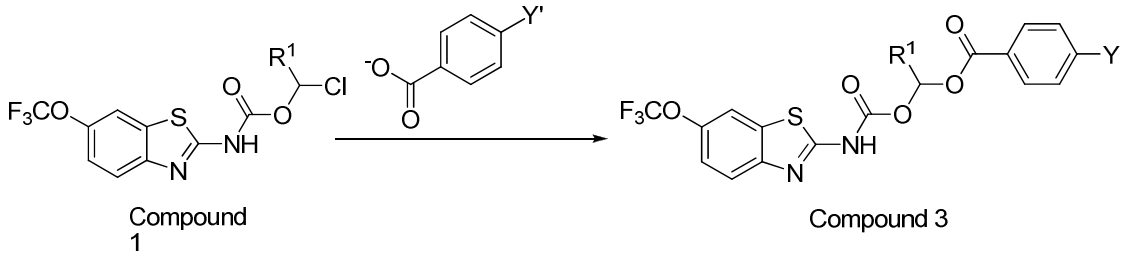


Scheme 1

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.

[0088] 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.



,

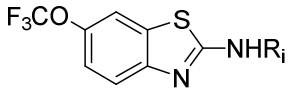
Scheme 2

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.

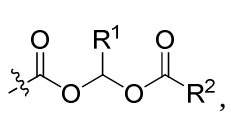
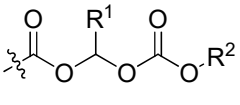
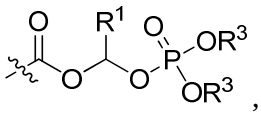
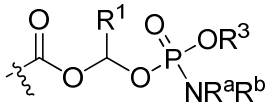
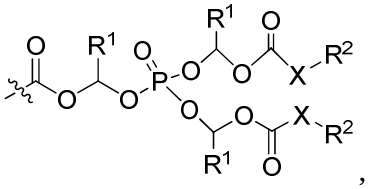
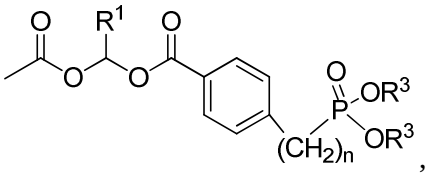
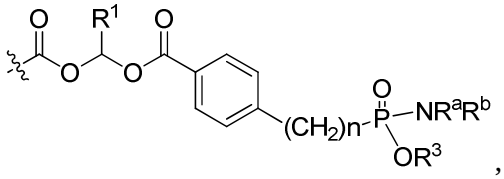
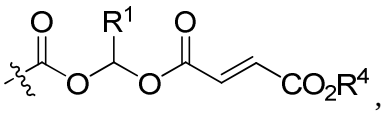
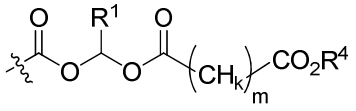
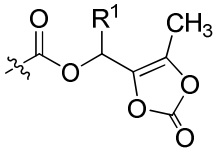
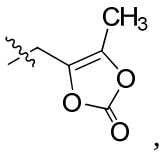
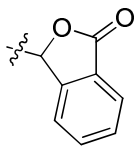
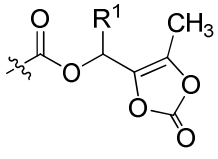
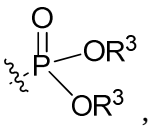
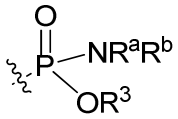
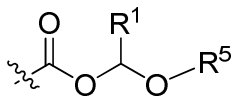
[0089] In one exemplary embodiment, the riluzole prodrug may be formed by Scheme 3 below. In Scheme 3, Compound 1 is reacted with protected phosphate and the resulting compound is deprotected to produce Compound 3.

WE CLAIM:

1. A prodrug of riluzole having the following formula:



wherein R_i is selected from:

,
,
,
,
,
,
,
,
,
,
,
,
,
,

and
,

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 O;

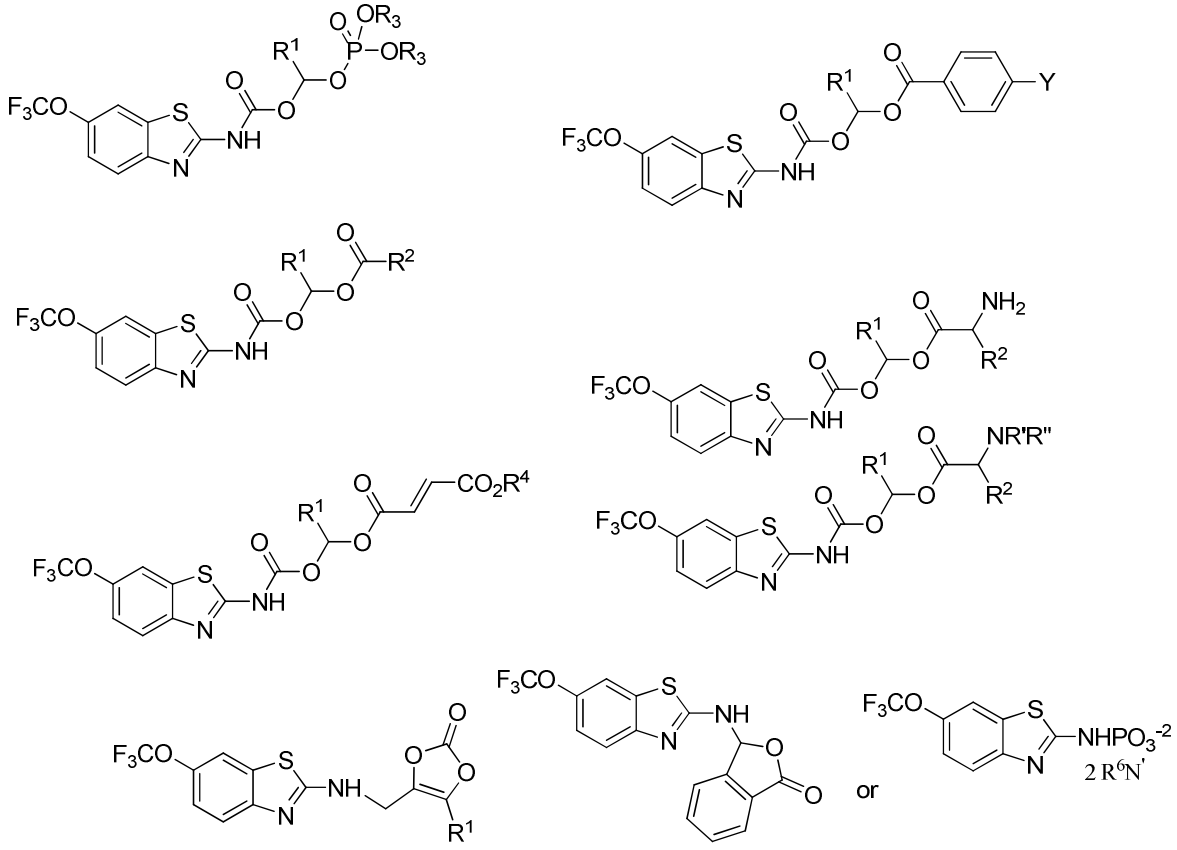
k is 1 or 2, m is 2-22, or $(CH_k)_m$ is saturated, unsaturated or conjugated hydrocarbon;

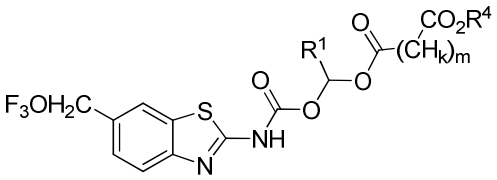
n is 0 – 2; and

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

wherein "substituted" refers to one or more substituents, which are the same or different, each replacing a hydrogen atom, wherein the one or more substituents are selected from F, Cl, Br, I, hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, oxo, 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, thioxo, or imino.

2. The prodrug of claim 1 selected from:





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;

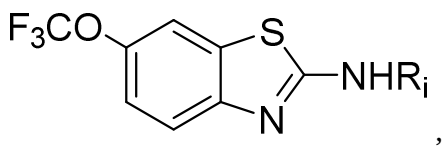
N' is a primary, secondary and tertiary amine which is substituted or unsubstituted, or metal salts;

Y is PO_3H, CH_2PO_3H or salt thereof; and

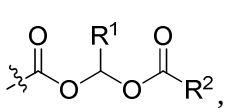
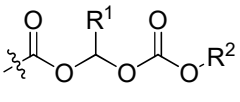
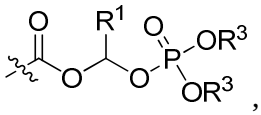
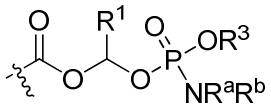
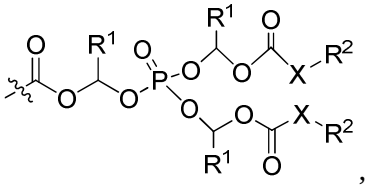
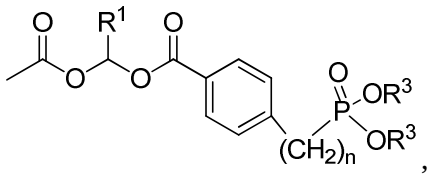
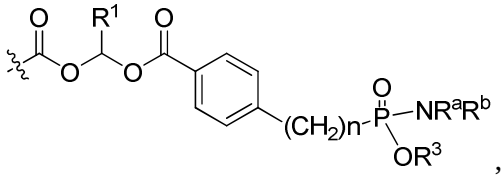
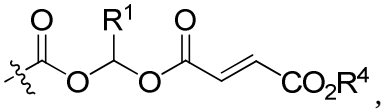
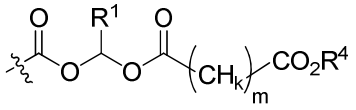
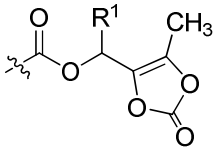
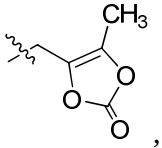
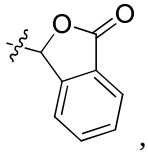
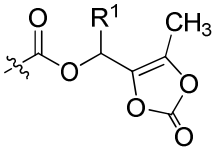
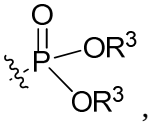
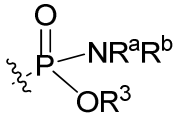
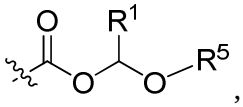
the metal is Na, K, Li, Ca, Mg, Ag or Zn,

wherein "substituted" refers to one or more substituents, which are the same or different, each replacing a hydrogen atom, wherein the one or more substituents are selected from F, Cl, Br, I, hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, oxo, 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, thioxo, or imino.

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


,

wherein R_i is selected from:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

and

,

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 O;

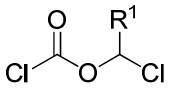
k is 1 or 2, m is 2-22, or $(CH_k)_m$ is saturated, unsaturated or conjugated hydrocarbon;

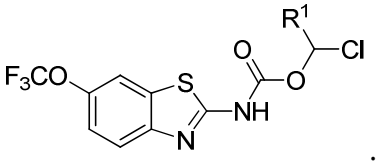
n is 0 – 2; and

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

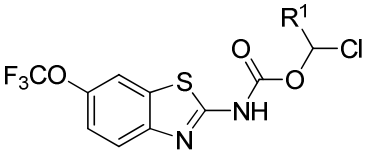
wherein "substituted" refers to one or more substituents, which are the same or different, each replacing a hydrogen atom, wherein the one or more substituents are selected from F, Cl, Br, I, hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, oxo, thio, imino, 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, thioxo, or imino.

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

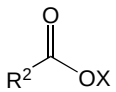


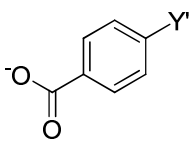
to produce .

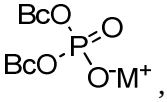
5. The method of claim 4, further comprising a step of reacting

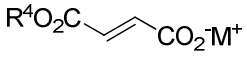
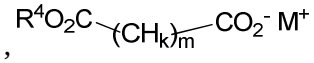
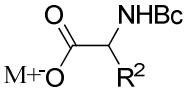
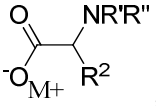


with a compound selected from:





,




and


wherein 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;

X is Na, K, Li, Ca, Mg, Ag, or Zn,

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;

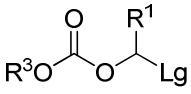
Bc is a protecting group;

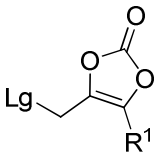
Y' is H, PO_3Bc_2, CH_2PO_2Bc, MPO_3Bc or salt thereof, or $N(R_a)_4^+$, where Ra is H or alkyl;

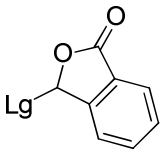
M is Na, K, Li, Mg, Ca, Ag or Zn; and

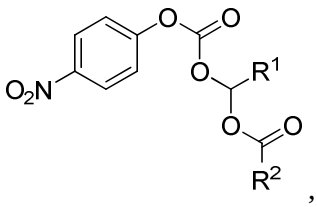
R' or R" are cyclic or acyclic alkyl,

wherein "substituted" refers to one or more substituents, which are the same or different, each replacing a hydrogen atom, wherein the one or more substituents are selected from F, Cl, Br, I, hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, oxo, 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, thioxo, or imino.

6. 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.

7. 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.

8. A method of synthesizing a riluzole prodrug, comprising a step of reacting a riluzole with , wherein Lg is a leaving group.

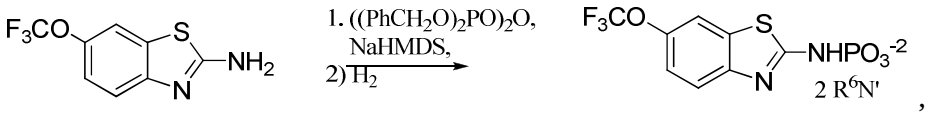
9. A method of synthesizing a riluzole prodrug, comprising a step of reacting riluzole with ,

wherein 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,

wherein "substituted" refers to one or more substituents, which are the same or different, each replacing a hydrogen atom, wherein the one or more substituents are selected from F, Cl, Br, I, hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, oxo, 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, thioxo, or imino.

10. A method of synthesizing a riluzole prodrug, comprising a step of reacting riluzole with $((PhCH_2O)_2PO)_2O$ and sodium bis(trimethylsilyl)amide (NaHMDS) and subsequently reacting the resulting compound with hydrogen:



,

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