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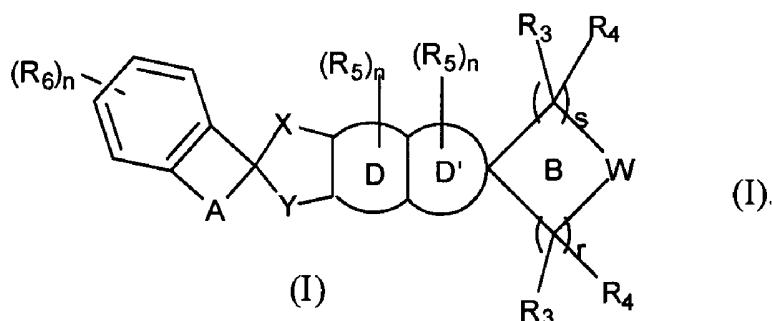
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(54) Title: SPIROCYCLIC COMPOUNDS AS VOLTAGE-GATED SODIUM CHANNEL MODULATORS



(57) Abstract: The present invention relates to compounds of Formula (I) along with processes for their preparation that are useful for treating, preventing and/or managing the diseases, disorders, syndromes or conditions modulated by VGSCs. The invention further relates to methods of treating, preventing managing and/or lessening the diseases, disorders, syndromes or conditions by modulators of VGSC of Formula (I).



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**SPIROCYCLIC COMPOUNDS AS VOLTAGE-GATED
SODIUM CHANNEL MODULATORS**

Related Applications

This application claims the benefit of Indian patent application nos. 1140/KOL/2010 filed on Oct 13, 2010 and 1141/KOL/2010 filed on Oct 13, 2010 all of which are hereby 5 incorporated by reference in their entirety.

Field of the Invention

The invention relates to spirocyclic compounds, their pharmaceutically acceptable salts thereof, and pharmaceutical compositions for the treatment, prevention, management, and /or lessening severity of diseases, disorders, syndromes or conditions which are 10 associated with the voltage-gated sodium channels (VGSC). The invention also relates to processes for the preparation of the compounds of the invention and to methods of treating, preventing, managing and/or lessening the severity of the diseases disorders, syndromes or conditions associated with voltage-gated sodium channels (VGSC).

Background of the Invention

15 Voltage-gated sodium channels play a crucial role in maintaining a specific membrane potential (intra- and extracellular ionic environments) across the mammalian cell membrane. The intracellular concentration of Na⁺ is kept low relative to the extracellular by active sodium pumps that eject three Na⁺ ions for every two K⁺ ions taken in. This generates a negative membrane potential (since more positive charge is pumped out and less taken in) 20 and maintains the Na⁺ concentration of 6 and 140 mM in the intra and extracellular milieu. On opening of the voltage-gated sodium channels (VGSC), Na⁺ rushes in and leads to depolarization of the membrane because of the associated positive charge. The entry of Na⁺ via VGSC's occurs in cells of the heart, central and peripheral nervous system and is essential to initiate the firing of an action potential.

25 VGSCs consist of a pore-forming alpha subunit and a stabilizing beta subunit, 9 isoforms of the alpha subunit have been identified till date (Nav1.1 to Nav1.9). All nine members of the family have >50% identity in the amino acid sequence in the extracellular

and transmembrane domain. The channels have also been further classified based on their sensitivity to the puffer fish toxin (tetrodotoxin, TTX). Channels Nav1.8, Nav1.9 and Nav1.5 are TTX resistant (TTX-R) whereas the remaining channels are sensitive to TTX (TTX-S). (England and Rawson. *Future Med. Chem.* (2010), 2, 775-790).

5 Nav1.1 is a tetrodotoxin sensitive ion channel that has been associated with epilepsy. More than 100 mutations have been reported in the Nav1.1 encoding gene that has been linked to epilepsy. Total loss of function mutations give rise to Severe Myoclonic Epilepsy of Infancy (SMEI or Dravet Syndrome), which is characterized by severe, intractable epilepsy and co-morbidities of ataxia and cognitive impairment. Mild loss of function
10 mutations have been associated with Familial Febrile Seizures. Missense Nav1.1 mutations lead to Generalized Epilepsy with Febrile Seizures Plus (GEFS+). Gain of function mutations of Nav1.1 have been reported to cause GEFS+ epilepsy. (Caterall *et al. J. Physiol.* (2010), 588, 1849-1859). Thus modulating Nav1.1 function could have therapeutic benefit in epilepsy and related disorders.

15 Nav1.3, is a tetrodotoxin (TTX)-sensitive sodium channel, and is expressed primarily during fetal development. Normally, Nav1.3 expression decreases following birth to very low levels throughout the nervous system. However, following injury such as that observed in axotomy, chronic constriction, varicella zoster virus infection, or an inflammatory insult, Nav1.3 levels increase in dorsal root ganglion neurons. Nav1.3 channels recover very rapidly
20 from inactivation during an action potential or burst of action potentials suggesting that these channels could play a role in sustaining high frequency firing or bursts of action potentials. (*Current Opinion in Pharmacology* (2008), 8, 50–56). A mutation in Nav1.3 (K354Q) has been linked to epilepsy.

25 Mutations in the Nav1.4 sodium channel are responsible for the hereditary myotonic syndromes. Myotonia is a neurological disorder that is characterized by voluntary muscle contractions followed by slow relaxations. Sodium channel blockers (e.g., Tocainide) are being used clinically for the symptomatic treatment of myotonia-associated muscle hyperexcitability. Thus, pharmacologically blocking Nav1.4 may benefit patients suffering

from hereditary myotonic syndrome (Catalano *et al.* *European Journal of Medicinal Chemistry* (2008), 43, 2535-2540).

Nav1.5 belongs to the TTX-resistant class of voltage-gated ion channels. Nav1.5 Na⁺ channels are responsible for the regenerative potentials that mediate the transmission of electrical signals in cardiac myocytes and cardiac fibres that relay electrical signals across the heart. Genetic mutations that reduce function of Nav1.5 are associated with long QT syndrome, Brugada syndrome, primary cardiac conduction disease and idiopathic ventricular fibrillation. Homozygous knock-out (KO) Nav1.5 mouse embryos die during mid-gestation, probably due to the severe cardiac malformations. Heterozygous KO mice (Nav1.5^{+/−}) mainly display slow atrial, atrio-ventricular (AV), and intra-ventricular conduction, as well as increased inducibility of ventricular arrhythmias. Nav1.5 has been proposed as a target for antiarrhythmic agents. Enhanced function of Nav1.5 has been linked to ischemia-reperfusion and ischemic heart diseases. It has been reported that increased intracellular sodium concentration leads to enhanced calcium flux, which in turn leads to cell death and tissue damage. Selective Nav1.5 blockers have been shown to possess anti-ischemic activity (Grand *et al.*, *J. Med. Chem.* (2008), 51, 3856–3866). Thus, Nav1.5 blockers can have therapeutic benefit in ischemic heart diseases. A novel splice form of Nav1.5 has been identified in breast cancer cells and the enhanced expression of this isoform was associated with strong metastatic potential in vitro and breast cancer progression in vivo. Based on these results Nav1.5 has been proposed to be a biomarker and a potential therapeutic target for breast cancer (Fraser *et al.* *Clin. Cancer Res.* (2005), 11, 5381-5389).

Expression of Nav1.6 has been shown to be increased in rat model for multiple sclerosis. Increased expression is seen in degenerate axons of MS lesions. Since sodium channel blockers are known to have anti inflammatory effects, it was proposed that controlled targeting Nav1.6 by selective blockers would have therapeutic potential against multiple sclerosis. Complete suppression of Nav1.6 function can have serious side effects: motor failure, ataxia, tremor, muscle weakness, and dystonia that are seen in Nav1.6 knockout mice. (Termin *et al.* *Ann. Rep. Med. Chem.* (2008), 43, 43-60). Sodium channel-mediated neuroprotection following ischemic stroke helps in reducing brain damage. Nav1.6

has been shown to play a role in mediating neuroprotection and small molecule Nav1.6 selective blockers did show neuroprotective effect (Clutterbuck *et al.* *J. Med. Chem.* (2009), 52, 2694–2707).

Gain of function mutations in the Nav1.7 gene in humans leads to inherited erythromelalgia (IEM). Another set of mutations lead to the development of paroxysmal extreme pain disorder (PEPD). Erythromelalgia is characterized by severe episodic burning pain associated with redness and warmth of the affected extremities. Patients describe attacks as an intense burning pain with accompanying redness in the distal extremities (feet, sometimes hands) in response to warm stimuli or moderate exercise.

PEPD attacks are most severe in the lower part of the body and can be triggered by a bowel movement or probing of the perianal area. They may also be accompanied by tonic non-epileptic seizures, bradycardia, and/or apnea. As the patients age, the pain pattern changes with pain primarily affecting the ocular and maxillary and/or mandibular areas rather than the rectal area. These attacks are often triggered by temperature changes (such as cold winds), eating, and/or emotional upsets (such as crying). (Fischer and Waxman. *Ann. N.Y. Acad. Sci.* 1184, (2010), 196–207).

Loss of function mutations in the human Nav1.7 gene lead to congenital insensitivity to pain which was observed for the first time in certain Pakistani families. Affected individuals displayed painless burns, fractures, and injuries of the lips and tongue. The patients did not have any autonomic or motor abnormalities, and reportedly had normal tear formation, sweating ability, reflexes, and intelligence. This genetic evidence clearly indicates that gain or loss of Nav1.7 function can lead to exacerbation or loss of pain sensation respectively. Thus, it may be possible to treat chronic pain by pharmacologically blocking Nav1.7. Moreover, Nav1.7 has also been implicated in epilepsy. Small molecule Nav1.7 blockers showed efficacy in *in vivo* epilepsy models. It has therefore been proposed that selective Nav1.7 blockers may lead to therapeutic benefit in epilepsy (Hoyt *et al.* *Bioorganic & Medicinal Chemistry Letters* (2008), 18, 1963–1966).

Expression of Nav1.7 is upregulated ~20 fold in prostate cancer. Moreover, the expression correlates with high metastatic potential in vitro. Prostate cancer could therefore be a potential therapeutic option for Nav1.7 blockers. (*Current Pharmaceutical Design* (2006), 12, 3681-3695; *Prostate Cancer and Prostatic Diseases* (2005), 8, 266–273).

5 Genetic evidence stems from the human gain of function as well as loss of function mutations that lead to inherited pain disorders and insensitivity to pain respectively. Non selective VGSC blockers have been shown to alleviate pain in animal models as well as in humans (e.g., Carbamazepine). Raloxifene, another non-selective sodium channel blocker, is also being developed for the treatment of neuropathic pain.

10 Nav1.8 is primarily expressed in the peripheral nervous system and is resistant to TTX-mediated block. Nav1.8 is known to be expressed in cerebellar neurons in both rodent models of multiple sclerosis and human patients where this abnormal Nav1.8 expression has been hypothesized to play a role in spasticity. Under all other conditions, however, Nav1.8 appears to be restricted to the peripheral nervous system. Nav1.8 is the dominant voltage-gated sodium channel driving action potential upstroke and conduction of unmyelinated peripheral nerves. Nav1.8 currents play a role in shaping the action potential waveform in nociceptive neurons due to slow inactivation rates that allow some channels to remain open following the action potential upstroke. (Krafft and Bannon *Current Opinion in Pharmacology* (2008), 8, 50–56). Nav1.8 channel expression is increased in the rat digital nerve and dorsal root ganglion (DRG) after intraplantar administration of complete Freund's adjuvant (CFA) or carrageenan (CARR), respectively. Likewise, local administration of prostaglandin-E2, adenosine, or serotonin produces an increase in TTX-R sodium current magnitude in peripheral nerves through modulation of the voltage-dependent properties of Nav1.8 and other sodium channels. Direct nerve injury (e.g., L5/L6 spinal nerve ligation) 15 also leads to immunocytochemical and electrophysiological changes in Nav1.8 channels suggesting a potential role for this channel in the sensation of neuropathic pain. Moreover, human patients with chronic neurogenic pain or chronic local hyperalgesia also show increased Nav1.8 channel expression proximal to a peripheral injury site. Nav1.8 knockout mice show a decreased sensitivity to mechanical stimuli and delayed development of thermal 20 25

hyperalgesia. Selective knockdown of Nav1.8 protein after Nav1.8 Antisense-oligonucleotide treatment reversed mechanical allodynia and thermal hyperalgesia after peripheral inflammation and nerve injury. (Jarvis *et al.* PNAS (2007), 104, 8520-8525).

5 Nav1.9 is a TTX-resistant channel found primarily within small sensory neurons (<30 μm diameter) of dorsal root ganglia (DRG) and trigeminal ganglia, but not in neurons and glia within the CNS, or in muscle. Studies in Nav1.9 KO mice indicate that it could play a role in bladder urodynamics and that blockade of this channel could be a potential therapeutic option for inflammation-mediated bladder dysfunction (Ritter *et al.* *Neuroscience Letters* (2009), 452, 28-32).

10 Voltage-gated sodium channels are implicated in various diseases and disease conditions, including but not limited to chronic pain, visceral pain, arrhythmia, multiple sclerosis, epilepsy and related disorders as well as cancer. Thus, small molecules targeting one or more of the relevant VGSCs is likely to alleviate the suffering from these conditions.

15 International publication nos. WO 2006/110917, WO 2007/109324, WO 2008/046049, WO 2008/046084, WO 2008/046087, WO 2008/060789, WO 2009/012242, WO 2010/035166, WO 2010/045197, WO 2010/045251, WO 2010/053998, WO 2010/078307, WO 2011/002708, WO 2011/026240, WO 2011/103196, WO 2011/056985, WO 2011/058766, WO 2011/088201 and *Bioorganic & Medicinal Chemistry Letters* (2011), 21, 3676-681 disclose compounds related to voltage-gated sodium channel (VGSC) 20 modulators for the treatment of various diseases mediated by VGSC modulation.

Summary of the Invention

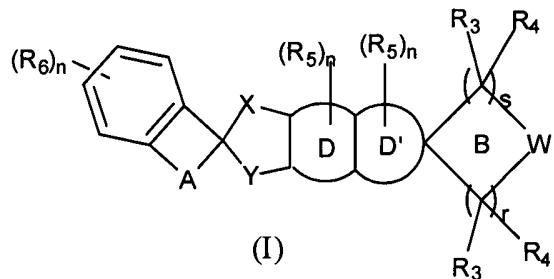
The invention relates to novel spirocyclic compounds, their pharmaceutically acceptable salts thereof, and pharmaceutical compositions for the treatment, prevention, management, and /or lessening severity of diseases, disorders, syndromes or conditions 25 which are associated with the voltage-gated sodium channels (VGSC). The invention also relates to processes for the preparation of the compounds of the invention and to methods of treating, preventing, managing and/or lessening the severity of the diseases disorders, syndromes or conditions associated with voltage-gated sodium channels (VGSC).

The details of one or more embodiments of the invention set forth below are illustrative in nature only and are not intended to limit the scope of the invention. Other features, objects and advantages of the inventions will be apparent from the description and claims.

5

Detailed Description of the Invention

In accordance with one aspect, the invention provides the compounds of Formula (I):



wherein,

D is a 5 or 6 membered aryl or heteroaryl ring;

10 D' is absent; or

D' is selected from a 4 to 7 membered carbocyclic or heterocyclic ring;

B is absent; or

B is selected from a carbocyclic or heterocyclic ring; provided that when D' is absent then B is also absent;

15 A is selected from -NRC(O)-, -NR-(CR₁R₂)_q-, -C(O)NR-, -NRS(O)₂-, -S(O)₂NR-, -NRC(S)-, -C(S)NR-, -NRC(O)-(CR₁R₂)_m-, -C(O)NR-(CR₁R₂)_m-, -(CR₁R₂)_m-NRC(O)-, -(CR₁R₂)_m-C(O)NR-, -(CR₁R₂)_m-NR-, -(CR₁R₂)_m-NR-(CR₁R₂)_m-, -NRC(O)NR-, -OC(O)NR-, -NRC(O)O-, NR-CR₁=CR₂-, -C(O)-CR₁=CR₂-, -N=C(R₁)- and -C(O)NRC(O)-;

20 R, which may be same or different at each occurrence, is independently selected from hydrogen, alkyl, haloalkyl, cyanoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, -C(O)R₁₂, -

C(O)OR₁₁, -(CR₁R₂)_m-NR₈R₉, -C(O)-NR₈R₉, -CR_aR_bC(O)NR₈R₉, -(CR_aR_b)_m-CR_aR_bR_c, and -S(O)_pR₁₂;

R₁ and R₂, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, cyano, nitro, -OR₁₀, -C(O)OR₁₁, and alkyl;

5 X is C₁-C₅ alkylene, wherein one or more CH₂ groups may independently be replaced by -O-, -C(O)-, -CR₃R₄-, -NR₈- or -S(O)_p-;

Y is selected from a bond, -O-, -S-, -C(O)-, -NR-, and -CR₃R₄-;

10 R₃ and R₄, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, cyano, nitro, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, -OR₁₀, -SR₁₀, -C(O)R₁₂, -OC(O)R₁₁, -CO(O)R₁₁, -NR₈R₉, -C(O)NR₈R₉, -NR₈C(O)R₁₂, -S(O)₂NR₈R₉ and -NR₇S(O)₂R₁₂; or

R₃ and R₄, together with the carbon atom to which they are attached, may form a substituted or unsubstituted 3 to 7 membered cyclic ring; wherein cyclic ring may be carbocyclic or heterocyclic;

15 with proviso that

i) when Y is a bond, B is absent, A is -NRC(O)-, -NR-(CR₁R₂)_q-, -NRS(O)₂-, -NRC(S)-, -NRC(O)-(CR₁R₂)_m-, -(CR₁R₂)_m-NRC(O)-, -NRC(O)NR-, -NRC(O)O-, or -N=C(R₁)-; X is C₁-C₅ alkylene, and only one of CH₂ group in X is replaced with -CR₃R₄- then

a) R₃ and R₄ both are not hydrogen;

20 b) R₃ and R₄ both are not fluorine; and

c) any one of R₃, R₄ is not -CH(OR₁₃);

ii) when Y is a bond, B is absent, A is -NRC(O)-, -NR-(CR₁R₂)_q-, -NRS(O)₂-, -NRC(S)-, -NRC(O)-(CR₁R₂)_m-, -(CR₁R₂)_m-NRC(O)-, -NRC(O)NR-, -NRC(O)O-, or -N=C(R₁)-; X is C₁-C₅ alkylene wherein at least one of CH₂ is independently replaced with O, C(O), NR₈,

25 S(O)_p and at least one of remaining CH₂ group is replaced with CR₃R₄ then R₃ and R₄ both are not hydrogen; and

iii) when Y is a bond, B is absent, A is $-NRC(O)-$, D ring is phenyl, D' ring is 1,4-dioxane, then X is not replaced with $-C(O)N(CH_3)-$ where C(O) is attached to the quaternary carbon;

W is selected from a bond, $-O-$, $-NR_8-$, $-S(O)_p-$, $-NR_8C(O)-$; CR_3R_4 , $-NR_8C(O)-NR_8-$, $-NR_8C(O)O-$, $-CR_3=N-$, $-C(=NR_8)-$, $-OC(O)-$ and $-OC(O)O-$;

5 R_5 , which may be same or different at each occurrence, is independently selected from halogen, cyano, nitro, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, $-OR_{10}$, $-SR_{10}$, $-S(O)_2R_{10}$, $-C(O)R_{12}$, $-OC(O)R_{11}$, $-NR_8R_9$, $-C(O)NR_8R_9$, $-NR_8C(O)R_{12}$, $-NR_8S(O)_2R_{12}$ and $-S(O)_2NR_8R_9$; provided that when R_5 is present on D' it may be attached on same or different carbon atom;

10 R_6 , which may be same or different at each occurrence, is independently selected from halogen, cyano, nitro, alkyl, haloalkyl, hydroxyalkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, $-OR_{10}$, $-SR_{10}$, $-C(O)R_{12}$, $-OC(O)R_{12}$, $-NR_8R_9$, $-C(O)NR_8R_9$, $-NR_8C(O)R_{12}$, $-NR_7S(O)_2R_{12}$ and $-S(O)_2NR_8R_9$;

15 R_7 , which may be same or different at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, $-C(O)R_{12}$ and $-S(O)_pR_{12}$;

20 R_8 and R_9 , which may be same or different at each occurrence, are independently selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, $-C(O)R_{12}$ and $-S(O)_pR_{12}$; or R_8 and R_9 , together with the nitrogen atom to which they are attached, may form a substituted or unsubstituted 3 to 14 membered heterocyclic ring;

25 R_{10} and R_{11} , which may be same or different at each occurrence, are independently selected from hydrogen, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, $-CR_aR_bC(O)NR_8R_9$ and $-(CR_aR_b)_m-CR_aR_bR_c$;

25 R_{12} , which may be same or different at each occurrence, is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl and heteroarylalkyl;

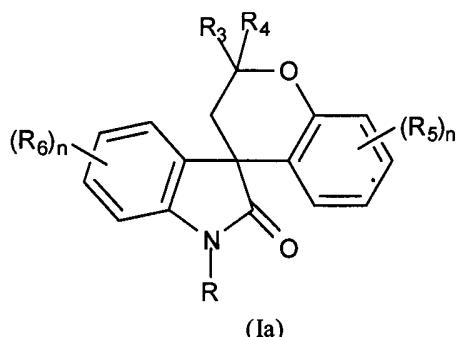
R_a, R_b and R_c, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, alkyl, heteroaryl and heterocycl; or R_a and R_b, together with the carbon atom to which they are attached, may form a substituted or unsubstituted 3 to 7 membered cyclic ring; wherein cyclic ring may be carbocyclic or heterocyclic;

- 5 ‘m’ is an integer ranging from 0 to 3, both inclusive;
‘n’ is an integer ranging from 0 to 4, both inclusive;
‘p’ is an integer ranging from 0 to 2, both inclusive;
‘q’ is an integer ranging from 1 to 2, both inclusive;
‘r’ and ‘s’ are independently an integer ranging from 0 to 4, both inclusive, provided
10 that the sum of ‘r’ and ‘s’ is at least 1 when ring B is present; and

wherein alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocycl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclalkyl wherever they occur may optionally be substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, oxo (=O), thio (=S),
15 alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclalkyl, heteroarylalkyl, -C(O)OR^x, -C(O)R^x, -C(S)R^x, -C(O)NR^xR^y, -NR^xC(O)NR^yR^z, -N(R^x)S(O)R^y, -N(R^x)S(O)₂R^y, -NR^xR^y, -NR^xC(O)R^y, -NR^xC(S)R^y, -NR^xC(S)NR^yR^z, -S(O)NR^xR^y, -S(O)₂NR^xR^y, -OR^x, -OC(O)R^x, -OC(O)NR^xR^y, -R^xC(O)OR^y, -R^xC(O)NR^yR^z, -R^xC(O)R^y, -SR^x, -S(O)R^x, and -S(O)₂R^x;
20 wherein each occurrence of R^x, R^y and R^z are independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclalkyl ring and heteroarylalkyl;

or a pharmaceutically acceptable salt thereof.

According to one embodiment are provided compounds of Formula (Ia):



or a pharmaceutically acceptable salt thereof;

wherein R, R₃, R₄, R₅, R₆ and 'n' are as defined above.

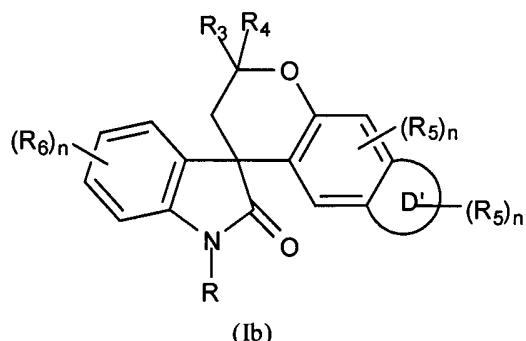
In a sub embodiment of Formula (Ia), compounds are provided in which R is
5 hydrogen alkyl, haloalkyl, cyanoalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl,
heterocyclalkyl or -C(O)R₁₂ wherein R₁₂ is substituted or unsubstituted aryl.

In a second sub embodiment of Formula (Ia), compounds are provided in which R₃ is
hydrogen or alkyl; and R₄ is alkyl, -C(O)R₁₂, or -C(O)OR₁₁ wherein R₁₁ and R₁₂ are
hydrogen or alkyl.

10 In a third sub embodiment of Formula (Ia), compounds are provided in which R₅ is
halogen, alkyl, -OR₁₀, wherein R₁₀ is hydrogen, alkyl, alkoxyalkyl, haloalkyl, aryl,
heteroaryl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, CR_aR_bC(O)NR₈R₉ or -(CR_aR_b)₁₋₂-CR_aR_bR_c wherein R_a, R_b and R_c are independently selected from hydrogen, alkyl,
heteroaryl and heterocyclyl (for example 2-oxooxazolidin-3-yl); or R_a and R_b together forms
15 a substituted or unsubstituted 3 to 7 heterocyclic ring; and 'n' is 1 or 2.

According to another embodiment are provided compounds of Formula (Ib):

12



or pharmaceutically acceptable salt thereof;

wherein R, R₃, R₄, R₅, R₆ and 'n' are as defined above; and

D' is 5 to 7 membered heterocyclic ring.

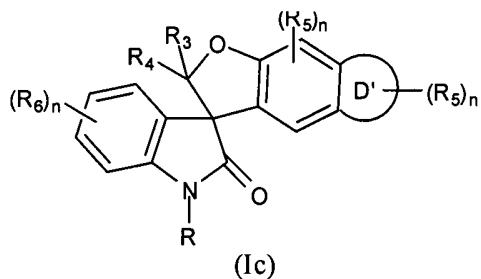
5 In a sub embodiment of Formula (Ib), compounds are provided in which D' is 5 or 6 membered heterocyclic ring for example 1, 3- dioxolane, or 1,4-dioxane.

In a second sub embodiment of Formula (Ib), compounds are provided in which R is hydrogen alkyl, haloalkyl, cyanoalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclalkyl or -C(O)R₁₂, wherein R₁₂ is aryl;

10 In a third sub embodiment of Formula (Ib), compounds are provided in which R₃ is hydrogen or alkyl; and R₄ is alkyl, -C(O)R₁₂, or -CO(O)R₁₁ wherein R₁₁ and R₁₂ are hydrogen or alkyl.

In a fourth sub embodiment of Formula (Ib), compounds are provided in which R₅ is halogen, alkyl and 'n' is 1 or 2.

15 According to another embodiment are provided compounds of Formula (Ic):

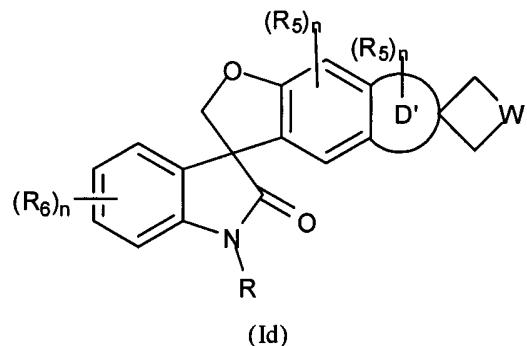


or a pharmaceutically acceptable salt thereof;

wherein, ring D' is 5 to 7 membered heterocyclic ring.

R, R₃, R₄, R₅, R₆ and 'n' are as defined herein above.

According to another embodiment are provided compounds of Formula (Id):



5

or pharmaceutically acceptable salt thereof;

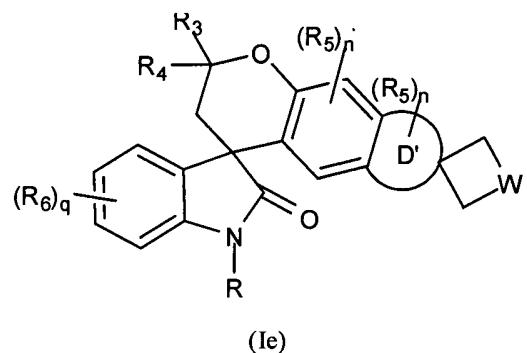
wherein, R, R₅, R₆ and 'n' are as defined herein above;

D' is 5 to 7 membered heterocyclic ring and

W is selected from a bond, -O-, -NR₈-, -S(O)_p-, -NR₈C(O)-; -CR₃R₄-, -NR₈C(O)-NR₈-

10 , -NR₈C(O)O-, -CR₃=N-, -C(=NR₈)-, -OC(O)- and -OC(O)O-.

According to another embodiment are provided compounds of Formula (Ie):



or pharmaceutically acceptable salt thereof;

wherein, R, R₃, R₄, R₅, R₆, 'n' and 'q', are as defined herein above;

D' is 5 to 7 membered heterocyclic ring; and

W is selected from a bond, -O-, -NR₈-, -S(O)_p-, -NR₈C(O)-; CR₃R₄, -NR₈C(O)-NR₈-, -NR₈C(O)O-, -CR₃=N-, -C(=NR₈)-, -OC(O)- and -OC(O)O-.

It should be understood that Formulae (I), (Ia), (Ib), (Ic), (Id) and (Ie) structurally

5 encompass all tautomers, stereoisomers, enantiomers, diastereomers, and pharmaceutically acceptable salts that may be contemplated from the chemical structures described herein.

In another aspect of the invention, there is provided a compound of Formula (I) useful in treating, preventing, managing and/or lessening the severity of the diseases, disorders, syndromes or conditions associated with VGSC.

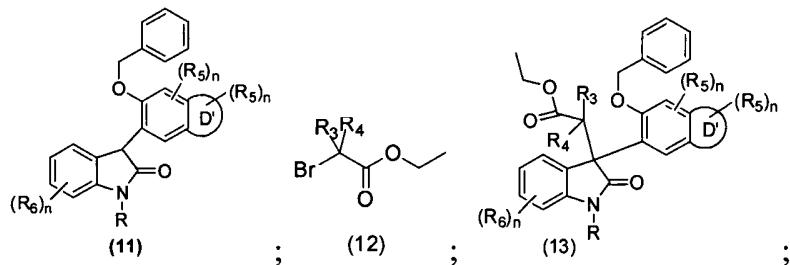
10 In another aspect, the invention provides a pharmaceutical composition comprising at least one compound of Formula (I) and at least one pharmaceutically acceptable excipient.

In another aspect, the invention provides a pharmaceutical composition of a compound of Formula (I) useful in treating, preventing, managing and/or lessening the severity of the diseases disorders, syndromes or conditions associated with VGSC in a 15 subject in need thereof by administering to the subject, one or more compounds described herein in an amount effective to cause modulation.

In another aspect of the invention are processes for the preparation of the compounds described herein.

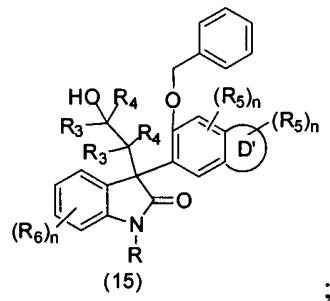
According to another embodiment are provided a process for the preparation compounds of 20 Formula (18):

a) alkylating compound (11) with compound (12) to give compound (13)

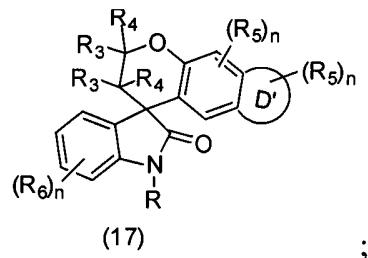


15

- b) treating compound (13) from step a) with an appropriately substituted Grignard reagent to give compound (15)

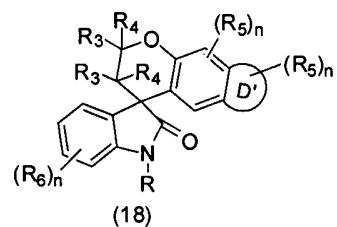


- c) deprotecting the benzylic hydroxyl group of compound (15) from step b)
5 followed by cyclisation to give compound (17)



and

- d) deprotecting compound (17) from step c) and alkylating with R-L where L is leaving group to give compound (18)



10

Definitions and Abbreviations:

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below.

For purposes of interpreting the specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa.

The terms "halogen" or "halo" means fluorine, chlorine, bromine, or iodine.

The term 'bond' means single bond.

5 The term "alkyl" refers to an alkane derived hydrocarbon radical that includes solely carbon and hydrogen atoms in the backbone, contains no unsaturation, has from one to six carbon atoms, and is attached to the remainder of the molecule by a single bond, *e.g.*, methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1- dimethylethyl (t-butyl) and the like. Unless set forth or recited to the contrary, all alkyl groups described or claimed
10 herein may be straight chain or branched, substituted or unsubstituted.

The term "alkylene" refers to a saturated divalent hydrocarbon radical that includes solely carbon and hydrogen atoms in the backbone. In particular, " C_1-C_5 alkylene" means a saturated divalent hydrocarbon radical with one to six carbon atoms *e.g.* methylene (- CH_2-), ethylene (- CH_2-CH_2-), 2,2-dimethylethylene, n-propylene, 2-methylpropylene, and the like.
15 Unless set forth or recited to the contrary, all alkylene groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

20 The term "alkenyl" refers to a hydrocarbon radical containing from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Non-limiting examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-but enyl, 2-but enyl and the like. Unless set forth or recited to the contrary, all alkenyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

25 The term "alkynyl" refers to a hydrocarbon radical containing to 10 carbon atoms and including at least one carbon- carbon triple bond. Non- limiting examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. Unless set forth or recited to the contrary, all alkynyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkoxy" refers to an alkyl group attached via an oxygen linkage. Non-limiting examples of such groups are -OCH₃ and -OC₂H₅. Unless set forth or recited to the contrary, all alkoxy groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

5 The term "cycloalkyl" refers to a non-aromatic mono or multicyclic ring system having 3 to 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups or spirobicyclic groups, *e.g.*, spiro(4,4)non-2-yl and the like. Unless set forth or recited to the contrary, all
10 cycloalkyl groups described or claimed herein may be substituted or unsubstituted.

15 The term "cycloalkylalkyl" refers to a cycloalkyl group as defined above, directly bonded to an alkyl group as defined above, *e.g.*, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl, etc. Unless set forth or recited to the contrary, all cycloalkylalkyl groups described or claimed herein may be substituted or
unsubstituted.

20 The term "haloalkyl" refers to an alkyl group as defined above that is substituted by one or more halogen atoms as defined above. Preferably, the haloalkyl may be monohaloalkyl, dihaloalkyl or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodine, bromine, chlorine or fluorine atom. Dihaloalkyl and polyhaloalkyl groups
25 can be substituted with two or more of the same halogen atoms or a combination of different halogen atoms. Preferably, a polyhaloalkyl is substituted with up to 12 halogen atoms. Non-limiting examples of a haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl and the like. A perhaloalkyl refers to an alkyl having all hydrogen atoms replaced with halogen atoms.

25 The term "hydroxyalkyl" refers to an alkyl group, as defined above that is substituted by one or more hydroxy groups. Preferably, the hydroxyalkyl is monohydroxyalkyl or

dihydroxyalkyl. Non-limiting examples of a hydroxyalkyl include 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, and the like.

The term "alkoxyalkyl" refers to an alkyl group, as defined above that is substituted by at least one alkoxy group as defined above, preferably one or two alkoxy groups, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, and the like. Unless set forth or recited to the contrary, all alkoxyalkyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "cyanoalkyl" refers to an alkyl group, as defined above that is substituted by one or more cyano groups (-CN). Preferably, the cyanoalkyl is monocyanoalkyl and the like.

The term "aryl" refers to an aromatic radical having 6 to 14 carbon atoms, including monocyclic, bicyclic and tricyclic aromatic systems, such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl and the like. Unless set forth or recited to the contrary, all aryl groups described or claimed herein may be substituted or unsubstituted.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., -CH₂C₆H₅ and -C₂H₄C₆H₅. Unless set forth or recited to the contrary, all arylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "heterocyclic ring" or "heterocyclyl ring" or "heterocyclyl", unless otherwise specified, refers to substituted or unsubstituted non-aromatic 3 to 15 membered ring which consists of carbon atoms and with one or more heteroatom(s) independently selected from N, O or S. The heterocyclic ring may be a mono-, bi- or tricyclic ring system, which may include fused, bridged or spiro ring systems and the nitrogen, carbon, oxygen or sulfur atoms in the heterocyclic ring may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized, the heterocyclic ring or heterocyclyl may optionally contain one or more olefinic bond(s), and one or two carbon atoms(s) in the heterocyclic ring or heterocyclyl may be interrupted with -C(O)-, -C(=N-alkyl)-, or -C(=N-cycloalkyl), etc. Non-limiting examples of heterocyclic rings include azepinyl, azetidinyl, benzodioxolyl, benzodioxanyl, chromanyl, dioxolanyl,

dioxaphospholanyl, decahydroisoquinolyl, indanyl, indolinyl, isoindolinyl, isochromananyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, oxazolinyl, oxazolidinyl, oxadiazolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, octahydroindolyl, octahydroisoindolyl, perhydroazepinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, piperidinyl, 5 phenothiazinyl, phenoazinyl, quinuclidinyl, tetrahydroisquinolyl, tetrahydrofuryl, tetrahydropyranly, thiazolinyl, thiazolidinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone and the like. The heterocyclic ring may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heterocycl groups described or claimed herein 10 may be substituted or unsubstituted.

The term "heteroaryl" unless otherwise specified, refers to a substituted or unsubstituted 5 to 14 membered aromatic heterocyclic ring with one or more heteroatom(s) independently selected from N, O or S. The heteroaryl may be a mono-, bi- or tricyclic ring system. The heteroaryl ring may be attached to the main structure at any heteroatom or 15 carbon atom that results in the creation of a stable structure. Non-limiting examples of a heteroaryl ring include oxazolyl, isoxazolyl, imidazolyl, furyl, indolyl, isoindolyl, pyrrolyl, triazolyl, triazinyl, tetrazolyl, thienyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, benzopyranyl, carbazolyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, naphthyridinyl, 20 pteridinyl, purinyl, quinoxaliny, quinolyl, isoquinolyl, thiadiazolyl, indolizinyl, acridinyl, phenazinyl, phthalazinyl and the like. Unless set forth or recited to the contrary, all heteroaryl groups described or claimed herein may be substituted or unsubstituted.

The term "heterocyclalkyl" refers to a heterocyclic ring radical directly bonded to an alkyl group. The heterocyclalkyl radical may be attached to the main structure at any 25 carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heterocyclalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "heteroarylalkyl" refers to a heteroaryl ring radical directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heteroarylalkyl groups described or claimed herein may be 5 substituted or unsubstituted.

Unless otherwise specified, the term "substituted" as used herein refers to a group or moiety having one or more substituents attached to the structural skeleton of the group or moiety. Such substituents include, but are not limited to hydroxy, halo, carboxyl, cyano, nitro, oxo (=O), thio (=S), alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, 10 cycloalkylalkyl, cycloalkenyl, amino, heteroaryl, heterocyclic ring, heterocyclalkyl, heteroarylalkyl, -C(O)OR^x, -C(O)R^x, -C(S)R^x, -C(O)NR^xR^y, -NR^xC(O)NR^yR^z, -N(R^x)S(O)R^y, -N(R^x)S(O)₂R^y, -NR^xR^y, -NR^xC(O)R^y, -NR^xC(S)R^y, -NR^xC(S)NR^yR^z, -S(O)NR^xR^y, -S(O)₂NR^xR^y, -OR^x, -OC(O)R^x, -OC(O)NR^xR^y, -R^xC(O)OR^y, -R^xC(O)NR^yR^z, -R^xC(O)R^y, -SR^x, -S(O)R^x, and -S(O)₂R^x; wherein each occurrence of R^x, R^y 15 and R^z are independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclalkyl ring and heteroarylalkyl.

The phrase "may optionally be substituted" refers to a moiety or group that may or may not be substituted. For example, "optionally substituted aryl" means that the aryl radical 20 may or may not be substituted and that the description includes both substituted and unsubstituted aryl radicals.

A "stereoisomer" refers to a compound having the same atoms bonded through the same bonds but having different three-dimensional orientations, which are not interchangeable. The invention contemplates various stereoisomers and mixtures thereof and 25 include enantiomers and diastereomers.

The term "or1", "or2", "or3" and "or4" is used to indicate stereochemistry at chiral centre. "or1", "or2", "or3" and "or4" indicates the stereochemistry at the chiral center could be

as draw (for example R) or the opposite one (for example S), but not the mixture of two possibilities.

The term "treating" or "treatment" of a state, disease, disorder, condition or syndrome includes: (a) preventing or delaying the appearance of clinical symptoms of the state, disease, disorder, condition or syndrome developing in a subject that may be afflicted with or predisposed to the state, disease, disorder, condition or syndrome but does not yet experience or display clinical or subclinical symptoms of the state, disease, disorder, condition or syndrome; (b) inhibiting the state, disease, disorder, condition or syndrome, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof; c) lessening the severity of a disease disorder or condition or at least one of its clinical or subclinical symptoms thereof; and/or (d) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The term "modulate" or "modulating" or "modulation" refers to a decrease or inhibition in the amount, quality, or effect of a particular activity, function or molecule; by way of illustration that antagonists of a voltage-gated sodium channels are modulators of VGSC. 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". For example, the compounds of invention are useful as modulators of the NAV1.7. 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 term "subject" includes mammals, preferably humans and other animals, such as domestic animals; e.g., household pets including cats and dogs.

A "therapeutically effective amount" refers to the amount of a compound that, when administered to a subject in need thereof, is sufficient to cause a desired effect. The

"therapeutically effective amount" will vary depending on the compound, the disease and its severity, age, weight, physical condition and responsiveness of the subject to be treated.

"Brine" refers to a saturated aqueous NaCl solution.

The following abbreviations are used throughout the specification:

5 "DMSO-D₆" refers to hexadeuterodimethyl sulfoxide;

"DMF" refers to N,N-dimethylformamide;

"J" refers to coupling constant in hertz (Hz);

"RT" refers to room temperature (22 to 26 °C);

"TLC" refers to thin layer chromatography

10 Pharmaceutically Acceptable Salts:

The compounds of the invention may form salts. In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Non-limiting examples of pharmaceutically acceptable salts are organic acid addition salts formed by addition of acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorate, α-ketoglutarate, α-glycerophosphate, formate, fumarate, propionate, glycolate, lactate, pyruvate, oxalate, maleate, and salicylate. Suitable inorganic salts may also be formed, including, sulfate, nitrate, bicarbonate, carbonate salts, hydrobromate and phosphoric acid.

20 Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

25 With respect to the overall compounds described by the Formula (I) the invention extends to stereoisomeric forms and to mixtures thereof. The different stereoisomeric forms

of the invention may be separated from one another by the method known in the art, or a given isomer may be obtained by stereospecific or asymmetric synthesis. Tautomeric forms and mixtures of compounds described herein are also contemplated.

Compound Screening:

5 The screening of compounds of the invention for VGSC modulatory activity can be achieved by using various *in vitro* and *in vivo* protocols. Some of the methods include measuring current (electrophysiology), estimating membrane potential (using membrane potential dyes or voltage specific dye pairs), measuring ion flux (*e.g.*, sodium or guanidium), measuring second messenger and transcription factor levels, measuring sodium concentration
10 or by Rubidium efflux assay. These assays can be performed in tissue slices or cell lines that endogenously express sodium channels (*e.g.* ND7/23, SHSY-5Y). Alternatively, one can also use cell lines stably expressing the Nav of interest (*e.g.*, stable cell lines generated in HEK293 cells or CHO cells).

Pharmaceutical Compositions:

15 The invention relates to pharmaceutical compositions containing the compound of Formula (I). In particular, the pharmaceutical compositions contain a therapeutically effective amount of at least one compound of Formula (I) and at least one pharmaceutically acceptable excipient (such as a carrier or diluent). Preferably, the pharmaceutical compositions include the compound(s) described herein in an amount sufficient to modulate
20 the ion flux through a voltage-dependent sodium channel to treat sodium channel mediated diseases such as pain when administered to a subject.

25 The compound of the invention may be incorporated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. The pharmaceutically acceptable excipient includes a 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.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicylic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents, preserving agents, salts for influencing osmotic pressure, buffers, sweetening agents, flavoring agents, colorants, or any combination of the foregoing. The pharmaceutical composition of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the subject by employing procedures known in the art.

The pharmaceutical compositions described herein may be prepared by conventional techniques known in the art. For example, the active compound can be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of an ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container, for example, in a sachet.

The pharmaceutical compositions may be administered in conventional forms, for example, capsules, tablets, aerosols, solutions, suspensions or products for topical application.

The route of administration may be any route which effectively transports the active compound of the invention to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal, parenteral, rectal, depot, subcutaneous, intravenous, intraurethral,

intramuscular, intranasal, ophthalmic (such as with an ophthalmic solution) or topical (such as with a topical ointment).

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and

5 lozenges. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Liquid formulations include, but are not limited to, syrups, emulsions, soft gelatin and sterile injectable liquids, such as aqueous or non-aqueous liquid suspensions or solutions. For parenteral application, particularly suitable are injectable solutions or suspensions formulation.

10 Liquid formulations include, but are not limited to, syrups, emulsions, suspensions, solutions, emulsions, soft gelatin and sterile injectable liquids, such as aqueous or non-aqueous liquid suspensions or solutions.

15 For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or 20 ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

For administration to human patients, the total daily dose of the compounds of the invention depends, of course, on the mode of administration. For example, oral administration may require a higher total daily dose, than an intravenous (direct into blood).
25 The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, and most typically 10 mg to 500 mg, according to the potency of the active component or mode of administration.

Suitable doses of the compounds for use in treating the diseases disorders, syndromes and conditions described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in humans based on preliminary evidence derived from the animal studies. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects for the patient. For example, the daily dosage of the Sodium channel modulator can range from about 0.1 to about 30.0 mg/kg. Mode of administration, dosage forms, suitable pharmaceutical excipients, diluents or carriers can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the invention.

10 **Methods of Treatment:**

In an embodiment the invention are provided compounds and pharmaceutical compositions that are useful in the treatment of diseases, disorders, syndromes and/or conditions modulated by Nav channel. The invention further provides a method of treating a disease, condition and/or disorder modulated by Nav channel in a subject in need thereof by 15 administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition of the invention.

One aspect of the invention provides methods for decreasing ion flow through voltage-gated sodium channels in a cell, comprising contacting a cell containing the target ion channels with a compound, associated to voltage-dependent gated ion channel, described 20 herein.

In another aspect of the invention, the methods are also useful for the diagnosis of conditions that can be treated by acting on ion flux through voltage-dependent gated ion channel, for determining if a patient will be responsive to therapeutic agents.

In still another aspect of the invention provides a method for the treatment of a disorder or condition through modulating a voltage-gated sodium channel. In this method, a 25 subject in need of such treatment is administered an effective amount of a compound described herein and/or according to Formula (I) described herein.

The compound of Formula (I), being a voltage-dependent gated sodium channel modulator, is potentially useful in the treating, preventing, managing and/or lessening of diseases, disorders, syndromes or conditions including but not limited to pain, erythromyalgia, neurological disorders, cardiovascular conditions, neuromuscular conditions, 5 multiple sclerosis, cancer, pruritis, benign prostatic hyperplasia (BPH) and the like.

Pain includes, but is not limited to, acute pain, musculoskeletal pain, post-operative pain, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain.

The compounds, compositions and methods of the invention are of particular use in treating, preventing, managing and/or lessening of pain including inflammatory, neuropathic, 10 nociceptive and idiopathic pain.

The compounds, compositions and methods of the invention are of particular use in treating, preventing, managing and/or lessening of pain including but not limited to postoperative pain, arthritis pain, osteoarthritis pain, pain associated with cancer including chemotherapy pain, neuropathic pain secondary to metastatic inflammation, neuralgic, 15 orofacial pain, burn pain, somatic pain, dental pain, sciatica pain, intestinal obstruction pain, visceral pain, colicky pain, myofacial pain, trauma pain, labour pain, trigeminal neuralgia, glossopharyngeal neuralgia, adiposis dolorosa, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, pain following stroke, 20 thalamic lesions, radiculopathy, chronic headache, migraine pain, familial hemiplegic migraine, conditions associated with cephalic pain, sinus headache, tension headache, cardiac pain arising from an ischemic myocardium, pain following stroke, neuropathy secondary to metastatic inflammation, pain due to connective tissue damage, and other forms of neuralgic, neuropathic, and idiopathic pain syndromes.

25 Idiopathic pain is pain of unknown origin, for example, phantom limb pain. Neuropathic pain is generally caused by injury or infection of the peripheral sensory nerves generally it includes, but is not limited to, pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and

vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies.

The compounds of the invention may be useful for treating certain types of inflammatory disease such as pancreatitis, which includes acute pancreatitis and chronic pancreatitis, is characterized by recurring or persistent abdominal pain with or without steatorrhea or diabetes mellitus, hereditary pancreatitis, pancreatic dysfunction. And it may also useful for treating the pain associated with pancreatitis and its related disorders.

The compounds of the invention may be useful for treating cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation.

Although no mutations in humans have been detected, Nav1.6 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, 8168-73). Nav1.7 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 Nav1.7 is also expressed in neuroendocrine cells associated with the autonomic system (Klugbauer, N., *et al. EMBO J.* (1995), 14, 1084-90) and as such has been implicated in autonomic processes. The compounds of the invention may be useful for treating Crohns disease, multiple sclerosis (MS) and pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), disseminated sclerosis, motor failure, ataxia, tremor, muscle weakness, and dystonia. 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).

The compounds of the invention may be useful for treating certain type of cancers for example prostate cancer, breast cancer, ovarian cancer, testicular cancer, thyroid neoplasia. The VGSC's are reported to have been expressed in prostate and breast cancer cells. Nav1.5

has been identified in breast cancer cells and the enhanced expression of this isoform was associated with strong metastatic potential in vitro and breast cancer progression in vivo. (Fraser *et al.* *Clin. Cancer Res.* (2005), 11, 5381-5389). Expression of Nav1.7 is upregulated ~20 fold in prostate cancer. Moreover, the expression correlates with high metastatic 5 potential in vitro. (*Current Pharmaceutical Design* (2006), 12, 3681-3695; *Prostate Cancer and Prostatic Diseases* (2005), 8, 266-273).

The compounds of invention may be useful in the treatment of epilepsy, partial and general tonic seizures, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions caused by stroke, glaucoma or neural trauma, neuromuscular conditions such as 10 restless leg syndrome and muscle paralysis or tetanus.

The compounds of invention may be useful in the treatment of pruritus and related diseases such as psoriatic pruritis, itch due to hemodialysis, aguagenic pruritis, itching caused by skin disorders, allergic itch, insect bite itch, itch caused by hypersensitivity such as dry skin, acne, eczema, psoriasis or injury, itch caused by vulvar vestibulitis and the similar itch.

15 The compounds of the invention may be useful in treating or preventing symptoms associated with BPH (benign prostate hyperplasia) including but not limited to acute urinary retention and urinary tract infection.

General Methods of Preparation:

The compounds described herein may be prepared by techniques known in the art. In 20 addition, the compounds described herein may be prepared by following the reaction sequence as depicted in Schemes 1 to 12. where D', R, R₃, R₄, R₅, R₆, and 'n' are as defined herein above, L is any leaving group such as halogen, X' is halogen, R' is H, substituted or unsubstituted alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, R" is hydrogen, alkyl etc.,. Further, in the following schemes, where specific bases, acids, reagents, 25 solvents, coupling agents, etc. are mentioned, it is understood that other bases, acids, reagents, solvents, coupling agents etc., known in the art may also be used and are therefore included within the scope of the present invention. Variations in reaction conditions, for

example, temperature and/or duration of the reaction, which may be used as known in the art are also within the scope of the present invention. All the isomers of the compounds described in these schemes, unless otherwise specified, are also encompassed within the scope of this invention.

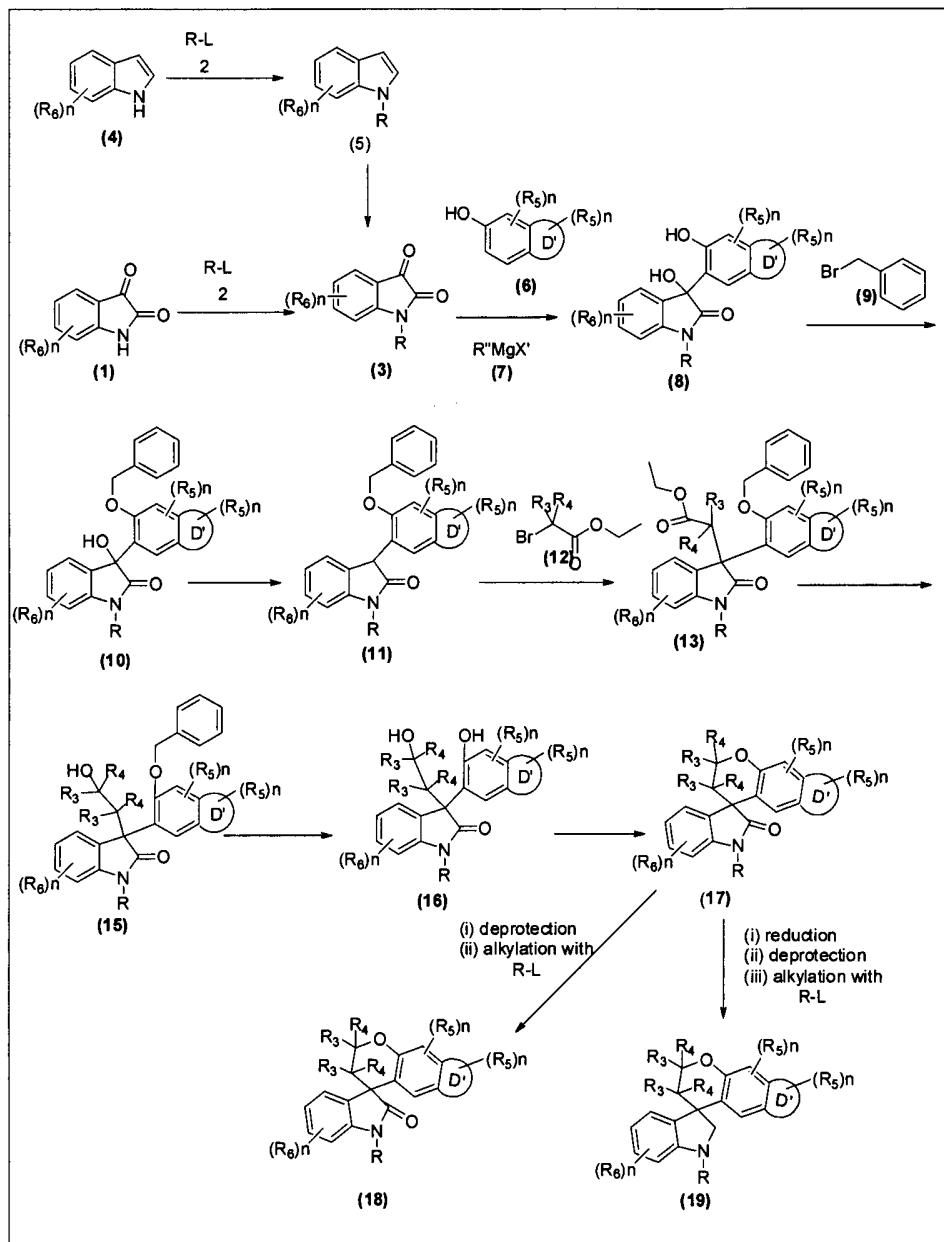
- 5 The compound of formula (18) and formula (19) can be prepared by sequential transformations as depicted in Scheme-1, where D', R, R₃, R₄, R₅, R₆, and 'n' are as defined herein above.

The compounds of formula (3) can be prepared by doing alkylation of isatin compound of formula (1) with alkylating agent of formula (2) using suitable base such NaH, Cs₂CO₃ or K₂CO₃ in solvents such as tetrahydrofuran (THF) or dimethylformamide (DMF).
10 The compound of formula (3) can also be prepared from indole compound of formula (4). The compound of formula (4) can be reacted with suitable alkylating agent of formula (2) followed by oxidation using *N*-bromosuccinimide (NBS) in dimethyl sulfoxide to afford the compound of formula (3). Phenoxy magnesium halide (Phenol compound of formula (6) is
15 treated with Grignard reagent of formula (7) at low temperature) can be reacted with the compound of formula (3) in suitable solvent such as, dichloromethane or tetrahydrofuran to afford the oxinole of formula (8). The compound of formula (8) is treated with benzyl halide of formula (9) in presence of a base such as Cs₂CO₃ and solvent such as DMF to afford mono benzylated compound of formula (10). The compound of formula (10) is treated with
20 trifluoroacetic acid and triethyl silane to obtain the dehydroxylated compound of formula (11). Alternatively, the same product can be prepared by treating the compound of formula (10) with thionylchloride/ triethylamine followed by reduction with zinc dust. The compound of formula (11) is then treated with an alkylating reagent such as ethyl boromoacetate (12) with a base such as NaH in a solvent such as THF or DMF to give the compound of formula
25 (13). The ester compound of formula (13) is then treated with Grignard reagent (Grignard complex appropriately substituted with R₃ or R₄) at low temperature in solvents such as, but not limited to THF or toluene to give disubstituted alcohol compound of formula (15). The debenzylation of compound of formula (15) is carried out using reagent such as ammonium

formate and Pd/C in solvents such as, but not limited to methanol or ethyl acetate to form compound of formula (16). The compound of formula (17) is synthesized through cyclization from compound of formula (16) using acid such as, but not limited to *p*-toluene sulfonic acid in solvent such as, but not limited to benzene or toluene. Compound (17) is transformed to 5 compound (18) by following the sequential transformations those are deprotection and alkylation with R-L (R is suitable substituent as defined herein above) using the methods known in the art of organic synthesis.

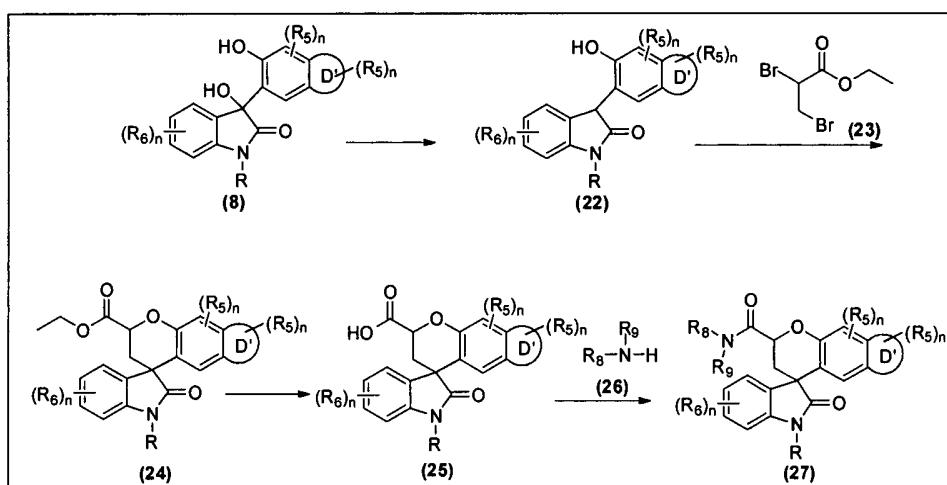
Alternatively, Compound (17) is then transformed to compound (19) by following the sequential transformations those are reduction, deprotection and alkylation with R-L (R is 10 suitable substituent as defined herein above) using the methods known in the art of organic synthesis.

Scheme-1



The compound of formula (22) is synthesized from compound of formula (8) using reagents such as, but not limited to trifluoroacetic acid and triethyl silane. The compound of formula (22) is further subjected for alkylation reaction using compound (23) and base such as but not limited to cesium carbonate in solvents such as, but not limited to DMF to result

compound of formula (24). The compound of formula (25) is obtained through hydrolysis of compound of formula (24) using base such as, but not limited to LiOH in solvent such as but not limited to THF and water. The compound of formula (27) is synthesized from compound of formula (25) using reagent such as, but not limited to 1-ethyl-3-(3-Dimethylaminopropyl)carbodiimide acrbodimide and N-hydroxy benzotrizole and compound of formula (26) in solvents such as, but not limited to dichloromethane.

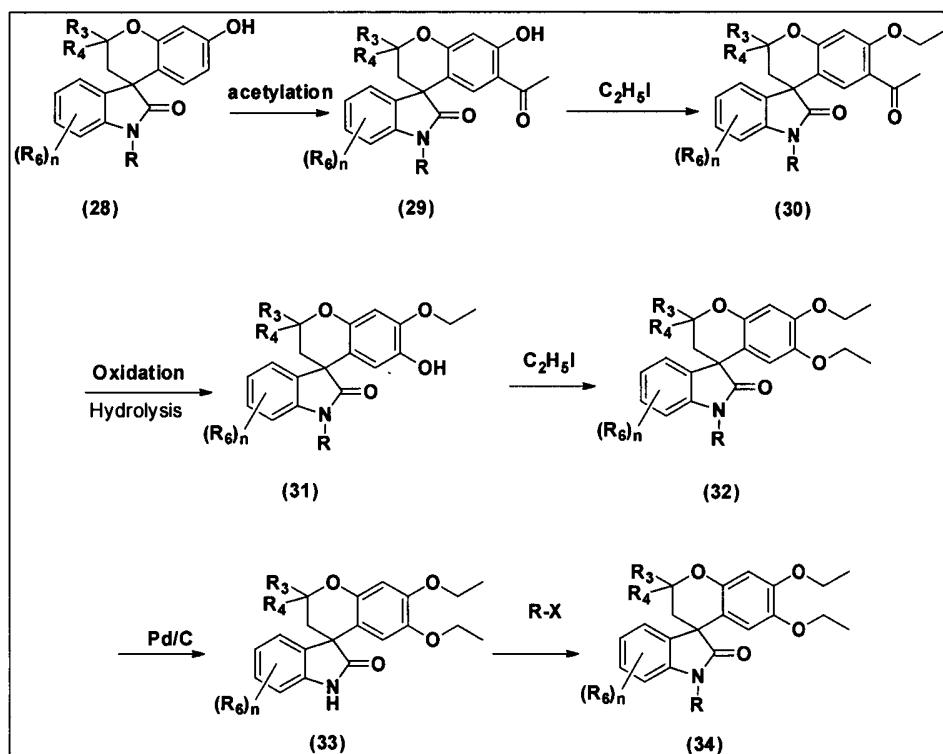
Scheme-2

10 The compound of formula (29) is synthesized from compound of formula (28) by Friedel Craft acylation reaction using reagents such as, but not limited to acetyl chloride and aluminium chloride and solvents such as but not limited to dichloromethane. The compound of formula (30) is synthesized from compound of formula (29) using reagent such as but not limited ethyl iodide and base such as but not limited to potassium carbonate in solvent such
15 as but not limited to DMF. The compound of formula (31) is synthesized by oxidation followed by hydrolysis using reagents such as but not limited to m-chloroperbenzoic acid in solvent such as but not limited to dichloromethane and hydrolysis is done using base such as but limited to sodium hydroxide in solvent methanol and water mixture. The compound of formula (32) is obtained through alkylation using ethyl iodide and base such as but not limited
20 to potassium carbonate in solvents such as but not limited to DMF. The compound of formula (33) is synthesized from compound of formula (32) using reagents such as but not

limited to ammonium formate and Pd/C in solvents such as but not limited to ethyl acetate. The compound of formula (34) is synthesized from compound of formula (33) using N-alkylation reaction.

Scheme-3

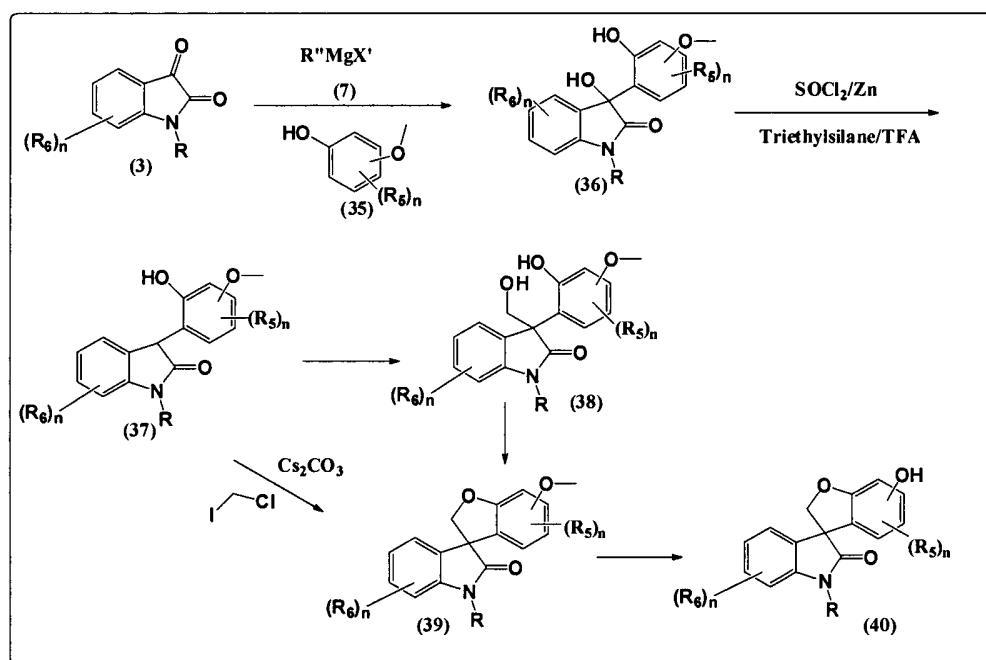
5



Compound of formula (39) can be prepared according to methods known in the art or by the methods disclosed in PCT published patent application WO2010/045251. The phenol of compound of formula (35) is treated with a Grignard reagent of formula (7) at low temperature to form the phenoxy magnesium halide Intermediate, which reacts with the compound of formula 3 in a solvent such as, but not limited to dichloromethane or tetrahydrofuran at 0-100°C to afford the compound of formula (36). The compound of formula (36) is treated with triethylsilane and trifluoroaceticacid to obtain the deoxygenated product of formula (37). Alternatively the same product can be prepared by treating the compound of formula (36) with thionylchloride and triethylamine followed by reduction with

zinc dust. The compound of formula (37) is then treated with an alkylating reagent such as but not limited to chloroiodomethane with a base such as Cs_2CO_3 in a solvent such as tetrahydrofuran or DMF to give the compound of formula (39). Alternatively the compound of formula (39) can be prepared from the compound of formula (38) by a Mitsunobu reaction, using a reagent such as triphenylphosphine or tributylphosphine and azadicarboxylate of diethyl or diisopropyl in a solvent such as tetrahydrofuran, dichloromethane etc., which in turn can be prepared from the compound of formula (37) using ytterbium (III) trifluoromethane sulfonate and formaldehyde or by treating a compound of formula 37 with a base such as lithium diisopropylamide (LDA), LiOH with formaldehyde. The compound of formula (39) is then demethylated by treating with BBr_3 in a halogenated solvent such as dichloromethane at -70°C -room temperature to afford a compound of formula (40).

Scheme-4

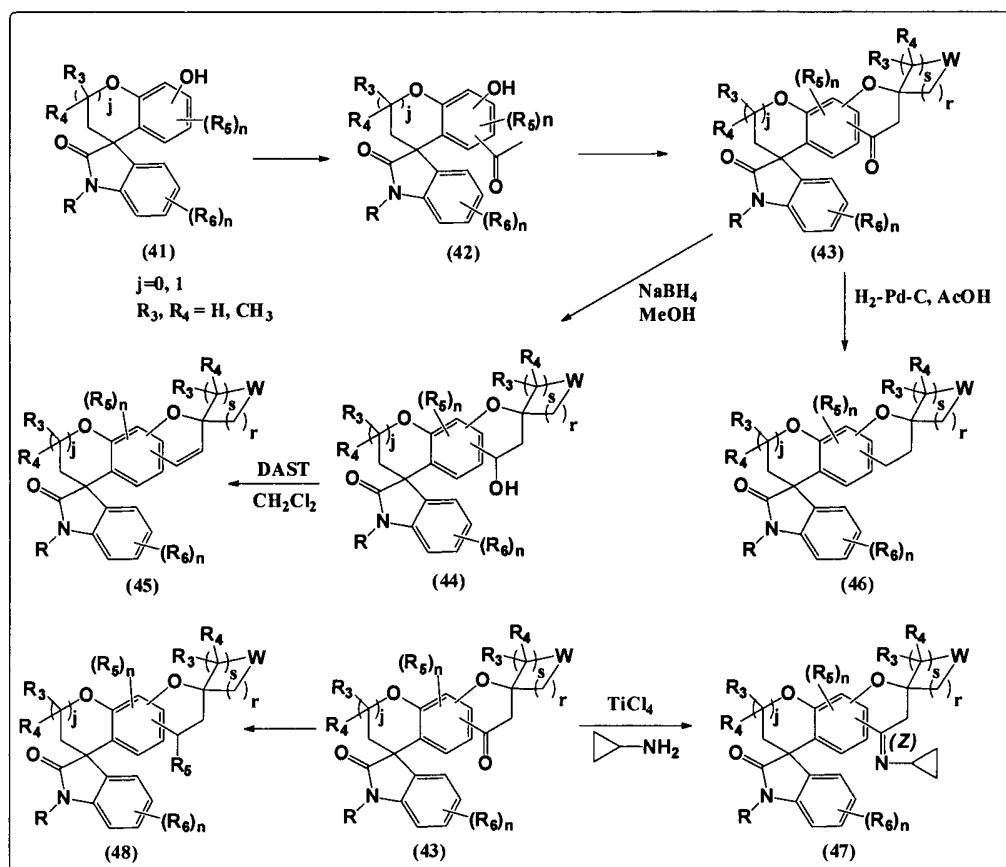


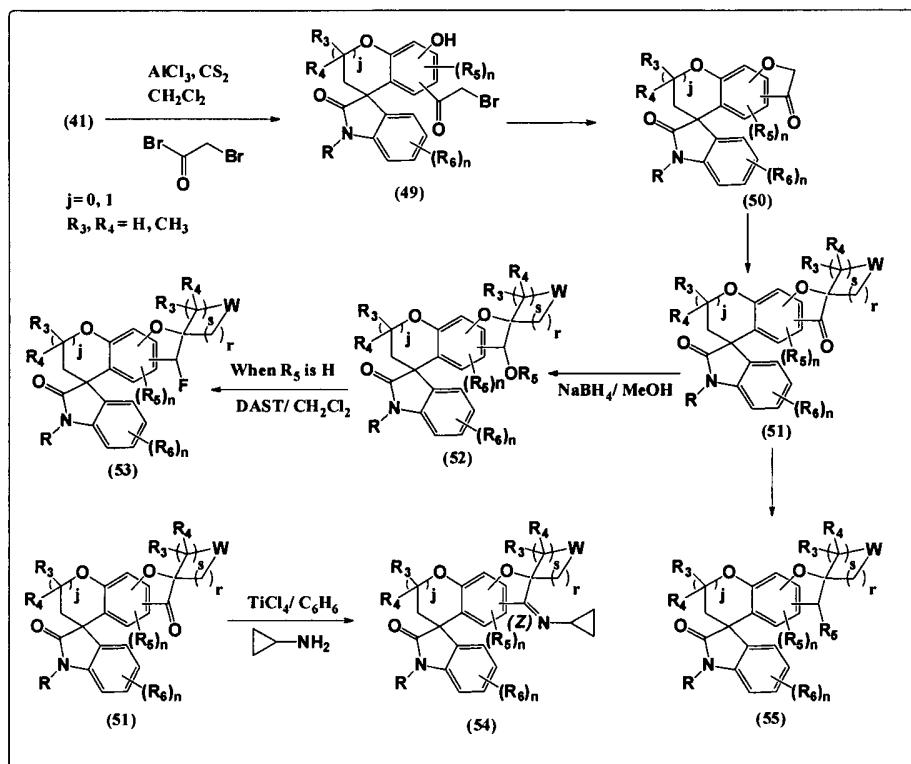
15 The compound of formula (41) is treated with acetylchloride in presence of aluminum chloride in a suitable solvent such as dichloromethane to obtain a compound of formula (42). The compound of formula 42 is then converted to the compound of formula (43) by refluxing with pyrrolidine and the corresponding cyclicketone in a suitable solvent such as methanol

(WO 200742906A1). Compound of formula (43) can be converted to compound of formula (44) by reduction with sodium borohydride in methanol, which can be converted to compound of formula (45) by treating with reagents such as but not limited to diethylamino sulphur trifluoride in a solvent such as dichloromethane. The carbonyl group of compound 5 (43) can also be converted to corresponding hydrocarbon compound (46) by refluxing in acetic acid with Pd/C under hydrogen atmosphere. The compound (43) can also be converted to imine of formula (47) by treating with titanium tetrachloride and cyclopropyl amine in benzene. Benzylic oxidation of compound of formula (46) can be done with reagents but not limited to ceric ammonium nitrate in solvents such as acetic acid, water and ether to obtain a 10 compound of formula (43). The carbonyl group of compound of formula (43) can be converted to R₅ using different methods known in the art to obtain a compound of formula (48).

The compound of formula (41) is then converted to compound of formula (49) by 15 treating with reagents such as bromoacetyl bromide and aluminum chloride in a solvent such as carbon disulphide methylene chloride. The compound of formula (49) can be converted to compound of formula (50) using a base such as but not limited to potassium carbonate in a solvent such as acetone via an intramolecular cyclisation. A spirocyclic ring on compound (50) can be generated by using the corresponding dibromide or diiodide, a base such as sodiumhydride and a suitable solvent such as THF to afford a compound of formula (51). 20 The carbonyl group of compound of formula (51) can be converted to corresponding alcohol (52) by reduction with sodium borohydride in methanol, which can be converted to corresponding fluoro derivative (53) by treating with diethylamino sulphur trifluoride in a solvent such as dichloromethane. The compound (51) can also be converted to corresponding imine of formula (54) by treating with titanium tetrachloride and cyclopropyl amine in a 25 solvent such as benzene. The carbonyl group of compound of formula (51) can also be converted to R₅ using different methods known in the literature to obtain a compound of formula (55).

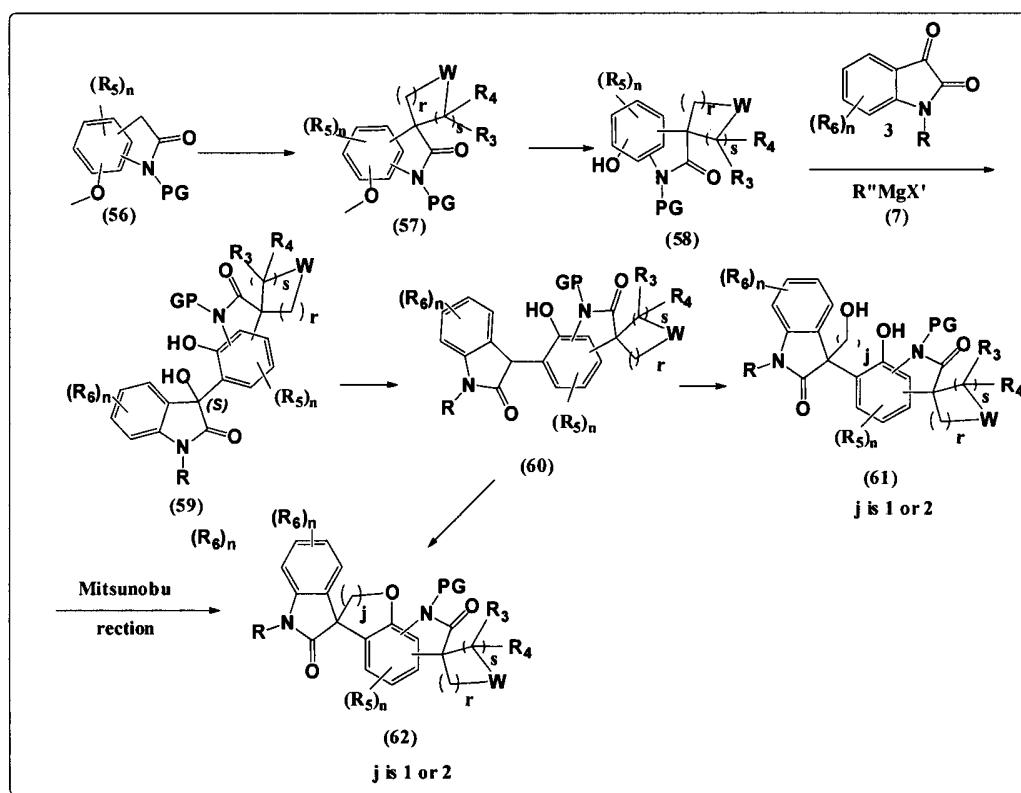
Scheme-5a

**Scheme-5b**



A compound of formula (56) can be prepared as described for structurally related compounds in the literature (*Synthetic Communication*, vol. 24, 4, 533-548, 1994). The spirocyclic ring of compound of formula (57) can be generated but not limited to, by using the corresponding dibromide or diiodide and a base such as sodiumhydride in a suitable solvent such as THF. The demethylation of compound of formula (57) can be carried out with BBr_3 in a suitable solvent such as dichloromethane at a temperature -78°C - room temperature to afford a compound of formula (58). The phenol of compound of formula (58) is treated with a Grignard reagent of formula (7) at low temperature to form the phenoxy magnesium halide Intermediate, which reacts with the keto carbonyl group of the isatin compound of formula (3) in a solvent such as, but not limited to dichloromethane or tetrahydrofuran to afford the oxindole of formula (59). The compound of formula (59) was treated with trimethylsilane and trifluoroaceticacid to obtain the deoxygenated product of formula (60). Alternatively the same product can be prepared by treating the compound of formula (59) with thionylchloride/triethylamine followed by reduction with zinc dust. The compound of formula (60) is then treated with an alkylating reagent such as but not limited to

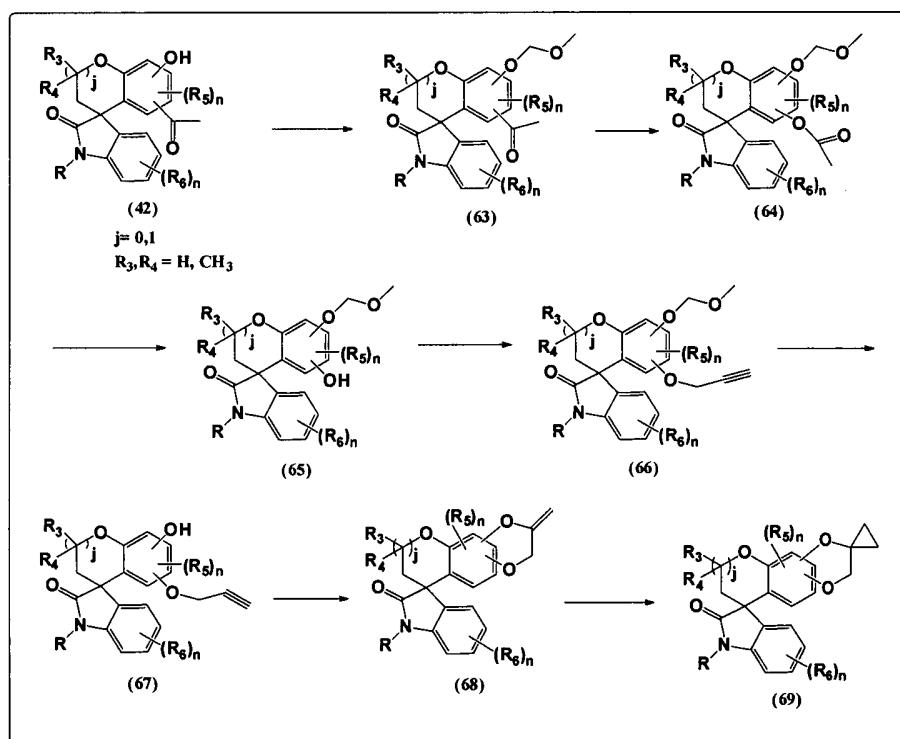
chloroiodomethane or dibromoethane with a base such as Cs_2CO_3 in a solvent such as tetrahydrofuran or DMF to give the compound of formula (62). Alternatively the compound of formula (62) can be prepared from the compound of formula (61) by a Mitsunobu reaction, using a phosphine reagent such as triphenylphosphine or tributylphosphine and 5 azadicarboxylate of diethyl or diisopropyl in a solvent such as tetrahydrofuran, dichloromethane etc., which in turn can be prepared from the compound of formula (60) using ytterbium (III) trifluoromethane sulfonate and formaldehyde or by treating with a base such as LDA, LiOH with formaldehyde.

Scheme-6

10

The compound of formula (42) is treated with MOM chloride in the presence of a base such as NaH and in a suitable solvent such as DMF to obtain a compound of formula (63). Baeyer-Villiger reaction of compound of formula (63) can give an ester of formula (64) and subsequent hydrolysis of the ester gives a phenol of formula (65). The phenol can be 15 alkylated using a base such as potassium carbonate but not limited to this method, with

propargylbromide to give a compound of formula (66). Compound of formula (67) can be obtained by the deprotection of MOM group using 50% TFA (trifluoroaceticacid) in dichloromethane at a temperature 0°C to room temperature and subsequent cyclisation can be carried out with CuI and a base such as triethylamine at a temperature 50-100°C to obtain a 5 compound of formula (68). The spirocyclopropane ring of compound of formula (69) can be generated using diethylzinc in a suitable solvent such as dichloromethane under reflux for 15-25 hours.

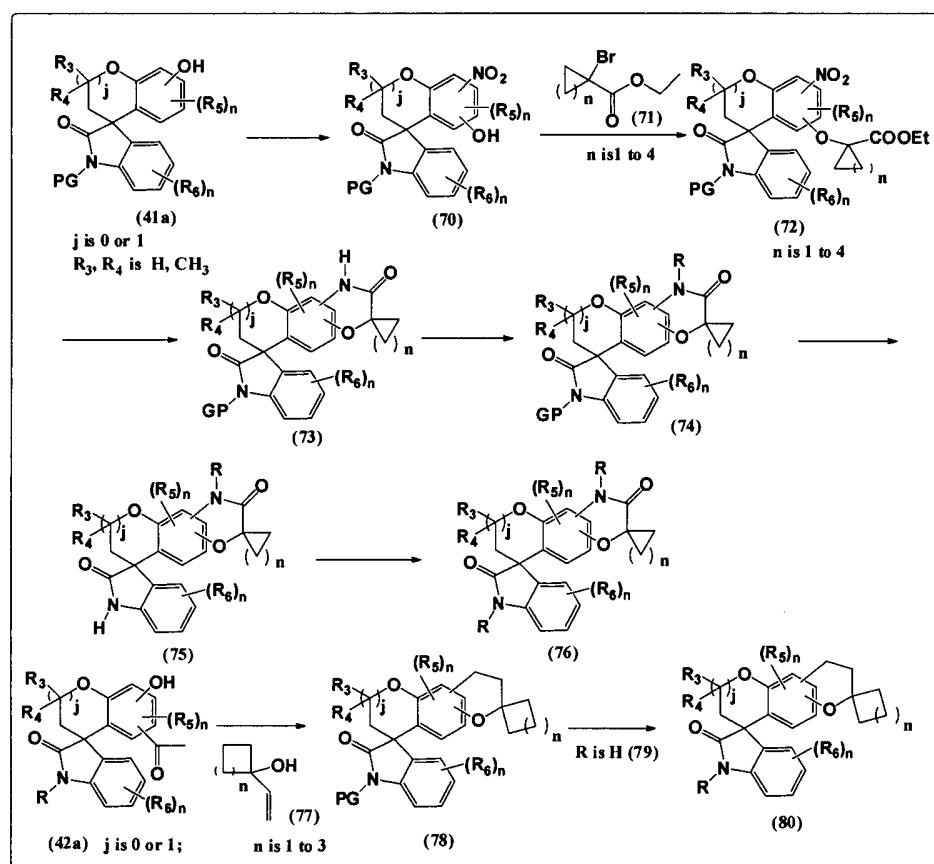
Scheme-7

10 A compound of formula (41)a is treated with KHSO_4 and sodium nitrite in a suitable solvent such as acetonitrile at 50°C to obtain a compound of formula (75). O-alkylation of compound of formula (70) with a compound of formula (71) using a base such as K_2CO_3 in a suitable solvent such as acetonitrile can afford a compound of formula (72). The nitro group of compound of formula (72) can be reduced with iron powder in a solvent such as acetic acid and at a temperature 60°C to afford a compound of formula (73) (*Bioorganic and Medicinal Chemistry*, vol.15, 17, 5912-5949, 2007). The amide nitrogen of compound of
 15

formula (73) can be protected with a suitable group using a base such as NaH and a polar solvent DMF to obtain a compound of formula (74). The protecting group of compound of formula (74) can be removed with reagents such as TFA and triflic acid in a suitable solvent such as dichloromethane to obtain a compound of formula (75) and subsequently alkylated 5 using a suitable base such as NaH in a solvent such as DMF to obtain a compound of formula (76).

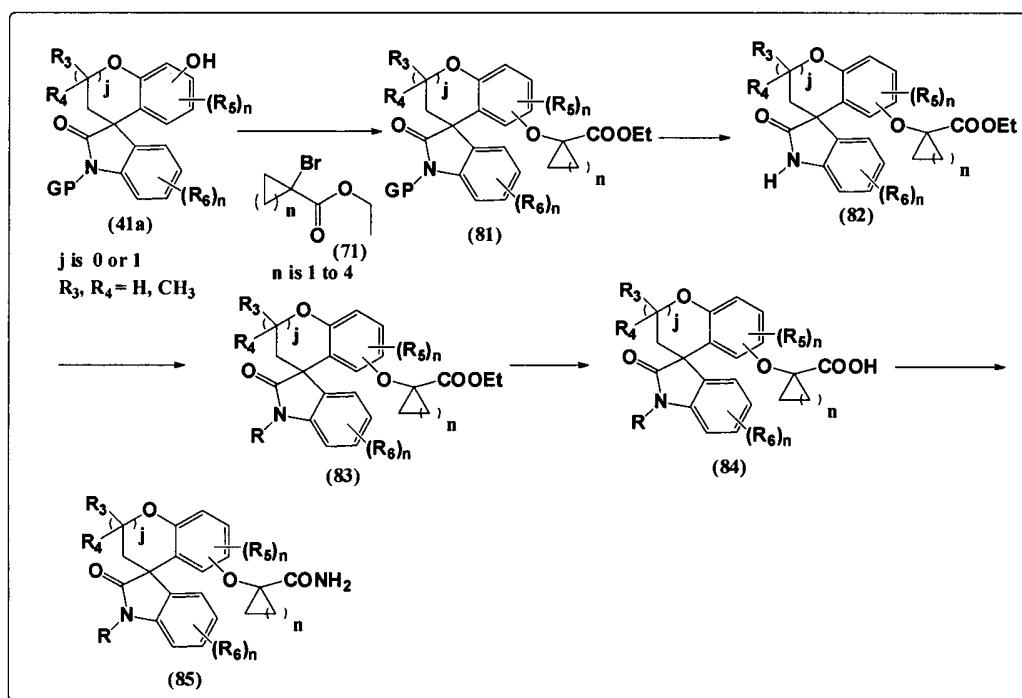
A compound of formula (42a) can be converted to a compound of formula (78) by treating with compound of formula (77) in presence of BF_3 - etherate and in a solvent such as dioxane at 110°C for 1-2 hours. The protecting group of compound of formula (78) can be 10 removed with a mild method such as TFA and triflic acid to afford a compound of formula (79). The amide nitrogen of compound of formula (79) can be protected with a suitable group using a base such as NaH and a polar solvent DMF to obtain a compound of formula (80).

Scheme-8



The hydroxy group of compound of formula (41a) can be alkylated with a compound of formula (71) using a base such as K_2CO_3 in a polar solvent such as DMF at 30-100°C or using microwave to obtain a compound of formula (81). The protecting group of compound of formula (81) can be removed using a suitable method known in the art to afford a 5 compound of formula (82) and subsequently the amide nitrogen of compound of formula (82) can be alkylated with a suitable group using a base such as NaH and a solvent like DMF at 0-100°C to afford a compound of formula (83). The ester group of compound of formula (83) can be hydrolysed using a base such as NaOH in a solvent such as methanol and water to obtain a compound of formula (84) and subsequently the carboxylic acid can be converted to 10 its amide using reagents such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), 1-hydroxybenzotriazole (HOBr) and aqueous NH_3 in a solvent such as dichloromethane at 0-room temperature for 15-25 hours to obtain a compound of formula (85).

Scheme-9

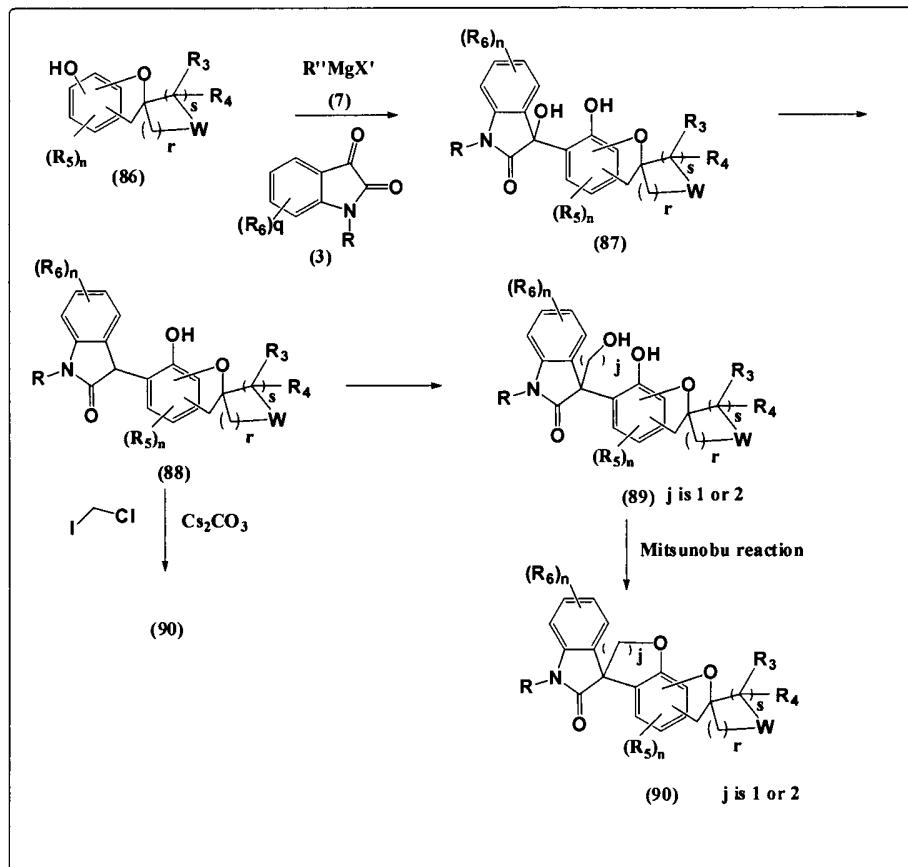


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A compound of formula (86) can be prepared as described for structurally related compounds in the literature. The phenol of compound of formula (86) is treated with a

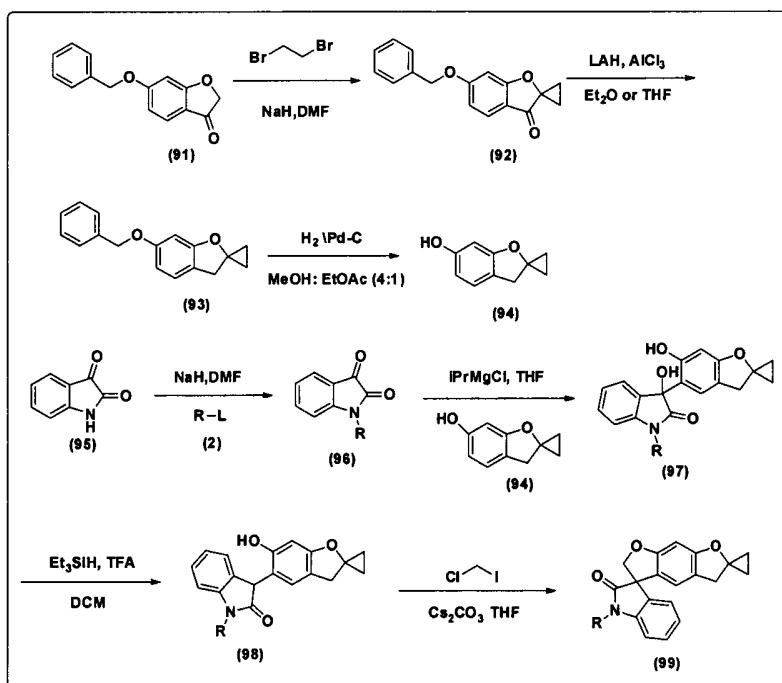
Grignard reagent of formula (7) at low temperature to form the phenoxy magnesium halide Intermediate, which reacts with the keto carbonyl group of the isatin compound of formula (3) in a solvent such as, but not limited to dichloromethane or tetrahydrofuran to afford the oxindole of formula (87). The compound of formula (87) is treated with trimethylsilane and 5 trifluoroacetic acid to obtain the deoxygenated product of formula (88). Alternatively the same product can be prepared by treating the compound of formula (87) with thionylchloride/triethylamine followed by reduction with zinc dust. The compound of formula (88) is then treated with an alkylating reagent such as but not limited to chloriodomethane or dibromoethane with a base such as Cs₂CO₃ in a solvent such as 10 tetrahydrofuran or DMF to give the compound of formula 90. Alternatively the compound of formula (90) can be prepared from the compound of formula (89) by a Mitsunobu reaction, using a phosphine reagent such as triphenylphosphine or tributylphosphine and azadicarboxylate of diethyl or diisopropyl in a solvent such as tetrahydrofuran, dichloromethane etc., which in turn can be prepared from the compound of formula 88 using 15 ytterbium (III) trifluoromethane sulfonate and formaldehyde or by treating with a base such as LDA, LiOH with formaldehyde.

Scheme-10



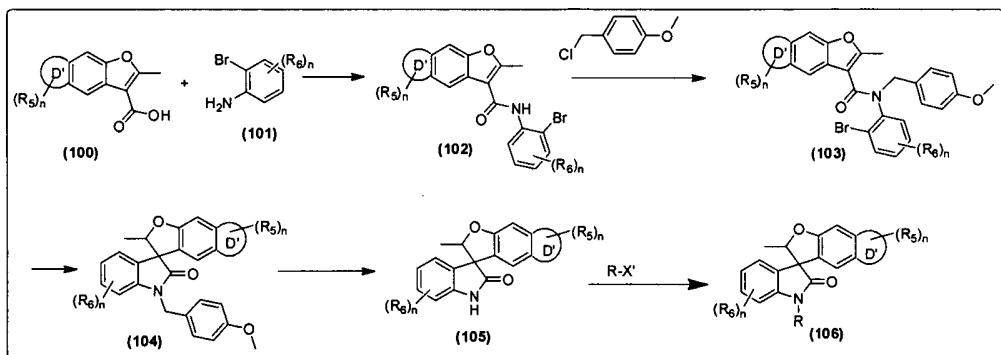
Compound (91) was treated with 1,2-dibromoethane in presence of a base such as NaH in a solvent such as DMF to obtain a compound (92) which was reduced with a mixture of lithium aluminium hydride (LAH) and AlCl_3 in ether to get a compound (93). Compound 5 (93) was then hydrogenated in ethyl acetate with Pd-C toyield compound (94). Compound (94) was treated with compound (96) in presence of isopropylmagnesium chloride to obtain dihydroxy compound (97), which was deoxygenated with TFA/triethylsilane in a solvent dichloromethane to produce a compound (98). Compound (98) was cyclised to form a compound (99) with chloroiodomethane using a base cesium carbonate and in a solvent such 10 as THF.

Scheme-11



The compound of formula (102) can be prepared by reacting compound of formula (100) with compound of formula (101) using reagents such as, but not limited to thionyl chloride, triethylamine in solvents such as but not limited to dichloromethane. The compound of formula (103) can be synthesized from compound of formula (102) by *N*-alkylation reaction. The compound of formula (103) further converted to compound of formula (104) using reagents such as, but not limited to tributyl tin hydride and azo bis isobutyronitrile (AIBN) in solvents such as but not limited to toluene. The compound of formula (105) can be prepared from compound of formula (104) using reagents such as but not limited to TFA and trifluoromethanesulfonic acid in solvent such as but not limited to dichloromethane. Finally the compound of formula (106) can be prepared by *N*-alkylation reaction of compound of formula (105).

Scheme-12



Experimental Procedures

Unless otherwise stated, work-up implies the following operations:

- 1) distribution of the reaction mixture between the organic and aqueous phase;
- 5 2) separation of layers;
- 3) drying the organic layer over sodium sulfate; and
- 4) filtration and evaporation of the organic solvent.

Purification, unless otherwise mentioned, implies purification by silica gel chromatographic techniques, generally using an ethyl acetate/petroleum ether mixture of
10 suitable polarity as the mobile phase.

Intermediates

Intermediate-1: 1-((Tetrahydrofuran-2-yl) methyl)-1*H*-indole:

To a stirred solution of NaH (10.25 g, 0.427 mol) in dry DMF (50.0 ml) at 0 °C was added a solution of indole (10.0g, 0.085mol) in 50.0 ml of dry DMF dropwise. The solution was
15 stirred for 1h at 0 °C. Meanwhile prepared a solution of tetrahydrofurfuryl chloride (12.88g, 0.106 mol) in 30.0 ml of dry DMF. This solution was added to the reaction mixture maintained at 0 °C dropwise. The course of reaction was monitored with TLC. After addition the reaction was stirred at room temperature overnight. The reaction mixture was quenched with addition of ice water, the phases were separated. The reaction mixture was extracted
20 with EtOAc (2 x 500 ml). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was

purified by column chromatography, with an isocratic elution of 40% ethyl acetate in petroleum ether to afford the title compound (13.0 g, 76 %) as brownish black oil. MS (ES+) m/z: 201.26 (M+1).

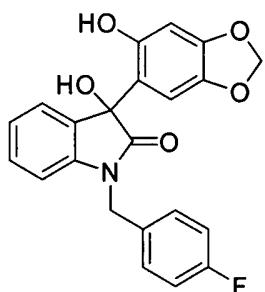
Intermediate-2: 1-((Tetrahydrofuran-2-yl) methyl) indoline-2, 3-dione:

- 5 To a ice cold solution of Intermediate-1 (10.0 g, 0.049 mol) in 100.0 ml of dry DMSO was added *N*-bromosuccinimide (NBS) (26.53g, 0.149 mol) lot wise. Temperature of reaction mixture was maintained between 0 °C to 5 °C. Reaction mixture was allowed to room temperature. Reaction mixture was then heated to reflux and maintained for 4.0 h. The course of the reaction was monitored my TLC. After completion of reaction, the reaction was
10 quenched with addition of ice water, the phases were separated. The reaction mixture was extracted with EtOAc (2 x 250 ml). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 40% ethyl acetate in petroleum ether to afford the title compound (9.0 g, 78 %) as orange oil. MS (ES+)
15 m/z: 231.25 (M+1).

Intermediate-3: 1-(4-Fluorobenzyl)indoline-2,3-dione:

- To a stirred solution of isatin (10 g, 67 mmol) in dry DMF (100 ml) at 0 °C was added NaH (2.1 g, 87.5 mmol) step wise. The solution was stirred for 1h at 0 °C. The *p*-fluorobenzyl bromide (11 mL, 81.1 mmol) was added dropwise. The course of reaction was monitored
20 with TLC. After addition the reaction was stirred at room temperature for 3 h. The reaction mixture was quenched with addition of ice water, the phases were separated. The reaction mixture was extracted with EtOAc (2 x 250 ml). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 40%
25 ethyl acetate in petroleum ether to afford the title compound (14 g, 82%) as an off white solid. MS (ES+) m/z: 256.1 (M+1).

Intermediate-4: 1-(4-Fluorobenzyl)-3-hydroxy-3-(6-hydroxybenzo [d][1,3]dioxol-5-yl)indolin-2-one:



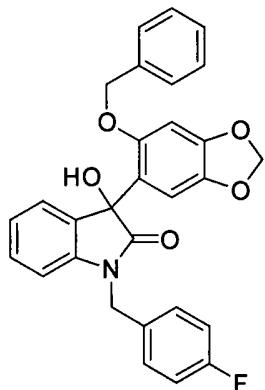
To an ice cooled solution of sesamol (2.70g, 19.5 mmol) in dry THF (75 mL) was added dropwise isopropyl magnesium chloride (10.80 mL, 21.5 mmol, 2.0 M in THF). The reaction mixture was stirred at 0 °C for 30 min, upon which time the colorless precipitate was formed.

5 The residue was partially dissolved in dichloromethane (50 mL) and the whole reaction mixture was added dropwise using dropping funnel to a solution of Intermediate-3 (5 g, 19.58 mmol) in dichloromethane (75 mL) at 0 °C. The course of reaction was monitored with TLC. After 8 h the reaction mixture was quenched with addition of saturated ammonium chloride (30 mL). The organic phase was evaporated *in vacuo* to dryness. The residue was extracted with EtOAc (2 x 100 ml). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 30% ethyl acetate in petroleum ether to afford the title compound (7.25 g, 98 %) as an off white solid.

10 15 ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.15 (s, 1H), 7.49-7.46 (m, 2H), 7.18-7.11 (m, 3H), 6.96-6.85 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.56 (s, 1H), 6.25 (s, 1H), 5.94 (d, *J* = 7.2 Hz, 2H), 4.95-4.78 (m, 2H); MS (ES+) m/z: 376.1 (M-18), 398.1(M+, 1 %), 416.1 (M+18, 20 %).

Intermediate-5: 3-(6-(Benzylxy)benzo[d][1,3]dioxol-5-yl)-1-(4-fluorobenzyl)-3-hydroxyindolin-2-one:

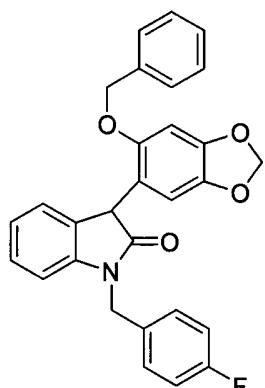
49



To a stirred solution of Intermediate-4 (200 mg, 0.55 mmol) and Cs₂CO₃ (198.9 mg, 0.61 mmol) in dry DMF (2 ml) at 0 °C was added benzyl bromide (0.064 ml, 0.56 mmol). The course of reaction was monitored with TLC. After 1.5 h the reaction mixture was quenched 5 with addition of ice water and the phases were separated. The reaction mixture was extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 10% ethyl acetate in petroleum ether to afford the title compound (210 mg, 87%) as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.94 (s, 1H), 7.32-7.19 (m, 6H), 7.13-7.06 (t, *J* = 8.8 Hz, 2H), 6.93-10 6.91 (m, 2H), 6.80-6.64 (m, 4H), 5.99 (d, *J* = 10.0 Hz, 2H), 4.68-4.55 (m, 2H), MS (ES+) m/z: 466.1 (M+1).

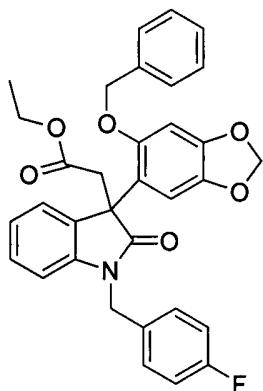
Intermediate-6: 3-(6-(Benzylxy)benzo[d][1,3]dioxol-5-yl)-1-(4-fluorobenzyl) indolin-2-one

:



To a stirred solution of Intermediate-5 (80 mg, 0.55 mmol) in dichloromethane (0.8 mL) at 0 °C was added trifluoroacetic acid (37 mg, 0.30 mmol). The solution turns dark brown color. After 5 min triethyl silane (38 mg, 0.30 mmol) was added and reaction mixture was stirred at room temperature. The course of reaction was monitored with TLC. After 3 h the reaction 5 mixture concentrated *in vacuo* to dryness. The residue was diluted with dichloromethane (5 mL) and washed with saturated ammonium chloride (2 mL) followed by water (5 mL). The organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 10% ethyl acetate in petroleum ether to afford the title compound (59 mg, 61%) as a off yellow 10 color solid. ¹H NMR (400 MHz, CDCl₃): δ 7.33-7.24 (m, 6H), 7.12-7.03 (m, 3H), 6.95-6.87 (m, 4H), 6.43-6.40 (m, 2H), 5.92 (d, *J* = 5.2 Hz, 2H), 4.81-4.45 (m, 3H).

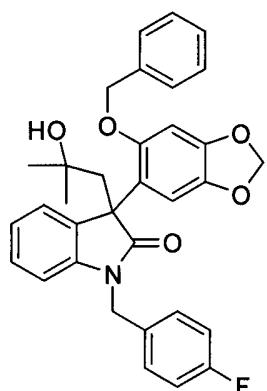
Intermediate-7: Ethyl 2-(3-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)-1-(4-fluoro benzyl)-2-oxoindolin-3-yl)acetate:



15 To an ice cooled solution of Intermediate-6 (600 mg, 1.35 mmol) in dry THF (10 mL) was added NaH (130 mg, 2.70 mmol) under N₂ atmosphere. The solution was stirred at 0 °C for 30 min in N₂ atmosphere. The ethyl bromoactetate (271 mg, 1.62 mmol) was added dropwise and reaction mixture was stirred at same temperature. The course of reaction was monitored with TLC. After 1.5 h the reaction mixture was quenched with ice water and reaction mixture 20 was concentrated *in vacuo* to nearly dryness. The solution residue was extracted with dichloromethane (2 × 15 mL) and washed with saturated ammonium chloride (10 mL) followed by water (15 mL). The organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography,

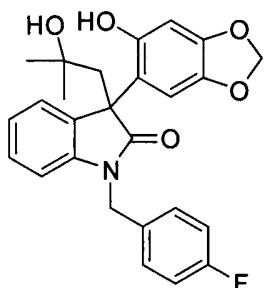
with an isocratic elution of 30 % ethyl acetate in petroleum ether to afford the title compound (180 mg, 72%) as a off white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 7.29-7.24 (m, 5H), 7.19-7.03 (m, 4H), 7.05-7.15 (m, 4H), 6.95-6.87 (m, 6H), 6.43-6.40 (m, 2H), 5.93 (d, J = 5.2 Hz, 2H), 4.57-4.48 (m, 2H), 3.80 (q, J = 7.2Hz, 2H), 3.44-3.18 (m, 2H), 0.90 (t, J = 6.8 Hz, 3H); MS (ES+) m/z: 554.1 (M+1).

Intermediate-8: 3-(6-(Benzylxy)benzo[*d*][1,3]dioxol-5-yl)-1-(4-fluorobenzyl)-3-(2-hydroxy-2-methyl propyl) indolin-2-one:

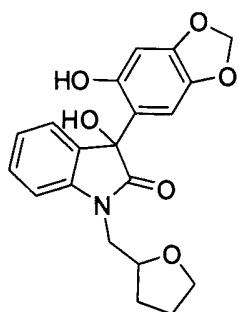


To an ice cooled solution of Intermediate-7 (400 mg, 0.722 mmol) in dry THF (6 mL) was added methyl magnesium bromide in dropwise manner (1.2 mL, 3.6 mmol) under N_2 atmosphere. The solution was stirred at room temperature under N_2 atmosphere. The course of reaction was monitored with TLC. After 3 h the reaction mixture was quenched with saturated ammonium chloride (2 mL) and reaction mixture was concentrated *in vacuo* to nearly dryness. The solution residue was extracted with dichloromethane (2×15 mL) and washed brine (15 mL). The organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 25% ethyl acetate in petroleum ether to afford the title compound (180 mg, 39 %) as a white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 7.44-7.42 (dd, J = 2.8, 8.4 Hz, 2H), 7.28-7.23 (m, 4H), 7.26-7.23 (m, 3H), 7.08-7.04 (m, 3H), 6.91-6.80 (m, 4H), 6.59-6.57 (m, 2H), 5.97 (s, 1H), 5.95 (s, 1H), 4.52-4.51 (m, 2H), 2.48 (m, 2H), 0.92 (s, 3H), 0.53 (s, 3H); MS (ES+) m/z: 522.2 (M- H_2O), 540.2 (M+1).

Intermediate-9: 1-(4-Fluorobenzyl)-3-(2-hydroxy-2-methylpropyl)-3-(6-hydroxyl benzo[*d*][1,3] dioxol-5-yl)-indolin-2-one:



- To a solution of Intermediate-8 (0.12 g, 0.22 mmol) in EtOAc (1.5 mL) was added ammonium formate (0.07 g, 1.11 mmol). The Pd/C (0.01 g, 10 %) was added carefully and reaction mixture was refluxed using guard tube. The course of reaction was monitored with 5 TLC. After 1h the reaction mixture was filtered through celite bed and washed with EtOAc (10 mL). After that, filtrate was extracted with water (10.0 mL). The organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 25 % ethyl acetate in petroleum ether to afford the title compound (0.09 g, 90.0 %) as a white solid.
- 10 ^1H NMR (400 MHz, DMSO-*d*₆): δ 9.29 (s, 1H), 7.51-7.54 (m, 2H), 7.05-7.15 (m, 4H), 6.98 (s, 1H), 6.84-6.88 (t, *J* = 7.2, 7.6 Hz, 1H), 6.70-6.72 (d, *J* = 7.6 Hz, 1H), 6.291(s, 1 H), 5.90-5.91 (s, 2H), 4.78-4.91(dd, *J* =15.6 Hz, 2H), 2.48 (m, 2H), 0.844 (s, 3H), 0.625 (s, 3H). MS (ES+) m/z: 432.1 (M+_{H2O}), 450.1(M+1).
- 15 Intermediate-10: 3-Hydroxy-3-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-1-((tetrahydrofuran-2-yl)methyl)indolin-2-one:

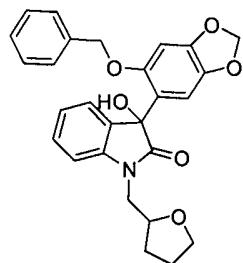


The title compound was prepared by following a procedure similar to that described in Intermediate-4 by using sesamol and Intermediate-2 (yield: 74 %). ^1H NMR (400 MHz, DMSO-*d*₆): δ 9.02 (s, 1H), 7.17-7.23 (m, 2H), 7.02-7.07 (m, 1H), 6.85-6.89 (m, 2H), 6.46-

6.47 (s, 1H), 6.22-6.23 (s, 1H), 5.92 (s, 1H), 5.91 (s, 1H), 4.09-4.12 (m, 1H), 3.76-3.78 (m, 3H) 1.86-1.93 (m, 2H), 1.68-1.75 (m, 2H); MS (ES+) m/z: 352.2 (M-OH).

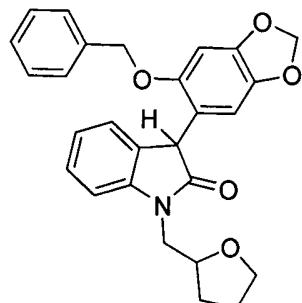
Intermediate-11: 3-(6-(Benzylloxy)benzo[d][1,3]dioxol-5-yl)-3-hydroxy-1-((tetrahydrofuran-2-yl)methyl) indolin-2-one:

5



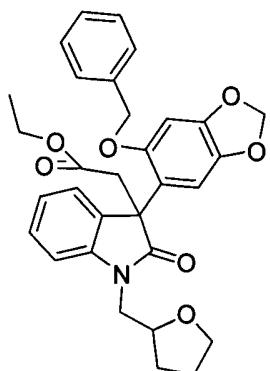
The title compound was prepared by following a procedure similar to that described in Intermediate-5 by using Intermediate-10 and benzyl bromide (yield: 88 %). ¹H NMR (400 MHz, DMSO-d₆): δ 7.36 (s, 1H), 7.20-7.25 (m, 4H), 6.74-6.92 (m, 5H), 6.67 (s, 1H), 5.98 (s, 1H), 5.96 (s, 1H), 4.58-4.66 (m, 2H), 3.85-3.90 (m, 1H), 3.41-3.74 (m, 4H), 1.72-1.84 (m, 3H), 1.44 (m, 1H); MS (ES+) m/z: 442.1 (M-OH).

Intermediate-12: 3-(6-(Benzylloxy)benzo[d][1,3]dioxol-5-yl)-1-((tetrahydrofuran-2-yl)methyl) indolin-2-one.



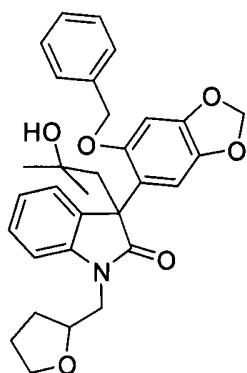
The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-11 (yield: 79 %). ¹H NMR (400 MHz, DMSO-d₆): δ 7.21-7.28 (m, 4H), 6.89-7.07 (m, 5H), 6.81 (d, 2H), 5.97 (s, 2H), 4.73-4.18 (m, 2H), 3.90 (m, 1H), 3.51-3.60 (m, 4H), 1.71-1.85 (m, 3H), 1.53 (m, 3H); MS (ES+) m/z: 444.1 (M+1).

Intermediate-13: Ethyl 2-(3-(6-(benzylloxy)benzo[d][1,3]dioxol-5-yl)-2-oxo-1-((tetrahydrofuran-2-yl)methyl)indolin-3-yl)acetate:



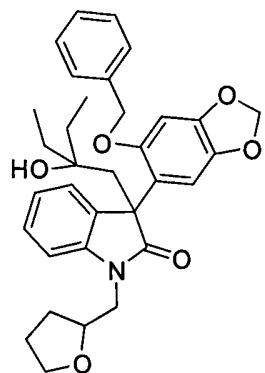
The title compound was prepared by following a procedure similar to that described in Intermediate-7 by using Intermediate-12 and ethyl bromoactetae (yield: 88 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.27-7.29 (m, 2H), 7.23-7.24 (m, 1H), 7.15-7.20 (m, 1H), 7.00-7.06 (m, 1H), 6.90-6.97 (m 2H), 6.82-6.86 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.66-4.68 (d, *J* = 11.2 Hz, 1H), 4.51-4.57 (d, *J* = 11.2 Hz, 1H), 4.04 (m, 1H), 3.77-3.89 (m, 3H), 3.51-3.70 (m, 2H), 3.30-3.43 (d, *J* = 14.4 Hz 1H), 3.13(d, *J* = 14.4 Hz, 1H), 1.58-2.04(m, 4H), 0.93-1.00(t, *J* = 6.8, 7.2 Hz, 3H); MS (ES+) m/z: 530.3 (M-15)

Intermediate-14: 3-(6-(Benzyl)benzo[1,3]dioxol-5-yl)-3-(2-hydroxy-2-methylpropyl)-1-((tetrahydrofuran-2-yl)methyl)indolin-2-one:



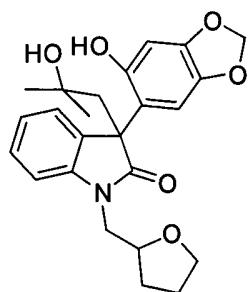
The title compound was prepared by following a procedure similar to that described in Intermediate-8 by using Intermediate-13 and methylmagnesium bromide (yield: 97 %). ¹H NMR (400 MHz, DMSO-*d*₆-D₂O): δ 7.17-7.25 (m, 4H), 6.73-6.90 (m, 5H), 6.55 (s, 2H), 5.90(d, *J* = 1.8 Hz, 2H), 4.63(d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 3.90 (m, 1H) 3.67-3.72(m, 1H), 3.48-3.57(m, 1H), 3.35 (m, 1H), 2.60 (m, 1H), 2.36 (m, 2H), 1.72-1.86 (m, 2H), 1.61-1.92(m, 2H), 0.71 (s, 3H), 0.71 (s, 3H); MS (ES+) m/z: 516.2(M+1).

Intermediate-15: 3-(6-(Benzylxy)benzo[*d*][1,3]dioxol-5-yl)-3-(2-ethyl-2-hydroxy butyl)-1-((tetrahydrofuran-2-yl)methyl)indolin-2-one:



The title compound was prepared by following a procedure similar to that described in
 5 Intermediate-8 by using Intermediate-13 and ethyl magnesium bromide (yield: 78 %). ¹H
 NMR (400 MHz, CDCl₃): δ 7.24-7.29 (m, 2H), 7.17-7.28 (m, 3H), 7.17- (m, 1H), 6.86-6.93
 (m, 3H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.42 (s, 1H), 5.91-5.94 (d, 2H), 4.63 (d, *J* = 10.8 Hz, 1H),
 4.45(d, *J* = 10.8Hz, 1H), 4.10 (m, 1H), 3.81-3.82 (m, 1H), 3.67-3.81 (m, 1H), 2.63 (d, *J* = 14.8
 Hz, 1H), 2.50 (d, *J* = 14.8 Hz, 1H), 2.44 (m, 1H), 1.86-1.98(m, 1H), 1.85 (m, 2H), 1.50-1.58
 10 (m, 3H), 1.26 (m, 2H), 1.03(m, 1H), 0.66-0.85(t, *J* = 7.2 Hz, 3H), 0.61-0.65(t, *J* = 7.2Hz,
 3H); MS (ES+) m/z: 526.2 (M-OH), 544.2(M+1).

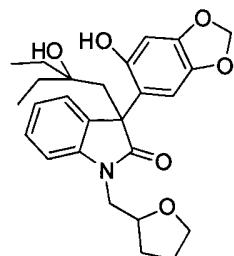
Intermediate-16: 3-(2-Hydroxy-2-methylpropyl)-3-(6-hydroxybenzo[*d*][1,3] dioxol-5-yl)-1-((tetra hydrofuran-2-yl)methyl)indolin-2-one:



15 The title compound was prepared by following a procedure similar to that described in
 Intermediate-9 by using Intermediate-14 (yield: 85 %). ¹H NMR (400 MHz, DMSO-d₆): δ
 9.33 (s, 1H), 7.04-7.18 (m, 3H), 6.89-6.92 (m, 2H), 6.30(m, 1H), 5.90 (s, 2H), 4.02-4.14 (m,

1H), 3.62-3.79 (m, 4H), 2.51 (m, 2H), 1.89-1.99 (m, 4H), 0.72(s, 3H), 0.78(s, 3H); MS (ES+) m/z: 408.2 (M-OH), 426.1 (M+1).

Intermediate-17: 3-(2-Ethyl-2-hydroxybutyl)-3-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-1-((tetra hydrofuran-2-yl)methyl)indolin-2-one:



5

The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-15 (yield: 99 %). ¹H NMR (400 MHz, DMSO-d₆): δ 9.50 (s, 1H), 7.30 (d, J = 7.2Hz, 1H), 7.15 (d, J = 8.0Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.83-6.90 (m, 2H), 6.31 (s, 1H), 5.87 (s, 1H), 5.86 (s, 1H), 4.13 (m, 1H), 3.69-3.77 (m, 2H), 10 3.50-3.63 (m, 2H), 2.56 (d, 1H), 2.39 (d, 1H), 1.68-1.91(m, 4H), 0.92(m, 2H) 0.84(m, 2H), 0.67(t, J = 7.2Hz, 3H), 0.58(t, J = 7.2 Hz, 3H); MS (ES+) m/z: 436.2 (M-OH), 454.1(M+1), 476.1(M+Na⁺).

Intermediate-18: 2,3-Dihydrobenzo[b][1,4]dioxine-6-carbaldehyde:

To a stirred solution of 3,4-dihydroxybenzaldehyde (55.24 g, 40.0 mmol) and K₂CO₃ (82.65 g, 44.0 mmol) in dry DMF (250 ml) at 0 °C was added dibromoethane (138.2 g, 100.0 mmol) over a period of 1 h. The reaction mixture was stirred at room temperature for over night. The course of reaction was monitored with TLC. The reaction mixture was quenched with addition of ice water, the phases were separated. The reaction mixture was extracted with EtOAc (2 x 500 ml). The combined organic extracts were washed with water and brine, 20 dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude brown color liquid compound was washed with NaOH solution and water to get free from the starting material. The crude liquid compound was obtained (50 g) in 76 % yield. ¹H NMR (400 MHz, CDCl₃): δ 9.78 (s, 1H), 7.40-7.36 (m, 2H), 6.95 (d, J = 8.8 Hz, 1H), 4.38 (m, 4H); MS (ES+) m/z 165.0 (M+1).

25 Intermediate-19: 2,3-Dihydrobenzo[b][1,4]dioxin-6-ol:

To a stirred solution of Intermediate-18 (50.0 g, 30.4 mmol) in dichloromethane (250 ml) was added *m*-chloroperbenzoic acid (63.29 g, 36.58 mmol) at room temperature and the reaction mixture was stirred for 16 h at reflux temperature. The course of reaction was monitored with TLC. The reaction mixture was quenched with addition of saturated NaHCO₃

5 and organic layer was washed with water (1 x 250 ml). The aqueous phase was again extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude liquid compound was dissolved in methanol (70 mL) and 4 N NaOH (250 mL) was added at 50 °C. The reaction mixture was stirred at same temperature for 2 h. The reaction mixture was acidified

10 with conc. HCl and methanol was evaporated under *vacuo*. The reaction mass was washed with water (2 x 100 mL) and liquid compound was extracted with EtOAc (2 x 250 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude liquid compound was purified with silica using EtOAc : Hexane (30 : 70) (30 %) eluent, which result light yellow color liquid compound (24.5 g;

15 56.25 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.85 (s, 1H), 7.44-7.41 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 4.38 (m, 4H); MS (ES+) m/z 153.0 (M+1).

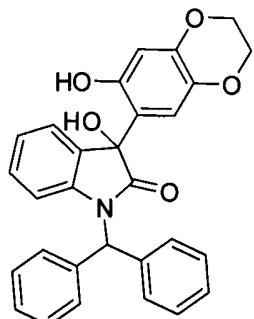
Intermediate-20: 1-Benzhydrylindoline-2,3-dione:

To a stirred solution of isatin (20.0 g, 136 mmol) in dry DMF (500 ml) at 0 °C was added NaH (4.1 g, 170 mmol) step wise. The solution was stirred for 1h at 0 °C. The benhydrin bromide (50 g, 200 mmol) was added lot wise. The color of the reaction mixture changes from brownish black to tar black. The course of reaction was monitored with TLC. After addition the reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with addition of ice water, the phases were separated. The reaction mixture was extracted with EtOAc (2 x 250 ml). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 40% ethyl acetate in petroleum ether to afford the title compound (40.0 g, 95%) as a bright orange solid.

20 ¹H NMR (400 MHz, CDCl₃): δ 7.12 (d, *J* = 8 Hz, 1H), 6.54 (dd, *J* = 8 Hz, 4 Hz, 1H), 6.41 (d, *J* = 4 Hz, 1H), 3.85 (s, 3H), 3.45 (s, 2H), 3.18 (s, 3H); MS (ES+) m/z 177.9 (M+1).

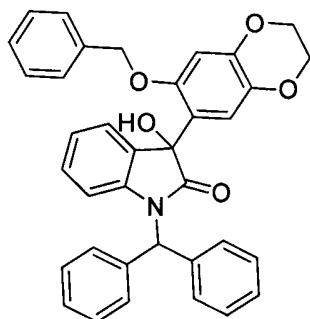
25

Intermediate-21: 1-Benzhydryl-3-hydroxy-3-(7-hydroxy-2,3-dihydrobenzo [b][1,4]dioxin-6-yl)indolin-2-one:



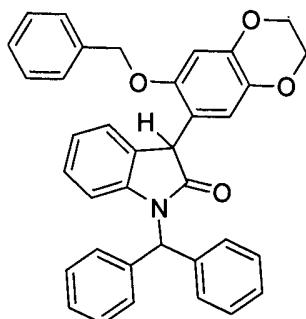
The title compound was prepared by following a procedure similar to that described in
5 Intermediate-4 by using Intermediate-19 and Intermediate-20 (yield: 54 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.04 (s, 1H), 7.40-7.29 (m, 10H), 7.24 (s, 1H), 3.85 (s, 1H), 6.96-6.89 (m, 4H), 6.52 (s, 1H), 6.29 (d, *J* = 7.6 Hz, 1H), 6.17 (s, 1H), 4.19 (m 4H); MS (ES+) m/z: 448.2 (M-H₂O).

Intermediate-22: 1-Benzhydryl-3-(7-(benzyloxy)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)3-hydroxy indolin-2-one:



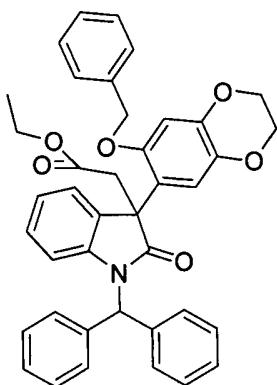
The title compound was prepared by following a procedure similar to that described in
15 Intermediate-5 by using Intermediate-21 and benzyl bromide (yield: 94 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.35-7.24 (m, 10H), 7.14-7.08 (m, 2H), 6.93-6.88 (m, 2H), 6.81 (s, 1H), 6.62-6.57 (m, 3H), 6.20 (s, 1H), 4.62 (d, *J* = 14.4 Hz, 1H), 4.33 (d, *J* = 14.4 Hz, 1H), 4.18 (m, 4H); MS (ES+) m/z: 538.2 (M-OH).

Intermediate-23: 1-Benzhydryl-3-(7-(benzyloxy)-2,3-dihydrobenzo[b][1,4]dioxin -6-yl)-3-indolin-2-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-22 (yield: 86 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.36-7.19 (m, 14H), 7.06 (m, 2H), 6.94-6.89 (m, 4H), 6.51-6.49 (m, 3H), 4.96-4.85 (m, 2H), 5 4.17 (m, 4H); MS (ES+) m/z: 540.3 (M+1,).

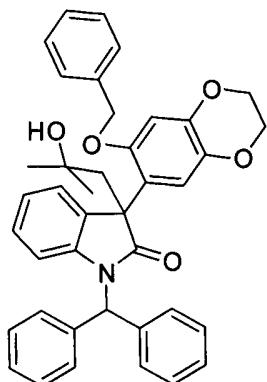
Intermediate-24: Ethyl-2-(1-benzhydryl-3-(7-(benzyloxy)-2,3-dihydrobenzo [b][1,4]dioxin-6-yl)-2-oxoindolin-3-yl)acetate:



The title compound was prepared by following a procedure similar to that described in Intermediate-7 by using Intermediate-23 and ethyl bromoactetate (yield: 88 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.37-7.25 (m, 10H), 7.20-7.01 (m, 5H), 6.91-6.87 (m, 4H), 6.82 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.30 (s, 1H), 4.66 (d, *J* = 13.6 Hz, 1H), 4.35 (d, *J* = 13.6 Hz, 1H), 4.13 (m, 4 H), 3.57 (d, *J* = 14.8 Hz, 1H), 3.14 (d, *J* = 14.8 Hz, 1H), 0.82(t, *J* = 7.2 Hz, 3H); MS (ES+) m/z: 540.3 (M+1,).

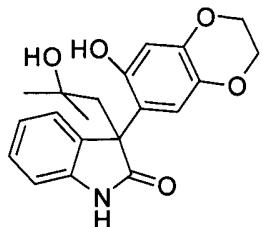
15 Intermediate-25: 1-Benzhydryl-3-(7-(benzyloxy)-2,3-dihydrobenzo[b][1,4]dioxin -6-yl)-3-(2-methylpropyl) indolin-2-one:

60



The title compound was prepared by following a procedure similar to that described in Intermediate-8 by using Intermediate-24 and methyl magnesium bromide (yield: 92 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.41-7.38 (m, 4H), 7.23-7.30 (m, 5H), 7.267.23 (m, 3H), 5 7.18-7.16 (m, 3H), 7.08 (d, *J* = 6.4 Hz, 1H), 6.95-6.90 (m, 3H), 6.85-6.81 (m, 3H), 6.39 (d, *J* = 8.0 Hz, 1H), 6.22 (s, 1H), 4.56 (d, *J* = 13.6 Hz, 1H), 4.16 (m, 4H), 2.56-2.49 (m, 2H), 1.02 (s, 3H), 0.60 (s, 3H); MS (ES+) m/z: 594.4 (M⁺-H₂O), 612.3 (M+1), 634.3 (M-Na⁺).

Intermediate-26: 3-(7-(Benzylxy)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-(2-hydroxypropyl)indolin-2-one:

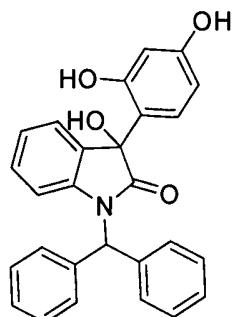


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The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-25 (yield: 86 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.57 (s, 1 H), 9.52 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.65 (s, 1H), 6.21 (s, 1H), 4.15-4.11 (m, 5H), 2.54 (d, *J* = 14.0 Hz, 1H), 2.44 (d, *J* = 14.0 Hz, 1H), 0.80 (s, 6H); MS (ES+) m/z: 338.2 (M-H₂O+1), 15 356.2 (M+1), 378.2 (M-Na⁺).

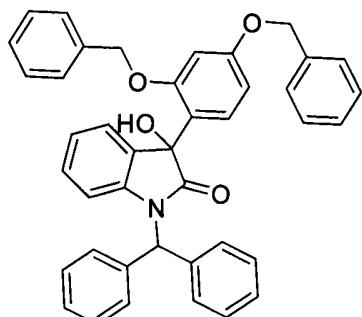
Intermediate-27: 1-Benzhydryl-3-(2,4-dihydroxyphenyl)-3-hydroxyindolin-2-one:

61



To an ice cooled solution of 3-hydroxy phenol (114 g, 363 mmol) in dry THF (500 mL) was added dropwise isopropyl magnesium chloride (378.0 mL, 756.0 mmol, 2.0 M in THF). The reaction mixture was stirred at 0 °C for 1 h, upon which time the colorless precipitate was formed. After that, the solution of Intermediate-20 (114 g, 363 mmol) in THF (450 ml) at 0 °C was added to the reaction mixture. The reaction mixture was stirred at ambient temperature for 16 h. The course of reaction was monitored with TLC. The reaction mixture was quenched with saturated ammonium chloride solution. The organic layer was washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated in *vacuo*. The obtained solid was dissolved in minimum quantity of ethyl acetate followed by precipitation using hexanes to afford the crude desired compound as colorless solid (122.0 g, 79.2 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.04 (m, 2H), 7.55-7.23 (m, 9H), 6.95-6.79 (m, 4H), 6.44-6.16 (m, 5H); MS (ES+) m/z: 406.0 (M-H₂O,).

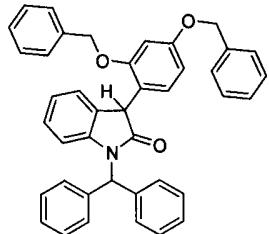
Intermediate-28: 1-Benzhydryl-3-(2,4-bis(benzyloxy)phenyl)-3-hydroxyindolin-2-one:



15

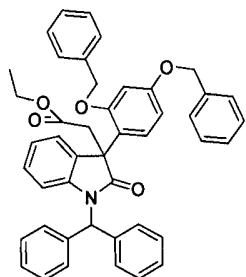
The title compound was prepared by following a procedure similar to that described in Intermediate-5 by using Intermediate-27 and benzyl bromide (yield: 86 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.79-7.29 (m, 9H), 7.27-7.08 (m, 10H), 6.96-6.81 (m, 4H), 6.66-6.57 (m, 4H), 6.34 (m, 1H), 5.02-4.33 (m, 4H); MS (ES+) m/z: 626.2 (M-Na⁺,).

Intermediate-29: 1-Benzhydryl-3-(2, 4-bis (benzyloxy) phenyl) indolin-2-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-28 (yield: 92 %). ¹H NMR (400 MHz, DMSO-d₆): δ 5 7.65-7.55 (m, 1H), 7.54-7.18 (m, 20H), 7.9-7.04 (m, 2H), 6.95-6.90 (m, 3H), 6.61-6.58 (m, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 5.08-4.49 (m, 4H); MS (ES+) m/z: 588.1 (M+1).

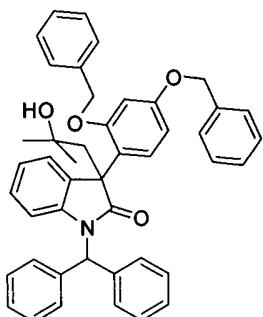
Intermediate-30: Ethyl-2-(1-benzhydryl-3-(2,4-bis(benzyloxy)phenyl)-2-oxoindolin-3-yl)acetate:



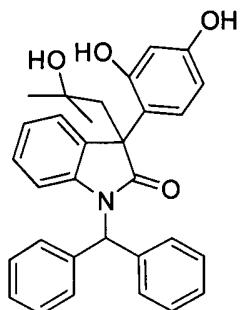
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The title compound was prepared by following a procedure similar to that described in Intermediate-7 by using Intermediate-29 and ethyl bromoactetae (yield: 83 %). ¹H NMR (400 MHz, DMSO-d₆): δ 7.39-7.26 (m, 15H), 7.20-7.18 (m, 4H), 7.13-7.11 (d, *J* = 8.0 Hz, 1H), 7.03 (m, 1H), 6.89-6.86 (m, 4H), 6.53-6.49 (m, 2H), 6.43 (m, 1H), 4.97 (s, 2H), 4.77 (d, *J* = 13.2 Hz, 1H), 4.38 (d, *J* = 13.2 Hz, 1H), 3.81 (m, 2H), 3.61 (d, *J* = 14.4 Hz, 1H), 3.16 (d, *J* = 14.4 Hz, 1H), 0.82(t, *J* = 7.2 Hz, 3H).

Intermediate-31: 1-Benzhydryl-3-(2,4-bis(benzyloxy)phenyl)-3-(2-hydroxy-2-methylpropyl)indolin-2-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-8 by using Intermediate-30 and methyl magnesium bromide (yield: 93 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.35-7.32 (m, 4H), 7.31-7.23 (m, 13H), 7.17-7.15 (m, 3H), 5 7.06 (d, *J* = 7.6 Hz, 1H), 6.96-6.92 (m, 2H), 6.83-6.80 (m, 3H), 6.51 (d, *J* = 8.8 Hz, 1H), 6.38 (d, *J* = 13.6 Hz, 1H), 6.35 (s, 1H), 4.95 (s, 2H), 4.67 (d, *J* = 13.6 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 2.68-2.49 (m, 2H), 1.04 (s, 3H), 0.62 (s, 3H); MS (ES+) m/z: 660.3 (M+1). Intermediate-32: 1-Benzhydryl-3-(2,4-dihydroxyphenyl)-3-(2-hydroxy-2-methylpropyl)indolin-2-one:

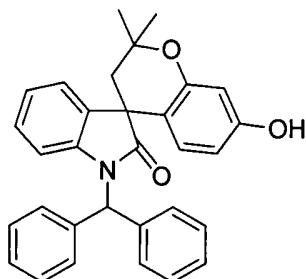


10

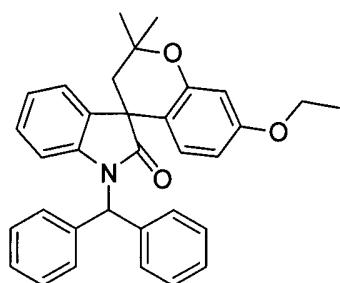
To a solution of Intermediate-31 (53.0 g, 80 mmol) in acetone (500 mL) was hydrogenated at atmospheric pressure over 10 % Pd/C (8.5 g, 80.0 mmol). The reaction mixture was stirred overnight at ambient temperature. The course of reaction was monitored with TLC. After completion of reaction, the reaction mixture was filtered through celite bed and washed with 15 EtOAc (5 × 250 mL). The organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was washed with *n*-pentane to result the crude compound (36.1 g, 94 %) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.43 (s, 1 H), 9.18 (s, 1H), 7.39-7.26 (m, 8H), 7.17-7.05 (m, 4H), 6.92-6.78(m, 3H), 6.25-6.14 (m, 3H),

4.07 (s, 1H), 2.56 (s, 1H), 1.98 (s, 1H) 0.85 (s, 3H), 0.60 (s, 3H); MS (ES+) m/z: 462.1 (M-H₂O+1), 480.1 (M+1).

Intermediate-33: 1'-Benzhydryl-7-hydroxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



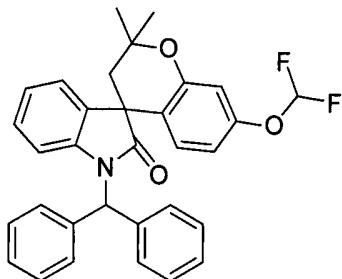
- 5 To a solution of Intermediate-32 (28.0 g, 58.4 mmol) in benzene (350ml) *p*-toluene sulphonic acid (11.1 g, 58.4 mmol) was added. The reaction mixture was refluxed for 5 h. After completion of reaction the mixture was diluted with EtOAc (100 mL) and organic layer was washed with saturated NaHCO₃ (2 × 250 mL), followed by brine (50 mL). The organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was purified by column chromatography, with an isocratic elution of 30 % ethyl acetate in petroleum ether to afford the title compound (20.4 mg, 76.0 %) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.50 (s, 1H), 7.45-7.32 (m, 5H), 7.30-7.24 (m, 5H), 7.10-7.01 (m, 2H), 6.96-6.89 (m, 2H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.23-6.13 (m, 3H), 2.38 (d, *J* = 14.4 Hz, 1H), 2.20 (d, *J* = 14.4 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H); MS (ES+) m/z: 462.2 (M+1).
- 10 15 Intermediate-34: 1'-Benzhydryl-7-ethoxy-2,2-dimethylspiro [chroman-4,3'-indolin]-2'-one:



- To an ice cooled solution of Intermediate-33 (0.25 g, 54.10 mmol) in dry DMF (5 mL) was added NaH (0.052 g, 54.10 mmol) under nitrogen atmosphere. The solution was stirred at 0 °C for 30 min. After that, ethyl iodide (0.08 mL, 108.3 mmol) was added and reaction 20 mixture was stirred for 1 h at ambient temperature. After completion of reaction, the mixture

was quenched with saturated ammonium chloride (5.0 mL) and solid compound was filtered and washed with water. The solid compound was dissolved in EtOAc (100 mL) and organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 20 % ethyl acetate in petroleum ether to afford the title compound (0.23 g, 81.1 %) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.43-7.34 (m, 6H), 7.32-7.25 (m, 4H), 7.10-7.02 (m, 2H), 6.96-6.90 (m, 2H), 6.57 (d, *J* = 7.6 Hz, 1H), 6.40-6.32 (m, 2H), 6.25 (d, *J* = 8.4 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, *J* = 6.8 Hz, 2H), 2.49 (d, *J* = 14.4 Hz, 1H), 2.24 (d, *J* = 14.4 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.29 (t, *J* = 6.8 Hz, 3H); MS (ES+) m/z: 489.8 (M+1,).

10 Intermediate-35: 1'-Benzhydryl-7-(difluoromethoxy)-2,2-dimethylspiro [chroman-4,3'-indolin]-2'-one:

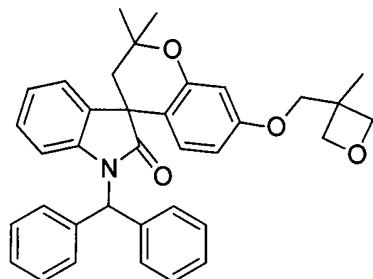


To the solution of Intermediate-33 (0.19 g, 0.41 mmol) in dry DMF (2 mL) was added cesium carbonate (0.40 g, 1.23 mmol) under nitrogen atmosphere. The solution was stirred at ambient temperature for 30 min. After that, sodium difluoroacetate (0.12 g, 0.82 mmol) was added and reaction mixture was heated at 100 °C for 45 min. After completion of reaction, the mixture was quenched with ice water (5.0 mL) and solid compound was filtered and washed with water. The solid compound was dissolved in EtOAc (100 mL) and organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 20 % ethyl acetate in petroleum ether to afford the title compound (0.17 g, 82 %) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.43-7.34 (m, 6H), 7.31-7.26 (m, 4H), 7.22 (s, 1H), 7.12-7.03 (m, 2H), 6.99-6.97 (m, 1H), 6.90 (s, 1H), 6.69-6.58 (m, 3H), 6.40 (d, *J* = 8.4 Hz, 1H), 2.45 (d, *J* = 14.4 Hz, 1H), 2.29 (d, *J* = 14.4 Hz, 1H), 1.50 (s, 3H), 1.47 (s, 3H); MS (ES+) m/z: 512.2 (M+1).

25 Intermediate-36: (3-Methyloxetan-3-yl) methyl 4-methylbenzenesulfonate:

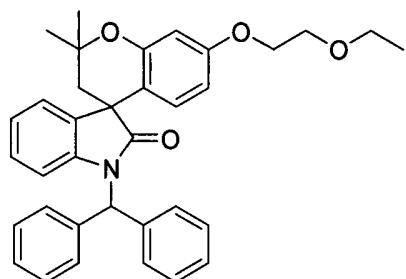
To an ice cooled solution of 3-methyloxetan-3-yl) methanol (5.0 g, 0.48 mmol) in dry dichloromethane (60 mL) was added triethylamine (7.4 g, 0.73mmol) followed by *p*-toluene sulfonyl chloride (10.2g, 0.53 mmol) under nitrogen atmosphere. The reaction was stirred at ambient temperature for 2 hours. After the completion of reaction, the reaction mixture was quenched with of ice water. The organic compound was extracted and organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 20 % ethyl acetate to result the desired compound (10.7g, 85.6 %). ^1H NMR (400 MHz, DMSO-*d*₆): δ 7.83 (d, *J* = 6.8 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H)), 4.25-4.18 (m, 4H), 4.11 (s, 2H), 2.43 (s, 3H), 1.18 (s, 3H); MS (ES+) m/z: 257.1 (M+1).

Intermediate-37: 1'-Benzhydryl-2, 2-dimethyl-7-((3-methyloxetan-3-yl) methoxy) spiro [chroman-4, 3'-indolin]-2'-one:



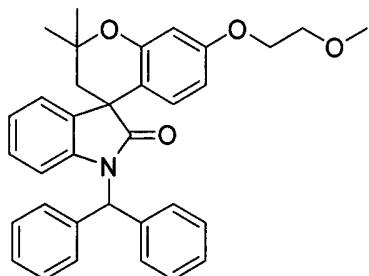
The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Intermediate-33 and Intermediate-36 (yield: 82 %). ^1H NMR (400 MHz, DMSO-*d*₆): δ 7.43-7.25 (m, 9H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.95-6.89 (m, 2H), 6.33 (s, 1H), 5.82 (s, 1H), 4.14-4.03 (m, 4H), 2.32 (d, *J* = 14.4 Hz, 1H), 2.09 (d, *J* = 14.4 Hz, 1H), 1.32 (d, *J* = 11.6 Hz, 6H); MS (ES+) m/z: 338.3 (M+1,).

Intermediate-38: 1'-Benzhydryl-7-(2-ethoxyethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



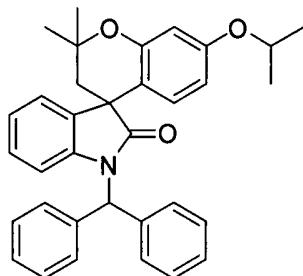
The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Intermediate-33 and 1-chloro-2-ethoxyethane (Yield: 88 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.45-7.25 (m, 10H), 7.11-7.03 (m, 2H), 6.97-6.90 (m, 2H), 5 6.58 (d, *J* = 8.0 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.25 (d, *J* = 8.0 Hz, 1H), 4.02-4.0 (m, 2H), 3.65-3.6 (m, 2H), 3.48-3.44 (m, 2H), 2.42 (d, *J* = 16.0 Hz, 1H), 2.24 (d, *J* = 16.0 Hz, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 534.1 (M+1).

Intermediate-39: 1'-Benzhydryl-7-(2-methoxyethoxy)-2,2-dimethylspiro [chroman-4,3'-10 indolin]-2'-one:



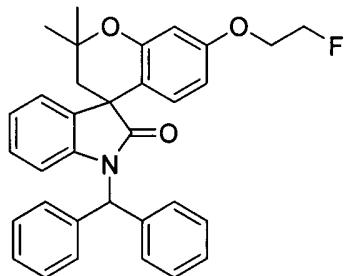
The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Intermediate-33 and 1-bromo-2-methoxyethane (yield: 81 %).

Intermediate-40: 1'-Benzhydryl-7-isopropoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Intermediate-33 and 2-bromo propane (yield: 89 %).

Intermediate-41: 1'-Benzhydryl-7-(2-fluoroethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:

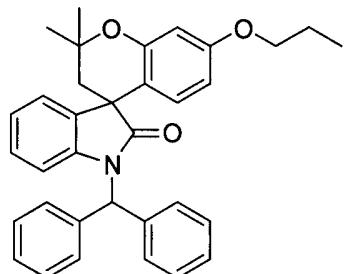


5

The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Intermediate-33 and 2-fluoroethyl 4-methylbenzenesulfonate (*Tetrahedron* (2005), **61**, 8410–8418) (yield: 88 %).

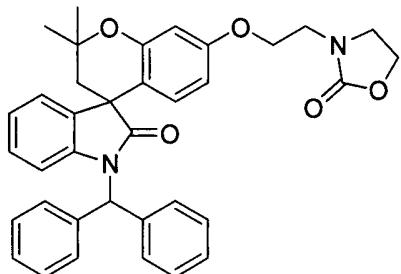
Intermediate-42: 1'-Benzhydryl-2,2-dimethyl-7-propoxyspiro[chroman-4,3'-indolin]-2'-one:

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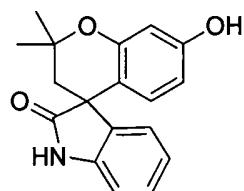
The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Intermediate-33 and 1-bromo propane (yield: 89 %).

Intermediate-43: 1'-Benzhydryl-2,2-dimethyl-7-(2-(2-oxooxazolidin-3-yl)ethoxy)spiro
15 [chroman-4,3'-indolin]-2'-one:



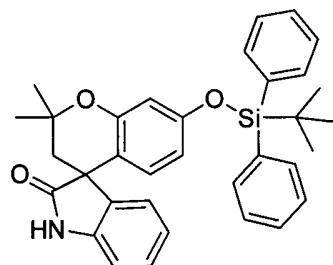
The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Intermediate-33 and 3-(2-hydroxyethyl)oxazolidin-2-one (yield: 70 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.43-7.25 (m, 9H), 7.11-7.03 (m, 2H), 6.97-6.89 (m, 2H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 8.0 Hz, 1H), 4.21-4.15 (m, 2H), 4.14-4.1 (m, 2H), 3.63-3.59 (m, 2H), 3.49-3.47 (m, 2H), 2.42 (d, *J* = 16.0 Hz, 1H), 2.25 (d, *J* = 16.0 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H); MS(ES+) m/z: 575.1 (M+1).

Intermediate-44: 7-Hydroxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



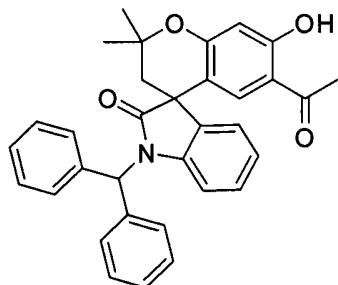
To a stirred solution of Intermediate-33 (1g, 2.169 mmol) in ethyl acetate was added Pd/C (2 g) and the whole suspension was stirred at room temperature for overnight under H₂ atmosphere. Excess of Pd/C was filter through celite bed, and the residue was washed with ethyl acetate (25 mL x 3). The organic layer was dried over Na₂SO₄ and concentrated under *vacuo*. The residue thus obtained was purified by column chromatography eluting 30% ethyl acetate/petroleum ether to furnish the title compound (0.5 g, 90%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.45 (s, 1H), 9.35 (s, 1H), 7.20 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.94-6.88 (m, 2H), 6.23-6.17 (m, 3H), 2.30 (d, *J* = 14.4 Hz, 1H), 2.07 (d, *J* = 14.4 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H).

Intermediate-45: 7-((Tert-butyldiphenylsilyl)oxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



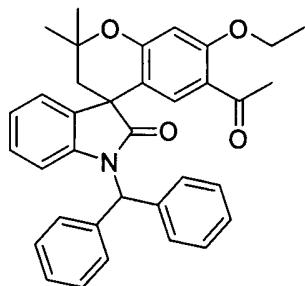
To a stirred solution of Intermediate-44 (0.2g, 0.677mmol) in dichloromethane was added imidazole (0.092g, 1.35mmol) and *tert*-butylchlorodiphenylsilane (0.371g, 1.35mmol). The whole suspension stirred at room temperature for overnight under nitrogen atmosphere. The reaction mixture was diluted with water (15ml) and extracted with dichloromethane (10mL x 5); the organic layer was dried over Na₂SO₄ and concentrated under *vacuo*. The residue thus obtained was purified by column chromatography eluting with 30% ethyl acetate/petroleum ether to get to afford the title compound (0.325g, 90%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.48 (s, 1H), 7.64-7.50 (m, 4H), 7.49-7.41 (m, 6H), 7.19-7.15 (m, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.92-6.86 (m, 2H), 6.23 (d, *J* = 2.0 Hz, 2H), 6.12 (d, *J* = 1.6 Hz, 1H), 2.30 (d, *J* = 14.4 Hz, 1H), 2.07 (d, *J* = 14.4 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H).

Intermediate-46: 6-Acetyl-1'-benzhydryl-7-hydroxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:

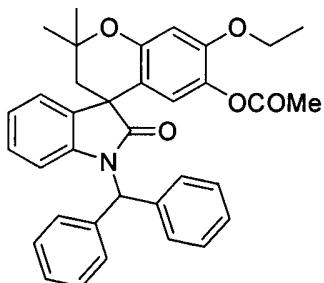


To a stirred solution of Intermediate-33 (2.0 g, 4.33 mmol) in DCM (dichloromethane) (45 mL) was added acetyl chloride (0.40 mL, 5.63 mmol) at 0°C, and the resulting solution was stirred for 10 min at rt. To the above solution was added aluminium chloride (2.022 g, 15.17mmol) portion wise under nitrogen atmosphere and the whole dark brown color solution was stirred for another 72 hr at room temperature. The reaction mixture was diluted with 1N HCl and aqueous phase was extracted with ethyl acetate (30 mL x 2); the organic layer was dried over Na₂SO₄ and concentrated under *vacuo*. The residue was purified by column chromatography with an isocratic elution of 6% ethyl acetate/petroleum ether to afford the title compound (0.6 g 25%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.89 (s, 1H), 7.44-7.27 (m, 10H), 7.18 (dd, *J* = 1.8 Hz, 7.6 Hz, 1H), 7.12-7.08 (m, 1H), 6.99 (m, 1H), 6.93 (s, 1H), 6.80 (s, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.41 (s, 1H), 2.41 (s, 3H), 2.32 (d, *J*=14.4 Hz, 1H), 2.18 (d, *J* = 14.4 Hz, 1H), 1.52 (s, 3H), 1.49 (s, 3H).

Intermediate-47: 6-Acetyl-1'-benzhydryl-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



- The title compound was prepared by following a procedure similar to that described in
 5 Intermediate-34 by using Intermediate-46, and iodoethane (Yield: 67 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.45-7.25 (m, 10H), 7.13 (dd, *J* = 1.8, 7.6 Hz, 1H), 7.05 (s, 1H), 7.00-6.91 (m, 3H), 6.60 (s, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.41 (d, *J* = 14.4 Hz, 1H), 2.30 (d, *J* = 14.4 Hz, 1H), 1.53 (s, 3H), 1.50 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H).
- 10 Intermediate-48: 1'-Benzhydryl-7-ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-6-yl acetate:

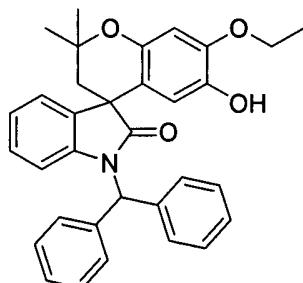


- To a stirred solution of Intermediate-47 (0.5 g, 1.034 mmol) in dichloromethane (5 ml) was added acetic acid (0.2 ml, 0.39 mmol) and was stirred for 30 minutes. The reaction mixture
 15 was cooled to 0°C and m-chloroperbenzoic acid (0.25 g, 1.48 mmol) was added and resulting solution was stirred at room temperature for 48 h. Excess of dichloromethane and acetic acid was evaporated *in vacuo*, the residue was diluted with ethyl acetate (10 ml) and added saturated aqueous NaHCO₃ solution (5 ml). The phases were separated and aqueous phase was extracted with ethyl acetate (2 x 10). The combined organic extract was washed with
 20 water (2 x 10 ml), brine (10 ml) and dried over anhydrous sodium sulphate, filtered and

concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford the title compound. Yield (0.4g, 80 %)

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.39-7.27 (m, 10H), 7.14 (dd, *J* = 1.8, 7.6 Hz, 1H), 7.05 (s, 1H), 7.00-6.91 (m, 2H), 6.52 (d, *J* = 0.8 Hz, 1H), 6.52 (s, 1H), 6.05 (s, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 2.46 (d, *J* = 14.4Hz, 1H) 2.25 (d, *J* = 14.4 Hz, 1H), 2.19 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H).

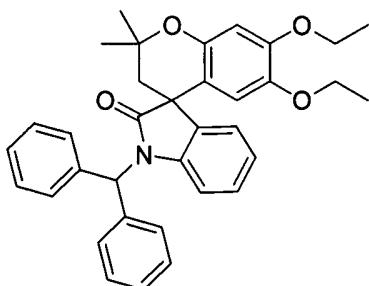
Intermediate-49: 1'-Benzhydryl-7-ethoxy-6-hydroxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



10

To a stirred solution of Intermediate-48 (0.4 g, 0.73 mmol) in methanol: water (1:1) (10 ml) was added sodium hydroxide (0.15 g, 3.65 mmol) in water (2 ml). The resultant suspension was stirred at room temperature for 5 h. The reaction mixture was cooled to 0°C and pH of the solution was adjusted to 7 by 1N HCl (20 ml) and the aqueous layer was diluted with ethyl acetate (15ml). The phases were separated and aqueous phase was extracted with ethyl acetate (2 x 30). The combined organic extracts were washed with water (2 x 20 ml), brine (20 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was triturated by n-pentane to afford the title compound in 90 % yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.42 (s, 1H), 7.45-7.26 (m, 10H), 7.14 (dd, *J* = 1.8, 7.6 Hz 1H), 7.04 (m, 1H), 6.97-6.95 (m, 1H), 6.89 (s, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 6.41 (s, 1H), 5.85 (s, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 2.32 (d, *J* = 14.4Hz, 1H) 2.15 (d, *J* = 14.4 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H) 1.29 (t, *J* = 7.2 Hz, 3H).

Intermediate-50: 1'-Benzhydryl-6,7-diethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Intermediate-49 and iodoethane (yield: 76 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.42-7.26 (m, 8H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.12-7.05 (m, 2H), 6.98-6.91 (m, 2H), 6.60 (d, *J* = 8.0 Hz 1H), 6.45 (s, 1H), 5.69 (s, 1H), 3.96 (q, *J* = 7.2 Hz, 2H), 3.43 (q, *J* = 7.2 Hz, 2H), 2.39 (d, *J* = 14.4 Hz, 1H), 2.23 (d, *J* = 14.4 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H)

Intermediate-51: 6-(Benzylxy)benzofuran-3(2H)-one:

Commercially available 6-hydroxy-2H-benzofuran-3-one (4.4 g, 29.3 mmol) was dissolved in 50 mL dry DMF and potassium carbonate (7.36 g, 53.3 mmol) was added, followed by slow addition of benzyl bromide (3.8 mL, 32.0 mmol). The reaction was stirred at room temperature for 18 h, filtered, and the filtrate poured into 250 mL cold water. The red solid obtained was filtered, washed with water, and dried to give 7.0 g (98 %). GCMS: 239.91 (M⁺).

Intermediate-52: 6-(Benzylxy)-2,2-dimethylbenzofuran-3(2H)-one:

To a solution of Intermediate-51 (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 (3x50.0 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 (400 MHz, CDCl₃): δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.47-7.34 (m, 5H), 6.71 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 5.08 (s, 2H), 1.45 (s, 6H); GCMS: 268.0 (M⁺).

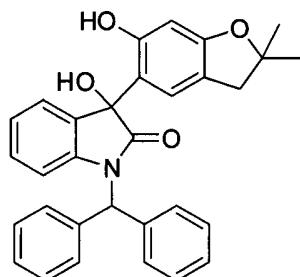
Intermediate-53: 6-(Benzylxy)-2,2-dimethyl-2,3-dihydrobenzofuran:

Lithium aluminum hydride (0.28 g, 7.45 mmol) was taken in ether (25 mL) under nitrogen atmosphere to which aluminum trichloride (1.1 g, 8.2 mmol) was added and stirred for 15 min. A mixture of Intermediate-52 (2.0 g, 7.45 mmol) and aluminum trichloride (1.1 g, 8.2 mmol) in diethyl ether (25 mL) was added to lithium aluminum hydride solution at room temperature. The reaction mixture was stirred at ambient temperature for 2 h and quenched with 1N NaOH solution (10.0 mL). The aqueous mixture was extracted with diethyl ether (3 x 25 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in *vacuo* to dryness to give the title compound (1.5 g, 79 %). This compound was taken as such for the next step. ¹H NMR (400 MHz, CDCl₃): δ 7.43-7.30 (m, 5H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.50 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 5.03 (s, 2H), 2.91(s, 2H), 1.34(s, 3H), 1.23(s, 3H); GCMS: 253.01 (M⁺).

Intermediate-54: 2,2-Dimethyl-2,3-dihydrobenzofuran-6-ol:

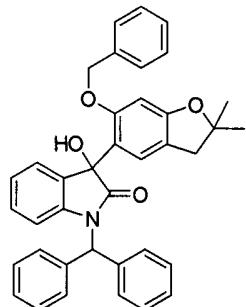
To a solution Intermediate-53 (1.4g, 5.51 mmol) in EtOAc (50 mL) was added Pd/C (1.0 g, 10 wt %) and the reaction mixture was stirred at room temperature under hydrogen gas atmosphere. The course of reaction was monitored with TLC. After 3h the reaction mixture was filtered through celite bed and washed with EtOAc (3 x 25 mL). The filtrate was concentrated under reduced pressure. The resulted solid compound was washed with n-pentane to afford the title compound (0.68 g, 70 %) as a white solid. GCMS: 162.96 (M).

20 **Intermediate-55: 1-Benzhydryl-3-hydroxy-3-(6-hydroxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl) indolin-2-one:**



The title compound was prepared by following a procedure similar to that described in Intermediate-4 by using Intermediate-20 and Intermediate-54 (Yield: 62 %). MS (ES+) m/z: 25 460.08 (M-18⁺).

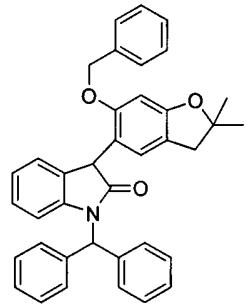
Intermediate-56: 1-Benzhydryl-3-(6-(benzyloxy)-2,2-dimethyl-2,3-dihydrobenzo furan-5-yl)-3-hydroxy indolin-2-one:



The title compound was prepared by following a procedure similar to that described in

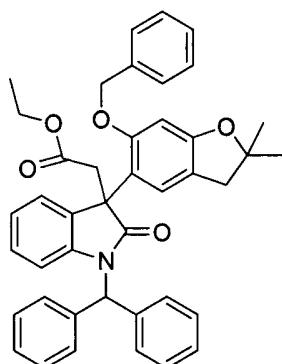
- 5 Intermediate-5 by using Intermediate-55 and benzyl bromide (Yield: 95 %). MS (ES+) m/z: 550.2 ($M-OH^+$).

Intermediate-57: 1-Benzhydryl-3-(6-(benzyloxy)-2,2-dimethyl-2,3-dihydrobenzo furan-5-yl) indolin-2-one:



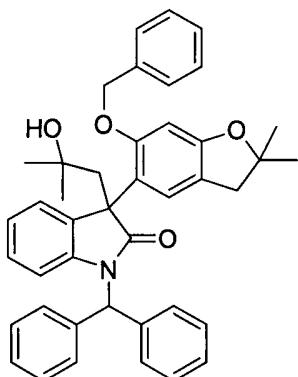
- 10 The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-56 (Yield: 81 %). MS (ES+) m/z: 552.1 ($M+1$).

Intermediate-58: 2-(1-Benzhydryl-3-(6-(benzyloxy)-2,2-dimethyl-2,3-dihydro benzofuran-5-yl)-2-oxoindolin-3-yl)acetate:



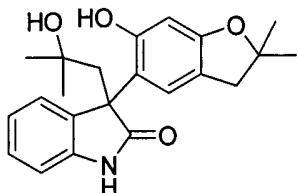
The title compound was prepared by following a procedure similar to that described in Intermediate-7 by using Intermediate-57 and ethyl bromoactetae (Yield: 78 %). MS (ES+) m/z: 638.3.1 (M+1).

- 5 Intermediate-59: 1-Benzhydryl-3-(6-(benzyloxy)-2,2-dimethyl-2,3-dihydrobenzo furan-5-yl)-3-(2-hydroxy-2-methylpropyl)indolin-2-one:



- The title compound was prepared by following a procedure similar to that described in Intermediate-8 by using Intermediate-58 and methyl magnesium bromide (Yield: 85 %). MS
10 (ES+) m/z: 624.3 (M+1).

Intermediate-60: 3-(6-Hydroxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(2-hydroxy-2-methylpropyl) indolin-2-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-59 (Yield: 84 %). MS (ES+) m/z: 368.1 (M+).

Intermediate-61: 6-(Benzyl)-2,3-dihydrobenzofuran:

The title compound was prepared by following a procedure similar to that described in

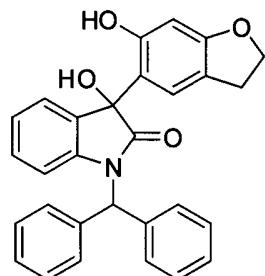
- 5 Intermediate-51 by using 6-hydroxybenzofuran-3(2H)-one and benzyl bromide (yield: 70 %).

¹H NMR (400 MHz, CDCl₃): δ 7.43-7.30 (m, 5H), 7.21 (d, J = 8.0 Hz, 1H), 6.50 (dd, J = 2.4, 8.0 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 5.03 (s, 2H), 2.91(s, 2H), 1.34 (s, 3H), 1.23 (s, 3H); GCMS: 253.01 (M+).

Intermediate-62: 2,3-Dihydrobenzofuran-6-ol:

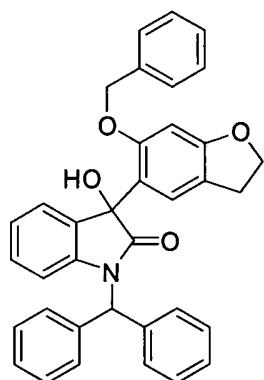
- 10 The title compound was prepared by following a procedure similar to that described in Intermediate-54 using Intermediate-61 (yield: 60%). GCMS: 162.96 (M+).

Intermediate-63: 1-Benzhydryl-3-hydroxy-3-(6-hydroxy-2,3-dihydrobenzofuran-5-yl)indolin-2-one:



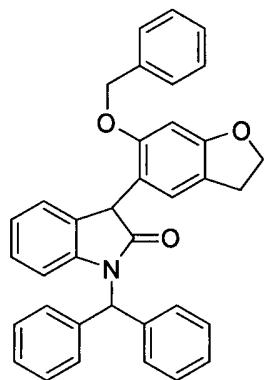
- 15 The title compound was prepared by following a procedure similar to that described in Intermediate-4 by using Intermediate-62 and Intermediate-20 (yield: 73 %).

Intermediate-64: 1-Benzhydryl-3-(6-(benzyloxy)-2,3-dihydrobenzofuran-5-yl)-3-hydroxyindolin-2-one:



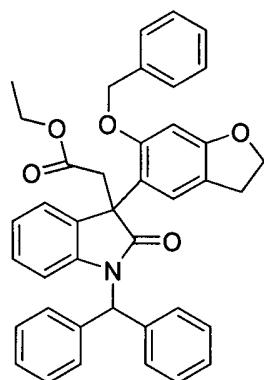
The title compound was prepared by following a procedure similar to that described in Intermediate-5 by using Intermediate-63 and benzyl bromide (yield: 83 %). MS (ES+) m/z: 522.2 ($M-OH^+$).

- 5 Intermediate-65: 1-Benzhydryl-3-(6-(benzyloxy)-2,3-dihydrobenzofuran-5-yl)indolin-2-one:



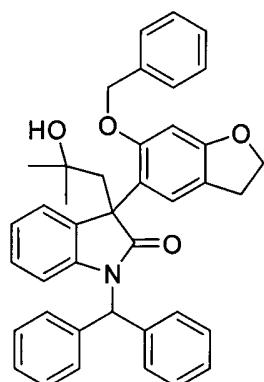
The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-64 (yield: 74 %).

- Intermediate-66: Ethyl 2-(1-benzhydryl-3-(6-(benzyloxy)-2,3-dihydrobenzofuran-5-yl)-2-oxoindolin-3-yl)acetate:
10



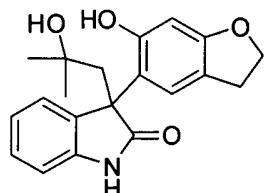
The title compound was prepared by following a procedure similar to that described in Intermediate-7 by using Intermediate-65 and ethyl bromoacetate (yield: 75 %). MS (ES+) m/z: 610.3 (M^+), 632.2($M^+ Na$).

- 5 Intermediate-67: 1-Benzhydryl-3-(6-(benzyloxy)-2,3-dihydrobenzofuran-5-yl)-3-(2-hydroxy-2-methylpropyl) indolin-2-one



The title compound was prepared by following a procedure similar to that described in Intermediate-8 by using Intermediate-66 and methyl magnesium bromide (yield: 89 %). MS (ES+) m/z: 578.3 ($M-OH^+$).

Intermediate-68: 3-(6-Hydroxy-2,3-dihydrobenzofuran-5-yl)-3-(2-hydroxy-2-methylpropyl)indolin-2-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-67 (yield: 45 %). MS (ES+) m/z: 322.1 ($M-OH^+$).

Intermediate-69: 3-Chloro-1-(2,4-dihydroxyphenyl)propan-1-one:

To a stirred mixture of resorcinol (10 g, 91 mmol) and 3-chloropropanoic acid (9.95 g, 92 mmol) was added trifluoromethanesulfonic acid (50 g, 333 mmol) in one portion. The solution was warmed to 80 °C for 30 min, cooled to room temperature over 15 min, and poured into dichloromethane (200 mL). The resulting solution was slowly poured into water (200 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL), dried over anhydrous sodium sulfate, and filtered.

Concentration under reduced pressure afforded the title compound (13.62 g, 67.9 mmol, 74.8 % yield) as an orange semisolid. The compound was used without any further purification.

Intermediate-70: 7-hydroxychroman-4-one:

To a stirred 2 M solution of sodium hydroxide (500 mL, 1000 mmol) at 5 °C was added Intermediate-69 13.6 g, 67.9 mmol) in one portion. The solution was warmed to room temperature over 2 h, re-cooled to 5 °C, and the pH was adjusted to ~2 with 6 M aqueous sulfuric acid (-50 mL). An orange precipitant formed which was collected by vacuum filtration and dried under reduced pressure. The filtrate was extracted with ethyl acetate (3 x 100 mL), washed with brine, and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave an orange solid. The two recovered solids were combined to give 7-hydroxychroman-4-one (9.0 g, 54.8 mmol, 81% yield). 1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, $J = 8.0$ Hz, 1H), 6.54 (dd, $J = 2.4, 8.0$ Hz, 1H), 6.40 (d, $J = 2.4$ Hz, 1H), 4.52 (m, 2H), 2.88 (m, 2H); GCMS: 163.9 (M^+).

Intermediate-71: 7-(Benzylxyloxy)chroman-4-one:

The title compound was prepared by following a procedure similar to that described in Intermediate-51 by using Intermediate-70 and benzyl bromide (yield: 90 %). GCMS: 239.91 (M^+).

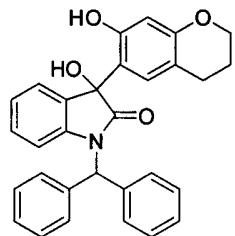
Intermediate-72: 7-(Benzylxyloxy)chroman:

The title compound was prepared by following a procedure similar to that described in Intermediate-53 by using Intermediate-71 (yield: 70 %). This compound was used without further purification for the next step. GCMS: 150.06(M⁺).

Intermediate-73: Chroman-7-ol:

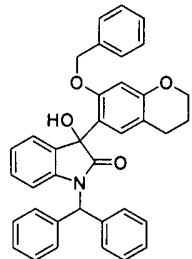
- 5 The title compound was prepared by following a procedure similar to that described in Intermediate-54 by using Intermediate-72 (yield: 60 % as white solid). GCMS: 162.96 (M⁺).

Intermediate-74: 1-Benzhydryl-3-hydroxy-3-(7-hydroxychroman-6-yl)indolin-2-one:



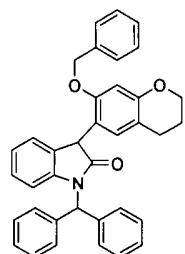
- 10 The title compound was prepared by following a procedure similar to that described in Intermediate-4 by using Intermediate-73 and Intermediate-20 (yield: 93 %). MS (ES+) m/z: 464.08 (M-18⁺).

Intermediate-75: 1-Benzhydryl-3-(7-(benzyloxy)chroman-6-yl)-3-hydroxyindolin-2-one:



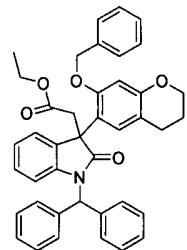
- 15 The title compound was prepared by following a procedure similar to that described in Intermediate-5 by using Intermediate-74 and benzyl bromide (yield: 97 %). MS (ES+) m/z: 536.2 (M-OH⁺).

Intermediate-76: 1-Benzhydryl-3-(7-(benzyloxy)chroman-6-yl)indolin-2-one:



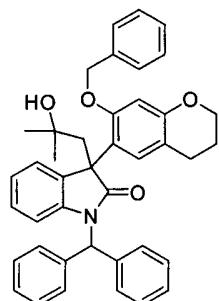
The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-75 (yield: 92 %). The crude compound was used as such for the next step without further purification.

- 5 Intermediate-77: Ethyl 2-(1-benzhydryl-3-(7-(benzyloxy)chroman-6-yl)-2-oxoindolin-3-yl)acetate:



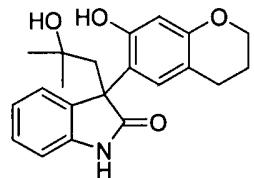
The title compound was prepared by following a procedure similar to that described in Intermediate-7 by using Intermediate-76 and ethyl bromoacetate (yield: 81 %). The crude 10 compound was used as such for the next step without further purification.

- Intermediate-78: 1-Benzhydryl-3-(7-(benzyloxy)chroman-6-yl)-3-(2-hydroxy-2-methylpropyl)indolin-2-one:



The title compound was prepared by following a procedure similar to that described in 15 Intermediate-8 by using Intermediate-77 and methyl magnesium bromide (yield: 94 %). MS (ES+) m/z: 610.3 (M⁺), 592.3 (M-OH).

Intermediate-79: 3-(2-Hydroxy-2-methylpropyl)-3-(7-hydroxychroman-6-yl) indolin-2-one:

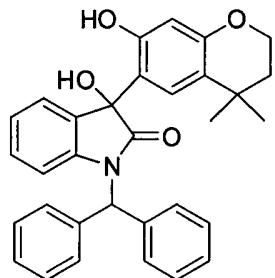


The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-78 (yield: 58 %). MS (ES+) m/z: 353.1 (M-OH).

5 Intermediate-80: 4,4-Dimethylchroman-7-ol:

The title compound was prepared according to the procedure reported in Patent US2006/100460 A1.

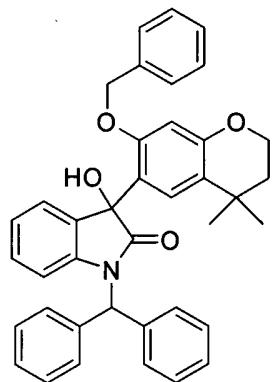
Intermediate-81: 1-Benzhydryl-3-hydroxy-3-(7-hydroxy-4,4-dimethylchroman-6-yl)indolin-2-one:



10

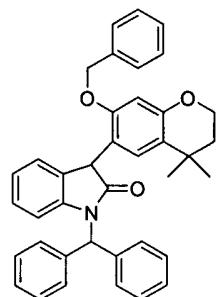
The title compound was prepared by following a procedure similar to that described in Intermediate-4 by using Intermediate-80 and Intermediate-20 (yield: 60 %). MS (ES+) m/z: 473.3 (M-18).

15 Intermediate-82: 1-Benzhydryl-3-(7-(benzyloxy)-4,4-dimethylchroman-6-yl)-3-hydroxyindolin-2-one:



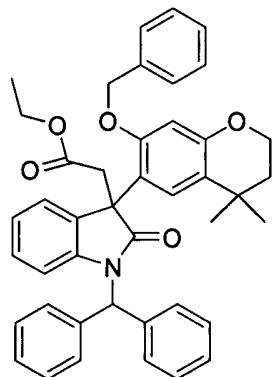
The title compound was prepared by following a procedure similar to that described in Intermediate-5 by using Intermediate-81 and benzyl bromide (yield: 85 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.37 (s, 1H), 7.37-7.28 (m, 8H), 7.13-7.07 (m, 4H), 6.93-6.82 (m, 3H), 6.66 (s, 1H), 6.63-6.58 (m, 3H), 6.02 (s, 1H), 4.63 (d, *J* = 14.0 Hz, 1H), 4.29 (d, *J* = 14.0 Hz, 1H), 4.06-3.99 (m, 2H), 1.74-1.71 (m, 2H), 1.30 (s, 6H); MS (ES+) m/z: 564.2 (M-OH).

Intermediate-83: 1-Benzhydryl-3-(7-(benzyloxy)-4,4-dimethylchroman-6-yl)indolin-2-one:



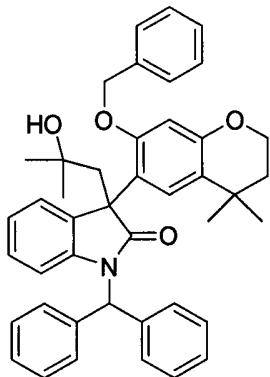
The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-82 (yield: 80 %). The crude compound was used 10 proceeded as such for the next step without further purification.

Intermediate-84: Ethyl 2-(1-benzhydryl-3-(7-(benzyloxy)-4,4-dimethylchroman-6-yl)-2-oxoindolin-3-yl)acetate:



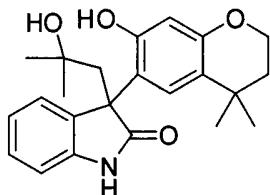
The title compound was prepared by following a procedure similar to that described in 15 Intermediate-7 by using Intermediate-83 and ethyl bromoacetate (Yield: 82 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.43-7.11 (m, 16H), 7.09-6.96 (m, 4H), 6.66-6.61 (m, 2H), 6.06 (s, 1H), 4.69 (d, *J* = 14.0 Hz, 1H), 4.35 (d, *J* = 14.0 Hz, 1H), 4.06-3.99 (m, 2H), 1.74-1.71 (m, 2H), 3.81-3.78 (m, 2H), 1.25-1.44 (m, 9H); MS (ES+) m/z: 652.3 (M⁺).

Intermediate-85: 1-Benzhydryl-3-(7-(benzyloxy)-4,4-dimethylchroman-6-yl)-3-(2-hydroxy-2-methylpropyl) indolin-2-one:



- The title compound was prepared by following a procedure similar to that described in
 5 Intermediate-8 by using Intermediate-84 and methyl magnesium bromide (Yield: 82 %).
 MS (ES+) m/z: 620.3 (M-OH⁺).

Intermediate-86: 3-(2-Hydroxy-2-methylpropyl)-3-(7-hydroxy-4,4-dimethyl chroman-6-yl)indolin-2-one:



- 10 The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-85 (Yield: 82 %). MS (ES+) m/z: 382.44(M⁺), 364.44 (M-OH).

Intermediate-87: 2,2-Dimethylchroman-7-ol:

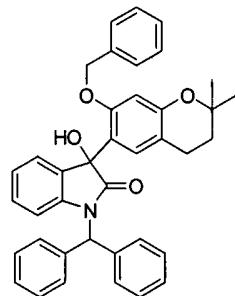
- The title compound was prepared according to the procedure reported in US2006/100460.
 15 ¹H NMR (400 MHz, CDCl₃): δ 7.18 (d, J = 8.0 Hz, 1H), 6.40 (dd, J = 2.4, 8.0 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 4.19-4.13 (m, 2H), 1.82-1.78 (m, 2H), 3.17 (s, 6H). MS(TIC) m/z: 177.08 (M-1⁺).

Intermediate-88: 1-Benzhydryl-3-hydroxy-3-(7-hydroxy-2,2-dimethylchroman-6-yl)indolin-2-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-4 by using Intermediate-87 and Intermediate-20 (yield: 85 %). MS (ES+) m/z: 475.08 ($M-17^+$).

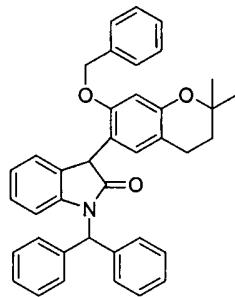
- 5 Intermediate-89: 1-Benzhydryl-3-(7-(benzyloxy)-2,2-dimethylchroman-6-yl)-3-hydroxyindolin-2-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-5 by using Intermediate-88 and benzyl bromide (yield: 92 %). MS (ES+) m/z:

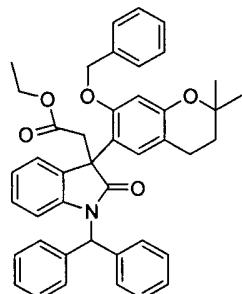
- 10 564.2 ($M-OH^+$).

Intermediate-90: 1-Benzhydryl-3-(7-(benzyloxy)-2,2-dimethylchroman-6-yl)indolin-2-one:



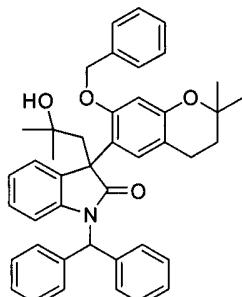
- The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-89 (yield: 83 %). The crude compound was proceed as
15 such for the next step without further purification.

Intermediate-91: Ethyl 2-(1-benzhydryl-3-(7-(benzyloxy)-2,2-dimethylchroman-6-yl)-2-oxoindolin-3-yl)acetate:



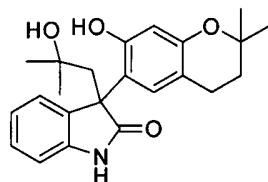
- The title compound was prepared by following a procedure similar to that described in
5 Intermediate-7 by taking Intermediate-90 and ethyl bromoacetate (yield: 75 %). MS (ES+) m/z: 652.3 (M+).

Intermediate-92: 1-Benzhydryl-3-(7-(benzyloxy)-2,2-dimethylchroman-6-yl)-3-(2-hydroxy-2-methylpropyl) indolin-2-one:



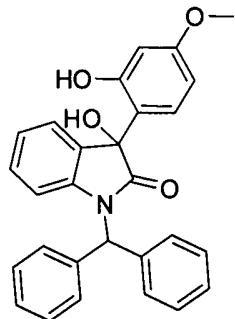
- 10 The title compound was prepared by following a procedure similar to that described in Intermediate-8 by using Intermediate-91 and methyl magnesium bromide (yield: 89 %). MS (ES+) m/z: 620.3(M-OH).

Intermediate-93: 3-(7-Hydroxy-2,2-dimethylchroman-6-yl)-3-(2-hydroxy-2-methylpropyl)indolin-2-one:



- 15 The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-92 (yield: 55 %). MS (ES+) m/z: 364.2 (M-OH⁺).

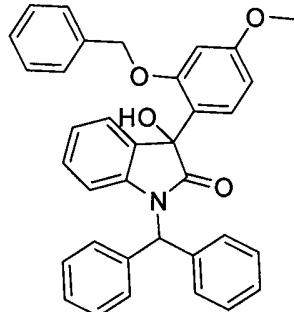
Intermediate-94: 1-Benzhydryl-3-hydroxy-3-(2-hydroxy-4-methoxyphenyl) indolin-2-one:



The title compound was prepared by following a procedure similar to that described in Intermediate-4 by using Intermediate-20 and 3-methoxyphenol (yield: 85 %). ¹H NMR (400

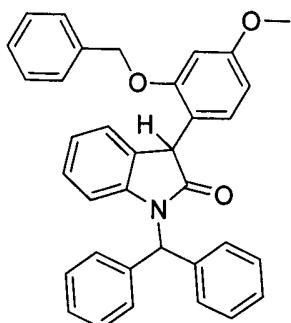
- 5 MHz, DMSO-*d*₆): δ 9.546 (s, 1H), 7.66-7.68 (m, 10H), 7.24 (d, *J* = 7.12 Hz, 1H), 7.172-
7.368 (m, 9H), 6.443-6.554 (m, 2H), 6.83-6.95 (m 4H), 6.20-6.32 (d, 2H); MS (ES+) m/z:
420.2 (M-OH).

Intermediate-95: 1-Benzhydryl-3-(2-(benzyloxy)-4-methoxyphenyl)-3-hydroxyindolin-2-one:



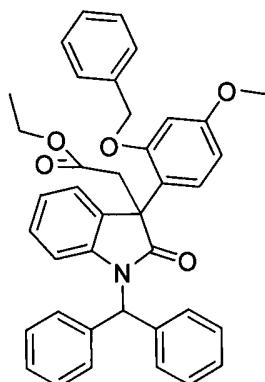
- 10 The title compound was prepared by following a procedure similar to that described in Intermediate-5 by using Intermediate-94 and benzyl bromide (yield: 96.2 %). ¹H NMR (400
MHz, DMSO-*d*₆): δ 7.78-7.80 (m, *J* = 8.8 Hz, 1H), 7.239-7.392 (m, 10H), 7.05-7.16 (m, 3H),
6.92-6.95 (t, *J* = 7.2 Hz, 1H), 6.83-6.80 (m, 2H), 6.55-6.63 (m, 4H), 6.25-6.26 (d, *J* = 2.4 Hz,
1H), 6.68 (s, 1H), 4.71-4.75 (d, *J* = 14.4 Hz, 1H), 4.38-4.37 (d, *J* = 14.4 Hz, 1H) 3.64 (s 3H);
15 MS (ES+) m/z: 510.2 (M-OH).

Intermediate-96: 1-Benzhydryl-3-(2-(benzyloxy)-4-methoxyphenyl)indolin-2-one



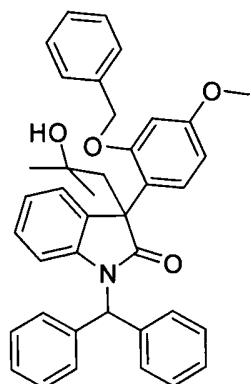
The title compound was prepared by following a procedure similar to that described in Intermediate-6 by using Intermediate-95.

Intermediate-97: Ethyl 2-(1-benzhydryl-3-(2-(benzyloxy)-4-methoxyphenyl)-2-oxoindolin-3-yl) acetate:



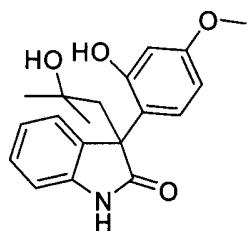
The title compound was prepared by following a procedure similar to that described in Intermediate-7 by taking Intermediate-96 and ethyl bromoacetate. (yield: 59 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.39-7.38 (m, 2H), 7.35-7.27 (m, 8H), 7.21-7.18 (m, 4H), 7.12-10 7.11(d 1H J=7.6Hz), 7.03 7.03(m, 1H), 6.89-6.86 (m, 4H), 6.54-6.52 (d, *J* = 8.0 Hz, 1H), 6.43-6.40 (dd, *J* = 2.4 Hz, 1H), 4.77-4.74 (d, *J* = 13.6 Hz, 1H), 4.38-4.34 (d *J* = 13.2 Hz, 1H), 3.85-3.74 (m, 1H), 3.62-3.58 (d, *J* = 14.8 Hz, 1H), 3.16-3.12 (d, *J* = 14.4 Hz, 1H), 0.84-0.81 (m, 3H); MS (ES+) m/z: 598.3 (M+1).

Intermediate-98: 1-Benzhydryl-3-(2-(benzyloxy)-4-methoxyphenyl)-3-(2-hydroxy -2-methyl propyl)indolin-2-one:



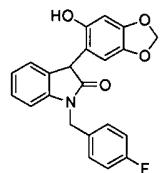
The title compound was prepared by following a procedure similar to that described in Intermediate-8 by using Intermediate-97 121 and methyl magnesium bromide (yield: 89.5 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.39 (m, 2H), 7.35-7.27 (m, 8H), 7.21-7.18 (m, 4H), 5 7.12-7.11(d, J = 7.6Hz, 1H), 7.03 (m, 1H), 6.89-6.86 (m, 4H), 6.54-6.52 (d, J = 8.0 Hz, 1H), 6.43-6.40 (dd, J = 2.4 Hz, 1H), 4.77-4.74 (d, 1H J =13.6Hz), 3.85-3.74 (m, 1H), 3.620-3.58 (d, J = 14.8 Hz, 1H), 3.16-3.12(d, J = 14.4 Hz, 1H), 0.84-0.81(m, 3H); MS (ES+) m/z: 598.3 (M+1).

Intermediate-99: 3-(2-Hydroxy-2-methylpropyl)-3-(2-hydroxy-4-methoxyphenyl) indolin-2-one:



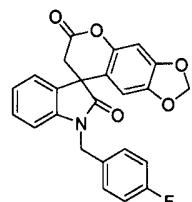
The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-98. ^1H NMR (400 MHz, DMSO- d_6): δ 10.55 (s, 1 H), 9.89 (s, 1H) , 7.15-7.10 (m, 3H), 6.89- 6.79 (m, 2H), 6.37-6.34 (dd, J = 2.8, 8.8 Hz, 1H), 15 6.27 (d, J = 2.8 Hz, 1H), 4.14 (s, 1H), 3.66 (s, 3H), 2.58-2.43 (m, 2H), 0.82(s, 3H); 0.79(s, 3H); MS (ES+) m/z: 310.2 (M-OH), 328.2 (M+1), 350.2 (M₊Na⁺).

Intermediate-100: 1-(4-Fluorobenzyl)-3-(6-hydroxybenzo[d][1,3]dioxol-5-yl) indolin-2-one:



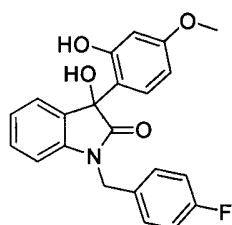
The title compound (10.5 g, 91.7 %) was prepared by following a procedure similar to that described in Intermediate-6 by taking Intermediate-4. ^1H NMR (400 MHz, DMSO- d_6): δ 9.15 (s, 1H), 7.46-7.42 (m, 2H), 7.17-7.12 (m, 3H), 6.97-6.89 (m, 2H), 6.82 (d, J = 7.6 Hz, 2H), 5 6.68 (s, 1H), 6.40 (s, 1H), 5.92 (d, J = 3.2 Hz, 1H), 5.00-4.80 (m, 3H); MS (ES+) m/z: 378.2 (M+1).

Intermediate-101: 1'-(4-Fluorobenzyl)spiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indoline]-2',6(7H)-dione:



10 To a stirred solution of Intermediate-100 (10.0 g, 26.5 mmol) and cesium carbonate (21.5 g, 1.11 mmol) in acetone (200.0 mL) was added bromoacetyl bromide (2.8 mL, 33.1 mmol). The reaction mixture was stirred at ambient temperature. After completion of reaction, the reaction mixture was concentrated under *vacuo*, followed by dilution with water. The organic compound was extracted with EtOAc (2 \times 250 mL). The organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 30% ethyl acetate in petroleum ether to afford solid the diastereomeric compounds (4.5 g, 40.6 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.37-7.29 (m, 4H), 7.19-7.12 (m, 3H), 7.08 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.01 (s, 2H), 5.89 (s, 1H), 4.88 (s, 2H), 2.58 (d, J = 14.4 Hz, 1H), 2.97 (d, J = 16.0 Hz, 1H); MS 15 (ES+) m/z: 418.1 (M+1).

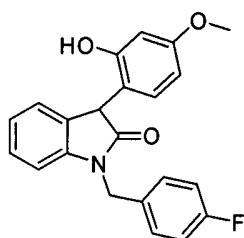
Intermediate-102: 1-(4-Fluorobenzyl)-3-hydroxy-3-(2-hydroxy-4-methoxyphenyl) indolin-2-one:



To a stirred solution of 3-methoxy phenol (0.85 ml, 7.84 mmol) in dry THF (5 ml) was added isopropylmagnesium chloride (2M in THF, 3.92 ml, 7.84 mmol) dropwise at 0°C. The resulting suspension was stirred for 1h at 0 °C which was added dropwise to the suspension 5 of Intermediate-3 (1g, 3.94 mmol) in dry THF (5 ml) at 0°C. After addition, the reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was quenched with addition of a saturated aqueous NH₄Cl solution (20 ml) and followed by EtOAc (50 ml). The phases were separated and the combined organic extract was washed with water (2 x 25 ml) and brine (25 ml), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to get the 10 residue which was purified by column chromatography over silica gel (mesh 100-200) with isocratic elution of 30% ethyl acetate in petroleum ether to afford the title compound (1.26 g, 64%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.40 (s, 1H), 7.64 (d, J= 8.8 Hz, 1H), 7.55-7.45 (m, 2H), 7.20-7.10 (m, 3H), 6.95-6.85 (m, 2H), 6.77 (d, J= 7.60 Hz, 1H), 6.53 (s, 1H), 6.49 (dd, J=8.40, J=2.40 Hz, 1H), 6.21(d, J= 2.4 Hz, 1H), 5.00-4.80 (m, 2H), 3.69 (s, 3H); MS (ES+) m/z : 362.1 (M-17)

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Intermediate-103: 1-(4-Fluorobenzyl)-3-(2-hydroxy-4-methoxyphenyl)indolin-2-one:

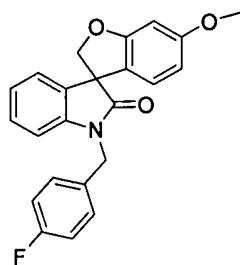


To a stirred solution of Intermediate-102 (1.5g, 3.95 mmol) in dry dichloromethane (15 ml) was added triethylsilane (3 ml, 18.78mmol) and trifluoroacetic acid (3 ml, 40.4mmol) 20 dropwise at 0°C. The resulting solution was stirred for 3h at 0-10°C. The reaction mixture was quenched with addition of saturated aqueous NH₄Cl solution (20 ml) and followed by

dichloromethane (50ml). The phases were separated and the combined organic extract was washed with water (2 x 25 ml) and brine (25 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue which was purified by column chromatography over silica gel (mesh 100-200) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford the title compound (0.92 g, 63%) as an off white solid.

¹H NMR (400 MHz, DMSO-d₆): δ 9.55 (s, 1H), 7.50-7.40 (m, 2H), 7.20-7.00 (m, 4H), 7.00-6.80 (m, 3H), 5.15-4.80 (m, 4H), 4.79 (s, 1H), 3.73 (s, 3H). MS (ES+) m/z : 364.2 (M+1)

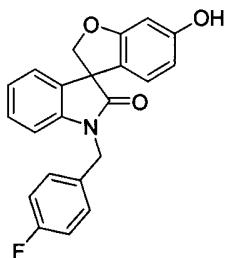
Intermediate-104: 1'-(4-Fluorobenzyl)-6-methoxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one:



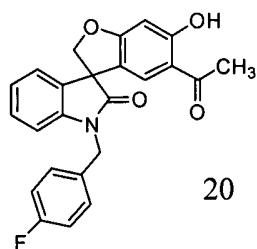
To a stirred solution of Intermediate-103 (10g, 27.52 mmol) in dry THF (75 ml) was added cesium carbonate (32.28 g, 99.069 mmol) at room temperature. The resulting suspension was stirred for 30 min. at room temperature and then chloroiodomethane (6 ml, 82.56 mmol) was added dropwise to the above suspension and stirred the reaction mixture at room temperature for 15 hours. The reaction mixture was quenched with the addition of water (50 ml) and followed by EtOAc (150 ml). The phases were separated and the combined organic extract was washed with water (2 x 50 ml) and brine(50 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue which was purified by column chromatography over silica gel (mesh 100-200) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (6.97 g, 67%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 7.45-7.35 (m, 2H), 7.30-7.15 (m, 4H), 7.10-7.00 (m, 2H), 6.59 (d, J= 2.0 Hz, 1H), 6.52 (d, J= 8.4 Hz, 1H), 6.38 (dd, J= 8.2, J= 2.0 Hz, 1H), 5.00-4.73 (m, 4H), 3.73 (s, 3H). MS (ES+) m/z: 376.1 (M+1).

Intermediate-105: 1'-(4-Fluorobenzyl)-6-hydroxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one

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- To a stirred solution of Intermediate-104 (0.97 g, 2.58 mmol) in dry dichloromethane (10 ml) was added boron tribromide (0.55 ml, 5.68 mmol) slowly at -78°C under nitrogen atmosphere. The resulting reddish coloured solution was allowed to warm to 0°C gradually within 0.5 h. The reaction mixture was cooled to -40°C and quenched with a saturated aqueous NaHCO₃ solution (15 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 25 ml). The combined organic extract was washed with water (2x20 ml), brine (20 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to obtain a residue, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford the title compound (0.8 g, 85%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.60 (s, 1H), 7.45-7.35 (m, 2H), 7.30-7.10 (m, 4H), 7.10-6.90 (m, 2H), 6.40 (d, J= 8.4 Hz, 1H), 6.35 (d, J= 2.0 Hz, 1H), 6.22 (dd, J=8.4, 2.4 Hz, 1H), 5.00-4.70 (m, 4H); MS (ES+) m/z: 362.0 (M+1)
- 15 Intermediate-106: 5-Acetyl-1'-(4-fluorobenzyl)-6-hydroxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one

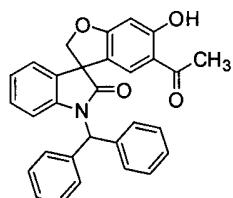


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To a stirred solution of Intermediate-105 (5 g, 13.84 mmol) in dry dichloromethane (50 ml) was added acetyl chloride (1.2 ml, 16.60 mmol) and then anhydrous aluminum chloride (6.45 g, 48.43 mmol) slowly at 0°C under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 48 h. The reaction mixture was cooled to 0°C and 1N HCl (50 ml) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic extract was washed with water (2x75 ml), brine (25 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (5 g, 90%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 7.50-7.40 (m, 2H), 7.30-7.15 (m, 4H), 7.10-7.00 (m, 3H), 6.56 (s, 1H), 5.00-4.85 (m, 4H), 2.38 (s, 3H); MS (ES+) m/z: 404 (M+1).

Intermediate-107: 5-Acetyl-1'-benzhydryl-6-hydroxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one

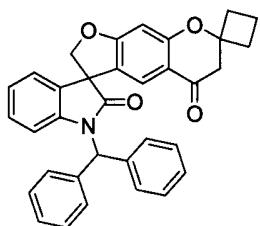
15



To a stirred solution of 1'-benzhydryl-6-hydroxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one, (prepared by following a procedure reported in WO2010/45251 A2, 2010) (5 g, 11.92 mmol) in dry dichloromethane (50 ml) was added acetyl chloride (1.0 ml, 14.30 mmol) and then anhydrous aluminum chloride (5.56 g, 41.70 mmol) slowly at 0°C under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 48 h. The reaction mixture was cooled to 0°C and 1N HCl (50 ml) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic extract was washed with water (2x75 ml), brine (25 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate

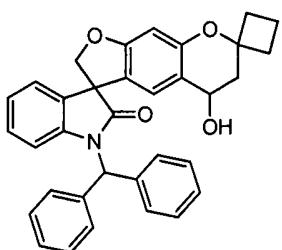
in petroleum ether to afford the title compound (2.0g, 36%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.81 (s, 1H), 7.43-7.34 (m, 8H), 7.33-7.27 (m, 3H), 7.16 (dt, J=7.6Hz , J=1.2Hz 1H), 7.02 (t, J=1.2Hz, 1H), 6.99 (s, 1H), 6.88(s, 1H), 6.63 (d, J=8.0Hz, 1H), 6.55 (s, 1H), 5.03-4.72 (m, 2H), 2.35(s, 3H) ; MS (ES+) m/z : 462.1 (M+1).

5 Intermediate-108:



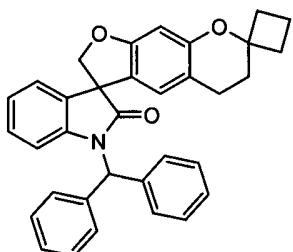
To a stirred solution of Intermediate-107 (4.1 g, 8.88 mmol) in methanol (40 ml) was added pyrrolidine (1.48 ml, 17.77 mmol) slowly at ambient temperature under nitrogen atmosphere. The resulting solution was stirred for 0.5 h. Then, cyclobutanone (1.33 ml, 17.77 mmol) was 10 added to the reaction mixture and heated to reflux for 16 h. The solvent was evaporated *in vacuo* and the residue was partitioned between 1N HCl (100 ml) and ethyl acetate (100ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extract was washed with water (2 x 50 ml), brine (50 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue, 15 which was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Intermediate-108 (2.8 g, 54%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 7.50-7.25 (m, 11H), 7.20-7.12 (m, 1H), 7.10-7.00 (m, 1H), 6.95(s, 1H), 6.88 (s, 1H), 6.65 (s, 1H), 6.62 (d, J=8.0Hz, 1H), 5.10-4.90 (m, 2H), 3.90-3.80 (m, 2H), 2.52-2.00(m, 2H), 2.85-2.65(m, 3H), 20 1.30-1.20(m, 1H) ; MS (ES+) m/z : 514.3 (M+1), 582.3 (80%).

Intermediate-109:



To a stirred solution of Intermediate-108 (0.94 g, 2.06 mmol) in methanol (10 ml) and THF (10ml) was added sodium borohydride (0.39 g, 10.31 mmol) slowly at 0°C under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 16 h. The solvent 5 was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (50 ml) and water (50 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extract was washed with water (2x20 ml) and brine (25 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue, which was purified by column chromatography over silica gel (100-200 10 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford Intermediate-109 (0.93 g) as an off white solid. ¹H NMR: (400 MHz, DMSO-d₆): δ 7.45-7.32 (m, 8H), 7.30-7.20 (m, 3H), 7.15-7.05 (m, 1H), 6.95-6.85 (m, 1H), 6.90 (s, 1H), 6.70-6.58 (m, 2H), 6.32 (s, 1H), 5.35-5.20 (m, 1H), 4.90-4.73 (m, 2H), 4.55-4.45 (m, 1H); 2.25-2.00 (m, 5H), 1.80-1.60(m, 3H); MS (ES+) m/z : 516.2 (M+1), 498.2 (M-17)

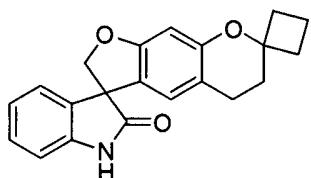
15 Intermediate-110:



A mixture of Intermediate-109 (0.9g, 1.97mmol), trifluoroacetic acid (5ml, 67.3mmol) and triethylsilane (5ml, 31.3mmol) in dichloromethane (15ml) was stirred at 0°C for 30 mins. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate

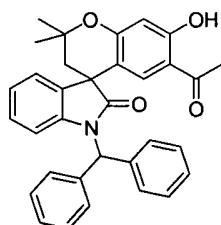
(50 ml) and water (50 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extract was washed with water (2x20 ml) and brine (25 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Intermediate-110 (0.71 g, 82%) as an off white solid. ^1H NMR: (400 MHz, CDCl_3): δ 7.40-7.30 (m, 8H), 7.15 (dd, $J=7.2\text{Hz}$, $J=1.2\text{Hz}$, 1H), 7.07 (s, 3H), 7.05-6.95 (m, 2H), 6.52 (dd, $J=7.2\text{Hz}$, $J=1.2\text{Hz}$, 1H), 6.41(s, 1H), 6.27(s, 1H), 5.00-4.65(m, 2H), 2.60-2.50 (m, 2H), 2.30-2.20 (m, 2H), 2.05-1.95 (m, 2H), 1.90-1.80(m, 3H), 1.58-1.56(m, 1H); MS (ES+) m/z : 500.3 (M+1).

Intermediate-111:



To a solid Intermediate-110 (0.7g, 1.58 mmol), 10% triflic acid in trifluoroacetic acid (20 ml) was added at 0°C and stirred for 1hr. Reaction mixture was quenched with addition of saturated aqueous Na_2CO_3 (100ml) followed by ethyl acetate (50ml) at 0°C. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extract was washed with water (2x20 ml) and brine (25 ml) and dried over anhydrous sodium sulphate. The solvent was concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 25% ethyl acetate in petroleum ether to afford Intermediate-111 (0.71 g, 82%) as an off white solid. ^1H NMR: (400 MHz, DMSO-d_6): δ 10.56 (S,1H), 7.22 (dt, $J=7.4\text{Hz}$, $J=2.8\text{Hz}$, 1H), 7.10 (d, $J=7.2\text{Hz}$, 1H), 6.96 (dt, $J=7.4\text{Hz}$, $J=2.8\text{Hz}$, 1H), 6.91(d, $J=7.6\text{Hz}$, 1H), 6.36 (s, 1H), 6.31 (s, 1H), 4.75-4.56 (m, 2H), 2.60-2.50 (m, 2H), 2.20-2.10 (m, 2H), 2.05-1.95 (m, 2H), 1.85-1.71 (m, 3H), 1.70-1.58 (m, 1H) ; MS (ES+) m/z : 334.5 (M+1).

Intermediate-112: 6-Acetyl-1'-benzhydryl-7-hydroxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one:



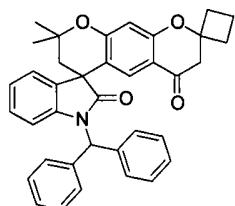
To a stirred solution of Intermediate-33 (28g, 60.66 mmol) in dry dichloromethane (800ml)

5 was added acetyl chloride (5.2ml, 9.05 mmol) and then anhydrous aluminium chloride (28.25g, 211.78 mmol) slowly lotwise at 0°C under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 48 h. The reaction mixture was cooled to 0°C and 1N HCl (500 ml) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 100 ml). The combined organic extracts were washed

10 with water (2x250 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (13.5g, 45%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 11.76 (s, 1H), 7.53-7.25 (m, 10H), 7.20-7.15 (m, 3H), 7.14-7.10 (m, 1H), 7.02-6.85 (m, 1H), 6.80 (s, 1H), 6.40 (s, 1H), 2.40-2.20 (m, 2H), 2.18 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H) ; MS (ES+) m/z : 484 (M+1).

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Intermediate-113:

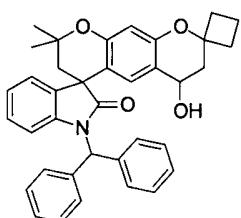


To a stirred solution of Intermediate-112 (10.1 g, 20.05 mmol) in methanol (100ml)

20 was added pyrrolidine (3.35ml, 40.11mmol) slowly at ambient temperature under nitrogen

atmosphere. The resulting solution was stirred for 0.5 h. Then, cyclobutanone (5.99ml, 80.22mmol) was added to the reaction mixture and heated to reflux for 16 h. The solvent was evaporated *in vacuo* and the residue was partitioned between 1N HCl (100 ml) and ethyl acetate (100ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed with water (2 x 50 ml), brine (50 ml) and dried over anhydrous sodium sulphate. The solvent was concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Intermediate-113 (9.0g, 80%) as an off white solid. ^1H NMR (400 MHz, CDCl₃): δ 7.50-7.30 (m, 10H), 7.16 (s, 1H), 7.10-7.05 (m, 2H), 7.00-6.90 (m, 2H), 6.50-6.45 (m, 2H), 2.70-2.60 (m, 2H), 2.50-2.25 (m, 4H), 2.15-2.05 (m, 2H), 1.95-1.85 (m, 1H), 1.70-1.50 (m, 7H); MS (ES+) m/z : 556.2 (M+1).

Intermediate-114 :

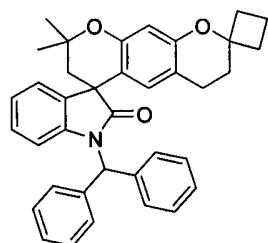


To a stirred solution of Intermediate-113 (9.0g, 16.19mmol) in methanol (45ml) and THF (45ml) was added sodium borohydride (1.84g, 48.59 mmol) slowly at 0°C under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 16 h. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (200ml) and water (200ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with water (2x20 ml) and brine (50 ml) and dried over anhydrous sodium sulphate. The solvent was concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford Intermediate-114 (8.9g, 98%) as an off white solid. ^1H NMR: (400 MHz, CDCl₃): δ 7.40-

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7.28 (m, 9H), 7.18-7.13 (m, 1H), 7.08-6.90 (m, 4H), 6.51-6.45 (m, 3H), 6.36 (d, $J=6.0\text{Hz}$, 1H), 4.60-4.48 (m, 1H), 2.50-2.45 (m, 1H), 2.30-2.15 (m, 5H), 2.05-1.80 (m, 4H), 1.70-1.50 (m, 6H) ; MS (ES+) m/z : 557.82 (M+1).

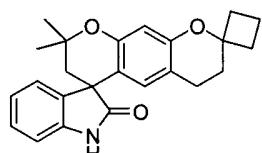
Intermediate-115:



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A mixture of Intermediate-114 (8.9g, 15.96mmol), trifluoroacetic acid (18ml) and triethylsilane (18ml) in dichloromethane (100ml) was stirred at 0°C for 2 h. The solvent was evaporated *in vacuo* and the residue was partitioned between dichloromethane (200ml) and a saturated aqueous NH₄Cl (250 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with water (2x50 ml) and brine (50 ml) and dried over anhydrous sodium sulphate. The solvent was concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Intermediate-115 (8.4g, 97%) as an off white solid. ¹H NMR: (400 MHz, CDCl₃): δ 7.45-7.30 (m, 10H), 7.18-7.16 (m, 1H), 7.10 (s, 1H), 7.00-6.90 (m, 2H), 6.52-6.49 (m, 1H), 6.35 (s, 1H), 6.05 (s, 1H), 2.50-2.40 (m, 3H), 2.30-2.20 (m, 3H), 2.05-1.95 (m, 2H); 1.90-1.80 (m, 3H), 1.70-1.60 (m, 1H), 1.56 (s, 3H), 1.51 (s, 3H); MS (ES+) m/z : 542.57 (M+1, 20%).

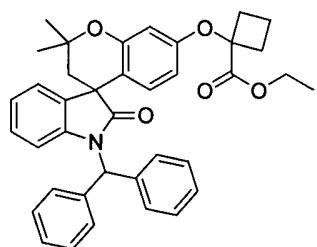
Intermediate-116 :



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To a stirred solution of Intermediate-115 (8.4 g, 15.51 mmol) in round bottom flask was added in ethyl acetate (150 ml), ammonium formate (20.0g, 317mmol) followed by 10% palladium on carbon (50% wt., 5.0g) and stirred the reaction mixture at 85°C for 3 h under a hydrogen atmosphere with the help of balloon .The reaction mixture was filtered on a Buchner 5 funnel through a celite bed. The filtrate was evaporated *in vacuo* to obtain a residue, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 25% ethyl acetate in petroleum ether to afford Intermediate-116 (5.5g, 94%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 10.50 (s, 1H), 7.19 (dt, *J*=8.0Hz, *J*=1.2Hz, 1H), 7.07 (d, *J*=8.0Hz, 1H), 6.95-6.88 (m, 2H), 6.20 (s, 1H), 6.10 (s, 1H), 2.50-2.38 10 (m, 2H), 2.32-2.26 (m, 1H), 2.15-2.04 (m, 3H), 2.01-1.92 (m, 2H), 1.85-1.70 (m, 3H), 1.68-1.55 (m, 1H), 1.42 (s, 3H), 1.40 (s, 3H); MS (ES+) m/z : 376.1 (M+1)

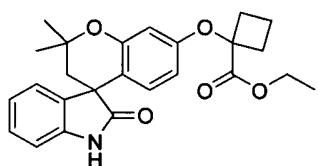
Intermediate-117: Ethyl 1-((1'-benzhydryl-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-7-yl) oxy)cyclobutanecarboxylate



15 To a stirred solution of Intermediate-33 (1.0 g, 2.17 mmol) in anhydrous DMF (10 ml) was added potassium carbonate (1.4g, 10.14 mmol) followed by ethyl-1-bromocyclobutane carboxylate, (0.35 ml, 2.17 mmol) at ambient temperature and then heated to 140°C for 6 hours under microwave condition. Reaction mixture was quenched with addition of water (100 ml) followed by ethyl acetate (100 ml). The phases were separated and the aqueous 20 phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extract was washed with water (3x50 ml), brine (50 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford the title compound (0.47g, 37%) as an off white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.29 (m, 11H), 7.10-7.15 (m, 2H), 6.98-6.88 (m, 2H), 6.30 (d, *J*=9.0Hz, 1H), 6.20 (d, *J*=2.4Hz, 1H), 6.12 (dd, *J*=8.8Hz, *J*=2.4Hz 1H), 4.19 (q, *J*=2.4Hz, 2H), 2.75-2.65 (m, 2H), 2.50-2.38 (m, 3H), 2.30-2.20 (m, 1H), 2.05-1.92 m, 2H), 1.55 (s, 3H), 1.49 (s, 3H), 1.26 (t, *J*=2.4Hz, 3H) ; MS (ES+) m/z : 588.2 (M+1).

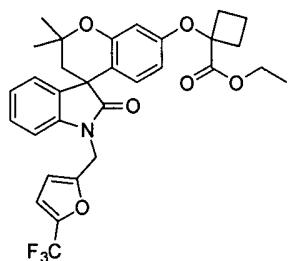
- 5 Intermediate-118: Ethyl1-((2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-7-yl) oxy)cyclobutanecarboxylate



To a stirred solution of Intermediate-117 (0.46 g, 0.787 mmol) in round bottom flask was added ethyl acetate (10 ml) followed by 10% palladium on carbon (50% wt., 0.1g) and stirred 10 the reaction mixture at 85°C under a hydrogen atmosphere with the help of ballon for 16 h. The reaction mixture was filtered on a Buchner funnel through a celite bed. The filtrate was evapourated in *vacuo* to obtain a residue, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 30% ethyl acetate in petroleum ether to afford the title compound (0.22 g, 65%) as an off white solid. ¹H NMR (400 MHz, DMSO-d6): δ 10.57 (s, 1H), 7.25-7.15 (m, 1H), 7.04 (d, *J*=7.2Hz, 1H), 6.01 (d, 2H), 6.31 (d, *J*=8.8Hz, 1H), 6.11 (dd, *J*=8.8Hz, *J*=2.8Hz, 1H), 6.01 (d, *J*=2.8Hz , 1H), 4.11 (q, *J*=7.2Hz, 2H), 2.70-2.58 (m, 2H), 2.40-2.30 (m, 3H), 2.15-2.05 (m, 1H), 1.95-1.85 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 1.07 (t, *J*=6.8Hz, 3H) ; MS (ES+) m/z : 422.1 (M+1)

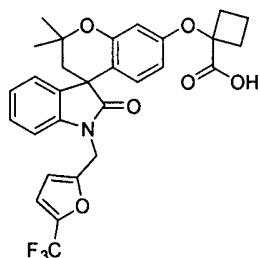
- Intermediate-119: Ethyl 1-((2,2-dimethyl-2'-oxo-1'-(5-(trifluoromethyl)furan-2-yl)methyl) 20 spiro[chroman-4,3'-indolin]-7-yl)oxy)cyclobutanecarboxylate

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To a stirred solution of Intermediate-118 (0.2g, 0.475mmol) in anhydrous DMF (5ml) was added 60% sodium hydride in mineral oil (0.028g, 0.708 mmol) followed by 2-bromomethyl-5-trifluoromethyl furan (0.12g, 0.522mmol) at 0°C and then stirred the reaction mixture at 0°C for 2 h. The reaction mixture was quenched with water (25 ml) followed by ethyl acetate (25 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 10 ml). The combined organic extract was washed with water (50 ml), brine (50 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford the title compound (0.25g, 92%) as an off white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.25-7.20 (m, 1H), 7.13-7.10 (m, 1H), 7.04-6.98 (m, 1H), 6.95-6.90 (m, 1H), 6.74-6.71 (m, 1H), 6.38-6.34 (m, 1H), 6.30 (d, *J*=8.4Hz, 1H), 6.19 (d, *J*=2.4Hz, 1H), 6.12 (dd, *J*=8.4Hz, *J*=2.4Hz, 1H), 5.10-4.85 (m, 2H), 4.18(q, *J*=7.2Hz , 2H), 2.75-2.65 (m, 2H), 2.45-2.35 (m, 3H), 2.25-2.15 (m, 1H), 2.00-1.90 (m, 2H), 1.55-1.45 (m, 6H), 1.15 (t, *J*=7.2Hz , 3H) ; MS (ES+) m/z : 570.2 (M+1).

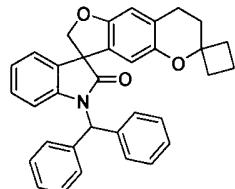
Intermediate-120: 1-((2,2-Dimethyl-2'-oxo-1'-(5-(trifluoromethyl)furan-2-yl) methyl)spiro [chroman-4,3'-indolin]-7-yl)oxy)cyclobutanecarboxylic acid



To a stirred solution of Intermediate-119 (0.25 g, 0.438 mmol) in methanol (5.0ml) and water (1.0 ml) was added Sodium hydroxide (0.08g, 2.0mmol) at ambient temperature and stirred for 16 h. The solvent was evaporated *in vacuo* and the residue was partitioned between 1N HCl (10ml) and ethyl acetate (10ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 5 ml). The combined organic extracts were washed with water (2 x 10 ml), brine (10 ml) and dried over anhydrous sodium sulphate. The solvent was concentrated *in vacuo* and the residue was purified by trituration with n-pentane to afford the title compound (0.16 g, 67%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 13.05 (s, 1H), 7.30-7.25 (m, 1H), 7.22-7.11(m, 3H), 7.05-6.95 (m, 1H), 6.75-6.70 (m, 1H), 6.36-6.26 (m, 1H), 6.22-6.20 (m, 1H), 6.05-6.00 (m, 1H), 5.15-4.98 (m, 2H), 2.70-2.60 (m, 2H), 2.40-2.15 (m, 4H), 1.95-1.85 (m, 2H), 1.48 (s, 3H), 1.44 (s, 3H); MS (ES+) m/z :542.04 (M+1).

Intermediate-121:

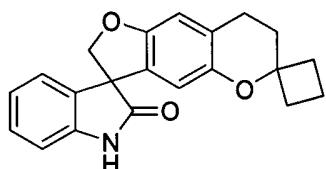
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To a stirred solution of 1'-benzhydryl-5-hydroxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one, (prepared by following a procedure reported in WO2010/45251 A2, 2010) (1g, 2.385mmol) and BF₃-etherate (1.68g, 11.92mmol) in 1,4-dioxane was added 1-vinyl cyclobutanol, Intermediate-82 (0.93g, 9.53mmol) in dioxane (10 mL) over 30 minutes at 110°C under nitrogen atmosphere. The reaction mixture was refluxed for 1 hour. The solution was diluted with water (40ml) and ethyl acetate (60ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 15 ml). The combined organic extract was washed with water (2x15 ml), brine (20 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get crude compound. It is purified by column chromatography on

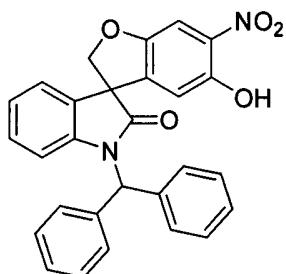
silica gel (100-200 mesh) with isocratic elution of 7% ethyl acetate in petroleum ether to afford Intermediate-121 as an off white solid (0.270 g 25%). ^1H NMR (400MHz, CDCl_3) δ 7.39-7.26 (m, 10H), 7.12 (d, $J=1.6$ Hz, 1H), 7.06 (s, 1H), 6.98-6.93 (m, 2H), 6.63 (s, 1H), 6.48 (d, $J=1.2$ Hz, 1H), 6.19 (s, 1H), 4.92 (d, $J=8.8$ Hz 1H), 4.65 (d, $J=8.8$ Hz 1H), 2.75 (t, $J=6.4$ Hz, 2H), 2.17 (t, $J=9.4$ Hz, 2H), 2.0-1.91 (m, 2H), 1.89-1.87 (m, 2H), 1.84-1.79 (m, 2H). MS (ES+) m/z : 500.3 (M+1)

Intermediate-122:



To a stirred solution of Intermediate-121 (0.270g, 0.540mmol) in trifluoroacetic acid (5ml) at 10 0°C was added 3 ml of 20% triflic acid in trifluoroacetic acid dropwise. The resultant black coloured solution was stirred at room temperature for 2 h. The reaction mixture was cooled to 0°C and neutralised by saturated aqueous Na_2CO_3 solution and added ethyl acetate (15ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 15 ml). The combined organic extract was washed with water (2 x 15ml), brine (20 ml) and dried 15 over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford Intermediate-122 (0.110g 60%) as an off white solid. ^1H NMR (400MHz, CDCl_3) δ 8.35 (s, 1H), 7.21 (d, $J=6.4$ Hz 1H), 7.13 (d, $J=7.6$ Hz 1H), 7.00 (d, $J=1.2$ Hz 1H), 6.92 (d, $J=8.0$ Hz 1H), 6.63 (s, 1H), 6.26 (s, 1H), 4.91 (d, $J=8.0$ Hz 1H), 4.64 (d, $J=8.0$ Hz 1H), 2.74 (t, $J=6.4$ Hz 2H), 2.17 (t, $J=2.8$ Hz 2H), 2.0-1.91 (m, 2H), 1.89-1.87 (m, 2H), 1.84-1.79 (m, 2H).

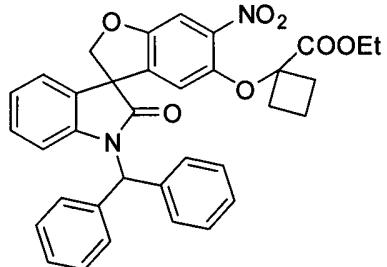
Intermediate-123: 1'-Benzhydryl-5-hydroxy-6-nitro-2H-spiro[benzofuran-3,3'-indolin]-2'-one



To a stirred solution of 1'-benzhydryl-5-hydroxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one, (prepared by followinga procedure reported in WO201045251) (1.3g, 3.0mmol) in acetonitrile (20ml) was added potassium hydrogen sulphate (1.63g, 12mmol) and sodium nitrite (0.828g, 12mmol). The reaction was heated at 50⁰C for 3h. The reaction mixture was cooled to room temperature and to this solution potassium hydrogen sulphate (0.4g, 3mmol) and sodium nitrite (0.2g, 3mmol) was added and further heated for 3 h. The reaction mixture was cooled to room temperature diluted with water (40ml) and added ethyl acetate (15ml). The phases were separated and aqueous phase was extracted with ethyl acetate (2 x 40ml).

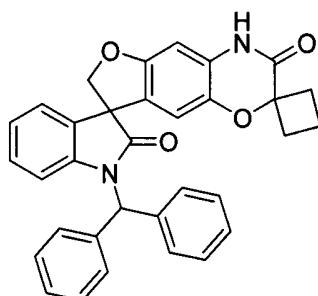
The combined organic extract was washed with water (2 x 25 ml), brine (25 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 7% ethyl acetate in petroleum ether to afford the title compound (0.350 g 25%) as an off yellow solid. ¹H NMR (400MHz, CDCl₃) δ 10.94 (s 1H), 7.48 (s, 1H), 7.45-7.24 (m, 11H), 7.17-7.10 (m, 1H), 7.04 (m, 1H), 6.87 (s, 1H), 6.61 (d, *J*=8.0Hz, 1H), 6.37 (s, 1H), 4.96 (d, *J*=9.2Hz, 1H), 4.85 (d, *J*=9.2Hz, 1H). MS (ES+) m/z : 464.2 (M+1).

Intermediate-124: Methyl 1-((1'-benzhydryl-6-nitro-2'-oxo-2H-spiro[benzofuran-3,3'-indolin]-5-yl)oxy)cyclobutanecarboxylate



To the solution of Intermediate-123 (0.350g, 0.754mmol) in acetonitrile (10ml) was added potassium carbonate (0.312g, 2.26mmol) and ethyl 1-bromocyclobutanecarboxylate (0.468g, 2.26mmol). The reaction was heated at 140°C for 3 h. The reaction mixture was cooled to room temperature and diluted with water (20ml) and added ethyl acetate (15ml). The phases 5 were separated and aqueous phase was extracted with ethyl acetate (2 x 15ml). The combined organic extracts were washed with water (2 x 15 ml), brine (15 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 10% ethyl acetate in petroleum ether to afford the title compound as an off white solid (0.140g 30%). ¹H NMR 10 (400MHz, CDCl₃) δ 7.46-7.26 (m, 11H), 7.07-7.04 (m, 1H), 7.02 (dd, *J*=1.8Hz, 7.6Hz, 2H), 6.98-6.96 (m, 1H), 6.52 (d, *J*=8.0Hz, 1H), 5.93 (s, 1H), 5.05 (d, *J*=9.2Hz, 1H), 4.78 (d, *J*=9.2Hz, 1H), 3.96-3.83 (m, 2H), 2.53-2.38 (m, 3H), 2.29-2.22 (m, 1H), 2.00-1.18 (m, 2H), 0.80 (t, *J*=7.2Hz 3H).

Intermediate-125:



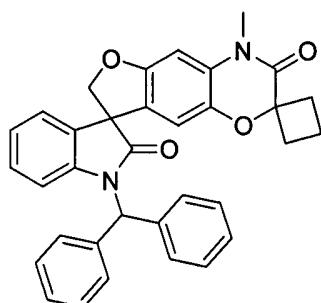
15

To a stirred solution of Intermediate-124 (0.140g 0.243mmol) in acetic acid was added iron powder (0.2g, 3.5mmol) and heated at 100°C for 3 h. The reaction mixture was cooled to room temperature and excess of Iron powder was filtered through celite bed, filtrate was evaporated to get a residue which was partitioned between ethyl acetate (15ml) and a 20 saturated aqueous NaHCO₃ solution (15ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 15ml). The combined organic extracts were washed with water (2 x 15 ml), brine (15 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography

over silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford Intermediate-125 (0.120g 90%). as an off white solid.

¹H NMR (400MHz, CDCl₃) δ 7.72 (s, 1H), 7.41-7.25 (m, 10H), 7.30 (dd, *J*=1.2Hz, 8.4Hz, 1H), 7.05-6.96 (m, 3H), 6.51 (d, *J*=0.8Hz, 1H), 6.35 (d, *J*=13.6Hz, 1H), 5.93 (s, 1H), 4.97 (d, 5 *J*=8.8Hz, 1H), 4.70 (d, *J*=8.8Hz, 1H), 2.60-2.59 (m, 1H), 2.53-2.49 (m, 1H), 2.26-2.18 (m, 2H), 1.95-1.88 (m, 2H). MS (ES+) m/z : 515.1 (M+1).

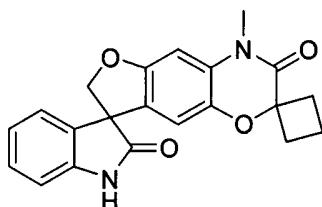
Intermediate-126:



To a stirred solution of Intermediate-125 (0.12g 0.233mmol) in *N,N*-dimethylformamide (5ml) at 0°C was added 60% sodium hydride in mineral oil (0.0071g, 0.279mmol) and was stirred for 15 minutes. To this iodomethane (0.039g, 0.279mmol) was added and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was cooled to 0°C and quenched with ice cold water (10ml) and added ethyl acetate (10ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 15ml). The combined organic extract was washed with water (2 x 10 ml), brine (15 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Intermediate- 126 (0.1g 90%) as an off white solid. ¹H NMR (400MHz, CDCl₃) δ 7.40-7.30 (m, 11H), 7.16 (dd, *J*=1.2Hz, *J*=7.2Hz, 1H), 7.07-7.04 (m, 1H), 7.02-6.99 (m, 1H), 6.50 (s, 1H), 6.53 (d, *J*=7.2Hz, 1H), 6.37 (s, 1H), 5.01 (d, *J*=8.8Hz, 1H), 4.74 (d, *J*=8.8Hz, 1H), 3.35 (s, 3H), 2.62-2.58 (m, 1H), 2.53-2.48 (m, 1H), 2.24-2.16 (m, 2H), 2.06-1.89 (m, 2H). MS (ES+) m/z : 529.2 (M+1).

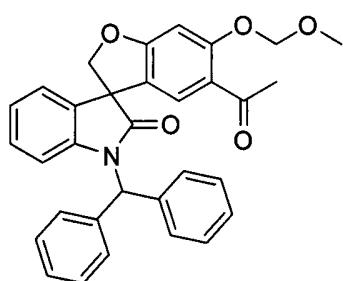
Intermediate-127:

110



To a stirred solution of Intermediate-126 (0.1g, 0.198mmol) in dichloromethane (10ml) at 0°C was added 3 ml 10% triflic acid in trifluoroacetic acid dropwise. The resultant black coloured solution was stirred at room temperature for 3 h. The reaction mixture was cooled to 5 0 °C and neutralised by a saturated aqueous Na₂CO₃ solution and then added ethyl acetate (15ml). The phases were separated and aqueous phase was extracted with ethyl acetate (2 x 15ml). The combined organic extracts were washed with water (2 x 10 ml), brine (15 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (100-200 mesh) with an isocratic elution of 10 30% ethyl acetate in petroleum ether to afford Intermediate- 127 (0.025g 40%) as an off white solid. ¹H NMR (400MHz, CDCl₃) δ 8.13 (s, 1H), 7.25 (s, 1H), 7.14 (dd, *J*=0.8Hz, *J*=7.6Hz, 1H), 7.06 (dd, *J*=0.8Hz, *J*=7.6Hz, 1H), 6.95 (d, *J*=7.6Hz, 1H), 6.57 (s, 1H), 6.47 (s, 1H), 4.97 (d, *J*=8.8Hz, 1H), 4.70 (d, *J*=8.8Hz, 1H), 3.33 (s, 3H), 2.59-2.56 (m, 1H), 2.55-2.45 (m, 1H), 2.22-2.12 (m, 2H), 1.92-1.85 (m, 2H). MS (ES+) m/z : 362.2 (M+1).

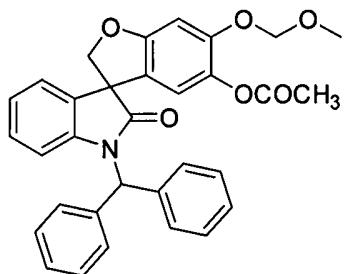
15 Intermediate-128: 5-Acetyl-1'-benzhydryl-6-(methoxymethoxy)-2H-spiro[benzo furan-3,3'-indolin]-2'-one



To a stirred solution of Intermediate-107 (5g, 10.834mmol) in N,N-dimethylformamide (40ml) at 0°C was added 60% sodium hydride in mineral oil (0.31g, 13mmol) and was stirred 20 for 15 minutes. To this chloro(methoxy) methane (1.04g, 13mmol) was added and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was cooled to 0°C and quenched with ice cold water (50ml) and added ethyl acetate (20ml). The phases

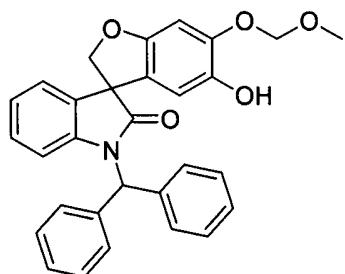
were separated and aqueous phase was extracted with ethyl acetate (2 x 40ml). The combined organic extract was washed with water (2 x 30 ml), brine (30 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford the title compound (5.0g 90%) as an off white solid. ¹H NMR (400MHz, CDCl₃) δ 7.42-7.29 (m, 11H), 7.16 (dd, J=1.2Hz, J=7.6Hz, 1H), 7.05-6.95 (m, 3H), 6.80 (s, 1H), 6.51 (d, J=7.6Hz, 1H), 5.28 (m, 2H), 5.05 (d, J=9.2Hz, 1H), 4.79 (d, J=9.2Hz, 1H), 3.51 (s, 3H), 2.53 (s, 3H).

Intermediate-129: 1'-Benzhydryl-6-(methoxymethoxy)-2'-oxo-2H-spiro[benzo furan-3,3'-indolin]-5-yl acetate



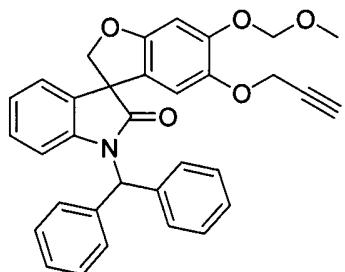
To a stirred solution of Intermediate-128 (5g 9.891mmol) in dichloromethane (50ml) was added acetic acid (2.26ml, 39.56mmol) and was stirred for 30 minutes. The reaction mixture was cooled to 0°C and m-chloroperbenzoic acid (2.56g 14.83mmol) was added and resulting solution was stirred at room temperature for 48 h. Excess of dichloromethane and acetic acid was evaporated *in vacuo*, the residue was diluted with ethyl acetate (60ml) and added saturated aqueous NaHCO₃ solution (50ml). The phases were separated and aqueous phase was extracted with ethyl acetate (2 x 40ml). The combined organic extract was washed with water (2 x 30 ml), brine (30 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford the title compound (3.3g 65%) as an off white solid. ¹H NMR (400MHz, CDCl₃) δ 7.42-7.29 (m, 11H), 7.16 (dd, J=1.2Hz, J=7.6Hz, 1H), 7.05-6.95 (m, 3H), 6.80 (s, 1H), 6.51 (d, J=7.6Hz, 1H), 5.28 (m, 2H), 5.05 (d, J=9.2Hz, 1H), 4.79 (d, J=9.2Hz, 1H), 3.51 (s, 3H), 2.21 (s, 3H).

Intermediate-130: 1'-Benzhydryl-5-hydroxy-6-(methoxymethoxy)-2H-spiro [benzo furan-3,3'-indolin]-2'-one



To a stirred solution of Intermediate-129 (0.440g 0.844 mmol) in methanol: water (1:1) (15ml) was added sodium hydroxide (0.572g, 4.226mmol) in water (2ml) . The resultant suspension was stirred at room temperature for 5 h. The reaction mixture was cooled to 0°C and pH of the solution was adjusted to 7 by 1N HCl (25ml) and the aqueous layer was diluted with ethyl acetate (15ml). The phases were separated and aqueous phase was extracted with ethyl acetate (2 x 30). The combined organic extracts were washed with water (2 x 30 ml), brine (30 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was triturated by n-pentane to afford the title compound (0.33g 80%) as an off white solid. ¹H NMR (400MHz, DMSO d₆) δ 8.72 (s, 1H), 7.46-7.28 (m, 11H), 7.20 (dd, J=1.2Hz, J=7.6Hz, 1H), 7.08 (s, 1H), 6.89 (s, 1H), 6.71 (s, 1H), 6.55 (d, J=0.8Hz, 1H), 6.09 (s, 1H), 5.12 (d, J=6.4Hz, 2H), 4.83 (d, J=9.2Hz, 1H), 4.71 (d, J=9.2Hz, 1H), 3.39 (s, 3H). MS (ES+) m/z : 480.2 (M+1).

Intermediate-131: 1'-benzhydryl-6-(methoxymethoxy)-5-(prop-2-yn-1-yloxy)-2H-spiro[benzofuran-3,3'-indolin]-2'-one

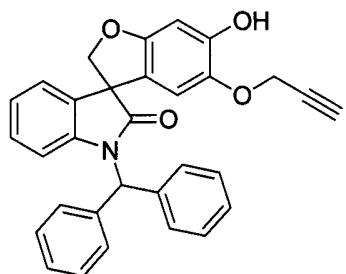


To a stirred solution of Intermediate-130 (0.8g 1.67mmol) in acetone (20ml) was added potassium carbonate (0.807g, 5.84mmol) and was stirred for 1 h, to this propargyl bromide

(0.496g, 4.17mmol) in acetone (15ml) was added carefully. The reaction mixture was heated to reflux for 16 h, reaction mixture was cooled to room temperature and was added potassium carbonate (4.17mmol) and propargyl bromide (2.0mmol); the reaction mixture was again heated to reflux for another 16 h. The reaction mixture was cooled to room temperature, 5 excess of acetone was evaporated *in vacuo*, and residue was diluted with ethyl acetate (30ml) and water (30ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 30ml). The combined organic extract was washed with water (2 x 30 ml), brine (30 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (100-200 mesh) 10 with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (0.8g 90%) as an off white solid.

¹H NMR (400MHz, CDCl₃) δ 7.38-7.28 (m, 10H), 7.16 (dd, *J*=1.2Hz, *J*=7.6Hz, 1H), 7.06-6.96 (m, 3H), 6.84 (s, 1H), 6.51-6.49 (m, 1H), 6.36 (s, 1H), 5.19 (s, 2H), 5.00 (d, *J*=8.8Hz, 1H), 4.73 (d, *J*=8.8Hz, 1H), 4.49 (m, 2H), 3.50 (s, 3H), 2.30 (s, 1H). MS (ES+) m/z : 518.2 15 (M+1).

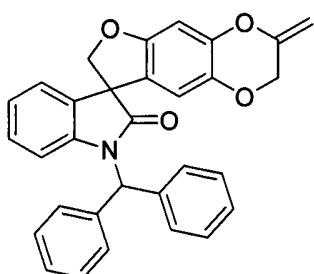
Intermediate-132: 1'-Benzhydryl-6-hydroxy-5-(prop-2-yn-1-yloxy)-2H-spiro [benzofuran-3,3'-indolin]-2'-one:



To a stirred solution of Intermediate-131 (0.8g 1.545mmol) in dichloromethane at 0°C was 20 added 1 ml trifluoroacetic acid : dichloromethane (1:1) dropwise. The resultant black coloured solution was stirred at 0°C for 20 minutes. Excess of TFA was evaporated *in vacuo*, residue was neutralised with an aqueous NaHCO₃ solution and the aqueous layer was diluted with ethyl acetate (25ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 30ml). The combined organic extracts were washed with water (2 x 30 ml), brine (20 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in* 25

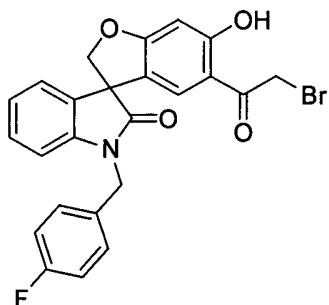
vacuo and the residue was triturated by n-pentane to afford the title compound (0.6g 80%) as an off white solid. ^1H NMR (400MHz, DMSO d_6) δ 7.44-7.28 (m, 10H), 7.19 (dd, $J=1.2\text{Hz}$, $J=7.6\text{Hz}$, 1H), 7.12-7.01 (m, 1H), 7.01- 6.98 (m, 1H), 6.88 (s, 1H), 6.59 (d, $J=8.0\text{Hz}$, 1H), 6.47 (d, $J=2.4\text{Hz}$, 1H), 6.23 (s, 1H), 4.87 (d, $J=8.0\text{Hz}$, 1H), 4.72 (d, $J=8.0\text{Hz}$, 1H), 4.49 (d, $J=2.4\text{Hz}$, 2H), 3.42 (m, 1H). MS (ES+) m/z : 474.2 (M+1).

Intermediate-133: 1'-Benzhydryl-3-methylene-3,7-dihydro-2H-spiro[[1,4]dioxino [2,3-f]benzofuran-8,3'-indolin]-2'-one:



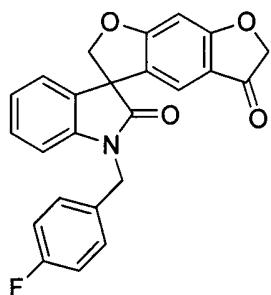
To a stirred solution of Intermediate-132 (0.6g 1.675mmol) in triethylamine (15ml) was added copper(I) iodide (0.0169g, 0.0887mmol). The resultant solution was stirred at room temperature for 30 minutes. Then it was heated to 100°C for 1 h. Excess of triethylamine was evaporated under *vacuo*, the residue was diluted with water (20ml) and ethyl acetate (20ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 20ml). The combined organic extract was washed with water (2 x 20 ml), brine (20 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (0.15g 25%) as an off white solid. ^1H NMR (400MHz, DMSO d_6) δ 7.38-7.28 (m, 10H), 7.14 (dd, $J=1.2\text{Hz}$, $J=7.6\text{Hz}$, 1H), 7.05-6.96 (m, 3H), 6.59 (s, 1H), 6.50 (dd, $J=1.2\text{Hz}$, $J=7.6\text{Hz}$, 1H), 6.25 (s, 1H), 4.97 (d, $J=8.8\text{Hz}$, 1H), 4.73 (d, $J=8.8\text{Hz}$, 1H), 4.70 (d, $J=7.2\text{Hz}$, 2H), 4.37 (s, 1H), 4.31 (d, $J=2\text{Hz}$, 1H). MS (ES+) m/z : 474.2 (M+1).

Intermediate-134: 5-(2-Bromoacetyl)-1'-(4-fluorobenzyl)-6-hydroxy-2H-spiro [benzofuran-3,3'-indolin]-2'-one:



To a stirred solution of 1'-(4-fluorobenzyl)-6-hydroxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one (prepared by following a procedure reported in WO201045251) (2 g, 5.54 mmol) in dry dichloromethane (50 ml) was added 2-bromoacetyl bromide (0.58 ml, 6.64 mmol) and then anhydrous aluminium chloride (2.58 g, 19.39 mmol) slowly at 0°C under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 48 h. The reaction mixture was cooled to 0°C and 1N HCl (50 ml) was added. The two phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with water (2x50 ml) and brine (50 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (1.5 g, 57%) as an off white solid. ¹H NMR(400 MHz, DMSO-d₆) δ 7.49-7.40 (m, 2 H), 7.32-7.26 (m, 2 H), 7.22-7.15 (m, 3 H), 7.12-7.05 (m, 2 H), 6.59 (s, 1 H), 5.00-4.61 (m, 4 H), 4.42 (s, 2 H). MS (ES+) m/z: 482.14 (M+), 484.0 (M+2).

Intermediate-135: 1'-(4-Fluorobenzyl)-2H-spiro[benzo[1,2-b:5,4-b']difuran-3,3'-indoline]-2',5-(6H)-dione:



To a stirred solution of Intermediate-134 (0.12 g, 0.248 mmol) in acetone (10 ml) was added anhydrous potassium carbonate (0.038 g, 0.273 mmol) at ambient temperature under a nitrogen atmosphere. The resulting solution was stirred at r.t. for 15 hours. The solvent was evaporated *in vacuo*. Water (20 ml), ethyl acetate (25ml) was added. The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed with water (2x15 ml), brine (20 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 18% ethyl acetate in petroleum ether to afford the title compound (0.09 g, 90%) as an off white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.32 (m, 2H), 7.29-7.26 (m, 1H), 7.19-7.15 (m, 1H), 7.15-7.05 (m, 3H), 7.01 (s, 1H), 6.86-6.80 (m, 1H), 6.67 (s, 1H), 5.16-5.00 (m, 2H), 4.90-4.86 (m, 2H), 4.65 (s, 2H); MS (ES+) m/z: 402.1 (M+1).

Intermediate-136: 6-Methoxy-1-methylindoline-2, 3-dione:

To a stirred suspension of commercially available 6-methoxyindoline-2,3-dione (0.2 g ,1.12 mmol) and sodium hydride (60% w/w dispersion in mineral oil, 0.067 g, 2.79 mmol) in dry DMF (5 ml) was added methyl iodide (0.084 ml, 1.35 mmol) slowly at 0 °C. The mixture was stirred at 0 °C for 45 min and quenched with water (10 ml) at 0 °C and added ethyl acetate. The two phases were separated and the aqueous phase was extracted with ethyl acetate (2x 25 ml). The combined organic layer was washed with water (2x20 ml), followed by brine (2x20 ml), dried over sodium sulfate and filtered. The filtrate was concentrated in vacuum to dryness to get a brown solid of 6-methoxy-1-methylindoline-2, 3-dione (0.140 g, 65%). ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 8 Hz, 1H), 6.57 (dd, J = 8 Hz, 4 Hz, 1H), 6.36 (d, J = 4 Hz, 1H), 3.93 (s, 3H), 3.22 (s, 3H); MS (ES+) m/z 191.9 (M+1), 213.9 (M+ Na)

Intermediate-137: 6-Methoxy-1-methylindolin-2-one:

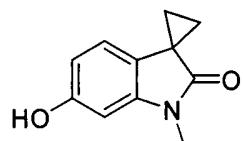
A stirred solution of Intermediate-136 (0.13 g, 0.680 mmol) in hydrazine hydrate (2 ml) was heated at 120 °C for 45 min. After cooling to room temperature, water (10 ml) was added. The aqueous phase was extracted in ethyl acetate (2 x 25 ml).The combined organic layer was washed with water (2x20 ml), followed by brine(20 ml), dried over sodium sulfate and

filtered. The filtrate was concentrated in vacuum to dryness and the residue was subjected to column chromatography over silica gel (100-200 mesh) using ethyl acetate-petroleum ether in the ratio (15:85) as an eluent to afford 6-methoxy-1-methylindolin-2-one as a yellow solid (0.055 g, 45%). ¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, J = 8 Hz, 1H), 6.54 (dd, J = 8 Hz, 4 Hz, 1H), 6.41 (d, J = 4 Hz, 1H), 3.85 (s, 3H), 3.45 (s, 2H), 3.18 (s, 3H); MS (ES+) m/z 177.9 (M+1).

Intermediate-138: 6'-Methoxy-1'-methylspiro[cyclopropane-1, 3'-indolin]-2'-one:

To a stirred solution of Intermediate-137 (0.05 g, 0.282 mmol) and 1, 2-dibromoethane (0.04 ml, 0.423 mmol) in dry DMF (1 ml) was added sodium hydride (60% w/w dispersion in mineral oil, 0.033 g, 0.847 mmol) slowly at 0 °C. The mixture was stirred at 0 °C for 1 h and quenched with methanol at -78 °C, added ethyl acetate(20 ml) followed by water(15 ml). The two phases were separated and the aqueous phase was extracted with ethyl acetate (2x 25 ml). The combined organic layer was washed with water (2x25 ml), followed by brine (20 ml) and dried over sodium sulfate. The filtrate was concentrated in vacuum to dryness and the residue was purified by column chromatography over silica gel (100-200 mesh) using 20% ethyl acetate in petroleum ether as an eluent to afford 6'-methoxy-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one as a brown solid (0.034 g, 59%). ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 8 Hz, 1H), 6.54-6.50 (m, 2 H), 3.82 (s, 3H), 3.26 (s, 3H), 1.68-1.59 (m, 2 H), 1.44-1.41 (m, 2 H); MS (ES+) m/z 204 (M+1).

Intermediate-139: 6'-Hydroxy-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one:

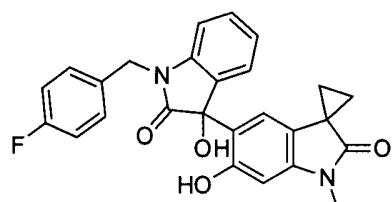


To a stirred solution of Intermediate-138 (0.15 g, 0.738 mmol) in dry dichloromethane (1 ml) was added boron tribromide 0.16 M solution (8.77 ml, 1.40 mmol) slowly at -78 °C. The mixture was stirred at 0 °C for 2.5 h and quenched with a saturated aqueous NaHCO₃ solution at -78 °C and added dichloromethane. The two phases were separated and the aqueous phase was extracted with dichloromethane (2 x 10 ml). The combined organic layer was washed with water (2x30 ml), followed by brine (30 ml) and dried over sodium sulfate.

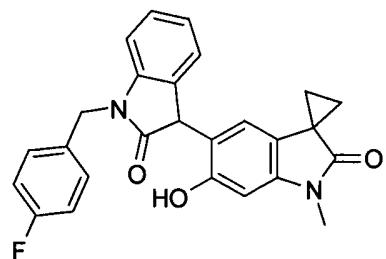
The filtrate was concentrated in vacuum to dryness and residue was subjected to column chromatography over silica gel (100-200 mesh) using ethyl acetate-petroleum ether in the ratio (40:60) as an eluent to afford the title compound (0.1 g, 71%). ¹H NMR (400 MHz, DMSO-d₆) δ 9.41 (s, 1H), 6.76 (d, J = 8 Hz, 1H), 6.48 (s, 1 H), 6.38 (d, J = 8 Hz, 1H), 3.14
5 (s, 3H), 1.46-1.37 (m, 4 H).

MS (ES+) m/z 190 (M+1), 212.0 (M+ Na).

Intermediate-140: 5'-(1-(4-Fluorobenzyl)-3-hydroxy-2-oxoindolin-3-yl)-6'-hydroxy-1'-methyl spiro[cyclopropane-1, 3'-indolin]-2'-one:

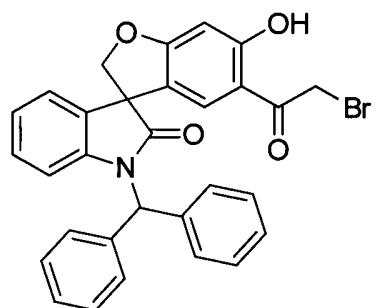


- 10 To a stirred solution of Intermediate-139 (0.07 g, 0.370 mmol) in dry tetrahydrofuran (2 ml) was added iso-propylmagnesium chloride (0.37 ml ,0.740 mmol, 2 M solution) slowly at 0 °C. After complete addition, a solid was precipitated out and this precipitate was added to 1-(4-fluorobenzyl)indoline-2,3-dione (Intermediate-3) (0.11g, 0.444 mmol) in dry tetrahydrofuran. The reaction mixture was refluxed at 70 °C for 24 h, the reaction mixture
15 was allowed to attain room temperature and quenched with a saturated aqueous NH₄Cl solution at room temperature. Ethyl acetate (10 ml) was added and the two phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 10 ml) and the combined organic layer was washed with water (15 ml), followed by brine (20 ml) and dried over sodium sulfate. The filtrate was concentrated in vacuum to dryness and the residue was
20 subjected to column chromatography over silica gel (100-200 mesh) using ethyl acetate-pet ether in the ratio(50:50) as an eluent to afford the title compound as an off white solid (0.11 g, 68%). ¹H NMR (400 MHz, DMSO-d₆) δ 9.50 (s, 1H), 7.52-7.48 (m, 2 H), 7.39 (s, 1 H), 7.19-7.14 (m, 3 H), 6.87 (d, J = 8 Hz, 2H), 6.77 (d, J = 8 Hz, 1H), 6.52 (s, 1H), 6.33 (s, 1H), 4.96-4.81 (m, 2H), 3.13 (s, 3H), 1.46-1.37 (m, 4 H). MS (ES+) m/z 445.1(M+1).
- 25 Intermediate-141: 5'-(1-(4-Fluorobenzyl)-2-oxoindolin-3-yl)-6'-hydroxy-1'-methyl spiro[cyclopropane-1,3'-indolin]-2'-one:



To a stirred solution of Intermediate-140 (0.11g,0.247) in dry dichloromethane (1 ml) was added triethylsilane (0.2 ml) and trifluoroacetic acid (0.25 ml) slowly at 0 °C and the mixture was stirred at 0-10 °C for 1 hour. The reaction mixture was concentrated in vacuum, added 5 dichloromethane (10 ml) and quenched with a saturated aqueous NH₄Cl solution at room temperature. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic layer was washed with water (20 ml), followed by brine (20 ml) and dried over sodium sulfate. The filtrate was concentrated in vacuum to dryness and the residue was subjected to column chromatography over silica gel 10 (100-200 mesh) using ethyl acetate-petroleum ether in the ratio(40:60) as an eluent to afford the title compound as off white solid (0.042 g, 42%). ¹H NMR (400 MHz, DMSO-d₆) δ 9.61 (s, 1H), 7.47-7.37 (m, 2 H), 7.19-7.14 (m, 4 H), 6.94-6.78 (m, 4 H), 6.45 (s, 1H), 5.01-4.76 (m, 2H), 3.14 (s, 3H), 1.45-1.43 (m, 4 H); MS (ES+) m/z 429.1(M+1).

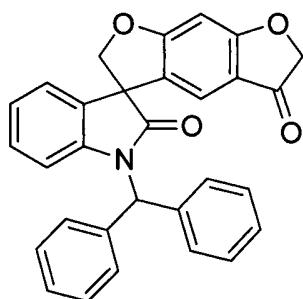
Intermediate-142:1'-Benzhydryl-5-(2-bromoacetyl)-6-hydroxy-2H-spiro[benzo furan-3,3'-indolin] -2'-one:



To a stirred solution of 1'-benzhydryl-6-hydroxy-2H-spiro[benzofuran-3,3'-indolin]-2'-one (prepared by following a procedure reported in WO2010/45197) (5g, 11.93 mmol) in dry dichloromethane (50 ml) was added 2-bromoacetyl bromide (1.25 ml, 2.89 g, 14.31 mmol) 20 and then anhydrous aluminium chloride (5.568 g, 41.76 mmol) slowly at 0°C under nitrogen

atmosphere. The resulting solution was stirred at ambient temperature for 48 h. The reaction mixture was cooled to 0°C and 1N HCl (100 ml) was added. The two phases were separated and the aqueous phase was extracted with dichloromethane (2 x 100 ml). The combined organic extracts were washed with water (2x100 ml), brine (10 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 12% ethyl acetate in petroleum ether to afford the title compound (3.4 g, 53%) as an off white solid. ¹H NMR(400 MHz, DMSO-d₆) δ: 11.95 (s,1H),7.45-7.32 (m,8H),7.31-7.26 (m,3H),7.17-7.12 (m,2H), -7.01(m,1H),6.88(s,1H),6.67-10 6.62(m,1H),6.58(s,1H),5.02(d,J=9.6Hz,1H),4.91(d,J=9.6Hz,1H),4.71-4.62(m,2H).MS (ES+) m/z: 540.1 (M+), 542.1 (M+2).

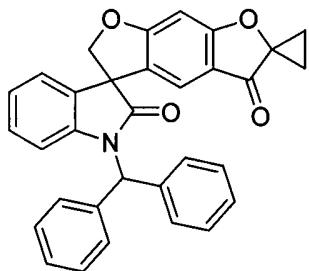
Intermediate-143:1'-Benzhydryl-2H-spiro[benzo[1,2-b:5,4-b']difuran-3,3'-indoline]-2',5(6H)-dione:



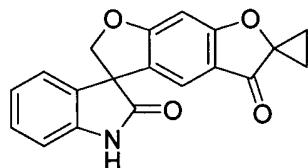
15 To a stirred solution Intermediate-142 (2.40 g, 4.44 mmol) in acetone (30 ml) was added anhydrous potassium carbonate (0.91 g, 6.66 mmol) at ambient temperature under a nitrogen atmosphere. The resulting suspension was stirred RT for 15 h. The solvent was evaporated *in vacuo*. Water (50 ml), ethyl acetate (50ml) was added. The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 30 ml). The combined organic extracts were washed with water (2x20 ml), brine (20 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (1. 9 g, 93%) as an off white solid. ¹H NMR

(400 MHz, DMSO-d₆)δ: 7.44-7.28 (m,11H),7.18-7.13 (m,1H),7.04-7.01 (m,1H), 6.89 (s,1H),6.87 (s,1H),6.69 (s,1H),6.63 (d,*J*=8.0 Hz,1H),5.11(d,*J*=10.0Hz,1H),4.99(d,*J*=10.0Hz,1H),4.76 (s,2H). MS (ES+) m/z: 460.1 (M+1).

5 Intermediate-144:

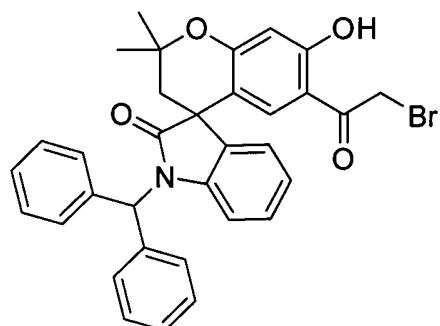


To a stirred solution of Intermediate-143 (1.9 g, 4.13 mmol) and 1, 2-dibromoethane (0.4 ml, 0.93 g, 4.96 mmol) in dry DMF (20 ml) was added sodium hydride (0.397 g, 16.55 mmol) slowly at 0 °C under nitrogen atmosphere. The resulting suspension was stirred at 0 °C for 45 min and heated at 50°C for 2 h. The reaction mixture was cooled to 0 °C and quenched by ice cold water (50 ml) slowly and added ethyl acetate (50 ml). The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 40 ml). The combined organic extracts were washed with water (2x 30 ml), brine (30 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 10% ethyl acetate in petroleum ether to afford Intermediate-144 (0.35 g, 18%) as an off white solid. ¹H NMR (400 MHz DMSO-d₆) δ: 7.46-7.26 (m, 1H),7.17-7.15 (m,1H), 7.02-6.98 (m, 2H), 6.87 (s,1H), 6.75 (s,1H), 6.63 (d, *J*=8.0Hz,1H), 5.11(d, *J*=9.6Hz, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 1.71-1.70 (m, 2H),1.34-1.33 (m, 2H) MS (ES+) m/z: 486.2 (M+1). Intermediate-145:



To a stirred solution of Intermediate-144 (0.35 g, 0.724 mmol) in dry DCM (8 ml) was added 10% triflic acid in TFA (1 ml) slowly at 0 °C under nitrogen atmosphere. The resulting solution was stirred 0 °C for 1 h. The reaction mixture was neutralized by an aqueous solution 5 of Na₂CO₃ and added ethyl acetate (40ml). The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (2x20 ml), brine (20 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica 10 gel (100-200 mesh), with an isocratic elution 20% ethyl acetate in petroleum ether to afford Intermediate-145 (0.2 g, 87%) as an off white solid. ¹H NMR (400 MHz DMSO-d₆) δ: 10.69 (s,1H),7.30-7.26 (m,1H),7.19(d,*J* =7.2Hz,1H),7.01-6.93 (m,4H),5.01 (d,*J* = 8.0Hz, 1H),4.89 (d,*J* = 8.0 Hz ,1H),1.73-1.67 (m, 2H),1.38-1.32 (m,2H) MS (ES+) m/z: 320.2 (M+1).

Intermediate-146: 1'-Benzhydryl-6-(2-bromoacetyl)-7-hydroxy-2,2-dimethylspiro [chroman-4,3'-indolin]-2'-one:

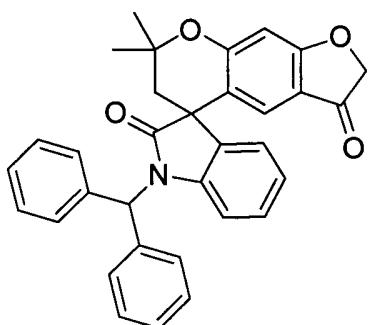


15

To a stirred solution of Intermediate-33 (5.0 g, 10.84 mmol) in dry dichloromethane (50ml) was added 2-bromoacetyl bromide (1.0 ml, 2.40 g, 11.93 mmol) and then anhydrous aluminium chloride (5.06 g, 37.96 mmol) slowly at 0°C under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 48 h. The reaction mixture was 20 cooled to 0°C and 1N HCl (50 ml) was added. The two phases were separated and the

aqueous phase was extracted with dichloromethane (2×50 ml). The combined organic extracts were washed with water (2×50 ml) and brine (50 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 10% ethyl acetate in petroleum ether to afford the title compound (3.90 g 61%) as an off white solid. ^1H NMR (400 MHz, DMSO-d₆) δ 11.20 (s, 1H), 7.45-7.26 (m, 10H), 7.15 (d, $J = 8.0$ Hz, 1H), 7.10-7.06 (m, 1H), 6.99-6.91 (m, 3H), 6.59 (d, $J = 8.0$ Hz, 1H), 6.44 (s, 1H), 4.65-4.53 (m, 2H), 2.45 (d, $J = 14.4$ Hz, 1H), 2.30 (d, $J = 14.4$ Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H) MS (ES+) m/z: 581.90 (M $^+$), 583.90(M+2).

10 Intermediate-147: 1'-Benzhydryl-7,7-dimethyl-6,7-dihydrospiro[furo[3,2-g] chromene-5,3'-indoline]-2',3(2H)-dione:

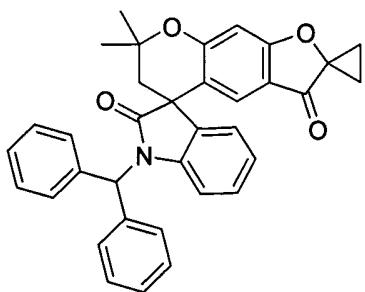


To a stirred solution of Intermediate-146 (3.85 g, 6.615 mmol) in acetone (30 ml) was added anhydrous potassium carbonate (1.36 g, 9.922 mmol) at ambient temperature under a nitrogen atmosphere. The resulting suspension was stirred at rt. for 15 h. The solvent was evaporated *in vacuo* and added water (50 ml) and ethyl acetate (50 ml). The two phases were separated and the aqueous phase was extracted with ethyl acetate (2×40 ml). The combined organic extracts were washed with water (2×30 ml), brine (20 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (2.3 g, 70%) as an off white solid. ^1H NMR (400 MHz, DMSO-d₆) δ : 7.44-7.33 (m, 6H), 7.31-7.26 (m, 5H), 7.18 (d, $J=8.0$ Hz, 1H), 7.12 (t, $J=8.0$ Hz, 1H), 7.00 (t, $J=8.0$ Hz, 1H), 6.90 (s, 1H), 6.75 (s, 1H), 6.66 (d, $J=8.0$ Hz, 1H), 4.69

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(s,2H),2.50 (d, $J = 14.8$ Hz ,1H), 2.35(d, $J = 14.8$ Hz ,1H),1.55(s, 3H), 1.51(s,3H). MS (ES+) m/z: 502.1 (M+).

Intermediate-148:



- 5 To a stirred solution of Intermediate-147 (0.5 g, 0.998 mmol) and 1, 2-dibromoethane (0.10 ml, 0.22 g, 1.19 mmol) in dry DMF (5 ml) was added sodium hydride (0.083 g, 3.493 mmol) slowly at 0 °C under nitrogen atmosphere. The resulting suspension was stirred at 0 °C for 45 min and heated at 50°C for 2 h. The reaction mixture was cooled to 0°C and quenched by ice cold water (50 ml) slowly and added ethyl acetate (50 ml). The two phases were separated
10 and the aqueous phase was extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with water (2x 15 ml), brine (20 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 10% ethyl acetate in petroleum ether to afford Intermediate-148 (0.14 g, 26%) as an off white solid.
15 ^1H NMR (400 MHz DMSO-d₆) δ :7.44-7.37(m, 6H),7.31-7.26 (m, 4H),7.20 (d, $J = 8.0$ Hz ,1H),7.13-7.10(m, 1H),7.00 (t, $J=8.0$ Hz,1H),6.91 (s,1H),6.84 (s,1H),6.66 (d, $J=8.0$ Hz,1H),6.10 (s,1H),2.50 (d, $J=14.4$ Hz,1H),2.37 (d, $J=14.4$ Hz,1H), 1.694-1.690 (m, 2H),1.55 (s,3H), 1.52 (s,3H),1.34-1.30 (m, 2H). MS (ES+) m/z 528.18 (M+1, 100)

Intermediate-149:



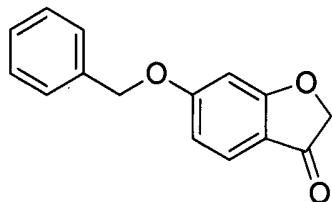
To a stirred solution of Intermediate-148 (0.53 g, 1.00 mmol) in dry DCM (10 ml) was added 10% trifilic acid in TFA (1.5 ml) slowly at 0°C under nitrogen atmosphere. The resulting solution was stirred 0°C for 1 hr. The reaction mixture was neutralized by an aqueous solution of Na₂CO₃ and added ethyl acetate (40ml). The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (2x20 ml) brine (20 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution 20% ethyl acetate in petroleum ether to afford

5 Intermediate-149 (0.28 g, 77%) as an off white solid.

10 Intermediate-149 (0.28 g, 77%) as an off white solid.

¹H NMR (400 MHz DMSO-d₆) δ : 10.67(s,1H), 7.25(t, J=8.0 Hz, 1H), 7.11 (d, J=7.2Hz, 1H), 6.97(t,J=8.0 Hz ,2H), 6.81(s,1H), 6.69 (s,1H), 2.49 (d, J=14.4Hz, 1H), 2.26 (d, J=14.4Hz,1H), 1.71-1.69 (m,2H), 1.53(s, 3H), 1.49(s, 3H), 1.36-1.31(m, 2H). MS (ES+) m/z: 362.1 (M+1).

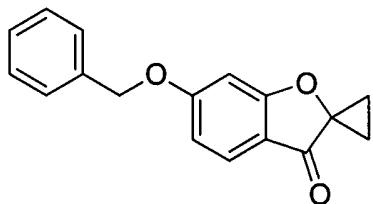
15 Intermediate-150: 6-(Benzylxy)benzofuran-3(2H)-one:



Intermediate-150 was prepared by following the procedure reported in *Journal of Organic Chemistry* (1997), 62, 5385 – 5391.

Intermediate-151: 6-(Benzylxy)-3H-spiro[benzofuran-2,1'-cyclopropan]-3-one:

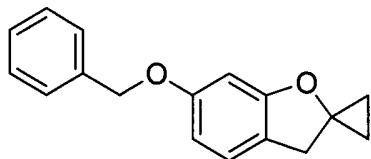
126



To a stirred solution of Intermediate-150 (0.3 g, 1.25mmol) and 1, 2-dibromoethane (0.16 ml, 0.35 g, 1.87 mmol) in dry DMF (5 ml) was added sodium hydride (0.12 g, 5.00 mmol) slowly at 0 °C under nitrogen atmosphere. The resulting suspension was stirred at 0 °C for 45 min and heated at 50°C for 2 h. The reaction mixture was cooled to 0 °C and quenched by ice cold water (50 ml) slowly and added ethyl acetate (50 ml). The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (2x 15 ml), brine (30ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 8% ethyl acetate in petroleum ether to afford 6-(benzyloxy)-3H-spiro[benzofuran-2,1'-cyclopropan]-3-one (0.075 g, 22%) as an off white solid.

¹H NMR (400 MHz DMSO-d₆)δ:7.59(d,J=8.8Hz,1H),7.46-7.33(m,5H),6.98(d, J=2.0Hz,1H),6.84(dd,J=8.8 Hz,2.0 Hz,1H),5.24(s,2H),1.74-1.70(m,2H),1.40-1.36 (m,2H).
MS (ES+) m/z 267.0 (M+1).

Intermediate-152: 6-(BenzylOxy)-3H-spiro[benzofuran-2,1'-cyclopropane]:



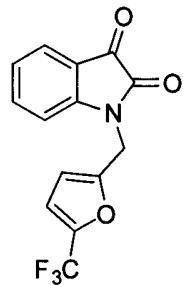
To a stirred suspension of aluminium chloride (0.35 g, 2.687 mmol) & Lithium aluminium hydride (0.092 g, 2.443 mmol) in dry diethyl ether (15 ml) was added Intermediate-151 (0.65 g, 2.443 mmol) slowly at 0°C under nitrogen atmosphere. The resulting suspension was brought to room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C and quenched by 0.5 N aqueous NaOH solution (15 ml) slowly and added ethyl acetate (50 ml).

The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with water (2x 25 ml), brine (20 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 4% ethyl acetate in petroleum ether to afford 6-(benzyloxy)-3H-spiro[benzofuran-2,1'-cyclopropane (0.43 g, 70%) as an off white solid. ¹H NMR (400 MHz DMSO-d₆) δ7.43-7.29(m,5H),7.09 (d,*J*=8.0Hz,1H), 6.49 (dd, *J*=6.0 Hz, 2.0 Hz,1H), 6.44(d, *J*=2.0Hz,1H),5.03 (s, 2H), 3.19 (s,2H), 1.06-1.03 (m, 2H), 0.75-0.72 (m, 2H). MS (ES+) m/z 253.53 (M+1).

Intermediate-153: 3H-Spiro[benzofuran-2,1'-cyclopropan]-6-ol:

10 In R.B. Flask to a stirred solution of Intermediate-152 (0.43 g, 1.70 mmol) in MeOH : EtOAc (4:1) (10 ml) was added 10% Pd-C (0.5 g) resulting suspension was stirred under hydrogen balloon atmosphere at room temperature for 3 h. The reaction mixture was filtered through celite pad washed with EtOAc (2 X 20 ml), and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 10% ethyl acetate in petroleum ether to afford 3H-spiro[benzofuran-2,1'-cyclopropan]-6-ol (0.22 g, 81%) as an off white solid. ¹H NMR (400 MHzDMSO-d₆):δ9.26(bs,1H), 6.95(d, *J*=8.0Hz,1H), 6.25(dd, *J*=8.0Hz,2.0Hz,1H),6.14(d,*J*=2.0Hz,1H),3.14(s,2H),1.04-1.01 (m,2H), 0.72-0.69 (m,2H). MS (ES+) m/z 163.0 (M+1).

Intermediate-154: 1-((5-(trifluoromethyl)furan-2-yl)methyl)indoline-2,3-dione:

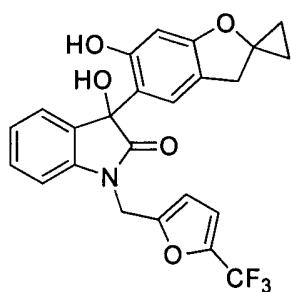


20

To a stirred solution of isatin (6.0 g, 40.78 mmol) in dry DMF (30 ml) at 0°C was added NaH (1.46 g, 61.17 mmol) lot wise. The solution was stirred for 1h at 0°C The 2-(bromomethyl)-5-(trifluoromethyl)furan (10.27 g, 44.85 mmol) was added dropwise. After addition, the

suspension was stirred at room temperature for 1h. The reaction mixture was quenched with addition of ice cold water (20ml) and added ethyl acetate (60 ml). The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 40 ml).The combined organic extracts were washed with water (200ml) and brine (200ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (mesh 100-200) with an isocratic elution of 16% ethyl acetate in petroleum ether to afford the title compound (3.8 g, 32%) as yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.64-7.59 (m, 2H), 7.13 (t,*J*=7.6 Hz, 1H), 7.04 (d,*J*=8.0 Hz, 1H), 6.75 (t,*J*=0.8 Hz, 1H), 6.45 (d,*J*=3.2 Hz, 1H), 4.93 (s, 2H).

10 Intermediate-155: 3-Hydroxy-3-(6-hydroxy-3H-spiro[benzofuran-2,1'-cyclo propan]-5-yl)-1-((5-(trifluoromethyl)furan-2-yl)methyl)indolin-2-one



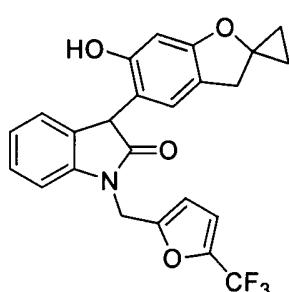
To a stirred solution of Intermediate-153 (1.0 g, 6.17 mmol) in dry THF (5 ml) at 0°C was added a 2M solution of isopropylmagnesium chloride in THF (3.40 ml, 6.79 mmol) dropwise. The resulting suspension was stirred for 1h at 0°C which was added dropwise to a suspension of 1-((5-(trifluoromethyl)furan-2-yl)methyl)indoline-2,3-dione (Intermediate-154) (2 g, 6.79 mmol) in dry THF (5 ml) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was cooled to 0 °C and quenched with addition of a saturated aqueous NH₄Cl solution (30 ml) and added EtOAc (20 ml). The two phases were separated and the aqueous phase was extracted with EtOAc (2 x 15 ml).The combined organic extract was washed with water (30 ml), brine (30 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (mesh 100-200) with an isocratic elution of 18%

ethyl acetate in petroleum ether to afford the title compound (1.1g, 40%) as an off white solid.

¹H NMR (400 MHz, DMSO-d₆): δ:9.19(s,1H),7.54(s,1H),7.47-7.18(m,2H),7.00-6.90 (m, 3H),6.58 (d, *J*=3.2 Hz,1H), 6.52 (s,1H), 6.03(s,1H), 4.99(s,2H), 3.28 (s,2H), 1.19-1.01

5 (m,2H), 0.75-.071(m,2H). m/z :440.04 (M-17)

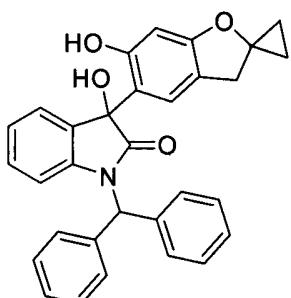
Intermediate-156: 3-(6-Hydroxy-3H-spiro[benzofuran-2,1'-cyclopropan]-5-yl)-1-((5-(trifluoromethyl)furan-2-yl)methyl)indolin-2-one:



To a stirred solution of Intermediate-155 (0.4 g, 0.875 mmol) in dry dichloromethane (10 ml) 10 at 0°C was added trifluoroacetic acid (0.8 ml, 1.19 g, 10.44 mmol) and then triethylsilane (0.8 ml, 0.58 g, 4.98 mmol) dropwise. The resulting solution was stirred for 3h at 0-10 0°C. The solvent was removed on a rotary evaporator at room temperature, the reaction mixture was cooled to 0 °C and quenched with addition of a saturated aqueous NH₄Cl solution (20 ml) and added dichloromethane (25 ml). The two phases were separated and the aqueous phase 15 was extracted with dichloromethane (2 x 15 ml). The combined organic extract was washed with water (25 ml), brine(25 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (mesh 100-200) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (0.28 g, 72%) as an off white solid. ¹HNMR(400MHz,DMSO-d₆):

20 89.45(s,1H),7.22-7.15(m,2H),7.05-6.93(m,3H),6.79 (s,1H),6.65 (d,*J*=2.8Hz,1H),6.21(s,1H),5.10-5.00 (m,2H), 4.81 (s,1H), 3.16 (s,2H), 1.04-1.01(m, 2H), 0.75-.072(m,2H).

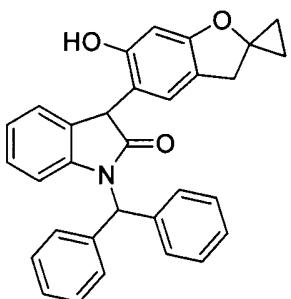
Intermediate-157: 1-Benzhydryl-3-hydroxy-3-(6-hydroxy-3H-spiro[benzofuran-2,1'-cyclopropan] -5-yl)indolin-2-one:



To a stirred solution of Intermediate-153 (0.20 g, 1.23 mmol) in dry THF (5 ml) at 0°C was added a 2M solution of isopropylmagnesium chloride in THF (1.23 ml, 2.46 mmol) dropwise. The resulting suspension was stirred for 1h at 0°C which was added dropwise to the 5 suspension of Intermediate-20 (0.46 g, 1.49 mmol) in dry THF (5 ml) at 0°C. After addition, the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with addition of a saturated aqueous NH₄Cl solution (10 ml) and extracted with EtOAc (2 x 20 ml). The phases were separated and the combined organic extract was washed with water (30 ml), brine (20 ml), dried over anhydrous sodium sulphate, filtered and 10 concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (mesh 100-200) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford the title compound (0.47 g, 81%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.40 (s,1H), 7.60(s,1H), 7.41-7.29 (m,10H), 6.95-6.88 (m,3H), 6.83-6.79 (m,1H), 6.51(s,1H), 6.28 (d, J=7.6Hz,1H), 6.10 (s,1H), 3.26 (s,2H), 1.10-1.02 (m,2H), 0.78-0.72(m,2H). m/z : 458.1

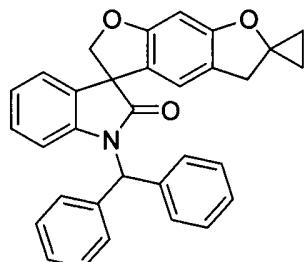
15 (M-17).

Intermediate-158: 1-Benzhydryl-3-(6-hydroxy-3H-spiro[benzofuran-2,1'-cyclopropan]-5-yl)indolin-2-one:



To a stirred solution of Intermediate-157 (0.37 g, 0.778 mmol) in dry dichloromethane (10ml) at 0°C was added trifluoroacetic acid (0.74 ml, 1.10 g, 9.66 mmol) and then triethylsilane (0.74 ml, 0.53 g, 4.63 mmol) dropwise. The resulting solution was stirred for 3 h at 0-10 0°C. Solvent was removed on rota vapour at RT, reaction mixture was cooled to 5 0°C and quenched with addition of saturated aqueous NH₄Cl solution (20 ml) and added dichloromethane (25 ml). The two phases were separated and the aqueous phase was extracted with dichloromethane (2 x 15 ml).The combined organic extract was washed with water (25 ml), brine(25 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (mesh 100-10 200) with an isocratic elution of 13% ethyl acetate in petroleum ether to afford the title compound (0.29 g, 82%) as an off white solid.¹H NMR (400 MHz, DMSO-d₆):δ 9.49(s,1H),7.42-7.27(m,10H),6.96-6.92(m,4H),6.85(t, J=7.2Hz,1H),6.36(d, J=7.6Hz,1H),6.21(s,1H),4.83(s,1H),3.19 (s,2H),1.06-1.03 (m, 2H),0.75-0.73(m, 2H).MS (ES+) m/z 460.2 (M+1).

15 Intermediate-159:



To a stirred solution of Intermediate-158 (0.3 g, 0.653 mmol) in dry THF (4 ml) was added cesium carbonate (0.84 g, 2.61 mmol) at room temperature. The resulting suspension was stirred for 30 min. at room temperature. Then, chloroiodomethane (0.069 ml, 0.17 g, 0.980 20 mmol) was added dropwise to the above suspension and stirred the reaction mixture at room temperature for 15 hours. The reaction mixture was cooled to 0°C and quenched with addition of water (10 ml) and added EtOAc (20 ml). The two phases were separated and the aqueous phase was extracted with EtOAc (2 x 15 ml).The combined organic extract was washed with water (20 ml),brine(25 ml), dried over anhydrous sodium sulphate, filtered and

concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (mesh 100-200) with an isocratic elution of 10% ethyl acetate in petroleum ether to afford Intermediate-159 (0.17 g, 56%) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ: 7.44-7.32(m,8H),7.27(d, J=7.2Hz,2H),7.26-7.21(m,1H),7.12-7.08(m,1H), 7.02 (t, J=7.2 Hz,1H), 6.89 (s,1H), 6.57 (d, J=8.0Hz,1H),6.41(d, J=7.6Hz,2H), 4.88 (d, J=9.2 Hz,1H), 4.77 (d, J=9.2 Hz,1H),3.10 (s,2H),1.05-1.01(m,2H),0.79-0.69(m,2H). MS (ES+) m/z 472.1.

Intermediate-160: 2-Methylbenzofuran-3-carboxylic acid:

The title compound was prepared by following a procedure similar to that described in *J. Org. Chem.* (2008), 73, 3481 – 3485.

10 Intermediate-161: *N*-(2-Bromophenyl)-2-methylbenzofuran-3-carboxamide:

To solution of Intermediate-160 (1 g, 5.68 mmol) in DCM (30.0 mL) was added triethylamine (2.9 g, 4.0 mL, 28.4 mmol) and thionylchloride (2.50 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 6 h and poured into CH₂Cl₂ (30.0 mL). The mixture was washed with 10 % HCl, dried over anhydrous sodium sulfate and filtered. The 15 filtrate was concentrated in *vacuo* to dryness. The crude product was dissolved DCM (30.0 mL) followed by the addition of 2-bromoaniline (4.42 g, 25.7 mmol). The reaction mixture was stirred at ambient temperature for 16 h and the solvent was removed under *vacuo*. To the residue was added ethyl acetate (50 mL) and water 20 (mL). The layers were separated and the organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was 20 concentrated in *vacuo* to dryness. The residue was subjected to column chromatography eluting with ethyl acetate/hexane (20 %) to give the title compound (1.2 g, 64 %) as a white solid.

Intermediate-162: *N*-(2-Bromophenyl)-*N*-(4-methoxybenzyl)-2-methylbenzofuran -3- carboxamide:

25 To a stirred solution of Intermediate-161 (1.0 g, 3.03 mmol) in dry DMF (20 mL) at 0 °C was added NaH (0.11 g, 4.54 mmol). The solution was stirred for 1h at 0 °C. To the above solution was added *p*-methoxybenzyl chloride (0.52 g, 3.33 mmol) drop wise at 0 °C. The reaction mixture was stirred at ambient temperature for overnight. Water (80 mL) was added followed by ethyl acetate (50 mL). The layers were separated and the organic layer 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 (10 %) to give the title compound (0.9 g, 66 %) as a solid compound

¹H NMR (400 MHz, DMSO-*d*₆): δ δ 7.52-7.46 (m, 2H), 7.41-7.36 (m, 2H), 7.22-7.1 (m, 4H), 7.04-6.98(m, 2H), 6.95-6.82 (m, 2H), 5.38 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H); MS(ES+) m/z: 450.1 (M+1), 450.2 (M+2).

Intermediate-163: 6-Methyl-[1,3]dioxolo[4,5-f]benzofuran-7-carboxylate

Above compound was synthesized according to the procedure mentioned as in *J. Org. Chem.* (2007), 72, 5337 – 5341.

10 Intermediate-164: 6-Methyl-[1,3]dioxolo[4,5-f]benzofuran-7-carboxylic acid:

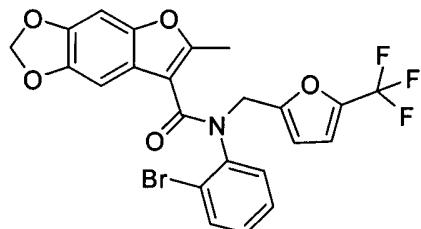
To a solution of Intermediate-163 (0.5g, 2.01 mmol) in a mixture of ethanol/water (1:1, 3mL) was added sodium hydroxide (161 mg, 4.02 mmol). The resulting mixture was refluxed for 2 h. The reaction mixture was concentrated in *vacuo* followed by the addition of water (5 mL). The mixture was extracted with ethyl acetate (15 mL). The aqueous layer was acidified with 15 2N HCl till pH 2. The precipitated solid was filtered and dried to give the title compound (0.31g, 70%) as a white solid.

Intermediate-165: *N*-(2-Bromophenyl)-6-methyl-[1,3]dioxolo[4,5-f]benzofuran-7-carboxamide.

The title compound was prepared by following a procedure similar to that described in

20 Intermediate-161, using Intermediate-164 (yield: 65 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.57(s, 1H), 7.74 (d d, *J* = 1.6 Hz, 8.0 Hz, 2H), 7.49-7.41 (m, 1H), 7.31 (s, 1H), 7.3 (s, 1H), 7.34-7.19 (m, 1H), 6.07 (s, 2H), 2.67 (s, 3H); MS(ES+) m/z: 374.1 (M+1), 376.1(M+2).

Intermediate-166: *N*-(2-Bromophenyl)-6-methyl-*N*-(5-(trifluoromethyl)furan-2-yl) methyl)-[1,3]dioxolo[4,5-f]benzofuran-7-carboxamide:

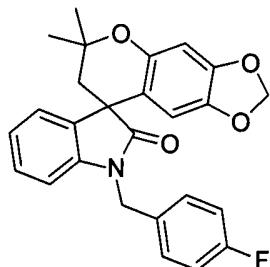


The title compound was prepared by following a procedure similar to that described in Intermediate-162, 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 79 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.5 (d, J = 8.0 Hz, 1H), 7.47-7.24 (m, 2H), 7.15-7.01 (m, 3H), 6.94 (s, 1H), 6.54 (s, 1H), 6.01 (s, 2H), 5.24 (d, J = 16.0 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 2.26 (s, 3H); MS(ES+) m/z: 522.1 (M+1), 524.0(M+2).

Examples

Example-1

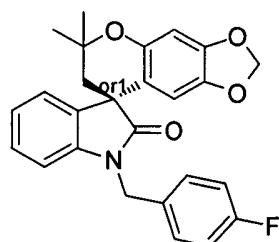
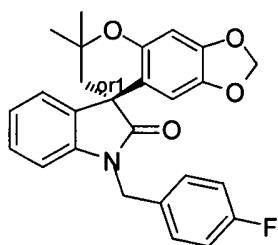
1'-(4-Fluorobenzyl)-6,6-dimethyl-6,7-dihydrospiro [[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-2'one



10

The title compound was prepared by following a procedure similar to that described in Intermediate-33 by using Intermediate-9 and *p*-toluene sulphonic acid (yield: 65 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.42-7.38 (m, 2H), 7.22-7.11 (m, 4H), 7.06-6.98 (m, 2H), 6.50 (s, 1H), 5.89 (s , 1H), 5.86 (s, 1H), 5.72 (s, 1H), 4.97-4.87 (m, 2H), 2.36-2.33 (d, J = 14.4 Hz, 1H), 2.17-2.13 (d, J = 14.4 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H); MS (ES+) m/z: 432.1 (M+1).

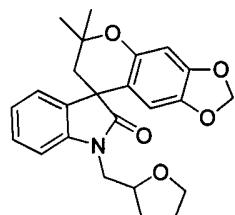
Example-2 and 3



Example-1 was separated on chiral column (CHIRAL PAK IA, 250 mm × 4.6, 5 µ) to obtain Example-2 (Retention time (RT) 10.57 minutes) and Example-3 (Retention time (RT) 14.20 minutes.

Example-4

- 5 6,6-Dimethyl-1'-((tetrahydrofuran-2-yl)methyl)-6,7-dihydrospiro[[1,3]dioxolo [4,5-g]chromene-8,3'-indolin]-2'-one

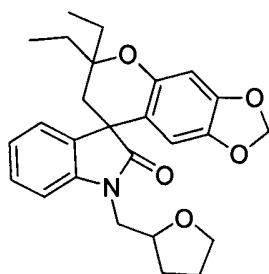


The title compound was prepared by following a procedure similar to that described in Intermediate-33 by using Intermediate-16 and *p*-toluene sulphonic acid (yield: 63 %).
 10 ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.27 (m, 1H), 7.189 (d, *J* = 8.0 Hz, 1H) 7.10 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.2,7.6 Hz, 1H), 6.48 (s, 1H), 5.92 (s, 1H), 5.89 (s, 1H), 5.86 (s, 1H), 4.22-4.19 (m, 1H), 3.84-3.79 (m, 1H) 3.69-3.76 (m, 2H), 3.65-3.61 (q, 1H), 2.28 (d, *J* = 14.4 Hz, 1H), 2.05 (d, *J* = 14.4 Hz, 1H), 1.99-1.79 (m, 3H), 1.63-1.58 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H); MS (ES+) m/z: 408.1 (M+1).

15

Example-5

- 6,6-Diethyl-1'-((tetrahydrofuran-2-yl)methyl)-6,7-dihydrospiro[[1,3]dioxolo [4,5-g]chromene-8,3'-indolin]-2'-one



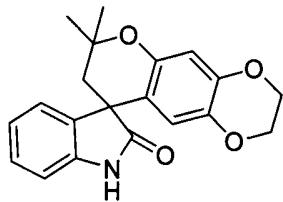
The title compound was prepared by following a procedure similar to that described
 20 in Intermediate-33 by using Intermediate-17 and *p*-toluene sulphonic acid (yield: 72 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.19-7.16 (m, 1H), 7.08-7.06 (d, *J* = 6.8 Hz, 1H), 7.02-6.98

(m, 1H), 6.50 (s, 1H)), 5.96 (s, 1H), 5.89 (s, 1H), 5.86 (s, 1H), 5.85 (s, 1H), 4.22-4.21 (m, 1H), 3.81-3.80 (m, 1H), 3.76-3.69 (m, 2H), 3.65-3.61 (m, 1H), 2.25 (d, $J = 14.4$ Hz, 1H), 2.07 (d, $J = 14.4$ Hz, 1H), 1.96-1.77 (m, 5H), 1.69-1.62 (m, 3H), 0.88-0.79 (m, 6H); MS (ES+) m/z: 436.1 (M+1).

5

Example-6

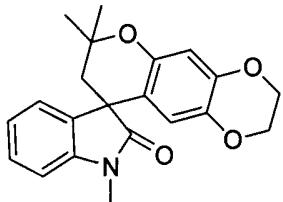
7,7-Dimethyl-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g] chromene-9,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Intermediate-33 by using Intermediate-26 and *p*-toluene sulphonic acid (yield: 87 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.51 (s, 1H), 7.20 (t, $J = 7.6$ Hz, 1H), 7.07 (d, $J = 7.6$ Hz, 1H), 6.95-6.89 (m, 2H), 6.33 (s, 1H), 5.82 (s, 1H), 4.14-4.03 (m, 4H), 2.32 (d, $J = 14.4$ Hz, 1H), 2.09 (d, $J = 14.4$ Hz, 1H), 1.32 (d, $J = 11.6$ Hz, 6H); MS (ES+) m/z: 338.3 (M+1).

Example-7

1',7,7-Trimethyl-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one

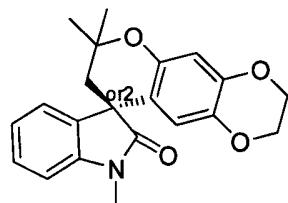
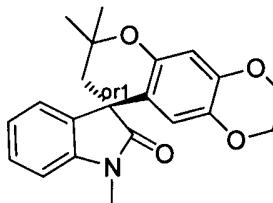


15

To an ice cooled solution of Example-6 (0.10g, 0.29 mmol) in dry DMF (1.5 mL) was NaH (14 mg, 0.35 mmol). The solution was stirred at 0 °C for 30 min. After that, methyl iodide (0.04 g, 0.29 mmol) was added and reaction mixture was stirred for 1 h at ambient temperature. After completion of reaction the mixture was quenched with saturated ammonium chloride (5.0 mL) and reaction mixture was extracted with EtOAc (2 × 100 mL) and organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 30 % ethyl acetate in petroleum ether to afford the title compound (0.8 g, 76.92 %) as a white

solid. ^1H NMR (400 MHz, CDCl_3): δ 7.25 (m, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.01 (t, $J = 7.6$ Hz, 1H), 6.85 (d, $J = 7.6$ Hz, 1H), 6.43 (s, 1H), 5.97 (s, 1H), 4.17-4.08 (m, 4H), 3.24 (s, 3H), 2.40 (d, $J = 14.4$ Hz, 1H), 2.16 (d, $J = 14.4$ Hz, 1H), 1.53 (s, 3H), 1.47 (s, 3H); MS (ES+) m/z: 352.2 (M+1).

5

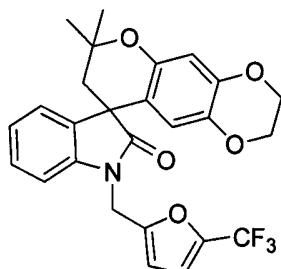
Example-8 and 9

Example-7 was separated to give Example-8 (Retention time (RT) 10.19 minutes and Example-9 Retention time (RT) 16.35 minutes) on chiral HPLC using CHIRAL PAK IC, 250 mm × 4.6, 5 μ ; Flow rate : 1 mL/ min; Mobile phase : Hexane: IPA (60 : 40 % v/v).

10

Example-10

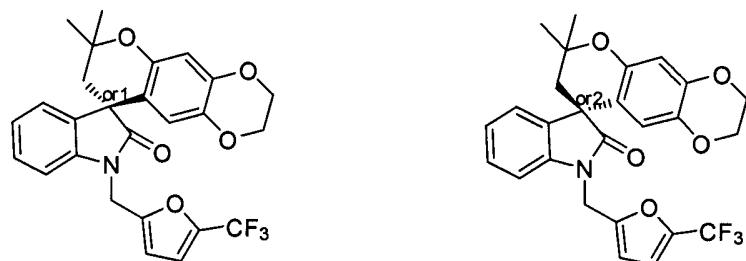
7,7-Dimethyl-1'-(5-trifluoromethyl)furan-2-yl)methyl-2,3,7,8tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-6 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 77 %). ^1H NMR (400 MHz, CDCl_3): δ 7.25-7.21 (m, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.02 (t, $J = 7.6$ Hz, 1H), 6.93 (d, $J = 7.6$ Hz, 1H), 6.72 (m, 1H), 6.44 (s, 1H), 6.35 (d, $J = 2.8$ Hz, 1H), 5.95 (s, 1H), 4.94 (s, 2 H), 4.16-4.08 (m, 4H), 2.39 (d, $J = 14.4$ Hz, 1H), 2.15 (d, $J = 14.4$ Hz, 1H), 1.54 (s, 3H), 1.47 (s, 3H); ^{19}F NMR (375 MHz, CDCl_3): δ -64.05; MS (ES+) m/z: 486.1 (M+1).

20

Example-11 and 12

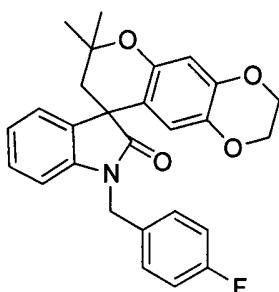


Example-10 separated to give Example-11 (Retention time (RT) 7.8 minutes and Example-12 Retention time (RT) 12.7 minutes) on chiral HPLC using CHIRAL PAK IC, 250 mm × 4.6, 5 μ ; Flow rate : 1 mL/ min; Mobile phase : Hexane: IPA (80 : 20 % v/v).

5

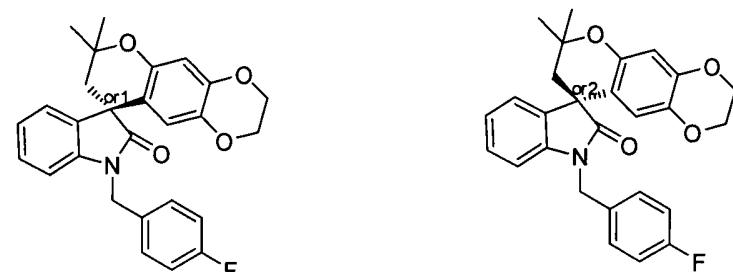
Example-13

1'-(4-Fluorobenzyl)-7,7-dimethyl- -2,3,7,8-tetrahydrospiro [[1,4]dioxino[2,3-g]chromene - 9,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described
10 in Example-7 by using Example-6 and 4-fluorobenzyl bromide (yield: 76 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.41-7.37 (m, 2H), 7.25-7.11 (m, 4H), 7.05-6.98 (m, 2H), 6.35 (s, 1H), 5.73 (s, 1H), 4.91 (s, 2H), 4.15-4.03 (m, 4H), 3.24 (s, 3H), 2.36 (d, J = 14.4 Hz, 1H), 2.16 (d, J = 14.4 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H); MS (ES+) m/z: 446.2 (M+1).

Example-14 and 15



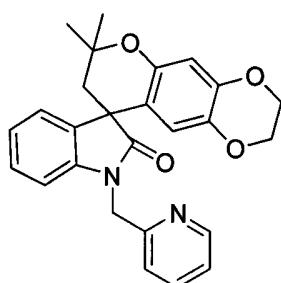
15

Example-13 separated to give Example-14 (Retention time (RT) 6.15 minutes and Example-15 Retention time (RT) 11.06 minutes) on chiral HPLC using CHIRAL PAK IC, 250 mm × 4.6, 5 μ ; Flow rate : 1 mL/ min; Mobile phase : A= *n*-hexane: IPA (90 : 10 % v/v), B = IPA, A: B= 85/15 (% V/V).

5

Example-16

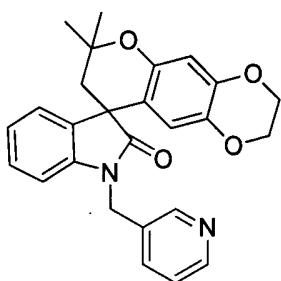
7,7-Dimethyl-1'-(pyridin-2-ylmethyl)-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g] chromene-9,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described
10 in Example-7 by using Example-6 and 2-(bromomethyl)-pyridine (yield: 47 %). ^1H NMR (400 MHz, DMSO- d_6): δ 8.47 (m, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 5.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.34 (s, 1H), 6.20 (s, 1H), 5.07 (q, J = 16.4, 18.0 Hz, 2H), 4.15-4.09 (m, 4H), 2.34 (d, J = 14.4 Hz, 1H), 2.19 (d, J = 14.4 Hz, 1H), 1.43 (d, J = 6.4 Hz, 6H); MS
15 (ES+) m/z: 429.2 (M+1).

Example-17

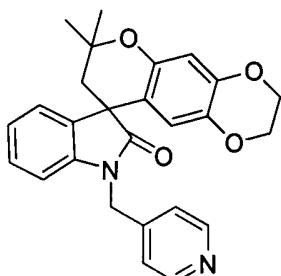
7,7-Dimethyl-1'-(pyridin-3-ylmethyl)-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g] chromene-9,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-6 and 3-(bromomethyl)-pyridine (yield: 66 %). ¹H NMR (400 MHz, DMSO-d₆): δ 8.61 (s, 1H), 8.50 (m, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.40-7.31 (m, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.13-6.99 (m, 3H), 6.36 (s, 1H), 5.73 (s, 1H), 4.98 (s, 2H), 4.15-4.09 (m, 4H), 2.37 (d, J = 14.4 Hz, 1H), 2.17 (d, J = 14.4 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H); MS (ES+) m/z: 429.2 (M+1).

Example-18

7,7-Dimethyl-1'-(pyridin-4-ylmethyl)-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g] chromene-9,3'-indolin]-2'-one

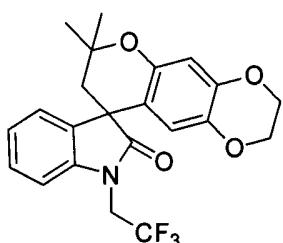


10

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-6 and 4-(bromomethyl)-pyridine (yield: 32 %). ¹H NMR (400 MHz, CDCl₃): δ 8.58 (s, 2H), 8.50 (m, 1H), 7.32-7.22 (m, 2H), 7.17-7.13 (m, 2H), 7.02-6.98 (m, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.46 (s, 1H), 5.99 (s, 1H), 4.96-4.87 (m, 2H), 4.20-4.06 (m, 4H), 2.46 (d, J = 14.0 Hz, 1H), 2.17 (d, J = 14.0 Hz, 1H), 1.55 (s, 3H), 1.49 (s, 3H); MS (ES+) m/z: 429.2 (M+1).

Example-19

7,7-Dimethyl-1'-(2,2,2-trifluoroethyl)-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g] chromene-9,3'-indolin]-2'-one

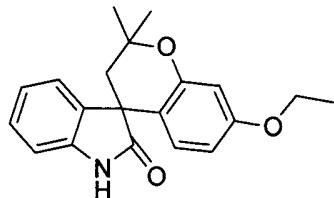


20

To the solution of Example-6 (0.30 g, 0.74 mmol) in dry DMF (2.5 mL) was added Cs₂CO₃ (1.0 g, 0.31 mmol). The solution was stirred at room temperature for 30 min. After that, 1,1,1-trifluoro-2-iodoethane (0.83 g, 0.39 mmol) was added and reaction mixture was stirred for overnight at ambient temperature. After completion of reaction the mixture was quenched 5 with addition of water (5.0 mL) and reaction mixture was extracted with EtOAc (2 × 100 mL) and organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 40 % ethyl acetate in petroleum ether to afford the title compound (0.24 g, 72.0 %) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.35-7.26 (m, 2H), 7.15-7.05 (m, 2H), 6.36 (s, 1H), 10 5.81 (s, 1H), 4.71-4.64 (m, 2H), 4.15-4.05 (m, 4H), 2.31 (d, *J* = 14.8 Hz, 1H), 2.18 (d, *J* = 14.8 Hz, 1H), 1.44 (d, *J* = 7.6 Hz, 6H); MS (ES+) m/z: 420.1 (M+1).

Example-20

7-Ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one

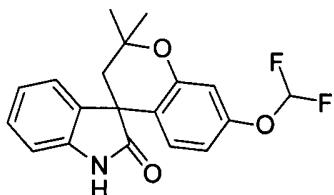


15 The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-34 (yield: 79 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.50 (s, 1 H), 7.21-7.17 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.94-6.89 (m, 2H), 6.37-6.29 (m, 3H), 3.94 (q, *J* = 6.8 Hz, 2H), 2.35 (d, *J* = 14.8 Hz, 1H), 2.12 (d, *J* = 14.8 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); MS (ES+) m/z: 324.3 (M+1).

20

Example-21

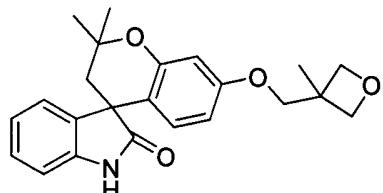
7-(Difluoromethoxy)-2,2-dimethylspiro [chroman-4, 3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-35 (yield: 87 % crude). MS (ES+) m/z: 346.3 (M+1).

Example-22

2,2-Dimethyl-7-((3-methyloxetan-3-yl)methoxy)spiro [chroman-4,3'-indolin]-2'-one

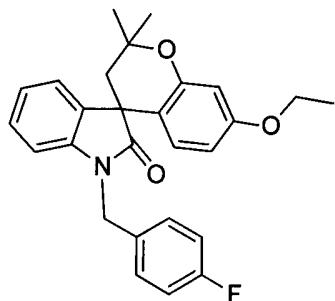


5

The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-37. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.57 (s, 1 H), 7.98-7.15 (m, 3H), 7.15 (m, 2H), 6.45-6.31(m, 2H), 4.44-4.33 (m, 4H), 4.39 (d, *J* = 15.2 Hz, 2H), 2.36 (d, *J* = 14.0 Hz, 1H), 2.13 (d, *J* = 14.0 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H); MS (ES+) m/z: 380.2 (M+1).

Example-23

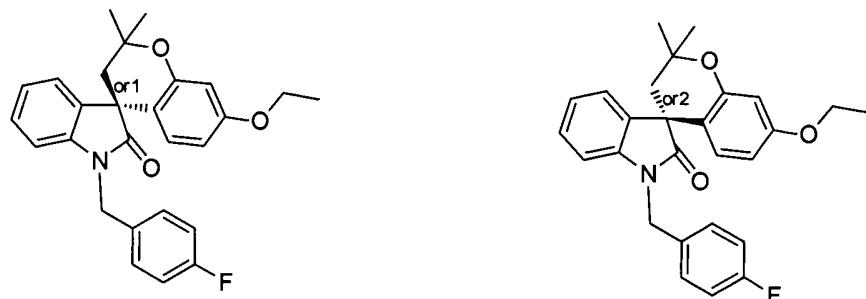
7-Ethoxy-1'-(4-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 4-(*p*-fluorobenzyl bromide) (yield: 63 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.41-7.39 (m, 2H), 7.38-7.17 (m, 3H), 7.15 (d, *J* = 6.8 Hz, 2H), 7.03-6.97 (m, 2H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.33 (dd, *J* = 2.8, 2.4 Hz, 1H), 6.21 (d, *J* = 8.8 Hz, 1H), 4.92 (s, 2H), 3.93 (m, 2H), 2.40 (d, *J* = 14.4 Hz, 1H), 2.20 (d, *J* = 14.4 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); MS (ES+) m/z: 433.1 (M+1).

20

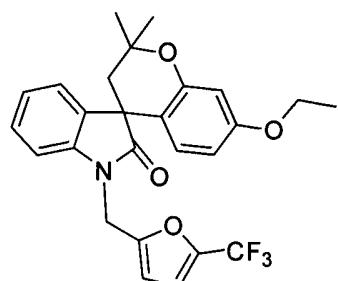
Example-24 and 25



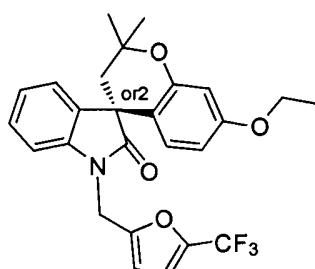
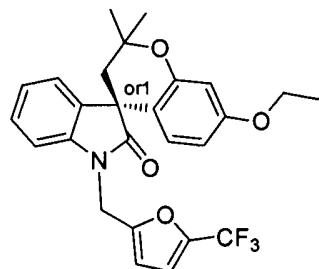
Example-23 was separated to give Example-24 (Retention time (RT) 5.83 minutes and Example-25 Retention time (RT) 6.94 minutes) on chiral HPLC using Phenomenex-CELL-2, 250 mm × 4.6, 5 μ ; Flow rate : 1.0 mL/ min; Mobile phase : A: *n*-Hexane: IPA (90 : 10 % v/v), B: IPA (100 %); A: B = 80/20 % v/v).

Example-26

7-Ethoxy-2, 2-dimethyl-1'-(5-trifluoromethyl) furan-2-yl) methyl) spiro [chroman-4, 3'-indolin]-2'-one



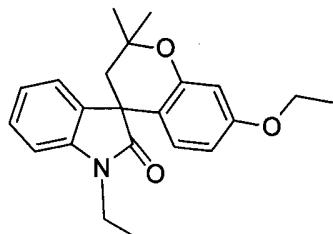
The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 54 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.26 (t, J = 8.0 Hz, 1H), 7.19-7.09 (m, 3H), 7.01 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 3.6 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.25-6.19 (m, 2H), 5.09 (m, 2H), 3.93 (q, J = 7.2 Hz, 2H), 2.40 (d, J = 14.8 Hz, 1H), 2.20 (d, J = 14.8 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); MS (ES+) m/z: 472.1 (M+1).

Example-27 and 28

The compound of Example-26 was separated to give Example-27 Retention time (RT) 3.91
 5 minutes and Example-28 Retention time (RT) 4.94 minutes on chiral HPLC using CHIRAL PAK IC, 250 mm × 4.6, 5 μ ; Flow rate : 1.5 mL/ min; Mobile phase : A= n-hexane: IPA (90 : 10 % v/v), B = IPA, A: B= 95/5 (% V/V).

Example-29

7-Ethoxy-1'-ethyl-2,2-dimethylspiro[chroman-4,3'-indolin] -2'-one

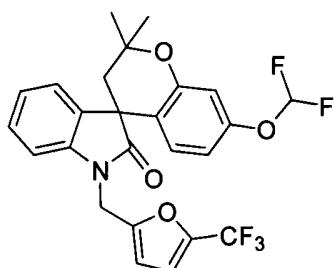


10

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and ethyl iodide (yield: 28 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.34-7.25 (m, 3H), 7.14-7.06 (m, 2H), 7.00 (t, J = 7.6 Hz, 1H), 6.38 (d, J = 2.8 Hz, 1H), 6.35 (dd, J = 2.4, 2.8 Hz, 1H), 6.23 (d, J = 8.4 Hz, 1H), 3.96 (m, 2H), 3.75 (m, 2H), 2.33 (d, J = 14.4 Hz, 1H), 2.14 (d, J = 14.4 Hz, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.30 (m, 6H); MS (ES+) m/z: 352.1 (M+1).

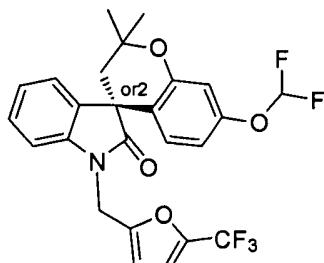
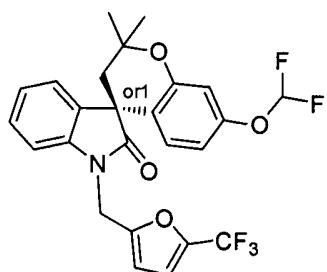
Example-30

7-(Difluoromethoxy)-2,2-dimethyl-1'-(5-trifluoromethyl)furan-2-ylmethyl) spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-21 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 29 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.29 (t, *J* = 7.6 Hz, 1H), 7.22-7.17 (m, 3H), 7.14 (d, *J* = 6.8 Hz, 1H), 7.05 (t, *J* = 6.4 Hz, 1H), 6.73 (d, *J* = 3.2 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H), 6.50 (dd, *J* = 2.4, 2.8 Hz, 1H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.10 (m, 2H), 2.40 (d, *J* = 14.8 Hz, 1H), 2.25 (d, *J* = 14.8 Hz, 1H), 1.51 (s, 3H), 1.46 (s, 3H); ¹⁹F NMR (375 MHz, DMSO-*d*₆): δ -62.71 (s, 3F), -82.30 (d, *J* = 14.4 Hz, 1F), -82.50 (d, *J* = 14.4 Hz, 1F); MS (ES+) m/z: 494.1 (M+1).

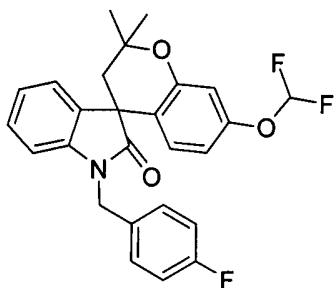
10

Example-31 and 32

15

Example-33

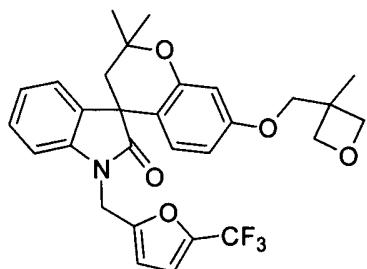
7-(Difluoromethoxy)-1'-(4-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



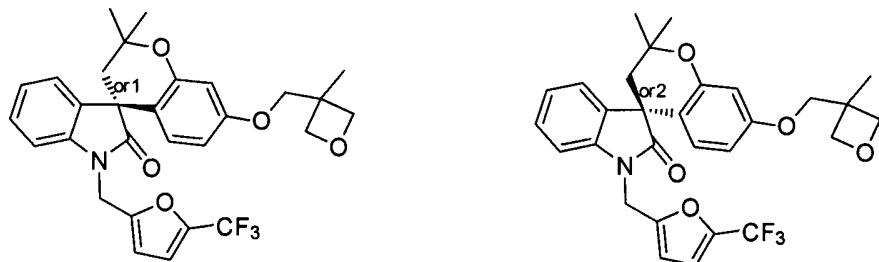
The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-21 and 4-(*p*-fluorobenzyl bromide) (yield: 31 %). ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.30 (m, 2H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 7.06-6.98 (m, 3H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.70 (d, $J = 2.4$ Hz, 1H), 6.64 (s, 1H), 6.51 (dd, $J = 2.4, 2.8$ Hz, 1H), 4.98 (m, 2H), 2.49 (d, $J = 14.4$ Hz, 1H), 2.27 (d, $J = 14.4$ Hz, 1H), 1.61 (s, 3H), 1.57 (s, 3H); MS (ES+) m/z: 454.1 (M+1).

Example-34

2,2-Dimethyl-7-((3-methyloxetan-3-yl)methoxy)-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-22 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 54 %). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.29 (t, $J = 8.0$ Hz, 1H), 7.20-7.15 (m, 2H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.03 (t, $J = 7.2$ Hz, 1H), 6.73 (d, $J = 3.2$ Hz, 1H), 6.48 (d, $J = 2.4$ Hz, 1H), 6.32-6.29 (dd, $J = 2.4, 2.8$ Hz, 1H), 6.38 (d, $J = 8.4$ Hz, 1H), 5.10 (m, 2H), 4.44 (d, $J = 5.6$ Hz, 2H), 4.27 (d, $J = 5.6$ Hz, 2H), 3.97 (s, 2H), 2.36 (d, $J = 14.4$ Hz, 1H), 2.20 (d, $J = 14.4$ Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.31 (s, 3H); MS (ES+) m/z: 528.1 (M+1).

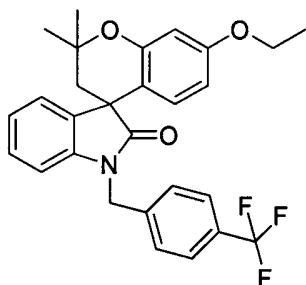


The Example-34 was separated to give Example-35 Retention time (RT) 8.66 minutes and Example-36 Retention time (RT) 13.38 minutes on chiral separation on chiral HPLC using CHIRAL PAK IC, 250 mm × 4.6, 5 μ ; Flow rate : 1.5 mL/ min; Mobile phase : A= n-hexane:

- 5 IPA (90 : 10 % v/v), B = IPA, A: B= 75/25 (% V/V).

Example-37

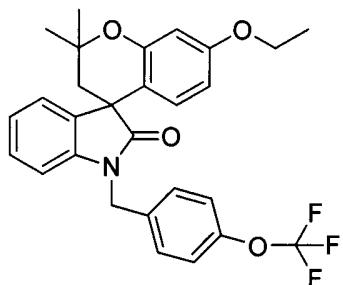
7-Ethoxy-2,2-dimethyl-1'-(4-(trifluoromethyl)benzyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-4-(trifluoromethyl) benzene (yield: 55 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.76 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.24-7.21 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.02-6.98 (m, 2H), 6.41 (d, J = 2.4 Hz, 1H), 6.36 (dd, J = 8.0, 2.4 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.04 (s, 2H), 3.98 (m, 2H), 2.23 (d, J = 16.0 Hz, 1H), 2.19 (d, J = 16.0 Hz, 1H), 1.52 (s, 3H), 1.46 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 482.23 (M+1).

Example-38

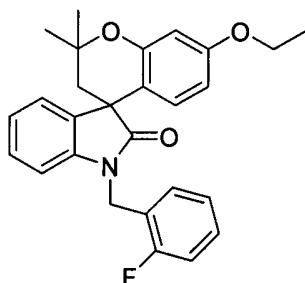
7-Ethoxy-2,2-dimethyl-1'-(4-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one

148

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-4-(trifluoromethoxy)benzene (yield: 52 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.47 (d, $J = 8.0$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.25-7.21 (m, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.04-6.98 (m, 2H), 6.40 (d, $J = 2.4$ Hz, 1H), 6.34 (dd, $J = 8.0, 2.4$ Hz, 1H), 6.24 (d, $J = 8.0$ Hz, 1H), 4.97 (s, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.41 (d, $J = 16.0$ Hz, 1H), 2.21 (d, $J = 16.0$ Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 498.1 (M+1).

Example-39

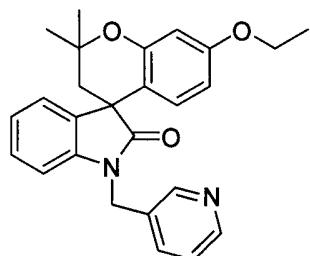
10 7-Ethoxy-1'-(2-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-2-fluorobenzene (yield: 45 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.38-7.28 (m, 1H), 7.27-7.14 (m, 4H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.01-6.93 (m, 2H), 6.40 (d, $J = 2.4$ Hz, 1H), 6.35 (dd, $J = 8.0, 2.4$, 1H), 6.28 (d, $J = 8.0$ Hz, 1H), 4.98 (s, 2H), 3.95 (q, $J = 7.2$ Hz, 2H), 2.38 (d, $J = 16.0$ Hz, 1H), 2.21 (d, $J = 16.0$ Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.27(t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 432.1 (M+1).

Example-40

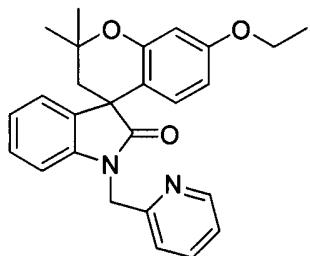
7-Ethoxy-2,2-dimethyl-1'-(pyridin-3-ylmethyl)spiro[chroman-4,3'-indolin]-2'-one

149

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 3-(bromomethyl)pyridine (yield: 56 %). ^1H NMR (400 MHz, DMSO- d_6): δ 8.01 (d, $J = 2.4$ Hz, 1H), 7.81-7.77 (m, 1H), 7.34-7.22 (m, 2H), 5 7.20-7.16 (m, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 6.97-6.95 (m, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 6.51 (d, $J = 8.0$ Hz, 1H), 6.39-6.34 (m, 2H), 5.03 (s, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.41(d, $J = 16.0$ Hz, 1H), 2.29 (d, $J = 16.0$ Hz, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 415.22 (M+1).

Example-41

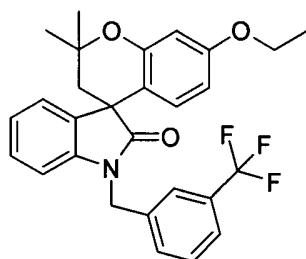
- 10 7-Ethoxy-2,2-dimethyl-1'-(pyridin-2-ylmethyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)pyridine (yield: 47 %). ^1H NMR (400 MHz, DMSO- d_6): δ 8.62 (s, 1H), 8.51 (s, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.41-7.37 (m, 1H), 7.25-7.22 (m, 1H), 7.18-6.98 (m, 3H), 6.42 (s, 1H), 6.33 (d, $J = 8.0$ Hz, 1H), 6.21(d, $J = 8.0$ Hz, 1H), 4.98 (s, 2H), 3.96 (q, $J = 7.2$ Hz, 2H), 2.40 (d, $J = 16.0$ Hz, 1H), 2.21 (d, $J = 16.0$ Hz, 1H), 1.51 (s, 3H), 1.44 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 415.29 (M+1).

Example-42

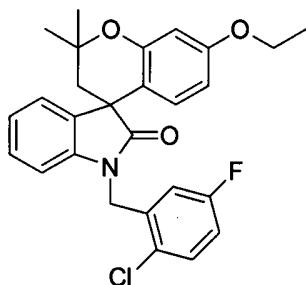
- 20 7-Ethoxy-2,2-dimethyl-1'-(3-(trifluoromethyl)benzyl)spiro[chroman-4,3'-indolin]-2'-one

150

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-3-(trifluoromethyl)benzene (yield: 62 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.76-7.57 (m, 4H), 7.26-7.21 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.06-6.99 (m, 2H), 6.44 (d, J = 2.4 Hz, 1H), 6.30 (dd, J = 8.0, 2.4 Hz, 1H), 6.21(d, J = 8.0 Hz, 1H), 5.07-4.98 (m, 2H), 3.97 (q, J = 7.2 Hz, 2H), 2.41(d, J = 16.0 Hz, 1H), 2.26 (d, J = 16.0 Hz, 1H), 1.55(s, 3H), 1.45(s, 3H), 1.27 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 482.11 (M+1).

Example 43

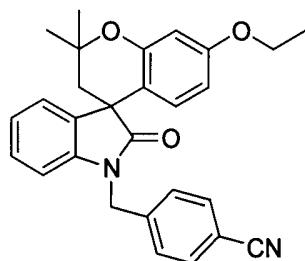
10 1'-(2-Chloro-5-fluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)-1-chloro-4-fluorobenzene (yield: 65 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.62-7.58 (m, 1H), 7.27-7.23 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.05-6.92 (m, 3H), 6.41(s, 1H), 6.34(s, 2H), 5.07-4.94 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 2.44 (d, J = 16.0 Hz, 1H), 2.26 (d, J = 16.0 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 465.67 (M+1).

Example-44

4-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzonitrile



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 4-(bromomethyl)benzonitrile (yield: 59 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.86 (d, $J = 8.0$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 2H), 7.24-7.20 (m, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.03-6.92 (m, 2H), 6.44 (d, $J = 2.4$ Hz, 1H), 6.36 (dd, $J = 8.0$, 2.4 Hz, 1H), 6.26 (d, $J = 8.0$ Hz, 1H), 5.04 (s, 2H), 3.98 (q, $J = 7.2$ Hz, 2H), 2.42 (d, $J = 16.0$ Hz, 1H), 2.23 (d, $J = 16.0$ Hz, 1H), 1.51(s, 3H), 1.46 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 439.17 (M+1).

Example-45

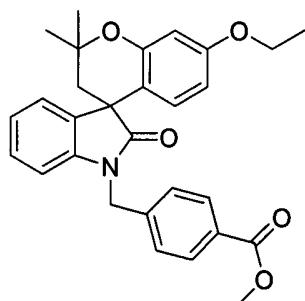
- 10 7-Ethoxy-1'-(6-fluoropyridin-2-yl)methyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)-6-fluoropyridine (yield: 60 %). ^1H NMR (400 MHz, DMSO- d_6): δ 8.03-7.97 (m, 1H), 7.34 (dd, $J = 8.0$, 2.4 Hz, 1H), 7.22-7.18 (m, 1H), 7.12-7.09 (m, 2H), 7.01-6.97 (m, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 6.57 (d, $J = 8.0$ Hz, 1H), 6.39 (d, $J = 2.4$ Hz, 1H), 6.33 (dd, $J = 8.0$, 2.4Hz, 1H), 5.08-4.95 (m, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.41 (d, $J = 16.0$ Hz, 1H), 2.2 (d, $J = 16.0$ Hz, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 433.16 (M+1).

Example-46

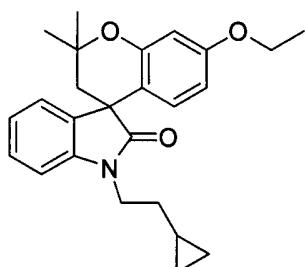
- 20 Methyl-4-((7-ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl) methyl)benzoate

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The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 4-(bromomethyl)benzoate (yield: 67 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.23-7.19 (m, 5 H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.02-6.96 (m, 2H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.28 (d, *J* = 8.0 Hz, 1H), 5.02 (s, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 2.42 (d, *J* = 16.0 Hz, 1H), 2.22 (d, *J* = 16.0 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 472.11 (M+1).

Example-47

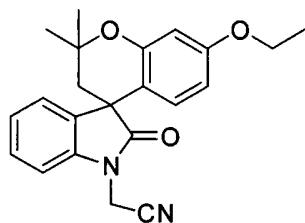
- 10 1'-(2-Cyclopropylethyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and (2-bromoethyl)cyclopropane (yield: 71 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.30-7.26 (m, 1H), 7.14-7.08 (m, 2H), 7.01 (m, 1H), 6.38-6.32 (m, 2H), 6.24 (d, *J* = 8.0 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.78 (m, 2H), 2.32 (d, *J* = 16.0 Hz, 1H), 2.15 (d, *J* = 16.0 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.70 (m, 1H), 0.39 (m, 2H), 0.04 (m, 2H); MS(ES+) m/z: 392.41 (M+1).

Example-48

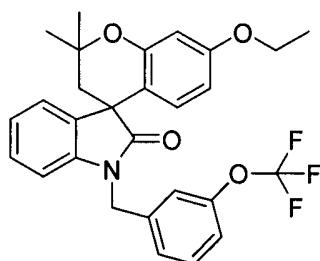
- 20 2-(7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)acetonitrile



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and bromo acetonitrile (yield: 76 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.4-7.36 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.15-7.07 (m, 2H), 6.4 (d, *J* = 2.4 Hz, 1H), 6.36 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.26 (d, *J* = 8.0 Hz, 1H), 5.0 (s, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 2.37 (d, *J* = 16.0 Hz, 1H), 2.18 (d, *J* = 16.0 Hz, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 363.1 (M+1).

Example-49

7-Ethoxy-2,2-dimethyl-1'-(3-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one

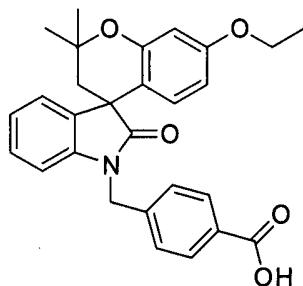


10

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-3-(trifluoromethoxy)benzene (yield: 59 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.53-7.49 (m, 1H), 7.38-7.22 (m, 4H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.06-6.98 (m, 2H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.31 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.22 (d, *J* = 8.0 Hz, 1H), 4.95-4.92 (m, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 2.39 (d, *J* = 16.0 Hz, 1H), 2.22 (d, *J* = 16.0 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 498.1 (M+1).

Example-50

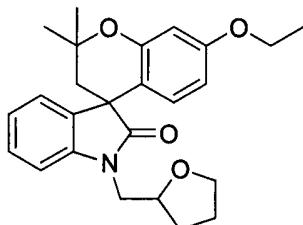
4-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzoic acid



To a solution of Example-46 (0.5g, 1.06 mmol) in a mixture of THF/water (2:1, 2mL) was added lithium hydroxide monohydrate (51 mg, 2.12 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated in *vacuo* followed by 5 the addition of water (5 mL). The mixture was extracted with ethyl acetate (15 mL). The aqueous layer was acidified with 2N HCl till pH 2. The precipitated solid was filtered and dried to give the title compound (0.41g, 85%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.91(br, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.23-7.19 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.01-6.97 (m, 2H), 6.41 (d, *J* = 2.4Hz, 1H), 6.36 (dd, *J* = 8.0, 2.4 10 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 1H), 5.01 (s, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 2.43 (d, *J* = 16.0 Hz, 1H), 2.23 (d, *J* = 16.0 Hz, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 458.04 (M+1).

Example-51

7-Ethoxy-2,2-dimethyl-1'-(tetrahydrofuran-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one



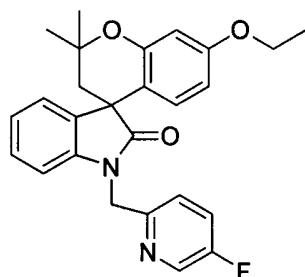
15

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and (tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (yield: 77 %). ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.24 (m, 1H), 7.18 (d, *J* = 8.0, 2.4 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.00-6.96 (m, 1H), 6.38-6.25 (m, 3H), 20 4.18 (m, 1H), 3.96 (q, *J* = 7.2 Hz, 2H), 3.83-3.72 (m, 3H), 3.63-3.62 (m, 1H), 2.23 (d, *J* =

16.0 Hz, 1H), 2.15 (d, J = 16.0 Hz, 1H), 1.95-1.90 (m, 3H), 1.62-1.59 (m, 1H), 1.47(s, 3H), 1.44 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 408.1 (M+1).

Example-52

7-Ethoxy-1'-(5-fluoropyridin-2-yl)methyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one

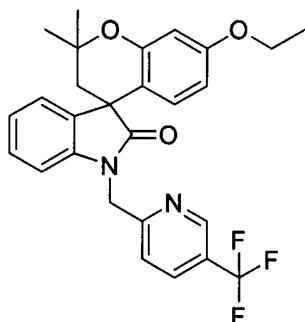


5

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)-5-fluoropyridine (yield: 80 %). ^1H NMR (400 MHz, DMSO- d_6): δ 8.53 (s, 1H), 7.68-7.71 (m, 1H), 7.47-7.43 (m, 1H), 7.21-7.17 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.99-6.91 (m, 2H), 6.43 (d, J = 8.0 Hz, 1H), 6.45-6.4 (m, 2H), 5.1-5.0 (m, 2H), 3.97 (q, J = 7.2 Hz, 2H), 2.40 (d, J = 16.0 Hz, 1H), 2.22 (d, J = 16.0 Hz, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 433.1 (M+1).

Example-53

7-Ethoxy-2,2-dimethyl-1'-(5-(trifluoromethyl)pyridin-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one



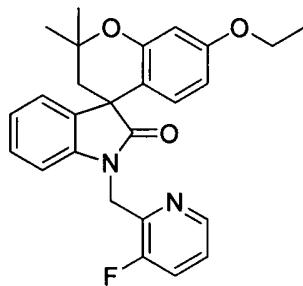
15

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)-5-(trifluoromethyl)pyridine (yield: 74 %). ^1H NMR (400 MHz, DMSO- d_6): δ 8.93 (s, 1H), 8.42 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.2-7.18 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.01-6.93 (m, 2H), 6.55 (d, J = 8.0 Hz, 1H),

6.41-6.38 (m, 2H), 5.18-5.17 (m, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.42 (d, $J = 16.0$ Hz, 1H), 2.23 (d, $J = 16.0$ Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 483.1 (M+1).

Example-54

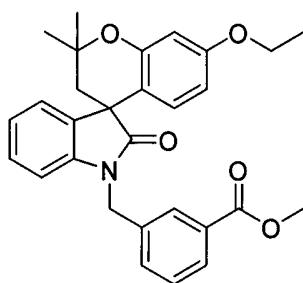
- 5 7-Ethoxy-1'-(3-fluoropyridin-2-yl)methyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)-3-fluoropyridine (yield: 67 %). ^1H NMR (400 MHz, CDCl_3): δ 8.36 (d, $J = 4.0$ Hz, 1H), 7.78-7.73 (m, 1H), 7.44-7.40 (m, 1H), 10 7.20-7.16 (m, 1H), 7.10 (d, $J = 8.0$ Hz, 1H), 6.98-6.94 (m, 2H), 6.62 (d, $J = 8.0$ Hz, 1H), 6.37-6.36 (m, 2H), 5.15 (s, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.37 (d, $J = 16.0$ Hz, 1H), 2.21(d, $J = 16.0$ Hz, 1H), 1.47(s, 3H), 1.45(s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 433.1 (M+1).

Example-55

- 15 Methyl-3-((7-ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl)benzoate

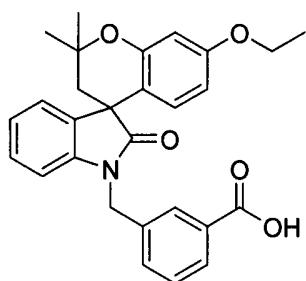


The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and methyl 3-(bromomethyl)benzoate (yield: 89 %). ^1H NMR (400 MHz, CDCl_3): δ 8.36 (d, $J = 4.0$ Hz, 1H), 7.78-7.73 (m, 1H), 7.44-7.40 (m, 1H), 20 7.20-7.16 (m, 1H), 7.10 (d, $J = 8.0$ Hz, 1H), 6.98-6.94 (m, 2H), 6.62 (d, $J = 8.0$ Hz, 1H),

6.37-6.36 (m, 2H), 5.15 (s, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.37 (d, $J = 16.0$ Hz, 1H), 2.21(d, $J = 16.0$ Hz, 1H), 1.47(s, 3H), 1.45(s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 433.1 (M+1).

Example-56

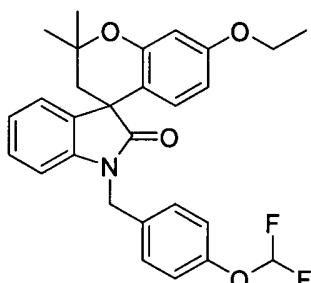
- 5 3-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzoic acid



The title compound was prepared by following a procedure similar to that described in Example-50 by using Example-55 (yield: 90 %). ^1H NMR (400 MHz, DMSO- d_6): δ 12.97(br, 1H), 7.87 (m, 2H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.52-7.48 (m, 1H), 7.23-7.21 (m, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.01-6.97 (m, 2H), 6.41 (d, $J = 2.4$ Hz, 1H), 6.32-6.31 (m, 1H), 5.09-4.93 (m, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.41 (d, $J = 16.0$ Hz, 1H), 2.23 (d, $J = 16.0$ Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 458.23 (M+1).

Example-57

- 15 1'-(4-(Difluoromethoxy)benzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



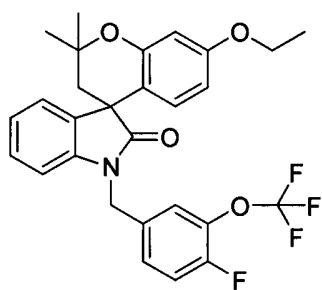
The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-4-(difluoromethoxy)benzene (yield: 61 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.46 (d, $J = 8.0$ Hz, 2H), 7.24-7.16 (m, 3H), 7.11(d, $J = 8.0$ Hz, 1H), 7.03-6.97 (m, 2H), 6.41(d, $J = 2.4$ Hz, 1H), 6.35 (dd, $J = 8.0, 2.4$ Hz,

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1H), 6.23 (d, $J = 8.0$ Hz, 1H), 4.93 (s, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.40 (d, $J = 16.0$ Hz, 1H), 2.22 (d, $J = 16.0$ Hz, 1H), 1.48 (s, 3H), 1.45(s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 480.1 (M+1).

Example-58

- 5 7-Ethoxy-1'-(4-fluoro-3-(trifluoromethoxy)benzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one

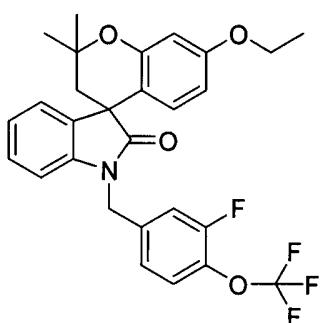


The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 4-(bromomethyl)-1-fluoro-2-(trifluoromethoxy) benzene (yield: 63 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.57-7.49 (m, 2H), 7.44-7.40 (m, 1H), 7.26-7.23 (m, 1H), 7.12-7.08 (m, 1H), 7.03-6.99 (m, 2H), 6.41 (d, $J = 2.4$ Hz, 1H), 6.31(dd, $J = 8.0, 2.4$ Hz, 1H), 6.19 (d, $J = 8.0$ Hz, 1H), 5.03-4.93 (m, 2H), 3.95 (q, $J = 7.2$ Hz, 2H), 2.38 (d, $J = 16.0$ Hz, 1H), 2.20 (d, $J = 16.0$ Hz, 1H), 1.50 (s, 3H), 1.44 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 516.1 (M+1).

15

Example-59

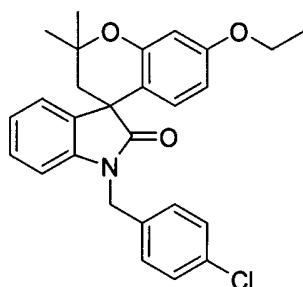
- 7-Ethoxy-1'-(3-fluoro-4-(trifluoromethoxy)benzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 4-(bromomethyl)-2-fluoro-1-(trifluoromethoxy)benzene (yield: 60 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.60-7.49 (m, 2H), 7.26-7.22 (m, 2H), 7.13-6.99 (m, 3H), 6.41 (d, J = 2.4 Hz, 1H), 6.33 (dd, J = 8.0, 2.4 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 5.03-4.94 (m, 2H), 3.96 (q, J = 7.2 Hz, 2H), 2.42 (d, J = 16.0 Hz, 1H), 2.23 (d, J = 16.0 Hz, 1H), 1.51 (s, 3H), 1.44 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 516.1 (M+1).

Example-60

1'-(4-Chlorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one

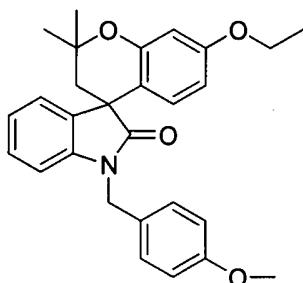


10

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-chloro-4-(chloromethyl) benzene (yield: 49 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.43 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.24-7.20 (m, 1H), 7.11(d, J = 8.0 Hz, 1H), 7.01(d, J = 8.0 Hz, 2H), 6.40 (d, J = 2.4 Hz, 1H), 6.35 (dd, J = 8.0, 2.4 Hz, 1H), 6.23 (d, J = 8.0 Hz, 1H), 4.93 (s, 2H), 3.97 (q, J = 7.2 Hz, 2H), 2.40 (d, J = 16.0 Hz, 1H), 2.20 (d, J = 16.0 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 448.23 (M+1).

Example-61

7-Ethoxy-1'-(4-methoxybenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



20

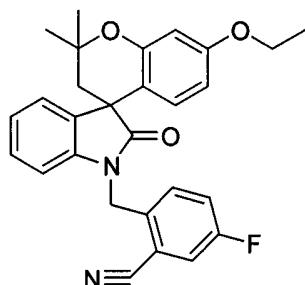
160

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(chloromethyl)-4-methoxybenzene (yield: 59 %).

¹H NMR (400 MHz, DMSO-d₆): δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.23-7.18 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.01-6.97 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.34 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.21 (d, *J* = 8.0 Hz, 1H), 4.89-4.84 (m, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 2.39 (d, *J* = 16.0 Hz, 1H), 2.19 (d, *J* = 16.0 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 444.1 (M+1).

Example-62

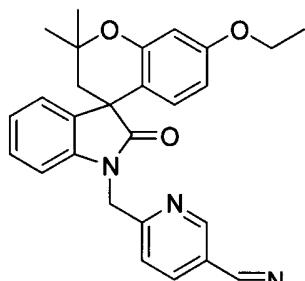
2-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl)-5-fluoro
10 benzonitrile



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)-5-fluorobenzonitrile (yield: 86 %).
¹H NMR (400 MHz, DMSO-d₆): δ 7.94-7.93 (m, 1H), 7.61-7.56 (m, 1H), 7.38-7.35 (m, 1H),
15 7.27-7.32 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.04-7.01 (m, 1H), 6.40-6.31 (m, 2H), 5.29-4.76 (m, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 2.44 (d, *J* = 16.0 Hz, 1H), 2.24 (d, *J* = 16.0 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 457.1 (M+1).

Example-63

6-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) nicotine nitrile

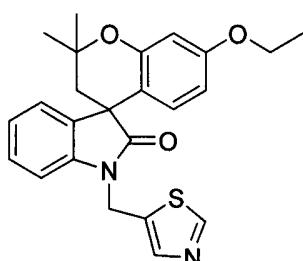


161

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 6-(bromomethyl)nicotinonitrile (yield: 69 %). ¹H NMR (400 MHz, CDCl₃): δ 8.83 (s, 1H), 7.82-7.89 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.18-7.12 (m, 2H), 7.01-6.97 (m, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.39 (d, J = 8.0 Hz, 1H), 6.33 (dd, J = 8.0, 2.4 Hz, 1H), 5.18-5.09 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 2.46 (d, J = 16.0 Hz, 1H), 2.25 (d, J = 16.0 Hz, 1H), 1.54 (s, 3H), 1.50 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 440.1 (M+1).

Example-64

7-Ethoxy-2,2-dimethyl-1'-(thiazol-5-ylmethyl)spiro[chroman-4,3'-indolin]-2'-one

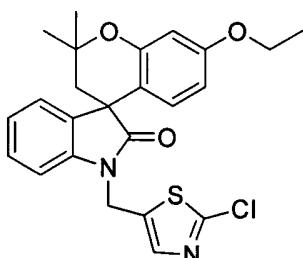


10

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 5-(bromomethyl)thiazole (yield: 62 %). ¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.24-7.20 (m, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.04-6.97 (m, 2H), 6.47 (d, J = 2.4 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 6.36 (d, J = 8.0 Hz, 1H), 5.37-5.21 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 2.48 (d, J = 16.0 Hz, 1H), 2.27 (d, J = 16.0 Hz, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 421.1 (M+1).

Example-65

1'-((2-Chlorothiazol-5-yl)methyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one

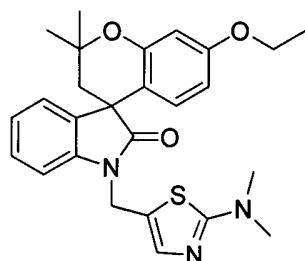


20

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-chloro-5-(chloromethyl) thiazole (yield: 70 %). ¹H NMR (400 MHz, CDCl₃): δ 7.56 (s, 1H), 7.24-7.22 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.04-7.01 (m, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.34 (dd, J = 8.0, 2.4 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.08-4.95 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 2.39 (d, J = 16.0 Hz, 1H), 2.212 (d, J = 16.0 Hz, 1H), 1.55 (s, 3H), 1.50 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 454.98 (M+1).

Example-66

10 1'-(2-(Dimethylamino)thiazol-5-yl)methyl)-7-ethoxy-2,2-dimethylspiro [chroman-4,3'-indolin]-2'-one

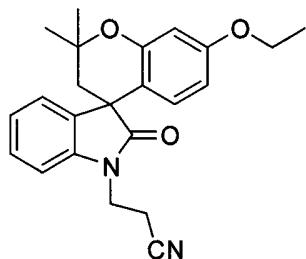


To a solution of Example-65 (0.20 g, 0.49 mmol) in N,N-dimethylformamide (6 mL) was added 2 M dimethyl amine in tetrahydrofuran (2.4 mL, 4.87 mmol) under nitrogen in a sealed tube. The reaction mixture was heated at 120 °C for 16 h. The reaction was quenched 15 with the water, and then extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over sodium sulfate, filtered, and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by flash chromatography with 30 % ethyl acetate in hexanes to afford the title compound (0.14 g, 70 %) as a colorless solid. ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.19 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 7.01-6.93 (m, 2H), 6.44 (d, J = 2.4 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H), 6.31 (dd, J = 8.0, 2.4 Hz, 1H), 5.03 (d, J = 16.0 Hz, 1H), 4.85 (d, J = 16.0 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.05 (s, 6H), 2.41 (d, J = 16.0 Hz, 1H), 2.20 (d, J = 16.0 Hz, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 464.1 (M+1).

Example-67

25 3-(7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)propanenitrile

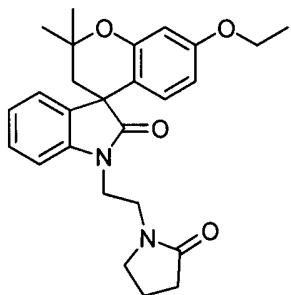
163



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 3-bromopropanenitrile (yield: 67 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.95-7.24 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.05-7.01 (m, 2H), 6.4 (d, J = 2.4 Hz, 1H), 6.36 (d, J = 8.0 Hz, 1H), 6.31 (dd, J = 8.0, 2.4 Hz, 1H), 4.03-3.19 (m, 4H), 2.97 (m, 2H), 2.35 (d, J = 16.0 Hz, 1H), 2.13 (d, J = 16.0 Hz, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 377.1 (M+1).

Example-68

7-Ethoxy-2,2-dimethyl-1'-(2-(2-oxopyrrolidin-1-yl)ethyl)spiro[chroman-4,3'-indolin]-2'-one

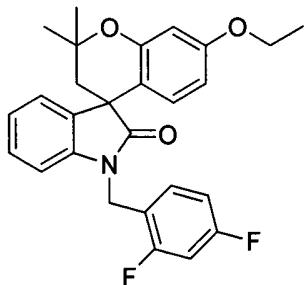


10

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(2-oxopyrrolidin-1-yl)ethyl 4-methylbenzenesulfonate (yield: 52 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.31-7.29 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.05 (m, 2H), 6.37 (s, 1H), 6.30 (s, 2H), 3.96-3.82 (m, 4H), 3.62 (m, 1H), 3.46-3.34 (m, 3H), 2.28 (d, J = 16.0 Hz, 1H), 2.1-2.01 (m, 3H), 1.8-1.74 (m, 2H), 1.47 (s, 3H), 1.42 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); MS(ES+) m/z: 435.1 (M+1).

Example-69

1'-(2,4-Difluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one

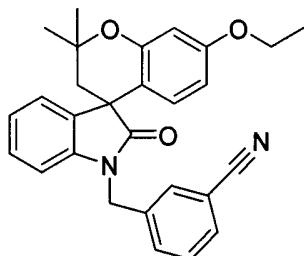
164

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-2,4-difluorobenzene (yield: 82 %).

¹H NMR (400 MHz, CDCl₃): δ 7.56 (m, 2H), 7.21-7.19 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.08-6.99 (m, 1H), 6.89-6.83 (m, 3H), 6.47 (d, *J* = 4.0 Hz, 1H), 6.33-6.32 (m, 1H), 5.01-4.9 (m, 2H), 4.0 (q, *J* = 7.2 Hz, 2H), 2.47 (d, *J* = 16.0 Hz, 1H), 2.25 (d, *J* = 16.0 Hz, 1H), 1.61 (s, 3H), 1.53 (s, 3H), 1.4 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 450.04 (M+1).

Example-70

3-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzonitrile



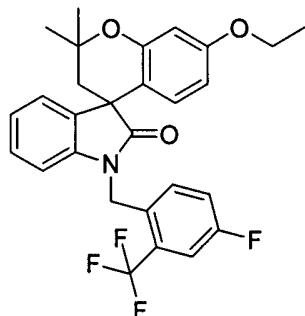
10

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 3-(bromomethyl)benzonitrile (yield: 72 %). ¹H NMR (400 MHz, CDCl₃): δ 7.7-7.59 (m, 3H), 7.54-7.46 (m, 1H), 7.23-7.17 (m, 2H), 7.05-7.02 (m, 1H), 6.75(d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 4.0 Hz, 1H), 6.39-6.32 (m, 2H), 5.03-4.92 (m, 2H), 4.01 (q, *J* = 7.2 Hz, 2H), 2.50 (d, *J* = 16.0 Hz, 1H), 2.28 (d, *J* = 16.0 Hz, 1H), 1.69 (s, 3H), 1.57 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 439.1 (M+1).

Example-71

7-Ethoxy-1'-(4-fluoro-2-(trifluoromethyl)benzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one

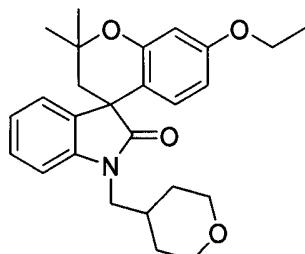
165



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-4-fluoro-2-(trifluoromethyl) benzene (yield: 48 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.70 (d, $J = 8.0$ Hz, 1H), 7.56-7.51 (m, 1H), 7.26-7.21 (m, 2H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.06-7.02 (m, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.45-6.36 (m, 3H), 5.13-5.01 (m, 2H), 3.98 (q, $J = 7.2$ Hz, 2H), 2.45 (d, $J = 16.0$ Hz, 1H), 2.28 (d, $J = 16.0$ Hz, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.3 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 500.1 (M+1).

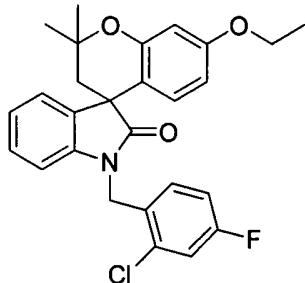
Example-72

10 7-Ethoxy-2,2-dimethyl-1'-(4-(bromomethyl)tetrahydro-2H-pyran-4-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 4-(bromomethyl)tetrahydro-2H-pyran (yield: 51 %).
15 ^1H NMR (400 MHz, CDCl₃): δ 7.24-7.22 (m, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 7.03-7.0 (m, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.46 (d, $J = 4.0$ Hz, 1H), 6.37-6.32 (m, 2H), 4.01-3.95 (m, 4H), 3.71-3.61 (m, 2H), 3.40-3.34 (m, 2H), 2.42 (d, $J = 16.0$ Hz, 1H), 2.22 (d, $J = 16.0$ Hz, 1H), 2.18 (m, 1H), 1.61-1.58 (m, 2H), 1.56 (s, 3H), 1.48 (s, 3H), 1.40 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 422.2 (M+1).

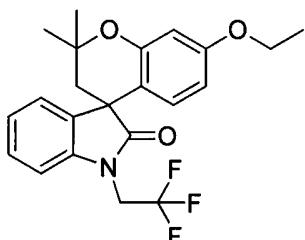
1'-(2-Chloro-4-fluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-2-chloro-4-fluorobenzene (yield: 5 64 %). ^1H NMR (400 MHz, CDCl_3): δ 7.18-7.13 (m, 4H), 7.01-6.97 (m, 1H), 6.94-6.89 (m, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 6.45 (d, $J = 4.0$ Hz, 1H), 6.38-6.32 (m, 2H), 5.02 (s, 2H), 3.98 (q, $J = 7.2$ Hz, 2H), 2.48 (d, $J = 16.0$ Hz, 1H), 2.25 (d, $J = 16.0$ Hz, 1H), 1.54 (s, 3H), 1.51 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 467.11 (M+1).

Example-74

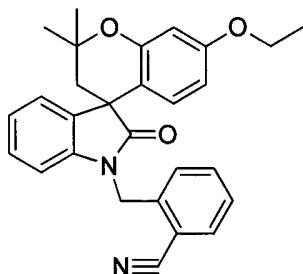
10 7-Ethoxy-2,2-dimethyl-1'-(2,2,2-trifluoroethyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1,1,1-trifluoro-2-iodoethane (yield: 53 %). ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.28 (m, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 7.08-7.06 (m, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 6.45 (d, $J = 4.0$ Hz, 1H), 6.38-6.32 (m, 2H), 4.37 (q, $J = 7.2$ Hz, 2H), 3.99 (q, $J = 7.2$ Hz, 2H), 2.40 (d, $J = 16.0$ Hz, 1H), 2.24 (d, $J = 16.0$ Hz, 1H), 1.56 (s, 3H), 1.51 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 406.1 (M+1).

Example-75

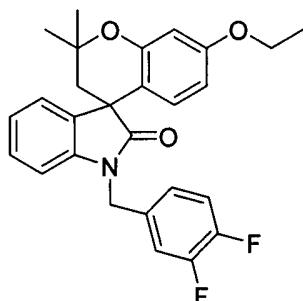
2-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzonitrile



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)benzonitrile (yield: 72 %). ^1H NMR (400 MHz, CDCl_3): δ 7.71 (d, $J = 8.0$ Hz, 1H), 7.55-7.53 (m, 1H), 7.41-7.35 (m, 2H), 7.19-7.12 (m, 2H), 7.01-6.97 (m, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.45 (d, $J = 4.0$ Hz, 1H), 6.36-6.31 (m, 2H), 5.17 (s, 2H), 3.98 (q, $J = 7.2$ Hz, 2H), 2.51 (d, $J = 16.0$ Hz, 1H), 2.26 (d, $J = 16.0$ Hz, 1H), 1.55 (s, 3H), 1.51 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 439.17 (M+1).

Example-76

1'-(3,4-Difluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



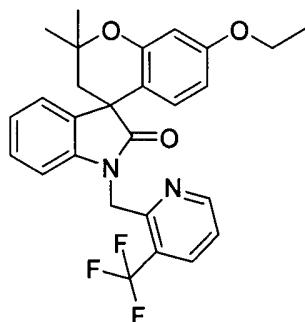
10

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-3,4-difluorobenzene (yield: 81 %). ^1H NMR (400 MHz, CDCl_3): δ 7.19-7.07 m, 3H), 7.05-7.02 (m, 2H), 7.01-6.97 (m, 1H), 6.74 (d, $J = 8.0$ Hz, 1H), 6.45 (d, $J = 4.0$ Hz, 1H), 6.31-6.29 (m, 2H), 4.9 (d, $J = 16.0$ Hz, 1H), 4.83 (d, $J = 16.0$ Hz, 1H), 3.98 (q, $J = 7.2$ Hz, 2H), 2.45 (d, $J = 16.0$ Hz, 1H), 2.23 (d, $J = 16.0$ Hz, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 450.04 (M+1).

Example-77

7-Ethoxy-2,2-dimethyl-1'-(3-(trifluoromethyl)pyridin-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one

20

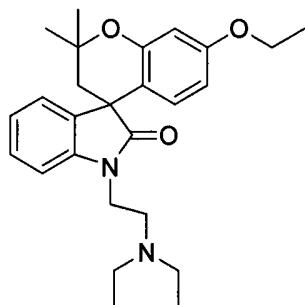
168

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)-3-(trifluoromethyl)pyridine (yield: 58 %). ^1H NMR (400 MHz, CDCl_3): δ 8.64 (d, $J = 4.0$ Hz, 1H), 8.01(d, $J = 4.0$ Hz, 1H), 7.54-5 7.32 (m, 2H), 7.16-7.12 (m, 1H), 7.01-6.98 (m, 1H), 6.90(d, $J = 8.0$ Hz, 1H), 6.615 (d, $J = 4.0$ Hz, 1H), 6.46 (d, $J = 4.0$ Hz, 1H), 6.42 (dd, $J = 4.0, 8.0$ Hz, 1H), 5.40 (d, $J = 16.0$ Hz, 1H), 5.21(d, $J = 16.0$ Hz, 1H), 4.01(q, $J = 7.2$ Hz, 2H), 2.56(d, $J = 16.0$ Hz, 1H), 2.34 (d, $J = 16.0$ Hz, 1H), 1.55 (s, 3H), 1.51(s, 3H), 1.40 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 483.1 (M+1).

10

Example-78

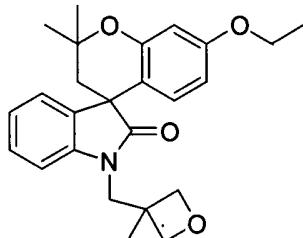
1'-(2-(Diethylamino)ethyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-chloro-N,N-diethyl ethanamine (yield: 37 %). ^1H NMR (400 MHz, CDCl_3): δ 7.26-7.23 (m, 1H), 7.20 (d, $J = 8.0$ Hz, 1H), 7.0-6.92 (m, 1H), 6.43-6.40 (m, 3H), 6.33 (dd, $J = 4.0, 8.0$ Hz, 1H), 3.98-3.91(m, 3H), 3.78-3.78 (m, 1H), 2.75-15 2.74 (m, 2H), 2.63-2.61 (m, 4H), 2.40 (d, $J = 16.0$ Hz, 1H), 2.20 (d, $J = 16.0$ Hz, 1H), 1.56 (s, 3H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.05 (m, 6H); MS(ES+) m/z: 423.29 (M+1).

Example-79

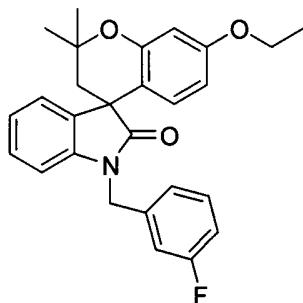
7-Ethoxy-2,2-dimethyl-1'-(3-methyloxetan-3-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and (3-methyloxetan-3-yl)methyl 4-methylbenzenesulfonate (*Journal of the American Chemical Society* (1999), 121, 5459 – 5466) (yield: 54 %). ¹H NMR (400 MHz, CDCl₃): δ 7.27-7.22 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.02-6.98 (m, 1H), 6.84 (dd, *J* = 4.0, 8.0 Hz, 1H), 6.45-6.41 (m, 2H), 6.35 (dd, *J* = 4.0, 8.0 Hz, 1H), 4.75-4.70 (m, 2H), 4.35-4.32 (m, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.88-3.78 (m, 2H), 2.42 (d, *J* = 16.0 Hz, 1H), 2.20 (d, *J* = 16.0 Hz, 1H), 1.58 (s, 3H), 1.52 (s, 3H), 1.46 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 408.42 (M+1).

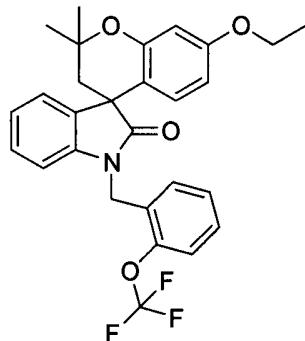
Example-80

7-Ethoxy-1'-(3-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-3-fluorobenzene (yield: 67 %). ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.28 (m, 1H), 7.19-7.11 (m, 3H), 7.03-6.95 (m, 3H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 4.0 Hz, 1H), 6.37-6.34 (m, 2H), 4.99 (m, 2H), 4.83 (d, *J* = 16.0 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 2H), 2.48 (d, *J* = 16.0 Hz, 1H), 2.26 (d, *J* = 16.0 Hz, 1H), 1.57 (s, 3H), 1.52 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); MS(ES+) m/z: 432.1 (M+1).

7-Ethoxy-2,2-dimethyl-1'-(2-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one

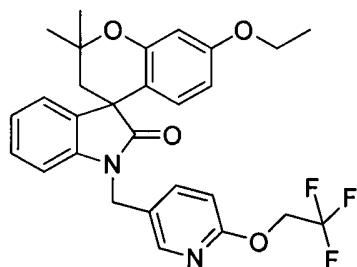


The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 1-(bromomethyl)-2-(trifluoromethoxy)benzene (yield: 80 %). ^1H NMR (400 MHz, CDCl_3): δ 7.35-7.26 (m, 2H), 7.25-7.23 (m, 2H), 7.21-7.13 (m, 2H), 7.01-6.98 (m, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 6.46 (d, $J = 4.0$ Hz, 1H), 6.40-6.32 (m, 2H), 5.04-4.98 (m, 2H), 3.97 (q, $J = 7.2$ Hz, 2H), 2.49 (d, $J = 16.0$ Hz, 1H), 2.26 (d, $J = 16.0$ Hz, 1H), 1.56 (s, 3H), 1.52 (s, 3H), 1.39 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 498.35 (M+1).

10

Example-82

7-Ethoxy-2,2-dimethyl-1'-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one



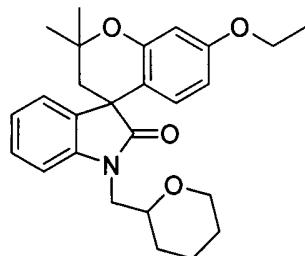
The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 5-(bromomethyl)-2-(2,2,2-trifluoroethoxy)pyridine (yield: 46 %). ^1H NMR (400 MHz, CDCl_3): δ 8.19 (d, $J = 4.0$ Hz, 1H), 7.67 (dd, $J = 4.0, 8.0$ Hz, 1H), 7.23-7.19 (m, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 7.03-7.01 (m, 1H), 6.86-6.81 (m, 2H), 6.74 (d, $J = 4.0$ Hz, 1H), 6.34-6.32 (m, 2H), 4.93 (d, $J = 16.0$ Hz, 1H), 4.82-4.72 (m, 3H),

4.01 (q, $J = 7.2$ Hz, 2H), 2.47 (d, $J = 16.0$ Hz, 1H), 2.24 (d, $J = 16.0$ Hz, 1H), 1.57 (s, 3H), 1.52 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 513.1 (M+1).

Example-83

7-Ethoxy-2,2-dimethyl-1'-(tetrahydro-2H-pyran-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one

5

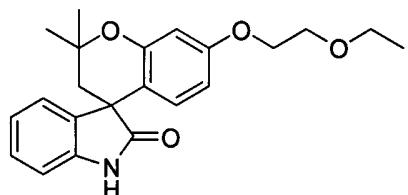


The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-20 and 2-(bromomethyl)tetrahydro-2H-pyran (yield: 56 %).

10 ^1H NMR (400 MHz, CDCl_3): δ 7.25 (d, $J = 8.0$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.06-6.97 (m, 2H), 6.49-6.40 (m, 2H), 6.34 (m, 1H), 3.98 (q, $J = 7.2$ Hz, 2H), 3.85-3.69 (m, 4H), 3.41-3.3 (m, 1H), 2.43 (d, $J = 16.0$ Hz, 1H), 2.24 (d, $J = 16.0$ Hz, 1H), 1.87-1.86 (m, 1H), 1.68-1.59 (m, 4H), 1.52 (t, $J = 7.2$ Hz, 3H), 1.48 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 422.29 (M+1).

Example-84

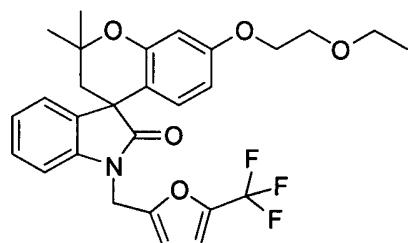
15 7-(2-Ethoxyethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-38 (Yield: 65 %). ^1H NMR (400 MHz, CDCl_3): δ 10.6 (s, 1H), 7.22-7.17 (m, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.94-6.94-6.89 (m, 2H), 6.40-6.35 (m, 2H), 6.32 (d, $J = 8.0$ Hz, 1H), 4.02-3.99 (m, 2H), 3.65-3.63 (m, 2H), 3.49-3.44 (m, 2H), 2.35 (d, $J = 16.0$ Hz, 1H), 2.13 (d, $J = 16.0$ Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H), 1.19 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 368.44 (M+1).

Example-85

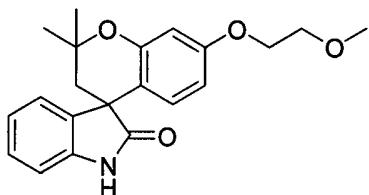
7-(2-Ethoxyethoxy)-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one)



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-84 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 51 %). ^1H NMR (400 MHz, DMSO d_6): δ 7.28-7.25 (m, 1H), 7.2-7.15 (m, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.03-7.01 (m, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 6.28-6.21 (m, 2H), 5.14-5.00 (m, 2H), 4.01-3.99 (m, 2H), 3.64-3.62 (m, 2H), 3.49 (q, J = 7.2 Hz, 2H), 2.36 (d, J = 16.0 Hz, 1H), 2.20 (d, J = 16.0 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.12 (s, 3H); MS(ES+) m/z: 515.81 (M+1).

Example-86

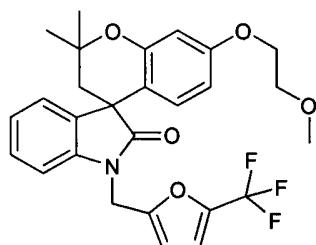
7-(2-Methoxyethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-39 (yield: 70 %).

Example-87

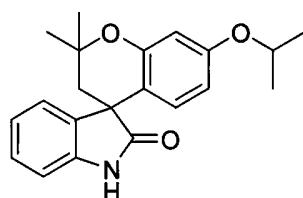
7-(2-Methoxyethoxy)-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-86 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 48 %). ^1H NMR (400 MHz, DMSO d_6): δ 7.28-7.25 (m, 1H), 7.19-7.15 (m, 2H), 7.11 (d, J = 8.0 Hz, 1H), 7.04-6.99 (m, 1H), 6.73 (d, J = 3.2 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.28-6.20 (m, 2H), 5.14-5.00 (m, 2H), 4.01-3.99 (m, 2H), 3.61-3.58 (m, 2H), 3.27 (s, 3H), 2.36 (d, J = 16.0 Hz, 1H), 2.20 (d, J = 16.0 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H); MS(ES+) m/z: 502.1 (M+1).

Example-88

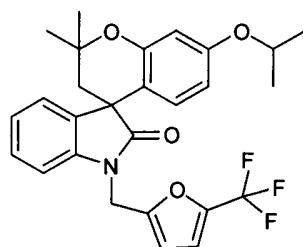
- 10 7-Isopropoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-40 (yield: 60 %).

Example-89

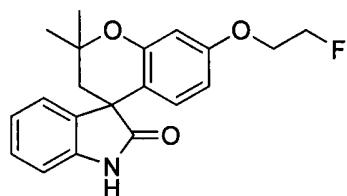
- 15 7-Isopropoxy-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-88 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 53 %). ^1H NMR (400 MHz, DMSO d_6): δ 7.28-7.24 (m, 1H), 7.19-7.11 (m, 3H), 7.03-6.99 (m, 1H), 6.73 (d, J = 3.2 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.23-6.18 (m, 2H), 5.14-4.99 (m, 2H), 5 4.54-4.45 (m, 2H), 2.35(d, J = 16.0 Hz, 1H), 2.19 (d, J = 16.0 Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H), 1.22 (d, J = 6.0 Hz, 6H); MS(ES+) m/z: 486.1 (M+1)

Example-90

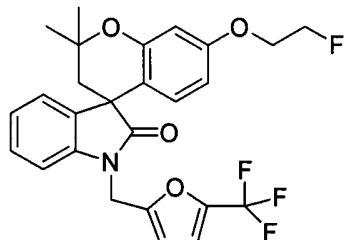
7-(2-Fluoroethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



10 The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-41 (yield: 62 %).

Example-91

7-(2-Fluoroethoxy)-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one



15

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-90 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 45 %). ^1H NMR (400 MHz, CDCl₃): δ 7.28-7.24 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.06-7.02 (m, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.75-6.74 (m, 1H), 6.49-6.48 (m, 1H), 6.39-6.37 (m, 2H), 20 4.92 (d, J = 16.0 Hz, 1H), 4.79-4.77 (m, 1H), 4.67-4.65 (m, 1H), 4.20-4.18 (m, 1H), 4.13-4.11 (m, 1H), 2.45 (d, J = 16.0 Hz, 1H), 2.25 (d, J = 16.0 Hz, 1H), 1.57 (s, 3H), 1.52 (s, 3H); MS(ES+) m/z: 489.9 (M+1).

Example-92

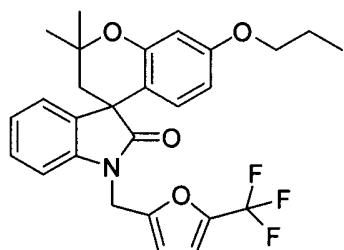
2,2-Dimethyl-7-propoxyspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described
5 in Intermediate-9 by using Intermediate-42 (yield: 69 %).

Example-93

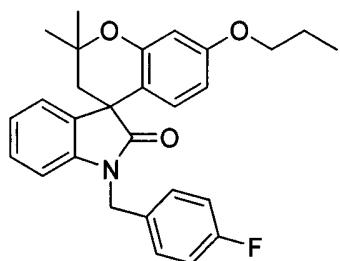
2,2-Dimethyl-7-propoxy-1'-((5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described
10 in Example-7 by using Example-92 and 2-(bromomethyl)-5-(trifluoro methyl)furan (yield: 48 %). ^1H NMR (400 MHz, CDCl_3): δ 7.27-7.16 (m, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 7.05-7.01 (m, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 6.75-6.74 (m, 1H), 6.49-6.46 (m, 1H), 6.39 (d, $J = 4.0$ Hz, 1H), 6.35-6.34 (m, 2H), 5.07 (d, $J = 16.0$ Hz, 1H), 4.93 (d, $J = 16.0$ Hz, 1H), 3.87(m, 2H),
15 2.44 (d, $J = 16.0$ Hz, 1H), 2.25 (d, $J = 16.0$ Hz, 1H), 1.80-1.75 (m, 2H), 1.54 (s, 3H), 1.52 (s, 3H), 1.08 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 486.1 (M+1).

Example-94

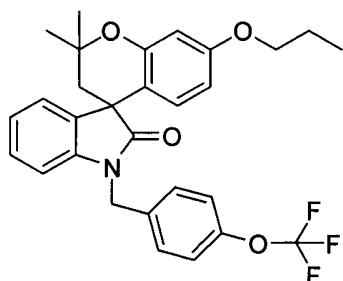
2,2-Dimethyl-7-propoxy-1'-((5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-92 and 1-(bromomethyl)-4-fluoro benzene (yield: 55 %). ^1H NMR (400 MHz, CDCl_3): δ 7.35-7.32 (m, 2H), 7.20-7.13 (m, 2H), 7.06-6.97 (m, 3H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.48 (d, $J = 4.0$ Hz, 1H), 6.34-6.33 (m, 2H), 5.01 (d, $J = 16.0$ Hz, 1H), 4.86 (d, $J = 16.0$ Hz, 1H), 3.88 (m, 2H), 2.49 (d, $J = 16.0$ Hz, 1H), 2.16 (d, $J = 16.0$ Hz, 1H), 1.81-1.75 (m, 2H), 1.55 (s, 3H), 1.53 (s, 3H), 1.01 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 446.1 (M+1).

Example-95

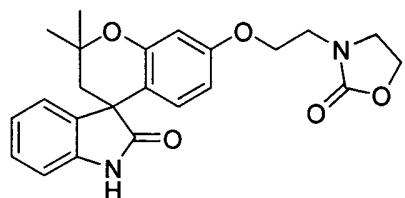
- 10 2,2-Dimethyl-7-propoxy-1'-(4-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-92 and 1-(bromomethyl)-4-(trifluoromethoxy)benzene (yield: 65 %). ^1H NMR (400 MHz, CDCl_3): δ 7.44-7.37 (m, 2H), 7.24-7.14 (m, 4H), 7.03-6.99 (m, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.48 (s, 1H), 6.34 (s, 1H), 5.02 (d, $J = 16.0$ Hz, 1H), 4.91 (d, $J = 16.0$ Hz, 1H), 3.88 (t, 2H), 2.49 (d, $J = 16.0$ Hz, 1H), 2.26 (d, $J = 16.0$ Hz, 1H), 1.80-1.75 (m, 2H), 1.57 (s, 3H), 1.53 (s, 3H), 1.03 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 512.1 (M+1).

Example-96

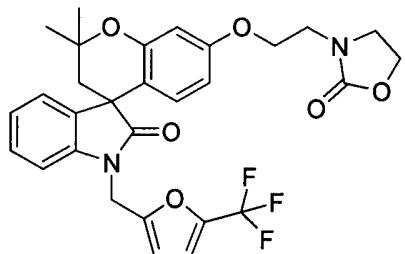
- 20 2,2-Dimethyl-7-(2-(2-oxooxazolidin-3-yl)ethoxy)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-43 (yield: 72 %). ^1H NMR (400 MHz, DMSO- d_6): δ 10.15 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.21-7.17 (m, 9H), 7.05 (d, J = 8.0 Hz, 1H), 6.94-6.89 (m, 2H), 6.43-6.31 (m, 3H), 4.25-4.17 (m, 2H), 4.05-4.03 (m, 2H), 3.63-3.59 (m, 2H), 3.49-3.47 (m, 2H), 2.43 (d, J = 16.0 Hz, 1H), 2.32 (d, J = 16.0 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H); MS(ES+) m/z: 409.1 (M+1).

Example-97

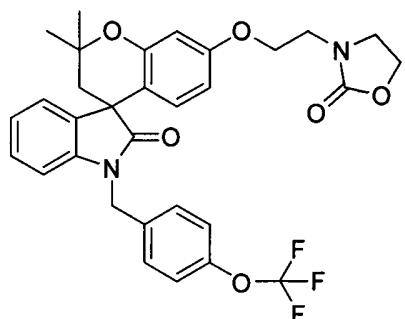
2,2-Dimethyl-7-(2-(2-oxooxazolidin-3-yl)ethoxy)-1'-(5-(trifluoromethyl)furan-2-yl)methylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-96 and 2-(bromomethyl)-5-(trifluoro methyl)furan (yield: 57 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.29-7.25 (m, 1H), 7.2 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 7.04-6.99 (m, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 6.29-6.21 (m, 2H), 5.14-5.0 (m, 2H), 4.25-4.13 (m, 2H), 4.01(q, J = 7.2 Hz, 2H), 3.63-3.61(m, 2H), 3.59-3.47(m, 2H), 2.43 (d, J = 16.0 Hz, 1H), 2.33 (d, J = 16.0 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H); MS(ES+) m/z: 557.1 (M+1).

Example-98

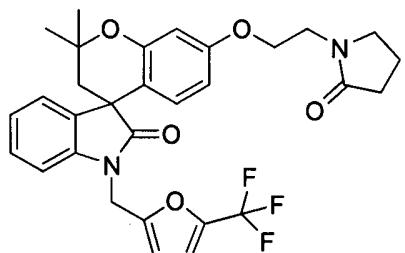
2,2-Dimethyl-7-(2-(2-oxooxazolidin-3-yl)ethoxy)-1'-(4-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-96 and 1-(bromomethyl)-4-(trifluoro methoxy)benzene (yield: 73 %). ^1H NMR (400 MHz, DMSO-d₆): δ 7.51 (d, $J = 8.0$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.29-7.22 (m, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.04-6.98 (m, 2H), 6.47 (d, $J = 2.4$ Hz, 1H), 6.38-6.35 (m, 1H), 6.27 (d, $J = 8.0$ Hz, 1H), 4.97 (s, 2H), 4.27-4.16 (m, 2H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.64-3.57 (m, 2H), 3.50-3.48 (m, 2H), 2.42 (d, $J = 16.0$ Hz, 1H), 2.23 (d, $J = 16.0$ Hz, 1H), 1.51 (s, 3H), 1.46 (s, 3H); MS(ES+) m/z: 583.1 (M+1).

Example-99

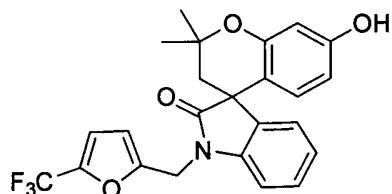
- 10 2,2-Dimethyl-7-(2-(2-oxopyrrolidin-1-yl)ethoxy)-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using 2,2-dimethyl-7-(2-(2-oxopyrrolidin-1-yl)ethoxy)spiro[chroman-4,3'-indolin]-2'-one (prepared from O-alkylation of Intermediate-33 then debenzylation by following the procedure described here in above). ^1H NMR (400 MHz, DMSO-d₆): δ 7.29-7.25 (m, 1H), 7.19 (m, 2H), 7.15 (d, $J = 8.0$ Hz, 1H), 7.04-7.01 (m, 1H), 6.72 (d, $J = 2.4$ Hz, 1H), 6.43 (d, $J = 2.4$ Hz, 1H), 6.28-6.21 (m, 2H), 5.14-5.00 (m, 2H), 3.98 (q, $J = 7.2$ Hz, 2H), 3.50 (m, 2H), 3.48 (m, 2H), 2.36 (d, $J = 16.0$ Hz, 1H), 2.2-2.17 (m, 3H), 1.9-1.84 (m, 2H), 20 1.49 (s, 3H), 1.45 (s, 3H); MS(ES+) m/z: 555.18 (M+1).

Example-100

7-Hydroxy-2,2-dimethyl-1'-((5-(trifluoromethyl)furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one

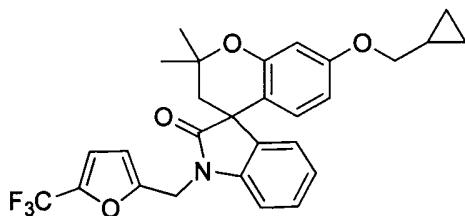


5

To a stirred solution of Intermediate-45 (0.32g 0.599mmol) in DMF (15mL) at 0°C was added sodium hydride (0.028g, 0.718mmol) at ambient temperature and the resulting reaction mixture was stirred for 15 minutes. To the above reaction mixture was added 2-(bromomethyl)-5-(trifluoromethyl)furan (0.150g, 0.658 mmol) and the resulting solution was stirred at room temperature for overnight. The reaction mixture was diluted with water (20mL) and extracted with ethyl acetate (20mL x2), the organic layer was dried over Na₂SO₄ and concentrated under *vacuo* to afford a solid. The residue was purified by column chromatography eluting with 20% ethyl acetate/petroleum ether to get the title compound (0.150 g 55%). ¹H NMR (400 MHz, DMSO-d₆): δ 9.40 (s, 1H), 7.26 (m, 1H), 7.19-7.18 (m, 1H), 7.15-7.09 (m, 2H), 7.01 (m, 1H), 6.72 (d, *J* = 3.2 Hz, 1H), 6.22 (t, 1H), 6.12 (d, *J* = 1.2 Hz, 1H), 5.12 (d, *J* = 16.4 Hz, 1H) 4.99 (d, *J* = 16.0 Hz, 1H), 2.31 (d, *J*=14.4 Hz, 1H) 2.15 (d, *J*=14.4 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H).

Example-101

7-(Cyclopropylmethoxy)-2,2-dimethyl-1'-((5-(trifluoromethyl)furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one



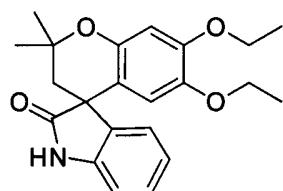
The title compound was prepared by following a procedure similar to that described in Intermediate-34 by using Example-100 and (bromomethyl) cyclopropane (Yield: 75 %).

¹H NMR (400 MHz, DMSO-d₆): δ 7.28-7.25 (m, 1H), 7.24-7.09 (m, 2H), 7.03-6.99 (m, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.38 (s, 1H), 6.27-6.19 (m, 2H), 5.13-4.99 (m, 2H), 3.37 (d, *J* = 6.8 Hz 2H), 2.58 (d, *J* = 16.0 Hz, 1H), 2.19 (d, *J* = 16.0 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.19-1.21 (m, 1H), 0.58-0.51 (m, 2H), 0.29-0.25 (m, 2H); MS(ES+) m/z: 497.99 (M+1)

5

Example-102

6,7-Diethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one

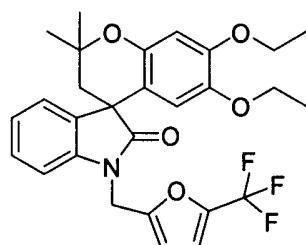


The title compound was prepared by following a procedure similar to that described in Intermediate-9 by using Intermediate-50 followed by debenzylation as described in Intermediate-9 (yield: 67 %). ¹H NMR (400 MHz, DMSO-d₆): δ 7.90 (s, 1H), 7.22 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.00 (m, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.47 (s, 1H), 6.08 (s, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.86-3.73 (q, *J* = 7.2 Hz, 2H), 2.45 (d, *J* = 14.4 Hz, 1H), 2.19 (d, *J* = 14.4 Hz, 1H), 1.57 (s, 3H), 1.51 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

15

Example-103

6,7-Diethoxy-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one



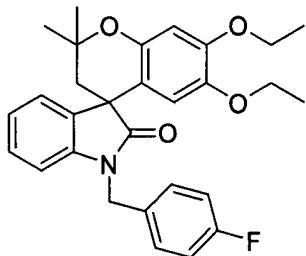
The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-102 and 2-(bromomethyl)-5-(trifluoro methyl)furan (yield: 58 %). ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.25 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.06-6.98 (m, 2H), 6.73 (s, 1H), 6.47 (s, 1H), 6.40-6.39 (m, 1H), 5.87 (s, 1H), 5.08 (d, *J* = 16.0 Hz,

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1H), 4.92 (d, $J = 16.0$ Hz, 1H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.73-3.62 (m, 2H), 2.42 (d, $J = 16.0$ Hz, 1H), 2.22 (d, $J = 16.0$ Hz, 1H), 1.58 (s, 3H), 1.51 (s, 3H), 1.42 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H); MS (ES+) m/z: 516.3 (M+1).

Example-104

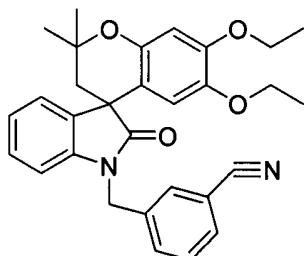
- 5 6,7-Diethoxy-1'-(4-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-102 and 1-(bromomethyl)-4-fluoro benzene (yield: 84 %). ^1H NMR (400 MHz, CDCl_3): δ 7.38-7.35 (m, 1H), 7.22-7.13 (m, 2H), 7.04-6.97 (m, 3H), 6.45 (s, 1H), 5.87 (s, 1H), 5.08 (d, $J = 16.0$ Hz, 1H), 4.77 (d, $J = 16.0$ Hz, 1H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.71-3.60 (m, 2H), 2.46 (d, $J = 16.0$ Hz, 1H), 2.24 (d, $J = 16.0$ Hz, 1H), 1.58 (s, 3H), 1.55 (s, 3H), 1.44 (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H); MS(ES+) m/z: 476.3 (M+1).

Example-105

- 3-((6,7-Diethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzonitrile



15

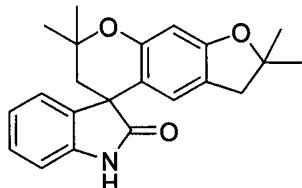
The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-102 and 3-(bromomethyl)benzonitrile (yield: 72 %). ^1H NMR (400 MHz, CDCl_3): δ 7.65-7.60 (m, 3H), 7.48-7.44 (m, 1H), 7.23-7.15 (m, 2H), 7.05-7.01 (m, 1H), 6.77-6.72 (m, 1H), 6.48 (s, 1H), 5.90 (s, 1H), 5.07 (d, $J = 16.0$ Hz, 1H), 4.92 (d, $J = 16.0$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.76-3.65 (m, 2H), 2.46 (d, $J = 16.0$ Hz, 1H), 2.25 (d,

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J=16.0 Hz, 1H), 1.58 (s, 3H), 1.52 (s, 3H), 1.45 (t, *J*= 7.2 Hz, 3H), 1.26 (t, *J*= 7.2 Hz, 3H); MS(ES+) m/z: 483.3 (M+1).

Example-106

2,2,7,7-Tetramethyl-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one

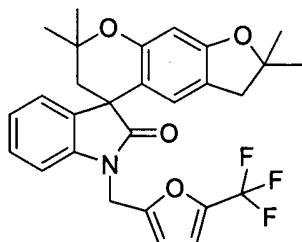


5

The title compound was prepared by following a procedure similar to that described in Intermediate-33 by using Intermediate-60 and *p*-toluene sulphonic acid (Yield: 85 %). ¹H NMR (400 MHz, CDCl₃): δ 7.45 (s, 1H), 7.24-7.17 (m, 2H), 7.04-7.01 (m, 1H), 6.62 (d, *J*= 4.0 Hz, 1H), 6.34 (s, 1H), 6.31 (s, 1H), 2.82-2.7 (m, 2H), 2.46 (d, *J*= 16.0 Hz, 1H), 2.21 (d, *J*= 16.0 Hz, 1H), 1.53 (s, 3H), 1.50 (s, 3H), 1.42 (s, 6H); MS (ES+) m/z: 350.1 (M+).

Example-107

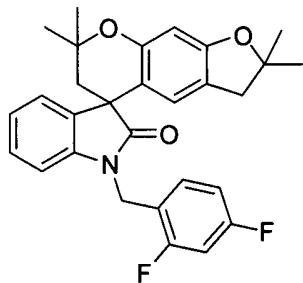
2,2,7,7-Tetramethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)-2,3,6,7-tetrahydro spiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-106 and 2-(bromomethyl)-5-(trifluoro methyl)furan (yield: 58 %). ¹H NMR (400 MHz, CDCl₃): δ 7.4 (d, *J*= 8.0 Hz, 1H), 7.20 (d, *J*= 8.0 Hz, 1H), 7.05-7.01 (m, 1H), 6.93 (d, *J*= 8.0 Hz, 1H), 6.74-6.73 (m, 1H), 6.4 (d, *J*= 4.0 Hz, 1H), 6.29 (s, 1H), 6.17 (s, 1H), 2.77-2.68 (m, 2H), 2.38 (d, *J*= 16.0 Hz, 1H), 2.21 (d, *J*= 16.0 Hz, 1H), 1.55 (s, 3H), 1.49 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H); MS(ES+) m/z: 498.1 (M+1).

Example-108

1'-(2,4-Difluorobenzyl)-2,2,7,7-tetramethyl-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one

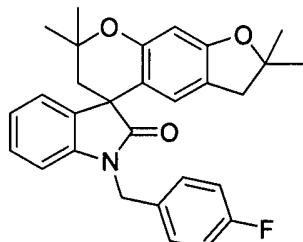


The title compound was prepared by following a procedure similar to that described
5 in Example-7 by using Example-106 and 1-(bromomethyl)-2,4-fluorobenzene (yield: 71 %).
¹H NMR (400 MHz, CDCl₃): δ 7.52-7.30 (m, 1H), 7.23-7.17 (m, 1H), 7.03-7.0 (m, 1H),
6.88-6.80 (m, 3H), 6.31 (s, 1H), 6.14 (s, 1H), 4.97 (s, 1H), 2.74 (s, 2H), 2.43 (d, J = 16.0 Hz,
1H), 2.21(d, J = 16.0 Hz, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H); MS(ES+)
m/z: 476.05 (M+1).

10

Example-109

1'-(4-Fluorobenzyl)-2,2,7,7-tetramethyl-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one



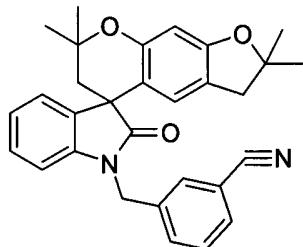
The title compound was prepared by following a procedure similar to that described
15 in Example-7 by using Example-106 and 1-(bromomethyl)-4-fluorobenzene (yield: 87 %).
¹H NMR (400 MHz, DMSO-d₆): δ 7.42-7.38 (m, 2H), 7.24-7.13 (m, 4H), 7.05-6.98 (m, 2H),
6.20 (s, 1H), 6.05 (s, 1H), 4.90 (s, 2H), 2.74 (m, 2H), 2.36 (d, J = 16.0 Hz, 1H), 2.17 (d, J =
16.0 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); MS(ES+) m/z: 458.1
(M+1).

20

Example-110

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3-((2,2,7,7-Tetramethyl-2'-oxo-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-1'-yl)methyl)benzonitrile

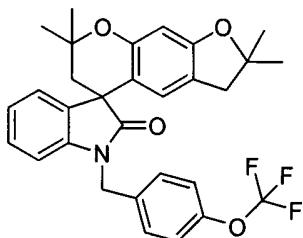


The title compound was prepared by following a procedure similar to that described
 5 in Example-7 by using Example-106 and 3-(bromomethyl)benzonitrile (yield: 76 %). ^1H
 NMR (400 MHz, CDCl_3): δ 7.83-7.78 (m, 2H), 7.68-7.54 (m, 2H), 7.26-7.22 (m, 1H), 7.17
 (d, $J = 8.0$ Hz, 1H), 7.08-7.0 (m, 2H), 6.21 (s, 1H), 6.05 (s, 1H), 2.79-2.69 (m, 2H), 2.39 (d,
 $J = 16.0$ Hz, 1H), 2.19 (d, $J = 16.0$ Hz, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.32 (s,
 3H); MS(ES+) m/z: 465.1 (M+1).

10

Example-111

2,2,7,7-Tetramethyl-1'-(4-(trifluoromethoxy)benzyl)-2,3,6,7-tetrahydrospiro[furo [3,2-g]chromene-5,3'-indolin]-2'-one

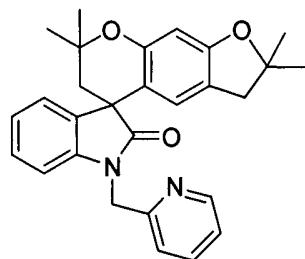


The title compound was prepared by following a procedure similar to that described in
 15 Example-7 by using Example-106 and 1-(bromomethyl)-4-(trifluoromethoxy)benzene
 (yield: 79 %). ^1H NMR (400 MHz, CDCl_3): δ 7.39 (d, $J = 8.0$ Hz, 1H), 7.21-7.17 (m, 4H),
 7.03-6.99 (m, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.31 (s, 1H), 6.14 (s, 1H), 4.95-4.93 (m, 2H),
 2.73-2.72 (m, 2H), 2.44 (d, $J = 16.0$ Hz, 1H), 2.22 (d, $J = 16.0$ Hz, 1H), 1.56 (s, 3H), 1.41 (s,
 3H), 1.39 (s, 3H), 1.22 (s, 3H); MS(ES+) m/z: 523.82 (M+1).

20

Example-112

2,2,7,7-Tetramethyl-1'-(pyridin-2-ylmethyl)-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-106 and 2-(bromomethyl)pyridine (yield: 73 %). ¹H NMR (400 MHz, CDCl₃): δ 8.57 (d, *J* = 4.0 Hz, 1H), 7.65-7.61 (m, 1H), 7.14-7.11 (m, 4H), 7.01-6.97 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.31 (s, 2H), 5.09 (s, 2H), 2.95-2.88 (m, 2H), 2.46 (d, *J* = 16.0 Hz, 1H), 2.24 (d, *J* = 16.0 Hz, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H); MS(ES+) m/z: 441.1 (M+1).

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Example-113

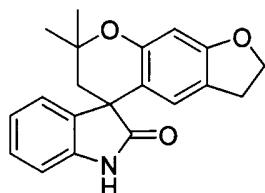
2-(2,2,7,7-Tetramethyl-2'-oxo-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-1'-yl)acetonitrile



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-106 and 2-bromo acetonitrile (yield: 62 %).

Example-114

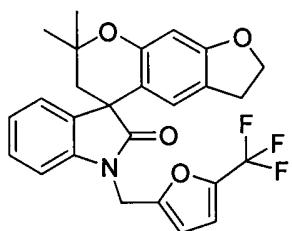
7,7-Dimethyl-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Intermediate-33 by using Intermediate-68 and *p*-toluene sulphonic acid (yield: 42 %). MS (ES+) m/z: 322.1 (M⁺).

Example-115

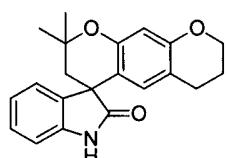
- 5 7,7-Dimethyl-1'-((5-(trifluoromethyl)furan-2-yl)methyl)-2,3,6,7-tetrahydrospiro [furo[3,2-g]chromene-5,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-114 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 58 %). ¹H NMR (400 MHz, CDCl₃): δ 7.25 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.05-7.01 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.74-6.72 (m, 1H), 6.39 (d, *J* = 4.0 Hz, 1H), 6.36 (s, 1H), 6.24 (s, 1H), 5.09 (d, *J* = 16.0 Hz, 1H), 4.90 (d, *J* = 16.0 Hz, 1H), 4.49-4.44 (m, 2H), 2.96-2.90 (m, 2H), 2.39 (d, *J* = 16.0 Hz, 1H), 2.21 (d, *J* = 16.0 Hz, 1H), 1.52 (s, 3H), 1.49 (s, 3H); MS(ES+) m/z: 470.1 (M⁺).

15 Example-116

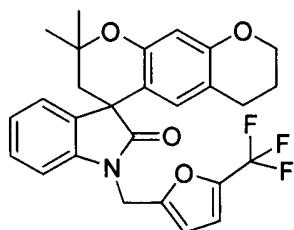
- 2',2'-Dimethyl-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g] chromen]-2-one



The title compound was prepared by following a procedure similar to that described in IntremEDIATE- 33 by using Intermediate-79 and *p*-toluene sulphonic acid (yield: 82 %). MS (ES+) m/z: 336.1 (M⁺).

Example-117

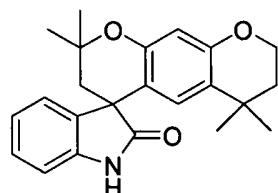
- 2',2'-Dimethyl-1-((5-(trifluoromethyl)furan-2-yl)methyl)-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g]chromen]-2-one



The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-116 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 43 %). ^1H NMR (400 MHz, CDCl_3): δ 7.26 (d, $J = 8.0$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.05-7.01 (m, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.74-6.73 (m, 1H), 6.38 (d, $J = 4.0$ Hz, 1H), 6.35 (s, 1H), 6.07 (s, 1H), 5.06 (d, $J = 16.0$ Hz, 1H), 4.90 (d, $J = 16.0$ Hz, 1H), 4.08-4.07 (m, 1H), 2.49-2.45 (m, 2H), 2.44 (d, $J = 16.0$ Hz, 1H), 2.20 (d, $J = 16.0$ Hz, 1H), 1.89-1.85 (m, 2H), 1.54 (s, 3H), 1.48 (s, 3H); MS(ES+) m/z: 484.1 (M+1).

Example-118

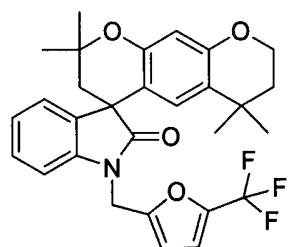
10 2',2',6',6'-Tetramethyl-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g] chromen]-2-one



The title compound was prepared by following a procedure similar to that described in Intermediate-33 by taking Intermediate-86 using *p*-toluene sulphonic acid (yield: 82 %). MS (ES+) m/z: 366.44 (M+).

Example-119

2',2',6',6'-Tetramethyl-1-((5-(trifluoromethyl)furan-2-yl)methyl)-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g]chromen]-2-one



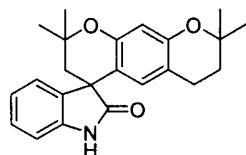
188

The title compound was prepared by following a procedure similar to that described in Example-7 by using Example-118 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 43 %). ^1H NMR (400 MHz, DMSO d_6): δ 7.32-7.15 (m, 3H), 7.15-7.01 (m, 2H), 6.69 (d, J = 2.4 Hz, 1H), 6.19 (s, 1H), 6.12 (s, 1H), 5.16 (d, J = 16.0 Hz, 1H), 5.01 (d, J = 16.0 Hz, 1H), 4.05-4.03 (m, 2H), 2.29 (d, J = 16.0 Hz, 1H), 2.15 (d, J = 16.0 Hz, 1H), 1.63-1.60 (m, 2H), 1.45 (s, 3H), 1.41 (s, 3H), 0.92 (s, 3H), 0.82 (s, 3H); MS(ES+) m/z: 512.09 (M+1).

Example-120

2',2',8',8'-Tetramethyl-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g]chromen]-2-one

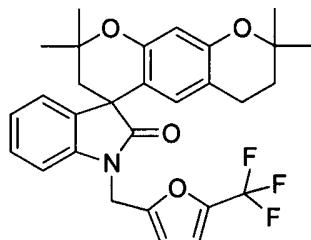
10



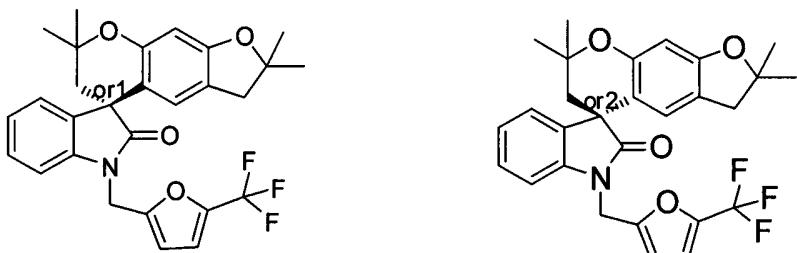
The title compound was prepared by following a procedure similar to that described in Intermediate-33 by using Intermediate-93 using *p*-toluene sulphonic acid (yield: 82 %).

Example-121

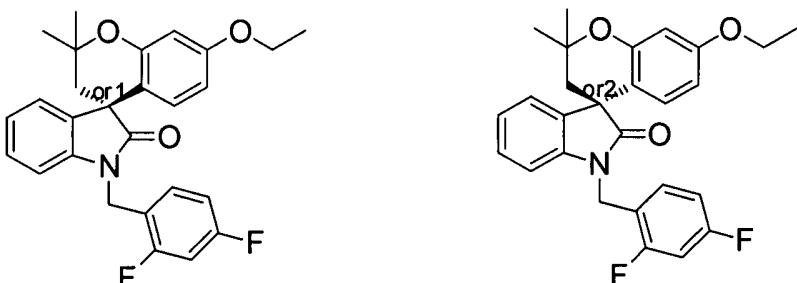
2',2',8',8'-Tetramethyl-1-((5-(trifluoromethyl)furan-2-yl)methyl)-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g]chromen]-2-one



The title compound was prepared by following a procedure similar to that described in Example-7 by taking Example-120 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield: 43 %). ^1H NMR (400 MHz, DMSO d_6): δ 7.26 (dd, J = 2.4, 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.32-7.05-7.01 (m, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.74-6.73 (m, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.37 (s, 1H), 6.33 (s, 1H), 5.06 (d, J = 16.0 Hz, 1H), 4.93 (d, J = 16.0 Hz, 1H), 2.46-2.42 (m, 2H), 2.38 (d, J = 16.0 Hz, 1H), 2.20 (d, J = 16.0 Hz, 1H), 1.68-1.65 (m, 2H), 1.53 (s, 3H), 1.48 (s, 3H), 1.27 (s, 6H); MS(ES+) m/z: 512.2 (M+1).

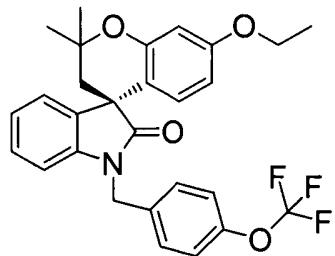
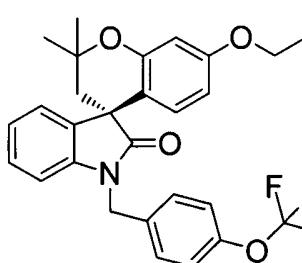
Example-122 and 123

The compound 2,2,7,7-tetramethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)-2,3,6,7-tetrahydrospiro [furo[3,2-g]chromene-5,3'-indolin]-2'-one was separated to give Example-
5 122 (Retention time (RT) 6.75 minutes (SOR:-2.84 (1% CHCl₃, MP: 182-184°C, Purity 99.71%) and Example-123 Retention time (RT) 7.20 minutes) (SOR:-1.84 (1% CHCl₃, Purity 99.28%) on chiral HPLC using Phenomenex-CELL-2 ,250mm x 4.6,5μ; Flow rate : 1.5 mL/ min; Mobile phase : A= n-hexane: IPA (95 : 5 % v/v), B = IPA.

Example-124 and 125

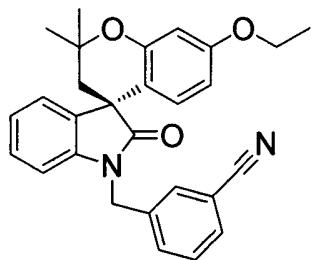
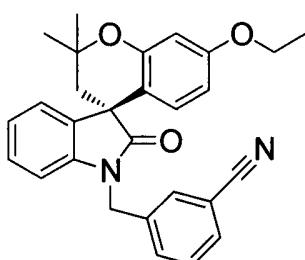
10 The compound 1'-(2,4-difluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one was separated to give Example-124 (Retention time (RT) 4.26 minutes (SOR:-0.52 (1% CHCl₃, MP: 135-137°C, Purity 99.73%) and Example-125 Retention time (RT) 5.32 minutes) (SOR:-2.52 (1% CHCl₃, MP: 135-137°C, Purity 99.27%) on chiral HPLC using CHIRAL
15 CEL OJ-H 250 X 4.6 MM, 5u; Flow rate : 1.5 mL/ min; Mobile phase : A= METHANOL(0.1%DEA) 85 %-15%ACN.

Example-126 and 127



The compound 7-ethoxy-2,2-dimethyl-1'-(4-(trifluoromethoxy)benzyl) spiro [chroman-4,3'-indolin]-2'-one was separated to give Example-126 (Retention time (RT) 6.63 minutes (SOR:-0.48 (1% CHCl₃, MP: 50-52°C, Purity 99.78%) and Example-127 Retention time (RT) 8.46 minutes) (SOR:-1.96 (1% CHCl₃, MP: 82-84°C, Purity 99.86%) on chiral HPLC using CHIRAL CEL OJ-H 250 X 4.6 MM, 5u; Flow rate : 1.5 mL/ min; Mobile phase : A= METHANOL(0.1%DEA) 95 %-5% CAN (acetonitrile).

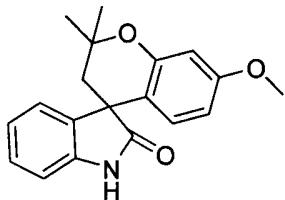
Example-128 and 129



10 The compound 3-((7-ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl)benzonitrile was separated to give Example-128 (Retention time (RT) 7.23 minutes (SOR:-7.76 (1% CHCl₃, Purity 99.91%) and Example-129 Retention time (RT) 9.74 minutes) (SOR:3.28 (1% CHCl₃, Purity 99.53%) on chiral HPLC using CHIRAL PAK IA ,250 mm x 4.6,5μ; Flow rate : 1.5 mL/ min; Mobile phase : A= *n*-hexane : IPA (90:10%v/v),
15 B=IPA.

Example-130

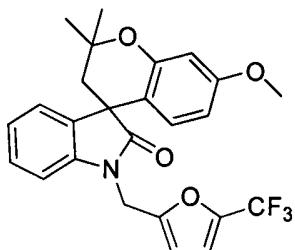
7-Methoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Intermediate-33 by taking Intermediate-99 using *p*-toluene sulphonic acid (yield: 61.5 %). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.53 (s, 1H), 7.22-7.18 (m, 1H), 7.06-7.04 (d, *J* = 7.2 Hz, 1H), 6.95-6.90 (m, 2H), 6.41 (d, *J* = 2 Hz, 1H), 6.38-6.32 (m, 2H), 3.66 (s, 3H), 2.36-2.33 (d, *J* = 14.4 Hz, 1H), 2.13-2.10 (d, *J* = 14.4 Hz, 1H), 1.48 (s, Hz, 3H), 1.44 (s, Hz, 3H); MS (ES+) m/z: 310.3 (M+1).

Example-131

7-Methoxy-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl) spiro[chroman -4,3'-indolin]-2'-one



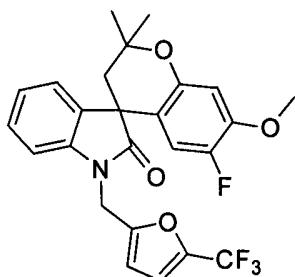
10

To a stirred solution of Example-130 (0.50 g, 1.61 mmol) in *N,N*-dimethylformamide (1.5 mL) was added sodium hydride (0.19 g, 4.04 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then 2-(bromomethyl)-5-(trifluoromethyl)furan (0.40 g, 1.77 mmol) was added. The mixture was stirred at ambient temperature for 2 h. After completion of reaction, the mixture was quenched with the ammonium chloride (10mL) and ice water (10.0 mL) and the solid compound extracted in EtOAc (10mL x 3) and organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 10 % ethyl acetate in petroleum ether to afford the title compound (0.50 g, 68.0 %) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.26 (t, *J* = 7.2 Hz, 1H), 7.18-7.09 (m, 3H), 7.017 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 2.8 Hz, 1H), 6.42 (d, *J* = 2.0 Hz, 1H), 6.27-6.20 (m, 2H), 5.06 (dd, *J* = 2.4, 2.0 Hz, 1H), 3.67 (s, 3H), 2.34 (d, *J* = 14.4Hz, 1H), 2.18 (d, *J* = 14.4Hz, 1H), 1.49 (s, 3H), 1.44 (s, 3H); MS (ES+) m/z: 458.2 (M+1).

25

Example-132

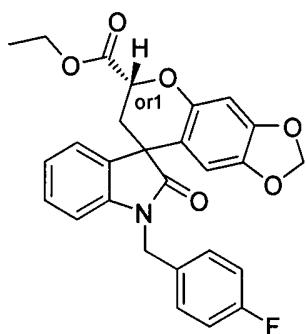
6-Fluoro-7-methoxy-2, 2-dimethyl-1'-(5-(trifluoromethyl) furan-2-yl) methyl) spiro
[chroman-4, 3'-indolin]-2'-one



To a stirred solution of stir Example-131 (0.2 g, 0.43 mmol) in acetonitrile (4.0 mL) was
5 added selectfluor® (0.15 g, 0.43 mmol). The reaction mixture was heated to reflux for overnight. The reaction mixture was cool to ambient temperature and 10mL water was added to it. The product was extracted in ethyl acetate (5mL x 3).The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuum. The residue was purified by column chromatography with ethyl
10 acetate in hexanes (12 %) to afford solid compound (0.43 g, 19.32 %). ¹H NMR (400 MHz,
DMSO-*d*₆): δ 7.28-7.25 (m, 1H), 7.13-7.11 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.06-7.02 (m, *J* = 7.2,
0.8 Hz, 1H), 6.94-6.82 (d, *J* = 8.4 Hz , 1H), 6.74-6.73 (m, 1H), 6.52 (d, *J* = 7.6Hz, 1H.), 6.36-
6.37 (d, *J* = 2.8 Hz, 1H), 6.13. (d *J* = 11.6 Hz, 1H), 4.97-4.90 (m, 2H), 3.82 (s, 3H), 2.40 (d,
J = 14.4 Hz, 1H), 2.20 (d, *J* = 14.4 Hz, 1H), 1.58 (s, 3H), 1.50 (s, 3H); MS (ES+) m/z:
15 476.1 (M+1).

Example-133

6-Ethyl 1'-(4-fluorobenzyl)-2'-oxo-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indoline]-6-carboxylate

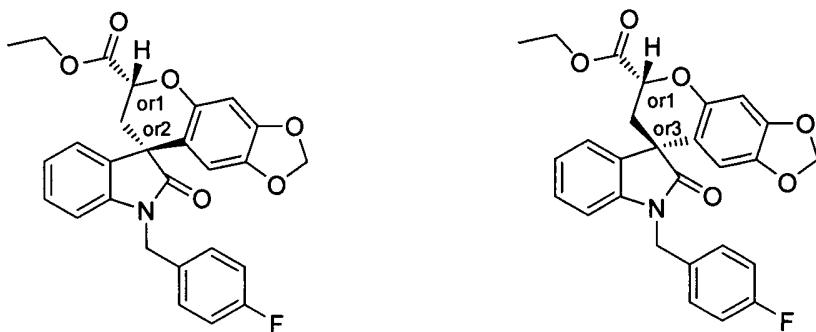


To a stirred solution of 1-(4-fluorobenzyl)-3-(6-hydroxybenzo[d][1,3]dioxol-5-yl)indolin-2-one (0.15 g, 0.44 mmol) and cesium carbonate (0.36 g, 1.11mmol) in DMF (1.0 mL) was added 1,2-dibromoethylpropionate (0.14 g, 0.44 mmol). The reaction mixture was stirred at ambient temperature. After completion of reaction, the reaction mixture was quenched with 5 ice water (5.0 mL) and the organic compound was extracted with EtOAc (2×50 mL). The organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 30% ethyl acetate in petroleum ether to afford solid the diastereomeric compounds (0.04 g and 0.01 g, 26.0 %).

10 Example-133a: 6-Ethyl 1'-(4-fluorobenzyl)-2'-oxo-6,7-dihydrospiro[[1,3]dioxolo [4,5-g]chromene-8,3'-indoline]-6-carboxylate
 ^1H NMR (400 MHz, CDCl₃): δ 7.30-7.27 (m, 2H), 7.25-7.21 (m, 1H), 7.05-7.00 (m, 4H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.662 (s, 1H), 5.85 (d, $J = 9.6$ Hz, 2H), 5.78 (s, 1H), 5.59 (t, $J = 6.4$ Hz, 1H), 5.01 (d, $J = 15.6$ Hz, 1H), 4.98 (d, $J = 15.6$ Hz, 1H), 4.31 (q, $J = 7.2$ Hz, 2H), 2.38 (d, $J = 2.0$ Hz, 1H), 2.36 (s, 1H), 1.30 (t, $J = 6.8$ Hz, 3H); MS (ES+) m/z: 476.2 (M+1).

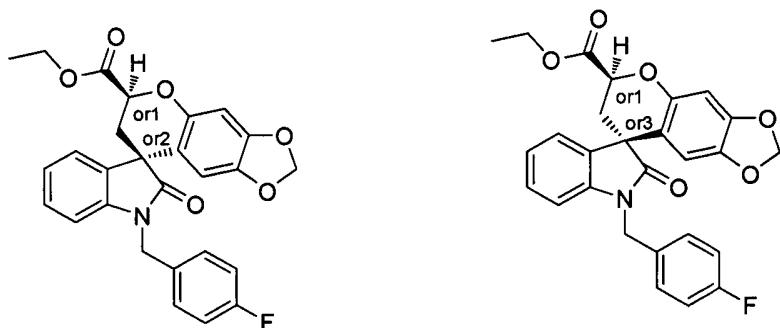
15 Example-133b 6-Ethyl 1'-(4-fluorobenzyl)-2'-oxo-6,7-dihydrospiro[[1,3]dioxolo [4,5-g]chromene-8,3'-indoline]-6-carboxylate: ^1H NMR ((400 MHz, CDCl₃): δ 7.35-7.25 (m, 2H), 7.22-(t, $J = 7.6$ Hz, 1H), 7.05-7.00 (m, 4H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.662 (s, 1H), 5.85 (d, $J = 9.6$ Hz, 2H), 5.78 (s, 1H), 5.59 (t, $J = 6.4$ Hz, 1H), 5.01 (d, $J = 15.6$ Hz, 1H), 4.98 (d, $J = 15.6$ Hz, 1H), 4.31 (q, $J = 7.2$ Hz, 2H), 2.38 (d, $J = 2.0$ Hz, 1H), 2.36 (s, 1H), 1.30 (t, $J = 6.8$ Hz, 3H); MS (ES+) m/z: 476.2 (M+1).

Example-134 and 135



The Example-133a was separated to give Example-134 Retention time (RT) 7.12 minutes and Example-135 Retention time (RT) 8.66 minutes on chiral HPLC using CHIRAL IC, 250 mm × 4.6, 5 μ ; Flow rate : 0.7 mL/ min; Mobile phase : Methanol (100 %).

Example-136 and 137

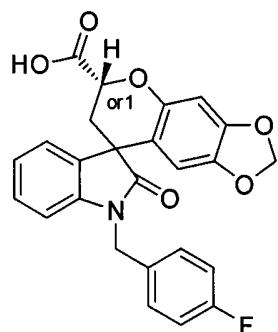


5

The Example-133b was separated to give Example-136 Retention time (RT) 12.87 minutes and Example-137 Retention time (RT) 18.38 minutes on chiral HPLC using CHIRAL IA, 250 mm × 4.6, 5 μ ; Flow rate : 1 mL/ min; Mobile phase : Hexane: IPA (60 : 40 % v/v).

Example-138

- 10 6-1'-(4-Fluorobenzyl)-2'-oxo-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene -8,3'-indoline]-6-carboxylic acid



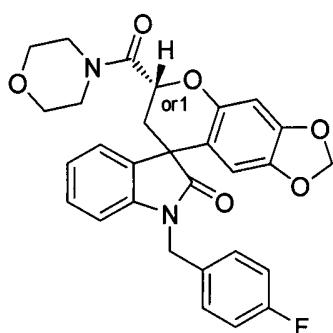
To a stirred solution of Example-133a (0.05 g, 0.44 mmol) in THF (2.0 mL) was added solution of LiOH (0.01 g, 0.52 mmol) in water (0.4 mL). The reaction mixture was stirred at ambient temperature. After completion of reaction, the reaction mixture was evaporated to dryness. The crude mass was diluted with water and extracted with EtOAc. The aqueous phase was acidified with 1N HCl and extracted with EtOAc (2 × 50 mL) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* get the white solid

compound (0.04 g, 91.0 %). ^1H NMR (400 MHz, DMSO- d_6): δ 13.29 (s, 1H), 7.38-7.35 (m, 2H), 7.29 (t, J = 6.8 Hz, 1H), 7.20-7.14 (m, 3H), 7.77-7.04 (m, 2H), 6.63 (s, 1H), 5.90 (s, 2H), 5.64 (s, 1H), 5.30 (d, J = 7.2 Hz, 1H), 4.93 (m, 2H), 2.38-2.28 (m, 2H); MS (ES+) m/z: 448.1 (M+1).

5

Example-139

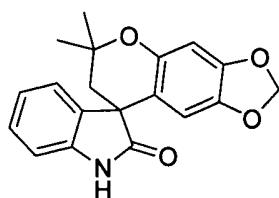
6-1'-(4-Fluorobenzyl)-6-(morpholine-4-carbonyl)-6,7-dihydrospiro [[1,3] dioxolo [4,5-g]chromene-8,3'-indolin]-2'-one



To a stirred solution of Example-138 (0.04 g, 0.08 mmol) in dichloromethane (5.0 mL) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.02 g, 0.13 mmol) and *N*-hydroxy benzotriazole (0.01 g, 0.10 mmol). The solution was stirred for 20 min at ambient temperature. After that, morpholine (0.01 g, 0.1 mmol) was added and reaction mixture was stirred for additional 2 h. After completion of reaction, the reaction mixture was quenched with ice water (5.0 mL) and the organic compound was extracted with EtOAc (2×50 mL).
10 The organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 40% ethyl acetate in petroleum ether to afford solid the diastereomeric compounds (0.02 g, 43.0 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.39-7.36 (m, 2H), 7.29 (t, J = 7.6Hz, 1H), 7.20-7.14 (m, 3H), 7.20-7.15 (m, 3H), 7.09-7.04 (s, 2H), 6.60 (s, 1H), 5.91(s, 2H), 5.67-5.66 (m, 2H), 4.91 (s, 2H), 3.66-3.43 (m, 8H), 2.37-2.13 (m, 2H); MS (ES+) m/z: 517.2 (M+1).
15
20

Example-140

6,6-Dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one

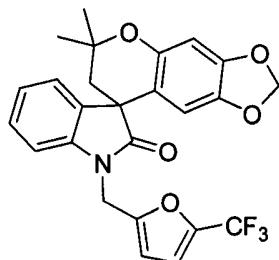


The title compound was prepared by following a procedure similar to that described in Intermediate-33 using 3-(2-hydroxy-2-methylpropyl)-3-hydroxy benzo[d][1,3]dioxol-5-ylindolin-2-one (prepared by following the procedure described herein above) (yield: 96 %).

5 MS (ES+) m/z: 324.2 (M+1)

Example-141

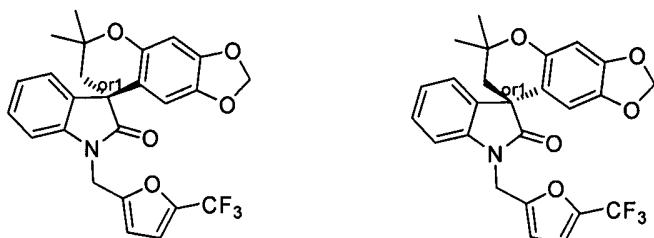
6,6-Dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)-6,7-dihydro spiro[[1,3] dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one



10 The title compound was prepared by following a procedure similar to that described in Example-7 using Example-140 (yield: 74.4 %). ^1H NMR (400 MHz, DMSO- d_6): δ 7.24 (t, $J = 7.2$ Hz, 1H), 7.18-7.10 (m, 3H), 7.02 (t, $J = 7.6$ Hz, 1H), 6.74 (s, 1H), 6.49 (s, 1H), 5.85 (d, $J = 7.6$ Hz, 2H), 5.73 (s, 1H), 5.13-4.99 (m, 2H), 2.31 (d, $J = 14.4$ Hz, 1H), 2.15 (d, $J = 14.4$ Hz, 1H), 1.45 (d, $J = 14.0$ Hz, 6H); MS (ES+) m/z: 472.1 (M+1).

15

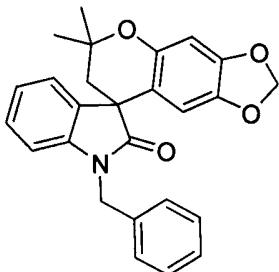
Example-142 and 143



The Example-141 was separated to give Example-142 Retention time (RT) 4.89 minutes and Example-143 Retention time (RT) 6.65 minutes on chiral HPLC using CHIRAL PAK IA, 250 mm × 4.6, 5 μ ; Flow rate : 1 mL/ min; Mobile phase : Hexane: IPA (80 : 20 % v/v).

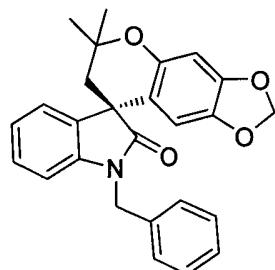
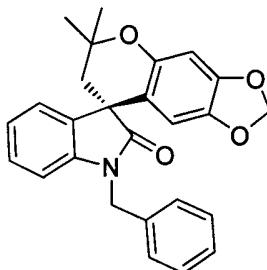
Example-144

- 5 1'-Benzyl-6,6-dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in Example-7 using Example-140 (yield: 77.6 %). ^1H NMR (400 MHz, DMSO): δ 7.34 (m, 4H), 7.28 (m, 1H) 7.22 (m, 1H) 7.12 (d, J = 7.2 Hz, 1H), 7.00(m, 2H), 6.49 (s, 1H), 5.89 (s, 1H), 5.86 (s, 1H), 5.75 (s, 1H), 4.92 (s, 2H), 2.35 (d, J = 14.4 Hz, 1H), 2.15 (d, J = 14.4 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H) ; MS (ES+) m/z: 414.2 (M+1).

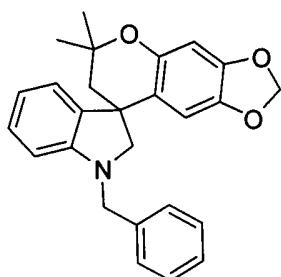
Example-145 and 146



The Example-144 was separated to give Example-145 Retention time (RT) 8.90 minutes and Example-146 Retention time (RT) 12.81 minutes on chiral HPLC using CHIRAL PAK IA, 250 mm × 4.6, 5 μ ; Flow rate : 1 mL/ min; Mobile phase : Hexane: IPA (80 : 20 % v/v).

Example-147

- 1'-Benzyl-6,6-dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indoline]

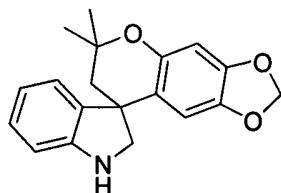


To a pre-cooled (5 °C) stirred suspension of LAH (0.28 g, 7.69 mmol) in anhydrous THF (20 mL) and under nitrogen atmosphere was added the Example-144 (2.0 mmol) in THF (20 mL), and the mixture was heated at reflux for 2 h. After cooling, the reaction mixture was quenched in saturated sodium sulphate solution (50 mL). The solids were removed by filtration and washed with Et₂O (3×15 mL). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 10% ethyl acetate in petroleum ether to afford the title compound (1.07g, 72.7%).

¹H NMR (400 MHz, CDCl₃): δ 7.34 (m, 5H), 7.08 (t, J = 7.6, 8.0 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.67 (m, 1H), 6.56 (d, J = 7.6 Hz, 1H), 6.46 (s, 1H), 6.28 (s, 1H), 5.80 (s, 2H), 4.34 (s, 2H), 3.52 (m, 2H), 2.18 (m, 2H), 1.36 (s, 3H), 1.23 (s, 3H); MS (ES+) m/z: 400.2 (M+1).

Example-148

15 6,6-Dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indoline]



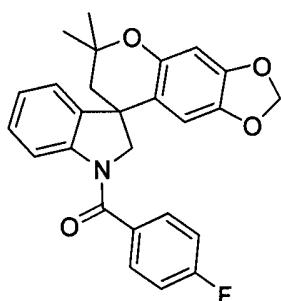
To a solution of Example-147 (0.22 g, 0.44 mmol) in dry EtOAc (20 mL) was added ammonium formate (0.41 g, 6.5 mmol). The Pd/C (0.02 g, 10 %) was added carefully and reaction mixture was refluxed using guard tube. The course of reaction was monitored with TLC. After 4 h the reaction mixture was filtered through celite bed and washed with EtOAc (5 × 50 mL)). After that, filtrate was extracted with water (50 mL). The organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was

washed with *n*-pentane to result the crude compound (0.11 g, 79.3 %) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.28 (m, 3 H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.38 (s, 1H), 6.23 (s, 1H), 5.86 (s, 1H), 5.81 (s, 1H), 4.21 (d, *J* = 11.2 Hz, 1H), 3.82 (d, *J* = 11.2 Hz, 1H), 2.34 (d, *J* = 14.8 Hz, 1H), 2.09 (d, *J* = 14.4 Hz, 1H), 1.49 (s, 3H); MS (ES+) m/z: 310.1 (M+1).

5

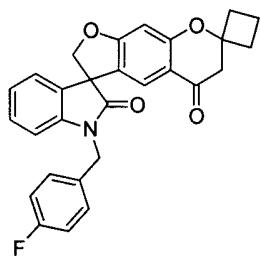
Example-149

(6,6-Dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-1'-yl)(4-fluorophenyl)methanone



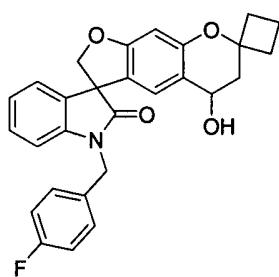
To a stirred solution of 4-fluoro benzoic acid (0.04 g, 0.28 mmol) in anhydrous DCM (1.5 mL) was added hydroxybenzotriazole hydrate (HOEt) (0.38 g, 0.28 mmol), diisopropylethyl amine (0.03 g, 0.28 mmol), and Example-148 (0.08 g, 0.25 mmol). After dissolution of complete HOEt, EDCI (0.05 g, 0.28 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. After completion of reaction, the reaction was diluted with dichloromethane (10 mL), followed by extraction with water (10mL x 2). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, with an isocratic elution of 9 % ethyl acetate in petroleum ether to afford the title compound (0.07 g, 71.1%). ¹H NMR (400 MHz, DMSO): δ 7.715 (m, 2 H), 7.34-7.04 (m, 5H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.37 (s, 1H), 6.24 (s, 1H), 5.88 (s, 1H), 5.86 (s, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.13 (d, *J* = 10.8 Hz, 1H), 2.30 (d, *J* = 14.4 Hz, 1H), 2.07 (d, *J* = 14.4 Hz, 1H), 1.35 (s, 3H), 1.11 (s, 3H); MS (ES+) m/z: 432.2 (M+1).

Example-150



To a stirred solution of Intermediate-106 (2 g, 4.96 mmol) in methanol (20 ml) was added pyrrolidine (0.83 ml, 9.91 mmol) slowly at ambient temperature under nitrogen atmosphere. The resulting solution was stirred for 0.5 h. Then, cyclobutanone (0.74 ml, 9.91 mmol) was 5 added to the reaction mixture and heated to reflux for 16 h. The solvent was evaporated *in vacuo* and the residue was partitioned between 1N HCl (50 ml) and ethyl acetate (50ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extract was washed with water (2x20 ml), brine (25 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get a residue. The 10 residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Example-150 (1.8 g, 80%) as an off white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.20 (m, 4H), 7.12-7.00 (m, 4H), 6.79 (d, *J*=8.00 Hz, 1H), 6.52 (s, 1H), 5.10-4.70 (m, 4H), 2.80 (s, 2H), 2.35-2.25 (m, 2H), 2.20-2.10 (m, 2H), 2.00-1.85 (m, 1H), 1.70-1.60 (m, 1H); MS (ES+) m/z : 456 (M+1).

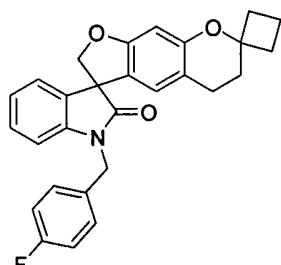
15

Example-151

To a stirred solution of Example-150 (0.645 g, 1.41 mmol) in methanol (10 ml) was added sodium borohydride (0.267 g, 7.06 mmol) slowly at 0°C under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 16 h. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (50 ml) and water (50 ml). The 20

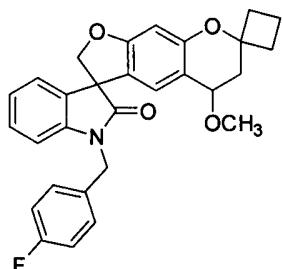
phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed with water (2x20 ml) and brine (25 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get a residue. The residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 20% ethyl acetate in petroleum ether to afford Example-151 (0.3 g, 45%) as an off white solid. ¹H NMR: (400 MHz, CDCl₃): δ 7.40-7.30 (m, 2H), 7.25-7.15 (m, 2H), 7.15-6.95 (m, 3H), 6.85-6.70 (m, 2H), 6.44 (s, 1H), 5.00-4.85 (m, 3H), 4.75-4.55 (m, 3H), 2.40-2.20 (m, 4H), 2.00-1.80 (m, 2H), 1.80-1.60 (m, 2H); MS (ES+) m/z : 440.2 (M+1).

Example-152

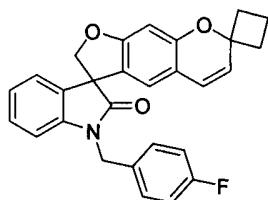


10

To a stirred solution of Example-150 (0.025 g, 0.055 mmol) in round bottom flask was added glacial acetic acid (1 ml) followed by 10% palladium on carbon (50% wt., 0.025g) and stirred the reaction mixture at 75°C for 16 h under a hydrogen atmosphere with the help of balloon. The reaction mixture was filtered on a Buchner funnel through a celite bed. The filtrate was 15 evaporated *in vacuo*, the residue was dissolved in ethyl acetate (5 ml) and washed with a saturated aqueous NaHCO₃ solution (5 ml). The combined organic extract was washed with brine (5 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to obtain a residue. The residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 10% ethyl acetate in petroleum ether to afford 20 Example-152(0.007 g, 28%) as an off white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.30-7.15 (m, 4H), 7.10-6.90 (m, 3H), 6.79 (d, J=8.00 Hz, 1H), 6.42 (s, 1H), 6.31 (s, 1H), 5.10-4.60 (m, 4H), 2.65-2.45 (m, 2H), 2.35-2.20 (m, 2H), 2.10-1.95 (m, 2H), 1.95-1.80 (m, 3H), 1.70-1.50 (m, 1H); MS (ES+) m/z : 442.1 (M+1)

Example-153

To a stirred solution of Example-151 (0.015 g, 0.033mmol) in dry *N,N*-dimethylformamide (1 ml) was added sodium hydride (60% w/w dispersion in mineral oil, 1.5 mg, 0.036 mmol) slowly at 0°C under nitrogen atmosphere. The resulting suspension was stirred at 0°C for 0.5 h. Then, methyl iodide (5.1 µl, 0.082 mmol) was added at 0°C and stirred at ambient temperature for 16 h. The reaction mixture was cooled to 0°C, added water (5 ml) and extracted with ethyl acetate (5 ml). The aqueous phase was again extracted with ethyl acetate (2x2 ml). The combined organic extracts were washed with water (2 ml), brine (2 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to yield a residue. The residue was purified by column chromatography over silica gel (100-200 mesh) with a isocratic elution of 15% ethyl acetate in petroleum ether to afford Example-153 (0.013 g, 85%) as an off white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.15 (m, 4H), 7.10-6.90 (m, 3H), 6.85-6.65 (m, 2H), 6.43 (s, 1H), 5.10-4.60 (m, 4H), 4.25-4.15 (m, 1H), 3.32 (s, 3H), 2.40-2.20 (m, 3H), 2.15-2.00 (m, 3H), 2.00-1.80 (m, 1H), 1.75-1.60 (m, 1H); MS (ES+) m/z : 472 (M+1).

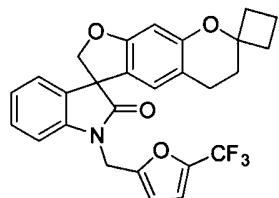
Example-154

To a stirred solution of Example-151 (0.1g, 0.22mmol) in anhydrous dichloromethane (2ml) was added DAST (*N,N*-diethylamino)sulphur trifluoride) (0.1ml) at -78°C slowly under nitrogen atmosphere and then stirred at ambient temperature for 3 h. The reaction mixture was quenched with water (25 ml) slowly followed by ethyl acetate (25 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with water (50 ml), brine (50 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get a residue, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Example-154 (0.013g, 13%) as an off white solid.

10 ^1H NMR (400 MHz, CDCl_3): δ 7.32 (t, $J=7.6\text{Hz}$, 2H), 7.21 (t, $J=7.6\text{Hz}$, 1H), 7.15 (d, $J=7.2\text{Hz}$, 1H), 7.03 (t, $J=8.0\text{Hz}$, 3H), 6.79 (d, , $J=8.0\text{Hz}$, 1H), 6.45 (s, 1H), 6.24 (s, 1H), 6.07 (d, , $J=10.0\text{Hz}$, 1H), 5.78 (d, $J=9.6\text{Hz}$, 1H), 5.00-4.60 (m, 4H), 2.50-2.40 (m, 2H), 2.18-2.13 (m, 2H), 1.90-1.80 (m, 1H), 1.70-1.60 (m, 1H); MS (ES+) m/z : 440.2 (M+1).

Example-155

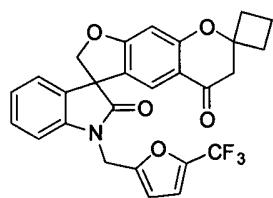
15



To a stirred solution of Intermediate-111 (0.3g, 0.89 mmol) in anhydrous DMF (3ml) was added 60% sodium hydride in mineral oil (0.032g, 1.35mmol) followed by 2-bromomethyl-5-trifluoromethyl furan (0.226g, 0.986mmol) at 0°C and then stirred at ambient temperature for 2 h. The reaction mixture was quenched with addition of water (25 ml) followed by ethyl acetate (25 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 10 ml). The combined organic extract was washed with water (50 ml), brine (50 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to obtain a residue. The residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Example-155 (0.3g, 70%) as an off white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.29 (dt, $J= 7.6\text{Hz}$, $J=$

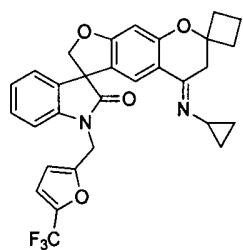
1.2Hz, 1H), 7.18 (dd, $J= 7.6\text{Hz}$, $J= 0.8\text{Hz}$, 1H), 7.07 (dt, $J= 7.6\text{Hz}$, $J= 1.2\text{Hz}$, 1H), 6.97 (d, $J= 8.0\text{Hz}$, 1H), 6.75-6.72 (m, 1H), 6.42-6.38 (m, 2H), 6.32 (s, 1H), 5.15-4.60 (m, 4H), 2.65-2.47 (m, 2H), 2.32-2.20 (m, 2H), 2.05-1.95 (m, 2H), 1.90-1.80 (m, 3H), 1.70-1.57 (m, 1H); MS (ES+) m/z : 482.2 (M+1).

5

Example-156

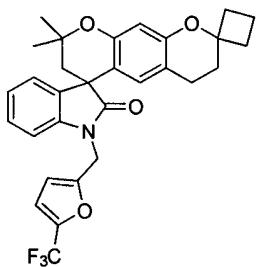
To a biphasic solution of Example-155 (0.03g, 0.062mmol) in acetic acid (0.5ml), diethyl ether (0.5ml) and water (0.5ml) was added ceric ammonium nitrate (0.2g, 0.365mmol) at ambient temperature lotwise and then stirred for 5 minutes. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate solution (25 ml) followed by ethyl acetate (10 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 10 ml). The combined organic extracts were washed with water (50 ml), brine (50 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get a residue. The residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 25% ethyl acetate in petroleum ether to afford Example-156 (0.015g, 48%) as an off white solid. ^1H NMR (400 MHz, CDCl₃): δ 7.32 (dt, $J= 7.6\text{Hz}$, $J= 1.2\text{Hz}$, 1H), 7.24 (s, 1H), 7.14 (dd, , $J= 7.6\text{Hz}$, $J= 1.2\text{Hz}$, 1H), 7.07 (dt, $J= 7.6\text{Hz}$, $J= 1.2\text{Hz}$, 1H), 7.02 (d, $J= 8.0\text{Hz}$, 1H), 6.75-6.72 (m, 1H), 6.50 (s, 1H), 6.40-6.37 (m, 1H), 5.05-4.70 (m, 4H), 2.77 (s, 2H), 2.35-2.25 (m, 2H), 2.18-2.08 (m, 2H), 1.95-1.85 (m, 1H), 1.70-1.57 (m, 1H); MS (ES+) m/z : 496.1(M+1).

Example-157



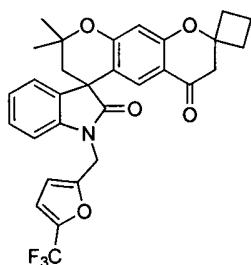
To a stirred solution of Example-156 (0.07g, 0.141 mmol) in anhydrous benzene (3ml) was added cyclopropylamine (0.05ml, 0.7mmol) followed by titanium tetrachloride (1M in dichloromethane 0.2ml, 0.211mmol) at 0°C and then the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was quenched by addition of water (10 ml) followed by ethyl acetate (10 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 5 ml). The combined organic extract was washed with water (10 ml), brine (15 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get a residue. The residue was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Example-157 (0.02g, 26%) as an off white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.33-7.27 (m, 2H), 7.17-7.13 (m, 1H), 7.10-7.02 (m, 1H), 7.00-6.95 (m, 1H), 6.75-6.50 (m, 1H), 6.46 (s, 1H), 6.38-6.35 (m, 1H), 5.00-4.60 (m, 4H), 3.00-2.95 (m, 2H), 2.35-2.20 (m, 2H), 2.10-2.00 (m, 2H), 1.95-1.85 (m, 1H), 1.75-1.60 (m, 1H), 0.95-0.82 (m, 2H), 0.80-0.65 (m, 2H); MS (ES+) m/z : 535.2 (M+1).

Example-158



The tile compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-116 and 2-bromomethyl-5-trifluoromethyl furan (Yield: 71 %). ^1H NMR (400 MHz, CDCl_3): δ 7.26-7.21 (m, 1H), 7.19-7.16 (m, 1H), 7.07-7.00 (m, 1H), 6.95-6.91 (m, 1H), 6.75-6.72 (m, 1H), 6.39-6.36 (m, 1H), 6.35 (s, 1H), 6.01 (s, 1H), 5 5.10-4.85 (m, 2H), 2.52-2.40 (m, 2H), 2.98-2.35 (m, 1H), 2.30-2.15 (m, 3H), 2.05-1.95 (m, 2H), 1.90-1.78 (m, 3H), 1.65-1.60 (m, 1H), 1.53 (s, 3H), 1.48 (s, 3H); MS (ES+) m/z : 524.11 ($M+1$).

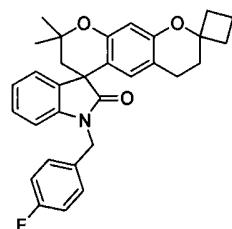
Example-159



10 The tile compound was prepared by following a procedure similar to that described in Example-156 by taking Example-158 (Yield: 65 %). ^1H NMR (400 MHz, CDCl_3): δ 7.32-7.27 (m, 1H), 7.15-7.02 (m, 3H), 7.00-6.95 (m, 1H), 6.80-6.75 (m, 1H), 6.50 (s, 1H), 6.40-6.37 (m, 1H), 5.10-4.88 (m, 2H), 2.77 (s, 2H), 2.45-2.20 (m, 3H), 2.15-2.05 (m, 2H), 1.95-1.85 (m, 2H), 1.75-1.65 (m, 1H), 1.61 (s, 3H), 1.53 (s, 3H); MS (ES+) m/z : 538.4 ($M+1$).

15

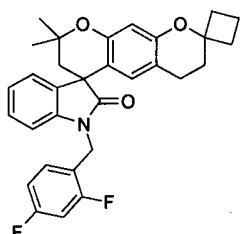
Example-160



The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-116 and 4-fluorobenzylbromide (Yield: 78%). ^1H NMR (400 MHz, CDCl_3): δ 7.38-7.33 (m, 2H), 7.23-7.16 (m, 2H), 7.08-6.98 (m, 3H), 6.83-6.77

(m, 1H), 6.37 (s, 1H), 6.07 (s, 1H), 5.05-4.85 (m, 2H), 2.55-2.40 (m, 3H), 2.32-2.18 (m, 3H), 2.05-1.95 (m, 2H), 1.90-1.80 (m, 3H), 1.70-1.60 (m, 1H), 1.57 (m, 3H), 1.51 (m, 3H); MS (ES+) m/z : 484.1 (M+1)

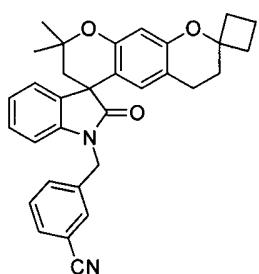
Example-161



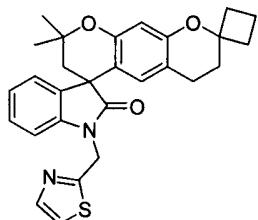
5

The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-116 and 2,4-difluorobenzyl bromide (yield: 52%). ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.28 (m, 1H), 7.23-7.15 (m, 2H), 7.03-6.97 (m, 1H), 6.90-6.80 (m, 3H), 6.35 (s, 1H), 6.05 (s, 1H), 4.96 (s, 2H), 2.47-2.37 (m, 3H), 2.30-2.15 (m, 3H), 2.05-1.92 (m, 2H), 1.88-1.77 (m, 3H), 1.65-1.57 (m, 1H), 1.55 (s, 3H), 1.49 (s, 3H); MS (ES+) m/z : 502.1 (M+1).

Example-162

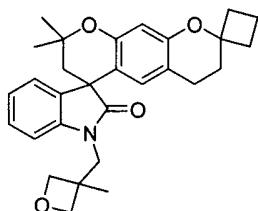


The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-116 and 3-bromomethyl benzonitrile (Yield: 53%). ¹H NMR (400 MHz, CDCl₃): δ 7.63-7.58 (m, 3H), 7.50-7.43 (m, 1H), 7.21-7.15 (m, 2H), 7.05-7.00 (m, 1H), 6.71 (d, J=7.6Hz, 1H), 6.35 (s, 1H), 6.05 (s, 1H), 5.06-4.86 (m, 2H), 2.58-2.40 (m, 3H), 2.30-2.18 (m, 3H), 2.05-1.95 (m, 2H), 1.90-1.77 (m, 3H), 1.65-1.58 (m, 1H), 1.55 (s, 3H), 1.49 (s, 3H); MS (ES+) m/z : 491.1 (M+1)

Example-163

The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-116 and 2-bromomethyl thiazole (Yield: 48%). ¹H

- 5 NMR (400 MHz, CDCl₃): δ 7.75 (d, *J*=3.2Hz, 1H), 7.31 (d, *J*=3.2Hz, 1H), 7.23-7.13 (m, 2H), 7.03-7.00 (m, 1H), 6.95 (d, *J*=8.0Hz, 1H), 6.34 (s, 1H), 6.18 (s, 1H), 5.40-5.20 (m, 2H), 2.55-2.37 (m, 3H), 2.30-2.18 (m, 3H), 2.05-1.92 (m, 2H), 1.90-1.78 (m, 3H), 1.65-1.58 (m, 1H), 1.57-1.45 (m, 6H); MS (ES+) m/z : 473.4 (M+1)

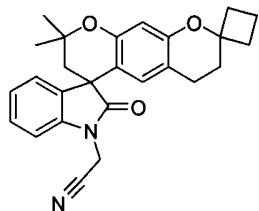
Example-164

10

The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-116 and Intermediate-36 (Yield: 57%). ¹H NMR (400

- MHz, CDCl₃): δ 7.27-7.19 (m, 2H), 7.07-7.00 (m, 1H), 6.87-6.83 (m, 1H), 6.36 (s, 1H), 6.21 (s, 1H), 4.82-4.75 (m, 2H), 4.40-4.30 (m, 2H), 3.83 (q, *J*=14.4Hz, 2H), 2.60-2.35 (m, 3H), 2.32-2.18 (m, 3H), 2.05-1.95 (m, 2H), 1.90-1.80 (m, 3H), 1.70-1.40 (m, 10H); MS (ES+) m/z : 460.11 (M+1).

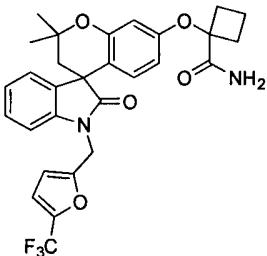
Example-165



The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-116 and bromoacetonitrile (yield: 55 %). ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.32 (m, 1H), 7.22-7.20 (m, 1H), 7.17-7.10 (m, 1H), 7.05-7.02 (m, 1H), 6.35 (s, 1H), 6.07(s, 1H), 4.70 (m, 2H), 2.60-2.33 (m, 3H), 2.30-2.16 (m, 3H), 2.05-1.95 (m, 2H), 1.90-1.78 (m, 3H), 1.67-1.57 (m, 1H), 1.53 (s, 3H), 1.48 (s, 3H); MS (ES+) m/z : 415.1 (M+1, 10%)

Example-166

10 1-((2,2-Dimethyl-2'-oxo-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-7-yl)oxy)cyclobutanecarboxamide

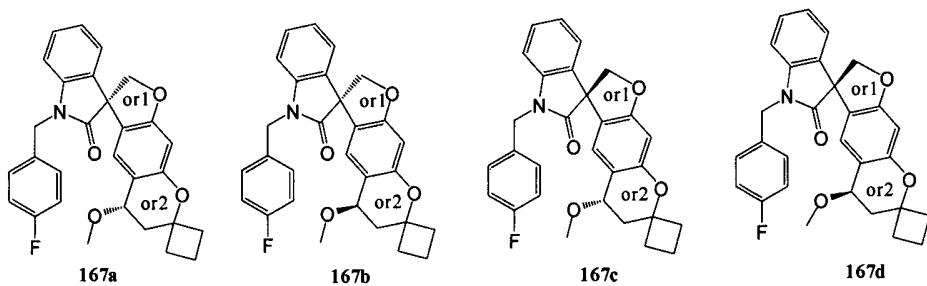


To a stirred solution of Intermediate-120 (0.1g, 0.185 mmol) in anhydrous dichloromethane (3ml) was added *N*-ethyl-*N'*-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.042g, 0.22mmol) followed by hydroxybenzotriazole (0.03g, 0.22mmol) at 0°C and then ammonium 15 hydroxide (0.1ml) was added. The reaction mixture was then stirred at ambient temperature for 16 hours and quenched by addition of water (10 ml) followed by dichloromethane (10 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 5ml). The combined organic extract was washed with water (2x10ml), brine (25ml) and dried over anhydrous sodium sulphate , filtered and concentrated *in vacuo* to get a residue, 20 which was purified by column chromatography over silica gel (100-200 mesh) with an

isocratic elution of 30% ethyl acetate in petroleum ether to afford the title compound (0.07g, 70%) as an off white solid. ^1H NMR (400 MHz, DMSO-d₆): δ 7.30-7.25 (m, 2H), 7.20-7.18 (m, 1H), 7.17-7.10 (m, 3H), 7.00 (t, $J=7.6\text{Hz}$, 1H), 6.72 (d, $J=3.2\text{Hz}$, 1H), 6.20 (d, $J=8.4\text{Hz}$, 1H), 6.08 (dd, $J=8.4\text{Hz}$, $J=2.4\text{Hz}$, 1H), 6.05 (d, $J=2.4\text{Hz}$, 1H), 5.15-4.97 (m, 2H), 2.60-2.57 (m, 2H), 2.35-2.10 (m, 4H), 1.90-1.70 (m, 2H), 1.48 (s, 3H), 1.44 (s, 3H); MS (ES+) m/z : 541.04 (M+1).

Example-167a to 167d

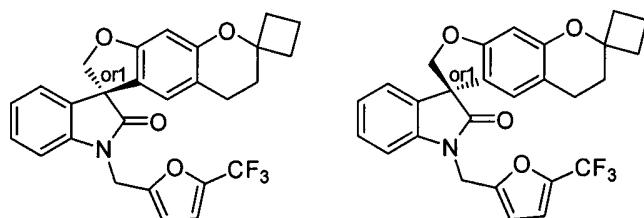
10



The above four isomer compounds (167a to 167d) of Example-153 were separated by a chiral column (lux cellulose-2, 250 x 4.6mm, 5u) with an isocratic elution of 40% isopropyl alcohol in hexane (flow rate 1ml/minute) with retention time 13.19, 15.72, 19.26 and 26.21 minutes respectively from 167a to 167d.

15

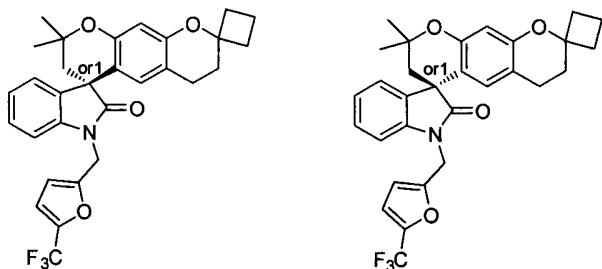
Example-168a to 168b



The Example-155 was separated to give Example-168a Retention time (RT) 7.4 minutes and Example-168b Retention time (RT) 10.10 minutes on chiral column (CHIRAL PAK IC

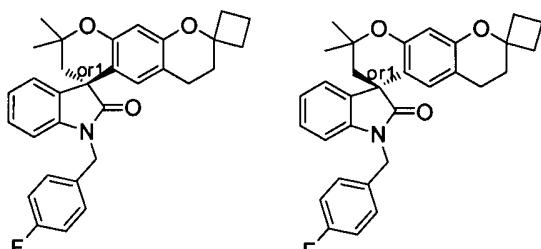
,250mm x 4.6,5 μ) with an isocratic elution of 40% isopropyl alcohol in hexane (flow rate 1ml/minute).

Example-169a to 169b



- 5 The Example-158 was separated to give Example-169a Retention time (RT) 5.67 minutes and Example-169b Retention time (RT) 6.7 minutes on chiral column (CHIRAL IA 250 x 4.6 5u) Flow rate : 1 mL/ min; Mobile phase : A= n-hexane: IPA (95 : 5 % v/v), B = IPA, A: B = 90/10 (% V/V).

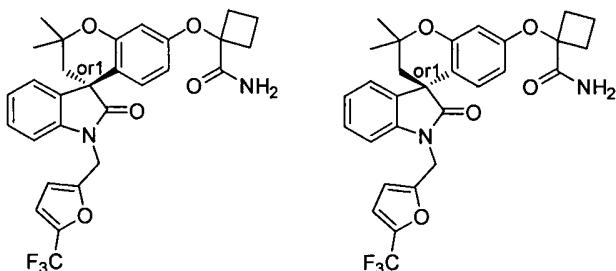
Example-170a to 170b



10

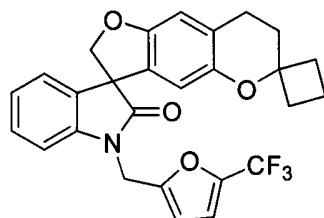
- The Example-160 was separated to give Example-170a Retention time (RT) 5.53 minutes and Example-170b Retention time (RT) 7.19 minutes on chiral column (CHIRAL IA 250 x 4.6 5u) Flow rate : 1 mL/ min; Mobile phase : A= n-hexane: IPA (90 : 10 % v/v), B = IPA, A: B = 70/30 (% V/V).

Example-171a to 171b



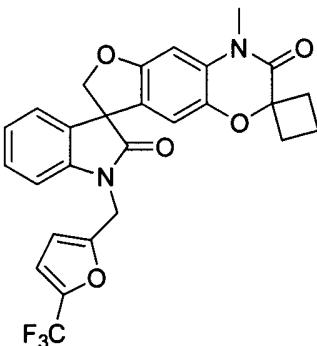
The Example-166 was separated to give Example-171a Retention time (RT) 8.29 minutes and Example-171b Retention time (RT) 11.52 minutes on chiral column (CHIRAL PAK IC, 250mm x 4.6,5 μ) Flow rate : 1 mL/ min; Mobile phase : A= n-hexane: IPA (90 : 10 % v/v), B = IPA, A: B = 80/20 (% V/V).

Example-172



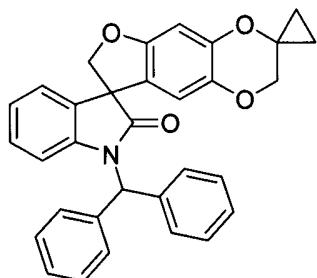
The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-122 and 2-(bromomethyl)-5-(trifluoromethyl)furan (Yield: 52%). ^1H NMR (400MHz, CDCl_3) δ 7.28 (dd, $J=1.2\text{Hz}$, $J=7.6\text{Hz}$, 1H), 7.16 (dd, $J=0.8\text{Hz}$, $J=8.4\text{Hz}$, 1H), 7.13 (m, 1H), 6.96 (d, $J=8.0\text{Hz}$ 1H), 6.74-6.73 (m, 1H), 6.62 (s, 1H), 6.37-6.36 (m, 1H), 6.13 (s, 1H), 5.00 (d, $J=16.0\text{Hz}$, 1H), 4.91 (d, $J=16.0\text{Hz}$ 1H), 4.88 (d, $J=8.0\text{Hz}$, 1H), 4.63 (d, $J=8.0\text{Hz}$, 1H), 2.73 (t, $J=6.4\text{Hz}$, 2H), 2.17 (t, $J=10.4\text{Hz}$ 2H), 2.0-1.91 (m, 2H), 1.89-1.87 (m, 2H), 1.80-1.78 (m, 1H), 1.63-1.58 (m, 1H). MS (ES+) m/z : 482.2 (M+1).

Example-173



The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-127 and 2-(bromomethyl)-5-(trifluoromethyl)furan (Yield: 55%). ^1H NMR (400MHz, CDCl_3) δ 7.32 (t, $J=7.6\text{Hz}$, 1H), 7.20 (dd, $J=0.8\text{Hz}$, $J=7.2\text{Hz}$, 1H), 7.09 (dd, $J=0.8\text{Hz}$, $J=7.6\text{Hz}$, 1H), 7.01 (d, $J=7.6\text{Hz}$, 1H), 6.76 (s, 1H), 6.57 (s, 1H), 6.41 (d, $J=2.8\text{Hz}$, 1H), 6.36 (s, 1H), 5.02 (d, $J=16.0\text{Hz}$, 1H), 4.96 (d, $J=9.2\text{Hz}$, 1H), 4.90 (d, $J=16.0\text{Hz}$, 1H), 4.70 (d, $J=9.2\text{Hz}$, 1H), 3.34 (s, 3H), 2.60-2.58 (m, 1H), 2.55-2.47 (m, 1H), 2.22-2.12 (m, 2H), 1.93-1.84 (m, 2H). MS (ES+) m/z : 511.09 (M+1).

Example-174



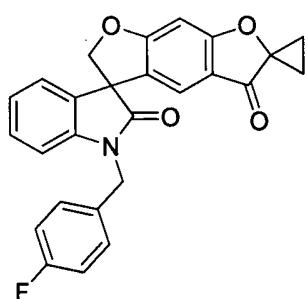
10

To a stirred solution of diethyl zinc in hexane (1.26ml, 1.267mmol) was added diiodomethane (0.338g, 1.267mmol); after 5 minutes a solution of Intermediate-133 (0.15g, 0.316mmol) in dichloromethane was added and the resultant solution was heated to reflux for 24 hours. The reaction mixture was cooled to room temperature and diluted with 15 dichloromethane (20ml), then added water (20ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 15ml). The combined organic extract was washed with water (2 x 15 ml), brine (20 ml) and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (100-200 mesh) with an isocratic elution of 10% ethyl acetate in petroleum ether

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to afford Example-174 (0.035g 20%) as an off white solid. ^1H NMR (400MHz, DMSO d₆) δ 7.39-7.28 (m, 10H), 7.17 (dd, $J=1.2\text{Hz}$, $J=7.6\text{Hz}$, 1H), 7.06 (s, 1H), 7.00-6.96 (m, 2H), 6.49 (d, $J=1.2\text{Hz}$, 1H), 6.43 (s, 1H), 6.25 (s, 1H), 4.95 (d, $J=8.8\text{Hz}$, 1H), 4.69 (d, $J=8.8\text{Hz}$, 1H), 4.00 (s, 2H), 1.05 (m, 2H), 0.74 (m, 2H). MS (ES+) m/z : 488.2 (M+1).

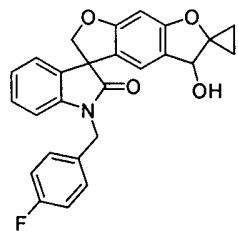
5

Example-175

To a stirred solution of Intermediate-135 (0.5 g, 1.24 mmol) and 1, 2-dibromoethane (0.16 ml, 1.87 mmol) in dry DMF (1 ml) was added sodium hydride (60% w/w dispersion in mineral oil, 0.15 g, 3.74 mmol) slowly at 0 °C under nitrogen atmosphere. The resulting 10 solution was warmed up to room temperature and heated at 50°C for 2 h. The reaction mixture was quenched by ice water (20 ml) and ethyl acetate (25ml) was added. The two phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed with water (2x20 ml) brine (20 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to get the residue which was 15 purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 18% ethyl acetate in petroleum ether to afford Example-175 (0.14 g, 26%) as an off white solid. ^1H NMR (400 MHz DMSO-d₆) δ 7.45-7.42 (m, 2H), 7.32-7.26 (m, 2H), 7.20-7.16 (m, 2H), 7.08-7.03 (m, 2H), 6.98 (s, 1H), 6.89 (s, 1H), 5.10-4.88(m, 4H), 1.98-1.70 (m, 2H), 1.39-1.33 (m, 2H); MS (ES+) m/z: 428.1 (M+1).

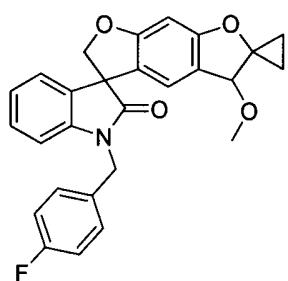
20

Example-176



The title compound was prepared by following a procedure similar to that described in Example-151 by taking Example-175 (yield: 65%). ^1H NMR (400 MHz CDCl_3) δ 7.34-7.31 (m, 2 H), 7.25-7.14 (m, 1 H), 7.06-7.02 (m, 4 H), 6.83-6.76 (m, 1 H), 6.75 (s, 1 H), 6.45 (s, 1 H), 5.06-4.97 (m, 2 H), 4.89-4.81 (m, 1 H), 4.79-4.74 (m, 2 H), 1.71-1.20 (m, 4 H). MS (ES+) m/z: 430.1 (M+1).

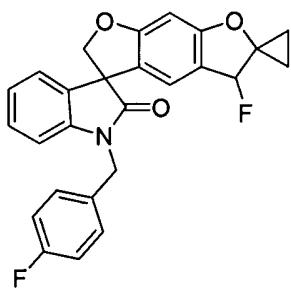
Example-177



To a stirred solution of Example-176 (0.03 g, 0.06 mmol) in dry *N,N*-dimethylformamide (1 ml) was added sodium hydride (60% w/w dispersion in mineral oil, 3 mg, 0.076 mmol) slowly at 0°C under nitrogen atmosphere. The resulting suspension was stirred at 0°C for 0.5 h. Then, methyl iodide (5.0 μl , 0.083 mmol) was added at 0°C and stirred at ambient temperature for 16 h. The reaction mixture was cooled to 0°C, water (5 ml) was added and extracted with ethyl acetate (5 ml). The aqueous phase was again extracted with ethyl acetate (2 x 2 ml). The combined organic extracts were washed with water (5 ml), brine (5 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with an isocratic elution of 15% ethyl acetate in petroleum ether to afford Example-177 (0.015 g, 50%) as an off white solid. ^1H NMR (400 MHz CDCl_3) δ 7.34-7.31 (m, 2 H), 7.25-7.13 (m, 2 H), 7.06-7.03 (m, 3 H), 6.8

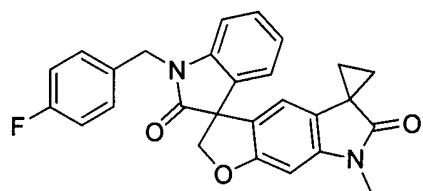
(d $J= 8$ Hz, 1 H), 6.65 (d $J= 8$ Hz, 1 H), 6.45 (s, 1 H), 5.04-4.99 (m, 2 H), 4.86-4.82 (m, 1 H), 4.75-4.63 (m, 2 H), 3.08 (s, 3 H), 1.29-1.16 (m, 4 H). MS (ES+) m/z: 444.1 (M+1).

Example-178



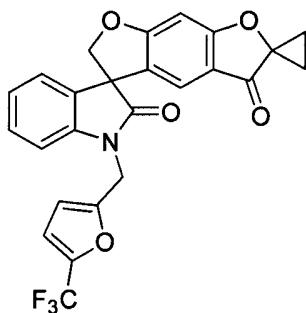
- 5 To a stirred solution of Example-176 (0.05 g 0.11 mmol) in dry dichloromethane (5 ml) was added (diethylamino) sulphur trifluoride (0.015 ml, 0.11 mmol) slowly at -78°C under nitrogen atmosphere. The resulting solution was stirred at -78 0°C for 0.5 h. The reaction mixture was quenched with a saturated aqueous NaHCO₃ solution at -78°C. The two phases were separated and the aqueous phase was extracted with dichloromethane (2 x 10 ml). The
10 combined organic extracts were washed with water (5 ml), brine (5 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated *in vacuo* to obtain a crude product, which was purified by column chromatography over silica gel (100-200 mesh) with an isocratic elution of 10 % ethyl acetate in petroleum ether to afford Example-178 (5.8 mg, 11%) as a brown solid. ¹H NMR (400 MHz CDCl₃) δ 7.39-7.34 (m, 2 H), 7.25-7.20 (m, 1 H), 7.16-7.14 (m, 1 H), 7.06-7.03 (m, 3 H), 6.82 (d $J= 8$ Hz, 1H), 6.74 (s, 1H), 6.30 (s, 1H), 5.04-
15 5.02 (m, 2 H), 4.84-4.75 (m, 2 H), 4.66-4.63 (m, 1 H), 1.24-1.20 (m, 4 H). MS (ES+) m/z: 432.1 (M+1).

Example-179

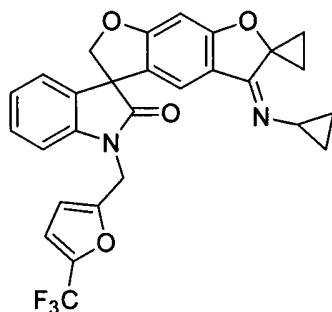


To a stirred solution of Intermediate-141 (0.036 g, 0.084 mmol) in dry tetrahydrofuran (2 ml) was added cesium carbonate (0.082 g 0.252 mmol) and chloroiodomethane (0.018 ml 0.252 mmol) slowly at 0 °C. The reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (5 ml) and water (3 ml). The two 5 phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 5 ml). The combined organic layer was washed with water (10 ml), followed by brine (2x5 ml) and dried over sodium sulfate. The filtrate was concentrated in vacuum to obtain a residue, which was subjected to column chromatography over silica gel (100-200 mesh) using methanol-dichloromethane in the ratio (2:98) as an eluent to afford the title compound as a brown solid 10 (0.011 g, 29%). ^1H NMR (400 MHz, CDCl_3) 7.30-7.26 (m, 2 H), 7.065-7.00 (m, 5 H), 6.83 (d, J = 8 Hz, 1H), 6.59 (s, 1H), 6.05 (s, 1H), 5.00-4.90 (m, 4 H), 3.27 (s, 3H), 1.53-1.29 (m, 4 H); MS (ES+) m/z 441.1(M+1), 463.1 (M+ Na).

Example-180

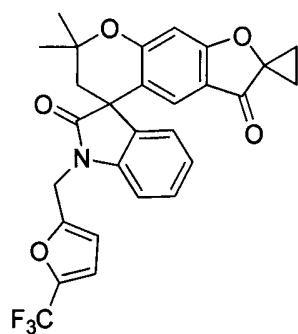


15 The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-145 and 2-(bromomethyl)-5-(trifluoromethyl) furan (Yield: 68%). ^1H NMR (400 MHz DMSO-d₆) δ 7.82-7.26(m,1H),7.22-7.19(m,3H),7.10-7.06(m,1H),6.98(s, 1H),6.87(s,1H),6.77(d, J = 3.2Hz,1H),5.07-4.97(m,4H), 1.73-1.67(m,2H),1.39-1.32(m,2H) MS (ES+) m/z: 468.1 (M+1).



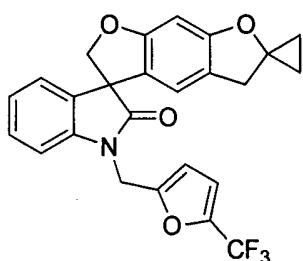
To a stirred solution of Example-180 (0.08 g, 0.1713 mmol) and cyclopropanamine (0.058 ml, 0.048 g, 0.8565 mmol) in dry benzene (3 ml) was added 1M solution of titanium tetrachloride in dichloromethane (0.034 ml, 0.2569 mmol) slowly at -5 °C under nitrogen atmosphere. The resulting suspension was warm up to room temperature and stirred for 16 h. The reaction mixture was cooled to 0°C and quenched by ice cold water (10 ml) slowly and added ethyl acetate (10 ml). The phases were separated and the aqueous phase was extracted in ethyl acetate (2 x 10 ml). The combined organic extract was washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (100-200 mesh), with a isocratic elution of 10% ethyl acetate in petroleum ether to afford the title compound (0.016 g, 18%) as a off white solid.¹H NMR (400 MHz DMSO-d₆) δ 7.36-7.30(m,1H), 7.26-7.16(m,4H), 7.10-7.03 (m, 1H), 6.80 (s,1H), 6.76-6.69(m,1H), 5.06-5.00(m,2H), 4.93 (d, J = 9.6Hz,1H), 4.83 (d, J = 9.6 Hz,1H), 3.05-3.03 (m,1H), 1.41-1.37 (m,2H), 1.07-0.83 (m,2H), 0.65-0.55 (m,2H), 0.46-0.40 (m,2H). MS (ES+) m/z: 507.1 (M+1,).

Example-182



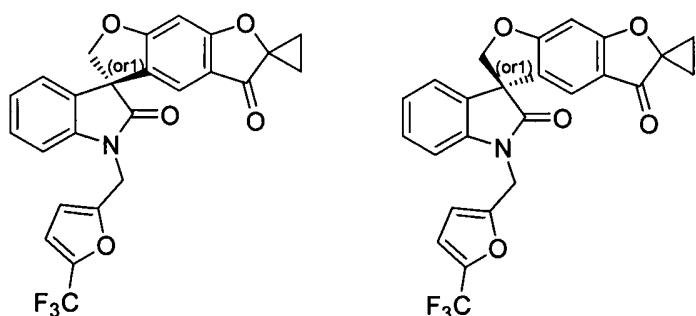
The title compound was prepared by following a procedure similar to that described in Example-7 by taking Intermediate-149 and 2-(bromomethyl)-5-(trifluoromethyl)furan (Yield: 64%). ^1H NMR (400 MHz DMSO-d₆) ^1H NMR (400 MHz DMSO-d₆) δ 7.35-7.31(m,1H),7.19-7.17 (m,3H),7.06 (t, $J=7.6\text{Hz}$,1H), 6.84 (s, 1H),6.71(d, $J = 2.8 \text{ Hz}$, 1H), 6.65 (s, 1H),5.08(s, 2H),2.42 (d, $J = 14.8 \text{ Hz}$,1H), 2.29 (d, $J=14.8 \text{ Hz}$,1H),1.72-1.64 (m, 2H),1.55 (s,3H),1.49 (s,3H),1.33-1.23 (m, 2H). MS (ES+) m/z: 510.05 (M+1).

Example-183



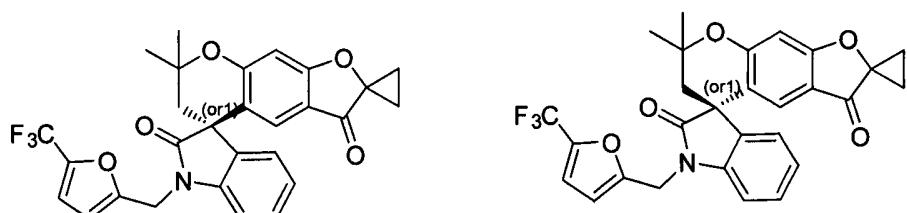
To a stirred solution of Intermediate-156 (0.15 g, 0.340 mmol) in dry THF (5 ml) was added cesium carbonate (0.44 g, 1.36 mmol) at room temperature. The resulting suspension was stirred for 30 min. at room temperature. Then, chloroiodomethane (0.036 ml, 0.089 g, 0.512 mmol) was added dropwise to the above suspension and stirred the reaction mixture at room temperature for 15 h. The reaction mixture was cooled to 0°C and quenched with addition of water (10 ml) and added EtOAc (20 ml).The two phases were separated and the aqueous phase was extracted with EtOAc (2 x 15 ml). The combined organic extract was washed with water (20 ml), brine (25 ml), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (mesh 100-200) with an isocratic elution of 15% ethyl acetate in petroleum ether to afford the title compound (0.05 g, 32%) as an off white solid. ^1H NMR (400 MHz,DMSO-d₆): δ 7.33-7.29 (m, 1H), 7.21-7.16 (m, 3H), 7.06 (t, $J=7.6\text{Hz}$,1H), 6.77(d, $J=3.6 \text{ Hz}$,1H), 6.42 (s,1H),6.37(s,1H), 5.13 (d, $J= 16.0\text{Hz}$, 1H), 4.99 (d, $J=16.0 \text{ Hz}$, 1H), 4.83 (d, $J= 9.6 \text{ Hz}$, 1H), 4.74 (d, $J= 9.6 \text{ Hz}$,1H), 3.06 (s, 2H), 1.07-0.99 (m, 2H), 0.85-0.77 (m, 2H). MS (ES+) m/z 453.98.

Example-184a and 184b



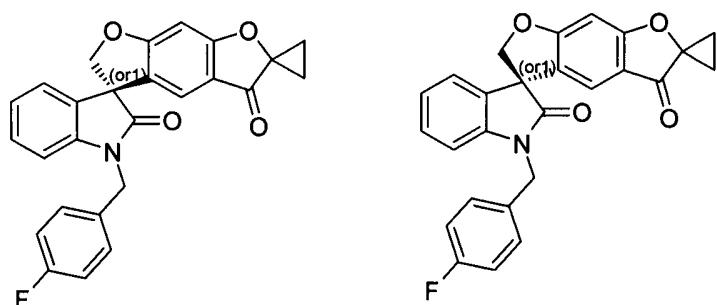
The Example-180 was separated to give Example-184a Retention time (RT) 5.96 minutes and Example-184b Retention time (RT) 14.74 minutes on chiral column (CHIRAL PAK IA, 250mm x 4.6, 5 μ) with an isocratic elution of 40% isopropyl alcohol in hexane (flow rate 1ml/minute).

Example-185a and 185b



The Example-182 was separated to give Example-185a Retention time (RT) 8.16 minutes and Example-185b Retention time (RT) 10.52 minutes on chiral column (CHIRAL PAK IA, 250mm x 4.6, 5 μ) with an isocratic elution of methanol-90% (0.1%DEA)_ACN_10% ACN (flow rate 0.5ml/minute).

Example-186a and 186b

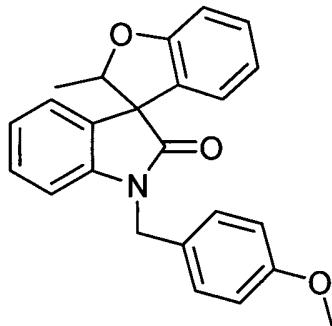


The Example-175 was separated to give Example-186a Retention time (RT) 8.36 minutes and Example-186b Retention time (RT) 9.91 minutes on chiral column (Phenomenex-

CELL-1,250mm x 4.6, 5 μ) with an isocratic elution of 35% isopropyl alcohol in hexane (flow rate 1ml/minute).

Example-187

1'-(4-Bethoxybenzyl)-2-methyl-2H-spiro[benzofuran-3,3'-indolin]-2'-one

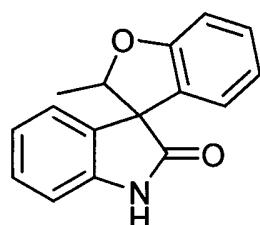


5

To a stirred solution Intermediate-162 (0.7g, 1.56 mmol) in toluene (10 mL) was added tributyl tinhydride (0.54g 1.87 mmol) and AIBN (25 mg 0.15 mmol). The reaction mixture was refluxed for 3 h at 100°C. The above reaction mixture was quenched with aqueous ammonia and extracted with ethyl acetate (3 x 20mL). The organic phase was washed with water and brine, and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in *vacuo* to afford a residue. The residue was purified by column chromatography eluting with 15 % ethyl acetate: hexane to afford a solid (0.4 g, 70 %). MS (ES+) m/z: 372.2 (M+1).

Example-188

15 2-Methyl-2H-spiro[benzofuran-3,3'-indolin]-2'-one



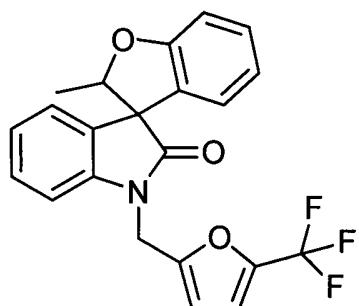
To a stirred solution of Example-187 (0.35 g, 0.92 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was added trifluoromethanesulfonic acid (1.41g, 9.2 mmol). The reaction mixture was stirred at ambient temperature for 16 hrs at room temperature and 20 concentrated in *vacuo*. The residue was basified with saturated aqueous sodium bicarbonate

and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography eluting with ethyl acetate / hexane (20%) to afford a solid (0.140 g, 60 %). MS (ES+) m/z: 252.2 (M+1).

5

Example 189

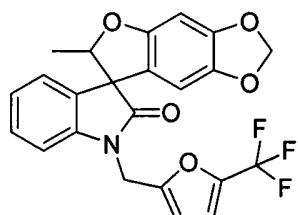
2-Methyl-1'-((5-(trifluoromethyl)furan-2-yl)methyl)-2H-spiro[benzofuran-3,3'-indolin]-2'-one



The title compound was prepared by following a procedure similar to that described in
10 Intermediate-162 using Example-188 and 2-(bromomethyl)-5-(trifluoromethyl)furan (yield:
80 %). MS(ES+) m/z: 400.2 (M+1).

Example 190

6-Methyl-1'-((5-(trifluoromethyl)furan-2-yl)methyl)-6H-spiro[[1,3]dioxolo[4,5-f]
benzofuran-7,3'-indolin]-2'-one



15

The title compound was prepared by following a procedure similar to that described in
Example 187 using Intermediate-166 (yield: 70 %). MS(ES+) m/z: 444.1 (M+1).

Pharmacological activity

Certain illustrative compounds within the scope of the invention are screened for NAV activity according to the procedure given below. The screening of the compounds may be carried by other methods and procedures known to skilled in the art.

Analysis of inhibition of sodium channels by test compounds:

5 ND7/23 cells that express endogenous different sodium channels were seeded in a 96-well plate at a density of 40000 cells/well and incubated at 37 °C / 5% CO₂ for 18-24 h. The assay was carried out using the Blue Membrane Potential Dye (Molecular Devices) following the manufacturer's instructions. Briefly, the cells were incubated with 1X blue membrane potential dye for 1 h. The cells were then treated with various concentrations of the test
10 compounds for 1 h followed by depolarization with 100 μM Veratridine. The fluorescence was read following excitation at 510-545 nm and emission at 565-625 nm in FLIPR. The "max-min" fluorescence values were used to calculate the % inhibition. IC₅₀ values were calculated by plotting % inhibition against concentration and curve fitting into a sigmoidal dose response.

15 Certain compounds of the present invention are shown to have functional activity as inhibitors of voltage gated sodium channels *in vitro*.

The compounds prepared were tested using the above assay procedure and the results obtained are given below. The IC₅₀ (nM) values of the compounds are set forth in Table-1 wherein "A" refers to an IC₅₀ value of less than 300 nM, "B" refers to an IC₅₀ value in range 20 of 300.01 nM to 1000 nM "C" refers to an IC₅₀ value in range of 1000.01 nM to 3000 nM and "D" refers to an IC₅₀ value in range of 3000.01nM to 10000 nM.

Table-1. Analysis of Inhibition of Sodium Channels

| Example No. | IC ₅₀ nM | Example No. | IC ₅₀ nM | Example No. | IC ₅₀ nM |
|-------------|---------------------|-------------|---------------------|-------------|---------------------|
| 1 | C | 104 | D | 154 | D |
| 2 | B | 105 | A | 155 | B |
| 3 | C | 107 | B | 156 | B |

| | | | | | |
|-----|---|-----|---|------|---|
| 4 | D | 124 | A | 167a | D |
| 5 | D | 128 | A | 167b | D |
| 7 | C | 131 | B | 167c | D |
| 8 | C | 132 | D | 167d | D |
| 9 | D | 134 | C | 168 | B |
| 10 | C | 135 | D | 168 | C |
| 11 | C | 136 | C | 172 | B |
| 12 | B | 137 | C | 175 | D |
| 13 | B | 138 | D | 176 | C |
| 16 | C | 141 | D | 177 | C |
| 17 | D | 143 | C | 178 | B |
| 26 | B | 149 | C | 180 | A |
| 32 | C | 150 | C | 186 | C |
| 36 | B | 151 | C | 184a | A |
| 97 | A | 152 | C | 186b | B |
| 103 | D | 153 | B | | |

Analysis of inhibition of Nav1.5 by test compounds:

HEK293 cells stably expressing hNav1.5 were seeded in a 96-well plate at a density of 80000 cells/well and incubated at 37 °C/5%CO₂ for 18-24 h. The assay was carried out
 5 using the Blue Membrane Potential Dye (Molecular Devices) following the manufacturer's instructions. Briefly, the cells were incubated with 1X blue membrane potential dye for 1 h. The cells were then treated with various concentrations of the test compounds for 1 h followed by depolarization with 100 µM Veratridine. The fluorescence was read following excitation at 510-545 nm and emission at 565-625 nm in FLIPR. The "max-min" 10 fluorescence values were used to calculate the % inhibition. IC₅₀ values were calculated by plotting % inhibition against concentration and curve fitting into a sigmoidal dose response.

Analysis of Inhibition of Nav1.4 by Test Compounds:

The CHO cells transfected with Nav1.4 were grown in complete Ham's F12 with 500ug/ml G418. The cells were seeded in a 96 well black clear bottom plate at a cell density of 25000 cells per well. The plates were incubated in a CO₂ incubator at 37°C for 48 h. 100uL of membrane potential blue dye was added and incubated for 45 min. The compound 5 dilutions were made during the incubation period. The compounds (serially diluted) were added to the cell plate and incubated for 10-15 min. 10x Veratridine (20uM final concentration) was added to the cell plate and the resulting changes in membrane potential were captured using FLIPR^{Tetra}.

In Vitro Metabolic Stability of Compounds in Various Species Liver Microsomes:

To evaluate the metabolic stability in liver microsomes - test compound(s) were added to an incubation mixture containing liver microsomes (0.125 mg/mL) and NADPH in potassium phosphate buffer (50 mM). Incubations were carried out at 37 °C in water bath shaker. Reaction was initiated with the addition of test item and aliquots of the reaction mixture were taken at 10, 20 and 30 min post-initiation. The reaction was terminated with 15 the stop solution containing internal standard. In general metabolic stability was assessed at 1 μM concentration in duplicate in presence or absence of NADPH. Samples were analyzed by LC-MSMS for the percentage of parent remaining at different incubation times. Slope of this regression was used to calculate the metabolic rate by using the equation:

Metabolic Rate = K*[S] / [P] (where K is the slope, S is the substrate concentration and P is 20 the protein concentration).

Table-2. Metabolic Stability

| Example No. | % remaining at 30 min in HLM (comp conc 1μM) | Example No. | % remaining at 30 min in HLM (comp Conc 1μM) |
|-------------|--|-------------|--|
| 14 | 44 | 44 | 85 |
| 19 | 47 | 69 | 73 |
| 25 | 77 | 71 | 97 |

| Example No. | % remaining at 30 min in HLM (comp conc 1µM) | Example No. | % remaining at 30 min in HLM (comp Conc 1µM) |
|-------------|--|-------------|--|
| 29 | 68 | 87 | 45 |
| 30 | 45 | 123 | 74 |
| 32 | 47 | 124 | 76 |
| 36 | 59 | 125 | 74 |
| 37 | 88 | 127 | 97 |
| 39 | 85 | 169b | 64 |
| 42 | 87 | 169a | 70 |
| 43 | 86 | | |

Analysis of CYP Inhibition for the Test Compounds:

The following is a method to evaluate the effect of a test compound (s) on the human CYP 3A4, 2C9, 2D6, 1A2 and 2C19 isozymes in human liver microsomes by monitoring production of selective metabolites using HPLC/LC-MS/MS. For each isozyme, an enzyme-substrate mixture will be prepared by premixing appropriate volumes of phosphate buffer, human liver microsomes and substrate. Test compound (s) will be added from working stock and plate will be placed at 37°C on a water bath shaker for 5 min (reactions will be carried out in micro titer plates) and then reaction initiated with the addition of NADPH. After 10 isozyme specific incubation time reaction will be quenched with acetonitrile containing internal standard followed by centrifugation for 10 min, separation of clear supernatant and quantification of metabolites. The response (area or ratio) of the metabolite in the sample without inhibitor was considered as 100% and the % reduction in the CYP activity at each inhibitor concentration was determined relative to no inhibitor area ratio. For IC₅₀ determination same inhibition will be carried out at 6 to 8 test compound concentrations.

Table-3. Analysis of CYP Inhibition

| Example No. | % inhibition CYP_3A4 at 1µM | % inhibition CYP_3A4 at 10µM | % inhibition CYP_2C9 at 1µM | % inhibition CYP_2C9 at 10µM |
|-------------|-----------------------------|------------------------------|-----------------------------|------------------------------|
| 32 | 0 | 0 | 0 | 22 |
| 29 | 5 | 13 | 0 | 48 |
| 28 | 9 | 42 | 0 | 58 |
| 89 | 23 | 84 | 0 | 53 |
| 34 | 32 | 73 | 3 | 74 |
| 129 | 25 | 49 | 4 | 70 |
| 69 | 9 | 29 | 8 | 36 |
| 107 | 32 | 60 | 8 | 51 |
| 15 | 5 | 29 | 10 | 65 |
| 40 | 12 | 41 | 10 | 53 |
| 36 | 27 | 68 | 11 | 63 |
| 27 | 17 | 72 | 14 | 53 |
| 132 | 21 | 50 | 15 | 77 |
| 39 | 10 | 24 | 19 | 51 |
| 19 | 0 | 21 | 23 | 56 |
| 70 | 15 | 32 | 26 | 73 |
| 127 | 30 | 61 | 26 | 49 |
| 123 | 8 | 30 | 31 | 54 |
| 37 | 6 | 11 | 33 | 60 |
| 122 | 16 | 45 | 37 | 67 |

FCA (Freund's Complete Adjuvant) -Induced Inflammatory Hyperalgesia:

An emulsion of Freund's Complete Adjuvant (FCA), containing heat killed *Mycobacterium tuberculosis* (4mg/ml) in incomplete Freund's adjuvant (IFA) and saline (1:1) 5 at a final concentration of 2 mg/ml, when injected (150 µl) into the plantar region of the paw

of rats, induced an inflammatory pain. Mechanical allodynia (7 days after injection) was assessed by measuring hind paw withdrawal thresholds with von Frey filaments. The 50% paw withdrawal threshold was determined using up and down method of Dixon and as per the Chaplan method.

5 **Table- 4. Induced Inflammatory Hyperalgesia**

| Example No. | Dose (mg/kg) | % Improvement (Mean ±SEM) in 50% Paw Withdrawal Threshold | |
|--------------------|---------------------|--|---------------|
| | | 1hr | 2hr |
| 24 | 30 | 14.9± 4.6 | 35.7± 3.4*** |
| 158 | 30 | 52.0 ± 18.6* | 31.2 ± 10.8** |

*p<.05, ***p<0.001 as compared to the CFA/Vehicle group by Dunnett test

Chronic constriction injury (CCI) - induced neuropathic pain (Bennett's model):

Chronic constriction injury (CCI) of sciatic nerve in rats induces mechanical allodynia in this Bennet's neuropathic pain model. Rats were anesthetized using ketamine / xylazine (50 / 5 mg/kg, i.p.) and the left sciatic nerve was exposed at mid thigh level through a small incision. Four loose ligatures of 4-0 chromic cat gut (Ethicon - Johnson & Johnson) at 1 mm space were placed around the sciatic nerve after the bifurcation of common sciatic nerve. After 10-15 days, mechanical allodynia was assessed by measuring hind paw withdrawal thresholds with von Frey filaments. The 50% paw withdrawal threshold was determined using up and down method of Dixon and as per the Chaplan method.

10 **Table- 5. Induced Neuropathic Pain**

| Example No. | Dose (mg/kg) | % Improvement (Mean ±SEM) in 50% Paw Withdrawal Threshold | |
|--------------------|---------------------|--|-------------|
| | | 1hr | 2hr |
| 158 | 30 | 42.4 ± 16.5 * | 31.5 ± 13.3 |

* $p<0.05$, compared to CCI/vehicle group by Dunnett's test

Thus, the compound of the present invention has been shown to decrease pain *in vivo*, indicating potential for use of the compounds of the present invention in the treating, preventing, managing or lessening the severity of the diseases disorders or conditions

- 5 associated with voltage gated sodium channel such as pain including inflammatory and neuropathic pain.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

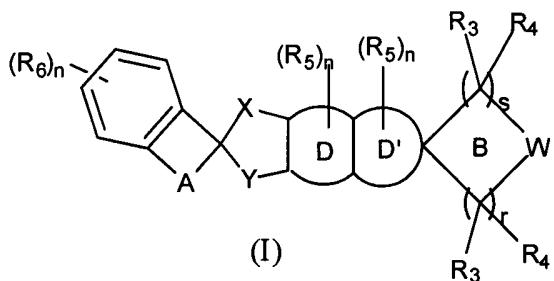
- 10 Although certain embodiments and examples have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments and examples without departing from the teachings thereof. All such modifications are intended to be encompassed within the below claims of the invention.

15

20

CLAIMS

1. A compound of Formula (I):



5 wherein,

D is a 5 or 6 membered aryl or heteroaryl ring;

D' is absent; or

D' is selected from a 4 to 7 membered carbocyclic or heterocyclic ring;

B is absent; or

10 B is selected from a carbocyclic or heterocyclic ring; provided that when D' is absent then B is also absent;

A is selected from $-NRC(O)-$, $-NR-(CR_1R_2)_q-$, $-C(O)NR-$, $-NRS(O)_2-$, $-S(O)_2NR-$, $-NRC(S)-$, $-C(S)NR-$, $-NRC(O)-(CR_1R_2)_m-$, $-C(O)NR-(CR_1R_2)_m-$, $-(CR_1R_2)_m-NRC(O)-$, $-(CR_1R_2)_m-C(O)NR-$, $-(CR_1R_2)_m-NR-$, $-(CR_1R_2)_m-NR-(CR_1R_2)_m-$, $-NRC(O)NR-$, $-OC(O)NR-$,
15 $-NRC(O)O-$, $NR-CR_1=CR_2-$, $-C(O)-CR_1=CR_2-$, $-N=C(R_1)-$ and $-C(O)NRC(O)-$;

R, which may be same or different at each occurrence, is independently selected from hydrogen, alkyl, haloalkyl, cyanoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclalkyl, $-C(O)R_{12}$, $-C(O)OR_{11}$, $-(CR_1R_2)_m-NR_8R_9$, $-C(O)-NR_8R_9$, $-CR_aR_bC(O)NR_8R_9$, $-(CR_aR_b)_m-CR_aR_bR_c$, and
20 $-S(O)_pR_{12}$;

R_1 and R_2 , which may be same or different at each occurrence, are independently selected from hydrogen, halogen, cyano, nitro, $-OR_{10}$, $-C(O)OR_{11}$, and alkyl;

X is C_1 - C_5 alkylene, wherein one or more CH_2 groups may independently be replaced by $-O-$, $-C(O)-$, $-CR_3R_4-$, $-NR_8-$ or $-S(O)_p-$;

5 Y is selected from a bond, $-O-$, $-S-$, $-C(O)-$, $-NR-$, and $-CR_3R_4-$;

R_3 and R_4 , which may be same or different at each occurrence, are independently selected from hydrogen, halogen, cyano, nitro, alkyl, haloalkyl, hydroxyalkyl, cyanoalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, $-OR_{10}$, $-SR_{10}$, $-C(O)R_{12}$, $-OC(O)R_{11}$, $-CO(O)R_{11}$, $-NR_8R_9$, $-C(O)NR_8R_9$, $-NR_8C(O)R_{12}$, $-S(O)_2NR_8R_9$ and $-NR_7S(O)_2R_{12}$; or

10 R_3 and R_4 , together with the carbon atom to which they are attached, may form a substituted or unsubstituted 3 to 7 membered cyclic ring; wherein cyclic ring may be carbocyclic or heterocyclic;

with proviso that

i) when Y is a bond, B is absent, A is $-NRC(O)-$, $-NR-(CR_1R_2)_q-$, $-NRS(O)_2-$, $-NRC(S)-$, $-NRC(O)-(CR_1R_2)_m-$, $-(CR_1R_2)_m-NRC(O)-$, $-NRC(O)NR-$, $-NRC(O)O-$, or $-N=C(R_1)-$; X is C_1 - C_5 alkylene, and only one of CH_2 group in X is replaced with $-CR_3R_4-$ then

- a) R_3 and R_4 both are not hydrogen;
- b) R_3 and R_4 both are not fluorine; and
- c) any one of R_3 , R_4 is not $-CH(OR_{13})$;

20 ii) when Y is a bond, B is absent, A is $-NRC(O)-$, $-NR-(CR_1R_2)_q-$, $-NRS(O)_2-$, $-NRC(S)-$, $-NRC(O)-(CR_1R_2)_m-$, $-(CR_1R_2)_m-NRC(O)-$, $-NRC(O)NR-$, $-NRC(O)O-$, or $-N=C(R_1)-$; X is C_1 - C_5 alkylene wherein at least one of CH_2 is independently replaced with O , $C(O)$, NR_8 , $S(O)_p$ and at least one of remaining CH_2 group is replaced with CR_3R_4 then R_3 and R_4 both are not hydrogen; and

25 iii) when Y is a bond, B is absent, A is $-NRC(O)-$, D ring is phenyl, D' ring is 1,4-dioxane, then X is not replaced with $-C(O)N(CH_3)-$ where $C(O)$ is attached to the quaternary carbon;

W is selected from a bond, -O-, -NR₈-, -S(O)_p-, -NR₈C(O)-; CR₃R₄, -NR₈C(O)-NR₈-, -NR₈C(O)O-, -CR₃=N-, -C(=NR₈)-, -OC(O)- and -OC(O)O-;

R₅, which may be same or different at each occurrence, is independently selected from halogen, cyano, nitro, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, -OR₁₀, -SR₁₀, -S(O)₂R₁₀, -C(O)R₁₂, -OC(O)R₁₁, -NR₈R₉, -C(O)NR₈R₉, -NR₈C(O)R₁₂, -NR₈S(O)₂R₁₂ and -S(O)₂NR₈R₉; provided that when R₅ is present on D' it may be attached on same or different carbon atom;

R₆, which may be same or different at each occurrence, is independently selected from halogen, cyano, nitro, alkyl, haloalkyl, hydroxyalkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, -OR₁₀, -SR₁₀, -C(O)R₁₂, -OC(O)R₁₂, -NR₈R₉, -C(O)NR₈R₉, -NR₈C(O)R₁₂, -NR₇S(O)₂R₁₂ and -S(O)₂NR₈R₉;

R₇, which may be same or different at each occurrence, is independently selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, -C(O)R₁₂ and -S(O)_pR₁₂;

R₈ and R₉, which may be same or different at each occurrence, are independently selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, -C(O)R₁₂ and -S(O)_pR₁₂; or R₈ and R₉, together with the nitrogen atom to which they are attached, may form a substituted or unsubstituted 3 to 14 membered heterocyclic ring;

R₁₀ and R₁₁, which may be same or different at each occurrence, are independently selected from hydrogen, alkyl, alkoxyalkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, -CR_aR_bC(O)NR₈R₉ and -(CR_aR_b)_m-CR_aR_bR_c;

R₁₂, which may be same or different at each occurrence, is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl and heteroarylalkyl;

R_a, R_b and R_c, which may be same or different at each occurrence, are independently selected from hydrogen, halogen, alkyl, heteroaryl and heterocyclyl; or R_a and R_b, together

with the carbon atom to which they are attached, may form a substituted or unsubstituted 3 to 7 membered cyclic ring; wherein cyclic ring may be carbocyclic or heterocyclic;

‘m’ is an integer ranging from 0 to 3, both inclusive;

‘n’ is an integer ranging from 0 to 4, both inclusive;

5 ‘p’ is an integer ranging from 0 to 2, both inclusive;

‘q’ is an integer ranging from 1 to 2, both inclusive;

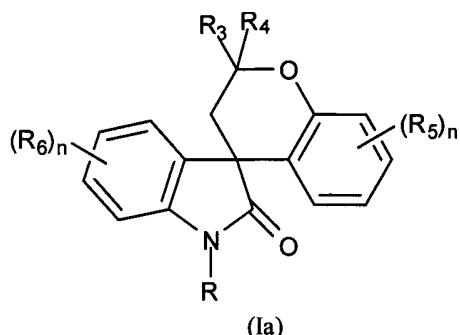
‘r’ and ‘s’ are independently an integer ranging from 0 to 4, both inclusive, provided that the sum of ‘r’ and ‘s’ is at least 1 when ring B is present; and

wherein alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxyalkyl,

10 cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl wherever they occur may optionally be substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, oxo (=O), thio (=S), alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclylalkyl, heteroarylalkyl, -C(O)OR^x, -C(O)R^x, -C(S)R^x, -C(O)NR^xR^y, -NR^xC(O)NR^yR^z, -N(R^x)S(O)R^y, -N(R^x)S(O)₂R^y, -NR^xR^y, -NR^xC(O)R^y, -NR^xC(S)R^y, -NR^xC(S)NR^yR^z, -S(O)NR^xR^y, -S(O)₂NR^xR^y, -OR^x, -OC(O)R^x, -OC(O)NR^xR^y, -R^xC(O)OR^y, -R^xC(O)NR^yR^z, -R^xC(O)R^y, -SR^x, -S(O)R^x, and -S(O)₂R^x; where each occurrence of R^x, R^y and R^z are independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic ring, heterocyclylalkyl ring and heteroarylalkyl;

or a pharmaceutically acceptable salt thereof.

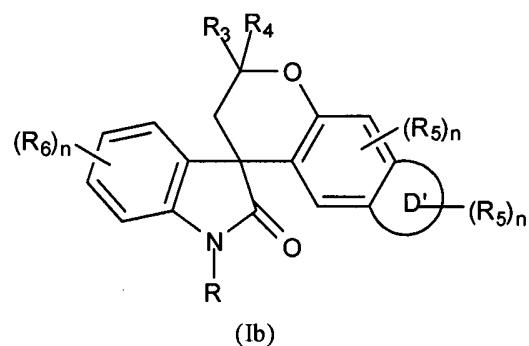
2. The compound of claim 1, having the Formula (Ia):



or a pharmaceutically acceptable salt thereof.

wherein R, R₃, R₄, R₅ and R₆ and 'n' are as defined in claim 1 or 2.

3. The compound of claim 1, having the Formula (Ib):



5

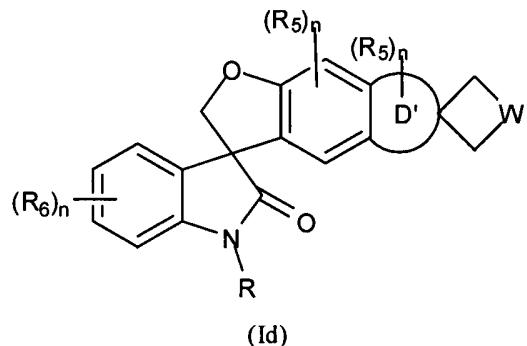
or a pharmaceutically acceptable salt thereof.

wherein,

D' is 5 to 7 membered heterocyclic ring; and

R, R₃, R₄, R₅ and R₆ and 'n' are as defined in claim 1 or 2.

- 10 4. The compound of claim 1, having the Formula (Id):



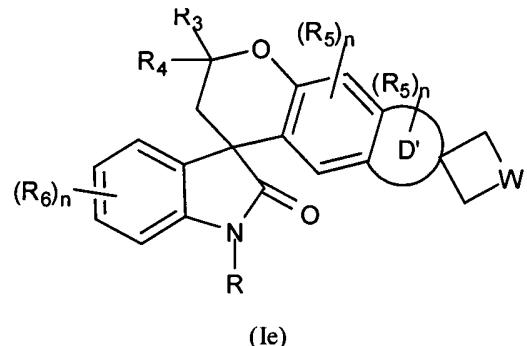
or a pharmaceutically acceptable salt thereof.

wherein,

D' is 5 to 7 membered heterocyclic ring; and

5 W, R, R₃, R₄, R₅ and R₆ and 'n' are as defined in claim 1 or 2.

5. The compound of claim 1, having the Formula (Ie):



or a pharmaceutically acceptable salt thereof.

wherein,

10 D' is 5 to 7 membered heterocyclic ring; and

W, R, R₃, R₄, R₅ and R₆ and 'n' are as defined in claim 1 or 2.

6. The compound of claim 1, wherein D is a substituted or unsubstituted 5 or 6 membered aryl or heteroaryl ring.

7. The compound of claim 6, wherein aryl is phenyl, wherein the

phenyl is optionally substituted with one or more R₅ wherein each R₅ is independently selected from halogen, alkyl or -OR₁₀; wherein R₁₀ is hydrogen, alkyl, haloalkyl, cycloalkylalkyl, heterocyclalkyl, CR_aR_bC(O)NR₈R₉ or -(CR_aR_b)_m-CR_aR_bR_c; wherein each of R_a, R_b and R_c are independently selected from hydrogen, alkyl, heteroaryl and heterocyclyl or R_a and R_b together form a substituted or unsubstituted 3 to 7 heterocyclic ring; and 'm' is 5 1 or 2.

8. The compound of claim 1, wherein D' is absent or a 5 to 7 membered heterocyclic ring.
9. The compound of claim 8, wherein the substituted heterocyclic ring is geminally substituted with substituted alkyl groups.
10. The compound of claim 8 or 9, wherein the heterocyclic ring is 1,3-dioxolane or 1,4-dioxane.
11. The compound of claim 1, wherein B is absent or a carbocyclic ring and 'r' and 's' are 1 or 2.
12. The compound of claim 1, 4 or 5, wherein W is CR₃R₄ or O, and 15 wherein R₃ and R₄ are hydrogen.
13. The compound of claim 11, wherein the carbocyclic ring is saturated and is selected from cyclopropane or cyclobutane.
14. The compound of claim 1, wherein A is -NRC(O)-, or -NR-, (CR₁R₂)_m- wherein R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl, aryl, heteroaryl, heterocyclyl, 20 cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclalkyl, -(CR₁R₂)_m-NR₈R₉, -C(O)R₁₂ or (CR_aR_b)_m-CR_aR_bR_c; R₁ and R₂ are hydrogen; R₁₂ is substituted or unsubstituted aryl; 'm' is 1 or 2 and R_a, R_b and R_c are as defined herein claim 7.
15. The compound of claim 14, wherein arylalkyl is substituted or unsubstituted benzyl, wherein substituent(s) one or more are independently selected from halogen, cyano, alkyl, 25 haloalkyl, alkoxy, haloalkoxy, -C(O)OH, or C(O)O-alkyl.

16. The compound of claim 14, wherein the heteroarylalkyl is substituted or unsubstituted pyridin-3-ylmethyl, pyridin-2-ylmethyl, pyridin-4-ylmethyl, thiazol-5-ylmethyl, wherein substituent(s) one or more are independently selected from halogen, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, -C(O)OH, C(O)O-alkyl or -NH₂ or -N(alkyl)₂.
- 5 17. The compound of claim 14, wherein heterocyclalkyl is tetrahydrofuran-2yl-methyl, tetrahydro-2*H*-pyran-2-ylmethyl, tetrahydro-2*H*-pyran-4-ylmethyl or 2-oxopyrrolidin-1-ylethyl.
18. The compound of claim 1, wherein Y is a bond.
19. The compound of claim 1, wherein X is C₁-C₅ alkylene wherein one or more CH₂ groups
10 in alkylene may independently be replaced by -O- or -CR₃R₄-wherein R₃ and R₄ are independently selected from hydrogen, alkyl, -C(O)NR₈R₉, -C(O)R₁₂, OC(O)R₁₂, or -CO(O)R₁₁ wherein R₁₁ and R₁₂ are hydrogen or alkyl; and R₈ and R₉ together form a substituted or unsubstituted 3 to 14 membered heterocyclic ring.
20. The compound of claim 19, wherein the heterocyclic ring is morpholine.
- 15 21. The compound of claim 1, wherein ring D is 5 or 6 membered aryl or heteroaryl ring, ring D' is absent, ring B is absent, A is -NRC(O)-, X is C₁-C₅ alkylene wherein one or more CH₂ groups may independently be replaced by -O- or -CR₃R₄-, Y is a bond and R₅ is halogen, alkyl, or -OR₁₀; wherein R₃ and R₄ are independently selected from hydrogen, alkyl, -C(O)NR₈R₉, -C(O)R₁₂, OC(O)R₁₂, or -CO(O)R₁₁ wherein R₁₁ and R₁₂ are hydrogen or alkyl; 20 and R₈ and R₉ together form a substituted or unsubstituted 3 to 14 membered heterocyclic ring; and R is as defined in claim 14.
22. The compound of claim 1, wherein ring D is 5 or 6 membered aryl or heteroaryl ring, ring D' is absent, ring B is absent, A is -NRC(O)-, X is C₁-C₅ alkylene wherein one or more CH₂ groups may independently be replaced by -O- or -CR₃R₄-, Y is a bond and R₅ is halogen, 25 alkyl, or -OR₁₀; wherein R₃ and R₄ are independently selected from hydrogen, alkyl, -C(O)NR₈R₉, -C(O)R₁₂, OC(O)R₁₂, or -CO(O)R₁₁ wherein R₁₁ and R₁₂ are hydrogen or alkyl; and R₈ and R₉ together form a substituted or unsubstituted 3 to 14 membered heterocyclic

ring; the sum of 'r' and 's' is 1 to 2; R is as defined in claim 14 and W is as defined in claim 1.

23. The compound of claim 1, which is selected from:

- 1'-((4-Fluorobenzyl)-6,6-dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one), [4,5-g]chromene-8,3'-indolin]-2'-one,
- 6,6-Dimethyl-1'-((tetrahydrofuran-2-yl)methyl)-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one,
- 6,6-Diethyl-1'-((tetrahydrofuran-2-yl)methyl)-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one,
- 10 7,7-Dimethyl-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one, 1',7,7-Trimethyl-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one,
- 7,7-Dimethyl-1'-((5-trifluoromethyl)furan-2-yl)methyl-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one,
- 15 1'-((4-Fluorobenzyl)-7,7-dimethyl-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one),
- 7,7-Dimethyl-1'-(pyridin-2-ylmethyl)-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one,
- 7,7-Dimethyl-1'-(pyridin-3-ylmethyl)-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one,
- 20 7,7-Dimethyl-1'-(pyridin-4-ylmethyl)-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one,
- 7,7-Dimethyl-1'-(2,2,2-trifluoroethyl)-2,3,7,8-tetrahydrospiro[[1,4]dioxino[2,3-g]chromene-9,3'-indolin]-2'-one,
- 7-Ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
- 25 7-(Difluoromethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,

- 2,2-Dimethyl-7-((3-methyloxetan-3-yl)methoxy)spiro [chroman-4,3'-indolin]-2'-one,
7-Ethoxy-1'-(4-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2, 2-dimethyl-1'-(5-trifluroromethyl) furan-2-yl) methyl)spiro [chroman-4, 3'-indolin]-2'-one,
- 5 7-Ethoxy-1'-ethyl-2,2-dimethylspiro[chroman-4,3'-indolin] -2'-one,
7-(Difluoromethoxy)-2, 2-dimethyl-1'-(5-trifluroromethyl) furan-2-yl)methyl)
spiro[chroman-4,3'-indolin]-2'-one,
7-(Difluoromethoxy)-1'-(4-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
2,2-Dimethyl-7-((3-methyloxetan-3-yl)methoxy)-1'-(5-(trifluoromethyl) furan-2-yl)methyl)
- 10 10 spiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(4-(trifluoromethyl)benzyl)spiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(4-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-1'-(2-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(pyridin-3-ylmethyl)spiro[chroman-4,3'-indolin]-2'-one,
- 15 7-Ethoxy-2,2-dimethyl-1'-(pyridin-2-ylmethyl)spiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(3-(trifluoromethyl)benzyl)spiro[chroman-4,3'-indolin]-2'-one,
1'-(2-Chloro-5-fluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
4-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl)benzonitrile,
7-Ethoxy-1'-(6-fluoropyridin-2-yl)methyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
- 20 Methyl-4-((7-ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzoate,
1'-(2-Cyclopropylethyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
2-(7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)acetonitrile,
7-Ethoxy-2,2-dimethyl-1'-(3-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one,

- 4-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzoic acid,
7-Ethoxy-2,2-dimethyl-1'-((tetrahydrofuran-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-1'-(5-fluoropyridin-2-yl)methyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(5-(trifluoromethyl)pyridin-2-yl)methyl)spiro [chroman-4,3'-
5 indolin]-2'-one,
7-Ethoxy-1'-(3-fluoropyridin-2-yl)methyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
Methyl-3-((7-ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl) methyl)benzoate,
3-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzoic acid,
1'-(4-(Difluoromethoxy)benzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
10 7-Ethoxy-1'-(4-fluoro-3-(trifluoromethoxy)benzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-
2'-one,
7-Ethoxy-1'-(3-fluoro-4-(trifluoromethoxy)benzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-
2'-one,
1'-(4-Chlorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
15 7-Ethoxy-1'-(4-methoxybenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
2-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl)-5-fluoro
benzonitrile,
6-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl)nicotine nitrile,
7-Ethoxy-2,2-dimethyl-1'-(thiazol-5-ylmethyl)spiro[chroman-4,3'-indolin]-2'-one,
20 1'-(2-Chlorothiazol-5-yl)methyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
1'-(2-(Dimethylamino)thiazol-5-yl)methyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-
indolin]-2'-one,
3-(7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)propanenitrile,
7-Ethoxy-2,2-dimethyl-1'-(2-(2-oxopyrrolidin-1-yl)ethyl)spiro[chroman-4,3'-indolin]-2'-one,

- 1'-(2,4-Difluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
3-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzonitrile,
7-Ethoxy-1'-(4-fluoro-2-(trifluoromethyl)benzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-
2'-one,
- 5 7-Ethoxy-2,2-dimethyl-1'-(tetrahydro-2H-pyran-4-yl)methyl)spiro[chroman-4,3'-indolin]-2'-
one,
1'-(2-Chloro-4-fluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(2,2,2-trifluoroethyl)spiro[chroman-4,3'-indolin]-2'-one,
2-((7-Ethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzonitrile,
- 10 1'-(3,4-Difluorobenzyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(3-(trifluoromethyl)pyridin-2-yl)methyl)spiro [chroman-4,3'-
indolin]-2'-one,
1'-(2-(Diethylamino)ethyl)-7-ethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(3-methyloxetan-3-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one,
- 15 7-Ethoxy-1'-(3-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(2-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one,
7-Ethoxy-2,2-dimethyl-1'-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methyl)spiro [chroman-
4,3'-indolin]-2'-one,
- 20 7-Ethoxy-2,2-dimethyl-1'-(tetrahydro-2H-pyran-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-
one,
7-(2-Ethoxyethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
7-(2-Ethoxyethoxy)-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-
4,3'-indolin]-2'-one,
7-(2-Methoxyethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,

- 7-(2-Methoxyethoxy)-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one,
- 7-Isopropoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
- 7-Isopropoxy-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one,
- 7-(2-Fluoroethoxy)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
- 7-(2-Fluoroethoxy)-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one,
- 2,2-Dimethyl-7-propoxyspiro[chroman-4,3'-indolin]-2'-one,
- 10 2,2-Dimethyl-7-propoxy-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one,
- 2,2-Dimethyl-7-propoxy-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one,
- 2,2-Dimethyl-7-propoxy-1'-(4-(trifluoromethoxy)benzyl)spiro[chroman-4,3'-indolin]-2'-one,
- 15 2,2-Dimethyl-7-(2-(2-oxooxazolidin-3-yl)ethoxy)spiro[chroman-4,3'-indolin]-2'-one,
- 2,2-Dimethyl-7-(2-(2-oxooxazolidin-3-yl)ethoxy)-1'-(5-(trifluoromethyl) furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-2'-one,
- 2,2-Dimethyl-7-(2-(2-oxooxazolidin-3-yl)ethoxy)-1'-(4-(trifluoromethoxy) benzyl)spiro[chroman-4,3'-indolin]-2'-one,
- 20 2,2-Dimethyl-7-(2-(2-oxopyrrolidin-1-yl)ethoxy)-1'-(5-(trifluoromethyl)furan-2-yl)methyl) spiro[chroman-4,3'-indolin]-2'-one,
- 7-Hydroxy-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl) spiro[chroman -4,3'-indolin]-2'-one,
- 25 7-(Cyclopropylmethoxy)-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl) spiro[chroman-4,3'-indolin]-2'-one,

6,7-Diethoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,

6,7-Diethoxy-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one,

6,7-Diethoxy-1'-(4-fluorobenzyl)-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,

5 3-((6,7-Diethoxy-2,2-dimethyl-2'-oxospiro[chroman-4,3'-indolin]-1'-yl)methyl) benzo nitrile,

2,2,7,7-Tetramethyl-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one,

2,2,7,7-Tetramethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)-2,3,6,7-tetrahydro spiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one,

1'-(2,4-Difluorobenzyl)-2,2,7,7-tetramethyl-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-

10 5,3'-indolin]-2'-one,

1'-(4-Fluorobenzyl)-2,2,7,7-tetramethyl-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one,

3-((2,2,7,7-Tetramethyl-2'-oxo-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-1'-yl)methyl)benzonitrile,

15 2,2,7,7-Tetramethyl-1'-(4-(trifluoromethoxy)benzyl)-2,3,6,7-tetrahydrospiro [furo[3,2-g]chromene-5,3'-indolin]-2'-one,

2,2,7,7-Tetramethyl-1'-(pyridin-2-ylmethyl)-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one,

20 2-(2,2,7,7-Tetramethyl-2'-oxo-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-1'-yl)acetonitrile,

7,7-Dimethyl-2,3,6,7-tetrahydrospiro[furo[3,2-g]chromene-5,3'-indolin]-2'-one,

7,7-Dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)-2,3,6,7-tetrahydro spiro[furo [3,2-g]chromene-5,3'-indolin]-2'-one,

2',2'-Dimethyl-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g] chromen]-2-one,

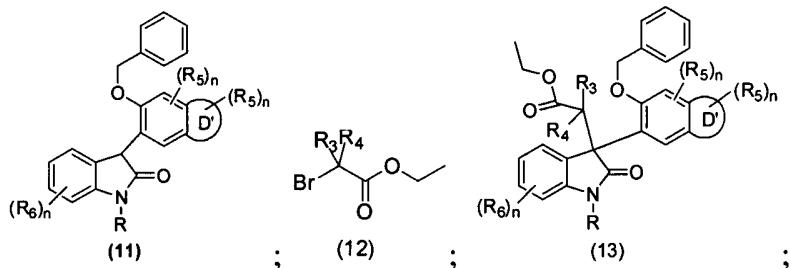
- 2',2'-Dimethyl-1-((5-(trifluoromethyl)furan-2-yl)methyl)-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g]chromen]-2-one,
- 2',2',6',6'-Tetramethyl-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano [3,2-g]chromen]-2-one,
- 5 2',2',6',6'-Tetramethyl-1-((5-(trifluoromethyl)furan-2-yl)methyl)-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g]chromen]-2-one,
- 2',2',8',8'-Tetramethyl-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g]chromen]-2-one,
- 10 2',2',8',8'-Tetramethyl-1-((5-(trifluoromethyl)furan-2-yl)methyl)-3',6',7',8'-tetrahydro-2'H-spiro[indoline-3,4'-pyrano[3,2-g]chromen]-2-one,
- 7-Methoxy-2,2-dimethylspiro[chroman-4,3'-indolin]-2'-one,
- 7-Methoxy-2,2-dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro [chroman-4,3'-indolin]-2'-one,
- 15 6-Fluoro-7-methoxy-2, 2-dimethyl-1'-(5-(trifluoromethyl) furan-2-yl) methyl) spiro [chroman-4, 3'-indolin]-2'-one,
- (6)-Ethyl-1'-(4-fluorobenzyl)-2'-oxo-6,7-dihydrospiro[[1,3]dioxolo[4,5-g] chromene-8,3'-indoline]-6-carboxylate,
- (6)-1'-(4-Fluorobenzyl)-2'-oxo-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene -8,3'-indoline]-6-carboxylic acid,
- 20 (6)-1'-(4-Fluorobenzyl)-6-(morpholine-4-carbonyl)-6,7-dihydrospiro[[1,3] dioxolo [4,5-g]chromene-8,3'-indolin]-2'-one,
- 6,6-Dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one,
- 6,6-Dimethyl-1'-(5-(trifluoromethyl)furan-2-yl)methyl)-6,7-dihydro spiro[[1,3] dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one,
- 25 1'-Benzyl-6,6-dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-2'-one,

- 1'-Benzyl-6,6-dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indoline],
6,6-Dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indoline],
(6,6-Dimethyl-6,7-dihydrospiro[[1,3]dioxolo[4,5-g]chromene-8,3'-indolin]-1'-yl) (4-fluorophenyl)methanone, and
- 5 1-((2,2-Dimethyl-2'-oxo-1'-(5-(trifluoromethyl)furan-2-yl)methyl)spiro[chroman-4,3'-indolin]-7-yl)oxy)cyclobutanecarboxamide
or a pharmaceutically acceptable salt thereof.
24. A pharmaceutical composition comprising one or more compounds of Formula (I) according to claim 1, and one or more pharmaceutically acceptable excipients.
- 10 25. A method of treating, preventing, managing and/or lessening diseases or disorders, syndromes or conditions associated with the modulation of voltage-gated sodium channels (VGSC) function in a subject in need thereof wherein the method comprises administering to the subject a therapeutically effective amount of a compound of claim 1 or 2 or a pharmaceutically acceptable salt thereof.
- 15 26. The method of claim 25, wherein the diseases, disorders, syndromes or conditions associated with the modulation of voltage-gated sodium channel (VGSC) functions are selected from the group consisting of pain and erythromyalgia.
- 20 27. The method of claim 25, wherein the diseases, disorders, syndromes or conditions associated with the modulation of voltage-gated sodium channel (VGSC) functions are selected from the group consisting of neurological disorders, cardiovascular conditions, neuromuscular conditions, multiple sclerosis, cancer, pruritis, or benign prostatic hyperplasia (BPH).
28. The method of claim 26, wherein the pain is neuropathic pain.
29. The method of claim 26, wherein the pain is inflammatory pain.
- 25 30. The method of claim 25, wherein the diseases, disorders, syndromes or conditions associated with the modulation of voltage-gated sodium channel (VGSC) function are

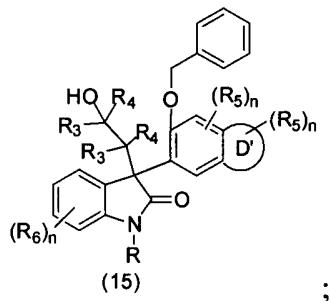
selected from the group consisting of postoperative pain, arthritis pain, osteoarthritis pain, pain associated with cancer including chemotherapy pain, neuropathic pain secondary to metastatic inflammation, neuralgic, orofacial pain, burn pain, somatic pain, dental pain, sciatica pain, intestinal obstruction pain, visceral pain, colicky pain, myofacial pain, trauma
5 pain, labour pain, trigeminal neuralgia, glossopharyngeal neuralgia, adiposis dolorosa, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflux sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, pain following stroke, thalamic lesions, radiculopathy, chronic headache, migraine pain, familial hemiplegic migraine, conditions associated with cephalic pain, sinus headache,
10 tension headache, cardiac pain arising from an ischemic myocardium, pain following stroke, neuropathy secondary to metastatic inflammation, pain due to connective tissue damage, and other forms of neuralgic, neuropathic, and idiopathic pain syndromes in a subject in need thereof comprising administering to the subject with a therapeutically effective amount.

31. A process for the preparation of a compound of Formula (I), the process comprising:

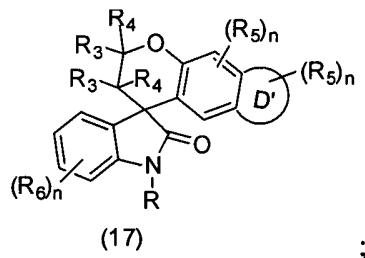
15 a) alkylating compound (11) with compound (12) to give compound (13)



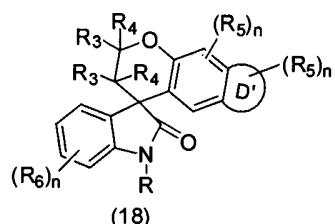
b) treating compound (13) from step a) with an appropriately substituted Grignard reagent to give compound (15)



- c) deprotecting the benzylic hydroxyl group of compound (15) from step b) followed by cyclisation to give compound (17)



- 5 d) deprotecting compound (17) from step c) and alkylating with R-L where L is leaving group to give compound (18)



32. The compound of claim 1, which is selected from Example-150 to Example-190 or its pharmaceutically acceptable salt there of.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2011/002392

A. CLASSIFICATION OF SUBJECT MATTER

| | | | | | |
|------|------------|------------|------------|------------|-----------|
| INV. | C07D491/10 | C07D491/20 | C07D491/22 | A61K31/407 | A61P25/00 |
| | A61P29/00 | | | | |

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y | WO 2006/110917 A2 (XENON PHARMACEUTICALS INC [CA]; CHAFFEEV MIKHAIL [CA]; CHOWDHURY SULTAN) 19 October 2006 (2006-10-19) cited in the application page 384; claim 1 page 485; claim 53 ----- | 1-32 |
| A | WO 2008/046049 A1 (XENON PHARMACEUTICALS INC [CA]; CADIEUX JEAN-JACQUES [CA]; CHOWDHURY S) 17 April 2008 (2008-04-17) cited in the application page 159; claim 1 ----- | 1-32 |
| A | WO 2008/046084 A2 (XENON PHARMACEUTICALS INC [CA]; CHAFFEEV MIKHAIL [CA]; CHOWDHURY SULTAN) 17 April 2008 (2008-04-17) cited in the application page 233; claim 1 ----- | 1-32 |
| | | -/- |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 January 2012

Date of mailing of the international search report

27/01/2012

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Authorized officer

Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2011/002392

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| Y | WO 2008/046087 A2 (XENON PHARMACEUTICALS INC [CA]; CHOWDHURY SULTAN [CA]; FU JIANMIN [CA]) 17 April 2008 (2008-04-17) cited in the application page 105; claim 1 page 136; claim 28 ----- | 1-32 |
| Y | WO 2008/060789 A2 (XENON PHARMACEUTICALS INC [CA]; CHAFEEV MIKHAIL [CA]; CHOWDHURY SULTAN) 22 May 2008 (2008-05-22) cited in the application page 376; example 2 page 380; claim 1 ----- | 1-32 |
| Y | WO 2010/045197 A1 (XENON PHARMACEUTICALS INC [CA]; CHAFEEV MIKHAIL [CA]; CHOWDHURY SULTAN) 22 April 2010 (2010-04-22) cited in the application page 139; claim 1 page 151; claim 32 ----- | 1-32 |
| A | WO 2010/045251 A2 (XENON PHARMACEUTICALS INC [CA]; CHAFEEV MIKHAIL [CA]; CHOWDHURY SULTAN) 22 April 2010 (2010-04-22) cited in the application page 804; claim 1 ----- | 1-32 |
| Y | WO 2010/053998 A1 (XENON PHARMACEUTICALS INC [CA]; CHOWDHURY SULTAN [CA]; FU JIANMIN [CA]) 14 May 2010 (2010-05-14) cited in the application page 105; claim 1 page 134; claim 40 ----- | 1-32 |
| A | WO 2010/078307 A1 (XENON PHARMACEUTICALS INC [CA]; CADIEUX JEAN-JACQUES [CA]; CHAFEEV MIK) 8 July 2010 (2010-07-08) cited in the application page 82; claim 5 ----- | 1-32 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2011/002392

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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