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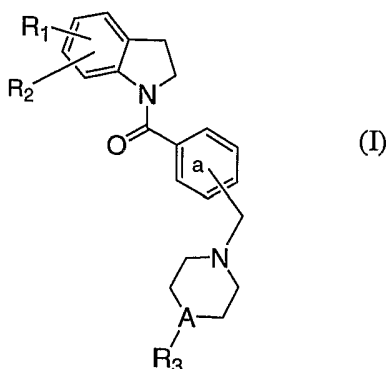
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(54) Title: DIHYDROINDOLYL METHANONES AS ALPHA 1A/1D ADRENORECEPTOR MODULATORS FOR THE TREATMENT OF BENIGN PROSTATIC HYPERTROPHY AND LOWER URINARY TRACT SYMPTOMS



(57) Abstract: The present invention relates to new compounds of Formula (I) and pharmaceutically acceptable forms thereof, use of the compounds as α_{1a} and/or α_{1d} adrenoreceptor modulators, including use of a pharmaceutical composition, medicine or medicament comprising said compounds, a process to prepare said compounds and a method for treating an α_{1a} and/or α_{1d} adrenoreceptor mediated disorder.

**DIHYDROINDOLYL METHANONES AS ALPHA 1A/1D
ADRENORECEPTOR MODULATORS FOR THE TREATMENT OF BENIGN
PROSTATIC HYPERTROPHY AND LOWER URINARY TRACT SYMPTOMS**

CROSS REFERENCE TO RELATED APPLICATIONS

- 5 This present application claims benefit of U.S. Provisional Patent Application Serial No. 60/653,218, filed February 15, 2005, which is incorporated herein by reference in its entirety and for all purposes.

FIELD OF THE INVENTION

- 10 The present invention relates to new compounds, more particularly new dihydroindolyl methanones as α_{1a}/α_{1d} adrenoreceptor modulators for the treatment of benign prostatic hypertrophy and/or lower urinary tract symptoms. The present invention also relates to pharmaceutical compositions comprising said new compounds, new processes to prepare these new compounds, to the use of these compounds as α_{1a}/α_{1d} adrenoreceptor modulators and new uses as a medicine as well as method of treatments.

15 **RELATED ART**

- The adrenergic receptors (ARs), through which norepinephrine and epinephrine exert their biological activities, are targets for many therapeutically important drugs. The α_1 -ARs play a dominant role in control of smooth muscle contraction and are important in control of blood pressure, nasal congestion, prostate function, and other processes (Harrison et al., Trends
20 Pharmacol Sci; 1991; 62-67). The α_1 -ARs were originally classified by pharmacological profiling into two subtypes, α_{1a} and α_{1b} (Morrow and Creese, Mol. Pharmacol; 1986; 29: 231-330; Minneman et al., Mol. Pharmacol; 1988; 33:509-514). Three genes encoding different α_1 -AR subtypes (α_{1a} , α_{1b} , and α_{1d}) have been cloned for a number of species, including human (Schwinn et al., J.Biol Chem; 1990; 265: 8183-8189; Ramarao et al., J Biol Chem; 1992;
25 267:21936-21945; Bruno et al., Biochem Biophys Res Commun; 1991; 179: 1485-1490). These three cloned α_1 -ARs are best differentiated from one another on the basis of the relative binding affinities of a series of antagonist compounds. There is general agreement that the α_{1a} - and α_{1b} -ARs correspond to the pharmacologically defined α_{1a} - and α_{1b} -ARs, while the functional role of the α_{1d} -AR is less clear, although it appears to mediate contraction of certain
30 blood vessels (Goetz et al., Eur J Pharmacol; 1991; 272:R5-R6). Like other ARs, the α_1 -ARs are members of the G-protein coupled receptor super family, and in most cells the primary functional response to activation of all α_1 -AR subtypes is an increase in intracellular Ca^{2+} .

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate and is the cause of lower urinary tract symptoms (LUTS) in a large segment of the elderly male

population. Symptoms such as straining, hesitancy, dribbling, weak stream, and incomplete emptying are classified as voiding or obstructive symptoms. Obstructive symptoms are primarily due to pressure upon the urethra from the physical mass of the enlarged prostate gland (the static component) and the increased tone of the smooth muscle of the prostate stroma and bladder neck (the dynamic component) (Caine, J Urol; 1986; 136: 1-4). Irritative or storage symptoms associated with BPH are frequency, urgency, nocturia, dysuria, and burning sensation. Patients feel that these symptoms are more disturbing than the obstructive symptoms. As the urine flow is reduced, due to the bladder outlet obstruction, the wall around the bladder base thickens and becomes hyperactive.

Functional studies have established that prostate smooth muscle tone is maintained through α_1 -ARs and that these receptors mediate the dynamic component of obstruction. α_1 -AR antagonists have successfully been used to treat the obstructive symptoms associated with BPH (Jardin et al., Scientific Communications Int; 1998; pp 559-632). Furthermore, the α_{1a} -AR subtype comprises the majority of α_1 -ARs in human prostatic smooth muscle and has been shown to mediate contraction in this tissue. Originally introduced as antihypertensive agents, α_1 -AR antagonists have become increasingly important in the management of BPH. α_1 -AR antagonists reduce smooth muscle tone in the prostate and lower urinary tract, thereby relaxing the bladder outlet and increasing urinary flow. The major disadvantage of non-selective α_1 -blockers is their adverse effect profile, particularly vasodilatation leading to dizziness, postural hypotension, asthenia, and occasionally syncope. For this reason, it would be desirable to block α_1 -ARs in the lower urinary tract without antagonizing the α_1 -ARs responsible for maintaining vascular tone.

A number of factors can be involved in lower urinary tract symptoms. Adrenergic stimulation of the bladder results in relaxation due to β -ARs, which dominate over contraction-mediating α_1 -ARs. Bladder contraction is primarily mediated by muscarinic receptors. Some studies indicate that the contribution from α_1 -ARs increases in hyperactive bladders due to bladder outlet obstruction or other conditions (Perlberg et al., Urology; 1982; 20:524-527); Restorick and Mundy, Br J Urol; 1989; 63: 32-35). However another study finds no change in α_1 -AR receptor function between normal and hypertrophic bladder due to outlet obstruction (Smith and Chapple, Neurolog Urodyn; 1994; 12: 414-415). It remains unclear, which α_1 -AR is dominant in the human bladder. One study reported a predominance of the α_{1a} subtype mRNA in the bladder dome, base, and trigone (Walden et al., J Urol; 1997; 157: 414-415). Another report found that the α_{1d} subtype is present as 66% of the α_1 -ARs at both the mRNA and protein levels, while the α_{1a} subtype is present as 34% of the total, with no evidence of the α_{1b} subtype (Malloy et al., J Urol; 1998; 160: 937-943). Drugs that selectively antagonize only

the α_{1a} -AR subtype appear to have little effect upon the irritative symptoms of BPH. Ro-70004, a α_{1a} subtype-selective compound was reported to be discontinued in clinical studies when it was found to have poor efficacy in treating these symptoms (Blue et al., Abstract 5th International Consultation on BPH (June 25-28) 2000). α_{1d} -ARs may be involved in mediating the irritative symptoms; however, the location of these α_{1d} -ARs is unknown (Piascik and Perez, J Pharmacol Exp Ther; 2001; 298: 403-410).

Studies have demonstrated Central Nervous Systems (CNS) inhibitory effects of α_1 antagonists upon the sympathetic and somatic outflow to the bladder in cats (Danuser and Thor, J Urol; 1995; 153: 1308-1312; Ramage and Wyllie, Eur J Pharmacol; 1995; 294: 645-650). Intrathecally administered doxazosin caused a decrease in micturition pressure in both normal rats and rats with bladder hypertrophy secondary to outlet obstruction (Ishizuka et al., Br J Pharmacol; 1996; 117:962-966). These effects may be due to a reduction in parasympathetic nerve activity in the spinal cord and ganglia. Other studies used spontaneously hypertensive rats, which have overactive bladders, to demonstrate that α_1 -AR antagonism only given intrathecally caused a return to normal micturition (Persson et al., Am J Physiol; 1998; 275:R1366-1373, Steers et al. 1999; Exp Physiol; 84:137-147.). Antagonists administered intra-arterially near the bladder, or ablation of peripheral noradrenergic nerves, had no effect upon the bladder overactivity in these animals, indicating that α_1 -ARs in the spinal cord control the bladder activity. Spinal α_1 -ARs may be important targets for pharmacological treatment of BPH symptoms in humans as well. All three α_1 -AR subtype mRNAs are found throughout the human spinal cord, however the α_{1d} subtype mRNA is present at twice the level of the other subtypes, particularly in the ventral sacral motor neurons and autonomic parasympathetic pathways. (Stafford-Smith et al., Mol Brain Res; 1998; 63:234-261). There may be clinical advantages to the pharmacological blockade of the α_{1d} -ARs in the CNS in reducing BPH symptoms.

Antagonism of α_{1d} -ARs in the CNS and bladder may be an important activity in reducing the irritative or filling symptoms of BPH and improving patient symptom scores. Tamsulosin (Flomax®, Yamanuchi and Boehringer Ingelheim) is a α_1 -AR antagonist, which is about 15-fold selective for the α_{1a} and α_{1d} subtypes over the α_{1b} subtype. Large clinical trials of BPH patients with tamsulosin showed improvement in both obstructive and irritative symptoms, however, cardiovascular and erectile dysfunction side effects were seen (Abrams et al. Br J Urol; 1995; 76:325-336; Chapple et al., Eur Urol; 1996; 29:155-167; Lepor, Urology; 1998; 51:892-900). Patients treated with non-selective α_1 antagonists also have improvement in both obstructive and irritative symptoms, although the risk of vascular side effects is greater. Generally, the α_{1a} subtype predominates in arteries at the mRNA and protein levels, while all

three subtypes are found in veins. The particular vessel bed is important in that the α_{1a} is the subtype found primarily in the splanchnic and coronary arteries, while the α_{1d} subtype is the predominant subtype found in the aorta. The α_1 -AR subtypes in the vasculature have been found to change with age. Contraction of the mammary artery is mediated by both α_{1a} and α_{1b} subtypes. The number of α_1 receptors in the mammary artery doubles with age; however, the α_{1b} subtype increases to a greater extent than the α_{1a} subtype (Raudner et al., Circulation; 1999; 100:2336-2343). The α_{1b} subtype may play a greater role in vascular tone in elderly patients. This suggests that an α_{1a} and α_{1d} -selective antagonist may have less effects upon the vasculature in elderly BPH patients, resulting in fewer cardiovascular side effects than are seen with non-selective α_1 antagonists, but provide relief from both obstructive and irritative symptoms.

A uroselective, cardiovascular-sparing α_1 -AR antagonist would be expected to provide symptomatic relief of BPH comparable to currently marketed non-selective agents such as terazosin/Hytrin[®], doxazosin/Cardura[®], alfuzosin/Xatral[®]/Uroxatral[®] and weakly selective tamsulosin/Flomax[®]/Harnal[®], without the undesirable side effects of postural hypotension, dizziness, and syncope. Ejaculatory dysfunction, or retrograde ejaculation, is a side effect seen in 10 to 35 % of patients using tamsulosin (Lepor, Urology; 1998; 51:901-906; Andersson and Wyllie, Brit J Urol Int; 2003; 92:876-877). This activity has been attributed to tamsulosin antagonism at the 5-HT_{1a} receptor. This often leads to discontinuation of treatment. Furthermore, the non-selective α_1 -AR antagonists and tamsulosin are contraindicated for use in conjunction with PDE inhibitors. There is likely to be high comorbidity between LUTS and erectile dysfunction patients. Patients being treated for LUTS with the current α_1 -AR blockers will find that they are excluded from using PDE inhibitors. An α_1 -AR antagonist with a receptor subtype binding profile, which is selective for the α_{1a} and α_{1d} subtypes, but with relatively little antagonism of the α_{1b} subtype may effectively treat both obstructive and irritative symptoms of BPH. Such a compound is likely to have a low cardiovascular side effect profile and allow for use in conjunction with PDE inhibitors. Also low binding activity at the 5-HT_{1a} receptor is likely to reduce the incidence of ejaculatory side effects.

LUTS also develop in women of a certain age. As in men, LUTS in women include both filling symptoms such as urgency, incontinence and nocturia, and voiding symptoms such as weak stream, hesitancy, incomplete bladder emptying and abdominal straining. The presence of this condition both in men and women suggests that at least part of the aetiology may be similar in the two sexes.

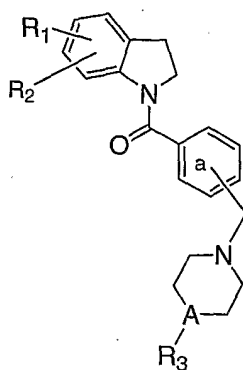
A (2,3-dihydro-indol-1-yl)-{4-[4-(2-isopropoxy-phenyl)-piperazine-1-ylmethyl]}-

phenyl}-methanone compound has been described as an antipsychotic having α_1 -AR activity (The Journal of Medicinal Chemistry, Vol. 41 (12), pp 1997 – 2009).

Accordingly, there is a need to provide dual selective α_{1a}/α_{1d} adrenoreceptor modulators, particularly dual selective α_{1a}/α_{1d} adrenoreceptor antagonists, in other words
 5 compounds that interact both with the α_{1a} and α_{1d} receptor but do not interact (or at least interact substantially less) with the α_{1b} receptor. The compounds of this invention are believed to be more efficacious drugs mainly for BPH/LUTS patients, and at the same time these compounds should show less unwanted side effects than the existing pharmaceuticals.

SUMMARY OF THE INVENTION

10 The present invention provides a compound of Formula (I)



and pharmaceutically acceptable forms thereof, wherein

“a” represents a point of attachment selected from the 3 or 4 position on the phenyl ring relative to the point of attachment of the methanone group for the compound of Formula (I),

“A” is a ring atom selected from CH or N,

- 15 R_1 is one substituent selected from the group consisting of hydrogen, -N-, halogen and nitro, wherein -N- is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkyl(C_{1-8} alkoxy), $C(O)(R^A)$, $C(O)O(R^A)$, $C(O)NH_2$, $C(O)NH(C_{1-8}alkyl)$, $C(O)N(C_{1-8}alkyl)_2$, $C(O)NH(R^A)$, $C(O)N(R^A)_2$, $C(O)NH(C_{1-8}alkyl-R^A)$, $C(O)N(C_{1-8}alkyl-R^A)_2$, $C(S)NH(R^A)$, $C(S)N(R^A)_2$,
 20 $C(S)NH(C_{1-8}alkyl-R^A)$, $C(S)N(C_{1-8}alkyl-R^A)_2$, $SO_2(C_{1-8}alkyl)$, $SO_2(R^A)$, SO_2NH_2 , $SO_2NH(C_{1-8}alkyl)$, $SO_2N(C_{1-8}alkyl)_2$, $SO_2NH(R^A)$, $C_{1-8}alkyl(R^A)$ and R^A ,
 R_2 is one substituent selected from the group consisting of hydrogen, -SO₂- and R^A , wherein -SO₂- is substituted with $C_{1-8}alkyl$, NH_2 , $NH(C_{1-8}alkyl)$ or $N(C_{1-8}alkyl)_2$,
 R^A is selected from the group consisting of C_{3-12} cycloalkyl, heterocyclyl, aryl and heteroaryl,
 25 wherein each is optionally substituted with one to three substituents independently selected from the group consisting of $C_{1-10}alkyl$, $C_{1-8}alkoxy$, $C_{1-8}alkyl(C_{1-8}alkoxy)_{1-2}$,

C₁₋₈alkyl(halogen)₁₋₃, C₁₋₈alkoxy(halogen)₁₋₃, C₁₋₈alkyl(hydroxy), NH₂, NH(C₁₋₈alkyl), N(C₁₋₈alkyl)₂, halogen, hydroxy, C(O)NH₂, C(O)NH(C₁₋₈alkyl), C(O)N(C₁₋₈alkyl)₂, NHC(O)H and NHC(O)(C₁₋₈alkyl),

R₃ is selected from the group consisting of C₁₋₈alkyl(R^B), -C(O)(C₁₋₈alkoxy) and R^B, and

- 5 R^B is selected from the group consisting of C₃₋₁₂cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₁₀alkyl, C₁₋₈alkoxy, C₁₋₈alkyl(C₁₋₈alkoxy)₁₋₂, C₁₋₈alkyl(halogen)₁₋₃, C₁₋₈alkoxy(halogen)₁₋₃, C₁₋₈alkyl(hydroxy), C₁₋₈alkoxy(hydroxy), cyano, halogen and hydroxy,
- 10 with the proviso that (2,3-dihydro-indol-1-yl)-{4-[4-(2-isopropoxy-phenyl)-piperazine-1-ylmethyl]-phenyl}-methanone is not included as a compound of Formula (I).

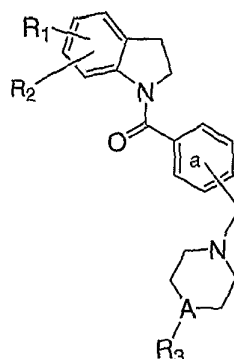
Examples of the invention include pharmaceutical compositions comprising a therapeutically effective amount of any of the compounds of Formula (I) described in the present application and a pharmaceutical acceptable carrier.

- 15 An example of the invention is a pharmaceutical composition made by combining any of the compounds of Formula (I) described in the present application and a pharmaceutically acceptable carrier.

- Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described in the present application and a pharmaceutically acceptable carrier.
- 20

The present invention further provides a method for treating a patient suffering from a disease or disorder mediated by dual selective α_{1a}/α_{1d} adrenoreceptor modulators comprising administering to the patient an effective amount of the compound of Formula (I) and pharmaceutically acceptable forms thereof.

An example of the invention includes a method for treating a patient suffering from a disease or disorder mediated by dual selective α_{1a}/α_{1d} adrenoreceptor modulators comprising administering to the patient an effective amount of a compound of Formula (II).



and pharmaceutically acceptable forms thereof, wherein

- 5 “a” represents a point of attachment selected from the 3 or 4 position on the phenyl ring relative to the point of attachment of the methanone group for the compound of Formula (II),

“A” is a ring atom selected from CH or N,

R₁ is one substituent selected from the group consisting of hydrogen, -N-, halogen and nitro,

- 10 wherein -N- is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl, C₁₋₈alkyl(C₁₋₈alkoxy), C(O)(R^A), C(O)O(R^A), C(O)NH₂, C(O)NH(C₁₋₈alkyl), C(O)N(C₁₋₈alkyl)₂, C(O)NH(R^A), C(O)N(R^A)₂, C(O)NH(C₁₋₈alkyl-R^A), C(O)N(C₁₋₈alkyl-R^A)₂, C(S)NH(R^A), C(S)N(R^A)₂, C(S)NH(C₁₋₈alkyl-R^A), C(S)N(C₁₋₈alkyl-R^A)₂, SO₂(C₁₋₈alkyl), SO₂(R^A), SO₂NH₂, SO₂NH(C₁₋₈alkyl), SO₂N(C₁₋₈alkyl)₂, SO₂NH(R^A), C₁₋₈alkyl(R^A) and R^A,

- 15 R₂ is one substituent selected from the group consisting of hydrogen, -SO₂- and R^A, wherein -SO₂- is substituted with C₁₋₈alkyl, NH₂, NH(C₁₋₈alkyl) or N(C₁₋₈alkyl)₂,

R^A is selected from the group consisting of C₃₋₁₂cycloalkyl, heterocyclyl, aryl and heteroaryl,

- 20 wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₁₀alkyl, C₁₋₈alkoxy, C₁₋₈alkyl(C₁₋₈alkoxy)₁₋₂, C₁₋₈alkyl(halogen)₁₋₃, C₁₋₈alkoxy(halogen)₁₋₃, C₁₋₈alkyl(hydroxy), NH₂, NH(C₁₋₈alkyl), N(C₁₋₈alkyl)₂, halogen, hydroxy, C(O)NH₂, C(O)NH(C₁₋₈alkyl), C(O)N(C₁₋₈alkyl)₂, NHC(O)H and NHC(O)(C₁₋₈alkyl),

R₃ is selected from the group consisting of C₁₋₈alkyl(R^B), -C(O)(C₁₋₈alkoxy) and R^B, and

R^B is selected from the group consisting of C₃₋₁₂cycloalkyl, heterocyclyl, aryl and heteroaryl,

- 25 wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₁₀alkyl, C₁₋₈alkoxy, C₁₋₈alkyl(C₁₋₈alkoxy)₁₋₂,

C₁₋₈alkyl(halogen)₁₋₃, C₁₋₈alkoxy(halogen)₁₋₃, C₁₋₈alkyl(hydroxy), C₁₋₈alkoxy(hydroxy), cyano, halogen and hydroxy.

It should be understood that pharmaceutically acceptable forms for compounds described and listed herein are meant to include all hydrates, solvates, polymorphs and pharmaceutically acceptable salts thereof. It should also be understood that unless otherwise indicated compounds of Formula (I) and Formula (II) are meant to comprise the stereochemically isomeric forms thereof.

An aspect of the invention is directed to methods for treating or preventing a disease or disorder mediated by dual selective α_{1a}/α_{1d} adrenoreceptor modulators, more particularly dual selective α_{1a}/α_{1d} adrenoreceptor antagonists such as, but not limited to, contractions of the prostate, bladder and other organs of the lower urinary tract without substantially affecting blood pressure. In this aspect, the method comprises administering the dual selective α_{1a}/α_{1d} adrenoreceptor modulator compounds of the present invention or a pharmaceutically acceptable form thereof to a patient suffering from contractions of the bladder and other organs of the lower urinary tract in an amount effective for the particular use.

Another aspect of the present invention is to provide a method for treating a patient suffering from Benign Prostatic Hyperplasia (BPH). In this aspect, the method comprises administering an effective amount of the modulator compounds of the present invention or a pharmaceutically acceptable form thereof to a patient suffering from BPH.

Another aspect of the present invention is to provide a method for treating a patient suffering from lower-urinary-tract-symptoms (LUTS), which include, but are not limited to, filling symptoms, urgency, incontinence and nocturia, as well as voiding problems such as weak stream, hesitancy, intermittency, incomplete bladder emptying and abdominal straining. In this aspect, the method comprises administering an effective amount of the modulator compounds of the present invention or a pharmaceutically acceptable form thereof to a patient suffering from LUTS.

A further aspect of the present invention is the use of the modulator compounds of the present invention or a pharmaceutically acceptable form thereof as a medicament. In this aspect, the use of the modulator compound or pharmaceutically acceptable form thereof includes the manufacture of a medicament for treating BPH and/or LUTS.

In another aspect of the present invention, the method for treating a patient suffering from BPH and/or LUTS includes administering an effective amount of a combination product comprising a modulator compound of the present invention in combination with a BPH and/or LUTS therapeutic agent. The BPH and/or LUTS therapeutic agent includes a 5 α -reductase agent (such as finasteride or dutasteride and the like or mixtures thereof), a NK-1 inhibitor, an

anti-androgen receptor agonist, an androgen receptor antagonist, a selective androgen receptor modulators, a PDE inhibitor, a urinary incontinence drugs (e.g. anti-muscarinics) or a 5HT-receptor modulator.

DETAILED DESCRIPTION OF THE INVENTION

5 An example of the present invention includes a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R_1 is one substituent selected from the group consisting of hydrogen, -N-, halogen and nitro, wherein -N- is substituted with two substituents independently selected from the group consisting of hydrogen, $C(O)(R^A)$, $C(O)O(R^A)$, $C(O)NH_2$, $C(O)NH(R^A)$, $C(O)N(R^A)_2$, $C(O)NH(C_{1-8}alkyl-R^A)$, $C(O)N(C_{1-8}alkyl-$
 10 $R^A)_2$, $C(S)NH(R^A)$, $C(S)N(R^A)_2$, $C(S)NH(C_{1-8}alkyl-R^A)$, $C(S)N(C_{1-8}alkyl-R^A)_2$, $SO_2(C_{1-8}alkyl)$, $SO_2(R^A)$, SO_2NH_2 , $SO_2NH(R^A)$, $C_{1-8}alkyl(R^A)$ and R^A .

Another example of the present invention includes a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R_1 is one substituent selected from the group consisting of hydrogen, -N-, halogen and nitro, wherein -N- is substituted with two
 15 substituents independently selected from the group consisting of hydrogen, $C(O)(R^A)$, $C(O)O(R^A)$, $C(O)NH_2$, $C(O)NH(R^A)$, $C(S)NH(R^A)$, $SO_2(C_{1-8}alkyl)$, $SO_2(R^A)$, SO_2NH_2 , $C_{1-8}alkyl(R^A)$ and R^A .

An example of the present invention includes a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R_2 is one substituent selected from the group consisting of hydrogen, - SO_2 - and R^A , wherein - SO_2 - is substituted with $C_{1-8}alkyl$ or
 20 $N(C_{1-8}alkyl)_2$.

An example of the present invention includes a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R^A is selected from the group consisting of $C_{3-12}cycloalkyl$, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with
 25 one to three substituents independently selected from the group consisting of $C_{1-10}alkyl$, $C_{1-8}alkoxy$, $C_{1-8}alkyl(C_{1-8}alkoxy)_{1-2}$, $C_{1-8}alkyl(halogen)_{1-3}$, $C_{1-8}alkoxy(halogen)_{1-3}$, NH_2 , $NH(C_{1-8}alkyl)$, $N(C_{1-8}alkyl)_2$, halogen, hydroxy and $NHC(O)(C_{1-8}alkyl)$.

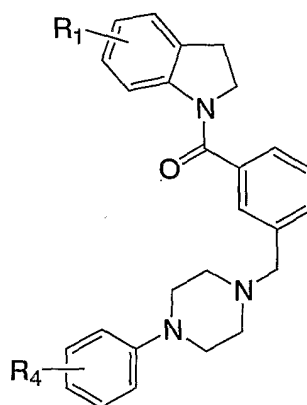
Another example of the present invention includes a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R^A is selected from the group consisting of
 30 $C_{3-12}cycloalkyl$, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of $C_{1-10}alkyl$, $C_{1-8}alkoxy$, $C_{1-8}alkyl(C_{1-8}alkoxy)_{1-2}$, $C_{1-8}alkyl(halogen)_{1-3}$, $N(C_{1-8}alkyl)_2$, halogen and $NHC(O)(C_{1-8}alkyl)$.

An example of the present invention includes a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R^B is selected from the group consisting of C_{3-12} cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-10} alkyl, C_{1-8} alkoxy, C_{1-8} alkyl(halogen)₁₋₃, C_{1-8} alkoxy(halogen)₁₋₃, cyano, halogen and hydroxy.

Another example of the present invention includes a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R^B is aryl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-10} alkyl, C_{1-8} alkoxy, C_{1-8} alkyl(halogen)₁₋₃, C_{1-8} alkoxy(halogen)₁₋₃, cyano, halogen and hydroxy.

Another example of the present invention includes a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R^B is aryl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8} alkoxy, C_{1-8} alkoxy(halogen)₁₋₃, cyano and hydroxy.

An example of the present invention includes a compound of Formula (Ia):



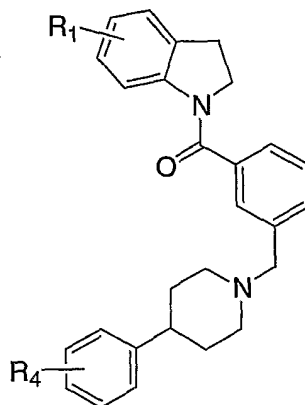
and pharmaceutically acceptable forms thereof, wherein R_1 , and R_4 are dependently selected from:

Cpd	R_1	R_4
1	5-NH ₂	2-OCH(CH ₃) ₂
2	5-NHSO ₂ -naphthalen-2-yl	2-OCH(CH ₃) ₂
3	5-NHSO ₂ -5-N(CH ₃) ₂ -naphthalen-1-yl	2-OCH(CH ₃) ₂
4	5-NHC(O)O-4-CH ₃ -phenyl	2-OCH(CH ₃) ₂
5	6-NH ₂	2-OCH(CH ₃) ₂
6	6-NHCH ₂ -2,6-F ₂ -phenyl	2-OCH(CH ₃) ₂
7	6-NHCH ₂ -2,6-(OCH ₃) ₂ -phenyl	2-OCH(CH ₃) ₂
8	5-NHCH ₂ -4-CF ₃ -phenyl	2-OCH(CH ₃) ₂
9	5-NHCH ₂ -2,6-F ₂ -phenyl	2-OCH(CH ₃) ₂
10	6-NHCH ₂ -4-(CH ₂) ₇ CH ₃ -phenyl	2-OCH(CH ₃) ₂

Cpd	R ₁	R ₄
11	6-NHCH ₂ -4-CH(OCH ₂ CH ₃) ₂ -phenyl	2-OCH(CH ₃) ₂
12	6-NHC(O)O-4-CH ₃ -phenyl	2-OCH(CH ₃) ₂
13	6-NHC(S)NH-phenyl	2-OCH(CH ₃) ₂
14	5-NHC(O)NH-2,4-Cl ₂ -phenyl	2-OCH(CH ₃) ₂
15	6-NHSO ₂ -4-NHC(O)CH ₃ -phenyl	2-OCH(CH ₃) ₂
16	6-NH-1,2,3,4-tetrahydro-naphthalen-2-yl	2-OCH(CH ₃) ₂
17	5-NHSO ₂ NH ₂	2-OCH(CH ₃) ₂
18	6-NHSO ₂ -5-Cl-3-CH ₃ -benzo[<i>b</i>]thien-2-yl	2-OCH(CH ₃) ₂
19	5-NHSO ₂ -4-NHC(O)CH ₃ -phenyl	2-OCH(CH ₃) ₂
20	6-NHSO ₂ NH ₂	2-OCH(CH ₃) ₂
21	5-NHC(O)NH-phenyl	2-OCH(CH ₃) ₂
22	6-NHC(O)NH-phenyl	2-OCH(CH ₃) ₂
23	5-NHCH ₂ -4-(CH ₂) ₇ CH ₃ -phenyl	2-OCH(CH ₃) ₂
24	5-NHCH ₂ -4-CH(OCH ₂ CH ₃) ₂ -phenyl	2-OCH(CH ₃) ₂
25	5-NHCH ₂ -2,6-(OCH ₃) ₂ -phenyl	2-OCH(CH ₃) ₂
26	5-NHC(O)-2,6-(OCH ₃) ₂ -phenyl	2-OCH(CH ₃) ₂
27	5-NHCH ₂ -benzo[1,3]dioxol-5-yl	2-OCH(CH ₃) ₂
28	6-NHC(O)-2,6-(OCH ₃) ₂ -phenyl	2-OCH(CH ₃) ₂
29	6-NH-4,7-(OCH ₃) ₂ -indan-2-yl	2-OCH(CH ₃) ₂
30	H	2-OCH ₃
31	H	2-CN
32	6-NHSO ₂ -5-N(CH ₃) ₂ -naphthalen-1-yl	2-OCH(CH ₃) ₂
40	6-NHC(O)-2,6-F ₂ -phenyl	2-OCH(CH ₃) ₂
41	6-NHCH ₂ -benzo[1,3]dioxol-5-yl	2-OCH(CH ₃) ₂
42	6-NHC(O)-4-OCH ₃ -phenyl	2-OCH(CH ₃) ₂
43	6-N[C(O)NH-2,6-F ₂ -phenyl] ₂	2-OCH(CH ₃) ₂
44	6-NHCH ₂ -2-F-phenyl	2-OCH(CH ₃) ₂
45	6-NHSO ₂ -2,6-F ₂ -phenyl	2-OCH(CH ₃) ₂
46	6-NHSO ₂ -4-CH ₃ -phenyl	2-OCH(CH ₃) ₂
47	6-NHSO ₂ CH ₂ CH ₃	2-OCH(CH ₃) ₂
48	6-NHC(O)-4-F-phenyl	2-OCH(CH ₃) ₂
49	6-NHC(O)NH ₂	2-OCH(CH ₃) ₂
63	H	2-OCH ₂ CF ₃
65	H	2-OCH ₂ CH(CH ₃) ₂
66	5-Br	2-OCH ₂ CH(CH ₃) ₂
67	5-Cl	2-OCH ₂ CH(CH ₃) ₂
68	5-F	2-OCH ₂ CH(CH ₃) ₂
69	H	2-OCH ₂ CH ₃

Cpd	R ₁	R ₄
73	6-NHC(O)NH-2,6-F ₂ -phenyl	2-OCH(CH ₃) ₂

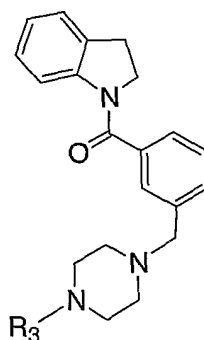
An example of the present invention includes a compound of Formula (Ib):



and pharmaceutically acceptable forms thereof, wherein R₁ and R₄ are dependently selected from:

Cpd	R ₁	R ₄
51	H	2-OCH(CH ₃) ₂
57	6-NHCH ₂ -2-F-phenyl	2-OCH(CH ₃) ₂
58	6-NHSO ₂ -2,6-F ₂ -phenyl	2-OCH(CH ₃) ₂
59	6-NHCH ₂ -2-F-phenyl	2-OCH ₃
60	6-NHC(O)NH-2,6-F ₂ -phenyl	2-OCH(CH ₃) ₂
61	6-NHSO ₂ -2,6-F ₂ -phenyl	2-OCH ₃

An example of the present invention includes a compound of Formula (Ic):

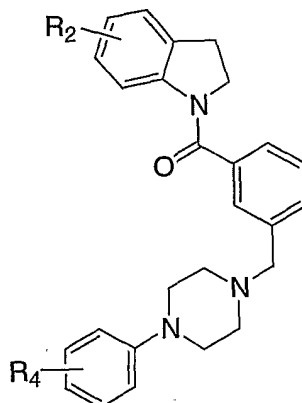


and pharmaceutically acceptable forms thereof, wherein R₃ is selected from:

Cpd	R ₃
54	C(O)OC(CH ₃) ₃
56	CH ₂ -2-OCH(CH ₃) ₂ -phenyl

Cpd	R ₃
64	CH ₂ -2-OCH ₃ -phenyl

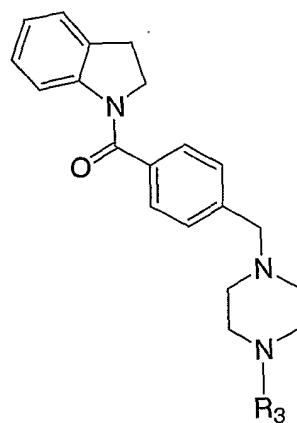
An example of the present invention includes a compound of Formula (Id):



and pharmaceutically acceptable forms thereof, wherein R₂ and R₄ are dependently selected from:

Cpd	R ₂	R ₄
70	5-SO ₂ N(Me) ₂	2-OCH ₂ CH(CH ₃) ₂
71	5-SO ₂ Me	2-OCH ₂ CH(CH ₃) ₂
72	5-Ph	2-OCH ₂ CH(CH ₃) ₂

An example of the present invention includes a compound of Formula (Ie):

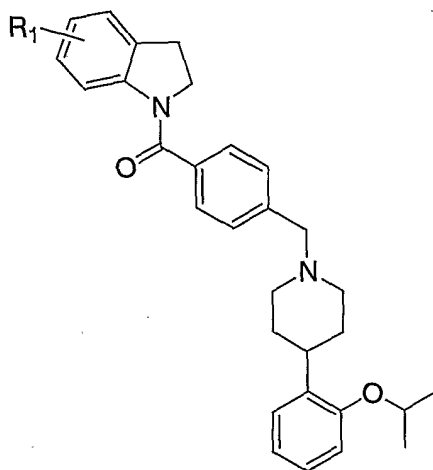


and pharmaceutically acceptable forms thereof, wherein R₃ is selected from:

Cpd	R ₃
52	CH ₂ -2-OCH(CH ₃) ₂ -phenyl
53	CH ₂ -2-OCH ₃ -phenyl
55	2-OCH ₂ CF ₃ -phenyl

Cpd	R ₃
62	CH ₂ -2-OH-phenyl

An example of the present invention includes a compound of Formula (If):

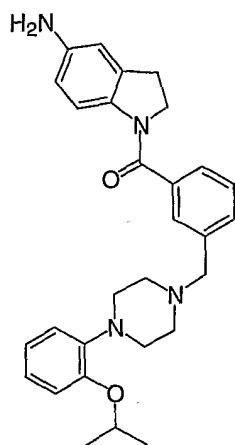


and pharmaceutically acceptable forms thereof, wherein R₁ is selected from:

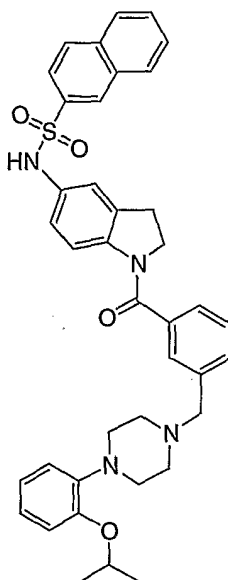
Cpd	R ₁
33	5-NH ₂
34	6-NH ₂
35	6-NO ₂
36	5-NHCH ₂ -4-CH(OCH ₂ CH ₃) ₂ -phenyl
37	6-NHCH ₂ -4-CH(OCH ₂ CH ₃) ₂ -phenyl
38	5-NO ₂
39	6-NHC(O)-2,6-(OCH ₃) ₂ -phenyl

Cpd	R ₁
50	H

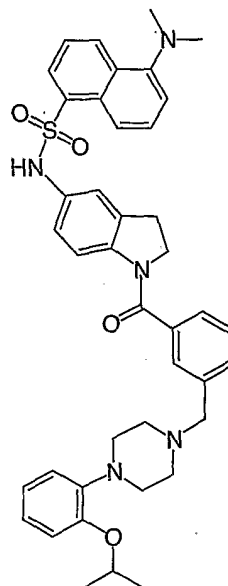
Another example of the present invention includes a compound selected from the group consisting of



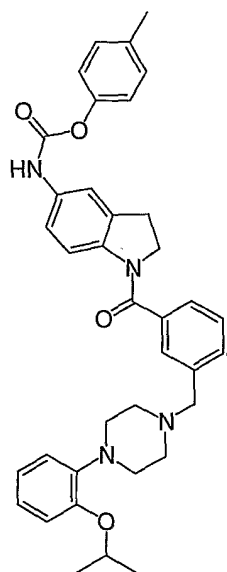
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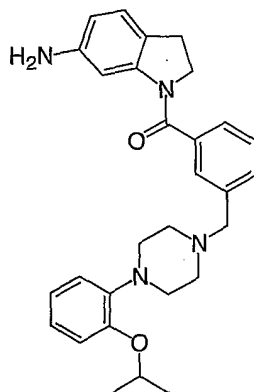
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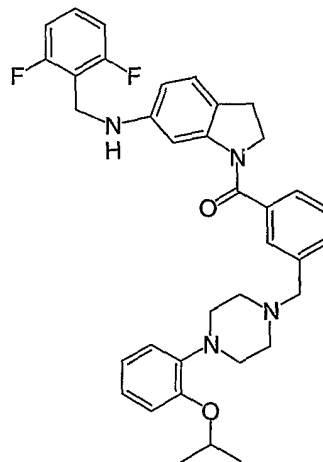
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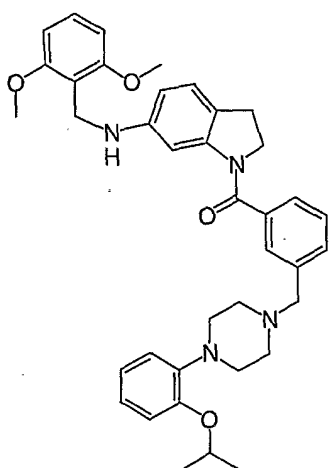


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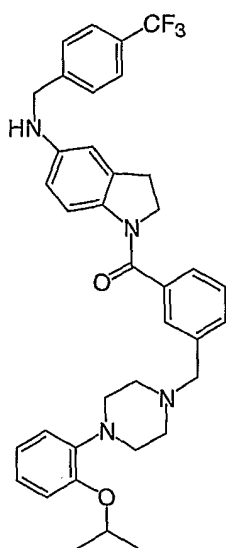


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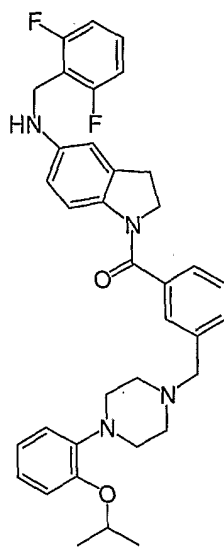
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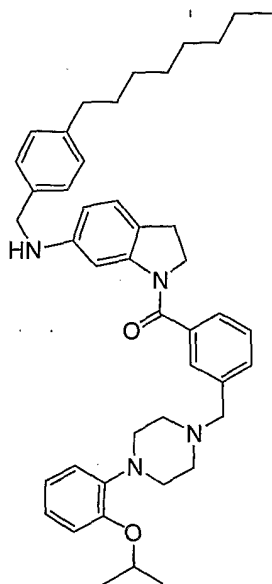
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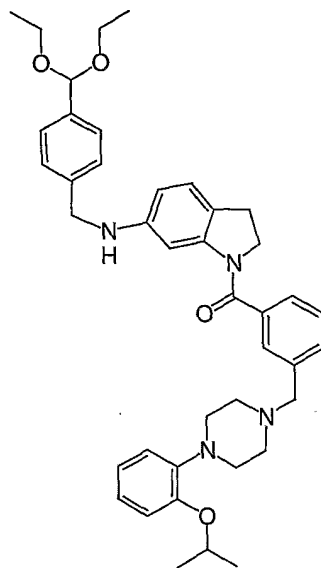
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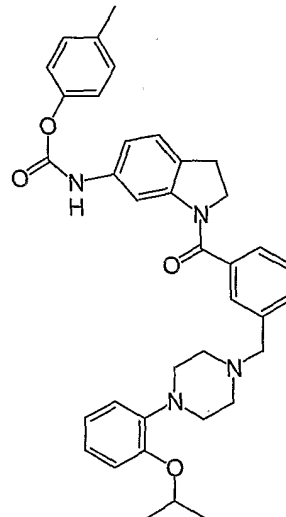
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Cpd 10

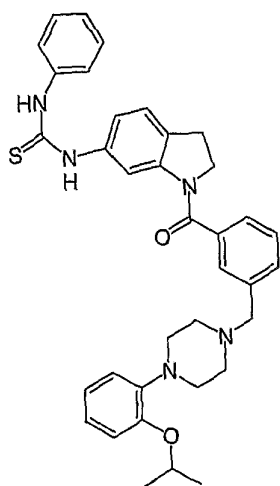
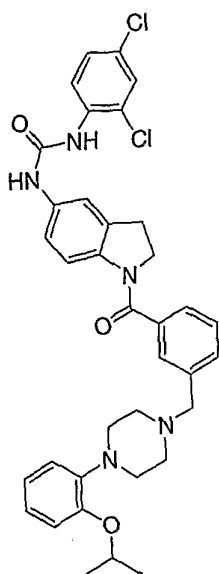
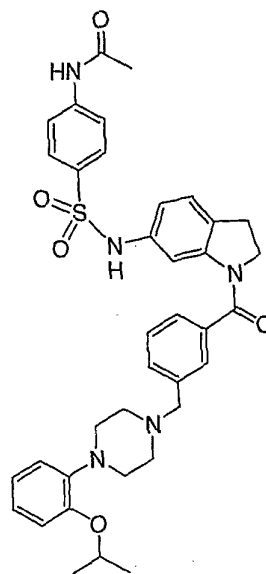


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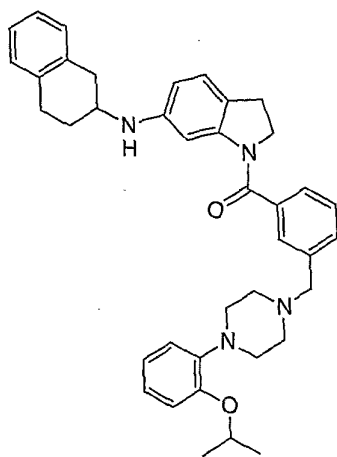


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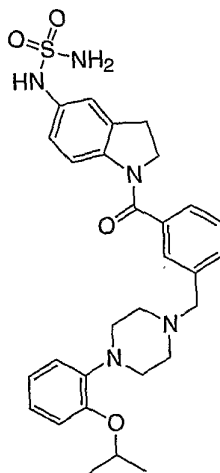
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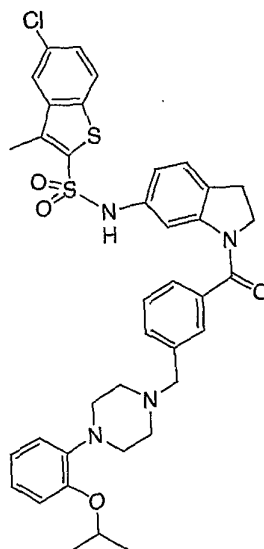
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Cpd 14



Cpd 15

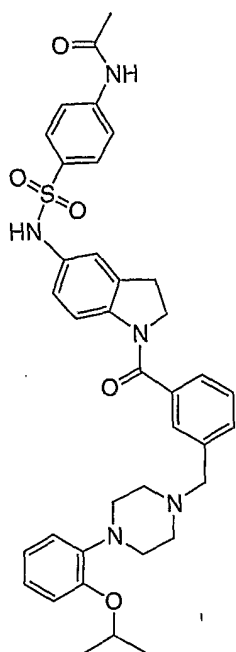
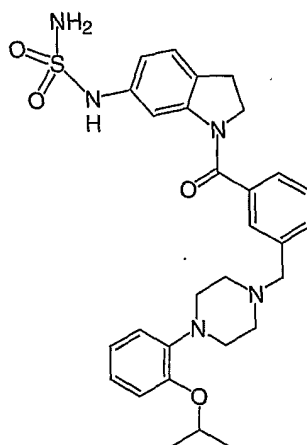
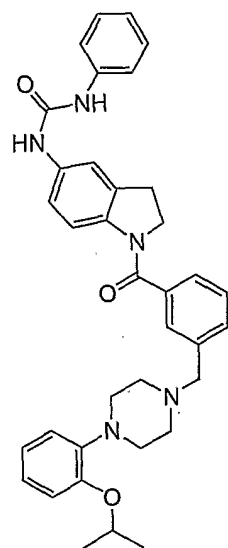


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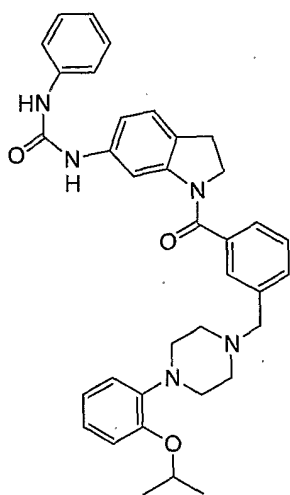
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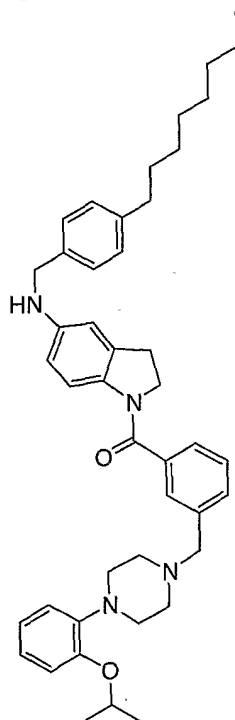
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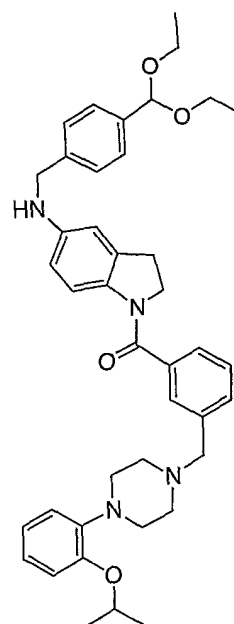
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Cpd 20



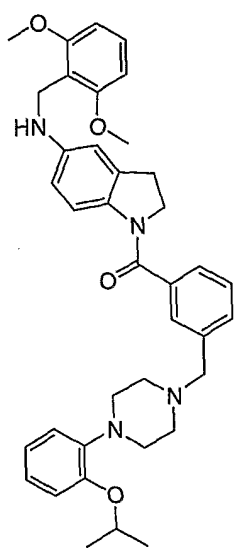
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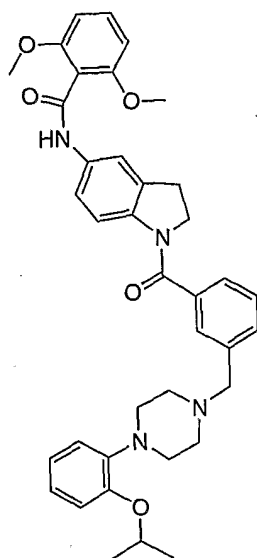
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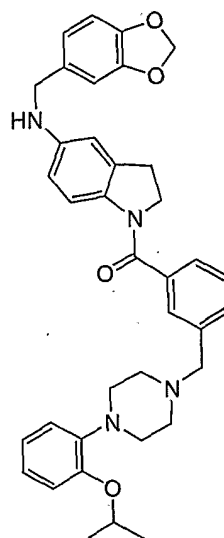
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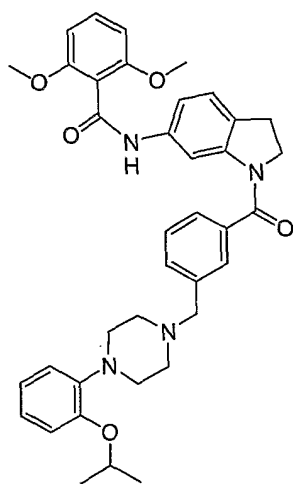
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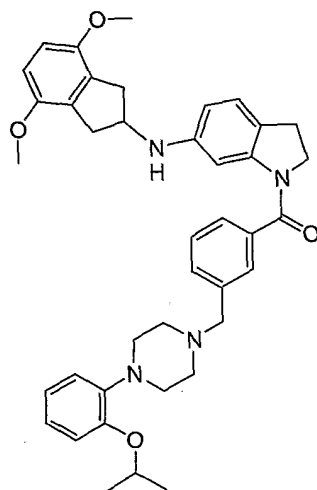
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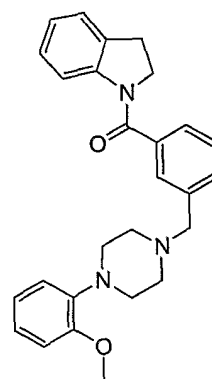
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Cpd 28

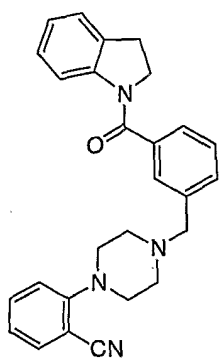
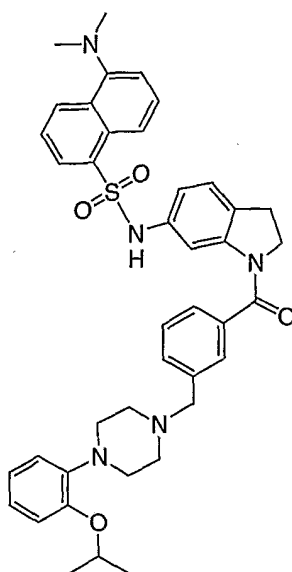
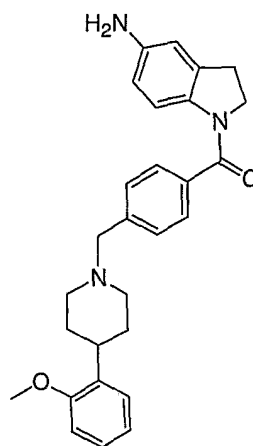


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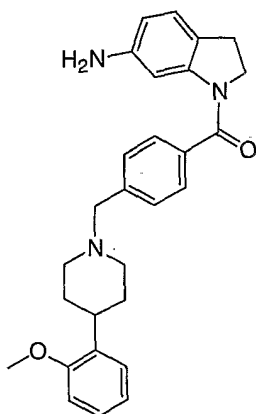


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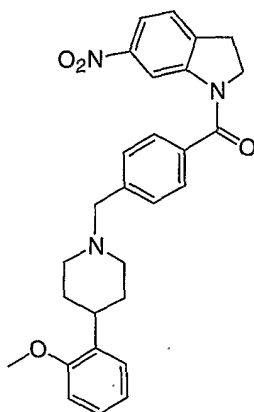
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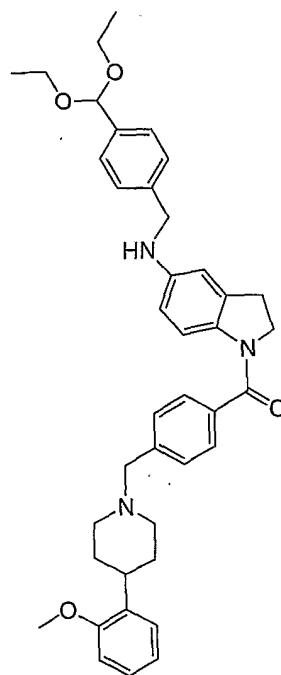
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Cpd 32



Cpd 33

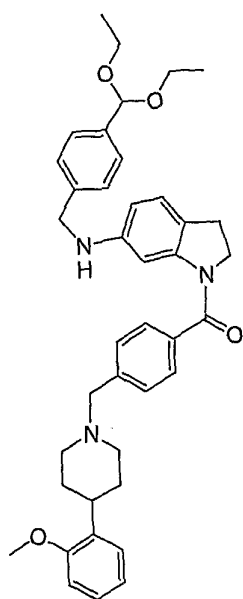


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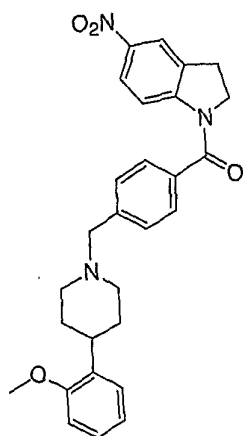
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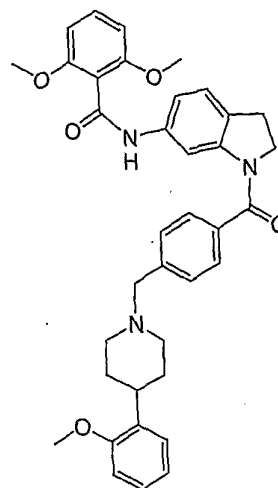
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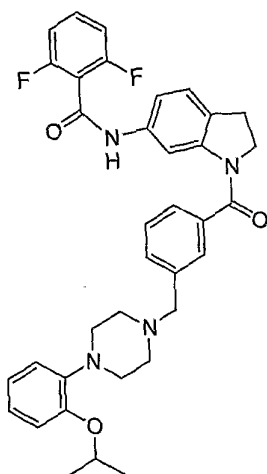
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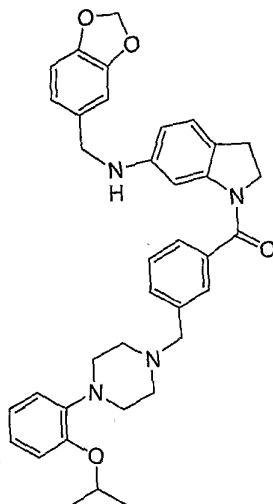
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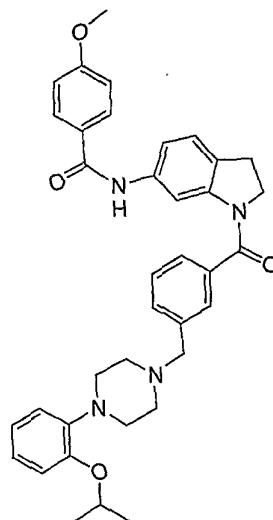
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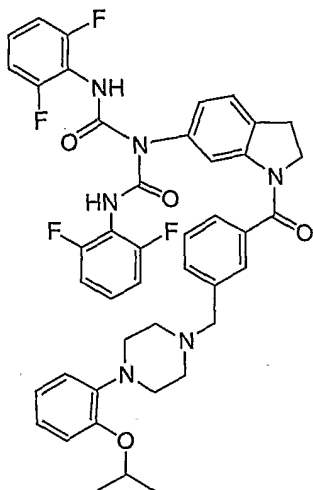
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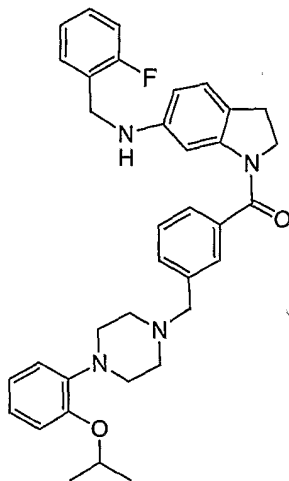
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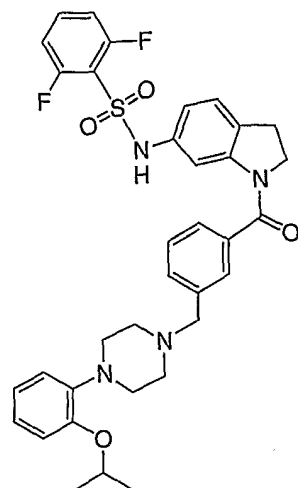
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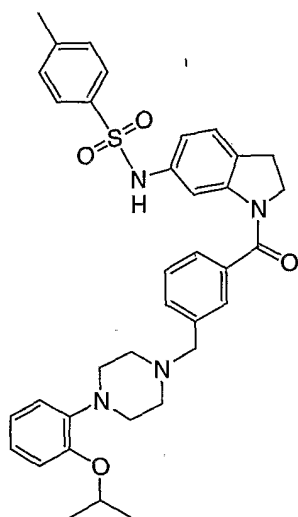
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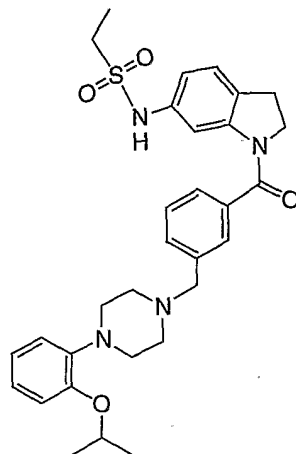
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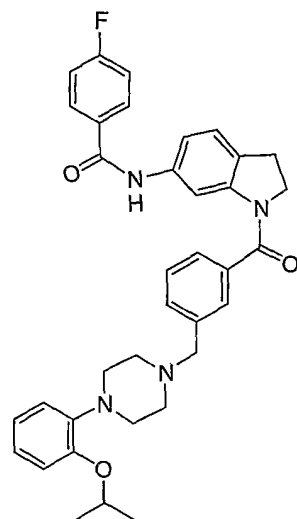
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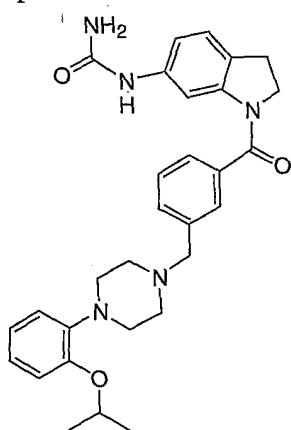
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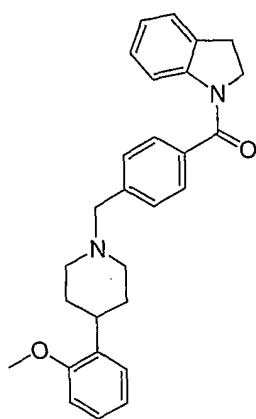
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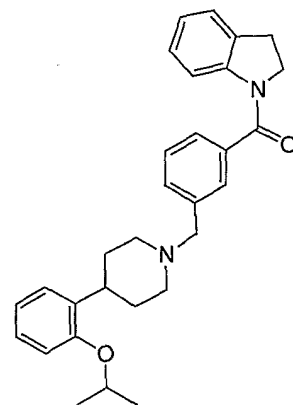
Cpd 48



Cpd 49

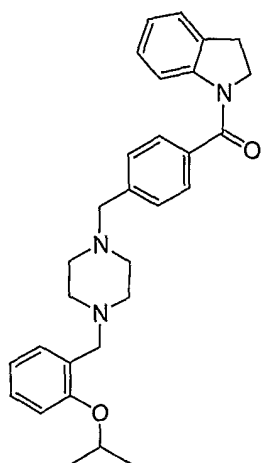


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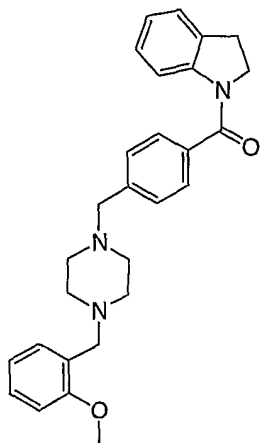


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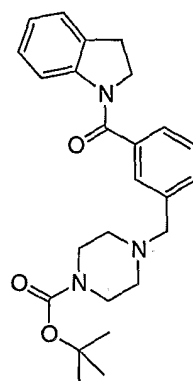
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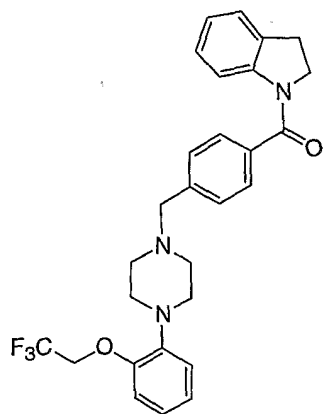
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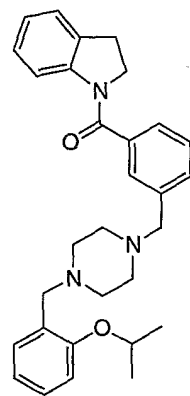
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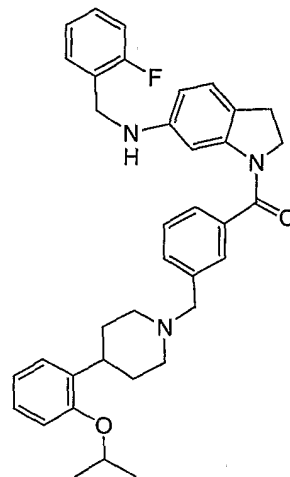
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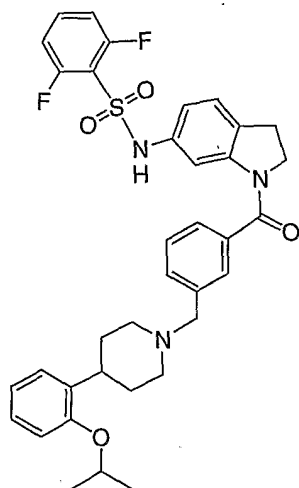
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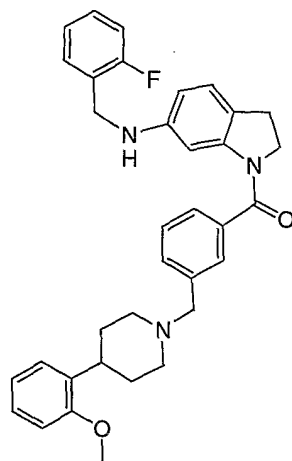
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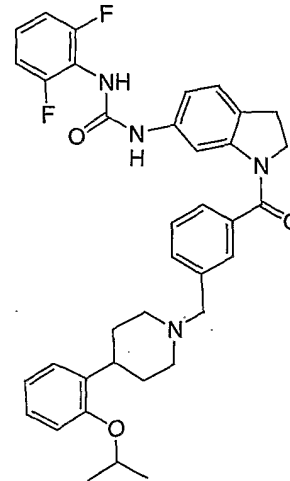
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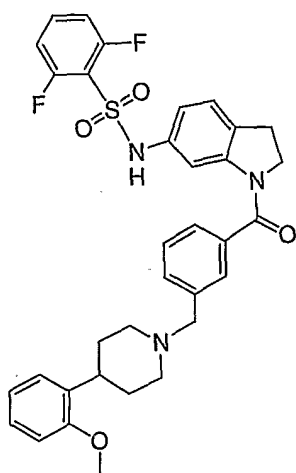
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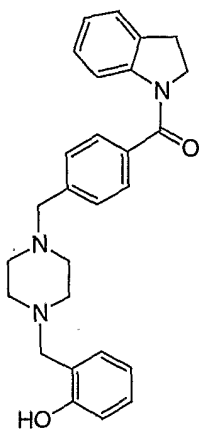
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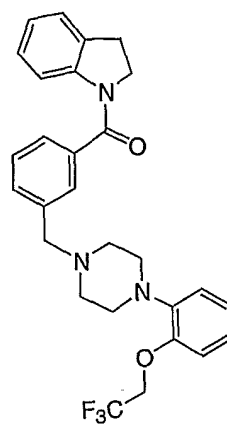
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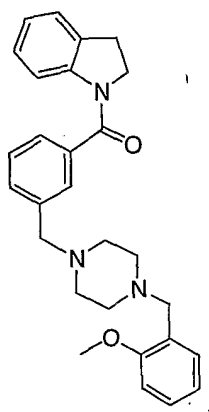
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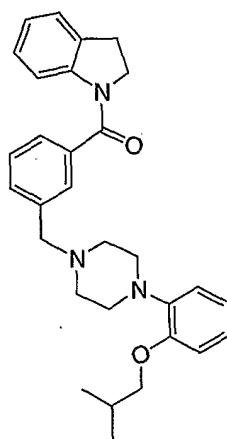
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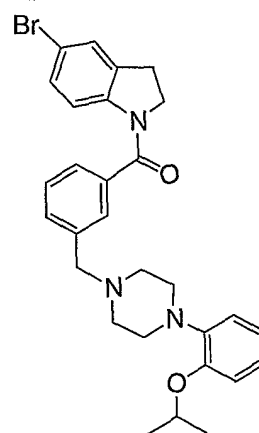
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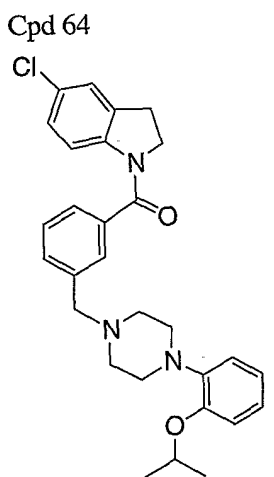
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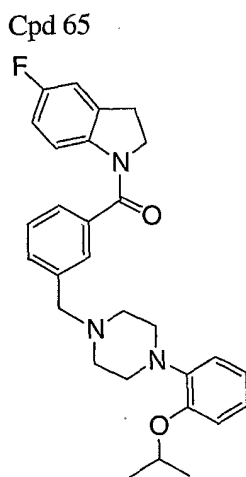
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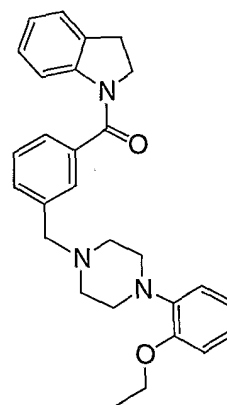
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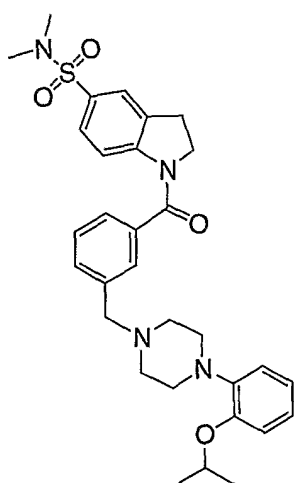
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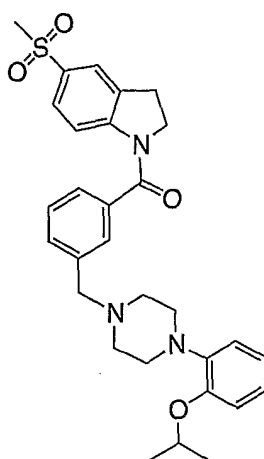
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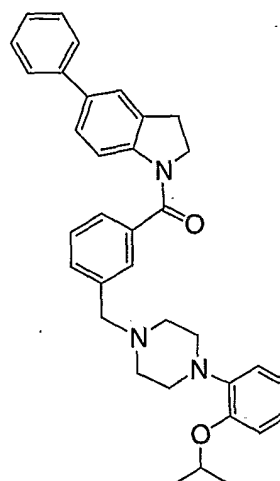


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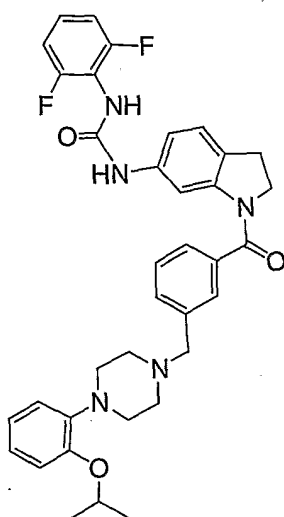


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Compound Forms

The compounds of the present invention may be present in the form of pharmaceutically acceptable salts. For use in medicines, the “pharmaceutically acceptable salts” of the compounds of this invention refer to non-toxic acidic/anionic or basic/cationic salt forms.

Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore when the compounds of the present invention carry an acidic moiety, suitable pharmaceutically acceptable salts 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. Thus, representative pharmaceutically acceptable salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate (or camphosulphonate), carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, fumarate, gluconate, glutamate, hydrabamine, hydrobromine, hydrochloride, iodide, isothionate, lactate, malate, maleate, mandelate, mesylate, nitrate, oleate, pamoate, palmitate, phosphate/diphosphate, salicylate, stearate, sulfate, succinate, tartrate, tosylate.

Certain compounds of the Formula (I) may exist in various stereoisomeric or tautomeric forms and mixtures thereof. The present invention encompasses all such dual α_{1a}/α_{1d} adrenoceptor inhibiting compounds, including active compounds in the form of essentially pure enantiomers, racemic mixtures, pure geometric isomers (such as *cis* and *trans* stereoisomers), mixtures of geometric isomers, and tautomers.

The term "isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. Such substances have the same number and kind of atoms but differ in structure. The structural difference may be in constitution (geometric isomers) or in an ability to rotate the plane of polarized light (optical isomers, or enantiomers).

The term "stereoisomer" refers to isomers of identical constitution that differ in the arrangement of their atoms in space. Enantiomers are stereoisomers wherein an asymmetrically substituted carbon atom acts as a chiral center. The term "chiral" refers to a molecule that is not superposable on its mirror image, implying the absence of an axis and a plane or center of symmetry. The term "enantiomer" refers to one of a pair of molecular species that are mirror images of each other and are not superimposable. The term "diastereomer" refers to stereoisomers that are not related as mirror images. The symbols "R" and "S" represent the configuration of substituents around a chiral carbon atom(s). The symbols "R*" and "S*" denote the relative configurations of substituents around a chiral carbon atom(s). Where the compounds of the present application have at least one stereocenter, they accordingly exist as enantiomers. Where the compounds according to the present invention possess two or more stereocenters, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The term "racemate" or "racemic mixture" refers to a compound of equimolar quantities of two enantiomeric species, wherein the compound is devoid of optical activity. The term "optical activity" refers to the degree to which a chiral molecule or nonracemic mixture of chiral molecules rotates the plane of polarized light.

The term "geometric isomer" refers to isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring or to a

bridged bicyclic system. Substituent atoms (other than H) on each side of a carbon-carbon double bond may be in an E or Z configuration. In the "E" (opposite sided) configuration, the substituents are on opposite sides in relationship to the carbon-carbon double bond; in the "Z" (same sided) configuration, the substituents are oriented on the same side in relationship to the carbon-carbon double bond. Substituent atoms (other than H) attached to a carbocyclic ring may be in a cis or trans configuration. In the "cis" configuration, the substituents are on the same side in relationship to the plane of the ring; in the "trans" configuration, the substituents are on opposite sides in relationship to the plane of the ring. Compounds having a mixture of "cis" and "trans" species are designated "cis/trans".

10 The compounds of the present invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the free base of each isomer of an isomeric pair using an optically active salt (followed by fractional crystallization and regeneration of the free base), forming an ester or amide of each of the isomers of an isomeric pair (followed by chromatographic separation and removal of the chiral auxiliary) or resolving an isomeric mixture of either a starting material or a final product using preparative TLC (thin layer chromatography) or a chiral HPLC column.

15 Furthermore, compounds of the present invention may have one or more polymorph or amorphous crystalline forms and as such are intended to be included in the scope of the invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such are also intended to be encompassed within the scope of this invention.

Chemical Nomenclature and Definitions

As used herein, the following terms are intended to have the following meanings (additional definitions are provided where needed throughout the Specification):

25 The term "C₁₋₈alkyl" whether used alone or as part of a substituent group, means a straight or branched chain monovalent hydrocarbon alkyl radical or alkylidyl linking group, wherein the radical is derived by the removal of one hydrogen atom from a single carbon atom and the linking group is derived by the removal of one hydrogen atom from each of two carbon atoms in the chain. Typical alkyl groups comprising from 1 to 8 carbon atoms include, for example methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, tertiary butyl, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 1-octyl, 2-octyl, 3-octyl and the like. Examples include C₁₋₈alkyl, C₁₋₆alkyl and C₁₋₄alkyl groups and the like.

35 The term "C₂₋₈alkenyl" whether used alone or as part of a substituent group, means a straight or branched chain monovalent hydrocarbon alkyl radical or alkylidyl linking group having at least one carbon-carbon double bond, whereby the double bond is derived by the

removal of one hydrogen atom from each of two adjacent carbon atoms of the radical or linking group. Atoms may be oriented about the double bond in either the cis or trans conformation. Typical alkenyl groups comprising from 2 to 8 carbon atoms include, for example, ethenyl, propenyl, allyl (2-propenyl), butenyl, pentenyl, hexenyl and the like. Examples include

5 C₂₋₈alkenyl and C₂₋₄alkenyl groups and the like.

The term "C₂₋₈alkynyl" whether used alone or as part of a substituent group, means a straight or branched chain monovalent hydrocarbon alkyl radical or alkyldiyl linking group having at least one carbon-carbon triple bond, whereby the triple bond is derived by the removal of two hydrogen atoms from each of two adjacent carbon atoms of the radical or

10 linking group. Typical alkynyl groups comprising from 2 to 8 carbon atoms include, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like. Examples include C₂₋₈alkynyl and C₂₋₄alkynyl groups and the like.

The term "C₁₋₈alkoxy" whether used alone or as part of a substituent group, refers to an alkyl or alkyldiyl radical attached through an oxygen linking atom. Typical alkoxy groups

15 comprising from 1 to 8 carbon atoms include, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy, octoxy and the like. Examples include C₁₋₈alkoxy or C₁₋₄alkoxy groups and the like.

The term "C₃₋₁₂cycloalkyl" whether used alone or as part of a substituent group, refers to a saturated or partially unsaturated, monocyclic or polycyclic hydrocarbon ring system

20 radical derived by the removal of one hydrogen atom from a single ring carbon atom. Typical cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1*H*-indenyl, indanyl, tetrahydro-naphthalenyl and the like. Examples include C₃₋₈cycloalkyl, C₅₋₈cycloalkyl or C₃₋₁₀cycloalkyl groups and the like.

The term "heterocyclyl" whether used alone or as part of a substituent group, refers to a

25 saturated or partially unsaturated monocyclic or polycyclic ring radical derived by the removal of one hydrogen atom from a single carbon or nitrogen ring atom. Typical heterocyclyl radicals include 2*H*-pyrrole, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, 2-imidazoliny (also referred to as 4,5-dihydro-1*H*-imidazolyl), imidazolidinyl, 2-pyrazoliny, pyrazolidinyl, tetrazolyl, tetrazolidinyl, piperidinyl, 1,4-dioxanyl, morpholiny, 1,4-dithianyl,

30 thiomorpholiny, piperaziny, azetidiny, azepany, hexahydro-1,4-diazepiny, hexahydro-1,4-oxazepany, tetrahydro-furyl, tetrahydro-thienyl, tetrahydro-pyrany, tetrahydro-pyridaziny, 1,3-benzodioxolyl (also referred to as benzo[1,3]dioxolyl) or 2,3-dihydro-1,4-benzodioxiny (also referred to as 2,3-dihydro-benzo[1,4]dioxiny) and the like.

The term "hetero" used as a prefix for a ring system refers to the replacement of at least

35 one ring carbon atom with one or more heteroatoms independently selected from N, S, O or P. Examples include rings wherein 1, 2, 3 or 4 ring members are a nitrogen atom; or, 0, 1, 2 or 3

ring members are nitrogen atoms and 1 member is an oxygen or sulfur atom. When allowed by available valences, up to two adjacent ring members may be heteroatoms; wherein one heteroatom is nitrogen and the other is one heteroatom selected from N, S or O.

The term "aryl," whether used alone or as part of a substituent group, refers to an aromatic monocyclic or polycyclic hydrocarbon ring radical derived by the removal of one hydrogen atom from a single carbon atom of the ring system. Typical aryl radicals include phenyl, naphthalenyl, fluorenyl, indenyl, azulenyl, anthracenyl and the like.

The term "aromatic" refers to a cycloalkylic hydrocarbon ring system having an unsaturated, conjugated π electron system.

The term "heteroaryl," whether used alone or as part of a substituent group, refers to an heteroaromatic monocyclic or polycyclic hydrocarbon ring radical derived by the removal of one hydrogen atom from a single ring carbon atom of the ring system. Typical heteroaryl radicals include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, indolyl, azaindolyl, isoindolyl, benzo[b]furyl, benzo[b]thienyl, indazolyl, azaindazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, 4*H*-quinoliziny, quinolinyl, isoquinolinyl, cinnolinyl, phthalziny, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl and the like.

The term "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted," refers to a core molecule on which one or more hydrogen atoms have been replaced with one or more functional radical moieties. The number that is allowed by available valences limits the amount of substituents. Substitution is not limited to the core molecule, but may also occur on a substituent radical, whereby the substituent radical becomes a linking group.

The term "independently selected" refers to one or more substituents selected from a group of substituents variable group, wherein the selected substituents may be the same or different.

The term "dependently selected" refers to one or more substituents specified in an indicated combination of structure variables.

Therapeutic Use

In an example of therapeutic use, the compounds of the present invention are modulators for the α_{1a} -AR and α_{1d} -AR subtypes and are useful for the treatment of BPH and/or LUTS.

In another example of therapeutic use, the modulator compounds are agonists, inverse-agonists or antagonists for each of the α_{1a} -AR and α_{1d} -AR subtypes. In another example, the

modulator compounds are selective antagonists for each of the α_{1a} -AR and α_{1d} -AR subtypes.

In another example of therapeutic use, the modulator compounds are agonists, inverse-agonists or antagonists for both the α_{1a} -AR and α_{1d} -AR subtypes. In another example, the modulator compounds are selective agonists for both the α_{1a} -AR and α_{1d} -AR subtypes. In another example, the modulator compounds are selective inverse-agonists for both the α_{1a} -AR and α_{1d} -AR subtypes. In another example, the modulator compounds are selective antagonists for both the α_{1a} -AR and α_{1d} -AR subtypes.

The binding affinities for instant compounds demonstrate selectivity as modulators for either the α_{1a} -AR or α_{1d} -AR subtype when compared to the binding affinities for other types of α_1 -ARs.

Furthermore, the binding affinities for instant compounds demonstrate selectivity as modulators for both the α_{1a} -AR and α_{1d} -AR subtypes when compared to the binding affinities for other types of α_1 -ARs.

Accordingly, the modulator compounds of the present invention are useful for treating, ameliorating or preventing a plurality of α_{1a} -AR and α_{1d} -AR mediated disorders or diseases. The usefulness of a compound of the present invention or pharmaceutical composition thereof as an α_{1a} -AR or α_{1d} -AR modulator or as a dual α_{1a} and α_{1d} -AR modulator can be determined according to the methods disclosed herein.

The term " α_{1a} -AR and α_{1d} -AR mediated disorder or disease" means disorders or diseases such as, but not limited to, contractions of the prostate, bladder and other organs of the lower urinary tract with or without an effect on blood pressure. The scope of such use includes the treatment of BPH and/or LUTS.

The term "LUTS" means disorders or diseases such as, but not limited to, filling symptoms, urgency, incontinence and nocturia, as well as voiding problems such as weak stream, hesitancy, intermittency, incomplete bladder emptying and abdominal straining.

The present invention thereby includes a method for treating, ameliorating or preventing an α_{1a} -AR and α_{1d} -AR mediated disorder or disease in a patient in need of such treatment comprising administering to the patient an effective amount of a compound of Formula (I) or pharmaceutical composition thereof.

The present invention thereby includes a method for treating, ameliorating or preventing BPH and/or LUTS in a patient in need of such treatment comprising administering to the patient an effective amount of a compound of Formula (I) or pharmaceutical composition thereof.

The term "patient" means an animal, preferably a mammal, most preferably a human, which has been the object of treatment, prevention, observation or experiment.

The term "administering" is to be interpreted liberally in accordance with the methods of the present invention. Such methods include therapeutically or prophylactically administering an effective amount of a composition or medicament of the present invention at different times during the course of a therapy or concurrently in a combination form.

- 5 Prophylactic administration can occur prior to the manifestation of symptoms characteristic of an α_{1a} and/or α_{1d} adrenoreceptor mediated disorder or disease such that the disorder or disease is treated, ameliorated, prevented or otherwise delayed in its progression. The methods of the present invention are further to be understood as embracing all therapeutic or prophylactic treatment regimens used by those skilled in the art.

- 10 The term "effective amount" refers to that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes treating, ameliorating or preventing the symptoms of a syndrome, disorder or disease being treated.

- 15 In an example of the method for treating, ameliorating or preventing an α_{1a} -AR and α_{1d} -AR mediated disorder or disease described herein, the method includes treating a patient suffering from BPH and/or LUTS comprising administering to the patient an effective amount of a combination product comprising a compound of Formula (I) or pharmaceutical composition thereof in combination with a BPH and/or LUTS therapeutic agent.

- 20 The BPH and/or LUTS therapeutic agent includes a human testosterone 5 α -reductase inhibitor agent or 5- α reductase isoenzyme 2 inhibitor agent (such as finasteride or dutasteride and the like or mixtures thereof), a NK-1 inhibitor, an anti-androgen receptor agonist, an androgen receptor antagonist, a selective androgen receptor modulators, a PDE inhibitor, a urinary incontinence drugs (e.g. anti-muscarinics) or a 5HT-receptor modulator.

- 25 With regard to the method for administering a combination product, the term "effective amount" means that amount of the compound of Formula (I) or pharmaceutical composition thereof in combination with that amount of the therapeutic agent, which have been adjusted to treat, ameliorate or prevent the symptoms of a syndrome, disorder or disease being treated.

- 30 As those skilled in the art will appreciate, the dosages of the compound of Formula (I) or pharmaceutical composition thereof and the therapeutic agent may be independently optimized and combined to achieve a synergistic result wherein the pathology is reduced more than it would be if either agent were used alone. In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted
- 35

accordingly.

In solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogenous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. An enteric layer can separate the two components. That enteric layer serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

An effective but non-toxic amount of the compound desired can be employed as a α_{1a}/α_{1d} antagonistic agent. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of

ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

5 The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective
10 amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium and elimination of a drug.

Compounds of Formula (I) may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever inhibition of the human α_{1a} -
15 AR or α_{1a} -AR is required. Such inhibition includes inhibition of the human α_{1a} -AR or α_{1d} -AR, selective inhibition of the human α_{1a} -AR or α_{1d} -AR, dual inhibition of the human α_{1a} -AR and α_{1d} -AR or selective, dual inhibition of the human α_{1a} -AR and α_{1d} -AR. The compounds of Formula (I) may be used alone at appropriate dosages defined by routine testing in order to obtain optimal antagonism of the human α_{1a} -AR or α_{1d} -AR while minimizing any potential
20 toxicity.

The daily dosage of the products may be varied over a wide range from about 0.001 to about 3,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0 and milligrams of the active ingredient for the symptomatic adjustment of the
25 dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 0.01 mg to about 3000 mg of active ingredient.

An effective amount of a compound of Formula (I) is a dosage level range of from about 0.0002 mg/kg to about 20 mg/kg of body weight per day. Preferably, the range is from
30 about 0.001 to 10 mg/kg of body weight per day. More preferably, the range is from about 0.001 mg/kg to 7 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

When compounds of Formula (I) are administered in a combination product, the compound of Formula (I) or pharmaceutical composition thereof and the therapeutic agent may
35 be co-administered or sequentially administered whereby the effects of BPH and/or LUTS is

treated, ameliorated or prevented.

The effective amount of the therapeutic agent selected from a human testosterone 5 α -reductase inhibitor agent or 5- α reductase isoenzyme 2 inhibitor agent (such as finasteride or durasteride and the like or mixtures thereof), a NK-1 inhibitor, an anti-androgen receptor agonist, an androgen receptor antagonist, a selective androgen receptor modulators, a PDE inhibitor, a urinary incontinence drugs (e.g. anti-muscarinics) or a 5HT-receptor modulator is a dosage level range of from about 0.0002 mg/kg to about 20 mg/kg of body weight per day. Preferably, the range is from about 0.001 to 10 mg/kg of body weight per day. More preferably, the range is from about 0.001 mg/kg to 7 mg/kg of body weight per day.

10 In one example of the combination product, the therapeutic agent is finasteride. The method for administering a combination product further comprises administering to the patient an effective amount of a compound of Formula (I) or pharmaceutical composition thereof in combination with finasteride.

The effective amount of finasteride administered in such a combination product is a dosage level range of from about 0.01 mg per day to about 50 mg per day. Preferably, the range is from about 0.2 mg per day to about 10 mg per day. More preferably, the range is from about 1 mg per day to about 7 mg per day. Most preferably, the dosage level is about 5 mg per day.

20 In yet another aspect, the present invention provides diagnostic compositions which are used for *in vivo* imaging of a α_{1a} and α_{1d} adrenoreceptors, comprising a compound of the present invention which is capable of being detected outside the body. Preferred are compositions comprising a compound of the present invention and a detectable label, such as a radioactive atom.

In yet another aspect the present invention provides compounds which are useful as ligands for use in assays relating to a α_{1a}/α_{1d} adrenoreceptors.

Synthetic Methods

Representative compounds of the present invention can be synthesized in accordance with the general synthetic schemes described below and are illustrated more particularly in the specific synthetic examples that follow. The general schemes and specific examples are offered by way of illustration; the invention should not be construed as being limited by the chemical reactions and conditions expressed. The methods for preparing the various starting materials used in the schemes and examples are well within the skill of persons versed in the art. No attempt has been made to optimize the yields obtained in any of the example reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

Synthetic routes

Where the processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-D-tartaric acid and/or (+)-di-*p*-toluoyl-L-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

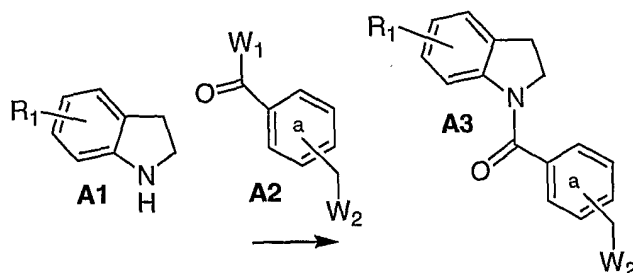
The terms used in describing the invention are commonly used and known to those skilled in the art. Some reagents are referred to as a chemical formula. Other reagents are referred to as abbreviations known to persons skilled in the art. When used herein, the following abbreviations have the indicated meanings:

Cpd	compound
DCM	dichloromethane
min/hr(s)/d(s)	minute/hour(s)/day(s)
M.P.	melting point in °C
MS	Mass Spectrum in m/z ($M+H^+$)
RT/rt/r.t.	room temperature
TEA	triethylamine
THF	tetrahydrofuran

Specific compounds which are representative of the invention may be prepared as per the following examples offered by way of illustration and not by way of limitation. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times,

temperatures, solvents and/or reagents. Additional compounds may be made according to the synthetic methods of the present invention by one skilled in the art, differing only in possible starting materials, reagents and conditions used in the instant methods.

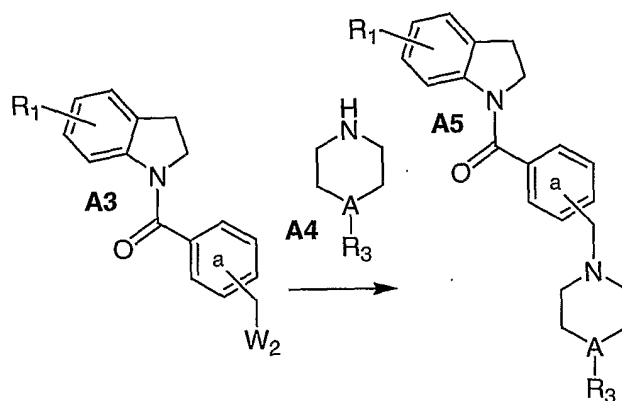
Scheme A



5

A solution of a substituted indole Compound A1 in DCM and TEA is cooled to about -60°C. A solution of a substituted Compound A2 (wherein W₁ is an appropriate leaving group, such as, for example, halo, more specifically chloride and wherein W₂ is an appropriate leaving group, such as, for example, halo, more specifically chloro) in DCM (wherein "a" represents a point of attachment on the phenyl ring of Compound A2 for the methylene-W₂ substituent) is then added dropwise to the solution of Compound A1. The reaction mixture is warmed to RT and stirred for about 5 hrs. The mixture is poured into cold water and the organic layer is separated, washed (preferably with brine), dried (preferably with Na₂SO₄) and concentrated in vacuo to give the methanone Compound A3.

10



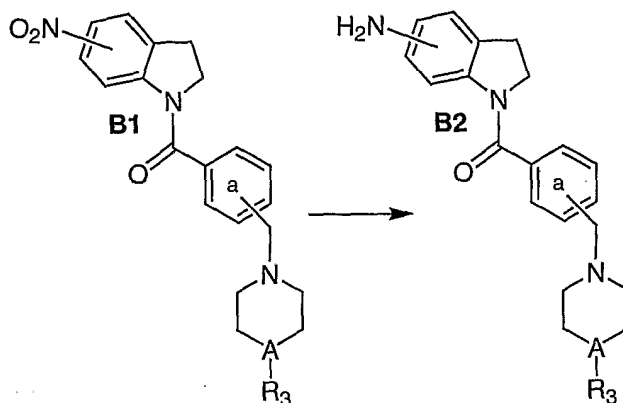
15

Compound A3 (wherein W₂ is an appropriate leaving group, such as, for example, halo, more specifically, chloro) is treated with a solution of a substituted heterocyclyl Compound A4 and potassium carbonate in acetonitrile. The reaction mixture is refluxed for about 4 hrs, then filtered, cooled and concentrated in vacuo. The residue is treated with water and extracted as needed (preferably twice) with DCM. The combined organic layers are washed (preferably with brine), dried (preferably with Na₂SO₄) and concentrated in vacuo to

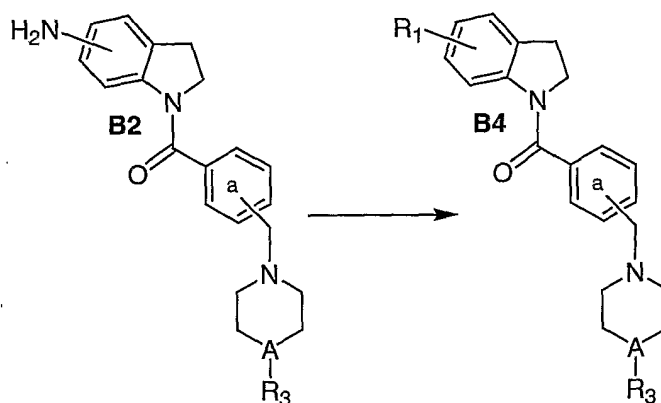
20

give a Compound **A5** of Formula (I).

Scheme B



When R₁ is nitro, as represented by Compound **B1**, the nitro substituent can be
 5 converted to a primary amine Compound **B2** by treating a solution of Compound **B1** in a
 mixture of THF:ethanol with hydrogen gas in the presence of a catalyst (10% Pd/C). The
 reaction mixture is shaken for about 2.5 hrs on a Parr apparatus, then filtered and concentrated
 in vacuo to give a solid which is purified via column chromatography (eluted preferably with a
 1:1:1 hexane:acetone:chloroform mixture and the like) to give the amine Compound **B2**.



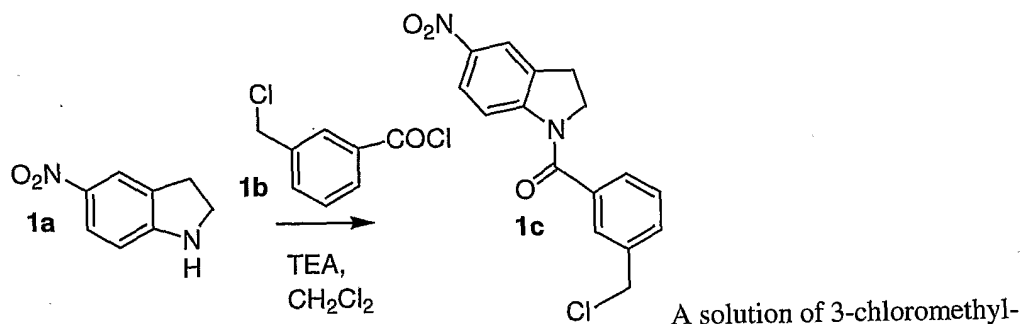
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To provide additional compounds representative of the scope of the present invention, a
 solution of Compound **B2** in DCM is further transformed into compounds **B4**, for instance by
 reductive alkylation, such can be done by treating with a solution of an appropriate aldehyde in
 glacial acetic acid and sodium triacetoxyborohydride to provide the reaction product
 15 Compound **B4**. Other transformations are also possible, such as, acylation and sulfonylation.
 These transformations can be performed according to art known techniques.

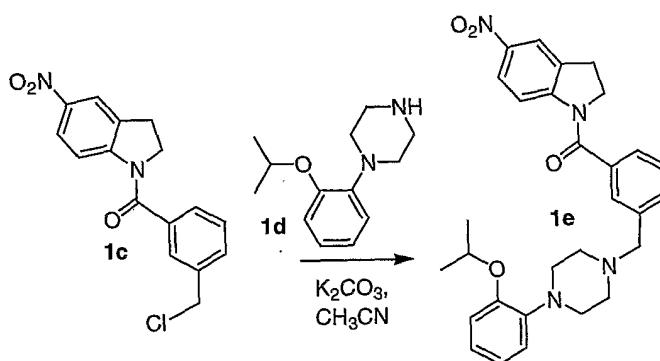
Examples of the present invention include compounds of Formula (I), wherein the R₁
 substituent can be other than a secondary or tertiary amine, which may be prepared by one
 skilled in the art substituting the appropriate starting materials, reagents and solvents.

Example 1

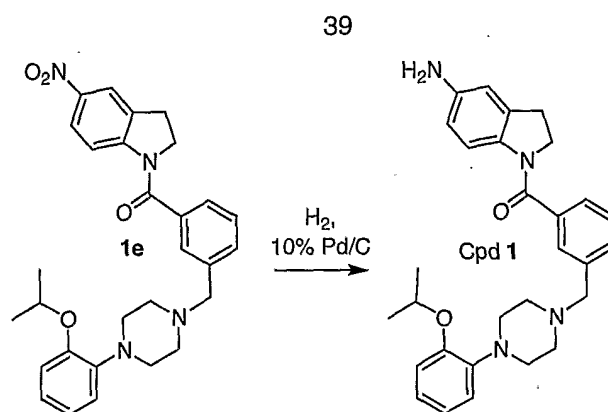
(5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone (Cpd 1)



- 5 benzoyl chloride Compound **1b** (11.5 g, 0.06 mol) in DCM (25 mL) was added dropwise to a cooled (-60°C) solution of 5-nitro-2,3-dihydro-1H-indole Compound **1a** (10 g, 0.06 mol) in DCM (200 mL) and TEA (10 mL, 0.07 mol). The reaction mixture was warmed to room temperature and stirred for 5 hrs. The mixture was poured into cold water and the organic layer was separated, washed with brine, dried (Na₂SO₄) and concentrated in vacuo to give the (3-chloromethyl-phenyl)-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound **1c** (20.69 g,
- 10 >100%) as a light yellow solid which contained residual DCM.



- Compound **1c** (11.75 g, 0.037 mol) was treated with 1-(2-isopropoxy-phenyl)-piperazine monofumarate Compound **1d** (12.46 g, 0.037 mol) and potassium carbonate (15.26 g, 0.11 mol) in acetonitrile (240 mL) and the resulting mixture was refluxed for 4 hrs. The reaction mixture was filtered, cooled and evaporated in vacuo to give a syrup which was treated with water and extracted twice with DCM. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated in vacuo to give {3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound **1e**
- 20 (20.26 g, >100%) as a light yellow solid which contained residual DCM.



Compound **1e** (6.1 g, 0.01 mol) in a mixture of THF:ethanol (50:100 mL) was treated with a catalyst (10% Pd/C, 0.60 g) and shaken for 2.5 h on a Parr apparatus under a hydrogen atmosphere, filtered and concentrated in vacuo to give a yellow solid which was purified via column chromatography (1:1:1 hexane:acetone:chloroform) to give Compound **1** (3.47 g, 74%) as a deep yellow solid. MS, m/z 471 (M+H); M.P. 137-139°C.

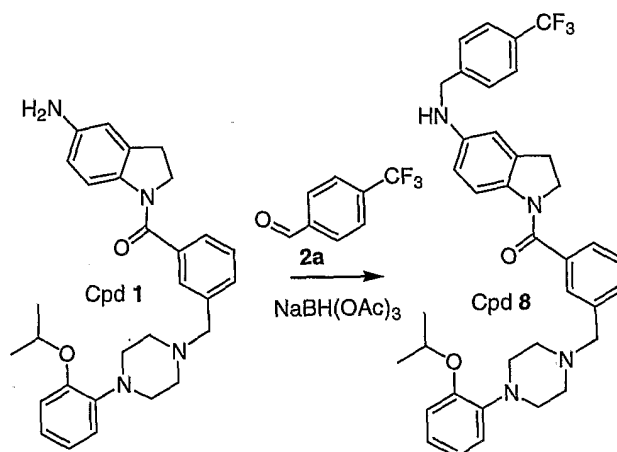
Following the procedure of Example 1, up until the preparation of intermediate **1e**, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS
30	(2,3-dihydro-indol-1-yl)-{3-[4-(2-methoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	428
31	(2,3-dihydro-indol-1-yl)-{3-[4-(2-cyano-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	423
54	4-[3-(2,3-dihydro-indole-1-carbonyl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester	422
56	(2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-benzyl)-piperazin-1-ylmethyl]-phenyl}-methanone	470
63	(2,3-dihydro-indol-1-yl)-(3-{4-[2-(2,2,2-trifluoro-ethoxy)-phenyl]-piperazin-1-ylmethyl}-phenyl)-methanone	496
64	(2,3-dihydro-indol-1-yl)-{3-[4-(2-methoxy-benzyl)-piperazin-1-ylmethyl]-phenyl}-methanone	442
65	(2,3-dihydro-indol-1-yl)-{3-[4-(2-isobutoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	470
66	(5-bromo-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	534
67	(5-chloro-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	490
68	(5-fluoro-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	474
69	(2,3-dihydro-indol-1-yl)-{3-[4-(2-ethoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	442
70	1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indole-5-sulfonic acid dimethylamide	563

Cpd	Name	MS
71	{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-(5-methanesulfonyl-2,3-dihydro-indol-1-yl)-methanone	534
72	{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-(5-phenyl-2,3-dihydro-indol-1-yl)-methanone	532

Example 2

{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-[5-(4-trifluoromethyl-benzylamino)-2,3-dihydro-indol-1-yl]-methanone (Cpd 8)



5

A solution of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 1 (0.15 g, 0.3 mmol) in DCM (4 mL) was treated with 4-trifluoromethyl-benzaldehyde Compound 2a (0.06 g, 0.3 mmol), glacial acetic acid (0.02 mL) and sodium triacetoxyborohydride (0.15 g, 0.7 mmol). The mixture was stirred under an inert atmosphere for 24 hrs, then treated with 1N NaOH (8 mL) and stirred for 60 min. The layers were separated. The organic layer was dried (Na₂SO₄), filtered and concentrated in vacuo to give Compound 8 (0.16 g) as an off white solid. MS *m/z* 629 (M+H⁺); M.P. 74-76°C.

10

Following the procedure of Example 2, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS	M.P.
9	[5-(2,6-difluoro-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	597	127-130
23	{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-[5-(4-octyl-benzylamino)-2,3-dihydro-indol-1-yl]-methanone	673	116-118
24	[5-(4-diethoxymethyl-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	663	---
25	[5-(2,6-dimethoxy-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	621	79-81

Cpd	Name	MS	M.P.
27	{5-[(benzo[1,3]dioxol-5-ylmethyl)-amino]-2,3-dihydro-indol-1-yl}-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	605	---

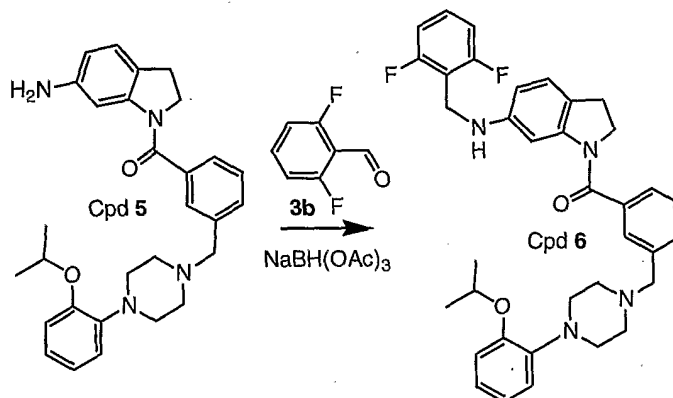
Example 3

(6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone (Cpd 5)

5

[6-(2,6-difluoro-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone (Cpd 6)

Using the procedure of Example 1, 6-nitro-2,3-dihydro-1H-indole Compound 3a was used in place of 5-nitro-2,3-dihydro-1H-indole Compound 1a to provide Compound 5.



10 Using the procedure of Example 2, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 5 was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 1 and 2,6-difluoro-benzaldehyde Compound 3b was used in place of 4-trifluoromethyl-benzaldehyde Compound 2a to provide Compound 6. MS m/z 597
15 ($M+H^+$); M.P. 137-139°C.

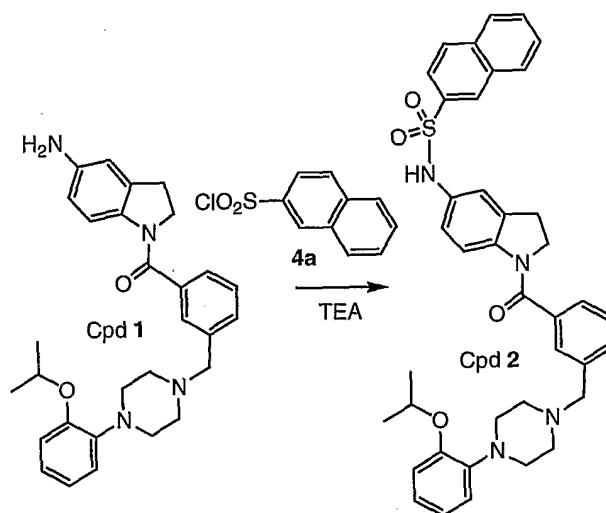
Following the procedure of Example 3, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS	M.P.
7	[6-(2,6-dimethoxy-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	621	---
10	{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-[6-(4-octyl-benzylamino)-2,3-dihydro-indol-1-yl]-methanone	673	---
11	[6-(2,6-dimethoxy-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	663	156-160

Cpd	Name	MS	M.P.
41	{6-[(benzo[1,3]dioxol-5-ylmethyl)-amino]-2,3-dihydro-indol-1-yl}-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	605	---
44	[6-(2-fluoro-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone	579	---

Example 4

naphthalene-2-sulfonic acid (1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)-amide (Cpd 2)



5

A solution of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 1 (0.15 g, 0.32 mmol) in DCM (5 mL) was treated with TEA (0.038 g, 0.37 mmol) and naphthalene-2-sulfonyl chloride Compound 4a (0.08 g, 0.35 mmol). The mixture was stirred for 8 hrs and then treated with water. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated in vacuo to give a residue which was purified via column chromatography (2:1:1 hexane:acetone:chloroform) to give Compound 2 (0.125 g) as a yellow solid. MS *m/z* 661 (M+H); M.P. 73-76°C.

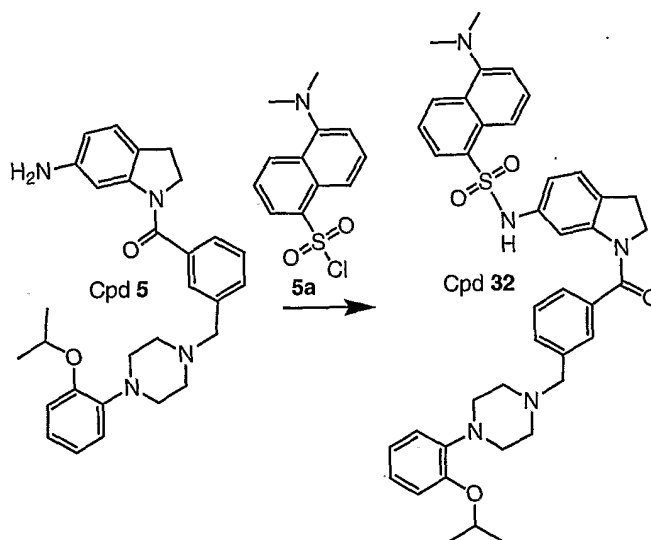
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Following the procedure of Example 4, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS	M.P.
3	5-dimethylamino-naphthalene-1-sulfonic acid (1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)-amide	704	80-83
19	N-[4-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)sulfamoyl]-phenyl]-acetamide	668	132-134

Example 5

5-dimethylamino-naphthalene-1-sulfonic acid (1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-amide (Cpd 32)



5

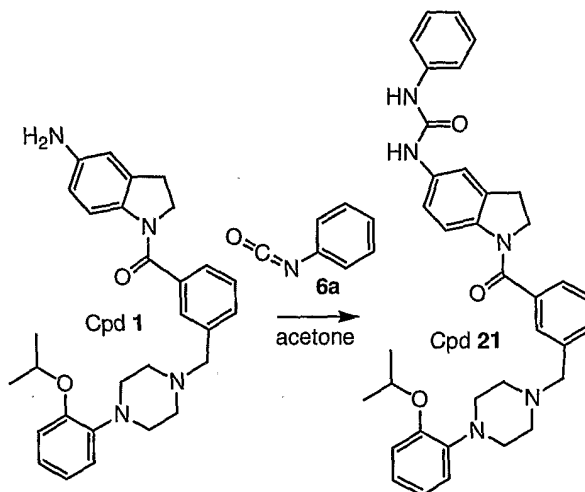
Using the procedure of Example 4, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **5** was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **1** and 5-dimethylamino-naphthalene-1-sulfonyl chloride Compound **5a** was used in place of naphthalene-2-sulfonyl chloride Compound **4a** to provide Compound **32**. MS m/z 704 ($M+H^+$); M.P. 137-139°C.

Following the procedure of Examples 4 and 5, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS	M.P.
15	N-[4-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)sulfamoyl]-phenyl]-acetamide	668	---
18	5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-amide	716	192-195
45	2,6-difluoro-N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-benzenesulfonamide	647	---
46	N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-4-methyl-benzenesulfonamide	625	---
47	ethanesulfonic acid (1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-amide	563	---

Example 6

1-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)-3-phenyl-urea (Cpd 21)



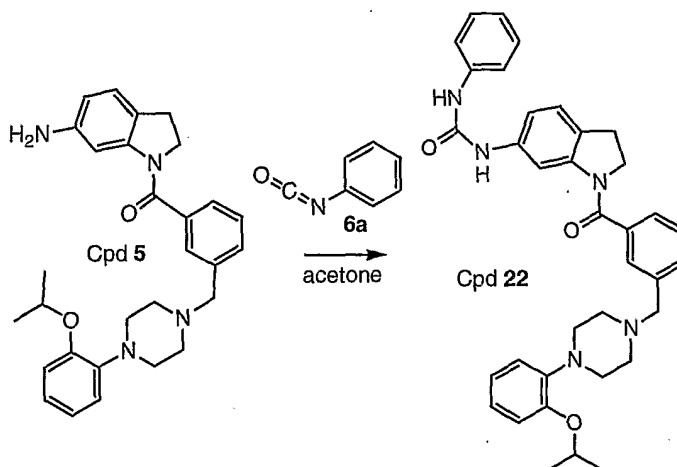
5 A solution of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **1** (0.15 g, 0.32 mmol) in acetone (5 mL) was treated with isocyanato-benzene Compound **6a** (0.038 g, 0.32 mmol). The reaction mixture was stirred at rt for 4 hrs, then concentrated in vacuo to a residue which was purified on a column (30:30:30:5 hexane:chloroform:acetone:methanol) to give Compound **21** as a colorless
10 syrup (0.08 g). MS *m/z* 590 (M+H).

Following the procedure of Example 6, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS
14	1-(2,4-dichloro-phenyl)-3-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)-urea	659

Example 7

1-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-3-phenyl-urea (Cpd 22)



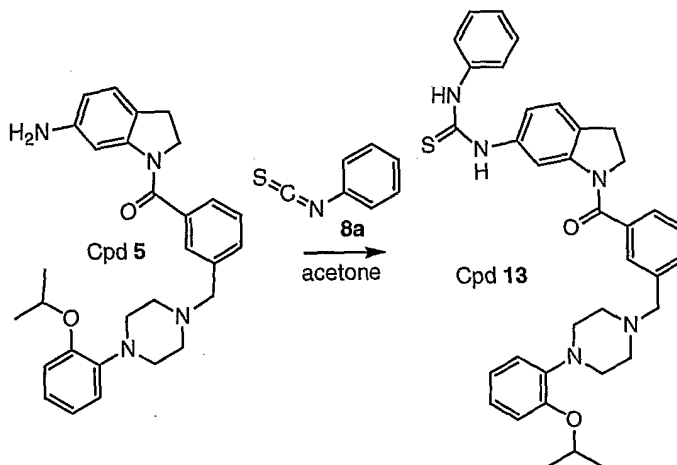
- 5 Using the procedure of Example 6, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 5 was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 1 to provide Compound 22. MS m/z 590 ($M+H^+$).

- 10 Following the procedure of Examples 6 and 7, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS
43	3-(2,6-difluoro-phenyl)-1-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-1-(2,6-difluorophenylaminocarbonyl)-urea	781
49	(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-urea	514
73	1-(2,6-difluoro-phenyl)-3-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-urea	611

Example 8

1-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-3-phenyl-thiourea (Cpd 13)



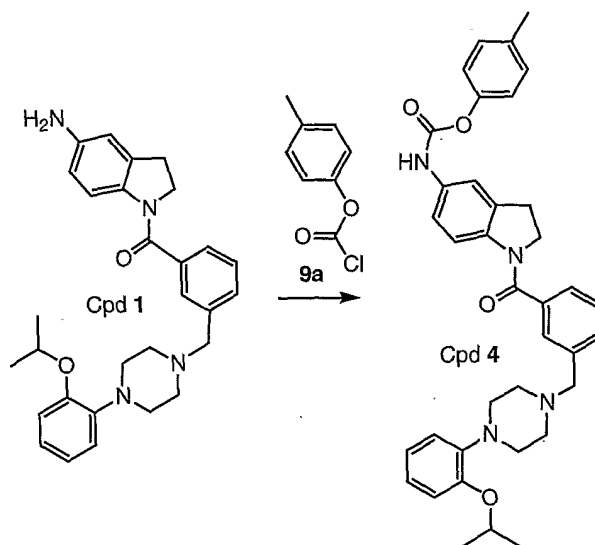
5

Using the procedure of Example 6, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 5 was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 1 and isothiocyanato-benzene Compound 8a was used in place of isocyanato-benzene Compound 6a to provide Compound 13. MS m/z 605 ($M+H^+$).

10

Example 9

(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}2,3-dihydro-1H-indol-5-yl)-carbamic acid p-tolyl ester (Cpd 4)



15

A solution of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 1 (0.15 g, 0.32 mmol) in DCM (5 mL) was treated

with TEA (0.054 mL, 0.37 mmol) and (4-methylphenyl)-carbonochloridic acid Compound **9a** (0.06 g, 0.32 mmol). The reaction mixture was stirred for 4 hrs, then poured into water. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated in vacuo to a residue which was purified by column chromatography (2:1:1 hexane:acetone:chloroform) to give

5 Compound **4** (0.10 g) as a white solid. MS m/z 605 ($\text{M}+\text{H}$); M.P. 166-168°C.

Example 10

(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-carbamic acid p-tolyl ester (Cpd **12**)

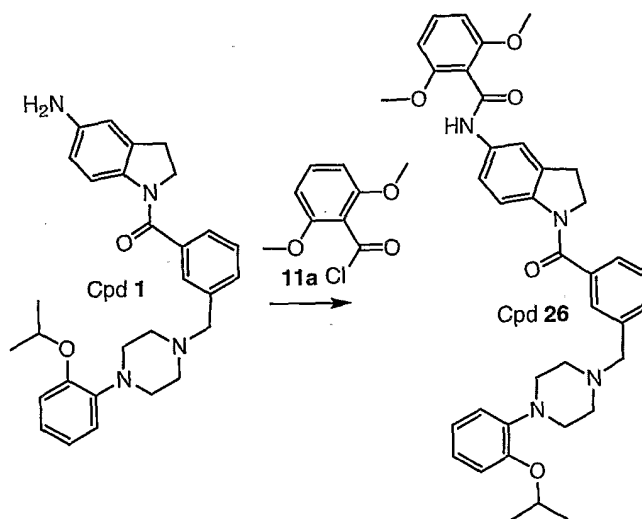
Using the procedure of Example 9, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **5** was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **1** to provide Compound **12**. MS m/z 605 ($\text{M}+\text{H}^+$).

10

Example 11

N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)-2,6-dimethoxy-benzamide (Cpd **26**)

15



A solution of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **1** (0.15 g, 0.32 mmol) in DCM (5 mL) was treated with TEA (0.054 mL, 0.37 mmol) and 2,6-dimethoxy-benzoyl chloride Compound **11a** (0.07 g, 0.32 mmol). The reaction mixture was stirred for 4 hrs and was then poured into water. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated in vacuo to a residue which was purified by column chromatography (2:1:1 hexane:acetone:chloroform) to give

20 Compound **26** (0.14 g) as a yellow solid. MS m/z 635 ($\text{M}+\text{H}^+$); M.P. 229-232°C.

Example 12

N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-2,6-dimethoxy-benzamide
(Cpd 28)

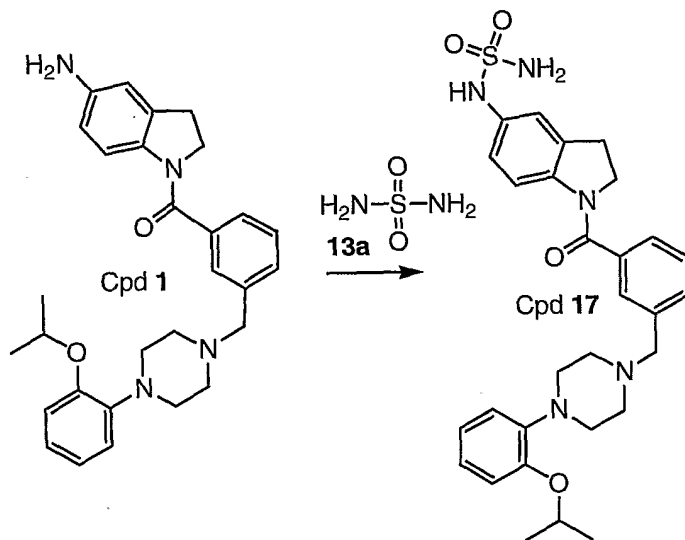
5 Using the procedure of Example 11, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 5 was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 1, to provide Compound 28. MS m/z 635 ($M+H^+$).

10 Following the procedure of Examples 11 and 12, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS
40	N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)-2,6-difluoro-benzamide	611
42	N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)-4-methoxy-benzamide	605
48	4-fluoro-N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-benzamide	593

Example 13

N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-5-yl)-sulfamide (Cpd 17)



15 A solution of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound 1 (0.30 g, 0.64 mmol) in dioxane (10 mL) was treated with sulfamide Compound 13a (0.30 g, 3.1 mmol). The reaction mixture was refluxed for 4 hrs and then was concentrated to a residue which was purified by column chromatography (30:30:1 acetone:chloroform: methanol) to give Compound 17 (0.075 g) as a brown solid. MS
20 m/z 550 ($M+H^+$).

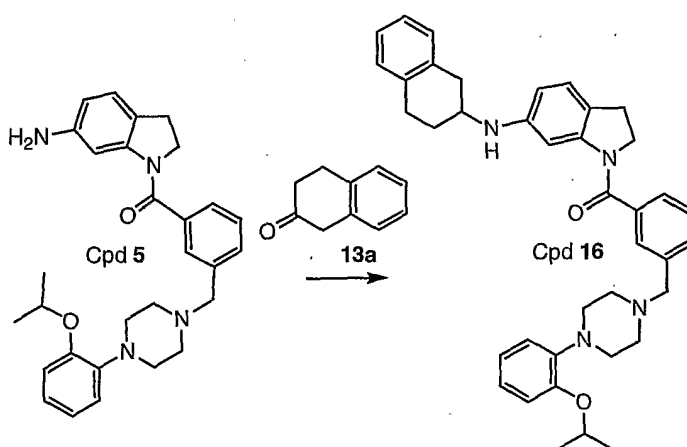
Example 14

N-(1-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-sulfamide (Cpd 20)

Using the procedure of Example 13, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **5** was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **1** to provide Compound **20**. MS m/z 550 ($M+H^+$).

Example 15

{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-[6-(1,2,3,4-tetrahydro-naphthalen-2-ylamino)-2,3-dihydro-indol-1-yl]-methanone (Cpd 16)

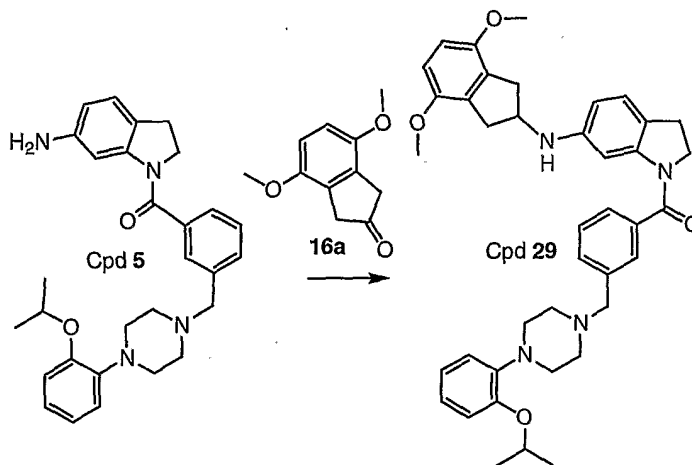


A solution of (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **5** (0.15 g, 0.3 mmol) in DCM (4 mL) was treated with 2-tetralone (also known as 3,4-dihydro-1H-naphthalen-2-one) Compound **13a** (0.046 g, 0.3 mmol), glacial acetic acid (0.02 mL) and sodium triacetoxyborohydride (0.15g, 0.7 mmol) and stirred under an inert atmosphere for 24 hrs. The reaction mixture was treated with 1N NaOH (8 mL) and stirred for 60 min, then the layers were separated. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give a residue which was purified by column chromatography (1:1:2 chloroform:acetone:hexanes) to give Compound **16** (0.049 g) as a syrup. MS m/z 601 ($M+H$).

50

Example 16

[6-(4,7-dimethoxy-indan-2-ylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone (Cpd 29)



5

Using the procedure of Example 15, 4,7-dimethoxy-2-indanone Compound 16a was used in place of 3,4-dihydro-1H-naphthalen-2-one Compound 13a to provide Compound 29. MS m/z 647 ($M+H^+$).

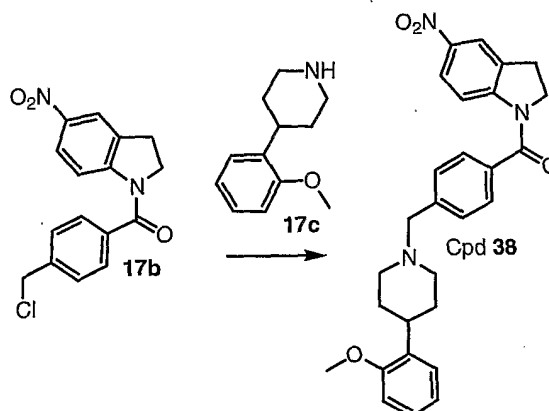
Example 17

10

(5-amino-2,3-dihydro-indol-1-yl)-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone (Cpd 33)
 {4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-(5-nitro-2,3-dihydro-indol-1-yl)-methanone (Cpd 38)

Using the procedure of Example 1, 4-chloromethyl-benzoyl chloride Compound 17a was used in place of 3-chloromethyl-benzoyl chloride Compound 1b to provide (4-chloromethyl-phenyl)-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound 17b.

15



Using the procedure of Example 1, Compound 17b was used in place of (3-chloromethyl-phenyl)-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound 1c and 4-(2-

methoxy-phenyl)-piperidine Compound **17c** was used in place of 1-(2-isopropoxy-phenyl)-piperazine monofumarate Compound **1d** to provide Compound **38**.

Using the procedure of Example 1, {4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound **38** was carried forward in place of {3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound **1e** to provide Compound **33**. MS m/z 442 ($M+H^+$).

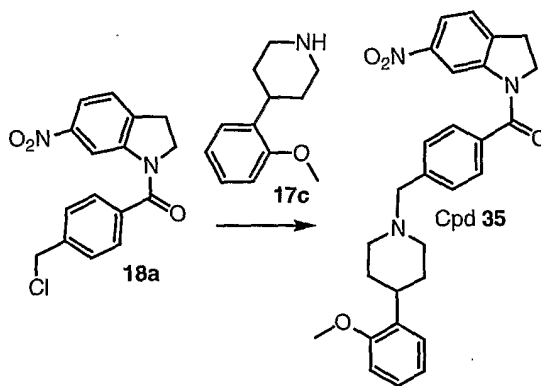
Following the procedure of Example 17, substituting the appropriate starting materials, reagents and solvents, the following compound(s) were prepared:

Cpd	Name	MS
50	(2,3-dihydro-indol-1-yl)-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone	427

Example 18

(6-amino-2,3-dihydro-indol-1-yl)-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone (Cpd **34**)
 {4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-(6-nitro-2,3-dihydro-indol-1-yl)-methanone (Cpd **35**)

Using the procedure of Example 1, 6-nitro-2,3-dihydro-1H-indole Compound **3a** was used in place of 5-nitro-2,3-dihydro-1H-indole Compound **1a**, 4-chloromethyl-benzoyl chloride Compound **17a** was used in place of 3-chloromethyl-benzoyl chloride Compound **1b** to provide (4-chloromethyl-phenyl)-(6-nitro-2,3-dihydro-indol-1-yl)-methanone Compound **18a**.



Using the procedure of Example 1, Compound **18a** was used in place of (3-chloromethyl-phenyl)-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound **1c** and 4-(2-methoxy-phenyl)-piperidine Compound **17c** was used in place of 1-(2-isopropoxy-phenyl)-piperazine monofumarate Compound **1d** to provide Compound **35**.

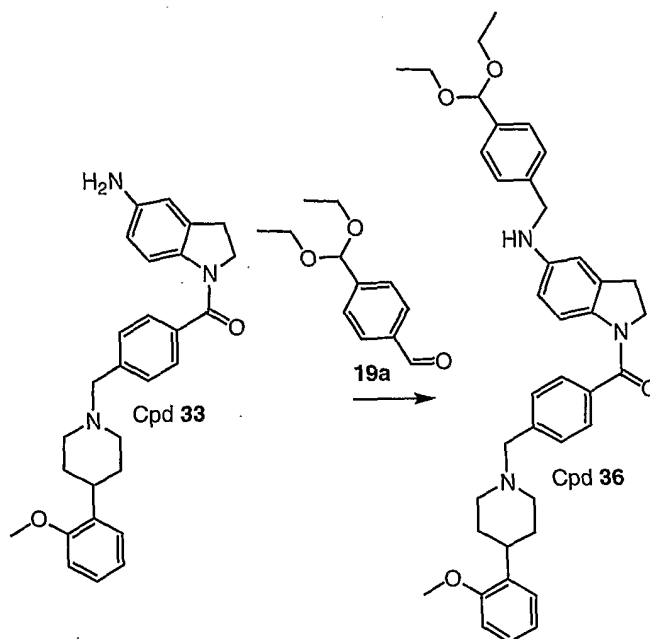
Using the procedure of Example 1, {4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-(6-nitro-2,3-dihydro-indol-1-yl)-methanone Compound **35** was carried forward in place of {3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-(5-nitro-2,3-dihydro-

indol-1-yl)-methanone Compound **1e** to provide Compound **34**. MS m/z 442 ($M+H^+$).

Example 19

[5-(4-diethoxymethyl-benzylamino)-2,3-dihydro-indol-1-yl]-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone (Cpd **36**)

5



Using the procedure of Example 2, (5-amino-2,3-dihydro-indol-1-yl)-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone Compound **33** was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **1** and 4-diethoxymethyl-benzaldehyde Compound **19a** was used in place of 4-trifluoromethyl-benzaldehyde Compound **2a** to provide Compound **36** as a brown solid. MS m/z 643 ($M+H^+$).

10

Example 20

[6-(4-diethoxymethyl-benzylamino)-2,3-dihydro-indol-1-yl]-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone (Cpd **37**)

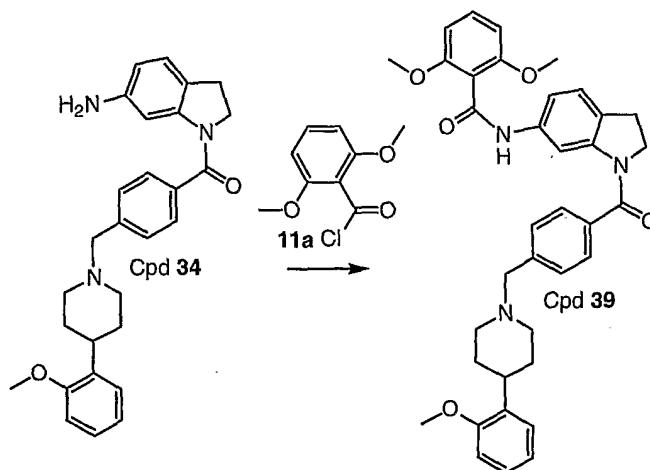
15

Using the procedure of Example 2, (6-amino-2,3-dihydro-indol-1-yl)-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone Compound **34** was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **1** and 4-diethoxymethyl-benzaldehyde Compound **19a** was used in place of 4-trifluoromethyl-benzaldehyde Compound **2a** to provide Compound **37** as a white solid. MS m/z 643 ($M+H^+$).

20

Example 21

2,6-dimethoxy-N-(1-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-benzamide (Cpd 39)



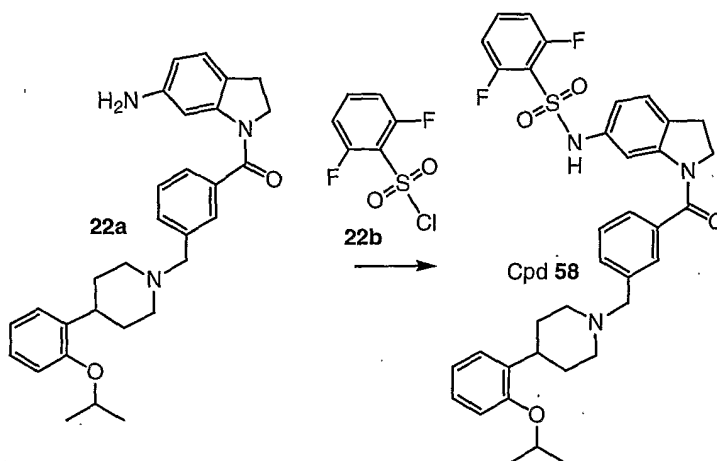
5

Using the procedure of Example 11, (6-amino-2,3-dihydro-indol-1-yl)-{4-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone Compound **34** was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **1** to provide Compound **39** as a brown solid. MS m/z 606 ($M+H^+$).

10

Example 22

2,6-difluoro-N-(1-{3-[4-(2-isopropoxy-phenyl)-piperidin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-benzenesulfonamide (Cpd 58)



15

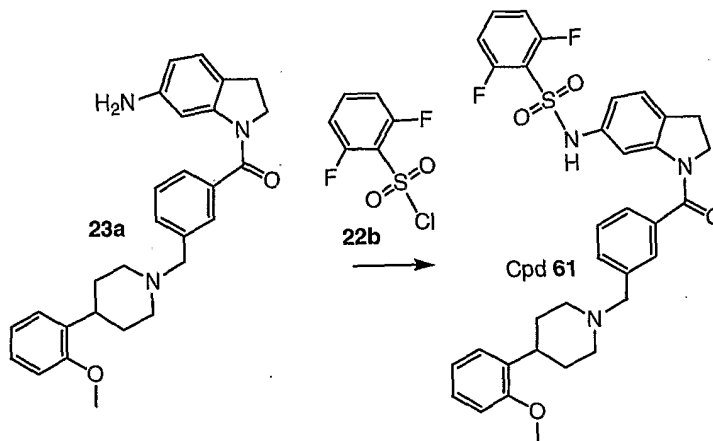
Using the procedure of Example 4, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone Compound **22a** was used in place of (5-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-

phenyl}-methanone Compound **1** and 2,6-difluoro-benzenesulfonyl chloride Compound **22b** was used in place of naphthalene-2-sulfonyl chloride Compound **4a** to provide Compound **58** as a cream-colored powder. MS m/z 646 ($M+H^+$).

Example 23

5

2,6-difluoro-N-(1-{3-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-benzenesulfonamide (Cpd **61**)

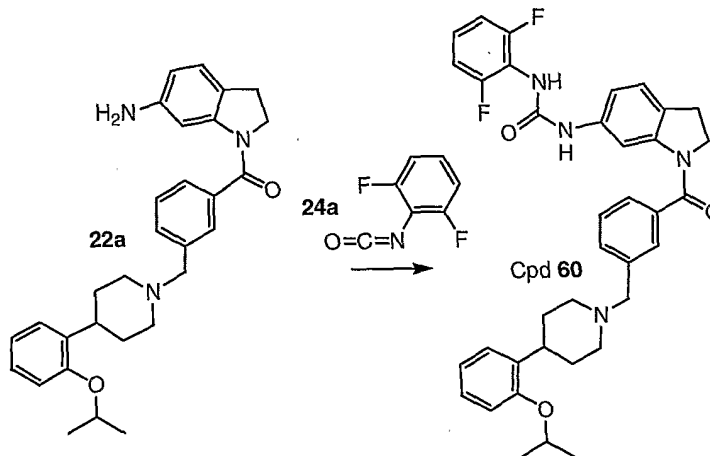


Using the procedure of Example 22, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone Compound **23a** was used in place of (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone Compound **22a** to provide Compound **61** as a cream-colored powder. MS m/z 618 ($M+H^+$).

Example 24

15

1-(2,6-difluoro-phenyl)-3-(1-{3-[4-(2-isopropoxy-phenyl)-piperidin-1-ylmethyl]-benzoyl}-2,3-dihydro-1H-indol-6-yl)-urea (Cpd **60**)

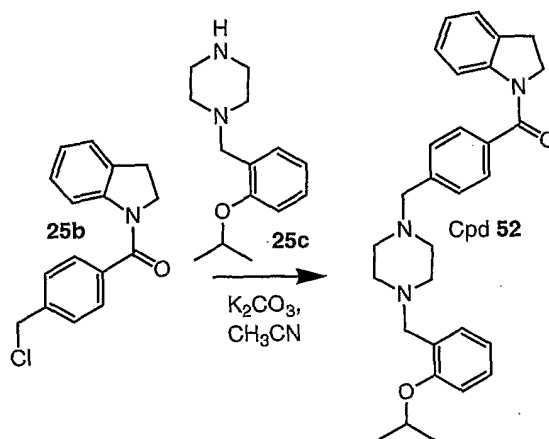


Using the procedure of Example 7, (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone Compound **22a** was used in place of (6-amino-2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperazin-1-ylmethyl]-phenyl}-methanone Compound **5**, and 1,3-difluoro-2-isocyanato-benzene Compound **24a** was used in place of isocyanato-benzene Compound **6a** to provide Compound **60** as a cream-colored powder. MS m/z 625 ($M+H^+$).

Example 25

(2,3-dihydro-indol-1-yl)-{4-[4-(2-isopropoxy-benzyl)-piperazin-1-ylmethyl]-phenyl}-methanone (Cpd **52**)

Using the procedure of Example 1, 2,3-dihydro-1H-indole Compound **25a** was used in place of 5-nitro-2,3-dihydro-1H-indole Compound **1a** and 4-chloromethyl-benzoyl chloride Compound **17a** was used in place of 3-chloromethyl-benzoyl chloride Compound **1b** to provide (4-chloromethyl-phenyl)-(2,3-dihydro-indol-1-yl)-methanone Compound **25b**.



Compound **25b** was used in place of (3-chloromethyl-phenyl)-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound **1c** and 1-(2-isopropoxy-benzyl)-piperazine monofumarate Compound **25c** was used in place of 1-(2-isopropoxy-phenyl)-piperazine monofumarate Compound **1d** to provide Compound **52**. MS m/z 470 ($M+H^+$).

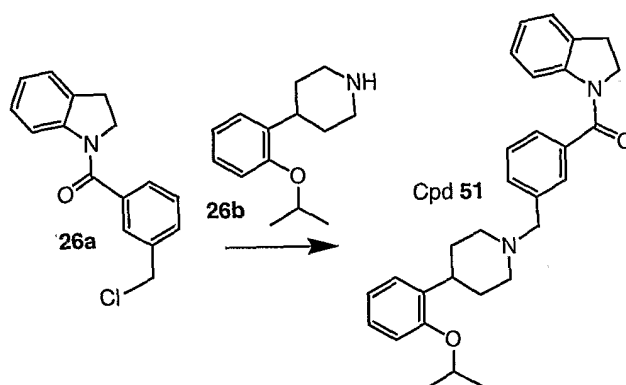
Following the procedure of Example 25, substituting the appropriate starting materials, reagents and solvents, the following compound(s) were prepared:

Cpd	Name	MS
53	(2,3-dihydro-indol-1-yl)-{4-[4-(2-methoxy-benzyl)-piperazin-1-ylmethyl]-phenyl}-methanone	442
55	(2,3-dihydro-indol-1-yl)-{4-[4-[2-(2,2,2-trifluoro-ethoxy)-phenyl]-piperazin-1-ylmethyl]-phenyl}-methanone	496
62	(2,3-dihydro-indol-1-yl)-{4-[4-(2-hydroxy-benzyl)-piperazin-1-ylmethyl]-phenyl}-methanone	428

Example 26

(2,3-dihydro-indol-1-yl)-{3-[4-(2-isopropoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone (Cpd 51)

Using the procedure of Example 1, 2,3-dihydro-1H-indole Compound 25a was used in place of 5-nitro-2,3-dihydro-1H-indole Compound 1a to provide (3-chloromethyl-phenyl)-(2,3-dihydro-indol-1-yl)-methanone Compound 26a.



Compound 26a was used in place of (3-chloromethyl-phenyl)-(5-nitro-2,3-dihydro-indol-1-yl)-methanone Compound 1c and 4-(2-isopropoxy-phenyl)-piperidine Compound 26b was used in place of 1-(2-isopropoxy-phenyl)-piperazine monofumarate Compound 1d to provide Compound 51. MS m/z 455 ($M+H^+$).

Following the procedure of Example 26, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

Cpd	Name	MS
57	[6-(2-fluoro-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-isopropoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone	578
59	[6-(2-fluoro-benzylamino)-2,3-dihydro-indol-1-yl]-{3-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-phenyl}-methanone	549

Biological Examples

15 α_1 -Adrenergic Receptor Binding Assay

Preparation of COS Cell Membranes

Membranes were prepared from COS-7 cells (African Green monkey kidney SV40-transformed cells) that had been transfected with one of the three α_1 -AR subtypes by the following method: COS cells from ten 100 mm tissue culture plates were scraped into a 5 mL volume of TE (a mixture of 50 mM tris(hydroxymethyl)aminomethane hydrochloride (Tris-HCl) and 5 mM ethylenediaminetetraacetic acid (EDTA) at pH 7.4). The cell suspension was disrupted with a Brinkman Polytron (at a setting of 8) for 10 sec. The disrupted cells were centrifuged at 1000 x g for 10 min at 4 °C. Supernatants were centrifuged at 34,500 x g for 20

min at 4 °C. The membrane pellets were suspended in a 2 mL volume of TNE (a mixture of 50 mM Tris-HCl, 5 mM EDTA and 150 mM NaCl at pH7.4). An aliquot of the membrane suspension was stored at -70 °C until use. The protein concentration was determined using a BioRad "DC" protein assay kit following membrane solubilization with Triton X-100.

5 Radio-ligand Binding Assay

Triplicate determinations of radio-ligand binding in the presence of increasing concentrations of testing compound were made. The reagents were added to 96-well polypropylene plate wells. Each assay well contained 140 μ L TNE, 25 μ L ^{125} I-2-(β -4-hydroxyphenyl)ethylaminomethyltetralone (^{125} I-HEAT) (specific activity 2200 Ci/mmol, Dupont-New England Nuclear, 50 pM final), 10 μ L testing compound dissolved in dimethyl sulfoxide (DMSO) (1 pM to 10 μ M in half-log increments, final), and 25 μ L appropriate α_1 -AR membrane subtype suspension in TNE (0.5 ng/ μ L for the α_{1a} and α_{1b} subtypes and 13 ng/ μ L for the α_{1d} subtype). The plate was incubated at rt for 1 hr. The contents of the wells were filtered through a glass filter (type C) (GF/C) membrane Unifilter plate (Packard Instruments) using the Packard Filtermate cell harvester. The filter plates were dried in a vacuum oven for 30 min at 40 °C. 25 μ L Microscint 20 liquid scintillation fluid (Packard Instruments) was added to each well. The radioactive content was analyzed in the TopCount microplate scintillation counter (Packard Instruments).

Data Analysis

The K_i values (in nM) shown in Table 1 were determined using GraphPad Prism software. K_d values used in the K_i calculation for the α_1 -AR subtypes for ^{125} I-HEAT were 81.5 nM for the α_{1a} -AR, 79 nM for the α_{1b} -AR and 50 nM for the α_{1d} -AR.

Table 1

Receptor Binding, K_i (nM)

Cpd	α_{1a} -AR	α_{1b} -AR	α_{1d} -AR
1	1.5	301	8.6
2	1.1	321	9.7
3	65	3452	98
4	2.4	96	20
5	1.9	143	2
6	2	856	2.4
7	11	684	16
8	14	389	15
9	26	2054	17
10	836	5000	250

Cpd	α 1a-AR	α 1b-AR	α 1d-AR
11	5	6259	7
12	3.3	495	5.7
13	33	305	4/3.11
14	22	5000	5000/4
15	1	91	700/5000
16	5.5	282	3.4
17	14	812	7.6
18	0.04	43	4
19	26	383	2.3
20	4.7/8.1	494/394	1.9/2.6
21	73	1395	12.5
22	39	251	5
23	195	5000	317
24	48	1472	15
25	67	1303	18
26	34	200	2
27	16.5	379	11
28	17	796	6.8
29	20.8	847	10.2/750
30	26/30.5	277.5/192.8	4.5/42
31	171	331	11.6/88
32	2.7	610	9.4
33	48.8	658.1	49.1
34	34.9	473.1	49.6
35	5.3	200.7	8.5
36	39.2	1012	40.2
37	75.6	909.4	98
38	124	461	44.2
39	74	595	41
40	31	208	1.5
41	31	208	1.5
42	3.8	447	5.8
43	7.8/3.4	204/185	2.8/3.2
44	1.3	5000	4.2
45	2.6	888	4
46	5.9	242	5.6
47	2.3	230	2.6
48	74	889	6
49	14	351	13
50	7.8	458	32

Cpd	α 1a-AR	α 1b-AR	α 1d-AR
51	0.8	106	1.6
52	122	1733	159
53	82	104	96
54	67.5	5000	5000
55	25.5	310	43
56	1197	655	1907
57	1.8	237	1.4
58	0.8/0.5	234/254.7	1.9/1
59	8.3	100.5	1.1
60	0.4	120.9	0.4
61	15.5	152.2	2.1
62			
63	0.1/2.1	10.6/117.3	0.5/1.9
64	105	146	101
65	65	909	42
66	1.3	82.8	0.3
67	2.1/12	1142/1260	14.7/22
68	13	288	13
69	0.36/15	2.8/170	0.25/4.3
70	107	1760	41
71	14/17.5	716/720	16/21
72	15	154	46
73	31	208	1.5

In Vivo Models

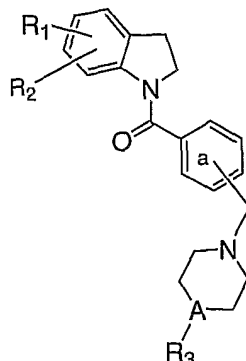
The ability of a test compound to relax prostatic smooth muscle tissue *in vivo* may be evaluated using the prostatic intraurethral pressure (IUP) and blood pressure (MAP) in the anesthetized canine model. Alternatively, the ability of a test compound to relax prostate smooth muscle tissue *in vivo* may be evaluated by evaluating the prostatic intraurethral pressure (IUP) and blood pressure (MAP) in the conscious canine model.

It is to be understood that the preceding description teaches the principles of the present invention, with examples thereof, which have emphasized certain aspects. It will also be understood that the practice of the invention encompasses all of the usual variations, adaptations and modifications as come within the scope of the following claims and their equivalents. However, numerous other equivalents not specifically elaborated on or discussed may nevertheless fall within the spirit and scope of the present invention and claims and are intended to be included.

Throughout this application, various publications are cited. The disclosure of all publications or patents cited herein are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats.

What is claimed is:

1. A compound of Formula (I)



or a pharmaceutically acceptable form thereof, wherein

“a” represents a point of attachment selected from the 3 or 4 position on the phenyl ring relative to the point of attachment of the methanone group for the compound of Formula (I),

“A” is a ring atom selected from CH or N,

R₁ is one substituent selected from the group consisting of hydrogen, -N-, halogen and nitro, wherein -N- is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl, C₁₋₈alkyl(C₁₋₈alkoxy), C(O)(R^A), C(O)O(R^A), C(O)NH₂, C(O)NH(C₁₋₈alkyl), C(O)N(C₁₋₈alkyl)₂, C(O)NH(R^A), C(O)N(R^A)₂, C(O)NH(C₁₋₈alkyl-R^A), C(O)N(C₁₋₈alkyl-R^A)₂, C(S)NH(R^A), C(S)N(R^A)₂, C(S)NH(C₁₋₈alkyl-R^A), C(S)N(C₁₋₈alkyl-R^A)₂, SO₂(C₁₋₈alkyl), SO₂(R^A), SO₂NH₂, SO₂NH(C₁₋₈alkyl), SO₂N(C₁₋₈alkyl)₂, SO₂NH(R^A), C₁₋₈alkyl(R^A) and R^A,

R₂ is one substituent selected from the group consisting of hydrogen, -SO₂- and R^A, wherein -SO₂- is substituted with C₁₋₈alkyl, NH₂, NH(C₁₋₈alkyl) or N(C₁₋₈alkyl)₂,

R^A is selected from the group consisting of C₃₋₁₂cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₁₀alkyl, C₁₋₈alkoxy, C₁₋₈alkyl(C₁₋₈alkoxy)₁₋₂, C₁₋₈alkyl(halogen)₁₋₃, C₁₋₈alkoxy(halogen)₁₋₃, C₁₋₈alkyl(hydroxy), NH₂, NH(C₁₋₈alkyl), N(C₁₋₈alkyl)₂, halogen, hydroxy, C(O)NH₂, C(O)NH(C₁₋₈alkyl), C(O)N(C₁₋₈alkyl)₂, NHC(O)H and NHC(O)(C₁₋₈alkyl),

R₃ is selected from the group consisting of C₁₋₈alkyl(R^B), -C(O)(C₁₋₈alkoxy) and R^B,

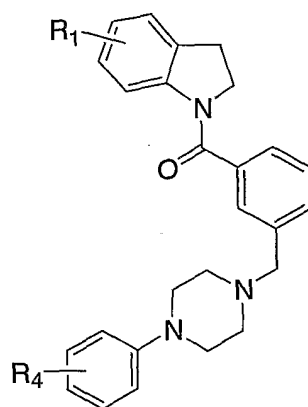
and

R^B is selected from the group consisting of C_{3-12} cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-10} alkyl, C_{1-8} alkoxy, C_{1-8} alkyl(C_{1-8} alkoxy)₁₋₂, C_{1-8} alkyl(halogen)₁₋₃, C_{1-8} alkoxy(halogen)₁₋₃, C_{1-8} alkyl(hydroxy), C_{1-8} alkoxy(hydroxy), cyano, halogen and hydroxy, with the proviso that (2,3-dihydro-indol-1-yl)-{4-[4-(2-isopropoxy-phenyl)-piperazine-1-ylmethyl]-phenyl}-methanone is not included as a compound of Formula (I).

2. A compound according to claim 1, wherein R_1 is one substituent selected from the group consisting of hydrogen, -N-, halogen and nitro, wherein -N- is substituted with two substituents independently selected from the group consisting of hydrogen, $C(O)(R^A)$, $C(O)O(R^A)$, $C(O)NH_2$, $C(O)NH(R^A)$, $C(O)N(R^A)_2$, $C(O)NH(C_{1-8}alkyl-R^A)$, $C(O)N(C_{1-8}alkyl-R^A)_2$, $C(S)NH(R^A)$, $C(S)N(R^A)_2$, $C(S)NH(C_{1-8}alkyl-R^A)$, $C(S)N(C_{1-8}alkyl-R^A)_2$, $SO_2(C_{1-8}alkyl)$, $SO_2(R^A)$, SO_2NH_2 , $SO_2NH(R^A)$, $C_{1-8}alkyl(R^A)$ and R^A .
3. A compound according to claim 1, wherein R_1 is one substituent selected from the group consisting of hydrogen, -N-, halogen and nitro, wherein -N- is substituted with two substituents independently selected from the group consisting of hydrogen, $C(O)(R^A)$, $C(O)O(R^A)$, $C(O)NH_2$, $C(O)NH(R^A)$, $C(S)NH(R^A)$, $SO_2(C_{1-8}alkyl)$, $SO_2(R^A)$, SO_2NH_2 , $C_{1-8}alkyl(R^A)$ and R^A .
4. A compound according to claim 1, wherein R_2 is one substituent selected from the group consisting of hydrogen, -SO₂- and R^A , wherein -SO₂- is substituted with $C_{1-8}alkyl$ or $N(C_{1-8}alkyl)_2$.
5. A compound according to claim 1, wherein R^A is selected from the group consisting of C_{3-12} cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-10} alkyl, C_{1-8} alkoxy, $C_{1-8}alkyl(C_{1-8}alkoxy)$ ₁₋₂, $C_{1-8}alkyl(halogen)$ ₁₋₃, $C_{1-8}alkoxy(halogen)$ ₁₋₃, NH_2 , $NH(C_{1-8}alkyl)$, $N(C_{1-8}alkyl)_2$, halogen, hydroxy and $NHC(O)(C_{1-8}alkyl)$.
6. A compound according to claim 1, wherein R^A is selected from the group consisting of C_{3-12} cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-10} alkyl, C_{1-8} alkoxy, $C_{1-8}alkyl(C_{1-8}alkoxy)$ ₁₋₂, $C_{1-8}alkyl(halogen)$ ₁₋₃, $N(C_{1-8}alkyl)_2$,

halogen and $\text{NHC(O)(C}_{1-8}\text{alkyl)}$.

7. A compound according to claim 1, wherein R^{B} is selected from the group consisting of C_{3-12} cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-10} alkyl, C_{1-8} alkoxy, C_{1-8} alkyl(halogen)₁₋₃, C_{1-8} alkoxy(halogen)₁₋₃, cyano, halogen and hydroxy.
8. A compound according to claim 1, wherein R^{B} is aryl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-10} alkyl, C_{1-8} alkoxy, C_{1-8} alkyl(halogen)₁₋₃, C_{1-8} alkoxy(halogen)₁₋₃, cyano, halogen and hydroxy.
9. A compound according to claim 1, wherein R^{B} is aryl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8} alkoxy, C_{1-8} alkoxy(halogen)₁₋₃, cyano and hydroxy.
10. A compound of formula (Ia):

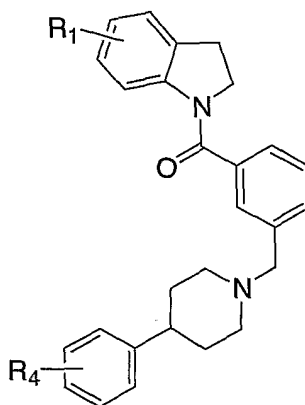


or a pharmaceutically acceptable form thereof, wherein

- 15 R_1 is selected from the group consisting of hydrogen, 5- NH_2 , 5- NHSO_2 -naphthalen-2-yl, 5- NHSO_2 -5- $\text{N(CH}_3)_2$ -naphthalen-1-yl, 5- NHC(O)O -4- CH_3 -phenyl, 6- NH_2 , 6- NHCH_2 -2,6- F_2 -phenyl, 6- NHCH_2 -2,6- $(\text{OCH}_3)_2$ -phenyl, 5- NHCH_2 -4- CF_3 -phenyl, 5- NHCH_2 -2,6- F_2 -phenyl, 6- NHCH_2 -4- $(\text{CH}_2)_7\text{CH}_3$ -phenyl, 6- NHCH_2 -4- $\text{CH(OCH}_2\text{CH}_3)_2$ -phenyl, 6- NHC(O)O -4- CH_3 -phenyl, 6- NHC(S)NH -phenyl, 5- NHC(O)NH -2,4- Cl_2 -phenyl, 6- NHSO_2 -4- NHC(O)CH_3 -phenyl, 6- NH -1,2,3,4-tetrahydro-naphthalen-2-yl, 5- NHSO_2NH_2 , 6- NHSO_2 -5- Cl -3- CH_3 -benzo[*b*]thien-2-yl, 5- NHSO_2 -4- NHC(O)CH_3 -phenyl, 6- NHSO_2NH_2 , 5- NHC(O)NH -phenyl,
- 20

- 5 6-NHC(O)NH-phenyl, 5-NHCH₂-4-(CH₂)₇CH₃-phenyl,
 5-NHCH₂-4-CH(OCH₂CH₃)₂-phenyl, 5-NHCH₂-2,6-(OCH₃)₂-phenyl,
 5-NHC(O)-2,6-(OCH₃)₂-phenyl, 5-NHCH₂-benzo[1,3]dioxol-5-yl,
 6-NHC(O)-2,6-(OCH₃)₂-phenyl, 6-NH-4,7-(OCH₃)₂-indan-2-yl,
 6-NHSO₂-5-N(CH₃)₂-naphthalen-1-yl, 6-NHC(O)-2,6-F₂-phenyl,
 6-NHCH₂-benzo[1,3]dioxol-5-yl, 6-NHC(O)-4-OCH₃-phenyl,
 6-N[C(O)NH-2,6-F₂-phenyl]₂, 6-NHCH₂-2-F-phenyl, 6-NHSO₂-2,6-F₂-phenyl,
 6-NHSO₂-4-CH₃-phenyl, 6-NHSO₂CH₂CH₃, 6-NHC(O)-4-F-phenyl,
 6-NHC(O)NH₂, 6-NHC(O)NH-2,6-F₂-phenyl, 5-Br, 5-Cl and 5-F; and
 10 R₄ is selected from the group consisting of hydrogen, 2-OCH(CH₃)₂, 2-OCH₃, 2-CN,
 2-OCH₂CF₃, 2-OCH₂CH(CH₃)₂ and 2-OCH₂CH₃.

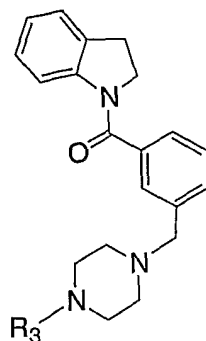
11. A compound of Formula (Ib):



or a pharmaceutically acceptable form thereof, wherein

- 15 R₁ is selected from the group consisting of hydrogen, 6-NHCH₂-2-F-phenyl,
 6-NHSO₂-2,6-F₂-phenyl, 6-NHCH₂-2-F-phenyl, 6-NHC(O)NH-2,6-F₂-phenyl,
 and 6-NHSO₂-2,6-F₂-phenyl; and
 R₄ is selected from the group consisting of 2-OCH(CH₃)₂ and 2-OCH₃.

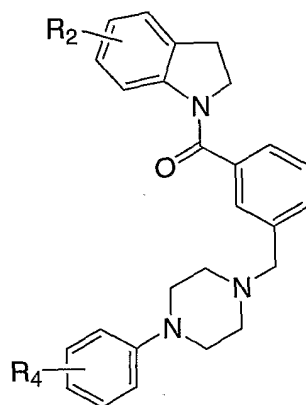
12. A compound of Formula (Ic):



or a pharmaceutically acceptable form thereof, wherein

R₃ is selected from the group consisting of C(O)OC(CH₃)₃, CH₂-2-OCH(CH₃)₂-phenyl and CH₂-2-OCH₃-phenyl.

- 5 13. A compound of Formula (Id):

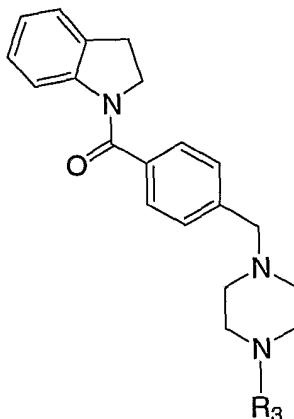


or a pharmaceutically acceptable form thereof, wherein

R₂ is selected from the group consisting of 5-SO₂N(Me)₂, 5-SO₂Me and 5-Ph; and

R₄ is 2-OCH₂CH(CH₃)₂.

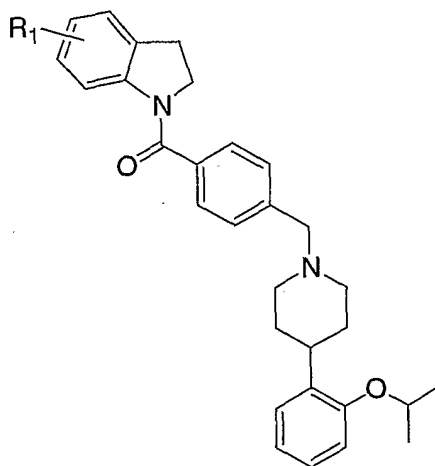
14. A compound of Formula (Ie):



or a pharmaceutically acceptable form thereof, wherein

R₃ is selected from the group consisting of CH₂-2-OCH(CH₃)₂-phenyl,
CH₂-2-OCH₃-phenyl, 2-OCH₂CF₃-phenyl, and CH₂-2-OH-phenyl.

15. A compound of Formula (If):



or a pharmaceutically acceptable form thereof, wherein

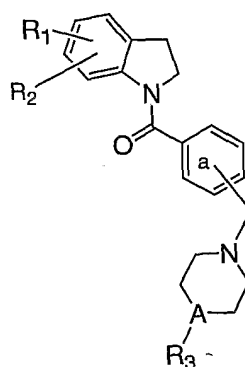
R₁ is selected from the group consisting of 5-NH₂, 6-NH₂, 6-NO₂,
5-NHCH₂-4-CH(OCH₂CH₃)₂-phenyl, 6-NHCH₂-4-CH(OCH₂CH₃)₂-phenyl,
5-NO₂, 6-NHC(O)-2,6-(OCH₃)₂-phenyl and hydrogen..

16. The compound of any of claim 1 to 15, wherein the compound is an α_{1a}/α_{1d} adrenoreceptor modulator.
17. The compound of claim 16, wherein the compound is a prodrug form thereof.

18. The compound of any of claim 1 to 17, wherein the compound is an isolated form thereof.
19. An α_{1a}/α_{1d} adrenoreceptor modulator characterized in that it is a compound as claimed in claim 1.
- 5 20. An α_{1a}/α_{1d} adrenoreceptor antagonist characterized in that it is a compound as claimed in claim 1.
21. The compound of claim 17, wherein the compound is a metabolite form thereof.
22. The compound of any of claim 1 to 18, wherein the compound is labeled with a ligand for use as a marker, and wherein the ligand is a radioligand selected from deuterium or tritium.
- 10 23. A pharmaceutical composition comprising an effective amount of the compound of any of claim 1 to 18 and a pharmaceutically acceptable carrier.
24. The pharmaceutical composition of claim 23, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.
- 15 25. A process for preparing a pharmaceutical composition comprising the step of intimately mixing the compound of any of claim 1 to 18 and a pharmaceutically acceptable carrier.
26. A medicament comprising an effective amount of the compound of any of claim 1 to 18.
- 20 27. The medicament of claim 26, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.
28. A medicine comprising an effective amount of the compound of any of claim 1 to 18.
29. The medicine of claim 28, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.
- 25 30. Use of the compound of any of claim 1 to 18 as an α_{1a}/α_{1d} adrenoreceptor antagonist comprising contacting one or both of the α_{1a} or α_{1d} adrenoreceptors with the compound.
31. The use of claim 30, wherein the use further comprises use of the compound in a

pharmaceutical composition, medicine or medicament for the treatment of an α_{1a}/α_{1d} adrenoreceptor mediated disease.

32. Use of the compound of any of claim 1 to 18 for the manufacture of a medicament for treating an α_{1a} adrenoreceptor, an α_{1d} adrenoreceptor or a dual α_{1a}/α_{1d} adrenoreceptor mediated disease.
- 5
33. A method of treating an α_{1a} adrenoreceptor, an α_{1d} adrenoreceptor or a dual α_{1a}/α_{1d} adrenoreceptor mediated disease, comprising administering to a patient in need of such treatment an effective amount of a compound of formula (II):



or a pharmaceutically acceptable form thereof, wherein

- 10 “a” represents a point of attachment selected from the 3 or 4 position on the phenyl ring relative to the point of attachment of the methanone group for the compound of Formula (I),

“A” is a ring atom selected from CH or N,

- 15 R_1 is one substituent selected from the group consisting of hydrogen, -N-, halogen and nitro, wherein -N- is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkyl(C_{1-8} alkoxy), $C(O)(R^A)$, $C(O)O(R^A)$, $C(O)NH_2$, $C(O)NH(C_{1-8}alkyl)$, $C(O)N(C_{1-8}alkyl)_2$, $C(O)NH(R^A)$, $C(O)N(R^A)_2$, $C(O)NH(C_{1-8}alkyl-R^A)$, $C(O)N(C_{1-8}alkyl-R^A)_2$, $C(S)NH(R^A)$, $C(S)N(R^A)_2$, $C(S)NH(C_{1-8}alkyl-R^A)$, $C(S)N(C_{1-8}alkyl-R^A)_2$, $SO_2(C_{1-8}alkyl)$, $SO_2(R^A)$, SO_2NH_2 , $SO_2NH(C_{1-8}alkyl)$, $SO_2N(C_{1-8}alkyl)_2$, $SO_2NH(R^A)$, $C_{1-8}alkyl(R^A)$ and R^A ,
- 20

R_2 is one substituent selected from the group consisting of hydrogen, $-SO_2-$ and R^A , wherein $-SO_2-$ is substituted with $C_{1-8}alkyl$, NH_2 , $NH(C_{1-8}alkyl)$ or $N(C_{1-8}alkyl)_2$,

- 25 R^A is selected from the group consisting of C_{3-12} cycloalkyl, heterocyclyl, aryl and

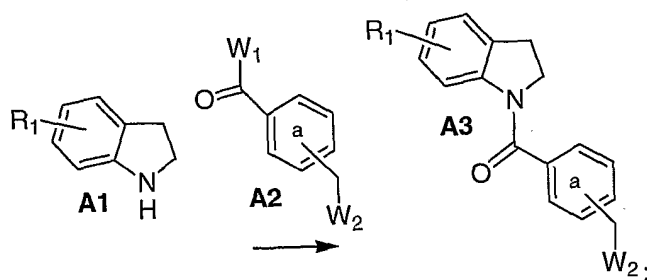
heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₁₀alkyl, C₁₋₈alkoxy, C₁₋₈alkyl(C₁₋₈alkoxy)₁₋₂, C₁₋₈alkyl(halogen)₁₋₃, C₁₋₈alkoxy(halogen)₁₋₃, C₁₋₈alkyl(hydroxy), NH₂, NH(C₁₋₈alkyl), N(C₁₋₈alkyl)₂, halogen, hydroxy, C(O)NH₂, C(O)NH(C₁₋₈alkyl), C(O)N(C₁₋₈alkyl)₂, NHC(O)H and NHC(O)(C₁₋₈alkyl),

R₃ is selected from the group consisting of C₁₋₈alkyl(R^B), -C(O)(C₁₋₈alkoxy) and R^B, and

R^B is selected from the group consisting of C₃₋₁₂cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₁₀alkyl, C₁₋₈alkoxy, C₁₋₈alkyl(C₁₋₈alkoxy)₁₋₂, C₁₋₈alkyl(halogen)₁₋₃, C₁₋₈alkoxy(halogen)₁₋₃, C₁₋₈alkyl(hydroxy), C₁₋₈alkoxy(hydroxy), cyano, halogen and hydroxyl.

34. The method of claim 33, wherein the compound is an α_{1a} adrenoreceptor, an α_{1d} adrenoreceptor or a dual α_{1a}/α_{1d} modulator.
35. The method of claim 34, wherein the compound is a prodrug form thereof.
36. The method of claim 34, wherein the compound is an isolated form thereof.
37. The method of claim 35, wherein the compound is a metabolite form thereof.
38. The method of claim 33, wherein the effective amount is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.
39. The method of claim 33, further comprising the use of an effective amount of the compound or a pharmaceutical composition, medicine or medicament thereof for the treatment of an α_{1a} adrenoreceptor, an α_{1d} adrenoreceptor or a dual α_{1a}/α_{1d} mediated disease.
40. The method of claim 39, wherein the pharmaceutical composition comprises an effective amount of the compound and a pharmaceutically acceptable carrier.
41. The method of claim 40, wherein the effective amount is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.
42. The method of claim 40, wherein the pharmaceutical composition is prepared by the step of intimately mixing the compound and a pharmaceutically acceptable carrier.

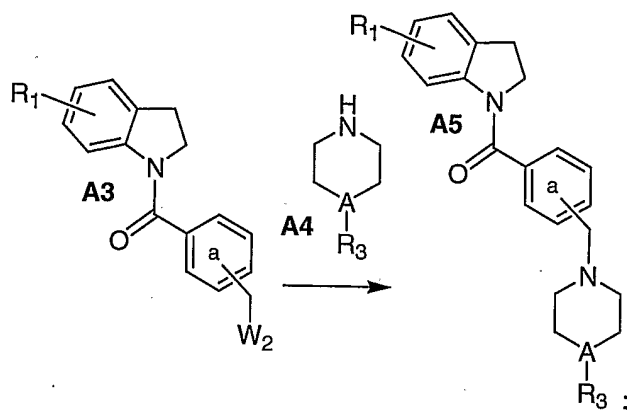
43. The method of claim 39, wherein the medicament comprises an effective amount of the compound.
44. The method of claim 43, wherein the effective amount is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.
- 5 45. The method of claim 39, wherein the medicine comprises an effective amount of the compound.
46. The method of claim 45, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.
47. The method of claim 39, further comprising contacting one or both of the α_{1a} or α_{1d} adrenoreceptors with the compound.
- 10 48. Use of the compound of claim 33 in the manufacture of a medicament for treating, preventing or ameliorating a kinase mediated disease, disorder or condition.
49. The method of claim 33, wherein the α_{1a} adrenoreceptor, α_{1d} adrenoreceptor or dual α_{1a}/α_{1d} adrenoreceptor mediated disease is LUTS.
- 15 49. The method of claim 33, wherein the α_{1a} adrenoreceptor, α_{1d} adrenoreceptor or dual α_{1a}/α_{1d} adrenoreceptor mediated disease is BPH.
50. Use of the compound of claim 33 for the manufacture of a medicament for treating an α_{1a} adrenoreceptor, an α_{1d} adrenoreceptor or a dual α_{1a}/α_{1d} adrenoreceptor mediated disease.
- 20 51. A process for preparing the compound of any of claim 1 to 18 or claim 33, comprising the steps of:
- a) reacting an intermediate of formula A1 with an intermediate of formula A2 resulting in an intermediate of formula A3:



- 25 b) reacting an intermediate of formula A3 with an intermediate of formula A4,

71

resulting in a compound of formula A5:



- c) converting compounds of formula A5 into compounds of general formula (I) by art-known functional group transformations and optionally preparing a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/05326

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 31/454(2006.01);31/496(2006.01);C07D 401/10(2006.01),403/10.

USPC: 514/254.09,323;544/373;546/201

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/254.09,323; 544/373; 546/201

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,569,659 A (REITZ) 29 October 1996 (29.10.1996), see especially column 2, lines 57-66, column 5, reaction scheme 1 and compound no 5 in Table 2.	1-10,13 and 15
X	REITZ et al. Orally Active Benzamide Antipsychotic Agents with Affinity for Dopamine D2, Serotonin 5-HT1A and Adrenergic $\alpha 1$ Receptors. Journal of Medicinal Chemistry. 01 May 1998, Vol.41, pages 1997-2009, especially page 2000, Table 1, entry for compound 49 and page 2003, Table 2, entry for compound 49.	33,36 and 38-50



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 May 2006 (26.05.2006)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Date of mailing of the international search report

14 JUL 2006

Authorized officer

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Telephone No. (571) 272-2717

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/05326

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1 (in part), 19, 20, 34, 35 and 37
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☒ Claims Nos.: 16-18, 21-32 and 51
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/05326

Continuation of Box II Reason 2:

Claims 1 (in part), 19, 20 and 34 embrace subject matter reciting a mode of action, namely as a modulator of certain subtypes of adrenoceptors which requires *apriori* testing in a particular environment. As none is indicated one cannot readily ascertain what structures are included/excluded by the claims' scope. Claim 1 (in part) embraces any "pharmaceutically acceptable form" of compounds of claim 1 while claims 35 and 37 are directed to "metabolite" or "prodrug" forms. In the absence of clear guidelines in the description pages as to structural makeup for such "forms" one cannot readily ascertain intended scope. Salts and stereoisomers are the only forms described.