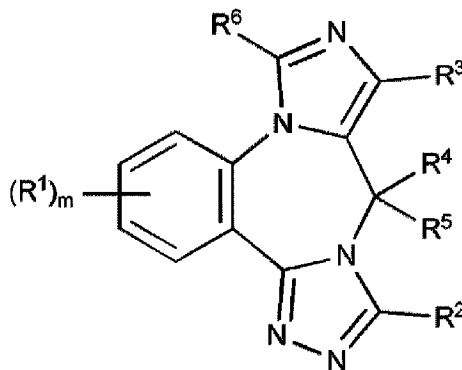




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(54) Title: BENZODIAZEPINE DERIVATIVES, COMPOSITIONS, AND METHODS FOR TREATING COGNITIVE IMPAIRMENT



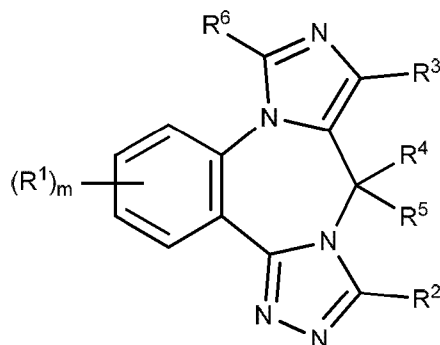
IV

(57) **Abrégé/Abstract:**

This invention relates to a compound of formula IV: (see formula IV), or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, for treating cognitive impairment associated with central nervous system (CNS) disorders. In particular, the cognitive impairment associated with central nervous system (CNS) disorders includes, without limitation, age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI (aMCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome, compulsive behavior, and substance addiction.

Abstract

This invention relates to a compound of formula IV:



IV,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, for treating cognitive impairment associated with central nervous system (CNS) disorders. In particular, the cognitive impairment associated with central nervous system (CNS) disorders includes, without limitation, age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI (aMCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease (AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome, compulsive behavior, and substance addiction.

BENZODIAZEPINE DERIVATIVES, COMPOSITIONS, AND METHODS FOR TREATING COGNITIVE IMPAIRMENT

[0001]

5

Field of the Invention

[0002] The invention relates to compounds, compositions and methods for treating cognitive impairment associated with central nervous system (CNS) disorders in a subject in need of treatment or at risk of said cognitive impairment.

10

Background of the Invention

[0003] Cognitive ability may decline as a normal consequence of aging or as a consequence of a central nervous disorder.

15

[0004] For example, a significant population of elderly adults experiences a decline in cognitive ability that exceeds what is typical in normal aging. Such age-related loss of cognitive function is characterized clinically by progressive loss of memory, cognition, reasoning, and judgment. Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age-Related Cognitive Decline (ARCD) or similar clinical groupings are among those related to such age-related loss of cognitive function. According to some estimates, there are more than 16 million people with AAMI in the U.S. alone, and MCI is estimated to affect 5.5 - 7 million in the U.S. over the age of 65.

20

[0005] Cognitive impairment is also associated with other central nervous system (CNS) disorders, such as dementia, Alzheimer's Disease (AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder (in particular, mania),

amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome, compulsive behavior, and substance addiction.

[0006] There is, therefore, a need for effective treatment of cognitive impairment
5 associated with central nervous system (CNS) disorders and to improve cognitive
function in patients diagnosed with, for example, age-related cognitive impairment, MCI,
amnesic MCI, AAMI, ARCD, dementia, AD, prodromal AD, PTSD, schizophrenia or
bipolar disorder (in particular, mania), amyotrophic lateral sclerosis (ALS), cancer-
therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD),
10 autism spectrum disorders, fragile X disorder, Rett syndrome, compulsive behavior, and
substance addiction and similar central nervous system (CNS) disorders with cognitive
impairment or at risk of developing them.

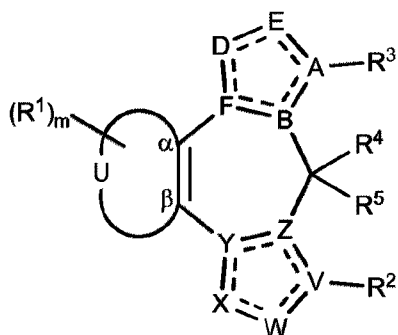
[0007] GABA_A receptors (GABA_A R) are pentameric assemblies from a pool of
different subunits (α 1-6, β 1-3, γ 1-3, δ , ϵ , π , θ) that form a Cl⁻ permeable channel that is
15 gated by the neurotransmitter γ -aminobutyric acid (GABA). Various pharmacological
effects, including anxiety disorders, epilepsy, insomnia, pre-anesthetic sedation, and
muscle relaxation, are mediated by different GABA_A subtypes.

[0008] Various studies have demonstrated that reduced GABA signaling is linked to
various CNS disorders with cognitive impairment. In particular, the α 5-containing
20 GABA_A Rs, which are relatively sparse in the mammalian brain, play a role in modifying
learning and memory. Previous studies demonstrated a reduction of hippocampal
expression of the α 5 subunit of the GABA_A receptor in rats with age-related cognitive
decline (*see* International Patent Publication WO 2007/019312). Such results suggest that
upregulation of α 5-containing GABA_A R function may be effective in the treatment of
25 cognitive impairment associated with said CNS disorders.

[0009] Thus, there is a need for positive allosteric modulators of α 5-containing GABA_A
R that are useful in therapeutic preparations for the treatment of cognitive impairment
associated with said CNS disorders.

Summary of the Invention

[0010] The present invention addresses the aforementioned need by providing a compound of formula I:



5

I,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein:

U and the two carbon atoms designated by α and β together form a 5- or 6- membered aromatic ring having 0-2 nitrogen atoms;

10 A is C, CR^6 , or N;

B and F are each independently selected from C, CR^6 , and N, wherein B and F cannot both be N;

D is selected from N, NR^7 , O, CR^6 or $\text{C}(\text{R}^6)_2$;

E is N, NR^7 , CR^6 or $\text{C}(\text{R}^6)_2$;

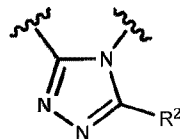
15 W is N, NR^7 , CR^6 or $\text{C}(\text{R}^6)_2$;

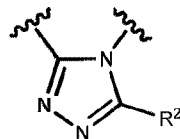
X is N, NR^7 , O, CR^6 or $\text{C}(\text{R}^6)_2$;

Y and Z are each independently selected from C, CR^6 , and N, wherein Y and Z cannot both be N;

V is C or CR^6 ,

20 or when Z is C or CR^6 , V is C, CR^6 , or N;



wherein when the ring formed by X, Y, Z, V and W is , then R^2 is $-\text{OR}^8$, $-\text{SR}^8$, $-(\text{CH}_2)_n\text{OR}^8$, $-(\text{CH}_2)_n\text{O}(\text{CH}_2)_n\text{R}^8$, $-(\text{CH}_2)_p\text{R}^8$ and $-(\text{CH}_2)_n\text{N}(\text{R}'')\text{R}^{10}$; and wherein R^2 is independently substituted with 0-5 R' ;

m and n are independently integers selected from 0-4;

p is an integer selected from 2-4;

each occurrence of the bond " --- " is either a single bond or a double bond;

each occurrence of R^1 , R^2 , R^4 , and R^5 are each independently selected from:

- 5 halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -N(R)₂, -SR, -SOR, -SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R, -C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR, -N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R, -C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂, and -P(O)(H)(OR);

R^3 is absent or is selected from:

- 15 halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -N(R)₂, -SR, -SOR, -SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R, -C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR, -N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R, -C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂, and -P(O)(H)(OR);

each R^6 is independently -H or -(C1-C6)alkyl;

- 25 each R^7 is independently -H or -(C1-C6)alkyl;

each R^8 is independently -(C1-C6)alkyl, -(C3-C10)-cycloalkyl, (C6-C10)-aryl, or 5- to 10- membered heteroaryl, wherein each occurrence of R^8 is independently substituted with 0-5 R^9 ;

each R^{10} is independently -(C3-C10)-cycloalkyl, 3- to 10- membered heterocyclyl-, (C6-

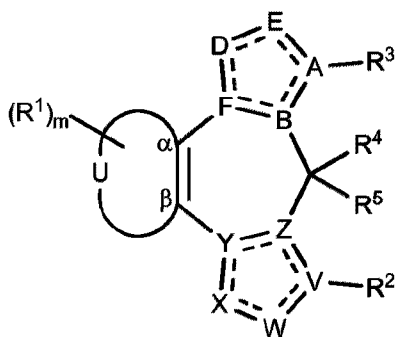
- 30 C10)-aryl, or 5- to 10- membered heteroaryl, wherein each occurrence of R^{10} is independently substituted with 0-5 R^9 ;

each R is independently selected from:

- H-,
 (C1-C12)-aliphatic-,
 (C3-C10)-cycloalkyl-,
 (C3-C10)-cycloalkenyl-,
 5 [(C3-C10)-cycloalkyl]-(C1-C12)-aliphatic-,
 [(C3-C10)-cycloalkenyl]-(C1-C12)-aliphatic-,
 [(C3-C10)-cycloalkyl]-O-(C1-C12)-aliphatic-,
 [(C3-C10)-cycloalkenyl]-O-(C1-C12)-aliphatic-,
 (C6-C10)-aryl-,
 10 (C6-C10)-aryl-(C1-C12)aliphatic-,
 (C6-C10)-aryl-O-(C1-C12)aliphatic-,
 (C6-C10)-aryl-N(R'')-(C1-C12)aliphatic-,
 3- to 10- membered heterocyclyl-,
 (3- to 10- membered heterocyclyl)-(C1-C12)aliphatic-,
 15 (3- to 10- membered heterocyclyl)-O-(C1-C12)aliphatic-,
 (3- to 10- membered heterocyclyl)-N(R'')-(C1-C12)aliphatic-,
 5- to 10- membered heteroaryl-,
 (5- to 10- membered heteroaryl)-(C1-C12)-aliphatic-,
 (5- to 10- membered heteroaryl)-O-(C1-C12)-aliphatic-; and
 20 (5- to 10- membered heteroaryl)-N(R'')-(C1-C12)-aliphatic-;
 wherein said heterocyclyl has 1-4 heteroatoms independently selected from N, NH, O, S,
 SO, and SO₂, and said heteroaryl has 1-4 heteroatoms independently selected from N,
 NH, O, and S;
 wherein each occurrence of R is independently substituted with 0-5 R';
 25 or when two R groups bound to the same atom, the two R groups may be taken together
 with the atom to which they are bound to form a 3- to 10-membered aromatic or non-
 aromatic ring having 0-4 heteroatoms independently selected from N, NH, O, S, SO,
 and SO₂, wherein said ring is optionally substituted with 0-5 R', and wherein said ring
 is optionally fused to a (C6-C10)aryl, 5- to 10- membered heteroaryl, (C3-
 30 C10)cycloalkyl, or a 3- to 10- membered heterocyclyl;
 wherein each occurrence of R' is independently selected from halogen, -R'', -OR'', oxo,
 -CH₂OR'', -CH₂NR''₂, -C(O)N(R'')₂, -C(O)OR'', -NO₂, -NCS, -CN, -CF₃, -OCF₃
 and -N(R'')₂;

wherein each occurrence of R'' is independently selected from H, -(C1-C6)-alkyl, (C3-C6)-cycloalkyl, 3- to 6- membered heterocyclyl, 5- to 10- membered heteroaryl-, (C6-C10)-aryl-, (5- to 10- membered heteroaryl)-(C1-C6)-alkyl-, (C6-C10)-aryl-(C1-C6)-alkyl-, (5- to 10- membered heteroaryl)-O-(C1-C6)-alkyl-, or (C6-C10)-aryl-O-(C1-C6)-alkyl-.

[0011] Some embodiments of this application provide a compound of formula I:



I,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein:

U and the two carbon atoms designated by α and β together form a 5- or 6- membered aromatic ring having 0-2 nitrogen atoms;

A is C, CR⁶, or N;

B and F are each independently selected from C, CR⁶, and N, wherein B and F cannot both be N;

D is selected from N, NR⁷, O, CR⁶ or C(R⁶)₂;

E is N, NR⁷, CR⁶ or C(R⁶)₂;

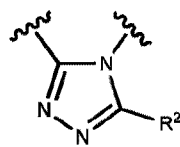
W is N, NR⁷, CR⁶ or C(R⁶)₂;

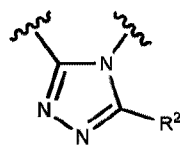
X is N, NR⁷, O, CR⁶ or C(R⁶)₂;

Y and Z are each independently selected from C, CR⁶, and N, wherein Y and Z cannot both be N;


V is C or CR⁶,

or when Z is C or CR⁶, V is C, CR⁶, or N;



wherein when the ring formed by X, Y, Z, V and W is , then R² is -OR⁸, -SR⁸, or -(CH₂)_nOR⁸;

m and n are each independently an integer selected from 0-4;

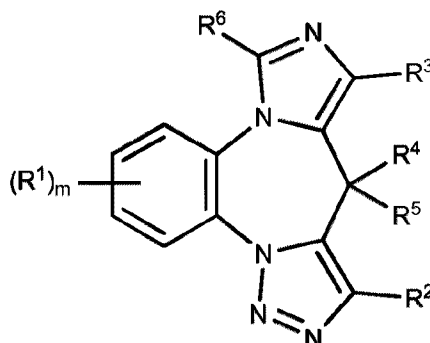
each occurrence of the bond “” is either a single bond or a double bond;

- 5 each occurrence of R¹, R², R⁴, and R⁵ are each independently selected from:
 - halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -N(R)₂, -SR, -SOR,
 - SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R,
 - (CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R,
 - C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂,
 - 10 -OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR,
 - N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R,
 - N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R,
 - C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂,
 - and -P(O)(H)(OR);
- 15 R³ is absent or is selected from:
 - halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -N(R)₂, -SR, -SOR,
 - SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R,
 - (CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R,
 - C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂,
 - 20 -OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR,
 - N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R,
 - N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R,
 - C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂,
 - and -P(O)(H)(OR);
- 25 each R⁶ is independently -H or -(C1-C6)alkyl;
- each R⁷ is independently -H or -(C1-C6)alkyl;
- each R⁸ is independently -(C1-C6)alkyl, -(C3-C10)-cycloalkyl, -(C6-C10)-aryl, or 5- to 10- membered heteroaryl, wherein each occurrence of R⁸ is independently substituted with 0-5 R⁹;
- 30 each R is independently selected from:
 - H-,

- (C1-C12)-aliphatic-,
 (C3-C10)-cycloalkyl-,
 (C3-C10)-cycloalkenyl-,
 [(C3-C10)-cycloalkyl]-(C1-C12)-aliphatic-,
 5 [(C3-C10)-cycloalkenyl]-(C1-C12)-aliphatic-,
 [(C3-C10)-cycloalkyl]-O-(C1-C12)-aliphatic-,
 [(C3-C10)-cycloalkenyl]-O-(C1-C12)-aliphatic-,
 (C6-C10)-aryl-,
 (C6-C10)-aryl-(C1-C12)aliphatic-,
 10 (C6-C10)-aryl-O-(C1-C12)aliphatic-,
 3- to 10- membered heterocyclyl-,
 (3- to 10- membered heterocyclyl)-(C1-C12)aliphatic-,
 (3- to 10- membered heterocyclyl)-O-(C1-C12)aliphatic-,
 5- to 10- membered heteroaryl-,
 15 (5- to 10- membered heteroaryl)-(C1-C12)-aliphatic-, and
 (5- to 10- membered heteroaryl)-O-(C1-C12)-aliphatic-;
 wherein said heterocyclyl has 1-4 heteroatoms independently selected from N, NH, O, S,
 SO, and SO₂, and said heteroaryl has 1-4 heteroatoms independently selected from N,
 NH, O, and S;
 20 wherein each occurrence of R is independently substituted with 0-5 R';
 or when two R groups bound to the same atom, the two R groups may be taken together
 with the atom to which they are bound to form a 3- to 10-membered aromatic or non-
 aromatic ring having 0-4 heteroatoms independently selected from N, NH, O, S, SO,
 and SO₂, wherein said ring is optionally substituted with 0-5 R', and wherein said ring
 25 is optionally fused to a (C6-C10)aryl, 5- to 10- membered heteroaryl, (C3-
 C10)cycloalkyl, or a 3- to 10- membered heterocyclyl;
 wherein each occurrence of R' is independently selected from halogen, -R'', -OR'', oxo,
 -CH₂OR'', -CH₂NR''₂, -C(O)N(R'')₂, -C(O)OR'', -NO₂, -NCS, -CN, -CF₃, -OCF₃
 and -N(R'')₂;
 30 wherein each occurrence of R'' is independently selected from H, -(C1-C6)-alkyl, (C3-
 C6)-cycloalkyl, 3- to 6- membered heterocyclyl, 5- to 10- membered heteroaryl-,
 (C6-C10)-aryl-, (5- to 10- membered heteroaryl)-(C1-C6)-alkyl-,
 (C6-C10)-aryl-(C1-C6)-alkyl-, (5- to 10- membered heteroaryl)-O-(C1-C6)-alkyl-, or

(C6-C10)-aryl-O-(C1-C6)-alkyl-.

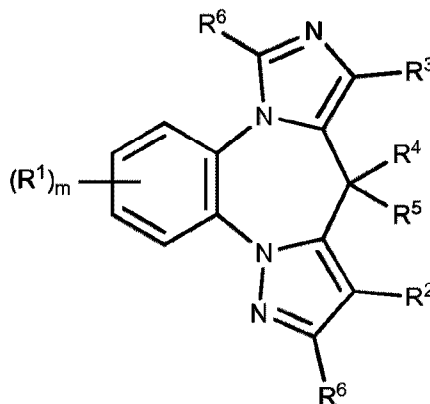
[0012] In another aspect, the present invention provides a compound of formula II:



II,

- 5 or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein m , R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined in formula I.

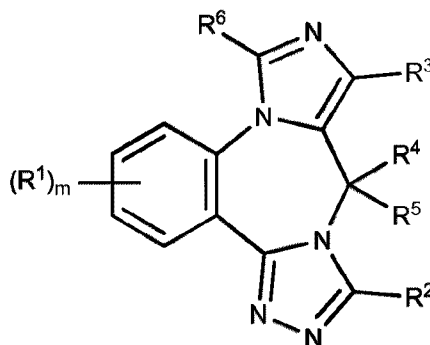
[0013] In another aspect, the present invention provides a compound of formula III:



III,

- 10 or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein m , R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined in formula I.

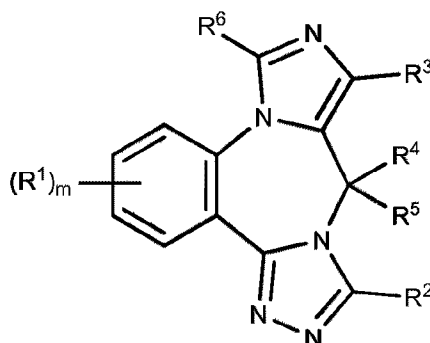
[0014] In another aspect, the present invention provides a compound of formula IV:



IV,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein R^2 is $-OR^8$, $-SR^8$, or $-(CH_2)_nOR^8$, wherein R^2 is independently substituted with 0-5 R' and wherein m , n , R^1 , R^3 , R^4 , R^5 , R^6 , and R^8 are as defined in formula I.

[0015] In another aspect, the present invention provides a compound of formula IV:



IV,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein R^2 is $-(CH_2)_nO(CH_2)_nR^8$, $-(CH_2)_pR^8$ or $-(CH_2)_nN(R'')R^{10}$, wherein R^2 is independently substituted with 0-5 R' and wherein m , n , p , R^1 , R^3 , R^4 , R^5 , R^6 , R^8 , R^{10} , and R'' are as defined herein.

[0016] The present invention also provides pharmaceutical compositions that comprise a compound of formulae I, II, III, or IV, or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

[0017] In some embodiments, compounds of formula I are GABA_A $\alpha 5$ receptor positive allosteric modulators. In some embodiments, compounds of formula II are GABA_A $\alpha 5$

receptor positive allosteric modulators. In some embodiments, compounds of formula III are GABA_A α 5 receptor positive allosteric modulators. In some embodiments, compounds of formula IV are GABA_A α 5 receptor positive allosteric modulators. Compounds of formula I, II, III or IV can be used to treat the conditions described herein, such as through activity as GABA_A α 5 receptor positive allosteric modulators.

[0018] In another aspect of the invention, there is provided a method for treating cognitive impairment associated with a CNS disorder in a subject in need of treatment or at risk of said cognitive impairment, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof. In some embodiments, the CNS disorder with cognitive impairment includes, without limitation, age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI (aMCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease (AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome, compulsive behavior, and substance addiction. In another aspect of the invention, there is provided a method of preserving or improving cognitive function in a subject in need thereof, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof. In certain embodiments of the invention, a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof is administered every 12 or 24 hours.

Detailed Description of the Figures

[0019] Figure 1 is a graph depicting the effects of administering methyl 3,5-diphenylpyridazine-4-carboxylate on the spatial memory retention of ten aged-impaired (AI) rats in an eight-arm Radial Arm Maze (RAM) test. The black bars refer to rats treated with vehicle alone; open bars refer to rats treated with methyl 3,5-diphenylpyridazine-4-carboxylate at different doses; hatched bar refers to rats treated with the combination of TB21007 and methyl 3,5-diphenylpyridazine-4-carboxylate.

[0020] Figure 2 is a graph showing the effect of methyl 3,5-diphenylpyridazine-4-carboxylate (administered intravenously) on the binding of Ro154513 in the hippocampus and cerebellum. Methyl 3,5-diphenylpyridazine-4-carboxylate blocked the binding of Ro154513 in the hippocampus but did not affect binding of Ro15413 in the cerebellum.

[0021] Figure 3 is a graph showing dose-dependent GABA_A α 5 receptor occupancy by methyl 3,5-diphenylpyridazine-4-carboxylate administered intravenously, with receptor occupancy determined either by the ratio between hippocampus (a region of high GABA_A α 5 receptor density) exposure of RO 15-4513 and cerebellum (a region with low GABA_A α 5 receptor density) exposure of RO 15-4513, or by using the GABA_A α 5 selective compound L-655,708 (10 mg/kg, i.v.) to define full occupancy.

[0022] Figure 4 is a graph showing exposure occupancy relationships for methyl 3,5-diphenylpyridazine-4-carboxylate in hippocampus. Methyl 3,5-diphenylpyridazine-4-carboxylate occupies about 32% of GABA_A α 5 receptors at exposures which are behaviorally active in aged-impaired rats.

[0023] Figures 5 is a graph depicting the effect of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate on the spatial memory retention of ten aged-impaired (AI) rats in an eight-arm Radial Arm Maze (RAM) test. Figure 5 shows the effect of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate on the spatial memory retention of ten aged-impaired (AI) rats in the RAM test, where the vehicle control was tested 3 times, and the different doses of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate were tested twice; In Figure 5, black bars refer to rats treated with vehicle alone and open bars refer to rats treated with ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate at different doses.

[0024] Figure 6 is a graph showing the effect of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate (administered intravenously) on the binding of Ro154513 in the hippocampus and cerebellum. Ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate blocked the binding of Ro154513 in the hippocampus but did not affect binding of Ro15413 in the cerebellum.

[0025] Figure 7 is a graph showing dose-dependent GABA_A α 5 receptor occupancy by ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate administered intravenously, as calculated by the ratio between hippocampus (a region of high GABA_A α 5 receptor density) exposure of RO 15-4513 and cerebellum (a region with low GABA_A α 5 receptor density) exposure of RO 15-4513 to define full occupancy..

[0026] Figure 8(A)-(C) are graphs showing the effect of 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one, as compared to vehicle dimethyl sulfoxide (DMSO), in aged-impaired rats using a Morris water maze behavioral task. Figure 8(A) shows the escape latency (i.e., the average time in seconds rats took to find the hidden platform in the water pool) during training in rats received 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one and rats received vehicle DMSO; Figure 8(B) shows the amount of time spent in target annulus and opposite annulus by rats received 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one and rats received vehicle DMSO; Figure 8(C) shows number of crossing in target annulus and opposite annulus by rats received 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one and rats received vehicle DMSO.

Detailed Description of the Invention

20 Definitions

[0027] Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

[0028] The methods and techniques of the present invention are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. "Principles of Neural Science," McGraw-Hill

Medical, New York, N.Y. (2000); Motulsky, "Intuitive Biostatistics," Oxford University Press, Inc. (1995); Lodish et al., "Molecular Cell Biology, 4th ed.," W. H. Freeman & Co., New York (2000); Griffiths et al., "Introduction to Genetic Analysis, 7th ed.," W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., "Developmental Biology, 6th ed.,"

5 Sinauer Associates, Inc., Sunderland, MA (2000).

[0029] Chemistry terms used herein are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms," Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

[0030] In case of conflict, the present specification, including its specific definitions,
10 will control.

[0031] Throughout this specification, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer (or components) or group of integers (or components), but not the exclusion of any other integer (or components) or group of integers (or components).

15 [0032] The singular forms "a," "an," and "the" include the plurals unless the context clearly dictates otherwise.

[0033] The term "including" is used to mean "including but not limited to".
"Including" and "including but not limited to" are used interchangeably.

[0034] The term "agent" is used herein to denote a chemical compound (such as an
20 organic or inorganic compound (including, such as, a compound of the present invention), a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, *e.g.*, a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants,
25 fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents which are known with respect to structure, and those which are not known with respect to structure. The $\alpha 5$ -containing GABA_A receptor agonist activity of such agents may render them suitable as "therapeutic agents" in the methods and compositions of this invention.

[0035] A “patient,” “subject,” or “individual” are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovine, porcine, etc.), companion animals (*e.g.*, canine, feline, etc.) and rodents (*e.g.*, mice and rats).

5 [0036] “Cognitive function” or “cognitive status” refers to any higher order intellectual brain process or brain state, respectively, involved in learning and/or memory including, but not limited to, attention, information acquisition, information processing, working memory, short-term memory, long-term memory, anterograde memory, retrograde memory, memory retrieval, discrimination learning, decision-making, inhibitory response
10 control, attentional set-shifting, delayed reinforcement learning, reversal learning, the temporal integration of voluntary behavior, expressing an interest in one’s surroundings and self-care, speed of processing, reasoning and problem solving and social cognition.

[0037] In humans, cognitive function may be measured, for example and without limitation, by the clinical global impression of change scale (CIBIC-plus scale); the Mini
15 Mental State Exam (MMSE); the Neuropsychiatric Inventory (NPI); the Clinical Dementia Rating Scale (CDR); the Cambridge Neuropsychological Test Automated Battery (CANTAB); the Sandoz Clinical Assessment-Geriatric (SCAG), the Buschke Selective Reminding Test (Buschke and Fuld, 1974); the Verbal Paired Associates subtest; the Logical Memory subtest; the Visual Reproduction subtest of the Wechsler Memory Scale-
20 Revised (WMS-R) (Wechsler, D. (1997) Wechsler Adult Intelligence Scale. 3rd Edition, The Psychological Corporation, San Antonio); the Benton Visual Retention Test, or the explicit 3-alternative forced choice task, or MATRICS consensus neuropsychological test battery. *See* Folstein et al., *J Psychiatric Res* 12: 189-98, (1975); Robbins et al., *Dementia* 5: 266-81, (1994); Rey, *L'examen clinique en psychologie*, (1964); Kluger et al., *J Geriatr Psychiatry Neurol* 12:168-79, (1999); Marquis et al., 2002 and Masur et al., 1994. Also
25 see Buchanan, R.W., Keefe, R.S.E., Umbricht, D., Green, M.F., Laughren, T., and Marder, S.R. (2011), The FDA-NIMH-MATRICES guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? *Schizophr. Bull.* 37, 1209–1217.

[0038] In animal model systems, cognitive function may be measured in various
30 conventional ways known in the art, including using a Morris Water Maze (MWM), Barnes circular maze, elevated radial arm maze, T maze or any other mazes in which the

animals use spatial information. Cognitive function can be assessed by reversal learning, extradimensional set shifting, conditional discrimination learning and assessments of reward expectancy. Other tests known in the art may also be used to assess cognitive function, such as novel object recognition and odor recognition tasks.

- 5 [0039] Cognitive function may also be measured using imaging techniques such as Positron Emission Tomography (PET), functional magnetic resonance imaging (fMRI), Single Photon Emission Computed Tomography (SPECT), or any other imaging technique that allows one to measure brain function. In animals, cognitive function may also be measured with electrophysiological techniques.
- 10 [0040] “Promoting” cognitive function refers to affecting impaired cognitive function so that it more closely resembles the function of a normal, unimpaired subject. Cognitive function may be promoted to any detectable degree, but in humans preferably is promoted sufficiently to allow an impaired subject to carry out daily activities of normal life at a level of proficiency as close as possible to a normal, unimpaired subject or an age-
- 15 matched normal, unimpaired subject.

- [0041] In some cases, “promoting” cognitive function in a subject affected by age-related cognitive refers to affecting impaired cognitive function so that it more closely resembles the function of an aged-matched normal, unimpaired subject, or the function of a young adult subject. Cognitive function of that subject may be promoted to any
- 20 detectable degree, but in humans preferably is promoted sufficiently to allow an impaired subject to carry out daily activities of normal life at a level of proficiency close as possible to a normal, unimpaired subject or a young adult subject or an age-matched normal unimpaired subject.

- [0042] “Preserving” cognitive function refers to affecting normal or impaired cognitive
- 25 function such that it does not decline or does not fall below that observed in the subject upon first presentation or diagnosis, or delays such decline.

[0043] “Improving” cognitive function includes promoting cognitive function and/or preserving cognitive function in a subject.

- [0044] “Cognitive impairment” refers to cognitive function in subjects that is not as
- 30 robust as that expected in a normal, unimpaired subject. In some cases, cognitive

function is reduced by about 5%, about 10%, about 30%, or more, compared to cognitive function expected in a normal, unimpaired subject. In some cases, “cognitive impairment” in subjects affected by aged-related cognitive impairment refers to cognitive function in subjects that is not as robust as that expected in an age-matched normal, unimpaired subject, or the function of a young adult subject (*i.e.* subjects with mean scores for a given age in a cognitive test).

[0045] “Age-related cognitive impairment” refers to cognitive impairment in aged subjects, wherein their cognitive function is not as robust as that expected in an age-matched normal subject or as that expected in young adult subjects. In some cases, cognitive function is reduced by about 5%, about 10%, about 30%, or more, compared to cognitive function expected in an age-matched normal subject. In some cases, cognitive function is as expected in an age-matched normal subject, but reduced by about 5%, about 10%, about 30%, about 50% or more, compared to cognitive function expected in a young adult subject. Age-related impaired cognitive function may be associated with Mild Cognitive Impairment (MCI) (including amnesic MCI and non-amnesic MCI), Age-Associated Memory Impairment (AAMI), and Age-related Cognitive Decline (ARCD).

[0046] “Cognitive impairment” associated with AD or related to AD or in AD refers to cognitive function in subjects that is not as robust as that expected in subjects who have not been diagnosed AD using conventional methodologies and standards.

[0047] “Mild Cognitive Impairment” or “MCI” refers to a condition characterized by isolated memory impairment unaccompanied other cognitive abnormalities and relatively normal functional abilities. One set of criteria for a clinical characterization of MCI specifies the following characteristics: (1) memory complaint (as reported by patient, informant, or physician), (2) normal activities of daily living (ADLs), (3) normal global cognitive function, (4) abnormal memory for age (defined as scoring more than 1.5 standard deviations below the mean for a given age), and (5) absence of indicators of dementia (as defined by DSM-IV guidelines). Petersen et al., *Srch. Neurol.* 56: 303-308 (1999); Petersen, “Mild cognitive impairment: Aging to Alzheimer's Disease.” Oxford University Press, N.Y. (2003). The cognitive deficit in subjects with MCI may involve any cognition area or mental process including memory, language, association, attention,

perception, problem solving, executive function and visuospatial skills. *See, e.g.,* Winbald et al., *J. Intern. Med.* 256:240-240, 2004; Meguro, *Acta. Neurol. Taiwan.* 15:55-57, 2008; Ellison et al., *CNS Spectr.* 13:66-72, 2008, Petersen, *Semin. Neurol.* 27:22-31, 2007. MCI is further subdivided into amnesic MCI (aMCI) and non-amnesic MCI, characterized by the impairment (or lack thereof) of memory in particular. MCI is defined as aMCI if memory is found to be impaired given the age and education level of the subject. If, on the other hand, the memory of the subject is found to be intact for age and education, but other non-memory cognitive domains are impaired, such as language, executive function, or visuospatial skills, MCI defines a non-amnesic MCI. aMCI and non-amnesic MCI can both be further subdivided into single or multiple domain MCI. aMCI-single domain refers to a condition where memory, but not other cognitive areas are impaired. aMCI-multiple domain refers to a condition where memory and at least one other cognitive area are impaired. Non-amnesic MCI is single domain or multiple domain dependent on whether or not more than one non-memory cognitive area is impaired. *See, e.g.,* Peterson and Negash, *CNS Spectr.* 13:45-53, 2008.

[0048] Diagnosis of MCI usually entails an objective assessment of cognitive impairment, which can be garnered through the use of well-established neuropsychological tests, including the Mini Mental State Examination (MMSE), the Cambridge Neuropsychological Test Automated Battery (CANTAB) and individual tests such as Rey Auditory Verbal Learning Test (AVLT), Logical Memory Subtest of the revised Wechsler Memory Scale (WMS-R) and the New York University (NYU) Paragraph Recall Test. *See* Folstein et al., *J Psychiatric Res* 12: 189-98 (1975); Robbins et al., *Dementia* 5: 266-81 (1994); Kluger et al., *J Geriatric Psychiatry Neurol* 12:168-79 (1999).

[0049] "Age-Associate Memory Impairment (AAMI)" refers to a decline in memory due to aging. A patient may be considered to have AAMI if he or she is at least 50 years old and meets all of the following criteria: a) The patient has noticed a decline in memory performance, b) The patient performs worse on a standard test of memory compared to young adults, c) All other obvious causes of memory decline, except normal aging, have been ruled out (in other words, the memory decline cannot be attributed to other causes such as a recent heart attack or head injury, depression, adverse reactions to medication, Alzheimer's disease, etc.).

[0050] "Age-Related Cognitive Decline (ARCD)" refers to declines in memory and cognitive abilities that are a normal consequence of aging in humans. This is also true in virtually all mammalian species. Age-Associated Memory Impairment refers to older persons with objective memory declines relative to their younger years, but cognitive
5 functioning that is normal relative to their age peers. Age-Consistent Memory Decline is a less pejorative label which emphasizes that these are normal developmental changes, are not pathophysiological, and rarely progress to overt dementia. The DSM-IV (1994) has codified the diagnostic classification of ARCD.

[0051] "Dementia" refers to a condition characterized by severe cognitive deficit that
10 interferes in normal activities of daily living. Subjects with dementia also display other symptoms such as impaired judgment, changes in personality, disorientation, confusion, behavior changes, trouble speaking, and motor deficits. There are different types of dementias, such as Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia.

[0052] Alzheimer's disease (AD) is characterized by memory deficits in its early phase. Later symptoms include impaired judgment, disorientation, confusion, behavior changes, trouble speaking, and motor deficits. Histologically, AD is characterized by beta-amyloid
15 plaques and tangles of protein tau.

[0053] Vascular dementia is caused by strokes. Symptoms overlap with those of AD,
20 but without the focus on memory impairment.

[0054] Dementia with Lewy bodies is characterized by abnormal deposits of alpha-synuclein that form inside neurons in the brain. Cognitive impairment may be similar to AD, including impairments in memory and judgment and behavior changes.

[0055] Frontotemporal dementia is characterized by gliosis, neuronal loss, superficial
25 spongiform degeneration in the frontal cortex and/or anterior temporal lobes, and Picks' bodies. Symptoms include changes in personality and behavior, including a decline in social skills and language expression/comprehension.

[0056] "Post traumatic stress disorder (PTSD)" refers to an anxiety disorder characterized by an immediate or delayed response to a catastrophic event, characterized by re-experiencing the trauma, psychic numbing or avoidance of stimuli associated with the trauma, and increased arousal. Re-experiencing phenomena include intrusive
5 memories, flashbacks, nightmares, and psychological or physiological distress in response to trauma reminders. Such responses produce anxiety and can have significant impact, both chronic and acute, on a patient's quality of life and physical and emotional health. PTSD is also associated with impaired cognitive performance, and older individuals with PTSD have greater decline in cognitive performance relative to control patients.

10 [0057] "Schizophrenia" refers to a chronic debilitating disorder, characterized by a spectrum of psychopathology, including positive symptoms such as aberrant or distorted mental representations (*e.g.*, hallucinations, delusions), negative symptoms characterized by diminution of motivation and adaptive goal-directed action (*e.g.*, anhedonia, affective flattening, avolition), and cognitive impairment. While abnormalities in the brain are
15 proposed to underlie the full spectrum of psychopathology in schizophrenia, currently available antipsychotics are largely ineffective in treating cognitive impairments in patients.

[0058] "Bipolar disorder" or "BP" or "manic depressive disorder" or "manic depressive illness" refers to a chronic psychological/mood disorder which can be characterized by
20 significant mood changes including periods of depression and euphoric manic periods. BP may be diagnosed by a skilled physician based on personal and medical history, interview consultation and physical examinations. The term "mania" or "manic periods" or other variants refers to periods where an individual exhibits some or all of the following characteristics: racing thoughts, rapid speech, elevated levels of activity and agitation as
25 well as an inflated sense of self-esteem, euphoria, poor judgment, insomnia, impaired concentration and aggression.

[0059] "Amyotrophic lateral sclerosis," also known as ALS, refers to a progressive, fatal, neurodegenerative disease characterized by a degeneration of motor neurons, the nerve cells in the central nervous system that control voluntary muscle movement. ALS
30 is also characterized by neuronal degeneration in the entorhinal cortex and hippocampus,

memory deficits, and neuronal hyperexcitability in different brain areas such as the cortex.

[0060] “Cancer-therapy-related cognitive impairment” refers to cognitive impairment that develops in subjects that are treated with cancer therapies such as chemotherapy and radiation. Cytotoxicity and other adverse side-effects on the brain of cancer therapies result in cognitive impairment in such functions as memory, learning and attention.

[0061] Parkinson’s disease (PD) is a neurological disorder characterized by a decrease of voluntary movements. The afflicted patient has reduction of motor activity and slower voluntary movements compared to the normal individual. The patient has characteristic “mask” face, a tendency to hurry while walking, bent over posture and generalized weakness of the muscles. There is a typical “lead-pipe” rigidity of passive movements. Another important feature of the disease is the tremor of the extremities occurring at rest and decreasing during movements.

[0062] “Autism,” as used herein, refers to an autism spectrum disorder characterized by a neural development disorder leading to impaired social interaction and communication by restricted and repetitive behavior. “Autism Spectrum Disorder” refers to a group of developmental disabilities that includes: autism; Asperger syndrome; pervasive developmental disorder not otherwise specified (PDD-NOS or atypical autism); Rett syndrome; and childhood disintegrative disorder.

[0063] Mental retardation is a generalized disorder characterized by significantly impaired cognitive function and deficits in adaptive behaviors. Mental retardation is often defined as an Intelligence Quotient (IQ) score of less than 70. Inborn causes are among many underlying causes for mental retardation. The dysfunction in neuronal communication is also considered one of the underlying causes for mental retardation (Myrrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* **2010**, 10, 207-214).

[0064] In some instances, mental retardation includes, but are not limited to, Down syndrome, velocariofacial syndrome, fetal alcohol syndrome, Fragile X syndrome, Klinefelter’s syndrome, neurofibromatosis, congenital hypothyroidism, Williams syndrome, phenylketonuria (PKU), Smith-Lemli-Opitz syndrome, Prader-Willi syndrome, Phelan-McDermid syndrome, Mowat-Wilson syndrome, ciliopathy, Lowe

syndrome and siderium type X-linked mental retardation. Down syndrome is a disorder that includes a combination of birth defects, including some degree of mental retardation, characteristic facial features and, often, heart defects, increased infections, problems with vision and hearing, and other health problems. Fragile X syndrome is a prevalent form of

5 inherited mental retardation, occurring with a frequency of 1 in 4,000 males and 1 in 8,000 females. The syndrome is also characterized by developmental delay, hyperactivity, attention deficit disorder, and autistic-like behavior. There is no effective treatment for fragile X syndrome.

[0065] Obsessive compulsive disorder ("OCD") is a mental condition that is most

10 commonly characterized by intrusive, repetitive unwanted thoughts (obsessions) resulting in compulsive behaviors and mental acts that an individual feels driven to perform (compulsion). Current epidemiological data indicates that OCD is the fourth most common mental disorder in the United States. Some studies suggest the prevalence of OCD is between one and three percent, although the prevalence of clinically recognized

15 OCD is much lower, suggesting that many individuals with the disorder may not be diagnosed. Patients with OCD are often diagnosed by a psychologist, psychiatrist, or psychoanalyst according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR) (2000) diagnostic criteria that include characteristics of obsessions and compulsions.

20 [0066] Substance addiction (*e.g.*, drug addiction, alcohol addiction) is a mental disorder. The addiction is not triggered instantaneously upon exposure to substance of abuse. Rather, it involves multiple, complex neural adaptations that develop with different time courses ranging from hours to days to months (Kauer J. A. *Nat. Rev. Neurosci.* **2007**, 8, 844-858). The path to addiction generally begins with the voluntary

25 use of one or more controlled substances, such as narcotics, barbiturates, methamphetamines, alcohol, nicotine, and any of a variety of other such controlled substances. Over time, with extended use of the controlled substance(s), the voluntary ability to abstain from the controlled substance(s) is compromised due to the effects of prolonged use on brain function, and thus on behavior. As such, substance addiction

30 generally is characterized by compulsive substance craving, seeking and use that persist even in the face of negative consequences. The cravings may represent changes in the underlying neurobiology of the patient which likely must be addressed in a meaningful

way if recovery is to be obtained. Substance addiction is also characterized in many cases by withdrawal symptoms, which for some substances are life threatening (e.g., alcohol, barbiturates) and in others can result in substantial morbidity (which may include nausea, vomiting, fever, dizziness, and profuse sweating), distress, and decreased ability to obtain recovery. For example, alcoholism, also known as alcohol dependence, is one such substance addiction. Alcoholism is primarily characterized by four symptoms, which include cravings, loss of control, physical dependence and tolerance. These symptoms also may characterize addictions to other controlled substances. The craving for alcohol, as well as other controlled substances, often is as strong as the need for food or water. Thus, an alcoholic may continue to drink despite serious family, health and/or legal ramifications.

[0067] “Treating” a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. Beneficial or desired clinical results include, but are not limited to, preventing or slowing the progression of the disease or disorder, or alleviation, amelioration, or slowing the progression, of one or more symptoms of cognitive impairment associated with CNS disorders, such as age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI (aMCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer’s Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson’s disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome, compulsive behavior, and substance addiction. In some embodiments, treatment comprises preventing or slowing the progression, of a CNS disorder (such as one as described herein). In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with that CNS disorder. In certain embodiments, the symptom to be treated is cognitive impairment or cognitive deficit. Treating age-related cognitive impairment further comprises slowing the conversion of age-related cognitive impairment (including, but not limited to MCI, ARCD and AAMI) into dementia (e.g., AD).

[0068] “Treating cognitive impairment” refers to taking steps to improve cognitive function in a subject with cognitive impairment so that the subject’s performance in one or more cognitive tests is improved to any detectable degree, or is prevented from further

decline. Preferably, that subject's cognitive function, after treatment of cognitive impairment, more closely resembles the function of a normal, unimpaired subject. Treatment of cognitive impairment in humans may improve cognitive function to any detectable degree, but is preferably improved sufficiently to allow the impaired subject to

5 carry out daily activities of normal life at the same level of proficiency as a normal, unimpaired subject. In some cases, "treating cognitive impairment" refers to taking steps to improve cognitive function in a subject with cognitive impairment so that the subject's performance in one or more cognitive tests is improved to any detectable degree, or is prevented from further decline. Preferably, that subject's cognitive function, after

10 treatment of cognitive impairment, more closely resembles the function of a normal, unimpaired subject. In some cases, "treating cognitive impairment" in a subject affecting by age-related cognitive impairment refers to takings steps to improve cognitive function in the subject so that the subject's cognitive function, after treatment of cognitive impairment, more closely resembles the function of an age-matched normal, unimpaired

15 subject, or the function of a young adult subject.

[0069] "Administering" or "administration of" a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, intravenously, subcutaneously, ocularly,

20 sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow, or controlled release of the compound or agent. Administering can also

25 be performed, for example, once, a plurality of times, and/or over one or more extended periods. In some aspects, the administration includes both direct administration, including self-administration, and indirect administration, including the act of prescribing a drug. For example, as used herein, a physician who instructs a patient to self-administer a drug, or to have the drug administered by another and/or who provides a patient with a

30 prescription for a drug is administering the drug to the patient.

[0070] Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age of the subject, whether the subject is

active or inactive at the time of administering, whether the subject is cognitively impaired at the time of administering, the extent of the impairment, and the chemical and biological properties of the compound or agent (*e.g.* solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, a compound or an agent is administered orally, *e.g.*,
 5 to a subject by ingestion, or intravenously, *e.g.*, to a subject by injection. In some embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

[0071] As used herein, a “ α 5-containing GABA_A receptor agonist,” “ α 5-containing
 10 GABA_A R agonist” or a “GABA_A α 5 receptor agonist” and other variations as used herein refer to a compound that enhances the function of α 5-containing GABA_A receptor (GABA_A R), *i.e.*, a compound that increase GABA-gated Cl⁻ currents. In some embodiments, α 5-containing GABA_A R agonist as used herein refers to a positive allosteric modulator, which potentiates the activity of GABA. α 5-containing GABA_A
 15 receptor agonists, suitable for use in the present invention, include the α 5-containing GABA_A receptor agonists of all formulas and specific α 5-containing GABA_A receptor agonists described herein, and their hydrates, solvates, polymorphs, salts (*e.g.*, pharmaceutically acceptable salts), isomers (*e.g.*, stereoisomers, E/Z isomers, and tautomers), and combinations thereof.

[0072] “Antipsychotic,” “antipsychotic agent,” “antipsychotic drug”, or “antipsychotic
 20 compound” refers to (1) a typical or an atypical antipsychotic; (2) an agent that is selected from dopaminergic agents, glutamatergic agents, NMDA receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs) agonists or positive allosteric modulators (PAMs) (*e.g.*,
 25 mGluR2/3 agonists or PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, AMPA/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic agents, serotonin receptor modulators, cholinergic agents, cannabinoid CB1 antagonists, neurokinin 3 antagonists,
 30 neurotensin agonists, MAO B inhibitors, PDE10 inhibitors, nNOS inhibits, neurosteroids, and neurotrophic factors, alpha-7 agonists or positive allosteric modulators (PAMs)PAMs, serotonin 2C agonists; and/or (3) an agent that is useful in treating one or

more signs or symptoms of schizophrenia or bipolar disorder (in particular, mania).

[0073] "Typical antipsychotics", as used herein, refer to conventional antipsychotics, which produce antipsychotic effects as well as movement related adverse effects related to disturbances in the nigrostriatal dopamine system. These extrapyramidal side effects (EPS) include Parkinsonism, akathisia, tardive dyskinesia and dystonia. See Baldessarini and Tarazi in Goodman & Gilman's The Pharmacological Basis of Therapeutics 10 Edition, 2001, pp. 485-520.

[0074] "Atypical antipsychotics", as used herein, refer to antipsychotic drugs that produce antipsychotic effects with little or no EPS and include, but are not limited to, aripiprazole, asenapine, clozapine, iloperidone, olanzapine, lurasidone, paliperidone, quetiapine, risperidone and ziprasidone. "Atypical" antipsychotics differ from conventional antipsychotics in their pharmacological profiles. While conventional antipsychotics are characterized principally by D₂ dopamine receptor blockade, atypical antipsychotics show antagonist effects on multiple receptors including the 5HT_a and 5HT_c serotonin receptors and varying degrees of receptor affinities. Atypical antipsychotic drugs are commonly referred to as serotonin/dopamine antagonists, reflecting the influential hypothesis that greater affinity for the 5HT₂ receptor than for the D₂ receptor underlies "atypical" antipsychotic drug action or "second generation" antipsychotic drugs. However, the atypical antipsychotics often display side effects, including, but not limited to, weight gain, diabetes (*e.g.*, type II diabetes mellitus), hyperlipidemia, QTc interval prolongation, myocarditis, sexual side effects, extrapyramidal side effects and cataract. Thus, atypical antipsychotics do not represent a homogeneous class, given their differences in the context of both alleviation of clinical symptoms and their potential for inducing side effects such as the ones listed above. Further, the common side effects of the atypical antipsychotics as described above often limit the antipsychotic doses that can be used for these agents.

[0075] Memantine is chemically known as 3,5-dimethyladamantan-1-amine or 3,5-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-amine, which is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with moderate affinity. The proprietary names for memantine include: Axura® and Akatinol® (Merz), Namenda® (Forest Laboratories), Ebixa® and Abixa® (Lundbeck), and Memox® (Unipharm). Memantine is approved for the treatment of moderate to severe Alzheimer's disease (AD) in the United States at a

dose of up to 28 mg/day. Derivatives or analogs of memantine, which include compounds that structurally or chemically resemble memantine, are also useful in the present invention. Such derivatives or analogs of memantine include, but are not limited to those compounds disclosed in U.S. Patents Nos. 3,391,142; 4,122,193; 4,273,774; and 5,061,703; U.S. Patent Application Publication US20040087658, US20050113458, US20060205822, US20090081259, US20090124659, and US20100227852; EP Patent Application Publication EP2260839A2; EP Patent EP1682109B1; and PCT Application Publication WO2005079779. Memantine, as used in the present invention, includes memantine and its derivatives and analogs, as well as hydrates, polymorphs, prodrugs, salts, and solvates thereof. Memantine, as used herein, also includes a composition comprising memantine or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof, wherein the composition optionally further comprises at least one additional therapeutic agent (such as a therapeutic agent useful for treating a CNS disorder or cognitive impairments associated thereof). In some embodiments, the memantine composition suitable for use in the present invention comprises memantine and a second therapeutic agent that is donepezil (under the trade name Aricept).

[0076] "Acetylcholinesterase inhibitor" or "AChE-I" as used herein refers to an agent that inhibits the ability of the cholinesterase enzyme to break down the neurotransmitter acetylcholine, thereby increasing the concentration and duration of acetylcholine, mainly in brain synapses or neuromuscular junctions. AChE-Is suitable for use in this application may include, for example, the subcategories of (i) reversible non-competitive inhibitors or reversible competitive inhibitors, (ii) irreversible, and (iii) quasi-irreversible inhibitors.

[0077] The term "simultaneous administration," as used herein, means that a $\alpha 5$ -containing GABA_A receptor agonist (*e.g.*, a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) and a second therapeutic agent (*e.g.*, an antipsychotic, memantine or an AChE-I), or their pharmaceutically acceptable salts, hydrates, solvates, or polymorphs, are administered with a time separation of no more than about 15 minutes, and in some embodiments no more than about 10 minutes. When the drugs are administered simultaneously, the $\alpha 5$ -containing GABA_A receptor agonist (*e.g.*, an $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) and a second therapeutic agent (*e.g.*, an antipsychotic, memantine or an AChE-I),

or their salts, hydrates, solvates, or polymorphs, may be contained in the same dosage (*e.g.*, a unit dosage form comprising both the $\alpha 5$ -containing GABA_A receptor agonist (*e.g.*, an $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) and a second therapeutic agent (*e.g.*, an antipsychotic, memantine or an AChE-I) or in discrete dosages (*e.g.*, the $\alpha 5$ -

5 containing GABA_A receptor agonist (*e.g.*, an $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) or its salt, hydrate, solvate, or polymorph is contained in one dosage form and a second therapeutic agent (*e.g.*, an antipsychotic, memantine or an AChE-I), or its salt, hydrate, solvate, or polymorph is contained in another dosage form).

[0078] The term "sequential administration" as used herein means that the $\alpha 5$ -

10 containing GABA_A receptor agonist (*e.g.*, a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) and a second therapeutic agent (*e.g.*, an antipsychotic, memantine or an AChE-I), or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, are administered with a time separation of more than about 15 minutes, and in some embodiments more than about one hour, or up to 12-24 hours. Either the $\alpha 5$ -containing

15 GABA_A receptor agonist (*e.g.*, a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) or a second therapeutic agent (*e.g.*, an antipsychotic, memantine or an AChE-I) may be administered first. The $\alpha 5$ -containing GABA_A receptor agonist (*e.g.*, a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) and a second therapeutic agent (*e.g.*, an antipsychotic, memantine or an AChE-I), or their salts, hydrates, solvents, or

20 polymorphs, for sequential administration may be contained in discrete dosage forms, optionally contained in the same container or package.

[0079] A "therapeutically effective amount" of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect, *e.g.* improving cognitive function in a subject, *e.g.*, a patient having cognitive impairment

25 associated with a CNS disorder. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject's size, health and age, the nature and extent of the cognitive

30 impairment or other symptoms of the CNS disorder (such as age-related cognitive impairment, Mild Cognitive Impairment (MCI), dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia , bipolar, ALS,

cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome, compulsive behavior, and substance addiction), and the therapeutics or combination of therapeutics selected for administration, and the mode of administration. The skilled worker can readily determine
5 the effective amount for a given situation by routine experimentation.

[0080] The compounds of the present invention also include prodrugs, analogs or derivatives. The term "prodrug" is art-recognized and is intended to encompass compounds or agents which, under physiological conditions, are converted into $\alpha 5$ -containing GABA_A R positive allosteric modulators. A common method for making a
10 prodrug is to select moieties which are hydrolyzed or metabolized under physiological conditions to provide the desired compound or agent. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal to a GABA_A $\alpha 5$ receptor positive allosteric modulator.

[0081] "Analog" is used herein to refer to a compound which functionally resembles another
15 chemical entity, but does not share the identical chemical structure. For example, an analog is sufficiently similar to a base or parent compound such that it can substitute for the base compound in therapeutic applications, despite minor structural differences.

[0082] "Derivative" is used herein to refer to the chemical modification of a compound. Chemical modifications of a compound can include, for example, replacement of
20 hydrogen by an alkyl, acyl, or amino group. Many other modifications are also possible.

[0083] The term "aliphatic" as used herein refers to a straight chained or branched alkyl, alkenyl or alkynyl. It is understood that alkenyl or alkynyl embodiments need at least two carbon atoms in the aliphatic chain. Aliphatic groups typically contains from 1 (or 2) to 12 carbons, such as from 1 (or 2) to 4 carbons.

[0084] The term "aryl" as used herein refers to a monocyclic or bicyclic carbocyclic aromatic ring system. Aryl as used herein includes a (C6-C12)-aryl-. For example, aryl as used herein can be a C6-C10 monocyclic or C8-C12 bicyclic carbocyclic aromatic ring system. In some embodiments, aryl as used herein can be a (C6-C10)-aryl-. Phenyl (or Ph) is an example of a monocyclic aromatic ring system. Bicyclic aromatic ring systems

include systems wherein both rings are aromatic, *e.g.*, naphthyl, and systems wherein only one of the two rings is aromatic, *e.g.*, tetralin.

[0085] The term "heterocyclic" as used herein refers to a monocyclic or bicyclic non-aromatic ring system having 1 to 4 heteroatom or heteroatom groups in each ring selected from O, N, NH, S, SO, or SO₂ in a chemically stable arrangement. Heterocyclic as used
 5 herein includes a 3- to 12- membered heterocycl- having 1-4 heteroatoms independently selected from O, N, NH, S, SO, or SO₂. For example, heterocyclic as used herein can be a 3- to 10- membered monocyclic or 8- to 12- membered bicyclic non-aromatic ring system having 1 to 4 heteroatom or heteroatom groups in each ring selected
 10 from O, N, NH, S, SO, or SO₂ in a chemically stable arrangement. In some embodiments, heterocyclic as used herein can be a 3- to 10- membered heterocycl- having 1-4 heteroatoms independently selected from O, N, NH, S, SO, or SO₂. In a bicyclic non-aromatic ring system embodiment of "heterocycl-," one or both rings may contain said heteroatom or heteroatom groups. In another bicyclic "heterocycl-"
 15 embodiment, one of the two rings may be aromatic. In yet another heterocyclic ring system embodiment, a non-aromatic heterocyclic ring may optionally be fused to an aromatic carbocycle.

[0086] Examples of heterocyclic rings include 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-
 20 tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3-thiazolidinyl, 4-
 25 thiazolidinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolane, benzodithiane, and 1,3-dihydro-imidazol-2-one.

[0087] The term "heteroaryl" as used herein refers to a monocyclic or bicyclic aromatic ring system having 1 to 4 heteroatom or heteroatom groups in each ring selected from O,
 30 N, NH or S in a chemically stable arrangement. Heteroaryl as used herein includes a 5- to 12- membered heteroaryl having 1-4 heteroatoms independently selected from O, N, NH or S. In some embodiments, heteroaryl as used herein can be a 5- to 10- membered

heteroaryl having 1-4 heteroatoms independently selected from O, N, NH or S. For example, heteroaryl as used herein can be a 5- to 10- membered monocyclic or 8- to 12-membered bicyclic aromatic ring system having 1 to 4 heteroatom or heteroatom groups selected from O, N, NH or S in one or both rings in a chemically stable arrangement. In
 5 such a bicyclic aromatic ring system embodiment of "heteroaryl":

- both rings are aromatic; and
- one or both rings may contain said heteroatom or heteroatom groups.

[0088] Examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, benzimidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl,
 15 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, purinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

[0089] The term "cycloalkyl or cycloalkenyl" refers to a monocyclic or fused or bridged
 20 bicyclic carbocyclic ring system that is not aromatic. For example, cycloalkyl or cycloalkenyl as used herein can be a C3-C10 monocyclic or fused or bridged C8-C12 bicyclic carbocyclic ring system that is not aromatic. Cycloalkenyl rings have one or more units of unsaturation. Preferred cycloalkyl or cycloalkenyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl,
 25 cycloheptenyl, norbornyl, adamantyl and decalinyl.

[0090] As used herein, the carbon atom designations may have the indicated integer and any intervening integer. For example, the number of carbon atoms in a (C1-C4)-alkyl group is 1, 2, 3, or 4. It should be understood that these designation refer to the total number of atoms in the appropriate group. For example, in a (C3-C10)-heterocyclyl the
 30 total number of carbon atoms and heteroatoms is 3 (as in aziridine), 4, 5, 6 (as in morpholine), 7, 8, 9, or 10.

[0091] "Pharmaceutically acceptable salt" is used herein to refer to an agent or a compound according to the invention that is a therapeutically active, non-toxic base and acid salt form of the compounds. The acid addition salt form of a compound that occurs in its free form as a base can be obtained by treating said free base form with an
5 appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclic, salicylic, p-aminosalicylic, pamoic and the like. See, *e.g.*, WO
10 01/062726.

[0092] Compounds containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt form, *e. g.* metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, *e. g.*, lithium,
15 sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, *e. g.* N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely, said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

[0093] Compounds and their salts can be in the form of a solvate, which is included
20 within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like. See, *e.g.*, WO 01/062726.

[0094] As used herein, the term "hydrate" refers to a combination of water with a compound wherein the water retains its molecular state as water and is either absorbed, adsorbed or contained within a crystal lattice of the substrate compound.

[0095] As used herein, the term "polymorph" refers to different crystalline forms of the
25 same compound and other solid state molecular forms including pseudo-polymorphs, such as hydrates (*e.g.*, bound water present in the crystalline structure) and solvates (*e.g.*, bound solvents other than water) of the same compound. Different crystalline polymorphs have different crystal structures due to a different packing of the molecules in the lattice.
30 This results in a different crystal symmetry and/or unit cell parameters which directly

influences its physical properties such the X-ray diffraction characteristics of crystals or powders. A different polymorph, for example, will in general diffract at a different set of angles and will give different values for the intensities. Therefore X-ray powder diffraction can be used to identify different polymorphs, or a solid form that comprises
5 more than one polymorph, in a reproducible and reliable way. Crystalline polymorphic forms are of interest to the pharmaceutical industry and especially to those involved in the development of suitable dosage forms. If the polymorphic form is not held constant during clinical or stability studies, the exact dosage form used or studied may not be comparable from one lot to another. It is also desirable to have processes for producing a
10 compound with the selected polymorphic form in high purity when the compound is used in clinical studies or commercial products since Impurities present may produce undesired toxicological effects. Certain polymorphic forms may exhibit enhanced thermodynamic stability or may be more readily manufactured in high purity in large quantities, and thus are more suitable for inclusion in pharmaceutical formulations.
15 Certain polymorphs may display other advantageous physical properties such as lack of hygroscopic tendencies, improved solubility, and enhanced rates of dissolution due to different lattice energies.

[0096] This application contemplates all the isomers of the compounds of formulae I-IV. "Isomer" as used herein includes optical isomers (such as stereoisomers, *e.g.*,
20 enantiomers and diastereoisomers), Z (zusammen) or E (entgegen) isomers, and tautomers. Many of the compounds useful in the methods and compositions of this invention have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30. The
25 invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds or mixtures thereof (including all possible mixtures of stereoisomers). See, *e.g.*, WO 01/062726. Furthermore, certain compounds which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the invention includes both mixture and separate individual isomers.
30 Multiple substituents on a piperidiny1 or the azepany1 ring can also stand in either cis or trans relationship to each other with respect to the plane of the piperidiny1 or the azepany1 ring. Some of the compounds may also exist in tautomeric forms. Such forms, although

not explicitly indicated in the formulae described herein, are intended to be included within the scope of the present invention. With respect to the methods and compositions of the present invention, reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the
 5 particular isomeric form is referred to specifically. See, *e.g.*, WO 01/062726.

[0097] The compounds of the invention enhance the function of $\alpha 5$ -containing GABA_A R, *i.e.*, they are $\alpha 5$ -containing GABA_A R agonists (*e.g.*, $\alpha 5$ -containing GABA_A receptor positive allosteric modulators) and are capable of increasing GABA-gated Cl⁻ currents.

[0098] The invention further provides pharmaceutical compositions comprising one or
 10 more compounds of the invention together with a pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical compositions of this application may further comprise a second therapeutic agent, such as an antipsychotic, memantine or an AChE-I.

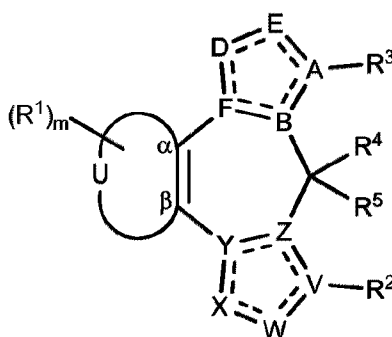
[0099] The invention further provides methods for treating cognitive impairment
 15 associated with said CNS disorders that are responsive to positive allosteric modulators of $\alpha 5$ -containing GABA_A receptor, *e.g.*, age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI (aMCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder,
 20 amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome,, compulsive behavior, and substance addiction. In certain embodiments, the method is a method of treating the age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI (aMCI), Age-Associated Memory Impairment
 25 (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome, compulsive behavior, and substance addiction. In certain embodiments,
 30 treatment comprises preventing or slowing the progression of a CNS disorder as described herein (such as those described herein). In certain embodiments, treatment

comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with the CNS disorder. In certain embodiments, the symptom to be treated is cognitive impairment or cognitive deficit. In another aspect of the invention, there is provided a method of preserving or improving cognitive function in a subject in need thereof, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

[0100] The various CNS disorders with cognitive impairment (*e.g.*, age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI (aMCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease (AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism spectrum disorders, fragile X disorder, Rett syndrome,, compulsive behavior, and substance addiction) may have a variety of etiologies. However, the symptom of cognitive impairment in each of the above-mentioned disorders may have overlapping causes. Thus, a composition or method of treatment that treats cognitive impairment in one CNS disorder may also treat cognitive impairment in another.

Benzodiazepine Derivatives

[0101] The present invention provides a compound of formula I:

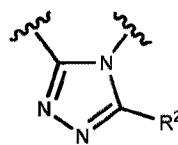


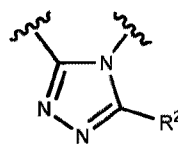
I,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein:

U and the two carbon atoms designated by α and β together form a 5- or 6- membered aromatic ring having 0-2 nitrogen atoms;

- A is C, CR⁶, or N;
 B and F are each independently selected from C, CR⁶, and N, wherein B and F cannot both be N;
 D is selected from N, NR⁷, O, CR⁶ or C(R⁶)₂;
 5 E is N, NR⁷, CR⁶ or C(R⁶)₂;
 W is N, NR⁷, CR⁶ or C(R⁶)₂;
 X is N, NR⁷, O, CR⁶ or C(R⁶)₂;
 Y and Z are each independently selected from C, CR⁶, and N, wherein Y and Z cannot both be N;
 10 V is C or CR⁶,
 or when Z is C or CR⁶, V is C, CR⁶, or N;



- wherein when the ring formed by X, Y, Z, V and W is , then R² is -OR⁸, -SR⁸, -(CH₂)_nOR⁸, -(CH₂)_nO(CH₂)_nR⁸, -(CH₂)_pR⁸ and -(CH₂)_nN(R'')R¹⁰; and wherein R² is independently substituted with 0-5 R';
 15 m and n are independently integers selected from 0-4;
 p is an integer selected from 2-4;
 each occurrence of the bond " $\overline{\text{---}}$ " is either a single bond or a double bond;
 each occurrence of R¹, R², R⁴, and R⁵ are each independently selected from:
 halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -N(R)₂, -SR, -SOR,
 20 -SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R,
 -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R,
 -C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂,
 -OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR,
 -N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R,
 25 -N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R,
 -C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂,
 and -P(O)(H)(OR);

R³ is absent or is selected from:

- halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -N(R)₂, -SR, -SOR,
 30 -SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R,
 -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R,

- $-\text{C}(\text{S})\text{OR}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{OC}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$,
 $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{C}(\text{S})\text{N}(\text{R})_2$, $-(\text{CR}_2)_{0-3}\text{NHC}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{N}(\text{R})\text{COR}$, $-\text{N}(\text{R})\text{N}(\text{R})\text{C}(\text{O})\text{OR}$,
 $-\text{N}(\text{R})\text{N}(\text{R})\text{CON}(\text{R})_2$, $-\text{N}(\text{R})\text{SO}_2\text{R}$, $-\text{N}(\text{R})\text{SO}_2\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$,
 $-\text{N}(\text{R})\text{C}(\text{S})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(\text{S})\text{N}(\text{R})_2$, $-\text{N}(\text{COR})\text{COR}$, $-\text{N}(\text{OR})\text{R}$,
5 $-\text{C}(=\text{NH})\text{N}(\text{R})_2$, $-\text{C}(\text{O})\text{N}(\text{OR})\text{R}$, $-\text{C}(=\text{NOR})\text{R}$, $-\text{OP}(\text{O})(\text{OR})_2$, $-\text{P}(\text{O})(\text{R})_2$, $-\text{P}(\text{O})(\text{OR})_2$,
and $-\text{P}(\text{O})(\text{H})(\text{OR})$;
each R^6 is independently $-\text{H}$ or $-(\text{C}1-\text{C}6)\text{alkyl}$;
each R^7 is independently $-\text{H}$ or $-(\text{C}1-\text{C}6)\text{alkyl}$;
each R^8 is independently $-(\text{C}1-\text{C}6)\text{alkyl}$, $-(\text{C}3-\text{C}10)\text{-cycloalkyl}$, $(\text{C}6-\text{C}10)\text{-aryl}$, or 5- to
10 10- membered heteroaryl, wherein each occurrence of R^8 is independently substituted
with 0-5 R' ;
each R^{10} is independently $-(\text{C}3-\text{C}10)\text{-cycloalkyl}$, 3- to 10- membered heterocyclyl-,
 $(\text{C}6-\text{C}10)\text{-aryl}$, or 5- to 10- membered heteroaryl, wherein each occurrence of R^{10} is
independently substituted with 0-5 R' ;
15 each R is independently selected from:
 $\text{H}-$,
 $(\text{C}1-\text{C}12)\text{-aliphatic-}$,
 $(\text{C}3-\text{C}10)\text{-cycloalkyl-}$,
 $(\text{C}3-\text{C}10)\text{-cycloalkenyl-}$,
20 $[(\text{C}3-\text{C}10)\text{-cycloalkyl}]\text{-(C}1\text{-C}12)\text{-aliphatic-}$,
 $[(\text{C}3-\text{C}10)\text{-cycloalkenyl}]\text{-(C}1\text{-C}12)\text{-aliphatic-}$,
 $[(\text{C}3-\text{C}10)\text{-cycloalkyl}]\text{-O-(C}1\text{-C}12)\text{-aliphatic-}$,
 $[(\text{C}3-\text{C}10)\text{-cycloalkenyl}]\text{-O-(C}1\text{-C}12)\text{-aliphatic-}$,
 $(\text{C}6-\text{C}10)\text{-aryl-}$,
25 $(\text{C}6-\text{C}10)\text{-aryl-(C}1\text{-C}12)\text{aliphatic-}$,
 $(\text{C}6-\text{C}10)\text{-aryl-O-(C}1\text{-C}12)\text{aliphatic-}$,
 $(\text{C}6-\text{C}10)\text{-aryl-N(R'')-(C}1\text{-C}12)\text{aliphatic-}$,
3- to 10- membered heterocyclyl-,
 $(3\text{- to }10\text{- membered heterocyclyl})\text{-(C}1\text{-C}12)\text{aliphatic-}$,
30 $(3\text{- to }10\text{- membered heterocyclyl})\text{-O-(C}1\text{-C}12)\text{aliphatic-}$,
 $(3\text{- to }10\text{- membered heterocyclyl})\text{-N(R'')-(C}1\text{-C}12)\text{aliphatic-}$,
5- to 10- membered heteroaryl-,
 $(5\text{- to }10\text{- membered heteroaryl})\text{-(C}1\text{-C}12)\text{-aliphatic-}$,

(5- to 10- membered heteroaryl)-O-(C1-C12)-aliphatic-; and

(5- to 10- membered heteroaryl)-N(R'')-(C1-C12)-aliphatic-;

wherein said heterocyclyl has 1-4 heteroatoms independently selected from N, NH, O, S, SO, and SO₂, and said heteroaryl has 1-4 heteroatoms independently selected from N,

5 NH, O, and S;

wherein each occurrence of R is independently substituted with 0-5 R';

or when two R groups bound to the same atom, the two R groups may be taken together with the atom to which they are bound to form a 3- to 10-membered aromatic or non-aromatic ring having 0-4 heteroatoms independently selected from N, NH, O, S, SO, and SO₂, wherein said ring is optionally substituted with 0-5 R', and wherein said ring is optionally fused to a (C6-C10)aryl, 5- to 10- membered heteroaryl, (C3- C10)cycloalkyl, or a 3- to 10- membered heterocyclyl;

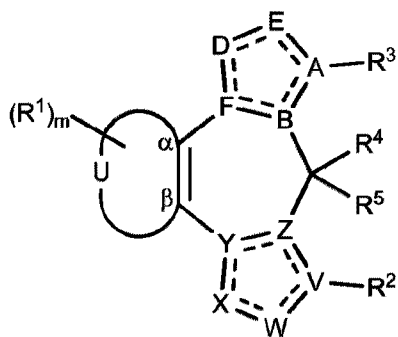
wherein each occurrence of R' is independently selected from halogen, -R'', -OR'', oxo, -CH₂OR'', -CH₂NR''₂, -C(O)N(R'')₂, -C(O)OR'', -NO₂, -NCS, -CN, -CF₃, -OCF₃ and -N(R'')₂;

15

wherein each occurrence of R'' is independently selected from H, -(C1-C6)-alkyl, (C3-C6)-cycloalkyl, 3- to 6- membered heterocyclyl, 5- to 10- membered heteroaryl-, (C6-C10)-aryl-, (5- to 10- membered heteroaryl)-(C1-C6)-alkyl-, (C6-C10)-aryl-(C1-C6)-alkyl-, (5- to 10- membered heteroaryl)-O-(C1-C6)-alkyl-, or (C6-C10)-aryl-O-(C1-C6)-alkyl-.

20

[0102] Some embodiments provide a compound of formula I:



I,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or

25 combination thereof, wherein:

U and the two carbon atoms designated by α and β together form a 5- or 6- membered

aromatic ring having 0-2 nitrogen atoms;

A is C, CR⁶, or N;

B and F are each independently selected from C, CR⁶, and N, wherein B and F cannot both be N;

5 D is selected from N, NR⁷, O, CR⁶ or C(R⁶)₂;

E is N, NR⁷, CR⁶ or C(R⁶)₂;

W is N, NR⁷, CR⁶ or C(R⁶)₂;

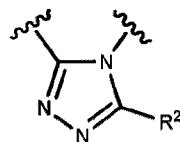
X is N, NR⁷, O, CR⁶ or C(R⁶)₂;

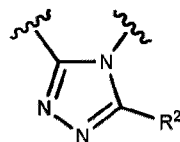
Y and Z are each independently selected from C, CR⁶, and N, wherein Y and Z cannot

10 both be N;


V is C or CR⁶,

or when Z is C or CR⁶, V is C, CR⁶, or N;



wherein when the ring formed by X, Y, Z, V and W is , then R² is -OR⁸, -SR⁸, or -(CH₂)_nOR⁸;

15 m and n are each independently an integer selected from 0-4;

each occurrence of the bond “” is either a single bond or a double bond;

each occurrence of R¹, R², R⁴, and R⁵ are each independently selected from: halogen, -R,

-OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -N(R)₂, -SR, -SOR,

-SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R,

20 -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R,

-C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂,

-OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR,

-N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R,

-N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R,

25 -C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂,

and -P(O)(H)(OR);

R³ is absent or is selected from:

halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -N(R)₂, -SR, -SOR,

-SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R,

30 -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R,

-C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂,

-OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR,
 -N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R,
 -N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R,
 -C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂,

5 and -P(O)(H)(OR);

each R⁶ is independently -H or -(C1-C6)alkyl;

each R⁷ is independently -H or -(C1-C6)alkyl;

each R⁸ is independently -(C1-C6)alkyl, -(C3-C10)-cycloalkyl, (C6-C10)-aryl, or 5- to
 10- membered heteroaryl, wherein each occurrence of R⁸ is independently substituted
 10 with 0-5 R';

each R is independently selected from:

H-,

(C1-C12)-aliphatic-,

(C3-C10)-cycloalkyl-,

15 (C3-C10)-cycloalkenyl-,

[(C3-C10)-cycloalkyl]-(C1-C12)-aliphatic-,

[(C3-C10)-cycloalkenyl]-(C1-C12)-aliphatic-,

[(C3-C10)-cycloalkyl]-O-(C1-C12)-aliphatic-,

[(C3-C10)-cycloalkenyl]-O-(C1-C12)-aliphatic-,

20 (C6-C10)-aryl-,

(C6-C10)-aryl-(C1-C12)aliphatic-,

(C6-C10)-aryl-O-(C1-C12)aliphatic-,

3- to 10- membered heterocyclyl-,

(3- to 10- membered heterocyclyl)-(C1-C12)aliphatic-,

25 (3- to 10- membered heterocyclyl)-O-(C1-C12)aliphatic-,

5- to 10- membered heteroaryl-,

(5- to 10- membered heteroaryl)-(C1-C12)-aliphatic-, and

(5- to 10- membered heteroaryl)-O-(C1-C12)-aliphatic-;

wherein said heterocyclyl has 1-4 heteroatoms independently selected from N, NH, O, S,

30 SO, and SO₂, and said heteroaryl has 1-4 heteroatoms independently selected from N,
 NH, O, and S;

wherein each occurrence of R is independently substituted with 0-5 R';

or when two R groups bound to the same atom, the two R groups may be taken together

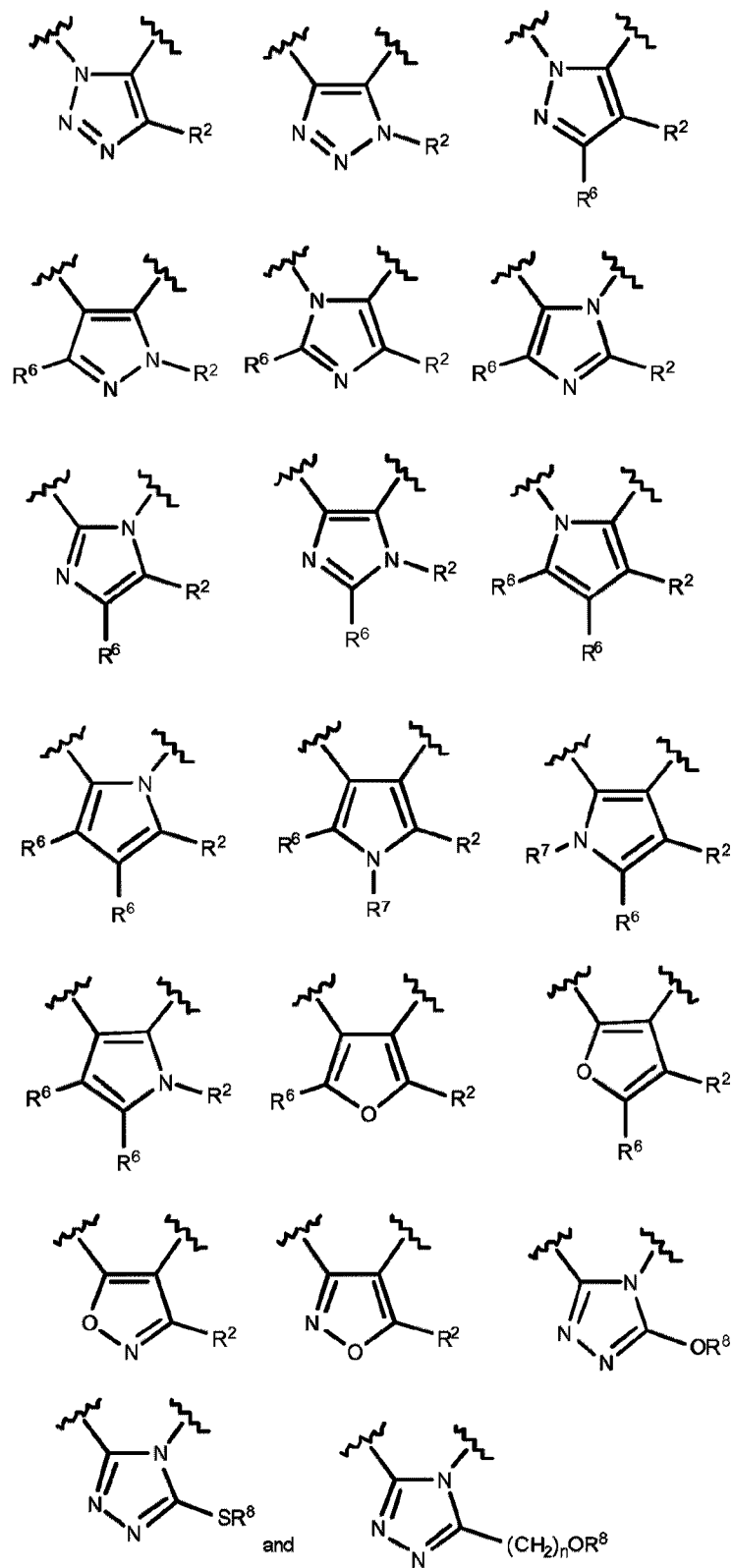
with the atom to which they are bound to form a 3- to 10-membered aromatic or non-aromatic ring having 0-4 heteroatoms independently selected from N, NH, O, S, SO, and SO₂, wherein said ring is optionally substituted with 0-5 R', and wherein said ring is optionally fused to a (C6-C10)aryl, 5- to 10- membered heteroaryl, (C3-
 5 C10)cycloalkyl, or a 3- to 10- membered heterocyclyl;

wherein each occurrence of R' is independently selected from halogen, -R'', -OR'', oxo, -CH₂OR'', -CH₂NR''₂, -C(O)N(R'')₂, -C(O)OR'', -NO₂, -NCS, -CN, -CF₃, -OCF₃ and -N(R'')₂;

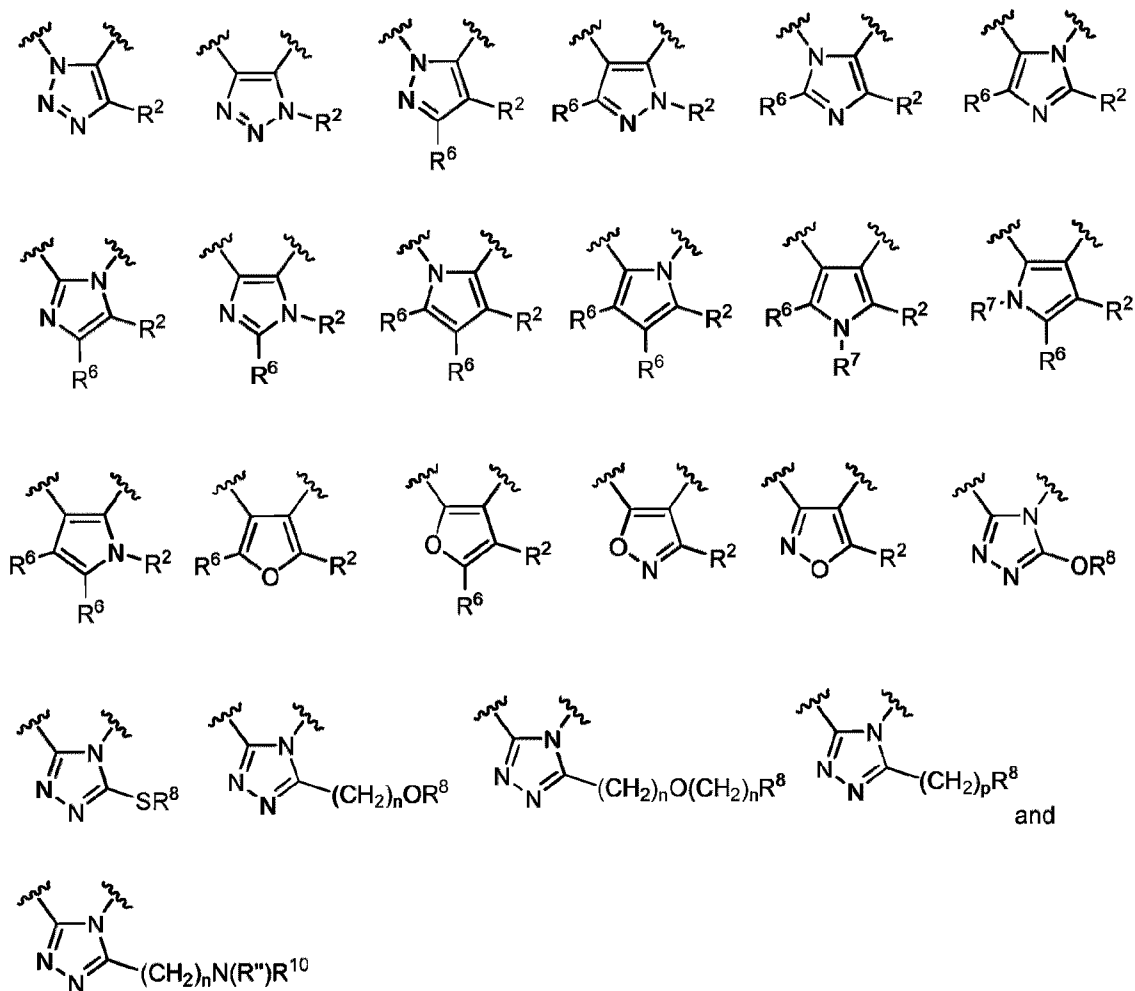
wherein each occurrence of R'' is independently selected from H, -(C1-C6)-alkyl, (C3-
 10 C6)-cycloalkyl, 3- to 6- membered heterocyclyl, 5- to 10- membered heteroaryl-, (C6-C10)-aryl-, (5- to 10- membered heteroaryl)-(C1-C6)-alkyl-, (C6-C10)-aryl-(C1-C6)-alkyl-, (5- to 10- membered heteroaryl)-O-(C1-C6)-alkyl-, or (C6-C10)-aryl-O-(C1-C6)-alkyl-.

[0103] In some embodiments of a compound of formula I, X, Y, Z, V and W together
 15 form X, Y, Z, V and W together form a 5-membered aromatic or non-aromatic ring having 1-4 nitrogen atoms, wherein said ring is substituted with 0-3 R⁶ and 0-2 R⁷. In some embodiments, X, Y, Z, V and W together form a 5-membered aromatic ring having 1-3 nitrogen atoms, wherein said ring is substituted with 0-2 R⁶ and 0-1 R⁷.

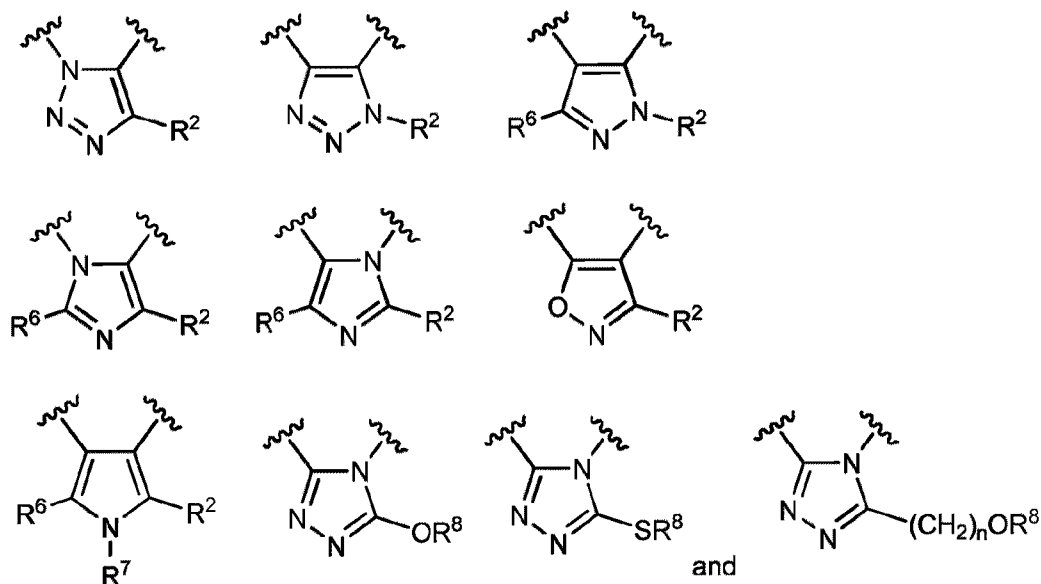
[0104] In certain embodiments, X, Y, Z, V and W form a ring that is selected from:



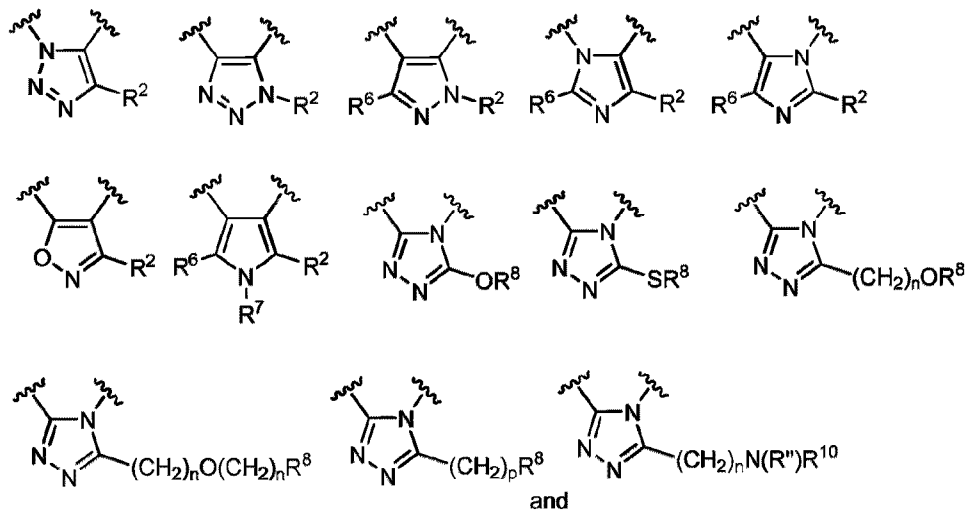
[0105] In some embodiments, X, Y, Z, V and W form a ring that is selected from:



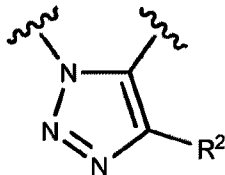
[0106] In some embodiments of a compound of formula I, W is N. In some embodiments, W is N, and X, Y, Z, V and W form a ring that is selected from:



[0107] In some embodiments, W is N, and X, Y, Z, V and W form a ring that is selected from:

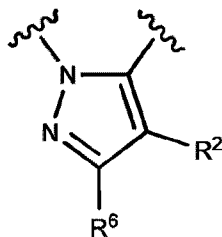


5 [0108] In certain embodiments of a compound of formula I, the ring formed by X, Y, Z, V and W is:

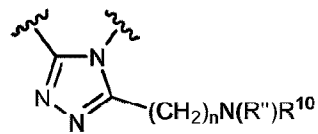
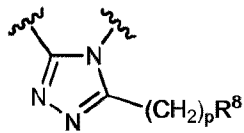
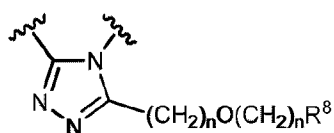
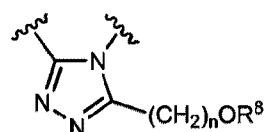
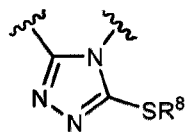
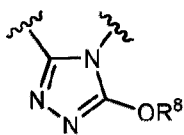


[0109] In certain embodiments of a compound of formula I, the ring formed by X, Y, Z,

V and W is:



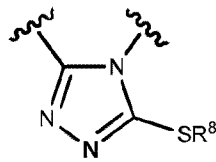
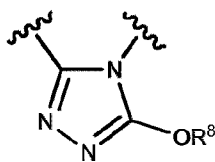
[0110] In certain embodiments of a compound of formula I, the ring formed by X, Y, Z, V and W is selected from:



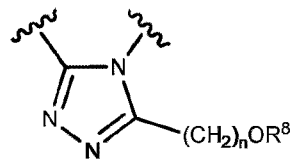
5

and

[0111] In certain embodiments of a compound of formula I, the ring formed by X, Y, Z, V and W is selected from:



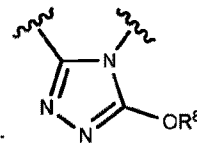
and



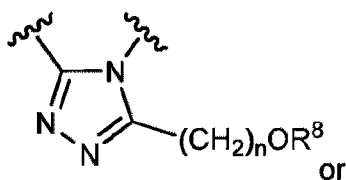
. In some

10 embodiments, the ring formed by X, Y, Z, V and W is:

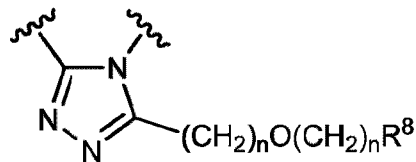
embodiments, the ring formed by X, Y, Z, V and W is:



. In some

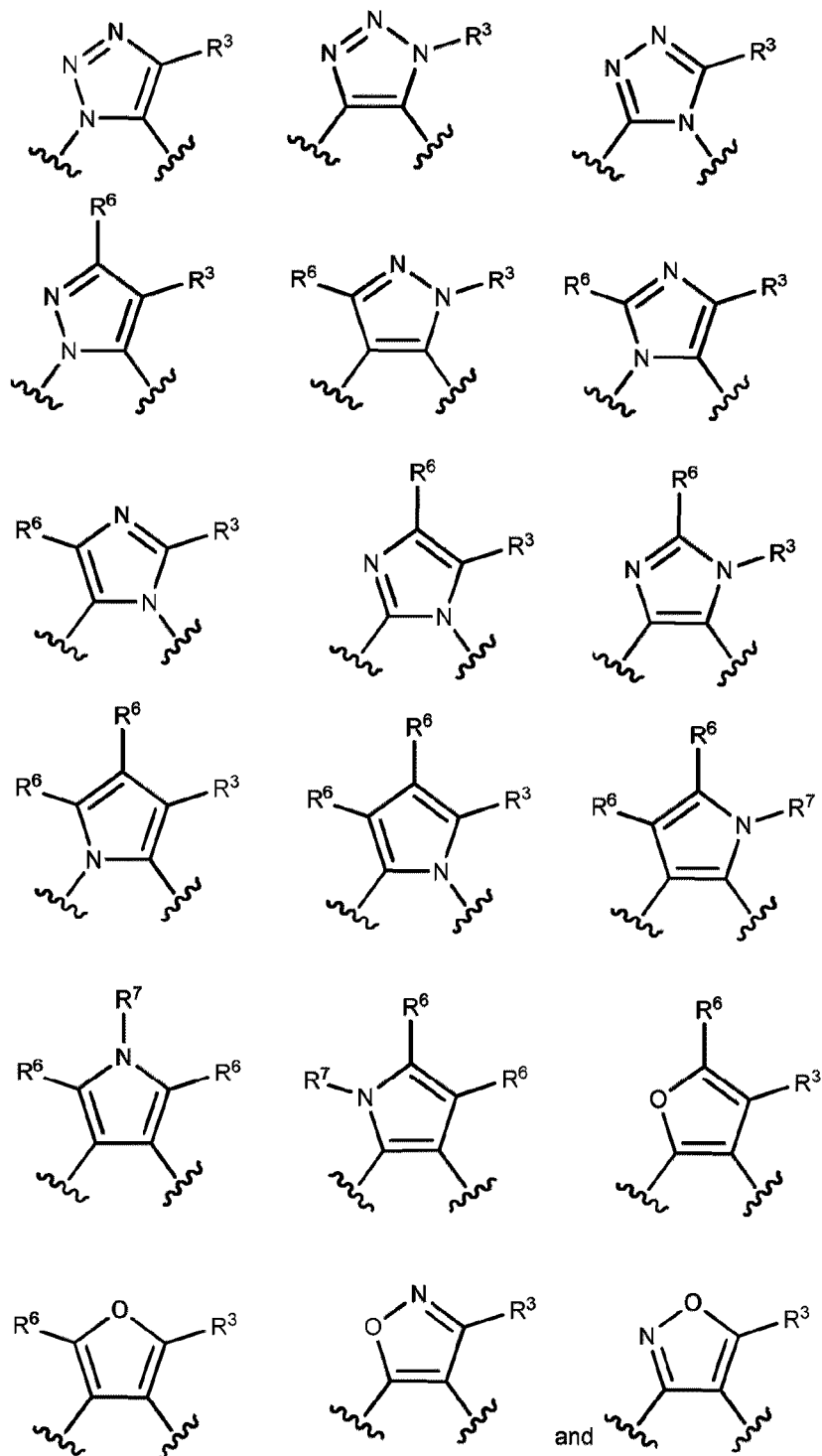


or

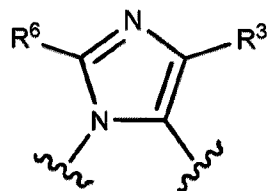


[0112] In some embodiments of a compound of formula I, A, B, D, E and F together form a 5-membered aromatic or non-aromatic ring having 1-4 nitrogen atoms, wherein said ring is substituted with 0-3 R⁶ and 0-2 R⁷. In certain embodiments, A, B, D, E and F together form a 5-membered aromatic ring having 1-3 nitrogen atoms, wherein said ring
5 is substituted with 0-2 R⁶ and 0-1 R⁷.

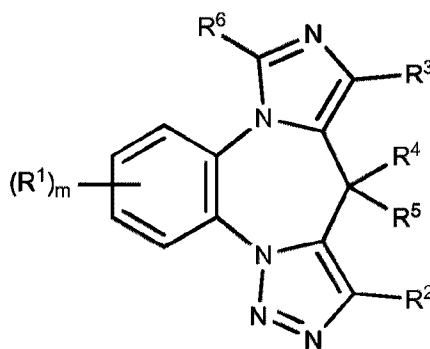
[0113] In some embodiments of a compound of formula I, A, B, D, E and F form a ring that is selected from:



[0114] In certain embodiments of a compound of formula I, the ring formed by A, B, D, F and E is:



[0115] In some embodiments of a compound of formula I, the compound has a structure of formula II:

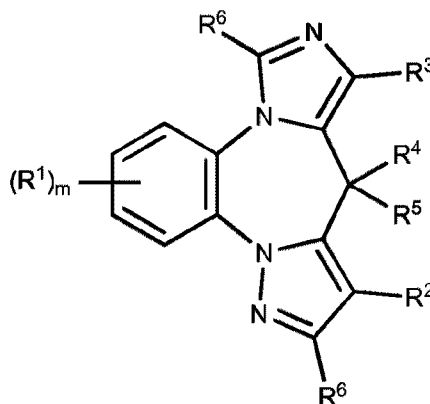


5

II,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein m, R¹, R², R³, R⁴, R⁵ and R⁶ are as defined in formula I.

[0116] In some embodiments of a compound of formula I, the compound has a structure of formula III:

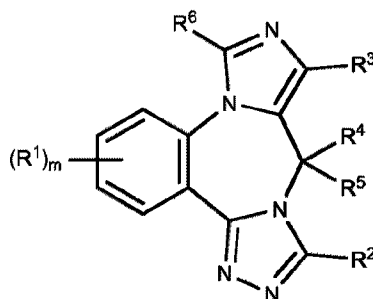


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III,

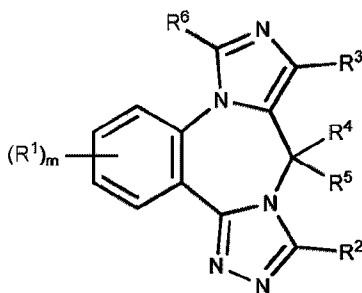
or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein m, R¹, R², R³, R⁴, R⁵ and R⁶ are as defined in formula I.

[0117] In some embodiments of a compound of formula I, the compound has a structure of formula IV:



IV,

- 5 or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein R^2 is $-OR^8$, $-SR^8$, or $-(CH_2)_nOR^8$, wherein R^2 is independently substituted with 0-5 R' and wherein m , n , R^1 , R^3 , R^4 , R^5 , R^6 , and R^8 are as defined in formula I. In some embodiments, R^2 is $-OR^8$. In some embodiments, R^2 is $-(CH_2)_nOR^8$.
- 10 [0118] In some embodiments of a compound of formula I, the compound has a structure of formula IV:



IV,

- or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein R^2 is $-(CH_2)_nO(CH_2)_pR^8$, $-(CH_2)_pR^8$ or $-(CH_2)_nN(R'')R^{10}$, wherein R^2 is independently substituted with 0-5 R' and wherein m , n , p , R^1 , R^3 , R^4 , R^5 , R^6 , R^8 , R^{10} , and R'' are as defined herein. In some embodiments, R^2 is $-(CH_2)_nO(CH_2)_pR^8$.
- 15

- [0119] In some embodiments of a compound of formula I, II, III, or IV, each occurrence of R^1 is selected from: halogen, $-R$, $-OR$, $-NO_2$, $-CN$, $-CF_3$, $-OCF_3$, $-N(R)_2$, $-N(R)SO_2R$,
- 20

- wherein each occurrence of R is independently substituted with 0-5 R'. In some embodiments, each occurrence of R¹ is independently selected from: halogen, -H, -(C1-C6)alkyl, -OH, -O((C1-C6)alkyl), -NO₂, -CN, -CF₃, -OCF₃, -NH₂, -N((C1-C6)alkyl)₂, -N((C1-C6)alkyl)SO₂((C1-C6)alkyl), and -NHSO₂((C1-C6)alkyl),
- 5 wherein said alkyl is independently substituted with 0-5 R'. In certain embodiments, each occurrence of R¹ is independently selected from: -H, -F, -Cl, -Br, -OH, -Me, -Et, -OMe, -OEt, -NO₂, -CN, -CF₃, -OCF₃, -NH₂, -NMe₂, -NEt₂, -NHSO₂Me, and -NHSO₂Et. In certain embodiments of a compound of any one of formulae I-IV, at least one R¹ is -OR. In some embodiments, the at least one R¹ is -O((C1-C6)alkyl), such as -OMe.
- 10 **[0120]** In some embodiments of a compound of formula I, II or III, R² is selected from: halogen, -R, -OR, -NO₂, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -CN, -CF₃, -C(O)NR₂, -C(O)OR, and -OCF₃, wherein each occurrence of R is independently substituted with 0-5 R'. In some embodiments, R² is selected from:
- H, -(C1-C6)alkyl, -CH₂-O((C1-C6)alkyl), -(C((C1-C6)alkyl)₂)₁₋₃-O((C1-C6)alkyl), -OH,
- 15 -O((C1-C6)alkyl), -NO₂, -CN, -CF₃, -OCF₃, (C3-C10)-cycloalkyl-, -C(O)N((C1-C6)alkyl)₂, -C(O)O((C1-C6)alkyl), 3- to 10- membered heterocyclyl-, (C6-C10)aryl-, 5- to 10- membered heteroaryl-, (C6-C10)aryl-(C1-C12)aliphatic-, (C6-C10)aryl-O-(C1-C12)aliphatic-,
- 20 (C6-C10)aryl-N(R'')-(C1-C12)aliphatic-, (C6-C10)aryl-(C1-C12)aliphatic-O-, (5- to 10-membered heteroaryl)-(C1-C12)-aliphatic-, (5- to 10-membered heteroaryl)-O-(C1-C12)-aliphatic-, (5- to 10-membered heteroaryl)-N(R'')-(C1-C12)-aliphatic-, (5- to 10-membered heteroaryl)-(C1-C12)-aliphatic-O-,
- 25 (3- to 10-membered heterocyclyl)-(C1-C12)aliphatic-, (3- to 10-membered heterocyclyl)-O-(C1-C12)aliphatic-, (3- to 10-membered heterocyclyl)-N(R'')-(C1-C12)aliphatic-, and (3- to 10- membered heterocyclyl)-(C1-C12)aliphatic-O-, wherein R² is independently substituted with 0-5 R'.
- 30 **[0121]** In some embodiments of a compound of formula I, II or III, R² is selected from: -H, -Me, -Et, propyl, isopropyl, butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CF₃, -C(O)OMe, -C(O)OEt, -OMe, -CH₂OMe, -CH₂OEt, -CH₂OPh,

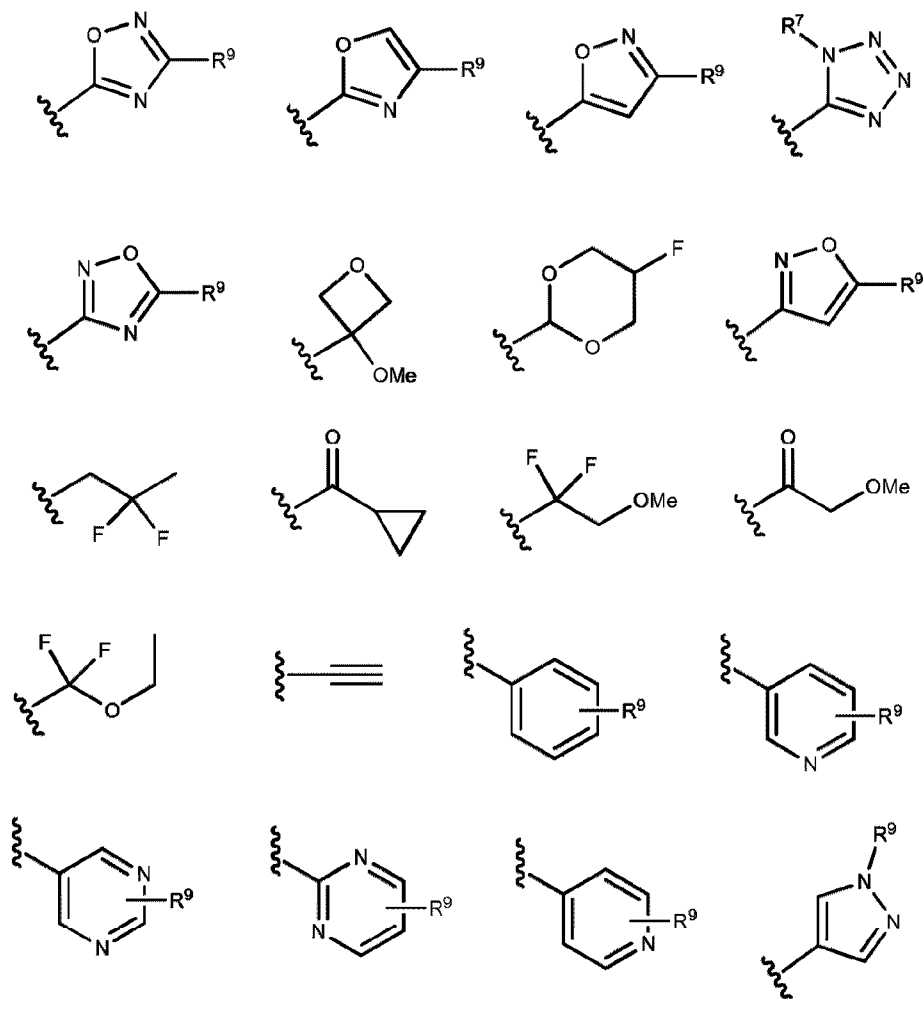
-CH₂-pyrrolidine, -CH₂-morpholine, -CH₂-pyridine, -CH₂Ph, wherein said R² is substituted with 0-3 R'. In some embodiments of a compound of formula I, II or III, R² is -Me substituted with 0-3 R' selected from -R'', -OR'', oxo, -CH₂OR'', -CH₂NR'',
 -C(O)N(R'')₂, -C(O)OR'', -NO₂, -NCS, -CN, -CF₃, -OCF₃ and -N(R'')₂, wherein R'' is
 5 independently selected from H, -(C1-C6)-alkyl, (C6-C10)-aryl-, and (C6-C10)-aryl-(C1-C6)-alkyl-. In some embodiment, R² is -Me that is independently substituted with 0-3 R' selected from -N(Me)₂, -N(Et)₂ and -N(Me)(CH₂Ph).

[0122] In some embodiments of a compound of formula I, II or III, R² is selected from: -CH₂Ph, -CH₂CH₂Ph, -Ph, -OCH₂Ph, -CH₂OPh, -OCH₂CH₂Ph, -CH₂CH₂OPh, -CH₂-
 10 pyrrolidine, -CH₂-morpholine, -CH₂-pyridine, and -CH₂Ph wherein said Ph, pyrrolidine, pyridine or morpholine is substituted with 0-5 R'. In some embodiments of a compound of formula I, II or III, R² is selected from: -CH₂Ph, -CH₂CH₂Ph, -Ph, -OCH₂Ph, -CH₂OPh, -OCH₂CH₂Ph, -CH₂CH₂OPh, -CH₂-pyrrolidine, -CH₂-morpholine, -CH₂-
 15 pyridine, and -CH₂Ph, wherein said Ph, pyrrolidine, pyridine or morpholine is substituted with 0-5 R' independently selected from halogen, (C1-C6)-alkyl, -OH, -O((C1-C6)-alkyl), -CH₂OH, -CH₂O(C1-C6)-alkyl, -CH₂N(C1-C6)-alkyl)₂, -C(O)O(C1-C6)-alkyl, -C(O)N(C1-C6)-alkyl)₂, -NO₂, -CN, -CF₃, -OCF₃ and -N(C1-C6)-alkyl)₂. In some of the above embodiments, the -Ph, pyrrolidine, pyridine or morpholine of R² is substituted with 0-5 R' independently selected from -F, -Cl, -CN, -Me, -Et, -OMe, and -OEt. In
 20 some embodiments of a compound of formula I, II or III, R² is -CH₂Ph, -CH₂OPh, -CH₂-pyridine, -CH₂-pyrrolidine, or -CH₂-morpholine wherein said -Ph, pyrrolidine, pyridine or morpholine is substituted with 0-3 R' independently selected from -F, -Cl, -CN, -Me, and -OMe.

[0123] In some embodiments of a compound of formula IV, R² is -OR⁸, -SR⁸,
 25 -(CH₂)_nOR⁸, -(CH₂)_nO(CH₂)_nR⁸, -(CH₂)_pR⁸ or -(CH₂)_nN(R'')R¹⁰, wherein each R⁸ is independently -(C1-C6)alkyl, -(C3-C10)-cycloalkyl, (C6-C10)-aryl, or 5- to 10-membered heteroaryl, wherein each occurrence of R⁸ is independently substituted with 0-5 R'; n is an integer selected from 0-4; p is an integer selected from 2-4; and each R¹⁰ is independently -(C3-C10)-cycloalkyl, 3- to 10- membered heterocyclyl-, (C6-C10)-aryl, or
 30 5- to 10- membered heteroaryl, wherein each occurrence of R¹⁰ is independently substituted with 0-5 R'. In some embodiments, R² is OR⁸. In some embodiments, R² is OR⁸, wherein R⁸ is (C6-C10)-aryl, substituted with 0-5 R'. In some embodiments, R² is

OR⁸, wherein R⁸ is (C6-C10)-aryl, substituted with 0-3 halogen (such as -F). In some embodiments, R² is -(CH₂)_nOR⁸ or -(CH₂)_nO(CH₂)_nR⁸. In some embodiments, R² is -(CH₂)_nOR⁸ or -(CH₂)_nO(CH₂)_nR⁸, wherein R⁸ is -(C1-C6)alkyl, (C6-C10)-aryl, or 5- to 10- membered heteroaryl, wherein each occurrence of R⁸ is independently substituted with 0-5 R'.

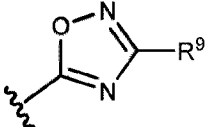
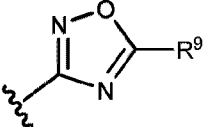
[0124] In some embodiments of a compound of formula I, II, III, or IV, R³ is selected from: halogen, -R, -CN, -CF₃, -SO₂R, -C(O)N(R)₂, -C(O)R and -C(O)OR, wherein each occurrence of R is independently substituted with 0-5 R'. In some embodiments, R³ is selected from: -F, -Br, -Cl, -(C1-C6)alkyl, -CN, -C≡C, -CF₃, -SO₂((C1-C6)alkyl), -C(O)N((C1-C6)alkyl)₂, -C(O)NH₂, -C(O)((C1-C6)alkyl), -SO₂((C6-C10)-aryl), -C(O)O((C1-C6)alkyl), -(C2-C6)-alkenyl, -(C2-C6)-alkynyl, -(C6-C10)-aryl, 5- to 10- membered heteroaryl-, and 3- to 10- membered heterocyclyl-, wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl or heterocyclyl- is independently substituted with 0-5 R'. In some embodiments of a compound of formula I, II, III, or IV, R³ is selected from: -H, -C(O)OMe, -C(O)Et, -C(O)NMe₂, -C(O)NH₂, -C(O)OEt, -C(O)OCH₂(*tert*-butyl), -C(O)OCH₂CF₃, -C(O)O(isopropyl), -C(O)NEt₂, -CHF₂, -CN, -C≡C, -SO₂Me, -SO₂Et, -SO₂Ph(Me), -CF₃, -CHF₂, -Me, -Et, -Br, -Cl, -CH₂Ph,



wherein R^9 is selected from $-H$, $-Me$, $-Et$, $-CF_3$, isopropyl, $-OMe$, $-OEt$, $-O$ -isopropyl, $-CH_2NMe_2$, $-tert$ -butyl and cyclopropyl.

[0125] In certain embodiments of a compound of formula I, II, III, or IV, R^3 is

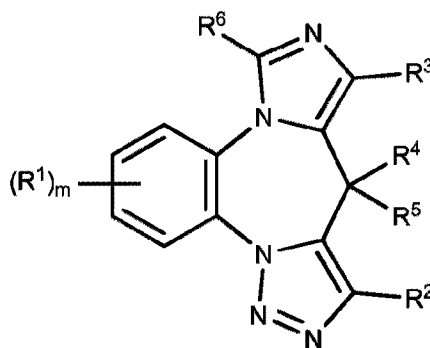
5 $-C(O)OMe$ or $-C(O)OEt$. In certain embodiments of a compound of formula I, II, III, or

IV, R^3 is  or , wherein R^9 is selected from $-H$, $-Me$, $-Et$, $-CF_3$, isopropyl, $-OMe$, $-OEt$, $-O$ -isopropyl, $-CH_2NMe_2$, $-tert$ -butyl and cyclopropyl.

[0126] In some embodiments of a compound of formula I, II, III, or IV, R^4 and R^5 are
 10 each independently selected from $-H$, halogen and $-R$, wherein each occurrence of R is independently substituted with 0-5 R' , or R^4 and R^5 may be taken together with the

carbon atom to which they are bound to form a 3- to 10-membered aromatic or non-aromatic ring having 0-3 additional heteroatoms independently selected from N, O, S, SO, and SO₂, wherein said ring is substituted with 0-5 R'. In some embodiments, R⁴ and R⁵ are each independently selected from -H, -Me, -Et, -F, or R⁴ and R⁵ are taken together with the carbon atom to which they are bound to form a 3- to 8-membered aliphatic ring. In certain embodiments, both R⁴ and R⁵ are -H.

[0127] In some embodiments, the present invention provides a compound of formula II:



II,

- or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein:
- m is 0-3;
- each R¹ is independently selected from: halogen, -H, -(C1-C6)alkyl, -OH, -O((C1-C6)alkyl), -NO₂, -CN, -CF₃, -OCF₃, wherein said alkyl is independently substituted with 0-5 R';
- R² is selected from: -(C1-C6)alkyl, -OH, -O((C1-C6)alkyl), -C(O)O((C1-C6)alkyl), (C6-C10)-aryl-(C1-C12)aliphatic-, (C6-C10)-aryl-O-(C1-C12)aliphatic-, (C6-C10)-aryl-(C1-C12)aliphatic-O-, (3- to 10- membered heterocyclyl)-(C1-C12)aliphatic-, (5- to 10- membered heteroaryl)-(C1-C12)-aliphatic-, (5- to 10- membered heteroaryl)-O-(C1-C12)-aliphatic-, and (5- to 10- membered heteroaryl)-(C1-C12)-aliphatic-O-, wherein said alkyl, aryl or heteroaryl is independently substituted with 0-5 R';
- R³ is selected from: -(C1-C6)alkyl, -SO₂(C1-C6)alkyl, -C(O)N((C1-C6)alkyl)₂, and -C(O)O((C1-C6)alkyl), wherein said alkyl is independently substituted with 0-5 R';
- R' is as defined herein;

R^4 and R^5 are each independently selected from -H, halogen and -(C1-C6)alkyl; and R^6 is selected from -H and -(C1-C6)alkyl.

[0128] In some of the embodiments of a compound of formula II, m is 0, 1 or 2; when m is 1 or 2, at least one occurrence of R^1 is halogen or -O((C1-C6)alkyl) (such as -F and -OMe);

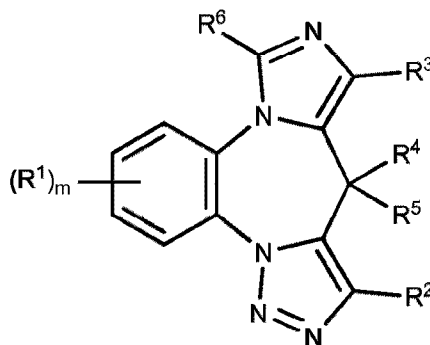
R^2 is selected from: -(C1-C6)alkyl (e.g., -Me), (C6-C10)-aryl-(C1-C12)aliphatic- (e.g., -CH₂Ph), (C6-C10)-aryl-O-(C1-C12)aliphatic- (e.g., -CH₂OPh) and (3- to 10-membered heterocyclyl)-(C1-C12)aliphatic- (e.g., -CH₂-pyrrolidine and -CH₂-morpholine), wherein said aryl (e.g., -Ph) or heterocyclyl (e.g., pyrrolidine or morpholine) is independently substituted with 0-5 R' independently selected from -F, -Me, and -OMe, and wherein said alkyl (e.g., -Me) is independently substituted with 0-3 R' selected from -N(Et)₂ and -N(Me)(CH₂Ph).

R^3 is -C(O)O((C1-C6)alkyl) (e.g., -COOEt);

R^4 and R^5 are both -H; and

R^6 is -H.

[0129] In some embodiments, the present invention provides a compound of formula II:



II,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or

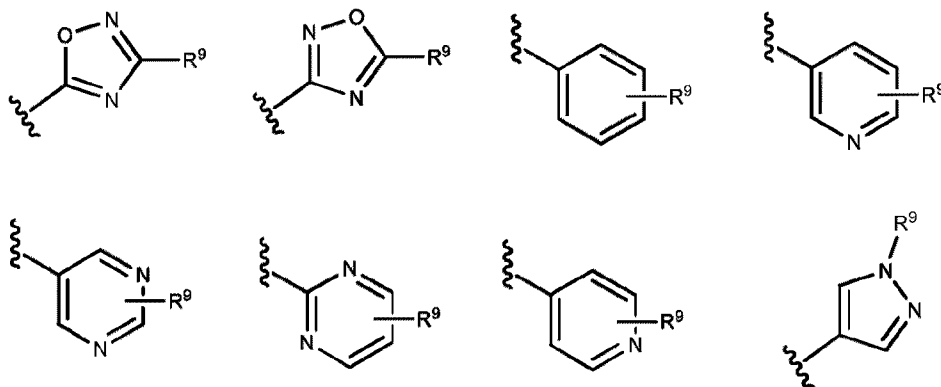
combination thereof, wherein:

m is 0-3;

each R^1 is independently selected from: halogen, -H, -(C1-C6)alkyl, -OH, -O((C1-C6)alkyl), -NO₂, -CN, -CF₃, -OCF₃, wherein R^1 is independently substituted with 0-5 R' ;

R^2 is selected from:

- (C1-C6)alkyl, -OH, -O((C1-C6)alkyl), -C(O)O((C1-C6)alkyl),
 (C6-C10)-aryl-(C1-C12)aliphatic-,
 (C6-C10)-aryl-O-(C1-C12)aliphatic-,
 (C6-C10)-aryl-N(R'')-(C1-C12)aliphatic-,
 5 (5- to 10- membered heteroaryl)-(C1-C12)aliphatic-,
 (5- to 10- membered heteroaryl)-O-(C1-C12)aliphatic-,
 (5- to 10- membered heteroaryl)-N(R'')-(C1-C12)aliphatic-,
 (3- to 10- membered heterocyclyl)-(C1-C12)aliphatic-,
 (3- to 10- membered heterocyclyl)-O-(C1-C12)aliphatic-,
 10 (3- to 10- membered heterocyclyl)-N(R'')-(C1-C12)aliphatic-,
 wherein R² is independently substituted with 0-5 R';
 R³ is selected from:
 -(C1-C6)alkyl, -C≡C, -CN, halogen, -SO₂((C6-C10)-aryl), -SO₂(C1-C6)alkyl),
 -C(O)N((C1-C6)alkyl)₂, -C(O)NH₂, -C(O)O((C1-C6)alkyl), -C(O)((C1-C6)alkyl), -
 15 (C6-C10)aryl, 5- to 10- membered heteroaryl, wherein R³ is independently substituted
 with 0-5 R';
 R⁴ and R⁵ are each independently selected from -H, halogen and -(C1-C6)alkyl;
 R⁶ is selected from -H and -(C1-C6)alkyl; and
 R' and R'' are as defined herein.
- 20 **[0130]** In some embodiments of a compound of formula II:
 m is 0, 1 or 2;
 when m is 1 or 2, at least one occurrence of R¹ is halogen or -O((C1-C6)alkyl);
 R² is selected from:
 -(C1-C6)alkyl, (C6-C10)-aryl-(C1-C12)aliphatic-, (C6-C10)aryl-O-(C1-
 25 C12)aliphatic-, (5- to 10- membered heteroaryl)-(C1-C12)aliphatic-, and (3- to 10-
 membered heterocyclyl)-(C1-C12)aliphatic-, wherein R² is independently substituted
 with 0-3 R';
 R³ is halogen, -CN, -C≡C, -C(O)NH₂, -(C1-C6)alkyl, -C(O)((C1-C6)alkyl), -C(O)O((C1-
 C6)alkyl), -SO₂(Ph(Me)),



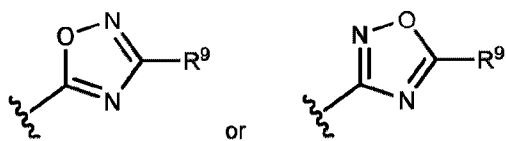
wherein R^3 is independently substituted with 0-3 R' , and wherein R^9 is selected from $-H$, $-Me$, $-Et$, $-CF_3$, isopropyl, $-OMe$, $-tert$ -butyl, and cyclopropyl;

R^4 and R^5 are both $-H$;

5 R^6 is $-H$; and

R' is as defined herein.

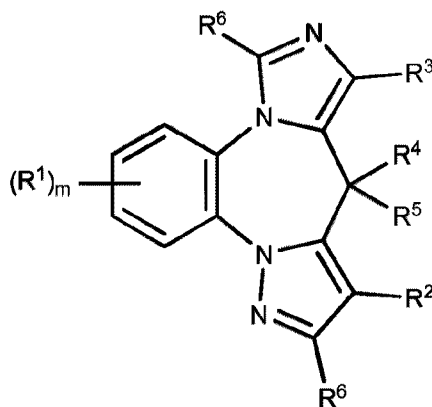
[0131] In some embodiments of a compound of formula II, R^3 is:



, wherein R^9 is selected from $-H$, $-Me$, $-Et$,

$-CF_3$, isopropyl, $-OMe$, and $-tert$ -butyl.

10 [0132] In some embodiments, the present invention provides a compound of formula III:



III,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or

combination thereof, wherein:

m is 0, 1, or 2, and when m is 1 or 2, at least one occurrence of R^1 is -O((C1-C6)alkyl) (such as -OMe);

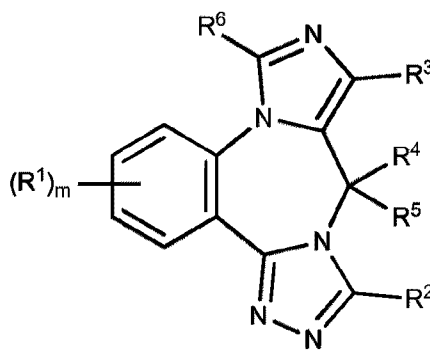
R^2 is selected from: -(C1-C6)alkyl (e.g., -Me) and (C6-C10)-aryl-(C1-C12)aliphatic- (e.g., -CH₂Ph);

R^3 is -C(O)O((C1-C6)alkyl) (e.g., -COOEt);

R^4 and R^5 are both -H; and

R^6 is -H.

[0133] In another aspect, the present invention provides a compound of formula IV:



IV,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein:

m is 0, 1, or 2, and when m is 1 or 2, at least one occurrence of R^1 is -O((C1-C6)alkyl) (such as -OMe);

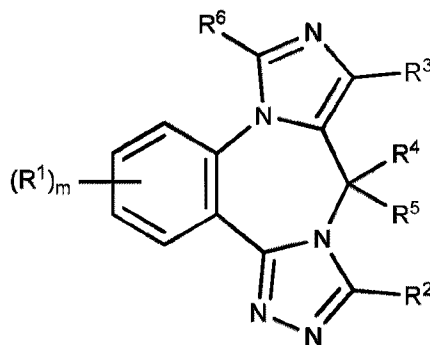
R^2 is OR^8 , wherein R^8 is (C6-C10)-aryl (such as phenyl), substituted with 0-3 halogen (such as -F);

R^3 is -C(O)O((C1-C6)alkyl) (e.g., -COOEt);

R^4 and R^5 are both -H; and

R^6 is -H.

[0134] In another aspect, the present invention provides a compound of formula IV:



IV,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof, wherein:

5 m is 0-3;

when m is 1 or 2, at least one occurrence of R¹ is -halogen or -O((C1-C6)alkyl);

each R¹ is independently selected from: halogen, -H, -(C1-C6)alkyl, -OH,

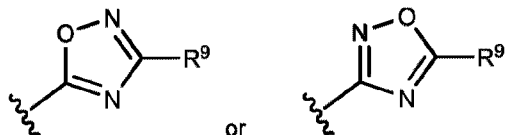
-O((C1-C6)alkyl), -NO₂, -CN, -CF₃, -OCF₃, wherein R¹ is independently substituted with 0-5 R²;

- 10 R² is selected from -OR⁸, -SR⁸, -(CH₂)ₙOR⁸, -(CH₂)ₙO(CH₂)ₙR⁸, -(CH₂)ₚR⁸ and -(CH₂)ₙN(R'')R¹⁰, wherein n is an integer selected from 0-4; p is an integer selected from 2-4; each R⁸ is independently -(C1-C6)alkyl, -(C3-C10)-cycloalkyl, (C6-C10)-aryl, or 5- to 10- membered heteroaryl, wherein each occurrence of R⁸ is independently substituted with 0-5 R²; each R¹⁰ is independently -(C3-C10)-
- 15 cycloalkyl, 3- to 10- membered heterocyclyl-, (C6-C10)-aryl, or 5- to 10- membered heteroaryl, wherein each occurrence of R¹⁰ is independently substituted with 0-5 R²; and wherein R² is independently substituted with 0-5 R²;

R³ is selected from:

-H, -CN, halogen, -(C1-C6)alkyl, -SO₂((C1-C6)alkyl), -C(O)N((C1-C6)alkyl)₂,

20 -C(O)((C1-C6)alkyl), -C(O)O((C1-C6)alkyl), and



, wherein R⁹ is selected from -Me, -Et,

isopropyl, -CF₃, -OMe, -OEt, -O-isopropyl, -CH₂NMe₂, and cyclopropyl; and wherein

R³ is independently substituted with 0-5 R²;

R^4 and R^5 are each independently selected from $-H$, halogen and $-(C1-C6)alkyl$;

R^6 is selected from $-H$ and $-(C1-C6)alkyl$; and

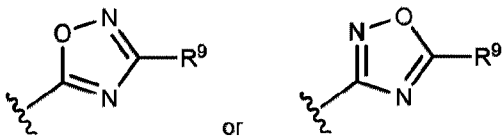
R' and R'' are as defined herein.

[0135] In some embodiments of a compound of formula IV:

5 m is 0, 1, or 2;

R^2 is $-OR^8$, $-(CH_2)_nOR^8$, $-(CH_2)_nO(CH_2)_nR^8$, wherein n is 1, and wherein R^8 is $-(C1-C6)alkyl$, $(C6-C10)aryl$ or 5- to 10- membered heteroaryl, wherein R^8 is independently substituted with 0-3 R' ;

R^3 is halogen, $-H$, $-CN$, $-(C1-C6)alkyl$, $-C(O)((C1-C6)alkyl)$, $-C(O)O((C1-C6)alkyl)$,

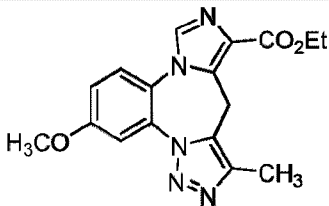
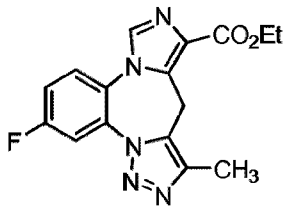
10  , wherein said alkyl is independently substituted with 0-3 R' ; R^9 is selected from $-Me$, $-Et$, isopropyl, and $-CF_3$;

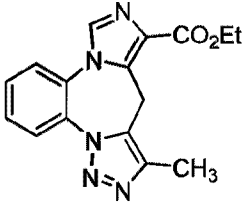
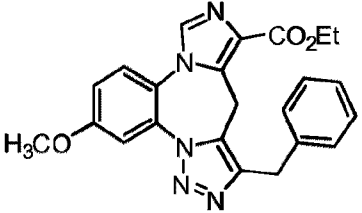
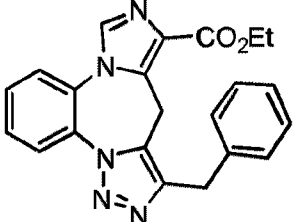
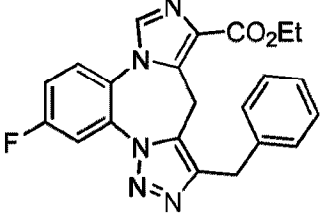
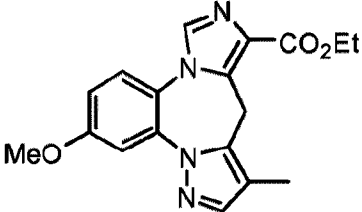
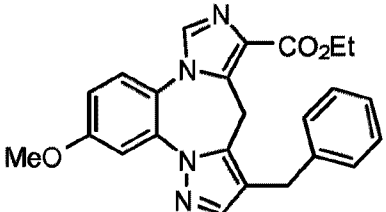
R^4 and R^5 are both $-H$;

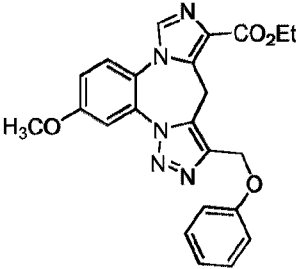
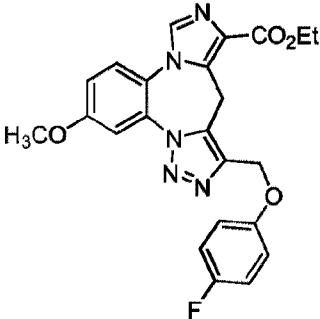
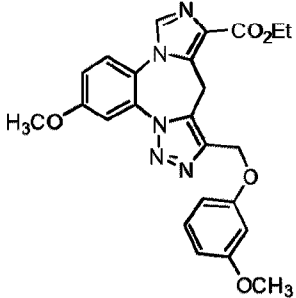
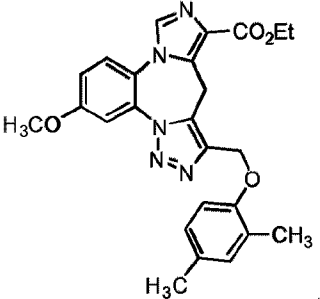
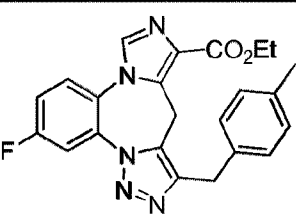
R^6 is $-H$; and

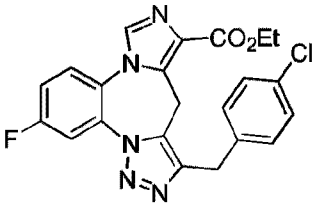
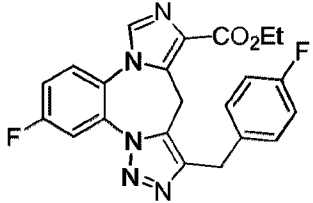
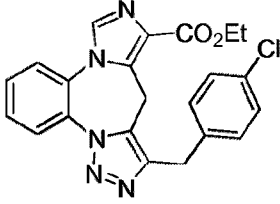
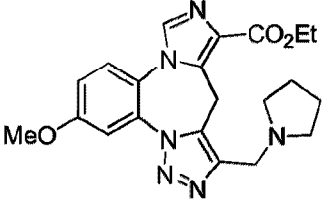
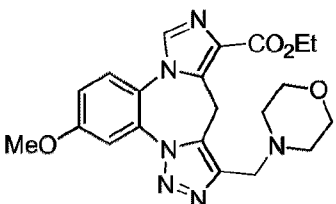
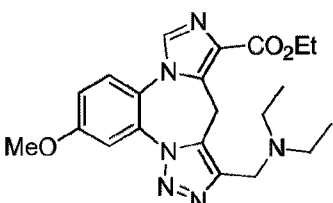
R' is as defined herein.

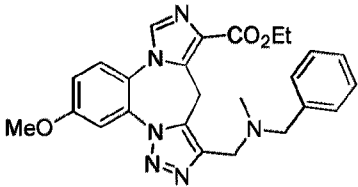
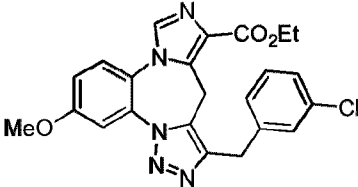
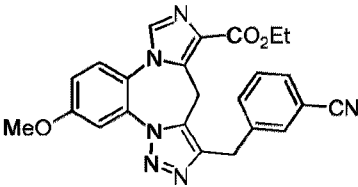
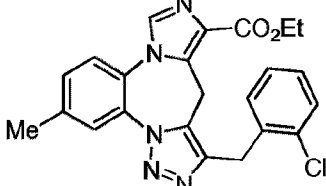
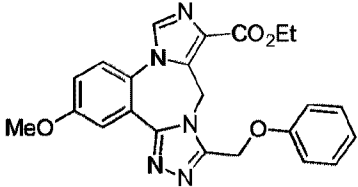
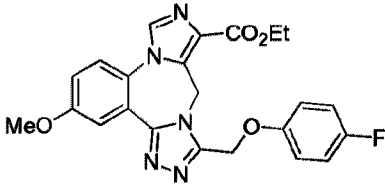
15 [0136] Examples of particular compounds of the present application include:

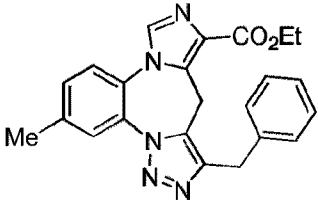
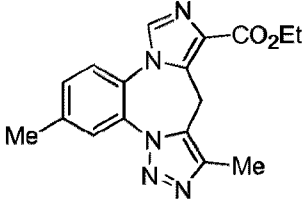
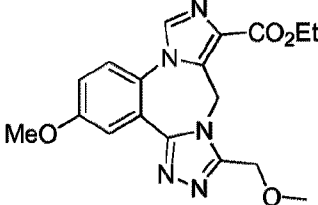
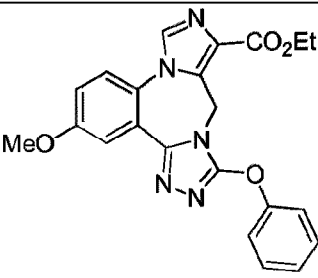
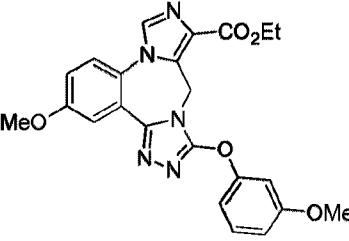
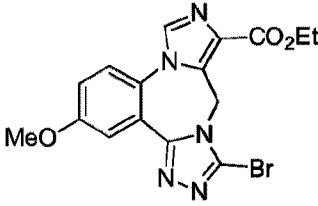
Compound	Structure
1	
2	

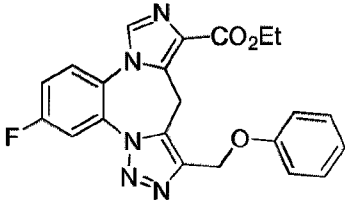
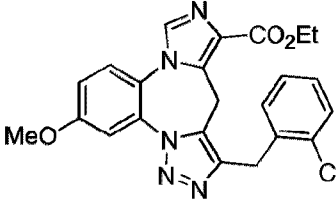
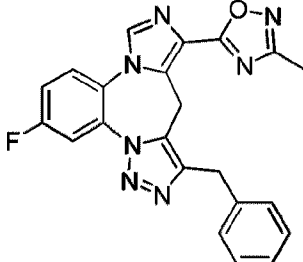
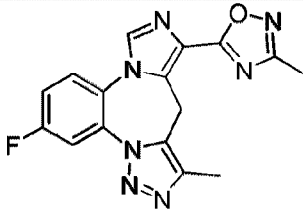
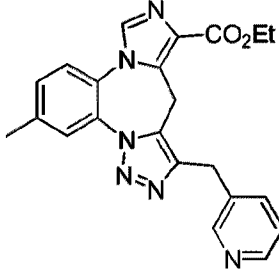
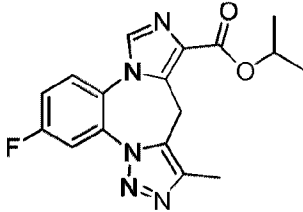
Compound	Structure
3	
4	
5	
6	
7	
8	

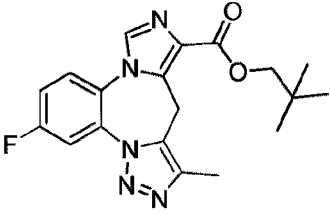
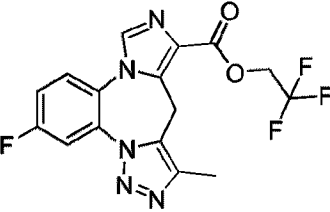
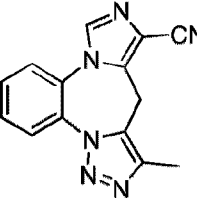
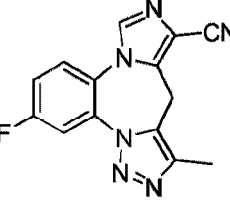
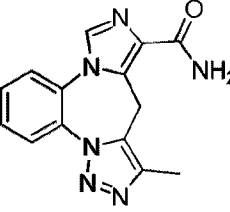
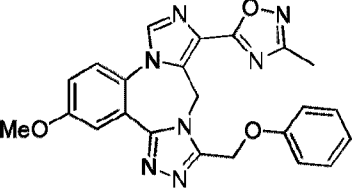
Compound	Structure
9	
10	
11	
12	
44	

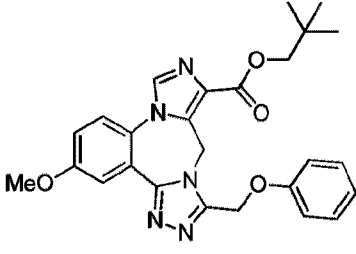
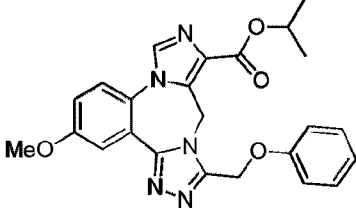
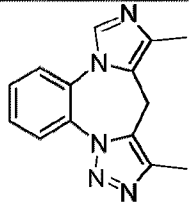
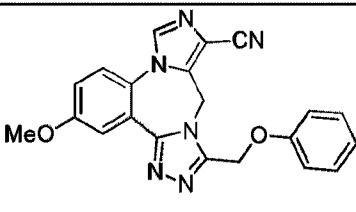
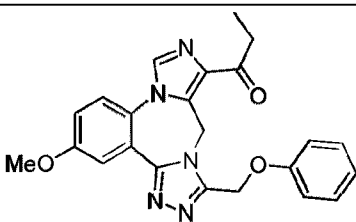
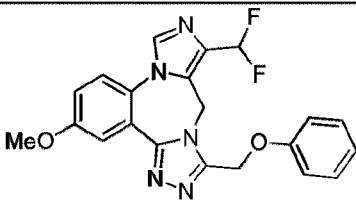
Compound	Structure
45	
46	
47	
48	
49	
50	

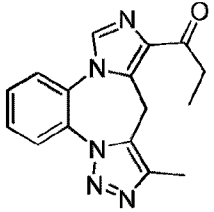
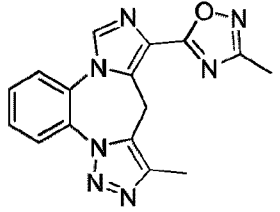
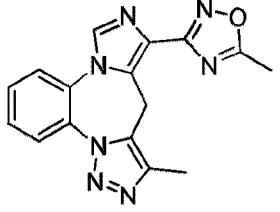
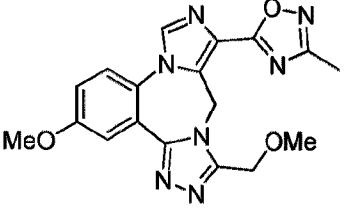
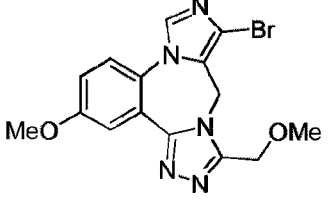
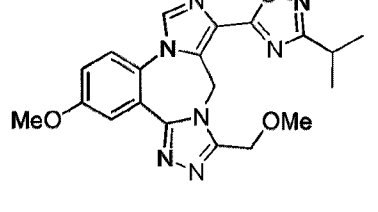
Compound	Structure
51	
52	
53	
54	
55	
56	

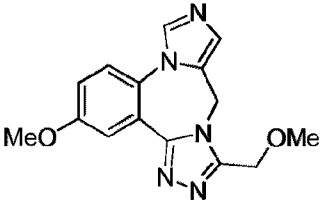
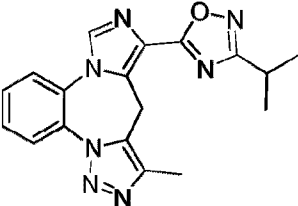
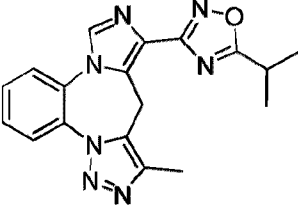
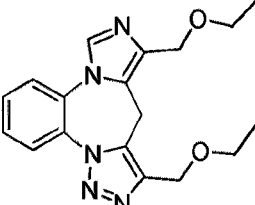
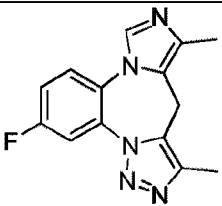
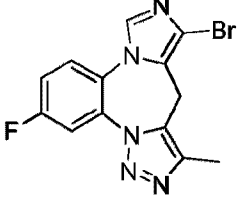
Compound	Structure
101	
102	
103	
104	
105	
106	

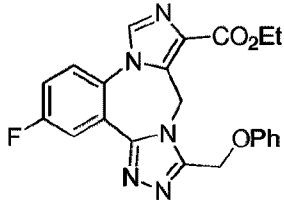
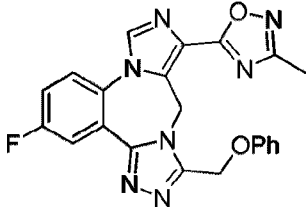
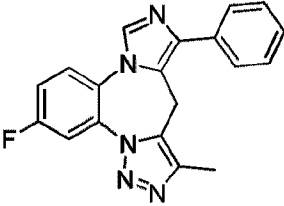
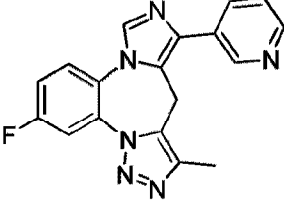
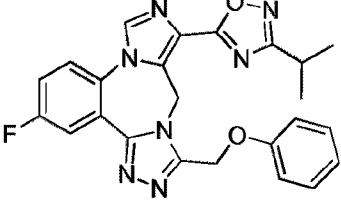
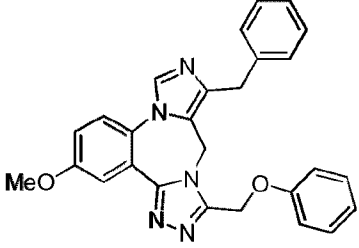
Compound	Structure
107	
108	
109	
110	
111	
112	

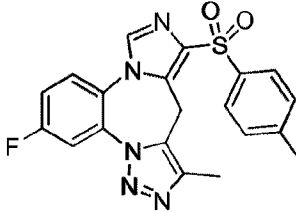
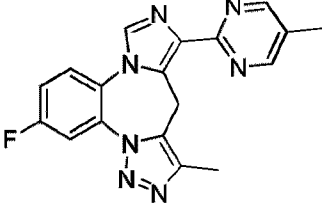
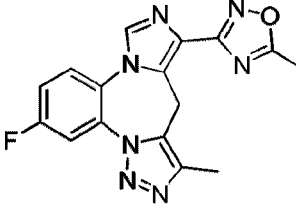
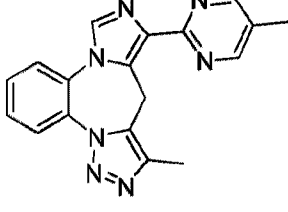
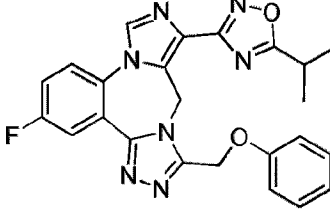
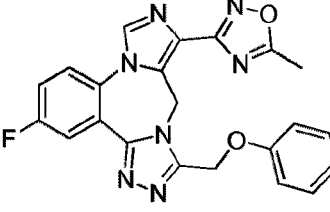
Compound	Structure
113	
114	
115	
116	
117	
118	

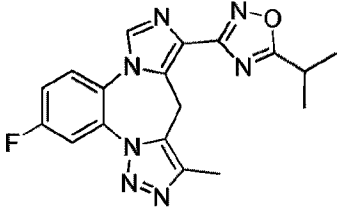
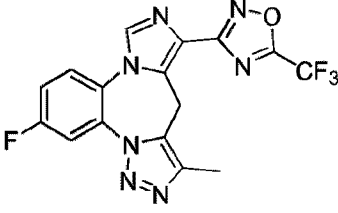
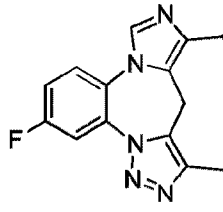
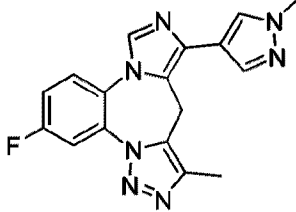
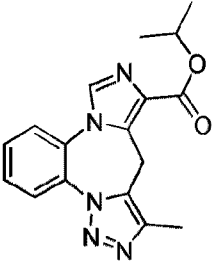
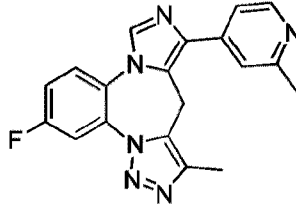
Compound	Structure
119	
120	
121	
122	
123	
124	

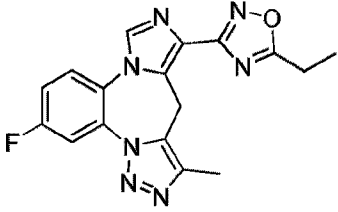
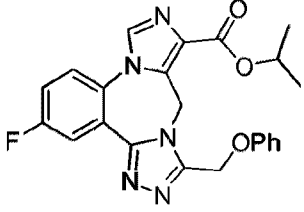
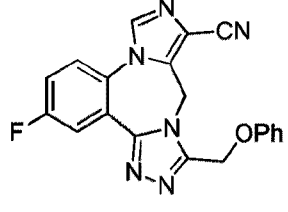
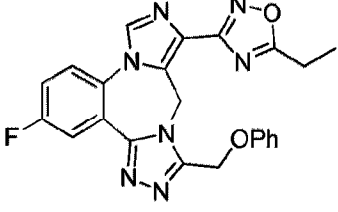
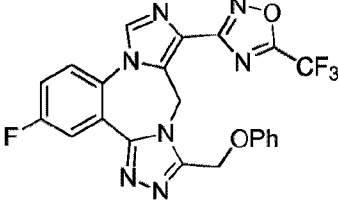
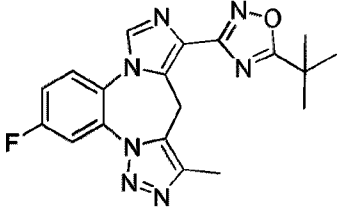
Compound	Structure
125	
126	
127	
128	
129	
130	

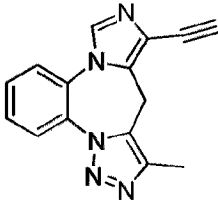
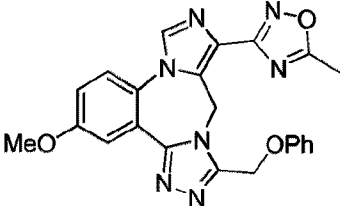
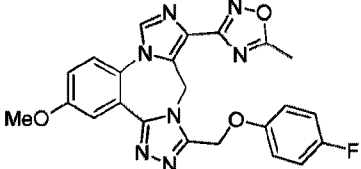
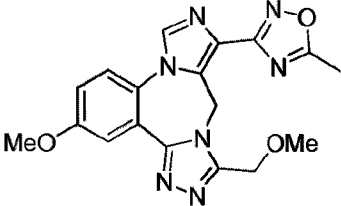
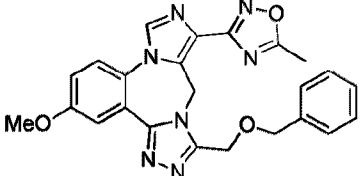
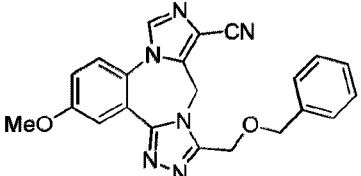
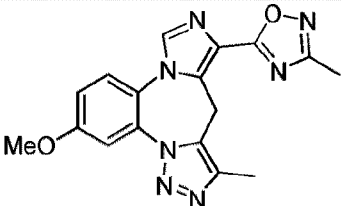
Compound	Structure
131	
132	
133	
134	
135	
136	

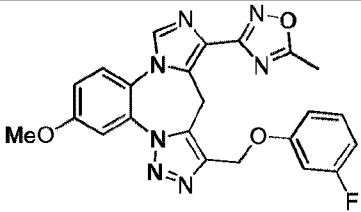
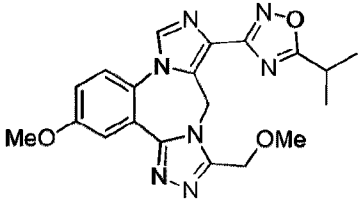
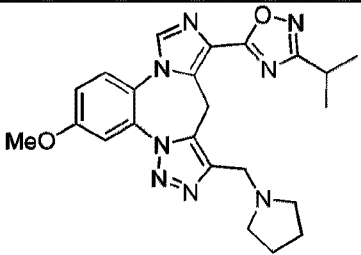
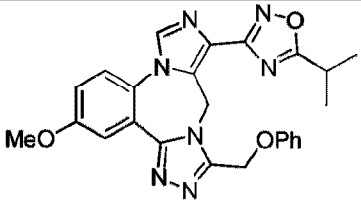
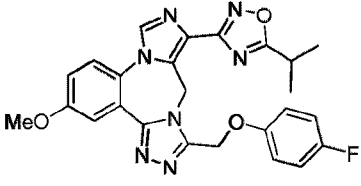
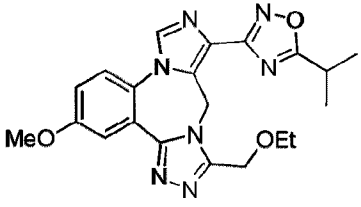
Compound	Structure
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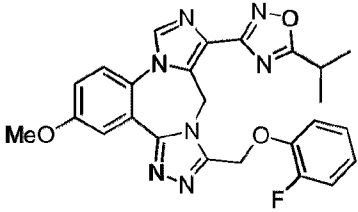
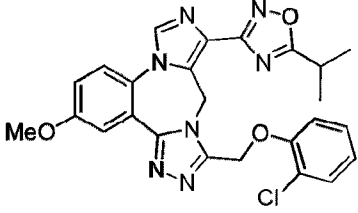
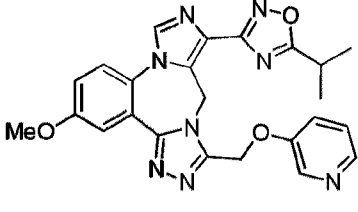
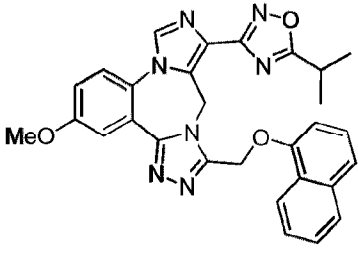
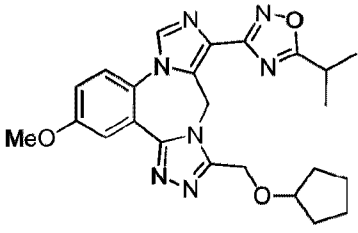
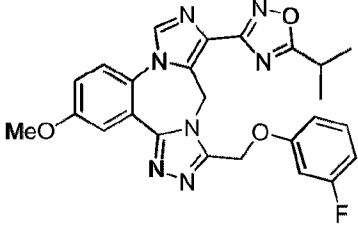
Compound	Structure
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Compound	Structure
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Compound	Structure
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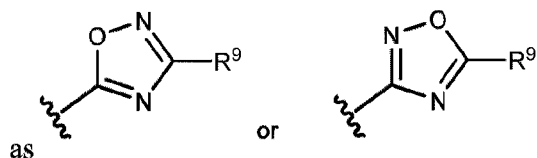
Compound	Structure
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Compound	Structure
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Compound	Structure
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and their pharmaceutically suitable salt, hydrate, solvate, polymorph, isomer or combination thereof.

[0137] The invention also includes various combinations of R^1 , R^2 and R^3 as described above. These combinations can in turn be combined with any or all of the values of the other variables described herein. For example, R^1 can be $-OR$ or halogen; ; R^2 can be (C1-C4)-alkyl-, $-OR^8$, $-(CH_2)_nOR^8$, or $-(CH_2)_nO(CH_2)_nR^8$; and optionally R^3 is $-C(O)OR$,
 5 or $-C(O)N(R)_2$. In another example, R^1 is $-OR$ or halogen; R^2 is (C1-C4)-alkyl-, $-OR^8$, $-(CH_2)_nOR^8$, or $-(CH_2)_nO(CH_2)_nR^8$; and R^3 is a 5- or 6-membered heteroaryl, such



can have the specific values of the groups described herein.

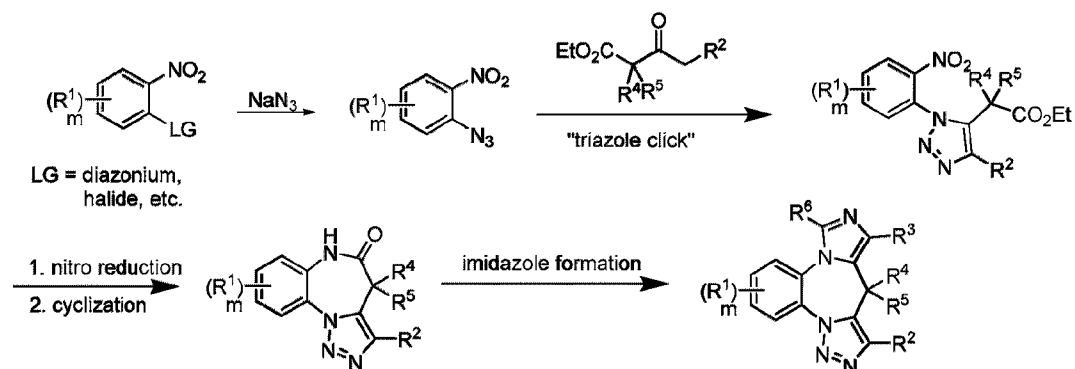
[0138] Any embodiment described herein is also intended to represent unlabeled forms
 10 as well as isotopically labeled forms of the compounds, unless otherwise indicated. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine,
 15 and chlorine, such as 2H , 3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{125}I , respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as 3H , ^{13}C , and ^{14}C , are present. Such isotopically labeled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example 2H or 3H), detection or imaging techniques,
 20 such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly preferred for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures
 25 disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0139] Any of the individual embodiments recited herein may define formula I, II, III, or IV individually or be combined to produce a preferred embodiment of this invention.

General Synthetic Methodology

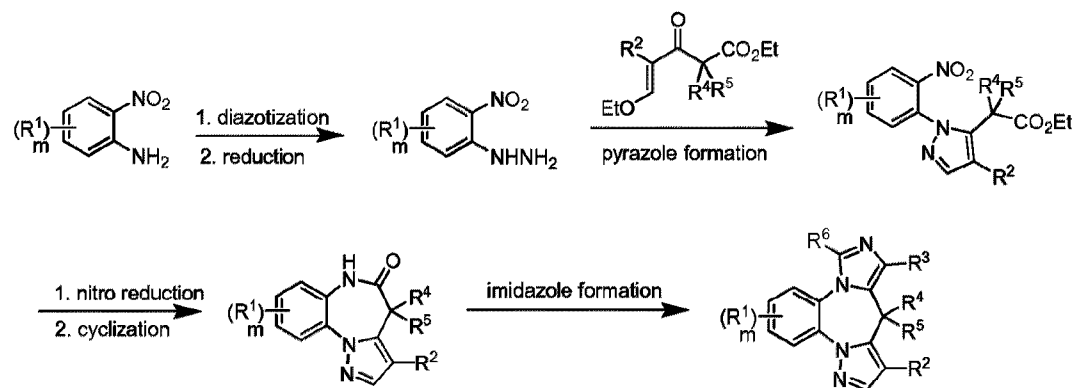
[0140] The compounds of this invention may be prepared in general by methods known to those skilled in the art. Schemes 1-10 below provide general synthetic routes for the preparation of compounds of formulae I-IV. Other equivalent schemes, which will be readily apparent to the ordinary skilled organic chemist, may alternatively be used to synthesize various portions of the molecules as illustrated by the general schemes below.

Scheme 1. General synthesis of a compound of formula I wherein X, Y, Z, V and W form a 1,2,3-triazole ring, or a compound of formula II.



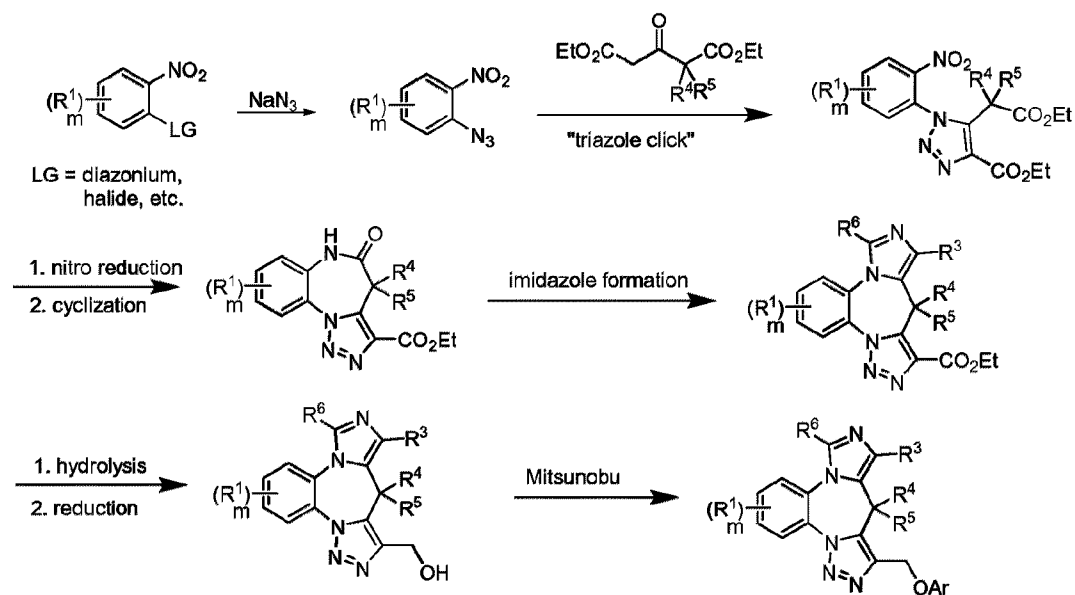
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Scheme 2. General synthesis of a compound of formula I or III, wherein X, Y, Z, V and W form a pyrazole ring.

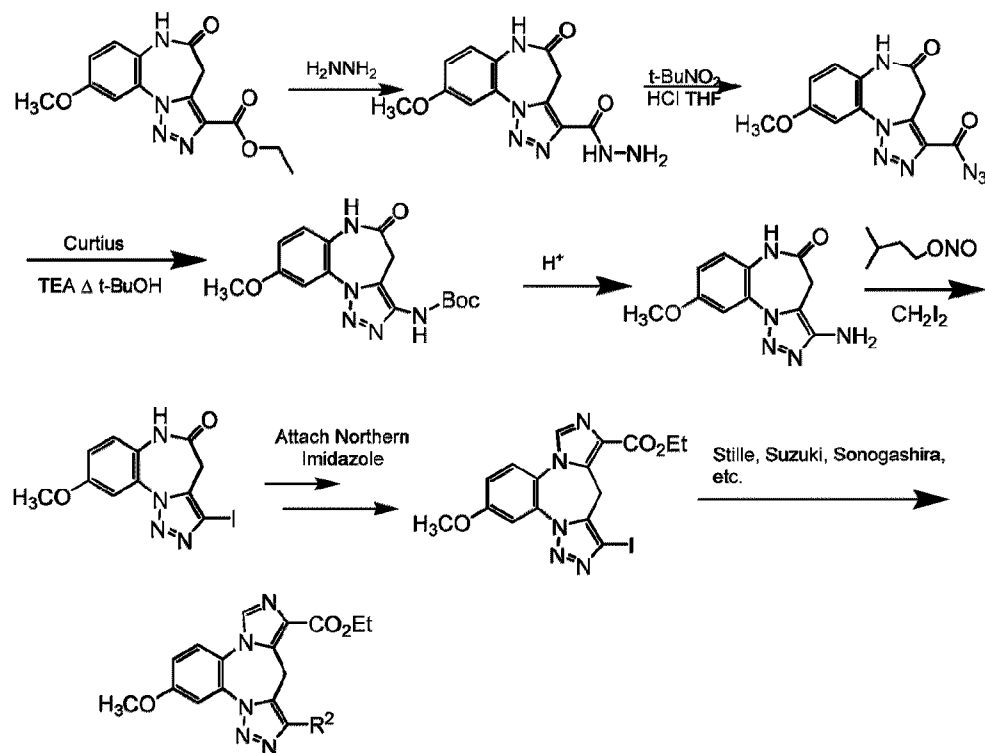


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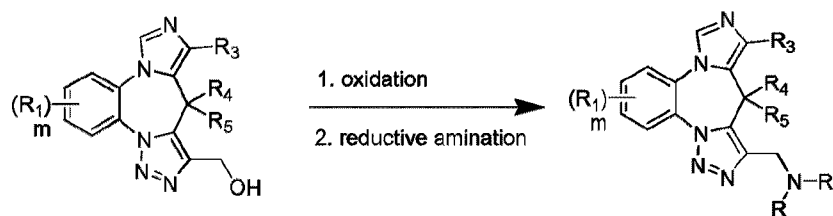
Scheme 3. General synthesis of a compound of formula I, wherein X, Y, Z, V and W form a phenoxy-substituted 1,2,3-triazole ring, or a compound of formula II.



5 **Scheme 4.** General synthesis of compounds of formula I or II to allow for divergent functionalization on the triazolo-ring formed by X, Y, Z, V and W.

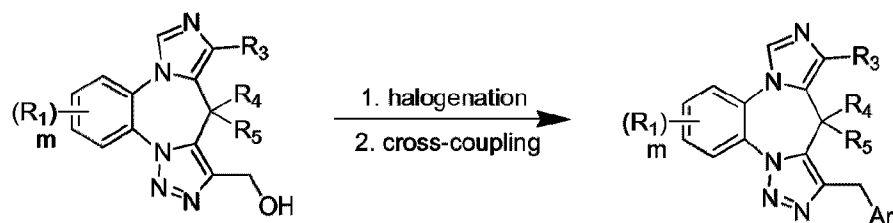


Scheme 5. General synthesis of a compound of formula I wherein X, Y, Z, V and W form an aminomethyl-substituted 1,2,3-triazole ring, or a compound of formula II.



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Scheme 6. General synthesis of a compound of formula I wherein X, Y, Z, V and W form an aralkyl-substituted or heteroaralkyl substituted 1,2,3-triazole ring, or a compound of formula II.

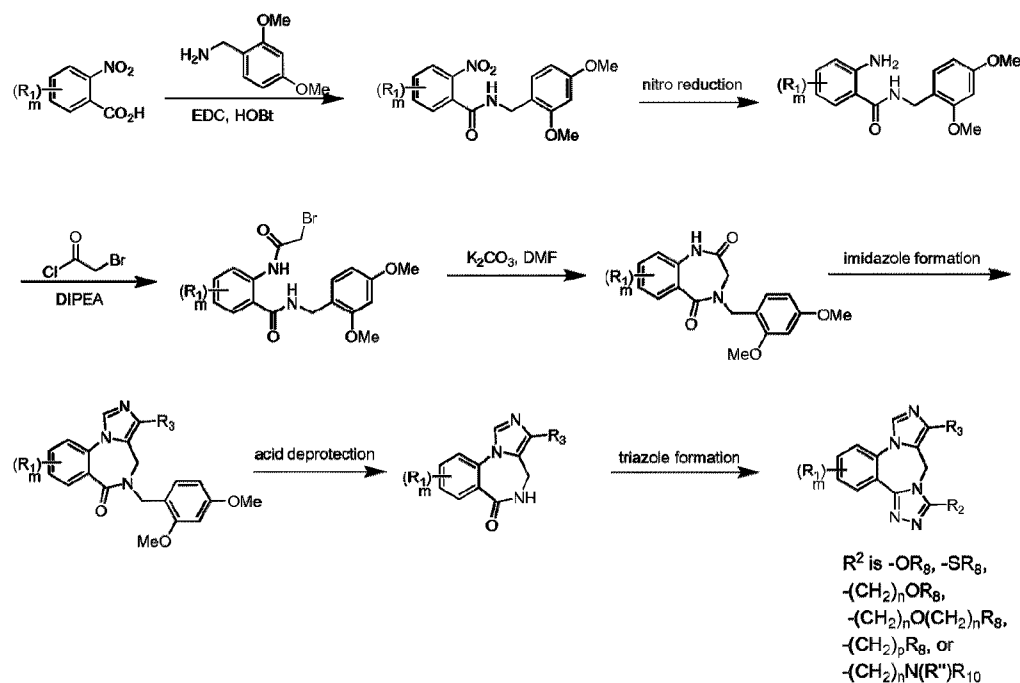


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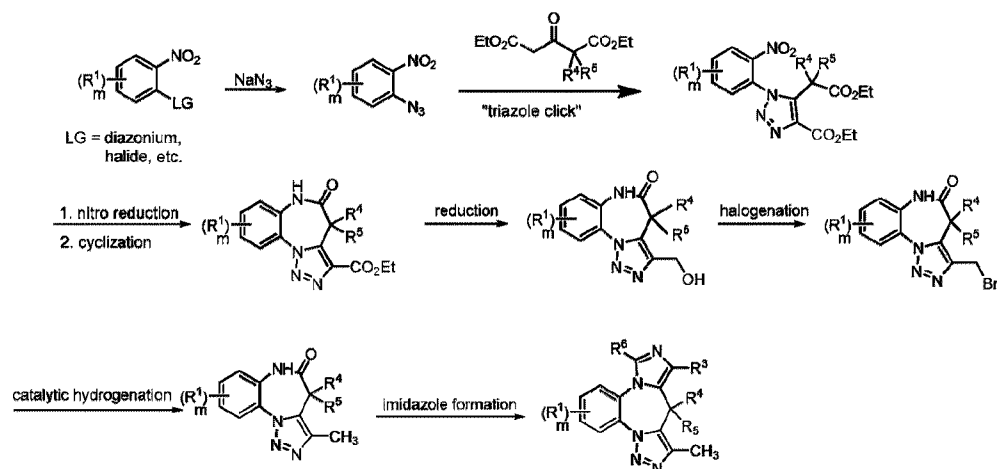
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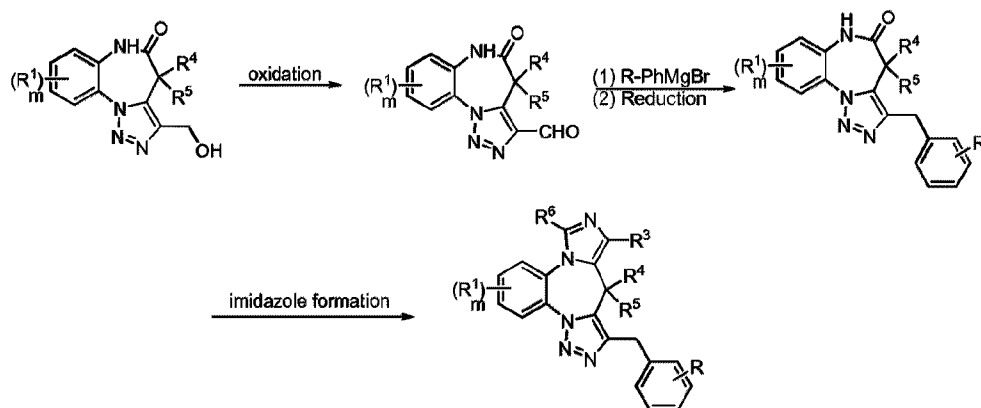
Scheme 7. General synthesis of a compound of formula I or IV, wherein X, Y, Z, V and W form a substituted 1,2,4-triazole ring.



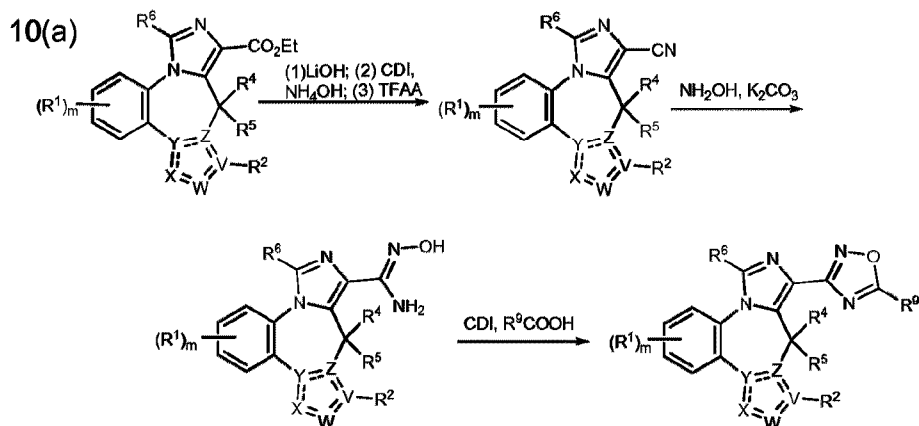
5 **Scheme 8.** General synthesis of a compound of formula I wherein X, Y, Z, V, and W form a methyl-substituted 1, 2, 3-triazole ring, or a compound of formula II.



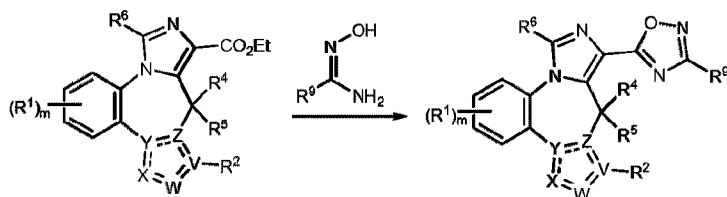
Scheme 9. General synthesis of a compound of formula I, wherein X, Y, Z, V, and W form a benzyl-substituted 1,2,3-triazole ring, or a compound of formula II.



5 **Scheme 10.** General synthesis of a compound of formula I, II, or IV wherein X, Y, Z, V and W form a substituted triazole ring, such as a 1,2,3-triazole ring or a 1,2,4-triazole ring, and the upper imidazole is substituted with a 1,2,4-oxadiazole ring as illustrated in 10(a) and 10(b).



10(b)



[0141] As would be recognized by skilled practitioners, compounds of formulae I-IV with variables other than those depicted above may be prepared by varying chemical reagents or the synthetic routes.

Pharmaceutical Compositions and Modes of Administration

- 5 [0142] The present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formulae I-IV, or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof.
- [0143] The basic nitrogen-containing groups present in the compounds of the invention may
 10 be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.
- 15 [0144] It will be appreciated that compounds and agents used in the compositions of this invention preferably should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier, however, can still be effectively administered directly into the central nervous system, *e.g.*, by an intraventricular or other neuro-compatible route.
- 20 [0145] In some embodiments of this invention, the $\alpha 5$ -containing GABA_A R positive allosteric modulator is formulated with a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers that may be used in these compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid,
 25 potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block
 30 polymers, polyethylene glycol and wool fat. In other embodiments, no carrier is used.

For example, the $\alpha 5$ -containing GABA_A R agonist (*e.g.*, a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) can be administered alone or as a component of a pharmaceutical formulation (therapeutic composition). The $\alpha 5$ -containing GABA_A R agonist (*e.g.*, a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator) may be
5 formulated for administration in any convenient way for use in human medicine.

[0146] In some embodiments, the therapeutic methods of the invention include administering the composition of a compound or agent topically, systemically, or locally. For example, therapeutic compositions of compounds or agents of the invention may be formulated for administration by, for example, injection (*e.g.*, intravenously,
10 subcutaneously, or intramuscularly), inhalation or insufflation (either through the mouth or the nose) or oral, buccal, sublingual, transdermal, nasal, or parenteral administration. The compositions of compounds or agents described herein may be formulated as part of an implant or device, or formulated for slow or extended release. When administered parenterally, the therapeutic composition of compounds or agents for use in this invention
15 is preferably in a pyrogen-free, physiologically acceptable form. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, Meade Publishing Co., Easton, PA.

[0147] In certain embodiments, pharmaceutical compositions suitable for parenteral administration may comprise the $\alpha 5$ -containing GABA_A R positive allosteric modulator
20 in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.
25 Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials,
30 such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0148] A composition comprising a $\alpha 5$ -containing GABA_A R positive allosteric modulator may also contain adjuvants, such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

[0149] In certain embodiments of the invention, compositions comprising a $\alpha 5$ -containing GABA_A R positive allosteric modulator can be administered orally, *e.g.*, in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and the like, each containing a predetermined amount of the $\alpha 5$ -containing GABA_A R positive allosteric modulator as an active ingredient.

[0150] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), one or more compositions comprising the $\alpha 5$ -containing GABA_A R positive allosteric modulator may be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of

a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0151] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the $\alpha 5$ -containing GABA_A R positive allosteric modulator, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol (ethanol), isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

[0152] Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol, and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0153] As described herein, the compounds, agents, and compositions thereof may be administered for slow, controlled or extended release. The term "extended release" is widely recognized in the art of pharmaceutical sciences and is used herein to refer to a controlled release of an active compound or agent from a dosage form to an environment over (throughout or during) an extended period of time, *e.g.* greater than or equal to one hour. An extended release dosage form will release drug at substantially constant rate over an extended period of time or a substantially constant amount of drug will be released incrementally over an extended period of time. The term "extended release" used herein includes the terms "controlled release," "prolonged release," "sustained release," "delayed release," or "slow release" as these terms are used in the pharmaceutical sciences. In some embodiments, the extended release dosage is administered in the form of a patch or a pump.

[0154] A person of ordinary skill in the art, such as a physician, is readily able to determine the required amount of $\alpha 5$ -containing GABA_A R positive allosteric modulator (s) to treat the subject using the compositions and methods of the invention. It is understood that the dosage regimen will be determined for an individual, taking into
5 consideration, for example, various factors that modify the action of $\alpha 5$ -containing GABA_A R positive allosteric modulator, the severity or stage of the disease, route of administration, and characteristics unique to the individual, such as age, weight, size, and extent of cognitive impairment.

[0155] It is well-known in the art that normalization to body surface area is an appropriate
10 method for extrapolating doses between species. To calculate the human equivalent dose (HED) from a dosage used in the treatment of age-dependent cognitive impairment in rats, the formula $HED (mg/kg) = rat\ dose (mg/kg) \times 0.16$ may be employed (see Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, December 2002, Center for Biologics Evaluation and Research). For example, using that formula, a
15 dosage of 10 mg/kg in rats is equivalent to 1.6 mg/kg in humans. This conversion is based on a more general formula $HED = animal\ dose\ in\ mg/kg \times (animal\ weight\ in\ kg/human\ weight\ in\ kg)^{0.33}$.

[0156] In certain embodiments of the invention, the dose of the $\alpha 5$ -containing GABA_A R positive allosteric modulator is between 0.0001 and 100 mg/kg/day (which, given a typical
20 human subject of 70 kg, is between 0.007 and 7000 mg/day).

[0157] In certain embodiments of the invention, the interval of administration is once every 12 or 24 hours. Administration at less frequent intervals, such as once every 6 hours, may also be used.

[0158] If administered by an implant, a device or a slow or extended release
25 formulation, the $\alpha 5$ -containing GABA_A R positive allosteric modulator can be administered one time, or one or more times periodically throughout the lifetime of the patient as necessary. Other administration intervals intermediate to or shorter than these dosage intervals for clinical applications may also be used and may be determined by one skilled in the art following the methods of this invention.

[0159] Desired time of administration can be determined by routine experimentation by one skilled in the art. For example, the $\alpha 5$ -containing GABA_A R positive allosteric modulator may be administered for a period of 1-4 weeks, 1-3 months, 3-6 months, 6-12 months, 1-2 years, or more, up to the lifetime of the patient.

- 5 [0160] In addition to $\alpha 5$ -containing GABA_A R positive allosteric modulator, the compositions of this invention can also include other therapeutically useful agents. These other therapeutically useful agents may be administered in a single formulation, simultaneously or sequentially with the $\alpha 5$ -containing GABA_A R positive allosteric modulator according to the methods of the invention.
- 10 [0161] It will be understood by one of ordinary skill in the art that the compositions described herein may be adapted and modified as is appropriate for the application being addressed and that the compositions described herein may be employed in other suitable applications. For example, the compositions of this application may further comprise a second therapeutic agent. Such other additions and modifications will not depart from the
- 15 scope hereof.

Pharmaceutical Compositions with Antipsychotics

- [0162] The compounds or the compositions of this application may be used in combination with an antipsychotic in treating cognitive impairment associated with schizophrenia or bipolar disorder in a subject having or at risk of said schizophrenia or
- 20 bipolar disorder (*e.g.*, mania). The antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof that is useful in the methods and compositions of this invention include both typical and atypical antipsychotics. In some embodiments, the compounds or the compositions of the present invention may be used to treat one or more positive and/or negative symptoms, as well as cognitive impairment, associated with
- 25 schizophrenia. In some embodiments, the compounds or the compositions of the present invention may be used to treat one or more symptoms, as well as cognitive impairment, associated with bipolar disorder (in particular, mania). In some embodiments of this invention, the compounds or the compositions of this invention prevent or slow the progression of cognitive impairment of schizophrenia or bipolar disorder (in particular,
- 30 mania) in said subject.

[0163] In some embodiments, the antipsychotics suitable for use in the present invention are selected from atypical antipsychotics. Such atypical antipsychotics include, but are not limited to, those disclosed in, for example, U.S. Patents 4,734,416; 5,006,528; 4,145,434; 5,763,476; 3,539,573; 5,229,382; 5,532,372; 4,879,288; 4,804,663; 4,710,500; 5 4,831,031; and 5,312,925, and EP Patents EP402644 and EP368388, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

[0164] In some embodiments, atypical antipsychotics suitable for use in the present invention include, but are not limited to, aripiprazole, asenapine, clozapine, iloperidone, olanzapine, lurasidone, paliperidone, quetiapine, risperidone and ziprasidone, and the 10 pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof. In some embodiments, the antipsychotic suitable for use herein is selected from aripiprazole (Bristol-Myers Squibb), olanzapine (Lilly) and ziprasidone (Pfizer), and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

[0165] In some embodiments, the antipsychotics suitable for use in the present 15 invention are typical antipsychotics, including, but not limited to, acepromazine, benperidol, bromazepam, bromperidol, chlorpromazine, chlorprothixene, clotiapine, cyamemazine, diazepam, dixyrazine, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, heptaminol, isopropamide iodide, levomepromazine, levosulpiride, loxapine, melperone, mesoridazine, molindone, oxypertine, oxyprothepine, penfluridol, perazine, 20 periciazine, perphenazine, pimozide, pipamperone, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, pyridoxine, sulpiride, sultopride, tetrabenazine, thioproperazine, thioridazine, tiapride, tiotixene, trifluoperazine, triflupromazine, trihexyphenidyl, and zuclopenthixol, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

25 [0166] In some embodiments of the present invention, the antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof may be selected from compounds that are dopaminergic agents (such as dopamine D₁ receptor antagonists or agonists, dopamine D₂ receptor antagonists or partial agonists, dopamine D₃ receptor antagonists or partial agonists, dopamine D₄ receptor antagonists), glutamatergic agents, 30 N-methyl-D-aspartate (NMDA) receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs)

- agonists or positive allosteric modulators (PAMs) (e.g., mGluR2/3 agonists or PAMs), glutamate receptor *glur5* positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs,
- 5 noradrenergic agents (such as α -2 adrenergic receptor agonists or antagonists and catechol-O-methyl transferase (COMT) inhibitors), serotonin receptor modulators (such as 5-HT_{2A} receptor antagonists, 5-HT_{1A} receptor partial agonists, 5-HT_{2C} agonists, and 5-HT₆ antagonists, serotonin 2C agonists), cholinergic agents (such as α -7 nicotinic
- 10 receptor agonists or PAMs, α 4- β 2 nicotinic receptor agonists, allosteric modulators of nicotinic receptors and acetylcholinesterase inhibitors, muscarinic receptor agonists and antagonists), cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, monoamine oxidase (MAO) B inhibitors, PDE10 inhibitors, neuronal nitric oxide synthase (nNOS) inhibitors, neurosteroids, and neurotrophic factors.
- 15 [0167] In some embodiments, an α 5-containing GABA_A receptor positive allosteric modulator as described herein and an antipsychotic as described herein, or their pharmaceutically acceptable salts, hydrates, solvates or polymorphs, are administered simultaneously, or sequentially, or in a single formulation, or in separate formulations packaged together. In other embodiments, the α 5-containing GABA_A receptor positive
- 20 allosteric modulator and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates or polymorphs, are administered via different routes. As used herein, “combination” includes administration by any of these formulations or routes of administration.

Pharmaceutical Compositions with Memantine

- 25 [0168] The compounds or the compositions of this application may be used in combination with memantine or a derivative or an analog thereof in treating cognitive impairment associated with central nervous system (CNS) disorders in a subject in need or at risk thereof, including, without limitation, subjects having or at risk for age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI, Age-Associated
- 30 Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD),

schizophrenia or bipolar disorder, amyotrophic lateral sclerosis (ALS) and cancer-therapy-related cognitive impairment.

[0169] Memantine, chemically also known as 3,5-dimethyladamantan-1-amine or 3,5-dimethyltricyclo[3.3.1.1^{3,7}]decan-1-amine, is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with moderate affinity. The proprietary names for memantine include: Axura® and Akatinol® (Merz), Namenda® (Forest Laboratories), Ebixa® and Abixa® (Lundbeck), and Memox® (Unipharm). Memantine is currently available in the U.S. and in over 42 countries worldwide. It is approved for the treatment of moderate to severe Alzheimer's disease (AD) in the United States at a dose of up to 28 mg/day. Memantine and some of its derivatives and analogs that are useful in the present invention are disclosed in U.S. Patents Nos. 3,391,142; 4,122,193; 4,273,774; and 5,061,703. Other memantine derivatives or analogs that are useful in the present invention include, but are not limited to, those compounds disclosed in U.S. Patent Application Publication US20040087658, US20050113458, US20060205822, US20090081259, US20090124659, and US20100227852; EP Patent Application Publication EP2260839A2; EP Patent EP1682109B1; and PCT Application Publication WO2005079779. Memantine, as used in the present invention, includes memantine and its derivatives and analogs, as well as hydrates, polymorphs, prodrugs, salts, and solvates thereof. Memantine, as used herein, also includes a composition comprising memantine or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof, wherein the composition optionally further comprises at least one additional therapeutic agent (such as a therapeutic agent useful for treating a CNS disorder or cognitive impairments associated thereof). In some embodiments, the memantine composition suitable for use in the present invention comprises memantine and a second therapeutic agent that is donepezil (under the trade name Aricept).

[0170] In other embodiments of the invention, the $\alpha 5$ -containing GABA_A receptor positive allosteric modulator and memantine (or the memantine derivative/analog), or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs are administered simultaneously, or sequentially, or in a single formulation or in separate formulations packaged together. In other embodiments, the $\alpha 5$ -containing GABA_A

receptor positive allosteric modulator and memantine (or the memantine derivative/analog), or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs are administered via different routes. As used herein, "combination" includes administration by any of these formulations or routes of administration.

Pharmaceutical Compositions with Acetylcholine Esterase Inhibitors (AChE-Is)

[0171] The compounds or the compositions of this application may be used in combination with an acetylcholine esterase inhibitor in treating cognitive impairment associated with central nervous system (CNS) disorders in a subject in need or at risk thereof, including, without limitation, subjects having or at risk for age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnesic MCI, Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia or bipolar disorder, amyotrophic lateral sclerosis (ALS) and cancer-therapy-related cognitive impairment.

[0172] AChE-Is known to a person of ordinary skill in the art may belong to the subcategories of (i) reversible non-competitive inhibitors or reversible competitive inhibitors, (ii) irreversible, and/or (iii) quasi-irreversible inhibitors.

[0173] In certain embodiment, AChE-Is useful in the present invention include those described in PCT applications WO2014039920 and WO2002032412; EP patents Nos. 468187; 481429-A; and U.S. Patents Nos. 4,816,456; 4,895,841; 5,041,455; 5,106,856; 5,602,176; 6,677,330; 7,340,299; 7,635,709; 8,058,268; 8,741,808; and 8,853,219.

[0174] In certain embodiment, typical AChE-Is that may be used in accordance with this invention include, but are not limited to, ungeremine, ladostigil, demecarium, echothiophate (Phospholine), edrophonium (Tensilon), tacrine (Cognex), Pralidoxime (2-PAM), pyridostigmine (Mestinon), physostigmine (serine, Antilirium), abmenonium (Mytelase), galantamine (Reminyl, Razadyne), rivastigmine (Exelon, SZD-ENA-713), Huperzine A, Icopezil, neostigmine (Prostigmin, Vagostigmin), Aricept (Donepezil, E2020), Lactucopicrin, monoamine acridines and their derivatives, piperidine and

piperazine derivatives, N-benzyl-piperidine derivatives, piperidiny-alkanoyl heterocyclic compounds, 4-(1-benzylpiperidyl)-substituted fused quinoline derivatives and cyclic amide derivatives. Other typical AChE-Is include carbamates and organophosphonate compounds such as Metrifonate (Trichlorfon). Benzazepinols such as galantamine are
5 also useful AChE-Is. In some embodiment, AChE-Is suitable for use in combination with the compounds and compositions of this application include: Donepezil (aricept), Galantamine (razadyne), or Rivastigmine (exelon).

[0175] In other embodiments of the invention, the $\alpha 5$ -containing GABA_A receptor positive allosteric modulator and the AChE-I, or their pharmaceutically acceptable salts,
10 hydrates, solvates, polymorphs, or prodrugs are administered simultaneously, or sequentially, or in a single formulation or in separate formulations packaged together. In other embodiments, the $\alpha 5$ -containing GABA_A receptor positive allosteric modulator and the AChE-I, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs are administered via different routes. As used herein, "combination" includes
15 administration by any of these formulations or routes of administration.

Methods of assessing cognitive impairment

[0176] Animal models serve as an important resource for developing and evaluating treatments for cognitive impairment associated with CNS disorders. Features that characterize cognitive impairment in animal models typically extend to cognitive
20 impairment in humans. Efficacy in such animal models is, thus, expected to be predictive of efficacy in humans. The extent of cognitive impairment in an animal model for a CNS disorder, and the efficacy of a method of treatment for said CNS disorder may be tested and confirmed with the use of a variety of cognitive tests.

[0177] A Radial Arm Maze (RAM) behavioral task is one example of a cognitive test,
25 specifically testing spacial memory (Chappell *et al. Neuropsychopharmacology* 37: 481-487, 1998). The RAM apparatus consists of, e.g., eight equidistantly spaced arms. A maze arm projects from each facet of a center platform. A food well is located at the distal end of each arm. Food is used as a reward. Blocks can be positioned to prevent entry to any arm. Numerous extra maze cues surrounding the apparatus may also be provided. After
30 habituation and training phases, spatial memory of the subjects may be tested in the RAM under control or test compound-treated conditions. As a part of the test, subjects are

pretreated before trials with a vehicle control or one of a range of dosages of the test compound. At the beginning of each trial, a subset of the arms of the eight-arm maze is blocked. Subjects are allowed to obtain food on the unblocked arms to which access is permitted during this initial "information phase" of the trial. Subjects are then removed
5 from the maze for a delay period, e.g., a 60 second delay, a 15 minute delay, a one-hour delay, a two-hour delay, a six hour delay, a 24 hour delay, or longer) between the information phase and the subsequent "retention test," during which the barriers on the maze are removed, thus allowing access to all eight arms. After the delay period, subjects are placed back onto the center platform (with the barriers to the previously blocked arms
10 removed) and allowed to obtain the remaining food rewards during this retention test phase of the trial. The identity and configuration of the blocked arms vary across trials. The number of "errors" the subjects make during the retention test phase is tracked. An error occurs in the trial if the subjects entered an arm from which food had already been retrieved in the pre-delay component of the trial, or if it re-visits an arm in the post-delay
15 session that had already been visited. A fewer number of errors would indicate better spatial memory. The number of errors made by the test subject, under various test compound treatment regimes, can then be compared for efficacy of the test compound in treating cognitive impairment associated with CNS disorders.

[0178] Another cognitive test that may be used to assess the effects of a test compound
20 on the cognitive impairment of a CNS disorder model animal is the Morris water maze. A water maze is a pool surrounded with a novel set of patterns relative to the maze. The training protocol for the water maze may be based on a modified water maze task that has been shown to be hippocampal-dependent (de Hoz *et al.*, *Eur. J. Neurosci.*, 22:745-54, 2005; Steele and Morris, *Hippocampus* 9:118-36, 1999). The subject is trained to locate a
25 submerged escape platform hidden underneath the surface of the pool. During the training trial, a subject is released in the maze (pool) from random starting positions around the perimeter of the pool. The starting position varies from trial to trial. If the subject does not locate the escape platform within a set time, the experimenter guides and places the subject on the platform to "teach" the location of the platform. After a delay
30 period following the last training trial, a retention test in the absence of the escape platform is given to assess spatial memory. The subject's level of preference for the location of the (now absent) escape platform, as measured by, e.g., the time spent in that location or the number of crossings of that location made by the mouse, indicates better

spatial memory, *i.e.*, treatment of cognitive impairment. The preference for the location of the escape platform under different treatment conditions, can then be compared for efficacy of the test compound in treating cognitive impairment associated with CNS disorders.

- [0179] There are various tests known in the art for assessing cognitive function in humans, for example and without limitation, the clinical global impression of change scale (CIBIC-plus scale); the Mini Mental State Exam (MMSE); the Neuropsychiatric Inventory (NPI); the Clinical Dementia Rating Scale (CDR); the Cambridge Neuropsychological Test Automated Battery (CANTAB); the Sandoz Clinical Assessment-Geriatric (SCAG), the Buschke Selective Reminding Test (Buschke and Fuld, 1974); the Verbal Paired Associates subtest; the Logical Memory subtest; the Visual Reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, D. (1997) Wechsler Adult Intelligence Scale. 3rd Edition, The Psychological Corporation, San Antonio); the Benton Visual Retention Test, or MATRICS consensus neuropsychological test battery which includes tests of working memory, speed of processing, attention, verbal learning, visual learning, reasoning and problem solving and social cognition. *See* Folstein et al., *J Psychiatric Res* 12: 189-98, (1975); Robbins et al., *Dementia* 5: 266-81, (1994); Rey, *L'examen clinique en psychologie*, (1964); Kluger et al., *J Geriatr Psychiatry Neurol* 12:168-79, (1999); Marquis et al., 2002 and Masur et al., 1994. Also see Buchanan, R.W., Keefe, R.S.E., Umbricht, D., Green, M.F., Laughren, T., and Marder, S.R. (2011) The FDA-NIMH-MATRICES guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? *Schizophr. Bull.* 37, 1209–1217. Another example of a cognitive test in humans is the explicit 3-alternative forced choice task. In this test, subjects are presented with color photographs of common objects consisting of a mix of three types of image pairs: similar pairs, identical pairs and unrelated foils. The second of the pair of similar objects is referred to as the "lure". These image pairs are fully randomized and presented individually as a series of images. Subjects are instructed to make a judgment as to whether the objects seen are new, old or similar. A "similar" response to the presentation of a lure stimulus indicates successful memory retrieval by the subject. By contrast, calling the lure stimulus "old" or "new" indicates that correct memory retrieval did not occur.
- [0180] In addition to assessing cognitive performance, the progression of age-related cognitive impairment and dementia, as well as the conversion of age-related cognitive

impairment into dementia, may be monitored by assessing surrogate changes in the brain of the subject. Surrogate changes include, without limitation, changes in regional brain volumes, perforant path degradation, and changes seen in brain function through resting state fMRI (R-fMRI) and fluorodeoxyglucose positron emission tomography (FDG-PET).

- 5 Examples of regional brain volumes useful in monitoring the progression of age-related cognitive impairment and dementia include reduction of hippocampal volume and reduction in volume or thickness of entorhinal cortex. These volumes may be measured in a subject by, for example, MRI. Aisen et al., *Alzheimer's & Dementia* 6:239-246 (2010). Perforant path degradation has been shown to be linked to age, as well as reduced
- 10 cognitive function. For example, older adults with more perforant path degradation tend to perform worse in hippocampus-dependent memory tests. Perforant path degradation may be monitored in subjects through ultrahigh-resolution diffusion tensor imaging (DTI). Yassa et al., *PNAS* 107:12687-12691 (2010). Resting-state fMRI (R-fMRI) involves imaging the brain during rest, and recording large-amplitude spontaneous low-
- 15 frequency (<0.1 Hz) fluctuations in the fMRI signal that are temporally correlated across functionally related areas. Seed-based functional connectivity, independent component analyses, and/or frequency-domain analyses of the signals are used to reveal functional connectivity between brain areas, particularly those areas whose connectivity increase or decrease with age, as well as the extent of cognitive impairment and/or dementia. FDG-
- 20 PET uses the uptake of FDG as a measure of regional metabolic activity in the brain. Decline of FDG uptake in regions such as the posterior cingulate cortex, temporoparietal cortex, and prefrontal association cortex has been shown to relate to the extent of cognitive decline and dementia. Aisen et al., *Alzheimer's & Dementia* 6:239-246 (2010), Herholz et al., *NeuroImage* 17:302-316 (2002).

25 **Age-Related Cognitive Impairment**

- [0181] The invention provides methods and compositions for treating age-related cognitive impairment or the risk thereof using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator (i.e., a compound of the invention), such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers,
- 30 or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression, of age-related cognitive impairment. In certain embodiments, treatment comprises alleviation, amelioration or slowing the

progression, of one or more symptoms associated with age-related cognitive impairment. In certain embodiments, treatment of age-related cognitive impairment comprises slowing the conversion of age-related cognitive impairment (including, but not limited to MCI, ARCD and AAMI) into dementia (*e.g.*, AD). The methods and compositions may be
5 used for human patients in clinical applications in the treating age-related cognitive impairment in conditions such as MCI, ARCD and AAMI or for the risk thereof. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications. In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with
10 age-related cognitive impairment, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

[0182] In some embodiments, a subject to be treated by the methods and compositions
15 of this invention exhibits age-related cognitive impairment or is at risk of such impairment. In some embodiments, the age-related cognitive impairment includes, without limitation, Age-Associated Memory Impairment (AAMI), Mild Cognitive Impairment (MCI) and Age-related Cognitive Decline (ARCD).

[0183] Animal models serve as an important resource for developing and evaluating
20 treatments for such age-related cognitive impairments. Features that characterize age-related cognitive impairment in animal models typically extend to age-related cognitive impairment in humans. Efficacy in such animal models is, thus, expected to be predictive of efficacy in humans.

[0184] Various animal models of age-related cognitive impairment are known in the art.
25 For example, extensive behavioral characterization has identified a naturally occurring form of cognitive impairment in an outbred strain of aged Long-Evans rats (Charles River Laboratories; Gallagher *et al.*, *Behav. Neurosci.* 107:618-626, (1993)). In a behavioral assessment with the Morris Water Maze (MWM), rats learn and remember the location of an escape platform guided by a configuration of spatial cues surrounding the maze. The
30 cognitive basis of performance is tested in probe trials using measures of the animal's spatial bias in searching for the location of the escape platform. Aged rats in the study

population have no difficulty swimming to a visible platform, but an age-dependent impairment is detected when the platform is camouflaged, requiring the use of spatial information. Performance for individual aged rats in the outbred Long-Evans strain varies greatly. For example, a proportion of those rats perform on a par with young adults. However, approximately 40-50% fall outside the range of young performance. This variability among aged rats reflects reliable individual differences. Thus, within the aged population some animals are cognitively impaired and designated aged-impaired (AI) and other animals are not impaired and are designated aged-unimpaired (AU). See, e.g., Colombo *et al.*, *Proc. Natl. Acad. Sci.* 94: 14195-14199, (1997); Gallagher and Burwell, *Neurobiol. Aging* 10: 691-708, (1989); Gallagher *et al.* *Behav. Neurosci.* 107:618-626, (1993); Rapp and Gallagher, *Proc. Natl. Acad. Sci.* 93: 9926-9930, (1996); Nicolle *et al.*, *Neuroscience* 74: 741-756, (1996); Nicolle *et al.*, *J. Neurosci.* 19: 9604-9610, (1999); International Patent Publication WO2007/019312 and International Patent Publication WO 2004/048551. Such an animal model of age-related cognitive impairment may be used to assay the effectiveness of the methods and compositions this invention in treating age-related cognitive impairment.

[0185] The efficacy of the methods and compositions of this invention in treating age-related cognitive impairment may be assessed using a variety of cognitive tests, including the Morris water maze and the radial arm maze, as discussed herein.

20 **Dementia**

[0186] The invention also provides methods and compositions for treating dementia using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression, of dementia. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with dementia. In certain embodiments, the symptom to be treated is cognitive impairment. In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with dementia, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically

acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof. In certain embodiments, the dementia is Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, or frontotemporal dementia. The methods and compositions may be used for human patients in clinical applications in treating dementia. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

[0187] Animal models serve as an important resource for developing and evaluating treatments for dementia. Features that characterize dementia in animal models typically extend to dementia in humans. Thus, efficacy in such animal models is expected to be predictive of efficacy in humans. Various animal models of dementia are known in the art, such as the PDAPP, Tg2576, APP23, TgCRND8, J20, hPS2 Tg, and APP + PS1 transgenic mice. Sankaranarayanan, *Curr. Top. Medicinal Chem.* 6: 609-627, 2006; Kobayashi et al. *Genes Brain Behav.* 4: 173-196. 2005; Ashe and Zahns, *Neuron*. 66: 631-45, 2010. Such animal models of dementia may be used to assay the effectiveness of the methods and compositions of this invention in treating dementia.

[0188] The efficacy of the methods and compositions of this invention in treating dementia, or cognitive impairment associated with dementia, may be assessed in animals models of dementia, as well as human subjects with dementia, using a variety of cognitive tests known in the art, as discussed herein.

Post Traumatic Stress Disorder

[0189] The invention also provides methods and compositions for treating post traumatic stress disorder (PTSD) using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression, of PTSD. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with PTSD. In certain embodiments, the symptom to be treated is cognitive impairment. In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with PTSD, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the

invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof. The methods and compositions may be used for human patients in clinical applications in treating PTSD. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those

5 applications.

[0190] Patients with PTSD (and, to a lesser degree trauma-exposed patients without PTSD) have smaller hippocampal volumes (Woon *et al.*, *Prog. Neuro-Psychopharm. & Biological Psych.* 34, 1181-1188; Wang *et al.*, *Arch. Gen. Psychiatry* 67:296-303, 2010). PTSD is also associated with impaired cognitive performance. Older individuals with

10 PTSD have greater declines in cognitive performance relative to control patients (Yehuda *et al.*, *Bio. Psych.* 60: 714-721, 2006) and have a greater likelihood of developing dementia (Yaffe *et al.*, *Arch. Gen. Psych.* 67: 608-613, 2010).

[0191] Animal models serve as an important resource for developing and evaluating treatments for PTSD. Features that characterize PTSD in animal models typically extend

15 to PTSD in humans. Thus, efficacy in such animal models is expected to be predictive of efficacy in humans. Various animal models of PTSD are known in the art.

[0192] One rat model of PTSD is Time-dependent sensitization (TDS). TDS involves exposure of the animal to a severely stressful event followed by a situational reminder of the prior stress. The following is an example of TDS. Rats are placed in a restrainer,

20 then placed in a swim tank and made to swim for a period of time, *e.g.*, 20 min. Following this, each rat is then immediately exposed to a gaseous anesthetic until loss of consciousness, and finally dried. The animals are left undisturbed for a number of days, *e.g.*, one week. The rats are then exposed to a “restress” session consisting of an initial stressor, *e.g.*, a swimming session in the swim tank (Liberzon *et al.*,

25 *Psychoneuroendocrinology* 22: 443-453, 1997; Harvery *et al.*, *Psychopharmacology* 175:494-502, 2004). TDS results in an enhancement of the acoustic startle response (ASR) in the rat, which is comparable to the exaggerated acoustic startle that is a prominent symptom of PTSD (Khan and Liberzon, *Psychopharmacology* 172: 225-229, 2004). Such animal models of PTSD may be used to assay the effectiveness of the

30 methods and compositions of this invention of the invention in treating PTSD.

[0193] The efficacy of the methods and compositions of this invention in treating PTSD, or cognitive impairment associated with PTSD, may also be assessed in animals models of PTSD, as well as human subjects with PTSD, using a variety of cognitive tests known in the art, as discussed herein.

5 **Schizophrenia and Bipolar Disorder**

[0194] The invention additionally provides methods and compositions for treating schizophrenia or bipolar disorder (in particular, mania) using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression of schizophrenia or bipolar disorder (in particular, mania). Schizophrenia is characterized by a wide spectrum of psychopathology, including positive symptoms such as aberrant or distorted mental representations (e.g., hallucinations, delusions), or dopamine dysregulation-associated symptoms (e.g., hyperdopaminergic responses, hyperdopaminergic behavioral responses, dopaminergic hyperactivity, or hyperlocomotor activity, or psychosis), negative symptoms characterized by diminution of motivation and adaptive goal-directed action (e.g., anhedonia, affective flattening, avolition), and cognitive impairment. In certain embodiments, treatment comprises alleviation, amelioration or slowing the progression of one or more positive and/or negative symptoms, as well as cognitive impairment, associated with schizophrenia. Further, there are a number of other psychiatric diseases such as schizotypal and schizoaffective disorder, other acute- and chronic psychoses and bipolar disorder (in particular, mania), which have an overlapping symptomatology with schizophrenia. In some embodiments, treatment comprises alleviation, amelioration or slowing the progression of one or more symptoms, as well as cognitive impairment, associated with bipolar disorder (in particular, mania). In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with schizophrenia or bipolar disorder, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof. The methods and compositions may be used for human patients in clinical applications in treating schizophrenia or bipolar disorder (in particular, mania).

The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

- [0195] Cognitive impairments are associated with schizophrenia. They precede the onset of psychosis and are present in non-affected relatives. The cognitive impairments associated with schizophrenia constitute a good predictor for functional outcome and are a core feature of the disorder. Cognitive features in schizophrenia reflect dysfunction in frontal cortical and hippocampal circuits. Patients with schizophrenia also present hippocampal pathologies such as reductions in hippocampal volume, reductions in neuronal size and dysfunctional hyperactivity. An imbalance in excitation and inhibition in these brain regions has also been documented in schizophrenic patients suggesting that drugs targeting inhibitory mechanisms could be therapeutic. *See, e.g., Guidotti et al., Psychopharmacology* 180: 191-205, 2005; Zierhut, *Psych. Res. Neuroimag.* 183:187-194, 2010; Wood *et al., NeuroImage* 52:62-63, 2010; Vinkers *et al., Expert Opin. Investig. Drugs* 19:1217-1233, 2009; Young *et al., Pharmacol. Ther.* 122:150-202, 2009.
- [0196] Animal models serve as an important resource for developing and evaluating treatments for schizophrenia. Features that characterize schizophrenia in animal models typically extend to schizophrenia in humans. Thus, efficacy in such animal models is expected to be predictive of efficacy in humans. Various animal models of schizophrenia are known in the art.
- [0197] One animal model of schizophrenia is protracted treatment with methionine. Methionine-treated mice exhibit deficient expression of GAD67 in frontal cortex and hippocampus, similar to those reported in the brain of postmortem schizophrenia patients. They also exhibit prepulse inhibition of startle and social interaction deficits (Tremonlizzo *et al., PNAS*, 99: 17095–17100, 2002). Another animal model of schizophrenia is methylaloxymethanol acetate (MAM)-treatment in rats. Pregnant female rats are administered MAM (20 mg/kg, intraperitoneal) on gestational day 17. MAM-treatment recapitulate a pathodevelopmental process to schizophrenia-like phenotypes in the offspring, including anatomical changes, behavioral deficits and altered neuronal information processing. More specifically, MAM-treated rats display a decreased density of parvalbumin-positive GABAergic interneurons in portions of the prefrontal cortex and hippocampus. In behavioral tests, MAM-treated rats display reduced latent inhibition.

Latent inhibition is a behavioral phenomenon where there is reduced learning about a stimulus to which there has been prior exposure with any consequence. This tendency to disregard previously benign stimuli, and reduce the formation of association with such stimuli is believed to prevent sensory overload. Low latent inhibition is indicative of psychosis. Latent inhibition may be tested in rats in the following manner. Rats are divided into two groups. One group is pre-exposed to a tone over multiple trials. The other group has no tone presentation. Both groups are then exposed to an auditory fear conditioning procedure, in which the same tone is presented concurrently with a noxious stimulus, e.g. an electric shock to the foot. Subsequently, both groups are presented with the tone, and the rats' change in locomotor activity during tone presentation is monitored. After the fear conditioning the rats respond to the tone presentation by strongly reducing locomotor activity. However, the group that has been exposed to the tone before the conditioning period displays robust latent inhibition: the suppression of locomotor activity in response to tone presentation is reduced. MAM-treated rats, by contrast show impaired latent inhibition. That is, exposure to the tone previous to the fear conditioning procedure has no significant effect in suppressing the fear conditioning. (see Lodge *et al.*, J. Neurosci., 29:2344-2354, 2009) Such animal models of schizophrenia may be used to assay the effectiveness of the methods and compositions of the invention in treating schizophrenia or bipolar disorder (in particular, mania).

[0198] MAM-treated rats display a significantly enhanced locomotor response (or aberrant locomotor activity) to low dose D-amphetamine administration. The MAM-treated rats also display a significantly greater number of spontaneously firing ventral tegmental dopamine (DA) neurons. These results are believed to be a consequence of excessive hippocampal activity because in MAM-treated rats, the ventral hippocampus (vHipp) inactivation (e.g., by intra-vHipp administration of a sodium channel blocker, tetrodotoxin (TTX), to MAM rats) completely reversed the elevated DA neuron population activity and also normalized the augmented amphetamine-induced locomotor behavior. The correlation of hippocampal dysfunction and the hyper-responsivity of the DA system is believed to underlie the augmented response to amphetamine in MAM-treated animals and psychosis in schizophrenia patients. See Lodge D. J. *et al.* *Neurobiology of Disease* (2007), 27(42), 11424-11430. The use of MAM-treated rats in the above study may be suitable for use to assay the effectiveness of the methods and compositions of the present invention in treating schizophrenia or bipolar disorder (in

particular, mania). For example, the methods and compositions of this invention may be evaluated, using MAM-treated animals, for their effects on the central hippocampus (vHipp) regulation, on the elevated DA neuron population activity and on the hyperactive locomotor response to amphetamine in the MAM-treated animals.

5 [0199] In MAM-treated rats, hippocampal (HPC) dysfunction leads to dopamine system hyperactivity. A benzodiazepine-positive allosteric modulator (PAM), selective for the $\alpha 5$ subunit of the GABA_A receptor, SH-053-2'F-R-CH₃, is tested for its effects on the output of the hippocampal (HPC). The effect of SH-053-2'F-R-CH₃ on the hyperactive locomotor response to amphetamine in MAM-treated animals is also examined. The
10 $\alpha 5$ GABAAR PAM reduces the number of spontaneously active DA neurons in the ventral tegmental area (VTA) of MAM rats to levels observed in saline-treated rats (control group), both when administered systemically and when directly infused into the ventral HPC. Moreover, HPC neurons in both saline-treated and MAM-treated animals show diminished cortical-evoked responses following the $\alpha 5$ GABAAR PAM treatment. In
15 addition, the increased locomotor response to amphetamine observed in MAM-treated rats is reduced following the $\alpha 5$ GABA_AR PAM treatment. See Gill K. M et al. *Neuropsychopharmacology* (2011), 1-9. The use of MAM-treated rats in the above study may be suitable for use in the present invention to assay the effectiveness of the methods and compositions of the invention in treating schizophrenia or bipolar disorder (in
20 particular, mania). For example, the methods and compositions of this invention may be evaluated, using MAM-treated animals, for their effects on the output of the hippocampal (HPC) and on the hyperactive locomotor response to amphetamine in the MAM-treated animals.

[0200] Administration of MAM to pregnant rats on embryonic day 15 (E15) severely
25 impairs spatial memory or the ability to learn the spatial location of four items on an eight-arm radial maze in the offspring. In addition, embryonic day 17 (E17) MAM-treated rats are able to reach the level of performance of control rats at the initial stages of training, but are unable to process and retrieve spatial information when a 30-min delay is interposed, indicating a significant impairment in working memory. See Gourevitch R. et al. (2004). *Behav. Pharmacol*, 15, 287-292. Such animal models of schizophrenia may be
30 used to assay the effectiveness of the methods and compositions of the invention in treating schizophrenia or bipolar disorder (in particular, mania).

[0201] Apomorphine-induced climbing (AIC) and stereotype (AIS) in mice is another animal model useful in this invention. Agents are administered to mice at a desired dose level (e.g., via intraperitoneal administration). Subsequently, e.g., thirty minutes later, experimental mice are challenges with apomorphine (e.g., with 1 mg/kg sc). Five minutes after the apomorphine injection, the sniffing-licking-gnawing syndrome (stereotyped behavior) and climbing behavior induced by apomorphine are scored and recorded for each animal. Readings can be repeated every 5 min during a 30-min test session. Scores for each animal are totaled over the 30-min test session for each syndrome (stereotyped behavior and climbing). If an effect reached at least of 50% inhibition, and ID₅₀ value (95% confidence interval) is calculated using a nonlinear least squares calculation with inverse prediction. Mean climbing and stereotype scores can be expressed as a percent of control values observed in vehicle treated (e.g., saline-treated) mice that receive apomorphine. See Grauer S. M. et al. *Psychopharmacology* (2009) 204, 37-48. This mouse model may be used to assay the effectiveness of the methods and compositions of the invention in treating schizophrenia or bipolar disorder (in particular, mania).

[0202] In another well-established preclinical model of schizophrenia, rats exposed chronically to ketamine, an uncompetitive *N-methyl-D-aspartate* (NMDA) receptor antagonist, produces positive and negative psychotic symptoms and cognitive impairment. Long-Evans male rats are injected intraperitoneally with ketamine (30 mg/kg, twice a day) for two weeks during adolescence (2 month-old). Rats are behaviorally tested when they reach adulthood (approximately 4-5 month-old) for the behavioral symptoms to ketamine exposure and for the efficacy of treatment to alleviate those symptoms. See, e.g., Enomoto et al. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 33 (2009) 668-675.

[0203] The efficacy of the methods and compositions of this invention in treating schizophrenia or cognitive impairment associated therewith may also be assessed in animal models of schizophrenia or bipolar disorder (in particular, mania), as well as human subjects with schizophrenia, using a variety of cognitive tests known in the art, as discussed herein.

Amyotrophic Lateral Sclerosis (ALS)

[0204] The invention additionally provides methods and compositions for treating ALS using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain
5 embodiments, treatment comprises preventing or slowing the progression, of ALS. In certain embodiments, treatment comprises alleviation, amelioration or slowing the progression, of one or more symptoms associated with ALS. In certain embodiments, the symptom to be treated is cognitive impairment. In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with
10 ALS, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof. The methods and compositions may be used for human patients in clinical applications in treating ALS. The dose of the composition and dosage interval for the method is, as described herein,
15 one that is safe and efficacious in those applications.

[0205] In addition to the degeneration of motor neurons, ALS is characterized by neuronal degeneration in the entorhinal cortex and hippocampus, memory deficits, and neuronal hyperexcitability in different brain areas such as the cortex.

[0206] The efficacy of the methods and compositions of this invention in treating ALS,
20 or cognitive impairment associated with ALS, may also be assessed in animal models of ALS, as well as human subjects with ALS, using a variety of cognitive tests known in the art, as discussed herein.

Cancer therapy-related cognitive impairment

[0207] The invention additionally provides methods and compositions for treating
25 cancer therapy-related cognitive impairment using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression, of cancer therapy-related cognitive impairment. In
30 certain embodiments, treatment comprises alleviation, amelioration or slowing the progression, of one or more symptoms associated with cancer therapy-related cognitive

impairment. In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with cancer therapy-related cognitive impairment, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof. The methods and compositions may be used for human patients in clinical applications in treating cancer therapy-related cognitive impairment. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

- 10 [0208] Therapies that are used in cancer treatment, including chemotherapy, radiation, or combinations thereof, can cause cognitive impairment in patients, in such functions as memory, learning and attention. Cytotoxicity and other adverse side-effects on the brain of cancer therapies are the basis for this form of cognitive impairment, which can persist for decades. (Dietrich *et al.*, *Oncologist* 13:1285-95, 2008; Soussain *et al.*, *Lancet* 15 374:1639-51, 2009).

- [0209] Cognitive impairment following cancer therapies reflects dysfunction in frontal cortical and hippocampal circuits that are essential for normal cognition. In animal models, exposure to either chemotherapy or radiation adversely affects performance on tests of cognition specifically dependent on these brain systems, especially the hippocampus (Kim *et al.*, *J. Radiat. Res.* 49:517-526, 2008; Yang *et al.*, *Neurobiol. Learning and Mem.* 93:487-494, 2010). Thus, drugs targeting these cortical and hippocampal systems could be neuroprotective in patients receiving cancer therapies and efficacious in treating symptoms of cognitive impairment that may last beyond the interventions used as cancer therapies.

- 25 [0210] Animal models serve as an important resource for developing and evaluating treatments for cancer therapy-related cognitive impairment. Features that characterize cancer therapy-related cognitive impairment in animal models typically extend to cancer therapy-related cognitive impairment in humans. Thus, efficacy in such animal models is expected to be predictive of efficacy in humans. Various animal models of cancer 30 therapy-related cognitive impairment are known in the art.

[0211] Examples of animal models of cancer therapy-related cognitive impairment include treating animals with anti-neoplastic agents such as cyclophosphamide (CYP) or with radiation, e.g., ^{60}Co gamma-rays. (Kim *et al.*, *J. Radiat. Res.* 49:517-526, 2008; Yang *et al.*, *Neurobiol. Learning and Mem.* 93:487-494, 2010). The cognitive function of animal models of cancer therapy-related cognitive impairment may then be tested with cognitive tests to assay the effectiveness of the methods and compositions of the invention in treating cancer therapy-related cognitive impairment. The efficacy of the methods and compositions of this invention in treating cancer therapy-related cognitive impairment, as well as human subjects with cancer therapy-related cognitive impairment, using a variety of cognitive tests known in the art, as discussed herein.

Parkinson's disease (PD)

[0212] Parkinson's disease (PD) is a neurological disorder characterized by a decrease of voluntary movements. The afflicted patient has reduction of motor activity and slower voluntary movements compared to the normal individual. The patient has characteristic "mask" face, a tendency to hurry while walking, bent over posture and generalized weakness of the muscles. There is a typical "lead-pipe" rigidity of passive movements. Another important feature of the disease is the tremor of the extremities occurring at rest and decreasing during movements.

[0213] Parkinson's disease, the etiology of which is unknown, belongs to a group of the most common movement disorders named parkinsonism, which affects approximately one person per one thousand. These other disorders grouped under the name of parkinsonism may result from viral infection, syphilis, arteriosclerosis and trauma and exposure to toxic chemicals and narcotics. Nonetheless, it is believed that the inappropriate loss of synaptic stability may lead to the disruption of neuronal circuits and to brain diseases. Whether as the result of genetics, drug use, the aging process, viral infections, or other various causes, dysfunction in neuronal communication is considered the underlying cause for many neurologic diseases, such as PD (Myrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* 2010, 10, 207-214).

[0214] Regardless of the cause of the disease, the main pathologic feature is degeneration of dopaminergic cells in basal ganglia, especially in substantia nigra. Due to premature death of the dopamine containing neurons in substantia nigra, the largest structure of the basal ganglia, the striatum, will have reduced input from substantia nigra

resulting in decreased dopamine release. The understanding of the underlying pathology led to the introduction of the first successful treatment which can alleviate Parkinson's disease. Virtually all approaches to the therapy of the disease are based on dopamine replacement. Drugs currently used in the treatment can be converted into dopamine after crossing the blood brain barrier, or they can boost the synthesis of dopamine and reduce its breakdown. Unfortunately, the main pathologic event, degeneration of the cells in substantia nigra, is not helped. The disease continues to progress and frequently after a certain length of time, dopamine replacement treatment will lose its effectiveness.

[0215] The invention provides methods and compositions for treating PD using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression of PD. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with PD. In certain embodiments, the symptom to be treated is cognitive impairment. For example, methods and compositions of the disclosure can be used to improve the motor/cognitive impairments symptomatic of Parkinson's disease. Moreover, methods and compositions of the disclosure may be useful for treating the memory impairment symptomatic of Parkinson's disease. In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with PD, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

[0216] There are a number of animal models for PD. Exemplary animal models for PD include the reserpine model, the methamphetamine model, the 6-hydroxydopamine (6-OHDA) model, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model, the paraquat (PQ)-Maneb model, the rotenone model, the 3-nitrotyrosine model and genetic models using transgenic mice. Transgenic models include mice that over express α -synuclein, express human mutant forms of α -synuclein, or mice that express LRKK2 mutations. See review of these models by Ranjita B. et al. (Ranjita B. et al. *BioEssays* 2002, 24, 308-318). Additional information regarding these animal models is readily available from Jackson Laboratories, as well as in numerous publications disclosing the use of these validated models.

[0217] The efficacy of the methods and compositions of this invention in treating PD, or cognitive impairment associated with PD, may be assessed in any of the above animal models of PD, as well as human subjects with PD, using a variety of cognitive tests known in the art, as discussed herein.

5 Autism

[0218] Autism is a neurodevelopmental disorder characterized by dysfunction in three core behavioral dimensions: repetitive behaviors, social deficits, and cognitive deficits. The repetitive behavior domain involves compulsive behaviors, unusual attachments to objects, rigid adherence to routines or rituals, and repetitive motor mannerisms such as stereotypies and self- stimulatory behaviors. The social deficit dimension involves deficits in reciprocal social interactions, lack of eye contact, diminished ability to carry on conversation, and impaired daily interaction skills. The cognitive deficits can include language abnormalities. Autism is a disabling neurological disorder that affects thousands of Americans and encompasses a number of subtypes, with various putative causes and few documented ameliorative treatments. The disorders of the autistic spectrum may be present at birth, or may have later onset, for example, at ages two or three. There are no clear cut biological markers for autism. Diagnosis of the disorder is made by considering the degree to which the child matches the behavioral syndrome, which is characterized by poor communicative abilities, peculiarities in social and cognitive capacities, and maladaptive behavioral patterns. The dysfunction in neuronal communication is considered one of the underlying causes for autism (Myrre van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* **2010**, 10, 207-214). Recent studies have shown that there is a GABA_A $\alpha 5$ deficit in autism spectrum disorder (ASD) and support further investigations of the GABA system in this disorder (Mendez MA, et al. *Neuropharmacology*. **2013**, 68:195-201).

[0219] The invention also provides methods and compositions for treating autism using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression of autism. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with autism. In certain embodiments, the symptom to be treated is

cognitive impairment or cognitive deficit. For example, methods and compositions of the disclosure can be used to improve the motor/cognitive deficits symptomatic of autism.

In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with autism, the method comprising the step of
5 administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

[0220] The valproic acid (VPA) rat model of autism using in vitro electrophysiological techniques, established by Rodier et al. (Rodier, P. M. et al. *Reprod. Toxicol.* **1997**, 11,

10 417-422) is one of the most exhaustively established insult-based animal models of autism and is based on the observation that pregnant women treated with VPA in the 1960s, during a circumscribed time window of embryogenesis, had a much higher risk of giving birth to an autistic child than the normal population. Offspring of VPA-exposed pregnant rats show several anatomical and behavioral symptoms typical of autism, such

15 as diminished number of cerebellar Purkinje neurons, impaired social interaction, repetitive behaviors as well as other symptoms of autism, including enhanced fear memory processing. See, Rinaldi T. et al. *Frontiers in Neural Circuits*, **2008**, 2, 1-7.

Another mouse model, BTBR T+tf/J (BTBR) mice, an established model with robust behavioral phenotypes relevant to the three diagnostic behavioral symptoms of autism--
20 unusual social interactions, impaired communication, and repetitive behaviors—was used to probe the efficacy of a selective negative allosteric modulator of the mGluR5 receptor, GRN-529. See, e.g., Silverman J. L. et al. *Sci Transl. Med.* **2012**, 4, 131. The efficacy of the methods and compositions of this invention in treating autism, or cognitive deficits associated with autism, may be assessed in the VPA-treated rat model of autism or the

25 BTBR T+tf/J (BTBR) mouse model, as well as human subjects with autism, using a variety of cognitive tests known in the art, as discussed herein.

Mental retardation

[0221] Mental retardation is a generalized disorder characterized by significantly impaired cognitive function and deficits in adaptive behaviors. Mental retardation is often
30 defined as an Intelligence Quotient (IQ) score of less than 70. Inborn causes are among many underlying causes for mental retardation. The dysfunction in neuronal communication is also considered one of the underlying causes for mental retardation

(Myrrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* **2010**, 10, 207-214).

[0222] In some instances, mental retardation includes, but are not limited to, Down syndrome, velocariofacial syndrome, fetal alcohol syndrome, Fragile X syndrome, Klinefelter's syndrome, neurofibromatosis, congenital hypothyroidism, Williams syndrome, phenylketonuria (PKU), Smith-Lemli-Opitz syndrome, Prader-Willi syndrome, Phelan-McDermid syndrome, Mowat-Wilson syndrome, ciliopathy, Lowe syndrome and siderium type X-linked mental retardation. Down syndrome is a disorder that includes a combination of birth defects, including some degree of mental retardation, characteristic facial features and, often, heart defects, increased infections, problems with vision and hearing, and other health problems. Fragile X syndrome is a prevalent form of inherited mental retardation, occurring with a frequency of 1 in 4,000 males and 1 in 8,000 females. The syndrome is also characterized by developmental delay, hyperactivity, attention deficit disorder, and autistic-like behavior. There is no effective treatment for fragile X syndrome.

[0223] The present invention contemplates the treatment of mild mental retardation, moderate mental retardation, severe mental retardation, profound mental retardation, and mental retardation severity unspecified. Such mental retardation may be, but is not required to be, associated with chromosomal changes, (for example Down Syndrome due to trisomy 21), heredity, pregnancy and perinatal problems, and other severe mental disorders. This invention provides methods and compositions for treating mental retardation using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression of mental retardation. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with mental retardation. In certain embodiments, the symptom to be treated is cognitive deficit/impairment. For example, methods and compositions of the disclosure can be used to improve the motor/cognitive impairments symptomatic of mental retardation. In some embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with mental retardation, the method comprising the step of administering to

said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

[0224] Several animal models have been developed for mental retardation. For example, a knockout mouse model has been developed for Fragile X syndrome. Fragile X syndrome is a common form of mental retardation caused by the absence of the FMR1 protein, FMRP. Two homologs of FMRP have been identified, FXR1P and FXR2P. FXR2P shows high expression in brain and testis, like FMRP. Both *Fxr2* and *Fmr1* knockout mice, and *Fmr1/Fxr2* double knockout mice are believed to be useful models for mental retardation such as Fragile X syndrome. See, Bontekoe C. J. M. et al. *Hum. Mol. Genet.* 2002, 11 (5): 487-498. The efficacy of the methods and compositions of this invention in treating mental retardation, or cognitive deficit/impairment associated with mental retardation, may be assessed in the these mouse models and other animal models developed for mental retardation, as well as human subjects with mental retardation, using a variety of cognitive tests known in the art, as discussed herein.

Compulsive behavior (obsessive-compulsive disorder)

[0225] Obsessive compulsive disorder ("OCD") is a mental condition that is most commonly characterized by intrusive, repetitive unwanted thoughts (obsessions) resulting in compulsive behaviors and mental acts that an individual feels driven to perform (compulsion). Current epidemiological data indicates that OCD is the fourth most common mental disorder in the United States. Some studies suggest the prevalence of OCD is between one and three percent, although the prevalence of clinically recognized OCD is much lower, suggesting that many individuals with the disorder may not be diagnosed. Patients with OCD are often diagnosed by a psychologist, psychiatrist, or psychoanalyst according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR) (2000) diagnostic criteria that include characteristics of obsessions and compulsions. Characteristics of obsession include: (1) recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and that cause marked anxiety or distress; (2) the thoughts, impulses, or images are not simply excessive worries about real-life problems; and (3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action. The person recognizes that the obsessional thoughts, impulses, or

images are a product of his or her own mind, and are not based in reality. Characteristics of compulsion include: (1) repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly; (2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts are not actually connected to the issue, or they are excessive.

[0226] Individuals with OCD typically perform tasks (or compulsion) to seek relief from obsession-related anxiety. Repetitive behaviors such as handwashing, counting, checking, or cleaning are often performed with the hope of preventing obsessive thoughts or making them go away. Performing these "rituals," however, only provides temporary relief. People with OCD may also be diagnosed with a spectrum of other mental disorders, such as generalized anxiety disorder, anorexia nervosa, panic attack, or schizophrenia.

[0227] The dysfunction in neuronal communication is considered one of the underlying causes for obsession disorder (Myrrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* **2010**, 10, 207-214). Studies suggest that OCD may be related to abnormal levels of a neurotransmitter called serotonin. The first-line treatment of OCD consists of behavioral therapy, cognitive therapy, and medications. Medications for treatment include serotonin reuptake inhibitors (SRIs) such as paroxetine (Seroxat™, Paxil®, Xetanor™, ParoMerck™, Rexetin™), sertraline (Zoloft®, Stimuloton™), fluoxetine (Prozac®, Bioxetin™), escitalopram (Lexapro®), and fluvoxamine (Luvox®) as well as the tricyclic antidepressants, in particular clomipramine (Anafranil®). Benzodiazepines are also used in treatment. As much as 40 to 60% of the patients, however, fail to adequately respond to the SRI therapy and an even greater proportion of patients fail to experience complete remission of their symptoms.

[0228] The invention provides methods and compositions for treating OCD using a $\alpha 5$ -containing GABA_A receptor agonist (e.g., a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator), such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression of OCD. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with OCD.

In certain embodiments, the symptom to be treated is cognitive impairment or cognitive deficit. For example, methods and compositions of the disclosure can be used to treat the cognitive deficits in OCD, and/or to improve cognitive function in patients with OCD. In some embodiments of the invention, there is provided a method of preserving or
5 improving cognitive function in a subject with OCD, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

[0229] A quinpirole-sensitized rat model has been developed for OCD. The compulsive
10 checking behavior of the quinpirole-sensitized rats is subject to interruption, which is an attribute characteristic of OCD compulsions. In addition, a schedule-induced polydipsia (SIP) rodent model of obsessive-compulsive disorder was used to evaluate the effects of the novel 5-HT_{2C} receptor agonist WAY-163909. *See, e.g.,* Rosenzweig-Lipson S. et al. *Psychopharmacology (Berl)* **2007**, 192, 159-70. The efficacy of the methods and
15 compositions of this invention in treating OCD, or cognitive impairment or cognitive deficits associated with OCD, may be assessed in the above animal models and other animal models developed for OCD, as well as human subjects with OCD, using a variety of cognitive tests known in the art, as discussed herein.

Substance addiction

[0230] Substance addiction (*e.g.*, drug substance addiction, alcohol substance addiction)
20 is a mental disorder. The substance addiction is not triggered instantaneously upon exposure to substance of abuse. Rather, it involves multiple, complex neural adaptations that develop with different time courses ranging from hours to days to months (Kauer J. A. *Nat. Rev. Neurosci.* **2007**, 8, 844-858). The path to substance addiction generally
25 begins with the voluntary use of one or more controlled substances, such as narcotics, barbiturates, methamphetamines, alcohol, nicotine, and any of a variety of other such controlled substances. Over time, with extended use of the controlled substance(s), the voluntary ability to abstain from the controlled substance(s) is compromised due to the effects of prolonged use on brain function, and thus on behavior. As such, substance
30 addiction generally is characterized by compulsive substance craving, seeking and use that persist even in the face of negative consequences. The cravings may represent changes in the underlying neurobiology of the patient which likely must be addressed in a

meaningful way if recovery is to be obtained. Substance addiction is also characterized in many cases by withdrawal symptoms, which for some substances are life threatening (e.g., alcohol, barbiturates) and in others can result in substantial morbidity (which may include nausea, vomiting, fever, dizziness, and profuse sweating), distress, and decreased ability to obtain recovery. For example, alcoholism, also known as alcohol dependence, is one such substance addiction. Alcoholism is primarily characterized by four symptoms, which include cravings, loss of control, physical dependence and tolerance. These symptoms also may characterize substance addictions to other controlled substances. The craving for alcohol, as well as other controlled substances, often is as strong as the need for food or water. Thus, an alcoholic may continue to drink despite serious family, health and/or legal ramifications.

[0231] Recent work exploring the effects of abusing alcohol, central stimulants, and opiates on the central nervous system (CNS) have demonstrated a variety of adverse effects related to mental health, including substance-induced impairments in cognition. See, Nyberg F. *Cognitive Impairments in Drug Addicts*, Chapter 9. In several laboratories and clinics substantial damages of brain function are seen to result from these drugs. Among the harmful effects of the abusing drugs on brain are those contributing to accelerated obsolescence. An observation that has received special attention during recent years is that chronic drug users display pronounced impairment in brain areas associated with executive and memory function. A remarked neuroadaptation caused by addictive drugs, such as alcohol, central stimulants and opiates involves diminished neurogenesis in the subgranular zone (SGZ) of the hippocampus. Indeed, it has been proposed that decreased adult neurogenesis in the SGZ could modify the hippocampal function in such a way that it contributes to relapse and a maintained addictive behavior. It also raises the possibility that decreased neurogenesis may contribute to cognitive deficits elicited by these abusing drugs.

[0232] The invention provides methods and compositions for treating substance addiction using a $\alpha 5$ -containing GABA_A receptor positive allosteric modulator, such as one selected from the compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, isomers, or combinations thereof as described herein. In certain embodiments, treatment comprises preventing or slowing the progression of substance addiction. In certain embodiments, treatment comprises alleviation, amelioration, or

slowing the progression of one or more symptoms associated with substance addiction. In certain embodiments, the symptom to be treated is cognitive impairment. For example, methods and compositions of the disclosure can be used to treat the cognitive impairment and/or to improve cognitive function in patients with substance addiction. In some

5 embodiments of the invention, there is provided a method of preserving or improving cognitive function in a subject with substance addiction, the method comprising the step of administering to said subject a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

- 10 [0233] Several animal models have been developed to study substance addiction. For example, a genetically selected Marchigian Sardinian alcohol-preferring (msP) rat models was developed to study the neurobiology of alcoholism. See, Ciccocioppo R. et al. *Substance addiction Biology* 2006, 11, 339-355. The efficacy of the methods and compositions of this invention in treating substance addiction, or cognitive impairment
- 15 associated with substance addiction, may also be assessed in animal models of substance addiction, as well as human subjects with substance addiction, using a variety of cognitive tests known in the art, as discussed herein.

Research Domain Criteria (RDoC)

- [0234] The invention further provides methods and compositions for treating
- 20 impairment in neurological disorders and neuropsychiatric conditions using a $\alpha 5$ -containing GABA_A R positive allosteric modulator or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof as described herein. In certain embodiments, treatment comprises alleviation, amelioration or slowing the progression, of one or more symptoms associated with such impairment. In another
- 25 aspect of the invention, there is provided methods and compositions for preserving or improving cognitive function in a subject in need thereof using a compound of the invention or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, isomer, or combination thereof.

- [0235] Research Domain Criteria (RDoC) are expected to augment clinical criteria,
- 30 such as DSM and ICD, for diagnosis of disease and disorders affecting the nervous

system (*see, e.g., Am. J. Psychiatry* 167:7 (2010)). The RDoC is intended to provide classification based on discoveries in genomics and neuroscience as well as clinical observation. The high expression of $\alpha 5$ -containing GABA_A receptors in specific neural circuits in the nervous system could be therapeutic targets for neural circuit dysfunction identified under RDoC.

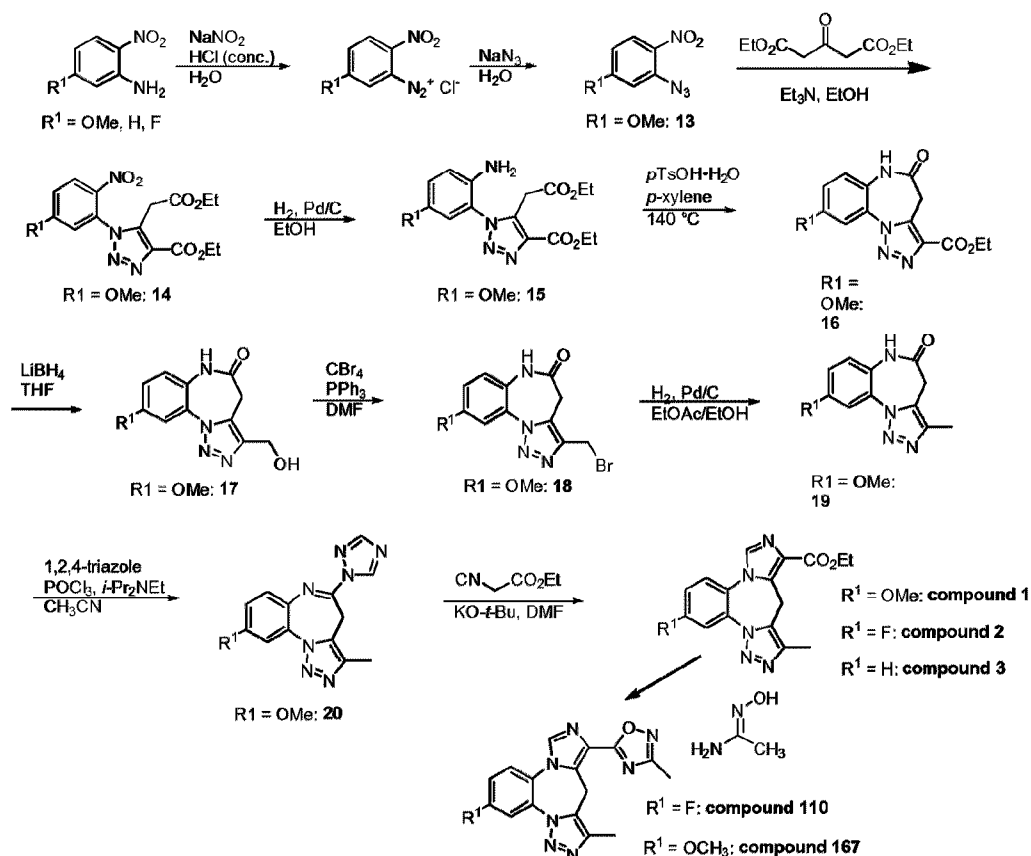
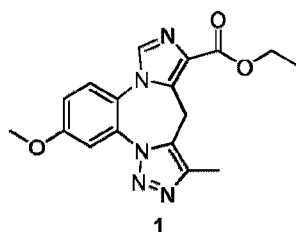
Assays for GABA_A $\alpha 5$ subunit binding and receptor positive allosteric modulator activity

[0236] The affinity of test compounds for a GABA_A receptor comprising the GABA_A $\alpha 5$ subunit may be determined using receptor binding assays that are known in the art. *See, e.g.,* U.S. Patent 7,642,267 and U.S. Patent 6,743,789.

[0237] The activity of the test compounds as a $\alpha 5$ -containing GABA_A R positive allosteric modulator may be tested by electrophysiological methods known in the art. *See, e.g.,* U.S. Patent 7,642,267 and Guidotti *et al.*, *Psychopharmacology* 180: 191-205, 2005. Positive allosteric modulator activity may be tested, for examples, by assaying GABA-induced chloride ion conductance of GABA_A receptors comprising the GABA_A $\alpha 5$ subunit. Cells expressing such receptors may be exposed to an effective amount of a compound of the invention. Such cells may be contacted *in vivo* with compounds of the invention through contact with a body fluid containing the compound, for example through contact with cerebrospinal fluid. *In vitro* tests may be done by contacting cells with a compound of the invention in the presence of GABA. Increased GABA-induced chloride conductance in cells expressing GABA_A receptors comprising the GABA_A $\alpha 5$ subunit in the presence of the test compound would indicate positive allosteric modulator activity of said compound. Such changes in conductance may be detected by, *e.g.,* using a voltage-clamp assay performed on *Xenopus* oocytes injected with GABA_A receptor subunit mRNA (including GABA_A $\alpha 5$ subunit RNA), HEK 293 cells transfected with plasmids encoding GABA_A receptor subunits, or *in vivo, ex vivo*, or cultured neurons.

[0238] It will be understood by one of ordinary skill in the art that the methods described herein may be adapted and modified as is appropriate for the application being addressed and that the methods described herein may be employed in other suitable applications, and that such other additions and modifications will not depart from the scope hereof.

5 Example 1: Synthesis of Compound 1



was used in the next step. To the diazonium salt in a crystallization dish under fast stirring at room temperature was added drop wise a solution of NaN₃ (1.93 g, 29.6 mmol) in H₂O (7 mL). After gas evolution stopped (3 h), it was filtered. The collected solid was re-crystallized from MeOH to give 4.342 g (yield 75% for 2 steps) of the product **13** as a yellow solid. To a mixture of the phenylazide **13** (1.94 g, 10 mmol) and diethyl 1,3-acetone-diacrylate (2.20 mL, 12 mmol) in EtOH (40 mL) at room temperature was added Et₃N (1.67 mL, 12 mmol). After the mixture was stirred at room temperature for 60 h, the initial suspension turned into a clear yellow solution. The solution was concentrated under vacuum and the residue was purified by chromatography (*RediSep* 24 g silica-gel column, 10% to 40% EtOAc in hexanes) to give 2.905 g of triazole **14** as a yellow solid. MS: [M+1] = 379.

[0241] The above triazole **14** (2.95 g, 7.66 mmol) in EtOH (50 mL) with Pd/C (10 wt%, 407 mg, 0.38 mmol) was stirred under H₂ (balloon) for 24 h. It was filtered through Celite™. The filtrate was concentrated and the residue was purified by chromatography (*RediSep* 24 g silica-gel column, 10% to 50% EtOAc in hexanes) to give 2.453 g of aniline **15** as a white solid. (70% yield for two steps.) MS: [M+1] = 349.

[0242] Compound **15** (2.45 g, 7.03 mmol) and catalytic amount of *p*-TsOH•H₂O (24 mg) in *p*-xylene (30 mL) were heated in a 140°C oil bath overnight. The mixture was cooled and filtered. The solid was washed with cold EtOAc. After drying, it gave 1.88 g (88% yield) of the lactam **16**. MS: [M+1] = 303.

[0243] To a suspension of the lactam ester **16** (837 mg, 2.77 mmol) in THF (20 mL) at room temperature was added LiBH₄ (2 M in THF, 1.39 mL, 2.78 mmol). After the mixture was stirred at room temperature for 60 h, more LiBH₄ (2 M in THF, 0.28 mL, 0.56 mmol) was added and it was stirred at room temperature for 24 additional h. A mixture of EtOAc/EtOH (10 mL/10 mL) was added to the reaction and it was concentrated in vacuo. The residue was taken up in EtOAc/CH₂Cl₂/MeOH and loose silica gel was added. After volatile solvents were evaporated, the solid was loaded onto a *RediSep* 24 g silica-gel column. Chromatography (solvent A: EtOAc, solvent B: 10:1 v/v CH₂Cl₂/MeOH; gradient eluent: A to B) gave 540 mg (75% yield) of the alcohol **17** as white solid. MS: [M+1] = 261.

[0244] To a solution of the alcohol **17** (105.4 mg, 0.40 mmol) and CBr₄ (336 mg, 1.01 mmol) in DMF (3 mL) was slowly added a solution of PPh₃ (255 mg, 0.97 mmol) in DMF (1 mL) over 20 min. After addition, TLC showed the reaction went completion. Water was added to quench the reaction and the mixture was extracted with EtOAc thrice.

5 The combined extracts were washed sequentially with H₂O, brine and dried over Na₂SO₄. Filtration and concentration gave the crude product. Chromatography (*RediSep* 12 g silica-gel column, CH₂Cl₂ to 30% EtOAc in CH₂Cl₂) gave 439.2 mg of a mixture of the bromide **18** ([M+1] = 324) and Ph₃PO. The above mixture (439 mg) in EtOAc/EtOH (8 mL/8 mL) with Pd/C (10 wt%, 200 mg, 0.19 mmol) was stirred under H₂ (balloon) for 2

10 h, then was filtered through Celite. The filtrate was concentrated and residue was purified by chromatography (*RediSep* 12 g silica-gel column, solvent A: 1:1 v/v CH₂Cl₂/hexanes, solvent B: EtOAc; gradient eluent: A to B) to give 99 mg (~80% yield for 2 steps) of product **19** as a white solid. MS: [M+1] = 245.

[0245] In a separate flask, 1,2,3-triazole (55.3 mg, 0.80 mmol) in CH₃CN (1 mL) at 0°C

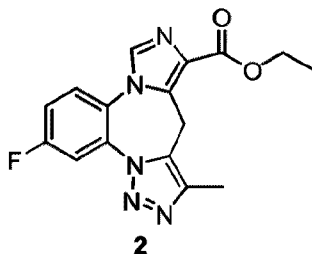
15 was treated with *i*-Pr₂NEt (146 µL, 0.84 mmol), followed by POCl₃ (23 µL, 0.25 mmol). The solution was stirred at 0°C for 2 h. The lactam **19** was added in one lot and the resulting suspension was heated in an 80°C oil bath for 20 h. Water was added to quench the reaction. It was extracted with EtOAc thrice. The combined extracts were washed with brine and dried over Na₂SO₄. Filtration and concentration gave 48.8 mg of the crude

20 product **20**, which was used directly in the next step. A solution of KO-*t*-Bu (37.2 mg, 0.33 mmol) in DMF (0.5 mL) was cooled to -50°C. Ethyl isocyanoacetate (40 µL, 0.36 mmol) was added drop wise. The mixture was stirred at -50°C for 1 h. The above crude product **20** in DMF (1 mL) was added drop wise. The mixture was allowed to warm to 10°C and stirred at 10°C for 1 h. Saturated NH₄Cl aqueous solution was added and it was

25 extracted with EtOAc thrice. The combined extracts were washed sequentially with water, brine and dried over Na₂SO₄. Filtration and concentration gave the crude product.

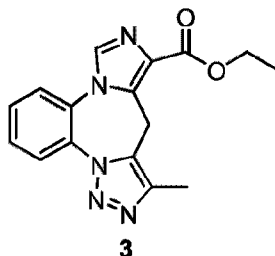
[0246] Chromatography (*RediSep* 12 g silica-gel column, solvent A: 1:1 v/v CH₂Cl₂/hexanes, solvent B: EtOAc; gradient eluent: 20% to 80% B in A) to give 15 mg (21% yield for 2 steps) of **Compound 1 (Example 1)** as an off-white solid. MS: [M+1] =

30 340. ¹H-NMR (500MHz, CDCl₃) δ: 7.74 (s, 1H), 7.63 (d, 1H, J=3Hz), 7.51 (d, 1H, J=8.5Hz), 7.14 (dd, 1H, J=3.0, 8.5Hz), 4.44 (q, 2H, J=7.0Hz), 3.95 (s, 3H), 2.44 (s, 3H), 1.45 (t, 3H, J=7.0Hz).

Example 2: Synthesis of Compound 2:

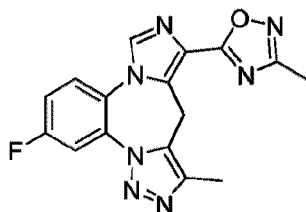
[0247] Compound of **Example 2** was synthesized in an analogous synthetic route as that described for **Example 1**, using 5-fluoro-2-nitro-aniline as the starting material to give **Compound 2** as a light brown solid: MS: [M+1] = 328. ¹H-NMR (500MHz, CDCl₃) δ: 7.90 (br dd, 1H, J=2.5, 8.5Hz), 7.77 (s, 1H), 7.62 (br dd, 1H, J=5.0, 9.0Hz), 7.35 (m, 1H), 4.45 (q, 2H, J=7.0Hz), 2.45 (s, 3H), 1.45 (t, 3H, J=7.0Hz).

10 **Example 3: Synthesis of Compound 3:**



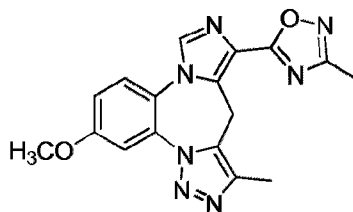
[0248] Compound of **Example 3** was synthesized in an analogous synthetic route as that described for **Example 1**, using 2-nitro-aniline as the starting material to give

15 **Compound 3** as a light yellow solid: MS: [M+1] = 310; ¹H-NMR (500MHz, CDCl₃) δ: 8.161 (br d, 1H, J=8.5Hz), 7.81 (s, 1H), 7.66 (m, 3H), 4.45 (q, 2H, J=7.0Hz), 2.45 (s, 3H), 1.46 (t, 3H, J=7.0Hz).

Example 4: Synthesis of Compound 110

[0249] Acetamide oxime was azeotroped three times in toluene before use. To a
 5 suspension of acetamide oxime (30 mg, 0.4 mmol) in THF (1 mL) was added NaH 60%
 in oil dispersion (16 mg, 0.4 mmol). The suspension was stirred at room temperature for
 15 min. The ester compound 2 (65 mg, 0.2 mmol) was added. The vial containing the
 ester was rinsed with THF (1 mL) which was added to the reaction mixture. The resulting
 brown suspension was stirred at room temperature for 30 mins then heated at 70 °C for 2h
 10 30 min. The suspension was quenched with MeOH. The solvent was evaporated and the
 crude oil was purified by chromatography (*RediSep* 4 g silica-gel column, eluted with
 70% EtOAc in Hexanes) to give 28 mg (41% yield) of product. MS: [M+1] = 338.
¹H NMR (CDCl₃) δ 7.92 (1H, dd, J= 2.5, 8.5 Hz), 7.90 (1H, s), 7.67 (1H, dd, J= 4.5, 9.5
 Hz), 7.38 (1H, m), 2.51 (3H, s), 2.46 (3H, s).

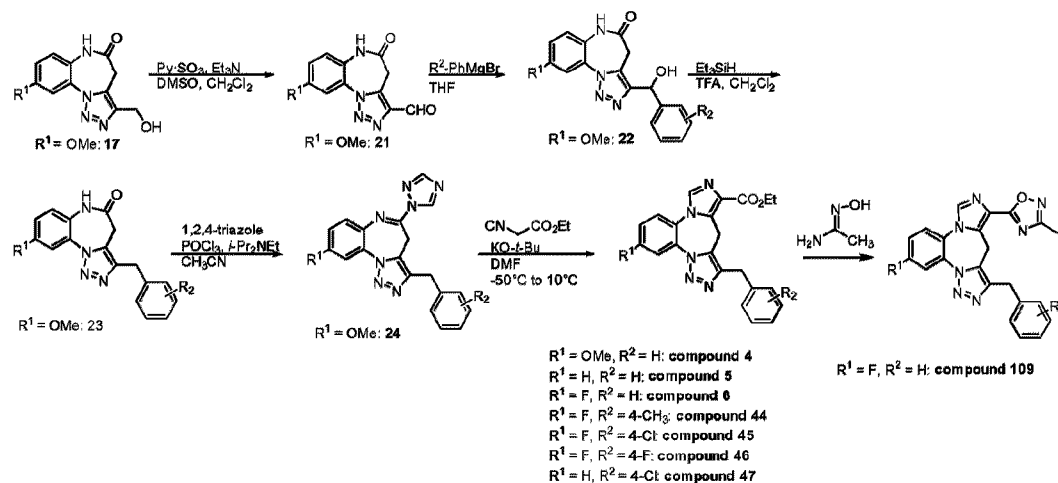
15

Example 5: Synthesis of Compound 167

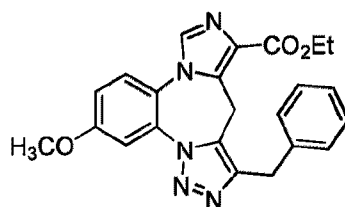
[0250] The compound was prepared analogously from **Compound 1** to give
 20 **Compound 167**: MS: [M+1] = 350. ¹H NMR (CDCl₃) δ 7.87 (1H, s), 7.65 (1H, d, J= 3
 Hz), 7.55 (1H, d, J= 9 Hz), 7.17 (1H, dd, J= 2.5, 9 Hz), 3.96 (3H, s), 2.5 (3H, s), 2.45
 (3H, s).

25

Scheme 12.



Example 6: Synthesis of Compound 4:



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[0251] To a solution of compound 17 prepared as in Example 1 (260 mg) in DMSO (4 mL) and CH_2Cl_2 (6 mL) was added Et_3N (0.7 mL, 5 mmol), followed by $\text{Py} \cdot \text{SO}_3$ (398 mg, 2.5 mmol). It was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with EtOAc thrice. The combined extracts were washed sequentially with H_2O , brine and dried over Na_2SO_4 . Filtration and concentration gave 198.5 mg of the crude aldehyde 21, which was used without further purification. To a suspension of aldehyde 21 (198.5 mg, 0.77 mmol) in THF (10 mL) at 0°C was added drop wise PhMgBr (1 M in THF, 1.54 mL, 1.54 mmol). It was stirred at 0°C for 30 min. Saturated NH_4Cl aqueous solution was added and it was extracted with EtOAc thrice.

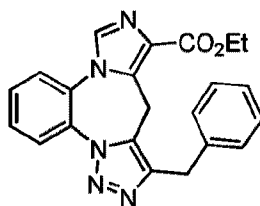
[0252] The combined extracts were washed with brine and dried over Na_2SO_4 . Filtration and concentration gave 252.9 mg of the benzyl alcohol 22 as a brown foamy solid. This was used in the next step without further purification. To a solution of the above crude alcohol 22 in CH_2Cl_2 (8 mL) with Et_3SiH (0.60 mL, 3.76 mmol) was added TFA (0.64 mL, 8.27 mmol). The reaction solution was stirred at room temperature for 4 h. After

concentration, the residue was purified by chromatography (*RediSep* 12 g silica-gel column, 20% to 80% EtOAc in hexanes) to give 34.1 mg (yield 12% for four steps) of the reduced product **23** as white foamy solid. MS: $[M+1] = 321$.

[0253] In a separate flask, a solution of 1,2,4-triazole (27 mg, 0.39 mmol) in CH_3CN (0.5 mL) at 0°C was treated with *i*- Pr_2NEt (72 μL , 0.41 mmol), followed by POCl_3 (11 μL , 0.12 mmol). The mixture was stirred at 0°C for 2 h. The lactam material **23** (32.2 mg, 0.1 mmol, solid) was added in one lot to the reaction mixture and it was heated in an 80°C oil bath for 20 h. The mixture was cooled to room temperature and creamy solid precipitate was observed. Water (0.5 mL) was added and it was stirred at room temperature for 5 min. The solid precipitate was collected by filtration, and washed with 0.5 mL of water, followed by drying under high vacuum to give 15.8 mg (yield 42%) of the adduct **24** as a off-white fluffy solid. MS: $[M+1] = 372$. A solution of KO-*t*-Bu (9.5 mg, 85 μmol) in DMF (0.5 mL) was cooled to -50°C . Ethyl isocyanoacetate (10.4 μL , 95 μmol) was added drop wise. The resulting mixture was stirred at -50°C for 1 h. The triazole amidine **24** (15.8 mg, 42 μmol , solid) was added in one lot. The stirred mixture was allowed to warm up to 10°C in 1 h and kept at 10°C for 1 h. Saturated NH_4Cl aqueous solution was added and it was extracted with EtOAc thrice. The combined extracts were washed sequentially with H_2O , brine and dried over Na_2SO_4 . Filtration and concentration gave the crude product. Chromatography (*RediSep* 4 g silica-gel column, Solvent A: 1:1 v/v CH_2Cl_2 /hexanes, solvent B: EtOAc; gradient eluent: A to 50% B in A) gave 16.8 mg (yield 95%) of the compound of **Example 6** as a white solid. MS: $[M+1] = 416$. $^1\text{H-NMR}$ (500MHz, CDCl_3) δ : 7.74 (s, 1H), 7.63 (d, 1H, $J=3.0\text{Hz}$), 7.50 (d, 1H, $J=9.0\text{Hz}$), 7.30 (br d, 2H, $J=7.0\text{Hz}$), 7.29 (br d, 2H, 7.5Hz), 7.20 (m, 1H), 7.13 (dd, 1H, $J=2.5, 9.0\text{Hz}$), 4.41 (q, 2H, $J=7.5\text{Hz}$), 4.17 (s, 2H), 3.95 (s, 3H), 1.43 (t, 3H, 7.5Hz).

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Example 7: Synthesis of Compound 5:



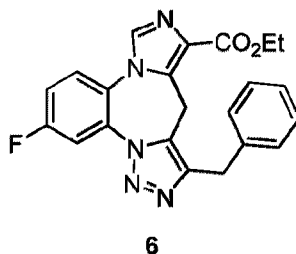
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[0254] Compound of **Example 7** was synthesized in an analogous synthetic route as that described for **Example 6**, using 2-nitro-aniline as the starting material to give

Compound 5 as a brown solid: MS: $[M+1] = 386$. $^1\text{H-NMR}$ (500MHz, CDCl_3) δ : 8.16

5 (br d, 1H, $J=7.0\text{Hz}$), 7.81 (s, 1H), 7.60-7.68 (m, 3H), 7.34 (br d, 2H, $J=8.0\text{Hz}$), 7.29 (br d, 2H, $J=7.0\text{Hz}$), 7.20 (m, 1H), 4.42 (q, 2H, $J=7.0\text{Hz}$), 4.18 (s, 2H), 1.44 (t, 3H, $J=7.0\text{Hz}$).

Example 8: Synthesis of Compound 6:

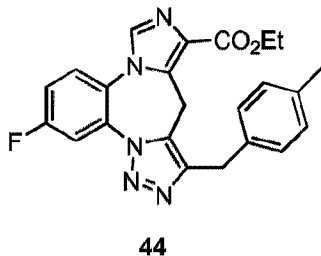


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[0255] Compound of **Example 8** was synthesized in an analogous synthetic route as that described for **Example 6**, using 5-fluoro-2-nitro-aniline as the starting material to give **compound 8** as a brown solid: MS: $[M+1] = 404$. $^1\text{H-NMR}$ (500MHz, CDCl_3) δ :

15 7.90 (dd, 1H, $J=3.5, 8.5\text{Hz}$), 7.77 (s, 1H), 7.61 (dd, 1H, $J=5.0, 10.5\text{Hz}$), 7.28-7.37 (m, 5H), 7.21 (m, 1H), 4.43 (q, 2H, $J=7.0\text{Hz}$), 4.17 (s, 2H), 1.44 (t, 3H, $J=7.0\text{Hz}$).

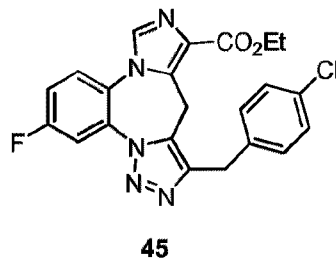
Example 9: Synthesis of Compound 44:



20 [0256] Compound of **Example 9** was synthesized in an analogous synthetic route as that described for **Example 6**, using 5-fluoro-2-nitro-aniline as the starting material to give the compound of **Example 9** as a brownish solid: MS: $[M+1] = 418$. $^1\text{H-NMR}$ (500MHz, CDCl_3) δ : 7.89 (br d, 1H, $J=9.5\text{Hz}$), 7.76 (s, 1H), 7.60 (dd, 1H, $J=5.5, 10.0\text{Hz}$), 7.35 (br t, 1H, $J=6.0\text{Hz}$), 7.22 (br d, 2H, $J=8.5\text{Hz}$), 7.09 (br d, 2H, $J=7.5\text{Hz}$),

4.43 (q, 2H, J=7.5Hz), 4.12 (s, 2H), 2.30 (s, 3H), 1.44 (t, 3H, J=7.5Hz).

Example 10: Synthesis of Compound 45:

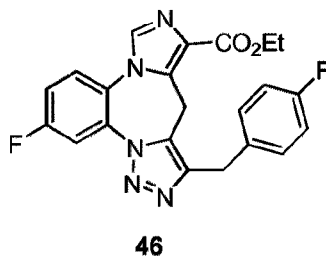


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[0257] Compound of **Example 10** was synthesized in an analogous synthetic route as that described for **Example 6**, using 5-fluoro-2-nitro-aniline as the starting material to give the compound of **Example 10** as a brownish solid: MS: [M+1] = 438. ¹H-NMR (500MHz, CDCl₃) δ: 7.90 (dd, 1H, J=3.0, 8.0Hz), 7.77 (s, 1H), 7.61 (dd, 1H, J=5.0, 9.0Hz), 7.36 (m, 1H), 7.25 (br s, 4H), 4.42 (q, 2H, J=7.0Hz), 4.14 (s, 2H), 1.44 (t, 3H, J=7.0Hz).

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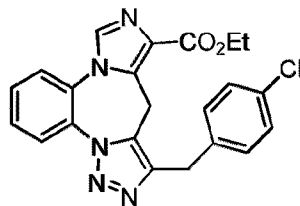
Example 11: Synthesis of Compound 46:



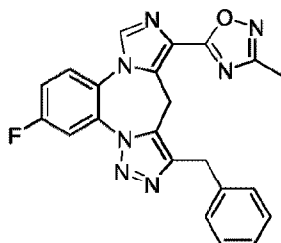
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[0258] Compound of **Example 11** was synthesized in an analogous synthetic route as that described for **Example 6**, using 5-fluoro-2-nitro-aniline as the starting material to give the compound of **Example 11** as a yellowish solid: MS: [M+1] = 422. ¹H-NMR (500MHz, CDCl₃) δ: 7.90 (dd, 1H, J=3.0, 8.5Hz), 7.77 (s, 1H), 7.61 (dd, 1H, J=5.0, 9.0Hz), 7.36 (m, 1H), 7.28 (m, 2H), 6.96 (m, 2H), 4.42 (q, 2H, J=7.5Hz), 4.14 (s, 2H), 1.44 (t, 3H, J=7.0Hz).

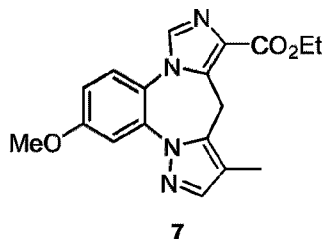
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Example 12: Synthesis of Compound 47:**47**

[0259] Compound of **Example 12** was synthesized in an analogous synthetic route as that described for **Example 6**, using 2-nitro-aniline as the starting material to give the compound of **Example 12** as a yellowish solid: MS: [M+1] = 420. ¹H-NMR (500 MHz, CDCl₃) δ: 8.16 (br d, 1H, J=7.0 Hz), 7.80 (s, 1H), 7.64 (m, 3H), 7.25 (m, 4H), 4.41 (q, 2H, J=7.0 Hz), 4.14 (s, 2H), 1.44 (t, 3H, J=8.0 Hz).

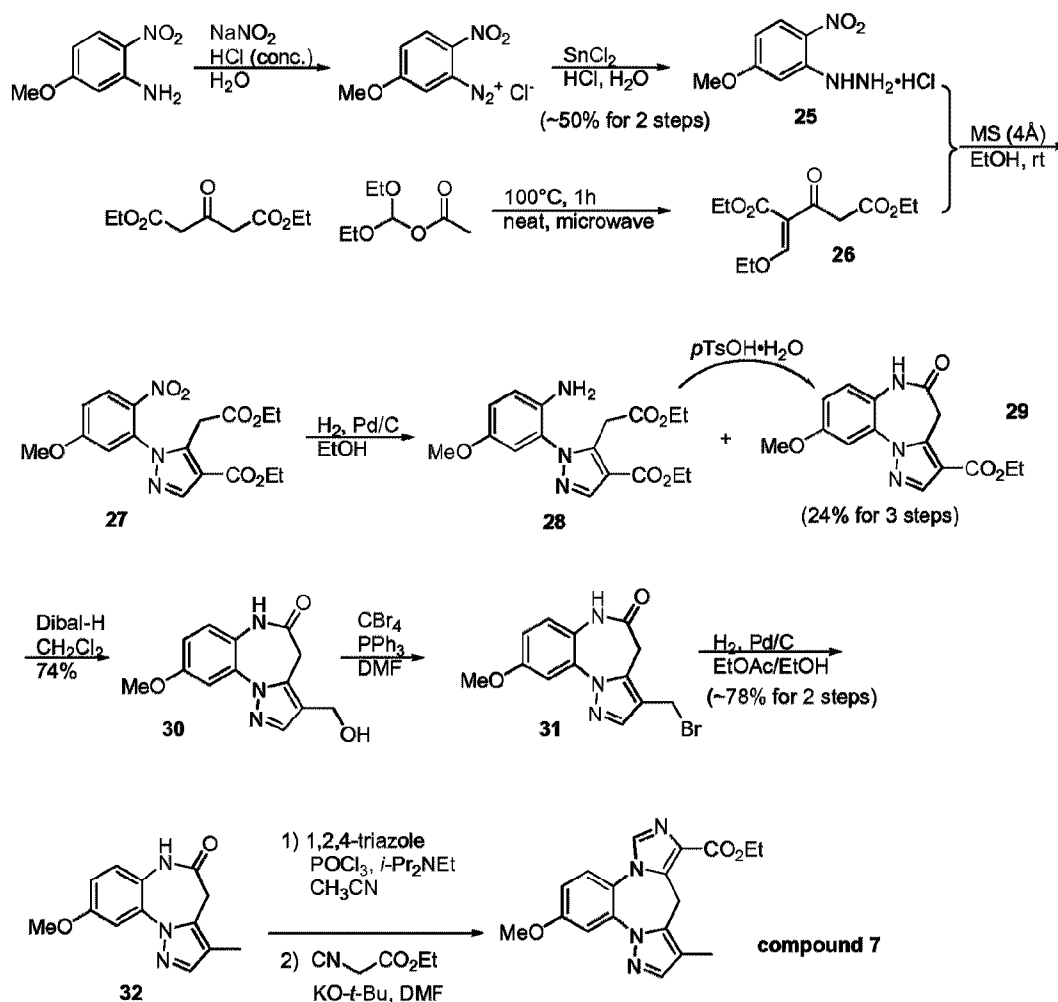
Example 13: Synthesis of Compound 109:**109**

[0260] Acetamide oxime (50 mg, 0.67 mmol) was azeotroped with toluene 3 times. THF (5mL) was added, then NaH 60% in oil dispersion (25 mg, 0.62 mmol). The suspension was stirred at room temperature for 30 min. 2 mL of this suspension was added to ester compound 6 (40 mg, 0.099 mmol) and the resulting solution was heated at 70 °C for 3h. The solution was quenched with water. The solution was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over MgSO₄. Filtration and concentration gave the crude product. Chromatography (*RediSep* 12 g silica-gel column. Eluted with 50% EtOAc in Hexanes) gave 6 mg (yield 20%) of the product **Compound 109** as yellow solid. MS: [M+1] = 414). ¹H-NMR (CDCl₃) δ 7.93 (1H, dd, J= 3, 8.5 Hz), 7.89 (1H, s), 7.65 (1H, dd, J= 5.5, 9 Hz), 7.38 (1H, m), 7.23 (5H, m), 4.2 (2H, s), 2.50 (3H, s).

Example 14: Synthesis of Compound 7:

[0261] To a stirred mixture of 5-methoxy-2-nitroaniline (5g, 29.7 mmol) in HCl (conc.
 5 12.9 mL) at 0°C was added drop wise a solution of NaNO₂ (2.05 g, 29.7 mmol) in H₂O (8 mL). The internal temperature was kept below 5°C. After addition, the mixture was allowed to warm up to room temperature in 1 h. The mixture was cooled to 0°C and a solution of SnCl₂•2H₂O (20.13 g, 89.2 mmol) in HCl (conc. 13 mL) was added slowly dropwise. After addition, it was stirred at room temperature for 2 h. The resulting yellow
 10 solid was collected by filtration and washed with cold (0°C) 6 N HCl. After drying in vacuum oven, it gave 3.245 g (yield 50%) of brown solid as aryl hydrazine **25**. MS: [M+H₂O+Na] = 224. In a separate flask, a mixture of diethyl 1,3-acetonediacrboxylate (2.426 g, 12 mmol) and diethoxymethyl acetate (1.946 g, 12 mmol) was heated under microwave radiation at 100°C for 1 h. The reaction mixture was concentrated in vacuo,
 15 and residual volatile component was co-distilled off with toluene (5ml) in vacuo to give condensation product **26**, which was used directly in the next step.

Scheme 13.



[0262] Product **26** from above was dissolved in EtOH (30 mL). Molecular sieves (4 Å, 2 g) and hydrazine hydrochloride **25** (2.19 g, 10 mmol) were added. The suspension was stirred at room temperature for 24 h. It was filtered through Celite and the solid was washed with EtOAc (10 mL X 3). The filtrate was concentrated. The residue was purified by chromatography (*RediSep* 40 g silica-gel column, 10% to 40% EtOAc in hexanes) to give 2.091 g of pyrrole **27** which was used without further purification in the next step. MS: [M+1] = 378.

[0263] The above nitro group on **27** (2.09 g, 5.5 mmol) was reduced in EtOH (40 mL) with Pd/C (10 wt%, 295 mg, 0.28 mmol) under H₂ (balloon) for 18 h. The mixture was filtered through Celite. The filtrate was concentrated and the residue was purified by

chromatography (*RediSep* 24 g silica-gel column, hexanes to 50% EtOAc in hexanes) to give 1.127g of the un-cyclized product **28** as a yellow sticky oil ($[M+1] = 348$), plus 154 mg of cyclized product **29** as a gray solid (MS: $[M+1] = 302$). The un-cyclized aniline **28** (1.127 g, 3.2 mmol) in *p*-xylene (20 mL) was treated with catalytic amount of *p*-TsOH•
5 H₂O (15 mg) in a 140°C oil bath for 20 h. The reaction mixture was cooled, concentrated, and the residue was triturated with cold (0°C) EtOAc. Filtration gave 559 mg of the lactam product **29** as a yellow solid. The total weight of the lactam product **29** combined is 713 mg (24% for 3 steps). MS: $[M+1] = 302$.

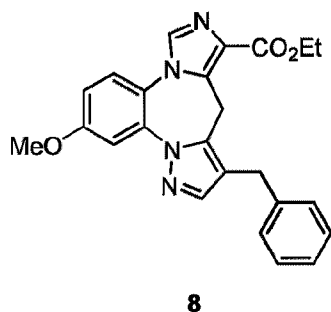
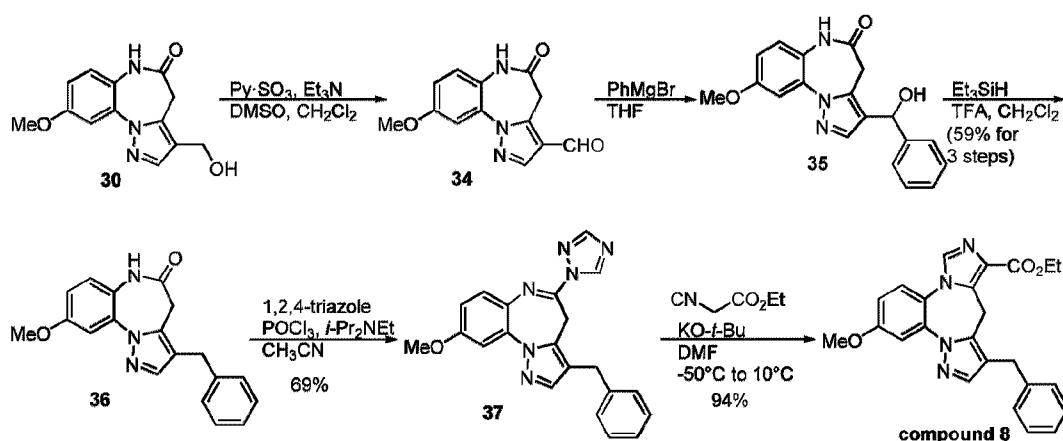
[0264] To a suspension of the ester **29** (566 mg, 1.88 mmol) in CH₂Cl₂ (35 mL) at -78°C
10 was added Dibal-H (1 M in hexane, 6.60 mL, 6.60 mmol). The suspension was stirred for 10 min at -78°C. The cold bath was removed and it was stirred for 20 min while the temperature rose to room temperature. At this point, TLC showed ~80% reaction completion. It was cooled to -78°C and more Dibal-H (1 M in hexane, 1.0 mL, 1.0 mmol) was added. After stirring at -78°C for 30 min, LCMS showed the reaction
15 proceeded to completion. The reaction was quenched by addition of Rochelle's salt aqueous solution (20%) followed by EtOAc. It was vigorously stirred at room temperature until it became a clear two-layer mixture. The layers were separated and the aqueous layer was extracted with EtOAc thrice. The combined organic phase was washed with brine and dried over Na₂SO₄. Filtration and concentration gave 480 mg of
20 the crude alcohol **30** as a slightly yellow solid. MS: $[M+1] = 260$.

[0265] To a solution of alcohol **30** (200 mg, 0.77 mmol) and CBr₄ (640 mg, 1.93 mmol) in DMF (8 mL) was added a solution of PPh₃ (486 mg, 1.85 mmol) in DMF (2 mL) slowly in 30 min. After addition, it was stirred at room temperature for 30 min. Water was added to quench the reaction and the mixture was extracted with EtOAc thrice. The
25 combined extracts were washed sequentially with H₂O, brine and dried over Na₂SO₄. Filtration and concentration gave the crude product. Chromatography (*RediSep* 12 g silica-gel column, solvent A: 1:1 v/v CH₂Cl₂/hexanes, solvent B: EtOAc; gradient eluent: 10% to 40% B in A) gave 221 mg of a mixture of the bromide **31** and Ph₃PO.

[0266] The above mixture in EtOAc/EtOH (8 mL/8 mL) with Pd/C (10 wt%, 200 mg,
30 0.19 mmol) was stirred under H₂ (balloon) for 1 h. It was filtered through Celite. The filtrate was concentrated and residue was purified by chromatography (*RediSep* 12 g

silica-gel column, solvent A: 1:1 v/v CH₂Cl₂/hexanes, solvent B: EtOAc; gradient eluent: 10% to 40% B in A) to give 146 mg of a mixture of the reduction product **32** ([M+1] = 244) and Ph₃PO.

[0267] In a separate flask, 1,2,4-triazole (81 mg, 1.17 mmol) in CH₃CN (1 mL) at 0°C
5 was treated with *i*-Pr₂NEt (214 µL, 1.23 mmol), followed by POCl₃ (34 µL, 0.36 mmol).
The solution was stirred at 0°C for 2 h. The lactam **32** (~60% purity by LCMS) was
added in one lot and the resulting suspension was heated in an 80°C oil bath for 18 h.
Water was added to quench the reaction. It was extracted with EtOAc thrice. The
combined extracts were washed sequentially with H₂O, brine and dried over Na₂SO₄.
10 Filtration and concentration gave 126.6 mg of the crude product **33** as a yellow glue,
which was used directly in the next reaction. MS: [M+1] = 295. A solution of KO- *t*-Bu
(97 mg, 0.86 mmol) in DMF (1 mL) was cooled to -50°C. Ethyl isocyanoacetate
(104 µL, 0.95 mmol) was added drop wise. The mixture was stirred at -50°C for 1 h.
The above crude product **33** in DMF (1.5 mL) was added drop wise. The mixture was
15 allowed to warm to 10°C and stirred at 10°C for 1 h. Saturated NH₄Cl aqueous solution
was added and it was extracted with EtOAc thrice. The combined extracts were washed
sequentially with water, brine and dried over Na₂SO₄. Filtration and concentration gave
the crude product. Chromatography (*RediSep* 12 g silica-gel column, solvent A: 1:1 v/v
CH₂Cl₂/hexanes, solvent B: EtOAc; gradient eluent: 10% to 40% B in A) to give 22 mg
20 of a white solid, which was further purified by preparative TLC (developed with 1:1 A/B)
to give 12.8 mg of the final product **Compound 7 (Example 14)** as a white solid. MS:
[M+1] = 339. ¹H-NMR (500MHz, CDCl₃) δ: 7.70 (s, 1H), 7.56 (s, 1H), 7.50 (d, 1H,
J=3.0Hz), 7.43 (d, 1H, J=8.5Hz), 7.00 (dd, 1H, J=2.5, 9.5Hz), 5.29 (br s, 1H), 4.44 (q,
2H, J=7.0Hz), 3.92 (s, 3H), 3.55 (br s, 1H), 2.17 (s, 3H), 1.45 (t, 3H, J=7.0Hz).

Example 15: Synthesis of Compound 8:**Scheme 14.**

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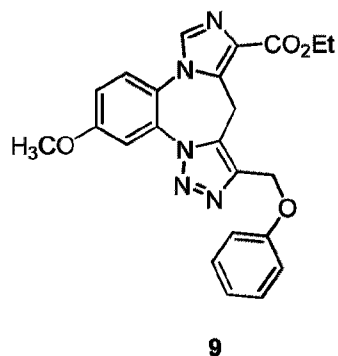
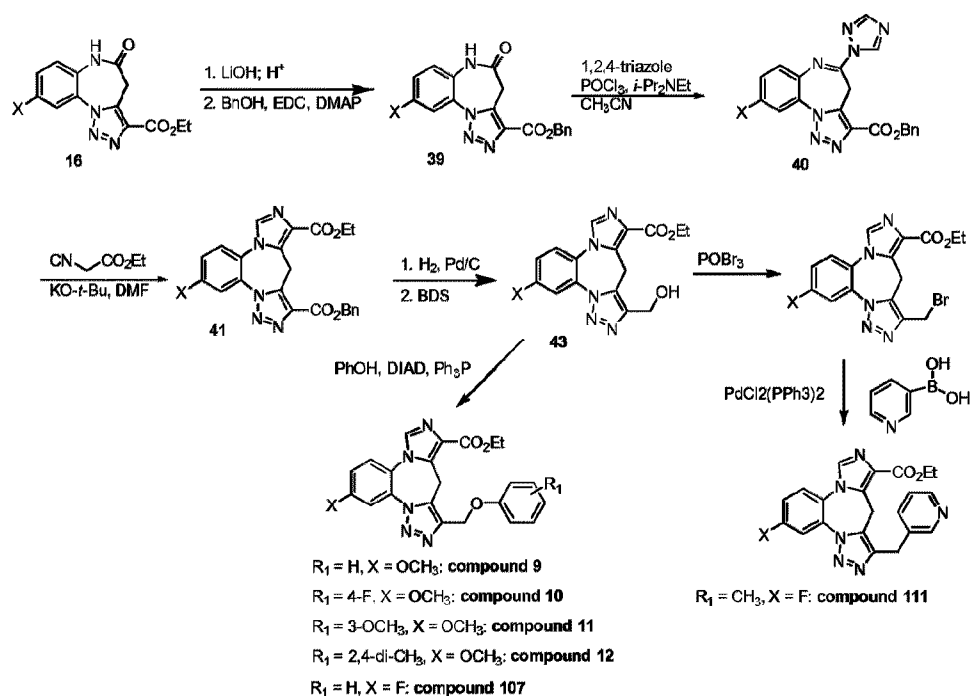
[0268] To a solution of the alcohol **30** (261 mg, 1.0 mmol) which was prepared in **Example 14** in DMSO (4 mL) and CH₂Cl₂ (6 mL) was added Et₃N (0.7 mL, 5 mmol), followed by Py•SO₃ (398 mg, 2.5 mmol). It was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with EtOAc thrice. The combined extracts were washed sequentially with H₂O, brine and dried over Na₂SO₄. Filtration and concentration gave 226 mg of the crude aldehyde **34** as a yellow solid. It was used in the next step without purification. MS: [M+1] = 258.

[0269] To a suspension of the crude aldehyde **34** (202 mg, 0.79 mmol) in THF (10 mL) at 0°C was added drop wise PhMgBr (1 M in THF, 1.58 mL, 1.58 mmol). It was stirred at 0°C for 30 min. Saturated NH₄Cl aqueous solution was added and it was extracted with EtOAc thrice. The combined extracts were washed with brine and dried over Na₂SO₄. Filtration and concentration gave 275 mg of the crude product **35** as a yellow

foamy solid, which was used in the next step without purification.

[0270] To a solution of the above crude alcohol **35** in CH₂Cl₂ (10 mL) with Et₃SiH (0.66 mL, 4.10 mmol) was added TFA (0.70 mL, 9.02 mmol). The reaction solution was stirred at room temperature for 1 h. After concentration, the residue was purified by chromatography (*RediSep* 24 g silica-gel column, 10% to 50% EtOAc in hexanes) to give 187.8 mg (yield 59% for three steps) of the product **36** as a gray solid. MS: [M+1] = 320.

[0271] In a separate flask, a solution of 1,2,4-triazole (127 mg, 1.83 mmol) in CH₃CN (1.6 mL) at 0°C was treated with *i*-Pr₂NEt (336 µL, 1.93 mmol), followed by POCl₃ (53 µL, 0.56 mmol). The mixture was stirred at 0°C for 2 h. Lactam **36** (150 mg, 0.47 mmol, solid) was added in one lot to the reaction mixture and it was heated in an 80°C oil bath for 18 h. The mixture was cooled to room temperature and solid precipitate was observed. Water (2.1 mL) was added and it was stirred at room temperature for 10 min. Filtration, washing the solid with 2 mL of water, followed by drying under high vacuum gave 118.8 mg (yield 69%) of the triazole amidine **37** as an off-white fluffy solid. MS: [M+1] = 371. A solution of KO-*t*-Bu (72 mg, 0.64 mmol) in DMF (2 mL) was cooled to -50°C. Ethyl isocyanoacetate (77 µL, 0.71 mol) was added drop wise. The resulting mixture was stirred at -50°C for 1 h. The triazole amidine **37** (118.8 mg, 42 µmol, solid) was added in lot. The stirred mixture was allowed to warm up to 10°C in 1 h and kept at 10°C for 1 h. Saturated NH₄Cl aqueous solution was added and it was extracted with EtOAc thrice. The combined extracts were washed sequentially with H₂O, brine and dried over Na₂SO₄. Filtration, concentration, then chromatography (*RediSep* 12 g silica-gel column. solvent A: 1:1 v/v CH₂Cl₂/hexanes, solvent B: EtOAc; gradient eluent: A to 40% B in A) gave 125.1 mg (yield 94%) of **Compound 8** as a white solid. MS: [M+1] = 415. ¹H-NMR (500 MHz; CDCl₃) δ: 7.72 (s, 1H), 7.54 (s, 1H), 7.51 (br s, 1H), 7.44 (br d, 1H, J=9.5Hz), 7.29 (br d, 2H, J=7.5Hz), 7.20 (m, 3H), 7.01 (br d, 1H, J=7.5Hz), 5.30 (br s, 1H), 4.38 (q, 2H, J=7.0Hz), 3.92 (br s, 5H), 3.54 (br s, 1H), 1.41 (t, 3H, J=7.0Hz).

Example 16: Synthesis of Compound 9:**Scheme 15.**

5

[0272] LiOH (1.09 g, 45.5 mmol) was added to a stirring solution of ester **16** (prepared in **Example 1**) (2.75g, 9.10 mmol) in THF (24 mL) and water (20 mL) at room temperature. MeOH (4mL) was added, and stirring continued for 2 h at room temperature at which point LCMS indicated complete consumption of the ester. Upon concentration in vacuo, the reaction mixture was acidified to pH 3-4 by adding 2N HCl (20 mL). After 20 min stirring, the reaction mixture was cooled to 0°C, a solid precipitate was collected by filtration, washed with 3-4 ml water, and dried to give 1.59 g (64%) of the

corresponding acid **38** as a grayish solid. MS: $[M+1] = 275$. To acid **38** (1.59 g, 5.8 mmol) suspended and stirred in DCM (30ml) was added EDC (5.6g, 29.2 mmol), benzyl alcohol (2.5 g, 23.2 mmol) and DMAP (3.54 g, 29.2 mmol). After 3 days of stirring at room temperature, the reaction was concentrated in vacuo. Water (80 mL) was added to the slurry, followed by diethyl ether (40 mL), and the mixture was stirred vigorously for 40 min, at which point the slurry turned into a precipitate, and was collected by suction filtration. The solid was washed with water and small amount of diethyl ether, and dried to give 1.65 g (78%) benzyl ester **39** as a white solid. MS: $[M+1] = 365$.

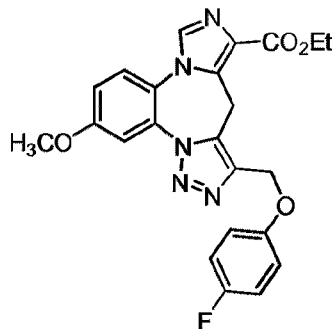
[0273] Compound 1,2,4-triazole (1.22 g, 17.7 mmol) in CH_3CN (15 mL) at 0°C was treated with *i*- Pr_2NEt (3.24 mL, 18.6 mmol), followed by POCl_3 (0.507 mL, 5.44 mmol). The solution was stirred at 0°C for 2 h. Benzyl ester **39** (1.65 g, 4.53 mmol) was added in lot and the resulting suspension was heated in an 80°C oil bath for 18 h. LCMS showed 5-10% starting lactam remained. In a separate flask, 1,2,4-triazole (307 mg, total 4.9 eq) in CH_3CN (3.8 mL) was treated with *i*- Pr_2NEt (0.82 mL, total 5.1 eq) and POCl_3 (0.127 mL; total 1.5 eq) at 0°C for 2 h. The resulting clear solution was transferred into the above reaction mixture. After 2 h heating at 80°C , the reaction was cooled to room temperature, water was added slowly to quench the reaction (10 min). Upon cooling in an ice bath, the solids formed were collected by filtration, washed with water (5ml), and dried to give 1.61g (86%) product **40** as a lightly yellow solid. MS: $[M+1] = 416$.

[0274] A solution of KO-*t*-Bu (0.739 g, 6.59 mmol) in DMF (11 mL) was cooled to -50°C . Ethyl isocyanoacetate (0.810 mL, 7.00 mmol) was added drop wise. The mixture was stirred at -50°C for 1 h. The above triazole intermediate **40** (1.61 g, 3.87 mmol) was added. The mixture was stirred at -50°C for 30 min, and slowly warmed to room temperature over 4-5 h. Saturated NH_4Cl aqueous solution (10 mL) was added, followed by EtOAc (10 mL). The mixture was sonicated to breakup solid chunks, then stirred thoroughly for 30 min. The precipitate was collected by filtration, washed with water, Et_2O , and dried to give crude product as a white solid. Filtrate was partitioned between water and EtOAc; aqueous layer was separated and extracted with EtOAc twice; the combined EtOAc layer was washed with brine and dried over MgSO_4 . Filtration and solvent removal gave a solid residue which was combined with the solid obtained above for chromatographic purification, using *RediSep* 24 g silica-gel column and gradient elution with 0.5 to 5% MeOH in DCM, to give 1.78 g (100%) imidazole **41** as a white

solid. MS: $[M+1] = 460$. The benzyl ester **41** (1.78 g, 3.87 mmol) was subjected to hydrogenolysis (hydrogen balloon) in the presence of catalytic amount of 10% Pd on charcoal in a solvent mixture of THF (40 mL), MeOH (20 mL) and EtOAc (20 mL) for 20 h. LCMS showed complete disappearance of the starting material. The solid catalyst
5 was removed by filtration over Celite, and rinsed repeatedly with ample amount of 30% MeOH in DCM until almost all products were recovered (TLC monitor). Filtrate containing the product was concentrated in vacuo to give 1.22 g (85%) of acid product **42** was obtained as a yellowish solid. MS: $[M+1] = 370$.

[0275] To the acid **42** (1.22 g, 3.30 mmol) suspended and stirred in THF (25mL) at 0°C
10 was added borane dimethylsulfide complex (2M THF; 19 mL, 38 mmol) dropwise. Ice bath was removed and the reaction mixture was stirred at room temperature for 16 h. Upon cooling in an ice bath, the reaction was carefully quenched with MeOH (20 mL), and then stirred at room temperature overnight. Solvents were removed in vacuo. MeOH was added and removed in vacuo two more times. ISCO purification (*RediSep* 24g
15 column) using a gradient of 1 to 8% MeOH in DCM gave 0.625 g (53%) of alcohol product **43** as a white solid. MS: $[M+1] = 356$.

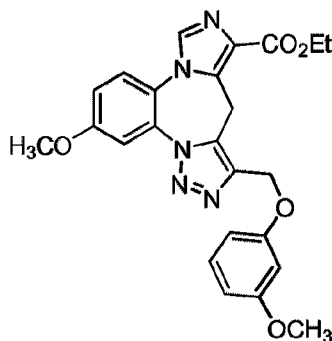
[0276] Diisopropyl azodicarboxylate (48.3 mg, 0.233 mmol) was added drop-wise into a stirring solution of alcohol **43** (37.5 mg, 0.106 mmol), phenol (14.9 mg, 0.158 mmol), and Ph_3P (55.6 mg, 0.212 mmol) in anhydrous THF (0.8 mL) at 0°C. Ice bath was
20 removed and stirring continued at room temperature for 16 h. LCMS showed complete disappearance of the starting alcohol. The reaction mixture was partitioned between sat. NaHCO_3 and EtOAc. The organic layer was separated and washed with water, brine, and dried over MgSO_4 . The desired product was isolated from the reaction mixture by two consecutive preparative TLC (4% MeOH in DCM, and hexanes/EtOAc/MeOH = 47.5 /
25 47.5 / 5, v/v/v) to give 5.3mg (12%) of product which is **Compound 9** as a white solid. MS: $[M+1] = 432$. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.77 (s, 1H), 7.63 (d, 1H, $J=3.5$ Hz), 7.53 (d, 1H, $J=9.0$ Hz), 7.31 (m, 2H), 7.17 (dd, 1H, $J=3.0, 8.5$ Hz), 7.08 (d, 2H, $J=7.0$ Hz), 6.99 (t, 1H, $J=6.5$ Hz), 5.30 (s, 2H), 4.40 (q, 2H, $J=7.0$ Hz), 3.96 (s, 3H), 1.38 (t, 3H, $J=7.0$ Hz).

Example 17: Synthesis of Compound 10:**10**

[0277] Compound of **Example 17** was synthesized in an analogous synthetic route as

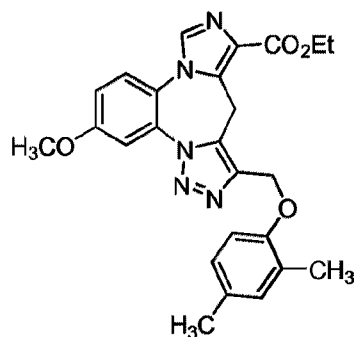
5 that described for **Example 16**, using 4-fluoro-phenol in the ultimate step to give
Compound 10 (4.9 mg) as a white solid: MS: $[M+1] = 450$. $^1\text{H-NMR}$ (500 MHz,
 CDCl₃) δ : 7.76 (s, 1H), 7.64 (d, 1H, $J=3.5$ Hz), 7.53 (d, 1H, $J=8.0$ Hz), 7.17 (dd, 1H,
 $J=2.5, 8.0\text{Hz}$), 7.01 (m, 4H), 5.26 (s, 2H), 4.40 (q, 2H, $J=7.0\text{Hz}$), 3.96 (s, 3H), 1.40 (t, 3H,
 $J=7.0\text{Hz}$).

10

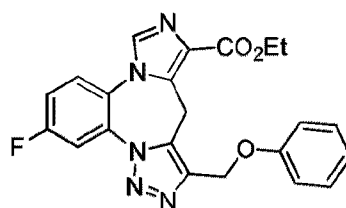
Example 18: Synthesis of Compound 11:**11**

[0278] Compound of **Example 18** was synthesized in an analogous synthetic route as

15 that described for **Example 16**, using 3-methoxy-phenol in the ultimate step to give
Compound 11 (6.1 mg) as a white solid: MS: $[M+1] = 462$. $^1\text{H-NMR}$ (500 MHz,
 CDCl₃) δ : 7.76 (s, 1H), 7.63 (d, 1H, $J=2.5$ Hz), 7.53 (d, 1H, $J=9.0\text{Hz}$), 7.15-7.22 (m, 2H),
 6.67 (m, 2H), 6.55 (br dd, 1H, $J=2.5, 8.0$ Hz), 5.28 (s, 2H), 4.39 (q, 2H, $J=7.0$ Hz), 3.96 (s,
 3H), 3.81 (s, 3H), 1.39 (t, 3H, $J=7.0$ Hz).

Example 19: Synthesis of Compound 12:**12**

- 5 [0279] Compound of **Example 19** was synthesized in an analogous synthetic route as that described for **Example 16**, using 2,4-dimethylphenol in the ultimate step to give **Compound 12** (3.1 mg) as a white solid: MS: [M+1] = 460. ¹H-NMR (500 MHz, CDCl₃) δ: 7.76 (s, 1H), 7.65 (d, 1H, J=3.0Hz), 7.53 (d, 1H, J=9.0 Hz), 7.17 (dd, 1H, J=2.5, 8.5 Hz), 6.98 (m, 3H), 5.26 (s, 2H), 4.37 (q, 2H, J=7.0 Hz), 3.96 (s, 3H), 2.26 (s, 10 3H), 2.20 (s, 3H), 1.36 (t, 3H, J=7.0Hz).

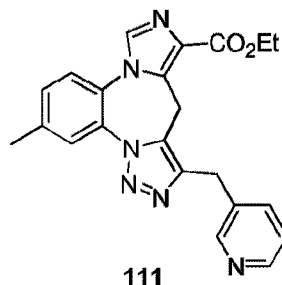
Example 20: Synthesis of Compound 107:**107**

- [0280] To a solution of alcohol **43** where X = F (prepared in an identical manner to example where X = OCH₃) (60 mg, 0.17 mmol) in THF (0.8 mL) was added phenol (30 mg, 0.32 mmol), triphenylphosphine (84 mg, 0.32 mmol). The reaction mixture was stirred at room temperature for 15 min. It was then cooled with an ice bath and DIAD (64 μL, 0.32 mmol) in THF (0.2 mL) was added slowly. The ice bath was removed and the reaction mixture was stirred at room temperature for 18h. LCMS indicated still the presence of some starting material. Phenol (10 mg), triphenylphosphine (28 mg) and DIAD (21 μL) were added to the reaction mixture and stirred for another hour. The solvent was evaporated and the crude material was purified by Chromatography (*RediSep*
- 15
- 20

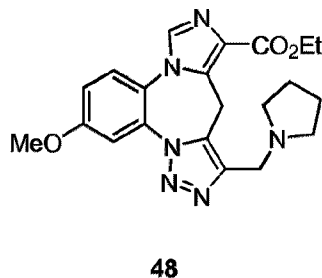
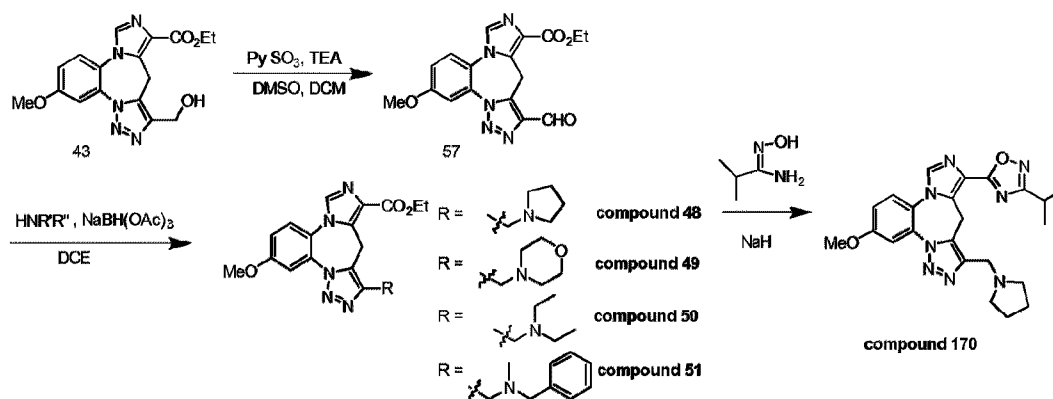
12 g silica-gel column. Eluting solvent: EtOAc) and prep TLC (eluting solvent: 5% MeOH/47.5%EtOAc/47.5% Hexanes) to give 11.4 mg (yield 16%) of the product

Compound 107. $[M+1] = 421$. $^1\text{H NMR}$ (CDCl_3) δ 7.92 (1H, dd, $J = 3.5, 8.5$ Hz), 7.80 (1H, s), 7.63 (1H, dd, $J = 5, 10$ Hz), 7.38 (1H, m), 7.31 (2H, t, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.00 (1H, t, $J = 8.5$ Hz), 5.3 (2H, s), 4.39 (2H, q, $J = 7$ Hz), 1.38 (3H, t, $J = 7$ Hz).

Example 21: Synthesis of Compound 111:



- [0281] To a suspension of alcohol **43** ($X = \text{Me}$) (160 mg, 0.47 mmol) in acetonitrile (9 mL) was added POBr_3 (405 mg, 1.41 mmol). The reaction mixture was heated at 80 C for 5 h. The reaction mixture was cooled down with an ice bath and sat. aq. NaHCO_3 solution was added. The resulting solution was extracted with DCM (3X). The combined organic phases were washed with brine and dried over MgSO_4 . The solvent was concentrated to afford the desired product, 166 mg, 88% yield, $[M+1] = 403$).
- [0282] To a suspension of the above alkyl bromide derivative (30 mg; 0.075 mmol) in deoxygenated DME (2.7 mL) was added 3-pyridine boronic acid (14 mg, 0.11 mmol) and a 2M Na_2CO_3 solution (0.22 mL, 0.44 mmol). The suspension was stirred at room temperature for 5 min, then $\text{PdCl}_2(\text{PPh}_3)_2$ (10 mg, 0.015 mmol) was added. The suspension was heated in a MW at 85 C for 1 hour. The reaction mixture was cooled and diluted with water and extracted with EtOAc (twice). The combined extracts were washed with brine and dried over MgSO_4 . Filtration and concentration gave the crude product which was purified by 2 prep TLC (eluting system: 3% MeOH in DCM) to give 5.3 mg (yield 18%) of the product **Compound 111**. MS: $[M+1] = 401$. $^1\text{H NMR}$ (CDCl_3) δ 8.66 (1H, bs), 8.48 (1H, bs), 7.96 (1H, s), 7.79 (1H, s), 7.66 (1H, d, $J = 8$ Hz), 7.50 (1H, d, $J = 8$ Hz), 7.43 (1H, d, $J = 7$ Hz), 7.23 (1H, m), 4.42 (2H, q, $J = 7$ Hz), 4.18 (2H, s), 2.54 (3H, s), 1.44 (3H, t, $J = 7$ Hz).

Example 22: Synthesis of Compound 48:**Scheme 16.**

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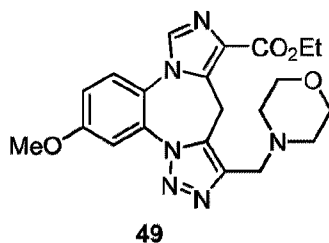
[0283] To alcohol **43** (186 mg, 0.523 mmol) stirring in DMSO (1 mL) and dichloromethane (2.5 mL) at room temperature was added triethylamine (0.394 mL, 2.82 mmol) and pyridine sulfur trioxide complex (225 mg, 1.41 mmol). After 3 h stirring, the reaction was quenched with water (5 mL), and extracted with ethyl acetate three times. The combined organic solution was washed with water, brine, and dried over MgSO_4 . The aldehyde product **57** was isolated by ISCO flash column chromatography (*RediSep* 4g column) using a gradient elution of 0.5 to 8% MeOH in DCM. 84.4 mg (46%) was obtained as a yellowish foamy solid. MS: $[M+1] = 354$.

[0284] To a stirring solution of aldehyde **57** (15.5 mg, 0.0439 mmol) in 1,2-dichloroethane (0.3 mL) at room temperature was added pyrrolidine (5.5 μL , 0.0658 mmol). After 2 min stirring, the solution turned clear, and NaBH(OAc)_3 (14.4 mg) was added. The reaction mixture was stirred for 4 h, and was quenched with saturated NaHCO_3 , and extracted with ethyl acetate three times. The combined organic layer was washed with water, brine, and dried over Na_2SO_4 . Prep TLC with 10% MeOH in DCM

20

gave 13.1 mg (73%) of the desired **Compound 48** as a clear filmy solid. MS: [M+1] = 409. ¹H-NMR (500MHz, CDCl₃) δ: 7.74 (s, 1H), 7.62 (d, 1H, J=3.0Hz), 7.51 (d, 1H, J=9.0Hz), 7.14 (dd, 1H, J=3.5, 9.0Hz), 4.42 (q, 2H, J=6.5Hz), 3.94 (s, 3H), 3.87 (br s, 2H), 2.65 (br s, 4H), 1.79 (br s, 4H), 1.44 (t, 3H, J=7.0Hz).

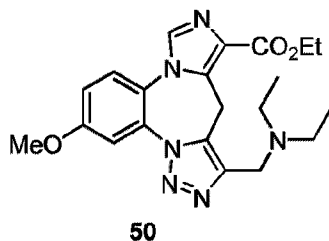
5 **Example 23: Synthesis of Compound 49:**



[0285] Compound of **Example 23** was synthesized in an analogous synthetic route as that described for **Example 22**, using morpholine in the ultimate step to give the compound of **Example 23** as a clear filmy solid: MS: [M+1] = 425. ¹H-NMR (500MHz, CDCl₃) δ: 7.75 (s, 1H), 7.63 (d, 1H, J=3.0 Hz), 7.52 (d, 1H, J=9.5 Hz), 7.15 (dd, 1H, J=3.0, 9.0 Hz), 4.42 (q, 2H, J=7.5 Hz), 3.95 (s, 3H), 3.76 (br s, 2H), 3.71 (br s, 4H), 2.57 (br s, 4H), 1.44 (t, 3H, J=8.0 Hz).

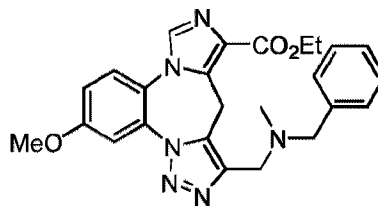
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15 **Example 24: Synthesis of Compound 50:**

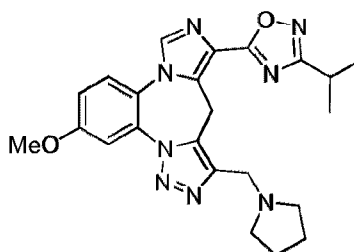


[0286] Compound of **Example 24** was synthesized in an analogous synthetic route as that described for **Example 22**, using diethylamine in the ultimate step to give the compound of **Example 24** as a clear filmy solid: MS: [M+1] = 411. ¹H-NMR (500 MHz, CDCl₃) δ: 7.74 (s, 1H), 7.64 (br d, 1H, J=3.0 Hz), 7.51 (d, 1H, J=9.0Hz), 7.15 (dd, 1H, J=2.5, 9.0 Hz), 4.43 (q, 2H, J=6.5 Hz), 3.96 (s, 3H), 3.86 (br s, 2H), 2.64 (br s, 4H), 1.44 (t, 3H, J=8.5 Hz), 1.15 (br s, 6H).

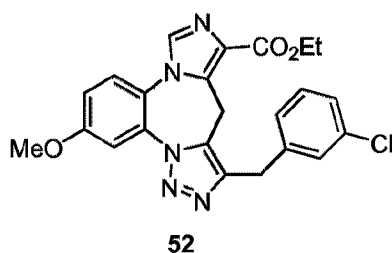
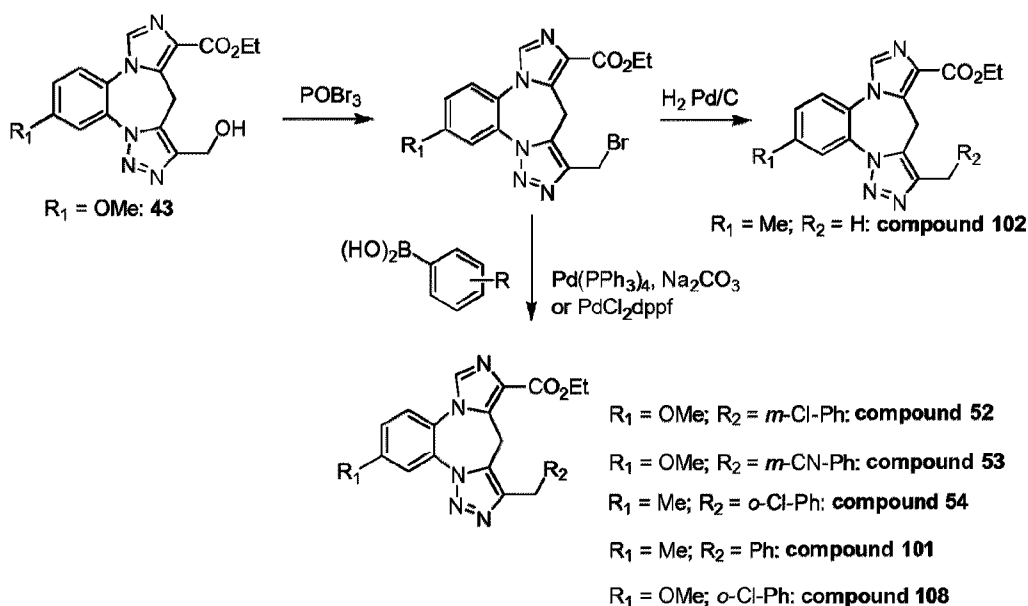
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Example 25: Synthesis of Compound 51:**51**

[0287] Compound of **Example 25** was synthesized in an analogous synthetic route as that described for **Example 22**, using methyl benzyl amine in the ultimate step to give the compound of **Example 25** as a clear filmy solid: MS: [M+1] = 459. ¹H-NMR (500 MHz, CDCl₃) δ: 7.75 (s, 1H), 7.63 (d, 1H, J=3.0 Hz), 7.51 (d, 1H, J=8.5 Hz), 7.36 (br d, 2H, J=8.0 Hz), 7.30 (m, 2H), 7.23 (m, 1H), 7.15 (dd, 1H, J=3.0, 9.0 Hz), 4.38 (q, 2H, J=7.5 Hz), 3.95 (s, 3H), 3.85 (br s, 2H), 3.63 (br s, 2H), 2.25 (s, 3H), 1.41 (t, 3H, J=7.0 Hz).

Example 26: Synthesis of Compound 170:**170**

[0288] Isobutyramidoxime (41.8 mg, 0.41 mmol) and ester **48** (27.9 mg, 0.0683 mmol) in a round bottom flask was azeotroped in toluene on a Rotavap several times, suspended in anhydrous THF (0.6 mL), and then cooled to 0°C. NaH (60% oil suspension; 10.9 mg, 0.273 mmol) was added. Ice bath was removed and the reaction mixture was stirred at RT for 20 min before being heated at 70°C for 6hrs, and cooled. Water (4 mL) was added, and the mixture was extracted with EtOAc three times. The combined organic solution was washed with brine and dried over MgSO₄. Prep. TLC with 10% MeOH in EtOAc gave 10.4 mg (34%) of the desired product **Compound 170** as a clear filmy solid. MS: [M+1] = 447.

Example 27: Synthesis of Compound 52:**5 Scheme 17.**

[0289] The starting alcohol **43** (160 mg, 0.45 mmol) was treated with phosphorous oxide tribromide (400 mg, 1.4 mmol) in acetonitrile (10ml) at 80°C for 5 h. The reaction was then cooled down to 0°C, quenched with sat. NaHCO₃, and extracted with

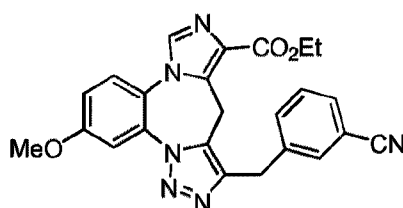
10 dichloromethane twice. Combined dichloromethane solution was washed with brine and dried over MgSO₄. Filtration and solvent removal in vacuo gave 173.3 mg (92%) of the bromide as a yellowish foamy solid. MS: [M+1] = 418.

[0290] To a suspension of bromide (55 mg, 0.131 mmol) in dimethoxyethane (2 ml; degassed) was added 2M Na₂CO₃ (0.39 ml, 0.78 mmol) and 3-chlorophenyl boronic acid

15 (42.2 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 2 min, then Pd(PPh₃)₄ (75 mg, 0.065 mmol) was added, and the suspension was heated in a 85°C

oil bath for 90 min. Upon cooling, the reaction mixture was diluted with EtOAc and washed with brine. The aqueous layer was separated and extracted with EtOAc three times. All organic layers were pooled and dried over Na₂SO₄, then filtered and solvent was removed in vacuo. The product was isolated by successive prep TLC purifications, using 20% hexanes in EtOAc followed by 5% MeOH in DCM. 9.6 mg product (Compound 52) was obtained as a brownish solid. MS: [M+1] = 450. ¹H-NMR (500 MHz, CDCl₃) δ: 7.75 (s, 1H), 7.64 (d, 1H, J=3.0 Hz), 7.51 (d, 1H, J=9.5 Hz), 7.31 (br s, 1H), 7.23 (br s, 1H), 7.17 (m, 3H), 4.43 (q, 2H, J=7.0Hz), 4.15 (s, 2H), 3.96 (s, 3H), 1.44 (t, 3H, J=8.0Hz).

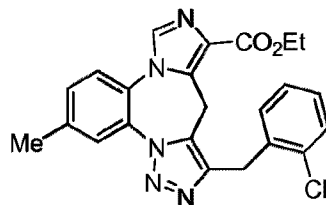
Example 28: Synthesis of Compound 53:



53

[0291] Compound of Example 28 was synthesized in an analogous synthetic route as that described for Example 27, using 3-cyanophenyl boronic acid in the ultimate step to give the compound of Example 28 as a brownish solid: MS: [M+1] = 441. ¹H-NMR (500 MHz, CDCl₃) δ: 7.75 (s, 1H), 7.66 (br s, 1H), 7.64 (d, 1H, J=3.0 Hz), 7.61 (br d, 1H, J=7.5 Hz), 7.39 (t, 1H, J=7.5 Hz), 7.16 (dd, 1H, J=3.5, 9.5 Hz), 4.45 (q, 2H, J=7.0H), 4.20 (s, 2H), 3.96 (s, 3H), 1.45 (t, 3H, J=7.0 Hz).

Example 29: Synthesis of Compound 54:

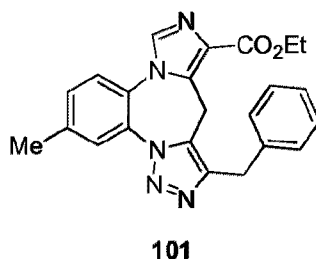


54

[0292] Compound of Example 29 was synthesized in an analogous synthetic route as

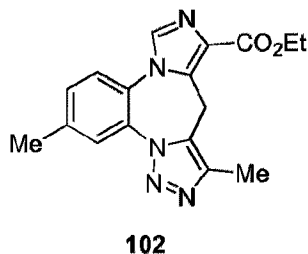
that described for **Example 27**, starting with the alcohol where R_1 = methyl, and using 2-chlorophenyl boronic acid in the ultimate step to give the compound of **Example 29** as a brownish solid: MS: $[M+1] = 434$.

5 **Example 30: Synthesis of Compound 101:**



[0293] Compound of **Example 30** was synthesized in an analogous synthetic route as that described for **Example 27**, starting with the alcohol where R_1 = methyl, and using
 15 phenyl boronic acid in the ultimate step to give the compound of **Example 30** as a brownish solid product which was purified by chromatography (*RediSep* 4 g silica-gel column. Eluting solvent: EtOAc) then a prep TLC (eluting system: 40% DCM/40% Hexanes/ 17% EtOAc/ 3% MeOH) to give 5.9 mg (yield 31%) of the product **Compound 101**. MS: $[M+1] = 402$. ^1H NMR (CDCl_3) δ 7.96 (1H, s), 7.77 (1H, s), 7.55 (1H, m), 7.47
 20 (1H, m), 7.32 (5H, m), 4.41 (2H, q, $J = 7$ Hz), 4.17 (2H, s), 2.53 (3H, s), 1.43 (3H, t, $J = 7$ Hz).

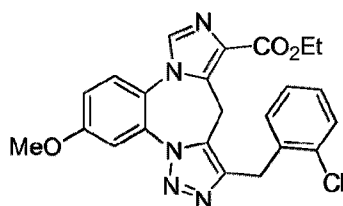
Example 31: Synthesis of Compound 102:



30 [0294] To a suspension of the bromide in EtOAc (2mL) and MeOH (2mL) was added activated 10% Pd/C (5 mg). The suspension was stirred under a hydrogen atmosphere for 48 h. The solution was filtered over celite. The filtrate was concentrated and purified by chromatography (*RediSep* 4 g silica-gel column. Eluting solvent: EtOAc) to give 15.9 mg

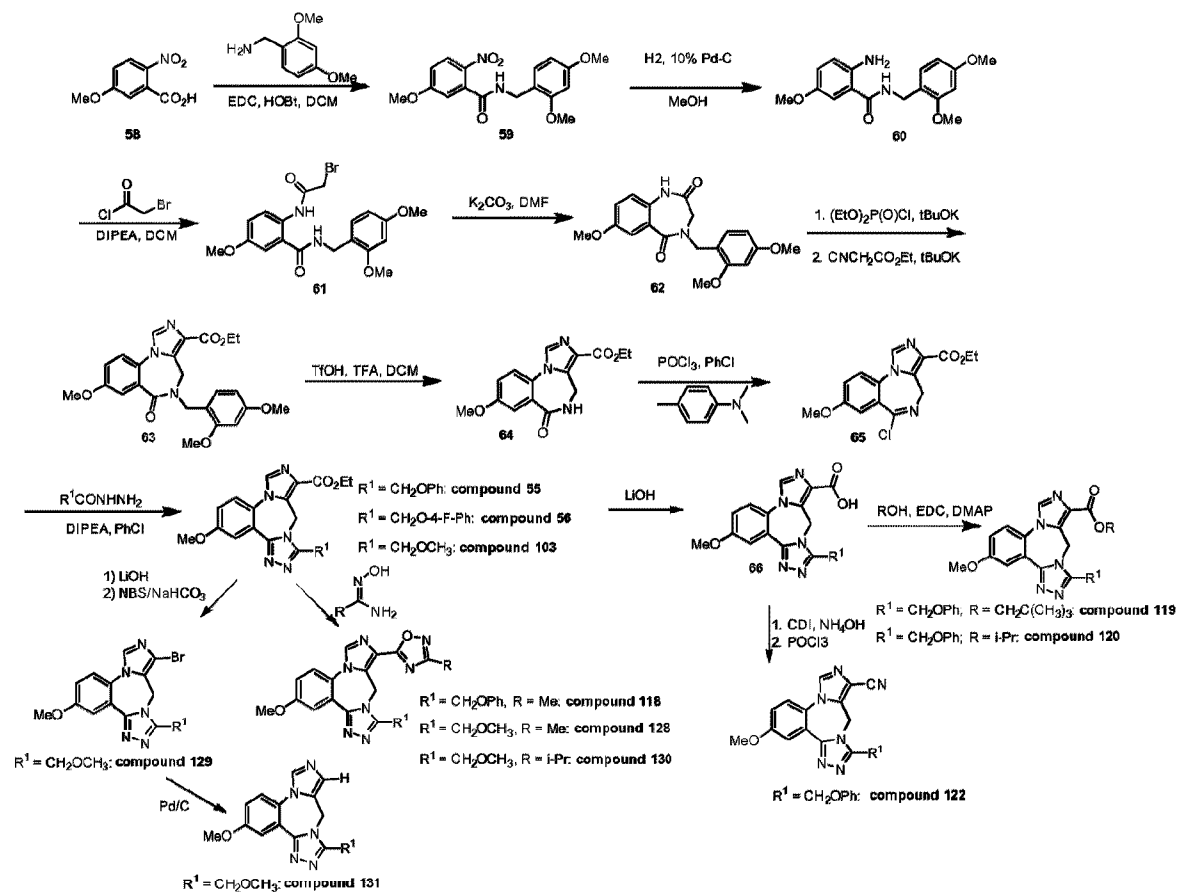
(33%) of the desired product **Compound 102**. MS: $[M+1] = 324$. ^1H NMR (CDCl_3) δ 7.96 (1H, s), 7.78 (1H, s), 7.49 (1H, d, $J = 9$ Hz), 7.42 (1H, d, $J = 8$ Hz), 4.43 (2H, q, $J = 7.5$ Hz), 2.53 (3H, s), 2.44 (3H, s), 1.45 (3H, t, $J = 7.5$ Hz).

5 Example 32: Synthesis of Compound 108:

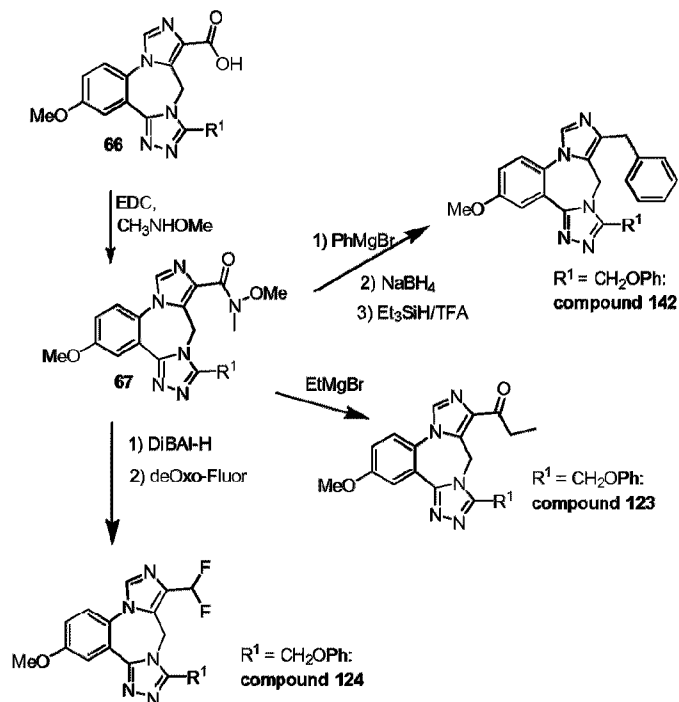


108

[0295] To a suspension of the bromide derivative where $R_1 = \text{OMe}$, (18 mg; 0.043 mmol) in deoxygenated DME (2 mL) was added 2-chlorophenyl boronic acid (10 mg, 0.065 mmol) and a 2M Na_2CO_3 solution (0.13 mL, 0.26 mmol). The suspension was stirred at room temperature for 15 min, then PdCl_2dppf (7 mg, 0.009 mmol) was added. The suspension was heated in an oil bath at 85 C for 1 hour. The reaction mixture was diluted with water and extracted with EtOAc (twice). The combined extracts were washed with brine and dried over Na_2SO_4 . Filtration and concentration gave the crude product which was purified by PrepTLC (eluting system: 5% MeOH/ 47.5% Hex/47.5% EtOAc) to give 3.5 mg (yield 18%) of the product **Compound 108**. MS: $[M+1] = 451$. ^1H NMR (CDCl_3) δ 7.77 (1H, s), 7.63 (1H, d, $J = 3$ Hz), 7.52 (1H, d, $J = 11.5$ Hz), 7.36 (1H, m), 7.31 (1H, m), 7.18 (2H, m), 7.14 (1H, dd, $J = 3, 9$ Hz), 4.38 (2H, q, $J = 7$ Hz), 4.27 (2H, s), 3.94 (3H, s), 1.41 (3H, t, $J = 7$ Hz).

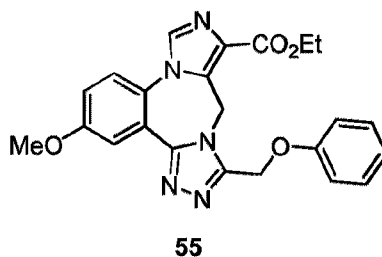


Scheme 18b.



5

Example 33: Synthesis of Compound 55:



55

[0296] To a solution of compound **58** (6.6 g, 33.5 mmol) in dichloromethane (100 mL) were added DIPEA (8.65 g, 67 mmol), HOBt (5.4 g, 36.85 mmol) and EDCI (9.6 g, 50.3 mmol). After about 15 min stirring, to the homogeneous reaction mixture was added a solution of 2,4-dimethoxybenzyl amine (5.6 g, 33.5 mmol) in dichloromethane (50 mL) dropwise under nitrogen atmosphere. The resulting mixture was stirred under nitrogen atmosphere at room temperature for 16h. The reaction mixture was washed successively with 1N NaOH (100 mL), water (100 mL) and brine (100 mL). The organic phase was then dried over Na₂SO₄ and evaporated to give a crude solid product **59** that crystallized from ethyl ether. Filtration and open air suction drying afforded an off-white solid pure

product 9.8g (96%), (MS: [M+1] = 347).

[0297] To a solution of compound **59** (9.8 g, 28.3 mmol) in MeOH/EtOAc (1:1, 100 mL) was added 10% wet Pd-C (1.8 g, 10% mmol). After three consecutive vacuuming and flushing with nitrogen, the heterogeneous reaction mixture was subjected to a balloon
5 hydrogenation at atmosphere pressure up until the absorption of hydrogen ceases, about 4h. The reaction mixture was filtered through a celite pad and evaporated to afford the pure desired product **60** as a brown oil 8.63g (96%), (MS: [M+1 = 317]). This product was used directly in the next step.

[0298] To a solution of compound **60** (8.63g, 27.3 mmol) in dichloromethane (100 mL)
10 was added triethylamine (5.5g, 54.6 mmol). The mixture was cooled with ice bath and treated with bromo acetyl chloride (5.2g, 32.76 mmol) under nitrogen atmosphere. The ice bath was removed and the mixture left stirring for 18h. The reaction mixture was washed successively with saturated NaHCO₃ (100 mL), water (100 mL) and brine (100 mL). The organic phase was then dried over Na₂SO₄ and evaporated to give a crude solid
15 product **61**. The crude product was crystallized from methanol, filtered and dried to afford a brown solid pure product 10.3 g (87%), [MS: 439].

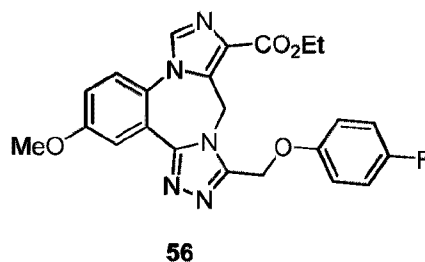
[0299] To a solution of compound **61** (10 g, 22.9 mmol) in DMF (1000 mL) was added K₂CO₃ (4.8 g, 45.8 mmol). The mixture was heated at 50 °C for 24h. LCMS showed a
20 complete conversion to the desired product. The mixture was cooled to room temperature and the inorganic solid was filtered. The solvent was removed under high vacuum. The resulting crude product **62** was crystallized from methanol, filtered and dried to give a pure brown solid product 6.4g (78%), (MS: [M+1] = 357).

[0300] To compound **62** (4.46 g, 12.52 mmol) dissolved in 2.5:1 THF/DMF (50 mL) at -20 °C was added *t*-BuOK (97%, 1.88 g, 16.28 mmol). The mixture was warmed to 25 °C,
25 and after stirring for 30 min was cooled again to -20 °C. Following dropwise addition of diethyl chlorophosphate (2.35 mL, 16.28 mmol), the mixture was stirred for 3 h while warming from -20 to 25 °C. The reaction mixture was re-cooled to 0 °C and to it was added ethyl isocyanoacetate (1.92 mL, 17.53 mmol). Subsequent cooling to -78 °C was followed by addition of *t*-BuOK (97%, 1.88 g, 16.28 mmol) and stirring at RT for 5 h.
30 Progress was monitored by LC/MS. The reaction was quenched by addition of 1:1

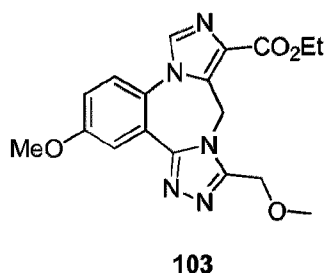
saturated NaHCO_3 / H_2O (140 mL), the precipitate was filtered, washed with H_2O and air dried overnight to afford 4.81 g (85%) of imidazole derivative **63** as a yellow solid (MS: $[\text{M}+1] = 452$).

[0301] To compound **63** (4.81 g, 10.65 mmol) in dichloromethane (35 mL) at 0 °C was
5 added trifluoroacetic acid (35 mL) followed by dropwise trifluoromethanesulfonic acid (1.9 mL, 21.31 mmol). The mixture was warmed to RT, stirred for 2 h, then concentrated to afford a residue which was dissolved in dichloromethane (120 mL). The crude solution was partitioned between chilled saturated NaHCO_3 and dichloromethane. The organic extractions were combined, dried (MgSO_4), filtered and concentrated to afford
10 3.2 g (99%) of deprotected product **64** (brown solid) of sufficient purity to take on the next step (MS: $[\text{M}+1] = 302$).

[0302] To lactam **64** (51.8 mg, 0.172 mmol) and N,N-dimethyl-*p*-toluidine (93.0 mg, 0.688 mmol) stirring in chlorobenzene (1 mL) under nitrogen was added POCl_3 (52.7 mg, 0.344 mmol). The reaction was then heated at 135 °C for 2 h. Upon cooling to room
15 temperature, phenoxy acetic acid hydrazide (228.4 mg, 1.36 mmol) was added in situ to the imino-chloride **65**, followed by DIPEA (90 μL). The reaction was stirred at room temperature for 30 min, then heated at 100 °C for 90 min. The reaction mixture was cooled, saturated NaHCO_3 (aq.) was added, and extracted with ethyl acetate three times; combined organic layer was washed with brine, and dried over MgSO_4 . After filtration
20 and concentration, the product as **Compound 55** was isolated by ISCO flash column chromatography (*RediSep* 4 g column, 1 to 10 % MeOH in DCM as eluting gradient) as a white solid, Wt: 8.6 mg. MS: $[\text{M}+1] = 432$. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.81 (s, 1H), 7.71 (d, 1H, $J=3.5$ Hz), 7.52 (d, 1H, $J=9.0$ Hz), 7.32 (m, 2H), 7.21 (dd, 1H, $J=2.5$, 8.5 Hz), 7.11 (d, 2H, $J=8.5$ Hz), 7.02 (m, 1H), 5.44 (s, 2H), 4.38 (q, 2H, $J=7.5$ Hz), 3.94
25 (s, 3H), 1.39 (t, 3H, $J=7.0$ Hz).

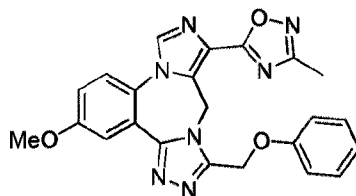
Example 34: Synthesis of Compound 56:

[0303] Compound of **Example 34** was synthesized in an analogous synthetic route as that described for **Example 33**, using 4-fluoro-phenoxy acetic acid hydrazide in the ultimate step to give the compound of **Example 34** as a yellowish solid: MS: [M+1] = 450. ¹H-NMR (500 MHz, CDCl₃) δ: 7.82 (s, 1H), 7.73 (d, 1H, J=3.5 Hz), 7.53 (d, 1H, J=10.0 Hz), 7.22 (dd, 1H, J=3.5, 9.0 Hz), 7.08-6.99 (m, 4H), 5.41 (s, 2H), 4.41 (q, 2H, J=7.0 Hz), 3.95 (s, 3H), 1.42 (t, 3H, J=6.5 Hz).

Example 35: Synthesis of Compound 103:

[0304] Compound of **Example 35** was synthesized in an analogous synthetic route as that described for **Example 33**, using 2-methoxy acetic acid hydrazide in the ultimate step to give the compound of **Example 35** as a yellowish solid: MS: [M+1] = 370.

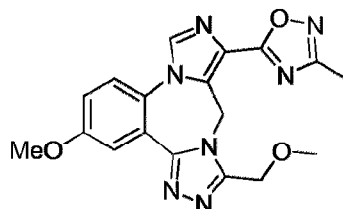
Example 36: Synthesis of Compound 118:



118

[0305] Acetamide oxime (8.4 mg, 0.108 mmol) was azeotroped in toluene three times on a Rotavap, then suspended in THF (1.0 mL). NaH (60% mineral suspension; 3.3 mg, 0.081 mmol) was added, and the mixture was stirred at RT for 10 min. Ester **55** (23.2 mg, 0.054 mmol) was added next. After 40 min stirring at RT, the reaction mixture was heated at 70°C for 4 h. Upon cooling, cold water (5 mL) was added to the reaction mixture, and ppts were collected by filtration, washed with water, and dried to give 9.7 mg (41%) of the desired product as a yellowish solid. MS: [M+1] = 442.

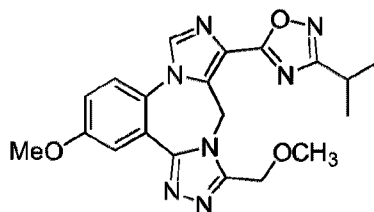
Example 37: Synthesis of Compound 128:



128

[0306] Compound of **Example 37** was synthesized in an analogous synthetic route as that described for **Example 36** above, using ester **Compound 103** in the ultimate step to give the compound of **Example 37** as a brownish solid: MS: [M+1] = 380.

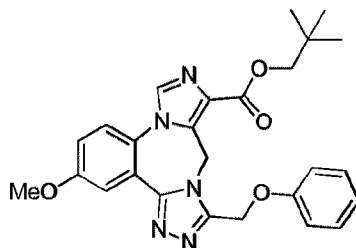
Example 38: Synthesis of Compound 130:



130

[0307] Compound of **Example 38** was synthesized in an analogous synthetic route as that described for **Example 36**, starting with ester **Compound 103** and condensing with isobutyramidoxime to give the compound of **Example 38** as a yellowish solid: MS: $[M+1] = 408$.

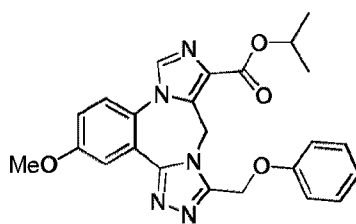
5 **Example 39: Synthesis of Compound 119:**



119

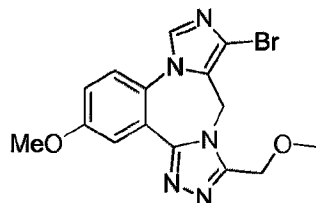
[0308] To the carboxylic acid (13.9 mg, 0.0345 mmol; obtained through LiOH hydrolysis of the precursor ester **55**) stirring in DCM (0.2 mL) was added Neopentyl alcohol (30.4 mg, 0.345 mmol), DMAP (4.2 mg, 0.0345 mmol), and EDC (20 mg, 0.104 mmol). After five hour stirring, the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl , sat. NaHCO_3 , brine, and dried over MgSO_4 . Silica gel chromatographic purification using a gradient of 0 to 8% MeOH in EtOAc gave 11.7mg (72%) of the desired product **Compound 119** as a yellowish solid. MS: $[M+1] = 474$.

Example 40: Synthesis of Compound 120:



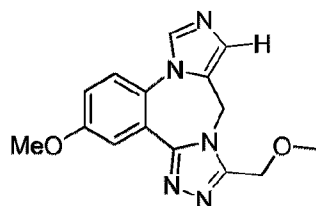
120

[0309] Compound of **Example 40** was synthesized in an analogous synthetic route as that described for **Example 39** above, using 2-propyl alcohol in the ultimate step to give the compound of **Example 40** as a yellowish solid: MS: $[M+1] = 446$.

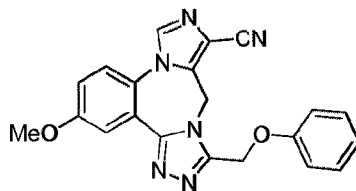
Example 41: Synthesis of Compound 129:**129**

[0310] **Compound 103 (Scheme 18a)** (66.1 mg, 0.179 mmol) was hydrolyzed in a solvent system of THF/water/MeOH (1.8 ml total, 6/5/1 ratio) by treating with LiOH (21.4 mg, 0.895 mmol) at RT for 2 h. Dil. HCl was added to acidify (pH ~3) the reaction mixture. The precipitate was collected by filtration, washed with water, and dried to give 49.0mg (80%) of the acid as a brownish solid.

[0311] The acid thus obtained was stirred in DMF (0.7 mL) at 0°C. NaHCO₃ (48.1 mg, 0.572 mmol) was added, followed by N-bromosuccinamide (96.7mg, 0.543 mmol). After overnight stirring, the reaction was diluted with EtOAc, and washed with sat. NaHCO₃. Aq. Layer was separated and extracted with EtOAc. Combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The product bromide was obtained by silica gel column chromatography with a gradient elution of 0 to 13% MeOH in EtOAc as a white solid (**Compound 129**). Wt: 28.6 mg (53%). MS: [M+1] = 377.

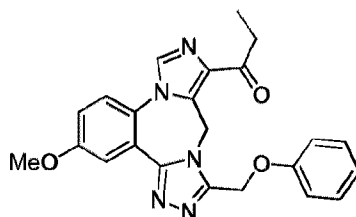
Example 42: Synthesis of Compound 131:**131**

[0312] **Compound 129** (22.6mg, 0.060 mmol) was hydrogenated over 10% Pd-C in EtOAc (1 mL) and MeOH (1 mL) for 16 h. Filtration over Celite, and solvent removal gave 14.9 mg (84%) of the des-bromo product **Compound 131** as a lightly yellowish solid. MS: [M+1] = 298.

Example 43: Synthesis of Compound 122:**122**

[0313] The phenoxy analog (Scheme 18a, R₁ = OPh) of acid 66 (20.4 mg, 0.0506 mmol) was suspended and stirred in DCM (0.5 mL) at RT. Carbonyl diimidazole (16.4 mg, 0.101 mmol) was added. After 2 h stirring, the resulting suspension was cooled to 0 °C, and ammonia (30 uL) was added dropwise. After 20min stirring, ice bath was removed and the reaction was allowed to proceed at RT for 1hr. The reaction was concentrated by removing DCM in vacuo. Water (3 mL) was added, and precipitate was collected by filtration, washed with water, and dried to give 16.2 mg of the crude primary amide which was used without further purification.

[0314] The primary amide (16.2mg, 0.0402 mmol) was treated with POCl₃ (46.2 mg, 0.302 mmol) in 1,4-dioxane (0.5 mL) at 95°C overnight. The reaction mixture was then quenched with sat. NaHCO₃ (5 mL), cooled to 0°C, and precipitate collected by suction filtration, washed with water, and dried to give 13.6 mg (88%) of the nitrile as a brownish solid, Compound 122. MS: [M+1] = 385.

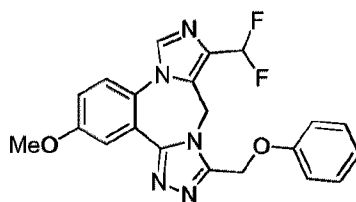
Example 44: Synthesis of Compound 123:**123**

[0315] To Acid 66 (15.8mg, 0.0392 mmol) stirring in THF (0.15 mL) and DCM (0.15ml) was added N,O-dimethylhydroxylamine HCl (4.6 mg, 0.047 mmol) and N-hydroxybenzotriazole hydrate (6.0 mg). EDC (11.3 mg, 0.0588 mmol) and triethylamine

(11.9 mg, 0.118 mmol) were then added, and the reaction was stirred at RT for 12hrs, diluted with EtOAc, washed with sat. NH_4Cl , brine, and dried over MgSO_4 . Filtration and solvent removal in vacuo gave 14.4 mg (82%) of the Weinreb amide which was used without further purification.

- 5 [0316] To the Weinreb amide (14.4 mg, 0.0323 mmol) stirring in THF (0.3 mL) at 0°C was added ethyl magnesium bromide etherate (3M; 0.323 mL). The reaction was allowed to warm to RT and stirred for 14 hrs, quenched with sat. NH_4Cl , extracted with EtOAc three times; combined organic layer washed with brine and dried over MgSO_4 . Filtration and solvent removal gave the crude ketone product which was purified by prep. TLC
10 using 8% MeOH in EtOAc. Wt: 4.6 mg (34%) of **Compound 123**. MS: $[\text{M}+1] = 416$.

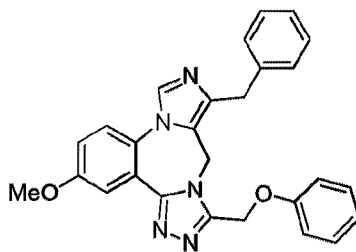
Example 45: Synthesis of Compound 124:



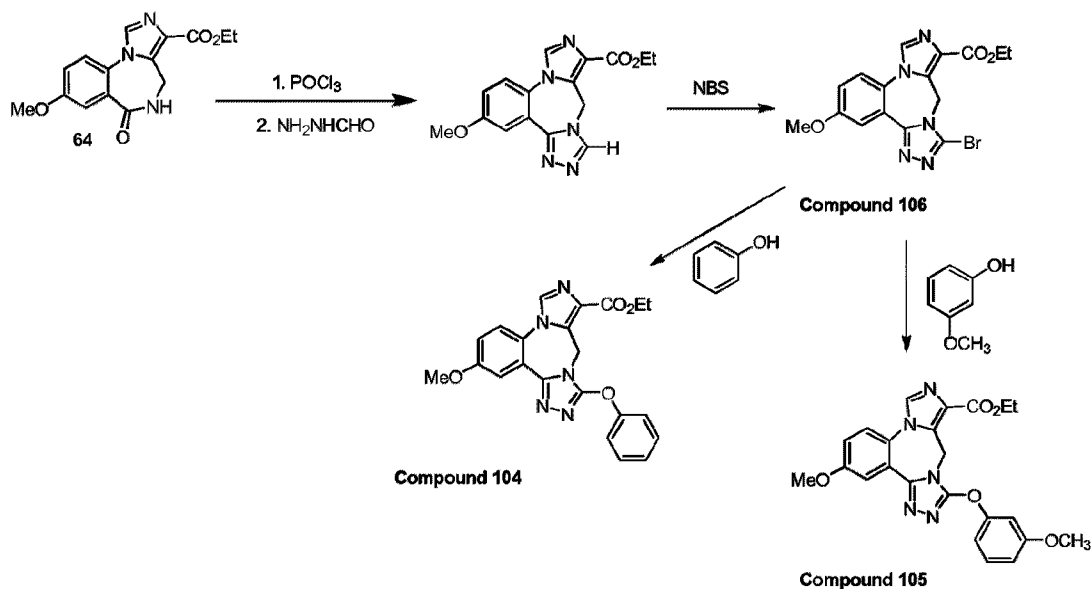
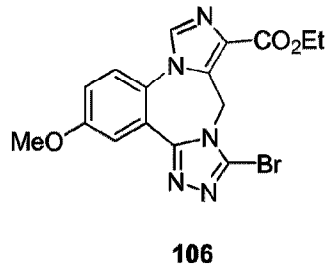
124

- [0317] Weinreb amide (18.0 mg, 0.0403 mmol) described above was treated with DIBAL (1M THF; 0.363 mL) at -78°C for 1hr, then still at -78°C quenched with Rochelle
15 salt solution (20%) overnight. The aq. solution was extracted with EtOAc three times; combined organic layer was washed with brine, and dried over MgSO_4 . Filtration and solvent removal in vacuo gave 13.7mg of the crude aldehyde which was used without further purification.

- [0318] The crude aldehyde (13.7 mg) in DCM (0.7 mL) at RT was treated with Deoxo-
20 Fluor (54.8 mg, 0.248 mmol) for 16hrs. The reaction was quenched with sat. NaHCO_3 (5 mL) for 20 min, extracted with EtOAc three times; combined organic layer washed with brine, and dried over MgSO_4 . Filtration and solvent removal followed by prep. TLC purification using 10% MeOH in EtOAc gave 7.5 mg (52%) of the desired difluoride **Compound 124** as a yellowish solid. MS: $[\text{M}+1] = 410$.

Example 46: Synthesis of Compound 142:**142**

[0319] Weinreb amide (8.8 mg, 0.0197 mmol) from above in THF (0.15 mL) at 0°C was treated with phenylmagnesium bromide (1M THF; 0.54 mL) for 2.5hrs, quenched with sat. NH₄Cl, extracted with EtOAc twice; combined organic layer washed with brine and dried over MgSO₄. Filtration and solvent removal gave the crude ketone which was used without further purification. The ketone in THF (0.5 mL) was treated with NaBH₄ (6 mg) at RT for 2 hrs, then quenched with sat. NH₄Cl, extracted with EtOAc three times; combined organic layer washed with brine, and dried over MgSO₄. Filtration and solvent removal gave the crude alcohol which was used without further purification. The thus obtained alcohol in DCM (1.4 mL) was treated with triethylsilane (86.4 mg, 0.75 mmol) and trifluoroacetic acid (171.0 mg, 1.5 mmol) at 40°C overnight, then concentrated in vacuo, diluted with EtOAc, washed with sat. NaHCO₃, brine, and dried over MgSO₄. Filtration and solvent removal gave the crude benzyl product which was purified by silica gel column chromatography using 0 to 12 % MeOH in EtOAc as eluent; 3.6 mg of **Compound 142** was obtained as a yellowish solid. MS: [M+1] = 450.

Scheme 19:**Example 47: Synthesis of Compound 106:**

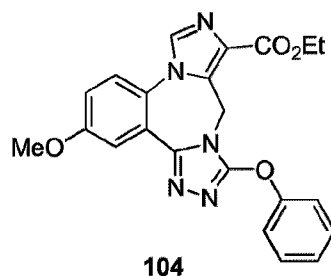
5

[0320] To lactam 64 (185.7 mg, 0.616 mmol) in chlorobenzene (5 mL) was added N,N -dimethyl-*p*-toluidine (333.3 mg, 2.465 mmol) and phosphorous oxychloride (188.9 mg, 1.232 mmol). The reaction mixture was heated at 135°C for 2hrs, cooled to RT, and formylhydrazide (296.0 mg, 4.93 mmol) was added, followed by diisopropyl ethyl amine (238.8 mg, 1.85mmol). Following 30 min stirring at RT, the reaction was heated at 100°C for 1 hr, cooled, and sat. NaHCO_3 (15 mL) added, extracted with EtOAc twice; combined organic layer washed with brine, and dried over MgSO_4 . Filtration and solvent removal gave the crude triazole product which was purified by silica gel column chromatography using 0 to 15% MeOH in EtOAc elution, 35.9mg (18%) was obtained as a brownish solid. MS: $[\text{M}+1] = 326$.

15

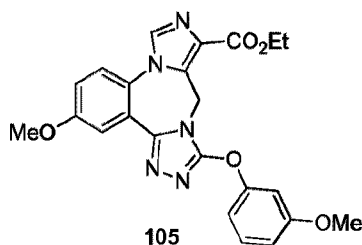
[0321] The triazole from above in DCM (1mL) was treated with N-bromosuccinamide (37.6 mg, 0.21 mmol) at 0°C. The reaction was allowed to warm to RT slowly, and proceeded at RT overnight, diluted with EtOAc, washed with sat. NaHCO₃, brine, and dried over MgSO₄. Filtration and solvent removal gave the crude bromide which was
 5 purified by silica gel column chromatography using 0 to 10% MeOH in EtOAc gradient; 22.9 mg (51%) of **Compound 106** was obtained as an off-white solid. [MS]: 406.

Example 48: Synthesis of Compound 104:



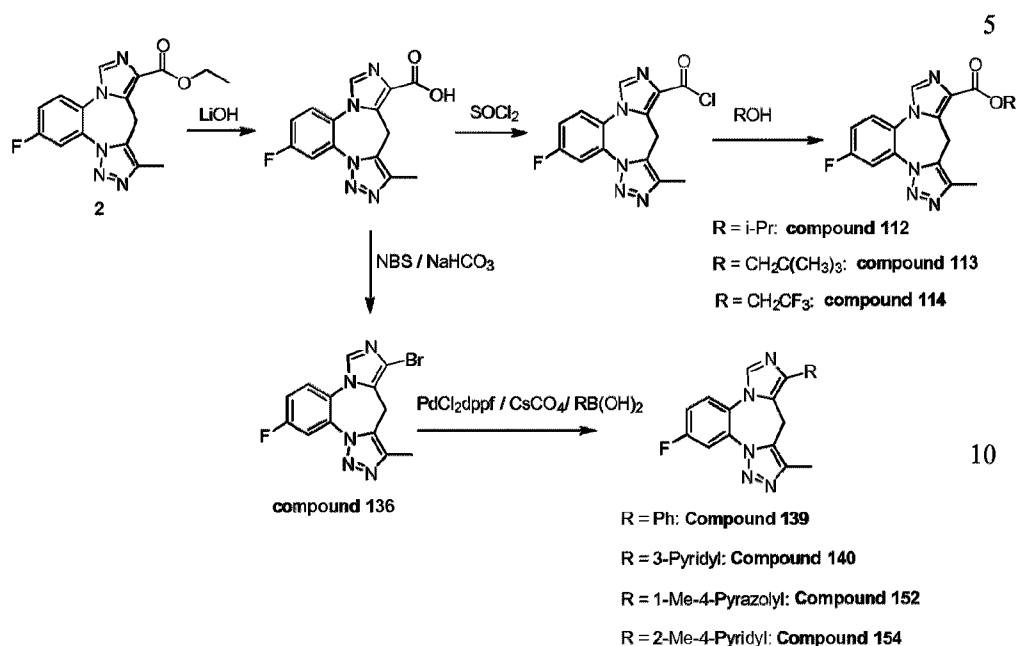
[0322] A microwave reaction vessel was charged with phenol (20.3 mg, 0.216 mmol),
 10 the bromide substrate from **Example 47** (29.1 mg, 0.0719 mmol), Cs₂CO₃ (117.0 mg, 0.360 mmol), diethyl 1,3-acetonedicarboxylate (14.5 mg, 0.0719 mmol), and DMF (0.5 ml). The vessel was flushed with nitrogen gas. CuI (6.8 mg, 0.036 mmol) was added, and the mixture was stirred at RT for 5min before heated @140°C under MW radiation conditions for 60 min. The reaction mixture was diluted with EtOAc, washed with water;
 15 aq. Layer separated and extracted with EtOAc twice; combined organic solution was washed with brine and dried over MgSO₄. Filtration and solvent removal gave the crude ether product which was purified by prep. TLC using 5% MeOH in DCM; 6.6 mg of **Compound 104** was obtained as a yellowish solid. MS: [M+1] = 418.

Example 49: Synthesis of Compound 105:



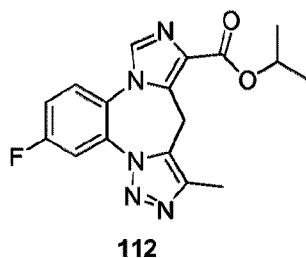
[0323] Compound of **Example 49** was synthesized in an analogous synthetic route as that described for **Example 48** above, using 3-methoxy phenol in the place of phenol, to give the compound of **Example 49** as a yellowish foamy solid: MS: $[M+1] = 448$.

Scheme 20:



Example 50: Synthesis of Compound 112:

15



[0324] To a solution of **Compound 2** (160 mg, 0.49 mmol) in THF (6 mL), water (5 mL) and MeOH (1 mL) was added LiOH (59 mg, 2.45 mmol). The solution was stirred at room temperature for 3 h. The solution was concentrated and the crude material was acidified with 1N HCl until pH 3-4. No solid was observed. EtOAc was added and the organic phase was extracted (3x). The combined extracts were washed with brine and dried over MgSO_4 . Filtration and concentration gave 112 mg (77% yield) of the desired carboxylic acid product as an orange solid MS: $[M+1] = 300$.

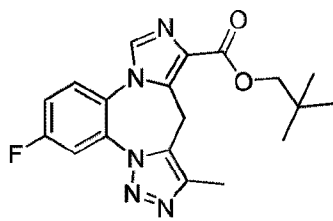
20

[0325] To a suspension of acid (30 mg, 0.1 mmol) in dichloroethane (0.2 mL) was added thionyl chloride (0.4 mL; 5 mmol) and DMF (20 μ L). The resulting solution was heated at 70 C for 1 hour. Another 0.2 mL of thionyl chloride was added and the solution was heated for another 30 min. The solvent was removed. The crude material was dried under vacuo.

[0326] The crude acid chloride (0.1 mmol) was suspended in isopropanol and stirred at room temperature for 18 h. The solvent was evaporated and the crude material was purified by chromatography. (*RediSep* 4 g silica-gel column, eluted with 10% MeOH in DCM) to give 8.6 mg (25% yield) of product **Compound 112** [M+1] =342).

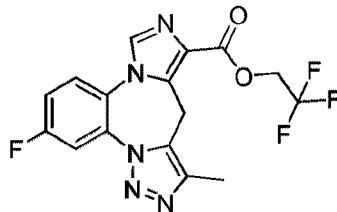
^1H NMR (CDCl_3) δ 7.90 (1H, d, J= 9 Hz), 7.79 (1H, bs), 7.63 (1H, bs), 7.36 (1H, bs), 3.48 (1H, m), 2.45 (3H, s), 1.43 (6H, d, J= 6.5 Hz).

Example 51: Synthesis of Compound 113:

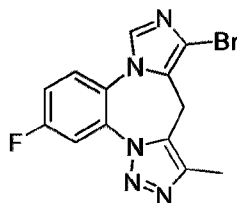


113

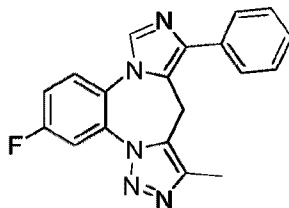
[0327] The crude acid chloride prepared above (0.066 mmol) was suspended in dichloroethane (1mL) and 2,2-dimethyl-1-propanol (300 mg, 3.4 mmol) was added. The solution was stirred at room temperature for 18 h. No product was formed. To the solution above, was added DMAP (5 mg, 0.004 mmol) and DCC (15 mg, 0.073 mmol). The solution was stirred at room temperature for 2 h. The reaction mixture was directly applied on a prep TLC (eluting system: 75 EtOAc in Hexanes) to give 7.2 mg (30% yield) of product **Compound 113**. MS: [M+1]=370. ^1H NMR (CDCl_3) δ 7.91 (1H, dd, J= 3, 9 Hz), 7.79 (1H, s), 7.61 (1H, dd, J= 4.5, 9 Hz), 7.35 (1H, m), 4.11 (2H, s), 2.44 (3H, s), 1.07 (9H,s).

Example 52: Synthesis of Compound 114:**114**

- [0328] The crude acid chloride prepared above (0.066 mmol) was suspended in dichloroethane (1mL) and 2,2,2-trifluoroethanol (0.1 mL, 1.4 mmol) followed by triethylamine (0.6 mL, 4.3 mmol) was added. The solution was stirred at room temperature for 2 h 30 min. The solvent was evaporated and the crude material was purified by chromatography. (*RediSep* 4 g silica-gel column, eluted with EtOAc) then purified with a prep TLC (eluting system: 70 % EtOAc in Hexanes) to give 8.1 mg (32% yield) of product **Compound 114** [M+1] = 382).
- 10 ^1H NMR (CDCl_3) δ 7.91 (1H, dd, J= 3.5, 9.5 Hz), 7.83 (1H, s), 7.63 (1H, dd, J= 4.5, 9.5 Hz), 7.35 (1H, m), 4.77 (2H, m), 2.43 (3H, s).

Example 53: Synthesis of Compound 136:**136**

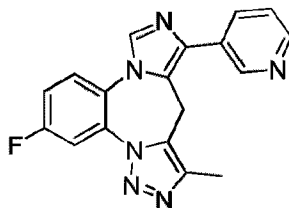
- 15 [0329] To a solution of acid prepared in **Example 50** (100 mg, 0.33 mmol) in DMF (1.5 mL) cooled with an ice bath was added NaHCO_3 (111 mg, 1.32 mmol) followed by NBS (117 mg, 0.66 mmol). The solution was stirred at room temperature for 14 h. The reaction mixture was diluted with water and extracted with EtOAc (5X). The combined extracts were washed with brine (2x) and dried over MgSO_4 . Filtration and concentration gave a crude product. Chromatography (*RediSep* 4 g silica-gel column, eluted with EtOAc) to give 93 mg (85% yield) of product **Compound 136** [M+1] = 334). ^1H NMR (CDCl_3) δ 7.87 (1H, dd, J= 2.5, 8.5 Hz), 7.72 (1H, s), 7.56 (1H, dd, J= 6, 10 Hz), 7.33 (1H, m), 2.44 (3H, s).
- 20

Example 54 Synthesis of Compound 139:**139**

[0330] General coupling procedure: To a solution of **Compound 136** (20 mg, 0.061 mmol) in degassed DME (0.9 mL) and water (0.1 mL) was added phenyl boronic acid (11 mg, 0.092 mmol), cesium carbonate (80 mg, 0.24 mmol) and Pd Cl₂dppf (5 mg, 0.066 mmol). The suspension was heated at 80 °C for one hour. The reaction mixture was diluted with water, extracted with EtOAc (3X). The combined extracts were washed with brine (2x) and dried over MgSO₄. Filtration and concentration gave a crude product which was purified by prep TLC (eluting system: 3% MeOH in EtOAc).

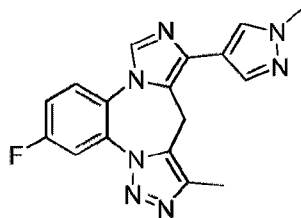
[0331] **Compound 139** was prepared using phenyl boronic acid. 10.8 mg (54% yield) of product was obtained. MS: [M+1] = 332. ¹H NMR (CDCl₃) δ 7.87 (1H, dd, J= 3.5, 9.5 Hz), 7.85 (1H, s), 7.63 (3H, m), 7.50 (2H, t, J= 6.5 Hz), 7.35 (2H, m), 2.41 (3H, s).

15

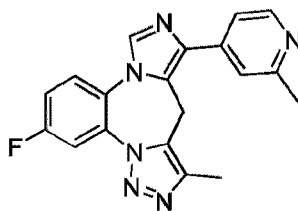
Example 55: Synthesis of Compound 140:**140**

[0332] **Compound 140** was prepared similarly using 3-pyridine boronic acid. 8.9 mg (27% yield) of product was obtained. MS: [M+1] = 333. ¹H NMR (CDCl₃) δ 8.86 (1H, s), 8.63 (1H, d, J= 5 Hz), 8.01 (1H, m), 7.90 (2H, m), 7.64 (1H, dd, J= 5.5, 9 Hz), 7.44 (1H, m), 7.36 (1H, m), 2.39 (3H, s).

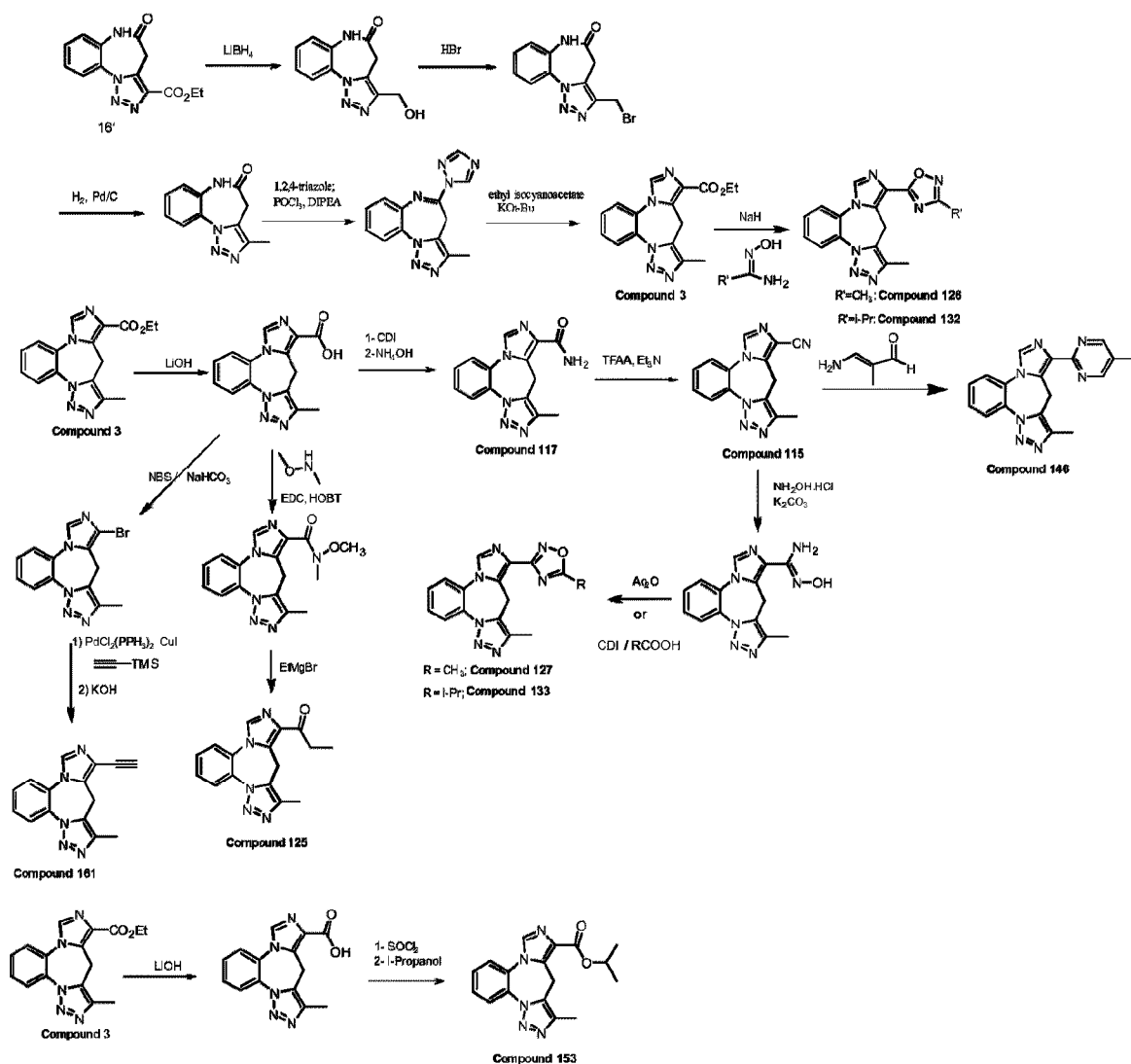
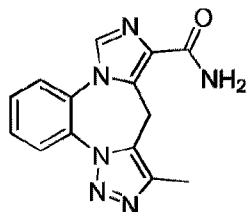
20

Example 56: Synthesis of Compound 152:**152**

[0333] **Compound 152** was prepared using 1-methylpyrazole-4-boronic acid, HCl. 12.5 mg (63% yield) of product was obtained. MS: $[M+1] = 336$. ^1H NMR ($\text{CDCl}_3 + \text{MeOD}_4$) δ 9.04 (1H, bs), 7.99 (1H, bs), 7.75 (2H, m), 7.41 (2H, m), 3.95 (3H, s), 2.32 (3H, s).

Example 57: Synthesis of Compound 154:**154**

10 [0334] **Compound 154** was prepared using 2-methylpyridine-4-boronic acid pinacol ester. 7.1 mg (34% yield) of product was obtained. MS: $[M+1] = 347$. ^1H NMR (CDCl_3) δ 8.6 (1H, d, $J = 6$ Hz), 7.89 (1H, dd, $J = 3.5, 8.5$ Hz), 7.87 (1H, s), 7.64 (1H, dd, $J = 5.5, 9$ Hz), 7.48 (1H, s), 7.36 (2H, m), 2.64 (3H, s), 2.41 (3H, s).

Scheme 21:**Example 58: Synthesis of Compound 117:****117**

- 5 [0335] In a 100 mL round-bottom flask, the lactam ester **16'** (2 g, 7.35 mmol; which was prepared in analogous fashion as **16** described in **Scheme 11**) was dissolved in 60

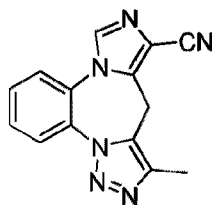
- mL of anhydrous THF. The solution was stirred at room temperature under a nitrogen atmosphere. LiBH_4 (2 M in THF, 4 mL, 8 mmol) was added slowly. The reaction mixture was stirred under a nitrogen atmosphere for 18 h. More LiBH_4 (2 M in THF, 2 mL, 4 mmol) was added slowly. The reaction mixture was stirred for another 24 h. A mixture of EtOAc/EtOH (20 mL/20 mL) was added to the reaction mixture and it was concentrated. The residue was taken up in MeOH and silica gel was added. After volatile solvents were evaporated, the solid was loaded onto a *RediSep* 40 g silica-gel column. The desired product was eluted with 5:1 v/v $\text{CH}_2\text{Cl}_2/\text{MeOH}$. The alcohol was obtained as a white solid (1.14 g, 67% yield). MS: $[\text{M}+1] = 231$.
- 10 [0336] The alcohol (1.14 g, 4.96 mmol) was suspended in 16 mL of HBr 33% in AcOH and heated at 80°C for 18 h. The solution was cooled down with an ice bath and diluted with EtOAc. A white solid could be observed. Slowly, a sat. aq. NaHCO_3 solution was added. Large amount of EtOAc and MeOH were used to solubilize the solid. The organic phase was extracted (3x) and the combined organic phases were washed with brine, dried over MgSO_4 . Filtration and concentration gave a crude product which was used in the next step without further purification. MS: $[\text{M}+1] = 293$.
- 15 [0337] To a solution of alkyl bromide derivative (4.96 mmol) in EtOAc (50 mL), MeOH (200 mL) and THF (50 mL) was added wet 10% Pd/C (250 mg) and the resulting suspension was stirred under a hydrogen atmosphere for 7 days. The suspension was filtered through Celite and the resulting solution was concentrated and co-evaporated with toluene. The crude product was used in the next step without further purification.
- 20 [0338] To a solution of 1,2,4-triazole (2.7 g, 39.7 mmol) in anhydrous CH_3CN (20 mL) at 0°C was added *i*- Pr_2NEt (7.6 mL, 43.6 mmol). Once all the triazole was dissolved, POCl_3 (1.11 mL, 11.9 mmol) was added. The mixture was stirred at 0°C for 2 h. The solution was transferred into the flask containing the lactam (4.96 mmol). The resulting solution was heated in an oil bath at 80°C for 16 h. The viscous mixture was cooled with an ice bath and the solvent evaporated. Diluted with EtOAc and water was added. It was extracted with EtOAc five times. The combined extracts were washed with brine and dried over MgSO_4 . Filtration and concentration gave a crude product, which was used directly in the next reaction. MS: $[\text{M}+1] = 266$.
- 25 [0339] A solution of KO^tBu (1.11 g, 9.92 mmol) in DMF (10 mL) was cooled to -50°C under a nitrogen atmosphere. Ethyl isocyanoacetate (1.2 mL, 10.9 mmol) was added slowly. The mixture was stirred between -60°C to -40°C for 1 h. The above crude 1,2,4-
- 30

triazolo intermediate from step 4 (4.96 mmol) in DMF (5 mL) was added slowly. The mixture was allowed to warm to room temperature over 16 h. Saturated NH_4Cl aqueous solution was added and it was extracted with EtOAc three times. The combined extracts were washed with brine (3x) and dried over MgSO_4 . Filtration and concentration gave a crude product. Chromatography (*RediSep* 24 g silica-gel column, eluted with 70% EtOAc in Hexanes) to give 296 mg (20% yield for 4 steps) of product. MS: $[\text{M}+1] = 310$.

[0340] To a solution of ester derivative (260 mg, 0.84 mmol) in THF (6 mL), water (5 mL) and MeOH (1 mL) was added LiOH (117 mg, 4.85 mmol). The solution was stirred at room temperature for 3 h. The solution was concentrated and the crude material was acidified with 1N HCl until pH 3-4. The solid was collected by multiple filtrations to give 178 mg (75% yield) of the desired product. MS: $[\text{M}+1] = 282$.

[0341] To a suspension of acid (80 mg, 0.28 mmol) in THF (2 mL) was added CDI (50 mg, 0.31 mmol). The suspension was heated at 65 C for 3 h. LCMS indicated that the reaction was incomplete. More CDI (10 mg) was added and the solution heated for another hour. The solution was cooled down to room temperature and a NH_4OH solution (1 mL) was added. The solution was stirred for one hour. The solid was collected by filtration to give 33 mg (42%) of the **Compound 117** as the desired product as a white solid. MS: $[\text{M}+1] = 281$. ^1H NMR (MeOD_4) δ 8.1 (1H, s), 7.9 (1H, s), 7.73 (3H, m), 7.07 (2H, s), 2.40 (3H, s).

Example 59: Synthesis of Compound 115:

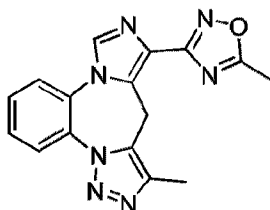


115

[0342] To a suspension of **Compound 117** (8 mg, 0.029 mmol) and triethylamine (8 μL ; 0.058 mmol) in THF (1 mL) was added trifluoroacetic anhydride (8 μL ; 0.058 mmol). The reaction mixture was stirred at room temperature for 16 h. LCMS indicated only 30% conversion. More trifluoroacetic anhydride (30 μL) and triethylamine (30 μL) were added. The solution became clear and stirred for another hour. The reaction was quenched with MeOH. The solvent was evaporated and the crude material was purified

by prep TLC (eluting system: 70% EtOAc in Hexanes) to give 6.6 mg (83%) of the Compound 115. MS: $[M+1] = 263$. ^1H NMR (CDCl_3) δ 8.17 (1H, d, $J = 7$ Hz), 7.88 (1H, s), 7.67 (3H, m), 2.46 (3H, s).

5 **Example 60: Synthesis of Compound 127:**



127

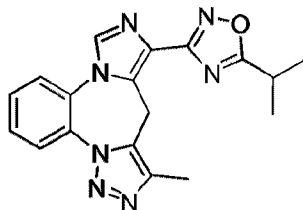
[0343] To a suspension of **Compound 115** (16 mg, 0.06 mmol) in EtOH (0.8 mL) and water (0.2 mL) was added hydroxylamine hydrochloride (6 mg, 0.09 mmol) and potassium carbonate (12 mg, 0.09 mmol). The suspension was heated at 80 °C for 16 h.

10 The solution was diluted with EtOAc and washed with water. Aq. Layer was separated and extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over MgSO_4 . Filtration and concentration gave 12.2 mg (67% yield) of the desired product. MS: $[M+1] = 296$.

[0344] A suspension of oxime (10 mg, 0.034 mmol) in acetic anhydride (0.5 mL) was heated at 110 °C for 1 hour. Then, the solution was heated at 130 °C for 1 hour. Finally, the temperature was increased to 140 °C and heated for another 2 h. The reaction mixture was cooled down and EtOH (1mL) was added to the reaction mixture which was heated for 16 h at 80 °C. The solvent was evaporated and the crude material was purified by prep TLC (eluting system: EtOAc) to give 6.1 mg (56% yield) of the desired product **Compound**

20 **127**. MS: $[M+1] = 320$. ^1H NMR (CDCl_3) δ 8.16 (1H, m), 7.92 (1H, s), 7.65 (3H, m), 2.68 (3H, s), 2.46 (3H, s).

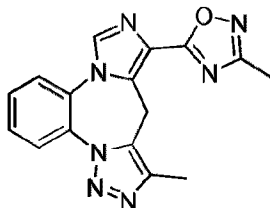
Example 61: Synthesis of Compound 133:



133

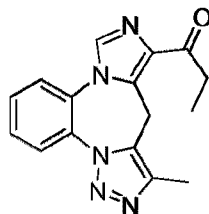
[0345] To a solution of isobutyric acid (19 μ L, 0.2 mmol) in THF (0.5 mL) was added CDI (10 mg, 0.062 mmol). The solution was stirred at room temperature for 2 h. The solution was then transferred into a vial containing the oxime derivative described above (12 mg, 0.041 mmol) and heated at 70 °C for 2 h. LCMS indicated that the reaction was incomplete. Another batch of reagent (isobutyric acid and CDI) was prepared and added to the reaction mixture which was heated at 70 °C for another hour. LCMS indicated that all starting material was consumed. The solvent was evaporated and the crude material was suspended in isobutyric acid (1 mL) and heated at 130 °C for one hour. The solvent was evaporated and the crude material was purified by Prep TLC (eluting system: 70% EtOAc in Hexanes) to give 6.7 mg (71%) of the desired product **Compound 133**. MS: [M+1] = 348. ¹H NMR (CDCl₃) δ 8.16 (1H, m), 7.92 (1H, s), 7.65 (3H, m), 3.32 (1H, m), 2.46 (3H, s), 1.5 (6H, d, J = 7 Hz).

Example 62: Synthesis of Compound 126:



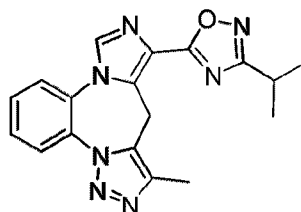
126

[0346] Acetamide oxime was azeotroped three times in toluene before use. To a suspension of acetamide oxime (24 mg, 0.32 mmol) in THF (1 mL) was added NaH 60% in oil dispersion (13 mg, 0.32 mmol). The suspension was stirred at room temperature for 15 min. Compound 3 (50 mg, 0.16 mmol) was added. The vial containing the ester was rinsed with DMF (1 mL) which was added to the reaction mixture. The resulting brown suspension was stirred at room temperature for 30 min then heated at 70 °C for 2 h. The suspension was quenched with water and the solution was kept in the fridge overnight. The solid was collected by multiple filtrations to give 16 mg (31% yield) of product **Compound 126**. MS: [M+1] = 320. ¹H NMR (CDCl₃) δ 8.18 (1H, m), 7.94 (1H, s), 7.67 (3H, m), 2.51 (3H, s), 2.46 (3H, s).

Example 63: Synthesis of Compound 125:**125**

[0347] To a suspension of the carboxylic acid derived from **Compound 3** (30 mg, 0.11 mmol), N,O-dimethylhydroxylamine hydrochloride (13 mg, 0.13 mmol), 1-
 5 hydroxybenzotriazole hydrate (17 mg, 0.11 mmol) and triethylamine (46 μ L, 0.33 mmol) in THF (0.3 mL) and DCM (0.3 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (32 mg, 0.17 mmol). The solution was stirred at room temperature for 16 h. The reaction mixture was quenched with a saturated ammonium chloride solution and extracted with EtOAc (3x). The combined extracts were washed
 10 with brine and dried over MgSO_4 . Filtration and concentration gave 31.2 mg (88% yield) of an orange solid which was used in the next step without further purification. MS: $[M+1] = 325$.

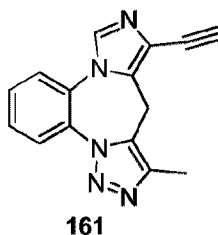
[0348] To a solution of above Weinreb amide derivative (31.2 mg, 0.093 mmol) in THF (0.5 mL) cooled at -78°C was added a solution of 3 M ethyl magnesium bromide (0.31
 15 mL, 0.93 mmol). The reaction mixture was stirred below -10°C over a period of 60 min. Then, it was quenched with a saturated ammonium chloride solution and extracted with EtOAc (2X). The combined extracts were washed with brine and dried over MgSO_4 . Filtration and concentration gave a crude product. Chromatography (*RediSep* 4 g silica-gel column, eluted with 80% EtOAc in Hexanes) to give 11.1 mg (41% yield) of product
 20 **Compound 125**. MS: $[M+1] = 294$. ^1H NMR (CDCl_3) δ 8.15 (1H, m), 7.76 (1H, s), 7.65 (3H, m), 3.08 (2H, q, $J = 7$ Hz), 2.44 (3H, s), 1.22 (3H, t, $J = 7$ Hz).

Example 64: Synthesis of Compound 132:**132**

[0349] To a solution of isobutyronitrile (2.6 mL; 29 mmol) in EtOH (30 mL) and water (10 mL) was added hydroxylamine hydrochloride (2.01 g, 29 mmol) and potassium carbonate (4 g, 29 mmol). The resulting suspension was heated at 80 °C for 16 h. The solvent was removed under vacuo. The residue was co-evaporated with toluene. The crude material was washed with EtOH and filtered to remove the sodium chloride. The filtrate was evaporated, co-evaporated with toluene several times and dried under vacuo to give 2 g (69%) of N-hydroxybutyramidine.

[0350] To a suspension of N-hydroxybutyramidine (47 mg, 0.46 mmol) in THF (1 mL) was added NaH 60% in oil dispersion (18 mg, 0.46 mmol). The suspension was stirred at room temperature for 30 min. Compound 3 (47 mg, 0.15 mmol) in THF (1 mL) was added. The resulting suspension was stirred at room temperature for 30 min then heated at 70 °C for 2 h. After one hour, only 50% conversion was observed. No change was observed after another hour. More reagent (N-hydroxybutyramidine and NaH) as described above was prepared and added to the reaction mixture which was heated for another 40 min. At this point, LCMS showed that the reaction was complete. The suspension was quenched with water. Some MeOH was added to help a complete dissolution, and the solution was extracted with EtOAc (3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Filtration and concentration gave a crude product. Chromatography (*RediSep* 4 g silica-gel column, eluted with EtOAc) to give 20 mg (38% yield) of product **Compound 132**. MS: [M+1] = 348. ¹H NMR (CDCl₃) δ 8.18 (1H, d, J = 8 Hz), 7.93 (1H, s), 7.69 (3H, m), 3.22 (1H, m), 2.46 (3H, s), 1.43 (6H, d, J = 9.5 Hz)

Example 65: Synthesis of Compound 161:

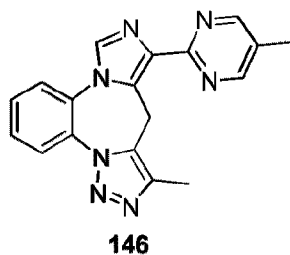


[0351] To a solution of acid derived from **Compound 3** (90 mg, 0.32 mmol) in DMF (2 mL) cooled with an ice bath was added NaHCO₃ (108 mg, 1.28 mmol) followed by NBS (114 mg, 0.64 mmol). The solution was stirred at room temperature for 18 h. The reaction

mixture was diluted with water and extracted with EtOAc (3X). The combined extracts were washed with brine (2x) and dried over MgSO₄. Filtration and concentration gave a crude product. Chromatography (*RediSep* 4 g silica-gel column, eluted with EtOAc) to give 54 mg (53% yield) of product. MS: [M+1]=316.

- 5 [0352] To a solution of bromide derivative (30 mg, 0.1 mmol) in dioxane (1 mL) and triethylamine (1 mL) was added TMS-acetylene (71 μ L, 0.5 mmol), CuI (2 mg, 0.01 mmol) and PdCl₂(PPh₃)₂ (7 mg, 0.01 mmol). The solution was heated at 110 °C for 6 h. More Pd catalyst (7mg) and TMS-acetylene (0.2 mL) were added and the reaction mixture heated for an additional 12 h. At this time, LCMS showed about 80% conversion.
- 10 More Pd catalyst (7mg) and TMS-acetylene (0.2 mL) were added and the reaction mixture heated for an additional 12 h. LCMS showed complete conversion. The reaction mixture was then diluted with water and extracted with EtOAc (3x). The combined extracts were washed with brine (2x) and dried over MgSO₄. Filtration and concentration gave a crude product. Chromatography (*RediSep* 4 g silica-gel column, eluted with 70%
- 15 EtOAc in Hexanes) to give 23 mg (69% yield) of product. MS: [M+1] =334.
- [0353] To a solution of alkyne derivative (23 mg, 0.069 mmol) in MeOH (0.6 mL) and H₂O (0.2 mL) was added KOH (4 mg, 0.076 mmol) at 0 C. The solution was let warm to room temperature over 16 h. The reaction mixture was diluted with a saturated aqueous ammonium chloride solution and extracted with EtOAc (2X). The combined extracts
- 20 were washed with brine (2x) and dried over MgSO₄. Filtration and concentration gave a crude product which was purified by prep TLC (eluting system: 80% EtOAc in Hexanes) to give 8.1 mg (45% yield) of product **Compound 161**. MS: [M+1]=262. ¹H NMR (CDCl₃) δ 8.13 (1H, m), 7.76 (1H, s), 7.62 (3H, m), 4.09 (2H, bs), 3.28 (1H, s), 2.44 (3H, s).

25 **Example 66: Synthesis of Compound 146:**

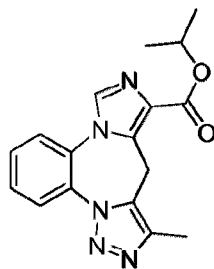


[0354] To a solution of 3-amino-2-methylacrolein (65 mg, 0.76 mmol) in anhydrous

THF (2 mL) was added NaH 60% in oil dispersion (30 mg, 0.76 mmol). The suspension was stirred at room temperature for 15 min. **Compound 115** (50 mg, 0.19 mmol) was added and the reaction mixture was heated at 65°C for 3 h. The reaction mixture was cooled down with an ice bath and water was added. The reaction mixture was stored in the fridge overnight. The solid was collected by filtration to give 27.5 mg (44% yield) of a white solid **Compound 146**. MS: $[M+1] = 330$. ^1H NMR (CDCl_3) δ 8.66 (2H, s), 8.15 (1H, m), 7.89 (1H, s), 7.65 (3H, m), 2.44 (3H, s), 2.36 (3H, s).

Example 67: Synthesis of Compound 153:

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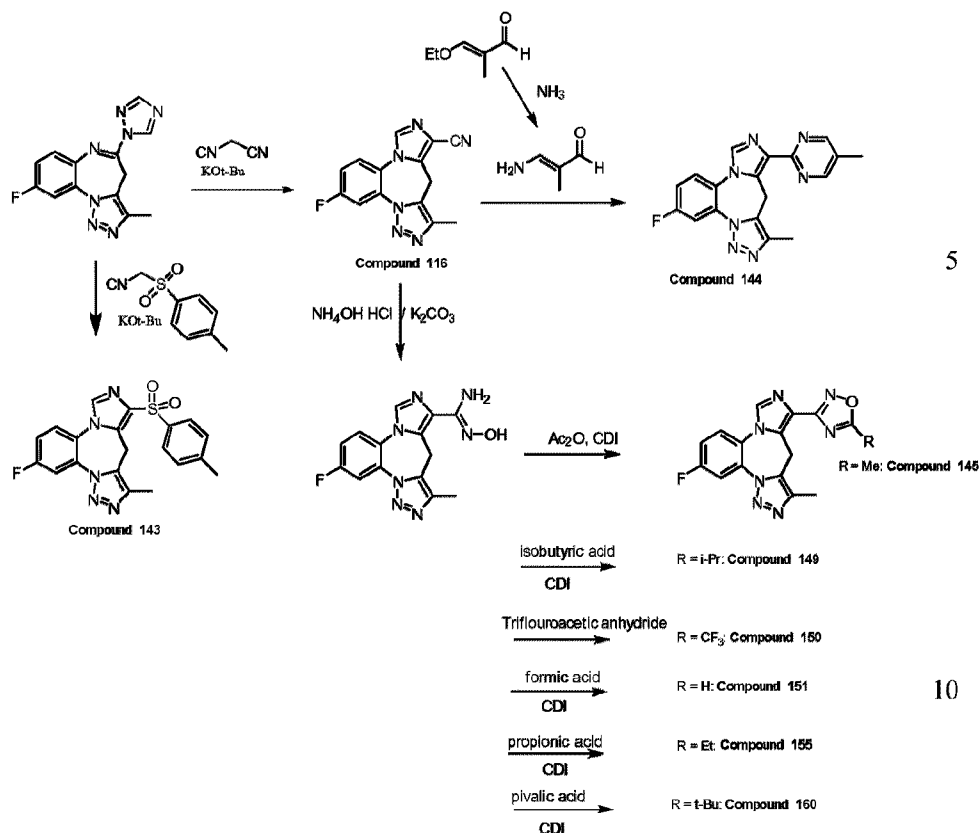


153

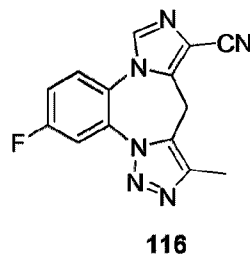
[0355] To a suspension of acid derived from **Compound 3** (30 mg, 0.11 mmol) in dichloroethane (0.2 mL) was added thionyl chloride (1 mL; 13.8 mmol) and DMF (20 μL). The resulting solution was heated at 70 °C for 1 hour. The solvent was removed. The crude material was dried under vacuo. The crude material was suspended in isopropanol (2 mL) and stirred at room temperature for 16 h. The solvent was evaporated, co-evaporated with methanol and the crude material was purified by prep TLC (eluting system: EtOAc) to give 7.2 mg (21% yield) of the product **Compound 153**. MS: $[M+1] = 324$. ^1H NMR (CDCl_3) δ 8.15 (1H, d, $J = 8$ Hz), 7.81 (1H, s), 7.64 (3H, m), 5.32 (1H, q, $J = 7$ Hz), 2.45 (3H, s), 1.43 (6H, d, $J = 7$ Hz).

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Scheme 22



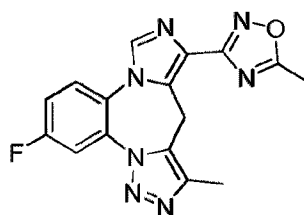
Example 68: Synthesis of Compound 116:



- [0356] An alternate route to the nitrile-substituted imidazole derivatives was also implemented. As an example, **Compound 116** was prepared from imino-derivative as shown in **Scheme 22**. A solution of isocyanatoacetonitrile (206 mg, 3.12 mmol) in DMF (7 mL) was cooled to -50°C under a nitrogen atmosphere. KOt-Bu (320 mg, 2.85 mmol) was added. The mixture was stirred at -50°C for 1 h. The imino derivative (prepared in identical fashion to the imino derivative shown above in **Scheme 21**) (350 mg, 1.24 mmol) was added slowly at -50°C . The mixture was allowed to warm to room

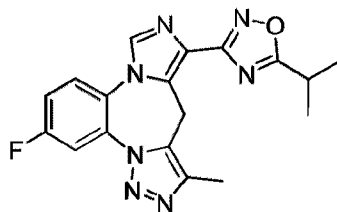
- temperature over 16 h. Saturated NH_4Cl aqueous solution was added and it was extracted with EtOAc three times. The combined extracts were washed with brine (3x) and dried over MgSO_4 . Filtration and concentration gave a crude product. Chromatography (*RediSep* 12 g silica-gel column, eluted with 70% EtOAc in Hexanes) to give 230 mg (70% yield) of the product **Compound 116**. MS: $[\text{M}+1] = 281$. ^1H NMR (CDCl_3) δ 7.92 (1H, dd, $J = 3, 8.5$ Hz), 7.81 (1H, s), 7.61 (1H, dd, $J = 4.5, 9$ Hz), 7.38 (1H, m), 2.47 (3H, s).

Example 69: Synthesis of Compound 145:

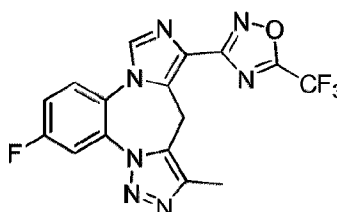


145

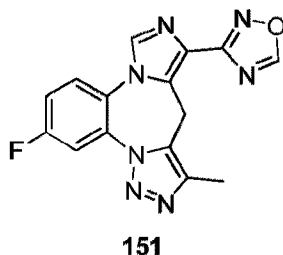
- [0357] To a suspension of cyanide derivative **Compound 116** (50 mg, 0.18 mmol) in EtOH (1.6 mL) and water (0.4 mL) was added hydroxylamine hydrochloride (17 mg, 0.24 mmol) and potassium carbonate (28 mg, 0.2 mmol). The suspension was heated at 80 °C for 30 min then cooled down to room temperature. A solid precipitate was collected by filtration to give 37.8 mg (68% yield) of the desired amino oxime product, $[\text{M}+1] = 314$.
- [0358] A suspension of amide oxime (10 mg, 0.032 mmol) in acetic anhydride (0.5 mL) was heated at 140 °C for 4 h. The reaction mixture was cooled down and EtOH (1 mL) was added to the reaction mixture which was heated for 16 h at 80 °C. The solvent was evaporated and the crude material was purified by prep TLC (eluting system: EtOAc) to give 6.6 mg (61% yield) of the desired product **Compound 145**. MS: $[\text{M}+1] = 338$.
- ^1H NMR (CDCl_3) δ 7.91 (1H, dd, $J = 3.5, 8.5$ Hz), 7.89 (1H, s), 7.65 (1H, dd, $J = 5.5, 10$ Hz), 7.35 (1H, m), 2.69 (3H, s), 2.45 (3H, s).

Example 70: Synthesis of Compound 149:**149**

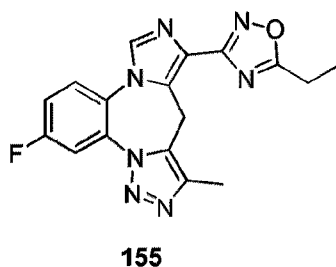
[0359] To a solution of isobutyric acid (30 μ L, 0.32 mmol) in THF (0.5 mL) was added CDI (16 mg, 0.096 mmol). The solution was stirred at room temperature for 2 h. The
 5 above amide oxime derivative (10 mg, 0.032 mmol) was added and the reaction mixture was heated at 70 C for 45 min. The solvent was evaporated and the crude material was suspended in isobutyric acid (1 mL) and heated at 130 °C for 3 h. The solvent was evaporated and the crude material was purified by Prep TLC (eluting system: 80% EtOAc in Hexanes) to give 10.6 mg (91%) of the desired product **Compound 149**. MS: [M+1] =
 10 366. ^1H NMR (CDCl_3) δ 7.90 (1H, dd, J= 3.5, 9 Hz), 7.89 (1H, s), 7.66 (1H, dd, J= 4.5, 8.5 Hz), 7.36 (1H, m), 3.32 (1H, q, J= 6.5 Hz), 2.46 (3H, s), 1.49 (6H, d, J= 8 Hz).

Example 71: Synthesis of Compound 150:**150**

[0360] A suspension of the above amide oxime (10 mg, 0.032 mmol) in trifluoroacetic anhydride (0.5 mL) was heated under reflux for 10 min. The solvent was evaporated and the crude material was purified by Prep TLC (eluting system: 80% EtOAc in Hexanes) to give 11.8 mg (94%) of the desired product **Compound 150**. MS: [M+1] = 392. ^1H NMR (CDCl_3) δ 7.92 (2H, m), 7.69 (1H, dd, J= 5.5, 9.5 Hz), 7.39 (1H, m), 2.45 (3H, s).

Example 72: Synthesis of Compound 151:

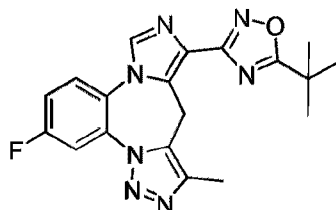
[0361] To a solution of formic acid (12 μ L, 0.32 mmol) in THF (0.5 mL) was added CDI (16 mg, 0.096 mmol). The solution was stirred at room temperature for 2 h. The
 5 above amide oxime derivative (10 mg, 0.032 mmol) was added and the reaction mixture was heated at 70 °C for 45 min. The solvent was evaporated and the crude material was suspended in formic acid (1 mL) and heated at 60 °C for 3 h. The solvent was evaporated and the crude material was purified by Prep TLC (eluting system: 80% EtOAc in Hexanes) to give 2.1 mg (20%) of the desired product **Compound 151**. MS: [M+1] =
 10 324. ^1H NMR (CDCl_3) δ 8.83 (1H, s), 7.92 (1H, dd, J= 3.5, 8 Hz), 7.91 (1H, s), 7.65 (1H, dd, J= 4.5, 9Hz), 7.37 (1H, m), 2.45 (3H, s).

Example 73: Synthesis of Compound 155:

[0362] To a solution of propionic acid (22 μ L, 0.29 mmol) in THF (0.5 mL) was added
 15 CDI (14 mg, 0.087 mmol). The solution was stirred at room temperature for 1 hour. The above amide oxime derivative (10 mg, 0.032 mmol) in THF (0.5 mL) was added and the reaction mixture was heated at 70 °C for 90 min. The solvent was evaporated and the crude material was suspended in propionic acid (1 mL) and heated at 130 °C for 1 h. The solvent was evaporated and the crude material was purified by Prep TLC (eluting system:
 20 80% EtOAc in Hexanes) to give 9.4 mg (94%) of the desired product **Compound 155**. MS: [M+1] = 352. ^1H NMR (CDCl_3) δ 7.91 (1H, dd, J= 2, 8.5 Hz), 7.88 (1H, s), 7.65 (1H,

dd, $J = 6, 9.5$ Hz), 7.36 (1H, m), 3.01 (2H, q, $J = 8.5$ Hz), 2.46 (3H, s), 1.48 (3H, t, $J = 8.5$ Hz).

Example 74: Synthesis of Compound 160:

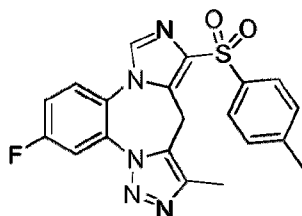


160

- 5 [0363] To a solution of pivalic acid (30 mg, 0.29 mmol) in THF (0.5 mL) was added CDI (14 mg, 0.087 mmol). The solution was stirred at room temperature for 1 hour. The above amide oxime derivative (10 mg, 0.032 mmol) in THF (0.5 mL) was added and the reaction mixture was heated at 70 °C for 90 min. The solvent was evaporated and the crude material was suspended in acetic acid (1 mL) and heated under reflux for 3 h. The
- 10 solvent was evaporated and the crude material was purified by Prep TLC (eluting system: 80% EtOAc in Hexanes) to give 7.4 mg (67%) of the desired product **Compound 160**. MS: $[M+1] = 380$. ^1H NMR (CDCl_3) δ 7.90 (1H, dd, $J = 2.7, 9$ Hz), 7.88 (1H, s), 7.65 (1H, dd, $J = 4.5, 9$ Hz), 7.35 (1H, m), 2.47 (3H, s), 1.53 (9H, s).

Example 75: Synthesis of Compound 143:

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143

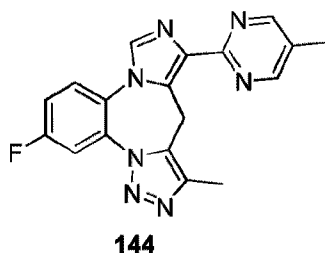
- [0364] A solution of KO^tBu (40 mg, 0.36 mmol) in DMF (3 mL) was cooled to -50 °C under a nitrogen atmosphere. p-Toluenesulfonylmethyl isocyanide (76 mg, 0.39 mmol) was added. The mixture was stirred at -50 °C for 1 h. The imino-derivative from **Scheme 22** (50 mg, 0.18 mmol) was added and the mixture was allowed to warm to room temperature over 16 h. Saturated NH_4Cl aqueous solution was added and it was extracted
- 20

with EtOAc five times. The combined extracts were washed with brine (3X) and dried over MgSO₄. Filtration and concentration gave the crude product. Chromatography (*RediSep* 4 g silica-gel column, eluted with 70% EtOAc in Hexanes) followed by a prep TLC (eluting system: 30% EtOAc in DCM) to give 22.2 mg (30% yield) of a white solid

5 **Compound 143**. MS: [M+1] = 410.

¹H NMR (CDCl₃) δ 7.91 (2H, d, J = 8 Hz), 7.87 (1H, dd, J = 2.5, 8.5 Hz), 7.74 (1H, s), 7.65 (1H, dd, J = 5.5, 9 Hz), 7.34 (3H, m), 2.50 (3H, s), 2.42 (3H, s).

Example 76: Synthesis of Compound 144:

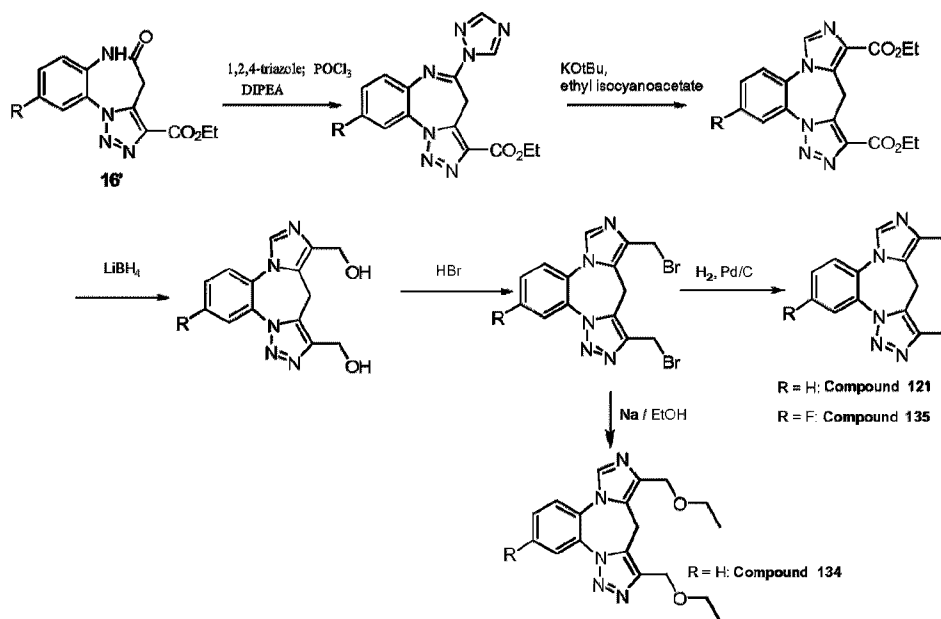


10 **[0365]** To 3-ethoxymethacrolein (100 mg, 0.88 mmol) was added 7 N ammonia in methanol (1.3 mL, 8.8 mmol). The solution was stirred at room temperature for 16 h. The solvent was evaporated and the crude yellow solid corresponding to 3-amino-2-methylacrolein was used in the next step without further purification.

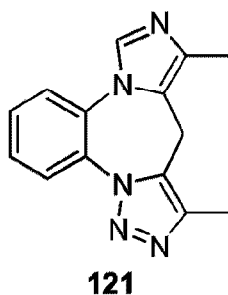
[0366] To a solution of 3-amino-2-methylacrolein (7 mg, 0.087 mmol) in anhydrous THF (1 mL) was added NaH 60% in oil dispersion (6 mg, 0.16 mmol). The suspension was stirred at room temperature for 15 min. The cyanide derivative (22 mg, 0.079 mmol) in THF (1 mL) was added and the reaction mixture was heated at 65 °C for 1 hour. As described above, a new batch of reagents was prepared with 3-amino-2-methylacrolein (20 mg) and NaH (20 mg) in THF (1 mL), and added to the reaction mixture which was heated at 65 °C for another hour. LCMS indicated completion of the reaction. The reaction mixture was quenched with methanol. The solvent was evaporated. The crude material was suspended in water and a solid was collected by filtration to give 5.2 mg (19% yield) of a light red solid **Compound 144**. MS: [M+1] = 348. ¹H NMR (CDCl₃) δ 8.67 (2H, s), 7.90 (1H, d, J = 9.5 Hz), 7.85 (1H, s), 7.65 (1H, dd, J = 4.5, 9 Hz), 7.34 (1H, m), 2.44 (3H, s), 2.36 (3H, s).

25

Scheme 23



Example 77: Synthesis of Compound 121:



- 5 [0367] To a solution of 1,2,4-triazole, (2.03 g, 29.4 mmol) in anhydrous CH_3CN (20 mL) at 0°C was added $i\text{-Pr}_2\text{NEt}$ (5.6 mL, 32.4 mmol). Once all the triazole was dissolved, POCl_3 (0.82 mL, 8.8 mmol) and compound 16' (1 g, 3.68 mmol) were added. The mixture was stirred at 0°C for 2 h. The resulting solution was heated in an oil bath at 80°C for 16 h. The mixture was cooled with an ice bath, diluted with EtOAc, and water
- 10 was added. It was extracted with EtOAc three times. The combined extracts were washed with brine and dried over MgSO_4 . Filtration and concentration gave 1.05 g (88% yield) of an orange solid which was used directly in the next step. MS: $[\text{M}+1] = 324$.

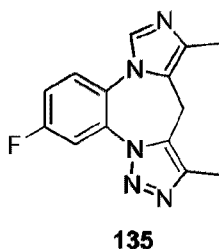
[0368] A solution of KOtBu (696 mg, 6.2 mmol) in DMF (15 mL) was cooled to -50°C

under a nitrogen atmosphere. Ethyl isocyanoacetate (0.75 mL, 6.8 mmol) was added slowly. The mixture was stirred at -50 °C for 1 h. The above crude product from step 1 (1 g, 3.1 mmol) was added and the mixture was allowed to warm to room temperature over 18 h. Saturated NH₄Cl aqueous solution was added and it was extracted with EtOAc
5 eight times. The combined extracts were washed with brine (3X) and dried over MgSO₄. Filtration and concentration gave the crude product. Chromatography (*RediSep* 24 g silica-gel column, eluted with 70% EtOAc in Hexanes) to give 950 mg (83% yield) of product. MS: [M+1] = 368.

[0369] To a solution of diester (200 mg, 0.54 mmol) in anhydrous THF (4 mL) stirred
10 at room temperature under a nitrogen atmosphere was added LiBH₄ (2 M in THF, 0.66 mL, 1.3 mmol). The reaction mixture was stirred under a nitrogen atmosphere for 24 h. A mixture of EtOAc/EtOH (3 mL/3 mL) was added to the reaction mixture and it was concentrated. The residue was taken up in MeOH and silica gel was added. After volatile solvents were evaporated, the solid was loaded onto a *RediSep* 4 g silica-gel
15 column. The desired product was eluted with 10:1 v/v CH₂Cl₂/MeOH. The diol was obtained as a solid (60 mg, 39% yield). MS: [M+1] = 284.

[0370] The diol (60 mg, 0.21 mmol) was suspended in 5 mL of HBr 33% in AcOH and heated at 80 °C for 18 h. The solution was cooled down with an ice bath and diluted with EtOAc. Slowly, a saturated aqueous NaHCO₃ solution was added. The solution was
20 extracted with EtOAc (3x), and the combined organic phases were washed with brine, dried over MgSO₄. Filtration and concentration gave a crude product which was used in the next step without further purification. MS: [M+1] = 408.

[0371] To a solution of dialkyl bromide derivative (0.21 mmol) in EtOAc (10 mL) and MeOH (10 mL) was added wet 10% Pd/C (catalytic amount) and the resulting suspension
25 was stirred under a hydrogen atmosphere for 60 h. The suspension was filtered through Celite and the resulting solution was concentrated. The crude product was purified by multiple prep TLC (eluting system: 3% MeOH in EtOAc) to give 6.2 mg (12% yield over 2 steps) of the desired product **Compound 121**. MS: [M+1] = 252. ¹H NMR (CDCl₃) δ 8.09 (1H, m), 7.74 (1H, s), 7.56 (3H, m), 7.90 (2H, m), 2.42 (3H, s), 2.29 (3H, s).

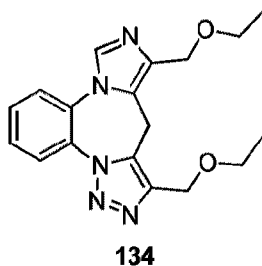
Example 78: Synthesis of Compound 135:

- [0372] **Compound 135** was synthesized in an analogous manner to **Compound 121** as follows: To a solution of 1,2,4-triazole (952 mg, 13.8 mmol) in anhydrous CH₃CN (20 mL) at 0°C was added *i*-Pr₂NEt (2.6 mL, 15.2 mmol). Once all the triazole was dissolved, POCl₃ (0.45 mL, 4.8 mmol) and the lactam ester (1 g, 3.45 mmol) was added. The mixture was stirred at 0°C for 2 h. The resulting solution was heated in an oil bath at 80°C for 16 h. The mixture was cooled with an ice bath, diluted with EtOAc, and water was added. It was extracted with EtOAc three times. The combined extracts were washed with brine and dried over MgSO₄. Filtration and concentration gave 1.03 g (87% yield) of an orange solid which was used directly in the next step. MS: [M+1]=342.
- A solution of KO^tBu (658 mg, 5.9 mmol) in DMF (15 mL) was cooled to -50°C under a nitrogen atmosphere. Ethyl isocyanoacetate (0.71 mL, 6.5 mmol) was added slowly. The mixture was stirred at -50°C for 1 h. The above crude product from step 1 (1 g, 2.9 mmol) was added and the mixture was allowed to warm to room temperature over 18 h. Saturated NH₄Cl aqueous solution was added and it was extracted with EtOAc eight times. The combined extracts were washed with brine (3X) and dried over MgSO₄. Filtration and concentration gave the crude product. Chromatography (*RediSep* 24 g silica-gel column, eluted with 70% EtOAc in Hexanes) to give 1.02 g (90% yield) of product. MS: [M+1] = 386.
- [0373] To a solution of diester (600 mg, 1.56 mmol) in anhydrous THF (8 mL) stirred at room temperature under a nitrogen atmosphere was added LiBH₄ (2 M in THF, 3.1 mL, 6.24 mmol). The reaction mixture was stirred under a nitrogen atmosphere for 24 h. A mixture of EtOAc/EtOH (10 mL/10 mL) was added to the reaction mixture and it was concentrated. The residue was taken up in MeOH and silica gel was added. After volatile solvents were evaporated, the solid was loaded onto a *RediSep* 12 g silica-gel column. The desired product was eluted with 10:1 v/v CH₂Cl₂/MeOH. The diol was obtained as a solid (187 mg, 40% yield). MS: [M+1] = 302.

[0374] The diol (80 mg, 0.27 mmol) was suspended in 7 mL of HBr 33% in AcOH and heated at 80°C for 48 h. The solution was cooled down with an ice bath and diluted with EtOAc. Slowly, a saturated aqueous NaHCO₃ solution was added. The solution was extracted (3x) and the combined organic phases were washed with brine, dried over
 5 MgSO₄. Filtration, concentration and co-evaporation with toluene gave 100 mg (88% yield) of a beige solid which was used in the next step without further purification. MS: [M+1] = 426.

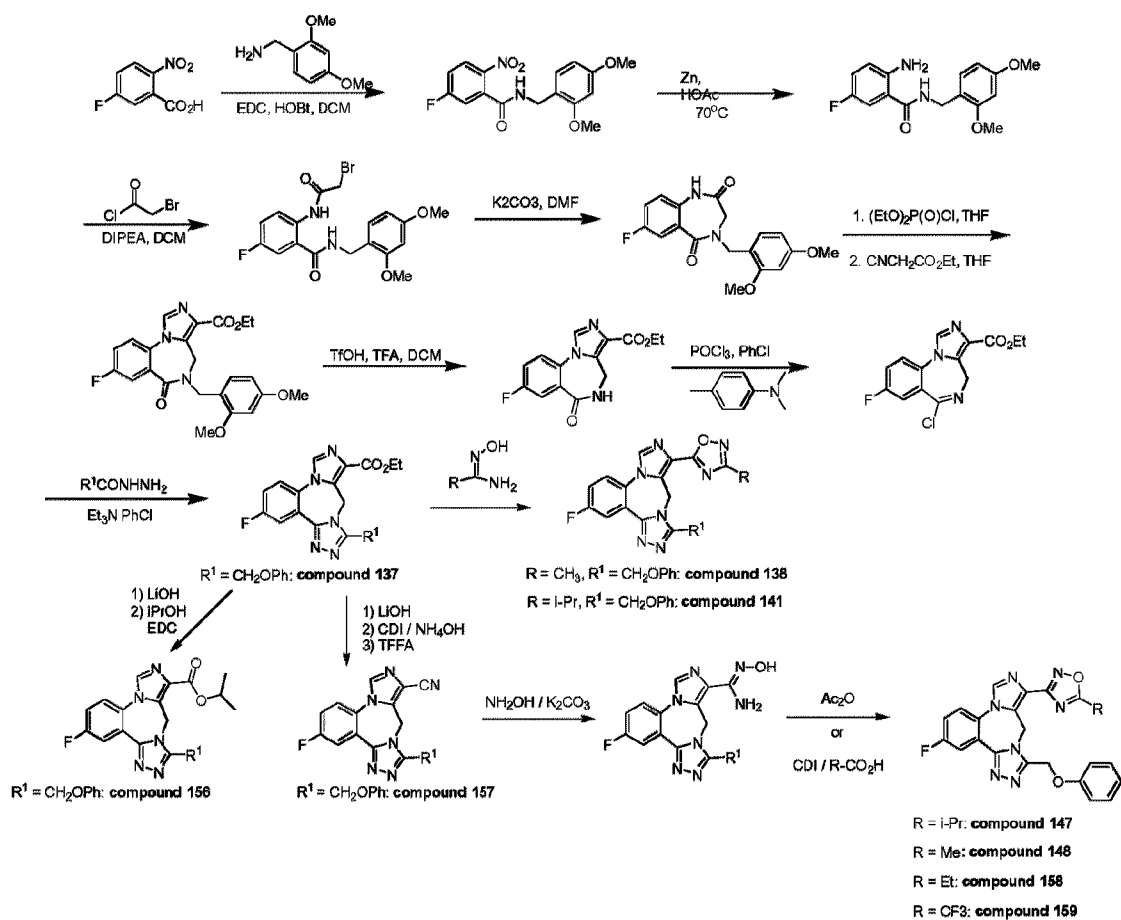
[0375] To a solution of dialkyl bromide derivative (70 mg, 0.16 mmol) in EtOAc (10 mL) and MeOH (10 mL) was added 10% Pd/C (catalytic amount) and the resulting
 10 suspension was stirred under a hydrogen atmosphere for 48 h. The suspension was filtered through Celite and the resulting solution was concentrated. The crude product was purified by multiple prep TLC (eluting system 1: 75% EtOAc in Hexanes; eluting system 2: 5% MeOH in EtOAc; eluting system 3: EtOAc) to give 4.1 mg (10% yield) of the desired product **Compound 135**. MS: [M+1] = 270. ¹H NMR (CDCl₃) δ 7.84 (1H, dd, J= 2.5, 9 Hz), 7.70 (1H, s), 7.54 (1H, dd, J= 5, 8 Hz), 7.30 (1H, m), 2.42 (3H, s), 2.28 (3H, s).
 15 s).

Example 79: Synthesis of Compound 134:

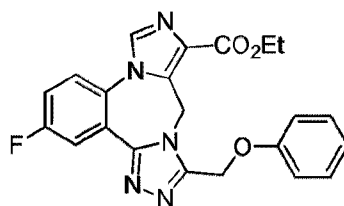


[0376] To a suspension of dialkyl bromide derivative described in **Scheme 23**, R = H, (30 mg, 0.074 mmol) in EtOH (1 mL), and heated at 80 °C was added a freshly prepared NaOEt 2M solution (75 μL, 0.15 mmol). The solution was heated for 10 min. The solvent was evaporated. The crude material was suspended in EtOAc and filtered. The filtrate was concentrated and purified by prep TLC (eluting system: EtOAc) to give 3.1 mg (12% yield) of the desired product **Compound 134**. MS: [M+1] = 340.
 20

Scheme 24



Example 80: Synthesis of Compound 137:



137

- 5 [0377] To a solution of 5-fluoro-2-nitrobenzoic acid (6.6g, 35.66 mmol) in dichloromethane (100 mL) were added DIPEA (9.22 g, 71.3 mmol), HOBt (6.0 g, 39.2 mmol) and EDCI (10.2 g, 53.5 mmol). After about 15 min stirring, to the reaction mixture was added a solution of 2,4-dimethoxybenzyl amine (5.96 g, 35.66 mmol) in dichloromethane (50 mL) dropwise under nitrogen atmosphere. The resulting mixture

was stirred under nitrogen atmosphere at room temperature for 16 h. The reaction mixture was washed successively with 1N HCl (100 mL), sat. NaHCO₃ (100 mL) and brine (100 mL). The organic phase was then dried over MgSO₄. Filtration and solvent removal in vacuo afforded a yellowish solid, wt: 9.3g (78%). MS: [M+1] = 335.

- 5 [0378] To the nitro benzene analog (9.3 g, 27.8 mmol) suspended and stirred in a solvent mixture of HOAc/THF/MeOH/H₂O (25/100/50/25 mL) at RT was added Zn powder. The mixture was heated to 70 °C for 20 hr, cooled, and filtered. Solid was rinsed with THF, and the combined filtrate was concentrated in vacuo. To the resulting slurry was added sat. NaHCO₃ slowly and carefully to avoid excessive forming formation
10 until pH reach 7 to 8. The mixture was extracted with EtOAc (3x); combined organic layer washed with brine, and dried over MgSO₄. Filtration and solvent removal gave the crude amine product as a dark brown gummy paste, wt: 8.7 g.

- [0379] To a solution of the aniline from above (8.7 g) in dichloromethane (150 mL) was added triethylamine (3.37 g, 33.4 mmol). The mixture was cooled with ice bath and
15 treated with bromo acetyl chloride (4.81g, 30.6 mmol) under nitrogen atmosphere. The ice bath was removed and the mixture left stirring for 72 hr. The reaction mixture was concentrated in vacuo, the resulting slurry treated with Et₂O (100 mL) and water (100 mL). Product precipitate was collected by filtration, and dried to give 5.6g product as a brown solid. Et₂O layer was separated from aq. Layer and diluted with DCM (50 mL),
20 washed with brine, and dried over MgSO₄. Filtration and solvent removal gave 5.3 g additional product as a foamy brown solid. Total wt: 11 g (100%).

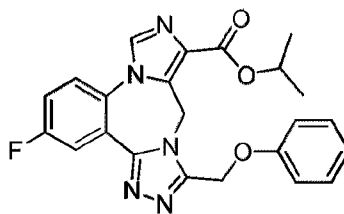
- [0380] To a solution of the bromide (11 g) in DMF (550 mL) was added K₂CO₃ (7.1 g, 51.7 mmol). The mixture was heated at 50 °C for 48hrs. The mixture was cooled to room temperature and the inorganic solid was filtered off. Filtrate was concentrated in vacuo,
25 treated with water/MeOH (60/10 mL), extracted with DCM (3x); combined organic layer was washed with brine and dried over MgSO₄. Filtration and solvent removal followed by silica gel column chromatography using 5 to 50% EtOAc in DCM gave 3.2 g (36%) of the 7-member lactam as a brownish solid. MS: [M+1] = 345.

- [0381] To the lactam (1.32 g, 3.83 mmol) dissolved and stirred in THF (20 mL) and
30 DMF (3 mL) at -20°C was added *t*-BuOK (0.645 g, 5.75 mmol). After 30min stirring at -20 °C, diethyl chlorophosphate (1.19 mL, 6.89 mmol) was added dropwise, and the

mixture was stirred for 3 h while warming from -20 to 20 °C. The reaction mixture was cooled to -78 °C and to it was added ethyl isocyanoacetate (0.791 mL, 6.89 mmol), followed by addition of *t*-BuOK (0.645 g, 5.75 mmol) and stirring continued overnight while temperature reached to RT. The reaction was quenched with saturated NH₄Cl,
5 extracted with EtOAc (2x); combined organic solution was washed with brine and dried over MgSO₄. Filtration and solvent removal gave a crude product which was purified by silica gel column chromatography using 15 to 100% EtOAc in DCM, wt: 0.861 g (47%), as a brown solid. MS: [M+1] = 440.

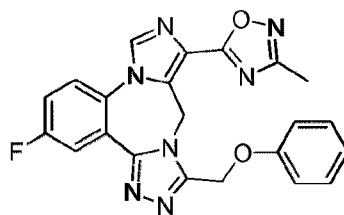
[0382] To the imidazole ester from above (861 mg) in dichloromethane (5 mL) at 0 °C
10 was added trifluoroacetic acid (5 mL) followed by trifluoromethanesulfonic acid (0.345 mL). The mixture was warmed to RT, stirred for 3 h, then concentrated to afford a residue which was dissolved in dichloromethane (50 mL). To which was added sat. NaHCO₃ (50 mL), followed by 20min stirring. pH of the top aq. Layer was tested basic, and was separated, extracted with DCM (3x); combined DCM solution washed with brine
15 and dried over MgSO₄. Filtration and solvent removal gave 0.58g (100%) of the lactam as a yellowish solid. MS: [M+1] = 290.

[0383] To lactam (209.1 mg, 0.723 mmol) and N,N-dimethyl-*p*-toluidine (234.7 mg, 1.74 mmol) stirring in chlorobenzene (2.5 mL) under nitrogen was added POCl₃ (133.0 mg, 0.867 mmol). The reaction was then heated at 135°C for 2 h. Upon cooling to room
20 temperature, phenoxy acetic acid hydrazide (189.0 mg, 1.08 mmol) was added, followed by DIPEA (0.455 mL). The reaction was stirred at room temperature for 30 min, then heated at 100°C for 60 min. The reaction mixture was cooled, saturated NH₄Cl (aq.) was added, and extracted with ethyl acetate three times; combined organic layer was washed with brine, and dried over MgSO₄. After filtration and concentration, the product was
25 isolated by ISCO flash column chromatography using 0 to 10% MeOH in EtOAc, wt: 116.7mg (36%) of **Compound 137** as a yellowish filmy solid. MS: [M+1] = 420.

Example 81: Synthesis of Compound 156:**156**

[0384] Ethyl ester **Compound 137** (244.2 mg, 0.582mmol) in a solvent system of THF/water/MeOH (6.0 mL total, 6/5/1 ratio) was treated with LiOH (69.7 mg, 2.91 mmol) at RT for 4hrs, concentrated in vacuo, acidified to pH~3, and precipitate collected by filtration. After water washing and drying, 179.3 mg (79%) of the acid was obtained as a yellowish solid. MS: [M+1] = 392.

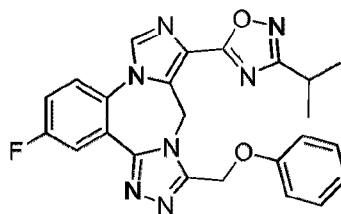
[0385] To the acid (10.8 mg, 0.0276 mmol) stirring in DCM (0.1ml) at RT was added EDCI (21.3 mg, 0.11 mmol), DMAP (6.7mg, 0.0552mmol) and isopropyl alcohol (13.2 mg, 0.221 mmol). After 12hrs, the reaction was diluted with EtOAc, washed with sat. NaHCO₃; aq. Layer separated and extracted with EtOAc, combined organic layer washed with brine, and dried over MgSO₄. Filtration and prep. TLC purification of the concentrate using 10% MeOH in EtOAc gave 8.7 mg (73%) of the isopropyl ester **Compound 156** as a yellowish foamy solid. MS: [M+1] = 434.

Example 82: Synthesis of Compound 138:**138**

[0386] Acetamide oxime (10.7 mg, 0.144 mmol) was azeotroped four times in toluene, and added to the ethyl ester **Compound 137** (9.5 mg, 0.0226 mmol). THF (0.3 mL) was added, followed by NaH 60% oil suspension (4.5 mg, 0.112 mmol). The reaction mixture was stirred at RT for 30 min, then heated at 70°C for 2 h, cooled to RT, and solvent

removed in vacuo, water (1.5 mL) added to quench the reaction, stirred for 20 min, and cooled to 4°C. Precipitate was collected by filtration, washed with water, and dried to give 5.2 mg (59%) of the oxadiazole product **Compound 138** as a light yellow solid. MS: [M+1] = 430.

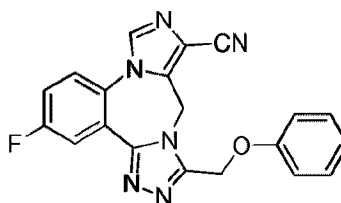
5 **Example 83: Synthesis of Compound 141:**



141

[0387] Compound of **Example 83** was synthesized in an analogous synthetic route as that described for **Example 82**, using isobutyramidoxime in place of acetamide oxime to give the compound of **Example 83** as a yellowish solid: MS: [M+1] = 458.

10 **Example 84: Synthesis of Compound 157:**



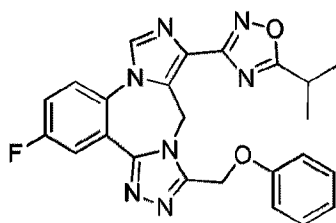
157

[0388] To the acid prepared above in **Example 81** (60.2 mg, 0.154 mmol) stirring in DCM (0.7 mL) at RT was added carbonyl diimidazole (49.9 mg, 0.308 mmol). The mixture was stirred for 40 min, then cooled to 0°C, and ammonia (0.112 ml) added, warmed to RT while stirring continued overnight. The reaction was concentrated, water (8 mL) added, and stirred well for 30 min. Resulting precipitate was collected by filtration, washed with water, and dried to give 51.1mg (85%) of the primary amide as a brownish solid. MS: [M+1] = 391.

[0389] The amide (51.1 mg) from above was treated with POCl₃ (200.8 mg, 1.31 mmol) in 1,4-dioxane (0.9 mL) at 90°C for 14hrs. Upon cooling to RT, the reaction was carefully

quenched with sat. NaHCO_3 (5 mL), stirred for 20 min. Precipitate was collected by filtration, washed with water, and dried to give 40.9 mg (85%) of nitrile product **Compound 157** as a brownish solid. MS: $[M+1] = 373$.

Example 85: Synthesis of Compound 147:



147

5

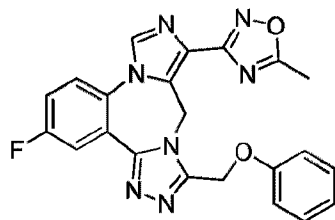
[0390] To the nitrile (45.8 mg, 0.123 mmol) in a round bottom flask was added hydroxylamine hydrochloride (14.5 mg, 0.209 mmol), K_2CO_3 (22.3 mg, 0.161 mmol), ethanol (0.6 mL), and water (0.15 mL). The reaction mixture was heated at 80°C for 30 min, cooled down, and concentrated in vacuo. The resulting slurry was treated with water (1.5 mL), sonicated to help mixing, and stirred at RT for 1 h before being cooled to 4°C . The resulting precipitate was collected by filtration, washed with cold water (1 mL), and dried to give 40.8 mg (82%) of the adduct as an off-white solid. MS: $[M+1] = 406$.

10

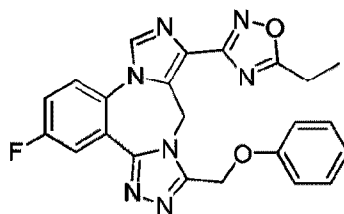
[0391] Isobutyric acid (31.4 mg, 0.582 mmol) was treated with carbonyl diimidazole (28.4 mg, 0.175 mmol) in THF (0.5 mL) for 2 hrs. The N-hydroxycarboxamide adduct (11.8 mg, 0.0291 mmol) was added, and the reaction was stirred at RT for 30 min. More isobutyric acid (0.5 mL) was added and the reaction mixture was heated at 110°C for 16 h, cooled, sat. NaHCO_3 (8 mL) added, and extracted with EtOAc (3x); combined organic layer washed with brine, and dried over MgSO_4 . Precp. TLC (5% MeOH in EtOAc) of the concentrated filtrate gave 11.2 mg (84%) of the oxadiazole **Compound 147** as a white solid. MS: $[M+1] = 458$.

15

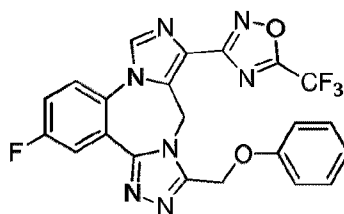
20

Example 86: Synthesis of Compound 148:**148**

[0392] Compound of **Example 86** was synthesized in an analogous synthetic route as that described for **Example 85**, using acetic acid in place of isobutyric acid to give the compound of **Example 86** as a white solid: MS: $[M+1] = 430$.

Example 87: Synthesis of Compound 158:**158**

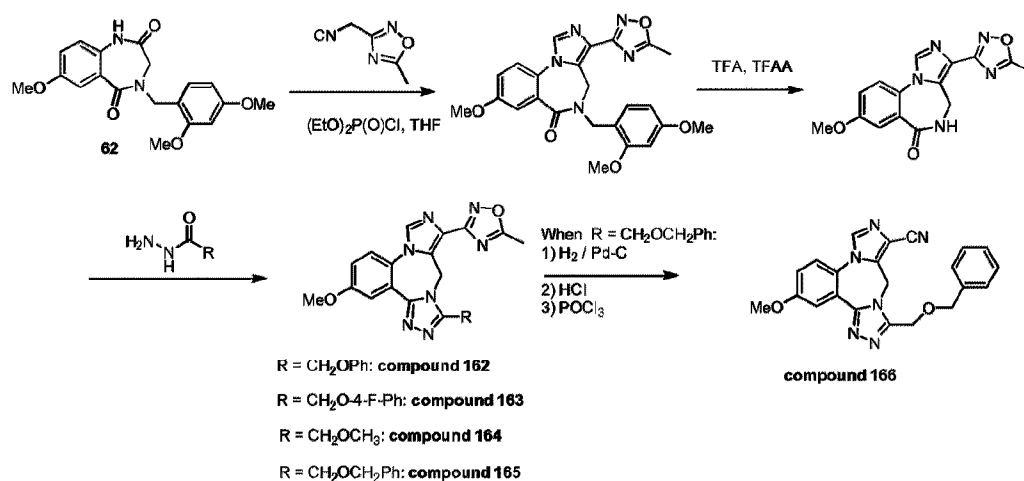
[0393] Compound of **Example 87** was synthesized in an analogous synthetic route as that described for **Example 85**, using propionic acid in place of isobutyric acid to give the compound of **Example 87** as a white solid: MS: $[M+1] = 444$.

Example 88: Synthesis of Compound 159:**159**

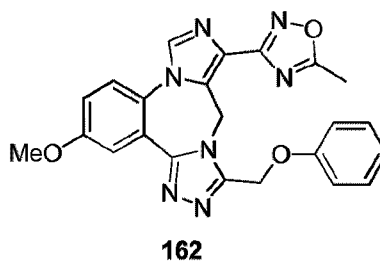
[0394] Trifluoroacetic anhydride (196.9 mg, 0.938 mmol) was added to the N-hydroxycarboxamide adduct (19.0 mg, 0.0469 mmol) suspended and stirred in THF (0.2

mL) at RT. After 30min stirring, the reaction was heated to 70°C for 1 h, cooled to RT, and diluted with EtOAc (10 mL), to which was added sat. NaHCO₃ and stirred for 30min. Aq. Layer was separated and extracted with EtOAc (1x); combined organic layer was washed with brine, and dried over MgSO₄. Filtration and solvent removal gave a paste to which was added nBuOH (5 ml) and HOAc (0.5 mL). This was heated at 115°C for 16 h, cooled and concentrated in vacuo, diluted with EtOAc, washed with sat. NaHCO₃, brine, and dried over MgSO₄. Prep. TLC (5% MeOH in EtOAc) of the concentrated filtrate gave 11.5 mg (51%) of the desired trifluoromethyl oxadiazole analog **Compound 159** as a yellowish solid. MS: [M+1] = 484.

10 **Scheme 25**



Example 89: Synthesis of Compound 162:

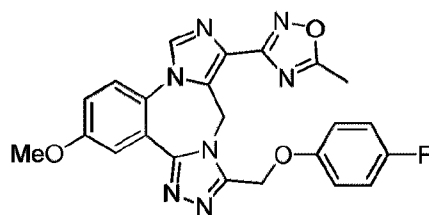


[0395] To lactam **62** (503.4 mg, 1.42 mmol) stirring in THF (2.9 ml) and DMF (0.8 mL) at -20°C was added tBuOK (240.2 mg). After 30 min stirring, diethyl chlorophosphate (377.7 mg, 2.12 mmol) was added dropwise, and the reaction mixture was slowly warmed to 8°C in 3 h before being cooled down to -20°C. 2.26 mL (2.26

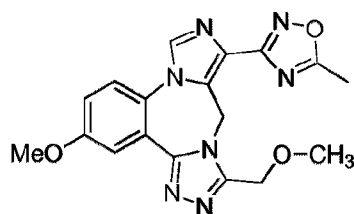
mmol) of oxadiazole isocyanate (ref. *JMC*, **1996**, 39, 170; prepared as 1M THF solution) was added. The reaction mixture was further cooled to -78°C, tBuOK (238.4 mg) was added, and the reaction was slowly warmed to RT overnight. Sat. NH₄Cl (5 mL) was added and the mixture was extracted with EtOAc (2x), washed with brine, and dried over
5 MgSO₄. Upon filtration and concentration, the product was isolated by silica gel column chromatography using a gradient elution of 0 to 10% MeOH in EtOAc to give 246.0 mg imidazole product as a yellowish solid. MS: [M+1] = 462.

[0396] The imidazole (246.0 mg, 0.533 mmol) obtained above was stirred in DCM (3 ml). Trifluoroacetic acid (3 mL) was added, followed by trifluoromethyl sulfonic acid
10 (160.0 mg, 1.07 mmol). After 3 h stirring, the reaction was diluted with DCM (20 mL), washed with sat. NaHCO₃; aq. Layer was separated and extracted with DCM (2x); combined DCM solution was washed with brine, and dried over MgSO₄. Filtration and solvent removal *in vacuo* gave 208.7 mg of the crude lactam product as a yellowish flaky solid. [M+1] = 312.

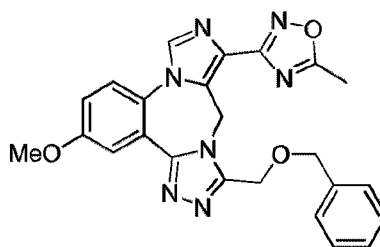
15 [0397] Phosphorous oxychloride (29.9 mg, 0.195 mmol) was added to a solution of the above obtained lactam (22.5 mg, 0.0723 mmol) and N,N-dimethyl-*p*-toluidine (51.8 mg, 0.383 mmol) stirring in chlorobenzene (0.45 mL) under nitrogen atmosphere. The reaction mixture was heated at 135°C for 3 h, then cooled to RT. Diisopropylethylamine (75.7 mg, 0.586 mmol) and phenoxyacetic hydrazide (50.1 mg, 0.302 mmol) was added,
20 and the reaction mixture was heated at 100°C for 14 h, cooled to RT, and partitioned between sat. NH₄Cl and EtOAc. Aq. Layer was separated and extracted with EtOAc; combined EtOAc solution was washed with brine, and dried over MgSO₄. Upon filtration and concentration, the product **Compound 162** was isolated by silica gel column chromatography using a gradient elution of 0 to 10% MeOH in EtOAc as a yellowish
25 solid. Wt: 11.8 mg (37%). MS: [M+1] = 442.

Example 90: Synthesis of Compound 163:**163**

[0398] Compound of **Example 90** was synthesized in an analogous synthetic route as that described for **Example 89**, using 4-fluorophenoxyacetic hydrazide in place of phenoxyacetic hydrazide to give the compound of **Example 90** as a yellowish solid:
 5 MS: [M+1] = 460.

Example 91: Synthesis of Compound 164:**164**

[0399] Compound of **Example 91** was synthesized in an analogous synthetic route as that described for **Example 89**, using methoxyacetic hydrazide in place of phenoxyacetic hydrazide to give the compound of **Example 91** as a yellowish solid: MS: [M+1] = 380.

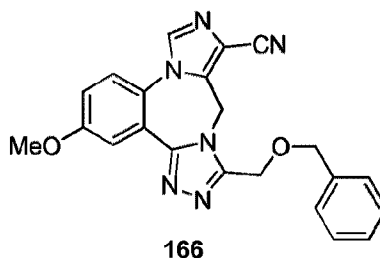
Example 92: Synthesis of Compound 165:**165**

[0400] **Preparation of benzyloxy acetic hydrazide:** carbonyl diimidazole (1.52 g, 9.39 mmol) was added to benzyloxy acetic acid (1.2 g, 7.22 mmol) stirring in THF (60 mL) at 0°C. Ice bath was removed and the stirring continued for 1 hr. The resulting cloudy solution was added to hydrazine (0.927 g, 28.9 mmol) stirring in THF (40 mL) at RT.

5 After 16hrs, the reaction mixture was concentrated to a slurry, to which was added water (120 mL), extracted with DCM (3x); combined DCM solution washed with brine, and dried over MgSO₄. Filtration and solvent removal gave 0.908 g (70%) of the hydrazide as a clear viscous oil. This was azeotroped in toluene a few times before use.

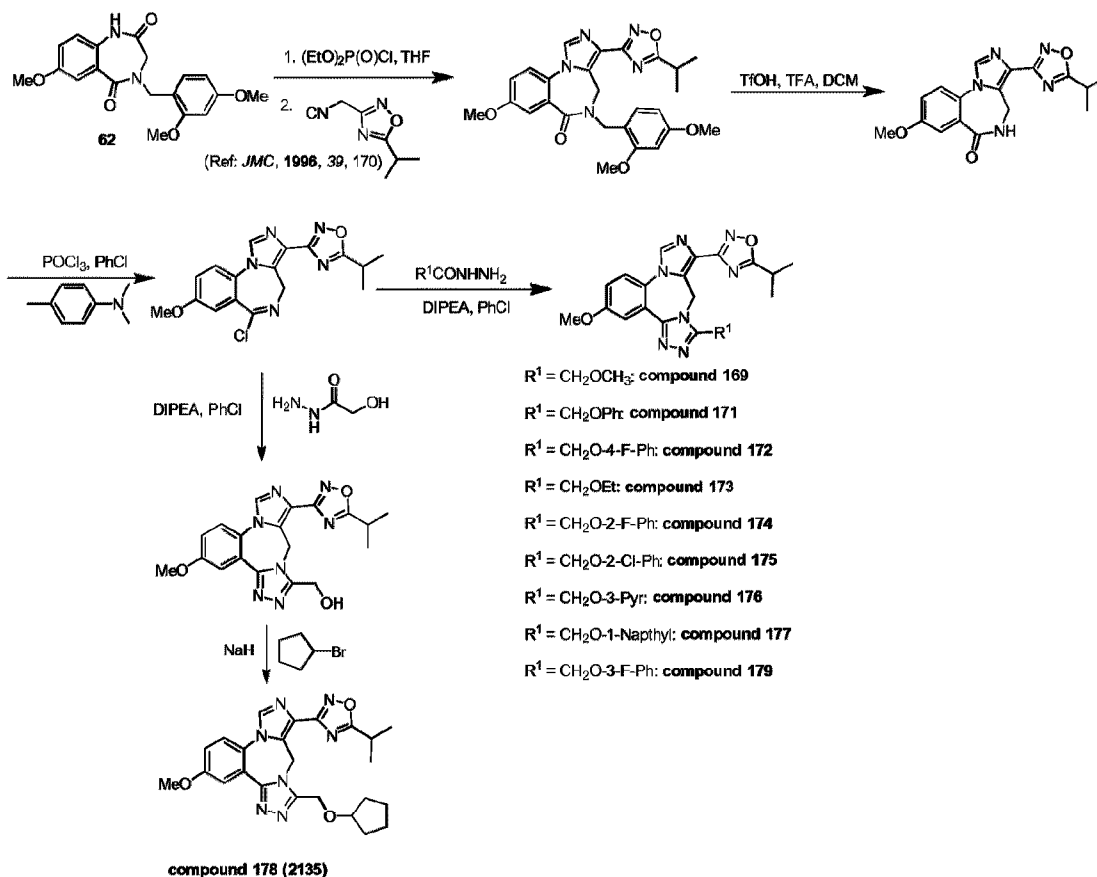
Compound of **Example 92** was synthesized in an analogous synthetic route as that described for **Example 89**, using benzyloxy acetic hydrazide in place of phenoxyacetic hydrazide to give the compound of **Example 92** as a yellowish solid: MS: [M+1] = 456.

Example 93: Synthesis of Compound 166:

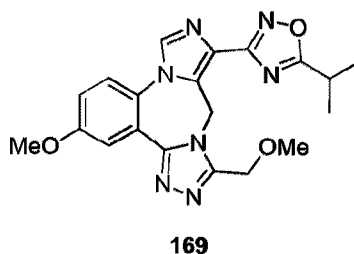


[0401] **Compound 165** from above (58.5 mg, 0.128 mmol) was treated with 10% Pd-C (catalytic) in EtOAc (4 mL) and MeOH (4 mL) under hydrogen atmosphere for 2 h. Catalyst was removed by filtration over Celite. To the filtrate was added conc. HCl (0.89 mL), and the mixture was stirred at RT for 16 h. Excess Na₂CO₃ (aq.) was added, and the solution was extracted with EtOAc (2x); combined organic solution was washed with brine, and dried over MgSO₄. Prep. TLC of the concentrated filtrate using 15% MeOH in EtOAc gave 14.9 mg of the primary amide ([M+1] = 417) as a yellowish solid. This primary amide was treated with phosphorous oxychloride (54.9 mg, 0.358 mmol) in 1,4-dioxane (1 mL) at 90°C for 14 h. Upon cooling, the reaction mixture was diluted with EtOAc, washed with sat. NaHCO₃; aq. layer separated and extracted with EtOAc (1x), combined organic solution was washed with brine, and dried over MgSO₄. Prep. TLC of the concentrated filtrate using 5% MeOH in EtOAc gave 5.2 mg of the desired nitrile product **Compound 166** as white needles. [M+1] = 399.

Scheme 26



Example 94: Synthesis of Compound 169:



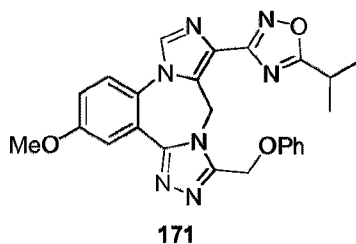
- [0402] To lactam **62** (2.23 g, 6.24 mmol) stirring in THF (10 mL) and DMF (3 mL) at -20 °C was added tBuOK (1.05 g, 9.36 mmol). After 30 min stirring, diethyl chlorophosphate (1.66 g, 9.36 mmol) was added dropwise, and the reaction mixture was slowly warmed to 8-10 °C in 3 h before being cooled down to -20 °C. 10.0 ml (10.0 mmol) of oxadiazole isocyanate (ref. *JMC*, 1996, 39, 170; prepared as 1M THF solution) was added. The reaction mixture was further cooled to -78 °C, tBuOK (1.05g, 9.36 mmol) was

added, and the reaction was slowly warmed to RT overnight. Sat. NH_4Cl (20 mL) was added and the mixture was extracted with EtOAc (3x), washed with brine, and dried over MgSO_4 . Upon filtration and concentration, the product was isolated by silica gel column chromatography using a gradient elution of 10 to 100% EtOAc in DCM to give 1.07 g (35%) imidazole product as a yellowish foamy solid. MS: $[\text{M}+1] = 490$.

[0403] The imidazole (1.07 g, 2.18 mmol) obtained above was stirred in DCM (11 mL). Trifluoroacetic acid (11 mL) was added, followed by trifluoromethyl sulfonic acid (0.656 g, 4.37 mmol). After 4 h stirring, the reaction was concentrated *in vacuo*, diluted with DCM (50 mL), washed with sat. NaHCO_3 aq. Layer was separated and extracted with DCM (2x); combined DCM solution was washed with brine, and dried over MgSO_4 . Filtration and solvent removal *in vacuo* gave 0.872 g of the crude lactam product as a brownish solid. $[\text{M}+1] = 340$.

[0404] Phosphorous oxychloride (51.0 mg, 0.333 mmol) was added to a solution of the above obtained lactam (45.0 mg, 0.133 mmol) and N,N-dimethyl-*p*-toluidine (89.6 mg, 0.663 mmol) stirring in chlorobenzene (0.60 mL) under nitrogen atmosphere. The reaction mixture was heated at 135°C for 3 h, then cooled to RT. Diisopropylethylamine (137.5 mg, 1.06 mmol) and methoxyacetic hydrazide (83.1 mg, 0.798 mmol) was added, and the reaction mixture was heated at 100°C for 4 h, cooled to RT, diluted with EtOAc, washed with sat. NaHCO_3 , brine, and dried over MgSO_4 . Upon filtration and concentration, the product **Compound 169** was isolated by silica gel column chromatography using a gradient elution of 0 to 13% MeOH in EtOAc as a brownish solid. Wt: 14.3 mg (26%). MS: $[\text{M}+1] = 408$.

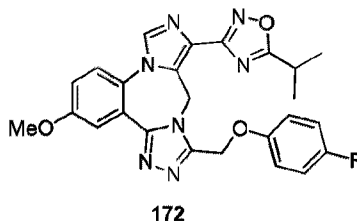
Example 95: Synthesis of Compound 171:



[0405] Compound of **Example 95** was synthesized in an analogous synthetic route as that described for **Example 94**, using phenoxyacetic hydrazide in place of methoxyacetic

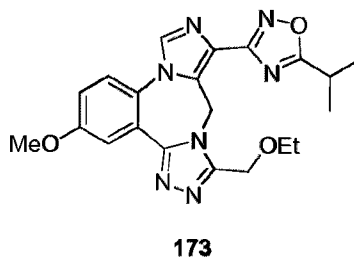
hydrazide to give the compound of **Example 95** as a yellowish solid: MS: $[M+1] = 470$.

Example 96: Synthesis of Compound 172:



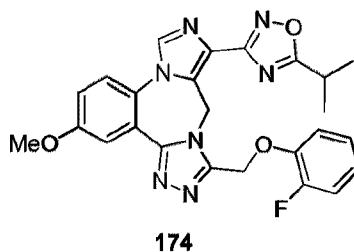
- [0406] Compound of **Example 96** was synthesized in an analogous synthetic route as that described for **Example 94**, using 4-fluoro-phenoxyacetic hydrazide in place of methoxyacetic hydrazide to give the compound of **Example 96** as a yellowish solid: MS: $[M+1] = 488$.

Example 97: Synthesis of Compound 173:



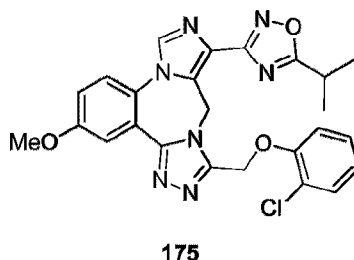
- [0407] Compound of **Example 97** was synthesized in an analogous synthetic route as that described for **Example 94**, using ethoxyacetic hydrazide in place of methoxyacetic hydrazide to give the compound of **Example 97** as a yellowish solid: MS: $[M+1] = 422$.

Example 98: Synthesis of Compound 174:



[0408] Compound of **Example 98** was synthesized in an analogous synthetic route as that described for **Example 94**, using 2-fluoro-phenoxyacetic hydrazide in place of methoxyacetic hydrazide to give the compound of **Example 98** as a yellowish solid: MS: [M+1] = 488.

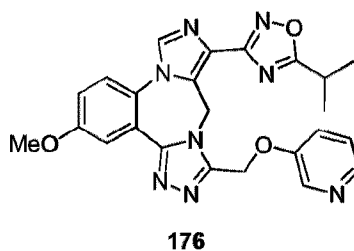
5 **Example 99: Synthesis of Compound 175:**



[0409] Compound of **Example 99** was synthesized in an analogous synthetic route as that described for **Example 94**, using 2-chloro-phenoxyacetic hydrazide in place of methoxyacetic hydrazide to give the compound of **Example 99** as a yellowish solid:

10 MS: [M+1] = 504.

Example 100: Synthesis of Compound 176:



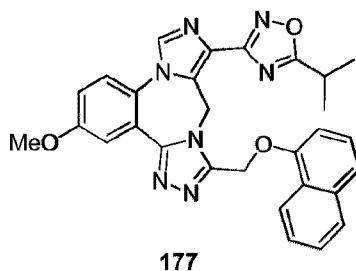
[0410] **Preparation of 3-pyridyloxy acetic hydrazide:** a solution of ethyl 3-pyridyloxy acetate (0.50 g, 2.76 mmol) and hydrazine (0.31 g, 9.66 mmol) in isopropyl alcohol (35 mL) was heated at 85°C for 30 hr, cooled, and concentrated in *vacuo*. The resulting white solid was dissolved in small amount of sat. NaCl solution, and extracted with EtOAc repeatedly. The combined organic solution was dried over MgSO₄. Filtration and solvent removal gave 177 mg of the desired acetic hydrazide as a white solid. Residual water moisture was removed by azeotroping in toluene.

20 Compound of **Example 100** was synthesized in an analogous synthetic route as that described for **Example 94**, using 3-pyridyloxy acetic hydrazide in place of

methoxyacetic hydrazide to give the compound of **Example 100** as a yellowish solid:

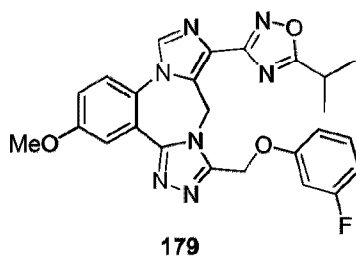
MS: $[M+1] = 471$.

Example 101: Synthesis of Compound 177:



- 5 [0411] Compound of **Example 101** was synthesized in an analogous synthetic route as that described for **Example 94**, using 1-naphthoxy acetic hydrazide in place of methoxyacetic hydrazide to give the compound of **Example 101** as an off white solid: MS: $[M+1] = 520$.

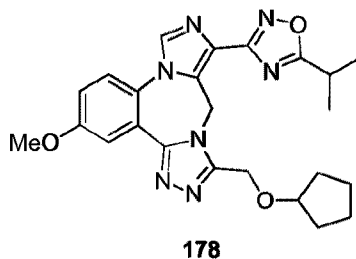
Example 102: Synthesis of Compound 179:



10

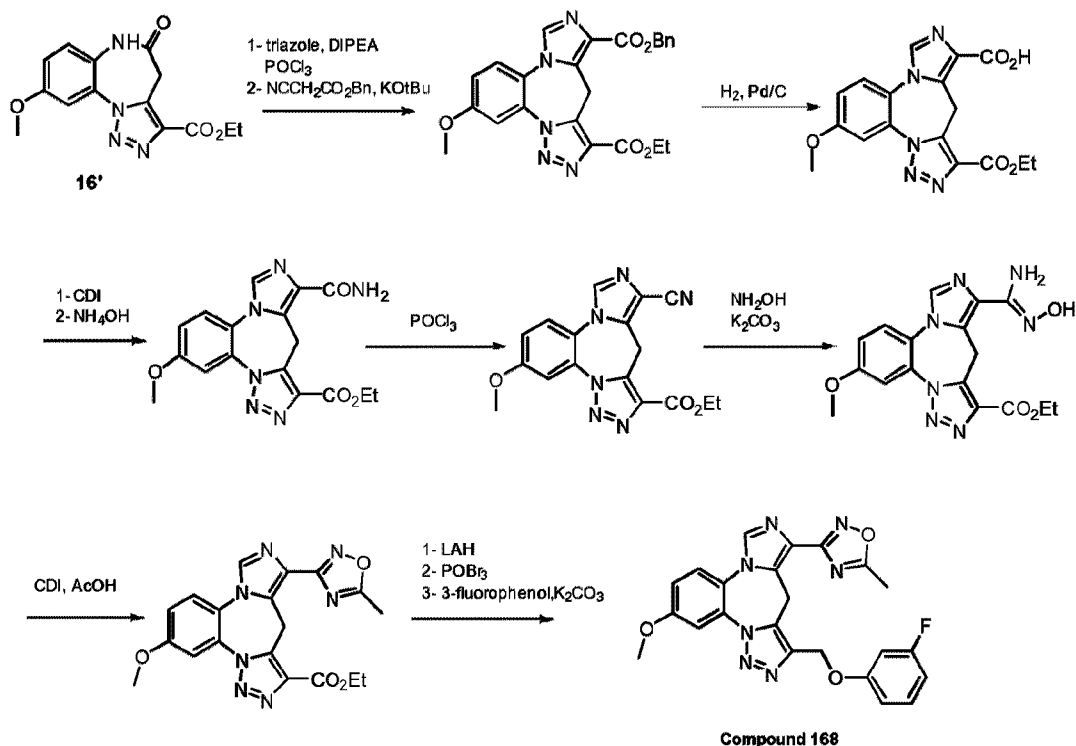
- [0412] Compound of **Example 102** was synthesized in an analogous synthetic route as that described for **Example 94**, using 3-fluorophenoxy acetic hydrazide in place of methoxyacetic hydrazide to give the compound of **Example 102** as a yellowish solid: MS: $[M+1] = 488$.

15

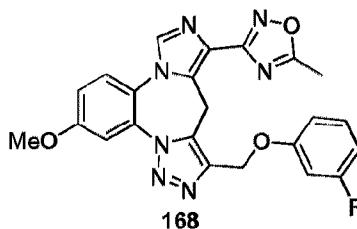
Example 103: Synthesis of Compound 178:

- [0413] Phosphorous oxychloride (64.8 mg, 0.422 mmol) was added to a solution of the oxadiazolyl imidazole lactam (57.5 mg, 0.169 mmol) and N,N-dimethyl-*p*-toluidine (114.6 mg, 0.847 mmol) stirring in chlorobenzene (0.70 ml) under nitrogen atmosphere. The reaction mixture was heated at 135°C for 3 h, then cooled to RT. Diisopropylethylamine (174.7 mg, 1.35 mmol), *t*-BuOH (0.3ml), and 2-hydroxy acetic hydrazide (91.3mg, 1.01mmol) was added. The reaction mixture was stirred at RT for 20min, then warmed at 50°C for one hour followed by 80°C heating for one hour before finally heated at 100°C overnight. Upon cooling to RT, the reaction was diluted with EtOAc, washed with brine, and dried over MgSO₄. Silica gel column chromatography of the concentrated filtrate using a gradient elution of 0 to 20% MeOH in EtOAc gave the desired hydroxymethyl triazole product as a yellowish solid. Wt: 18.1 mg (27%). MS: [M+1] = 394.
- [0414] To a solution of hydroxymethyl triazole from above (18.1 mg, 0.046 mmol), cyclopentyl bromide (274.0 mg, 1.84 mmol), and HMPA (16.5 mg, 0.092 mmol) stirring in THF (0.5 ml) was added NaH (60% suspension; 18.4 mg, 0.46 mmol). After 10min, the reaction was heated at 100°C for 6hrs, cooled, quenched with sat. NaHCO₃, and extracted with EtOAc (2x), washed with brine, and dried over MgSO₄. Prep. TLC of the concentrated filtrate using 8% MeOH in EtOAc gave 5.5mg (26%) of the desired ether **Compound 178** as a yellowish solid. [M+1] = 462.

Scheme 27



Example 104: Synthesis of Compound 168:



[0415] To a suspension of benzyl glycinate hydrochloride (5 g, 24.8 mmol) in DCM (100 mL) was added EDC.HCl (6.2 g, 33.2 mmol) and triethylamine (5.2 mL, 37.2 mmol). The suspension was cooled down to -50 °C then formic acid (1.4 mL, 37.2 mmol) in DCM (5 mL) was added. The reaction mixture was stirred at -50 °C for one hour then at 4 °C for 3 h. The solution was diluted with 1N HCl and extracted with DCM (2x). The combined organic phases were washed with brine and dried over MgSO₄. Filtration and concentration gave 3.89 g (81% yield) of formylated glycine as an oil (M+1= 194)

[0416] To a solution of formylated glycine derivative (1 g, 5.2 mmol) in DCM (30 mL) was added triethylamine (3.2 mL, 23 mmol). The solution was cooled down to -50 °C and

POCl₃ (1.9 mL, 20.8 mmol) was added slowly. The solution was stirred at – 50 C for 10 min, then stirred at room temperature for 40 min. The solution turned light red-brown. It was diluted with DCM and a 20% sodium carbonate solution (100 mL) was added. The reaction mixture was stirred vigorously for 15 min. The organic phase was separated
5 twice and dried over MgSO₄. Filtration and concentration to give the desired benzyl isocyanoacetate in quantitative yield which was used in the next step without further purification.

[0417] To a solution of 1,2,4-triazole (914 mg, 13.2 mmol) in anhydrous CH₃CN (20 mL) at 0°C was added *i*-Pr₂NEt (2.5 mL, 14.6 mmol). Once all the triazole was dissolved,
10 POCl₃ (0.43 mL, 4.6 mmol) was added. The mixture was stirred at 0°C for 2 h. The lactam ester 16' (1 g, 3.31 mmol) was added. The resulting solution was heated in an oil bath at 80°C for 16 h. The mixture was cooled with an ice bath. Diluted with EtOAc then water was added. Aq. layer was separated and extracted with EtOAc four times. The combined organic extracts was washed with brine and dried over MgSO₄. Filtration and
15 concentration gave a light yellow solid which was used directly in the next step (M+1=354).

[0418] A solution of benzyl isocyanoacetate (892 mg, 5.1 mmol) in DMF (10 mL) was cooled to -50°C under a nitrogen atmosphere. KO^tBu (514 mg, 4.6 mmol) was added. The mixture was stirred at -50°C for 1 h. The triazole derivative prepared above (900 mg,
20 2.55 mmol) in DMF (5 mL) was added slowly at -50 °C. The mixture was allowed to warm to room temperature over 16 h. Saturated aqueous NH₄Cl solution was added and it was extracted with EtOAc three times. The combined extracts were washed with brine (3x) and dried over MgSO₄. Filtration and concentration gave a crude product. Chromatography (*RediSep* 24 g silica-gel column, eluted with 70% EtOAc in Hexanes) to
25 give 886 mg (76% yield) of product (M+1=460).

[0419] To a solution of benzyl ester derivative (770 mg, 1.68 mmol) in EtOAc (10 mL) and MeOH (30 mL) was added wet Pd/C (60 mg) and the resulting suspension was stirred under a hydrogen atmosphere for 48 h. The suspension was filtered through Celite and the resulting solution was concentrated. The crude debenzylated product (530 mg, 86%yield)
30 was used in the next step without further purification (M+1= 370).

[0420] To a suspension of acid (530 mg, 1.44 mmol) in DCM (10 mL) was added CDI (931 mg, 5.75 mmol). The solution was stirred at room temperature for 2 h. The solution was cooled down with an ice bath and a NH₄OH solution (6 mL) was added. The solution

was stirred for 30 min and it was concentrated. The solid was collected by filtration and washed with water to give 422 mg (80%) of the desired product as a brown solid. (M+1= 369).

[0421] To a suspension of primary amide derivative (422 mg, 1.15 mmol) in dioxane
5 (10 mL) was added POCl₃ (160 µL, 1.7 mmol). The suspension was heated at 90 °C for 2 h. The resulting solution was cooled down with an ice bath and quenched with a saturated aqueous NaHCO₃ solution. The solid was collected by filtration to give 308 mg (77% yield) of the desired cyanide derivative. (M+1= 351).

[0422] To a suspension of cyanide derivative (150 mg, 0.44 mmol) in EtOH (4 mL) and
10 water (1 mL) was added hydroxylamine hydrochloride (40 mg, 0.57 mmol) and potassium carbonate (67 mg, 0.48 mmol). The suspension was stirred at room temperature for 16 h. LCMS indicated about 50% conversion. More hydroxylamine hydrochloride (40 mg, 0.57 mmol) and potassium carbonate (67 mg, 0.48 mmol) were added, and stirred for another 24 h. The solution was diluted with EtOAc and washed
15 with water. The combined organic phases were washed with brine, dried over MgSO₄. Filtration and concentration gave 145 mg (86% yield) of the desired product. (M+1= 384).

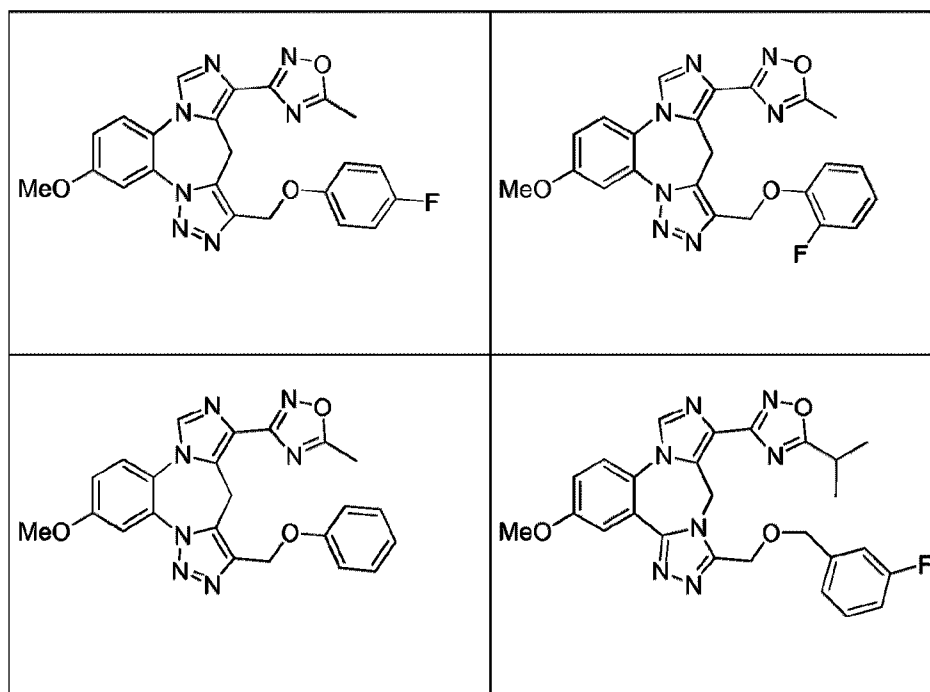
[0423] To a solution of acetic acid (0.22 mL, 3.8 mmol) in THF (5 mL) was added CDI
(123 mg, 0.76 mmol). The solution was stirred at room temperature for 2 h. The solution
20 was then poured into a flask containing the oxime derivative (145 mg, 0.38 mmol) and heated at 70 °C for 1 hour. The solvent was evaporated and the crude material was suspended in acetic acid (8 mL) and heated at 130 °C for one hour. The solvent was evaporated and the crude material was triturated with water to give 134 mg (86%) of the desired product (M+1= 408).

[0424] To a suspension of ester derivative (50 mg, 0.12 mmol) in THF (1 mL) was
25 added lithium aluminum hydride (7 mg, 0.18 mmol). The suspension was stirred at room temperature for 2 h. LCMS indicated about 70% conversion along some other side products and some remaining starting material. More lithium aluminum hydride (4 mg) was added and the reaction mixture was stirred at room temperature for another 30 min.
30 The reaction mixture was quenched with 1N HCl. The solution was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over MgSO₄. Filtration and concentration gave 20 mg (45% yield) of the desired alcohol product. (M+1= 366).

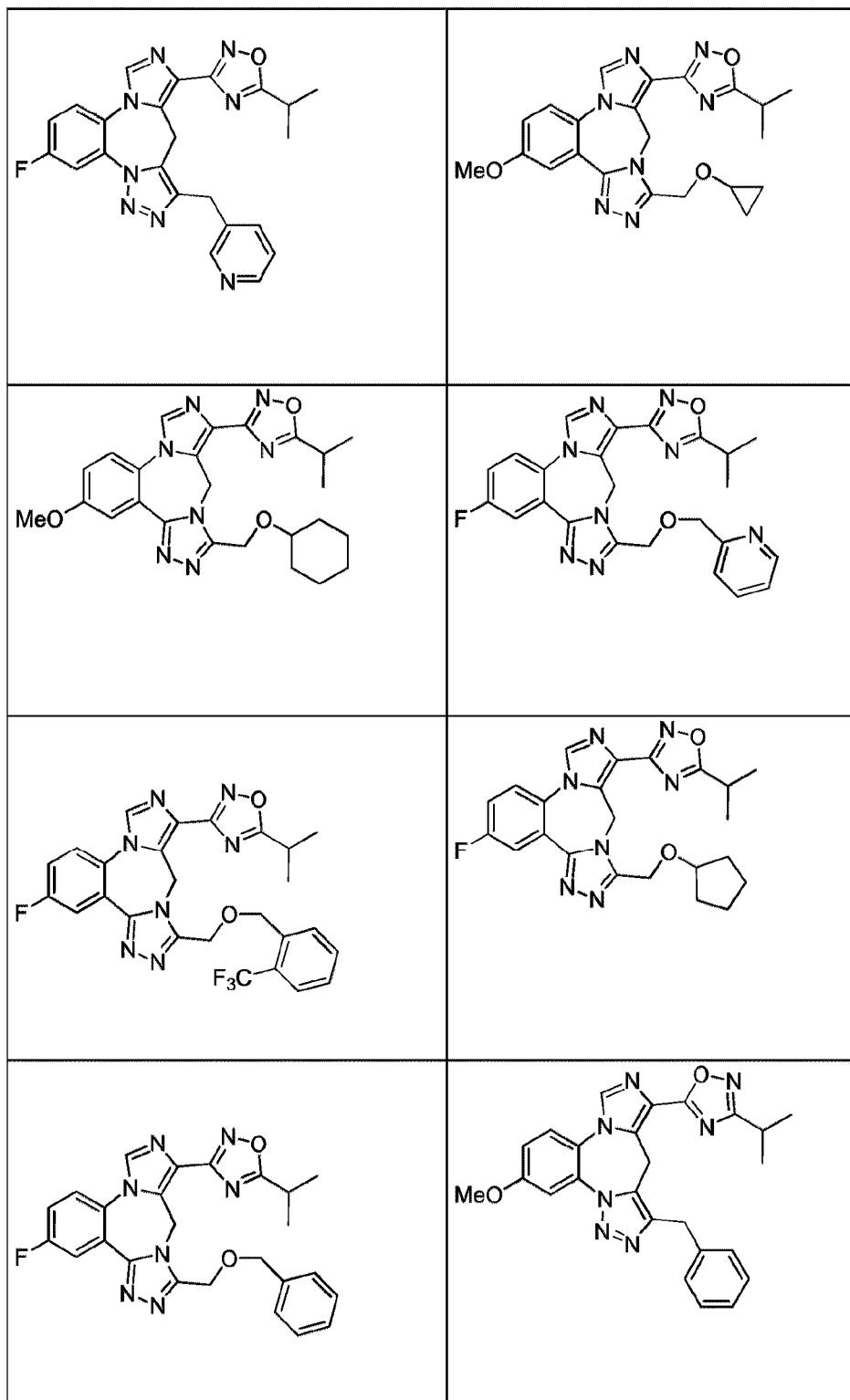
[0425] To a suspension of alcohol (20 mg, 0.055 mmol) in dioxane (1 mL) was added POBr₃ (31 mg, 0.11 mmol). The reaction mixture was heated at 110 °C for 1 hour. The reaction mixture was cooled down with an ice bath and sat. aq. NaHCO₃ solution was added. The resulting solution was extracted with EtOAc (3X). The combined organic phases were washed with brine and dried over MgSO₄. The solvent was concentrated to give 22 mg (96% yield) of the desired product (M+1= 428).

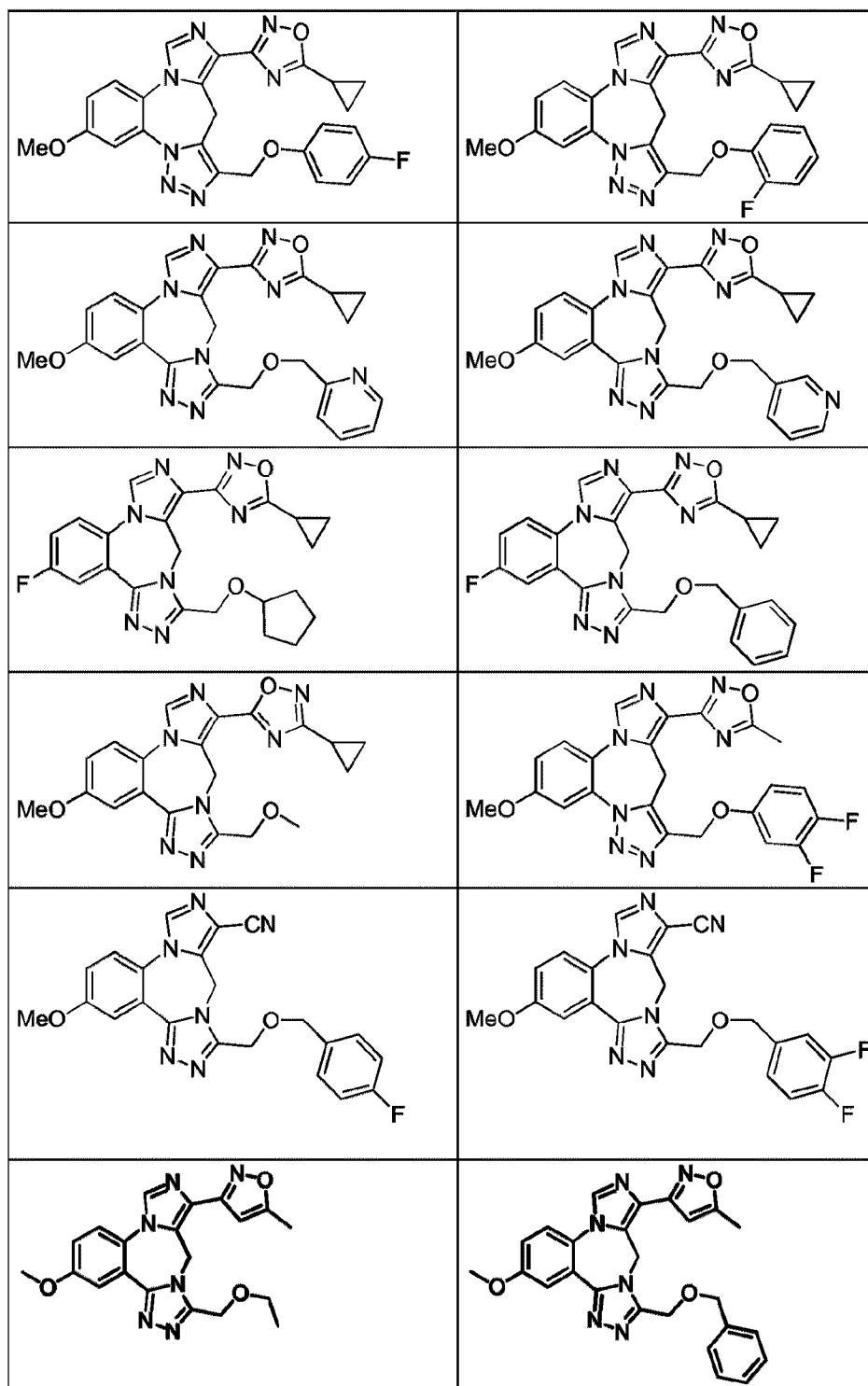
[0426] To a vial containing alkyl bromide derivative (22 mg, 0.052 mmol) was added 3-fluorophenol (58 mg, 0.52 mmol) in dioxane (1 mL) and potassium carbonate (72 mg, 0.52 mmol). The reaction mixture was heated at 90 °C for 1 hour. The reaction mixture was diluted with sat. aq. NaHCO₃ solution. The resulting solution was extracted with EtOAc (3X). The combined organic phases were washed with brine and dried over MgSO₄. Filtration and concentration gave a crude product. Purification by prep TLC (eluting system: EtOAc) to give 5 mg (21% yield) of the desired product **Compound 168** (M+1= 460). ¹H NMR (CDCl₃) δ 7.87 (1H, s), 7.65 (1H, d, J= 3.5 Hz), 7.57 (1H, d, J= 10 Hz), 7.24 (1H, m), 7.19 (1H, dd, J= 3.5, 9 Hz), 6.77 (1H, dd, J= 2.5, 9.5 Hz), 6.72 (2H, m), 5.26 (2H, s), 3.97 (3H, s), 2.48 (3H, s).

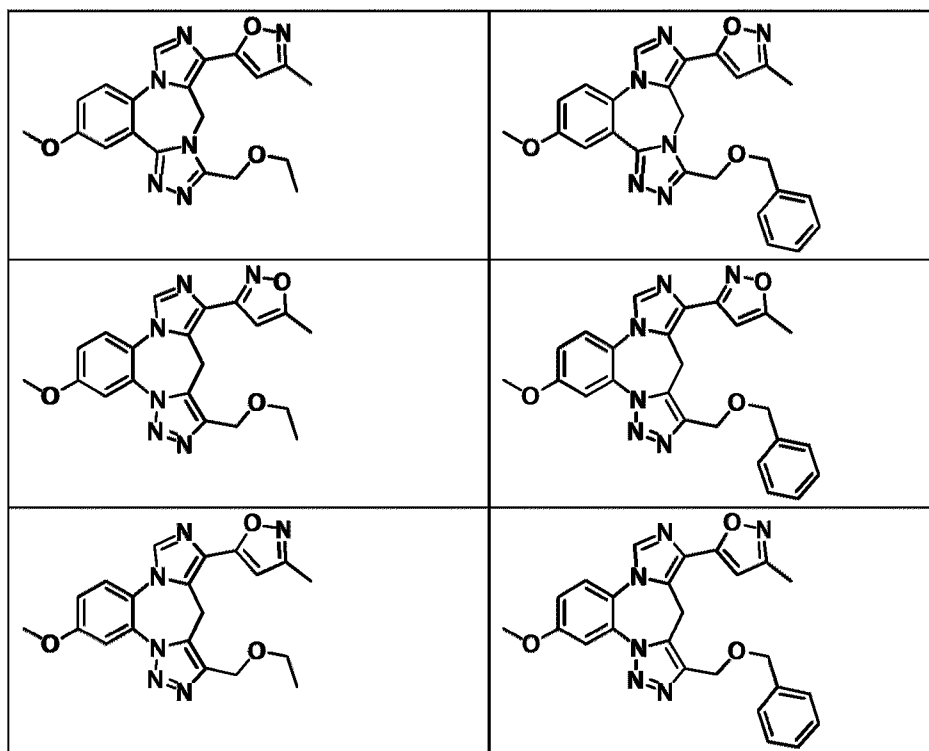
[0427] Implementing reactions similar and analogous to those shown in Schemes 1 through 27, the following compounds are also specifically contemplated in this application:











Example 105: Assessing $\alpha 5$ -containing GABA_A Receptor (GABA_AR) positive allosteric modulator activity

[0428] *Step 1: Establish clones of GABA_AR subunits ($\alpha 5$, $\beta 3$, $\gamma 2$, $\alpha 1$, $\alpha 2$ and $\alpha 3$) and prepare the corresponding cRNAs:* Human clones of GABA_A-R $\alpha 5$, $\beta 3$, $\gamma 2$, $\alpha 1$, $\alpha 2$ and $\alpha 3$ subunits are obtained from commercial resources (e.g., OriGene and Genescript). These clones are engineered into pRC, pCDM, pcDNA, and pBluescript KSM vector (for oocyte expression) or other equivalent expression vectors. Conventional transfection agents (e.g., FuGene, Lipofectamine 2000, or others) are used to transiently transfect host cells.

[0429] *Step 2 - Functional GABA_AR Assay of $\alpha 5\beta 3\gamma 2$, $\alpha 1\beta 3\gamma 2$, $\alpha 2\beta 3\gamma 2$, and $\alpha 3\beta 3\gamma 2$, subtypes in Xenopus oocyte expression system:* cRNAs encoding $\alpha 5$, $\beta 3$, $\gamma 2$, $\alpha 1$, $\alpha 2$ and $\alpha 3$ subunits are transcribed *in vitro* using T3 mMESSAGE mMACHINE Kit (Ambion) and injected (in a ratio of $\alpha:\beta:\gamma = 2:2:1$ or other optimized conditions) into oocytes freshly prepared from Xenopus laevis. After two days of culturing, GABA-gated Cl⁻ currents from oocytes are performed using TEVC setups (Warner Instruments, Inc., Foster City, CA). GABA, benzodiazepine, and diazepam are used as reference compounds to validate the system.

[0430] *Step 3 - Evaluate test compounds for positive allosteric modulator activity on the $\alpha 5\beta 3\gamma 2$ subtype and test off-target activity on the $\alpha 1$ to $\alpha 3$ coupled $\beta 3\gamma 2$ subtypes when the $EC_{50}=5\mu M$ selectivity cut-off is reached:* The GABA-gated Cl^- current from oocytes are measured in the TEVC setup in the presence of the test compounds. The positive
 5 allosteric modulator activity of each the test compounds is tested in a 5-point dose-response assay. The test compounds include some reference compounds (literature EC_{50} values for the $\alpha 5\beta 3\gamma 2$ subtype are in the range of 3-10 μM). EC_{50} s in the $\alpha 5\beta 3\gamma 2$ subtype are obtained for each compound. If the EC_{50} in $\alpha 5\beta 3\gamma 2$ is $\leq 5\mu M$, then the EC_{50} of the other three subtypes ($\alpha 1\beta 2\gamma 2$, $\alpha 2\beta 3\gamma 2$, and $\alpha 3\beta 3\gamma 2$) is further determined
 10 individually in order to test for selectivity of the compounds in the $\alpha 5\beta 3\gamma 2$ subtype over other subtypes.

[0431] *Step 4 – Evaluate further test compounds on the $\alpha 5\beta 3\gamma 2$ subtype and test off-target activities when the $EC_{50}=0.5\mu M$ selectivity cut-off is reached:* The second batch of test compounds are tested using the same strategy, but with a lower EC_{50} cutoff (0.5
 15 μM). Again, the EC_{50} s of the $\alpha 5\beta 3\gamma 2$ subtype for each of the compounds is determined. The $\alpha 1$ to $\alpha 3$ coupled $\beta 3\gamma 2$ subtypes are tested only if the EC_{50} for the $\alpha 5$ -containing receptor is $< 0.5 \mu M$.

Example 106: Evaluating Compounds for Binding and Positive Allosteric Modulator Activity on the GABA_A $\alpha 5$ Receptors

20 (A) Binding activity of test compounds on GABA_AR

[0432] Tissue culture and Membrane Preparation: The binding was performed on Ltk cells stably expressing GABA_A receptors: $\alpha 1\beta 1\gamma 2$, $\alpha 2\beta 3\gamma 2$, $\alpha 3\beta 3\gamma 2$ and $\alpha 5\beta 3\gamma 2$ (provided by Merck Co., NJ, USA). Cells were seeded in 100 mm culture plates in DMEM/F12 medium containing 10% serum and antibiotics in 5% CO₂ and allowed to grow for 1-2
 25 days. GABA_AR expression was then induced by dexamethasone as follows: 0.5 μM for 1 day for $\alpha 5$ containing and 2 μM for 3 days for $\alpha 1$, $\alpha 2$ and $\alpha 3$ containing GABA_ARs. After induction, cells were collected by scraping into Dulbecco's Phosphate buffered saline (DPBS, pH 7.4, Invitrogen, Carlsbad, CA, USA) and centrifuged at 150 x g for 10 min. The pellet was washed twice by re-suspension and centrifugation. The cell pellets from at
 30 least 5 different preps were combined, suspended in the binding assay buffer (50 mM KH₂PO₄; 1 mM EDTA; 0.2 M KCl, pH 7.4) and membranes prepared by sonication (3-5 times, 30 sec) using Branson Sonifier 150 (G.Heinmann, Germany). Protein content was

determined using BCA assay (Bio-Rad Labs, Reinach, Switzerland) with Bovine Serum Albumin (Sigma Aldrich, St. Louis, MO, USA) as the standard. Aliquots were prepared and stored at -20°C for further use in binding assays.

- [0433] Ligand Binding: Saturation binding curves were obtained by incubating
 5 membranes with increasing concentrations (0.01 – 8 nM) of [³H]Ro15-1788 (Flumazepil, 75-85 Ci/mmol, PerkinElmer, MA, USA), with nonspecific binding measured in the presence of 10 μM diazepam. Inhibition of [³H]Ro15-1788 binding of the test compounds was performed at concentrations of the radioligand at or lower than the K_d values for α1, α2, α3 and α5 containing GABA_ARs determined from the saturation curves.
- 10 [0434] All binding assays were performed for 1 h at 4°C in assay buffer. The total assay volume was 0.5 ml containing 0.2 mg/ml protein for α5 and 0.4 mg/ml for α1, α2, and α3 containing GABA_AR membranes. Incubations were terminated by filtration through GF/B filters using a 24-Cell Harvester (Brandel, Gaithersburg, MD, USA) followed by 3 washes with ice-cold assay buffer. Filters were transferred to scintillation vials, 5 ml
 15 scintillation liquid added, vortex-mixed and kept in dark. Next day, radioactivity was obtained using a scintillation counter (Beckman Coulter, Brea, CA, USA). All assays were performed in triplicate.

- [0435] Data Analyses: Saturation and inhibition curves were obtained using GraphPad Prism software (GraphPad Software, Inc., CA, USA). The equilibrium dissociation
 20 constants (K_i values) of the unlabeled ligand were determined using Cheng-Prusoff equation $K_i = IC_{50} / (1 + S/K_d)$, where IC₅₀ is the concentration of unlabeled ligand that inhibits 50% of [³H] ligand binding, S is the concentration of radioligand and K_d is the equilibrium dissociation constant of the radioactive ligand. A log range of the compounds (1 nM – 10 μM) was used to determine the K_i values which are presented as Mean ± SD
 25 from triplicate assays.

(B) positive allosteric modulator activity of test compounds on α5β2γ2 subtype GABA_AR

[0436] Compounds of the present invention were initially screened at 100 nM for their ability to potentiate an EC₂₀ concentration of GABA in oocytes containing GABA_A receptors (α5β2γ2), using a protocol essentially similar to the one presented above.

[0437] On day 1, 1ng/32nL of GABA_A $\alpha 5\beta 2\gamma 2$ cDNA was injected into one oocyte. Test starts on day 2. The cDNA injected to the oocytes was a mix of alpha, beta and gamma, their ratio is 1:1:10 (by weight) and the total weight of the mixed 3 subunits to be injected in one oocyte was 1ng in 32 nl volume. The injected oocytes can also be tested
 5 on day 3. In such case, the cDNA amount injected to the oocytes should be reduced by 20%.

[0438] Compounds of the present invention were tested using the following procedures.

[0439] GABA dose-response

- 1). 8 oocytes were placed in 8 chambers of OpusXpress and superfused with Modified
 10 Barth's Saline (MBS) at 3mL/min. Glass electrodes back-filled with 3M KCl (0.5-3 megaohms) were used. Membrane potential of oocytes was voltage-clamped at -60mV.
- 2). Average EC₂₀ GABA obtained from previous tests were applied for five-six times to stabilize oocytes. Oocytes were washed with MBS for 5-10 min between each GABA applications.
- 15 3). Run GABA dose-response to obtain EC₂₀ GABA value.

[0440] Control test (Diazepam or methyl 3,5-diphenylpyridazine-4-carboxylate)

- 1). New oocytes was used to run new test.
- 2). EC₂₀ GABA was applied for five-six times to stabilize oocytes. Oocytes were washed with MBS for 5-10 min between each GABA applications.
- 20 3). EC₂₀ GABA was applied to obtain current (I_{GABA}). Oocytes were washed with MBS for 5-10 min.
- 4). 1 μ M diazepam or methyl 3,5-diphenylpyridazine-4-carboxylate was pre-applied for 40 sec, followed by co-application of 1 μ M diazepam or methyl 3,5-diphenylpyridazine-4-carboxylate and EC₂₀ GABA to obtain I_{test}. I_{test} was divided by I_{GABA} to obtain
 25 potentiation (%).

[0441] Test compounds at multiple doses

- 1). Repeat the above steps 1), 2) and 3) in the control test.
- 2). The first concentration of a test compound was pre-applied for 40 sec followed by co-application of the test compound of the same concentration and EC₂₀ GABA to obtain
 30 I_{test}. Divide I_{test} by I_{GABA} to obtain potentiation (%).

3). Discard all tested oocytes, new oocytes were used and the above steps 1) and 2) were repeated to test second concentration of the same compound. Each oocyte was used for only one concentration test for a single test compound. The steps were repeated for other test compounds.

- 5 [0442] In some embodiments, the compounds of this application have a binding affinity (as represented by K_i) at $\alpha 5$ -containing GABA_ARs of less than 200 nM, less than 180 nM, less than 150 nM, or less than 100 nM. In some embodiments, the compounds of this application have a binding affinity (as represented by K_i) at $\alpha 5$ -containing GABA_ARs of less than 50 nM. In some embodiments, the compounds of this application have a
10 binding affinity (as represented by K_i) at $\alpha 5$ -containing GABA_ARs of less than 10 nM.

- [0443] In some embodiments, the compounds of this application are selective for $\alpha 5$ -containing GABA_ARs over $\alpha 1$ -containing GABA_ARs. In some embodiments, the compounds of this application are more than 50-fold, more than 100-fold, more than 500-fold or more than 1000-fold selective for $\alpha 5$ -containing GABA_ARs over $\alpha 1$ -containing
15 GABA_ARs.

[0444] In some embodiments, the compounds of this application have an EC_{50} at the $\alpha 5$ -containing GABA_ARs of less than 500 nM, less than 100 nM or less than 50 nM. In some embodiments, the compounds of this application have an EC_{50} at the $\alpha 5$ -containing GABA_ARs of less than 25 nM.

- 20 [0445] In some embodiments, the compounds of this application potentiate $\alpha 5$ -containing GABA_ARs for more than 10%, more than 25%, more than 50%, or more than 75% at 100 nM. In some embodiments, the compounds of this application potentiate $\alpha 5$ -containing GABA_ARs for more than 10%, more than 25%, more than 50%, or more than 75% at 1000 nM.

- 25 [0446] Screening results of the binding and PAM functional activity tests are summarized in Tables 1 and 2 below.

[0447] The following Table 1 illustrates the ranges of GABA $\alpha 5$ binding K_i 's associated with compounds of this invention:

Table 1

GABA α 5 Binding K_i Values (nM)		
< 99 nM	100 – 1000 nM	> 1000 nM
Compounds 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 44, 55, 101, 103, 105, 107, 108, 114, 128, 153, 158, 162, 163, 164, 166, 169, 171, 172, 173, 174, 175, 177, 179, 5, 47, 48, 49, 51, 52, 53, 54, 56, 102, 104, 106, 111, 112, 118, 120, 126, 127, 130, 133, 137, 145, 147, 148, 149, 155, 156, 157, 160, 165, 168, 178, 45, 46, 109, 122, 129, 132, 150, 151, 159, 161, 167, 176	Compounds 50, 110, 113, 115, 119, 124, 125, 134, 136, 138, 139, 141, 143, 144, 146, 170,	Compounds 116, 117, 121, 123, 131, 135, 140, 142, 143, 152, 154,

[0448] The following Table 2 illustrates the ranges of GABA α 5 functional potentiation associated with compounds of this invention:

5 **Table 2**

GABA α 5 Functional Data	
20 – 49% @ 100 nM	> 50% @ 100 nM
Compounds 1, 2, 9, 11, 48, 45, 55, 109, 110, 111, 118, 120, 126, 127, 128, 130, 132, 137, 147, 148, 153, 155, 158, 162, 163, 175	Compounds 113, 114, 145, 149, 160, 171, 172, 173, 174, 176, 177, 178, 179

[0449] Selected compounds of this invention demonstrate > 10-fold binding selectivity versus GABA α 1, GABA α 2, or GABA α 3.

Example 107: Effect of Methyl 3,5-diphenylpyridazine-4-carboxylate in Aged-Impaired (AI) Rats

[0450] Methyl 3,5-diphenylpyridazine-4-carboxylate, corresponding to compound number 6 in van Niel et al. *J. Med. Chem.* **48**:6004-6011 (2005), is a selective $\alpha 5$ -
5 containing GABA_A R agonist. It has an $\alpha 5$ *in vitro* efficacy of +27 (EC₂₀). The effect of methyl 3,5-diphenylpyridazine-4-carboxylate in aged-impaired rats was studied using a RAM task. Moreover, receptor occupancy by methyl 3,5-diphenylpyridazine-4-carboxylate in $\alpha 5$ -containing GABA_A receptor was also studied.

(A) Effect of Methyl 3,5-diphenylpyridazine-4-carboxylate in Aged-Impaired Rats Using a
10 Radial Arm Maze (RAM) Behavioral Task

[0451] The effects of methyl 3,5-diphenylpyridazine-4-carboxylate on the *in vivo* spatial memory retention of aged-impaired (AI) rats were assessed in a Radial Arm Maze (RAM) behavioral task using vehicle control and four different dosage levels of methyl 3,5-diphenylpyridazine-4-carboxylate (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg and 3 mg/kg, ip).
15 RAM behavioral tasks were performed on eight AI rats. All five treatment conditions (vehicle and four dosage levels) were tested on all eight rats.

[0452] The RAM apparatus used consisted of eight equidistantly-spaced arms. An elevated maze arm (7 cm width x 75 cm length) projected from each facet of an octagonal center platform (30 cm diameter, 51.5 cm height). Clear side walls on the arms were 10
20 cm high and were angled at 65° to form a trough. A food well (4 cm diameter, 2 cm deep) was located at the distal end of each arm. Froot LoopsTM (Kellogg Company) were used as rewards. Blocks constructed of PlexiglasTM (30 cm height x 12 cm width) could be positioned to prevent entry to any arm. Numerous extra maze cues surrounding the apparatus were also provided.

25 [0453] The AI rats were initially subjected to a pre-training test (Chappell *et al. Neuropharmacology* **37**: 481-487, 1998). The pre-training test consisted of a habituation phase (4 days), a training phase on the standard win-shift task (18 days) and another training phase (14 days) in which a brief delay was imposed between presentation of a subset of arms designated by the experimenter (*e.g.*, 5 arms available and 3 arms blocked)
30 and completion of the eight-arm win-shift task (*i.e.*, with all eight arms available).

[0454] In the habituation phase, rats were familiarized to the maze for an 8-minute session on four consecutive days. In each of these sessions, food rewards were scattered on the RAM, initially on the center platform and arms and then progressively confined to the arms. After this habituation phase, a standard training protocol was used, in which a food pellet was located at the end of each arm. Rats received one trial each day for 18 days. Each daily trial terminated when all eight food pellets had been obtained or when either 16 choices were made or 15 minutes had elapsed. After completion of this training phase, a second training phase was carried out in which the memory demand was increased by imposing a brief delay during the trial. At the beginning of each trial, three arms of the eight-arm maze were blocked. Rats were allowed to obtain food on the five arms to which access was permitted during this initial “information phase” of the trial. Rats were then removed from the maze for 60 seconds, during which time the barriers on the maze were removed, thus allowing access to all eight arms. Rats were then placed back onto the center platform and allowed to obtain the remaining food rewards during this “retention test” phase of the trial. The identity and configuration of the blocked arms varied across trials.

[0455] The number of “errors” the AI rats made during the retention test phase was tracked. An error occurred in the trial if the rats entered an arm from which food had already been retrieved in the pre-delay component of the trial, or if the rat re-visited an arm in the post-delay session that it had already visited.

[0456] After completion of the pre-training test, rats were subjected to trials with more extended delay intervals, *i.e.*, a two-hour delay, between the information phase (presentation with some blocked arms) and the retention test (presentation of all arms). During the delay interval, rats remained off to the side of the maze in the testing room, on carts in their individual home cages. AI rats were pretreated 30 – 40 minutes before daily trials with a one-time shot of the following five conditions: 1) vehicle control - 5% dimethyl sulfoxide, 25% polyethylene glycol 300 and 70% distilled water; 2) methyl 3,5-diphenylpyridazine-4-carboxylate at 0.1 mg/kg; 3) methyl 3,5-diphenylpyridazine-4-carboxylate at 0.3 mg/kg; 4) methyl 3,5-diphenylpyridazine-4-carboxylate at 1 mg/kg; and 5) methyl 3,5-diphenylpyridazine-4-carboxylate at 3 mg/kg; through intraperitoneal (i.p.) injection. Injections were given every other day with intervening washout days. Each AI rat was treated with all five conditions within the testing period. To

counterbalance any potential bias, drug effect was assessed using ascending-descending dose series, *i.e.*, the dose series was given first in an ascending order and then repeated in a descending order. Therefore, each dose had two determinations.

[0457] Parametric statistics (paired t-tests) was used to compare the retention test performance of the AI rats in the two-hour delay version of the RAM task in the context of different doses of methyl 3,5-diphenylpyridazine-4-carboxylate and vehicle control (see Figure 1). The average numbers of errors that occurred in the trials were significantly fewer with methyl 3,5-diphenylpyridazine-4-carboxylate treatment of 3 mg/kg (average no. of errors \pm standard error of the mean (SEM) = 1.31 ± 0.40) than using vehicle control (average no. of errors \pm SEM = 3.13 ± 0.62). Relative to vehicle control treatment, methyl 3,5-diphenylpyridazine-4-carboxylate significantly improved memory performance at 3 mg/kg ($t(7) = 4.233$, $p = 0.004$).

[0458] The therapeutic dose of 3 mg/kg became ineffective when the AI rats were concurrently treated with 0.3 mg/kg of TB21007, a $\alpha 5$ -containing GABA_A R inverse agonist. The average numbers of errors made by rats with the combined TB21007/methyl 3,5-diphenylpyridazine-4-carboxylate treatment (0.3 mg/kg TB21007 with 3 mg/kg methyl 3,5-diphenylpyridazine-4-carboxylate) was 2.88 ± 1.32 , and was no different from rats treated with vehicle control (3.13 ± 1.17 average errors). Thus, the effect of methyl 3,5-diphenylpyridazine-4-carboxylate on spatial memory is a GABA_A $\alpha 5$ receptor-dependent effect (see Figure 1).

(B) Effect of Methyl 3,5-diphenylpyridazine-4-carboxylate on $\alpha 5$ -containing GABA_A Receptor Occupancy

Animals

[0459] Adult male Long Evans rats (265-295 g, Charles River, Portage, MI, $n=4$ /group) were used for GABA_A $\alpha 5$ receptor occupancy studies. Rats were individually housed in ventilated stainless-steel racks on a 12:12 light/dark cycle. Food and water were available ad libitum. In additional studies to evaluate compound exposures at behaviorally active doses, young or aged Long Evan rats ($n= 2-4$ /group) were used for these studies.

Compounds

[0460] Ro 15-4513 was used as a receptor occupancy (RO) tracer for GABA_A $\alpha 5$ receptor sites in the hippocampus and cerebellum. Ro 15-4513 was chosen as the tracer

based on its selectivity for GABA_Aα5 receptors relative to other alpha subunit containing GABA_A receptors and because it has been successfully used for GABA_Aα5 RO studies in animals and humans (*see, e.g.,* Lingford-Hughes et al., *J. Cereb. Blood Flow Metab.* 22:878-89 (2002); Pym et al, *Br. J. Pharmacol.* 146: 817-825 (2005); and Maeda et al., *Synapse* 47: 200-208 (2003)). Ro 15-4513 (1 µg/kg), was dissolved in 25% hydroxyl-propyl beta-cyclodextrin and administered i.v. 20' prior to the RO evaluations. Methyl 3,5-diphenylpyridazine-4-carboxylate (0.1 – 10 mg/kg) was synthesized by Nox Pharmaceuticals (India) and was dissolved in 25% hydroxyl-propyl beta-cyclodextrin and administered i.v. 15' prior to tracer injection. Compounds were administered in a volume of 0.5 ml/kg except for the highest dose of methyl 3,5-diphenylpyridazine-4-carboxylate (10 mg/kg) which was administered in a volume of 1 ml/kg due to solubility limitations.

Tissue preparation and analysis

[0461] The rats were sacrificed by cervical dislocation 20' post tracer injection. The whole brain was rapidly removed, and lightly rinsed with sterile water. Trunk blood was collected in EDTA coated eppendorf tubes and stored on wet ice until study completion. Hippocampus and cerebellum were dissected and stored in 1.5 ml eppendorf tubes, and placed on wet ice until tissue extraction. In a drug naïve rat, six cortical brain tissues samples were collected for use in generating blank and standard curve samples.

[0462] Acetonitrile containing 0.1% formic acid was added to each sample at a volume of four times the weight of the tissue sample. For the standard curve (0.1-30 ng/g) samples, a calculated volume of standard reduced the volume of acetonitrile. The sample was homogenized (FastPrep-24, Lysing Matrix D; 5.5 m/s, for 60 seconds or 7-8 watts power using sonic probe dismembrator; Fisher Scientific) and centrifuged for 16-minutes at 14,000 rpm. The (100 µl) supernatant solution was diluted by 300 µl of sterile water (pH 6.5). This solution was then mixed thoroughly and analyzed via LC/MS/MS for Ro 15-4513 (tracer) and methyl 3,5-diphenylpyridazine-4-carboxylate.

[0463] For plasma exposures, blood samples were centrifuged at 14000 rpm for 16 minutes. After centrifuging, 50ul of supernatant (plasma) from each sample was added to 200 µl of acetonitrile plus 0.1% formic acid. For standard curve (1-1000 ng/ml) samples, a calculated volume of standard reduced the volume of acetonitrile. Samples were sonicated for 5 minutes in an ultrasonic water bath, followed by centrifugation for 30

minutes, at 16000 RPM. 100ul of supernatant was removed from each sample vial and placed in a new glass auto sample vial, followed by the addition of 300 µl of sterile water (pH 6.5). This solution was then mixed thoroughly and analyzed via LC/MS/MS for methyl 3,5-diphenylpyridazine-4-carboxylate.

- 5 [0464] Receptor occupancy was determined by the ratio method which compared occupancy in the hippocampus (a region of high GABA_Aα5 receptor density) with occupancy in the cerebellum (a region with low GABA_Aα5 receptor density) and additionally by a high dose of the GABA_Aα5 negative allosteric modulator L-655,708 (10 mg/kg, i.v.) to define full occupancy.
- 10 [0465] Vehicle administration followed by tracer administration of 1 µg/kg, i.v., of Ro 15-4513 resulted in > 5-fold higher levels of Ro 15-4513 in hippocampus (1.93 ± 0.05 ng/g) compared with cerebellum (0.36 ± 0.02 ng/g). Methyl 3,5-diphenylpyridazine-4-carboxylate (0.01 – 10 mg/kg, i.v.) dose-dependently reduced Ro 15-4513 binding in hippocampus, without affecting cerebellum levels of Ro 15-4513 (Figure 2) with a dose
- 15 of 10 mg/kg, i.v., demonstrating >90% occupancy (Figure 3). Both methods of calculating RO yielding very similar results with ED50 values for methyl 3,5-diphenylpyridazine-4-carboxylate as 1.8 mg/kg or 1.1 mg/kg based on the ratio method or using L-755,608 to define occupancy .

- [0466] Methyl 3,5-diphenylpyridazine-4-carboxylate exposure was below the
- 20 quantification limits (BQL) at 0.01 mg/kg, i.v., in both plasma and hippocampus and but was detectable at low levels in hippocampus at 0.1 mg/kg, i.v. (see Table 3). Hippocampal exposure was linear as a 10-fold increase in dose from 0.1 to 1 mg/kg, i.v., resulted in a 12-fold increase in exposure. Increasing the dose from 1 to 10 mg/kg, i.v., only increased the exposure by ~5-fold. Plasma exposure increased 12-fold as the dose
- 25 increased from 1 to 10 mg/kg, i.v.

Table 3: % GABA_A α5 Receptor Occupancy by methyl 3,5-diphenylpyridazine-4-carboxylate (0.01-10 mg/kg, i.v.). Hippocampus and Plasma Exposure of methyl 3,5-diphenylpyridazine-4-carboxylate by Treatment Group in young Long Evans rats.

Dose (mg/kg, i.v.)	%RO (L-655,708 Method) (SEM)	%RO (Ratio Method) (SEM)	Plasma ng/mL (SEM)	Hippocampus ng/g (SEM)
0.01	19.2 (11.1)	15.7 (9.1)	BQL	BQL
0.1	16.4 (4.9)	13.4 (4.0)	BQL	14.6 (3.5)
1	38.5 (11.2)	31.5 (9.1)	62.8 (6.1)	180.0 (10.3)
10	110.0 (6.6)	90.2 (5.4)	763.5 (85.7)	947.2 (51.3)

[0467] Additional studies were conducted in aged Long-Evans rats in order to determine the exposures at the behaviorally relevant doses in the cognition studies. Exposure in young Long-Evans rats was also determined to bridge with the receptor occupancy studies that were conducted in young Long-Evans rats. Exposures in young and aged Long-Evans rats were relatively similar (Table 4, Figure 4). Increasing the dose 3-fold from 1 to 3 mg/kg, ip resulted in a greater than dose-proportional increase in exposure in young and aged rats in both hippocampus and plasma with increases ranging from 4.5 to 6.6-fold.

10 **Table 4:** Hippocampus and Plasma Exposure of methyl 3,5-diphenylpyridazine-4-carboxylate in Young Long Evans Rats by Treatment Group

	Young	Young	Aged	Aged
Dose (mg/kg, ip)	Hippocampus ng/g (SEM)	Plasma ng/mL (SEM)	Hippocampus ng/g (SEM)	Plasma ng/mL (SEM)
1	25.9 (1.7)	20.0 (1.4)	38.8 (21.7)	45.2 (29.6)
3	129.1 (22.4)	132.9 (19.5)	177.5 (19.5)	196 (18.2)

[0468] In the RO studies, an exposure of 180 ng/g in hippocampus (1 mg/kg, i.v.) represented 32-39% receptor occupancy depending on method used to determine RO.

15 This exposure is comparable to that observed in aged rats at 3 mg/kg, i.p., suggesting that 30-40% RO is required for cognitive efficacy in this model.

[0469] These studies demonstrated that methyl 3,5-diphenylpyridazine-4-carboxylate produced dose-dependent increase in GABA_A α5 receptor occupancy. Methyl 3,5-

diphenylpyridazine-4-carboxylate also demonstrated good brain exposure with brain/plasma ratios > 1. The studies further demonstrated that methyl 3,5-diphenylpyridazine-4-carboxylate was producing its cognitive enhancing effects by positive allosteric modulation at the GABA_A α 5 subtype receptor.

- 5 **Example 108: Effect of Ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate in Aged-Impaired (AI) Rats**
[0470] Ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate, corresponding to compound number 49 in Achermann et al. *Bioorg. Med. Chem. Lett.*, 19:5746-5752 (2009), is a selective α 5-containing GABA_A
 10 R agonist.

- [0471]** The effect of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate on the *in vivo* spatial memory retention of aged-impaired (AI) rats was assessed in a Radial Arm Maze (RAM) behavioral task that is essentially similar to the task as described in Example 107 (A),
 15 using vehicle control (25% cyclodextrin, which was tested 3 times: at the beginning, middle and end of ascending/descending series) and six different doses levels (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg, each dose was tested twice) of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate. The same experiment was repeated using the same
 20 vehicle control and doses of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate, where the vehicle control was tested 5 times, the 3 mg/kg dose of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate was tested 4 times, and the other doses of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate were tested twice.
 25

- [0472]** Parametric statistics (paired t-tests) was used to compare the retention test performance of the AI rats in the four-hour delay version of the RAM task in the context of different doses of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate and vehicle control (*see Figure 5*).
 30 Relative to vehicle control treatment, ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate significantly improved memory

performance at 3 mg/kg ($t(7) = 4.13$, $p = 0.004$, or $t(7) = 3.08$, $p = 0.018$) and at 10 mg/kg ($t(7) = 2.82$, $p = 0.026$).

[0473] The effect of ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate on $\alpha 5$ -containing GABA_A receptor occupancy was also studied following a procedure that is essentially similar to the one as described in Example 107(B) (*see above*). This study demonstrated that ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate (0.01 – 10 mg/kg, i.v.) reduced Ro 15-4513 binding in hippocampus, without affecting cerebellum levels of Ro 15-4513 (Figure 6) with a dose of 10 mg/kg, i.v., demonstrating >90% occupancy (Figure 7).

Example 109: Effect of 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one in Aged-Impaired Rats Using a Morris Water Maze Behavioral Task

[0474] 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one, corresponding to compound 44 in Chambers et al. *J. Med. Chem.* 46:2227-2240 (2003) is a selective $\alpha 5$ -containing GABA_A R agonist.

[0475] The effects of 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one on the *in vivo* spatial memory retention of aged-impaired (AI) rats were assessed in a Morris water maze behavioral task. A water maze is a pool surrounded with a novel set of patterns relative to the maze. The training protocol for the water maze may be based on a modified water maze task that has been shown to be hippocampal-dependent (de Hoz et al., *Eur. J. Neurosci.*, 22:745-54, 2005; Steele and Morris, *Hippocampus* 9:118-36, 1999).

[0476] Cognitively impaired aged rats were implanted unilaterally with a cannula into the lateral ventricle. Stereotaxic coordinates were 1.0 mm posterior to bregma, 1.5 mm lateral to midline, and 3.5 mm ventral to the skull surface. After about a week of recovery, the rats were pre-trained in a water maze for 2 days (6 trials per day) to locate a submerged escape platform hidden underneath the surface of the pool, in which the escape platform location varied from day to day. No intracerebroventricular (ICV) infusion was given during pre-training.

[0477] After pre-training, rats received ICV infusion of either 100 µg 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one (n = 6) in 5 µl DMSO or vehicle DMSO (n = 5) 40 min prior to water maze training and testing. Training consisted of 8 trials per day for 2 days where the hidden escape platform remained in the same location. Rats were given 60 seconds to locate the platform with a 60 seconds inter-trial interval. The rats were given a probe test (120 seconds) 24 hr after the end of training where the escape platform was removed. During the training, there were 4 blocks, where each block had 4 training trials.

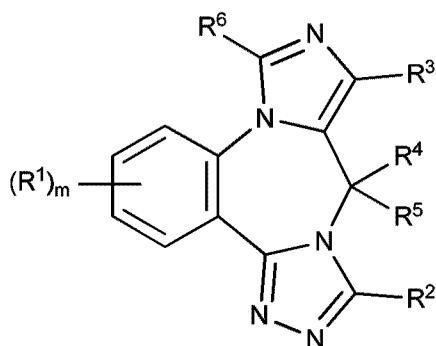
[0478] Rats treated with vehicle and 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one found the escape platform about the same time at the beginning of training (block 1). In this block of training, rats treated with vehicle and 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one both spent about 24 seconds to find the escape platform. However, rats treated with 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one were able to find the platform more proficiently (i.e., quicker) at the end of training (block 4) than those treated with vehicle alone. In block 4, rats treated with 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one spent about 9.6 seconds to find the escape platform, while rats treated with vehicle spent about 19.69 seconds. These results suggest that 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one improved the learning of the water maze task in rats (see **Figure 8(A)**).

[0479] During a test trial 24 hr after training, the escape platform was removed. The search/swim pattern of the rats was used to measure whether the rats remember where the escape platform was located during pre-trial training in order to test for the long-term memory of the rats. In this trial, “target annulus” is a designated area 1.5 times the size of the escape platform around the area where the platform was located during pre-trial training. “Opposite annulus” is a control area of the same size as the size of the target annulus, which is located opposite to the target annulus in the pool. If the rats had good long term memory, they would tend to search in the area surrounding the location where the platform was during the pre-trial training (i.e., the “target” annulus; and not the “opposite” annulus). “Time in annulus” is the amount of time in seconds that the rat spent in the target or opposite annulus area. “Number (#) of crossings” in annulus is the number of times the rat swam across the target or opposite annulus area.

- [0480] Rats received vehicle spent the same amount of time in the target annulus and opposite annulus, indicating that these rats did not seem to remember where the platform was during the pre-trial training. By contrast, rats treated with 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one spent significantly more time in the target annulus, and crossed the “target annulus” more often, as compared to the time they spent in, or the number of times they crossed the “opposite annulus”. These results suggest that 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one improved the long-term memory of rats in the water maze task (see, **Figures 8(B) and 8(C)**).
- [0481] Compounds of the present invention demonstrated positive allosteric modulatory effect on the GABA_A $\alpha 5$ receptor (*See, e.g.,* Example 106). These compounds will enhance the effects of GABA at the GABA_A $\alpha 5$ receptor. Therefore, compounds of the present invention should produce cognitive enhancing effects in aged-impaired animals (such as rats), similar to the effects produced by other GABA_A $\alpha 5$ receptor selective agonists, such as methyl 3,5-diphenylpyridazine-4-carboxylate, ethyl 3-methoxy-7-methyl-9H-benzo[f]imidazo[1,5-a][1,2,4]triazolo[4,3-d][1,4]diazepine-10-carboxylate, and 6,6 dimethyl-3-(3-hydroxypropyl)thio-1-(thiazol-2-yl)-6,7-dihydro-2-benzothiophen-4(5H)-one (*See, e.g.,* Examples 28-30).

Claims:

1. A compound of formula IV:



IV,

or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, wherein:

R^2 is $-OR^8$, $-SR^8$, $-(CH_2)_nOR^8$, $-(CH_2)_nO(CH_2)_nR^8$, $-(CH_2)_pR^8$ or $-(CH_2)_nN(R'')R^{10}$; and wherein R^2 is independently substituted with 0-5 R' ;

m and n are independently integers selected from 0-4;

p is an integer selected from 2-4;

each occurrence of R^1 , R^4 , and R^5 are each independently selected from:

halogen, $-R$, $-OR$, $-NO_2$, $-NCS$, $-CN$, $-CF_3$, $-OCF_3$, $-SiR_3$, $-N(R)_2$, $-SR$, $-SOR$, $-SO_2R$, $-SO_2N(R)_2$, $-SO_3R$, $-(CR_2)_{1-3}R$, $-(CR_2)_{1-3}-OR$, $-(CR_2)_{0-3}-C(O)NR(CR_2)_{0-3}R$, $-(CR_2)_{0-3}-C(O)NR(CR_2)_0-3OR$, $-C(O)R$, $-C(O)C(O)R$, $-C(O)CH_2C(O)R$, $-C(S)R$, $-C(S)OR$, $-C(O)OR$, $-C(O)C(O)OR$, $-C(O)C(O)N(R)_2$, $-OC(O)R$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-C(S)N(R)_2$, $-(CR_2)_0-3NHC(O)R$, $-N(R)N(R)COR$, $-N(R)N(R)C(O)OR$, $-N(R)N(R)CON(R)_2$, $-N(R)SO_2R$, $-N(R)SO_2N(R)_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(S)R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-N(COR)COR$, $-N(OR)R$, $-C(=NH)N(R)_2$, $-C(O)N(OR)R$, $-C(=NOR)R$, $-OP(O)(OR)_2$, $-P(O)(R)_2$, $-P(O)(OR)_2$, or $-P(O)(H)(OR)$;

R^3 is selected from:

halogen, $-R$, $-OR$, $-NO_2$, $-NCS$, $-CN$, $-CF_3$, $-OCF_3$, $-SiR_3$, $-N(R)_2$, $-SR$, $-SOR$, $-SO_2R$, $-SO_2N(R)_2$, $-SO_3R$, $-(CR_2)_{1-3}R$, $-(CR_2)_{1-3}-OR$, $-(CR_2)_{0-3}-C(O)NR(CR_2)_{0-3}R$, $-(CR_2)_{0-3}-C(O)NR(CR_2)_0-$

OR , $-C(O)R$, $-C(O)C(O)R$, $-C(O)CH_2C(O)R$, $-C(S)R$, $-C(S)OR$, $-C(O)OR$, $-C(O)C(O)OR$, $-C(O)C(O)N(R)_2$, $-OC(O)R$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-C(S)N(R)_2$, $-(CR_2)_0$,
 $_3NHC(O)R$, $-N(R)N(R)COR$, $-N(R)N(R)C(O)OR$, $-N(R)N(R)CON(R)_2$, $-N(R)SO_2R$, $-N(R)SO_2N(R)_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(S)R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-N(COR)COR$, $-N(OR)R$, $-C(=NH)N(R)_2$, $-C(O)N(OR)R$, $-C(=NOR)R$, $-OP(O)(OR)_2$, $-P(O)(R)_2$, $-P(O)(OR)_2$, or $-P(O)(H)(OR)$;

each R^6 is independently $-H$ or $-(C1-C6)alkyl$;

each R^8 is independently $-(C1-C6)alkyl$, $-(C3-C10)-cycloalkyl$, $(C6-C10)-aryl$, or 5- to 10- membered heteroaryl, wherein each occurrence of R^8 is independently substituted with 0-5 R' ;

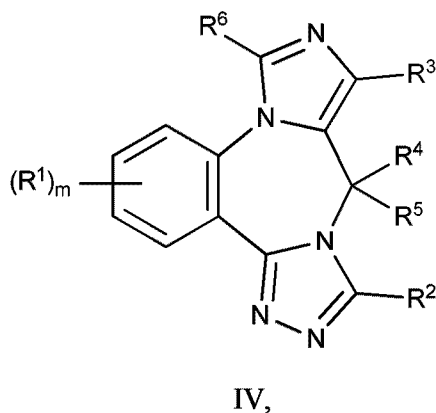
each R^{10} is independently $-(C3-C10)-cycloalkyl$, 3- to 10- membered heterocyclyl-, $(C6-C10)-aryl$, or 5- to 10- membered heteroaryl, wherein each occurrence of R^{10} is independently substituted with 0-5 R' ;

each R is independently selected from:

H -,
 $(C1-C12)-aliphatic$ -,
 $(C3-C10)-cycloalkyl$ -,
 $(C3-C10)-cycloalkenyl$ -,
 $[(C3-C10)-cycloalkyl]-(C1-C12)-aliphatic$ -,
 $[(C3-C10)-cycloalkenyl]-(C1-C12)-aliphatic$ -,
 $[(C3-C10)-cycloalkyl]-O-(C1-C12)-aliphatic$ -,
 $[(C3-C10)-cycloalkenyl]-O-(C1-C12)-aliphatic$ -,
 $(C6-C10)-aryl$ -,
 $(C6-C10)-aryl-(C1-C12)aliphatic$ -,
 $(C6-C10)-aryl-O-(C1-C12)aliphatic$ -,
 $(C6-C10)-aryl-N(R'')-(C1-C12)aliphatic$ -,
 3- to 10- membered heterocyclyl-,
 (3- to 10- membered heterocyclyl)-(C1-C12)aliphatic-,
 (3- to 10- membered heterocyclyl)-O-(C1-C12)aliphatic-,
 (3- to 10- membered heterocyclyl)- $N(R'')$ -(C1-C12)aliphatic-,
 5- to 10- membered heteroaryl-,
 (5- to 10- membered heteroaryl)-(C1-C12)-aliphatic-,

(5- to 10- membered heteroaryl)-O-(C1-C12)-aliphatic-; or
 (5- to 10- membered heteroaryl)-N(R'')-(C1-C12)-aliphatic-;
 wherein each occurrence of R other than hydrogen is independently substituted
 with 0-5 R';
 or when two R groups bound to the same atom, the two R groups may be taken
 together with the atom to which they are bound to form a 3- to 10-membered
 aromatic or non-aromatic ring having 0-4 heteroatoms independently selected
 from N, NH, O, S, SO, or SO₂, wherein said ring is optionally substituted with
 0-5 R', and wherein said ring is optionally fused to a (C6-C10)aryl, 5- to 10-
 membered heteroaryl, (C3-C10)cycloalkyl, or a 3- to 10- membered
 heterocyclyl;
 wherein each occurrence of R' is independently selected from halogen, -
 R'', -OR'', oxo, -CH₂OR'', -CH₂NR''₂, -C(O)N(R'')₂, -C(O)OR'', -
 NO₂, -NCS, -CN, -CF₃, -OCF₃, or -N(R'')₂;
 wherein each occurrence of R'' is independently selected from H, -(C1-C6)-alkyl,
 (C3-C6)-cycloalkyl, 3- to 6- membered heterocyclyl, 5- to 10- membered
 heteroaryl-, (C6-C10)-aryl-, (5- to 10- membered heteroaryl)-(C1-C6)-alkyl-,
 (C6-C10)-aryl-(C1-C6)-alkyl-, (5- to 10- membered heteroaryl)-O-(C1-C6)-
 alkyl-, or (C6-C10)-aryl-O-(C1-C6)-alkyl-
 wherein said heterocyclyl has 1-4 heteroatoms independently selected from N, NH,
 O, S, SO, or SO₂, and said heteroaryl has 1-4 heteroatoms independently
 selected from N, NH, O, or S.

2. A compound of formula IV:



or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, wherein:

R² is -OR⁸, -SR⁸, or -(CH₂)_nOR⁸;

m and n are independently integers selected from 0-4;

each occurrence of R¹, R⁴, and R⁵ are each independently selected from:

halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -
N(R)₂, -SR, -SOR, -SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -
(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R, -C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR, -N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R, -C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂, or -P(O)(H)(OR);

R³ is selected from:

halogen, -R, -OR, -NO₂, -NCS, -CN, -CF₃, -OCF₃, -SiR₃, -
N(R)₂, -SR, -SOR, -SO₂R, -SO₂N(R)₂, -SO₃R, -(CR₂)₁₋₃R, -(CR₂)₁₋₃-OR, -
(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃R, -(CR₂)₀₋₃-C(O)NR(CR₂)₀₋₃OR, -C(O)R, -C(O)C(O)R, -C(O)CH₂C(O)R, -C(S)R, -C(S)OR, -C(O)OR, -C(O)C(O)OR, -C(O)C(O)N(R)₂, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -C(S)N(R)₂, -(CR₂)₀₋₃NHC(O)R, -N(R)N(R)COR, -N(R)N(R)C(O)OR, -N(R)N(R)CON(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(S)R, -N(R)C(O)N(R)₂, -N(R)C(S)N(R)₂, -N(COR)COR, -N(OR)R, -C(=NH)N(R)₂, -C(O)N(OR)R, -C(=NOR)R, -OP(O)(OR)₂, -P(O)(R)₂, -P(O)(OR)₂, or -P(O)(H)(OR);

each R⁶ is independently -H or -(C1-C6)alkyl;

each R⁸ is independently -(C1-C6)alkyl, -(C3-C10)-cycloalkyl, (C6-C10)-aryl, or 5- to 10- membered heteroaryl, wherein each occurrence of R⁸ is independently substituted with 0-5 R';

each R is independently selected from:

H-,
(C1-C12)-aliphatic-,

(C3-C10)-cycloalkyl-,
 (C3-C10)-cycloalkenyl-,
 [(C3-C10)-cycloalkyl]-(C1-C12)-aliphatic-,
 [(C3-C10)-cycloalkenyl]-(C1-C12)-aliphatic-,
 [(C3-C10)-cycloalkyl]-O-(C1-C12)-aliphatic-,
 [(C3-C10)-cycloalkenyl]-O-(C1-C12)-aliphatic-,
 (C6-C10)-aryl-,
 (C6-C10)-aryl-(C1-C12)aliphatic-,
 (C6-C10)-aryl-O-(C1-C12)aliphatic-,
 3- to 10- membered heterocyclyl-,
 (3- to 10- membered heterocyclyl)-(C1-C12)aliphatic-,
 (3- to 10- membered heterocyclyl)-O-(C1-C12)aliphatic-,
 5- to 10- membered heteroaryl-,
 (5- to 10- membered heteroaryl)-(C1-C12)-aliphatic-, or
 (5- to 10- membered heteroaryl)-O-(C1-C12)-aliphatic-;

wherein each occurrence of R other than hydrogen is independently substituted
 with 0-5 R';

or when two R groups bound to the same atom, the two R groups may be taken
 together with the atom to which they are bound to form a 3- to 10-membered
 aromatic or non-aromatic ring having 0-4 heteroatoms independently selected
 from N, NH, O, S, SO, or SO₂, wherein said ring is optionally substituted with
 0-5 R', and wherein said ring is optionally fused to a (C6-C10)aryl, 5- to 10-
 membered heteroaryl, (C3-C10)cycloalkyl, or a 3- to 10- membered
 heterocyclyl;

wherein each occurrence of R' is independently selected from halogen, -
 R'', -OR'', oxo, -CH₂OR'', -CH₂NR''₂, -C(O)N(R'')₂, -C(O)OR'', -
 NO₂, -NCS, -CN, -CF₃, -OCF₃ or -N(R'')₂;

wherein each occurrence of R'' is independently selected from H, -(C1-C6)-alkyl,
 (C3-C6)-cycloalkyl, 3- to 6- membered heterocyclyl, 5- to 10- membered
 heteroaryl-, (C6-C10)-aryl-, (5- to 10- membered heteroaryl)-(C1-C6)-alkyl-,
 (C6-C10)-aryl-(C1-C6)-alkyl-, (5- to 10- membered heteroaryl)-O-(C1-C6)-
 alkyl-, or (C6-C10)-aryl-O-(C1-C6)-alkyl-;

wherein said heterocyclyl has 1-4 heteroatoms independently selected from N, NH,
 O, S, SO, or SO₂, and said heteroaryl has 1-4 heteroatoms independently

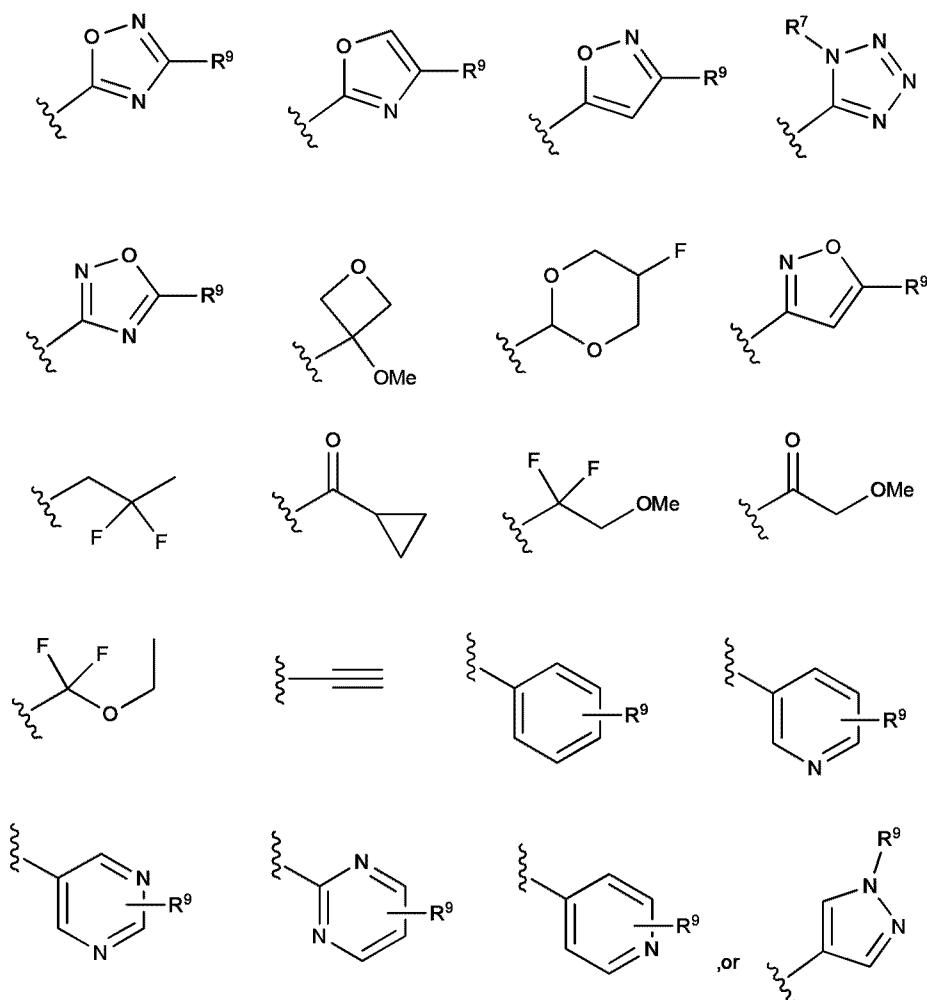
selected from N, NH, O, or S.

3. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 1 wherein R^2 is OR^8 , SR^8 , $(CH_2)_nOR^8$, $-(CH_2)_nO(CH_2)_nR^8$, $-(CH_2)_pR^8$ or $-(CH_2)_nN(R'')R^{10}$, wherein each R^8 is independently $-(C1-C6)alkyl$, $-(C3-C10)-cycloalkyl$, $(C6-C10)-aryl$, or 5- to 10- membered heteroaryl, wherein each occurrence of R^8 is independently substituted with 0-5 R' ; n is an integer selected from 0-4; p is an integer selected from 2-4; and each R^{10} is independently $-(C3-C10)-cycloalkyl$, 3- to 10- membered heterocyclyl-, $(C6-C10)-aryl$, or 5- to 10- membered heteroaryl, wherein each occurrence of R^{10} is independently substituted with 0-5 R' .
4. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 3, wherein R^2 is OR^8 .
5. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 3, wherein R^2 is $-(CH_2)_nOR^8$ or $-(CH_2)_nO(CH_2)_nR^8$.
6. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 4, wherein R^8 is $(C6-C10)-aryl$, independently substituted with 0-5 R' .
7. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 5, wherein R^8 is $-(C1-C6)alkyl$, $(C6-C10)-aryl$, or 5- to 10- membered heteroaryl, wherein each

occurrence of R⁸ is independently substituted with 0-5 R'.

8. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to any one of claims 1-7, wherein each occurrence of R¹ is selected from:
halogen, -R, -OR, -NO₂, -CN, -CF₃, -OCF₃, -N(R)₂, or -N(R)SO₂R, wherein each occurrence of R other than hydrogen is independently substituted with 0-5 R'.
9. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 8, wherein each occurrence of R¹ is independently selected from: halogen, -H, -(C1-C6)alkyl, -OH, -O((C1-C6)alkyl), -NO₂, -CN, -CF₃, -OCF₃, -NH₂, -N((C1-C6)alkyl)₂, -N((C1-C6)alkyl)SO₂((C1-C6)alkyl), or -NHSO₂((C1-C6)alkyl), wherein said alkyl is independently substituted with 0-5 R'.
10. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 9, wherein each occurrence of R¹ is independently selected from: -H, -F, -Cl, -Br, -OH, -Me, -Et, -OMe, -OEt, -NO₂, -CN, -CF₃, -OCF₃, -NH₂, -NMe₂, -NEt₂, -NHSO₂Me, or -NHSO₂Et.
11. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 8, wherein at least one R¹ is -OR.
12. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 11, wherein the at least one R¹ is -O((C1-C6)alkyl).

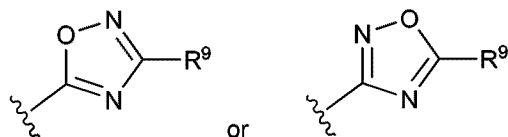
13. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 12, wherein the at least one R¹ is –OMe.
14. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to any one of claims 1-13, wherein R³ is selected from:
halogen, -R, -CN, -CF₃, -SO₂R, -C(O)N(R)₂, -C(O)R or -C(O)OR, wherein each occurrence of R other than hydrogen is independently substituted with 0-5 R'.
15. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 14, wherein R³ is selected from:
-H, -F, -Br, -Cl, -(C1-C6)alkyl, -CN, -CF₃, -SO₂((C1-C6)alkyl), -C(O)N((C1-C6)alkyl)₂, -C(O)NH₂, -C(O)((C1-C6)alkyl), -SO₂((C6-C10)-aryl), -C(O)O((C1-C6)alkyl), -(C2-C6)-alkenyl, -(C2-C6)-alkynyl, -(C6-C10)-aryl, 5- to 10- membered heteroaryl-, or 3- to 10- membered heterocyclyl-, wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl or heterocyclyl- is independently substituted with 0-5 R'.
16. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 15, wherein R³ is selected from: -H, -C(O)OMe, -C(O)Et, -C(O)NMe₂, -C(O)NH₂, -C(O)OEt, -C(O)OCH₂(*tert*-butyl), -C(O)OCH₂CF₃, -C(O)O(isopropyl), -C(O)NEt₂, -CN, -SO₂Me, -SO₂Et, -SO₂Ph(Me), -CF₃, -CHF₂, -Me, -Et, -Br, -Cl, -CH₂Ph,



wherein R^9 is selected from $-H$, $-Me$, $-Et$, $-CF_3$, isopropyl, $-OMe$, $-OEt$, $-O$ -isopropyl, $-CH_2NMe_2$, *-tert-butyl* or cyclopropyl.

17. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 16 wherein R^3 is $-C(O)OMe$ or $-C(O)OEt$.

18. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 16, wherein R^3 is:



, wherein R⁹ is selected from –H, –Me, –Et, –CF₃, isopropyl, –OMe, –OEt, –O-isopropyl, –CH₂NMe₂, –*tert*-butyl or cyclopropyl.

19. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to any one of claims 1-18, wherein R⁴ and R⁵ are each independently selected from –H, halogen or –R, wherein each occurrence of R other than hydrogen is independently substituted with 0-5 R', or R⁴ and R⁵ may be taken together with the carbon atom to which they are bound to form a 3- to 10-membered aromatic or non-aromatic ring having 0-3 additional heteroatoms independently selected from N, O, S, SO, or SO₂, wherein said ring is substituted with 0-5 R'.
20. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 19, wherein R⁴ and R⁵ are each independently selected from –H, –Me, –Et, or –F, or R⁴ and R⁵ are taken together with the carbon atom to which they are bound to form a 3- to 8-membered aliphatic ring.
21. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 20, wherein both R⁴ and R⁵ are –H.
22. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 1 or 2, wherein: m is 0, 1, or 2, and when m is 1 or 2, at least one occurrence of R¹ is –O((C1-C6)alkyl);

R² is OR⁸, wherein R⁸ is (C6-C10)-aryl, substituted with 0-3 halogen;

R³ is -C(O)O((C1-C6)alkyl);

R⁴ and R⁵ are both -H; and

R⁶ is -H.

23. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 1, wherein: m is 0-3;

when m is 1 or 2, at least one occurrence of R¹ is -halogen or -O((C1-C6)alkyl);

each R¹ is independently selected from: halogen, -H, -(C1-C6)alkyl, -OH,

-O((C1-C6)alkyl), -NO₂, -CN, -CF₃, or -OCF₃,

wherein the said (C1-C6)alkyl is independently substituted with 0-5 R';

R² is selected from -OR⁸, -SR⁸, -(CH₂)_nOR⁸, -(CH₂)_nO(CH₂)_nR⁸, -(CH₂)_pR⁸ or -

(CH₂)_nN(R'')R¹⁰, wherein n is an integer selected from 0-4; p is an integer

selected from 2-4; each R⁸ is independently -(C1-C6)alkyl, -(C3-C10)-

cycloalkyl, (C6-C10)-aryl, or 5- to 10- membered heteroaryl, wherein each

occurrence of R⁸ is independently substituted with 0-5 R'; each R¹⁰ is

independently -(C3-C10)-cycloalkyl, 3- to 10- membered heterocycl-yl, (C6-

C10)-aryl, or 5- to 10- membered heteroaryl, wherein each occurrence of R¹⁰ is

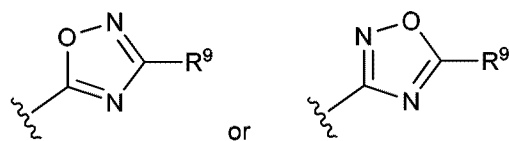
independently substituted with 0-5 R'; and wherein R² is independently

substituted with 0-5 R';

R³ is selected from:

-H, -CN, halogen, -(C1-C6)alkyl, -SO₂((C1-C6)alkyl), -C(O)N((C1-

C6)alkyl)₂, -C(O)((C1-C6)alkyl), -C(O)O((C1-C6)alkyl),



, wherein R⁹ is selected from -Me, -

Et, isopropyl, -CF₃, -OMe, -OEt, -O-isopropyl, -CH₂NMe₂, or cyclopropyl;

wherein the said alkyl of R³ is independently substituted with 0-5 R';

R⁴ and R⁵ are each independently selected from -H, halogen or -(C1-C6)alkyl; and

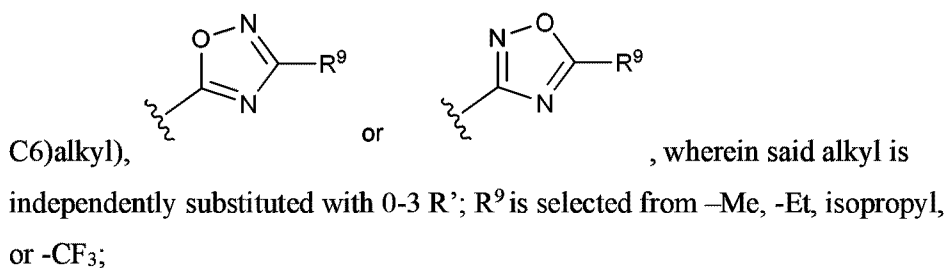
R⁶ is selected from -H or -(C1-C6)alkyl.

24. The compound, or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 23, wherein:

m is 0, 1, or 2;

R² is OR⁸, -(CH₂)_nOR⁸, or -(CH₂)_nO(CH₂)_nR⁸, wherein n is 1, and wherein R⁸ is - (C1-C6)alkyl, (C6-C10)-aryl or 5- to 10- membered heteroaryl, wherein R⁸ is independently substituted with 0-3 R⁷;

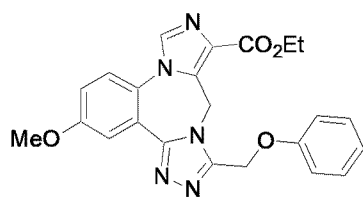
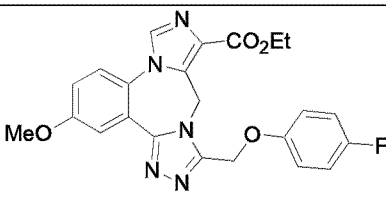
R³ is halogen, -H, -CN, -(C1-C6)alkyl, -C(O)((C1-C6)alkyl), -C(O)O((C1-



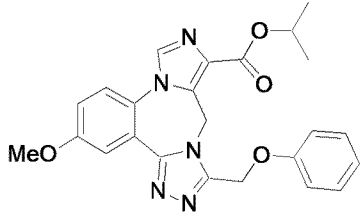
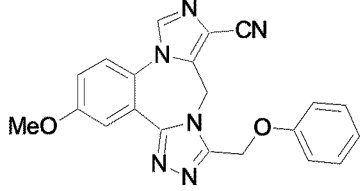
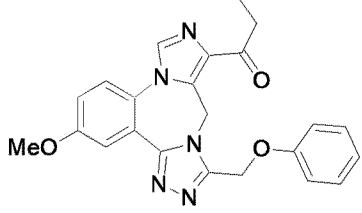
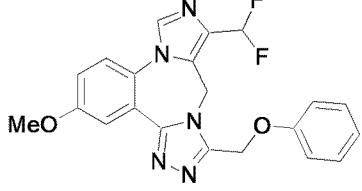
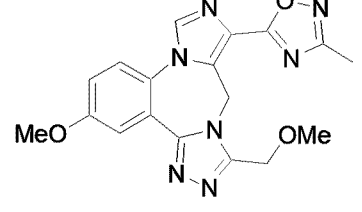
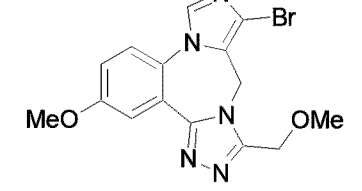
R⁴ and R⁵ are both -H; and

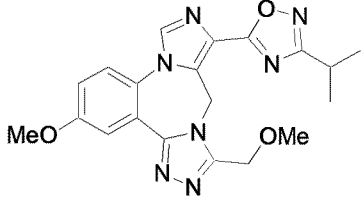
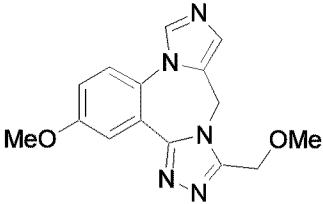
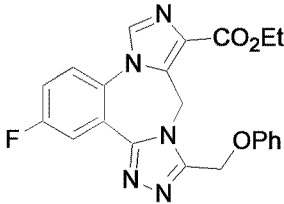
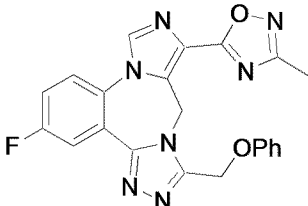
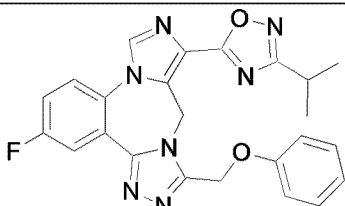
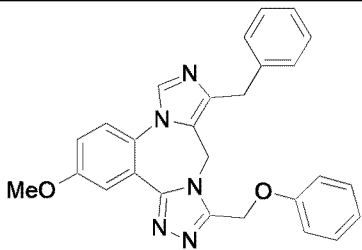
R⁶ is -H.

25. A compound selected from:

Compound	Structure
55	
56	

Compound	Structure
103	
104	
105	
106	
118	
119	

Compound	Structure
120	
122	
123	
124	
128	
129	

Compound	Structure
130	
131	
137	
138	
141	
142	

Compound	Structure
147	
148	
156	
157	
158	
159	

Compound	Structure
162	
163	
164	
165	
166	
169	
171	

Compound	Structure
172	
173	
174	
175	
176	
177	

polymorph thereof.

30. The pharmaceutical composition according to claim 28, wherein the second therapeutic agent is memantine, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.
31. The pharmaceutical composition according to claim 28, wherein the second therapeutic agent is an AChE-I selected from Donepezil, Galantamine, and Rivastigmine, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.
32. The compound or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof according to any one of the claims 1-25 for the manufacture of a medicament for the treatment of cognitive impairment associated with a central nervous system (CNS) disorder in a subject in need thereof.
33. The pharmaceutical composition according to any one of claims 26-31 for the manufacture of a medicament for the treatment of cognitive impairment associated with a central nervous system (CNS) disorder in a subject in need thereof.
34. The compound or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 32, wherein the CNS disorder is age-related cognitive impairment.
35. The compound or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 32, wherein the CNS disorder is mild cognitive impairment (MCI).
36. The compound or the pharmaceutically acceptable salt, hydrate, solvate,

polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 32, wherein the CNS disorder is amnesic mild cognitive impairment (aMCI).

37. The compound or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 32, wherein the CNS disorder is dementia.

38. The compound or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 32, wherein the CNS disorder is Alzheimer's disease.

39. The compound or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof, according to claim 32, wherein the CNS disorder is schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), post-traumatic stress disorder (PTSD), associated with cancer therapy, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, or substance addiction.

40. The pharmaceutical composition according to claim 33, wherein the CNS disorder is age-related cognitive impairment.

41. The pharmaceutical composition according to claim 33, wherein the CNS disorder is mild cognitive impairment (MCI).

42. The pharmaceutical composition according to claim 33, wherein the CNS disorder is amnesic mild cognitive impairment (aMCI).

43. The pharmaceutical composition according to claim 33, wherein the CNS disorder is dementia.

44. The pharmaceutical composition according to claim 33, wherein the CNS disorder is Alzheimer's disease.
45. The pharmaceutical composition according to claim 33, wherein the CNS disorder is schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), post-traumatic stress disorder (PTSD), associated with cancer therapy, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, or substance addiction.
46. Use of a compound or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof according to any one of the claims 1-25 for the treatment of cognitive impairment associated with a central nervous system (CNS) disorder in a subject in need thereof.
47. Use of a pharmaceutical composition according to any one of claims 26-31, for the treatment of cognitive impairment associated with a central nervous system (CNS) disorder in a subject in need thereof.
48. The use of a compound or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof according to claim 46, wherein the CNS disorder is age-related cognitive impairment.
49. The use of a compound or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof according to claim 46, wherein the CNS disorder is mild cognitive impairment (MCI).
50. The use of a compound or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof according to claim 46, wherein the CNS disorder is amnesic mild cognitive impairment (aMCI).

51. The use of a compound or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof according to claim 46, wherein the CNS disorder is dementia.
52. The use of a compound or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof according to claim 46, wherein the CNS disorder is Alzheimer's disease.
53. The use of a compound or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, enantiomer, diastereomer, Z (zusammen) isomer, E(entgegen) isomer, tautomer or combination thereof according to claim 46, wherein the CNS disorder is schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), post-traumatic stress disorder (PTSD), associated with cancer therapy, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, or substance addiction.
54. The use of a pharmaceutical composition according to claim 47, wherein the CNS disorder is age-related cognitive impairment.
55. The use of a pharmaceutical composition according to claim 47, wherein the CNS disorder is mild cognitive impairment (MCI).
56. The use of a pharmaceutical composition according to claim 47, wherein the CNS disorder is amnesic mild cognitive impairment (aMCI).
57. The use of a pharmaceutical composition according to claim 47, wherein the CNS disorder is dementia.
58. The use of a pharmaceutical composition according to claim 47, wherein the CNS disorder is Alzheimer's disease.
59. The use of a pharmaceutical composition according to claim 47, wherein the

CNS disorder is schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), post-traumatic stress disorder (PTSD), associated with cancer therapy, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, or substance addiction.

Figure 1

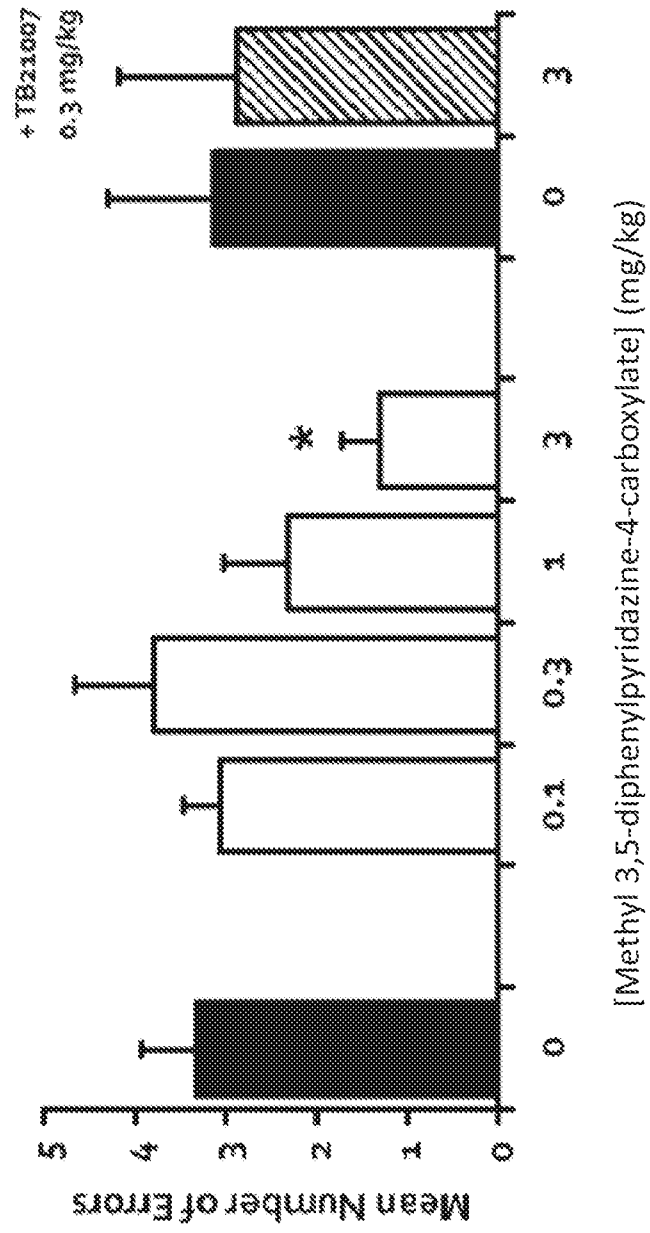


Figure 2

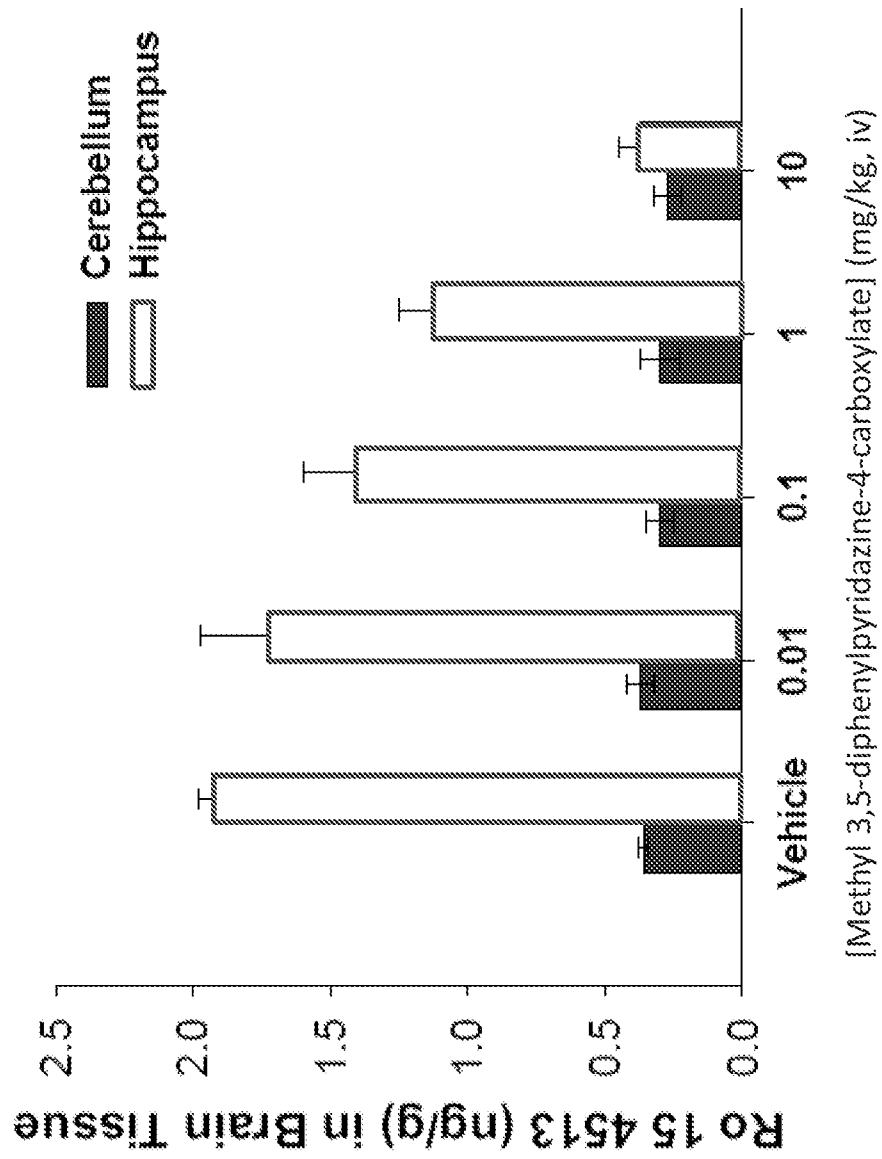


Figure 3

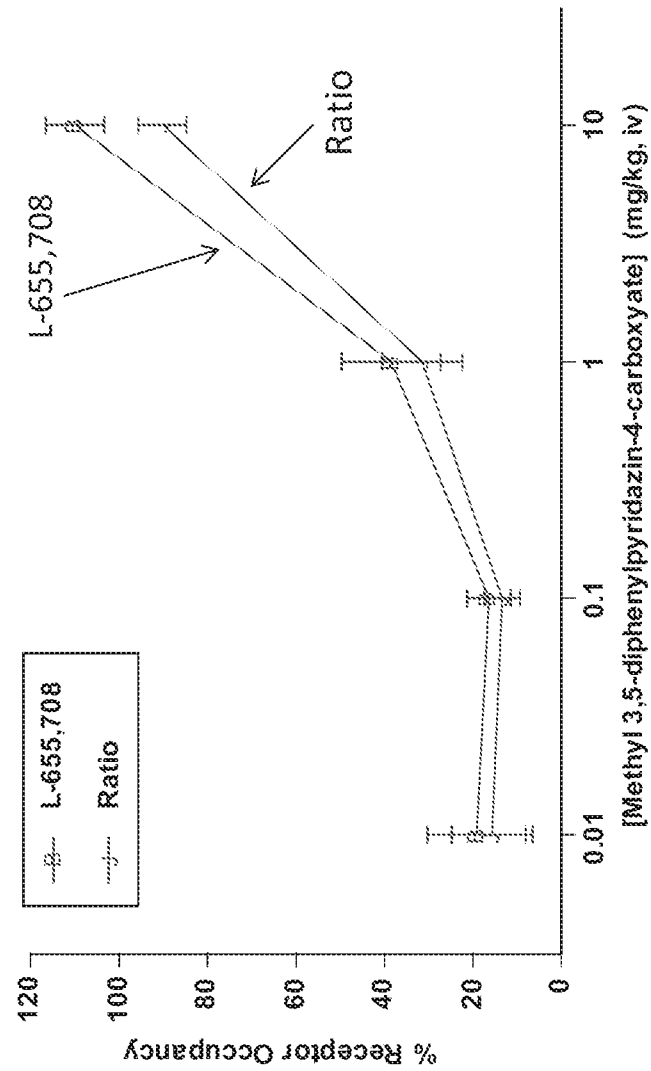


Figure 4

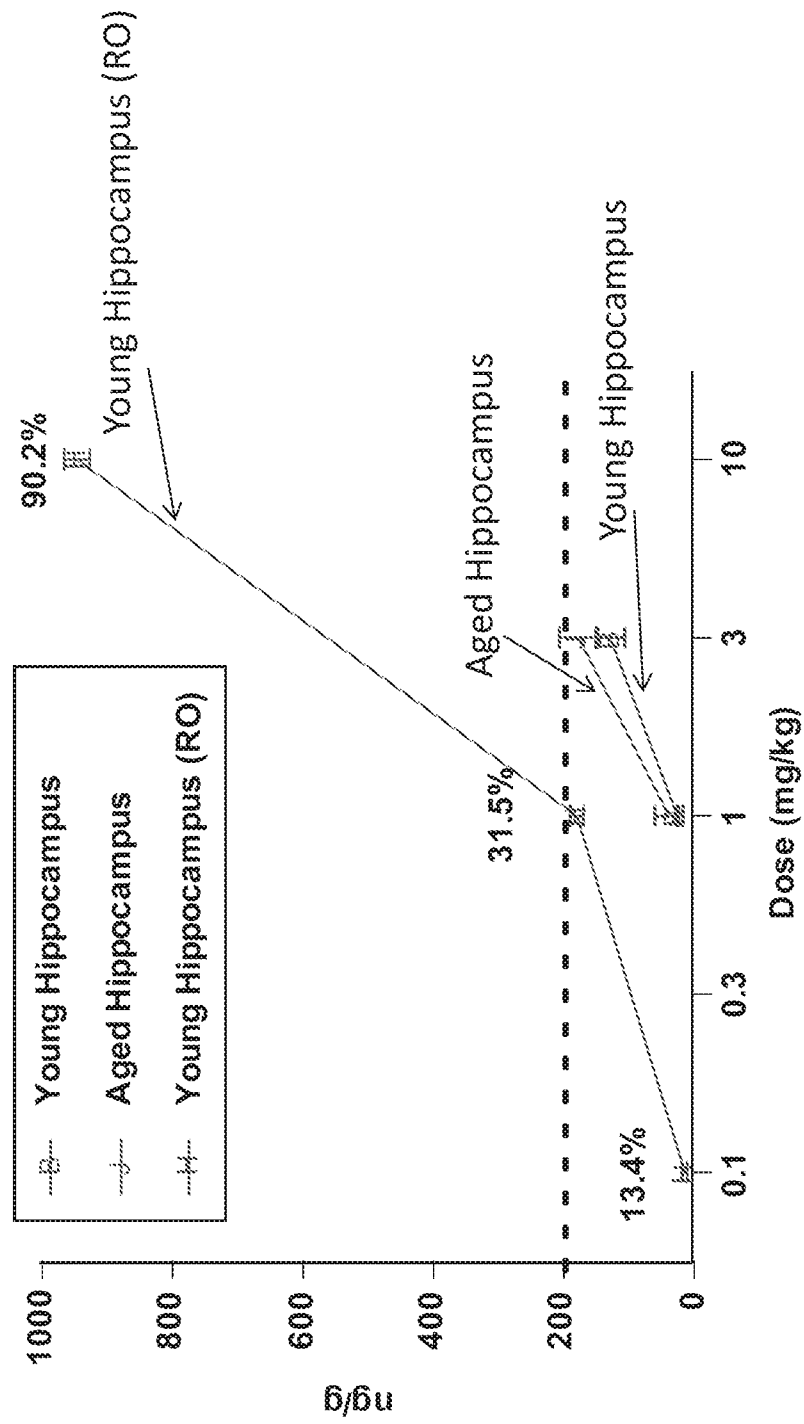


Figure 5

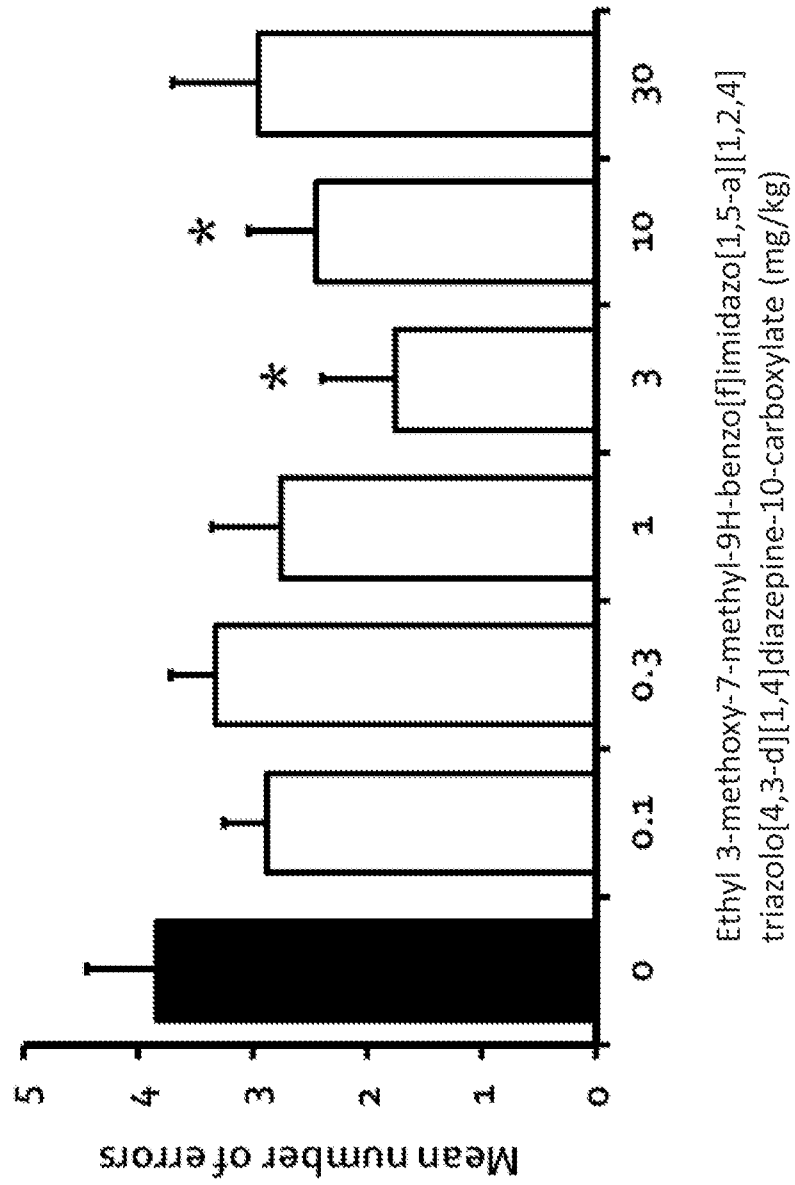


Figure 6

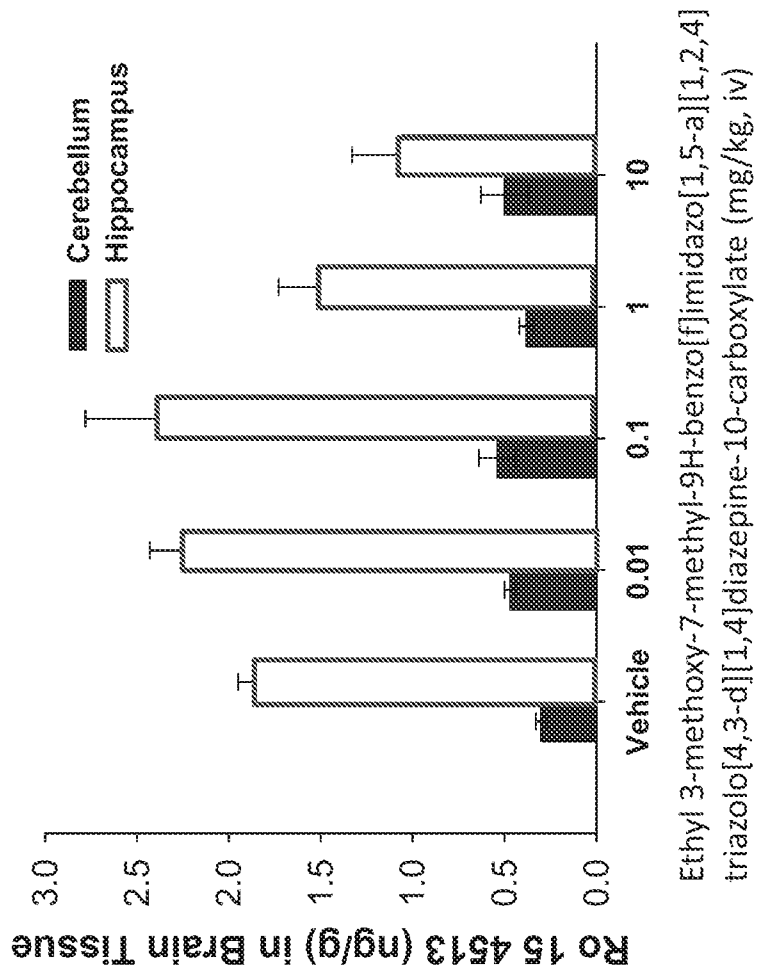


Figure 7

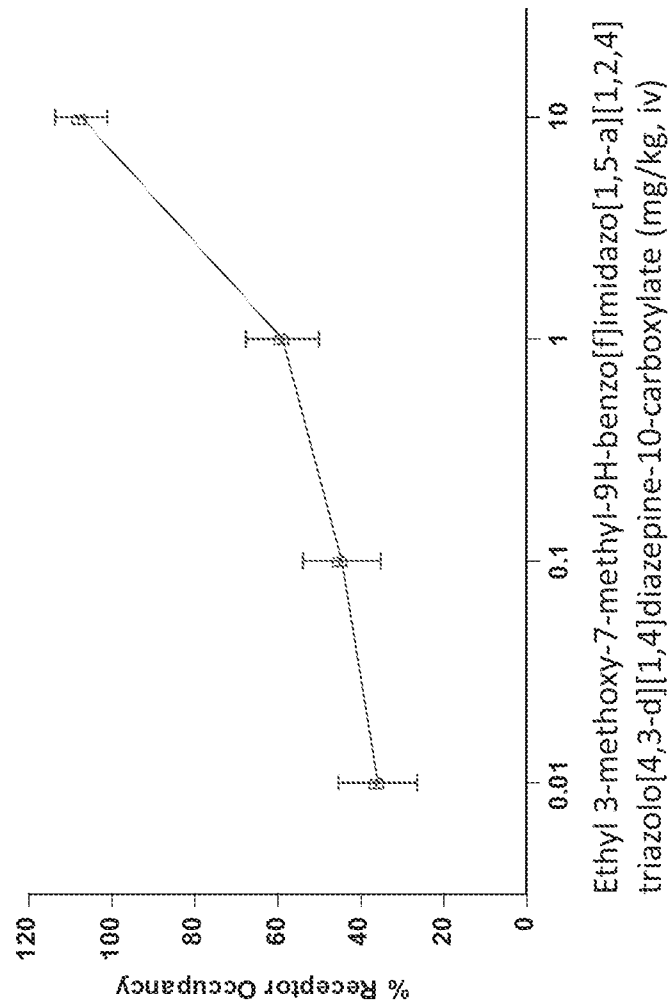


Figure 8(A)

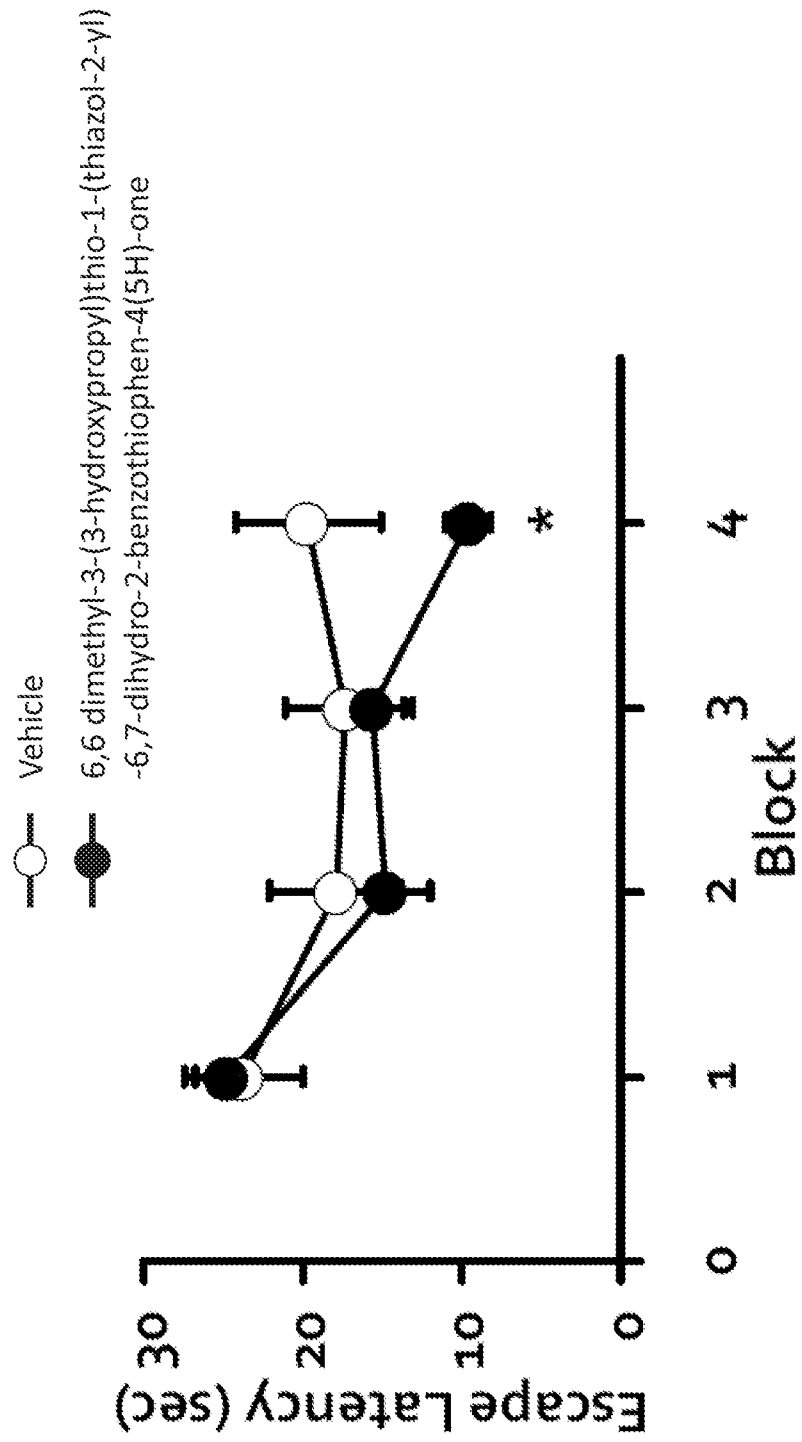


Figure 8(B)

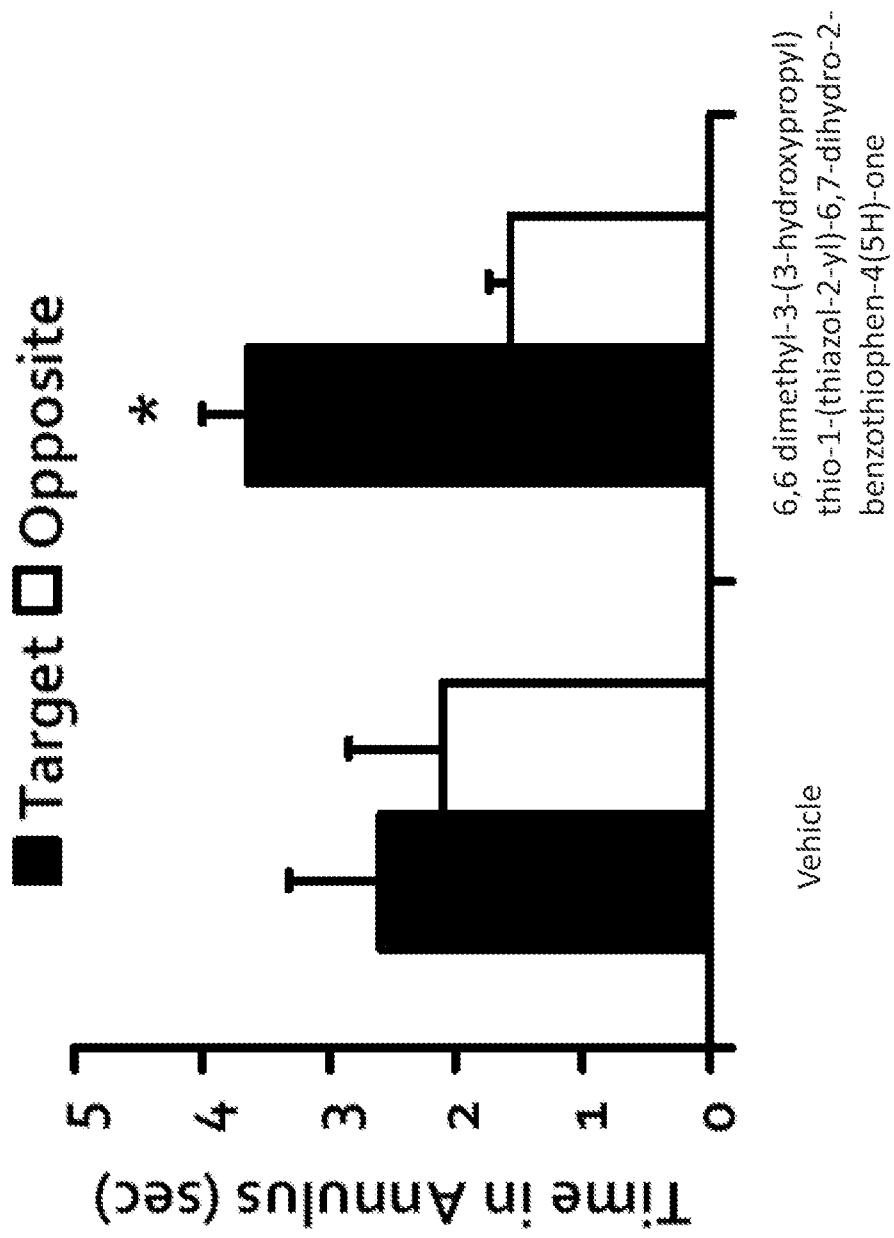
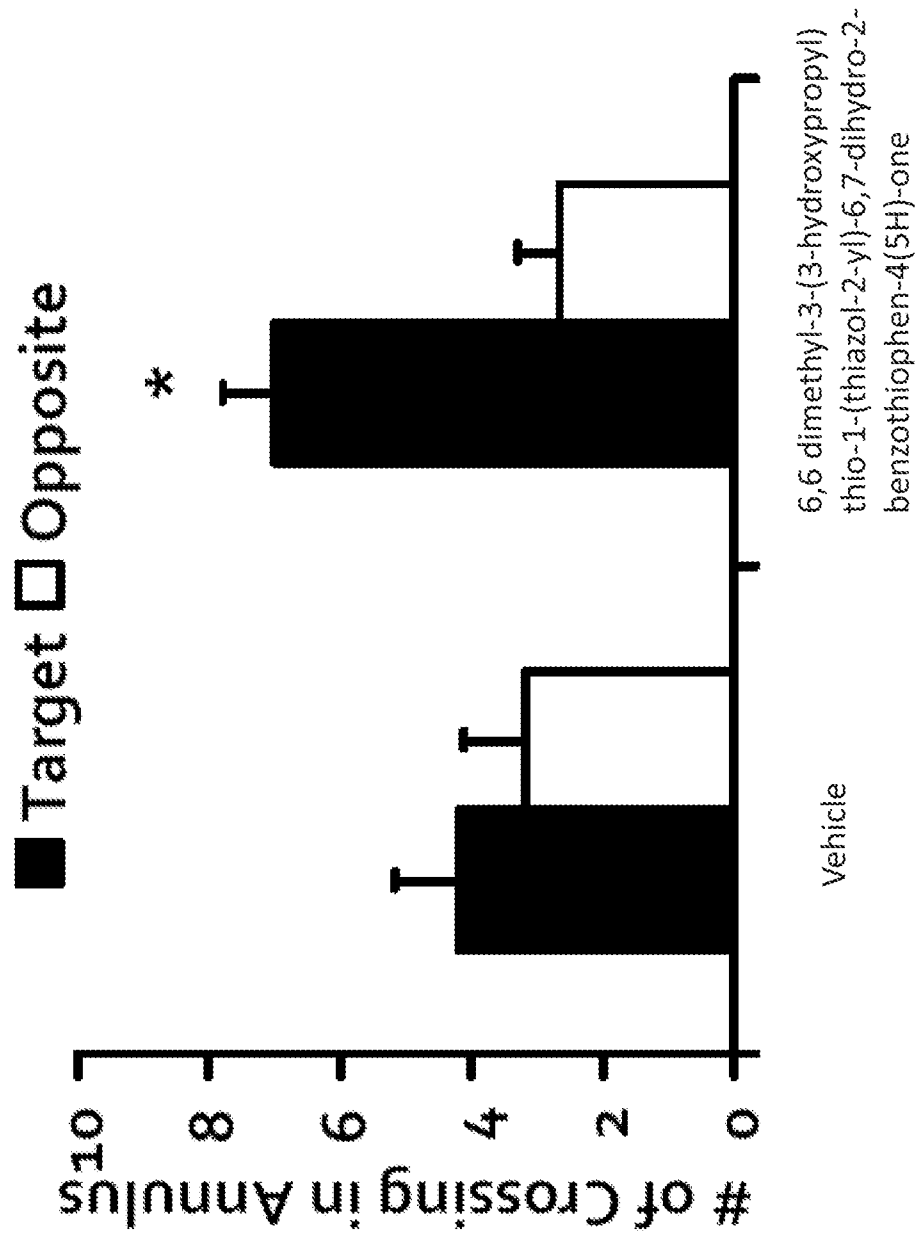
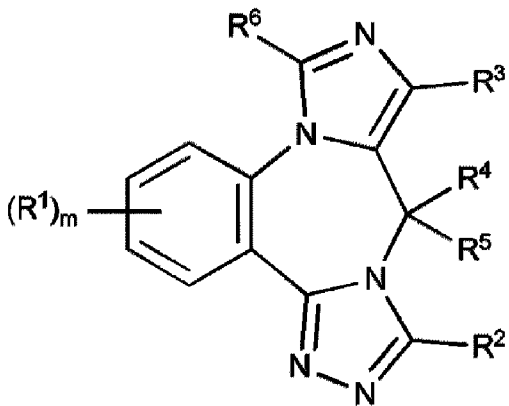


Figure 8(C)





IV