(19) DANMARK

(10) **DK/EP 3999042 T3**

Patent- og Varemærkestyrelsen

(12) Oversættelse af europæisk patentskrift

(51) Int.Cl.: ***A 61 K 31/05 (2006.01)*** ***A 61 K 31/352 (2006.01)*** ***A 61 K 31/47 (2006.01)***

(45) Oversættelsen bekendtgjort den: **2023-11-06**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2023-10-11**

(86) Europæisk ansøgning nr.: **20751200.5**

(86) Europæisk indleveringsdag: **2020-07-17**

(87) Den europæiske ansøgnings publiceringsdag: **2022-05-25**

(86) International ansøgning nr.: **GB2020051723**

(87) Internationalt publikationsnr.: **WO2021014132**

(30) Prioritet: **2019-07-19 GB 201910389**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **GW Research Limited, Sovereign House Vision Park , Chivers Way , Histon, Cambridge, Cambridgeshire CB24 9BZ, Storbritannien**

(72) Opfinder: **SILCOCK, Alan, GW Pharma Limited, Sovereign House Vision Park, Chivers Way, Histon, Cambridge Cambridgeshire CB24 9BZ, Storbritannien**
WHALLEY, Benjamin, GW Pharma Limited, Sovereign House Vision Park, Chivers Way, Histon, Cambridge Cambridgeshire CB24 9BZ, Storbritannien
GRAY, Royston, GW Pharma Limited, Sovereign House Vision Park, Chivers Way, Histon, Cambridge Cambridgeshire CB24 9BZ, Storbritannien
STRAKER, Hannah, GW Pharma Limited, Sovereign House Vision Park, Chivers Way, Histon, Cambridge Cambridgeshire CB24 9BZ, Storbritannien
TSE, Karen, GW Pharma Limited, Sovereign House Vision Park, Chivers Way, Histon, Cambridge Cambridgeshire CB24 9BZ, Storbritannien
COBB, Alexander, Department of Chemistry King's College London, 7 Trinity Street, London SE1 1DB, Storbritannien
BRYANT, Laura, 9 Leighcroft Gardens, Leigh-on-sea Essex SS9 4NP, Storbritannien

(74) Fuldmægtig i Danmark: **NORDIC PATENT SERVICE A/S, Bredgade 30, 1260 København K, Danmark**

(54) Benævnelse: **CANNABINOIDDERIVATER SOM FARMACEUTISK AKTIVE FORBINDELSER OG FREMGANGSMÅDER TIL FREMSTILLING DERAF**

(56) Fremdragne publikationer:
EP-A1- 3 061 450
WO-A1-2014/062965
WO-A2-01/95899

DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to a group of cannabinoid derivatives as pharmaceutically active compounds and methods of preparation thereof.

[0002] The cannabinoid derivatives of the invention are analogues 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 derivatives of the invention.

BACKGROUND TO THE INVENTION

[0003] 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 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*).

[0004] Cannabis plants comprise a highly complex mixture of compounds. At least 568 unique molecules have been identified. Among these compounds are cannabinoids, terpenoids, sugars, fatty acids, flavonoids, other hydrocarbons, nitrogenous compounds, and amino acids.

[0005] 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 cannabinoid acids Δ9-tetrahydrocannabinolic acid (Δ9-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.

[0006] There are currently four cannabinoid-based pharmaceutical approved products on the market. These are: dronabinol (Marinol®) which is a synthetic tetrahydrocannabinol (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.

[0007] 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.

[0008] 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.

[0009] 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.

[0010] 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.

[0011] The synthetic production of the metabolite of CBD, 7-hydroxy-cannabidiol, (7-OH CBD) is disclosed in WO 01/95899. The compound was tested in a model of inflammation and found to be effective. The application goes on to suggest that the compound may be of use as an analgesic, anti-anxiety, anti-convulsant, neuroprotective, anti-psychotic and antiinflammatory based on the mechanisms the compound displays in the model of inflammation.

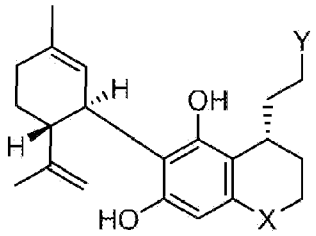
[0012] WO 2014/062965 A1 discloses cannabinoid derivatives and the uses of the compounds in the fields of treating epilepsy, pain, inflammation and cancer.

[0013] The present invention relates to novel cannabinoid compounds which are biologically active and hence useful in the treatment of diseases. Such novel compounds may be administered by a wide variety of routes including but not limited to oral, transdermal, buccal, nasal, pulmonary, rectal or ocular. Such compounds may be used for the treatment or prevention of a medical condition such as epilepsy, pain, inflammation and cancer.

BRIEF SUMMARY OF THE DISCLOSURE

[0014] In accordance with a first aspect of the present invention there is provided a compound of general Formula I or a salt thereof,

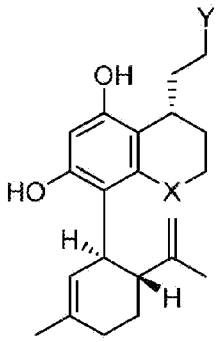
Formula I



where X is either CH_2; O; NBoc; NFMoc; NZ; NTs; NAc; NC(O)iPr; NBz or NH and Y is either H or OH.

[0015] In accordance with a second aspect of the present invention there is provided a compound of general Formula II or a salt thereof,

Formula II



where X is either CH_2; O; NBoc; NFMoc; NZ; NTs; NAc; NC(O)iPr; NBz or NH and Y is either H or OH.

[0016] In accordance with a third aspect of the present invention there is provided a pharmaceutical composition comprising the compound of general Formula I or Formula II.

[0017] Preferably the pharmaceutical composition is selected from a tablet, a capsule, a granule, an oral solution, a powder for inhalation, a sprinkle, an oral solution and a suspension.

[0018] Preferably 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.

[0019] In accordance with a fourth aspect of the present invention there is provided a compound of general Formula I or Formula II for use as a medicament.

[0020] In accordance with a fifth aspect of the present invention there is provided a compound of general Formula I or Formula II for use in the treatment of epilepsy.

[0021] In accordance with a seventh aspect of the present invention there is provided a process for the production of a compound of general Formula I or Formula II comprising reacting a resorcinol unit of Structure 1a-j via a Friedel-Crafts 1,4-addition to produce compounds of Structures 2a to 2j or 3a to 3j followed by subsequent steps to produce the compounds of general Formula I or Formula II via intermediates.

[0022] In accordance with an eighth aspect of the present invention there is provided an intermediate formed in the process of the production of a compound of general Formula I or Formula II.

DEFINITIONS

[0023] "Cannabinoids" are a group of compounds including the endocannabinoids, the phytocannabinoids and those which are neither endocannabinoids or phytocannabinoids, hereinafter "syntho-cannabinoids".

[0024] "Endocannabinoids" are endogenous cannabinoids, which are high affinity ligands of CB1 and CB2 receptors.

[0025] "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.

[0026] "Syntho-cannabinoids" are those compounds that are not found endogenously or in the cannabis plant. Examples include WIN 55212 and rimonabant.

[0027] 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.

[0028] 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.

[0029] 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) thorough 98% (w/w) to 99% % (w/w) and greater.

DETAILED DESCRIPTION OF THE INVENTION

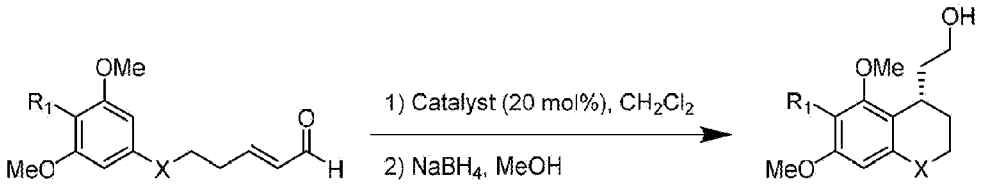
[0030] The following describes the production of the novel cannabinoid derivatives as claimed

in the present invention. The structure and absolute configuration of the compounds produced were determined by X-ray crystallographic analysis, using a molybdenum X-Ray source.

EXAMPLE 1: METHOD OF MANUFACTURE OF NORMAL CBD DERIVATIVES

[0031] This example describes a novel method of synthesis which was used to produce novel analogues of normal CBD which demonstrated pharmacological activity. Scheme 1 below describes the initial reaction which was used to produce the primary intermediate and Scheme 2 describes the production of the normal CBD derivatives which were formed via a number of intermediates.

Scheme 1: Friedel-Crafts 1,4-addition reaction



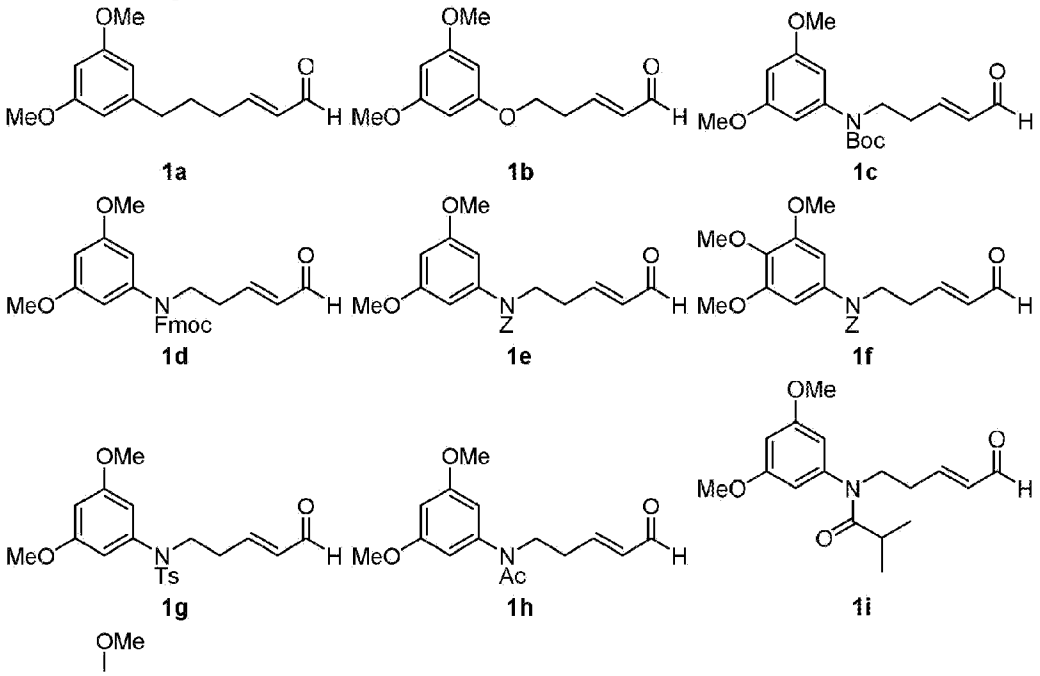
1a-j **2a-j**

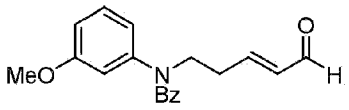
Where R_1 = H or OMe and X = CH_2; O; NBoc; NFMoc; NZ; NTs; NAc; NC(O)iPr; NBz or NH

[0032] The resorcinol unit, in Structures 1a to 1j (shown below), underwent a Friedel-Crafts 1,4-addition reaction as shown in Scheme 1 to produce compounds of Structures 2a to 2j described below.

[0033] Various catalysts were tested. Silylated Jørgensen-Hayashi type gave poor yields but excellent selectivity. MacMillan-type catalysts gave better yields but poorer enantioselectivities.

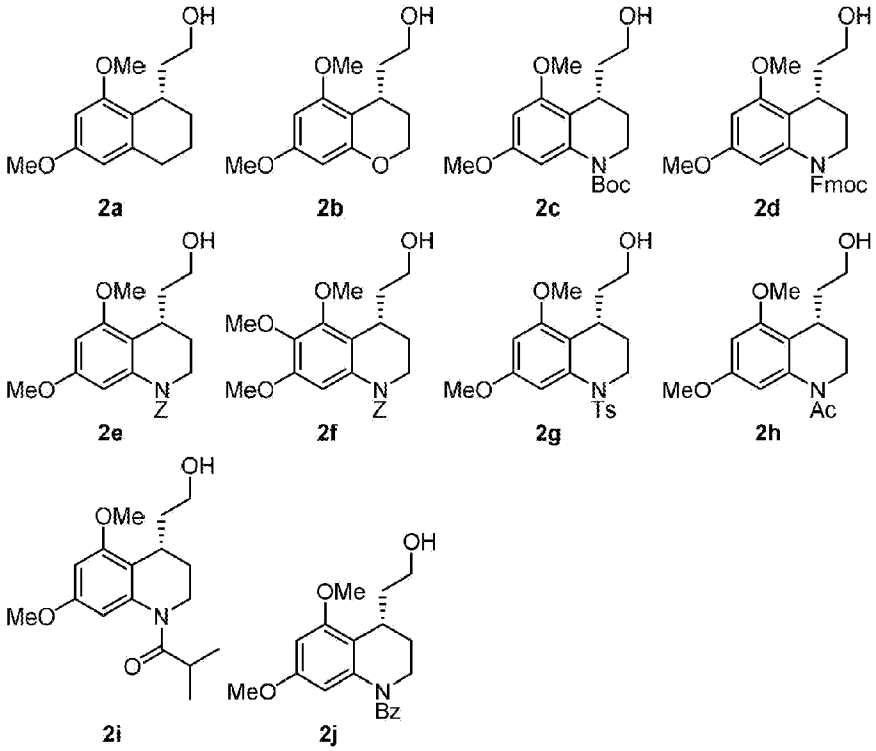
Structures 1a-j





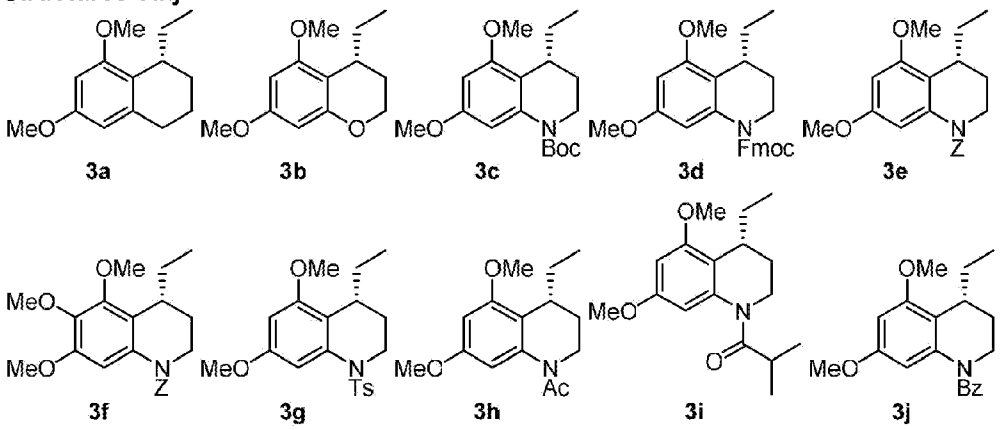
1j

Structures 2a-j



2a 2b 2c 2d 2e 2f 2g 2h 2i 2j

Structures 3a-j



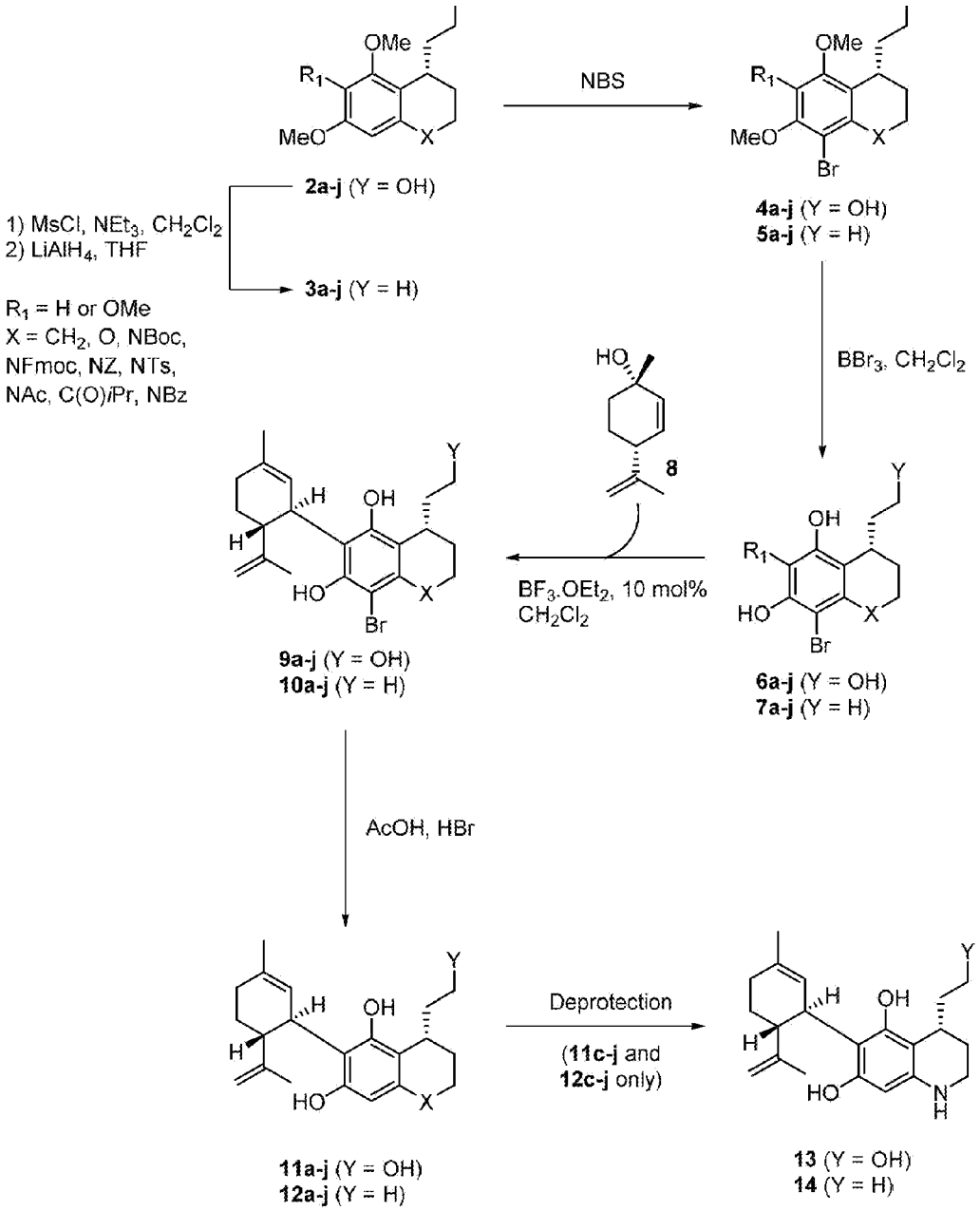
3a 3b 3c 3d 3e 3f 3g 3h 3i 3j

[0034] The compound of Structures 2a to 2j or 3a to 3j (shown above) were then reacted as shown in Scheme 2 below to derive two different normal CBD derivatives 11a to 11j or 12a to 12j.

[0035] Deprotection of the derivatives 11 c-j and 12 c-j further produced compounds 13 and 14.

Scheme 2: Synthesis of normal CBD analogues

Y Y

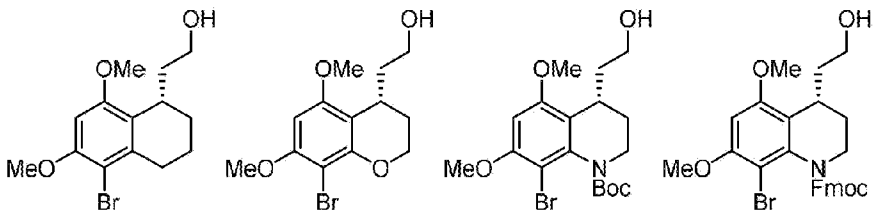


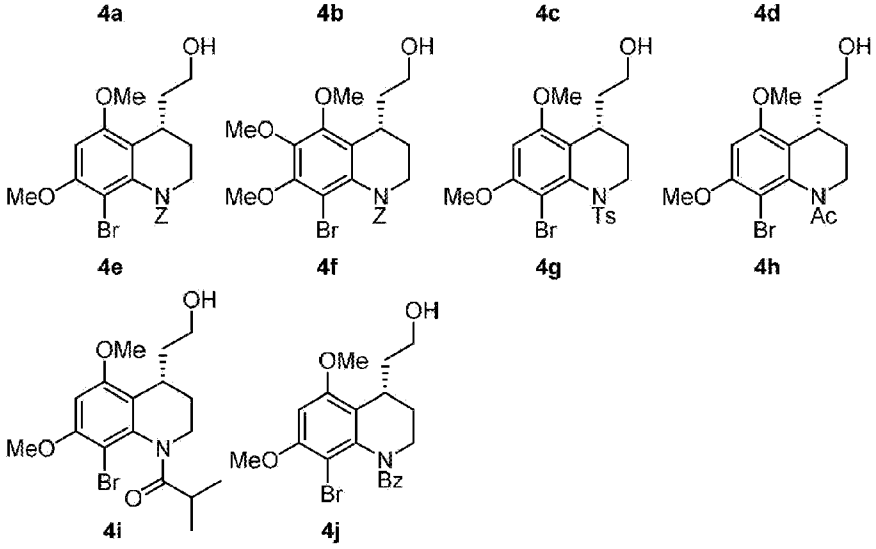
NBS: *N*-bromosuccinimide

Synthesis of intermediates 4a to 4j or 5a to 5j:

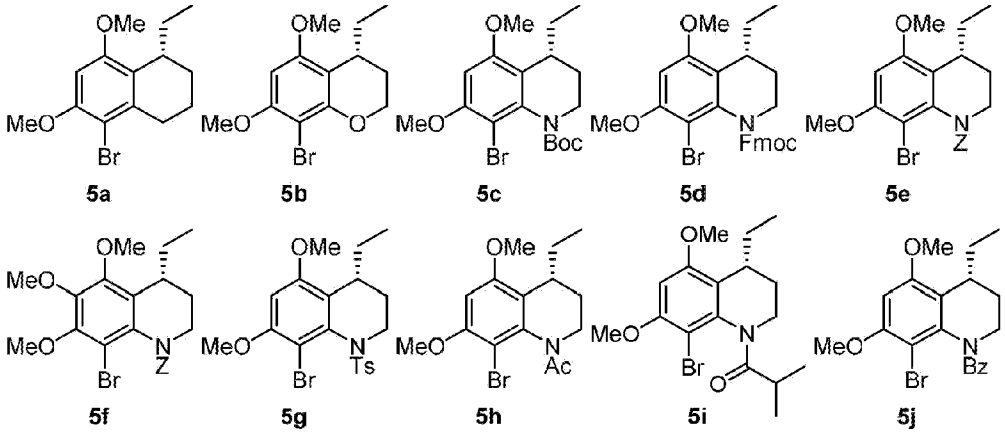
[0036] Intermediates 2a-2j or 3a-3j were brominated with N-bromosuccinimide (NBS) to create arylbromide system compounds 4a-4j or 5a-5j shown below.

Structures 4a-4j





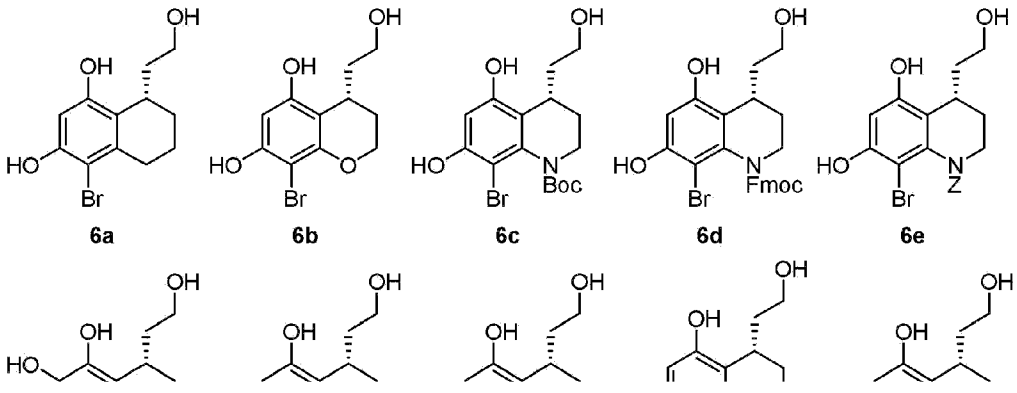
Structures 5a-5j

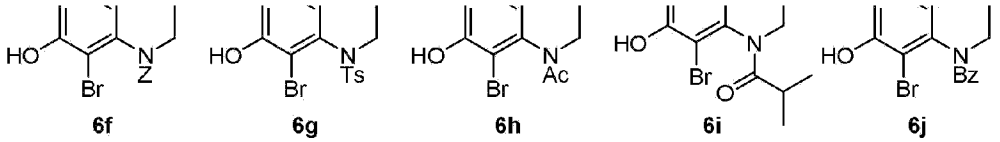


Synthesis of intermediates 6a to 6j or 7a to 7j

[0037] Intermediates 4a-4j or 5a-5j were O-demethylated with boron tribromide in the presence of dichloromethane which resulted in the deprotected chiral resorcinol compounds as described in 6a to 6j or 7a to 7j depicted below.

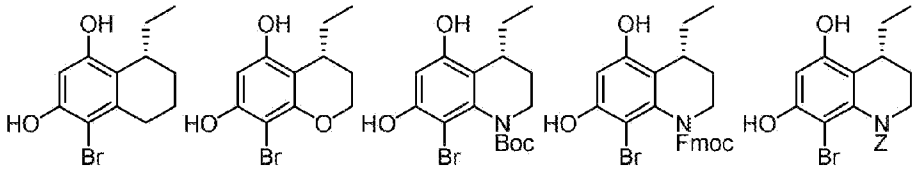
Structures 6a-6j



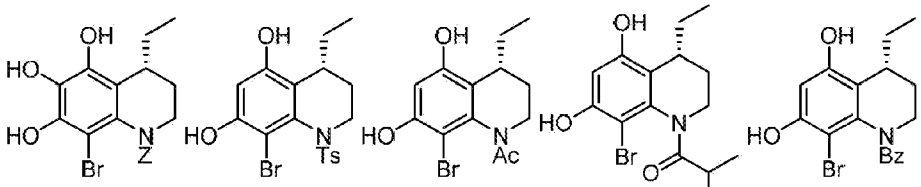


6f **6g** **6h** **6i** **6j**

Structures 7a-7j



7a **7b** **7c** **7d** **7e**

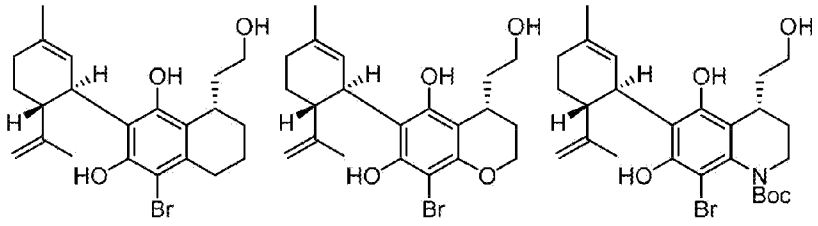


7f **7g** **7h** **7i** **7j**

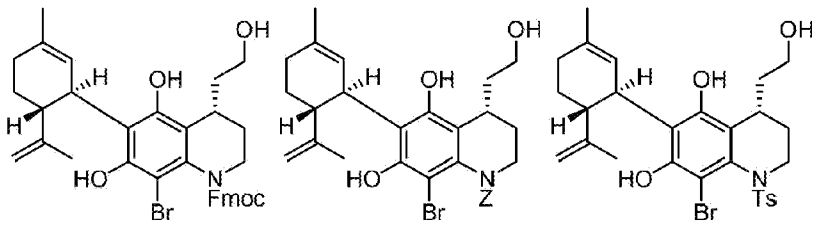
Synthesis of intermediates 9a to 9j (except 9f) or 10a to 10j (except 10f)

[0038] Coupling of the brominated intermediates of 6a-6j or 7a-7j with menthadienol (shown as structure 8 in Scheme 2) in the presence of boron trifluoride diethyl etherate produced the intermediates 9a to 9j (except 9f which is not possible) or 10a to 10j (except 10f which is not possible). These structures are depicted below.

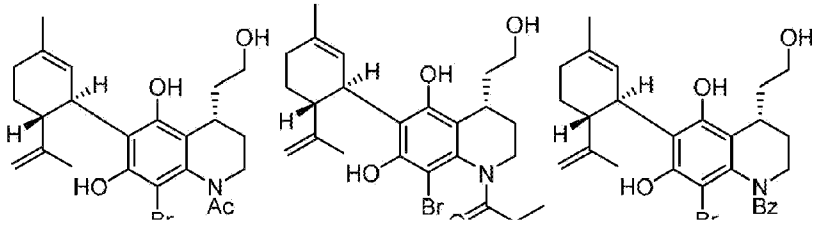
Structures 9a-j (note 9f is not possible)

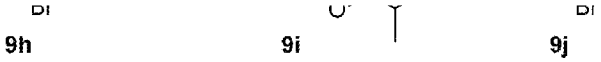


9a **9b** **9c**



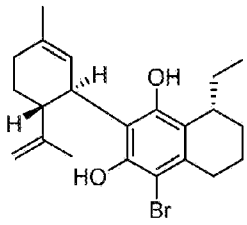
9d **9e** **9g**



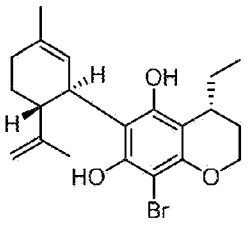


9h 9i 9j

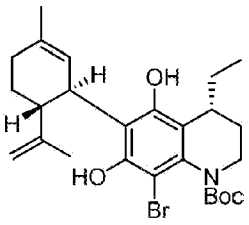
Structures 10a-j (note 10f is not possible)



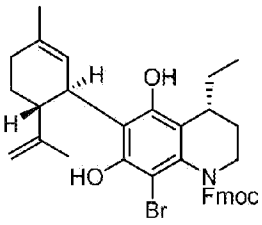
10a



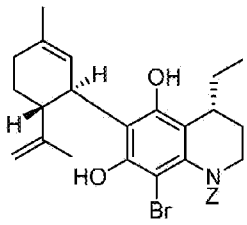
10b



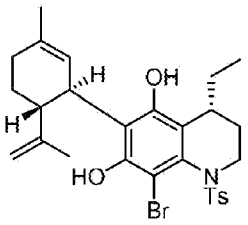
10c



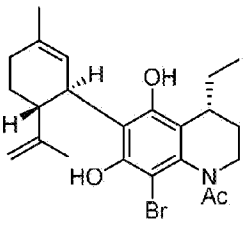
10d



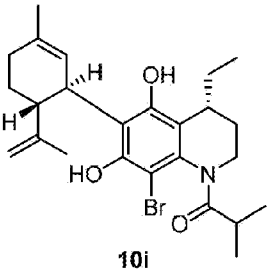
10e



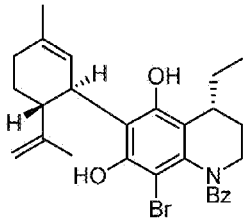
10g



10h



10i

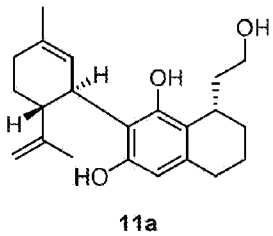


10j

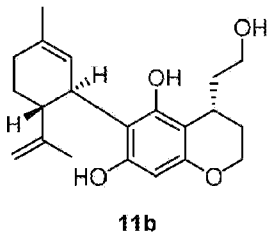
Synthesis of normal CBD derivatives 11a to 11j (except 11f) or 12a to 12j (except 12f)

[0039] 9a to 9j (except 9f) or 10a to 10j (except 10f) were debrominated with acetic acid and hydrogen bromide to produce the normal CBD derivatives 11a to 11j (except 11f) or 12a to 12j (except 12f) shown below.

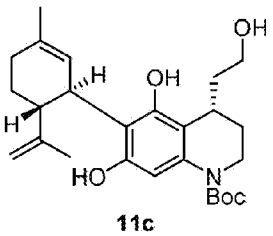
Structures 11a-j (note 11f is not possible)



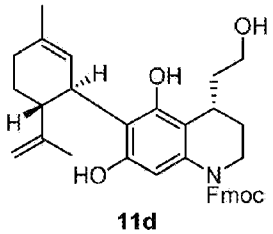
11a



11b



11c



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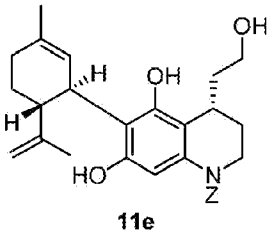

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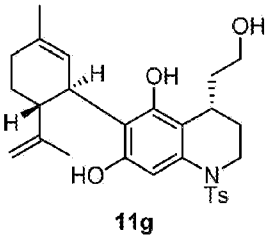
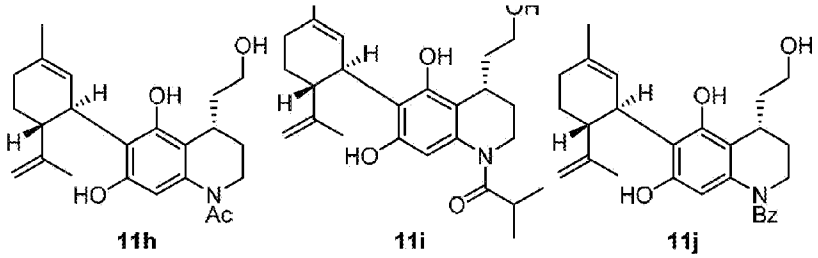
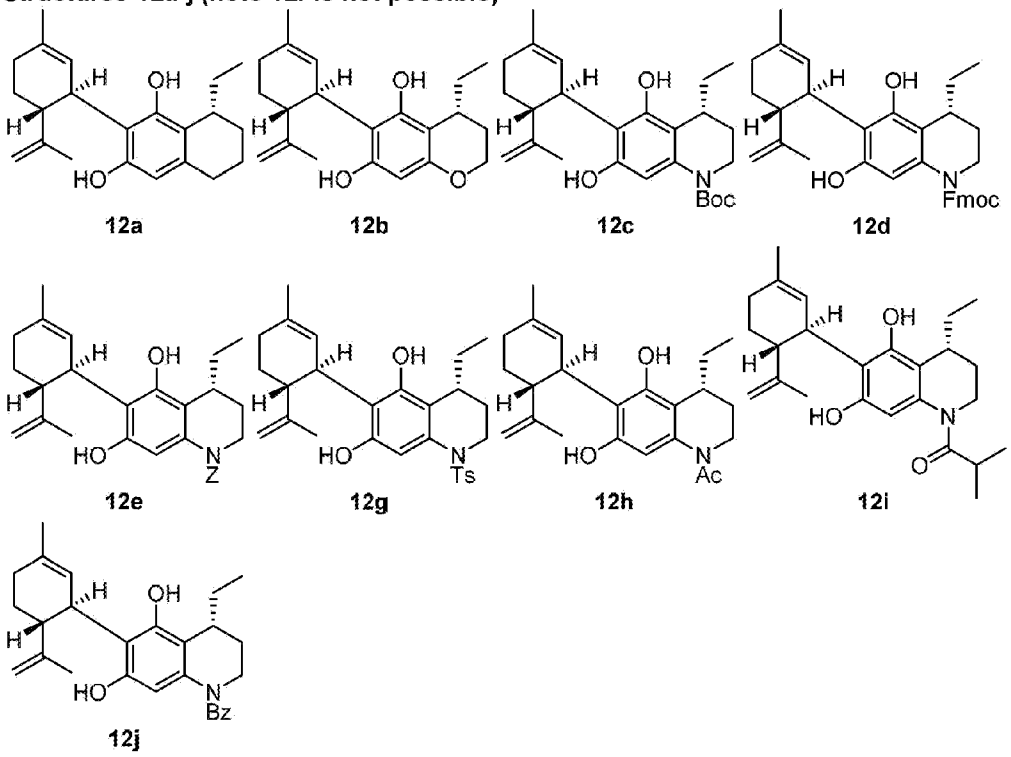


11g

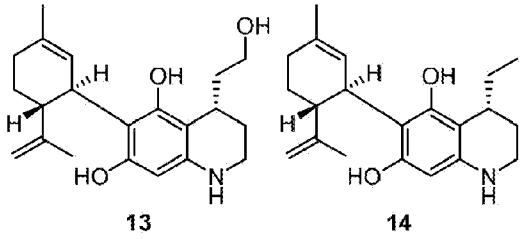


Structures 12a-j (note 12f is not possible)



[0040] Furthermore, the N-protected moieties compounds 11c-11j (except 11f) and 12c to 12j (except 12f) can be deprotected to give the two NH derivatives, compounds 13 and 14, shown below.

Structures 13 and 14

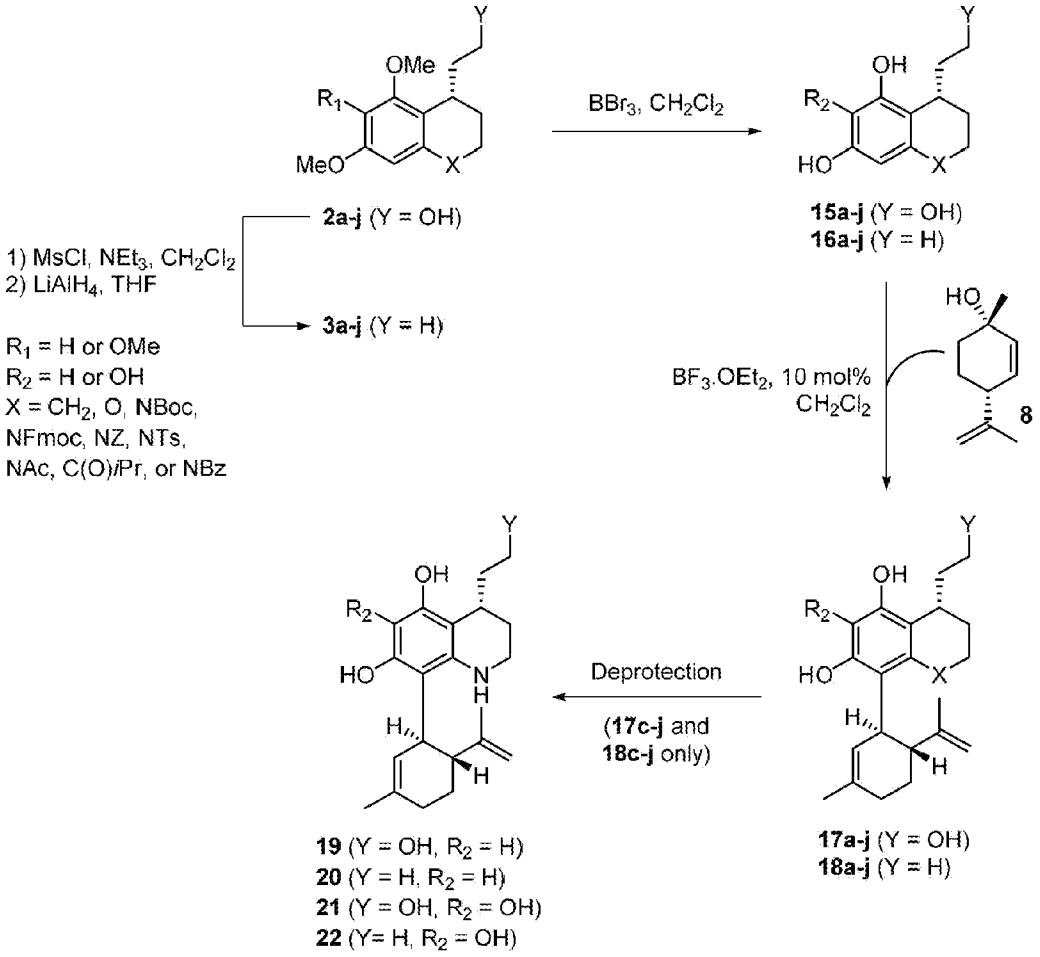


EXAMPLE 2: METHOD OF MANUFACTURE OF ABNORMAL CBD DERIVATIVES

[0041] This example describes a novel method of synthesis which was used to produce novel analogues of abnormal CBD which demonstrated pharmacological activity. Scheme 1 depicted

in Example 1 describes the initial reaction which was used to produce the primary intermediates 2a to 2j and 3a to 3j and Scheme 3 describes the production of the abnormal CBD derivatives which were formed via a number of intermediates.

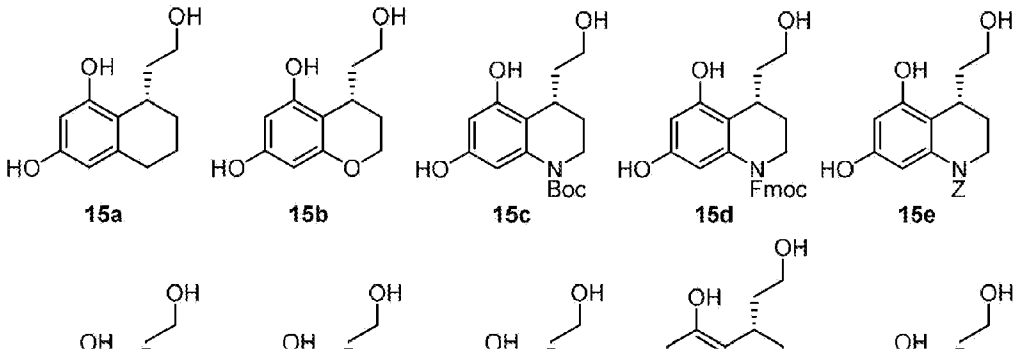
Scheme 3: Synthesis of abnormal CBD analogues



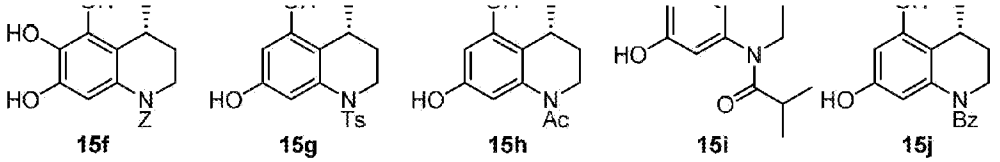
Synthesis of intermediates 15a to 15j or 16a to 16j

[0042] Intermediates 2a to 2j or 3a to 3j were O-demethylated with boron tribromide in the presence of dichloromethane which resulted in the deprotected chiral resorcinol compounds as described in 15a to 15j or 16a to 16j below.

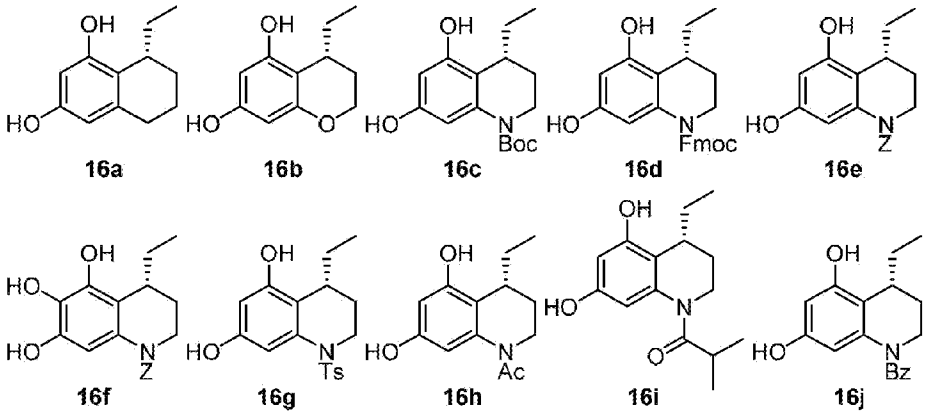
Structures 15a-j



15a **15b** **15c** **15d** **15e**



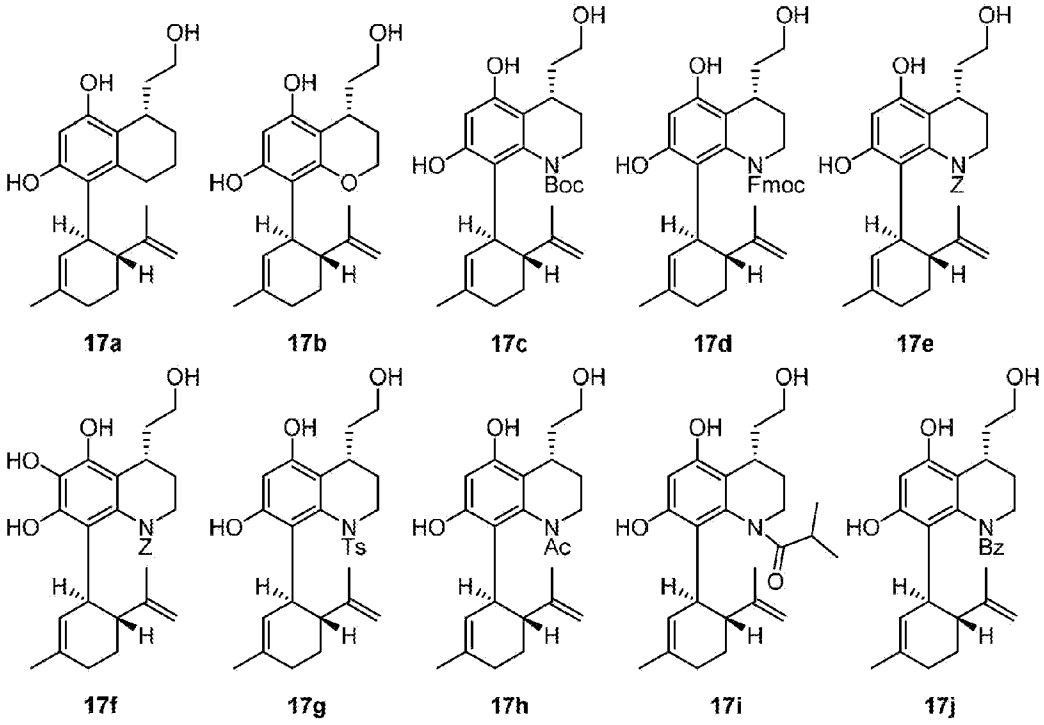
Structures 16a-j



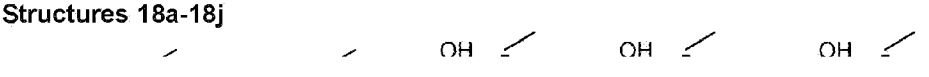
Synthesis of abnormal CBD derivatives 17a to 17j or 18a to 18j

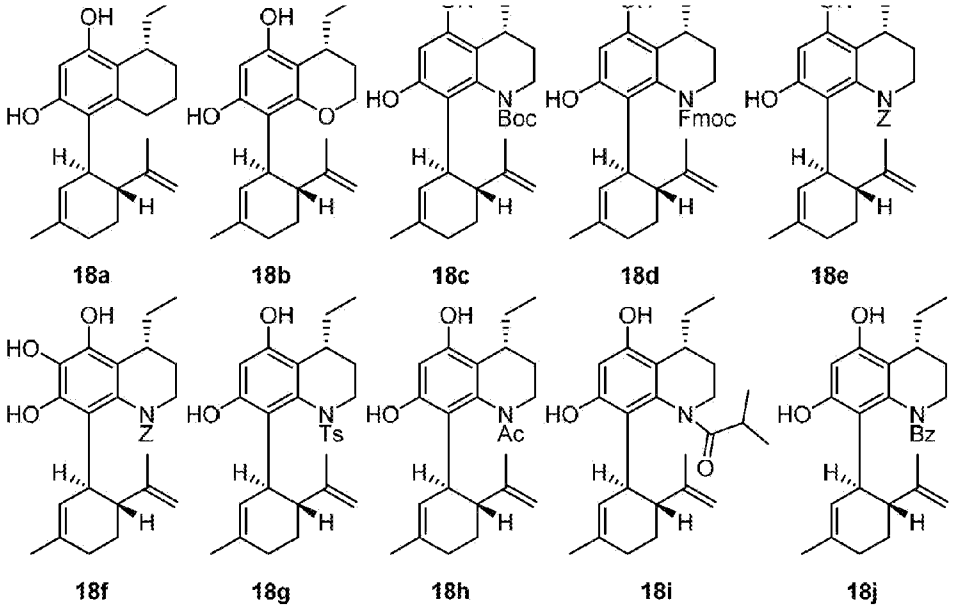
[0043] Coupling of the intermediates of 15a-15j or 16a-16j with menthadienol (shown as structure 8 in Scheme 3) in the presence of boron trifluoride diethyl etherate produced the abnormal CBD derivatives 17a to 17j or 18a to 18j depicted below.

Structures 17a-17j



Structures 18a-18j

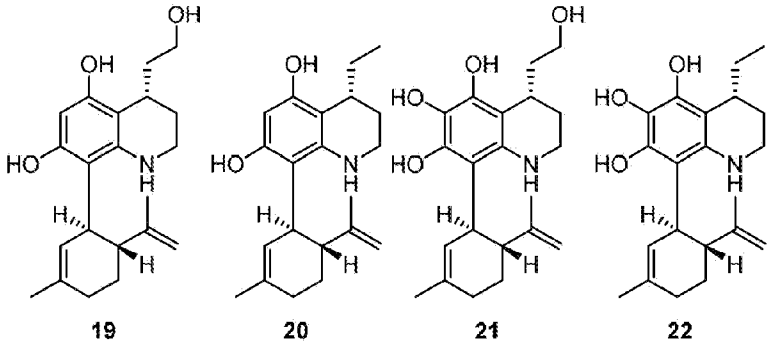




Synthesis of compounds19 to 22

[0044] Deprotection of 17c to 17j or 18c to 18j produced the compounds 19 to 22 described below.

Structures 19, 20, 21, 22



CONCLUSION:

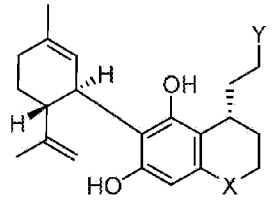
[0045] The application of the novel routes of synthesis to produce novel cannabidiol analogues and their intermediates is of benefit.

[0046] Compounds of the general formulas I and II are as detailed below and are equivalent to the compounds of structures 11a to 11j (except 11f), 12a to 12j (except 11f), 17a to 17j and 17a to 17j. Such compounds may provide improved or new therapeutic treatment options.

[0047] Deprotection of particular compounds has been found to produce additional novel

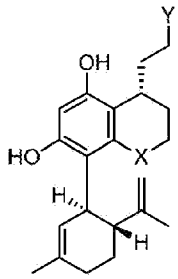
molecules which provide additional improved or new therapeutic benefit. Such compounds include 13, 14, 19, 20, 21 and 22.

Formula I



where X is either CH_2; O; NBoc; NFMoc; NZ; NTs; NAc; NC(O)iPr; NBz or NH and Y is either H or OH.

Formula II



where X is either CH_2; O; NBoc; NFMoc; NZ; NTs; NAc; NC(O)iPr; NBz or NH and Y is either H or OH.

EXAMPLE 3: EVALUATION OF CANNABINOID DERIVATIVES FOR ANTICONVULSANT ACTIVITY USING THE MAXIMAL ELECTROSHOCK SEIZURE THRESHOLD (MEST) TEST IN THE MOUSE

[0048] The efficacy of exemplary cannabinoid derivatives according to Formula I and Formula II were tested in a mouse model of generalised seizure, the maximal electroshock seizure threshold (MEST) test.

[0049] 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).

[0050] 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.

[0051] Conversely, a reduction in seizure threshold is indicative of a pro-convulsant effect as observed with known convulsant agents such as picrotoxin.

[0052] 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 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:

[0053] Naive mice were acclimatised to the procedure room in their home cages for up to 7 days, with food and water available ad libitum.

[0054] 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 at 200 mg/kg, or diazepam at 2.5 mg/kg.

[0055] Animals were individually assessed for the production of a tonic hind limb extensor convulsion at 60 min post-dose for vehicle, 30-120 min post-dose for test compound (dependant on compound) and 30 min post-dose for diazepam, from a single electroshock.

[0056] 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.

[0057] Data generated from each treatment group were used to calculate the CC_{50} ± SEM values for the treatment group.

Test Compounds:

[0058] Vehicle: (5% ethanol, 5% solutol in 90% Saline) was prepared as follows: 2 mL of ethanol, 2 mL of solutol were warmed to 60°C, in 36 mL of saline (1:1:18).

[0059] Positive control: diazepam was used at 2.5mg/kg.

[0060] The test compounds used were 12a, 12b, 18a and 18b. Test compounds were administered at 200mg/kg (i.p.) in a 1:1:18 ethanol: solutol: saline formulation.

Sample Collection:

[0061] 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 collection were performed following decapitation.

[0062] 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 10 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 cap cryovials, weighed and frozen on cardice.

Statistical analysis

[0063] 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) ± standard error.

[0064] Test compound effects were also calculated as percentage change in CC_{50} from the vehicle control group.

[0065] Significant difference between drug-treated animals and controls were assessed according to Litchfield and Wilcoxon (1949).

Results

[0066] Figures 1 to 4 and Tables 1 to 4 describe the data produced in this experiment.

[0067] In the vehicle group, the CC_{50} value was calculated to be 21mA.

[0068] In the diazepam (2.5 mg/kg) treated group, administered i.p. 30 minutes before the test, the CC_{50} value was 35mA. This result was statistically significant ($p<0.001$) compared to the vehicle control.

[0069] In the test compound treatment groups, administered i.p. between 30 and 120 minutes before the test, all four compounds produced a statistically significant CC_{50} value compared to vehicle.

[0070] Such data are indicative that these compounds will be of therapeutic benefit.

Table 1: Evaluation of effect of Compound 12a in the MEST test

Treatment	Dose (mg/kg)	Test time post dose (min)	N	CC_{50} +/- SEM	Significance	% change from vehicle
Vehicle	-	60	12	21.0 +/- 0.5	-	-
Diazepam	2.5	30	12	35.0 +/- 1.1	P<0.001	66%
Compound 12a	200	60	8	54.0 +/- 0.2	P<0.001	157%

Table 2: Evaluation of effect of Compound 12b in the MEST test

Treatment	Dose (mg/kg)	Test time post dose (min)	N	CC_{50} +/- SEM	Significance	% change from vehicle
Vehicle	-	60	12	21.0 +/- 0.5	-	-
Diazepam	2.5	30	12	35.0 +/- 1.1	P<0.001	66%
Compound 12b	200	30	12	43.8 +/- 0.2	P<0.001	109%

Table 3: Evaluation of effect of Compound 18a in the MEST test

Treatment	Dose (mg/kg)	Test time post dose (min)	N	CC_{50} +/- SEM	Significance	% change from vehicle
Vehicle	-	60	12	21.0 +/- 0.5	-	-
Diazepam	2.5	30	12	35.0 +/- 1.1	P<0.001	66%
Compound 18a	200	120	12	41.8 +/- 0.5	P<0.001	99%

Table 4: Evaluation of effect of Compound 18b in the MEST test

Treatment	Dose (mg/kg)	Test time post dose (min)	N	CC_{50} +/- SEM	Significance	% change from vehicle
Vehicle	-	60	12	21.0 +/- 0.5	-	-
Diazepam	2.5	30	12	35.0 +/- 1.1	P<0.001	66%
Compound 18b	200	120	12	40.3 +/- 0.8	P<0.001	92%

Conclusions

[0071] These data demonstrate a therapeutic effect for the compounds of Formula I and Formula II.

[0072] These data are significant as they provide heretofore unknown evidence that these novel cannabinoid derivatives may be of therapeutic value.

[0073] The compounds tested were those detailed as Compound 12a, Compound 12b, Compound 18a and Compound 18b. Such compounds are examples of the cannabinoid derivatives of general Formula I and Formula II.

[0074] Clearly as all compounds showed efficacy in the MEST test such therapeutic efficacy can be attributed to the cannabinoid derivatives of general Formula I and Formula II of the invention.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO0195899A [0011]
- WO2014062965A1 [0012]

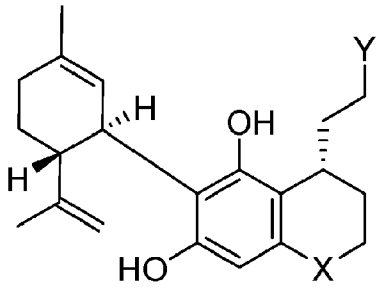
Non-patent literature cited in the description

- **ROGER PERTWEE**The Handbook of Cannabis3-15 [0008]

PATENTKRAV

1. Forbindelse med den almene formel I eller et salt deraf

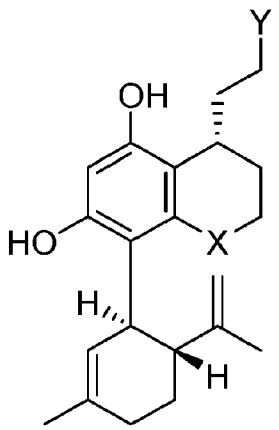
Formel I



hvor X enten er CH_2; O; NBoc; NFMoc; NZ; NTs; NAc; NC(O)iPr; NBz eller NH og Y enten er H eller OH.

2. Forbindelse med den almene formel II eller et salt deraf

Formel II



hvor X enten er CH_2; O; NBoc; NFMoc; NZ; NTs; NAc; NC(O)iPr; NBz eller NH og Y enten er H eller OH.

3. Farmaceutisk sammensætning, der omfatter en forbindelse ifølge krav 1 eller krav 2.

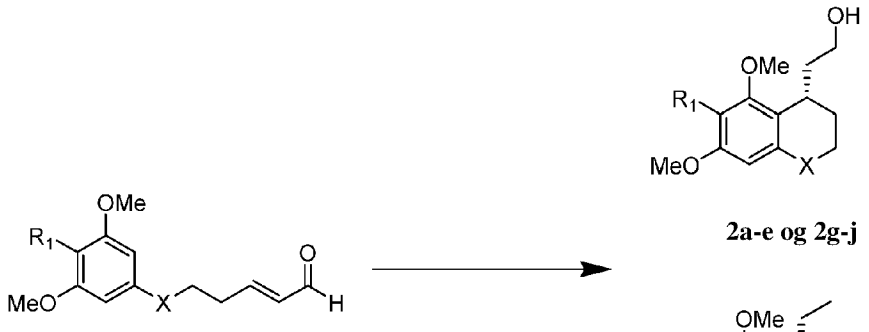
4. Farmaceutisk sammensætning ifølge krav 3, hvor den farmaceutiske sammensætning vælges blandt en tablet, en kapsel, et granulat, et inhalationspulver, et drys, en oral opløsning og en suspension.

5. Farmaceutisk sammensætning ifølge krav 3 eller krav 4, hvor sammensætningen endvidere omfatter en eller flere af: et hjælpestof valgt blandt et bærestof, en olie, et sprængmiddel, et smøremiddel, et stabiliseringsmiddel, et smagsstof, et antioxidant, et fortyndingsmiddel og en anden farmaceutisk virksom forbindelse.

6. Forbindelse ifølge krav 1 eller krav 2 til anvendelse som et lægemiddel.

7. Forbindelse ifølge krav 1 eller krav 2 til anvendelse i behandlingen af epilepsi.

8. Fremgangsmåde til fremstilling af en forbindelse med den almene formel I ifølge krav 1, eller almene formel II ifølge krav 2, og som omfatter omsætning af en resorcinolenhed med strukturen 1a-e eller 1g-j via en Friedel-Crafts 1,4-addition for at fremstille forbindelser med strukturerne 2a-e eller 2g-j, eller 3a-e eller 3g-j:



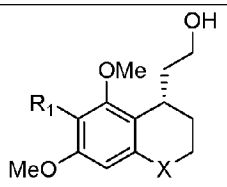
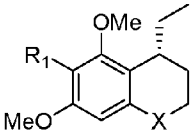
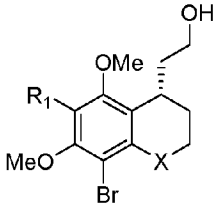
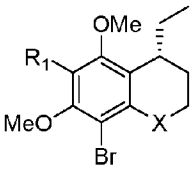
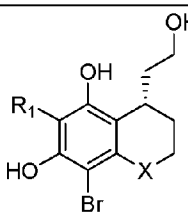
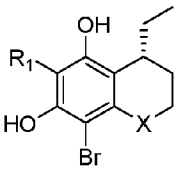
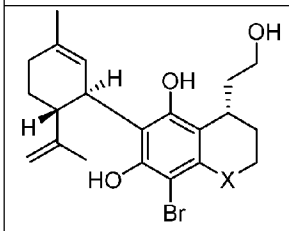
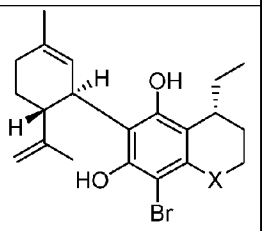
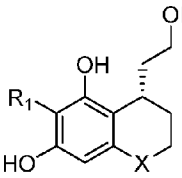
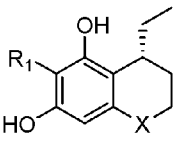
1a-e og 1g-j

2a-e og 2g-j

3a-e og 3g-j

R_1 = H; X = CH_2; O; NBoc; NFmoc; NZ; NTs; NAc; NC(O)iPr; eller NBz efterfulgt af efterfølgende trin for at fremstille forbindelserne med den almen formel I eller II via mellemprodukter.

9. Mellemprodukt dannet i processen med fremstilling af en forbindelse med den almene formel I eller formel II, hvor mellemproduktet vælges fra:

 **2a-e og 2g-j**	 **3a-e og 3g-j**
 **4a-e og 4g-j**	 **5a-e og 5g-j**
 **6a-e og 6g-j**	 **7a-e og 7g-j**
 **9a-e og 9g-j**	 **10a-e og 10g-j**
 **15a-e og 15g-j**	 **16a-e og 16g-j**

hvor R_1 = H, og X = CH_2; O; NBoc; NFmoc; NZ; NTs; NAc; NC(O)iPr; eller NBz.

DRAWINGS

Figure 1. Effect of Compound 12a on the electroshock-induced generalised seizure threshold (MEST) in the mouse

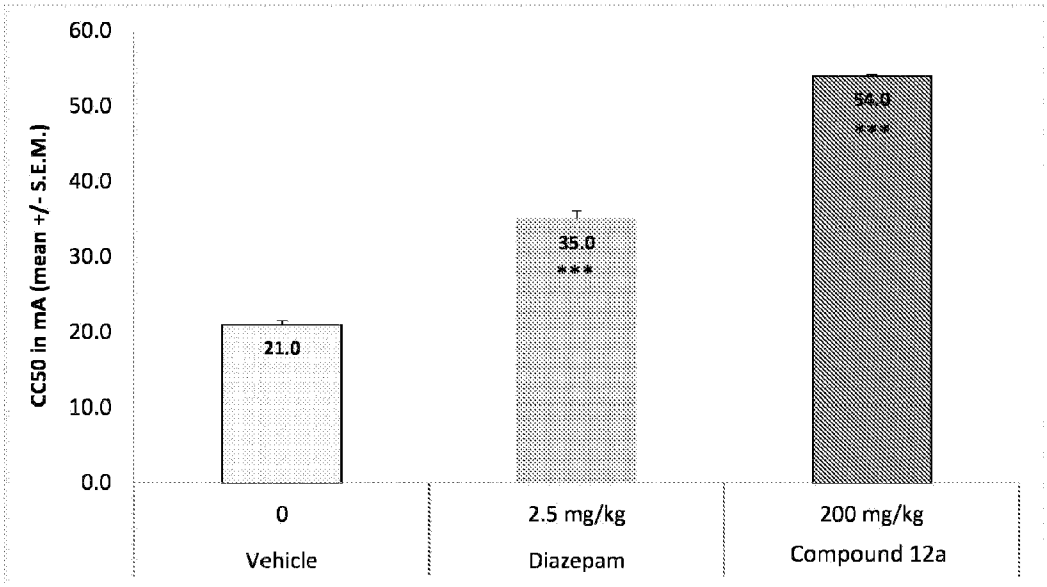


Figure 2. Effect of Compound 12b on the electroshock-induced generalised seizure threshold (MEST) in the mouse

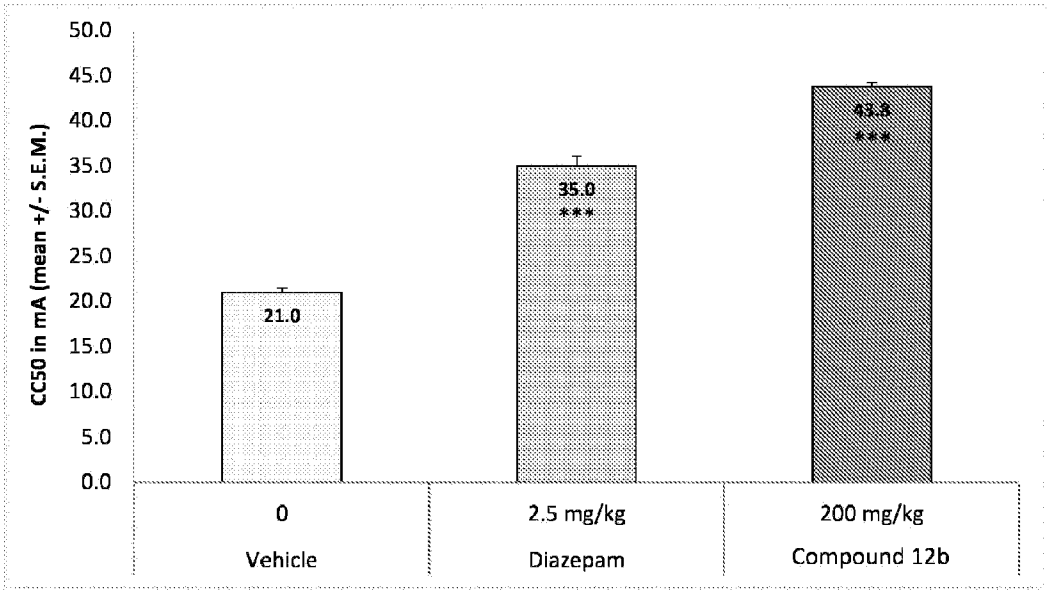


Figure 3. Effect of Compound 18a on the electroshock-induced generalised seizure threshold (MEST) in the mouse

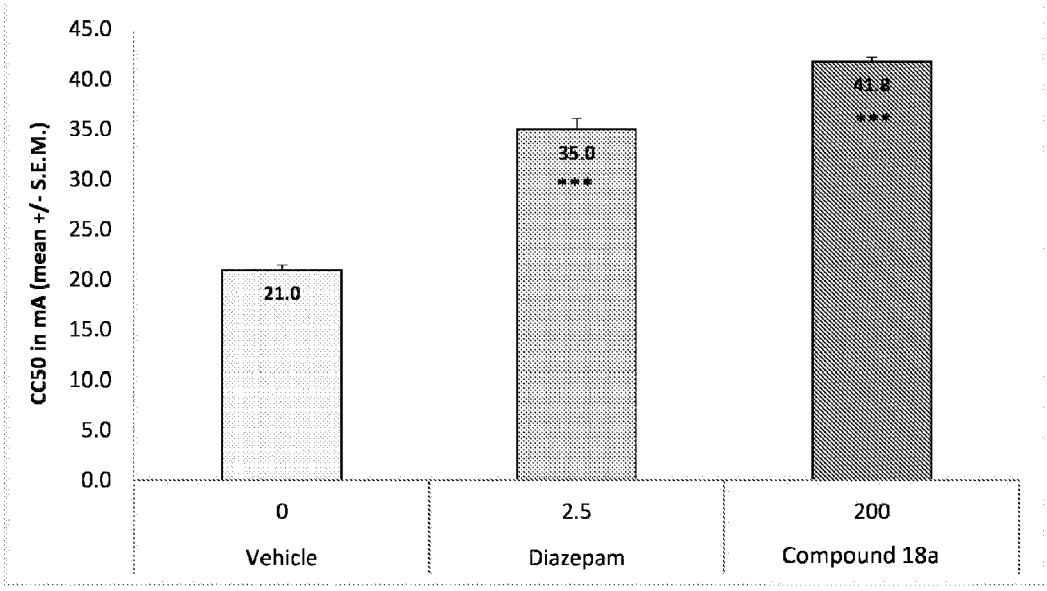


Figure 4. Effect of Compound 18b on the electroshock-induced generalised seizure threshold (MEST) in the mouse