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(54) Title: OXINDOLE COMPOUNDS AND THEIR USES AS THERAPEUTIC AGENTS

(57) Abstract: This invention is directed to oxindole compounds that are useful for the treatment and/or prevention of sodium channel-mediated diseases or conditions, such as pain. Pharmaceutical compositions comprising the compounds and methods of using the compounds are also disclosed.

OXINDOLE COMPOUNDS AND THEIR USES AS THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention is directed to oxindole compounds. In particular, this invention is directed to oxindole compounds that are sodium channel blockers and are therefore useful in treating sodium channel-mediated diseases or conditions, such as pain, as well as other diseases and conditions associated with the mediation of sodium channels.

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
5 with function, this family of proteins are considered prime points of therapeutic intervention. Na_v1.1 and Na_v1.2 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_v1.1 and Na_v1.2 result in severe epileptic states and in some cases mental decline (Rhodes, T.H., et al., *Proc. Natl. Acad. Sci. USA*
10 (2004), 101(30):11147-52; Kamiya, K., et al., *J. Biol. Chem.* (2004), 279(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_v1.3 is broadly expressed throughout the body (Raymond, C.K., et al., *op. cit.*). It has been demonstrated to have its expression upregulated in the dorsal horn
15 sensory neurons of rats after nervous system injury (Hains, B.D., et al., *J. Neurosci.* (2003), 23(26):8881-92). Many experts in the field have considered Na_v1.3 as a suitable target for pain therapeutics (Lai, J., et al., *Curr. Opin. Neurobiol.* (2003), (3):291-72003; Wood, J.N., et al., *J. Neurobiol.* (2004), 61(1):55-71; Chung, J.M., et al.,
20 *Novartis Found Symp.* (2004), 261:19-27; discussion 27-31, 47-54).

Na_v1.4 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
25 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_v1.5, is expressed mainly in the heart ventricles and atria (Raymond, C.K., et al., *op. cit.*), and can be found in the sinovial node, ventricular node and possibly Purkinje cells. The rapid upstroke of the cardiac action
30 potential and the rapid impulse conduction through cardiac tissue is due to the opening of Na_v1.5. As such, Na_v1.5 is central to the genesis of cardiac arrhythmias. Mutations in human Na_v1.5 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
35 blocker therapy has been used extensively in treating cardiac arrhythmias. The first

antiarrhythmic drug, quinidine, discovered in 1914, is classified as a sodium channel blocker.

Na_v1.6 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_v1.6 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_v1.7 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_v1.7 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_v1.7 null mutants; deleting Na_v1.7 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_v1.7 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_v1.7 blockers active in a subset of neurons is supported by the finding that two human heritable pain conditions, primary erythralgia and familial rectal pain, have been shown to map to Na_v1.7 (Yang, Y., et al., *J. Med. Genet.* (2004), 41(3):171-4).

The expression of Na_v1.8 is essentially restricted to the DRG (Raymond, C.K., et al., *op. cit.*). There are no identified human mutations for Na_v1.8. However, Na_v1.8-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_v1.8 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_v1.8) subunit.

The tetrodotoxin insensitive, peripheral sodium channel Na_v1.9, disclosed by Dib-Hajj, S.D., et al. (see Dib-Hajj, S.D., et al., *Proc. Natl. Acad. Sci. USA* (1998), 95(15):8963-8) was shown to reside solely in the dorsal root ganglia. It has been demonstrated that Na_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 (Cestèle, S. et al., *Biochimie* (2000), Vol. 82:883-892).

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.

Management of Acute and Chronic Pain

Drug therapy is the mainstay of management for acute and chronic pain in all age groups, including neonates, infants and children. The pain drugs are classified by the American Pain Society into three main categories: 1) non-opioid analgesics-acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDs), including salicylates (e.g. aspirin), 2) opioid analgesics and 3) co-analgesics.

Non-opioid analgesics such as acetaminophen and NSAIDs are useful for acute and chronic pain due to a variety of causes including surgery, trauma, arthritis and cancer. NSAIDs are indicated for pain involving inflammation because acetaminophen lacks anti-inflammatory activity. Opioids also lack anti-inflammatory activity. All NSAIDs inhibit the enzyme cyclooxygenase (COX), thereby inhibiting prostaglandin synthesis and reducing the inflammatory pain response. There are at

least two COX isoforms, COX-1 and COX-2. Common non-selective COX inhibitors include, ibuprofen and naproxen. Inhibition of COX-1, which is found in platelets, GI tract, kidneys and most other human tissues, is thought to be associated with adverse effects such as gastrointestinal bleeding. The development of selective COX-2
5 NSAIDs, such as Celecoxib, Valdecoxib and Rofecoxib, have the benefits of non-selective NSAIDs with reduced adverse effect profiles in the gut and kidney. However, evidence now suggests that chronic use of certain selective COX-2 inhibitors can result in an increased risk of stroke occurrence.

The use of opioid analgesics is recommended by the American Pain Society to
10 be initiated based on a pain-directed history and physical that includes repeated pain assessment. Due to the broad adverse effect profiles associated with opiate use, therapy should include a diagnosis, integrated interdisciplinary treatment plan and appropriate ongoing patient monitoring. It is further recommended that opioids be added to non-opioids to manage acute pain and cancer related pain that does not
15 respond to non-opioids alone. Opioid analgesics act as agonists to specific receptors of the mu and kappa types in the central and peripheral nervous system. Depending on the opioid and its formulation or mode of administration it can be of shorter or longer duration. All opioid analgesics have a risk of causing respiratory depression, liver failure, addiction and dependency, and as such are not ideal for long-term or chronic
20 pain management.

A number of other classes of drugs may enhance the effects of opioids or NSAIDs, have independent analgesic activity in certain situations, or counteract the side effects of analgesics. Regardless of which of these actions the drug has, they are collectively termed "coanalgesics". Tricyclic antidepressants, antiepileptic drugs, local
25 anaesthetics, glucocorticoids, skeletal muscle relaxants, anti-spasmodic agents, antihistamines, benzodiazepines, caffeine, topical agents (e.g. capsaicin), dextroamphetamine and phenothiazines are all used in the clinic as adjuvant therapies or individually in the treatment of pain. The antiepileptic drugs in particular have enjoyed some success in treating pain conditions. For instance, Gabapentin, which
30 has an unconfirmed therapeutic target, is indicated for neuropathic pain. Other clinical trials are attempting to establish that central neuropathic pain may respond to ion channel blockers such as blockers of calcium, sodium and/or NMDA (N-methyl-D-aspartate) channels. Currently in development are low affinity NMDA channel blocking agents for the treatment of neuropathic pain. The literature provides substantial pre-
35 clinical electrophysiological evidence in support of the use of NMDA antagonists in the

treatment of neuropathic pain. Such agents also may find use in the control of pain after tolerance to opioid analgesia occurs, particularly in cancer patients.

Systemic analgesics such as NSAIDs and opioids are to be distinguished from therapeutic agents which are useful only as local analgesics/anaesthetics. Well known
5 local analgesics such as lidocaine and xylocaine are non-selective ion channel blockers which can be fatal when administered systemically. A good description of non-selective sodium channel blockers is found in Madge, D. et al., *J. Med. Chem.* (2001), 44(2):115-37.

Several sodium channel modulators are known for use as anticonvulsants or
10 antidepressants, such as carbamazepine, amitriptyline, lamotrigine and riluzole, all of which target brain tetrodotoxin-sensitive (TTX-S) sodium channels. Such TTX-S agents suffer from dose-limiting side effects, including dizziness, ataxia and somnolence, primarily due to action at TTX-S channels in the brain.

Sodium Channels Role in Pain

15 Sodium channels play a diverse set of roles in maintaining normal and pathological states, including the long recognized role that voltage gated sodium channels play in the generation of abnormal neuronal activity and neuropathic or pathological pain (Chung, J.M. et al.). Damage to peripheral nerves following trauma or disease can result in changes to sodium channel activity and the development of
20 abnormal afferent activity including ectopic discharges from axotomised afferents and spontaneous activity of sensitized intact nociceptors. These changes can produce long-lasting abnormal hypersensitivity to normally innocuous stimuli, or allodynia. Examples of neuropathic pain include, but are not limited to, post-herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, chronic lower back pain, phantom limb pain,
25 and pain resulting from cancer and chemotherapy, chronic pelvic pain, complex regional pain syndrome and related neuralgias.

There has been some degree of success in treating neuropathic pain symptoms by using medications, such as gabapentin, and more recently pregabalin, as short-term, first-line treatments. However, pharmacotherapy for neuropathic pain has
30 generally had limited success with little response to commonly used pain reducing drugs, such as NSAIDs and opiates. Consequently, there is still a considerable need to explore novel treatment modalities.

There remains a limited number of potent effective sodium channel blockers with a minimum of adverse events in the clinic. There is also an unmet medical need

to treat neuropathic pain and other sodium channel associated pathological states effectively and without adverse side effects. The present invention provides compounds, methods of use and compositions that include these compounds to meet these critical needs.

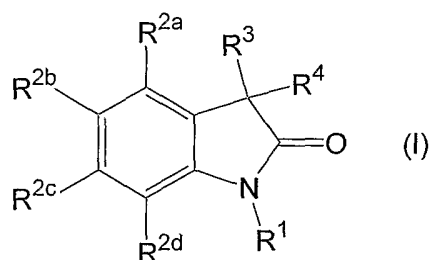
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SUMMARY OF THE INVENTION

The present invention is directed to oxindole compounds that are useful for the treatment and/or prevention of sodium channel-mediated diseases or conditions, such as pain. The compounds of the present invention are also useful for the treatment of other sodium channel-mediated diseases or conditions, including, but not limited to central nervous conditions such as epilepsy, anxiety, depression and bipolar disease; cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular conditions such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome.

15

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



wherein:

R¹ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, -R⁹-C(O)R⁶, -R⁹-C(O)OR⁶, -R⁹-C(O)N(R⁵)R⁶, -R⁹-OR⁶, -R⁹-CN, -R¹⁰-P(O)(OR⁶)₂ or -R¹⁰-O-R¹⁰-OR⁶;

20

or R¹ is aralkyl substituted by -C(O)N(R⁷)R⁸ where:

R⁷ is hydrogen, alkyl, aryl or aralkyl; and

25

R⁸ is hydrogen, alkyl, haloalkyl, -R¹⁰-CN, -R¹⁰-OR⁶, -R¹⁰-N(R⁵)R⁶, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

or R⁷ and R⁸, together with the nitrogen to which they are attached, form a N-heterocyclyl or N-heteroaryl;

and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,

heterocyclalkyl, heteroaryl and heteroaryl groups 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, $-R^9-CN$, $-R^9-OR^6$, heterocycl and heteroaryl;

5 or R^1 is aralkyl substituted by one or more substituents selected from the group consisting of $-R^9-OR^6$, $-R^9-C(O)OR^6$, halo, haloalkyl, alkyl, nitro, cyano, aryl (optionally substituted by cyano), aralkyl (optionally substituted by one or more alkyl groups), heterocycl 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:

10 each R^{11} is hydrogen, alkyl, aryl or aralkyl;

each R^{12} is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, 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 $-R^{10}-CN$;

15 R^{13} is hydrogen, alkyl, aryl, aralkyl or $-C(O)R^6$;

and wherein each aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, 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, $-R^9-CN$, $-R^9-OR^6$, $-R^9-C(O)R^6$, heterocycl and heteroaryl;

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

25 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, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, 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;

35 and wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl,

- heterocyclyl, heterocyclalkyl, 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;
- 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, aralkynyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)X$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-OC(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-R^9-Si(R^6)_3$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, $-N[N(R^5)C(O)OR^6]C(O)OR^6$ 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, heterocyclalkyl, 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, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;
- or R^3 and R^4 together may form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$ (where R^{9a} 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^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 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.

In another aspect, the invention provides methods for the treatment of pain 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 present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, $Na_v1.4$, $Na_v1.5$, $Na_v1.6$, $Na_v1.7$, $Na_v1.8$, or $Na_v1.9$ is implicated in the disease state.

In another aspect, the invention provides methods of treating a range of sodium channel-mediated diseases or conditions, for example, pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritic, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses,

familial erythermalgia, primary erythermalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions caused by stroke, glaucoma or neural trauma, tachy-arrhythmias, atrial fibrillation and ventricular fibrillation.

5 In another aspect, the invention provides methods of treating a range of sodium channel-mediated disease or condition through inhibition of ion flux through a voltage-dependent sodium channel 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.

10 In another aspect, the invention provides pharmaceutical compositions comprising the compounds of the invention, as set forth above, and pharmaceutically acceptable excipients. In one embodiment, the present invention relates to a pharmaceutical composition comprising a compound of the invention in a pharmaceutically acceptable carrier and in an amount effective to treat diseases or
15 conditions related to pain when administered to an animal, preferably a mammal, most preferably a human.

 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
20 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.

DETAILED DESCRIPTION OF THE INVENTION

25 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-C₁₂alkyl describes an alkyl group, as defined below, having a total of 7 to 12 carbon atoms, and C₄-C₁₂cycloalkylalkyl describes a
30 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.

 Accordingly, as used in the specification and appended claims, unless specified

to the contrary, the following terms have the meaning indicated:

"Amino" refers to the -NH_2 radical.

"Cyano" refers to the -CN radical.

"Hydroxyl" refers to the -OH radical.

5 "Imino" refers to the =NH substituent.

"Nitro" refers to the -NO_2 radical.

"Oxo" refers to the =O substituent.

"Thioxo" refers to the =S substituent.

"Trifluoromethyl" refers to the -CF_3 radical.

10 "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 (*t*-butyl),
 15 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, -OR^{14} , -OC(O)-R^{14} , $\text{-N(R}^{14})_2$, -C(O)R^{14} , -C(O)OR^{14} , $\text{-C(O)N(R}^{14})_2$, $\text{-N(R}^{14})\text{C(O)OR}^{17}$, $\text{-N(R}^{15})\text{C(O)R}^{17}$, $\text{-N(R}^{15})\text{S(O)}_t\text{R}^{17}$ (where *t* is 1 to 2),
 20 $\text{-S(O)}_t\text{OR}^{17}$ (where *t* is 1 to 2), $\text{-S(O)}_t\text{R}^{17}$ (where *t* is 0 to 2), and $\text{-S(O)}_t\text{N(R}^{15})_2$ (where *t* is 1 to 2) where each R^{15} 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^{17} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl,
 25 heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted unless otherwise indicated.

"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
 30 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, -OR^{15} , -OC(O)-R^{15} ,
 35 $\text{-N(R}^{15})_2$, -C(O)R^{15} , -C(O)OR^{15} , $\text{-C(O)N(R}^{15})_2$, $\text{-N(R}^{15})\text{C(O)OR}^{17}$, $\text{-N(R}^{15})\text{C(O)R}^{17}$,

-N(R¹⁵)S(O)_tR¹⁷ (where t is 1 to 2), -S(O)_tOR¹⁷ (where t is 1 to 2), -S(O)_tR¹⁷ (where t is 0 to 2), and -S(O)_tN(R¹⁵)₂ (where t is 1 to 2) where each R¹⁵ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl; and
 5 each R¹⁷ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted unless otherwise indicated.

"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely
 10 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 alkylene 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 alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two
 15 carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilyl, -OR¹⁵, -OC(O)-R¹⁵, -N(R¹⁵)₂, -C(O)R¹⁵, -C(O)OR¹⁵, -C(O)N(R¹⁵)₂, -N(R¹⁵)C(O)OR¹⁷, -N(R¹⁵)C(O)R¹⁷, -N(R¹⁵)S(O)_tR¹⁷ (where t is 1 to 2), -S(O)_tOR¹⁷
 20 (where t is 1 to 2), -S(O)_tR¹⁷ (where t is 0 to 2), and -S(O)_tN(R¹⁵)₂ (where t is 1 to 2) where each R¹⁵ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl; and each R¹⁷ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or
 25 heteroarylalkyl, and where each of the above substituents is unsubstituted unless otherwise indicated.

"Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely
 30 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
 35 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, oxo, trimethylsilyl, $-OR^{15}$, $-OC(O)-R^{15}$, $-N(R^{15})_2$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})_2$, $-N(R^{15})C(O)OR^{17}$, $-N(R^{15})C(O)R^{17}$, $-N(R^{15})S(O)_tR^{17}$ (where t is 1 to 2), $-S(O)_tOR^{17}$ (where t is 1 to 2), $-S(O)_tR^{17}$ (where t is 0 to 2), and $-S(O)_tN(R^{15})_2$ (where t is 1 to 2) where each R^{15} 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^{17} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted unless otherwise indicated.

"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, $-OR^{15}$, $-OC(O)-R^{15}$, $-N(R^{15})_2$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})_2$, $-N(R^{15})C(O)OR^{17}$, $-N(R^{15})C(O)R^{17}$, $-N(R^{15})S(O)_tR^{17}$ (where t is 1 to 2), $-S(O)_tOR^{17}$ (where t is 1 to 2), $-S(O)_tR^{17}$ (where t is 0 to 2), and $-S(O)_tN(R^{15})_2$ (where t is 1 to 2) where each R^{15} 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^{17} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted unless otherwise indicated.

"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, heterocyclalkyl, heteroaryl, heteroarylalkyl, -OR¹⁵, -OC(O)-R¹⁵, -N(R¹⁵)₂, -C(O)R¹⁵, -C(O)OR¹⁵, -C(O)N(R¹⁵)₂, -N(R¹⁵)C(O)OR¹⁷, -N(R¹⁵)C(O)R¹⁷, -N(R¹⁵)S(O)_tR¹⁷ (where t is 1 to 2), -S(O)_tOR¹⁷ (where t is 1 to 2), -S(O)_tR¹⁷ (where t is 0 to 2), and -S(O)_tN(R¹⁵)₂ (where t is 1 to 2) where each R¹⁵ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl; and each R¹⁷ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted.

"Alkoxy" refers to a radical of the formula -OR_a where R_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_a-O-R_a where each R_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 a multicyclic hydrocarbon ring system consisting only of hydrogen and carbon and containing from 6 to 19 carbon atoms, where the ring system may be partially saturated. Aryl groups include, but are not limited to groups such as fluorenyl, phenyl, naphthyl, indene, dihydronaphthyl, tetrahydronaphthyl and dihydroindenyl. 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, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, heteroaryl, heteroarylalkyl, -R¹⁶-OR¹⁵, -R¹⁶-OC(O)-R¹⁵, -R¹⁶-N(R¹⁵)₂, -R¹⁶-C(O)R¹⁵, -R¹⁶-C(O)OR¹⁵, -R¹⁶-C(O)N(R¹⁵)₂, -R¹⁶-N(R¹⁵)C(O)OR¹⁷, -R¹⁶-N(R¹⁵)C(O)R¹⁷, -R¹⁶-N(R¹⁵)S(O)_tR¹⁷ (where t is 1 to 2), -R¹⁶-S(O)_tOR¹⁷ (where t is 1 to 2), -R¹⁶-S(O)_tR¹⁷ (where t is 0 to 2), and -R¹⁶-S(O)_tN(R¹⁵)₂ (where t is 1 to 2) where each R¹⁵ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl; each R¹⁶ is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R¹⁷ is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted.

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above and R_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.

5 "Aryloxy" refers to a radical of the formula $-OR_b$ where R_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 $-R_cR_b$ where R_c is an alkenyl radical as defined above and R_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 $-OR_b$ where R_b 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, decalyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^{16}-OR^{15}$, $-R^{16}-OC(O)-R^{15}$, $-R^{16}-N(R^{15})_2$, $-R^{16}-C(O)R^{15}$, $-R^{16}-C(O)OR^{15}$, $-R^{16}-C(O)N(R^{15})_2$, $-R^{16}-N(R^{15})C(O)OR^{17}$, $-R^{16}-N(R^{15})C(O)R^{17}$, $-R^{16}-N(R^{15})S(O)_tR^{17}$ (where t is 1 to 2), $-R^{16}-S(O)_tOR^{17}$ (where t is 1 to 2), $-R^{16}-S(O)_tR^{17}$ (where t is 0 to 2), and $-R^{16}-S(O)_tN(R^{15})_2$ (where t is 1 to 2) where each R^{15} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl; each R^{16} is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R^{17} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl,

heterocyclalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted.

"Cycloalkylalkyl" refers to a radical of the formula $-R_aR_d$ where R_a is an alkyl radical as defined above and R_d 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.

"Heterocycl" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocycl 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 heterocycl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocycl radical may be partially or fully saturated. Examples of such heterocycl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranlyl, thiomorpholyl, thiamorpholyl, 1-oxo-thiomorpholyl, and 1,1-dioxo-thiomorpholyl. Unless stated otherwise specifically in the specification, the term "heterocycl" is meant to include heterocycl 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, thioxo, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^{16}-OR^{15}$, $-R^{16}-OC(O)-R^{15}$, $-R^{16}-N(R^{15})_2$, $-R^{16}-C(O)R^{15}$, $-R^{16}-C(O)OR^{15}$, $-R^{16}-C(O)N(R^{15})_2$, $-R^{16}-N(R^{15})C(O)OR^{17}$, $-R^{16}-N(R^{15})C(O)R^{17}$, $-R^{16}-N(R^{15})S(O)_tR^{17}$ (where t is 1 to 2), $-R^{16}-S(O)_tOR^{17}$ (where t is 1 to 2), $-R^{16}-S(O)_tR^{17}$ (where t is 0 to 2), and $-R^{16}-S(O)_tN(R^{15})_2$ (where t is 1 to 2) where each R^{15} is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl or heteroarylalkyl; each R^{16} is

independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R^{17} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted.

5 "N-heterocyclyl" is a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. An N-heterocyclyl radical may be optionally substituted as described above for heterocyclyl radicals.

"Heterocyclalkyl" refers to a radical of the formula $-R_aR_e$ 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 heterocyclalkyl radical may be optionally substituted as defined above for an alkyl group. The heterocycl part of the heterocyclalkyl radical may be optionally substituted as defined above for
15 a heterocycl group.

"Heteroaryl" refers to a 3- to 18-membered fully or partially aromatic ring radical which consists of three to twelve carbon atoms and from one to five 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
20 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 quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzoaxazolyl, benzothiazolyl, benzothiadiazolyl,
25 benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzo-1,3-dioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl,
30 indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl,
35 thiadiazolyl, 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, halo, haloalkyl, haloalkenyl, cyano, oxo, thioxo, nitro, oxo, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^{16}-OR^{15}$, $-R^{16}-OC(O)-R^{15}$, $-R^{16}-N(R^{15})_2$, $-R^{16}-C(O)R^{15}$, $-R^{16}-C(O)OR^{15}$, $-R^{16}-C(O)N(R^{15})_2$, $-R^{16}-N(R^{15})C(O)OR^{17}$, $-R^{16}-N(R^{15})C(O)R^{17}$, $-R^{16}-N(R^{15})S(O)_tR^{17}$ (where t is 1 to 2), $-R^{16}-S(O)_tOR^{17}$ (where t is 1 to 2), $-R^{16}-S(O)_tR^{17}$ (where t is 0 to 2), and $-R^{16}-S(O)_tN(R^{15})_2$ (where t is 1 to 2) where each R^{15} is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R^{16} is independently a direct bond or a straight or branched alkylene or alkenylene chain; and each R^{17} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted.

"N-heteroaryl" is a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An N-heteroaryl radical may be optionally substituted as described above for heteroaryl radicals.

"Heteroarylalkyl" refers to a radical of the formula $-R_aR_f$ where R_a is an alkyl radical as defined above and R_f 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 $-R_bR_f$ where R_b is an alkenyl radical as defined above and R_f 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.

"Analgesia" refers to an absence of pain in response to a stimulus that would

normally be painful.

"Allodynia" refers to a condition in which a normally innocuous sensation, such as pressure or light touch, is perceived as being extremely painful.

"Prodrugs" is meant to indicate a compound that may be converted under
5 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
10 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):7-9, 21-24 (Elsevier, Amsterdam)).

A discussion of prodrugs is provided in Higuchi, T., *et al.*, "Pro-drugs as Novel
15 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
20 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,
25 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.

30 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
35 iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I ,

and ^{125}I , respectively. These radiolabelled 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
5 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.* ^3H , 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.* ^2H , may afford certain
10 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
15 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.

20 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
25 compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabelled 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
30 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
35 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.

"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 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, 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, propionic 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
5 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,
10 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
15 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
20 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
25 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
30 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 sodium channel-mediated disease or condition in the mammal, preferably a human. The amount of a compound of the invention
35 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;
- 10 (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, *i.e.*, relieving pain without addressing the underlying disease or condition.

15 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
20 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
25 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
30 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*
35 geometric isomers. Likewise, all tautomeric forms are also intended to be included.

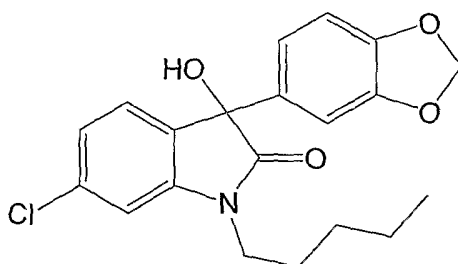
A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose
5 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
10 (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 1,3-dihydroindol-2-one structure. For
15 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.

20 Thus, for example, a compound of formula (I) wherein R¹ is pentyl, R^{2a}, R^{2b} and R^{2d} are each hydrogen, R^{2c} is chloro, R³ is -OH and R⁴ 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-
25 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 $-R^9-C(O)R^6$, $-R^9-C(O)OR^6$, $-R^9-OR^6$, $-R^9-CN$, $-R^{10}-P(O)(OR^6)_2$, $-R^{10}-O-R^{10}-OR^6$, hydrogen, alkyl, haloalkyl, cycloalkylalkyl, heterocyclalkyl, aryl (optionally substituted by one or more substituents selected from the group consisting of halo and $-R^9-C(O)OR^6$), aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, $-R^9-OR^6$ and $-R^9-C(O)OR^6$), 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, heterocyclalkyl, heterocyclalkylalkyl, 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, heterocyclalkyl, heterocyclalkylalkyl, 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, heterocyclalkyl, heterocyclalkylalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$ 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;
- 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, heterocyclalkyl 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 $-R^9-OR$), $-R^9-OR^6$, $-R^9-OC(O)R^6$, $-R^9-N(R^5)R^6$, $-R^9-C(O)R^5$, $-R^9-C(O)X$, $-R^9-C(O)OR^6$ and $-N(R^6)C(O)OR^6$, wherein X is chloro or bromo;
- R^4 is independently selected from the group consisting of alkyl, aryl, aralkyl, aralkynyl, heteroaryl, heteroarylalkyl, $-R^9-C(O)R^5$, $-N(R^6)C(O)N(R^5)R^6$, $-R^9-NO_2$, $-R^9-N(R^5)R^6$, $-R^9-C(O)OR^6$, $-N[N(R^5)C(O)OR^6]C(O)OR^6$, $-R^9-N(R^6)C(O)OR^6$ and

$-R^9-Si(R^6)_3$,

wherein each of the aryl, aralkynyl, heteroaryl and heteroarylalkyl 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,

heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

or R^3 and R^4 together may form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$ (where R^{9a} 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^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 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.

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, aryl or aralkyl, where each aryl and aralkyl group for R^1 is independently 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^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo, aryl, heteroaryl and $-R^9-OR^6$, wherein each of the aryl and heteroaryl 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, -R⁹-CN, -R⁹-NO₂, -R⁹-OR⁶,
 5 -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, alkyl, halo, -R⁹-OR⁶ or -R⁹-OC(O)R⁶;

R⁴ is independently selected from the group consisting of alkyl, aryl, aralkynyl,
 10 heteroaryl, heteroarylalkyl, -R⁹-C(O)R⁵, -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,
 15 cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl,
 heterocyclylalkyl, heteroaryl, heteroarylalkyl, 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;

20 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;

25 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
 30 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, heteroaryl, -R⁹-OR⁶ and
 35 -R⁹-C(O)OR⁶;

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

wherein each of the aryl and heteroaryl 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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 $-R^9-OC(O)R^6$;

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

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 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 aryl or aralkyl each optionally substituted by one or more substituents selected from the group consisting of 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, halo and alkyl;

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

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

each R^5 is alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and optionally substituted heteroaryl;

each R^6 is hydrogen or alkyl; and

each R^9 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, wherein:

- R^1 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, $-R^9-OR^6$ and $-R^9-C(O)OR^6$);
- R^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo, aryl, heteroaryl and $-R^9-OR^6$, wherein each of the aryl and heteroaryl 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$ 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 $-R^9-OC(O)R^6$;
- R^4 is heterocyclylalkyl, heteroaryl or heteroarylalkyl, each 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$ 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;
- 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:

- R¹ is aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, -R⁹-OR⁶ and -R⁹-C(O)OR⁶);
- R^{2a}, R^{2b}, R^{2c} and R^{2d} are each independently selected from the group consisting of
- 5 hydrogen, alkyl, halo, phenyl, benzodioxolyl and -R⁹-OR⁶,
- R³ is hydrogen, halo, -R⁹-OR⁶ or -R⁹-OC(O)R⁶;
- R⁴ is heterocyclalkyl, heteroaryl or heteroarylalkyl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, heterocycl, and -R⁹-OR⁶;
- 10 each 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 heterocycl and optionally substituted heteroaryl; and
- 15 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:

- 20 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);
- R^{2a}, R^{2b}, R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo, aryl, heteroaryl and -R⁹-OR⁶,
- 25 wherein each of the aryl and heteroaryl 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, heterocycl, heterocyclalkyl, 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;
- 30 R³ is hydrogen or -R⁹-OR⁶;
- R⁴ is aryl, aralkyl or aralkynyl,
- 35 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 alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, -R⁹-CN, -R⁹-NO₂,
 5 -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,
 10 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
 15 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
 20 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);

R^{2a}, R^{2b}, R^{2c} and R^{2d} are each independently selected from the group consisting of
 25 hydrogen, alkyl, halo, aryl, heteroaryl and -R⁹-OR⁶,

wherein each of the aryl and heteroaryl 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, -R⁹-CN, -R⁹-NO₂, -R⁹-OR⁶,
 30 -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 -R⁹-OR⁶;

35 R⁴ is aryl, aralkyl or aralkynyl,

wherein each of the aryl, aralkyl and aralkynyl groups for R^4 is optionally substituted by one or more substituents selected from the group consisting of halo, heteroaryl 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 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.

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, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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 hydrogen, alkyl or $-R^9-OR^6$;

R^4 is independently selected from the group consisting of alkyl, aryl, aralkynyl, heteroaryl, heteroarylalkyl, $-R^9-C(O)R^5$, $-R^9-N(R^6)C(O)OR^6$, $-N(R^6)C(O)N(R^5)R^6$,

$-R^9-NO_2$, $-R^9-N(R^5)R^6$, $-R^9-C(O)OR^6$, and $-R^9-Si(R^6)_3$,

wherein each of the aryl, aralkynyl, heteroaryl and heteroarylalkyl 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,

heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$,

$-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$,

$-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl,

aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9-OR^6$,

$-R^9-N(R^5)R^6$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$,

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, $-R^9-CN$,

$-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$,

$-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

R³ is hydrogen, alkyl or -R⁹-OR⁶;

R⁴ is heteroaryl 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, 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;

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 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, halo, haloalkyl, aryl, aralkyl, -R⁹-OR⁶, -R⁹-C(O)OR⁶ and -R⁹-C(O)N(R⁵)R⁶;

R³ is hydrogen, alkyl or -R⁹-OR⁶;

R⁴ is heteroaryl optionally substituted by one or more substituents selected from the group consisting of halo, -R⁹-OR⁶ and -N(R⁶)C(O)R⁵;

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

5 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

10 above in the Summary of the Invention, wherein:

R¹ 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 and halo;

R³ is hydrogen or -R⁹-OR⁶;

15 R⁴ is independently selected from the group consisting of -R⁹-C(O)R⁵ and -R⁹-N(R⁶)C(O)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; and

20 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.

25 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, haloalkyl, -R⁹-OR⁶, heteroaryl and -R⁹-C(O)OR⁶);

R^{2a}, R^{2b}, R^{2c} and R^{2d} are each hydrogen;

30 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;

R³ is -R⁹-C(O)X, -R⁹-C(O)OR⁶ and -R⁹-C(O)N(R⁵)R⁶ where X is bromo or chloro;

35 R⁴ is independently selected from the group consisting of -R⁹-C(O)R⁵ 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 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 alkyl or aralkyl optionally substituted by one or more substituents selected from the group consisting of halo and $-R^9-C(O)OR^6$;

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, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$ 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;

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 and R^4 together form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$,

where R^{9a} 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^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 alkyl or aralkyl optionally substituted by one or more substituents selected from the group consisting of halo and $-R^9-C(O)OR^6$;

R^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo and haloalkyl;

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 and R^4 together form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$,

where R^{9a} 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^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, wherein:

- R^1 is alkyl or aralkyl optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, $-R^9-OR^6$, heteroaryl and $-R^9-C(O)OR^6$;
- 5 R^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo and haloalkyl;
- 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;
- 10 R^3 is independently selected from the group consisting of $-N[N(R^5)C(O)OR^6]C(O)OR^6$, $-R^9-N(R^5)R^6$ and $-N(R^6)C(O)OR^6$;
- R^4 is independently selected from the group consisting of alkyl, aryl, heteroaryl, and $-R^9-C(O)R^5$,
- wherein each of the aryl and heteroaryl groups for R^4 is optionally substituted
- 15 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, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally
- 20 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 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:

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

-R⁹-OR⁶);

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^{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;

R³ is hydrogen, -R⁹-OR⁶ or heteroaryl optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and -R⁹-OR⁶;

R⁴ is independently selected from the group consisting of alkyl, aryl, aralkyl, heteroaryl, -R⁹-Si(R⁶)₃, -R⁹-NO₂ and -R⁹-C(O)R⁵, wherein each of the aryl, aralkyl and heteroaryl groups for R⁴ is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and -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; 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.

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

The scope of the invention described herein is not intended to include compounds disclosed in the following patents and patent applications: PCT Published Patent Application WO 86/03749; PCT Published Patent Application WO 91/01306; PCT Published Patent Application WO 91/04974; PCT Published Patent Application WO 91/06545; PCT Published Patent Application WO 93/12786; PCT Published Patent Application WO 00/06556; U.S. Patent No. 4,440,785; U.S. Patent No. 4,670,566; U.S. Patent No. 5,453,516; U.S. Patent No. 6,046,341; and U.S. Patent No. 6,090,818; the disclosures of which are incorporated in full by reference herein in their entireties; or the compounds disclosed in Singh, B. *et al.*, *J. Med. Chem.* (1994), Vol. 37, pp. 248-254.

UTILITY AND TESTING OF THE COMPOUNDS OF THE INVENTION

The present invention relates to compounds, pharmaceutical compositions and methods of using the compounds and pharmaceutical compositions for the treatment of sodium channel-mediated diseases, preferably diseases related to pain, central
5 nervous conditions such as epilepsy, anxiety, depression and bipolar disease; cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular conditions such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain
10 syndrome, by administering to a patient in need of such treatment an effective amount of a sodium channel blocker modulating, especially inhibiting, agent.

In general, the present invention provides a method for treating a patient for, or protecting a patient from developing, a sodium channel-mediated disease, especially pain, comprising administering to an animal, such as a mammal, especially a human
15 patient in need thereof, a therapeutically effective amount of a compound of the invention or a pharmaceutical composition comprising a compound of the invention wherein the compound modulates the activity of one or more voltage-dependent sodium channels.

The general value of the compounds of the invention in mediating, especially
20 inhibiting, the sodium channel ion flux can be determined using the assays described below in the Biological Assays section. Alternatively, the general value of the compounds in treating conditions and diseases may be established in industry standard animal models for demonstrating the efficacy of compounds in treating pain. Animal models of human neuropathic pain conditions have been developed that result
25 in reproducible sensory deficits (allodynia, hyperalgesia, and spontaneous pain) over a sustained period of time that can be evaluated by sensory testing. By establishing the degree of mechanical, chemical, and temperature induced allodynia and hyperalgesia present, several physiopathological conditions observed in humans can be modeled allowing the evaluation of pharmacotherapies.

30 In rat models of peripheral nerve injury, ectopic activity in the injured nerve corresponds to the behavioural signs of pain. In these models, intravenous application of the sodium channel blocker and local anesthetic lidocaine can suppress the ectopic activity and reverse the tactile allodynia at concentrations that do not affect general behaviour and motor function (Mao, J. and Chen, L.L, *Pain* (2000), 87: 7-17).

Allometric scaling of the doses effective in these rat models, translates into doses similar to those shown to be efficacious in humans (Tanelian, D.L. and Brose, W.G., *Anesthesiology* (1991), 74(5):949-951). Furthermore, Lidoderm®, lidocaine applied in the form of a dermal patch, is currently an FDA approved treatment for post-herpetic neuralgia (Devers, A. and Glaser, B.S., *Clin. J. Pain* (2000), 16(3):205-8).

Sodium channel blockers have clinical uses in addition to pain. Epilepsy and cardiac arrhythmias are often targets of sodium channel blockers. Recent evidence from animal models suggest that sodium channel blockers may also be useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and in patients with multiple sclerosis (MS) (Clare, J.J. et al., *op. cit.* and Anger, T. et al., *op. cit.*).

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 instant invention are sodium channel blockers and are therefore useful for treating diseases and conditions in humans and other organisms, including all those human diseases and conditions which are the result of aberrant voltage-dependent sodium channel biological activity or which may be ameliorated by modulation of voltage-dependent sodium channel biological activity.

As defined herein, a sodium channel-mediated disease or condition refers to a disease or condition which is ameliorated upon modulation of the sodium channel and includes, but is not limited to, pain, central nervous conditions such as epilepsy, anxiety, depression and bipolar disease; cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular conditions such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome.

A sodium channel-mediated disease or condition also includes pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, glossopharyngeal neuralgia, neuropathy secondary to metastatic infiltration, adiposis dolorosa, thalamic

lesions, hypertension, autoimmune disease, asthma, drug addiction (e.g. opiate, benzodiazepine, amphetamine, cocaine, alcohol, butane inhalation), Alzheimer, dementia, age-related memory impairment, Korsakoff syndrome, restenosis, urinary dysfunction, incontinence, parkinson's disease, cerebrovascular ischemia, neurosis, 5 gastrointestinal disease, sickle cell anemia, transplant rejection, heart failure, myocardial infarction, reperfusion injury, intermittent claudication, angina, convulsion, respiratory disorders, cerebral or myocardial ischemias, long-QT syndrome, Catecholeminergic polymorphic ventricular tachycardia, ophthalmic diseases, spasticity, spastic paraplegia, myopathies, myasthenia gravis, paramyotonia congenita, 10 hyperkalemic periodic paralysis, hypokalemic periodic paralysis, alopecia, anxiety disorders, psychotic disorders, mania, paranoia, seasonal affective disorder, panic disorder, obsessive compulsive disorder (OCD), phobias, autism, Aspergers Syndrome, Retts syndrome, disintegrative disorder, attention deficit disorder, aggressivity, impulse control disorders, thrombosis, pre clampsia, congestive cardiac 15 failure, cardiac arrest, Freidrich's ataxia, Spinocerebellar ataxia, myelopathy, radiculopathy, systemic lupus erythamatosi, granulomatous disease, olivo-ponto-cerebellar atrophy, spinocerebellar ataxia, episodic ataxia, myokymia, progressive pallidal atrophy, progressive supranuclear palsy and spasticity, traumatic brain injury, cerebral oedema, hydrocephalus injury, spinal cord injury, anorexia nervosa, bulimia, 20 Prader-Willi syndrome, obesity, optic neuritis, cataract, retinal haemorrhage, ischaemic retinopathy, retinitis pigmentosa, acute and chronic glaucoma, macular degeneration, retinal artery occlusion, Chorea, Huntington's chorea, cerebral edema, proctitis, post-herpetic neuralgia, eudynia, heat sensitivity, tosaroidosis, irritable bowel syndrome, Tourette syndrome, Lesch-Nyhan Syndrome, Brugado syndrome, Liddle syndrome, 25 Crohns disease, multiple sclerosis and the pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), disseminated sclerosis, diabetic neuropathy, peripheral neuropathy, charcot marie tooth syndrome, arthritic, rheumatoid arthritis, osteoarthritis, chondrocalcinosis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, 30 rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schitzophrenia, sodium channel toxin related illnesses, familial erythremalgia, primary erythremalgia, rectal pain, cancer, narcotic drug addiction, epilepsy, partial and general tonic seizures, febrile seizures, absence seizures (petit mal), myoclonic seizures, atonic seizures, clonic seizures, Lennox Gastaut, West Syndrome (infantile spasms), multiresistant 35 seizures, seizure prophylaxis (anti-epileptogenic), familial Mediterranean fever

syndrome, gout, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions caused by stroke or neural trauma, tachy-arrhythmias, atrial fibrillation and ventricular fibrillation and as a general or local anaesthetic..

As used herein, the term "pain" refers to all categories of pain and is
5 recognized to include but not limited to neuropathic pain, inflammatory pain, nociceptive pain, idiopathic pain, neuralgic pain, orofacial pain, burn pain, burning mouth syndrome, somatic pain, visceral pain, myofacial pain, dental pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, reflex sympathetic dystrophy, brachial plexus avulsion, neurogenic bladder,
10 chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, acute pain (e.g. musculoskeletal and post-operative pain), chronic headache, migraine headache, familial hemiplegic migraine, conditions associated with cephalic pain, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, pain following stroke, thalamic lesions, radiculopathy, HIV pain, post-herpetic pain, non-
15 cardiac chest pain, irritable bowel syndrome and pain associated with bowel disorders and dyspepsia, pain associated with narcotic drug addiction withdrawal and combinations thereof.

The compounds identified in the instant specification inhibit the ion flux through a voltage-dependent sodium channel. Preferably, the compounds are state or
20 frequency dependent modifiers 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 (Cestèle, S., et al., *op. cit.*). These compounds may also be
25 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.

The present invention readily affords many different means for identification of
30 sodium channel modulating agents that are useful as therapeutic agents. Identification of modulators of sodium channel 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,
35 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.

A competitive binding assay with known sodium channel toxins such as tetrodotoxin, alpha-scorpion toxins, aconitine, BTX and the like, may be suitable for identifying potential therapeutic agents with high selectivity for a particular sodium channel. The use of BTX in such a binding assay is well known and is described in McNeal, E.T., et al., *J. Med. Chem.* (1985), 28(3):381-8; and Creveling, C.R., et al., *Methods in Neuroscience, Vol. 8: Neurotoxins* (Conn PM Ed) (1992):25-37, Academic Press, New York.

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-guanidine influx or determine cell depolarization using fluorescent dyes such as the FRET based and other fluorescent assays or a radiolabelled binding assay employing radiolabelled 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
5 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
10 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 channel, such as the open state, closed
15 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
20 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
25 assay can use radioactive $^{22}\text{[Na]}$ and $^{14}\text{[C]}$ 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.

30 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
35 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
5 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
10 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
15 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
20 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.
25 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 pain, especially chronic pain or other conditions such
30 as arrhythmias and epilepsy 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%.
35 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 IC_{50} value) should be less than 10 μM , preferably below 1 μM and most preferably below 50 nM. The IC_{50} ("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 IC_{50} s 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 $\text{Na}_v1.1$, $\text{Na}_v1.2$, $\text{Na}_v1.3$, $\text{Na}_v1.4$, $\text{Na}_v1.5$, $\text{Na}_v1.6$, $\text{Na}_v1.7$, $\text{Na}_v1.8$, or $\text{Na}_v1.9$ 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 $\text{Na}_v1.1$, $\text{Na}_v1.2$, $\text{Na}_v1.3$, $\text{Na}_v1.4$, $\text{Na}_v1.5$, $\text{Na}_v1.6$, $\text{Na}_v1.7$, $\text{Na}_v1.8$, or $\text{Na}_v1.9$ 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.

Pharmaceutical Compositions of the Invention and Administration

The present invention also relates to pharmaceutical composition containing the compounds of the invention disclosed herein. In one embodiment, the present invention relates to a composition comprising compounds of the invention in a pharmaceutically acceptable carrier and in an amount effective to modulate, preferably inhibit, ion flux through a voltage-dependent sodium channel to treat sodium channel

mediated diseases, such as pain, when administered to an animal, preferably a mammal, most preferably a human patient.

The pharmaceutical compositions useful herein also contain a pharmaceutically acceptable carrier, including any suitable diluent or excipient, which includes any
5 pharmaceutical agent that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which may be administered without undue toxicity. Pharmaceutically acceptable carriers include, but are not limited to, liquids, such as water, saline, glycerol and ethanol, and the like. A thorough discussion of pharmaceutically acceptable carriers, diluents, and other excipients is presented in
10 REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Pub. Co., N.J. current edition).

Those skilled in the art know how to determine suitable doses of the compounds for use in treating the diseases and conditions contemplated herein. Therapeutic doses are generally identified through a dose ranging study in humans
15 based on preliminary evidence derived from animal studies. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects for the patient.

A typical regimen for treatment of sodium channel-mediated disease comprises administration of an effective amount over a period of one or several days, up to and
20 including between one week and about six months, or it may be chronic. It is understood that the dosage of a diagnostic/pharmaceutical compound or composition of the invention administered *in vivo* or *in vitro* will be dependent upon the age, sex, health, and weight of the recipient, severity of the symptoms, kind of concurrent treatment, if any, frequency of treatment, the response of the individual, and the nature
25 of the diagnostic/pharmaceutical effect desired. 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., Berkow et al., eds., The Merck Manual, 16th edition, Merck and Co., Rahway, N.J., 1992;
30 Goodman et al., eds., Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th 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
35 Pharmaceutical Sciences, 18th edition, Mack Publishing Co., Easton, PA (1990);

Katzung, 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.

5 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. Effective amounts of a diagnostic pharmaceutical compound or
10 composition of the invention are from about 0.1 μ g to about 100 mg/Kg body weight, administered at intervals of 4-72 hours, for a period of 2 hours to 1 year, and/or any range or value therein, such as 0.0001-0.001, 0.001-0.01, 0.01-0.1, 0.1-1.0, 1.0-10, 5-10, 10-20, 20-50 and 50-100 mg/Kg, at intervals of 1-4, 4-10, 10-16, 16-24, 24-36, 36-48, 48-72 hours, for a period of 1-14, 14-28, or 30-44 days, or 1-24 weeks, or any
15 range or value therein. 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
20 (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
25 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
30 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
35 invention as desired.

The composition may be intended for rectal administration, in the form, e.g., of a suppository which will melt in the rectum and release the drug. A typical suppository formulation will generally consist of active ingredient with a binding and/or lubricating agent such as a gelatine or cocoa butter or other low melting vegetable or synthetic wax or fat.

A typical formulation for intramuscular or intrathecal administration will consist of a suspension or solution of active in an oil or solution of active ingredient in an oil, for example arachis oil or sesame oil. A typical formulation for intravenous or intrathecal administration will consist of sterile isotonic aqueous solution containing, for example active ingredient and dextrose or sodium chloride or a mixture of dextrose and sodium chloride.

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)TM 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 devices 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.

COMBINATION THERAPY

The compounds of the invention may be usefully combined with one or more other compounds of the invention or one or more other therapeutic agent or as any combination thereof, in the treatment of sodium channel-mediated diseases and conditions. For example, a compound of formula (I) may be administered simultaneously, sequentially or separately in combination with other therapeutic agents, including, but not limited to:

- opiates analgesics, e.g. morphine, heroin, cocaine, oxymorphone, levorphanol, levallorphan, oxycodone, codeine, dihydrocodeine, propoxyphene, nalmefene, fentanyl, hydrocodone, hydromorphone, meripidine, methadone, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine and pentazocine;
- non-opiate analgesics, e.g. acetaminophen, salicylates (e.g. aspirin);
- nonsteroidal antiinflammatory drugs (NSAIDs), e.g. ibuprofen, naproxen, fenoprofen, ketoprofen, celecoxib, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin and zomepirac;
- anticonvulsants, e.g. carbamazepine, oxcarbazepine, lamotrigine, valproate, topiramate, gabapentin and pregabalin;
- antidepressants such as tricyclic antidepressants, e.g. amitriptyline, clomipramine, desipramine, imipramine and nortriptyline;
- COX-2 selective inhibitors, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, and lumiracoxib;
- alpha-adrenergics, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, and 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- barbiturate sedatives, e.g. amobarbital, aprobarbital, butabarbital, butabital,

- mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal and thiopental;
- tachykinin (NK) antagonists, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (ccR,9R)-7- $\square$; 3,5- bis(trifluoromethyl)benzyl $\square$;-8,9,10,11-tetrahydro-9-methyl-5 (4- methylphenyl)-7H- $\square$;1,4 $\square$;diazocino $\square$;2,1-g $\square$; $\square$;1,7 $\square$;- naphthyridine-6-13-dione (TAK 637), 5- $\square$; $\square$;(2R,3S)-2- $\square$;(1 R)-1- $\square$;3,5-bis(trifluoromethyl)phenyl $\square$;ethoxy-3-(4 fluorophenyl)-4- morpholinyl $\square$;-methyl $\square$;-1,2-dihydro-3H-1,2,4-triazol-3-one (MK 869) , ap rep itant, lane p itant, dapitant and 3- $\square$; $\square$;2- methoxy-5 (trifluoromethoxy)phenyl $\square$;-methylamino $\square$;-2-phenylpiperidine (2S, 3S);
 - coal-tar analgesics, in particular paracetamol;
 - serotonin reuptake inhibitors, e.g. paroxetine, sertraline, norfluoxetine (fluoxetine desmethyl metabolite), metabolite demethylsertraline, '3 fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine, trazodone and fluoxetine;
 - noradrenaline (norepinephrine) reuptake inhibitors, e.g. maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®)), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine, and venlafaxine duloxetine neuroleptics sedative/anxiolytics;
 - dual serotonin-noradrenaline reuptake inhibitors, such as venlafaxine, venlafaxine metabolite O- desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
 - acetylcholinesterase inhibitors such as donepezil;
 - 5-HT₃ antagonists such as ondansetron;
 - metabotropic glutamate receptor (mGluR) antagonists;
 - local anaesthetic such as mexiletine and lidocaine;
 - corticosteroid such as dexamethasone;
 - antiarrhythmics, e.g. mexiletine and phenytoin;
 - muscarinic antagonists, e.g. , tolterodine, propiverine, tropium t chloride,

darifenacin, solifenacin, temiverine and ipratropium;

- cannabinoids;
- vanilloid receptor agonists (e.g. resiniferatoxin) or antagonists (e.g. capsazepine);
- 5 • sedatives, e.g. glutethimide, meprobamate, methaqualone, and dichloralphenazone;
- anxiolytics such as benzodiazepines,
- antidepressants such as mirtazapine,
- topical agents (e.g. lidocaine, capsaicin and resiniferotoxin);
- 10 • muscle relaxants such as benzodiazepines, baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol and orphenadrine;
- anti-histamines or H1 antagonists;
- NMDA receptor antagonists;
- 5-HT receptor agonists/antagonists;
- 15 • PDEV inhibitors;
- Tramadol®;
- cholinergic (nicotinic) analgesics;
- alpha-2-delta ligands;
- prostaglandin E2 subtype antagonists;
- 20 • leukotriene B4 antagonists;
- 5-lipoxygenase inhibitors; and
- 5-HT3 antagonists.

Sodium channel-mediated diseases and conditions that may be treated and/or prevented using such combinations include but not limited to, pain, central and

25 peripherally mediated, acute, chronic, neuropathic as well as other diseases with associated pain and other central nervous disorders such as epilepsy, anxiety, depression and bipolar disease; or cardiovascular disorders such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular disorders such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural

30 trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome.

As used herein "combination" refers to any mixture or permutation of one or more compounds of the invention and one or more other compounds of the invention or one or more additional therapeutic agent. Unless the context makes clear

otherwise, "combination" may include simultaneous or sequentially delivery of a compound of the invention with one or more therapeutic agents. Unless the context makes clear otherwise, "combination" may include dosage forms of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise,

5 "combination" may include routes of administration of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include formulations of a compound of the invention with another therapeutic agent. Dosage forms, routes of administration and pharmaceutical compositions include, but are not limited to, those described herein.

10 KITS-OF-PARTS

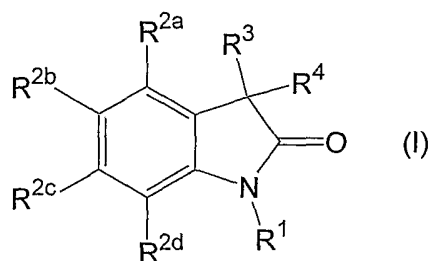
The present invention also provides kits that contain a pharmaceutical composition which includes one or more compounds of the above formulae. The kit also includes instructions for the use of the pharmaceutical composition for modulating the activity of ion channels, for the treatment of pain, as well as other utilities as

15 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

20 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):



25 wherein R^1 , R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^3 and R^4 are as defined herein, 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 diarylalkylsilyl (e.g., *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, 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 Green, T.W. and P.G.M. Wuts, *Protective Groups in Organic Synthesis* (1999), 3rd Ed., Wiley. The protecting 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.

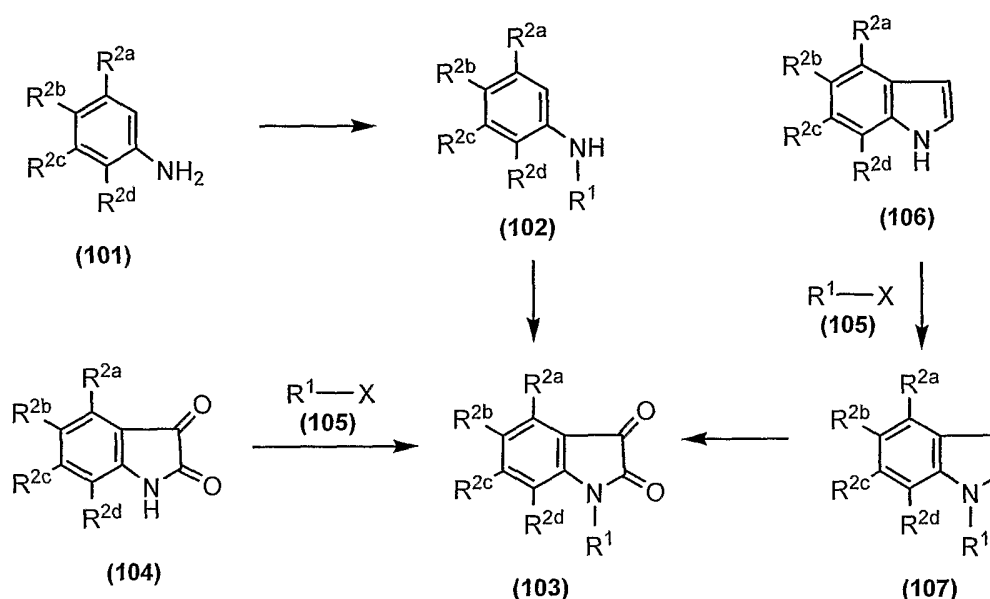
The following Reaction Schemes illustrate methods to make compounds of this invention. It is understood that one skilled in the art would be able to make these compounds by similar methods or by methods known to one skilled in the art. It is also understood that one skilled in the art would be able to 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: Reactions, Mechanisms, and Structure*, 5th edition (Wiley, December 2000)) or

prepared as described in this invention.

In the following Reaction Schemes, the various R groups (e.g., R¹, 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, X is Cl or Br, and R¹¹ is an alkyl group.

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

REACTION SCHEME 1



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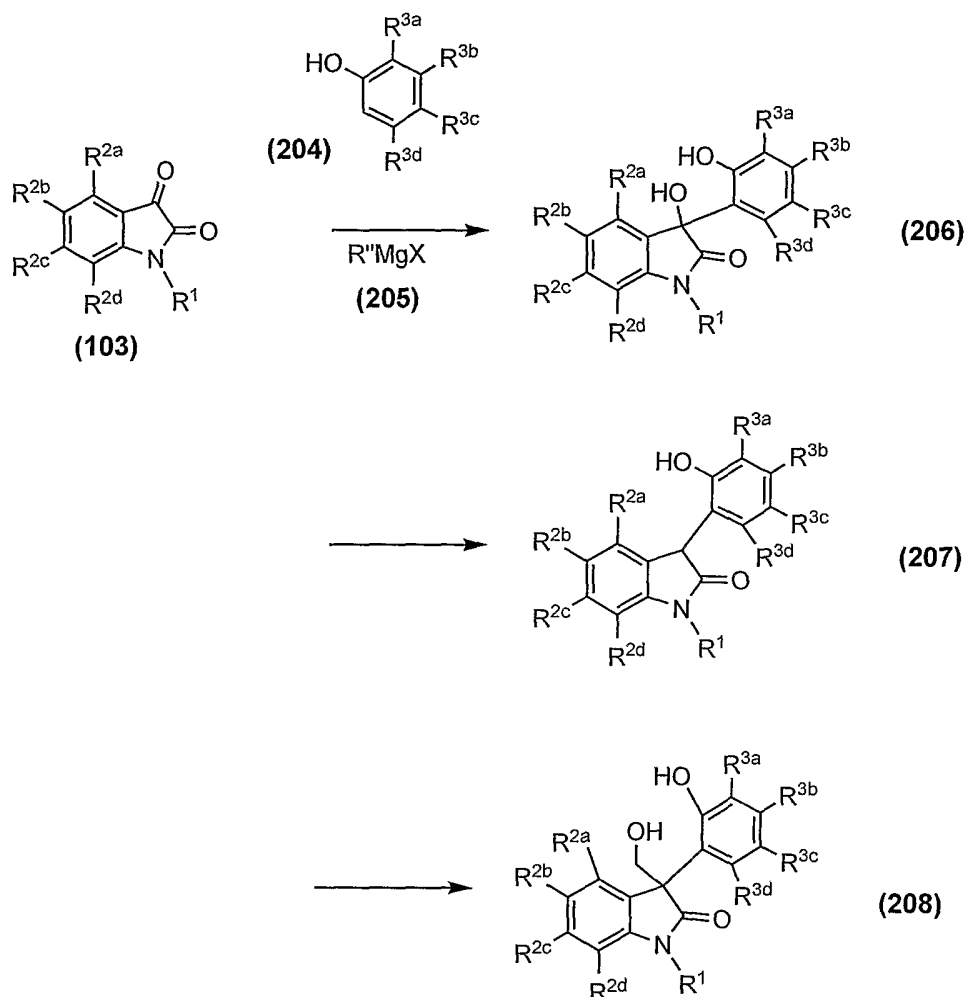
The R¹ group can be introduced to an amino compound of formula (101) either by reductive amination, which is well-known to those skilled in the art, or formation of an amide by reacting with a corresponding acyl chloride followed by reduction, which is also well-known to those skilled in the art, to 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).

20

In general, the compounds of formula (I) of the invention where R³ is hydrogen,

-OH or -CH₂OH can be synthesized following the general procedure as described below in REACTION SCHEME 2.

REACTION SCHEME 2

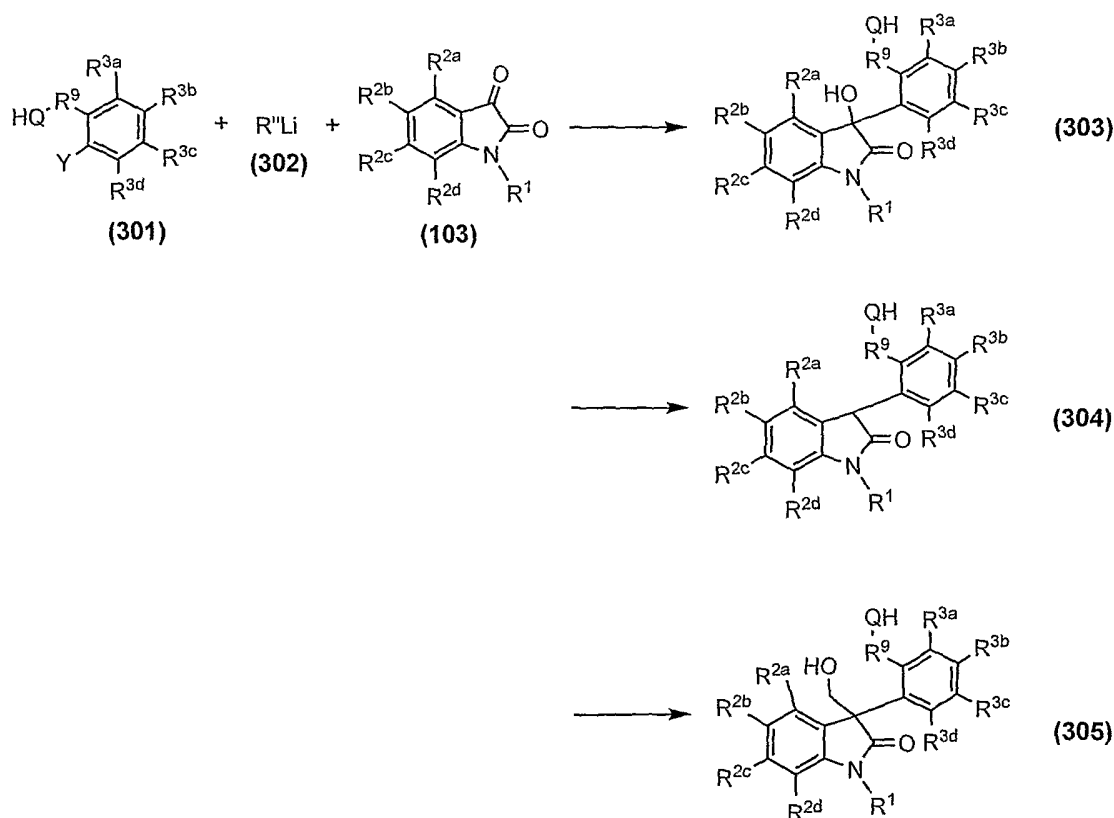


- 5 The phenol compound of formula (204) is treated with a Grignard reagent of formula (205) at low temperature (0 °C) to form the phenoxymagnesium halide intermediate which reacts with the keto-carbonyl group of the isatin compound of formula (103) in a solvent, such as, but not limited to, methylene chloride or toluene, to afford the oxindole of formula (206) (Formula (I), R³ = -OH). The compound of formula
- 10 (207) (Formula (I), R³ = 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 SOCl₂/NEt₃ and reduction with Zn dust. The compound of formula (207) 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 (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, iPr_2NH or LDA, and subsequently reacting with formaldehyde.

Alternatively, the compound of formula (I) of the invention where R^3 is hydrogen, $-OH$, or $-CH_2-OH$ 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

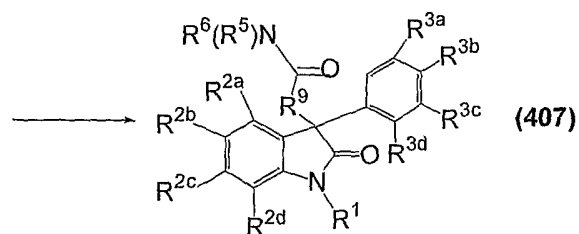
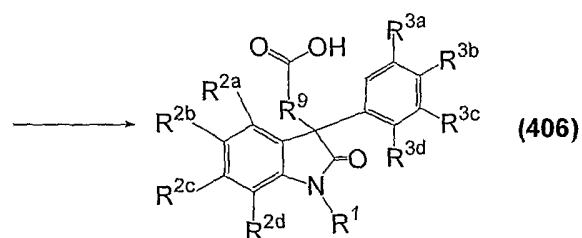
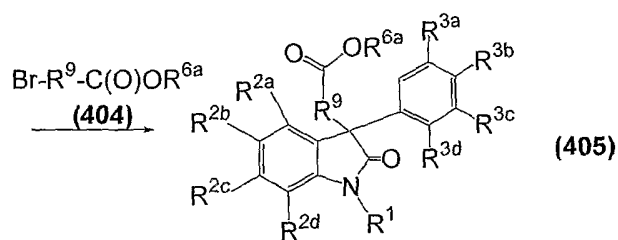
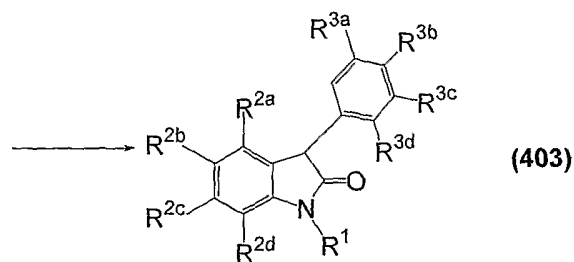
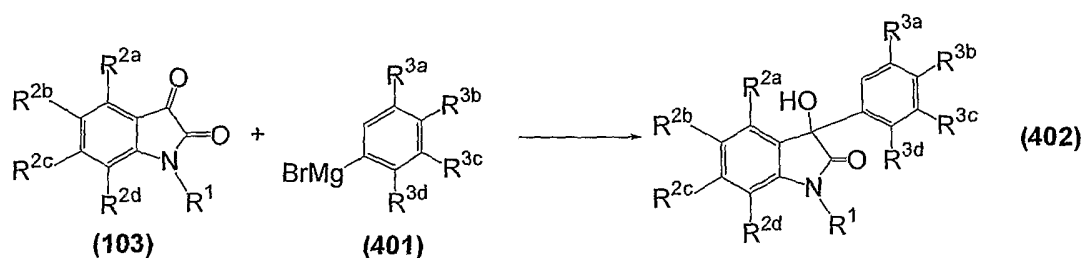


A compound of formula (301) is treated with a lithium reagent of formula (302), such as, but not limited to, $n-BuLi$, at low temperature followed by the reaction with keto-carbonyl group of the isatin compound of formula (103) in a solvent, such as, but

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 $SOCl_2/NEt_3$ 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), $R^3 = -CH_2OH$). 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, iPr_2NH or LDA, and subsequently reacting with formaldehyde.

Alternatively, the compound of formula (I) of the invention where R^3 is hydrogen, $-OH$, $-R^9-C(O)OR^{6a}$, $-R^9-C(O)OH$, $-R^9-C(O)N(R^5)R^6$ can be synthesized following the general procedure as described below in REACTION SCHEME 4 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 group (*i.e.*, phenyl) as defined in the specification for optional substituents for aryl groups, R'' is an alkyl group, R^9 is as defined above in the Summary of the Invention and Q is $-O-$, $-S-$, $-N(R^6)-$, R^5 is as described above in the Summary of the Invention, R^{6a} 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, R^9 is as described above in the Summary of the Invention.

REACTION SCHEME 4

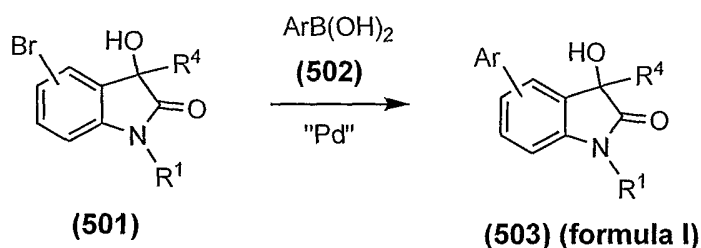


The Grignard reagent of formula (401) reacts with keto-carbonyl group of the isatin compound of formula (103) in a solvent, such as, but not limited to, methylene chloride or toluene to afford the oxindole of formula (402) (Formula (I), R³ = -OH). The compound of formula (403) (Formula (I), R³ = H) is 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 triethylsilane. The compound of formula (403) can also be achieved by treating the compound of formula (402) with $\text{SOCl}_2/\text{NEt}_3$ 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), $\text{R}^3 = -\text{R}^9-\text{C}(\text{O})\text{OR}^{6a}$) which is subjected to saponification to generate the carboxylic acid of formula (406) (Formula (I), $\text{R}^3 = -\text{R}^9-\text{C}(\text{O})\text{OH}$). 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), $\text{R}^3 = -\text{R}^9-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$) following procedures known to the skilled in the art.

Alternatively, the compound of formula (I) of the invention where R^2 is aryl can be synthesized following the general procedure as described below in REACTION SCHEME 5 where the various R groups (e.g., R^1 , R^4 , etc.) are defined as in the Summary of the Invention for compounds of formula (I).

REACTION SCHEME 5.

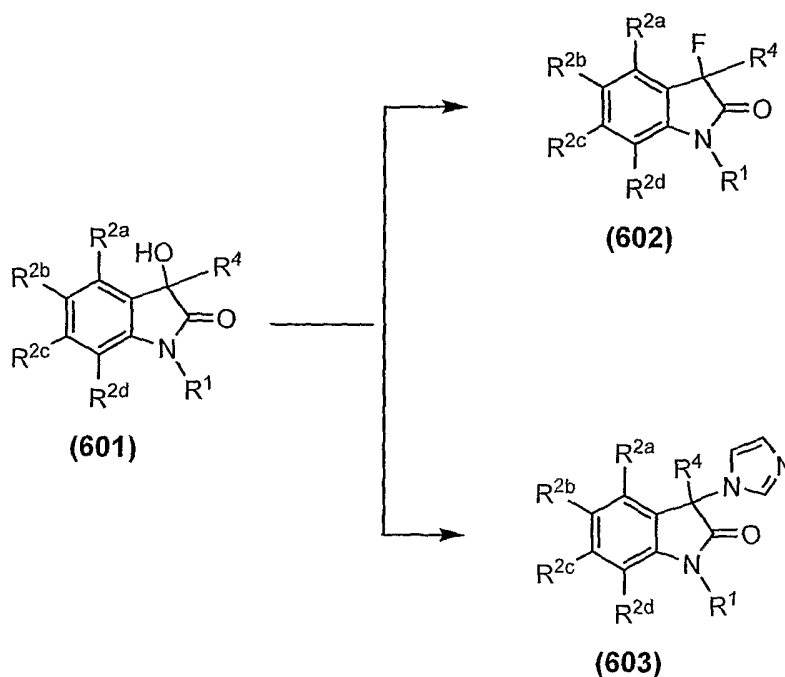


The compound of formula (501) can react with an arylboronic acid of formula (502) in the presence of a palladium catalyst such as, but not limited to, palladium acetate, tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0) with or without a ligand such as, but not limited to, triphenylphosphine, tri(o-tolyl)phosphine, 1,1'-bis(diphenylphosphino)ferrocene or 2-(di-*tert*-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 tetrahydrofuran, 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 R^3 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).

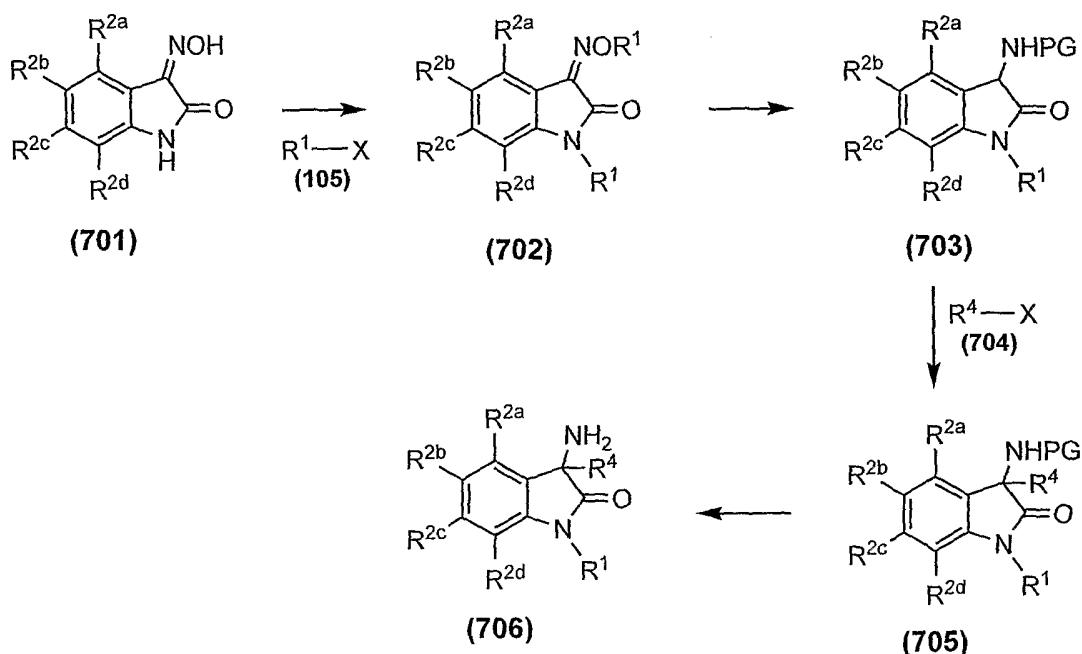
REACTION SCHEME 6



- 5 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,
- 10 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).

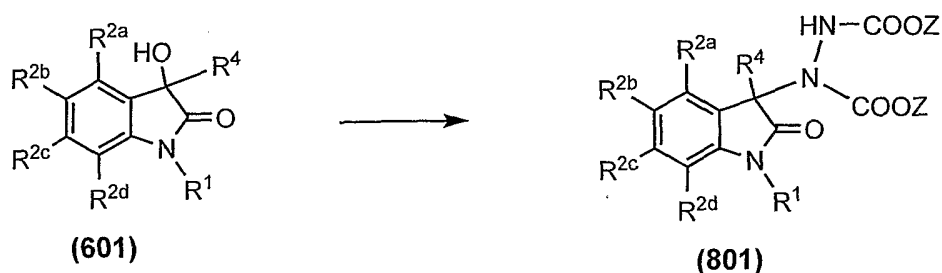
REACTION SCHEME 7



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) by treating 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 *N,N*-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-1*H*-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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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-1*H*-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 5-fluoro-1*H*-indole-2,3-dione, and 1-bromopentane with 4-chlorobenzyl bromide, the title compound was obtained as a red solid: ¹H NMR (300 MHz, CDCl₃) 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)-1*H*-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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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)-1*H*-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, CDCl_3) 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)-1*H*-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)-1*H*-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, CDCl_3) 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)-1*H*-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, CDCl_3) δ 7.60 (d,

1H), 7.55-7.45 (m, 1H), 7.12-7.06 (t, 1H), 6.80 (d, 1H), 6.50 (s, 2H), 3.79 (s, 9H); MS (ES+) m/z 350.2 (M + 23).

PREPARATION 8

Synthesis of 1-cyclohexylmethyl-1*H*-indole-2,3-dione

5 Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with cyclohexymethyl bromide, the title compound was obtained as a red solid (37%): ^1H NMR (300 MHz, CDCl_3) 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).

10 PREPARATION 9

Synthesis of 1-(2-trifluoromethylbenzyl)-1*H*-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, CDCl_3)
15 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*H*-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
20 compound was obtained as an orange solid (39%): ^1H NMR (300 MHz, CDCl_3) 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*H*-indole-2,3-dione

25 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, CDCl_3) 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).

30 PREPARATION 12

Synthesis of 1-[2-(4-chlorophenyl)-ethyl]-1*H*-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) δ 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

5 Synthesis of 1-(4-chlorobenzyl)-5-methyl-1*H*-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-1*H*-indole-2,3-dione, the title compound was obtained as a red solid: ^1H NMR (300 MHz, CDCl_3) δ 7.43-7.22 (m, 6H), 6.61 (d, 1H), 4.86 (s, 2H), 1.79 (s, 3H).

10 PREPARATION 14

Synthesis of 1-thiophen-2-yl-methyl-1*H*-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 ($M + 23$).

15 PREPARATION 15

Synthesis of 1-(2-methoxybenzyl)-1*H*-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 ($M + 23$).

20 PREPARATION 16

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

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace 1-bromopentane with 1-chloromethylnaphthylene, the title compound was obtained as an orange solid (59%): ^1H NMR (300 MHz, CDCl_3) δ 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)-1*H*-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) δ 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-1*H*-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
5 was obtained as an orange solid (81%): MS (ES+) *m/z* 260.2 (*M* + 23).

PREPARATION 19

Synthesis of 1-(3-methoxybenzyl)-1*H*-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
10 compound was obtained as an orange solid (66%): MS (ES+) *m/z* 290.2 (*M* + 23).

PREPARATION 20

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

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 7-fluoro-1*H*-indole-2,3-dione (Martin, K., et al,
15 *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)-1*H*-indole-2,3-dione

20 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

25 Synthesis of 1-(3-trifluoromethyl-4-chlorobenzyl)-1*H*-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).

30

PREPARATION 23

Synthesis of 1-(5-chloro-thiophen-2-yl-methyl)-1*H*-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%): ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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*H*-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%): ^1H NMR (300 MHz, CDCl_3) δ 8.99 (dd, 1H),
10 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).

PREPARATION 25

Synthesis of 1-(2-iodo-benzyl)-1*H*-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
15 compound was obtained as a solid (67%): ^1H NMR (300 MHz, CDCl_3) δ 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).

PREPARATION 26

20 Synthesis of 1-hexyl-1*H*-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%): ^1H NMR (300 MHz, CDCl_3) δ 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,
25 6H), 0.88 (t, 3H).

PREPARATION 27

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

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 4,7-dichloro-1*H*-indole-2,3-dione, the title
30 compound was obtained as a solid (89%): ^1H NMR (300 MHz, CDCl_3) δ 7.41 (d, 1H), 6.98 (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 28

Synthesis of 4-chloro-1-pentyl-1*H*-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 4-chloro-1*H*-indole-2,3-dione, the title compound
5 was obtained as a solid (98%): ¹H NMR (300 MHz, CDCl₃) δ 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-1*H*-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 6-chloro-1*H*-indole-2,3-dione (Rossiter, S.
10 *Tetrahedron Lett.* (2002), 43(26): 4671-4), the title compound was obtained as a solid (74%): ¹H NMR (300 MHz, CDCl₃) δ 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

15 Synthesis of 5-bromo-1-(4-chlorobenzyl)-1*H*-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 5-bromo-1*H*-indole-2,3-dione, and 1-bromopentane with 4-chlorobenzyl bromide, the title compound was obtained as a
solid (39%): ¹H NMR (300 MHz, CDCl₃) δ 7.70 (d, 1H), 7.58 (dd, 1H), 7.30 (d, 2H), 7.22
20 (d, 2H), 6.63 (d, 1H), 4.87 (s, 2H).

PREPARATION 31

Synthesis of 5,7-dimethyl-1-pentyl-1*H*-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 5,7-dimethyl-1*H*-indole-2,3-dione, the title
25 compound was obtained as a solid (44%): ¹H NMR (300 MHz, CDCl₃) δ 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)-1*H*-indole-2,3-dione

30 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: ¹H NMR (300 MHz, CDCl₃) δ 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*H*-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: ¹H NMR (300 MHz, CDCl₃) δ 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)-1*H*-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: ¹H NMR (300 MHz, CDCl₃) δ 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)-1*H*-indole-2,3-dione

To a suspension of sodium hydride (1.61 g, 41.9 mmol, 60% dispersion in mineral oil) in anhydrous *N,N*-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: ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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*H*-indole-2,3-dione

Following the procedure as described in PREPARATION 1, and making non-critical variations to replace isatin with 7-(trifluoromethyl)-1*H*-indole-2,3-dione

(Maginnity, *J. Am. Chem. Soc.* (1951):3579), the title compound was obtained as a solid(41%): ^1H NMR (300 MHz, CDCl_3) δ 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

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

To a mixture of isatin (10.0 g, 67.9 mmol) in anhydrous CH_2Cl_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
10 ether to give the title compound (13.5 g, 70%): ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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

15 Synthesis of 1-(1,3-benzodioxol-5-yl)-1*H*-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-(methylenedioxy)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
20 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%): ^1H NMR (300 MHz, CDCl_3) δ 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

25 Synthesis of 4-bromo-1-pentyl-1*H*-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
30 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: ^1H NMR (300 MHz, CDCl_3) δ 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}C NMR (75 MHz, CDCl_3) δ 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*H*-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 *N*-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: ^1H NMR (300 MHz, CDCl_3) δ 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}C NMR (75 MHz, CDCl_3) δ 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.

20 PREPARATION 41

Synthesis of ethyl (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 (2-bromoethyl)cyclopropane with ethyl bromoacetate, the title compound was obtained (79%) as a light yellow powder: ^1H NMR (300 MHz, CDCl_3) δ 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-1*H*-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: ^1H NMR (300 MHz, CDCl_3) δ 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*H*-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-

5 (bromomethyl)benzoate, the title compound was obtained (84%) as a orange solid: ¹H-NMR (300 MHz, CDCl₃) δ 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*H*-indole-2,3-dione

10 Following the procedure as described in PREPARATION 35, and making non-critical variations to replace (2-bromoethyl)cyclopropane with 2-(3-bromopropyl)-1*H*-isoindole-1,3(2*H*)-dione, the title compound was obtained (92%): ¹H NMR (300 MHz, CDCl₃) δ 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

15 Synthesis of 1-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-1*H*-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)-1*H*-isoindole-1,3(2*H*)-dione, the title compound was obtained (75%): ¹H NMR (300 MHz, 20 CDCl₃) δ 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)-1*H*-indole-2,3-dione

25 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-(benzyloxy)propyl]-1*H*-indole-2,3-dione

30 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: ¹H NMR (300 MHz, CDCl₃) δ 7.57-6.92 (m, 9H), 4.50 (s, 2H), 3.84 (t, 2H), 3.54 (t, 2H),

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*H*-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, CDCl_3) 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

10 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, CDCl_3) 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(2*H*)-one

To a stirred solution of 6-(benzyloxy)benzofuran-3(2*H*)-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, CDCl_3) 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 ($M + 1$).

30

PREPARATION 51

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

To a solution of 6-(benzyloxy)-2,2-dimethylbenzofuran-3(2*H*)-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%): ¹H NMR (300 MHz, CDCl₃) δ 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%): ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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-(trifluoromethyl)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-1*H*-indol-1-yl)acetate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace isatin with 4-chloro-1*H*-indole-2,3-dione, and (2-bromoethyl)cyclopropane with ethyl bromoacetate, the title compound was obtained (95%) as a solid: ¹H NMR (300 MHz, CDCl₃) δ 7.48 (t, 1H), 7.08 (d, 1H), 6.67 (d, 1H), 4.47 (s, 2H), 4.23 (q, 2H), 1.27 (t, 3H); MS (ES+) *m/z* 268.6 (M + 1).

PREPARATION 59

Synthesis of 1-hexyl-1*H*-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)-1*H*-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 *N,N*-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 *in vacuo* to dryness. The residue was triturated with ether to afford the title compound (10.6 g, 85%) as a brown solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 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 NMR (75 MHz, DMSO-*d*₆) δ 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]-1*H*-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, $\text{DMSO}-d_6$) 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); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) 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.

5

PREPARATION 62.

Synthesis of 1-(diphenylmethyl)-5-methyl-1*H*-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)dibenzene, the title compound was obtained (74%) as a

10 bright orange solid: ^1H NMR (300 MHz, CDCl_3) δ 7.42-7.26 (m, 11H), 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-1*H*-indol-1-yl)acetate

Following the procedure as described in PREPARATION 35, and making non-critical variations to replace isatin with 5-chloro-1*H*-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, CDCl_3) 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

20 Synthesis of methyl (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 (2-bromoethyl)cyclopropane with methyl bromoacetate, the title compound was obtained (72%): ^1H NMR (300 MHz, CDCl_3) 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 ($M + 1$).

25

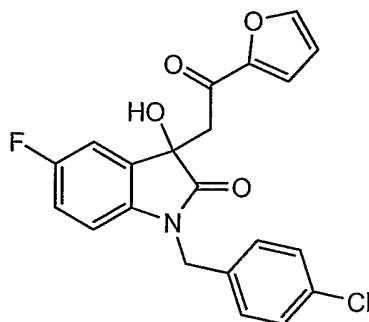
PREPARATION 65

Synthesis of 7-fluoro-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 7-fluoroisatin, and 1-bromopentane with 2-(bromomethyl)-5-(trifluoromethyl)furan, the title compound was obtained (34%):
30 MS (ES+) m/z 336.2 ($M + 23$).

EXAMPLE 1

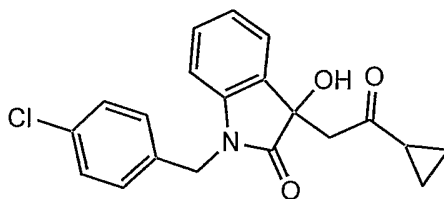
Synthesis of 1-(4-chlorobenzyl)-5-fluoro-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



5 A solution of 1-(4-chlorobenzyl)-5-fluoro-1*H*-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-*d*₆) 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-*d*₆) 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

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

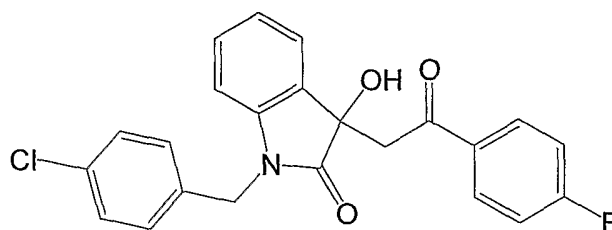


Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-cyclopropyl-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-1*H*-indole-2,3-dione, the title compound was obtained (48%): mp 102-103 °C; ¹H NMR (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

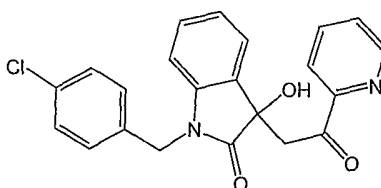
Synthesis of 1-(4-chlorobenzyl)-3-[2-(4-fluorophenyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-(4-fluoro-phenyl)-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a white solid (55%): mp 156-160 °C; 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* 432.0 (M + 23).

EXAMPLE 4

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

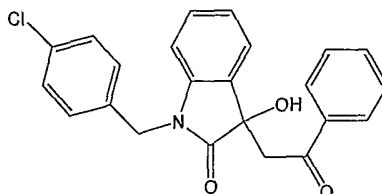


Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-pyridin-2-yl-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a white solid (28%): mp 185 °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

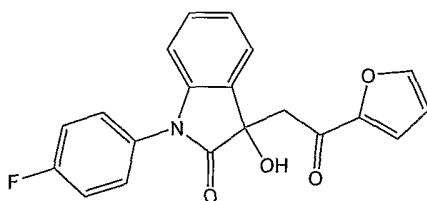
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2H-indol-2-one



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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a white solid (64%): mp 190 °C (dec.); ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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

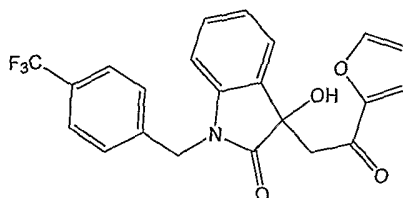
Synthesis of 1-(4-fluorophenyl)-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-1H-indole-2,3-dione with 1-(4-fluorophenyl)-1H-indole-2,3-dione, the title compound was obtained as a white solid (43%): mp 185 °C (dec.); ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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; MS (ES+) 352.1 ($M + 1$), 374.0 ($M + 23$).

EXAMPLE 7

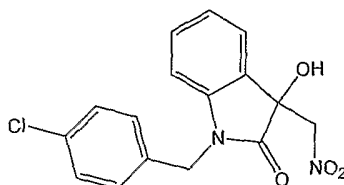
Synthesis of 3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1-(4-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-1H-indole-2,3-dione with 1-(4-trifluoromethylbenzyl)-1H-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),
 10 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



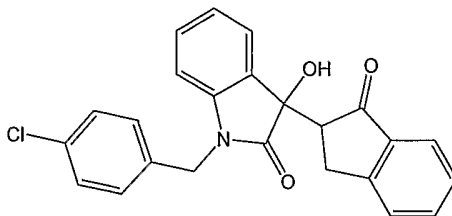
15

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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-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.

20

EXAMPLE 9

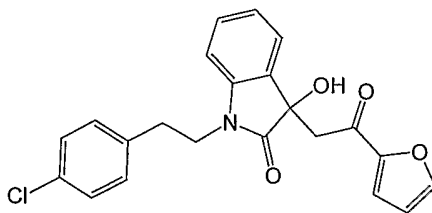
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(1-oxoindan-2-yl)-1,3-dihydroindol-2H-2-one



5 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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-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

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

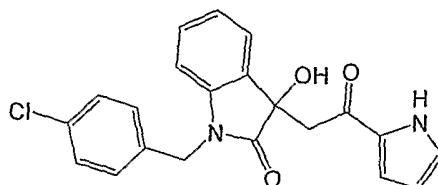


Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-1H-indole-2,3-dione with 1-(4-chlorophenylethyl)-1H-indole-2,3-dione, the title compound was obtained as a white solid (39%): mp 128-132 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.61-7.60 (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, 131.0, 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

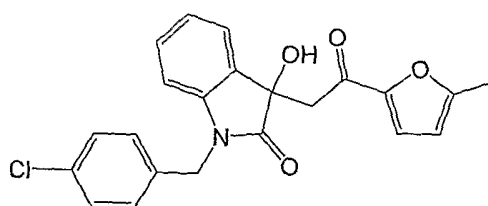
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-[2-oxo-2-(1H-pyrrol-2-yl)-ethyl]-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-(1H-pyrrol-2-yl)-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-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

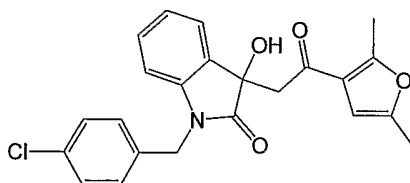
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-[2-(5-methylfuran-2-yl)-2-oxoethyl]-1,3-dihydro-2H-indol-2-one



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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-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, 131.1, 129.7, 129.6, 128.9, 124.2, 122.6, 121.8, 109.8, 109.4, 73.3, 45.5, 42.6, 14.0.

EXAMPLE 13

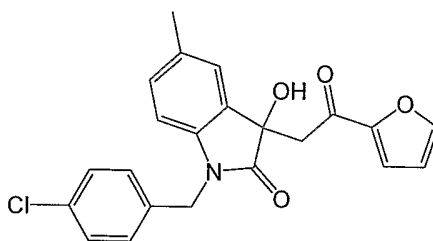
Synthesis of 1-(4-chlorobenzyl)-3-[2-(2,5-dimethylfuran-3-yl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



5 Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 1-(2,5-dimethyl-furan-3-yl)-ethanone, and 1-(4-chlorobenzyl)-5-fluoro-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-1*H*-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 (d, 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-2*H*-indol-2-one

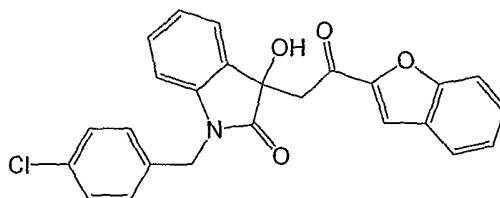


15

Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-5-methyl-1*H*-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

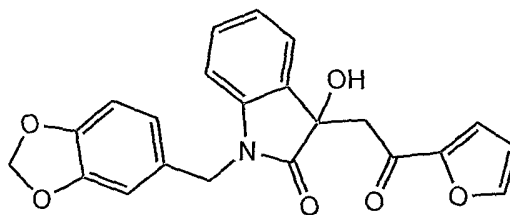
Synthesis of 3-(2-benzofuran-2-yl-2-oxo-ethyl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



5 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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-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),
10 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

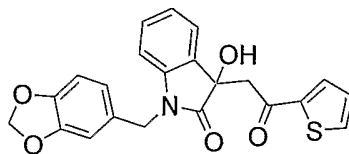
15 Synthesis of 1-(1,3-benzodioxol-5-ylmethyl)-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2H-indol-2-one



20 Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 1-(4-chlorobenzyl)-5-fluoro-1H-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-*d*₆) 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,
25 109.8, 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

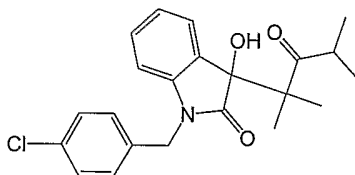


5 Following the procedure as described in EXAMPLE 1, and making non-critical variations to replace 2-acetylfuran with 2-acetylthiophene, and 1-(4-chlorobenzyl)-5-fluoro-1H-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-1H-indole-2,3-dione, the title compound was obtained as a yellow solid (36%): 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),
 10 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-*d*₆) 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.

15

EXAMPLE 18

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



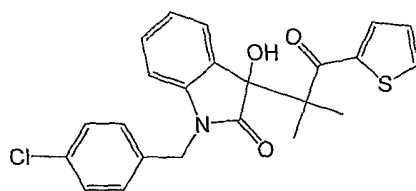
To a solution of methylaniline (2.20 g, 20.0 mmol) in benzene (10.0 mL) was
 20 added ethylmagnesium bromide (10.0 mL, 2 M) at 0 °C and a solution of 2,4-dimethylpentan-3-one (2.10 g, 19.0 mmol) in benzene (5.00 mL) during 10-15 min. The reaction mixture was stirred at 15 °C for 30 min and cooled down to -13 °C followed by the addition of a solution of 1-(4-chlorobenzyl)-1H-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
 25 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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) δ 177.0, 143.1, 134.1, 133.5, 129.8, 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.

5

EXAMPLE 19

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

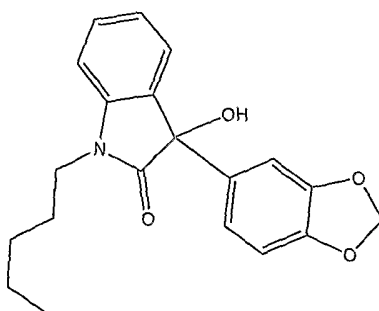


Following the procedure as described in EXAMPLE 18, and making non-critical variations to replace 2,4-dimethylpentan-3-one with 2-methyl-1-thiophen-2-yl-propan-1-one, the title compound was obtained as a colorless solid (35%): mp 130-132 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.82-7.79 (m, 1H), 7.66-7.62 (m, 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); ^{13}C NMR (75 MHz, CDCl_3) δ 200.2, 176.5, 143.1, 134.3, 134.2, 133.6, 133.5, 129.9, 129.0, 128.9, 128.8, 128.0, 125.5, 123.1, 80.8, 51.7, 43.2, 22.0, 21.5.

15

EXAMPLE 20

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



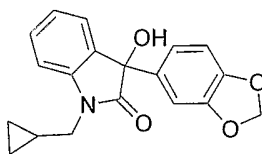
To a solution of 1-pentyl-1*H*-indole-2,3-dione (1.00 g, 4.60 mmol) in anhydrous tetrahydrofuran (30.0 mL) was added a solution of 3,4-(methylenedioxy)phenylmagnesium bromide (5.10 mL, 5.10 mmol, 1.0 M solution in toluene/THF, 50:50) under nitrogen at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, at ambient temperature for 6 h, quenched with saturated ammonium

20

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-2*H*-indol-2-one



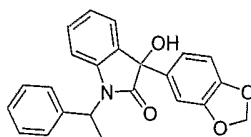
15

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-cyclopropylmethyl-1*H*-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 177.2, 147.7, 147.1, 143.2, 136.0, 133.4, 129.8, 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).

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EXAMPLE 22

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



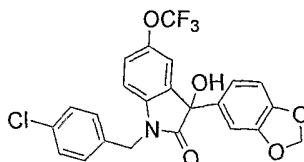
25

Following the procedure as described in EXAMPLE 20, and making non-critical

variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(1-phenylethyl)-1*H*-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), 6.95 (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-2*H*-indol-2-one

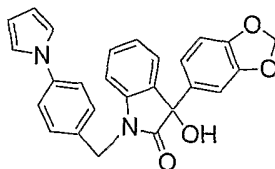


Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-5-trifluoromethoxy-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (38%): mp 138-140 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.27 (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, 140.7, 134.0, 133.3, 133.0, 129.3, 128.6, 122.9, 122.1, 119.0, 118.8, 118.7, 110.2, 108.4, 106.1, 101.4, 77.7, 43.6; MS (ES+) *m/z* 460 (M - 17).

20

EXAMPLE 24

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



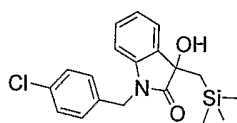
Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(4-pyrrol-1-yl-benzyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (31%): mp 195-198 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.51 (d, 2H), 7.37 (d, 2H), 7.31 (t, 2H), 7.24 (t, 1H), 7.17 (d, 1H), 7.02 (d, 1H), 6.98 (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-*d*₆) 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).

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EXAMPLE 25

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

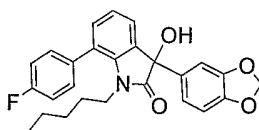


Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with (trimethylsilyl)methylmagnesium chloride, and 1-pentyl-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (65%): mp 121-122 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.36 (d, 1H), 7.28-7.17 (m, 5H), 7.04 (dd, 1H), 6.69 (d, 1H), 4.81 (ABq, 2H), 3.02 (br, 1H), 1.56 (s, 2H), -0.29 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) 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.

15

EXAMPLE 26

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



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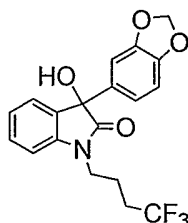
Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 7-(4-fluorophenyl)-1-pentyl-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (17%): mp 149-151 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.29 (m, 2H), 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, ²*J*_{CF} = 12 Hz), 134.3, 133.2, 133.1, 131.5-131.2 (m), 125.0, 124.2, 122.9, 118.8, 115.4-114.7 (m),

25

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



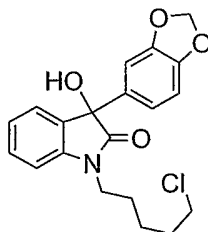
5

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(4,4,4-trifluorobutyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (37%): mp 119-121 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.34 (dt, 1H), 7.28 (d, 1H), 7.09 (t, 1H), 6.89-6.86 (m, 2H), 6.78-6.70 (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); ^{13}C NMR (75 MHz, CDCl_3) 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).

10

EXAMPLE 28

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



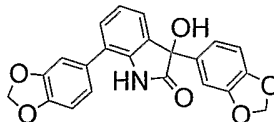
Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(5-chloropentyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (67%): mp 131-132 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.35-7.25 (m, 2H), 7.06 (t, 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); ^{13}C NMR (75 MHz, CDCl_3) 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).

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EXAMPLE 29

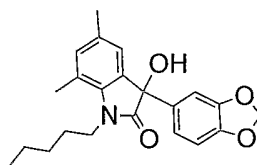
Synthesis of 3,7-bis(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical
 5 variations to replace 1-pentyl-1*H*-indole-2,3-dione with 7-(1,3-benzodioxol-5-yl)-1*H*-
 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,
 10 130.1, 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-2*H*-
 indol-2-one

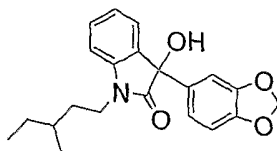


15

Following the procedure as described in EXAMPLE 20, and making non-critical
 variations to replace 1-pentyl-1*H*-indole-2,3-dione with 5,7-dimethyl-1-pentyl-1*H*-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),
 20 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

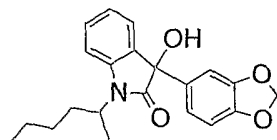
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methylpentyl)-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(3-methylpentyl)-1*H*-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),
10 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

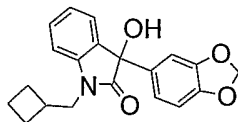
15 Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(1-methylpentyl)-1,3-dihydro-2H-indol-2-one



 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(1-methylpentyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (47%): mp 152-154 °C;
20 ¹H NMR (300 MHz, CDCl₃) δ 7.27-7.23 (m, 2H), 7.05-6.99 (m, 2H), 6.85 (d, 1H), 6.79 (dd, 1H), 6.70 (d, 1H), 5.90 (dd, 2H), 4.40-4.28 (m, 1H), 3.83 (br, 1H), 2.10-1.97 (1H), 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*
25 336 (*M* - 17).

EXAMPLE 33

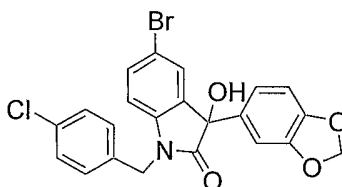
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-cyclobutylmethyl-3-hydroxy-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-cyclobutylmethyl-1H-indole-2,3-dione, the title compound was obtained (32%) as a colorless solid: mp 124-125 °C; 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

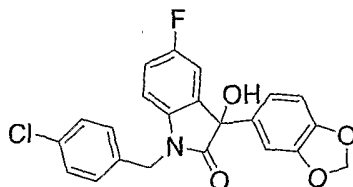
15 Synthesis of 3-(1,3-benzodioxol-5-yl)-5-bromo-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



20 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-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 °C; 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-*d*₆) 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

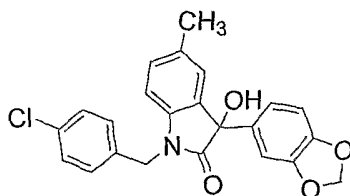
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-5-fluoro-3-hydroxy-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-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 °C; ¹H NMR (300 MHz, DMSO-*d*₆) 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); ¹³C NMR (75 MHz, DMSO-*d*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

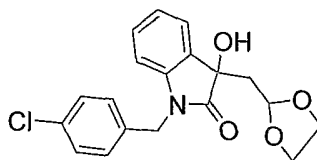
15 Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-methyl-1,3-dihydro-2H-indol-2-one



20 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-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; ¹H NMR (300 MHz, DMSO-*d*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); ¹³C NMR (75 MHz, CDCl₃) δ 177.2, 147.7, 147.2, 140.1, 135.9, 135.7, 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

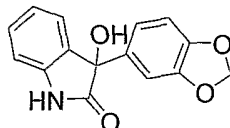
Synthesis of 1-(4-chlorobenzyl)-3-(1,3-dioxolan-2-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



5 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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as colorless solid (69%): mp 166-169 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.38 (d, 1H), 7.28-7.22 (m, 5H),
 10 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); ¹³C 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

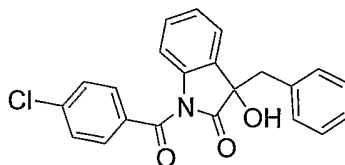
15 Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with isatin, the title compound was obtained (36%): mp 177-180 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.4 (s, 1H), 7.23-
 20 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); ¹³C NMR (75 MHz, DMSO-*d*₆) 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

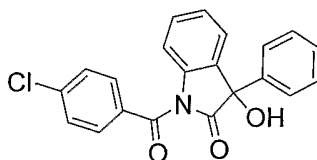
Synthesis of 3-benzyl-1-(4-chlorobenzoyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with benzylmagnesium bromide, and 1-pentyl-1*H*-indole-2,3-dione with 1-(4-chlorobenzoyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (58%): mp 168-170 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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

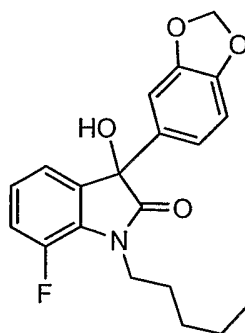
Synthesis of 1-(4-chlorobenzoyl)-3-hydroxy-3-phenyl-1,3-dihydroindol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with phenylmagnesium bromide, and 1-pentyl-1*H*-indole-2,3-dione with 1-(4-chlorobenzoyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (80%): mp 141-143 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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

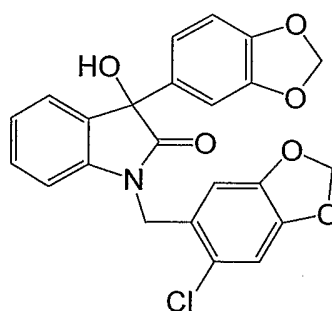
Synthesis of 3-(1,3-benzodioxol-5-yl)-7-fluoro-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 7-fluoro-1-pentyl-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (69%): mp 102-104 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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

15 Synthesis of 3-(1,3-benzodioxol-5-yl)-1-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-hydroxy-1,3-dihydro-2*H*-indol-2-one

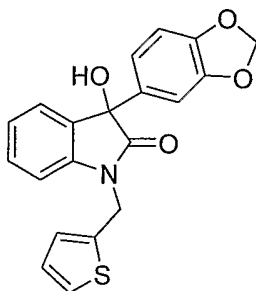


20 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (33%): mp 153-155 °C; ¹H NMR (300 MHz, CDCl₃) 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, CDCl_3) 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

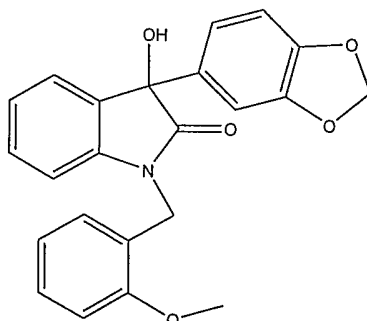
- 5 Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-thiophen-2-ylmethyl-1,3-dihydro-2H-indol-2-one



- Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-thiophen-2-ylmethyl-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (39%): mp 141-142 °C; ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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

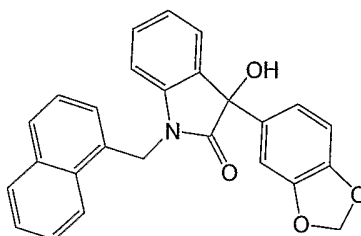


- 20 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(2-methoxybenzyl)-1H-indole-

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-1,3-dihydro-2*H*-indol-2-one



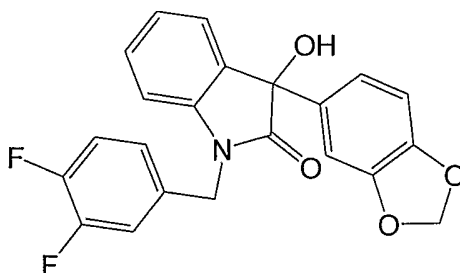
10

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-naphthalen-1-ylmethyl-1*H*-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), 7.17-7.11 (m, 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).

20

EXAMPLE 46

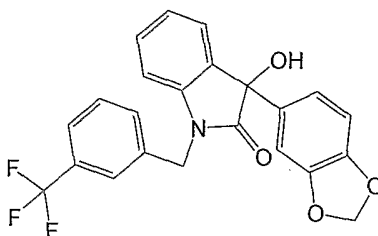
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(3,4-difluorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(3,4-difluoro-benzyl)-1*H*-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, 2H), 7.13-7.00 (m, 4H), 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, 123.4, 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

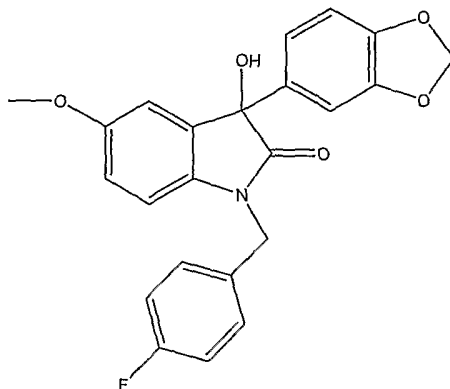
10 Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-trifluoromethylbenzyl)-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(3-trifluoromethyl-benzyl)-1*H*-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

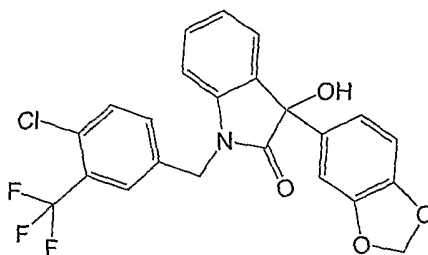
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-3-hydroxy-5-methoxy-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(4-fluorobenzyl)-5-methoxy-1H-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
10 (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* 390 (M - 17).

EXAMPLE 49

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

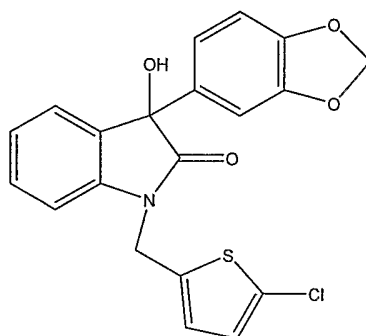


20 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(3-trifluoromethyl-4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (33%): mp 133-135 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.58 (s, 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); ^{13}C NMR (75 MHz, CDCl_3) 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

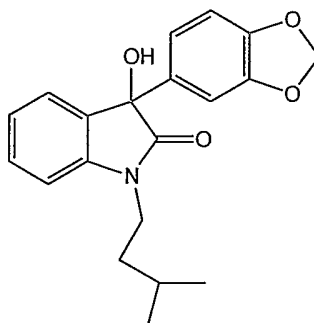
- 5 Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(5-chlorothiophen-2-ylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



- Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(5-chloro-thiophen-2-ylmethyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (30%): mp 164-165 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.26 (m, 2H), 7.11-7.06 (m, 1H), 6.92-6.72 (m, 6H), 5.94 (d, 2H), 4.95 (q, 2H), 3.02 (br, 1H); ^{13}C NMR (75 MHz, CDCl_3) 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 ($M - 17$).

- 15 EXAMPLE 51

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

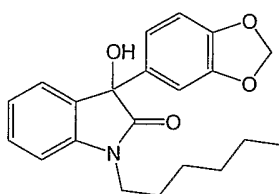


- Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(3-methylbutyl)-1H-indole-2,3-

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

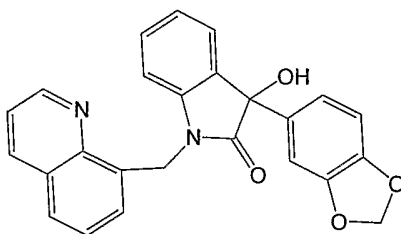
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-hexyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-hexyl-1*H*-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-2*H*-indol-2-one

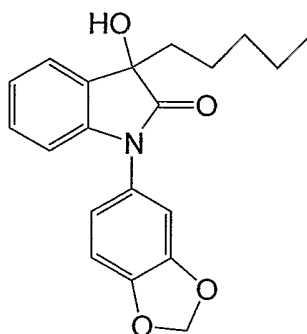


Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-quinolin-8-ylmethyl-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (43%): mp 187-189 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.98 (dd, 1H), 8.17 (dd, 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); ^{13}C NMR (75 MHz, CDCl_3) 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

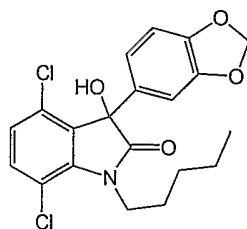
Synthesis of 1-(1,3-benzodioxol-5-yl)-3-hydroxy-3-pentyl-1,3-dihydro-2H-indol-2-one



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-1H-indole-2,3-dione with 1-(1,3-benzodioxol-5-yl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (30%): mp 88-90 °C; ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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

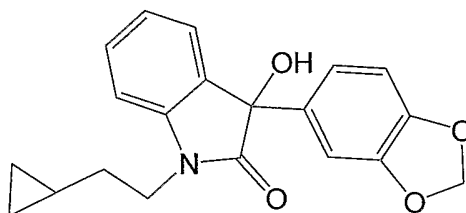
Synthesis of 3-(1,3-benzodioxol-5-yl)-4,7-dichloro-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-4,7-dichloro-1*H*-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, 1H), 6.92 (d, 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

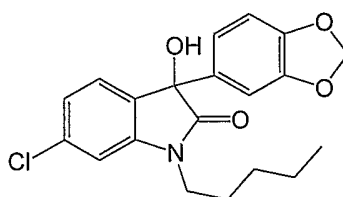
- 10 Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(2-cyclopropylethyl)-1*H*-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 (ES+) *m/z* 320 (M - 17).

EXAMPLE 57

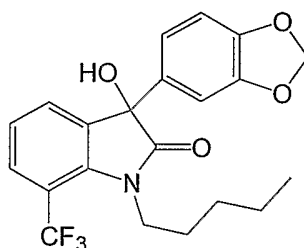
- Synthesis of 3-(1,3-benzodioxol-5-yl)-6-chloro-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-6-chloro-1*H*-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 177.2, 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

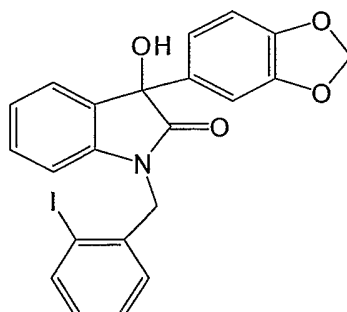
- 10 Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-7-trifluoromethyl-1,3-dihydro-2*H*-indol-2-one



- Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-7-trifluoromethyl-1*H*-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

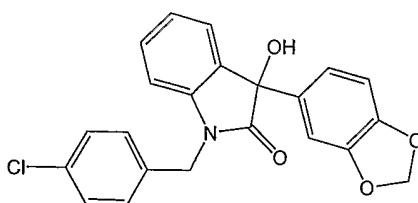
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(2-iodobenzyl)-1,3-dihydro-2*H*-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(2-iodobenzyl)-1*H*-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),
10 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

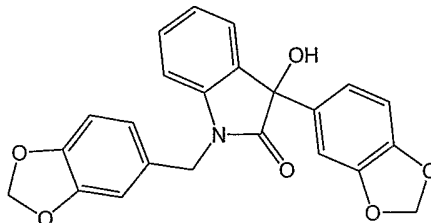
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



15 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (76%): mp 177-178 °C;
20 ¹H NMR (300 MHz, CDCl₃) δ 7.30-6.70 (m, 11H), 5.93 (dd, 2H), 4.94 (d, 1H), 4.79 (d, 1H), 3.23 (br, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 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

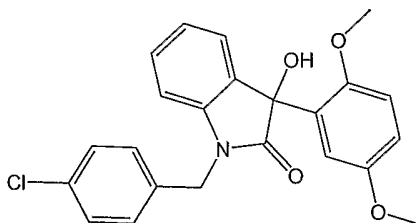
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(1,3-benzodioxol-5-ylmethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (67%): mp 172-173 °C; ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C
10 NMR (75 MHz, CDCl₃) δ 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

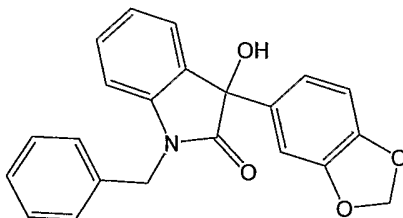
Synthesis of 1-(4-chlorobenzyl)-3-(2,5-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2*H*-
15 indol-2-one



 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with 2,5-dimethoxymagnesium bromide, and 1-pentyl-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless
20 solid (47%): ¹H NMR (300 MHz, CDCl₃) δ 7.56 (d, 1H), 7.35-7.09 (m, 6H), 6.96 (t, 1H), 6.70 (d, 1H), 6.55 (m, 1H), 6.38 (d, 1H), 4.98 (d, 1H), 4.79 (d, 1H), 3.79 (s, 3H), 3.57 (br, 1H), 3.43 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.4, 160.7, 156.8, 143.6, 136.3, 133.2, 132.5, 130.1, 129.1, 128.9, 128.1, 123.8, 122.5, 122.4, 108.9, 105.0, 99.3, 74.9,
25 65.4, 55.8, 55.7, 42.7, 15.6.

EXAMPLE 63

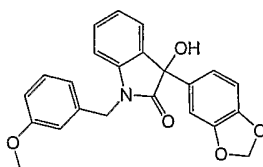
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-benzyl-3-hydroxy-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-benzyl-1H-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 (d, 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

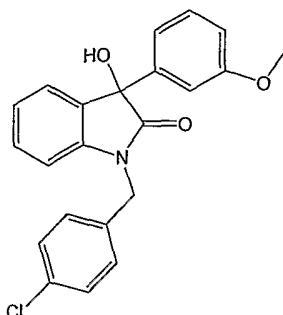
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methoxybenzyl)-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(3-methoxybenzyl)-1H-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

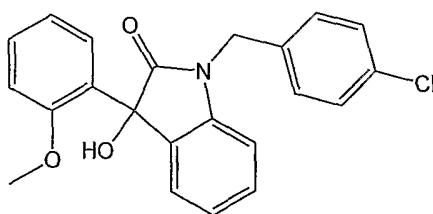
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(3-methoxyphenyl)-1,3-dihydro-2H-indol-2-one



5 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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-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

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

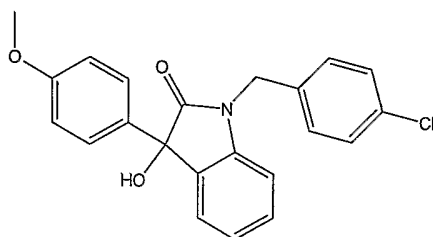


20 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with 2-methoxyphenylmagnesium bromide, and 1-pentyl-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (44%): mp 175-176 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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, 130.2, 130.1, 129.4, 129.2, 129.0, 123.9, 122.5, 120.8, 112.0, 109.0, 75.1, 55.8, 42.7.

EXAMPLE 67

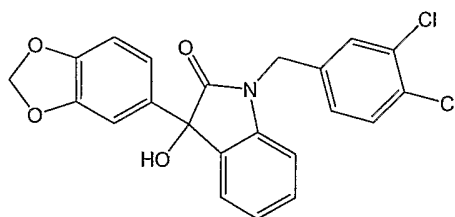
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2*H*-indol-2-one



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-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (63%): mp 195-196 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, DMSO-*d*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

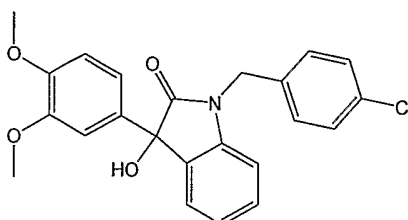
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(3,4-dichlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(3,4-dichlorobenzyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (59%): mp 177-179 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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

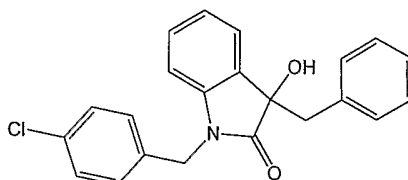
Synthesis of 1-(4-chlorobenzyl)-3-(3,4-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



- 5 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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (50%): mp 155-158 °C; ¹H NMR (300 MHz, CDCl₃) 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);
- 10 MS (ES+) *m/z* 432.5 (M + 23).

EXAMPLE 70

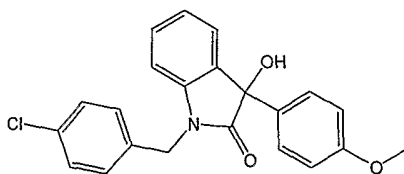
Synthesis of 3-benzyl-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



- 15 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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (33%): mp 210 °C (dec.); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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.
- 20

EXAMPLE 71

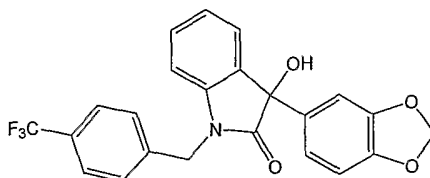
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2H-indol-2-one



5 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-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (63%): mp 195-196 °C; ¹H NMR (300 MHz, CDCl₃) 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);
 10 ¹³C NMR (75 MHz, CDCl₃) δ 177.5, 159.3, 142.6, 135.8, 133.6, 132.6, 129.7, 129.1, 127.3, 125.1, 123.4, 114.1, 109.8, 77.1, 55.5, 42.5.

EXAMPLE 72

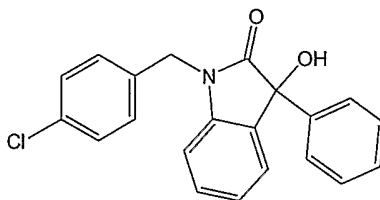
15 Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-trifluoromethylbenzyl)-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione and 1-(4-trifluorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (73%): mp 164-166 °C;
 20 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,
 25 101.6, 77.2, 42.1.

EXAMPLE 73

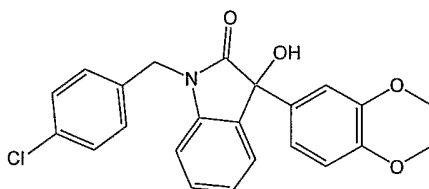
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-phenyl-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical
 5 variations to replace 3,4-(methylenedioxy)phenylmagnesium bromide with
 phenylmagnesium bromide and 1-pentyl-1H-indole-2,3-dione with 1-(4-chlorobenzyl)-
 1H-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, 142.7, 141.7, 135.8,
 10 133.6, 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

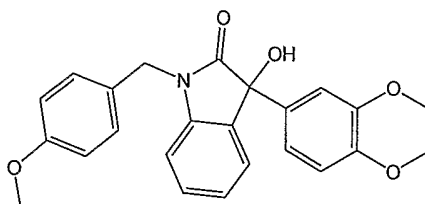


15

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-1H-indole-2,3-dione
 with 1-(4-chlorobenzyl)-1H-indole-2,3-dione, the title compound was obtained as a
 20 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 75

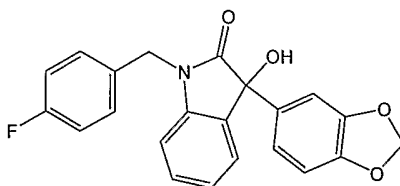
Synthesis of 3-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2H-indol-2-one



5 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-1H-indole-2,3-dione with 1-(4-methoxybenzyl)-1H-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),
 10 7.02 (t, 1H), 6.95 (d, 1H), 6.86-6.74 (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

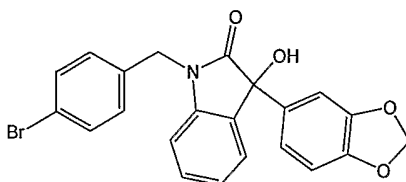
15 Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(4-fluorobenzyl)-1H-indole-
 20 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, 133.0, 132.9, 129.9, 129.8, 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

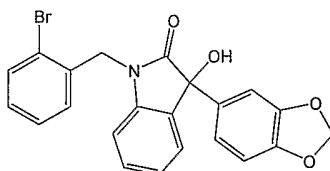
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-bromobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(4-bromobenzyl)-1*H*-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), 4.76 (d, 1H), 3.28 (br, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.3, 147.8, 147.3, 142.6, 136.2,
10 135.6, 133.3, 132.0, 130.0, 129.8, 125.2, 123.4, 121.1, 119.3, 109.9, 108.3, 106.9, 101.6, 77.2, 42.7.

EXAMPLE 78

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

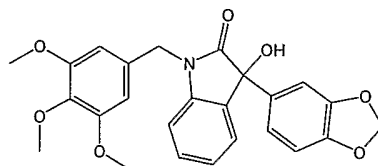


15

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(2-bromobenzyl)-1*H*-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,
20 135.0, 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

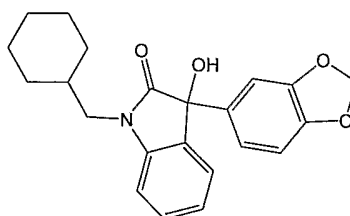
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3,4,5-trimethoxybenzyl)-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(3,4,5-trimethoxybenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (33%): mp 158-161 °C; 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-2H-indol-2-one

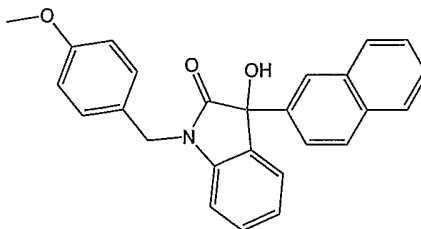


15

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(cyclohexylmethyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (28%): mp 164-165 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.35-6.70 (m, 7H), 5.90 (q, 2H), 3.65-3.42 (m, 2H), 3.25 (br, 1H), 1.90-1.60 (m, 6H), 1.25-0.95 (m, 5H); 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

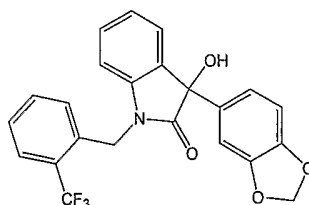
Synthesis of 3-hydroxy-1-(4-methoxybenzyl)-3-naphthalen-2-yl-1,3-dihydro-2*H*-indol-2-one



5 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-1*H*-indole-2,3-dione with 1-(4-methoxybenzyl)-1*H*-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),
 10 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

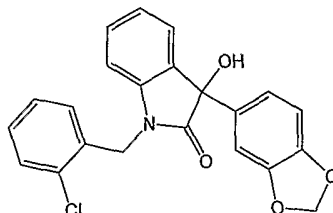
15 Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(2-trifluoromethylbenzyl)-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(2-trifluoromethylbenzyl)-1*H*-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),
 20 5.10 (d, 1H), 3.15 (br, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆) 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

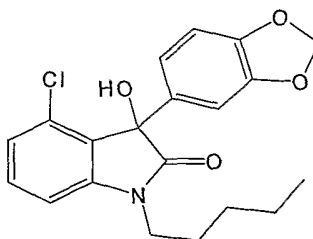
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(2-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-(2-chlorobenzyl)-1H-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 (s, 2H), 5.11 (d, 1H), 4.96 (d, 1H), 3.15 (br, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 177.3, 147.8, 147.3, 142.7, 135.5, 10
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

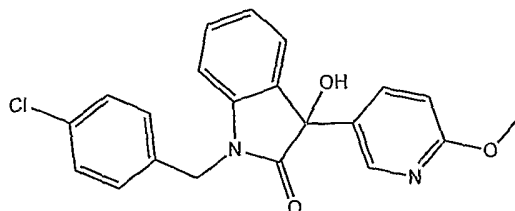


15

Following the procedure as described in EXAMPLE 20, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-pentyl-4-chloro-1H-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).
20

EXAMPLE 85

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

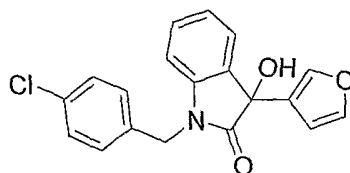


5 To a solution of 5-bromo-2-methoxypyridine (1.88 g, 10.0 mmol) in anhydrous THF (25.0 mL) was added a solution of *t*-BuLi (5.88 mL, 10.0 mmol, 1.7 M in pentane) at -78 °C. The yellow solution was stirred for 0.5 h, and added to a solution of 1-(4-chlorobenzyl)-1H-indole-2,3-dione (1.36 g, 5.00 mmol) in anhydrous THF (25.0 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h and at ambient temperature
10 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 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 (4/1) to give the title compound (0.35 g, 18%) as a yellow solid:
15 mp 182-184 °C; ¹H NMR (300 MHz, DMSO-*d*₆) 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-*d*₆) 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).

20

EXAMPLE 86

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

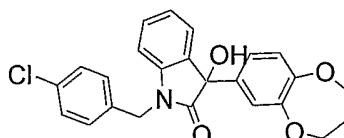


Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 3-bromofuran, the title compound
25 was obtained (9%) as a colorless solid: mp 128-130 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.60 (t, 1H), 7.41-7.30 (m, 6H), 7.23 (dt, 1H), 7.03 (d, 1H), 6.90 (d, 1H), 6.68 (s, 1H),

6.51 (dd, 1H), 4.86 (s, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 176.6, 144.3, 142.3, 142.1, 140.6, 135.8, 132.5, 132.1, 129.8, 129.6, 129.1, 126.7, 124.9, 123.3, 109.9, 109.8, 72.6, 42.4; MS (ES+) m/z 322 (M - 17).

EXAMPLE 87

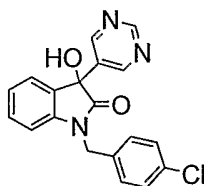
- 5 Synthesis of 1-(4-chlorobenzyl)-3-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



- 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-1,5-benzodioxepine, the title compound was obtained as a colorless solid (16%): mp 188-190 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) 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); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 177.2, 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

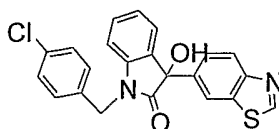
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-pyrimidin-5-yl-1,3-dihydro-2H-indol-2-one



- 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 °C; ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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

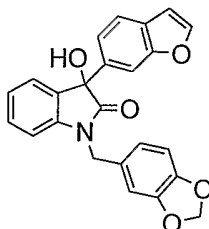
Synthesis of 3-(1,3-benzothiazol-6-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



5 Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 6-bromo-1,3-benzothiazole, the title compound was obtained as a colorless solid (13%): mp 185-187 °C; ¹H NMR (300 MHz, DMSO-*d*₆) 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-*d*₆) δ 175.4, 174.6, 152.4, 142.7, 136.8, 135.3, 132.6, 131.1, 130.6, 130.0, 129.6,
10 129.1, 125.4, 124.9, 124.8, 123.6, 118.5, 110.4, 77.8, 42.6; MS (ES+) *m/z* 406 (M + 1).

EXAMPLE 90

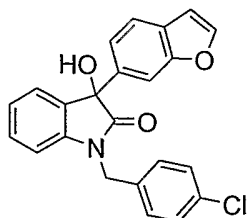
Synthesis of 1-(1,3-benzodioxol-5-ylmethyl)-3-(1-benzofuran-6-yl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



15 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)-1*H*-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (11%): mp > 200 °C; ¹H
20 NMR (300 MHz, DMSO-*d*₆) 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;
25 MS (ES+) *m/z* 382 (M - 17).

EXAMPLE 91

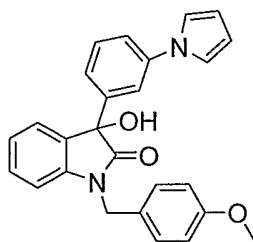
Synthesis of 3-(1-benzofuran-6-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



5 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-*d*₆) 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

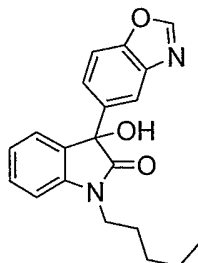
Synthesis of 3-hydroxy-1-(4-methoxybenzyl)-3-(3-pyrrol-1-ylphenyl)-1,3-dihydro-2*H*-indol-2-one



15 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)-1*H*-indole-2,3-dione with 1-(4-methoxybenzyl)-1*H*-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, CDCl₃) 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

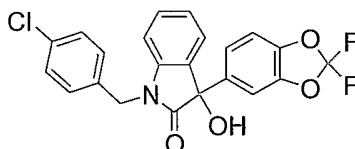
Synthesis of 3-(1,3-benzoxazol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 5-bromobenzoxazole, and 1-(4-chlorobenzyl)-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (21%): mp 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

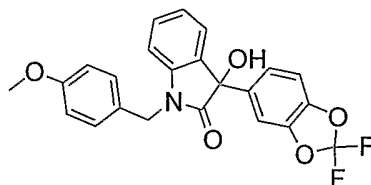
Synthesis of 1-(4-chlorobenzyl)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 5-bromo-2,2-difluoro-1,3-benzodioxole, the title compound was obtained as a colorless solid (20%): mp 150-152 °C; ¹H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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

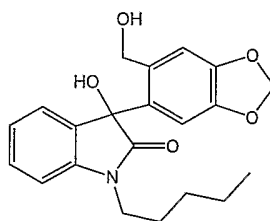
Synthesis of 3-(2,2-difluoro-1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with 5-bromo-2,2-difluoro-1,3-benzodioxole, and 1-(4-chlorobenzyl)-1H-indole-2,3-dione with 1-(4-methoxybenzyl)-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (31%): mp 88-90 °C; ¹H NMR (300 MHz, CDCl₃) 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

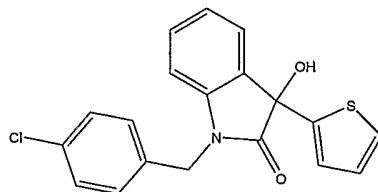
Synthesis of 3-hydroxy-3-[6-(hydroxymethyl)-1,3-benzodioxol-5-yl]-1-pentyl-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 85, and making non-critical variations to replace 5-bromo-2-methoxypyridine with (6-bromo-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

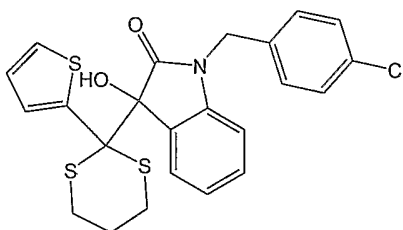


To a solution of thiophene (0.84 g, 10.0 mmol) in THF (50.0 mL) was added
 5 n-BuLi (6.50 mL, 1.6 M, 11.0 mmol) at -35°C . The reaction mixture was stirred at -30°C for 30 min. The generated lithiated species was added into a solution of 1-(4-chlorobenzyl)-1H-indole-2,3-dione (2.70 g, 10.0 mmol) in THF (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 NH_4Cl solution and the solvent was evaporated under
 10 reduced pressure. The residue was subjected to column chromatography (SiO_2 , $\text{MeOH}:\text{CH}_2\text{Cl}_2$ - 1:20-1:10) to give 1.21 g (34%) of the title compound as a colorless solid: mp $140-143^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 7.50-6.85 (m, 11H), 6.68 (d, 1H), 4.85 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) 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.

15

EXAMPLE 98

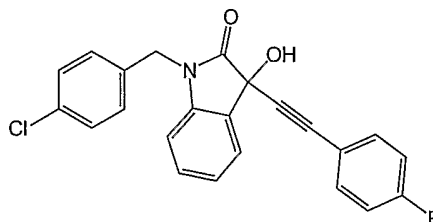
Synthesis of 1-(4-chlorobenzyl)-3-hydroxy-3-[2-(2-thienyl)-1,3-dithian-2-yl]-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 97, and making non-critical
 20 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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) δ 174.6, 144.7, 143.3, 135.5, 132.4, 131.0, 130.1, 129.7, 128.8, 128.8, 128.7, 127.0, 126.5, 121.7, 108.8,
 25 80.7, 62.4, 42.7, 27.5, 24.5.

EXAMPLE 99

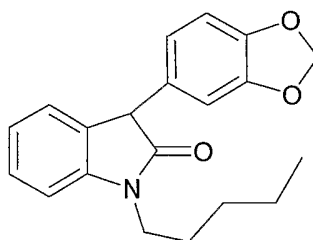
Synthesis of 1-(4-chlorobenzyl)-3-(4-fluorophenylethynyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



5 Following the procedure as described in EXAMPLE 97, and making non-critical variations to replace thiophene with 1-ethynyl-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, 66.8, 40.2; 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



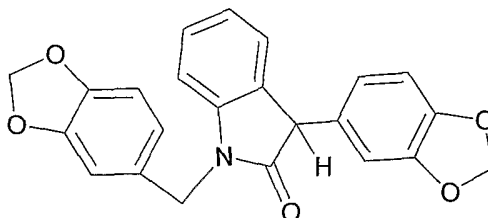
15 To a solution of 1-pentyl-1H-indole-2,3-dione (1.42 g, 5.32 mmol) in anhydrous THF (30.0 mL) was added a solution of 3,4-(methylenedioxy)phenylmagnesium bromide (5.90 mL, 1.0 M solution in toluene/THF, 50:50) under nitrogen at -78 °C. The reaction mixture was stirred at -78 °C for 1 h and at ambient temperature for 4 h, and quenched with saturated ammonium chloride (30.0 mL). The mixture was extracted
20 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 *i*Pr₂NEt (1.82 g, 2.50 mL, 17.9 mmol) and SOCl₂ (2.50 mL) at 0 °C. The reaction
25 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, CDCl₃) δ 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, CDCl₃) δ 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).

15

EXAMPLE 101

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

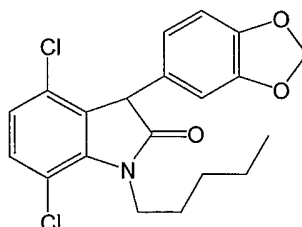


Following the procedure as described in EXAMPLE 100, and making non-critical variations to replace 1-pentyl-1*H*-indole-2,3-dione with 1-(1,3-benzodioxol-5-ylmethyl)-1*H*-indole-2,3-dione, the title compound was obtained as a colorless solid (37%): mp 117-118 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.21 (t, 1H), 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, CDCl₃) δ 176.1, 148.1, 148.0, 147.2, 147.1, 143.3, 130.2, 129.7, 128.9, 128.4, 125.1, 122.8, 121.9, 121.2, 120.9, 109.2, 108.7, 108.6, 108.4, 107.9, 101.1, 51.7, 43.8. Anal. Calcd for C₂₃H₁₇NO₄: C, 71.31; H, 4.42; N, 3.62. Found: C, 70.89; H, 4.44; N, 3.59.

25

EXAMPLE 102

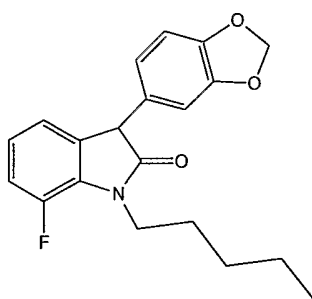
Synthesis of 3-(1,3-benzodioxol-5-yl)-4,7-dichloro-1-pentyl-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 100, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-pentyl-4,7-dichloro-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (48%): mp 84-86 °C; ¹H NMR (300 MHz, CDCl₃) δ 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, CDCl₃) δ 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

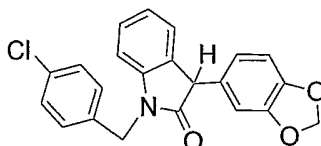
Synthesis of 3-(1,3-benzodioxol-5-yl)-7-fluoro-1-pentyl-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 100, and making non-critical variations to replace 1-pentyl-1H-indole-2,3-dione with 1-pentyl-7-fluoro-1H-indole-2,3-dione, the title compound was obtained as a colorless solid (71%): mp 95-97 °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

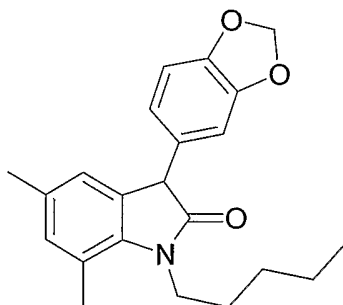
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-1,3-dihydro-2H-indol-2-one



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 °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

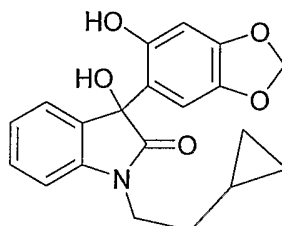


Following the procedure as described in EXAMPLE 104, and making non-critical variations to replace 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one with 3-(1,3-benzodioxol-5-yl)-3-hydroxy-5,7-dimethyl-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained as a colorless solid (43%): mp 111-114 °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, CDCl₃) δ 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

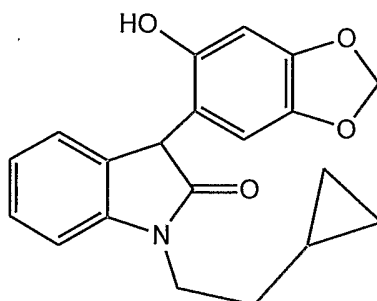
- 5 Synthesis of 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one



- 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 °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 °C. A solution of 1-(2-cyclopropylethyl)-1H-indole-2,3-dione (1.77 g, 8.23 mmol) in dichloromethane (20.0 mL) was added to the above solution at 0 °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: ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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

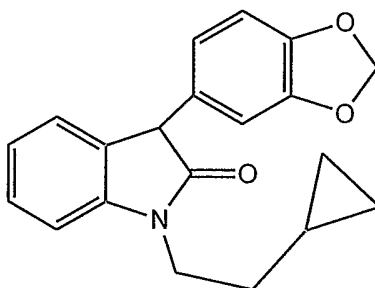
Synthesis of 1-(2-cyclopropylethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one



- 5 To a solution of 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-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
- 10 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: ¹H NMR (300 MHz, CDCl₃) δ 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
- 15 (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); ¹³C NMR (75 MHz, CDCl₃) δ 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

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



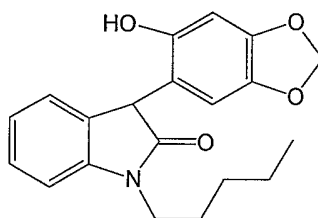
Following the procedure as described in EXAMPLE 104, and making non-

critical variations to replace 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one with 3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained as a colorless solid (96%): mp 87-89 °C; ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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, 101.1, 51.6, 40.3, 32.4, 8.7, 4.4, 4.3; MS (ES+) *m/z* 322 (M + 1).

10

EXAMPLE 109

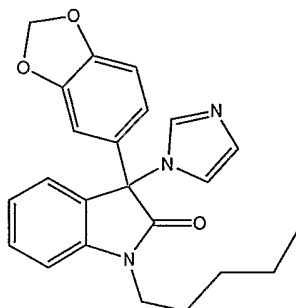
Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



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-2*H*-indol-2-one with 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained as a colorless solid (70%): mp 101-103 °C; ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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

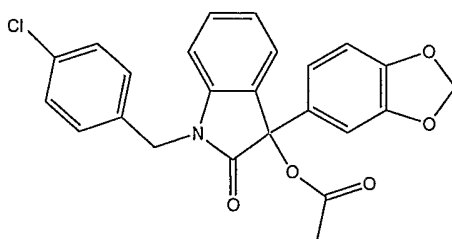
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-imidazol-1-yl-1-pentyl-1,3-dihydro-2*H*-indol-2-one



5 A mixture of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-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
10 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,
15 107.4, 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-1*H*-indol-3-yl acetate



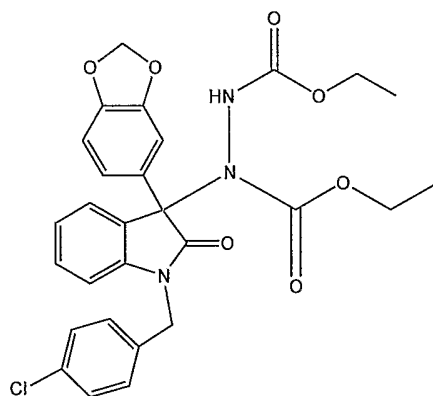
20

To a solution of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (0.39 g, 1.00 mmol) in CH₂Cl₂ (15.0 mL) was added ⁱPr₂NEt (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
 5 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,
 10 124.2, 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-1*H*-indol-3-yl]hydrazine-1,2-dicarboxylate



15

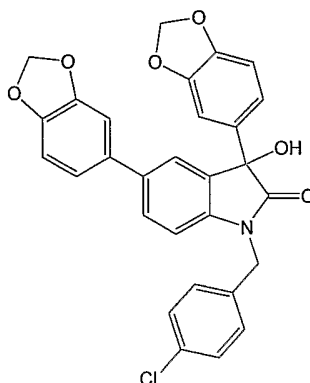
A mixture of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (1.00 g, 2.54 mmol), triphenylphosphine (0.99 g, 3.81 mmol) and diethyl azodicarboxylate (0.66 g, 3.81 mmol) in CH₂Cl₂ was stirred at ambient temperature for 16 h. The reaction mixture was diluted with CH₂Cl₂ (30.0 mL) and
 20 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,
 25 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-117); Anal. Calc'd for $C_{28}H_{26}N_3O_7$: 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

5

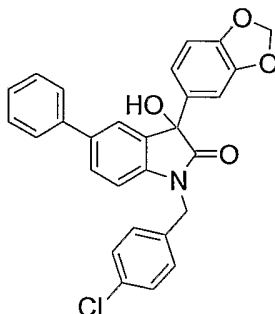


A mixture of 3-(1,3-benzodioxol-5-yl)-5-bromo-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one (0.47 g, 1.00 mmol) and $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol) in anhydrous dioxane (12.0 mL) was stirred at ambient temperature for 10 min under nitrogen followed by the additions of a solution of 3,4-methylenedioxyphenylboronic acid (0.23 g, 1.50 mmol) in ethanol (1.00 mL), aqueous solution of 2.0 M Na_2CO_3 (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, $DMSO-d_6$) 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); ^{13}C NMR (75 MHz, $DMSO-d_6$) 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, 101.6, 77.8, 42.6; MS (ES+) m/z 536 (M + 23), 496 (M - 17).

20

EXAMPLE 114

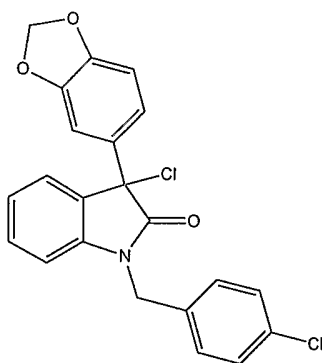
Synthesis of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-indol-2-one



5 Following the procedure as described in EXAMPLE 113, 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-*d*₆) 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),
 10 3.47 (br, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆) 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

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

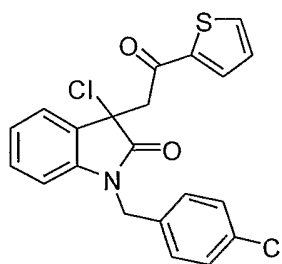


20 To a solution of 3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (2.00 g, 5.09 mmol) in CH₂Cl₂ (75.0 mL) was added pyridine (0.60 g, 7.63 mmol) followed by SOCl₂ (0.72 g, 6.11 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and quenched by the addition 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

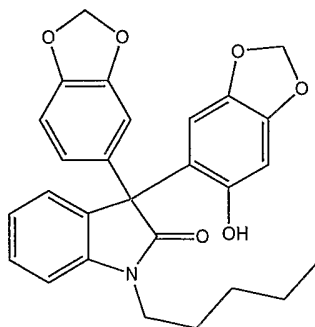
Synthesis of 3-chloro-1-(4-chlorobenzyl)-3-[2-oxo-2-(2-thienyl)ethyl]-1,3-dihydro-2H-indol-2-one



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-2H-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

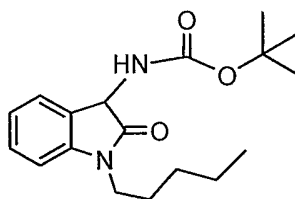
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 5 A mixture of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-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%)
- 10 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, 108.3, 107.0,
- 15 102.1, 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).
- 20

EXAMPLE 118

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



A. Synthesis of 1-pentyl-1*H*-indole-2,3-dione 3-(*O*-pentyloxime)

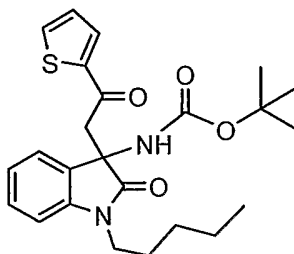
To a solution of 1*H*-indole-2,3-dione 3-oxime (10.0 g, 61.7 mmol) in DMF (100 mL) was added NaH (5.33 g, 139 mmol, 60% in mineral oil) in portions at 0 °C over 10 min. The reaction mixture was stirred for 30 min followed by the addition of 1-
5 bromopentane (9.50 mL, 77.1 mmol). The reaction mixture 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
10 was crystallized from ether to give the title compound (5.56 g, 30%) as a colorless solid: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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,
15 13.9; MS (ES+) *m/z* 302 (M + 1).

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

To a mixture of 1-pentyl-1*H*-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
20 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-
25 147 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₆N₂O₃: C, 67.90; H, 8.23; N, 8.80. Found: C, 68.16; H, 7.97;
30 N, 8.81.

EXAMPLE 119

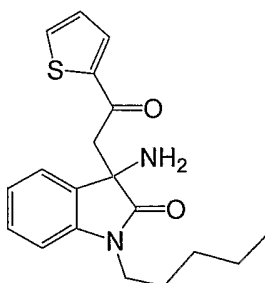
Synthesis of *tert*-butyl {2-oxo-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-2,3-dihydro-1*H*-indol-3-yl}carbamate



5 A mixture of *tert*-butyl (2-oxo-1-pentyl-2,3-dihydro-1*H*-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
 10 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: ¹H NMR (300 MHz, CDCl₃) δ 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,
 15 9H), 0.89 (t, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 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-2*H*-indol-2-one



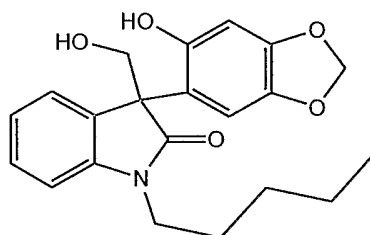
20

To a solution of *tert*-butyl {2-oxo-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-2,3-dihydro-1*H*-indol-3-yl}carbamate (0.46 g, 1.06 mmol) in CH₂Cl₂ (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 NaHCO₃ and diluted with CH₂Cl₂ (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; ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₁₉H₂₂N₂O₂S: 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

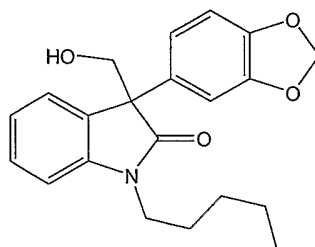


To a solution of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one (3.39 g, 10.0 mmol) in anhydrous CH₂Cl₂ (40 mL) was added triethyl amine (6.07 g, 60.0 mmol) and chlorotrimethylsilane (4.35 g, 40.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and diluted with anhydrous CH₂Cl₂ (100 mL). The mixture was washed with H₂O (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 CH₂Cl₂ (100 mL). The mixture was washed with saturated NaHCO₃ (50.0 mL), saturated ammonium chloride (50.0 mL) and H₂O (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 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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

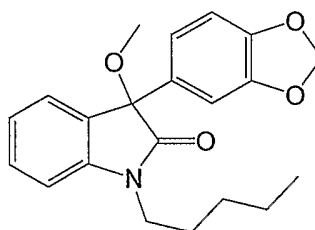
- 10 Synthesis of 3-(1,3-benzodioxol-5-yl)-3-hydroxymethyl-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 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*H*-indol-2-one with 3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained as a colorless solid: mp 110-113 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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

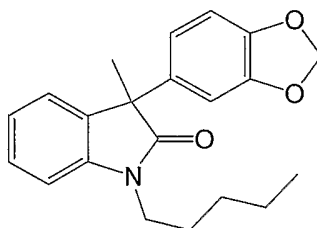
Synthesis of 3-(1,3-benzodioxol-5-yl)-3-methoxy-1-pentyl-1,3-dihydro-indol-2-one



To a solution of 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-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 °C. The mixture was stirred at 0 °C for one hour and quenched with ammonium chloride solution. The mixture was
5 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),
10 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).

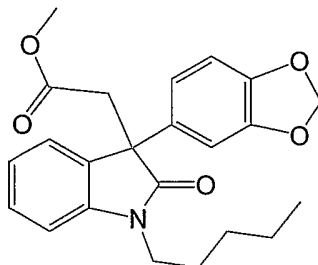
EXAMPLE 124

15 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-2*H*-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
20 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
25 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-1*H*-indol-3-yl]acetate

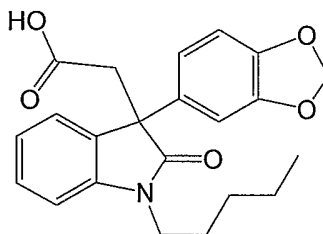
5 A solution of 3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one (1.00 g, 3.10 mmol) and methyl bromoacetate (0.44 mL, 4.60 mmol) in THF (20 mL) was degassed by bubbling through argon for one hour. Sodium hydride (0.19 g, 4.60 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h and quenched with ammonium chloride solution. The mixture was poured into water (150 mL), and

10 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: ¹H NMR (300 MHz, CDCl₃) δ 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,

15 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); ¹³C NMR (75 MHz, CDCl₃) δ 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).

20

EXAMPLE 126

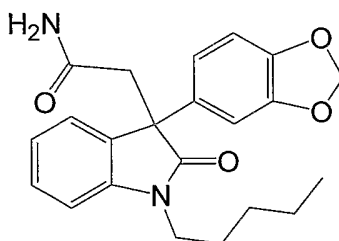
Synthesis of [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]acetic acid

To a solution of methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-

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: ^1H NMR (300 MHz, CDCl_3) δ 7.29 (td, 1H), 7.21 (dd, 1H), 7.05 (td, 1H), 6.87 (d, 1H), 6.76 (d, 1H), 6.72-6.64 (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) δ 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

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



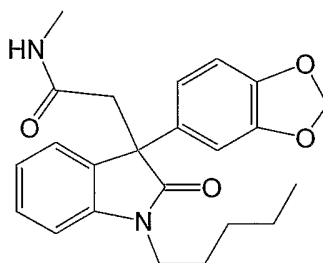
A. To a solution of [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetic acid (0.28 g, 0.73 mmol) and oxalyl chloride (0.32 mL, 3.70 mmol) in toluene (10.0 mL) was added one drop of DMF and the mixture was stirred at ambient temperature overnight. The mixture was concentrated under 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 the acid chloride (0.05 g, 0.12 mmol) in dichloromethane (1.00 mL) at ambient temperature. The mixture was stirred 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: ^1H NMR (300 MHz, CDCl_3) δ 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), 3.27 (d, 1H), 2.98 (d, 1H), 1.74-1.59 (m, 2H), 1.38-1.22 (m, 4H), 0.85 (t, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 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

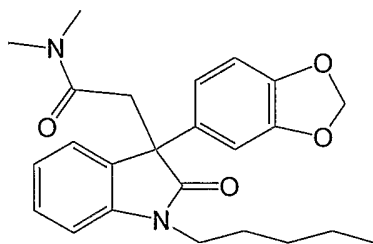
Synthesis of 2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]-*N*-methylacetamide



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%): ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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

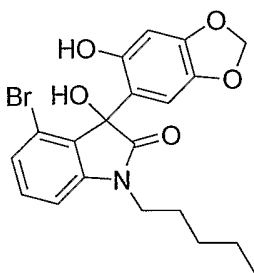
Synthesis of 2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]-*N,N*-dimethylacetamide



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%): ^1H NMR (300 MHz, CDCl_3) δ 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); ^{13}C NMR (CDCl_3 , 75 MHz) δ 178.7, 168.5, 147.8, 146.8, 144.1, 133.9, 132.5, 128.1, 124.0, 121.8, 120.1, 108.6, 108.0, 107.6, 101.1, 53.2, 41.7, 40.3, 37.3, 35.4, 29.1, 26.9, 22.3, 14.0; MS (ES+) m/z 409.1 ($M + 1$).

EXAMPLE 130

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

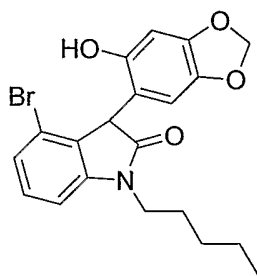


To a solution of 1,3-benzodioxol-5-ol (12.8 g, 92.9 mmol) in tetrahydrofuran (200 mL) was added isopropylmagnesium chloride solution (50.7 mL, 101 mmol, 2.0 M in ether) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, upon which time the colorless precipitate was formed. After the solvent was removed under reduced pressure, the residue was dissolved in methylene chloride (100 mL) and added to a solution of 4-bromo-1-pentyl-1H-indole-2,3-dione (25.0 g, 84.5 mmol) in dichloromethane (100 mL) via a canula over 10 min at 0 °C. The reaction mixture was stirred at ambient temperature for 16 h, quenched with saturated ammonium chloride solution (100 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers was washed with brine, 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 to give the title compound (34.9 g, 97%) as a brown gummy material: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) 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); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 177.6, 152.6, 149.1, 144.8, 141.2, 131.7, 127.7, 127.6, 121.0, 113.8, 108.3, 106.7, 101.7, 101.4, 80.5, 40.5, 28.8, 26.7 22.2, 13.9.

EXAMPLE 131

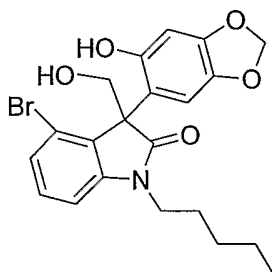
- 5 Synthesis of 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one



- To a solution of 4-bromo-3-hydroxy-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 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 (16.5 g, 49%) as a brown solid: ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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).

EXAMPLE 132

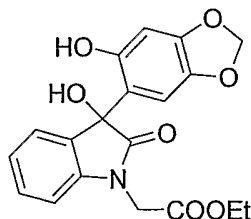
Synthesis of 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one



- 5 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
- 10 magnesium sulfate and filtered. The filtrate was concentrated *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,
- 15 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 *in vacuo* to dryness to yield the title compound (6.32 g, 79%) as a fluffy solid: ¹H NMR (300 MHz, CDCl₃) δ 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),
- 20 3.70-3.65 (m, 2H), 1.68-1.57 (m, 2H), 1.36-1.29 (m, 4H), 0.83 (t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 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 .

EXAMPLE 133

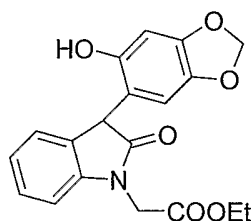
Synthesis of ethyl [3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



5 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with ethyl (2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)acetate, the title compound was obtained (95%): ¹H NMR (300 MHz, DMSO-*d*₆) δ 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-)
10 *m/z* 370.2 (M - 1).

EXAMPLE 134

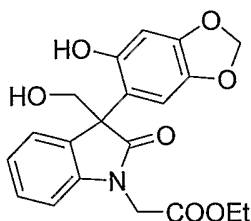
Synthesis of ethyl [3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



15 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*H*-indol-2-one with ethyl [3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained (84%) as a white powder: ¹H NMR (DMSO-*d*₆, 300 MHz) δ 9.37 (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).
20

EXAMPLE 135

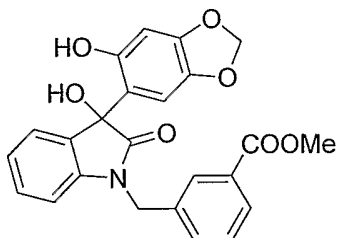
Synthesis of ethyl [3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



5 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*H*-indol-2-one with ethyl [3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained as a white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.03 (s, 1H), 7.17-6.85 (m, 5H), 6.22 (s, 1H), 5.83 (s, 2H),
10 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

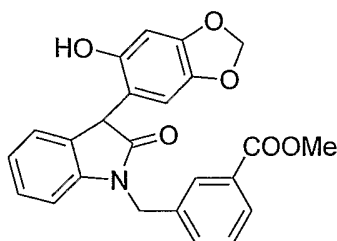
Synthesis of methyl 3-[[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate



15 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with methyl 3-[[2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate, the title compound was obtained (96%): ¹H NMR (300 MHz, CDCl₃) δ 8.65 (s, 1H), 7.92 (s, 1H), 7.85 (d, 1H),
20 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 (s, 1H), 4.83 (dd, 2H), 3.80 (s, 3H);
¹³C NMR (75 MHz, CDCl₃) δ 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-1*H*-indol-1-yl]methyl]benzoate

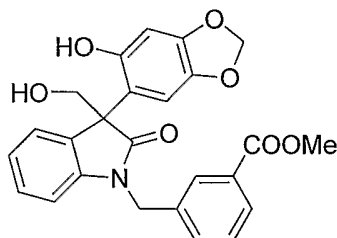


5 Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one with methyl 3-[[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate,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

10

EXAMPLE 138

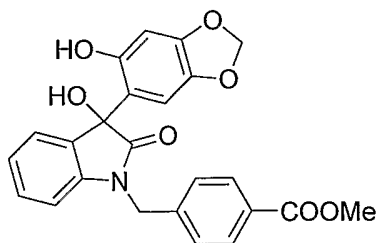
Synthesis of methyl 3-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate



15 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*H*-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

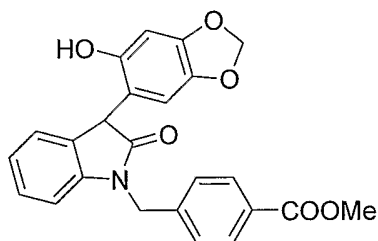
Synthesis of methyl 4-[[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate



- 5 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-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

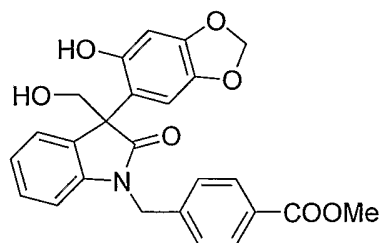
- 10 Synthesis of methyl 4-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate



- 15 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-2*H*-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, 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-1*H*-indol-1-yl]methyl]benzoate

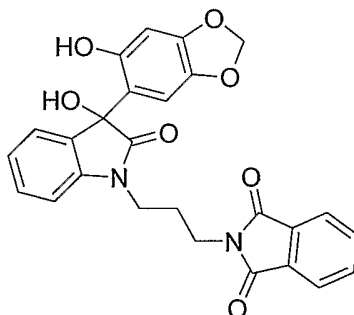


5 Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with methyl 4-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate, the title compound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

10

EXAMPLE 142

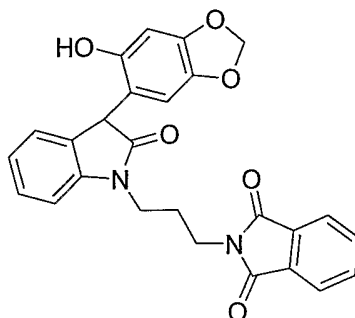
Synthesis of 2-{3-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione



15 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 1-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-1*H*-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, 1H), 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

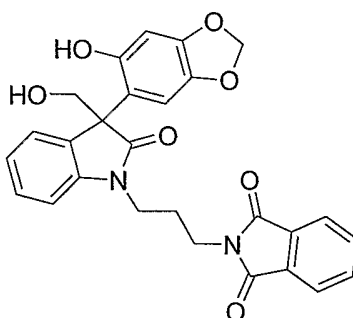
Synthesis of 2-{3-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione



5 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*H*-indol-2-one with 2-{3-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione, the title compound was obtained (94%): ¹H NMR (300 MHz, CDCl₃) δ 7.81-7.78 (m, 2H), 7.70-7.67 (m, 2H), 7.32-7.27 (m, 2H), 7.12-7.07 (m, 1H), 6.90-6.87 (m, 1H), 6.54 (s, 1H),
10 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

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

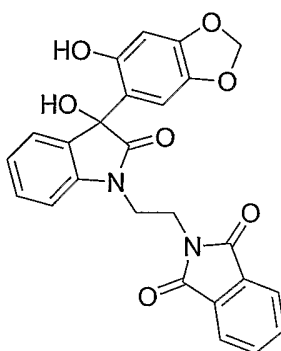


20 Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with 2-{3-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione, 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), 7.68-7.61 (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, 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,
 5 36.1, 26.5; MS (ES+) *m/z* 487.3 (M + 1).

EXAMPLE 145

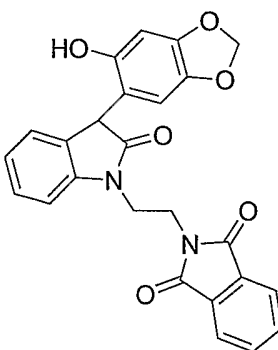
Synthesis of 2-{2-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione



10 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 1-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-1*H*-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);
 15 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-1*H*-indol-1-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione

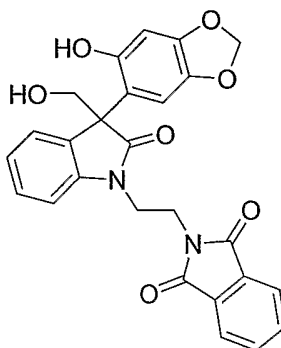


20 Following the procedure as described in EXAMPLE 131, and making non-

critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with 2-{2-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-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).

EXAMPLE 147

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



10

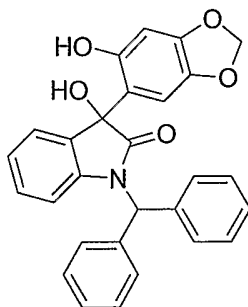
Following the procedure as described in EXAMPLE 132, making variation to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with 2-{2-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione, the title compound was 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)

15

EXAMPLE 148

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

20

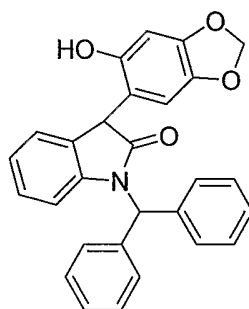


Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 1-(diphenylmethyl)-1*H*-indole-2,3-dione, the title compound was obtained (99%) as an off-white powder: MS (ES+) m/z 474.5 ($M + 23$).

5

EXAMPLE 149

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

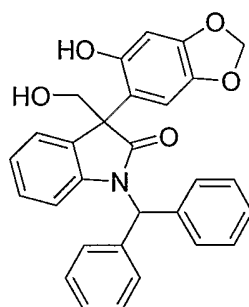


Following the procedure as described in EXAMPLE 107, and making the variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one, the title compound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

10

EXAMPLE 150

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



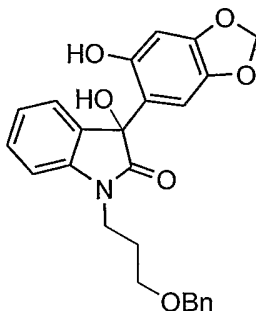
Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained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

20

(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



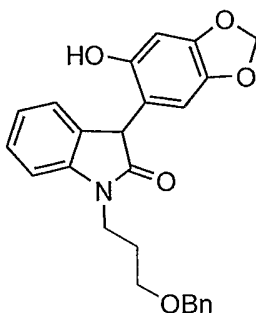
5

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,), 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).

10

EXAMPLE 152

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



15

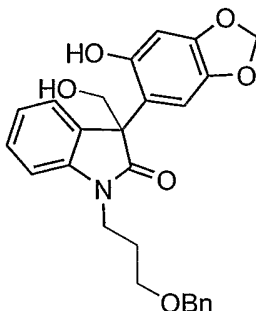
Following the procedure as described in EXAMPLE 131, and making non-critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 1-[3-(benzyloxy)propyl]-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound 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,

20

2H), 2.03-1.93 (m, 2H); MS (ES+) m/z 418.3 (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



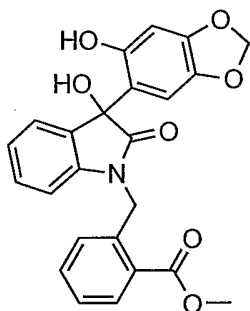
5

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).

10

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



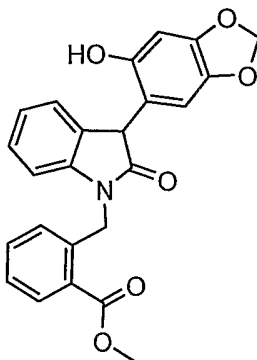
15

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- d_6) 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).

20

EXAMPLE 155

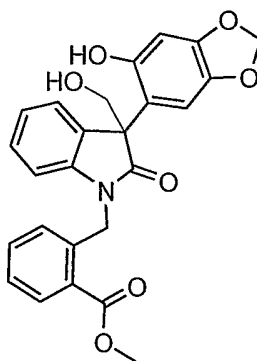
Synthesis of methyl 2-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate



5 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*H*-indol-2-one with methyl 2-[[3-hydroxy-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 (100%) as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) 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

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

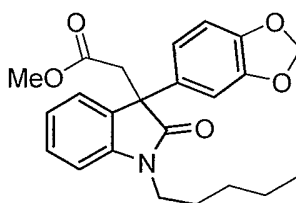


A solution of methyl 2-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate (17.1 g, 40.0 mmol) and paraformaldehyde (10.3 g, 330 mmol) in THF (500 mL) was degassed by bubbling through argon for 2 hours. To this solution was added lithium diisopropylamide solution (45.1 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- d_6) δ 9.20 (s, 1H), 7.95 (dd, 1H), 7.53-7.33 (m, 3H), 7.08-6.82 (m, 4H), 6.53 (d, 1H), 6.25 (s, 1H), 5.93-5.86 (m, 2H), 5.31-5.07 (m, 3H), 4.26-4.17 (m, 1H), 4.00-3.92 (m, 1H), 3.88 (s, 3H); MS (ES+) m/z 448.3 (M + 1).

EXAMPLE 157

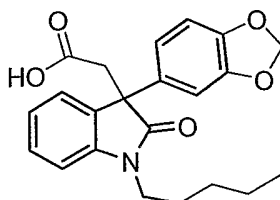
Synthesis of methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1H-indol-3-yl]acetate



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 (20.0 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: ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 158

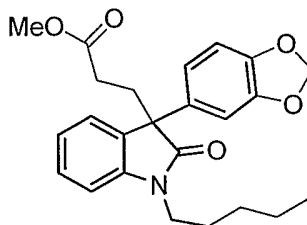
Synthesis of [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]acetic acid



To a solution of methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-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 water (150 mL) was added. The solution was extracted with ethyl acetate/hexanes (1/3 v/v, 50.0 mL). The water layer was acidified with 1 N HCl solution until the pH value reached 2 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 to afford the title compound (5.00 g, 88%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.29 (td, 1H), 7.21 (dd, 1H), 7.05 (td, 1H), 6.87 (d, 1H), 6.76 (d, 1H), 6.72-6.64 (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); ¹³C NMR (75 MHz, CDCl₃) δ 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 159

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

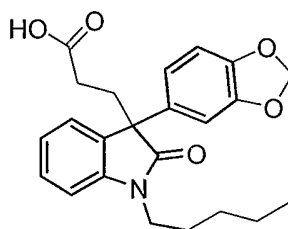


Following the procedure as described in EXAMPLE 157, and making non-critical variations to replace methyl bromoacetate with methyl 3-bromopropionate, the

title compound was obtained (76%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 160

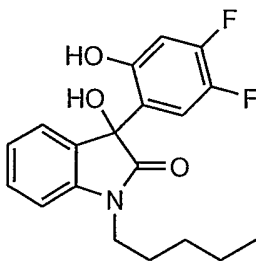
Synthesis of 3-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]propanoic acid



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

EXAMPLE 161

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

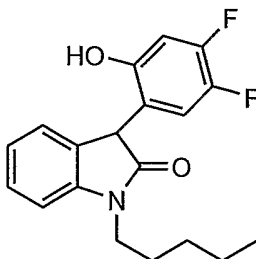


Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 1-pentyl-1*H*-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 3, 4-difluorophenol, the title compound was obtained (31%): ^1H NMR (300 MHz, CDCl_3) δ 9.69-9.65 (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 162

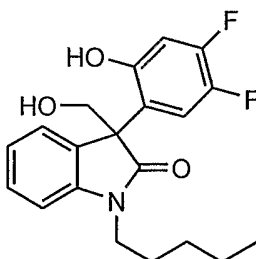
- 5 Synthesis of 3-(4,5-difluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 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*H*-indol-2-one with 3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (98%):
 10 ^1H NMR (300 MHz, CDCl_3) 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 163

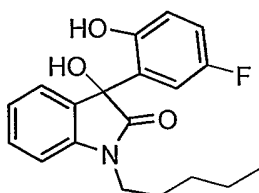
- 15 Synthesis of 3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 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-2*H*-indol-2-one with 3-(4,5-difluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (96%): MS (ES+) m/z 344 ($M - 17$), 384 ($M + 23$).

EXAMPLE 164

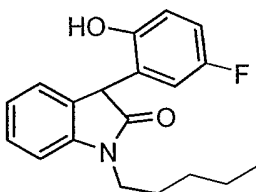
Synthesis of 3-(5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 5 Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-1*H*-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 4-fluorophenol, 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
10 (m, 4H), 0.87 (t, 3H); MS (ES+) *m/z* 312 (M - 17), 352 (M + 23).

EXAMPLE 165

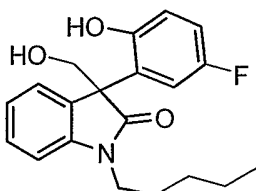
Synthesis of 3-(5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- To a solution of 3-(5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-
15 2*H*-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 166

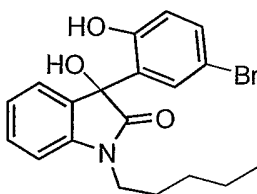
Synthesis of 3-(5-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one



- 5 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
- 10 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), 6.57-6.49 (m, 1H), 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).

15 EXAMPLE 167

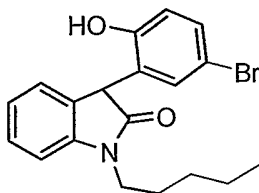
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one



- Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 4-bromophenol, the title compound
- 20 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 168

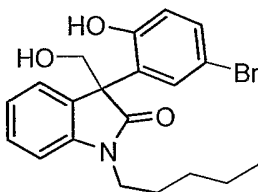
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



To a solution of 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-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 169

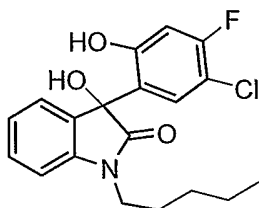
10 Synthesis of 3-(5-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 166, and making non-critical variations to replace 3-(5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-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 170

20 Synthesis of 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one

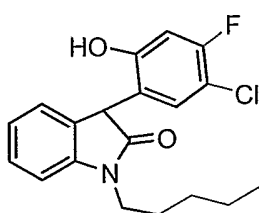


Following the procedure as described in EXAMPLE 130, and making non-

critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-1*H*-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 4-chloro-3-fluorophenol, the title compound was obtained (33%): ¹H NMR (300 MHz, CDCl₃) δ 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 171

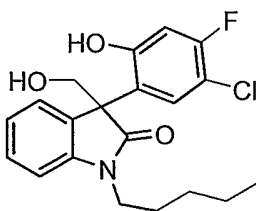
Synthesis of 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



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-2*H*-indol-2-one with 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (99%): ¹H NMR (300 MHz, CDCl₃) δ 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 172

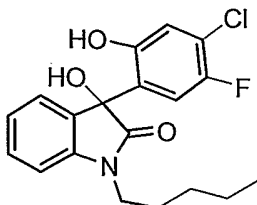
Synthesis of 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



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-2*H*-indol-2-one with 3-(5-chloro-4-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (46%): MS (ES+) *m/z* 360 (M - 17), 400 (M + 23).

EXAMPLE 173

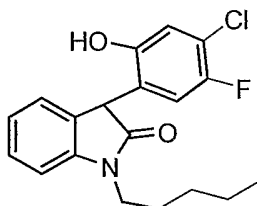
Synthesis of 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 5 Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-1*H*-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 174

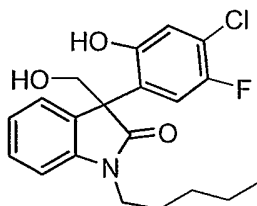
- 10 Synthesis of 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 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-2*H*-indol-2-one with 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained: MS (ES+) *m/z* 348 (*M* + 1).
- 15

EXAMPLE 175

Synthesis of 3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



20

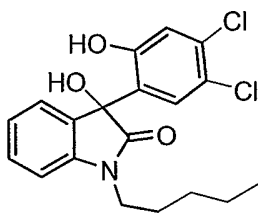
Following the procedure as described in EXAMPLE 132, and making non-

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

5

EXAMPLE 176

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

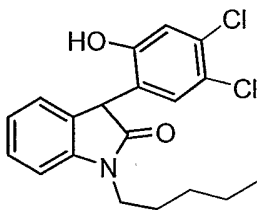


Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-1*H*-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 3,4-dichlorophenol, the title compound was obtained (26%): ¹H NMR (300 MHz, CDCl₃) δ 9.60 (s, 1H), 7.50-7.40 (m, 2H), 7.22 (td, 1H), 7.11 (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).

15

EXAMPLE 177

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

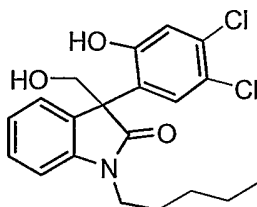


Following the procedure as described in EXAMPLE 168, and making non-critical variations to replace 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one with 3-(4,5-dichloro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (86%): 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).

25

EXAMPLE 178

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

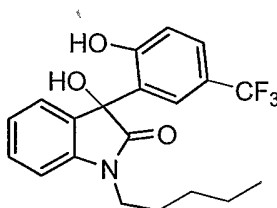


5 Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 3-(4,5-dichloro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z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

10

EXAMPLE 179

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

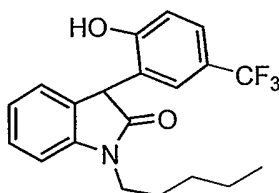


15 Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1H-indole-2,3-dione with 1-pentyl-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with α, α, α -trifluorocresol, the title compound was obtained (46%): ^1H NMR (300 MHz, CDCl_3) δ 9.75 (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), 1.40-1.27 (m, 4H), 0.88 (t, 3H); MS (ES+) m/z 362 (M - 17), 402 (M + 23).

20

EXAMPLE 180

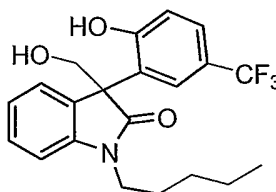
Synthesis of 3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 5 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-2*H*-indol-2-one with 3-hydroxy-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2*H*-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),
 10 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 181

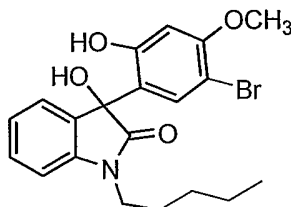
Synthesis of 3-(hydroxymethyl)-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 15 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*H*-indol-2-one with 3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained: MS (ES+) *m/z* 376 (M - 17),
 20 416 (M + 23).

EXAMPLE 182

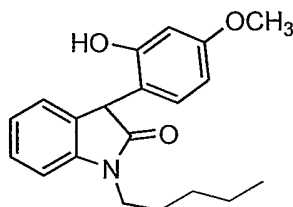
Synthesis of 3-(5-bromo-2-hydroxy-4-methoxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 5 Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-1*H*-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, CDCl₃) 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).
- 10

EXAMPLE 183

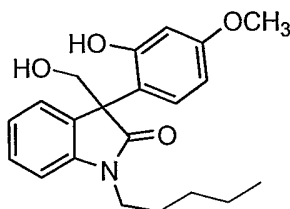
Synthesis of 3-(2-hydroxy-4-methoxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 15 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-2*H*-indol-2-one with 3-(5-bromo-2-hydroxy-4-methoxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (83%): ¹H NMR (300 MHz, CDCl₃) 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).
- 20

EXAMPLE 184

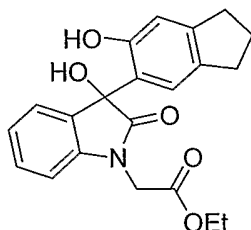
Synthesis of 3-(2-hydroxy-4-methoxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one



5 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, CDCl₃) 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),
10 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 185

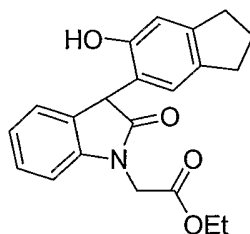
Synthesis of ethyl [3-hydroxy-3-(6-hydroxy-2,3-dihydro-1H-inden-5-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate



15 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 title compound was obtained (84%): ¹H NMR (300 MHz, CDCl₃) δ 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),
20 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).

EXAMPLE 186

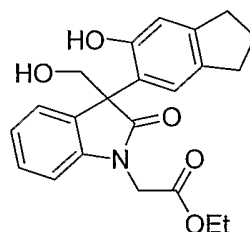
Synthesis of ethyl [3-(6-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



5 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-2*H*-indol-2-one with ethyl [3-hydroxy-3-(6-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained: ¹H NMR (300 MHz, CDCl₃) δ 8.50-7.90 (br, 1H), 7.40-7.32 (m, 2H), 7.38 (td, 1H), 6.94 (s, 1H),
10 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 187

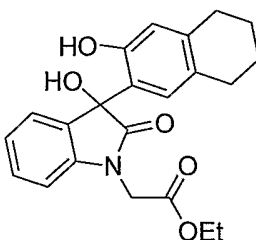
Synthesis of ethyl [3-(6-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



15 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*H*-indol-2-one with ethyl [3-(6-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained: MS (ES+) *m/z* 364 (*M* -
20 17), 404 (*M* + 23).

EXAMPLE 188

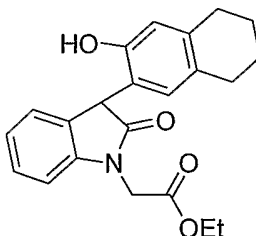
Synthesis of ethyl [3-hydroxy-3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



5 Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with ethyl (2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)acetate, and 1,3-benzodioxol-5-ol with 5, 6, 7, 8-tetrahydronaphthalen-2-ol, the title compound was obtained (81%): ¹H NMR (300 MHz, CDCl₃) δ 8.61 (s, 1H), 7.54 (dd, 1H), 7.38 (td, 1H), 7.20 (t, 1H), 6.80 (d, 1H), 6.76 (s, 1H), 6.50 (s, 1H), 4.45 (ABq, 2H), 4.21 (q, 2H), 4.18-4.14 (br, 1H), 2.73-2.47 (m, 4H), 1.77-1.63 (m, 4H), 1.24 (t, 3H); MS (ES+) *m/z* 364 (M - 17), 404 (M + 23)

EXAMPLE 189

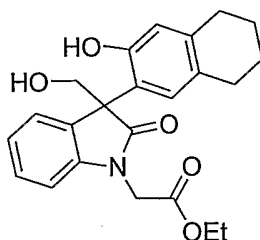
Synthesis of ethyl [3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



15 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-2*H*-indol-2-one with ethyl [3-hydroxy-3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained: ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.32 (m, 2H), 7.20 (t, 1H), 6.84 (d, 1H), 6.78 (s, 1H), 6.61 (s, 1H), 5.12 (s, 1H), 4.47 (ABq, 2H), 4.21 (q, 2H), 2.76-2.44 (m, 4H), 1.78-1.64 (m, 4H), 1.24 (t, 3H); MS (ES+) *m/z* 366 (M + 1).

EXAMPLE 190

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

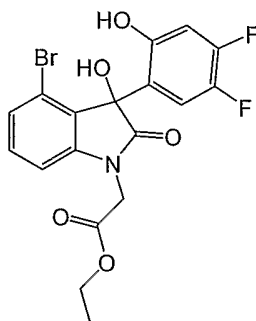


5 Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with ethyl [3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate, the title compound was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

10

EXAMPLE 191

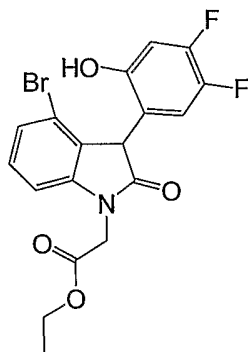
Synthesis of ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate



15 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 3,4-difluorophenol, the title compound was obtained as a white solid (42%); MS (ES+) *m/z* 424 (*M* - 17), 426 (*M* - 17), 464 (*M* + 23), 466 (*M* + 23).

EXAMPLE 192

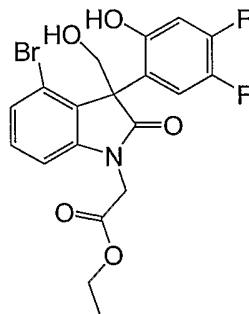
Synthesis of ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1H-indol-1-yl]acetate



5 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
10 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%): ¹H NMR (300 MHz, CDCl₃) δ 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).

15 EXAMPLE 193

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

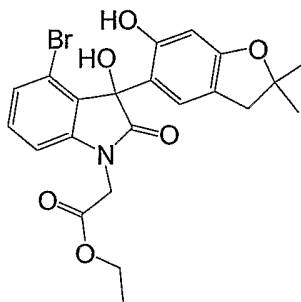


Following the procedure as described in EXAMPLE 132, and making non-
20 critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-

dihydro-2*H*-indol-2-one with ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained (83%): MS (ES+) *m/z* 456.3 (*M* + 1), 458.3 (*M* + 1).

EXAMPLE 194

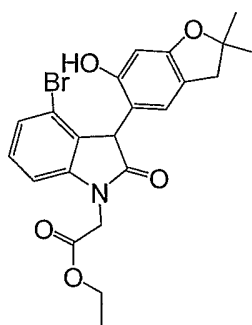
- 5 Synthesis of ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



- Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with ethyl (4-bromo-2,3-dioxo-2,3-dihydro-1*H*-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).
- 10

EXAMPLE 195

- 15 Synthesis of 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

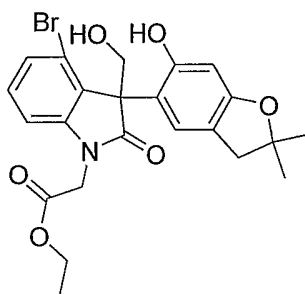


- A mixture of ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate (1.32 g, 2.80 mmol), triethylsilane (2.00 mL, 12.2 mmol) and trifluoroacetic acid (0.94 mL, 12.2 mmol) in dichloromethane (50.0 mL) was stirred at 35 °C for 3 hours. The mixture diluted with dichloromethane (100 mL), washed with water, dried over anhydrous sodium sulfate
- 20

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%): ^1H 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 196

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



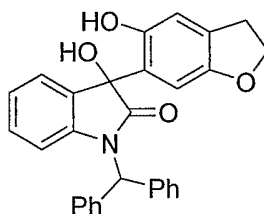
10

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-1H-indol-1-yl]acetate, the title compound was obtained (25%): MS (ES+) m/z 490.5 ($M + 1$), 492.5 ($M + 1$).

15

EXAMPLE 197

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



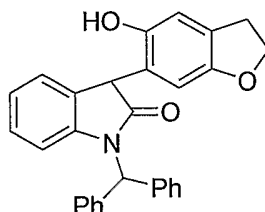
20

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, R.J., 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 198

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



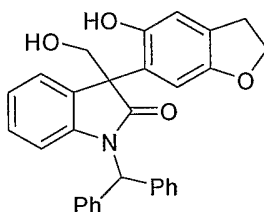
5

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*H*-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-indol-2-one, the title

10 compound was obtained: MS (ES+) m/z 434.4 ($M + 1$).

EXAMPLE 199

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



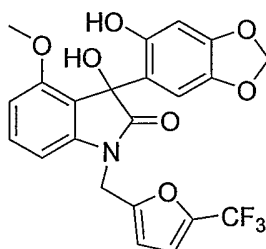
15

To a solution of 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-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 ($M + 23$).

20

EXAMPLE 200

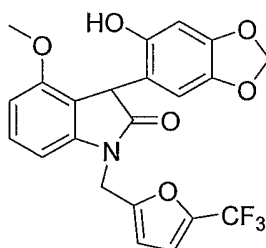
Synthesis of 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one



- 5 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1*H*-indole-2,3-dione, the title compound was obtained (56%): MS (ES+) *m/z* 486.4 (*M* + 23).

EXAMPLE 201

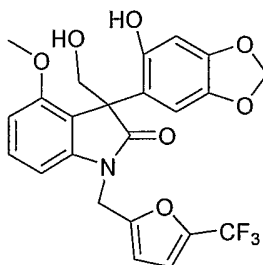
- 10 Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one



- 15 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*H*-indol-2-one with 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (86%): MS (ES+) *m/z* 448.4 (*M* + 1).

EXAMPLE 202

Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one

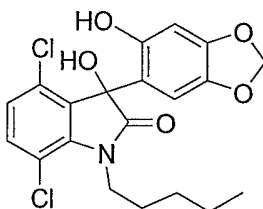


5 Following the procedure as described in EXAMPLE 201, and making non-critical variations to replace 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-indol-2-one with 3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (64%): MS (ES+) *m/z* 500.4 (M + 23)..

10

EXAMPLE 203

Synthesis of 4,7-dichloro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



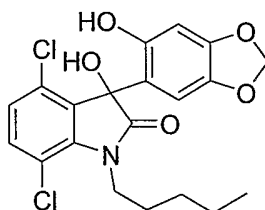
A. Synthesis of 4,7-dichloro-1-pentyl-1*H*-indole-2,3-dione

15 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*H*-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

20 (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 ($M + 1$).

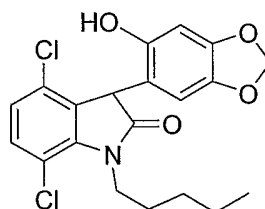
B. Synthesis of 4,7-dichloro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one



- 5 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, CDCl_3) 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),
10 1.34-1.21 (m, 4H), 0.84 (t, 3H); MS (ES+) m/z 408.2 ($M - 17$).

EXAMPLE 204

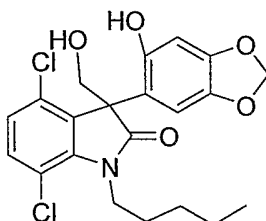
Synthesis of 4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one



- 15 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 4,7-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, CDCl_3) 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 205

Synthesis of 4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one

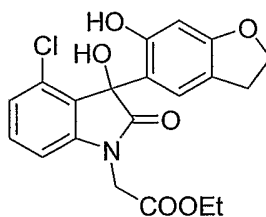


5 Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with 4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (94%) as a gummy solid: MS (ES+) *m/z* 439.3 (*M* + 1).

10

EXAMPLE 206

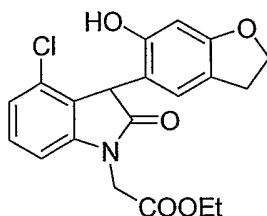
Synthesis of ethyl [4-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



15 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with ethyl (4-chloro-2,3-dioxo-2,3-dihydro-1*H*-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 207

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

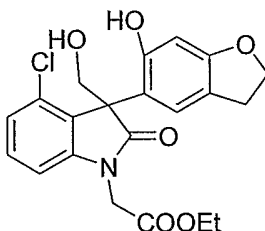


5 Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one with ethyl [4-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, 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).

10

EXAMPLE 208

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



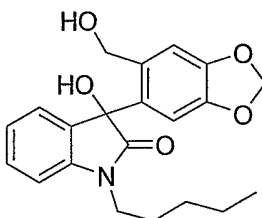
15

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*H*-indol-2-one with ethyl [4-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained (99%) as a gummy solid: MS (ES+) *m/z* 418.7 (M + 1).

20

EXAMPLE 209

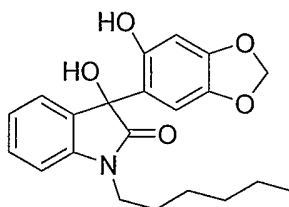
Synthesis of 3-hydroxy-3-[6-(hydroxymethyl)-1,3-benzodioxol-5-yl]-1-pentyl-1,3-dihydro-2H-indol-2-one



- 5 To a stirred solution of (6-bromo-1,3-benzodioxol-5-yl)methanol (1.27 g, 5.50 mmol) in THF (45.0 mL) was added n-BuLi (5.00 mL, 2.0 M, 10.0 mmol) dropwise at -75 °C. The reaction mixture was stirred at -75 °C for 45 min followed by the addition of a solution of 1-pentyl-1H-indole-2,3-dione (1.00 g, 4.60 mmol) in THF (20.0 mL) at -75 °C. The resulting mixture was stirred at ambient temperature for 12 hrs and
- 10 quenched with ammonium chloride solution (5.00 mL). More ethyl acetate and water were added and separated. The organic layer was concentrated *in vacuo* to dryness. The residue was subjected to column chromatography eluting with 50% EtOAc:Hexanes to yield the title compound (0.29 g, 25%) as a solid: 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),
- 15 5.90-5.87 (m, 2H), 4.77 (dd, 2H), 3.75-3.56 (m, 2H), 1.75-1.58 (m, 2H), 1.26-1.35 (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 210

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

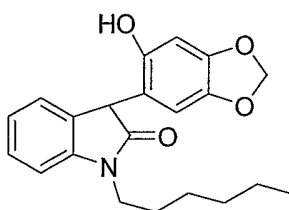


- Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-hexyl-1H-indole-2,3-dione, the title compound was obtained (53%) as a colorless solid: ¹H NMR
- 25

(300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 211

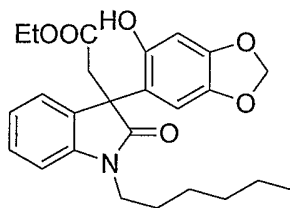
Synthesis of 1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one



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*H*-indol-2-one with 1-hexyl-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (98%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 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 212

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

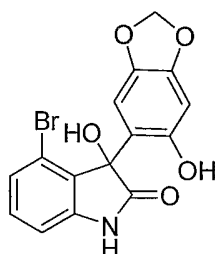


To a solution of diisopropylamine (1.14 g, 11.0 mmol) in THF (10.0 mL) was added *n*-butyl lithium (7.00 mL, 11.0 mmol, 1.6 M solution in hexane) at -75 °C. The resulting mixture was stirred at -75 °C for half an hour and added slowly to a solution of 1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one 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 213

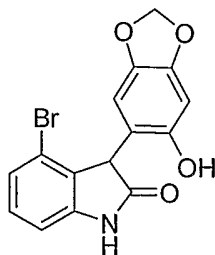
Synthesis of 4-bromo-3-(6-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 4-bromoisatin, the title compound was obtained (95%) as a beige solid: ¹H 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); ¹³C 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 214

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



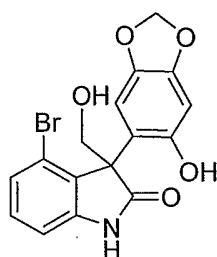
Following the procedure as described in EXAMPLE 131, and making non-

critical variations to replace 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with 4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-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).

5

EXAMPLE 215

Synthesis of 4-bromo-3-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-3-(hydroxymethyl)indolin-2-one

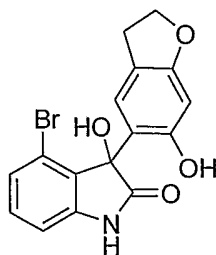


Following the procedure as described in EXAMPLE 212, and making non-critical variations to replace 1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one with 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one, and ethyl bromoacetate with *para*-formaldehyde, the title compound was obtained (70%) as a colorless solid: ¹H 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); ¹³C 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, 109.3, 107.9, 101.2, 97.6, 63.5, 57.4.

15

EXAMPLE 216

Synthesis of 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one



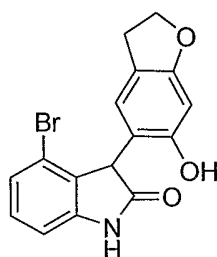
20

Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 4-bromoisatin, and 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol, the title

compound was obtained (78%) as a colorless solid: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) 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); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) 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 217

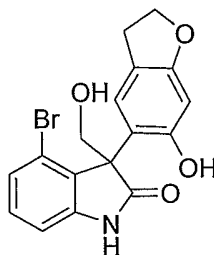
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one



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*H*-indol-2-one with 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (62%) as a solid: MS (ES+) m/z 346.5 ($M + 1$), 348.5 ($M + 1$).

EXAMPLE 218

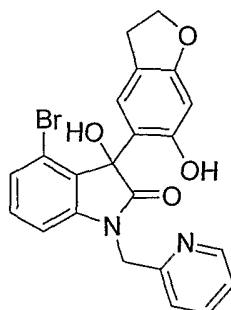
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydrobenzofuran-5-yl)-3-(hydroxymethyl)indolin-2-one



Following the procedure as described in EXAMPLE 212, and making non-critical variations to replace 1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one with 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one, and ethyl bromoacetate with *para*-formaldehyde, the title compound was obtained.

EXAMPLE 219

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

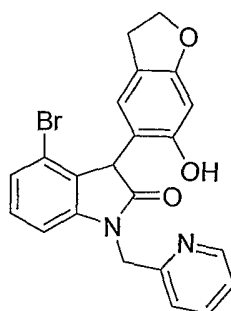


5 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 4-bromo-1-(pyridin-2-ylmethyl)-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 2,3-dihydrobenzofuran-6-ol, the title compound was obtained (91%) as a colorless solid: mp >225 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.29 (s, 1H), 8.54 (d, 1H), 7.70 (dt, 1H),
 10 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); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 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).

15

EXAMPLE 220

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

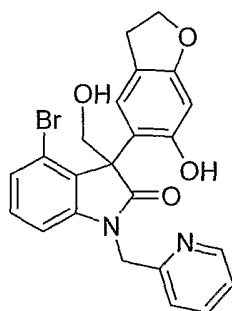


20 To a solution of 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one (1.12 g, 2.48 mmol) in anhydrous dichloromethane (25.0 mL) was added triethylamine (1.40 mL, 9.91 mmol) and SOCl₂ (0.40 mL, 4.96 mmol) at 0 °C. The reaction mixture was 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 221

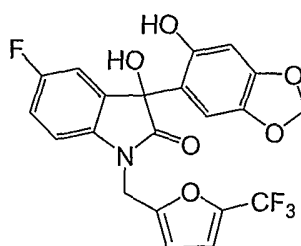
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2H-indol-2-one



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 222

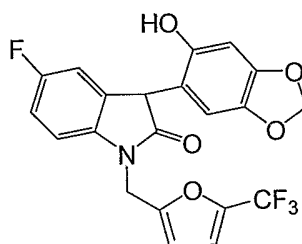
Synthesis of 5-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2H-indol-2-one



Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 5-fluoro-1-
 {[5-(trifluoromethyl)-2-furyl]methyl}-1*H*-indole-2,3-dione, the title compound was
 obtained (66%) as a pale yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.15 (s, 1H),
 5 7.21 (s, 1H), 7.15 (dd, 1H), 7.08-6.95 (m, 2H), 6.74 (s, 1H), 6.54 (s, 1H), 6.22 (d, 1H),
 5.90 (d, 2H), 4.96 (s, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 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 223

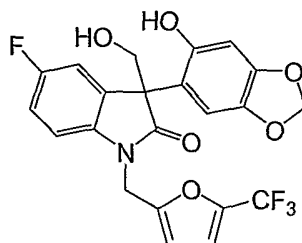
Synthesis of 5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-
 {[5-(trifluoromethyl)-2-furyl]methyl}-1,3-dihydro-2*H*-indol-2-one



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-
 15 pentyl-1,3-dihydro-2*H*-indol-2-one with 5-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-
 {[5-(trifluoromethyl)-2-furyl]methyl}-1,3-dihydro-2*H*-indol-2-one, the
 title compound was obtained (72%) as a pale yellow solid: ¹H NMR (300 MHz, DMSO-
*d*₆) δ 9.31 (s, 1H), 7.13 (dd, 1H), 7.02 (dd, 2H), 6.82 (d, 1H), 6.59 (d, 2H), 6.39 (s, 1H),
 20 5.87 (d, 2H), 5.07-4.96 (m, 2H), 4.84 (s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 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 224

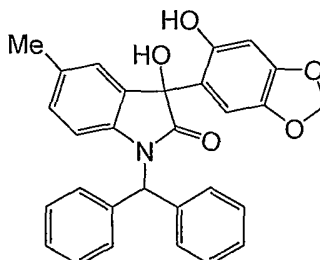
Synthesis of 5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one



5 A mixture of 5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-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),
 10 washed with 10% aqueous HCl (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:hexanes (50%) to give the title compound (0.65 g, 59%) as a colorless solid: mp 92-95 °C; ¹H 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), 5.09 (br, 1H), 4.97 (ABq, 2H), 4.01 (ABq, 2H); ¹³C 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 225

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



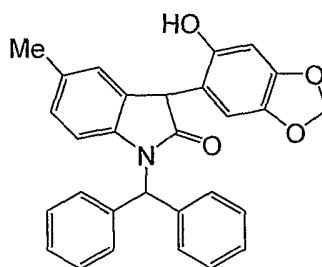
Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 1-

(diphenylmethyl)-5-methyl-1*H*-indole-2,3-dione, the title compound was obtained (92%) as a colorless solid: ^1H NMR (300 MHz, CDCl_3) δ 9.23 (br s, 1H), 7.40-7.15 (m, 11H), 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 ($M - 17$).

5

EXAMPLE 226

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

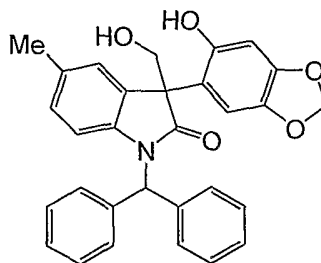


Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (84%) as a colorless solid: ^1H 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 ($M + 1$).

15

EXAMPLE 227

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



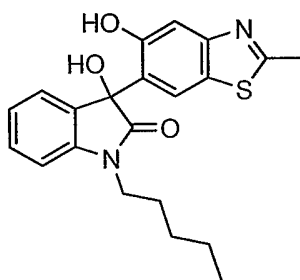
20

To a solution of 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-2*H*-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 228

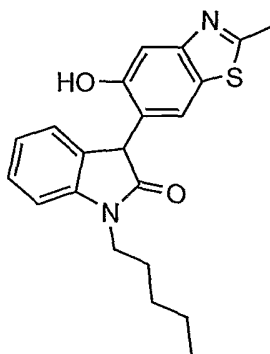
- 10 Synthesis of 3-hydroxy-3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one



- 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-*d*₆) 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), 1.80-1.60 (m, 2H), 1.50-1.31 (m, 4H), 0.90 (t, 3H); MS (ES+) *m/z* 383.4 (M + 1).

EXAMPLE 229

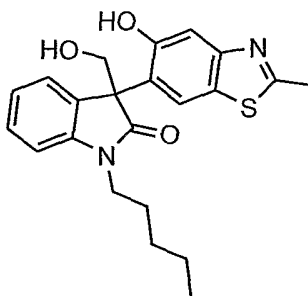
Synthesis of 3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 5 A suspension of 3-hydroxy-3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2*H*-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 230

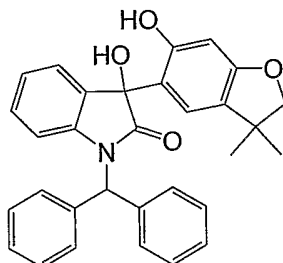
- 10 Synthesis of 3-(hydroxymethyl)-3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one



- 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-2*H*-indol-2-one with 3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained: MS (ES+) *m/z* 367.5 (M + 1).
- 15

EXAMPLE 231

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

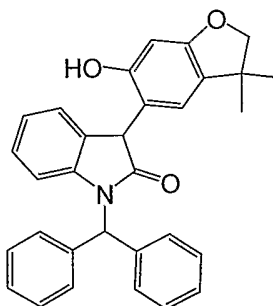


5 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1H-indole-2,3-dione with 1-(diphenylmethyl)-1H-indole-2,3-dione, and 1,3-benzodioxol-5-ol with 3,3-dimethyl-2,3-dihydro-1-benzofuran-6-ol, the title compound was obtained: MS (ES+) m/z 478.5 (M + 1).

10

EXAMPLE 232

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

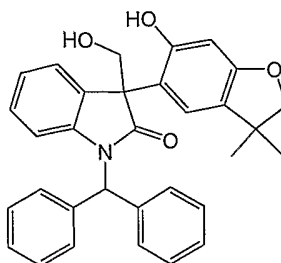


15 Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one, the title compound was obtained (73%): ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.20 (m, 12H), 7.11-7.04 (m, 2H), 6.97 (s, 1H), 6.58 (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).

20

EXAMPLE 233

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

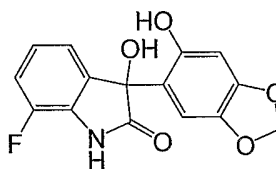


- 5 Following the procedure as described in EXAMPLE 199, and making non-critical variations to replace 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-indol-2-one with 1-(diphenylmethyl)-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained: MS (ES+) *m/z* 492.5 (M + 1)

10

EXAMPLE 234

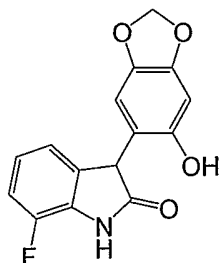
Synthesis of 7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one



- 15 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 7-fluoro-1*H*-indole-2,3-dione, the title compound was obtained (80%): ¹H NMR (300 MHz, DMSO-*d*₆) 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 235

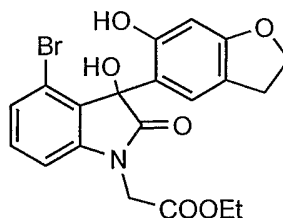
Synthesis of 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one



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*H*-indol-2-one with 7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (100%): ¹H NMR (300 MHz, DMSO-*d*₆) 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 236

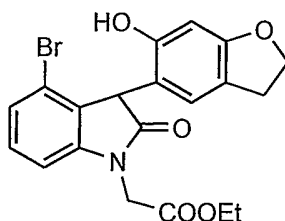
Synthesis of ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with ethyl (4-bromo-2,3-dioxo-2,3-dihydro-1*H*-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 237

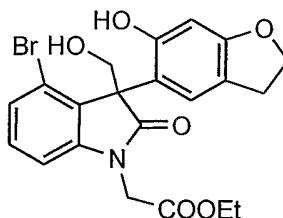
Synthesis of ethyl [4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



5 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-2*H*-indol-2-one with ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-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 238

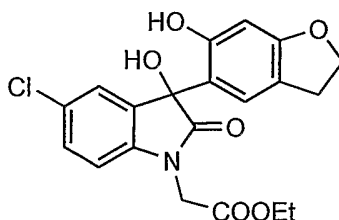
Synthesis of ethyl [4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



15 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*H*-indol-2-one with ethyl [4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained (99%):
20 MS (ES+) *m/z* 463.2 (M + 1).

EXAMPLE 239

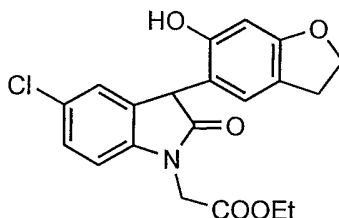
Synthesis of ethyl [5-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



5 Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with ethyl (5-chloro-2,3-dioxo-2,3-dihydro-1*H*-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),
10 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 240

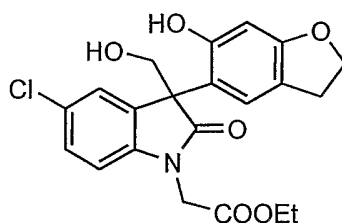
Synthesis of ethyl [5-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



15 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*H*-indol-2-one with ethyl [5-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound
20 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 241

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

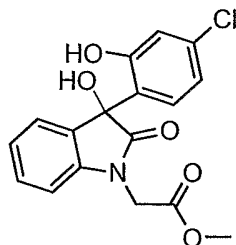


5 Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with ethyl [5-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained (99%): MS (ES+) *m/z* 418.7 (*M* + 1).

10

EXAMPLE 242

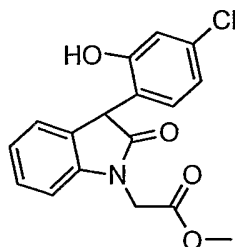
Synthesis of methyl [3-(4-chloro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



15 Following the procedure as described in EXAMPLE 130, and making non-critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with methyl (2,3-dioxo-2,3-dihydro-1*H*-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),
20 372.4 (*M* + 23).

EXAMPLE 243

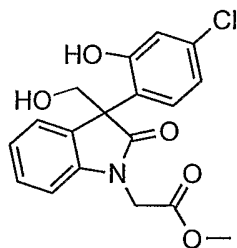
Synthesis of methyl [3-(4-chloro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



5 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*H*-indol-2-one with methyl [3-(4-chloro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-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 244

Synthesis of methyl [3-(4-chloro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



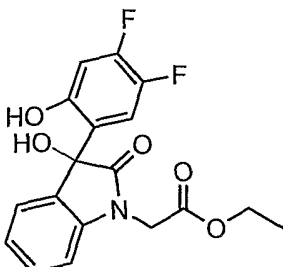
15

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*H*-indol-2-one with methyl [3-(4-chloro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained: MS (ES+) *m/z* 362.5 (*M* + 1)

20 364.5 (*M* + 1).

EXAMPLE 245

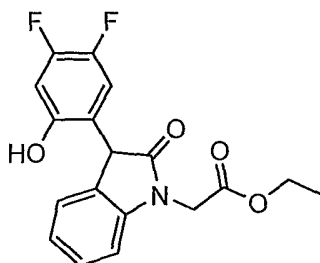
Synthesis of ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



- 5 Following the procedure as described in EXAMPLE 106, and non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with ethyl (2,3-dioxo-2,3-dihydro-1*H*-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 246

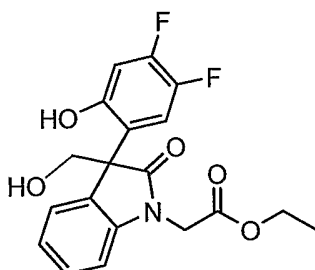
- 10 Synthesis of ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate



- 15 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*H*-indol-2-one with ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-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 247

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

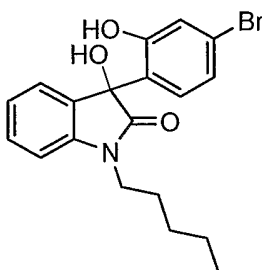


5 Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one with methyl [3-(4-chloro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate, the title compound was obtained: MS (ES+) *m/z* 378.3 (*M* + 1), 361.3 (*M* - 17).

10

EXAMPLE 248

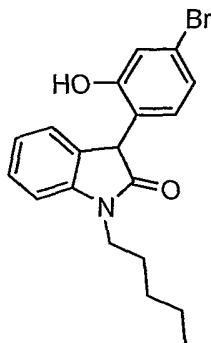
Synthesis of 3-(4-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one



15 Following the procedure as described in EXAMPLE 128, and making non-critical variations to replace 4-bromo-1-pentyl-1*H*-indole-2,3-dione with 1-pentyl-1*H*-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
20 (*M* + 1), 393.4 (*M* + 1).

EXAMPLE 249

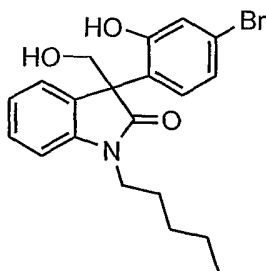
Synthesis of 3-(4-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2H-indol-2-one



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 3-(4-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2H-indol-2-one, the title compound was obtained (91%) as a white powder: ^1H NMR (300 MHz, CDCl_3) δ 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 250

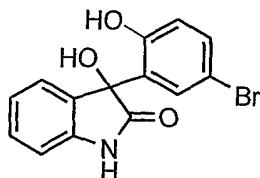
Synthesis of 3-(4-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one



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-2H-indol-2-one, the title compound was obtained: R_f = 0.5 (EtOAc/Hexanes, $\frac{1}{4}$).

EXAMPLE 251

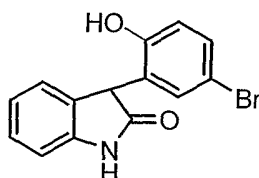
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-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 252

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



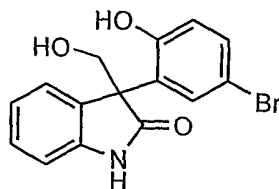
10

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*H*-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1,3-dihydro-2*H*-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).

15

EXAMPLE 253

Synthesis of 3-(5-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one



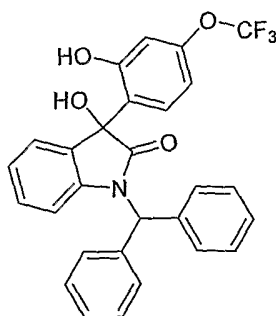
20

Following the procedure as described in EXAMPLE 224, 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-2*H*-indol-2-one with 3-(5-bromo-2-

hydroxyphenyl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained: MS (ES+) m/z 334.2 ($M + 1$), 336.2 ($M + 1$).

EXAMPLE 254

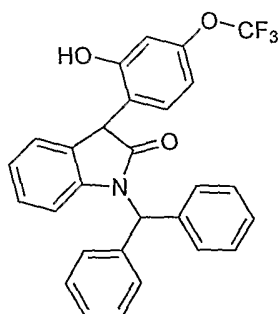
Synthesis of 1-(diphenylmethyl)-3-hydroxy-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2*H*-indol-2-one



Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 1-(diphenylmethyl)-1*H*-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 255

Synthesis of 1-(diphenylmethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2*H*-indol-2-one



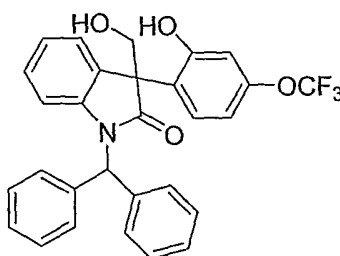
15

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*H*-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (82%): MS (ES+) m/z 498.4 ($M + 23$).

20

EXAMPLE 256

Synthesis of 1-(diphenylmethyl)-3-(hydroxymethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2H-indol-2-one

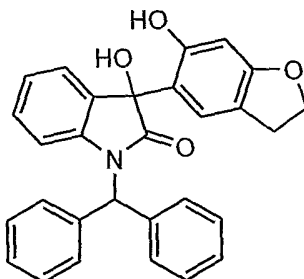


5 Following the procedure as described in EXAMPLE 132, and making non-critical variations to replace 4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one with 1-(diphenylmethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2H-indol-2-one, the title compound was obtained: MS (ES+) m/z 488 ($M - 17$), 528 ($M + 23$).

10

EXAMPLE 257

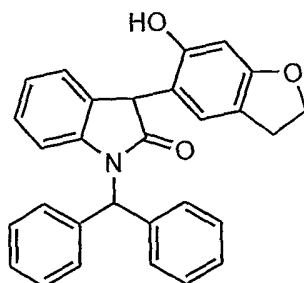
Synthesis of 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2H-indol-2-one



15 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 258

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

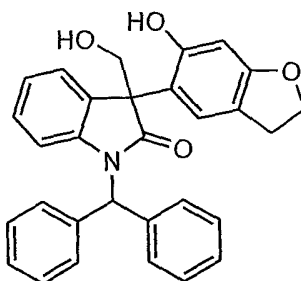


5 Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one with 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (67%) as a white solid: MS (ES+) m/z 434.3 ($M + 1$).

10

EXAMPLE 259

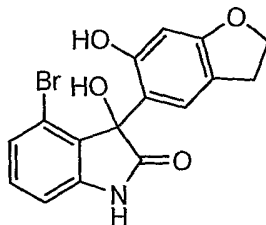
Synthesis of 1-(diphenylmethyl)-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one



15 Following the procedure as described in EXAMPLE 199, and making non-critical variations to replace 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-indol-2-one with 1-(diphenylmethyl)-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (45%) as a white solid: MS (ES+) m/z 464.5 ($M + 1$).

EXAMPLE 260

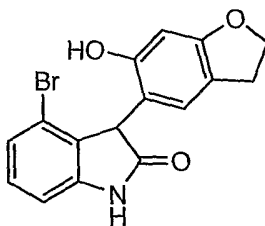
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one



5 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)-1*H*-indole-2,3-dione with 4-bromo-1*H*-indole-2,3-dione, the title compound was obtained (78%) as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) 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),
 10 5.90 (s, 1H), 4.45 (t, 2H), 3.05 (t, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) 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 261

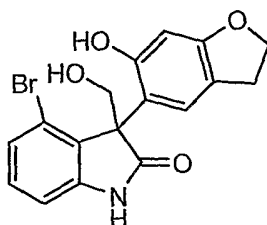
15 Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one



20 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*H*-indol-2-one with 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-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 262

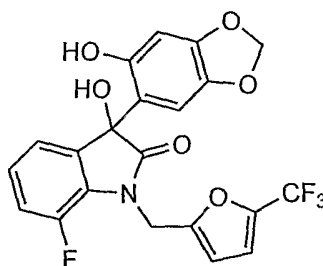
Synthesis of 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one



5 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-2*H*-indol-2-one, the title compound was obtained (16%): $R_f = 0.21$ (EtOAc/Hexanes, 7/3).

EXAMPLE 263

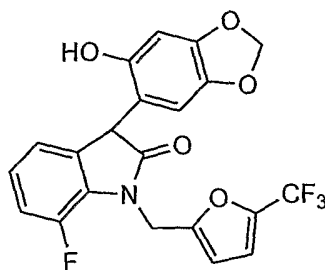
10 Synthesis of 7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one



15 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 7-fluoro-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1*H*-indole-2,3-dione, the title compound was obtained (75%): MS (ES+) m/z 474.3 ($M + 23$).

EXAMPLE 264

Synthesis of 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one

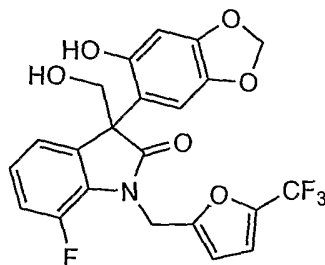


5 Following the procedure as described in EXAMPLE 107, and making non-critical variations to replace 1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one with 7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (65%): MS (ES+) *m/z* 436.4 (*M* + 1).

10

EXAMPLE 265

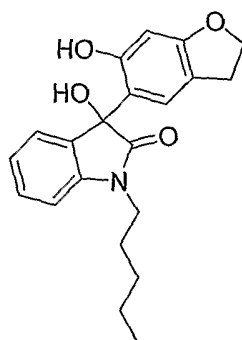
Synthesis of 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one



15 Following the procedure as described in EXAMPLE 199, and making non-critical variations to replace 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-indol-2-one with 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained (67%): MS (ES+) *m/z* 488.4 (*M* + 23).

EXAMPLE 266

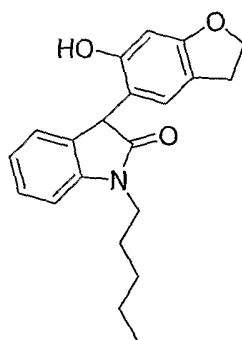
Synthesis of 3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one



5 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 267

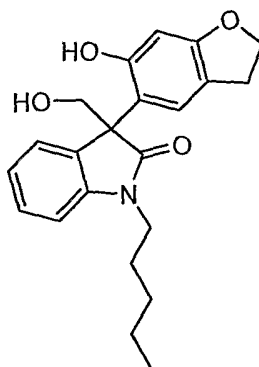
10 Synthesis of 3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2H-indol-2-one



15 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 268

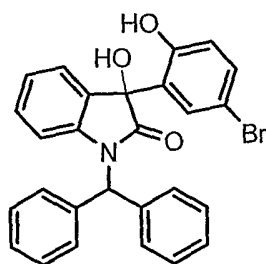
Synthesis of 3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2H-indol-2-one



5 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 ($M + 23$).

10 EXAMPLE 269

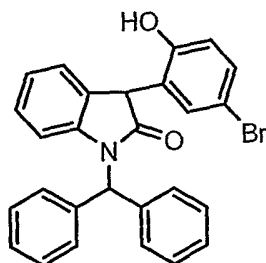
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one



15 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 270

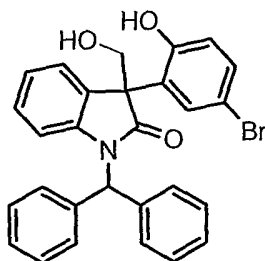
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-1,3-dihydro-2*H*-indol-2-one



5 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-2*H*-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-3-hydroxy-1,3-dihydro-2*H*-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, 10 1H), 6.57-6.51 (m, 1H), 5.04 (s, 1H); MS (ES+) *m/z* 471.2 (M + 1), 473.2 (M + 1).

EXAMPLE 271

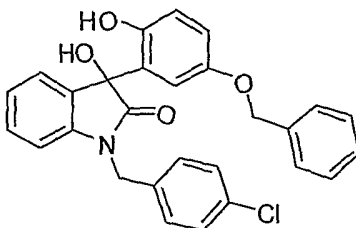
Synthesis of 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one



15 Following the procedure as described in EXAMPLE 199, and making non-critical variations to replace 1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-indol-2-one with 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-1,3-dihydro-2*H*-indol-2-one, the title compound was obtained: MS (ES+) *m/z* 500.4 (M + 1), 502.4 (M + 1).

EXAMPLE 272

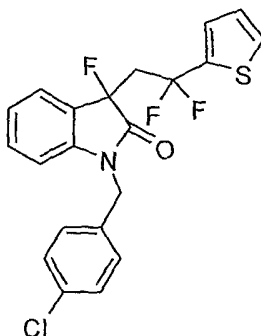
3-[5-(benzyloxy)-2-hydroxyphenyl]-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one



5 Following the procedure as described in EXAMPLE 106, and making non-critical variations to replace 1-(2-cyclopropylethyl)-1*H*-indole-2,3-dione with 1-(4-chlorobenzyl)-1*H*-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),
10 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 273

15 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 CH₂Cl₂ (20.0 mL) was
20 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; ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, 1H), 7.64 (d, 1H), 7.39-7.21 (m, 6H), 7.12 (t, 1H), 7.01 (t, 1H),
5 6.64 (d, 1H), 4.92 (ABq, 2H), 4.08-4.05 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 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

10 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.

15 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
20 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 ¹⁴C-guanidine hydrochloride in combination with various known sodium channel
25 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
30 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

CELL LINE	mRNA Expression	Functional Characterization
CHO-K1 (Chinese Hamster Ovary; recommended host cell line) ATTC accession number CCL-61	• $\text{Na}_v1.4$ expression has been shown by RT-PCR • No other Na_v expression has been detected	• The 18-20-fold increase in [^{14}C] Guanidine influx was completely blocked using TTX. ($\text{Na}_v1.4$ is a TTX sensitive channel)
L6 (rat myoblast cell) ATTC Number CRL-1458	• Expression of $\text{Nav}1.4$ and 1.5	• The 10-15 fold increase in [^{14}C] Guanidine influx was only partially blocked by TTX ($\text{Na}_v1.5$ is TTX resistant)
SH-SY5Y (Human neuroblastoma) ATTC Number CRL-2266	• Published Expression of $\text{Na}_v1.9$ and $\text{Na}_v1.7$ (Blum et al)	• The 10-16-fold increase in [^{14}C] Guanidine influx above background. • was partially blocked by TTX ($\text{Na}_v1.9$ is TTX resistant)
SK-N-BE2C (a human neuroblastoma cell line) ATCC Number CRL-2268	• Expression of $\text{Na}_v1.8$	• Stimulation of BE2C cells with pyrethroids results in a 6 fold increase in [^{14}C] Guanidine influx above background. • TTX partially blocked influx ($\text{Na}_v1.8$ is TTX resistant)
PC12 (rat pheochromocytoma) ATTC Number CRL-1721	• Expression of $\text{Na}_v1.2$ expression	• The 8-12-fold increase in [^{14}C] Guanidine influx was completely blocked using TTX. ($\text{Na}_v1.2$ 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 % CO₂ 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 ($\text{fit} = (A + ((B - A) / (1 + ((C/x)^D))))$).

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, Na_v1.5.

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 37C° 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 Mohm $\tilde{s}$. 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 (K_r and K_i , 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 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_{rest}) and the currents during the inactivated state ($I_{inactivated}$) were used to calculate steady-state affinity of compounds. Based on the Michaelis-Menton model of inhibition, the K_r and K_i was calculated as the concentration of compound needed to cause 50% inhibition of the I_{rest} or the $I_{inactivated}$, respectively.

$$\% \text{ inhibition} = \frac{V_{\max} * [\text{Drug}]^h}{[\text{Drug}]^h + K_m^h}$$

5 $V_{\max}$ 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 ($\frac{1}{2}V_{\max}$) of the I_{rest} or $I_{\text{inactivated}}$, the drug concentration is numerically equal to K_m and approximates the K_r and K_i , respectively.

BIOLOGICAL EXAMPLE 3

Analgesia Induced by sodium channel Blockers

10 Heat Induced Tail Flick Latency Test

In this test, the analgesia effect produced by administering a compound of the invention was observed through heat-induced tail-flick in mice. The test includes a heat source consisting of a projector lamp with a light beam focused and directed to a point on the tail of a mouse being tested. The tail-flick latencies, which were assessed
15 prior to drug treatment, and in response to a noxious heat stimulus, i.e., the response time from applying radiant heat on the dorsal surface of the tail to the occurrence of tail flick, were measured and recorded at 40, 80, 120, and 160 minutes.

For the first part of this study, 65 animals underwent assessment of baseline tail flick latency once a day over two consecutive days. These animals were then
20 randomly assigned to one of the 11 different treatment groups including a vehicle control, a morphine control, and 9 compounds at 30 mg/Kg were administered intramuscularly. . Following dose administration, the animals were closely monitored for signs of toxicity including tremor or seizure, hyperactivity, shallow, rapid or depressed breathing and failure to groom. TThe optimal incubation time for each
25 compound was determined via regression analysis. The analgesic activity of the test compounds was expressed as a percentage of the maximum possible effect (%MPE) and was calculated using the following formula:

$$30 \quad \% \text{ MPE} = \frac{\text{Postdrug latency} - \text{Predrug latency}}{\text{Cut-off time (10s)} - \text{Predrug latency}} \times 100\%$$

where:

Postdrug latency= the latency time for each individual animal taken before the
35 tail is removed (flicked) from the heat source after receiving drug.

Predrug latency= the latency time for each individual animal taken before the tail is flicked from the heat source prior to receiving drug.

Cut-off time (10 s)= is the maximum exposure to the heat source.

Acute Pain (Formalin Test)

5 The formalin test is used as an animal model of acute pain. In the formalin test, animals were briefly habituated to the plexiglass test chamber on the day prior to experimental day for 20 minutes. On the test day, animals were randomly injected with the test articles. At 30 minutes after drug administration, 50 µL of 10% formalin was injected subcutaneously into the plantar surface of the left hind paw of the rats. Video
10 data acquisition began immediately after formalin administration, for duration of 90 minutes.

 The images were captured using the Actimatrix Limelight software which stores files under the *.lmi extension, and then converts it into the MPEG-4 coding. The videos are then analyzed using behaviour analysis software "The Observer 5.1",
15 (Version 5.0, Noldus Information Technology, Wageningen, The Netherlands). The video analysis was done by watching the animal behaviour and scoring each according to type, and defining the length of the behaviour (Dubuisson and Dennis, 1977). Scored behaviours include: (1) normal behaviour, (2) putting no weight on the paw, (3) raising the paw, (4) licking/biting or scratching the paw. Elevation, favoring, or
20 excessive licking, biting and scratching of the injected paw indicate a pain response. Analgesic response or protection from compounds is indicated if both paws are resting on the floor with no obvious favoring, excessive licking, biting or scratching of the injected paw.

 Analysis of the formalin test data is done according to two factors: (1) Percent
25 Maximal Potential Inhibitory Effect (%MPIE) and (2) pain score. The %MPIEs was calculated by a series of steps, where the first is to sum the length of non-normal behaviours (behaviours 1,2,3) of each animal. A single value for the vehicle group was obtained by averaging all scores within the vehicle treatment group. The following calculation yields the MPIE value for each animal:

30
$$\text{MPIE (\%)} = 100 - [(\text{treatment sum/average vehicle value}) \times 100\%]$$

 The pain score is calculated from a weighted scale as described above. The duration of the behaviour is multiplied by the weight (rating of the severity of the response), and divided by the total length of observation to determine a pain rating for

each animal. The calculation is represented by the following formula:

$$\text{Pain rating} = [0(T_0) + 1(T_1) + 2(T_2) + 3(T_3)] / (T_0 + T_1 + T_2 + T_3)$$

Compounds of the present invention were shown to be efficacious within a range of 30 mg/Kg and 0.1 mg/Kg.

5 CFA Induced Chronic Inflammatory Pain

In this test, tactile allodynia was assessed with calibrated von Frey filaments. Following a full week of acclimatization to the vivarium facility, 150 μ L of the "Complete Freund's Adjuvant" (CFA) emulsion (CFA suspended in an oil/saline (1:1) emulsion at a concentration of 0.5 mg/mL) was injected subcutaneously into the plantar surface of the left hind paw of rats under light isoflurane anaesthesia. Animals were allowed to recover from the anaesthesia and the baseline thermal and mechanical nociceptive thresholds of all animals are assessed one week after the administration of CFA. All animals were habituated to the experimental equipment for 20 minutes on the day prior to the start of the experiment. The test and control articles were administered to the animals, and the nociceptive thresholds measured at defined time points after drug administration to determine the analgesic responses to each of the six available treatments. The time points used were previously determined to show the highest analgesic effect for each test compound.

Thermal nociceptive thresholds of the animals were assessed using the Hargreaves test. Animals were placed in a Plexiglas enclosure set on top of an elevated glass platform with heating units. The glass platform is thermostatically controlled at a temperature of approximately 30 °C for all test trials. Animals were allowed to accommodate for 20 minutes following placement into the enclosure until all exploration behaviour ceases. The Model 226 Plantar/Tail Stimulator Analgesia Meter (IITC, Woodland Hills, CA) was used to apply a radiant heat beam from underneath the glass platform to the plantar surface of the hind paws. During all test trials, the idle intensity and active intensity of the heat source were set at 1 and 45 respectively, and a cut off time of 20 seconds was employed to prevent tissue damage.

The response thresholds of animals to tactile stimuli were measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA) following the Hargreaves test. Animals were placed in an elevated Plexiglas enclosure set on a mire mesh surface. After 10 minutes of accommodation, pre-calibrated Von Frey hairs were applied perpendicularly to the plantar surface of both paws of the

animals in an ascending order starting from the 0.1 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continues until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force was used because it represent
5 approximately 10% of the animals' body weight and it serves to prevent raising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus. The compounds of the present invention were shown to be efficacious within a range of 30 mg/Kg and 0.1 mg/Kg.

Postoperative Models of Nociception

10 In this model, the hypealgesia caused by an intra-planar incision in the paw is measured by applying increased tactile stimuli to the paw until the animal withdraws its paw from the applied stimuli. While animals were anaesthetized under 3.5% isoflurane, which was delivered via a nose cone, a 1 cm longitudinal incision was made using a number 10 scalpel blade in the plantar aspect of the left hind paw
15 through the skin and fascia, starting 0.5 cm from the proximal edge of the heel and extending towards the toes. Following the incision, the skin was apposed using 2, 3-0 sterilized silk sutures. The injured site was covered with Polysporin and Betadine. Animals were returned to their home cage for overnight recovery.

The withdrawal thresholds of animals to tactile stimuli for both operated
20 (ipsilateral) and unoperated (contralateral) paws can be measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals were placed in an elevated Plexiglas enclosure set on a mire mesh surface. After at least 10 minutes of acclimatization, pre-calibrated Von Frey hairs were applied perpendicularly to the plantar surface of both paws of the animals in an ascending
25 order starting from the 10 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continued until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force is used because it represent approximately 10% of the animals' body weight and it serves to prevent raising of the entire limb due to the use
30 of stiffer hairs, which would change the nature of the stimulus.

Compounds of the present invention were shown to be efficacious within a range of 30 mg/Kg and 0.1 mg/Kg.

Neuropathic pain model: Chronic Constriction Injury

Briefly, an approximately 3 cm incision was made through the skin and the fascia at the mid thigh level of the animals' left hind leg using a no. 10 scalpel blade. The left sciatic nerve was exposed via blunt dissection through the *biceps femoris* with care to minimize haemorrhagia. Four loose ligatures were tied along the sciatic nerve using 4-0 non-degradable sterilized silk sutures at intervals of 1 to 2 mm apart. The tension of the loose ligatures was tight enough to induce slight constriction of the sciatic nerve when viewed under a dissection microscope at a magnification of 4 fold. In the sham-operated animal, the left sciatic nerve was exposed without further manipulation. Antibacterial ointment was applied directly into the wound, and the muscle was closed using sterilized sutures. Betadine was applied onto the muscle and its surroundings, followed by skin closure with surgical clips.

The response thresholds of animals to tactile stimuli were measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals were placed in an elevated Plexiglas enclosure set on a mire mesh surface. After 10 minutes of accommodation, pre-calibrated Von Frey hairs were applied perpendicularly to the plantar surface of both paws of the animals in an ascending order starting from the 0.1 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continues until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force is used because it represents approximately 10% of the animals' body weight and it serves to prevent raising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus. Compounds of the present invention were shown to be efficacious within a range of 30 mg/Kg and 0.1 mg/Kg.

Thermal nociceptive thresholds of the animals were assessed using the Hargreaves test. Following the measurement of tactile thresholds, animals were placed in a Plexiglass enclosure set on top of an elevated glass platform with heating units. The glass platform is thermostatically controlled at a temperature of approximately 24 to 26 °C for all test trials. Animals were allowed to accommodate for 10 minutes following placement into the enclosure until all exploration behaviour ceases. The Model 226 Plantar/ Tail Stimulator Analgesia Meter (IITC, Woodland Hills, CA) was used to apply a radiant heat beam from underneath the glass platform to the plantar surface of the hind paws. During all test trials, the idle intensity and active

intensity of the heat source were set at 1 and 55 respectively, and a cut off time of 20 seconds was used to prevent tissue damage.

BIOLOGICAL EXAMPLE 4

Aconitine Induced Arrhythmia Test

5 The antiarrhythmic activity of compounds of the invention is demonstrated by the following test. Arrhythmia was provoked by intravenous administration of aconitine (2.0 µg/Kg) dissolved in physiological saline solution. Test compounds were intravenously administered 5 minutes after the administration of aconitine. Evaluation of the anti-arrhythmic activity was conducted by measuring the time from the aconitine
10 administration to the occurrence of extrasystole (ES) and the time from the aconitine administration to the occurrence of ventricular tachycardia (VT).

 In rats under isoflurane anaesthesia (1/4 to 1/3 of 2%), a tracheotomy was performed by first creating an incision in the neck area, then isolating the trachea and making a 2 mm incision to insert tracheal tube 2 cm into the trachea such that the
15 opening of the tube was positioned just on top of the mouth. The tubing was secured with sutures and attached to a ventilator for the duration of the experiment.

 Incisions (2.5 cm) were then made into the femoral areas and using a blunt dissection probe, the femoral vessels were isolated. Both femoral veins were cannulated, one for pentobarbital anaesthetic maintenance (0.02-0.05 mL) and one for
20 the infusion and injection of drug and vehicle. The femoral artery was cannulated with the blood pressure gel catheter of the transmitter.

 The ECG leads were attached to the thoracic muscle in the Lead II position (upper right/above heart – white lead and lower left/below heart – red lead). The leads were secured with sutures.

25 All surgical areas were covered with gauze moistened with 0.9% saline. Saline (1-1.5 mL of a 0.9% solution) was supplied to moisten the areas post-surgery. The animals' ECG and ventilation were allowed to equilibrate for at least 30 minutes.

 The arrhythmia was induced with a 2 µg/Kg/min aconitine infusion for 5 minutes. During this time the ECG was recorded and continuously monitored. An
30 intravenous bolus injection of test compound (10, 30 or 100 µg/Kg) resulted in a complete return to normal baseline ECG.

BIOLOGICAL EXAMPLE 5

Ischemia Induced Arrhythmia Test

Rodent models of ventricular arrhythmias, in both acute cardioversion and

prevention paradigms have been employed in testing potential therapeutics for both atrial and ventricular arrhythmias in humans. Cardiac ischemia leading to myocardial infarction is a common cause of morbidity and mortality. The ability of a compound to prevent ischemia-induced ventricular tachycardia and fibrillation is an accepted model for determining the efficacy of a compound in a clinical setting for both atrial and ventricular tachycardia and fibrillation.

Anaesthesia is first induced by pentobarbital (i.p.), and maintained by an i.v. bolus infusion. Male SD rats have their trachea cannulated for artificial ventilation with room air at a stroke volume of 10 ml/Kg, 60 strokes/minute. The right femoral artery and vein are cannulated with PE50 tubing for mean arterial blood pressure (MAP) recording and intravenous administration of compounds, respectively.

The chest was opened between the 4th and 5th ribs to create a 1.5 cm opening such that the heart was visible. Each rat was placed on a notched platform and metal restraints were hooked onto the rib cage opening the chest cavity. A suture needle was used to penetrate the ventricle just under the lifted atrium and exited the ventricle in a downward diagonal direction so that a >30% to <50% occlusion zone (OZ) would be obtained. The exit position was ~0.5 cm below where the aorta connects to the left ventricle. The suture was tightened such that a loose loop (occluder) was formed around a branch of the artery. The chest was then closed with the end of the occluder accessible outside of the chest.

Electrodes were placed in the Lead II position (right atrium to apex) for ECG measurement as follows: one electrode inserted into the right forepaw and the other electrode inserted into the left hind paw.

The body temperature, MAP, ECG, and heart rate were constantly recorded throughout the experiment. Once the critical parameters had stabilized, a 1-2 minute recording was taken to establish the baseline values. Infusion of the compound or control substances was initiated once baseline values were established. After a 5-minute infusion of compound or control, the suture was pulled tight to ligate the LCA and create ischemia in the left ventricle. The critical parameters were recorded continuously for 20 minutes after ligation, unless the MAP reached the critical level of 20-30 mmHg for at least 3 minutes, in which case the recording was stopped because the animal would be declared deceased and was then sacrificed. The ability of the compound to prevent arrhythmias and sustain near-normal MAP and HR was scored and compared to control.

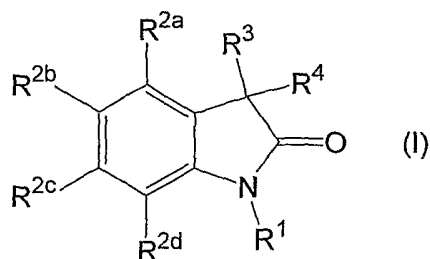
* * * * *

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.

- 5 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 compound of formula (I):



wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, $-R^9-C(O)R^6$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-R^9-OR^6$, $-R^9-CN$, $-R^{10}-P(O)(OR^6)_2$ 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 groups 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 $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, $-R^9-CN$, $-R^9-OR^6$, $-R^9-C(O)R^6$, 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, $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, 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, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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, aralkynyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)X$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-OC(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-R^9-Si(R^6)_3$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, $-N[N(R^5)C(O)OR^6]C(O)OR^6$ 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, heterocyclalkyl, 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, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

or R^3 and R^4 together may form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$ (where R^{9a} 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^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 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.

2. The compound of Claim 1 wherein:

R^1 is $-R^9-C(O)R^6$, $-R^9-C(O)OR^6$, $-R^9-OR^6$, $-R^9-CN$, $-R^{10}-P(O)(OR^6)_2$, $-R^{10}-O-R^{10}-OR^6$, hydrogen, alkyl, haloalkyl, cycloalkylalkyl, heterocyclylalkyl, aryl (optionally substituted by one or more substituents selected from the group consisting of halo and $-R^9-C(O)OR^6$), aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, $-R^9-OR^6$ and $-R^9-C(O)OR^6$), 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$ 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;

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 $-R^9-OR$), $-R^9-OR^6$, $-R^9-OC(O)R^6$, $-R^9-N(R^5)R^6$, $-R^9-C(O)R^5$, $-R^9-C(O)X$, $-R^9-C(O)OR^6$ and

$-N(R^6)C(O)OR^6$, wherein X is chloro or bromo;

R^4 is independently selected from the group consisting of alkyl, aryl, aralkyl, aralkynyl, heteroaryl, heteroarylalkyl, $-R^9-C(O)R^5$, $-N(R^6)C(O)N(R^5)R^6$, $-R^9-NO_2$, $-R^9-N(R^5)R^6$, $-R^9-C(O)OR^6$, $-N[N(R^5)C(O)OR^6]C(O)OR^6$, $-R^9-N(R^6)C(O)OR^6$ and $-R^9-Si(R^6)_3$,

wherein each of the aryl, aralkynyl, heteroaryl and heteroarylalkyl 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, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

or R^3 and R^4 together may form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$ (where R^{9a} 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^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 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.

3. The compound of Claim 2 wherein:

R^1 is hydrogen, alkyl, aryl or aralkyl, where each aryl and aralkyl group for R^1 is independently 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^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo, aryl, heteroaryl and $-R^9-OR^6$, wherein each of the aryl and heteroaryl 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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, alkyl, halo, $-R^9-OR^6$ or $-R^9-OC(O)R^6$;

R^4 is independently selected from the group consisting of alkyl, aryl, aralkynyl, heteroaryl, heteroarylalkyl, $-R^9-C(O)R^5$, $-N(R^6)C(O)N(R^5)R^6$, $-R^9-NO_2$, $-R^9-N(R^5)R^6$, $-R^9-C(O)OR^6$ and $-R^9-Si(R^6)_3$, wherein each of the aryl, aralkynyl, heteroaryl and heteroarylalkyl 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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.

4. The compound of Claim 3 wherein:

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

wherein each of the aryl and heteroaryl 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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 $-R^9-OC(O)R^6$;

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

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 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.

5. The compound of Claim 4 wherein:

R^1 is aryl or aralkyl each optionally substituted by one or more substituents selected from the group consisting of 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, halo and alkyl;

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

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

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.

6. The compound of Claim 5 selected from the group consisting of the following:

1-(4-chlorobenzyl)-5-fluoro-3-[2-(2-furyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-(2-cyclopropyl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-[2-(4-fluorophenyl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-pyridin-2-ylethyl)-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-indol-2-one;
1-(4-fluorophenyl)-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1-(4-trifluoromethylbenzyl)-1,3-dihydro-2*H*-indol-2-one;
1-[2-(4-chlorophenyl)-ethyl]-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-[2-oxo-2-(1*H*-pyrrol-2-yl)-ethyl]-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-[2-(5-methylfuran-2-yl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-[2-(2,5-dimethylfuran-3-yl)-2-oxoethyl]-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-(2-furan-2-yl-2-oxoethyl)-3-hydroxy-5-methyl-1,3-dihydro-2*H*-indol-2-one;
3-(2-benzofuran-2-yl-2-oxo-ethyl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(1,1,3-trimethyl-2-oxobutyl)-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-(1,1-dimethyl-2-oxo-2-thiophen-2-yl-ethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one; and
3-chloro-1-(4-chlorobenzyl)-3-[2-oxo-2-(2-thienyl)ethyl]-1,3-dihydro-2*H*-indol-2-one.

7. The compound of Claim 3 wherein:

R^1 is aralkyl (optionally substituted by one or more substituents selected from the group consisting of halo, haloalkyl, heteroaryl, $-R^9-OR^6$ and $-R^9-C(O)OR^6$); R^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo, aryl, heteroaryl and $-R^9-OR^6$, wherein each of the aryl and heteroaryl 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$ 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 $-R^9-OC(O)R^6$;

R^4 is heterocyclalkyl, heteroaryl or heteroarylalkyl, each 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$ 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;

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.

8. The compound of Claim 7 wherein:

R^1 is aralkyl (optionally substituted by one or more substituents selected from the

group consisting of halo, haloalkyl, heteroaryl, $-R^9-OR^6$ and $-R^9-C(O)OR^6$;
 R^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of
hydrogen, alkyl, halo, phenyl, benzodioxolyl and $-R^9-OR^6$,
 R^3 is hydrogen, halo, $-R^9-OR^6$ or $-R^9-OC(O)R^6$;
 R^4 is heterocyclalkyl, heteroaryl or heteroarylalkyl, each optionally substituted by one
or more substituents selected from the group consisting of alkyl, halo,
heterocycl, and $-R^9-OR^6$;
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 heterocycl 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.

9. The compound of Claim 8 selected from the group consisting of the
following:
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)-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-2*H*-indol-2-one;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3-(1-benzofuran-6-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;

3-(2,2-difluoro-1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-methoxybenzyl)-1,3-dihydro-2*H*-indol-2-one;

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

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

3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-1,3-dihydro-2*H*-indol-2-one;
3,5-bis(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-chloro-1-(4-chlorobenzyl)-1,3-dihydro-2*H*-indol-2-one;
methyl 3-[[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
methyl 3-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
methyl 3-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
methyl 4-[[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
methyl 4-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
methyl 4-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one;
methyl 2-[[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
methyl 2-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
methyl 2-[[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]methyl]benzoate;
1-(diphenylmethyl)-3-hydroxy-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-indol-2-one;
1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-1,3-dihydro-2*H*-indol-2-one;
1-(diphenylmethyl)-3-(5-hydroxy-2,3-dihydro-1-benzofuran-6-yl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one;
1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-

2*H*-indol-2-one;
 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-5-methyl-1,3-dihydro-2*H*-indol-2-one;
 1-(diphenylmethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-5-methyl-1,3-dihydro-2*H*-indol-2-one;
 1-(diphenylmethyl)-3-hydroxy-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one;
 1-(diphenylmethyl)-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one;
 1-(diphenylmethyl)-3-(6-hydroxy-3,3-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one; and
 1-(4-chlorobenzyl)-3-(2,2-difluoro-2-thiophen-2-ylethyl)-3-hydroxy-1,3-dihydroindol-2-one.

10. The compound of Claim 3 wherein:

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

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

wherein each of the aryl and heteroaryl 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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 or $-R^9-OR^6$;

R^4 is aryl, aralkyl or aralkynyl,

wherein each of the aryl, aralkyl and aralkynyl 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$,

$-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$; $-R^9-C(O)OR^6$,
 $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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.

11. The compound of Claim 10 wherein:

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

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

wherein each of the aryl and heteroaryl 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$,
 $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$; $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$,
 $-N(R^6)C(O)R^5$, 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 $-R^9-OR^6$;

R^4 is aryl, aralkyl or aralkynyl,

wherein each of the aryl, aralkyl and aralkynyl groups for R^4 is optionally
substituted by one or more substituents selected from the group
consisting of halo, heteroaryl 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 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.

12. The compound of Claim 11 selected from the group consisting of the following:

1-(4-chlorobenzyl)-3-(2,5-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(3-methoxyphenyl)-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(2-methoxyphenyl)-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-(3,4-dimethoxyphenyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
3-benzyl-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-(4-methoxyphenyl)-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-hydroxy-3-phenyl-1,3-dihydro-2*H*-indol-2-one;
3-hydroxy-1-(4-methoxybenzyl)-3-naphthalen-2-yl-1,3-dihydro-2*H*-indol-2-one;
3-hydroxy-1-(4-methoxybenzyl)-3-(3-pyrrol-1-ylphenyl)-1,3-dihydro-2*H*-indol-2-one;
1-(4-chlorobenzyl)-3-(4-fluorophenylethynyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(4,5-difluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(5-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(5-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(5-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(5-chloro-4-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(5-chloro-4-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4-chloro-5-fluoro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4-chloro-5-fluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4,5-dichloro-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4,5-dichloro-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4,5-dichloro-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-hydroxy-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2*H*-indol-2-one ;

3-(hydroxymethyl)-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(5-bromo-2-hydroxy-4-methoxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(2-hydroxy-4-methoxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(2-hydroxy-4-methoxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4-bromo-2-hydroxyphenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4-bromo-2-hydroxyphenyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(4-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;

3-(5-bromo-2-hydroxyphenyl)-1,3-dihydro-2*H*-indol-2-one;

3-(5-bromo-2-hydroxyphenyl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one;

1-(diphenylmethyl)-3-hydroxy-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2*H*-indol-2-one;

1-(diphenylmethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2*H*-indol-2-one;

1-(diphenylmethyl)-3-(hydroxymethyl)-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-1,3-dihydro-2*H*-indol-2-one;

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

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

1-(diphenylmethyl)-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one;
 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-1,3-dihydro-2*H*-indol-2-one;
 3-(5-bromo-2-hydroxyphenyl)-1-(diphenylmethyl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one; and
 3-[5-(benzyloxy)-2-hydroxyphenyl]-1-(4-chlorobenzyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one.

13. The compound of Claim 2 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, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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 hydrogen, alkyl or $-R^9-OR^6$;

R^4 is independently selected from the group consisting of alkyl, aryl, aralkynyl, heteroaryl, heteroarylalkyl, $-R^9-C(O)R^5$, $-R^9-N(R^6)C(O)OR^6$, $-N(R^6)C(O)N(R^5)R^6$, $-R^9-NO_2$, $-R^9-N(R^5)R^6$, $-R^9-C(O)OR^6$, and $-R^9-Si(R^6)_3$, wherein each of the aryl, aralkynyl, heteroaryl and heteroarylalkyl 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, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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.

14. The compound of Claim 13 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, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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, 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, halo, haloalkyl, haloalkenyl,

cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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.

15. The compound of Claim 14 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 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, halo, haloalkyl, aryl, aralkyl, $-R^9-OR^6$, $-R^9-C(O)OR^6$ 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 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 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.

16. The compound of Claim 15 selected from the group consisting of the following:

- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-1-(cyclopropylmethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-7-(4-fluorophenyl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(4,4,4-trifluorobutyl)-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-1-(5-chloropentyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
- 3,7-bis(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-5,7-dimethyl-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methylpentyl)-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(1-methylpentyl)-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-1-cyclobutylmethyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-7-fluoro-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-(3-methylbutyl)-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-1-hexyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-4,7-dichloro-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-6-chloro-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-3-hydroxy-1-pentyl-7-trifluoromethyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-4-chloro-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzoxazol-5-yl)-3-hydroxy-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 1-(4-chlorobenzyl)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;
- 3-hydroxy-3-[6-(hydroxymethyl)-1,3-benzodioxol-5-yl]-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
- 3-(1,3-benzodioxol-5-yl)-4,7-dichloro-1-pentyl-1,3-dihydro-2*H*-indol-2-one;

3-(1,3-benzodioxol-5-yl)-7-fluoro-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(1,3-benzodioxol-5-yl)-5,7-dimethyl-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
1-(2-cyclopropylethyl)-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
1-(2-cyclopropylethyl)-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
3-(1,3-benzodioxol-5-yl)-1-(2-cyclopropylethyl)-1,3-dihydro-2*H*-indol-2-one;
3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-hydroxymethyl-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-methoxy-1-pentyl-1,3-dihydro-indol-2-one;
3-(1,3-benzodioxol-5-yl)-3-methyl-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-2*H*-indol-2-one;
4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
4,7-dichloro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
4,7-dichloro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
3-hydroxy-3-[6-(hydroxymethyl)-1,3-benzodioxol-5-yl]-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
1-hexyl-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
ethyl [1-hexyl-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetate ;
4-bromo-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
4-bromo-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-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-2*H*-indol-2-one;
4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-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-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
 3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
 3-(hydroxymethyl)-3-(5-hydroxy-2-methyl-1,3-benzothiazol-6-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
 7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
 7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;
 4-bromo-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one;
 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1,3-dihydro-2*H*-indol-2-one;
 4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one;
 3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one;
 3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one; and
 3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1-pentyl-1,3-dihydro-2*H*-indol-2-one.

17. The compound of Claim 13 wherein:

R¹ 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 and halo;

R³ is hydrogen or -R⁹-OR⁶;

R⁴ is independently selected from the group consisting of -R⁹-C(O)R⁵ and -R⁹-N(R⁶)C(O)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; 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.

18. The compound of Claim 2 wherein:

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

19. The compound of Claim 18 selected from the group consisting of the following:

3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl acetate;
 methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]acetate;
 [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]acetic acid;
 2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]acetamide;
 2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]-*N*-methylacetamide;
 2-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]-*N,N*-dimethylacetamide;
 methyl [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]acetate;
 [3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-yl]acetic acid;
 methyl 3-[3-(1,3-benzodioxol-5-yl)-2-oxo-1-pentyl-2,3-dihydro-1*H*-indol-3-

yl]propanoate; and

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

20. The compound of Claim 2 wherein:

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

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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, wherein each of the cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$ 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;

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 and R^4 together form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$,

where R^{9a} 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^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.

21. The compound of Claim 20 wherein:

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

R^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo and haloalkyl;

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 and R^4 together form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$,

where R^{9a} 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^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.

22. The compound of Claim 2 wherein:

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

R^{2a} , R^{2b} , R^{2c} and R^{2d} are each independently selected from the group consisting of hydrogen, alkyl, halo and haloalkyl;

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 $-N[N(R^5)C(O)OR^6]C(O)OR^6$,

$-R^9-N(R^5)R^6$ and $-N(R^6)C(O)OR^6$;

R^4 is independently selected from the group consisting of alkyl, aryl, heteroaryl, and

$-R^9-C(O)R^5$,

wherein each of the aryl and heteroaryl groups 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, 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.

23. The compound of Claim 22 selected from the group consisting of the following:

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

1-[3-(1,3-benzodioxol-5-yl)-1-(4-chlorobenzyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]hydrazine-1,2-dicarboxylate;

tert-butyl {2-oxo-3-[2-oxo-2-(2-thienyl)ethyl]-1-pentyl-2,3-dihydro-1*H*-indol-3-yl}carbamate; and

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

24. The compound of Claim 2 wherein:

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

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 hydrogen, $-R^9-OR^6$ or heteroaryl optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl and $-R^9-OR^6$;

R^4 is independently selected from the group consisting of alkyl, aryl, aralkyl, heteroaryl, $-R^9-Si(R^6)_3$, $-R^9-NO_2$ and $-R^9-C(O)R^5$,

wherein each of the aryl, aralkyl and heteroaryl groups for R^4 is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl 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 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.

25. The compound of Claim 24 selected from the group consisting of the following:

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

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

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

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

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

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

3-(1,3-benzodioxol-5-yl)-1-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;

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

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

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

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

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

1-(1,3-benzodioxol-5-ylmethyl)-3-(1-benzofuran-6-yl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one;

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

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

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

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

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

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

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

2-{3-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]propyl}-1*H*-isoindole-1,3(2*H*)-dione;

2-{2-[3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione;

2-{2-[3-(6-hydroxy-1,3-benzodioxol-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione;

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

1-[3-(benzyloxy)propyl]-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;

1-[3-(benzyloxy)propyl]-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one;

1-(3-benzyloxypropyl)-3-(6-hydroxybenzo[1,3]dioxol-5-yl)-3-hydroxymethyl-1,3-dihydro-2*H*-indol-2-one;

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

ethyl [3-(6-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [3-(6-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [3-hydroxy-3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [3-(hydroxymethyl)-3-(3-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [4-bromo-3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [4-bromo-3-hydroxy-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
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;
ethyl [4-bromo-3-(6-hydroxy-2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one;
3-(6-hydroxy-1,3-benzodioxol-5-yl)-4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one;
3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-4-methoxy-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one;
ethyl [4-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [4-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;
ethyl [4-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-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-2*H*-indol-2-one;

4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2*H*-indol-2-one;

4-bromo-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-1-(pyridin-2-ylmethyl)-1,3-dihydro-2*H*-indol-2-one;

5-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one;

5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one;

5-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-3-(hydroxymethyl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one;

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

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

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

ethyl [5-chloro-3-hydroxy-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;

ethyl [5-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;

ethyl [5-chloro-3-(6-hydroxy-2,3-dihydro-1-benzofuran-5-yl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;

methyl [3-(4-chloro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;

methyl [3-(4-chloro-2-hydroxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;

methyl [3-(4-chloro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;

ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;

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

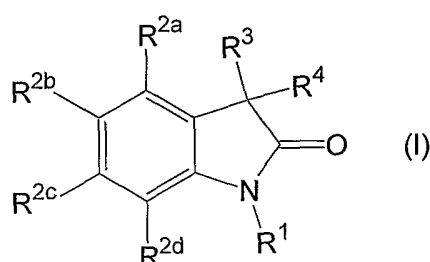
ethyl [3-(4,5-difluoro-2-hydroxyphenyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate;

7-fluoro-3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-dihydro-2*H*-indol-2-one;

7-fluoro-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1-[[5-(trifluoromethyl)-2-furyl]methyl]-1,3-

dihydro-2*H*-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-2*H*-indol-2-one.

26. A method of treating, preventing or ameliorating a disease or a condition of a mammal selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I):



wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, $-R^9-C(O)R^6$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-R^9-OR^6$, $-R^9-CN$, $-R^{10}-P(O)(OR^6)_2$ 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 groups 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 $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, heterocyclalkyl, 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, heterocyclalkyl, 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, $-R^9-CN$, $-R^9-OR^6$, $-R^9-C(O)R^6$, heterocyclyl and heteroaryl;

or R^1 is heterocyclalkyl or heteroarylalkyl where the heterocyclalkyl or the heteroaryl group is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, 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, heterocyclalkyl, 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, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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;

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, -R⁹-CN, -R⁹-NO₂, -R⁹-OR⁶, -R⁹-N(R⁵)R⁶, -N=C(R⁵)R⁶, -S(O)_mR⁵, -R⁹-C(O)R⁵, -R⁹-C(O)X, -C(S)R⁵, -C(R⁵)₂C(O)R⁶, -R⁹-OC(O)R⁶, -R⁹-C(O)OR⁶, -C(S)OR⁵, -R⁹-C(O)N(R⁵)R⁶, -C(S)N(R⁵)R⁶, -R⁹-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, -R⁹-S(O)_nN(R⁵)R⁶, -N(R⁶)C(=NR⁵)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, 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;

or R³ and R⁴ together may form =NS(O)₂R⁶, =N-R¹⁵, =N-O-R⁶ or =R^{9a}-C(O)R⁶ (where R^{9a} 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 -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-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;

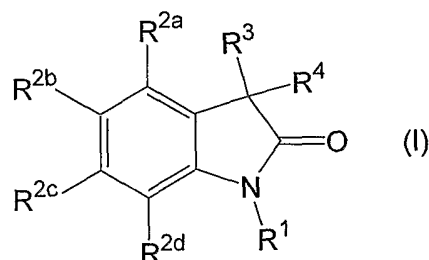
as a stereoisomer, enantiomer, tautomer thereof or mixtures thereof;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

27. A method of claim 26, wherein said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, pain associated with narcotic drug addiction withdrawal and combinations thereof.

28. A method of claim 26, wherein said disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, to sarcoidosis, irritable bowel syndrome, Crohn's disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritic, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythralgia, primary erythralgia, familial rectal pain, cancer, narcotic drug addiction, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions caused by stroke or neural trauma, tachy-arrhythmias, atrial fibrillation and ventricular fibrillation.

29. A method of treating pain through inhibition of ion flux through a voltage-dependent sodium channel in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I):



wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, $-R^9-C(O)R^6$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-R^9-OR^6$, $-R^9-CN$, $-R^{10}-P(O)(OR^6)_2$ 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, heterocyclalkyl, 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, heterocyclalkyl, heteroaryl and heteroaryl groups 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 $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, heterocyclalkyl, 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, $-R^9-CN$, $-R^9-OR^6$, $-R^9-C(O)R^6$, 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, $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^5)N(R^5)R^6$, 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, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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, aralkynyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)X$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-OC(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-R^9-Si(R^6)_3$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, $-N[N(R^5)C(O)OR^6]C(O)OR^6$ 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, heterocyclalkyl, 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, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

or R^3 and R^4 together may form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$ (where R^{9a} 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 $-R^9-OR^6$);

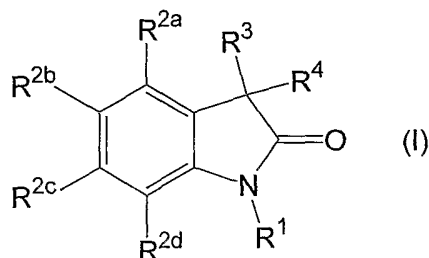
each R^5 and R^6 is independently selected from group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl and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

30. A method of decreasing ion flux through a voltage-dependent sodium channel in a cell in a mammal, wherein the method comprises contacting the cell with a compound of formula (I):



wherein:

R^1 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, $-R^9-C(O)R^6$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-R^9-OR^6$, $-R^9-CN$, $-R^{10}-P(O)(OR^6)_2$ 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, heterocyclalkyl, 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, heterocyclalkyl, heteroaryl and heteroaryl groups 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 $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, $-R^9-CN$, $-R^9-OR^6$, $-R^9-C(O)R^6$, 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, $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, 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, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$;

$-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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, aralkynyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)X$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-OC(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-R^9-Si(R^6)_3$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, $-N[N(R^5)C(O)OR^6]C(O)OR^6$ 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, alkynyl, halo, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

or R^3 and R^4 together may form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$ (where R^{9a} 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^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;

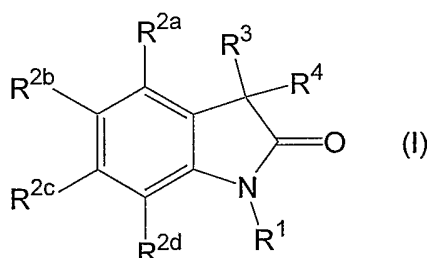
each R⁹ is a direct bond or an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain or an optionally substituted straight or branched alkynylene chain; and

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.

31. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of formula (I):



wherein:

R¹ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, -R⁹-C(O)R⁶, -R⁹-C(O)OR⁶, -R⁹-C(O)N(R⁵)R⁶, -R⁹-OR⁶, -R⁹-CN, -R¹⁰-P(O)(OR⁶)₂ or -R¹⁰-O-R¹⁰-OR⁶;

or R¹ is aralkyl substituted by -C(O)N(R⁷)R⁸ where:

R⁷ is hydrogen, alkyl, aryl or aralkyl; and

R⁸ is hydrogen, alkyl, haloalkyl, -R¹⁰-CN, -R¹⁰-OR⁶, -R¹⁰-N(R⁵)R⁶, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

or R⁷ and R⁸, 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 groups for R⁷ and R⁸ 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 $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, $-R^9-CN$, $-R^9-OR^6$, $-R^9-C(O)R^6$, 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, $-R^9-OR^6$, $-R^9-C(O)OR^6$, 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, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, 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, haloalkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

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, aralkynyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, $-R^9-\dot{C}N$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-N=C(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)X$, $-C(S)R^5$, $-C(R^5)_2C(O)R^6$, $-R^9-OC(O)R^6$, $-R^9-C(O)OR^6$, $-C(S)OR^5$, $-R^9-C(O)N(R^5)R^6$, $-C(S)N(R^5)R^6$, $-R^9-Si(R^6)_3$, $-N(R^6)C(O)R^5$, $-N(R^6)C(S)R^5$, $-N(R^6)C(O)OR^6$, $-N(R^6)C(S)OR^5$, $-N(R^6)C(O)N(R^5)R^6$, $-N(R^6)C(S)N(R^5)R^6$, $-N(R^6)S(O)_nR^5$, $-N(R^6)S(O)_nN(R^5)R^6$, $-R^9-S(O)_nN(R^5)R^6$, $-N(R^6)C(=NR^6)N(R^5)R^6$, $-N[N(R^5)C(O)OR^6]C(O)OR^6$ 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, heterocyclalkyl, 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, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, oxo, $-R^9-CN$, $-R^9-NO_2$, $-R^9-OR^6$, $-R^9-N(R^5)R^6$, $-S(O)_mR^5$, $-R^9-C(O)R^5$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^5)R^6$, $-N(R^6)C(O)R^5$, 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;

or R^3 and R^4 together may form $=NS(O)_2R^6$, $=N-R^{15}$, $=N-O-R^6$ or $=R^{9a}-C(O)R^6$ (where R^{9a} 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 R¹⁵ is a N-heterocyclyl optionally substituted by alkyl, haloalkyl or -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-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.