

CANNABINOID DERIVATIVE AS A PHARMACEUTICALLY ACTIVE COMPOUND AND METHOD OF PREPARATION THEREOF

RELATED APPLICATIONS

- 5 [0001] The present application is related to, and claims the benefit of, GB 2019784.4 filed on 15 December 2020 (15.12.2020), the contents of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

- [0002] The present invention relates to a cannabinoid derivative as a pharmaceutically active compound and method of preparation thereof.
- 10 [0003] The cannabinoid derivative of the invention is an analogue of cannabidiol (CBD). CBD is a non-psychoactive cannabinoid which has been used to treat various diseases and disorders. While such treatments hold promise, there remains a need in the art for more effective treatments and this has been brought about by way of the cannabinoid derivative of the invention.

15 BACKGROUND TO THE INVENTION

- [0004] Cannabinoids are natural and synthetic compounds structurally or pharmacologically related to the constituents of the cannabis plant or to the endogenous agonists (endocannabinoids) of the cannabinoid receptors CB1 or CB2. The only way in nature in which these compounds are produced is by the cannabis plant. Cannabis is a
- 20 genus of flowering plants in the family *Cannabaceae*, comprising the species *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis* (sometimes considered as part of *Cannabis sativa*).

- [0005] Cannabis plants comprise a highly complex mixture of compounds. At least 568 unique molecules have been identified. Among these compounds are cannabinoids,
- 25 terpenoids, sugars, fatty acids, flavonoids, other hydrocarbons, nitrogenous compounds, and amino acids.

- [0006] Cannabinoids exert their physiological effects through a variety of receptors including, but not limited to, adrenergic receptors, cannabinoid receptors (CB1 and CB2), GPR55, GPR3, or GPR5. The principle cannabinoids present in cannabis plants are
- 30 cannabinoid acids Δ^9 -tetrahydrocannabinolic acid (Δ^9 -THCA) and cannabidiolic acid (CBDA) with small amounts of their respective neutral (decarboxylated) cannabinoids. In addition, cannabis may contain lower levels of other minor cannabinoids.

- [0007] There are currently four cannabinoid-based pharmaceutical approved products on the market. These are: dronabinol (Marinol®) which is a synthetic tetrahydrocannabinol
- 35 (THC) approved for the treatment of loss of appetite in AIDS and the treatment of severe

nausea and vomiting caused by cancer chemotherapy; nabilone (Cesamet®) which is a synthetic cannabinoid and an analog of THC which is approved for the treatment of nausea and vomiting caused by cytotoxic chemotherapy unresponsive to conventional antiemetics; nabiximols (Sativex®) a mixture of two cannabis plant extracts approved for the treatment of neuropathic pain, spasticity, overactive bladder, and other symptoms of multiple sclerosis; and highly purified botanical CBD (Epidiolex®) approved in the United States for the treatment of Dravet syndrome and Lennox-Gastaut syndrome in children and adults over the age of 2 years.

[0008] As can be seen above cannabinoids are a class of compounds which may be derived naturally from the cannabis plant or produced semi-synthetically or synthetically via chemical synthesis.

[0009] More than 100 different cannabinoids have been identified. These cannabinoids can be split into different groups as follows: phytocannabinoids; endocannabinoids and synthetic cannabinoids (which may be novel cannabinoids or synthetically produced versions of phytocannabinoids or endocannabinoids). The Handbook of Cannabis, Roger Pertwee, Chapter 1, pages 3 to 15 details the cannabinoids known to date.

[0010] Cannabidiol (CBD) is a major cannabinoid constituent of Cannabis species, such as the hemp plant (*Cannabis sativa*). Unlike other cannabinoids, such as THC, cannabidiol does not bind to CB1 or CB2 receptors, or its binding to the receptors is negligible in terms of inducing a pharmacological effect. Thus, cannabidiol does not cause the central or peripheral nervous system effects mediated by the CB1 or CB2 receptors. CBD has little or no psychotropic (cannabimimetic) activity and its molecular structure and properties are substantially different from those of other cannabinoids.

[0011] Cannabidiol administration has been the subject of research in an attempt to provide an alternative treatment for various diseases and disorders which may respond to such treatment.

[0012] Whilst literature such as Gong *et al.* (2019) have described possible synthetic routes to generate C4'-substituted derivatives of CBD, giving a broad range of compounds that could be potentially generated and potentially be tested, there is no provision of any data to suggest the efficacy of such compounds, let alone that any specific compounds would be of particular benefit compared to others in the treatment of a disease.

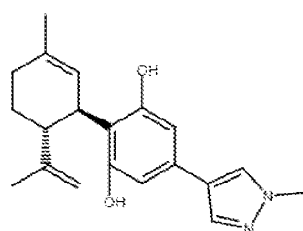
[0013] The present invention has been devised in light of these considerations.

BRIEF SUMMARY OF THE INVENTION

[0014] At its most general, the present invention relates to a synthetic cannabinoid compound which is biologically active and hence useful in the treatment of diseases. Such a novel compound may be administered by a wide variety of routes including but not limited to oral, transdermal, buccal, nasal, pulmonary, rectal or ocular. Such compound may be used for the treatment or prevention of a medical condition such as epilepsy.

[0015] The cannabidiol derivative of the invention is (1'R,2'R)-5'-methyl-4-(1-methyl-1H-pyrazol-4-yl)-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol, and will be referred to as the compound of formula (I) or compound 1 throughout.

[0016] In a first aspect of the invention there is provided a compound of formula (I), or a salt thereof:



formula (I)

[0017] In a second aspect of the invention there is a pharmaceutical composition comprising the compound of the first aspect and one or more additional ingredients selected from carriers, diluents (e.g. oils), excipients, adjuvants, fillers, buffers, binders, disintegrants, preservatives, antioxidants, lubricants, stabilisers, solubilisers, surfactants, masking agents, colouring agents, flavouring agents, and sweetening agents.

[0018] Preferably the pharmaceutical composition of the second aspect is in a form selected from a liquid, a solution, a suspension, an emulsion, a syrup, an electuary, a mouthwash, a drop, a tablet, a granule, a powder, a lozenge, a pastille, a capsule, a cachet, a pill, an ampoule, a bolus, a suppository, a pessary, a tincture, a gel, a paste, an ointment, a cream, a lotion, an oil, a foam, a spray, and an aerosol.

[0019] In a third aspect of the invention there is provided a compound of the first aspect, or the pharmaceutical composition of the second aspect, for use in a method of treatment.

[0020] Preferably, the method of treatment in the third aspect is a method of treatment of epilepsy, generalised seizure or tonic-clonic seizure.

[0021] In a fourth aspect of the invention there is provided a compound of the first aspect, or the pharmaceutical composition of the second aspect, for use as a medicament.

[0022] Preferably, the medicament of the fourth aspect is a medicament for treating epilepsy, generalised seizure or tonic-clonic seizure.

[0023] In a fifth aspect of the invention there is provided a method of treatment comprising administering to a subject in need of treatment a therapeutically effective amount of the compound of the compound of the first aspect or the pharmaceutical composition of the second aspect.

[0024] These and other aspects and embodiments of the invention are described in further detail below.

BRIEF SUMMARY OF THE DRAWINGS

[0025] Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which:

5 [0026] **Figure 1** shows the evaluation of the test compound, as shown as formula (I), in the MEST test in the mouse as described in Example 2.

[0027] **Figure 2** shows pharmacokinetics of compound **1** in rat as described in Example 3.

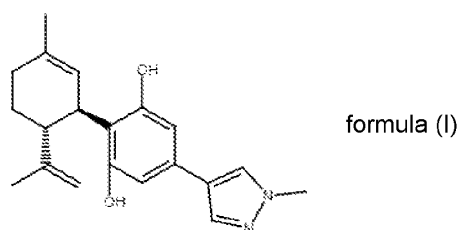
[0028] **Figure 3** shows specific PK parameters A) AUC_{last} and B) C_{max} of compound **1** in rat as described in Example 3.

DETAILED DESCRIPTION OF THE INVENTION

10 [0029] The present invention provides a synthetic cannabinoid compound which is biologically active and hence useful in the treatment of diseases.

Synthetic Cannabinoid

[0030] The invention provides a compound of formula (I):



15 [0031] The compound of the invention is (1'R,2'R)-5-methyl-4-(1-methyl-1H-pyrazol-4-yl)-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol.

Salts

[0032] In some embodiments, the compound of formula (I) is provided in free base form.

[0033] Alternatively, it may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the compound, for example, a pharmaceutically-acceptable salt.

20 Examples of pharmaceutically acceptable salts are discussed in "Pharmaceutical Salts: Properties, Selection, and Use", 2nd Edition, 2002, Stahl and Wermuth (Eds), Wiley-VCH, Weinheim, Germany.

[0034] Accordingly, in some embodiments the compound of formula (I) is provided as a salt, for example in a protonated form together with a suitable counter anion.

25 [0035] Suitable counter anions include both organic and inorganic anions. Example of suitable inorganic anions include those derived from inorganic acids, including chloride (Cl⁻),

bromide (Br⁻), iodide (I⁻), sulfate (SO₄²⁻), sulfite (SO₃²⁻), nitrate (NO₃⁻), nitrite (NO₂⁻), phosphate (PO₄³⁻), and phosphite (PO₃³⁻). Examples of suitable organic anions include 2-acetoxybenzoate, acetate, ascorbate, aspartate, benzoate, camphorsulfonate, cinnamate, citrate, edetate, ethanedisulfonate, ethanesulfonate, formate, fumarate, gluconate, glutamate, glycolate, hydroxymalate, carboxylate, lactate, laurate, lactate, maleate, malate, methanesulfonate, oleate, oxalate, palmitate, phenylacetate, phenylsulfonate, propionate, pyruvate, salicylate, stearate, succinate, sulfanilate, tartarate, toluenesulfonate, and valerate. Examples of suitable polymeric organic anions include those derived from tannic acid and carboxymethyl cellulose.

- 10 [0036] Alternatively, in some embodiments the compound of formula (I) is provided as a salt, for example in a deprotonated form together with a suitable counter cation.

- [0037] Suitable counter cations include both organic and inorganic cations. Examples of suitable inorganic cations include alkali metal ions such as Na⁺ and K⁺, alkaline earth cations such as Ca²⁺ and Mg²⁺, and other cations such as Al³⁺. Examples of suitable organic cations include the ammonium ion (i.e., NH₄⁺) and substituted ammonium ions (e.g., NH₃R⁺, NH₂R₂⁺, NHR₃⁺, NR₄⁺). Examples of substituted ammonium ions include 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 N(CH₃)₄⁺.
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Solvates

[0038] In some embodiments, the compound of formula (I) is provided in desolvated form, for example, in dehydrated form.

- [0039] Alternatively, it may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the compound.
- 25

[0040] Accordingly, in some embodiments the compound of formula (I) is provided in the form of a solvate (a complex of solute (e.g., compound, salt of compound) and solvent). Examples of solvates include hydrates, for example, a mono-hydrate, a di-hydrate and a tri-hydrate.

30 Methods of Synthesis

[0041] Methods for the synthesis of the compound of formula (I) are set out in the worked examples. Additional information relevant to the synthesis of synthetic cannabinoids can be found in Gong *et al.* (2019).

Pharmaceutical Compositions

- 35 [0042] While it is possible for the compound of formula (I) to be administered alone, it is preferable to administer a pharmaceutical composition (e.g., a formulation, preparation, or

medicament) comprising the compound of formula (I) together with one or more other pharmaceutically acceptable ingredients.

5 **[0043]** Accordingly, the invention provides a pharmaceutical composition comprising a compound of formula (I), or a salt thereof, together with one or more pharmaceutically acceptable ingredients.

[0044] Suitable pharmaceutically acceptable ingredients (e.g. carriers, diluents, excipients, etc.) can be found in standard pharmaceutical texts, for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000, pub. Lippincott, Williams & Wilkins; and Handbook of Pharmaceutical Excipients, 2nd edition, 1994.

10 **[0045]** Examples of suitable pharmaceutically acceptable ingredients include pharmaceutically acceptable carriers, diluents (e.g. oils), excipients, adjuvants, fillers, buffers, binders, disintegrants, preservatives, antioxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents.

15 **[0046]** In a preferred embodiment, the pharmaceutical composition comprises, one or more of: an excipient selected among a carrier, an oil, a disintegrant, a lubricant, a stabilizer, a flavouring agent, an antioxidant, a diluent and another pharmaceutically effective compound.

20 **[0047]** The pharmaceutical composition may be in any suitable form. Examples of suitable forms include liquids, solutions (e.g., aqueous, nonaqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), 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, pessaries, tinctures, gels, pastes, ointments, creams, lotions, oils, 25 foams, sprays, and aerosols.

[0048] In a preferred embodiment, the form of the pharmaceutical composition is selected from a tablet, a capsule, a granule, a powder for inhalation, a sprinkle, an oral solution and a suspension.

Medical Treatment

30 **[0049]** The inventors have found that the compound of formula (I) is biologically active. The worked examples demonstrate that the compound of formula (I) displays anticonvulsant activity in a mouse model. As such, the compound of formula (I) and its salts, as well as pharmaceutical compositions comprising the compound of formula (I) or its salts, will be useful in medical treatment.

35 **[0050]** Accordingly, the invention provides a compound of formula (I), or a salt thereof, for use in a method of treatment, for example for use in a method of treatment of the human or animal body by therapy (i.e. a method of therapy).

[0051] The invention also provides a compound of formula (I), or a salt thereof, for use as a medicament.

[0052] The invention also provides a method of treatment comprising administering to a subject in need of treatment a therapeutically effective amount of compound (I), or a salt thereof.

[0053] The invention also provides the use of compound (I), or a salt thereof, for the manufacture of a medicament.

Conditions Treated

[0054] The inventors have found that the compound of formula (I) displays anticonvulsant activity in a mouse model of generalised seizure. Accordingly, the compound of formula (I), its salts, as well as pharmaceutical compositions comprising the compound of formula (I) or its salts, will be useful in the treatment of certain conditions associated with seizure.

[0055] Similarly, the compound of formula (I), its salts, as well as pharmaceutical compositions comprising the compound of formula (I) or its salts, will be useful as medicaments for treating (and in the manufacture of medicaments for treating) certain conditions associated with seizure.

[0056] In a preferred embodiment, the condition associated with seizure is epilepsy.

[0057] In one embodiment, the condition associated with seizure is generalised seizure, such as generalised seizure associated with epilepsy.

[0058] In one embodiment, the condition associated with seizure is tonic-clonic seizures, such as tonic-clonic seizures associated with epilepsy.

The Subject/Patient

[0059] The method of treatment typically comprises administering a compound of formula (I), or a salt thereof, to a subject or patient.

[0060] 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, orang-utan, gibbon), or a human. Furthermore, the subject/patient may be any of its forms of development, for example, an infant or child.

[0061] In a preferred embodiment, the subject/patient is a human, more preferably an adult human.

[0062] The subject/patient may also be a non-human mammal used in laboratory research, such as a rodent. Rodents include rats, mice, guinea pigs and chinchillas.

Routes of Administration

[0063] The method of treatment may comprise administering a compound of formula (I), or a salt thereof, to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

- 5 [0064] The route of administration may be 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
10 example, by injection or infusion, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; or by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

15 Dosages

[0065] The method of treatment typically comprises administering a therapeutically effective amount of a compound of formula (I), or a salt thereof, to a subject.

- [0066] Appropriate dosages of the compound of formula (I), its salts, as well as pharmaceutical compositions comprising the compound of formula (I) or its salts, can vary
20 from patient to patient. Determining the optimal dosage will generally involve balancing 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 compound of formula (I), the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other active agents,
25 compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The dosage and route of administration will ultimately be at the discretion of the 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
30 side-effects.

[0067] Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating clinician.

Other Aspects and Embodiments

[0068] Each and every compatible combination of the embodiments described above is explicitly disclosed herein, as if each and every combination was individually and explicitly recited.

- 5 [0069] Various further aspects and embodiment of the present invention will be apparent to those skilled in the art in view of the present disclosure.

[0070] Where used, "and/or" is to be taken as a specific disclosure of each of the relevant components or features alone as well as a specific disclosure of the combination of the components or features. For example, "A and/or B" is to be taken as specific disclosure of
10 each of i) A, ii) B, and iii) A and B, just as if each were set out individually.

[0071] Unless context dictates otherwise, the descriptions and definitions of the features set out above are not limited to any particular aspect or embodiment of the invention and apply equally to all aspects and embodiments which are described.

DEFINITIONS

- 15 [0072] The following definitions are provided in order to aid understanding of the invention.

[0073] "Cannabinoids" are a group of compounds including the endocannabinoids, the phytocannabinoids and those which are neither endocannabinoids or phytocannabinoids, hereinafter "syntho-cannabinoids".

- 20 [0074] "Endocannabinoids" are endogenous cannabinoids, which are high affinity ligands of CB1 and CB2 receptors.

[0075] "Phytocannabinoids" are cannabinoids that originate in nature and can be found in the cannabis plant. The phytocannabinoids can be present in an extract including a botanical drug substance, isolated, or reproduced synthetically.

- 25 [0076] "Syntho-cannabinoids" are those compounds that are not found endogenously or in the cannabis plant. Examples include WIN 55212 and rimonabant.

[0077] An "isolated phytocannabinoid" is one which has been extracted from the cannabis plant and purified to such an extent that all the additional components such as secondary and minor cannabinoids and the non-cannabinoid fraction have been removed.

- 30 [0078] A "synthetic cannabinoid" is one which has been produced by chemical synthesis. This term includes modifying an isolated phytocannabinoid, by, for example, forming a pharmaceutically acceptable salt thereof.

[0079] A "substantially pure" cannabinoid is defined as a cannabinoid which is present at greater than 95% (w/w) pure. More preferably greater than 96% (w/w) through 97% (w/w) through 98% (w/w) to 99% (w/w) and greater.

- 35 [0080] Epilepsy is considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one

unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (A practical clinical definition of epilepsy by the International League Against Epilepsy (ILAE), 2014).

- 5 [0081] The term "generalized seizure" ("generalized onset seizures") refers to seizures conceptualized as originating at some point within the brain and rapidly engaging bilaterally distributed networks (Operational Classification of Seizure Types by the ILAE, 2017).

- [0082] A "tonic-clonic seizure" occurs in two phases, a tonic phase typically involving muscle stiffening and loss of consciousness, and a clonic phase typically involving
10 rhythmically jerking of the limbs.

- [0083] The term "pharmaceutically acceptable" 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,
15 commensurate with a reasonable benefit/risk ratio. Each ingredient (e.g. carrier, diluent, excipient, etc.) must also be "acceptable" in the sense of being compatible with the other ingredients of the composition.

- [0084] The term "therapeutically-effective amount" pertains to that amount of a compound, or a material, composition or dosage form comprising a compound, which is effective for
20 producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

WORKED EXAMPLES

[0085] Certain aspects and embodiments of the invention will not be illustrated by way of example and with reference to the figures described above.

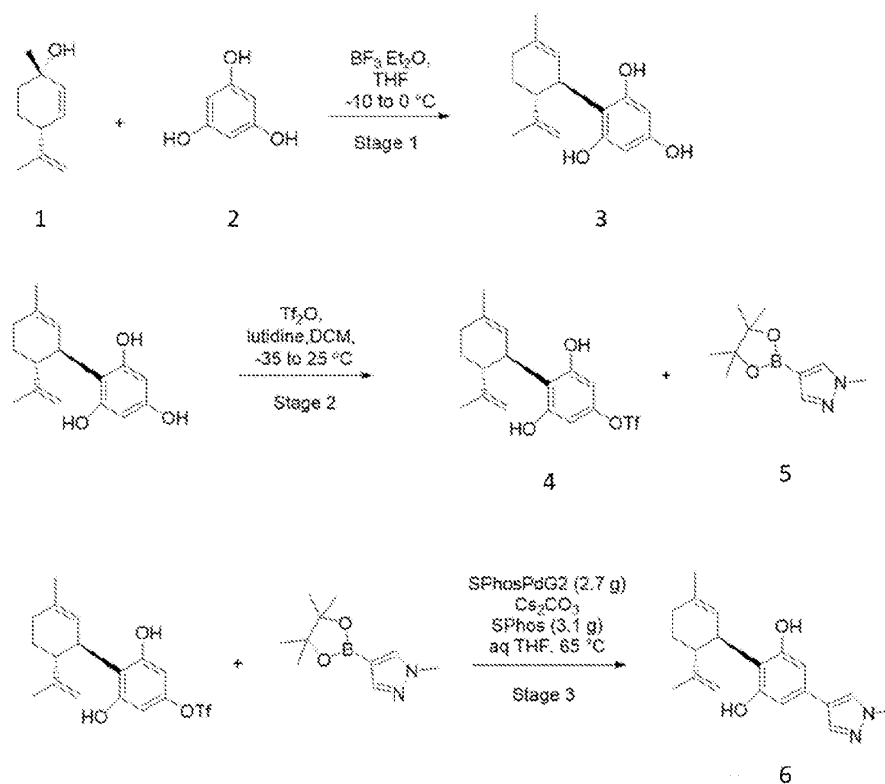
25 Example 1: Synthetic Production Method for CBD Derivative

[0086] This example describes a novel method of synthesis which was used to produce a novel analogue of CBD which demonstrated pharmacological activity. Scheme 1 below describes the three stages of the reaction which was used to produce the CBD derivative, formed via a number of intermediates.

- 30 [0087] The cannabidiol derivative of the invention is (1'R,2'R)-5'-methyl-4-(1-methyl-1H-pyrazol-4-yl)-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol, and will be referred to as the compound of formula (I) or compound 1 throughout.

- [0088] Analytical data of compound 1 is as follows: ¹H NMR (500 MHz, DMSO) δ 8.88 (s, 2H), 7.81 (s, 1H), 7.53 (s, 1H), 6.32 (s, 2H), 5.11 (m, 1H), 4.51 (m, 1H), 4.42 (dd, J = 3.0, 1.6
35 Hz, 1H), 3.86 (m, 1H), 3.80 (s, 3H), 3.05 (ddd, J = 13.2, 10.5, 2.8 Hz, 1H), 2.09 (m, 1H), 1.97 (m, 1H), 1.69 (m, 1H), 1.63 (m, 1H), 1.56 (s, 3H), 1.55 (s, 3H). MS (ES⁺): m / z 325.2 (M+1). HPLC purity 99.2%.

Scheme 1: Synthesis of CBD derivative



Compound	Name
1	Menthadienol
2	Benzene-1,3,5-triol (Phloroglucinol)
3	(1'R,2'R)-5'-Methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,4,6-triol
4	(1'R,2'R)-2,6-Dihydroxy-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate
5	1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole
6	(1'R,2'R)-5'-methyl-4-(1-methyl-1H-pyrazol-4-yl)-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol

5 **[0089]** (1S,4R)-1-Methyl-4-(prop-1-en-2-yl)cyclohex-2-en-1-ol (Menthadienol) was coupled with Phloroglucinol using $\text{BF}_3 \cdot \text{OEt}_2$ to give the trihydroxybenzene derivative in moderate yield.

[0090] Treatment with trifluoromethanesulphonic anhydride in a regioselective triflation gave the aryl triflate in a good yield.

[0091] The aryl triflate and pyrazole boronate were coupled in a Suzuki reaction, catalysed by palladium. The title compound was afforded, in a good yield, after IMS crystallisation.

Example 2: Evaluation of Cannabinoid Derivative for Anticonvulsant Activity using the Maximal Electroshock Seizure Threshold (MEST) Test in the Mouse

5 [0092] The efficacy of the cannabinoid derivative according to formula (I) was tested in a mouse model of generalised seizure, the maximal electroshock seizure threshold (MEST) test.

[0093] The maximal electroshock seizure threshold (MEST) test is widely utilized preclinically to evaluate pro- or anti-convulsant properties of test compounds (Loscher et al., 1991).

10 [0094] In the MEST test the ability of a drug to alter the seizure threshold current required to induce hind limb tonic extensor convulsions is measured according to an "up and down" method of shock titration (Kimball et al., 1957). An increase in seizure threshold is indicative of anti-convulsant effect. Antiepileptic drugs including the sodium channel blockers (e.g. lamotrigine) with clinically proven efficacy against generalised tonic-clonic seizures all exhibit anti-convulsant properties in this test in the mouse.

15 [0095] Conversely, a reduction in seizure threshold is indicative of a pro-convulsant effect as observed with known convulsant agents such as picrotoxin.

[0096] The ability of a test compound to alter the stimulus intensity, expressed as current (mA), required to induce the presence of tonic hind limb extensor convulsions, is assessed in the MEST. The outcome of the presence (+) or absence (0) of tonic hind limb extensor
20 convulsions observed from a current to produce tonic hind limb extension in 50% of animals in the treatment group (CC_{50}) determines the seizure threshold for the treatment group and the effects were then compared to the CC_{50} of the vehicle control group.

Methods

Study Details:

25 [0097] Naïve mice were acclimatised to the procedure room in their home cages for up to 7 days, with food and water available ad libitum.

[0098] All animals were weighed at the beginning of the study and randomly assigned to treatment groups based on a mean distribution of body weight across groups. All animals were dosed at 10 mL/kg via intraperitoneal (i.p) injection, with either vehicle, test compound
30 at 2, 20 or 200 mg/kg or diazepam at 2.5 mg/kg.

[0099] Animals were individually assessed for the production of a tonic hind limb extensor convulsion at 30 min post-dose for vehicle, 30 min post-dose for test compound and 30 min post-dose for diazepam, from a single electroshock.

35 [0100] The first animal within a treatment group was given a shock at the expected or estimated CC_{50} current. For subsequent animals, the current was lowered or raised depending on the convulsions outcome from the preceding animal, in intervals of 5 mA.

[0101] Data generated from each treatment group were used to calculate the $CC_{50} \pm SEM$ values for the treatment group.

Test Compounds:

5 [0102] Vehicle: (5% ethanol, 10% solutol, 85% Saline) was prepared as follows: 1 mL of ethanol, 2 mL of solutol were warmed to 60°C, in 17 mL of saline (1:2:17).

[0103] Positive control: diazepam was used at 2.5mg/kg.

[0104] The test compound, described herein as compound 1, is as shown as formula (I). Test compound was administered at 2, 20 and 200mg/kg (i.p.) in a 1:2:17 ethanol:solutol:0.9% saline formulation.

10 *Sample Collection:*

[0105] Each animal was humanely killed immediately after production of a convulsion by destruction of the brain from striking the cranium, followed by the confirmation of permanent cessation of the circulation from decapitation under The Humane Killing of Animals under Schedule 1 to the Animals (Scientific Procedures) Act 1986. Terminal blood and brain
15 collection were performed following decapitation.

[0106] Blood was collected in Lithium-heparin tubes and centrifuged at 4°C for 10 minutes at 1500 x g. The resulting plasma was removed (>100 µL) and split into 2 aliquots of 0.5 mL Eppendorf tubes containing 100 µL of ascorbic acid (100 mg/mL) for stabilisation. Brains were removed, washed in saline and halved. Each half was placed into separate 2 mL screw
20 cap cryovials, weighed and frozen on cardice.

Statistical analysis

[0107] The data for each treatment group were recorded as the number of +’s and 0’s at each current level employed and this information is then used to calculate the CC_{50} value (current required for 50% of the animals to show seizure behaviour) $\pm$ standard error.

25 [0108] Test compound effects were also calculated as percentage change in CC_{50} from the vehicle control group.

[0109] Significant difference between drug-treated animals and controls were assessed according to Litchfield and Wilcoxon (1949).

Results

30 [0110] Figure 1 and Table 1 describe the data produced in this experiment.

[0111] In the vehicle group, the CC_{50} value was calculated to be 24.3mA.

[0112] In the diazepam (2.5 mg/kg) treated group, administered i.p. 30 minutes before the test, the CC_{50} value was 78.5mA. This result was statistically significant ($p < 0.001$) compared

to the vehicle control. One animal in the diazepam group, was not dosed due to welfare issues from fighting.

- [0113] In the test compound treatment group, administered i.p. 30 minutes before the test, Compound 1 produced a statistically significant CC_{50} value compared to vehicle at all three doses of the compound.

[0114] Such data are indicative that this compound will be of therapeutic benefit.

Table 1: Evaluation of effect of compound 1 in the MEST test

Treatment	Dose (mg/kg)	Test time post dose (min)	N	$CC_{50} \pm SEM$	Significance	% change from vehicle
Vehicle	-	30	12	24.3 ± 0.4	-	-
Diazepam	2.5	30	11	78.5 ± 1.0	$P < 0.001$	223%
Compound 1	2	30	12	30.8 ± 1.0	$P < 0.001$	27%
Compound 1	20	30	12	52.5 ± 1.3	$P < 0.001$	116%
Compound 1	200	30	12	197.5 ± 20.4	$P < 0.001$	712%

Conclusions

- [0115] These data demonstrate a therapeutic effect for the compound of formula (I).
- 10 [0116] These data are significant as they provide heretofore unknown evidence that this novel cannabinoid derivative may be of therapeutic value.
- [0117] Clearly the compound produced a dose-related increase in MEST, suggesting that this compound exhibits anticonvulsive properties. Significant effects were observed at 2, 20 and 200 mg/kg, when compared to vehicle.
- 15 **EXAMPLE 3: EVALUATION OF PHARMACOKINETIC PROPERTIES OF CANNABINOID DERIVATIVE**
- [0118] The plasma pharmacokinetics of compound 1 was assessed following oral dose administration to male Wistar Han Rats.

Methods

Study Details:

- [0119] The Wistar Han Rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies. Animals were socially housed (up to 3 animals of the same group) in polycarbonate cages containing appropriate bedding equipped with water bottles and may be provided with items such as devices for hiding in, paper and/or objects for chewing, unless contraindicated by study procedures. Pelleted rodent diet were provided ad libitum throughout the study, except during designated procedures.
- 10 [0120] The 9 male animals were 8 to 10 weeks old at initiation of dosing.

Test compound:

- [0121] Vehicle: 1% Ethanol /12% Kolliphor HS-15/ 87% Saline (w/w/v).
- [0122] Dose formulation was prepared as follows: test item was dissolved in ethanol. Kolliphor HS-15 and saline was heated separately to 60°C, and the required amount of heated Kolliphor HS-15 added to the test item / ethanol solution. The mixture was stirred at 60°C until homogenous. Hot saline was added to the mixture to meet dose level requirements, and stirred at 60°C until a homogenous solution. Prior to release, the formulations were allowed to cool to ≤40°C. Subsequently, the formulations were stored at room temperature until dosing.

20 Treatment:

- [0123] Groups 1, 2 and 3: The test item was administered to the appropriate animals by oral gavage. The dose was given using a plastic feeding tube.

Table 2: Study Design

Group No.	Dose level (mg/kg)	Dose volume (mL/kg)	No. of animals	Animal No.
1	15	10	3	1-3
2	45	10	3	4-6
3	150	10	3	7-9

Sample Collection:

- 25 [0124] PK Sample Collection: From animals in Group 1 to 3 blood was collected according to the PK sample collection table (outlined in Table 3). Approximately 0.2 mL blood samples

was taken from the jugular vein and collected into tubes containing K2 EDTA as anti-coagulant and stored on ice.

- [0125] Sample Processing and Storage: Whole blood was processed to plasma by centrifugation (3000g for 10 minutes at 5°C) within 1 hour of collection. Plasma samples were transferred into labelled polypropylene tubes and stored at < -75°C until shipment.

Table 3: Bioanalytical Sample Collection

Group No.	PK Sample Collection Time Points (post dose)						
	15 min	30 min	1h	2h	4h	8h	24h
1	1-3	1-3	1-3	1-3	1-3	1-3	1-3
2	4-6	4-6	4-6	4-6	4-6	4-6	4-6
3	7-9	7-9	7-9	7-9	7-9	7-9	7-9

Results

- [0126] Figures 2 to 3 and Table 4 provide the data produced in this experiment. Bioavailability was found to be high across concentrations with T_{max} at 1 hour for 15 and 45 mg/kg dose groups. Exposure and C_{max} increase in a linear fashion with dose in rat (Fig 3).

Table 4: Rat Pharmacokinetics of compound 1

PK Parameter	15 mg/kg	45 mg/kg	150 mg/kg
Measured Dose (mg/kg)	15	101	204
C_{max} (ng/mL)	1126	4006	6730
T_{max} (h)	1.00	1.00	8.0
$t_{1/2}$ (h)	3.3	3.6	4.3
AUC_{last} (ng/mL.hr)	4247	47854	101383
AUC_{inf} (ng/mL.hr)	5326	48346	104914
Bioavailability (%)	69.6	96.4	107

Conclusions

- [0127] The data provided in this Example allowed determination of the intrinsic pharmacokinetics of the test compound (compound 1) to enable its proper characterisation. Favourable pharmacokinetic data demonstrate suitability of this novel compound as a treatment option for conditions associated with seizure.

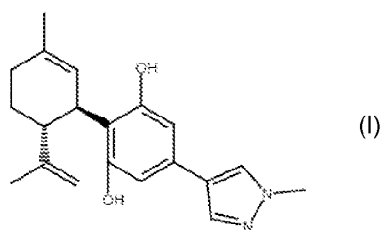
REFERENCES

[0128] A number of publications are cited above 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. The contents of each of these references is
5 incorporated herein.

1. Gong et al., "Synthesis of CBD and Its Derivatives Bearing Various C4'-Side Chains with a Late-Stage Diversification Method", *J. Org. Chem*, **2020**, Vol. 85, pp. 2704–2715.

CLAIMS

1. A compound of formula (I), or a salt thereof,



2. A pharmaceutical composition comprising the compound of claim 1 and one or more additional ingredients selected from carriers, diluents (e.g. oils), excipients, adjuvants, fillers, buffers, binders, disintegrants, preservatives, antioxidants, lubricants, stabilisers, solubilisers, surfactants, masking agents, colouring agents, flavouring agents, and sweetening agents.
3. The pharmaceutical composition of claim 2 in a form selected from a liquid, a solution, a suspension, an emulsion, a syrup, an electuary, a mouthwash, a drop, a tablet, a granule, a powder, a lozenge, a pastille, a capsule, a cachet, a pill, an ampoule, a bolus, a suppository, a pessary, a tincture, a gel, a paste, an ointment, a cream, a lotion, an oil, a foam, a spray, and an aerosol.
4. The compound of claim 1, or the pharmaceutical composition of claim 2 or claim 3, for use in a method of treatment.
5. The compound of claim 1, or the pharmaceutical composition of claim 2 or claim 3, for use in the treatment of epilepsy.
6. The compound of claim 1, or the pharmaceutical composition of claim 2 or claim 3, for use in the treatment of generalised seizure.
7. The compound of claim 1, or the pharmaceutical composition of claim 2 or claim 3, for use in the treatment of tonic-clonic seizure.
8. The compound of claim 1, or the pharmaceutical composition of claim 2 or claim 3, for use as a medicament.
9. The compound of claim 1, or the pharmaceutical composition of claim 2 or claim 3, for use as a medicament for treating epilepsy.

10. The compound of claim 1, or the pharmaceutical composition of claim 2 or claim 3, for use as a medicament for treating generalised seizure.
11. The compound of claim 1, or the pharmaceutical composition of claim 2 or claim 3, for use as a medicament for treating tonic-clonic seizure.
12. A method of treatment comprising administering to a subject in need of treatment a therapeutically effective amount of the compound of claim 1 or the pharmaceutical composition of claim 2 or claim 3.