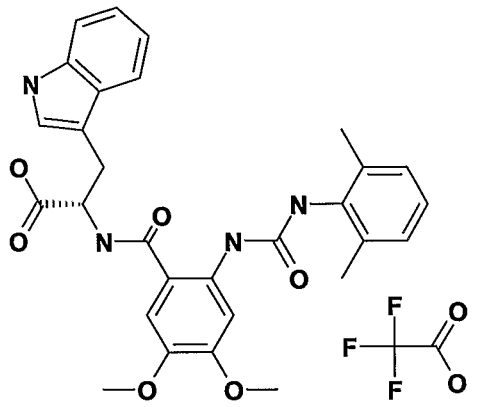
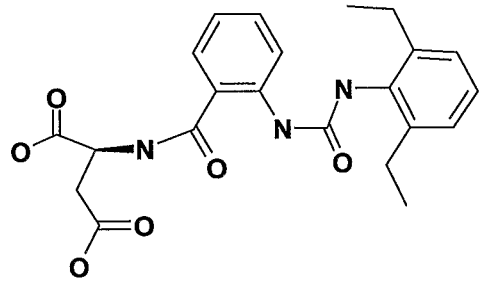
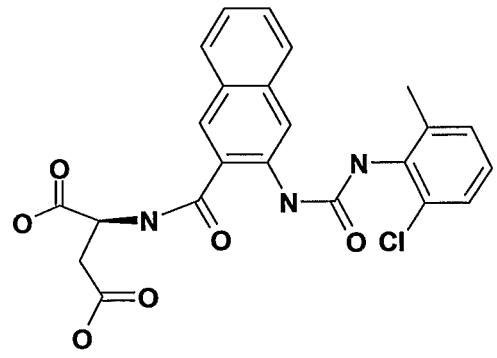
61		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-histidine trifluoroacetate	492.2	0.45
62		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine	502.4	0.26
63		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-arginine	511.4	2.73
64		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-tyrosine	518.4	0.45

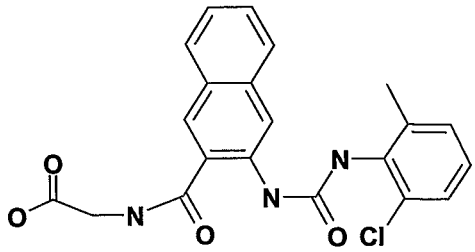
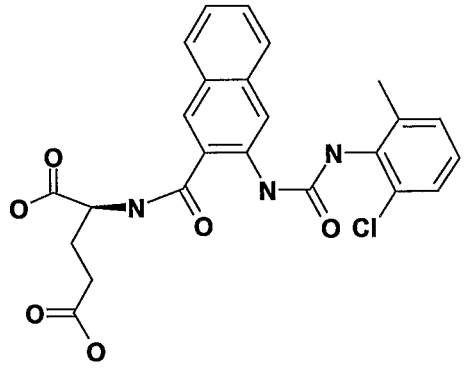
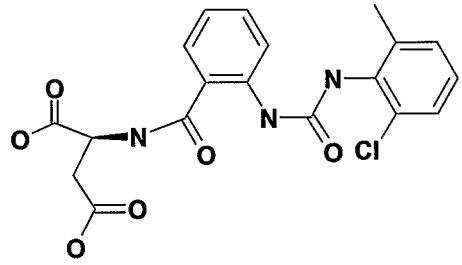
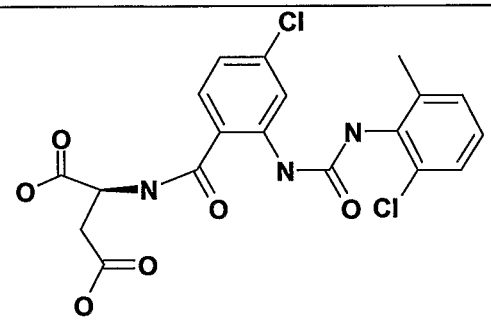
65		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-tryptophan trifluoroacetate	541.4	0.27
66		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-aspartic acid	456.4	7.16
67		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-L-aspartic acid	480.4	19.80
68		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-leucine	454.4	7.54

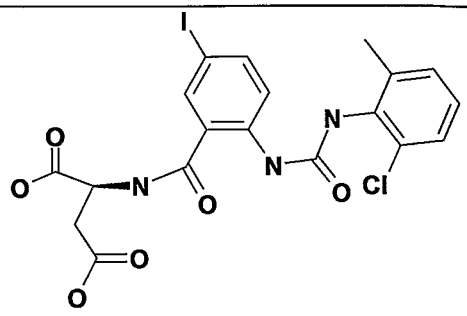
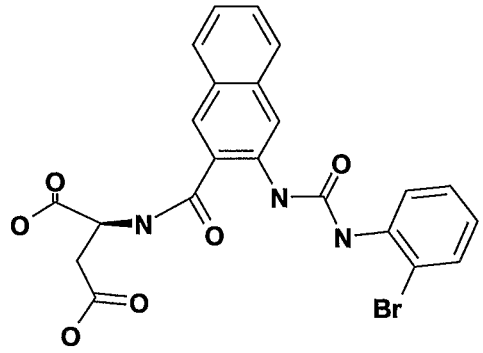
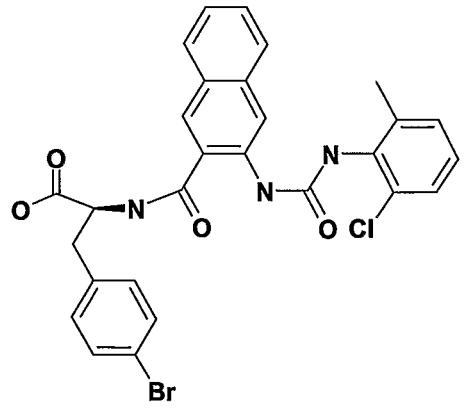
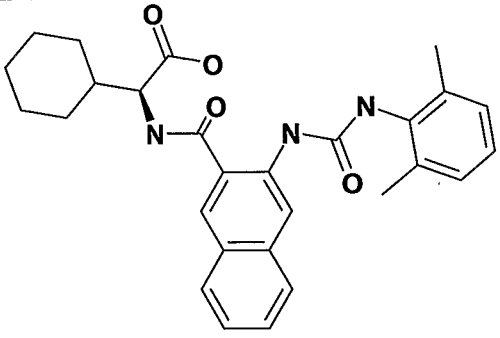
69		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-L-leucine	478.4	13.80
70		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-isoleucine	454.4	5.97
71		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-L-isoleucine	478.4	22.30
72		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-phenylalanine	488.4	10.90

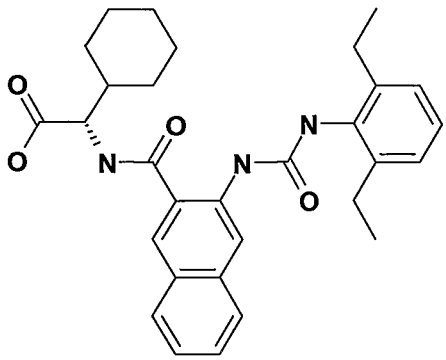
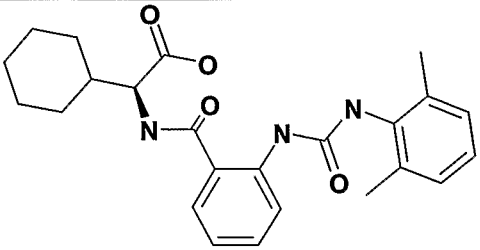
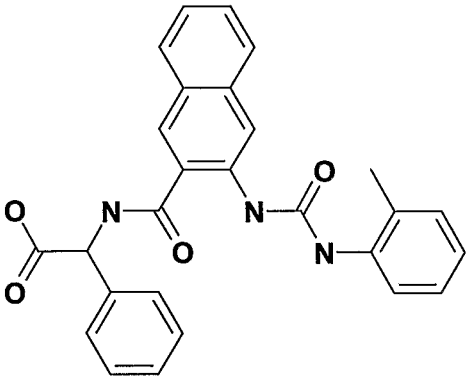
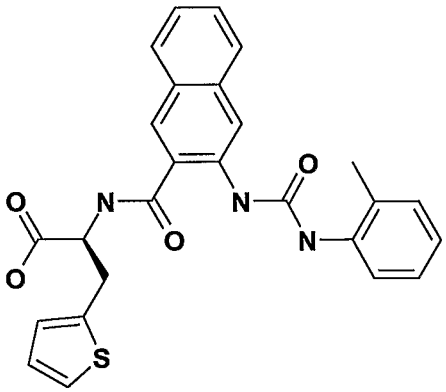
73		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-L-phenylalanine	512.4	11.60
74		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-tryptophan trifluoroacetate	527.4	6.58
75		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-L-tryptophan trifluoroacetate	551.4	0.76
76		N-[2-({[(2-chlorophenyl) amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-tryptophan trifluoroacetate	513.4	3.74

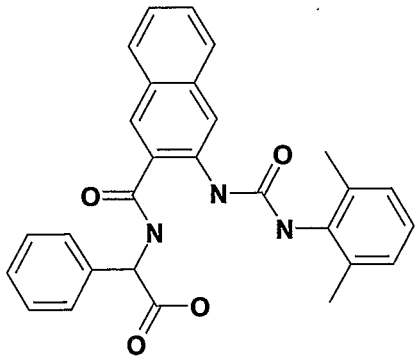
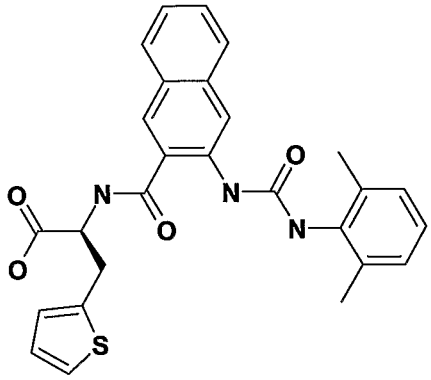
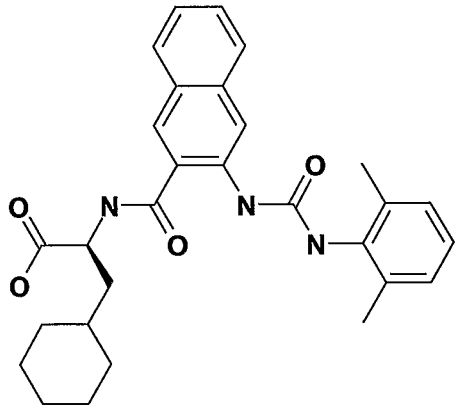
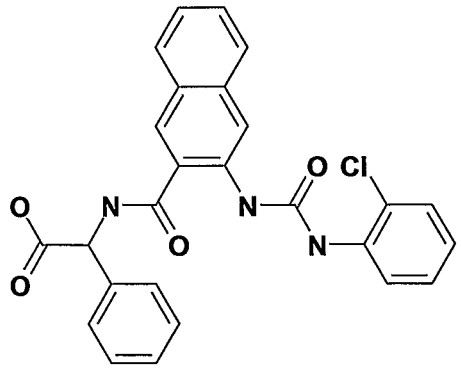
77		N-[2-({[(2-chlorophenyl) amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-L-tryptophan trifluoroacetate	537.2	9.05
78		N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-aspartic acid	436.2	9.11
79		N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-leucine	434.4	18.70
80		N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-isoleucine	434.4	8.73

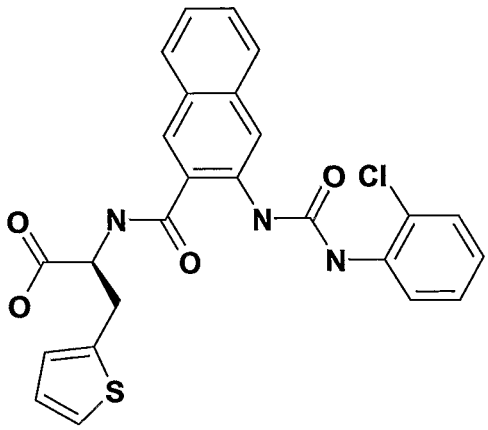
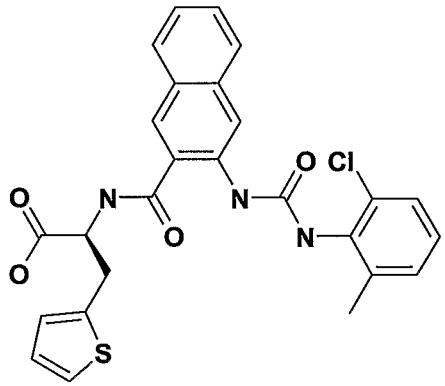
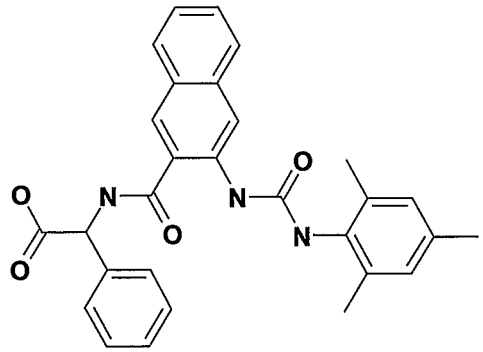
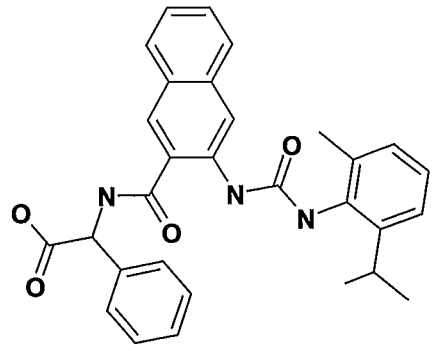
81		N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-phenylalanine	468.4	14.70
82		N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-L-tryptophan trifluoroacetate	531.4	9.41
83		N-[2-({[(2,6-diethylphenyl)amino]carbonyl}amino)benzoyl]-L-aspartic acid	428.0	34.15
84		N-[3-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid	470.2	0.39

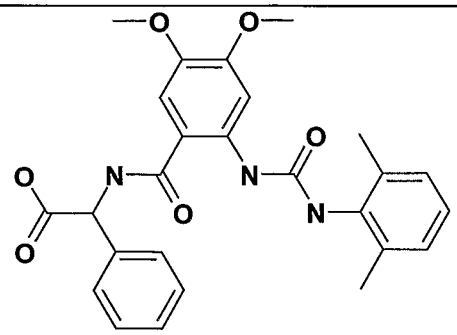
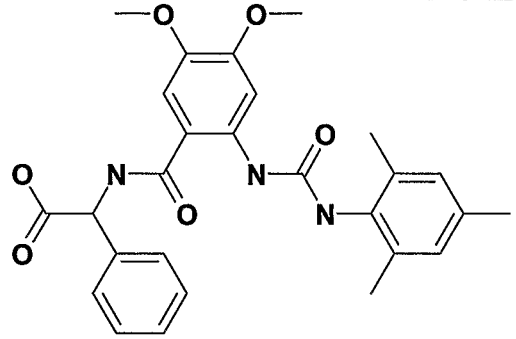
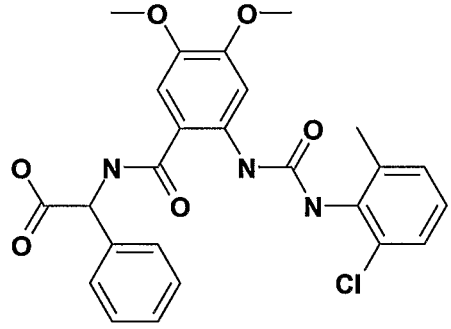
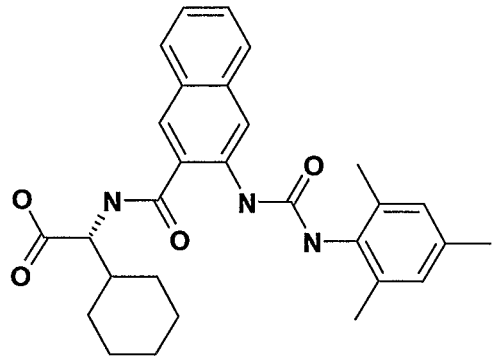
85		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] glycine	412.2	0.57
86		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-glutamic acid	464.2	0.70
87		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)benzoyl]-L-aspartic acid	419.8	24.50
88		N-[4-chloro-2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)benzoyl]-L-aspartic acid	454.0	5.20

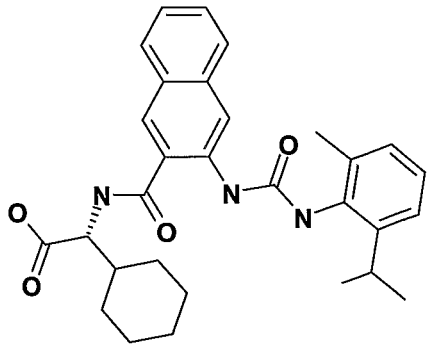
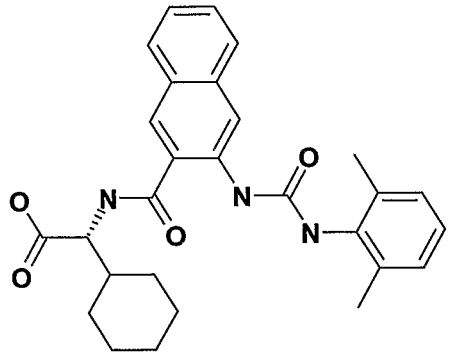
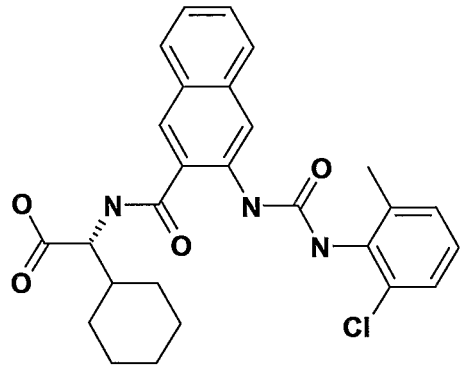
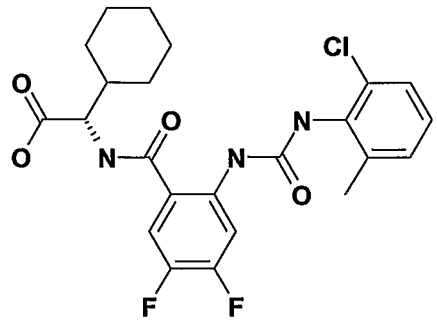
89		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-5-iodobenzoyl]-L-aspartic acid	546.0	17.45
90		N-[3-({[(2-bromophenyl) amino]carbonyl}amino)-2-naphthoyl]-L-aspartic acid	500.1	22.95
91		4-bromo-N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-L-phenylalanine	580.0	7.88
92		(2S)-cyclohexyl{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}acetic acid	474.4	0.12

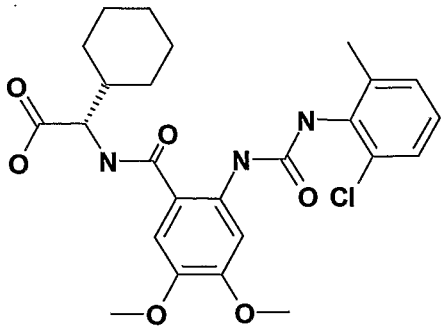
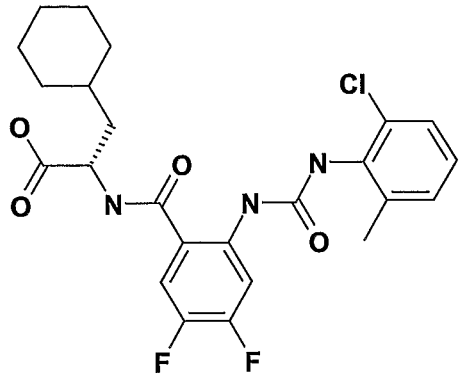
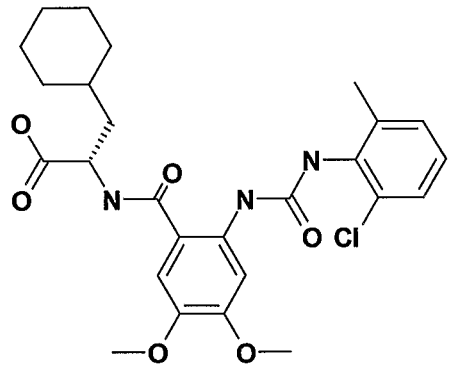
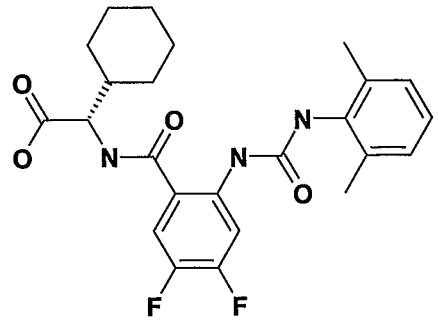
93		(2S)-cyclohexyl({[3-({[(2,6-diethylphenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}amino) ethanoic acid	502.4	0.59
94		(2S)-cyclohexyl{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)benzoyl] amino}acetic acid	424.2	0.53
95		{[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] amino}(phenyl) acetic acid	454.2	9.89
96		N-{[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-3-(2-thienyl)-L-alanine	474.4	5.07

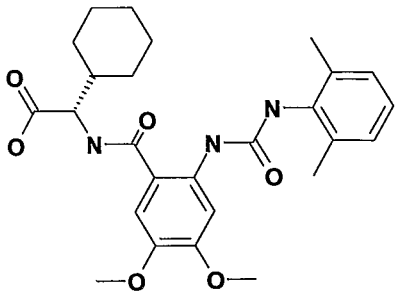
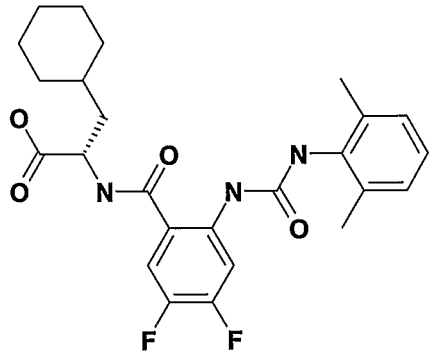
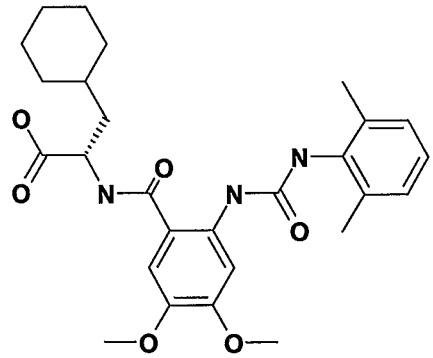
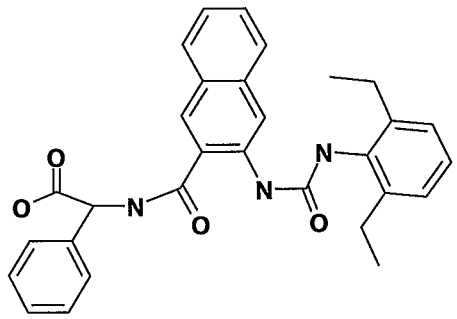
97		{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(phenyl) acetic acid	468.2	0.66
98		N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-(2-thienyl)-L-alanine	488.4	0.54
99		3-cyclohexyl-N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-L-alanine	488.6	0.49
100		{[3-({[(2-chlorophenyl)amino]carbonyl}amino)-2-naphthoyl]amino}(phenyl) acetic acid	474.4	7.63

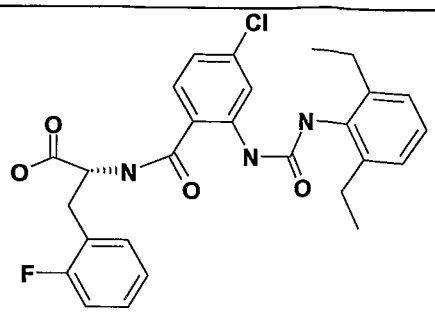
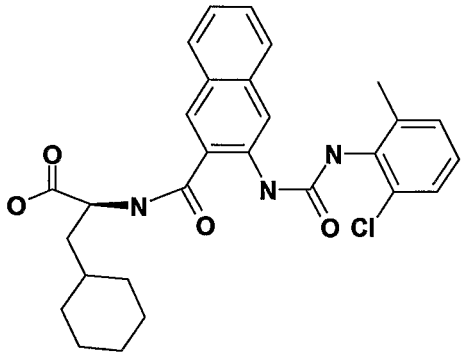
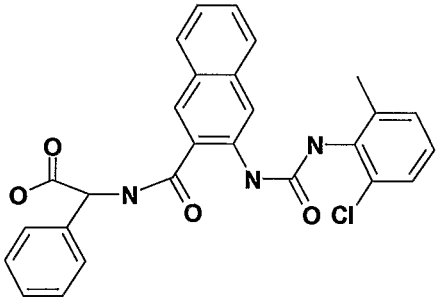
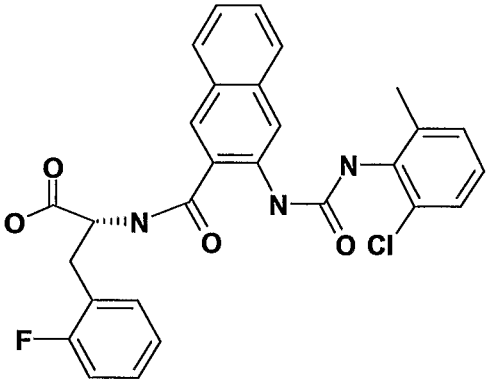
101		N-{[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-3-(2-thienyl)-L-alanine	494.2	2.78
102		N-{[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-3-(2-thienyl)-L-alanine	508.4	0.36
103		phenyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl] carbonyl}amino)acetic acid	482.2	0.06
104		{[3-({[(2-isopropyl-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] amino}(phenyl) acetic acid	496.4	1.04

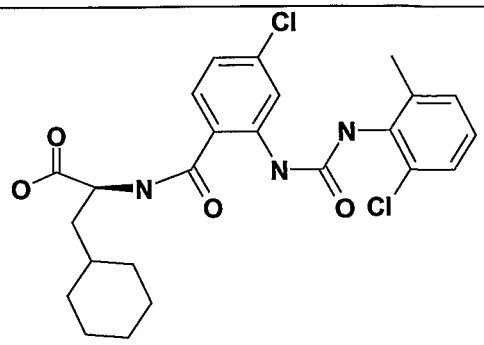
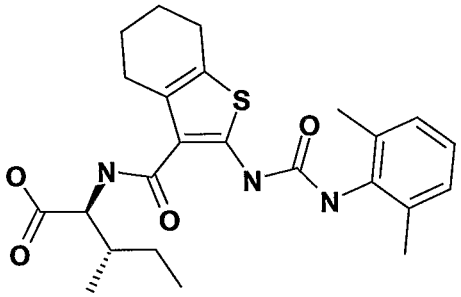
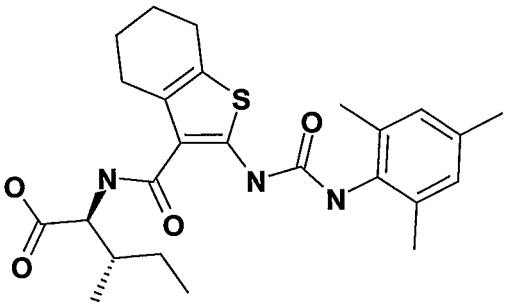
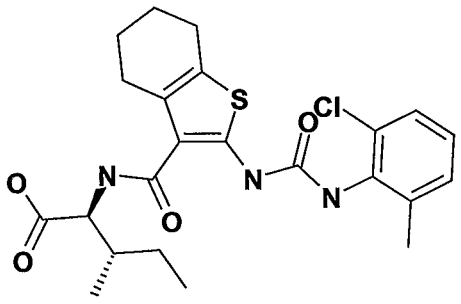
105		{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]amino}(phenyl)acetic acid	478.2	19.60
106		[(2-{[(mesitylamino)carbonyl]amino}-4,5-dimethoxybenzoyl)amino](phenyl)acetic acid	492.4	4.23
107		{[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5-dimethoxybenzoyl]amino}(phenyl)acetic acid	498.2	12.20
108		(2R)-cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl)amino]acetic acid	488.4	3.29

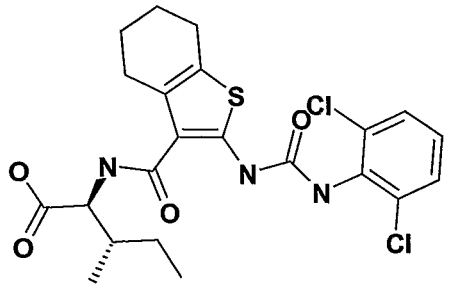
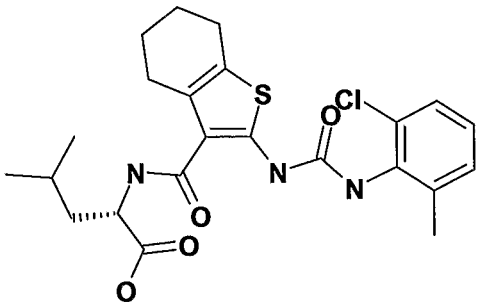
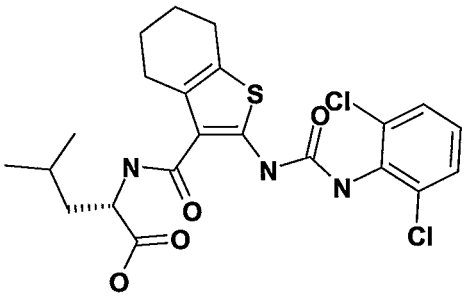
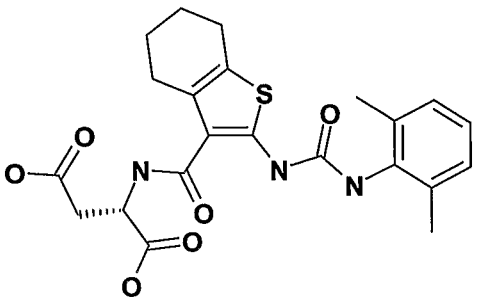
109		(2R)-cyclohexyl{[3-({[(2-isopropyl-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] amino}acetic acid	502.4	19.80
110		(2R)-cyclohexyl{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl] amino}acetic acid	474.4	12.00
111		(2R)-{[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] amino} (cyclohexyl) acetic acid	494.2	4.15
112		(2S)-{[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-difluorobenzoyl]amino} (cyclohexyl) acetic acid	480.4	0.86

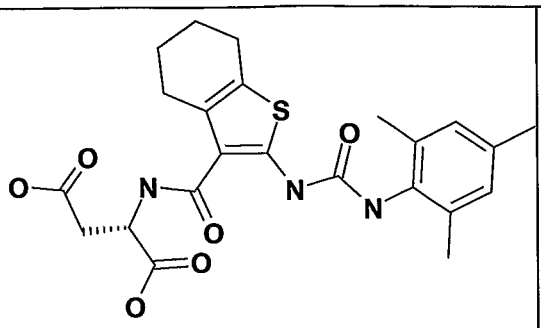
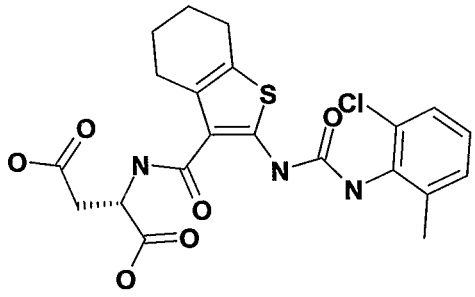
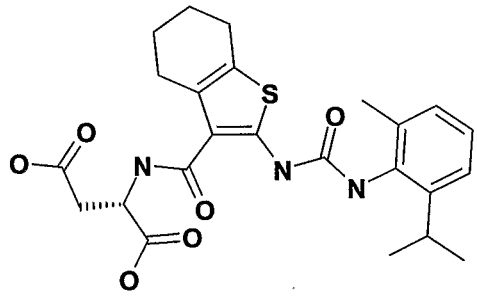
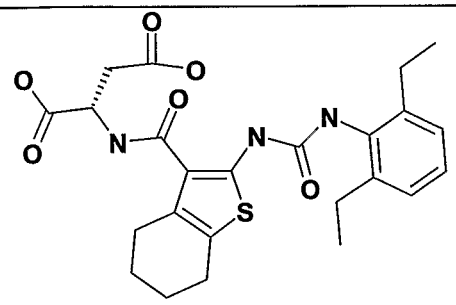
113		(2S)-{[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]amino} (cyclohexyl) acetic acid	504.4	7.04
114		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-difluorobenzoyl]-3-cyclohexyl-L-alanine	494.4	18.70
115		N-[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-3-cyclohexyl-L-alanine	518.4	13.00
116		(2S)-cyclohexyl{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]amino}acetic acid	460.4	1.63

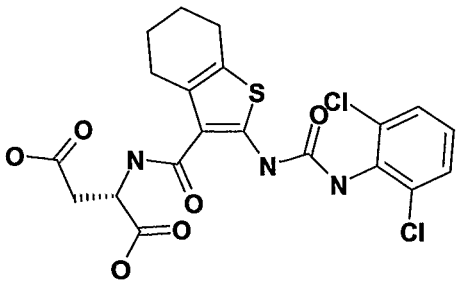
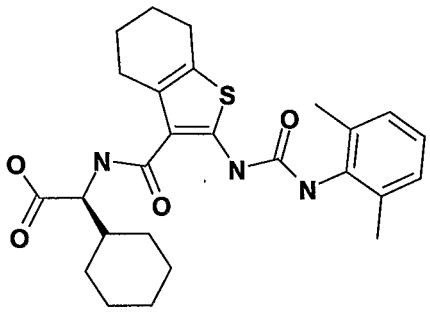
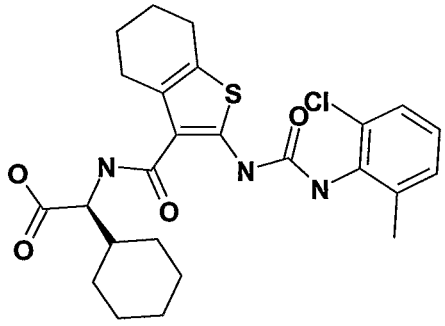
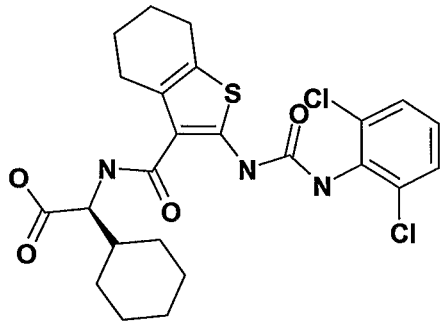
117		(2S)-cyclohexyl{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]amino} acetic acid	484.4	14.70
118		3-cyclohexyl-N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-difluorobenzoyl]-L-alanine	474.4	15.70
119		3-cyclohexyl-N-[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5-dimethoxy-benzoyl]-L-alanine	498.4	13.60
120		{[3-({[(2,6-diethylphenyl) amino]carbonyl}amino)-2-naphthoyl] amino}(phenyl) acetic acid	496.0	24.55

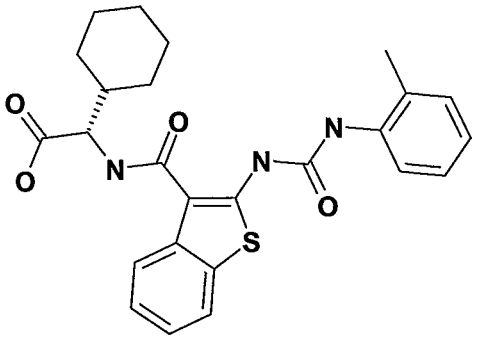
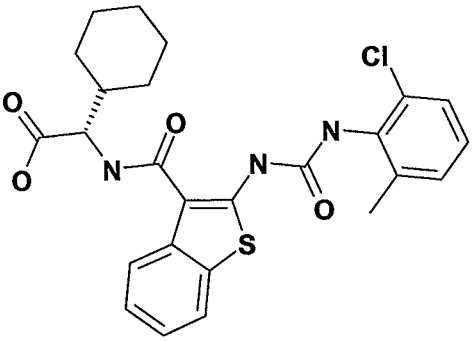
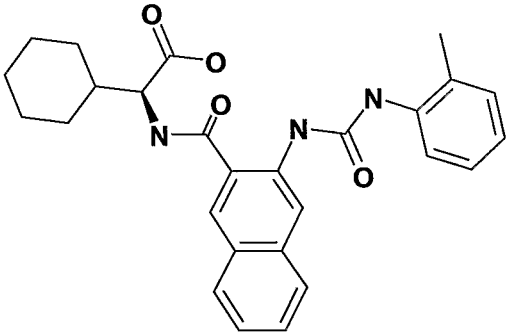
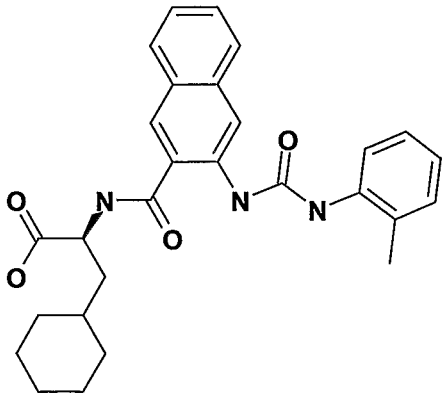
121		N-[4-chloro-2-({[(2,6-diethylphenyl) amino]carbonyl}amino)benzoyl]-2-fluoro-D-phenylalanine	512.2	3.44
122		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-3-cyclohexyl-L-alanine	508.4	2.23
123		({[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}amino)(phenyl)acetic acid	488.4	0.27
124		N-[3-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-2-naphthoyl]-2-fluoro-D-phenylalanine	520.0	5.82

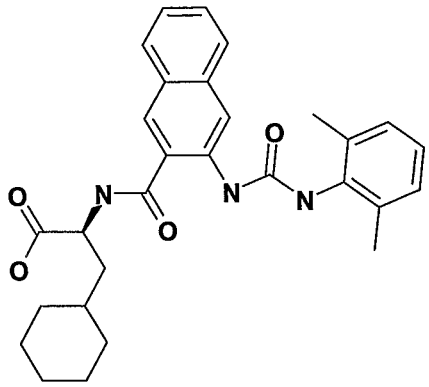
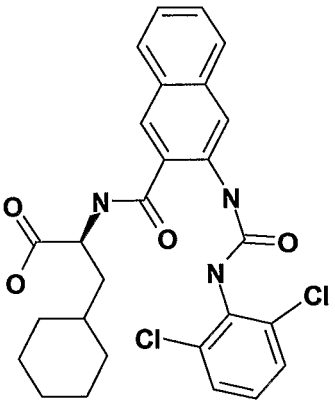
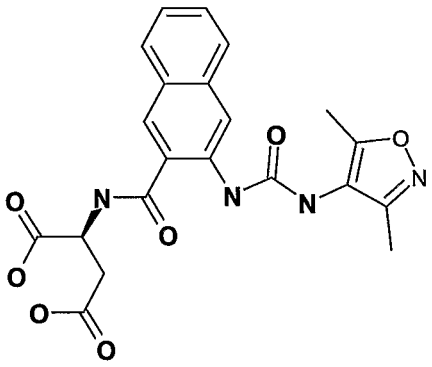
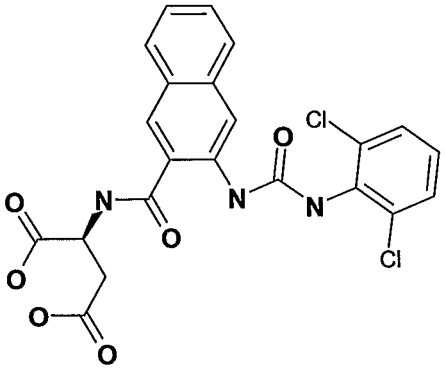
125		N-[4-chloro-2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)benzoyl]-3-cyclohexyl-L-alanine	492.0	28.60
126		N-{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-isoleucine	458.2	13.90
127		N-[(2-{[(mesitylamino)carbonyl]amino}-4,5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-L-isoleucine	472.4	18.20
128		N-{[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-isoleucine	479	14.80

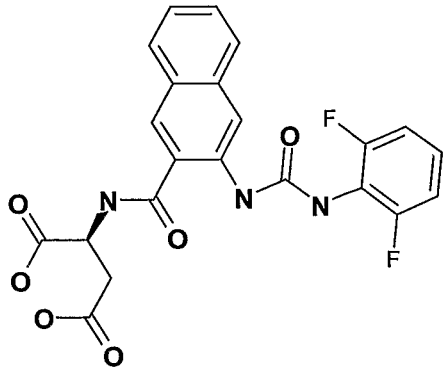
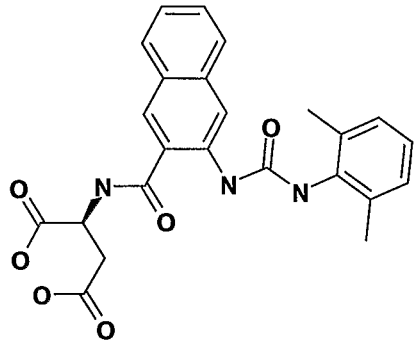
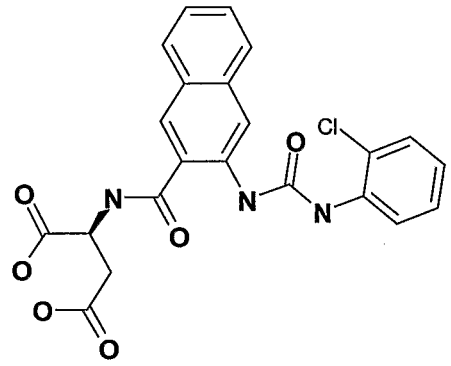
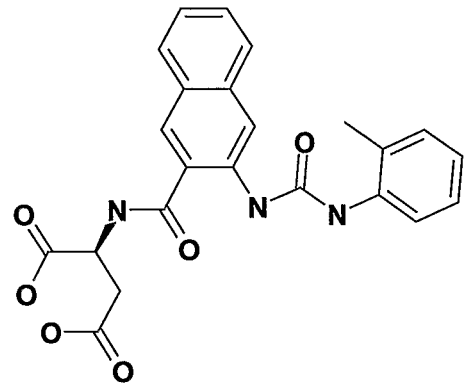
129		N-{[2-({[(2,6-dichlorophenyl) amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-isoleucine	499.2	7.97
130		N-{[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-leucine	479.2	18.00
131		N-{[2-({[(2,6-dichlorophenyl) amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-leucine	499.4	9.96
132		N-{[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid	460.2	5.25

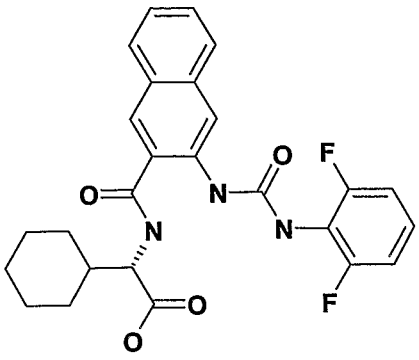
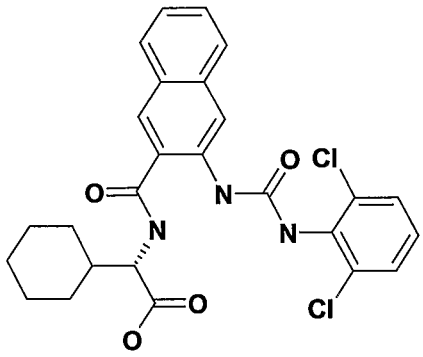
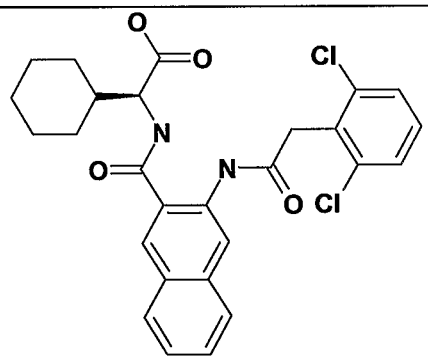
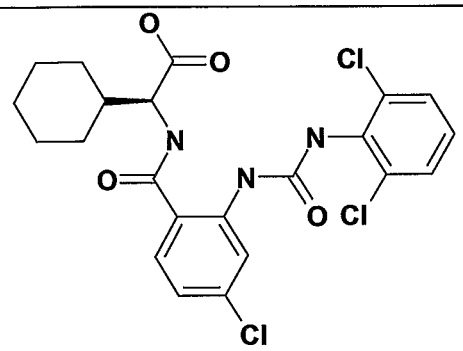
133		N-[(2-{[(mesitylamino)carbonyl]amino}-4,5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-L-aspartic acid	474.4	2.38
134		N-{[2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid	480.4	3.66
135		N-{[2-({[(2-isopropyl-6-methylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid	488.2	17.90
136		N-{[2-({[(2,6-diethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid	488.6	4.58

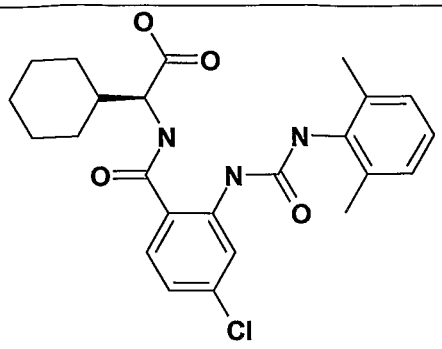
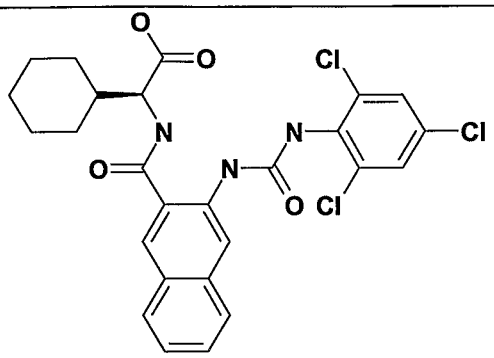
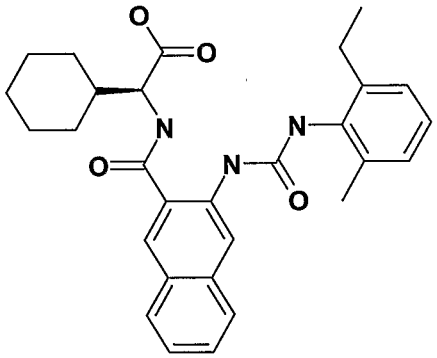
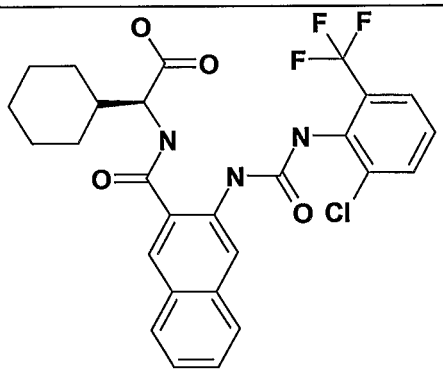
137		N-{[2-({[(2,6-dichlorophenyl) amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl}-L-aspartic acid	501.4	4.15
138		(2S)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl} amino)acetic acid	484.4	5.56
139		(2S)-({[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl} amino) (cyclohexyl) acetic acid	505.2	3.26
140		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl) amino]carbonyl}amino)-4,5,6,7-tetrahydro-1-benzothien-3-yl]carbonyl} amino) acetic acid	525.2	5.50

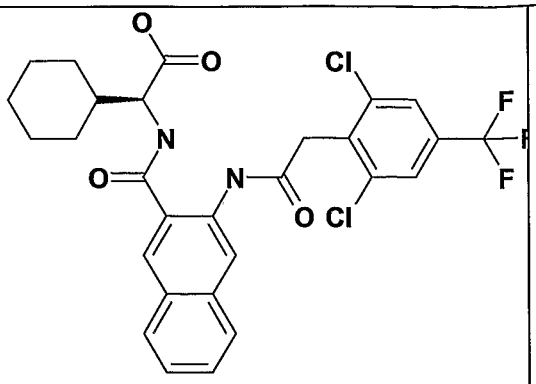
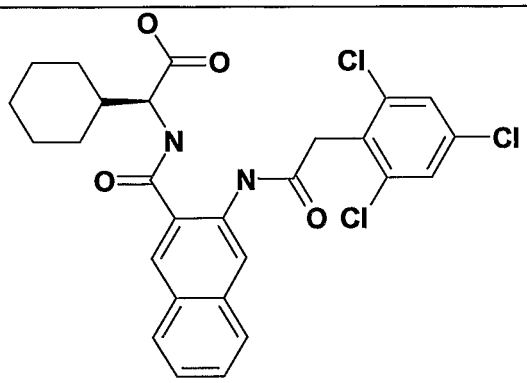
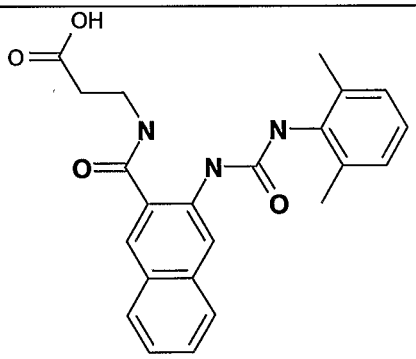
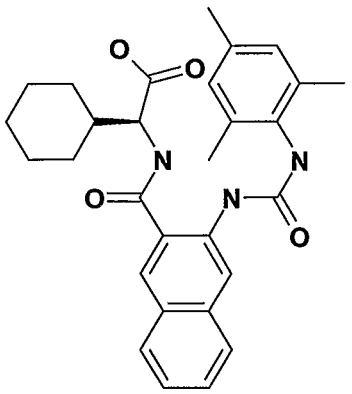
141		(2S)-cyclohexyl({[2-({[(2-methylphenyl) amino]carbonyl}amino)-1-benzothien-3-yl]carbonyl} amino) acetic acid	466.4	8.71
142		(2S)-({[2-({[(2-chloro-6-methylphenyl) amino]carbonyl}amino)-1-benzothien-3-yl]carbonyl} amino) (cyclohexyl) acetic acid	500.2	1.51
143		(2S)-cyclohexyl{[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthoyl] amino}acetic acid	460.8	30.34
144		3-cyclohexyl-N-{[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-alanine	474.6	16.80

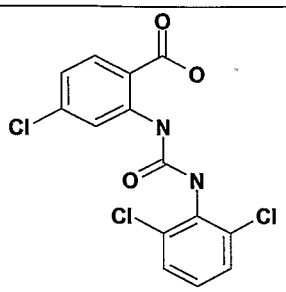
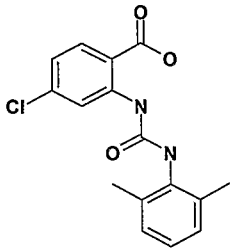
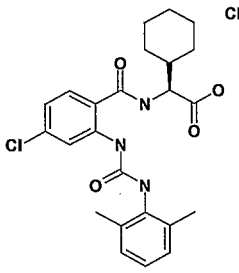
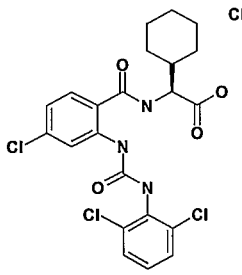
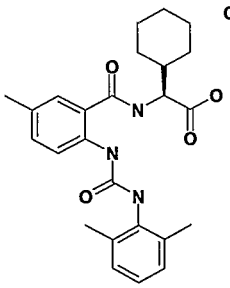
145		3-cyclohexyl-N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-alanine	488.8	0.59
146		3-cyclohexyl-N-{[3-({[(2,6-dichlorophenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-alanine	528.4	0.54
147		N-{[3-({[(3,5-dimethyl-4-isoxazolyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-aspartic acid	441.6	29.10
148		N-{[3-({[(2,6-dichlorophenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-aspartic acid	490.4	0.23

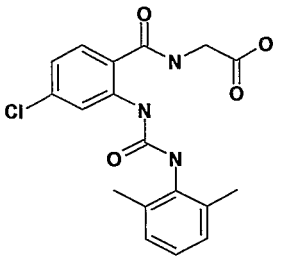
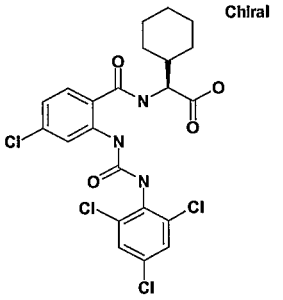
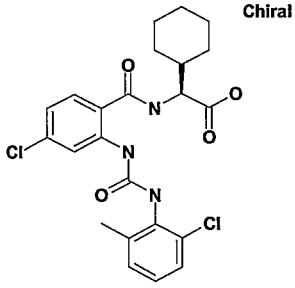
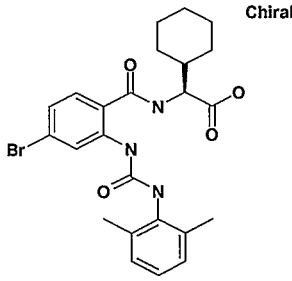
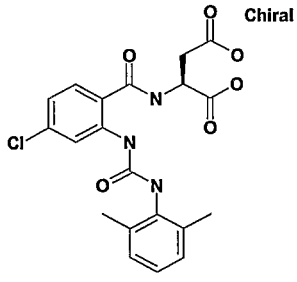
149		N-{[3-({[(2,6-difluorophenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-aspartic acid	458.6	5.02
150		N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-aspartic acid	450.4	0.12
151		N-{[3-({[(2-chlorophenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-aspartic acid	456.4	1.55
152		N-{[3-({[(2-methylphenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}-L-aspartic acid	436.4	1.23

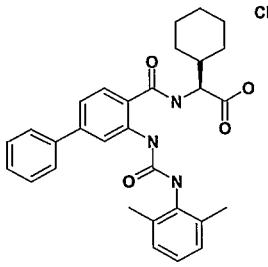
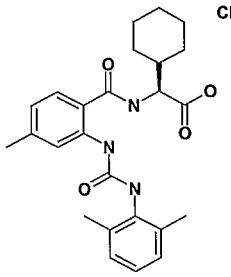
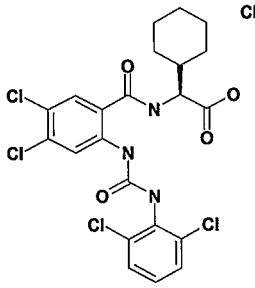
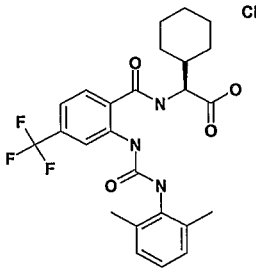
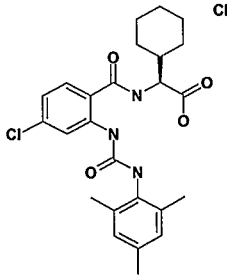
153		(2S)-cyclohexyl({[3-({[(2,6-difluorophenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}amino)ethanoic acid	482.2	4.85
154		(2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl) amino]carbonyl}amino)-2-naphthalenyl] carbonyl}amino)acetic acid	514.6	0.10
155		(2S)-cyclohexyl{[(3-{[(2,6-dichlorophenyl) acetyl]amino}-2-naphthalenyl) carbonyl]amino}ethanoic acid	513.6	6.80
156		(2S)({[4-chloro-2-({[(2,6-dichlorophenyl) amino]carbonyl}amino)phenyl] carbonyl}amino) (cyclohexyl) ethanoic acid	[M-H] =496	0.082

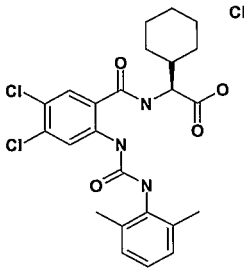
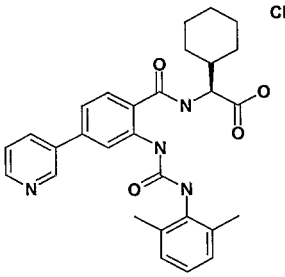
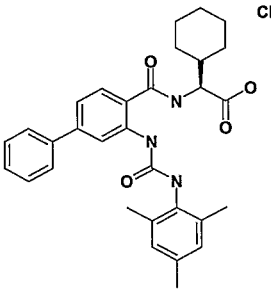
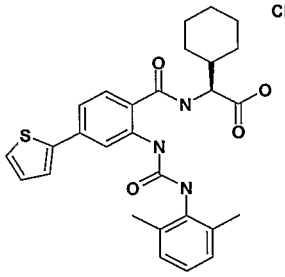
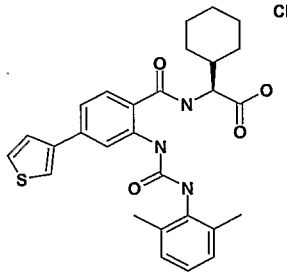
157		(2S)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl) ethanoic acid	[M-H] =456	0.242
158		(2S)-cyclohexyl{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthoyl]amino}ethanoic acid	[M-H] =546	0.079
159		(2S)-cyclohexyl{[3-({[(2-ethyl-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino}ethanoic acid	[M-H] =486	0.058
160		(2S)-({3-[({[2-chloro-6-(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthoyl}amino)(cyclohexyl)ethanoic acid	[M-H] =546	0.068

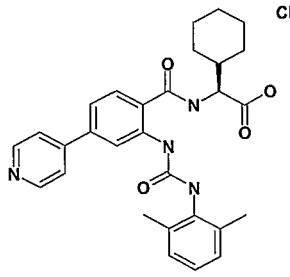
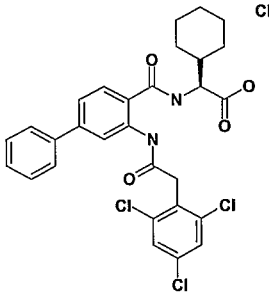
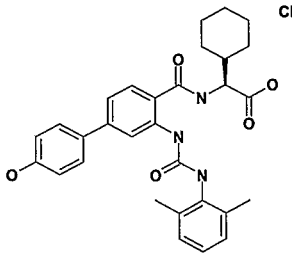
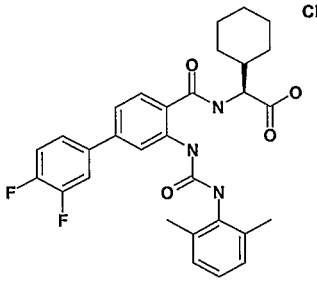
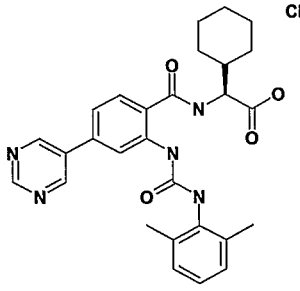
161		(2S)-cyclohexyl{[3-({[2,6-dichloro-4-(trifluoromethyl)phenyl]acetyl} amino)-2-naphthoyl] amino}ethanoic acid	[M-H] =579	0.11
162		(2S)-cyclohexyl[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-2-naphthoyl) amino]ethanoic acid	[M-H] =546	0.046
163		N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl]-beta-alanine	[M-H] =404	0.509
164		(2S)-cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl) amino]ethanoic acid	[M-H] =486	0.006

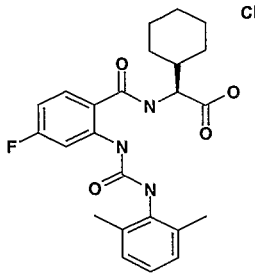
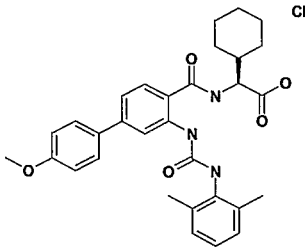
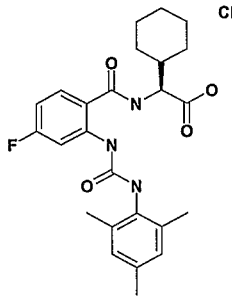
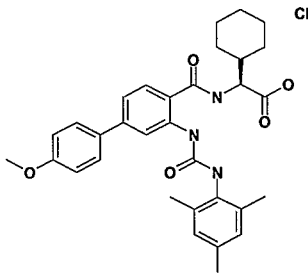
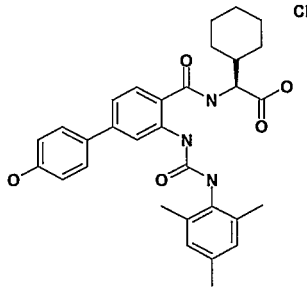
165		4-Chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino) benzoic acid	358 (M-H)	15.1
166		2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)benzoic acid	317 (M-H)	8.64
167		(2*S*)-({[4-chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	456 (M-H)	0.39
168		(2*S*)-({[4-chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	496 (M-H)	0.2
169		(2*S*)Cyclohexyl({[2({[(2,6dimethylphenyl)amino]carbonyl}amino)-5-methylphenyl]carbonyl}amino)ethanoic acid	436 (M-H)	0.68

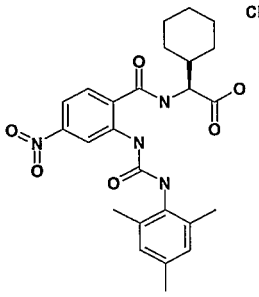
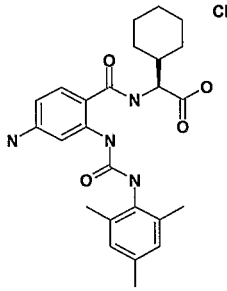
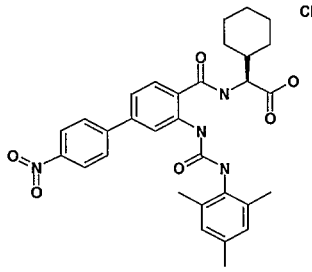
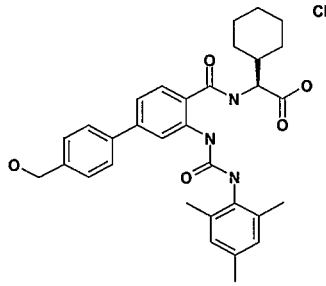
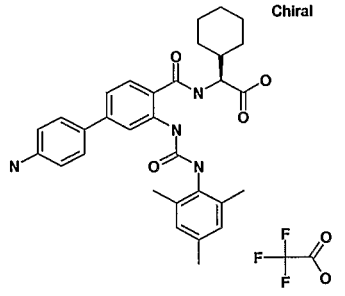
170		*N*{[4chloro2({[(2,6dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}glycine	374 (M-H)	2.91
171	 Chiral	(2*S*)-({[4-Chloro-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	532 (M-H)	0.33
172	 Chiral	(2*S*)-({[4-chloro-2-({[(2-chloro-6-methylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	476 (M-H)	0.18
173	 Chiral	(2*S*)-({[4-Bromo-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	502,504 (M, M+2)	0.31
174	 Chiral	*N*-{[4-Chloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartic acid	432 (M-H)	0.77

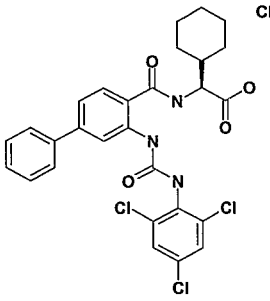
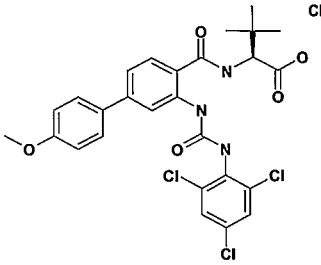
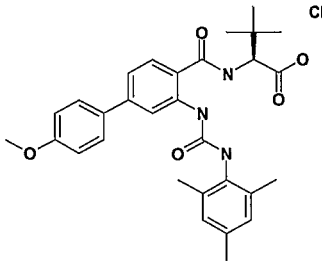
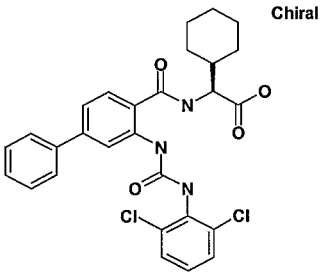
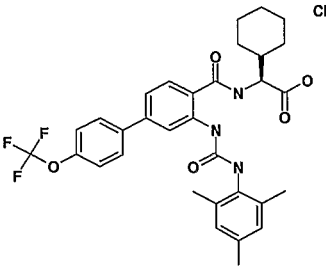
175	 Chiral	(2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	498 (M-H)	0.163
176	 Chiral	(2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-methylphenyl]carbonyl}amino)ethanoic acid	436 (M-H)	0.75
177	 Chiral	(2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	531 (M-H)	0.1
178	 Chiral	(2*S*)-cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(trifluoromethyl)phenyl]carbonyl}amino)ethanoic acid	490 (M-H)	2.33
179	 Chiral	(2*S*)-({[4-Chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	470 (M-H)	0.035

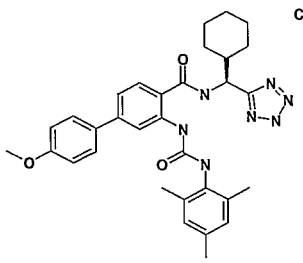
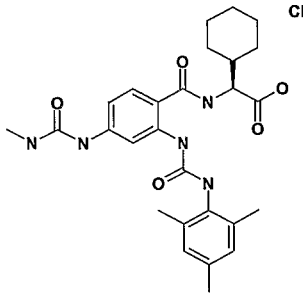
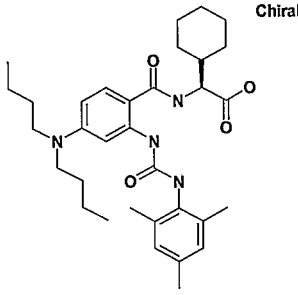
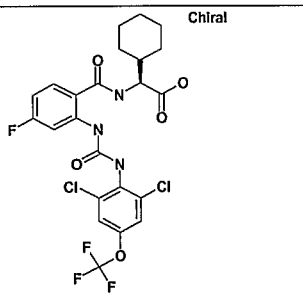
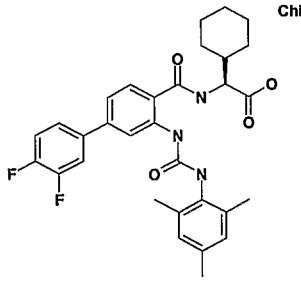
180	 Chiral	(2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	490 (M-H)	0.094
181	 Chiral	(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-pyridinyl)phenyl]carbonyl}amino)ethanoic acid	499 (M-H)	0.099
182	 Chiral	: (2*S*)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	512 (M-H)	0.017
183	 Chiral	(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(2-thienyl)phenyl]carbonyl}amino)ethanoic acid	504 (M-H)	0.1
184	 Chiral	(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-thienyl)phenyl]carbonyl}amino)ethanoic acid	504 (M-H)	0.22

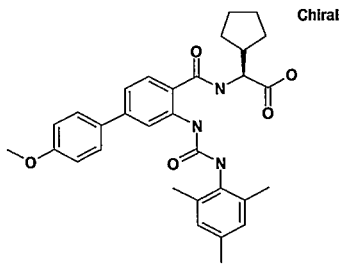
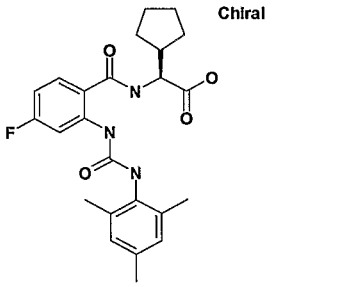
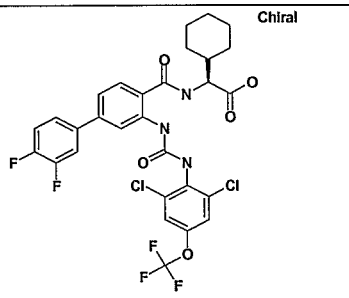
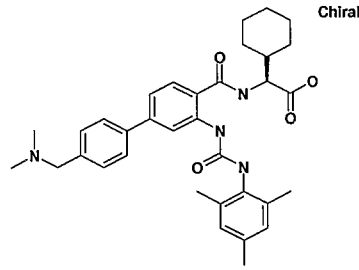
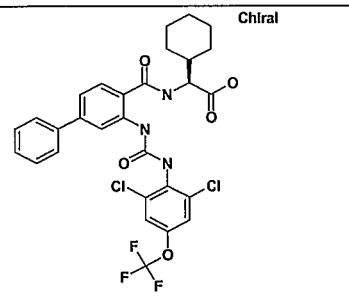
185	 Chiral	(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(4-pyridinyl)phenyl]carbonyl}amino)ethanoic acid	501 (M+H)	0.17
186	 Chiral	(2*S*)-Cyclohexyl{[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-4-biphenylyl)carbonyl]amino}ethanoic acid	573 (M)	0.341
187	 Chiral	(2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-hydroxy-4-biphenylyl]carbonyl}amino)ethanoic acid	516 (M+H)	0.034
188	 Chiral	(2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}amino)ethanoic acid	534 (M-H)	0.074
189	 Chiral	(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(5-pyrimidinyl)phenyl]carbonyl}amino)ethanoic acid	500 (M-H)	0.33

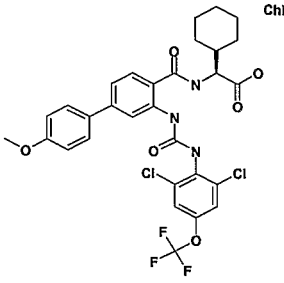
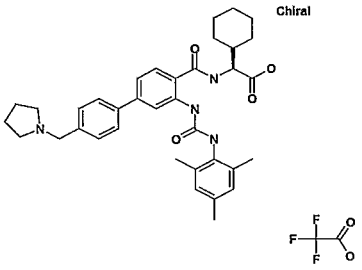
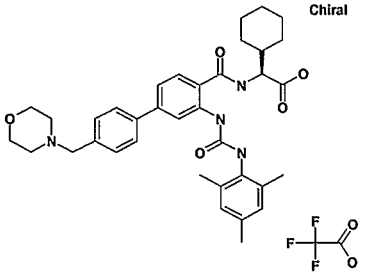
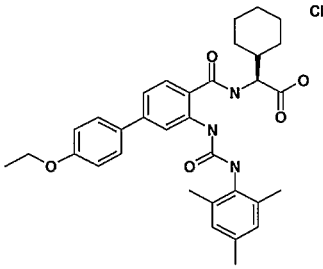
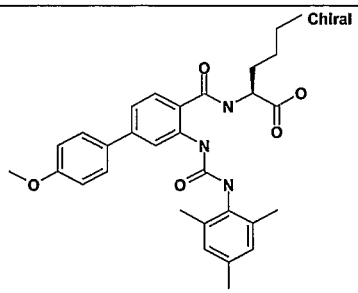
190		(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid	440 (M-H)	0.7
191		(2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid	530 (M+H)	0.032
192		(2*S*)-Cyclohexyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	456 (M+H)	0.12
193		(2*S*)-Cyclohexyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	542 (M-H)	0.007
194		2S)-Cyclohexyl({[4'-hydroxy-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	530 (M+H)	0.011

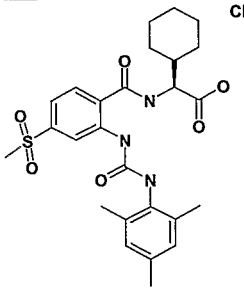
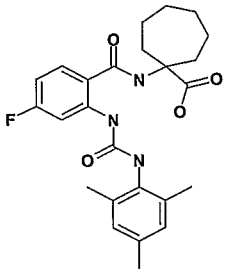
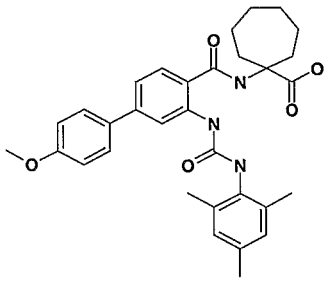
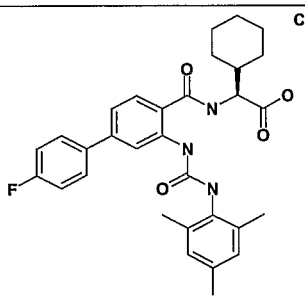
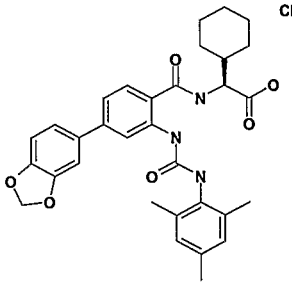
195		(2*S*)-Cyclohexyl({[4-nitro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	483 (M+H)	0.55
196		(2*S*)-({[4-Amino-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	453 (M+H)	0.11
197		(2*S*)-Cyclohexyl({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	559 (M+H)	0.014
198		(2*S*)-Cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	542 (M-H)	0.027
199		(2*S*)-({[4'-Amino-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid	529 (M+H)	0.004

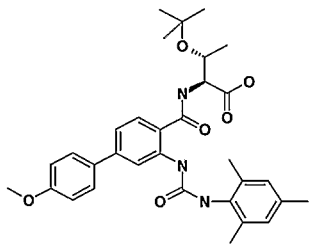
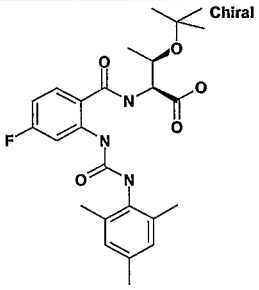
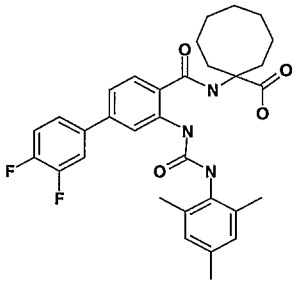
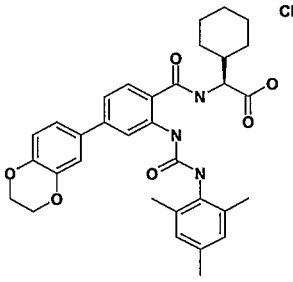
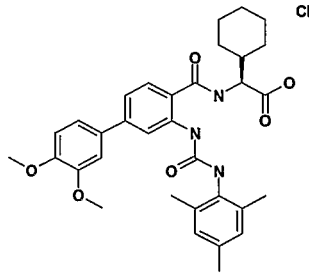
200	 Chiral	(2*S*)-Cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	574 (M)	0.13
201	 Chiral	3-Methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valine	577 (M-H)	0.67
202	 Chiral	3-Methyl-*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-valine	518 (M+H)	0.14
203	 Chiral	(2*S*)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	538 (M-H)	0.075
204	 Chiral	(2*S*)-Cyclohexyl({[4'-[(trifluoromethyl)oxy]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	598 (M+H)	0.19

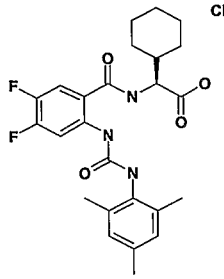
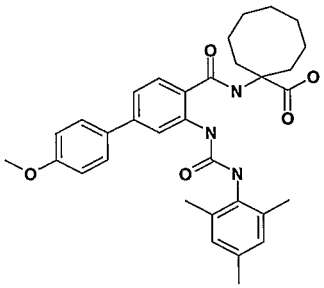
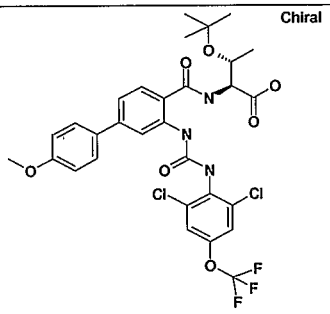
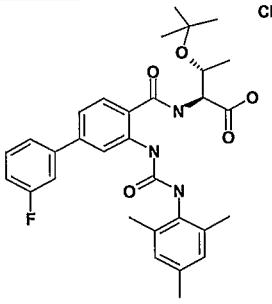
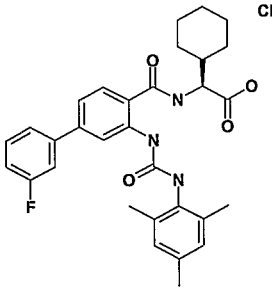
205	 Chiral	*N*-[(*S*)-cyclohexyl(1*H*-tetrazol-5-yl)methyl]-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylcarboxamide	566 (M-H)	0.14
206	 Chiral	(2*S*)-Cyclohexyl({[4-{[(methylamino)carbonyl]amino}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	510 (M+H)	0.096
207	 Chiral	(2*S*)-Cyclohexyl({[4-(dibutylamino)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	565 (M+H)	16.1
208	 Chiral	(2*S*)-Cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]amino}ethanoic acid	564 (M-H)	0.13
209	 Chiral	(2*S*)-Cyclohexyl({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	550 (M+H)	0.014

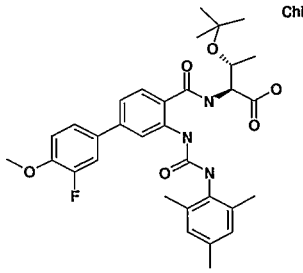
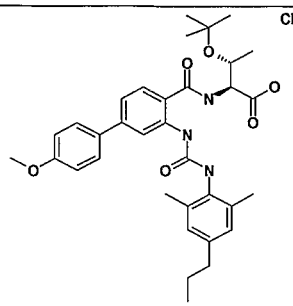
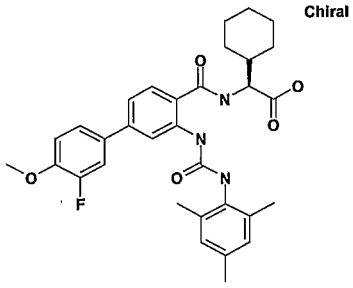
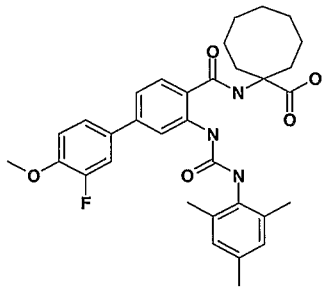
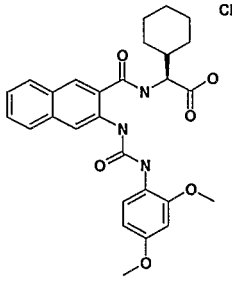
210		(2*S*)-Cyclopentyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) ethanoic acid	528 (M-H)	0.014
211		(2*S*)-Cyclopentyl({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	440 (M-H)	0.29
212		(2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3',4'-difluoro-4-biphenylyl)carbonyl]amino} ethanoic acid	658 (M-H)	0.017
213		(2*S*)-Cyclohexyl({[4'-[(dimethylamino)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) ethanoic acid	571 (M+H)	0.024
214		(2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-biphenylyl)carbonyl]amino} ethanoic acid	622 (M-H)	0.023

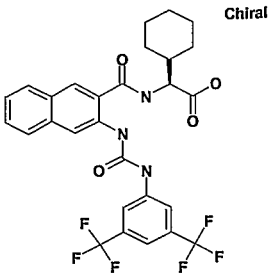
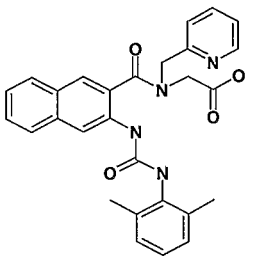
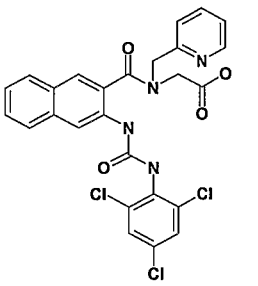
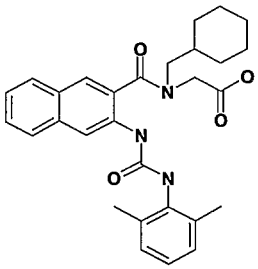
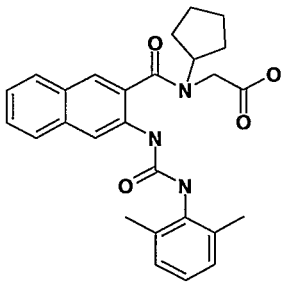
215		(2*S*)-Cyclohexyl({[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}amino) ethanoic acid	652 (M-H)	0.009
216		(2*S*)-Cyclohexyl({[4'-(1-pyrrolidinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) ethanoic acid	595 (M-H)	0.006
217		(2*S*)-cyclohexyl({[4'-(4-morpholinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) ethanoic acid	611 (M-H)	0.009
218		(2*S*)-Cyclohexyl({[4'-(ethyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) ethanoic acid	556 (M-H)	0.007
219		*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-norleucine	516 (M-H)	0.015

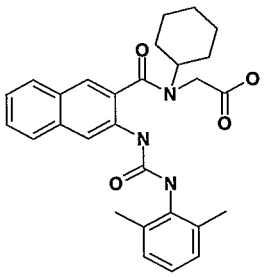
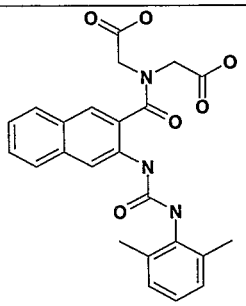
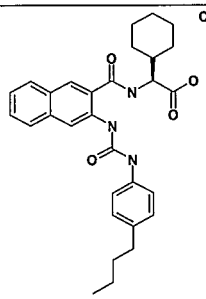
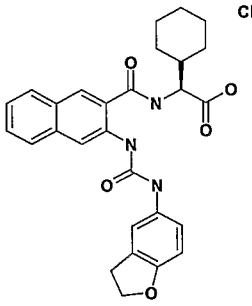
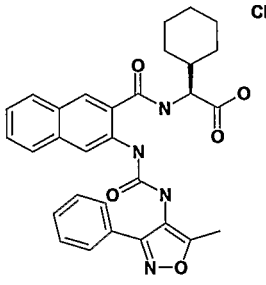
220	 Chiral	(2*S*)-Cyclohexyl({[4-(methylsulfonyl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	514 (M-H)	1.96
221		-({[4-Fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)cycloheptanecarboxylic acid	454 (M-H)	0.3
222		1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) cycloheptanecarboxylic acid	542 (M-H)	0.024
223	 Chiral	(2*S*)-Cyclohexyl({[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) ethanoic acid	530 (M-H)	0.009
224	 Chiral	(2*S*)-({[4-(1,3-Benzodioxol-5-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	556 (M-H)	0.003

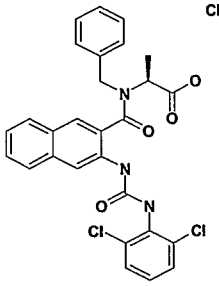
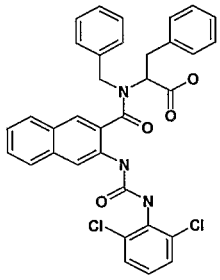
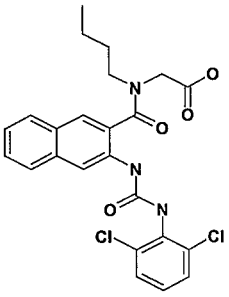
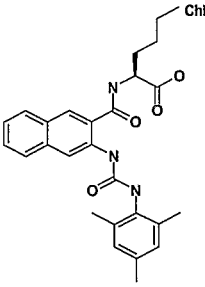
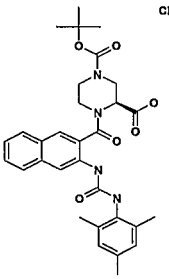
225	 Chiral	O-(1,1-Dimethylethyl)-N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine	560 (M-H)	0.002
226	 Chiral	*O*-(1,1-Dimethylethyl)-*N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-threonine	472 (M-H) (APCI)	0.53
227		1-({[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) cyclooctanecarboxylic acid	564 (M+H)	0.001
228	 Chiral	(2*S*)-Cyclohexyl({[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	572 (M+H)	0.004
229	 Chiral	(2*S*)-({[3',4'-Bis(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid	574 (M+H)	0.003

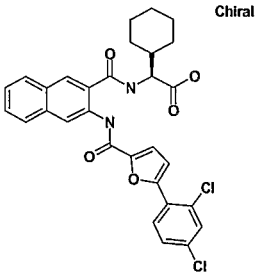
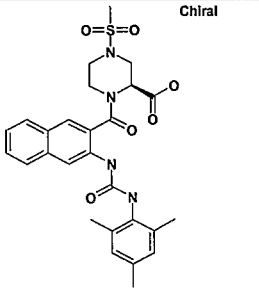
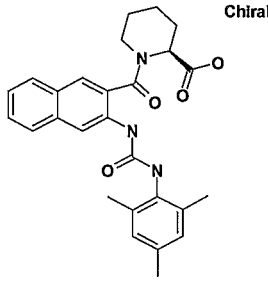
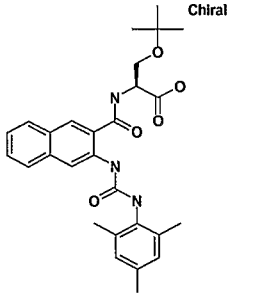
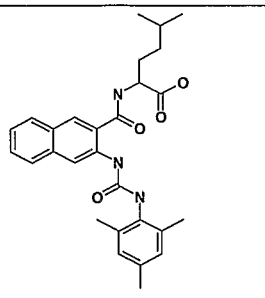
230	 Chiral	(2*S*)-Cyclohexyl({[4,5-difluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid	474 (M+H)	0.058
231		1-({[4'-(Methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) cyclooctanecarboxylic acid	558 (M+H)	0.001
232	 Chiral	N-{[3-{[({2,6-Dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine	672 (M+H)	0.007
233	 Chiral	O-(1,1-Dimethylethyl)-N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine	550 (M+H)	0.023
234	 Chiral	(2S)-Cyclohexyl({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino) ethanoic acid	532 (M+H)	0.024

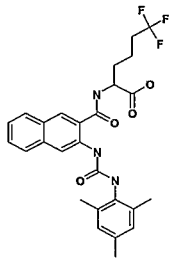
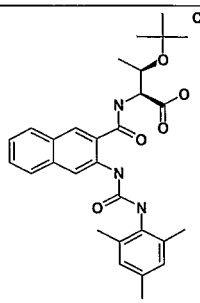
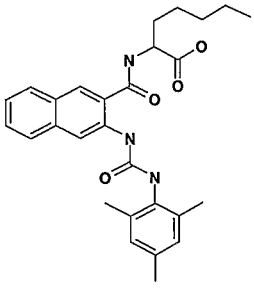
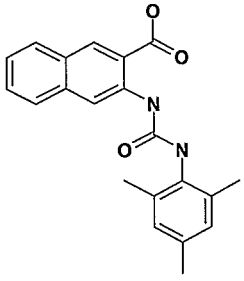
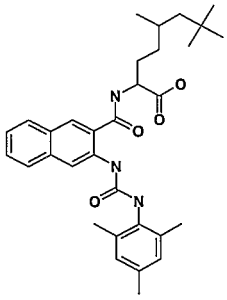
235	 Chiral	O-(1,1-Dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine	580 (M+H)	0.013
236	 Chiral	O-(1,1-Dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-threonine	590 (M+H)	0.004
237	 Chiral	(2S)-Cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	562 (M+H) (APCI)	0.02
238		1-({[3'-Fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid	574 (M-H)	0.01
239	 Chiral	(2S)-[({3-[({[2,4-bis(methyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoic acid	506 (M+H)	2.38

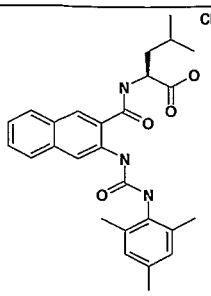
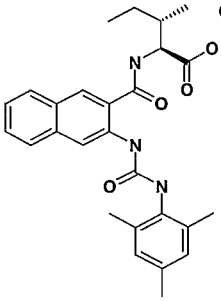
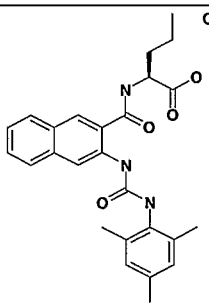
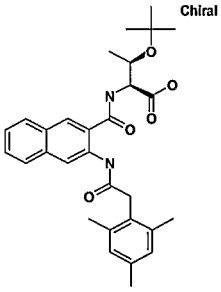
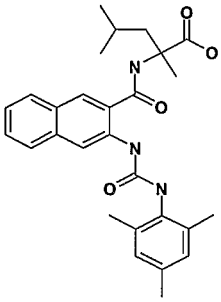
240	 Chiral	(2S)-[({3-[({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino](cyclohexyl)ethanoic acid	582 (M+H)	8.18
241		N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-N-(2-pyridinylmethyl)glycine	483 (M+H)	3.61
242		N-(2-pyridinylmethyl)-N-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine	557 (M+H)	2.86
243		N-(cyclohexylmethyl)-N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine	488 (M+H)	1.77
244		N-cyclopentyl-N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine	460 (M+H)	0.97

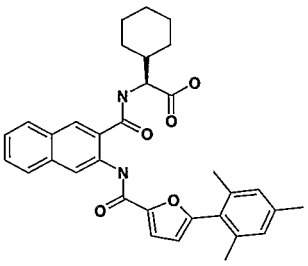
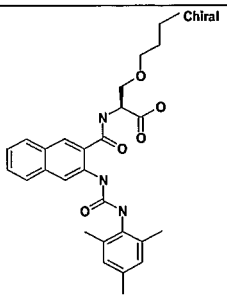
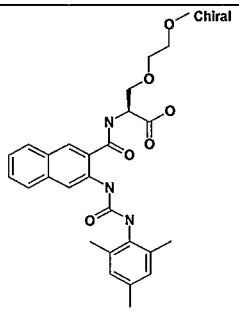
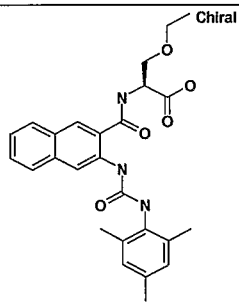
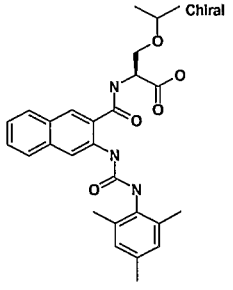
245		N-cyclohexyl-N-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine	474 (M+H)	2.13
246		2,2'-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}imino)diacetic acid (non-preferred name)	450 (M+H)	2.12
247	Chiral 	(2S)-({[3-({[(4-butylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	502 (M+H)	10.42
248	Chiral 	(2S)-cyclohexyl{[(3-{[(2,3-dihydro-1-benzofuran-5-ylamino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid	488 (M+H)	15.13
249	Chiral 	(2S)-cyclohexyl({[3-({[(5-methyl-3-phenyl-4-isoxazolyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	527 (M+H)	17.4

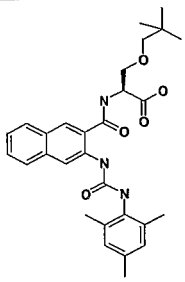
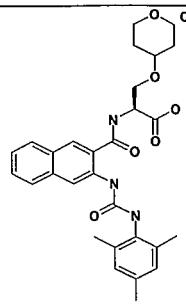
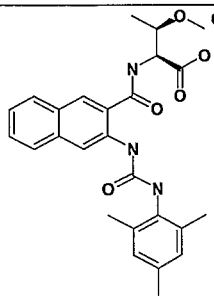
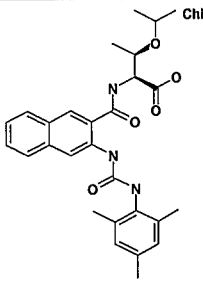
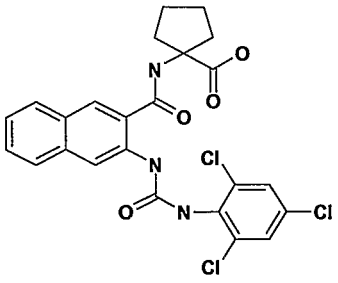
250	 Chiral	N-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-N-(phenylmethyl)-L-alanine	536 (M+H)	7.77
251		N-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-N-(phenylmethyl)phenylalanine	611 (M-H)	12.2
252		N-butyl-N-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine	488 (M+H)	0.65
253	 Chiral	N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine	462 (M+H)	0.016
254	 Chiral	(2S)-4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylic acid	561 (M+H)	0.81

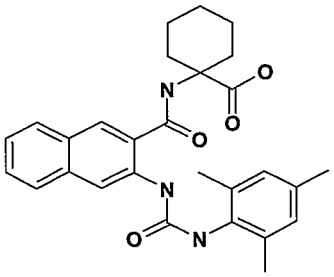
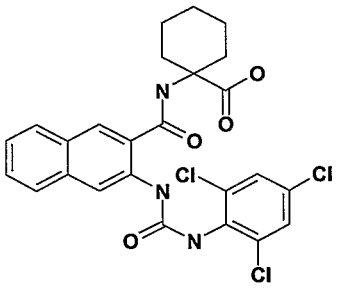
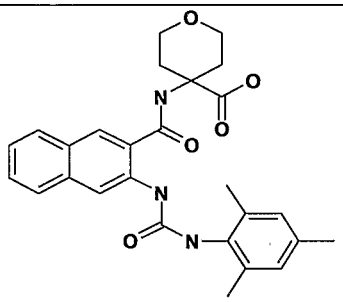
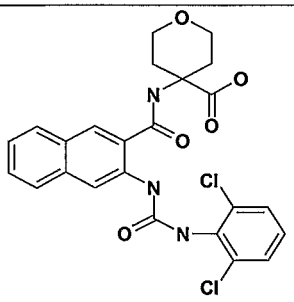
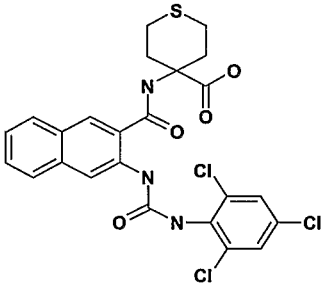
255	 Chiral	(2S)-cyclohexyl({[3-({[5-(2,4-dichlorophenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	563 (M-H)	2.6
256	 Chiral	(2S)-4-(methylsulfonyl)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperazinecarboxylic acid	539 (M+H)	17.42
257	 Chiral	(2S)-1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-piperidinecarboxylic acid	460 (M+H)	18.43
258	 Chiral	O-(1,1-dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine	492 (M+H)	0.018
259		5-methyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine	476 (M+H)	0.056

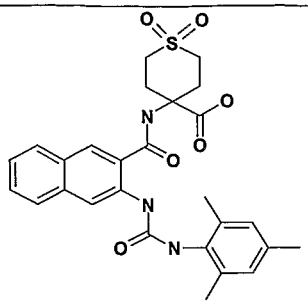
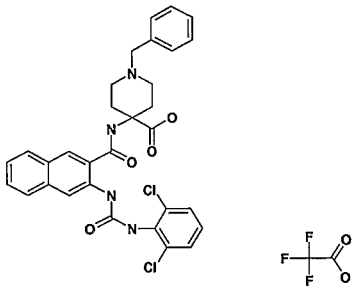
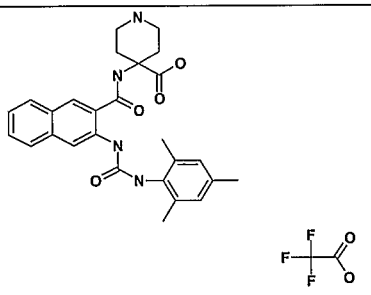
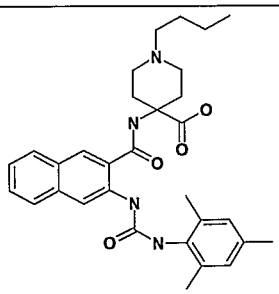
260		6,6,6-trifluoro-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine	516 (M+H)	0.067
261		O-(1,1-dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine	506 (M+H)	0.005
262		2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)heptanoic acid	476 (M+H)	0.14
263		3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxylic acid	349 (M+H)	3.46
264		5,7,7-trimethyl-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)octanoic acid	532 (M+H)	0.12

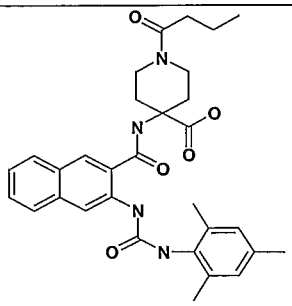
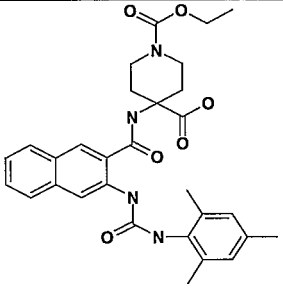
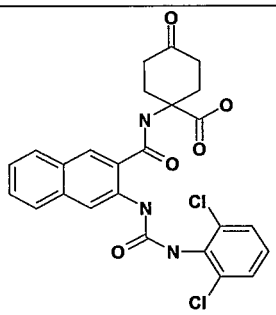
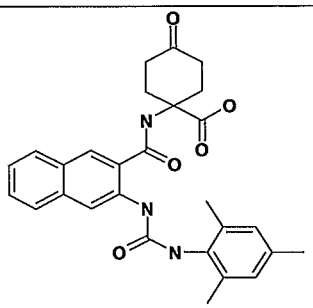
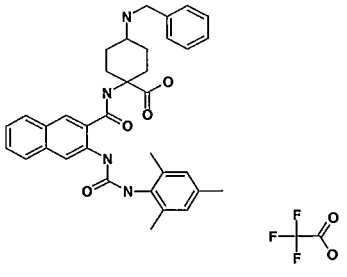
265		N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-leucine	462 (M+H)	0.07
266		N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-isoleucine	462 (M+H)	0.052
267		N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline	448 (M+H)	0.026
268		O-(1,1-dimethylethyl)-N-[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]-L-threonine	505 (M+H)	0.05
269		2-methyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}leucine	476 (M+H)	0.21

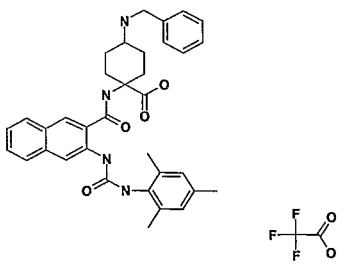
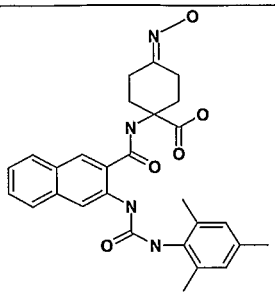
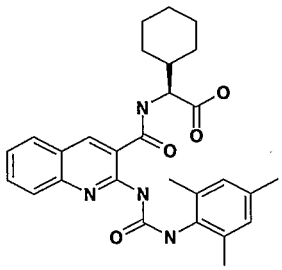
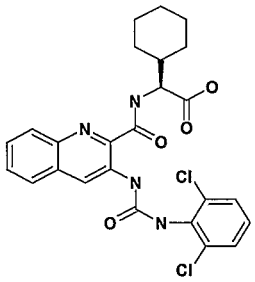
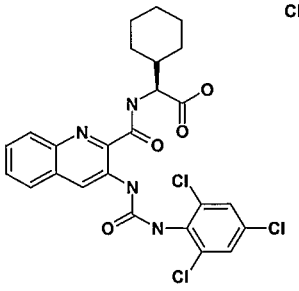
270		(2S)-cyclohexyl({[3-({[5-(2,4,6-trimethylphenyl)-2-furanyl]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	539 (M+H)	10.3
271		O-butyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine	492 (M+H)	0.053
272		O-[2-(methyloxy)ethyl]-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine	494 (M+H)	0.038
273		O-ethyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine	464 (M+H)	0.056
274		O-(1-methylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine	478 (M+H)	0.04

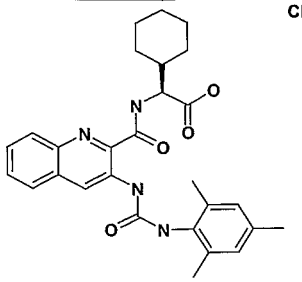
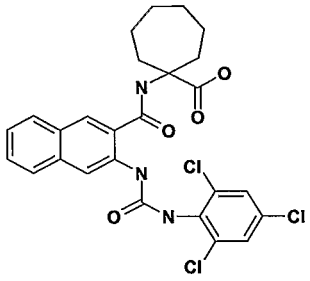
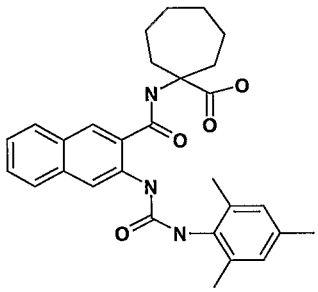
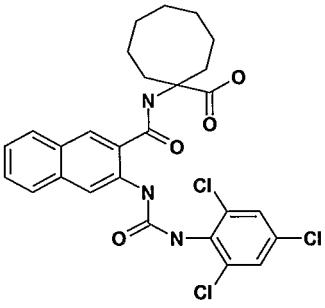
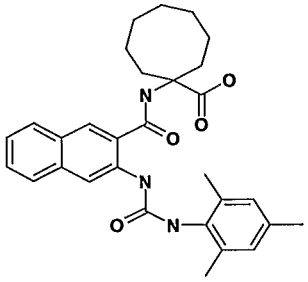
275		O-(2,2-dimethylpropyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine	506 (M+H)	0.041
276		O-(tetrahydro-2H-pyran-4-yl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine	520 (M+H)	0.045
277		O-methyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine	464 (M+H)	0.24
278		O-(1-methylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine	492 (M+H)	0.017
279		1-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylic acid	521	3

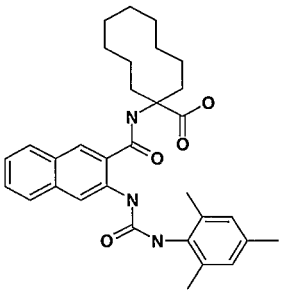
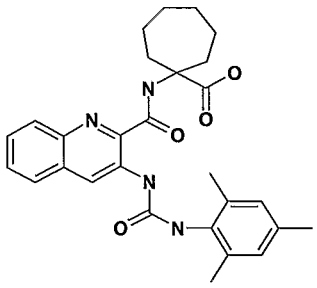
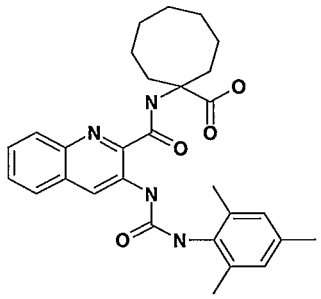
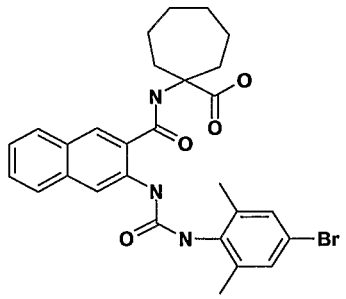
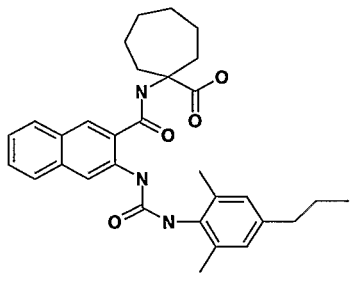
280		1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid	474	0.3
281		1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid	534	1.62
282		4-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2H-pyran-4-carboxylic acid	476	1.15
283		4-({[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2H-pyran-4-carboxylic acid	502	7.18
284		4-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2H-thiopyran-4-carboxylic acid	553	2.31

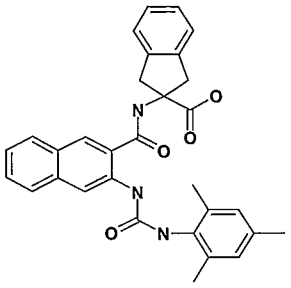
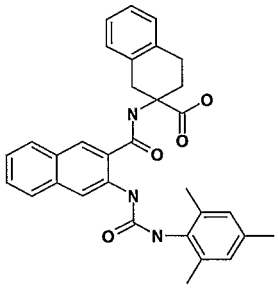
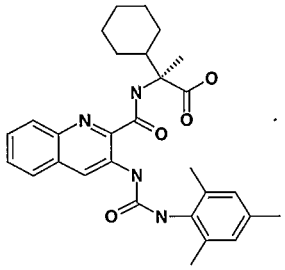
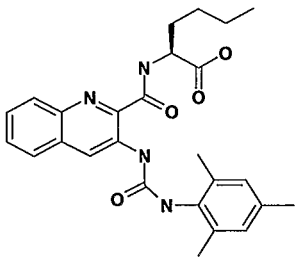
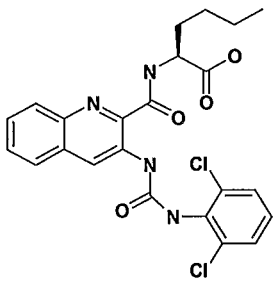
285		4-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)tetrahydro-2H-thiopyran-4-carboxylic acid 1,1-dioxide	524	3.31
286		4-({[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1-(phenylmethyl)-4-piperidinecarboxylic acid	492	1.38
287		1-{[(1,1-Dimethylethyl)oxy]carbonyl}-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid	575	0.43
288		4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid trifluoroacetate	475	6.17
289		1-Butyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid	531	4.39

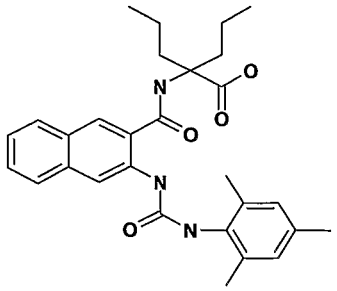
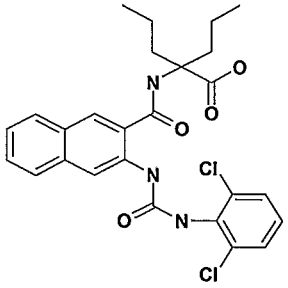
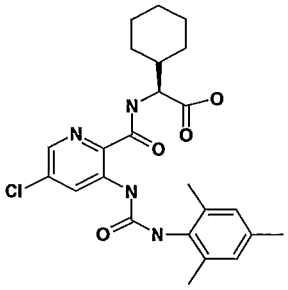
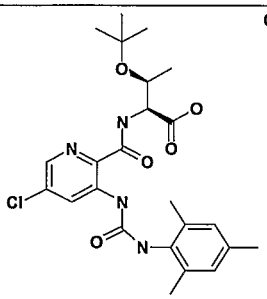
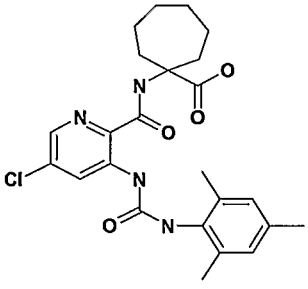
290		1-Butanoyl-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid	545	1.24
291		1-[(Ethyloxy)carbonyl]-4-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-piperidinecarboxylic acid	547	0.61
292		1-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-4-oxocyclohexanecarboxylic acid	515	6.59
293		4-Oxo-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid	488	1.67
294		4-[(phenylmethyl)amino]-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid	579	2.53

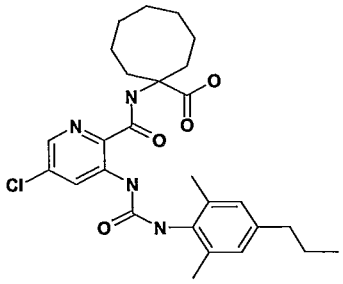
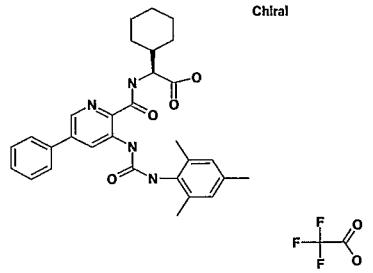
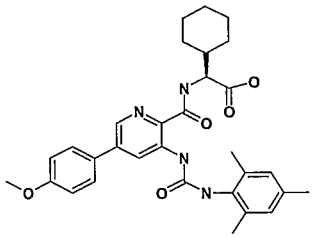
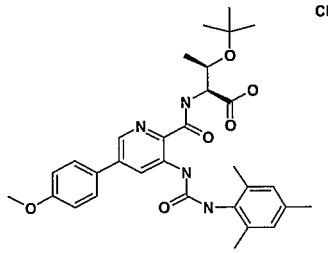
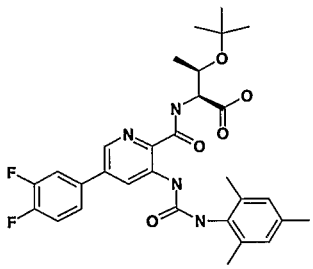
295		4-[(phenylmethyl)amino]-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid	579	5.56
296		4-(hydroxyimino)-1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclohexanecarboxylic acid	503	0.54
297	Chiral 	(2S)-cyclohexyl({[2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-quinolinyl]carbonyl}amino)ethanoic acid	489	15.6
298	Chiral 	(2S)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid	515	0.15
299	Chiral 	(2S)-Cyclohexyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid	551	0.48

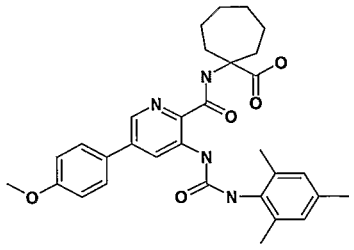
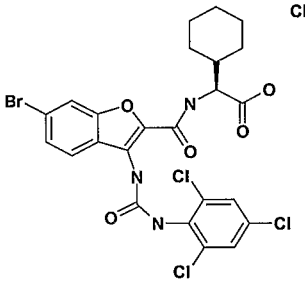
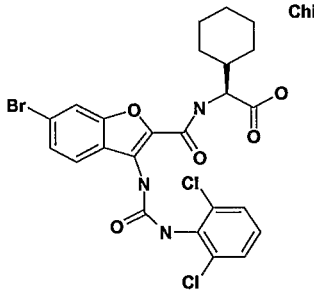
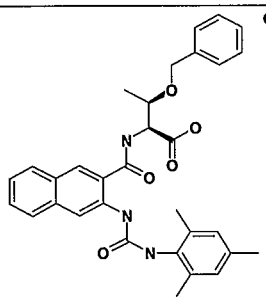
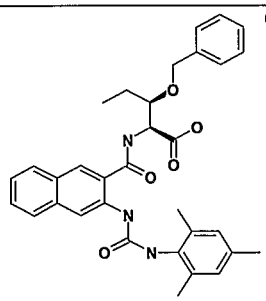
300	Chiral 	(2S)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino) ethanoic acid	489	0.027
301		1-({[3-({[(2,4,6-Trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid	549	0.35
302		1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid	488	0.036
303		1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid	563	0.057
304		1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid	502	0.005

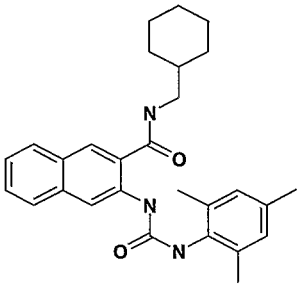
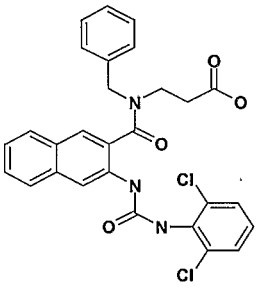
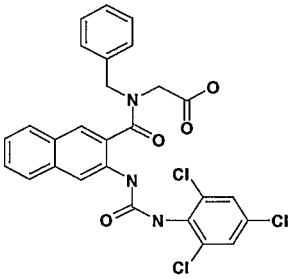
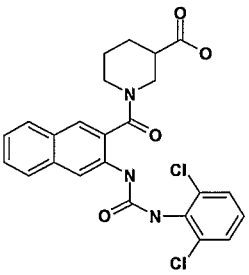
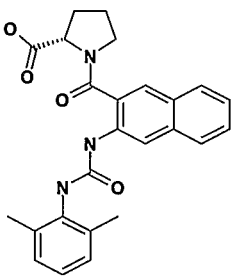
305		1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclodecanecarboxylic acid	530	0.006
306		1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cycloheptanecarboxylic acid	489	0.011
307		1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cyclooctanecarboxylic acid	503	0.002
308		1-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid	553	0.25
309		1-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid	516	0.011

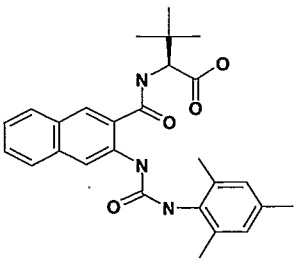
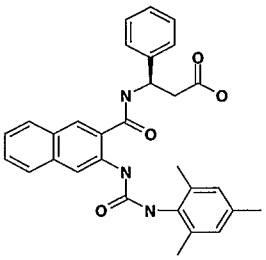
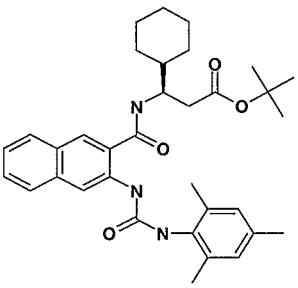
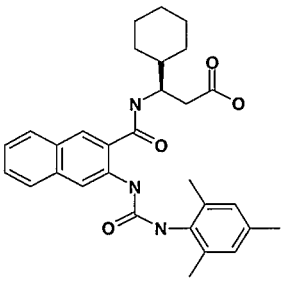
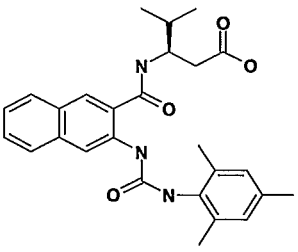
310		2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-2,3-dihydro-1H-indene-2-carboxylic acid	508	0.064
311		2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid	522	0.037
312	Chiral 	2-Cyclohexyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-D-alanine	503	0.23
313	Chiral 	N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucine	463	0.16
314	Chiral 	N-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}-L-norleucine	489	1.8

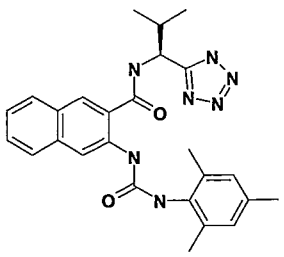
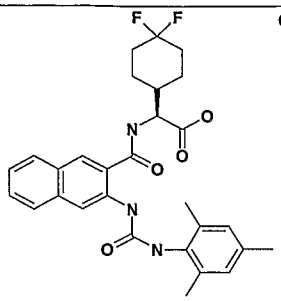
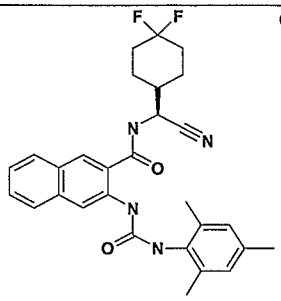
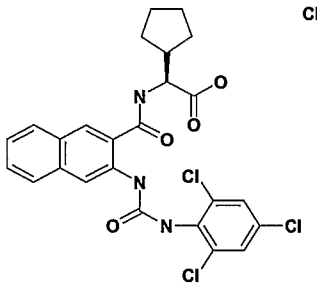
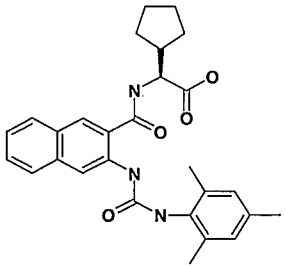
315		2-Propyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norvaline	490	0.73
316		*N*-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-2-propylnorvaline	516	0.36
317	Chiral 	(2S)-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)(cyclohexyl)ethanoic acid	473	0.92
318	Chiral 	N-{[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine	491	4.28
319		1-({[5-chloro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylic acid	473	0.47

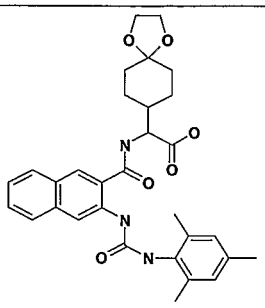
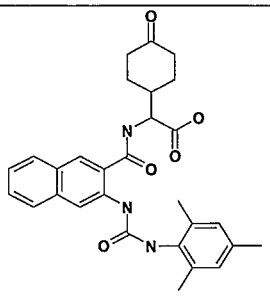
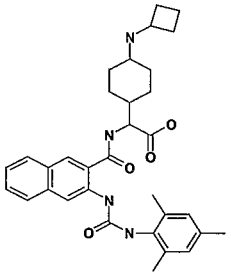
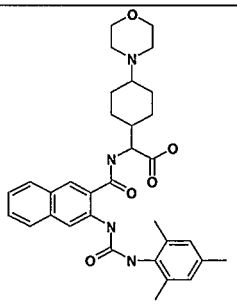
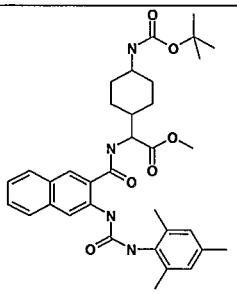
320		1-({[5-Chloro-3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylic acid	515	0.038
321	 Chiral	(2S)-Cyclohexyl({[5-phenyl-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)ethanoic acid	515	0.15
322	 Chiral	(2S)-Cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)ethanoic acid	545	0.083
323	 Chiral	O-(1,1-dimethylethyl)-N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-L-threonine	563	0.17
324	 Chiral	N-{[5-(3,4-Difluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine	569	0.47

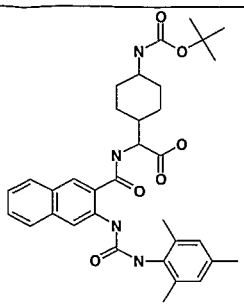
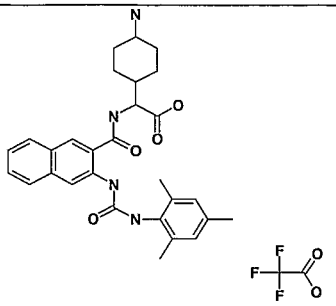
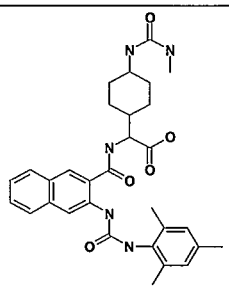
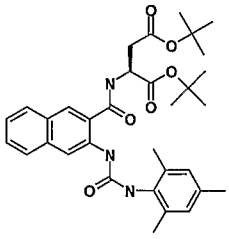
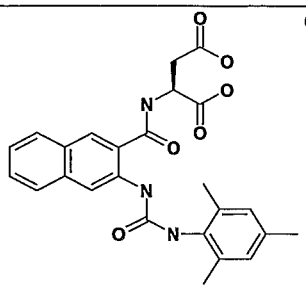
325		1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylic acid	545	0.031
326	 Chiral	(2S)-({[6-Bromo-3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoic acid	618	7.39
327	 Chiral	(2S)-({[6-Bromo-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-1-benzofuran-2-yl]carbonyl}amino)(cyclohexyl)ethanoic acid	584	9.87
328	 Chiral	O-(phenylmethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine	539	0.022
329	 Chiral	(3R)-3-[(phenylmethyl)oxy]-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline	554	0.025

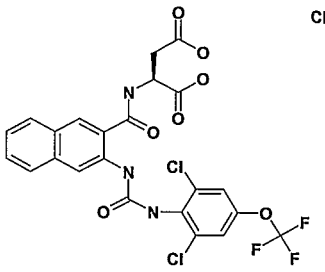
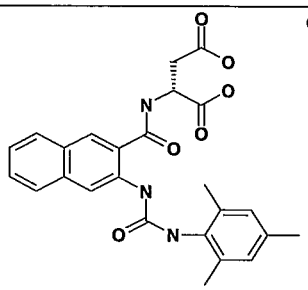
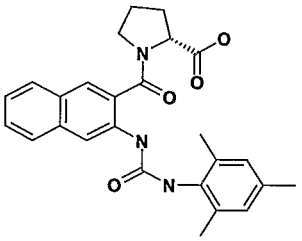
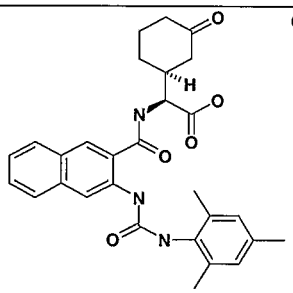
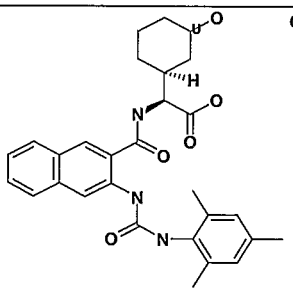
330		N-(cyclohexylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide	444	14.4
331		N-{[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-N-(phenylmethyl)- -alanine	536	2.18
332		N-(phenylmethyl)-N-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}glycine	577	4.35
333		1-{[3-({[(2,6-Dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-3-piperidinecarboxylic acid	486	9.27
334	Chiral 	1-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-proline	430 (M-H)	0.42

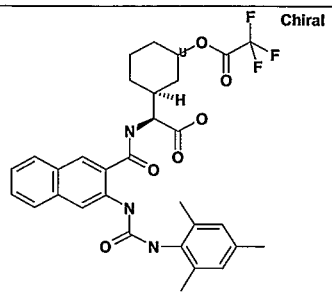
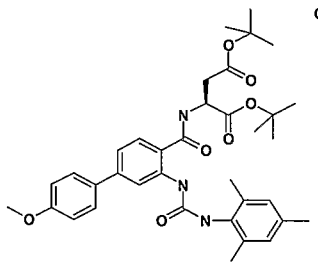
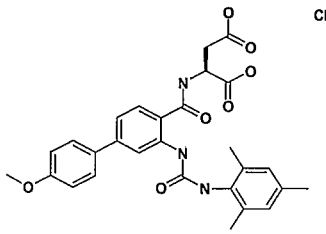
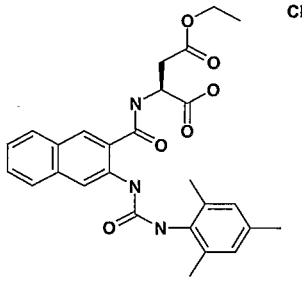
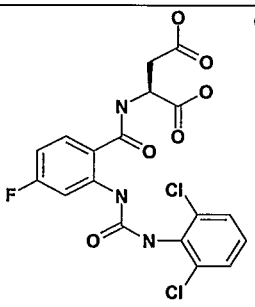
335	Chiral 	3-methyl-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-valine	460 (M-H)	0.3
336	Chiral 	(3*R*)-3-phenyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoic acid	494 (M-H)	0.61
337	Chiral 	1,1-dimethylethyl (3*R*)-3-cyclohexyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoate	556 (M-H)	5.26
338	Chiral 	(3*R*)-3-cyclohexyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)propanoic acid	500 (M-H)	2.13
339	Chiral 	(3*R*)-4-methyl-3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)pentanoic acid	460 (M-H)	1.56

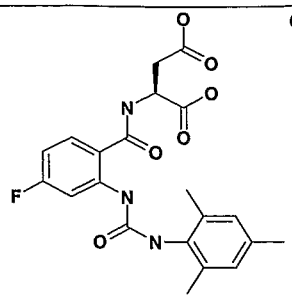
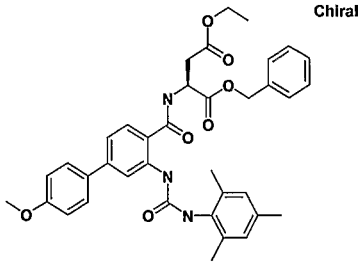
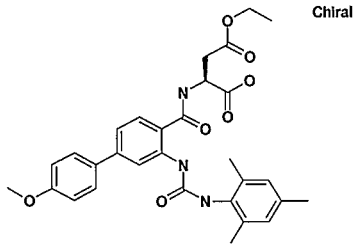
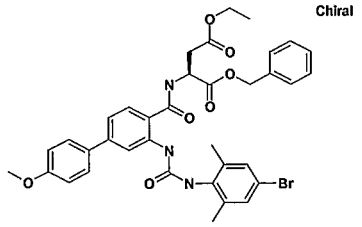
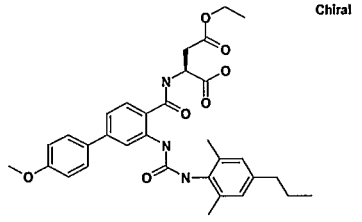
340	 Chiral	*N*-[(1*S*)-2-methyl-1-(1*H*-tetrazol-5-yl)propyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide	470 (M-H)	0.34
341	 Chiral	(2*S*)-(4,4-difluorocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	522 (M-H)	0.032
342	 Chiral	*N*-[(*S*)-cyano(4,4-difluorocyclohexyl)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenecarboxamide	503 (M-H)	8.6
343	 Chiral	(2*S*)-cyclopentyl({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	533 (M-H)	0.13
344	 Chiral	(2*S*)-cyclopentyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	472 (M-H)	0.013

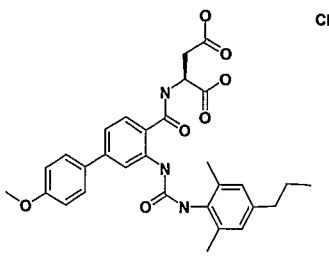
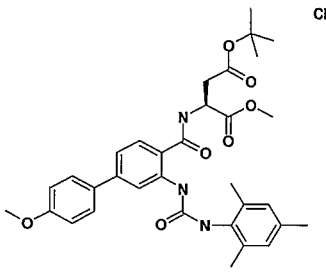
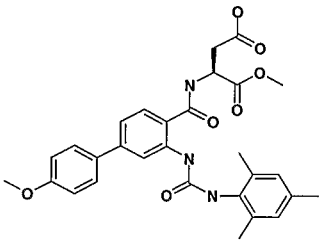
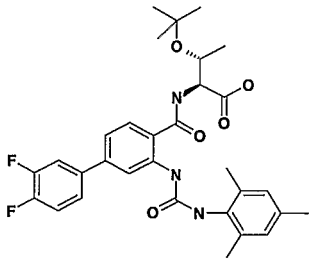
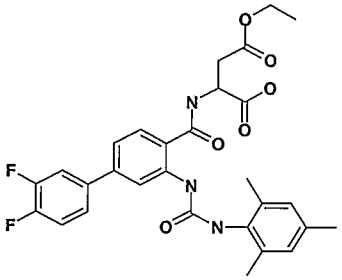
345		1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid	544 (M-H)	0.034
346		(4-oxocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid	500 (M-H)	0.17
347		(cis and trans)-[4-(cyclobutylamino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid	557 (M+H) APCI	0.81
348		(cis and trans)-[4-(4-morpholinyl)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid	572 (M-H)	1.86
349		(cis and trans)-methyl [4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetate	615 (M-H)	6.89

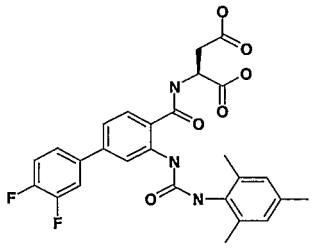
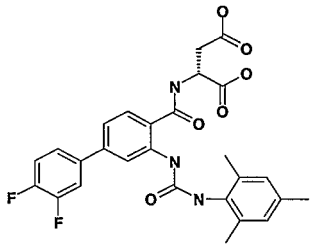
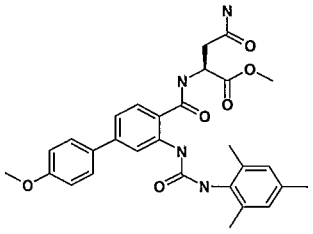
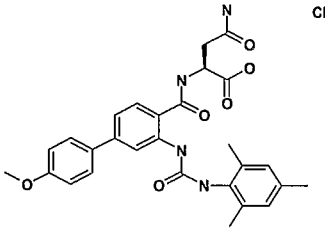
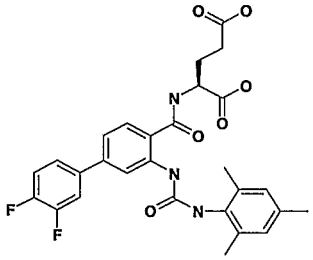
350		(cis and trans)-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid	601 (M-H)	0.044
351		(cis and trans)-(4-aminocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid trifluoroacetate	501 (M-H)	2.37
352		(cis and trans)-(4-{[(methylamino)carbonyl]amino}cyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid	558 (M-H)	0.1
353	 Chiral	bis(1,1-dimethylethyl) *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartate	574 (M-H)	5.08
354	 Chiral	*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid	462 (M-H)	0.061

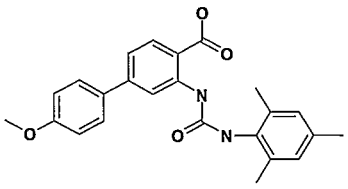
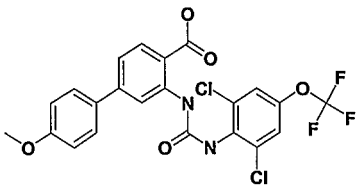
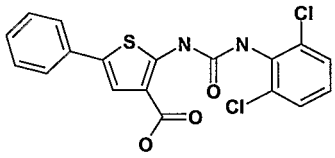
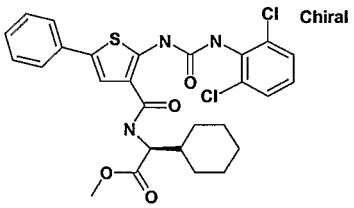
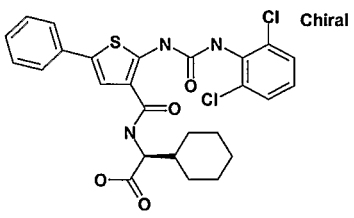
355	 Chiral	*N*-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-aspartic acid	572 (M-H)	0.014
356	 Chiral	*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-aspartic acid	462 (M-H).	0.1
357	 Chiral	1-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-proline	444 (M-H)	2.47
358	 Chiral	(2*S*)-[(1*S*)-3-oxocyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	500 (M-H)	0.075
359	 Chiral	(2*S*)-[(1*S*)-3-hydroxycyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	502 (M-H)	0.006

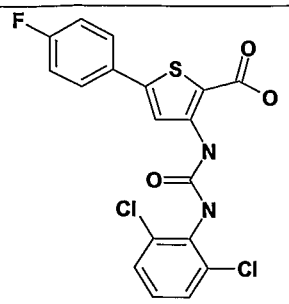
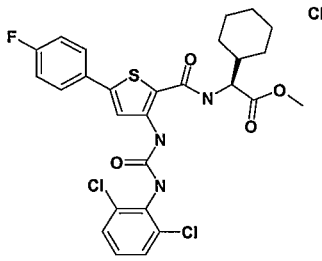
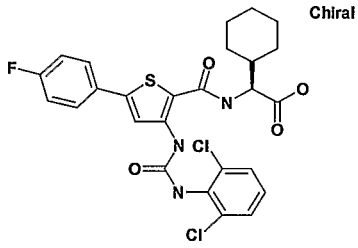
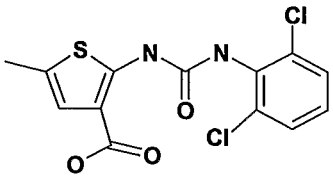
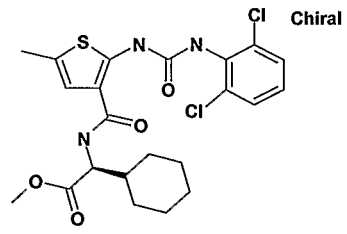
360	 Chiral	(2*S*)-{(1*S*)-3-[(trifluoroacetyl)oxy]cyclohexyl}({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	598 (M-H)	0.011
361	 Chiral	bis(1,1-dimethylethyl) *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate	630 (M-H) APCI	6.07
362	 Chiral	*N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid	518 (M-H)	0.006
363	 Chiral	(2*S*)-4-(ethyloxy)-4-oxo-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid	490 (M-H)	0.36
364	 Chiral	*N*-{[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-aspartic acid	456 (M-H)	1.28

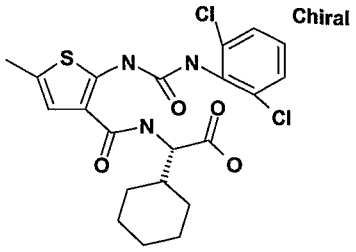
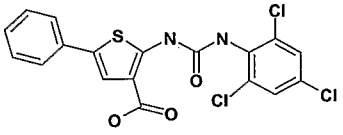
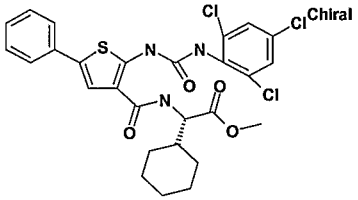
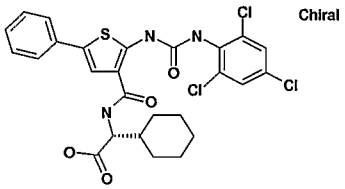
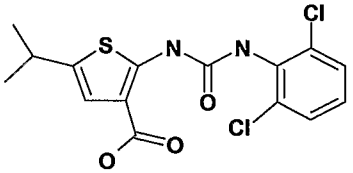
365	 Chiral	*N*-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-aspartic acid	430 (M-H)	1.68
366	 Chiral	4-ethyl 1-(phenylmethyl) *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate	638 (M+H)	11.1
367	 Chiral	(2S)-4-(ethyloxy)-2-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid	546 (M-H)	0.64
368	 Chiral	4-ethyl 1-(phenylmethyl) *N*-{[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartate	703 (M+H)	5.58
369	 Chiral	(2*S*)-2-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid	574 (M-H) APCI	0.094

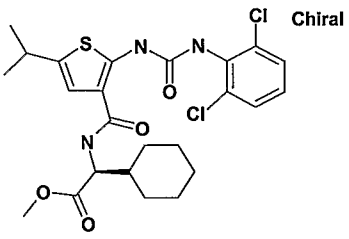
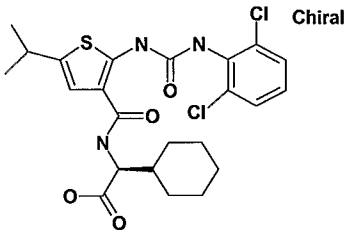
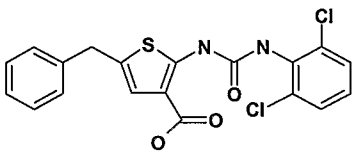
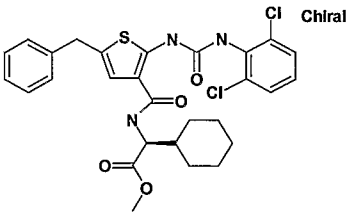
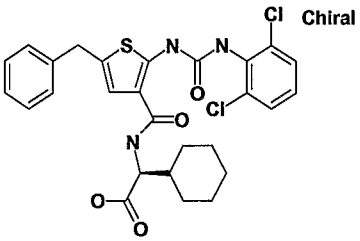
370	 Chiral	*N*-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartic acid	547 (M-H) APCI	0.002
371	 Chiral	4-(1,1-dimethylethyl) 1-methyl *N*-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartate	588 (M-H)	13.54
372	 Chiral	(3*S*)-4-(methyloxy)-3-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid	532 (M-H)	0.99
373	 Chiral	*N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine	566 (M-H)	0.005
374		(2*S*)-2-({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid	554 (M+H) APCI	0.82

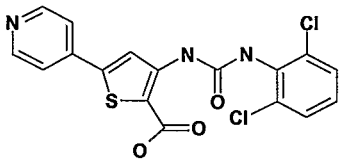
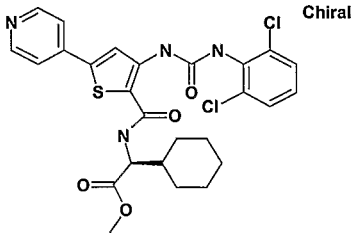
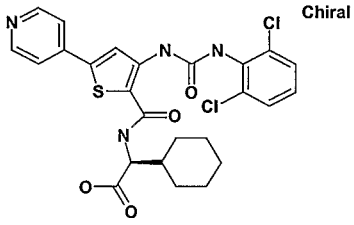
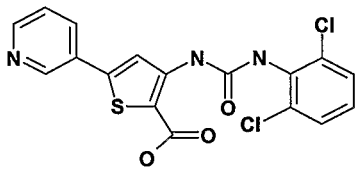
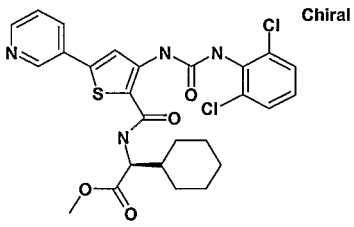
375	 Chiral	*N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid	524 (M-H) APCI	0.043
376	 Chiral	*N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-D-aspartic acid	524 (M-H) APCI	0.11
377	 Chiral	methyl N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparaginate	531 (M-H) APCI	9.13
378	 Chiral	N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparagine	517 (M-H) APCI	0.1
379	 Chiral	*N*-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-glutamic acid	538 (M-H) APCI	0.084

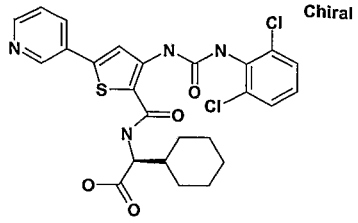
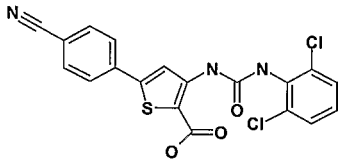
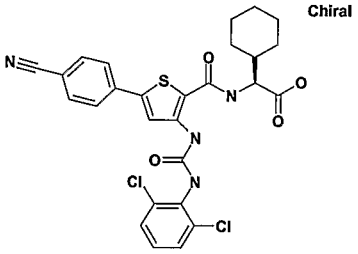
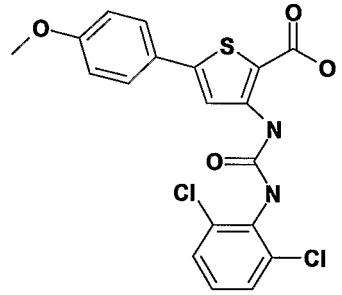
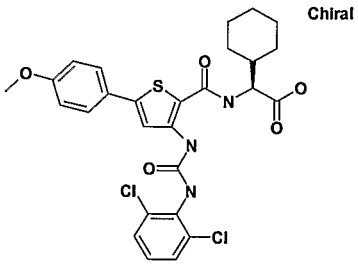
380		4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylcarboxylic acid	403 (M-H)	1.99
381		3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylcarboxylic acid	517 (M+H)	3.42
382		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thiophenecarboxylic acid	407	1.17
383		methyl (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thienyl]carbonyl}amino)ethanoate	560	2.37
384		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-3-thienyl]carbonyl}amino)ethanoic acid	555	0.23

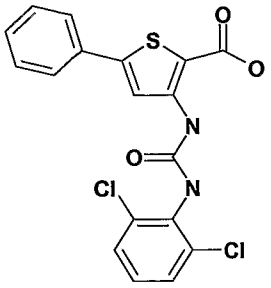
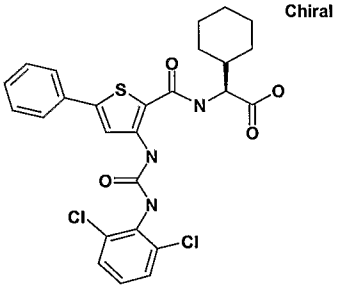
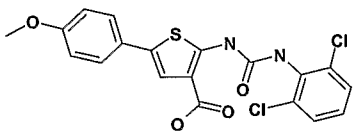
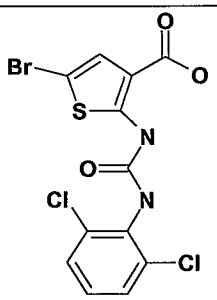
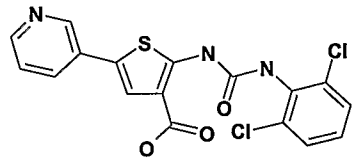
385		3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thiophenecarboxylic acid	425	1.14
386		methyl (2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thienyl]carbonyl}amino)ethanoate	578	4.3
387		(2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-2-thienyl]carbonyl}amino)ethanoic acid	564	0.43
388		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thiophenecarboxylic acid	345	19.69
389		methyl (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thienyl]carbonyl}amino)ethanoate	498	15.6

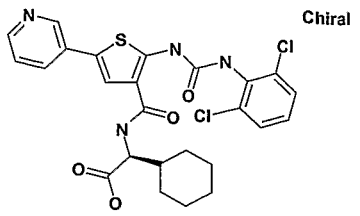
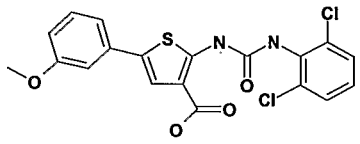
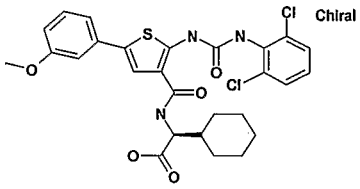
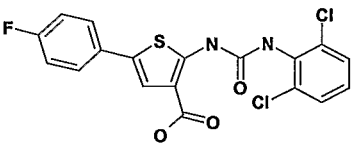
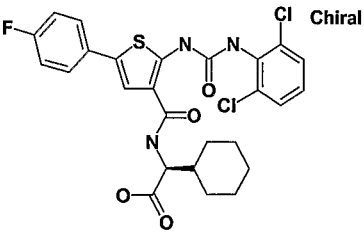
390		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-methyl-3-thienyl]carbonyl}amino)ethanoic acid	484	17.51
391		5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid	441	6.78
392		methyl (2S)-cyclohexyl({[5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoate	594	1.32
393		(2R)-cyclohexyl({[5-phenyl-2-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid	580	0.84
394		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thiophenecarboxylic acid	373	19.26

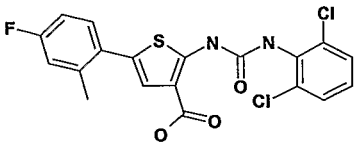
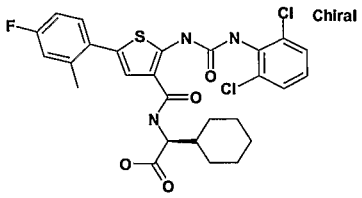
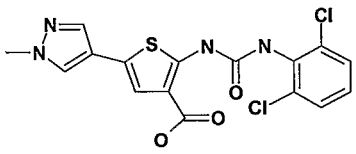
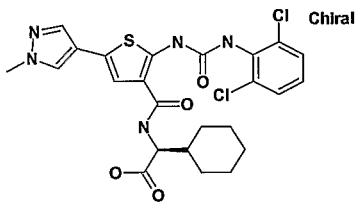
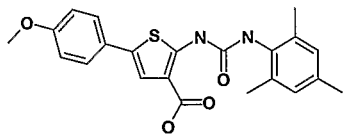
395		methyl (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thienyl]carbonyl}amino)ethanoate	526	4.49
396		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methylethyl)-3-thienyl]carbonyl}amino)ethanoic acid	580	1.75
397		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thiophenecarboxylic acid	421	14.28
398		methyl (2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thienyl]carbonyl}amino)ethanoate	575	3.06
399		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(phenylmethyl)-3-thienyl]carbonyl}amino)ethanoic acid	561	6.7

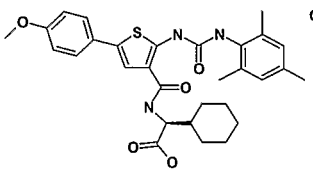
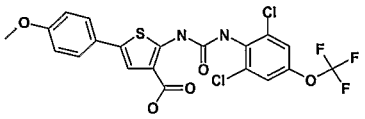
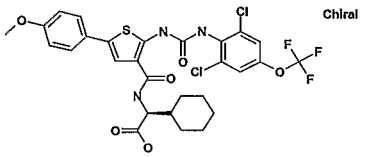
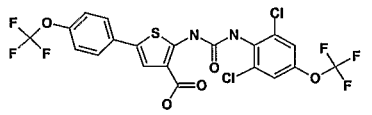
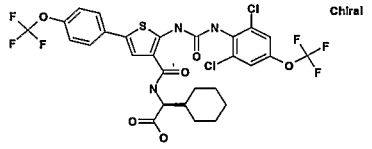
400		3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thiophenecarboxylic acid	408	1.83
401	 Chiral	methyl (2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thienyl]carbonyl}amino)ethanoate	562	14.88
402	 Chiral	(2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-pyridinyl)-2-thienyl]carbonyl}amino)ethanoic acid	548	0.17
403		3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thiophenecarboxylic acid	408	4.22
404	 Chiral	methyl (2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thienyl]carbonyl}amino)ethanoate	562	13.18

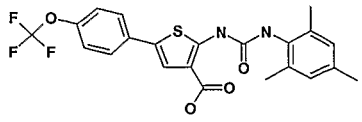
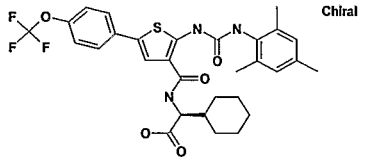
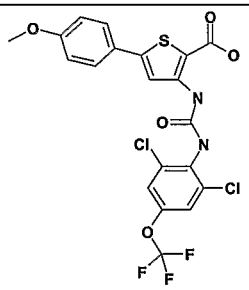
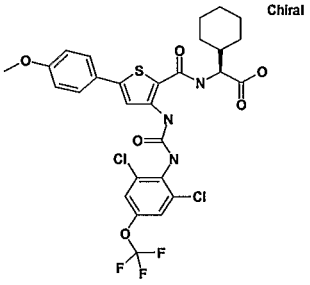
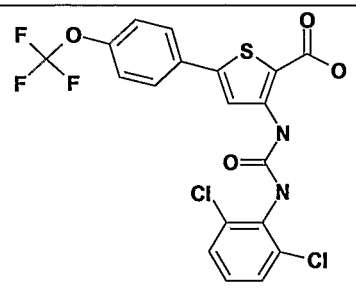
405		(2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-2-thienyl]carbonyl}amino)ethanoic acid	548	0.23
406		5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid	432	1.11
407		(2S)-({[5-(4-cyanophenyl)-3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)(cyclohexyl)ethanoic acid	571	0.37
408		3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid	437	1.15
409		(2S)-cyclohexyl[({3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid	576	0.093

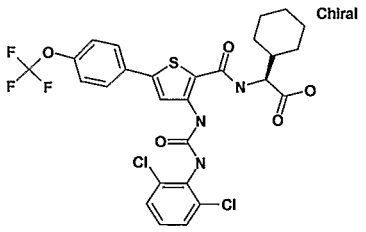
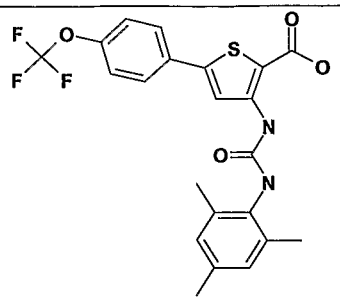
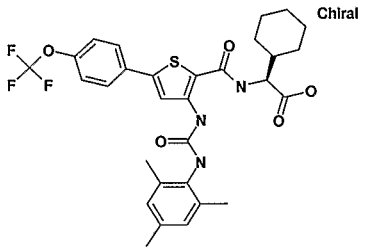
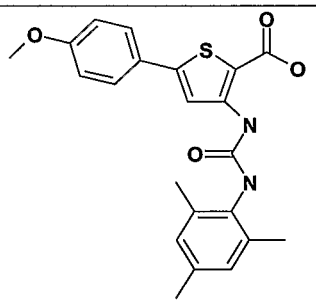
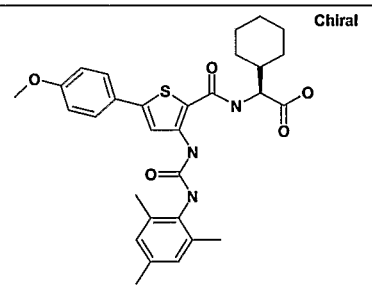
410		3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-2-thiophenecarboxylic acid	407	0.89
411		(2S)-cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-phenyl-2-thienyl]carbonyl}amino)ethanoic acid	546	0.12
412		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylic acid	437	1.04
413		5-bromo-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid	410	10.6
414		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thiophenecarboxylic acid	408	2.72

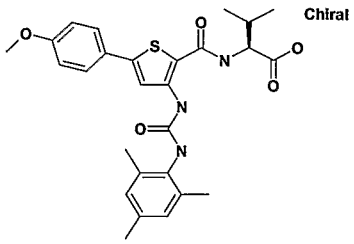
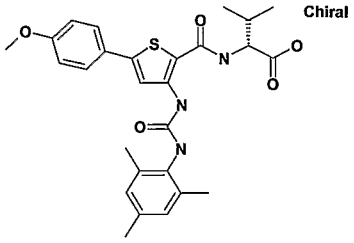
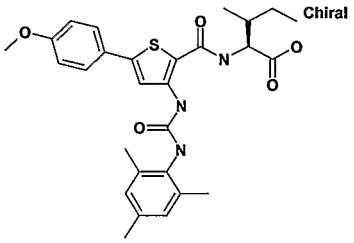
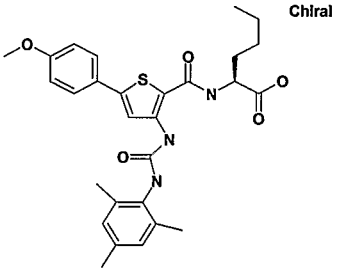
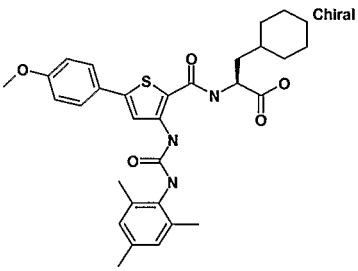
415		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(3-pyridinyl)-3-thienyl]carbonyl}amino)ethanoic acid	546	0.77
416		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thiophenecarboxylic acid	437	4.13
417		(2S)-cyclohexyl[({2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[3-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoic acid	576	0.36
418		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thiophenecarboxylic acid	425	2.97
419		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluorophenyl)-3-thienyl]carbonyl}amino)ethanoic acid	564	0.6

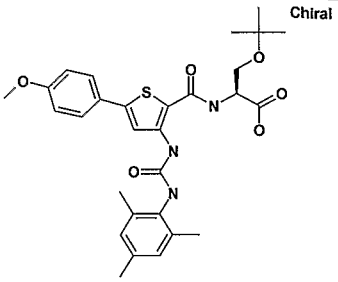
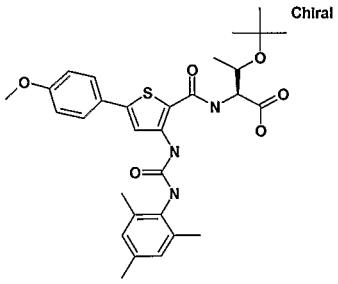
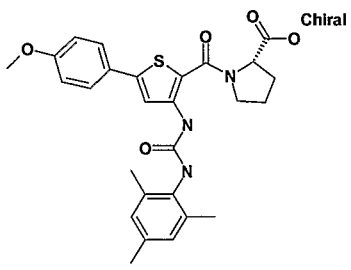
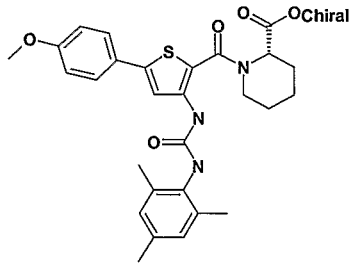
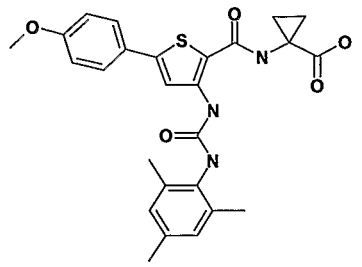
420		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thiophenecarboxylic acid	439	5.64
421		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(4-fluoro-2-methylphenyl)-3-thienyl]carbonyl}amino)ethanoic acid	564	1.39
422		2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1H-pyrazol-4-yl)-3-thiophenecarboxylic acid	411	6.34
423		(2S)-cyclohexyl({[2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-(1-methyl-1H-pyrazol-4-yl)-3-thienyl]carbonyl}amino)ethanoic acid	550	0.26
424		5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid	411	0.29

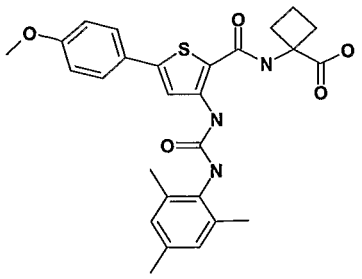
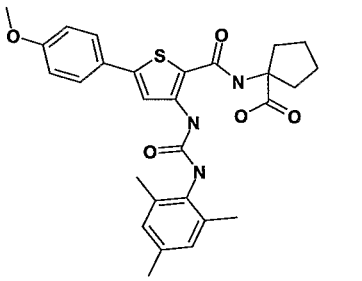
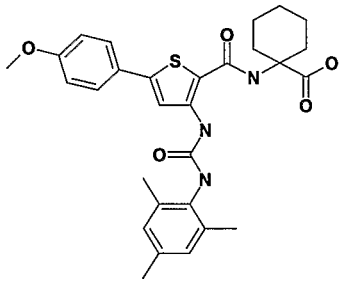
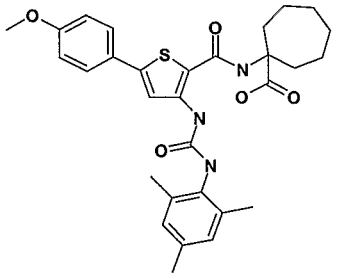
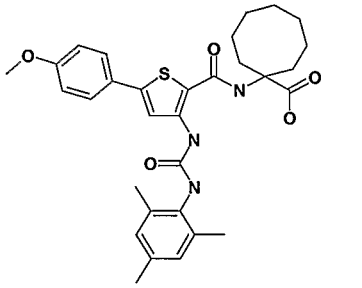
425	 Chiral	(2S)-cyclohexyl({[5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid	550	0.016
426		2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thiophenecarboxylic acid	521	1.31
427	 Chiral	(2S)-cyclohexyl[({2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoic acid	660	0.027
428		2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thiophenecarboxylic acid	575	1.22
429	 Chiral	(2S)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thienyl)carbonyl]amino}ethanoic acid	714	0.096

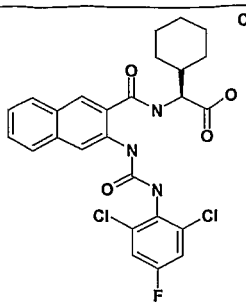
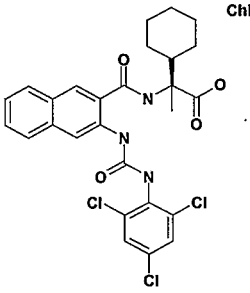
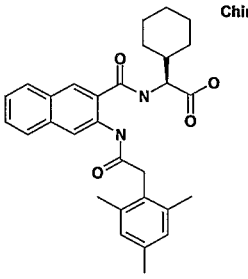
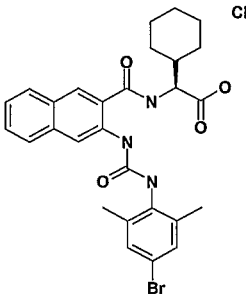
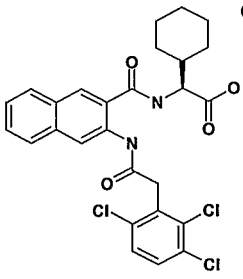
430		5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thiophenecarboxylic acid	465	0.74
431		(2S)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid	630	0.33
432		3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thiophenecarboxylic acid	521	2.7
433		(2S)-cyclohexyl[({3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid	660	0.08
434		3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thiophenecarboxylic acid	491	2.12

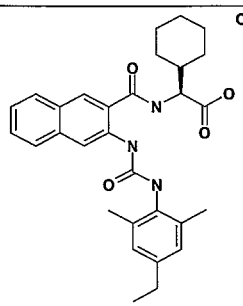
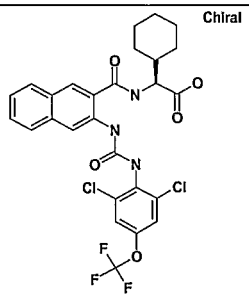
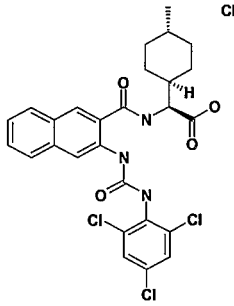
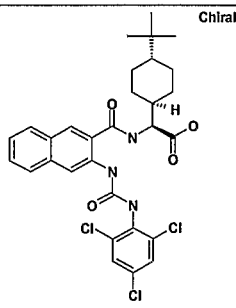
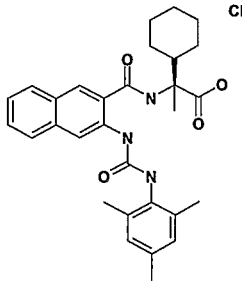
435		(2S)-cyclohexyl{[(3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-{4-[(trifluoromethyl)oxy]phenyl}-2-thienyl)carbonyl]amino}ethanoic acid	630	1.63
436		5-{4-[(trifluoromethyl)oxy]phenyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid	465	1.57
437		(2S)-cyclohexyl({[5-{4-[(trifluoromethyl)oxy]phenyl}-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoic acid	604	0.22
438		5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thiophenecarboxylic acid	411	0.33
439		(2S)-cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoic acid	550	0.012

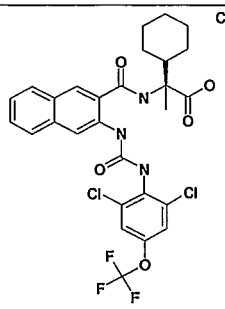
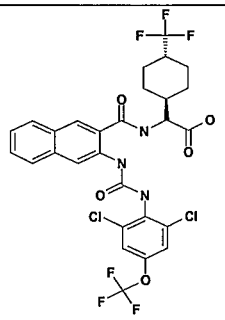
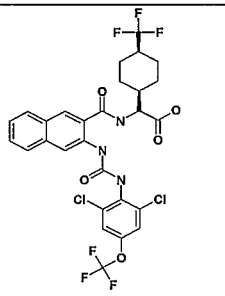
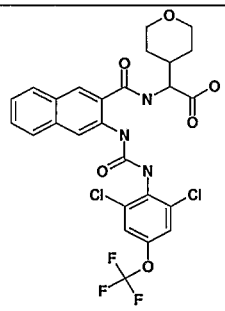
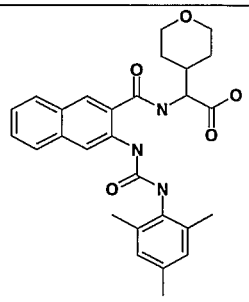
440		N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-valine	510	0.1
441		N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-D-valine	510	2.11
442		N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-isoleucine	524	0.051
443		N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-norleucine	524	0.043
444		3-cyclohexyl-N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-alanine	564	0.11

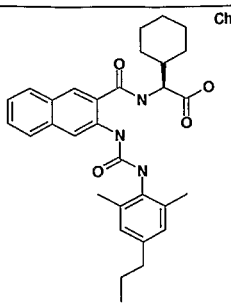
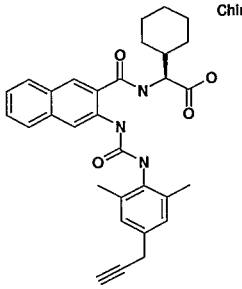
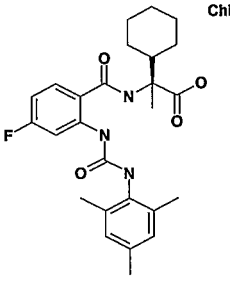
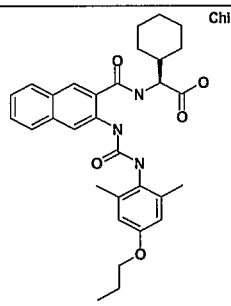
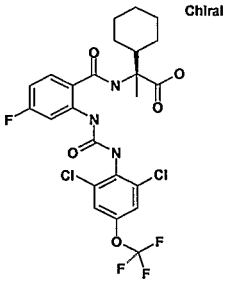
445		O-(1,1-dimethylethyl)-N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-serine	554	0.082
446		O-(1,1-dimethylethyl)-N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-threonine	568	0.031
447		1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-proline	508	0.026
448		(2S)-1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-2-piperidinecarboxylic acid	522	0.37
449		1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopropanecarboxylic acid	494	0.34

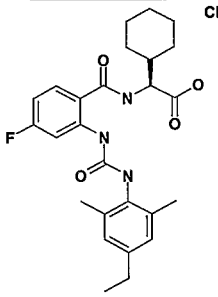
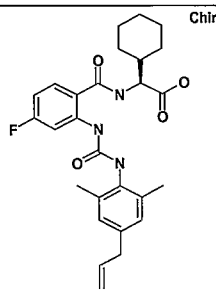
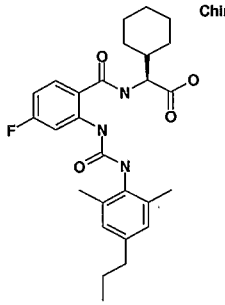
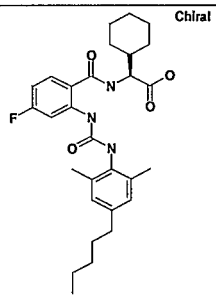
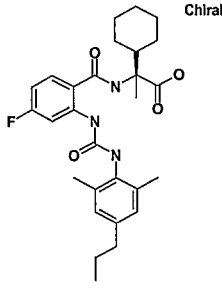
450		1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclobutanecarboxylic acid	508	0.25
451		1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopentanecarboxylic acid	522	0.047
452		1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid	536	0.003
453		1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cycloheptanecarboxylic acid	550	0.004
454		1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclooctanecarboxylic acid	564	0.001

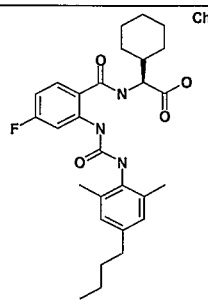
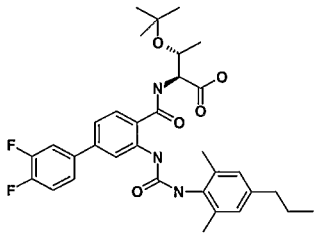
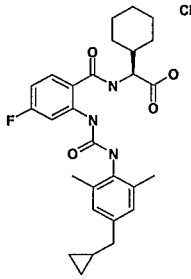
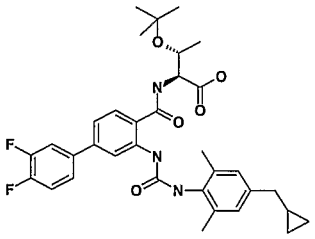
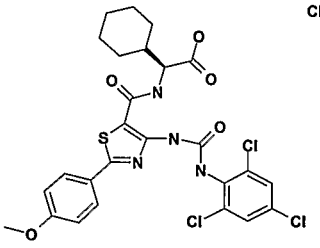
455	 Chiral	(2S)-cyclohexyl({[3-({[(2,6-dichloro-4-fluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	530 (M-H)	0.086
456	 Chiral	2-cyclohexyl-N-{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine	560 (M-H)	0.23
457	 Chiral	(2S)-cyclohexyl{[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid	485 (M-H)	0.064
458	 Chiral	(2S)-({[3-({[(4-bromo-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	550 (M-H)	0.22
459	 Chiral	(2S)-cyclohexyl{[(3-{[(2,3,6-trichlorophenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid	545 (M-H)	0.18

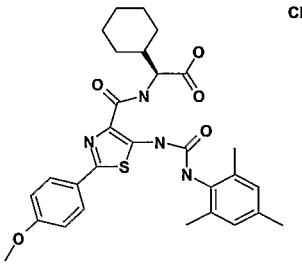
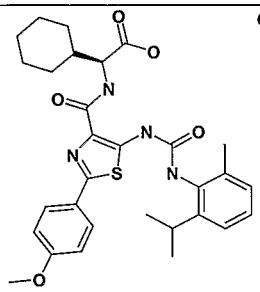
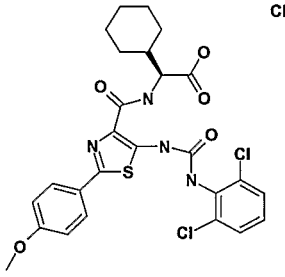
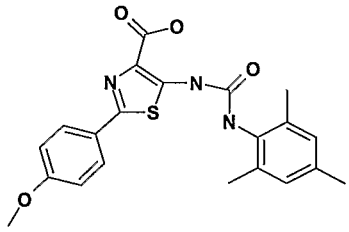
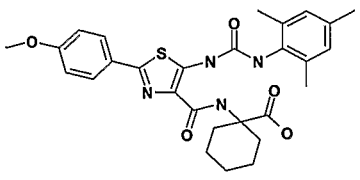
460	 Chiral	(2S)-cyclohexyl({[3-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	500 (M-H)	0.002
461	 Chiral	(2S)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid	596 (M-H)	0.005
462	 Chiral	(2S)-(trans-4-methylcyclohexyl)({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	560 (M-H)	0.056
463	 Chiral	(2S)-[trans-4-(1,1-dimethylethyl)cyclohexyl]({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	602 (M-H)	0.56
464	 Chiral	2-cyclohexyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine	500 (M-H)	0.008

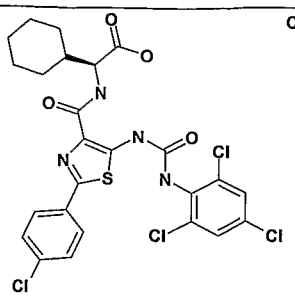
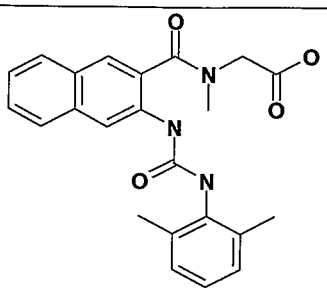
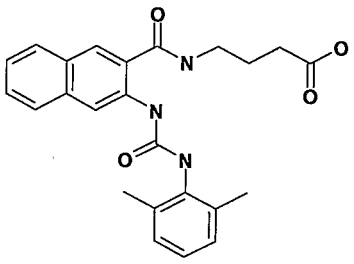
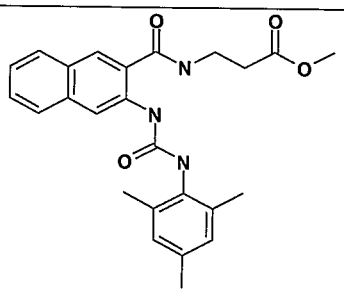
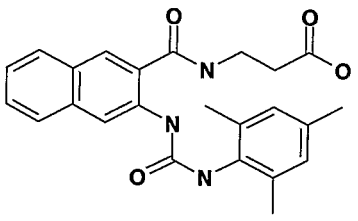
465	 Chiral	2-cyclohexyl-N-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-alanine	610 (M-H)	0.006
466		{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[trans-4-(trifluoromethyl)cyclohexyl]acetic acid	664 (M-H)	0.013
467		{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[cis-4-(trifluoromethyl)cyclohexyl]acetic acid	664 (M-H)	0.035
468		{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(tetrahydro-2H-pyran-4-yl)acetic acid	558 (M-H)	0.015
469		tetrahydro-2H-pyran-4-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid	488 (M-H)	0.059

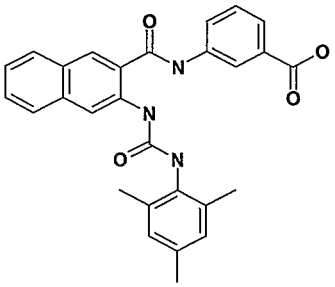
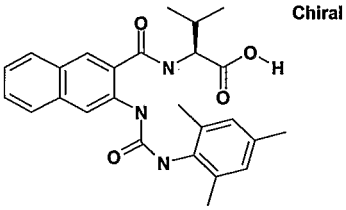
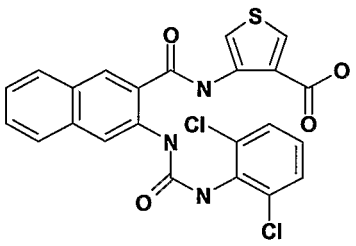
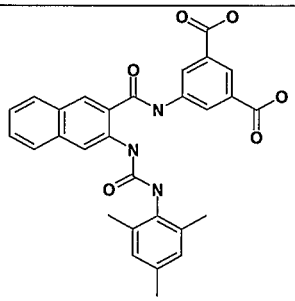
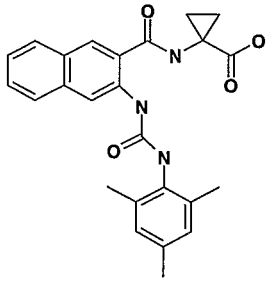
470	 Chiral	(2S)-cyclohexyl({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	514 (M-H)	0.002
471	 Chiral	(2S)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propyn-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid	510 (M-H)	0.003
472	 Chiral	2-cyclohexyl-N-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-L-alanine	468 (M-H)	0.16
473	 Chiral	(2S)-cyclohexyl[({3-[({[2,6-dimethyl-4-(propyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid	530 (M-H)	0.001
474	 Chiral	2-cyclohexyl-N-[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-fluorophenyl)carbonyl]-L-alanine	578 (M-H)	0.145

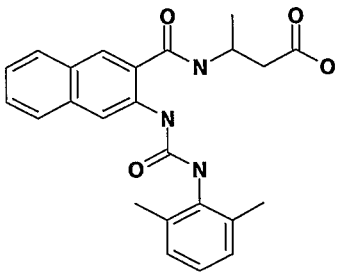
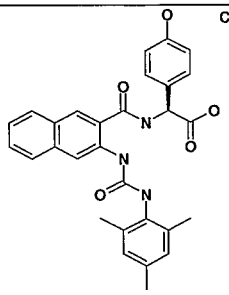
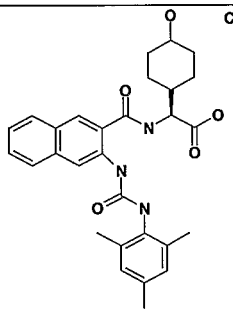
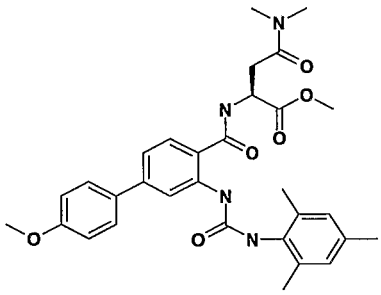
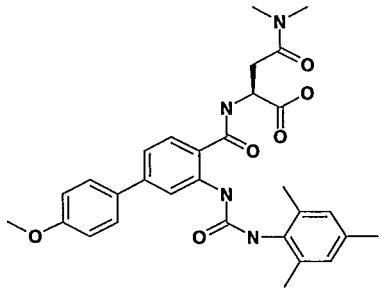
475	 Chiral	(2S)-cyclohexyl({[2-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid	468 (M-H)	0.051
476	 Chiral	(2S)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid	480 (M-H)	0.03
477	 Chiral	(2S)-cyclohexyl({[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid	482 (M-H)	0.008
478	 Chiral	(2S)-cyclohexyl({[2-({[(2,6-dimethyl-4-pentylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid	510 (M-H)	0.003
479	 Chiral	2-cyclohexyl-N-{[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-alanine	496 (M-H)	0.004

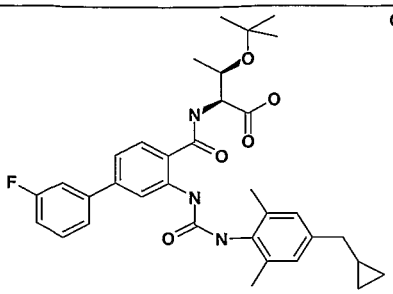
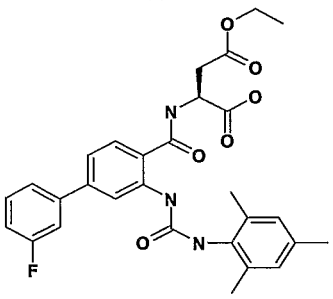
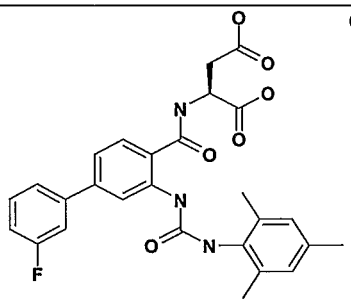
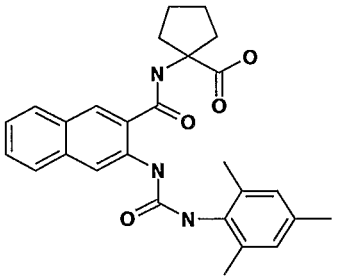
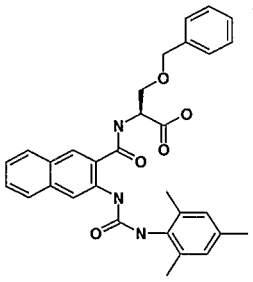
480	 Chiral	(2S)-({[2-({[(4-butyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoic acid	496 (M-H)	0.02
481	 Chiral	O-(1,1-dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-L-threonine	594 (M-H)	0.0004
482	 Chiral	(2S)-cyclohexyl[({2-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid	494 (M-H)	0.005
483	 Chiral	N-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-O-(1,1-dimethylethyl)-L-threonine	606 (M-H)	0.001
484	 Chiral	(2S)-cyclohexyl({[2-[4-(methyloxy)phenyl]-4-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1,3-thiazol-5-yl]carbonyl}amino)ethanoic acid	611 (M + H)	5

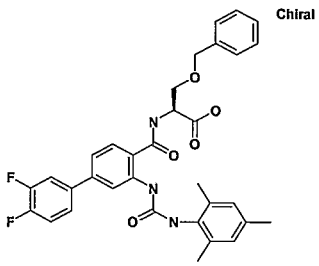
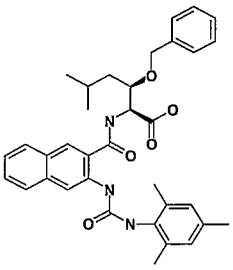
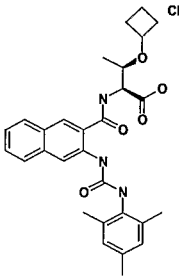
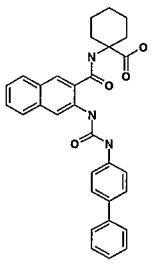
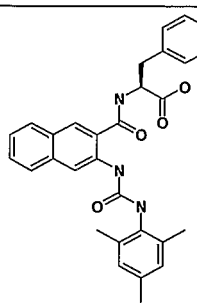
485	 Chiral	(2S)-cyclohexyl({[2-[4-(methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)ethanoic acid	551 (M + H), 573 (M + Na)	0.7
486	 Chiral	(2S)-cyclohexyl[({5-[({[2-methyl-6-(1-methylethyl)phenyl]amino}carbonyl)amino]-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino]ethanoic acid	565 (M + H), 587 (M + Na)	1.78
487	 Chiral	(2S)-cyclohexyl[({5-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-[4-(methyloxy)phenyl]-1,3-thiazol-4-yl}carbonyl)amino]ethanoic acid	577 (M + H), 599 (M + Na)	0.74
488		2-[4-(Methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazole-4-carboxylic acid		8.23
489		1-({[2-[4-(Methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylic acid	537 (M + H), 559 (M + Na)	0.034

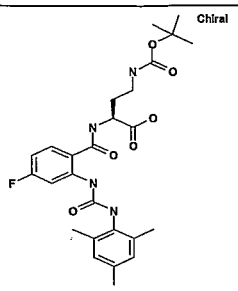
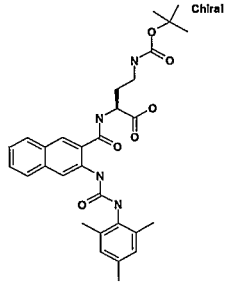
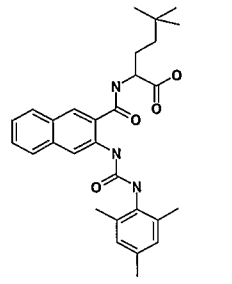
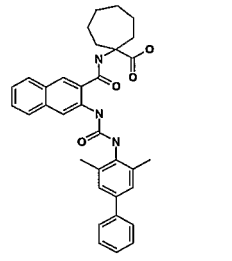
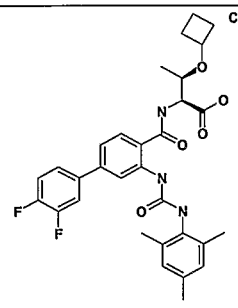
490	 Chiral	(2S)-({[2-(4-chlorophenyl)-5-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)(cyclohexyl)ethanoic acid	615 (M + H)	0.17
491		*N*-{[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-*N*-methylglycine	NMR in example	2.11
492		4-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid	NMR in example	7.52
493		methyl *N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-beta-alaninate	NMR in example	9.86
494		*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-beta-alanine	NMR in example	0.36

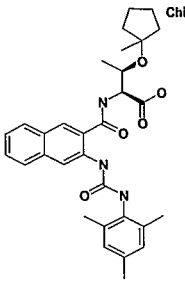
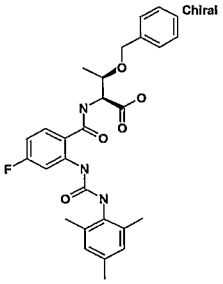
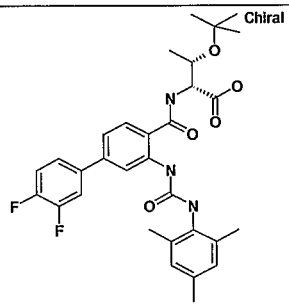
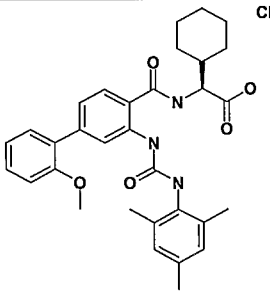
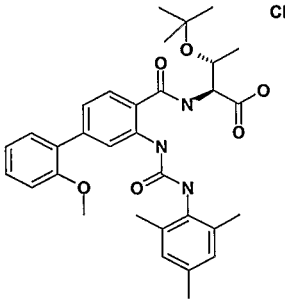
495		3-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)benzoic acid	NMR in example	0.3
496		*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-valine	NMR in example	0.29
497		4-({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-3-thiophenecarboxylic acid	NMR in example	17.66
498		5-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,3-benzenedicarboxylic acid	512 (M+H)	0.11
499		1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopropanecarboxylic acid	NMR in example	0.51

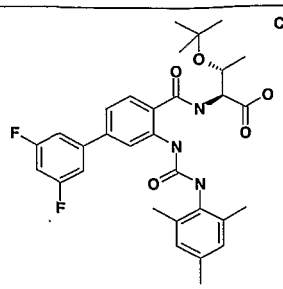
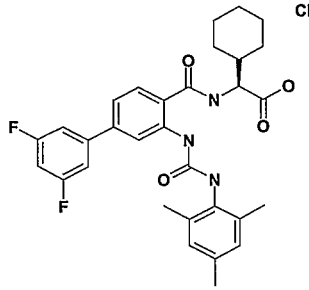
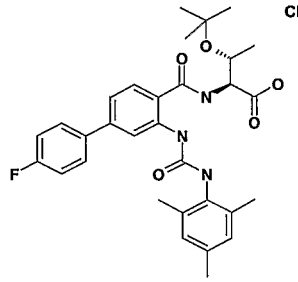
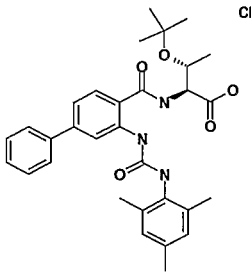
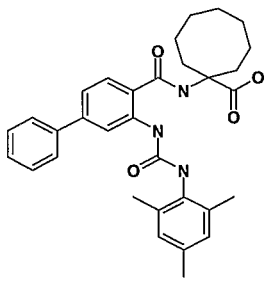
500		3-({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid	NMR in example	2.14
501	 Chiral	(2*S*)-(4-hydroxyphenyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	496(M-H)	0.012
502	 Chiral	(2*S*)-(4-hydroxycyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	502(M-H)	0.013
503	 Chiral	Methyl N4,N4-dimethyl-N2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparaginate	ACPI 561 (M+H)	11.1
504	 Chiral	N^4,N^4-dimethyl-N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparagine	APCI 547 (M+H)	0.032

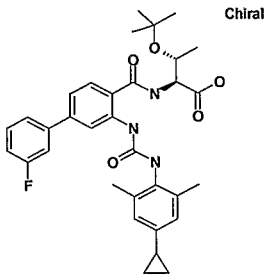
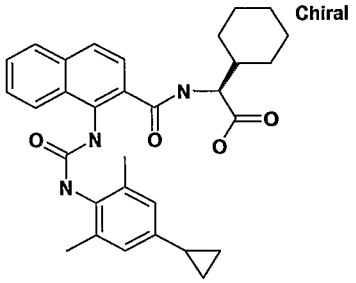
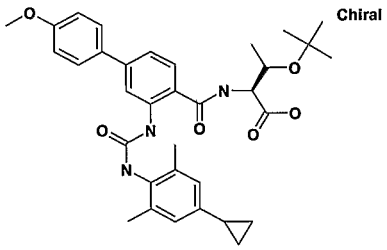
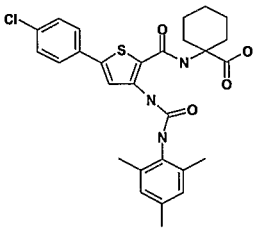
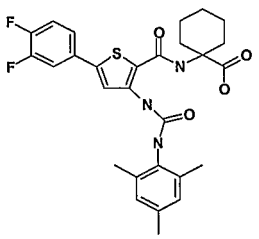
505	 Chiral	*N*-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threonine	APCI 588 (M-H)	0.003
506	 Chiral	(2*S*)-4-(ethyloxy)-2-({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)-4-oxobutanoic acid	APCI 536 (M+H)	1.09
507	 Chiral	*N*-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid	APCI 508 (M+H)	0.053
508		1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclopentanecarboxylic acid	460 (M+H)	0.279
509	 Chiral	*O*-(Phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine	526 (M+H)	0.028

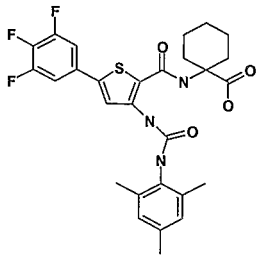
510		*N*-{[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(phenylmethyl)-L-serine	588 (M+H)	0.042
511		(3*R*)-5-Methyl-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine	582 (M+H)	0.077
512		O-cyclobutyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine	504 (M+H)	0.011
513		1-{[(3-{[(4-biphenylylamino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}cyclohexanecarboxylic acid	508 (M+H)	7.43
514		N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-phenylalanine	496 (M+H)	0.052

515		(2S)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)butanoic acid	517 (M+H)	1.9
516		(2S)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid	549 (M+H)	0.089
517		5,5-dimethyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine	489 (M+H)	0.019
518		1-({[3-({[(3,5-dimethyl-4-biphenylyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid	550 (M+H)	0.34
519		O-cyclobutyl-N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine	566 (M+H)	0.007

520		O-(1-methylcyclopentyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine	566 (M+H)	0.006
521		N-{[4-fluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}-O-(phenylmethyl)-L-threonine	532 (M+H)	0.134
522		N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-D-threonine	568 (M+H)	0.675
523		(2S)-cyclohexyl({[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	544 (M+H)	0.008
524		O-(1,1-Dimethylethyl)-N-{[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine	562 (M+H)	0.011

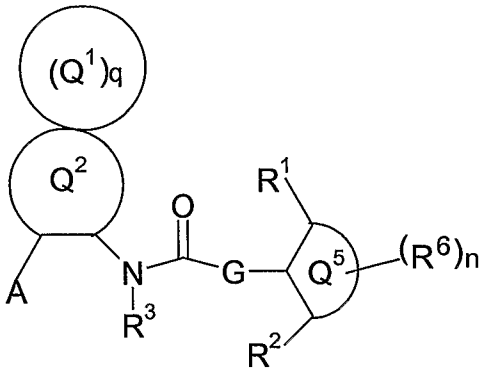
525	 Chiral	N-{[3',5'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine	566 (M-H)	0.007
526	 Chiral	(2S)-Cyclohexyl({[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid	550 (M+H) (APCI)	0.005
527	 Chiral	O-(1,1-Dimethylethyl)-N-{[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine	550 (M+H) (APCI)	0.003
528	 Chiral	O-(1,1-Dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine	532 (M+H) (APCI)	0.003
529		1-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid	528 (M+H) (APCI	0.002

530		N-{[3-({[(4-Cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine	576 (M+H) (APCI	0.021
531		(2S)-cyclohexyl({[3-({[(4-cyclopropylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid	514 (M+H)	0.019
532		N-{[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine	588 (M+H)	0.011
533		1-({[5-(4-chlorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid	540 (M + H)	0.003
534		1-({[5-(3,4-difluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid	542 (M + H)	0.104

535		1-({[5-(3,4,5-trifluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid	560 (M + H)	0.206

What is claimed is:

1. A compound of Formula 1 comprising:



Formula 1

a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof

wherein:

A is $C(=O)NQ^3Q^4$ or $C(=O)OH$;

Q^1 and Q^2 are fused together;

Q^1 is selected from the group consisting of (i) a 5- or 6- membered aromatic ring, (ii) a 5- or 6- membered cycloalkyl ring, (iii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, or sulfur, and (iv) a 4- to 8- membered heterocyclic ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, or sulfur; and q is 0 or 1;

Q^2 is selected from the group consisting of (i) a 5- or 6- membered aromatic ring and (ii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, or sulfur;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, alkoxy, monoalkylamino, and dialkylamino;

R^3 is hydrogen or a C_{1-6} alkyl;

Q^3 and Q^4 are each independently selected from the group consisting of (i) hydrogen, (ii) C_{1-6} alkyl, (iii) $-CR^4R^5Z$, where Z is a 5- or 6- membered

heteroaryl having at least one heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur, (iv) aryl, and (v) $-CR^4R^5COOH$;

R^4 and R^5 are each independently selected from the group consisting of (i) hydrogen, (ii) a C_{1-6} alkyl, (iii) a 4- to 8- membered cycloalkyl, (iv) a 5- or 6- membered aryl, (v) a 5- or 6- membered heteroaryl, (vi) a 5- or 6- membered aralkyl, (vii) a 5- or 6- membered heteroarakyl, having at least one heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, (viii) a 4- to 8- membered cycloalkylalkyl, and (ix) a 4- to 8- membered heterocyclic ring;

R^4 and R^5 are taken together can form a (i) 3-10 membered cycloalkyl or (ii) a 4-8 membered heterocyclic ring;

G is selected from the group consisting of carbon, nitrogen, oxygen, and sulfur;

Q^5 is selected from the group consisting of (i) a 5- or 6- membered aromatic ring and (ii) a 5- or 6- membered heteroaromatic ring having at least one heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur;

R^6 is selected from the group consisting of (i) C_{1-6} alkyl, (ii) halogen, (iii) alkoxy, (iv) cyano, (v) hydroxyl, (vi) haloalkyl, (vii) a mono- or dialkyl- amino, (viii) 3-5 membered cycloalkyl, (ix) 3-5 membered cycloalkylalkyl, (x) alkenyl, (xi) alkynyl, and (xii) acyl; and n is 0 or 1.

2. The compound of Claim 1 wherein q is 1.

3. The compound of Claim 1 wherein Q^1 is cyclohexyl or phenyl.

4. The compound of Claim 3 wherein Q^1 is phenyl.

5. The compound of Claim 1 wherein Q^2 is substituted.

6. The compound of Claim 5 wherein Q^2 is substituted with an alkoxy or a halo.

7. The compound of Claim 1 wherein Q^2 is selected from the group

consisting of an unsubstituted aromatic ring, a dimethoxy substituted aromatic ring, and a mono- or dihalosubstituted aromatic ring.

8. The compound of Claim 1 wherein Q^2 is an unsubstituted phenyl.

9. The compounds of claim 1 wherein q is 0.

10. The compound of claim 9 wherein Q^2 is substitiuted phenyl, substitiuted thienyl, or substitiuted pyridyl ring.

11. The compound of claim 10 wherein Q^2 is substituted with mono- or di-halo, mono- or di-alkyl, or mono or di-alkoxy.

12. The compound of claim 10 wherein Q^2 is substituted with an aryl ring.

13. The compound of claim 12 wherein said aryl is a phenyl ring.

14. The compound of claim 13 wherein said phenyl ring is substituted.

15. The compound of claim 14 wherein said phenyl is substituted with a halo or alkoxy group.

16. The compound of Claim 1 wherein R^1 and R^2 are each independently selected from the group consisting of halo and C_{1-6} alkyl.

17. The compound of Claim 1 wherein R^1 is choro and R^2 is methyl or vice versa.

18. The compound of Claim 1 wherein R^1 and R^2 are each chloro.

19. The compound of Claim 1 wherein R^1 and R^2 are each methyl.

20. The compound of Claim 1 wherein R^3 is hydrogen.

21. The compound of Claim 1 wherein Q^3 and Q^4 are each independently selected from the group consisting of (i) $-CR^4R^5Z$ where Z is tetrazole, (ii) $-CR^4R^5COOH$, and (iii) hydrogen.

22. The compound of Claim 1 wherein Q^3 is $-CR^4R^5COOH$ and Q^4 is hydrogen.

23. The compound of Claim 1 wherein R^4 and R^5 are selected from the group consisting of (i) hydrogen, (ii), cycloalkyl, (iii) aryl, (iv) substituted or unsubstituted C_{1-6} alkyl, and (v) aralkyl.

24. The compound of Claim 21 wherein R^4 and R^5 are selected from the group consisting of hydrogen, aryl, cycloalkyl, and substituted and unsubstituted C_{1-6} alkyl.

25. The compound of Claim 24 wherein said substituted C_{1-6} alkyl is substituted with alkoxy or –COOH.

26. The compound of Claim 1 wherein R^4 and R^5 taken together form a (i) 3-10 membered cycloalkyl or (ii) a 4-8 membered heterocyclic ring.

27. The compound of Claim 1 wherein G is carbon or nitrogen.

28. The compound of Claim 1 wherein Q^5 is a substituted or unsubstituted 6-membered aromatic ring.

29. The compound of Claim 28 wherein Q^5 is phenyl, alkylphenyl, or halophenyl.

30. The compound of Claim 1 wherein Q^2 is phenyl and q is l.

31. The compound of Claim 1 wherein R^6 is C_{1-5} alkyl, halomethyl, alkoxy, or halo.

32. The compound of Claim 1 wherein R^6 is methyl, ethyl, n-propyl, cyclopropylmethyl, chloro, or trifluoromethoxy.

33. The compound of Claim 1 wherein Q^2 is a susbtituted or unsubstituted heteroaromatic ring.

34. The compound of Claim 26 wherein Q^2 is a 5-membered heteroaromatic ring with one sulfur as the heteroatom.

35. The compound of Claim 1 wherein said compound is selected from the group consisting of

N-[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthoyl] glycine;

Phenyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(2S)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(2S)({[4-chloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl] carbonyl}amino)(cyclohexyl) ethanoic acid;

(2S)-Cyclohexyl{[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthoyl]amino} ethanoic acid;

(2S)-Cyclohexyl{[3-({[(2-ethyl-6-methylphenyl)amino]carbonyl}amino)-2-naphthoyl]amino} ethanoic acid;

(2S)-({3-[({[2-Chloro-6-(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthoyl}amino)(cyclohexyl) ethanoic acid;

(2S)-Cyclohexyl[(3-{[(2,4,6-trichlorophenyl)acetyl]amino}-2-naphthoyl) amino]ethanoic acid;

(2S)-Cyclohexyl[(3-{[(mesitylamino)carbonyl]amino}-2-naphthoyl)

amino]ethanoic acid;

(2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dichlorophenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-({[4-Chloro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid;

(2*S*)-Cyclohexyl({[4,5-dichloro-2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(3-pyridinyl)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[2-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4-(2-thienyl)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-hydroxy-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,6- dimethylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2S)-Cyclohexyl({[4'-hydroxy-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-nitro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-(hydroxymethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-({[4'-Amino-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid;

(2*S*)-Cyclohexyl({[3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4-{[(methylamino)carbonyl]amino}-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclopentyl({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-3',4'-difluoro-4-biphenylyl)carbonyl]amino}ethanoic acid;

(2*S*)-Cyclohexyl({[4'-[(dimethylamino)methyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4-biphenylyl)carbonyl]amino}ethanoic acid;

(2*S*)-Cyclohexyl({[3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-(1-pyrrolidinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-cyclohexyl({[4'-(4-morpholinylmethyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-Cyclohexyl({[4'-(ethyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-norleucine;

1-({[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cycloheptanecarboxylic acid;

(2*S*)-Cyclohexyl({[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

(2*S*)-({[4-(1,3-Benzodioxol-5-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)(cyclohexyl)ethanoic acid;

O-(1,1-Dimethylethyl)-N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

1-({[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid;

(2*S*)-Cyclohexyl({[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid;

(2*S*)-({[3',4'-Bis(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)(cyclohexyl)ethanoic acid;

(2*S*)-Cyclohexyl({[4,5-difluoro-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)phenyl]carbonyl}amino)ethanoic acid;

1-({[4'-(Methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid;

N-{[3-{[({2,6-Dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine;

O-(1,1-Dimethylethyl)-N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

(2S)-Cyclohexyl({[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

O-(1,1-Dimethylethyl)-N-{[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

O-(1,1-Dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-threonine;

(2S)-Cyclohexyl({[3'-fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

1-({[3'-Fluoro-4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine;

O-(1,1-dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

5-methyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine;

6,6,6-trifluoro-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine;

O-(1,1-dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-leucine;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-isoleucine;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline;

O-(1,1-dimethylethyl)-N-[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]-L-threonine;

O-butyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-[2-(methyloxy)ethyl]-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-ethyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-(1-methylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-(2,2-dimethylpropyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-(tetrahydro-2H-pyran-4-yl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

O-(1-methylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

(2S)-Cyclohexyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)ethanoic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid;

1-({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclooctanecarboxylic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cyclodecanecarboxylic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cycloheptanecarboxylic acid;

1-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-quinolinyl]carbonyl}amino)cyclooctanecarboxylic acid;

1-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)cycloheptanecarboxylic acid;

2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-2,3-dihydro-1H-indene-2-carboxylic acid;

2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid;

1-({[5-Chloro-3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cyclooctanecarboxylic acid;

(2S)-Cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)ethanoic acid;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-pyridinyl]carbonyl}amino)cycloheptanecarboxylic acid;

O-(phenylmethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

(3R)-3-[(phenylmethyl)oxy]-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norvaline;

(2*S*)-(4,4-difluorocyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2*S*)-cyclopentyl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

1,4-dioxaspiro[4.5]dec-8-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(cis and trans)-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(cis and trans)-(4-{[(methylamino)carbonyl]amino}cyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-aspartic acid;

N-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-aspartic acid;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-D-aspartic acid;

(2*S*)-[(1*S*)-3-oxocyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2*S*)-[(1*S*)-3-hydroxycyclohexyl]({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2*S*)-{(1*S*)-3-[(trifluoroacetyl)oxy]cyclohexyl}({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

N-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid;

(2*S*)-2-({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}amino)-4-(ethyloxy)-4-oxobutanoic acid;

N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-L-aspartic acid;

N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(1,1-dimethylethyl)-L-threonine;

N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid;

N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparagine;

N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-glutamic acid;

(2S)-cyclohexyl[({3-({[(2,6-dichlorophenyl)amino]carbonyl}amino)-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl({[5-[4-(methyloxy)phenyl]-2-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-3-thienyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl[({2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-3-thienyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl{[(2-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-{4-[(trifluoromethyl)oxy]phenyl}-3-thienyl)carbonyl]amino}ethanoic acid;

(2S)-cyclohexyl[({3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-5-[4-(methyloxy)phenyl]-2-thienyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)ethanoic acid;

N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-valine;

N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-isoleucine;

N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-norleucine;

O-(1,1-dimethylethyl)-N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-serine;

O-(1,1-dimethylethyl)-N-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-threonine;

1-{[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}-L-proline;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclopentanecarboxylic acid;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cycloheptanecarboxylic acid;

1-({[5-[4-(methyloxy)phenyl]-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclooctanecarboxylic acid;

(2S)-cyclohexyl({[3-({[(2,6-dichloro-4-fluorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl{[(3-{[(2,4,6-trimethylphenyl)acetyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid;

(2S)-cyclohexyl({[3-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}ethanoic acid;

(2S)-(trans-4-methylcyclohexyl)({[3-({[(2,4,6-trichlorophenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

2-cyclohexyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-alanine;

2-cyclohexyl-N-[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]-L-alanine;

{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[trans-4-(trifluoromethyl)cyclohexyl]acetic acid;

{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}[cis-4-(trifluoromethyl)cyclohexyl]acetic acid;

{[(3-{[({2,6-dichloro-4-[(trifluoromethyl)oxy]phenyl}amino)carbonyl]amino}-2-naphthalenyl)carbonyl]amino}(tetrahydro-2H-pyran-4-yl)acetic acid;

tetrahydro-2H-pyran-4-yl({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)acetic acid;

(2S)-cyclohexyl({[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl[({3-[({[2,6-dimethyl-4-(2-propyn-1-yl)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl[({3-[({[2,6-dimethyl-4-(propyloxy)phenyl]amino}carbonyl)amino]-2-naphthalenyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl({[2-({[(4-ethyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl[({2-[({[2,6-dimethyl-4-(2-propen-1-yl)phenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid;

(2S)-cyclohexyl({[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid;

(2S)-cyclohexyl({[2-({[(2,6-dimethyl-4-pentylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)ethanoic acid;

2-cyclohexyl-N-{[2-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}-L-alanine;

(2S)-({[2-({[(4-butyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4-fluorophenyl]carbonyl}amino)(cyclohexyl)ethanoic acid;

O-(1,1-dimethylethyl)-N-{[3-({[(2,6-dimethyl-4-propylphenyl)amino]carbonyl}amino)-3',4'-difluoro-4-biphenylyl]carbonyl}-L-threonine;

(2S)-cyclohexyl[({2-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-4-fluorophenyl}carbonyl)amino]ethanoic acid;

N-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3',4'-difluoro-4-biphenylyl}carbonyl)-O-(1,1-dimethylethyl)-L-threonine;

1-({[2-[4-(Methyloxy)phenyl]-5-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]carbonyl}amino)cyclohexanecarboxylic acid;

(2*S*)-(4-hydroxyphenyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

(2*S*)-(4-hydroxycyclohexyl)({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

N^4,N^4-dimethyl-N^2-{[4'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-asparagine;

N-({3-[({[4-(cyclopropylmethyl)-2,6-dimethylphenyl]amino}carbonyl)amino]-3'-fluoro-4-biphenylyl}carbonyl)-*O*-(1,1-dimethylethyl)-L-threonine;

N-{[3'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-aspartic acid;

O-(Phenylmethyl)-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-serine;

N-{[3',4'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-*O*-(phenylmethyl)-L-serine;

(3*R*)-5-Methyl-3-[(phenylmethyl)oxy]-*N*-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-norleucine;

O-cyclobutyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-phenylalanine;

(2S)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-({[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)butanoic acid;

5,5-dimethyl-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}norleucine;

O-cyclobutyl-N-{[3',4'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

O-(1-methylcyclopentyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}-L-threonine;

(2S)-cyclohexyl({[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

O-(1,1-Dimethylethyl)-N-{[2'-(methyloxy)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

N-{[3',5'-Difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine;

(2S)-Cyclohexyl({[3',5'-difluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)ethanoic acid;

O-(1,1-Dimethylethyl)-N-{[4'-fluoro-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

O-(1,1-Dimethylethyl)-N-{[3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}-L-threonine;

1-({[3-({[(2,4,6-Trimethylphenyl)amino]carbonyl}amino)-4-biphenylyl]carbonyl}amino)cyclooctanecarboxylic acid;

N-{[3-({[(4-Cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-3'-fluoro-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine;

(2S)-cyclohexyl({[3-({[(4-cyclopropylphenyl)amino]carbonyl}amino)-2-naphthalenyl]carbonyl}amino)ethanoic acid;

N-{[3-({[(4-cyclopropyl-2,6-dimethylphenyl)amino]carbonyl}amino)-4'-(methyloxy)-4-biphenylyl]carbonyl}-O-(1,1-dimethylethyl)-L-threonine;

1-({[5-(4-chlorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid; and

1-({[5-(3,4-difluorophenyl)-3-({[(2,4,6-trimethylphenyl)amino]carbonyl}amino)-2-thienyl]carbonyl}amino)cyclohexanecarboxylic acid

36. A pharmaceutical composition comprising a compound of Claim 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and at least one excipient.

37. A method of treating a mammal suffering from diabetes, a condition associated with diabetes, or both comprising the administration of a compound of Claim 1, a pharmaceutically acceptable salt, solvate, or physiologically functional

derivative thereof.

38. The method of Claim 37 wherein said mammal is a human.

39. A method of treating a mammal suffering from diabetes, a condition associated with diabetes, or both comprising the administration to said mammal of a pharmaceutical composition comprising a compound of Claim 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and at least one excipient.

40. The method of Claim 39 wherein said mammal is a human.

41. A method of treating a mammal suffering from tissue ischemia, myocardial ischemia, or both comprising the administration of a compound of Claim 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

42. The method of Claim 41 wherein said mammal is a human.

43. A method of treating a mammal suffering from tissue ischemia, myocardial ischemia, or both comprising the administration to said mammal of a pharmaceutical composition of a compound of Claim 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and at least one excipient.

44. The method of Claim 43 wherein said mammal is a human.

45. A process of making a compound of Claim 1 comprising a solid-phase synthesis using at least one isocyanate.

46. A process of making a compound of Claim 1 comprising a solid-phase synthesis using at least one urea carboxylic acid.

47. A process of making a compound of Claim 1 comprising a solution-phase synthesis using at least one urea carboxylic acid.

48. A process of making a compound of Claim 1 comprising a solid-phase synthesis using at least one acid chloride.

49. A process of making a compound of Claim 1 comprising a solution-phase synthesis using at least one isocyanate.

50. A process of making a compound of Claim 1 comprising a solution-phase synthesis using at least one carboxylic acid.

51. The use of a compound of Claim 1 or a pharmaceutically acceptable salt, solvate, or physiological functional derivative thereof for the manufacture of a medicine.

52. The use according to Claim 51 wherein the medicine is for the treatment of at least one of diabetes, a condition associated with diabetes, tissue ischemia, and myocardial ischemia.

53. The use of a pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt, solvate, or physiological functional derivative thereof for the manufacture of a medicine.

54. The use according to Claim 53 wherein the medicine is for the treatment of at least one of diabetes, a condition associated with diabetes, tissue ischemia, and myocardial ischemia.