Abstract: Disclosed are compounds of General Formula I: wherein R₁, R₂, R₃, X and Y are described herein, as well as pharmaceutically acceptable salts, solvates, and stereoisomers thereof. Pharmaceutical compositions comprising such compounds, as well as methods of use, and treatment for neuropsychiatric disorders including pain, sleep, mood, anxiety, eating and addictive disorders, are also provided.
wo 2011/137220


Published:

— with international search report (Art. 21(3))
SMALL MOLECULE NEUROPEPTIDE S ANTAGONISTS FOR THE TREATMENT OF ADDICTIVE DISORDERS, MOOD, ANXIETY AND SLEEP DISORDERS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/328,900, filed on April 28, 2010, the entire contents of which are incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Neuropeptide S (NPS) is believed to affect arousal, wakefulness, propensity for movement, asthma and other allergic responses, stress associated with several anxiety disorders, and other physiological functions. NPS is the endogenous ligand for the Neuropeptide S receptor (NPSR), which is also known as TGR23 and vasopressin receptor-related receptor 1 (VRR1) (Genbank accession no. BD183774, BD183814, BD183773). The NPSR is a G-protein coupled receptor (GPCR). NPS acts as an agonist at the NPSR, causing dose dependent intracellular Ca++ mobilization, as well as increasing adenylyl cyclase accumulation, as measured by cAMP assay. NPS signalling through its G-protein-coupled receptor is also implicated in asthma susceptibility.

[0003] Neuropsychiatric disorders including, for example, mood, anxiety, eating, and sleep related disorders, as well as alcoholism and drug addiction are major causes of mortality and morbidity. Patient relapse into drug seeking and use, after an interval of sobriety, is a key component of the addictive syndrome, with approximately two-thirds of patients relapsing within 3 months of initiating abstinence.

[0004] Therefore, there still exists a need to find improved treatments for neuropsychiatric disorders.

BRIEF SUMMARY OF THE INVENTION

[0005] In accordance with an embodiment, the present invention provides a compound of General Formula I:
or a salt, solvate or stereoisomer thereof, wherein $R_1$ and $R_2$ are the same or different moieties and each are selected from the group consisting of: H, C$_6$H$_{11}$ alkyl, C$_6$H$_{11}$ aryl C$_6$ alkyl, heterocyclyl C$_6$ alkyl, C$_6$ alkylamino C$_6$ alkyl, C$_6$ dialkylamino C$_6$ alkyl, C$_6$-C$_{14}$ aryl alkylamino, C$_6$-C$_{14}$ aryl alkylamino C$_6$ alkyl C$_6$ aryl C$_6$ alkenyl, C$_6$-C$_{14}$ aryl C$_6$ alkenyl C$_6$ alkylamino alkoxy, and C$_6$-C$_{14}$ aryl C$_6$ alkenyl C$_6$ alkylamino alkoxy.

In accordance with an embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein $R_1$ is selected from the group consisting of: H, C$_6$H$_{11}$ alkyl, C$_6$H$_{11}$ aryl C$_6$ alkyl, C$_6$H$_{11}$ aryl C$_6$ alkylamino, C$_6$-C$_{14}$ aryl C$_6$ alkenyl, C$_6$-C$_{14}$ aryl C$_6$ alkylamino C$_6$ alkyl C$_6$ C$_6$ alkenyl, and C$_6$-C$_{14}$ aryl C$_6$ alkylamino C$_6$ alkyl, thio Q-C$_6$ alkyl, thio C$_2$-C$_6$ alkenyl, thio C$_2$-C$_6$ alkynyl, C$_2$-C$_6$ aryl, C$_2$-C$_6$ acyloxy, C$_2$-C$_6$ acyloxy, C$_2$-C$_6$ acyl, amido, sulphonamido, C$_6$H$_{11}$ alkyl, C$_2$-C$_6$ arylamino, and C$_2$-C$_6$ alkynyl, wherein each of alkyl, aryl, or heterocyclyl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxy, carboxy, phosphoryl, phosphonoyl, phosphono C$_6$ alkyl, carboxy C$_6$ alkyl, dicarboxy C$_6$ alkyl, dicarboxy halo C$_6$ alkyl, sulfonyl, cyano, nitro, alkoxy, alkylthio, acyl, acyloxy, thioacetyl, acylthio, amino, alkylamino, dialkylamino, trialkylamino, guanidine, aldehyde, ureido, and aminocarbonyl, wherein $R_3$ is selected from the group consisting of thio, oxy, and hydroxyl, wherein X is selected from the group consisting of a phosphorous atom and a carbon atom, wherein when X=C, $R_3$=hydroxyl, when X=P, $R_3$ is selected from the group consisting of a sulfur atom and an oxygen atom, and wherein Y is selected from the group consisting of a nitrogen atom and a carbon atom.
wherein each of alkyl, aryl, or heterocyclyl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxy, and carboxy, wherein \( R_2 \) is selected from the group consisting of H, Ci-C_6 alkyl, C_6-Ci_4 aryl, and C_6-Ci_4 aryl Ci-C_6 alkyl, wherein each of alkyl, aryl, or heterocyclyl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxy, and carboxy, wherein \( R_3 \) is selected from the group consisting of thio, oxy, and hydroxyl, wherein \( X \) is selected from the group consisting of a phosphorous atom and a carbon atom, wherein when \( X=C \), \( R_3=OH \), wherein when \( X=P \), \( R_3 \) is selected from the group consisting of a sulfur atom and an oxygen atom; and wherein \( Y \) is selected from the group consisting of a nitrogen atom and a carbon atom.

[0007] In another embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein \( R_i \) is selected from the group consisting of: H, C_1-C_6 alkyl, C_6-Ci_4 aryl Ci-C_6 alkyl, C_6-Ci_4 aryl Ci-C_6 alkylamino, C_6-Ci_4 aryl Ci-C_6 alkenyl, C_6-Ci_4 aryl Ci-C_6 alkylamino alkoxy, and C_6-Ci_4 aryl Ci-C_6 alkoxy, wherein the aryl, or heterocyclyl moiety is substituted with one or more halo groups.

[0008] In a further embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein the aryl, or heterocyclyl moiety of \( R_i \) is substituted with one or more fluoro groups.

[0009] In an embodiment, the present invention provides compounds having the following General Formula I:

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\end{array}
\]

wherein \( \text{R}_1 \) and \( \text{R}_2 \) are the same or different moieties and each comprise a hydrocarbon group which can be optionally substituted, \( \text{R}_3 \) is either S, O, or OH, and \( X \) is either a phosphate.
atom or a carbon atom, wherein when $X=C$, $R_3=\text{OH}$; and when $X=P$, $R_3=S$, or $O$, and wherein $Y$ is either $N$ or $C$, and pharmaceutically acceptable salts, solvates or stereoisomers thereof.

[0010] In a further embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein $R_1$ is selected from the group consisting of: H, $\text{C}_1$-$\text{C}_6$ alkyl, $\text{C}_6$-$\text{C}_{14}$ aryl, $\text{C}_6$-$\text{C}_{14}$ aryl $\text{Cl}$-$\text{C}_6$ alkenyl, wherein the aryl moiety is substituted with one or more halo groups, wherein $R_2$ is selected from the group consisting of: H, $\text{C}_1$-$\text{C}_6$ alkyl and $\text{C}_6$-$\text{C}_{14}$ aryl, wherein $R_3=S$, wherein $X=P$, and wherein $Y=N$.

[0011] In another embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein $R_1$ is selected from the group consisting of: H, $\text{C}_1$-$\text{C}_6$ alkyl, $\text{C}_6$-$\text{C}_{14}$ aryl, and $\text{C}_6$-$\text{C}_{14}$ aryl $\text{Cl}$-$\text{C}_6$ alkyl, wherein $R_2$ is selected from the group consisting of: H, $\text{C}_1$-$\text{C}_6$ alkyl and $\text{C}_6$-$\text{C}_{14}$ aryl, wherein $R_3=S$, wherein $X=P$, and wherein $Y=N$.

[0012] In yet another embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein $R_1$ is selected from the group consisting of: H, $\text{C}_1$-$\text{C}_6$ alkyl, $\text{C}_6$-$\text{C}_{14}$ aryl, and $\text{C}_6$-$\text{C}_{14}$ aryl $\text{Cl}$-$\text{C}_6$ alkyl, wherein $R_2$ is selected from the group consisting of: H, and $\text{C}_1$-$\text{C}_6$ alkyl, wherein $R_3=S$, wherein $X=P$, and wherein $Y=N$.

[0013] In another embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein the compound is one of the following:

Example 1

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\begin{array}{c}
\text{Example 1} \\
\end{array}
\]

Example 2

\[
\begin{array}{c}
\text{Example 2} \\
\end{array}
\]
Example 3

Example 6

Example 7

Example 8

Example 9
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Example 48

Example 49

; and
In another embodiment, the present invention provides a pharmaceutical composition comprising at least one of the above identified compounds of General Formula I, as set forth above, or a salt, solvate or stereoisomer thereof, and a pharmaceutically acceptable carrier.

In a further embodiment, the present invention provides a pharmaceutical composition comprising a compound of General Formula I, as set forth above, or salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier, and at least one other compound, salt, solvate, or stereoisomer thereof, suitable for use in treating a neuropsychiatric disorder. In an embodiment, the compound suitable for use in treating a neuropsychiatric disorder is selected from the group consisting of the following drug classes: antipsychotics, antidepressants and anxiolytics.

In accordance with an embodiment, the present invention provides a method of treating a neuropsychiatric disorder in a subject comprising administering a therapeutically effective amount of a compound of General Formula I, as set forth above, or a salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier. In another embodiment, the neuropsychiatric disorders being treated by the methods of the present invention comprise pain, sleep, mood, anxiety, eating and addictive disorders. In an embodiment, the anxiety disorders being treated by the methods of the present invention are selected from the group consisting of: panic disorder, social phobia and obsessive-compulsive disorder. In a further embodiment, it is contemplated that the eating disorders being treated by the methods of the present invention are selected from the group consisting of: anorexia nervosa and bulimia.

It is contemplated that in a further embodiment, the addictive disorders being treated by the methods of the present invention are selected from the group consisting of:
alcohol addiction, tobacco addiction, nicotine addiction, and intoxication and inhalation disorders associated with alcohol, tobacco and nicotine addiction.

In accordance with an embodiment, the present invention provides a method of treating a Neuropeptide S Receptor related disorder in a subject comprising administering a therapeutically effective amount of a compound of General Formula I, as set forth above, or a salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

Figure 1 is a depiction IC₅₀ inhibition curves for Examples 7, 8 and 9, showing inhibition of intracellular calcium (Ca²⁺) production.

Figure 2 is a depiction IC₅₀ inhibition curves for Examples 7, 8 and 9, showing inhibition of cAMP production.

Figure 3 is binding competition curves for Y¹⁰-NPS labeled with I²⁵I and Examples 7, 30, and 32, depicting their relative binding affinity for the NPSR.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, the development of the compounds of General Formula I, and their salts, solvates, and stereoisomers thereof, have activity as NPS antagonists (NPSAs), and the present invention provides a clinically useful treatment for alcohol and drug addiction. In addition, because mood, anxiety, eating, and sleep related behaviors are often closely linked with addictive processes, and are also affected by the NPS system, the NPSAs of the present invention will also be useful in these clinical areas.

In accordance with an embodiment, the present invention provides a compound of General Formula I:
or a salt, solvate or stereoisomer thereof, wherein R₁ and R₂ are the same or different moieties and each are selected from the group consisting of: H, C₁₋₆ alkyl, C₆₋₄ aryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, C₁₋₆ alkylamino C₁₋₆ alkyl, C₁₋₆ dialkylamino C₁₋₆ alkyl, C₆₋₁₄ aryl C₁₋₆ alkylamino C₁₋₆ alkyl, C₁₋₆ alkythio C₁₋₆ alkyl, C₁₋₆ alkylthiocarbonyl C₁₋₆ alkyl, C₂₋₆ C₁₋₄ aryloxy, C₁₋₆ C₂₋₄ arylamino alkoxy, and C₁₋₆ aryl Ci-C₆ alkoxy,

![Chemical Structure](image)

[0024] In accordance with an embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein R₁ is selected from the group consisting of: H, C₁₋₆ alkyl, C₆₋₄ aryl C₁₋₆ alkyl, C₆₋₁₄ aryl Ci-C₆ alkyamino, C₆₋₁₄ aryl Ci-C₆ alkenyl, C₆₋₁₄ aryl Ci-C₆ alkylamino alkoxy, and C₆₋₁₄ aryl Ci-C₆ alkoxy,
wherein each of alkyl, aryl, or heterocyclyl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxy, and carboxy, wherein \( R_2 \) is selected from the group consisting of \( H, C_1-C_6 \) alkyl, \( C_6-Ci_4 \) aryl, and \( C_6-Ci_4 \) aryl \( C_i-C_6 \) alkyl, wherein each of alkyl, aryl, or heterocyclyl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxy, and carboxy, wherein \( R_3 \) is selected from the group consisting of thio, oxy, and hydroxyl, wherein \( X \) is selected from the group consisting of a phosphorous atom and a carbon atom, wherein when \( X=C, R_3=OH \), wherein when \( X=P, R_3 \) is selected from the group consisting of a sulfur atom and an oxygen atom; and wherein \( Y \) is selected from the group consisting of a nitrogen atom and a carbon atom.

[0025] In another embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein \( R_i \) is selected from the group consisting of: \( H, C_1-C_6 \) alkyl, \( C_6-Ci_4 \) aryl \( C_i-C_6 \) alkyl, \( C_6-Ci_4 \) aryl \( C_i-C_6 \) alkenyl, \( C_6-Ci_4 \) aryl \( C_i-C_6 \) alkylamino alkoxy, and \( C_6-Ci_4 \) aryl \( C_i-C_6 \) alkoxy, wherein the aryl, or heterocyclyl moiety is substituted with one or more halo groups.

[0026] In a further embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein the aryl, or heterocyclyl moiety of \( R_1 \) is substituted with one or more fluoro groups.

[0027] In an embodiment, the present invention provides compounds having the following General Formula I:

\[
\begin{align*}
\text{wherein } & R_1 \text{ and } R_2 \text{ are the same or different moieties and each comprise a hydrocarbon group which can be optionally substituted, } R_3 \text{ is either } S, O, \text{ or } OH, \text{ and } X \text{ is either a phosphate}\end{align*}
\]
atom or a carbon atom, wherein when X=C, R_3=OH; and when X=P, R_3=S, or O, and wherein Y is either N or C, and pharmaceutically acceptable salts, solvates or stereoisomers thereof.

[0028] In a further embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein R_1 is selected from the group consisting of: H, C_1-C_6 alkyl, C_6-Ci_4 aryl, C_6-Ci_4 aryl C_6-Ci_4 alkyl and C_6-Ci_4 aryl Ci-C_6 alkenyl, wherein the aryl moiety is substituted with one or more halo groups, wherein R_2 is selected from the group consisting of: H, C_1-C_6 alkyl and C_6-Ci_4 aryl, wherein R_3=S, wherein X=P, and wherein Y=N.

[0029] In another embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein R_1 is selected from the group consisting of: H, C_1-C_6 alkyl, C_6-Ci_4 aryl, and C_6-Ci_4 aryl Ci-C_6 alkyl, wherein R_2 is selected from the group consisting of: H, C_1-C_6 alkyl and C_6-Ci_4 aryl, wherein R_3=S, wherein X=P, and wherein Y=N.

[0030] In yet another embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein R_1 is selected from the group consisting of: H, C_1-C_6 alkyl, C_6-Ci_4 aryl, and C_6-Ci_4 aryl Ci-C_6 alkyl, wherein R_2 is selected from the group consisting of: H, and C_1-C_6 alkyl, wherein R_3=S, wherein X=P, and wherein Y=N.

[0031] In another embodiment, the present invention provides a compound of General Formula I, or a salt, solvate, or stereoisomer thereof, wherein the compound is one of the following:

Example 1

![Example 1](image)

Example 2

![Example 2](image)
Example 10

Example 11

Example 12

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Example 37
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Example 40
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Example 42

Example 43
Example 47

Example 48

Example 49

and
In another embodiment, the present invention provides a pharmaceutical composition comprising at least one of the above identified compounds of General Formula I, as set forth above, or a salt, solvate or stereoisomer thereof, and a pharmaceutically acceptable carrier.

In a further embodiment, the present invention provides a pharmaceutical composition comprising a compound of General Formula I, as set forth above, or salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier, and at least one other compound, salt, solvate, or stereoisomer thereof, suitable for use in treating a neuropsychiatric disorder. In an embodiment, the compound suitable for use in treating a neuropsychiatric disorder is selected from the group consisting of the following drug classes: antipsychotics, antidepressants and anxiolytics.

In accordance with an embodiment, the present invention provides a method of treating a neuropsychiatric disorder in a subject comprising administering a therapeutically effective amount of a compound of General Formula I, as set forth above or a salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

In accordance with an embodiment, the present invention provides a method of treating a neuropsychiatric disorder in a subject comprising administering a therapeutically effective amount of a compound of General Formula I, as set forth above, or a salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier. In another embodiment, the neuropsychiatric disorders being treated by the methods of the present invention comprise pain, sleep, mood, anxiety, eating and addictive disorders. In an embodiment, the anxiety disorders being treated by the methods of the present invention are selected from the group consisting of: panic disorder, social phobia and obsessive-compulsive disorder. In a further
embodiment, it is contemplated that the eating disorders being treated by the methods of the present invention are selected from the group consisting of: anorexia nervosa and bulimia.

[0036] In a further embodiment, the addictive disorders being treated by the methods of the present invention are selected from the group consisting of: alcohol addiction, tobacco addiction, nicotine addiction, and intoxication and inhalation disorders associated with alcohol, tobacco and nicotine addiction.

[0037] In accordance with an embodiment, the present invention provides a method of treating a a Neuropeptide S Receptor related disorder in a subject comprising administering a therapeutically effective amount of a compound of General Formula 1, as set forth above, or a salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[0038] In accordance with another embodiment, the present invention provides a method of binding a Neuropeptide S receptor in a host cell comprising contacting the Neuropeptide S receptor with an effective amount of a compound of General Formula 1, as set forth above, or a salt, solvate, or stereoisomer thereof.

[0039] In accordance with an embodiment, the present invention provides a compound of General Formula 1, as set forth above, or salt, solvate, or stereoisomer thereof, wherein the composition includes a pharmaceutically and physiologically acceptable carrier, in an amount effective for use in a medicament, preferably for use as a medicament for treating a neuropsychiatric disorder in a subject, preferably wherein the neuropsychiatric disorder comprises pain, sleep, mood, anxiety, eating and addictive disorders, or for use as a medicament for treating an anxiety disorder, preferably wherein the anxiety disorders are selected from the group consisting of: panic disorder, social phobia and obsessive-compulsive disorder, or for use as a medicament for treating an eating disorder, preferably wherein the eating disorders are selected from the group consisting of: anorexia nervosa and bulimia, or for use as a medicament for treating an addictive disorder, preferably wherein the addictive disorders are selected from the group consisting of: alcohol addiction, tobacco addiction, nicotine addiction, and intoxication and inhalation disorders associated with alcohol, tobacco and nicotine addiction, when administered to the subject in an effective amount.

[0040] In another embodiment, the present invention provides a compound of General Formula 1, as set forth above, or salt, solvate, or stereoisomer thereof, wherein the composition includes a pharmaceutically and physiologically acceptable carrier, in an amount
effective for use in a medicament, preferably for use as a medicament for treating a neuropsychiatric disorder in a subject, wherein the effective amount of the compound of General Formula 1, or a salt, solvate, or stereoisomer thereof, administered to the subject is in a range of between about 0.001 mg/kg/day to about 1000 mg/kg/day, preferably, at least about 0.01 mg/kg/day to about 100 mg/kg/day, more preferably about 0.1 mg/kg/day to about 10 mg/kg/day, still more preferably about 0.5 mg/kg/day to about 5 mg/kg/day.

[0041] In a further embodiment, the compounds of General Formula 1, as set forth above, or a salt, solvate, or stereoisomer thereof, can function as NPS receptor antagonists (NPSAs), and in conjunction with a pharmaceutically acceptable carrier, are capable of being used in the treatment of NPS related disorders. As such, the terms "NPSA" and "compounds of General Formula 1, or a salt, solvate, or stereoisomer thereof are used interchangeably in the specification.

[0042] In an embodiment, the present invention also provides a method of treating a neuropsychiatric disorder in a subject, comprising administering to the subject, a therapeutically effective amount of at least one of the above identified compounds and a pharmaceutically acceptable carrier. In accordance with the present invention, the method of treating a neuropsychiatric disorder includes, but is not limited to, disorders related to pain, sleep, mood, anxiety, eating and addictive disorders.

[0043] In another embodiment, the present invention provides a method for treating or suppressing the symptoms of eating disorders in a subject, comprising administering to a patient in need of treatment a therapeutically effective amount of at least one of the above identified compounds, and a pharmaceutically acceptable carrier. In accordance with the present invention, the eating disorders being treated by the compounds and methods of the present invention can include, for example, anorexia nervosa and bulimia. In accordance with the present invention, the method for treating or suppressing the symptoms of eating disorders in a subject may also include administering to the subject, a pharmaceutical composition comprising, in a therapeutically effective amount, at least one of the above identified compounds, and at least one other compound suitable for use in treating a neuropsychiatric disorder, and a pharmaceutically acceptable carrier.

[0044] In a further embodiment, the present invention provides a method for treating or suppressing the symptoms of addictive disorders in a subject, including, for example, alcohol addiction, tobacco addiction, nicotine addiction, and intoxication and inhalation disorders.
associated with alcohol, tobacco and nicotine addiction, the method comprising administering
to the patient, a therapeutically effective amount of at least one of the above identified
compounds and a pharmaceutically acceptable carrier. In accordance with the present
invention, the method for treating or suppressing the symptoms of addictive disorders in a
subject may also include administering to the subject, a pharmaceutical composition
comprising, in a therapeutically effective amount, at least one of the above identified
compounds, and at least one other compound suitable for use in treating a neuropsychiatric
disorder, and a pharmaceutically acceptable carrier.

[0045] In yet another embodiment, the present invention provides a method for treating
or suppressing the symptoms of anxiety disorders in a subject, comprising administering to a
patient in need of treatment a therapeutically effective amount of at least one of the above
identified compounds, and a pharmaceutically acceptable carrier. In accordance with the
present invention, the anxiety disorders being treated by the compounds and methods of the
present invention can include, for example, panic disorder, social phobia or obsessive-
compulsive disorder.

[0046] In accordance with the present invention, the method for treating or suppressing
the symptoms of anxiety disorders in a subject may also include administering to the subject,
a pharmaceutical composition comprising, in a therapeutically effective amount, at least one
of the above identified compounds, and at least one other compound suitable for use in
treating a neuropsychiatric disorder, and a pharmaceutically acceptable carrier.

[0047] In accordance with the present invention, in an embodiment, the at least one other
compound suitable for use in treating a neuropsychiatric disorder can include, for example, a
compound from the classes of drugs known as antipsychotics, antidepressants and
anxiolytics, and other drugs known to be effective in treating a neuropsychiatric disorder.

[0048] In an embodiment, NPSAs and preparations that comprise NPSAs may be
administered to subjects in effective dosages and by effective routes of administration to
cause, for example, decreased arousal, decreased awakening, decreased alertness, decreased spontaneou
movement, sleep, somnolence, sedation, normalized sleep patterns, normalized sleep stages, increased duration of sleep, bronchodilation, relaxation of bronchial smooth
muscle and/or other effects as described herein. Thus, NPSAs (including, e.g., compounds of
General Formula I, as set forth above, and salts, solvates, and stereoisomers thereof) and
preparations that comprise NPSAs, are useful for treating neuropsychiatric disorders,
including, for example, insomnia, sleep disorders, decreased duration of sleep or frequent awakening, disorders that cause excessive spontaneous movement, some behavioral disorders, bronchitis, obstructive pulmonary disease, asthma, allergic conditions and other disorders as described herein.

As used herein, including, e.g., General Formula I, the term "hydrocarbon group" of the "hydrocarbon group which may be substituted" represented by R<sub>1</sub> and R<sub>2</sub> may be exemplified by a straight-chained or cyclic hydrocarbons (e.g., alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, a branched or straight-chain alkylamino, dialkylamino, or alkyl or dialkylaminoalkyl, or thioalkyl, thioalkenyl, thioalkynyl, arylxy, thioaryl, thioheteroaryl, acyloxy, thioacyl, amido, sulphonamido, etc.), or the like. Among these, straight-chained or cyclic hydrocarbon having 1 to 16 carbon atoms are preferred.

As used herein, examples of the term "alkyl" preferably include a C<sub>1</sub>-6 alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) and the like.

As used herein, examples of the term "alkenyl" preferably include C<sub>2</sub>-6 alkenyl (e.g., vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, etc.) and the like.

As used herein, examples of the term "alkynyl" preferably include C<sub>2</sub>-6 alkynyl (e.g., ethynyl, propargyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-hexynyl, etc.) and the like.

The term "hydroxyalkyl" embraces linear or branched alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. Examples include hydroxymethyl, hydroxyethyl, hydroxypropyl, etc. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals having alkyl portions of one to about ten carbon atoms, such as a methoxy group. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide haloalkoxy or haloalkoxyalkyl groups.
The term "alkylamino" includes monoalkylamino. The term "monoalkylamino" means an amino, which is substituted with an alkyl as defined herein. Examples of monoalkylamino substituents include, but are not limited to, methylamino, ethylamino, isopropylamino, t-butylamino, and the like. The term "dialkylamino" means an amino, which is substituted with two alkyls as defined herein, which alkyls can be the same or different. Examples of dialkylamino substituents include dimethylamino, diethylamino, ethylisopropylamino, diisopropylamino, dibutylamino, and the like.

The terms "alkylthio," "alkenylthio" and "alkynylthio" group mean a group consisting of a sulphur atom bonded to an alkyl-, alkenyl- or alkynyl-group, which is bonded via the sulphur atom to the entity to which the group is bonded. Included within the NPSAs of the present invention are the tautomeric forms of the disclosed compounds, isomeric forms including diastereoisomers, and the pharmaceutically-acceptable salts thereof.

The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases.

The NPSAs of the present invention contain basic nitrogen atoms, and the described salts made in accordance with embodiments of the invention were generated by alkylation of the N1 nitrogen of a imidazo[1,2-a]pyridine. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid, and such organic acids as maleic acid, succinic acid and citric acid. Other pharmaceutically acceptable salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium and magnesium, or with organic bases, such as dicyclohexylamine. All of these salts may be prepared by conventional means by reacting, for example, the appropriate acid or base with the corresponding NPSAs of the present invention.

Salts formed from free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

For use in medicines, the salts of the NPSAs should be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of the present invention include, for
example, acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid, such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maieic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

[0060] In addition, embodiments of the invention include hydrates of the NPSAs of the present invention. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like. Hydrates of the NPSAs of the present invention may be prepared by contacting the NPSA with water under suitable conditions to produce the hydrate of choice.

[0061] In an embodiment, the pharmaceutical compositions of the present invention comprise the compounds of the present invention, for example, the compounds of General Formula I, and/or their salts, solvates, or stereoisomers thereof, together with a pharmaceutically acceptable carrier.

[0062] The compounds and pharmaceutical compositions of the present invention are suitably used as therapeutic agents for NPSR related disorders including, for example, addictive disorders, anxiety disorders, eating disorders, obsessive compulsive disorders and social phobias. According to another embodiment of the present invention, a method is provided for treating NPSR-related disorders in a subject, comprising administering to the subject, at least one NPSA of the present invention, or its salt, solvate, or stereoisomer thereof, in an amount effective to treat the NPSR related disorder in the subject.

[0063] Accordingly, in a further embodiment, the present invention provides a method for blocking the endogenous agonist of an NPSR, by contacting the NPSR with an effective amount of at least one NPSA of the present invention, or its salt, solvate, or stereoisomer thereof, under conditions effective to cause the NPSA compounds to bind the NPSR. Without being limited to any particular theory, it is believed the binding of the at least one NPSA to the NPSR will inhibit the endogenous agonist of the NPSR, and initiate the suppression or treatment of symptoms of neuropsychiatric disorders in a subject, including, for example, disorders related to pain, sleep, mood, anxiety, eating and addictive disorders.

[0064] As defined herein, in one or more embodiments, "contacting" means that the one or more NPSAs of the present invention are introduced into a sample having at least one NPSR, or NPSR complex, and appropriate enzymes or reagents, in a test tube, flask, tissue
culture, chip, array, plate, microplate, capillary, or the like, and incubated at a temperature and time sufficient to permit binding of the at least one NPSA to the NPSR or an NPSR complex. Methods for contacting the samples with the NPSAs, and other specific binding components are known to those skilled in the art, and may be selected depending on the type of assay protocol to be run. Incubation methods are also standard and are known to those skilled in the art.

Another embodiment of the invention further provides a host cell comprising a Neuropeptide S receptor (NPSR). As used herein, the term "host cell" refers to any type of cell that can contain the NPSR. The host cell can be a eukaryotic cell, e.g., plant, animal, fungi, or algae, or can be a prokaryotic cell, e.g., bacteria or protozoa. The host cell can be a cultured cell or a primary cell, i.e., isolated directly from an organism, e.g., a human. The host cell can be an adherent cell or a suspended cell, i.e., a cell that grows in suspension. Suitable host cells are known in the art and include, for instance, DH5α E. coli cells, Chinese hamster ovarian cells, monkey VERO cells, COS cells, HEK293 cells, and the like. For purposes of testing or binding the NPSR with one of the compounds of the present invention, the host cell is preferably a eukaryotic cell, e.g., a CHO cell. For purposes of testing or screening the ability of the compounds to bind or antagonize the NPSR, the host cell is preferably a mammalian cell. Most preferably, the host cell is a human cell.

Also provided by an embodiment of the invention is a population of cells comprising at least one host cell described herein. The population of cells can be a heterogeneous population comprising the host cell comprising the NPSR. Alternatively, the population of cells can be a substantially homogeneous population, in which the population comprises mainly of host cells (e.g., consisting essentially of) comprising the NPSR. The population also can be a clonal population of cells, in which all cells of the population are clones of a single host cell comprising the NPSR.

In another embodiment, the term "contacting" means that the at least one NPSA of the present invention is introduced into a subject receiving treatment for a neuropsychiatric disorder, and the at least one NPSA is allowed to come in contact with the NPSR or NPSR complex in vivo.

The subject referred to in the inventive methods can be any subject. Preferably, the subject is a mammal. As used herein, the term "mammal" refers to any mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and
mammals of the order Logomorpha, such as rabbits. It is preferred that the mammals are from the order Camivora, including Felines (cats) and Canines (dogs). It is more preferred that the mammals are from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). It is most preferred that the mammals are of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). An especially preferred mammal is the human.

In a further embodiment, the present invention provides a method of treating a subject having or displaying symptoms of neuropsychiatric disorders, including, for example, disorders related to pain, sleep, mood, anxiety, eating and addictive disorders, the method comprising administering to the subject, a pharmaceutical composition comprising at least one NPSA, and at least one other compound suitable for use in treating a neuropsychiatric disorder, with a pharmaceutically acceptable carrier, in an effective amount to inhibit, suppress or treat symptoms of the neuropsychiatric disorder.

The compounds suitable for use in treating a neuropsychiatric disorders in the present invention, include, for example, drugs in the following classes: antipsychotics, antidepressants, anxiolytics and other classes of drugs known to those of skill in the art.

Several types of antidepressant medications are well-known, and commonly used to treat depressive disorders, include, for example, selective serotonin reuptake inhibitors (SSRIs), tricyclics, and monoamine oxidase inhibitors (MAOIs).

Several types of medications for treatment of anxiety disorders (such as phobias, obsessive compulsive disorders) and seizure disorders include, for example, benzodiazepines, such as diazepam, triazolam, midazolam, lorazepam, chlordiazepoxide, alprazolam, and other benzodiazepine-based medications.

"Typical" antipsychotic drugs, useful in the present invention include, for example, chlorpromazine, emonopride, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, pimozide, perphenazine, raclopride, remoxipride, spiperone, thioridazine, thiothixene, and trifluoperazine. Typical antipsychotics are believed to act by blocking dopaminergic receptors (dopamine receptor antagonists), primarily dopamine D₂ receptors, thereby reducing dopaminergic transmission in the brain. Examples of "atypical" antipsychotics useful in the present invention include, but are not limited to, asenapine olanzapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, amisulpride, ziprasidone, and mirtazapine.
[0074] Embodiments of the invention include a process for preparing pharmaceutical products comprising the NPS antagonist compounds. The term "pharmaceutical product" means a composition suitable for pharmaceutical use (pharmaceutical composition), as defined herein. Pharmaceutical compositions formulated for particular applications comprising the NPSAs of the present invention are also part of this invention, and are to be considered an embodiment thereof.

[0075] As used herein, the term "treat," as well as words stemming therefrom, includes preventative as well as disorder remittive treatment. The terms "reduce," "suppress," and "inhibit," as well as words stemming therefrom, have their commonly understood meaning of lessening or decreasing. These words do not necessarily imply 100% or complete treatment, reduction, suppression, or inhibition.

[0076] In an embodiment, the pharmaceutical compositions of the present invention comprise the NPSAs of the present invention together with a pharmaceutically acceptable carrier. With respect to pharmaceutical compositions described herein, the pharmaceutically acceptable carrier can be any of those conventionally used, and is limited only by physico-chemical considerations, such as solubility and lack of reactivity with the active compound(s), and by the route of administration. The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, and diluents, are well-known to those skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active agent(s), and one which has little or no detrimental side effects or toxicity under the conditions of use.

[0077] The carriers or diluents used herein may be solid carriers or diluents for solid formulations, liquid carriers or diluents for liquid formulations, or mixtures thereof.

[0078] Solid carriers or diluents include, but are not limited to, gums, starches (e.g., corn starch, pregelatinized starch), sugars (e.g., lactose, mannitol, sucrose, dextrose), cellulosic materials (e.g., microcrystalline cellulose), acrylics (e.g., polymethylacrylate), calcium carbonate, magnesium oxide, talc, or mixtures thereof.

[0079] For liquid formulations, pharmaceutically acceptable carriers may be, for example, aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include, for example, water, alcoholic/aqueous solutions, cyclodextrins, emulsions or suspensions, including saline and buffered media.
Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, fish-liver oil, sesame oil, cottonseed oil, corn oil, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include, for example, oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

Parenteral vehicles (for subcutaneous, intravenous, intraarterial, or intramuscular injection) include, for example, sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's and fixed oils. Formulations suitable for parenteral administration include, for example, aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

Intravenous vehicles include, for example, fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Examples are sterile liquids such as water and oils, with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. In general, water, saline, aqueous dextrose and related sugar solutions, and glycols such as propylene glycols or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions.

In addition, in an embodiment, the NPSAs of the present invention may further comprise, for example, binders (e.g., acacia, cornstarch, gelatin, caromer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g., cornstarch, potato starch, alginic acid, silicon dioxide, croscarmelose sodium, crospovidone, guar gum, sodium starch glycolate), buffers (e.g., Tris-HCl, acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g. sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., cremophor, glycerol, polyethylene glycerol, benzalkonium chloride, benzyl benzoate, cyclodextrins, sorbitan esters, stearic acids), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g., hydroxypropyl cellulose, hydroxypropylmethyl cellulose), viscosity increasing agents (e.g., caromer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweetners (e.g., aspartame,
citric acid), preservatives (e.g., thimerosal, benzyl alcohol, parabens), lubricants (e.g., stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g., colloidal silicon dioxide), plasticizers (e.g., diethyl phthalate, triethyl citrate), emulsifiers (e.g., carborner, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g., ethyl cellulose, acrylates, polymethacrylates), and/or adjuvants.

The choice of carrier will be determined, in part, by the particular NPSA, as well as by the particular method used to administer the NPSA. Accordingly, there are a variety of suitable formulations of the pharmaceutical compositions of the invention. The following formulations for parenteral, subcutaneous, intravenous, intramuscular, intraarterial, intrathecal and interperitoneal administration are exemplary, and are in no way limiting. More than one route can be used to administer the NPSAs, and in certain instances, a particular route can provide a more immediate and more effective response than another route.

Suitable soaps for use in parenteral formulations include, for example, fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include, for example, (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-P-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

The parenteral formulations will typically contain, for example, from about 0.5% to about 25% by weight of the NPSAs in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants, for example, having a hydrophilic-lipophilic balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5% to about 15% by weight. Suitable surfactants include, for example, polyethylene glycol sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.
The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets.

Injectable formulations are in accordance with the invention. The requirements for effective pharmaceutical carriers for injectable compositions are well-known to those of ordinary skill in the art (see, e.g., *Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Company, Philadelphia, PA, Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Trissel, 15th ed., pages 622-630 (2009)).

For purposes of the invention, the amount or dose of the NPSAs administered should be sufficient to effect, e.g., a therapeutic or prophylactic response, in the subject over a reasonable time frame. The dose will be determined by the efficacy of the particular NPSA and the condition of a subject, as well as the body weight of a subject to be treated.

The dose of the NPSA also will be determined by the existence, nature and extent of any adverse side effects that might accompany the administration of a particular NPSA. Typically, an attending physician will decide the dosage of the NPSA with which to treat each individual subject, taking into consideration a variety of factors, such as age, body weight, general health, diet, sex, NPSA to be administered, route of administration, and the severity of the condition being treated. By way of example, and not intending to limit the invention, the dose of the NPSA can be between about 0.001 mg/kg/day to about 1000 mg/kg/day, preferably, at least about 0.01 mg/kg/day to about 100 mg/kg/day, more preferably, about 0.1 mg/kg/day to about 10 mg/kg/day, still more preferably, about 0.5 mg/kg/day to about 5 mg/kg/day. In an alternate embodiment, the dose of the NPSA administered to the subject is in a range of between about 0.1 mg/kg/day to about 10 mg/kg/day, preferably, at least about 0.5 mg/kg/day to about 4 mg/kg/day, more preferably, about 1 mg/kg/day to about 2 mg/kg/day, and most preferably about 1 mg/kg/day.

Alternatively, the NPSA can be modified into a depot form, such that the manner in which the NPSA is released into the body to which it is administered is controlled with respect to time and location within the body (see, for example, U.S. Patent No. 4,450,150). Depot forms of NPSAs can be, for example, an implantable composition comprising the NPSA and a porous or non-porous material, such as a polymer, wherein the NPSA is
encapsulated by or diffused throughout the material and/or degradation of the non-porous material. The depot is then implanted into the desired location within the body and the NPSAs are released from the implant at a predetermined rate.

[0092] In one embodiment, the NPSAs provided herein can be controlled release compositions, i.e., compositions in which the one or more NPSAs are released over a period of time after administration. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils). In another embodiment the composition is an immediate release composition, i.e., a composition in which all or substantially all of the NPSA is released immediately after administration.

[0093] In yet another embodiment, the NPSAs can be delivered in a controlled release system. For example, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, or other modes of administration. In an embodiment, a pump may be used. In one embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity to the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Design of Controlled Release Drug Delivery Systems, Xiaoling Li and Bhaskara R. Jasti eds. (McGraw-Hill, 2006)).

[0094] The NPSA compositions of the present invention may also include incorporation of the active ingredients into or onto particulate preparations of polymeric compounds such as polylactic acid, polylactic acid, hydrogels, etc., or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance.

[0095] In accordance with the present invention, NPSAs may be modified by, for example, the covalent attachment of water-soluble polymers such as polyethylene glycol, copolymers of polyethylene glycol and polypropylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinylpyrrolidone or polyproline. The modified compounds are known to exhibit substantially longer half-lives in blood following intravenous injection, than do the corresponding unmodified compounds. Such modifications may also increase the NPSAs' solubility in aqueous solution, eliminate aggregation, enhance the physical and chemical stability of the compound, and greatly reduce the immunogenicity and reactivity of the compound. As a result, the desired in vivo biological activity may be achieved by the
administration of such polymer-compound adducts less frequently, or in lower doses than with the unmodified compound.

EXAMPLES

[0096] Unless otherwise stated, all reactions were earned out under an atmosphere of dry argon or nitrogen in dried glassware. Indicated reaction temperatures refer to those of the reaction bath, while room temperature (rt) is noted as about 25 °C. All solvents were of anhydrous quality purchased from Aldrich Chemical Co. (Sigma-Aldrich, St. Louis, MO) and used as received. Commercially available starting materials and reagents were purchased from Aldrich and were used as received.

[0097] Analytical thin layer chromatography (TLC) was performed with Sigma Aldrich TLC plates (5 x 20 cm, 60 A, 250 μm) (Sigma-Aldrich). Visualization was accomplished by irradiation under a 254 nm UV lamp. Chromatography on silica gel was performed using forced flow (liquid) of the indicated solvent system on Biotage KP-Sil pre-packed cartridges and using the Biotage SP-1 automated chromatography system (Biotage AB, Uppsala, Sweden). Reverse phase preparative purification was performed on a Waters semi-preparative HPLC (Waters, Billerica, MA). The column used was a Phenomenex Luna C18 (5 micron, 30 x 75 mm) (Phenomenex, Torrance, CA) at a flow rate of 45 ml/min. The mobile phase consisted of acetonitrile (AcCN) and water (each containing 0.1% trifluoroacetic acid (TFA)). A gradient of 10% to 50% AcCN over 8 minutes was used during the purification. Fraction collection was triggered by UV detection (220 nM).

[0098] H and 13C NMR spectra were recorded on a Varian Inova 400 MHz spectrometer (Varian Instruments, Palo Alto, CA). Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl3 7.27 ppm, 77.00 ppm, DMSO-d6 2.50 ppm, 39.51 ppm for 1H, 13C respectively). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, m = multiplet), coupling constants, and number of protons.

[0099] Analytical analysis was performed on an Agilent LC/MS (Agilent Technologies, Santa Clara, CA). Method 1: A 7 minute gradient of 4 to 100% AcCN (containing 0.025% TFA) in water (containing 0.05% TFA) was used with an 8 minute run time at a flow rate of 1 ml/min. A Phenomenex Luna C18 column (3 micron, 3 x 75 mm) was used at a temperature of 50 °C. Method 2: A 3 minute gradient of 4 to 100% AcCN (containing
0.025% TFA) in water (containing 0.05% TFA) was used with a 4.5 minute run time at a flow rate of 1 ml/min. A Phenomenex Luna C18 column (3 micron, 3 x 100 mm) was used at a temperature of 50 °C.

Purity determination was performed using an Agilent Diode Array Detector. Mass determination was performed using an Agilent 6130 mass spectrometer with electrospray ionization in the positive mode (Agilent Technologies). Unless otherwise stated all compounds were >95% purity.

Molecular weight confirmation was confirmed using an Agilent Time-Of-Flight Mass Spectrometer. A 3 minute gradient from 4 to 100% AcCN (0.1% formic acid) in water (0.1% formic acid) was used with a 4 minute run time at a flow rate of 1 ml/minute. A Zorbax SB-C18 column (3.5 micron, 2.1 x 30 mm (Agilent Technologies), was used at a temperature of 50 °C. Confirmation of molecular formula was confirmed using electrospray ionization in the positive mode with the Agilent Masshunter software (version B.02).

EXAMPLE 1

The synthesis of 3-(diphenylphosphino)imidazo[1,2-a]pyridine is described below.

\[
\text{Ph}_2P\text{Ph} \xrightarrow{\text{Cl}} \text{N}\text{N}^{\text{Ph}} \xrightarrow{\text{N}} \text{P} \text{Ph}^{\text{N}}
\]

Chlorodiphenylphosphine (1.40 g, 6.35 mmol) and iodos trimethylsilane (1.27 g, 6.35 mmol) were mixed in toluene (4 ml) and stirred for about 2 hours. This mixture was transferred to a premixed solution of imidazo[1,2-a]pyridine (500 mg, 4.23 mmol) and triethylamine (2.35 ml, 16.9 mmol) in pyridine (10 ml). The reaction was allowed to stir overnight, concentrated in vacuo, and concentrated with toluene (X2) to remove pyridine. The crude mixture was dissolved in dichloromethane (DCM) and purified by silica gel chromatography (0 to 100% ethyl acetate (EtOAc)/DCM) to provide 3-(diphenylphosphino)imidazo [1,2-a]pyridine (550 mg, 1.82 mmol, 43.0 % yield). 1H NMR (400 MHz, DMSO-4) δ ppm 6.94 (td, J=6.8, 1.4 Hz, 1 H), 7.36 (m, 12 H), 7.71 (m, 1 H),
8.16 (m, J=6.8, 2.1, 1.1, 1.1 Hz, 1 H); LC/MS: Method 1, retention time 4.500 min; HRMS (m/z) calculated for C_{19}H_{16}N_{2}P^{+} (M+H)^{+} 303.1046, found 303.1049.

EXAMPLE 2

[0104] The synthesis of 3-(diphenylphosphoryl) imidazo[1,2-a]pyridine, HCl is described below.

[0105] 3-(Diphenylphosphino)imidazo[1,2-a]pyridine (125 mg, 0.413 mmol) was dissolved in tetrahydrofuran (THF) and treated with excess 30% hydrogen peroxide (300 mg, 2.65 mmol). The reaction was stirred for 16 hours, then diluted with EtOAc and washed with water. The organic layer was dried (MgSO₄), filtered, concentrated, and purified by reverse phase HPLC. The TFA salt obtained was dissolved in DCM, treatment with excess HCl (4M in ethanol) and then concentration *in vacuo* (twice) to obtain the HCl salt 3-(diphenylphosphoryl) imidazo[1,2-a]pyridine, HCl (45 mg, 0.13 mmol, 31% yield). 1H NMR (400 MHz, DMSO-d₆) δ ppm 7.39 (m, 1 H), 7.63 (m, 4 H), 7.75 (m, 6 H), 7.87 (m, 1 H), 7.94 (s, 1 H), 8.00 (m, 1 H), 8.78 (d, J=6.8 Hz, 1 H); LC/MS: Method 1, retention time 3.693 minutes; HRMS (m/z) calculated for C_{19}H_{16}N_{2}O_{2}P^{+} (M+H)^{+} 319.0995, found 319.0995.

EXAMPLE 3

[0106] The synthesis of 3-(diphenylphosphorothioyl)imidazo[1,2-a]pyridine, HCl is described below.

[0107] 3-(Diphenylphosphino)imidazo[1,2-a]pyridine (125 mg, 0.413 mmol) was dissolved in THF and treated with excess sulfur (50 mg, 1.6 mmol). The reaction was stirred for 16 hours, then diluted with EtOAc and washed with water. The organic layer was dried
(MgSO₄), filtered, concentrated, and purified by reverse phase HPLC. The TFA salt obtained was dissolved in DCM, treatment with excess HCl (4M in ethanol) and then concentration in vacuo (twice) to obtain the HCl salt 3-(diphenylphosphorothioyl)imidazo[1,2-a]pyridine, HCl (50 mg, 0.135 mmol, 33 % yield). 1H NMR (400 MHz, DMSO-<δ>) δ ppm 7.19 (t, J=6.8 Hz, 1 H), 7.38 (br. s., 1 H), 7.66 (m, 7 H), 7.80 (m, 4 H), 7.89 (d, J=9.2 Hz, 1 H), 8.52 (d, J=6.7 Hz, 1 H); LC/MS: Method 1, retention time 4.845 minutes; HRMS (m/z) calculated for C₁₃H₇N₂PS (M+H)+ 335.0766, found 335.0771.

EXAMPLE 4

[0108] The synthesis of 2-amino-1-(prop-2-ynyl)pyridinium, Br⁻ is described below.

[0109] Pyridin-2-amine (9.5 g, 0.10 mol) and 3-bromoprop-1-yne (10 ml, 0.10 mol) were taken in ethanol (50 ml) and refluxed for 2 hours. The reaction was left to cool overnight. A light yellow solid precipitated out of the reaction. This was filtered via a Buchner funnel, washed with cold ethanol, and air dried to obtain 2-amino-1-(prop-2-ynyl)pyridinium, Br⁻ (10 g, 47 mmol, 47 % yield). 1H NMR (400 MHz, DMSO-<δ>) δ ppm 3.82 (t, J=2.5 Hz, 1 H), 5.08 (d, J=2.5 Hz, 2 H), 6.95 (td, J=6.9, 1.4 Hz, 1 H), 7.11 (m, 1 H), 7.91 (ddd, J=8.9, 7.1, 1.7 Hz, 1 H), 8.17 (m, 1 H), 8.63 (br. s., 2 H).

EXAMPLE 5

[0110] The synthesis of 2-methylimidazo[1,2-a]pyridine is described below.

[0111] 2-Amino-1-(prop-2-ynyl)pyridinium bromide (6.0 g, 28 mmol) was mixed with copper(I) iodide (0.537 g, 2.82 mmol), PdCl₂(PPh₃)₂ (0.495 g, 0.705 mmol) in DMF (50 mL), treated with triethylamine (12 ml, 87 mmol) and stirred overnight by which the light orange solution had turned brown. The reaction was concentrated, adsorbed on to silica gel and then
purified by flash silica gel chromatography (0 to 100% DCM/EtOAc), to provide 2-methylimidazo[1,2-a]pyridine (2.69 g, 20.35 mmol, 72 % yield). 1H NMR (400 MHz, Chloroform-δ) δ ppm 2.46 (s, 3 H), 6.72 (m, 1 H), 7.1 1 (ddd, J=9.0, 6.8, 1.4 Hz, 1 H), 7.33 (s, 1 H), 7.54 (m, 1 H), 8.03 (dt, J=6.8, 1.2 Hz, 1 H).

EXAMPLE 6

The synthesis of 3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine is described below.

\[ \text{Ph-P-Ph} \quad \text{Si} \quad \text{N} \quad \text{N} \quad \text{S} \quad \rightarrow \quad \text{Ph} \quad \text{S} \]

General Procedure A: Chlorodiphenylphosphine (3.89 ml, 26.4 mmol) and iodotrimethylsilane (5.29 g, 26.4 mmol) were stirred in toluene (10 ml) for 2 hours. This was added to a premixed solution of 2-methylimidazo[1,2-a]pyridine (2.33 g, 17.6 mmol) and triethylamine (9.78 ml, 70.5 mmol) in pyridine (10.0 ml), and stirred 12 hours. Sulfur (0.565 g, 17.6 mmol) was added and stirred for another 6 hours. The reaction was concentrated, then concentrated again with toluene (to remove pyridine), and diluted with benzene. The solids (presumed to be triethylamine (Et₃N) and pyridine salts) were filtered, and the filtrate, adsorbed over silica and subjected to purification by flash silica gel chromatography (0 to 75% EtOAc in DCM) to provide 3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine (3.02 g, 8.67 mmol, 49.2 % yield). 1H NMR (400 MHz, DMSO-d₆) δ ppm 1.57 (m, 3 H), 6.96 (m, J=6.7, 6.7, 1.0, 0.7 Hz, 1 H), 7.44 (m, 1 H), 7.60 (m, 4 H), 7.68 (m, 3 H), 7.78 (m, 4 H), 8.35 (dt, J=6.8, 1.2 Hz, 1 H).

EXAMPLE 7

The synthesis of 3-(diphenylphosphorothioyl)-1,2-dimethyl-lH-imidazo[1,2-a]pyridin-4-iium, MeS0₄⁻ is described below.
General Procedure B: 3-(Diphenylphosphorothioyl)-2-methylimidazo[1,2-ajpyridine (90 mg, 0.26 mmol) and dimethyl sulfate (0.05 ml, 0.52 mmol) were taken in dioxane (2 ml). The contents were heated in a sealed tube at 100 °C for 16 hours. The reaction was cooled and the solid obtained was filtered, washed with diethyl ether, and air dried to obtain 3-(diphenylphosphorothioyl)-1,2-dimethyl-1H-imidazo[1,2-a]pyridin-4-ium, MeSO₄⁺ (50 mg, 0.11 mmol, 41 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.67 (m, 3 H), 3.91 (s, 3 H), 7.54 (t, J=7.0 Hz, 1 H), 7.68 (td, J=7.6, 3.5 Hz, 4 H), 7.77 (m, 2 H), 7.87 (m, 4 H), 8.15 (t, J=8.3 Hz, 1 H), 8.39 (m, 1 H), 8.66 (d, J=6.8 Hz, 1 H); LC/MS: Method 1, retention time 4.545 minutes; HRMS (m/z) calculated for C₂₀Hᵡ₂N₂P₆S⁺ (M)⁺ 363.1079, found 363.1080.

EXAMPLE 8

The synthesis of 3-(diphenylphosphorothioyl)-1-methyl-1H-imidazo[1,2-alpyridin-4-ium, MeSO₄⁺ is described below.

3-(Diphenylphosphorothioyl)imidazo[1,2-a]pyridine (150 mg, 0.449 mmol) was reacted with dimethyl sulfate (0.086 ml, 0.897 mmol), according to General Procedure B, to obtain 3-(Diphenylphosphorothioyl)-1-methyl-1H-imidazo[1,2-a]pyridin-4-ium, MeSO₄⁺ (70 mg, 0.15 mmol, 34 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 4.02 (s, 3 H), 7.65 (m, 5 H), 7.77 (m, 2 H), 7.86 (m, 4 H), 8.08 (dd, J=2.0, 0.4 Hz, 1 H), 8.21 (m, 1 H), 8.3 (m, 1 H), 8.72 (m, 1 H); LC/MS: Method 1, retention time 4.468 minutes; HRMS (m/z) calculated for C₂₀Hᵡ₈N₂PS⁺ (M)⁺ 349.0923, found 349.0925.
EXAMPLE 9

[0118] The synthesis of 1-benzyl-3-(diphenylphosphorothioyl)-1H-imidazo[1,2-a]pyridin-4-ium, Br- is described below.

\[
\begin{align*}
\text{Br} & \quad \text{Ph}_{2}P \quad \text{S} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

[0119] 3-Diphenylphosphorothioyl)imidazo[1,2-a]pyridine (124 mg, 0.371 mmol) and (bromomethyl)benzene (0.055 ml, 0.463 mmol) were reacted according to General Procedure B, to obtain 1-benzyl-3-(diphenylphosphorothioyl)-1H-imidazo[1,2-a]pyridin-4-iun bromide (75 mg, 0.15 mmol, 40 % yield). 1H NMR (400 MHz, DMSO-d_6) δ ppm 5.73 (s, 2 H), 7.40 (m, 5 H), 7.67 (m, 5 H), 7.77 (m, 2 H), 7.89 (m, 4 H), 8.21 (ddd, J=9.2, 7.2, 1.2 Hz, 1 H), 8.29 (d, J=2.3 Hz, 1 H), 8.37 (m, 1 H), 8.75 (m, 1 H); LC/MS: Method 1, retention time 5.069 minutes; HRMS (m/z) calculated for C_{26}H_{22}N_{2}PS^+ (M)+ 425.1236, found 425.1242.

EXAMPLE 10

[0120] The synthesis of 3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine, HCl is described below.

\[
\begin{align*}
\text{S} & \quad \text{Ph}_{2}P \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

[0121] 3-(Diphenylphosphino)-2-methylimidazo[1,2-a]pyridine (209 mg, 0.660 mmol) was dissolved in THF (5 ml), treated with excess sulfur (200 mg, 6.24 mmol), and stirred for 16 hours. The reaction was adsorbed onto silica gel, purified by flash silica gel chromatography and then reverse phase HPLC. Fractions from the reverse phase HPLC were treated with saturated aqueous NaHCO_3, and extracted with DCM. The organic phases were concentrated, dried (MgSO_4), redissolved in minimal DCM, and then treated with excess 1M HCl in ethanol to precipitate a white solid. The mixture was concentrated, dissolved in
minimal DCM, treated with ethanol to cause precipitation. The solid obtained was filtered to provide 3-((diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine, HCl (55 mg, 0.14 mmol, 22% yield). 1H NMR (400 MHz, chloroform-d) δ ppm 1.64 (m, 3 H), 6.70 (m, 1 H), 7.27 (m, 1 H), 7.46 (m, 4 H), 7.55 (m, 3 H), 7.77 (m, 4 H), 8.62 (dt J=6.8, 1.2 Hz, 1 H); LC/MS: Method 1, retention time 4.697 minutes; HRMS (m/z) calculated for C$_{20}$H$_{18}$N$_2$PS$^+$ (M+H)$^+$ 349.0923, found 349.0927.

EXAMPLE 1

[0122] The synthesis of imidazo[1,2-a]pyridin-3-yldiphenylmethanol is described below.

[0123] 3-Bromoimidazo[1,2-a]pyridine (172 mg, 0.873 mmol) was dissolved in THF (5 ml), cooled to -15 °C under nitrogen. Isopropylmagnesiumchloride-lithium chloride (1.5 ml, 1.5 mmol) was added and the reaction gradually warmed to 10 °C. A solution of benzophenone (175 mg, 0.960 mmol) in THF (1 ml) was added via syringe, and the reaction warmed to room temperature. The reaction was quenched by addition of saturated aqueous NH$_4$Cl, and then extracted with EtOAc. The organic layer was separated, concentrated, and purified by reverse phase HPLC which provided the TFA salt. This was converted to its free base by dissolution in EtOAc, and then treatment with saturated aqueous NaHCO$_3$. The organic phase was dried (MgSO$_4$), filtered, and concentrated. The oily residue was dissolved in minimal DCM, treated with ethanol, and sonicated to cause precipitation of a solid which was filtered and air dried to provide imidazo[1,2-a]pyridin-3-yldiphenylmethanol (80 mg, 0.266 mmol, 17.76% yield). 1H NMR (400 MHz, Chloroform-J) δ ppm 3.05 (s, 1 H), 6.63 (m, 1 H), 7.01 (s, 1 H), 7.18 (m, 1 H), 7.35 (m, 8 H), 7.61 (m, 1 H), 8.06 (m, 1H); LC/MS: Method 1, retention time 4.143 minutes; HRMS (m/z) calculated for C$_{20}$H$_{17}$N$_2$O$^+$ (M+H)+ 301.1335, found 301.1337.
The synthesis of 3-(diphenylphosphoryl)-2-methylimidazo[1,2-a]pyridine, HCl is described below.

3-Bromo-2-methylimidazo[1,2-a]pyridine (290 mg, 1.37 mmol, not completely pure) was dissolved in THF (5 ml), cooled to -15 °C under nitrogen. Isopropylmagnesiumchloride-lithium chloride (2 ml, 2 mmol) was added and the reaction allowed to warm to 10 °C, at which point it was determined by thin layer chromatography (TLC) (1:1 DCM:EtOAc) that the halogen-metal exchange was complete. A solution of chlorodiphenylphosphine (300 mg, 1.36 mmol) in THF (1 ml) was added via syringe and the reaction was allowed to gradually warm to room temperature. The reaction was quenched by addition of saturated aqueous NH₄Cl, extracted with EtOAc. The organic layer was separated, purified by silica gel chromatography (0 to 100% EtOAc/DCM). The product, which was not completely pure by 1H NMR, was taken in THF and treated with excess 30% hydrogen peroxide, and stirred overnight. Water was added, extracted with EtOAc, then concentrated, and the residue purified by reverse phase HPLC. The fractions were treated with saturated aqueous NaHCO₃, extracted with EtOAc, dried (MgSO₄), filtered, and concentrated, redissolved in DCM, and converted to HCl salt by treatment with excess 1M HCl in Et₂O and then further concentrated.

The residue was then redissolved in DCM and treated with ethanol to cause precipitation. The solid obtained was filtered and washed with ethanol, to obtain 3-(diphenylphosphoryl)-2-methylimidazo[1,2-a]pyridine, HCl (30 mg, 0.08 mmol, 5.9 % yield). 1H NMR (400 MHz, DMSO-d₆) δ ppm 1.82 (d, J=1.2 Hz, 3 H), 7.24 (m, 1 H), 7.68 (m, 11 H), 7.85 (d, J=8.6 Hz, 1 H), 8.84 (d, J=6.7 Hz, 1 H); LC/MS: Method 1, retention time 3.734 minutes; HRMS (m/z) calculated for C₂₀H₁₅N₂OP⁺ (M+H)⁺ 333.1151, found 333.1157.
EXAMPLE 13

[0127] The synthesis of (2-methylimidazo[1,2-a]pyridin-3-yl)diphenylmethanol is described below.

\[
\begin{align*}
\text{Br} & \quad \text{Ph} \quad \text{O} \quad \text{MgCl}_2 \cdot \text{LiCl} \\
\text{N} & \quad \text{N} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{HO} & \quad \text{Ph}
\end{align*}
\]

[0128] 3-Bromo-2-methylimidazo[1,2-a]pyridine (220 mg, 1.042 mmol, not completely pure) was dissolved in THF (5 ml), and cooled to -15 °C under nitrogen. Isopropylmagnesiumchloride-lithium chloride (2.7 ml, 2.70 mmol) was added and the reaction was allowed to warm to 10 °C. A solution of benzophenone (208 mg, 1.141 mmol) in THF (1 ml) was added via syringe and the reaction warmed to room temperature. The reaction was quenched by addition of saturated aqueous NH₄Cl and then extracted with EtOAc. The organic layer was separated and then purified by silica gel chromatography (0 to 100% EtOAc in DCM) to provide (2-methylimidazo[1,2-a]pyridin-3-yl)diphenylmethanol (100 mg, 0.318 mmol, 30.5 % yield). 1H NMR (400 MHz, DMSO-\(d_6\)) δ ppm 1.38 (s, 3 H), 6.65 (m, 1 H), 6.93 (s, 1 H), 7.14 (ddd, \(J=9.0, 6.7, 1.4\) Hz, 1 H), 7.23 (m, 4 H), 7.33 (m, 6 H), 7.43 (dt, \(J=9.0, 1.2\) Hz, 1 H), 8.11 (dt, \(J=7.0, 1.3\) Hz, 1 H); LC/MS: Method 1, retention time 4.290 minutes; HRMS (m/z) calculated for C\(_{22}\)H\(_{19}\)N\(_2\)O (M+H)+ 315.1492, found 315.1495.

EXAMPLE 14

[0129] The synthesis of 3-(hydroxydiphenylmethyl)-1,2-dimethylimidazo[1,2-a]pyridin-1-i um, TFA⁻ is described below.

\[
\begin{align*}
\text{Ph} & \quad \text{HO} & \quad \text{Ph} & \quad \text{O} & \quad \text{SO}_2
\end{align*}
\]

[0130] General Procedure C: (2-Methylimidazo[1,2-a]pyridin-3-yl)diphenylmethanol (32 mg, 0.102 mmol) and dimethyl acetate (15 \(\mu\)l, 0.157 mmol) were heated in a sealed tube overnight. An oily residue was observed suspended in dioxane. The reaction was concentrated, purified with reverse phase HPLC (25 to 70% AcCN in Water, 0.1% TFA) to
provide 3-(hydroxydiphenylmethyl)-1,2-dimethylimidazo[1,2-a]pyridin-l-ium, TFA· (25 mg, 0.057 mmol, 55.5 % yield). The counter anion (MeSO₄⁻) was assumed to be exchanged out with TFA·. 1H NMR (400 MHz, DMSO-d₆) δ ppm 1.49 (s, 3 H), 3.88 (s, 3 H), 7.37 (m, 11 H), 7.60 (m, 1 H), 7.99 (m, 1 H), 8.25 (d, J=9.2 Hz, 1 H), 8.58 (d, J=7.0 Hz, 1 H); LC/MS: Method 1, retention time 4.321 minutes; HRMS (m/z) calculated for C₂₂H₂₁N₂O⁺ (M)⁺ 329.1648, found 329.1656.

EXAMPLE 15

[0131] The synthesis of 3-(hydroxydiphenylmethyl)-1-methylimidazo[1,2-a]pyridin-1-ium, TFA· is described below.

[0132] Imidazo[1,2-a]pyridin-3-yl diphenylmethanol (48 mg, 0.16 mmol) and dimethyl sulfate (25 µl, 0.26 mmol) were reacted according to General Procedure C, to obtain 3-(hydroxydiphenylmethyl)-1-methylimidazo[1,2-a]pyridin-1-ium, TFA· (35 mg, 0.082 mmol, 51.1 % yield). 1H NMR (400 MHz, DMSO-d₄) δ ppm 7.41 (m, 11 H), 7.56 (s, 1 H), 8.05 (ddd, J=9.1, 7.1, 1.2 Hz, 1 H), 8.24 (dt, J=9.2, 1.1 Hz, 1 H), 8.39 (m, 1 H); LC/MS: Method 1, retention time 4.074 minutes; HRMS (m/z) calculated for C₂₁H₁₉N₂O⁺ (M)⁺ 315.1492, found 315.1497.

EXAMPLE 16

[0133] The synthesis of 3-(diphenylphosphorothioyl)-1,2-dimethyl-1H-indole is described below.
General Procedure D: A solution of chlorodiphenylphosphine (1310 mg, 5.94 mmol) in toluene (5 ml) was treated with iodo(trimethyl)silane (1000 mg, 5.00 mmol) and stirred for 1 hour. This was added to a stirring solution of 1,2-dimethyl-1H-indole (650 mg, 4.48 mmol) and triethylamine (2.5 ml, 17.94 mmol) in pyridine (8 ml). A portion (approximately a fifth) of the reaction was removed and treated with excess sulfur (300 mg, 9.36 mmol), and stirred overnight. The reaction was concentrated, redissolved in DCM, and subjected to purification by silica gel chromatography (0 to 100 % EtOAc/DCM). The crude residue (white powder) obtained was suspended in diethyl ether, filtered, and air dried to obtain 3-(diphenylphosphorothioyl)-1,2-dimethyl-1H-indole (130 mg, 0.360 mmol, 40.1 % yield). 1H NMR (400 MHz, DMSO-d6) δ ppm 2.17 (d, J=1.4 Hz, 3 H), 3.72 (s, 3 H), 6.36 (dt, J=8.0, 1.0 Hz, 1 H), 6.78 (ddd, J=8.2, 7.1, 1.2 Hz, 1 H), 7.10 (ddd, J=8.2, 7.0, 1.2 Hz, 1 H), 7.53 (m, 5 H), 7.59 (m, 2 H), 7.82 (m, 4 H); LC/MS: Method 1, retention time 6.915 minutes; HRMS (m/z) calculated for C22H21NPS+(M+H)+ 362.127, found 362.134.

EXAMPLE 17

The synthesis of 3-(diphenylphosphorothioyl)-1-methyl-1H-indole (SPA02-002) is described below.

[0134] Chlorodiphenylphosphine (1310 mg, 5.94 mmol), iodo(trimethyl)silane (1000 mg, 5.00 mmol), 1-methyl-1H-indole (640 mg, 4.88 mmol), and triethylamine (2.5 ml, 17.94 mmol) were reacted according to General Procedure D. A portion of the reaction (approximately a fifth) was treated with excess sulfur to produce 3-(diphenylphosphorothioyl)-1-methyl-1H-indole (130 mg, 0.374 mmol, 38.9 % yield). 1H NMR (400 MHz, OMSO-d6) δ ppm 3.85 (s, 3 H), 7.05 (ddd, J=8.1, 7.0, 1.1 Hz, 1 H), 7.25 (ddd, J=8.3, 7.1, 1.3 Hz, 1 H), 7.30 (dt, J=8.0, 1.0 Hz, 1 H), 7.44 (d, J=4.5 Hz, 1 H), 7.56 (m, 7 H), 7.74 (m, 4 H); LC/MS: Method 1, retention time 6.793 minutes; HRMS (m/z) calculated for C21H19NPS+(M+H)+ 348.0970, found 348.0974.
EXAMPLE 18

[0136] The synthesis of 3-(diphenylphosphoryl)-1,2-dimethyl-1H-indole is described below.

[0137] Chlorodiphenylphosphine, iodotrimethylsilane, 1,2-dimethyl-1H-indole, and triethylamine were reacted according to General Procedure D, and then a fifth of the reaction was treated with excess 30% hydrogen peroxide, to produce 3-(diphenylphosphoryl)-1,2-dimethyl-1H-indole. 1H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.46 (m, 3 H), 3.73 (s, 3 H), 6.58 (d, J=8.0 Hz, 1 H), 6.84 (m, 1 H), 7.11 (m, 1 H), 7.51 (m, 5 H), 7.61 (m, 6 H); LC/MS: Method 1, retention time 5.696 minutes; HRMS (m/z) calculated for C$_{22}$H$_{27}$NOP$^+$(M+H)$^+$ 346.1355, found 346.1356.

EXAMPLE 19

[0138] The synthesis of 3-(diphenylphosphoryl)-1-methyl-1H-indole is described below.

[0139] Chlorodiphenylphosphine, iodotrimethylsilane, 1-methyl-1H-indole, and triethylamine were reacted according to General Procedure D, and then a fifth of the reaction was treated with excess 30% hydrogen peroxide, to produce 3-(diphenylphosphorothioyl)-1-methyl-1H-indole. 1H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.84 (s, 3 H), 7.04 (m, 1 H), 7.24 (m, 2 H), 7.44 (d, J=3.9 Hz, 1 H), 7.55 (m, 7 H), 7.68 (m, 4 H); LC/MS: Method 1, retention time 5.469 minutes; HRMS (m/z) calculated for C$_{23}$H$_{31}$NOP$^+$(M+H)$^+$ 332.1202, found 332.1202.
EXAMPLE 20

The synthesis of 3-(diphenylphosphorothioyl)-1-methyl-2-phenyl-1H-indole is described below.

\[
\text{Ph} - \text{P} - \text{Ph} \quad \text{Ph} - \text{Si} - \text{Ph} - \text{N} \quad \text{S} \quad \rightarrow \quad \text{Ph} - \text{P} - \text{S} - \text{Ph} - \text{N} \quad \text{S} = \text{P}
\]

I-Methyl-2-phenyl-1H-indole was treated according to General Procedure A, to yield 3-(diphenylphosphorothioyl)-1-methyl-2-phenyl-1H-indole. 1H NMR (400 MHz, DMSO-\(d_6\)) δ ppm 3.53 (s, 3 H), 6.95 (m, 2 H), 7.09 (m, 2 H), 7.15 (m, 1 H), 7.25 (m, 7 H), 7.35 (m, 2 H), 7.62 (m, 1 H), 7.73 (m, 4 H); LC/MS: Method 1, retention time 7.299 minutes; HRMS (m/z) calculated for \(\text{C}_{27}\text{H}_{23}\text{NPS}^+\) (M+H)+ 424.1283, found 410.1287.

EXAMPLE 21

The synthesis of 3-(diphenylphosphorothioyl)-1H-indole is described below.

\[
\text{Ph} - \text{P} - \text{Ph} \quad \text{Ph} - \text{Si} - \text{N} \quad \rightarrow \quad \text{Ph} - \text{P} - \text{S} - \text{N}
\]

Chlorodiphenylphosphine (1.88 g, 8.54 mmol) and iodotrimethylsilane (1.16 ml, 8.54 mmol) were dissolved in toluene (5 ml), stirred for 2 hours and then transferred to a premixed solution of triethylamine (2.59 g, 25.6 mmol), 1H-indole (1.00 g, 8.54 mmol), and pyridine (5 ml). The reaction was stirred overnight, concentrated, and then purified by flash silica gel chromatography, to provide 3-(diphenylphosphorothioyl)-1H-indole (0.60 g, 1.8 mmol, 21 % yield). 1H NMR (400 MHz, DMSO-\(d_6\)) δ ppm 7.00 (ddd, \(J=8.1, 7.0, 1.1\) Hz, 1 H), 7.18 (ddd, \(J=8.3, 7.0, 1.4\) Hz, 1 H), 7.31 (dt, \(J=8.0, 1.1\) Hz, 1 H), 7.35 (d, \(J=4.5\) Hz, 1 H), 7.55 (m, 7 H), 7.74 (m, 4 H), 11.94 (br. s., 1 H); LC/MS: Method 1, retention time 6.353 minutes; HRMS (m/z) calculated for \(\text{C}_{27}\text{H}_{23}\text{NPS}^+\) (M+H)+ 348.0970, found 348.0973.
The major reaction product, 1,3-bis(diphenylphosphorothioyl)-1H-indole could also be refluxed with aqueous KOH in ethanol, to provide the title compound.

**EXAMPLE 22**

The synthesis of 3-(diphenylphosphorothioyl)-2-methyl-1H-indole is described below.

![Chemical Structure]

**General Procedure E: Chlorodiphenylphosphine** (3.36 g, 15.3 mmol) and iodotrimethylsilane (2.075 ml, 15.25 mmol) were dissolved in toluene (5 ml), stirred for 2 hours, and then transferred to a premixed solution of triethylamine (6.34 ml, 45.7 mmol), 2-methyl-1H-indole (2.00 g, 15.3 mmol), and pyridine (5 ml). After stirring overnight, excess sulfur (2.444 g, 76 mmol) was added. The reaction was stirred for another 6 hours, then concentrated, diluted with ethanol, aqueous 2.5 M KOH (-10 eq) was added, refluxed for 2 hours, cooled, and concentrated.

The reaction mixture was then diluted with toluene, and the precipitated solids (presumed to be Et₃N and pyridium salts) were filtered off. The filtrate was concentrated and taken up in DCM. Hexanes were also added to cause further precipitation. The resulting solids were then filtered off. The mixture was adsorbed on silica gel and subjected purification by flash column chromatography (0 to 100% EtOAc/hexanes), to obtain a mixture of the required product and an unidentified impurity. On addition of DCM and letting stand, a white solid precipitate formed, which was filtered and identified as pure 3-(diphenylphosphorothioyl)-2-methyl-1H-indole (0.8 g, 2.3 mmol, 15 % yield). 1H NMR (400 MHz, DMSO-4) δ ppm 2.05 (s, 3 H), 6.52 (d, J=8.0 Hz, 1 H), 6.76 (ddd, J=8.2, 7.1, 1.0 Hz, 1 H), 7.03 (m, 1 H), 7.37 (dt, J=8.1, 1.0 Hz, 1 H), 7.55 (m, 6 H), 7.81 (m, 4 H), 11.87 (br. s., 1 H); LC/MS: Method 1, retention time 6.466 minutes; HRMS (m/z) calculated for C₂₁H₁₉NPS⁺(M+H)⁺ 348.0970, found 348.0973.
EXAMPLE 23

[0148] The synthesis of 3-(diphenylphosphorothioyl)-2-phenyl-lH-indole is described below.

\[
\text{Ph} \quad \begin{array}{c}
\text{P} \\
\text{Ph}
\end{array} \quad \text{S}
\]

Chlorosilanes then KOH

[0149] 2-Phenyl-lH-indole was treated according to General Procedure E, to produce 3-(diphenylphosphorothioyl)-2-phenyl-lH-indole. 1H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 6.65 (m, 1 H), 6.84 (ddd, \(J=8.3, 7.1, 1.1\) Hz, 1 H), 7.11 (m, 4 H), 7.26 (m, 4 H), 7.34 (m, 2 H), 7.43 (m, 2 H), 7.48 (dt, \(J=8.0, 1.0\) Hz, 1 H), 7.84 (m, 4 H), 12.21 (m, 1 H); LC/MS: Method 1, retention time 6.929 minutes; HRMS (m/z) calculated for \(C_{26}H_{24}INPS^+(M+H)^+\) 410.127, found 410.135.

EXAMPLE 24

[0150] The synthesis of N-benzyl-3-(diphenylphosphorothioyl)-lH-indole-1-carboxamide is described below.

\[
\text{Ph} \quad \begin{array}{c}
\text{P} \\
\text{Ph}
\end{array} \quad \text{S}
\]

[COC1]3 \quad \text{NH}_2

[0151] General Procedure F: Benzylamine (50 mg, 0.47 mmol) in THF (2 ml) was treated with triphosgene (58 mg, 0.20 mmol). A solid was observed to precipitate out of the solution. This solution was stirred for 30 minutes. A solution of 3-(diphenylphosphorothioyl)-lH-indole (50 mg, 0.150 mmol), Et\(_3\)N (200 \(\mu\)L, 1.435 mmol) in THF was then added to the reaction mixture, along with a small crystal of 4-dimethylaminopyridine (DMAP) (5 mg, 0.041 mmol). The reaction stirred for 2 hours and
worked up with water/EtOAc. The reaction contained unreacted 3-(diphenylphosphorothioyl)-1H-indole and product, and was purified by HPLC to provide N-benzyl-3-(diphenylphosphorothioyl)-1H-indole-1-carboxamide. 1H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 4.46 (d, \(J=5.9\) Hz, 2 H), 7.13 (ddd, \(J=8.1, 7.0, 1.1\) Hz, 1 H), 7.29 (m, 3 H), 7.35 (m, 4 H), 7.55 (m, 4 H), 7.61 (m, 2 H), 7.81 (m, 4 H), 7.96 (d, \(J=5.5\) Hz, 1 H), 8.25 (dt, \(J=8.3, 0.8\) Hz, 1 H), 9.11 (t, \(J=5.9\) Hz, 1 H); LC/MS: Method 1, retention time 7.169 minutes; HRMS (m/z) calculated for C\(_{28}\)H\(_{24}\)N\(_2\)OPS\(^+\) (M+H\(^+\)) + 467.1341, found 467.1341.

**EXAMPLE 25**

[0152] The synthesis of 3-(diphenylphosphorothioyl)-N-(4-fluorobenzyl)-1H-indole-1-carboxamide is described below.

![Chemical structure](image)

[0153] 4-Fluorobenzylamine was reacted with 3-(diphenylphosphorothioyl)-1H-indole according to General Procedure F, to produce 3-(diphenylphosphorothioyl)-N-(4-fluorobenzyl)-1H-indole-1-carboxamide. 1H NMR (400 MHz, DMSO-4) \(\delta\) ppm 4.45 (d, \(J=5.7\) Hz, 2 H), 7.15 (m, 3 H), 7.31 (m, 2 H), 7.40 (m, 2 H), 7.55 (m, 4 H), 7.62 (m, 2 H), 7.81 (m, 4 H), 7.96 (d, \(J=5.5\) Hz, 1 H), 8.25 (m, 1 H), 9.11 (t, \(J=5.8\) Hz, 1 H); LC/MS: Method 1, retention time 7.188 minutes; HRMS (m/z) calculated for C\(_{28}\)H\(_{24}\)FN\(_2\)OPS\(^+\) (M+H\(^+\)) + 485.1247, found 485.1237.

**EXAMPLE 26**

[0154] The synthesis of N-benzyl-3-(diphenylphosphorothioyl)-2-methyl-1H-indole-1-carboxamide is described below.
Benzylamine was reacted with 3-(diphenylphosphorothioyl)-2-methyl-1H-indole according to General Procedure F, to produce N-benzyl-3-(diphenylphosphorothioyl)-2-methyl-1H-indole-1-carboxamide. 1H NMR (400 MHz, DMSO-\textit{d}_6) δ ppm 2.11 (d, J=1.6 Hz, 3 H), 4.52 (d, J=5.9 Hz, 2 H), 6.51 (dt, J=8.1, 1.0 Hz, 1 H), 6.87 (ddd, J=8.2, 7.1, 1.1 Hz, 1 H), 7.15 (ddd, J=8.4, 7.2, 1.3 Hz, 1 H), 7.29 (m, 1 H), 7.38 (m, 4 H), 7.49 (m, 1 H), 7.55 (m, 4 H), 7.62 (m, 2 H), 7.85 (m, 4 H), 9.37 (t, J=5.9 Hz, 1 H); LC/MS: Method 1, retention time 7.090 minutes; HRMS (m/z) calculated for C_{29}H_{26}N_2OPS^+(M+H)^+ 481.1498, found 481.1499.

EXAMPLE 27

4-Fluorobenzylamine was reacted with 3-(diphenylphosphorothioyl)-2-methyl-1H-indole according to General Procedure F, to produce 3-(diphenylphosphorothioyl)-N-(4-fluorobenzyl)-2-methyl-1H-indole-1-carboxamide. 1H NMR (400 MHz, DMSO-\textit{i}^\text{V}) δ ppm 2.11 (s, 3 H), 4.51 (d, J=5.9 Hz, 2 H), 6.52 (d, J=8.0 Hz, 1 H), 6.88 (m, 1 H), 7.18 (m, 3 H),
7.46 (m, 3 H), 7.59 (m, 6 H), 7.85 (m, 4 H), 9.36 (t, J=5.9 Hz, 1 H); LC/MS: Method 1, retention time 7.107 minutes; HRMS (m/z) calculated for C_{29}H_{25}FN_{2}OPS^{+}(M+H)^{+} 499.1404.

EXAMPLE 28

The synthesis of 3-(diphenylphosphorothioyl)-N-(4-fluorobenzyl)-2-phenyl-lH-indole-l-carboxamide is described below.

4-Fluorobenzylamine was reacted with 3-(diphenylphosphorothioyl)-2-phenyl-lH-indole according to General Procedure F, to produce 3-(diphenylphosphorothioyl)-N-(4-fluorobenzyl)-2-phenyl-lH-indole-l-carboxamide. 1H NMR (400 MHz, DMSO-\(\alpha\)) \(\delta\) ppm 4.25 (d, J=6.1 Hz, 2 H), 6.98 (m, 8 H), 7.10 (m, 1 H), 7.19 (m, 2 H), 7.27 (m, 5 H), 7.37 (m, 2 H), 7.55 (dt, J=8.3, 0.7 Hz, 1 H), 7.73 (m, 4 H), 9.13 (t, J=6.0 Hz, 1 H); LC/MS: Method 1, retention time 7.345 minutes; HRMS (m/z) calculated for C_{34}H_{27}FN_{2}OPS^{+}(M+H)^{+} 561.1560, found 561.1559.

EXAMPLE 29

The synthesis of 3-(diphenylphosphorothioyl)-2-methylimidazo[l,2-a]pyridine is described below.
3-(Diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine (62 mg, 0.178 mmol) and 2-bromo-l-phenylethanone (75 mg, 0.377 mmol) were reacted according to General Procedure B, to produce 3-(diphenylphosphorothioyl)-2-methyl-1-(2-oxo-2-phenylethyl)imidazo[1,2-a]pyridin-1-ium, Br⁻ (85 mg, 0.155 mmol, 87 % yield). ¹H NMR (400 MHz, DMSO-d₄) δ ppm 1.62 (s, 3 H), 6.37 (s, 2 H), 7.66 (m, 7 H), 7.79 (m, 3 H), 7.91 (m, 4 H), 8.11 (dd, J=8.4, 1.4 Hz, 2 H), 8.18 (m, 1 H), 8.44 (m, 1 H), 8.76 (d, J=6.8 Hz, 1 H); LC/MS: Method 1, retention time 5.391 minutes; HRMS (m/z) calculated for C₂₉H₂₆N₂OPS⁺ (M)+ 467.1341, found 467.1346.

EXAMPLE 30

The synthesis of 1-cinnamyl-3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridin-1-ium, Br⁻ is described below.

3-(Diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine (62 mg, 0.178 mmol) and (E)-(3-bromoprop-1-enyl)benzene were reacted according to General Procedure B, to produce 1-cinnamyl-3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridin-1-ium, Br⁻. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.75 (d, J=1.4 Hz, 3 H), 5.28 (m, 2 H), 6.43 (m, 1 H), 6.86 (d, J=16.0 Hz, 1 H), 7.32 (m, 3 H), 7.44 (m, 2H), 7.59 (td, J=7.1, 1.3 Hz, 1 H), 7.68 (m, 4 H), 7.78 (m, 2 H), 7.91 (m, 4 H), 8.20 (ddd, J=9.2, 7.2, 1.2 Hz, 1 H), 8.48 (m, 1 H), 8.70 (m, 1 H); LC/MS: Method 1, retention time 5.744 minutes; HRMS (m/z) calculated for C₂₉H₂₆N₂OPS⁺ (M)+ 465.1549, found 453.1553.

EXAMPLE 31

The synthesis of 3-(diphenylphosphorothioyl)-2-methyl-1-phenethylimidazo[1,2-a]pyridin-1-ium, Br⁻ is described below.
[0165] 3-(Diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine and (2-bromoethyl)benzene were reacted according to General Procedure B, to produce 3-(diphenylphosphorothioyl)-2-methyl-1-phenethylimidazo[1,2-a]pyridin-1-ium \( \text{Br}^- \). 1H NMR (400 MHz, DMSO-4) \( \delta \) ppm 1.41 (d, \( J=1.4 \) Hz, 3 H), 3.07 (t, \( J=6.6 \) Hz, 2 H), 4.66 (t, \( J=6.8 \) Hz, 2 H), 7.11 (m, 2 H), 7.23 (m, 3 H), 7.49 (td, \( J=7.1, 1.3 \) Hz, 1 H), 7.66 (m, 4 H), 7.78 (m, 6 H), 8.04 (m, 1 H), 8.22 (m, 1 H), 8.65 (m, 1 H); LC/MS: Method 1, retention time: 5.180 minutes; HRMS (\( m/z \)) calculated for \( C_{28}H_{26}N_2PS^+(M)^+ \) 453.1549, found 453.1555.

EXAMPLE 32

[0166] The synthesis of 3-(diphenylphosphorothioyl)-2-methyl-1-(3-phenylpropyl)imidazo[1,2-a]pyridin-1-ium, TFA is described below.

[0167] 3-(Diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine and (3-bromopropyl)benzene were reacted according to General Procedure B, to produce and purified by reverse phase HPLC, 3-(diphenylphosphorothioyl)-2-methyl-1-(3-phenylpropyl)imidazo[1,2-a]pyridin-1-ium, TFA\(^-\). 1H NMR (400 MHz, DMSO-\( d_6 \) \( \delta \) ppm 1.65 (m, 3 H), 2.05 (qd, \( J=8.0, 7.7 \) Hz, 2 H), 2.71 (m, 2 H), 4.42 (t, \( J=7.7 \) Hz, 2 H), 7.17 (m, 5 H), 7.52 (tt, \( J=7.0, 0.6 \) Hz, 1 H), 7.64 (m, 4 H), 7.74 (m, 2 H), 7.83 (m, 4 H), 8.13 (m, 1 H), 8.41 (m, 1 H), 8.62 (d, \( J=7.0 \) Hz, 1 H); LC/MS: Method 1, retention time: 5.407 minutes; HRMS (\( m/z \)) calculated for \( C_{29}H_{29}N_2PS^+(M)^+ \) 467.1705, found 467.1709.
EXAMPLE 33

[0168] The synthesis of \( \text{1-benzyl-3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridin-1-ium} \), TFA is described below.

\[
\text{Ph}_2\text{P} \quad \text{N} \quad \text{S} \quad \text{Ph} \quad \text{Br} \quad \rightarrow \quad \text{Ph}_{\text{Ph}} \quad \text{P} \quad \text{S} \quad \text{Ph} \quad \text{Ph} \quad \text{N} \quad \text{S} \quad \text{Ph} \quad \text{Ph}
\]

3-Diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridine and (bromomethyl)benzene were reacted according to General Procedure B, to provide \( \text{1-Benzyl-3-(diphenylphosphorothioyl)-2-methylinmidazo[1,2-a]pyridin-1-ium} \), TFA-. \( \text{1H NMR} \) (400 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) ppm 1.64 (m, 3 H), 5.76 (m, 2 H), 7.30 (m, 2 H), 7.39 (m, 3 H), 7.60 (m, 1 H), 7.68 (m, 4 H), 7.77 (m, 2 H), 7.91 (m, 4 H), 8.19 (m, 1 H), 8.44 (m, 1 H), 8.70 (d, \( J=6.8 \) Hz, 1 H); \( \text{LC/MS: Method} \) 1, retention time: 5.160 minutes; \( \text{HRMS (m/z)} \) calculated for \( \text{C}_{27}\text{H}_{24}\text{N}_2\text{PS}^+(\text{M})^+ \) 439.1392, found 439.1398.

EXAMPLE 34

[0169] The synthesis of \( \text{1-benzyl-3-(diphenylphosphorothioyl)-2-methyl-1H-indole} \) is described below.

\[
\text{Ph}_2\text{P} \quad \text{Br} \quad \rightarrow \quad \text{Ph}_{\text{Ph}} \quad \text{P} \quad \text{S} \quad \text{Ph} \quad \text{Ph} \quad \text{N} \quad \text{S} \quad \text{Ph} \quad \text{Ph} \quad \text{H}
\]

[0170] General Procedure G: 3-(Diphenylphosphorothioyl)-2-methyl-1H-indole (40 mg, 0.115 mmol) and benzyl bromide (39.4 mg, 0.230 mmol) in DMF (2 ml) were treated with 95% sodium hydride (7.27 mg, 0.288 mmol) and stirred overnight. The reaction was quenched with careful addition of 1 ml of water, dried under a stream of nitrogen, and the residue was dissolved in DMSO, with slight amounts of MeOH, and then purified by reverse phase HPLC, to provide \( \text{1-benzyl-3-(diphenylphosphorothioyl)-2-methyl-1H-indole} \). \( \text{1H} \)
NMR (400 MHz, DMSO-**d**6) δ ppm 2.13 (m, 3 H), 5.53 (s, 2 H), 6.37 (d, J=8.0 Hz, 1 H), 6.80 (m, 1 H), 7.02 (m, 2 H), 7.07 (m, 1 H), 7.26 (m, 1 H), 7.34 (m, 2 H), 7.57 (m, 7 H), 7.84 (m, 4 H); LC/MS: Method 1, retention time: 7.308 minutes; HRMS (m/z) calculated for C_{28}H_{25}NPS^+(M+H)^+ 438.1440, found 439.1445.

**EXAMPLE 35**

[0171] The synthesis of 3-(diphenylphosphorothioyl)-2-methyl-l-phenethyl-lH-indole is described below.

![Synthesis of 3-(diphenylphosphorothioyl)-2-methyl-l-phenethyl-lH-indole](image)

[0172] 3-(Diphenylphosphorothioyl)-2-methyl-l-phenethyl-lH-indole was synthesized according to General Procedure G, from 3-(diphenylphosphorothioyl)-2-methyl-lH-indole and 2-bromoethylbenzene. 1H NMR (400 MHz, DMSO-4) δ ppm 1.74 (m, 3 H), 3.03 (m, 2 H), 4.43 (t, J=6.8 Hz, 2 H), 6.39 (d, J=8.0 Hz, 1 H), 6.81 (td, J=7.6, 1.0 Hz, 1 H), 7.05 (m, 2 H), 7.13 (m, 1 H), 7.26 (m, 3 H), 7.56 (m, 7 H), 7.76 (m, 4 H); LC/MS: Method 1, retention time: 7.393 minutes; HRMS (m/z) calculated for C_{29}H_{27}NPS^+(M+H)^+ 452.1596, found 452.1604.

**EXAMPLE 36**

[0173] The synthesis of 3-(diphenylphosphorothioyl)-2-methyl-l-(3-phenylpropyl)-lH-indole is described below.

![Synthesis of 3-(diphenylphosphorothioyl)-2-methyl-l-(3-phenylpropyl)-lH-indole](image)
3-(Diphenylphosphorothioyl)-2-methyl-l-(3-phenylpropyl)-lH-indole, was synthesized according to General Procedure G, from 3-(diphenylphosphorothioyl)-2-methyl-lH-indole and 3-bromopropylbenzene: 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.99 (qd, J=7.7, 7.5 Hz, 2 H), 2.13 (m, 3 H), 2.67 (m, 2 H), 4.21 (m, 2 H), 6.34 (d, J=8.0 Hz, 1 H), 6.77 (m, 1 H), 7.08 (m, 1 H), 7.24 (m, 5 H), 7.47 (dd, J=8.3, 1.1 Hz, 1 H), 7.56 (m, 6 H), 7.82 (m, 4 H); LC/MS: Method 1, retention time: 7.579 minutes; HRMS (m/z) calculated for C_{39}H_{30}NPS+ (M+H)+ 466.1753, found 466.1752.

EXAMPLE 37

The synthesis of 3-(diphenylphosphorothioyl)-2-methyl-l-(3-phenylpropyl)-lH-indole is described below.

[0176] 1-Cinnamyl-3-(diphenylphosphorothioyl)-2-methyl-lH-indole was synthesized according to General Procedure G, from 3-(diphenylphosphorothioyl)-2-methyl-lH-indole and 2-cinnamyl bromide. 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (d, 3 H), 5.04 (d, J=4.9 Hz, 2 H), 6.37 (m, 2 H), 6.44 (m, 1 H), 6.80 (m, 1 H), 7.10 (m, 1 H), 7.23 (m, 1 H), 7.31 (m, 2 H), 7.40 (m, 2 H), 7.57 (m, 7 H), 7.86 (m, 4 H); LC/MS: Method 1, retention time: 7.578 minutes.

EXAMPLE 38

The synthesis of 3-(diphenylphosphorothioyl)-2-methyl-l-(4-phenylbutyl)imidazo[l,2-a]pyridin-l-ium, Br is described below.
1H NMR (400 MHz, DMSO-$d_6$) δ ppm 1.73 (m, 7 H), 2.62 (m, 2 H), 4.43 (m, 2 H), 7.18 (m, 3 H), 7.28 (m, 2 H), 7.55 (td, $J$=7.0, 1.4 Hz, 1 H), 7.68 (m, 4 H), 7.78 (m, 2 H), 7.89 (m, 4 H), 8.15 (ddd, $J$=9.1, 7.1, 1.2 Hz, 1 H), 8.42 (dd, $J$=9.1, 1.1 Hz, 1 H), 8.64 (m, 1 H); LC/MS: Method 1, retention time 5.638 minutes; HRMS (m/z) calculated for $C_{30}H_{30}N_2P S^+$ (M) $+^+$ 481.1868, found 481.1871.

EXAMPLE 39

The synthesis of 3-(diphenylphosphorothioyl)-2-methyl-1-(5-phenylpentyl)imidazo[1,2-a]pyridin-1-ium, TFA$^-$ is set forth below.

1H NMR (400 MHz, DMSO-$d_6$) δ ppm 1.39 (m, 2 H), 1.61 (m, 2 H), 1.70 (s, 3 H), 1.76 (m, 2 H), 2.57 (t, $J$=7.4 Hz, 2 H), 4.39 (t, $J$=7.7 Hz, 2 H), 7.16 (m, 3 H), 7.26 (m, 2 H), 7.55 (m, 1 H), 7.68 (td, $J$=7.6, 3.5 Hz, 4 H), 7.78 (m, 2 H), 7.89 (ddd, $J$=14.7, 8.3, 1.3 Hz, 4 H), 8.15 (m, 1 H), 8.43 (m, 1 H), 8.65 (d, $J$=7.0 Hz, 1 H); LC/MS: Method 1, retention time 5.738 min; HRMS (m/z) calculated for $C_{23}H_{28}N_2P S^+$ (M) $+^+$ 495.2030, found 495.2033.
EXAMPLE 40

[0181] The synthesis of l-cinnamyl-3-(diphenylphosphorothioyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-ium, Br- is set forth below.

[0182] Step 1: Preparation of 2-(4-fluorophenyl)imidazo[1,2-a]pyridine. 2-Bromo-l-(4-fluorophenyl)ethanone (1.15 g, 5.31 mmol) and pyridin-2-amine (500 mg, 5.31 mmol) in ethanol (10 ml) were heated in a microwave vessel at 150 °C for 30 minutes. The reaction was cooled, concentrated, diluted with dichloromethane, and washed with saturated aqueous NaHCO₃. The organic layer was separated, dried (MgSO₄) and purified via flash silica gel column chromatography (0 to 100% EtOAc/DCM) to provide 2-(4-fluorophenyl)imidazo[1,2-a]pyridine (0.67 g, 3.2 mmol, 59% yield). 1H NMR (400 MHz, DMSO-⁶) δ ppm 1H NMR (400 MHz, DMSO-₆) δ ppm 6.90 (td, J = 6.7, 1.4 Hz, 1 H), 7.26 (m, 3 H), 7.57 (m, 1 H), 8.00 (m, 2 H), 8.38 (d, J = 0.8 Hz, 1 H), 8.52 (dt, J = 6.8, 1.2 Hz, 1 H); LC/MS: Method 2, retention time 2.624 minutes.

[0183] Step 2: Preparation of 3-(Diphenylphosphorothioyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridine. Chlorodiphenylphosphine (2.22 g, 10.1 mmol) was dissolved in toluene (2.5 ml) and treated with iodotrimethylsilane (1.37 ml, 10.1 mmol) under nitrogen at room temperature for 45 minutes. A solution of 2-(4-fluorophenyl)imidazo[1,2-a]pyridine (0.61 g, 2.9 mmol), triethylamine (2.40 ml, 17.3 mmol) in pyridine (2.5 ml) was added to this mixture at rt under nitrogen. The mixture was stirred for 7 hours and then treated with sulfur (0.369 g, 11.5 mmol) and stirred for another 16 hours. The reaction was
concentrated, diluted with toluene and then concentrated again in vacuo (X2). The residue was adsorbed onto silica gel and then purified by flash silica gel column chromatography (5 to 100% EtOAc/DCM) to provide 3-(diphenylphosphorothioyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridine (891 mg, 2.080 mmol, 72.3% yield). 1H NMR (400 MHz, chloroform-δ) δ ppm: 6.62 (m, 2 H), 6.75 (m, 1 H), 7.16 (m, 2 H), 7.24 (m, 4 H), 7.37 (ddd, J=7.8, 6.8, 1.2 Hz, 3 H), 7.71 (m, 5 H), 8.43 (d, J=7.0 Hz, 1 H); LC/MS: Method 2, retention time 3.544 minutes.

[0184] Final synthesis of 1-cinnamyl-3-(diphenylphosphorothioyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-l-i um, Br-.

3-(Diphenylphosphorothioyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridine and (E)-(3-bromoprop-1-enyl)benzene were reacted according to general procedure B to provide title compound. 1H NMR (400 MHz, chloroform-J) δ ppm: 5.18 (m, 1 H), 6.09 (dt, J=15.8, 6.4 Hz, 1 H), 6.44 (d, J=15.8 Hz, 1 H), 6.79 (t, J=8.7 Hz, 2 H), 7.25 (m, 1 H), 7.34 (m, 9 H), 7.45 (m, 2 H), 7.55 (m, 2 H), 7.99 (m, 5 H), 8.16 (m, 1 H), 8.16 (dd, J=9.1, 1.1 Hz, 1 H), 5.18 (m, 1 H); LC/MS: Method 1, retention time 5.732 minutes; HRMS (m/z) calculated for C_{34}H_{27}FN_{2}PS^{+}(M)^{+} 545.1615, found 545.1617.

[0185] The following compounds were prepared by General procedure B and then purified by flash silica gel chromatography or reverse phase HPLC. The synthesis of (E)-1-(3-(4-chlorophenyl)allyl)-3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridin-l-ium, TFA<sup>-</sup> is set forth below.
1H NMR (400 MHz, DMSO-d6) δ ppm 1.75 (d, 3 H), 5.28 (m, 2 H), 6.47 (m, 1 H), 6.84 (d, J=16.0 Hz, 1 H), 7.41 (m, 2 H), 7.47 (m, 2 H), 7.59 (td, J=7.1, 1.2 Hz, 1 H), 7.69 (m, 4 H), 7.78 (m, 2 H), 7.91 (m, 4 H), 8.20 (ddd, J=9.2, 7.2, 1.2 Hz, 1 H), 8.47 (m, 1 H), 8.70 (m, 1 H); LC/MS: Method 1, retention time 5.503 minutes; HRMS (m/z) calculated for C$_{29}$H$_{25}$ClN$_{2}$P$_{2}$S$_{2}$+ (M)$^{+}$ 499.1168, found 499.1166.

EXAMPLE 42

The synthesis of (E)-3-(diphenylphosphorothioyl)-(3-(4-fluorophenyl)allyl)-2-methylimidazo[1,2-a]pyridin-1-ium, TFA$^-$ is provided below.

LC/MS: Method 1, retention time 5.313 minutes; HRMS (m/z) calculated for C$_{20}$H$_{25}$F$_{2}$N$_{2}$P$_{2}$S$_{2}$+ (M)$^{+}$ 483.1466, found 483.1465.

EXAMPLE 43

The synthesis of (E)-3-(diphenylphosphorothioyl)-1-(3-(4-fluorophenyl)allyl)-2-methylimidazo[1,2-a]pyridin-1-ium, TFA$^-$ is provided below.
[0190] 1H NMR (400 MHz, DMSCW_6) δ ppm 1.75 (d, J=1.4 Hz, 3 H), 3.75 (s, 3 H), 5.27 (m, 2 H), 5.75 (s, 1 H), 6.86 (m, 2 H), 7.01 (m, 2 H), 7.26 (m, 1 H), 7.59 (m, 1 H), 7.69 (m, 4 H), 7.78 (td, J=7.6, 1.6 Hz, 2 H), 7.91 (ddd, J=14.7, 8.4, 1.4 Hz, 4 H), 8.20 (m, 1 H), 8.48 (d, J=9.2 Hz, 1 H), 8.70 (m, 1 H); LC/MS: Method 1, retention time 5.305 minutes; HRMS (m/z) calculated for C_{30}H_{28}N_{2}OPS^+ (M)^+ 495.1661, found 495.1661.

EXAMPLE 44

[0191] The synthesis of (E)-1-(3-(2-chlorophenyl)allyl)-3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridin-l-ium, TFA^- is provided below.

[0192] 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.76 (d, J=1.4 Hz, 3 H), 5.39 (m, 2 H), 6.46 (dt, J=15.8, 6.2 Hz, 1 H), 7.10 (d, J=16.0 Hz, 1 H), 7.33 (m, 2 H), 7.46 (m, 1 H), 7.65 (m, 6 H), 7.78 (m, 2 H), 7.91 (m, 4 H), 8.21 (ddd, J=8.9, 7.3, 1.2 Hz, 1 H), 8.50 (dd, J=9.2, 1.2 Hz, 1 H), 8.70 (m, 1 H); LC/MS: Method 1, retention time 5.440 minutes; HRMS (m/z) calculated for C_{29}H_{27}Cl_{2}N_{2}PS^+ (M)^+ 499.1168, found 499.1170.

EXAMPLE 45

[0193] The synthesis of (E)-1-(3-(4-bromophenyl)allyl)-3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridin-l-ium, TFA^- is set forth below.
[0194] 1H NMR (400 MHz, DMSCW₆) δ ppm 1.74 (d, J=1.4 Hz, 3 H), 5.26 (dd, J=6.1, 1.2 Hz, 2 H), 6.47 (m, 1 H), 6.81 (d, J=16.2 Hz, 1 H), 7.40 (d, J=8.6 Hz, 2 H), 7.57 (m, 3 H), 7.68 (m, 4 H), 7.78 (m, 2 H), 7.90 (m, 4 H), 8.19 (m, 1 H), 8.46 (dd, J=9.2, 1.2 Hz, 1 H), 8.70 (dd, J=6.9, 1.1 Hz, 1 H); LC/MS: Method 1, retention time 5.555 minutes; HRMS (m/z) calculated for C₂₉H₂₅BrN₂PS⁺(M)+543.0660, found 543.0657.

EXAMPLE 46

[0195] The synthesis of (E)-1-(3-(3-chlorophenyl)allyl)-3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridin-1-ium, TFA⁻ is provided below.

[0196] 1H NMR (400 MHz, DMSO-d⁶) δ ppm 1.75 (m, 3 H), 5.29 (m, 2 H), 6.53 (dt, J=15.9, 6.1 Hz, 1 H), 6.82 (d, J=15.8 Hz, 1 H), 7.36 (m, 3 H), 7.54 (m, 1 H), 7.60 (m, 1 H), 7.69 (m, 4 H), 7.78 (m, 2 H), 7.90 (m, 4 H), 8.20 (m, 1 H), 8.46 (m, 1 H), 8.71 (d, J=7.0 Hz, 1 H); LC/MS: Method 1, retention time 5.520 minutes; HRMS (m/z) calculated for C₂₉H₂₅C₁N₂PS⁺(M)+499.168, found 499.163.

EXAMPLE 47

[0197] The synthesis of (E)-3-(diphenylphosphorothioyl)-2-methyl-1-(3-(4'-CF₃CF(trifluoromethyl)phenyl)allyl)imidazo[1,2-a]pyridin-1-ium, TFA⁻ is set forth below.
[0198] 1H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.75 (d, J=1.4 Hz, 3 H), 5.32 (dd, J=6.7, 0.9 Hz, 2 H), 6.62 (dt, J=16.1, 6.0 Hz, 1 H), 6.92 (d, J=16.0 Hz, 1 H), 7.59 (td, J=7.0, 1.2 Hz, 1 H), 7.68 (m, 8 H), 7.78 (m, 2 H), 7.91 (m, 4 H), 8.20 (ddd, J=8.9, 7.3, 1.2 Hz, 1 H), 8.47 (dd, J=9.2, 1.0 Hz, 1 H), 8.71 (m, 1 H); LC/MS: Method 1, retention time 5.592 minutes; HRMS (m/z) calculated for C$_3$H$_2$SF$_3$N$_2$PS$^+$ (M)$^+$ 533.1427, found 533.1426.

EXAMPLE 48

[0199] The synthesis of (E)-l-(3-(3-bromophenyl)allyl)-3-(diphenylphosphorothioyl)-2-methylimidazo[1,2-a]pyridin-1-ium, TFA$^-$ is provided below.

[0200] 1H NMR (400 MHz, chloroform-d) δ ppm 1.79 (d, J=0.4 Hz, 3 H), 5.35 (m, 2 H), 6.20 (m, 1 H), 6.57 (d, J=15.1 Hz, 1 H), 7.18 (t, J=7.7 Hz, 1 H), 7.26 (m, 2 H), 7.40 (m, 1 H), 7.47 (t, J=1.7 Hz, 1 H), 7.63 (m, 6 H), 7.96 (m, 5 H), 8.13 (m, 1 H), 8.81 (d, J=6.8 Hz, 1 H); LC/MS: Method 1, retention time 5.552 minutes; HRMS (m/z) calculated for C$_{29}$H$_{23}$BrN$_2$PS$^+$ (M)$^+$ 543.0660, found 543.0662.
EXAMPLE 49

[0201] The synthesis of (E)-l-(3-(3-bromo-4-fluorophenyl)allyl)-3-
(diphenylphosphorothioyl)-2-methylimidazo[l,2-a]pyridin-l-ium, TFA\(^-\) is set forth below.

![Chemical structure](image)

[0202] \( ^1\)H NMR (400 MHz, chloroform-\(\delta\) ppm 1.79 (d, \(J=1.4\) Hz, 3 H), 5.35 (m, 2 H),
6.14 (m, 1 H), 6.58 (d, \(J=15.8\) Hz, 1 H), 7.07 (t, \(J=8.3\) Hz, 1 H), 7.27 (m, 2 H), 7.53 (dd,
\(J=6.6, 2.2\) Hz, 1 H), 7.59 (m, 4 H), 7.67 (m, 2 H), 7.96 (m, 5 H), 8.13 (d, \(J=9.2\) Hz, 1 H), 8.80
(d, \(J=6.7\) Hz, 1 H); LC/MS: Method 1, retention time 5.566 minutes; HRMS (m/z) calculated for
\(C_{29}H_{24}BrF_{2}N_{2}PS^+ (M)^+\) 561.0564, found 561.0565.

EXAMPLE 50

[0203] The synthesis of (E)-3-(diphenylphosphorothioyl)-2-methyl-l-(3-(naphthalen-2-
yl)allyl)imidazo[l,2-a]pyridin-l-ium, Br\(^-\) is provided below.

![Chemical structure](image)

[0204] LC/MS: Method 1, retention time 5.633 minutes; HRMS (m/z) calculated for
\(C_{33}H_{28}N_{2}PS^+ (M)^+\), 515.1712 found 515.1706.
EXAMPLE 51

[0205] In the following example, measurement of the inhibition of intracellular calcium stimulation of cells *in vitro*, after treating with one or more NPSAs of the present invention, using an intracellular calcium assay, is disclosed.

[0206] Intracellular calcium was measured using a BD PBX NW calcium assay kit (BD Bioscience, Rockville, MD). A Chinese hamster ovary cell line (CHO) stably expressing the NPSR (CHO-NPSR) was generated using standard tissue culture methods for CHO cells known in the art. The cells were maintained in F12 medium containing 10% FBS, 100 units/ml Penicillin, 100 μg/ml Streptomycin, and 200 μg/ml Geneticin (Invitrogen, Carlsbad, CA) at 37 °C, 5% CO₂. Cells were seeded at 3 μl/well with 1500 cells in black, tissue culture treated, clear bottom 1536-well plates (Greiner Bio-One, Monroe, NC). After overnight incubation at 37 °C 5% C0₂, cells were loaded with 3 μl of the calcium dye prepared as manufacture's instruction and incubated for another 1 hour. 23 nl of test compounds prepared in DMSO were then added using a pintool station (Kalypsys, San Diego, CA). Fluorescence was monitored over time as cells were challenged with EC₈₀ of agonists (80 nM NPS for NPSR or 1 nM vasopressin for Vasopressin Vlb receptor) in a FDSS-7000 detector (Hamamatsu, Bridgewater, NJ). The basal fluorescence signal was first recorded for 10 seconds at 1 Hz, followed by addition of 2 μl agonist prepared in HBSS buffer supplemented with 0.1% BSA, and the antagonist response of compounds was recorded for another 170 seconds. The CCD binning was set to 2x2. The time-course fluorescence responses were expressed in terms of fluorescent change over background. The maximal fluorescent response was exported into a text file using the instrument's software data export utility. Concentration-response curves were fitted and EC₅₀/IC₅₀ were calculated with the GraphPad Prism® software (GraphPad, San Diego, CA), and are shown in Figure 1.

EXAMPLE 52

[0207] In the following example, measurement of the inhibition of cyclic AMP release in CHO-NPSR cells *in vitro*, after treating with one or more NPSAs of the present invention, using a cAMP assay, is disclosed.

[0208] Intracellular cAMP level was measured using LANCE cAMP detection kit (Perkin Elmer, Waltham, MA). After overnight incubation at 37 °C 5% CO₂, CHO-NPSR cells were
seeded at 4 µi/well with 2000 cells in white, tissue culture treated 1536-well plates. The cells were then treated with the addition of 1µi of stimulation buffer (IX PBS buffer, 0.1% BSA, 0.05% Tween-20, 500 µM Ro 20-1724 (Sigma-Aldrich), EC80 of NPS) to each well, and then the cells were incubated at 37 °C, 5 % CO₂ for 30 minutes. 1.25 µi of D2 conjugated cAMP, and 1 µi of cryptate conjugated anti-cAMP antibody were then added to the wells. D2 conjugated cAMP and cryptate conjugated anti-cAMP antibody were both prepared in cell lysis buffer according to the manufacturer's instructions. After 30 minutes, plates were then read in ViewLux plate reader (Perkin Elmer, Waltham, MA) using the TRF detection mode optimized for HTRF.

[0209] About 23 nl of each of the NPSAs of the present invention, were added to each well by a pintool station, followed by addition of 1 µi stimulation buffer (IX HBSS buffer, 0.1% BSA, 5 mM HEPES, 500 µM RO-201724, 1.5% Alexa-647 conjugated anti-cAMP antibody stock, 100 nM NPS) by a BioRAPTR flying reagent dispenser (Beckman Coulter, Fullerton, CA). Cells were then incubated at 37 °C for 1 hour and 1 µl of detection reagent (IX detection buffer provided by the manufacturer, 1% TritonX-100, biotin labeled cAMP 1:250 dilution, Eu-W8044 1:750 dilution) were added. After 1 hour incubation at room temperature, plates were measured using the ViewLux ultraHTS microplate imager (Perkin Elmer) under LANCE setting (Figure 2).

EXAMPLE 53

[0210] In the following example, a competition binding assay for measurement of the inhibition of binding of radiolabeled NPS to NPS receptors after treatment with one or more NPSAs of the present invention, is disclosed.

[0211] Y¹⁰-NPS labeled with ^1²^5I was obtained from NEN Perkin Elmer (Boston, MA). In the competition binding assay, increasing concentrations of unlabeled human NPS or NPSAs were used to compete with 0.15nM [¹²⁵I]Y¹⁰-NPS. Non-specific binding was determined in the presence of 1 µM unlabeled NPS. CHO-NPSR cells were first seeded into 24-well plates and cultured until reaching about 95% confluence. Cells were then washed once with 1 ml PBS and incubated with radioligand with, or without compounds, in DMEM medium containing 0.1% bovine serine albumin, at room temperature for about 90 minutes. Cells were washed twice with ice-cold PBS and lysed with 0.5ml IN NaOH. Bound
radioactivity was counted in a gamma counter. Data from duplicate were analyzed using
GraphPad Prism (GraphPad, San Diego, CA), and the results are shown in Figure 3.

[0212] All references, including publications, patent applications, and patents, cited
herein are hereby incorporated by reference to the same extent as if each reference were
individually and specifically indicated to be incorporated by reference and were set forth in
its entirety herein.

[0213] The use of the terms "a" and "an" and "the" and similar referents in the context of
describing the invention (especially in the context of the following claims) are to be
construed to cover both the singular and the plural, unless otherwise indicated herein or
clearly contradicted by context. The terms "comprising," "having," "including," and
"containing" are to be construed as open-ended terms (i.e., meaning "including, but not
limited to,"") unless otherwise noted. Recitation of ranges of values herein are merely
intended to serve as a shorthand method of referring individually to each separate value
falling within the range, unless otherwise indicated herein, and each separate value is
incorporated into the specification as if it were individually recited herein. All methods
described herein can be performed in any suitable order unless otherwise indicated herein or
otherwise clearly contradicted by context. The use of any and all examples, or exemplary
language (e.g., "such as") provided herein, is intended merely to better illuminate the
invention and does not pose a limitation on the scope of the invention unless otherwise
claimed. No language in the specification should be construed as indicating any non-claimed
element as essential to the practice of the invention.

[0214] Preferred embodiments of this invention are described herein, including the best
mode known to the inventors for carrying out the invention. Variations of those preferred
embodiments may become apparent to those of ordinary skill in the art upon reading the
foregoing description. The inventors expect skilled artisans to employ such variations as
appropriate, and the inventors intend for the invention to be practiced otherwise than as
specifically described herein. Accordingly, this invention includes all modifications and
equivalents of the subject matter recited in the claims appended hereto as permitted by
applicable law. Moreover, any combination of the above-described elements in all possible
variations thereof is encompassed by the invention unless otherwise indicated herein or
otherwise clearly contradicted by context.
CLAIM(S):

1. A compound of General Formula I:

or a salt, solvate, or stereoisomer thereof;

wherein R1 and R2 are the same or different moieties and each are selected from the
group consisting of: H, C1-C6 alkyl, C6-Ci4 aryl C1-C6 alkyl, heterocyclyl C1-C6 alkyl, C1-C6
alkylamino C1-C6 alkyl, C1-C6 dialkylamino C1-C6 alkyl, C6-Ci4 aryl C1-C6 alkylamino C1-C6
alkyl, C1-C6 alkylthio C1-C6 alkyl, C6-Ci4 arylthio, C6-Ci4 aryl C1-C6 alkylthio d-C6 alkyl,
C1-C6 alkylsulfonyl C1-C6 alkyl, C6-Ci4 arylsulfonyl C1-C6 alkyl, C6-Ci4 arylsulfanyl C1-C6
alkyl, hydroxy C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkoxy C1-C6 alkyl, C3-Ci8 cycloalkyl,
heterocyclyl, C6-Ci4 aryl, C6-Ci4 aryl C1-C6alkyl, C1-C6 alkylamino, di C1-C6 alkylamino, di
Ci-C6 alkylamino Ci-C6 alkyl, thio Ci-C6 alkyl, thio C2-C6 alkenyl, thio C2-C6 alkynyl, C6-
Ci4 arlyoxy, C2-C6 acyloxy, thio C2-C6 acyl, amido, sulphonamido, Ci-C6 alkyl, C2-C6
alkenyl, and C2-C6 alkynyl, wherein each of alkyl, aryl, or heterocyclyl moiety may be
unsubstituted or substituted with one or more substituents selected from the group consisting
of halo, hydroxy, carboxy, phosphoryl, phosphonyl, phosphono Ci-C6 alkyl, carboxy Ci-C6
alkyl, dicarboxy Ci-C6 alkyl, dicarboxy halo Ci-C6 alkyl, sulfonyl, cyano, nitro, alkoxy,
alkylthio, acyl, acyloxy, thioacyl, acylthio, aryloxy, amino, alkylamino, dialkylamino,
trialkylamino, guanidine, aldehydo, ureido, and aminocarbonyl;

wherein R3 is selected from the group consisting of thio, oxy, and hydroxyl;

wherein X is selected from the group consisting of a phosphorous atom and a carbon
atom;
wherein when \( X = C \), \( R_3 = \text{hydroxyl} \);

when \( X = P \), \( R_3 \) is selected from the group consisting of a sulfur atom and an oxygen atom; and

wherein \( Y \) is selected from the group consisting of a nitrogen atom and a carbon atom.

2. The compound, salt, solvate, or stereoisomer of claim 1, wherein \( R_i \) is selected from the group consisting of: \( H \), \( \text{Ci-C}_6 \text{alkyl} \), \( \text{C}_6\text{-Cl}_4 \text{aryl} \), \( \text{C}_6\text{-Ci}_4 \text{aryl} \text{Ci-C}_6 \text{alkyl} \), aryl \( \text{Ci-C}_6 \text{alkyl} \), aryloxy, \( \text{Ci-C}_6 \text{alkylamino} \), \( \text{C}_6\text{-Cl}_4 \text{aryl} \text{Ci-C}_6 \text{alkenyl} \), \( \text{C}_6\text{-Cl}_4 \text{aryl} \text{Ci-C}_6 \text{alkylamino alkoxy} \), and \( \text{C}_6\text{-C}_4 \text{aryl} \text{Ci-C}_6 \text{alkoxy} \);

wherein each of alkyl, aryl, or heterocyclyl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxy, and carboxy;

wherein \( R_2 \) is selected from the group consisting of \( H \), \( \text{Ci-C}_6 \text{alkyl} \), \( \text{C}_6\text{-Cl}_4 \text{aryl} \), and \( \text{C}_6\text{-C}_4 \text{aryl} \text{Ci-C}_6 \text{alkyl} \);

wherein each of alkyl, aryl, or heterocyclyl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxy, and carboxy;

wherein \( R_3 \) is selected from the group consisting of thio, oxy, and hydroxyl;

wherein \( X \) is selected from the group consisting of a phosphorous atom and a carbon atom;

wherein when \( X = C \), \( R_3 = \text{OH} \);

wherein when \( X = P \), \( R_3 \) is selected from the group consisting of a sulfur atom and an oxygen atom; and

wherein \( Y \) is selected from the group consisting of a nitrogen atom and a carbon atom.

3. The compound, salt, solvate, or stereoisomer of either of claims 1 or 2, wherein \( R_i \) is selected from the group consisting of: \( H \), \( \text{Ci-C}_6 \text{alkyl} \), \( \text{C}_6\text{-Cl}_4 \text{aryl} \), \( \text{C}_6\text{-C}_4 \text{aryl} \text{Ci-C}_6 \text{alkyl} \),
4. The compound, salt, solvate, or stereoisomer of any one of claims 1-3, wherein the aryl, or heterocyclyl moiety is substituted with one or more fluoro groups.

5. A compound having the following General Formula I:

wherein \( R_1 \) and \( R_2 \) are the same or different moieties and each comprise a hydrocarbon group which can be optionally substituted, \( R_3 \) is either S, O, or OH, and X is either a phosphate atom or a carbon atom, wherein when \( X=C \), \( R_3=\text{OH} \); and when \( X=P \), \( R_3=S, \text{ or } O \), and wherein Y is either N or C, and pharmaceutically acceptable salts, solvates or stereoisomers thereof.

6. The compound, salt, solvate, or stereoisomer of any one of claims 1-5, wherein \( R_1 \) is selected from the group consisting of: H, C\(_6\)-alkyl, C\(_6\)-aryl, C\(_6\)-aryl C\(_6\)-alkyl and C\(_6\)-aryl C\(_6\)-alkenyl;

wherein the aryl moiety is substituted with one or more halo groups;

wherein \( R_2 \) is selected from the group consisting of: H, C\(_6\)-alkyl and C\(_6\)-aryl;

wherein \( R_3=S \);
wherein X=P; and

wherein Y=N.

7. The compound, salt, solvate, or stereoisomer of any one of claims 1-6, wherein \( R_1 \) is selected from the group consisting of: H, Ci-C\(_6\) alkyl, C\(_6\)-Ci\(_4\) aryl, and C\(_6\)-Ci\(_4\) aryl Ci-C\(_6\) alkyl;

wherein \( R_2 \) is selected from the group consisting of: H, Ci-C\(_6\) alkyl and C\(_6\)-Ci\(_4\) aryl;

wherein \( R_3 = S \);

wherein X=P; and

wherein Y=N.

8. The compound, salt, solvate, or stereoisomer of any one of claims 1-7, wherein \( R_1 \) is selected from the group consisting of: H, Ci-C\(_6\) alkyl, C\(_6\)-Ci\(_4\) aryl, and C\(_6\)-Ci\(_4\) aryl Ci-C\(_6\) alkyl;

wherein \( R_2 \) is selected from the group consisting of: H, and C\(_1\)-Ci\(_6\) alkyl;

wherein \( R_3 = S \);

wherein X=P; and

wherein Y=N.

9. The compound, salt, solvate, or stereoisomer of any one of claims 1-8, wherein the compound is one of the following:

![Example 1](image-url)
Example 2

Example 3

Example 6

Example 7

Example 8
Example 9

Example 10

Example 11

Example 12

Example 13
Example 14

Example 15

Example 16

Example 17

Example 18
Example 19

Example 20

Example 21

Example 22

Example 23
Example 24

Example 25

Example 26
Example 27

![Chemical Structure 27]

Example 28

![Chemical Structure 28]

Example 29

![Chemical Structure 29]
Example 30

Example 31

Example 32

Example 33
Example 34

Example 35

Example 36

Example 37
Example 38

Example 39

Example 40
Example 41

Example 42

Example 43
Example 44

Example 45

Example 46
Example 47

Example 48

Example 49

; and
10. A pharmaceutical composition comprising a compound, salt, solvate, or stereoisomer of any one of claims 1-9, and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition comprising a compound, salt, solvate, or stereoisomer of any one of claims 1-9, and at least one other compound, salt, solvate, or stereoisomer thereof, suitable for use in treating a neuropsychiatric disorder.

12. The pharmaceutical composition of claim 11, wherein the compound, salt, solvate, or stereoisomer suitable for use in treating a neuropsychiatric disorder is selected from the group consisting of the following drug classes: antipsychotics, antidepressants and anxiolytics.

13. A method of treating a neuropsychiatric disorder in a subject comprising administering a therapeutically effective amount of a compound, salt, solvate, or stereoisomer of any one of claims 1-9.

14. The method of treating a neuropsychiatric disorder of claim 13, wherein the neuropsychiatric disorder being treated comprises pain, sleep, mood, anxiety, eating and addictive disorders.

15. The method of claim 14, wherein the anxiety disorder being treated is selected from the group consisting of: panic disorder, social phobia and obsessive-compulsive disorder.

16. The method of claim 14, wherein the eating disorders being treated are selected from the group consisting of: anorexia nervosa and bulimia.
17. The method of claim 14, wherein the addictive disorders being treated are selected from the group consisting of: alcohol addiction, tobacco addiction, nicotine addiction, and intoxication and inhalation disorders associated with alcohol, tobacco and nicotine addiction.

18. A method of treatment of a Neuropeptide S receptor related disorder in a subject comprising administering a therapeutically effective amount of a compound, salt, solvate, or stereoisomer of any one of claims 1-9.

19. A method of binding a Neuropeptide S receptor in a host cell comprising contacting the Neuropeptide S receptor with an effective amount of a compound, salt, solvate, or stereoisomer of any one of claims 1-9.

20. A pharmaceutical composition comprising a compound, salt, solvate, or stereoisomer of any one of claims 1-9, wherein the composition includes a pharmacologically and physiologically acceptable carrier, in an amount effective for use in a medicament, preferably for use as a medicament for treating a neuropsychiatric disorder in a subject, preferably wherein the neuropsychiatric disorder comprises pain, sleep, mood, anxiety, eating and addictive disorders, or for use as a medicament for treating an anxiety disorder, preferably wherein the anxiety disorders are selected from the group consisting of: panic disorder, social phobia and obsessive-compulsive disorder, or for use as a medicament for treating an eating disorder, preferably wherein the eating disorders are selected from the group consisting of: anorexia nervosa and bulimia, or for use as a medicament for treating an addictive disorder, preferably wherein the addictive disorders are selected from the group consisting of: alcohol addiction, tobacco addiction, nicotine addiction, and intoxication and inhalation disorders associated with alcohol, tobacco and nicotine addiction, when administered to the subject in an effective amount.

21. The pharmaceutical composition of claim 20, wherein the therapeutically effective amount of the compound, salt, solvate, or stereoisomer of any one of claims 1-6 administered to the subject is in a range of between about 0.001 mg/kg/day to about 1000 mg/kg/day, preferably, at least about 0.01 mg/kg/day to about 100 mg/kg/day, more preferably, at least about 0.1 mg/kg/day to about 10 mg/kg/day.
FIGURE 2.
FIGURE 3.

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**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/US2011/034276

**A. CLASSIFICATION OF SUBJECT MATTER**

C07D 209/08 C07D 209/42

**CLASSIFICATION**

**INV.** C07D209/08 C07D209/42 C07 F9/547 C07 F9/553

**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D C07 F

**DOCUMENTATION SEARCHED**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**Electronic data base consulted during the international search (name of data base and, where practical, search terms used)**

EPO-Internal, CHEM ABS Data, BEI LSTEI N Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>X</td>
<td>WO 2004/067529 AI (LILLY CO ELI [US]; BELL MI CHAEL GREGORY [US]; GAVARDI NAS KONSTANTINOS) 12 Aug 2004 (2004-08-12) page 228; claim 1 page 237; claim 42</td>
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<td>A</td>
<td>WO 02/44120 AI (KAROBILO AB [SE]; GILLENER MI KAEL [SE]; HAGBERG LARS [SE]; KOCH EVA [SE]) 6 June 2002 (2002-06-06) page 46 - page 48; examples 47-51</td>
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<td>A</td>
<td>WO 2009/156072 AI (BAYER SCHERING PHARMA AG [DE]; KLOKHOFOF PETER [DE]; BRUENS ASTRI D [DE];) 30 December 2009 (2009-12-30) page 462; claim 1</td>
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**X** Further documents are listed in the continuation of Box C. **X** See patent family annex.

- **"A"** document defining the general state of the art which is not considered to be of particular relevance
- **"E"** earlier document but published on or after the international filing date
- **"L"** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **"O"** document referring to an oral disclosure, use, exhibition or other means
- **"P"** document published prior to the international filing date but later than the priority date claimed

**Date of the actual completion of the international search**

30 June 2011

**Date of mailing of the international search report**

13/07/2011

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

**Authorized officer**

Jeanjean Fabien
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