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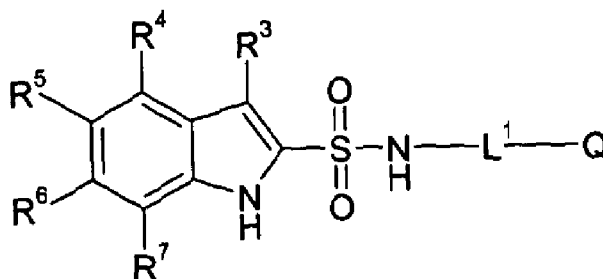
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(54) **Title:** N- (ARYLALKYL) - 1H- INDOLE- 2 - SULFONIC ACID AMIDE COMPOUNDS AND THEIR THERAPEUTIC USE AS CANNABINOID ALLOSTERIC MODULATORS



(57) **Abstract:** The present invention pertains generally to the field of therapeutic compounds. More specifically the present invention pertains to certain N-(arylalkyl)-1H-indole-2-sulfonic acid amide compounds that, *inter alia*, inhibit cannabinoid receptor signalling. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit cannabinoid receptor signalling; to treat disorders that are ameliorated by the inhibition of cannabinoid receptor signalling; to treat metabolic syndrome, type-2 diabetes, dyslipidaemia, obesity, eating disorders, cardiovascular diseases and disorders, and other conditions as described herein.

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N- (ARYLALKYL) - 1H- INDOLE- 2 - SULFONIC ACID AMIDE COMPOUNDS AND THEIR THERAPEUTIC USE AS CANNABINOID ALLOSTERIC MODULATORS

RELATED APPLICATION

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This application is related to United Kingdom (GB) patent application number 1103419.6 filed 28 February 2011, the contents of which are incorporated herein by reference in their entirety.

10

TECHNICAL FIELD

The present invention pertains generally to the field of therapeutic compounds. More specifically the present invention pertains to certain *N*-(arylalkyl)-1*H*-indole-2-sulfonic acid amide compounds that, *inter alia*, inhibit cannabinoid receptor signalling.

15

The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit cannabinoid receptor signalling; to treat disorders that are ameliorated by the inhibition of cannabinoid receptor signalling; to treat metabolic syndrome, type-2 diabetes, dyslipidaemia, obesity, eating disorders, cardiovascular diseases and disorders, and other conditions as described herein.

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BACKGROUND

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A number of publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

30

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

35

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

40

Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values

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are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

5 This disclosure includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

Physiological Role and Therapeutic Potential of Cannabinoid Receptors

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The endocannabinoid system encompasses a family of endogenous eicosanoid ligands, known as "endocannabinoids". Prominent examples include arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), both of which are synthesised on demand and are rapidly hydrolysed by the enzymes fatty acid amide hydrolase (FAAH) and monoacyl glycerol lipase (MAG lipase) respectively (see, e.g., Di Marzo, 2004).
15 Levels of the endocannabinoids are altered in certain disease states, where they have an autoprotective role (see, e.g., Pertwee, 2005). Mammalian tissues express at least two types of cannabinoid receptor, CB1 and CB2, both G protein coupled receptors (GPCR).

20

Cannabinoid receptors have been shown to play an important role in a many areas of human physiology and are treatments or potential treatments for a number of human medical conditions. Cannabinoid receptor agonists are already in use (e.g., Marinol®, Solvay; Nabilone®, Eli Lilly; Sativex®, GW Pharmaceuticals) as treatments for chemotherapy-induced nausea; for the control of pain and the treatment of spasticity in
25 patients with multiple sclerosis; and as appetite enhancers for patients with HIV / AIDS or undergoing chemotherapy.

30

Other studies have demonstrated a role in inflammation for both the CB1 and CB2 receptors and the ability of drugs which antagonize these receptors to be used as anti-inflammatory agents in the treatment of a number of disorders, including rheumatoid arthritis, psoriasis and inflammatory bowel disease (see, e.g., Croci *et al.*, 2003).

35

More recently there has been intense interest in the therapeutic properties of drugs which act as antagonists at CB1. These include SR141716A (Acomplia®, Sanofi-Aventis) and taranabant (Merck) for which clinical trials demonstrated efficacy in facilitation of weight loss, treatment of type-2 diabetes and cessation of smoking. The inventors have previously shown that similar compounds are able to prevent bone loss and therefore may be used in the treatment of disorders involving excessive or inappropriate bone loss, including osteoporosis, Paget's disease of bone, and bone cancers (see,
40 e.g., Greig *et al.*, 2004; Idris *et al.*, 2005).

The outlook was sufficiently promising that a number of drugs reached late stage clinical trials or were marketed. However, rejection by the FDA and eventual withdrawal in Europe of the first such drug to reach the market effectively terminated this approach, in

spite of the apparent therapeutic benefit. The primary problems were caused both by down-regulation of the receptor (due to the property of inverse agonism) leading to a reduction in efficacy and reversal of weight loss on cessation of treatment, and the CNS effects, which included suicidal thought, nausea and depression.

5

It has long been suggested that the toxicological issues associated with cannabinoid antagonism could be avoided if a drug only tuned down excessive receptor activation, rather than turned it off completely. This effect can be achieved by the use of allosteric modulators and the therapeutic potential of cannabinoid receptor modulation harnessed without the associated side effects of global activation or inhibition of the receptor (see, e.g., Di Marzo, 2008).

10

Advantages of Allosteric Modulation of Receptors

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It is now acknowledged that numerous GPCRs contain allosteric binding sites for endogenous and/or synthetic ligands, which are discrete from the agonist-binding site, which is known as the orthosteric site (the normal binding site for the endogenous ligand) (see, e.g., Christopoulos *et al.*, 2002). The binding of an allosteric modulator delivers a conformational change which impacts the affinity and/or efficacy of orthosteric ligands, thereby influencing the behaviour of a receptor and tuning the pre-existing actions of the endogenous ligands (see, e.g., May *et al.*, 2003). The action may increase or decrease the affinity of the endogenous ligand and its association or dissociation rate constant, and may either increase or decrease the intracellular signalling caused by the binding of the endogenous ligand. Thus, allosteric modulators may be defined as positive or negative according to whether they enhance or inhibit the transmission of signalling caused by the endogenous ligand binding.

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Allosteric modulators (acting at a site away from that which binds the normal ligand) play an increasingly prominent role in therapeutics, and are recognized particularly as a promising approach to achieving receptor selectivity.

30

Allosteric modulation has a number of advantages, including more subtle modulation or resetting of receptor activity than seen with intervention at the orthosteric site. As an allosteric modulator can only act in the presence of the natural ligand, it allows for drug therapy that more effectively maintains normal receptor function. That is, many synthetic drugs will remain bound to the receptor for a lengthy period, or have been designed to have improved metabolic stability (as required to reach the site of activity), thus causing an extended effect and either desensitization or continued and excessive activation of the receptor. On the other hand, the endogenous ligand is often rapidly broken down or recycled, causing only a transient activation or deactivation and thus avoiding such changes as receptor expression levels. Thus, allosteric modulation may be less likely to cause side-effects, as the pharmacological effects more closely model normal physiology. (See, e.g., Conn *et al.*, 2009; Gao *et al.*, 2006).

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Furthermore, the endogenous ligand is generally synthesized and released on demand at the site in which the action is required; rapid breakdown ensures that the effects on distant receptors sites in other tissue types is kept to a minimum. Likewise, in disease states, receptor over-activation or under-activation may be restricted to particular tissues and it is desirable only to modulate at these sites; altering receptor activity at other sites may lead in turn to undesirable harmful effects. Synthetic ligands tend to be delivered systemically and thus affect a variety of tissue types, but cannot usually be designed to have the same binding characteristics as the endogenous ligand, due to the requirements for metabolic and chemical stability. Thus, tuning of the signal from the endogenous ligand also has the advantage of introducing tissue selectivity and thus affecting only the tissues affected by the disease state, giving a more effective therapy.

Furthermore, with less evolutionary pressure and lower sequence conservation between receptor sub-types, the allosteric sites of many receptors offer greater opportunities for selectivity, whereas the orthosteric sites of many receptors can be too similar to allow a drug to distinguish between them (as they often must bind the same endogenous ligand, e.g., a neurotransmitter). An example of this has been the development of sub-type specific muscarinic acetylcholine receptor (M) and metabotropic glutamate receptor (mGluR) allosteric modulators, following repeated failure to achieve selectivity with orthosteric modulators. General reviews on the growing importance and promise of allosteric modulation can be found in, e.g., Conn *et al.*, 2009. Reviews regarding the potential of cannabinoids can be found in, e.g., Ross, 2007.

Furthermore, allosteric modulation may offer an approach to targeting the activities of orthosteric receptors which are regarded as “un-druggable”, in that the physiochemical characteristics of the binding site (the mixture of hydrophobic and polar groups lining the pocket) may be incompatible with the physicochemical attributes required of a drug with sufficient solubility, membrane permeability and metabolic stability to reach the site of action. In these cases, an allosteric site may be found which has better compatibility with drug-like substances.

Furthermore, allosteric modulation may offer an approach to targeting diseases in which receptor number has been reduced (e.g., Parkinson’s disease, in which the number dopaminergic neurons is diminished).

A number of receptors have been shown to be amenable to positive or negative allosteric modulation by small molecules, including the GABA (against which diazepam acts), adenosine, muscarinic and metabotropic glutamate receptors (see, e.g., Soudijn *et al.*, 2004; Gao *et al.*, 2006).

Recent reviews highlight the emerging lucrative drug discovery potential of developing positive and negative allosteric modulators of GPCRs (see, e.g., Wang *et al.*, 2009). Similarly, there are key advantages in targeting drugs to allosteric sites on the cannabinoid CB1 receptor: reduced side-effect profile; greater receptor-subtype

selectivity; reduced drug-induced alterations in receptor coupling mechanisms (see, e.g., Ross, 2007). In particular, allosteric modulators possess specific advantages when considering the treatment of multi-factorial syndromes, such as metabolic disorders (see, e.g., Wang *et al.*, 2009).

5

In 2005, the first evidence was published indicating that the cannabinoid CB1 receptor contains an allosteric binding site and compounds were identified that unexpectedly are allosteric enhancers of agonist binding affinity, but are functionally allosteric inhibitors of agonist signalling efficacy (see, e.g., Price *et al.*, 2005). Allosteric enhancers have the potential to treat anxiety, depression, multiple sclerosis, pain and other disorders in which cannabinoid activation has been shown to play a beneficial role; enhancers would be free of psychoactive side-effects associated with direct agonism of CB1. Allosteric inhibitors have the potential to treat metabolic syndrome (obesity, type-2 diabetes and associated conditions), drug addiction and other conditions in which excessive activation of the cannabinoid system has been implicated.

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Cannabinoid Allosteric Modulators and Greater Receptor-Subtype Selectivity

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Generating receptor ligands with high subtype-selectivity is often hampered by the large extent of sequence homology within the orthosteric binding domain across receptor subtypes (see, e.g., Rees, 2002). Whilst a number of ligands that are selective for the cannabinoid CB1 and CB2 receptor have been developed to date, issues of receptor subtype selectivity remain. A number of well-established cannabinoid receptor agonists and antagonists have affinity for an orphan receptor GPR55 and the TRPV1 channel (see, e.g., Ryberg *et al.*, 2007; Ross, 2003). Targeting the allosteric site on the CB1 receptor may be a key strategy for generation of highly subtype-specific compounds.

Allosteric Modulators and Reduced Side-Effect Profile

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There is ample evidence that the levels of endocannabinoids are increased in both physiological and pathophysiological situations, in which an autoprotective action of the endocannabinoids has been also implicated (see, e.g., Pertwee, 2005).

35

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Hypothetically, positive allosteric modulators (allosteric enhancers) would selectively magnify this autoprotective effect, but have no effect on CB1 receptors that are not bound by endocannabinoid thus avoiding global CNS effects. By triggering activation of the endocannabinoid system without causing the unwanted psychotropic effects, positive allosteric modulation of the CB1 receptor would signify a nexus in cannabinoid research. Proof of principle for the concept that enhancing endocannabinoid signalling is a beneficial therapeutic strategy can be found in the effects of inhibitors of the enzymes responsible for the rapid intracellular hydrolysis of anandamide and 2AG. FAAH inhibitors are anxiolytic and antidepressant and both FAAH and MAG lipase (MAGL) inhibitors are antinociceptive; neither displays the psychoactive effects that are characteristic of direct CB1 receptor agonism (see, e.g., Cravatt *et al.*, 2004;

Piomelli *et al.*, 2006; Guindon *et al.*, 2007). Allosteric enhancement of the actions of anandamide and 2AG may be preferable to the global increased levels of endocannabinoid associated with inhibition of FAAH or MAG lipase respectively. Positive allosteric modulators (PAMs) would thereby afford a strategy which specifically targets known CB1 receptor signalling. In contrast, inhibition of the enzymatic breakdown of the endocannabinoids may potentially augment signalling associated with additional putative receptor targets for these eicosanoids (e.g., GPR55), thus introducing potential unexpected side-effects. In addition, in the presence of FAAH or MAGL inhibitors the increased levels of endocannabinoids may lead to enhanced production of by-products of other metabolic pathways (e.g., COX2) again potentially introducing unexpected side-effects. The latter two issues would not be encountered with PAMs that specifically target the CB1 receptor.

As with all allosteric enhancers, CB1 allosteric enhancers have a safety advantage over agonists in that they are less prone to overdose or toxic effect; the maximum ceiling of activity is controlled by the natural amount of endogenous ligand already in existence. Thus, positive allosteric modulators of the CB1 receptor have the advantage that they would not be expected to cause the psychotropic effects seen with agonists; allosteric inhibitors (negative modulators) of the CB1 receptor have the advantage that they would not be expected to cause the nausea and depression seen with inverse agonists. In both cases, tissue selectivity and subtle tuning (rather than global activation or complete blockage) of receptor function is expected to give an outcome more resembling normal physiology, with fewer side-effects than intervention at the orthosteric site.

Therapeutic Indications for Cannabinoid Positive Allosteric Modulators

The side effects of anti-depressants and anxiolytics are frequently reported in the scientific literature and popular media. Moreover, their efficacy is often challenged, and there is therefore a huge requirement for better drugs. Neuropathic pain is also an underserved medical need, with NSAIDs and opioids often proving inadequate (e.g., for the treatment of multiple sclerosis). The endocannabinoids are one of the body's most important natural painkillers, released on demand as and when they are required. Currently available compounds (agonists) indiscriminately activate this system throughout the body, causing unacceptable psychotropic side effects. Positive allosteric modulation has the advantage of increasing endocannabinoid effects only at the site of release (e.g., in the spinal cord or at the site of inflammation), thus providing side-effect-free pain relief where required. Compounds which increase levels of endocannabinoids by preventing their breakdown (FAAH inhibitors) are being pursued by many pharmaceutical companies and are in Phase II clinical trials for the treatment of depression and anxiety and in Phase I clinical trials for neuropathic pain. However, these have a relatively indiscriminate action and, unlike positive allosteric modulators, are likely to still have undesired side-effects. The potential for modulation of the cannabinoid system for the treatment of pain has been extensively reviewed (see, e.g., Pertwee, 2007).

Therapeutic Indications for Cannabinoid Negative Allosteric Modulators

5 It has become clear over recent decades that lifestyle-related intervention is no longer sufficient for the control of obesity, a modern plague associated with many cardiovascular complications. The possibility of pharmacological assistance is being widely investigated, but safety concerns and poor efficacy have severely limited the number of drugs to reach the market.

10 As described previously, drugs which block cannabinoid receptor activation were expected to find widespread use for the treatment of obesity, addiction and metabolic syndrome (see, *e.g.*, Wadman, 2006). These were either withdrawn from the market, or clinical development halted, once the side-effects of depression and suicidal thought became apparent. These events demonstrate that centrally-acting cannabinoid inverse agonists could not be used safely for the treatment of obesity.

15 Alongside other health risks, obesity is associated with insulin resistance and impaired glucose tolerance; the endocannabinoid system is a powerful regulator of the overactive systemic metabolism seen in type-2 diabetes.

20 Cannabinoid antagonists have been proposed as useful therapeutic agents in this field, but again the lack of a safe agent has thus far prevented clinical exploitation. Centrally acting CB1 antagonists such as Acomplia® and taranabant were all expected to find use in the treatment of type-2 diabetes (see, *e.g.*, Patti, 2010). Whilst some of the beneficial effects of these agents on metabolism could be attributed to reduction in body fat, some
25 of the effects are believed to relate to their peripheral activity. This has been demonstrated by chronic treatment with Acomplia® that not only resulted in reduction of body weight gain, but also in significant improvement in lipid profiles (reduced triglycerides and cholesterol), and glucose tolerance in obese humans and rodents (see, *e.g.*, Bensaid *et al.*, 2003; Scheen *et al.*, 2006). Evidence suggests that the activation of
30 CB1 receptors in these peripheral tissues promotes lipogenesis, lipid storage, insulin secretion, glucagon secretion and adiponectin modulation (see, *e.g.*, Cota *et al.* 2003; Osei-Hyiaman *et al.*, 2005; Bermudez-Silva *et al.*, 2008). CB1 receptors and endocannabinoids are present in peripheral tissues involved in metabolic dysfunction associated with obesity, including adipose tissue, liver, skeletal muscle and pancreas,
35 and there is evidence for the upregulation of the endocannabinoid system in these tissues in experimental and human obesity (see, *e.g.*, Kunos *et al.*, 2009). Furthermore, a peripherally-restricted CB1 receptor antagonist does not affect behavioural responses in mice with genetic or diet-induced obesity, but it does cause weight-independent improvements in glucose homeostasis, fatty liver, and plasma lipid profile (see,
40 *e.g.*, Tam *et al.*, 2010). These findings confirm a prominent role for peripheral CB1 receptors on the modulation of metabolism (see, *e.g.*, Son *et al.*, 2010).

Taken together, these data indicate that use of either a CB1 receptor negative allosteric modulator or a peripherally-acting negative allosteric modulator (allosteric inhibitor) would

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be expected to be useful in therapy for, e.g., type-2 diabetes, but would be expected to lack the side-effects seen with centrally acting CB1 receptor antagonists that target the orthosteric site.

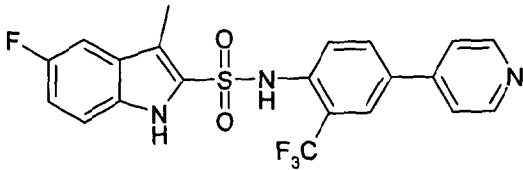
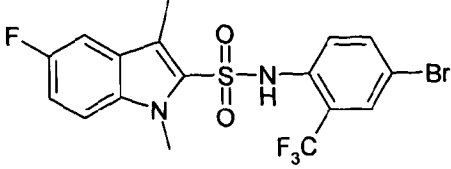
- 5 Without wishing to be bound by any particular theory, the inventors believe that the use of allosteric modulators will have the same therapeutic utility as currently proposed for orthosteric (direct) agonists, antagonists, partial agonists and inverse agonists, but with reduced side-effects. Without wishing to be bound by any particular theory, the inventors also believe that the compounds of the class described herein act as allosteric
 10 modulators of the cannabinoid receptors.

1H-Indole-2-Sulfonic Acid Amides

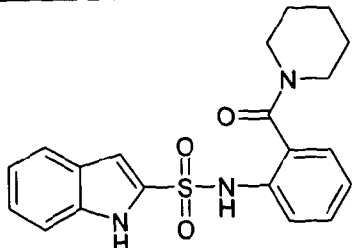
A number of 1H-indole-2-sulfonic acid amides have been described.

15

Banner et al, 2008, describes certain compounds, including the following compounds, which allegedly act as chymase inhibitors.

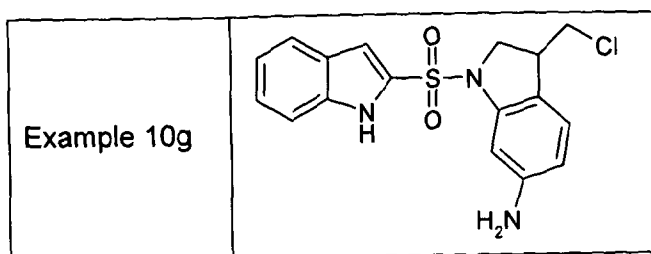
Example 29, page 38	
Example 30, page 42	

- 20 Allison et al., 2006, describes certain compounds, including the following compound, which allegedly act as cholecystokinin-2 receptor antagonists.

Example 36	
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- 25 Milbank et al., 1999, describes certain compounds, including the following compound, which allegedly act as DNA alkylating agents.

- 9 -

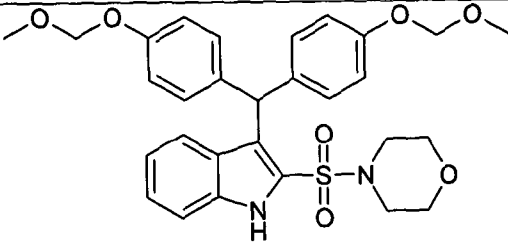
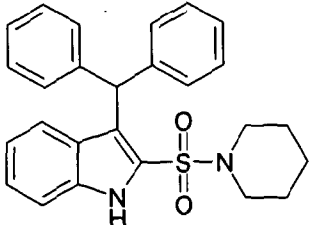
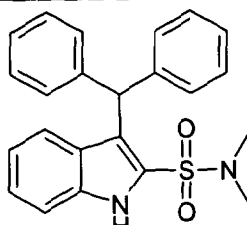


Kobayashi *et al.*, 2004, describes certain compounds, including the following compounds, which allegedly act as Factor Xa inhibiting anti-coagulants.

Reference Example 138, column 171	
Reference Example 228, column 196	
Example in Column 47	
Example in Column 48	
Example in Column 48	
Example in Column 48	

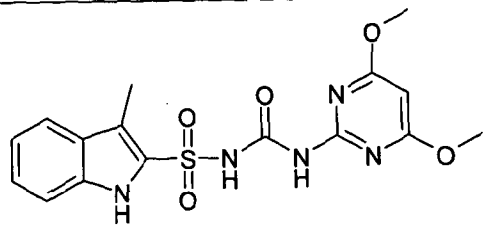
5

Machii *et al.*, 1996, describes certain compounds, including the following compounds, which allegedly are useful in the treatment of osteoporosis.

Example 246	
Example 263	
Example 265	

Zimmerman *et al.*, 1988, describes certain compounds, including the following compound, which allegedly are useful as herbicides.

5

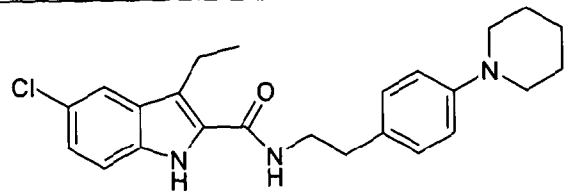
Example in Column 31	
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1H-Indole-2-Carboxylic Acid Amides as Cannabinoid Modulators

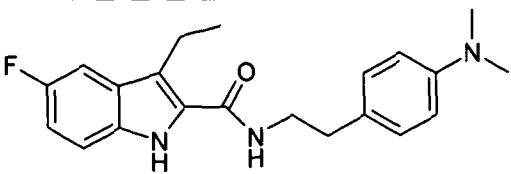
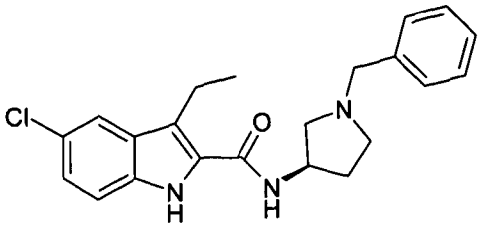
Some 1H-indole-2-carboxylic acid amides have been described as cannabinoid modulators.

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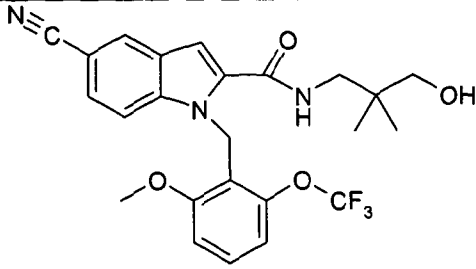
Price *et al.*, 2005, describes certain compounds, including the following compounds, which allegedly act as negative allosteric modulators.

Org 27569	
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- 11 -

Org 27759	
Org 29647	

Cowley *et al.*, 2011, describes certain compounds, including the following compound, which allegedly act as an antagonist of the CB1 receptor.

Compound 26i	
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The present inventors have identified a new a class of 1*H*-indole-2-sulfonic acid amides, as described herein, that address, for example, one or more of needs discussed above, and additionally have surprising and unexpected properties.

- 10 Without wishing to be bound to any particular theory, the inventors believe that the NISA compounds described herein have drug-like properties superior to those of previously described compounds for this indication, most especially in terms of retaining potency as negative allosteric modulators of the cannabinoid receptor, whilst improving physicochemical properties such as improved metabolic stability and peripheral
- 15 restriction. The NISA compounds described herein are sulfonamides which, in general comparison with amides, have improved metabolic stability, especially in acidic conditions such as the stomach. Furthermore, sulfonamides are more polar than amides, making them less likely to pass the blood-brain barrier (BBB). As a number of the side effects from exisiting drugs that target the cannabinoid system are centrally-mediated, drugs that
- 20 do not pass the blood-brain barrier (i.e., which are peripherally restricted) are less likely to show undesired side-effects. Brain permeability is closely related to topographical polar surface area (tPSA). As a general rule, drugs with tPSA of $< 60 \text{ \AA}^2$ (0.6 nm^2) will pass through the BBB, while those with tPSA of $> 60 - 70 \text{ \AA}^2$ ($0.6 - 0.7 \text{ nm}^2$) become progressively less likely to pass through the BBB as tPSA further increases. (See,
- 25 *e.g.*, Kerns *et al.*, 2008). Replacement of amide for sulfonamide increases the tPSA by $17 \text{ \AA}^2$ (0.17 nm^2). Consequently, the NISA compounds are much more likely to remain restricted to the periphery than, *e.g.*, structurally similar amide compounds. Furthermore,

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sulfonamides (being more polar than amides) are expected to have higher solubility than amides. If a drug is to show oral activity, it must first be dissolved, to permit absorption from the gastrointestinal tract.

- 5 Furthermore, the NISA compounds described herein may also have other advantages over the corresponding amide compounds because of their mode of action: the amide ("Org") compounds described by Price *et al.*, 2005, all increase the binding of the endogenous ligand, but reduce the efficacy (i.e., the ligand binds more strongly but activation of the signalling pathway is reduced). In contrast, the NISA compounds
- 10 described herein do not increase the binding of the endogenous ligand but do reduce the efficacy (i.e., the ligand binding is *not* increased, but activation of the signalling pathway *is* reduced). This not only demonstrates clear differences between the NISA compounds described herein and the corresponding amide compounds, but may also provide a therapeutic advantage, for example, to provide compounds which are more effective for
- 15 long-term use, for example, by avoiding potential changes in receptor expression levels caused by desensitisation.

SUMMARY OF THE INVENTION

One aspect of the invention pertains to certain *N*-(arylalkyl)-1*H*-indole-2-sulfonic acid amide compounds (referred to herein as NISA compounds), as described herein.

5

Another aspect of the invention pertains to a composition (e.g., a pharmaceutical composition) comprising an NISA compound, as described herein, and a pharmaceutically acceptable carrier or diluent.

10 Another aspect of the invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising the step of mixing an NISA compound, as described herein, and a pharmaceutically acceptable carrier or diluent.

15 Another aspect of the present invention pertains to a method of inhibiting cannabinoid receptor (e.g., CB1) signalling function (e.g., in a cell), *in vitro* or *in vivo*, comprising contacting the cell with an effective amount of an NISA compound, as described herein.

20 Another aspect of the present invention pertains to a method of treatment comprising administering to a subject in need of treatment a therapeutically-effective amount of an NISA compound, as described herein, preferably in the form of a pharmaceutical composition.

25 Another aspect of the present invention pertains to an NISA compound as described herein for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to use of an NISA compound, as described herein, in the manufacture of a medicament for use in treatment.

30 In one embodiment, the treatment is treatment of a disorder that is ameliorated by the inhibition of cannabinoid receptor (e.g., CB1) signalling.

In one embodiment, the treatment is treatment of metabolic syndrome.

35 In one embodiment, the treatment is treatment of type-2 diabetes.

In one embodiment, the treatment is treatment of dyslipidaemia

In one embodiment, the treatment is treatment of obesity.

40 In one embodiment, the treatment is treatment of an eating disorder.

In one embodiment, the treatment is treatment of a cardiovascular disease or disorder.

- 14 -

In one embodiment, the treatment is treatment of a cardiovascular disease or disorder *associated with cardiovascular disease*.

5 In one embodiment, the treatment is treatment of hypertension, congestive heart failure, cardiac hypertrophy, peripheral artery disease, atherosclerosis, stroke, kidney disease, myocardial infarction, steatohepatitis, or cardiotoxicity associated with chemotherapy.

10 In one embodiment, the treatment is treatment of a non-alcoholic fatty liver disease (NAFLD) associated with metabolic syndrome.

In one embodiment, the treatment is treatment of a disease or disorder characterised by an addiction component.

15 In one embodiment, the treatment is treatment of addiction or withdrawal, for example, smoking addiction and/or smoking withdrawal, alcohol addiction and/or alcohol withdrawal, drug addiction and/or drug withdrawal.

In one embodiment, the treatment is smoking cessation therapy.

20 In one embodiment, the treatment is treatment of a bone disease or disorder.

In one embodiment, the treatment is treatment of osteoporosis, Paget's disease of bone, or bone related cancer.

25 In one embodiment, the treatment is treatment of breast cancer.

In one embodiment, the treatment is treatment of a disease or disorder characterised by an inflammatory or autoimmune component.

30 In one embodiment, the treatment is treatment of rheumatoid arthritis, inflammatory bowel disease, or psoriasis.

In one embodiment, the treatment is treatment of a psychiatric disease or disorder.

35 In one embodiment, the treatment is treatment of anxiety, mania, or schizophrenia.

In one embodiment, the treatment is treatment of a disease or disorder characterised by impairment of memory and/or loss of cognitive function.

40 In one embodiment, the treatment is treatment of memory impairment, loss of cognitive function, Parkinson's disease, Alzheimer's disease, or dementia.

- 15 -

Another aspect of the present invention pertains to a kit comprising (a) an NISA compound, as described herein, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the compound.

5

Another aspect of the present invention pertains to an NISA compound *obtainable* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

- 10 Another aspect of the present invention pertains to an NISA compound *obtained* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

- 15 Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

- 20 As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

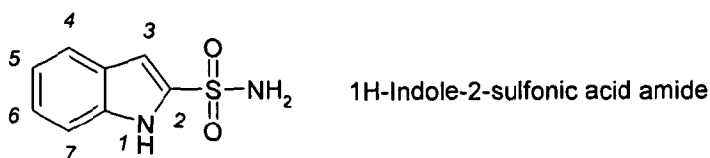
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph illustrating the data described below, and shows the effects of ABD1012 in inhibiting the maximum level of stimulation (E_{max}) caused by the cannabinoid agonist CP55,940, as measured using the β -arrestin assay. The graph shows that ABD1012 is a highly potent inhibitor of cannabinoid receptor signalling and reduces the level of stimulation (E_{max} , efficacy) by 50% at a concentration of close to 100 nM (IC_{50} = 120 nM, as calculated by GraphPad Prism). Each symbol represents the mean percentage of stimulation above basal $\pm$ S.E.M ($n = 3$).

Figure 2 a graph illustrating the data described below, and shows the effects of CP55940, ORG27569 and ABD1027 on the specific binding of [^{3} H]CP55940 in the equilibrium binding assay using mouse brain membranes. Each symbol represents the mean percentage of specific binding $\pm$ SEM. The graph shows that CP55940 causes a reduction in [^{3} H]CP55940 binding, as would be expected, causing 100% displacement of the radioligand from the orthosteric site. In contrast, ORG27569 causes an increase in [^{3} H]CP55940 binding, although it inhibits agonist signalling in functional studies, making ORG27569 an enhancer of agonist binding affinity but an inhibitor of agonist signalling efficacy (see, e.g., Price *et al.*, 2005). The graph also demonstrates that ABD1027 does not affect [^{3} H]CP55940 binding and thus does not bind to the orthosteric site, although it inhibits agonist signalling in functional studies (as shown in biological study 1). An allosteric inhibitor which has little or no effect on agonist affinity, such as ABD1027, may represent a compound with less complex pharmacology, which may be more effective in vivo: for example use of a compound which increases ligand binding, such as ORG27569 may lead to a reduction in the levels of receptor expression and a consequent reduction in compound efficacy over time or a departure from normal pharmacology.

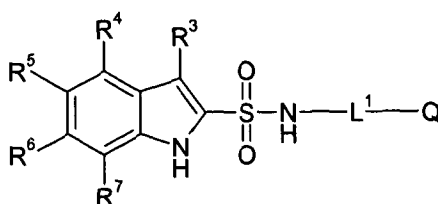
DETAILED DESCRIPTION OF THE INVENTIONCompounds

- 5 One aspect of the present invention relates to certain compounds which are structurally related to 1*H*-indole-2-sulfonic acid amide.



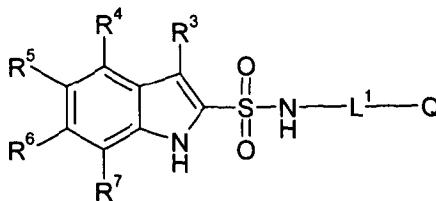
- 10 More particularly, the present invention relates to certain *N*-(arylalkyl)-1*H*-indole-2-sulfonic acid amides.

Thus, one aspect of the present invention pertains to compounds selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates,
 15 and solvates thereof, wherein -Q, -L¹-, -R³-, -R⁴-, -R⁵-, -R⁶-, and -R⁷ are as defined herein (for convenience, collectively referred to herein as "*N*-(arylalkyl)-1*H*-indole-2-sulfonic acid amide compounds" or "NISA compounds"):



- 20 Some embodiments of the invention include the following:

(1) A compound selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



- 25 wherein:

-Q is independently -Q¹ or -Q²;

- 30 -Q¹ is independently -Q^{1C} or -Q^{1H};

- 18 -

-Q^{1C} is independently phenyl or naphthyl, and is optionally substituted with one or more substituents -W¹;

5 -Q^{1H} is independently pyridyl, and is optionally substituted with one or more substituents -W¹;

-Q² is independently -Q^{2A}-Q^{2B};

10 -Q^{2A}- is independently -Q^{2AC}- or -Q^{2AH}-;

-Q^{2AC}- is independently phenylene or naphth-di-yl, and is optionally substituted with one or more substituents -W²;

15 -Q^{2AH}- is independently pyrid-di-yl, and is optionally substituted with one or more substituents -W²;

-Q^{2B} is independently -Q^{2BC} or -Q^{2BH};

20 -Q^{2BC} is independently phenyl or naphthyl, and is optionally substituted with one or more substituents -W¹;

-Q^{2BH} is independently C₅₋₆heteroaryl or C₉₋₁₀heteroaryl, and is optionally substituted with one or more substituents -W¹;

25 each -W¹ is independently:

30 -F, -Cl, -Br, -I,
 -R^{W1}, -R^{W2},
 -R^{W4}, -R^{W5},
 -OH, -OR^W,
 -CF₃, -OCF₃,
 -CN, -NO₂,
 -SH, -SR^W,
 -NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
 35 -C(=O)R^W,
 -C(=O)OH, -C(=O)OR^W,
 -NHC(=O)R^W, -NR^{WC}(=O)R^W,
 -C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
 -S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2},
 40 -NHS(=O)₂R^W, -NR^{WS}(=O)₂R^W,
 -S(=O)₂R^W, or -S(=O)₂CF₃;

each $-W^2$ is independently:

- 5
- F, -Cl, -Br, -I,
 - $-R^{W1}$, $-R^{W2}$,
 - $-R^{W4}$, $-R^{W5}$,
 - OH, $-OR^W$,
 - $-CF_3$, $-OCF_3$,
 - CN, $-NO_2$,
 - SH, $-SR^W$,
 - 10 $-NH_2$, $-NHR^W$, $-NR^W_2$, $-NR^{WN1}R^{WN2}$,
 - $-C(=O)R^W$,
 - $-C(=O)OH$, $-C(=O)OR^W$,
 - $-NHC(=O)R^W$, $-NR^WC(=O)R^W$,
 - $-C(=O)NH_2$, $-C(=O)NHR^W$, $-C(=O)NR^W_2$, $-C(=O)NR^{WN1}R^{WN2}$,
 - 15 $-S(=O)_2NH_2$, $-S(=O)_2NHR^W$, $-S(=O)_2NR^W_2$, $-S(=O)_2NR^{WN1}R^{WN2}$,
 - $-NHS(=O)_2R^W$, $-NR^WS(=O)_2R^W$,
 - $-S(=O)_2R^W$, or $-S(=O)_2CF_3$;

each $-R^W$ is independently $-R^{W1}$, $-R^{W2}$, or $-R^{W3}$;

20

each $-R^{W1}$ is independently saturated aliphatic C_{1-4} alkyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, $-CF_3$, -OH, $-OR^{W11}$, and $-OCF_3$, wherein each $-R^{W11}$ is independently saturated aliphatic C_{1-4} alkyl;

25

each $-R^{W2}$ is independently saturated C_{3-6} cycloalkyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, $-R^{W22}$, $-CF_3$, -OH, $-OR^{W22}$, $-OCF_3$, -CN, and $-NO_2$, wherein each $-R^{W22}$ is independently saturated aliphatic C_{1-4} alkyl;

30

each $-R^{W3}$ is independently phenyl or benzyl, and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, $-R^{W33}$, $-CF_3$, -OH, $-OR^{W33}$, $-OCF_3$, -CN, and $-NO_2$, wherein each $-R^{W33}$ is independently saturated aliphatic C_{1-4} alkyl;

35

each $-R^{W4}$ is independently aliphatic C_{2-6} alkenyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, $-CF_3$, -OH, $-OR^{W44}$, and $-OCF_3$, wherein each $-R^{W44}$ is independently saturated aliphatic C_{1-4} alkyl;

40

each $-R^{W5}$ is independently aliphatic C_{2-6} alkynyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, $-CF_3$, -OH, $-OR^{W55}$, and $-OCF_3$, wherein each $-R^{W55}$ is independently saturated aliphatic C_{1-4} alkyl;

each $-NR^{WN1}R^{WN2}$ is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is optionally substituted with one or more substituents selected from: $-R^{WN3}$, $-C(=O)R^{WN3}$, and $-S(=O)_2R^{WN3}$, wherein each $-R^{WN3}$ is independently saturated aliphatic C_{1-4} alkyl;

- 20 -

-L¹- is independently saturated aliphatic C₁₋₄alkylene, and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^L, and -OCF₃, wherein each -R^L is independently saturated aliphatic C₁₋₄alkyl;

5

-R³ is independently -H or -R^{3A};

-R⁴ is independently -H or -R^{4A};

-R⁵ is independently -H or -R^{5A};

-R⁶ is independently -H or -R^{6A};

10

-R⁷ is independently -H or -R^{7A};

each of -R^{3A}, -R^{4A}, -R^{5A}, -R^{6A}, and -R^{7A} is independently:

15

-F, -Cl, -Br, -I,

-R^{A1}, -R^{A2}, -R^{A3},

-R^{A4}, -R^{A5},

-OH, -OR^A,

-CF₃, -OCF₃,

-CN, -NO₂,

20

-SH, -SR^A,

-NH₂, -NHR^A, -NR^A₂, -NR^{AN1}R^{AN2},

-NHC(=O)R^A, -NR^AC(=O)R^A,

-C(=O)R^A,

-C(=O)OH, -C(=O)OR^A,

25

-C(=O)NH₂, -C(=O)NHR^A, -C(=O)NR^A₂, -C(=O)NR^{AN1}R^{AN2},

-S(=O)₂R^A, -S(=O)₂CF₃,

-S(=O)₂NH₂, -S(=O)₂NHR^A, -S(=O)₂NR^A₂, -S(=O)₂NR^{AN1}R^{AN2},

-NHS(=O)₂R^A, or -NR^AS(=O)₂R^A;

30

each -R^A is independently -R^{A1}, -R^{A2}, or -R^{A3};

each -R^{A1} is independently saturated aliphatic C₁₋₄alkyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^{A11}, and -OCF₃, wherein each -R^{A11} is independently saturated aliphatic C₁₋₄alkyl;

35

each -R^{A2} is independently saturated C₃₋₆cycloalkyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -R^{A22}, -CF₃, -OH, -OR^{A22}, -OCF₃, -CN, and -NO₂, wherein each -R^{A22} is independently saturated aliphatic C₁₋₄alkyl;

40

each -R^{A3} is independently phenyl or benzyl, and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -R^{A33}, -CF₃, -OH, -OR^{A33}, -OCF₃, -CN, and -NO₂, wherein each -R^{A33} is independently saturated aliphatic C₁₋₄alkyl;

each $-R^{A4}$ is independently aliphatic C_{2-6} alkenyl and is optionally substituted with one or more substituents selected from: $-F$, $-Cl$, $-Br$, $-I$, $-CF_3$, $-OH$, $-OR^{A44}$, and $-OCF_3$, wherein each $-R^{A44}$ is independently saturated aliphatic C_{1-4} alkyl;

5 each $-R^{A5}$ is independently aliphatic C_{2-6} alkynyl and is optionally substituted with one or more substituents selected from: $-F$, $-Cl$, $-Br$, $-I$, $-CF_3$, $-OH$, $-OR^{A55}$, and $-OCF_3$, wherein each $-R^{A55}$ is independently saturated aliphatic C_{1-4} alkyl;

10 each $-NR^{AN1}R^{AN2}$ is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is optionally substituted with one or more substituents selected from: $-R^{AN3}$, $-C(=O)R^{AN3}$, and $-S(=O)_2R^{AN3}$, wherein each $-R^{AN3}$ is independently saturated aliphatic C_{1-4} alkyl.

15 For the avoidance of doubt, it is not intended that any two or more of $-R^3$, $-R^4$, $-R^5$, $-R^6$, and $-R^7$ together form a ring fused to the ring(s) to which they are attached. For example, it is not intended that $-R^3$ and $-R^4$ together form a ring fused to the rings to which they are attached. Similarly, it is not intended that $-R^4$ and $-R^5$ together form a ring fused to the ring to which they are attached.

20 The Group -Q-

(2) A compound according to (1), wherein $-Q$ is independently $-Q^1$.

25 (3) A compound according to (1), wherein $-Q$ is independently $-Q^2$.

The Group $-Q^1$ -

(4) A compound according to any one of (1) to (3), wherein $-Q^1$, if present, is independently $-Q^{1C}$.

30 (5) A compound according to any one of (1) to (3), wherein $-Q^1$, if present, is independently $-Q^{1H}$.

The Group $-Q^2$ -

35 (6) A compound according to any one of (1) to (5), wherein $-Q^{2A}$, if present, is independently $-Q^{2AC}$.

40 (7) A compound according to any one of (1) to (5), wherein $-Q^{2A}$, if present, is independently $-Q^{2AH}$.

(8) A compound according to any one of (1) to (5), wherein $-Q^{2B}$, if present, is independently $-Q^{2BC}$.

- 22 -

(9) A compound according to any one of (1) to (5), wherein $-Q^{2B}$, if present, is independently $-Q^{2BH}$.

5 (10) A compound according to any one of (1) to (5), wherein $-Q^2$, if present, is independently $-Q^{2AC}-Q^{2BC}$.

(11) A compound according to any one of (1) to (5), wherein $-Q^2$, if present, is independently $-Q^{2AC}-Q^{2BH}$.

10 (12) A compound according to any one of (1) to (5), wherein $-Q^2$, if present, is independently $-Q^{2AH}-Q^{2BC}$.

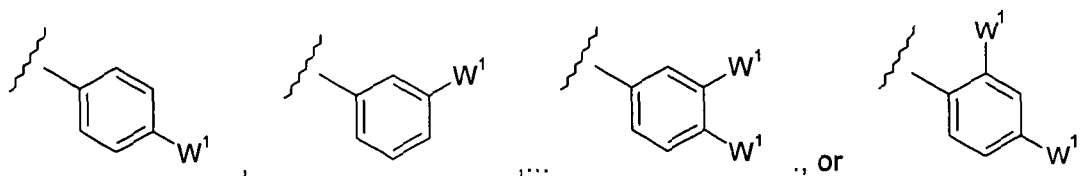
(13) A compound according to any one of (1) to (5), wherein $-Q^2$, if present, is independently $-Q^{2AH}-Q^{2BH}$.

15

The Group $-Q^{1C}$

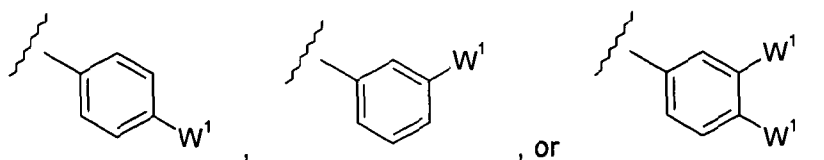
20 (14) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently phenyl, and is optionally substituted with one or more substituents $-W^1$.

(15) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently:

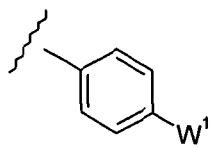


25

(16) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently:

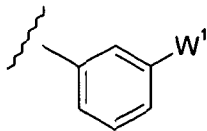


30 (17) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently:

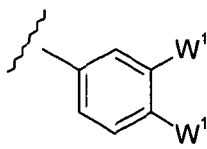


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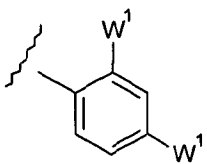
(18) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently:



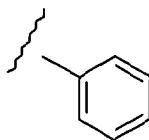
5 (19) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently:



10 (20) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently:



(21). A compound according to any one of (1) to (13), where $-Q^{1C}$, if present, is independently:



15

(22) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently naphthyl, and is optionally substituted with one or more substituents $-W^1$.

20 (23) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently naphth-1-yl, and is optionally substituted with one or more substituents $-W^1$.

25 (24) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently naphth-2-yl, and is optionally substituted with one or more substituents $-W^1$.

(25) A compound according to any one of (1) to (13), wherein $-Q^{1C}$, if present, is independently naphthyl.

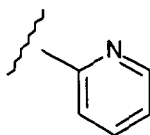
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The Group -Q^{1H}

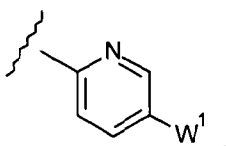
(26) A compound according to any one of (1) to (25), wherein -Q^{1H}, if present, is pyridin-2-yl, and is and is optionally substituted with one or more substituents -W¹.

5



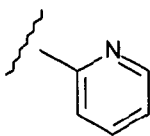
(27) A compound according to any one of (1) to (25), wherein -Q^{1H}, if present, is independently:

10



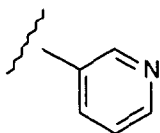
(28) A compound according to any one of (1) to (25), wherein -Q^{1H}, if present, is independently:

15



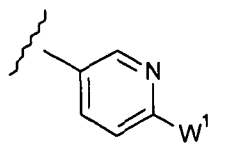
(29) A compound according to any one of (1) to (25), wherein -Q^{1H}, if present, is pyridin-3-yl, and is and is optionally substituted with one or more substituents -W¹.

20



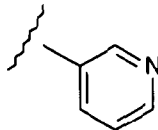
(30) A compound according to any one of (1) to (25), wherein -Q^{1H}, if present, is independently:

25

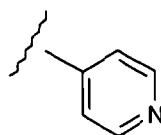


- 25 -

(31) A compound according to any one of (1) to (25), wherein $-Q^{1H}$, if present, is independently:



- 5 (32) A compound according to any one of (1) to (25), wherein $-Q^{1H}$, if present, is pyridin-4-yl, and is optionally substituted with one or more substituents $-W^1$.



- 10 (33) A compound according to any one of (1) to (25), wherein $-Q^{1H}$, if present, is pyridin-4-yl.

The Group $-Q^{2AC}$ -

15

(34) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently phenylene, and is optionally substituted with one or more substituents $-W^2$.

20

(35) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently para-phenylene or meta-phenylene, and is optionally substituted with one or more substituents $-W^2$.

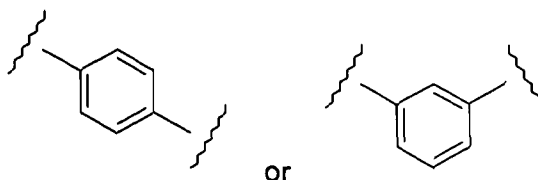
25

(36) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently para-phenylene, and is optionally substituted with one or more substituents $-W^2$.

30

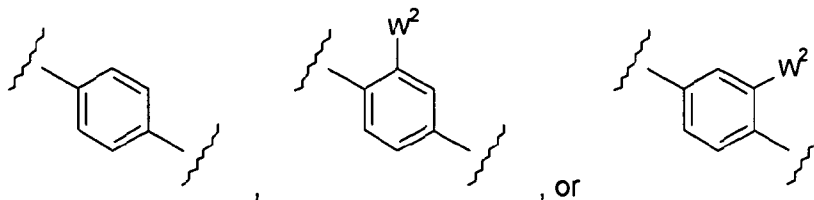
(37) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently meta-phenylene, and is optionally substituted with one or more substituents $-W^2$.

(38) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently:

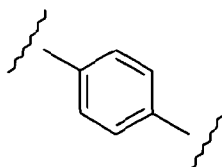


- 26 -

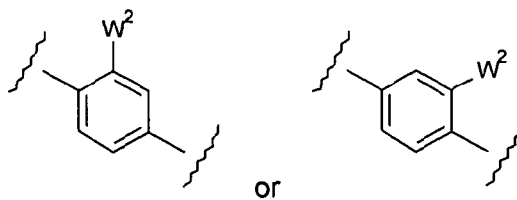
(39) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently:



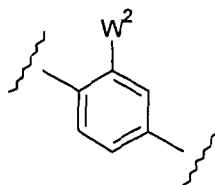
5 (40) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently:



10 (41) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently:

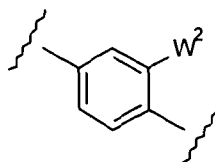


(42) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently:



15

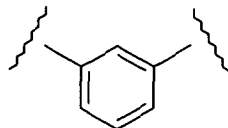
(43) A compound according to any one of (1) to (33), wherein $-Q^{2AC}$ -, if present, is independently:



20

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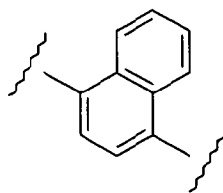
(44) A compound according to any one of (1) to (33), wherein $-Q^{2AC}-$, if present, is independently:



5 (45) A compound according to any one of (1) to (33), wherein $-Q^{2AC}-$, if present, is independently naphth-di-yl, and is optionally substituted with one or more substituents $-W^2$.

10 (46) A compound according to any one of (1) to (33), wherein $-Q^{2AC}-$, if present, is independently naphth-1,4-di-yl, and is optionally substituted with one or more substituents $-W^2$.

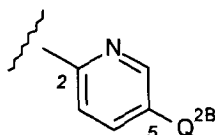
(47) A compound according to any one of (1) to (28), wherein $-Q^{2AC}-$, if present, is independently:



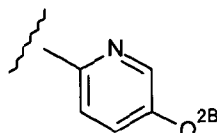
15

The Group $-Q^{2AH}-$

20 (48) A compound according to any one of (1) to (47), wherein $-Q^{2AH}-$, if present, is independently pyrid-2,5-di-yl, and is optionally substituted with one or more substituents $-W^2$.

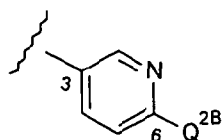


25 (49) A compound according to any one of (1) to (47), wherein $-Q^{2AH}-Q^{2B}$, if present, is independently:

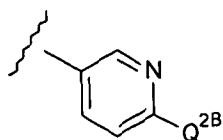


30 (50) A compound according to any one of (1) to (47), wherein $-Q^{2AH}-$, if present, is independently pyrid-3,6-di-yl, and is optionally substituted with one or more substituents $-W^2$.

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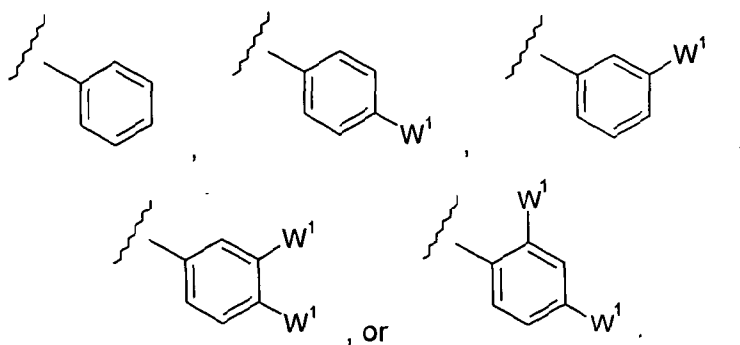
- (51) A compound according to any one of (1) to (47), wherein $-Q^{2AH}-Q^{2B}$, if present, is independently:



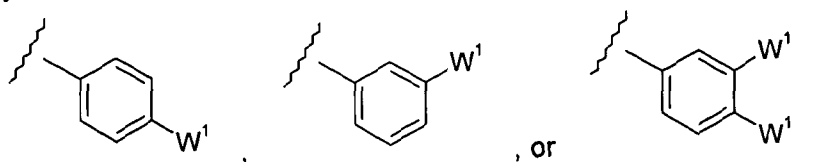
The Group $-Q^{2BC}$

- (52) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently phenyl, and is optionally substituted with one or more substituents $-W^1$.

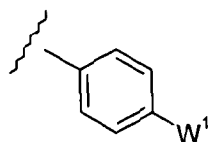
- (53) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently:



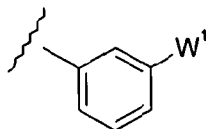
- (54) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently:



- (55) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently:

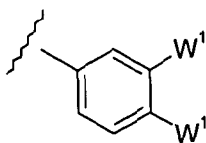


(56) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently:



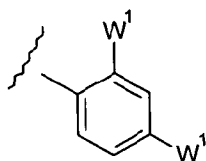
5

(57) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently:



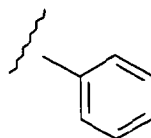
10

(58) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently:



15

(59) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently:



20

(60) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently naphthyl, and is optionally substituted with one or more substituents $-W^1$.

(61) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently naphth-1-yl, and is optionally substituted with one or more substituents $-W^1$.

25

(62) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently naphth-2-yl, and is optionally substituted with one or more substituents $-W^1$.

30

(63) A compound according to any one of (1) to (51), wherein $-Q^{2BC}$, if present, is independently naphthyl.

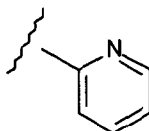
The Group -Q^{2BH}

- 5 (64) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzoimidazolyl, indazolyl, benzofuranyl, benzothienyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, quinoliny, isoquinoliny, cinnoliny, quinoxaliny, quinazoliny, or phthalazinyl, and is optionally substituted with one or more substituents -W¹.
- 10 (65) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently C₅₋₆heteroaryl, and is optionally substituted with one or more substituents -W¹.
- 15 (66) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, or pyrazinyl, and is optionally substituted with one or more substituents -W¹.
- 20 (67) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, or isothiazolyl, and is optionally substituted with one or more substituents -W¹.
- 25 (68) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently thienyl, pyridyl, pyridazinyl, pyrimidinyl, or pyrazinyl, and is optionally substituted with one or more substituents -W¹.
- 30 (69) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently pyridyl, pyridazinyl, pyrimidinyl, or pyrazinyl, and is optionally substituted with one or more substituents -W¹.
- 35 (70) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently thienyl, pyridyl, pyrimidinyl, or pyrazinyl, and is optionally substituted with one or more substituents -W¹.
- (71) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently pyridyl, pyrimidinyl, or pyrazinyl, and is optionally substituted with one or more substituents -W¹.
- 40 (72) A compound according to any one of (1) to (63), wherein -Q^{2BH}, if present, is independently pyridyl or thienyl, and is optionally substituted with one or more substituents -W¹.

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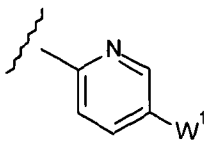
(73) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is independently pyridyl, and is optionally substituted with one or more substituents $-W^1$.

- 5 (74) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is pyridin-2-yl, and is and is optionally substituted with one or more substituents $-W^1$.



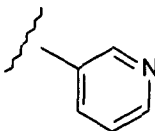
- 10 (75) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is pyridin-2-yl, and is and is optionally substituted with one or more substituents $-W^1$.

(76) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is independently:

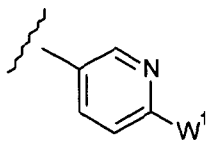


- 15 (77) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is pyridin-2-yl.

- 20 (78) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is pyridin-3-yl, and is and is optionally substituted with one or more substituents $-W^1$.



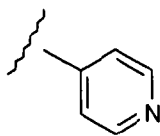
- 25 (79) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is independently:



- 30 (80) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is pyridin-3-yl.

(81) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is pyridin-4-yl, and is and is optionally substituted with one or more substituents $-W^1$.

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(82) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is pyridin-4-yl.

5

(83) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is independently thienyl, and is optionally substituted with one or more substituents $-W^1$.

10 (84) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is independently thienyl.

(85) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is independently pyrimidinyl, and is optionally substituted with one or more substituents $-W^1$.

15 (86) A compound according to any one of (1) to (63), wherein $-Q^{2BH}$, if present, is independently pyrimidinyl.

The Group $-W^1$

20 (87) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently:

- F, -Cl, -Br, -I,
- R^{W1}, -R^{W2},
- R^{W4}, -R^{W5},
- 25 -OH, -OR^W,
- SH, -SR^W,
- CF₃, -OCF₃,
- NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
- C(=O)R^W,
- 30 -C(=O)OH, -C(=O)OR^W,
- NHC(=O)R^W, -NR^WC(=O)R^W,
- C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
- S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2},
- NHS(=O)₂R^W, -NR^WS(=O)₂R^W, or
- 35 -S(=O)₂R^W.

(88) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently:

- F, -Cl, -Br, -I,
- 40 -R^{W1}, -R^{W2},
- OH, -OR^W,
- SH, -SR^W,

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- CF₃, -OCF₃,
 -NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
 -C(=O)OH, -C(=O)OR^W,
 -NHC(=O)R^W, -NR^WC(=O)R^W,
 5 -C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
 -S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2}, or
 -S(=O)₂R^W.

10 (89) A compound according to any one of (1) to (86), wherein each -W¹, if present, is independently:

- F, -Cl, -Br, -I,
 -R^{W1}, -R^{W2},
 -OH, -OR^W,
 -CF₃, -OCF₃,
 15 -NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
 -NHC(=O)R^W, -NR^WC(=O)R^W,
 -C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
 -S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2}, or
 -S(=O)₂R^W.

20

(90) A compound according to any one of (1) to (86), wherein each -W¹, if present, is independently:

- F, -Cl, -Br, -I,
 -R^{W1}, -R^{W2},
 25 -OH, -OR^W,
 -CF₃, -OCF₃,
 -NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
 -S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2},
 -NHS(=O)₂R^W, -NR^WS(=O)₂R^W, or
 30 -S(=O)₂R^W.

(91) A compound according to any one of (1) to (86), wherein each -W¹, if present, is independently:

- F, -Cl, -Br, -I,
 35 -R^{W1}, -R^{W2},
 -OH, -OR^W,
 -CF₃, -OCF₃,
 -NH₂, -NHR^W, -NR^W₂, or -NR^{WN1}R^{WN2}.

40 (92) A compound according to any one of (1) to (86), wherein each -W¹, if present, is independently -F, -Cl, -Br, -I, -R^{W1}, -CF₃, -OH, -OR^W, -OCF₃, -NH₂, -NHR^W, -NR^W₂, or -NR^{WN1}R^{WN2}.

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- (93) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently -F, -Cl, -Br, -I, $-R^{W1}$, $-CF_3$, -OH, $-OR^W$, or $-OCF_3$.
- 5 (94) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently -F, -Cl, -Br, -I, $-R^{W1}$, $-CF_3$, -OH, $-OR^{W1}$, or $-OCF_3$.
- (95) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently $-NH_2$, $-NHR^W$, $-NR^W_2$, or $-NR^{WN1}R^{WN2}$.
- 10 (96) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently -F, -Cl, -Br, -I, and $-R^{W1}$.
- (97) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently $-R^{W1}$.
- 15 (98) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently -F, -Cl, -Br, or -I.
- (99) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently -F.
- 20 (100) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently -Cl.
- (101) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently -OH or $-OR^W$.
- 25 (102) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently -OH.
- 30 (103) A compound according to any one of (1) to (86), wherein each $-W^1$, if present, is independently $-OR^W$.
- The Group $-W^2$
- 35 (104) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently:
- 40 -F, -Cl, -Br, -I,
 $-R^{W1}$, $-R^{W2}$,
 $-R^{W4}$, $-R^{W5}$,
 -OH, $-OR^W$,
 $-SR^W$,
 $-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^W$, $-NR^W_2$, $-NR^{WN1}R^{WN2}$,

- 35 -

- 5
- C(=O)R^W,
 - C(=O)OH, -C(=O)OR^W,
 - NHC(=O)R^W, -NR^WC(=O)R^W,
 - C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
 - S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2},
 - NHS(=O)₂R^W, -NR^WS(=O)₂R^W, or
 - S(=O)₂R^W.

10 (105) A compound according to any one of (1) to (103), wherein each -W², if present, is independently:

- 15
- F, -Cl, -Br, -I,
 - R^{W1}, -R^{W2},
 - OH, -OR^W,
 - CF₃, -OCF₃,
 - NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
 - C(=O)OH, -C(=O)OR^W,
 - NHC(=O)R^W, -NR^WC(=O)R^W,
 - C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
 - S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2},

20

 - NHS(=O)₂R^W, -NR^WS(=O)₂R^W, or
 - S(=O)₂R^W.

(106) A compound according to any one of (1) to (103), wherein each -W², if present, is independently:

- 25
- F, -Cl, -Br, -I,
 - R^{W1}, -R^{W2},
 - OH, -OR^W,
 - CF₃, -OCF₃,
 - NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},

30

 - NHC(=O)R^W, -NR^WC(=O)R^W,
 - C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
 - S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2}, or
 - S(=O)₂R^W.

35 (107) A compound according to any one of (1) to (103), wherein each -W², if present, is independently:

- 40
- F, -Cl, -Br, -I,
 - R^{W1}, -R^{W2},
 - OH, -OR^W,
 - CF₃, -OCF₃,
 - NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
 - S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2}, or
 - S(=O)₂R^W.

(108) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently:

- 5 -F, -Cl, -Br, -I,
 $-R^{W1}$, $-R^{W2}$,
 -OH, $-OR^W$,
 $-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^W$, $-NR^{W2}$, or $-NR^{WN1}R^{WN2}$.

10 (109) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -F, -Cl, -Br, -I, $-R^{W1}$, $-CF_3$, -OH, $-OR^W$, $-OCF_3$, $-NH_2$, $-NHR^W$, $-NR^{W2}$, or $-NR^{WN1}R^{WN2}$.

15 (110) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -F, -Cl, -Br, -I, $-R^{W1}$, $-CF_3$, -OH, $-OR^W$, or $-OCF_3$.

(111) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -F, -Cl, -Br, -I, $-R^{W1}$, $-CF_3$, -OH, $-OR^{W1}$, or $-OCF_3$.

20 (112) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently $-NH_2$, $-NHR^W$, $-NR^{W2}$, or $-NR^{WN1}R^{WN2}$.

(113) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -F, -Cl, -Br, -I, and $-R^{W1}$.

25 (114) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently $-R^{W1}$.

(115) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -F, -Cl, -Br, or -I.

30 (116) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -F.

35 (117) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -Cl.

(118) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -OH or $-OR^W$.

40 (119) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently -OH.

(120) A compound according to any one of (1) to (103), wherein each $-W^2$, if present, is independently $-OR^W$.

The Group -R^W

5 (121) A compound according to any one of (1) to (120), wherein each -R^W, if present, is independently -R^{W1} or -R^{W2}.

(122) A compound according to any one of (1) to (120), wherein each -R^W, if present, is independently -R^{W1} or -R^{W3}.

10 (123) A compound according to any one of (1) to (120), wherein each -R^W, if present, is independently -R^{W1}.

The Group -R^{W1}

15 (124) A compound according to any one of (1) to (123), wherein each -R^{W1}, if present, is independently saturated aliphatic C₁₋₄alkyl and is optionally substituted with one or more substituents selected from: -OH and -OR^{W11}, wherein each -R^{W11} is independently saturated aliphatic C₁₋₄alkyl.

20 (125) A compound according to any one of (1) to (123), wherein each -R^{W1}, if present, is independently saturated aliphatic C₁₋₄alkyl.

(126) A compound according to any one of (1) to (123), wherein each -R^{W1}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

25 (127) A compound according to any one of (1) to (123), wherein each -R^{W1}, if present, is independently -Me or -Et.

30 (128) A compound according to any one of (1) to (123), wherein each -R^{W1}, if present, is independently -Me.

The Group -R^{W11}

35 (129) A compound according to any one of (1) to (128), wherein each -R^{W11}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

(130) A compound according to any one of (1) to (128), wherein each -R^{W11}, if present, is independently -Me or -Et.

40 (131) A compound according to any one of (1) to (128), wherein each -R^{W11}, if present, is independently -Me.

The Group -R^{W2}

5 (132) A compound according to any one of (1) to (131), wherein each -R^{W2}, if present, is independently saturated C₃₋₆cycloalkyl and is optionally substituted with one or more substituents selected from: -R^{W22}, -OH, and -OR^{W22}, wherein each -R^{W22} is independently saturated aliphatic C₁₋₄alkyl.

10 (133) A compound according to any one of (1) to (131), wherein each -R^{W2}, if present, is independently saturated C₃₋₆cycloalkyl and is optionally substituted with one or more substituents selected from: -OH and -OR^{W22}, wherein each -R^{W22} is independently saturated aliphatic C₁₋₄alkyl.

15 (134) A compound according to any one of (1) to (131), wherein each -R^{W2}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(135) A compound according to any one of (1) to (131), wherein each -R^{W2}, if present, is independently cyclopropyl.

The Group -R^{W22}

20 (136) A compound according to any one of (1) to (135), wherein each -R^{W22}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

25 (137) A compound according to any one of (1) to (135), wherein each -R^{W22}, if present, is independently -Me or -Et.

(138) A compound according to any one of (1) to (135), wherein each -R^{W22}, if present, is independently -Me.

30 The Group -R^{W3}

35 (139) A compound according to any one of (1) to (138), wherein each -R^{W3}, if present, is independently phenyl or benzyl, and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -R^{W33}, -CF₃, -OH, -OR^{W33}, and -OCF₃, wherein each -R^{W33} is independently saturated aliphatic C₁₋₄alkyl.

(140) A compound according to any one of (1) to (138), wherein each -R^{W3}, if present, is independently phenyl or benzyl.

40 (141) A compound according to any one of (1) to (138), wherein each -R^{W3}, if present, is independently phenyl.

(142) A compound according to any one of (1) to (138), wherein each -R^{W3}, if present, is independently benzyl.

The Group -R^{W33}

5 (143) A compound according to any one of (1) to (142), wherein each -R^{W33}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

(144) A compound according to any one of (1) to (142), wherein each -R^{W33}, if present, is independently -Me or -Et.

10 (145) A compound according to any one of (1) to (142), wherein each -R^{W33}, if present, is independently -Me.

The Group -R^{W4}

15 (146) A compound according to any one of (1) to (145), wherein each -R^{W4}, if present, is independently aliphatic C₂₋₄alkenyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^{W44}, and -OCF₃, wherein each -R^{W44} is independently saturated aliphatic C₁₋₄alkyl.

20 (147) A compound according to any one of (1) to (145), wherein each -R^{W4}, if present, is independently aliphatic C₂₋₄alkenyl and is optionally substituted with one or more substituents selected from: -OH and -OR^{W44}, wherein each -R^{W44} is independently saturated aliphatic C₁₋₄alkyl.

25 (148) A compound according to any one of (1) to (145), wherein each -R^{W4}, if present, is independently aliphatic C₂₋₄alkenyl.

30 (149) A compound according to any one of (1) to (145), wherein each -R^{W4}, if present, is independently -CH=CH₂, -CH=CH-CH₃, or -CH=CH-CH₂-CH₃, and is optionally substituted with one or more substituents selected from: -OH and -OR^{W44}, wherein each -R^{W44} is independently saturated aliphatic C₁₋₄alkyl (e.g., -CH=CHOH).

35 (150) A compound according to any one of (1) to (145), wherein each -R^{W4}, if present, is independently -CH=CH₂, -CH=CH-CH₃, or -CH=CH-CH₂-CH₃.

The Group -R^{W44}

40 (151) A compound according to any one of (1) to (150), wherein each -R^{W44}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

(152) A compound according to any one of (1) to (150), wherein each -R^{W44}, if present, is independently -Me or -Et.

(153) A compound according to any one of (1) to (150), wherein each $-R^{W44}$, if present, is independently -Me.

The Group $-R^{W5}$

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(154) A compound according to any one of (1) to (153), wherein each $-R^{W5}$, if present, is independently aliphatic C_{2-4} alkynyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, $-CF_3$, -OH, $-OR^{W55}$, and $-OCF_3$, wherein each $-R^{W55}$ is independently saturated aliphatic C_{1-4} alkyl.

10

(155) A compound according to any one of (1) to (153), wherein each $-R^{W5}$, if present, is independently aliphatic C_{2-4} alkynyl and is optionally substituted with one or more substituents selected from: -OH and $-OR^{W55}$, wherein each $-R^{W55}$ is independently saturated aliphatic C_{1-4} alkyl.

15

(156) A compound according to any one of (1) to (153), wherein each $-R^{W5}$, if present, is independently aliphatic C_{2-4} alkynyl.

(157) A compound according to any one of (1) to (153), wherein each $-R^{W5}$, if present, is independently $-C\equiv CH$, $-C\equiv C-CH_3$, or $-C\equiv C-CH_2-CH_3$, and is optionally substituted with one or more substituents selected from: -OH and $-OR^{W55}$, wherein each $-R^{W55}$ is independently saturated aliphatic C_{1-4} alkyl.

20

(158) A compound according to any one of (1) to (153), wherein each $-R^{W5}$, if present, is independently $-C\equiv CH$, $-C\equiv C-CH_3$, or $-C\equiv C-CH_2-CH_3$.

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The Group $-R^{W55}$

(159) A compound according to any one of (1) to (158), wherein each $-R^{W55}$, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

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(160) A compound according to any one of (1) to (158), wherein each $-R^{W55}$, if present, is independently -Me or -Et.

(161) A compound according to any one of (1) to (158), wherein each $-R^{W55}$, if present, is independently -Me.

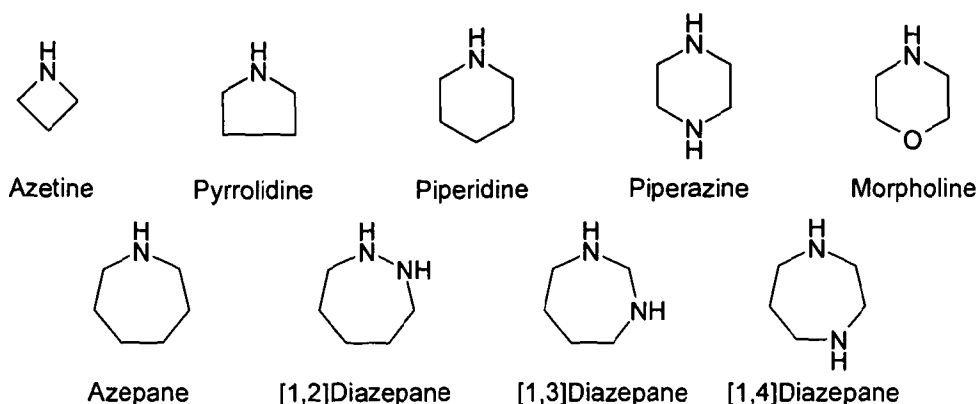
35

The Group $-NR^{WN1}R^{WN2}$

(162) A compound according to any one of (1) to (161), wherein each $-NR^{WN1}R^{WN2}$, if present, is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is optionally substituted with one or more substituents $-R^{WN3}$, wherein each $-R^{WN3}$ is independently saturated aliphatic C_{1-4} alkyl.

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- (163) A compound according to any one of (1) to (161), wherein each $-NR^{WN1}R^{WN2}$,
 5 if present, is independently pyrrolidino, piperidino, piperazino, morpholino, or azepano, and is optionally substituted with one or more substituents $-R^{WN3}$, wherein each $-R^{WN3}$ is independently saturated aliphatic C_{1-4} alkyl.
- (164) A compound according to any one of (1) to (161), wherein each $-NR^{WN1}R^{WN2}$,
 10 if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is optionally substituted with one or more substituents $-R^{WN3}$, wherein each $-R^{WN3}$ is independently saturated aliphatic C_{1-4} alkyl.
- (165) A compound according to any one of (1) to (161), wherein each $-NR^{WN1}R^{WN2}$,
 15 if present, is independently piperidino, piperazino, or morpholino, and is optionally substituted with one or more substituents $-R^{WN3}$, wherein each $-R^{WN3}$ is independently saturated aliphatic C_{1-4} alkyl.
- (166) A compound according to any one of (1) to (161), wherein each $-NR^{WN1}R^{WN2}$,
 20 if present, is independently piperidino, piperazino, or morpholino.
- (167) A compound according to any one of (1) to (161), wherein each $-NR^{WN1}R^{WN2}$,
 if present, is independently piperidino.
- (168) A compound according to any one of (1) to (161), wherein each $-NR^{WN1}R^{WN2}$,
 25 if present, is independently morpholino.

The Group $-R^{WN3}$

- (169) A compound according to any one of (1) to (168), wherein each $-R^{WN3}$, if present, is
 30 independently -Me, -Et, -nPr, -iPr, or -tBu.
- (170) A compound according to any one of (1) to (168), wherein each $-R^{WN3}$, if present, is
 35 independently -Me or -Et.

(171) A compound according to any one of (1) to (168), wherein each $-R^{WN3}$, if present, is independently -Me.

The Group $-L^1$ -

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(172) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently saturated aliphatic C_{1-4} alkylene.

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(173) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, or $-CH_2CH_2CH(CH_3)-$.

15

(174) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently $-CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(175) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

20

(176) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently $-CH_2-$, $-CH(CH_3)-$, or $-CH_2CH_2-$.

(177) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently $-CH_2-$ or $-CH_2CH_2-$.

25

(178) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently $-CH_2-$.

30

(179) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently $-CH(CH_3)-$.

(180) A compound according to any one of (1) to (171), wherein $-L^1$ - is independently $-CH_2CH_2-$.

The Group $-R^L$

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(181) A compound according to any one of (1) to (180), wherein each $-R^L$, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

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(182) A compound according to any one of (1) to (180), wherein each $-R^L$, if present, is independently -Me or -Et.

(183) A compound according to any one of (1) to (180), wherein each $-R^L$, if present, is independently -Me.

The Group -R³

(184) A compound according to any one of (1) to (183), wherein -R³ is independently -H.

- 5 (185) A compound according to any one of (1) to (183), wherein -R³ is independently -R^{3A}.

The Group -R⁴

- 10 (186) A compound according to any one of (1) to (185), wherein -R⁴ is independently -H.

(187) A compound according to any one of (1) to (185), wherein -R⁴ is independently -R^{4A}.

- 15 The Group -R⁵

(188) A compound according to any one of (1) to (187), wherein -R⁵ is independently -H.

- 20 (189) A compound according to any one of (1) to (187), wherein -R⁵ is independently -R^{5A}.

The Group -R⁶

- 25 (190) A compound according to any one of (1) to (189), wherein -R⁶ is independently -H.

(191) A compound according to any one of (1) to (189), wherein -R⁶ is independently -R^{6A}.

The Group -R⁷

- 30 (192) A compound according to any one of (1) to (191), wherein -R⁷ is independently -H.

(193) A compound according to any one of (1) to (191), wherein -R⁷ is independently -R^{7A}.

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The Group -R^{3A}

(194) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently:

- 40 -F, -Cl, -Br, -I,
 -R^{A1}, -R^{A2}, -R^{A3},
 -R^{A4}, -R^{A5},
 -OH, -OR^A,
 -CF₃, -OCF₃,

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- NH₂, -NHR^A, -NR^A₂, -NR^{AN1}R^{AN2},
 -NHC(=O)R^A, -NR^AC(=O)R^A,
 -C(=O)R^A,
 -C(=O)OH, -C(=O)OR^A,
 5 -C(=O)NH₂, -C(=O)NHR^A, -C(=O)NR^A₂, -C(=O)NR^{AN1}R^{AN2},
 -S(=O)₂R^A, -S(=O)₂CF₃,
 -S(=O)₂NH₂, -S(=O)₂NHR^A, -S(=O)₂NR^A₂, -S(=O)₂NR^{AN1}R^{AN2},
 -NHS(=O)₂R^A, or -NR^AS(=O)₂R^A.
- 10 (195) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently:
 -F, -Cl, -Br, -I,
 -R^{A1}, -R^{A2}, -R^{A3},
 -R^{A4}, -R^{A5},
 15 -OH, -OR^A,
 -CF₃, -OCF₃,
 -NH₂, -NHR^A, -NR^A₂, -NR^{AN1}R^{AN2},
 -NHC(=O)R^A, -NR^AC(=O)R^A,
 -C(=O)R^A,
 20 -C(=O)OH, -C(=O)OR^A,
 -C(=O)NH₂, -C(=O)NHR^A, -C(=O)NR^A₂, or -C(=O)NR^{AN1}R^{AN2}.
- (196) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently:
 25 -F, -Cl, -Br, -I,
 -R^{A1}, -R^{A2}, -R^{A3},
 -R^{A4}, -R^{A5},
 -OH, -OR^A,
 -CF₃, -OCF₃,
 30 -NH₂, -NHR^A, -NR^A₂, or -NR^{AN1}R^{AN2}.
- (197) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently:
 35 -F, -Cl, -Br, -I,
 -R^{A1}, -R^{A2}, -R^{A3},
 -R^{A4}, -R^{A5},
 -OH, -OR^A,
 -CF₃, or -OCF₃.
- 40 (198) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently:
 -F, -Cl, -Br, -I,
 -R^{A1},
 -OH, -OR^A,

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-CF₃, or -OCF₃.

(199) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently: -R^{A1}, -R^{A2}, -R^{A3}, -R^{A4}, or -R^{A5}.

5

(200) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently: -R^{A1}.

(201) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently: -R^{A2}.

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(202) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently: -R^{A3}.

(203) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently: -R^{A4}.

15

(204) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently: -R^{A5}.

20

(205) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently saturated aliphatic C₁₋₄alkyl and is optionally substituted with one or more substituents selected from: -OH and -OR^{3AA}, wherein each -R^{3AA} is independently saturated aliphatic C₁₋₄alkyl.

25

(206) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently -Me, -CH₂OR^{3AA}, or -Et.

(207) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently saturated aliphatic C₁₋₄alkyl.

30

(208) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

(209) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently -Me.

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(210) A compound according to any one of (1) to (193), wherein -R^{3A}, if present, is independently -Et.

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The Group -R^{3AA}

(211) A compound according to any one of (1) to (210), wherein each -R^{3AA}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

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(212) A compound according to any one of (1) to (210), wherein each $-R^{3AA}$, if present, is independently -Me or -Et.

- 5 (213) A compound according to any one of (1) to (210), wherein each $-R^{3AA}$, if present, is independently -Me.

The Group $-R^{4A}$

- 10 (214) A compound according to any one of (1) to (213), wherein $-R^{4A}$, if present, is independently:

-F, -Cl, -Br, -I,
 $-R^{A1}$, $-R^{A2}$, $-R^{A3}$,
 $-R^{A4}$, $-R^{A5}$,
 15 -OH, $-OR^A$,
 $-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^A$, $-NR^A_2$, $-NR^{AN1}R^{AN2}$,
 $-NHC(=O)R^A$, $-NR^AC(=O)R^A$,
 $-C(=O)R^A$,
 20 $-C(=O)OH$, $-C(=O)OR^A$,
 $-C(=O)NH_2$, $-C(=O)NHR^A$, $-C(=O)NR^A_2$, $-C(=O)NR^{AN1}R^{AN2}$,
 $-S(=O)_2R^A$, $-S(=O)_2CF_3$,
 $-S(=O)_2NH_2$, $-S(=O)_2NHR^A$, $-S(=O)_2NR^A_2$, $-S(=O)_2NR^{AN1}R^{AN2}$,
 $-NHS(=O)_2R^A$, or $-NR^AS(=O)_2R^A$;

- 25 (215) A compound according to any one of (1) to (213), wherein $-R^{4A}$, if present, is independently:

-F, -Cl, -Br, -I,
 $-R^{A1}$, $-R^{A2}$, $-R^{A3}$,
 30 $-R^{A4}$, $-R^{A5}$,
 $-OH$, $-OR^A$,
 $-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^A$, $-NR^A_2$, $-NR^{AN1}R^{AN2}$,
 $-NHC(=O)R^A$, $-NR^AC(=O)R^A$,
 35 $-C(=O)R^A$,
 $-C(=O)OH$, $-C(=O)OR^A$,
 $-C(=O)NH_2$, $-C(=O)NHR^A$, $-C(=O)NR^A_2$, or $-C(=O)NR^{AN1}R^{AN2}$.

- 40 (216) A compound according to any one of (1) to (213), wherein $-R^{4A}$, if present, is independently:

-F, -Cl, -Br, -I,
 $-R^{A1}$, $-R^{A2}$, $-R^{A3}$,
 $-R^{A4}$, $-R^{A5}$,
 $-OH$, $-OR^A$,

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-CF₃, -OCF₃,
 -NH₂, -NHR^A, -NR^A₂, or -NR^{AN1}R^{AN2}.

5 (217) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently:

-F, -Cl, -Br, -I,
 -R^{A1},
 -OH, -OR^A,
 -CF₃, or -OCF₃.

10

(218) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently: -F, -Cl, -Br, -I, or -R^{A1}.

15 (219) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently -R^{A1}.

(220) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently: -F, -Cl, -Br, or -I.

20 (221) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently: -F, -Cl, -Br, or -Me.

(222) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently -F.

25

(223) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently -Cl.

30 (224) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently -Br.

(225) A compound according to any one of (1) to (213), wherein -R^{4A}, if present, is independently -Me.

35 The Group -R^{5A}

(226) A compound according to any one of (1) to (225), wherein -R^{5A}, if present, is independently:

40 -F, -Cl, -Br, -I,
 -R^{A1}, -R^{A2}, -R^{A3},
 -R^{A4}, -R^{A5},
 -OH, -OR^A,
 -CF₃, -OCF₃,
 -NH₂, -NHR^A, -NR^A₂, -NR^{AN1}R^{AN2},

- 5
 -NHC(=O)R^A, -NR^AC(=O)R^A,
 -C(=O)R^A,
 -C(=O)OH, -C(=O)OR^A,
 -C(=O)NH₂, -C(=O)NHR^A, -C(=O)NR^A₂, -C(=O)NR^{AN1}R^{AN2},
 -S(=O)₂R^A, -S(=O)₂CF₃,
 -S(=O)₂NH₂, -S(=O)₂NHR^A, -S(=O)₂NR^A₂, -S(=O)₂NR^{AN1}R^{AN2},
 -NHS(=O)₂R^A, or -NR^AS(=O)₂R^A;

10 (227) A compound according to any one of (1) to (225), wherein -R^{5A}, if present, is independently:

- 15
 -F, -Cl, -Br, -I,
 -R^{A1}, -R^{A2}, -R^{A3},
 -R^{A4}, -R^{A5},
 -OH, -OR^A,
 -CF₃, -OCF₃,
 -NH₂, -NHR^A, -NR^A₂, -NR^{AN1}R^{AN2},
 -NHC(=O)R^A, -NR^AC(=O)R^A,
 -C(=O)R^A,
 -C(=O)OH, -C(=O)OR^A,
 20 -C(=O)NH₂, -C(=O)NHR^A, -C(=O)NR^A₂, or -C(=O)NR^{AN1}R^{AN2}.

(228) A compound according to any one of (1) to (225), wherein -R^{5A}, if present, is independently:

- 25
 -F, -Cl, -Br, -I,
 -R^{A1}, -R^{A2}, -R^{A3},
 -R^{A4}, -R^{A5},
 -OH, -OR^A,
 -CF₃, -OCF₃,
 -NH₂, -NHR^A, -NR^A₂, or -NR^{AN1}R^{AN2}.

30

(229) A compound according to any one of (1) to (225), wherein -R^{5A}, if present, is independently:

- 35
 -F, -Cl, -Br, -I,
 -R^{A1},
 -OH, -OR^A,
 -CF₃, or -OCF₃.

(230) A compound according to any one of (1) to (225), wherein -R^{5A}, if present, is independently: -F, -Cl, -Br, -I, -R^{A1}, -OH, or -OR^A.

40

(231) A compound according to any one of (1) to (225), wherein -R^{5A}, if present, is independently: -F, -Cl, -Br, -I, or -R^{A1}.

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(232) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently $-R^{A1}$.

5 (233) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently $-OH$ or $-OR^A$.

(234) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently: $-F$, $-Cl$, $-Br$, or $-I$.

10 (235) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently: $-F$, $-Cl$, $-Br$, or $-Me$.

(236) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently $-F$.

15 (237) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently $-Cl$.

20 (238) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently $-Br$.

(239) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently $-Me$.

25 (240) A compound according to any one of (1) to (225), wherein $-R^{5A}$, if present, is independently $-OMe$.

The Group $-R^{6A}$

30 (241) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently:

35 $-F$, $-Cl$, $-Br$, $-I$,
 $-R^{A1}$, $-R^{A2}$, $-R^{A3}$,
 $-R^{A4}$, $-R^{A5}$,
 $-OH$, $-OR^A$,
 $-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^A$, $-NR^A_2$, $-NR^{AN1}R^{AN2}$,
 $-NHC(=O)R^A$, $-NR^AC(=O)R^A$,
 $-C(=O)R^A$,
40 $-C(=O)OH$, $-C(=O)OR^A$,
 $-C(=O)NH_2$, $-C(=O)NHR^A$, $-C(=O)NR^A_2$, $-C(=O)NR^{AN1}R^{AN2}$,
 $-S(=O)_2R^A$, $-S(=O)_2CF_3$,
 $-S(=O)_2NH_2$, $-S(=O)_2NHR^A$, $-S(=O)_2NR^A_2$, $-S(=O)_2NR^{AN1}R^{AN2}$,
 $-NHS(=O)_2R^A$, or $-NR^AS(=O)_2R^A$;

(242) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently:

- 5 $-F, -Cl, -Br, -I,$
- $-R^{A1}, -R^{A2}, -R^{A3},$
- $-R^{A4}, -R^{A5},$
- $-OH, -OR^A,$
- $-CF_3, -OCF_3,$
- $-NH_2, -NHR^A, -NR^A_2, -NR^{AN1}R^{AN2},$
- 10 $-NHC(=O)R^A, -NR^AC(=O)R^A,$
- $-C(=O)R^A,$
- $-C(=O)OH, -C(=O)OR^A,$
- $-C(=O)NH_2, -C(=O)NHR^A, -C(=O)NR^A_2, \text{ or } -C(=O)NR^{AN1}R^{AN2}.$

15 (243) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently:

- $-F, -Cl, -Br, -I,$
- $-R^{A1}, -R^{A2}, -R^{A3},$
- $-R^{A4}, -R^{A5},$
- 20 $-OH, -OR^A,$
- $-CF_3, -OCF_3,$
- $-NH_2, -NHR^A, -NR^A_2, \text{ or } -NR^{AN1}R^{AN2}.$

25 (244) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently:

- $-F, -Cl, -Br, -I,$
- $-R^{A1},$
- $-OH, -OR^A,$
- 30 $-CF_3, \text{ or } -OCF_3.$

(245) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently: $-F, -Cl, -Br, -I, \text{ or } -R^{A1}.$

35 (246) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently $-R^{A1}.$

(247) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently: $-F, -Cl, -Br, \text{ or } -I.$

40 (248) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently: $-F, -Cl, -Br, \text{ or } -Me.$

(249) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently $-F.$

(250) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently -Cl.

5 (251) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently -Br.

(252) A compound according to any one of (1) to (240), wherein $-R^{6A}$, if present, is independently -Me.

10

The Group $-R^{7A}$

(253) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently:

15

-F, -Cl, -Br, -I,
 $-R^{A1}$, $-R^{A2}$, $-R^{A3}$,
 $-R^{A4}$, $-R^{A5}$,
 -OH, $-OR^A$,

20

$-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^A$, $-NR^A_2$, $-NR^{AN1}R^{AN2}$,
 $-NHC(=O)R^A$, $-NR^AC(=O)R^A$,
 $-C(=O)R^A$,
 $-C(=O)OH$, $-C(=O)OR^A$,
 $-C(=O)NH_2$, $-C(=O)NHR^A$, $-C(=O)NR^A_2$, $-C(=O)NR^{AN1}R^{AN2}$,

25

$-S(=O)_2R^A$, $-S(=O)_2CF_3$,
 $-S(=O)_2NH_2$, $-S(=O)_2NHR^A$, $-S(=O)_2NR^A_2$, $-S(=O)_2NR^{AN1}R^{AN2}$,
 $-NHS(=O)_2R^A$, or $-NR^AS(=O)_2R^A$;

(254) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently:

30

-F, -Cl, -Br, -I,
 $-R^{A1}$, $-R^{A2}$, $-R^{A3}$,
 $-R^{A4}$, $-R^{A5}$,
 -OH, $-OR^A$,

35

$-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^A$, $-NR^A_2$, $-NR^{AN1}R^{AN2}$,
 $-NHC(=O)R^A$, $-NR^AC(=O)R^A$,
 $-C(=O)R^A$,

40

$-C(=O)OH$, $-C(=O)OR^A$,
 $-C(=O)NH_2$, $-C(=O)NHR^A$, $-C(=O)NR^A_2$, or $-C(=O)NR^{AN1}R^{AN2}$.

(255) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently:

-F, -Cl, -Br, -I,

- 52 -

- 5 $-R^{A1}$, $-R^{A2}$, $-R^{A3}$,
 $-R^{A4}$, $-R^{A5}$,
 $-OH$, $-OR^A$,
 $-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^A$, $-NR_2^A$, or $-NR^{AN1}R^{AN2}$.

(256) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently:

- 10 $-F$, $-Cl$, $-Br$, $-I$,
 $-R^{A1}$,
 $-OH$, $-OR^A$,
 $-CF_3$, or $-OCF_3$.

- 15 (257) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently: $-F$, $-Cl$, $-Br$, $-I$, or $-R^{A1}$.

(258) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently $-R^{A1}$.

- 20 (259) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently: $-F$, $-Cl$, $-Br$, or $-I$.

(260) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently: $-F$, $-Cl$, $-Br$, or $-Me$.

- 25 (261) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently $-F$.

- 30 (262) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently $-Cl$.

(263) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently $-Br$.

- 35 (264) A compound according to any one of (1) to (252), wherein $-R^{7A}$, if present, is independently $-Me$.

The Group $-R^A$

- 40 (265) A compound according to any one of (1) to (264), wherein each $-R^A$, if present, is independently $-R^{A1}$ or $-R^{A2}$.

(266) A compound according to any one of (1) to (264), wherein each $-R^A$, if present, is independently $-R^{A1}$ or $-R^{A3}$.

(267) A compound according to any one of (1) to (264), wherein each $-R^A$, if present, is independently $-R^{A1}$.

5 The Group $-R^{A1}$

(268) A compound according to any one of (1) to (267), wherein each $-R^{A1}$, if present, is independently saturated aliphatic C_{1-4} alkyl and is optionally substituted with one or more substituents selected from: $-OH$ and $-OR^{A11}$, wherein each $-R^{A11}$ is independently
10 saturated aliphatic C_{1-4} alkyl.

(269) A compound according to any one of (1) to (267), wherein each $-R^{A1}$, if present, is independently saturated aliphatic C_{1-4} alkyl.

15 (270) A compound according to any one of (1) to (267), wherein each $-R^{A1}$, if present, is independently $-Me$, $-Et$, $-nPr$, $-iPr$, or $-tBu$.

(271) A compound according to any one of (1) to (267), wherein each $-R^{A1}$, if present, is independently $-Me$ or $-Et$.
20

(272) A compound according to any one of (1) to (267), wherein each $-R^{A1}$, if present, is independently $-Me$.

The Group $-R^{A11}$

25

(273) A compound according to any one of (1) to (272), wherein each $-R^{A11}$, if present, is independently $-Me$, $-Et$, $-nPr$, $-iPr$, or $-tBu$.

(274) A compound according to any one of (1) to (272), wherein each $-R^{A11}$, if present, is
30 independently $-Me$ or $-Et$.

(275) A compound according to any one of (1) to (272), wherein each $-R^{A11}$, if present, is independently $-Me$.

35 The Group $-R^{A2}$

(276) A compound according to any one of (1) to (275), wherein each $-R^{A2}$, if present, is independently saturated C_{3-6} cycloalkyl and is optionally substituted with one or more substituents selected from: $-R^{A22}$, $-OH$, and $-OR^{A22}$, wherein each $-R^{A22}$ is independently
40 saturated aliphatic C_{1-4} alkyl.

(277) A compound according to any one of (1) to (275), wherein each $-R^{A2}$, if present, is independently saturated C_{3-6} cycloalkyl and is optionally substituted with one or more

substituents selected from: -OH and -OR^{A22}, wherein each -R^{A22} is independently saturated aliphatic C₁₋₄alkyl.

5 (278) A compound according to any one of (1) to (275), wherein each -R^{A2}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(279) A compound according to any one of (1) to (275), wherein each -R^{A2}, if present, is independently cyclopropyl.

10 The Group -R^{A22}

(280) A compound according to any one of (1) to (279), wherein each -R^{A22}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

15 (281) A compound according to any one of (1) to (279), wherein each -R^{A22}, if present, is independently -Me or -Et.

(282) A compound according to any one of (1) to (279), wherein each -R^{A22}, if present, is independently -Me.

20

The Group -R^{A3}

25 (283) A compound according to any one of (1) to (282), wherein each -R^{A3}, if present, is independently phenyl or benzyl, and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -R^{A33}, -CF₃, -OH, -OR^{A33}, and -OCF₃, wherein each -R^{A33} is independently saturated aliphatic C₁₋₄alkyl.

(284) A compound according to any one of (1) to (282), wherein each -R^{A3}, if present, is independently phenyl or benzyl.

30

(285) A compound according to any one of (1) to (282), wherein each -R^{A3}, if present, is independently phenyl.

35 (286) A compound according to any one of (1) to (282), wherein each -R^{A3}, if present, is independently benzyl.

The Group -R^{A33}

40 (287) A compound according to any one of (1) to (286), wherein each -R^{A33}, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

(288) A compound according to any one of (1) to (286), wherein each -R^{A33}, if present, is independently -Me or -Et.

(289) A compound according to any one of (1) to (286), wherein each $-R^{A33}$, if present, is independently -Me.

The Group $-R^{A4}$

5

(290) A compound according to any one of (1) to (289), wherein each $-R^{A4}$, if present, is independently aliphatic C_{2-4} alkenyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, $-CF_3$, -OH, $-OR^{A44}$, and $-OCF_3$, wherein each $-R^{A44}$ is independently saturated aliphatic C_{1-4} alkyl.

10

(291) A compound according to any one of (1) to (289), wherein each $-R^{A4}$, if present, is independently aliphatic C_{2-4} alkenyl and is optionally substituted with one or more substituents selected from: -OH and $-OR^{A44}$, wherein each $-R^{A44}$ is independently saturated aliphatic C_{1-4} alkyl.

15

(292) A compound according to any one of (1) to (289), wherein each $-R^{A4}$, if present, is independently aliphatic C_{2-4} alkenyl.

(293) A compound according to any one of (1) to (289), wherein each $-R^{A4}$, if present, is independently $-CH=CH_2$, $-CH=CH-CH_3$, or $-CH=CH-CH_2-CH_3$, and is optionally substituted with one or more substituents selected from: -OH and $-OR^{A44}$, wherein each $-R^{A44}$ is independently saturated aliphatic C_{1-4} alkyl (e.g., $-CH=CHOH$).

20

(294) A compound according to any one of (1) to (289), wherein each $-R^{A4}$, if present, is independently $-CH=CH_2$, $-CH=CH-CH_3$, or $-CH=CH-CH_2-CH_3$.

25

The Group $-R^{A44}$

(295) A compound according to any one of (1) to (294), wherein each $-R^{A44}$, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

30

(296) A compound according to any one of (1) to (294), wherein each $-R^{A44}$, if present, is independently -Me or -Et.

(297) A compound according to any one of (1) to (294), wherein each $-R^{A44}$, if present, is independently -Me.

35

The Group $-R^{A5}$

(298) A compound according to any one of (1) to (297), wherein each $-R^{A5}$, if present, is independently aliphatic C_{2-4} alkynyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, $-CF_3$, -OH, $-OR^{A55}$, and $-OCF_3$, wherein each $-R^{A55}$ is independently saturated aliphatic C_{1-4} alkyl.

40

(299) A compound according to any one of (1) to (297), wherein each $-R^{A5}$, if present, is independently aliphatic C_{2-4} alkynyl and is optionally substituted with one or more substituents selected from: $-OH$ and $-OR^{A55}$, wherein each $-R^{A55}$ is independently saturated aliphatic C_{1-4} alkyl.

5

(300) A compound according to any one of (1) to (297), wherein each $-R^{A5}$, if present, is independently aliphatic C_{2-4} alkynyl.

10 (301) A compound according to any one of (1) to (297), wherein each $-R^{A5}$, if present, is independently $-C\equiv CH$, $-C\equiv C-CH_3$, or $-C\equiv C-CH_2-CH_3$, and is optionally substituted with one or more substituents selected from: $-OH$ and $-OR^{A55}$, wherein each $-R^{A55}$ is independently saturated aliphatic C_{1-4} alkyl.

15 (302) A compound according to any one of (1) to (297), wherein each $-R^{A5}$, if present, is independently $-C\equiv CH$, $-C\equiv C-CH_3$, or $-C\equiv C-CH_2-CH_3$.

The Group $-R^{A55}$

20 (303) A compound according to any one of (1) to (302), wherein each $-R^{A55}$, if present, is independently $-Me$, $-Et$, $-nPr$, $-iPr$, or $-tBu$.

(304) A compound according to any one of (1) to (302), wherein each $-R^{A55}$, if present, is independently $-Me$ or $-Et$.

25 (305) A compound according to any one of (1) to (302), wherein each $-R^{A55}$, if present, is independently $-Me$.

The Group $-NR^{AN1}R^{AN2}$

30 (306) A compound according to any one of (1) to (305), wherein each $-NR^{AN1}R^{AN2}$, if present, is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is optionally substituted with one or more substituents $-R^{AN3}$, wherein each $-R^{AN3}$ is independently saturated aliphatic C_{1-4} alkyl.

35 (307) A compound according to any one of (1) to (305), wherein each $-NR^{AN1}R^{AN2}$, if present, is independently pyrrolidino, piperidino, piperazino, morpholino, or azepano, and is optionally substituted with one or more substituents $-R^{AN3}$, wherein each $-R^{AN3}$ is independently saturated aliphatic C_{1-4} alkyl.

40 (308) A compound according to any one of (1) to (305), wherein each $-NR^{AN1}R^{AN2}$, if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is optionally substituted with one or more substituents $-R^{AN3}$, wherein each $-R^{AN3}$ is independently saturated aliphatic C_{1-4} alkyl.

- 57 -

(309) A compound according to any one of (1) to (305), wherein each $-NR^{AN1}R^{AN2}$, if present, is independently piperidino, piperazino, or morpholino, and is optionally substituted with one or more substituents $-R^{AN3}$, wherein each $-R^{AN3}$ is independently saturated aliphatic C_{1-4} alkyl.

5

(310) A compound according to any one of (1) to (305), wherein each $-NR^{AN1}R^{AN2}$, if present, is independently piperidino, piperazino, or morpholino.

10 (311) A compound according to any one of (1) to (305), wherein each $-NR^{AN1}R^{AN2}$, if present, is independently piperidino.

(312) A compound according to any one of (1) to (305), wherein each $-NR^{AN1}R^{AN2}$, if present, is independently morpholino.

15 The Group $-R^{WN3}$

(313) A compound according to any one of (1) to (312), wherein each $-R^{AN3}$, if present, is independently -Me, -Et, -nPr, -iPr, or -tBu.

20 (314) A compound according to any one of (1) to (312), wherein each $-R^{AN3}$, if present, is independently -Me or -Et.

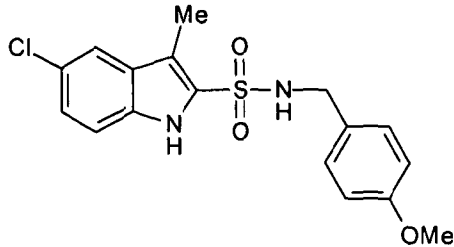
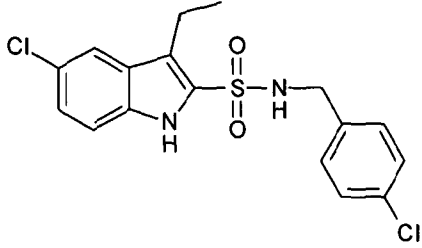
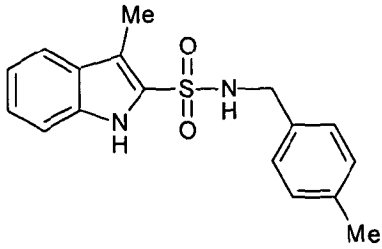
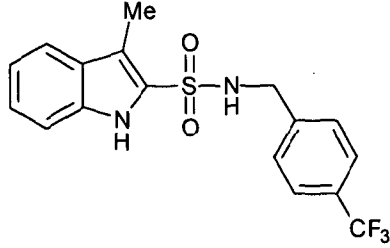
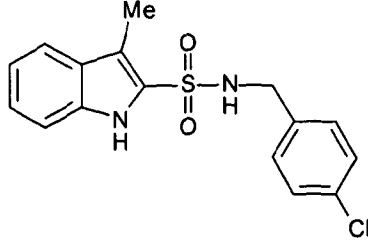
(315) A compound according to any one of (1) to (312), wherein each $-R^{AN3}$, if present, is independently -Me.

25

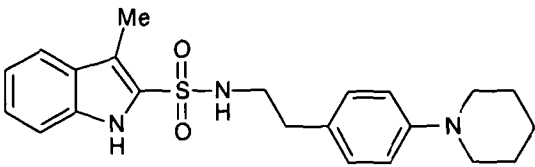
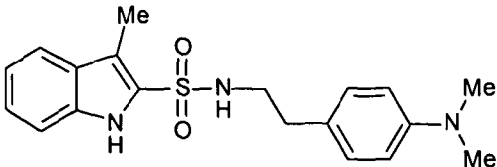
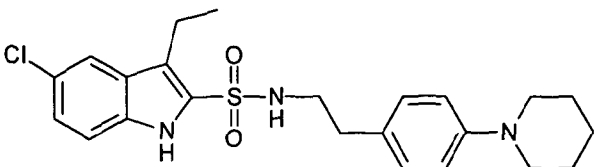
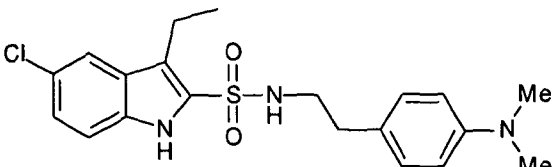
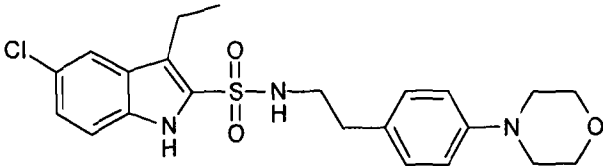
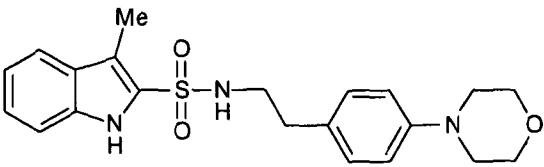
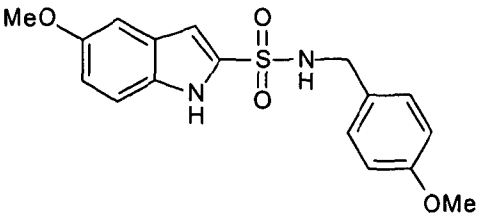
Specific Compounds

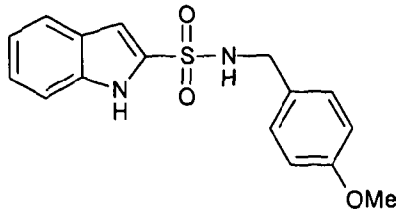
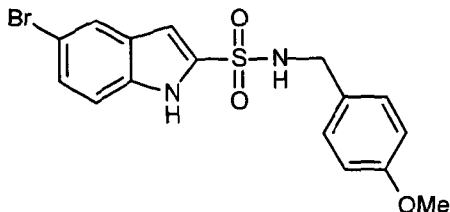
(316) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

5

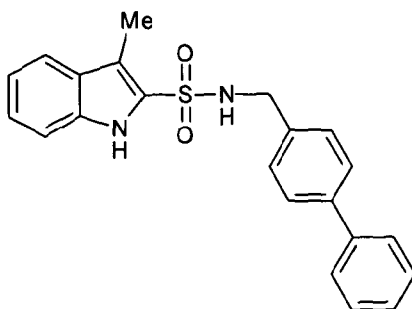
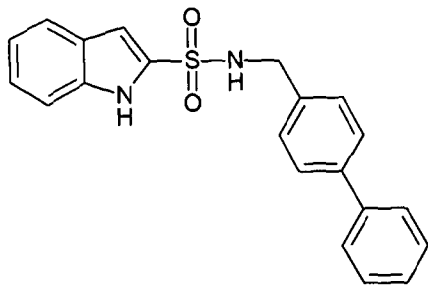
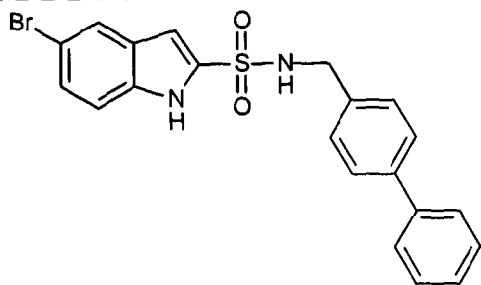
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2.	ABD0962	19	
3.	ABD0965	21	
4.	ABD0968	23	
5.	ABD0972	25	

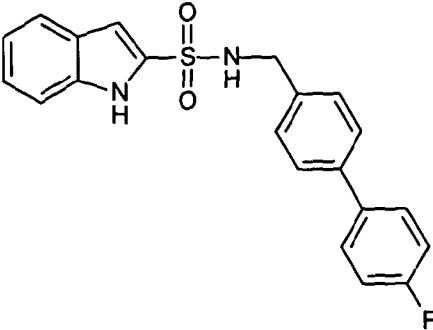
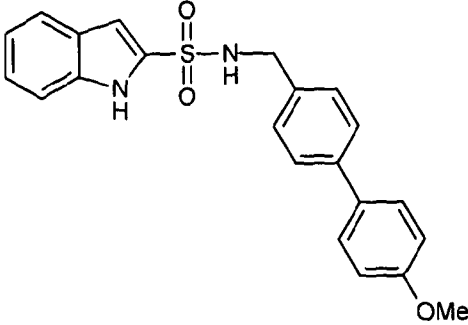
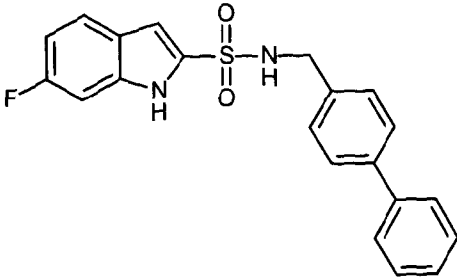
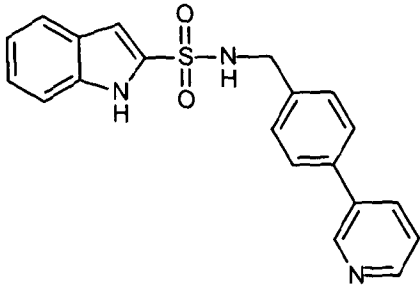
#	ABD No.	Synthesis	Structure
6.	ABD0975	27	 <chem>COc1ccc(cc1)CN(S(=O)(=O)c2c(C)c[nH]3ccccc23)</chem>
7.	ABD0979	31	 <chem>c1ccc[nH]1CN(S(=O)(=O)c2c(C)c[nH]3ccccc23)</chem>
8.	ABD0983	33	 <chem>c1ccncc1CN(S(=O)(=O)c2c(C)c[nH]3ccccc23)</chem>
9.	ABD0984	35	 <chem>Clc1cc(Cl)ccc1CN(S(=O)(=O)c2c(C)c[nH]3ccccc23)</chem>
10.	ABD0986	37	 <chem>c1ccccc1CN(S(=O)(=O)c2c(C)c[nH]3ccccc23)</chem>
11.	ABD0989	39	 <chem>Clc1ccccc1CN(S(=O)(=O)c2c(C)c[nH]3ccccc23)</chem>
12.	ABD1002	41	 <chem>c1ccccc1CCN(S(=O)(=O)c2c(C)c[nH]3ccccc23)</chem>

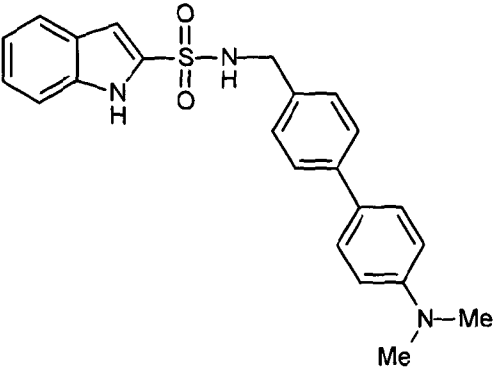
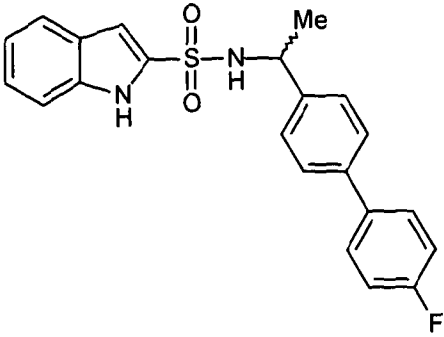
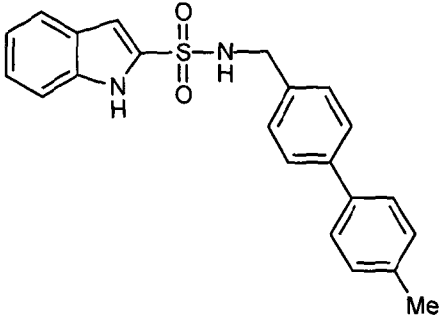
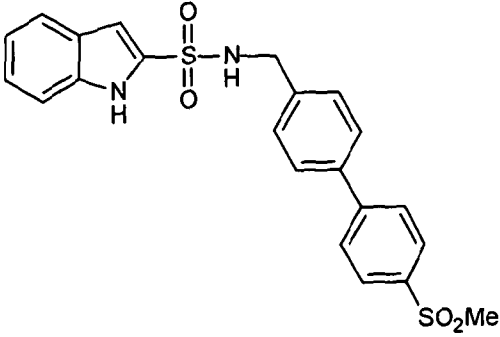
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14.	ABD1006	49	
15.	ABD1012	51	
16.	ABD1014	53	
17.	ABD1016	57	
18.	ABD1018	59	
19.	ABD1022	64	

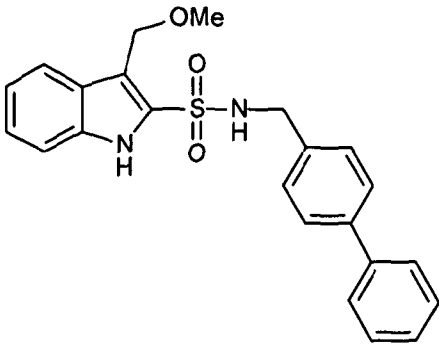
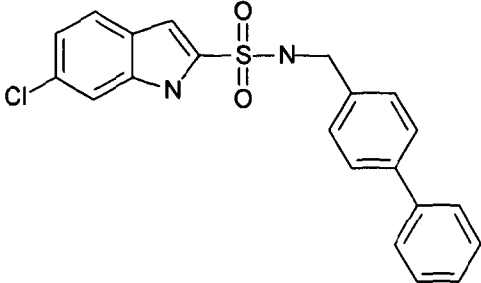
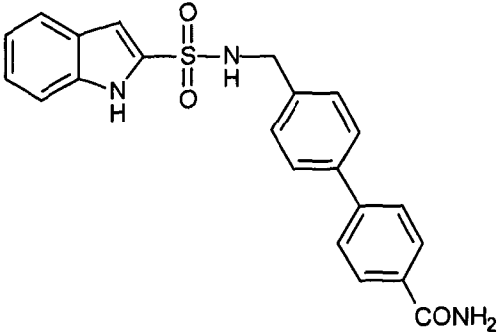
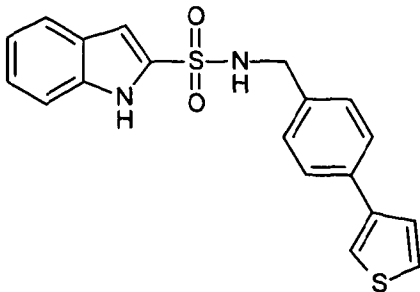
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21.	ABD1031	90	

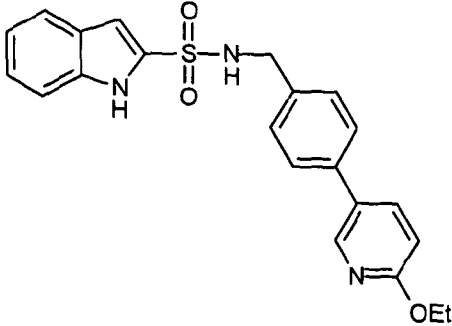
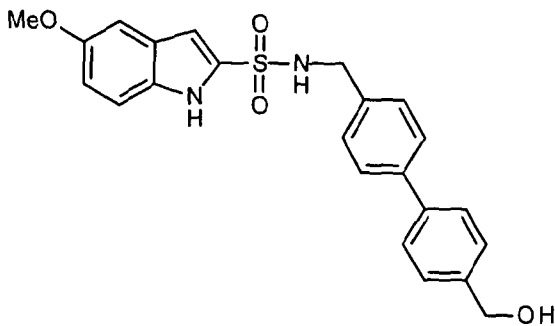
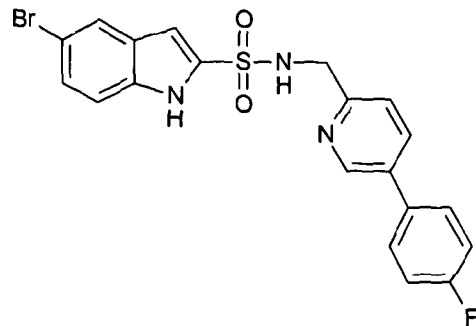
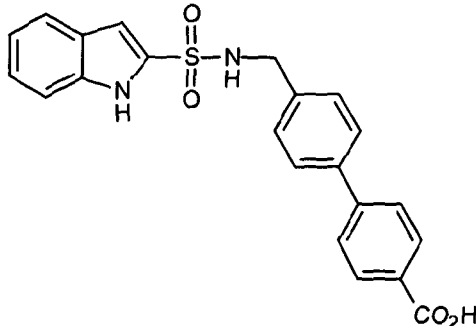
(317) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

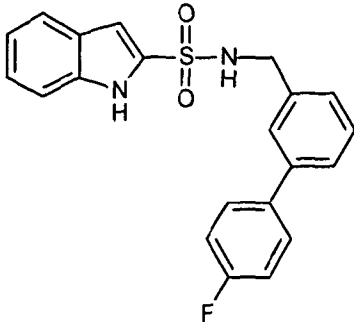
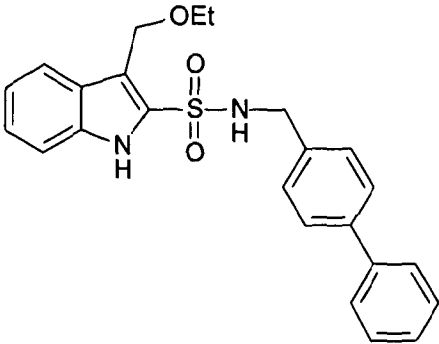
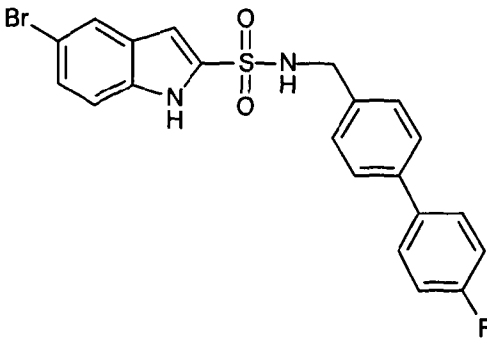
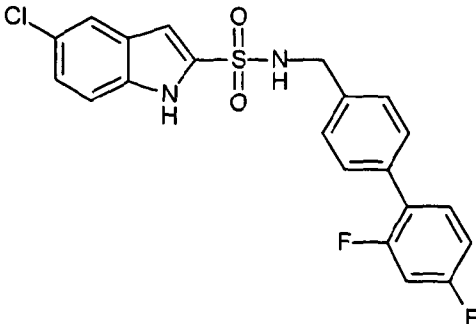
#	ABD No.	Synthesis	Structure
1.	ABD0978	29	
2.	ABD1025	70	
3.	ABD1026	75	

#	ABD No.	Synthesis	Structure
4.	ABD1027	78	
5.	ABD1028	80	
6.	ABD1029	85	
7.	ABD1030	88	

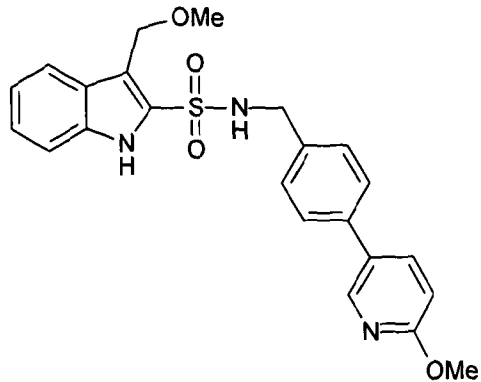
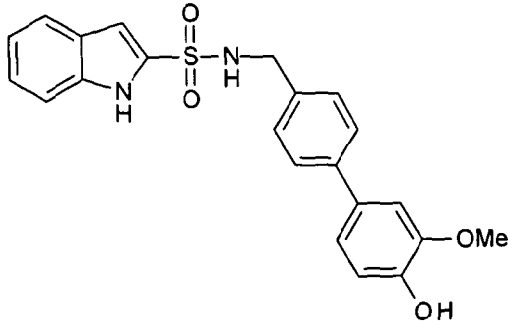
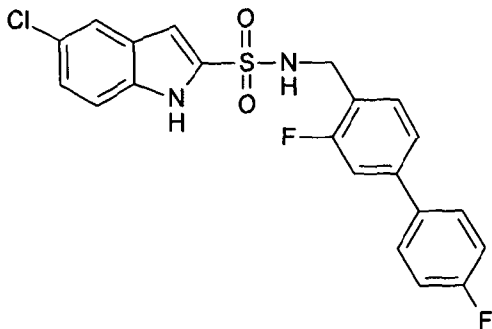
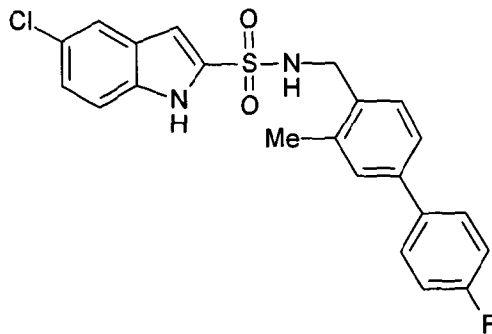
#	ABD No.	Synthesis	Structure
8.	ABD1032	92	
9.	ABD1033	95	
10.	ABD1034	97	
11.	ABD1035	99	

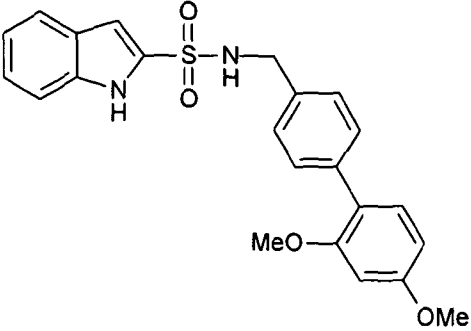
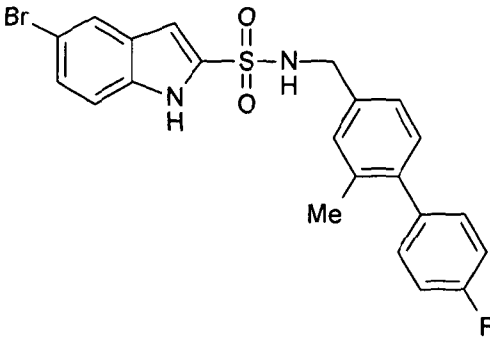
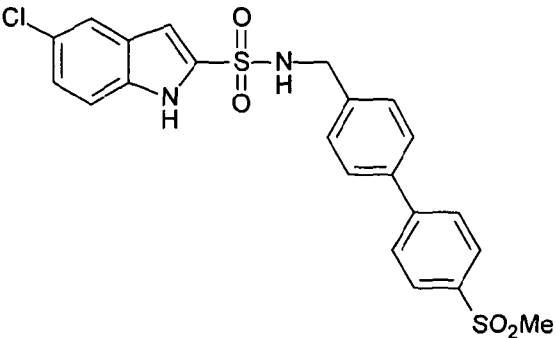
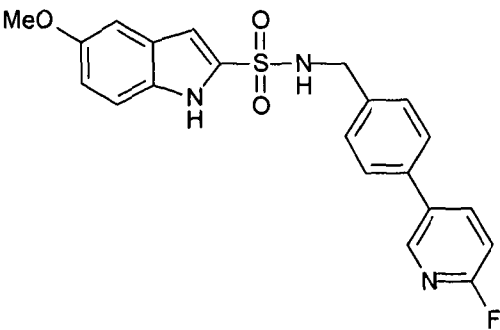
#	ABD No.	Synthesis	Structure
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13.	ABD1037	110	
14.	ABD1038	112	
15.	ABD1042	114	

#	ABD No.	Synthesis	Structure
16.	ABD1045	117	
17.	ABD1046	120	
18.	ABD1047	124	
19.	ABD1048	126	

#	ABD No.	Synthesis	Structure
20.	ABD1049	129	
21.	ABD1050	130	
22.	ABD1054	132	
23.	ABD1055	138	

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#	ABD No.	Synthesis	Structure
24.	ABD1056	140	
25.	ABD1057	142	
26.	ABD1058	146	
27.	ABD1059	149	

#	ABD No.	Synthesis	Structure
28.	ABD1060	150	
29.	ABD1062	154	
30.	ABD1064	156	
31.	ABD1066	158	

Combinations

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., -Q, -L¹-, -R³, -R⁴, -R⁵, -R⁶, -R⁷, -Q¹, -Q², -Q^{1C}, -Q^{1H}, -Q^{2A}-, -Q^{2B}-, -Q^{2AC}-, -Q^{2AH}-, -Q^{2BC}-, -Q^{2BH}-, -W¹, -W², -R^W, -R^{W1}, -R^{W2}, -R^{W3}, -R^{W4}, -R^{W5}, -R^{W11}, -R^{W22}, -R^{W33}, -R^{W44}, -R^{W55}, -NR^{WN1}R^{WN2}, -R^{WN3}, -R^L, -R^{3A}, -R^{4A}, -R^{5A}, -R^{6A}, -R^{7A}, -R^A, -R^{A1}, -R^{A2}, -R^{A3}, -R^{A4}, -R^{A5}, -R^{A11}, -R^{A22}, -R^{A33}, -R^{A44}, -R^{A55}, -NR^{AN1}R^{AN2}, -R^{AN3}, etc.) are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (i.e., compounds that can be isolated, characterised, and tested for biological activity). In addition, all sub-combinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

Substantially Purified Forms

One aspect of the present invention pertains to NISA compounds, as described herein, in substantially purified form and/or in a form substantially free from contaminants.

In one embodiment, the compound is in substantially purified form and/or in a form substantially free from contaminants.

In one embodiment, the compound is in a substantially purified form with a purity of least 50% by weight, e.g., at least 60% by weight, e.g., at least 70% by weight, e.g., at least 80% by weight, e.g., at least 90% by weight, e.g., at least 95% by weight, e.g., at least 97% by weight, e.g., at least 98% by weight, e.g., at least 99% by weight.

Unless specified, the substantially purified form refers to the compound in any stereoisomeric or enantiomeric form. For example, in one embodiment, the substantially purified form refers to a mixture of stereoisomers, i.e., purified with respect to other compounds. In one embodiment, the substantially purified form refers to one stereoisomer, e.g., optically pure stereoisomer. In one embodiment, the substantially purified form refers to a mixture of enantiomers. In one embodiment, the substantially purified form refers to an equimolar mixture of enantiomers (i.e., a racemic mixture, a racemate). In one embodiment, the substantially purified form refers to one enantiomer, e.g., optically pure enantiomer.

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In one embodiment, the compound is in a form substantially free from contaminants wherein the contaminants represent no more than 50% by weight, *e.g.*, no more than 40% by weight, *e.g.*, no more than 30% by weight, *e.g.*, no more than 20% by weight, *e.g.*, no more than 10% by weight, *e.g.*, no more than 5% by weight, *e.g.*, no more than 3% by weight, *e.g.*, no more than 2% by weight, *e.g.*, no more than 1% by weight.

Unless specified, the contaminants refer to other compounds, that is, other than stereoisomers or enantiomers. In one embodiment, the contaminants refer to other compounds and other stereoisomers. In one embodiment, the contaminants refer to other compounds and the other enantiomer.

In one embodiment, the compound is in a substantially purified form with an optical purity of at least 60% (*i.e.*, 60% of the compound, on a molar basis, is the desired stereoisomer or enantiomer, and 40% is undesired stereoisomer(s) or enantiomer), *e.g.*, at least 70%, *e.g.*, at least 80%, *e.g.*, at least 90%, *e.g.*, at least 95%, *e.g.*, at least 97%, *e.g.*, at least 98%, *e.g.*, at least 99%.

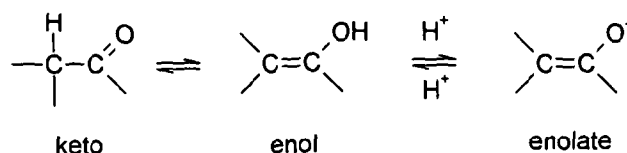
Isomers

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, *cis*- and *trans*-forms; *E*- and *Z*-forms; *c*-, *t*-, and *r*-forms; *endo*- and *exo*-forms; *R*-, *S*-, and *meso*-forms; *D*- and *L*-forms; *d*- and *l*-forms; (+) and (-) forms; *keto*-, *enol*-, and *enolate*-forms; *syn*- and *anti*-forms; *synclinal*- and *anticlinal*-forms; α - and β -forms; *axial* and *equatorial* forms; *boat*-, *chair*-, *twist*-, *envelope*-, and *halfchair*-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (*i.e.*, isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, -OCH₃, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, -CH₂OH. Similarly, a reference to *ortho*-chlorophenyl is not to be construed as a reference to its structural isomer, *meta*-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (*e.g.*, C₁₋₇alkyl includes *n*-propyl and *iso*-propyl; butyl includes *n*-, *iso*-, *sec*-, and *tert*-butyl; methoxyphenyl includes *ortho*-, *meta*-, and *para*-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, *keto*-, *enol*-, and *enolate*-forms, as in, for example, the following tautomeric pairs: *keto/enol* (illustrated below), *imine/enamine*, *amide/imino alcohol*, *amidine/amidine*, *nitroso/oxime*, *thioketone/enethiol*, *N-nitroso/hydroxyazo*, and *nitro/aci-nitro*.

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Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D), and ^3H (T); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including mixtures (e.g., racemic mixtures) thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

15 Salts

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., $-\text{COOH}$ may be $-\text{COO}^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{3+} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-\text{NH}_2$ may be $-\text{NH}_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous. Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, gluceptonic, gluconic, glutamic, glycolic, hydroxymaleic,

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hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but
5 are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

10

Solvates and Hydrates

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the compound. The term "solvate" is used herein in the conventional sense to
15 refer to a complex of solute (*e.g.*, compound, salt of compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a a hemi-hydrate, a mono-hydrate, a di-hydrate, a tri-hydrate, *etc.*

Unless otherwise specified, a reference to a particular compound also includes solvate
20 (*e.g.*, hydrate) forms thereof.

Typical procedures for making and identifying suitable hydrates and solvates are well known to those in the art; see for example, pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in
25 Pharmaceutical Solids, ed. Harry G. Britain, Vol. 95, Marcel Dekker, Inc., New York, 1999.

Hydrates and solvates can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared
30 spectroscopy, powder X-ray diffraction (XRPD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide quick and efficient services for identifying solvates and hydrates on a routine basis. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE), Avantium Technologies (Amsterdam) and Aptuit (Greenwich, CT).

35

For the avoidance of doubt, it is understood that the phrase "pharmaceutically acceptable salts and solvates thereof" and the phrase "pharmaceutically acceptable salt or solvate thereof" embrace pharmaceutically acceptable solvates (*e.g.*, hydrates) of the compounds, pharmaceutically acceptable salts of the compounds, as well as
40 pharmaceutically acceptable solvates (*e.g.*, hydrates) of pharmaceutically acceptable salts of the compounds.

Chemically Protected Forms

It may be convenient or desirable to prepare, purify, and/or handle the compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Greene and P. Wuts; 4th Edition; John Wiley and Sons, 2006).

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH₃); a benzyloxy amide (-NHCO-OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethoxy amide (-NH-Teoc), as a 2,2,2-trichloroethoxy amide (-NH-Troc),

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as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O●).

5 For example, a carboxylic acid group may be protected as an ester for example, as: an C₁₋₇alkyl ester (e.g., a methyl ester; a t-butyl ester); a C₁₋₇haloalkyl ester (e.g., a C₁₋₇trihaloalkyl ester); a triC₁₋₇alkylsilyl-C₁₋₇alkyl ester; or a C₅₋₂₀aryl-C₁₋₇alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

10 For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

Prodrugs

15 It may be convenient or desirable to prepare, purify, and/or handle the compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which, when metabolised (e.g., *in vivo*), yields the desired active compound. Typically, the prodrug is inactive, or less active than the desired active compound, but may provide advantageous handling, administration, or metabolic properties.

20 For example, active compounds which have a hydroxyl or carboxylic acid group may be converted to prodrugs which are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, 25 where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Chemical Synthesis

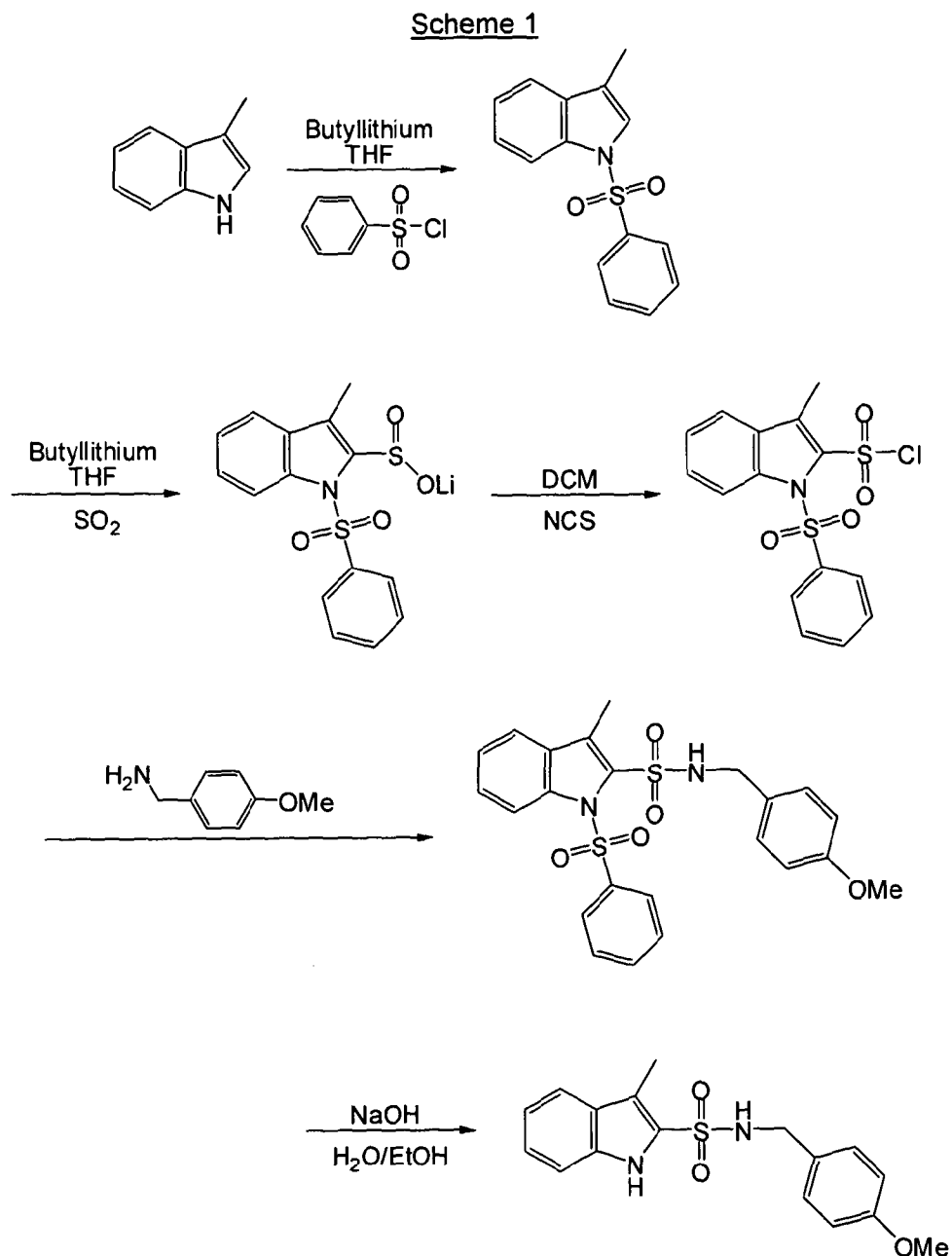
30 Methods for the chemical synthesis of *N*-(arylalkyl)-1*H*-indole-2-sulfonic acid amide ("NISA") compounds (as described herein) are described herein. These and/or other well-known methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional NISA compounds (as described herein).

35 In one approach, an appropriate *N*-protected indole is sulfonylated and then chlorinated to give the corresponding sulfonyl chloride, which is then reacted with a range of amines to give the desired indole-2-sulfonic acid amides. (See, e.g., Graham *et al.*, 1990). For example, the indole is deprotonated with a base, for example, sodium hydride or butyl lithium, and *N*-protected by reaction with suitable group, for example, benzenesulfonyl chloride. Further deprotonation, for example, with butyl lithium, is achieved at the 40 2-position and the resulting anion is reacted with sulfur dioxide to give the corresponding lithium sulfinatate salt. The lithium sulfinatate salt is then chlorinated by reaction with a suitable agent, for example, *N*-chlorosuccinimide, to give the corresponding sulfonyl chloride, which is then coupled with an amine, for example, benzylamine, to give an

indole-2-sulfonic acid amide. Finally, the protecting group is removed, for example, with ethanolic sodium hydroxide, to give the target compound.

An example of such a method is shown in the following scheme.

5



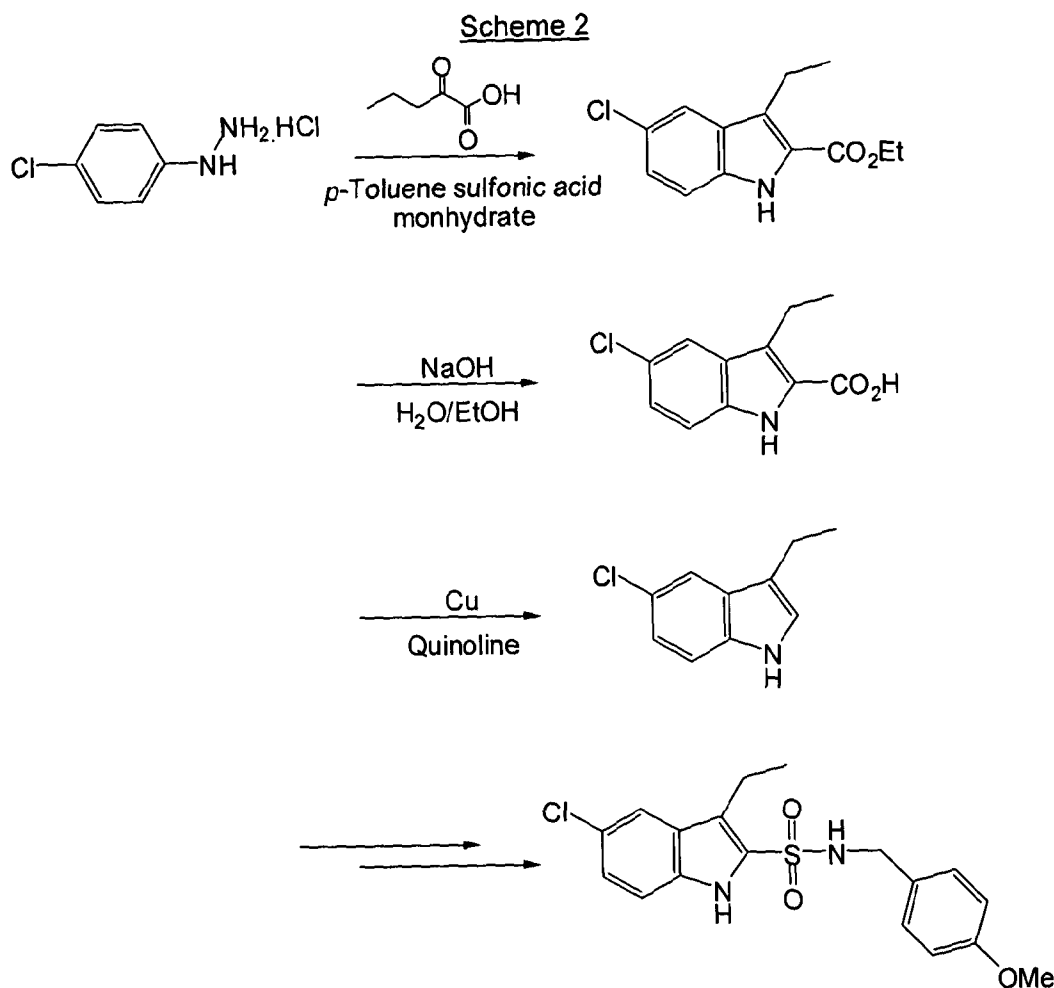
10

In another approach, a substituted indole is prepared from the required phenylhydrazine using a Fisher-indole synthesis. For example, 4-chlorophenylhydrazine hydrochloride is reacted with 2-oxovaleric acid, in the presence of *p*-toluenesulfonic acid to give an ethyl indole-2-carboxylate. The ester is hydrolysed, for example, with ethanolic sodium hydroxide, and the carboxylate is removed, for example, with copper in quinoline (see, for

example, Liu *et al.*, 1997). The desired indole-2-sulfonic acid amide is then prepared, for example, as described in Scheme 1 above.

An example of such a method is shown in the following scheme.

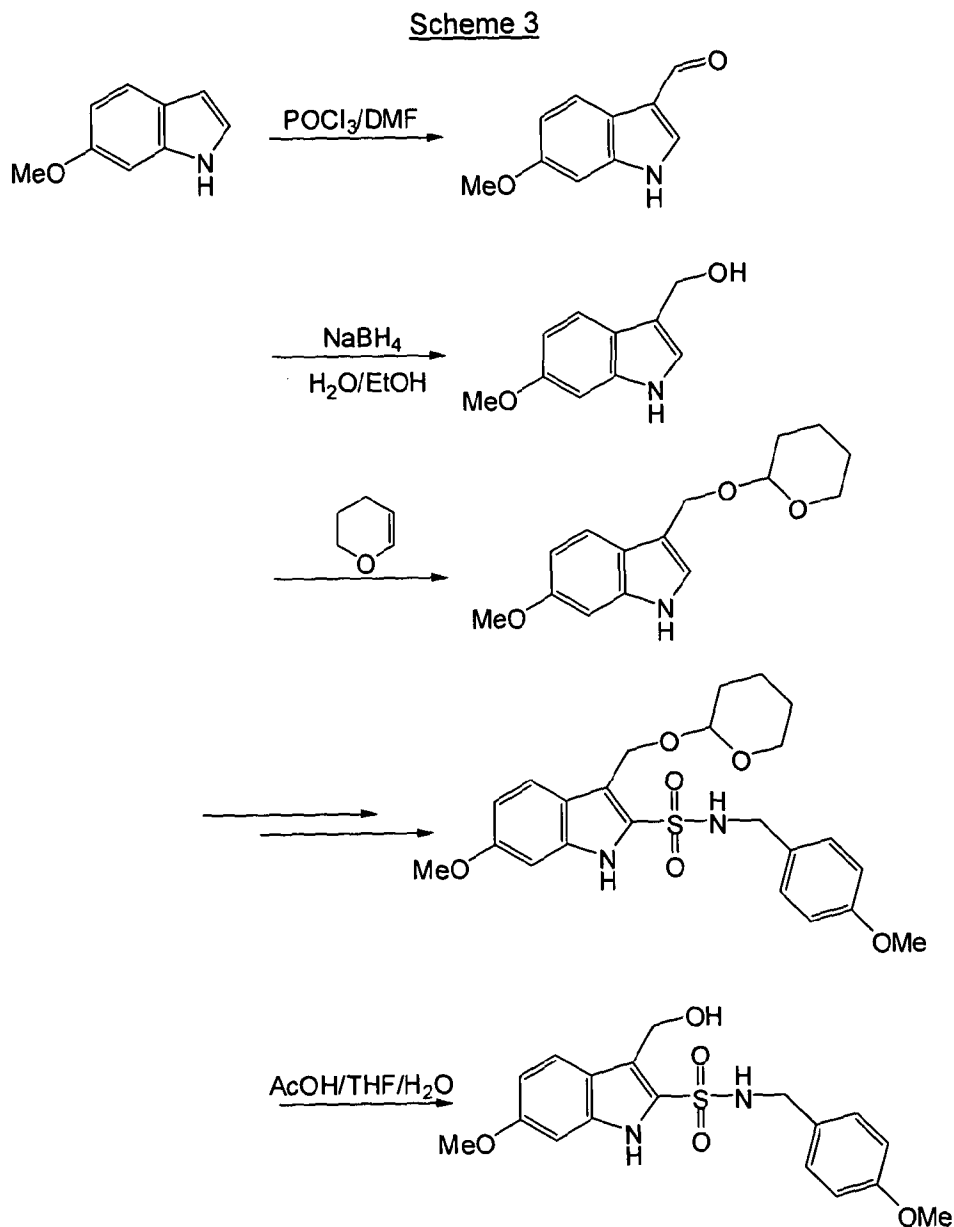
5



- In another approach, a range of substituents can be introduced at the 3-position of the indole via the corresponding 3-carboxaldehyde, which may be prepared from the required indole by a Vilsmeier-Haack formylation (see, *e.g.*, Sundberg, 1990). For example, the indole is reacted with a mixture of phosphoryl trichloride and anhydrous DMF in refluxing DCM, to give the corresponding 3-carboxaldehyde. The aldehyde is then reduced, for example, with lithium aluminium hydride or sodium borohydride, to give the corresponding
- 10 alcohol. The alcohol is then further protected, for example, as a benzyl ether (OBn), as a *t*-butyldiphenyl silyl ether (OTBDPS), or as a tetrahydropyranyl ether (OTHP), by reaction with benzyl chloride, *t*-butyldiphenyl silyl chloride, or dihydropyran, respectively (see, *e.g.*, Greene and Wuts, Protective Groups in Organic Synthesis, 1999, J. Wiley, New York, pp. 49-54). The desired indole-2-sulfonic acid amide is then prepared by further
- 15 sulfonation, for example, as described in Scheme 1 above. Finally, the protecting group is removed, for example, the benzyl group is removed by hydrogenation, the silyl ether group is removed by reaction with tertiarybutylammonium fluoride and the
- 20

tetrahydropyranyl group is removed under acidic conditions. Other methods of protection and deprotection of alcohols are outlined, for example, in Greene and Wuts, Protective Groups in Organic Synthesis, 1999, J. Wiley, New York, pp. 49-54).

- 5 An example of such a method is shown in the following scheme.



- 10 In another approach, the indole-3-carboxaldehyde is oxidised to give the corresponding 3-hydroxyindole derivative using a modified Baeyer-Villiger oxidation (see, *e.g.*, Hickman *et al.*, 2000), for example, with *m*-chloroperbenzoic acid and *p*-toluenesulfonic acid. The alcohol is then protected, *e.g.*, as described in Scheme 3 above, or further reacted to give the corresponding ether, for example, by selective
- 15 methylation using dimethylsulfate. If required, the methyl ether is removed after

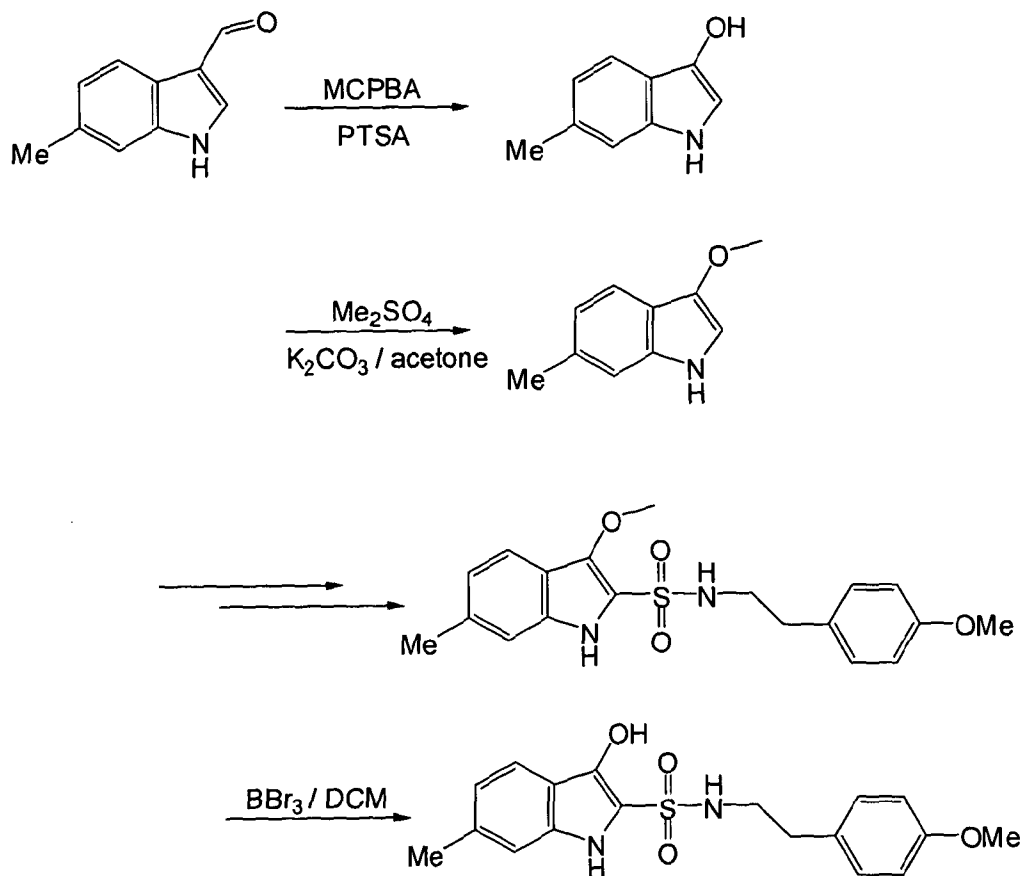
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preparation of the indole-2-sulfonic acid amide, to give the corresponding 3-hydroxy derivative, for example, by demethylation using boron tribromide.

An example of such a method is shown in the following scheme.

5

Scheme 4



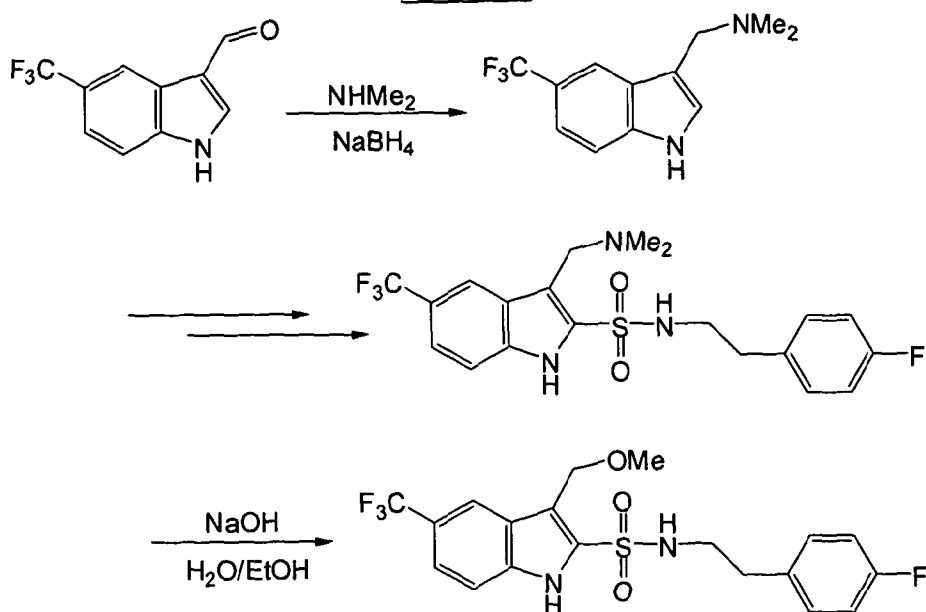
10 In another approach, an alkylamine is introduced into the 3-position of the indole by reductive amination of the carboxaldehyde, *e.g.*, using an amine and sodium cyanoborohydride or sodium borohydride. Further alkaline hydrolysis can be used to give a base-catalysed rearrangement and formation of the corresponding ethoxymethylether.

An example of such a method is shown in the following scheme.

15

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Scheme 5

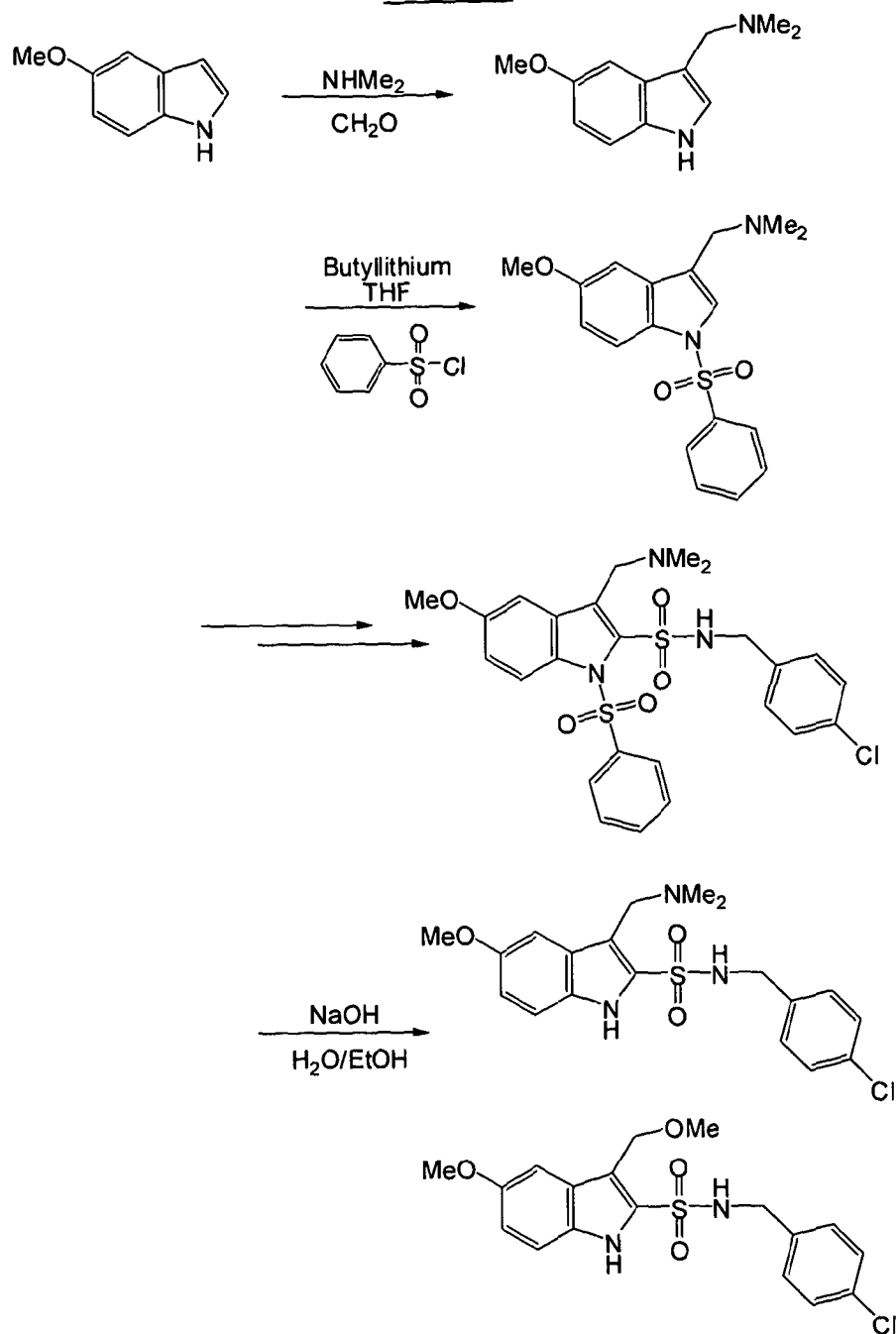


In another approach, the amine is introduced by a Mannich reaction (see, e.g., Brehm *et al.*, 1950) using the unsubstituted indole, e.g., using formaldehyde and dimethylamine. The resultant indole is then *N*-protected, e.g., with benzenesulfonyl chloride, and then 2-sulfonylated, for example, as described in Scheme 1 above. Base-catalysed removal of the *N*-benzenesulfonyl group can lead either to the amine or to rearrangement and formation of the corresponding 2-ethoxymethyl derivative.

An example of such a method is shown in the following scheme.

- 80 -

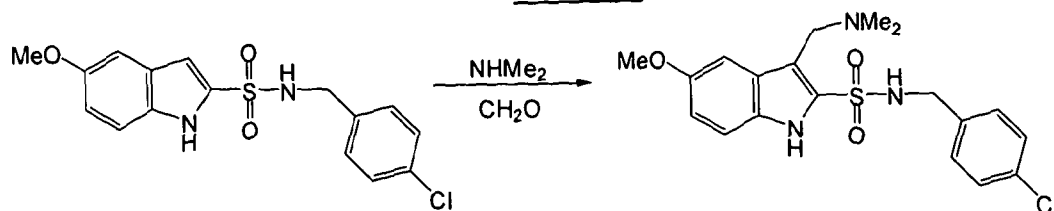
Scheme 6



- 5 In another approach, the amine is introduced directly onto the indole-2-sulfonic acid amide by a Mannich reaction, for example, by reaction with dimethylamine and formaldehyde in glacial acetic acid.

An example of such a method is shown in the following scheme.

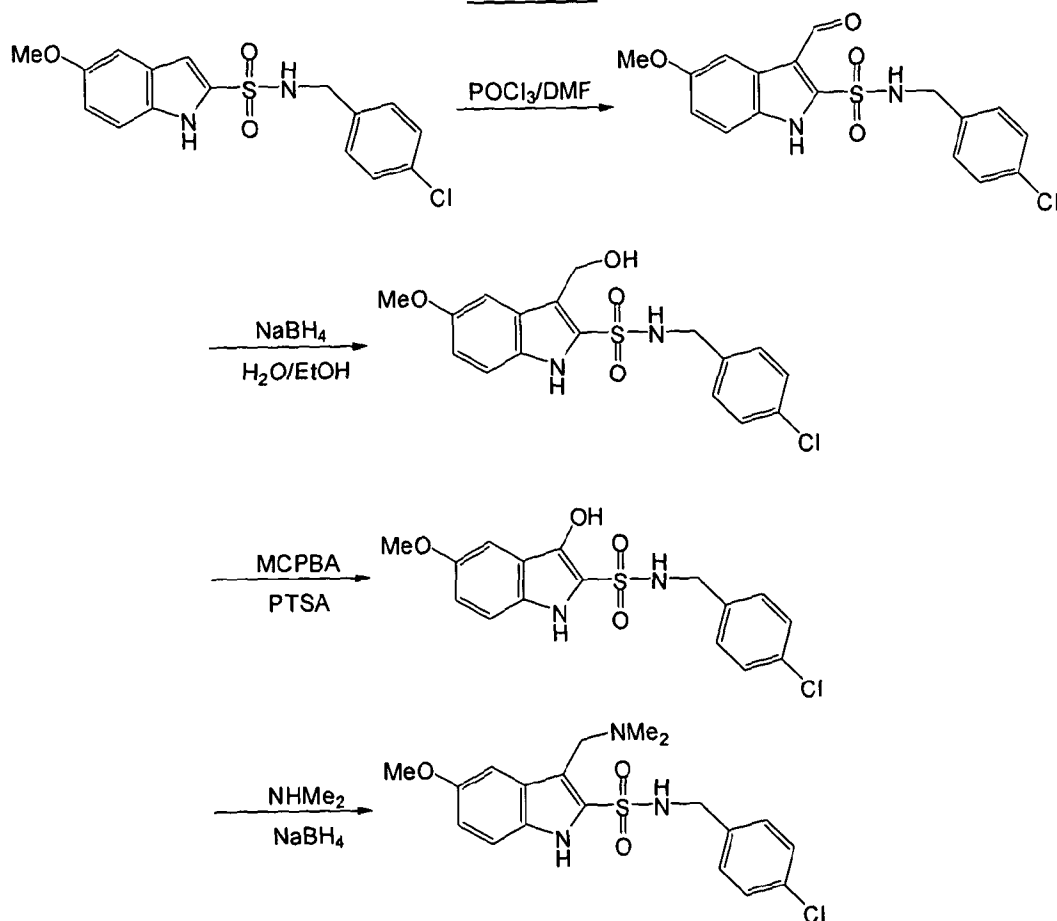
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Scheme 7

- In another approach, the aldehyde is introduced directly onto the indole-2-sulfonic acid amide by a Vilsmeier-Haach formylation. For example, the indole is reacted with a mixture of phosphoryl trichloride and anhydrous dimethylformamide (DMF) in refluxing dichloromethane (DCM), to give the corresponding 3-carboxaldehyde. The aldehyde is then reduced, and further reacted as described above to give a range of ethers and amines, for example, reduced with sodium borohydride to give a 3-methoxyindole or
- oxidised with 3-chloroperoxybenzoic acid (MCPBA) to give a 3-hydroxyindole, or subjected to reductive amination, for example, with dimethylamine and NaBH₃(CN) or NaBH₄, to give a 3-methylamino derivative.

An example of such a method is shown in the following scheme.

15

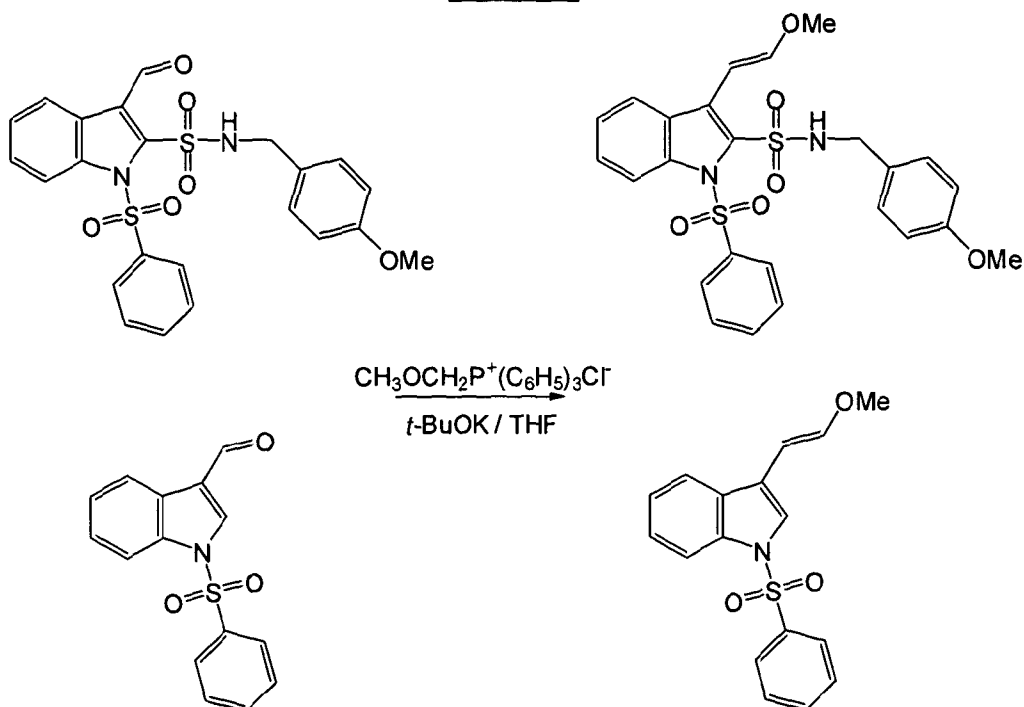
Scheme 8

In another approach, the aldehyde is reacted with a Wittig reagent to give a 3-vinylindole. For example, the *N*-protected indole-3-carboxylaldehyde is reacted with $\text{CH}_3\text{OCH}_2\text{P}^+(\text{C}_6\text{H}_5)_3\text{Cl}^-$ in tetrahydrofuran (THF) in the presence of potassium tertiary butoxide, to give the corresponding 3-(2-methoxy)vinyl indole.

5

An example of such a method is shown in the following scheme.

Scheme 9



10

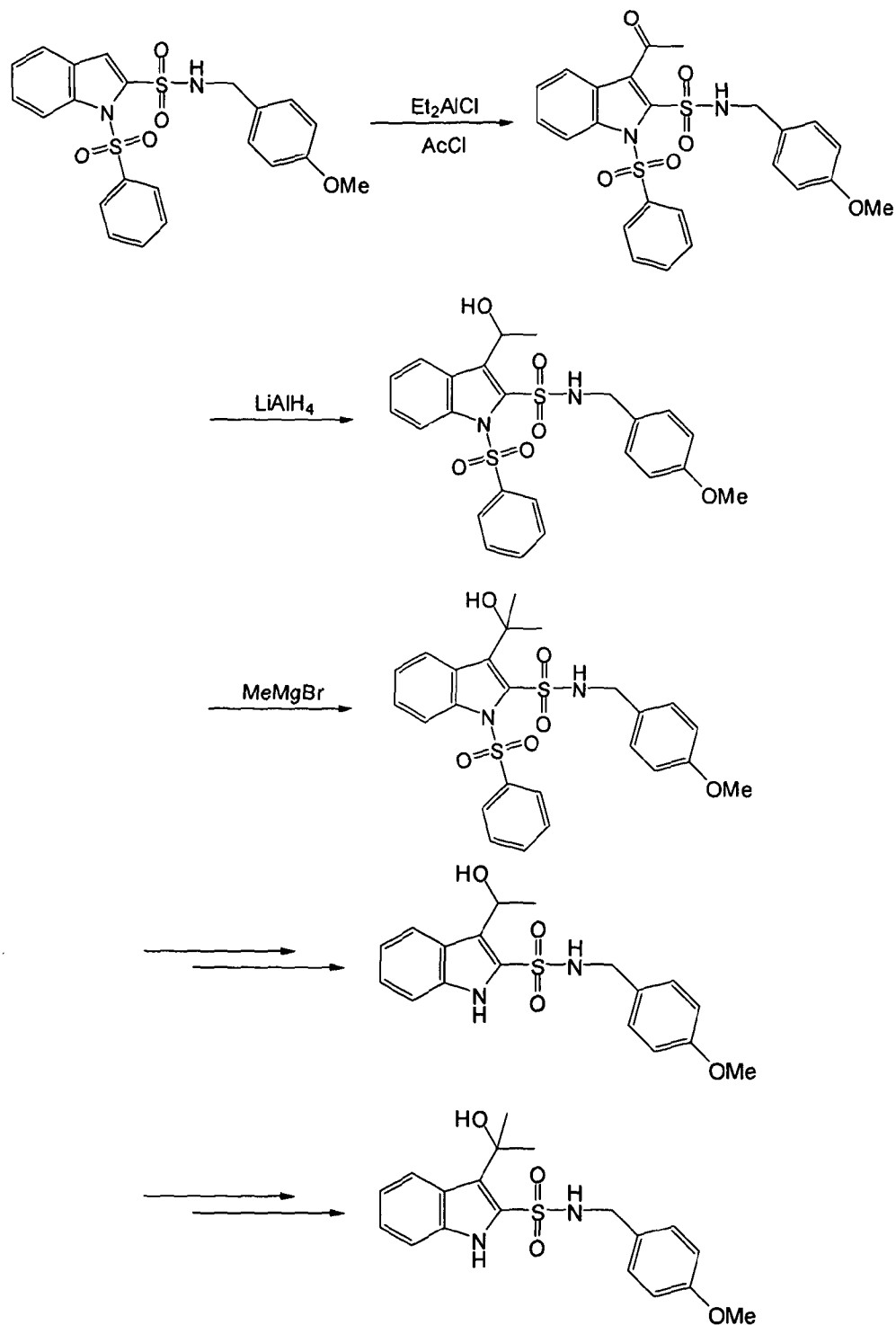
In another approach, the indole is acylated at the 3-position by Friedel-Crafts acylation, for example, by reaction with acetyl chloride in the presence of diethylaluminium chloride. The acyl group is then further reduced, for example, with LiAlH_4 , to give a secondary alcohol, or with a Grignard reagent, for example, methylmagnesium bromide, to give a tertiary alcohol.

15

An example of such a method is shown in the following scheme.

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Scheme 10

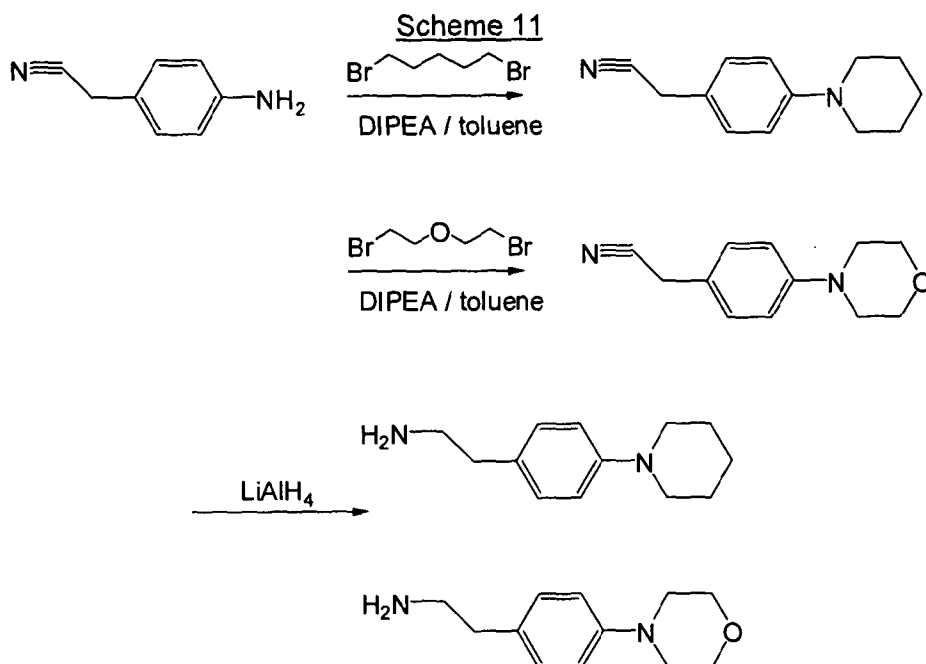


- 5 In another approach, the amine to which the sulfonyl chloride is coupled is prepared by reduction of a suitable nitrile compound, for example by reduction of a substituted phenylacetonitrile with lithium aluminium hydride. Prior to this, the phenylacetonitrile may be prepared by reaction of a suitable aromatic amine with a dibromoalkane or dibromoether, for example, 4-aminophenylacetonitrile can be reacted with

1,5-dibromopentane in toluene in the presence of diisopropylethylamine, or in dimethylformamide in the presence of K_2CO_3 .

An example of such a method is shown in the following scheme.

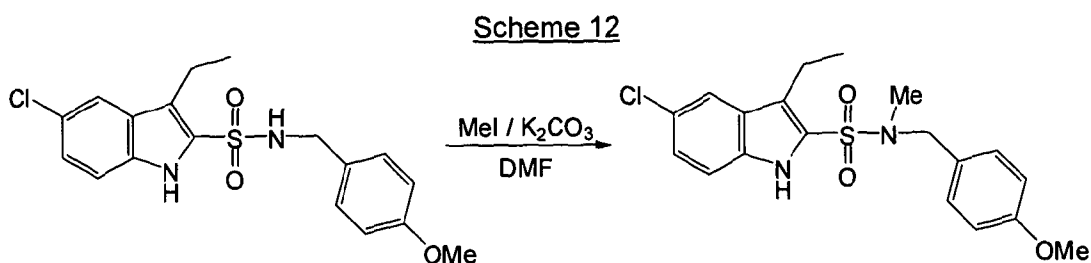
5



10 In another approach, the sulfonic acid amide nitrogen is further substituted, for example, with a methyl group, by reaction with methyl iodide in dimethylformamide (DMF), in the presence of potassium carbonate.

An example of such a method is shown in the following scheme.

15

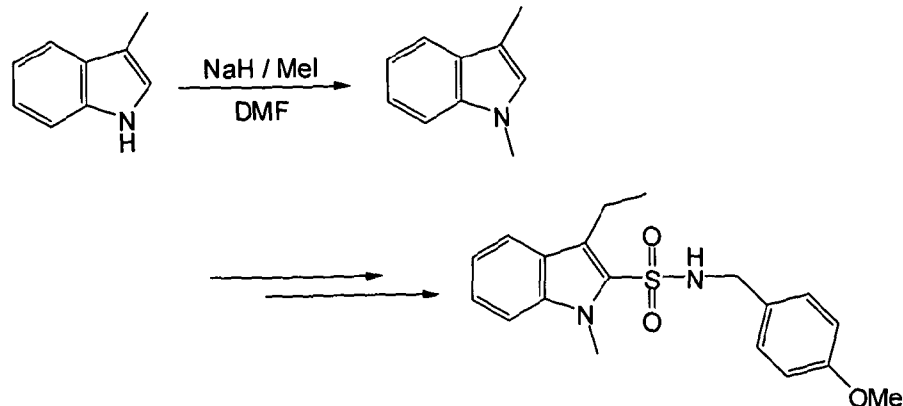


20 In another approach, the indole nitrogen is further substituted, for example with a methyl group, for example, by deprotonation with NaH and reaction with methyl iodide in dimethylformamide (DMF). The methylated indole is then further sulfonylated at the 2-position, for example, as described in Scheme 1 above.

An example of such a method is shown in the following scheme.

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Scheme 13

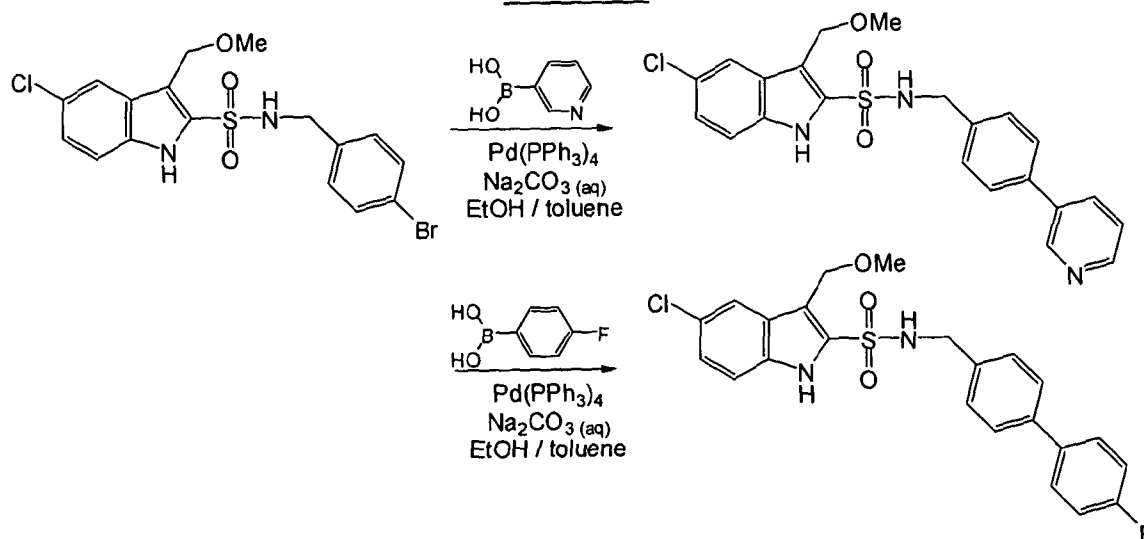


In another approach, further substituents may be added to the benzylamine moiety, for example by Suzuki coupling of an aryl or heteroarylboronic acid with a bromobenzyl side group facilitated by a palladium catalyst, for example $\text{Pd}(\text{PPh}_3)_4$.

An example of such a method is shown in the following scheme.

10

Scheme 14

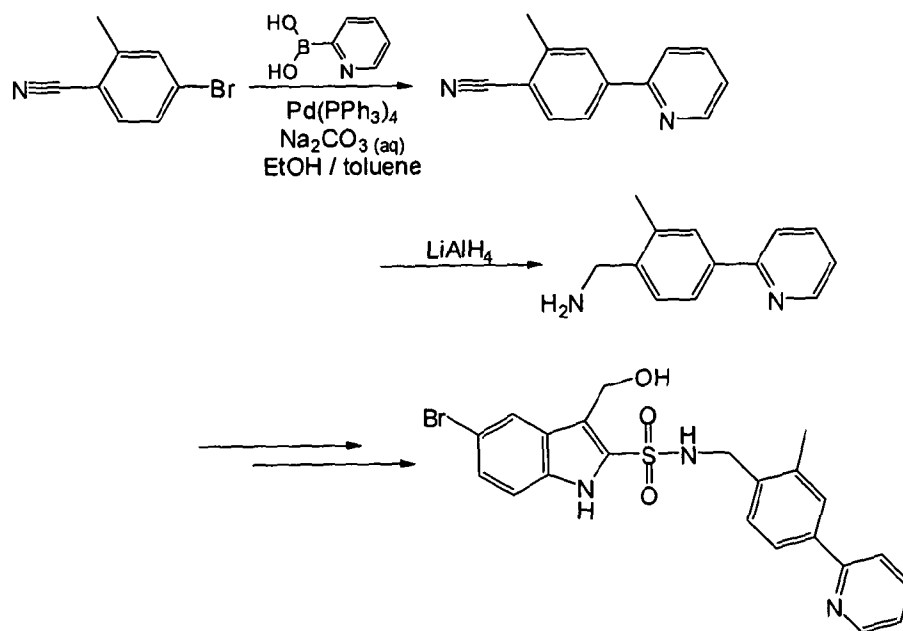


In another approach, the desired biaryl side chain can be prepared prior to coupling with the sulfonyl chloride, prepared as described above, using Suzuki coupling of the protected amine. For example the appropriate bromobenzylamine can be BOC protected, using di-*tert*-butyl dicarbonate, and coupled with the required aryl or heteroarylboronic acid, facilitated by a suitable palladium catalyst, for example $\text{Pd}(\text{PPh}_3)_4$, and the BOC protecting group removed with a reagent such as trifluoroacetic acid or ethanolic HCl. If required, the bromobenzylamine can be prepared from the appropriate bromobenzonitrile derivatives.

An example of such a method is shown in the following scheme.

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Scheme 15



Compositions

One aspect of the present invention pertains to a composition (e.g., a pharmaceutical composition) comprising an NISA compound, as described herein, and a
5 pharmaceutically acceptable carrier, diluent, or excipient.

Another aspect of the present invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising mixing an NISA compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

10

Uses

The NISA compounds, as described herein, are useful, for example, in the treatment of disorders (e.g., diseases) that are ameliorated by the inhibition of cannabinoid receptor
15 (e.g., CB1) signalling, as described herein.

Use in Methods of Inhibiting Cannabinoid Receptor (e.g., CB1) Signalling

One aspect of the present invention pertains to a method of inhibiting cannabinoid receptor (e.g., CB1) signalling in a cell, *in vitro* or *in vivo*, comprising contacting the cell with an effective amount of an NISA compound, as described herein.

Suitable assays for determining cannabinoid receptor (e.g., CB1) signalling inhibition are described herein and/or are known in the art.

25

In one embodiment, the method is performed *in vitro*.

In one embodiment, the method is performed *in vivo*.

In one embodiment, the NISA compound is provided in the form of a pharmaceutically acceptable composition.

30

Any type of cell may be treated, including but not limited to, adipose, lung, gastrointestinal (including, e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

35

One of ordinary skill in the art is readily able to determine whether or not a candidate compound inhibits a cannabinoid receptor (e.g., CB1). For example, suitable assays are described herein.

For example, a sample of cells may be grown *in vitro* and a compound brought into contact with said cells, and the effect of the compound on those cells observed. As an example of "effect," the morphological status of the cells (e.g., alive or dead, etc.) may be determined. Where the compound is found to exert an influence on the cells, this may be

40

used as a prognostic or diagnostic marker of the efficacy of the compound in methods of treating a patient carrying cells of the same cellular type.

Use in Methods of Therapy

5

Another aspect of the present invention pertains to an NISA compound, as described herein, for use in a method of treatment of the human or animal body by therapy.

Use in the Manufacture of Medicaments

10

Another aspect of the present invention pertains to use of an NISA compound, as described herein, in the manufacture of a medicament for use in treatment.

In one embodiment, the medicament comprises the NISA compound.

15

Methods of Treatment

Another aspect of the present invention pertains to a method of treatment comprising administering to a patient in need of treatment a therapeutically effective amount of an NISA compound, as described herein, preferably in the form of a pharmaceutical composition.

20

Disorders Treated - Disorders Ameliorated by the Inhibition of Cannabinoid Receptor (e.g., CB1) Signalling

25

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of a disorder (e.g., a disease) that is ameliorated by the inhibition of cannabinoid receptor (e.g., CB1) signalling.

30

Disorders Treated

In one embodiment, the treatment is treatment of metabolic syndrome.

35 In one embodiment, the treatment is treatment of type-2 diabetes.

In one embodiment, the treatment is treatment of dyslipidaemia

In one embodiment, the treatment is treatment of obesity.

40

In one embodiment, the treatment is treatment of an eating disorder.

In one embodiment, the treatment is treatment of a cardiovascular disease or disorder.

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In one embodiment, the treatment is treatment of a cardiovascular disease or disorder associated with cardiovascular disease.

- 5 In one embodiment, the treatment is treatment of hypertension, congestive heart failure, cardiac hypertrophy, peripheral artery disease, atherosclerosis, stroke, kidney disease, myocardial infarction, steatohepatitis, or cardiotoxicity associated with chemotherapy.

In one embodiment, the treatment is treatment of a non-alcoholic fatty liver disease (NAFLD) associated with metabolic syndrome.

10

In one embodiment, the treatment is treatment of a disease or disorder characterised by an addiction component.

- 15 In one embodiment, the treatment is treatment of addiction or withdrawal, for example, smoking addiction and/or smoking withdrawal, alcohol addiction and/or alcohol withdrawal, drug addiction and/or drug withdrawal.

In one embodiment, the treatment is smoking cessation therapy.

- 20 In one embodiment, the treatment is treatment of a bone disease or disorder.

In one embodiment, the treatment is treatment of osteoporosis, Paget's disease of bone, or bone related cancer.

- 25 In one embodiment, the treatment is treatment of breast cancer.

In one embodiment, the treatment is treatment of a disease or disorder characterised by an inflammatory or autoimmune component.

- 30 In one embodiment, the treatment is treatment of rheumatoid arthritis, inflammatory bowel disease, or psoriasis.

In one embodiment, the treatment is treatment of a psychiatric disease or disorder.

- 35 In one embodiment, the treatment is treatment of anxiety, mania, or schizophrenia.

In one embodiment, the treatment is treatment of a disease or disorder characterised by impairment of memory and/or loss of cognitive function.

- 40 In one embodiment, the treatment is treatment of memory impairment, loss of cognitive function, Parkinson's disease, Alzheimer's disease, or dementia.

Treatment

The term "treatment," as used herein in the context of treating a disorder, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the disorder, and includes a reduction in the rate of progress, a halt in the rate of progress, alleviation of symptoms of the disorder, amelioration of the disorder, and cure of the disorder. Treatment as a prophylactic measure (i.e., prophylaxis) is also included. For example, use with patients who have not yet developed the disorder, but who are at risk of developing the disorder, is encompassed by the term "treatment."

For example, treatment includes the prophylaxis of type-2 diabetes, reducing the incidence of type-2 diabetes, alleviating the symptoms of type-2 diabetes, etc.

The term "therapeutically-effective amount," as used herein, pertains to that amount of a compound, or a material, composition or dosage form comprising a compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Combination Therapies

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. For example, the compounds described herein may also be used in combination therapies, e.g., in conjunction with other agents. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; gene therapy; and controlled diets.

One aspect of the present invention pertains to a compound as described herein, in combination with one or more (e.g., 1, 2, 3, 4, etc.) additional therapeutic agents, as described below.

The particular combination would be at the discretion of the physician who would select dosages using his common general knowledge and dosing regimens known to a skilled practitioner.

The agents (i.e., the compound described herein, plus one or more other agents) may be administered simultaneously or sequentially, and may be administered in individually varying dose schedules and via different routes. For example, when administered sequentially, the agents can be administered at closely spaced intervals (e.g., over a period of 5-10 minutes) or at longer intervals (e.g., 1, 2, 3, 4 or more hours apart, or even

longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

5 The agents (i.e., the compound described here, plus one or more other agents) may be formulated together in a single dosage form, or alternatively, the individual agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

10 Examples of additional agents/therapies that may be co-administered/combined with treatment with the NISA compounds described herein include the following:

15 Compounds used in the treatment of type-2 diabetes and obesity, such as insulin and insulin analogues; dipeptidyl peptidase-4 (DPP-4) inhibitors; glucagon-like peptide-1 analogues; hypoglycaemic agents, such as alpha-glucosidase inhibitors; biguanides; sulfonyl ureas; thiazolidinediones; weight loss therapies, such as appetite suppressing agents, serotonin reuptake inhibitors, noradrenaline reuptake inhibitors, β_3 -adrenoceptor agonists, and lipase inhibitors.

20 Compounds used in the treatment of cardiovascular disease and dysfunction, such as diuretics; angiotensin-converting enzyme (ACE) inhibitors; angiotensin II antagonists; beta-blockers; calcium antagonists, such as nifedipine; HMG-CoA-reductase inhibitors, such as statins; other lipid modulating agents, such as fibrates; bile acid-binding resins; drugs used to treat cardiac dysfunction, such as digoxin, aldosterone antagonists, and organic nitrates.

25 Compounds used to assist smoking cessation, such as norepinephrine-dopamine reuptake inhibitors, such as bupropion.

30 Compounds used in the treatment of bone diseases and disorders, such as anti-resorptive agents, such as bisphosphonates; anabolic agents, such as parathyroid hormone; RANKL inhibitors, such as denosumab; estrogen replacement and selective estrogen receptor modulators, such as raloxifene.

35 Compounds used in the treatment of breast cancer, such as compounds which modulate tubulin polymerisation, such as paclitaxel; targeted therapies, such as antibodies against specific cell surface markers on tumour cells, such as antibodies against the HER2 oncoprotein, such as trastuzumab.

40 Compounds used in the treatment of a disease or disorder with an inflammatory or autoimmune component, such as non-steroidal anti-inflammatory drugs (NSAIDs); disease-modifying anti-rheumatic drugs (DMARDs), such as immunosuppressants; anti-TNF agents, such as infliximab, etanercept, and adalimumab; and anti B-cell therapies, such as rituximab.

- Compounds used in the treatment of a psychiatric disease or disorder, such as GABA_A modulators, such as benzodiazepines; 5HT_{1A} receptor agonists, such as buspirone; beta blockers; antipsychotics, such as dopamine receptor blockers and other drugs which modulate monoamine receptors, transporters or metabolism, for example, tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors; lithium; and anti-epileptic drugs, such as those which block sodium channels, those which block T-type calcium channels, or those which block GABA transaminase or reuptake, including phenytoin, carbamazepine, valproate and vigabatrin.
- 10 Compounds classes used in the treatment of a disease or disorder characterised by impairment of memory and/or loss of cognitive function, such as dopamine agonists and anticholinesterases.

Other Uses

- 15 The NISA compounds described herein may also be used as cell culture additives to inhibit cannabinoid receptor (e.g., CB1) signalling, *etc.*
- 20 The NISA compounds described herein may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.
- 25 The NISA compounds described herein may also be used as a standard, for example, in an assay, in order to identify other active compounds, other inhibitors of cannabinoid receptor (e.g., CB1) signalling, *etc.*

Kits

- 30 One aspect of the invention pertains to a kit comprising (a) an NISA compound as described herein, or a composition comprising an NISA compound as described herein, e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the compound or composition.
- 35 The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

Routes of Administration

- 40 The NISA compound or pharmaceutical composition comprising the NISA compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

The Subject/Patient

The subject/patient may be a chordate, a vertebrate, a mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject/patient may be any of its forms of development, for example, a foetus.

In one preferred embodiment, the subject/patient is a human.

Formulations

While it is possible for an NISA compound to be administered alone, it is preferable to present it as a pharmaceutical formulation (e.g., composition, preparation, medicament) comprising at least one NISA compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents. The formulation may further comprise other active agents, for example, other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising mixing at least one NISA compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, e.g., carriers, diluents, excipients, etc. If formulated as discrete units (e.g., tablets, etc.), each unit contains a predetermined amount (dosage) of the compound.

5 The term "pharmaceutically acceptable," as used herein, pertains to compounds, ingredients, materials, compositions, dosage forms, *etc.*, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (*e.g.*, human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, *etc.* must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

10 Suitable carriers, diluents, excipients, *etc.* can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 5th edition, 2005.

15 The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the compound with carriers (*e.g.*, liquid carriers, finely divided solid carrier, *etc.*), and then shaping the product, if
20 necessary.

The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

25 Formulations may suitably be in the form of liquids, solutions (*e.g.*, aqueous, non-aqueous), suspensions (*e.g.*, aqueous, non-aqueous), emulsions (*e.g.*, oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, tablets (including, *e.g.*, coated tablets), granules, powders, lozenges, pastilles, capsules (including, *e.g.*, hard and soft gelatin capsules), cachets, pills, ampoules, boluses, suppositories,
30 pessaries, tinctures, gels, pastes, ointments, creams, lotions, oils, foams, sprays, mists, or aerosols.

Formulations may suitably be provided as a patch, adhesive plaster, bandage, dressing, or the like which is impregnated with one or more compounds and optionally one or more
35 other pharmaceutically acceptable ingredients, including, for example, penetration, permeation, and absorption enhancers. Formulations may also suitably be provided in the form of a depot or reservoir.

40 The compound may be dissolved in, suspended in, or admixed with one or more other pharmaceutically acceptable ingredients. The compound may be presented in a liposome or other microparticulate which is designed to target the compound, for example, to blood components or one or more organs.

Formulations suitable for oral administration (*e.g.*, by ingestion) include liquids, solutions (*e.g.*, aqueous, non-aqueous), suspensions (*e.g.*, aqueous, non-aqueous), emulsions (*e.g.*, oil-in-water, water-in-oil), elixirs, syrups, electuaries, tablets, granules, powders, capsules, cachets, pills, ampoules, boluses.

5 Formulations suitable for buccal administration include mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs. Lozenges typically comprise the compound in a flavored basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the compound in an inert matrix, such as gelatin and glycerin,
10 or sucrose and acacia. Mouthwashes typically comprise the compound in a suitable liquid carrier.

Formulations suitable for sublingual administration include tablets, lozenges, pastilles, capsules, and pills.

15 Formulations suitable for oral transmucosal administration include liquids, solutions (*e.g.*, aqueous, non-aqueous), suspensions (*e.g.*, aqueous, non-aqueous), emulsions (*e.g.*, oil-in-water, water-in-oil), mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

20 Formulations suitable for non-oral transmucosal administration include liquids, solutions (*e.g.*, aqueous, non-aqueous), suspensions (*e.g.*, aqueous, non-aqueous), emulsions (*e.g.*, oil-in-water, water-in-oil), suppositories, pessaries, gels, pastes, ointments, creams, lotions, oils, as well as patches, adhesive plasters, depots, and reservoirs.

25 Formulations suitable for transdermal administration include gels, pastes, ointments, creams, lotions, and oils, as well as patches, adhesive plasters, bandages, dressings, depots, and reservoirs.

30 Tablets may be made by conventional means, *e.g.*, compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (*e.g.*, povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (*e.g.*, lactose,
35 microcrystalline cellulose, calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc, silica); disintegrants (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (*e.g.*, sodium lauryl sulfate); preservatives (*e.g.*, methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, sorbic acid); flavours, flavour enhancing agents, and sweeteners.

40 Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided

with a coating, for example, to affect release, for example an enteric coating, to provide release in parts of the gut other than the stomach.

5 Ointments are typically prepared from the compound and a paraffinic or a water-miscible ointment base.

10 Creams are typically prepared from the compound and an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

15 Emulsions are typically prepared from the compound and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

25 Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulfate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

40 Formulations suitable for intranasal administration, where the carrier is a liquid, include, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the compound.

Formulations suitable for intranasal administration, where the carrier is a solid, include, for example, those presented as a coarse powder having a particle size, for example, in

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the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

5 Formulations suitable for pulmonary administration (e.g., by inhalation or insufflation therapy) include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide, or other suitable gases.

10 Formulations suitable for ocular administration include eye drops wherein the compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the compound.

15 Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols, for example, cocoa butter or a salicylate; or as a solution or suspension for treatment by enema.

20 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the compound, such carriers as are known in the art to be appropriate.

25 Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the compound is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additionally contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient.

30 Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the compound in the liquid is from about 1 ng/mL to about 10 µg/mL, for example from about 10 ng/mL to about 1 µg/mL. The formulations may be

35 presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile

40 powders, granules, and tablets.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the NISA compounds, and compositions comprising the NISA compounds, can vary from patient to

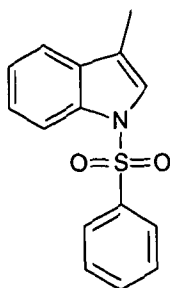
patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular NISA compound, the route of administration, the time of administration, the rate of excretion of the NISA compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the disorder, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of NISA compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (*e.g.*, in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of the NISA compound is in the range of about 10 μg to about 250 mg (more typically about 100 μg to about 25 mg) per kilogram body weight of the subject per day. Where the compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

EXAMPLESChemical Synthesis

- 5 The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Synthesis 13-Methyl-1-(phenylsulfonyl)-1*H*-indole (**ABD0945d**)

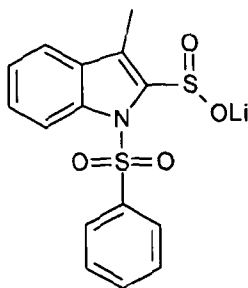
10

Method A: 3-Methyl indole (14.5 g) was dissolved in dry tetrahydrofuran (150 mL) and cooled in an ethanol/CO₂ bath under N₂. 1.6 M Butyllithium (72 mL) was added dropwise and the mixture stirred for 1 h whilst warming to 0°C. The mixture was again cooled in the ethanol/CO₂ bath and benzene sulfonyl chloride (23 g) was added dropwise. The mixture then allowed slowly to warm to room temperature for 2 h. The mixture was poured into 2% Na₂CO₃, extracted with ether, washed with sat. Na₂CO₃ solution, dried and evaporated to give the title compound as a white crystalline solid.

15

¹³C NMR (DMSO-*d*₆): δ 9.3, 113.2, 118.7, 119.9, 123.4, 124.7, 126.5, 129.7, 129.9, 131.4, 134.3, 134.5 and 137.2.

20

Synthesis 2Lithium 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD0945c**)

25

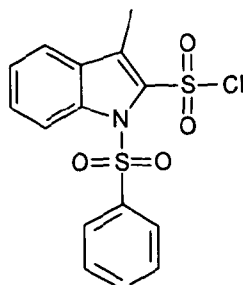
Method B: A solution of 1.6 M n-butyllithium in hexane (43 mL, 70 mmol) was added dropwise over 1 h to a solution of 3-methyl-1-(phenylsulfonyl)-1*H*-indole (**ABD0945d**) (18 g, 66 mmol) in dry tetrahydrofuran (100 mL), under nitrogen, and cooled to -70°C. After an additional 30 minutes, dry sulfur dioxide gas was introduced over the solution surface for 15 minutes to give a copious precipitate. This suspension was allowed to

- 100 -

warm to room temperature over 2 h, diluted with petroleum spirit (250 mL), and the white precipitate was collected by filtration to give the lithium sulfinatate salt as a white powder.

Synthesis 3

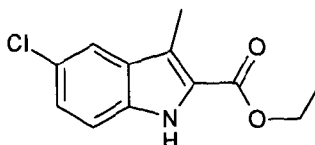
5 3-Methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**)



10 Method C: Lithium 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD0945c**) (6 g) was suspended in methylene chloride (50 mL) and cooled to 5°C, and *N*-chlorosuccinimide (2.4 g) was added portionwise. After 2 h, the mixture was filtered, and the solvent was evaporated to give a brown oil which solidified on standing.

Synthesis 4

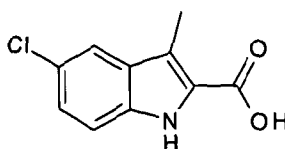
Ethyl 5-chloro-3-methyl-1*H*-indole-2-carboxylate (**ABD0956g**)



15 Method D: 4-Chlorophenylhydrazine hydrochloride (3.98 g) was suspended in absolute ethanol (140 mL), 2-ketovaleric acid (2.54 mL) and *p*-toluenesulfonic acid monohydrate (21 g) were added and the resulting reaction mixture was refluxed for 20 h. After removal of ethanol under reduced pressure the residue was extracted with dichloromethane, washed twice with saturated NaHCO₃ solution, dried over MgSO₄, and evaporated under
20 reduced pressure to give crude product which was recrystallized from light petroleum and EtOAc to give the title compound as white needles.

Synthesis 5

5-Chloro-3-methyl-1*H*-indole-2-carboxylic acid (**ABD0956f**)



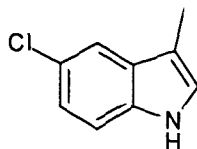
25 Method E: Ethyl 5-chloro-3-methyl-1*H*-indole-2-carboxylate (**ABD0956g**) (1 g) was dissolved in ethanol (30 mL) and 5% NaOH (15 mL) was added. The reaction mixture was kept at 40°C with stirring overnight. After removal of ethanol under reduced pressure, the residue was then taken into water, precipitated out at pH 1 using 5% HCl

and the precipitate extracted with EtOAc, dried over MgSO₄ and evaporated under reduced pressure to give the title compound as a white solid.

Synthesis 6

5

5-Chloro-3-methyl-1*H*-indole (**ABD0956e**)



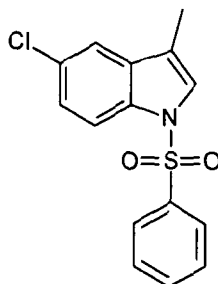
Method F: 5-Chloro-3-methyl-1*H*-indole-2-carboxylic acid (**ABD0956f**) (2 g) and copper powder (1.2 g) were mixed in toluene (50 mL) and purged with N₂ for 5 minutes. The mixture was microwaved for 25 minutes at 250°C. After cooling to room temperature, the reaction mixture was acidified with 6 N HCl and the copper powder was removed by filtration. The filtrate was extracted twice with EtOAc, washed with saturated NaHCO₃ solution, brine, dried over MgSO₄, and evaporated under reduced pressure to give a crude product which was purified by flash chromatography on silica gel.

¹³C NMR (CDCl₃): δ 9.5, 111.6, 112.0, 118.4, 122.1, 123.1, 124.9, 129.4 and 134.6.
¹H NMR (CDCl₃): δ 2.32 (3H, s), 7.00 (1H, s), 7.17 (1H, dd, *J* = 2.0, 8.4 Hz), 7.24 (1H, d, *J* = 8.4 Hz), 7.57 (1H, s) and 7.88 (1H, br s).

Synthesis 7

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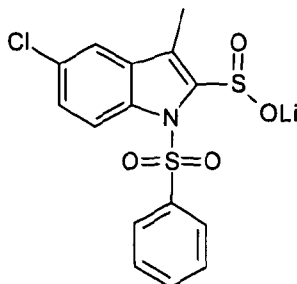
5-Chloro-3-methyl-1-(phenylsulfonyl)-1*H*-indole (**ABD0956d**)



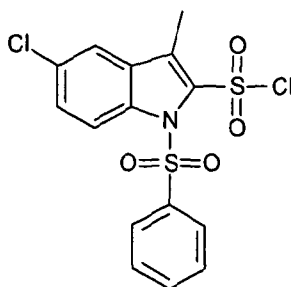
Using a method analogous to Method A, with 5-chloro-3-methyl-1*H*-indole (**ABD0956e**), the title compound was obtained as a white powder.

¹³C NMR (CDCl₃): δ 9.6, 114.7, 118.3, 119.3, 124.4, 124.9, 126.7, 129.1, 129.3, 133.1, 133.6, 133.8 and 138.1. ¹H NMR (CDCl₃): δ 2.00 (3H, s), 7.01 (1H, dd, *J* = 2.0, 8.4 Hz), 7.07 (1H, s), 7.16 - 7.19 (3H, m), 7.26 - 7.30 (1H, m), 7.57 - 7.59 (2H, m) and 7.65 (1H, d, *J* = 8.4 Hz).

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Synthesis 8Lithium 5-chloro-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD0956c**)

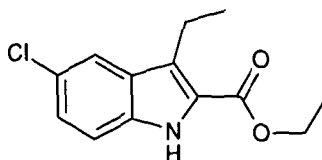
5 Using a method analogous to Method B, with 5-chloro-3-methyl-1-(phenylsulfonyl)-1*H*-indole (**ABD0956d**), the title compound was obtained as a yellow solid.

Synthesis 95-Chloro-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0956b**)

10 Using a method analogous to Method C, with lithium 5-chloro-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD0956c**), the title compound was obtained as a white powder on crystallisation from DCM/petrol.

Synthesis 10

15 Ethyl 5-chloro-3-ethyl-1*H*-indole-2-carboxylate (**ABD0962g**)



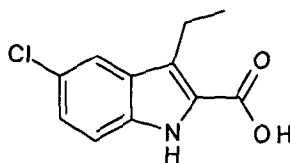
Using a method analogous to Method D, with 4-chlorophenylhydrazine hydrochloride and 2-oxovaleric acid, the title compound was obtained as white needles on crystallisation from EtOAc/petrol.

20

¹³C NMR (CDCl₃): δ 14.4, 15.4, 18.0, 61.0, 112.9, 120.1, 124.0, 125.6, 125.9, 126.1, 128.6, 134.2 and 162.0. ¹H NMR (CDCl₃): δ 1.27 (3H, t, *J* = 7.6 Hz), 1.46 (3H, t, *J* = 6.8 Hz), 3.07 (2H, q, *J* = 6.8 Hz), 4.44 (2H, q, *J* = 7.2 Hz), 7.30 - 7.24 (2H, m), 7.66 (1H, s) and 9.00 (1H, br s).

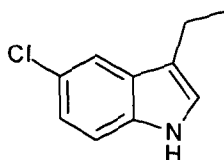
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Synthesis 115-Chloro-3-ethyl-1*H*-indole-2-carboxylic acid (**ABD0962f**)

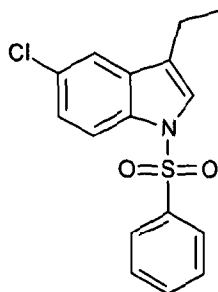
Using a method analogous to Method E, with ethyl 5-chloro-3-ethyl-1*H*-indole-2-carboxylate (**ABD0962g**) the title compound was obtained as a white solid.

¹³C NMR (DMSO-*d*₆): δ 16.1, 17.7, 114.5, 119.7, 124.2, 124.6, 125.0, 125.4, 128.3, 134.9 and 163.5. ¹H NMR (DMSO-*d*₆): δ 1.15 (3H, t, *J* = 7.6 Hz), 3.01 (2H, q, *J* = 7.2 Hz), 7.22 (1H, dd, *J* = 2.0, 9.2 Hz), 7.39 (1H, d, *J* = 7.6 Hz), 7.69 (1H, d, *J* = 2.0 Hz) and 11.55 (1H, br s).

Synthesis 125-Chloro-3-ethyl-1*H*-indole (**ABD0962e**)

Using a method analogous to Method F, with 5-chloro-3-ethyl-1*H*-indole-2-carboxylic acid (**ABD0962f**), the title compound was obtained as a white solid.

¹³C NMR (CDCl₃): δ 14.4, 18.2, 112.0, 118.5, 118.6, 121.9, 122.1, 124.8, 128.6 and 134.7. ¹H NMR (CDCl₃): δ 1.34 (3H, t, *J* = 7.6 Hz), 2.75 (2H, q, *J* = 7.6 Hz), 7.00 (1H, s), 7.15 (1H, dd, *J* = 2.0, 8.4 Hz), 7.25 (1H, d, *J* = 8.4 Hz), 7.59 (1H, d, *J* = 2.0 Hz) and 7.88 (1H, br s).

Synthesis 135-Chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole (**ABD0962d**)

Using a method analogous to Method A, with 5-chloro-3-ethyl-1*H*-indole (**ABD0962e**), the title compound was obtained as a yellow solid.

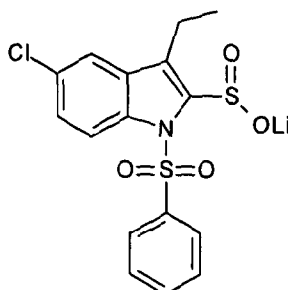
¹³C NMR (CDCl₃): δ 13.1, 18.0, 114.8, 119.3, 123.3, 124.9, 124.9, 126.6, 129.0, 129.3, 132.3, 133.8, 133.8 and 138.1. ¹H NMR (CDCl₃): δ 1.29 (3H, t, *J* = 7.6 Hz), 2.62 (2H, q, *J*

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= 7.6 Hz), 7.26 (1H, dd, $J = 2.0, 8.8$ Hz), 7.33 (1H, s), 7.41 - 7.45 (3H, m), 7.51 - 7.55 (1H, m), 7.83 - 7.85 (2H, m) and 7.91 (1H, d, $J = 8.8$ Hz).

Synthesis 14

5 Lithium 5-chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD0962c**)

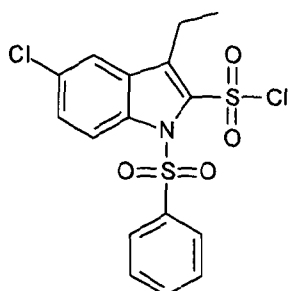


Using a method analogous to Method B, with 5-chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole (**ABD0962d**), the title compound was obtained as a white powder.

10

Synthesis 15

5-Chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0962b**)

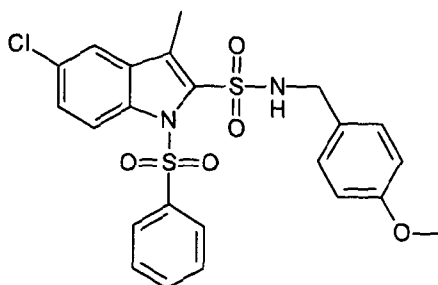


Using a method analogous to Method C, with lithium 5-chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD0962c**), the title compound was obtained as a white powder

15 on crystallisation from DCM/petrol.

Synthesis 16

5-Chloro-*N*-(4-methoxybenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0956a**)



20

Method G: 5-Chloro-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0956b**) (0.5 g) was dissolved in DCM (30 mL) and cooled in a water bath. 4-Methoxybenzylamine (1.5 mL) was added and the mixture stirred for 4 h. The mixture

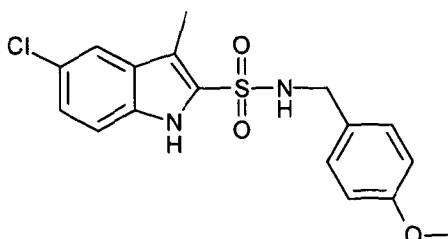
- 105 -

was poured into acidified water (250 mL) and extracted with ethyl acetate (200 mL). The organic was washed with water (4 x 200 mL), dried and evaporated to give an oil. Trituration with diethyl ether and addition of petrol gave the title compound as a white solid.

5

Synthesis 17

5-Chloro-*N*-(4-methoxybenzyl)-3-methyl-1*H*-indole-2-sulfonamide (**ABD0956**)



Method H: 5-Chloro-*N*-(4-methoxybenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0956a**) (1g) was suspended in 10% NaOH (25 mL) and ethanol (25 mL) and heated to reflux for 4 h, giving a clear solution. The organic solvent was evaporated under vacuum and the aqueous extracted with ethyl acetate, dried and evaporated to give the title compound as a white solid upon recrystallisation from ether/petrol.

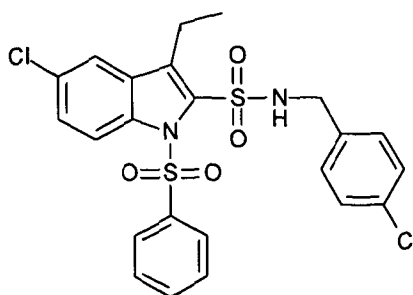
15

^{13}C NMR (DMSO- d_6): δ 8.7, 45.3, 55.0, 113.3, 113.5, 114.8, 119.6, 124.2, 124.9, 128.4, 128.8, 129.3, 131.6, 133.7 and 158.4. ^1H NMR (DMSO- d_6): δ 2.38 (3H, s), 3.64 (3H, s), 3.98 (2H, s), 6.73 (2H, d, J = 8.2 Hz), 7.10 (2H, d, J = 8.2 Hz), 7.25 (1H, d, J = 8.8 Hz), 7.40 (1H, d, J = 8.8 Hz), 7.70 (1H, s), 8.26 (1H, s) and 11.77 (1H, s).

20

Synthesis 18

5-Chloro-*N*-(4-chlorobenzyl)-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0962a**)



Using a method analogous to Method G, with 5-chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0962b**) and 4-chlorobenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

^{13}C NMR (DMSO- d_6): δ 14.7, 18.2, 45.8, 117.5, 120.6, 126.8, 127.8, 128.5, 129.1, 129.5, 129.6, 129.8, 131.7, 133.6, 134.9, 135.2, 135.9, 136.1 and 136.1. ^1H NMR (DMSO- d_6): δ 1.04 (3H, t, J = 7.3 Hz), 2.89 (2H, q, J = 7.3 Hz), 4.22 (2H, m), 7.10 (2H, d, J = 8.2 Hz),

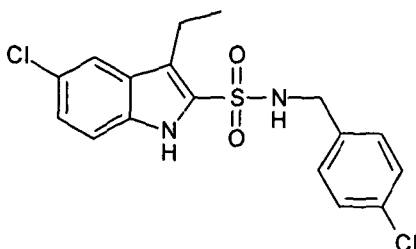
30

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7.24 (2H, d, $J = 8.2$ Hz), 7.51 (1H, m), 7.53 (2H, d, $J = 8.2$ Hz), 7.63 (1H, t, $J = 7.6$ Hz), 7.75 (1H, s), 7.86 (2H, d, $J = 7.6$ Hz), 8.04 (1H, m), 8.05 (1H, d, $J = 8.8$ Hz).

Synthesis 19

5 5-Chloro-*N*-(4-chlorobenzyl)-3-ethyl-1*H*-indole-2-sulfonamide (**ABD0962**)



Using a method analogous to Method H with 5-chloro-*N*-(4-chlorobenzyl)-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0962a**), the title compound was obtained as a white powder on crystallisation from ether/petrol.

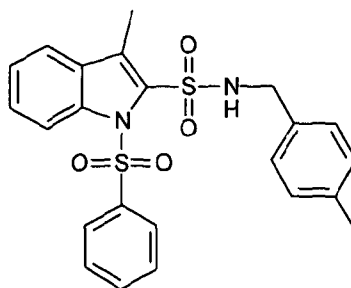
10

^{13}C NMR (DMSO- d_6): δ 15.7, 16.7, 45.0, 114.3, 119.1, 119.9, 124.3, 124.6, 127.4, 128.0, 129.2, 130.8, 131.7, 133.9 and 136.8. ^1H NMR (DMSO- d_6): δ 1.17 (3H, t, $J = 7.3$ Hz), 2.89 (2H, q, $J = 7.3$ Hz), 4.08 (2H, m), 7.25 (5H, m), 7.42 (1H, d, $J = 8.5$ Hz), 7.69 (1H, s), 8.42 (1H, br s) and 11.78 (1H, br s).

15

Synthesis 20

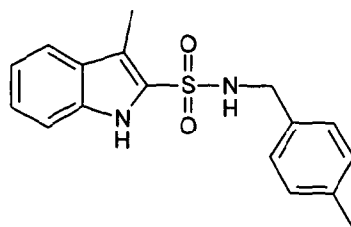
3-Methyl-*N*-(4-methylbenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0965a**)



20 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 4-methylbenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

Synthesis 21

N-(4-Methylbenzyl)-3-methyl-1*H*-indole-2-sulfonamide (**ABD0965**)



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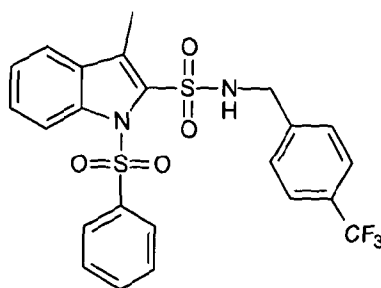
Using a method analogous to Method H with 3-methyl-*N*-(4-methylbenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0965a**), the title compound was obtained as a white powder on crystallisation from ether/petrol.

- 5 ¹³C NMR (DMSO-*d*₆): δ 8.8, 20.7, 45.6, 112.4, 113.8, 119.5, 119.9, 124.4, 127.3, 127.4, 128.7, 129.9, 134.7, 135.4 and 136.2. ¹H NMR (DMSO-*d*₆): δ 2.21 (3H, s), 2.44 (3H, s), 4.02 (2H, m), 7.03 (2H, d, *J* = 8.5 Hz), 7.09 (1H, m), 7.11 (2H, d, *J* = 8.2 Hz), 7.26 (1H, t, *J* = 8.2 Hz), 7.42 (1H, d, *J* = 8.2 Hz), 7.62 (1H, d, *J* = 7.9 Hz). MS, *m/z*: Calcd, 314.11; Found, 313.02 (M-1).

10

Synthesis 22

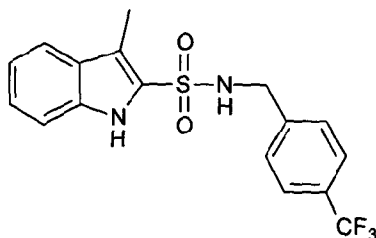
3-Methyl-1-(phenylsulfonyl)-*N*-(4-(trifluoromethyl)benzyl)-1*H*-indole-2-sulfonamide (**ABD0968a**)



- 15 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 4-trifluoromethyl-benzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

Synthesis 23

20 3-Methyl-*N*-(4-(trifluoromethyl)benzyl)-1*H*-indole-2-sulfonamide (**ABD0968**)



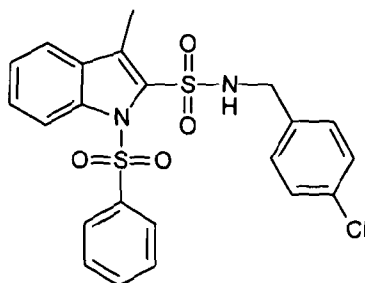
Using a method analogous to Method H with 3-methyl-1-(phenylsulfonyl)-*N*-(4-(trifluoromethyl)benzyl)-1*H*-indole-2-sulfonamide (**ABD0968a**), the title compound was obtained as a white powder on purification by column chromatography.

25

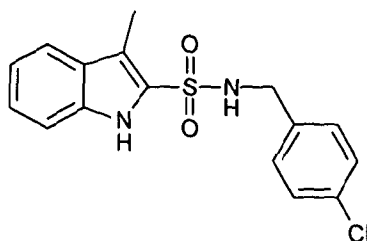
¹³C NMR (DMSO-*d*₆): δ 8.8, 45.2, 112.4, 114.0, 119.5, 120.0, 124.4, 124.9, 127.2, 127.4, 127.9, 128.0, 129.5, 135.4 and 142.8. ¹H NMR (DMSO-*d*₆): δ 2.43 (3H, s), 4.16 (2H, m), 7.08 (1H, t, *J* = 7.0 Hz), 7.25 (1H, t, *J* = 7.0 Hz), 7.40 (1H, d, *J* = 8.2 Hz), 7.46 (2H, d, *J* = 8.2 Hz), 7.55 (3H, m), 8.40 (1H, s), and 11.60 (1H, s).

30

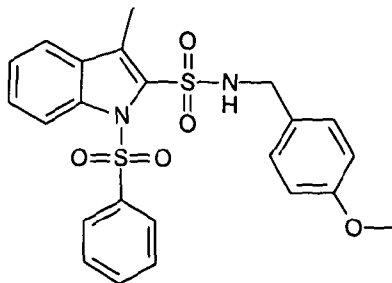
- 108 -

Synthesis 24*N*-(4-Chlorobenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0972a**)

- 5 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 4-chlorobenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

Synthesis 25*N*-(4-Chlorobenzyl)-3-methyl-1*H*-indole-2-sulfonamide (**ABD0972**)

- 10 Using a method analogous to Method H with *N*-(4-chlorobenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0972a**), the title compound was obtained as white needles on crystallisation from ether / petrol.
- 15 ¹³C NMR (DMSO-*d*₆): δ 11.0, 45.7, 115.3, 121.2, 124.6, 126.8, 127.9, 129.1, 129.4, 129.6, 130.6, 131.7, 136.2 and 136.6. MS, *m/z*: Calcd, 334.05; Found, 332.95 (M-1).

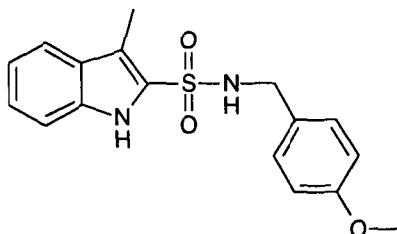
Synthesis 26*N*-(4-Methoxybenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0975a**)

- 20 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 4-methoxybenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

- ¹³C NMR (DMSO-*d*₆): δ 11.0, 46.1, 54.7, 113.0, 113.2, 115.4, 121.3, 124.5, 126.8, 126.9, 128.6, 128.8, 129.1, 130.1, 132.8, 134.7, 136.5, 136.8 and 158.2. ¹H NMR (DMSO-*d*₆): δ 2.38 (3H, s), 3.48 (3H, s), 4.15 (2H, d, *J* = 5.8 Hz), 6.55 (2H, d, *J* = 8.5 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 7.32 (1H, t, *J* = 7.3 Hz), 7.49 (2H, m), 7.59 (2H, d, *J* = 7.9 Hz), 7.72 (1H, t, *J* = 6.4 Hz), 7.88 (2H, d, *J* = 7.3 Hz) and 8.04 (1H, d, *J* = 8.2 Hz).

Synthesis 27

N-(4-Methoxybenzyl)-3-methyl-1*H*-indole-2-sulfonamide (**ABD0975**)



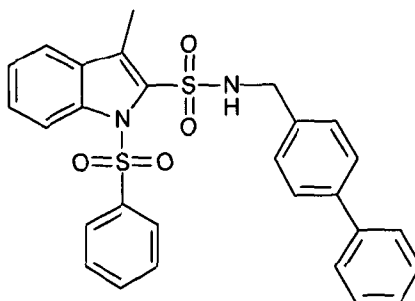
- 10 Using a method analogous to Method H with *N*-(4-methoxybenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0975a**), the title compound was obtained as white needles on filtration and washing with ether.

- 15 ¹³C NMR (DMSO-*d*₆): δ 8.8, 45.3, 55.0, 112.4, 113.5, 113.7, 119.4, 119.9, 124.4, 127.3, 129.0, 129.6, 129.9, 135.4 and 158.4. ¹H NMR (DMSO-*d*₆): δ 2.44 (3H, s), 3.66 (3H, s), 4.00 (2H, d, *J* = 6.1 Hz), 6.78 (2H, d, *J* = 8.5 Hz), 7.09 (1H, t, *J* = 7.6 Hz), 7.14 (2H, d, *J* = 8.5 Hz), 7.26 (1H, t, *J* = 7.6 Hz), 7.42 (1H, d, *J* = 7.9 Hz), 7.61 (1H, d, *J* = 7.9 Hz), 8.16 (1H, t, *J* = 6.1 Hz) and 11.6 (1H, s). MS, *m/z*: Calcd, 330.10; Found, 329.99 (M).

20

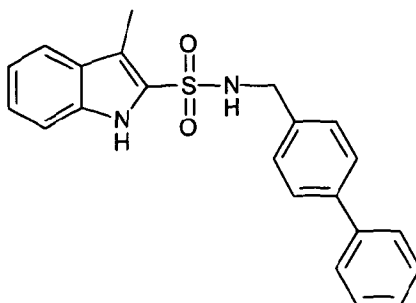
Synthesis 28

N-(Biphenyl-4-ylmethyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0978a**)



- 25 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 4-phenylbenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

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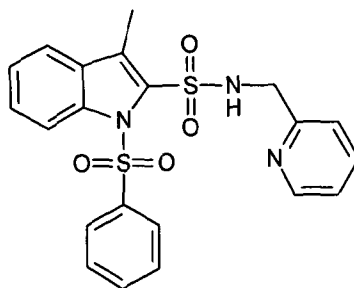
Synthesis 29*N*-(Biphenyl-4-ylmethyl)-3-methyl-1*H*-indole-2-sulfonamide (**ABD0978**)

- 5 Using a method analogous to Method H with *N*-(biphenyl-4-ylmethyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0978a**), the title compound was obtained as white needles by filtration on recrystallisation from ether/petrol.

- 10 ¹³C NMR (DMSO-*d*₆): δ 8.9, 45.5, 112.4, 113.8, 119.6, 120.2, 124.5, 126.4, 126.7, 127.3, 127.4, 127.9, 128.9, 129.8, 135.4, 137.0, 139.0 and 139.9. ¹H NMR (DMSO-*d*₆): δ 2.46 (3H, s), 4.11 (2H, m), 7.08 (1H, t, *J* = 7.6 Hz), 7.25 (1H, t, *J* = 7.9 Hz), 7.32 (2H, d, *J* = 7.9 Hz), 7.37 (1H, m), 7.42 (2H, d, *J* = 6.1 Hz), 7.46 (1H, m), 7.52 (2H, d, *J* = 7.9 Hz), 7.57 (2H, d, *J* = 8.8 Hz), 7.61 (1H, d, *J* = 8.8 Hz), 8.32 (1H, s) and 11.6 (1H, s).

Synthesis 30

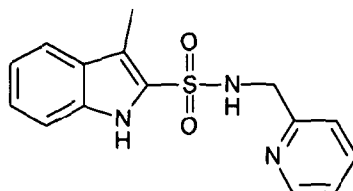
- 15 3-Methyl-1-(phenylsulfonyl)-*N*-(pyridin-2-ylmethyl)-1*H*-indole-2-sulfonamide (**ABD0979a**)



- 20 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 2-picolylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

¹H NMR (DMSO-*d*₆): δ 2.40 (3H, s), 4.32 (2H, s), 7.05 (1H, t, *J* = 7.3 Hz), 7.39 (2H, m), 7.53 (3H, m), 7.64 (3H, m), 7.87 (2H, m), 7.92 (1H, d, *J* = 7.6 Hz), 8.05 (1H, d, *J* = 8.2 Hz) and 8.29 (1H, d, *J* = 4.6 Hz).

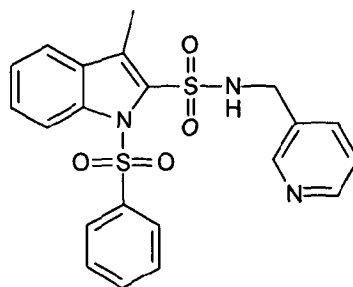
- 111 -

Synthesis 313-Methyl-*N*-(pyridin-2-ylmethyl)-1*H*-indole-2-sulfonamide (**ABD0979**)

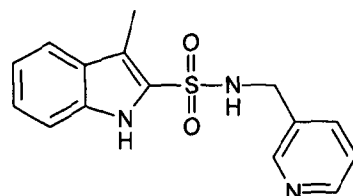
- 5 Using a method analogous to Method H with 3-methyl-1-(phenylsulfonyl)-*N*-(pyridin-2-ylmethyl)-1*H*-indole-2-sulfonamide (**ABD0979a**), the title compound was obtained as white needles by filtration on recrystallisation from ether/petrol.

¹³C NMR (DMSO-*d*₆): δ 8.8, 47.6, 112.4, 114.0, 119.6, 120.1, 121.3, 122.3, 124.6, 127.3, 129.7, 135.4, 136.7, 148.7 and 157.3.

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Synthesis 323-Methyl-1-(phenylsulfonyl)-*N*-(pyridin-3-ylmethyl)-1*H*-indole-2-sulfonamide (**ABD0983a**)

- 15 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 3-picolylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

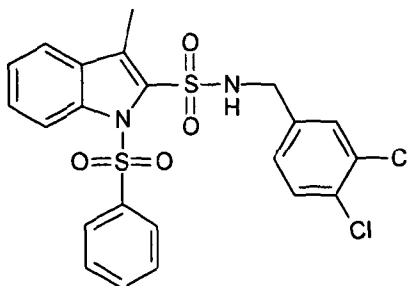
Synthesis 333-Methyl-*N*-(pyridin-3-ylmethyl)-1*H*-indole-2-sulfonamide (**ABD0983**)

20

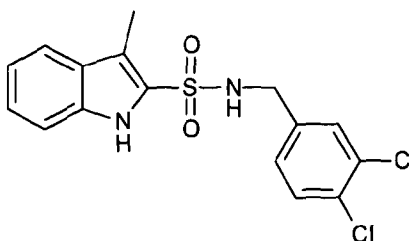
Using a method analogous to Method H with 3-methyl-1-(phenylsulfonyl)-*N*-(pyridin-3-ylmethyl)-1*H*-indole-2-sulfonamide (**ABD0983a**), the title compound was obtained as white needles by filtration on recrystallisation from ether/petrol.

- 25 ¹³C NMR (DMSO-*d*₆): δ 8.8, 43.4, 112.5, 114.0, 119.9, 120.3, 123.2, 124.6, 127.2, 129.5, 133.4, 135.3, 135.4, 148.5 and 149.0. ¹H NMR (DMSO-*d*₆): δ 2.43 (3H, s), 4.10 (2H, s), 7.10 (1H, m), 7.23 (2H, m), 7.43 (1H, m), 7.58 (2H, s), 8.36 (1H, s) and 8.42 (1H, s).

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Synthesis 34*N*-(3,4-Dichlorobenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0984a**)

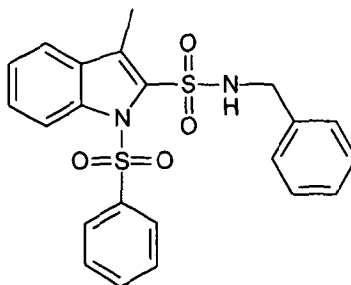
- 5 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 3,4-dichlorobenzylamine, the title compound was obtained as a white powder on crystallisation from ether / petrol.

Synthesis 35*N*-(3,4-Dichlorobenzyl)-3-methyl-1*H*-indole-2-sulfonamide (**ABD0984**)

10

Using a method analogous to Method H with *N*-(3,4-dichlorobenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0984a**), the title compound was obtained as a white powder on filtration and washing with ether.

- 15 ¹H NMR (DMSO-*d*₆): δ 2.41 (3H, s), 4.09 (2H, d, *J* = 6.1 Hz), 7.07 (1H, t, *J* = 7.9 Hz), 7.20 (1H, m), 7.26 (1H, d, *J* = 7.0 Hz), 7.36 (1H, s), 7.42 (2H, m), 7.58 (1H, d, *J* = 7.9 Hz), 8.24 (1H, t, *J* = 6.1 Hz), and 11.57 (1H, s).

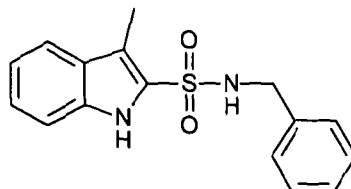
Synthesis 36*N*-Benzyl-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0986a**)

Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and benzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

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- ¹³C NMR (DMSO-*d*₆): δ 11.0, 46.4, 115.7, 121.4, 124.7, 126.9, 127.2, 128.0, 128.4, 128.5, 129.4, 129.6, 130.2, 132.7, 134.7, 136.6, 136.8 and 137.4. ¹H NMR (DMSO-*d*₆): δ 2.40 (3H, s), 4.22 (2H, d, *J* = 6.1 Hz), 7.01 (1H, m), 7.10 (2H, t, *J* = 7.3 Hz), 7.27 (2H, d, *J* = 7.0 Hz), 7.35 (1H, d, *J* = 7.3 Hz), 7.47 (3H, m), 7.59 (2H, d, *J* = 7.9 Hz), 7.72 (1H, t, *J* = 6.4 Hz), 7.88 (2H, d, *J* = 7.3 Hz) and 8.04 (1H, d, *J* = 8.2 Hz).

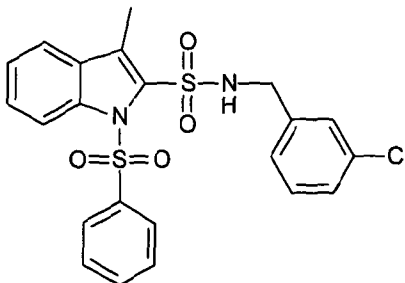
Synthesis 37*N*-Benzyl-3-methyl-1*H*-indole-2-sulfonamide (**ABD0986**)

- 10 Using a method analogous to Method H with *N*-benzyl-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0986a**), the title compound was obtained as a white powder on filtration and washing with ether.

- ¹³C NMR (DMSO-*d*₆): δ 8.8, 45.8, 112.5, 113.8, 119.5, 119.7, 120.1, 124.7, 127.2, 127.3, 128.2, 129.9, 135.5 and 137.9. ¹H NMR (DMSO-*d*₆): δ 2.46 (3H, s), 4.08 (2H, s), 7.10 (1H, t, *J* = 7.9 Hz), 7.24 (6H, m), 7.44 (1H, d, *J* = 8.2 Hz), 7.62 (1H, d, *J* = 7.9 Hz), 8.24 (1H, s), and 11.60 (1H, s).

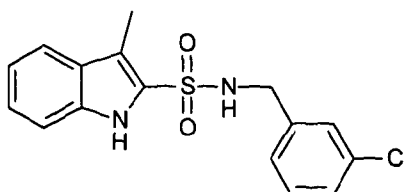
Synthesis 38

- 20 *N*-(3-Chlorobenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0989a**)



Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 3-chlorobenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

25

Synthesis 39*N*-(3-Chlorobenzyl)-3-methyl-1*H*-indole-2-sulfonamide (**ABD0989**)

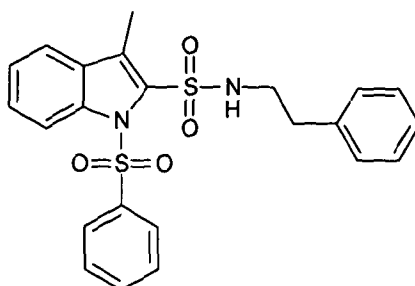
- 114 -

Using a method analogous to Method H with *N*-(3-chlorobenzyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD0989a**), the title compound was obtained as a white powder on recrystallisation from ether/petrol.

- 5 ^1H NMR ($\text{DMSO}-d_6$): δ 2.43 (3H, s), 4.10 (2H, s), 7.09 (1H, t, $J = 7.6$ Hz), 7.24 (5H, m), 7.41 (1H, d, $J = 7.9$ Hz), 7.60 (1H, d, $J = 7.9$ Hz), 8.33 (1H, s) and 11.60 (1H, s).

Synthesis 40

3-Methyl-*N*-phenethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1002a**)



10

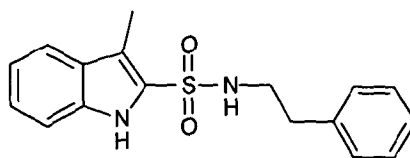
Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and phenylethylamine, the title compound was obtained as an oil which solidified on trituration with ether.

- 15 ^{13}C NMR (CDCl_3): δ 11.1, 36.0, 44.7, 115.9, 120.9, 124.5, 126.7, 127.5, 128.5, 128.7, 128.9, 129.5, 130.8, 131.6, 134.2, 137.3, 137.3 and 137.7. ^1H NMR (CDCl_3): δ 2.56 (3H, s), 2.88 (2H, t, $J = 7.6$ Hz), 3.34 (2H, q, $J = 6.8$ Hz), 6.06 (1H, br s), 7.16 - 7.58 (11H, m), 7.98 (2H, d, $J = 8.0$ Hz) and 8.24 (1H, d, $J = 8.4$ Hz).

20

Synthesis 41

3-Methyl-*N*-phenethyl-1*H*-indole-2-sulfonamide (**ABD1002**)



Using a method analogous to Method H with 3-methyl-*N*-phenethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1002a**), the title compound was obtained as a white powder.

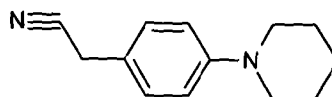
25

- 30 ^{13}C NMR (CDCl_3): δ 9.0, 35.5, 43.9, 112.0, 117.1, 120.6, 120.7, 125.8, 126.9, 127.9, 128.1, 128.7, 128.8, 135.4 and 137.4. ^1H NMR (CDCl_3): δ 2.39 (3H, s), 2.66 (2H, t, $J = 6.4$ Hz), 3.19 (2H, q, $J = 6.4$ Hz), 4.63 (1H, br s), 6.90 - 6.95 (2H, m), 7.06 - 7.20 (4H, m), 7.25 - 7.35 (2H, m), 7.55 (1H, d, $J = 7.6$ Hz), 8.61 (1H, br s).

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Synthesis 42

2-(4-(Piperidin-1-yl)phenyl)acetonitrile



5 Method I: To a stirred solution of 4-aminophenylacetonitrile (2.5 g) in toluene (75 mL), 1,5-dibromopentane (2.58 mL) and DIPEA (7.9 mL) were added. The reaction mixture was refluxed for 20 h in an oil bath. After cooling, toluene was added and red brown precipitate (Br-salt) was collected by filtration. The filtrate was washed with water, dried over anhydrous MgSO₄, and evaporated under reduced pressure to give the title compound as a pale pink solid.

10

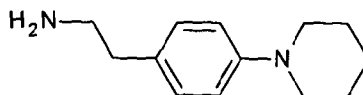
¹³C NMR (CDCl₃): δ 22.8, 24.3, 25.7, 50.4, 116.7, 118.5, 119.7, 128.7 and 151.9.

¹H NMR (CDCl₃): δ 1.57 – 1.69 (6H, m), 3.15 (4H, t, *J* = 4.5 Hz), 3.64 (2H, s), 6.91 (2H, d, *J* = 8.3 Hz) and 7.17 (2H, d, *J* = 8.3 Hz).

15

Synthesis 43

2-(4-(Piperidin-1-yl)phenyl)ethanamine

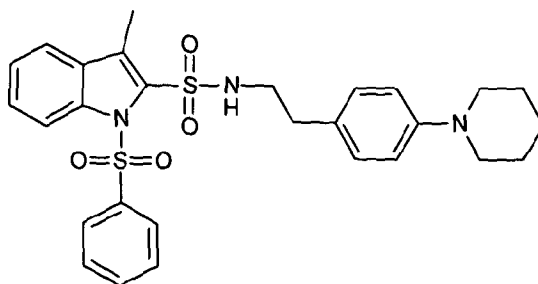


20 Method J: A solution of 2-(4-(piperidin-1-yl)phenyl)acetonitrile (2 g) in ether (35 mL) was added to a suspension of LiAlH₄ (3.8 g) in ether (15 mL) at 0°C under N₂. The mixture was stirred overnight at room temperature. A saturated solution of Na₂SO₄ was slowly added at 0°C and the mixture stirred for a further 30 minutes and then quenched with addition of water. The reaction mixture was filtered and the residue washed with ether (3 x 100 mL). The organic layer was washed with brine, dried over MgSO₄ and evaporated under reduced pressure to yield the title compound as a pale yellow oil.

25

¹³C NMR (CDCl₃): δ 24.3, 26.0, 39.3, 43.8, 51.0, 116.8, 129.4, 130.6 and 150.8. ¹H NMR (CDCl₃): δ 1.30 (2H, br s), 1.53 – 1.68 (6H, m), 2.63 (2H, t, *J* = 6.5 Hz), 2.89 (2H, t, *J* = 6.8 Hz), 3.09 (4H, t, *J* = 4.8 Hz), 6.86 (2H, d, *J* = 8.7 Hz) and 7.05 (2H, d, *J* = 8.8 Hz).

30

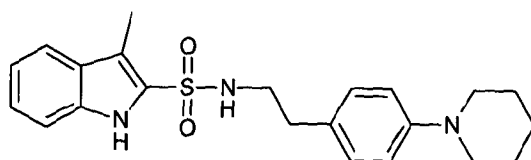
Synthesis 443-Methyl-1-(phenylsulfonyl)-*N*-(4-(piperidin-1-yl)phenethyl)-1*H*-indole-2-sulfonamide (ABD1004a)

Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 2-(4-(piperidin-1-yl)phenyl)ethanamine, the title compound was obtained as a white solid after purification by column chromatography.

- 5 ¹³C NMR (CDCl₃): δ 11.1, 24.3, 25.8, 35.0, 44.9, 50.7, 115.9, 116.8, 120.9, 124.5, 127.5, 128.1, 128.5, 128.9, 129.2, 129.5, 130.8, 131.7, 134.1, 137.3, 137.4 and 151.1. ¹H NMR (CDCl₃): δ 1.27 - 1.23 (2H, m), 1.36 - 1.42 (4H, m), 2.26 (3H, s), 2.49 (2H, t, *J* = 7.2 Hz), 2.79 (4H, t, *J* = 5.2 Hz), 2.98 (2H, q, *J* = 6.8 Hz), 5.74 (1H, t, *J* = 6.4 Hz), 6.54 (2H, d, *J* = 8.4 Hz), 6.73 (2H, d, *J* = 8.4 Hz), 7.03 - 7.12 (3H, m), 7.19 - 7.29 (3H, m), 7.68 (2H, d, *J* = 8.4 Hz) and 7.95 (1H, d, *J* = 8.8 Hz).
- 10

Synthesis 45

3-Methyl-*N*-phenethyl-1*H*-indole-2-sulfonamide (**ABD1004**)

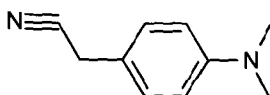


- 15 Using a method analogous to Method H with 3-methyl-1-(phenylsulfonyl)-*N*-(4-(piperidin-1-yl)phenethyl)-1*H*-indole-2-sulfonamide (**ABD1004a**), the title compound was obtained as a white powder.

- 20 ¹³C NMR (CDCl₃): δ 9.0, 24.2, 25.8, 34.4, 44.0, 50.6, 111.9, 116.7, 116.9, 120.6, 120.6, 125.7, 127.4, 128.1, 129.3, 135.3 and 151.2. ¹H NMR (CDCl₃): δ 1.55 - 1.60 (2H, m), 1.67 - 1.73 (4H, m), 2.47 (3H, s), 2.66 (2H, t, *J* = 6.4 Hz), 3.11 (4H, t, *J* = 5.2 Hz), 3.23 (2H, q, *J* = 6.4 Hz), 4.51 (1H, t, *J* = 6.0 Hz), 6.80 (2H, d, *J* = 8.8 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 7.18 - 7.22 (1H, m), 7.34 - 7.35 (2H, m), 7.64 (1H, d, *J* = 7.6 Hz) and 8.46 (1H, br s). MS, *m/z*: Calcd, 397.18; Found, 397.04 (M).
- 25

Synthesis 46

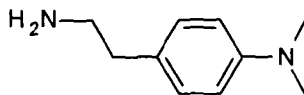
2-(4-(Dimethylamino)phenyl)acetonitrile



- 30 To a mixture of 4-aminobenzylcyanide (1.32 g) and 37% aqueous formaldehyde (8 mL) in acetonitrile (40 mL), NaBH₃CN (1.9 g) was added. After addition of glacial acetic acid (1 mL) dropwise, the reaction mixture was stirred for 2 h at room temperature. An additional glacial acetic acid (1 mL) was then added and the stirring was continued for further 30 minutes. Et₂O (150 mL) was added and reaction mixture was washed with 1 M KOH (3 x 40 mL) and brine. The ether layer was dried over MgSO₄ and evaporated
- 35 *in vacuo* to give the title compound as a pale brown solid.

- ¹³C NMR (CDCl₃): δ 22.7, 40.6, 112.8, 117.1, 118.8, 128.8 and 150.2. ¹H NMR (CDCl₃): δ 2.95 (6H, s), 3.63 (2H, s), 6.71 (2H, d, *J* = 8.8 Hz) and 7.16 (2H, d, *J* = 8.5 Hz).

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Synthesis 474-(2-Aminoethyl)-*N,N*-dimethylaniline

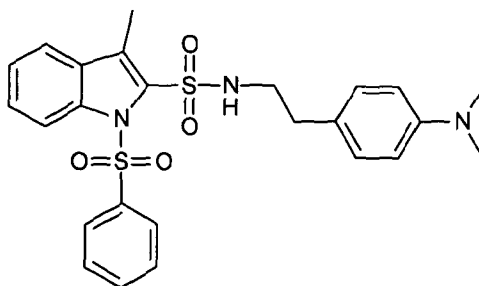
5 Using a method analogous to Method J, with 2-(4-(dimethylamino)phenyl)acetonitrile, the title compound was obtained as a reddish brown oil.

¹³C NMR (CDCl₃): δ 37.3, 40.9, 42.9, 113.0, 127.2, 129.5 and 149.4. ¹H NMR (CDCl₃): δ 2.72 (2H, t, *J* = 4.5 Hz), 2.81 - 3.04 (8H, m), 4.65 (2H, br s), 6.68 (2H, d, *J* = 8.3 Hz) and 7.07 (2H, d, *J* = 7.3 Hz).

10

Synthesis 48

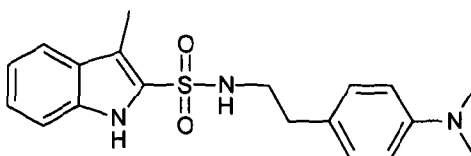
N-(4-(Dimethylamino)phenethyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide
(**ABD1006a**)



15 Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 4-(2-aminoethyl)-*N,N*-dimethylaniline, the title compound was obtained as a white solid after purification by column chromatography.

20 ¹³C NMR (CDCl₃): δ 11.1, 34.9, 40.7, 45.1, 113.0, 115.9, 120.9, 124.4, 125.4, 127.5, 128.4, 128.9, 129.3, 129.5, 130.7, 131.7, 134.1, 137.3, 137.4 and 149.5. ¹H NMR (CDCl₃): δ 2.55 (3H, s), 2.78 (2H, t, *J* = 7.6 Hz), 2.88 (6H, m), 3.28 (2H, q, *J* = 6.8 Hz), 6.03 (1H, t, *J* = 6.4 Hz), 6.64 (2H, d, *J* = 8.8 Hz), 7.01 (2H, d, *J* = 8.8 Hz), 7.33 - 7.31 (3H, m), 7.48 - 7.58 (3H, m), 8.00 (2H, d, *J* = 8.0 Hz) and 8.24 (1H, d, *J* = 8.4 Hz).

25

Synthesis 493-Methyl-*N*-phenethyl-1*H*-indole-2-sulfonamide (**ABD1006**)

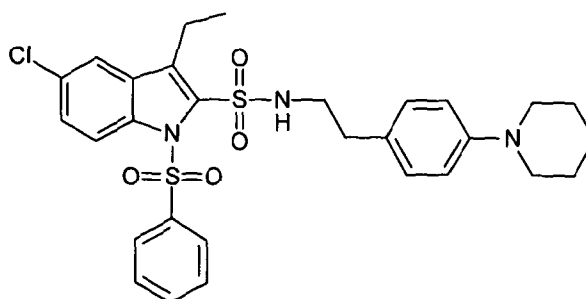
30 Using a method analogous to Method H with *N*-(4-(dimethylamino)phenethyl)-3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1006a**), the title compound was obtained as a white powder.

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¹³C NMR (CDCl₃): δ 34.3, 40.6, 44.2, 112.0, 113.0, 117.0, 120.6, 124.8, 125.6, 128.1, 129.3, 135.3 and 149.6. ¹H NMR (CDCl₃): δ 2.40 (3H, s), 2.57 (2H, t, *J* = 6.8 Hz), 2.82 (6H, m), 3.15 (2H, q, *J* = 6.8 Hz), 4.51 (1H, t, *J* = 6.0 Hz), 6.52 (2H, d, *J* = 8.8 Hz), 6.81 (2H, d, *J* = 8.8 Hz), 7.10 - 7.14 (1H, m), 7.26 - 7.28 (2H, m), 7.56 (1H, d, *J* = 8.0 Hz) and 8.46 (1H, br s).

Synthesis 50

5-Chloro-3-ethyl-1-(phenylsulfonyl)-*N*-(4-(piperidin-1-yl)phenethyl)-1*H*-indole-2-sulfonamide (**ABD1012a**)

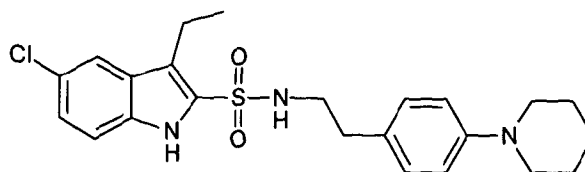


Using a method analogous to Method G, with 5-chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0962b**) and 2-(4-(piperidin-1-yl)phenyl)ethanamine, the title compound was obtained as a white solid after purification by column chromatography.

¹³C NMR (CDCl₃): δ 14.8, 18.6, 24.3, 25.8, 35.0, 45.0, 50.7, 116.8, 117.3, 120.4, 127.5, 127.9, 128.5, 129.0, 129.2, 130.0, 130.5, 132.7, 134.3, 135.6, 135.8, 137.0 and 151.1. ¹H NMR (CDCl₃): δ 1.13 (3H, t, *J* = 7.6 Hz), 1.46 - 1.51 (2H, m), 1.57 - 1.64 (4H, m), 2.70 (2H, t, *J* = 7.6 Hz), 2.94 (2H, q, *J* = 7.2 Hz), 3.01 (4H, t, *J* = 5.2 Hz), 3.23 (2H, q, *J* = 7.2 Hz), 5.96 (1H, t, *J* = 6.0 Hz), 6.74 (2H, d, *J* = 8.4 Hz), 6.95 (2H, d, *J* = 8.4 Hz), 7.31 - 7.38 (3H, m), 7.45 - 7.49 (2H, m), 7.88 (2H, d, *J* = 8.4 Hz) and 8.11 (1H, d, *J* = 8.4 Hz).

Synthesis 51

5-Chloro-3-ethyl-*N*-(4-(piperidin-1-yl)phenethyl)-1*H*-indole-2-sulfonamide (**ABD1012**)



Using a method analogous to Method H with 5-chloro-3-ethyl-1-(phenylsulfonyl)-*N*-(4-(piperidin-1-yl)phenethyl)-1*H*-indole-2-sulfonamide (**ABD0962b**), the title compound was obtained as a white powder.

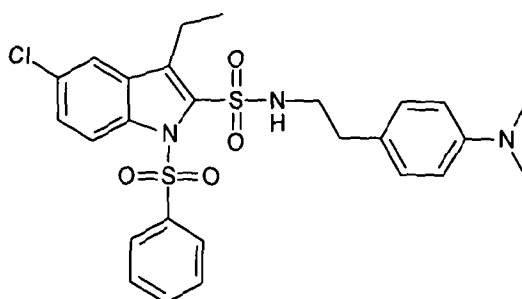
¹³C NMR (CDCl₃): δ 15.4, 17.5, 24.2, 25.8, 34.5, 44.2, 50.6, 113.4, 116.7, 120.0, 122.8, 126.0, 126.3, 127.3, 128.1, 128.8, 129.2, 133.8 and 151.1. ¹H NMR (CDCl₃): δ 1.15 (3H, t, *J* = 7.6 Hz), 1.47 - 1.51 (2H, m), 1.58 - 1.64 (4H, m), 2.57 (2H, t, *J* = 6.8 Hz), 2.84 (2H, q, *J* = 7.6 Hz), 3.01 (4H, t, *J* = 4.8 Hz), 3.14 (2H, q, *J* = 6.8 Hz), 4.66 (1H, t, *J* = 6.4 Hz),

6.70 (2H, d, $J = 8.4$ Hz), 6.81 (2H, d, $J = 8.4$ Hz), 7.18 - 7.20 (2H, m), 7.54 (1H, s), 8.68 (1H, br s). MS, m/z : Calcd, 445.16; Found, 445.01 (M).

5

Synthesis 52

5-Chloro-*N*-(4-(dimethylamino)phenethyl)-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1014a**)



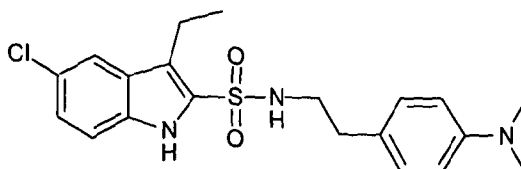
10 Using a method analogous to Method G, with 5-chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0962b**) and 4-(2-aminoethyl)-*N,N*-dimethylaniline, the title compound was obtained as a oil after purification by column chromatography.

15 ^{13}C NMR (CDCl_3): δ 14.8, 18.6, 34.9, 40.6, 45.2, 113.0, 117.3, 120.3, 125.2, 127.5, 128.5, 129.0, 129.2, 130.0, 130.4, 132.7, 134.3, 135.4, 135.8, 137.1 and 149.5. ^1H NMR (CDCl_3): δ 1.13 (3H, t, $J = 7.6$ Hz), 2.70 (2H, t, $J = 7.6$ Hz), 2.80 (6H, s), 2.91 (2H, q, $J = 7.2$ Hz), 3.23 (2H, q, $J = 7.2$ Hz), 5.95 (1H, t, $J = 6.0$ Hz), 6.53 (2H, d, $J = 8.4$ Hz), 6.93 (2H, d, $J = 8.4$ Hz), 7.31 - 7.37 (3H, m), 7.44 - 7.48 (2H, m), 7.87 (2H, d, $J = 8.4$ Hz) and 8.10 (1H, d, $J = 9.2$ Hz).

20

Synthesis 53

5-Chloro-*N*-(4-(dimethylamino)phenethyl)-3-ethyl-1*H*-indole-2-sulfonamide (**ABD1014**)



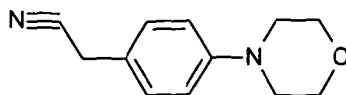
25 Using a method analogous to Method H with 5-chloro-*N*-(4-(dimethylamino)phenethyl)-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1014a**), the title compound was obtained as a white powder.

30 ^{13}C NMR (CDCl_3): δ 15.4, 17.5, 34.4, 40.8, 44.3, 113.2, 113.4, 120.0, 122.9, 126.0, 126.2, 128.1, 128.7, 129.3 and 133.9. ^1H NMR (CDCl_3): δ 1.18 (3H, t, $J = 7.6$ Hz), 2.58 (2H, t, $J = 6.4$ Hz), 2.82 - 2.89 (6H, m), 2.91 (2H, q, $J = 7.2$ Hz), 3.16 (2H, q, $J = 7.6$ Hz), 4.81 (1H, t, $J = 6.0$ Hz), 6.53 (2H, d, $J = 8.4$ Hz), 6.83 (2H, d, $J = 8.4$ Hz), 7.20 (2H, s), 7.56 (1H, s) and 8.85 (1H, br s). MS, m/z : Calcd, 405.13; Found, 404.97 (M).

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Synthesis 54

2-(4-Morpholinophenyl)acetonitrile



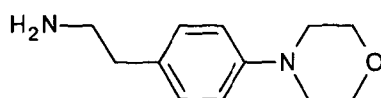
- 5 Using a method analogous to Method I with 4-aminophenylacetonitrile and 2-bromoethylether, the title compound was obtained as a pale yellow solid.

^{13}C NMR (CDCl_3): δ 22.8, 49.1, 66.8, 116.0, 118.0, 120.8, 128.8 and 151.0. ^1H NMR (CDCl_3): δ 3.14 (4H, t, J = 4.8 Hz), 3.66 (2H, s), 3.85 (4H, t, J = 4.5 Hz), 6.89 (2H, d, J = 8.8 Hz) and 7.21 (2H, d, J = 8.3 Hz).

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Synthesis 55

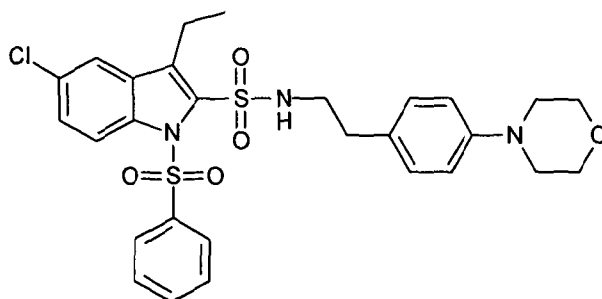
2-(4-Morpholinophenyl)ethanamine



- 15 Using a method analogous to Method J with 2-(4-morpholinophenyl)acetonitrile, the title compound was obtained as a pale yellow oil.

^{13}C NMR (CDCl_3): δ 39.0, 43.6, 49.6, 66.9, 115.9, 129.5, 131.3 and 149.7. ^1H NMR (CDCl_3): δ 1.92 (2H, br s), 2.65 (2H, t, J = 6.8 Hz), 2.90 (2H, t, J = 6.8 Hz), 3.10 (4H, t, J = 4.8 Hz), 3.84 (4H, t, J = 4.8 Hz), 6.85 (2H, d, J = 8.5 Hz) and 7.09 (2H, d, J = 8.3 Hz).

20

Synthesis 565-Chloro-3-ethyl-*N*-(4-morpholinophenethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1016a**)

- 25 Using a method analogous to Method G, with 5-chloro-3-ethyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0962b**) and 2-(4-morpholinophenyl)ethanamine, the title compound was obtained as a oil after purification by column chromatography.

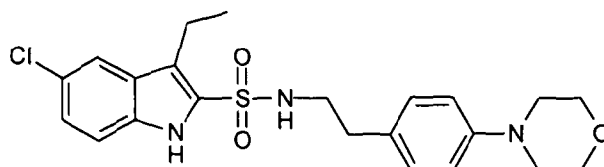
- 30 ^{13}C NMR (CDCl_3): δ 14.8, 18.6, 35.0, 44.9, 49.4, 66.9, 116.0, 117.3, 120.4, 127.5, 128.5, 128.9, 129.0, 129.4, 130.0, 130.5, 132.7, 134.4, 135.5, 135.8, 137.0 and 150.1. ^1H NMR (CDCl_3): δ 1.13 (3H, t, J = 7.6 Hz), 2.72 (2H, t, J = 6.8 Hz), 2.93 (2H, q, J = 7.6 Hz), 3.01 (4H, t, J = 4.4 Hz), 3.24 (2H, q, J = 7.2 Hz), 3.77 (4H, t, J = 4.4 Hz), 5.95 (1H, t, J = 6.0

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Hz), 6.72 (2H, d, $J = 8.0$ Hz), 6.98 (2H, d, $J = 8.0$ Hz), 7.31 - 7.38 (3H, m), 7.45 - 7.49 (2H, m), 7.86 (2H, d, $J = 8.8$ Hz) and 8.10 (1H, d, $J = 9.2$ Hz).

Synthesis 57

5-Chloro-3-ethyl-*N*-(4-morpholinophenethyl)-1*H*-indole-2-sulfonamide (**ABD1016**)



Using a method analogous to Method H with 5-chloro-3-ethyl-*N*-(4-morpholinophenethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1016a**), the title compound was obtained as a white powder.

10

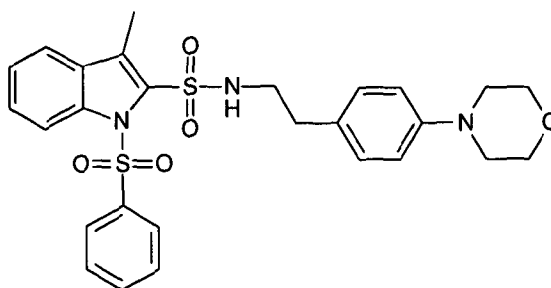
^{13}C NMR (CDCl_3): δ 15.4, 17.5, 34.5, 44.2, 49.3, 66.9, 113.3, 115.9, 120.1, 122.8, 126.1, 126.3, 128.1, 128.4, 128.8, 129.4, 133.8 and 150.2. ^1H NMR (CDCl_3): δ 1.23 (3H, t, $J = 7.2$ Hz), 2.67 (2H, t, $J = 6.4$ Hz), 2.93 (2H, q, $J = 7.6$ Hz), 3.08 (4H, t, $J = 4.0$ Hz), 3.23 (2H, q, $J = 6.4$ Hz), 3.85 (4H, t, $J = 4.0$ Hz), 4.78 (1H, t, $J = 5.6$ Hz), 6.74 (2H, d, $J =$

15

8.4 Hz), 6.93 (2H, d, $J = 8.4$ Hz), 7.28 (2H, s), 7.63 (1H, s) and 8.81 (1H, br s).

Synthesis 58

3-Methyl-*N*-(4-morpholinophenethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1018a**)



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Using a method analogous to Method G, with 3-methyl-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD0945b**) and 2-(4-morpholinophenyl) ethanamine, the title compound was obtained as a oil after purification by column chromatography.

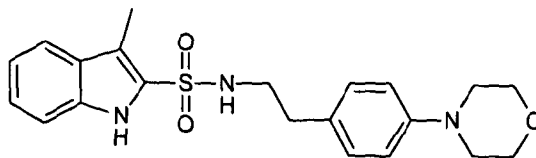
25

^{13}C NMR (CDCl_3): δ 11.1, 35.0, 44.8, 49.4, 66.9, 115.9, 116.0, 120.9, 124.5, 127.5, 128.5, 128.9, 129.0, 129.4, 129.5, 130.7, 131.7, 134.1, 137.2, 137.3 and 150.1. ^1H NMR (CDCl_3): δ 2.55 (3H, s), 2.80 (2H, t, $J = 6.8$ Hz), 3.09 (4H, t, $J = 4.8$ Hz), 3.30 (2H, q, $J = 7.2$ Hz), 3.84 (4H, t, $J = 4.8$ Hz), 6.02 (1H, t, $J = 6.0$ Hz), 6.81 (2H, d, $J = 8.8$ Hz), 7.06 (2H, d, $J = 8.8$ Hz), 7.33 - 7.41 (3H, m), 7.48 - 7.58 (3H, m), 7.97 (2H, d, $J = 8.4$ Hz) and

30

8.22 (1H, d, $J = 8.4$ Hz).

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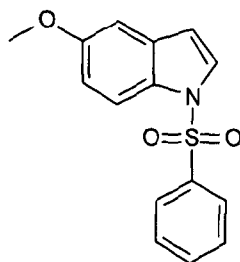
Synthesis 593-Methyl-*N*-(4-morpholinophenethyl)-1*H*-indole-2-sulfonamide (**ABD1018**)

- 5 Using a method analogous to Method H with 3-methyl-*N*-(4-morpholinophenethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1018a**), the title compound was obtained as a white powder.

- 10 ^{13}C NMR (CDCl_3): δ 9.0, 34.5, 44.1, 49.3, 66.9, 112.1, 116.0, 117.1, 120.6, 120.6, 125.7, 127.9, 128.0, 128.6, 129.4, 135.5 and 150.1. ^1H NMR (CDCl_3): δ 2.40 (3H, s), 2.57 (2H, t, $J = 6.8$ Hz), 2.99 (4H, t, $J = 4.8$ Hz), 3.14 (2H, q, $J = 6.8$ Hz), 3.76 (4H, t, $J = 4.8$ Hz), 4.71 (1H, t, $J = 6.4$ Hz), 6.65 (2H, d, $J = 8.4$ Hz), 6.84 (2H, d, $J = 8.4$ Hz), 7.09 - 7.13 (1H, m), 7.23 - 7.29 (2H, m), 7.56 (1H, d, $J = 8.4$ Hz) and 8.71 (1H, br s).

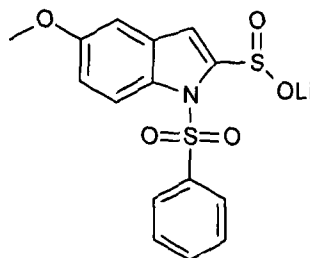
Synthesis 60

- 15 5-Methoxy-1-(phenylsulfonyl)-1*H*-indole (**ABD1022d**)



Using a method analogous to Method A, with 5-methoxy-1*H*-indole, the title compound was obtained as a white powder.

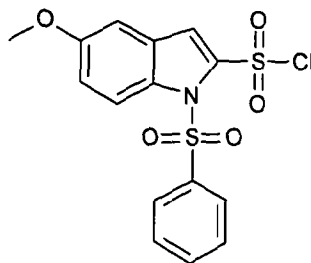
- 20 ^{13}C NMR ($\text{DMSO}-d_6$): δ 55.3, 104.1, 110.1, 113.5, 113.9, 126.6, 127.7, 128.7, 129.8, 131.7, 134.5, 137.0 and 156.1.

Synthesis 61Lithium 5-methoxy-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1022c**)

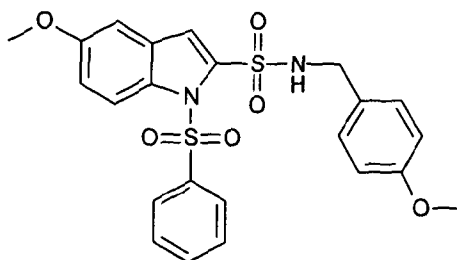
25

Using a method analogous to Method B, with 5-methoxy-1-(phenylsulfonyl)-1*H*-indole (**ABD1022d**), the title compound was obtained as a pale brown solid.

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Synthesis 625-Methoxy-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1022b**)

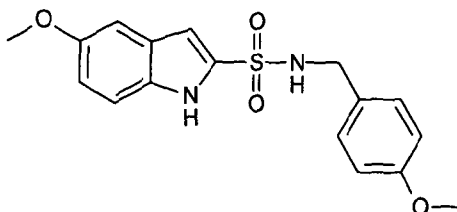
- 5 Using a method analogous to Method C, with lithium 5-methoxy-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1022c**), the title compound was obtained as a pale orange solid on recrystallisation from methanol.

Synthesis 635-Methoxy-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1022a**)

10

Using a method analogous to Method G, with 5-methoxy-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1022b**) and 4-methoxybenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

15

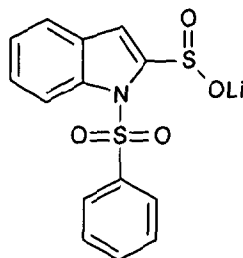
Synthesis 645-Methoxy-*N*-(4-methoxybenzyl)-1*H*-indole-2-sulfonamide (**ABD1022**)

- 20 Using a method analogous to Method H with 5-methoxy-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1022a**), the title compound was obtained as a white powder on recrystallisation from ether/petrol.

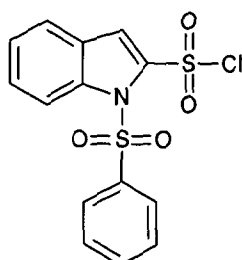
¹³C NMR (DMSO-*d*₆): δ 45.7, 55.1, 55.3, 102.1, 104.6, 113.4, 113.6, 115.7, 126.5, 128.9, 129.7, 131.9, 134.6, 154.1 and 158.5. ¹H NMR (DMSO-*d*₆): δ 3.69 (3H, s), 3.76 (3H, s), 4.02 (2H, s), 6.82 (1H, s), 6.86 (2H, d, *J* = 5.1 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 7.12 (1H, s), 7.18 (2H, d, *J* = 8.5 Hz), 7.36 (1H, d, *J* = 9.1 Hz), 8.20 (1H, br s) and 11.92 (1H, br s).

25

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Synthesis 65Lithium 1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1023c**)

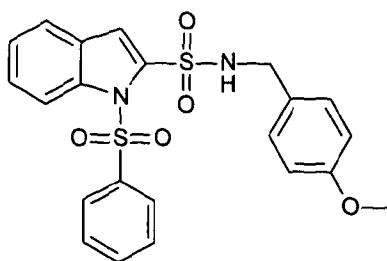
- 5 Using a method analogous to Method B, with 1-(phenylsulfonyl)-1*H*-indole, the title compound was obtained as a pale brown solid.

Synthesis 661-(Phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1023b**)

- 10 Using a method analogous to Method C, with lithium 1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1023c**), the title compound was obtained as a pale orange solid on recrystallisation from methanol.

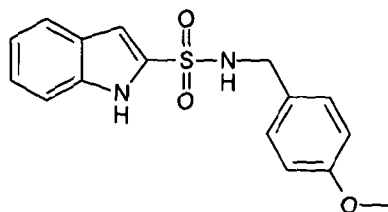
Synthesis 67

- 15 *N*-(4-Methoxybenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1023a**)



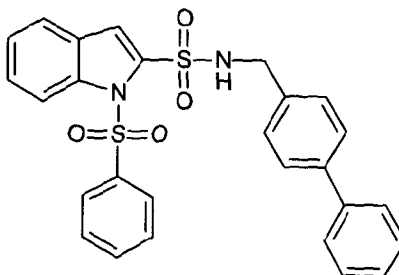
Using a method analogous to Method G, with 1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1023b**) and 4-methoxybenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

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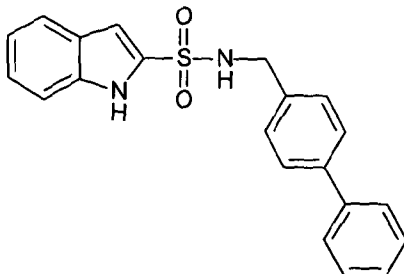
Synthesis 68*N*-(4-Methoxybenzyl)-1*H*-indole-2-sulfonamide (**ABD1023**)

Using a method analogous to Method H with *N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1023a**), the title compound was obtained as a white powder on recrystallisation from ether/petrol.

¹³C NMR (DMSO-*d*₆): δ 45.7, 55.0, 105.1, 112.7, 113.6, 120.4, 121.9, 124.3, 126.1, 128.9, 129.6, 134.6, 136.8 and 158.5.

Synthesis 69*N*-(Biphenyl-4-ylmethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1025a**)

Using a method analogous to Method G, with 1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1023b**) and 4-phenylbenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

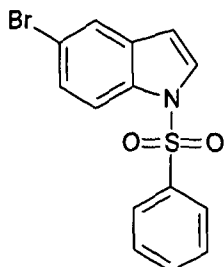
Synthesis 70*N*-(Biphenyl-4-ylmethyl)-1*H*-indole-2-sulfonamide (**ABD1025**)

Using a method analogous to Method H with *N*-(biphenyl-4-ylmethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1025a**), the title compound was obtained as a white powder on washing with ether.

¹³C NMR (DMSO-*d*₆): δ 45.9, 105.0, 112.7, 120.5, 121.9, 124.3, 126.1, 126.5, 126.8, 127.4, 128.2, 129.0, 134.6, 136.8, 137.2, 139.1 and 139.9. ¹H NMR (DMSO-*d*₆): δ 4.19

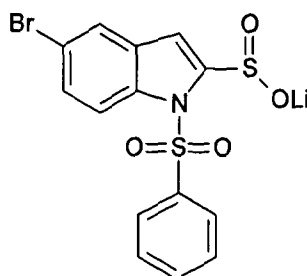
(2H, s), 7.02 (1H, s), 7.12 (1H, t, $J = 7.9$ Hz), 7.29 (1H, t, $J = 7.9$ Hz), 7.38 (2H, d, $J = 7.6$ Hz), 7.41 (1H, m), 7.47 (2H, d, $J = 7.9$ Hz), 7.51 (1H, m), 7.58 (2H, d, $J = 7.9$ Hz), 7.62 (2H, d, $J = 7.0$ Hz), 7.68 (1H, d, $J = 7.9$ Hz), 8.37 (1H, br s) and 12.06 (1H, br s)

5

Synthesis 715-Bromo-1-(phenylsulfonyl)-1*H*-indole (**ABD1026d**)

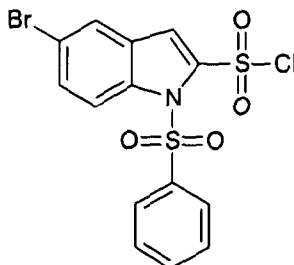
Using a method analogous to Method A, with 5-bromo-1*H*-indole, the title compound was obtained as a brown oil which solidified on standing.

10

Synthesis 72Lithium 5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1026c**)

Using a method analogous to Method B, with 5-bromo-1-(phenylsulfonyl)-1*H*-indole (**ABD1026d**), the title compound was obtained as a pale brown solid.

15

Synthesis 735-Bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1026b**)

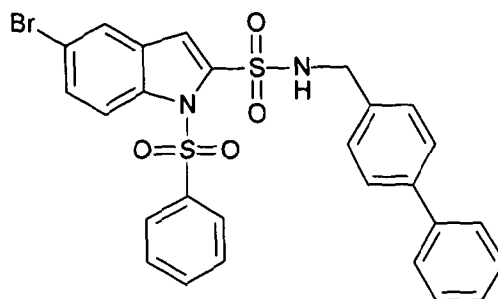
20

Using a method analogous to Method C, with lithium 5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1026c**), the title compound was obtained as a pale orange solid on recrystallisation from methanol.

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Synthesis 74

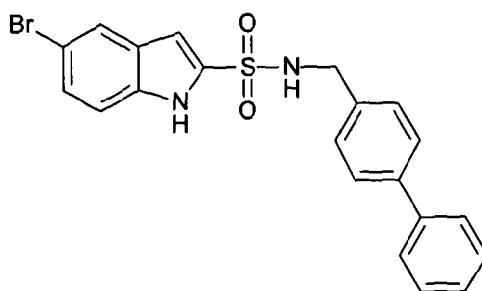
N-(Biphenyl-4-ylmethyl)-5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide
(**ABD1026a**)



- 5 Using a method analogous to Method G, with 5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1026b**) and 4-phenylbenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

Synthesis 75

10 *N*-(Biphenyl-4-ylmethyl)-5-bromo-1*H*-indole-2-sulfonamide (**ABD1026**)



Using a method analogous to Method H with *N*-(biphenyl-4-ylmethyl)-5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1026a**), the title compound was obtained as a white powder on washing with ether.

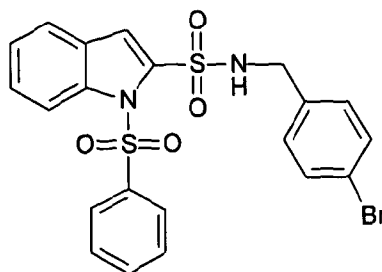
15

¹³C NMR (DMSO-*d*₆): δ 45.9, 104.6, 112.9, 114.7, 124.1, 126.5, 126.8, 127.4, 127.7, 127.9, 128.3, 128.9, 135.4, 136.0, 136.9, 139.1 and 139.9. ¹H NMR (DMSO-*d*₆): δ 4.19 (2H, d, *J* = 5.8 Hz), 6.96 (1H, s), 7.34 – 7.59 (11H, m), 7.88 (1H, s), 8.42 (1H, m) and 12.26 (1H, s). MS, *m/z*: Calcd, 440.0; Found, 441.1 (*M*+*H*).

20

Synthesis 76

N-(4-Bromobenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1027b**)

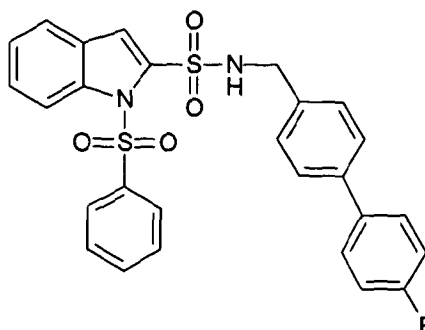


Using a method analogous to Method G, with 1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1023b**) and 4-bromobenzylamine, the title compound was obtained as a yellow oil, recrystallised from ether/petrol to give a pale yellow solid.

5

Synthesis 77

N-((4'-Fluorobiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1027a**)

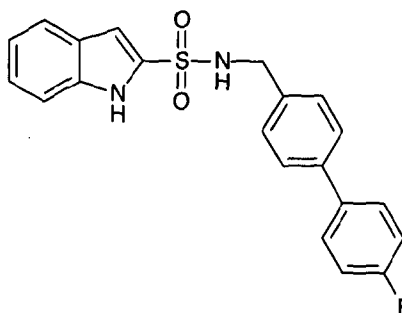


Method K: *N*-(Biphenyl-4-ylmethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (see previous synthesis) **ABD1027b** (1.0 g) was dissolved in a mixture of toluene (15 mL) and ethanol (15 mL). 4-Fluorophenylboronic acid (1 g) was added followed by (PPh₃)₄Pd (0.15 g). The mixture was stirred vigorously under N₂ and 2 M Na₂CO₃ (15 mL) added. The mixture was refluxed with stirring for 3 h under an atmosphere of N₂. The organic solvents were removed under vacuum, the residue dissolved in ethyl acetate and washed with water and saturated NaCl solution. After drying (Na₂SO₄), the solvent was evaporated and the brown residue was purified by column chromatography (ethyl acetate/petrol), the residue recrystallised from ether/petrol and the title compound was obtained as a white powder

20

Synthesis 78

N-((4'-Fluorobiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1027**)



Using a method analogous to Method H with *N*-((4'-fluorobiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1027a**), the title compound was obtained as a pale brown powder on washing with ether.

25

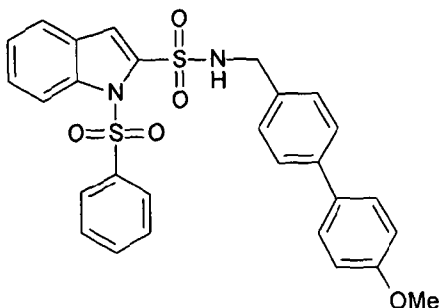
¹³C NMR (DMSO-*d*₆): δ 45.8, 105.0, 112.6, 115.7, 120.4, 121.8, 124.5, 126.1, 126.4, 126.7, 128.3, 134.6, 136.3, 136.8, 137.2, 138.1 and 161.9 (d, *J* = 244.0 Hz). ¹H NMR

- 129 -

(DMSO- d_6): δ 4.22 (2H, s), 6.97 (1H, s), 7.20 – 7.75 (12H, m), 8.34 (1H, m) and 12.07 (1H, s)

Synthesis 79

- 5 *N*-((4'-Methoxybiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1028a**)

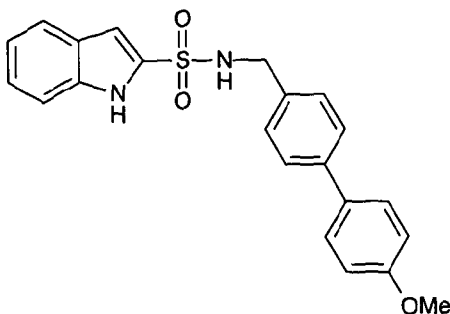


Using a method analogous to Method K, with **ABD1027b** and 4-methoxyphenylboronic acid, the title compound was obtained as a white powder

10

Synthesis 80

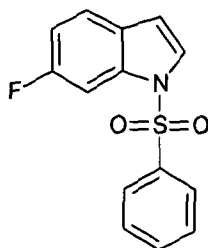
- N*-((4'-Methoxybiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1028**)



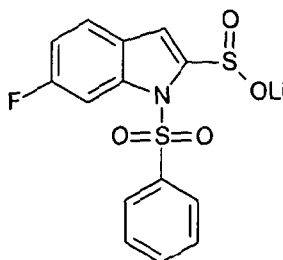
- 15 Using a method analogous to Method H with *N*-((4'-methoxybiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1028a**), the title compound was obtained as a pale brown powder on washing with ether.

- 20 ^{13}C NMR (DMSO- d_6): δ 45.9, 55.2, 105.3, 112.7, 114.3, 120.4, 121.9, 124.4, 126.0, 126.1, 127.9, 128.1, 132.2, 134.6, 136.3, 136.8, 138.8 and 158.9. ^1H NMR (DMSO- d_6): δ 3.78 (3H, s), 4.17 (2H, d, $J = 5.2$ Hz), 7.02 (3H, s), 7.29 (1H, t, $J = 8.2$ Hz), 7.35 (2H, d, $J = 8.2$ Hz), 7.36 (1H, m), 7.54 (5H, m), 7.68 (1H, d, $J = 7.3$ Hz), 8.30 (1H, s) and 12.05 (1H, s).

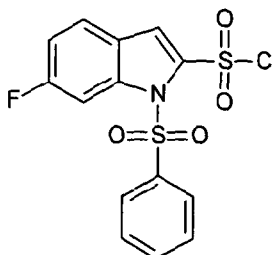
- 130 -

Synthesis 816-Fluoro-1-(phenylsulfonyl)-1*H*-indole (**ABD1029d**)

- 5 Using a method analogous to Method A, with 6-fluoro-1*H*-indole, the title compound was obtained as a brown oil which solidified on standing.

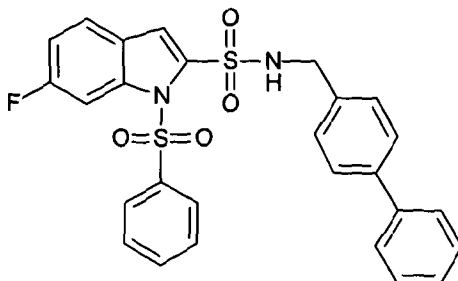
Synthesis 82Lithium 6-fluoro-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1029c**)

- 10 Using a method analogous to Method B, with 6-fluoro-1-(phenylsulfonyl)-1*H*-indole (**ABD1029d**), the title compound was obtained as a pale brown solid.

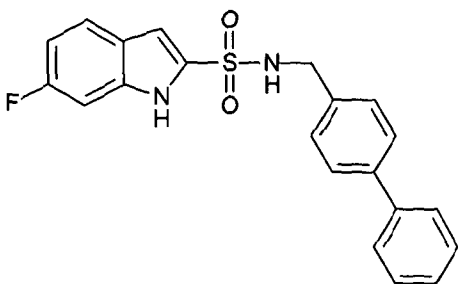
Synthesis 836-Fluoro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1029b**)

- 15 Using a method analogous to Method C, with lithium 6-fluoro-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1029c**), the title compound was obtained as a pale orange solid on recrystallisation from methanol.

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Synthesis 84*N*-(Biphenyl-4-ylmethyl)-6-fluoro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1029a**)

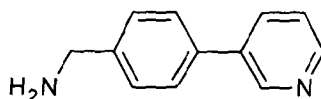
- 5 Using a method analogous to Method G, with 6-fluoro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1029b**) and 4-phenylbenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

Synthesis 85*N*-(Biphenyl-4-ylmethyl)-6-fluoro-1*H*-indole-2-sulfonamide (**ABD1029**)

- 10 Using a method analogous to Method H with *N*-(biphenyl-4-ylmethyl)-6-fluoro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1029a**), the title compound was obtained as a white powder on washing with ether.
- 15 ¹H NMR (DMSO-*d*₆): δ 4.18 (2H, d, *J* = 5.8 Hz), 7.03 (2H, m), 7.22 (1H, d, *J* = 9.5 Hz), 7.35 – 7.45 (5H, m), 7.55 – 7.61 (4H, m), 7.68 (1H, t, *J* = 5.5 Hz), 8.38 (1H, t, *J* = 6.7 Hz) and 12.16 (1H, s).

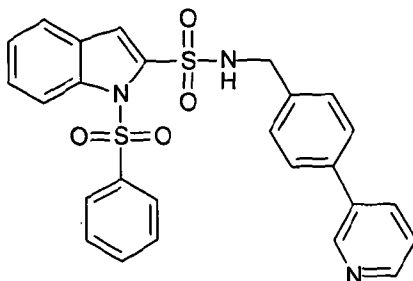
Synthesis 86

(4-(Pyridin-3-yl)phenyl)methanamine

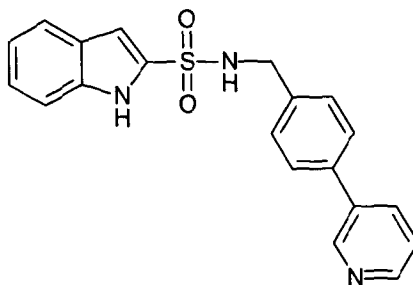


- 20 Using a method analogous to Method K, with 4-bromobenzylamine and 3-pyridylboronic acid, the title compound was obtained as a clear oil which solidified on standing.

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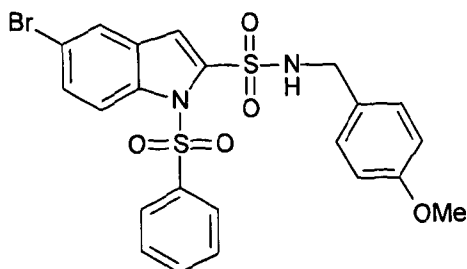
Synthesis 871-(Phenylsulfonyl)-*N*-(4-(pyridin-3-yl)benzyl)-1*H*-indole-2-sulfonamide (**ABD1030a**)

- 5 Using a method analogous to Method G, with 1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1023b**) and (4-(pyridin-3-yl)phenyl)methanamine, the title compound was obtained as a pale yellow solid on recrystallisation from ether/petrol.

Synthesis 88*N*-(4-(Pyridin-3-yl)benzyl)-1*H*-indole-2-sulfonamide (**ABD1030**)

- 10 Using a method analogous to Method H with 1-(phenylsulfonyl)-*N*-(4-(pyridin-3-yl)benzyl)-1*H*-indole-2-sulfonamide (**ABD1030a**), the title compound was obtained as a pale brown powder, which gave a white solid on recrystallisation from ether/petrol.
- 15 ¹³C NMR (DMSO-*d*₆): δ 45.8, 105.2, 112.5, 120.5, 121.8, 123.7, 124.0, 126.1, 126.6, 128.3, 134.2, 134.6, 135.3, 136.0, 136.8, 138.0, 143.8 and 144.2. ¹H NMR (DMSO-*d*₆): δ 4.20 (2H, s), 7.00 (1H, s), 7.10 (1H, t, *J* = 7.9 Hz), 7.26 (1H, t, *J* = 8.5 Hz), 7.43 (4H, m), 7.63 (3H, m), 7.99 (1H, d, *J* = 8.5 Hz), 8.38 (1H, br s), 8.54 (1H, s), 8.84 (1H, s) and 12.05 (1H, br s).

20

Synthesis 895-Bromo-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1031a**)

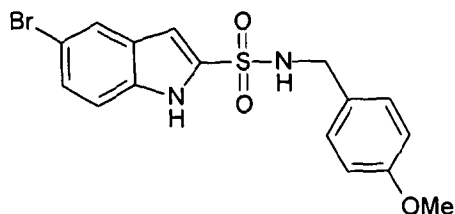
- 133 -

Using a method analogous to Method G, with 5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1026b**) and 4-methoxybenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

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Synthesis 90

5-Bromo-*N*-(4-methoxybenzyl)-1*H*-indole-2-sulfonamide (**ABD1031**)



10

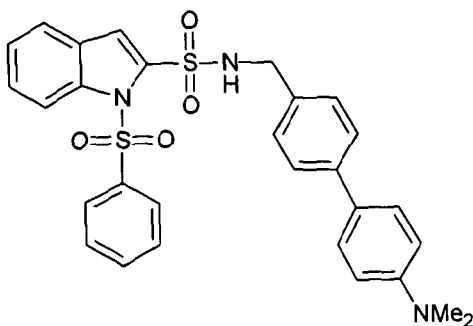
Using a method analogous to Method H with 5-bromo-*N*-(4-methoxybenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1031a**), the title compound was obtained as a white powder on washing with ether.

¹³C NMR (DMSO-*d*₆): δ 45.7, 55.1, 102.4, 112.8, 113.7, 114.8, 124.3, 126.9, 127.9, 129.0, 129.5, 135.4, 136.1 and 158.5.

15

Synthesis 91

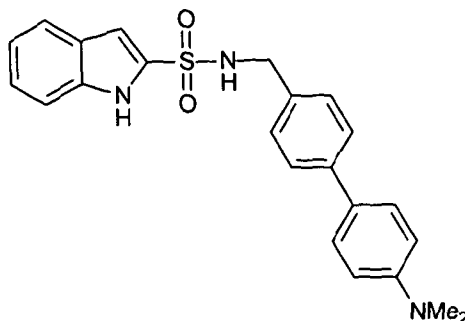
N-((4'-(Dimethylamino)biphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1032a**)



20

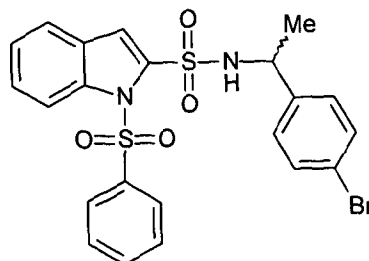
Using a method analogous to Method K, with **ABD1027b** and 4-dimethylaminophenylboronic acid, the title compound was obtained as a white powder

- 134 -

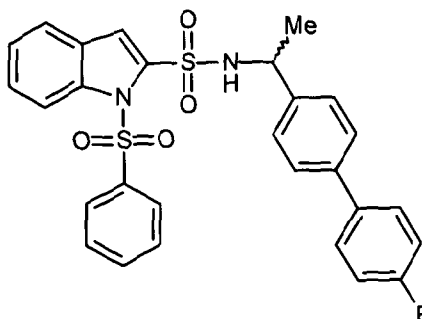
Synthesis 92*N*-((4'-(Dimethylamino)biphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1032**)

Using a method analogous to Method H with *N*-((4'-(dimethylamino)biphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1032a**), the title compound was obtained as a pale brown powder on washing with ether.

¹³C NMR (DMSO-*d*₆): δ 40.1, 46.0, 105.1, 112.4, 112.7, 120.3, 121.9, 124.7, 125.3, 126.1, 127.2, 127.3, 128.2, 134.6, 135.4, 136.8, 139.3 and 149.9. ¹H NMR (DMSO-*d*₆): δ 2.92 (6H, s), 4.14 (2H, s), 6.76 (2H, m), 7.02 (1H, m), 7.13 (2H, m), 7.31 (3H, m), 7.49 (4H, m), 7.68 (1H, m), 8.28 (1H, br s) and 12.02 (1H, br s).

Synthesis 93*N*-(1-(4-Bromophenyl)ethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1033b**)

Using a method analogous to Method G, with 1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1023b**) and 4-bromo-α-methylbenzylamine, the title compound was obtained as a yellow oil, recrystallised from ether/petrol to give a pale yellow solid.

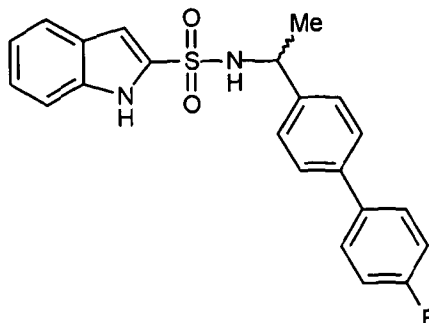
Synthesis 94*N*-(1-(4'-Fluorobiphenyl-4-yl)ethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1033a**)

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Using a method analogous to Method K, with **ABD1033b** and 4-fluorophenylboronic acid, the title compound was obtained as a white powder.

Synthesis 95

5 *N*-(1-(4'-Fluorobiphenyl-4-yl)ethyl)-1*H*-indole-2-sulfonamide (**ABD1033**)



Using a method analogous to Method H with *N*-(1-(4'-fluorobiphenyl-4-yl)ethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1033a**), the title compound was obtained as a pale brown powder on washing with ether.

10

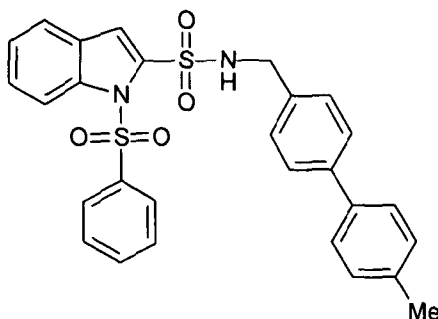
¹³C NMR (DMSO-*d*₆): δ 23.3, 52.6, 105.1, 112.5, 115.7, 120.4, 121.9, 124.4, 126.1, 126.5, 126.6, 128.7, 135.2, 136.5, 136.7, 137.8, 142.9 and 161.8 (d, *J* = 244.2 Hz).

¹H NMR (DMSO-*d*₆): δ 1.31 (3H, d, *J* = 7.0 Hz), 4.57 (1H, m), 6.83 (1H, s), 7.20 – 7.60 (12 H, m), 8.37 (1H, d, *J* = 7.0 Hz) and 10.88 (1H, s).

15

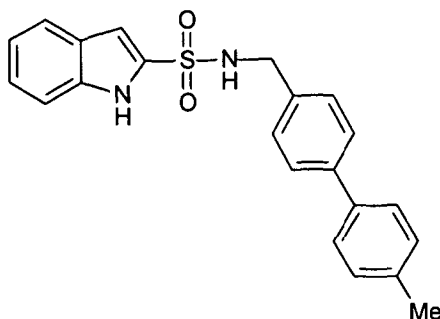
Synthesis 96

N-((4'-Methylbiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1034a**)



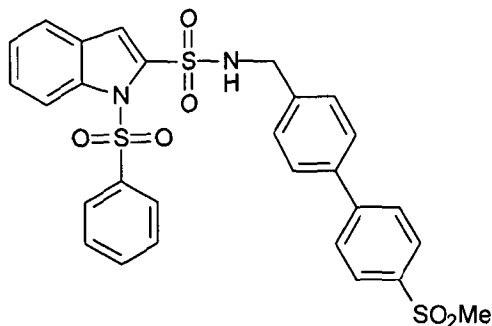
20 Using a method analogous to Method K, with **ABD1027b** and 4-methylphenylboronic acid, the title compound was obtained as a white powder

- 136 -

Synthesis 97*N*-((4'-Methylbiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1034**)

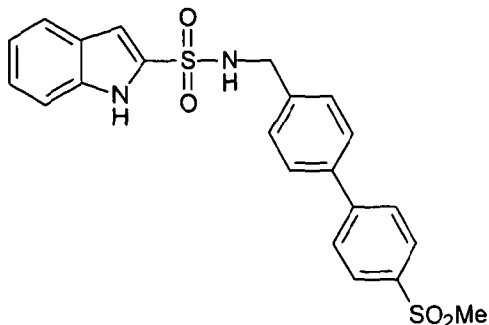
Using a method analogous to Method H with *N*-((4'-methylbiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1034a**), the title compound was obtained as a pale brown powder on washing with ether.

¹H NMR (DMSO-*d*₆): δ 2.33 (3H, s), 4.17 (2H, d, *J* = 4.9 Hz), 7.00 (1H, s), 7.12 (1H, t, *J* = 8.2 Hz), 7.26 (3H, m), 7.35 (2H, d, *J* = 8.2 Hz), 7.54 (5H, m), 7.68 (1H, d, *J* = 7.9 Hz), 8.30 (1H, s) and 12.03 (1H, s).

Synthesis 98*N*-((4'-Methanesulfonylbiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1035a**)

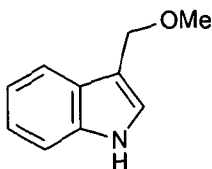
Using a method analogous to Method K, with **ABD1027b** and 4-methanesulfonylphenylboronic acid, the title compound was obtained as a white powder

- 137 -

Synthesis 99*N*-((4'-Methanesulfonylbiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1035**)

Using a method analogous to Method H with *N*-((4'-methanesulfonylbiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1035a**), the title compound was obtained as a pale brown powder on washing with ether.

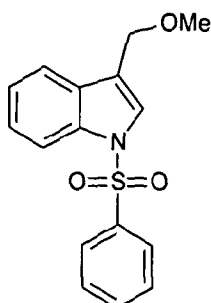
¹³C NMR (DMSO-*d*₆): δ 43.6, 45.8, 105.3, 112.7, 120.6, 121.8, 124.4, 126.1, 127.3, 127.6, 128.0, 128.1, 128.5, 134.5, 137.3, 138.6, 139.5 and 144.8. ¹H NMR (DMSO-*d*₆): δ 3.26 (3H, s), 4.22 (2H, s), 7.01 (1H, s), 7.11 (1H, t, *J* = 7.9 Hz), 7.28 (1H, t, *J* = 8.2 Hz), 7.43 (2H, d, *J* = 7.9 Hz), 7.49 (1H, d, *J* = 8.5 Hz), 7.67 (3H, d, *J* = 8.8 Hz), 7.88 (2H, d, *J* = 8.2 Hz), 8.00 (2H, d, *J* = 7.9 Hz), 8.36 (1H, br s) and 12.08 (1H, br s).

Synthesis 1003-(Methoxymethyl)-1*H*-indole

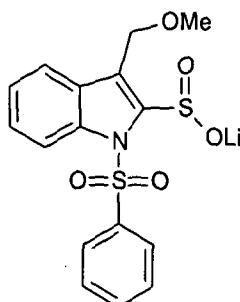
The title compound was prepared by the method described by Geismann and Arman (1952). Briefly, sodium (3.5 g) was dissolved in methanol (150 mL) and chilled in an ice bath. Gramine (10 g) was added and stirred until dissolution had occurred. Methyl iodide (21 g) was added and the mixture stirred overnight, a precipitate was observed within a few minutes. The mixture was filtered and the methanolic filtrate poured into water (250 mL) giving a pink / orange crystalline solid.

¹³C NMR (DMSO-*d*₆): δ 56.6, 65.8, 111.5, 111.7, 118.6, 118.7, 121.3, 125.1, 127.1 and 136.4. ¹H NMR (DMSO-*d*₆): δ 3.24 (3H, s), 4.57 (2H, s), 7.05 (1H, t, *J* = 8.2 Hz), 7.11 (1H, t, *J* = 7.9 Hz), 7.32 (1H, s), 7.38 (1H, t, *J* = 7.9 Hz), 7.59 (1H, d, *J* = 7.0 Hz) and 11.03 (1H, s).

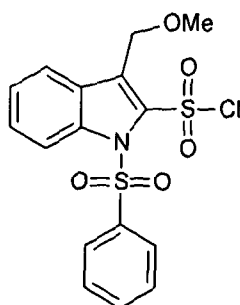
- 138 -

Synthesis 1013-(Methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole (**ABD1036d**)

- 5 Using a method analogous to Method A, with 3-(methoxymethyl)-1*H*-indole, the title compound was obtained as a brown oil which solidified on standing.

Synthesis 102Lithium 3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1036c**)

- 10 Using a method analogous to Method B, with 3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole (**ABD1036d**), the title compound was obtained as a pale brown solid.

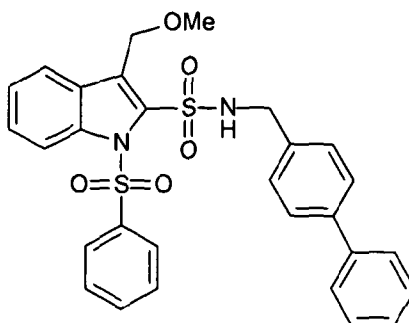
Synthesis 1033-(Methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1036b**)

- 15 Using a method analogous to Method C, with lithium 3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1036c**), the title compound was obtained as a pale orange solid on recrystallisation from methanol.

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Synthesis 104

N-(Biphenyl-4-ylmethyl)-3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide
(**ABD1036a**)

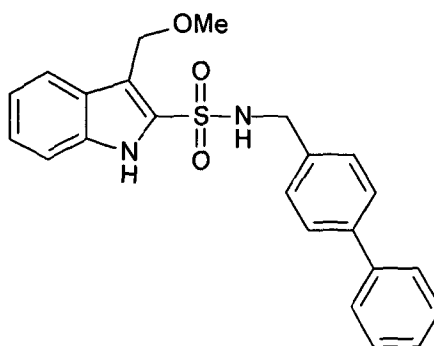


- 5 Using a method analogous to Method G, with 3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1036b**) and 4-phenylbenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

¹³C NMR (DMSO-*d*₆): δ 46.1, 57.7, 64.5, 115.3, 122.4, 124.7, 126.2, 126.5, 129.9, 127.6,
10 128.1, 128.4, 128.9, 128.8, 129.4, 129.6, 134.2, 134.9, 136.4, 136.5, 136.6, 139.1 and 139.8. ¹H NMR (DMSO-*d*₆): δ 3.19 (3H, s), 4.30 (2H, s), 4.82 (2H, s), 7.30 – 7.50 (13H, m), 7.62 (1H, m), 7.73 (1H, d, *J* = 7.6 Hz), 7.92 (2H, d, *J* = 7.0 Hz) and 8.05 (2H, m).

Synthesis 105

- 15 *N*-(Biphenyl-4-ylmethyl)-3-(methoxymethyl)-1*H*-indole-2-sulfonamide (**ABD1036**)

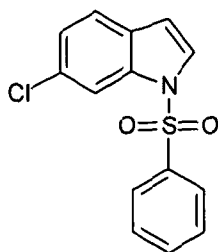


Using a method analogous to Method H (substituting methanol for ethanol) with *N*-(biphenyl-4-ylmethyl)-3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1036a**), the title compound was obtained as a white solid on washing with ether.

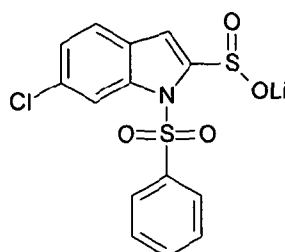
20 ¹³C NMR (DMSO-*d*₆): δ 45.5, 57.3, 63.6, 112.8, 114.3, 120.2, 120.8, 124.6, 126.5, 126.7, 126.8, 127.5, 128.0, 129.0, 131.6, 135.4, 137.0, 139.1 and 139.9. ¹H NMR (DMSO-*d*₆): δ 3.37 (3H, s), 4.15 (2H, d, *J* = 5.5 Hz), 4.84 (2H, s), 7.12 (1H, t, *J* = 7.9 Hz), 7.29 – 7.60 (11H, m), 7.74 (1H, d, *J* = 7.6 Hz), 8.33 (1H, t, *J* = 5.5 Hz) and 11.90 (1H, s).

25

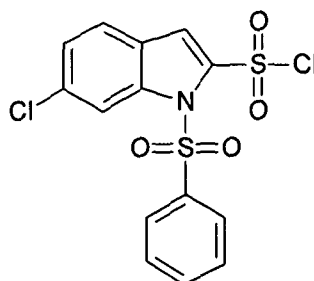
- 140 -

Synthesis 1066-Chloro-1-(phenylsulfonyl)-1*H*-indole (**ABD1037d**)

- 5 Using a method analogous to Method A, with 6-chloro-1*H*-indole, the title compound was obtained as a brown oil which solidified on standing.

Synthesis 107Lithium 6-Chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1037c**)

- 10 Using a method analogous to Method B, with 6-chloro-1-(phenylsulfonyl)-1*H*-indole (**ABD1037d**), the title compound was obtained as a pale brown solid.

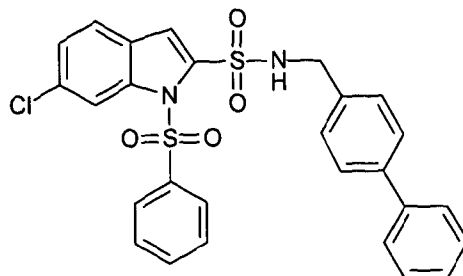
Synthesis 1086-Chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1037b**)

- 15 Using a method analogous to Method C, with lithium 6-chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1037c**), the title compound was obtained as a pale orange solid.

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Synthesis 109

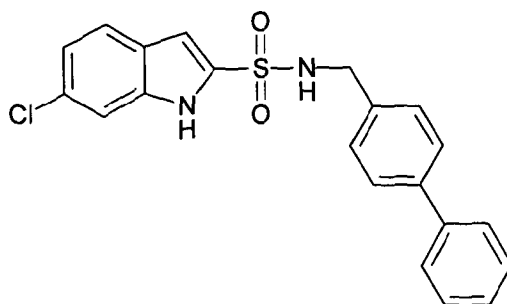
N-(Biphenyl-4-ylmethyl)-6-chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide
(**ABD1037a**)



- 5 Using a method analogous to Method G, with 6-chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1037b**) and 4-phenylbenzylamine, the title compound was obtained as a white powder on crystallisation from ether/petrol.

Synthesis 110

10 *N*-(Biphenyl-4-ylmethyl)-6-chloro-1*H*-indole-2-sulfonamide (**ABD1037**)

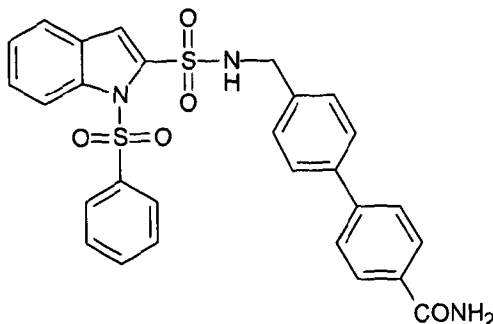


Using a method analogous to Method H with *N*-(biphenyl-4-ylmethyl)-6-chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1037a**), the title compound was obtained as a white powder on washing with ether.

15

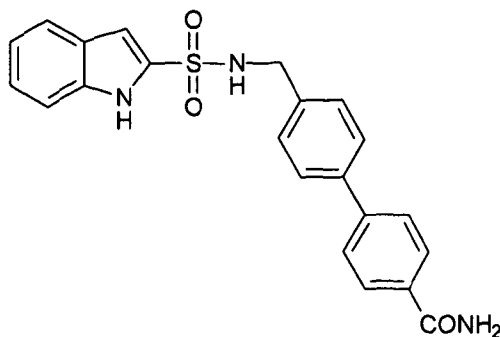
Synthesis 111

4'-((1-(Phenylsulfonyl)-1*H*-indole-2-sulfonamido)methyl)biphenyl-4-carboxamide
(**ABD1038a**)



- 20 Using a method analogous to Method K, with **ABD1027b** and 4-carbamoylphenylboronic acid, the title compound was obtained as a white powder

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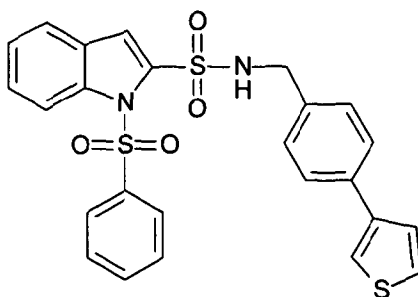
Synthesis 1124'-((1*H*-Indole-2-sulfonamido)methyl)biphenyl-4-carboxamide (**ABD1038**)

5 Using a method analogous to Method H with 4'-((1-(phenylsulfonyl)-1*H*-indole-2-sulfonamido)methyl)biphenyl-4-carboxamide (**ABD1038a**), the title compound was obtained as a pale brown powder on washing with ether.

10 ¹³C NMR (DMSO-*d*₆): δ 45.8, 105.4, 112.7, 120.5, 121.9, 124.6, 126.1, 126.7, 126.9, 128.3, 129.6, 130.1, 134.5, 136.8, 137.9, 138.1, 144.0 and 167.2. ¹H NMR (DMSO-*d*₆): δ 4.20 (2H, d, *J* = 5.2 Hz), 7.00 (1H, s), 7.11 (1H, t, *J* = 7.9 Hz), 7.28 (1H, t, *J* = 8.5 Hz), 7.41 (2H, d, *J* = 7.9 Hz), 7.49 (1H, d, *J* = 7.9 Hz), 7.65 (2H, d, *J* = 7.0 Hz), 7.75 (2H, d, *J* = 8.2 Hz), 8.01 (2H, d, *J* = 7.9 Hz), 8.34 (1H, m), 12.04 (1H, s) and 12.96 (1H, br s).

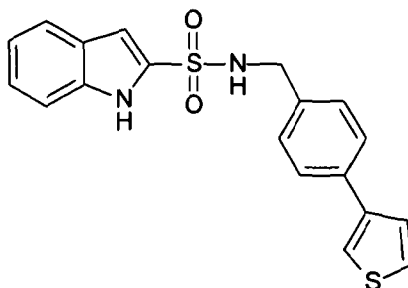
Synthesis 113

15 1-(Phenylsulfonyl)-*N*-(4-(thiophen-3-yl)benzyl)-1*H*-indole-2-sulfonamide (**ABD1042a**)



Using a method analogous to Method K, with **ABD1027b** and 3-thienylboronic acid, the title compound was obtained as a white powder.

20

Synthesis 114*N*-(4-(Thiophen-3-yl)benzyl)-1*H*-indole-2-sulfonamide (**ABD1042**)

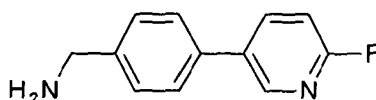
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Using a method analogous to Method H with 1-(phenylsulfonyl)-*N*-(4-(thiophen-3-yl)benzyl)-1*H*-indole-2-sulfonamide (**ABD1042a**), the title compound was obtained as a pale brown powder on washing with ether.

- 5 ¹H NMR (DMSO-*d*₆): δ 4.15 (2H, d, *J* = 5.5 Hz), 7.01 (1H, s), 7.12 (1H, t, *J* = 7.0 Hz), 7.28 (1H, m), 7.33 (2H, d, *J* = 7.3 Hz), 7.51 (2H, m), 7.65 (2H, d, *J* = 7.9 Hz), 7.66 (2H, m), 7.83 (1H, s), 8.27 (1H, m) and 12.04 (1H, s).

Synthesis 115

- 10 (4-(6-Fluoropyridin-3-yl)phenyl)methanamine (**ABD1045b**)

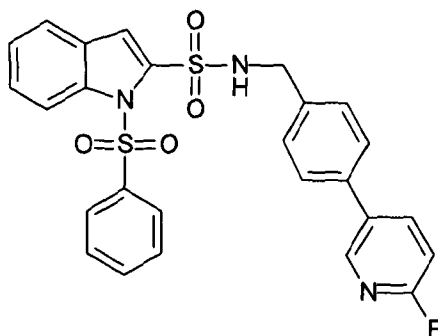


Using a method analogous to Method K, with 4-bromobenzylamine and 2-fluoropyridine-5-boronic acid, the title compound was obtained as a clear oil which solidified on standing.

15

Synthesis 116

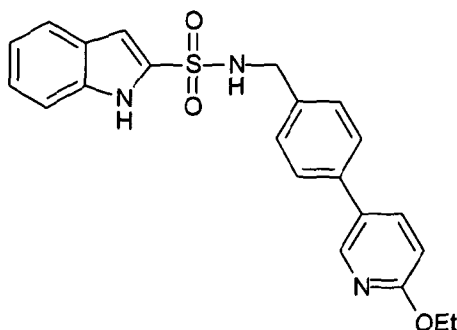
- N*-(4-(6-Fluoropyridin-3-yl)benzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1045a**)



- 20 Using a method analogous to Method G, with 1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1023b**) and (4-(6-fluoropyridin-3-yl)phenyl)methanamine (**ABD1045b**), the title compound was obtained as a pale yellow solid on recrystallisation from ether/petrol.

Synthesis 117

- 25 *N*-(4-(6-Ethoxypyridin-3-yl)benzyl)-1*H*-indole-2-sulfonamide (**ABD1045**)



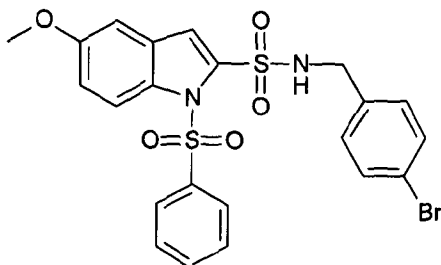
Using a method analogous to Method H with *N*-(4-(6-fluoropyridin-3-yl)benzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1045a**), the title compound was obtained as a white powder.

- 5 ¹H NMR (DMSO-*d*₆): δ 1.33 (3H, t, *J* = 6.4 Hz), 4.15 (2H, s), 4.33 (2H, q, *J* = 7.0 Hz), 6.86 (1H, d, *J* = 8.5 Hz), 6.98 (1H, s), 7.11 (1H, t, *J* = 7.0 Hz), 7.27 (1H, t, *J* = 8.8 Hz), 7.36 (2H, d, *J* = 7.9 Hz), 7.46 (1H, d, *J* = 7.0 Hz), 7.57 (2H, d, *J* = 7.9 Hz), 7.66 (1H, d, *J* = 7.0 Hz), 7.93 (1H, d, *J* = 8.5 Hz), 8.34 (1H, s), 8.42 (1H, s) and 12.02 (1H, s). MS, *m/z*: Calcd, 407.13; Found, 408.18 (M+H).

10

Synthesis 118

5-Methoxy-*N*-(4-bromobenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1046b**)

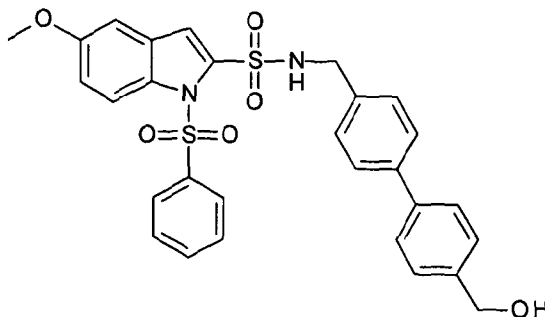


- 15 Using a method analogous to Method G, with 5-methoxy-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1022b**) and 4-bromobenzylamine, the title compound was obtained as a clear oil after purification by column chromatography.

Synthesis 119

N-((4'-(Hydroxymethyl)biphenyl-4-yl)methyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1046a**)

20



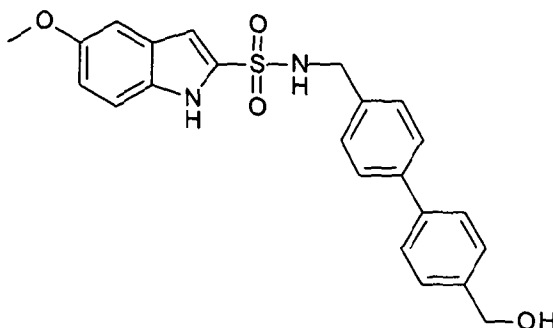
Using a method analogous to Method K, with **ABD1046b** and 4-hydroxymethylphenylboronic acid, the title compound was obtained as a pale pink powder.

25

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Synthesis 120

N-((4'-(Hydroxymethyl)biphenyl-4-yl)methyl)-5-methoxy-1*H*-indole-2-sulfonamide (**ABD1046**)

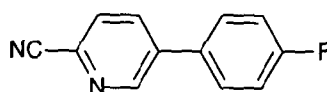


- 5 Using a method analogous to Method H with *N*-((4'-(hydroxymethyl)biphenyl-4-yl)methyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1046a**), the title compound was obtained as a white solid.

¹H NMR (DMSO-*d*₆): δ 3.86 (3H, s), 4.19 (2H, m), 4.56 (2H, s), 5.24 (1H, t, *J* = 5.8 Hz),
10 6.84 (1H, m), 7.24 (1H, m), 7.37 (5H, m), 7.56 (5H, m), 8.43 (1H, s) and 12.23 (1H, s)

Synthesis 121

5-(4-Fluorophenyl)picolinonitrile (**ABD1047c**)

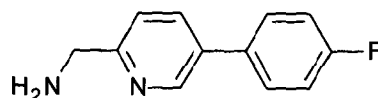


- 15 Using a method analogous to Method K, with 5-bromo-2-pyridinecarbonitrile and 4-fluorophenylboronic acid, the title compound was obtained as a white solid from DCM/petrol.

¹H NMR (CDCl₃): δ 7.22 (2H, m), 7.58 (2H, m), 7.76 (1H, d, *J* = 8.8 Hz), 7.97 (1H, dd,
20 *J* = 7.6, 2.4 Hz), 8.90 (1H, s).

Synthesis 122

(5-(4-Fluorophenyl)pyridin-2-yl)methanamine (**ABD1047b**)



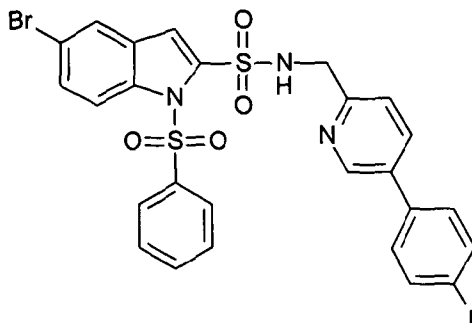
- 25 5-(4-Fluorophenyl)picolinonitrile (**ABD1047b**) (1 g) was dissolved in THF (20 mL) and cooled in an ethanol / CO₂ bath. 1 M LiAlH₄ in THF (13 mL) was added and the mixture stirred at below -50°C for 2 h. The reaction was quenched by the dropwise addition of 1 : 10 water : THF (20 mL), diluted with ethyl acetate, stirred with 1 M NaOH and filtered through Ceelite®. The organic phase was separated, washed with 1 M NaOH, brine and
30 dried. Evaporation gave the title compound as an amorphous brown solid.

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^{13}C NMR ($\text{DMSO}-d_6$): δ 47.4, 116.3 (d, $J = 21.7$ Hz), 121.5, 129.2 (d, $J = 8.5$ Hz), 132.9, 134.1, 134.9, 147.0, 162.1 and 162.5 (d, $J = 243.1$ Hz).

Synthesis 123

5 5-Bromo-*N*-((5-(4-fluorophenyl)pyridin-2-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1047a**)

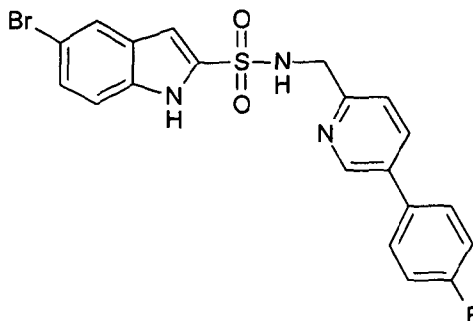


5-Bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1026c**) (1.5 g) was dissolved in THF (30 mL) and cooled in a water bath. (5-(4-Fluorophenyl)pyridin-2-yl)-methanamine (**ABD1047b**) (1.2 g) was added and the mixture stirred overnight. DMAP (0.5 g) was added and a precipitate was seen, the mixture was stirred for a further 2 h, diluted with ethyl acetate and poured into water (250 mL). The organic was washed with water and saturated NaCl solution, dried and evaporated to a red gum. Trituration with ether gave the crude product as a pale brown powder.

15

Synthesis 124

5-Bromo-*N*-((5-(4-fluorophenyl)pyridin-2-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1047**)

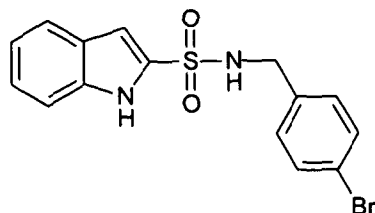


Using a method analogous to Method H with 5-bromo-*N*-((5-(4-fluorophenyl)pyridine-2-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1047a**), the title compound was obtained as a pale brown solid after washing with ether.

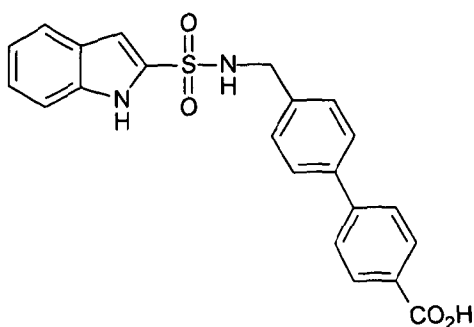
^{13}C NMR ($\text{DMSO}-d_6$): δ 48.1, 105.2, 113.3, 115.1, 116.3 (d, $J = 20.9$ Hz), 122.0, 124.5, 127.4, 128.2, 129.3 (d, $J = 7.7$ Hz), 133.7, 133.7, 135.0, 135.8, 136.3, 147.0, 156.5 and 162.6 (d, $J = 243.1$).

25

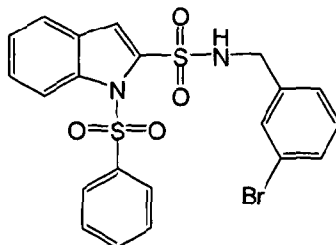
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Synthesis 125*N*-(4-Bromobenzyl)-1*H*-indole-2-sulfonamide (**ABD1048a**)

- 5 Using a method analogous to Method H with *N*-(4-bromobenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1027b**), the title compound was obtained as a pale brown solid on recrystallisation from ether/petrol.

Synthesis 1264'-((1*H*-Indole-2-sulfonamido)methyl)biphenyl-4-carboxylic acid (**ABD1048**)

- 10 Using a method analogous to Method K, with **ABD1048b** and 4-carboxyphenylboronic acid, after partitioning between dilute HCl and ethyl acetate, the title compound was obtained as a pale brown powder.
- 15 ¹³C NMR (DMSO-*d*₆): δ 46.3, 105.7, 113.0, 120.9, 122.3, 124.8, 126.5, 127.1, 127.3, 128.7, 130.0, 130.4, 135.0, 137.3, 138.3, 138.5, 144.4 and 167.6.

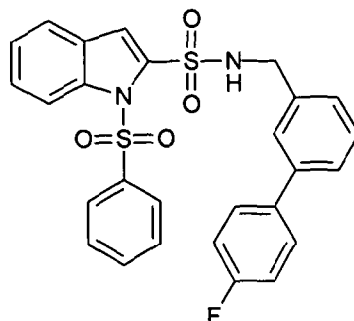
Synthesis 127*N*-(3-Bromobenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1049b**)

- 20 Using a method analogous to Method G, with 1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1027b**) and 3-bromobenzylamine, the title compound was obtained as a pale yellow solid after crystallisation from ether/petrol.

- 148 -

Synthesis 128

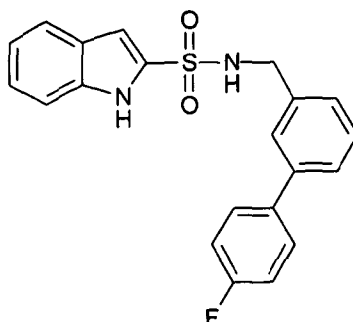
N-((4'-Fluorobiphenyl-3-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide
(**ABD1049a**)



- 5 Using a method analogous to Method K, with **ABD1049b** and 4-fluorophenylboronic acid, the title compound was obtained as a white powder after purification by column chromatography.

Synthesis 129

10 *N*-((4'-Fluorobiphenyl-3-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1049**)

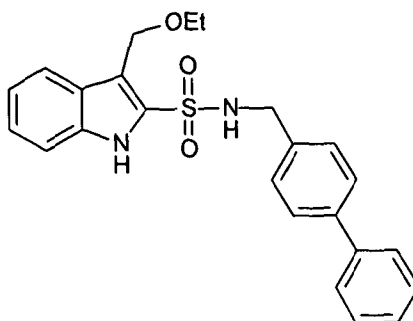


Using a method analogous to Method H with *N*-((4'-fluorobiphenyl-3-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1049a**), the title compound was obtained as a white solid on recrystallisation from ether/petrol.

15

¹³C NMR (DMSO-*d*₆): δ 46.6, 105.7, 113.1, 116.1 (d, *J* = 20.9 Hz), 120.9, 122.3, 124.8, 125.9, 126.2, 126.5, 127.1, 129.0 (d, *J* = 7.7 Hz), 129.3, 135.1, 136.8 (d, *J* = 3.1 Hz), 137.2, 139.0, 139.6 and 162.2 (d, *J* = 242.3 Hz).

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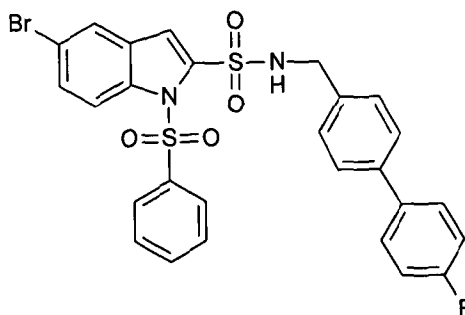
Synthesis 130*N*-(Biphenyl-4-ylmethyl)-3-(ethoxymethyl)-1*H*-indole-2-sulfonamide (**ABD1050**)

Using a method analogous to Method H with *N*-(biphenyl-4-ylmethyl)-3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1036a**), the title compound was obtained as a white solid on washing with ether.

¹³C NMR (DMSO-*d*₆): δ 15.3, 45.5, 61.8, 64.7, 112.5, 114.8, 120.1, 120.9, 124.7, 126.6, 126.7, 126.9, 127.4, 128.2, 128.8, 131.2, 135.5, 137.0, 139.1 and 139.9. ¹H NMR (DMSO-*d*₆): δ 1.11 (3H, t, *J* = 7.0 Hz), 3.50 (2H, q, *J* = 6.7 Hz), 4.15 (2H, d, *J* = 5.5 Hz), 4.87 (2H, s), 7.12 (1H, t, *J* = 7.9 Hz), 7.32 – 7.57 (11H, m), 7.75 (1H, d, *J* = 7.6 Hz), 8.32 (1H, t, *J* = 5.5 Hz) and 11.88 (1H, s).

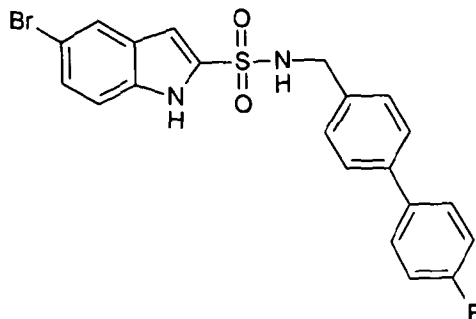
Synthesis 131

5-Bromo-*N*-((4'-fluorobiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1054a**)



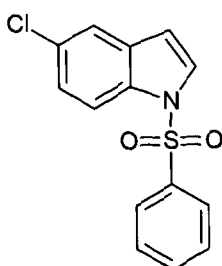
Using a method analogous to Method G, with 5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1026b**) and (4'-fluorobiphenyl-4-yl)methanamine, the title compound was obtained as a pale yellow solid after crystallisation from ether/petrol.

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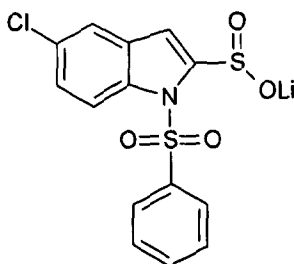
Synthesis 1325-Bromo-*N*-((4'-fluorobiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1054**)

Using a method analogous to Method H with 5-bromo-*N*-((4'-fluorobiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1054a**), the title compound was obtained as a white solid after crystallisation from ether/petrol.

¹³C NMR (DMSO-*d*₆): δ 46.3, 113.3, 115.1, 116.1 (d, *J* = 20.9 Hz), 124.5, 126.9, 127.4, 128.3, 128.6, 129.0 (d, *J* = 7.7 Hz) 135.8, 136.4, 136.7, 136.8, 137.3, 138.4, 162.2 (d, *J* = 243.1 Hz). MS, *m/z*: Calcd, 458.01; Found, 459.09 (M+H).

Synthesis 1335-Chloro-1-(phenylsulfonyl)-1*H*-indole (**ABD1055e**)

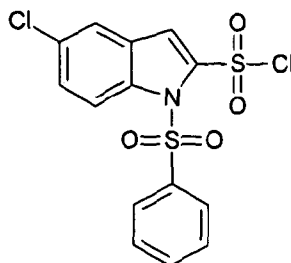
Using a method analogous to Method A, with 5-chloro-1*H*-indole, the title compound was obtained as a brown oil which solidified on standing.

Synthesis 134Lithium 5-Chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1055d**)

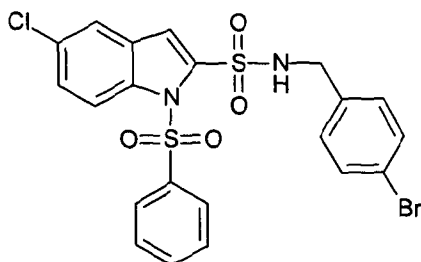
20

Using a method analogous to Method B, with 5-chloro-1-(phenylsulfonyl)-1*H*-indole (**ABD1055e**), the title compound was obtained as a pale brown solid.

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Synthesis 1355-Chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1055c**)

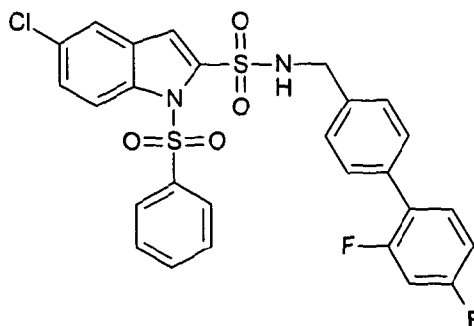
- 5 Using a method analogous to Method C, with lithium 5-chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfinate (**ABD1055d**), the title compound was obtained as a pale orange solid on recrystallisation from methanol.

Synthesis 136*N*-(4-Bromobenzyl)-5-chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1055b**)

10

- Using a method analogous to Method G, with 5-chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1055c**) and 4-bromobenzylamine, the title compound was obtained as a yellow solid after purification by column chromatography.

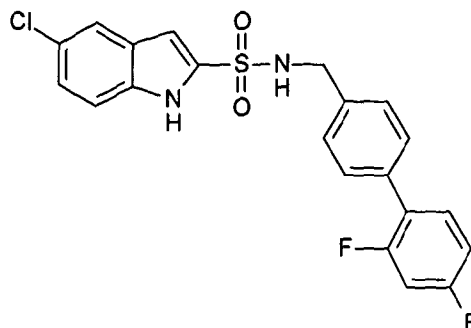
15

Synthesis 1375-Chloro-*N*-((2',4'-difluorobiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1055a**)

20

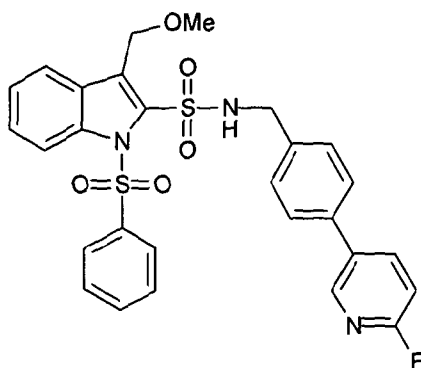
- Using a method analogous to Method K, with **ABD1055b** and 2,4-difluorophenylboronic acid, the title compound was obtained as a brown powder

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Synthesis 1385-Chloro-*N*-((2',4'-difluorobiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1055**)

5 Using a method analogous to Method H with 5-chloro-*N*-((2',4'-difluorobiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1055a**), the title compound was obtained as a white solid after crystallisation from ether/petrol.

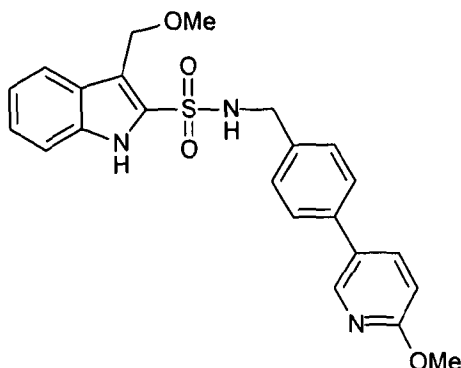
¹³C NMR (DMSO-*d*₆): δ 46.3, 104.8 (d, *J* = 27.1), 105.1, 112.4 (dd, *J* = 20.9, 3.1 Hz), 114.7, 121.4, 125.0, 125.1, 125.4, 127.6, 128.3, 129.0, 132.2 (dd, *J* = 10.0, 5.4 Hz),
10 133.6, 135.6, 136.6, 137.9, 159.5 (dd, *J* = 250, 21.7 Hz) and 162.3 (dd, *J* = 250, 20.7 Hz).

Synthesis 139*N*-(4-(6-Fluoropyridin-3-yl)benzyl)-3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1056a**)

15

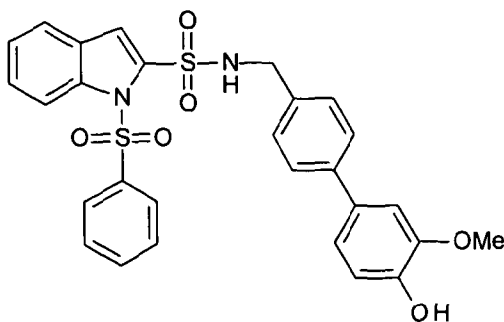
Using a method analogous to Method G, with 3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1036b**) and (4-(6-fluoropyridin-3-yl)phenyl)methanamine (**ABD1045b**), the title compound was obtained as a white solid by filtration.

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Synthesis 140**3-(Methoxymethyl)-*N*-(4-(6-methoxypyridin-3-yl)benzyl)-1*H*-indole-2-sulfonamide (ABD1056)**

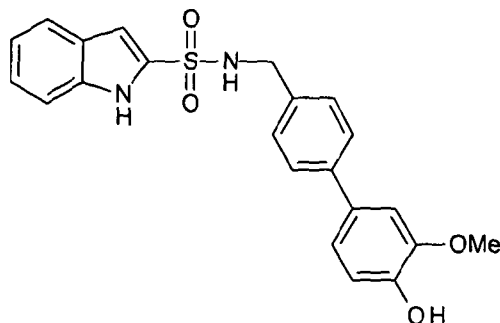
- 5 Using a method analogous to Method H with *N*-(4-(6-fluoropyridin-3-yl)benzyl)-3-(methoxymethyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1056a**) (substituting methanol for ethanol), the title compound was obtained as a white powder on recrystallisation from ether/petrol.
- 10 ¹H NMR (DMSO-*d*₆): δ 3.40 (3H, s), 3.89 (3H, s), 4.15 (2H, s), 4.84 (2H, s), 6.89 (1H, d, *J* = 7.9 Hz), 7.11 (1H, m), 7.35 (3H, m), 7.51 (3H, m), 7.72 (1H, d, *J* = 8.2 Hz), 7.90 (1H, d, *J* = 7.9 Hz), 8.42 (2H, m) and 11.92 (1H, s). MS, *m/z*: Calcd, 437.13; Found, 438.17 (*M*+*H*).

15

Synthesis 141***N*-((4'-Hydroxy-3'-methoxybiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (ABD1057a)**

- Using a method analogous to Method K, with **ABD1027b** and 4-hydroxy-3-methoxyphenylboronic acid, the title compound was obtained as a clear brown oil.
- 20

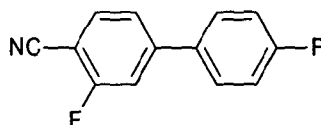
- 154 -

Synthesis 142*N*-((4'-Hydroxy-3'-methoxybiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1057**)

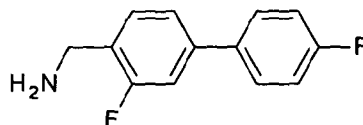
5 Using a method analogous to Method H with *N*-((4'-hydroxy-3'-methoxybiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1057a**), the title compound was obtained as a pale brown powder on on recrystallisation from ether/petrol.

¹³C NMR (DMSO-*d*₆): δ 46.4, 56.1, 105.6, 111.2, 113.0, 116.3, 119.5, 120.9, 122.3, 124.8, 126.5, 126.5, 128.5, 131.6, 135.1, 136.4, 137.3, 139.8, 146.8 and 148.4.

10

Synthesis 1433,4'-Difluorobiphenyl-4-carbonitrile (**ABD1058c**)

15 Using a method analogous to Method K, with 4-bromo-2-fluorobenzonitrile and 4-fluorophenylboronic acid, the title compound was obtained as a white solid from ethyl acetate/petrol

Synthesis 144(3,4'-Difluorobiphenyl-4-yl)methanamine (**ABD1058b**)

20

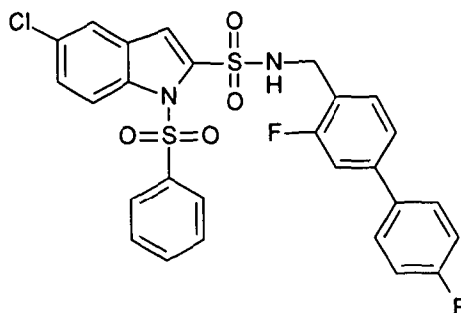
Method L: 3,4'-Difluorobiphenyl-4-carbonitrile (**ABD1058c**) (2 g) was dissolved in THF (20 mL) and cooled in an ethanol / CO₂ bath. 1 M LiAlH₄ in THF (30 mL) was added and the mixture stirred at below room temperature overnight. The reaction was quenched by the dropwise addition of 1 : 10 water : THF (20 mL), diluted with ethyl acetate, stirred with 1 M NaOH and filtered through Ceelite®. The organic phase was separated, washed with 1 M NaOH, brine and dried. Evaporation gave the title compound as a thick oil, used without further purification.

25

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Synthesis 145

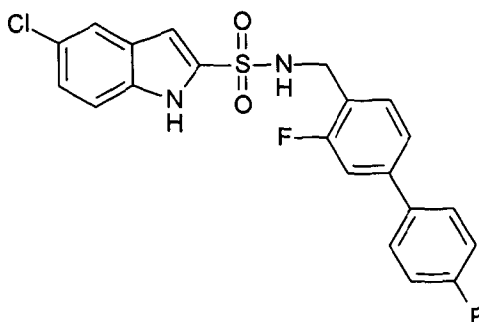
5-Chloro-*N*-((3,4'-difluorobiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1058a**)



- 5 Using a method analogous to Method G, with 5-chloro-1-(phenylsulfonyl)-1*H*-indole-2-sulfonyl chloride (**ABD1055c**) and (3,4'-difluorobiphenyl-4-yl)methanamine, the title compound was obtained as a pale yellow solid on crystallisation from ether/petrol.

Synthesis 146

- 10 5-Chloro-*N*-((3,4'-difluorobiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1058**)



Using a method analogous to Method H with 5-chloro-*N*-((3,4'-difluorobiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1058a**), the title compound was obtained as a white powder on purification by column chromatography.

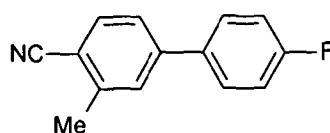
15

¹³C NMR (DMSO-*d*₆): δ 40.0 (hidden), 105.2, 113.5 (d, *J* = 22.5 Hz), 114.7, 116.2 (d, *J* = 21.7 Hz), 121.4, 122.8, 123.8 (d, *J* = 14.7 Hz), 125.0, 125.4, 127.0 (d, *J* = 23.2 Hz), 129.2 (d, *J* = 7.7 Hz), 131.0 (d, *J* = 4.6 Hz), 135.4, 135.6, 136.4, 141.0 (d, *J* = 7.7 Hz), 160.6 (d, *J* = 243.9 Hz) and 162.6 (d, *J* = 243.9 Hz). ¹H NMR (DMSO-*d*₆): δ 4.20 (2H, s), 6.92 (1H, s), 7.25 (3H, m), 7.40 (4H, m), 7.64 (2H, m), 7.96 (1H, s), 8.38 (1H, br s) and 12.17 (1H, br s).

20

Synthesis 146

4'-Fluoro-3-methylbiphenyl-4-carbonitrile (**ABD1059c**)



25

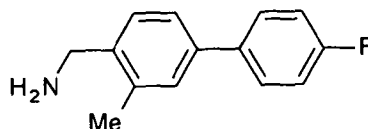
- 156 -

Using a method analogous to Method K, with 4-bromo-2-methylbenzonitrile and 4-fluorophenylboronic acid, the title compound was obtained as a white solid from ethyl acetate/petrol

5

Synthesis 147

(4'-Fluoro-3-methylbiphenyl-4-yl)methanamine (**ABD1059b**)

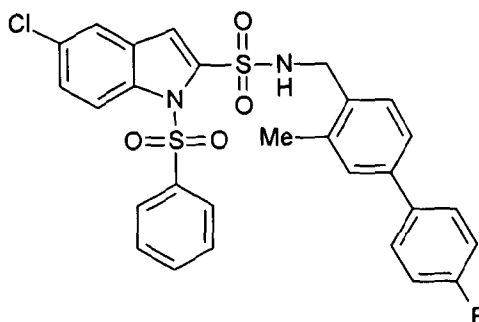


Using a method analogous to Method L, with 4'-fluoro-3-methylbiphenyl-4-carbonitrile, the title compound was obtained as a thick brown oil.

10

Synthesis 148

5-Chloro-N-((4'-fluoro-3-methylbiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1H-indole-2-sulfonamide (**ABD1059a**)

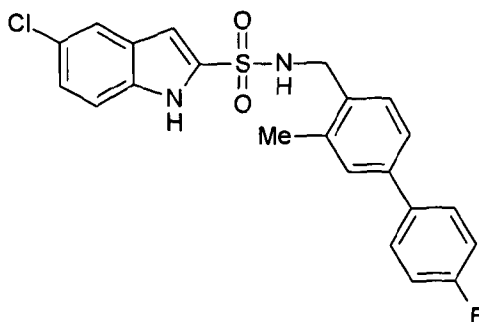


15

Using a method analogous to Method G, with 5-chloro-1-(phenylsulfonyl)-1H-indole-2-sulfonyl chloride (**ABD1055c**) and (4'-fluoro-3-methylbiphenyl-4-yl)methanamine, the title compound was obtained as a clear oil after purification by column chromatography.

Synthesis 149

5-Chloro-N-((4'-fluoro-3-methylbiphenyl-4-yl)methyl)-1H-indole-2-sulfonamide (**ABD1059**)



Using a method analogous to Method H with 5-chloro-N-((4'-fluoro-3-methylbiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1H-indole-2-sulfonamide (**ABD1059a**), the title compound was obtained as a white powder on purification by column chromatography and washing with ether.

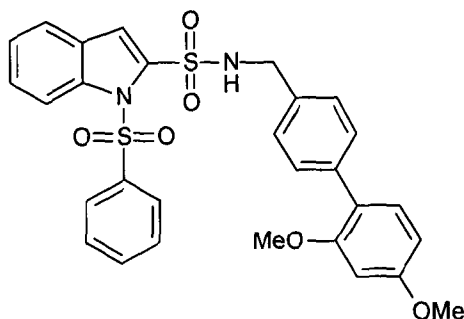
25

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¹³C NMR (DMSO-*d*₆): δ 19.1, 44.5, 105.1, 114.7, 116.1 (d, *J* = 20.9 Hz), 121.4, 124.3, 124.9, 125.3, 127.6, 128.7, 129.0 (d, *J* = 8.6 Hz), 129.5, 135.0, 135.6, 136.8, 136.8, 137.1, 138.7 and 162.2 (d, *J* = 242.3 Hz). ¹H NMR (DMSO-*d*₆): δ 2.28 (3H, s), 4.13 (d, *J* = 5.6 Hz), 6.96 (1H, s), 7.25 – 7.39 (6H, m), 7.47 (1H, d, *J* = 8.8 Hz), 7.61 (2H, m), 7.72 (1H, s), 8.21 (1H, t, *J* = 6.1 Hz) and 12.20 (1H, s)

Synthesis 149

N-((2',4'-Dimethoxybiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1060a**)

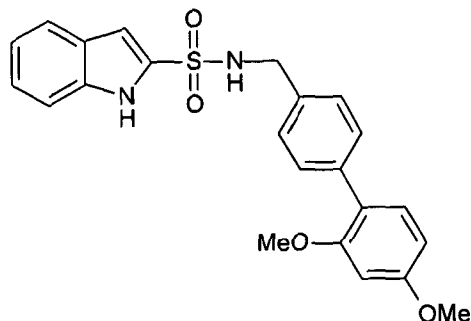


10

Using a method analogous to Method K, with **ABD1027b** and 2,4-dimethoxyphenylboronic acid, the title compound was obtained as a pale yellow oil.

Synthesis 150

N-((2',4'-Dimethoxybiphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1060**)



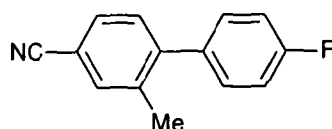
20

Using a method analogous to Method H with *N*-((2',4'-dimethoxybiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1060a**), the title compound was obtained as a white solid on recrystallisation from ether/petrol.

¹³C NMR (DMSO-*d*₆): δ 46.5, 55.7, 55.9, 99.4, 105.6, 105.7, 113.1, 120.9, 122.3, 122.6, 124.8, 126.5, 127.7, 129.5, 131.3, 135.1, 136.3, 137.3, 137.5, 157.6 and 160.5

Synthesis 151

4'-Fluoro-2-methylbiphenyl-4-carbonitrile (**ABD1062c**)

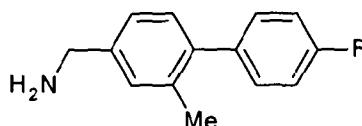


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- 158 -

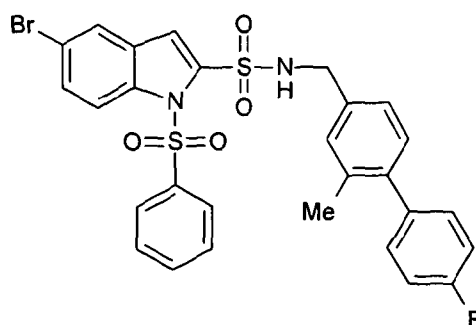
Using a method analogous to Method K, with 4-bromo-3-methylbenzonitrile and 4-fluorophenylboronic acid, the title compound was obtained as a white solid from ethyl acetate/petrol

5

Synthesis 152**(4'-Fluoro-2-methylbiphenyl-4-yl)methanamine (ABD1062b)**

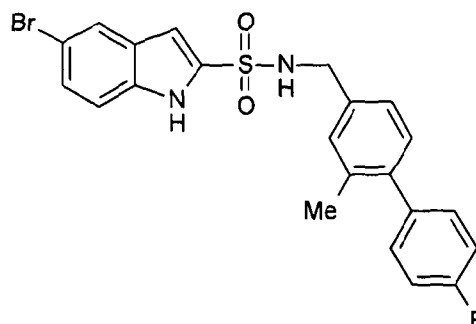
Using a method analogous to Method L, with 4'-fluoro-2-methylbiphenyl-4-carbonitrile (**ABD1062c**), the title compound was obtained as a thick brown oil.

10

Synthesis 153**5-Bromo-N-((4'-fluoro-2-methylbiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1H-indole-2-sulfonamide (ABD1062a)**

15 Using a method analogous to Method G, with 5-bromo-1-(phenylsulfonyl)-1H-indole-2-sulfonyl chloride (**ABD1026b**) and (4'-fluoro-2-methylbiphenyl-4-yl)methanamine (**ABD1062b**), the title compound was obtained as a clear oil after column chromatography.

20

Synthesis 154**5-Bromo-N-((4'-fluoro-2-methylbiphenyl-4-yl)methyl)-1H-indole-2-sulfonamide (ABD1062)**

25

Using a method analogous to Method H with 5-bromo-N-((4'-fluoro-2-methylbiphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1H-indole-2-sulfonamide (**ABD1062a**), the title compound was obtained as a white powder on washing with ether.

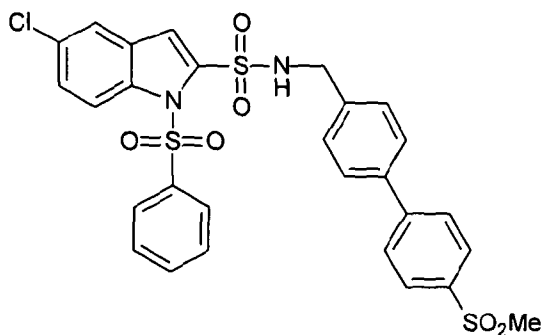
- 159 -

^1H NMR ($\text{DMSO}-d_6$): δ 2.05 (3H, s), 4.14 (2H, d, $J = 6.0$ Hz), 6.89 (1H, s), 7.02 (1H, d, $J = 7.6$ Hz), 7.06 (1H, s), 7.09 (1H, d, $J = 8.0$ Hz), 7.20 (4H, m), 7.38 (2H, m), 7.84 (1H, s), 8.34 (1H, t, $J = 6.2$ Hz) and 12.15 (1H, s)

5

Synthesis 155

5-Chloro-*N*-((4'-(methylsulfonyl)biphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1064a**)



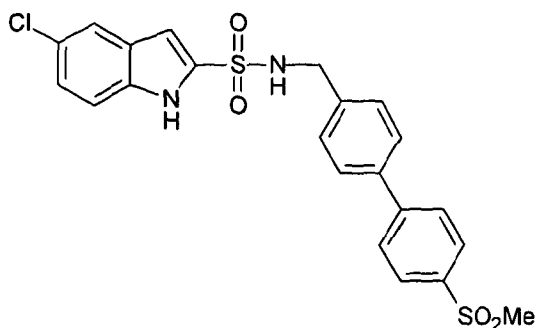
10

Using a method analogous to Method K, with **ABD1055b** and 4-methanesulfonyl-phenylboronic acid, the title compound was obtained as a brown powder on repeated addition of ether followed by evaporation.

15

Synthesis 156

5-Chloro-*N*-((4'-(methylsulfonyl)biphenyl-4-yl)methyl)-1*H*-indole-2-sulfonamide (**ABD1064**)

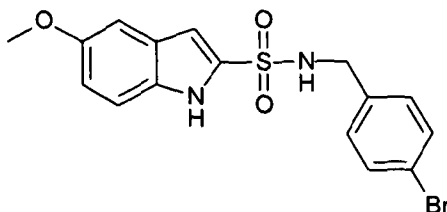


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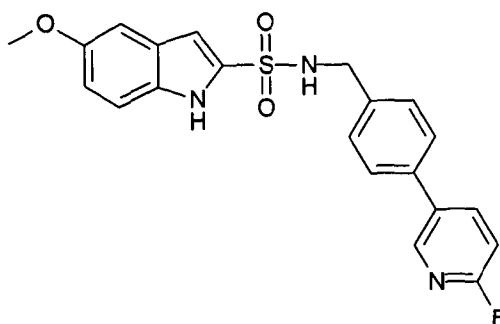
Using a method analogous to Method H with 5-chloro-*N*-((4'-(methylsulfonyl)biphenyl-4-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1064a**), the title compound was obtained as a white solid after recrystallisation from ether.

^{13}C NMR ($\text{DMSO}-d_6$): δ 44.1, 46.2, 105.2, 114.7, 121.4, 125.0, 125.4, 127.5, 127.6, 127.9, 128.0, 128.7, 135.6, 136.6, 137.7, 138.8, 139.9 and 145.2.

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Synthesis 157*N*-(4-Bromobenzyl)-5-methoxy-1*H*-indole-2-sulfonamide (**ABD1066a**)

- 5 Using a method analogous to Method H with 5-methoxy-*N*-(4-bromobenzyl)-1-(phenylsulfonyl)-1*H*-indole-2-sulfonamide (**ABD1046b**), the title compound was obtained as a white solid after recrystallisation from ether.

Synthesis 158*N*-(4-(6-Fluoropyridin-3-yl)benzyl)-5-methoxy-1*H*-indole-2-sulfonamide (**ABD1066**)

- 10 Using a method analogous to Method K, with *N*-(4-bromobenzyl)-5-methoxy-1*H*-indole-2-sulfonamide (**ABD1066a**) and 6-fluoro-3-pyridinylboronic acid, the title compound was obtained as a pale red solid from ethyl acetate/petrol.
- 15 ¹³C NMR (DMSO-*d*₆): δ 46.2, 55.7, 102.6, 105.4, 110.0 (d, *J* = 37.2 Hz), 113.9, 116.0, 126.9, 127.1, 128.7, 132.4, 134.3 (d, *J* = 4.7 Hz), 135.0, 135.1, 138.4, 140.6 (d, *J* = 7.8 Hz), 145.7 (d, *J* = 14.7 Hz), 154.5 and 163.0 (d, *J* = 234.6 Hz). ¹H NMR (DMSO-*d*₆): δ 3.73 (3H, s), 4.16 (2H, d, *J* = 6.0 Hz), 6.89 (1H, s), 6.90 (1H, dd, *J* = 9.2, 2.4 Hz), 7.10 (1H, d, *J* = 2.4 Hz), 7.23 (1H, dd, *J* = 8.4, 2.4 Hz), 7.34 (1H, d, *J* = 9.2 Hz), 7.38 (2H, d, *J* = 8.0 Hz), 7.60 (2H, d, *J* = 8.0 Hz), 8.19 (1H, td, *J* = 8.4, 2.4 Hz), 8.25 (1H, t, *J* = 6.0 Hz), 8.47 (1H, d, *J* = 2.4 Hz) and 11.83 (1H, s).
- 20

Biological Studies

Cannabinoid (CB) Receptor Allosteric Modulators - Functional Characteristics

- 5 Cannabinoid receptor allosteric ligands may be functionally characterised, for example, according to:
- (1) their effect upon agonist binding; and/or
 - (2) their effect upon agonist-induced signalling efficacy.
- 10 For example, allosteric interactions at the cannabinoid CB1 receptor have recently been described (see, *e.g.*, Price *et al.*, 2005). Three compounds, ORG27569, ORG29647 and ORG27759, produce a slowing of the dissociation of radiolabelled CB1 receptor agonist CP55940 from the CB1 receptor in mouse brain membranes. This slowing of the dissociation of the agonist is indicative of an allosteric modulator (see, *e.g.*, Price *et al.*,
- 15 2005). These three ORG compounds also induce an increase in the binding of CP55940 in an equilibrium binding assay and a decrease in the binding of a radiolabelled inverse agonist SR141716A. Thus, these modulators display a markedly divergent effect on orthosteric ligand affinity versus efficacy; they are allosteric *enhancers* of agonist binding affinity and allosteric *inhibitors* of agonist signalling efficacy.
- 20 Irrespective of mechanism, ligands can be classified solely on their overall functional effects: ligands which amplify the effect of an agonist are known as allosteric enhancers or positive allosteric modulators; ligands which suppress the effect of an agonist are known as allosteric inhibitors or negative allosteric modulators.

25

Assays Used to Investigate Allosteric Modulation

In order to fully investigate the effects of allosteric modulators, it is important to investigate the effects on both agonist affinity and efficacy.

30

- The radioligand equilibrium binding assay can be used to determine the effects on binding. When an allosteric ligand binds, it can either increase or decrease the dissociation rates of radiolabelled ligands. The use of functional assays to find allosteric modulators is also widely used as a screening mechanism and is required in order to
- 35 define the overall modulatory effect, positive or negative. It is possible to find allosteric modulators that affect signalling but don't affect affinity, which could be missed using the radioligand binding assays (equilibrium and dissociation) (see, *e.g.*, Christopolous *et al.*, 2004). Functional assays such as the β -arrestin and [^{35} S]GTP γ S binding assays represent an excellent starting point for G-protein coupled receptor based drug discovery
- 40 where the main purpose of drug discovery is to find compounds that exert functional effects.

Binding Assays

Radioligand equilibrium binding assays are used to investigate whether or not the compound under investigation has an effect on the affinity of the orthosteric ligand binding. When an allosteric ligand binds, it can either increase or decrease the dissociation rates of radiolabelled ligands. Using this method to look for allosteric modulators of orthosteric agonist affinity can be advantageous. If the modulator has an allosteric effect on the affinity of an orthosteric agonist for its receptor, there may be a displacement (full or partial), no displacement, or even an enhancement of orthosteric ligand binding. However, orthosteric and allosteric ligands share the ability to appear to fully "displace" an orthosteric ligand in an equilibrium binding assay. When a compound appears to "fully displace" the orthosteric ligand, it might be assumed it is acting at the orthosteric site but it may be acting at the allosteric site. This assay is useful in determining the effect the allosteric compound has on the affinity of the orthosteric compound. However, it is normally used along with another assay in order to correctly identify and confirm an allosteric action and prevent misidentification. This is often an important step in a full characterisation of an allosteric modulator, particularly those modulators which affect orthosteric binding affinity or of those that differentially affect orthosteric functional efficacy (see, e.g., Price *et al.*, 2005).

Functional Assays

Functional assays are used to find allosteric modulators, and are also widely used as a screening mechanism and are required in order to define the overall modulatory effect, positive or negative. It is possible to identify allosteric modulators that affect signalling but don't affect affinity, and which could be missed using only a radioligand binding assay (equilibrium and dissociation) (see, e.g., Christopoulos *et al.*, 2004).

Negative allosteric modulators will cause a characteristic decrease in efficacy ($E_{\max}$) of an orthosteric agonist in a functional assay. In contrast, competitive antagonists cause no change in agonist efficacy, but do cause a decrease in the potency (EC_{50}). Positive allosteric modulators will show a characteristic increase in the efficacy ($E_{\max}$) of the orthosteric agonist.

PathHunter™ β -Arrestin Assays

β -Arrestins are multifunctional intracellular proteins that interact with a structurally diverse group of cell surface receptors including GPCRs, to regulate cellular functions (see, e.g., Violin *et al.*, 2007).

PathHunter™ enzyme fragment complementation is the most important method to measure β -arrestin recruitment. PathHunter™ β -Arrestin assays developed by DiscoverRX are revolutionary high-throughput screening assays for monitoring GPCR

activation following ligand stimulation, without an imaging instrument, fluorescent protein tag, or radioactivity.

5 Instead, the assays detect GPCR activation through binding of β -arrestin to the expressed GPCR of interest, and measure the interaction of the two proteins using enzyme fragment complementation (EFC). The EFC approach offers a range of benefits for screening; including signal amplification and robust performance.

10 In this assay, the β -galactosidase enzyme (β -gal) is split into two inactive fragments. The larger portion of β -gal, termed EA for enzyme acceptor, is fused to the C-terminus of β -arrestin. The smaller, complementing fragment of β -gal, the ProLink™ tag, is expressed as a fusion protein with the GPCR of interest at the C-terminus. Upon activation, the GPCR is bound by β -arrestin. The interaction of β -arrestin and the GPCR forces the interaction of ProLink and EA, thus allowing complementation of the two
15 fragments of β -gal and the formation of a functional enzyme capable of hydrolyzing substrate and generating a fluorescence signal.

Using the PathHunter™ CB1 kit from DiscoverRX, a cannabinoid CB1 receptor agonist is added and activates the receptor, EA, which is fused to the C-terminus of β -arrestin, and
20 then interacts with the ProLink™ tag which is fused to the CB1 receptor. This will result in the fluorescence signal that is recorded by a luminescence plate reader. The fluorescence signal is directly related to the activation of the receptor, therefore a higher concentration of agonist will yield a larger fluorescence signal. The cannabinoid agonist is added in increasing concentrations to obtain an agonist dose response curve. With
25 pre-incubation of a potential allosteric modulator, either an enhancement of agonist signalling with an allosteric enhancer or a decrease in the maximal response of the agonist with an allosteric inhibitor is expected.

30 All raw data are obtained as luminescence (relative light units), and are normalised and presented as a percentage of the maximal response for the cannabinoid CB1 receptor agonist CP55,940 (2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-5-(2-methyloctan-2-yl)phenol).

[³⁵S]GTPγS Binding Assay

35 The [³⁵S]GTPγS binding assay was initially used and characterized with purified receptor and G-protein complexes in phospholipid vesicles using β -adrenergic receptors (see, e.g., Asano *et al.*, 1984). It is now common for this assay to be done using cell membranes that possess the receptor of interest (see, e.g., Harrison *et al.*, 2003).

40 All G-protein coupled receptors must function through an interaction and activation of G-proteins (see, e.g., Milligan, 2003). The [³⁵S]GTPγS binding assay measures the amount of G-protein activation after a ligand binds to the G-protein coupled receptor (see, e.g., Harrison *et al.*, 2003). In its inactive state, the G-protein exists as a heterodimer

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(G α (GDP) $\beta\gamma$) with GDP bound to the G α subunit. When the G-protein is activated by a ligand binding to the receptor, there is an exchange of GDP to GTP at the G α subunit; this is known as the guanine nucleotide exchange (see, e.g., Harrison *et al.*, 2003). This binding of the GTP to the G α subunit leads to the dissociation of the $\beta\gamma$ subunit, which will in turn lead to the downstream effects exerted by the activation of the particular G-protein (see, e.g., Milligan, 2003). The G α (GDP) $\beta\gamma$ heterodimer is then reformed by GTPase which reforms the G α to GDP which then leads to the binding of the $\beta\gamma$ complex (see, e.g., Harrison *et al.*, 2003). The guanine nucleotide exchange is an event that happens very early in the signal transduction cascade, making this assay an excellent measure of pharmacological characteristics and the efficacy of ligands binding to the receptor (see, e.g., Milligan, 2003).

[³⁵S]GTP γ S is an analogue of GTP; it is non-hydrolysable and therefore resistant to the GTPase activity of the G α subunit. In the [³⁵S]GTP γ S binding assay, [³⁵S]GTP γ S is used to replace the naturally occurring GTP. As this analogue is not hydrolysed by the GTPase, the GDP is not then able to reassociate with the G α subunit, meaning that there will then be a build up of membrane bound [³⁵S]GTP γ S (see, e.g., Milligan, 2003). The amount of [³⁵S]GTP γ S bound is then quantified through filtration onto fibre glass filters which will retain any radioactivity. These filters are then used in a liquid scintillation counter. The data collected are expressed as a percentage over the amount of basal binding.

Biological Study 1

Initial screening of candidate compounds was performed using an *in vitro* assay to determine functional characteristics.

The PathHunter™ β -Arrestin assay (from DiscoverX, Fremont, USA) was performed as follows. HEK293 CB1 β -arrestin cells were plated 48 hours before use and incubated at 37°C, 5% CO₂ in a humidified incubator. Test compounds were dissolved in dimethylsulfoxide (DMSO) and diluted in optimized cell culture (OCC, as supplied by DiscoverX) media to the required concentrations. 5 μ L of test compound or vehicle solution was added to each well and incubated for 60 minutes at 37°C, 5% CO₂ in a humidified incubator. 5 μ L of increasing concentrations of anandamide was added to each well followed by a 90-minute incubation at 37°C, 5% CO₂ in a humidified incubator. 55 μ L of detection reagent (as supplied by DiscoverX) was then added, followed by a further 90 minute incubation at room temperature in the dark. Chemiluminescence, reported in relative light units (RLU – a dimensionless value, standardised as a % of maximum stimulation with anandamide), was measured on a standard luminescence plate reader.

Data were plotted as % of maximal stimulation (E_{max}) caused by agonist versus the logarithm of concentration of agonist, in the presence or absence of a fixed concentration of test compound (modulator) or vehicle. For example, stimulation in the presence of

agonist alone will give a value for stimulation expressed in RLU, which can be expressed as a range from 0% (at lowest agonist concentration, e.g., 1 nM) to 100% (at the highest agonist concentration, e.g., 10 μ M). Addition of a test compound which is a negative allosteric modulator at a fixed concentration (e.g., 100 nM) will give reduced RLU values leading to a reduction in the maximum stimulation elicited by the agonist, which can be expressed as a % of the control (agonist alone). The concentration of modulator which produces a 50% reduction in the E_{max} of the agonist is defined as the IC_{50} . An example of this is shown in Figure 1.

Figure 1 is a graph illustrating the data described herein, and shows the effects of ABD1012 in inhibiting the maximum level of stimulation (E_{max}) caused by the cannabinoid agonist CP55,940, as measured using the β -arrestin assay. The graph shows that ABD1012 is a highly potent inhibitor of cannabinoid receptor signalling and reduces the level of stimulation (E_{max} , efficacy) by 50% at a concentration of close to 100 nM (IC_{50} = 120 nM, as calculated by GraphPad Prism). Each symbol represents the mean percentage of stimulation above basal $\pm$ S.E.M ($n = 3$).

The graph also demonstrates that ABD1012 is an allosteric inhibitor (negative allosteric modulator) because it gives a reduction in E_{max} which is not overcome by higher concentrations of agonist; this is in contrast to the rightward shift of the curve, without a reduction in E_{max} , that would be seen with a competitive orthosteric antagonist.

All values are expressed as the mean, and variability is expressed as S.E.M or as 95% confidence limits. All data were analysed using GraphPad Prism 5 and fitted to a sigmoidal dose response curve; the IC_{50} value was obtained as the concentration of the inhibitor that reduces the agonist E_{max} to 50% of the maximum response obtained for the agonist.

The following compounds were studied using the PathHunter™ β -Arrestin assay as described above:

ABD0956, ABD0962, ABD0965, ABD0968, ABD0972, ABD0975, ABD0978, ABD0979, ABD0983, ABD0984, ABD0986, ABD0989, ABD1002, ABD1004, ABD1006, ABD1012, ABD1014, ABD1016, ABD1018, ABD1022, ABD1023, ABD1025, ABD1026, ABD1027, ABD1028, ABD1029, ABD1030, ABD1032, ABD1033, ABD1034, ABD1035, ABD1036, ABD1037, ABD1038, ABD1042, ABD1045, ABD1046, ABD1047, ABD1048, ABD1049, ABD1050, ABD1054, ABD1055, ABD1056, ABD1057, ABD1058, ABD1059, ABD1060, ABD1062, ABD1064.

All of the compounds have an IC_{50} for allosteric inhibition of less than 10 μ M.

The following compounds have an IC_{50} for allosteric inhibition of less than 1 μM :

ABD0956, ABD0965, ABD0968, ABD0972, ABD0975, ABD0978, ABD0984, ABD0989,
 ABD1002, ABD1004, ABD1006, ABD1012, ABD1014, ABD1016, ABD1022, ABD1023,
 5 ABD1025, ABD1026, ABD1027, ABD1028, ABD1029, ABD1030, ABD1032, ABD1033,
 ABD1034, ABD1035, ABD1036, ABD1037, ABD1042, ABD1045, ABD1046, ABD1047,
 ABD1049, ABD1050, ABD1054, ABD1055, ABD1056, ABD1057, ABD1058, ABD1060,
 ABD1062, ABD1064.

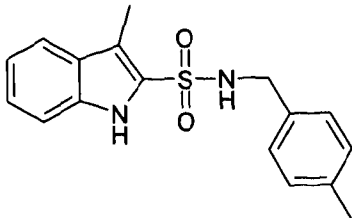
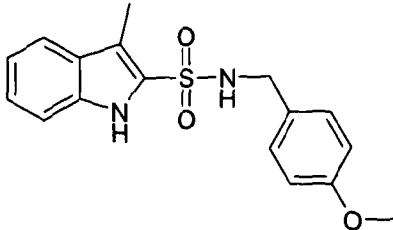
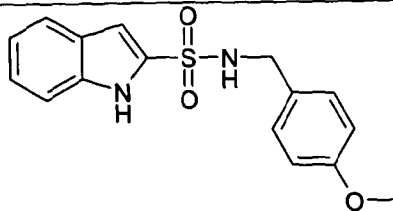
10 The following compounds have an IC_{50} for allosteric inhibition of less than 200 nM:

ABD1027, ABD1028, ABD1025, ABD1032, ABD1034, ABD1037, ABD1055, ABD1029,
 ABD1026, ABD1030, ABD0978, ABD1047, ABD1045, ABD1042, ABD1054, ABD1035,
 ABD1064, ABD1050, ABD1058, ABD1060, ABD1057, ABD1036, ABD1033, ABD1056,
 15 ABD1046, ABD1012, ABD1062, ABD1014, ABD1049.

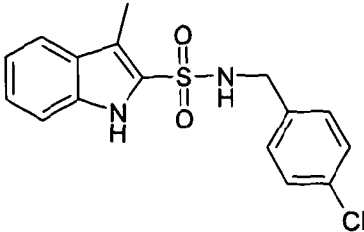
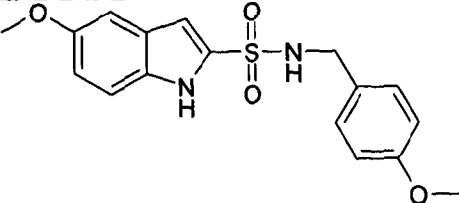
The following compounds have an IC_{50} for allosteric inhibition of less than 50 nM:

ABD0978, ABD1025, ABD1026, ABD1027, ABD1028, ABD1029, ABD1030, ABD1032,
 20 ABD1033, ABD1034, ABD1035, ABD1036, ABD1037, ABD1042, ABD1045, ABD1047,
 ABD1050, ABD1054, ABD1055, ABD1057, ABD1058, ABD1060, ABD1064.

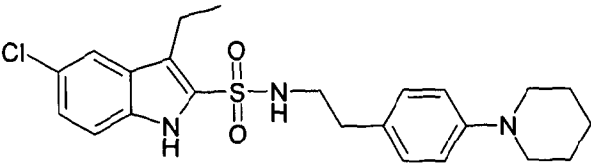
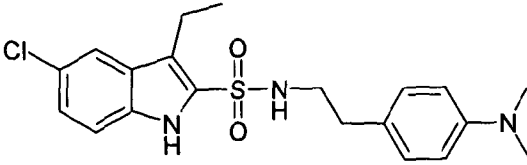
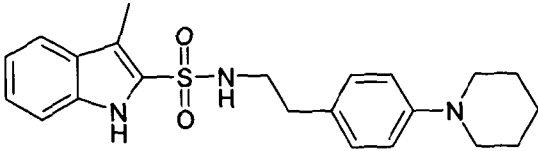
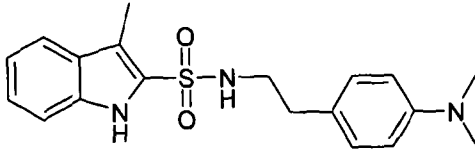
Data for several specific compounds (where $-L^1-$ is $-CH_2-$ and $-Q$ is $-Q^1$) are shown below.

Compound	Structure	IC_{50} (nM)
ABD0965		200
ABD0975		200
ABD1023		200

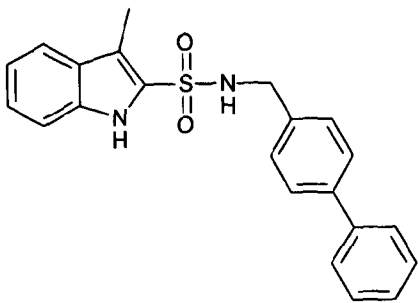
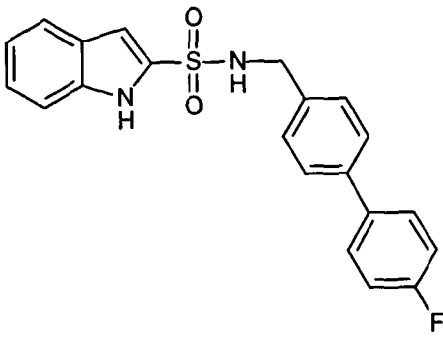
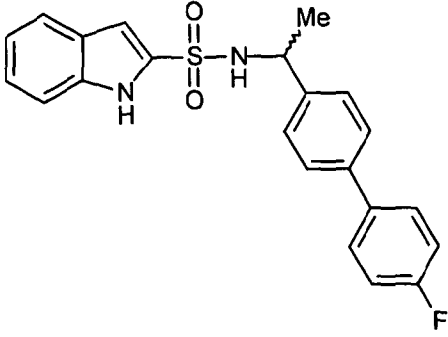
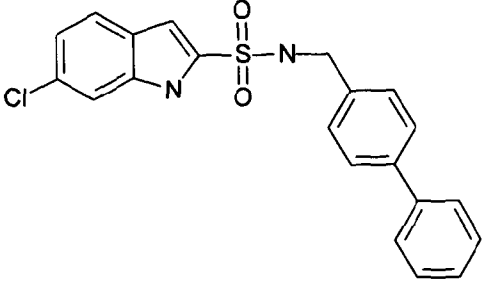
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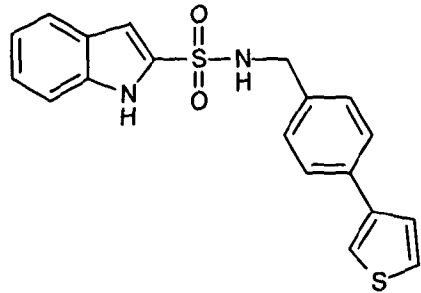
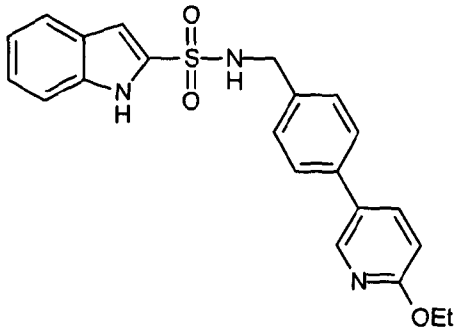
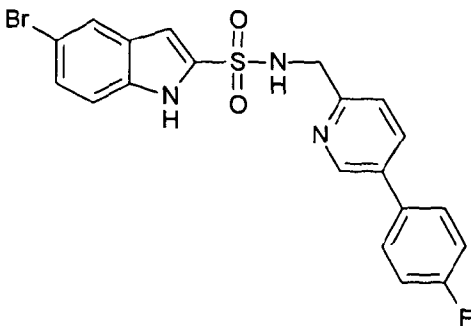
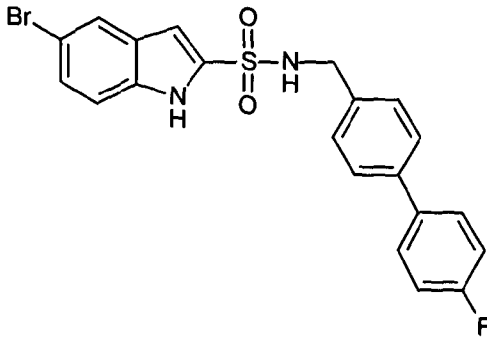
Compound	Structure	IC ₅₀ (nM)
ABD0972		300
ABD1022		400

Data for several specific compounds (where -L¹- is -CH₂CH₂- and -Q is -Q¹) are shown below.

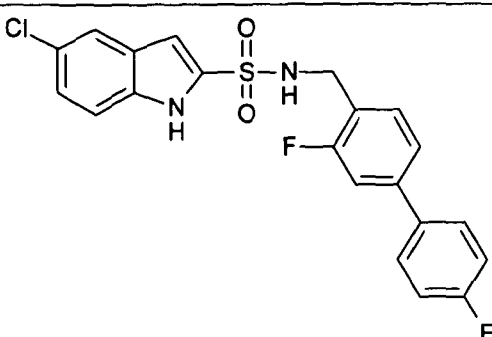
Compound	Structure	IC ₅₀ (nM)
ABD1012		120
ABD1014		130
ABD1004		200
ABD1006		300

Data for several specific compounds (where $-L^1$ is $-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-$ and $-Q$ is $-\text{Q}^2$) are shown below.

Compound	Structure	IC ₅₀ (nM)
ABD0978		8
ABD1027		1
ABD1033		41
ABD1037		4

Compound	Structure	IC ₅₀ (nM)
ABD1042		12
ABD1045		10
ABD1047		9
ABD1054		12

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Compound	Structure	IC ₅₀ (nM)
ABD1058		21

Biological Study 2

Equilibrium binding assays were carried out using [³H]CP55940 (the cannabinoid receptor agonist) at a concentration of 0.7 nM. 1 mg/mL bovine serum albumin (BSA) and 50 mM Tris buffer was used in a total assay volume of 500 μ L containing 0.01% DMSO. Binding was initiated by adding 33 μ g of mouse brain membranes. Assays were incubated at 37°C for 60 minutes and the reaction was stopped by the addition of ice cold wash buffer that contained 50 mM Tris buffer and 1 mg/mL BSA followed by vacuum filtration using a 24-well sampling manifold Brandel cell harvester and Whatman GF/B glass-fibre filters that had been soaked in the same wash buffer at 4°C for at least 24 hours. Each reaction tube was washed five times with a 500 μ L aliquot of buffer. The filters were then oven-dried for 60 minutes and then placed in 5 mL scintillation vials with 4 mL of scintillation fluid, and radioactivity was quantified by liquid scintillation spectrometry. Specific binding is defined as the difference between the binding that occurred in the presence of, and absence of, 1 μ M CP55940 and varied between 70% and 90% of the total binding (adapted from Thomas *et al.*, 2005).

Figure 2 a graph illustrating the data described herein, and shows the effects of CP55940, ORG27569 and ABD1027 on the specific binding of [³H]CP55940 in the equilibrium binding assay using mouse brain membranes. Each symbol represents the mean percentage of specific binding $\pm$ SEM. The graph shows that CP55940 causes a reduction in [³H]CP55940 binding, as would be expected, causing 100% displacement of the radioligand from the orthosteric site. In contrast, ORG27569 causes an increase in [³H]CP55940 binding, although it inhibits agonist signalling in functional studies, making ORG27569 an enhancer of agonist binding affinity but an inhibitor of agonist signalling efficacy (see, e.g., Price *et al.*, 2005). The graph also demonstrates that ABD1027 does not affect [³H]CP55940 binding and thus does not bind to the orthosteric site, although it inhibits agonist signalling in functional studies (as shown in biological study 1). An allosteric inhibitor which has little or no effect on agonist affinity, such as ABD1027, may represent a compound with less complex pharmacology, which may be more effective in vivo: for example use of a compound which increases ligand binding, such as ORG27569 may lead to a reduction in the levels of receptor expression and a consequent reduction in compound efficacy over time or a departure from normal pharmacology.

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described

5 embodiments should be regarded as illustrative rather than restrictive, and it should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention.

REFERENCES

- A number of publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.
- 10 Allison *et al.*, 2006, "Identification and Optimization of Anthranilic Sulfonamides as Novel, Selective Cholecystokinin-2 Receptor Antagonists", J. Med. Chem., Vol. 49, pp. 6371-6390.
- Asano *et al.*, 1984, "Reconstitution of catecholamine-stimulated binding of Guanosine 5'-O-(3-Thiotriphosphate) to the stimulatory GTP-binding protein of adenylate cyclase," Biochemistry, Vol. 23, pp. 5460-5467.
- 15 Banner *et al.*, 2008, "Sulfonamide Derivatives as Chymase Inhibitors," international patent application publication number WO 2008/084004 A1 published 17 July 2008.
- Barth *et al.*, 2008a, "Dérivés de N-[(1,5-diphényl-1H-pyrazol-3-yl)méthyl]sulphonamide antagonistes des récepteurs CB1 des cannabinoïdes", European patent application publication number EP 1878723 A1, published 16 January 2008.
- 20 Barth *et al.*, 2008b, "1,5-Diarylpyrrole derivatives, preparation method thereof and application of the same in therapeutics", United States patent application publication number US 2008/0015245 A1, published 17 January 2008.
- Barth *et al.*, 2008c, "Derivatives of 4,5-diarylpyrrole, preparation method thereof and application of the same in therapeutics", United States patent application publication number US 2008/0176924 A1, published 24 July 2008.
- 25 Barth *et al.*, 2008d, "N-[(4,5-diphenylpyrimidin-2-yl)méthyl]amine derivatives, the preparation thereof and their therapeutic use", United States patent application publication number US 2008/0176867 A1, published 24 July 2008.
- 30 Barth *et al.*, 2008e, "Heterocyclic derivatives, preparation and therapeutic use thereof", United States patent application publication number US 2008/0269303 A1, published 30 October 2008.
- Barth *et al.*, 2008f, "Diaryltriazolemethylamine derivatives, preparation and therapeutic use thereof", United States patent application publication number US 2008/0293794 A1, published 27 November 2008.
- 35 Barth *et al.*, 2009, "Aminomethylpyridine derivatives, method for preparing same and therapeutic use thereof", United States patent application publication number US 2009/0203699 A1, published 13 August 2009.
- Barth *et al.*, 2010, "5,6-Diarylpyridines substituted in the 2- and 3-position, preparation thereof and therapeutic use thereof", United States patent application publication number US 2010/0256202 A1, published 07 October 2010.
- 40 Bensaid *et al.*, 2003, "The cannabinoid CB1 receptor antagonist SR141716 increases Acip30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells," Mol. Pharmacol., Vol. 63, pp 908-914.

- Bermúdez-Silva *et al.*, 2008, "Presence of functional cannabinoid receptors in human endocrine pancreas," Diabetologia, Vol. 51, pp. 476-487.
- Brehm *et al.*, 1950, "The Preparation of Mannich bases related to Gramine," J. Org. Chem., Vol. 15, pp. 685-687.
- 5 Christopoulos *et al.*, 2002, "G protein-coupled receptor allosterism and complexing," Pharmacol. Rev., Vol. 54, pp. 323-374.
- Christopoulos *et al.*, 2004, "G-protein-coupled receptor allosterism: the promise and the problem(s)," Biochemical society transactions, Vol. 32, pp. 873-877.
- Conn *et al.*, 2009, "Allosteric modulators of GPCRs: a novel approach for the treatment of
10 CNS disorders," Nat. Rev. Drug Disc., Vol. 8, pp. 41-54 (January 2009).
- Cota *et al.*, 2003, "The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis," J. Clin. Invest., Vol. 112, pp. 423-431.
- Cowley *et al.*, 2011, "The Discovery of novel indole-2-carboxamides as cannabinoid CB1
15 receptor antagonists", Bioorg. Med. Chem. Lett., Vol. 21, pp. 497-501.
- Cravatt *et al.*, 2004, "The endogenous cannabinoid system and its role in nociceptive behaviour," J. Neurobiol., Vol. 61, pp. 149-160.
- Croci *et al.*, 2003, "Role of cannabinoid CB1 receptors and tumor necrosis factor-alpha in the gut and systemic anti-inflammatory activity of SR 141716 (rimonabant) in
20 rodents," Brit. J. Pharmacol., Vol. 140, pp. 115-122.
- Di Marzo *et al.*, 2004, "The endocannabinoid system and its therapeutic exploitation," Nat. Rev. Drug Disc., Vol. 3, pp. 771-784.
- Di Marzo, 2008, "Targeting the endocannabinoid system: to enhance or reduce?" Nat. Rev. Drug Disc., Vol. 7, pp. 438-455.
- 25 Gao *et al.*, 2006, "Keynote review: Allosterism in membrane receptors," Drug Disc. Today, Vol. 11, pp. 191-202.
- Geismann and Arman, 1952, "The Reaction of Gramine with Methyl Iodide. The Preparation and Properties of Gramine Methiodide," J. Am. Chem. Soc., Vol. 74, pp. 3916-3919.
- 30 Graham *et al.*, 1990, "Topically Active Carbonic Anhydrase Inhibitors. 3. Benzofuran- and Indole-2-sulfonamides," J. Med. Chem., Vol. 33, pp. 749-754.
- Greig *et al.*, 2004, international patent application publication number WO 2004/078261 A1 published 16 September 2004.
- Guindon *et al.*, 2007, "The antinociceptive effects of intraplantar injections of
35 2-Arachidonoylglycerol are mediated by cannabinoid CB2 receptors," Br. J. Pharmacol., Vol. 150, pp. 693-701.
- Harrison *et al.*, 2003, "The [35S]GTPγS binding assay: approaches and applications in pharmacology," Life Sciences, Vol. 74, pp. 489-508.
- Hickman *et al.*, 2000, "A Concise synthesis of 3-hydroxyindole-2-carboxylates by a
40 modified Baeyer-Villiger oxidation," Tet. Lett., Vol. 41, pp. 8217-8220.
- Idris *et al.*, 2005, "Regulation of bone mass, bone loss and osteoclast function by cannabinoid receptors", Nat. Med., Vol. 11, pp. 774-779.
- Kerns *et al.*, 2008, "Chapter 10: Blood-Brain Barrier", in Drug-like Properties: Concepts, Structure Design and Methods (Elsevier, Oxford, UK), p. 130.

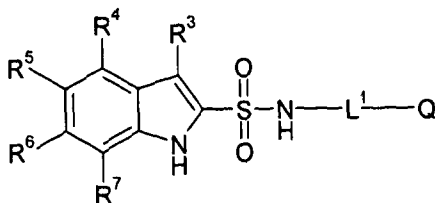
- Kobayashi *et al.*, 2004, "Sulfonyl Derivatives," US Patent No. 6,747,023 granted 08 June 2004.
- Kunos *et al.*, 2009, "Should peripheral CB(1) cannabinoid receptors be selectively targeted for therapeutic gain?" Trends Pharmacol. Sci., Vol. 30, pp. 1-7.
- 5 Liu *et al.*, 1997, "Regiospecific Bromination of 3-Methylindoles with NBS and Its Application to the Concise Synthesis of Optically Active Unusual Tryptophans Present in Marine Cyclic Peptides," J. Org. Chem., Vol. 62, pp. 7447-7456.
- Machii *et al.*, 1996, "Indole Derivatives," US Patent No. 5,891,902 granted 06 April 1999.
- May *et al.*, 2003, "Allosteric modulators of G-protein-coupled receptors," Curr. Opin. Pharmacol., Vol. 3, pp. 551-556.
- 10 Milbank *et al.*, 1999, "Synthesis of 1-Substituted 3-(Chloromethyl)-6-aminoindoline (6-Amino-seco-CI) DNA Minor Groove Alkylating Agents and Structure-Activity Relationships for Their Cytotoxicity," J. Med. Chem., Vol. 42, pp. 649-658.
- Milligan, 2003, "Principles: extending the utility of [³⁵S]GTPγS binding assays," Trends Pharmacol. Sci., Vol. 24, pp. 87-90.
- 15 Osei-Hyiaman *et al.*, 2005, "Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity," J. Clin. Invest., Vol. 115, pp. 1298-1305.
- Patti, 2010, "Rehashing endocannabinoid antagonists: can we selectively target the periphery to safely treat obesity and type 2 diabetes?," J. Clin. Invest., Vol. 120, pp. 2646-2648.
- 20 Pertwee, 2005, "The Therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids," AAPS Journal, Vol. 7, pp. E625-E654.
- 25 Pertwee, 2007, "Cannabinoids and multiple sclerosis," Mol. Neurobiol., Vol. 36, pp. 45-59.
- Piomelli *et al.*, 2006, "Pharmacological profile of the selective FAAH inhibitor KDS-4103 (URB597)," CNS Drug Reviews, Vol. 12, pp. 1-38.
- Price *et al.*, 2005, "Allosteric Modulation of the Cannabinoid CB1 Receptor," Mol. Pharmacol., Vol. 68, pp. 1484-1495.
- 30 Rees *et al.*, 2002, "GPCR drug discovery through the exploitation of allosteric drug binding sites," Receptors and Channels, Vol. 8, pp. 261-268.
- Ross, 2003, "Anandamide and Vanilloid TRPV1 Receptors," Br. J. Pharmacol., Vol. 140, pp. 790-801.
- Ross, 2007, "Allosterism and cannabinoid CB(1) receptors: the shape of things to come," Trends Pharmacol. Sci., Vol. 28, pp. 567-572.
- 35 Ross, 2009, "The Enigmatic pharmacology of GPR55," Trends Pharmacol. Sci., Vol. 30, pp. 156-163.
- Ryberg *et al.*, 2007, "The orphan receptor GPR55 is a novel cannabinoid receptor," Br. J. Pharmacol., Vol. 152, pp. 1092-1101.
- 40 Scheen *et al.*, 2006, "Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study," Lancet, Vol. 368, pp. 1660-1672.

- Son *et al.*, 2010, "Peripherally acting CB1-receptor antagonist: the relative importance of central and peripheral CB1 receptors in adiposity control," Int. J. Obesity, Vol. 34, pp. 547-556.
- 5 Soudijn *et al.*, 2004, "Allosteric modulation of G protein-coupled receptors: perspectives and recent developments," Drug Disc Today, Vol. 9, pp. 752-758.
- Sundberg, 1990, "Chapter 11, Introduction of Substituents at C3," in Indoles (Academic Press, San Diego, London), p. 115.
- Tam *et al.*, 2010, "Peripheral CB1 cannabinoid receptor blockade improves cardiometabolic risk in mouse models of obesity," J. Clin. Invest., Vol. 120, 10 pp. 2953-2966.
- Thomas *et al.*, 2005, "Evidence that the plant cannabinoid Δ^9 -tetrahydrocannabivarin is a cannabinoid CB1 and CB2 receptor antagonist." Brit. J. Pharmacol., Vol. 146, pp. 917-926.
- Violin *et al.*, 2007, "Beta-arrestin-biased ligands at seven-transmembrane receptors," 15 Trends Pharmacol. Sci., Vol. 28, pp. 416-422.
- Wadman, 2006, "Rimonabant adds appetizing choice to slim obesity market," Nat. Med., Vol. 12, p. 27.
- Wang *et al.*, 2009, "Allosteric modulators of G protein-coupled receptors: future therapeutics for complex physiological disorders," J. Pharmacol. Exp. Ther., 20 Vol. 331, pp. 340-348.
- Zimmerman *et al.*, 1988, "Herbicidal indole sulfonamides," US Patent No. 4,764,610 granted 16 August 1988.

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CLAIMS

1. A compound selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



5

wherein:

-Q is independently -Q¹ or -Q²;

10

-Q¹ is independently -Q^{1C} or -Q^{1H};

-Q^{1C} is independently phenyl or naphthyl, and is optionally substituted with one or more substituents -W¹;

15

-Q^{1H} is independently pyridyl, and is optionally substituted with one or more substituents -W¹;

-Q² is independently -Q^{2A}-Q^{2B};

20

-Q^{2A}- is independently -Q^{2AC}- or -Q^{2AH}-;

-Q^{2AC}- is independently phenylene or naphth-di-yl, and is optionally substituted with one or more substituents -W²;

25

-Q^{2AH}- is independently pyrid-di-yl, and is optionally substituted with one or more substituents -W²;

-Q^{2B} is independently -Q^{2BC} or -Q^{2BH};

30

-Q^{2BC} is independently phenyl or naphthyl, and is optionally substituted with one or more substituents -W¹;

-Q^{2BH} is independently C₅₋₆heteroaryl or C₉₋₁₀heteroaryl, and is optionally substituted with one or more substituents -W¹;

35

each -W¹ is independently:

-F, -Cl, -Br, -I,

-R^{W1}, -R^{W2},

-R^{W4}, -R^{W5},

40

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5 -OH, -OR^W,
 -CF₃, -OCF₃,
 -CN, -NO₂,
 -SH, -SR^W,
 -NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
 -C(=O)R^W,
 -C(=O)OH, -C(=O)OR^W,
 -NHC(=O)R^W, -NR^WC(=O)R^W,
 10 -C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
 -S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2},
 -NHS(=O)₂R^W, -NR^WS(=O)₂R^W,
 -S(=O)₂R^W, or -S(=O)₂CF₃;

each -W² is independently:

15 -F, -Cl, -Br, -I,
 -R^{W1}, -R^{W2},
 -R^{W4}, -R^{W5},
 -OH, -OR^W,
 20 -CF₃, -OCF₃,
 -CN, -NO₂,
 -SH, -SR^W,
 -NH₂, -NHR^W, -NR^W₂, -NR^{WN1}R^{WN2},
 -C(=O)R^W,
 25 -C(=O)OH, -C(=O)OR^W,
 -NHC(=O)R^W, -NR^WC(=O)R^W,
 -C(=O)NH₂, -C(=O)NHR^W, -C(=O)NR^W₂, -C(=O)NR^{WN1}R^{WN2},
 -S(=O)₂NH₂, -S(=O)₂NHR^W, -S(=O)₂NR^W₂, -S(=O)₂NR^{WN1}R^{WN2},
 -NHS(=O)₂R^W, -NR^WS(=O)₂R^W,
 30 -S(=O)₂R^W, or -S(=O)₂CF₃;

each -R^W is independently -R^{W1}, -R^{W2}, or -R^{W3};

35 each -R^{W1} is independently saturated aliphatic C₁₋₄alkyl and is optionally
 substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH,
 -OR^{W11}, and -OCF₃, wherein each -R^{W11} is independently saturated aliphatic
 C₁₋₄alkyl;

40 each -R^{W2} is independently saturated C₃₋₆cycloalkyl and is optionally
 substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -R^{W22},
 -CF₃, -OH, -OR^{W22}, -OCF₃, -CN, and -NO₂, wherein each -R^{W22} is independently
 saturated aliphatic C₁₋₄alkyl;

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each -R^{W3} is independently phenyl or benzyl, and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -R^{W33}, -CF₃, -OH, -OR^{W33}, -OCF₃, -CN, and -NO₂, wherein each -R^{W33} is independently saturated aliphatic C₁₋₄alkyl;

each -R^{W4} is independently aliphatic C₂₋₆alkenyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^{W44}, and -OCF₃, wherein each -R^{W44} is independently saturated aliphatic C₁₋₄alkyl;

each -R^{W5} is independently aliphatic C₂₋₆alkynyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^{W55}, and -OCF₃, wherein each -R^{W55} is independently saturated aliphatic C₁₋₄alkyl;

each -NR^{WN1}R^{WN2} is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is optionally substituted with one or more substituents selected from: -R^{WN3}, -C(=O)R^{WN3}, and -S(=O)₂R^{WN3}, wherein each -R^{WN3} is independently saturated aliphatic C₁₋₄alkyl;

-L¹- is independently saturated aliphatic C₁₋₄alkylene, and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^L, and -OCF₃, wherein each -R^L is independently saturated aliphatic C₁₋₄alkyl;

-R³ is independently -H or -R^{3A};
 -R⁴ is independently -H or -R^{4A};
 -R⁵ is independently -H or -R^{5A};
 -R⁶ is independently -H or -R^{6A};
 -R⁷ is independently -H or -R^{7A};

each of -R^{3A}, -R^{4A}, -R^{5A}, -R^{6A}, and -R^{7A} is independently:

-F, -Cl, -Br, -I,
 -R^{A1}, -R^{A2}, -R^{A3},
 -R^{A4}, -R^{A5},
 -OH, -OR^A,
 -CF₃, -OCF₃,
 -CN, -NO₂,
 -SH, -SR^A,
 -NH₂, -NHR^A, -NR^A₂, -NR^{AN1}R^{AN2},
 -NHC(=O)R^A, -NR^AC(=O)R^A,
 -C(=O)R^A,
 -C(=O)OH, -C(=O)OR^A,
 -C(=O)NH₂, -C(=O)NHR^A, -C(=O)NR^A₂, -C(=O)NR^{AN1}R^{AN2},

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-S(=O)₂R^A, -S(=O)₂CF₃,
 -S(=O)₂NH₂, -S(=O)₂NHR^A, -S(=O)₂NR^A₂, -S(=O)₂NR^{AN1}R^{AN2},
 -NHS(=O)₂R^A, or -NR^AS(=O)₂R^A;

5 each -R^A is independently -R^{A1}, -R^{A2}, or -R^{A3};

each -R^{A1} is independently saturated aliphatic C₁₋₄alkyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^{A11}, and -OCF₃, wherein each -R^{A11} is independently saturated aliphatic C₁₋₄alkyl;

10

each -R^{A2} is independently saturated C₃₋₆cycloalkyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -R^{A22}, -CF₃, -OH, -OR^{A22}, -OCF₃, -CN, and -NO₂, wherein each -R^{A22} is independently saturated aliphatic C₁₋₄alkyl;

15

each -R^{A3} is independently phenyl or benzyl, and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -R^{A33}, -CF₃, -OH, -OR^{A33}, -OCF₃, -CN, and -NO₂, wherein each -R^{A33} is independently saturated aliphatic C₁₋₄alkyl;

20

each -R^{A4} is independently aliphatic C₂₋₆alkenyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^{A44}, and -OCF₃, wherein each -R^{A44} is independently saturated aliphatic C₁₋₄alkyl;

25

each -R^{A5} is independently aliphatic C₂₋₆alkynyl and is optionally substituted with one or more substituents selected from: -F, -Cl, -Br, -I, -CF₃, -OH, -OR^{A55}, and -OCF₃, wherein each -R^{A55} is independently saturated aliphatic C₁₋₄alkyl;

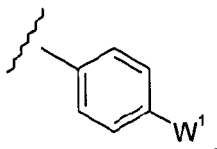
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each -NR^{AN1}R^{AN2} is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is optionally substituted with one or more substituents selected from: -R^{AN3}, -C(=O)R^{AN3}, and -S(=O)₂R^{AN3}, wherein each -R^{AN3} is independently saturated aliphatic C₁₋₄alkyl.

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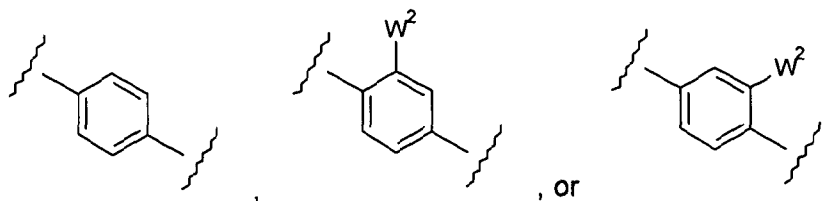
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2. A compound according to claim 1, wherein -Q is independently -Q¹.
3. A compound according to claim 1, wherein -Q is independently -Q².
- 5 4. A compound according to claim 1 or 2, wherein -Q¹ is independently -Q^{1C}.
5. A compound according to claim 1 or 2, wherein -Q¹ is independently -Q^{1H}.
6. A compound according to claim 1 or 3, wherein -Q² is independently -Q^{2AC}-Q^{2BC}.
- 10 7. A compound according to claim 1 or 3, wherein -Q² is independently -Q^{2AC}-Q^{2BH}.
8. A compound according to claim 1 or 3, wherein -Q² is independently -Q^{2AH}-Q^{2BC}.
- 15 9. A compound according to claim 1 or 3, wherein -Q² is independently -Q^{2AH}-Q^{2BH}.
10. A compound according to any one of claims 1, 2, and 4, wherein -Q^{1C} is independently phenyl, and is optionally substituted with one or more substituents -W¹.
- 20 11. A compound according to any one of claims 1, 2, and 4, wherein -Q^{1C} is independently:

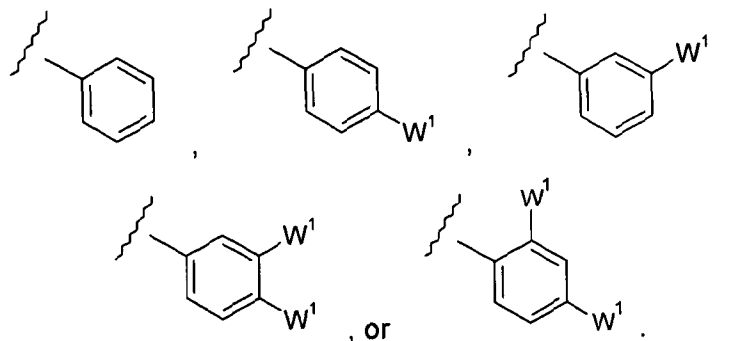


- 25 12. A compound according to any one of claims 1, 2, and 5, wherein -Q^{1H} is pyridin-2-yl, and is and is optionally substituted with one or more substituents -W¹.
13. A compound according to any one of claims 1, 2, and 5, wherein -Q^{1H} is pyridin-3-yl, and is and is optionally substituted with one or more substituents -W¹.
- 30 14. A compound according to any one of claims 1, 2, and 5, wherein -Q^{1H} is pyridin-4-yl, and is and is optionally substituted with one or more substituents -W¹.
15. A compound according to any one of claims 1, 3, 6, and 7, wherein -Q^{2AC}- is independently phenylene, and is optionally substituted with one or more substituents -W².
- 35 16. A compound according to any one of claims 1, 3, 6, and 7, wherein -Q^{2AC}- is independently para-phenylene, and is optionally substituted with one or more substituents -W².
- 40

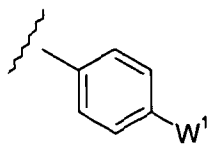
17. A compound according to any one of claims 1, 3, 6, and 7, wherein $-Q^{2AC}$ - is independently:



18. A compound according to any one of claims 1, 3, 8, and 9, wherein $-Q^{2AH}$ - is independently pyrid-2,5-di-yl, and is optionally substituted with one or more substituents $-W^2$.
19. A compound according to any one of claims 1, 3, 8, and 9, wherein $-Q^{2AH}$ - is independently pyrid-3,6-di-yl, and is optionally substituted with one or more substituents $-W^2$.
20. A compound according to any one of claims 1, 3, 6, and 8, wherein $-Q^{2BC}$ - is independently phenyl, and is optionally substituted with one or more substituents $-W^1$.
21. A compound according to any one of claims 1, 3, 6, and 8, wherein $-Q^{2BC}$ - is independently:

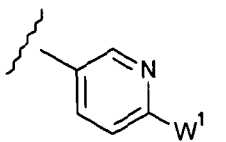


22. A compound according to any one of claims 1, 3, 6, and 8, wherein $-Q^{2BC}$ is independently:



23. A compound according to any one of claims 1, 3, 7, and 9, wherein $-Q^{2BH}$ is independently C_{5-6} heteroaryl, and is optionally substituted with one or more substituents $-W^1$.

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24. A compound according to any one of claims 1, 3, 7, and 9, wherein $-Q^{2BH}$ is independently pyridyl or thienyl, and is optionally substituted with one or more substituents $-W^1$.
- 5 25. A compound according to any one of claims 1, 3, 7, and 9, wherein $-Q^{2BH}$ is independently pyridyl, and is optionally substituted with one or more substituents $-W^1$.
- 10 26. A compound according to any one of claims 1, 3, 7, and 9, wherein $-Q^{2BH}$ is independently:
- 
27. A compound according to any one of claims 1 to 26, wherein each $-W^1$, if present, is independently:
- 15 $-F$, $-Cl$, $-Br$, $-I$,
 $-R^{W1}$, $-R^{W2}$,
 $-OH$, $-OR^W$,
 $-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^W$, $-NR^{W2}$, $-NR^{WN1}R^{WN2}$,

20 $-S(=O)_2NH_2$, $-S(=O)_2NHR^W$, $-S(=O)_2NR^{W2}$, $-S(=O)_2NR^{WN1}R^{WN2}$,
 $-NHS(=O)_2R^W$, $-NR^WS(=O)_2R^W$, or
 $-S(=O)_2R^W$.

28. A compound according to any one of claims 1 to 26, wherein each $-W^1$, if present, is independently $-F$, $-Cl$, $-Br$, $-I$, $-R^{W1}$, $-CF_3$, $-OH$, $-OR^W$, $-OCF_3$, $-NH_2$, $-NHR^W$, $-NR^{W2}$, or $-NR^{WN1}R^{WN2}$.

25 29. A compound according to any one of claims 1 to 26, wherein each $-W^1$, if present, is independently $-NH_2$, $-NHR^W$, $-NR^{W2}$, or $-NR^{WN1}R^{WN2}$.

30 30. A compound according to any one of claims 1 to 26, wherein each $-W^1$, if present, is independently $-R^{W1}$.

31. A compound according to any one of claims 1 to 26, wherein each $-W^1$, if present, is independently $-F$, $-Cl$, $-Br$, or $-I$.

35 32. A compound according to any one of claims 1 to 26, wherein each $-W^1$, if present, is independently $-OH$ or $-OR^W$.

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33. A compound according to any one of claims 1 to 32, wherein each $-W^2$, if present, is independently:
 $-F$, $-Cl$, $-Br$, $-I$,
 $-R^{W1}$, $-R^{W2}$,
 $-OH$, $-OR^W$,
 $-CF_3$, $-OCF_3$,
 $-NH_2$, $-NHR^W$, $-NR^{W2}$, $-NR^{WN1}R^{WN2}$,
 $-S(=O)_2NH_2$, $-S(=O)_2NHR^W$, $-S(=O)_2NR^{W2}$, $-S(=O)_2NR^{WN1}R^{WN2}$, or
 $-S(=O)_2R^W$.
34. A compound according to any one of claims 1 to 32, wherein each $-W^2$, if present, is independently $-F$, $-Cl$, $-Br$, $-I$, $-R^{W1}$, $-CF_3$, $-OH$, $-OR^W$, $-OCF_3$, $-NH_2$, $-NHR^W$, $-NR^{W2}$, or $-NR^{WN1}R^{WN2}$.
35. A compound according to any one of claims 1 to 32, wherein each $-W^2$, if present, is independently $-NH_2$, $-NHR^W$, $-NR^{W2}$, or $-NR^{WN1}R^{WN2}$.
36. A compound according to any one of claims 1 to 32, wherein each $-W^2$, if present, is independently $-R^{W1}$.
37. A compound according to any one of claims 1 to 32, wherein each $-W^2$, if present, is independently $-F$, $-Cl$, $-Br$, or $-I$.
38. A compound according to any one of claims 1 to 32, wherein each $-W^2$, if present, is independently $-OH$ or $-OR^W$.
39. A compound according to any one of claims 1 to 38, wherein each $-R^W$, if present, is independently $-R^{W1}$.
40. A compound according to any one of claims 1 to 39, wherein each $-R^{W1}$, if present, is independently $-Me$, $-Et$, $-nPr$, $-iPr$, or $-tBu$.
41. A compound according to any one of claims 1 to 39, wherein each $-R^{W1}$, if present, is independently $-Me$.
42. A compound according to any one of claims 1 to 41, wherein each $-NR^{WN1}R^{WN2}$, if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is optionally substituted with one or more substituents $-R^{WN3}$, wherein each $-R^{WN3}$ is independently saturated aliphatic C_{1-4} alkyl.
43. A compound according to any one of claims 1 to 42, wherein $-L^1$ is independently saturated aliphatic C_{1-4} alkylene.

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44. A compound according to any one of claims 1 to 42, wherein -L¹- is independently -CH₂-, -CH(CH₃)-, or -CH₂CH₂-.
- 5 45. A compound according to any one of claims 1 to 42, wherein -L¹- is independently -CH₂- or -CH(CH₃)-.
46. A compound according to any one of claims 1 to 42, wherein -L¹- is independently -CH₂CH₂-.
- 10 47. A compound according to any one of claims 1 to 46, wherein -R³ is independently -H.
48. A compound according to any one of claims 1 to 46, wherein -R³ is independently -R^{3A}.
- 15 49. A compound according to any one of claims 1 to 48, wherein -R⁴ is independently -H.
50. A compound according to any one of claims 1 to 48, wherein -R⁴ is independently -R^{4A}.
- 20 51. A compound according to any one of claims 1 to 50, wherein -R⁵ is independently -H.
- 25 52. A compound according to any one of claims 1 to 50, wherein -R⁵ is independently -R^{5A}.
53. A compound according to any one of claims 1 to 52, wherein -R⁶ is independently -H.
- 30 54. A compound according to any one of claims 1 to 52, wherein -R⁶ is independently -R^{6A}.
55. A compound according to any one of claims 1 to 54, wherein -R⁷ is independently -H.
- 35 56. A compound according to any one of claims 1 to 54, wherein -R⁷ is independently -R^{7A}.

57. A compound according to any one of claims 1 to 56, wherein $-R^{3A}$, if present, is independently:
-F, -Cl, -Br, -I,
- R^{A1} ,
5 -OH, -OR^A,
-CF₃, or -OCF₃.
58. A compound according to any one of claims 1 to 56, wherein $-R^{3A}$, if present, is independently: $-R^{A1}$.
- 10 59. A compound according to any one of claims 1 to 58, wherein $-R^{4A}$, if present, is independently:
-F, -Cl, -Br, -I,
- R^{A1} ,
15 -OH, -OR^A,
-CF₃, or -OCF₃.
60. A compound according to any one of claims 1 to 58, wherein $-R^{4A}$, if present, is independently: -F, -Cl, -Br, -I, or $-R^{A1}$.
- 20 61. A compound according to any one of claims 1 to 60, wherein $-R^{5A}$, if present, is independently:
-F, -Cl, -Br, -I,
- R^{A1} ,
25 -OH, -OR^A,
-CF₃, or -OCF₃.
62. A compound according to any one of claims 1 to 60, wherein $-R^{5A}$, if present, is independently: -F, -Cl, -Br, -I, $-R^{A1}$, -OH, or -OR^A.
- 30 63. A compound according to any one of claims 1 to 62, wherein $-R^{6A}$, if present, is independently:
-F, -Cl, -Br, -I,
- R^{A1} ,
35 -OH, -OR^A,
-CF₃, or -OCF₃.
64. A compound according to any one of claims 1 to 62, wherein $-R^{6A}$, if present, is independently: -F, -Cl, -Br, -I, or $-R^{A1}$.
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65. A compound according to any one of claims 1 to 64, wherein $-R^{7A}$, if present, is independently:
 -F, -Cl, -Br, -I,
 -R^{A1},
 -OH, -OR^A,
 -CF₃, or -OCF₃.
66. A compound according to any one of claims 1 to 64, wherein $-R^{7A}$, if present, is independently: -F, -Cl, -Br, -I, or -R^{A1}.
67. A compound according to any one of claims 1 to 66, wherein each $-R^A$, if present, is independently $-R^{A1}$.
68. A compound according to any one of claims 1 to 67, wherein each $-R^{A1}$, if present, is independently saturated aliphatic C₁₋₄alkyl.
69. A compound according to any one of claims 1 to 68, wherein each $-NR^{AN1}R^{AN2}$, if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is optionally substituted with one or more substituents $-R^{AN3}$, wherein each $-R^{AN3}$ is independently saturated aliphatic C₁₋₄alkyl.
70. A compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, hydrates, and solvates thereof:
 ABD0956, ABD0962, ABD0965, ABD0968, ABD0972, ABD0975, ABD0978,
 ABD0979, ABD0983, ABD0984, ABD0986, ABD0989, ABD1002, ABD1004,
 ABD1006, ABD1012, ABD1014, ABD1016, ABD1018, ABD1022, ABD1023,
 ABD1025, ABD1026, ABD1027, ABD1028, ABD1029, ABD1030, ABD1031,
 ABD1032, ABD1033, ABD1034, ABD1035, ABD1036, ABD1037, ABD1038,
 ABD1042, ABD1045, ABD1046, ABD1047, ABD1048, ABD1049, ABD1050,
 ABD1054, ABD1055, ABD1056, ABD1057, ABD1058, ABD1059, ABD1060,
 ABD1062, ABD1064, and ABD1066.
71. A pharmaceutical composition comprising a compound according to any one of claims 1 to 70, and a pharmaceutically acceptable carrier or diluent.
72. A method of preparing a pharmaceutical composition comprising the step of mixing a compound according to any one of claims 1 to 70, and a pharmaceutically acceptable carrier or diluent.
73. A method of inhibiting cannabinoid receptor (e.g., CB1) signalling in a cell, *in vitro* or *in vivo*, comprising contacting the cell with an effective amount of a compound according to any one of claims 1 to 70.

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74. A compound according to any one of claims 1 to 70 for use in a method of treatment of the human or animal body by therapy.
- 5 75. A compound according to claim 1 for use in a method of treatment of a disorder that is ameliorated by the inhibition of cannabinoid receptor (e.g., CB1) signalling.
76. Use of a compound according to any one of claims 1 to 70 in the manufacture of a medicament for the treatment of a disorder that is ameliorated by the inhibition of cannabinoid receptor (e.g., CB1) signalling.
- 10 77. A method of treatment of a disorder that is ameliorated by the inhibition of cannabinoid receptor (e.g., CB1) signalling comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 70.
- 15 78. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of metabolic syndrome.
- 20 79. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of type-2 diabetes.
80. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of dyslipidaemia
- 25 81. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of obesity.
82. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of an eating disorder.
- 30 83. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of a cardiovascular disease or disorder.
- 35 84. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of a cardiovascular disease or disorder *associated with* cardiovascular disease.
- 40 85. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of hypertension, congestive heart failure, cardiac hypertrophy, peripheral artery disease, atherosclerosis, stroke, kidney disease, myocardial infarction, steatohepatitis, or cardiotoxicity associated with chemotherapy.

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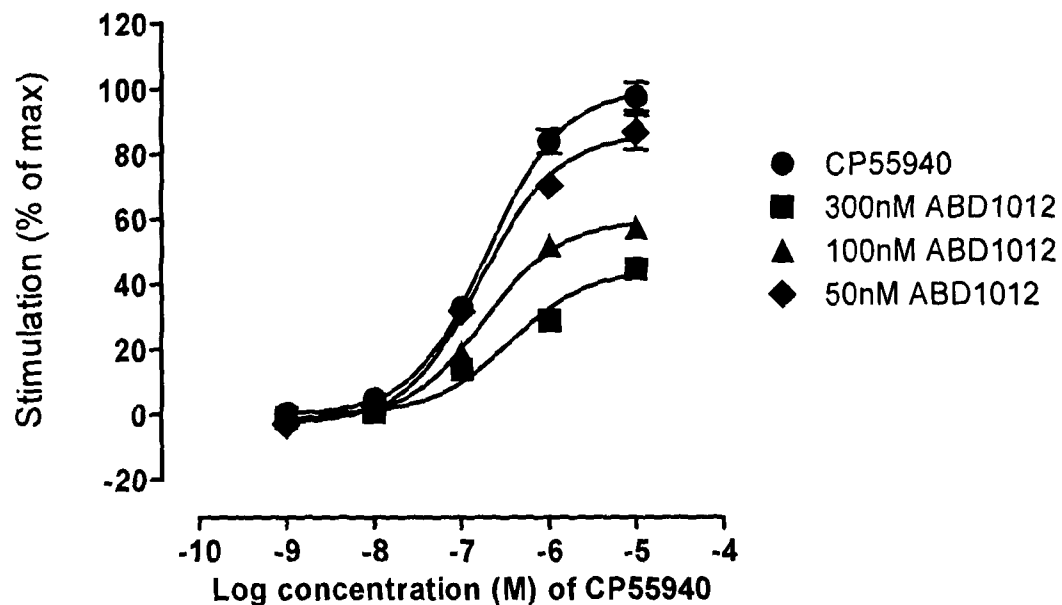
86. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of a non-alcoholic fatty liver disease (NAFLD) associated with metabolic syndrome.
- 5 87. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of a disease or disorder characterised by an addiction component.
- 10 88. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of addiction or withdrawal, for example, smoking addiction and/or smoking withdrawal, alcohol addiction and/or alcohol withdrawal, drug addiction and/or drug withdrawal.
- 15 89. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is smoking cessation therapy.
- 20 90. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of a bone disease or disorder.
91. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of osteoporosis, Paget's disease of bone, or bone related cancer.
- 25 92. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of breast cancer.
- 30 93. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of a disease or disorder characterised by an inflammatory or autoimmune component.
- 35 94. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of rheumatoid arthritis, inflammatory bowel disease, or psoriasis.
95. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of a psychiatric disease or disorder.
- 40 96. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of anxiety, mania, or schizophrenia.

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97. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of a disease or disorder characterised by impairment of memory and/or loss of cognitive function.
- 5 98. A compound according to claim 75, use according to claim 76, or a method according to claim 77, wherein the treatment is treatment of memory impairment, loss of cognitive function, Parkinson's disease, Alzheimer's disease, or dementia.

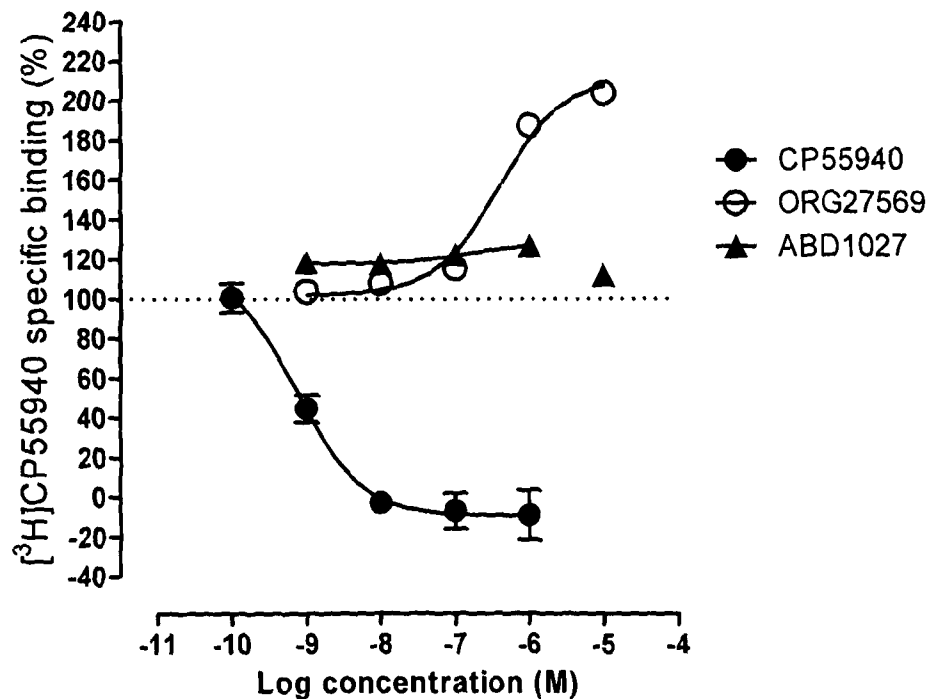
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FIGURE 1



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FIGURE 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2012/000193

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D209/30 C07D401/12 C07D409/12 A61K31/404 A61P3/00 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		
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, WPI Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/002133 A1 (SCHERING CORP [US]; SHANKAR BANDARPALLE B [US]; GILBERT ERIC [US]; RIZ) 5 January 2006 (2006-01-05) claim 1 -----	1-99
A	WO 03/042174 A1 (SCHERING CORP [US]) 22 May 2003 (2003-05-22) claim 1 -----	1-99
A	TONG LING ET AL.: "Expansion of SAR studies on triaryl bis sulfone cannabinoid CB2 receptor ligands", BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 20, no. 22, 31 August 2010 (2010-08-31), pages 6785-6789, XP009158183, table I -----	1-99
☐ 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 5 April 2012		Date of mailing of the international search report 24/04/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2012/000193

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006002133	A1	05-01-2006	AT 444066 T 15-10-2009
		CA 2571058 A1 05-01-2006	
		CN 101005838 A 25-07-2007	
		EP 1768667 A1 04-04-2007	
		ES 2332416 T3 04-02-2010	
		HK 1097189 A1 26-02-2010	
		JP 2008503585 A 07-02-2008	
		WO 2006002133 A1 05-01-2006	
WO 03042174	A1	22-05-2003	AR 037352 A1 03-11-2004
		BR 0214164 A 28-09-2004	
		CA 2466440 A1 22-05-2003	
		CN 1585749 A 23-02-2005	
		CN 101684091 A 31-03-2010	
		EC SP045104 A 28-06-2004	
		EP 1444203 A1 11-08-2004	
		HU 0401924 A2 28-01-2005	
		JP 2005509032 A 07-04-2005	
		JP 2010018635 A 28-01-2010	
		KR 20050044417 A 12-05-2005	
		MX PA04004674 A 12-08-2004	
		NZ 532291 A 25-11-2005	
		PE 07202003 A1 29-08-2003	
		WO 03042174 A1 22-05-2003	
		ZA 200403685 A 23-05-2005	