Title: USE OF OXINDOLE COMPOUNDS AS THERAPEUTIC AGENTS

Abstract: This invention is directed to methods of using oxindole compounds for the treatment and/or prevention of diseases or conditions such as hypercholesterolemia, benign prostatic hyperplasia, pruritis and cancer.
USE OF OXINDOLE COMPOUNDS AS THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention is directed to methods of using oxindole compounds as therapeutic agents. In particular, this invention is directed to the use of certain oxindole compounds in treating diseases or conditions such as hypercholesterolemia, benign prostatic hyperplasia, pruritis and cancer.

BACKGROUND OF THE INVENTION

Voltage-gated sodium channels, transmembrane proteins that initiate action potentials in nerve, muscle and other electrically excitable cells, are a necessary component of normal sensation, emotions, thoughts and movements (Catterall, W.A., Nature (2001), Vol. 409, pp. 988-990). These channels consist of a highly processed alpha subunit that is associated with auxiliary beta subunits. The pore-forming alpha subunit is sufficient for channel function, but the kinetics and voltage dependence of channel gating are in part modified by the beta subunits (Goldin et al., Neuron (2000), Vol. 28, pp. 365-368). Each alpha-subunit contains four homologous domains, I to IV, each with six predicted transmembrane segments. The alpha-subunit of the sodium channel, forming the ion-conducting pore and containing the voltage sensors regulating sodium ion conduction has a relative molecular mass of 260,000. Electrophysiological recording, biochemical purification, and molecular cloning have identified ten different sodium channel alpha subunits and four beta subunits (Yu, F.H., et al., Sci. STKE (2004), 253; and Yu, F.H., et al., Neurosci. (2003), 20:7577-85).

The hallmarks of sodium channels include rapid activation and inactivation when the voltage across the plasma membrane of an excitable cell is depolarized (voltage-dependent gating), and efficient and selective conduction of sodium ions through conducting pores intrinsic to the structure of the protein (Sato, C., et al., Nature (2001), 409:1047-1051). At negative or hyperpolarized membrane potentials, sodium channels are closed. Following membrane depolarization, sodium channels open rapidly and then inactivate. Channels only conduct currents in the open state and, once inactivated, have to return to the resting state, favoured by membrane hyperpolarization, before they can reopen. Different sodium channel subtypes vary in the voltage range over which they activate and inactivate as well as their activation and inactivation kinetics.

The sodium channel family of proteins has been extensively studied and shown
to be involved in a number of vital body functions. Research in this area has identified variants of the alpha subunits that result in major changes in channel function and activities, which can ultimately lead to major pathophysiological conditions. Implicit with function, this family of proteins are considered prime points of therapeutic intervention. Na/1.1 and Na/1.2 are highly expressed in the brain (Raymond, C.K., et al., J. Biol. Chem. (2004), 279(44):46234-41) and are vital to normal brain function. In humans, mutations in Na/1.1 and Na/1.2 result in severe epileptic states and in some cases mental decline (Rhodes, T.H., et al., Proc. Natl. Acad. Sci. USA (2004),101(30):11147-52; Kamiya, K., et al., J. Biol. Chem. (2004), 24(11):2690-8; Pereira, S., et al., Neurology (2004), 63(1):191-2). As such both channels have been considered as validated targets for the treatment of epilepsy (see PCT Published Patent Publication No. WO 01/38564).


Na/1.4 expression is essentially limited to muscle (Raymond, C.K., et al., op. cit.). Mutations in this gene have been shown to have profound effects on muscle function including paralysis, (Tamaoka A., Intern. Med. (2003), (9):769-70). Thus, this channel can be considered a target for the treatment of abnormal muscle contractility, spasm or paralysis.

The cardiac sodium channel, Na/1.5, is expressed mainly in the heart ventricles and atria (Raymond, C.K., et al., op. cit.), and can be found in the sinoval node, ventricular node and possibly Purkinje cells. The rapid upstroke of the cardiac action potential and the rapid impulse conduction through cardiac tissue is due to the opening of Na/1.5. As such, Na/1.5 is central to the genesis of cardiac arrhythmias. Mutations in human Na/1.5 result in multiple arrhythmic syndromes, including, for example, long QT3 (LQT3), Brugada syndrome (BS), an inherited cardiac conduction defect, sudden unexpected nocturnal death syndrome (SUNDS) and sudden infant death syndrome (SIDS) (Liu, H. et al., Am. J. Pharmacogenomics (2003), 3(3):173-9). Sodium channel blocker therapy has been used extensively in treating cardiac arrhythmias. The first antiarrhythmic drug, quinidine, discovered in 1914, is classified as a sodium channel
Na/1.6 encodes an abundant, widely distributed voltage-gated sodium channel found throughout the central and peripheral nervous systems, clustered in the nodes of Ranvier of neural axons (Caldwell, J.H., et al., Proc. Natl. Acad. Sci. USA (2000), 97(10): 5616-20). Although no mutations in humans have been detected, Na\textsubscript{v}1.6 is thought to play a role in the manifestation of the symptoms associated with multiple sclerosis and has been considered as a target for the treatment of this disease (Craner, M.J., et al., Proc. Natl. Acad. Sci. USA (2004), 101(21): 8168-73).

Na/I.7 was first cloned from the pheochromocytoma PC12 cell line (Toledo-Aral, J. J., et al., Proc. Natl. Acad. Sci. USA (1997), 94:1527-1532). Its presence at high levels in the growth cones of small-diameter neurons suggested that it could play a role in the transmission of nociceptive information. Although this has been challenged by experts in the field as Na\textsubscript{v}1.7 is also expressed in neuroendocrine cells associated with the autonomic system (Klugbauer, N., et al., EMBO J. (1995), 14(6): 1084-90) and as such has been implicated in autonomic processes. The implicit role in autonomic functions was demonstrated with the generation of Na/I.7 null mutants; deleting Na\textsubscript{v}1.7 in all sensory and sympathetic neurons resulted in a lethal perinatal phenotype. (Nassar, et al., Proc. Natl. Acad. Sci. USA (2004), 101(34): 12706-11.) In contrast, by deleting the Na/I.7 expression in a subset of sensory neurons that are predominantly nociceptive, a role in pain mechanisms, was demonstrated (Nassar, et al., op. cit.). Further support for Na/I.7 blockers active in a subset of neurons is supported by the finding that two human heritable pain conditions, primary erythermalgia and familial rectal pain, have been shown to map to Na/I.7 (Yang, Y., et al., J. Med. Genet. (2004), 41(3): 171-4).

The expression of Na\textsubscript{v}1.8 is essentially restricted to the DRG (Raymond, C.K., et al., op. cit.). There are no identified human mutations for Na\textsubscript{v}1.8. However, Nav1.8-null mutant mice were viable, fertile and normal in appearance. A pronounced analgesia to noxious mechanical stimuli, small deficits in noxious thermoreception and delayed development of inflammatory hyperalgesia suggested to the researchers that Na\textsubscript{v}1.8 plays a major role in pain signalling (Akopian, A. N., et al., Nat. Neurosci. (1999), 2(6): 541-8). Blocking of this channel is widely accepted as a potential treatment for pain (Lai, J, et al., op. cit; Wood, J.N., et al., op. cit; Chung, J.M., et al., op. cit). PCT Published Patent Application No. WO03/037274A2 describes pyrazole-amides and sulfonamides for the treatment of central or peripheral nervous system conditions, particularly pain and chronic pain by blocking sodium channels associated
with the onset or recurrence of the indicated conditions. PCT Published Patent Application No. WO03/037890A2 describes piperidines for the treatment of central or peripheral nervous system conditions, particularly pain and chronic pain by blocking sodium channels associated with the onset or recurrence of the indicated conditions.

The compounds, compositions and methods of these inventions are of particular use for treating neuropathic or inflammatory pain by the inhibition of ion flux through a channel that includes a PN3 (Na\textsubscript{v1.8}) subunit.

The tetrodotoxin insensitive, peripheral sodium channel Nay/1.9, disclosed by Dib-Hajj, S.D., et al. (see Dib-Hajj, S.D., et al., Proc. Natl. Acad. ScL USA (1998), 95(15):8963-8) was shown to reside solely in the dorsal root ganglia. It has been demonstrated that Na\textsubscript{v1.9} underlies neurotrophin (BDNF)-evoked depolarization and excitation, and is the only member of the voltage gated sodium channel superfamily to be shown to be ligand mediated (Blum, R., Kafitz, K.W., Konnerth, A., Nature (2002), 419 (6908):687-93). The limited pattern of expression of this channel has made it a candidate target for the treatment of pain (Lai, J., et al., op. cit; Wood, J.N., et al., op. cit.) Chung, J.M. et al., op. cit.)

NaX is a putative sodium channel, which has not been shown to be voltage gated. In addition to expression in the lung, heart, dorsal root ganglia, and Schwann cells of the peripheral nervous system, NaX is found in neurons and ependymal cells in restricted areas of the CNS, particularly in the circumventricular organs, which are involved in body-fluid homeostasis (Watanabe, E., et al., J. Neurosci. (2000), 20(20):7743-51). NaX-null mice showed abnormal intakes of hypertonic saline under both water- and salt-depleted conditions. These findings suggest that the NaX plays an important role in the central sensing of body-fluid sodium level and regulation of salt intake behaviour. Its pattern of expression and function suggest it as a target for the treatment of cystic fibrosis and other related salt regulating maladies.

Studies with the sodium channel blocker tetrodotoxin (TTX) used to lower neuron activity in certain regions of the brain, indicate its potential use in the treatment of addiction. Drug-paired stimuli elicit drug craving and relapse in addicts and drug-seeking behavior in rats. The functional integrity of the basolateral amygdala (BLA) is necessary for reinstatement of cocaine-seeking behaviour elicited by cocaine-conditioned stimuli, but not by cocaine itself. BLA plays a similar role in reinstatement of heroin-seeking behavior. TTX-induced inactivation of the BLA on conditioned and heroin-primed reinstatement of extinguished heroin-seeking behaviour in a rat model (Fuchs, R.A. and See, R.E., Psychopharmacology (2002) 160(4):425-33).
This closely related family of proteins has long been recognised as targets for therapeutic intervention. Sodium channels are targeted by a diverse array of pharmacological agents. These include neurotoxins, antiarrhythmics, anticonvulsants and local anesthetics (Clare, J.J., et al., Drug Discovery Today (2000) 5:506-520). All of the current pharmacological agents that act on sodium channels have receptor sites on the alpha subunits. At least six distinct receptor sites for neurotoxins and one receptor site for local anesthetics and related drugs have been identified (Cestele, S. et al., Biochimie (2000), Vol. 82, pp. 883-892).

The small molecule sodium channel blockers or the local anesthetics and related antiepileptic and antiarrhythmic drugs, interact with overlapping receptor sites located in the inner cavity of the pore of the sodium channel (Catterall, W.A., Neuron (2000), 26:13-25). Amino acid residues in the S6 segments from at least three of the four domains contribute to this complex drug receptor site, with the IVS6 segment playing the dominant role. These regions are highly conserved and as such most sodium channel blockers known to date interact with similar potency with all channel subtypes. Nevertheless, it has been possible to produce sodium channel blockers with therapeutic selectivity and a sufficient therapeutic window for the treatment of epilepsy (e.g. lamotrigine, phenytoin and carbamazepine) and certain cardiac arrhythmias (e.g. lignocaine, tocainide and mexiletine). However, the potency and therapeutic index of these blockers is not optimal and have limited the usefulness of these compounds in a variety of therapeutic areas where a sodium channel blocker would be ideally suited.

SUMMARY OF THE INVENTION

The present invention is directed to the use of oxindole compounds for the treatment and/or prevention of diseases or conditions, such as hypercholesterolemia, benign prostatic hyperplasia, pruritis, and cancer.

Accordingly, in one aspect, the invention provides compounds of formula (I):

\[
\text{R}^1 \text{ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl,}
\]

wherein:

\( R^1 \) is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl,
cycloalkylalkyl, heteroaryl, heterocyclyl, -R^9-C(O)R^6, -R^9-C(O)OR^6, -R^9-C(O)N(R^5)R^6, -R^9-OR^6, -R^9-N(R^5)R^6, aryl and aralkyl;

R^2_a, R^2_b, R^2_c and R^2_d are each independently selected from the group consisting of

R^2_a, R^2_b, R^2_c and R^2_d are each independently selected from the group consisting of·
hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R³-CN, -R³-NO₂, -R³-OR⁶, -R³-N(R⁵)R⁶, -N=C(R⁵)R⁶, -S(O)₇R⁵, -R³-C(O)R⁵, -C(S)R⁵, -C(R⁵)₂C(O)R⁶, -R³-C(O)OR⁶,
-C(S)OR⁵, -R³-C(O)N(R⁵)R⁶, -C(S)N(R⁵)R⁶, -N(R⁶)C(O)R⁵, -N(R⁶)C(S)R⁵,
-N(R⁶)C(O)OR⁶, -N(R⁶)C(S)OR⁵, -N(R⁶)C(O)N(R⁵)R⁶, -N(R⁶)C(S)N(R⁵)R⁶,
-N(R⁶)S(O)₇R⁵, -N(R⁶)S(O)₇N(R⁵)R⁶, -R³-S(O)₇N(R⁵)R⁶, -N(R⁶)C(=N⁶)N(R⁵)R⁶,
and -N(R⁶)C(=N-CN)N(R⁵)R⁶, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;
and wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralenyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R⁵, R⁶, R⁷ and R⁸ is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl,
-R³-CN, -R³-NO₂, -R³-OR⁶, -R³-N(R⁵)R⁶, -S(O)₇R⁵, -R³-C(O)R⁵,
-R³-C(O)OR⁶, -R³-C(O)N(R⁵)R⁶, -N(R⁶)C(O)R⁵, -N(R⁶)C(S)R⁵,
-N(R⁶)C(O)OR⁶, -N(R⁶)C(S)OR⁵, -N(R⁶)C(O)N(R⁵)R⁶, -N(R⁶)C(S)N(R⁵)R⁶,
-N(R⁶)S(O)₇R⁵, -N(R⁶)S(O)₇N(R⁵)R⁶, -R³-S(O)₇N(R⁵)R⁶, -N(R⁶)C(=N⁶)N(R⁵)R⁶,
wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;
or R⁵ and R⁶, R⁷ and R⁸, or R⁷ and R⁸, together with the carbon ring atoms to which they are directly attached, may form a fused ring selected from cycloalkyl, aryl, heterocyclyl and heteroaryl;
R⁹ and R⁴ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R³-CN, -R³-NO₂, -R³-OR⁶, -R³-N(R⁵)R⁶, -S(O)₇R⁵, -R³-C(O)R⁵,
-R³-C(O)X, -C(S)R⁵, -C(R⁵)₂C(O)R⁶, -R³-OC(O)R⁶, -R³-C(O)OR⁶,
-C(S)OR⁵, -R³-C(O)N(R⁵)R⁶, -C(S)N(R⁵)R⁶, -R³-Si(R⁶)₃, -N(R⁶)C(O)R⁵,
-N(R⁶)C(S)R⁵, -N(R⁶)C(O)OR⁶, -N(R⁶)C(S)OR⁵, -N(R⁶)C(O)N(R⁵)R⁶,
-N(R⁶)C(S)N(R⁵)R⁶, -N(R⁶)S(O)₇N(R⁵)R⁶, -R³-S(O)₇N(R⁵)R⁶, -N[R(R⁶)C(O)OR⁶]C(O)OR⁶ and
-N(R⁶)C(N=C(R⁵)R⁶)N(R⁵)R⁶,
wherein X is bromo or chloro, each m is independently 0, 1, or 2 and each n is independently 1 or 2; and
wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralenyl, heterocyclyl,
heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl groups for R³ and R⁴ is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyln, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, -R³-CN, -R³-NO₂, -R³-OR⁶, -R³-N(R⁵)R⁶, -S(O)₆R⁵, -R³-C(O)R⁵, -R³-C(O)OR⁶, -R³-C(O)N(R⁵)R⁶, -N(R⁵)C(O)R⁵, and -N(R⁶)S(O)₆R⁵, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2; or R³ and R⁴ together may form =NS(O)₂R⁶, =N-R₁⁰, =N-O-R⁶ or =R³a-C(O)R⁶ (where R³a is a straight or branched alkenylene chain wherein the alkenylene chain is attached to the carbon to which R³ and R⁴ is attached through a double bond and R¹⁰ is a N-heterocyclyl optionally substituted by alkyl, haloalkyl or -R³-OR⁶); each R⁵ and R⁶ is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl; or when R⁵ and R⁶ are each attached to the same nitrogen atom, then R⁵ and R⁶, together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl; each R⁹ is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; and each R¹⁰ is an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In another aspect, the invention provides methods of treating or preventing hypercholesterolemia in a mammal, preferably a human, wherein the methods comprise administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention as set forth above.

In another aspect, the invention provides methods of treating or preventing benign prostatic hyperplasia in a mammal, preferably a human, wherein the methods comprise administering to the mammal in need thereof a therapeutically effective
amount of a compound of the invention as set forth above.

In another aspect, the invention provides methods of treating or preventing pruritis in a mammal, preferably a human, wherein the methods comprise administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention as set forth above.

In another aspect, the invention provides methods of treating or preventing cancer in a mammal, preferably a human, wherein the methods comprise administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention as set forth above.

In another aspect, the invention provides pharmaceutical compositions comprising the compounds of the invention, as set forth above, and pharmaceutically acceptable excipients.

In another aspect, the invention provides pharmaceutical therapy in combination with one or more other compounds of the invention or one or more other accepted therapies or as any combination thereof to increase the potency of an existing or future drug therapy or to decrease the adverse events associated with the accepted therapy. In one embodiment, the present invention relates to a pharmaceutical composition combining compounds of the present invention with established or future therapies for the indications listed in the invention.

In another aspect, this invention is directed to the use of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or the use of a pharmaceutical composition of the invention, comprising a pharmaceutically acceptable excipient and a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, in the preparation of a medicament for the treatment and/or prevention of hypercholesterolemia, benign prostatic hyperplasia, pruritis, and/or cancer in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Certain chemical groups named herein are preceded by a shorthand notation indicating the total number of carbon atoms that are to be found in the indicated chemical group. For example; C₇-C₁₂ alkyl describes an alkyl group, as defined below,
having a total of 7 to 12 carbon atoms, and \( \text{C}_4\text{-C}_{12} \) cycloalkylalkyl describes a
cycloalkylalkyl group, as defined below, having a total of 4 to 12 carbon atoms. The
total number of carbons in the shorthand notation does not include carbons that may
exist in substituents of the group described. For example, the following terms have the
meaning indicated:

"C\( \text{r}\) C\( \text{t}_{10}\) alkyl" refers to an alkyl radical as defined below containing one to ten
carbon atoms. The C\( \text{t}_{10}\) alkyl radical may be optionally substituted as defined below
for an alkyl group.

"C\( \text{r}\) C\( \text{t}_{12}\) alkylnyl" refers to an alkylnyl radical as defined below containing two to
twelve carbon atoms. The C\( \text{r}\) C\( \text{t}_{12}\) alkylnyl radical may be optionally substituted as
defined below for an alkenyl group.

"C\( \text{r}\) C\( \text{t}_{12}\) alkoxy" refers to an alkoxy radical as defined below containing one to
twelve carbon atoms. The alkoxy part of the C\( \text{r}\) C\( \text{t}_{12}\) alkoxy radical may be optionally
substituted as defined below for an alkyl group.

"C\( \text{r}\) C\( \text{t}_{12}\) alkoxyalkyl" refers to an alkoxyalkyl radical as defined below containing
two to twelve carbon atoms. Each alkoxy part of the C\( \text{r}\) C\( \text{t}_{12}\) alkoxyalkyl radical may be
optionally substituted as defined below for an alkyl group.

"C\( \text{t}_{7}\) C\( \text{t}_{12}\) aralkyl" refers to an aralkyl group as defined below containing seven to
twelve carbon atoms. The aralkyl part of the C\( \text{t}_{7}\) C\( \text{t}_{12}\) aralkyl radical may be optionally
substituted as described below for an aryl group. The alkyl part of the C\( \text{t}_{7}\) C\( \text{t}_{12}\) aralkyl
radical may be optionally substituted as defined below for an alkyl group.

"C\( \text{t}_{7}\) C\( \text{t}_{12}\) aralkenyl" refers to an aralkenyl group as defined below containing
seven to twelve carbon atoms. The aralkenyl part of the C\( \text{t}_{7}\) C\( \text{t}_{12}\) aralkenyl radical may be
optionally substituted as described below for an aryl group. The alkenyl part of the
C\( \text{t}_{7}\) C\( \text{t}_{12}\) aralkenyl radical may be optionally substituted as defined below for an alkenyl
group.

"C\( \text{r}\) C\( \text{t}_{12}\) cycloalkyl" refers to a cycloalkyl radical as defined below having three to
twelve carbon atoms. The C\( \text{r}\) C\( \text{t}_{12}\) cycloalkyl radical may be optionally substituted as
defined below for a cycloalkyl group.

"C\( \text{r}\) C\( \text{t}_{12}\) cycloalkylalkyl" refers to a cycloalkylalkyl radical as defined below
having four to twelve carbon atoms. The C\( \text{r}\) C\( \text{t}_{12}\) cycloalkylalkyl radical may be
optionally substituted as defined below for a cycloalkylalkyl group.

In addition to the foregoing, as used in the specification and appended claims,
unless specified to the contrary, the following terms have the meaning indicated:

"Amino" refers to the \(-\text{NH}_2\) radical.
"Cyano" refers to the -CN radical.
"Hydroxyl" refers to the -OH radical.
"Imino" refers to the =NH substituent.
"Nitro" refers to the -NO₂ radical.
"Oxo" refers to the =O substituent.
"Thioxo" refers to the -SO₂ radical.
"Trifluoromethyl" refers to the -CF₃ radical.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms, preferably one to eight carbon atoms or one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (iso-propyl), n-butyl, n-pentyl, 1,1-dimethylethyl (f-butyl), 3-methylhexyl, 2-methylhexyl, and the like. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilyl, -OR₁₄, -OC(O)-R₁₄, -N(R₁₄)₂, -C(O)R₁₄, -C(O)OR₁₄, -C(O)N(R₁₄)₂, -N(R₁₄)C(O)OR₁₄, -N(R₁₄)C(O)R₁₄, -N(R₁₄)S(O)₁₆ (where t is 1 to 2), -S(O)₂OR₁₆ (where t is 1 to 2), -S(O)₆R₁₆ (where t is Oto 2), and -S(O)₂N(R₁₄)₂ (where t is 1 to 2) where each R₁₄ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to twelve carbon atoms, preferably one to eight carbon atoms and which is attached to the rest of the molecule by a single bond, e.g., ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilyl, -OR₁₄, -OC(O)-R₁₄, -N(R₁₄)₂, -C(O)R₁₄, -C(O)OR₁₄, -C(O)N(R₁₄)₂, -N(R₁₄)C(O)OR₁₄, -N(R₁₄)C(O)R₁₄, -N(R₁₄)S(O)₁₆ (where t is 1 to 2), -S(O)₂OR₁₆ (where t is 1 to 2), -S(O)₆R₁₆ (where t is Oto 2), and -S(O)₂N(R₁₄)₂ (where t is 1 to 2) where each R₁₄ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more
halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R\textsubscript{16} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkenylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, e.g., methylene, ethylene, propylene, n-butylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, o xo, trimethylsilanyl, -OR\textsubscript{14}, -OC(O)-R\textsubscript{14}, -N(R\textsubscript{14})\textsubscript{2}, -C(O)R\textsubscript{14}, -C(O)OR\textsubscript{14}, -C(O)N(R\textsubscript{14})\textsubscript{2}, -N(R\textsubscript{14})C(O)OR\textsubscript{16}, -N(R\textsubscript{14})C(O)R\textsubscript{16}, -N(R\textsubscript{14})S(O)\textsubscript{1}R\textsubscript{16} (where t is 1 to 2), -S(O)\textsubscript{1}OR\textsubscript{16} (where t is 1 to 2), -S(O)\textsubscript{1}R\textsubscript{16} (where t is Oto 2), and -S(O)\textsubscript{2}N(R\textsubscript{14})\textsubscript{2} (where t is 1 to 2) where each R\textsubscript{14} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R\textsubscript{16} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkenylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, e.g., ethenylene, propenylene, n-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, o xo, trimethylsilanyl, -OR\textsubscript{14}, -OC(O)-R\textsubscript{14}, -N(R\textsubscript{14})\textsubscript{2}, -C(O)R\textsubscript{14}, -C(O)OR\textsubscript{14}, -C(O)N(R\textsubscript{14})\textsubscript{2}, -N(R\textsubscript{14})C(O)OR\textsubscript{16}, -N(R\textsubscript{14})C(O)R\textsubscript{16}, -N(R\textsubscript{14})S(O)\textsubscript{1}R\textsubscript{16} (where t is 1 to 2), -S(O)\textsubscript{1}OR\textsubscript{16} (where t is 1 to 2), -S(O)\textsubscript{1}R\textsubscript{16} (where t is Oto 2), and -S(O)\textsubscript{2}N(R\textsubscript{14})\textsubscript{2} (where t is 1 to 2) where each R\textsubscript{14} is independently hydrogen, alkyl,
haloalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each $R^{16}$ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

“Alkynylene” or “alkynylene chain” refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one triple bond and having from two to twelve carbon atoms, e.g., propynylene, n-butynylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkynylene chain may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilyl, -OR$^{14}$, -OC(O)-R$^{14}$, -N(R$^{14}$)$_2$, -C(O)R$^{14}$, -C(O)OR$^{14}$, -C(O)N(R$^{14}$)$_2$, -N(R$^{14}$)C(O)OR$^{16}$, -N(R$^{14}$)C(O)R$^{16}$, -N(R$^{14}$)S(O)$_2$R$^{16}$ (where $t$ is 1 to 2), -S(O)$_2$OR$^{16}$ (where $t$ is 1 to 2), -S(O)$_2$R$^{16}$ (where $t$ is Oto 2), and -S(O)$_2$N(R$^{14}$)$_2$ (where $t$ is 1 to 2) where each R$^{14}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

“Alkynyl” refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to twelve carbon atoms, preferably one to eight carbon atoms and which is attached to the rest of the molecule by a single bond, e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -OR$^{14}$, -OC(O)-R$^{14}$, -N(R$^{14}$)$_2$, -C(O)R$^{14}$, -C(O)OR$^{14}$, -C(O)N(R$^{14}$)$_2$, -N(R$^{14}$)C(O)OR$^{16}$, -N(R$^{14}$)C(O)R$^{16}$, -N(R$^{14}$)S(O)$_2$R$^{16}$ (where $t$ is 1 to 2), -S(O)$_2$OR$^{16}$ (where $t$ is 1 to 2), -S(O)$_2$R$^{16}$ (where $t$ is Oto 2), and -S(O)$_2$N(R$^{14}$)$_2$ (where $t$ is 1 to 2) where each R$^{14}$ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R$^{16}$ is alkyl,
haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Alkoxy" refers to a radical of the formula -OR\textsubscript{a} where R\textsubscript{a} is an alkyl radical as defined above containing one to twelve carbon atoms. The alkyl part of the alkoxy radical may be optionally substituted as defined above for an alkyl radical.

"Alkoxyalkyl" refers to a radical of the formula -R\textsubscript{a}-O-R\textsubscript{a} where each R\textsubscript{a} is independently an alkyl radical as defined above. The oxygen atom may be bonded to any carbon in either alkyl radical. Each alkyl part of the alkoxyalkyl radical may be optionally substituted as defined above for an alkyl group.

"Aryl" refers to aromatic monocyclic or multicyclic hydrocarbon ring system consisting only of hydrogen and carbon and containing from 6 to 18 carbon atoms, where the ring system may be partially saturated. Aryl groups include, but are not limited to, groups such as fluorenyl, phenyl and naphthyl. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from the group consisting of alkyl, akenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, heteroaryl, heteroarylalkyl, -R\textsuperscript{15}-OR\textsubscript{14}, -R\textsuperscript{15}-OC(O)-R\textsuperscript{14}, -R\textsuperscript{15}-N(R\textsuperscript{14})\textsubscript{2}, -R\textsuperscript{15}-C(O)R\textsuperscript{14}, -R\textsuperscript{15}-C(O)OR\textsuperscript{14}, -R\textsuperscript{15}-C(O)N(R\textsuperscript{14})\textsubscript{2}, -R\textsuperscript{15}-N(R\textsuperscript{14})C(O)OR\textsuperscript{16}, -R\textsuperscript{15}-N(R\textsuperscript{14})C(O)R\textsuperscript{16}, -R\textsuperscript{15}-N(R\textsuperscript{14})S(O)\textsubscript{t}R\textsuperscript{16} (where t is 1 to 2), -R\textsuperscript{15}-S(O)\textsubscript{t}R\textsuperscript{16} (where t is 0 to 2), and -R\textsuperscript{15}-S(O)\textsubscript{t}N(R\textsuperscript{14})\textsubscript{2} (where t is 1 to 2) where each R\textsuperscript{14} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R\textsuperscript{15} is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R\textsuperscript{16} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Aralkyl" refers to a radical of the formula -R\textsubscript{a}R\textsubscript{b} where R\textsubscript{a} is an alkyl radical as defined above and R\textsubscript{b} is one or more aryl radicals as defined above, e.g., benzyl, diphenylmethyl and the like. The aryl radical(s) may be optionally substituted as described above.

"Aryloxy" refers to a radical of the formula -OR\textsubscript{b} where R\textsubscript{b} is an aryl group as defined above. The aryl part of the aryloxy radical may be optionally substituted as defined above.

"Aralkenyl" refers to a radical of the formula -R\textsubscript{c}R\textsubscript{b} where R\textsubscript{c} is an alkenyl radical as defined above and R\textsubscript{b} is one or more aryl radicals as defined above, which may be optionally substituted as described above. The aryl part of the aralkenyl radical may
be optionally substituted as described above for an aryl group. The alkenyl part of the aralkenyl radical may be optionally substituted as defined above for an alkenyl group.

"Aralkyloxy" refers to a radical of the formula -ORₜ where Rₜ is an aralkyl group as defined above. The aralkyl part of the aralkyloxy radical may be optionally substituted as defined above. 

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalinyl, and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, oxo, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaryalkyl, -R¹₅-OR¹⁴, -R¹₅-OC(O)-R¹⁴, -R¹₅-N(R¹⁴)₂, -R¹₅-C(O)R¹⁴, -R¹₅-C(O)OR¹⁴, -R¹₅-C(O)N(R¹⁴)₂, -R¹₅-N(R¹⁴)C(O)OR¹⁶, -R¹₅-N(R¹⁴)C(O)R¹⁶, -R¹₅-N(R¹⁴)S(O)ₙR¹⁶ (where t is 1 to 2), -R¹₅-S(O)ₙOR¹⁶ (where t is 1 to 2), -R¹₅-S(O)ₙR¹⁶ (where t is 0 to 2), and -R¹₅-S(O)ₙN(R¹⁴)₂ (where t is 1 to 2) where each R¹⁴ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaryalkyl; each R¹⁵ is independently a direct bond or a straight or branched alkyne or alkylene chain; and each R¹⁶ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaryalkyl.

"Cycloalkylalkyl" refers to a radical of the formula -Rₐ₁Rₜₜ where Rₐ is an alkyl radical as defined above and Rₜ is a cycloalkyl radical as defined above. The alkyl radical and the cycloalkyl radical may be optionally substituted as defined above.

"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like. The alkyl part of the haloalkyl radical may be optionally substituted as defined above for an alkyl group.
"Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thiényl[1,3]dithianyl, decahydroisoquinoly, imidazoliny1, imidazolidiny1, isothiazolidiny1, isoazolidiny1, morpholiny1, octahydroindolyl, octahydroisoindolyl, 2-oxopiperaziny1, 2-oxopiperidiny1, 2-oxopyrrolidiny1, oxazolidiny1, piperidiny1, piperaziny1, 4-piperidony1, pyrrolidiny1, pyrazolidiny1, thiazolidiny1, tetrahydrofurany1, trithiany1, tetrahydropyranyl, thiomorpholiny1, thiamorpholiny1, 1-oxo-thiomorpholiny1, and 1,1-dioxo-thiomorpholiny1. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, oxo, thio, nitro, aryl, alaryl, cycloalkyl, cycloalkilalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaryllalkyl, -R_{15}^-OR_{14}^-, -R_{15}^--OC(O)--R_{14}^-, -R_{15}^-N(R_{14})_{2}^-, -R_{15}^-C(O)R_{14}^-, -R_{15}^-C(O)OR_{14}^-, -R_{15}^-C(O)N(R_{14})_{2}^-, -R_{15}^-N(R_{14})C(O)OR_{16}^-, -R_{15}^-N(R_{14})C(O)R_{16}^-, -R_{15}^-N(R_{14})S(O)_{1}^--R_{16}^-(where t is 1 to 2), -R_{15}^-S(O)_{1}^--OR_{16}^-(where t is 1 to 2), -R_{15}^-S(O)_{1}^--R_{16}^-(where t is 0 to 2), and -R_{15}^-S(O)_{1}^--N(R_{14})_{2}^-(where t is 1 to 2) where each R_{14} is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, alaryl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaryllalkyl; each R_{15} is independently a direct bond or a straight or branched alkyne or alkenylene chain; and each R_{16} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, alaryl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaryllalkyl.

"Heterocyclylalkyl" refers to a radical of the formula -R_{a}^--R_{e}^- where R_{a} is an alkyl radical as defined above and R_{e} is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. The alkyl part of the heterocyclylalkyl radical may be optionally substituted as defined above for an alkyl group. The heterocyclyl part of the heterocyclylalkyl radical may be optionally substituted as defined above for a heterocyclyl group.

"Heteroaryl" refers to a 5- to 18-membered aromatic ring radical which consists
of one to seventeen carbon atoms and from one to ten heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quatemized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzoazoxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxany1, benzonaphthofuranyl, benzoazoxazolyl, benzodioxinyl, benzopyran, benzopyranon, benzofurany1, benzothieny1 (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofurany1, dibenzo thiophenyl, furanyl, furanony1, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indoliny1, isoindoliny1, isoquinolyl, indoliziny1, isoazolyl, naphthyridinyl, oxadiazolyl, 2-oxazepiny1, oxazolyl, oxiranyl, 1-phenyl-1H-pyrroly1, phenaziny1, phenothiaziny1, phenoxaziny1, phthalaziny1, pteridinyl, purinyl, pyrroly1, pyrazolyl, pyridinyl, pyraziny1, pyrimidy1, pyridaziny1, pyrroly1, quinazoliny1, quinoliny1, quinolinyl, quinuclidiny1, isoquinoliny1, tetrahydroquinoliny1, thiazolyl, thiazoliny1, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, the term “heteroaryl” is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkoxy, halo, haloalkyl, haloalkeny1, cyano, oxo, thioxo, nitro, oxo, ary1, aralkyl, cycloalkyl, cycloalkylalkyl, heterocycly1, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R<sup>15</sup>-OR<sup>14</sup>, -R<sup>15</sup>-OC(O)-R<sup>14</sup>, -R<sup>15</sup>-N(R<sup>14</sup>)<sub>2</sub>, -R<sup>15</sup>-C(O)R<sup>14</sup>, -R<sup>15</sup>-C(O)OR<sup>14</sup>, -R<sup>15</sup>-C(O)N(R<sup>14</sup>)<sub>2</sub>, -R<sup>15</sup>-N(R<sup>14</sup>)<sub>2</sub>-O(R<sup>14</sup>)OR<sup>16</sup>, -R<sup>15</sup>-N(R<sup>14</sup>)<sub>2</sub>-O(R<sup>14</sup>)=O(R<sup>16</sup>), -R<sup>15</sup>-N(R<sup>14</sup>)S(O)R<sup>16</sup> (where t is 1 to 2), -R<sup>15</sup>-S(O)OR<sup>16</sup> (where t is 1 to 2), -R<sup>15</sup>-S(O)R<sup>16</sup> (where t is 0 to 2), and -R<sup>15</sup>-S(O)N(R<sup>14</sup>)<sub>2</sub> (where t is 1 to 2) where each R<sup>14</sup> is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, ary1, aralkyl, heterocycly1, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R<sup>15</sup> is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R<sup>16</sup> is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, ary1, aralkyl, heterocycly1, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

"Heteroarylalkyl" refers to a radical of the formula -R<sub>a</sub>R<sub>b</sub> where R<sub>a</sub> is an alkyl radical as defined above and R<sub>b</sub> is a heteroaryl radical as defined above. The heteroaryl part of the heteroarylalkyl radical may be optionally substituted as defined above for a heteroaryl group. The alkyl part of the heteroarylalkyl radical may be
optionally substituted as defined above for an alkyl group.

"Heteroarylalkenyl" refers to a radical of the formula -R_bR_i where R_b is an alkenyl radical as defined above and R_i is a heteroaryl radical as defined above. The heteroaryl part of the heteroarylalkenyl radical may be optionally substituted as defined above for a heteroaryl group. The alkenyl part of the heteroarylalkenyl radical may be optionally substituted as defined above for an alkenyl group.

"Trihaloalkyl" refers to an alkyl radical, as defined above, that is substituted by three halo radicals, as defined above, e.g., trifluoromethyl. The alkyl part of the trihaloalkyl radical may be optionally substituted as defined above for an alkyl group.

"Trihaloalkoxy" refers to a radical of the formula -OR_g where R_g is a trihaloalkyl group as defined above. The trihaloalkyl part of the trihaloalkoxy group may be optionally substituted as defined above for a trihaloalkyl group.

"Prodrugs" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted in vivo to an active compound of the invention. Prodrugs are typically rapidly transformed in vivo to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam)). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, Ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound of the invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound of the invention. Prodrugs include compounds of the invention wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound of the invention is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group,
respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol or amide derivatives of amine functional groups in the compounds of the invention and the like.

The invention disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of formula (I) being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as $^2$H, $^3$H, $^{11}$C, $^{12}$C, $^{13}$C, $^{14}$C, $^{13}$N, $^{15}$N, $^{15}$O, $^{17}$O, $^{16}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F, $^{36}$Cl, $^{123}$I, and $^{125}$I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action on the sodium channels, or binding affinity to pharmacologically important site of action on the sodium channels. Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* $^3$H, and carbon-14, *i.e.* $^{14}$C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* $^2$H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as $^{11}$C, $^{18}$F, $^{15}$O and $^{13}$N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples and Preparations as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically are identified by administering a
radiolabeled compound of the invention in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Mammal" includes humans and both domestic animals such as laboratory animals and household pets, (e.g. cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution. When a functional group is described as "optionally substituted," and in turn, substituents on the functional group are also "optionally substituted" and so on, for the purposes of this invention, such iterations are limited to five.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, caproic acid, caprylic acid, and caproic acid.
acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, proionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

Often crystallizations produce a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The
compound of the invention may be true solvates, while in other cases, the compound of the invention may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

"Therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a mammal, preferably a human, is sufficient to effect treatment, as defined below, of a disease or condition in the mammal, preferably a human. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, the manner of administration, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition of interest, and includes:

(i) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;
(ii) inhibiting the disease or condition, i.e., arresting its development;
(iii) relieving the disease or condition, i.e., causing regression of the disease or condition; or
(iv) relieving the symptoms resulting from the disease or condition.

As used herein, the terms "disease" and "condition" may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

The compounds of the invention, or their pharmaceutically acceptable salts may contain one or more asymmetric centres and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids. The
present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallisation. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centres of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

Also within the scope of the invention are intermediate compounds of formula (I) and all polymorphs of the aforementioned species and crystal habits thereof.

The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program, wherein the compounds of the invention are named herein as derivatives of the central core structure, i.e., the 2-oxindole structure. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. In chemical structure diagrams, all bonds are identified, except for some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

Thus, for example, a compound of formula (I) wherein R^1 is pentyl, R^{2a}, R^{2b} and R^{2d} are each hydrogen, R^{2c} is chloro, R^3 is -OH and R^4 is benzo-1,3-dioxolyl, i.e., a compound of the following formula:
is named herein as 3-(1,3-benzodioxol-5-yl)-6-chloro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one.

**EMBODIMENTS OF THE INVENTION**

Of the various aspects of the invention set forth above in the Summary of the Invention, certain embodiments are preferred.

One embodiment is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

- $R^1$ is $-R^9$-C(O)$R^6$, $-R^3$-C(O)$R^6$, $-R^3$-CN, $-R^{10}$-P(O)(OR)$^6$, $-R^{10}$-O$-R^{10}$-OR$^6$,
- hydrogen, alkyl, haloalkyl, cycloalkylalkyl, heterocyclylalkyl, aryl (optionally substituted by one or more substituents selected from the group consisting of halo and $-R^9$-C(O)$R^6$), aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, $-R^9$-OR$^6$ and $-R^9$-C(O)$R^6$), heteroaryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and $-R^9$-OR$^6$), or heteroarylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and $-R^9$-OR$^6$);

- $R^{2a}$, $R^{2b}$, $R^{2c}$ and $R^{2d}$ are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9$-OR$^6$, $-R^9$-N($R^5$)$R^6$, $-R^9$-C(O)$R^5$, $-R^9$-C(O)OR$^6$, $-R^9$-C(O)N($R^5$)$R^6$, and $-N(R^6)$C(O)$R^5$, wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for $R^{2a}$, $R^{2b}$, $R^{2c}$ and $R^{2d}$ is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9$-CN, $-R^9$-NO$^2$, $-R^9$-OR$^6$, $-R^9$-N($R^5$)$R^6$, $-S(O)_m$R$^5$, $-R^9$-C(O)$R^5$, $-R^9$-C(O)OR$^6$, $-R^9$-C(O)N($R^5$)$R^6$, $-N(R^6)$C(O)$R^5$ and $-N(R^6)$S(O)$_n$R$^5$, wherein each $m$ is
independently 0, 1, or 2 and each n is independently 1 or 2; 
or $R_{2a}$ and $R_{2b}$, $R_{2b}$ and $R_{2c}$, or $R_{2c}$ and $R_{2d}$, together with the carbon ring atoms to 
which they are directly attached, may form a fused ring selected from aryl, 
heterocyclyl and heteroaryl;

$R^3$ is independently selected from the group consisting of hydrogen, alkyl, halo, 
haloalkyl, heteroaryl (optionally substituted by one or more substituents 
selected from the group consisting of alkyl, halo, haloalkyl and $-R_{2a}$-OR), 
$-R_{2a}$-OR$^6$, $-R_{2a}$-OC(O)R$^6$, $-R_{2a}$-N(R$^5$)R$^6$, $-R_{2a}$-C(O)R$^5$, $-R_{2a}$-C(O)OR$^6$ 
and $-N(R_{2a})C(O)OR^6$, wherein X is chloro or bromo;

$R^4$ is independently selected from the group consisting of alkyl, aryl, aralkyl, 
aralkynyl, heteroaryl, heteroaryllalkyl, $-R_{2a}$-C(O)R$^5$, $-N(R_{2a})C(O)N(R_{2a})R_{2a}$, 
$-R_{2a}$-N(R$^5$)R$^6$, $-R_{2a}$-C(O)OR$^6$, $-N[N(R_{2a})C(O)OR_{2a}]C(O)OR^6$, $-R_{2a}$-N(R$^6$)C(O)OR$^6$ 
and $-R_{2a}$-Si(R$^6$)$_3$,

wherein each of the aryl, aralkynyl, heteroaryl and heteroaryllalkyl groups for $R^4$ 
is optionally substituted by one or more substituents selected from the 
group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, 
cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, 
heteroaryllalkyl, heteroaryl, heteroaryllalkyl, oxo, $-R_{2a}$-CN, $-R_{2a}$-NO$_2$, 
$-R_{2a}$-OR$^6$, $-R_{2a}$-N(R$^5$)R$^6$, $-S(O)_mR^5$, $-R_{2a}$-C(O)R$^5$, $-R_{2a}$-C(O)OR$^6$, 
$-R_{2a}$-C(O)N(R$^5$)R$^6$, $-N(R_{2a})C(O)R^5$, and $-N(R_{2a})S(O)_nR^6$, wherein each m is 
independently 0, 1, or 2 and each n is independently 1 or 2;

or $R^3$ and $R^4$ together may form =NS(O)$_2$R$^6$, =N-R$_{15}$, =N-O-R$_6$ or $=R_{2a}$-C(O)R$^6$ (where 
$R_{2a}$ is a straight or branched alkenylene chain wherein the alkenylene chain is 
attached to the carbon to which $R^3$ and $R^4$ is attached through a double bond 
and $R_{15}$ is a N-heterocyclyl optionally substituted by alkyl, haloalkyl or $-R_{2a}$-OR$^6$);

each $R^5$ and $R^6$ is independently selected from group consisting of hydrogen, alkyl, 
alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, 
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally 
substituted aralkyl, optionally substituted heterocyclyl and optionally substituted 
heteroaryl;

or when $R^5$ and $R^6$ are each attached to the same nitrogen atom, then $R^5$ and $R^6$, 
together with the nitrogen atom to which they are attached, may form a 
N-heterocyclyl or N-heteroaryl;

each $R^9$ is a direct bond or an optionally substituted straight or branched alkyene 
chain, an optionally substituted straight or branched alkenylene chain or an
optionally substituted straight or branched alkynylene chain; and
each R\textsuperscript{1} is an optionally substituted straight or branched alkylene chain, an optionally
substituted straight or branched alkenylene chain or an optionally substituted
straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth
above in the Summary of the Invention, wherein:

R\textsuperscript{1} is hydrogen, alkyl, aryl or aralkyl, where each aryl and aralkyl group for R\textsuperscript{1} is
independently optionally substituted by one or more substituents selected from
the group consisting of halo, haloalkyl, heteroaryl, -R\textsuperscript{9}.OR\textsuperscript{6} and -R\textsuperscript{9}.C(O)OR\textsuperscript{6};

R\textsuperscript{2a}, R\textsuperscript{2b}, R\textsuperscript{2c} and R\textsuperscript{2d} are each independently selected from the group consisting of
hydrogen, alkyl, halo, aryl, heteroaryl and -R\textsuperscript{9}.OR\textsuperscript{6},
wherein each of the aryl and heteroaryl group for R\textsuperscript{2a}, R\textsuperscript{2b}, R\textsuperscript{2c} and R\textsuperscript{2d} is
optionally substituted by one or more substituents selected from the
group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl,
cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl,
heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R\textsuperscript{9}.CN, -R\textsuperscript{9}.NO\textsubscript{2}, -R\textsuperscript{9}.OR\textsuperscript{6},
-R\textsuperscript{9}.N(R\textsuperscript{5})R\textsuperscript{6}, -S(O)\textsubscript{m}R\textsuperscript{5}, -R\textsuperscript{9}.C(O)R\textsuperscript{5}, -R\textsuperscript{9}.C(O)OR\textsuperscript{6}, -R\textsuperscript{9}.C(O)N(R\textsuperscript{5})R\textsuperscript{6},
-N(R\textsuperscript{6})C(O)R\textsuperscript{5}, and -N(R\textsuperscript{6})S(O)\textsubscript{m}R\textsuperscript{5}, where each m is independently 0, 1, or 2 and each n is independently 1 or 2;

R\textsuperscript{3} is hydrogen, alkyl, halo, -R\textsuperscript{9}.OR\textsuperscript{6} or -R\textsuperscript{9}.OC(O)R\textsuperscript{6};

R\textsuperscript{4} is independently selected from the group consisting of alkyl, aryl, alkenyl,
heteroaryl, heteroarylalkyl, -R\textsuperscript{9}.C(O)R\textsuperscript{5}, -N(R\textsuperscript{5})C(O)N(R\textsuperscript{5})R\textsuperscript{6}, -R\textsuperscript{9}.NO\textsubscript{2},
-R\textsuperscript{9}.N(R\textsuperscript{5})R\textsuperscript{6}, -R\textsuperscript{9}.C(O)OR\textsuperscript{6} and -R\textsuperscript{9}.Si(R\textsuperscript{6})\textsubscript{3},
wherein each of the aryl, alkenyl, heteroaryl and heteroarylalkyl groups for R\textsuperscript{4}
is optionally substituted by one or more substituents selected from the
group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl,
cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl,
heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, -R\textsuperscript{9}.CN, -R\textsuperscript{9}.NO\textsubscript{2},
-R\textsuperscript{9}.OR\textsuperscript{6}, -R\textsuperscript{9}.N(R\textsuperscript{5})R\textsuperscript{6}, -S(O)\textsubscript{m}R\textsuperscript{5}, -R\textsuperscript{9}.C(O)R\textsuperscript{5}, -R\textsuperscript{9}.C(O)OR\textsuperscript{6},
-R\textsuperscript{9}.C(O)N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{6})C(O)R\textsuperscript{5}, and -N(R\textsuperscript{6})S(O)\textsubscript{m}R\textsuperscript{5}, where each m is
independently 0, 1, or 2 and each n is independently 1 or 2;

each R\textsuperscript{5} and R\textsuperscript{6} is independently selected from group consisting of hydrogen, alkyl,
alkenyl, alkenyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocyclyl and optionally substituted
heteroaryl;
or when \( R^5 \) and \( R^6 \) are each attached to the same nitrogen atom, then \( R^5 \) and \( R^6 \),
together with the nitrogen atom to which they are attached, may form a
N-heterocyclyl or N-heteroaryl; and

5 each \( R^9 \) is a direct bond or an optionally substituted straight or branched alkenylene
chain, an optionally substituted straight or branched alkenylene chain or an
optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth
above in the Summary of the Invention, wherein:

10 \( R^1 \) is aryl or aralkyl each optionally substituted by one or more substituents selected
from the group consisting of halo, haloalkyl, heteroaryl, \(-R^9\)-OR\(^6\) and
\(-R^9\)-C(O)OR\(^6\);

\( R^{ca}, R^{cb}, R^{cc} \) and \( R^{cd} \) are each independently selected from the group consisting of
hydrogen, alkyl, halo, aryl, heteroaryl and \(-R^9\)-OR\(^6\),

15 wherein each of the aryl and heteroaryl group for \( R^{ca}, R^{cb}, R^{cc} \) and \( R^{cd} \) is
optionally substituted by one or more substituents selected from the
group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl,
cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl,
heterocyclylalkyl, heteroaryl, heteroarylalkyl, \(-R^9\)-CN, \(-R^9\)-NO\(_2\), \(-R^9\)-OR\(^6\),
\(-R^9\)-N(R\(^5\))R\(^6\), \(-S(O)\)_\(m\)R\(^5\), \(-R^9\)-C(O)R\(^5\), \(-R^9\)-C(O)OR\(^6\), \(-R^9\)-C(O)N(R\(^5\))R\(^6\),
\(-N(R^6)C(O)R^5\) and \(-N(R^6)S(O)_nR^5\), wherein each \( m \) is independently 0, 1, or 2 and each \( n \) is independently 1 or 2;

\( R^3 \) is hydrogen, halo, \(-R^9\)-OR\(^6\) or \(-R^9\)-OC(O)OR\(^6\);

\( R^4 \) is \(-R^9\)-C(O)R\(^5\);

20 each \( R^5 \) and \( R^6 \) is independently selected from group consisting of hydrogen, alkyl,
alkenyl, alkynyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocyclyl and optionally substituted
heteroaryl;
or when \( R^5 \) and \( R^6 \) are each attached to the same nitrogen atom, then \( R^5 \) and \( R^6 \),
together with the nitrogen atom to which they are attached, may form a
N-heterocyclyl or N-heteroaryl; and

25 each \( R^9 \) is a direct bond or an optionally substituted straight or branched alkenylene
chain, an optionally substituted straight or branched alkenylene chain or an
optionally substituted straight or branched alkynylene chain.
Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R¹ is aryl or aralkyl each optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl and -R⁰-OR⁶;

R²a, R²b, R²c and R²d are each independently selected from the group consisting of hydrogen, halo and alkyl;

R₃ is hydrogen, halo, -R⁰-OR⁶ or -R⁰-OC(O)R⁶;

R⁴ is -R⁰-C(O)R⁵;

each R⁵ is alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

each R⁶ is hydrogen or alkyl; and

each R⁹ is a direct bond or an optionally substituted straight or branched alkylene chain.

Another embodiment of the invention is a compound of formula (I) selected from the group consisting of:

1-(4-chlorobenzyl)-5-fluoro-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-(2-cyclopropyl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-[2-(4-fluorophenyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-pyridin-2-ylethyl)-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2H-indol-2-one;

1-(4-fluorophenyl)-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;

3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1-(4-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one;

1-[2-(4-chlorophenyl)-ethyl]-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-hydroxy-3-[2-oxo-2-(1H-pyrrol-2-yl)-ethyl]-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-hydroxy-3-[2-oxo-2-(1H-pyrryl-2-yl)-ethyl]-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-hydroxy-3-[2-(5-methylfuran-2-yl)-2-oxoethyl]-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-hydroxy-3-[2-(5-methylfuran-2-yl)-2-oxoethyl]-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-hydroxy-3-[2-(2,5-dimethylfuran-3-yl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzyl)-3-[2-(furan-2-yl-2-oxoethyl)]-3-hydroxy-5-methyl-1,3-dihydro-2H-indol-2-one;
3-(2-benzofuran-2-yl-2-oxo-ethyl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(1,1,3-trimethyl-2-oxobutyl)-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-(1,1-dimethyl-2-oxo-2-thiophen-2-yl-ethyl)-3-hydroxy-1,3-dihydro-
2H-indol-2-one; and
3-chloro-1-(4-chlorobenzyl)-3-[2-oxo-2-(2-thienyl)ethyl]-1,3-dihydro-2H-indol-2-one.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R1 is aralkyl (optionally substituted by one or more substituents selected from the
10 group consisting of halo, haloalkyl, heteroaryl, -R5−OR6 and -R5−C(O)R6);
R2a, R2b, R2c and R2d are each independently selected from the group consisting of
hydrogen, alkyl, halo, aryl, heteroaryl and -R5−OR6,
wherein each of the aryl and heteroaryl group for R2a, R2b, R2c and R2d is
15 optionally substituted by one or more substituents selected from the
group consisting of alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl,
cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl,
heterocyclylalkyl, heteroaryl, heteroarylmethyl,
20 -R5−C(O)R6, -R5−C(O)R5, -R5−C(O)OR6, -R5−C(O)NR5R6,
-N(R6)C(O)R5 and -N(R6)S(O)R5, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;
R3 is hydrogen, halo, -R5−OR6 or -R5−OC(O)R6;
R4 is heterocyclylalkyl, heteroaryl or heteroarylmethyl, each optionally substituted by one
25 or more substituents selected from the group consisting of alkyl, alkenyl,
alcohol, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,
aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylmethyl,
-R5−CN,
-R5−NO2, -R5−OR6, -R5−N(R5)R6, -S(O)mR5, -R5−C(O)R5, -R5−C(O)OR6,
30 -R5−C(O)N(R5)R6, -N(R6)C(O)R5 and -N(R6)S(O)nR5, wherein each m is
independently 0, 1, or 2 and each n is independently 1 or 2;
each R5 and R6 is independently selected from group consisting of hydrogen, alkyl,
alcohol, alkenyl, haloalkyl, alkoxycarbonyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocyclyl and optionally substituted
heteroaryl;
or when R5 and R6 are each attached to the same nitrogen atom, then R5 and R6,
35 together with the nitrogen atom to which they are attached, may form a
N-heterocyclyl or N-heteroaryl; and each R\(^9\) is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R\(^1\) is aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, -R\(^6\)-OR\(^6\) and -R\(^8\)-C(O)OR\(^6\));

R\(^2\), R\(^3\), R\(^4\) and R\(^8\) are each independently selected from the group consisting of hydrogen, alkyl, halo, phenyl, benzodioxolyl and -R\(^6\)-OR\(^6\),

R\(^3\) is hydrogen, halo, -R\(^8\)-OR\(^6\) or -R\(^8\)-OC(O)R\(^6\);

R\(^4\) is heterocyclylalkyl, heteroaryl or heteroarylalkyl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, heterocyclyl, and -R\(^8\)-OR\(^6\);

each R\(^6\) is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl; and

each R\(^9\) is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, selected from the group consisting of:

1-(4-chlorobenzyl)-3-hydroxy-3-(1-oxoindan-2-yl)-1,3-dihydroindol-2H-2-one;

3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(1-phenylethyl)-1,3-dihydro-2H-indol-2-one;

3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-(trifluoromethoxy)-1,3-dihydro-2H-indol-2-one;

3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-[4-(1H-pyrrol-1-yl)benzyl]-1,3-dihydro-2H-indol-2-one;

3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-[4-(1H-pyrrol-1-yl)benzyl]-1,3-dihydro-2H-indol-2-one;

3-(1,3-benzodioxol-5-yl)-5-bromo-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;

3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-5-fluoro-3-hydroxy-1,3-dihydro-2H-indol-2-one;

3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-methyl-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-(1,3-dioxolan-2-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(2-methoxybenzyl)-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-naphthalen-1-ylmethyl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(3,4-difluorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one;
S-Cl,S-benzodioxol-5-yl)-1-(4-fluorobenzylO-S-hydroxy-S-methoxy-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(4-chloro-3-trifluoromethylbenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(3-trifluoromethylbenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(4-bromobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(2-bromobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3,4,5-trimethoxybenzyl)-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(2-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(2-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-furan-3-yl-3-hydroxy-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-pyrimidin-5-yl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzothiazol-6-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(1-benzofuran-6-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(2,2-difluoro-1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-thiophen-2-yl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-hydroxy-3-[2-(2-thienyl)-1,3-dithian-2-yl]-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-phenyl-1,3-dihydro-2H-indol-2-one;
3,5-bis(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-phenyl-1,3-dihydro-2H-indol-2-one;
1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
2H-indol-2-one;
1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2H-indol-2-one;
1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one;
1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-2H-indol-2-one;
1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-5-methyl-1,3-dihydro-2H-indol-2-one;
1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one;
1-(diphenylmethyl)-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one;
1-(diphenylmethyl)-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-(2,2-difluoro-2-thiophen-2-ylethyl)-3-hydroxy-1,3-dihydroindol-2-one.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R1 is hydrogen, alkyl, or aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, -R9-OR6 and -R9-C(O)OR6);

R2a, R2b, R2c and R2d are each independently selected from the group consisting of hydrogen, alkyl, halo, aryl, heteroaryl and -R9-OR6,

wherein each of the aryl and heteroaryl group for R2a, R2b, R2c and R2d is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R9-CN, -R9-NO2, -R9-OR6, -R9-N(R5)R6, -S(O)mR5, -R9-C(O)R5, -R9-C(O)OR6, -R9-C(O)N(R5)R6, -N(R6)C(O)R5, and -N(R6)S(O)nR5, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;

R3 is hydrogen or -R9-OR6;
$\text{R}^4$ is aryl, aralkyl or aralkynyl,
wherein each of the aryl, aralkyl and aralkynyl groups for $\text{R}^4$ is optionally
substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, -$\text{R}^9$-CN, -$\text{R}^9$-NO$_2$, -$\text{R}^9$-$\text{OR}^6$, -$\text{R}^9$-$\text{N(R}^5$-$\text{R}^6$, -$\text{S(O)}_m$-$\text{R}^5$, -$\text{R}^9$-$\text{C(O)}$-$\text{OR}^6$, -$\text{R}^9$-$\text{C(O)}$-$\text{N(R}^5$-$\text{R}^6$, -$\text{N(R}^6$-$\text{C(O)}$-$\text{R}^5$, and -$\text{N(R}^6$-$\text{S(O)}_n$-$\text{R}^5$, wherein each $m$ is independently 0, 1, or 2 and each $n$ is independently 1 or 2;

each $\text{R}^5$ and $\text{R}^6$ is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkylnyl, haloalkyl, alkoxynl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted heterocycl and optionally substituted heteroaryl;

or when $\text{R}^5$ and $\text{R}^6$ are each attached to the same nitrogen atom, then $\text{R}^5$ and $\text{R}^6$, together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl; and

each $\text{R}^9$ is a direct bond or an optionally substituted straight or branched alkyene chain, an optionally substituted straight or branched alkylene chain or an optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

$\text{R}^1$ is hydrogen, alkyl or aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, -$\text{R}^9$-$\text{OR}^6$ and -$\text{R}^9$-$\text{C(O)}$-$\text{OR}^6$);

$\text{R}^{2a}$, $\text{R}^{2b}$, $\text{R}^{2c}$ and $\text{R}^{2d}$ are each independently selected from the group consisting of hydrogen, alkyl, halo, aryl, heteroaryl and -$\text{R}^9$-$\text{OR}^6$,

wherein each of the aryl and heteroaryl group for $\text{R}^{2a}$, $\text{R}^{2b}$, $\text{R}^{2c}$ and $\text{R}^{2d}$ is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -$\text{R}^9$-$\text{CN}$, -$\text{R}^9$-$\text{NO}_2$, -$\text{R}^9$-$\text{OR}^6$, -$\text{R}^9$-$\text{N(R}^5$-$\text{R}^6$, -$\text{S(O)}_m$-$\text{R}^5$, -$\text{R}^9$-$\text{C(O)}$-$\text{R}^5$, -$\text{R}^9$-$\text{C(O)}$-$\text{OR}^6$, -$\text{R}^9$-$\text{C(O)}$-$\text{N(R}^5$-$\text{R}^6$, -$\text{N(R}^6$-$\text{C(O)}$-$\text{R}^5$, and -$\text{N(R}^6$-$\text{S(O)}_n$-$\text{R}^5$, wherein each $m$ is independently 0, 1, or 2 and each $n$ is independently 1 or 2;
R³ is \(-\text{R⁹-OR⁶}\);
R⁴ is aryl, aralkyl or aralkynyl,
wherein each of the aryl, aralkyl and aralkynyl groups for R⁴ is optionally
substituted by one or more substituents selected from the group
consisting of halo, heteroaryl and \(-\text{R⁹-OR⁶}\);
each R⁵ and R⁶ is independently selected from group consisting of hydrogen, alkyl,
alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocyclyl and optionally substituted
heteroaryl;
or when R⁵ and R⁶ are each attached to the same nitrogen atom, then R⁵ and R⁶,
together with the nitrogen atom to which they are attached, may form a
N-heterocycl or N-heteroaryl; and
each R⁹ is a direct bond or an optionally substituted straight or branched alkylene
chain.

Another embodiment of the invention is a compound of formula (I), as set forth
above in the Summary of the Invention, selected from the group consisting of:
1-(4-chlorobenzyl)-3-(2,5-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(3-methoxyphenyl)-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(2-methoxyphenyl)-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-(3,4-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-benzyl-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-phenyl-1,3-dihydro-2H-indol-2-one;
3-hydroxy-1-(4-methoxybenzyl)-3-naphthalen-2-yl-1,3-dihydro-2H-indol-2-one;
3-hydroxy-1-(4-methoxybenzyl)-3-(3-pyrrol-1-ylphenyl)-1,3-dihydro-2H-indol-2-one;
1-(4-chlorobenzyl)-3-(4-fluorophenylethynyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(5-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(5-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(5-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2/-/indol-2-one;
3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2/-/-indol-2-one;
3-(5-chloro-4-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one;
3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2/-/-indol-2-one;
3-(4-chloro-5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one;
3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(4,5-dichloro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(4,5-dichloro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(4,5-dichloro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-hydroxy-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(hydroxymethyl)-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2/-/-indol-2-one;
3-(diphenylmethyl)-3-hydroxy-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(diphenylmethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one;
1-(diphenylmethyl)-3-(hydroxymethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one;
Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R1 is hydrogen, alkyl, haloalkyl or cycloalkylalkyl;

R2a, R2b, R2c and R2d are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R9-OR6, -R9-N(R5)R6, -R9-C(O)R5, -R9-C(O)OR6, -R9-C(O)N(R5)R6, -N(R5)C(O)R5, wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R2a, R2b, R2c and R2d is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R9-CN, -R9-NO2, -R9-OR6, -R9-N(R5)R6, -S(O)mR5, -R9-C(O)R5, -R9-C(O)OR6, -R9-C(O)N(R5)R6, -N(R6)C(O)R5, and -N(R6)S(O)nR6, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;

or R2a and R2b, R2b and R2c, or R2c and R2d, together with the carbon ring atoms to which they are directly attached, may form a fused ring selected from aryl, heterocyclyl and heteroaryl;

R3 is hydrogen, alkyl or -R9-OR6;

R4 is independently selected from the group consisting of alkyl, aryl, aralkynyl,
heteroaryl, heteroarylalkyl, -R9-C(O)R5, -R9-N(R6)C(O)OR6, -N(R6)C(O)N(R5)R6,
-R9-NO2, -R9-N(R5)R6, -R9-C(O)OR6, and -R9-Si(R6)3,
wherein each of the aryl, aralkynyl, heteroaryl and heteroarylalkyl groups for R4
is optionally substituted by one or more substituents selected from the
group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl,
cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl,
heterocyclylalkyl, heterocyclylalkyl, oxo, -R9-CN, -R9-NO2,
-R9-OR6, -R9-N(R5)R6, -S(O)mR5, -R9-C(O)R5, -R9-C(O)OR6,
-R9-C(O)N(R5)R6, -N(R6)C(O)R5, and -N(R6)S(O)nR5, wherein each m is
independently 0, 1, or 2 and each n is independently 1 or 2;
each R5 and R6 is independently selected from group consisting of hydrogen, alkyl,
alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocyclyl and optionally substituted
heteroaryl;
or when R5 and R6 are each attached to the same nitrogen atom, then R5 and R6,
together with the nitrogen atom to which they are attached, may form a
N-heterocyclyl or N-heteroaryl; and
each R9 is a direct bond or an optionally substituted straight or branched alkylene
chain, an optionally substituted straight or branched alkenylene chain or an
optionally substituted straight or branched alkynylene chain.
Another embodiment of the invention is a compound of formula (I), as set forth
above in the Summary of the Invention, wherein:
R1 is hydrogen, alkyl, haloalkyl or cycloalkylalkyl;
R2a, R2b, R2c and R2d are each independently selected from the group consisting of
hydrogen, alkyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl,
aralkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkyl, heterocyclylalkyl, -R9-OR6,
-R9-N(R5)R6, -R9-C(O)R5, -R9-C(O)OR6, -R9-C(O)N(R5)R6, -N(R6)C(O)R5,
wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl,
heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R2a, R2b, R2c
and R2d is optionally substituted by one or more substituents selected from
the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl,
haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl,
heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R9-CN,
-R9-NO2, -R9-OR6, -R9-N(R5)R6, -S(O)mR5, -R9-C(O)R5, -R9-C(O)OR6,
-R^9-C(O)N(R^5)R^6, -N(R^6)C(O)R^5, and -N(R^6)S(O)\textsubscript{n}R^5, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;

R^3 is hydrogen, alkyl or -R^9-OR^6;

R^4 is heteroaryl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaryalkyl, oxo, -R^3-CN, -R^3-NO\textsubscript{2}, -R^3-N(R^5)R^6, -S(O)\textsubscript{m}R^5, -R^9-C(O)R^5, -R^9-C(O)OR^6, -R^9-C(O)N(R^5)R^6, -N(R^6)C(O)R^5, and -N(R^6)S(O)\textsubscript{n}R^5, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;

each R^5 and R^6 is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

or when R^5 and R^6 are each attached to the same nitrogen atom, then R^5 and R^6, together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl; and

each R^9 is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R^1 is hydrogen, alkyl, haloalkyl or cycloalkylalkyl;

R^{2a}, R^{2b}, R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, aryl and heteroaryl, wherein each of the aryl and heteroaryl group for R^{2a}, R^{2b}, R^{2c} and R^{2d} is optionally substituted by one or more substituents selected from the group consisting of alkyl, haloalkyl, aryl, alaryl, -R^9-OR^6, -R^9-C(O)OR^6 and -R^9-C(O)N(R^5)R^6;

R^3 is hydrogen, alkyl or -R^9-OR^6;

R^4 is heteroaryl optionally substituted by one or more substituents selected from the group consisting of halo, -R^9-OR^6 and -N(R^6)C(O)R^5;

each R^5 and R^6 is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

or when R⁵ and R⁶ are each attached to the same nitrogen atom, then R⁵ and R⁶, together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl; and each R⁹ is a direct bond or an optionally substituted straight or branched alkyene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, selected from the group consisting of:

- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one;
- 3-(1,S-benzodioxol-δ-yO:i-cyclopropylmethyO-S-hydroxy-l,S-dihydro^H-indol^-one;
- 3-(1,3-benzodioxol-5-yl)-7-(4-fluorophenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2/-/-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(4,4,4-trifluorobutyl)-1,3-dihydro-2H-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-1-(5-chloropentyl)-3-hydroxy-1,3-dihydro-2/-/-indol-2-one;
- 3,7-bis(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-5,7-dimethyl-1-pentyl-1,3-dihydro-2H-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methylpentyl)-1,3-dihydro-2H-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(1-methylpentyl)-1,3-dihydro-2H-indol-2-one;
- 3-(1,S-benzodioxol-δ-yO:i-cyclobutylmethyl-S-hydroxy-l,S-dihydro^H-indol^-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-7-trifluoromethyl-1,3-dihydro-2H-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-4-chloro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-7-trifluoromethyl-1,3-dihydro-2H-indol-2-one;
- 1-(4-chlorobenzyl)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one.
3-hydroxy-3-[6-(hydroxymethyl)-1,3-benzodioxol-5-yl]-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-4,7-dichloro-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-7-fluoro-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-5,7-dimethyl-1-pentyl-1,3-dihydro-2H-indol-2-one;
1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
1-(2-cyclopropylethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-hydroxymethyl-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-methoxy-1-pentyl-1,3-dihydro-indol-2-one;
4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-1,3-dihydro-2H-indol-2-one;
3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
4,7-dichloro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
1-hexyl-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
ethyl[1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-3-y]acetate;
4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-3-(hydroxymethyl)indolin-2-one;
4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-2,3-dihydrobenzofuran-5-yl)-3-(hydroxymethyl)indolin-2-one;
3-hydroxy-3-(5-hydroxy-2-methyl-1-benzothiazoi-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(5-hydroxy-2-methyl-1-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(hydroxymethyl)-3-(5-hydroxy-2-methyl-1-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one;
3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;
3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one;

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R1 is hydrogen, alkyl, haloalkyl or cycloalkylalkyl;
R2a, R2b, R2c and R2d are each independently selected from the group consisting of hydrogen and halo;
R3 is hydrogen or -R8-OR5;
R4 is independently selected from the group consisting of -R8-C(O)R5 and
-R8-N(R6)C(O)OR6;
each R5 and R6 is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl; and
each R9 is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkyne chain.
Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R^1 is alkyl or aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, -R^3-OR^6, heteroaryl and -R^3-C(O)OR^6);

R^2a, R^2b, R^2c and R^2d are each hydrogen;
or R^2a and R^2b, R^2b and R^2c, or R^2c and R^2d, together with the carbon ring atoms to which they are directly attached, may form a fused ring selected from aryl, heterocyclyl and heteroaryl;

R^3 is -R^9-C(O)X, -R^9-C(O)OR^6 and -R^9-C(O)N(R^5)R^6 where X is bromo or chloro;

R^4 is independently selected from the group consisting of -R^9-C(O)R^5 and heteroaryl optionally substituted by one or more substituents selected from the group consisting of halo and R^9-OR^6;
each R^5 and R^6 is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl;
or when R^5 and R^6 are each attached to the same nitrogen atom, then R^5 and R^6, together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl; and

each R^9 is a direct bond or an optionally substituted straight or branched alkyne chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, selected from the group consisting of:

3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-2-oxo-2,3-dihydro-1/-/-indol-3-yl acetate;
methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1/-/-indol-3-yl]acetate;
[3-(i ^-benzodioxol-S-yl^-oxo-i-pentyl^-S-dihydro-1H-indol-S-yOacetic acid;
2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetamide;
2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]-/Λ,Λ-
dimethylacetamide;
methyl 3-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-
yl]propanoate; and
3-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]propanoic acid.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

R¹ is alkyl or aralkyl optionally substituted by one or more substituents selected from
the group consisting of halo and -R³-C(O)OR⁶;

R²a, R²b, R²c and R²d are each independently selected from the group consisting of
hydrogen, alkyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl,
aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R⁸-OR⁶,
-R⁸-N(R⁵)R⁶, -R⁸-C(O)R⁶, -R⁸-C(O)OR⁶, -R⁸-C(O)N(R⁵)R⁶, -N(R⁶)C(O)R⁶,
wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl,
heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R²a, R²b, R²c
and R²d is optionally substituted by one or more substituents selected
from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl,
haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl,
heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R⁸-CN,
-R⁸-NO₂, -R⁸-OR⁶, -R⁸-N(R⁵)R⁶, -S(O)ₘR⁶, -R⁸-C(O)R⁶, -R⁸-C(O)OR⁶,
-R⁸-C(O)N(R⁵)R⁶, -N(R⁶)C(O)R⁵ and -N(R⁶)S(O)ₙR⁶, wherein each m is
independently 0, 1, or 2 and each n is independently 1 or 2;
or R²a and R²b, R²b and R²c, or R²c and R²d, together with the carbon ring atoms to
which they are directly attached, may form a fused ring selected from aryl,
heterocyclyl and heteroaryl;

R³ and R⁴ together form =NS(O)₂R⁶, =N-R¹⁵, =N-O-R⁶ or =R²-N=C(O)R⁶,
where R²a is a straight or branched alkenylene chain wherein the alkenylene
chain is attached to the carbon to which R³ and R⁴ is attached through a
double bond and R¹⁵ is a N-heterocyclyl optionally substituted by alkyl,
haloalkyl or -R⁸-OR⁶;
each R⁵ and R⁶ is independently selected from group consisting of hydrogen, alkyl,
alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocyclyl and optionally substituted
heteroaryl;
or when R⁵ and R⁶ are each attached to the same nitrogen atom, then R⁵ and R⁶,
together with the nitrogen atom to which they are attached, may form a
N-heterocyclyl or N-heteroaryl; and

each R⁹ is a direct bond or an optionally substituted straight or branched alkylene
chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkyne chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

5 \( R^1 \) is alkyl or aralkyl optionally substituted by one or more substituents selected from the group consisting of halo and \(-R^9\cdot C(O)\cdot R^6\);

10 \( R^{ca}, R^{cb}, R^{cc} \) and \( R^{cd} \) are each independently selected from the group consisting of hydrogen, alkyl, halo and haloalkyl;

or \( R^{ca} \) and \( R^{cb} \), \( R^{cc} \) and \( R^{cd} \), together with the carbon ring atoms to which they are directly attached, may form a fused ring selected from aryl, heterocyclyl and heteroaryl;

R\(^3\) and R\(^4\) together form \( =N\cdot S(O)\cdot R^6, =N\cdot R^{15}, =N\cdot O\cdot R^6 \) or \( =R^9\cdot C(O)\cdot R^6 \),

where \( R^9 \) is a straight or branched alkenylene chain wherein the alkenylene chain is attached to the carbon to which \( R^3 \) and \( R^4 \) is attached through a double bond and \( R^{15} \) is a N-heterocyclyl optionally substituted by alkyl, haloalkyl or \(-R^9\cdot OR^6\);

each \( R^6 \) is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

and each \( R^9 \) is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkyne chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:

\( R^1 \) is alkyl or aralkyl optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, \(-R^9\cdot OR^6\), heteroaryl and \(-R^9\cdot C(O)OR^6\);

\( R^{ca}, R^{cb}, R^{cc} \) and \( R^{cd} \) are each independently selected from the group consisting of hydrogen, alkyl, halo and haloalkyl;

or \( R^{ca} \) and \( R^{cb} \), \( R^{cc} \) and \( R^{cd} \), together with the carbon ring atoms to which they are directly attached, may form a fused ring selected from aryl, heterocyclyl and heteroaryl;

\( R^3 \) is independently selected from the group consisting of \(-N[N(R^9)\cdot C(O)\cdot OR^6]\cdot C(O)\cdot OR^6, -R^9\cdot N(R^9)\cdot R^6 \) and \(-N(R^9)\cdot C(O)\cdot OR^6\);
R^4 is independently selected from the group consisting of alkyl, aryl, heteroaryl, and -R^6-C(O)R^5,
wherein each of the aryl and heteroaryl group for R^4 is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and haloalkyl; each R^5 and R^6 is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkylnyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl; or when R^5 and R^6 are each attached to the same nitrogen atom, then R^5 and R^6, together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl; and each R^9 is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, selected from the group consisting of:
3-(1,3-benzodioxol-5-yl)-3-imidazol-1-yl-1-pentyl-1,3-dihydro-2H-indol-2-one;
1-[3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]hydrazine-1,2-dicarboxylate;
terb-butyl [2-oxo-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-2,3-dihydro-1H-indol-3-yl]carbamate; and
3-amino-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-1,3-dihydro-2H-indol-2-one.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, wherein:
R^1 is -R^8-C(O)R^8, -R^8-C(O)OR^8, -R^8-OR^8, alkyl, aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, -R^8-OR^8, heteroaryl and -R^8-C(O)OR^8), heteroaryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and -R^8-OR^8), or heteroarylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and -R^8-OR^8);
R^2a, R^2b, R^2c and R^2d are each independently selected from the group consisting of hydrogen, alkyl, halo or haloalkyl;
or $R_2^a$ and $R_2^b$, $R_2^b$ and $R_2^c$, or $R_2^c$ and $R_2^d$, together with the carbon ring atoms to which they are directly attached, may form a fused ring selected from aryl, heterocyclyl and heteroaryl;

$R_3^i$ is hydrogen, -$R_9^a$-OR or heteroaryl optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and -$R_9^a$-OR;

$R_4^i$ is independently selected from the group consisting of alkyl, aryl, aralkyl, heteroaryl, -$R_9^a$-Si($R_6^i$), -$R_9^a$-NO$_2$ and -$R_9^a$-C($R_5^i$), wherein each of the aryl, aralkyl and heteroaryl group for $R_4^i$ is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and -$R_9^a$-OR;

each $R_5^i$ and $R_6^i$ is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl; and each $R_9^i$ is a direct bond or an optionally substituted straight or branched alkenylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain.

Another embodiment of the invention is a compound of formula (I), as set forth above in the Summary of the Invention, selected from the group consisting of:

1-(4-chlorobenzyl)-3-hydroxy-3-nitromethyl-1,3-dihydro-2/-/-indol-2-one;

1-(1,3-benzodioxol-5-ylmethyl)-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one;

1-(1,3-benzodioxol-5-ylmethyl)-3-hydroxy-3-[2-oxo-2-(2-thienyl)ethyl]-1,3-dihydro-2H-indol-2-one;

i-C$^\text{chlorobenzyO}$-S-hydroxy-S$^\text{trimethylsilylOMethylJ}-I$.S-dihydro$^H$-indol$^\wedge$-one;

3-benzyl-1-(4-chlorobenzoyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;

1-(4-chlorobenzoyl)-3-hydroxy-3-phenyl-1,3-dihydroindol-2-one;

3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-quinolin-8-ylmethyl-1,3-dihydro-2H-indol-2-one;

3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-thiophen-2-ylmethyl-1,3-dihydro-2H-indol-2-one;

S-Cl.S-benzodioxol-$\delta$-yO-i-C$^5$-chlorothiophen$^\wedge$-ylmethyO-S-hydroxy-I$.S-dihydro$^H$-indol-2-one;

3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-quinolin-8-ylmethyl-1,3-dihydro-2H-indol-2-one;
1-(1,3-benzodioxol-5-yl)-3-hydroxy-3-pentyl-1,3-dihydro-2H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
i-CIS-benzodioxol-5-ylmethyO-S-CIS-benzofuran-0-yO-S-hydroxy-S-dihydro^H-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one;
etyl [3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
etyl [3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
etyl [3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
2-{3-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]propyl}-1H-isoyndole-1,3(2/-/)-dione;
2-{3-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]propyl}-1H-isoyndole-1,3(2H)-dione;
2-{3-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]propyl}-1H-isoyndole-1,3(2H)-dione;
2-{2-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]ethyl}-1H-isoyndole-1,3(2H)-dione;
2-{2-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]ethyl}-1H-isoyndole-1,3(2H)-dione;
2-{2-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]ethyl}-1H-isoyndole-1,3(2H)-dione;
1-[3-(benzyloxy)propyl]-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
1-[3-(benzyloxy)propyl]-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one;
1-[3-(benzyloxy)propyl]-3-(6-hydroxybenzo[1,3]dioxol-5-yl)-3-hydroxymethyl-1,3-dihydro-2H-indol-2-one;
etyl [3-hydroxy-3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
etyl [3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
etyl [3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-
1H-indol-1-yl]acetate;
ethyl [3-hydroxy-3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [3-(hydroxymethyl)-3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-bromo-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one;
ethyl [4-bromo-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-bromo-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one;
3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-4-methoxy-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one;
ethyl [4-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one;
4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one;
ylmethyl)-1,3-dihydro-2H-indol-2-one;
5-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-\{[5-(trifluoromethyl)-2-furyl]methyl\}-1,3-dihydro-2H-indol-2-one;
5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-\{[5-(trifluoromethyl)-2-furyl]methyl\}-1,3-dihydro-2H-indol-2-one;
5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-\{[5-(trifluoromethyl)-2-furyl]methyl\}-1,3-dihydro-2H-indol-2-one;
ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [5-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
methyl [3-(4-chloro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
methyl [3-(4-chloro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
methyl [3-(4-chloro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate;
7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-\{[5-(trifluoromethyl)-2-furyl]methyl\}-1,3-dihydro-2H-indol-2-one;
7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-\{[5-(trifluoromethyl)-2-furyl]methyl\}-1,3-dihydro-2H-indol-2-one; and
7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-\{[5-(trifluoromethyl)-2-furyl]methyl\}-1,3-dihydro-2H-indol-2-one.
One embodiment of the invention is the method of treating or preventing hypercholesterolemia in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I) as set forth above for the embodiments of the compounds of formula (I).

Another embodiment of the invention is the method of treating or preventing benign prostatic hyperplasia in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I) as set forth above for the embodiments of the compounds of formula (I).

Another embodiment of the invention is the method of treating or preventing pruritis in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I) as set forth above for the embodiments of the compounds of formula (I).

Another embodiment of the invention is the method of treating or preventing cancer in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I) as set forth above for the embodiments of the compounds of formula (I).

Specific embodiments of the compounds of formula (I) are described in more detail below in the Preparation of the Compounds of the Invention.


UTILITY AND TESTING OF THE COMPOUNDS OF THE INVENTION

The compounds of the invention modulate, preferably inhibit, ion flux through a voltage-dependent sodium channel in a mammal, especially in a human. Any such modulation, whether it be partial or complete inhibition or prevention of ion flux, is sometimes referred to herein as "blocking" and corresponding compounds as
"blockers". In general, the compounds of the invention modulates the activity of a sodium channel downwards, inhibits the voltage-dependent activity of the sodium channel, and/or reduces or prevents sodium ion flux across a cell membrane by preventing sodium channel activity such as ion flux.

The compounds of the invention inhibit the ion flux through a voltage-dependent sodium channel. Preferably, the compounds are state or frequency dependent modifers of the sodium channels, having a low affinity for the rested/closed state and a high affinity for the inactivated state. These compounds are likely to interact with overlapping sites located in the inner cavity of the sodium conducting pore of the channel similar to that described for other state-dependent sodium channel blockers (Cestele, S., et al., op. cit.). These compounds may also be likely to interact with sites outside of the inner cavity and have allosteric effects on sodium ion conduction through the channel pore.

Any of these consequences may ultimately be responsible for the overall therapeutic benefit provided by these compounds.

Accordingly, while not wishing to be bound to any particular mechanism of action, the compounds and pharmaceutical compositions of the invention are useful in the treatment and/or prevention of benign prostatic hyperplasia (BPH), hypercholesterolemia, cancer and/or pruritis (itch) in a mammal, preferably a human.

Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is one of the most common diseases affecting aging men. BPH is a progressive condition which is characterized by a nodular enlargement of prostatic tissue resulting in obstruction of the urethra. Consequences of BPH can include hypertrophy of bladder smooth muscle, a decompensated bladder, acute urinary retention and an increased incidence of urinary tract infection.

BPH has a high public health impact and is one of the most common reasons for surgical intervention among elderly men. Attempts have been made to clarify the etiology and pathogenesis and, to that end, experimental models have been developed. Spontaneous animal models are limited to the chimpanzee and the dog.

BPH in man and the dog share many common features. In both species, the development of BPH occurs spontaneously with advanced age and can be prevented by early/prepubertal castration. A medical alternative to surgery is very desirable for treating BHP and the consequences.

The prostatic epithelial hyperplasia in both man and the dog is androgen sensitive, undergoing involution with androgen deprivation and resuming epithelial
hyperplasia when androgen is replaced. Cells originating from the prostate gland have been shown to express high levels of voltage gated sodium channels. Immunostaining studies clearly demonstrated evidence for voltage gated sodium channels in prostatic tissues (Prostate Cancer Prostatic Dis. 2005; 8(3):266-73).

Hypercholesterolemia, i.e., elevated blood cholesterol, is an established risk factor in the development of, e.g., atherosclerosis, coronary artery disease, hyperlipidemia, stroke, hyperinsulinemias, hypertension, obesity, diabetes, cardiovascular diseases (CVD), myocardial ischemia, and heart attack. Thus, lowering the levels of total serum cholesterol in individuals with high levels of cholesterol has been known to reduce the risk of these diseases. The lowering of low density lipoprotein cholesterol in particular is an essential step in the prevention of CVD. Although there are a variety of hypercholesterolemia therapies, there is a continuing need and a continuing search in this field of art for alternative therapies.

The invention provides compounds which are useful as antihypercholesterolemia agents and their related conditions. The present compounds may act in a variety of ways. While not wishing to be bound to any particular mechanism of action, the compounds may be direct or indirect inhibitors of the enzyme acyl CoA: cholesterol acyl transferase (ACAT) that results in inhibition of the esterification and transport of cholesterol across the intestinal wall. Another possibility may be that the compounds of the invention may be direct or indirect inhibitors of cholesterol biosynthesis in the liver. It is possible that some compounds of the invention may act as both direct or indirect inhibitors of ACAT and cholesterol biosynthesis.

Pruritus, commonly known as itch, is a common dermatological condition. While the exact causes of pruritus are complex and poorly understood, there has long been acknowledged to have interactions with pain. In particular, it is believed that sodium channels likely communicate or propagate along the nerve axon the itch signals along the skin. Transmission of the itch impulses results in the unpleasant sensation that elicits the desire or reflex to scratch.

From a neurobiology level, it is believed that there is a shared complexity of specific mediators, related neuronal pathways and the central processes of itch and pain and recent data suggest that there is a broad overlap between pain- and itch-related peripheral mediators and/or receptors (Ikoma et al., Nature Reviews Neuroscience, 7:535-547, 2006). Remarkably, pain and itch have similar mechanisms of neuronal sensitization in the peripheral nervous system and the central nervous
system but exhibits intriguing differences as well.

For example, the mildly painful stimuli from scratching are effective in abolishing the itch sensation. In contrast, analgesics such as opioids can generate severe pruritus. The antagonistic interaction between pain and itch can be exploited in pruritus therapy, and current research concentrates on the identification of common targets for future analgesic and antipruritic therapy.

Compounds of the present invention have been shown to have analgesic effects in a number of animal models at oral doses ranging from 1 mg/kg to 100 mg/kg. The compounds of the invention can also be useful for treating pruritus.

The types of itch or skin irritation, include, but are not limited to:

a) psoriatic pruritis, itch due to hemodyalisis, aquagenic pruritus, and itching caused by skin disorders (e.g., contact dermatitis), systemic disorders, neuropathy, psychogenic factors or a mixture thereof;

b) itch caused by allergic reactions, insect bites, hypersensitivity (e.g., dry skin, acne, eczema, psoriasis), inflammatory conditions or injury;

c) itch associated with vulvar vestibulitis; and

d) skin irritation or inflammatory effect from administration of another therapeutic such as, for example, antibiotics, antivirals and antihistamines.

The compounds of the invention are also useful in treating or preventing certain hormone sensitive cancers, such as prostate cancer (adenocarcinoma), breast cancer, ovarian cancer, testicular cancer, thyroid neoplasia. The voltage gated sodium channels have been demonstrated to be expressed in prostate and breast cancer cells. Up-regulation of neonatal Na(v)1.5 occurs as an integral part of the metastatic process in human breast cancer and could serve both as a novel marker of the metastatic phenotype and a therapeutic target (Clin. Cancer Res. 2005, Aug. 1; 11(15): 5381-9). Functional expression of voltage-gated sodium channel alpha-subunits, specifically Na/I.7, is associated with strong metastatic potential in prostate cancer (CaP) in vitro. Voltage-gated sodium channel alpha-subunits immunostaining, using antibodies specific to the sodium channel alpha subunit was evident in prostatic tissues and markedly stronger in CaP vs non-CaP patients (Prostate Cancer Prostatic Dis. 2005;8(3):266-73)

The compounds of the invention are also useful in treating or preventing symptoms associated with BPH such as, but not limited to, acute urinary retention and urinary tract infection.
endocrine imbalances or endocrinopathies such as congenital adrenal hyperplasia, hyperthyroidism, hypothyroidism, osteoporosis, osteomalacia, rickets, Cushing's Syndrome, Conn's syndrome, hyperaldosteronism, hypogonadism, hypergonadism, infertility, fertility and diabetes.

The present invention readily affords many different means for identification of therapeutic agents, especially as sodium channel modulating agents. Identification of the therapeutic agents can be assessed using a variety of in vitro and in vivo assays, e.g., measuring current, measuring membrane potential, measuring ion flux, (e.g. sodium or guanidinium), measuring sodium concentration, measuring second messengers and transcription levels, and using e.g., voltage-sensitive dyes, radioactive tracers, and patch-clamp electrophysiology.

One such protocol involves the screening of chemical agents for ability to modulate the activity of a sodium channel thereby identifying it as a modulating agent. A typical assay described in Bean et al., J. General Physiology (1983), 83:613-642, and Leuwer, M., et al., Br. J. Pharmacol (2004), 141(1):47-54, uses patch-clamp techniques to study the behaviour of channels. Such techniques are known to those skilled in the art, and may be developed, using current technologies, into low or medium throughput assays for evaluating compounds for their ability to modulate sodium channel behaviour.


These assays can be carried out in cells, or cell or tissue extracts expressing the channel of interest in a natural endogenous setting or in a recombinant setting. The assays that can be used include plate assays which measure Na+ influx through surrogate markers such as 14C-guanidinium influx or determine cell depolarization using fluorescent dyes such as the FRET based and other fluorescent assays or a radiolabeled binding assay employing radiolabeled aconitine, BTX, TTX or STX. More direct measurements can be made with manual or automated electrophysiology systems. The guanidine influx assay is explained in more detail below in the Biological Assays section.
Throughput of test compounds is an important consideration in the choice of screening assay to be used. In some strategies, where hundreds of thousands of compounds are to be tested, it is not desirable to use low throughput means. In other cases, however, low throughput is satisfactory to identify important differences between a limited number of compounds. Often it will be necessary to combine assay types to identify specific sodium channel modulating compounds.

Electrophysiological assays using patch clamp techniques is accepted as a gold standard for detailed characterization of sodium channel compound interactions, and as described in Bean et al., op. cit. and Leuwer, M., et al., op. cit. There is a manual low-throughput screening (LTS) method which can compare 2-10 compounds per day; a recently developed system for automated medium-throughput screening (MTS) at 20-50 patches (i.e. compounds) per day; and a technology from Molecular Devices Corporation (Sunnyvale, CA) which permits automated high-throughput screening (HTS) at 1000-3000 patches (i.e. compounds) per day.

One automated patch-clamp system utilizes planar electrode technology to accelerate the rate of drug discovery. Planar electrodes are capable of achieving high-resistance, cells-attached seals followed by stable, low-noise whole-cell recordings that are comparable to conventional recordings. A suitable instrument is the PatchXpress 7000A (Axon Instruments Inc, Union City, CA). A variety of cell lines and culture techniques, which include adherent cells as well as cells growing spontaneously in suspension are ranked for seal success rate and stability. Immortalized cells (e.g. HEK and CHO) stably expressing high levels of the relevant sodium ion channel can be adapted into high-density suspension cultures.

Other assays can be selected which allow the investigator to identify compounds which block specific states of the sodium channel, such as the open state, closed state or the resting state, or which block transition from open to closed, closed to resting or resting to open. Those skilled in the art are generally familiar with such assays.

Binding assays are also available, however these are of only limited functional value and information content. Designs include traditional radioactive filter based binding assays or the confocal based fluorescent system available from Evotec OAI group of companies (Hamburg, Germany), both of which are HTS.

Radioactive flux assays can also be used. In this assay, channels are stimulated to open with veratridine or aconitine and held in a stabilized open state with a toxin, and channel blockers are identified by their ability to prevent ion influx. The
assay can use radioactive $^{22}$Na and $^{14}$C guanidinium ions as tracers. FlashPlate & Cytostar-T plates in living cells avoids separation steps and are suitable for HTS. Scintillation plate technology has also advanced this method to HTS suitability. Because of the functional aspects of the assay, the information content is reasonably good.

Yet another format measures the redistribution of membrane potential using the FLIPR system membrane potential kit (HTS) available from Molecular Dynamics (a division of Amersham Biosciences, Piscataway, NJ). This method is limited to slow membrane potential changes. Some problems may result from the fluorescent background of compounds. Test compounds may also directly influence the fluidity of the cell membrane and lead to an increase in intracellular dye concentrations. Still, because of the functional aspects of the assay, the information content is reasonably good.

Sodium dyes can be used to measure the rate or amount of sodium ion influx through a channel. This type of assay provides a very high information content regarding potential channel blockers. The assay is functional and would measure Na+ influx directly. CoroNa Red, SBFI and/or sodium green (Molecular Probes, Inc. Eugene OR) can be used to measure Na influx; all are Na responsive dyes. They can be used in combination with the FLIPR instrument. The use of these dyes in a screen has not been previously described in the literature. Calcium dyes may also have potential in this format.

In another assay, FRET based voltage sensors are used to measure the ability of a test compound to directly block Na influx. Commercially available HTS systems include the VIPR™ II FRET system (Aurora Biosciences Corporation, San Diego, CA, a division of Vertex Pharmaceuticals, Inc.) which may be used in conjunction with FRET dyes, also available from Aurora Biosciences. This assay measures sub-second responses to voltage changes. There is no requirement for a modifier of channel function. The assay measures depolarization and hyperpolarizations, and provides ratiometric outputs for quantification. A somewhat less expensive MTS version of this assay employs the FLEXstation™ (Molecular Devices Corporation) in conjunction with FRET dyes from Aurora Biosciences. Other methods of testing the compounds disclosed herein are also readily known and available to those skilled in the art.

These results provide the basis for analysis of the structure-activity relationship (SAR) between test compounds and the sodium channel. Certain substituents on the core structure of the test compound tend to provide more potent inhibitory compounds.
SAR analysis is one of the tools those skilled in the art may now employ to identify preferred embodiments of the compounds of the invention for use as therapeutic agents.

Modulating agents so identified are then tested in a variety of *in vivo* models so as to determine if they alleviate the diseases or conditions, especially benign prostatic hyperplasia (BPH), hypercholesterolemia, cancer and pruritus (itch), with minimal adverse events. The assays described below in the Biological Assays Section are useful in assessing the biological activity of the instant compounds.

Typically, a successful therapeutic agent of the present invention will meet some or all of the following criteria. Oral availability should be at or above 20%.

Animal model efficacy is less than about 0.1 µg to about 100 mg/Kg body weight and the target human dose is between 0.1 µg to about 100 mg/Kg body weight, although doses outside of this range may be acceptable ("mg/Kg" means milligrams of compound per kilogram of body mass of the subject to whom it is being administered).

The therapeutic index (or ratio of toxic dose to therapeutic dose) should be greater than 100. The potency (as expressed by IC₅₀ value) should be less than 10 µM, preferably below 1 µM and most preferably below 50 nM. The IC₅₀ ("Inhibitory Concentration - 50%") is a measure of the amount of compound required to achieve 50% inhibition of ion flux through a sodium channel, over a specific time period, in an assay of the invention. Compounds of the present invention in the guanidine influx assay have demonstrated IC₅₀ ranging from less than a nanomolar to less than 10 micromolar.

In an alternative use of the invention, the compounds of the invention can be used in *in vitro* or *in vivo* studies as exemplary agents for comparative purposes to find other compounds also useful in treatment of, or protection from, the various diseases disclosed herein.

Another aspect of the invention relates to inhibiting Na/1.1, NaV1.2, Na/I.3, NaV/1.4, Na/I.5, NaV1.6, Na/I.7, Na/I.8, or NaV1.9 activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Inhibition of NaV1.1, NaV1.2, Na/I.3, NaV1.4, NaV1.5, NaV1.6, Na/I.7, Na/I.8,
or Na/1.9 activity in a biological sample is useful for a variety of purposes that are
known to one of skill in the art. Examples of such purposes include, but are not limited
to, the study of sodium ion channels in biological and pathological phenomena; and the
comparative evaluation of new sodium ion channel inhibitors.

5 A compound of the invention, as set forth above in the Summary of the
Invention, as a stereoisomer, enantiomer or tautomer or mixtures thereof, or a
pharmaceutically acceptable salt, solvate or prodrug thereof, and/or a pharmaceutical
composition of the invention, comprising a pharmaceutically acceptable excipient and
one or more compounds of the invention, as set forth above in the Summary of the
Invention, as a stereoisomer, enantiomer or tautomer or mixtures thereof, or a
pharmaceutically acceptable salt, solvate or prodrug thereof, can also be used in the
preparation of a medicament for the treatment and/or prevention of
hypercholesterolemia, benign prostatic hyperplasia, pruritis, and/or cancer in a
mammal.

15 PHARMACEUTICAL COMPOSITIONS OF THE INVENTION AND ADMINISTRATION

Administration of the compounds of the invention, or their pharmaceutically
acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be
carried out via any of the accepted modes of administration of agents for serving
similar utilities. The pharmaceutical compositions of the invention can be prepared by
combining a compound of the invention with an appropriate pharmaceutically
acceptable carrier, diluent or excipient, and may be formulated into preparations in
solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders,
granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres,
and aerosols. Typical routes of administering such pharmaceutical compositions
include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual,
rectal, vaginal, and intranasal. The term parenteral as used herein includes
subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion
techniques. Pharmaceutical compositions of the invention are formulated so as to
allow the active ingredients contained therein to be bioavailable upon administration of
the composition to a patient. Compositions that will be administered to a subject or
patient take the form of one or more dosage units, where for example, a tablet may be
a single dosage unit, and a container of a compound of the invention in aerosol form
may hold a plurality of dosage units. Actual methods of preparing such dosage forms
are known, or will be apparent, to those skilled in this art; for example, see The
Science and Practice of Pharmacy, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease or condition of interest in accordance with the teachings of this invention.

A pharmaceutical composition of the invention may be in the form of a solid or liquid. In one aspect, the carrier(s) are particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup, injectable liquid or an aerosol, which is useful in, for example, inhalatory administration.

When intended for oral administration, the pharmaceutical composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the pharmaceutical composition may be formulated into a powder, granule, compressed tablet, pill, capsule, chewing gum, wafer or the like form. Such a solid composition will typically contain one or more inert diluents or edible carriers. In addition, one or more of the following may be present: binders such as carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, Primogel, com starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin; a flavoring agent such as peppermint, methyl salicylate or orange flavoring; and a coloring agent.

When the pharmaceutical composition is in the form of a capsule, for example, a gelatin capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or oil.

The pharmaceutical composition may be in the form of a liquid, for example, an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred composition contain, in addition to the present compounds, one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer. In a composition intended to be administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent may be included.

The liquid pharmaceutical compositions of the invention, whether they be
solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

A liquid pharmaceutical composition of the invention intended for either parenteral or oral administration should contain an amount of a compound of the invention such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. Preferred oral pharmaceutical compositions contain between about 4% and about 50% of the compound of the invention. Preferred pharmaceutical compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01 to 10% by weight of the compound prior to dilution of the invention.

The pharmaceutical composition of the invention may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the compound of the invention from about 0.1 to about 10% w/v (weight per unit volume).

The pharmaceutical composition of the invention may be intended for rectal administration, in the form, for example, of a suppository, which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without
limitation, lanolin, cocoa butter and polyethylene glycol.

The pharmaceutical composition of the invention may include various materials, which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials that form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule.

The pharmaceutical composition of the invention in solid or liquid form may include an agent that binds to the compound of the invention and thereby assists in the delivery of the compound. Suitable agents that may act in this capacity include a monoclonal or polyclonal antibody, a protein or a liposome.

The pharmaceutical composition of the invention may consist of dosage units that can be administered as an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system that dispenses the active ingredients. Aerosols of compounds of the invention may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, and the like, which together may form a kit. One skilled in the art, without undue experimentation may determine preferred aerosols.

The pharmaceutical compositions of the invention may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy. Generally, a therapeutically effective daily dose is (for
a 70 kg mammal) from about 0.001 mg/kg \((i.e., 0.7 \text{ mg})\) to about 100 mg/kg \((i.e., 7.0 \text{ gm})\); preferably a therapeutically effective dose is (for a 70 kg mammal) from about 0.01 mg/kg \((i.e., 7 \text{ mg})\) to about 50 mg/kg \((i.e., 3.5 \text{ gm})\); more preferably a therapeutically effective dose is (for a 70 kg mammal) from about 1 mg/kg \((i.e., 70 \text{ mg})\) to about 25 mg/kg \((i.e., 1.75 \text{ gm})\).

The ranges of effective doses provided herein are not intended to be limiting and represent preferred dose ranges. However, the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one skilled in the relevant arts. (see, e.g., Berkowet al., eds., The Merck Manual, 16\text{th} edition, Merck and Co., Rahway, NJ., 1992; Goodman et al., eds., Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10\text{th} edition, Pergamon Press, Inc., Elmsford, N.Y., (2001); Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics, 3rd edition, ADIS Press, LTD., Williams and Wilkins, Baltimore, MD. (1987), Ebadi, Pharmacology, Little, Brown and Co., Boston, (1985); Osolci et al., eds., Remington's Pharmaceutical Sciences, 18\text{th} edition, Mack Publishing Co., Easton, PA (1990); Katuzng, Basic and Clinical Pharmacology, Appleton and Lange, Norwalk, CT (1992)).

The total dose required for each treatment can be administered by multiple doses or in a single dose over the course of the day, if desired. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. The diagnostic pharmaceutical compound or composition can be administered alone or in conjunction with other diagnostics and/or pharmaceuticals directed to the pathology, or directed to other symptoms of the pathology. The recipients of administration of compounds and/or compositions of the invention can be any vertebrate animal, such as mammals. Among mammals, the preferred recipients are mammals of the Orders Primate (including humans, apes and monkeys), Arteriodactyla (including horses, goats, cows, sheep, pigs), Rodenta (including mice, rats, rabbits, and hamsters), and Carnivora (including cats, and dogs). Among birds, the preferred recipients are turkeys, chickens and other members of the same order. The most preferred recipients are humans.

For topical applications, it is preferred to administer an effective amount of a pharmaceutical composition according to the invention to target area, e.g., skin surfaces, mucous membranes, and the like, which are adjacent to peripheral neurons which are to be treated. This amount will generally range from about 0.0001 mg to
about 1 g of a compound of the invention per application, depending upon the area to be treated, whether the use is diagnostic, prophylactic or therapeutic, the severity of the symptoms, and the nature of the topical vehicle employed. A preferred topical preparation is an ointment, wherein about 0.001 to about 50 mg of active ingredient is used per cc of ointment base. The pharmaceutical composition can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such compositions include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive. Such transdermal patches may be used to provide continuous pulsatile, or on demand delivery of the compounds of the present invention as desired.

The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. Controlled release drug delivery systems include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Pat. Nos. 3,845,770 and 4,326,525 and in P. J. Kuzma et al, Regional Anesthesia 22 (6): 543-551 (1997), all of which are incorporated herein by reference.

The compositions of the invention can also be delivered through intra-nasal drug delivery systems for local, systemic, and nose-to-brain medical therapies. Controlled Particle Dispersion (CPD)™ technology, traditional nasal spray bottles, inhalers or nebulizers are known by those skilled in the art to provide effective local and systemic delivery of drugs by targeting the olfactory region and paranasal sinuses.

The invention also relates to an intravaginal shell or core drug delivery device suitable for administration to the human or animal female. The device may be comprised of the active pharmaceutical ingredient in a polymer matrix, surrounded by a sheath, and capable of releasing the compound in a substantially zero order pattern on a daily basis similar to devises used to apply testosterone as described in PCT Patent No. WO 98/50016.

Current methods for ocular delivery include topical administration (eye drops), subconjunctival injections, periocular injections, intravitreal injections, surgical implants and iontophoresis (uses a small electrical current to transport ionized drugs into and through body tissues). Those skilled in the art would combine the best suited excipients with the compound for safe and effective intra-ocular administration.

The most suitable route will depend on the nature and severity of the condition
being treated. Those skilled in the art are also familiar with determining administration methods (oral, intravenous, inhalation, sub-cutaneous, rectal etc.), dosage forms, suitable pharmaceutical excipients and other matters relevant to the delivery of the compounds to a subject in need thereof.

5 **KITS-OF-PARTS**

The present invention also provides kits that contain a pharmaceutical composition which includes one or more compounds of the invention. The kit also includes instructions for the use of the pharmaceutical composition for modulating the activity of ion channels, for the treatment of benign prostatic hyperplasia (BPH), hypercholesterolemia, cancer and pruritis (itch), as well as other utilities as disclosed herein. Preferably, a commercial package will contain one or more unit doses of the pharmaceutical composition. For example, such a unit dose may be an amount sufficient for the preparation of an intravenous injection. It will be evident to those of ordinary skill in the art that compounds which are light and/or air sensitive may require special packaging and/or formulation. For example, packaging may be used which is opaque to light, and/or sealed from contact with ambient air, and/or formulated with suitable coatings or excipients.

**PREPARATION OF THE COMPOUNDS OF THE INVENTION**

The following Reaction Schemes illustrate methods to make compounds of this invention, *i.e.*, compounds of formula (I):

```
\[
\begin{array}{c}
\text{R}^2b \\
\text{R}^2c \\
\text{R}^2d \\
\text{R}^2a \\
\text{R}^3 \\
\text{R}^4 \\
\end{array}
\]
```

wherein \( \text{R}^1 \), \( \text{R}^{2a} \), \( \text{R}^{2b} \), \( \text{R}^{2c} \), \( \text{R}^{2d} \), \( \text{R}^3 \) and \( \text{R}^4 \) are as defined above in the Summary of the Invention, as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

It will also be appreciated by those skilled in the art that in the process described below the functional groups of intermediate compounds may need to be
protected by suitable protecting groups. Such functional groups include hydroxy,
amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include
trialkylsilyl or dialkylsilyl (e.g., f-butylidemethylsilyl, f-butylidiphenylsilyl or
trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for
amino, amidino and guanidino include benzyl, f-butoxycarbonyl, benzylxoyxycarbonyl,
and the like. Suitable protecting groups for mercapto include -C(O)-R" (where R" is
alkyl, aryl or arylalkyl), p-methoxybenzyl, trityl and the like. Suitable protecting groups
for carboxylic acid include alkyl, aryl or arylalkyl esters.

Protecting groups may be added or removed in accordance with standard
techniques, which are known to one skilled in the art and as described herein.

The use of protecting groups is described in detail in Greene, T.W. and P.G.M.
group may also be a polymer resin such as a Wang resin or a 2-chlorotrityl-chloride
resin.

It will also be appreciated by those skilled in the art, although such protected
derivatives of compounds of this invention may not possess pharmacological activity
as such, they may be administered to a mammal and thereafter metabolized in the
body to form compounds of the invention which are pharmacologically active. Such
derivatives may therefore be described as "prodrugs". All prodrugs of compounds of
this invention are included within the scope of the invention.

The following Reaction Schemes illustrate methods to make compounds of this
invention. It is understood that one skilled in the art would be able to make these
compounds by similar methods or by methods known to one skilled in the art. It is also
understood that one skilled in the art would be able to make in a similar manner as
described below other compounds of formula (I) not specifically illustrated below by
using the appropriate starting components and modifying the parameters of the
synthesis as needed. In general, starting components may be obtained from sources
such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI,
and Fluorochem USA, etc. or synthesized according to sources known to those skilled
in the art (see, e.g., Smith, M.B. and J. March, Advanced Organic Chemistry.
prepared as described in this invention.

In the following Reaction Schemes, the various R groups (e.g., R¹, R², etc.) are
defined as in the Summary of the Invention for compounds of formula (I) unless
specifically defined otherwise, R²a, R²b, R²c and R²d are optional substituents for the
aryl (i.e., phenyl) as defined in the specification for optional substituents for aryl groups, X is Cl or Br, and R\textsuperscript{11} is an alkyl group.

REACTION SCHEME 1 illustrates the synthesis of isatin compounds used in this invention.

The R\textsuperscript{1} group can be introduced to an amino compound of formula (101) either by reductive amination, which is well-known to those skilled in the art, or formation of an amide by reacting with a corresponding acyl chloride followed by reduction, which is also well-known to those skilled in the art, to form a higher order substituted amino compound of formula (102). Reaction of the compound of formula (102) with oxalyl chloride gives the compound of formula (103). Alternatively, the compound of formula (103) can be obtained by alkylation of the compound of formula (104) with the chloro or bromo compound of formula (105). Alternatively, alkylation of indole compound of formula (106) with the chloro or bromo compound of formula (105) provides the compound of formula (107). Treatment of the compound of formula (107) with N-bromosuccinimide in a solvent such as, but not limited to, dimethylsulfoxide affords the product of formula (103).

In general, the compounds of formula (I) of the invention where R\textsuperscript{3} is hydrogen, -OH or -CH\textsubscript{2}OH can be synthesized following the general procedure as described below in REACTION SCHEME 2.
The phenol compound of formula (204) is treated with a Grignard reagent of formula (205) at low temperature (0 °C) to form the phenoxy magnesium halide intermediate which reacts with the keto-carbonyl group of the isatin compound of formula (103) in a solvent, such as, but not limited to, methylene chloride or toluene, to afford the oxindole of formula (206) (Formula (I), R^3 = -OH). The compound of formula (207) (Formula (I), R^3 = H) is obtained after the removal of the hydroxyl group at C-3 position of the oxindole by treating the compound of formula (206) with silane such as triethylsilane. The compound of formula (207) can also be achieved by treating the compound of formula (206) with SOCl_2/NEt_3 and reduction with Zn dust. The compound of formula (207) is treated with a silyl compound, such as, but not limited to, trimethyssilyl chloride, to generate the silyl ether intermediate which is treated with ytterbium (III) trifluoromethanesulfonate and formaldehyde to afford the compound of
formula (208) (Formula (I), R^3 = -CH_2OH). Alternatively, the compound of formula (208) can be obtained by treating the compound of formula (207) with a base, such as, but not limited to, LiOH, JPr_2NH or LDA, and subsequently reacting with formaldehyde.

Alternatively, the compound of formula (I) of the invention where R^3 is hydrogen, -OH, or -CH_2OH can be synthesized following the general procedure as described below in REACTION SCHEME 3 where the various R groups (e.g., R^1, R^{2a}, etc.) are defined as in the Summary of the Invention for compounds of formula (I) unless specifically defined otherwise, R^{3a}, R^{3b}, R^{3c} and R^{3d} are optional substituents for the aryl (i.e., phenyl) as defined in the specification for optional substituents for aryl groups, Y is bromo or iodo, R'' is an alkyl group, and R^9 is as defined above in the Summary of the Invention and Q is -O-, -S-, -N(R^6)-.

REACTION SCHEME 3

A compound of formula (301) is treated with a lithium reagent of formula (302), such as, but not limited to, n-BuLi, at low temperature followed by the reaction with keto-carbonyl group of the isatin compound of formula (103) in a solvent, such as, but not limited to, THF, to afford the oxindole of formula (303) (Formula (I), R^3 = -OH). The compound of formula (304) (Formula (I), R^3 = H) is obtained after the removal of the
hydroxyl group at C-3 position of the oxindole by treating the compound of formula (303) with silane such as triethylsilane. The compound of formula (304) can also be achieved by treating the compound of formula (303) with SOCl₂/NEt₃ and reduction with Zn dust. Compound of formula (304) is treated with a silyl compound, such as, but not limited to, trimethylsilyl chloride to generate the silyl ether intermediate which is treated with ytterbium (III) trifluoromethanesulfonate and formaldehyde to afford the compound of formula (305) (Formula (I), R₃ = -CH₂OH). Alternatively, compound of formula (305) can be obtained by treating the compound of formula (304) with a base, such as, but not limited to, LiOH, JPr₂NH or LDA, and subsequently reacting with formaldehyde.

Alternatively, the compound of formula (I) of the invention where R₃ is hydrogen, -OH, -R⁹-C(O)OR₆, -R⁹-C(O)OH, -R⁹-C(O)N(R⁵)R⁶ can be synthesized following the general procedure as described below in REACTION SCHEME 4 where the various R groups (e.g., R¹, R²a, etc.) are defined as in the Summary of the Invention for compounds of formula (I) unless specifically defined otherwise, R³a, R³b, R³c and R³d are optional substituents for the aryl group (i.e., phenyl) as defined in the specification for optional substituents for aryl groups, R" is an alkyl group, R⁹ is as defined above in the Summary of the Invention and Q is -O-, -S-, -N(R⁶)-. R⁵ is as described above in the Summary of the Invention, R⁶a is alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl, R₇ is as described above in the Summary of the Invention.
The Grignard reagent of formula (401) reacts with keto-carbonyl group of the isatin compound of formula (103) in a solvent, such as, but not limited to, methylene chloride or toluene to afford the oxindole of formula (402) (Formula (I), \( R^3 = -\text{OH} \)). The compound of formula (403) (Formula (I), \( R^3 = \text{H} \)) is obtained after the removal of the...
hydroxyl group at C-3 position of the oxindole by treating the compound of formula (402) with silane such as triethyilsilane. The compound of formula (403) can also be achieved by treating the compound of formula (402) with SOCl₂/NET₃ and reduction with Zn dust. Compound of formula (403) is alkylated at C-3 position of oxindole ring with a compound of formula (404) to afford the compound of formula (405) (Formula (I), R³ = -R⁹-C(O)OR⁸) which is subjected to saponification to generate the carboxylic acid of formula (406) (Formula (I), R³ = -R⁹-C(O)OH). This carboxylic acid is converted to an acid chloride that can react with an appropriate amine to form the amide product of formula (407) (Formula (I), R³ = -R⁹-C(O)N(R⁵)R⁶) following procedures known to the skilled in the art.

Alternatively, the compound of formula (I) of the invention where R² is aryl can be synthesized following the general procedure as described below in REACTION SCHEME 5 where the various R groups (e.g., R¹, R⁴, etc.) are defined as in the Summary of the Invention for compounds of formula (I).

REACTION SCHEME 5.

The compound of formula (501) can react with an arylboronic acid of formula (502) in the presence of a palladium catalyst such as, but not limited to, palladium acetate, tetrakis(triphenylphospine)palladium(0), tris(dibenzylideneacetone)dipalladium(0) with or without a ligand such as, but not limited to, triphenylphosphate, tri(o-tolyl)phospine, 1,1'-bis(diphenylphosphino)ferrocene or 2-(di-terf-butylphosphino)biphenyl, a base such as, but not limited to, sodium carbonate, cesium carbonate, or sodium bicarbonate, in a solvent such as, but not limited to, dimethoxyethane, dioxane, or tetrahedrofuran, to provide the coupled product (503) as a compound of formula (I) (See Kotha, S., et al, *Tetrahedron* (2002), 58:9633 and Miyaura, N., et al, *Chem. Rev.* (1995), 95:2457).

Alternatively, the compound of formula (I) of the invention where R³ is fluoro or a nitrogen containing heterocyclic ring can be synthesized following the general procedure as described below in REACTION SCHEME 6 where the various R groups
(e.g., R², R⁴, etc.) are defined as in the Summary of the Invention for compounds of formula (I).

REACTION SCHEME 6

Treatment of 3-hydroxyl compound of formula (601) with a fluorinating reagent such as, but not limited to, (diethylamino)sulfur trifluoride, in a solvent such as, but not limited to, dichloromethane or chloroform, provides the fluorinated product (602) as compound of formula (I). Compound of formula (601) can react with a nitrogen containing heterocyclic compound such as, but not limited to, 1,1'-carbonyl diimidazole, to generate the imidazole compound of formula (603) as a compound of formula (I).

Alternatively, the compound of formula (I) of the invention where R³ is an amino group can be synthesized following the general procedure as described below in REACTION SCHEME 7 where the various R groups (e.g., R¹, R², R⁴, etc.) are defined as in the Summary of the Invention for compounds of formula (I).
The oxime compound (701) can be alkylated with the chloro or bromo compound of formula (105) to generate the compound of formula (702), which can be reduced with a reducing agent such as, but not limited to, zinc dust in acetic acid. In the presence of a protecting group source such as, but not limited to, di-tert-butyl dicarbonate, the protected compound of formula (703) can be obtained. The \( R^4 \) group can be introduced to the compound of formula (703) with a base such as, but not limited to, potassium carbonate, in a solvent such as, but not limited to, acetone, acetonitrile or \( \Lambda,\Lambda\text{-dimethylformamide} \), followed by reaction with an electrophile of formula (704). Removal of the protecting group on the compound of formula (705) provides the amino compound of formula (706) as a compound of formula (I).

Alternatively, the compound of formula (I) of the invention where \( R^3 \) is an hydrazine group (Z is ethyl, isopropyl or tert-butyl) can be synthesized following the general procedure as described below in REACTION SCHEME 8 where the various \( R \) groups (e.g., \( R^1, R^2, R^4 \), etc.) are defined as in the Summary of the Invention for compounds of formula (I).
REACTION SCHEME 8

Treatment of compound of formula (601) with a phosphine compound such as, but not limited to, triphenylphosphine or tributylphosphine, and diethyl, diisopropyl or di-tert-butyl azodicarboxylate in a solvent such as, but not limited to, dichloromethane, tetrahydrofuran or ethyl acetate, provides the hydrazine compound (801) as formula (I).

The following Preparations are directed to intermediates used in the preparation of the compounds of formula (I), and the following Examples are directed to compounds of formula (I).

PREPARATION 1

Synthesis of 1-pentyl-1H-indole-2,3-dione

To a solution of isatin (3.00 g, 20.4 mmol) in DMF (40.0 ml) was added sodium hydride (1.10 g, 26.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min followed by the addition of 1-bromopentane (3.30 ml, 26.5 mmol). The mixture was stirred at 0 °C for 3 hours and poured into water (200 ml). The suspension was extracted with ethyl acetate (3 x 200 ml). The combined organic layers was washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to flash column chromatography to afford an orange solid (2.80 g, 62 %) as the title compound: ^1^H NMR (300 MHz, CDCl_3) δ 7.60-7.52 (m, 2H), 7.08 (td, 1H), 6.87 (d, 1H), 3.69 (t, 2H), 1.74-1.61 (m, 2H), 1.40-1.28 (m, 4H), 0.88 (t, 3H); ^1^C NMR (75 MHz, CDCl_3) δ 183.6, 158.1, 151.0, 138.4, 125.3, 123.5, 117.5, 110.2, 40.2, 29.0, 26.9, 22.2, 13.9.

PREPARATION 2

Synthesis of 1-(4-chlorobenzyl)-5-fluoro-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 5-fluoro-1H-indole-2,3-dione, and 1-bromopentane with 4-chlorobenzyl bromide, the title compound was obtained as a red solid: ^1^H NMR (300 MHz, CDCl_3) δ 7.34-7.16 (m, 6H), 6.71-6.65 (m, 1H), 4.88 (s, 2H);
MS (ES+) m/z 312.5 (M + 23).

PREPARATION 3
Synthesis of 1-(4-chlorobenzyl)-7H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-
critical variations to replace 1-bromopentane with 4-chlorobenzyl chloride, the title
compound was obtained as an orange solid (90%): 1H NMR (300 MHz, CDCl₃) δ 7.59
(d, 1H), 7.48 (t, 1H), 7.31-7.24 (m, 4H), 7.09 (t, 1H), 6.72 (d, 1H), 4.87 (s, 2H); 13C
NMR (75 MHz, CDCl₃) δ 183.0, 158.2, 150.4, 138.4, 134.1, 133.1, 129.3, 128.8, 125.6,
124.1, 117.7, 110.8, 43.4; MS (ES+) m/z 294.5 (M + 23).

PREPARATION 4
Synthesis of 1-(1,3-benzodioxol-5-ylmethyl)-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-
critical variations to replace 1-bromopentane with 5-(chloromethyl)-1,3-benzodioxole,
the title compound was obtained as an orange solid (70%): 1H NMR (300 MHz, CDCl₃)
δ 7.59 (d, 1H), 7.48 (dt, 1H), 7.08 (dt, 1H), 6.82-6.72 (d, 1H), 5.92 (s, 2H), 4.80 (s, 2H);
MS (ES+) m/z 304.2 (M + 23).

PREPARATION 5
Synthesis of 1-(4-trifluoromethylbenzyl)-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-
critical variations to replace 1-bromopentane with 4-trifluoromethylbenzyl chloride, the title
compound was obtained as an orange solid (38%): MS (ES+) m/z 328.2 (M + 23).

PREPARATION 6
Synthesis of 1-(4-methoxybenzyl)-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-
critical variations to replace 1-bromopentane with 4-methoxybenzyl bromide, the title
compound was obtained as a red solid (61%): 1H NMR (300 MHz, CDCl₃) δ 7.58 (m,
1H), 7.50-7.42 (m, 1H), 7.28-7.25 (m, 2H), 7.10-7.02 (m, 1H), 6.89-6.76 (m, 3H), 4.87
(s, 2H), 3.77 (s, 3H); MS (ES+) m/z 290.2 (M + 23).

PREPARATION 7
Synthesis of 1-(3,4,5-trimethoxybenzyl)-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-
critical variations to replace 1-bromopentane with 3,4,5-trimethoxybenzyl chloride, the title
compound was obtained as a solid (57%): 1H NMR (300 MHz, CDCl₃) δ 7.60 (d,
PREPARATION 8
Synthesis of 1-cyclohexylmethyl-1/-/-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with cyclohexylmethyl bromide, the title compound was obtained as a red solid (37%): ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.52 (m, 2H), 7.07 (t, 1H), 6.87 (d, 1H), 3.52 (d, 2H); 1.80-1.60 (m, 6H), 1.28-0.70 (m, 5H); MS (ES+) m/z 266.3 (M + 23).

PREPARATION 9
Synthesis of 1-(2-trifluoromethylbenzyl)-1/-/-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 2-trifluoromethylbenzyl chloride, the title compound was obtained as an orange solid (67%): ¹H NMR (300 MHz, CDCl₃) δ 7.77-7.63 (m, 2H), 7.50-7.37 (m, 3H), 7.21-7.15 (m, 1H), 7.12 (t, 1H), 6.59 (d, 1H), 5.15 (s, 2H); MS (ES+) m/z 328.2 (M + 23).

PREPARATION 10
Synthesis of 1-(2-chlorobenzyl)-1/-/-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 2-chlorobenzyl chloride, the title compound was obtained as an orange solid (39%): ¹H NMR (300 MHz, CDCl₃) δ 7.63-7.57 (m, 1H), 7.52-7.39 (m, 2H), 7.28-7.07 (m, 4H), 6.75 (d, 1H), 5.05 (s, 2H).

PREPARATION 11
Synthesis of 1-(4-fluorobenzyl)-1/-/-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 4-fluorobenzyl bromide, the title compound was obtained as an orange solid (55%): ¹H NMR (300 MHz, CDCl₃) δ 7.62-7.58 (m, 1H), 7.51-7.45 (m, 1H), 7.33-7.26 (m, 2H), 7.11-6.98 (m, 3H), 6.77-6.72 (m, 1H), 4.88 (s, 2H); MS (ES+) m/z 278.2 (M + 23).

PREPARATION 12
Synthesis of 1-[2-(4-chlorophenyl)-ethyl]-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 1-(2-bromoethyl)-4-chlorobenzene,
the title compound was obtained as a red solid (28%): \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.60-7.50 (m, 2H), 7.28-7.06 (m, 5H), 6.77-6.71 (d, 1H), 3.91 (t, 2H), 2.96 (t, 2H); MS (ES+) \( m/z \) 308.5 (M + 23).

**PREPARATION 13**

Synthesis of 1-(4-chlorobenzyl)-5-methyl-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 4-chlorobenzyl chloride, and isatin with 5-methyl-7H-indole-2,3-dione, the title compound was obtained as a red solid: \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.43-7.22 (m, 6H), 6.61 (d, 1H), 4.86 (s, 2H), 1.79 (s, 3H).

**PREPARATION 14**

Synthesis of 1-thiophen-2-yl-methyl-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 2-chloromethylthiophene, the title compound was obtained as a red solid (80%): MS (ES+) \( m/z \) 266.2 (M + 23).

**PREPARATION 15**

Synthesis of 1-(2-methoxybenzyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 2-methoxybenzyl chloride, the title compound was obtained as an orange solid (42%): MS (ES+) \( m/z \) 290.2 (M + 23).

**PREPARATION 16**

Synthesis of 1-naphthalen-1-ylmethyl-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 1-chloromethylnapthylene, the title compound was obtained as an orange solid (59%): \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.05-8.07 (m, 1H), 7.87-7.90 (m, 1H), 7.77-7.83 (m, 1H), 7.50-7.62 (m, 3H), 7.37-7.42 (m, 3H), 7.03-7.09 (m, 1H), 6.73 (d, 1H), 5.40 (s, 2H); MS (ES+) \( m/z \) 310.2 (M + 23).

**PREPARATION 17**

Synthesis of 1-(3-trifluoromethylbenzyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 3-trifluoromethylbenzyl bromide, the title compound was obtained as a red solid (78%): \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.46-7.64 (m, 6H), 7.07-7.15 (m, 1H), 6.73 (d, 1H), 4.96 (s, 2H); MS (ES+) \( m/z \) 328.3 (M + 23).
PREPARATION 18

Synthesis of 1-benzyl-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with benzyl bromide, the title compound was obtained as an orange solid (81%): MS (ES+) m/z 260.2 (M + 23).

PREPARATION 19

Synthesis of 1-(3-methoxybenzyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 3-methoxybenzyl chloride, the title compound was obtained as an orange solid (66%): MS (ES+) m/z 290.2 (M + 23).

PREPARATION 20

Synthesis of 7-fluoro-1-pentyl-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 7-fluoro-7H-indole-2,3-dione (Martin, K., et al, Org. Syn. (2002), 79:23), the title compound was obtained as an orange solid (23%): 1H NMR (300 MHz, CDCl3) δ 7.40-7.43 (m, 1H), 7.28-7.32 (m, 1H), 7.02-7.08 (m, 1H), 3.81-3.87 (m, 2H), 1.61-1.74 (m, 2H), 1.31-1.36 (m, 4H), 0.88 (t, 3H).

PREPARATION 21

Synthesis of 1-(3,4-difluoro-benzyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 3,4-difluorobenzyl bromide, the title compound was obtained as a solid (44%): 1H NMR (300 MHz, CDCl3) δ 7.61-7.63 (m, 1H), 7.47-7.53 (m, 1H), 7.06-7.18 (m, 4H), 6.74 (d, 1H), 4.86 (s, 2H).

PREPARATION 22

Synthesis of 1-(3-trifluoromethyl-4-chlorobenzyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 3-trifluoromethyl-4-chlorobenzyl bromide, the title compound was obtained as a solid (51%): 1H NMR (300 MHz, CDCl3) δ 7.44-7.65 (m, 4H), 7.09-7.26 (m, 2H), 6.72 (d, 1H), 4.92 (s, 2H).

PREPARATION 23

Synthesis of 1-(5-chloro-thiophen-2-yl-methyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 2-bromomethyl-5-chloro-thiophene,
the title compound was obtained as a solid (74%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.62 (dt, 1H), 7.53 (dd, 1H), 7.20 (d, 1H), 7.13-7.08 (m, 2H), 6.95 (d, 1H), 4.99 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 183.2, 158.4, 150.1, 138.4, 137.5, 128.3, 127.9, 127.0, 125.1, 123.9, 118.2, 111.4, 38.6.

5 PREPARATION 24

Synthesis of 1-quinolin-8-ylmethyl-1/-/-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 8-bromomethyl-quinoline, the title compound was obtained as a solid (42%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.99 (dd, 1H), 8.20 (dd, 1H), 7.78 (dd, 1H), 7.69-7.67 (m, 1H), 7.58 (dd, 1H), 7.53-7.37 (m, 3H), 7.06-6.98 (m, 2H), 5.68 (s, 2H).

10 PREPARATION 25

Synthesis of 1-(2-iodo-benzyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 2-iodobenzyl bromide, the title compound was obtained as a solid (67%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.89 (dd, 1H), 7.64 (dd, 1H), 7.51-7.45 (m, 1H), 7.29-7.26 (m, 1H), 7.14-7.07 (m, 2H), 7.02-6.96 (m, 1H), 6.66 (dd, 1H), 4.95 (s, 2H).

15 PREPARATION 26

Synthesis of 1-hexyl-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 1-bromohexane, the title compound was obtained as a solid (76%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.43-7.40 - (m, 1H), 7.35-7.28 (m, 2H), 7.08-7.02 (m, 1H), 3.87-3.81 (m, 2H), 1.74-1.61 (m, 2H), 1.36-1.31 (m, 6H), 0.88 (t, 3H).

20 PREPARATION 27

Synthesis of 4,7-dichloro-1-pentyl-1/-/-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 4,7-dichloro-7H-indole-2,3-dione, the title compound was obtained as a solid (89%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.41 (d, 1H), 6.98 (d, 1H), 4.1 1-4.06 (m, 2H), 1.75-1.66 (m, 2H), 1.36-1.31 (m, 4H), 0.89 (t, 3H).
PREPARATION 28
Synthesis of 4-chloro-1-pentyl-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 4-chloro-1H-indole-2,3-dione, the title compound was obtained as a solid (98%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71 (d, 1H), 7.41 (m, 1H), 6.95 (d, 1H), 4.11-4.06 (m, 2H), 1.75-1.66 (m, 2H), 1.36-1.31 (m, 4H), 0.89 (t, 3H).

PREPARATION 29
Synthesis of 6-chloro-1-pentyl-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 6-chloro-1H-indole-2,3-dione (Rossiter, S. Tetrahedron Lett. (2002), 43(26): 4671-4), the title compound was obtained as a solid (74%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.79 (s, 1H), 7.52 (d, 1H), 7.24 (d, 1H), 4.11-4.06 (m, 2H), 1.75-1.66 (m, 2H), 1.36-1.31 (m, 4H), 0.89 (t, 3H).

PREPARATION 30
Synthesis of 5-bromo-1-(4-chlorobenzyl)-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 5-bromo-1H-indole-2,3-dione, and 1-bromopentane with 4-chlorobenzyl bromide, the title compound was obtained as a solid (39%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.70 (d, 1H), 7.58 (dd, 1H), 7.30 (d, 2H), 6.63 (d, 1H), 4.87 (s, 2H).

PREPARATION 31
Synthesis of 5,7-dimethyl-1-pentyl-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 5,7-dimethyl-1H-indole-2,3-dione, the title compound was obtained as a solid (44%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.24 (s, 1H), 6.81 (s, 1H), 3.88-3.83 (m, 2H), 2.47 (s, 3H), 2.22 (s, 3H), 1.67-1.63 (m, 2H), 1.35-1.32 (m, 4H), 0.88 (t, 3H).

PREPARATION 32
Synthesis of 1-(5-chloropentyl)-1H-indole-2,3-dione
Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 1-bromo-5-chloropentane, the title compound was obtained as a solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.32 (d, 1H), 7.29-7.27 (m, 1H), 7.09 (m, 1H), 6.80 (d, 1H), 3.83-3.61 (m, 2H), 3.49 (t, 2H), 1.84-1.68 (m,
4H, 1.55-1.47 (m, 2H).

PREPARATION 33

Synthesis of 1-cyclobutylmethyl-1/-/-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with bromomethylcyclobutane, the title compound was obtained as a solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.01 (d, 1H), 6.99-6.97 (m, 1H), 6.81-6.76 (m, 1H), 6.54 (d, 1H), 3.60 (dd, 1H), 3.35 (dd, 1H), 2.58-2.47 (m, 2H), 1.83-1.71 (m, 2H), 1.59-1.51 (m, 3H).

PREPARATION 34

Synthesis of 1-(1-phenylethyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with (1-bromoethyl)benzene, the title compound was obtained as a solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.24 (m, 7H), 7.11-7.05 (m, 1H), 6.85 (d, 1H), 5.81-5.74 (d, 2H), 1.83 (d, 3H).

PREPARATION 35

Synthesis of 1-(2-cyclopropylethyl)-1H-indole-2,3-dione

To a suspension of sodium hydride (1.61 g, 41.9 mmol, 60% dispersion in mineral oil) in anhydrous $\Lambda/\Lambda$-dimethylformamide (25.0 ml) was added isatin (6.17 g, 41.9 mmol) at 0°C. The reaction mixture was stirred for 0.5 h followed by the addition of (2-bromoethyl)cyclopropane (Maercker, A., et al, Justus Liebigs Ann. Chem. (1972), 759:132-157) (9.25 g, 61.2 mmol). The resulting mixture was stirred at ambient temperature for 16 h and quenched with water (50.0 ml). The mixture was extracted with ethyl acetate (3 x 100.0 mL). The combined organic layers was washed with water (3 x 50.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness to yield the title compound (6.50 g, 90%) as a viscous gum: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.57-7.51 (m, 2H), 7.05 (t, 1H), 6.88 (d, 1H), 3.79-3.74 (m, 2H), 1.59-1.52 (m, 2H), 0.70-0.61 (m, 1H), 0.44-0.38 (m, 2H), 0.05-0.02 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) 5 183.7, 158.2 151.2, 138.3, 125.4, 123.6, 117.5, 110.2, 40.3, 32.2, 8.6, 4.3.

PREPARATION 36

Synthesis of 1-pentyl-7-trifluoromethyl-1/-/-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 7-(trifluoromethyl)-1H-indole-2,3-dione.
(Maginnity, J. Am. Chem. Soc. (1951):3579), the title compound was obtained as a solid(41%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.76-7.85 (m, 2H), 7.19 (t, 1H), 3.83-3.89 (m, 2H), 1.58-1.65 (m, 2H), 1.29-1.33 (m, 4H), 0.89 (t, 3H).

PREPARATION 37

Synthesis of 1-(4-chlorobenzoyl)-1H-indole-2,3-dione

To a mixture of isatin (10.0 g, 67.9 mmol) in anhydrous CH$_2$Cl$_2$ (400 mL) was added diisopropylethylamine (17.6 g, 136 mmol) and 4-chlorobenzoyl chloride (14.2 g, 74.7 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 16 h upon which time yellow precipitate formed. The solid was filtered-off, washed with ether to give the title compound (13.5 g, 70%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.92 (d, 1H), 7.87 (d, 2H), 7.79-7.74 (m, 2H), 7.58 (d, 2H), 7.35 (t, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 180.5, 167.4, 157.7, 148.2, 138.3, 137.9, 133.1, 132.0, 128.7, 125.9, 124.9, 120.5, 116.6.

PREPARATION 38

Synthesis of 1-(1,3-benzodioxol-5-yl)-1H-indole-2,3-dione

To a solution of isatin (0.66 g, 4.51 mmol) in dry dichloromethane (20.0 mL) was added 3,4-(methylene dioxy)phenylboronic acid (1.50 g, 9.04 mmol), copper acetate (0.82 g, 4.52 mmol) and pyridine (0.71 g, 9.04 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 72 hrs and quenched with water. The mixture was extracted with ethyl acetate. The organic solution was concentrated in vacuo. The precipitated solid was filtered and washed with ether and dried to give the title compound (0.20 g, 17%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.66 (dd, 1H), 7.52 (dt, 1H), 7.21-7.09 (m, 2H), 6.87-6.83 (m, 3H), 6.05 (s, 2H).

PREPARATION 39

Synthesis of 4-bromo-1-pentyl-1H-indole

To a mixture of sodium hydride (2.54 g, 66.3 mmol, 60% dispersion in mineral oil) in anhydrous N,N-dimethylformamide (50.0 mL) was added 4-bromoindole (10.0 g, 51.0 mmol) at 0 °C. The reaction mixture was stirred for 0.5 h followed by the addition of 1-bromopentane (9.25 g, 61.2 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 6 h and quenched with brine solution (20.0 mL). The reaction mixture was diluted with water (100 mL) and extracted with ether (3 x 200 mL). The combined organic layers was washed with brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The
residue was subjected to column chromatography eluting with hexane (100%) to give the title compound (13.3 g, 98%) as a yellow oil: \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta 7.30-7.27\) (m, 2H), 7.14 (t, 1H), 6.88 (t, 1H), 6.55 (d, 1H), 4.08 (t, 2H), 1.87-1.77 (m, 2H), 1.39-1.22 (m, 4H), 0.89 (t, 3H); \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta 136.3, 129.2, 128.4, \) 122.2, 122.1, 114.9, 108.7, 101.3, 46.8, 29.9, 29.1, 22.3, 13.9.

**PREPARATION 40**

Synthesis of 4-bromo-1-pentyl-1/-/-indole-2,3-dione

To a solution of 4-bromo-1-pentylindole (25.0 g, 93.9 mmol) in anhydrous dimethylsulfoxide (350 mL) was added \(\Lambda\)-bromosuccinimide (50.2 g, 282 mmol) in portions over 30 min. The reaction mixture was heated at 60 °C for 3 h, upon which time the internal temperature increased to 120 °C. After cooling down to ambient temperature, the reaction mixture was poured onto ethyl acetate/water (1/1, 600 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 500 mL). The combined organic layers was washed with water (3 x 500 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness to yield the title compound (25.7 g, 92%) as a yellow solid: \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta 7.38\) (t, 1H), 7.21 (t, 1H), 6.82 (d, 1H), 3.68 (t, 2H), 1.72-1.59 (m, 2H), 1.39-1.25 (m, 4H), 0.86 (t, 3H); \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta 180.9, 157.2, 152.6, 138.4, 128.3, 121.7, 116.3, 108.9, 40.4, 28.9, 26.9, 22.3, 13.9.

**PREPARATION 41**

Synthesis of ethyl (2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with ethyl bromoacetate, the title compound was obtained (79%) as a light yellow powder: \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta 7.64-7.54\) (m, 2H), 7.16-7.11 (m, 1H), 6.77 (d, 1H), 4.47 (s, 2H), 4.22 (q, 2H), 1.26 (t, 3H); MS(ES+) m/z 256.2 (M + 23).

**PREPARATION 42**

Synthesis of methyl 3-[(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)methyl]benzoate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with methyl 3-(bromomethyl)benzoate, the title compound was obtained (84%) as a orange solid: \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta 7.99-7.95\) (m, 2H), 7.60 (d, 1H), 7.53-7.47 (m, 2H), 7.43 (d, 1H), 7.09 (t, 1H), 6.43 (d, 1H), 4.95 (s, 2H), 3.89 (s, 3H).
PREPARATION 43
Synthesis of methyl 4-[(2,3-dioxo-2,3-dihydro-1/-/-indol-1-yl)methyl]benzoate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with methyl 4-(bromomethyl)benzoate, the title compound was obtained (84%) as an orange solid: \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta 8.00\) (d, 2H), 7.61 (d, 1H), 7.46 (t, 1H), 7.38 (d, 2H), 7.09 (t, 1H), 6.69 (d, 1H), 4.96 (s, 2H), 3.88 (s, 3H); MS (ES+) \(m/z\) 296.1 (M + 1).

PREPARATION 44
Synthesis of 1-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-1/-/-indole-2,3-dione

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione, the title compound was obtained (92%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.80-7.79\) (m, 4H), 7.61-7.56 (m, 1H), 7.49-7.46 (m, 1H), 7.18-7.16 (m, 1H), 7.07-7.05 (m, 1H), 3.72-3.60 (m, 4H), 1.97-1.92 (m, 2H).

PREPARATION 45
Synthesis of 1-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-1/-/-indole-2,3-dione

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with 2-(2-bromoethyl)-1H-isoindole-1,3(2H)-dione, the title compound was obtained (75%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.85-7.78\) (m, 4H), 7.65 (td, 1H), 7.55 (dd, 1H), 7.25 (d, 1H), 7.12 (t, 1H), 4.00-3.80 (m, 4H); MS (ES+) \(m/z\) 321.0 (M + 1), 343.0 (M + 23).

PREPARATION 46
Synthesis of 1-(diphenylmethyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with 1,1'-(bromomethylene)dibenzene, the title compound was obtained (68%) as an orange solid: MS (ES+) \(m/z\) 336.4 (M + 23).

PREPARATION 47
Synthesis of 1-[3-(benzylxyo)propyl]-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 39, and making non-critical variations to replace 4-bromoindole with isatin, and 1-bromopentane with benzyl 3-bromopropyl ether, the title compound was obtained (95%) as a pale yellow syrup: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.57-6.92\) (m, 9H), 4.50 (s, 2H), 3.84 (t, 2H), 3.54 (t, 2H), 3.00-2.80 (m, 4H), 1.97-1.92 (m, 2H), 1.00-0.80 (m, 3H); MS (ES+) \(m/z\) 309.0 (M + 1), 331.0 (M + 31).
2.03-1.94 (m, 2H); MS (ES+) m/z 296.3 (M + 1), 318.3 (M + 23).

**PREPARATION 48**

Synthesis of methyl 2-[(2,3-dioxo-2,3-dihydro-1/-/-indol-1-yl)methyl]benzoate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with methyl 2-(bromomethyl)benzoate, the title compound was obtained (68%) as a yellow solid: 1H NMR (300 MHz, CDCl₃) δ 8.05 (dd, 1H), 7.64 (dd, 1H), 7.50-7.31 (m, 3H), 7.22 (d, 1H), 7.10 (t, 1H), 6.72 (d, 1H), 5.41 (s, 2H), 3.95 (s, 3H).

**PREPARATION 49**

Synthesis of ethyl (4-bromo-2,3-dioxo-2,3-dihydro-1 H-indol-1 -yl)acetate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace isatin with 4-bromoisatin, and (2-bromoethyl)cyclopropane with ethyl bromoacetate, the title compound was obtained as a yellow solid (68%): 1H NMR (300 MHz, CDCl₃) δ 7.39 (t, 1H), 7.27(dd, 1H), 6.71 (dd, 1H), 4.47 (s, 2H), 4.23 (q, 2H), 1.27 (t, 3H); MS (ES+) m/z 312 (M + 1), 314 (M + 1), 334 (M + 23), 336 (M + 23).

**PREPARATION 50**

Synthesis of 6-(benzyloxy)-2,2-dimethylbenzofuran-3(2H)-one

To a stirred solution of 6-(benzyloxy)benzofuran-3(2H)-one (Adams, J. L., et al, *J. Med. Chem.* (1996), 39(26):5035-46) (1.60 g, 6.67 mmol) in DMF (50.0 mL) were added sodium hydride (0.59 g, 14.7 mmol) and iodomethane (1.46 mL, 23.3 mmol) at 0°C. The reaction mixture was stirred at ambient temperature for 16 h and quenched with saturated ammonium chloride (50.0 mL). The aqueous mixture was extracted with ethyl acetate (3 x 50.0 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography (ethyl acetate/hexane, 1/10) to give the title compound (0.85 g, 47%): 1H NMR (300 MHz, CDCl₃) δ 7.55 (d, 1H), 7.44-7.30 (m, 5H). 6.69 (dd, 1H), 6.54 (d, 1H), 5.10 (s, 2H), 1.43 (s, 6H); MS (ES+) m/z 269.5 (M + 1).

**PREPARATION 51**

Synthesis of 2,2-dimethyl-2,3-dihydrobenzofuran-6-ol

To a solution of 6-(benzyloxy)-2,2-dimethylbenzofuran-3(2H)-one (0.85 g, 3.20 mmol) in methanol (100 mL) was added palladium hydroxide (0.22 g 20 wt. % loading,
0.32 mmol). The resulting mixture was hydrogenated for 16 hours under 60 psi of hydrogen. The reaction mixture was filtered through celite, washed with methanol. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography (ethyl acetate/hexane, 1/5) to give the title compound (0.46 g, 88%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.92 (d, 1H), 6.30-6.21 (m, 2H), 4.77 (s, 1H), 2.90 (s, 2H), 1.44 (s, 6H).

**PREPARATION 52**

Synthesis of 4-(benzyloxy)-1-bromo-2-(2-methylallyloxy)benzene

To a solution of 5-(benzyloxy)-2-bromophenol (Simas, A.B.C., et al, *Synthesis*, 1999):1017-21) (8.15 g, 29.3 m mol) in DMF (150.0 mL) was added potassium carbonate (4.46 g, 32.2 mmol) slowly at 0°C. The mixture was stirred at ambient temperature for half an hour followed by the addition of 3-bromo-2-methylpropene (3.35 mL, 32.2 mmol) during half an hour at 0°C. The mixture was stirred at ambient temperature overnight, quenched with saturated ammonium chloride (50.0 mL). The aqueous mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo. The residue was subjected to column chromatography (ethyl acetate/hexane, 1/20) to give the title compound (10.0 g, 94%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.43-7.29 (m, 5H), 6.53 (d, 1H), 6.45 (dd, 1H), 5.15-4.94 (m, 4H), 4.43 (s, 2H), 1.82 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 159.1, 155.6, 140.1, 136.5, 133.1, 128.6, 128.1, 127.5, 112.9, 107.2, 103.3, 102.0, 72.4, 70.3, 19.3.

**PREPARATION 53**

Synthesis of 6-(benzyloxy)-3,3-dimethyl-2,3-dihydrobenzofuran

To a solution of 4-(benzyloxy)-1-bromo-2-(2-methylallyloxy)benzene (5.00 g, 15.1 mmol) in benzene (400 mL) was added tributyltin hydride (7.42 mL, 27.2 mmol) and benzoyl peroxide (0.70 g, 2.90 mmol) at 0°C. The resulting mixture was refluxed at 100°C overnight. After cooling down to ambient temperature, the mixture was washed with water, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography (ethyl acetate/hexane, 1/20) to give the title compound (3.48 g, 91%): MS (ES+) \(m/z\) 255.6 (M + 1).

**PREPARATION 54**

Synthesis of 3,3-dimethyl-2,3-dihydro-1-benzofuran-6-ol

To a solution of 6-(benzyloxy)-3,3-dimethyl-2,3-dihydrobenzofuran (3.48 g, 13.7...
mmol) in methanol (200 ml) was added Pd/C (1.45 g) and the mixture was hydrogenated under 40 psi of hydrogen overnight. The reaction mixture was filtered through celite, washed with methanol. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography (ethyl acetate/hexane, 1/7) to give the title compound (1.66 g, 74%): MS (ES+) m/z 165.4 (M + 1).

PREPARATION 55
Synthesis of ethyl 2-(2-(tert-butoxycarbonylamino)-6-methoxyphenyl)-2-oxoacetate
To a solution of tert-butyl 3-methoxyphenylcarbamate (25.6 g, 0.11 mol) in THF (300 mL) was added n-BuLi (0.25 mol, 1.6 M solution in pentane) at -78 °C. The resulted solution was stirred at 0 °C for 3 hours and re-cooled to -78 °C followed by the addition of diethyl oxalate (20.1 g, 0.14 mol). The mixture was stirred at -78 °C for 45 min and at ambient temperature for one hour, and quenched with 1 N HCl. The mixture was extracted with ether. The organic solution was dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography to give 3.70 g (27% based on recovered starting material) of the title compound: MS (ES+) m/z 324.3 (M + 1).

PREPARATION 56
Synthesis of 4-methoxyindoline-2,3-dione
A mixture of ethyl 2-(2-(tert-butoxycarbonylamino)-6-methoxyphenyl)-2-oxoacetate (3.70 g, 110 mmol) and 10% H₂SO₄ (100.0 mL) was heated at 100 °C for 10 hours. After cooling down to ambient temperature, the reaction mixture was extracted with ether (3 x 100.0 mL). The combined ether solution was washed with water (2 x 50.0 mL), dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography to give 0.37 g (19%) of the title compound: MS (ES+) m/z 200.1 (M + 23).

PREPARATION 57
Synthesis of 4-methoxy-1-[[5-(trifluoromethyl)-2-furyl][methyl]-1 H-indole-2,3-dione
Following the procedure as described in PREPARATION 39, and making non-critical variations to replace 4-bromoindole with 4-methoxyindoline-2,3-dione, and 1-bromopentane with 2-(bromomethyl)-5-(trifloromethyl)furan, the title compound was obtained (26%): MS (ES+) m/z 348.2 (M + 23).
PREPARATION 58

Synthesis of ethyl (4-chloro-2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace isatin with 4-chloro-1H-indole-2,3-dione, and (2-bromoethyl)cyclopropane with ethyl bromoacetate, the title compound was obtained (95%) as a solid: \( ^1H \text{NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 7.48 (t, 1H), 7.08 (d, 1H), 6.67 (d, 1H), 4.47 (s, 2H), 4.23 (q, 2H), 1.27 (t, 3H); \text{MS (ES+)} m/z 268.6 (M + 1). \)

PREPARATION 59

Synthesis of 1-hexyl-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with n-bromohexane, the title compound was obtained (90%) as a viscous gum which was directly used.

PREPARATION 60

Synthesis of 4-bromo-1-(pyridin-2-ylmethyl)-1H-indole-2,3-dione

To a solution of 4-bromoisatin (8.94 g, 39.5 mmol) in anhydrous \( N,N \)-dimethylformamide (100 mL) was added sodium hydride (3.34 g, 86.9 mmol, 60% dispersion in mineral oil) in portions at 0 °C. The brown reaction mixture was stirred for 30 min followed by the addition of a solution of 2-(bromomethyl)pyridine hydrobromide (10.0 g, 39.5 mmol) neutralized with sodium hydride (1.52 g, 39.5 mmol, 60% dispersion in mineral oil) in \( \Lambda,\Lambda \)-dimethylformamide at 0 °C. The reaction mixture was stirred for 16 h and quenched with water (100 mL). The reaction mixture was extracted with diethyl ether (3 x 100 mL) and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers was washed with water (5 x 200 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated \textit{in vacuo} to dryness. The residue was triturated with ether to afford the title compound (10.6 g, 85%) as a brown solid: \( ^1H \text{NMR} (300 \text{ MHz}, \text{DMSO-d}_6) \delta 8.53 (d, 1H), 7.67 (t, 1H), 7.30 (t, 2H), 7.25-7.19 (m, 2H), 6.94 (d, 1H), 5.04 (s, 2H); ^13C \text{NMR} (75 \text{ MHz}, \text{DMSO-d}_6) \delta 180.5, 157.3, 154.2, 152.3, 149.5, 138.4, 137.5, 128.6, 123.3, 122.3, 121.5, 116.4, 110.3, 45.8. \)

PREPARATION 61

Synthesis of 5-fluoro-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace isatin with 5-fluoroisatin, and (2-bromoethyl)cyclopropane with 2-(bromomethyl)-5-(trifluoromethyl)furan, the title compound was obtained (59%)
as a red solid: ¹H NMR (300 MHz, DMSOd ₆) δ 7.54-7.50 (m, 1H), 7.47-7.44 (m, 1H), 7.20 (dd, 1H), 7.14-7.13 (m, 1H), 6.75 (d, 1H), 4.99 (s, 2H); ¹³C NMR (75 MHz, DMSO-d₆) δ 182.4 (d), 160.7, 158.5 (d), 157.5, 153.0 (d), 146.5 (d), 139.9 (q), 124.3, 119.3 (d), 114.5 (d), 112.7 (d), 112.0 (d), 110.5, 36.8.

PREPARATION 62

Synthesis of 1-(diphenylmethyl)-5-methyl-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace isatin with 5-methylisatin, and (2-bromoethyl)cyclopropane with 1,1'-((bromomethylene)disobenzene, the title compound was obtained (74%) as a bright orange solid: ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.26 (m, 1H), 7.09 (d, 1H), 6.95 (s, 1H), 6.37 (d, 1H), 2.24 (s, 3H).

PREPARATION 63

Synthesis of ethyl (5-chloro-2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace isatin with 5-chloro-1H-indole-2,3-dione, and (2-bromoethyl)cyclopropane with ethyl 2-bromoacetate, the title compound was obtained (98%) as a solid: ¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, 1H), 7.54 (dd, 1H), 6.74 (d, 1H), 4.46 (s, 2H), 4.23 (q, 2H), 1.27 (t, 3H); MS (ES+) m/z 268.6 (M + 1).

PREPARATION 64

Synthesis of methyl (2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with methyl bromoacetate, the title compound was obtained (72%): ¹H NMR (300 MHz, CDCl₃) δ 7.64-7.53 (m, 2H), 7.14 (t, 1H), 6.77 (d, 1H), 4.48 (s, 2H), 3.76 (s, 3H); MS (ES+) m/z 220.4 (M + 1).

PREPARATION 65

Synthesis of 7-fluoro-1-[(5-(trifluoromethyl)-2-furylmethyl)-1H-indole-2,3-dione

Following the procedure as described in PREPARATION 39, and making non-critical variations to replace 4-bromoindole with 7-fluoroisatin, and 1-bromopentane with 2-(bromomethyl)-5-(trifluoromethyl)furan, the title compound was obtained (34%): MS (ES+) m/z 336.2 (M + 23).
EXAMPLE 1

Synthesis of 1-(4-chlorobenzyl)-5-fluoro-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one

A solution of 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione (2.89 g, 10.0 mmol), 2-acetylfuran (1.10 g, 10.0 mmol) and 3 drops of diisopropylamine in absolute EtOH (50.0 mL) was refluxed for 1 hour and stirred at ambient temperature for overnight. The solid was filtered off and recrystallized from ethanol to give 1.89 g (47%) of the title compound as a white solid: 1H NMR (300 MHz, DMSO-CD3) δ 7.96-7.91 (m, 1H), 7.50-7.26 (m, 6H), 7.02-6.94 (m, 1H), 6.75-6.65 (m, 2H), 6.44 (s, 1H), 4.94-4.76 (dd, 2H), 3.93 (d, 1H), 3.47 (d, 1H); 13C NMR (75 MHz, DMSO-CD3) δ 184.8, 177.0, 160.5, 157.3, 151.8, 148.7, 139.6, 135.7, 133.1, 133.0, 132.5, 129.7, 128.9, 120.0, 115.8, 115.5, 113.1, 112.5, 112.2, 110.3, 110.2, 73.4, 45.8, 42.7.

EXAMPLE 2

Synthesis of 1-(4-chlorobenzyl)-3-(2-cyclopropyl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-cyclopropyl-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained (48%): mp 102-103 0C; 1H NMR (300 MHz, CDCl3) δ 7.38-7.15 (m, 6H), 7.02 (t, 1H), 6.63 (d, 1H), 4.88 (d, 1H), 4.79 (d, 1H), 4.54 (br, 1H), 3.38 (d, 1H), 3.12 (d, 1H), 1.95-1.84 (m, 1H), 1.11-0.85 (m, 4H); 13C NMR(75 MHz, CDCl3) δ 207.1, 177.2, 143.4, 135.9, 132.4, 131.4, 129.7, 129.5, 128.9, 124.0, 122.6, 109.3, 73.0, 50.5, 42.6, 21.1, 10.8, 10.6.

EXAMPLE 3

Synthesis of 1-(4-chlorobenzyl)-3-[2-(4-fluorophenyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-(4-fluorophenyl)-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (55%): mp 156-160 0C; 1H NMR (300 MHz, CDCl3) δ 7.94-7.90 (m, 2H), 7.40-6.99 (m, 9H), 6.68 (d, 1H), 4.95 (d, 1H), 4.82 (d, 1H), 4.16 (s, 1H), 3.85 (d, 1H), 3.56 (d, 1H); 13C NMR (75 MHz, CDCl3) δ 195.7, 177.3, 167.4, 164.0, 143.7, 136.0, 133.2, 133.2, 132.4, 131.6, 131.6, 131.5, 129.7, 129.5, 128.9, 123.9, 122.6, 116.3, 116.0, 109.4, 73.2, 46.4, 42.6; MS (ES+) m/z
EXAMPLE 4

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-pyridin-2-ylethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with i-pyridin-2-yl-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (28%): mp 185 °C (dec); ¹H NMR (300 MHz, CDCl₃) δ 8.65 (d, 1H), 8.12 (d, 1H), 7.92 (t, 1H), 7.59 (t, 1H), 7.35-7.15 (m, 8H), 4.90 (d, 1H), 4.78 (d, 1H), 3.85 (d, 1H), 3.59 (d, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 198.3, 177.4, 152.5, 149.7, 143.7, 138.0, 136.0, 138.0, 136.0, 132.4, 131.5, 129.7, 129.5, 128.9, 128.5, 123.9, 122.6, 121.7, 73.3, 45.6, 42.6; MS (ES+) m/z 393.1 (M + 1).

EXAMPLE 5

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-phenyl-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (64%): mp 190 °C (dec); ¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, 2H), 7.60-7.15 (m, 9H), 7.00 (t, 1H), 6.67 (d, 1H), 4.95 (d, 1H), 4.85 (d, 1H), 4.25 (s, 1H), 3.87 (d, 1H), 3.59 (d, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 197.9, 176.5, 142.7, 136.3, 134.0, 133.9, 133.6, 130.0, 129.0, 128.8, 128.2, 124.1, 123.3, 109.5, 74.5, 44.7, 43.4.

EXAMPLE 6

Synthesis of 1-(4-fluorophenyl)-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-fluorophenyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (43%): mp 185 °C (dec); ¹H NMR (300 MHz, CDCl₃) δ 7.55-7.0 (m, 9H), 6.74 (d, 1H), 6.52 (m, 1H), 4.09 (s, 1H), 3.8 (d, 1H), 3.49 (d, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 185.0, 176.7, 176.7, 163.2, 160.0, 151.8, 148.7, 144.4, 131.4, 131.3, 130.8, 130.7, 129.8, 129.4, 129.3, 124.5, 123.1, 120.0, 117.2, 116.9, 113.1, 109.1, 73.2, 73.1, 73.1, 46.6;
EXAMPLE 7
Synthesis of 3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1-(4-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-7/-/-indole-2,3-dione with 1-(4-trifluoromethylbenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (61%): mp 148-150 °C; 1H NMR (300 MHz, CDCl3) δ 7.58 (s, 1H), 7.40 (d, 1H), 7.24-7.20 (m, 4H), 7.02 (q, 3H), 6.63 (d, 1H), 6.53 (m, 1H), 4.88 (d, 1H), 4.80 (d, 1H), 4.50 (br, 1H), 3.90 (d, 1H), 3.42 (d, 1H); 13C NMR (75 MHz, CDCl3) δ 185.0, 177.2, 152.4, 152.3, 151.8, 149.2, 149.1, 148.8, 143.2, 134.3, 131.1, 129.8, 124.1, 122.8, 120.2, 113.1, 112.3, 112.1, 109.4, 73.1, 45.7, 42.2.

EXAMPLE 8
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-nitromethyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with nitromethane, and 1-(4-chlorobenzyl)-5-fluoro-7/-/-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (52%): mp 123 °C (dec); 1H NMR (300 MHz, CDCl3, δ 7.45-7.20 (m, 6H), 7.10 (t, 1H), 6.7 (d, 1H), 5.02-4.73 (m, 4H), 3.75 (s, 1H); 13C NMR (75 MHz, CDCl3) δ 175.3, 142.8, 133.9, 133.2, 131.3, 129.2, 128.7, 128.4, 125.7, 124.7, 124.5, 124.1, 78.0, 73.4, 43.7.

EXAMPLE 9
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(1-oxoindan-2-yl)-1,3-dihydroindol-2H-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with indan-1-one, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (77%): mp 154-157 °C; 1H NMR (300 MHz, CDCl3) δ 7.82 (d, 1H), 7.58 (t, 1H), 7.4-7.05 (m, 9H), 6.7 (d, 1H), 5.82 (s,1H), 4.81 (d, 1H), 4.61 (d, 1H), 3.38-3.31 (m, 1H), 2.98 (q, 1H), 2.35 (dd, 1H); 13C NMR (75 MHz, CDCl3) δ 207.4, 175.9, 152.9, 142.7, 136.7, 135.6, 134.2, 133.6, 130.4, 129.0, 129.0, 128.3, 128.0, 126.3, 124.3, 124.3, 123.7, 109.4, 78.2, 50.6, 43.2, 28.7; MS (ES+) m/z 426 (M + 23).
EXAMPLE 10

Synthesis of 1-[2-(4-chlorophenyl)-ethyl]-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorophenylethyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (39%): mp 128-132 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.61-7.60 (m, 1H), 7.42 (d, 1H), 7.33-7.12 (m, 6H), 7.50 (t, 1H), 6.82 (d, 1H), 6.58-6.55 (m, 1H), 4.42 (br, 1H), 4.10-3.99 (m, 1H), 3.90-3.79 (m, 1H), 3.55 (d, 1H), 3.2 (d, 1H), 3.0 (t, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 184.2, 176.3, 151.4, 148.1, 143.1, 137.6, 131.6, 131.0, 130.8, 130.5, 129.2, 128.3, 123.7, 121.8, 119.3, 112.6, 108.5, 72.6, 45.5, 40.6, 32.1; MS (ES+) m/z 418.1 (M+23).

EXAMPLE 11

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-[2-oxo-2-(1H-pyrrol-2-yl)-ethyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-(7H-pyrrol-2-yl)-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (18%): mp 202 °C (dec); ¹H NMR (300 MHz, CDCl₃) δ 11.6 (s, 1H), 7.46-6.85 (m, 8H), 6.67 (d, 1H), 6.22 (s, 1H), 6.17-6.11 (m, 1H), 4.83 (dd, 2H), 3.80 (d, 1H), 3.38 (d, 1H), 3.31 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 185.6, 177.4, 143.6, 136.0, 132.3, 131.8, 131.4, 129.7, 129.4, 128.9, 126.3, 124.0, 122.5, 117.7, 110.4, 109.2, 73.4, 45.6, 42.6; MS (ES+) m/z 403.1 (M+23).

EXAMPLE 12

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-[2-(5-methylfuran-2-yl)-2-oxoethyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-(5-methyl-furan-2-yl)-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (51%): mp 162-163 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.40 (dd, 1H), 7.30-7.10 (m, 6H), 7.00 (t, 1H), 6.65 (d, 1H), 6.15 (d, 1H), 4.91 (d,1H), 4.81 (d, 1H), 4.65 (br, 1H), 3.60 (d, 1H), 3.27 (d, 1H), 2.36 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 183.8, 177.2, 158.7, 150.8, 143.5, 135.9, 132.4,
EXAMPLE 13
Synthesis of 1-(4-chlorobenzyl)-3-(2-(2,5-dimethylfuran-3-yl)-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-(2,5-dimethylfuran-3-yl)-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (24%): 1H NMR (300 MHz, CDCl₃) δ 7.44-7.15 (m, 6H), 7.00 (t, 1H), 6.65 (d, 1H), 6.09 (s, 1H), 4.92 (d, 1H), 4.81 (d, 1H), 4.78 (s, 1H), 3.45 (d, 1H), 3.18 (s, 1H), 2.51 (s, 3H), 2.21 (s, 3H); MS (ES+) m/z 432.1 (M + 23).

EXAMPLE 14
Synthesis of 1-(4-chlorobenzyl)-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-5-methyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-5-methyl-7H-indole-2,3-dione, the title compound was obtained as a white solid (54%): mp 183-185 °C; 1H NMR (300 MHz, CDCl₃) δ 7.58 (s, 1H), 7.30-7.18 (m, 6H), 6.98 (d, 1H), 6.53 (m, 2H), 4.90 (d, 1H), 4.80 (d, 1H), 4.33 (br, 1H), 3.52 (d, 1H), 3.35 (d, 1H), 2.25 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 184.8, 177.1, 151.9, 148.6, 141.1, 136.0, 132.3, 131.5, 131.1, 129.7, 129.6, 128.8, 124.8, 119.8, 113.1, 109.2, 73.2, 45.8, 42.6, 21.0; MS (ES+) m/z 418.1 (M + 23).

EXAMPLE 15
Synthesis of 3-(2-benzofuran-2-yl-2-oxo-ethyl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-benzofuran-2-yl-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a white solid (33%): mp 185 °C (dec); 1H NMR (300 MHz, CDCl₃) δ 7.68 (d, 1H), 7.55-7.18 (m, 10H), 7.05 (t, 1H), 7.68 (d, 1H), 4.95 (d, 1H), 4.81 (d, 1H), 4.25 (s, 1H), 3.87 (d, 1H), 3.51 (d, 1H); 13C NMR (75 MHz, CDCl₃) δ 187.0, 177.1, 155.5, 151.9, 143.5, 135.9, 132.4, 130.9, 129.7, 129.2, 128.9, 127.1, 124.6, 124.3, 124.3, 122.7, 115.7, 112.7, 109.5, 73.3, 46.2, 42.6; MS (ES+) m/z
454.1 (M + 23).

EXAMPLE 16

Synthesis of 1-(1,3-benzodioxol-5-ylmethyl)-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-7/-/-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-1H-indole-2,3-dione, the title compound was obtained as a white solid (54%): mp 175-177 °C; 1H NMR (300 MHz, DMSO-c6) δ 7.52 (d, 1H), 7.38 (dd, 1H), 7.21-7.16 (m, 2H), 6.98 (dt, 1H), 6.82-6.80 (m, 2H), 6.74-6.71 (m, 2H), 6.51 (dd, 1H), 5.90 (s, 2H), 4.78 (ABq, 2H); 13C NMR (75 MHz, CDCl3) δ 186.8, 176.2, 152.3, 148.1, 147.2, 142.6, 129.9, 129.6, 129.3, 124.1, 123.2, 120.8, 118.4, 112.4, 109.8, 108.4, 107.9, 101.1, 74.6, 43.9, 43.8; MS (ES+) m/z 414 (M + 23).

EXAMPLE 17

Synthesis of 1-(1,3-benzodioxol-5-ylmethyl)-3-hydroxy-3-[2-oxo-2-(2-thienyl)ethyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 2-acetylthiophene, and 1-(4-chlorobenzyl)-5-fluoro-7/-/-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-1H-indole-2,3-dione, the title compound was obtained as a yellow solid (36%): mp 186-187 °C; 1H NMR (300 MHz, CDCl3) δ 8.00 (dd, 1H), 7.94 (dd, 1H), 7.34 (dd, 1H), 7.19 (dd, 1H), 7.12 (dd, 1H), 6.96-6.86 (m, 3H), 6.83 (d, 1H), 6.73 (d, 1H), 6.30 (s, 1H), 5.95 (d, 2H), 4.76 (br, 1H), 3.82 (ABq, 2H); 13C NMR (75 MHz, DMSO-d6) δ 189.8, 177.1, 147.9, 146.9, 143.7, 143.7, 135.9, 134.6, 131.2, 130.6, 129.5, 129.3, 123.9, 122.5, 121.1, 109.5, 108.6, 108.3, 101.4, 73.2, 46.5, 43.0; MS (ES+) m/z 430 (M + 23). Anal. Calcd for C22H17NO5S: C, 64.85; H, 4.21; N, 3.44. Found: C, 64.73; H, 4.25; N, 3.70.

EXAMPLE 18

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(1,3-trimethyl-2-oxobutyl)-1,3-dihydro-2H-indol-2-one

To a solution of methylaniline (2.20 g, 20.0 mmol) in benzene (10.0 mL) was added ethylmagnesium bromide (10.0 mL, 2 M) at 0 °C and a solution of 2,4-dimethylpentan-3-one (2.10 g, 19.0 mmol) in benzene (5.00 mL) during 10-15 min. The reaction mixture was stirred at 15 °C for 30 min and cooled down to -13 °C followed by the addition of a solution of 1-(4-chlorobenzyl)-7H-indole-2,3-dione (3.50 g,
13.0 mmol) in THF (100 ml). The reaction mixture was stirred at -10 °C for 1 hour and ambient temperature for 2 hours and quenched with NH₄Cl solution. The reaction mixture was concentrated in vacuo to dryness. The residue was subjected to column chromatography to yield 1.10 g (22%) of colorless solid as the title compound: mp 105-107 °C; 1H NMR (300 MHz, CDCl₃) δ 7.38-7.18 (m, 6H), 7.01 (t, 1H), 6.65 (d, 1H), 6.12 (s, 1H), 4.87 (d, 1H), 4.72 (d, 1H), 3.09-3.04 (m, 1H), 1.38 (s, 3H), 1.18 (s, 3H), 1.16 (d, 3H), 1.08 (d, 3H); 13C NMR (75 MHz, CDCl₃) δ 177.4, 147.8, 147.5, 142.8, 134.3, 132.0, 129.7, 124.9, 123.3, 129.0, 128.8, 128.3, 125.4, 123.1, 109.2, 81.5, 50.2, 43.1, 36.8, 20.9, 20.1, 19.5, 18.9.

EXAMPLE 19

Synthesis of 1-(4-chlorobenzyl)-3-(1,1-dimethyl-2-oxo-2-thiophen-2-yl-ethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 18, and making non-critical variations to replace 2,4-dimethylpentan-3-one with 2-methyl-1-thiophen-2-yl-propan-1-one, the title compound was obtained as a colorless solid (35%): mp 130-132 °C; 1H NMR (300 MHz, CDCl₃) δ 7.82-7.79 (m, 1H), 7.66-7.62 (m, 1H), 7.37-7.35 (m, 1H), 7.30-6.97 (m, 7H), 6.67 (d, 1H), 5.52 (br, 1H), 4.90 (d, 1H), 4.70 (d, 1H), 1.55 (s, 6H); 13C NMR (75 MHz, CDCl₃) δ 200.2, 176.5, 143.1, 134.3, 134.2, 133.6, 133.5, 129.9, 129.0, 128.9, 128.5, 128.0, 125.5, 123.1, 80.8, 51.7, 43.2, 22.0, 21.5.

EXAMPLE 20

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

To a solution of 1-pentyl indole-2,3-dione (1.00 g, 4.60 mmol) in anhydrous tetrahydrofuran (30.0 mL) was added a solution of 3,4-(methyleneoxy)phenylmagnesium bromide (5.10 mL, 5.10 mmol, 1.0 M solution in toluene/THF, 50:50) under nitrogen at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, at ambient temperature for 6 h, quenched with saturated ammonium chloride (30.0 mL) and separated. The aqueous layer was extracted with ethyl acetate (3 x 50.0 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/heptane (3/7) to give a gummy material which was crystallized from ether/hexane to afford 0.33 g (21%) of colorless solid as the title compound: mp 85-87 °C; 1H NMR (300 MHz, CDCl₃) δ 7.34-7.24 (m, 2H), 7.04 (dt, 1H), 6.89-6.86 (m, 2H), 6.79 (dd, 1H), 6.69 (d, 1H), 5.90 (dd, 2H), 3.75 (dt, 1H), 3.60 (dt, 1H), 1.73-1.63 (m, 2H), 1.35-1.30 (m, 4H), 0.87 (t, 3H); 13C NMR (75 MHz, CDCl₃) δ 177.4, 147.8, 147.5, 142.8, 134.3, 132.0, 129.7, 124.9, 123.3,
118.9, 109.0, 108.1, 106.3, 101.2, 77.7, 40.3, 29.0, 27.0, 22.2, 14.0; MS (ES+) m/z 322 (M - 17).

EXAMPLE 21

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(cyclopropylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 1-cyclopropylmethyl-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (12%): mp 142-145 °C; 1H NMR (300 MHz, CDCl₃) δ 7.30 (t, 1H), 7.16-7.12 (m, 2H), 7.00 (t, 1H), 6.86 (d, 1H), 6.79 (d, 1H), 6.67 (s, 1H), 6.61 (d, 1H), 5.95 (d, 2H), 3.54 (d, 1H), 3.33 (s, 1H), 1.20-1.09 (m, 1H), 0.44-0.42 (m, 2H), 0.34-0.25 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 177.4, 148.2, 148.1, 145.5, 143.2, 128.8, 127.6, 126.6, 124.9, 124.9, 123.0, 119.2, 109.6, 108.2, 106.6, 101.5, 77.2, 43.8, 9.7, 3.93; MS (ES+) m/z 306 (M - 17).

EXAMPLE 22

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(1-phenylethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 1-(1-phenylethyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (24%): mp 148-150 °C; 1H NMR (300 MHz, CDCl₃) δ 7.37-7.22 (m, 6H), 7.08 (dt, 1H), 6.99 (dd, 1H), 6.85 (d, 1H), 6.84 (dd, 1H), 6.76 (d, 1H), 6.52 (d, 1H), 5.94 (dd, 2H), 5.77 (q, 1H), 3.25 (br, 1H), 1.83 (d, 3H); 13C NMR (75 MHz, CDCl₃) δ 177.5, 148.1, 147.7, 141.4, 139.0, 134.2, 131.9, 129.5, 128.8, 127.6, 126.6, 124.9, 123.2, 118.8, 111.5, 108.3, 106.3, 101.3, 77.5, 49.7, 16.1; MS (ES+) m/z 356 (M - 17).

EXAMPLE 23

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-(trifluoromethoxy)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-5-trifluoromethoxy-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (38%): mp 138-140 °C; 1H NMR (300 MHz, CDCl₃) δ 7.31-7.27 (m, 2H), 7.21-7.15 (m, 3H), 7.10-7.06 (m, 1H), 6.88 (d, 1H), 6.78-6.74 (m, 2H), 6.70 (d, 1H), 5.65 (dd, 2H), 4.85 (ABq, 2H), 3.72 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.4, 148.2, 148.1, 145.5,
EXAMPLE 24

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-[4-(1/-/-pyrrol-1-yl)benzyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 1-(4-pyrrol-1-yl-benzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (31%): mp 195-198 °C; 1H NMR (300 MHz, DMSO-d$_6$) δ 7.51 (d, 2H), 7.37 (d, 2H), 7.31 (t, 2H), 7.24 (t, 1H), 7.17 (d, 1H), 7.02 (d, 1H), 6.88 (d, 1H), 6.81-6.78 (m, 2H), 6.56 (dd, 1H), 6.21 (t, 2H), 5.96 (d, 2H), 4.87 (s, 2H), 3.30 (s, 1H); 13C NMR (75 MHz, DMSO-Of) δ 177.2, 147.7, 147.3, 142.7, 139.5, 135.6, 133.6, 133.3, 129.8, 129.1, 125.1, 123.3, 119.9, 119.4, 119.2, 110.9, 109.9, 108.3, 106.8, 101.6, 77.2, 42.6; MS (ES+) m/z 447 (M + 23), 407 (M - 17).

EXAMPLE 25

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-[(trimethylsilyl)methyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with (trimethylsilyl)methylmagnesium chloride, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (65%): mp 121-122 °C; 1H NMR (300 MHz, CDCl$_3$) δ 7.36 (d, 1H), 7.28-7.24 (m, 1H), 7.15-7.03 (m, 4H), 6.91-6.85 (m, 2H), 6.74 (d, 1H), 5.93 (s, 2H), 4.81 (ABq, 2H), 3.02 (br, 1H), 1.56 (s, 2H), -0.29 (s, 9H); 13C NMR (75 MHz, CDCl$_3$) δ 178.4, 141.8, 133.8, 133.6, 131.1, 129.6, 129.0, 128.9, 124.3, 123.3, 109.3, 75.6, 43.2, 28.4, -1.01.

EXAMPLE 26

Synthesis of 3-(1,3-benzodioxol-5-yl)-7-(4-fluorophenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 7-(4-fluorophenyl)-1-pentyl-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (17%): mp 149-151 °C; 1H NMR (300 MHz, CDCl$_3$) δ 7.39-7.29 (m, 2H), 7.28-7.24 (m, 1H), 7.15-7.03 (m, 4H), 6.91-6.85 (m, 2H), 6.74 (d, 1H), 5.93 (s, 2H), 3.47-3.32 (m, 2H), 3.25-3.16 (m,
1H), 1.64 (br, 1H), 1.24-1.11 (m, 2H), 1.08-0.99 (m, 2H), 0.84-0.66 (m, 4H); 13C NMR (75 MHz, CDCl3) δ 178.5, 164.1, 160.8, 148.0, 147.7, 139.4, 134.5 (d, 2JCF = 12 Hz), 134.3, 133.2, 133.1, 131.5-131.2 (m), 125.0, 124.2, 122.9, 118.8, 115.4-14.7 (m), 108.3, 106.2, 101.3, 76.9, 41.9, 28.4, 27.3, 22.1, 13.9; MS (ES+) m/z 416 (M - 17).

EXAMPLE 27
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(4,4,4-trifluorobutyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(4,4,4-trifluorobutyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (37%): mp 119-121 °C; 1H NMR (300 MHz, CDCl3) δ 7.34 (dt, 1H), 7.28 (d, 1H), 7.09 (t, 1H), 6.89-6.86 (m, 2H), 6.79-6.70 (m, 2H), 5.92 (s, 2H), 3.86-3.68 (m, 2H), 3.53 (s, 1H), 2.23-2.06 (m, 2H), 2.02-1.96 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 177.5, 148.0, 147.8, 142.1, 133.8, 131.6, 130.0, 128.6, 125.3, 124.9, 123.8, 118.9, 108.7, 108.2, 106.2, 101.3, 77.6, 39.0, 31.9, 31.5, 31.1, 30.7, 20.3, 20.3; MS (ES+) m/z 362 (M - 17).

EXAMPLE 28
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(5-chloropentyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(5-chloropentyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (67%): mp 131-132 °C; 1H NMR (300 MHz, CDCl3) δ 7.35-7.25 (m, 2H), 7.06 (t, 1H), 6.89-6.87 (m, 2H), 6.82-6.79 (m, 1H), 6.71 (d, 1H), 5.91 (2H), 3.83-3.73 (m, 1H), 3.70-3.60 (m, 1H), 3.49 (t, 2H), 1.84-1.68 (m, 4H), 1.55-1.45 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 177.4, 148.0, 147.7, 142.7, 134.0, 131.7, 129.9, 125.1, 123.5, 118.9, 108.9, 108.2, 106.3, 101.2, 77.6, 44.7, 40.0, 32.0, 26.7, 24.1; MS (ES+) m/z 356 (M - 17).

EXAMPLE 29
Synthesis of 3,7-bis(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 7-(1,3-benzodioxol-5-yl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (20%): mp 112-115 °C; 1H NMR (300 MHz, CDCl3) δ 8.06 (s, 1H), 7.24-7.20 (m, 2H), 7.10 (t, 1H), 6.96 (d, 1H), 6.88-6.82 (m, 4H), 6.72 (d, 1H), 5.99 (dd, 2H), 5.92 (s, 2H), 3.64 (br, 1H); 13C
NMR (75 MHz, CDCl₃) δ 179.3, 148.3, 148.0, 147.7, 147.3, 137.7, 133.7, 132.4, 130.8, 130.1, 124.7, 124.0, 123.8, 121.6, 119.0, 109.0, 108.6, 108.2, 106.3, 101.4, 101.3, 78.2; MS (ES-) m/z 388 (M - 1).

**EXAMPLE 30**

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-5,7-dimethyl-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 5,7-dimethyl-1-pentyl-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (41%): mp 120-121 °C; ¹H NMR (300 MHz, CDCl₃) δ 6.89-6.78 (m, 4H), 6.70 (d, 1H), 5.89 (s, 2H), 3.85 (t, 2H), 3.46 (s, 1H), 2.47 (s, 3H), 2.22 (s, 3H), 1.67-1.63 (m, 2H), 1.35-1.33 (m, 4H), 0.88 (t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 178.2, 147.8, 147.4, 138.0, 134.7, 134.1, 132.9, 132.8, 123.6, 119.6, 118.7, 108.1, 106.1, 101.1, 77.5, 42.0, 29.2, 28.8, 22.4, 20.7, 18.8, 14.0; MS (ES+) m/z 350 (M - 17).

**EXAMPLE 31**

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methylpentyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(3-methylpentyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (28%): ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.24 (m, 2H), 7.05 (t, 1H), 6.90-6.85 (m, 2H), 6.81-6.78 (m, 1H), 6.70 (d, 1H), 5.90 (s, 2H), 3.68-3.58 (m, 1H), 3.47-3.36 (m, 1H), 2.06-1.95 (m, 1H), 1.43-1.13 (m, 4H), 0.92-0.82 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 177.4, 147.9, 147.6, 143.3, 143.2, 131.7, 129.7, 124.9, 123.3, 109.3, 109.2, 108.2, 106.3, 101.2, 77.6, 46.6, 36.6, 31.5, 20.0, 17.6, 14.3; MS (ES+) m/z 336 (M - 17).

**EXAMPLE 32**

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(1-methylpentyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(1-methylpentyl)-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (47%): mp 152-154 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.27-7.23 (m, 2H), 7.05-6.99 (m, 2H), 6.85 (d, 1H), 6.79 (d, 1H), 5.90 (dd, 2H), 4.40-4.28 (m, 1H), 3.83 (br, 1H), 2.10-1.97 (1H), 1.43-1.13 (m, 4H), 0.92-0.82 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 177.4, 147.9, 147.6, 143.3, 143.2, 131.7, 129.7, 124.9, 123.3, 109.3, 109.2, 108.2, 106.3, 101.2, 77.6, 46.6, 36.6, 31.5, 20.0, 17.6, 14.3; MS (ES+) m/z 336 (M - 17).
1.79-1.65 (m, 1H), 1.46 (d, 3H), 1.32-1.19 (m, 4H), 0.89-0.80 (m, 3H); 13C NMR (75 MHz, CDCl3) δ 177.5, 147.9, 147.5, 142.3, 134.5, 132.2, 129.6, 125.1, 123.0, 118.8, 110.3, 108.2, 106.2, 101, 168: 77.5, 48.9, 32.8, 28.9, 22.4, 18.1, 14.0; MS (ES+) m/z 336 (M - 17).

EXAMPLE 33
Synthesis of 3-(1,3-benzodioxol-5-yO-i-cyclobutylmethyl-S-hydroxy-i,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-cyclobutylmethyl-7H-indole-2,3-dione, the title compound was obtained (32%) as a colorless solid: mp 124-125 0C; 1H NMR (300 MHz, CDCl3) δ 7.30 (t, 1H), 7.24 (d, 1H), 7.04 (t, 1H), 6.89 (m, 2H), 6.81 (dd, 1H), 6.71 (d, 1H), 5.91 (dd, 2H), 3.86 (dd, 1H), 3.62 (dd, 1H), 2.86 (m, 1H), 2.09-1.98 (m, 2H), 1.89-1.78 (m, 4H); 13C NMR (75 MHz, CDCl3) δ 176.5, 146.6, 146.3, 141.8, 133.1, 130.5, 128.4, 123.6, 122.0, 117.5, 107.9, 106.9, 104.9, 100.0, 76.4, 44.1, 32.5, 25.0, 24.9, 17.0; MS (ES+) m/z 320 (M - 17).

EXAMPLE 34
Synthesis of 3-(1,3-benzodioxol-5-yl)-5-bromo-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 5-bromo-1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained (61%) as a colorless solid: mp 179-180 0C; 1H NMR (300 MHz, CDCl3) δ 7.44 (dd, 1H), 7.40-7.37 (m, 2H), 7.32-7.30 (m, 3H), 6.95-6.87 (m, 3H), 6.81 (d, 1H), 6.56 (d, 1H), 5.97 (d, 2H), 4.86 (dd, 2H); 13C NMR (75 MHz, DMSO-d6) δ 176.7, 147.9, 147.5, 141.8, 135.6, 134.8, 132.7, 132.5, 129.7, 129.1, 127.8, 119.1, 115.2, 112.1, 108.4, 106.7, 101.6, 77.1, 42.6; MS (ES+) m/z 472 (M + 23).

EXAMPLE 35
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-5-fluoro-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 5-fluoro-1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (44%): mp 145-147 0C; 1H NMR (300 MHz, DMSO-d6) δ 7.32 (d, 4H), 7.13-7.04 (m, 2H), 6.97-6.90 (m,
3H), 6.80 (d, 1H), 6.56 (dd, 1H), 5.97 (d, 2H), 4.86 (dd, 2H); $^{13}$C NMR (75 MHz, DMSO-
C$_6$) δ 177.0, 160.9, 157.8, 147.8, 147.4, 138.7, 135.6, 135.1, 135.0, 134.9, 132.6,
129.7, 129.1, 119.2, 116.0, 113.0, 112.7, 110., 108.3, 106.7, 101.1, 77.3, 42.6; MS
(ES+) m/z 394 (M - 17).

EXAMPLE 36

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-methyl-1,3-
dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical
variations to replace 1-pentyl-7H-indole-2,3-dione with 5-methyl-1-(4-chlorobenzyl)-1H-
indole-2,3-dione, the title compound was obtained (53%) as a colorless solid: mp 122-
124 °C; $^1$H NMR (300 MHz, DMSO-C$_6$) δ 7.34 (dd, 4H), 7.03 (d, 1H), 6.98 (s, 1H), 6.86-
6.78 (m, 3H), 6.75 (s, 1H), 6.56 (dd, 1H), 5.96 (d, 2H), 4.83 (ABq, 2H), 2.19 (s, 3H); $^{13}$C
NMR (75 MHz, CDC$_6$) δ 177.2, 147.7, 147.2, 140.1, 135.9, 135.1, 133.4, 132.5, 129.9,
129.7, 129.0, 119.1, 109.6, 108.3, 106.7, 101.5, 77.3, 42.5, 21.0; MS (ES+) m/z 394 (M - 17).

EXAMPLE 37

Synthesis of 1-(4-chlorobenzyl)-3-(1,3-dioxolan-2-ylmethyl)-3-hydroxy-1,3-dihydro-2/-/-
indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical
variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with (1,3-
dioxolan-2-ylmethyl)magnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-
chlorobenzyl)-7/-/-indole-2,3-dione, the title compound was obtained as colorless solid
(69%): mp 166-169 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.38 (d, 1H), 7.28-7.22 (m, 5H),
7.05 (t, 1H), 6.64 (d, 1H), 5.18 (t, 1H), 4.82 (ABq, 2H), 4.14 (br, 1H), 3.89-3.79 (m, 4H),
2.30 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 177.3, 142.8, 135.9, 132.4, 130.8, 129.7,
129.6, 128.9, 124.9, 122.7, 109.4, 100.7, 73.3, 64.5, 64.3, 42.5, 31.2; MS (ES+) m/z
382 (M + 23).

EXAMPLE 38

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical
variations to replace 1-pentyl-7H-indole-2,3-dione with isatin, the title compound was
obtained (36%): mp 177-180 °C; $^1$H NMR (300 MHz, DMSO-d$_6$) δ 10.4 (s, 1H), 7.23-
7.13 (m, 2H), 7.06 (d, 1H), 6.92 (t, 1H), 6.86 (d, 1H), 6.79 (dd, 1H), 6.65 (d, 1H), 6.59
(br, 1H), 3.69 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-CD$_3$) δ 178.8, 159.6, 143.6, 142.4, 134.1, 129.7, 129.6, 125.2, 122.5, 118.0, 112.9, 112.0, 110.3, 77.7, 55.5.

**EXAMPLE 39**

Synthesis of 3-benzyl-1-(4-chlorobenzoyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methyleneedioxy)phenylmagnesium bromide with benzylmagnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzoyl)-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (58%): mp 168-170 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.54 (d, 1H), 7.42 (t, 12H), 7.37-7.28 (m, 4H), 7.22-7.14 (m, 4H), 6.85 (d, 2H), 3.31 (ABq, 2H), 3.09 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.3, 167.8, 139.8, 139.4, 133.1, 131.9, 130.8, 130.4, 130.3, 128.8, 128.5, 128.3, 127.6, 125.5, 124.5, 115.1, 45.6; MS (ES+) m/z 399 (M + 23).

**EXAMPLE 40**

Synthesis of 1-(4-chlorobenzoyl)-3-hydroxy-3-phenyl-1,3-dihydroindol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methyleneedioxy)phenylmagnesium bromide with phenylmagnesium bromide, and 1-pentyl-7A7-indole-2,3-dione with 1-(4-chlorobenzoyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (80%): mp 141-143 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.90 (d, 1H), 7.67 (d, 1H), 7.53-7.50 (m, 2H), 7.47-7.39 (m, 2H), 7.35-7.34 (m, 4H), 7.28-7.19 (m, 3H), 7.02 (d, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.1, 167.9, 139.8, 139.5, 139.1, 131.9, 130.8, 130.7, 130.4, 128.9, 128.8, 128.7, 128.3, 126.0, 125.5, 125.2, 115.5; MS (ES+) m/z 386 (M + 23).

**EXAMPLE 41**

Synthesis of 3-(1,3-benzodioxol-5-yl)-7-fluoro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7A7-indole-2,3-dione with 7-fluoro-1-pentyl-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (69%): mp 102-104 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.01-6.99 (m, 3H), 6.88-6.71 (m, 3H), 5.93 (s, 2H), 3.87-3.81 (m, 2H), 3.02 (br, 1H), 1.73-1.69 (m, 2H), 1.36-1.32 (m, 4H), 0.86-0.91 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 174.8, 145.9, 145.6, 132.4, 131.6, 122.0, 121.9, 118.6, 118.6, 116.6, 115.9, 115.6, 106.1, 103.9, 99.1, 75.5, 40.2, 26.6, 26.4, 20.1, 11.8; MS (ES+) m/z 340.3 (M - 17).
EXAMPLE 42
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (33%): mp 153-155 °C; 1H NMR (300 MHz, CDCl₃) δ 7.24 (m, 2H), 7.06 (m, 1H), 6.95 (d, 1H), 6.78 (m, 4H), 6.59 (s, 1H), 5.90 (m, 4H), 4.91 (q, 2H), 3.16 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.7, 148.0, 147.3, 142.2, 137.8, 131.4, 130.0, 125.8, 124.7, 123.8, 119.0, 109.9, 109.8, 108.2, 107.8, 106.4, 101.9, 101.3, 41.2; MS (ES+) m/z 420.1 (M - 17).

EXAMPLE 43
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-thiophen-2-ylmethyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-thiophen-2-ylmethyl-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (39%): mp 141-142 °C; 1H NMR (300 MHz, CDCl₃) δ 7.29-7.19 (m, 3H), 7.04 (m, 2H), 6.94-6.90 (m, 3H), 6.83-6.80 (m, 1H), 6.71 (d, 1H), 5.92-5.91(m, 2H), 5.05 (ABq, 2H), 3.22 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.0, 148.0, 147.7, 142.0, 137.8, 133.9, 131.6, 129.8, 127.0, 126.7, 125.5, 125.0, 123.7, 118.9, 109.5, 106.3, 101.2, 39.0; MS (ES+) m/z 348.1 (M - 17).

EXAMPLE 44
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(2-methoxybenzyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(2-methoxybenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (63%): mp 148-150 °C; 1H NMR (300 MHz, CDCl₃) δ 7.27-7.14 (m, 4H), 7.01 (t, 1H), 6.92 (d, 1H), 6.89-6.81 (m, 4H), 6.72 (d, 1H), 5.92 (dd, 2H), 4.93 (ABq, 2H), 3.84 (s, 3H), 2.80 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.5, 157.1, 147.9, 147.6, 142.9, 134.3, 131.5, 129.8, 128.9, 128.5, 124.7, 123.3, 123.3, 120.7, 118.9, 110.4, 110.0, 108.28, 106.4, 101.2, 55.3, 39.1; MS (ES+) m/z 372 (M - 17).
EXAMPLE 45

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-naphthalen-1-ylmethyl-1H-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-naphthalen-1-ylmethyl-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (26%): mp 93-95 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.07-8.03 (m, 1H), 7.89-7.77 (m, 2H), 7.55-7.43 (m, 2H), 7.40-7.27 (m, 3H), 7.17-7.1 1H), 7.04-6.97 (m, 2H), 6.86-6.71 (m, 3H), 5.93 (dd, 2H), 5.63-5.57 (m, 1H), 5.18-5.16 (m, 1H), 3.42 (br, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.5, 148.0, 147.8, 142.9, 133.9, 133.9, 131.5, 131.0, 130.2, 130.0, 129.9, 128.6, 126.7, 126.1, 125.3, 124.9, 123.3, 122.9, 119.1, 119.0, 110.2, 108.2, 106.4, 101.3, 77.8, 42.6; MS (ES+) m/z 392.2 (M - 17).

EXAMPLE 46

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(3,4-difluorobenzyl)-3-hydroxy-1H-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(3,4-difluorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (52%): mp 200-201 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.21-7.20 (m, 1H), 7.04-7.03 (m, 2H), 6.91 (d, 1H), 6.81-6.71 (m, 3H), 5.93 (dd, 2H), 4.84 (q, 2H), 3.44 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.5, 148.1, 147.9, 142.0, 133.7, 132.4, 131.4, 129.9, 125.2, 123.9, 123.4, 123.3, 118.9, 117.9, 117.7, 116.5, 116.3, 109.4, 108.3, 106.3, 101.3, 77.7, 43.0; MS (ES+) m/z 378.1 (M - 17).

EXAMPLE 47

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-trifluoromethylbenzyl)-1H-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(3-trifluoromethylbenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (74%): mp 133-135 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.53-7.42 (m, 4H), 7.31-7.21 (m, 2H), 7.09-7.04 (m, 4H) 6.93 (d, 1H), 5.93 (dd, 2H), 4.94 (q, 2H), 2.81 (br, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.5, 148.1, 147.9, 142.1, 136.5, 133.8, 131.4, 130.5, 130.0, 125.1, 124.8, 124.8, 124.0, 123.9, 123.9, 118.9, 109.4, 108.3, 106.3, 101.3, 77.7, 43.5; MS (ES+) m/z 410 (M - 17).
EXAMPLE 48

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-3-hydroxy-5-methoxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(4-fluorobenzyl)-5-methoxy-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (31%): mp 127-129°C; 1H NMR (300 MHz, CDCl₃) δ 7.25-7.21 (m, 2H), 7.00-6.94 (m, 2H), 6.88 (dd, 2H), 6.81-6.77 (m, 1H), 6.74-6.69 (m, 2H), 6.63-6.60 (m, 1H), 5.91 (dd, 2H), 4.81 (q, 2H), 3.69 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 177.4, 163.9, 160.7, 156.7, 148.0, 147.7, 135.4, 134.0, 132.9, 131.3, 131.2, 129.1, 129.0, 118.9, 115.9, 115.7, 114.6, 111.7, 110.2, 108.2, 106.3, 101.3, 78.1, 55.8, 43.4; MS (ES+) m/z 382 (M - 17).

EXAMPLE 49

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chloro-3-trifluoromethylbenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(3-trifluoromethyl-4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (33%): mp 133-135°C; 1H NMR (300 MHz, CDCl₃) δ 7.58 (s, 1H), 7.43-7.24 (m, 4H), 7.10-7.05 (m, 1H), 6.91 (d, 1H), 6.78-6.67 (m, 3H), 5.93 (d, 2H), 4.89 (q, 2H), 3.46 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.6, 148.1, 147.9, 141.8, 134.7, 133.6, 132.1, 131.8, 131.5, 130.0, 128.7, 126.3, 126.2, 125.3, 124.4, 124.1, 118.9, 109.2, 108.3, 106.3, 101.3, 77.7, 43.0; MS (ES+) m/z 444 (M - 17).

EXAMPLE 50

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(5-chlorothiophen-2-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(5-chlorothiophen-2-ylmethyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (30%): mp 164-165°C; 1H NMR (300 MHz, CDCl₃) δ 7.32-7.26 (m, 2H), 7.1 1-7.06 (m, 1H), 6.92-6.72 (m, 6H), 5.94 (d, 2H), 4.95 (q, 2H), 3.02 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 174.6, 145.8, 145.6, 139.6, 134.3, 131.5, 129.4, 127.8, 127.7, 124.0, 123.8, 123.0, 121.7, 116.8, 107.2, 106.1, 104.1, 99.1, 75.4, 37.0; MS (ES+) m/z 382 (M - 17).
EXAMPLE 51

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methylbutyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(3-methylbutyl)-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (48%): mp 129-131 °C; 1H NMR (300 MHz, CDCl₃) δ 7.33-7.24 (m, 2H), 7.07-7.02 (m, 1H), 6.88-6.69 (m, 4H), 5.91 (dd, 2H), 3.82-3.58 (m, 2H), 2.89 (br, 1H), 1.71-1.50 (m, 3H), 0.96 (dd, 6H); 13C NMR (75 MHz, CDCl₃) δ 177.2, 147.9, 147.6, 142.8, 134.2, 131.8, 129.8, 125.0, 123.3, 118.8, 108.9, 108.2, 106.2, 101.2, 77.6, 77.5, 38.7, 35.9, 26.1, 22.5, 22.4; MS (ES+) m/z 323.1 (M - 17).

EXAMPLE 52

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-hexyl-3-hydroxy-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 1-hexyl-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (30%): mp 88-90 °C; 1H NMR (300 MHz, CDCl₃) δ 7.33-7.24 (m, 2H), 7.07-7.02 (m, 1H), 6.89-6.69 (m, 4H), 5.90 (s, 2H), 3.80-3.55- (m, 2H), 2.02 (br, 1H), 1.74-1.60- (m, 2H), 1.36-1.23- (m, 6H), 0.85 (t, 3H); 13C NMR (75 MHz, CDCl₃) δ 177.3, 147.9, 147.6, 142.8, 134.2, 131.8, 129.8, 124.9, 123.3, 118.8, 109.0, 108.2, 106.2, 101.2, 77.6, 77.5, 40.3, 31.4, 27.3, 26.6, 22.5, 14.0; MS (ES+) m/z 337 (M - 17).

EXAMPLE 53

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-quinolin-8-ylmethyl-1,3-dihydro-2H-indole-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-quinolin-8-ylmethyl-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (43%): mp 187-189 °C; 1H NMR (300 MHz, CDCl₃) δ 8.98 (dd, 1H), 8.17 (dd, 1H), 7.51-7.35 (m, 3H), 7.29-7.24 (m, 2H), 7.13-7.08 (m, 1H), 7.01-6.96 (m, 2H), 6.91-6.81 (m, 2H), 6.74 (d, 1H), 5.92 (dd, 2H), 5.64 (q, 2H), 2.14 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.9, 149.7, 148.0, 147.7, 145.9, 142.8, 136.6, 134.2, 133.3 131.5, 129.8, 128.3, 127.6, 127.5, 126.5, 124.7, 123.4, 121.4, 119.1, 110.2, 108.2, 106.5, 101.2, 77.9, 39.7; MS (ES+) m/z 411.6 (M + 1).
EXAMPLE 54

Synthesis of 1-(1,3-benzodioxol-5-yl)-3-hydroxy-3-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with pentylmagnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(1,3-benzodioxol-5-yl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (30%): mp 85-90 °C; 1H NMR (300 MHz, CDCl₃) δ 7.41-7.38 (m, 1H), 7.25-7.20 (m, 1H), 7.12-7.07 (m, 1H), 6.91-6.88 (m, 1H), 6.82-6.74 (m, 3H), 6.01-5.93 (m, 2H), 2.70 (br, 1H), 2.12-1.83 (m, 2H), 1.28-1.00 (m, 6H), 0.87-0.78 (m, 3H); 13C NMR (75 MHz, CDCl₃) δ 178.1, 148.5, 147.5, 143.7, 129.7, 129.5, 127.6, 124.1, 123.5, 120.4, 120.2, 109.6, 108.8, 107.8, 101.8, 77.5, 77.2, 39.1, 31.7, 28.2, 22.9, 22.7, 22.3, 14.0, 13.9; MS (ES+) m/z 323.2 (M - 17).

EXAMPLE 55

Synthesis of 3-(1,3-benzodioxol-5-yl)-4,7-dichloro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-pentyl-4,7-dichloro-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (32%): mp 82-84 °C; 1H NMR (300 MHz, CDCl₃) δ 7.24-7.19 (m, 2H), 6.83-6.79 (m, 1H), 6.91-6.89 (m, 1H), 6.83 (d, 1H), 6.75-6.68 (m, 2H), 5.90-5.83 (m, 2H), 4.02-3.97 (m, 2H), 1.74-1.53 (m, 2H), 1.33-1.20 (m, 4H), 0.87-0.82 (m, 3H); 13C NMR (75 MHz, CDCl₃) δ 176.5, 151.1, 148.0, 147.9, 141.1, 140.6, 133.4, 131.3, 131.0, 130.6, 125.0, 118.9, 114.2, 108.2, 108.0, 107.6, 106.7, 106.2, 101.3, 101.0, 98.3, 77.7, 77.5, 42.0, 34.7, 29.2, 22.7, 14.1; MS (ES+) m/z 390 (M - 17).

EXAMPLE 56

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(2-cyclopropylethyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (30%): mp 110-112 °C; 1H NMR (300 MHz, CDCl₃) δ 7.33-7.25 (m, 2H), 7.05 (d, 1H), 6.91-6.89 (m, 2H), 6.83-6.79 (m, 1H), 6.73-6.70 (m, 1H), 5.91 (d, 2H), 3.92-3.68 (m, 2H), 3.68-3.22 (br, 1H), 1.68-1.50 (m, 2H), 0.73-0.65 (m, 1H), 0.47-0.34 (m, 2H), 0.08-0.03 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 177.1, 147.9, 147.7, 143.1, 134.1, 131.5, 129.8, 125.0, 123.2, 118.9, 109.0, 108.2, 106.3, 101.2, 77.4, 77.2, 40.4, 32.4, 8.6, 4.4, 4.3; MS
EXAMPLE 57

Synthesis of 3-(1,3-benzodioxol-5-yO-6-chloro-S-hydroxy-i-pentyl-i-3,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-pentyl-6-chloro-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (79%): mp 103-105 °C; 1H NMR (300 MHz, CDCl3) δ 7.24-7.15 (m, 1H), 7.04-7.00 (m, 1H), 6.87-6.80 (m, 2H), 6.75-6.69 (m, 2H), 5.92-5.91 (m, 2H), 3.66 (m, 2H), 3.49-3.32 (br, 1H), 1.72-1.59 (m, 2H), 1.38-1.23 (m, 4H), 0.90-0.85 (m, 3H); 13C NMR (75 MHz, CDCl3) δ 177.6, 148.1, 147.8, 142.2, 139.7, 136.8, 107.0, 106.1, 103-105 °C; 13C NMR (75 MHz, CDCl3) δ 177.2, 148.0, 147.8, 144.1, 135.6, 133.6, 130.1, 125.9, 123.2, 118.7, 109.7, 108.3, 106.1, 101.3, 77.4, 40.5, 29.0, 26.9, 22.3, 13.9; MS (ES+) m/z 356 (M-17).

EXAMPLE 58

Synthesis of 3-(1,3-benzodioxol-5-yI)-3-hydroxy-1-pentyl-7-trifluoromethyl-7/-/-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-pentyl-7-trifluoromethyl-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (89%): mp 115-117 °C; 1H NMR (300 MHz, CDCl3) δ 7.58 (d, 1H), 7.40 (d, 1H), 7.10 (t, 1H), 6.82-6.80 (m, 1H), 6.75-6.67 (m, 2H), 5.90 (s, 2H), 4.23 (s, 1H), 3.87-3.81 (m, 2H), 1.63-1.58 (m, 2H), 1.32-1.19 (m, 4H), 0.89-0.84 (m, 3H); 13C NMR (75 MHz, CDCl3) δ 178.9, 148.0, 147.8, 138.0, 134.9, 128.6, 127.8, 122.9, 121.6, 119.8, 119.0, 118.7, 113.7, 112.9, 108.3, 107.0, 106.0, 101.3, 77.5, 42.8, 28.9, 22.3, 18.2, 14.0; MS (ES+) m/z 390 (M-17).

EXAMPLE 59

Synthesis of 3-(1,3-benzodioxol-5-yI)-3-hydroxy-1-(2-iodobenzyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 1-(2-iodobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (45%): mp 130-132 °C; 1H NMR (300 MHz, CDCl3) δ 7.86 (d, 1H), 7.31 (dd, 1H), 7.24-7.17 (m, 2H), 7.07 (dt, 1H) 6.98-6.92 (m, 3H), 6.86 (dd, 1H), 6.74 (d, 1H), 6.65 (d, 1H), 5.94 (dd, 2H), 4.92 (q, 2H), 2.90 (br, 1H); 13C NMR (75 MHz, CDCl3) δ 177.6, 148.1, 147.8, 142.2, 139.7, 136.8,
133.9, 131.3, 130.0, 129.4, 128.8, 127.0, 125.0, 123.8, 119.1, 110.0, 108.3, 106.5, 101.3, 97.7, 77.9, 49.1; MS (ES+) m/z 467 (M - 17).

EXAMPLE 60
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (76%): mp 177-178 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.30-6.70 (m, 11H), 5.93 (dd, 2H), 4.94 (d, 1H), 4.79 (d, 1H), 3.23 (br, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 177.7, 148.0, 147.7, 142.1, 133.9, 133.9, 133.7, 131.7, 129.8, 129.1, 128.7, 125.1, 123.8, 119.0, 109.6, 108.2, 106.4, 101.3, 77.8, 43.3.

EXAMPLE 61
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (67%): mp 172-173 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.29-7.20 (m, 2H), 7.09-7.02 (t, 1H), 6.92 (d, 1H), 6.83-6.71 (m, 6H), 5.94-5.90 (m, 4H), 4.88 (d, 1H), 4.73 (d, 1H), 3.2 (br, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 177.2, 148.0, 147.8, 147.3, 147.1, 142.7, 135.6, 133.3, 130.5, 129.7, 125.0, 123.3, 121.2, 119.2, 110.0, 108.7, 108.3, 108.2, 106.8, 101.6, 101.5, 77.2, 42.9.

EXAMPLE 62
Synthesis of 1-(4-chlorobenzyl)-3-(2,5-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phennylmagnesium bromide with 2,5-dimethoxymagnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (47%): \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.56 (d, 1H), 7.35-7.09 (m, 6H), 6.92 (d, 1H), 6.83-6.71 (m, 6H), 5.94-5.90 (m, 4H), 4.88 (d, 1H), 4.73 (d, 1H), 3.2 (br, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 177.4, 160.7, 156.8, 143.6, 136.3, 133.9, 131.3, 130.0, 129.4, 128.8, 127.0, 125.0, 123.8, 119.1, 110.0, 108.3, 106.5, 101.3, 97.7, 77.9, 49.1; MS (ES+) m/z 467 (M - 17).
EXAMPLE 63

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-benzyl-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 1-benzyl- 7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (82%): mp 171-172 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.18 (m, 7H), 7.22 (t, 1H), 6.93 (d, 1H), 6.85-6.72 (m, 3H), 5.93 (q, 2H), 5.0 (d, 1H), 4.81 (s, 1H), 3.25 (br, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.2, 147.8, 147.3, 142.8, 136.8, 135.7, 133.3, 129.8, 129.1, 127.9, 127.7, 125.1, 123.3, 119.2, 109.9, 108.3, 106.8, 101.6, 77.2, 43.2.

EXAMPLE 64

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methoxybenzyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 1-(3-methoxybenzyl)-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (60%): mp 145-148 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.18 (m, 3H), 7.40 (t, 1H), 6.94-6.70 (m, 7H), 5.93 (q, 2H), 5.01 (d, 1H), 4.73 (d, 1H), 3.72 (s, 3H), 3.28 (br, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.7, 160.0, 147.9, 147.6, 142.4, 137.0, 134.2, 131.8, 129.9, 129.7, 124.9, 123.6, 119.5, 119.0, 113.4, 112.6, 109.8, 108.2, 106.5, 101.2, 77.8, 55.2, 43.9.

EXAMPLE 65

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(3-methoxyphenyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with 3-methoxyphenylmagnesium bromide, and 1-pentyl-7/-/-indole-2,3-dione with 1-(4-chlorobenzyl)-7/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (48%): mp 175-176 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.17 (m, 7H), 7.08-6.98 (m, 2H), 6.9-6.8 (m, 2H), 6.73 (d, 1H), 4.97 (d, 1H), 4.78 (d, 1H), 3.77 (s, 3H), 3.31 (br, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.2, 159.7, 143.3, 142.6, 135.8, 133.5, 132.6, 129.8, 129.7, 129.1, 125.1, 123.4, 118.0, 113.3, 11.9, 109.9, 77.4, 55.4, 42.6.
EXAMPLE 66
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(2-methoxyphenyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with 2-methoxyphenylmagnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (44%): mp 175-176 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.71 (d, 1H), 7.38-6.62 (m, 9H), 6.81 (d, 1H), 6.72 (d, 1H), 4.98 (d, 1H), 4.81 (d, 1H), 3.61 (br, 1H), 3.43 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.2, 155.8, 143.7, 136.3, 132.8, 132.5, 130.2, 130.1, 129.4, 129.2, 129.0, 127.5, 123.9, 122.5, 120.8, 112.0, 109.0, 75.1, 55.8, 42.7.

EXAMPLE 67
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with 4-methoxyphenylmagnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (63%): mp 195-196 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.28-6.71 (m, 11H), 5.93 (m, q, 2H), 4.93 (d, 1H), 4.75 (d, 1H), 3.76 (s, 3H), 3.16 (br, 1H); $^{13}$C NMR (75 MHz, DMSO-Cl$_6$) δ 177.2, 159.1, 147.8, 147.3, 142.8, 135.7, 133.4, 129.7, 129.2, 128.6, 125.0, 123.2, 119.2, 114.5, 110.0, 108.2, 106.8, 101.6, 77.2, 55.5, 42.6.

EXAMPLE 68
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(3,4-dichlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(3,4-dichlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (59%): mp 177-179 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.40-7.22 (m, 4H), 7.14-7.08 (m, 2H), 6.92 (s, 1H), 6.82-6.70 (m, 3H), 5.95-5.93 (m, 2H), 4.94 (d, 1H), 4.77 (d, 1H), 3.15 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.3, 147.8, 147.3, 137.4, 135.4, 133.3, 131.8, 131.3, 130.6, 129.9, 129.7, 128.1, 125.2, 123.5, 119.2, 109.8, 108.3, 106.8, 101.6, 77.2, 42.1.
EXAMPLE 69

Synthesis of 1-(4-chlorobenzyl)-3-(3,4-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with 3,4-dimethoxyphenylmagnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (50%): mp 155-158 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.33-7.20 (m, 6H), 7.10-7.02 (m, 2H), 6.78-6.72 (m, 3H), 4.99 (d, 1H), 4.74 (d, 1H), 3.83 (s, 6H), 3.20 (br, 1H); MS (ES+) m/z 432.5 (M + 23).

EXAMPLE 70

Synthesis of 3-benzyl-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with benzylmagnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (33%): mp 210 °C (dec); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.45-6.85 (m, 11H), 6.51 (d, 1H), 6.35 (d, 1H), 5.0 (d, 1H), 4.35 (d, 1H), 3.40 (d, 1H), 3.30 (d, 1H), 3.11 (br, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.4, 142.5, 135.3, 135.0, 132.1, 130.9, 130.6, 129.5, 129.0, 128.8, 128.2, 127.0, 124.9, 122.7, 109.3, 77.2, 44.0, 42.2.

EXAMPLE 71

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with 4-methoxyphenylmagnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (63%): mp 195-196 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.33-7.18 (m, 8H), 7.05 (t, 1H), 6.84 (d, 2H), 6.72 (d, 1H), 4.95 (d, 1H), 4.78 (d, 1H), 3.78 (s, 3H), 3.24 (br, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.5, 159.3, 142.6, 135.8, 133.6, 132.6, 129.7, 129.1, 127.3, 125.1, 123.4, 14.1, 109.8, 77.1, 55.5, 42.5.
EXAMPLE 72

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione and 1-(4-trifluorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (73%): mp 164-166 °C; 1H NMR (300 MHz, CDCl₃) δ 7.33-7.24 (m, 3H), 7.10 (t, 1H), 6.94-6.87 (m, 3H), 6.80-6.69 (m, 4H), 5.94 (s, 2H), 4.87 (d, 1H), 4.77 (d, 1H), 3.30 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.4, 152.5, 152.4, 152.4, 152.3, 149.2, 149.2, 149.1, 149.0, 147.8, 147.3, 142.2, 140.3, 140.1, 139.9, 137.0, 136.8, 136.6, 135.3, 134.2, 134.1, 134.1, 134.0, 133.3, 130.0, 125.2, 123.6, 119.2, 112.4, 112.4, 112.2, 112.2, 109.8, 108.2, 106.8, 101.6, 77.2, 42.1.

EXAMPLE 73

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-phenyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (88%): mp 144-145 °C; 1H NMR (300 MHz, CDCl₃) δ 7.60-6.82 (m, 13H), 4.88 (br, 2H); 13C NMR (75 MHz, CDCl₃) δ 177.4, 142.7, 141.7, 135.8, 133.6, 132.6, 129.8, 129.7, 129.1, 128.7, 128.1, 125.9, 125.1, 123.5, 109.9, 77.6, 42.6; MS (ES+) m/z 350.4 (M + 1).

EXAMPLE 74

Synthesis of 1-(4-chlorobenzyl)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with (2,3-dihydro-1,4-benzodioxin-6-yl)magnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (37%): mp 184-185 °C; 1H NMR (300 MHz, CDCl₃) δ 7.30-7.18 (m, 4H), 7.04 (t, 1H), 6.92 (d, 2H), 6.82 (m, 2H), 6.7 (d, 2H), 4.95 (d, 1H), 4.78 (d, 1H), 4.21 (s, 4H), 3.3 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.3, 143.5, 143.5, 142.6, 135.8, 134.6, 133.4, 132.6, 129.7, 129.1, 125.1, 123.4, 118.8, 117.2, 115.0, 109.8, 77.0, 64.5, 42.5.
EXAMPLE 7

Synthesis of 3-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with (2,3-dihydro-1,4-benzodioxin-6-yl)magnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-methoxybenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (45%): mp 197-198 °C; 1H NMR (300 MHz, CDCl₃) δ 7.29-7.17 (m, 4H), 7.02 (t, 1H), 6.92-6.74 (m, 5H), 4.93 (d, 1H), 4.76 (d, 1H), 4.22 (s, 4H), 3.76 (s, 3H), 3.0 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.2, 159.1, 143.5, 143.4, 142.8, 134.8, 133.4, 129.6, 129.2, 128.6, 125.0, 123.2, 118.8, 117.2, 115.0, 114.5, 109.9, 77.0, 64.5, 55.5, 42.61.

EXAMPLE 76

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(4-fluorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (68%): mp 195-196 °C; 1H NMR (300 MHz, CDCl₃) δ 7.30-7.20 (m, 4H), 7.09-6.96 (m, 3H), 6.91 (d, 1H), 6.83-6.71 (m, 3H), 5.93 (q, 2H), 4.94 (d, 1H), 4.79 (d, 1H), 3.25 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.2, 163.6, 160.4, 147.8, 147.3, 142.6, 135.6, 133.3, 1330, 132.9, 129.9, 129.8, 125.1, 123.4, 119.2, 116.0, 115.7, 109.9, 108.3, 106.8, 101.6, 77.2, 42.5.

EXAMPLE 77

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-bromobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(4-bromobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (46%): mp 179-180 °C; 1H NMR (300 MHz, CDCl₃) δ 7.45-6.70 (m, 11H), 5.93 (q, 2H), 4.94 (d, 1H), 4.79 (d, 1H), 3.25 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.3, 163.6, 160.4, 147.8, 147.3, 142.6, 135.6, 133.3, 1330, 132.9, 129.9, 129.8, 125.1, 123.4, 119.2, 116.0, 115.7, 109.9, 108.3, 106.8, 101.6, 77.2, 42.7.
EXAMPLE 78
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(2-bromobenzyl)-3-hydroxy-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(2-bromobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (29%): 1H NMR (300 MHz, CDCl₃) δ 7.58 (d, 1H), 7.33-6.68 (m, 10H), 5.94 (q, 2H), 5.08 (d, 1H), 4.94 (d, 1H), 3.4 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.3, 147.8, 147.4, 142.7, 135.4, 135.0, 133.3, 133.2, 130.0, 129.9, 128.4, 128.0, 125.2, 123.6, 122.6, 119.4, 109.7, 108.5, 108.3, 107.0, 101.6, 77.3, 43.8.

EXAMPLE 79
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3,4,5-trimethoxybenzyl)-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(3,4,5-trimethoxybenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (33%): mp 158-161 ⁰C; 1H NMR (300 MHz, CDCl₃) δ 7.30-6.70 (m, 7H), 6.46 (s, 2H), 5.92 (s, 2H), 5.07 (d, 1H), 4.61 (d, 1H), 3.79 (s, 3H), 3.76 (s, 6H), 3.20 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.8, 153.5, 147.9, 147.6, 142.3, 134.2, 131.8, 131.1, 129.7, 124.9, 123.7, 118.9, 109.7, 108.1, 106.3, 103.9, 101.3, 77.8, 60.8, 56.0, 44.0.

EXAMPLE 80
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-cyclohexylmethyl-3-hydroxy-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(cyclohexylmethyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (28%): mp 164-165 ⁰C; 1H NMR (300 MHz, CDCl₃) δ 7.35-6.70 (m, 7H), 5.92 (s, 2H), 5.07 (d, 1H), 4.61 (d, 1H), 3.79 (s, 3H), 3.76 (s, 6H), 3.20 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.8, 147.8, 147.5, 143.3, 134.3, 131.9, 129.6, 124.9, 123.3, 118.9, 109.3, 108.1, 106.4, 101.2, 77.6, 46.6, 36.3, 30.9, 26.2, 25.7, 25.7.
EXAMPLE 81
Synthesis of 3-hydroxy-1-(4-methoxybenzyl)-3-naphthalen-2-yl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with naphthyl-2-magnesium bromide, and 1-pentyl-7H-indole-2,3-dione with 1-(4-methoxybenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (55%): mp 163-165 °C; 1H NMR (300 MHz, CDCl₃) δ 8.05-6.88 (m, 15H), 5.15 (d, 1H), 4.81 (d, 1H), 3.80 (s, 3H), 3.27 (br, 1H); 13C NMR (75 MHz, CDCl₃) δ 177.0, 159.3, 142.9, 136.5, 134.2, 133.5, 130.1, 130.0, 129.9, 129.4, 129.3, 128.5, 126.3, 125.9, 125.7, 125.6, 124.7, 123.3, 77.6, 55.6, 43.1.

EXAMPLE 82
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(2-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(2-trifluoromethylbenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (65%): mp 168-170 °C; 1H NMR (300 MHz, CDCl₃) δ 7.74-6.58 (m, 11H), 5.95 (q, 2H), 5.17 (d, 1H), 5.10 (d, 1H), 3.15 (br, 1H); 13C NMR (75 MHz, DMSO-d₆) δ 177.5, 147.8, 147.3, 142.6, 135.4, 134.5, 133.4, 133.3, 130.0, 128.4, 127.2, 127.0, 126.8, 126.8, 126.7, 126.6, 125.3, 123.7, 109.5, 108.2, 106.9, 101.6, 77.2, 40.2, 40.2.

EXAMPLE 83
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(2-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-(2-chlorobenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (60%): mp 144-146 °C; 1H NMR (300 MHz, CDCl₃) δ 7.43-6.70 (m, 11H), 5.93 (q, 2H), 5.17 (d, 1H), 5.10 (d, 1H), 3.15 (br, 1H); 13C NMR (75 MHz, DMSO-d₆) δ 177.3, 147.8, 147.3, 142.7, 135.5, 133.5, 133.3, 132.5, 130.1, 129.9, 129.6, 128.3, 127.9, 125.2, 123.5, 119.4, 109.7, 108.2, 107.0, 101.6, 77.3, 41.3.
EXAMPLE 84

Synthesis of 3-(1,3-benzodioxol-5-yl)-4-chloro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-4H-indole-2,3-dione with 1-pentyl-4-chloro-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (45%): mp 140-142 °C; 1H NMR (300 MHz, CDCl₃) δ 7.28 (dd, 1H), 7.01 (d, 1H), 6.85-6.71 (m, 4H), 5.92-5.90 (m, 2H), 3.75-3.53 (m, 2H), 3.26-3.21 (s, 1H), 1.72-1.62 (m, 2H), 1.34-1.28 (m, 4H), 0.87-0.82 (m, 3H); 13C NMR (75 MHz, CDCl₃) δ 175.6, 148.0, 147.8, 144.9, 131.8, 131.2, 128.1, 124.0, 118.9, 108.9, 107.4, 106.2, 101.3, 78.2, 40.5, 28.9, 26.9, 22.3, 13.9; MS (ES+), m/z 356 (M - 17).

EXAMPLE 85

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(6-methoxypyridin-3-yl)-1,3-dihydro-2H-indol-2-one

To a solution of 5-bromo-2-methoxypyridine (1.88 g, 10.0 mmol) in anhydrous THF (25.0 mL) was added a solution of t-BuU (5.88 mL, 10.0 mmol, 1.7 M in pentane) at -78 °C. The yellow solution was stirred for 0.5 h, and added to a solution of 1-(4-chlorobenzyl)-1H-indole-2,3-dione (1.36 g, 5.00 mmol) in anhydrous THF (25.0 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h and at ambient temperature for 3 h. The reaction was quenched with the addition of saturated ammonium chloride (30.0 mL) and extracted with ethyl acetate (3 x 30.0 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/hexane (4:1) to give the title compound (0.35 g, 18%) as a yellow solid: mp 182-184 °C; 1H NMR (300 MHz, DMSO-d₆) δ 7.98 (dd, 1H), 7.53 (dd, 1H), 7.40-7.27 (m, 4H), 7.24 (dt, 2H), 7.04 (dt, 1H), 6.96 (d, 1H), 6.91 (s, 1H), 6.76 (dd, 1H), 4.86 (ABq, 2H); 13C NMR (75 MHz, DMSO-d₆) δ 176.9, 163.7, 144.5, 142.6, 137.5, 135.7, 132.6, 132.4, 130.3, 130.1, 129.7, 129.1, 125.2, 123.6, 110.7, 110.0, 75.9, 53.7, 42.6; MS (ES+) m/z 380 (M).
δ 7.60 (t, 1H), 7.41-7.30 (m, 6H), 7.23 (dt, 1H), 7.03 (d, 1H), 6.90 (d, 1H), 6.68 (s, 1H), 6.51 (dd, 1H), 4.86 (s, 2H); 13C NMR (75 MHz, DMSO-d6) δ 175.4, 174.6, 152.4, 142.7, 136.8, 135.3, 132.6, 131.1, 130.6, 130.0, 129.6, 129.3, 124.9, 123.3, 109.9, 109.8, 72.6, 42.4; MS (ES+) m/z 322 (M - 17).

EXAMPLE 87

Synthesis of 1-(4-chlorobenzyl)-3-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 7-bromo-3,4-dihydro-2H-indol-2-one, the title compound was obtained as a colorless solid (16%): mp 188-190 0C; 1H NMR (300 MHz, DMSO-d6) δ 7.39-7.31 (m, 4H), 7.23 (t, 1H), 7.16 (d, 1H), 7.01 (t, 1H), 6.93 (d, 1H), 6.88-6.84 (m, 1H), 6.76-6.74 (m, 2H), 4.91-4.80 (m, 2H), 4.05 (br, 4H), 3.30 (br, 1H), 2.03 (s, 2H); 13C NMR (75 MHz, DMSO-d6) δ 117.2, 151.0, 150.9, 142.6, 136.7, 135.3, 133.3, 132.6, 129.8, 129.7, 129.1, 125.1, 123.4, 121.7, 120.9, 119.3, 109.8, 76.9, 70.9, 70.8, 42.5, 32.0; MS (ES+) m/z 404 (M - 17).

EXAMPLE 88

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-pyrimidin-5-yl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 5-bromopyrimidine, the title compound was obtained as a colorless solid (14%): mp 155-157 0C; 1H NMR (300 MHz, CDCl3) δ 9.03 (s, 1H), 8.71 (s, 2H), 7.32-7.23 (m, 4H), 7.18 (d, 1H), 7.10 (t, 1H), 6.79 (d, 1H), 4.83 (ABq, 2H); 13C NMR (75 MHz, CDCl3) δ 176.0, 154.7, 142.2, 134.0, 133.9, 133.4, 130.9, 129.6, 129.3, 128.7, 125.3, 124.3, 110.1, 75.3, 43.6; MS (ES+) m/z 352 (M + 1).

EXAMPLE 89

Synthesis of 3-(1H-benzothiazol-6-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 6-bromo-1H-benzothiazole, the title compound was obtained as a colorless solid (13%): mp 185-187 0C; 1H NMR (300 MHz, DMSO-d6) δ 8.42 (d, 1H), 7.82 (s, 1H), 7.61 (d, 1H), 7.58 (d, 1H), 7.48-7.41 (m, 4H), 7.25 (d, 2H), 7.00 (t, 1H), 6.95 (t, 1H), 4.97 (ABq, 2H); 13C NMR (75 MHz, DMSO-d6) δ 175.4, 174.6, 152.4, 142.7, 136.8, 135.3, 132.6, 131.1, 130.6, 130.0, 129.6.
EXAMPLE 90

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 6-bromobenzofuran, and 1-(4-chlorobenzyl)-7H-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (11%): mp > 200 °C; ¹H NMR (300 MHz, DMSO-CD₆) δ 7.84 (d, 1H), 7.61 (d, 1H), 7.43 (d, 1H), 7.37-7.17 (m, 3H), 7.02 (t, 1H), 6.91-6.87 (m, 4H), 5.96 (s, 2H), 4.84 (ABq, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 174.9, 174.6, 158.0, 156.4, 154.9, 153.8, 142.6, 135.5, 135.4, 132.6, 130.7, 130.5, 130.3 130.2, 130.0, 129.5, 129.2, 127.9, 127.7, 125.3, 125.0, 124.4, 123.6, 123.5, 123.5, 121.9, 115.9, 113.8, 111.7, 110.3, 110.2, 104.9, 104.6, 74.5, 74.4, 42.6; MS (ES+) m/z 382 (M - 17).

EXAMPLE 91

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 6-bromobenzofuran, the title compound was obtained as a colorless solid (8%): mp > 200 °C (dec); ¹H NMR (300 MHz, DMSO-CZ₂) δ 7.84 (d, 1H), 7.60 (dd, 1H), 7.50-7.35 (m, 6H), 7.30-7.17 (m, 2H), 7.03 (t, 1H), 6.96 (d, 1H), 6.91 (s, 1H), 4.94 (ABq, 2H), 3.29 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 174.9, 174.6, 156.4, 154.9, 142.6, 135.5, 135.4, 132.6, 130.5, 130.3, 129.5, 129.1, 127.9, 127.7, 125.3, 125.0, 123.6, 121.9, 115.9, 113.8, 111.6, 110.2, 104.9, 104.6, 74.5, 74.4, 42.6; MS (ES+) m/z 372 (M - 17).

EXAMPLE 92

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 3-(1-pyrrolyl)bromobenzene, and 1-(4-chlorobenzyl)-7H-indole-2,3-dione with 1-(4-methoxybenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (7%): ¹H NMR (300 MHz, CDCl₃) δ 7.39 (t, 1H), 7.34 (d, 1H), 7.30-7.21 (m, 5H), 7.04 (d, 1H), 6.98 (t, 2H), 6.87-6.82 (m,
4H); 6.29 (t, 2H), 5.00 (d, 1H), 4.85 (s, 1H), 4.72 (d, 1H), 3.76 (s, 3H); 13C NMR (75 MHz, CDCl 3 ) δ 177.2, 159.3, 142.6, 142.1, 141.0, 131.5, 130.0, 129.9, 128.8, 127.5, 124.9, 123.7, 122.4, 120.3, 119.3, 117.4, 114.3, 110.5, 109.9, 77.8, 55.3, 43.6; MS (ES+) m/z 411 (M + 1), 393 (M - 17).

EXAMPLE 93

Synthesis of 3-(1,3-benzoxazol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxpyridine with 5-bromobenzoaxazole, and 1-(4-chlorobenzyl)-7H-indole-2,3-dione with 1-pentyl-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (21%): m p 189-191 °C; 1H NMR (300 MHz, DMSO-d 6 ) δ 7.95 (d, 1H), 7.72-7.67 (m, 2H), 7.54 (d, 1H), 7.36 (t, 2H), 7.12 (d, 1H), 7.03 (t, 1H), 3.69 (t, 2H), 1.65-1.52 (m, 2H), 1.35-1.22 (m, 4H), 0.80 (t, 3H); 13C NMR (75 MHz, DMSO-(d 6 )) δ 173.1, 165.4, 149.9, 143.2, 142.3, 131.1, 129.1, 129.0, 125.4, 123.3, 123.2, 117.3, 113.4, 110.1, 74.6, 40.8, 28.7, 26.9, 22.2, 14.3; MS (ES+) m/z 357 (M + 1), 319 (M - 17).

EXAMPLE 94

Synthesis of 1-(4-chlorobenzyl)-3-(2,2-difluoro-1,3-benzoxazol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxpyridine with 5-bromo-2,2-difluoro-1,3-benzoxazole, the title compound was obtained as a colorless solid (20%): m p 150-152 °C; 1H NMR (300 MHz, CDCl 3 ) δ 7.36 (dd, 1H), 7.30 (s, 3H), 7.27-7.22 (m, 2H), 7.10 (t, 1H), 7.06-6.97 (m, 3H), 6.73 (d, 1H), 4.90 (ABq, 2H), 3.73 (br, 1H); 13C NMR (75 MHz, CDCl 3 ) δ 175.8, 143.8, 142.6, 139.9, 133.8, 133.6, 130.5, 129.2, 129.1, 128.8, 128.7, 124.9, 123.9, 123.8, 123.2, 121.0, 109.8, 109.7, 75.5, 43.7; MS (ES+) m/z 430 (M + 1).

EXAMPLE 95

Synthesis of 3-(2,2-difluoro-1,3-benzoxazol-5-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxpyridine with 5-bromo-2,2-difluoro-1,3-benzoxazole, and 1-(4-chlorobenzyl)-7H-indole-2,3-dione with 1-(4-methoxybenzyl)-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (31%): m p 88-90 °C; 1H NMR (300 MHz, CDCl 3 ) δ 7.36 (d, 1H), 7.27 (d, 2H), 7.21 (d, 2H), 7.07 (d,
1H), 7.03-6.95 (m, 2H), 6.84 (d, 2H), 6.78 (d, 1H), 4.86 (ABq, 2H), 4.21 (br, 1H), 3.76 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 175.9, 159.2, 143.8, 142.8, 139.9, 130.3, 129.5, 128.8, 127.1, 124.8, 123.7, 123.6, 123.4, 121.1, 114.2, 110.0, 109.5, 75.6, 55.3, 43.9; MS (ES+) m/z 448 (M + 23).

EXAMPLE 96

Synthesis of 3-hydroxy-3-[6-(hydroxymethyl)-1,3-benzodioxol-5-yl]-1-pentyl-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with (6-bromo-1,3-benzodioxol-5-yl)methanol (Mann, J., et al, J. Chem. Soc. Perkin Trans. 1 (1984):2081-8), the title compound was obtained as a colorless solid (45%): mp 120-122 °C; 1H NMR (300 MHz, CDCl₃) δ 7.38-7.24 (m, 2H), 7.11 (t, 1H), 6.91 (d, 1H), 6.81 (s, 1H), 6.43 (s, 1H), 5.90-5.87 (m, 2H), 4.77 (dd, 2H), 3.75-3.56 (m, 2H), 1.58-1.75 (m, 2H), 1.35-1.26 (m, 2H), 0.89-0.83 (m, 3H); 13C NMR (75 MHz, CDCl₃) δ 177.8, 147.4, 147.2, 142.8, 133.5, 132.2, 131.1, 130.1, 125.3, 123.8, 111.4, 109.2, 108.1, 101.5, 79.5, 64.7, 40.4, 29.0, 26.8, 22.3, 13.9; MS (ES+) m/z 352.1 (M - 17).

EXAMPLE 97

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-thiophen-2-yl-1,3-dihydro-2H-indol-2-one

To a solution of thiophene (0.84 g, 10.0 mmol) in THF (50.0 mL) was added n-BuLi (6.50 mL, 1.6 M, 11.0 mmol) at -35 °C. The reaction mixture was stirred at -30 °C for 30 min. The generated lithiated species was added into a solution of 1-(4-chlorobenzyl)-7H-indole-2,3-dione (2.70 g, 10.0 mmol) in THF (50.0 mL) at -78 °C and the resulting mixture was stirred at ambient temperature for 16 h. The reaction mixture was quenched with saturated NH₄Cl solution and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography (SiO₂, MeOH:CH₂Cl₂ - 1:20-1:10) to give 1.21 g (34%) of the title compound as a colorless solid: mp 140-143 °C; 1H NMR (300 MHz, CDCl₃) δ 7.50-6.85 (m, 11H), 6.68 (d, 1H), 4.85 (s, 2H); 13C NMR (75 MHz, CDCl₃) δ 176.0, 145.3, 142.2, 135.7, 132.6, 132.4, 130.2, 129.6, 129.1, 127.1, 127.0, 125.3, 123.4, 110.0, 75.5, 42.6.

EXAMPLE 98

Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-[2-(2-thienyl)-1,3-dithian-2-yl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 97, and making non-critical
variations to replace thiophene with 2-(2-thienyl)-1,3-dithiane, the title compound was obtained as a colorless solid (26%): mp 166 °C (dec); 1H NMR (300 MHz, CDCl₃) δ 7.53 (d, 1H), 7.28-6.80 (m, 10H), 6.40 (d, 1H), 4.85 (d, 1H), 4.44 (d, 1H), 4.03 (s, 1H), 3.00-2.75 (m, 4H), 2.00-1.86 (m, 2H); 13C NMR (75 MHz, CDCl₃) δ 174.6, 144.7, 143.3, 135.5, 132.4, 131.0, 130.1, 129.7, 128.8, 128.7, 127.0, 126.5, 121.7, 108.8, 80.7, 62.4, 42.7, 27.5, 24.5.

EXAMPLE 99
Synthesis of 1-(4-chlorobenzyl)-3-(4-fluorophenylethynyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 97, and making non-critical variations to replace thiophene with 1-ethyl-4-fluorobenzene, the title compound was obtained as a colorless solid (71%): mp 153-154 °C; 1H NMR (300 MHz, CDCl₃) δ 7.60 (m, 1H), 7.30-7.00 (m, 10H), 6.68 (d, 1H), 4.88 (s, 2H), 3.70 (s, 1H); 13C NMR (75 MHz, CDCl₃) δ 171.1, 161.3, 158.1, 132.8, 132.8, 128.8, 128.7, 128.0, 127.0, 126.6, 125.9, 122.4, 121.3, 121.1, 121.0, 116.2, 115.9, 114.6, 114.3, 107.7, 86.4, 81.3, 81.2, 66.8, 60.2; MS (ES+) m/z 391.6 (M + 1), 413.8 (M + 23).

EXAMPLE 100
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one
To a solution of 1-pentyl-1H-indole-2,3-dione (1.42 g, 5.32 mmol) in anhydrous THF (30.0 mL) was added a solution of 3,4-(methylenedioxy)phenylmagnesium bromide (5.90 mL, 1.0 M solution in toluene/THF, 50:50) under nitrogen at -78 °C. The reaction mixture was stirred at -78 °C for 1 h and at ambient temperature for 4 h, and quenched with saturated ammonium chloride (30.0 mL). The mixture was extracted with ethyl acetate (3 x 50.0 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness to give 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one. The crude product was dissolved in CH₂Cl₂ (30.0 mL) followed by the additions of 'Pr₂NEt (1.82 g, 2.50 mL, 17.9 mmol) and SOCl₂ (2.50 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 6 h and poured into CH₂Cl₂ (30.0 mL). The mixture was washed with 10% HCl, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The crude product was dissolved in acetic acid/THF (30.0 mL/2.50 mL) followed by the addition of Zn dust (9.50 g, 143 mmol). The reaction mixture was heated at reflux for 6 h and cooled down to ambient temperature. The mixture was filtered and the residue was washed with...
ethyl acetate (100 ml). The filtrate was washed with water (3 x 15.0 ml), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/hexane (30%) to give the title compound (0.11 g, 6%) as a gummy material: \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.29 (t, 1H), 7.14 (d, 1H), 7.02 (t, 1H), 6.88 (d, 1H), 6.75 (d, 1H), 6.68 (dd, 1H), 6.59 (d, 1H), 5.90 (s, 2H), 4.48 (s, 1H), 3.79-3.63 (m, 2H), 1.73-1.64 (m, 2H), 1.36-1.31 (m, 4H), 0.88 (t, 3H); \( ^13C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 175.9, 148.0, 147.1, 143.9, 130.5, 129.2, 128.4, 125.1, 122.5, 121.9, 108.6, 108.4, 101.1, 51.7, 40.2, 29.0, 27.1, 22.4, 14.0; MS (ES+) m/z 324 (M+1).

**EXAMPLE 101**

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-ylmethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 100, and making non-critical variations to replace 1-pentylM-//-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-1/-/-indole-2,3-dione, the title compound was obtained as a colorless solid (37%): mp 117-118 °C; \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.21 (t, 1H), 7.14 (d, 1H), 7.01 (t, 1H), 6.81-6.74 (m, 4H), 6.72-6.68 (m, 2H), 6.61 (d, 1H), 5.91 (s, 2H), 5.90 (s, 2H), 4.81 (ABq, 2H), 4.57 (s, 1H); \( ^13C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 176.1, 148.1, 148.0, 147.2, 147.1, 143.3, 130.2, 129.7, 128.9, 128.4, 125.1, 122.8, 121.2, 120.9, 109.2, 108.7, 108.6, 108.4, 107.9, 101.1, 51.7, 43.8. Anal. Calcd for C\(_{25}\)H\(_{17}\)NO\(_4\): C, 71.31; H, 4.42; N, 3.62. Found: C, 70.89; H, 4.44; N, 3.59.

**EXAMPLE 102**

Synthesis of 3-(1,3-benzodioxol-5-yl)-4,7-dichloro-1-pentyl-1,3-dihydro-2H-indole-2,3-dione

Following the procedure as described in EXAMPLE 100, and making non-critical variations to replace 1-pentyl-7H-indole-2,3-dione with 1-pentyl-4,7-dichloro-7H-indole-2,3-dione, the title compound was obtained as a colorless solid (48%): mp 84-86 °C; \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.24-7.18 (m, 1H), 6.91 (d, 1H), 6.74 (d, 1H), 6.61-6.51 (m, 2H), 5.91 (s, 2H), 4.46 (s, 1H), 4.06-3.99 (m, 2H), 1.71-1.60 (m, 2H), 1.33-1.28 (m, 4H), 0.88-0.84 (m, 3H); \( ^13C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 175.4, 148.0, 147.2, 141.3, 132.1, 130.2, 129.1, 128.1, 123.8, 121.7, 113.5, 108.6, 108.2, 101.2, 51.5, 41.8, 29.5, 28.7, 22.4, 14.01; MS (ES+) m/z 394 (M+1).
EXAMPLE 103

Synthesis of 3-(1,3-benzodioxol-5-yl)-7-fluoro-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 100, and making non-
critical variations to replace 1-pentyl-7/-/-indole-2,3-dione with 1-pentyl-7-fluoro-1/-/-
indole-2,3-dione, the title compound was obtained as a colorless solid (71%): mp 95-97
0°C; 1H NMR (300 MHz, CDCl₃) δ 7.05-6.89 (m, 3H), 6.75 (d, 1H), 6.67-6.63 (m, 1H),
6.56 (d, 1H), 5.91 (s, 2H), 4.49 (s, 1H), 3.89-3.79 (m, 2H), 1.70-1.61 (m, 2H), 1.36-1.29
(m, 4H), 0.89-0.84 (m, 3H); 13C NMR (75 MHz, CDCl₃) δ 175.5, 148.9, 148.1, 147.2,
145.7, 132.0, 132.0, 130.6, 130.5, 130.0, 123.1, 123.0, 121.9, 121.0, 120.9, 116.5,
116.3, 108.6, 108.5, 101.2, 51.9, 51.9, 42.2, 28.8, 28.7, 22.3, 14.0; MS (ES+) m/z 342
(M + 1).

EXAMPLE 104

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

To a colorless solution of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-
hydroxy-1,3-dihydro-2H-indol-2-one (2.00 g, 5.90 mmol) in anhydrous CH₂Cl₂ (40.0
mL) was added trifluoroacetic acid (2.06 g, 17.7 mmol) followed by triethyl silane (2.02
g, 17.7 mmol) at 0°C. The brown reaction solution was stirred at 0°C for 45 minutes
and diluted with CH₂Cl₂ (60.0 mL). The mixture was washed with water (3 x 25.0 mL).
The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate
was concentrated in vacuo to dryness. The residue was crystallized from ethyl acetate
and ether to give the title compound (1.84 g, 83%) as a colorless solid: mp 161-163 0°C;
1H NMR (300 MHz, CDCl₃) δ 7.29-7.20 (m, 5H), 7.17-7.14 (m, 1H), 7.02 (dt, 1H), 6.79-
6.70 (m, 3H), 6.60 (d, 1H), 5.93 (dd, 2H), 4.88 (ABq, 2H), 4.59 (s, 1H); 13C NMR (75
MHz, CDCl₃) δ 176.2, 148.1, 147.2, 143.2, 134.4, 133.6, 130.1, 129.0, 128.9, 128.8,
128.4, 125.3, 123.0, 121.9, 109.0, 108.6, 101.2, 51.6, 43.3; MS (ES+) m/z 378 (M + 1).

EXAMPLE 105

Synthesis of 3-(1,3-benzodioxol-5-yl)-5,7-dimethyl-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 104, and making non-
critical variations to replace 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-
dihydro-2H-indol-2-one with 3-(1,3-benzodioxol-5-yl)-3-hydroxy-5,7-dimethyl-1-pentyl-
1,3-dihydro-2H-indol-2-one, the title compound was obtained as a colorless solid
(43%): mp 111-114 0°C; 1H NMR (300 MHz, CDCl₃) δ 6.84 (s, 1H), 6.77 (d, 1H), 6.74 (s,
1H), 6.65 (dd, 1H), 6.54 (d, 1H), 5.90 (s, 2H), 4.42 (s, 1H), 3.95-3.83 (m, 2H), 2.50 (s,
3H), 2.23 (s, 3H), 1.72-1.60 (m, 2H), 1.38-1.31 (m, 4H), 0.88 (t, 3H); 13C NMR (75
MHz, CDCl$_3$ $\delta$ 177.2, 148.0, 147.0, 138.9, 132.7, 132.2, 130.9, 130.3, 123.8, 122.0, 119.1, 108.6, 108.5, 101.1, 51.6, 42.0, 29.4, 28.8, 22.4, 20.7, 18.8, 14.0; MS (ES$^+$) m/z 352 (M + 1);

**EXAMPLE 106**

Synthesis of 1-(2-cyclopipylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

To a solution of 1,3-benzodioxol-5-ol (1.25 g, 9.06 mmol) in THF (20.0 mL) was added dropwise a solution of isopropylmagnesium chloride solution (4.53 mL, 9.06 mmol, 2.0 M in THF) at 0 $^\circ$C over 5 min. The reaction mixture was stirred for 0.5 h upon which time colorless precipitate was formed. After the solvent was removed under reduced pressure, the residue was dissolved in dichloromethane (20.0 mL) and cooled to 0 $^\circ$C. A solution of 1-(2-cyclopipylethyl)-1H-indole-2,3-dione (1.77 g, 8.23 mmol) in dichloromethane (20.0 mL) was added to the above solution at 0 $^\circ$C. The resulting mixture was stirred at ambient temperature for 16 h and quenched with saturated ammonium chloride solution (30.0 mL). The organic layer was separated and washed with water (3 x 25.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was crystallized from ethyl acetate and ether to give the title compound (2.22 g, 76%) as a colorless solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.52 (s, 1H), 7.46 (d, 1H), 7.37 (dt, 1H), 7.18 (dt, 1H), 6.90 (d, 1H), 6.56 (s, 1H), 6.23 (s, 1H), 5.84 (dd, 2H), 4.55 (s, 1H), 3.87-3.63 (m, 2H), 1.64-1.44 (m, 2H), 0.68-0.55 (m, 1H), 0.41-0.27 (m, 2H), -0.02-(-0.07) (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) 5 179.1, 152.4, 148.8, 142.7, 141.3, 130.3, 129.1, 126.3, 123.7, 117.3, 109.5, 106.9, 101.9, 101.4, 79.3, 40.6, 32.2, 8.6, 4.3, 4.2; MS (ES$^+$) m/z 337.6 (M - 17).

**EXAMPLE 107**

Synthesis of 1-(2-cyclopipylethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

To a solution of 1-(2-cyclopipylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one (2.22 g, 6.27 mmol) in dichloromethane (30.0 mL) was added trifluoroacetic acid (2.12 g, 18.8 mmol) and triethylsilane (2.14 g, 18.8 mmol). The brown solution was stirred at ambient temperature for 0.5 h and concentrated in vacuo to dryness. The residue was diluted with dichloromethane (100 mL), washed with water (3 x 50.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column
chromatography eluting with ethyl acetate/hexane (20/80) to give the title compound (1.69 g, 80%) as a brown solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.21-9.10 (br, 1H), 7.38-7.30 (m, 2H), 7.16 (t, 1H), 6.96 (d, 1H), 6.63 (s, 1H), 6.33 (s, 1H), 5.84 (dd, 2H), 5.01 (s, 1H), 3.87-3.72 (m, 2H), 1.66-1.46 (m, 2H), 0.69-0.59 (m, 1H), 0.43-0.30 (m, 2H), 0.09-0.06 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.8, 151.3, 147.6, 144.1, 141.5, 128.7, 126.2, 123.1, 115.2, 109.5, 109.4, 106.5, 101.5, 101.2, 47.4, 40.5, 32.2, 8.6, 4.3, 4.2; MS (ES+) m/z 338.3 (M + 1).

EXAMPLE 108

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 104, and making non-critical variations to replace 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one with 3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one, the title compound was obtained as a colorless solid (96%): mp 87-89 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30-7.24 (m, 1H), 7.14 (d, 1H), 7.02 (t, 1H), 6.89 (d, 1H), 6.76-6.66 (m, 2H), 6.59 (d, 1H), 5.89 (s, 2H), 4.47 (s, 1H), 3.89-3.71 (m, 2H), 1.68-1.48 (m, 2H), 0.74-0.62 (m, 1H), 0.44-0.38 (m, 2H), 0.05-0.01 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 176.0, 148.0, 147.1, 144.0, 130.4, 129.0, 128.3, 125.1, 122.5, 121.9, 108.7, 108.5, 108.5, 101.5, 51.6, 40.3, 32.4, 8.7, 4.4, 4.3; MS (ES+) m/z 322 (M + 1).

EXAMPLE 109

Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 104, and making non-critical variations to replace 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one with 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained as a colorless solid (70%): mp 101-103 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.67 (br, 1H), 7.39-7.29 (m, 2H), 7.18-7.13 (m, 1H), 6.94 (d, 1H), 6.62 (s, 1H), 6.32 (s, 1H), 5.84 (dd, 2H), 5.01 (s, 1H), 3.71-3.63 (m, 2H), 1.71-1.61 (m, 2H), 1.35-1.27 (m, 4H), 0.86 (t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.8, 151.3, 147.6, 144.0, 141.5, 128.7, 126.4, 126.2, 123.1, 115.3, 109.4, 106.5, 101.5, 101.2, 77.4, 47.4, 40.5, 31.6, 29.0, 27.0, 22.7, 22.3, 14.1, 13.9; MS (ES+) m/z 340 (M + 1).
EXAMPLE 110

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-imidazol-1-yl-1-pentyl-1,3-dihydro-2H-indol-2-one

A mixture of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one (0.34 g, 1.01 mmol), 1,1'-carbonyl diimidazole (0.21 g, 1.31 mmol) in anhydrous CH₂Cl₂ was stirred at ambient temperature for 17 h under nitrogen. The solvent was removed under reduced pressure and the residue was subjected to column chromatography eluting with ethyl acetate/hexane (10% to 50%, gradient) to give the title compound (0.21 g, 54%) as gummy material: ¹H NMR (300 MHz, CDCl₃) δ 7.57 (s, 1H), 7.38 (dt, 1H), 7.29 (d, 1H), 7.11 (d, 1H), 7.08-7.03 (m, 2H), 6.95 (d, 1H), 6.72 (d, 1H), 6.67 (d, 1H), 6.61 (dd, 1H), 5.94 (dd, 2H), 3.80-3.69 (m, 2H), 1.74-1.65 (m, 2H), 1.37-1.28 (m, 4H), 0.86 (t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 148.4, 148.3, 142.4, 136.6, 131.2, 130.5, 129.4, 128.5, 125.8, 123.4, 120.5, 118.5, 109.7, 108.3, 107.4, 101.6, 68.3, 40.6, 28.9, 26.9, 22.2, 13.9; MS (ES+) m/z 390 (M + 1), 322 (M - 67).

EXAMPLE 111

Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-2-oxo-2,3-dihydro-1H-indol-3-y1 acetate

To a solution of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one (0.39 g, 1.00 mmol) in CH₂Cl₂ (15.0 mL) was added Pr₂NEt (0.74 g, 1.00 mL, 5.74 mmol) followed by the addition of acetyl chloride (1.10 g, 1.00 mL, 14.1 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 3 h and quenched by the addition of saturated ammonium chloride (10.0 mL). The organic layer was washed with water (2 x 10.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/hexane (10% to 30%, gradient) to give the title compound (0.14 g, 31%) as a colorless solid: mp 146-148 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.29-7.21 (m, 6H), 7.08 (t, 1H), 7.00 (s, 1H), 6.72-6.63 (m, 3H), 5.95 (dd, 1H), 4.85 (ABq, 2H), 2.16 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.9, 169.1, 148.4, 148.1, 143.2, 134.0, 133.4, 130.1, 130.0, 128.9, 128.7, 127.9, 124.2, 123.2, 120.2, 109.6, 108.0, 107.4, 101.4, 80.9, 43.6, 20.5; MS (ES+) m/z 376 (M - 60).
EXAMPLE 112

Synthesis of diethyl 1-{3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-2-oxo-2,3-dihydro-1H-indol-3-yl}hydrazine-1,2-dicarboxylate

A mixture of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2/-/indol-2-one (1.00 g, 2.54 mmol), triphenylphosphine (0.99 g, 3.81 mmol) and diethyl azodicarboxylate (0.66 g, 3.81 mmol) in CH₂Cl₂ was stirred at ambient temperature for 16 h. The reaction mixture was diluted with CH₂Cl₂ (30.0 mL) and washed with H₂O (3 x 25.0 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was crystallized from ethyl acetate and ether to give the title compound (0.82 g, 58%) as a colorless solid: mp > 220 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.03 (d, 1H), 7.26-7.09 (m, 8H), 6.68 (d, 1H), 6.59 (d, 1H), 5.94-5.91 (m, 3H), 4.84 (ABq, 2H), 4.14-3.96 (m, 4H), 1.16 (t, 3H), 1.03 (t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.7, 155.9, 154.4, 148.2, 147.8, 141.8, 134.2, 133.3, 129.2, 128.9, 128.5, 126.9, 126.6, 123.6, 122.9, 110.0, 109.1, 107.8, 101.4, 72.1, 62.9, 62.0, 43.6, 14.4, 14; MS (ES+) m/z 337 (M+1 17); Anal. Calc’d for C₉₈H₂₆N₉O₇: C, 60.93; H, 4.75; N, 7.61. Found: C, 60.67; H, 4.75; N, 7.61.

EXAMPLE 113

Synthesis of 3,5-bis(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

A mixture of 3-(1,3-benzodioxol-5-yl)-5-bromo-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one (0.47 g, 1.00 mmol) and Pd(PPh₃)₄ (0.12 g, 0.10 mmol) in anhydrous dioxane (12.0 mL) was stirred at ambient temperature for 10 min under nitrogen followed by the additions of a solution of 3,4-methylenedioxy)phenylboronic acid (0.23 g, 1.50 mmol) in ethanol (1.00 mL) , aqueous solution of 2.0 M Na₂CO₃ (2.00 mL). The reaction mixture was heated at reflux for 16 h, cooled to ambient temperature and concentrated under reduced pressure. The residue was diluted with ethyl acetate (30.0 mL), washed with saturated ammonium chloride solution (2 x 10.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was triturated with ethyl acetate to give the title compound (0.35 g, 69%) as a beige solid: ¹H NMR (300 MHz, DMSO-CD₆) δ 7.48 (dd, 1H), 7.41-7.33 (m, 5H), 7.11 (d, 1H), 6.99-6.95 (m, 3H), 6.90 (d, 1H), 6.86 (s, 1H), 6.80 (d, 1H), 6.62 (d, 1H), 5.99 (s, 2H), 5.96 (d, 2H), 4.89 (ABq, 2H); ¹³C NMR (75 MHz, DMSO-CD₆) δ 177.2, 148.4, 147.8, 147.3, 147.0, 141.6, 135.8, 135.5 (2C), 134.5, 133.9, 132.6, 129.7, 129.1,127.9, 123.1, 120.2, 119.2, 110.3, 109.1, 108.3, 107.2, 106.9,
10.16, 77.8, 42.6; MS (ES+) m/z 536 (M + 23), 496 (M - 17).

EXAMPLE 114
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-phenyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 115, and making non-critical variations to replace 3,4-methylenedioxyphenylboronic acid with phenylboronic acid, the title compound was obtained as a colorless solid (56%): 1H NMR (300 MHz, DMSO-CD6) δ 7.51 (d, 1H), 7.48-7.43 (m, 3H), 7.37 (d, 2H), 7.31-7.23 (m, 6H), 6.95 (d, 1H), 6.86 (dd, 1H), 6.79 (d, 1H), 6.74 (d, 1H), 5.93 (d, 2H), 4.98 (d, 1H), 4.82 (d, 1H), 3.47 (br, 1H); 13C NMR (75 MHz, DMSOD) δ 177.5, 148.1, 147.9, 141.9, 140.3, 137.3, 133.9, 133.8, 133.7, 132.0, 129.2, 128.8, 128.7, 128.6, 127.3, 126.8, 124.0, 119.0, 109.9, 108.3, 106.3, 101.3, 77.8, 43.5; MS (ES+) m/z 492 (M + 23), 452 (M - 18).

EXAMPLE 115
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-chloro-1-(4-chlorobenzyl)-1,3-dihydro-2H-indol-2-one

To a solution of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one (2.00 g, 5.09 mmol) in CH2Cl2 (75.0 mL) was added pyridine (0.60 g, 7.63 mmol) followed by SOCl2 (0.72 g, 6.11 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and quenched by the addition of saturated ammonium chloride solution (5.00 mL). The organic layer was washed with saturated ammonium chloride (2 x 15.0 mL). The combined aqueous layers was extracted with CH2Cl2 (25.0 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/hexane (30%) to give the title compound (0.64 g, 31%) as a yellow solid: 1H NMR (300 MHz, CDCl3) δ 7.30-7.24 (m, 5H), 7.20-7.17 (m, 2H), 7.11 (t, 1H), 7.01 (s, 1H), 6.75-6.70 (m, 3H), 5.91 (dd, 2H), 4.85 (dd, 2H); 13C NMR (75 MHz, CDCl3) δ 175.2, 147.9, 147.8, 143.3, 134.1, 133.7, 132.4, 130.1, 129.1, 128.7, 127.7, 125.9, 123.5, 120, 109.5, 108.0, 107.4, 101.2, 83.6, 53.2, 43.3; MS (ES+) m/z 430 (M + 23).

EXAMPLE 116
Synthesis of 3-chloro-1-(4-chlorobenzyl)-3-[2-oxo-2-(2-thienyl)ethyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 115, and making non-
critical variations to replace 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-
dihydro-2H-indol-2-one with 3-hydroxy-1-(4-chlorobenzyl)-3-[2-oxo-2-(2-thienyl)ethyl]-
1,3-dihydro-2/-/-indol-2-one, the title compound was obtained as a colorless solid
(30%): mp 129-131 °C; 1H NMR (300 MHz, CDCl₃) δ 8.13 (dd, 1H), 8.00 (dd, 1H), 7.55
(d, 1H), 7.48-7.34 (m, 4H), 7.27-7.21 (m, 2H), 6.99 (dt, 1H), 6.91 (d, 1H), 4.97 (s, 2H),
4.43 (ABq, 2H), 3.32 (s, 1H); 13C NMR (75 MHz, CDCl₃) δ 188.7, 173.6, 142.6, 142.3,
136.6, 135.4, 132.6, 130.8, 129.6, 129.4, 129.3, 129.1, 124.2, 123.5, 110.2, 62.6, 46.8,
42.9; MS (ES+ m/e 439 (M + 23), 402 (M + 23 - 35).

EXAMPLE 117

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-
dihydro-2H-indol-2-one

A mixture of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-
2-one (1.00 g, 2.95 mmol), sesamole (1.63 g, 11.8 mmol) and p-toluene sulfonic acid
(2.24 g, 11.8 mmol) in 1,2-dichloroethane (25.0 mL) was heated at 80 °C for 12 h.

After cooling to ambient temperature, the mixture was diluted with ethyl acetate (30.0
mL), washed with saturated ammonium chloride (10.0 mL) and brine (10.0 mL). The
combined aqueous layers was extracted with ethyl acetate (2 x 50.0 mL) and the
combined organic layers was dried over anhydrous sodium sulfate and filtered. The
filtrate was concentrated in vacuo to dryness. The residue was subjected to column
chromatography eluting with ethyl acetate/hexane (gradient 20% to 50%) to give a
solid as the title compound that was crystallized from ether and hexane (0.32 g, 24%) as
a colorless solid: mp 75-76 °C; 1H NMR (300 MHz, CDCl₃) δ 9.51 (s, 1H), 7.33-7.27
(m, 1H), 7.10 (d, 1H), 6.95 (d, 1H), 6.68 (d, 1H), 6.56-6.53 (m, 1H), 6.44 (s, 1H), 5.90-
5.88 (m, 2H), 5.83 (d, 1H), 3.87-3.70 (m, 2H), 1.78-1.69 (m, 2H), 1.36-1.31 (m, 4H),
0.88 (t, 3H); 13C NMR (75 MHz, CDCl₃) δ 180.8, 152.7, 148.3, 148.1, 146.9, 141.3,
140.8, 134.4, 132.7, 128.6, 126.9, 123.5, 119.5, 117.0, 109.7, 108.4, 106.3, 107.0,
102.1, 101.3, 101.2, 61.5, 40.7, 31.6, 29.0, 27.0, 22.3, 14.0; MS (ES+) m/z 482 (M +
23), 460 (M + 1).

EXAMPLE 118

Synthesis of tert-butyl (2-oxo-1-pentyl-2,3-dihydro-1 H-indol-3-yl)carbamate

A. Synthesis of 1-pentyl-7/-/-indole-2,3-dione 3-(O-pentylxime)

To a solution of 1/-/-indole-2,3-dione 3-oxime (10.0 g, 61.7 mmol) in DMF (100
mL) was added NaH (5.33 g, 139 mmol, 60% in mineral oil) in portions at 0 °C over 10

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The reaction mixture was stirred for 30 min followed by the addition of 1-bromopentane (9.50 ml, 77.1 mmol). The reaction mixture was stirred at ambient temperature for 16 h and quenched with water (150 ml). The mixture was extracted with ethyl acetate (3 x 200 ml) and the combined organic layers was washed with saturated ammonium chloride (100 ml), brine (50.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was crystallized from ether to give the title compound (5.56 g, 30%) as a colorless solid: ^1^H NMR (300 MHz, CDCl$_3$) δ 7.92 (d, 1H), 7.33 (d, 1H), 7.01 (d, 1H), 6.79 (d, 1H), 4.48-4.42 (m, 2H), 3.71-3.65 (m, 2H), 1.84-1.75 (m, 2H), 1.75-1.59 (m, 2H), 1.40-1.24 (m, 4H), 0.90-0.83 (m, 6H); ^13^C NMR (75 MHz, CDCl$_3$) δ 163.5, 143.9, 143.5, 132.2, 127.7, 122.7, 115.9, 108.6, 77.5, 39.9, 29.0, 28.8, 28.0, 27.2, 22.4, 22.3, 14.0, 13.9; MS (ES+) m/z 302 (M + 1).

B. Synthesis of tert-butyl (2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl)carbamate

To a mixture of 1-pentyl-7H-indole-2,3-dione 3-(O-pentyl-oxime) (3.84 g, 12.7 mmol), Zn (dust) (3.32 g, 50.9 mmol) in acetic acid (30.0 mL) was added di-tert-butyl dicarbonate (5.55 g, 25.4 mmol). The resulting mixture was stirred at ambient temperature for 16 h. The solid was filtered off and washed with ethyl acetate (100 mL). The filtrate was washed with water (3 x 50.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate:hexane (5% to 30%, gradient) to give the title compound (2.10 g, 52%) as a colorless solid: mp 145-147 °C; ^1^H NMR (300 MHz, CDCl$_3$) δ 7.37 (d, 1H), 7.29-7.24 (m, 1H), 7.03 (t, 1H), 6.80 (d, 1H), 5.10 (br, 2H), 3.74-3.46 (m, 2H), 1.70-1.60 (m, 2H), 1.43 (s, 9H), 1.37-1.30 (m, 4H), 0.87 (t, 3H); ^13^C NMR (75 MHz, CDCl$_3$) δ 174.4, 155.8, 143.1, 129.1, 127.1, 124.7, 122.7, 108.5, 80.5, 53.6, 40.3, 29.0, 28.2, 27.1, 22.4, 14.0; MS (ES+) m/z 341 (M + 23). Anal. Calcd for C$_{18}$H$_{26}$N$_2$O$_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 68.16; H, 7.97; N, 8.81.

**EXAMPLE 119**

Synthesis of tert-butyl [2-oxo-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-2,3-dihydro-1H-indol-3-yl]carbamate

A mixture of tert-butyl (2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl)carbamate (0.64 g, 2.00 mmol), 2-bromo-1-thiophen-2-yl-ethanone (0.45 g, 2.20 mmol) and potassium carbonate (1.67 g, 12.0 mmol) in acetone (50.0 mL) was stirred at ambient
temperature for 18 h. The solid was filtered, the residue was rinsed with ethyl acetate and the solvent was removed under reduced pressure. The residue was subjected to column chromatography eluting with ethyl acetate/hexane (gradient 10% to 30%) to give a solid as the title compound that was crystallized from ether and hexane (0.48 g, 54%) as a colorless solid: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.63 (dd, 1H), 7.46 (dd, 1H), 7.29 (d, 1H), 7.26-7.20 (m, 2H), 7.03 (dd, 1H), (d, 1H), 6.84 (d, 1H), 6.41 (br, 1H), 3.89-3.80 (m, 2H), 3.46 (d, 1H), 3.13 (d, 1H), 1.73-1.67 (m, 2H), 1.42-1.33 (m, 4H), 1.26 (s, 9H), 0.89 (t, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 189.0, 184.9, 175.6, 153.9, 143.9, 142.7, 135.2, 133.2, 130.0, 128.4, 124.1, 122.4, 108.5, 80.2, 60.1, 44.3, 40.4, 29.1, 28.1, 27.0, 22.4, 14.1; MS (ES+) \(m/z\) 442 (M + 23).

**EXAMPLE 120**

Synthesis of 3-amino-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-1,3-dihydro-2H-indol-2-one

To a solution of tert-butyl \{2-oxo-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-2,3-dihydro-1H-indol-3-yl\} carbamate (0.46 g, 1.06 mmol) in CH\(_2\)Cl\(_2\) (25.0 mL) was added trifluoroacetic acid (5.00 mL) at 0 °C. The reaction solution was stirred at ambient temperature for 16 h and neutralized with saturated NaHCO\(_3\) and diluted with CH\(_2\)Cl\(_2\) (25.0 mL). The organic layer was separated and washed with water (3 x 25.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/hexane (gradient 1% to 30%) to afford the title compound (0.25 g, 71%) as a colorless solid: mp 167-169 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.65 (dd, 1H), 7.57 (dd, 1H), 7.38 (d, 1H), 7.27 (t, 1H), 7.07 (dd, 1H), 6.98 (t, 1H), 6.86 (d, 1H), 3.78-3.62 (m, 3H), 3.49-3.42 (m, 1H), 1.81 (br, 2H), 1.76-1.66 (m, 2H), 1.41-1.33 (m, 4H), 0.89 (t, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 198.1, 189.0, 179.0, 143.8, 143.3, 134.0, 132.3, 129.3, 128.1, 123.8, 122.5, 108.7, 77.2, 58.6, 47.1, 40.3, 29.1, 27.0, 22.4, 14.1; MS (ES+) \(m/z\) 343 (M + 1), 217. Anal. Calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_2\)S: C, 66.64; H, 6.48; N, 8.18. Found: C, 66.85; H, 6.45; N, 8.27.

**EXAMPLE 121**

Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

To a solution of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one (3.39 g, 10.0 mmol) in anhydrous CH\(_2\)Cl\(_2\) (40 mL) was added triethyl amine (6.07 g, 60.0 mmol) and chlorotrimethylsilane (4.35 g, 40.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and diluted with anhydrous CH\(_2\)Cl\(_2\) (100
ml). The mixture was washed with H$_2$O (3 x 50.0 ml), dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo to dryness.

The gummy yellow residue was dissolved in anhydrous THF (40.0 ml) followed by the additions of formaldehyde solution (2.75 mL, 100 mmol, 37 wt% in water) and ytterbium (III) trifluoromethanesulfonate (1.55 g, 2.50 mmol). The reaction mixture was stirred at ambient temperature for 36 h and diluted with CH$_2$Cl$_2$ (100 mL). The mixture was washed with saturated NaHCO$_3$ (50.0 mL), saturated ammonium chloride (50.0 mL) and H$_2$O (50.0 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The gummy residue was subjected to column chromatography eluting with ethyl acetate/hexane (10% to 40%, gradient) to give the title compound (2.49 g, 67%) as a beige solid: mp 125-127 ⁰C; $^1$H NMR (300 MHz, CDCl$_3$) δ 10.85-10.63 (br, 1H), 7.48-7.35 (m, 2H), 7.28-7.19 (m, 1H), 6.96 (d, 1H), 6.52 (d, 2H), 5.82 (dd, 2H), 4.63 (d, 1H), 4.11 (d, 1H), 3.70 (d, 2H), 2.04-1.74 (br, 1H), 1.65 (td, 2H), 1.31-1.24 (m, 4H), 0.84 (t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 180.3, 152.6, 148.13, 143.2, 141.3, 129.2, 129.1, 126.2, 123.3, 112.4, 109.6, 108.2, 101.9, 101.3, 64.6, 59.8, 40.6, 31.6, 28.9, 26.9, 22.7, 22.2, 14.1, 13.9; MS (ES+) $m/z$ 370 (M + 1).

EXAMPLE 122

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxymethyl-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 121, and making non-critical variations to replace 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one with 3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained as a colorless solid: mp 110-113 ⁰C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.35-7.26 (m, 2H), 7.09 (td, 1H), 6.94-6.89 (m, 2H), 6.85 (dd, 1H), 6.73 (d, 1H), 5.90 (s, 2H), 4.30-4.03 (m, 2H), 3.80-3.61 (m, 2H), 2.14-1.74 (br, 1H), 1.73-1.58 (m, 2H), 1.38-1.23 (m, 4H), 0.85 (t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 177.5, 148.0, 147.1, 143.5, 130.7, 130.5, 128.7, 124.9, 122.7, 120.7, 108.9, 108.4, 107.9, 101.2, 67.2, 57.9, 40.2, 29.0, 27.1, 22.3, 14.0; MS (ES+) $m/z$ 375.19 (M + 22).

EXAMPLE 123

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-methoxy-1-pentyl-1,3-dihydro-indol-2-one

To a solution of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one (0.82 g, 2.40 mmol) in THF (20.0 mL) was added sodium hydride (0.15 g, 3.60 mmol) and iodomethane (0.30 mL, 4.80 mmol) at 0 ⁰C. The mixture was stirred at
0 °C for one hour and quenched with ammonium chloride solution. The mixture was poured into water (150 ml.) and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo. The residue was subjected to flash column chromatography to afford a colorless oil (0.66 g, 77%) as the title compound: 1H NMR (300 MHz, CDCl₃) δ 7.36 (td, 1H), 7.25 (dd, 1H), 7.10 (td, 1H), 6.97 (d, 1H), 6.9 (d, 1H), 6.74-6.65 (m, 2H), 5.91-5.88 (m, 2H), 3.76-3.60 (m, 2H), 3.18 (s, 3H), 1.72-1.59 (m, 2H), 1.37-1.22 (m, 4H), 0.85 (t, 3H); 13C NMR (75 MHz, CDCl₃) δ 174.9, 147.8, 147.7, 143.9, 132.7, 130.1, 128.0, 125.8, 123.0, 119.9, 108.8, 107.9, 107.3, 101.1, 83.5, 53.0, 40.1, 29.0, 27.0, 22.3, 13.9; MS (ES+) m/z 375.9 (M + 23), 322.2 (M - 31).

EXAMPLE 124

Synthesis of 3-(1,3-benzodioxol-5-yl)-3-methyl-1-pentyl-1,3-dihydro-indol-2-one

A solution of 3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one (0.54 g, 1.70 mmol) and iodomethane (0.52 mL, 8.40 mmol) in THF (20 mL) was degassed by bubbling through argon for one hour. Sodium hydride (0.20 g, 5.10 mmol) was added at 0 °C. The mixture was stirred at 0 °C for one hour and quenched with ammonium chloride solution. The mixture was poured into water (150 mL) and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo. The residue was subjected to flash column chromatography to afford a colorless oil (0.35 g, 61%) as the title compound: 1H NMR (300 MHz, CDCl₃) δ 7.28 (td, 1H), 7.16-7.12 (m, 1H), 7.05 (td, 1H), 6.90 (d, 1H), 6.76-6.73 (m, 1H), 6.72-6.67 (m, 2H), 5.90-5.87 (m, 2H), 3.79-3.60 (m, 2H), 1.73-1.61 (m, 5H), 1.36-1.23 (m, 4H), 0.86 (t, 3H); 13C NMR (75 MHz, CDCl₃) δ 179.3, 147.8, 146.7, 142.6, 135.2, 134.8, 128.0, 124.2, 122.6, 119.9, 108.6, 108.1, 107.5, 101.1, 51.7, 40.1, 29.0, 27.1, 23.8, 22.3, 14.0; MS (ES+) m/z 359.9 (M + 23).

EXAMPLE 125

Synthesis of methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetate

A solution of 3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one (1.00 g, 3.10 mmol) and methyl bromoacetate (0.44 mL, 4.60 mmol) in THF (20 mL) was degassed by bubbling through argon for one hour. Sodium hydride (0.19 g, 4.60 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h and quenched with ammonium chloride solution. The mixture was poured into water (150 mL), and extracted with ethyl acetate (200 mL). The organic layer was washed with water, dried
over sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to flash column chromatography to afford the title compound (0.94 g, 76%) as a colorless oil: \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.30 (td, 1H), 7.25 (dd, 1H), 7.06 (td, 1H), 6.89 (d, 1H), 6.81 (d, 1H), 6.74-6.65 (m, 2H), 5.90-5.87 (m, 2H), 3.71-3.64 (m, 2H), 3.45 (d, 1H), 3.41 (s, 3H), 3.18 (d, 1H), 1.74-1.60 (m, 2H), 1.39-1.22 (m, 4H), 0.85 (t, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 177.8, 170.0, 147.9, 147.0, 143.9, 133.1, 131.3, 128.6, 124.6, 122.3, 119.9, 108.7, 108.1, 107.4, 101.2, 52.8, 51.6, 41.8, 40.4, 29.0, 26.8, 22.3, 14.0; MS (ES+) \( m/z \) 418.1 (M + 23), 396.1 (M + 1).

**EXAMPLE 126**

Synthesis of [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1/-/-indol-3-yl]acetic acid

To a solution of methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetate (5.90 g, 15.0 mmol) in THF/water (2/1 v/v, 120 ml) was added lithium hydroxide monohydrate (1.26 g, 28.0 mmol). The mixture was stirred at ambient temperature overnight. Most THF was removed under vacuum and 150 ml of water was added. The solution was extracted with ethyl acetate/hexanes (1/3 v/v, 50 ml). The water layer was acidified with 1 N HCl solution until the pH value reached 2 then extracted with ethyl acetate (200 ml). The organic layer was washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness to afford the title compound (5.00 g, 88%) as a white solid: \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.29 (td, 1H), 7.21 (dd, 1H), 7.05 (td, 1H), 6.87 (d, 1H), 6.76 (d, 1H), 6.71-6.64 (m, 2H), 5.90-5.86 (m, 2H), 3.65 (t, 2H), 3.43 (d, 1H), 3.11 (d, 1H), 1.70-1.55 (m, 2H), 1.36-1.22 (m, 4H), 0.85 (t, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 178.2, 174.0, 148.0, 147.1, 143.4, 132.6, 131.4, 128.7, 124.4, 122.7, 119.8, 108.9, 108.2, 107.2, 101.2, 52.6, 41.5, 40.4, 29.0, 26.6, 22.3, 14.0; MS (ES+) \( m/z \) 404.0 (M + 23), 382.0 (M + 1).

**EXAMPLE 127**

**A.** To a solution of [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetic acid (0.28 g, 0.73 mmol) and oxalyl chloride (0.32 mL, 3.70 mmol) in toluene (10.0 mL) was added one drop of DMF and the mixture was stirred at ambient temperature overnight. The mixture was concentrated under vacuum to afford a brown oil as the desired acid chloride compound.
B. Ammonium hydroxide (1.00 mL, 28% solution, excess) and sodium bicarbonate (0.05 g, 0.58 mmol) were mixed in a mixture solvent of water/dichloromethane (10.0 mL, 1/1, v/v) followed by the addition of a solution of the acid chloride (0.05 g, 0.12 mmol) in dichloromethane (1.00 mL) at ambient temperature. The mixture was sirred at ambient temperature for one hour and separated. The organic layer was washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated under vacuum to dryness to afford a white solid (0.03 g, 78%) as the title compound: \( ^{1}H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.32-7.23 (m, 2H), 7.06 (td, 1H), 6.87 (d, 1H), 6.82 (d, 1H), 6.76 (dd, 1H), 6.68 (d, 1H), 6.40-6.27 (br, 1H), 5.92-5.86 (m, 2H), 5.36-5.22 (br, 1H), 3.78-3.60 (m, 2H), 3.39-3.25 (m, 2H), 2.96 (s, 3H), 2.74 (s, 3H), 1.78-1.59 (m, 4H), 1.37-1.26 (m, 4H), 0.85 (t, 3H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 178.6, 170.9, 148.1, 147.1, 142.7, 133.0, 131.8, 128.6, 124.7, 122.8, 119.8, 108.9, 108.3, 107.2, 101.2, 53.6, 43.6, 40.4, 29.0, 26.8, 22.3, 14.0; MS (ES+) m/z 403.1 (M + 23), 381.1 (M + 1).

EXAMPLE 128

Synthesis of 2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]-\( \text{N}\)-methylacetamide

Following the procedure as described in EXAMPLE 127, and making non-critical variations to replace ammonium hydroxide with methylamine, the title compound was obtained as a colorless solid (86%): \( ^{1}H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.30-7.23 (m, 2H), 7.05 (td, 1H), 6.87 (d, 1H), 6.81 (d, 1H), 6.75 (dd, 1H), 6.68 (d, 1H), 6.40-6.27 (br, 1H), 5.90-5.86 (m, 2H), 3.80-3.61 (m, 2H), 3.25 (d, 1H), 2.95 (d, 1H), 2.56 (d, 3H), 1.73-1.59 (m, 2H), 1.37-1.26 (m, 4H), 0.86 (t, 3H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 178.7, 169.2, 148.0, 147.0, 142.6, 133.1, 132.0, 128.5, 124.7, 122.8, 119.8, 108.9, 108.3, 107.7, 101.2, 53.9, 43.9, 40.4, 29.0, 27.0, 26.2, 22.3, 14.0; MS (ES+) m/z 417.1 (M + 23), 395.1 (M + 1).

EXAMPLE 129

Synthesis of 2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]-\( \text{N,\text{/ V}}\)-dimethylacetamide

Following the procedure as described in EXAMPLE 127, and making non-critical variations to replace ammonium hydroxide with dimethylamine, the title compound was obtained as a colorless solid (93%): \( ^{1}H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.30-7.23 (m, 2H), 7.03 (td, 1H), 6.93 (d, 1H), 6.88 (d, 1H), 6.78 (dd, 1H), 6.66 (d, 1H), 5.89-5.86 (m, 2H), 3.85-3.54 (m, 2H), 3.39-3.25 (m, 2H), 2.96 (s, 3H), 2.74 (s, 3H), 1.78-
1.56 (m, 2H), 1.35-1.19 (m, 4H), 0.82 (t, 3H); 13C NMR (CDCl₃, 75 MHz) δ 178.7,
168.5, 147.8, 146.8, 144.1, ... was diluted with dichloromethane (200
mL), washed with saturated ammonium chloride solution (50.0
mL), brine (3 x 50.0
mL), stirred for 3 min. The reaction mixture was was
filtered and the filtrate was concentrated in vacuo to dryness. The residue was subjected to column
chromatography eluting with ethyl acetate-hexane to give the title compound (34.9 g, 97%) as a brown gummy material: 1H NMR (300 MHz, DMSO-d₆) δ 8.95 (s, 1H), 7.29-
7.21 (m, 2H), 6.88-6.81 (m, 1H), 6.55, (s, 1H), 6.14 (s, 1H), 5.86 (dd, 2H), 4.24 (s, 1H),
3.70-3.52 (m, 2H), 1.69-1.55 (m, 2H), 1.31-1.24 (m, 4H), 0.83 (t, 3H); 13C NMR (75
MHz, DMSO-d₆) δ 177.6, 152.6, 149.1, 144.8, 141.2, 131.7, 127.7, 127.6, 121.0, 113.8,

EXAMPLE 131

Synthesis of 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-
dihydro-2/-/-indol-2-one

To a solution of 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-
pentyl-1,3-dihydro-2H-indol-2-one (34.9 g, 80.4 mmol) in dichloromethane (100 mL)
was added trifluoroacetic acid (18.7 g, 161 mmol) and triethyl silane (18.3 g, 161
mmol). The brown solution was stirred at ambient temperature for 3 h and
concentrated in vacuo to dryness. The residue was diluted with dichloromethane (200
mL), washed with saturated ammonium chloride solution (50.0 mL), brine (3 x 50.0
mL), dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated
in vacuo to dryness. The residue was subjected to column
chromatography eluting with ethyl acetate-hexane to give the title compound (34.9 g, 97%) as a brown gummy material: 1H NMR (300 MHz, DMSO-d₆) δ 8.95 (s, 1H), 7.29-
7.21 (m, 2H), 6.88-6.81 (m, 1H), 6.55, (s, 1H), 6.14 (s, 1H), 5.86 (dd, 2H), 4.24 (s, 1H),
3.70-3.52 (m, 2H), 1.69-1.55 (m, 2H), 1.31-1.24 (m, 4H), 0.83 (t, 3H); 13C NMR (75
MHz, DMSO-d₆) δ 177.6, 152.6, 149.1, 144.8, 141.2, 131.7, 127.7, 127.6, 121.0, 113.8,
mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated \textit{in vacuo} to dryness. The residue was crystallized from ether to give the title compound (16.5 g, 49%) as a brown solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.29-7.21 (m, 2H), 7.14 (dd, 1H), 6.58 (s, 1H), 6.10 (s, 1H), 5.85 (dd, 2H), 5.01 (s, 1H), 3.75-3.55 (m, 2H), 1.69-1.56 (m, 2H), 1.35-1.21 (m, 4H), 0.86 (t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.9, 150.9, 147.6, 145.4, 141.6, 130.3 127.1 126.8, 120.8, 113.3 108.0, 106.7, 101.5, 101.2, 59.9, 48.6, 40.7, 28.9, 26.9, 22.3 13.9; MS (ES$^+)$ m/z 418.3 (M + 1), 420.3 (M + 1).

\textbf{EXAMPLE 132}

Synthesis of 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

To a solution of 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one (7.50 g, 17.9 mmol) in dry dichloromethane (150 mL) was added triethylamine (10.9 g, 108 mmol) and chloromethylsilane (7.80 g, 71.8 mmol) at 0°C. The reaction mixture was stirred at 0°C for 2 h and diluted with dichloromethane (100 mL). The mixture was washed with water (3 x 50.0 mL), dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated \textit{in vacuo} to dryness. The residue was dissolved in THF (150 mL) followed by the additions of formaldehyde solution (4.90 mL, 179 mmol, 37 wt% in water) and ytterbium (III) trifluoromethanesulfonate (1.11 g, 1.79 mmol). The resulting mixture was stirred at ambient temperature for 36 h. After the solvent was removed under reduced pressure, the residue was diluted with dichloromethane (200 mL), washed with saturated sodium bicarbonate (50.0 mL), saturated ammonium chloride (50.0 mL) and water (100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated \textit{in vacuo} to dryness to yield the title compound (6.32 g, 79%) as a fluffy solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.28 (s, 1H), 7.10 (t, 1H), 7.00 (dd, 1H), 6.89 (dd, 1H), 6.83 (s, 1H), 6.27 (s, 1H), 6.85 (dd, 2H), 4.52-4.41 (m, 2H), 3.90 (dd, 1H), 3.70-3.65 (m, 2H), 1.68-1.57 (m, 2H), 1.36-1.29 (m, 4H), 0.83 (t, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.1, 150.3, 147.2, 147.2, 140.5, 129.6, 129.2, 125.6, 118.4, 114.8, 109.2, 106.9, 101.0, 98.2, 62.6, 57.6, 39.9, 28.9, 26.7, 22.2, 13.5.

\textbf{EXAMPLE 133}

Synthesis of ethyl [3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 106, and making non-
critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with ethyl (2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate, the title compound was obtained (95%): $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.08 (s, 1H), 7.21-7.13 (m, 2H), 6.93-6.86 (m, 3H), 6.57 (s, 1H), 6.19 (s, 1H), 5.88 (m, 2H), 4.47 (m, 2H), 4.13 (q, 2H), 1.19 (t, 3H); MS (ES-) m/z 370.2 (M - 1).

EXAMPLE 134

Synthesis of ethyl [3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (84%) as a white powder: $^1$H NMR (DMSOd$_6$, 300 MHz) 59.37 (s, 1H), 7.19 (m, 1H), 7.01-6.90 (m, 3H), 6.43 (s, 2H), 5.84 (m, 2H), 4.86 (s, 1H), 4.56 (s, 2H), 4.13 (q, 2H), 1.18 (t, 3H); MS (ES+) m/z 378.2 (M + 23).

EXAMPLE 135

Synthesis of ethyl [3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained as a white powder: $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.03 (s, 1H), 7.17-6.85 (m, 5H), 6.22 (s, 1H), 5.83 (s, 2H), 5.04 (t, 1H), 4.56-4.08 (m, 5H), 3.69 (m, 1H), 1.18 (t, 3H); MS (ES+) m/z 408.1 (M + 23).

EXAMPLE 136

Synthesis of methyl 3-[[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]methyl]benzoate

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with methyl 3-[[2,3-dioxo-2,3-dihydro-1H-indol-1-yl]methyl]benzoate, the title compound was obtained (96%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.65 (s, 1H), 7.92 (s, 1H), 7.85 (d, 1H), 7.41-7.38 (m, 1H), 7.32-7.24 (m, 2H), 7.19-7.13 (m, 1H), 7.04-6.9 (m, 1H), 6.63 (d,
1H), 6.44 (s, 1H), 6.39 (s, 1H), 5.79 (s, 2H), 5.05 (dd, 2H), 3.80 (s, 3H);
13C NMR (75 MHz, CDCl3) 5 178.7, 167.0, 151.0, 148.5, 142.1, 141.1, 135.7, 131.6, 130.5, 130.1, 129.1, 129.0, 128.4, 125.5, 123.9, 116.7, 109.7, 106.5, 101.3, 100.5, 78.6, 60.6, 52.4, 43.6; MS (ES+) m/z 456.1 (M + 23).

EXAMPLE 137
Synthesis of methyl 3-[(3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]benzoate

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with methyl 3-[(3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1/-/-indol-1-yl)methyl]benzoate, the title compound was obtained (98%): MS (ES+) m/z 418.2 (M + 1).

EXAMPLE 138
Synthesis of methyl 3-[(3-(6-hydroxy-1 ,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1 H-indol-1 -yl)methyl]benzoate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1 ,3-benzodioxol-5-yl)-1-pentyl-1 ,3-dihydro-2H-indol-2-one with methyl 3-[(3-(6-hydroxy-1 ,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1 H-indol-1 -yl)methyl]benzoate, the title compound was obtained (81%): MS (ES+) m/z 470.3 (M + 23), 448.3 (M + 1)

EXAMPLE 139
Synthesis of methyl 4-[(3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1 H-indol-1 -yl)methyl]benzoate

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with methyl 4-[(2,3-dioxo-2,3-dihydro-1 H-indol-1 -yl)methyl]benzoate, the title compound was obtained (79%): MS (ES+) /m/z 416.1 (M -17).

EXAMPLE 140
Synthesis of methyl 4-[(3-(6-hydroxy-1 ,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1 -yl)methyl]benzoate

Following the procedure as described in EXAMPLE 107, and making the variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with methyl 4-[(3-hydroxy-3-(6-hydroxy-1 ,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1 H-indol-1 -yl)methyl]benzoate,
5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl][methyl]benzoate, the title compound was obtained (98%) as a solid: MS (ES+) m/z 418.1 (M + 1).

**EXAMPLE 141**

Synthesis of methyl 4-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl][methyl]benzoate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with methyl 4-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl][methyl]benzoate, the title compound was obtained (81%): MS (ES+) m/z 448.1 (M + 1).

**EXAMPLE 142**

Synthesis of 2-{3-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl][propyl]-1H-isoindole-1,3(2H)-dione

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-1H-indole-2,3-dione, the title compound was obtained (96%): ¹H NMR (300 MHz, CDCl₃) δ 7.86-7.78 (m, 4H), 7.21-7.13 (m, 2H), 7.00-6.97 (m, 1H), 6.87-6.85 (m, 2H), 6.15 (s, 2H), 5.86-5.84 (m, 2H), 3.69-3.65 (m, 4H), 2.46-2.45 (m, 1H), 1.94-1.87 (m, 2H); MS (ES+) m/z 473.4 (M - 17).

**EXAMPLE 143**

Synthesis of 2-{3-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl][propyl]-1H-isoindole-1,3(2H)-dione

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 2-{3-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl][propyl]-1H-isoindole-1,3(2H)-dione, the title compound was obtained (94%): ¹H NMR (300 MHz, CDCl₃) δ 7.81-7.78 (m, 2H), 7.70-7.67 (m, 1H), 7.32-7.27 (m, 2H), 7.12-7.07 (m, 1H), 6.90-6.87 (m, 1H), 6.54 (s, 1H), 6.45 (s, 1H), 5.86 (dd, 2H), 4.82 (s, 1H), 3.96-3.66 (m, 4H), 2.17-2.04 (m, 2H); MS (ES+) m/z 457.0 (M + 1).
EXAMPLE 144

Synthesis of 2-{3-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]propyl}-1H-isooindole-1,3(2H)-dione

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 2-[3-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]propyl]-1H-isooindole-1,3(2H)-dione, the title compound was obtained (94%) as a foam solid: ¹H NMR (300 MHz, CDCl₃) δ 9.20 (s, 1H), 7.81-7.79 (m, 2H), 7.35-7.25 (m, 2H), 7.16-7.14 (m, 1H), 6.90 (d, 1H), 6.80 (s, 1H), 6.48 (s, 1H), 5.86 (dd, 2H), 4.64 (d, 1H), 3.67-4.13 (m, 5H), 2.18-2.05 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 180.6, 168.6, 151.2, 147.8, 143.2, 141.2, 134.2, 131.9, 130.0, 128.7, 125.1, 123.2, 113.9, 108.7, 108.3, 101.3, 100.6, 64.9, 58.0, 37.6, 36.1, 26.5; MS (ES⁺) m/z 487.3 (M + 1).

EXAMPLE 145

Synthesis of 2-[2-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]ethyl]-1H-isooindole-1,3(2H)-dione

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-1H-indole-2,3-dione, the title compound was obtained (99%): ¹H NMR (300 MHz, CD₃OD) δ 7.85-7.68 (m, 4H), 7.29 (td, 1H), 7.18-6.96 (m, 3H), 6.88 (s, 1H), 6.16 (s, 1H), 5.85 (s, 1H), 5.82 (s, 1H), 4.01-3.81 (m, 4H); MS (ES⁺) m/z 441 (M - 17), 458 (M + 23).

EXAMPLE 146

Synthesis of 2-[2-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]ethyl]-1H-isooindole-1,3(2H)-dione

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 2-[2-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]ethyl]-1H-isooindole-1,3(2H)-dione, the title compound was obtained (90%) as a white solid: ¹H NMR (300 MHz, CD₃OD) δ 10.15-10.05 (br, 1H), 8.66-8.58 (m, 4H), 8.07-7.70 (m, 4H), 7.12 (s, 1H), 7.18 (s, 1H), 6.70 (s, 1H), 6.69 (s, 1H), 5.50 (s, 1H), 4.91-4.56 (m, 4H); MS (ES⁺) m/z 443 (M + 1).

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EXAMPLE 147

Synthesis of 2-{2-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]ethyl}-1/-/-isoindole-1,3(2H)-dione

Following the procedure as described in EXAMPLE 132, making variation to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 2-[2-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]ethyl]-1/-/-isoindole-1,3(2H)-dione, the title compound was obtained (56%): ¹H NMR (300 MHz, CD₃OD) δ 9.97 (s, 1H), 8.72-8.62 (m, 4H), 8.07-7.67 (m, 5H), 7.01 (s, 1H), 6.71 (s, 1H), 6.70 (s, 1H), 5.79 (t, 1H), 4.88-4.50 (m, 6H); MS (ES+) m/z 455 (M - 17), 473 (M + 1), 495 (M + 23)

EXAMPLE 148

Synthesis of 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-(diphenylmethyl)-1/-/-indole-2,3-dione, the title compound was obtained (99%) as an off-white powder: MS (ES+) m/z 474.5 (M + 23).

EXAMPLE 149

Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making the variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2/-/-indol-2-one, the title compound was obtained (84%) as an off-white solid: MS (ES+) m/z 458.4 (M + 23).

EXAMPLE 150

Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2/-/-indol-2-one, the title compound was obtained (56%): MS (ES+) m/z 488.3 (M + 23)
EXAMPLE 151
Synthesis of 1-[3-(benzyloxy)propyl]-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with 1-[3-(benzyloxy)propyl]-1H-indole-2,3-dione, the title compound was obtained (70%): 1H NMR (300 MHz, CDCl₃) δ 9.42 (s, 1H), 7.32-7.16 (m, 8H), 6.96 (d, 1H), 6.61 (s, 1H), 6.23 (s, 1H), 5.86-5.83 (m, 2H), 4.44 (s, 2H), 3.88-3.73 (m, 2H), 3.46 (t, 2H), 2.06-1.85 (m, 2H); MS (ES+) m/z 416.3 (M - 17), 456.3 (M + 23).

EXAMPLE 152
Synthesis of 1-[3-(benzyloxy)propyl]-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 1-[3-(benzyloxy)propyl]-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (92%): 1H NMR (300 MHz, CDCl₃) δ 7.42-6.95 (m, 9H), 6.56 (s, 1H), 6.24 (s, 1H), 5.86 (ABq, 1H), 5.81 (AB, 1H), 4.99 (s, 1H), 4.42 (s, 2H), 3.91-3.76 (m, 2H), 3.46 (t, 2H), 2.03-1.93 (m, 2H); MS (ES+) m/z 448.3 (M + 1).

EXAMPLE 153
Synthesis of 1-(3-benzyloxypropyl)-3-(6-hydroxybenzo[1,3]dioxol-5-yl)-3-hydroxymethyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 1-[3-(benzyloxy)propyl]-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (93%): MS (ES+) m/z 448.2 (M + 1).

EXAMPLE 154
Synthesis of methyl 2-[[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]methyl]benzoate

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with methyl 2-[[2,3-dioxo-2,3-dihydro-1H-indol-1-yl]methyl]benzoate, the title compound was obtained (97%) as a colorless solid: 1H NMR (300 MHz, DMSO-d₆) δ 9.29 (s, 1H), 7.97
(dd, 1H), 7.53-7.36 (m, 3H), 7.28 (s, 1H), 7.10 (td, 1H), 6.96-6.83 (m, 2H), 6.59 (d, 2H), 6.25 (s, 1H), 5.95-5.86 (m, 2H), 5.31-5.07 (m, 2H), 3.88 (s, 3H); MS (ES+) m/z 456.1 (M + 23).

EXAMPLE 155

5 Synthesis of methyl 2-[(3-(6-hydroxy-1,3-benzodioxol-5-y1)-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]benzoate

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]benzoate, the title compound was obtained (100%) as a white solid: 1H NMR (300 MHz, DMSO-CD6) δ 9.32 (s, 1H), 7.94 (dd, 1H), 7.50-7.34 (m, 2H), 7.26 (d, 1H), 7.08 (t, 1H), 7.00-6.86 (m, 2H), 6.76 (s, 1H), 6.64 (d, 1H), 6.38 (s, 1H), 5.93-5.86 (m, 2H), 5.34-5.12 (m, 2H), 4.83 (s, 1H), 3.87 (s, 3H); MS (ES+) m/z 418.2 (M + 1).

EXAMPLE 156

Synthesis of methyl 2-[(3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]benzoate

A solution of methyl 2-[(3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]benzoate (17.1 g, 40.0 mmol) and paraformaldehyde (10.3 g, 330 mmol) in THF (500 mL) was degassed by bubbling through argon for 2 hours. To this solution was added lithium diisopropylamide solution (45.1 mL, 2 M solution, 90.0 mmol) slowly at -78 °C. The mixture was stirred at ambient temperature overnight and quenched with saturated ammonium chloride solution. The mixture was concentrated in vacuo to remove THF followed by the addition of ethyl acetate (500 mL). The organic layer was washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was recrystallized from ethyl acetate/hexanes to give the title compound (13.7 g, 75%): 1H NMR (300 MHz, DMSO-CD6) δ 9.20 (s, 1H), 7.95 (dd, 1H), 7.53-7.33 (m, 3H), 7.08 (t, 1H), 7.00-6.82 (m, 2H), 6.53 (d, 1H), 6.25 (s, 1H), 5.93-5.86 (m, 2H), 5.34-5.12 (m, 2H), 4.83 (s, 1H), 3.87 (s, 3H); MS (ES+) m/z 448.3 (M + 1).

EXAMPLE 157

Synthesis of methyl 3-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]propanoate

Following the procedure as described in EXAMPLE 157, and making non-
critical variations to replace methyl bromoacetate with methyl 3-bromopropionate, the
title compound was obtained (76%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ
7.28 (td, 1H), 7.17 (dd, 1H), 7.06 (td, 1H), 6.89 (d, 1H), 6.84 (d, 1H), 6.77 (dd, 1H),
6.68 (d, 1H), 5.89-5.84 (m, 2H), 3.67 (t, 2H), 3.53 (s, 3H), 2.69-2.56 (m, 1H), 2.54-2.41
(m, 1H), 2.21-2.08 (m, 1H), 1.99-1.86 (m, 1H), 1.72-1.59 (m, 2H), 1.38-1.24 (m, 4H),
0.85 (t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.8, 173.1, 147.9, 146.9, 143.2, 133.5,
131.6, 128.5, 124.9, 122.6, 120.1, 108.7, 108.1, 107.6, 101.1, 55.2, 51.6, 40.2, 32.4,
29.5, 29.1, 27.1, 22.3, 14.0; MS (ES+) m/z 410.1 (M + 1), 432.0 (M + 23).

EXAMPLE 158

Synthesis of 3-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-
yl]propanoic acid

Following the procedure as described in EXAMPLE 158, and making non-
critical variations to replace methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-
dihydro-1H-indol-3-yl]acetate with methyl 3-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-
2,3-dihydro-1/-/-indol-3-yl]propanoate, the title compound was obtained (92%) as a
colorless solid: MS (ES-) m/z 394.2 (M - 1).

EXAMPLE 159

Synthesis of 3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1
,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-
critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-pentyl-
1/-/-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 3,4-difluorophenol, the title
compound was obtained (31%): ¹H NMR (300 MHz, CDCl₃) δ 9.69-9.65 (br, 1H), 7.51-
7.41 (m, 2H), 7.26-7.21 (m, 1H), 6.99-6.57 (m, 3H), 4.18-4.14 (br, 1H), 3.78-3.58 (m,
2H), 1.76-1.62 (m, 2H), 1.40-1.28 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 330 (M - 17),
370 (M + 23).

EXAMPLE 160

Synthesis of 3-(4,5-difluoro-2-hydroxyphenyl)-1-pentyl-1
,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-
critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1
,3-
benzodioxol-5-yl)-1 ,3-dihydro-2H-indol-2-one with 3-(4,5-difluoro-2-hydroxyphenyl)-3-
hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (98%):
¹H NMR (300 MHz, CDCl₃) δ 7.46-7.19 (m, 3H), 7.03-6.68 (m, 3H), 5.03 (s, 1H), 3.76-
3.67 (m, 2H), 1.76-1.62 (m, 2H), 1.40-1.28 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 332 (M + 1).

EXAMPLE 161
Synthesis of 3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(4,5-difluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (96%): MS (ES+) m/z 344 (M - 17), 384 (M + 23).

EXAMPLE 162
Synthesis of 3-(5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-H-indole-2,3-dione with 1-H-indole-2,3-dione and 1,3-benzodioxol-5-ol with 4-flurophenol, the title compound was obtained (53%): 1H NMR (300 MHz, CDCl₃) δ 9.42-9.14 (br, 1H), 7.53-6.86 (m, 6H), 6.56-6.48 (m, 1H), 4.58-4.28 (br, 1H), 3.79-3.58 (m, 2H), 1.77-1.61 (m, 2H), 1.41-1.24 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 312 (M + 1), 352 (M + 23).

EXAMPLE 163
Synthesis of 3-(5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

To a solution of 3-(5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one (2.42 g, 7.35 mmol) in dichloromethane (10.0 mL) were added trifluoroacetic acid (1.00 mL) and triethylsilane (1.00 mL) at ambient temperature. The reaction mixture was stirred at 40 °C for 15 hrs and concentrated in vacuo to dryness. The residue was triturated with ether to give the title compound (2.10 g, 91%) as a solid: MS (ES+) m/z 314 (M + 1).

EXAMPLE 164
Synthesis of 3-(5-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

To a solution of 3-(5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one (2.10 g, 6.70 mmol) in THF (20.0 mL) were added paraformaldehyde (1.76 g, 58.8 mmol) and lithium diisopropylamide (7.35 mL, 2.0 M in THF, 14.7 mmol) at 0 °C. The
reaction mixture was stirred at 0°C for 2 hrs followed by the addition of ammonium chloride solution (10.0 ml.) and ethyl acetate (100 ml.). The organic layer was washed with water and brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo to dryness to give the title compound: ¹H NMR (300 MHz, CDCl₃) δ 9.55-9.10 (br, 1H), 7.53-6.86 (m, 6H), 4.74-4.30 (br, 1H), 4.18-4.07 (m, 2H), 3.79-3.60 (m, 2H), 1.77-1.61 (m, 2H), 1.41-1.24 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 326 (M - 17), 366 (M + 23).

EXAMPLE 165
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1/-/-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 4-bromophenol, the title compound was obtained (41%): ¹H NMR (300 MHz, CDCl₃) δ 9.46-9.25 (br, 1H), 7.51-6.80 (m, 7H), 4.73-4.51 (br, 1H), 3.79-3.56 (m, 2H), 1.76-1.60 (m, 2H), 1.41-1.22 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 377 (M - 17), 379 (M - 17), 412 (M + 23), 414 (M + 23).

EXAMPLE 166
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

To a solution of 3-(5-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one (2.22 g, 5.64 mmol) in dichloromethane (10.0 mL) were added trifluoroacetic acid (1.00 mL) and triethylsilane (1.00 mL) at ambient temperature. The reaction mixture was stirred at 50°C for 15 hrs and concentrated in vacuo to dryness to give the title compound: MS (ES+) m/z 374 (M + 1), 376 (M + 1).

EXAMPLE 167
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 164, and making non-critical variations to replace 3-(5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 386 (M - 17), 388 (M - 17), 426 (M + 23), 428 (M + 23).
EXAMPLE 168
Synthesis of 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 4-chloro-3-fluorophenol, the title compound was obtained (33%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.80 (s, 1H), 7.52-7.41 (m, 2H), 7.23 (t, 1H), 6.96 (d, 1H), 6.84 (d, 1H), 6.80 (d, 1H), 4.15 (s, 1H), 3.79-3.58 (m, 2H), 1.76-1.62 (m, 2H), 1.40-1.28 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 346 (M - 17), 386 (M + 23).

EXAMPLE 169
Synthesis of 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 166, and making non-critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (99%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.0-9.70 (br, 1H), 7.45-7.18 (m, 3H), 6.98 (d, 1H), 6.90-6.82 (m, 2H), 5.01 (s, 1H), 3.75-3.66 (m, 2H), 1.76-1.62 (m, 2H), 1.40-1.28 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 348 (M + 1).

EXAMPLE 170
Synthesis of 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (46%): MS (ES+) m/z 360 (M - 17), 400 (M + 23).

EXAMPLE 171
Synthesis of 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 3-chloro-4-fluorophenol, the title compound was obtained (14%): MS (ES+) m/z 346 (M - 17), 386 (M + 23).
EXAMPLE 172
Synthesis of 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 166, and making non-critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 348 (M + 1).

EXAMPLE 173
Synthesis of 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (50% for two steps): MS (ES+) m/z 360 (M - 17), 400 (M + 23).

EXAMPLE 174
Synthesis of 3-(4,5-dichloro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 3,4-dichlorophenol, the title compound was obtained (26%): 1H NMR (300 MHz, CDCl₃) δ 9.60 (s, 1H), 7.50-7.40 (m, 2H), 7.22 (td, 1H), 7.1 1 (s, 1H), 6.95 (d, 1H), 6.86 (s, 1H), 4.31-4.12 (br, 1H), 3.79-3.59 (m, 2H), 1.76-1.62 (m, 2H), 1.40-1.27 (m, 4H), 0.88 (t, 3H); MS (ES+) m/z 363 (M - 17), 403 (M + 23).

EXAMPLE 175
Synthesis of 3-(4,5-dichloro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 166, and making non-critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(4,5-dichloro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (86%): 1H NMR (300 MHz, CDCl₃) δ 10.0-9.50 (br, 1H), 7.42 (t, 1H), 7.32 (d, 1H), 7.22 (td, 1H), 7.09 (s, 1H), 6.95 (d, 1H), 6.93 (s, 1H), 5.04(s, 1H), 3.77-3.68 (m, 2H), 1.77-1.62 (m, 2H), 1.40-1.27 (m, 4H), 0.88 (t, 3H); MS (ES+) m/z 348 (M + 1).
EXAMPLE 176
Synthesis of 3-(4,5-dichloro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(4,5-dichloro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 376 (M - 17), 416 (M + 23).

EXAMPLE 177
Synthesis of 3-hydroxy-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione and 1,3-benzodioxol-5-ol with α,α,α-trifluorocresol, the title compound was obtained (46%): 1H NMR (300 MHz, CDCl₃) δ 9.75 (s, 1H), 7.50-7.39 (m, 3H), 7.21 (td, 1H), 7.10-7.02 (m, 2H), 6.96 (d, 1H), 4.26 (s, 1H), 3.82-3.59 (m, 2H), 1.77-1.63 (m, 2H), 1.40-1.30 (m, 4H), 0.88 (t, 3H); MS (ES+) m/z 362 (M - 17), 402 (M + 23).

EXAMPLE 178
Synthesis of 3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 166, and making non-critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (78%): 1H NMR (300 MHz, CDCl₃) δ 8.20-8.00 (br, 1H), 7.43-7.14 (m, 5H), 7.02 (d, 1H), 6.95 (d, 1H), 5.11 (s, 1H), 3.82-3.72 (m, 2H), 1.79-1.66 (m, 2H), 1.40-1.27 (m, 4H), 0.88 (t, 3H); MS (ES+) m/z 364 (M + 1).

EXAMPLE 179
Synthesis of 3-(hydroxymethyl)-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2H-indol-2-one
dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 376 (M - 17), 416 (M + 23).

EXAMPLE 180
Synthesis of 3-(5-bromo-2-hydroxy-4-methoxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 4-bromo-3-methoxyphenol, the title compound was obtained (48%): 1H NMR (300 MHz, CDCl$_3$) δ 9.85 (s, 1H), 7.52-7.38 (m, 2H), 7.22 (td, 1H), 6.94 (d, 1H), 6.89 (s, 1H), 6.63 (s, 1H), 4.13-4.03 (br, 1H), 3.86 (s, 3H), 3.80-3.57 (m, 2H), 1.75-1.63 (m, 2H), 1.40-1.25 (m, 4H), 0.88 (t, 3H); MS (ES+) m/z 402 (M - 17), 404 (M - 17), 442 (M + 23), 444 (M + 23).

EXAMPLE 181
Synthesis of 3-(2-hydroxy-4-methoxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 166, and making non-critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(5-bromo-2-hydroxy-4-methoxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (83%): 1H NMR (300 MHz, CDCl$_3$) δ 9.78-9.20 (br, 1H), 7.43-7.31 (m, 2H), 7.19 (t, 1H), 6.97 (d, 1H), 6.79 (d, 1H), 6.70-6.64 (m, 1H), 6.38 (dd, 1H), 5.02 (s, 1H), 3.77 (s, 3H), 3.70 (t, 2H), 1.75-1.63 (m, 2H), 1.40-1.25 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 326 (M + 1).

EXAMPLE 182
Synthesis of 3-(2-hydroxy-4-methoxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(2-hydroxy-4-methoxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (41%): 1H NMR (300 MHz, CDCl$_3$) δ 10.79 (s, 1H), 7.51-7.37 (m, 2H), 7.26 (td, 1H), 6.99 (d, 1H), 6.95 (d, 1H), 6.59 (d, 1H), 6.34 (dd, 1H), 4.67 (d, 1H), 4.14 (d, 1H), 3.76 (s, 3H), 3.78-3.69 (m, 2H), 1.75-1.63 (m, 2H), 1.40-1.25 (m, 4H), 0.87 (t, 3H); MS (ES+) m/z 338 (M - 17), 378 (M + 23).
EXAMPLE 183

Synthesis of ethyl \([3\text{-hydroxy-3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-2-oxo-2,3-
dihydro-1H-indol-1-yl}]acetate\)

Following the procedure as described in EXAMPLE 130, and making non-
critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with ethyl (2,3-
dioxo-2,3-dihydro-1H-indol-1-yl)acetate, and 1,3-benzodioxol-5-ol with 5-indanol, the

\[\begin{align*}
\text{title compound was obtained (84%): } & H \text{ NMR (300 MHz, } CDCl_3) \delta 8.76 (s, 1H), 7.55 (d, 1H), 7.38 (td, 1H), 7.20 (t, 1H), 6.9 (s, 1H), 6.80 (d, 1H), 6.65 (s, 1H), 4.45 (ABq, 2H), 4.32-4.25 (br, 1H), 4.20 (q, 2H), 2.83 (t, 2H), 2.74-2.65 (m, 2H), 2.06-1.94 (m, 2H), 1.27 (t, 3H); MS (ES+) m/z 350 (M - 17), 390 (M + 23).
\end{align*}\]

EXAMPLE 184

Synthesis of ethyl \([3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate\)

Following the procedure as described in EXAMPLE 166, and making non-
critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-
dihydro-2/-/-indol-2-one with ethyl \([3\text{-hydroxy-3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-2-oxo-2,3-
dihydro-1H-indol-1-yl}]acetate\), the title compound was obtained: \[ H \text{ NMR (300 MHz, } CDCl_3) \delta 8.50-7.90 (br, 1H), 7.40-7.32 (m, 2H), 7.38 (td, 1H), 6.94 (s, 1H), 6.84 (d, 1H), 6.75 (s, 1H), 5.16 (s, 1H), 4.48 (ABq, 2H), 4.21 (q, 2H), 2.85 (t, 2H), 2.81-2.61 (m, 2H), 2.09-1.92 (m, 2H), 1.25 (t, 3H); MS (ES+) m/z 352 (M + 1).
\]

EXAMPLE 185

Synthesis of ethyl \([3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-3-(hydroxymethyl)-2-oxo-
2,3-dihydro-1H-indol-1-yl]acetate\)

Following the procedure as described in EXAMPLE 132, and making non-
critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-
dihydro-2/-/-indol-2-one with ethyl \([3\text{-hydroxy-3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-2-oxo-2,3-
dihydro-1H-indol-1-yl}]acetate\), the title compound was obtained: MS (ES+) m/z 364 (M - 17), 404 (M + 23).

EXAMPLE 186

Synthesis of ethyl \([3\text{-hydroxy-3-(3-hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-2-oxo-
2,3-dihydro-iH-indol-1-yl}]acetate\)

Following the procedure as described in EXAMPLE 130, and making non-
critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with ethyl (2,3-
dioxo-2,3-dihydro-1H-indol-1-yl)acetate, and 1,3-benzodioxol-5-ol with 5,6,7,8-
tetrahydronaphthalen-2-ol, the title compound was obtained (81%): \( ^1 \text{H} \text{NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 8.61 (s, 1\text{H}), 7.54 (dd, 1\text{H}), 7.38 (td, 1\text{H}), 7.20 (t, 1\text{H}), 6.80 (d, 1\text{H}), 6.76 (s, 1\text{H}), 6.50 (s, 1\text{H}), 4.45 (ABq, 2\text{H}), 4.21 (q, 2\text{H}), 4.18-4.14 (br, 1\text{H}), 2.73-2.47 (m, 4\text{H}), 1.77-1.63 (m, 4\text{H}), 1.24 (t, 3\text{H}); \text{MS} (\text{ES}^+) \text{m/z} 364 (\text{M} - 17), 404 (\text{M} + 23) \)

**EXAMPLE 187**

Synthesis of ethyl [3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1\text{H}-indol-1-yl]acetate

Following the procedure as described in **EXAMPLE 166**, and making non-critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [3-hydroxy-3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1\text{H}-indol-1-yl]acetate, the title compound was obtained: \( ^1 \text{H} \text{NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 7.42-7.32 (m, 2\text{H}), 7.20 (t, 1\text{H}), 6.84 (d, 1\text{H}), 6.78 (s, 1\text{H}), 6.61 (s, 1\text{H}), 5.12 (s, 1\text{H}), 4.47 (ABq, 2\text{H}), 4.21 (q, 2\text{H}), 2.76-2.44 (m, 4\text{H}), 1.78-1.64 (m, 4\text{H}), 1.24 (t, 3\text{H}); \text{MS} (\text{ES}^+) \text{m/z} 366 (\text{M} + 1). \)

**EXAMPLE 188**

Synthesis of ethyl [3-(hydroxymethyl)-3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1\text{H}-indol-1-yl]acetate

Following the procedure as described in **EXAMPLE 132**, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1\text{H}-indol-1-yl]acetate, the title compound was obtained: \text{MS} (\text{ES}^+) \text{m/z} 378 (\text{M}-17), 418 (\text{M} + 23).

**EXAMPLE 189**

Synthesis of ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1\text{H}-indol-1-yl]acetate

Following the procedure as described in **EXAMPLE 106**, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with ethyl (4-bromo-2,3-dioxo-2,3-dihydro-1\text{H}-indol-1-yl)acetate and 1,3-benzodioxol-5-ol with 3,4-difluorophenol, the title compound was obtained as a white solid (42%); \text{MS} (\text{ES}^+) \text{m/z} 424 (\text{M} - 17), 426 (\text{M} - 17), 464 (\text{M} + 23), 466 (\text{M} + 23).
EXAMPLE 190

Synthesis of ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

A mixture of ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate (0.90 g, 2.00 mmol), triethylsilane (2.00 mL, 12.2 mmol) and trifluoroacetic acid (0.94 mL, 12.2 mmol) was heated at 90°C for two days. After cooling down to ambient temperature, the mixture was diluted with ethyl acetate (200 mL), washed with water, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography (ethyl acetate/hexanes, 1/3) to give the title compound (0.37 g, 43%): \(^\text{1}H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.22 (m, 3H), 6.82-6.71 (m, 2H), 6.52 (t, 1H), 5.10 (s, 1H), 4.45 (s, 2H), 4.21 (q, 2H), 1.23 (t, 3H); MS (ES+) m/z 426.4 (M + 1), 428.4 (M + 1).

EXAMPLE 191

Synthesis of ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (83%): MS (ES+) m/z 456.3 (M + 1), 458.3 (M + 1).

EXAMPLE 192

Synthesis of ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with ethyl (4-bromo-2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate and 1,3-benzodioxol-5-ol with 2,2-dimethyl-2,3-dihydrobenzofuran-6-ol, the title compound was obtained: MS (ES+) m/z 498.5 (M + 23), 500.5 (M + 23).

EXAMPLE 193

Synthesis of ethyl [4-bromo-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

A mixture of ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate (1.32 g, 2.80 mmol),
triethylsilane (2.00 mL, 12.2 mmol) and trifluoroacetic acid (0.94 mL, 12.2 mmol) in dichloromethane (50.0 mL) was stirred at 35°C for 3 hours. The mixture diluted with dichloromethane (100 mL), washed with water, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography (ethyl acetate/hexane, 1/3) to give the title compound (1.04 g, 81%): $^1$H NMR (300 MHz, CDCl$_3$) δ 7.32-7.15 (m, 2H), 6.74 (d, 1H), 6.50-6.36 (br, 2H), 5.04 (s, 1H), 4.51-4.34 (m, 2H), 4.25-4.14 (m, 2H), 2.92-2.69 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.23 (t, 3H); MS (ES+) m/z 460.5 (M + 1), 462.5 (M + 1).

EXAMPLE 194

Synthesis of ethyl [4-bromo-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [4-bromo-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1 H-indol-1-yl]acetate, the title compound was obtained (25%): MS (ES+) m/z 490.5 (M + 1), 492.5 (M + 1).

EXAMPLE 195

Synthesis of 1-(diphenylmethyl)-3-hydroxy-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-5-ol, (Alabaster, RJ. , et al.; Synthesis (1988), 12:950-2) and 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-(diphenylmethyl)-1H-indole-2,3-dione, the title compound was obtained: MS (ES+) m/z 472.2 (M + 23).

EXAMPLE 196

Synthesis of 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2H/-/indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 434.4 (M + 1).
EXAMPLE 197
Synthesis of 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one

To a solution of 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2H-indol-2-one (1.01 g, 2.30 mmol) in THF (50.0 mL) was added paraformaldehyde (1.00 g, 30.0 mmol). Argon was bubbled through the reaction mixture for one hour followed by the addition of diisopropylamine (1.00 g, 10.0 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 20 hours and diluted with ethyl acetate (100 mL). The resulting mixture was washed with water (2 x 50.0 mL), dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness to give 0.67 g (65%) of the title compound: MS (ES+) m/z 486.4 (M + 23).

EXAMPLE 198
Synthesis of 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[5-(trifluoromethyl)-2-furil]methyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 4-methoxy-1-[5-(trifluoromethyl)-2-furil]methyl]-1,3-dihydro-2H-indole-2,3-dione, the title compound was obtained (56%): MS (ES+) m/z 486.4 (M + 23).

EXAMPLE 199
Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[5-(trifluoromethyl)-2-furil]methyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[5-(trifluoromethyl)-2-furil]methyl]-1,3-dihydro-2H-indol-2-one, the title compound was obtained (86%): MS (ES+) m/z 448.4 (M + 1).

EXAMPLE 200
Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-4-methoxy-1-[5-(trifluoromethyl)-2-furil]methyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 198, and making non-critical variations to replace 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2H-indol-2-one with 3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[5-(trifluoromethyl)-2-furil]methyl]-1,3-dihydro-2H-indol-2-one, the title compound was
obtained (64%): MS (ES+) m/z 500.4 (M + 23).

EXAMPLE 201
Synthesis of 4,7-dichloro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one

A. Synthesis of 4,7-dichloro-1-pentyl-1/-/-indole-2,3-dione

To a mixture of sodium hydride (0.17 g, 6.94 mmol, 60% dispersion in mineral oil) in anhydrous N, N-dimethylformamide (5.00 mL) was added a solution of 4,7-dichloro-1/-/-indole-2,3-dione (1.00 g, 4.60 mmol) in N, N-dimethylformamide (5.00 mL) at 0 °C. The brown reaction mixture was stirred for 0.5 h followed by the addition of a solution of 1-bromopentane (0.84 g, 5.55 mmol) in anhydrous N, N-dimethylformamide (5.00 mL). The reaction mixture was stirred at ambient temperature for 16 h and poured into wet ethyl ether (30.0 mL). After the organic layer was separated, it was washed with water (2 x 20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The gummy residue was dried under vacuum and the solid was triturated with ether to give the title compound (0.98 g, 98%): MS (ES+) m/z 286.2 (M + 1).

B. Synthesis of 4,7-dichloro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 4,7-dichloro-1-pentyl-1H-indole-2,3-dione, the title compound was obtained (68%) as a white solid: 1H NMR (300 MHz, CDCl₃) δ 8.61 (br, 1H), 7.26 (t, 1H), 7.03 (d, 1H), 6.52 (s, 1H), 6.12 (s, 1H), 5.86 (dd, 2H), 4.21 (br, 1H), 4.01-3.96 (m, 2H), 1.73-1.58 (m, 2H), 1.34-1.21 (m, 4H), 0.84 (t, 3H); MS (ES+) m/z 408.2 (M - 17).

EXAMPLE 202
Synthesis of 4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 4,7-dichloro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (72%) as a white solid: 1H NMR (300 MHz, CDCl₃) δ 7.27-7.23 (m, 1H), 7.03 (d, 1H), 6.55 (s, 1H), 6.04 (s, 1H), 5.84 (dd, 2H), 5.03 (s, 1H), 4.09-3.99 (m, 2H), 1.72-
1.62 (m, 2H), 1.33-1.24 (m, 4H), 0.86 (t, 3H); MS (ES+) m/z 409.2 (M + 1).

EXAMPLE 203

Synthesis of 4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (94%) as a gummy solid: MS (ES+) m/z 439.3 (M + 1).

EXAMPLE 204

Synthesis of ethyl [4-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with ethyl (4-chloro-2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate, the title compound was obtained (75%) as a white solid: 1H NMR (300 MHz, CDCl₃) δ 8.70 (br, 1H), 7.31 (t, 1H), 7.12 (d, 1H), 6.68 (d, 1H), 6.46 (d, 2H), 4.53-4.46 (m, 2H), 5.09-4.40 (d, 2H), 4.18 (q, 2H), 3.08-2.88 (m, 2H), 1.23 (t, 3H); MS (ES+) m/z 387.8 (M - 17).

EXAMPLE 205

Synthesis ethyl [4-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with ethyl [4-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (75%) as a white solid: 1H NMR (300 MHz, CDCl₃) δ 7.33-7.27 (m, 2H), 7.12 (d, 1H), 6.71 (d, 1H), 6.50-6.48 (m, 1H), 5.10 (s, 1H), 4.54-4.42 (m, 4H), 4.19 (q, 2H), 3.11-2.90 (m, 2H), 1.23 (t, 3H); MS (ES+) m/z 388.8 (M + 1).

EXAMPLE 206

Synthesis of ethyl [4-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (94%) as a gummy solid: MS (ES+) m/z 439.3 (M + 1).
dihydro-2H-indol-2-one with ethyl [4-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (99%) as a gummy solid: MS (ES+) m/z 418.7 (M + 1).

**EXAMPLE 207**

Synthesis of 1-hexyl-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-hexyl-1H-indole-2,3-dione, the title compound was obtained (53%) as a colorless solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.44 (br, 1H), 7.47-7.44 (m, 1H), 7.40-7.34 (m, 1H), 7.17 (t, 1H), 6.89 (d, 1H), 6.55 (s, 1H), 6.21 (s, 1H), 5.84-5.82 (m, 2H), 4.58 (br, 1H), 3.71-3.56 (m, 2H), 1.67-1.62 (m, 2H), 1.32-1.21 (m, 6H), 0.84-0.80 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 179.0, 152.3, 148.8, 142.5, 141.3, 130.3, 129.2, 126.1, 123.7, 117.2, 109.5, 106.8, 101.9, 101.4, 79.2, 40.4, 31.3, 27.1, 26.4, 22.4, 13.9; MS (ES+) m/z 352.5 (M + 17).

**EXAMPLE 208**

Synthesis of 1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 1-hexyl-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (98%) as a white solid: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38-7.13 (m, 3H), 6.94 (d, 1H), 6.60 (s, 1H), 6.32 (s, 1H), 5.84 (dd, 2H), 5.02 (s, 1H), 3.74-3.63 (m, 2H), 1.70-1.61 (m, 2H), 1.37-1.19 (m, 6H), 0.83 (t, 3H); MS (ES+) m/z 354.2 (M + 1).

**EXAMPLE 209**

Synthesis of ethyl [1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetate

To a solution of diisopropylamine (1.14 g, 11.0 mmol) in THF (10.0 mL) was added n-butyl lithium (7.00 mL, 11.0 mmol, 1.6 M solution in hexane) at -75 °C. The resulting mixture was stirred at -75 °C for half an hour and added slowly to a solution of 1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one in THF (20.0 mL) at -75 °C. After stirring at -75 °C for another half an hour, ethyl bromoacetate was added. The mixture was stirred at ambient temperature for 18 hrs and quenched with saturated ammonium chloride solution. The organic solvent was removed in vacuo and
the aqueous residue was diluted with ethyl acetate (100 ml). The organic layer was washed with saturated ammonium chloride (25.0 ml), brine (50.0 ml), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* to dryness. The residue was subjected to column chromatography eluting with 40% EtOAc/Hexanes to yield the title compound (0.19 g, 8%) as an oil: MS (ES+) *m/z* 440.5 (M + 1).

**EXAMPLE 210**

Synthesis of 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 4-bromoisatin, the title compound was obtained (95%) as a beige solid: \(^1\)H NMR (300 MHz, DMSO-d$_6$) δ 10.40 (s, 1H), 9.09 (s, 1H), 7.22 (s, 1H), 7.04 (t, 1H), 6.90 (d, 1H), 6.75 (d, 1H), 6.43 (br, 1H), 6.21 (s, 1H), 5.88 (d, 2H); \(^{13}\)C NMR (75 MHz, DMSO-d$_6$) δ 178.0, 148.7, 147.0, 145.8, 139.5, 131.3, 130.8, 125.4, 118.8, 118.4, 109.4, 108.9, 101.0, 97.4, 76.6; MS (ES+) *m/z* 366.4 (M + 1), 364.5 (M + 1).

**EXAMPLE 211**

Synthesis of 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (95%) as a cream solid: MS (ES+) *m/z* 348.5 (M + 1), 346.3 (M + 1).

**EXAMPLE 212**

Synthesis of 4-bromo-3-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-3-(hydroxymethyl)indolin-2-one

Following the procedure as described in EXAMPLE 209, and making non-critical variations to replace 1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one, and ethyl bromoacetate with para-formaldehyde, the title compound was obtained (70%) as a colorless solid: \(^1\)H NMR (300 MHz, DMSO-d$_6$) δ 9.00 (br, 1H), 7.13-6.95 (m, 3H), 6.84 (d, 1H), 6.16 (d, 1H), 5.90-5.84 (m, 2H), 5.16-4.83 (m, 2H); \(^{13}\)C NMR (75 MHz, DMSO-d$_6$) δ 177.8, 150.4, 147.1, 146.8, 139.8, 130.2, 129.3, 125.8, 117.7, 115.8,
EXAMPLE 213
Synthesis of 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 4-bromoisonatin, and 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol, the title compound was obtained (78%) as a colorless solid: 

\[
\begin{align*}
\text{H NMR} (300 \text{ MHz}, \text{DMSO-CD}_6) & \delta 10.36 (s, 1H), 9.15 (s, 1H), 7.49 (1H), 7.04 (t, 1H), 6.89 (d, 1H), 6.74 (d, 1H), 6.35 (br, 1H), 5.90 (s, 1H), 4.45 (t, 2H), 3.05 (t, 2H); \\
\text{C NMR} (75 \text{ MHz}, \text{DMSO-CD}_6) & \delta 178.4, 160.2, 154.0, 145.7, 131.6, 130.7, 125.5, 125.4, 118.9, 117.7, 116.1, 108.8, 96.8, 76.9, 71.8, 29.1; \\
\text{MS (ES-)} & m/z 344.4 (M - 17), 360.4 (M - 1).
\end{align*}
\]

EXAMPLE 214
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (62%) as a solid: 

\[
\begin{align*}
\text{MS (ES+)} & m/z 346.5 (M + 1), 348.5 (M + 1).
\end{align*}
\]

EXAMPLE 215
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydrobenzofuran-5-yl)-3-(hydroxymethyl)indolin-2-one

Following the procedure as described in EXAMPLE 209, and making non-critical variations to replace 1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one, and ethyl bromoacetate with para-formaldehyde, the title compound was obtained.

EXAMPLE 216
Synthesis of 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 4-bromo-1-
(pyridin-2-ylmethyl)-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol, the title compound was obtained (91%) as a colorless solid: mp >225 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 9.29 (s, 1H), 8.54 (d, 1H), 7.70 (dt, 1H), 7.61 (br, 1H), 7.32-7.26 (m, 2H), 7.07 (d, 1H), 7.00 (d, 1H), 6.72 (d, 1H), 6.60 (br, 1H), 6.02 (s, 1H), 4.91 (ABq, 2H), 4.47 (t, 2H), 3.06 (d, 2H); \(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 176.9, 160.4, 156.3, 153.8, 149.6, 146.1, 137.5, 130.9, 130.8, 126.5, 125.8, 123.1, 121.5, 118.8, 117.3, 116.4, 108.3, 96.7, 76.6, 71.9, 45.7, 29.1; MS (ES\(^+\)) \(m/z\) 455.4 (M + 1), 437.4 (M - 17).

EXAMPLE 217

Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one

To a solution of 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one (1.12 g, 2.48 mmol) in anhydrous dichloromethane (25.0 mL) was added triethylamine (1.40 mL, 9.91 mmol) and SOCl\(_2\) (0.40 mL, 4.96 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and quenched with water (30.0 mL). The organic layer was separated, washed with water (3 x 30.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness to give a gummy material. The residue was dissolved in acetic acid/tetrahydrofuran (3.0 mL/22.0 mL) followed by the addition of zinc dust (0.81 g, 12.4 mmol) in one portion. The reaction mixture was stirred at ambient temperature for 16 h. After the solid was filtered, the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (100 mL), washed with water (3 x 30.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness to give the title compound (1.50 g, 77%) as a gummy material: MS (ES\(^+\)) \(m/z\) 437.3 (M + 1).

EXAMPLE 218

Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (34%): MS (ES\(^+\)) \(m/z\) 468.4 (M + 1).
EXAMPLE 219

Synthesis of 5-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 5-fluoro-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one, the title compound was obtained (66%) as a pale yellow solid: \(^1\)H NMR (300 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 9.15 (s, 1H), 7.21 (s, 1H), 7.15 (dd, 1H), 7.08-6.95 (m, 2H), 6.47 (s, 1H), 6.54 (s, 1H), 6.22 (d, 1H), 5.90 (d, 2H), 4.96 (s, 2H); \(^{13}\)C NMR (75 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 176.7, 160.6, 157.4, 154.0, 148.6, 147.4, 140.1 (m), 139.6 (m), 134.7 (d, \(^2\)J\(_{CF}\) = 29.4 Hz), 121.3, 119.5, 117.7, 115.1 (d, \(^1\)J\(_{CF}\) = 92.1 Hz), 114.5, 111.8 (d, \(^1\)J\(_{CF}\) = 97.5 Hz), 109.7, 109.6, 107.2, 101.3, 97.8, 75.1, 36.9; MS (ES\(^+\)) m/z 450.3 (M + 1).

EXAMPLE 220

Synthesis of 5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 5-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (72%) as a pale yellow solid: \(^1\)H NMR (300 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 9.31 (s, 1H), 7.13 (dd, 1H), 7.02 (dd, 2H), 6.82 (d, 1H), 6.59 (d, 2H), 6.39 (s, 1H), 5.87 (d, 2H), 5.07-4.96 (m, 2H), 4.84 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 176.1, 160.5, 157.4, 153.9, 150.5, 147.5, 140.2, 139.6, 139.1, 132.3 (d, \(^2\)J\(_{CF}\) = 33.3 Hz), 115.3, 114.5 (m), 114.2, 113.9, 111.9 (d, \(^1\)J\(_{CF}\) = 98.7 Hz), 109.9, 109.7 (d, \(^2\)J\(_{CF}\) = 32.7 Hz), 101.3, 98.3, 48.5, 36.8; MS (ES\(^+\)) m/z 436.2 (M + 1).

EXAMPLE 221

Synthesis of 5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one

A mixture of 5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one (3.64 g, 8.41 mmol), para-formaldehyde (2.52 g, 84.1 mmol) and lithium hydroxide monohydrate (1.06 g, 25.2 mmol) in tetrahydrofuran (84.0 mL) and water (10.0 mL) was stirred at 0 °C for 4 h. After the solvent was removed in vacuo, the residue was dissolved in ethyl acetate (100 mL), washed with 10% aqueous HCl (3 x 25.0 mL), dried over anhydrous sodium sulfate
and filtered. The filtrate was concentrated \textit{in vacuo} to dryness. The residue was subjected to column chromatography eluting with ethyl acetate:hexanes (50\%) to give the title compound (0.65 g, 59\%) as a colorless solid: mp 92-95 0\C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.11 (s, 1H), 7.12 (d, 1H), 6.99-6.87 (m, 3H), 6.80 (dd, 1H), 6.48 (d, 1H), 6.23 (s, 1H), 5.89 (d, 2H), 4.97 (ABq, 2H), 4.01 (ABq, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 177.9, 154.3, 154.3, 150.3, 146.9, 140.1, 117.2, 115.2, 114.5, 113.6, 113.3, 111.9, 111.5, 109.3, 108.7, 108.6, 108.3, 101.37, 98.1, 56.2, 49.2, 37.0; MS (ES+) m/z 466.2 (M + 1), 448.2 (M - 17).

EXAMPLE 222

Synthesis of 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1/-/-indole-2,3-dione with 1-(diphenylmethyl)-5-methyl-1H-indole-2,3-dione, the title compound was obtained (92\%) as a colorless solid: $^1$H NMR (300 MHz, CDCl$_3$) δ 9.23 (br s, 1H), 7.40-7.15 (m, 1H), 6.90-6.85 (m, 2H), 6.57 (s, 1H), 6.33 (d, 1H), 6.31 (s, 1H), 5.87 (s, 2H), 4.46 (br, 1H), 2.28 (s, 3H); MS (ES+) m/z 448.4 (M - 17).

EXAMPLE 223

Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2/-/-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-2/-/-indol-2-one, the title compound was obtained (84\%) as a colorless solid: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.37-7.25 (m, 9H), 7.22-7.17 (m, 2H), 7.10 (s, 1H), 6.91 (s, 1H), 6.86 (d, 1H), 6.63 (s, 1H), 6.40 (s, 1H), 6.38 (d, 1H), 5.88 (ABq, 2H), 5.07 (s, 1H), 2.23 (s, 3H); MS (ES+) m/z 450.3 (M + 1).

EXAMPLE 224

Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-5-methyl-1,3-dihydro-2H-indol-2-one

To a solution of 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-2H-indol-2-one (1.61 g, 3.60 mmol) and para-formaldehyde (0.43 g,
14.6 mmol) in dichloromethane (60.0 mL) was added diisopropylamine (7.20 mmol). After stirring at ambient temperature for 3 h, the reaction was quenched with saturated aqueous ammonium chloride (60.0 mL). The organic layer was separated and washed with water (3 x 100 mL), dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/hexanes (20-60%) to afford the title compound (1.07 g, 63%) as a colorless solid: 1H NMR (300 MHz, CDCl₃) δ 10.09 (br, 1H), 7.37-7.16 (m, 12H), 6.99 (s, 1H), 6.87 (d, 1H), 6.62 (s, 1H) 6.54 (s, 1H), 6.37 (d, 1H), 5.87 (d, 2H), 4.45 (ABq, 2H), 2.33 (s, 3H); MS (ES+) m/z 480.4 (M + 1).

EXAMPLE 225
Synthesis of 3-hydroxy-3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 2-methyl-1,3-benzothiazol-5-ol, the title compound was obtained (81%) as a colorless solid: 1H NMR (300 MHz, DMSO-d₆) δ 9.90 (br, 1H), 9.05 (br, 1H), 7.78 (d, 1H), 7.25 (dd, 1H), 7.10-6.95 (m, 2H), 6.90-6.80 (m, 2H), 3.81-3.58 (m, 2H), 2.75 (br, 3H), 2.00-1.60 (m, 2H), 1.50-1.31 (m, 4H), 0.90 (t, 3H); MS (ES+) m/z 383.4 (M + 1).

EXAMPLE 226
Synthesis of 3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one
A suspension of 3-hydroxy-3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one (0.50 g, 1.31 mmol) in hydroiodic acid (10.0 mL) was refluxed for 1.5 days. The reaction mixture was concentrated in vacuo to dryness to give the title compound.

EXAMPLE 227
Synthesis of 3-(hydroxymethyl)-3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 367.5 (M + 1).
EXAMPLE 228
Synthesis of 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-(diphenylmethyl)-2,3-dihydro-1-benzofuran-6-ol, the title compound was obtained: MS (ES+) m/z 478.5 (M + 1).

EXAMPLE 229
Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (73%): 1H NMR (300 MHz, CDCl₃) δ 7.38-7.20 (m, 12H), 7.11-7.04 (m, 2H), 6.97 (s, 1H), 6.57-6.51 (m, 1H), 6.50 (s, 1H), 5.08 (s, 1H), 4.19 (s, 2H), 1.25 (s, 3H), 1.18 (s, 3H); MS (ES+) m/z 426.6 (M + 1).

EXAMPLE 230
Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 197, and making non-critical variations to replace 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 492.5 (M + 1).

EXAMPLE 231
Synthesis of 7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 7-fluoro-1,3-dihydro-2H-indol-2-one, the title compound was obtained (80%): 1H NMR (300 MHz, DMSO-d₆) δ 10.66 (s, 1H), 9.11 (s, 1H), 7.18 (s, 1H), 7.07-6.98 (m, 1H), 6.83-6.74 (m, 1H), 6.66 (d, 1H), 6.48 (s, 1H), 6.18 (s, 1H), 5.92-5.85 (m, 2H); MS (ES+) m/z 304.5 (M + 1).
EXAMPLE 232

Synthesis of 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (100%): ¹H NMR (300 MHz, DMSO-d₆) δ 10.84 (s, 1H), 9.22 (s, 1H), 7.01 (t, 1H), 6.87-6.78 (m, 1H), 6.71 (d, 1H), 6.62 (s, 1H), 6.35 (s, 1H), 5.90-5.85 (m, 2H), 4.67 (s, 1H); MS (ES+) m/z 288.5 (M + 1).

EXAMPLE 233

Synthesis of ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1/-/-indole-2,3-dione with ethyl (4-bromo-2,3-dioxo-2,3-dihydro-1/-/-indol-1-yl)acetate, and 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol, the title compound was obtained (68%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.66 (br, 1H), 7.31-7.19 (m, 3H), 6.73 (dd, 1H), 6.49-6.45 (m, 1H), 5.09-4.36 (m, 4H), 4.20 (q, 2H), 3.14-2.90 (m, 2H), 1.23 (t, 3H); MS (ES+) m/z 432.2 (M - 17).

EXAMPLE 234

Synthesis of ethyl [4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1/-/-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 107, and making no-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (81%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.19 (m, 3H), 6.75 (d, 1H), 6.50-6.45 (m, 1H), 5.08 (s, 1H), 5.09-4.36 (m, 4H), 4.20 (q, 2H), 3.14-2.90 (m, 2H), 1.23 (t, 3H); MS (ES+) m/z 433.3 (M + 1).
EXAMPLE 235

Synthesis of ethyl [4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (99%): MS (ES+) m/z 463.2 (M + 1).

EXAMPLE 236

Synthesis of ethyl [5-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1,3-dihydro-2H-indole-2,3-dione with ethyl [5-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, and 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol, the title compound was obtained (85%) as a white solid: 1H NMR (300 MHz, CDCl3) δ 8.70 (br, 1H), 7.31-7.24 (m, 2H), 6.92 (d, 1H), 6.68 (s, 1H), 6.46 (s, 1H), 4.53-4.46 (m, 2H), 5.09-4.40 (d, 2H), 4.18 (q, 2H), 3.08-2.88 (m, 2H), 1.23 (t, 3H); MS (ES+) m/z 387.8 (M - 17).

EXAMPLE 237

Synthesis of ethyl [5-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [5-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (94%) as a white solid: 1H NMR (300 MHz, CDCl3) δ 7.30-7.24 (m, 2H), 6.72 (d, 1H), 6.66 (s, 1H), 6.39 (s, 1H), 5.05 (s, 1H), 4.53-4.46 (m, 4H), 4.21 (q, 2H), 3.14-2.94 (m, 2H), 1.25 (t, 3H); MS (ES+) m/z 388.8 (M + 1).

EXAMPLE 238

Synthesis of ethyl [5-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [5-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (99%) as a white solid: 1H NMR (300 MHz, CDCl3) δ 8.70 (br, 1H), 7.31-7.24 (m, 2H), 6.92 (d, 1H), 6.68 (s, 1H), 6.46 (s, 1H), 4.53-4.46 (m, 2H), 5.09-4.40 (d, 2H), 4.18 (q, 2H), 3.08-2.88 (m, 2H), 1.23 (t, 3H); MS (ES+) m/z 463.2 (M + 1).
yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (99%): MS (ES+) m/z 418.7 (M + 1).

EXAMPLE 239
Synthesis of methyl [3-(4-chloro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with methyl (2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate, and 1,3-benzodioxol-5-ol with 3-chlorophenol, the title compound was obtained (29%) as a yellow solid: 1H NMR (300 MHz, CDCl₃) δ 9.10 (s, 1H), 7.48 (d, 1H), 7.38 (t, 1H), 7.19 (t, 1H), 7.01 (br s, 1H), 6.80-6.64 (m, 3H), 5.28 (br s, 1H), 4.51 (d, 1H), 4.44 (d, 1H), 3.75 (s, 3H); MS (ES+) m/z 370.5 (M + 23), 372.4 (M + 23).

EXAMPLE 240
Synthesis of methyl [3-(4-chloro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1H-indole-2,3-dione with methyl [3-(4-chloro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (83%) as a semi-solid; 1H NMR (300 MHz, CDCl₃) δ 7.36 (t, 1H), 7.29 (bd, 1H), 7.18 (t, 1H), 6.95 (br, 1H), 6.86-6.78 (m, 3H), 5.13 (brs, 1H), 4.55 (d, 1H), 4.45 (d, 1H), 3.75 (s, 3H); MS (ES+) m/z 332.5 (M + 1), 334.5 (M + 1).

EXAMPLE 241
Synthesis of methyl [3-(4-chloro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1H-indole-2,3-dihydro-2H-indol-2-one with methyl [3-(4-chloro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained: MS (ES+) m/z 362.5 (M + 1) 364.5 (M + 1).
EXAMPLE 242

Synthesis of ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 106, and non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with ethyl (2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetate, the title compound was obtained as a brown oil: MS (ES+) m/z 364.3 (M + 1), 348.5 (M - 17).

EXAMPLE 243

Synthesis of ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained (83%) as a light yellow oil: 1H NMR (300 MHz, CDCl₃) δ 7.39 (t, 1H), 7.34 (d, 1H), 7.26-7.22 (m, 1H), 6.92-6.82 (m, 2H), 6.73 (dd, 1H), 5.11 (br, 1H), 4.50 (d, 1H), 4.43 (d, 1H), 4.21 (q, 2H), 1.23 (t, 3H); MS (ES+) m/z 448.5 (M + 1).

EXAMPLE 244

Synthesis of ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with methyl [3-(4-chloro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was obtained: MS (ES+) m/z 378.3 (M + 1), 361.3 (M - 17).

EXAMPLE 245

Synthesis of 3-(4-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indole-2-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 3-bromophenol, the title compound was obtained (48%) as a white solid: 1H NMR (300 MHz, CDCl₃) δ 9.66 (br, 1H), 7.50-7.38 (m, 2H), 7.24-7.16 (m, 2H), 6.98-6.86 (m, 2H), 6.64 (d, 1H), 4.15 (br, 1H), 3.80-3.55 (m, 2H), 1.75-1.62 (m, 2H), 1.40-1.34 (m, 4H), 0.89 (t, 3H); MS (ES+) m/z 391.4
EXAMPLE 246

Synthesis of 3-(4-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(4-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2/-/-indol-2-one, the title compound was obtained (91%) as a white powder: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40 (t, 1H), 7.31 (d, 1H) 7.24-7.23 (m, 2H), 7.01-6.91 (m, 2H), 6.74 (d, 1H), 5.05 (br, 1H), 3.80-3.65 (m, 2H), 1.75-1.63 (m, 2H), 1.38-1.29 (m, 4H), 0.88 (t, 3H); MS (ES+) $m/z$ 374.4 (M + 1), 376.4 (M + 1).

EXAMPLE 247

Synthesis of 3-(4-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(4-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one, the title compound was obtained: $R_f = 0.5$ (EtOAc/Hexanes, %).

EXAMPLE 248

Synthesis of 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with isatin, 1,3-benzodioxol-5-ol with 4-bromophenol, the title compound was obtained (71%) as a yellowish solid: MS (ES+) $m/z$ 319.4 (M + 1), 321.4 (M + 1).

EXAMPLE 249

Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2/-/-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one, the title compound was obtained (98%) as a white powder: MS (ES+) $m/z$ 306.2 (M + 1), 304.2 (M+1).
EXAMPLE 250

Synthesis of 3-(5-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 221, and making non-critical variations to replace 5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[(5-(trifluoromethyl)-2-furyl)methyl]-1,3-dihydro-2H-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 334.2 (M + 1), 336.2 (M + 1).

EXAMPLE 251

Synthesis of 1-(diphenylmethyl)-3-hydroxy-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1/-/-indole-2,3-dione with 1-(diphenylmethyl)-1/-/-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 3-(trifluoromethoxy)phenol, the title compound was obtained (75%): MS (ES+) m/z 514.5 (M + 23).

EXAMPLE 252

Synthesis of 1-(diphenylmethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2H-indol-2-one, the title compound was obtained (82%): MS (ES+) m/z 498.4 (M + 23).

EXAMPLE 253

Synthesis of 1-(diphenylmethyl)-3-(hydroxymethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 488 (M - 17), 528 (M + 23).
EXAMPLE 254
Synthesis of 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-
yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-
critical variations to replace 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol
(Foster et al., J. Chem. Soc. 1948:2254-2258) and 1-(2-cyclopropylethyl)-1H-indole-
2,3-dione with 1-(diphenylmethyl)-1H-indole-2,3-dione, the title compound was
obtained (68%) as a white solid: MS (ES+) m/z 450.4 (M + 1).

EXAMPLE 255
Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-2,3-dihydro-1H-indol-2-
ol)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-
critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-(diphenylmethyl)-1H-indole-2,3-dione, the title compound was
obtained (67%) as a white solid: MS (ES+) m/z 434.3 (M + 1).

EXAMPLE 256
Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-2,3-dihydro-1H-indol-2-
ol)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 197, and making non-
critical variations to replace 1-(diphenylmethyl)-1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol and
1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 4-bromo-1H-indole-2,3-dione, the title compound was obtained (45%) as a white solid: MS (ES+) m/z 464.5 (M + 1).

EXAMPLE 257
Synthesis of 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-
yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-
critical variations to replace 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol and
1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 4-bromo-1H-indole-2,3-dione, the title compound was obtained (78%) as a white solid: ¹H NMR (300 MHz, DMSO-CD₆) δ 10.36 (s, 1H), 9.15 (s, 1H), 7.49 (1H), 7.04 (t, 1H), 6.89 (d, 1H), 6.74 (d, 1H), 6.35 (br, 1H), 5.90 (s, 1H), 4.45 (t, 2H), 3.05 (t, 2H); ¹³C NMR (75 MHz, DMSO-d₆) δ 178.4, 160.2, 154.0, 145.7, 131.6, 130.7, 125.5, 125.4, 118.9, 117.7, 116.1, 108.8, 96.8, 76.9, 71.8,
29.1; MS (ES-) m/z 344.4 (M - 17), 360.4 (M - 1).

EXAMPLE 258
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1 -benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (62%) as a white solid: MS (ES+) m/z 346.5 (M + 1), 348.5 (M + 1).

EXAMPLE 259
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1 -benzofuran-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 166, and making non-critical variations to replace 3-(5-fluoro-2-hydroxyphenyl)-1-pentylindolin-2-one with 4-bromo-3-(6-hydroxy-2,3-dihydro-1 -benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (16%): Rf = 0.21 (EtOAc/Hexanes, 7/3).

EXAMPLE 260
Synthesis of 7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-\{5-(trifluoromethyl)-2-furyl\}[methyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 7-fluoro-1-[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2H-indole-2,3-dione, the title compound was obtained (75%): MS (ES+) m/z 474.3 (M + 23).

EXAMPLE 261
Synthesis of 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-\{5-(trifluoromethyl)-2-furyl\}[methyl]-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-\{5-(trifluoromethyl)-2-furyl\}[methyl]-1,3-dihydro-2H-indol-2-one, the title compound was obtained (65%): MS (ES+) m/z 436 A (M + 1).
EXAMPLE 262
Synthesis of 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-{[5-(trifluoromethyl)-2-furyl]methyl}-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 197, and making non-critical variations to replace 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-{[5-(trifluoromethyl)-2-furyl]methyl}-1,3-dihydro-2H-indol-2-one, the title compound was obtained (67%): MS (ES+) m/z 488.4 (M + 23).

EXAMPLE 263
Synthesis of 3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol, the title compound was obtained (90%) as a white powder: MS (ES+) m/z 376.3 (M + 23).

EXAMPLE 264
Synthesis of 3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (76%): MS (ES+) m/z 338.3 (M + 1).

EXAMPLE 265
Synthesis of 3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one
Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (46%): MS (ES+) m/z 368.3 (M + 1), 380.4 (M + 23).
EXAMPLE 266
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-(diphenylmethyl)-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 4-bromophenol, the title compound was obtained (90%) as an orange solid: MS (ES+) m/z 486.2 (M + 1), 488.2 (M + 1).

EXAMPLE 267
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 168, and making non-critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one, the title compound was obtained (99%) as a white powder: 1H NMR (300 MHz, CDCl₃) δ 7.39-7.20 (m, 11H), 7.11-7.06 (m, 4H), 6.82 (d, 1H), 6.57-6.51 (m, 1H), 5.04 (s, 1H); MS (ES+) m/z 471.2 (M + 1), 473.2 (M + 1).

EXAMPLE 268
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 197, and making non-critical variations to replace 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2H-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 500.4 (M + 1), 502.4 (M + 1).

EXAMPLE 269
3-[5-(benzyloxy)-2-hydroxyphenyl]-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 4-(benzyloxy)phenol, the title compound was obtained (100%) as a colorless solid: mp 172-175 °C; 1H NMR (300 MHz, CDCl₃) δ 8.52 (br, 1H), 7.36 (dd, 1H), 7.32-7.27 (m, 5H), 7.25-7.21 (m, 3H), 7.18-7.15 (m, 2H), 7.09 (dt, 1H), 6.87 (d, 1H), 6.80 (dd, 1H), 6.69 (d, 1H), 4.89-4.72 (m,
5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.7, 151.5, 149.8, 142.2, 136.9, 133.7, 133.5, 130.2, 129.4, 129.1, 128.6, 128.5, 127.9, 127.6, 126.0, 125.9, 124.1, 119.8, 116.1, 114.4, 109.8, 79.1, 65.9, 43.4; MS (ES$^+$) m/z 494 (M + 23), 454 (M - 17).

EXAMPLE 270

5 Synthesis of 1-(4-chlorobenzyl)-3-(2,2-difluoro-2-thiophen-2-ylethyl)-3-hydroxy-1,3-dihydroindol-2-one

To a solution of 1-(4-chlorobenzyl)-5-ylmethyl-3-hydroxy-3-(2-oxo-2-thiophen-2-ylethyl)-1,3-dihydroindol-2-one (0.57 g, 1.50 mmol) in anhydrous CH$_2$Cl$_2$ (20.0 mL) was added (diethylamino)sulfur trifluoride (0.73 g, 4.50 mmol) at -78 °C and stirred for 2 h. The reaction solution was poured onto water and the organic layer was separated. The organic layer was washed with brine (2 x 10.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/hexane (5% to 30%) to give a solid. The solid was crystallized from ethyl acetate and ether to afford the title compound (0.32 g, 51%) as a tan yellow solid: mp 121-123 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.76 (d, 1H), 7.64 (d, 1H), 7.39-7.21 (m, 6H), 7.12 (t, 1H), 7.01 (t, 1H), 6.64 (d, 1H), 4.92 (ABq, 2H), 4.08-4.05 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 187.0 (d), 172.0 (d), 144.1 (d), 142.9 (d), 134.8, 133.7, 133.6, 132.9, 131.6 (d), 128.9 (d), 128.4, 125.1 (d), 124.4 (d), 123.2 (d), 109.9 (d), 91.8, 89.4, 43.9 (d), 43.5; MS (ES$^+$) m/z 422 (M + 1).

BIOLOGICAL ASSAYS

Various techniques are known in the art for testing the activity of compounds of the invention. In order that the invention described herein may be more fully understood, the following biological assays are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

BIOLOGICAL EXAMPLE 1

Guanidine Influx Assay (in vitro assay)

This example describes an in vitro assay for testing and profiling test agents against human or rat sodium channels stably expressed in cells of either an endogenous or recombinant origin. The assay is also useful for determining the IC$_{50}$ of a sodium channel blocking compound. The assay is based on the guanidine flux assay described by Reddy, N.L., et al., J. Med. Chem. (1998), 41(17):3298-302.
The guanidine influx assay is a radiotracer flux assay used to determine ion flux activity of sodium channels in a high-throughput microplate-based format. The assay uses $^{14}$C-guanidine hydrochloride in combination with various known sodium channel modulators, to assay the potency of test agents. Potency is determined by an IC$_{50}$ calculation. Selectivity is determined by comparing potency of the compound for the channel of interest to its potency against other sodium channels (also called 'selectivity profiling').

Each of the test agents is assayed against cells that express the channels of interest. Voltage gated sodium channels are either TTX sensitive or insensitive. This property is useful when evaluating the activities of a channel of interest when it resides in a mixed population with other sodium channels. The following Table 1 summarizes cell lines useful in screening for a certain channel activity in the presence or absence of TTX.

**TABLE 1**

<table>
<thead>
<tr>
<th>CELL LINE</th>
<th>mRNA Expression</th>
<th>Functional Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHO-K1 (Chinese Hamster Ovary;</td>
<td>• Na$_v$1.4 expression has been</td>
<td>• The 18-20-fold increase in $^{14}$C Guanidine influx was completely showed by RT-PCR</td>
</tr>
<tr>
<td>recommended host cell line)</td>
<td>shown by RT-PCR</td>
<td>Guanidine influx was completely blocked using TTX. (Na$_v$1.4 is a TTX sensitive channel)</td>
</tr>
<tr>
<td>ATTC accession number CCL-61</td>
<td>• No other Na$_v$ expression has</td>
<td></td>
</tr>
<tr>
<td></td>
<td>been detected</td>
<td></td>
</tr>
<tr>
<td>L6 (rat myoblast cell) ATTC</td>
<td>• Expression of Nav1.4 and 1.5</td>
<td>• The 10-15 fold increase in $^{14}$C Guanidine influx was only partially blocked by TTX (Na$_v$1.5 is TTX resistant</td>
</tr>
<tr>
<td>Number CRL-1458</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SH-SY5Y (Human neuroblastoma)</td>
<td>• Published Expression of Nav1.9 and</td>
<td>• The 10-16-fold increase in $^{14}$C Guanidine influx above background.</td>
</tr>
<tr>
<td>ATTC Number CRL-2266</td>
<td>Nav1.7 (Blum et al)</td>
<td>• was partially blocked by TTX (Na$_v$1.9 is TTX resistant)</td>
</tr>
<tr>
<td>CELL LINE</td>
<td>mRNA Expression</td>
<td>Functional Characterization</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| SK-N-BE2C (a human neuroblastoma cell line) ATCC Number CRL-2268 | Expression of NaV1.8     | • Stimulation of BE2C cells with pyrethroids results in a 6 fold increase in [14C] Guanidine influx above background.  
• TTX partially blocked influx (NaV1.8 is TTX resistant) |
| PC12 (rat pheochromocytoma) ATCC Number CRL-1721                | Expression of Na\(_1\)2 expression | • The 8-12-fold increase in [14C] Guanidine influx was completely blocked using TTX. (Na\(_1\)2 is a TTX sensitive channel) |

It is also possible to employ recombinant cells expressing these sodium channels. Cloning and propagation of recombinant cells are known to those skilled in the art (see, for example, Klugbauer, N., et al., *EMBO J.* (1995), 14(6):1084-90; and Lossin, C., et al., *Neuron* (2002), 34:877-884)

Cells expressing the channel of interest are grown according to the supplier or in the case of a recombinant cell in the presence of selective growth media such as G418 (Gibco/Invitrogen). The cells are disassociated from the culture dishes with an enzymatic solution (1X) Trypsin/EDTA (Gibco/Invitrogen) and analyzed for density and viability using haemocytometer (Neubauer). Disassociated cells are washed and resuspended in their culture media then plated into Scintiplates (Beckman Coulter Inc.) (approximately 100,000 cells/well) and incubated at 37 °C/5 % CO\(_2\) for 20-24 hours. After an extensive wash with Low sodium HEPES-buffered saline solution (LNHBSS) (150 mM Choline Chloride, 20 nM HEPES (Sigma), 1mM Calcium Chloride, 5mM Potassium Chloride, 1 mM Magnesium Chloride, 10 mM Glucose) agents diluted with LNHBSS are added to each well. (Varying concentrations of test agent may be used). The activation/radiolabel mixture contains aconitine (Sigma), and 14C-guanidine hydrochloride (ARC).

After loading the cells with test agent and activation/radiolabel mixture, the Scintiplates are incubated at ambient temperature. Following the incubation, the Scintiplates are extensively washed with LNHBSS supplemented with guanidine (Sigma). The Scintiplates are dried and then counted using a Wallac MicroBeta TriLux (Perkin-Elmer Life Sciences). The ability of the test agent to block sodium channel activity is determined by comparing the amount of 14C-guanidine present inside the
cells expressing the different sodium channels. Based on this data, a variety of
calculations, as set out elsewhere in this specification, may be used to determine
whether a test agent is selective for a particular sodium channel.

IC$_{50}$ value of a test agent for a specific sodium channel may be determined
using the above general method. IC$_{50}$ may be determined using a 3, 8, 10, 12 or 16
point curve in duplicate or triplicate with a starting concentration of 1, 5 or 10µM diluted
serially with a final concentration reaching the sub-nanomolar, nanomolar and low
micromolar ranges. Typically the mid-point concentration of test agent is set at 1 µM,
and sequential concentrations of half dilutions greater or smaller are applied (e.g. 0.5
µM; 5 µM and 0.25 µM; 10 µM and 0.125 µM; 20 µM etc.). The IC$_{50}$ curve is calculated
using the 4 Parameter Logistic Model or Sigmoidal Dose-Response Model formula (fit
= (A+((B-A)/(1+((C/x) ^ D))))).

The fold selectivity, factor of selectivity or multiple of selectivity, is calculated by
dividing the IC$_{50}$ value of the test sodium channel by the reference sodium channel, for
example, Nay1.5.

Representative compounds of the invention, when tested in the above assay
using a known cell line that expresses a sodium channel, demonstrated an IC$_{50}$ (nM)
activity level as set forth below in Table 2 wherein "A" refers to an IC$_{50}$ activity level of
from 1 nM to 10 nM, "B" refers to an IC$_{50}$ activity level from 10 nM to 100 nM, "C" refers
to an IC$_{50}$ activity level from 100 nM to 1000 nM, and "D" refers to an IC$_{50}$ activity level
equal to or greater than 1000 nM. The Synthetic Example numbers provided in Table
2 correspond to the Synthetic Examples herein:

<table>
<thead>
<tr>
<th>Synthetic Example #</th>
<th>Compound Name</th>
<th>Activity Level (IC$_{50}$ nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-(4-chlorobenzyl)-5-fluoro-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>1-(4-chlorobenzyl)-3-[2-cyclopropyl-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>1-(4-chlorobenzyl)-3-[2-(4-fluorophenyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC&lt;sub&gt;50&lt;/sub&gt; nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>4</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-pyridin-2-yethyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>6</td>
<td>1-(4-fluorophenyl)-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1-(4-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-nitromethyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>9</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-(1-oxoindan-2-yl)-1,3-dihydroindol-2H-2-one</td>
<td>D</td>
</tr>
<tr>
<td>10</td>
<td>1-[2-(4-chlorophenyl)-ethyl]-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>11</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-[2-oxo-2-(1H-pyrrol-2-yl)-ethyl]-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>12</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-[2-(5-methylfuran-2-yl)-2-oxoethyl]-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>13</td>
<td>1-(4-chlorobenzyl)-3-[2-(2,5-dimethylfuran-3-yl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC&lt;sub&gt;50&lt;/sub&gt; nM)</td>
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<td>---------------------</td>
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</tr>
<tr>
<td>14</td>
<td>1-(4-chlorobenzyl)-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-5-methyl-1,3-dihydro-2H-indol-2-one</td>
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<td>15</td>
<td>3-(2-benzofuran-2-yl-2-oxo-ethyl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
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</tr>
<tr>
<td>16</td>
<td>1-(1,3-benzodioxol-5-ylmethyl)-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>17</td>
<td>1-(1,3-benzodioxol-5-ylmethyl)-3-hydroxy-3-[2-oxo-2-(2-thienyl)ethyl]-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>18</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-(1,1,3-trimethyl-2-oxobutyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>19</td>
<td>1-(4-chlorobenzyl)-3-(1,1-dimethyl-2-oxo-2-thiophen-2-yl-ethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>20</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>21</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(cyclopropylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>22</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(1-phenylethyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>23</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-(trifluoromethoxy)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC&lt;sub&gt;50&lt;/sub&gt; nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>24</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-[4-(1H-pyrrol-1-yl)benzyl]-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>25</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-[(trimethylsilyl)methyl]-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>26</td>
<td>3-(1,3-benzodioxol-5-yl)-7-(4-fluorophenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>27</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(4,4,4-trifluorobutyl)-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>28</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(5-chloropentyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>29</td>
<td>3,7-bis(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>30</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-5,7-dimethyl-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>31</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methylpentyl)-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>32</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(1-methylpentyl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>33</td>
<td>3-(1,3-benzodioxol-5-yl)--1-cyclobutylmethyl-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>34</td>
<td>3-(1,3-benzodioxol-5-yl)-5-bromo-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC&lt;sub&gt;50&lt;/sub&gt; nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>35</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-5-fluoro-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>36</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-methyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>37</td>
<td>1-(4-chlorobenzyl)-3-(1,3-dioxolan-2-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>38</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>39</td>
<td>3-benzyl-1-(4-chlorobenzoyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>40</td>
<td>1-(4-chlorobenzoyl)-3-hydroxy-3-phenyl-1,3-dihydropindol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>41</td>
<td>3-(1,3-benzodioxol-5-yl)-7-fluoro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>42</td>
<td>3-(1,3-benzodioxol-5-yl)-1-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>43</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-thiophen-2-ylmethyl-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>44</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(2-methoxybenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>45</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-naphthalen-1-ylmethyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC&lt;sub&gt;50&lt;/sub&gt; nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>46</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(3,4-difluorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>47</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>48</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-3-hydroxy-5-methoxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>49</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-chloro-3-trifluoromethylbenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>50</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(5-chlorothiophen-2-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>51</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methylbutyl)-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>52</td>
<td>3-(1,3-benzodioxol-5-yl)-1-hexyl-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
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<td>53</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-quinolin-8-ylmethyl-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>54</td>
<td>1-(1,3-benzodioxol-5-yl)--3-hydroxy-3-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>55</td>
<td>3-(1,3-benzodioxol-5-yl)-4,7-dichloro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC$_{50}$ nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>56</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>57</td>
<td>3-(1,3-benzodioxol-5-yl)-6-chloro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
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<tr>
<td>58</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-7-trifluoromethyl-1,3-dihydro-2H-indol-2-one</td>
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</tr>
<tr>
<td>59</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(2-iodobenzyl)-1,3-dihydro-2H-indol-2-one</td>
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</tr>
<tr>
<td>60</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>61</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-yimethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>62</td>
<td>1-(4-chlorobenzyl)-3-(2,5-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>63</td>
<td>3-(1,3-benzodioxol-5-yl)-1-benzyl-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>64</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methoxybenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>65</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-(3-methoxyphenyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC$_{50}$ nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>66</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-(2-methoxyphenyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>67</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>68</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(3,4-dichlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>69</td>
<td>1-(4-chlorobenzyl)-3-(3,4-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
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<td>70</td>
<td>3-benzyl-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
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<tr>
<td>72</td>
<td>3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
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<td>73</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-phenyl-1,3-dihydro-2H-indol-2-one</td>
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</tr>
<tr>
<td>74</td>
<td>1-(4-chlorobenzyl)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>75</td>
<td>3-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>76</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>77</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-bromobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC$_{50}$ nM)</td>
</tr>
<tr>
<td>---------------------</td>
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</tr>
<tr>
<td>78</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(2-bromobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>80</td>
<td>3-(1,3-benzodioxol-5-yl)-1-cyclohexylmethyl-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>83</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(2-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>84</td>
<td>3-(1,3-benzodioxol-5-yl)-4-chloro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>85</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-(6-methoxypyridin-3-yl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>86</td>
<td>1-(4-chlorobenzyl)-3-furan-3-yl-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>87</td>
<td>1-(4-chlorobenzyl)-3-(3,4-dihydro-2H-1,5-benzodioxeepin-7-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>88</td>
<td>1-(4-chlorobenzyl)-3-hydroxy-3-pyrimidin-5-yl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>89</td>
<td>3-(1,3-benzothiazol-6-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>90</td>
<td>1-(1,3-benzodioxol-5-ylmethyl)-3-(1-benzofuran-6-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>91</td>
<td>3-(1-benzofuran-6-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC&lt;sub&gt;50&lt;/sub&gt; nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>92</td>
<td>3-hydroxy-1-(4-methoxybenzyl)-3-(3-pyrrol-1-ylphenyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>93</td>
<td>3-(1,3-benzoxazol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>94</td>
<td>1-(4-chlorobenzyl)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>95</td>
<td>3-(2,2-difluoro-1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>96</td>
<td>3-hydroxy-3-[6-(hydroxymethyl)-1,3-benzodioxol-5-yl]-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>99</td>
<td>1-(4-chlorobenzyl)-3-(4-fluorophenylethynyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>100</td>
<td>3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>101</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-ylmethyl)-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>102</td>
<td>3-(1,3-benzodioxol-5-yl)-4,7-dichloro-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>103</td>
<td>3-(1,3-benzodioxol-5-yl)-7-fluoro-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>104</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>105</td>
<td>3-(1,3-benzodioxol-5-yl)-5,7-dimethyl-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC₅₀ nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>107</td>
<td>1-(2-cyclopropylethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>108</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-1,3-dihydro-2H-indol-2-one</td>
<td>B</td>
</tr>
<tr>
<td>109</td>
<td>3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>110</td>
<td>3-(1,3-benzodioxol-5-yl)-3-imidazol-1-yl-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>111</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-2-oxo-2,3-dihydro-1H-indol-3-yl acetate</td>
<td>D</td>
</tr>
<tr>
<td>112</td>
<td>1-[3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-2-oxo-2,3-dihydro-1H-indol-3-ylhydrazine-1,2-dicarboxylate</td>
<td>D</td>
</tr>
<tr>
<td>113</td>
<td>3,5-bis(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>114</td>
<td>3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-phenyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>115</td>
<td>3-(1,3-benzodioxol-5-yl)-3-chloro-1-(4-chlorobenzyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>116</td>
<td>3-chloro-1-(4-chlorobenzyl)-3-[2-oxo-2-(2-thienyl)ethyl]-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>117</td>
<td>3-(1,3-benzodioxol-5-yl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level (IC&lt;sub&gt;50&lt;/sub&gt; nM)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>118</td>
<td>tert-butyl (2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl)carbamate</td>
<td>D</td>
</tr>
<tr>
<td>119</td>
<td>tert-butyl [2-oxo-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-2,3-dihydro-1H-indol-3-yl]carbamate</td>
<td>D</td>
</tr>
<tr>
<td>120</td>
<td>3-amino-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>121</td>
<td>3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>122</td>
<td>3-{(1,3-benzodioxol-5-yl)}-3-hydroxymethyl-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>123</td>
<td>3-{(1,3-benzodioxol-5-yl)}-3-methoxy-1-pentyl-1,3-dihydro-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>124</td>
<td>3-{(1,3-benzodioxol-5-yl)}-3-methyl-1-pentyl-1,3-dihydro-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>125</td>
<td>methyl [3-{(1,3-benzodioxol-5-yl)}-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetate</td>
<td>D</td>
</tr>
<tr>
<td>126</td>
<td>[3-{(1,3-benzodioxol-5-yl)}-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetic acid</td>
<td>D</td>
</tr>
<tr>
<td>127</td>
<td>2-[3-{(1,3-benzodioxol-5-yl)}-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetamide</td>
<td>D</td>
</tr>
<tr>
<td>128</td>
<td>2-[3-{(1,3-benzodioxol-5-yl)}-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]-N-methylacetamide</td>
<td>D</td>
</tr>
<tr>
<td>129</td>
<td>2-[3-{(1,3-benzodioxol-5-yl)}-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]-N,N-dimethylacetamide</td>
<td>D</td>
</tr>
<tr>
<td>Synthetic Example #</td>
<td>Compound Name</td>
<td>Activity Level</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>136</td>
<td>methyl 3-[(3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]benzoate</td>
<td>C</td>
</tr>
<tr>
<td>144</td>
<td>2-[(3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1H-indol-1-yl)propyl]-1H-isoindole-1,3(2H)-dione</td>
<td>D</td>
</tr>
<tr>
<td>157</td>
<td>methyl 3-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]propanoate</td>
<td>D</td>
</tr>
<tr>
<td>207</td>
<td>1-hexyl-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one</td>
<td>C</td>
</tr>
<tr>
<td>216</td>
<td>4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>221</td>
<td>5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>225</td>
<td>3-hydroxy-3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>263</td>
<td>3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
<tr>
<td>269</td>
<td>3-[5-(benzyl oxy)-2-hydroxy phenyl]-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one</td>
<td>D</td>
</tr>
</tbody>
</table>
BIOLOGICAL EXAMPLE 2

Electrophysiological Assay (In vitro assay)

Cells expressing the channel of interest were cultured in DMEM growth media (Gibco) with 0.5mg/mL G418, +/-1% PSG, and 10% heat-inactivated fetal bovine serum at 37°C and 5% CO₂. For electrophysiological recordings, cells were plated on 10mm dishes.

Whole cell recordings were examined by established methods of whole cell voltage clamp (Bean et al., op. cit.) using an Axopatch 200B amplifier and Clampex software (Axon Instruments, Union City, CA). All experiments were performed at ambient temperature. Electrodes were fire-polished to resistances of 2-4 Mohms. Voltage errors and capacitance artifacts were minimized by series resistance compensation and capacitance compensation, respectively. Data were acquired at 40 kHz and filtered at 5 kHz. The external (bath) solution consisted of: NaCl (140 mM), KCl (5 mM), CaCl₂ (2 mM), MgCl₂ (1 mM), HEPES (10 mM) at pH 7.4. The internal (pipette) solution consisted of (in mM): NaCl (5), CaCl₂ (0.1) MgCl₂ (2), CsCl (10), CsF (120), HEPES (10), EGTA (10), at pH 7.2.

To estimate the steady-state affinity of compounds for the resting and inactivated state of the channel (Kᵣ and Kᵢ, respectively), 12.5 ms test pulses to depolarizing voltages from -60 to +90 mV from a holding potential of -110 mV was used to construct current-voltage relationships (I-V curves). A voltage near the peak of the IV-curve (-30 to 0 mV) was used as the test pulse throughout the remainder of the experiment. Steady-state inactivation (availability) curves were then constructed by measuring the current activated during a 8.75 ms test pulse following 1 second conditioning pulses to potentials ranging from -110 to -10 mV. To monitor channels at steady-state, a single “diary” protocol with a holding potential of -110 mV was created to record the resting state current (10 ms test pulse), the current after fast inactivation (5 ms pre-pulse of -80 to -50 mV followed by a 10 ms test pulse), and the current during various holding potentials (35 ms ramp to test pulse levels). Compounds were

<table>
<thead>
<tr>
<th>Synthetic Example #</th>
<th>Compound Name</th>
<th>Activity Level (IC₅₀ nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>270</td>
<td>1-(4-chlorobenzyl)-3-(2,2-difluoro-2-thiophen-2-ylethyl)-3-hydroxy-1,3-dihydroindol-2-one</td>
<td>D</td>
</tr>
</tbody>
</table>

196
applied during the "diary" protocol and the block was monitored at 15 s intervals.

After the compounds equilibrated, the voltage-dependence of the steady-state inactivation in the presence of the compound was determined. Compounds that block the resting state of the channel decreased the current elicited during test pulses from all holding potentials, whereas compounds that primarily blocked the inactivated state decreased the current elicited during test pulses at more depolarized potentials. The currents at the resting state ($I_{\text{rest}}$) and the currents during the inactivated state ($I_{\text{activated}}$) were used to calculate steady-state affinity of compounds. Based on the Michaelis-Menten model of inhibition, the $K_r$ and $K_w$ was calculated as the concentration of compound needed to cause 50% inhibition of the $I_{\text{rest}}$ or the $I_{\text{inactivated}}$, respectively.

$$% \text{ inhibition} = \frac{V_g V_{\text{max}} [\text{Drug}]^h}{[\text{Drug}]^h + K_m^h}$$

$V_{\text{max}}$ is the rate of inhibition, $h$ is the Hill coefficient (for interacting sites), $K_m$ is Michaelis-Menten constant, and $[\text{Drug}]$ is the concentration of the test compound. At 50% inhibition ($V_g V_{\text{max}}$) of the $I_{\text{rest}}$ or $I_{\text{activated}}$, the drug concentration is numerically equal to $K_m$ and approximates the $K_r$ and $K_w$, respectively.

**BIOLOGICAL EXAMPLE 3**

*In Vivo* Assay for Benign Prostate Hyperplasia (BPH)

The effectiveness of the compounds of the present invention for treating BPH was demonstrated by the following *in vivo* assay.

Dogs were dosed orally with compounds of the present invention at oral doses of between 0 mg/kg and 100 mg/kg for a period of 4 weeks. A control group received placebo. The animals were sacrificed and the prostate glands dissected out, dabbed dry and then weighed. Compounds of the present invention were shown to be efficacious in a dose dependent manner within a range of 5 mg/kg and 100 mg/kg in significantly reducing the weight of the prostate in dogs when compared to the vehicle treated (0 mg/kg) controls. These compounds had no adverse events, making them ideal candidates for the safe treatment of BPH and the associated symptoms, such as, but not limited to, acute urinary retention and urinary tract infection.

**BIOLOGICAL EXAMPLE 4**

*In Vivo* Assay for Antihypercholesterolemia Efficacy and Antiatherosclerotic Efficacy

The compounds of this invention possess antihypercholesterolemia efficacy
and antiatherosclerotic efficacy, as evidenced by their activity in the assays described below.

Dogs have cardiovascular systems similar to that of humans, making them ideal for studying the effects of medicinal compounds designed to treat cardiovascular disorders.

Dogs were dosed orally at a range of 0 mg/kg to 100 mg/kg daily with compounds of the present invention for a period of 2-4 weeks. After 2 and 4 weeks the animals were bled and their serum collected for total cholesterol analysis and compared to the animals dosed with vehicle alone (0 mg/kg).

The measurement of cholesterol is one of the most common tests performed in the clinical laboratory setting. Simple fluorometric methods for the sensitive quantitation of total cholesterol in plasma or serum are commonly used. In one assay, cholesteryl esters in the sample are first hydrolyzed by cholesterol esterase. All cholesterol, whether previously esterified or existing free in the circulation, is then oxidized by cholesterol oxidase to the corresponding ketone and hydrogen peroxide. ADHP (10-acetyl-3,7-dihydroxyphenoxazine) is utilized as a highly sensitive and stable probe for hydrogen peroxide. Horseradish peroxidase catalyzes the reaction of ADHP with hydrogen peroxide to yield the highly fluorescent product resorufin, which can be monitored using excitation wavelengths of 565-580 nm and emission wavelengths of 585-595 nm.

The compounds of the invention exhibited the ability to affect a significant drop in total serum cholesterol when administered in the above assay to dogs in a daily oral dose range of 5-100 mg/kg over a 2- and 4-week period.

**BIOLOGICAL EXAMPLE 5**

*In Vivo* Assay for Treatment of Pruritis

The compounds of the invention can be evaluated for their activity as antipruritic agents by *in vivo* test using rodent models. One established model for peripherally elicited pruritus is through the injection of serotonin into the rostral back area (neck) in hairless rats. Prior to serotonin injections (e.g., 2 mg/ml, 50 µL), a dose of a compound of the present invention can be applied systemically through oral, intravenous or intraperitoneal routes or topically to a circular area fixed diameter (e.g. 18 mm). Following dosing, the serotonin injections are given in the area of the topical dosing. After serotonin injection the animal behaviour is monitored by video recording for 20 min-1.5 h, and the number of scratches in this time compared to vehicle treated
animals. Thus, application of a compound of the current invention could suppress serotonin-induced scratching in rats.

* * * *

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.
WHAT IS CLAIMED IS

1. A method of treating or preventing hypercholesterolemia in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I):

\[
\begin{align*}
R^1 & \text{ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, } \\
& \quad \text{ -R}^2 \text{-C(O)R}^6, \text{ -R}^3 \text{-C(O)OR}^6, \\
& \quad \text{ -R}^4 \text{-C(O)N(R}^5 \text{)R}^6, \text{ -R}^3 \text{-OR}^6, \text{ -R}^4 \text{-CN, -R}^{10} \text{-P(O)(OR}^6 \text{)}_2 \text{ or -R}^{10} \text{-O-R}^{10} \text{-OR}^6; \\
\text{or R}^1 & \text{ is aralkyl substituted by -C(O)N(R}^7 \text{)R}^8 \text{ where:} \\
R^7 & \text{ is hydrogen, alkyl, aryl or aralkyl; and} \\
R^8 & \text{ is hydrogen, alkyl, haloalkyl, -R}^{10} \text{-CN, -R}^{10} \text{-OR}^6, \text{ -R}^{10} \text{-N(R}^5 \text{)R}^6, \text{ aryl, aralkyl,} \\
& \quad \text{ cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or} \\
& \quad \text{ heteroarylalkyl;} \\
\text{or R}^7 & \text{ and R}^8, \text{ together with the nitrogen to which they are attached, form a} \\
& \quad \text{N-heterocyclyl or N-heteroaryl;} \\
\text{and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,} \\
& \quad \text{ heterocyclylalkyl, heteroaryl and heteroaryl group for R}^7 \text{ and R}^8 \text{ is} \\
& \quad \text{ optionally substituted by one or more substituents selected from the} \\
& \quad \text{ group consisting of alkyl, cycloalkyl, aryl, aralkyl, halo, haloalkyl,} \\
& \quad \text{ -R}^9 \text{-CN, -R}^9 \text{-OR}^6, \text{ heterocyclyl and heteroaryl;} \\
\text{or R}^1 & \text{ is aralkyl substituted by one or more substituents selected from the group} \\
& \quad \text{ consisting of -R}^9 \text{-OR}^6, \text{ -R}^9 \text{-C(O)OR}^6, \text{ halo, haloalkyl, alkyl, nitro, cyano, aryl} \\
& \quad \text{ (optionally substituted by cyano), aralkyl (optionally substituted by one or more} \\
& \quad \text{ alkyl groups), heterocyclyl and heteroaryl;} \\
\text{or R}^1 & \text{ is -R}^{10} \text{-N(R}^{11} \text{)R}^{12}, \text{ -R}^{10} \text{-N(R}^{13} \text{)C(O)R}^{12} \text{ or -R}^{10} \text{-N(R}^{11} \text{)C(O)N(R}^{11} \text{)R}^{12} \text{ where:} \\
& \quad \text{ each R}^{11} \text{ is hydrogen, alkyl, aryl or aralkyl;} \\
& \quad \text{ each R}^{12} \text{ is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,}
\end{align*}
\]

200
heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl,
-R\textsuperscript{10}OC(O)R\textsuperscript{6}, -R\textsuperscript{10}C(O)OR\textsuperscript{6}, -R\textsuperscript{10}C(O)N(R\textsuperscript{5})R\textsuperscript{6}, -R\textsuperscript{10}C(O)R\textsuperscript{6}, -R\textsuperscript{10}OR\textsuperscript{6}, or -R\textsuperscript{10}CN;
R\textsuperscript{13} is hydrogen, alkyl, aryl, aralkyl or -C(O)R\textsuperscript{6};
and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,
heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R\textsuperscript{11} and R\textsuperscript{12} is optionally substituted by one or more substituents selected from the
group consisting of alkyl, cycloalkyl, aryl, aralkyl, halo, haloalkyl, nitro,
-R\textsuperscript{9}CN, -R\textsuperscript{9}OR\textsuperscript{6}, -R\textsuperscript{9}C(O)R\textsuperscript{6}, heterocyclyl and heteroaryl;
or R\textsuperscript{1} is heterocyclylalkyl or heteroarylalkyl where the heterocyclylalkyl or the heteroaryl group is optionally substituted by one or more substituents selected from the
group consisting of alkyl, halo, haloalkyl, -R\textsuperscript{9}OR\textsuperscript{6}, -R\textsuperscript{9}C(O)OR\textsuperscript{6}, aryl and
aralkyl;
R\textsuperscript{2a}, R\textsuperscript{2b}, R\textsuperscript{2c} and R\textsuperscript{2d} are each independently selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkeny1, cycloalkyl,
cycloalkylalkyl, aryl, aralkyl, aralkeny1, heterocyclyl, heterocyclylalkyl,
heteroaryl, heterocyclylalkyl, heterocyclylalkyl, heterocyclylalkyl,
heteroaryl, heterocyclylalkyl, heteroaryl, heterocyclylalkyl,
-R\textsuperscript{9}CN, -R\textsuperscript{9}NO\textsubscript{2}, -R\textsuperscript{9}OR\textsuperscript{6}, -R\textsuperscript{9}N(R\textsuperscript{5})R\textsuperscript{6},
-N=C(R\textsuperscript{5})R\textsuperscript{6}, -S(O)\textsubscript{m}R\textsuperscript{5}, -R\textsuperscript{9}C(O)R\textsuperscript{5}, -C(S)R\textsuperscript{5}, -C(R\textsuperscript{5})\textsubscript{2}C(O)R\textsuperscript{6}, -R\textsuperscript{9}C(O)OR\textsuperscript{6},
-C(S)OR\textsuperscript{5}, -R\textsuperscript{9}C(O)N(R\textsuperscript{5})R\textsuperscript{6}, -C(S)N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{9})C(O)R\textsuperscript{5},
-N(R\textsuperscript{9})C(S)R\textsuperscript{5}, -N(R\textsuperscript{9})C(O)OR\textsuperscript{6}, -N(R\textsuperscript{9})C(S)OR\textsuperscript{5}, -N(R\textsuperscript{9})C(O)N(R\textsuperscript{5})R\textsuperscript{6},
-N(R\textsuperscript{9})C(S)N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{9})S(O)\textsubscript{m}R\textsuperscript{5}, -N(R\textsuperscript{9})S(O)\textsubscript{m}N(R\textsuperscript{5})R\textsuperscript{6}, -R\textsuperscript{9}S(O)\textsubscript{m}N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{9})C(=NR\textsuperscript{6})N(R\textsuperscript{5})R\textsuperscript{6},
and -N(R\textsuperscript{9})C(=N-CN)N(R\textsuperscript{5})R\textsuperscript{6}, wherein each m is independently 0, 1, or 2 and each
n is independently 1 or 2;
and wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkeny1,
heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for
R\textsuperscript{2a}, R\textsuperscript{2b}, R\textsuperscript{2c} and R\textsuperscript{2d} is optionally substituted by one or more
substituents selected from the group consisting of alkyl, alkenyl, alkynyl,
halo, haloalkyl, haloalkeny1, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,
aralkeny1, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl,
-R\textsuperscript{9}CN, -R\textsuperscript{9}NO\textsubscript{2}, -R\textsuperscript{9}OR\textsuperscript{6}, -R\textsuperscript{9}N(R\textsuperscript{5})R\textsuperscript{6}, -S(O)\textsubscript{m}R\textsuperscript{5}, -R\textsuperscript{9}C(O)R\textsuperscript{5},
-R\textsuperscript{9}C(O)OR\textsuperscript{6}, -R\textsuperscript{9}C(O)N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{9})C(O)R\textsuperscript{5},
-N(R\textsuperscript{9})C(S)R\textsuperscript{5}, -N(R\textsuperscript{9})C(O)OR\textsuperscript{6}, -N(R\textsuperscript{9})C(S)OR\textsuperscript{5}, -N(R\textsuperscript{9})C(O)N(R\textsuperscript{5})R\textsuperscript{6},
-N(R\textsuperscript{9})C(S)N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{9})S(O)\textsubscript{m}R\textsuperscript{5}, -N(R\textsuperscript{9})S(O)\textsubscript{m}N(R\textsuperscript{5})R\textsuperscript{6}, -R\textsuperscript{9}S(O)\textsubscript{m}N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{9})C(=NR\textsuperscript{6})N(R\textsuperscript{5})R\textsuperscript{6},
and -N(R\textsuperscript{9})C(=N-CN)N(R\textsuperscript{5})R\textsuperscript{6}, wherein each m is independently 0, 1, or 2 and each
n is independently 1 or 2;
or R\textsuperscript{2a} and R\textsuperscript{2b}, R\textsuperscript{2b} and R\textsuperscript{2c}, or R\textsuperscript{2c} and R\textsuperscript{2d}, together with the carbon ring atoms to
which they are directly attached, may form a fused ring selected from
cycloalkyl, aryl, heterocyclyl and heteroaryl;

R³ and R⁴ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R³-CN, -R³-NO₂, -R³-OR⁶, -R³-N(R⁵)R⁶, -N=C(R⁵)R⁶, -S(O)⁰R⁵, -R³-C(O)R⁵, -R³-C(O)X, -C(S)R⁵, -C(R⁵)₂C(O)R⁶, -R³-OC(O)R⁶, -R³-C(O)OR⁶, -C(S)OR⁵, -R³-C(O)N(R⁵)R⁶, -C(S)N(R⁵)R⁶, -R³-Si(R⁶)₃, -N(R⁶)C(O)R⁵, -N(R⁶)C(S)R⁵, -N(R⁶)C(O)OR⁶, -N(R⁶)C(S)OR⁵, -N(R⁶)C(O)N(R⁵)R⁶, -N(R⁶)C(S)N(R⁵)R⁶, -N(R⁶)S(O)ₙR⁵, -N(R⁶)S(O)ₙN(R⁵)R⁶, -R³-S(O)ₙN(R⁵)R⁶, -N(R⁶)C(=NR⁶)N(R⁵)R⁶, -N[N(R⁵)C(O)OR⁶]C(O)OR⁶ and -N(R⁶)C(N=C(R⁵)R⁶)N(R⁵)R⁶,

wherein X is bromo or chloro, each m is independently 0, 1, or 2 and each n is independently 1 or 2; and

wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl groups for R³ and R⁴ is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, alkoxy, -R³-CN, -R³-NO₂, -R³-OR⁶, -R³-N(R⁵)R⁶, -S(O)ₙR⁵, -R³-C(O)R⁵, -R³-C(O)OR⁶, -R³-C(O)N(R⁵)R⁶, -N(R⁶)C(O)R⁵, and -N(R⁶)S(O)ₙR⁶, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;

or R³ and R⁴ together may form =NS(O)₂R⁶, =N-R¹⁵, =N-O-R⁶ or =R³a-C(O)R⁶ (where R³a is a straight or branched alkenylene chain wherein the alkenylene chain is attached to the carbon to which R³ and R⁴ is attached through a double bond and R¹⁵ is a N-heterocyclyl optionally substituted by alkyl, haloalkyl or -R³-OR⁶);

each R⁵ and R⁶ is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

or when R⁵ and R⁶ are each attached to the same nitrogen atom, then R⁵ and R⁶, together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl;

each R⁹ is a direct bond or an optionally substituted straight or branched alkenylene
chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkyne chain; and each \( R^{10} \) is an optionally substituted straight or branched alkenylene chain, an optionally substituted straight or branched alkyne chain or an optionally substituted straight or branched alkyne chain; as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

2. A method of treating or preventing benign prostatic hyperplasia in a mammal, wherein the methods comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I):

\[
\text{(I)}
\]

wherein:
\( R^1 \) is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, \(-R^9-C(O)R^6\), \(-R^9-C(O)OR^6\), \(-R^9-C(O)NR^5R^6\), \(-R^9-OR^6\), \(-R^9-CN\), \(-R^{10}-P(O)(OR^6)_2\) or \(-R^{10}-O-R^{10}-OR^6\);

or \( R^1 \) is aralkyl substituted by \(-C(O)N(R^7)R^8\) where:

\( R^7 \) is hydrogen, alkyl, aryl or aralkyl; and

\( R^8 \) is hydrogen, alkyl, haloalkyl, \(-R^{10}-CN\), \(-R^{10}-OR^6\), \(-R^{10}-N(R^5)R^6\), aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

or \( R^7 \) and \( R^8 \), together with the nitrogen to which they are attached, form a N-heterocyclyl or N-heteroaryl;

and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaryl group for \( R^7 \) and \( R^8 \) is optionally substituted by one or more substituents selected from the group consisting of alkyl, cycloalkyl, aryl, aralkyl, halo, haloalkyl, \(-R^9-CN\), \(-R^9-OR^6\), heterocyclyl and heteroaryl;

or \( R^1 \) is aralkyl substituted by one or more substituents selected from the group
consisting of -R^8-OR^6, -R^8-C(O)OR^6, halo, haloalkyl, alkyl, nitro, cyano, aryl (optionally substituted by cyano), aralkyl (optionally substituted by one or more alkyl groups), heterocyclyl and heteroaryl;  

or R^1 is -R^{10-}N(R^{11})R^{12}, -R^{10-}N(R^{13})C(O)R^{12} or -R^{10-}N(R^{11})C(O)N(R^{11})R^{12} where:  
each R^{11} is hydrogen, alkyl, aryl or aralkyl;  
each R^{12} is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, 
-R^{10-}OC(O)R^6, -R^{10-}C(O)OR^6, -R^{10-}C(O)N(R^5)R^6, -R^{10-}C(O)R^6, -R^{10-}OR^6,  
or -R^{10-}CN;  
R^{13} is hydrogen, alkyl, aryl, aralkyl or -C(O)R^6;  
and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R^{11} and R^{12} is optionally substituted by one or more substituents selected from the group consisting of alkyl, cycloalkyl, aryl, aralkyl, halo, haloalkyl, nitro, -R^8-CN, -R^8-OR^6, -R^8-C(O)R^6, heterocyclyl and heteroaryl;  
or R^1 is heterocyclylalkyl or heteroarylalkyl where the heterocyclylalkyl or the heteroaryl group is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, -R^8-OR^6, -R^8-C(O)OR^6, aryl and aralkyl;  

R^{2a}, R^{2b}, R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R^8-CN, -R^8-NO_2, -R^8-OR^6, -R^8-N(R^5)R^6, 
-N-S(C)OR^5, -R^8-C(O)N(R^5)R^6, -C(S)N(R^5)R^6, -N(R^6)C(O)N(R^5)R^6, -N(R^6)C(S)R^5, 
-N(R^6)C(O)OR^6, -N(R^6)C(S)OR^5, -N(R^6)C(O)N(R^5)R^6, -N(R^6)C(S)N(R^5)R^6,  
-N(R^6)S(O)_nR^6, -N(R^6)S(O)_nN(R^5)R^6, -R^8-S(O)_nN(R^5)R^6, -N(R^6)C(=NR^6)N(R^5)R^6,  
and -N(R^6)C(=NN-N)N(R^5)R^6, wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;  
and wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R^{2a}, R^{2b}, R^{2c} and R^{2d} is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl,
-R^3-CN, -R^3-NO_2, -R^3-OR^6, -R^3-N(R^5)R^6, -S(O)_mR^5, -R^3-C(O)R^5,
-R^3-C(O)OR^6, -R^3-C(O)N(R^5)R^6, -N(R^6)C(O)R^5, and -N(R^6)S(O)_nR^6,
wherein each m is independently 0, 1, or 2 and each n is independently
1 or 2;

or R^{3a} and R^{2b}, R^{2b} and R^{3c}, or R^{2c} and R^{2d}, together with the carbon ring atoms to
which they are directly attached, may form a fused ring selected from
cycloalkyl, aryl, heterocyclyl and heteroaryl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen,
alkyl, alkenyl, alkylnyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl,
aryl, aralkyl, aralkynyl, aralkynyl, heterocyclyl, heterocyclylalkyl, heteroaryl,
heteroarylalkyl, -R^3-CN, -R^3-NO_2, -R^3-OR^6, -R^3-N(R^5)R^6, -N-S(C(R^5))R^6, -S(O)_mR^5,
-R^3-C(O)R^5, -R^3-C(O)X, -C(S)R^5, -C(R^5)C(O)R^6, -R^3-OC(O)R^6, -R^3-C(O)OR^6,
-C(S)OR^5, -R^3-C(O)N(R^5)R^6, -C(S)N(R^5)R^6, -R^3-Si(R^6)_3, -N(R^6)C(O)R^5,
-N(R^6)C(S)(S)OR^5, -N(R^6)C(S)OR^5, -N(R^6)C(O)N(R^5)R^6,
-N(R^6)C(S)N(R^5)R^6, -N(R^6)S(O)_nR^5, -N(R^6)S(O)_nN(R^5)R^6, -R^3-S(O)_nN(R^5)R^6,
-N(R^6)C(=NR^6)N(R^5)R^6, -N[N(R^5)C(O)OR^6]C(O)OR^6 and
-N[R^6]C(N=C(R^5)R^6)]N(R^5)R^6,
wherein X is bromo or chloro, each m is independently 0, 1, or 2 and each n is
independently 1 or 2; and

wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, aralkynyl,
heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl groups for
R^3 and R^4 is optionally substituted by one or more substituents selected from
the group consisting of alkyl, alkenyl, alkylnyl, halo, haloalkyl,
haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl,
heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, -R^3-CN,
-R^3-NO_2, -R^3-OR^6, -R^3-N(R^5)R^6, -S(O)_mR^5, -R^3-C(O)R^5, -R^3-C(O)OR^6,
-R^3-C(O)N(R^5)R^6, -N(R^6)C(O)R^5, and -N(R^6)S(O)_nR^6, wherein each m is
independently 0, 1, or 2 and each n is independently 1 or 2;

or R^{3} and R^{4} together may form =NS(O)_2R^6, =N-R^{15}, =N-O-R^6 or =R^{3a}.C(O)R^6 (where
R^{3a} is a straight or branched alkenylene chain wherein the alkenylene chain is
attached to the carbon to which R^3 and R^4 is attached through a double bond
and R^{15} is a N-heterocyclyl optionally substituted by alkyl, haloalkyl or -R^3-OR^6);

each R^6 and R^6 is independently selected from group consisting of hydrogen, alkyl,
alkenyl, alkylnyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl,
optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl;
or when R\textsuperscript{5} and R\textsuperscript{6} are each attached to the same nitrogen atom, then R\textsuperscript{5} and R\textsuperscript{6},
together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl;
each R\textsuperscript{9} is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; and
each R\textsuperscript{10} is an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain;
as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

3. A method of treating or preventing pruritis in a mammal, wherein the methods comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I):

\[
\begin{align*}
R^1 \text{ is } & \text{hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, } -R^8-C(O)R^6, -R^8-C(O)OR^6, \\
& -R^8-C(O)N(R^5)R^6, -R^8-OR^6, -R^8-CN, -R^{10}-P(O)(OR^6) \text{ or } -R^{10}-O-R^{10}-OR^6; \\
or & R^1 \text{ is aralkyl substituted by } -C(O)N(R^7)R^8 \text{ where:}
\end{align*}
\]

R\textsuperscript{7} is hydrogen, alkyl, aryl or aralkyl; and
R\textsuperscript{8} is hydrogen, alkyl, haloalkyl, -R\textsuperscript{10}-CN, -R\textsuperscript{10}-OR\textsuperscript{6}, -R\textsuperscript{10}-N(R\textsuperscript{5})R\textsuperscript{6}, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;
or R\textsuperscript{7} and R\textsuperscript{8}, together with the nitrogen to which they are attached, form a N-heterocyclyl or N-heteroaryl;
and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,
heterocyclylalkyl, heteroaryl and heteroaryl group for $R^7$ and $R^8$ is
optionally substituted by one or more substituents selected from the
group consisting of alkyl, cycloalkyl, aryl, aralkyl, halo, haloalkyl,
-R$_a$-CN, -R$_a$-OR$_b$, heterocyclyl and heteroaryl;
or $R^1$ is aralkyl substituted by one or more substituents selected from the group
consisting of -R$_a$-OR$_b$, -R$_a$-C(O)OR$_b$, halo, haloalkyl, alkyl, nitro, cyano, aryl
(optionally substituted by cyano), aralkyl (optionally substituted by one or more
alkyl groups), heterocyclyl and heteroaryl;
or $R^1$ is -R$_a$-N(R$_b$)R$_c$ or -R$_a$-N(R$_b$)C(O)R$_c$ or -R$_a$-N(R$_b$)C(O)N(R$_c$)R$_d$ where:
each R$_b$ is hydrogen, alkyl, aryl or aralkyl;
each R$_c$ is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,
heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for $R^1$ and $R^2$
is optionally substituted by one or more substituents selected from the
 group consisting of alkyl, cycloalkyl, aryl, aralkyl, halo, haloalkyl, nitro,
-R$_a$-CN, -R$_a$-OR$_b$, -R$_a$-C(O)R$_b$, heterocyclyl and heteroaryl;
or $R^1$ is heterocyclylalkyl or heteroarylalkyl where the heterocyclylalkyl or the heteroaryl
group is optionally substituted by one or more substituents selected from the
group consisting of alkyl, halo, haloalkyl, -R$_a$-OR$_b$, -R$_a$-C(O)OR$_b$, aryl and
aralkyl;
$R^{2a}$, $R^{2b}$, $R^{2c}$ and $R^{2d}$ are each independently selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl,
cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl,
nitro, heteroaryl, heteroarylalkyl, -R$_a$-CN, -R$_a$-NO$_b$, -R$_a$-OR$_b$, -R$_a$-N(R$_b$)R$_c$,
-N$_b$=C(R$_b$)R$_c$, -S(O)$_n$R$_b$, -R$_a$-C(O)R$_c$, -C(S)R$_b$, -C(R$_b$)$_2$C(O)R$_c$, -R$_a$-C(O)OR$_b$,
-C(S)OR$_b$, -R$_a$-C(O)N(R$_b$)R$_c$, -C(S)N(R$_b$)R$_c$, -N(R$_b$)C(O)R$_c$, -N(R$_b$)C(S)R$_c$,
-N(R$_b$)C(O)OR$_b$, -N(R$_b$)C(S)OR$_b$, -N(R$_b$)C(O)N(R$_c$)R$_d$, -N(R$_b$)C(S)N(R$_c$)R$_d$,
-N(R$_b$)S(O)$_n$R$_c$, -N(R$_b$)S(O)$_n$N(R$_c$)R$_d$, -R$_a$-S(O)$_n$N(R$_c$)R$_d$, -N(R$_b$)C(=NR$_b$)N(R$_c$)R$_d$,
and -N(R$_b$)C(=N-CN)N(R$_c$)R$_d$, wherein each m is independently 0, 1, or 2 and
each n is independently 1 or 2;
and wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, 
heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for
R\textsuperscript{2a}, R\textsuperscript{2b}, R\textsuperscript{2c} and R\textsuperscript{2d} is optionally substituted by one or more
substituents selected from the group consisting of alkyl, alkenyl, alkynyl,
halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,
aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl,
-R\textsuperscript{9}-CN, -R\textsuperscript{9}-NO\textsubscript{2}, -R\textsuperscript{9}-OR\textsuperscript{6}, -R\textsuperscript{9}-N(R\textsuperscript{5})R\textsuperscript{6}, -S(O)\textsubscript{m}R\textsuperscript{5}, -R\textsuperscript{9}-C(O)R\textsuperscript{5},
-R\textsuperscript{9}-C(O)OR\textsuperscript{6}, -R\textsuperscript{9}-C(O)N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{6})C(O)R\textsuperscript{5}, and -N(R\textsuperscript{5})S(O)\textsubscript{n}R\textsuperscript{5},
wherein each m is independently 0, 1, or 2 and each n is independently
1 or 2;
or R\textsuperscript{2a} and R\textsuperscript{2b}, R\textsuperscript{2b} and R\textsuperscript{2c}, or R\textsuperscript{2c} and R\textsuperscript{2d}, together with the carbon ring atoms to
which they are directly attached, may form a fused ring selected from
cycloalkyl, aryl, heterocyclyl and heteroaryl;
R\textsuperscript{3} and R\textsuperscript{4} are each independently selected from the group consisting of hydrogen,
alcohol, alkenyl, alkenyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl,
aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl,
heteroarylalkyl, -R\textsuperscript{9}-CN, -R\textsuperscript{9}-NO\textsubscript{2}, -R\textsuperscript{9}-OR\textsuperscript{6}, -R\textsuperscript{9}-N(R\textsuperscript{5})R\textsuperscript{6}, -N=R(C(R\textsuperscript{5})R\textsuperscript{6}, -S(O)\textsubscript{m}R\textsuperscript{6},
-R\textsuperscript{9}-C(O)R\textsuperscript{5}, -R\textsuperscript{9}-C(O)X, -C(S)R\textsuperscript{5}, -C(R\textsuperscript{5})\textsubscript{2}C(O)R\textsuperscript{5}, -R\textsuperscript{9}-OC(O)R\textsuperscript{5}, -R\textsuperscript{9}-C(O)OR\textsuperscript{6},
-C(S)OR\textsuperscript{5}, -R\textsuperscript{9}-C(O)N(R\textsuperscript{5})R\textsuperscript{6}, -C(S)N(R\textsuperscript{5})R\textsuperscript{6}, -R\textsuperscript{9}-Si(R\textsuperscript{6})\textsubscript{3}, -N(R\textsuperscript{6})C(O)R\textsuperscript{5},
-N(R\textsuperscript{5})C(S)R\textsuperscript{5}, -N(R\textsuperscript{6})C(O)OR\textsuperscript{5}, -N(R\textsuperscript{6})C(S)OR\textsuperscript{5}, -N(R\textsuperscript{6})C(O)N(R\textsuperscript{5})R\textsuperscript{6},
-N(R\textsuperscript{5})C(S)N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{6})S(O)\textsubscript{n}R\textsuperscript{5}, -N(R\textsuperscript{6})S(O)\textsubscript{n}N(R\textsuperscript{5})R\textsuperscript{6},
-N(R\textsuperscript{5})C(=NR\textsuperscript{6})N(R\textsuperscript{5})R\textsuperscript{6}, -N[N(R\textsuperscript{5})C(O)OR\textsuperscript{6}]C(O)OR\textsuperscript{6} and
-N(R\textsuperscript{5})C(N=C(R\textsuperscript{5})R\textsuperscript{6})N(R\textsuperscript{5})R\textsuperscript{6},
wherein X is bromo or chloro, each m is independently 0, 1, or 2 and each n is
independently 1 or 2; and
wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, aralkynyl,
heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl groups for
R\textsuperscript{3} and R\textsuperscript{4} is optionally substituted by one or more substituents selected from
the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, 
haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl,
heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, -R\textsuperscript{9}-CN,
-R\textsuperscript{9}-NO\textsubscript{2}, -R\textsuperscript{9}-OR\textsuperscript{6}, -R\textsuperscript{9}-N(R\textsuperscript{5})R\textsuperscript{6}, -S(O)\textsubscript{m}R\textsuperscript{5}, -R\textsuperscript{9}-C(O)R\textsuperscript{5}, -R\textsuperscript{9}-C(O)OR\textsuperscript{6},
-R\textsuperscript{9}-C(O)N(R\textsuperscript{5})R\textsuperscript{6}, -N(R\textsuperscript{6})C(O)R\textsuperscript{5}, and -N(R\textsuperscript{5})S(O)\textsubscript{n}R\textsuperscript{5}, wherein each m is
independently 0, 1, or 2 and each n is independently 1 or 2;
or R\textsuperscript{3} and R\textsuperscript{4} together may form =N=SO\textsubscript{2}R\textsuperscript{6}, =N-R\textsuperscript{15}, =N-O-R\textsuperscript{5} or =R\textsuperscript{9a}-C(O)R\textsuperscript{6} (where
R\(^{3a}\) is a straight or branched alkenylene chain wherein the alkenylene chain is attached to the carbon to which R\(^{3}\) and R\(^{4}\) is attached through a double bond and R\(^{15}\) is a N-heterocyclyl optionally substituted by alkyl, haloalkyl or -R\(^{9}\)-OR\(^{6}\); each R\(^{9}\) and R\(^{6}\) is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl; or when R\(^{5}\) and R\(^{6}\) are each attached to the same nitrogen atom, then R\(^{5}\) and R\(^{6}\), together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl; each R\(^{3}\) is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; and each R\(^{10}\) is an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

4. A method of treating or preventing cancer in a mammal, wherein the methods comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I):

![Chemical Structure](image)

wherein:
R\(^{1}\) is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkeny, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, -R\(^{2}\)-C(O)R\(^{6}\), -R\(^{3}\)-C(O)OR\(^{6}\), -R\(^{8}\)-C(O)N(R\(^{5}\))R\(^{6}\), -R\(^{8}\)-OR\(^{6}\), -R\(^{8}\)-CN, -R\(^{10}\)-P(O)(OR\(^{6}\))\(_{2}\) or -R\(^{10}\)-O-R\(^{10}\)-OR\(^{6}\); or R\(^{1}\) is aralkyl substituted by -C(O)N(R\(^{7}\))R\(^{8}\) where:
R seven is hydrogen, alkyl, aryl or aralkyl; and
R eight is hydrogen, alkyl, haloalkyl, -R eleven-CN, -R eleven-OR six, -R eleven-N(R five)R six, ary1, aralkyl,
cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;
or R seven and R eight, together with the nitrogen to which they are attached, form a
N-heterocyclyl or N-heteroaryl;
and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,
heterocyclylalkyl, heteroaryl and heteroaryl group for R seven and R eight is
optionally substituted by one or more substituents selected from the group
consisting of alkyl, cycloalkyl, aryl, aralkyl, halo, haloalkyl,
-R eight-CN, -R eight-OR six, heterocyclyl and heteroaryl;
or R one is aralkyl substituted by one or more substituents selected from the group
consisting of -R eight-OR six, -R eight-C(O)OR six, halo, haloalkyl, alkyl, nitro, cyano, aryl
(optionally substituted by cyano), aralkyl (optionally substituted by one or more
alkyl groups), heterocyclyl and heteroaryl;
or R one is -R ten-N(R eleven)R twelve, -R ten-N(R twelve)C(O)R twelve or -R ten-N(R eleven)C(O)N(R eleven)R twelve where:
each R eleven is hydrogen, alkyl, aryl or aralkyl;
each R twelve is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl,
heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl,
-R ten-OC(O)R six, -R ten-C(O)OR six, -R ten-C(O)N(R five)R six, -R ten-C(O)R six, -R ten-OR six,
or -R ten-CN;
R thirteen is hydrogen, alkyl, aryl, aralkyl or -C(O)R six;
and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,
heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R eleven and R twelve
is optionally substituted by one or more substituents selected from the group
consisting of alkyl, cycloalkyl, aryl, aralkyl, halo, haloalkyl, nitro,
-R eight-CN, -R eight-OR six, -R eight-C(O)R six, heterocyclyl and heteroaryl;
or R one is heterocyclylalkyl or heteroarylalkyl where the heterocyclylalkyl or the heteroaryl
group is optionally substituted by one or more substituents selected from the group
consisting of alkyl, halo, haloalkyl, -R eight-OR six, -R eight-C(O)OR six, ary1 and
aralkyl;
R two, R three and R four are each independently selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl,
cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl,
heteroaryl, heteroarylalkyl, -R eight-CN, -R eight-NO two, -R eight-OR six, -R eight-N(R five)R six,
-N=C(R\(^5\))R\(^6\), -S(O)\(_m\)R\(^5\), -R\(^8\)-C(O)R\(^5\), -C(S)R\(^5\), -C(R\(^5\))\(_2\)C(O)R\(^6\), -R\(^8\)-C(O)OR\(^6\),
-C(S)OR\(^5\), -R\(^8\)-C(O)N(R\(^5\))R\(^6\), -C(S)N(R\(^5\))R\(^5\), -N(R\(^6\)-C(O)R\(^5\),
-N(R\(^5\))C(O)OR\(^6\), -N(R\(^5\))C(S)OR\(^5\), -N(R\(^5\))C(O)N(R\(^5\))R\(^6\), -N(R\(^5\))C(S)N(R\(^5\))R\(^6\),
-N(R\(^6\))S(O)\(_n\)R\(^5\), -N(R\(^6\))S(O)\(_n\)N(R\(^5\))R\(^6\), -R\(^8\)-S(O)\(_n\)N(R\(^5\))R\(^6\), -N(R\(^6\))C(=NR\(^6\))N(R\(^5\))R\(^6\),
and -N(R\(^6\))C(=N-CN)N(R\(^5\))R\(^6\), wherein each m is independently 0, 1, or 2 and each n is independently 1 or 2;

and wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl groups for R\(^2a\), R\(^2b\), R\(^2c\) and R\(^2d\) is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, heterocyclyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl, -R\(^9\)-CN, -R\(^9\)-NO\(_2\), -R\(^9\)-OR\(^6\), -R\(^9\)-N(R\(^5\))R\(^6\), -S(O)\(_m\)R\(^5\), -R\(^8\)-C(O)R\(^5\),
-R\(^8\)-C(O)OR\(^6\), -R\(^8\)-C(O)X, -C(S)R\(^5\), -C(R\(^5\))\(_2\)C(O)R\(^6\), -R\(^8\)-OC(O)R\(^6\), -R\(^8\)-C(O)OR\(^6\),
-C(S)OR\(^5\), -R\(^8\)-C(O)N(R\(^5\))R\(^6\), -C(S)N(R\(^5\))R\(^6\), -R\(^8\)-Si(R\(^6\))\(_3\), -N(R\(^6\))C(O)R\(^5\),
-N(R\(^6\))C(S)R\(^5\), -N(R\(^6\))C(O)OR\(^6\), -N(R\(^6\))C(S)OR\(^5\), -N(R\(^6\))C(O)N(R\(^5\))R\(^6\),
-N(R\(^6\))C(S)N(R\(^5\))R\(^6\), -N(R\(^6\))S(O)\(_n\)R\(^5\), -N(R\(^6\))S(O)\(_n\)N(R\(^5\))R\(^6\), -R\(^8\)-S(O)\(_n\)N(R\(^5\))R\(^6\),
-N(R\(^6\))C(=NR\(^6\))N(R\(^5\))R\(^6\), -N[R(R\(^6\))-C(O)OR\(^6\)]C(O)OR\(^6\) and
-N[R(R\(^6\))C(N=C(R\(^5\)))R\(^6\)]N(R\(^5\))R\(^6\),
wherein X is bromo or chloro, each m is independently 0, 1, or 2 and each n is independently 1 or 2;

or R\(^2a\) and R\(^2b\), R\(^2b\) and R\(^2c\), or R\(^2c\) and R\(^2d\), together with the carbon ring atoms to which they are directly attached, may form a fused ring selected from cycloalkyl, aryl, heterocyclyl and heteroaryl;

R\(^3\) and R\(^4\) are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R\(^9\)-CN, -R\(^9\)-NO\(_2\), -R\(^9\)-OR\(^6\), -R\(^9\)-N(R\(^5\))R\(^6\), -S(O)\(_m\)R\(^5\), -R\(^8\)-C(O)R\(^5\),
-R\(^8\)-C(O)OR\(^6\), -C(S)R\(^5\), -C(R\(^5\))\(_2\)C(O)R\(^6\), -R\(^8\)-OC(O)R\(^6\), -R\(^8\)-C(O)OR\(^6\),
-C(S)OR\(^5\), -R\(^8\)-C(O)N(R\(^5\))R\(^6\), -C(S)N(R\(^5\))R\(^6\), -R\(^8\)-Si(R\(^6\))\(_3\), -N(R\(^6\))C(O)R\(^5\),
-N(R\(^6\))C(S)R\(^5\), -N(R\(^6\))C(O)OR\(^6\), -N(R\(^6\))C(S)OR\(^5\), -N(R\(^6\))C(O)N(R\(^5\))R\(^6\),
-N(R\(^6\))C(S)N(R\(^5\))R\(^6\), -N(R\(^6\))S(O)\(_n\)R\(^5\), -N(R\(^6\))S(O)\(_n\)N(R\(^5\))R\(^6\), -R\(^8\)-S(O)\(_n\)N(R\(^5\))R\(^6\),
-N(R\(^6\))C(=NR\(^6\))N(R\(^5\))R\(^6\), -N[R(R\(^6\))-C(O)OR\(^6\)]C(O)OR\(^6\) and
-N[R(R\(^6\))C(N=C(R\(^5\)))R\(^6\)]N(R\(^5\))R\(^6\),
wherein X is bromo or chloro, each m is independently 0, 1, or 2 and each n is independently 1 or 2;

and wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, aralkynyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl groups for R\(^3\) and R\(^4\) is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl,
haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl,
heterocycyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, \(-\text{R}^9\)-CN, \(-\text{R}^9\)-NO\(_2\), \(-\text{R}^9\)-OR\(_6\), \(-\text{R}^9\)-C(\text{O})R\(_5\), \(-\text{R}^9\)-C(\text{O})OR\(_6\),
\(-\text{R}^9\)-C(\text{O})N(R\(_5\))R\(_6\), \(-\text{R}^9\)-C(\text{O})R\(_5\), and \(-\text{N}(\text{R}^6)\text{S(\text{O})}_n\text{R}^5\), wherein each \(m\) is independently 0, 1, or 2 and each \(n\) is independently 1 or 2;
or \(\text{R}^3\) and \(\text{R}^4\) together may form \(\text{=NS(\text{O})}_2\text{R}^6\), \(\text{=N-}\text{R}^{15}\), \(\text{=N-O-R}^6\), or \(\text{=R}^{9a}\text{-C(\text{O})R}^6\) (where \(\text{R}^{9a}\) is a straight or branched alkenylene chain wherein the alkenylene chain is attached to the carbon to which \(\text{R}^3\) and \(\text{R}^4\) is attached through a double bond and \(\text{R}^{15}\) is a N-heterocyclyl optionally substituted by alkyl, haloalkyl or \(-\text{R}^9\text{-OR}^6\);
each \(\text{R}^5\) and \(\text{R}^6\) is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and optionally substituted heteroaryl;
or when \(\text{R}^5\) and \(\text{R}^6\) are each attached to the same nitrogen atom, then \(\text{R}^5\) and \(\text{R}^6\), together with the nitrogen atom to which they are attached, may form a N-heterocyclyl or N-heteroaryl;
each \(\text{R}^9\) is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; and each \(\text{R}^{10}\) is an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain;
as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof;
or a pharmaceutically acceptable salt, solvate or prodrug thereof.