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(54) **AMINE PRODRUGS OF PHARMACEUTICAL COMPOUNDS**

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(57) **ABSTRACT**

Disclose are amine prodrugs and methods of synthesis thereof. In particular, the amine prodrug comprises a drug molecule and at least one or more prodrug appendage moieties and the method for synthesis the amine prodmg comprises a step of coupling the drag molecule and at least one or more prodrug appendage moieties. Also disclosed are exemplary riluzole prodrugs and methods of synthesis thereof.

AMINE PRODRUGS OF PHARMACEUTICAL COMPOUNDS

CROSS REFERENCE TO RELATED A.PPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application Ser. No. 62/257,533 filed Nov. 19, 2015, the disclosure of which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention relates to amine prodrugs and methods of synthesis thereof. The amine prodrug comprises a drug molecule and at least one or more prodrug appendage moieties. The method of synthesis thereof comprises a step of coupling the drug molecule and at least one or more prodrug appendage moieties.

BACKGROUND

[0003] Discovery of novel prodrugs has been an integral part in current pharmaceutical industry. A prodrug is an alternative form of a drug and is used instead to improve absorbed, distributed, metabolized and excreted (ADME) properties of the drug. The prodrug is administered in an inactive or less active form, and is subsequently converted to its active drug through a normal metabolic process, such as hydrolysis or other chemical reactions, in a subject.

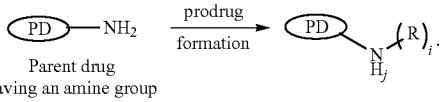
[0004] Among commercially available prodrug products, amine prodrugs such as Capecitabine (Xeloda), Docarpamine, Prulifloxacin, Gabapentin enacabril, and Altrofloxacin have been successfully introduced into market. The primary or secondary amine prodrugs have been made substantially and further prodrugs of tertiary amine or quaternary amine have been also made and are being advanced into clinical development as well. (Prodrugs of Amines, Ana L. Simphcio et al, Molecules, 2008,13 519-547; Prodrugs of Amines, Jeffrey Krise et al, Prodrugs, Challenges and Rewards Part 1 and Part 2, Springer N.Y., 2007; Drug Synthesis II, presentation by Tapio Nevalainen, University of Eastern Finland, 2012.)

[0005] As such, other amine prodrugs are potential candidates for drug development.

SUMMARY OF THE INVENTION

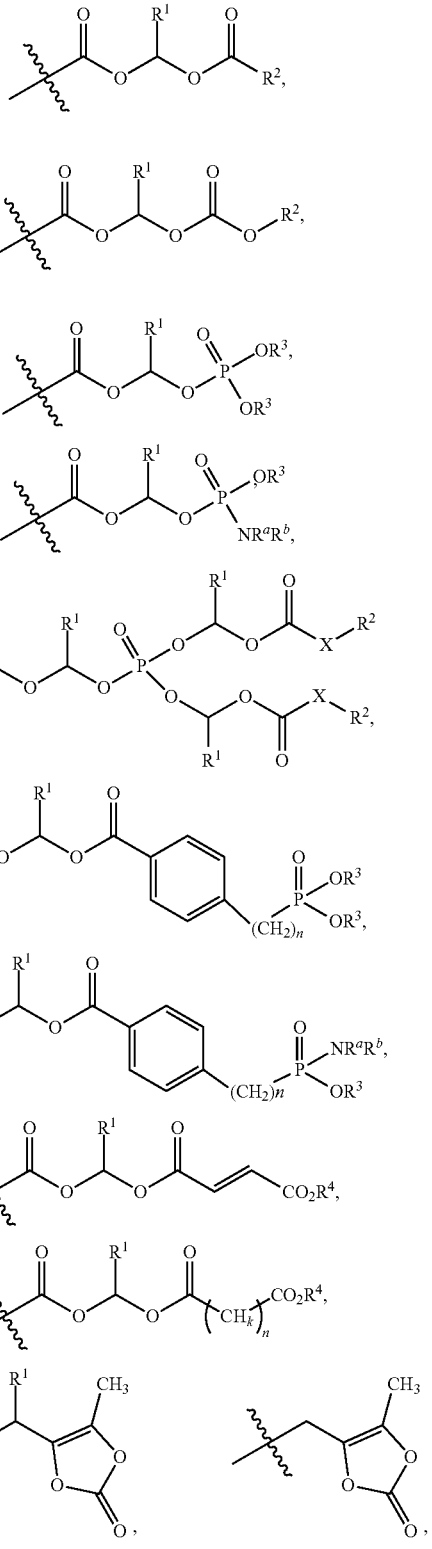
[0006] The present invention provides amine prodrug and methods of synthesis thereof.

[0007] In one aspect, the present invention provides a prodrug which comprises a drug molecule and at least one or more prodrug appendage moieties. The prodrug may be as:



[0008] In particular, the prodrug appendage moiety may be coupled to amine of the drug molecule. In this prodrug of the present invention, i may be 1 or 2 and j may be 0 or 1. For example, i is 1 and j is 1; or i is 2 and j is 0.

[0009] The prodrug appendage moiety may be independently selected from the group of consisting of:



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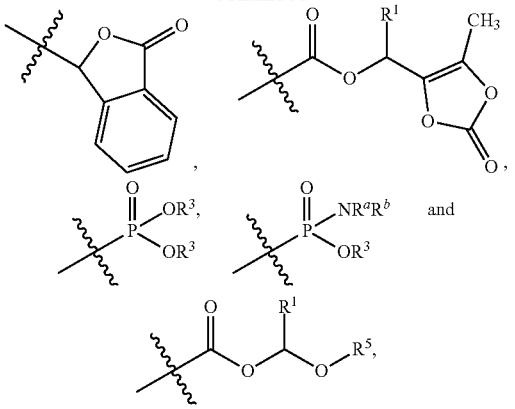


[0010] where R^1 may be H, alkyl or particularly C_1-C_8 alkyl;

[0011] R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted.

[0012] R^3 may be H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine;

[0013] R^4 may be H, metal, ammonium salt, or alkyl;

[0014] R^5 may be a substituted or unsubstituted natural amino acid;

[0015] R^a or R^b may be H, alkyl or aryl; or NR^a or NR^b may be an amino acid;

[0016] X may be C or O;

[0017] k may be 1 or 2, m may be 2-22, or $(CH_k)_m$ may be saturated, unsaturated or conjugated hydrocarbon;

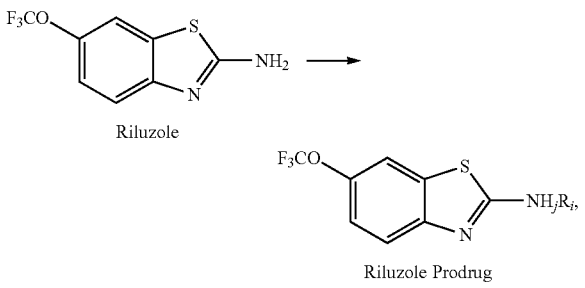
[0018] n may be 0-2; and

[0019] the metal may be Na, K, Li, Ca, Mg, Ag or Zn.

[0020] In an exemplary embodiment, and the drug molecule may be riluzole.

[0021] In another aspect, the present invention provides a method of preparing a prodrug.

[0022] In one embodiment, a method of preparing a riluzole prodrug is provided. The method comprises a step of coupling one or more prodrug appendage moieties to a riluzole molecule as described below.

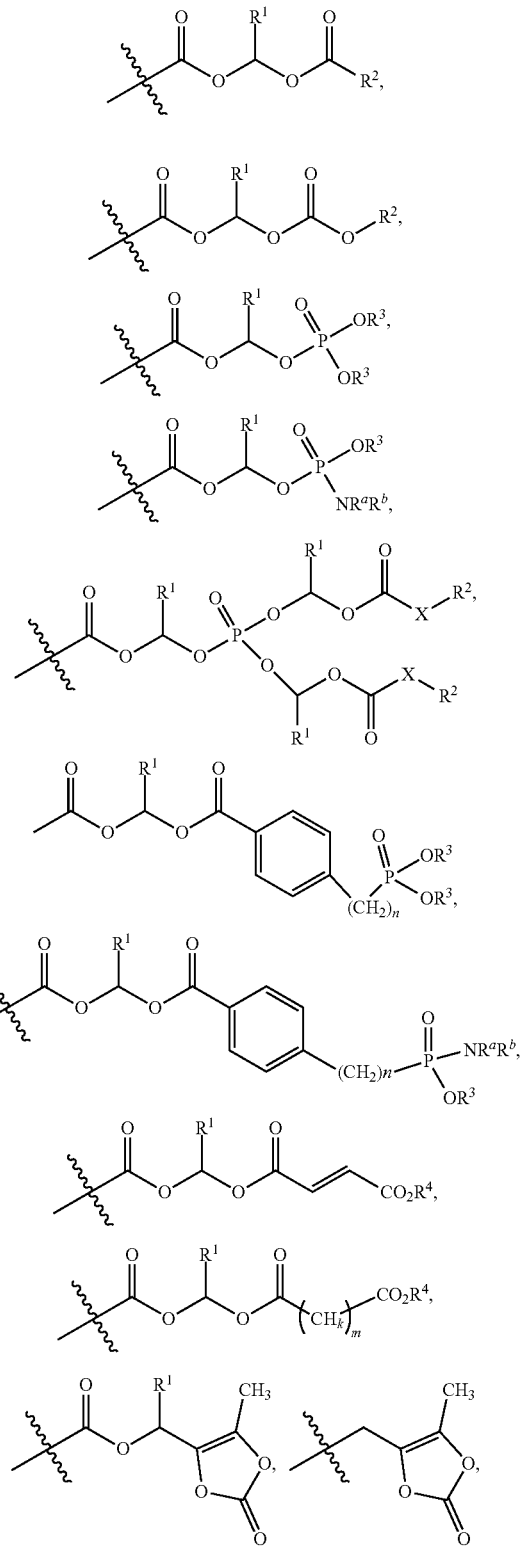


Riluzole

Riluzole Prodrug

[0023] In particular, the prodrug appendage moiety may be coupled to amine of the riluzole molecule where i may be 1 or 2 and j may be 0 or 1. For example, i is 1 and j is 1; or i is 2 and j is 0.

[0024] The prodrug appendage mu e independently selected from the group of consisting of:



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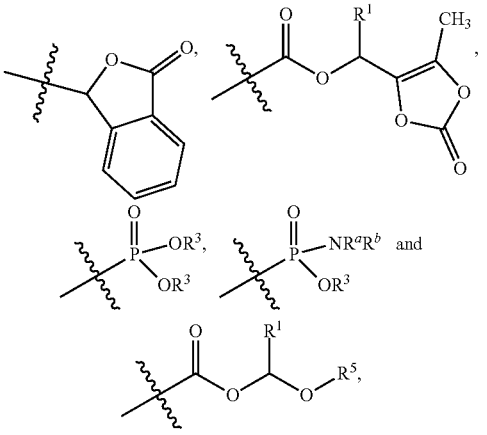


[0025] where R^1 may be H, alkyl or particularly C_1-C_8 alkyl;

[0026] R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted.

[0027] R^3 may be H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine;

[0028] R^4 may be H, metal, ammonium salt, or alkyl;

[0029] R^5 may be a substituted or unsubstituted natural amino acid;

[0030] R^a or R^b may be H, alkyl or aryl; or NR^a or NR^b may be an amino acid;

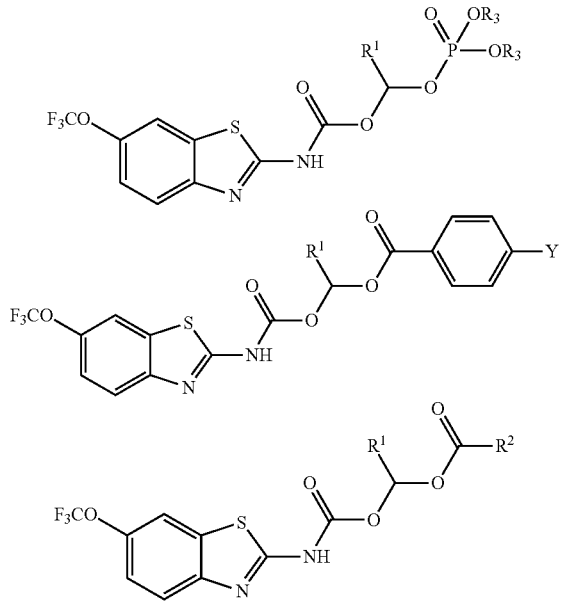
[0031] X may be C or O;

[0032] k may be 1 or 2, in may be 2-22, or $(CH_k)_m$ may be saturated, unsaturated or conjugated hydrocarbon;

[0033] n may be 0-2; and

[0034] the metal may be Na, K, Li, Ca, Mg, Ag or Zn.

[0035] Exemplary riluzole prodrug may be:



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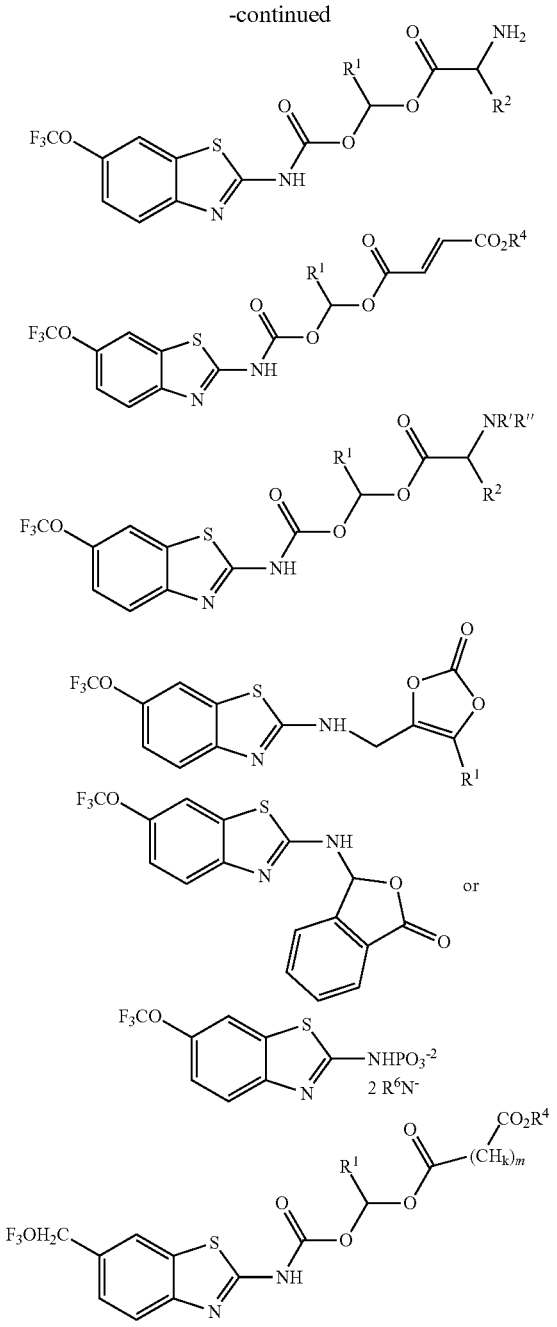
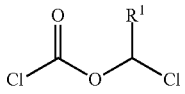


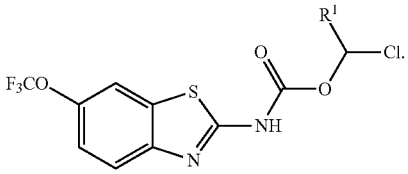
where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; R^3 may be H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine; R^4 may be H, metal, ammonium salt, or alkyl; R^6 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl; N' may be a primary, secondary and tertiary amine which may be substituted or unsubstituted, or metal salts; and Y may be PO_3H, CH_2PO_2H or salt thereof. In particular, the metal may be Na, K, Li, Ca, Mg, Ag or Zn.

[0036] The present invention also provides a method of synthesizing a riluzole prodrug.

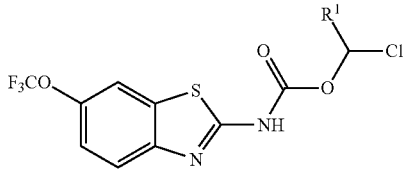
[0037] In one embodiment, the method comprises a step of reacting riluzole with



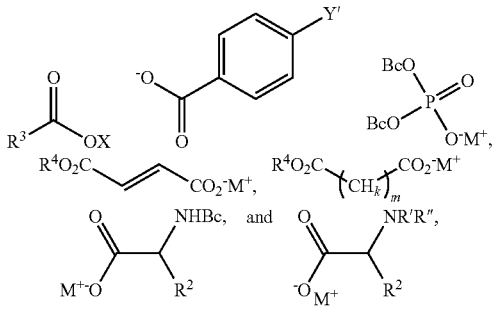
to produce



[0038] The method further comprises a step of reacting



with a compound selected from the group consisting of:



[0039] where R^1 may be H, alkyl or particularly C_1-C_8 alkyl;

[0040] R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted;

[0041] R^4 may be H, metal, ammonium salt, or alkyl;

[0042] k may be 1 or 2, m may be 2-22, or $(CH_k)_m$ may be saturated, unsaturated or conjugated hydrocarbon;

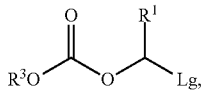
[0043] Bc may be a protecting group;

[0044] Y' may be H, PO_3Bc_2, CH_2PO_2Bc, MPO_3Bc or salt thereof, or $N(R_a)_2$, where Ra is H or alkyl;

[0045] M may be a metal such as Na, K, Li, Ca, Mg, Ag or Zn; and

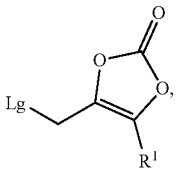
[0046] R' or R" may be cyclic or acyclic alkyl.

[0047] In one embodiment, the method of synthesizing a riluzole prodrug comprises a step of reacting a riluzole, with CO_2, Cs_2CO_3 and reacting the resulting compound with



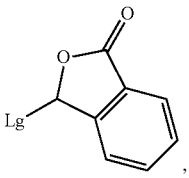
wherein Lg is a leaving group.

[0048] In one embodiment, the method of synthesizing a riluzole prodrug comprises a step of reacting a riluzole with



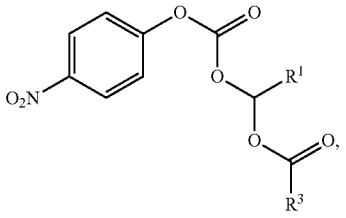
wherein Lg is a leaving group and where R^1 may be H, or C_1-C_8 alkyl

[0049] In one embodiment, the method of synthesizing a riluzole prodrug comprises a step of reacting a riluzole with



wherein Lg is a leaving group.

[0050] In one embodiment, the method of synthesizing a riluzole prodrug comprises a step of reacting riluzole with

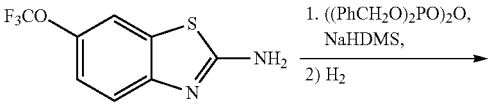


[0051] wherein R^1 may be H, alkyl or particularly C_1-C_8 alkyl;

[0052] R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; and

[0053] R^3 may be H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine.

[0054] In one embodiment, the method of synthesizing a riluzole prodrug comprises a step of reacting riluzole with $((PhCH_2O)_2PO)_2O$ and sodium bis(trimethylsilyl)amide (NaHMDS) and subsequently reacting the resulting compound with hydrogen:



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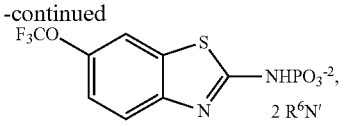


[0055] where R^6 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl; and N' may be a primary, secondary and tertiary amine which may be substituted or unsubstituted, or metal salts.

[0056] Other aspects of the invention are disclosed infra.

DETAILED DESCRIPTION OF THE INVENTION

[0057] The following is a detailed, description provided to aid those skilled in the art in practicing the present invention. These of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present disclosure. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The terminology used in the description is for describing particular embodiments only and is not intended to be limiting. All publications, patent applications, patents, figures and other references mentioned herein are expressly incorporated by reference in their entirety.

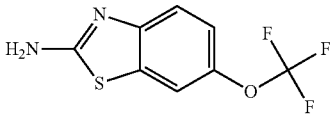
[0058] The following terms are used to describe the present invention. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present invention.

[0059] As used in the description of the invention and the appended claims, the singular forms "a", "an" and "the" are used interchangeably and intended to include the plural forms as well and fall within each meaning, unless the context clearly indicates otherwise. Also, as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the listed items, as well as the lack of combinations when interpreted in the alternative ("or"). Singular word forms are intended to include plural word forms and are likewise used herein interchangeably where appropriate and fall within each meaning, unless expressly stated otherwise.

[0060] The term "prodrug" as used herein, is a precursor of a drug which may be administered in an altered or less active form. The prodrug may be converted into the active drug form in physiological environments by hydrolysis or other metabolic pathways. The prodrug may provide improved physiochemical or physiological characteristics to enhance therapeutic effects of the drug.

[0061] The term "prodrug appendage moiety" as used herein, refers to a chemical group or moiety covalently or non-covalently attached to a drug molecule, thereby produce a prodrug form of the drug. The prodrug appendage moiety may not alter pharmacokinetic core or properties of the drug molecules by intramolecular rearrangement or cleavage. In certain embodiments, multiple prodrug appendage moieties may be attached to the drug molecule, without limitation. In addition, the prodrug appendage moiety may couple one or more of the drug molecules, without limitation.

[0062] The term "riluzole", as used herein, refers to a drug, 6-(trifluoromethoxy)benzothiazol-2-amine, which is generally used to treat amyotrophic lateral sclerosis (ALS). It is also available in the market as RILUTEK®.



6-(trifluoromethoxy)benzothiazol-2-amine

[0063] As used herein, the term "leaving group," or "LG", as used herein, refers to any group that leaves in the course of a chemical reaction involving the group and includes but is not limited to halogen, brosylate, mesylate, tosylate, tritlate, p-nitrobenzoate, phosphonate groups, for example,

[0064] As used herein, the term "alkyl" refers to a straight-chained or branched hydrocarbon group containing 1 to 18 (e.g., C_1-C_{18}, inclusive; and any sub-range thereof) carbon atoms. The term "lower alkyl" refers to a C1-C6 alkyl chain. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl (n-, sec-, tert-), and pivaloyl. Alkyl groups may be optionally substituted with one or more substituents.

[0065] The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicyclic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups bridged cyclic group or spirobicyclic groups e.g spiro(4,4)non-2-yl.

[0066] As used herein, the term "halogen" or "halide" means —F, —Cl, —Br or —I.

[0067] As used herein, the term "haloalkyl" means and alkyl group in which one or more (including all) the hydrogen radicals are replaced by a halo group, wherein each halo group is independently selected from —F, —Cl, —Br, and —I. The term "halomethyl" means a methyl in which one to three hydrogen radical(s) have been replaced by a halo group. Representative haloalkyl groups include trifluoromethyl, difluoromethyl, bromethyl, 1,2-dichloreethyl, 4-iodobutyl, 2-fluoropentyl, and the like. The term "perhaloalkyl" refers to a alkyl group in which all hydrogen atoms are replaced by a halo group (e.g., trifluoromethyl, pentafluoroethyl). In certain embodiments, the haloalkyl may be an activated alkyl.

[0068] The term "cycloalkyl" refers to a hydrocarbon 3-8 membered monocyclic or 7-14 membered bicyclic ring system having at least one non-aromatic ring. Cycloalkyl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a cycloalkyl group may be substituted by a substituent. Representative examples of cycloalkyl group include cyclopropyl, cyclopentyl, cyclohexyl, cyclobutyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl.

[0069] The term "aryl" refers to a hydrocarbon monocyclic, bicyclic or tricyclic aromatic ring system. Aryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, 4, 5 or 6 atoms of each ring of an aryl group may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl, anthracenyl, fluorenyl, indenyl, azulenyl, and the like.

[0070] The term "heteroaryl" refers to an aromatic monocyclic, bicyclic, or tricyclic ring system having 1-4 ring heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or

1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and the remainder ring atoms being carbon (with appropriate hydrogen atoms unless otherwise indicated). Heteroaryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a heteroaryl group may be substituted by a substituent. Examples of heteroaryl groups include pyridyl, 1-oxo-pyridyl, furanyl, benzol[1,3]dioxolyl, benzo[1,4]dioxinyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl, imidazolyl thiazolyl, isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, thiadiazolyl, isoquinolinyl, indazolyl, benzoxazolyl, benzofuryl, indolizinyl, imidazopyridyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, quinazolinyl, purinyl, pyrrolo[2,3]pyrimidinyl, pyrazolo[3,4]pyrimidinyl, and benzo(b)thienyl, 3H-thiazolo[2,3c][1,2,4]thiadiazolyl, imidazo[1,2-d]-1,2,4-thiadiazolyl, imidazo[2,1-b]-1,3,4-thiadiazolyl. 1H,2H-furo[3,4-d]-1,2,3-thiadiazolyl, 1H-pyrazolo[5,1-c]-1,2,4-triazolyl, pyrrolo[3,4-d]-1,2,3 triazolyl, cyclopentatriazolyl, 3H-pyrrolo[3,4-c]isoxazolyl, 1H,3H-pyrrolo[1,2-c]oxazolyl, pyrrolol[2,1b]oxazolyl, and the like.

[0071] As used herein the term "substituent" or "substituted" means that a hydrogen radical on a compound or group (such as, for example, alkyl, alkenyl, alkynyl, alkylene, aryl aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cyclyl, heterocycloalkyl, or heterocyclyl group) is replaced with any desired group that does not substantially adversely affect the stability of the compound. In one embodiment, desired substituents are those which do not adversely affect the activity of a compound. The term "substituted" refers to one or more substituents (which may be the same or different), each replacing a hydrogen atom. Examples of substituents include, but are not limited to, halogen (F, Cl, Br, or I), hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, oxo (i.e., carbonyl), thio, imino, formyl, carbamido, carbamyl, carboxyl, thioureido, thiocyanato, sulfoamido, sulfonylalkyl, sulfonylaryl, alkyl, alkenyl, alkoxy, mercaptoalkoxy, aryl, heteroaryl, cyclyl, heterocyclyl, wherein alkyl, alkenyl, alkyloxy, aryl, heteroaryl, cyclyl, and heterocyclyl are optionally substituted with alkyl, aryl, heteroaryl, halogen, hydroxyl, amino, mercapto, cyano, nitro, oxo (=O), thioxo (=S), or imino (=NR), wherein R is as defined herein. The substituents on any group (such as, for example, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl) can be at any atom of that group, wherein any group that can be substituted (such as, for example, alkyl, alkenyl, alkynyl, aryl, aralkyl, beteroaryl, beteroaralkyl, cycloalkyl, cyclyl, heterocycloalkyl, and heterocyclyl) can be optionally substituted with one or more substituents (which may be the same or different), each replacing a hydrogen atom. Examples of suitable substituents include, but not limited to alkyl, alkenyl, alkynyl, cyclyl, cycloalkyl, heterocycloalkenyl, heterocycloalkyl, arylalkyl, beteroarylalkyl, aryl, heteroaryl, halogen, haloalkyl, cyano, nitro, alkoxy, aryloxy, hydroxyl, hydroxylalkyl, oxo (i.e., carbonyl), carboxyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkylcarbonyloxy, aryloxycarbonyl, heteroaryloxy, heteroaryloxycarbonyl, thio, mercapto, mercaptoalkyl, arylsulfonyl, amino, aminoalkyl, dialkylamino, alkylcarbonylamino, alkylaminocarbonyl, or alkoxycarbonylamino; alkylamine, arylamino, diarylamino, alkylcarbonyl, or arylamino-substituted aryl; arylalkylamino, aralkylaminocarbonyl, amino, alkylaminosulfonyl, arylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, imino, carbamido, carbamyl, thioureido, thiocyanato, sulfoamido, sulfonylalkyl, sulfonylaryl, or mercaptoalkoxy.

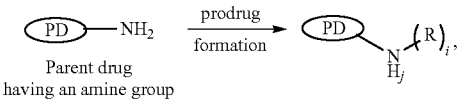
[0072] Additional suitable substituents on alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cyclyl, heterocycloalkyl, and heterocyclyl include, without limitation halogen, CN, NO_2, OR^{15}, SR^{15}, $S(O)_2OR^{15}$, $NR^{15}R^{16}$, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, (=O), (=S), (=NR^{15}), $C(O)OR^{15}$, $C(O)NR^{15}R^{16}$, $OC(O)NR^{15}R^{16}$, $NR^{15}C(O)NR^{15}$, R^{16}, $C(NR^{16})NR^{15}R^{16}$, $NR^{15}C(NR^{16})NR^{15}R^{16}$, $S(O)_2NR^{15}R^{16}$, R^{17}, C(O)H, $C(O)R^{17}$, $NR^{15}C(O)R^{17}$, $Si(R^{15})_3$, $OSi(R^{15})_3$, $Si(OH)_2R^{15}$, $P(O)(OR^{15})_2$, $S(O)R^{17}$, or $S(O)_2R^{17}$. Each R^{15} is independently hydrogen, C_1-C_6 alkyl optionally substituted with cycloalkyl, aryl, heterocyclyl, aryl, or heteroaryl. Each R^{16} is independently hydrogen, C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl aryl, or heteroaryl. Each R^{17} is independently C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl and C_1-C_4 alkyl in each R^{15}, R^{16} and R^{17} can optionally be substituted with halogen, CN, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, COOH, $C(O)OC_1$-C_4 alkyl, NH_2, C_1-C_4 alkylamino, or C_1-C_4 dialkylamino.

[0073] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed, groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0074] The compounds disclosed in the present invention are available from commercial sources or may be synthesized using reagents and techniques known in the art, including those delineated herein. The chemicals used in the synthetic routes may include, for example, solvents, reagents, catalysts, and protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds herein. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations,* VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis,* 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis,* John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis,* John Wiley and Sons (1995) and subsequent editions thereof.

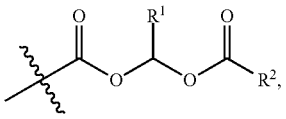
Prodrug Appendage Moiety

[0075] In one aspect, a novel design of amine prodrugs is provided in the current invention. In particular, the prodrugs may include a parent drug molecule having at least one amine group and at least one prodrug appendage moiety attached to an amine of the parent drug molecule.



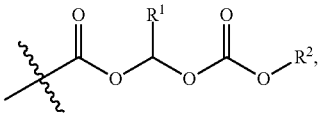
where R is a prodrug appendage moiety where i may be 1 or 2 and j may be 0 or 1. For example, i is 1 and j is 1; or i is 2 and j is 0.

[0076] In certain exemplary embodiment, R is



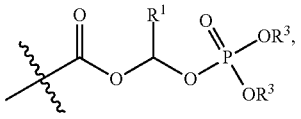
where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted.

[0077] In certain exemplary embodiments, R is



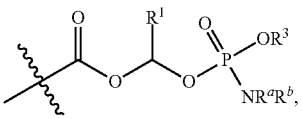
where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; and R^2 may be alkyl, cycloalkyl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted.

[0078] In certain exemplary embodiments, R is



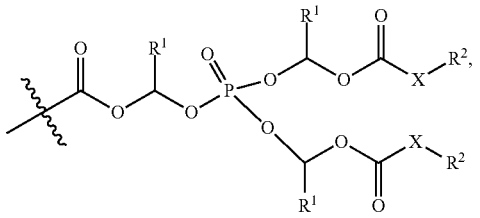
where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; and R^3 may be H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine The metal may be Na. K, Li, Ca, Mg, Ag or Zn.

[0079] In certain exemplary embodiments, R is



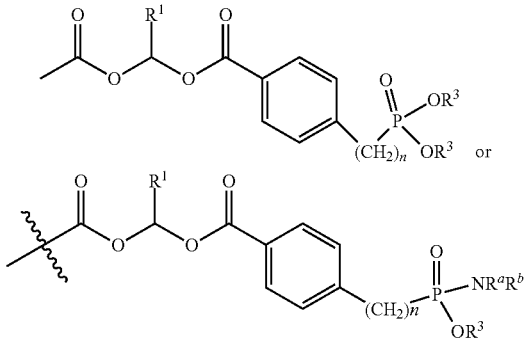
where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; and R^3 may be H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine; and R^a or R^b may be H, alkyl or aryl, or NR^a or NR^b may be an amino acid. The metal may be Na, K, Li, Ca, Mg, Ag or Zn. Aryl, or NR^a or NR^b may be an amino acid. The metal may be Na, K, Li, Ca, Mg, Ag or Zn.

[0080] In certain exemplary embodiments, R is



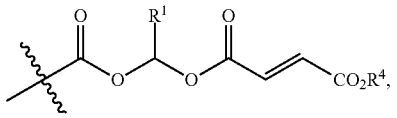
where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; and X is C or O.

[0081] In certain exemplary embodiments, R is



where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; R^2 may be alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; and R^3 may be H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine; and R^a or R^b may be H, alkyl or aryl, or NR^a or NR^b may be an amino acid. n may be 0- b **2**.

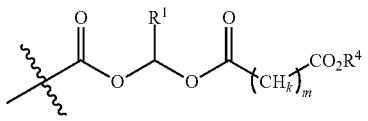
[0082] In certain exemplary embodiments, R is



where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; and R^4 may be H, metal, ammonium salt, or alkyl;

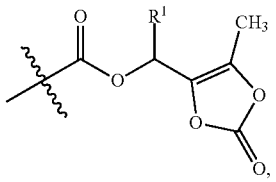
[0083] In particular, the metal may be Na, K, Li, Ca, Mg, Ag or Zn.

[0084] In certain exemplary embodiments, R is,



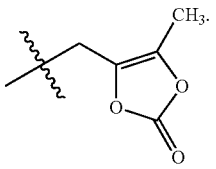
where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; and R^4 may be H, metal, ammonium salt, or alkyl; k may be 1 or 2, m may be 2-22, or $(CH_k)_m$ may be saturated, unsaturated or conjugated hydrocarbon. In particular, the metal may be Na, K, Li, Ca, Mg, Ag or Zn.

[0085] In certain exemplary embodiments, R is

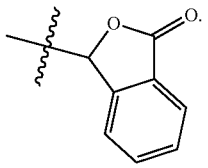


where R^1 may be H, alkyl or particularly C_1-C_8 alkyl.

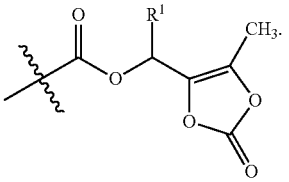
[0086] In certain exemplary embodiments, R is



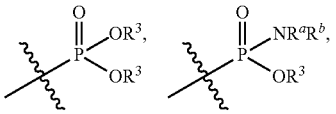
[0087] In certain exemplary embodiments, R is



[0088] In certain exemplary embodiments, R is

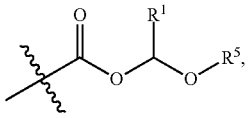


[0089] In certain exemplary embodiments, R is



where R^3 may be H, metal, alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted, or a substituted or unsubstituted primary, secondary or tertiary amine; R^a or R^b may be H, alkyl or aryl, or NR^a or NR^b may be an amino acid.

[0090] In certain exemplary embodiments, R is

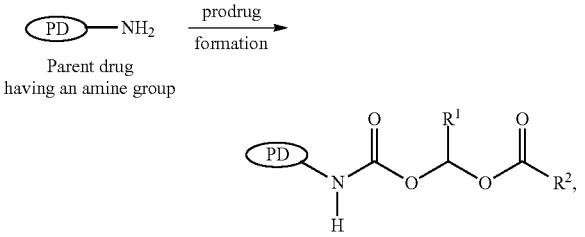


where R^1 may be H, alkyl or particularly C_1-C_8 alkyl; and R^5 may be a substituted or unsubstituted natural amino acid;

[0091] In certain embodiment, i is 1 and j is 1.

[0092] In certain embodiment, i is 2 and j is 0.

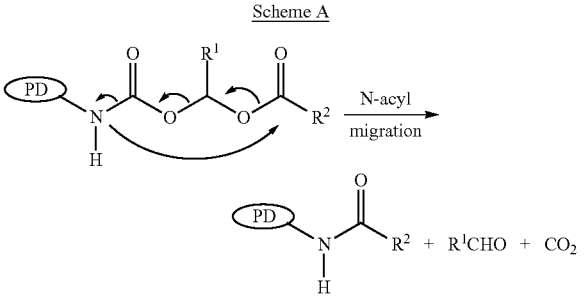
[0093] In an exemplary embodiment, the amine prodrug may be N-acyloxy carbamate prodrug formed as below.



[0094] where R^1 is be H or CH_3; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or alkyl, which may be substituted or unsubstituted.

[0095] In certain exemplary embodiments, when the amine of the prodrug is a primary or secondary amine, the N-acyloxy carbamate prodrug itself may further be converted into an N-acyl compound spontaneously by intramolecular O to N acyl migration. As shown Scheme A, the N-acyl compound may be released as consequence and may substantially provide a stable carbamate compound.

Scheme A



[0096] In certain exemplary embodiments, the amine prodrugs may have improved physiochemical stability, thereby providing advantages in isolation, crystallinity, solid state stability, solubility, formulation and the like.

[0097] In certain exemplary embodiments, the amine prodrugs may have improved physiological stability when the prodrugs are taken and ingested by the subject. For example, the N-acyloxy carbamate drugs may be converted or released into the drug form more efficiently in the subject without adverse effect.

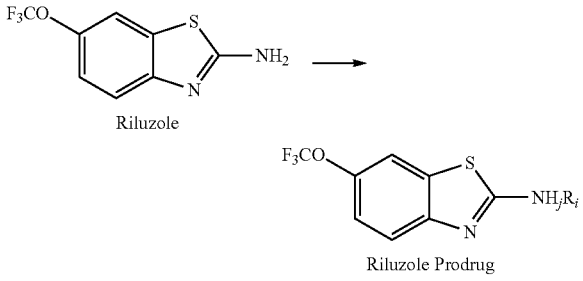
[0098] In certain exemplary embodiments, the amine prodrugs of the invention may have specificity to a certain enzymatic reaction. In yet certain embodiments, the prodrugs may be under metabolic pathway to release the active drug by enzymatic or biochemical reaction.

[0099] In certain embodiments, the amine prodrugs of the invention may provide improved cell permeability to a target cell.

[0100] In certain embodiments, the appendage moiety of the amine prodrug may provide improved physiochemical stability, improved physiological stability, or specificity to particular enzymes.

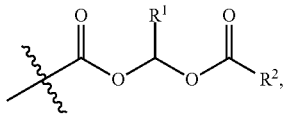
Riluzole Prodrugs

[0101] In one aspect, the current invention provides riluzole prodrugs. The riluzole prodrug may include a riluzole and at least one or more of prodrug appendage moieties attached to an amine of the riluzole at its aromatic amine.



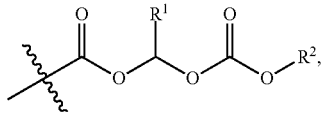
[0102] In one embodiment, the riluzole may be coupled to one or more of prodrug appendage moieties (R) to form riluzole prodrugs, in certain embodiments, i is 1 or 2 and j is 0 or 1. For example, i is 1 and j is 1; or i is 2 and j is 0.

[0103] In certain exemplary embodiment, R is



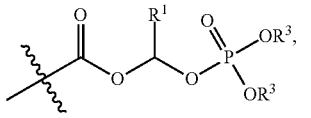
where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted.

[0104] In certain exemplary embodiments, R is



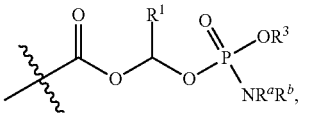
where R^1 is H alkyl or particularly C_1-C_8 alkyl; and R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted.

[0105] In certain exemplary embodiments, R is



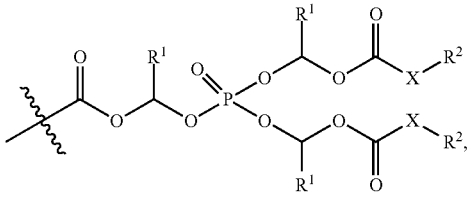
where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted, and R^3 is H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine.

[0106] In certain exemplary embodiments, R is



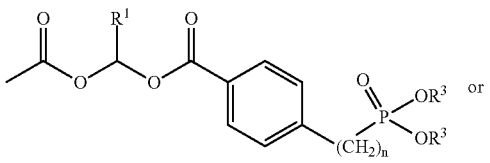
where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; R^3 is H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine; and R^a or R^b is H, alkyl or aryl or NR^a NR^b is an amino acid.

[0107] In certain exemplary embodiments, R is



where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, halo alkyl, which may be substituted or unsubstituted; and X is C or O.

[0108] In certain exemplary embodiments, R is



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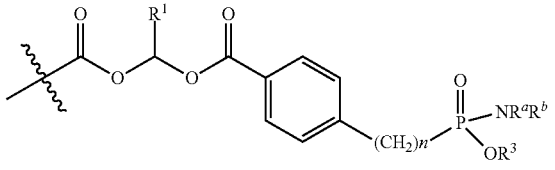
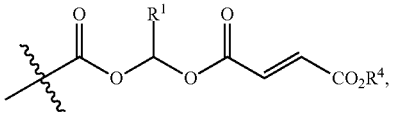


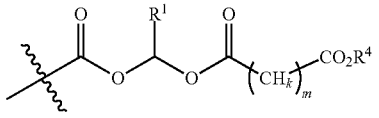
where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; R^3 is H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine; and R^a or $R^b$is H, alkyl or aryl or NR^a or NR^b is an amino acid.

[0109] In certain exemplary embodiments, R is



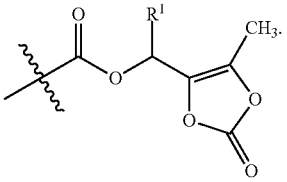
where R^1 is H, alkyl or particularly C_1-C_8 alkyl; and R^4 is H, metal, ammonium salt, or alkyl. In particular, the metal is Na, K, Li, Ca, Mg, Ag or Zn.

[0110] In certain exemplary embodiments, R is,



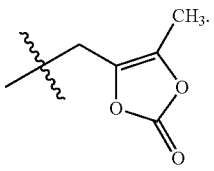
where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^4 is H, metal, ammonium salt, or alkyl; k is 1 or 2, m is 2-22 or $(CH_k)_m$ is saturated, unsaturated or conjugated hydrocarbon. In particular, the metal is Na, K, Li, Ca, Mg, Ag or Zn.

[0111] In certain exemplary embodiments, R is

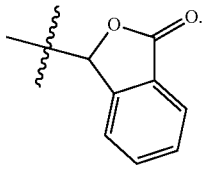


where R^1 is H, alkyl or particularly C_1-C_8 alkyl.

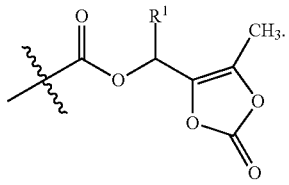
[0112] In certain exemplary embodiments, R is



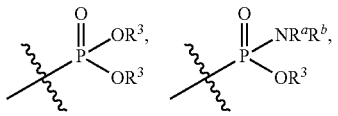
[0113] In certain exemplary embodiments, R is



[0114] In certain exemplary embodiments, R is

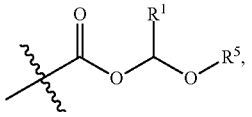


[0115] In certain exemplary embodiments, R is



where R^3 is H, metal, alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted, or a substituted or unsubstituted primary, secondary or tertiary amine; R^a or R^b is H, alkyl, aryl or NR^a or NR^b may be an amino acid.

[0116] In certain exemplary embodiments, R is

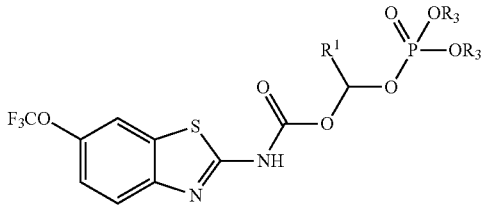


where R^1 is H, alkyl or particularly C_1-C_8 alkyl R^5 is a substituted or unsubstituted natural amino acid.

[0117] In certain embodiment, i is 1 and j is 1.

[0118] In certain embodiment, i is 2 and j is 0.

[0119] Exemplary riluzole prodrug may be, but not limited to,



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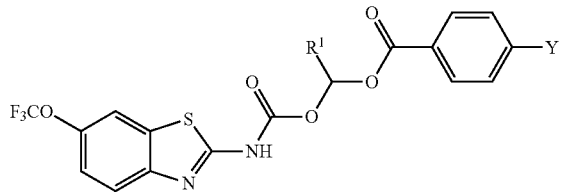
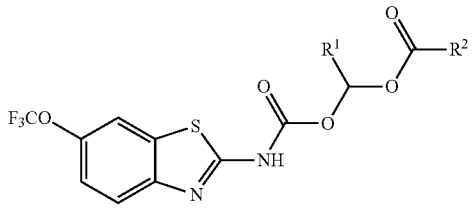
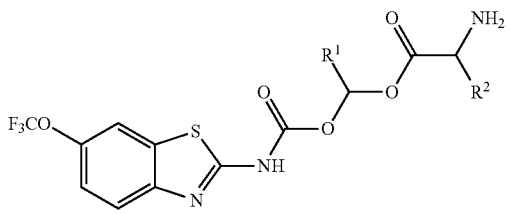
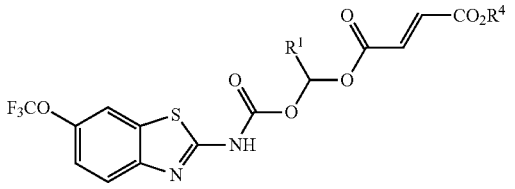
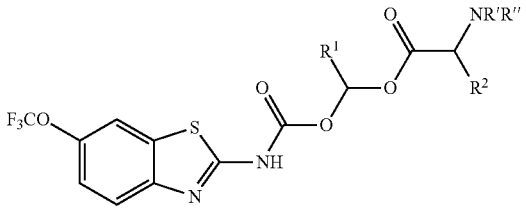
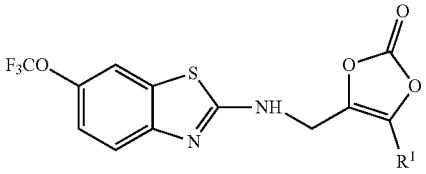


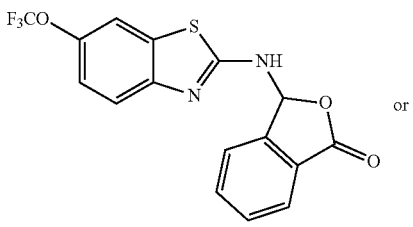




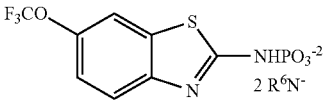








or



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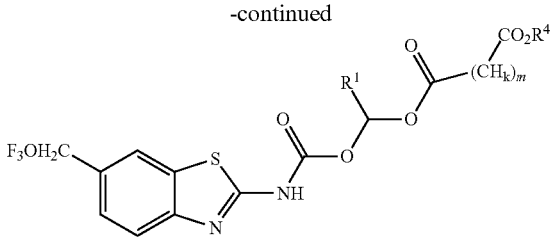
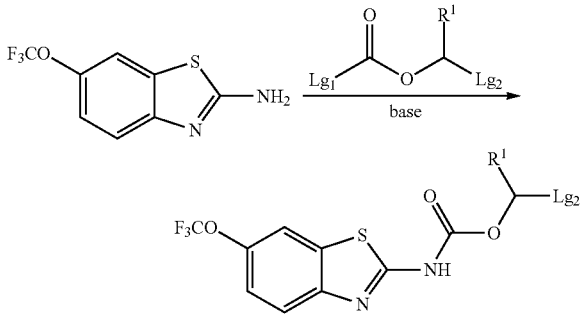


[0120] where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; R^3 is H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine; R^4 is H, metal, ammonium salt, or alkyl; R^6 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl; k is 1 or 2, in is 2-22, or $(CH_k)_m$ is saturated, unsaturated or conjugated hydrocarbon; N' is a primary, secondary and tertiary amine which may be substituted or unsubstituted, or metal salts; and Y is PO_3H, CH_2PO_3H or salt thereof. In particular, the metal is Na, K, Li, Ca, Mg, Ag or Zn.

Synthesis of Riluzole Prodrugs

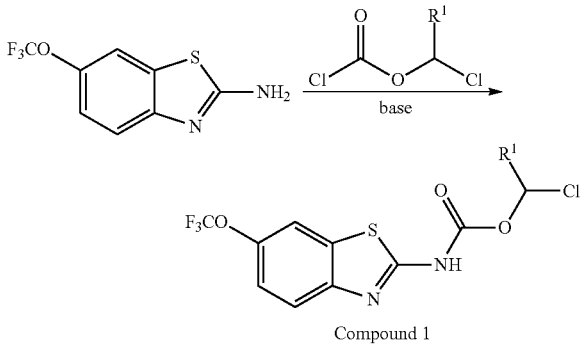
[0121] In one aspect, the riluzole prodrugs may be synthesized via intermediate form.

[0122] In one embodiment, the riluzole may be activated to produce an intermediate b reaction with methyl carboxyl group in basic condition.



[0123] The intermediate may include a good leaving group, such as halide, and may be susceptible to a nucleophilic attack from other nucleophiles. Exemplary leaving group may be, but not limited to, Cl, Br, or I.

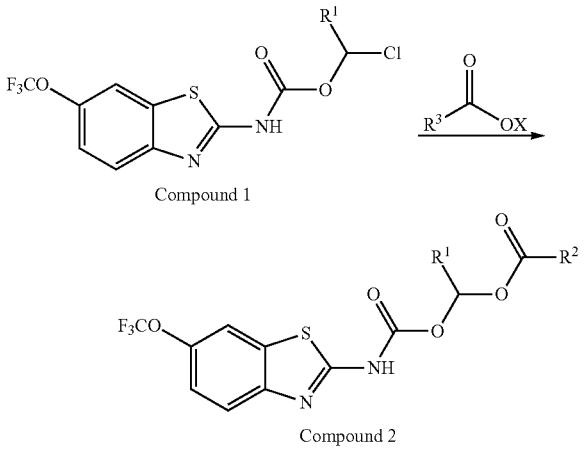
[0124] Exemplary reaction may be described as follows:



Compound 1

[0125] In one exemplary embodiment, the riluzole prodrug may be formed by Scheme 1. below. In Scheme 1, Compound 1 is reacted with carboxylate metal to produce Compound 2.

Scheme 1



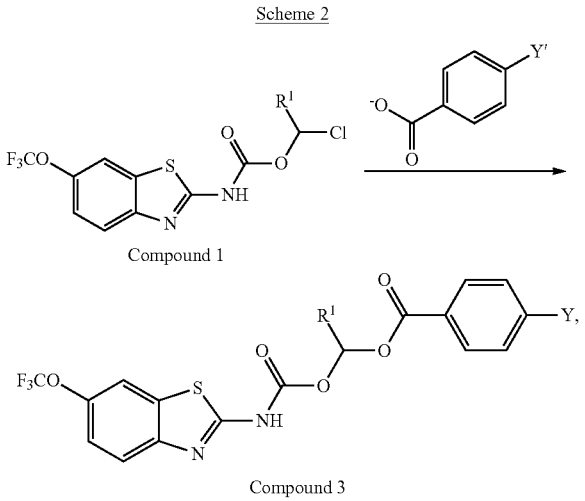
Compound 1

Compound 2

[0126] where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; and X is Na, K, Li, Ag or Zn. Further, the metal is Na, K, Li, Ca, Mg, Ag or Zn.

[0127] In one exemplary embodiment, the riluzole prodrug may be formed by Scheme 2 below. In Scheme 2, Compound 1 is reacted with phenyl carboxylate under basic condition to produce Compound 3.

Scheme 2



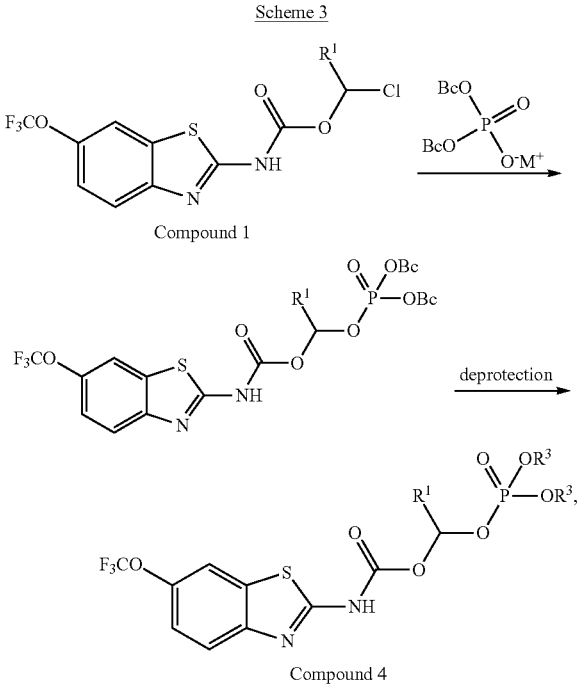
Compound 1

Compound 3

[0128] where R^1 is H, alkyl or particularly C_1-C_8 alkyl;Y is PO_3H, CH_2PO_3H or salts thereof; and Y' is H, PO_3Bc_2, CH_2PO_2Bc, MPO_3Bc or salt thereof, or $N(R_a)_4^+$, where Ra is H or alkyl.

[0129] In one exemplary embodiment, the riluzole prodrug may be formed by Scheme 3 below. In Scheme 3, Compound 1 is reacted with protected phosphate and the resulting compound is deprotected to produce Compound 3.

Scheme 3



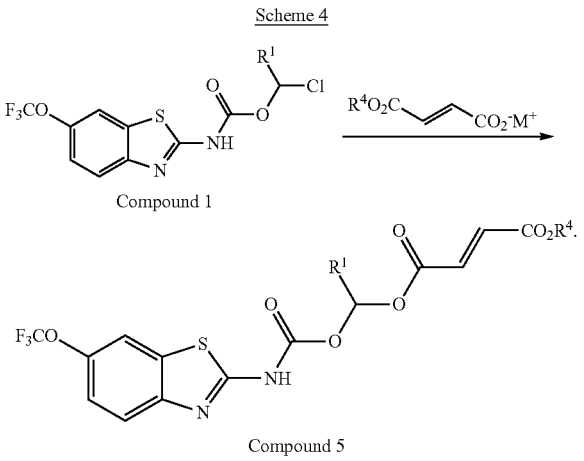
Compound 1

Compound 4

[0130] where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted; R^3 is H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine; and Bc is a protecting group. M is a metal including Na, K, Li, Ca, Mg, Ag or Zn.

[0131] In one exemplary embodiment, the riluzole prodrug may be formed by Scheme 4 and Scheme 4' below. In Scheme 4, Compound 1 is reacted with fumarase to produce Compound 5

Scheme 4

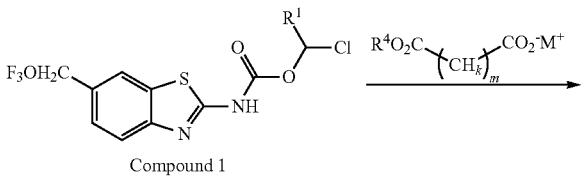


Compound 1

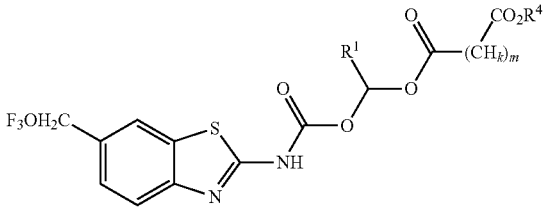
Compound 5

[0132] In Scheme 4', Compound 1 is reacted with a saturate, unsaturated, or conjugated dicarboxylic acid to produce Compound 5'.

Scheme 4'



Compound 1

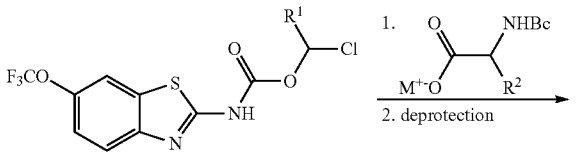


Compound 5'

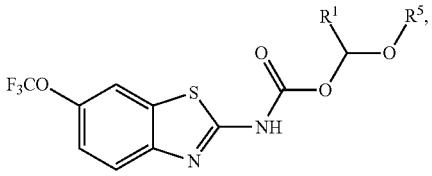
[0133] In Schemes 4 and 4', R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^4 is H, metal ammonium salt, or alkyl; k is 1 or 2, is 2-22, or $(CH_k)_m$ is saturated, unsaturated or conjugated hydrocarbon; and M is a metal including Na, K, Li, Mg, Ca, Ag or Zn.

[0134] In one exemplary embodiment, the riluzole prodrug may be formed by Scheme 5 below. In Scheme 5, Compound 1 is reacted with protected aminoacetate and the resulting compound is deprotected to produce Compound 6.

Scheme 5



Compound 1

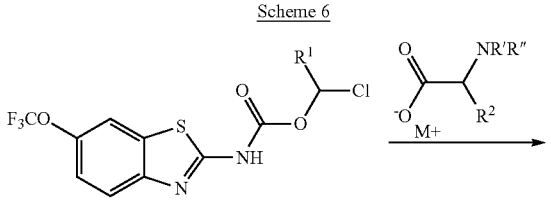


Compound 6

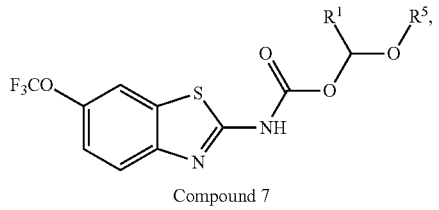
[0135] where R^1 is H, alkyl or particularly C_1-C_8 alkyl; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted ; and R^5 is a substituted or unsubstituted natural amino acid; and M is a metal including Na, K, Li, Mg, Ca, Ag or Zn. Bc is a protecting group.

[0136] In one exemplary embodiment, the riluzole prodrug may be formed by Scheme 6 below. In Scheme 6, Compound 1 is reacted with aminoacetate to produce Compound 7.

Scheme 6



Compound 1



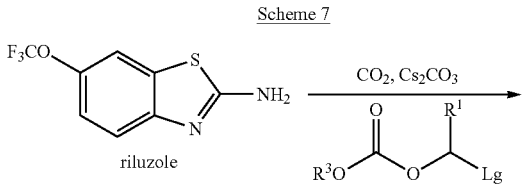
Compound 7

[0137] where R^1 is H, alkyl or particularly C_1-C_8 alkyl; and R^5 is a substituted or unsubstituted natural amino acid; and X is Na, K, Li, Ag or Zn.

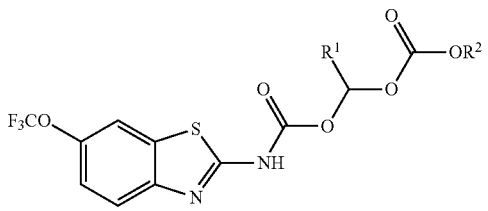
[0138] In another embodiment, the riluzole prodrug nay be formed using cesium carbonate for carbamination of amine efficiently.

[0139] In one exemplary embodiment, the riluzole prodrug may be formed in N-acyloxy carbamate form. In Scheme 7, activated carboxylic acid and carbon dioxide are condensed with riluzole to form the prodrug (compound 8).

Scheme 7



riluzole

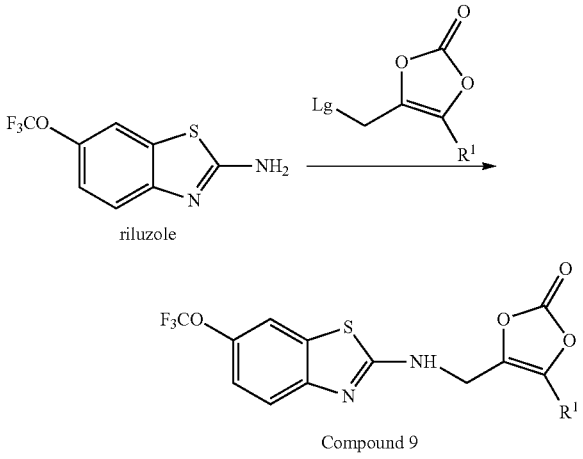


Compound 8

[0140] where R^1 is H, alkyl or particularly C_1-C_8 alkyl; Lg is a leaving group; R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which may be substituted or unsubstituted. In particular, Lg may be a halide, such as F, Cl, Br and I.

[0141] In Scheme 8, riluzole is reacted with 4-methyl 1,3-dioxol-2 one to produce Compound 9. In an exemplary embodiment, the prodrug may be synthesized as follows.

Scheme 8



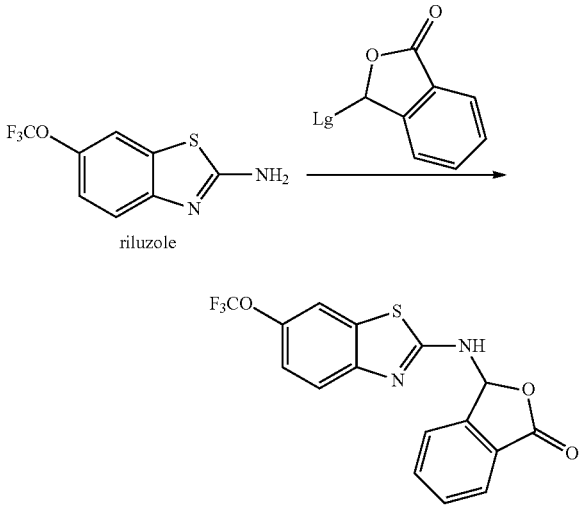
Compound 9

[0142] where R^1 is H, alkyl or particularly C_1-C_8 Lg is a leaving group Lg is a leaving group. Particularly, Lg, may be a halide, such as F, Cl, Br and I.

[0143] In Scheme 9, riluzole is reacted with isobenzofurane-1-one to produce Compound 10.

[0144] In an exemplary embodiment, the prodrug may be synthesized as follows.

Scheme 9

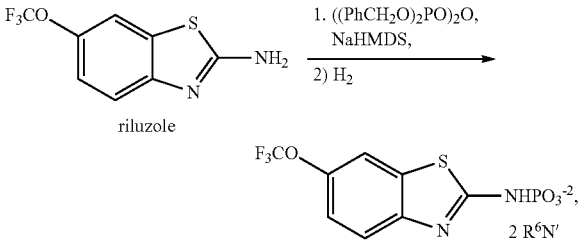


Compound 10

[0145] In particular, Lg is a leaving group, Lg may be a halide, such as F, Br and I.

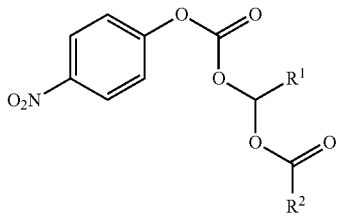
[0146] In Scheme 10, riluzole is reacted with $((PhCH_2O)_2PO)_2O$ and sodium bis(trimethylsilyl)amide (NaHMDS) and the resulting compound is reacted with hydrogen gas to produce compound 11.

[0147] In an exemplary embodiment, the prodrug may be synthesized as follows:



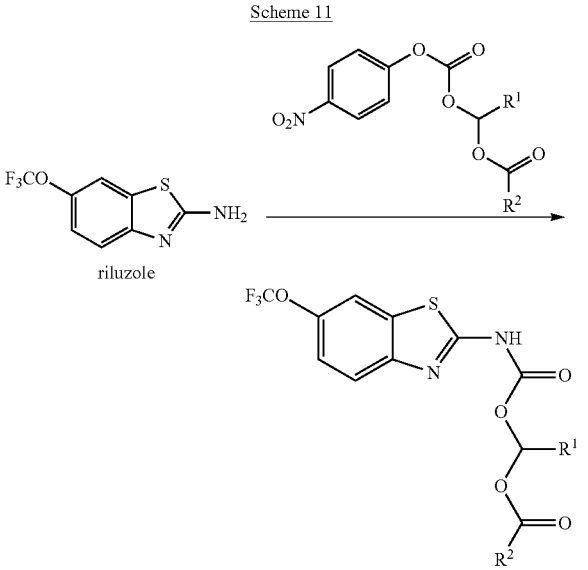
[0148] where R^6 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl; and N' is a primary, secondary and tertiary amine which is substituted or unsubstituted, or metal salts.

[0149] In one exemplary embodiment, N-acyloxy carbamate prodrug may also be synthesized using



((4-nitrophenoxy)carbonyloxy)methyl formate,
where R^1 is H, alkyl or particularly C_1-C_8 alkyl; and R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which is substituted or unsubstituted. Exemplary reaction scheme is shown as follows. In Scheme 11, riluzole is reacted with ((4-nitrophenoxy)carbonyloxy)methyl formate to produce Compound 12.

Scheme 11



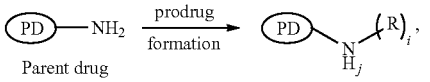
Compound 12

[0150] The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

[0151] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

We claim:

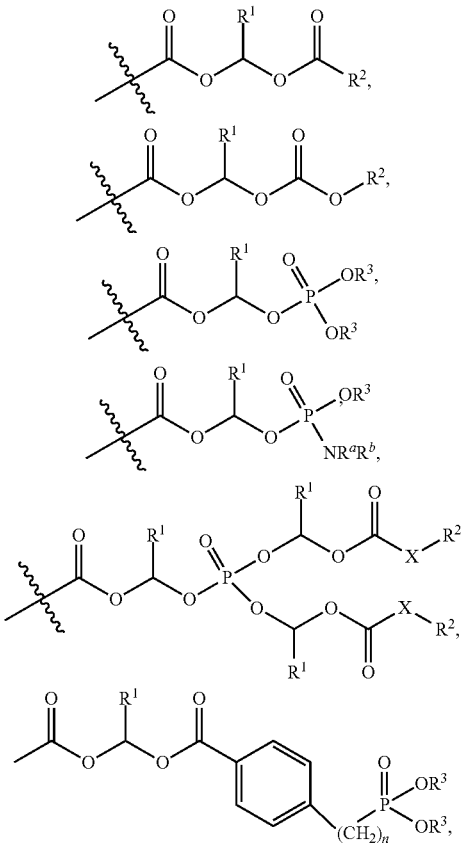
1. A prodrug comprising a drug molecule and at least one or more prodrug appendage moieties, the prodrug is formed as:



Parent drug having an amine group

wherein the prodrug appendage moiety is coupled to amine of the drug molecule, and i is 1 or 2 and j is 0 or 1.

2. The prodrug of claim **1**, wherein prodrug appendage moiety is independently selected from the group of consisting of:



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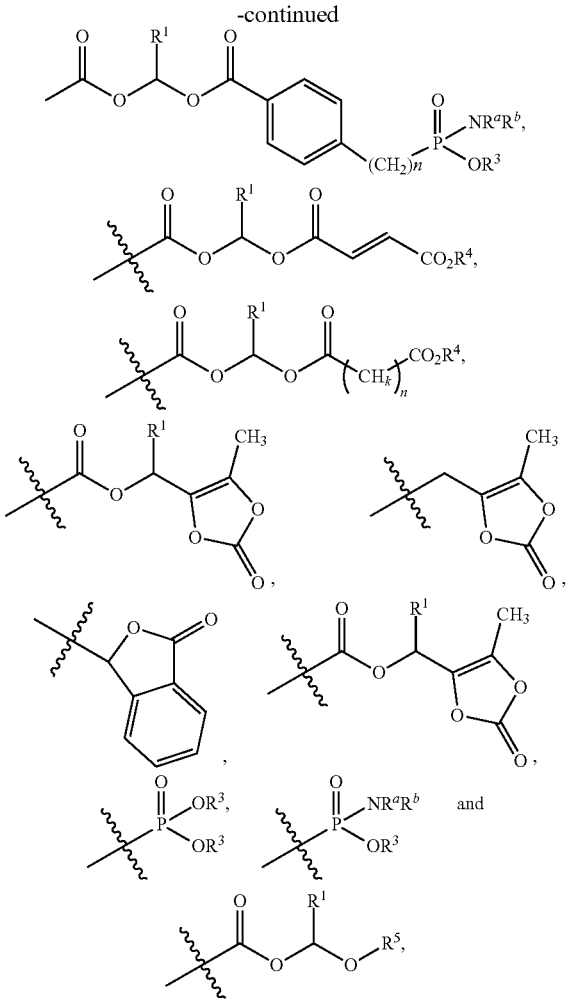


where R^1 is H, alkyl or particularly C_1-C_8 alkyl;

R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which is substituted or unsubstituted.

R^3 is H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine;

R^4 is H, metal, ammonium salt or alkyl;

R^5 is a substituted or unsubstituted natural amino acid;

R^a or R^b is H, alkyl or aryl; or NR^a or NR^b is an amino acid;

X is C or O;

k is 1 or 2, m is 2-22, or $(CH_k)_m$ is saturated, unsaturated or conjugated hydrocarbon;

n is0-2;

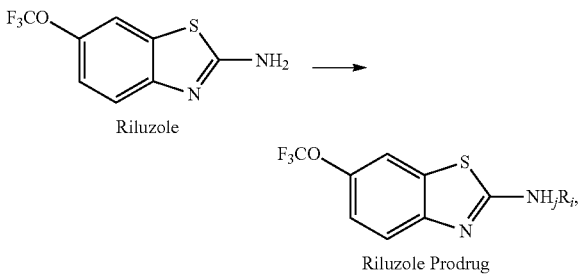
the metal is Na, K, Li, Ca, Mg, Ag or Zn.

3. The prodrug of claim **1** wherein i is 1 and j is 1,

4. The prodrug of claim **1**, wherein i is 2 and j is 0.

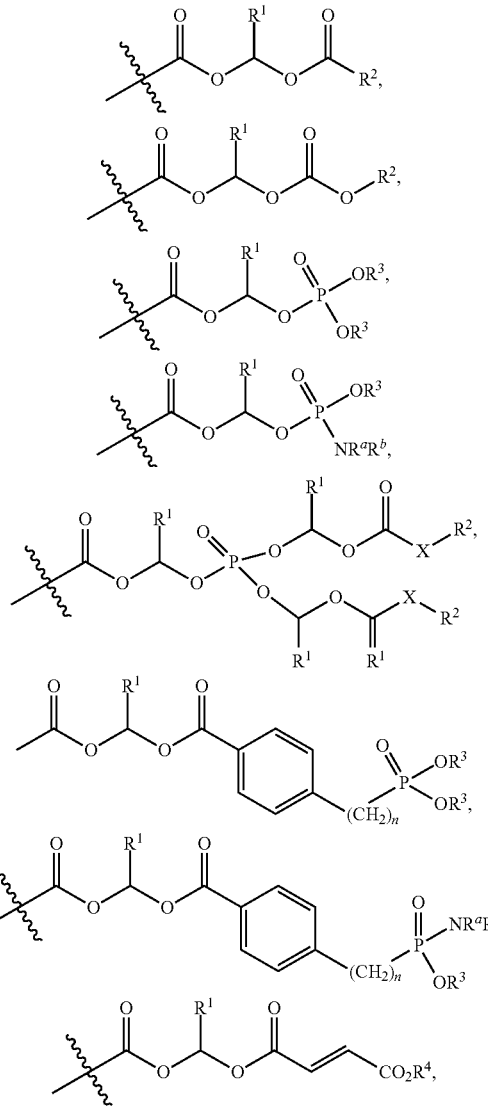
5. The prodrug of claim **1**, wherein the drug molecule riluzole.

6. A method of preparing a riluzole prodrug, comprising a step of coupling one or more prodrug appendage moieties to a riluzole molecule



wherein the prodrug appendage moiety is coupled to amine of the riluzole molecule, and i is 1 or 2 and j is 0 or 1.

7. The method of claim **6**, wherein each prodrug appendage moiety is independently selected from the group of consisting of:



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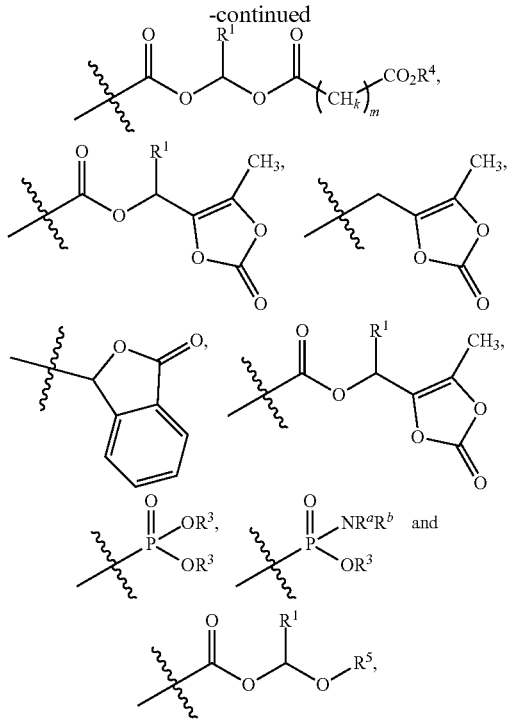


where R^1 is H, alkyl or particularly C_1-C_8 alkyl;

R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which is substituted or unsubstituted,

R^3 is H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine;

R^4 is H, metal, ammonium salt or alkyl;

R^5 is a substituted or unsubstituted natural amino acid;

R^a or R^b is H, alkyl or aryl; or NR^a or NR^b is an amino acid;

X is C or O;

k is 1 or 2, m is 2-22, or $(CH_k)_m$ is saturated, unsaturated or conjugated hydrocarbon;

n is 0-2;

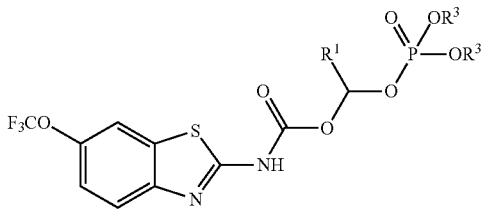
is 2-12; and

the metal is Na, K, Li, Mg, Ca, Ag or Zn.

8. The method of claim **6**, wherein i is 1 and is 1.

9. The method of claim **6**, wherein i is 2 and j is 0.

10. The method of claim **6**, wherein the riluzole prodrug is selected from the group consisting of:



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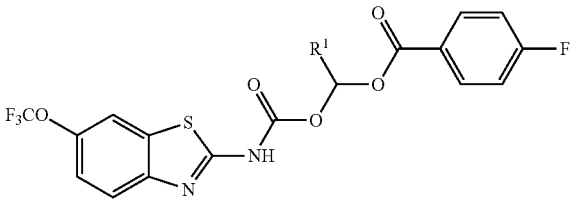
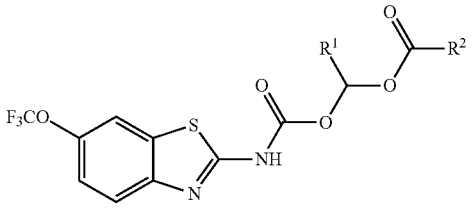
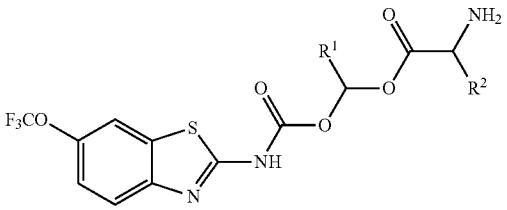
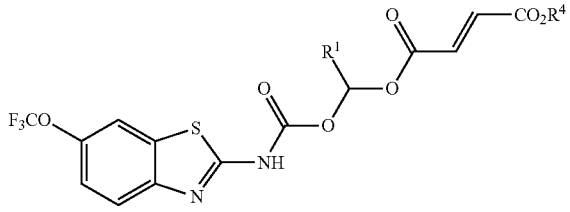
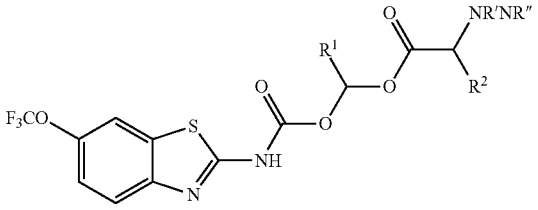
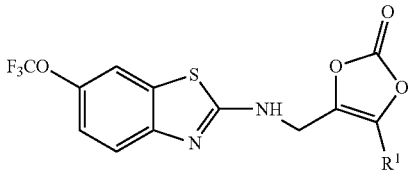


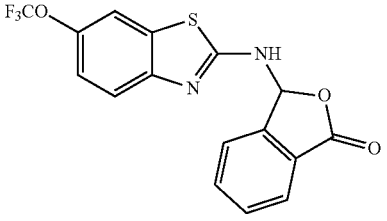




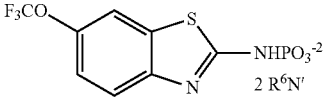








or



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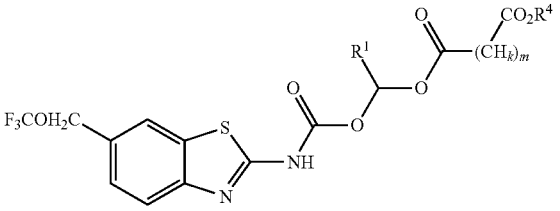


where R_1 is H, alkyl, or particularly C_1-C_8 alkyl;

R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which is substituted or unsubstituted;

R^3 is H, metal, R^2 or a substituted or unsubstituted primary, secondary or tertiary amine;

R^4 is H, metal, ammonium salt or alkyl;

R^5 is a substituted or unsubstituted natural amino acid;

R^6 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl;

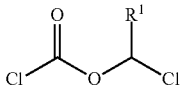
k is 1 or 2, m is 2-22, or $(CH_k)_m$ is saturated, unsaturated or conjugated hydrocarbon;

N' is a primary, secondary and tertiary amine which is substituted or unsubstituted, or metal salts;

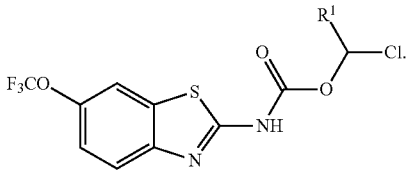
Y is PO_3H, CH_2PO_3H or salt thereof; and

the metal is Na, K, Li, Ca, Mg, Ag or Zn.

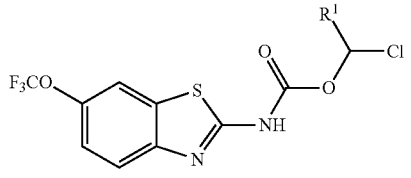
11. A method of synthesizing a riluzole prodrug, comprising a step of reacting riluzole with



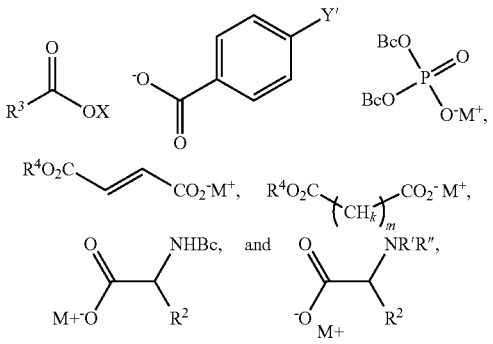
to produce



12. The method of claim **11**, further comprising a step of reacting



with a compound selected from the group consisting of:



wherein R^2 is H, alkyl or particularly C_1-C_8 alkyl

R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which is substituted or unsubstituted;

R^4 is H, metal, ammonium salt, or alkyl,

k is 1 or 2, m is 2-22, or $(CH_k)_m$ is saturated, unsaturated pr conjugated hydrocarbon;

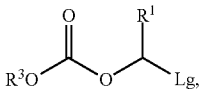
Bc is a protecting group;

Y' is H, PO_3Bc_2, CH_2PO_2Bc, or salt thereof, or $N(R_a)_4^+$, where Ra is H or alkyl;

M is Na, K, Li, Mg, Ca, Ag or Zn; and

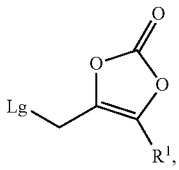
R' or R" are cyclic or acyclic alkyl.

13. A method of synthesizing a riluzole prodrug, comprising a step of reacting a riluzole, with CO_2, Cs_2CO_3 and reacting the resulting compound with



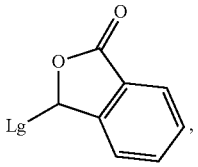
wherein Lg is a leaving group.

14. A method of synthesizing a riluzole prodrug, comprising a step of reacting a riluzole with



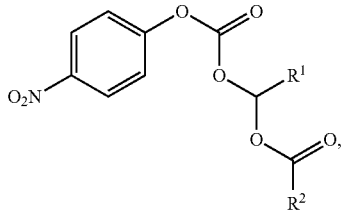
wherein Lg is a leaving group and where R^1 is H, or C_1-C_8 alkyl.

15. A method of synthesizing a riluzole prodrug, comprising a step of reacting a riluzole with



wherein Lg is a leaving group.

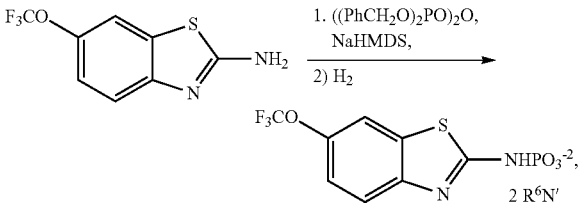
16. A method of synthesizing a riluzole prodrug, comprising a step of reacting riluzole with



wherein R^I is H, alkyl or particularly C_1-C_8 alkyl: and

R^2 is alkyl, cycloalkyl, aryl, or heteroaryl, or halo alkyl, which is substituted or unsubstituted.

17. A method of synthesizing a riluzole prodrug, col prising a step of reacting riluzole with $((PhCH_2O)_2PO)_2O$ and sodium his(trimethylsily)amide (NaHMDS) and subsequently reacting the resulting compound with hydrogen:



wherein R^6 is alkyl, cycloalkyl, aryl,or heteroaryl, or haloalkyl; N' is a primary, secondary and tertiary amine N, which is substituted or unsubstituted, or metal salts.

* * * * *