

DERIVATIVES OF SUBSTITUTED MORPHOLINES AND USES THEREOF**CROSS-REFERENCE TO RELATED APPLICATIONS**

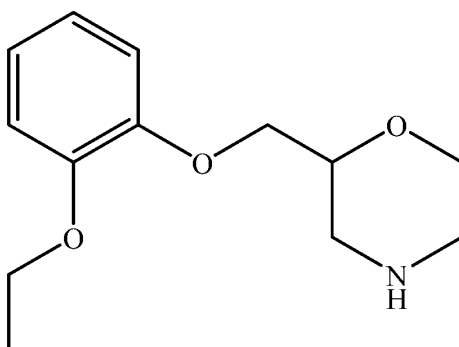
This application claims priority to U.S. Provisional Application No. 63/162,671, filed March 18, 2021, the entire contents of which are incorporated herein.

FIELD

[0001] The present technology generally relates to derivatives of substituted morpholines and their uses in pharmaceutical compositions and for the treatment of central nervous system (CNS) disorders.

BACKGROUND

[0002] (R,S)-2-[(2-ethoxyphenoxy)methyl]morpholine:



is a bicyclic morpholine derivative, assigned CAS No. 46817-91-8 (CAS No. 35604-67-2 for the HCl salt). It is characterized by the formula $C_{13}H_{19}NO_3$, with a molecular mass of 237.295 g/mol.

[0003] 2-((2-ethoxyphenoxy)methyl)morpholine is known to have several desirable pharmacologic uses, including treatment of depression, nocturnal enuresis, narcolepsy, sleep disorders, and alcoholism, among others. 2-((2-ethoxyphenoxy)methyl)morpholine was previously marketed in several European countries for the treatment of major depressive disorder

(MDD). 2-((2-ethoxyphenoxy)methyl)morpholine is an inhibitor of the reuptake of norepinephrine ("NRI"), but may also enhance the release of serotonin from neuronal stores.

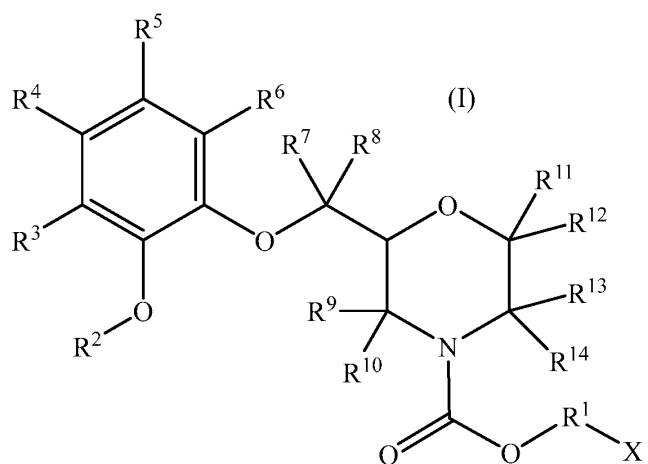
[0004] However, treatment with 2-((2-ethoxyphenoxy)methyl)morpholine has been associated with numerous side effects including nausea, vomiting, loss of appetite, increased erythrocyte sedimentation, EKG and EEG anomalies, epigastric pain, diarrhea, constipation, vertigo, orthostatic hypotension, edema of the lower extremities, dysarthria, tremor, psychomotor agitation, mental confusion, inappropriate secretion of antidiuretic hormone, increased transaminases, and seizure.

[0005] In order to minimize the side effects associated with 2-((2-ethoxyphenoxy)methyl)morpholine, chemists have synthesized derivatives and analogs that retain the pharmacologic properties of 2-((2-ethoxyphenoxy)methyl)morpholine. Derivatives of substituted morpholines have been previously disclosed in the art, for example in UK Patent 1 243 391 and UK Patent 1 260 886. In a different approach, the present inventors synthesize novel derivatives of substituted morpholines. Prodrugs are a class of derivatives that in many instances have little or no pharmacological activity, which are converted *in vivo* to therapeutically active compounds. In some instances, the prodrug itself may possess biological activity. Prodrug activation may occur by enzymatic or non-enzymatic cleavage of the temporary bond between the carrier and the drug molecule, or a sequential or simultaneous combination of both.

[0006] The newly synthesized derivatives of substituted morpholines, with the derivatization of the amine group of the morpholine in the structure of 2-((2-ethoxyphenoxy)methyl)morpholine produce chemically stable compounds to serve as novel compounds. These derivatives of 2-((2-ethoxyphenoxy)methyl)morpholine can be used in pharmaceutical compositions and for the treatment of central nervous system (CNS) disorders.

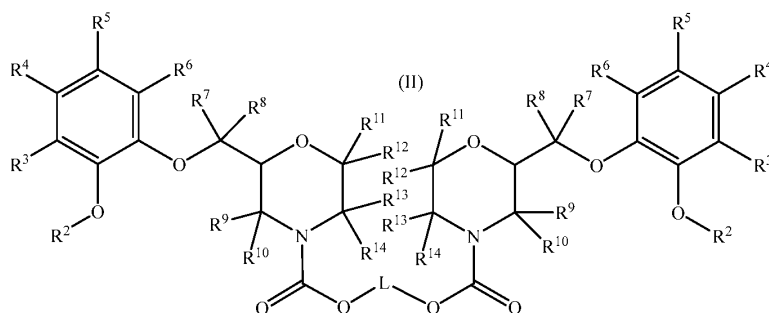
SUMMARY

[0007] In one aspect, derivatives of substituted morpholines are provided, including a compound of Formula I, a stereoisomer thereof, or a salt thereof:



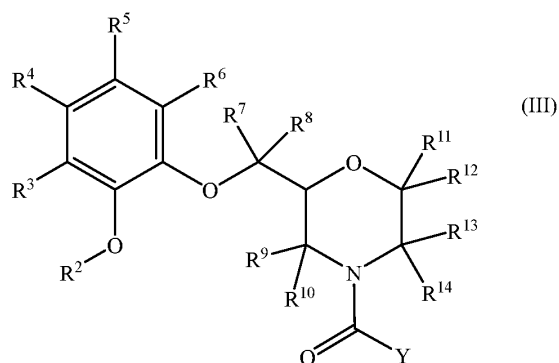
In Formula I, R^1 may be alkyl, heterocyclyl, or a pyridyl, R^2 may be alkyl, aryl, heteroaryl, or heterocyclyl, R^3 - R^{14} may be each independently H, F, Cl, Br, I, CN, NO_2 , alkyl, aryl, heteroaryl, or heterocyclyl; and X may be H, F, Cl, Br, I, an amino acid residue, a substituted amino acid residue, alkyl, ester.

[0008] In some embodiments, the present technology relates to derivatives of substituted morpholines according to the compound of Formula II, stereoisomer thereof, and/or a salt thereof:



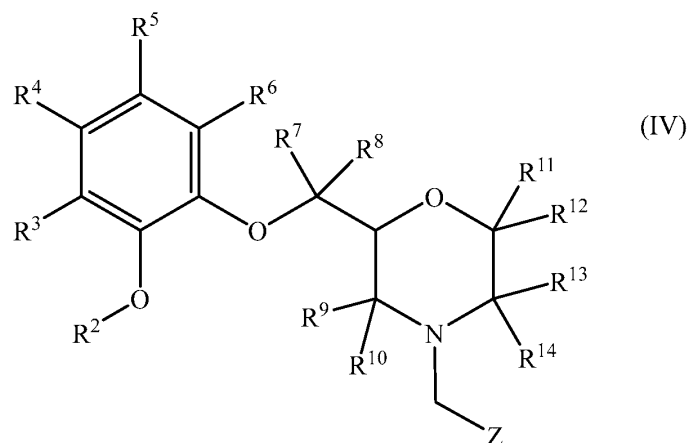
In Formula II, L may be alkyl, a substituted pyridinecarboxylic acid, or a substituted azanediyl acetate; R^2 may be alkyl, aryl, heteroaryl, or heterocyclyl; and R^3 - R^{14} may be each independently H, F, Cl, Br, I, CN, NO_2 , alkyl, aryl, heteroaryl, or heterocyclyl.

[0009] In some embodiments, the present technology relates to derivatives of substituted morpholines according to the compound of Formula III, a stereoisomer thereof, and/or a salt thereof:



In Formula III, Y may be F, Cl, Br, I, an amino acid residue, a substituted amino acid residue, alkyl, or ester; R² may be alkyl, aryl, heteroaryl, or heterocyclyl; and R³-R¹⁴ may be each independently H, F, Cl, Br, I, CN, NO₂, alkyl, aryl, heteroaryl, or heterocyclyl.

[0010] In some embodiments, derivatives of substituted morpholines are provided according to Formula IV, a stereoisomer thereof, and/or a salt thereof:



In Formula IV, Z may be H, F, Cl, Br, I, an amino acid residue, a substituted amino acid residue, or a nitrogen-containing group; R² may be alkyl, aryl, heteroaryl, or heterocyclyl; and R³-R¹⁴ may be each independently H, F, Cl, Br, I, CN, NO₂, alkyl, aryl, heteroaryl, or heterocyclyl.

[0011] In any of the above embodiments, R² may be CH₂CH₃. In any of the above embodiments, R³–R¹⁴ may each be H.

[0012] In some aspects, a composition is provided that includes derivatives of substituted morpholines of Formula I, II, III, or IV, their stereoisomers and/or salts thereof and at least one pharmaceutically acceptable excipient or carrier.

[0013] In some aspects, treatment of a central nervous system (“CNS”) disorder is provided, the treatment including administering to a subject in need thereof a pharmaceutical composition that includes a derivative of substituted morpholines, including of a compound of Formula I, II, III, or IV.

[0014] In some aspects, a method is provided for making a derivative of substituted morpholines, including of a compound of Formula I, II, III, or IV, their stereoisomers and/or salts thereof comprising contacting 2-((2-ethoxyphenoxy)methyl)morpholine or a salt thereof, Intermediate 1, Intermediate 2, or Intermediate 3 with a reactive compound suitable for forming the compound of Formula I, II, III, or IV.

DETAILED DESCRIPTION

[0015] Definitions. The following terms are used throughout as defined below.

[0016] As used herein, the term “viloxazine” or 2-((2-ethoxyphenoxy)methyl)morpholine means (R,S)-2-[(2-ethoxyphenoxy)methyl]morpholine] includes a pharmaceutically acceptable salt or ester thereof, including either a single (–) enantiomer or a single (+) enantiomer, or in the form of a racemic mixture or a non-racemic mixture of enantiomers with varying amounts of (–) and (+) enantiomers.

[0017] As used herein and in the appended claims, singular articles such as “a” and “an” and “the” and similar referents in the context of describing the elements (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein merely intended to serve as shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate

value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, “such as”) provided herein, is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0018] As used herein, “about” will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art, given the context in which it is used, “about” will mean up to plus or minus 10% of the particular term.

[0019] Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Compounds comprising radioisotopes such as tritium, C¹⁴, P³², and S³⁵ are thus within the scope of the present technology. Procedures for inserting such labels into the compounds of the present technology will be readily apparent to those skilled in the art based on the disclosure herein.

[0020] In general, “substituted” refers to an organic group as defined below (*e.g.*, an alkyl group) in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Thus, a substituted group is substituted with one or more substituents, unless otherwise specified. In some embodiments, a substituted group is substituted with 1, 2, 3, 4, 5, or 6 substituents. Examples of substituent groups include: halogens (*i.e.*, F, Cl, Br, and I); hydroxyls; alkoxy, alkenoxy, aryloxy, aralkyloxy, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxy, and heterocyclylalkoxy groups; carbonyls (oxo); carboxylates; esters; urethanes; oximes; hydroxylamines; alkoxyamines; aralkoxyamines; thiols; sulfides; sulfoxides; sulfones; sulfonyls; pentafluorosulfanyl (*i.e.*, SF₅), sulfonamides; amines; N-oxides; hydrazines; hydrazides; hydrazones; azides; amides; ureas; amidines; guanidines;

enamines; imides; isocyanates; isothiocyanates; cyanates; thiocyanates; imines; nitro groups; nitriles (i.e., CN); and the like.

[0021] The term “carboxylate” as used herein refers to the conjugate base a carboxylic acid with the chemical formula --COO .

[0022] The term “ester” as used herein refers to --COOR^2 - and --C(O)O-G groups. R^2 is a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein. G is a carboxylate protecting group. Carboxylate protecting groups are well known to one of ordinary skill in the art. An extensive list of protecting groups for the carboxylate group functionality may be found in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein and which is hereby incorporated by reference in its entirety and for any and all purposes as if fully set forth herein.

[0023] The term “amide” (or “amido”) includes C- and N-amide groups, i.e., $\text{C(O)NR}^3\text{R}^4$, and --NRC(O)-R groups, respectively. R^3 and R^4 are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein. Amido groups therefore include but are not limited to carbamoyl groups (--C(O)NH_2) and formamide groups (NHC(O)H). In some embodiments, the amide is $\text{--NRC(O)-(C}_{1-5}\text{ alkyl)}$ and the group is termed “carbonylamino,” and in others the amide is --NHC(O)-alkyl and the group is termed “alkanoylamino.”

[0024] The term “amine” (or “amino”) as used herein refers to $\text{--NR}^5\text{R}^6$ groups, wherein R^5 and R^6 are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein. In some embodiments, the amine is alkylamino, dialkylamino, arylamino, or alkylarylamino. In other embodiments, the amine is NH_2 , methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropylamino, phenylamino, or benzylamino.

[0025] The term “halogen” or “halo” as used herein refers to bromine (Br), chlorine (Cl), fluorine (F), or iodine (I). In some embodiments, the halogen is chlorine (Cl).

[0026] The term “polypeptide” or “peptide” as used herein refers to two or more amino acids linked by a peptide (*i.e.*, amide) bond between the carboxyl terminus of one amino acid and the amino terminus of another. The term “peptide” may be combined with a prefix indicating the number of amino acids in the peptide, *e.g.*, a “pentapeptide” is a peptide of five amino acids.

[0027] The term “amino acid” is recognized in the art and generally refers to a natural or unnatural alpha or beta amino acid. The term “amino acid” includes, but is not limited to, anyone of the twenty-one standard L-amino acids commonly found in naturally occurring peptides.

[0028] The term “amino acid residue with hydrophobic side chain” as used herein refers to the following amino acids: alanine (Ala), valine (Val), isoleucine (Ile), Leucine (Leu), methionine (Met), phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp). In some embodiment, the amino acid residue with hydrophobic side chain is valine (Val). In other embodiment, the amino acid residue with hydrophobic side chain is phenylalanine (Phe).

[0029] The term “acetyl” as used herein refers to a methyl group bonded to a carbonyl group ($\text{CH}_3\text{CO}-$).

[0030] The term “pyridine” group as used herein refers to a group with the heterocyclic organic compound with the chemical formula $\text{C}_5\text{H}_5\text{N}$.

[0031] The term “pyridinecarboxylic acid” as used herein refers to compound having a pyridine ring and a carboxyl group.

[0032] The term “azanediy” as used herein refers to a functional group having the formula $-\text{NH}$; the group is bonded to the rest of the compound by two single bonds.

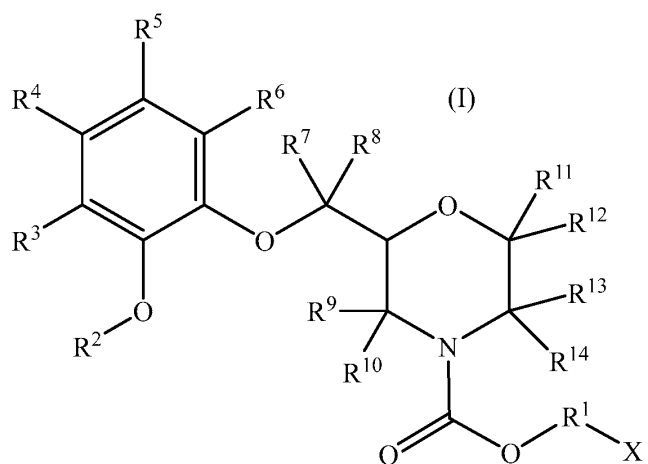
[0033] Pharmaceutically acceptable salts of compounds described herein are within the scope of the present technology and include acid or base addition salts which retain the desired pharmacological activity and is not biologically undesirable (*e.g.*, the salt is not unduly toxic, allergenic, or irritating, and is bioavailable). When the compound of the present technology has a basic group, such as, for example, an amino group, pharmaceutically acceptable salts can be formed with inorganic acids (such as hydrochloric acid, hydroboric acid, nitric acid, sulfuric

acid, and phosphoric acid), organic acids (*e.g.*, alginate, formic acid, acetic acid, benzoic acid, gluconic acid, fumaric acid, oxalic acid, tartaric acid, lactic acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, naphthalene sulfonic acid, and p-toluenesulfonic acid) or acidic amino acids (such as aspartic acid and glutamic acid). When the compound of the present technology has an acidic group, such as for example, a carboxylic acid group, it can form salts with metals, such as alkali and earth alkali metals (*e.g.*, Na⁺, Li⁺, K⁺, Ca²⁺, Mg²⁺, or Zn²⁺), ammonia or organic amines (*e.g.*, dicyclohexylamine, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, or triethanolamine) or basic amino acids (*e.g.* arginine, lysine, or ornithine). Such salts can be prepared in situ during isolation and purification of the compounds or by separately reacting the purified compound in its free base or free acid form with a suitable acid or base, respectively, and isolating the salt thus formed.

[0034] Stereoisomers of compounds (also known as optical isomers) include all chiral, diastereomeric, and racemic forms of a structure, unless the specific stereochemistry is expressly indicated. Thus, compounds used in the present technology include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these stereoisomers are all within the scope of the present technology.

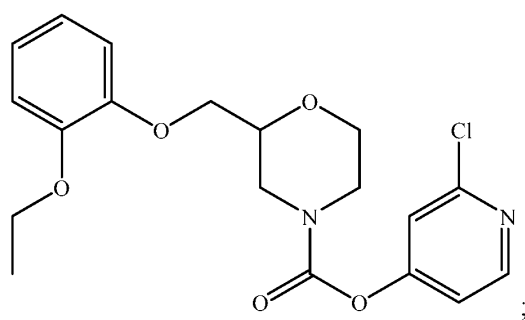
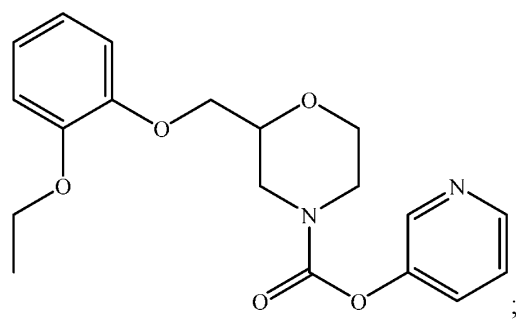
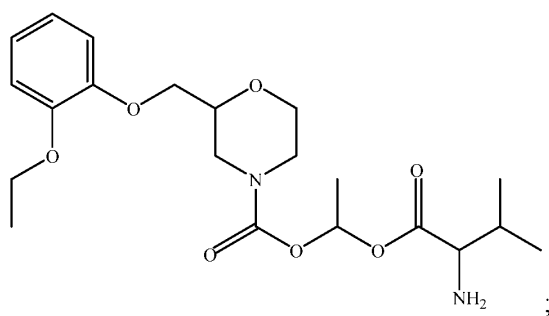
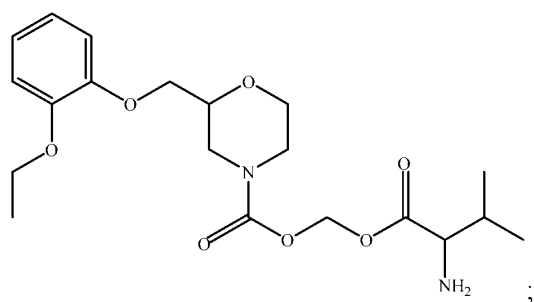
[0035] The term “pharmaceutically acceptable excipient” refers to those substances that are well accepted by the industry and regulatory agencies such as those listed in monographs published in compendia such as USP-NF, Food Chemicals Codex, Code of Federal Regulations (CFR), FDA Inactive Ingredients Guide and in 21 CFR parts 182 and 184 that lists substances that are generally regarded as safe (GRAS) food ingredients.

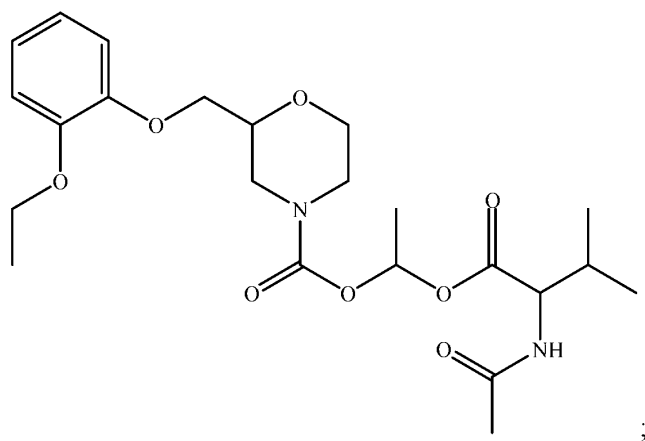
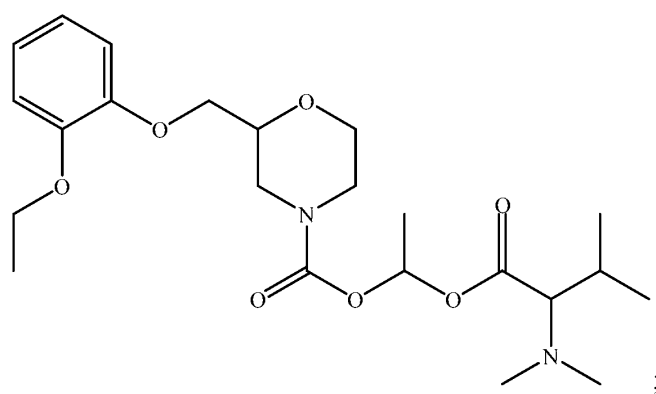
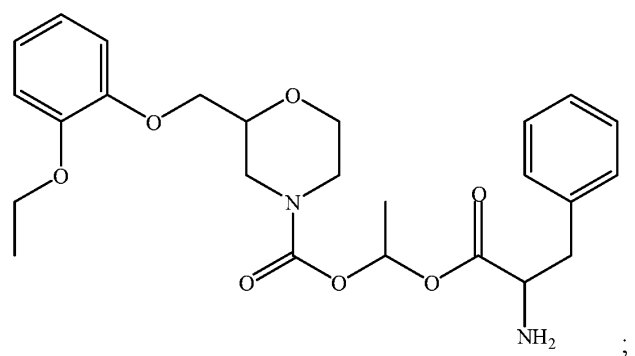
[0036] In one aspect, a compound represented by Formula I is provided, or a stereoisomer thereof or a pharmaceutically acceptable salt thereof:

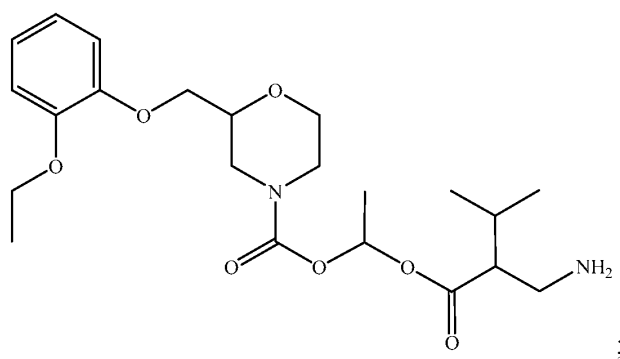
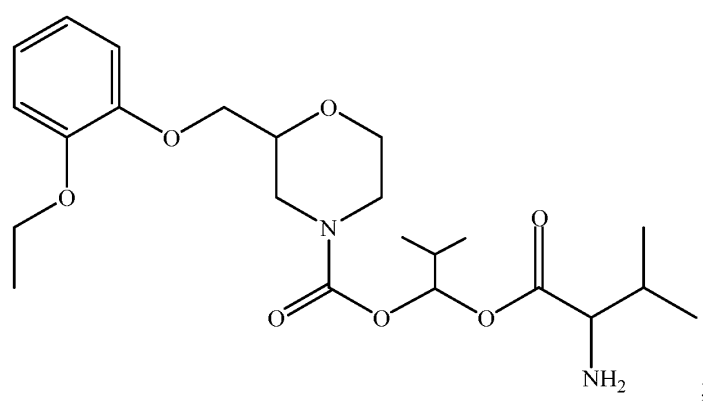
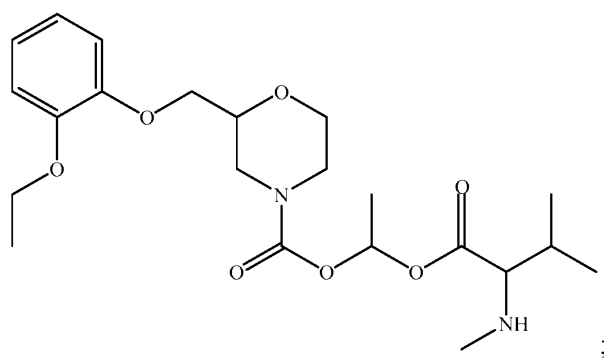


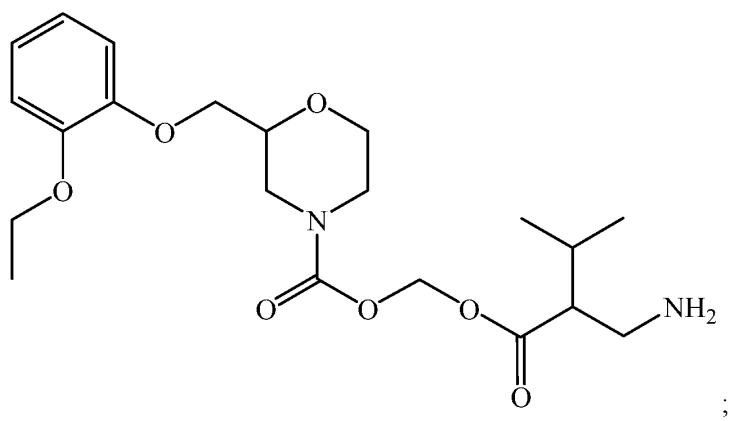
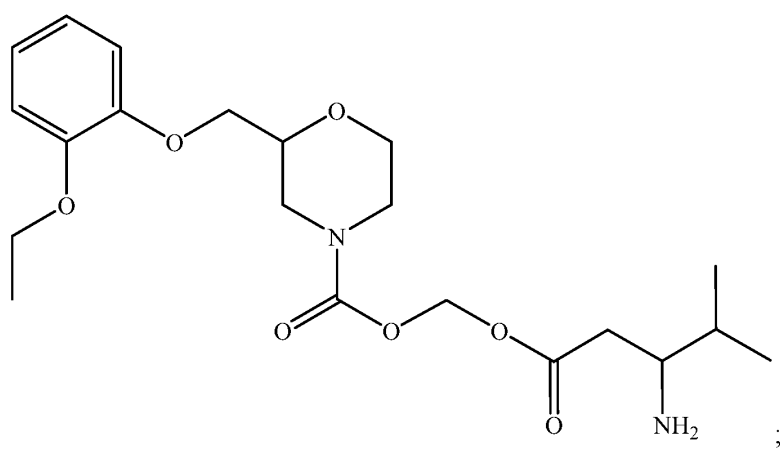
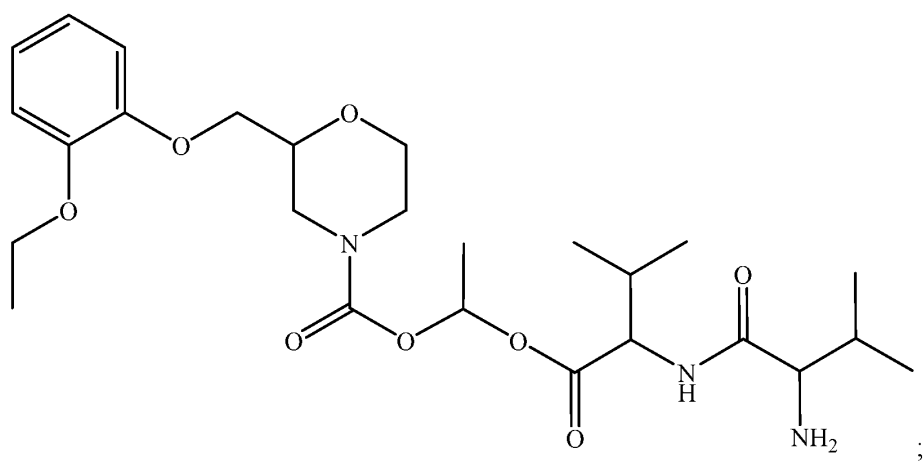
In the compound of Formula I, R^1 may be alkyl, heterocyl, or a pyridyl; R^2 may be alkyl, aryl, heteroaryl, or heterocycl; R^3 - R^{14} may be each independently H, F, Cl, Br, I, CN, NO_2 , alkyl, aryl, heteroaryl, or heterocycl; and X may be H, halogen, an amino acid residue, a substituted amino acid residue, alkyl, ester. In some preferred embodiments, R^2 is ethyl. In any of the above embodiments, R^1 may be CH_2 , CH_2CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, $(\text{CH}_3)_2\text{C}$, $(\text{CH}_3)_2\text{CHCH}_2$, or $(\text{CH}_3)_3\text{CCH}_2$. In any of the above embodiments, X may be an amino acid residue. In such embodiments, the amino acid residue may further include a hydrophobic side chain. In any of the above embodiments, the amino acid residue may be valine or phenylalanine. In any of the above embodiments, each of R^3 - R^{14} may be independently H, F, Cl, Br, I, or alkyl. In some such embodiments, each of R^3 - R^{14} may be independently H or C_1 - C_6 alkyl. In some embodiments, R^3 - R^{14} are all H. In any of the above embodiments, R^1 may be CH_2CH_2 or $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$. In various embodiments above, R_1 may be CH_2 or C_2H_5 , and/or X may be an ester. In various embodiments above, R^1 may be a pyridyl group and X may be F, Cl, Br, or I.

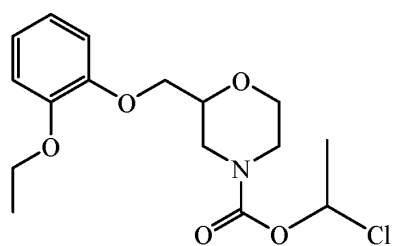
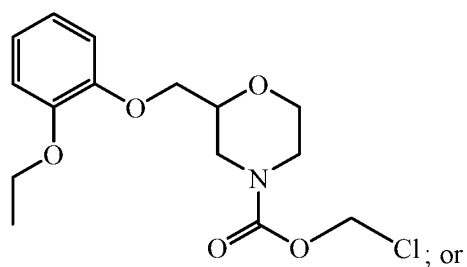
[0037] In various embodiments, the compound represented by Formula I is one or more of the following compounds, with the understanding that where chiral centers are present each representation includes any R, S, or racemic structures as well:



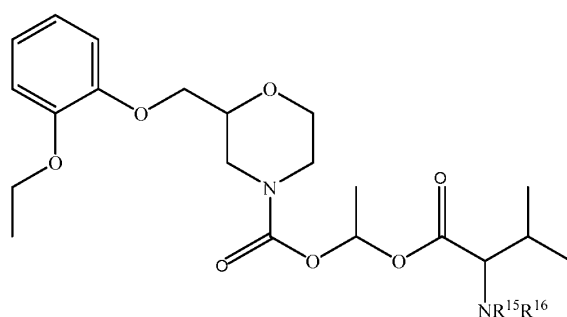






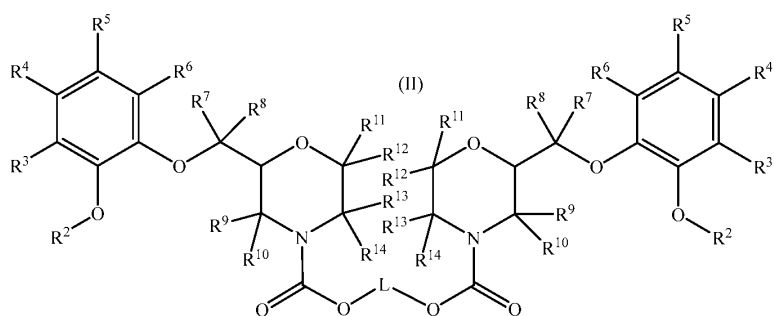


[0038] In some embodiments, the compound represented by Formula I is:



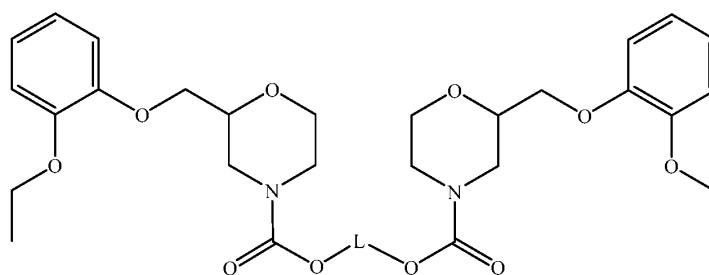
In the above formula, R^{15} may be H, alkyl, or $-C(O)OR^{17}$; R^{16} may be H, alkyl, or $-C(O)OR^{17}$; and R^{17} may be H or alkyl. In some embodiments, R^{15} may be alkyl and R^{16} may be H or alkyl. In such embodiments, R^{15} may be methyl and R^{16} may be H or methyl. In some embodiments, R^{15} and R^{16} are methyl. In some embodiments, R^{15} is $-C(O)OR^{17}$, R^{16} is H, and R^{17} is methyl.

[0039] In another aspect, a compound represented by Formula II is provided, or a stereoisomer thereof, and/or a salt thereof:

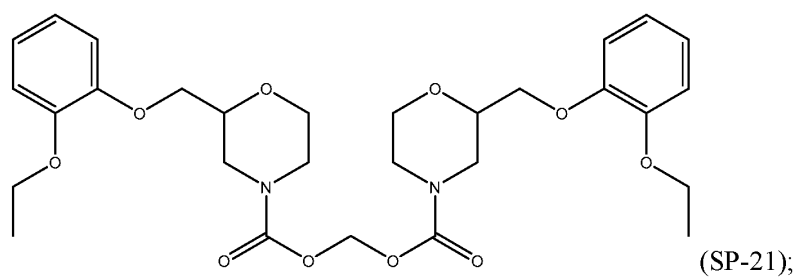


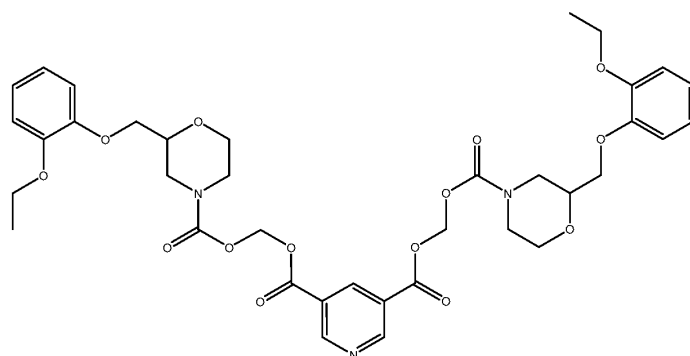
In Formula II, L is alkyl, a substituted pyridinecarboxylic acid, or a substituted azanediyl acetate; R^2 is alkyl, aryl, heteroaryl, or heterocyclyl; and R^3 - R^{14} are each independently H, F, Cl, Br, I, CN, NO_2 , alkyl, aryl, heteroaryl, or heterocyclyl. In some embodiments, R^2 is ethyl.

[0040] In some embodiments, the compound represented by Formula II is:

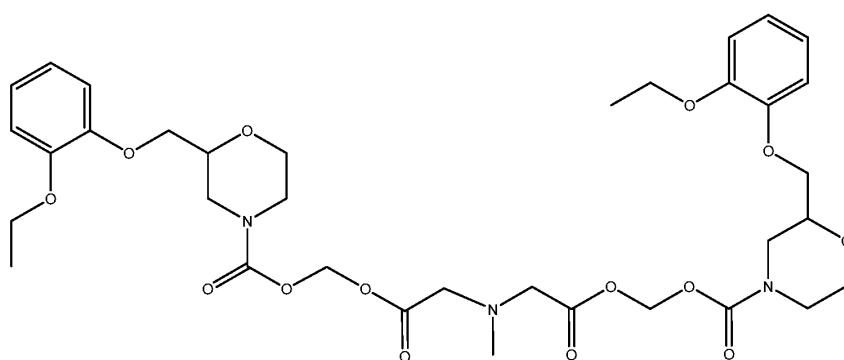


[0041] In various embodiments, the compound of Formula II is one or more of the following:



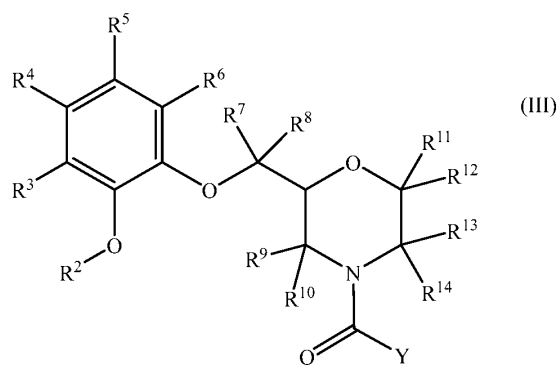


(SP-30); or



(SP-31).

[0042] In another aspect, a compound represented by Formula III is provided, or a stereoisomer thereof, and/or a salt thereof:

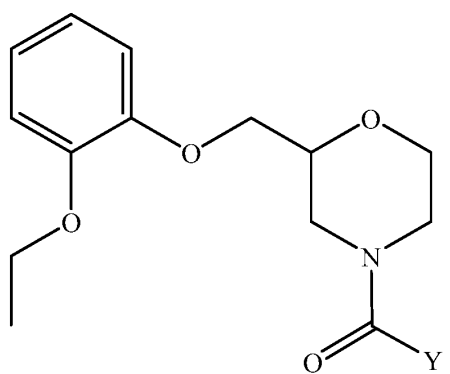


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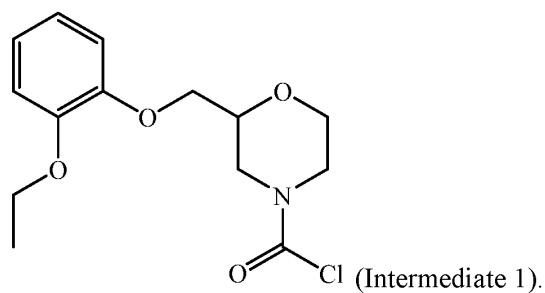
In Formula III, Y may be F, Cl, Br, I, an amino acid residue, a substituted amino acid residue, alkyl, or ester; R² may be alkyl, aryl, heteroaryl, or heterocyclyl; and R³-R¹⁴ may be each

independently H, F, Cl, Br, I, CN, NO₂, alkyl, aryl, heteroaryl, or heterocyclyl. In some embodiments, R² is ethyl.

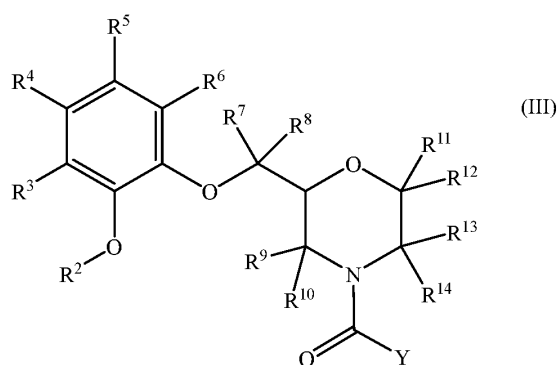
[0043] In some embodiments, the compound represented by Formula III is:



[0044] In some embodiments, the compound represented by Formula III is:

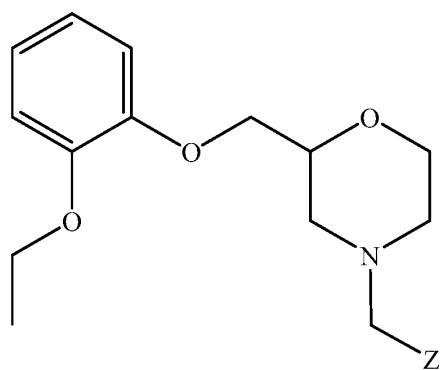


[0045] In another aspect, a compound represented by Formula IV is provided, or a stereoisomer thereof, and/or a salt thereof:

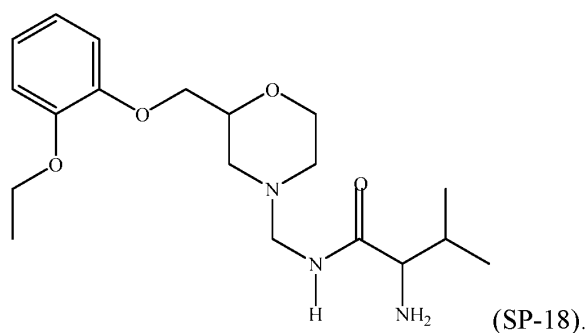


In Formula III, Z may be H, F, Cl, Br, I, an amino acid residue, a substituted amino acid residue, or a nitrogen-containing group; R^2 may be alkyl, aryl, heteroaryl, or heterocyclyl; and R^3 - R^{14} may be each independently H, F, Cl, Br, I, CN, NO_2 , alkyl, aryl, heteroaryl, or heterocyclyl. In some embodiments, R^2 is ethyl.

[0046] In some embodiments, the compound represented by Formula IV is:



[0047] In some embodiments, the compound represented by Formula IV is:



[0048] In some embodiments, a composition includes a derivative of substituted morpholines of Formula I, II, III, or IV, stereoisomers thereof, and/or salts thereof, and at least one pharmaceutically acceptable excipient or carrier.

[0049] In some embodiments, a pharmaceutical composition includes comprising a derivative of substituted morpholines of Formula I, II, III, or IV, stereoisomers thereof, and/or salts thereof with a pharmaceutically acceptable carrier or excipient. The pharmaceutical

formulation may be in an appropriate dosage form. Illustrative dosage forms include, but are not limited to, injections, oral forms, suppositories, caches, pouches, transdermal, and the like.

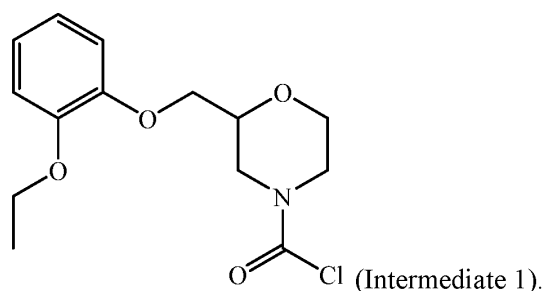
[0050] In another aspect, treatment of a CNS disorder is provided by administering a composition including a derivative of substituted morpholines of Formulae I, II, III, or IV, or salts thereof as described herein to a subject in need thereof.

[0051] In another aspect, a method is provided for administering to a subject a composition including a compound of Formula I, II, III, or IV or salts thereof. In one aspect, the subject is a mammal. In further embodiments, the mammalian subject is a human. In particular embodiments, the mammalian subject is an adult human or a human child.

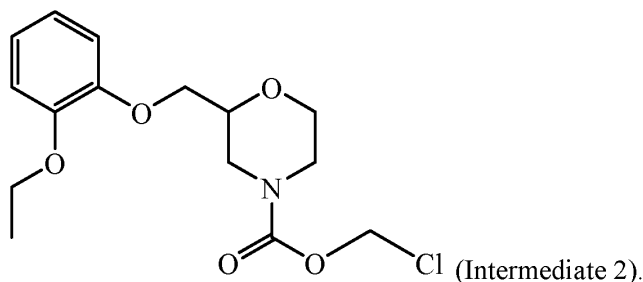
[0052] In some embodiments, the methods described herein include administering the derivative of substituted morpholines of Formula I, II, III, or IV, stereoisomers thereof, and/or salts thereof along with at least one additional pharmaceutical agent. In some embodiments, the at least one additional pharmaceutical agent is another agent for a CNS disorder. In further embodiments, the at least one additional pharmaceutical agent is 2-((2-ethoxyphenoxy)methyl)morpholine or a salt thereof.

[0053] In one embodiment, the derivative of substituted morpholines may be prepared from 2-((2-ethoxyphenoxy)methyl)morpholine or a salt thereof.

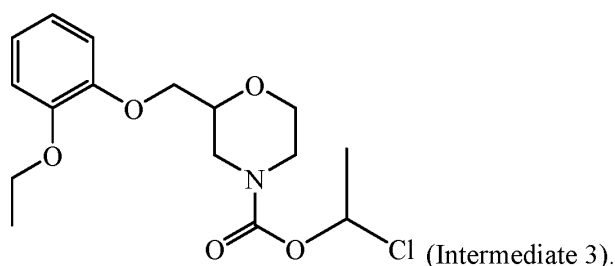
[0054] In one embodiment, the derivative of substituted morpholines may be prepared by reacting 2-((2-ethoxyphenoxy)methyl)morpholine or a salt thereof with sodium bicarbonate to form the intermediate 1 having the following structure:



[0055] In one embodiment, the derivative of substituted morpholines may be prepared by reacting 2-((2-ethoxyphenoxy)methyl)morpholine or a salt thereof with 1-chloromethyl chloroformate forming the Intermediate 2 having the following structure:



[0056] In one embodiment, the derivative of substituted morpholines can be prepared by reacting 2-((2-ethoxyphenoxy)methyl)morpholine or a salt thereof with 1-chloroethyl chloroformate forming the Intermediate 3 having the following structure:



[0057] In one embodiment, the derivatives of substituted morpholines of Formula I, II, III, or IV are prepared by reacting 2-((2-ethoxyphenoxy)methyl)morpholine or a salt thereof with the Intermediate 1, Intermediate 2, or Intermediate 3.

[0058] In another embodiment, a method of making the derivatives of substituted morpholines of Formula I, II, III, or IV are provided.

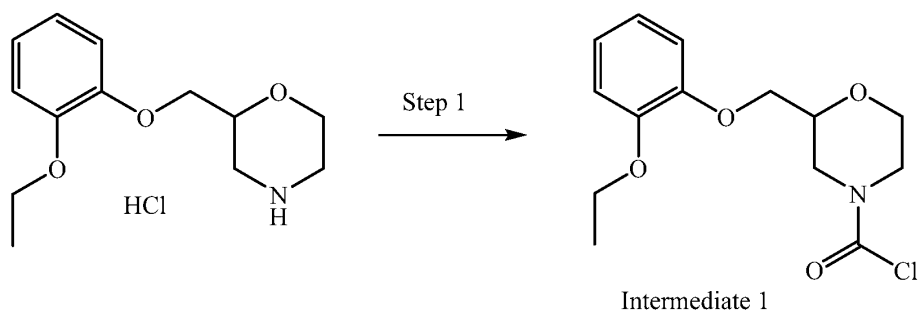
[0059] The derivatives of substituted morpholines may be analyzed by liquid chromatography-mass spectrometry (LCMS) and nuclear magnetic resonance (NMR) spectroscopy.

[0060] The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

[0061] Procedures for making the Intermediates. It is understood that while in some structures, chiral centers are indicated in either an R or S configuration, the other configuration is also disclosed herein.

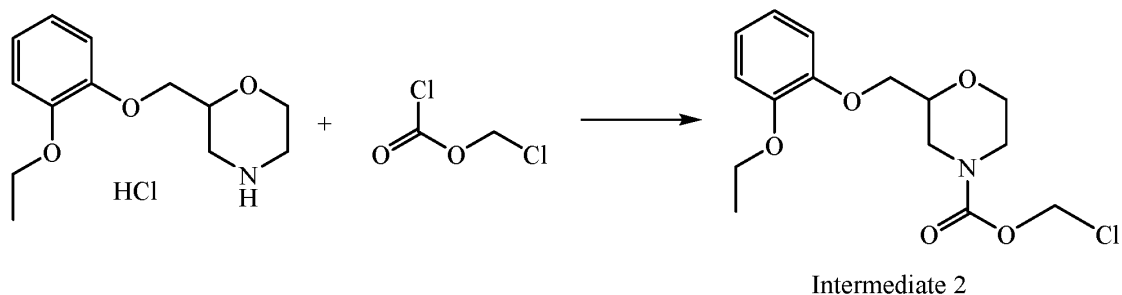
[0062] Intermediate 1: Synthesis of 2-((2-ethoxyphenoxy)methyl)morpholine-4-carbonyl chloride.



[0063] A solution of 2-((2-ethoxyphenoxy)methyl)-morpholine hydrochloride (500 mg, 1.83 mmol) in dichloromethane (50 ml) was added dropwise to a slurry of sodium bicarbonate (460 mg, 5.48 mmol). The reaction mixture was stirred for 30 minutes. A solution of triphosgene (358 mg, 1.21 mmol) in dichloromethane (25 ml) was added at 10-15°C over 15 minutes. The reaction mixture was stirred at room temperature for 3 hours. The reaction mass was filtered to remove sodium chloride and the filtrate is concentrated under vacuum to give 438 mg of ethyl methyl carbamoyl chloride as a light yellow oil (yield: 80%).

[0064] ¹H NMR (CDCl₃, 400MHz): δ ppm 6.88-6.91 (m, 4H), 4.39-4.47 (br t, 1H), 3.96-4.25 (m, 6H), 3.83-3.87 (br t, 1H), 3.61-3.71 (br t, 1H), 3.03-3.38 (m, 2H), 1.44 (t, 3H).

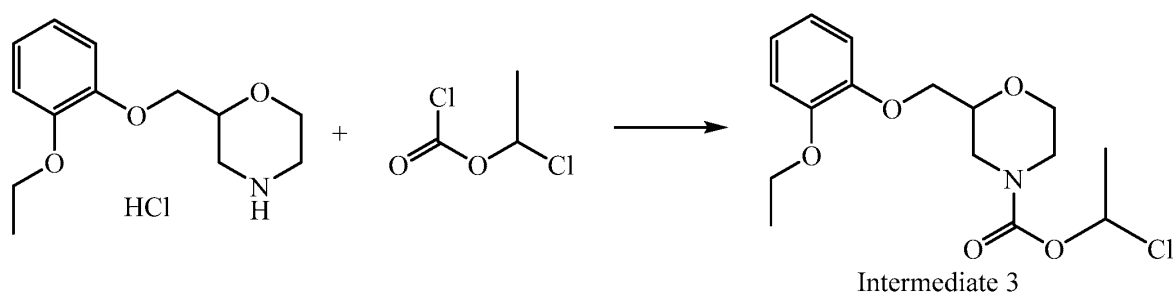
[0065] Intermediate 2: chloromethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate.



[0066] To a stirred ice cold mixture of 2-((2-ethoxyphenoxy)methyl)morpholine hydrochloride (1.3 gm, 4.52 mmol), trimethylamine (1.01 gm, 9.95 mmol) dichloromethane was added dropwise 1-chloromethyl chloroformate. The reaction mixture was stirred at 10-15°C, allowed to attain room temperature and stirred for 5 hours. The precipitated solids were filtered and the filtrate was concentrated. The crude product was purified by column chromatography (hexane:EtOAc 7:3) to afford 1.2 gm (80%) of white solid.

[0067] ^1H NMR (CDCl_3 , 400MHz): δ ppm 1.46 (t, 3 H), 1.59 (s, 4 H), 3.05 (d, 2 H), 3.63 (d, 1H), 3.92 - 4.02 (m, 2 H), 4.04 - 4.15 (m, 4 H), 4.23 (br. s., 1 H), 5.76 - 5.86 (m, 2 H), 6.84-7.00 (m, 4 H).

[0068] Intermediate 3: 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate.



[0069] To a stirred ice cold mixture of 2-((2-ethoxyphenoxy)-methyl)morpholine hydrochloride (2 gm, 6.96 mmol), trimethylamine (1.01 g, 9.95 mmol) dichloromethane was added dropwise 1-chloroethyl chloroformate (1.19 g, 83.5 mmol). The reaction mixture was stirred at 10-15°C and allowed to attain room temperature and stirred for 5 h. Precipitated solids

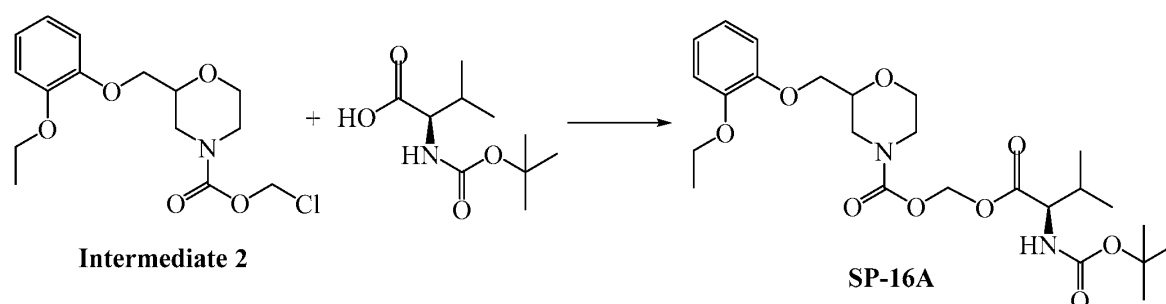
were filtered and the filtrate was concentrated. The crude product was purified by column chromatography (hexane:EtOAc 7:3) to afford 1.42 gm (59.3%) of white solid.

[0070] ^1H NMR (400 MHz, CDCl_3): δ ppm 1.39-1.51 (m, 3 H), 1.83 (d, 3 H), 2.92-3.12 (m, 2 H), 3.54-3.72 (m, 1 H), 3.85 (br. s., 1 H), 3.89-4.13 (m, 7 H), 4.20 (d, 1 H), 6.61 (m, 1 H), 6.84-7.01 (m, 4 H).

[0071] Procedures for Synthesizing the Compounds of Formula I, II, III or IV:

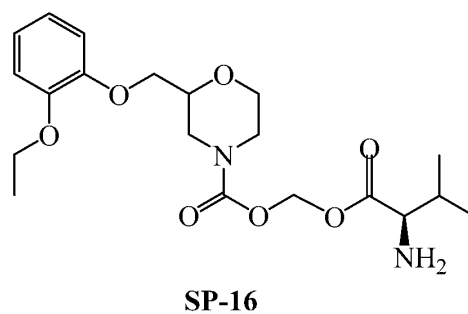
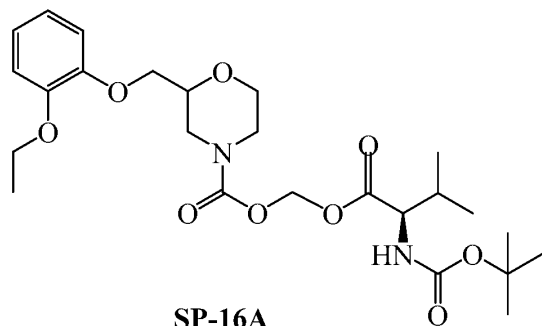
[0072] SP-16: ((D-valyl)oxy)methyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate.

Step 1.



[0073] A reaction mixture of N-Boc-D-Valine (175 mg, 0.80 mmol), cesium carbonate (130 mg, 0.4 mmol), in methanol (3.3 ml) was stirred at room temperature for 3 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added chloromethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 2) (177 mg, 0.52 mmol). The resulting mixture was stirred at 80°C for 20 hours. DMF was evaporated under vacuum, residue dissolved in chloroform and purified by column chromatography (hexane:EtOAc 1:1) to afford 112 mg (39.4%) of semi-solid oil.

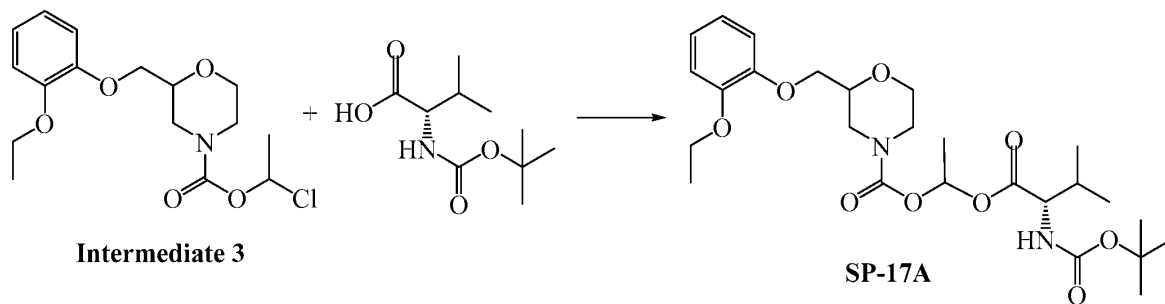
Step 2:



[0074] A solution of SP-16A (65 mg, 0.12 mmol) and 2M HCl in dioxane stirred at room temperature overnight. Solvent was evaporated and dried under vacuum to obtain 50 mg (95.6%) of pure desired product (SP-16) as a brown semisolid. LCMS: Purity: 96.27% by ELS detector. MS: M+H=411.14. ¹H NMR (CDCl₃, 400MHz): δ ppm 1.12 (t, 6 H), 1.44 (t, 3 H), 2.46 (br. s, 1 H), 2.90 - 3.10 (m, 2H), 3.52-3.66 (m, 1 H), 3.85-4.20 (m, 10 H), 5.83 (br. s, 1 H), 5.95 (d, 1 H), 6.85-6.96 (m, 4 H), 8.24 (br. s, 2 H).

[0075] SP-17: 1-((L-valyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate.

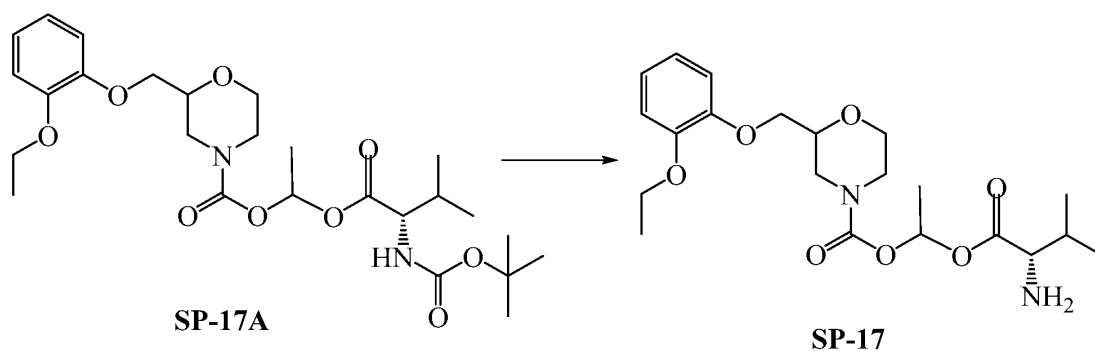
Step 1.



[0076] A reaction mixture of N-Boc-L-Valine (175 mg, 0.80 mmol), cesium carbonate (130 mg, 0.4 mmol), in methanol (3.3 ml) was stirred at room temperature for 3 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added chloromethyl 2 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 3) (184 mg, 0.52 mmol). The resulting mixture was stirred at 80°C for 20 hours.

DMF was evaporated under vacuum, residue dissolved in chloroform and purified by column chromatography (hexane:EtOAc 8:2) to obtain 141 mg (48.3%) of semisolid oil.

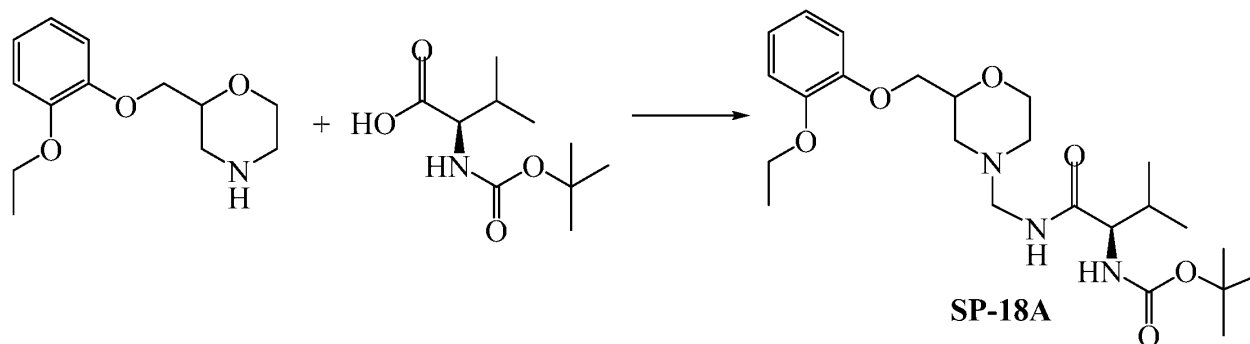
Step 2:



[0077] A solution of SP-17A (65 mg, 0.11 mmol) and 2M HCl in dioxane stirred at room temperature overnight. The solvent was then evaporated and the product dried under vacuum to obtain 51 mg (92.4%) of pure desired product (SP-17) as a brown solid. LCMS: Purity: 100% by ELS detector. MS: M+H= 425.17. ¹H NMR (CDCl₃, 400MHz): δ ppm 1.12 (t, 6 H), 1.44 (t, 3 H), 2.46 (br. s., 1 H), 2.90-3.10 (m, 2 H), 3.52-3.66 (m, 1 H), 3.85-4.20 (m, 10 H), 5.83 (br. s., 1 H), 5.95 (d, 1 H), 6.85-6.96 (m, 4 H), 8.24 (br. s., 2 H).

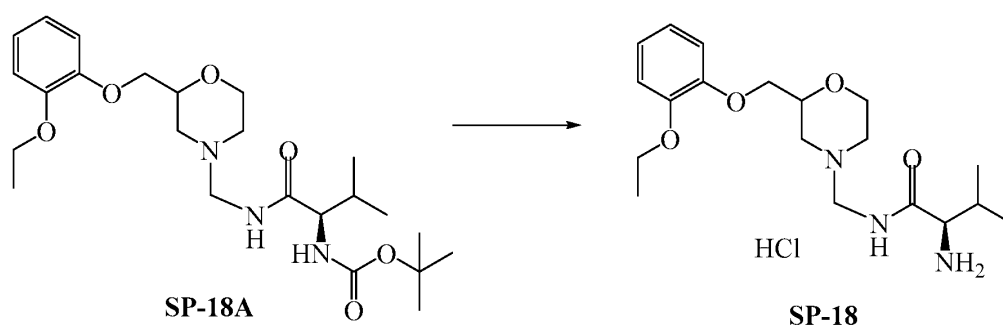
[0078] SP-18: (2R)-2-amino-N-((2-((2-ethoxyphenoxy)methyl)morpholino)methyl)-3-methylbutanamide bis hydrochloride salt.

Step 1:



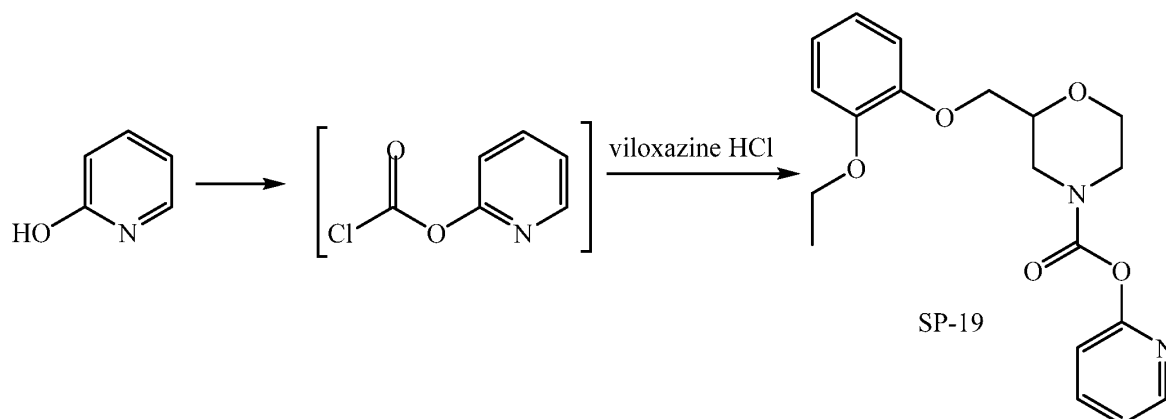
[0079] To a solution of 2-((2-ethoxyphenoxy)methyl)-morpholine hydrochloride (108 mg, 0.4 mmol) and polyformaldehyde (50 mg) in THF (2 ml) was added a slurry of sodium bicarbonate (92 mg, 1.1 mmol). The reaction mixture was stirred for 48 hours minutes. The reaction mass was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in chloroform and purified by column chromatography (hexane: EtOAc 8:1) to obtain 80 mg (43%) of semi-solid oil.

Step 2:



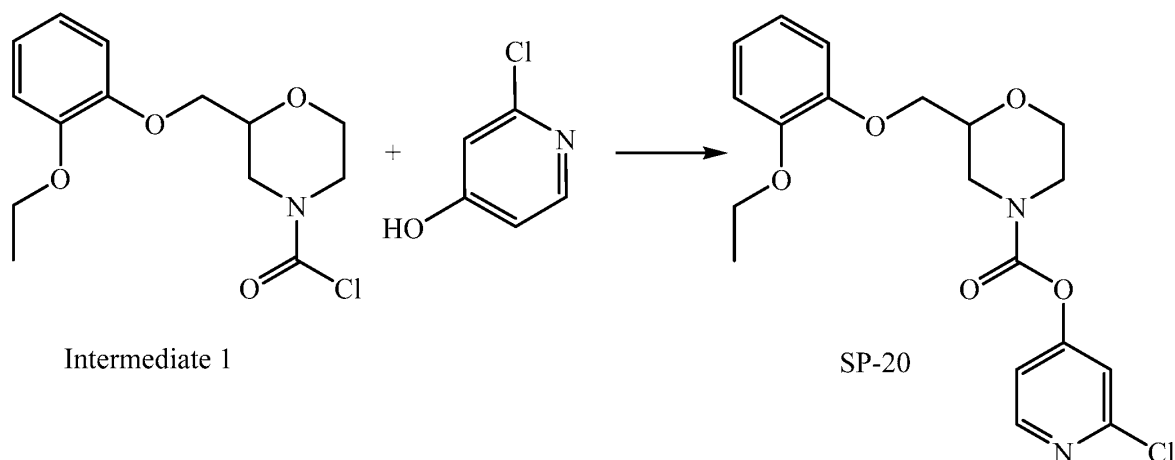
[0080] Solution of SP-18A (70 mg, 0.15 mmol) and 2M HCl in dioxane was stirred at room temperature overnight. The solvent was evaporated and dried under vacuum to obtain 50 mg (76%) of pure desired product (SP-18) as a brown solid. LCMS: $M+H = 366.20$. Purity 98.73% by ELS detector. ^1H NMR (CDCl_3 , 400MHz): δ ppm 9.8-10.5 (br m, 1H), 8.2-8.5 (br s, 2 H), 6.75-7.1 (m, 4H), 4.2-5.0 (m, 4H), 3.9-4.2 (m, 6H), 3.70-3.87 (m, 2H), 3.0-3.5 (br s, 1H), 1.75-2.25 (m, 4H), 1.3-1.5 (m, 3H), 1.1 (br s, 6H).

[0081] SP-19: Pyridin-2-yl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate



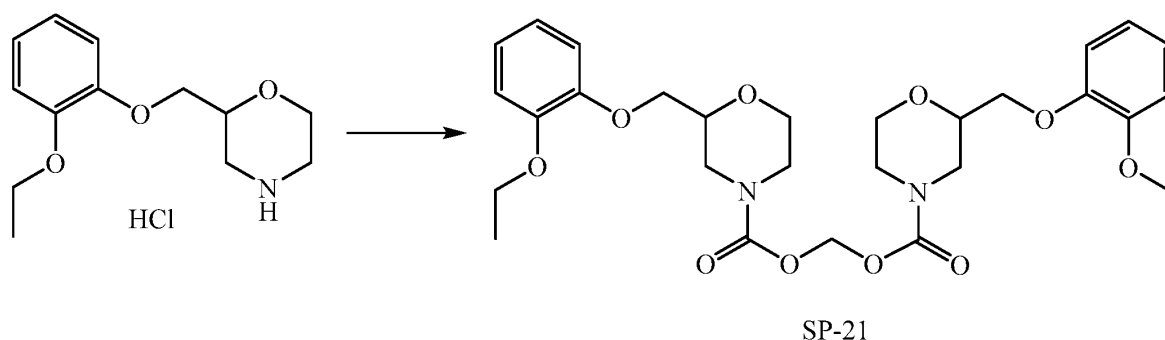
[0082] A solution of triphosgene (163 mg, 0.55 mmol) in dichloromethane (DCM; 1 ml) was stirred in an ice bath at 0-5°C temperature for 15 min and a solution of 2-hydroxypyridine (150 mg, 1.58 mmol), *N,N*-diisopropylethylamine (DIPEA; 208 mg, 1.61 mmol) in DCM (1 ml) was added dropwise. The reaction mixture allowed to attain room temperature. The completion of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture was evaporated, reconstituted with DCM and evaporated (X 3) to remove excess of triphosgene. Residue was reconstituted with DCM, and a solution of 2-((2-ethoxyphenoxy)methyl)morpholine hydrochloride (363mg, 1.26 mmol) and TEA (13.6 mg, 1.34 mmol) in DCM added and stirred overnight at room temperature. The reaction mixture was absorbed on silica and was purified by column chromatography using hexane – ethyl acetate (2:1) to obtain the target compound (SP-19) as a semisolid 56 mg (12.3%). LCMS: M+H= 359.08. Purity 100% by ELS detector. ¹H NMR (400 MHz, CDCL₃): δ 1.25-1.46 (m, 3 H), 3.02-3.34 (m, 2 H), 3.69-3.76 (m, 1 H), 3.95–4.16 (m, 7 H), 4.28–4.42 (d, 1 H), 6.85-6.99 (m, 4 H), 7.11 (dd, 1 H), 7.21 (dd, 1 H), 7.75 - 7.83 (m, 1 H), 8.39 (dd, 1 H).

[0083] SP-20: 2-Chloropyridin-4-yl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate.



[0084] To a stirred and ice-cooled solution of 2-chloro-4-hydroxy pyridine, (95 mg, 0.73 mmol) in anhydrous THF (10 mL) was added 2-((2-ethoxyphenoxy)methyl)morpholine-4-carbonyl chloride (Intermediate 1) (273 mg, 0.33 mmol), followed by a dropwise addition of NaH (60% in oil, 35 mg, 0.146 mmol). The reaction mixture was stirred for 14 hours at room temperature under argon. After evaporation of the solvent in vacuo, water (5 mL) was added and extracted with ether (3 × 10 mL). The organic phase was washed with dilute NaOH (pH 10- 11), dried, and evaporated to dryness in vacuum. Purification by column chromatography (hexane:EtOAc 2:1) afforded 83 mg (29%) of a semisolid (SP-20). LCMS: Purity 100% by ELS detector. MS: M+H=393.08. ¹H NMR (CDCl₃, 400MHz): δ ppm 1.38-1.47 (m, 3 H), 3.04-3.32 (m, 2 H), 3.70 (t, 1 H) 3.9-3.93 (m, 1 H), 4.03-4.08 (m, 5 H), 4.15-4.18 (m, 1 H), 4.30-4.35 (m, 1 H), 6.87-6.99 (m, 4 H), 7.11-7.12 (m, 1 H), 7.23 (d, 1 H), 8.37 (d, 1 H).

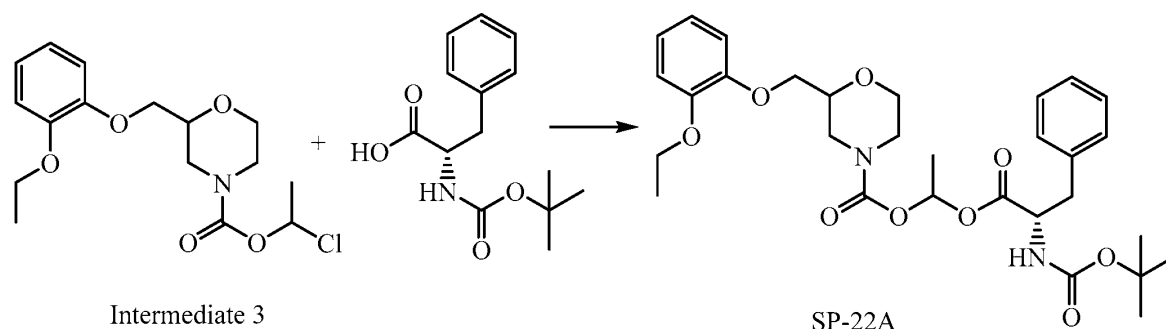
[0085] SP-21: Methylene bis(2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate).



[0086] A solution of 2-((2-ethoxyphenoxy)methyl)morpholine hydrochloride (108 mg, 0.4 mmol) and methylene dibromide (50 mg) in DMF (2 ml) was added a slurry of cesium carbonate (100 mg, 1.2 mmol). Carbon dioxide gas was passed into the reaction for 30 minutes and the mixture stirred at room temperature for 48 hours. The reaction mass was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in chloroform and purified by column chromatography (hexane:EtOAc 4:1) to afford 52 mg (22.6%) of a solid. Purity 100% by ELS detector. MS: M+H= 575.15. ¹H NMR (CDCl₃, 400MHz): δ ppm 6.7-7.00 (m, 8H), 5.83 (s, 2H), 3.8-4.2 (m, 16H), 3.5-3.6 (m, 2H), 2.8-3.0 (m, 4H), 1.43-1.47 (t, 6H).

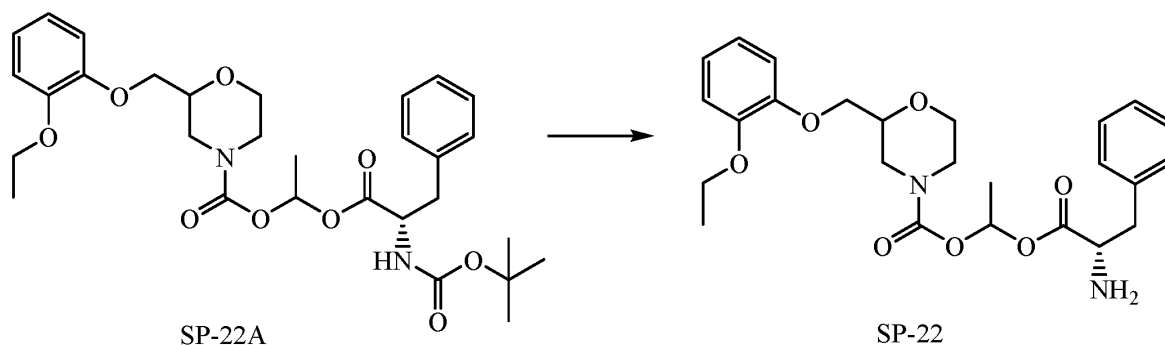
[0087] SP-22: 1-((L-phenylalanyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate.

Step 1.



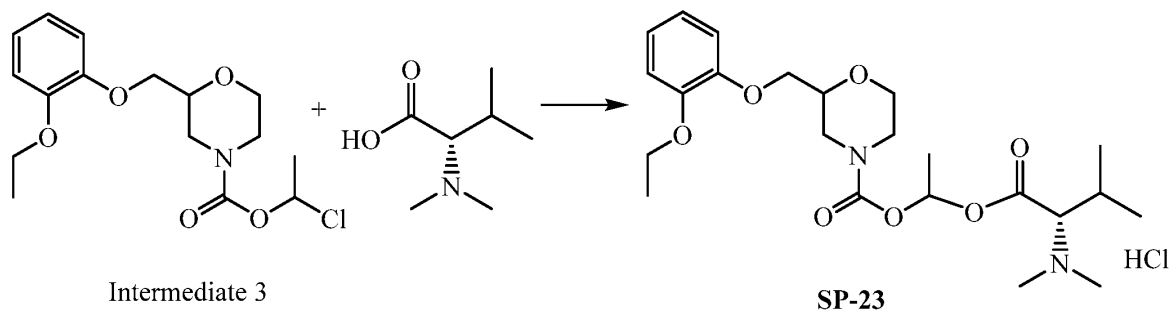
[0088] A reaction mixture of N-Boc-phenylalanine (175 mg, 0.66 mmol), cesium carbonate (107 mg, 0.33 mmol), in methanol (1.3 ml) were stirred at room temperature for 3 hours, then methanol was evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 3) (150 mg, 0.42 mmol). The resulting mixture was stirred at 80°C for 20 hours. The DMF was then evaporated under vacuum, the residue dissolved in chloroform, and then purified by column chromatography (hexane:EtOAc 8:2) to afford 232 mg (61%) of semi-solid oil.

Step 2:



[0089] Solution of SP-22A (140 mg, 0.238 mmol) and 2M HCl in dioxane was stirred at room temperature overnight. The solvent was evaporated and dried under vacuum to obtain 58 mg (52%) of pure desired product as a light brown solid. LCMS: Purity: 100% by ELS detector. MS: M+H=495.24. ¹H NMR (CDCl₃, 400MHz): δ ppm 1.25 - 1.50 (m, 6 H), 2.95 - 3.06 (m, 2 H), 3.35-3.71 (m, 4 H) 3.76- 4.13 (m, 8 H) 4.34 – 4.40 (m, 2 H) 6.85 - 6.92 (m, 5 H), 7.25-7.36 (m, 5 H), 8.70 (br. s., 1 H), 8.79 (br. s., 1 H).

[0090] SP-23 1-((dimethyl-L-valyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate, hydrochloride.

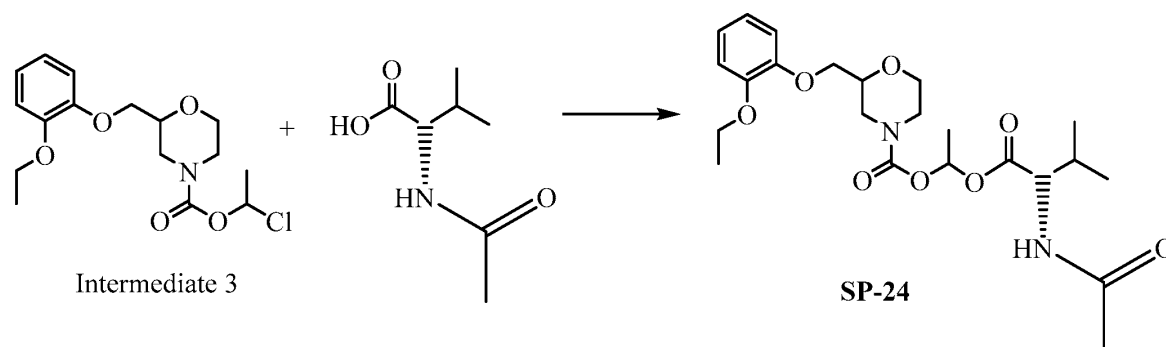


[0091] A reaction mixture of L-Val-N,N-dimethyl (100 mg, 0.68 mmol), cesium carbonate (110 mg, 0.34 mmol), in methanol (0.75 ml) were stirred at room temperature for 3 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 3) (160 mg, 0.44 mmol). The resulting mixture was stirred at 80°C for 20 hours.

The DMF was evaporated under vacuum, residue dissolved in chloroform and purified by column chromatography (hexane:EtOAc 3:2) to afford 91 mg (45.7%) of semisolid.

[0092] 77 mg of the parent compound was dissolved in 2 ml of chloroform and 0.17 ml of 2M HCl in dioxane was added. The reaction mixture was stirred at room temperature for 2 hours. The solvent was then evaporated under Argon and then under vacuum to obtain 81 mg of an oil. LCMS: Purity: 99.61% by ELS detector. MS: M+H= 453.30 M+Na=475.28. ¹H NMR (CDCl₃, 400MHz): δ ppm 0.89 (dd, 3 H), 0.97 (d, 3 H), 1.45 (t, 3 H), 1.53 (d, 3 H), 1.63 (s, 1 H), 2.01 (dt, 6.54 Hz, 1 H), 2.31 (s, 6 H), 2.72 (m, 1 H), 3.04 (br. s., 2 H), 3.59 (d, 1 H), 3.81–4.18 (m, 8 H), 6.88–6.91 (m, 5 H).

[0093] SP-24: 1-((Acetyl-L-valyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate.

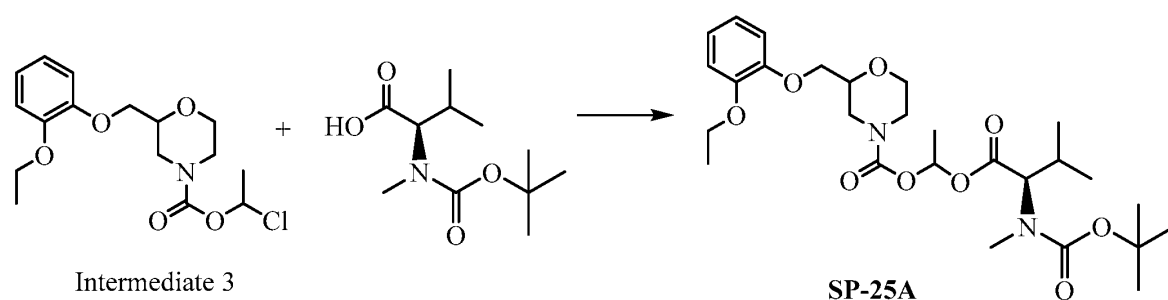


[0094] A reaction mixture of N-acetylvaline (120 mg, 0.69 mmol), cesium carbonate (110 mg, 0.34 mmol), in methanol (0.9 ml) were stirred at room temperature for 3 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 3) (160 mg, 0.44 mmol). The resulting mixture was stirred at 80°C for 20 hours. The DMF was evaporated under vacuum, residue dissolved in chloroform and purified by column chromatography (hexane:EtOAc 3:2) to afford 75 mg (37%) of oil. LCMS: Purity: 100% by ELS detector. MS: M+H= 473.26 M+Na=495.24. ¹H NMR (CDCl₃, 400MHz): δ ppm 0.82–1.03 (m, 3 H), 0.93 (d, 3 H), 1.45 (br. s., 3 H), 1.52–1.53 (m, 3 H), 2.04 (d, 3 H), 2.17 (m, 1 H), 2.94 – 3.10 (m, 2 H),

3.57-3.60 (m, 1H), 3.84 - 4.17 (m, 8 H), 4.55-4.62 (m, 1 H), 5.97 (br. s., 1 H), 6.89-6.95 (m, 5 H).

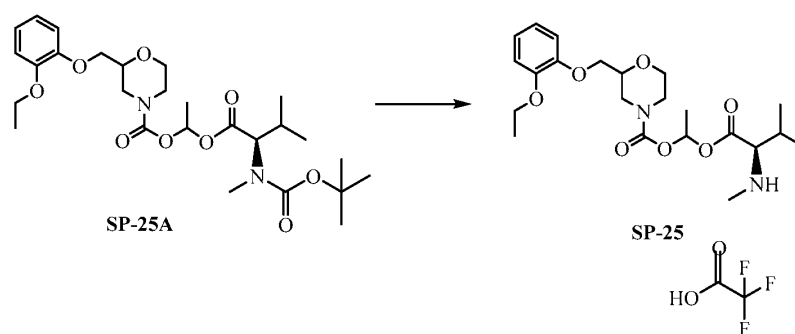
[0095] SP-25: 1-((methyl-D-valyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate, trifluoroacetic acid salt.

Step 1.



[0096] A reaction mixture of N-Boc-D-Valine (160 mg, 0.69 mmol), cesium carbonate (110 mg, 0.35 mmol), in methanol (1.2 ml) was stirred at room temperature for 3 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 3) (160 mg, 0.44 mmol). The resulting mixture was stirred at 80°C for 20 hours. DMF was evaporated under vacuum, residue dissolved in chloroform and purified by column chromatography (hexane:EtOAc 2:1) to afford 90 mg (36.1%) of semi-solid oil.

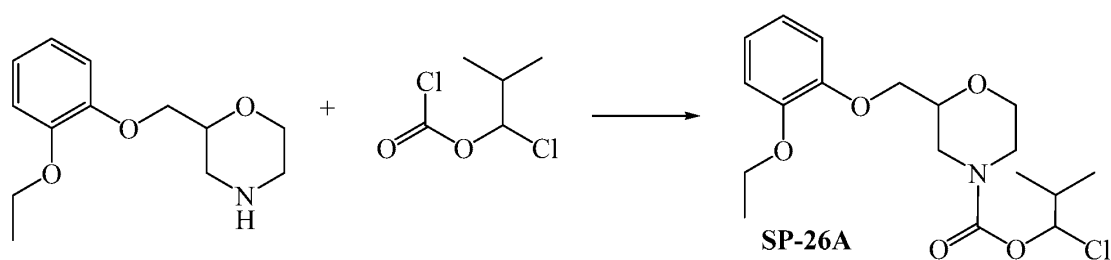
Step 2:



[0097] Solution of SP-25A (50 mg, 0.09 mmol) in DCM (1 ml) and TFA (0.1 ml) was stirred at room temperature overnight (18 hours). The solvent was then evaporated and dried under vacuum to obtain 35.8 mg (85.3%) of pure desired product as a yellow oil. LCMS: Purity: 100% by ELS detector. MS: M+H=439.24 ¹H NMR (CDCl₃, 400MHz): δ 0.98 - 1.15 (m, 6 H), 1.36 - 1.49 (m, 3 H), 1.57 (d, 3 H), 2.37 (br. s., 1 H), 2.78 (s, 3 H), 2.88 - 3.10 (m, 2 H), 3.14 (d, 1 H), 3.49 - 3.64 (m, 1 H), 3.67 (br. s., 1 H), 3.84 (br. s., 1 H), 3.89 (br. s., 1 H), 3.97 (br. s., 2 H), 4.00 - 4.11 (m, 3H), 4.16 (d, 2 H), 6.84 - 7.00 (m, 5 H).

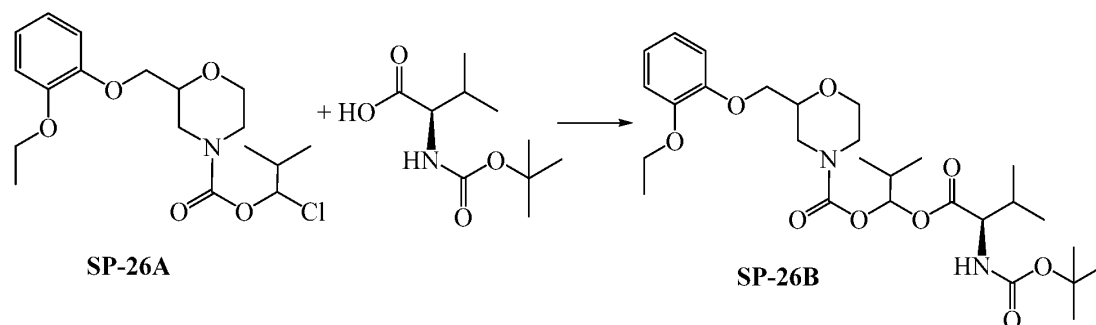
[0098] SP-26: 1-((D-valyl)oxy)-2-methylpropyl 2-((2-ethoxyphenoxy)methyl)-morpholine-4-carboxylate HCl salt.

Step 1:



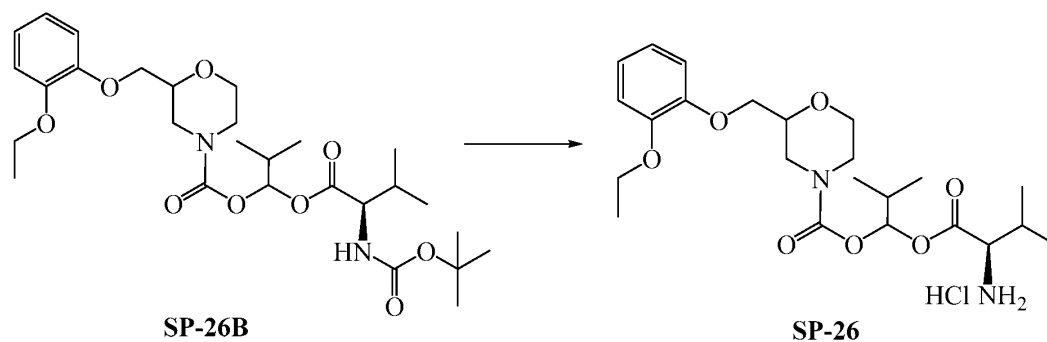
[0099] To a stirred ice cold mixture of 2-((2-ethoxyphenoxy)-methyl)morpholine hydrochloride (350 mg, 1.22 mmol), trimethylamine (271 mg, 2.68 mmol) dichloromethane was added dropwise 1-chloro-2-methylpropylchloroformate (210 mg, 1.46 mmol). The reaction mixture was stirred at 10-15°C and allowed to attain room temperature and stirred for 2 hours. Precipitated solids were filtered and the filtrate was concentrated. The crude product was purified by column chromatography (hexane:EtOAc 4:1) to afford 0.55 gm (59.3%) of oil. ¹H NMR (CDCl₃, 400MHz): δ ppm 1.06-1.09 (m, 6 H), 1.43-1.46 (t, 3 H), 2.18-2.22 (m, 1 H), 2.95-3.20 (m, 2 H), 3.55-3.69 (m, 1 H), 3.86-4.27 (m, 8 H), 6.36-6.37 (d, 1H), 6.86-6.97 (m, 4 H).

Step 2.



[0100] A reaction mixture of N-Boc-D-Valine (200 mg, 0.92 mmol), cesium carbonate (150 mg, 0.46 mmol), in methanol (1.5 ml) were stirred at room temperature for 2 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added 1-chloro-2-methylpropyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-26A) (230 mg, 0.59 mmol). The resulting mixture was stirred at 80°C for 20 hours. DMF was evaporated under vacuum, residue dissolved in chloroform and purified by column chromatography (hexane:EtOAc 4:1) to afford 170 mg (52.1 %) of semisolid oil.

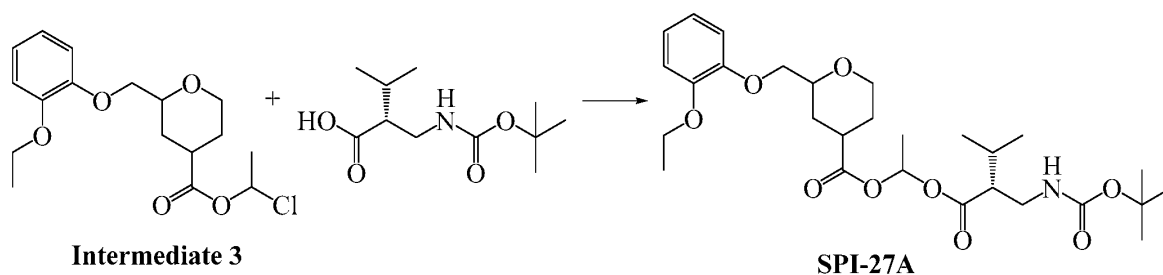
Step 3:



[0101] Solution of SP-26B (110 mg, 0.2 mmol) in dioxane (1 ml) and 2M HCl in dioxane (0.4 ml) stirred at room temperature overnight (18 hours). The solvent was then evaporated and dried under vacuum to obtain 80 mg (88%) of pure desired product as an oil. LCMS: Purity: 100% by ELS detector. MS: M+H=453.22. ¹H NMR (CDCl₃, 400MHz): δ ppm 0.92-1.04 (m, 6 H), 1.04-1.23 (m, 6 H), 1.42 (t, 3 H), 2.09 (br, 1 H), 2.48 (br, 1 H), 2.89-3.17 (m, 1 H), 3.49-4.25 (m, 13 H), 6.81-6.73 (m, 1H), 6.88-6.92 (m, 4 H), 8.70-8.76 (d, 2 H).

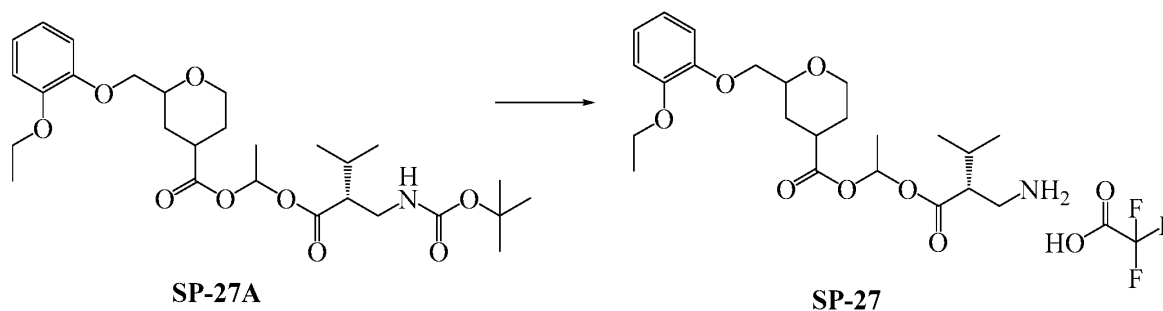
[0102] SP-27: 1-(((R)-2-(aminomethyl)-3-methylbutanoyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate trifluoroacetic acid salt.

Step 1.



[0103] A reaction mixture of N-Boc-3-amino-2-isopropionic acid (100 mg, 0.43 mmol), cesium carbonate (70 mg, 0.22 mmol), in methanol (0.75 ml) were stirred at room temperature for 2 hours ("h"), then methanol evaporated, residue reconstituted with DMF (0.75 ml). To the reaction mixture was added chloromethyl 2 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 3) (99 mg, 0.28 mmol). The resulting mixture was stirred at 80°C for 20 hours. The DMF was evaporated under vacuum, the residue dissolved in chloroform and purified by column chromatography (hexane:EtOAc 4:1) to afforded 117 mg (77.6%) of semi-solid.

Step 2:

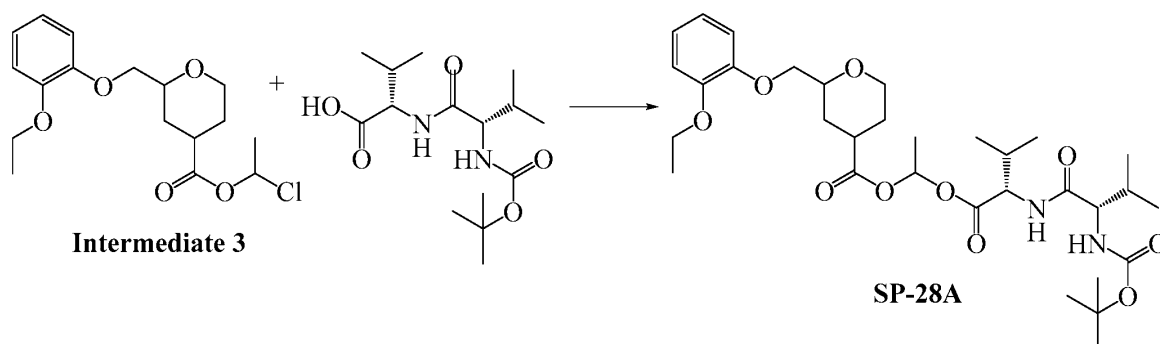


[0104] A solution of SP-27A (58 mg, 0.012 mmol) in chloroform (1 ml) and TFA (0.2 ml) stirred at room temperature for 24 hours. The solvent was then evaporated and dried under vacuum to obtain 52 mg (90%) of pure desired product as oil. LCMS: Purity: 100% by ELS

detector. MS: M+H=439.21. ^1H NMR (CDCl_3 , 400MHz): δ ppm 0.86-1.04 (m, 6 H), 1.35-1.49 (m, 3 H), 1.53 (br. s., 3 H), 2.96-3.09 (m, 1 H), 3.10-3.31 (m, 2 H), 3.79-3.91 (m, 2 H), 3.92-4.16 (m, 6 H), 6.85-7.01 (m, 4 H), 7.65 (br. s., 3 H).

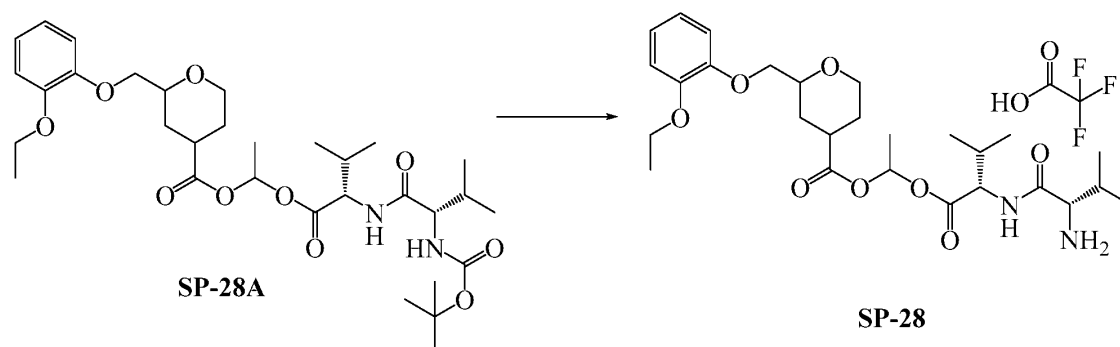
[0105] SP-28: 1-(((R)-2-(aminomethyl)-3-methylbutanoyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate trifluoroacetic acid salt.

Step 1.



[0106] A reaction mixture of Boc-Val-Val (150 mg, 0.47 mmol), cesium carbonate (80 mg, 0.24 mmol), in methanol (1.13 ml) was stirred at room temperature for 2 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 3) (110 mg, 0.3 mmol). The resulting mixture was stirred at 80°C for 18 hours. The DMF was evaporated under vacuum, residue dissolved in DCM and purified by column chromatography (hexane:EtOAc 1:1) to afford 35 mg (11.9%) of semi-solid.

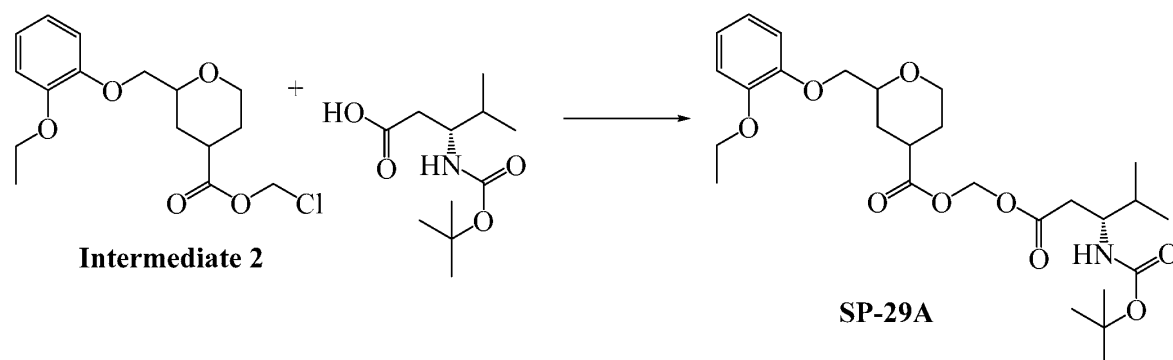
Step 2:



[0107] Solution of SP-28A (32 mg, 0.005 mmol) in chloroform (1 ml) and TFA (0.085 ml) was stirred at room temperature for 6 hours. The solvent was then evaporated and dried under vacuum to obtain 33 mg (98%) of pure desired product as yellow semi-solid. LCMS: Purity: 100% by ELS detector. MS: M+H= 524.27. ¹H NMR (CDCl₃, 400MHz): δ ppm 0.87-1.16 (m, 11 H), 1.36-1.56 (m, 6 H), 2.18 (br. s., 2 H), 2.99-3.05 (m, 2 H), 3.59-4.24 (m, 11 H), 6.18 (br. s., 2 H), 6.84 - 7.05 (m, 5H), 7.34-7.53 (m, 1 H), 8.10 (br. s., 2 H).

[0108] SP-29: (((R)-3-amino-4-methylpentanoyl)oxy)methyl 2-((2-ethoxyphenoxy)-methyl)morpholine-4-carboxylate, trifluoroacetic acid salt

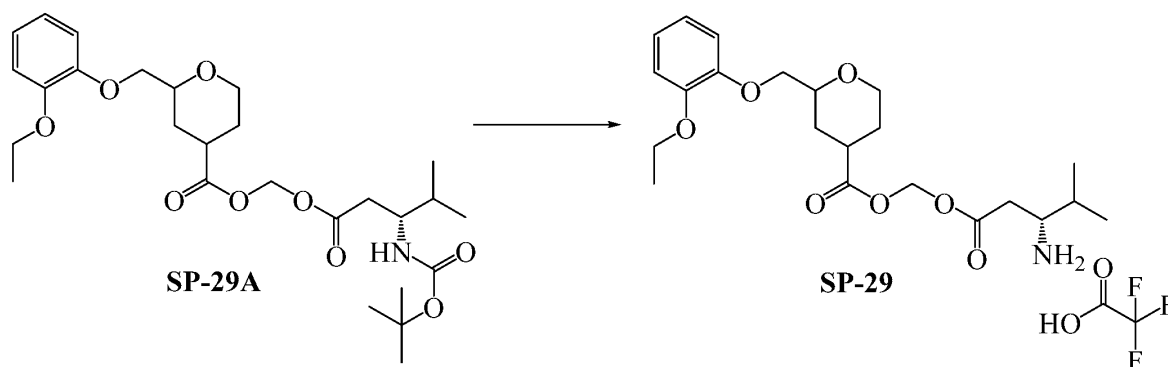
Step 1.



[0109] A reaction mixture of Boc-L-β-leucine (150 mg, 0.65 mmol), cesium carbonate (110 mg, 0.146 mmol), in methanol (1.13 ml) was stirred at room temperature for 2 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added chloromethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 2) (140 mg,

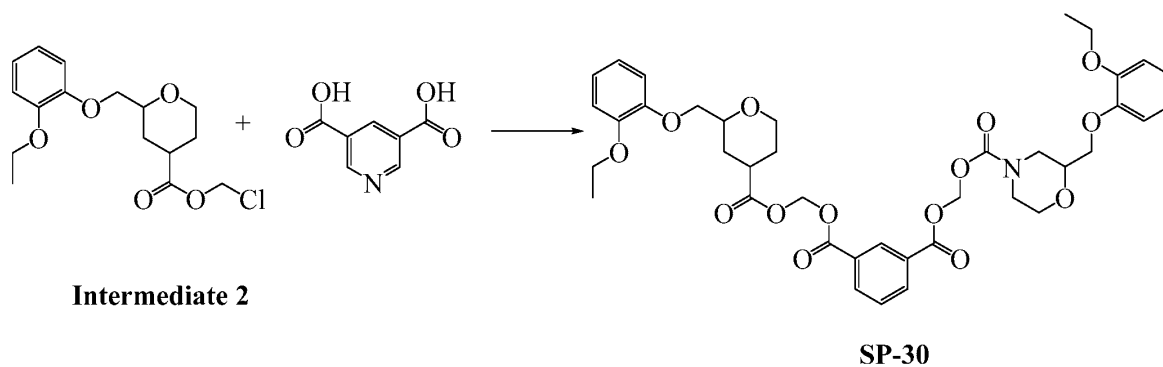
0.42 mmol). The resulting mixture was stirred at 80°C for 18 hours. The DMF was evaporated under vacuum, residue dissolved in DCM and purified by column chromatography (hexane:EtOAc 4:1) to afford 120 mg (54.5%) of semi-solid.

Step 2:



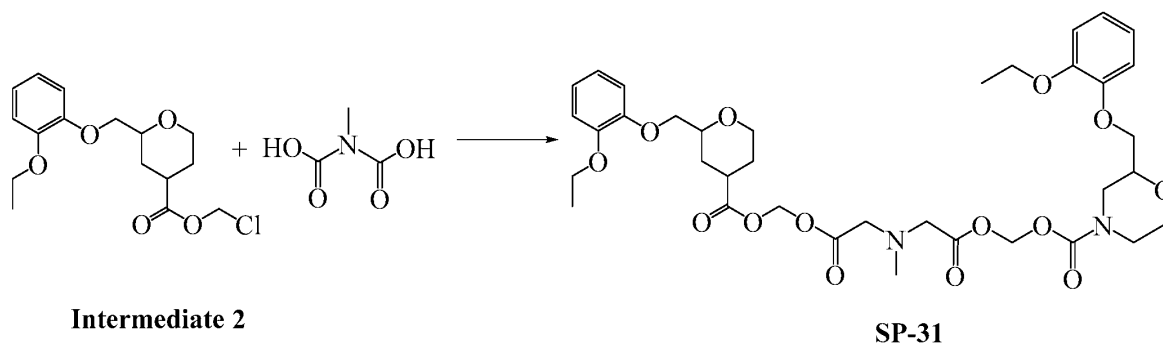
[0110] Solution of SP-29A (58 mg, 0.11 mmol) in chloroform (1 ml) and TFA (0.55 ml) stirred at room temperature for 24 hours. The solvent was then evaporated and dried under vacuum to obtain 50 mg (90%) of pure desired product as oil. LCMS: Purity: 100% by ELS detector. MS: M+H= 425.19. ¹H NMR (CDCl₃, 400MHz): δ ppm 1.03 (dd, 6 H), 1.36-1.48 (m, 3 H), 2.04 (m, 1 H), 2.79 (d, 2 H), 2.93-3.22 (m, 2 H), 3.46 (br. s. 1 H), 3.57-3.65 (m, 1 H), 3.90-4.18 (m, 6 H), 5.72-5.91 (m, 2 H), 6.86-7.02 (m, 3 H), 7.43-7.73 (m, 3 H), 8.35 (br. s., 3 H).

[0111] SP-30: Bis(((2-((2-ethoxyphenoxy)methyl)morpholine-4-carbonyl)oxy)methyl)pyridine-3,5-dicarboxylate



[0112] A reaction mixture of 3,5-pyridinedicarboxylic acid (75 mg, 0.4 mmol), cesium carbonate (190 mg, 0.6 mmol), in methanol (0.6 ml) was stirred at room temperature for 2 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added chloromethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 2) (370 mg, 1.1 mmol). The resulting mixture was stirred at 80°C for 18 hours. DMF was evaporated under vacuum, residue dissolved in DCM and purified by column chromatography (hexane:EtOAc 1:1) to afford 56 mg (18.5%) of semi-solid oil. LCMS: Purity: 100 % by ELS detector. MS: M+H= 754.21. ¹H NMR (CDCl₃, 400MHz): δ ppm 1.44 (t, 6 H), 2.92-3.21 (m, 4 H), 3.57-3.67 (m, 2 H), 3.84 (br. s, 2 H) 3.93-4.12 (m, 12 H), 4.18-4.27 (m, 2 H), 6.07-6.11 (m, 4 H), 6.82-7.04 (m, 8 H), 8.93 (s, 1 H), 9.43 (s, 2 H).

[0113] SP-31: ((2,2'-(methylazanediyl)bis(acetyl))bis(oxy))bis(methylene) bis(2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate).

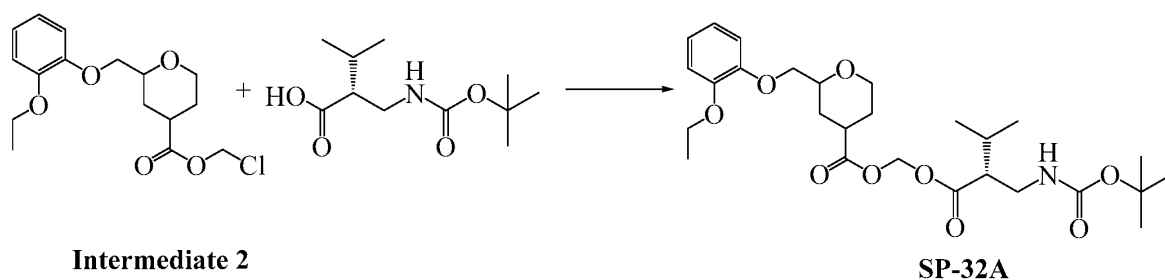


[0114] A reaction mixture of methyliminodiacetic acid (50 mg, 0.3 mmol), cesium carbonate (144 mg, 0.4 mmol), in methanol (0.4 ml) was stirred at room temperature for 2 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added chloromethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 2) (280 mg, 0.8 mmol). The resulting mixture was stirred at 80°C for 18 hours. DMF was evaporated under vacuum, residue dissolved in DCM and purified by column chromatography (hexane:EtOAc 1:1). Resulting product re-purified by reverse phase C18 column using acetonitrile and water gradient mixture to obtain 30.5 mg (13.8%) of pure semisolid-oil product. LCMS: Purity: 100 % by ELS detector. MS: M+H= 734.23. ¹H NMR (CDCl₃, 400MHz): δ

ppm 1.43–1.48 (t, 6 H), 2.55 (s, 3 H), 2.89 - 3.18 (m, 4 H), 3.51-3.69 (m, 6 H), 3.82-4.24 (m, 16 H), 5.82 (s, 4 H), 6.83-7.00 (m, 8 H).

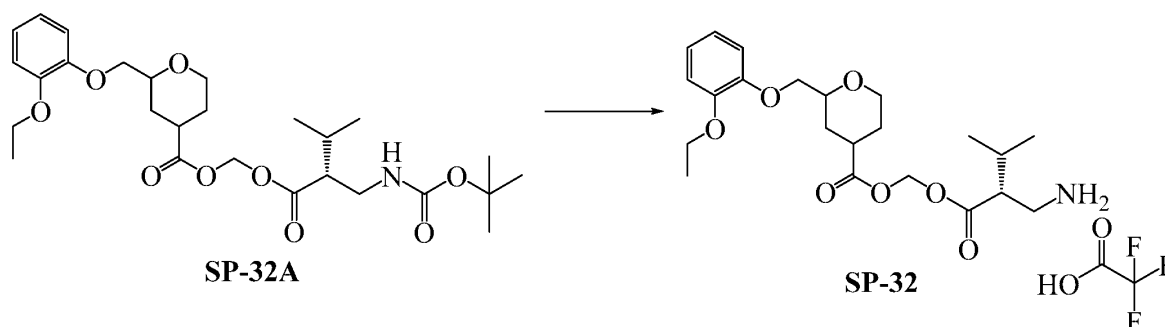
[0115] SP-32: (((R)-2-(aminomethyl)-3-methylbutanoyl)oxy)methyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate, trifluoroacetic acid salt.

Step 1.



[0116] A reaction mixture of N-Boc-3-amino-2-isopropylpropionic acid (10 mg, 0.4 mmol), cesium carbonate (78 mg, 0.2 mmol), in methanol (0.85 ml) was stirred at room temperature for 2 hours, then methanol evaporated, residue reconstituted with DMF (1 ml). To the reaction mixture was added chloromethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 2) (95 mg, 0.3 mmol). The resulting mixture was stirred at 80°C for 18 hours. The DMF was evaporated under vacuum, residue dissolved in DCM and purified by column chromatography (hexane:EtOAc 4:1) to afford 80 mg (50.8%) of semi-solid.

Step 2:



[0117] Solution of SP-32A (65 mg, 0.124 mmol) in chloroform (1 ml) and TFA (0.23 ml) was stirred at room temperature for 24 hours. Solvent evaporated and dried under vacuum to obtain 49 mg (93%) of pure desired product as a semisolid-oil. LCMS: Purity: 100% by ELS detector. MS: M+H=425.18. ¹H NMR (CDCl₃, 400MHz): δ ppm 0.95 (d, 3 H), 0.93 (d, 3 H), 1.40-1.48 (m, 3 H), 2.13 (br. s., 1 H), 2.72-2.83 (m, 1 H), 2.90-3.16 (m, 3 H), 3.20-3.32 (m, 1 H), 3.51-3.67 (m, 1 H), 3.84 (d, 1 H), 3.91-4.20 (m, 7 H), 5.74-5.86 (m, 2 H), 6.83-7.01 (m, 4 H).

[0118] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the technology in its broader aspects as defined in the following claims.

[0119] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising,” “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed technology. Additionally, the phrase “consisting essentially of” will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase “consisting of” excludes any element not specified.

[0120] The present disclosure is not to be limited in terms of the particular embodiments described in this application. Many modifications and variations can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and compositions within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. The present disclosure is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure

is not limited to particular methods, reagents, compounds, compositions or biological systems, which can of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

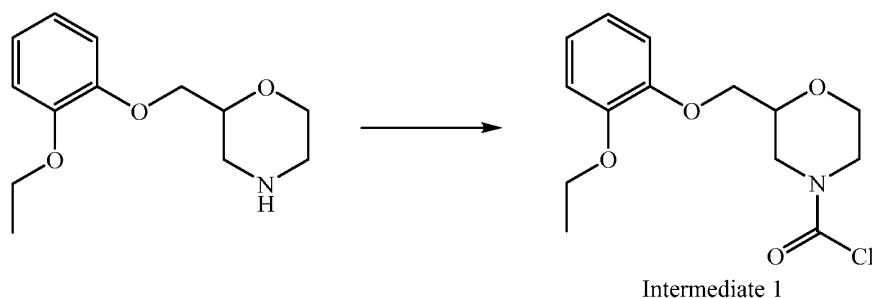
[0121] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0122] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, *etc.* As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, *etc.* As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member.

[0123] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

[0124] In an embodiment, a process for preparing 2-((2-ethoxyphenoxy)methyl)morpholine-4-carbonyl chloride (Intermediate 1) is provided, comprising:

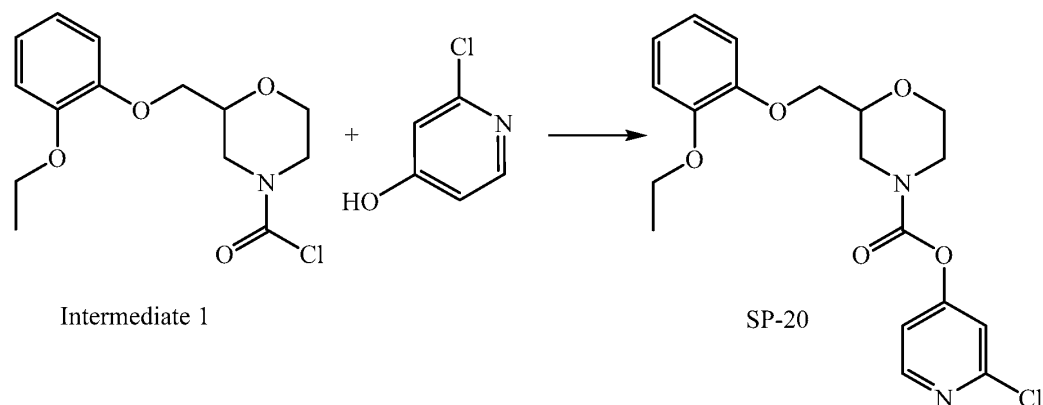
reacting 2-((2-ethoxyphenoxy)methyl)-morpholine with a reaction mixture comprising triphosgene



[0125] In further embodiments, the reaction mixture comprises dichloromethane. In other embodiments, the reaction mixture comprises sodium bicarbonate.

[0126] In some embodiments, Intermediate 1 is used to prepare 2-chloropyridin-4-yl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-20), comprising:

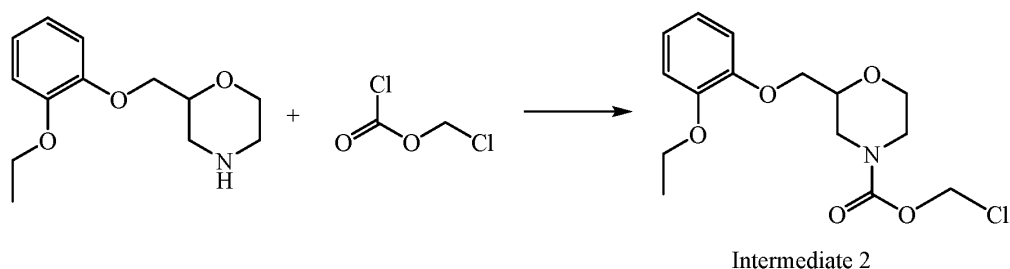
reacting 2-((2-ethoxyphenoxy)methyl)morpholine-4-carbonyl chloride (Intermediate 1) and a reaction mixture comprising 2-chloro-4-hydroxy pyridine



[0127] In further embodiments, this reaction mixture further comprises anhydrous tetrahydrofuran.

[0128] In some embodiments, a process for preparing chloromethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 2) is provided, comprising:

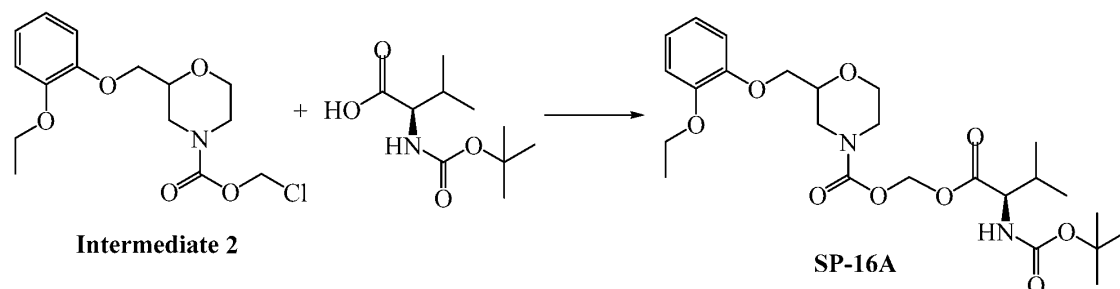
reacting 2-((2-ethoxyphenoxy)methyl)-morpholine with a reaction mixture comprising 1-chloromethyl chloroformate



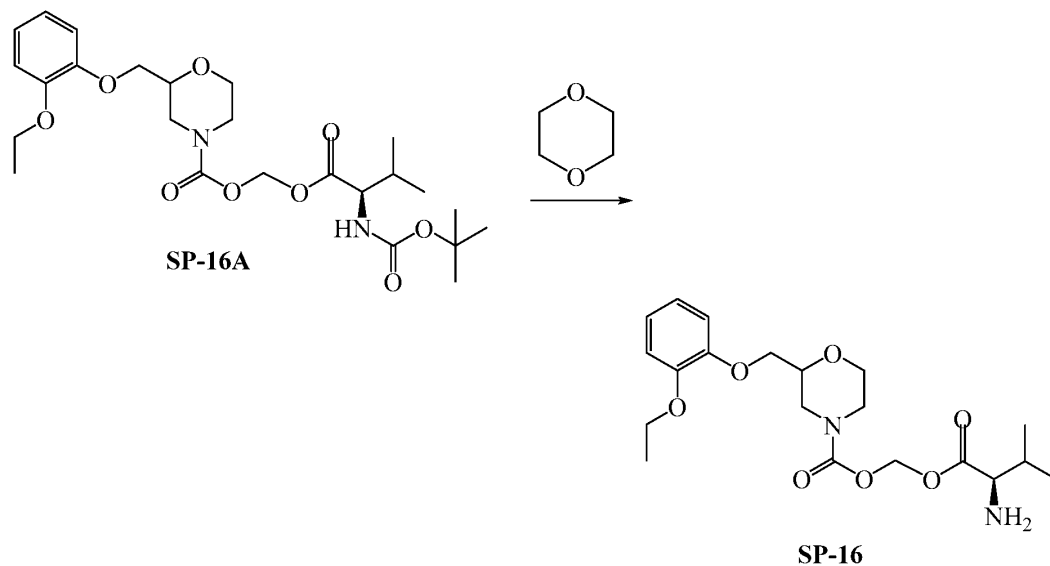
[0129] In further embodiments, this reaction mixture comprises trimethylamine. In other embodiments, this reaction mixture comprises dichloromethane.

[0130] In some embodiments, Intermediate 2 is used to prepare ((D-valyl)oxy)methyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-16), comprising:

(a) forming (SP-16A) by reacting Intermediate 2 with a reaction mixture comprising N-Boc-D-Valine; and



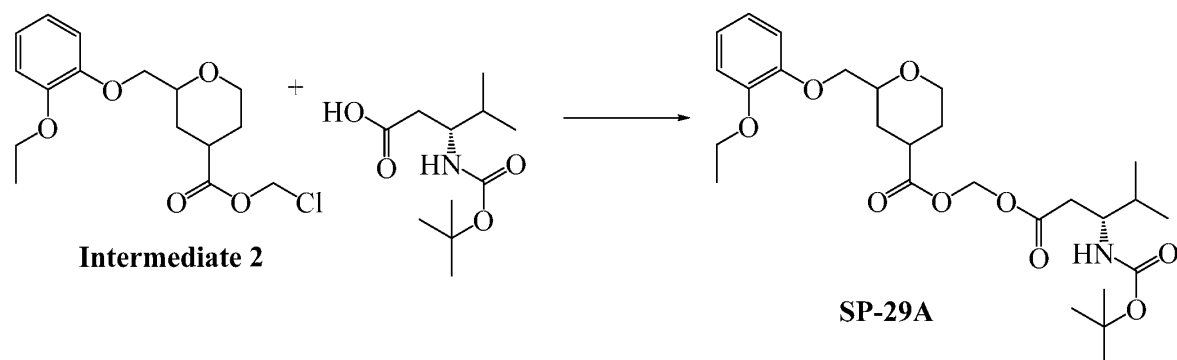
(b) reacting SP-16A with dioxane in an organic acid



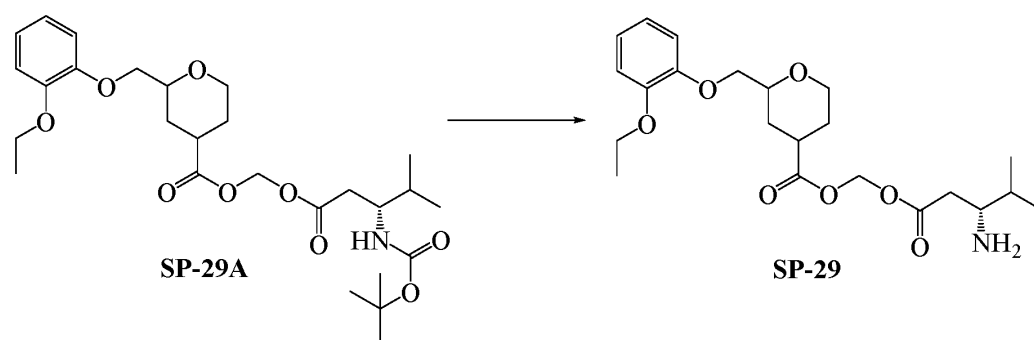
[0131] In further embodiments, the reaction mixture comprises cesium carbonate. In other embodiments, the reaction mixture comprises methanol. In some embodiments, the organic acid is hydrochloric acid.

[0132] In some embodiments, Intermediate 2 is used to prepare (((R)-3-amino-4-methylpentanoyl)oxy)methyl 2-((2-ethoxyphenoxy)-methyl)morpholine-4-carboxylate (SP-29), comprising:

(a) forming SP-29A by reacting Intermediate 2 and a reaction mixture comprising Boc-L- β -leucine; and



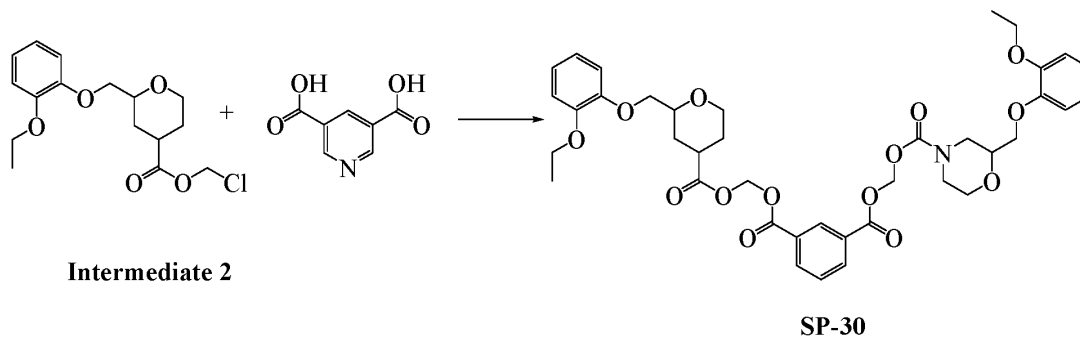
(b) stirring SP-29A in chloroform and trifluoroacetic acid



[0133] In further embodiments, this reaction mixture comprises cesium carbonate. In other embodiments, the reaction mixture comprises methanol.

[0134] In other embodiments, Intermediate 2 is used to prepare bis(((2-((2-ethoxyphenoxy)methyl)morpholine-4-carbonyl)oxy)methyl)pyridine-3,5-dicarboxylate (SP-30), comprising:

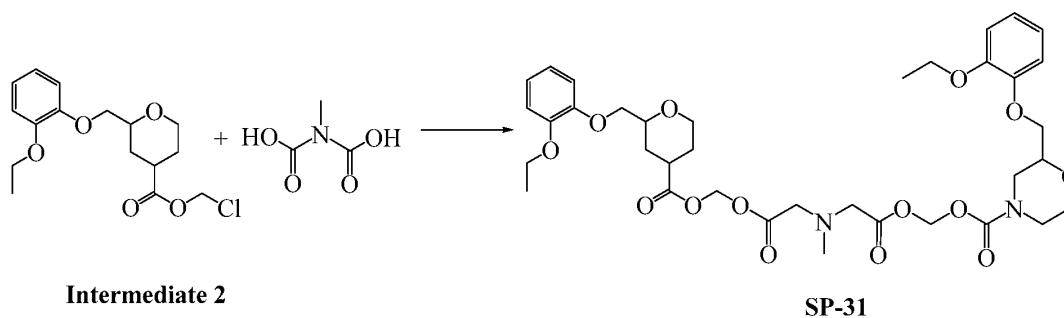
reacting Intermediate 2 and a reaction mixture comprising 3,5-pyridinedicarboxylic acid



[0135] In further embodiments, this reaction mixture comprises cesium carbonate. In other embodiments, the reaction mixture comprises methanol.

[0136] In some embodiments, Intermediate 2 is used to prepare ((2-2'-(methylazanediy)bis(acetyl))bis(oxy))bis(methylene) bis(2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate) (SP-31), comprising:

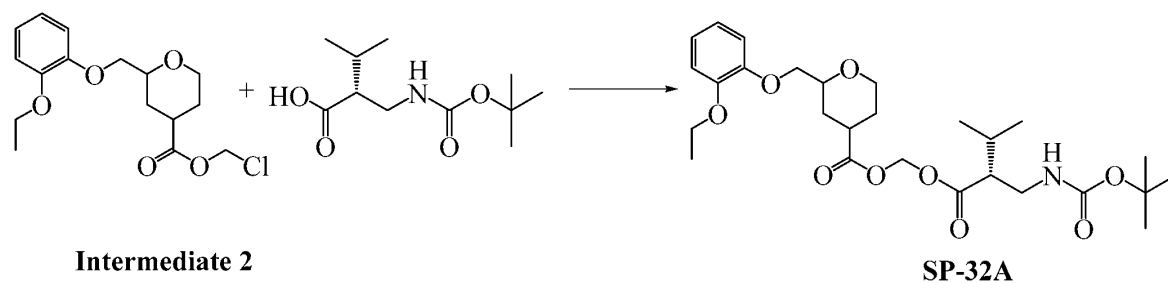
reacting chloromethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 2) and a reaction mixture comprising methyliminodiacetic acid



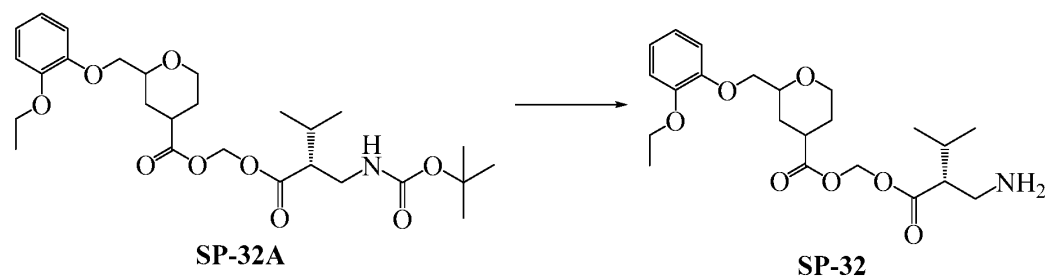
[0137] In further embodiments, this reaction mixture comprises cesium carbonate. In other embodiments, the reaction mixture comprises methanol.

[0138] In other embodiments, Intermediate 2 is used to prepare (((R)-2-(aminomethyl)-3-methylbutanoyl)oxy)methyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate, trifluoroacetic acid salt (SP-32), comprising:

(a) forming SP-32A by reacting Intermediate 2 and a reaction mixture comprising N-Boc-3-amino-2-isopropylpropionic acid; and



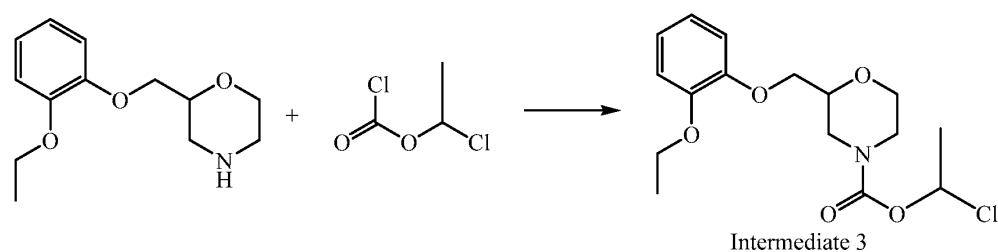
(b) stirring SP-32A in chloroform and trifluoroacetic acid



[0139] In further embodiments, this reaction mixture comprises cesium carbonate. In other embodiments, the reaction mixture comprises methanol.

[0140] In another embodiment, a process for preparing 1-chloroethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (Intermediate 3) is provided, comprising:

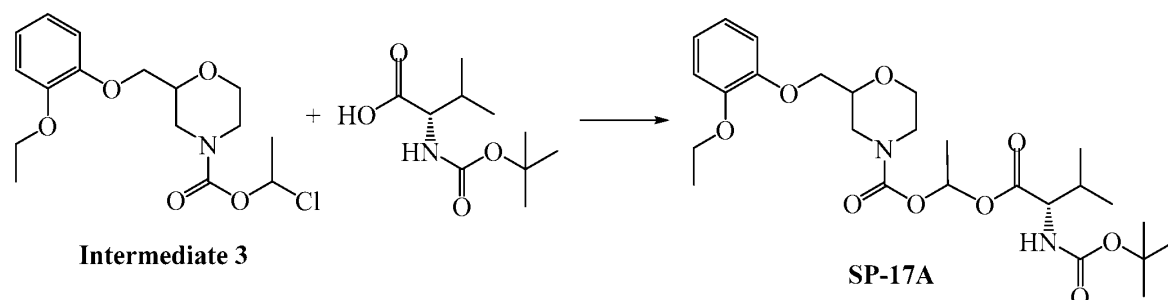
reacting 2-((2-ethoxyphenoxy)methyl)morpholine with a reaction mixture comprising 1-chloroethyl chloroformate



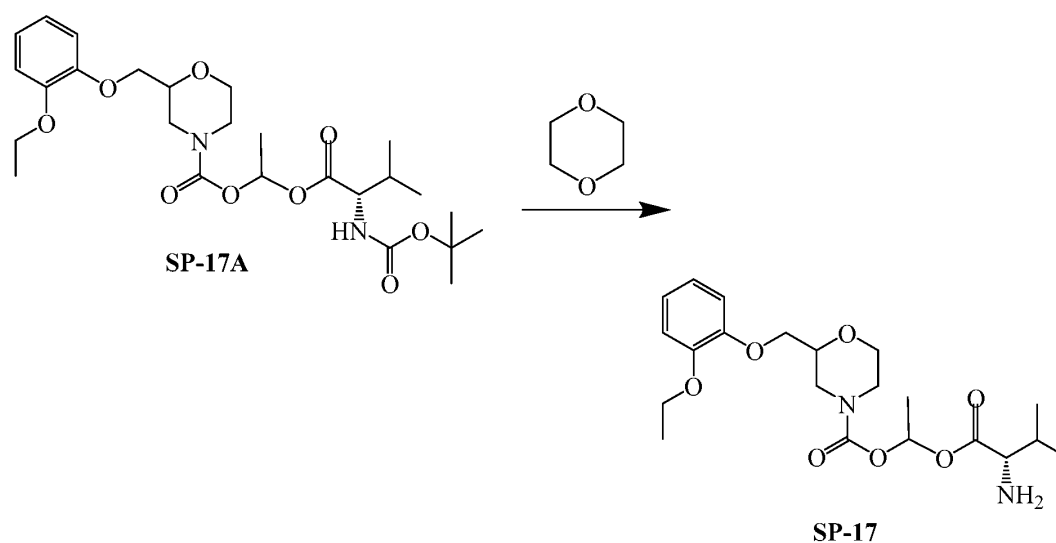
[0141] In further embodiments, this reaction mixture comprises trimethylamine. In other embodiments, the reaction mixture comprises dichloromethane.

[0142] In some embodiments, Intermediate 3 is used to prepare 1-((L-valyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-17), comprising:

(a) forming SP-17A by reacting Intermediate 3 and a reaction mixture comprising N-Boc-L-Valine; and



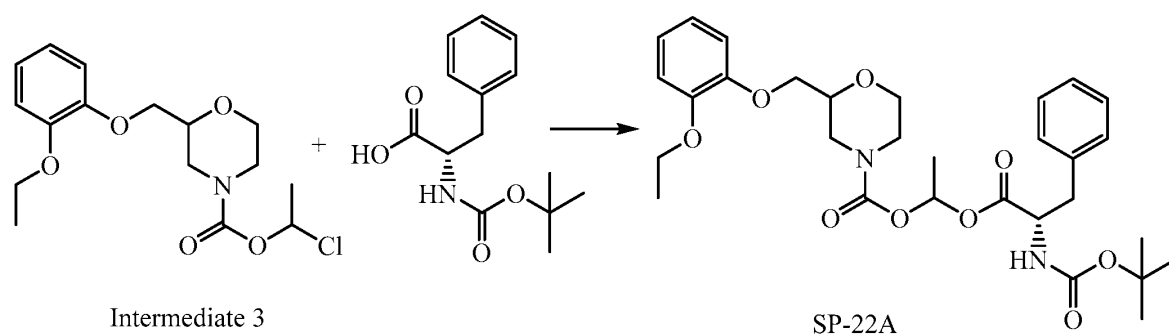
(b) reacting SP-17A with dioxane in an organic acid



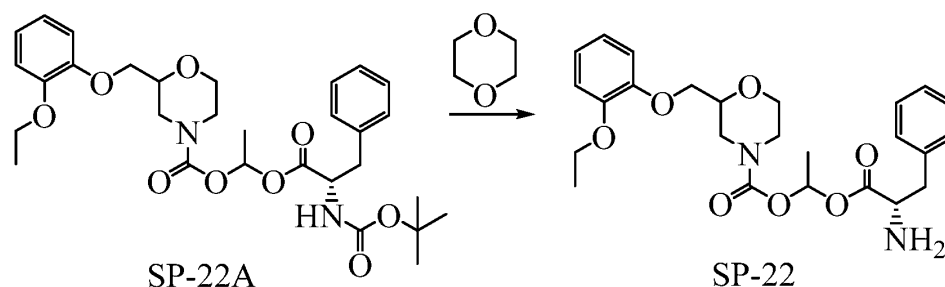
[0143] In further embodiments, this reaction mixture comprises methanol. In other embodiments, the reaction mixture comprises cesium carbonate. In some further embodiments, the organic acid is hydrochloric acid.

[0144] In some embodiments, Intermediate 3 is used to prepare 1-((l-phenylalanyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-22), comprising:

(a) forming SP-22A by reacting Intermediate 3 with a reaction mixture comprising N-Boc-phenylalanine; and



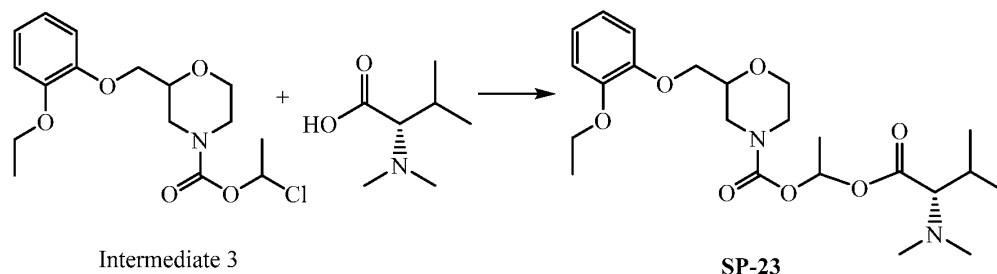
(b) reacting SP-22A with dioxane in an organic acid



[0145] In further embodiments, this reaction mixture further comprises cesium carbonate. In other embodiments, the reaction mixture further comprises methanol. In alternative embodiments, the organic acid is hydrochloric acid.

[0146] In some embodiments, Intermediate 3 is used to prepare 1-((dimethyl-L-valyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-23), comprising:

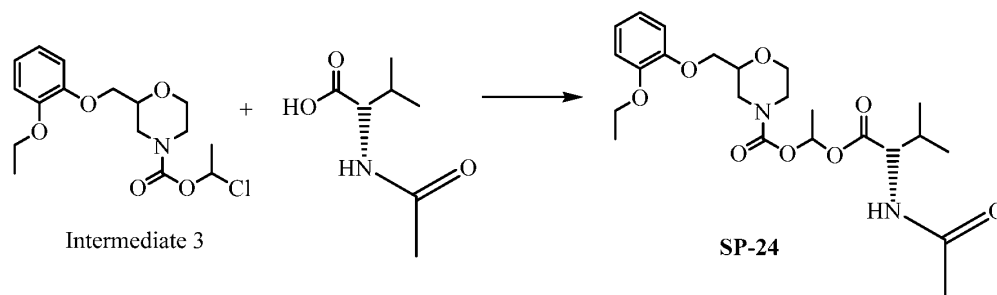
reacting Intermediate 3 with a reaction mixture comprising L-Val-N,N-dimethyl



[0147] In further embodiments, this reaction mixture comprises cesium carbonate. In some embodiments, the reaction mixture comprises methanol.

[0148] In some embodiments, Intermediate 3 is used to prepare 1-((Acetyl-L-valyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-24), comprising:

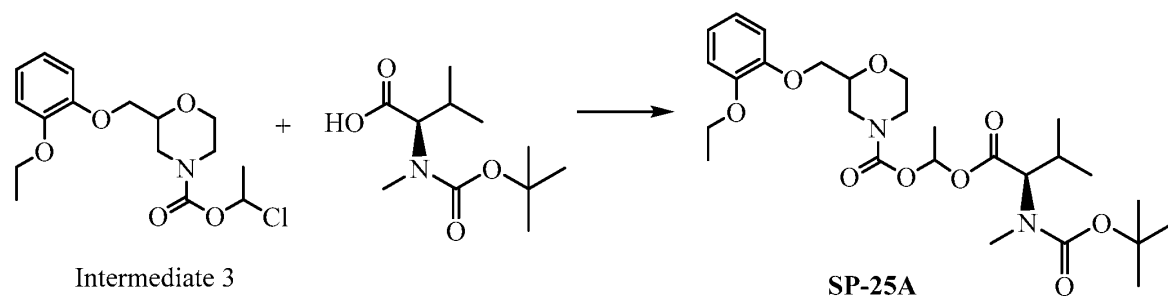
reacting Intermediate 3 with a reaction mixture comprising N-acetylvaline



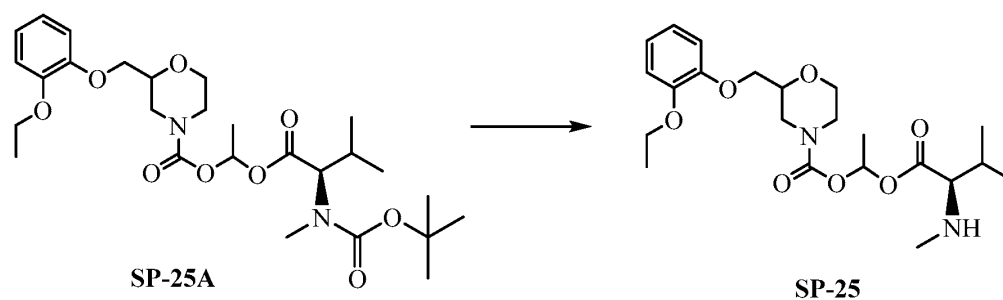
[0149] In further embodiments, this reaction mixture comprises cesium carbonate. In some embodiments, the reaction mixture comprises methanol.

[0150] In some embodiments, Intermediate 3 is used to prepare 1-((methyl-D-valyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-25), comprising:

(a) forming SP-25A by reacting Intermediate 3 with a reaction mixture comprising N-Boc-D-Valine; and



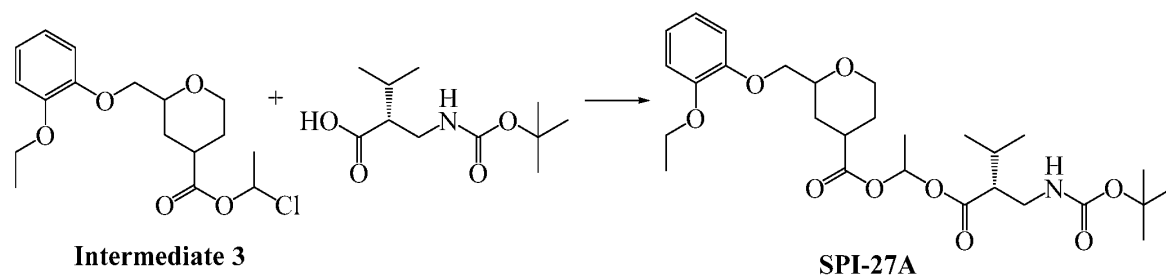
(b) reacting SP-25A with dichloromethane and trifluoroacetic acid



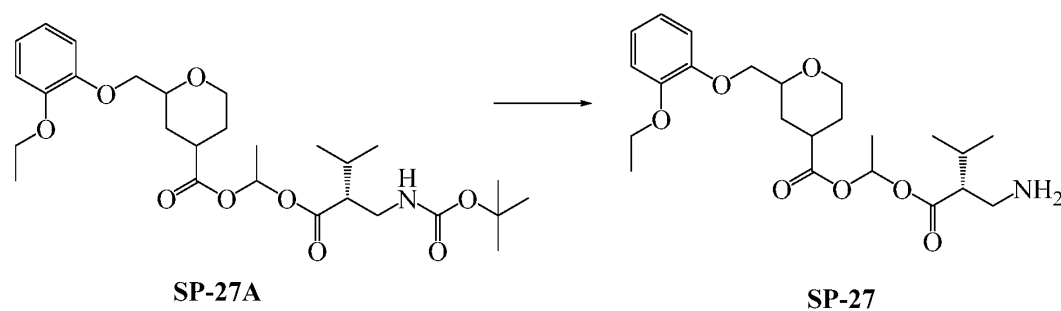
[0151] In further embodiments, this reaction mixture comprises methanol. In some embodiments, the reaction mixture comprises cesium carbonate.

[0152] In some embodiments, Intermediate 3 is used to prepare 1-(((R)-2-(aminomethyl)-3-methylbutanoyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-27), comprising:

(a) forming SP-27A by reacting Intermediate 3 and a reaction mixture comprising N-Boc-3-amino-2-isopropionic acid; and



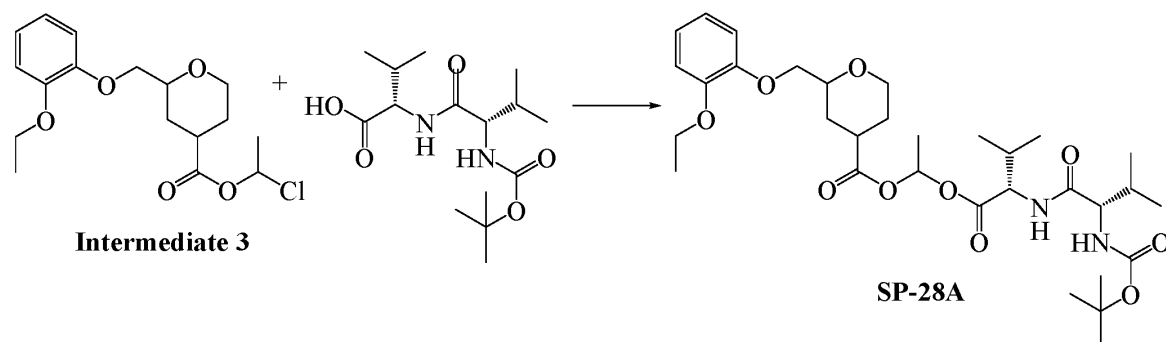
(b) stirring a solution of SP-27A in chloroform and trifluoroacetic acid



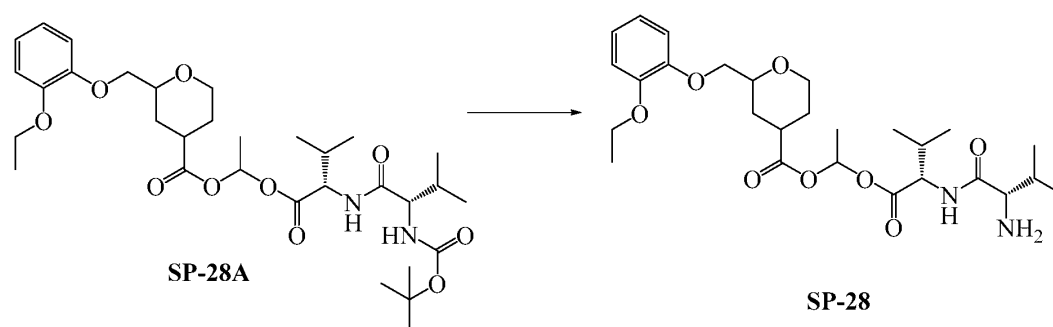
[0153] In further embodiments, this reaction mixture further comprises cesium carbonate. In other embodiments, the reaction mixture further comprises methanol.

[0154] In some embodiments, Intermediate 3 is used to prepare 1-(((R)-2-(aminomethyl)-3-methylbutanoyl)oxy)ethyl 2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-28), comprising:

(a) forming SP-28A by reacting Intermediate 3 with a reaction mixture comprising Boc-Val-Val; and



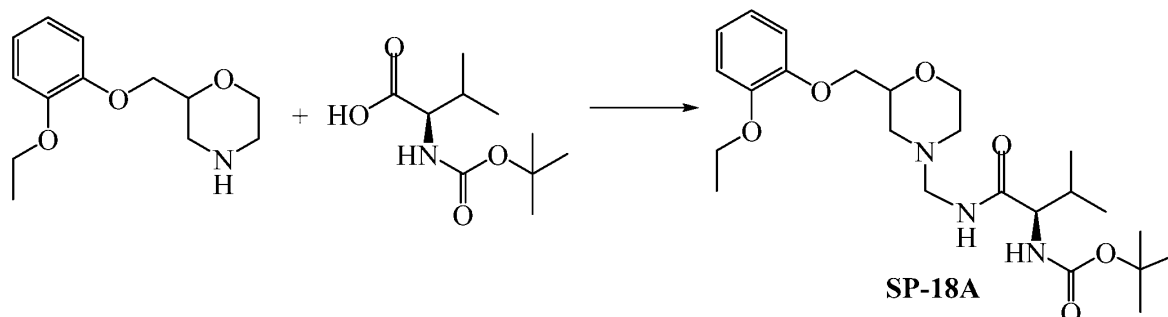
(b) stirring a solution of SP-28A in chloroform and trifluoroacetic acid



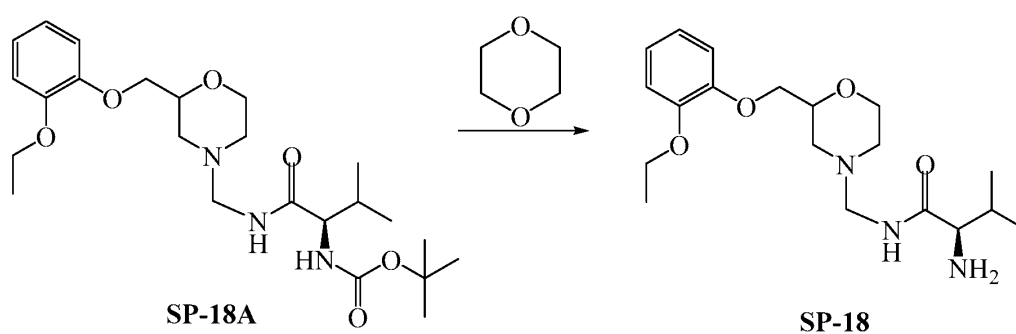
[0155] In further embodiments, this reaction mixture further comprises cesium carbonate. In some embodiments, the reaction mixture further comprises methanol.

[0156] In one embodiment, a process for preparing (2R)-2-amino-N-((2-((2-ethoxyphenoxy)methyl)morpholino)methyl)-3-methylbutanamide (SP-18) is provided, comprising:

(a) forming SP-18A by reacting 2-((2-ethoxyphenoxy)methyl)morpholine and a reaction mixture comprising polyformaldehyde; and



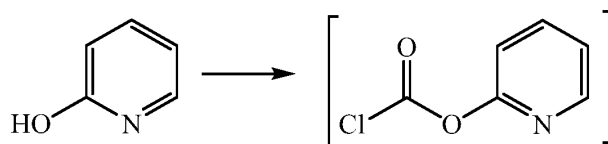
(b) reacting SP-18A with dioxane in an organic acid



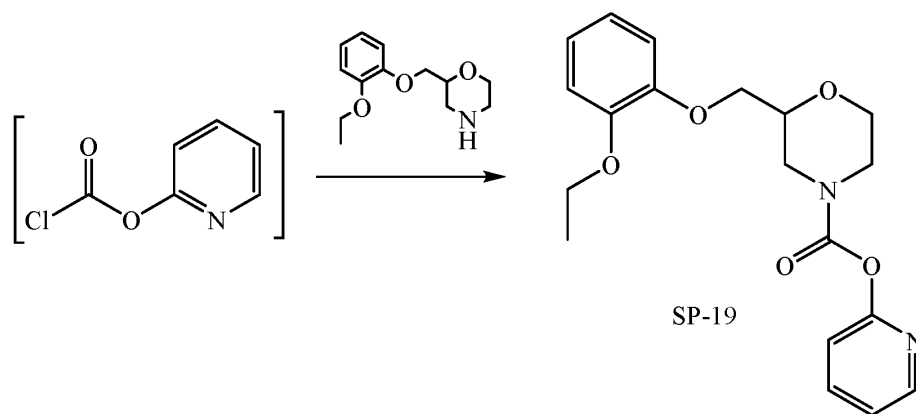
[0157] In further embodiments, this reaction mixture further comprises tetrahydrofuran. In some embodiments, the organic acid is hydrochloric acid.

[0158] In another embodiment, a process for preparing pyridine-2-yl 2((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-19) is provided, comprising:

(a) forming pyridine-2-yl carbonochloridate by reacting 2-hydroxypyridine with a reaction mixture comprising N,N-diisopropylethylamine; and



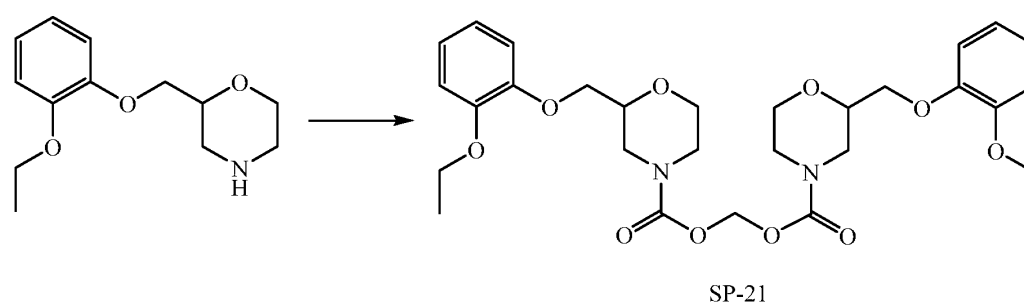
(b) reacting the pyridine-2-yl carbonochloridate with a second reaction mixture comprising 2-((2-ethoxyphenoxy)methyl)morpholine



[0159] In further embodiments, this reaction mixture comprises triphosgene. In some embodiments, the reaction mixture comprises dichloromethane. In other embodiments, the second reaction mixture comprises dichloromethane. In yet other embodiments, the second reaction mixture comprises triethylamine.

[0160] In one embodiment, a process for preparing methylene bis(2-((2-ethoxyphenoxy)methyl)morpholine-4-carboxylate (SP-21) is provided, comprising:

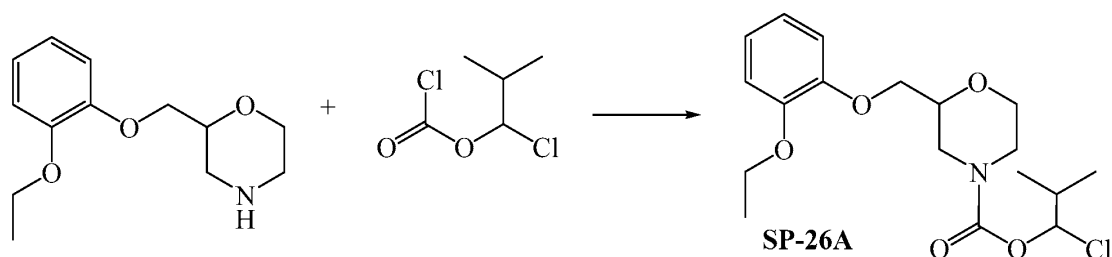
reacting 2-((2-ethoxyphenoxy)methyl)morpholine with a reaction mixture comprising methylene dibromide



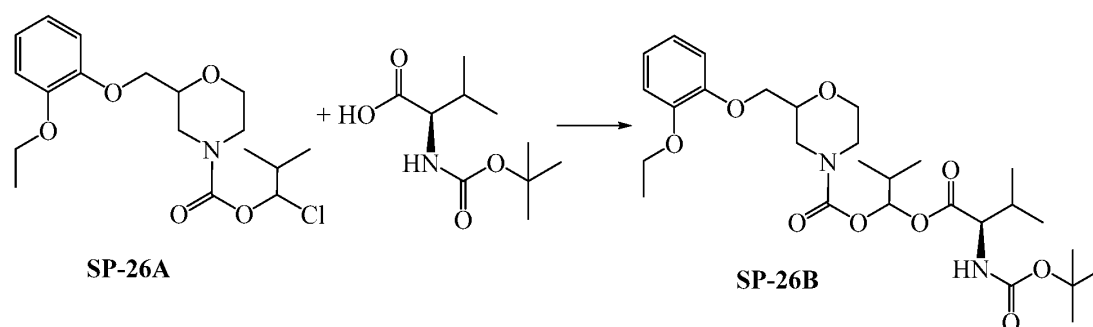
[0161] In further embodiments, the reaction mixture comprises dimethyl formamide. In some embodiments, carbon dioxide gas is passed over the reaction mixture.

[0162] In another embodiment, a process for preparing 1-((D-valyl)oxy)-2-methylpropyl 2-((2-ethoxyphenoxy)methyl)-morpholine-4-carboxylate (SP-26) is provided, comprising:

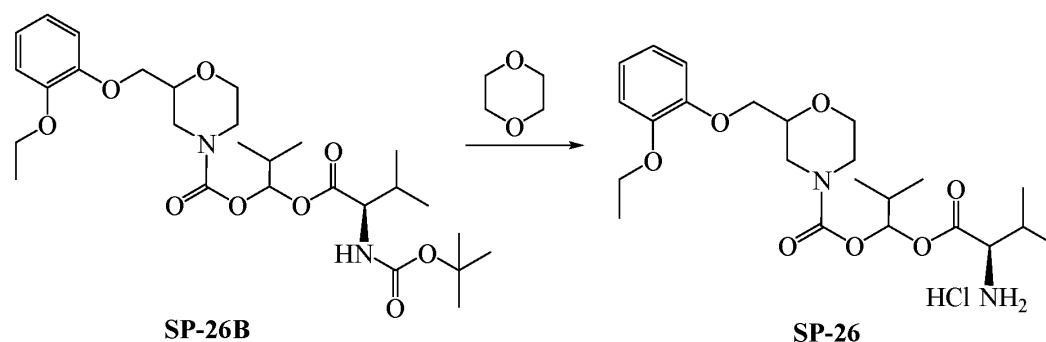
(a) forming SP-26A by reacting 2-((2-ethoxyphenoxy)-methyl)morpholine and a first reaction mixture comprising 1-chloro-2-methylpropylchloroformate;



(b) forming SP-26B by reacting SP-26A and a second reaction mixture comprising N-Boc-D-Valine; and



(c) reacting SP-26B with dioxane in an organic acid

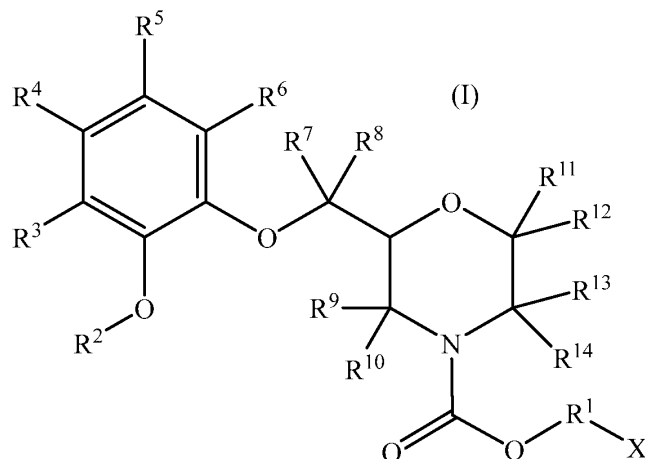


[0163] In a further embodiment, the first reaction mixture comprises trimethylamine. In some embodiments, the first reaction mixture comprises dichloromethane. In other embodiments, the second reaction mixture comprises cesium carbonate. In some embodiments, the second reaction mixture comprises methanol. In other embodiments, the organic acid is hydrochloric acid.

[0124] Other embodiments are set forth in the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I, a stereoisomer thereof, or a salt thereof:



wherein:

R^1 is alkyl, heterocyclyl, or a pyridyl;

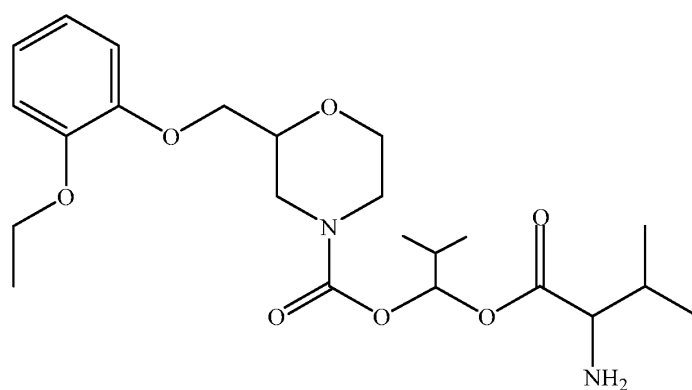
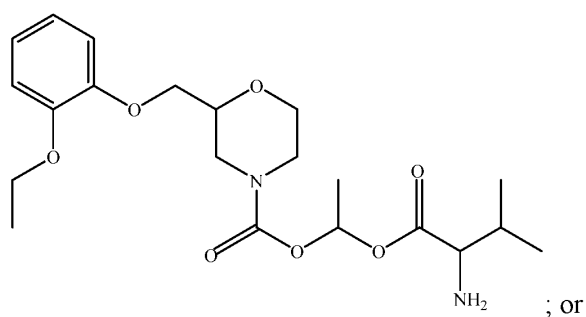
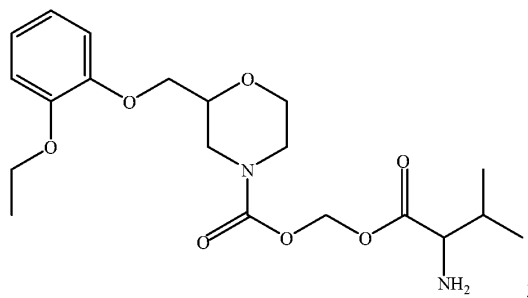
R^2 is alkyl, aryl, heteroaryl, or heterocyclyl;

R^3 - R^{14} are each independently H, F, Cl, Br, I, CN, NO₂, alkyl, aryl, heteroaryl, or heterocyclyl; and

X is H, halogen, an amino acid residue, a substituted amino acid residue, alkyl, ester.

2. The compound of Claim 1, wherein R^1 is CH₂, CH₂CH₂, CH₃CH, CH₂CH₂CH₂, CH₂CH₂CH₂CH₂, (CH₃)₂C, (CH₃)₂CHCH, or (CH₃)₃CCH.
3. The compound of Claim 2, wherein X is an amino acid residue.
4. The compound of Claim 3, wherein the amino acid residue comprises a hydrophobic side chain.
5. The compound of Claim 4, wherein the amino acid residue with a hydrophobic side chain is valine.
6. The compound of Claim 5, wherein R_1 is CH₂, CH₃CH, or (CH₃)₂CHCH.

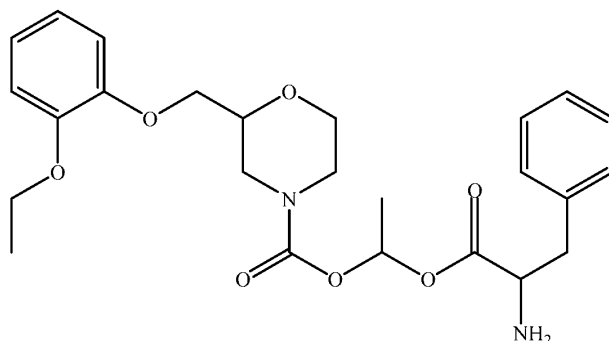
7. The compound of Claim 6 that is:



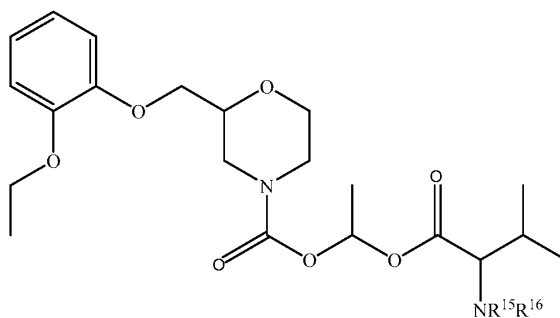
8. The compound of Claim 4, wherein the amino acid residue with a hydrophobic side chain is phenylalanine.

9. The compound of Claim 8, wherein R_1 is CH_3CH .

10. The compound of Claim 9 having the structure



11. The compound of Claim 3, wherein each of R^3 - R^{14} is independently H, F, Cl, Br, I, or alkyl.
12. The compound of Claim 11, wherein each of R^3 - R^{14} are each independently H or C_1 - C_6 alkyl.
13. The compound of Claim 12, wherein R^3 - R^{14} are all H.
14. The compound of Claim 13, wherein R^1 is CH_2 , CH_2CH_2 , CH_3CH , $CH_2CH_2CH_2CH_2$, or $CH_3CH_2CH_2CH$, or $(CH_3)_3CCH$.
15. The compound of Claim 1 which is:



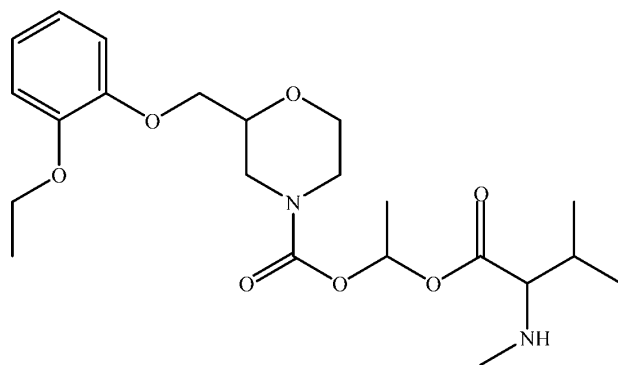
wherein:

- R^{15} is H, alkyl, $-C(O)OR^{17}$, or $-C(O)R^{17}$;
- R^{16} is H, alkyl, $-C(O)OR^{17}$, or $-C(O)R^{17}$; and
- R^{17} is H or alkyl.

16. The compound of Claim 15, wherein R^{15} is alkyl and R^{16} is H or alkyl.

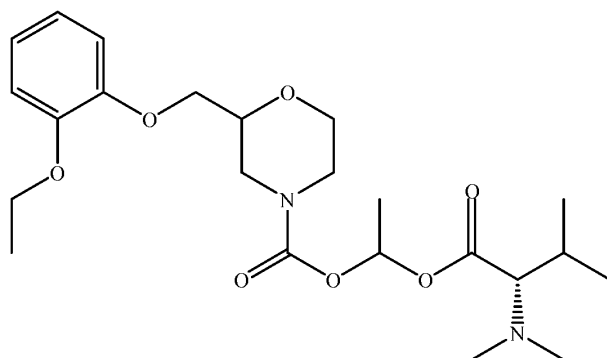
17. The compound of Claim 16, wherein R^{15} is methyl and R^{16} is H or methyl.

18. The compound of Claim 17 having the structure:



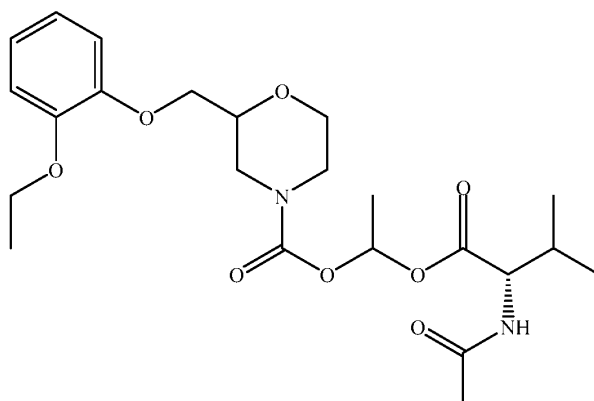
19. The compound of Claim 17, wherein R^{15} and R^{16} are methyl.

20. The compound of Claim 19 having the structure:



21. The compound of Claim 15, wherein R^{15} is $-C(O)R^{17}$, R^{16} is H, and R^{17} is methyl.

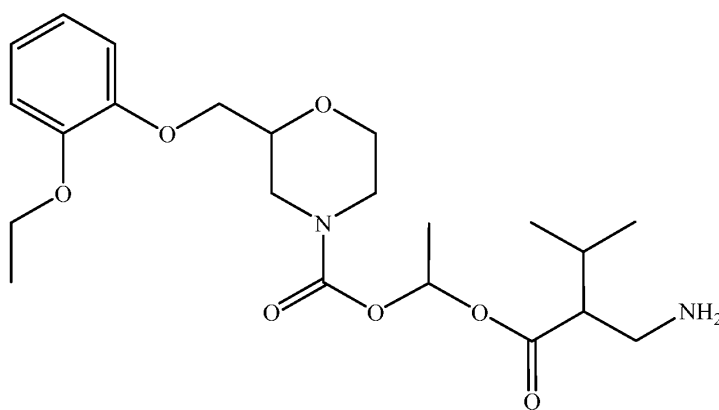
22. The compound of Claim 21 having the structure:

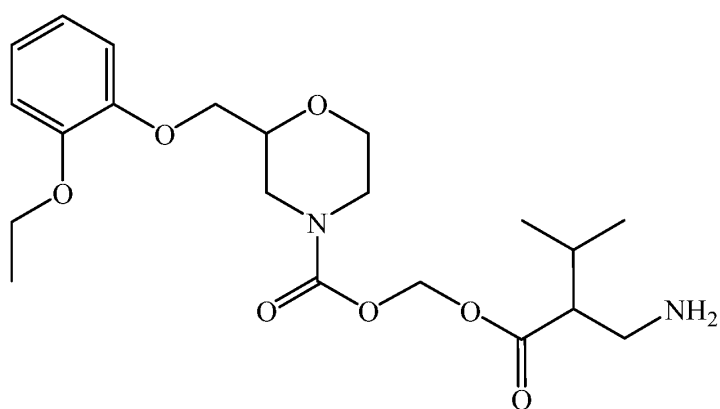
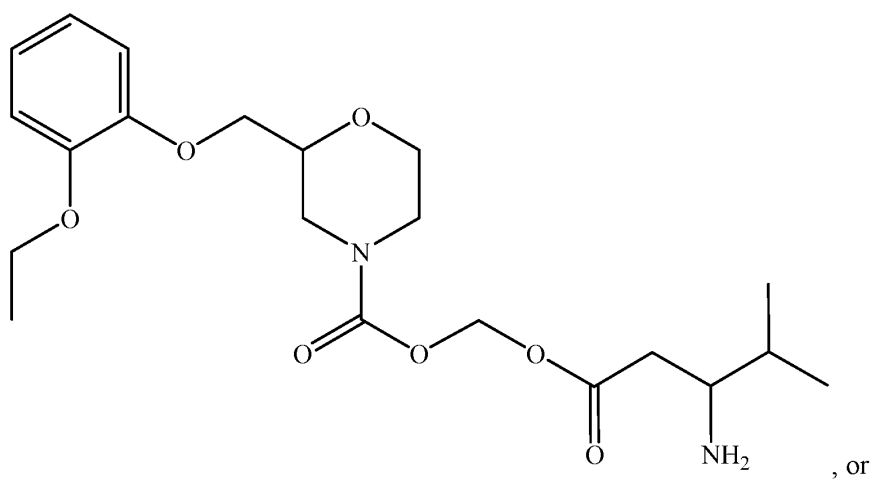
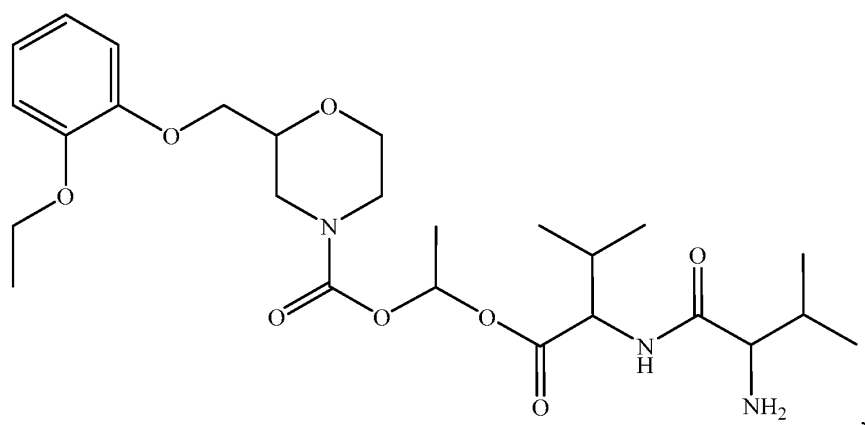


23. The compound of Claim 1, wherein R₁ is CH₂ or CH₃CH.

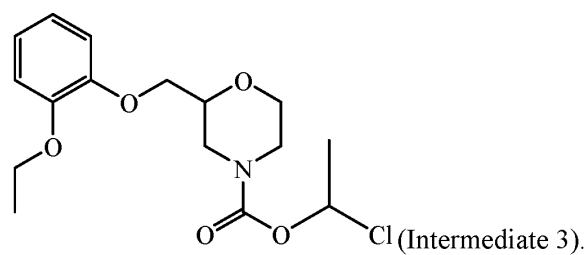
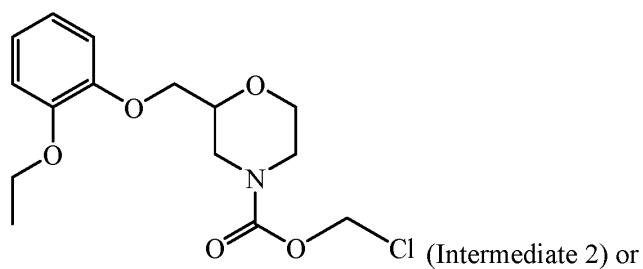
24. The compound of Claim 23, wherein X is an ester.

25. The compound of Claim 24 which is:



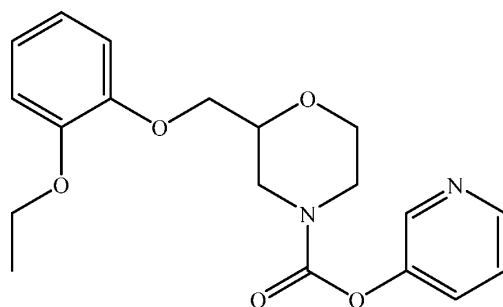


26. The compound of Claim 1 which is:



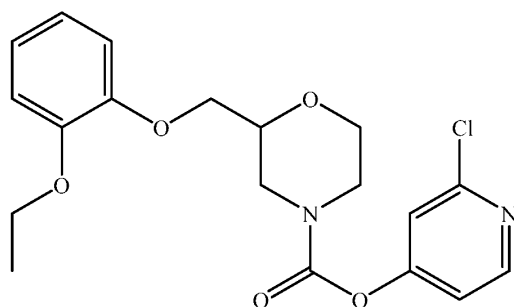
27. The compound of Claim 1, wherein R^1 is a pyridyl group and X is H.

28. The compound of Claim 27 that is:

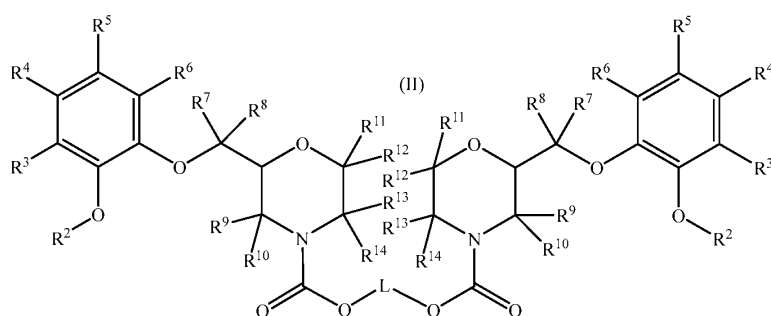


29. The compound of Claim 1, wherein R^1 is a pyridyl group and X is F, Cl, Br, or I.

30. The compound of Claim 29 that is:



31. A compound of Formula II, stereoisomer thereof, and/or a salt thereof:



wherein:

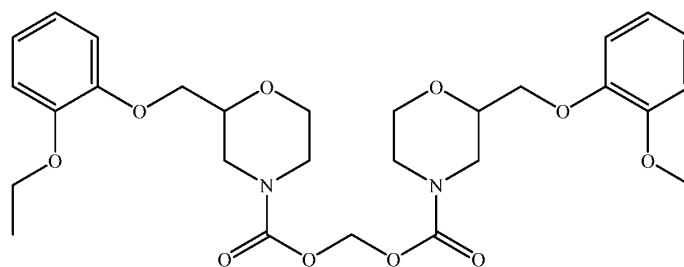
L is alkyl, a substituted pyridinecarboxylic acid, or a substituted azanediyl acetate;

R² is alkyl, aryl, heteroaryl, or heterocyclyl; and

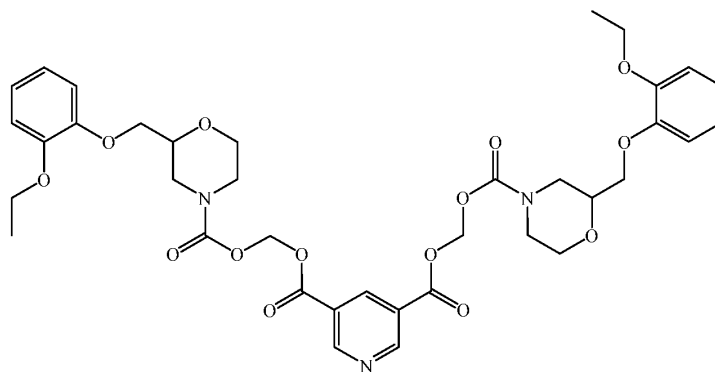
R³-R¹⁴ are each independently H, F, Cl, Br, I, CN, NO₂, alkyl, aryl, heteroaryl, or heterocyclyl.

32. The compound of Claim 31, wherein L is CH₂.

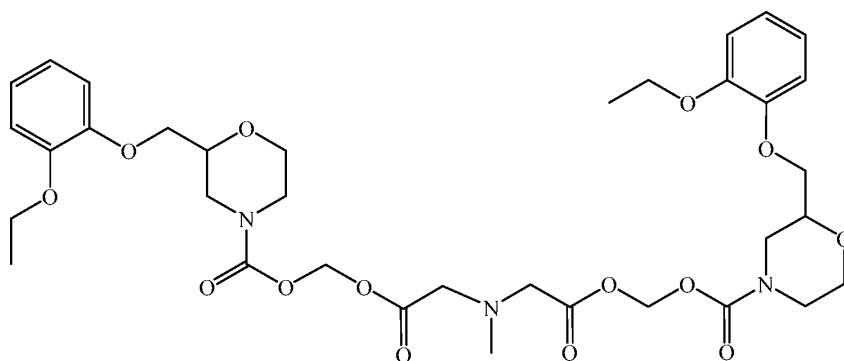
33. The compound of Claim 31 or 32 that is:



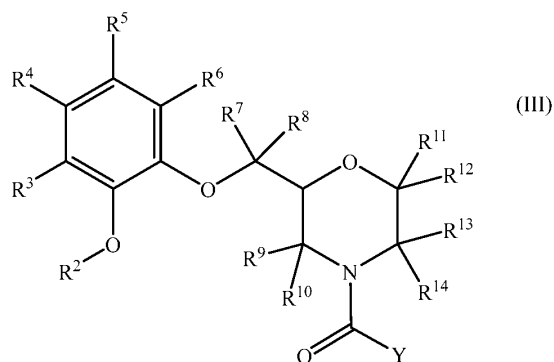
34. The compound of Claim 31, wherein L is a substituted pyridinecarboxylic acid group.
35. The compound of Claim 34, wherein the substituted pyridinecarboxylic acid group is a dimethyl pyridine-dicarboxylate.
36. The compound of claim 31 or 35 that is:



37. The compound of Claim 31, wherein the substituted azanediyl acetate group is a methylazanediyl acetate.
38. The compound of Claim 31 or 37 that is:



39. A compound of Formula III, a stereoisomer thereof, and/or a salt thereof:



wherein:

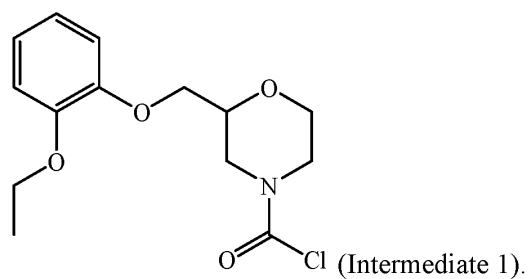
Y is F, Cl, Br, I, an amino acid residue, a substituted amino acid residue, alkyl, or ester;

R² is alkyl, aryl, heteroaryl, or heterocyclyl; and

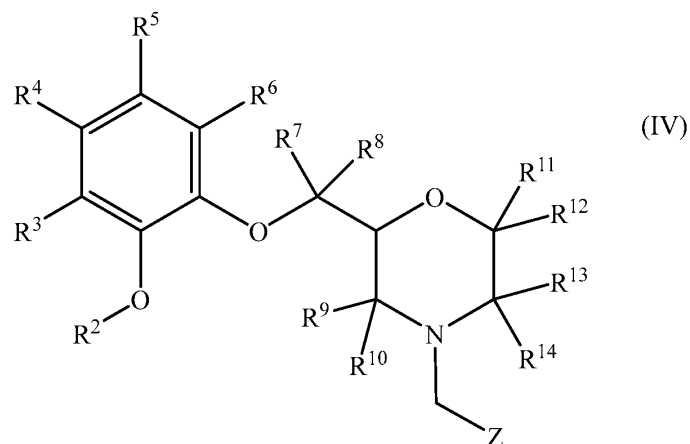
R³-R¹⁴ are each independently H, F, Cl, Br, I, CN, NO₂, alkyl, aryl, heteroaryl, or heterocyclyl.

40. The compound of Claim 39, wherein Y is Cl.

41. The compound of Claim 39 or 40 that is:



42. A compound of Formula IV, a stereoisomer thereof, and/or a salt thereof:



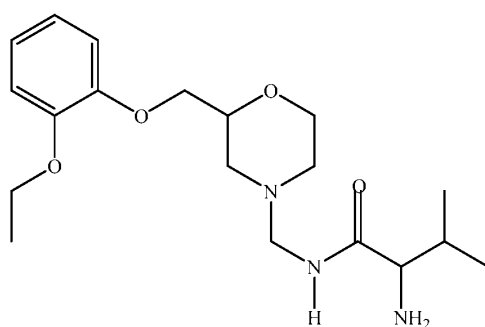
wherein:

Z is H, F, Cl, Br, I, an amino acid residue, a substituted amino acid residue, or a nitrogen-containing group;

R² is alkyl, aryl, heteroaryl, or heterocyclyl; and

R³-R¹⁴ are each independently H, F, Cl, Br, I, CN, NO₂, alkyl, aryl, heteroaryl, or heterocyclyl.

43. The compound of Claim 42, wherein Z is a nitrogen-containing group.
44. The compound of Claim 43, wherein the nitrogen-containing group is an amide.
45. The compound of Claim 42 or 44 that is:



46. A composition comprising a compound of any one of claims 1, 31, 39, or 42, and a pharmaceutically acceptable excipient.

47. A method for the treatment of a central nervous system disorder, the method comprising administering to a subject the composition of Claim 46.
48. A method of making a compound of Formula I, II, III, or IV by contacting 2-((2-ethoxyphenoxy)methyl)morpholine or a salt thereof, Intermediate 1, Intermediate 2, or Intermediate 3 with a reactive compound suitable for forming the compound of Formula I, II, III, or IV.