

Substituted Enaminones, their Derivatives and Uses Thereof

This application claims the benefit of U.S. Provisional Application No. 60/569,465, filed May 6, 2004, the subject matter of which is incorporated herein in its entirety.

5 Field of the Invention

This invention is in the field of medicinal chemistry. In particular, the invention relates to substituted enaminones and their derivatives and the discovery that these compounds modulate the effect of γ -aminobutyric acid (GABA) on the GABA_A receptor complex in a therapeutically relevant fashion and may be used to ameliorate CNS disorders amenable to modulation of the
10 GABA_A receptor complex.

Background of the Invention

GABA is the most abundant inhibitory neurotransmitter in the mammalian brain. GABA controls brain excitability by exerting inhibitory functions on neuronal membranes by altering their permeability to specific ions. Binding of GABA to the GABA_A-type (GABA_A) receptor
15 increases the permeability of neuronal membranes to chloride ions (Cl⁻). In most neurons the relative Cl⁻ ion concentration is greater outside than inside the membrane. Thus, selective permeability to Cl⁻ initiated by GABA binding forces Cl⁻ into the cell. The majority of fast inhibitory synaptic transmission is a result of GABA binding to the GABA_A receptors. GABA_A receptors are ubiquitously expressed throughout the CNS with almost all neurons staining for
20 their presence. The GABA_A receptor is a hetero-pentameric protein structure of the nicotinic acetylcholine receptor superfamily. Native GABA_A receptors are formed from at least 19 related subunits. The subunits are grouped into α , β , δ , ϵ , π , and ρ families. The most prevalent combination of GABA_A receptors is a stoichiometric combination of the 2 x α , 2 x β , and 1 x γ subunits, with the remaining subunits relegated to substituting for the γ subunit during specific
25 development expression or in highly specific brain region localization. The adult brain predominately expresses the $\alpha_1\beta_2\gamma_2$ subunit combination (60%) with the $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_n\gamma_2$ subunits comprising the majority (35%) of the remaining receptors. The relative effects of GABA are influenced by the GABA_A receptor subunit expressed in a specific brain region or neuronal circuit.

30 The neurophysiological effects of GABA result from a conformational change that occurs when GABA binds to the GABA_A receptor. The GABA_A receptor and the associated ion channel complex (GRC) recognize many compounds that allosterically enhance the ability of GABA to

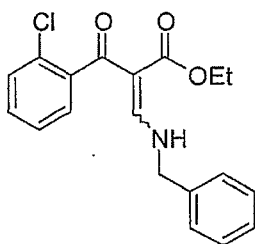
bind to the GABA_A receptor. The allosteric modulators have distinct sites on the GRC. These sites are separate and unique from the site that recognizes GABA. The most widely studied and characterized class of allosteric modulator of the GRC are those that interact with the benzodiazepine(BZ)-site.

5 Alternative sites for modulating the GRC have been described. For example, neuroactive steroids are non-hormonal steroids that bind and functionally modulate the GRC. The current role of neuroactive steroids in GABA_A receptor pharmacology is supported by overwhelming evidence. Electrophysiological and biochemical techniques have confirmed the capacity of neuroactive steroids to allosterically modulate the GRC through a unique site of action.
10 Experimentally, neuroactive steroids exhibit a pharmacological profile similar, but not identical, to the benzodiazepines. Neuroactive steroids have anxiolytic, anticonvulsant, and sedative-hypnotic properties.

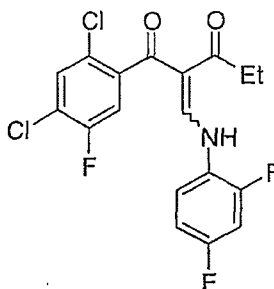
It is well-documented that the GRC is responsible for the mediation of anxiety, seizure activity, and sedation. Thus, GABA and drugs that act like GABA or facilitate the effects of
15 GABA (e.g., the therapeutically useful barbiturates and benzodiazepines (BZs) such as Valium) produce their therapeutically useful effects by interacting with specific modulatory sites on the GRC receptor complex.

Related Art

Sayyed, I. A. et al. (Synthetic Comm. 2000, 30(14), 2533) disclose the synthesis of the
20 following compound as a synthetic intermediate:



Palomo Coll, A. in Spanish patent 2049640 (1994) discloses the following compound as
a synthetic intermediate:



Summary of the Invention

The present invention is related to the discovery that certain substituted enaminones represented by Formula I act as enhancers of GABA-facilitated Cl^- flux mediated through the GABA_A receptor complex (GRC).

5 The invention is related to treating disorders responsive to enhancement of GABA action on GABA receptors in a mammal by administering an effective amount of a compound of Formula I as described herein.

The compounds of the present invention, being ligands for GABA_A receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous
10 system (CNS). In one aspect, the compounds are useful for the treatment and/or prevention of disorders of the CNS involving neuronal hyperexcitability. Such disorders include but are not limited to anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and
15 generalized or substance-induced anxiety disorder, neuroses, convulsions, migraine, and depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder.

Another aspect of the present invention is directed to the use of the compounds of Formula I as enhancers of GABA-facilitated Cl^- flux mediated through the GABA_A receptor
20 complex. Also, an aspect of the present invention is to provide a pharmaceutical composition useful for treating disorders responsive to the enhancement GABA-facilitated Cl^- flux mediated through the GRC, containing an effective amount of a compound of Formula I in a mixture with one or more pharmaceutically acceptable carriers or diluents.

Compounds useful in the present invention have not been heretofor reported. Thus, the
25 present invention is also directed to novel substituted enaminones having the structure of Formula I. Without being bound by theory proposed herein, it is believed that the compound of Formula I or pharmaceutically acceptable salts thereof act by binding to a site other than a site that binds [^3H]-flunitrazepam, barbiturates, loreclezole, [^3H]-muscimol or $3\alpha,20\alpha$ -pregnanediol, thereby altering chloride conductance through the GABA_A receptor complex in a therapeutically
30 usefully fashion.

Further, the present invention is directed to ^3H , ^{35}S , ^{36}Cl , ^{14}C and ^{125}I radiolabeled compounds of Formula I and their use as radioligands for their binding site on the GRC.

Additional embodiments and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended
5 claims.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

Brief Description of the Drawings

10 Figure 1: Dose response of ethyl 2-chloro- α -[[4-ethynylphenyl]amino]methylene]- β -oxo-benzenepropionate, α -[[4-ethynylphenyl]-amino]methylene]-2-chloro- β -oxo-N-propyl-benzenepropanamide, 5 α -pregnan-3 α -ol-20-one, and clonazepam on 0.2 nM [³H]flunitrazepam binding in rat cortex.

Figure 2: Dose response of 5 α -pregnan-3 α , 20 α -diol in the absence and presence of 30
15 nM ethyl 2-chloro- α -[[4-ethynylphenyl]amino]methylene]- β -oxo-benzenepropionate or 100 nM α -[[4-ethynylphenyl]amino]methylene]-2-chloro- β -oxo-N-propyl-benzenepropanamide on 2 nM [³⁵S]TBPS binding in rat cortex.

Figure 3: Dose response of ethyl 2-chloro- α -[[4-ethynylphenyl]amino]methylene]- β -oxo-benzenepropionate, α -[[4-ethynylphenyl]amino]methylene]-2-chloro- β -oxo-N-propyl-
20 benzenepropanamide, and γ -aminobutyric acid on 5 nM [³H]muscimol binding in rat cortex.

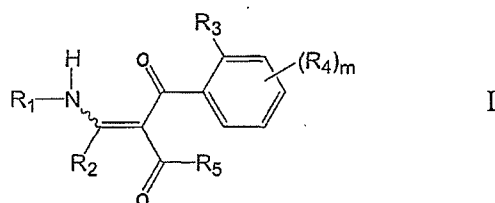
Figure 4: Dose response of loreclezole in the presence and absence of 300 nM ethyl 2-chloro- α -[[4-ethynylphenyl]amino]methylene]- β -oxo-benzenepropionate on 0.2 nM [³H]flunitrazepam binding in rat cortex.

Figure 5: Dose response of pentobarbital in the presence and absence of 300 nM ethyl 2-
25 chloro- α -[[4-ethynylphenyl]amino]methylene]- β -oxo-benzenepropionate on 0.2 nM [³H]flunitrazepam binding in rat cortex.

Detailed Description of the Invention

In one embodiment, there is provided substituted enaminones represented by Formula I:

5



I

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₁ is selected from the group consisting of aryl, heteroaryl, aralkyl and R₁₆R₁₇N-, each unsubstituted or substituted;

5 R₂ is selected from the group consisting of hydrogen and unsubstituted or substituted C₁₋₁₀alkyl;

R₃ is selected from the group consisting of fluoro, chloro, bromo, iodo, C₁₋₁₀alkoxy, nitro, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl and unsubstituted or substituted C₁₋₁₀alkyl;

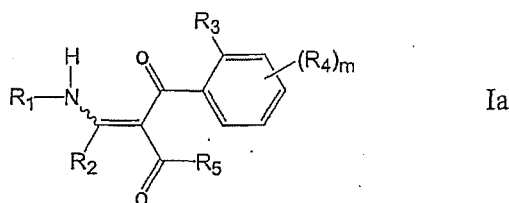
10 each R₄ is independently selected from the group consisting of halogen, nitro, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R₅ is selected from the group consisting of C₁₋₁₀alkyl, C₁₋₁₀alkoxy, -NH₂, C₁₋₁₀alkylamino, di(C₁₋₁₀)alkylamino and aryl, each unsubstituted or substituted;

15 R₁₆ and R₁₇ are each independently C₃₋₁₂cycloalkyl, aryl, heteroaryl, C₁₋₁₀alkyl, each unsubstituted or substituted, or R₁₆ and R₁₇ together with the nitrogen atom to which they are attached form an unsubstituted or substituted 4, 5, or 6 membered ring; and

m is 0, 1, 2, 3 or 4; with the proviso that when R₅ is -OEt, then R₄ is not halogen, and the compound of Formula I is not the compounds ethyl α-[(benzyl)aminomethylene]-2-chloro-β-oxobenzenepropionate and 1-(2,4-dichloro-5-fluorophenyl)-2-[[2,4-difluorophenyl]amino]methylene]-1,3-pentanedione.

In another embodiment, there is provided substituted enaminones represented by Formula Ia:



Ia

25 or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₁ is selected from the group consisting of aryl, heteroaryl, aralkyl and R₁₆R₁₇N-, each unsubstituted or substituted;

R_2 is selected from the group consisting of hydrogen and unsubstituted or substituted C_{1-10} alkyl;

R_3 is selected from the group consisting of hydrogen, halo, halo C_{1-10} alkyl, perhalo C_{1-10} alkyl, amino, cyano, nitro, hydroxy, thio, C_{1-20} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C_{1-10} alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

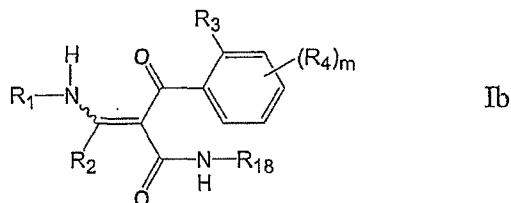
each R_4 is independently selected from the group consisting of halogen, nitro, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, aralkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, each unsubstituted or substituted, or wherein R_3 and an adjacent R_4 together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R_5 is selected from the group consisting of C_{1-10} alkyl, CH_3O- , C_{3-10} alkoxy, $-NH_2$, C_{1-10} alkylamino, di(C_{1-10})alkylamino and aryl, each unsubstituted or substituted;

R_{16} and R_{17} are each independently C_{3-12} cycloalkyl, aryl, heteroaryl, C_{1-10} alkyl, each unsubstituted or substituted, or R_{16} and R_{17} together with the nitrogen atom to which they are attached form an unsubstituted or substituted 4, 5, or 6 membered ring; and

m is 0, 1, 2, 3 or 4. In a particular variation of the above compound of Formula Ia, the compound is the compound wherein R_5 is not CH_3CH_2O- .

In one aspect, there is provided a compound of the Formula Ib:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_1 is selected from the group consisting of aryl, heteroaryl, aralkyl and $R_{16}R_{17}N-$, each unsubstituted or substituted;

R_2 is selected from the group consisting of hydrogen and unsubstituted or substituted C_{1-10} alkyl;

R_3 is selected from the group consisting of hydrogen, halo, halo C_{1-10} alkyl, perhalo C_{1-10} alkyl, amino, cyano, nitro, hydroxy, thio, C_{1-20} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C_{1-10} alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

each R_4 is independently selected from the group consisting of hydrogen, halo, nitro, halo C_{1-10} alkyl, perhalo C_{1-10} alkyl, amino, cyano, nitro, hydroxy, thio, C_{1-20} alkyl, C_{2-10} alkenyl,

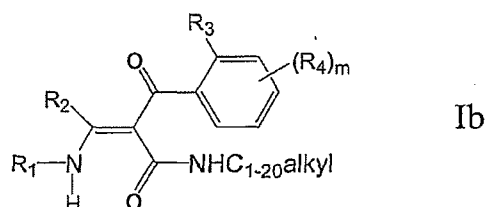
C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R₁₆ and R₁₇ are each independently C₃₋₁₂cycloalkyl, aryl, heteroaryl, C₁₋₁₀alkyl, each unsubstituted or substituted, or R₁₆ and R₁₇ together with the nitrogen atom to which they are attached form an unsubstituted or substituted 4, 5, or 6 membered ring; and

R₁₈ is selected from the group consisting of optionally substituted C₁₋₁₀alkyl, arylalkyl, and heterocycloalkyl; and

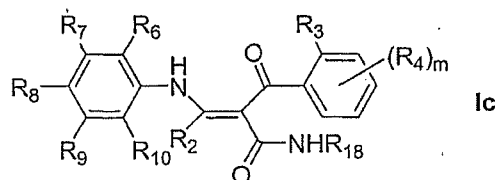
m is 0, 1, 2, 3 or 4.

In another aspect of the compound of the Formula I, when R₅ is C₁₋₁₀alkylamino, the stereochemistry of the enaminone is such that the -NHR₁ is syn with the -COR₅ group as shown in Formula Ib below.



In another aspect of the compound of Formula Ib, the group -NHC₁₋₂₀alkyl is selected from the group consisting of -NHC₂₋₁₀alkyl. In another aspect, the group C₂₋₁₀alkyl is *iso*-propyl, propyl, *sec*-butyl, *tert*-butyl, 2-methyl-1-butyl and 3-methyl-1-butyl.

In another aspect, there is provided a compound comprising the Formula Ic:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₂ is selected from the group consisting of hydrogen, methyl and ethyl;

R₃ is selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

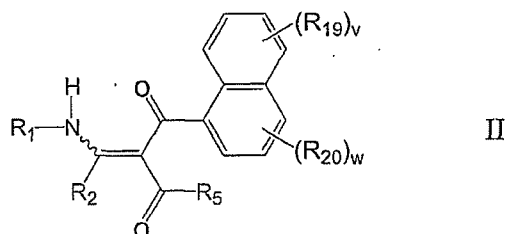
each R₄ is independently selected from the group consisting of hydrogen, halo, nitro, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl,

C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

5 R₆, R₇, R₈, R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, halo, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, cycloalkyl, arylC₁₋₁₀alkyl and heteroarylC₁₋₁₀alkyl; or R₆ and R₇, or R₇ and R₈, or R₈ and R₉, or R₉ and R₁₀ are taken together with the carbon atoms to which they are attached to form an unsubstituted or substituted fused 5 or 6 membered saturated, partially unsaturated ring, aryl or heteroaryl;

10 R₁₈ is selected from the group consisting of C₁₋₁₀alkyl, arylalkyl and heterocycloalkyl, each unsubstituted or substituted; and m is 0, 1, 2, 3 or 4.

In another aspect, there is provided a compound comprising the Formula II:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

15 R₁ is selected from the group consisting of aryl, heteroaryl, aralkyl and R₁₆R₁₇N-, each unsubstituted or substituted;

R₂ is selected from the group consisting of hydrogen and unsubstituted or substituted C₁₋₁₀alkyl;

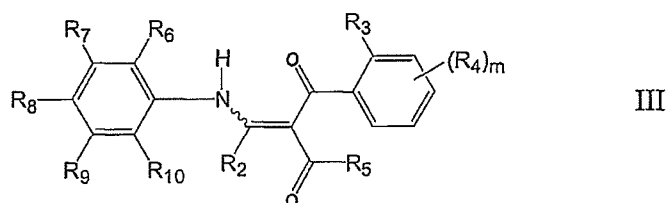
20 R₅ is selected from the group consisting of C₁₋₁₀alkyl, C₁₋₁₀alkoxy, -NH₂, C₁₋₁₀alkylamino, di(C₁₋₁₀)alkylamino and aryl, each unsubstituted or substituted;

R₁₆ and R₁₇ are each independently C₃₋₁₂cycloalkyl, aryl, heteroaryl, C₁₋₁₀alkyl, each unsubstituted or substituted, or R₁₆ and R₁₇ together with the nitrogen atom to which they are attached form an unsubstituted or substituted 4, 5, or 6 membered ring;

25 R₁₉ and R₂₀ are each independently selected from the group consisting of halo, cyano, nitro, halo(C₁₋₁₀)alkyl, perhalo(C₁₋₅)alkyl, aryl, heteroaryl, cycloalkyl, C₁₋₁₀alkyl, aryl(C₁₋₁₀)alkyl, cycloalkyl(C₁₋₁₀)alkyl, hydroxy(C₁₋₁₀)alkyl, amino(C₁₋₁₀)alkyl, alkoxy(C₁₋₁₀)alkyl, amino, hydroxyl, thio, C₁₋₁₀alkoxy and C₁₋₁₀alkylthiol; and

v and w are each independently 0, 1, 2 or 3.

In yet another aspect, there is provided a compound comprising the Formula III:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₂ is selected from the group consisting of hydrogen and unsubstituted or substituted C₁₋₁₀alkyl;

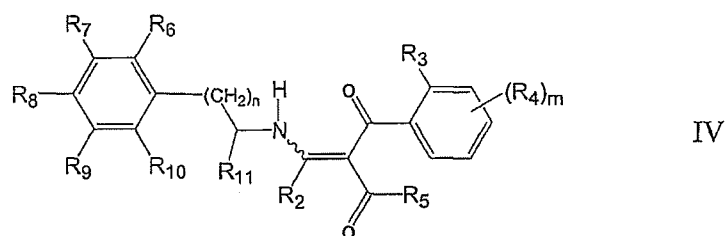
R₃ is selected from the group consisting of fluoro, chloro, bromo, iodo, C₁₋₁₀alkoxy, nitro, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl and unsubstituted or substituted C₁₋₁₀alkyl;

each R₄ is independently selected from the group consisting of halogen, nitro, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R₅ is selected from the group consisting of C₁₋₁₀alkyl, C₁₋₁₀alkoxy, -NH₂, C₁₋₁₀alkylamino, di(C₁₋₁₀)alkylamino and aryl, each unsubstituted or substituted;

R₆, R₇, R₈, R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, halo, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, cycloalkyl, arylC₁₋₁₀alkyl and heteroarylC₁₋₁₀alkyl; or R₆ and R₇, or R₇ and R₈, or R₈ and R₉, or R₉ and R₁₀ are taken together with the carbon atoms to which they are attached to form an unsubstituted or substituted fused 5 or 6 membered saturated, partially unsaturated ring, aryl or heteroaryl; and m is 0, 1, 2, 3 or 4.

In another aspect, there is provided a compound comprising the Formula IV:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₂ is selected from the group consisting of hydrogen and unsubstituted or substituted C₁₋₁₀alkyl;

R₃ is selected from the group consisting of fluoro, chloro, bromo, iodo, C₁₋₁₀alkoxy, nitro, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl and unsubstituted or substituted C₁₋₁₀alkyl;

each R₄ is independently selected from the group consisting of halogen, nitro, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, each

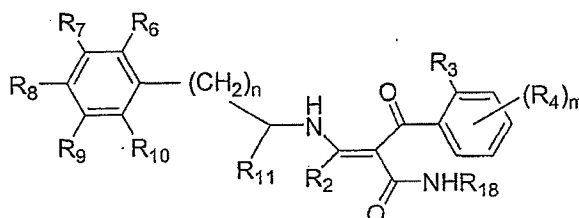
unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R₅ is selected from the group consisting of C₁₋₁₀alkyl, C₁₋₁₀alkoxy, -NH₂, C₁₋₁₀alkylamino, di(C₁₋₁₀)alkylamino and aryl, each unsubstituted or substituted;

5 R₆, R₇, R₈, R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, halo, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, cycloalkyl, arylC₁₋₁₀alkyl and heteroarylC₁₋₁₀alkyl; or R₆ and R₇, or R₇ and R₈, or R₈ and R₉, or R₉ and R₁₀ are taken together with the carbon atoms to which they are attached to form an unsubstituted or substituted fused 5 or 6 membered saturated, partially unsaturated ring, aryl or heteroaryl;

10 R₁₁ is hydrogen or is an unsubstituted or substituted C₁₋₁₀alkyl; m is 0, 1, 2, 3 or 4; and n is 0, 1, 2, 3, 4 or 5.

In yet another aspect, there is provided a comprising the Formula IVa:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

15 R₂ is selected from the group consisting of hydrogen, methyl and ethyl;

R₃ is selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

20 each R₄ is independently selected from the group consisting of halogen, nitro, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

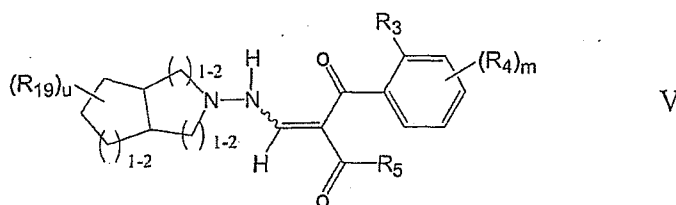
R₅ is selected from the group consisting of C₁₋₁₀alkyl, C₁₋₁₀alkoxy, -NH₂, 25 C₁₋₁₀alkylamino, di(C₁₋₁₀)alkylamino and aryl, each unsubstituted or substituted;

R₆, R₇, R₈, R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, halo, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, cycloalkyl, arylC₁₋₁₀alkyl and heteroarylC₁₋₁₀alkyl; or R₆ and R₇, or R₇ and R₈, or R₈ and R₉, or R₉ and R₁₀ are taken together with the carbon atoms to which they are attached to form an unsubstituted or substituted fused 5 30 or 6 membered saturated, partially unsaturated ring, aryl or heteroaryl;

R_{11} is hydrogen or is an unsubstituted or substituted C_{1-10} alkyl;

R_{18} is selected from the group consisting of C_{1-10} alkyl, arylalkyl and heterocycloalkyl, each unsubstituted or substituted; and m is 0, 1, 2, 3 or 4; and n is 0, 1, 2, 3, 4 or 5.

In another aspect, there is provided a compound comprising the Formula V:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

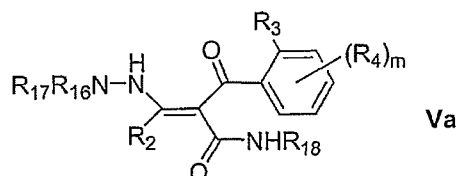
R_3 is selected from the group consisting of hydrogen, halo, halo C_{1-10} alkyl, perhalo C_{1-10} alkyl, amino, cyano, nitro, hydroxy, thio, C_{1-20} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C_{1-10} alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

each R_4 is independently selected from the group consisting of hydrogen, halo, halo C_{1-10} alkyl, perhalo C_{1-10} alkyl, amino, cyano, nitro, hydroxy, thio, C_{1-20} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C_{1-10} alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted, or wherein R_3 and an adjacent R_4 together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R_5 is selected from the group consisting of alkyl, alkoxy, amino, alkylamino, dialkylamino and aryl, each unsubstituted or substituted;

each R_{19} is independently selected from the group consisting of halogen, C_{1-10} alkyl, C_{2-10} alkynyl, C_{1-10} alkoxy, aralkyl and cycloalkyl, each unsubstituted or substituted; m is 0, 1, 2, 3 or 4; and u is 0, 1 or 2.

In yet another aspect, there is provided a compound comprising the Formula Va:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_2 is selected from the group consisting of hydrogen and unsubstituted or substituted C_{1-10} alkyl;

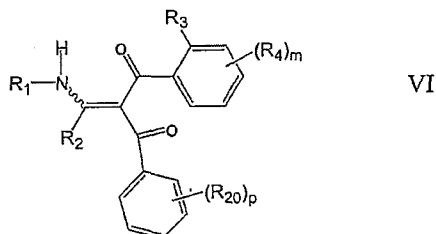
R₃ is selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

5 each R₄ is independently selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or
10 substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R₁₆ and R₁₇ are each independently C₃₋₁₂cycloalkyl, aryl, heteroaryl, C₁₋₁₀alkyl, each unsubstituted or substituted, or R₁₆ and R₁₇ together with the nitrogen atom to which they are attached form an unsubstituted or substituted 4, 5, or 6 membered ring;

R₁₈ is selected from the group consisting of C₁₋₁₀alkyl, arylalkyl, and heterocycloalkyl,
15 each unsubstituted or substituted; and m is 0, 1, 2, 3 or 4.

In yet another aspect, there is provided a compound comprising the Formula VI:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₁ is selected from the group consisting of aryl, heteroaryl, aralkyl and R₁₆R₁₇N-, each
20 unsubstituted or substituted;

R₂ is selected from the group consisting of hydrogen and unsubstituted or substituted C₁₋₁₀alkyl;

R₃ is selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group,
25 sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

each R₄ is independently selected from the group consisting of halogen, nitro, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, each

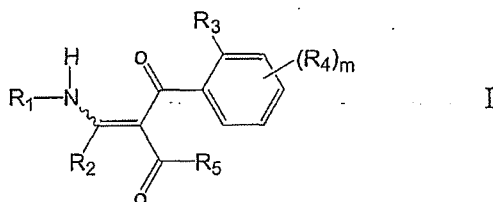
unsubstituted or substituted, or wherein R_3 and an adjacent R_4 together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R_{16} and R_{17} are each independently C_{3-12} cycloalkyl, aryl, heteroaryl, C_{1-10} alkyl, each unsubstituted or substituted, or R_{16} and R_{17} together with the nitrogen atom to which they are
5 attached form an unsubstituted or substituted 4, 5, or 6 membered ring; and

each R_{20} is independently selected from the group consisting of halo, cyano, nitro, halo(C_{1-10})alkyl, perhalo(C_{1-5})alkyl, aryl, heteroaryl, C_{1-10} alkyl, aryl(C_{1-10})alkyl, alkoxy(C_{1-10})alkyl, amino, hydroxyl, thio and C_{1-10} alkoxy, and m and p are each independently 0, 1, 2, 3 or 4.

10 In one variation of the above compound, R_8 is selected from the group consisting of C_{1-10} alkyl, halogen, and C_{1-10} alkoxy; and R_6 , R_7 , R_9 and R_{10} are hydrogen. In another variation of the above compound, R_3 is selected from the group consisting of methyl, trifluoromethyl and chloro; and m is 0.

In one embodiment, there is provided a pharmaceutical composition, comprising the
15 compound of Formula I:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_1 is selected from the group consisting of aryl, heteroaryl, aralkyl and $R_{16}R_{17}N-$, each unsubstituted or substituted;

20 R_2 is selected from the group consisting of hydrogen and unsubstituted or substituted C_{1-10} alkyl;

R_3 is selected from the group consisting of fluoro, chloro, bromo, iodo, C_{1-10} alkoxy, nitro, halo C_{1-10} alkyl, perhalo C_{1-10} alkyl and unsubstituted or substituted C_{1-10} alkyl;

each R_4 is independently selected from the group consisting of halogen, nitro, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, aralkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl,
25 each unsubstituted or substituted, or wherein R_3 and an adjacent R_4 together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

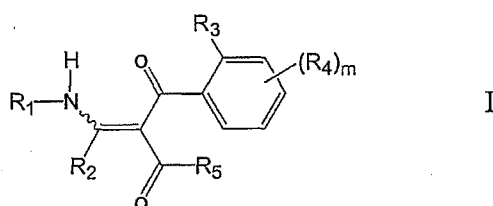
R_5 is selected from the group consisting of optionally substituted C_{1-10} alkyl, C_{1-10} alkoxy, $-NH_2$, C_{1-10} alkylamino, di(C_{1-10})alkylamino and aryl;

R_{16} and R_{17} are each independently C_{3-12} cycloalkyl, aryl, heteroaryl, C_{1-10} alkyl, each unsubstituted or substituted, or R_{16} and R_{17} together with the nitrogen atom to which they are attached form an unsubstituted or substituted 4, 5, or 6 membered ring; and m is 0, 1, 2, 3 or 4; with the proviso that when R_5 is -OEt, then R_4 is not halogen, and the compound of Formula I is not the compounds ethyl α -[(benzyl)aminomethylene]-2-chloro- β -oxobenzenepropionate and 1-(2,4-dichloro-5-fluorophenyl)-2-[[2,4-difluorophenyl]amino]methylene]-1,3-pentanedione; and a pharmaceutically-acceptable carrier selected from the group consisting of excipients and auxiliaries.

Also provided herein are the above compounds wherein the compounds are present as a single stereoisomer and mixtures of stereoisomers and their pharmaceutically acceptable salts. In addition, there is provided the pharmaceutical compositions of the above compounds wherein the composition is formulated for oral administration, parenteral, intraavenous, transdermal, sublingual, intramuscular, rectal, intranasal, intraocular or subcutaneous administration.

In yet another aspect, there is provided a pharmaceutical composition comprising each of the above compound and a pharmaceutically-acceptable carrier selected from the group consisting of excipients and auxiliaries.

In another aspect, there is provided a method for the treatment of CNS disorders amenable to modulation of the GABA_A receptor complex which comprises administering to a patient in need of such treatment a compound of Formula I:



20

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein each of the variables are as defined above. In one variation of the above method, the CNS disorder is an anxiety disorder. In another variation, the CNS disorder is convulsions. In another variation, the CNS disorder is insomnia. In yet another variation, the CNS disorder is a major depressive or bipolar disorder. In yet another variation, the CNS disorder is chronic or acute pain. In another variation, the CNS disorder is a neuroses. In a particular variation, the CNS disorder is withdrawal-induced convulsions from substance abuse. In yet another particular variation, the CNS disorder is a phobia. In another variation of the above method, the CNS disorder is a panic disorder.

25

In one variation of the above method, the CNS disorder is a generalized anxiety disorder. In another variation, the CNS disorder is an obsessive-compulsive disorder. In yet another variation, the CNS disorder is a post traumatic and acute stress disorder. In another variation, the CNS disorder is a migraine. In one particular variation of the method, the CNS disorder is a bipolar manic disorder; or a cognition deficit disorder. In a particular variation of the above method, the CNS disorder is selected from the group consisting of anxiety and stress related disorders, depression and other affective disorders, epilepsy and other seizure disorders, insomnia and related sleep disorders, acute and chronic pain and cough.

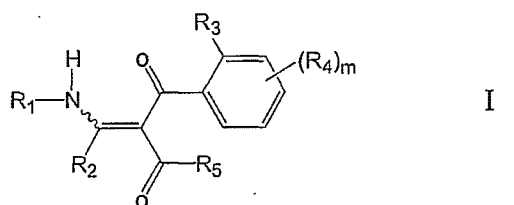
In another aspect, there is provided a method for the treatment of disorders related to learning and memory comprising the steps of administering to a patient in need of such a treatment a compound of the Formula I above. In one variation of the method, the disorder relating to learning and memory is selected from the group consisting of mild cognitive impairment, age related cognitive decline, senile dementia, Alzheimer's disease, sleep disorders involving reduced wakefulness. In another variation, the sleep disorder involving reduced wakefulness is selected from the group consisting of narcolepsy and idiopathic hypersomnia. In yet another variation, there is provided a method wherein the compound of Formula I or a pharmaceutically acceptable salt thereof acts by binding to a site other than a site that binds [³H]-flunitrazepam, barbiturates, loreclezole, [³H]-muscimol or 3 α ,20 α -pregnanediol, thereby altering chloride conductance through the GABA_A receptor complex in a therapeutically useful fashion. In yet another aspect, there is provided a method for the treatment of CNS disorders amenable to modulation of the GABA_A receptor complex which comprises administering to a patient in need of such treatment a compound of Formula I.

α 7 Nicotinic Acetylcholine Receptor Modulators:

The present invention is also related to the discovery that certain substituted enaminones represented by Formulae I-VI act as novel modulators of α 7 nicotinic acetylcholine receptors (nAChRs). The invention is related with treating disorders responsive to enhancement of acetylcholine action on α 7 nAChRs in a mammal by administering an effective amount of a compound of Formulae I-VI as described herein. The compounds of the present invention, being ligands for α 7 nAChRs, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include neurodegenerative diseases, senile dementias and schizophrenia. Another aspect of the present invention is directed to the use of the compounds of Formulae I-VI as enhancers of acetylcholine-facilitated monovalent and divalent cation flux mediated through the α 7 nAChR. Also, an aspect of the present invention is

to provide a pharmaceutical composition useful for treating disorders responsive to the enhancement of acetylcholine-facilitated monvalent and divalent cation mediated flux through the nAChR, containing an effective amount of a compound of Formulae I-VI in a mixture with one or more pharmaceutically acceptable carriers or diluents.

In one aspect, there is provided a method for the treatment of CNS disorders amenable to modulation of the nAChR complex which comprises administering to a patient in need of such treatment a compound of Formula I:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₁ is selected from the group consisting of aryl, heteroaryl, aralkyl and R₁₆R₁₇N-, each unsubstituted or substituted;

R₂ is selected from the group consisting of hydrogen and unsubstituted or substituted C₁₋₁₀alkyl;

R₃ is selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

each R₄ is independently selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R₅ is selected from the group consisting of optionally substituted C₁₋₁₀alkyl, C₁₋₁₀alkoxy, -NH₂, C₁₋₁₀alkylamino, di(C₁₋₁₀)alkylamino and aryl;

R₁₆ and R₁₇ are each independently C₃₋₁₂cycloalkyl, aryl, heteroaryl, C₁₋₁₀alkyl, each unsubstituted or substituted, or R₁₆ and R₁₇ together with the nitrogen atom to which they are attached form an unsubstituted or substituted 4, 5, or 6 membered ring; and m is 0, 1, 2, 3 or 4.

In another aspect, there is provided a method for the treatment of neurodegenerative disorders, which comprises administering to a patient in need of such treatment an effective

amount of compound of the Formulae I-VI. In yet another aspect, there is provided a method for the treatment of senile dementias, which comprises administering to a patient in need of such treatment an effective amount of compound of the Formulae I-VI. In another aspect, there is provided a method for the treatment of schizophrenia, which comprises administering to a patient in need of such treatment an effective amount of compound of the Formulae I-VI. In yet another aspect, there is provided a method for the treatment of cognition deficit disorders, which comprises administering to a patient in need of such treatment an effective amount of compound of the Formulae I-VI. In another aspect, there is provided a method for the treatment of disorders related to learning and memory such as mild cognitive impairment, age related cognitive decline, senile dementia, Alzheimer's disease, by inhibition of mono and divalent cation conductance through the site mediating the action of compound of the above Formulae I-VI.

Compounds of Formulae I-VI include:

Ethyl 2-chloro- β -oxo- α -[[[4-(1,2,3,4-tetrahydronaphthyl-1-amino)phenyl]amino]-methylene]benzenepropionate;

Ethyl 2-chloro-5-nitro- β -oxo- α -[[[4-(1,2,3,4-tetrahydronaphthyl-1-amino)-phenyl]amino]methylene]benzenepropionate;

Ethyl 2-chloro- α -[(cyclohexylamino)methylene]- β -oxobenzenepropionate;

Ethyl 2-chloro- α -[(4-iodophenyl)aminomethylene]- β -oxo-benzenepropionate;

Ethyl α -[(4-bromophenyl)aminomethylene]-2-chloro- β -oxo-benzenepropionate;

Ethyl 2-chloro- α -[(4-methoxyphenyl)aminomethylene]- β -oxo-benzene-propionate;

Ethyl 2-chloro- α -[(3-chloro-4-fluorophenyl)aminomethylene]- β -oxo-benzene-propionate;

Ethyl 2-chloro- α -[(4-fluorophenyl)aminomethylene]- β -oxo-benzenepropionate;

Ethyl α -[(4-iodophenyl)aminomethylene]- β -oxo-1-naphthalenepropionate;

Ethyl α -[(4-fluorophenyl)aminomethylene]- β -oxo-1-naphthalenepropionate;

Ethyl α -[(benzyl)aminomethylene]- β -oxo-1-naphthalenepropionate;

Ethyl β -oxo- α -[(2-phenylethyl)aminomethylene]-1-naphthalenepropionate;

Ethyl β -oxo- α -[(3-phenylpropyl)aminomethylene]-1-naphthalenepropionate;

Ethyl β -oxo- α -[(4-phenylbutyl)aminomethylene]-1-naphthalenepropionate;

Ethyl 2-chloro- α -[(3-phenylpropyl)aminomethylene]- β -oxo-benzenepropionate;

Ethyl 2-chloro- α -[(3,3-diphenylpropyl)aminomethylene]- β -oxo-benzenepropionate;

- Ethyl 2-chloro- β -oxo- α -[(4-phenylbutyl)aminomethylene]-benzenepropionate;
 Ethyl 2-bromo- α -[(4-fluorophenyl)aminomethylene]- β -oxo-benzenepropionate;
 Ethyl α -[(4-fluorophenyl)aminomethylene]-2-nitro- β -oxo-benzenepropionate;
 Ethyl α -[(4-fluorophenyl)aminomethylene]-2-methyl- β -oxo-benzenepropionate;
 5 Ethyl 2-methyl- β -oxo- α -[(4-phenylbutyl)aminomethylene]-benzenepropionate;
 Ethyl 2-nitro- β -oxo- α -[(4-phenylbutyl)aminomethylene]-benzenepropionate;
 Ethyl 2-ethoxy- β -oxo- α -[(4-phenylbutyl)aminomethylene]-benzenepropionate;
 Methyl 2-chloro- α -[(4-iodophenyl)aminomethylene]- β -oxo-benzenepropionate;
 Ethyl α -[(4-iodophenyl)aminomethylene]- β -oxo-2-trifluoromethyl-benzenepropionate;
 10 Ethyl α -[(4-iodophenyl)aminomethylene]-2-methyl- β -oxo-benzenepropionate;
 Ethyl α -[(4-methoxyphenyl)aminomethylene]- β -oxo-2-trifluoromethyl-
 benzenepropionate;
 Ethyl 2-bromo- α -[(4-iodophenyl)aminomethylene]- β -oxo-benzenepropionate;
 Ethyl 2-chloro- α -[(4-methylphenyl)aminomethylene]- β -oxo-benzenepropionate;
 15 Ethyl α -[(4-butylphenyl)aminomethylene]-2-chloro- β -oxo-benzenepropionate;
 Ethyl 2-chloro- α -[(4-isopropylphenyl)aminomethylene]- β -oxo-benzene-propionate;
 Ethyl 2-bromo- α -[(4-iodophenyl)aminomethylene]- β -oxo-benzenepropionate;
 2-Chloro- α -[[[(4-cyanophenyl)amino]methylene]-N-ethyl- β -oxo-benzenepropanamide;
 2-Chloro-N-ethyl- α -[[[(4-iodophenyl)amino]methylene]- β -oxo-benzenepropanamide;
 20 2-Chloro- α -[[[(4-iodophenyl)amino]methylene]- β -oxo-N-(2-propynyl)-
 benzenepropanamide;
 2-Chloro- α -[[[(4-ethynylphenyl)amino]methylene]- β -oxo-N-propyl-benzenepropanamide;
 α -[[[(4-Ethynylphenyl)amino]methylene]-2-methyl- β -oxo-N-propyl-
 benzenepropanamide;
 25 α -[[[(4-Cyanophenyl)amino]methylene]-2-methyl- β -oxo-N-propyl-benzenepropanamide;
 α -[[[(4-Ethynylphenyl)amino]methylene]-2-methyl- β -oxo-N-(2-propynyl)-
 benzenepropanamide;
 2-Chloro- α -[[[(4-cyanophenyl)amino]methylene]- β -oxo-N-propyl-benzenepropanamide;
 Ethyl α -[(4-iodophenyl)aminomethylene]-2-methyl- β -oxo-benzenepropionate;
 30 2-Chloro-N-ethyl- α -[(isoxazolyl-3-amino)methylene]- β -oxo-benzenepropanamide;
 α -[(4-Ethynylphenyl)aminomethylene]- β -oxo-N-propyl-1-naphthalenepropanamide;

2-Chloro- α -[(isoxazolyl-3-amino)methylene]- β -oxo-N-propyl-benzenepropanamide;
2-Chloro-N-ethyl- β -oxo- α -[(1,2,4-triazolyl-4-amino)methylene]benzene-propanamide;
Ethyl α -[(4-ethynylphenyl)aminomethylene]-2-fluoro- β -oxobenzenepropionate;
 α -[(4-Ethynylphenyl)aminomethylene]- β -oxo-N-propyl-1-naphthalenepropanamide; and
5 2-Chloro-N-ethyl- β -oxo- α -[(pyrazinyl)amino]-benzenepropanamide.

For use in medicine, the salts of the compounds of Formulae I-VI will 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 this invention include acid addition salts
10 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, sulfuric acid, methanesulfonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts
15 thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts. Standard methods for the preparation of pharmaceutically acceptable salts and their formulations are well known in the art, and are disclosed in various references, including for example, "Remington: The Science and Practice of Pharmacy", A. Gennaro, ed., 20th edition,
20 Lippincott, Williams & Wilkins, Philadelphia, PA.

The present invention includes within its scope prodrugs of the compounds of Formulae I-VI above. In general, such prodrugs will be functional derivatives of the compounds of Formulae I-VI that are readily convertible in vivo into the required compound of Formulae I-VI. Conventional procedures for the selection and preparation of suitable prodrug derivatives are
25 described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed
30 within the scope of the present invention.

"Disease" means any unhealthy condition of an animal or any unhealthy condition of an animal that may be caused by medical therapy to the animal from a therapy. Example of a

disease caused by therapy include, for example, therapies that may result in one or more side effects.

"Halogen" or "halo" means fluorine, bromine, chlorine and iodine. Useful halogens include fluorine, chlorine, bromine and iodine.

5 "Alkyl" means a straight or branched, saturated or unsaturated aliphatic radical with the number of carbon atoms depicted. An alkyl group may comprise a heteroatom, such as an oxygen, nitrogen or sulfur inserted within or in the chain of the alkyl group. Useful alkyl groups include straight chain and branched C₁₋₂₀alkyl groups. In one aspect, the alkyl group of the present invention comprises the C₅₋₂₀alkyl groups. Typical C₅₋₂₀alkyl groups include n-penyl, n-
10 hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tricedyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl, n-octadecyl, n-nonadecyl and eicosanyl groups. An alkyl group may also be represented with another group, such as an "arylalkyl" group, such as a benzyl group. See below.

An "aryl" group may be a monocyclic, bicyclic or polycyclic ring system wherein each
15 ring is aromatic, or when fused or connected to one or more rings to form a polycyclic ring system. An aryl ring may also be fused with a non-aromatic ring. An aryl ring may also contain a heteroatom to form a hetroaryl ring. Useful aryl groups are C₆₋₁₄aryl, especially C₆₋₁₀aryl. Typical C₆₋₁₄aryl groups include phenyl, naphthyl, anthracyl, indenyl and biphenyl groups.

An "arylalkyl" or "aralkyl" group includes any of the above-mentioned C₁₋₂₀alkyl groups
20 substituted with any of the above-mentioned C₆₋₁₀aryl groups. Similarly, a substituted C₁₋₁₀alkyl may also represent an arylalkyl or aralkyl group (or heteroarylalkyl, etc ...) when the C₁₋₁₀alkyl group is substituted with an aryl group. Useful arylalkyl groups include benzyl, phenethyl and phenylpropyl. When a combination group such as a arylalkyl or aralkyl group is represented, the group is attached at the latter or last represented group. For example, an "arylC₁₋₁₀alkyl" group,
25 such as a benzyl group, for example, is attached at the bond represented here as arylC₁₋₁₀alkyl- or benzyl-.

Useful cycloalkylalkyl groups include any of the above-mentioned C₁₋₂₀alkyl groups substituted with any of the previously mentioned cycloalkyl groups. A cycloalkyl group may also comprise one or more heteroatoms in the cyclic group. Examples of useful cycloalkylalkyl
30 groups include cyclohexylmethyl and cyclopropylmethyl groups.

Useful halomethyl groups include C₁₋₂₀alkyl groups substituted with one or more fluorine, chlorine, bromine or iodine atoms, including fluoromethyl, difluoromethyl,

trifluoromethyl and 1,1-difluoroethyl groups. Perhaloalkyl group include, for example, trifluoromethyl and pentafluoroethyl groups.

Useful hydroxyalkyl groups include C₁₋₂₀alkyl groups substituted by hydroxy group, including hydroxymethyl, 1- and 2-hydroxyethyl and 1-hydroxypropyl groups.

5 Useful alkoxy groups include oxygen substitution by one of the C₁₋₂₀alkyl groups described above. Examples of such alkoxy groups include methoxy, ethoxy, propoxy, butoxy, and the like.

Useful alkylthio groups include sulfur substitution by one of the C₁₋₂₀alkyl groups described above including for example, thiomethyl, thiobutyl, decyl- and hexadecylthio groups.

10 An "amino" group is -NH₂. An alkylamino and dialkylamino groups, for example, include the groups -NHR₁₂ and -NR₁₂R₁₃, wherein each R₁₂ and R₁₃ are independently substituted or unsubstituted C₁₋₂₀alkyl groups. Example of such groups include -NHMe, -NHEt, -NHcyclohexyl, -NHCH₂phenyl, -N(Me)₂, and the like. Useful dialkylaminoalkyl groups include any of the above-mentioned C₁₋₁₀alkyl groups, each substituted or unsubstituted. Also, a
15 substituted amino group may include for example, -NHMe, -NHEt, -NHcyclohexyl, -N(Me)₂ and the like, and -NHCOMe, -NHCOEt, -NHCONHMe, and the like.

"Imino" means the group -C(=N)- that may be attached to another ligand such as an -NR_aR_b or an -OR_a group, for example, to form a -C(=N)NR_aR_b or a -C(=N)OR_a, respectively.

20 Useful alkylthiol groups include any of the above-mentioned C₁₋₁₀alkyl groups substituted by a -SH group.

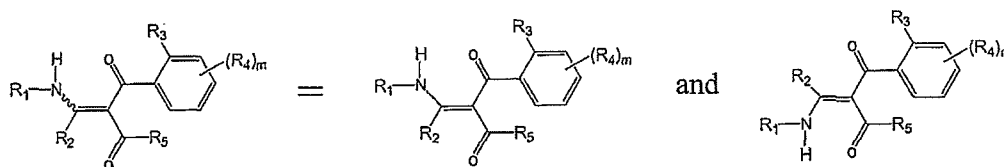
"Carbonyl" means the group -C(O)- that may be attached to another ligand such as an -NR_aR_b or an -OR_a group, for example, to form a -C(O)NR_aR_b or a -C(O)OR_a, respectively. Additional examples of carbonyl groups include a carboxy group, aldehyde, acid halide or ketone. A carboxy or carboxyl group is -COOH.

25 "Heterocyclic" means a saturated or partially unsaturated 3-7 membered monocyclic or 7-10 membered bicyclic ring system, which consists of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic
30 rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on carbon or nitrogen if the resulting compound is stable. Examples include, but are not limited to pyrrolidine, piperidine, piperazine, morpholine, quinoline, 1,2,3,4-tetrahydroquinoline, and the like.

"Heteroaryl" means wholly unsaturated 5 and 6 membered monocyclic, or 9 and 10 membered bicyclic ring system for example, which consists of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on carbon or nitrogen if the resulting compound is stable. Examples include, but are not limited to thiophene, benzothiophene, imidazole, pyridine, pyrimidine, quinoline, naphthyridine, purine and the like. The heteroaryl groups may be unsubstituted or substituted.

"Substituted or unsubstituted" means that a group may consist of only hydrogen substituents (unsubstituted) or may further comprise one or more non-hydrogen substituents (substituted) that are not otherwise specified. For example, *tert*-butyl group may be an example of a propyl group that is substituted by a methyl group. Examples of substituents include, but are not limited to, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkylene, amide, amino, aryl, carbamoyl, carbonyl group, cycloalkyl, ester, halo, heteroaryl, oxo, hydroxy or nitro groups, each of which may also be substituted or unsubstituted as valency permits. Optional substituents on R₁ to R₂₀ include any one or more of halo, cyano, nitro, halo(C₁₋₂₀)alkyl, perhalo(C₁₋₂₀)alkyl, aryl, cycloalkyl, C₁₋₂₀alkyl, aryl(C₁₋₂₀)alkyl, cycloalkyl(C₁₋₂₀)alkyl, hydroxy(C₁₋₂₀)alkyl, amino(C₁₋₂₀)alkyl, alkoxy(C₁₋₂₀)alkyl, amino, hydroxy, thiol, alkoxy and C₁₋₂₀alkylthiol groups mentioned above. In one aspect, a preferred optional substituents include halo, (C₁₋₆)alkyl, halo(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, C₁₋₂₁₀alkoxy and amino.

"Isomers" mean any compound with an identical molecular formula but having a difference in the nature or sequence of bonding or arrangement of the atoms in space. Examples of such isomers include, for example, E and Z isomers of double bonds, enantiomers, and diastereomers. Compounds of the present invention depicting a bond with a "squiggly line" representation is intended to encompass a single isomer and/or both isomers of the double bond as shown below.



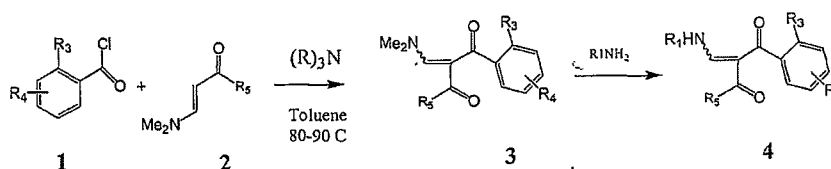
"Prodrug" means a compound that may be converted *in vivo* metabolically into a compound of the present invention. For example, the prodrug of a compound of the present invention may or may not have biological activity as an agonist. Examples of prodrugs are

known in the art. Examples of prodrugs are provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the *A.C.S. Symposium Series*; and in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both references of which are incorporated herein by reference. Prodrugs may also be considered to be analogs or derivatives of the compounds of the present invention.

The preparation of the compounds of the present invention may be performed using the standard methods known in the art of organic synthesis. Reaction transformation using compounds having functional groups may be performed on compounds with functional groups that may be protected. A "protected" compound or derivatives means derivatives of a compound where one or more reactive site or sites or functional groups are blocked with protecting groups. Protected derivatives are useful in the preparation of the compounds of the present invention or in themselves, the protected derivatives may be the biologically active agent. An example of a comprehensive text listing suitable protecting groups may be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

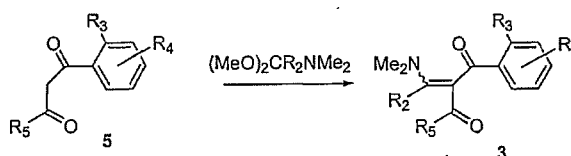
The synthesis of compounds of Formulae II and III is in Scheme 1. Compound 2 with $R_5 = \text{OEt}$ is commercially available from Acros. Compound 2 with $R_5 = \text{OMe}$ can be prepared from dimethylamine and methyl propiolate according to Navarro-Vazquez *et al. J. Org. Chem.* **2002**, 67(10), 3220. The corresponding amides can be prepared as described by Nuvolet, A. *et al. J. Chem. Soc. Perkin Trans. 1*, **1989**, 1007-1011 and Dabrowski, J. *et al. Tetrahedron*, **1976**, 32, 1025-1029.

Scheme 1:



Intermediate 3 can also be prepared as shown in Scheme 2:

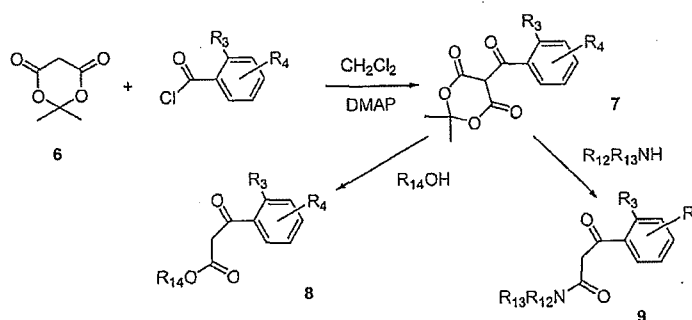
Scheme 2



With $R_5 = \text{alkyl}$, compound 5 can be prepared according to Collins, J. L. *et al. US* 6,498,174 or by using the method of Atkins, R. J., *et al. Organic Process Research & Development* **1997**, 1, 185-197 or Popic, *et al. Synthesis* **1991**, 195-198. For $R_5 = \text{alkoxy}$,

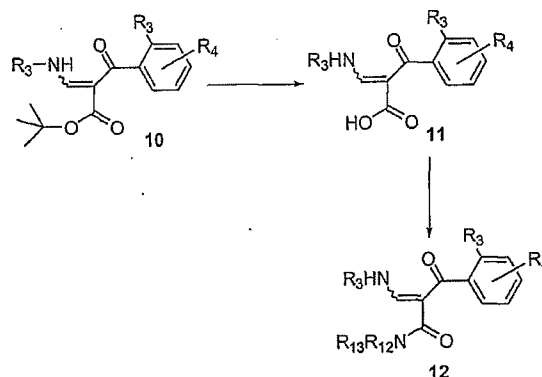
compound **5** is prepared according to the method of Oikawa, Y. *et al. J. Org. Chem.* **1978**, 43(10), 2087-2088. For $R_5 = \text{NMe}_2$, compound **3** is prepared from **2** ($R_5 = \text{NMe}_2$) by using the method of Grohe, K. U.S. patent 4,699,992. Compound **5** with $R_5 = \text{amino}$ or alkoxy is prepared as shown in Scheme 3, starting from Meldrum's acid (**6**), synthesis of acyl Meldrum's acid (**7**): Yamamoto, Y. *et al. Chem. Pharm. Bull.* **1987**, 35, 1860-70; reaction of acyl Meldrum's acid with amines: Andrews, I. P. *et al. Tetrahedron Lett.* **1995**, 36(42), 7743-46; Pak, C. S. *et al. Synthesis* **1992**, 1213-1214; Moya, P. *et al. J. Org. Chem.* **1998**, 63, 8530-35.

Scheme 3



Amides (**12**, Scheme 4) can also be prepared from the corresponding tert-butyl ester (**10**) prepared as in Scheme 3 above ($R_{14}\text{OH} = \text{tert-butanol}$). Reaction of the tert-butyl ester with trifluoroacetic acid in the presence of thioanisole gave the acid (**11**). Standard methods for amide bond formation were then used (isobutyl chloroformate and triethylamine; carbonyl diimidazole, dicyclohexylcarbodiimide, etc.).

Scheme 4



In Vitro Binding Assay 1

$[^{35}\text{S}]$ TBPS binding assay. The cortex from male Sprague-Dawley rats (weighing 160-200 g) was removed immediately after decapitation and dissected over ice. A P_2 homogenate was prepared for binding assay as previously described (Gee, *Mol. Pharmacol.* 30: 218-225, 1986.). The tissue was homogenized in 0.32 M sucrose (J. T. Baker Chemical Co., Phillipsburg, NJ,

USA) with a Teflon-coated pestle, followed by centrifugation at 1,000X g for 10 min. The supernatant was collected and centrifuged at 9,000X g for 20 min. The resultant P₂ pellet was resuspended in ice-cold 50 mM sodium potassium phosphate (J.T. Baker) buffer (pH 7.4) containing 200 mM NaCl (J.T. Baker) and used immediately in binding assays. A 2nM concentration of [³⁵S]TBPS (86 Ci/mmol; New England Nuclear, Boston, MA, USA) was incubated with 100 µl of tissue homogenate (10% w/v) in the presence or absence of 5 µM GABA (Sigma Chem. Co., St. Louis, MO) and 5 µl aliquots of test drug dissolved in dimethyl sulfoxide (Sigma Chem. Co.) (≤ 10 µl of solvent used in all assays). At the concentration (≤ 1%) used, dimethyl sulfoxide had no effect on specific [³⁵S]TBPS binding. All assays were brought to a final volume of 1 ml with 50 mM sodium potassium phosphate buffer (pH 7.4) containing 200 mM NaCl. Non-specific binding was defined as binding in the presence of 2µM TBPS (NEN, Boston, MA) and accounted for ~30% of the total binding. Assays were terminated after a 90-min steady-state incubation at 25 °C by rapid filtration through glass fiber filters (no. 32; Schleicher & Schuell, Keene, N.H.). Filter-bound radioactivity was quantified by liquid scintillation spectrophotometry. The data were evaluated by nonlinear regression (GraphPad, Inc., San Diego, CA) to obtain IC₅₀ (concentration at which half-maximal inhibition of radioligand occurs) values.

Electrophysiological Assay 1:

Pregnant Sprague-Dawley rats, incubating embryos of 17-19 days gestation, were sacrificed by cervical dislocation. The embryos were removed under aseptic conditions and the brains quickly excised and placed in Hank's balanced salt solution (HBSS, Gibco) at ambient room temperature (18-22 °C). The hippocampi were dissected out and chopped into fragments (~ 2 mm³) and transferred into an enzyme solution containing (in mM): NaCl 116, KCl 5.4, NaHCO₃ 26, NaH₂PO₄ 1, CaCl₂ 1.5, MgSO₄ 1, EDTA 0.5, glucose 25, cysteine 1, and papain 20 U/ml (Sigma) and incubated at 37 °C, 5% CO₂, 100% relative humidity for 1 hr. Tissue fragments were washed in HBSS containing 1 mg/ml of bovine serum albumin (BSA) and 1 mg/ml of ovomucoid (both Sigma). Tissue was transferred into a further 3-4 ml of this solution and gently triturated into a single cell suspension using a fire-polished Pasteur pipette. The single cell suspension was layered on to 5 ml HBSS containing 10 mg/ml of BSA and 10 mg/ml of ovomucoid and centrifuged at 100 X g for 10 min. The supernatant was discarded and the cells resuspended in 3-4 ml of glutamine-free minimal essential media (MEM, Gibco) supplemented with heat-inactivated fetal calf serum (5% v/v Gibco), heat-inactivated horse serum (5% v/v Gibco), streptomycin and penicillin (50 µg/ml and 5000 i.u./ml, respectively),

glutamine and glucose (final concentrations 2 mM and 20 mM [Gibco and BDH] respectively). Approximately $1-2 \times 10^5$ cells were plated out on to each 35 mm (Falcon "Primaria") tissue culture dish which contained ~ 1 ml of the sera-enriched MEM. The plates were maintained at 37 °C, in 5% CO₂, and 100% relative humidity until used in electrophysiological studies.

5 Background proliferation of non-neuronal elements was suppressed with cytosine arabinoside (10 µM, Sigma) for 48 hr 7 days after initial dissociation.

The compounds of the present invention that evoked membrane currents were recorded from hippocampal neurons using the whole cell configuration of the patch-clamp technique. Neurons were voltage clamped at -60 mV using a List electronics L/M EPC-7 converter head

10 stage and amplifier. Cells were perfused with an external (bath) recording solution containing (in mM): NaCl 140, KCl 2.8, MgCl₂ 2, CaCl₂ 1 and HEPES-NaOH 10 (pH 7.2). Tetrodotoxin (TTX, 0.3 µM) was included in the recording solution to suppress synaptic activity. The external solution was delivered (at ~2 ml/min) by a Watson-Marlow flow pump via non-sterile tubing which was connected to a plastic cannula (tip dia 1 mm). The input cannula was mounted on a

15 Prior[®] micromanipulator and was positioned in close (< 1mm) proximity to the cell under study. Bath solution was withdrawn from the dish via a 19G needle connected by flexible tubing to an aquarium suction pump. The recording electrode was filled with an internal solution composed of (in mM): CsCl or KCl 140, MgCl₂ 2, CaCl₂ 0.1, EGTA 1.1 (free Ca²⁺ ~ 10⁻⁸ M), HEPES-NaOH 10, and ATP-Mg²⁺ 2. The recording electrodes were fabricated from glass hematocrit

20 tubes (Kimble sodalime tubes 73811) on a Narishige PB7 two stage electrode puller. Electrodes were coated within 100 µm of the tip with "Sylgard" (Dow Corning) and fire polished just before use. The compounds were applied locally to the soma of a voltage-clamped neuron by pressure ejection (1.4 Kpa, 10-80 msec, 0.1-0.033 Hz) from the tip of a modified recording pipette using a Picospritzer II device (General Valve Corporation). The compound-containing pipette was

25 positioned within 0.1 mm of the cell using a Leitz micromanipulator. The microscope and micromanipulators were all mounted on a vibration-free isolation air table (Wentworth) placed inside a Faraday cage. The compound-evoked whole cell currents were monitored on a storage oscilloscope (Tektronix 2212), recorded, after digital pulse code modulation (frequency response 14 kHz, Sony PCM 701), and displayed on Multitrace (Electromed) pen chart recorder

30 (frequency response 0.5 kHz). All drugs, other than the compounds of the present invention, were applied to cells via the superfusion system. Compound-evoked whole cell currents were measured at their peak. Responses in the presence of drugs expressed as the arithmetic mean ± SEM of responses in the absence (control) or drugs.

Electrophysiology Assay 2

GABA_A subunit transfected HEK cells are maintained at 37 °C and 5% CO₂ using Dulbecco's Modified Eagle's Medium with L-glutamine and no sodium pyruvate (Irvine Scientific #9031, Irvine CA) and supplemented with 10% fetal bovine serum (Irvine Scientific #3000), 10 U/ml hygromycin B (Calbiochem #400051), and an antibiotic cocktail consisting of 100 µg/ml streptomycin sulfate, 0.25 µg/ml amphotericin B, 100 units/ml penicillin G (Gibco 15240-096, Gaithersburg MD). Cells are passed by 2 X wash with phosphate buffered saline (PBS) pH 7.4 and lifted using 1 X trypsin/EDTA solution in PBS (0.5 mg/ml trypsin, 0.2 mg/ml EDTA, Irvine Scientific #9342) when confluency reaches ~90%.

GABA_A subunit transfected HEK cells are grown to ~70% confluency on slide. Cells are transferred to a bath that is continuously perfused with extracellular saline. The extracellular medium contained 145 mM NaCl, 3 mM KCl, 1.5 mM CaCl₂, 1 mM MgCl₂, 5.5 mM d-glucose, and 10 mM HEPES, pH 7.4 at an osmolarity of 320-330 mosM. Recordings are performed at room temperature using the whole cell patch clamp technique. The patch pipette solution contained 147 mM *N*-methyl-D-glucamine hydrochloride, 5 mM CsCl, 5 mM K₂ATP, 5 mM HEPES, 1 mM MgCl₂, 0.1 mM CaCl₂, and 1.1 mM EGTA, pH 7.2, at an osmolarity of 315 mosM. Pipette-to-bath resistance is typically 3-5 Mohms. Cells are voltage clamped at -60 mV, and the chloride equilibrium potential was approximately 0 mV. Drugs are dissolved in extracellular medium and rapidly applied to the cell by local perfusion. A motor driven multi-channel switching system exchanged solutions in approximately 20 ms.

In vivo Pharmacology

Anticonvulsant assay: Adult male non-Swiss albino (NSA) mice (25-30 g) are used in these studies. Time to peak anti-convulsant effect was determined against picrotoxin (Sigma) induced seizures. Mice were injected with picrotoxin (3.15 mg/kg s.c.) at various time points up to 60 minutes after the injection of drug (30 mg/kg i.p.) and the time that maximum protection was observed was defined as the time of peak effect. 6 Animals were used per dose of test drug. Mice are injected (i.p.) with various doses of drug dissolved in DMSO or vehicle (DMSO 5 µl/g body weight) at time of peak effect before administration (s.c.) of a CD₉₇ dose of metrazol (85 mg/kg), (+)-bicuculline (2.7 mg/kg), or picrotoxin (3.15 mg/kg), or vehicle (0.9% saline 5 µl/g body weight). Immediately after the injection mice are observed for a period of 45-60 minutes. The number of animals with tonic/clonic convulsions is recorded.

Vogel conflict

Adult male rats are randomly divided into groups of 6 rats/group. Animals were deprived of water overnight (16hr). Food was freely available at time of thirsting. Thirty minutes after injection (i.p.) of test drug, control drug (diazepam), or vehicle control rats are placed in a square plexiglass box containing a stainless steel bottom connected to one side of a drinkometer circuit. At the other side of the drinkometer circuit a water bottle, placed so the drink tube extends into the plexiglass box, is connected. When a subject drinks from the bottle the circuit is closed and an electric shock is delivered at the tube after seven licks are recorded. The number of licks in a 10 min session is recorded.

Light-dark transition

Male NSA mice (25-30g) are used. The apparatus consists of an open-topped box divided into small and large area by a partition that has a hole at floor level. The small compartment is painted black and the large compartment white. The white compartment was illuminated with light and the black compartment with red light. The time spent in the light compartment and the number of transitions between compartments are recorded during a 3 min test session. Vehicle or test compounds are administered 30 min prior to the test. Diazepam is administered (i.p.) at 2 mg/kg.

Example 1*Ethyl 2-chloro- α -[(dimethylamino)methylene]- β -oxo-benzenepropanoate*

A mixture of ethyl 3,3-dimethylaminoacrylate (4.68 g, 32.7 mmol) and N,N-diisopropylethylamine (12 mL, 8.9 g, 69 mmol) was stirred at rt and a solution of 2-chlorobenzoyl chloride (5.72 g, 32.7 mmol) in 30 mL of toluene was added over 5 mins. The yellow solution that formed was placed in an oil bath at 85-90 °C. After 3 h, the mixture that formed was filtered and the solid was washed with toluene (4 x 25 mL). The pooled toluene washes were extracted with water (3 x 50 mL) and brine (1 x 30 mL), dried (Na₂SO₄), filtered and concentrated. The dark filtrate was concentrated and the oily residue was triturated with hexanes (100 mL). The solid that formed was isolated by filtration and washed with hexanes (25 mL). The crude product was dissolved in a minimum volume of EtOAc and added to 16.5 cm of flash silica gel in a 5 cm dia. column. Elution with 100% EtOAc afforded an oil that solidified after trituration with hexanes. The solid, weight 5.68 g (62%), exhibited mp 70-71.5 °C.

The following compounds were prepared by using the method described above:

ethyl 4-chloro- α -[(dimethylamino)methylene]- β -oxo-benzenepropanoate;

ethyl 2-chloro- α -[(dimethylamino)methylene]-4-fluoro-3-methyl- β -oxo-benzenepropanoate, mp 104.5-106.5 °C;

ethyl α -[(dimethylamino)methylene]- β -oxo-1-naphthalenepropanoate, oil after flash chromatography with 4:1 hexanes/EtOAc;

5 ethyl 2-chloro- α -[(dimethylamino)methylene]-5-nitro- β -oxo-benzenepropanoate (03DJH60B);

ethyl α -[(dimethylamino)methylene]-2-methyl- β -oxo-benzenepropanoate oil after flash chromatography;

ethyl 2-bromo- α -[(dimethylamino)methylene]- β -oxo-benzenepropanoate;

10 ethyl α -[(dimethylamino)methylene]- β -oxo-2-trifluoromethyl benzenepropanoate; and
ethyl α -[(dimethylamino)methylene]-2-nitro- β -oxo-benzenepropanoate.

Example 2

Methyl 2-chloro- α -[(dimethylamino)methylene]- β -oxo-benzenepropanoate

A mixture of methyl 2-chlorobenzoylacetate (Acros; 266 mg, 1.25 mmol) and *N,N*-
15 dimethylformamide dimethylacetal (161 mg, 1.35 mmol) was stirred at rt under N₂ for 2 weeks. The reaction was then concentrated in vacuo and the residue was adsorbed on silica gel and chromatographed. Elution with 3:1 EtOAc/hexanes afforded 193 mg of the title compound as a yellow solid.

Example 3

20 **1,1-Dimethylethyl 2-chloro- α -[(4-iodophenyl)amino]methylene]- β -oxo-benzenepropanoate**

1,1-Dimethylethyl 2-chlorobenzoylacetate. A solution of 5-(2-chlorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (539 mg, 1.91 mmol) in 17 mL of toluene was treated with 0.6 mL (465 mg, 6.27 mmol) of 2-methyl-2-propanol and heated at 80-85 °C. After 4.5 h, the reaction was allowed to cool and concentrated in vacuo. The crude product was adsorbed onto 2
25 g of flash silica and added to 22.5 cm of flash silica in a 2 cm dia. column. Elution with 9:1 hexanes/EtOAc gave 416 mg (86%) of the β -ketoester as an oil.

1,1-Dimethylethyl 2-chloro- α -[(dimethylamino)methylene]- β -oxo-benzenepropanoate. 1,1-Dimethylethyl 2-chlorobenzoylacetate (87 mg, 0.342 mmol) and *N,N*-dimethylformamide dimethyl acetal (50 μ L, 45 mg, 0.375 mmol) were stirred in 1 mL of
30 toluene. After 6 d, the reaction was concentrated in vacuo and the residue was subjected to flash chromatography. Elution with 1:1 hexanes/EtOAc afforded 61 mg (58%) of the title compound as an oil that solidified on standing, mp 97-99 °C.

1,1-Dimethylethyl 2-chloro- α -[[[4-iodophenyl]amino]methylene]- β -oxo-benzenepropanoate. A solution of 1,1-dimethylethyl 2-chloro- α -[(dimethylamino)methylene]- β -oxo-benzenepropanoate (25.5 mg, 0.082 mmol) in 1 mL of toluene was treated with 4-iodoaniline (17.9 mg, 0.082 mmol) added as a solid in one portion. After stirring overnight, the reaction was concentrated in vacuo and the residue was adsorbed onto silica gel and added to 19.5 cm of flash silica in a 2 cm dia. column. Elution with 5:1 hexanes/EtOAc gave the title compound as a solid.

Example 4

2-Chloro- α -[[[4-cyanophenyl]amino]methylene]- β -oxo-N-propyl-benzenepropanamide

5-(2-Chlorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione. A solution of 4-(dimethylamino)pyridine (33.96 g, 278 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (20.0 g, 139 mmol) in 50 mL of CH_2Cl_2 was cooled in an ice-salt bath to -10°C . A solution of 2-chlorobenzoyl chloride (29.2 g, 167 mmol) in 20 mL of CH_2Cl_2 was added dropwise via addition funnel over 1 h. After stirring cold for 1 h, the reaction was allowed to warm to rt and stirred for an additional 3 h. The resulting yellow-orange solution was then extracted with an aq. 10% HCl solution (200 mL) and 200 mL of brine. After drying with MgSO_4 , the mixture was filtered and the solvent was removed in vacuo. The resulting orange oil was triturated with hexanes (3 x 50 mL), affording the title compound (20 g) as a yellow solid.

2-Chloro- β -oxo-N-propylbenzenepropanamide. A suspension of 5-(2-chlorobenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.06 g, 7.30 mmol) in 100 mL of toluene was treated with neat propylamine (550 μL , 395 mg, 6.70 mmol) added dropwise via syringe. The reaction was then heated at $80-90^\circ\text{C}$ for 4 h. Once at rt, the reaction was concentrated to dryness. The residue was adsorbed onto flash silica gel and added to 19 cm of flash silica gel in a 5 cm dia. column. Elution with 4:1 hexanes/EtOAc afforded 851 mg (53%) of the title compound as a yellow oil.

2-Chloro- α -[(dimethylamino)methylene]- β -oxo-N-propylbenzenepropanamide. A solution of 789 mg (3.29 mmol) of 2-chloro- β -oxo-N-propyl-benzenepropanamide in 5 mL of CH_2Cl_2 was treated with neat N,N-dimethylformamide dimethylacetal (450 μL , 402 mg, 3.38 mmol) added dropwise via syringe. The reaction was allowed to stir overnight and then concentrated in vacuo. Flash chromatography (11 cm in a 5 cm column) eluting with 2% MeOH/ CH_2Cl_2 afforded 756 mg (79%) of the title compound as a yellow foam. Trituration with hexanes gave a yellow solid, mp $76-78^\circ\text{C}$.

2-Chloro- β -oxo-N-propyl- α -[[[(4-trifluoromethyl)phenyl]amino]methylene]-benzenepropanamide. To 2-chloro- α -[(dimethylamino)methylene]- β -oxo-N-propylbenzenepropanamide (63.5 mg, 0.215 mmol) was added 4-(trifluoromethyl)aniline (27 μ L, 34.6 mg, 0.215 mmol) and toluene (3 mL). The mixture was heated at reflux for 3 h. Once at rt, the reaction was concentrated in vacuo. The residue was adsorbed onto flash silica gel and added to 20 cm of flash silica gel in a 2 cm dia. column. Elution with 6:1 hexanes/EtOAc afforded 57 mg the desired product as a solid, mp 96-97.5 °C.

The following compounds were prepared by using the method described above:

5-(2-chloro-4-fluoro-3-methylbenzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, yellow-orange solid after trituration with hexanes;

2-chloro- β -oxo-N-propylbenzenepropanamide, light yellow oil after chromatography with 4:1 hexanes/EtOAc;

2-chloro-N-ethyl- β -oxobenzenepropanamide, light yellow oil after chromatography with 4:1 hexanes/EtOAc;

4-chloro- β -oxo-N-propylbenzenepropanamide, light yellow solid after chromatography with 1.5:1 hexanes/EtOAc;

2-fluoro- β -oxo-N-propylbenzenepropanamide, light brown oil after chromatography with 1.5:1 hexanes/EtOAc;

2-chloro- α -[(dimethylamino)methylene]-N-ethyl- β -oxo-N-benzenepropanamide, light yellow solid, mp 97.5-100 °C after chromatography with 2.5 % MeOH/CH₂Cl₂;

2,2-dimethyl-5-(2-methylbenzoyl)-1,3-dioxane-4,6-dione, red-orange semisolid after trituration with hexanes;

2-methyl- β -oxo-N-propyl-benzenepropanamide, light yellow oil after chromatography with 2:1 hexanes/EtOAc;

2-methyl- β -oxo-N-(2-propynyl)-benzenepropanamide, light yellow oil after chromatography with 2:1 hexanes/EtOAc;

α -[(dimethylamino)methylene]-2-methyl- β -oxo-N-propyl-benzenepropanamide, light yellow oil after chromatography with 2.5 % MeOH/CH₂Cl₂;

α -[(dimethylamino)methylene]-2-methyl- β -oxo-N-(2-propynyl)-benzenepropanamide, light yellow oil after chromatography with 2.5 % MeOH/CH₂Cl₂. ¹H NMR (500 MHz, CDCl₃) δ 8.97 (br s, 1H), 7.29-7.14 (m, 5H), 4.16 (dd, 2H, J = 5.3, 2.5 Hz), 3.03 (br s, 6H), 2.31 (s, 3H), 2.20 (t, 1H, J = 2.5 Hz);

2-chloro- α -[[[4-iodophenyl]amino]methylene]- β -oxo-N-propyl-benzenepropanamide;

2-chloro-N-ethyl- α -[[[4-iodophenyl]amino]methylene]- β -oxo-benzenepropanamide; ^1H NMR (500 MHz, CDCl_3) δ 12.96 (d, 1H, $J = 12.2$ Hz), 9.52 (br s, 1H), 7.66 (d, 1H, $J = 12.5$ Hz), 7.60 (d, 2H, $J = 8.5$ Hz), 7.47 (d, 1H, $J = 7.9$ Hz), 7.41 (dt, 1H, $J = 7.6, 1.5$ Hz), 7.37 (dt, 1H, $J = 7.4, 0.7$ Hz), 7.31 (d, 1H, $J = 7.4, 1.7$ Hz), 6.66 (d, 2H, $J = 8.6$ Hz), 3.46 (br s, 2H), 1.29 (t, 3H, $J = 7.3$ Hz);

α -[[[4-ethynylphenyl]amino]methylene]-2-methyl- β -oxo-N-propyl-benzenepropanamide, mp 160-161.5 °C after chromatography with 7:1 hexanes/EtOAc (R_f 0.36). ^1H NMR (500 MHz, CDCl_3) δ 12.90 (d, 1H, $J = 12.6$ Hz), 9.73 (br s, 1H), 7.77 (d, 1H, $J = 12.5$ Hz), 7.40 (d, 2H, $J = 8.7$ Hz), 7.36 (dt, 1H, $J = 7.5, 1.4$ Hz), 7.29-7.25 (m, 2H), 7.21 (d, 1H, $J = 6.3$ Hz), 6.79 (d, 2H, $J = 8.7$ Hz), 3.40 (q, 2H, $J = 6.5$ Hz), 3.07 (s, 1H), 2.32 (s, 3H), 1.69 (sextet, 2H, $J = 7.3$ Hz), 1.04 (t, 3H, $J = 7.4$ Hz). Anal Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.09; H, 6.45; 7.91.;

α -[[[4-ethynylphenyl]amino]methylene]-2-methyl- β -oxo-N-(2-propynyl)-benzenepropanamide;

α -[[[4-cyanophenyl]amino]methylene]-2-methyl- β -oxo-N-propyl-benzenepropanamide;

α -[[[1-azabicyclo[3.3.0]octyl]-1-amino]methylene]-2-chloro- β -oxo-N-propyl-benzenepropanamide, mp 111.5-113 °C after chromatography with 5:1 hexanes/EtOAc (R_f 0.34);

2-chloro- α -[[[4-ethynylphenyl]amino]methylene]- β -oxo-N-propyl-benzenepropanamide;

2-chloro- α -[[[4-fluorophenyl]amino]methylene]- β -oxo-N-propyl-benzenepropanamide, mp 95-96 °C;

2-chloro- α -[[[4-iodophenyl]amino]methylene]- β -oxo-N-(2-propynyl)-benzenepropanamide;

2-chloro-N-ethyl- β -oxo- α -[(pyrazinyl)amino]-benzenepropanamide, white solid, mp 134.5-137 °C after chromatography with 2% MeOH/ CH_2Cl_2 (R_f 0.6);

2-chloro- α -[(isoxazolyl-3-amino)methylene]- β -oxo-N-propyl-benzenepropanamide, white solid, mp 116.5-118.5 °C after chromatography with 1% MeOH/ CH_2Cl_2 ;

2-chloro-N-ethyl- β -oxo- α -[(1,2,4-triazolyl-4-amino)methylene]-benzenepropanamide, white solid that precipitated from toluene, washed twice with toluene, mp 189.5-190 °C;

2-chloro-N-ethyl- α -[(isoxazolyl-3-amino)methylene]- β -oxo-benzenepropanamide, white solid, mp 139-140 °C after chromatography with 2% MeOH/ CH_2Cl_2 (R_f 0.7); and

2-chloro- α -[(4-ethynylphenyl)aminomethylene]- β -oxo-N-propyl-1-naphthalenepropanamide, off white solid, mp 155-156 °C after chromatography with 8:1 hexanes/EtOAc (R_f 0.25).

Example 5

5 Ethyl 2-chloro- α -[(3-chloro-4-fluorophenyl)amino]methylene]- β -oxo-benzenepropionate

A solution of ethyl 2-chloro- α -[(dimethylamino)methylene]- β -oxo-benzenepropanoate (50 mg, 0.177 mmol) in 1 mL of EtOH was treated with neat 3-chloro-4-fluoroaniline (25.8 mg, 0.177 mmol). After stirring at rt until complete by TLC, the reaction was concentrated in vacuo. The residue was subjected to flash chromatography (1:1 EtOAc/hexanes), affording 42.6 mg
10 (63%) of the product as a white solid, mp 96-102 °C. ^1H NMR (400 MHz, CDCl_3 9:1 ratio of alkene isomers, major isomer NMR given) δ 12.66 (d, 1H, $J = 12.8$ Hz), 8.50 (d, 1H, $J = 13.2$ Hz), 7.37-7.16 (m, 7H), 4.01 (q, 2H, $J = 7.1$ Hz), 0.93 (t, 2H, $J = 7.1$ Hz).

Example 6

Ethyl 2-chloro- β -oxo- α -[[4-(4-phenylbutyl)amino]methylene]-benzenepropionate

15 A solution of 4-phenylbutylamine (24.5 mg, 0.164 mmol) in 1 mL of EtOH was treated with solid ethyl 2-chloro- α -[(dimethylamino)methylene]- β -oxo-benzenepropanoate (46.5 mg, 0.165 mmol). After stirring at rt for 5 m, the reaction was concentrated in vacuo and the residue was subjected to flash chromatography, (10 cm of silica gel in a 2 cm dia. column; elution with 100% CH_2Cl_2), affording 60.4 mg (96%) of the title compound as a white solid, mp 90-92 °C.
20 By ^1H NMR the compound is a 4.5:1 mixture of double bond isomers. ^1H NMR (CDCl_3 , 400 MHz) major isomer δ 11.06 (br m, 1H), 8.11 (d, 1H, $J = 14.0$ Hz), 7.34-7.17 (m, 9H), 3.94 (q, 2H, $J = 7.1$ Hz), 3.43 (m, 2H), 2.68 (m, 2H), 1.73 (m, 4H), 0.88 (t, 3H, $J = 7.1$ Hz). ^1H NMR (CDCl_3 , 400 MHz) minor isomer (only peaks that are shifted from major isomer are given) δ 9.52 (br m, 1H), 8.17 (d, 1H, $J = 9.4$ Hz), 3.89 (q, 2H, $J = 7.1$ Hz), 0.77 (t, 3H, $J = 7.1$ Hz).

25

Example 7

Ethyl 2-chloro- β -oxo- α -[[[4-(1,2,3,4-tetrahydronaphthyl-1-amino)phenyl]amino]methylene]-benzenepropionate

4-(1,2,3,4-Tetrahydronaphthyl-1-amino)nitrobenzene. A solution of 4-fluoro-1-nitrobenzene (2.82 g, 20.0 mmol) in 10 mL of DMSO was treated with neat 1,2,3,4-tetrahydro-1-aminonaphthalene (3.0 mL, 3.08 g, 20.9 mmol) added dropwise via syringe. The resulting
30 orange solution was stirred at rt. After 6 d, the reaction was added to cold water/EtOAc. The aq. layer was washed with EtOAc (3 x 50 mL) and the pooled organic layers were washed with 100

mL of a 0.7 M aq. HCl solution, water and brine. After drying (Na_2SO_4), the mixture was filtered and the solvent removed in vacuo. The residue was triturated with 100 mL of hexanes, giving 2.35 g of the desired product as a bright yellow solid.

4-(1,2,3,4-Tetrahydronaphthyl-1-amino)aniline. A suspension of nitro compound (1.06 g, 3.93 mmol) in 115 mL of glacial HOAc was treated with solid Zn metal (1.32 g, 20.2 mmol) added in portions. After 25 m, an additional 1.14 g of Zn was added. After 30 m, the mixture was filtered. The solid was washed with HOAc (2 x 25 mL). The HOAc was then removed in vacuo and the residue was partitioned between EtOAc and a half saturated aq. NaHCO_3 solution (50 mL of each). The organic layer was separated, washed with 25 mL each of a half saturated aq. NaHCO_3 solution and brine, dried (Na_2SO_4), filtered and concentrated to dryness. The aniline (891 mg, 95%) was isolated as an air sensitive solid.

Ethyl 2-chloro- β -oxo- α -[[4-(1,2,3,4-tetrahydronaphthyl-1-amino)phenyl]amino]methylene]-benzenepropionate. A solution of ethyl 2-chloro- α -[(dimethylamino)methylene]- β -oxo-benzenepropionate (1.027 g, 3.65 mmol) in EtOH (10 mL) and 4-(1,2,3,4-tetrahydronaphthyl-1-amino)aniline (869 mg, 3.65 mmol) was as added as a solid in one portion. After stirring at rt for 4 d, the solid precipitate that formed was isolated by filtration and washed with EtOH (3 x 10 mL). The yellow-green solid that resulted was adsorbed onto flash silica gel and subjected to column chromatography. Elution with 6:1 hexanes/EtOAc gave a yellow oil. Trituration with hexanes gave 623 mg (36%) of a yellow solid, mp 118-121 °C. ^1H NMR (400 MHz, CDCl_3 , 4.6:1 ratio of alkene isomers, major isomer NMR given) δ 12.87 (d, 1H, J = 13.7 Hz), 8.54 (d, 1H, J = 13.7 Hz), 7.38-7.17 (m, 8H), 7.14 (d, 2H, J = 8.8 Hz), 6.69 (d, 2H, J = 8.7 Hz), 4.63 (m, 1H), 4.04-3.94 (m, 4H), 2.90-2.74 (m, 2H), 2.01-1.80 (m, 4H), 0.92 (t, 3H, J = 7.1 Hz).

The following compounds were prepared as described in the foregoing examples:

Ethyl 2-chloro- α -[[4-ethynylphenyl]amino]methylene]- β -oxo-benzenepropionate, mp 128.5-133 °C;

ethyl 2-bromo- α -[[4-fluorophenyl]amino]methylene]- β -oxo-benzenepropionate, mp 83.5-84.5 °C;

ethyl α -[(benzyl)aminomethylene]- β -oxo-1-naphthalenepropionate, mp 142-143.5 °C;

ethyl β -oxo- α -[(2-phenylethyl)aminomethylene]-1-naphthalenepropionate, mp 131-133 °C;

ethyl β -oxo- α -[(3-phenylpropyl)aminomethylene]-1-naphthalenepropionate, mp 86-88 °C;

ethyl α -[(octyl)aminomethylene]- β -oxo-1-naphthalenepropionate, mp 88-89 °C;

ethyl α -[(octyl)aminomethylene]- β -oxo-1-naphthalenepropionate, mp 72-73 °C;

5 ethyl 2-methyl- β -oxo- α -[(4-phenylbutyl)aminomethylene]-benzenepropionate, mp 87-88 °C;

ethyl 2-nitro- β -oxo- α -[(4-phenylbutyl)aminomethylene]-benzenepropionate, mp 120-121.5 °C;

10 ethyl α -[[[(4-fluorophenyl)amino]methylene]-2-nitro- β -oxo-benzenepropionate, mp 109-110 °C;

ethyl α -[[[(4-iodophenyl)amino]methylene]- β -oxo-2-trifluoromethyl-benzene-propionate, mp 110-111 °C;

ethyl α -[[[(4-methoxyphenyl)amino]methylene]- β -oxo-2-trifluoromethyl-benzene-propionate, mp 80-83 °C;

15 ethyl 2-chloro- β -oxo- α -[(4-phenylbutyl)aminomethylene]-benzenepropionate, mp 91-92 °C;

ethyl 2-bromo- β -oxo- α -[(4-phenylbutyl)aminomethylene]-benzenepropionate, mp 96-97 °C;

20 ethyl β -oxo- α -[(4-phenylbutyl)aminomethylene]-2-trifluoromethyl-benzenepropionate, mp 104-106 °C;

ethyl 2-chloro- α -[[[(2-naphthyl)amino]methylene]- β -oxo-benzenepropionate, mp 121-122 °C;

ethyl 2-chloro- α -[[[(3,4-methylenedioxy)phenyl]amino]methylene]- β -oxo-benzenepropionate, mp 99-101 °C;

25 ethyl 2-chloro- α -[[[(4-iodophenyl)amino]methylene]- β -oxo-benzenepropionate (05DJH133A; RMG 20062). Prepared as a 23:1 mixture of double bond isomers, mp 152-153 °C. ¹H NMR (CDCl₃, 400 MHz) major isomer δ 12.65 (d, 1H, J = 13.1 Hz), 8.58 (d, 1H, J = 13.4 Hz), 7.73 (d, 2H, J = 8.5 Hz), 7.37-7.24 (m, 4H), 7.04 (d, 2H, J = 8.6 Hz), 4.01 (q, 2H, J = 7.1 Hz), 0.93 (d, 3H, J = 7.1 Hz);

30 methyl 2-chloro- α -[[[(4-iodophenyl)amino]methylene]- β -oxo-benzenepropionate, mp 159.5-160.5 °C;

ethyl 2-chloro- β -oxo- α -[[[(2-phenoxy)ethyl]amino]methylene]-benzenepropionate, mp 134.5-135.5 °C;

ethyl 2-chloro- α -[[[(1-methyl-3-phenylpropyl)amino]methylene]- β -oxo-benzenepropionate, mp 82.5-85 °C;

5 ethyl 2-chloro- β -oxo- α -[[[(2-phenylamino)ethyl]amino]methylene]-benzenepropionate (05DJH151C);

ethyl 2-chloro- α -[[[(4-hydroxyphenyl)amino]methylene]- β -oxo-benzenepropionate, mp 197.5-198.5 °C;

10 ethyl 2-chloro- α -[[[(4-chlorophenyl)amino]methylene]- β -oxo-benzenepropionate, mp 121.5-122.5 °C;

ethyl 2-chloro- α -[[[(3-chlorophenyl)amino]methylene]- β -oxo-benzenepropionate (05DJH110A);

ethyl 2-chloro- α -[[[(2-chlorophenyl)amino]methylene]- β -oxo-benzenepropionate (05DJH110A);

15 ethyl 2-chloro- α -[[[(4-methylphenyl)amino]methylene]- β -oxo-benzenepropionate, mp 106-108 °C;

ethyl 2-chloro- α -[[[(4-methoxyphenyl)amino]methylene]- β -oxo-benzenepropionate, mp 96-97 °C;

20 ethyl 2-chloro- α -[[[(4-isopropylphenyl)amino]methylene]- β -oxo-benzenepropionate, mp 83-85 °C;

ethyl α -[[[(4-butylphenyl)amino]methylene]-2-chloro- β -oxo-benzenepropionate (05DJH108D);

ethyl 2-chloro- β -oxo- α -[[[(4-trifluoromethylphenyl)amino]methylene]-benzenepropionate, mp 127-131 °C;

25 ethyl 2-chloro- α -[[[(4-ethylphenyl)amino]methylene]- β -oxo-benzenepropionate, mp 80-84 °C;

ethyl 2-chloro- α -[[[(4-methylthio)phenyl]amino]methylene]- β -oxo-benzenepropionate, mp 127-128 °C;

30 ethyl 2-chloro- α -[[[4-(methylsulfinyl)phenyl]amino]methylene]- β -oxo-benzenepropionate and ethyl 2-chloro- α -[[[4-(methylsulfonyl)phenyl]amino]-methylene]- β -oxo-benzenepropionate.

Reaction of ethyl 2-chloro- α -[[[(4-methylthio)phenyl]amino]methylene]- β -oxo-benzenepropionate with 1.5 eq. of 3-chloroperoxybenzoic acid gave a mixture of the corresponding sulfoxide and sulfone which were separated by chromatography (2% MeOH/CH₂Cl₂);

5 ethyl 2-chloro- α -[[[(4-propylphenyl)amino]methylene]- β -oxo-benzenepropionate;

ethyl 2-chloro- β -oxo- α -[[[(4-trifluoromethoxyphenyl)amino]methylene]-
benzenepropionate, mp 98.5-103.5 °C; and

ethyl α -[[[(4-butylphenyl)amino]methylene]-2-nitro- β -oxo-benzenepropiona

Example 8

10 *2-Chloro- α -[[[(4-iodophenyl)amino]methylene]- β -oxobenzenepropanoic acid*

A solution of 1,1-dimethylethyl 2-chloro- α -[[[(4-iodophenyl)amino]methylene]- β -oxobenzenepropanoate (17.9 mg, 0.037 mmol) in CH₂Cl₂ was treated with thioanisole (17.5 μ L, 18.5 mg, 0.15 mmol) and trifluoroacetic acid (35 μ L, 52 mg, 0.454 mmol) at 0 °C. The reaction was stirred at rt for 45 m and concentrated in vacuo. The residue was purified by flash
15 chromatography (2.5 % MeOH/CH₂Cl₂), affording 13 mg of the acid as a white solid, mp 202.5-205 °C. MS 450 (M + Na⁺) 100, 428 (M⁺) 27.

Example 9

2-Chloro-N,N-dimethyl- α -[[[(4-iodophenyl)amino]methylene]- β -oxobenzenepropanamide

To a suspension of 2-chloro- α -[[[(4-iodophenyl)amino]methylene]- β -
20 oxobenzenepropanoic acid (43 mg, 0.10 mmol) in 1 mL of CH₂Cl₂ was added N,N'-dicyclohexylcarbodiimide (21 mg, 0.10 mmol). The mixture was cooled in an ice bath and 50 μ L (0.10 mmol) of a 2M solution of dimethylamine in THF was added. The reaction mixture was stirred at rt for 16 h. The formed DCU was removed by filtration. The filtrate was washed with water and evaporated to dryness. The title compound (22 mg, 50 %) was isolated by column
25 chromatography (5% MeOH in CH₂Cl₂); MS 410 (M - 45), 455(M + 1), 477(M + Na⁺).

The following compounds were prepared as described in the foregoing examples:

2-Chloro-N-[(2-dimethylamino)ethyl]- α -[[[(4-iodophenyl)amino]methylene]- β -
oxobenzenepropanamide, mp 145-147 °C, MS: 497 (100); 520(22).

Example 10

30 *1,3-Diphenyl-2-[[[(4-iodophenyl)amino]methylene]-1,3-propanedione*

2-[(Dimethylamino)methylene]-1,3-diphenyl-1,3-propanedione: To a solution of dibenzoylmethane (1.072 g, 4.78 mmol) in 6 mL of toluene was added neat N,N-

dimethylformamide dimethylacetal (0.7 mL, 630 mg, 5.25 mmol) dropwise via syringe. The resulting solution was stirred at rt for 1 h and then heated at reflux for 16 h. Once at rt, the reaction was concentrated in vacuo. The residue was dissolved in a minimum of CH₂Cl₂ and added to 13 cm of flash silica gel in a 5 cm dia. column. Elution with 1 L of 1%, 500 mL of 2% and 300 mL of 3% MeOH/ CH₂Cl₂ gave 975 mg of the desired product as a semisolid. Trituration with 50 mL of hexanes gave 772 mg of the title compound as a light yellow solid, mp 123-124 °C (lit mp 120 °C, Schenone, P. *et al. J. Het. Chem.* 1982, 19(6), 1355-61).

1,3-Diphenyl-2-[[4-iodophenyl]amino]methylene]-1,3-propanedione: A solution of 1,3-diphenyl-2-[(dimethylamino)methylene]-1,3-propanedione (317 mg, 1.13 mmol) in 5.5 mL of MeOH was treated with solid 4-iodoaniline (245 mg, 1.12 mmol). The resulting solution was stirred at rt overnight. The resulting precipitate was isolated by filtration and washed with MeOH. The title compound was isolated as a light yellow solid.

Additional compounds prepared are as follows:

α -[[4-chlorophenyl]amino]methylene]-N-isopropyl- β -oxobenzenepropanamide;

4-chloro- α -[[4-ethoxyphenyl]amino]methylene]-N-propyl- β -oxobenzene-propanamide;

α -[[4-chlorophenyl]amino]methylene]-N-isopropyl- β -oxobenzenepropanamide; ¹H

NMR (400 MHz, CDCl₃) δ 12.83 (d, 1H, J = 12.4 Hz), 9.50 (d, 1H, J = 6.5 Hz), 7.93 (d, 1H, J = 12.4 Hz), 7.53-7.44 (m, 5H), 7.25 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 4.19 (octet, 1H, J = 6.7 Hz), 1.28 (d, 6H, J = 6.4 Hz).

2-chloro- α -[[4-chlorophenyl]amino]methylene]-N-isopropyl- β -oxobenzene-propanamide; TOF MS ES+ m/z 399, 401 (M + Na⁺);

2-chloro- α -[[4-chlorophenyl]amino]methylene]-N-ethyl- β -oxobenzenepropanamide; TOF MS ES+ m/z 285, 287 (M + Na⁺);

2-chloro- α -[[4-ethoxyphenyl]amino]methylene]-N-ethyl- β -oxobenzene-propanamide;

¹H NMR (400 MHz, CDCl₃) δ 12.89 (d, 1H, J = 12.5 Hz), 9.59 (s, 1H), 7.60 (d, 1H, J = 12.7 Hz), 7.46-7.29 (m, 4H), 6.82 (m, 4H), 3.96 (q, 2H, J = 7.0 Hz), 3.45 (br m, 2H), 1.38 (t, 3H, J = 6.9 Hz), 1.28 (t, 3H, J = 7.2 Hz);

2-chloro- α -[[4-chlorophenyl]amino]methylene]-N-propyl- β -oxobenzene-propanamide; TOF MS ES+ m/z 399, 401 (M + Na⁺);

2-chloro- α -[[4-chlorophenyl]amino]methylene]-N-(1-methylpropyl)- β -oxobenzene-propanamide; (07TBCJ71) ¹H NMR (400 MHz, CDCl₃) δ 13.00 (d, 1H, J = 12.2 Hz), 9.46 (d, 1H, J = 7.6 Hz), 7.64 (d, 1H, J = 12.4 Hz), 7.48-7.24 (m, 6H), 6.83 (d, 2H, J = 8.8 Hz), 4.04 (m,

1H), 1.63 (m, 2H), 1.27 (d, 3H, J = 6.6 Hz), 1.00 (t, 3H, J = 7.6 Hz). TOF MS ES+ m/z 413, 415 (M + Na⁺);

2-chloro-N-ethyl- α -[[α -methyl-4-fluorobenzyl)amino]methylene]- β -oxobenzene-propanamide;

5 2-chloro-N-ethyl- α -[[α -methylbenzyl)amino]methylene]- β -oxobenzene-propanamide;

2-chloro-N-propyl- α -[(2-methyl-1-phenylhydrazino)methylene]- β -oxobenzene-propanamide;

2-chloro- α -[[4-iodophenyl)amino]methylene]-N-methyl- β -oxobenzene-propanamide; ¹H NMR (400 MHz, CDCl₃) δ 12.94 (d, 1H, J = 12.4 Hz), 9.48 (br s, 1H), 7.65 (d, 1H, J = 12.4 Hz), 7.60 (d, 2H, J = 8.7 Hz), 6.65 (d, 2H, J = 8.7 Hz), 2.97 (d, 3H, J = 4.6 Hz);

2-chloro- α -[[4-chlorophenyl)amino]methylene]-N-methyl- β -oxobenzene-propanamide; TOF MS ES+ m/z 371, 373 (M + Na⁺);

2-chloro- α -[[4-chlorophenyl)amino]methylene]-N-(α -methylbenzyl)- β -oxobenzene-propanamide;

15 α -[[4-chlorophenyl)amino]methylene]-N-isopropyl- β -oxobenzenepropanamide; ¹H NMR (400 MHz, CDCl₃) δ 12.83 (d, 1H, J = 12.4 Hz), 9.50 (d, 1H, J = 6.5 Hz), 7.93 (d, 1H, J = 12.4 Hz), 7.53-7.44 (m, 5H), 7.25 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 4.19 (octet, 1H, J = 6.7 Hz), 1.28 (d, 6H, J = 6.4 Hz).

4-chloro- α -[[4-ethoxyphenyl)amino]methylene]-N-propyl- β -oxobenzene-propanamide;

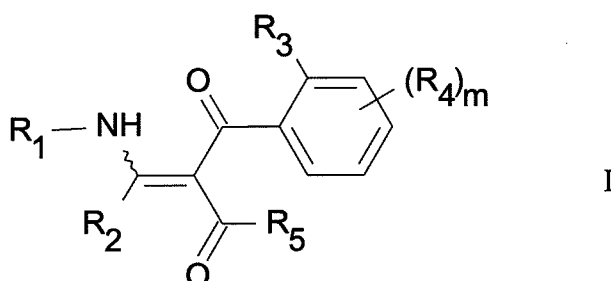
20

Table 1: Inhibition of [³⁵S]TBPS binding by Enaminones

Compound	[³⁵ S]TBPS IC ₅₀ (μ M)	I _{max} (%)
ethyl 2-chloro- α -[[4-ethynylphenyl)-amino]methylene]- β -oxobenzenepropionate	0.01	95
ethyl 2-chloro- α -[[4-iodophenyl)-amino]methylene]- β -oxobenzenepropionate	0.02	86
α -[[4-ethynylphenyl)amino]methylene]-2-methyl- β -oxo-N-propyl-benzenepropanamide	0.02	95
ethyl 2-chloro- α -[[4-cyanophenyl)-amino]methylene]- β -oxobenzenepropionate	0.06	100
2-methyl- α -[[4-methylphenyl)amino]methylene]- β -oxo-N-propyl-benzenepropanamide	0.10	100
ethyl α -[[4-fluorophenyl)amino]methylene]- β -oxo-1-naphthalenepropionate	0.20	81
ethyl 2-chloro- α -[[2-chlorophenyl)-amino]methylene]- β -oxobenzenepropionate	0.42	100

WHAT IS CLAIMED IS:

1. A compound comprising the Formula I:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R₁ is selected from the group consisting of aryl, heteroaryl and aralkyl, each unsubstituted or substituted;

R₂ is selected from the group consisting of hydrogen and unsubstituted or substituted C₁₋₁₀alkyl;

R₃ is selected from the group consisting of fluoro, chloro, bromo, iodo, C₁₋₁₀alkoxy, nitro, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl and unsubstituted or substituted C₁₋₁₀alkyl;

each R₄ is independently selected from the group consisting of halogen, nitro, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R₅ is selected from the group consisting of C₁₋₁₀alkoxy, -NH₂, C₁₋₁₀alkylamino, di(C₁₋₁₀)alkylamino and aryl, each unsubstituted or substituted;

and

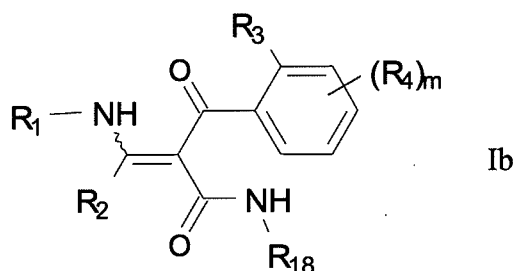
m is 0, 1, 2, 3 or 4; with the proviso that when R₅ is -OEt, then R₄ is not halogen, and the compound of Formula I is not ethyl α-[(benzyl)aminomethylene]-2-chloro-β-oxobenzenepropionate.

2. A compound according to claim 1:

wherein:

R₅ is selected from the group consisting of CH₃O-, C₃₋₁₀alkoxy, -NH₂, C₁₋₁₀alkylamino, di(C₁₋₁₀)alkylamino and aryl, each unsubstituted or substituted.

3. The compound of Formula Ib:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R₁ is selected from the group consisting of aryl, heteroaryl, aralkyl and R₁₆R₁₇N-, each unsubstituted or substituted;

R₂ is selected from the group consisting of hydrogen and unsubstituted or substituted C₁₋₁₀alkyl;

R₃ is selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted;

each R₄ is independently selected from the group consisting of hydrogen, halo, haloC₁₋₁₀alkyl, perhaloC₁₋₁₀alkyl, amino, cyano, nitro, hydroxy, thio, C₁₋

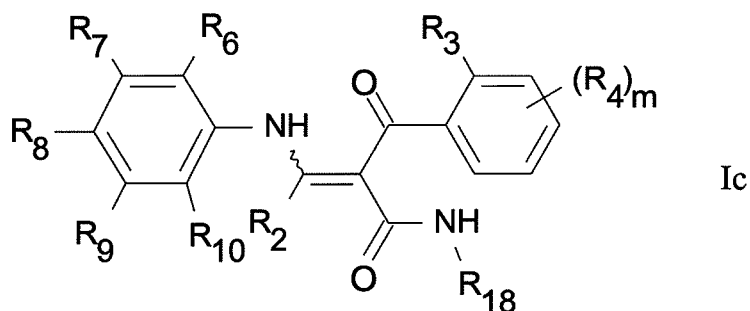
₂₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, C₁₋₁₀alkoxy, aryloxy, heteroaryloxy, carbonyl group, sulfonyl group, sulfinyl group, imino group, each unsubstituted or substituted, or wherein R₃ and an adjacent R₄ together form a fused unsubstituted or substituted 5 or 6 membered cycloalkyl, aryl or heteroaryl ring;

R₁₆ and R₁₇ are each independently C₃₋₁₂cycloalkyl, aryl, heteroaryl, C₁₋₁₀alkyl, each unsubstituted or substituted, or R₁₆ and R₁₇ together with the nitrogen atom to which they are attached form an unsubstituted or substituted 4, 5 or 6 membered ring;

R₁₈ is selected from the group consisting of optionally substituted C₁₋₁₀alkyl, arylalkyl and heterocycloalkyl; and

m is 0, 1, 2, 3 or 4.

4. A compound of Claim 3 comprising the Formula Ic:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

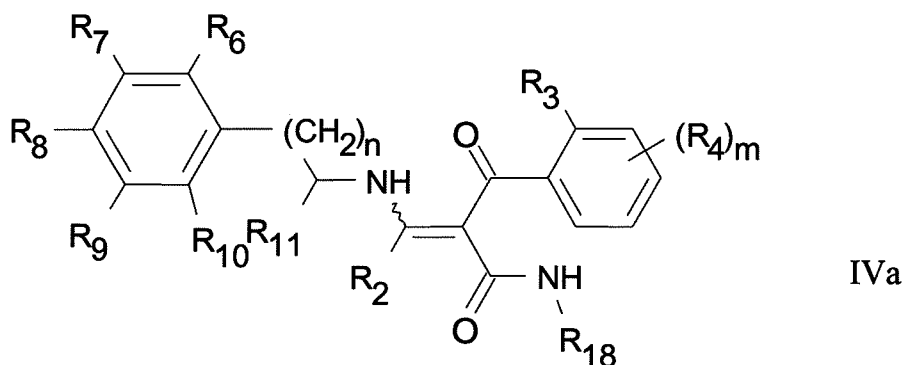
R₂ is selected from a group consisting of hydrogen, methyl and ethyl;

R₃, R₄, R₁₈ and m are as defined in claim 3; and

R₆, R₇, R₈, R₉ and R₁₀ are each independently selected from the group consisting of hydrogen, halo, C₁₋₁₀alkyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, aralkyl, cycloalkyl, arylC₁₋₁₀alkyl and heteroarylC₁₋₁₀alkyl; or R₆ and R₇, or R₇ and R₈, or R₈ and R₉, or R₉ and R₁₀ are taken together with the carbon atoms to which they are

attached to form an unsubstituted or substituted fused 5 or 6 membered saturated, partially unsaturated ring, aryl or heteroaryl.

5. A compound of Claim 3 comprising the Formula IVa:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_2 is selected from the group consisting of hydrogen, methyl and ethyl;

R_3 , R_4 , R_{18} and m are as defined in claim 3;

R_6 , R_7 , R_8 , R_9 and R_{10} are each independently selected from the group consisting of hydrogen, halo, C_{1-10} alkyl, C_{2-10} alkynyl, C_{1-10} alkoxy, aralkyl, cycloalkyl, aryl C_{1-10} alkyl and heteroaryl C_{1-10} alkyl; or R_6 and R_7 , or R_7 and R_8 , or R_8 and R_9 , or R_9 and R_{10} are taken together with the carbon atoms to which they are attached to form an unsubstituted or substituted fused 5 or 6 membered saturated, partially unsaturated ring, aryl or heteroaryl;

R_{11} is hydrogen or is an unsubstituted or substituted C_{1-10} alkyl; and

n is 0, 1, 2, 3, 4 or 5.

6. A compound of Claim 3 that is:

2-Chloro- α -[[(4-cyanophenyl)amino]methylene]-N-ethyl- β -oxo-benzenepropanamide;

2-Chloro-N-ethyl- α -[[4-iodophenyl]amino]methylene]- β -oxo-benzenepropanamide;

2-Chloro- α -[[4-iodophenyl]amino]methylene]- β -oxo-N-(2-propynyl)-benzenepropanamide;

2-Chloro- α -[[4-ethynylphenyl]amino]methylene]- β -oxo-N-propyl-benzenepropanamide;

α -[[4-Ethynylphenyl]amino]methylene]-2-methyl- β -oxo-N-propyl-benzenepropanamide;

α -[[4-Cyanophenyl]amino]methylene]-2-methyl- β -oxo-N-propyl-benzenepropanamide;

α -[[4-Ethynylphenyl]amino]methylene]-2-methyl- β -oxo-N-(2-propynyl)-benzenepropanamide;

2-Chloro- α -[[4-cyanophenyl]amino]methylene]- β -oxo-N-propyl-benzenepropanamide;

2-Chloro-N-ethyl- α -[(isoxazolyl-3-amino)methylene]- β -oxo-benzenepropanamide;

α -[(4-Ethynylphenyl)aminomethylene]- β -oxo-N-propyl-1-naphthalenepropanamide;

2-Chloro- α -[(isoxazolyl-3-amino)methylene]- β -oxo-N-propyl-benzenepropanamide;

2-Chloro-N-ethyl- β -oxo- α -[(1,2,4-triazolyl-4-amino)methylene]benzenepropanamide;

α -[(4-Ethynylphenyl)aminomethylene]- β -oxo-N-propyl-1-naphthalenepropanamide;

2-Chloro-N-ethyl- β -oxo- α -[(pyrazinyl)amino]-benzenepropanamide;

α -[[[4-chlorophenyl]amino]methylene]-N-isopropyl- β -oxobenzene-propanamide;

2-chloro- α -[[[4-chlorophenyl]amino]methylene]-N-isopropyl- β -oxobenzene-propanamide;

2-chloro- α -[[[4-chlorophenyl]amino]methylene]-N-ethyl- β -oxobenzene-propanamide;

2-chloro- α -[[[4-ethoxyphenyl]amino]methylene]-N-ethyl- β -oxobenzene-propanamide;

2-chloro- α -[[[4-chlorophenyl]amino]methylene]-N-propyl- β -oxobenzene-propanamide;

2-chloro- α -[[[4-chlorophenyl]amino]methylene]-N-(1-methylpropyl)- β -oxobenzene-propanamide;

2-chloro-N-ethyl- α -[[[α -methyl-4-fluorobenzyl]amino]methylene]- β -oxobenzene-propanamide;

2-chloro-N-ethyl- α -[[[α -methylbenzyl]amino]methylene]- β -oxobenzene-propanamide;

2-chloro-N-propyl- α -[2-methyl-1-phenylhydrazino]methylene]- β -oxobenzene-propanamide;

2-chloro- α -[[[4-iodophenyl]amino]methylene]-N-methyl- β -oxobenzene-propanamide;

2-chloro- α -[[[4-chlorophenyl]amino]methylene]-N-methyl- β -oxobenzene-propanamide; and

2-chloro- α -[[[4-chlorophenyl]amino]methylene]-N-(α -methylbenzyl)- β -oxobenzene-propanamide.

7. A pharmaceutical composition comprising the compound of Claim 1 or 3 and a pharmaceutically-acceptable carrier selected from the group consisting of excipients and auxiliaries.
8. A pharmaceutical composition comprising the compound of Claim 4 and a pharmaceutically-acceptable carrier selected from the group consisting of excipients and auxiliaries.
9. A pharmaceutical composition comprising the compound of Claim 5 and a pharmaceutically-acceptable carrier selected from the group consisting of excipients and auxiliaries.
10. A pharmaceutical composition comprising the compound of Claim 6 and a pharmaceutically-acceptable carrier selected from the group consisting of excipients and auxiliaries.
11. A compound as defined in Claim 1 or 3 for the treatment of a CNS disorder amenable to modulation of the GABA_A receptor complex.
12. The compound of Claim 11, wherein the CNS disorder is selected from the group consisting of an anxiety disorder, insomnia, a major depressive and a bipolar disorder.
13. The compound of Claim 11, wherein the CNS disorder is convulsions or withdrawal-induced convulsions from substance abuse.
14. The compound of Claim 11, wherein the CNS disorder is chronic or acute pain.
15. The compound of Claim 11, wherein the CNS disorder is selected from the group consisting of a neuroses, a phobia, a panic disorder, a generalized anxiety disorder, an obsessive-compulsive disorder and a bipolar manic disorder.
16. The compound of Claim 11, wherein the CNS disorder is a post traumatic and acute stress disorder.

17. The compound of Claim 11, wherein the CNS disorder is a migraine.
18. The compound of Claim 11, wherein the CNS disorder is a cognition deficit disorder.
19. The compound of Claim 11, wherein the CNS disorder is selected from the group consisting of anxiety and stress related disorders, depression and other affective disorders, epilepsy and other seizure disorders, insomnia and related sleep disorders, acute and chronic pain, and cough.
20. A compound as defined in Claim 1 or 3 for the treatment of a disorder related to learning and memory.
21. The Compound of Claim 20, wherein the disorder relating to learning and memory is selected from the group consisting of mild cognitive impairment, age related cognitive decline, senile dementia, Alzheimer's disease and sleep disorders involving reduced wakefulness.
22. The compound of Claim 21, wherein the sleep disorder involving reduced wakefulness is selected from the group consisting of narcolepsy and idiopathic hypersomnia.
23. A compound as defined in Claim 1 or 3 for the treatment of a CNS disorder amenable to modulation of the nAChR complex.
24. A compound as defined in Claim 1 or 3 for the treatment of a neurodegenerative disorder.
25. A compound as defined in Claim 1 or 3 for the treatment of a senile dementia.
26. A compound as defined in Claim 1 or 3 for the treatment of schizophrenia.
27. A compound as defined in Claim 1 or 3 for the treatment of a cognition deficit disorder.