(12) STANDARD PATENT (11) Application No. AU 2007244978 B2
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Abnormal Cannabidiols as agents for lowering intraocular pressure

(51) International Patent Classification(s)
C07C 39/08 (2006.01) ***A61K 31/4427*** (2006.01)
A61K 31/05 (2006.01) ***A61K 31/445*** (2006.01)
A61K 31/34 (2006.01) ***A61K 31/4523*** (2006.01)
A61K 31/35 (2006.01) ***A61K 31/50*** (2006.01)
A61K 31/381 (2006.01) ***A61K 31/501*** (2006.01)
A61K 31/382 (2006.01) ***A61K 31/502*** (2006.01)
A61K 31/4353 (2006.01) ***C07D 211/00*** (2006.01)
A61K 31/44 (2006.01)

(21) Application No: **2007244978** (22) Date of Filing: **2007.04.24**

(87) WIPO No: **WO07/127711**

(30) Priority Data

(31) Number	(32) Date	(33) Country
11/409,868	**2006.04.24**	**US**
11/409,570	**2006.04.24**	**US**
11/409,871	**2006.04.24**	**US**

(43) Publication Date: **2007.11.08**
(44) Accepted Journal Date: **2013.05.30**

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(56) Related Art
Adams et al. (1940) J. Am. Chem. Soc. 62: 1770-1775
Pisanenko et al. (1976) Pharmaceutical Chemistry Journal 10(10): 35-36
US 2002/161041
US 2003/180234
CAplus accession number 1972:460212
US 2002/137961
WO 2006/007227
US 2005/282902
WO 2003/091189

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
8 November 2007 (08.11.2007)

PCT

(10) **International Publication Number**
WO 2007/127711 A3

(51) **International Patent Classification:**
A61K 31/05 (2006.01) *A61K 31/501* (2006.01)
A61K 31/34 (2006.01) *A61K 31/4427* (2006.01)
A61K 31/35 (2006.01) *A61K 31/502* (2006.01)
A61K 31/381 (2006.01) *A61K 31/445* (2006.01)
A61K 31/382 (2006.01) *A61K 31/4523* (2006.01)
A61K 31/4353 (2006.01) *C07C 39/08* (2006.01)
A61K 31/50 (2006.01) *C07D 211/00* (2006.01)
A61K 31/44 (2006.01)

(21) **International Application Number:** PCT/US2007/067267

(22) **International Filing Date:** 24 April 2007 (24.04.2007)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
11/409,871 24 April 2006 (24.04.2006) US
11/409,570 24 April 2006 (24.04.2006) US
11/409,868 24 April 2006 (24.04.2006) US

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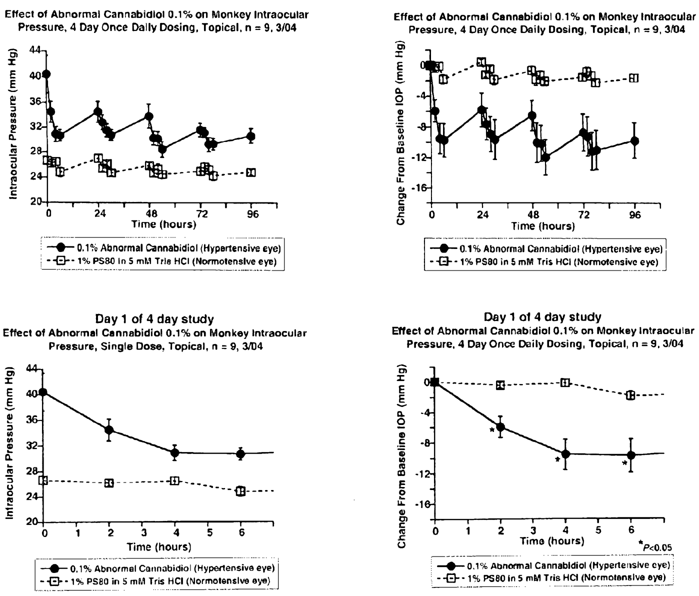
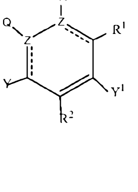
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

[Continued on next page]

(54) **Title:** ABNORMAL CANNABIDIOLS AS AGENTS FOR LOWERING INTRAOCULAR PRESSURE

(57) **Abstract:** The present invention provides a method of treating glaucoma or ocular hypertension which comprises applying to the eye of a person in need thereof an amount sufficient to treat glaucoma or ocular hypertension of a compound of formula (I), wherein Y, Q, Z, R, R^1 and R^2 are as defined in the specification. The present invention further comprises pharmaceutical compositions, e.g. ophthalmic compositions, including said compound.





(I)

WO 2007/127711 A3

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 27 March 2008

17909ABC(AP)

ABNORMAL CANNABIDIOLS AS AGENTS FOR LOWERING INTRAOCULAR PRESSURE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the use of Abnormal Cannabidiols to lower the intraocular pressure of mammals and thus are useful in treating glaucoma.

2. Background of the Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical α-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

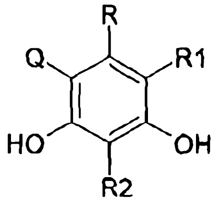
Certain Abnormal Cannabidiols are disclosed in Howlett et al, "International Union of Pharmacology. XXVII. Classification of Cannabinoid Receptors", Pharmacological Reviews 54: 161-202, 2002.

Reference is made to Published U.S. Patent Application Numbers 2005/0282902, 2005/0282912 and 2005/0282913 to Chen et al which were published on December 22, 2005 and are herein incorporated by reference thereto. (June Chen is a co-inventor of each of said published patent applications and the present patent application.)

Summary of the Invention

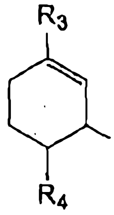
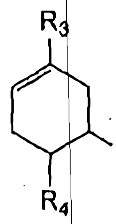
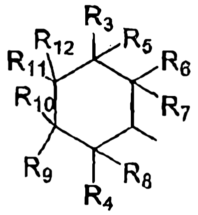
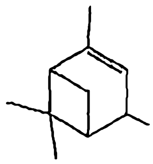
We have found that Abnormal Cannabidiols are potent ocular hypotensive agents. We have further found that Abnormal Cannabidiols and homologues and derivatives thereof, are especially useful in the treatment of glaucoma and surprisingly, cause no or significantly lower ocular surface hyperemia than the other compounds that are useful in lowering intraocular pressure, e.g. $PGF_{2\alpha}$ and lower alkyl esters thereof.

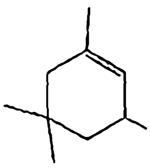
A first aspect of the invention provides a compound for treating glaucoma or ocular hypertension having the formula II:



(II)

wherein Q is selected from the group consisting of: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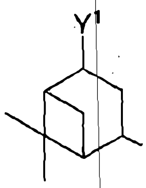

wherein Y^1 is R^3 and R^5, or =O, or OH;

R is a halogen;

R^1 is selected from the group consisting of H and halogen;

R^2 is independently selected from the group consisting of H, C_{1-5} alkyl, halogen, XC_{1-5} alkyl, C_{1-5} alkylOR^{13}, C_{1-5} alkylN(R^{13})$_2$, N(R^{13})$_2$, XC $_{1-5}$ alkylN(R^{13})$_2$ and XC $_{1-5}$ alkylOR^{13}; wherein X is O or S(O)$_n$; and n is 0 or an integer of from 1 to 2;

R^3 is selected from the group consisting of H, hydroxyl C_{1-5} alkyl, C_{1-5} alkylOR^{13} and C_{1-5} alkylN(R^{13})$_2$;

R^4 is selected from the group consisting of H, C_{1-5} alkenyl, C_{2-5} alkyl, C_{1-5} alkylOR^{13} and C_{1-5} alkylN(R^{13})$_2$;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} are independently selected from the group consisting of H, C_{1-5} alkyl, C_{1-5} alkylOR^{13} and OR^{13}; and

R^{13} is selected from the group consisting of H, C_{1-5} alkyl and C_{3-8} cyclic alkyl.

A second aspect of the invention provides a pharmaceutical composition which is an ophthalmic solution comprising a therapeutically effective amount of a compound as defined in the first aspect.

A third aspect of the invention provides a pharmaceutical product comprising a container adapted to dispense the contents in metered form, and an ophthalmic solution therein as defined in the second aspect.

A fourth aspect of the invention provides a method of treating glaucoma or ocular hypertension comprising applying to the eye of a subject in need thereof a sufficient amount of a compound as defined in the first aspect.

A fifth aspect of the invention provides a method for treating glaucoma or intraocular pressure comprising applying to the eye of a subject in need thereof a sufficient amount of a combination of a compound as defined in the first aspect, and a drug selected from the group consisting of a β-blocker, an adrenergic agonist, a carbonic anhydrase inhibitor, a cholinergic agonist, a chlolinesterase inhibitor, a glutamate antagonist, a prostamide and a prostaglandin.

A sixth aspect of the invention provides a use of a compound as defined in the first aspect in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension.

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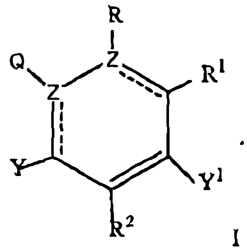
A seventh aspect of the invention provides a use of a compound as defined in the first aspect in the manufacture of a medicament for the treatment of glaucoma or intraocular pressure, wherein the compound is intended for administration with a drug selected from the group consisting of a β-blocker, an adrenergic agonist, a carbonic anhydrase inhibitor, a cholinergic agonist, a chlolinesterase inhibitor, a glutamate antagonist, a prostamide and a prostaglandin.

The present invention relates to methods of treating ocular hypertension which comprises administering an effective amount of a compound represented by



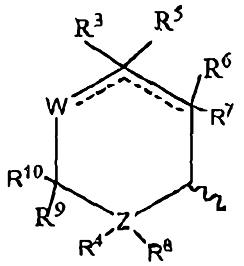
I

wherein Y is selected from the group consisting of keto and hydroxyl;

Y^1 is selected from the group consisting of hydroxyl, keto, halogen and C_1-C_5 alkyl;

Z is N or C;

Q is selected from the group consisting of phenyl, halogen-substituted phenyl, 5 or 6 member heterocyclic radicals, wherein the hetero atom is nitrogen, oxygen or sulfur,



wherein W is a direct bond or $C(R^{11})(R^{12})$;

a dotted line represents the presence or absence of a double bond;

the wavy line represents a direct bond;

Q and Y may form a condensed ring wherein Y is –C(O)-NR3- and Q is –C(Q')- wherein Q' is R3 or said C is a spiro atom and Q', together with said C, represents a carbocyclic or heterocyclic ring having from 3 to 6 carbon atoms and said hetero atom is N, O or S;

R is selected from the group consisting of H, halogen and C_{1-5} alkyl;

R^1 is selected from the group consisting of H and halogen;

R^2 is selected from the group consisting of H, C_{1-5} alkyl, halogen, XC_{1-5} alkyl, C_{1-5} alkylOR^{13}, C_{1-5} alkylN(R^{13} $)_2$,

N(R^{13} $)_2$, XC_{1-5} alkylN(R^{13} $)_2$ and XC_{1-5} alkylOR^{13}; wherein

X is O or S(O $)_n$;

n is 0 or an integer of from 1 to 2;

R^3 is selected from the group consisting of H, hydroxyl, oxo, C_{1-5} alkyl, C_{1-5} alkylOR^{13} and C_{1-5} alkylN(R^{13} $)_2$;

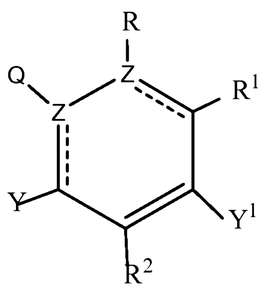
R^4 is selected from the group consisting of H, C_{1-5} alkenyl, C_{1-5} alkyl, C_{1-5} alkylOR^{13} and C_{1-5} alkylN(R^{13} $)_2$;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} are independently selected from the group consisting of H, C_{1-5} alkyl, C_{1-5} alkylOR^{13} and OR^{13}; and

R^{13} is selected from the group consisting of H, C_{1-5} alkyl and C_{3-8} cyclic alkyl, or two R^{13} groups, together with N, may form a cyclic ring such as a piperidine or morpholine ring; and provided that R^8 and R^{12} may, together, form a cyclic ring, and R^3 and R^5 may, together, represent O, and

when Q is menthadiene, R^1 and R^2 are H and Y is hydroxyl, R may not be H or alkyl.

Preferably, the compound of formula I is

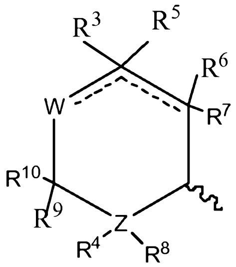


I'

wherein Y is selected from the group consisting of keto and hydroxyl;

Z is N or C;

Q is selected from the group consisting of



wherein W is a direct bond or $C(R^{11})(R^{12})$;

a dotted line represents the presence or absence of a double bond;

wherein R is selected from the group consisting of H, halogen, e.g. bromo or chloro; and C_{1-5} alkyl; R^1 is selected from the group consisting of H, halogen, e.g. bromo or chloro;

R^2 is independently selected from the group consisting of H, C_{1-5} alkyl, halogen, XC_{1-5} alkyl, C_{1-5} alkylOR^{13}, C_{1-5} alkyl$N(R^{13})_2$, $N(R^{13})_2$, XC_{1-5} alkyl$N(R^{13})_2$ and XC_{1-5} alkylOR^{13};

X is O or $S(O)_n$;

n is 0 or an integer of from 1 to 2;

R^3 is selected from the group consisting of H, hydroxyl, C_{1-5} alkyl, C_{1-5} alkylOR^{13} and C_{1-5} alkylN(R^{13})$_2$;

R^4 is selected from the group consisting of H, C_{1-5} alkenyl, e.g. isopropenyl, C_{1-5} alkyl, C_{1-5} alkylOR^{13} and C_{1-5} alkylN(R^{13})$_2$;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} are independently selected from the group consisting of H, C_{1-5} alkyl, C_{1-5} alkylOR^{13} and OR^{13}; and

R^{13} is selected from the group consisting of H, C_{1-5} alkyl and C_{3-8} cyclic alkyl, or two R^{13} groups, together with N, may form a cyclic ring such as a piperidine or morpholine ring; and provided that any of said alkyl groups may be substituted with a hetero atom containing radical, wherein said heteroatom is R^8 and R^{12} may, together, form a cyclic ring;
and R^3 and R^5 may, together, represent O, and
when Q is menthadiene, R^1 and R^2 are H and Y is hydroxyl, R may not be H or alkyl.

In a further aspect, the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I) or (I'), in admixture with an non-toxic, pharmaceutically acceptable liquid vehicle. Such pharmaceutical compositions may be ophthalmic solutions which are useful in treating ocular hyptension and/or glaucoma. Finally, the present invention provides certain novel compounds which are useful in treating ocular hypertension and/or glaucoma.

Brief Description of the Figures

Figure 1 shows the effect of abnormal cannabidiol on intraocular pressure.

Figure 2 shows the effect of the compound of Example 4 intraocular pressure.

Figure 3 shows the effect of the compound of Example 3 intraocular pressure.

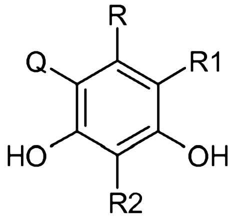
Figure 4 shows the effect of the compound of Example 6 intraocular pressure.

Figure 5 shows the effect of the compound of Example 5 intraocular pressure.

Detailed Description of the Invention

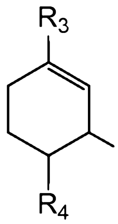
The present invention relates to the use of Abnormal Cannabidiols as ocular hypotensives. These therapeutic agents are represented by compounds having the formula I or I', above.

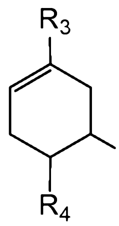
In one embodiment of the invention, the compound is selected from the group consisting of abnormal Cannabidiols and analogues thereof represented by formula II

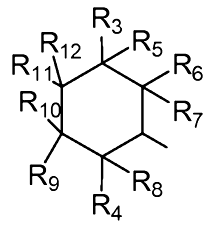


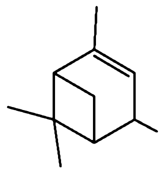
II

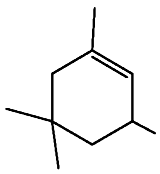
wherein Q is selected from the group consisting of







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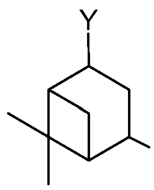

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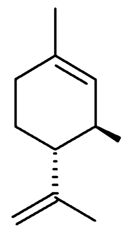
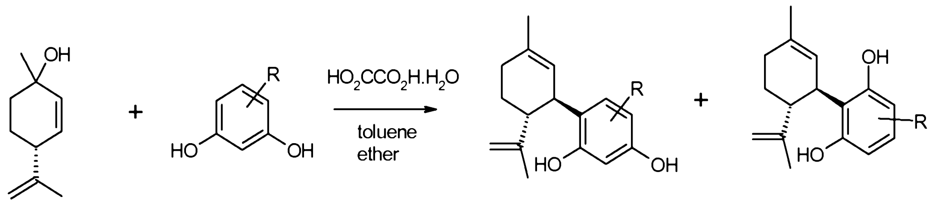
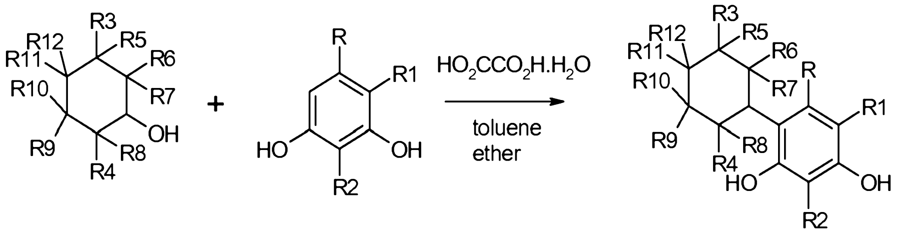
A particularly preferred group represented by Q is menthadiene or



In this class of compounds, preferably, R is selected from the group consisting of hydrogen, methyl, bromo and chloro and R^1 is selected from the group consisting of hydrogen, methyl and chloro.

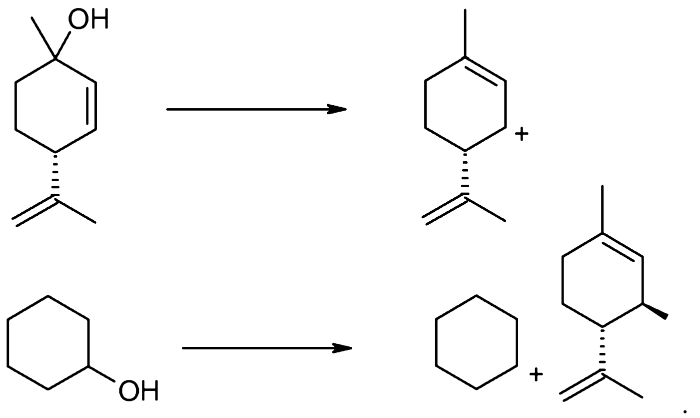
Compounds of this type may be prepared by condensation of a cyclic alkene or cyclic alcohol with a suitably substituted benzene-1,3-diol. The reaction is catalysed by an acid such as oxalic acid dihydrate or p-toluenesulphonic acid. The reaction is carried out in a solvent or mixture of solvents such as toluene, diethyl ether or dichloromethane. A mixture of the two isomers is obtained and the desired product is separated by chromatography. The reaction scheme is illustrated below.



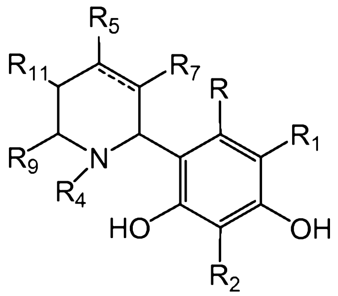


The synthesis of the starting materials is well known.

The mechanism of the reaction is the result of the formation of a carbocation by elimination of OH or a starting material containing a functional group such as acetate which can also be eliminated to give the carbocation can be used.

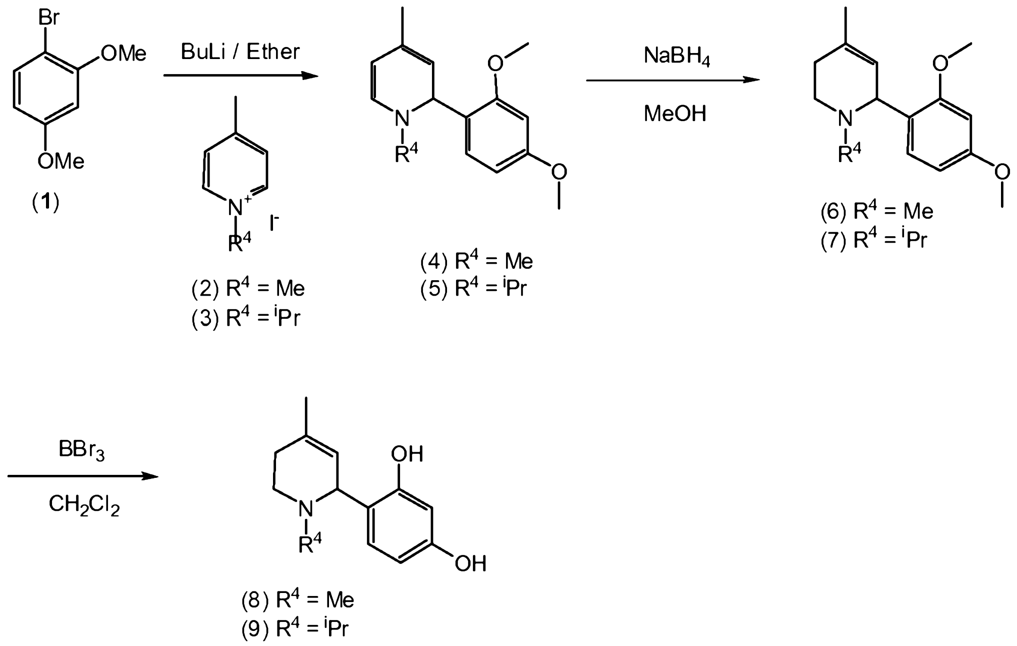


In another embodiment of the invention the compound is tetrahydropyridine represented by formula III

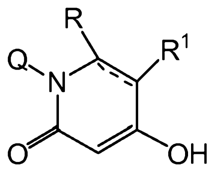


III.

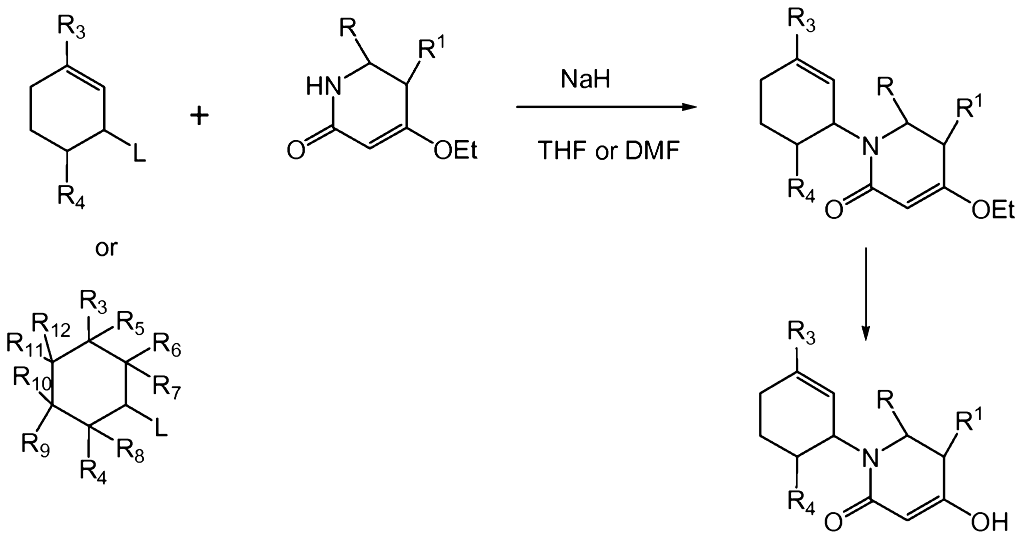
These tetrahydropyridine compounds may be synthesized according to the following reaction scheme wherein Me is methyl, Bu is butyl and iPr is isopropyl.



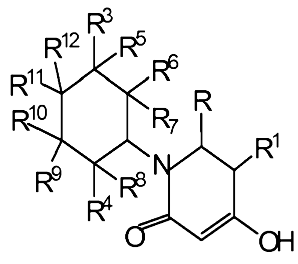
In a further embodiment of the invention, the compound is a piperidinedione represented by the formula IV


IV.

These compounds may be synthesized according to the following reaction scheme wherein Et is ethyl, THF is tetrahydrofuran and DMF is dimethyl formamide.



or



Where L is a leaving group such bromine, iodine or tosyl.

Compounds of formula I' wherein Y and Y^1 are keto are known as piperidine-2, 4-diones and may be synthesized as described by H. Nishino, et al., Teterahedron 2005, 11107-11124. The corresponding cyclohexane-1, 3 diones may be prepared as described in EP 291114 and EP 310186. Compounds of formula I' wherein Y is keto and Y^1 is hydroxyl are known as 4-hydroxypyridin-2-ones and may be prepared as described by Castillo, et al. in Bull. Soc. Chim. Fr. 1982, 257-261.

The compounds wherein $Y=Y^1$=hydroxyl may be prepared by dehydrogenation of the corresponding cyclohexane –1, 3 diones by the method described by E.D. Berymann, et a., JACS, 1953, 3226. Compounds of formula I' wherein both of Z is N, Y is oxo and Y^1 is hydroxyl may be prepared as described in WO 2005/007632 and J. Het. Chem. 1989, 169-176.

In all of the above formulae, as well as in those provided hereinafter, the straight lines represent bonds. Where there is no symbol for the atoms between the bonds, the appropriate carbon-containing radical is to be inferred.

Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five unit doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 μl.

The compounds disclosed herein for use in the method of this invention, i.e. the treatment of glaucoma or elevated intraocular pressure, may also be used in combination with other drugs useful for the treatment of glaucoma or elevated intraocular pressure.

For the treatment of glaucoma or elevated intraocular pressure, combination treatment with the following classes of drugs are contemplated:

β-Blockers (or β-adrenergic antagonists) including carteolol, levobunolol, metipranolol, timolol hemihydrate, timolol maleate, β1-selective antagonists such as betaxolol, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Adrenergic Agonists including

non-selective adrenergic agonists such as epinephrine borate, epinephrine hydrochloride, and dipivefrin, and the like, or pharmaceutically acceptable salts or prodrugs thereof; and

α_2-selective adrenergic agonists such as apraclonidine, brimonidine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Carbonic Anhydrase Inhibitors including acetazolamide, dichlorphenamide, methazolamide, brinzolamide, dorzolamide, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Cholinergic Agonists including

direct acting cholinergic agonists such as carbachol, pilocarpine hydrochloride, pilocarpine nitrate, pilocarpine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

chlolinesterase inhibitors such as demecarium, echothiophate, physostigmine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Glutamate Antagonists such as memantine, amantadine, rimantadine, nitroglycerin, dextrophan, detromethorphan, CGS-19755, dihydropyridines, verapamil, emopamil, benzothiazepines, bepridil, diphenylbutylpiperidines, diphenylpiperazines, HOE 166 and related drugs, fluspirilene, eliprodil, ifenprodil, CP-101,606, tibalosine, 2309BT, and 840S, flunarizine, nicardipine, nifedimpine, nimodipine, barnidipine, lidoflazine, prenylamine lactate, amiloride, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Prostamides such as bimatoprost, or pharmaceutically acceptable salts or prodrugs thereof; and

Prostaglandins including travoprost, UFO-21, chloprostenol, fluprostenol, 13,14-dihydro-chloprostenol, isopropyl unoprostone, latanoprost and the like.

The invention is further illustrated by the following non-limiting Examples.

Example 1

Intraocular Pressure

Intraocular pressure was measured by applanation pneumatonometry in conscious animals. The test compound was administered topically to one eye while vehicle was given to the fellow eye in a masked fashion. Ocular normotensive Beagle dogs (males, females) were dosed once daily for five days. Laser-induced unilaterally ocular hypertensive Cynomolgus monkeys (females) were dosed once daily for 4 days. Student's paired *t*-test was used for statistical comparisons. Differences were considered statistically significant if the *P*-value is less than 0.05.

The results are shown in the Figures.

The figures show the change from baseline IOP of Monkey dosed with 0.1% of the active compound versus time.

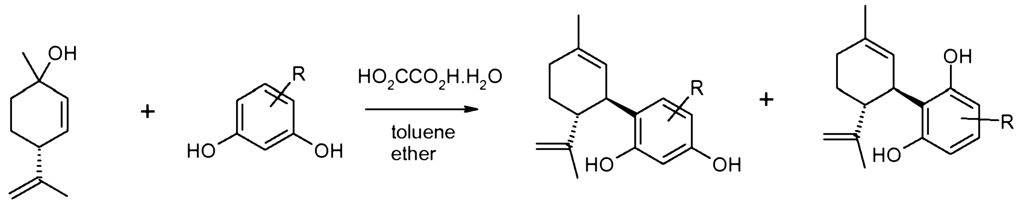
Example 2

Determination of Abnormal Cannabidiol Activity

Abnormal Cannabidiol receptor activity may be measured in accordance with the procedure disclosed in (Wagner JA et al., *Hypertension* 33 [part II], 429 (1999); Járai Z et al., *PNAS* 96, 14136 (1999), which is hereby incorporated by reference in its entirety.

Experimental Details for Synthesis of Abnormal Cannabidiols

General Route



Example 3

5-methyl-4-(6-Isoprenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol

(4R)-1-Methyl-4-isoprenylcyclohex-2-ene-1-ol (300mg, 2mmoles) was dissolved in toluene (20ml) and 5-methylresorcinol (248mg, 2mmoles) was added in diethyl ether (5ml). Oxalic acid dihydrate (252mg, 2mmoles) was added and the reaction mixture heated with stirring at 80° for 5 hours. The reaction mixture was allowed to cool and diluted with diethyl ether (30ml). The ether solution was washed twice with aqueous sodium bicarbonate and dried over anhydrous magnesium sulphate. The solvents were evaporated under reduced pressure to give the crude product as a brown oil (800mg). The product was purified using a silica column eluted with ethyl acetate : isohexane 1 : 9 going to ethyl acetate : isohexane 2 : 8.
The product was isolated as a yellow gum (106mg)

Example 4

4-(6-Isoprenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol

The named compound is prepared according to the method described in Example 3 except that resorcinol is substituted for 5-methylresorcinol.

^{1}H NMR (300MHz, $CDCl_3$) 6.2 (M, 2H), 6.1 (S, 1H), 5.55 (M, 1H), 4.7 (M, 1H), 4.55 (S, 1H), 4.5 (M, 1H), 3.55 (M, 1H), 2.5 (M, 1H), 2.2 (M, 2H), 2.15 (S, 3H), 1.85 (M, 2H), 1.8 (S, 3H), 1.6 (S, 3H)

Also prepared in a similar manner were

Example 5

5-Chloro-4-(6-Isoprenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol

^{1}H NMR (300MHz, $CDCl_3$) 6.4 (M, 1H), 6.3 (M, 1H), 6.25 (S, 1H), 5.6 (M, 1H), 4.7 (brS, 1H), 4.65 (M, 1H), 4.4 (M, 1H), 4.0 (M, 1H), 2.5 (M, 1H), 2.25 (M, 1H), 2.15 (M, 1H), 1.85 (M, 2H), 1.8 (S, 3H), 1.6 (S, 3H)

Example 6

4-(6-Isoprenyl-3-methylcyclohex-2-enyl)-5-methoxybenzene-1,3-diol

^{1}H NMR (300MHz, $CDCl_3$) 6.15 (brS, 1H), 6.0 (M, 2H), 5.6 (M, 1H), 4.65 (brS, 1H), 4.5 (M, 1H), 4.35 (M, 1H), 3.95 (M, 1H), 3.7 (S, 3H), 2.4 (M, 1H), 2.25 (1H, M), 2.1 (M, 1H), 1.8 (M, 2H), 1.8 (S, 3H), 1.65 (S, 3H)

Example 7

2-(6-Isoprenyl-3-methylcyclohex-2-enyl)-5-methoxybenzene-1,3-diol

^{1}H NMR (300MHz, $CDCl_3$) 6.0 (brS, 2H), 5.55 (M, 1H), 4.7 (M, 1H), 4.6 (M, 1H), 3.8 (M, 1H), 3.75 (S, 3H), 2.4 (M, 1H), 2.2 (M, 1H), 2.1 (M, 1H), 1.8 (S, 3H), 1.8 (M, 2H)

Example 8

Synthesis of 6-Chloro-4-(6-Isoprenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol

4-Chlororesorcinol (350mg, 2.4mmoles) was dissolved in toluene (30ml) and diethyl ether (20ml) and p-toluenesulphonic acid (91mg, 0.48mmoles) was added.

(4R)-1-Methyl-4-isoprenylcyclohex-2-ene-1-ol (500mg, 3mmoles) in toluene (10ml) was added and the reaction mixture was stirred at room temperature for 6 hours. Diluted with diethyl ether (30ml) and washed twice with aqueous sodium bicarbonate. Dried over anhydrous magnesium sulphate and the solvent was evaporated under reduced pressure to give a yellow gum (800mg). Purified using a silica column eluted with ethyl acetate : isohexane 9:1 going to ethyl acetate : isohexane 8:2. The product was isolated as a yellow gum (95mg)

^1H NMR (300MHz, $CDCl_3$) 6.9 (S, 1H), 6.5 (S, 1H), 5.5 (S, 1H), 5.45 (M, 1H), 5.35 (S, 1H), 4.7 (M, 1H), 4.6 (M, 1H), 3.35 (M, 1H), 2.2 (M, 3H), 1.8 (M, 3H), 1.75 (M, 2H), 1.6 (S, 3H)

Example 9

Synthesis of 4-Cyclohexylbenzene-1,3-diol

This compound was prepared as described in JACS, 1953, 2341.

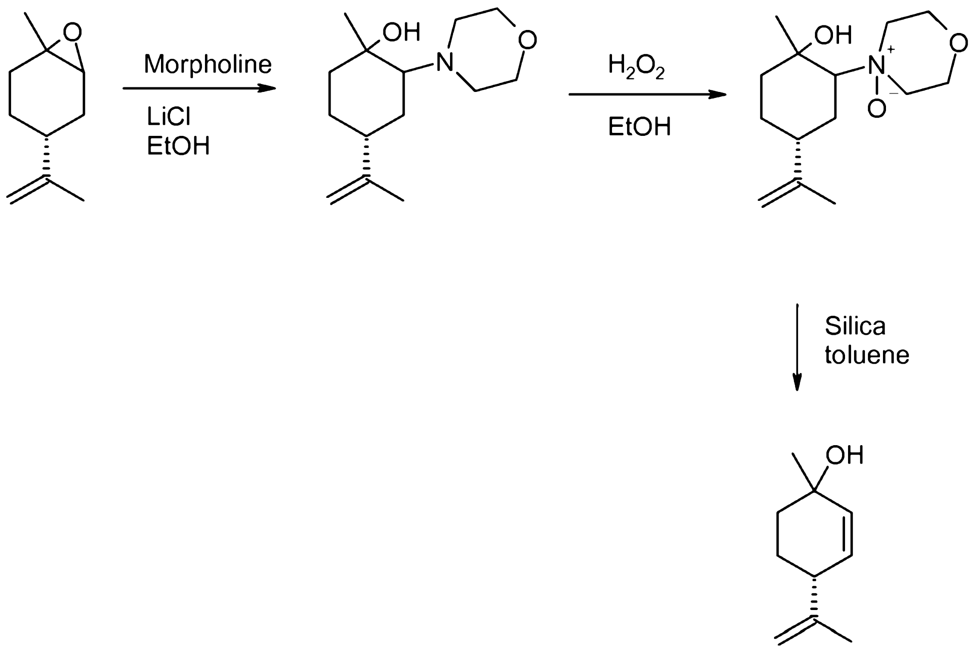
Resorcinol (2.2g, 0.02 moles) was mixed with cyclohexanol (1g, 0.01moles) and zinc (II) chloride (0.48g, 0.0035moles) and the reaction mixture heated to 150° with stirring. After heating 2 hours, the reaction mixture was allowed to cool and then dissolved in ethyl acetate. Washed with water and dried over anhydrous magnesium sulphate. The solvent was evaporated to give a brown oil (3.0g). Excess resorcinol was evaporated by heating in a Kugelrohr oven under reduced pressure (200°, 2mmHg). Purified using a silica column eluted with ethyl acetate : isohexane 2:8 to give the product as a yellow oil (0.5g). Trituration with isohexane gave the product as a white solid (0.2g).

^1H NMR (300MHz, $CDCl_3$) 7.0 (D, 1H J = 8Hz), 6.4 (M, 1H), 6.3 (M, 1H), 4.7 (S, 1H), 4.55 (S, 1H), 2.7 (M, 1H), 1.8 (M, 5H), 1.4 (M, 5H)

Example 10

Synthesis of 4R-Isoprenyl-1-methylcyclohex-2-enol

The synthesis of 4R-Isoprenyl-1-methylcyclohex-2-enol was carried out as described in WO2004096740.



Example 11

4-Isoprenyl-1-methyl-2-morpholin-4-yl-cyclohexanol

(+)-Limonene oxide (13.2g, 0.087moles) was dissolved in ethanol (40ml) and lithium chloride (5.9g, 0.14moles) was added with stirring. Morpholine (11.4g, 0.13moles) was added and the reaction mixture was heated at 60° for 48hours. The solvent was evaporated under reduced pressure and the residue taken up in dichloromethane. Washed with water. Extracted into 2M hydrochloric acid and washed with dichloromethane. Basified to pH 10 by addition of 2M sodium hydroxide. Extracted with diethyl ether and washed with water. Dried over anhydrous magnesium sulphate and evaporated the solvent under reduced pressure to give the product as a yellow oil (10.3g)

^{1}H NMR (300MHz, $CDCl_3$) 4.95 (M, 1H), 4.85 (M, 1H), 3.7 (M, 4H), 2.75 (M, 2H), 2.5 (M, 4H), 2.1 (M, 1H), 1.95 (M, 1H), 1.75 (S, 3H), 1.6 (M, 4H), 1.2 (S, 3H)

Example 12

4-Isoprenyl-1-methyl-2-(4-oxy-morpholin-4-yl)-cyclohexanol

4-Isoprenyl-1-methyl-2-morpholin-4-yl-cyclohexanol (17.7g, 0.074 moles) was dissolved in ethanol (100ml) and 35% hydrogen peroxide (37ml, 0.325moles) was added. Heated with stirring at 50° for 6 hours. 5% palladium on carbon (100mg) was added in order to decompose the excess peroxide. Stirred at room temperature for 3 hours. (Peroxide test papers gave a negative result.)
Filtered through a pad of HiFlo to remove the palladium on carbon and the solvent was evaporated under reduced pressure to give the product as a yellow oil (22.2g).

^{1}H NMR (300MHz, $CDCl_3$) 5.5 (M, 1H), 4.85 (M, 1H), 4.5 (M, 2H), 3.7 (M, 4H), 3.4 (M, 3H), 2.95 (M, 1H), 2.65 (M, 1H), 2.25 (M, 1H), 2.0 (M, 1H), 1.85 (M, 1H), 1.75 (M, 1H), 1.75 (S, 3H), 1.55 (M, 1H), 1.55 (S, 3H)

Example 13

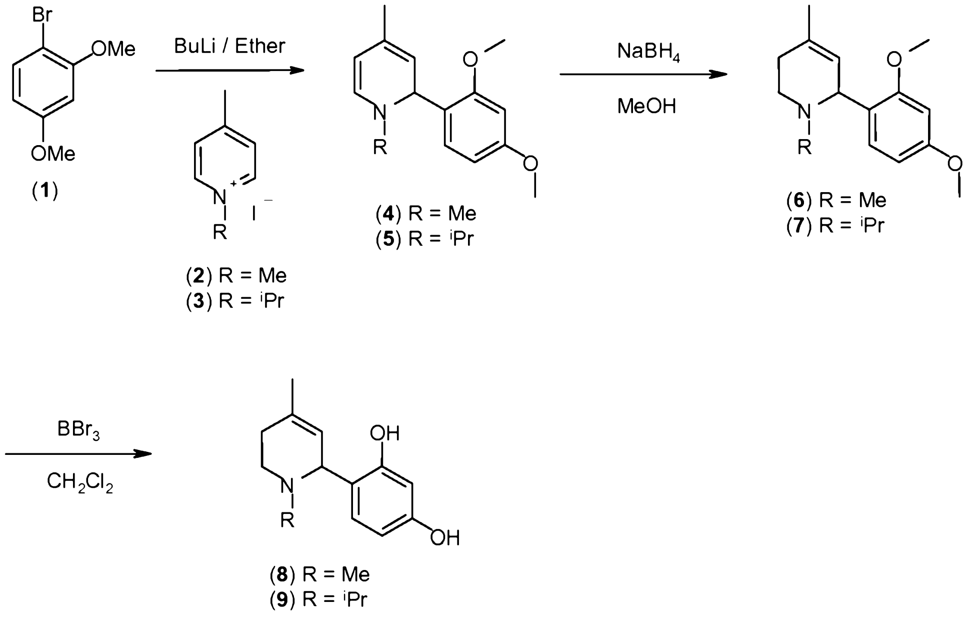
4R-Isoprenyl-1-methylcyclohex-2-enol

4-Isoprenyl-1-methyl-2-morpholin-4-yl-cyclohexanol (4.6g, 0.018

moles) was dissolved in toluene (80ml) and silica (1.1g) was added. The reaction mixture was heated to reflux with stirring. Water generated in the reaction was removed using Dean and Stark apparatus. After refluxing overnight, the silica was removed by filtration and the filtrate evaporated under reduced pressure to give a brown oil
(4.0g). Dissolved in dichloromethane and washed with 2M hydrochloric acid. Washed with water and dried over anhydrous magnesium sulphate. The solvent was removed by evaporation under reduced pressure to give the product as a brown oil
(1.3g).

^{1}H NMR (300MHz, $CDCl_3$) 5.7 (M, 2H), 4.8 (M, 2H), 2.7 (M, 1H), 1.8 (M, 2H), 1.75 (S, 3H), 1.65 (M, 2H), 1.3 (S, 3H)

Experimental details for Synthesis of Tetrahydropyridines



Scheme 1

Example 14

Preparation of 2-(2,4-Dimethoxyphenyl)-1,4-dimethyl-1,2-dihydropyridine.

To a stirred solution of 2,4-dimethoxybromobenzene (**1**) (0.5g, 2.3mmol) in diethyl ether (10ml) cooled at -78^0C under nitrogen was added a solution of n-butyl lithium (1.0ml, 2.5mmol of 2.5M solution in hexane) drop wise. The mixture was stirred at -78^oC for 2 hours and then 1,4-dimethyl pyridinium iodide (**2**) (0.54g, 2.5mmol) was added as a solid. The resultant mixture was allowed to warm to room temperature and stirred at room temperature for 18 hours. The mixture was diluted with water (20ml) and extracted with diethyl ether (2 x 15ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to yield 2-(2,4-dimethoxyphenyl)-1,4-dimethyl-1,2-dihydropyridine (**4**) (0.5g, 93%) as a brown oil, ^{1}H NMR

$CDCl_3$??1.7 (s, 3H), 2.7 (s, 3H), 3.8(s, 6H), 4.45 (dd, 1H, J = 2,7) 4.85 (m, 1H), 5.4 (d, 1H, J = 4), 6.05 (d, 1H, J = 7), 6.45 (d, 1H, J = 3), 6.55 (m, 1H), 7.5 (d, 1H, J = 9).

By proceeding in a similar manner starting from 2,4-dimethoxybromobenzene (**1**) and 1- isopropyl-4-methyl pyridinium iodide (**3**), 2-(2,4-dimethoxyphenyl)-1-isopropyl-4-methyl-1,2-dihydropyidine (**5**) was prepared, ^{1}H NMR $CDCl_3$? (d, 6H J = 7), 1.7 (s, 3H), 3.15 (m, 1H), 3.7 (s, 6H), 4.5 (d, 1H J = 8), 4.8 (m,1H), 5.5(5, 1H J = 5), 6.3 (d, 1H J = 7), 6.45 (d, 1H J = 2), 6.55 (m, 1H), 7.55 (d, 1H J = 8).

Example 15

Preparation of 6-(2,4-Dimethoxyphenyl)-1,4-dimethyl-1,2,3,6-tetrahydro-pyridine (6).

To a stirred solution of 2-(2,4-dimethoxyphenyl)-1,4-dimethyl-1,2-dihydropyridine(**4**) (0.48g, 2.06mmol) in methanol (5ml) at room temperature was added sodium borohydride (98mg, 2.51mmol), gas evolution commenced immediately, the resulting mixture was stirred for 3 hours. At this time the solvent was evaporated and the residue suspended in water (5ml) and extracted with ethyl acetate (2 x 10ml). The organic extract was then extracted with 2M hydrochloric acid (2 x 15ml). The aqueous layer was basified with 2M sodium hydroxide and extracted with ethyl acetate (2 x 20ml), the organic extract was dried over anhydrous magnesium sulphate, filtered and evaporated to yield 6-(2,4-dimethoxyphenyl)-1,4-dimethyl-1,2,3,6-tetrahydropyridine (**6**) (350mg, 73%) as a yellow oil, ^{1}H NMR $CDCl_3$ δ?1.55 (s, 3H), 1.9 (m, 1H), 2.2 (s, 3H), 2.5(m, 2H), 2.95 (m, 1H), 3.8 (s, 6H), 4.1 (m, 1H), 5.2 (m, 1H), 6.5 (m, 2H), 7.3 (d, 1H J = 4).

By proceeding in a similar manner starting from 2-(2,4-dimethoxyphenyl)-1-isopropyl-4-methyl-1,2-dihydropyidine (**5**), 6-(2,4-dimethoxyphenyl)-1-

isopropyl-4-methyl-1,2,3,6-tetrahydropyridine (**7**) was prepared, ^{1}H NMR $CDCl_3$ δ 0.95 (d, 3H *J* = 6), 1.05 (d, 3H *J* = 6), 1.7 (s, 3H), 1.9 (m, 1H), 2.5 (m, 1H), 2.85 (m, 1H), 3.0 (m,1H), 3.8 (s, 6H), 4.6 (s, 1H), 5.2 (s, 1 H), 6.45 (d, 1H *J* = 3), 6.5 (dd, 1H *J* =3,8), 7.4 (d, 1H *J* = 8).

Example 16

Preparation 4-(1,4-Dimethyl-1,2,5,6-tetrahydropyridin-2-yl)-benzene-1,3-diol (8)

To a stirred solution of 6-(2,4-dimethoxyphenyl)-1,4-dimethyl-1,2,3,6-tetrahydro-pyridine (**6**) (300mg, 1.27mmol) in dichloromethane (20ml) cooled at 0^0C under nitrogen was added boron tribromide (3.1ml, 3.18mmol of 1.0M solution in dichloromethane), the resultant dark solution was allowed to warm to room temperature and stirred for 1 hour. The solution was poured onto ice and basified with sodium bicarbonate. The layers were separated and the aqueous layer was extracted with dichloromethane (20ml), the combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated to a gum (200mg). The material was purified on a 10g silica cartridge eluting with methanol/dichloromethane/ammonia (7:92:1) to yield 4-(1,4-dimethyl-1,2,5,6-tetrahydropyridin-2-yl)-benzene-1,3-diol (**8**) (93mg, 35%) as a gum, ^{1}H NMR D6-acetone ??1.67 (s, 3H), 1.97 (m,1H), 2.3 (s, 3H), 2.42 (m, 1H), 2.74 (m, 1H), 3.08 (m, 1H), 3.74 (s, 1H), 5.15 (s, 1H), 6.2 (d, 1H *J* = 2), 6.27 (dd, 1H *J* =2,8), 6.82 (d, 1H *J* = 8), 9.4 (bs, 2H).

By proceeding in a similar manner starting from 6-(2,4-dimethoxyphenyl)-1-isopropyl-4-methyl-1,2,3,6-tetrahydropyridine (**7**), 4-(1-isopropyl-4-methyl-1,2,5,6-tetra-hydropyridin-2-yl)-benzene-1,3-diol (**9**) was prepared, NMR D6-acetone δ 0.81 (d, 3H *J* = 7), 0.98 (d, 3H *J* = 7), 1.52 (s, 3H), 1.84 (m, 1H), 2.15(m, 1H), 2.29(m, 1H), 2.94 (m, 2H), 4.09 (s, 1H), 4.97 (s, 1H), 6.05 (d, 1H *J* = 3), 6.11(dd, *J* = 3,8), 6.68 (d, *J* = 8), 9.6 (bs, 2H).

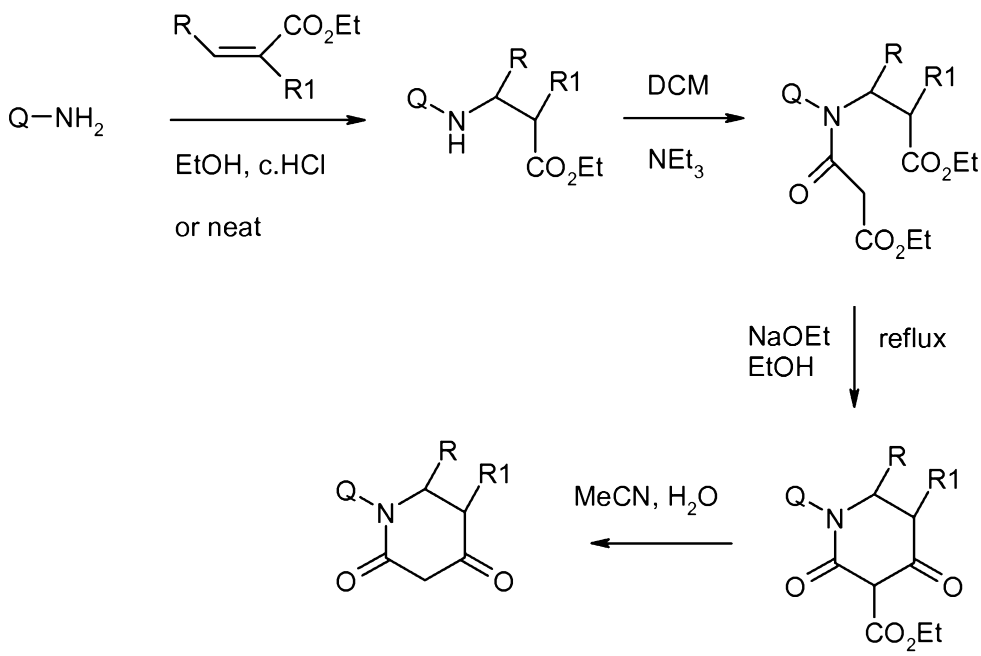
Example 17

Preparation of 1- Isopropyl-4-methyl pyridinium iodide (3).

To a stirred solution of 4-picoline (2.5g, 26.8mmol) in acetonitrile (50ml) was added isopropyl iodide (9.1g, 53.6mmol) drop wise, the resultant mixture was heated at 90°C for 24 hours. After cooling the solvent was evaporated to give a red solid which on trituration with ethyl acetate yielded 1- isopropyl-4-methyl pyridinium iodide (6.01g, 85%) as a cream solid, ^{1}H NMR D6-DMSO δ?1.6 (d, 6H, *J* = 7), 2.6 (s, 3H), 4.95 (m, 1H), 8.0 (d, 2H *J* = 6), 9.05 (d, 2H *J* = 6).

Preparation of 1-Aryl-piperidine2,4-diones

Scheme



Example 18

Preparation of Ethyl 3-(3-Chlorophenylamino)propionate

3-Chloroaniline (3.8g, 0.03moles) was dissolved in ethanol (5ml) and ethyl acrylate (3.3g, 0.033moles) was added in ethanol (5ml). Concentrated hydrochloric acid (1ml) was added and the reaction mixture was heated at reflux for 48 hours. Evaporated to a low bulk and dissolved the residue in dichloromethane and water. Basified to pH 9 with aqueous ammonia and separated. Evaporated off the dichloromethane under reduced pressure to give the crude product as a yellow oil (5.4g) Purified using a silica column eluted with isohexane:ethyl acetate 9:1 to give the required product (3.5g, 51%) as a colourless oil.

^{1}H NMR $CDCl_3$ δ 1.30 (t, 3H, J = 6.5Hz), 2.65 (t, 2H, J = 6Hz), 3.45 (q, 2H J = 6Hz), 4.20 (q, 2H, J = 6.5Hz), 6.50 (m, 1H), 6.60 (m, 1H), 6.70 (m, 1H), 7.10 (m, 1H)

Example 19

Preparation of *N*-(3-Chlorophenyl)-*N*-(2-ethoxycarbonyl-ethyl)-malonamic acid ethyl ester

Ethyl 3-(3-Chlorophenylamino)propionate (3.5g, 0.0154moles) was dissolved in dichloromethane (40ml) and ethyl malonyl chloride (2.55g, 0.017moles) was added dropwise in dichloromethane (10ml) with stirring and cooling in order to keep the reaction temperature below 20°. Triethylamine (1.72g, 0.017moles) was added dropwise in dichloromethane (10ml). The reaction temperature was kept below 20° by ice bath cooling. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. Washed with 2M hydrochloric acid, water and sodium bicarbonate solution. Dried over anhydrous magnesium sulphate, filtered and evaporated to give the required product as an orange oil. (4.5g, 86%)

^{1}H NMR $CDCl_3$ δ 1.25 (m, 6H), 2.65 (t, 2H, J = 7Hz), 3.20 (s, 2H), 4.10 (m, 4H), 7.15 (m, 1H), 7.30 (m, 1H), 7.40 (m, 2H)

Example 20

Preparation of Ethyl 1-(3-chlorophenyl)piperidine-2,4-dione carboxylate

Sodium (0.7g, 0.029moles) was dissolved in ethanol (90ml) and *N*-(3-Chlorophenyl)-*N*-(2-ethoxycarbonyl-ethyl)-malonamic acid ethyl ester (4.5g, 0.0132moles) was added in ethanol (30ml). The reaction mixture was heated at reflux overnight. The ethanol was evaporated off and the residue dissolved in water. Washed with diethyl ether and acidified to pH2 with concentrated sulphuric acid. Extracted with dichloromethane and the combined dichloromethane extracts were combined. Washed with water and dried over anhydrous magnesium sulphate. Filtered and evaporated to give the product as an orange oil (2.8g, 72%)

^{1}H NMR $CDCl_3$ δ 1.40 (t, 3H, J = 5Hz), 2.85 (t, 2H, J = 6Hz), 3.85 (t, 2H J = 6Hz), 4.40 (q, 2H, J = 5Hz), 7.20 (m, 2H), 7.30 (m, 1H), 7.35 (m, 1H)

Example 21

Preparation of 1-(3-Chlorophenyl)piperidine-2,4-dione

Ethyl 1-(3-chlorophenyl)piperidine-2,4-dione carboxylate (2.8g, 0.0095moles) was dissolved in acetonitrile (100ml)/water (10ml) and refluxed for 2 hours. Evaporated to a low bulk and dissolved in dichloromethane. Washed with water and dried over anhydrous magnesium sulphate. Filtered and evaporated to give the product as an orange oil (2.2g). Purified using a silica column eluted with dichloromethane:ethyl acetate 9:1 to give the required product as a pale yellow gum (1.2g, 59%)

^{1}H NMR $CDCl_3$ δ 2.80 (t, 2H, J = 6Hz), 3.55 (s, 2H), 4.05 (t, 2H, J = 6Hz), 7.20 (m, 1H), 7.30 (m, 1H), 7.35 (m, 1H), 7.40 (m, 1H)

Also prepared in a similar manner were

1-Phenylpiperidine-2,4-dione

^{1}H NMR $CDCl_3$, ppm) δ 2.80 (t, 2H, J = 6Hz), 3.6 (s, 2H), 4.05 (t, 2H, J = 6Hz), 7.30 (m, 3H), 7.45 (m, 2H)

1-(3-Methylphenyl)piperidine-2,4-dione

^{1}H NMR ($CDCl_3$, ppm) δ 2.40 (s, 3H), 2.80(t, 2H, J = 6.5Hz), 3.6 (s, 2H), 4.05 (t, 2H, J = 6.5Hz), 7.30 (m, 3H), 7.45 (m, 2H)

1-(4-Fluorophenyl)piperidine-2,4-dione

^{1}H NMR $CDCl_3$, ppm) δ 2.80 (t, 2H, J = 6Hz), 3.55 (s, 2H), 4.0 (t, 2H, J = 6Hz), 7.1 (m, 2H), 7.25 (m, 2H)

1-(3,5-Difluorophenyl)piperidine-2,4-dione

^{1}H NMR ($CDCl_3$, ppm) δ 2.80 (t, 2H, J = 6Hz), 3.58 (s, 2H), 4.04 (t, 2H, J = 6Hz), 6.68-6.83 (m, 1H), 6.84-6.99 (m, 2H).

1-(3,5-Dichlorophenyl)piperidine-2,4-dione

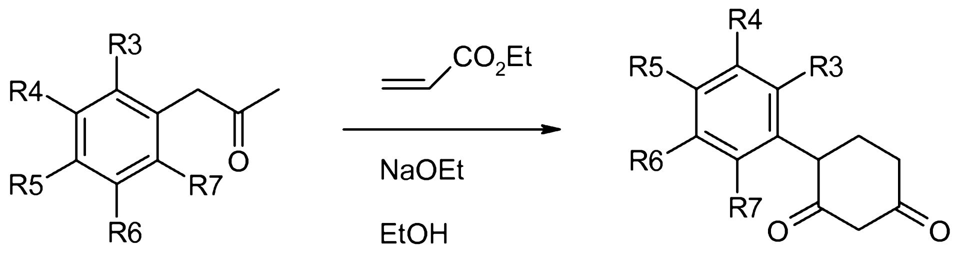
^{1}H NMR ($CDCl_3$, ppm) δ 2.80 (t, 2H, J = 6Hz), 3.58 (s, 2H), 4.02 (t, 2H, J = 6Hz), 7.20-7.36 (m, 3H).

1-(4-Methylpyrid-2-yl)piperidine-2,4-dione

^{1}H NMR ($CDCl_3$, ppm) δ 2.41 (s, 3H), 2.75 (t, 2H, J = 6Hz), 3.62 (s, 2H), 4.44 (t, 2H, J = 6Hz), 6.94-7.02 (m, 1H), 7.72-7.79 (m, 1H), 8.25-8.36 (m, 1H).

Preparation of Cyclohexane-1,3-diones

Scheme



Example 22

Preparation of 4-(4-Fluorophenyl)cyclohexane-1,3-dione

Sodium (0.3g, 0.013moles) was dissolved in ethanol (50ml) and 4-Fluorophenylacetone (2.0g, 0.013moles) was added in ethanol (10ml). Ethyl acrylate (1.3g, 0.013moles) was and the reaction mixture was heated at reflux overnight. The reaction mixture was allowed to cool and evaporated under reduced pressure to give a brown gum. Dissolved in water and washed with diethyl ether. The aqueous layer was acidified to pH2 with conc. Hydrochloric acid and extracted with dichloromethane. The extracts were combined and washed with water. Dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated to give an orange oil. (1.7g) This was purified using a silica column eluted with dichloromethane:ethyl acetate 8:2 and then dichloromethane:ethyl acetate 2:1 to give a colorless gum. (0.428g) This was triturated with diethyl ether/isohexane to give 4-(4-Fluorophenyl)cyclohexane-1,3-dione (0.28g) as a white solid.

^{1}H NMR (CD_3OD, ppm) δ 2.1 (m, 1H), 2.3 (m, 1H), 2.4 (m, 2H), 3.7 (m, 1H), 4.9 (s, 2H), 7.1 (m, 2H), 7.2 (m, 2H).

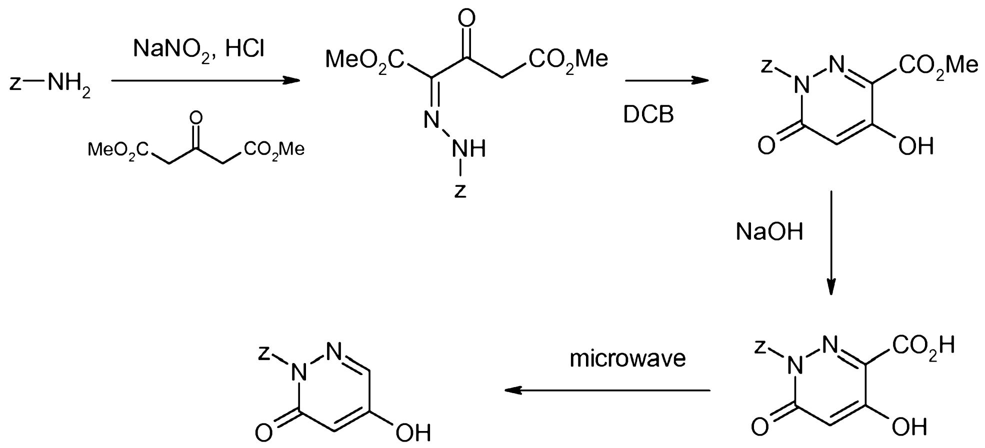
Also prepared in a similar manner

4-Phenylcyclohexane-1,3-dione

^{1}H NMR (CD_3OD, ppm) δ 2.15 (m, 1H), 2.3 (m, 3H), 3.7 (m, 1H), 4.9 (s, 2H), 7.2 (m, 3H), 7.3 (m, 2H).

Preparation of Pyridazin-3-ones

Scheme



Example 23

3-Oxo-2-phenylhydrazono)pentanedioic acid dimethylester

To a mixture of aniline (1.86g, 20mmol) in concentrated hydrochloric acid (10ml) and water (20ml) at a temperature below 5°C was added a solution of sodium nitrite (1.38g, 20mmol) in water (15ml) drop wise. The resultant mixture was stirred for 15 minutes and then it was poured into a solution of dimethylacetonedicarboxylate (3.48g, 20mmol) and sodium acetate (12g, 0.146mol) in ethanol (12ml) and water (40ml) causing an immediate precipitation. The suspension was stirred for 1 hour and then extracted with ethyl acetate (3 x 125ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to yield 3-oxo-2-phenylhydrazono)pentanedioic acid dimethyl ester as a red oil (5.58g, quantitative) consisting of a mixture of *E* and Z isomers about the hydrazone

^{1}H NMR $CDCl_3$ δ □̃□̃□̃ (singlets, 8H), 7.1-7.5 (m, 5H), 12.8 (s, 1H).

Example 24

Methyl 4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate

3-Oxo-2-phenylhydrazono)pentanedioic acid dimethyl ester (12.5mmol) was dissolved in dichlorobenzene and heated at reflux for 24 hours and then allowed to cool to room temperature. The solvent was evaporated and the residue triturated with ether to give methyl 4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate a beige solid (2.4g, 78%)

^{1}H NMR $CDCl_3$ δ 4.0 (s, 3H), 6.4 (s, 1H), 7.4-7.6 (m, 5H), 10.3 (s, 1H).

Example 25

4-Hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid

Methyl 4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate (0.8g, 3.24mmol) was suspended in sodium hydroxide solution (20ml of 2.0M) and heated at reflux for 1 hour. The mixture was allowed to cool to room temperature, acidified with 2M hydrochloric acid and extracted with ethyl acetate (3 x 15ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to yield 4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid as a yellow solid (0.6g, 80%)

^{1}H NMR $CDCl_3$ δ 6.3 (s, 1H), 7.35-7.7 (m, 5H).

Example 26

5-Hydroxy-2-phenyl-2H-pyridazin-3-one

4-Hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid (400mg, 1.72mmol) was heated at 270°C in a microwave for 3 minutes. The resultant black mixture was extracted into saturated sodium bicarbonate (15ml). The sodium bicarbonate solution was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 15ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to a crude solid (300mg). This was purified on a 10g SPE cartridge eluting with dichloromethane/ ethyl acetate (80:20 to 60:40) to yield 5-hydroxy-2-phenyl-2H-pyridazin-3-one (60mg) as a beige solid

^{1}H NMR D6 DMSO δ 6.05 (d, 1H, J = 2.7 Hz), 7.4-7.6 (m, 5H), 7.85 (d, 1H, J = 2.7 Hz), 11.6 (s, 1H).

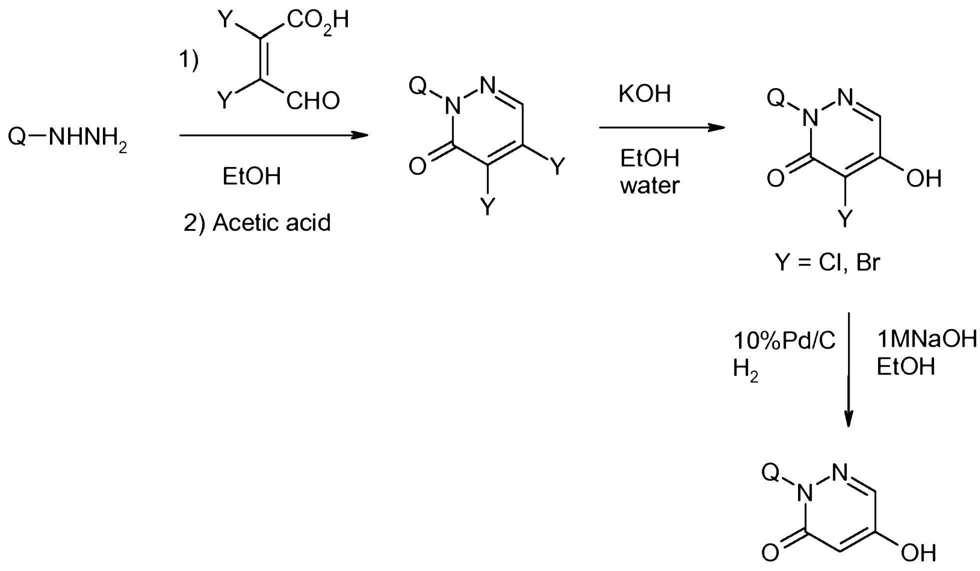
The following compounds are also active in the method of the present invention:

2-(4-Chlorophenyl)-5-hydroxy-2H-pyridazin-3-one

5-Hydroxy-2-(3-trifluoromethylphenyl)-2H-pyridazin-3-one

The following synthesis is described in J. Het. Chem. 1989, 26, 169-176

Scheme



Example 27

2-(3,5-Difluorophenyl)-5-hydroxypyridazin-3-one

4-Bromo-2-(3,5-difluorophenyl)-5-hydroxypyridazin-3-one (0.6g, 1.98mmoles) was dissolved in ethanol (50ml) and 1M sodium hydroxide (4ml) was added. 10% Palladium on carbon (0.15g) was added and the flask was placed under an atmosphere of hydrogen (balloon) with stirring. The reaction mixture was stirred overnight at room temperature. Filtered off the catalyst using Hyflo and evaporated to dryness. Added 2M hydrochloric acid and extracted into ethyl acetate. Washed with water and dried over anhydrous magnesium sulphate. Filtered and evaporated the filtrate to give a white solid. Triturated with diethyl ether to give the product as a white solid. (0.32g, 72%)

^{1}H NMR DMSOd6 δ 12.2 (br s, 1H), 7.9 (d, 1H, J = 3Hz), 7.3 (m, 5H), 6.1 (d, 1H, J = 3Hz)

Also prepared in a similar manner

2-(2,5-Difluorophenyl)-5-hydroxypyridazin-3-one

^{1}H NMR DMSOd6 δ 11.8 (br s, 1H), 7.85 (d, 1H, J = 2.5Hz), 7.4 (m, 4H), 6.1 (d, 1H, J = 2.5Hz)

Example 28

4-Bromo-2-(3,5-difluorophenyl)-5-hydroxypyridazin-3-one

4,5-Dibromo-2-(3,5-difluorophenyl)pyridazin-3-one (1.5g, 0.0041moles) was suspended in ethanol (50ml) and potassium hydroxide (0.8g, 0.0123moles) was added in water (8ml). Refluxed for 4 hours with stirring. Evaporated to a low bulk and diluted with water. Acidified to pH2 with conc. hydrochloric acid and extracted with ethyl acetate. Washed with water and dried with anhydrous magnesium sulphate. Filtered and evaporated the filtrate to give an orange solid. Triturated with diethyl ether and dried in a desiccator to give the product as a cream solid. (0.7g, 56%)

^{1}H NMR DMSOd6 δ 12.5 (br s, 1H), 7.9 (s, 1H), 7.35 (m, 3H) ; ^{19}F NMR δ 110

Also prepared in a similar manner

4-Bromo-2-(2,5-difluorophenyl)-5-hydroxypyridazin-3-one

^{1}H NMR DMSOd6 δ 7.9 (s, 1H), 7.5 (m, 3H) ; ^{19}F NMR δ 117, 126

4-Bromo-2-(2,5-dichlorophenyl)-5-hydroxypyridazin-3-one

^{1}H NMR DMSOd6 δ 7.9 (s, 1H), 7.8 (d, 1H, J = 2.5Hz), 7.7 (d, 1H, J = 8.5Hz), 7.6 (d,d, 1H, J = 2.5, 8.5Hz)

Example 29

4,5-Dibromo-2-(3,5-difluorophenyl)pyridazin-3-one

Mucobromic acid (2.8g, 0.011moles) was dissolved in ethanol (75ml) and 3,5-difluorophenyl hydrazine hydrochloride (1.8g, 0.01moles) was added. After 30 minutes, triethylamine (1.4ml, 0.01moles) was added. The reaction mixture was stirred at room temperature for 3 hours. Evaporated to a low bulk and the residue was suspended in glacial acetic acid (80ml). Refluxed with stirring overnight to give a brown solution. Evaporated to dryness and triturated with methanol to give the required product as a pale brown solid. (3.4g, 93%)

^{1}H NMR DMSOd6 δ 8.3 (s, 1H), 7.4 (m, 3H); ^{19}F NMR δ 109

Also prepared in a similar manner

4,5-Dibromo-2-(2,5-dichlorophenyl)pyridazin-3-one

^{1}H NMR DMSOd6 δ 7.9 (s, 1H), 7.45 (m, 1H), 7.4 (m, 2H)

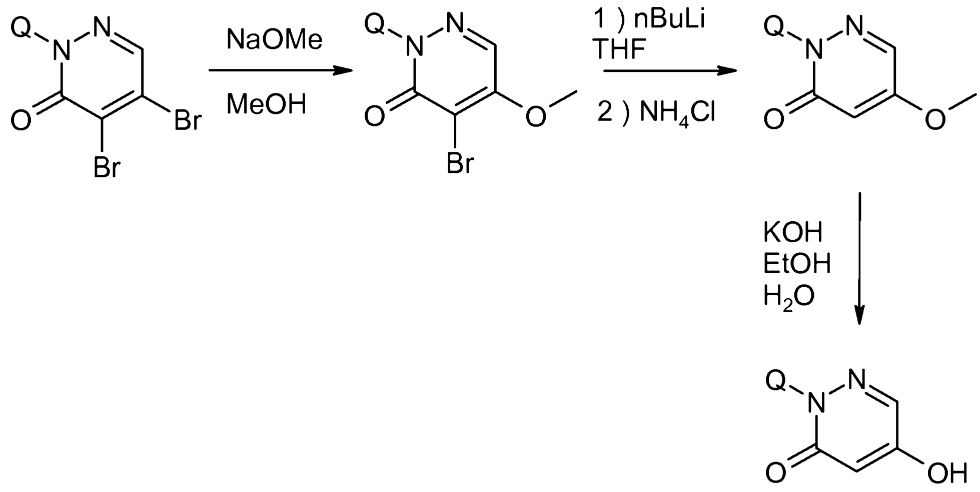
4,5-Dibromo-2-(3,5-dichlorophenyl)pyridazin-3-one

^{1}H NMR DMSOd6 δ 8.35 (s, 1H), 7.8 (m, 1H), 7.7(m,2H)

4,5-Dibromo-2-(2,5-difluorophenyl)pyridazin-3-one

^{1}H NMR DMSOd6 δ 8.35 (s, 1H), 7.5 (m, 3H)

Scheme



Example 30

2-(3,5-Dichlorophenyl)-5-hydroxypyridazin-3-one

2-(3,5-Dichlorophenyl)-5-methoxypyridazin-3-one (0.25g, 0.92mmoles) was suspended in ethanol (40ml) and potassium hydroxide (0.12g, 1.8mmoles) was added in water (5ml). Refluxed overnight with stirring to give a yellow solution. Evaporated to dryness and added 2M hydrochloric acid. Extracted with ethyl acetate (x2) and washed with water and dried over anhydrous magnesium sulphate. Filtered and evaporated to give a yellow solid. Triturated with dichloromethane to give a pale yellow solid. (0.1g, 42%)

^{1}H NMR DMSOd6 δ 7.75 (d, 1H, J = 3Hz), 7.6 (m, 2H), 7.5 (m, 1H), 6.25 (d, 1H, J = 3Hz)

Also prepared in a similar manner

2-(2,5-Dichlorophenyl)-5-hydroxypyridazin-3-one

^{1}H NMR DMSOd6 δ 10.9 (br s, 1H), 7.7 (d, 1H, J = 3Hz), 7.4 (m, 1H), 7.35 (m, 1H), 7.3 (m, 1H), 6.2 (d, 1H, J = 3Hz)

Example 31

2-(3,5-Dichlorophenyl)-5-methoxypyridazin-3-one

4-Bromo-2-(3,5-dichlorophenyl)-5-methoxypyridazin-3-one (2.5g,0.0071moles) was dissolved in THF (250ml) and cooled to –50° under nitrogen. 1.6M n-Butyl lithium (6.7ml, 0.011moles) was added dropwise with stirring. Allowed to warm to –20° over 1 hour. Added 1 equivalent of 1.6M n-Butyl lithium (4.4ml, 0.0071moles) dropwise. Stirred at –20° for 30minutes. Poured into ammonium chloride solution and stirred for 15minutes. Extracted with EtOAc (x2) and washed with water. Dried over anhydrous magnesium sulphate, filtered and evaporated to give a brown solid. (3.0g) Purified using MPLC (silica, eluted with dichloromethane: EtOAc 9:1) to give a yellow solid. (0.25g, 13%) Not pure used directly in the next reaction.

^{1}H NMR DMSOd6 δ 7.7 (d, 1H, J = 3Hz), 7.6 (d, 2H, J = 2Hz), 7.5 (d, 1H, J = 2Hz), 6.2 (d, 1H, J = 3Hz)

Also prepared in a similar manner

2-(2,5-Dichlorophenyl)-5-methoxypyridazin-3-one

^1H NMR DMSOd6 δ 7.95 (d, 1H, J = 3Hz), 7.75 (d, 1H, J = 2.5Hz), 7.7 (d, 1H, J = 8Hz), 7.6 (d, d, 1H, J = 2.5, 8Hz), 6.45 (d, 1H, J = 3Hz)

Example 32

4-Bromo-2-(3,5-dichlorophenyl)-5-methoxypyridazin-3-one

Sodium (0.28g, 0.012moles) was dissolved in methanol (100ml) and a suspension of 4,5-Dibromo-2-(3,5-dichlorophenyl)pyridazin-3-one (4.0g, 0.01moles) in methanol (60ml) was added. Refluxed overnight. Evaporated to dryness and added water. Filtered off the solid and dried in a dessicator. Triturated with ether and dried in a dessicator. (3.1g, 89%)

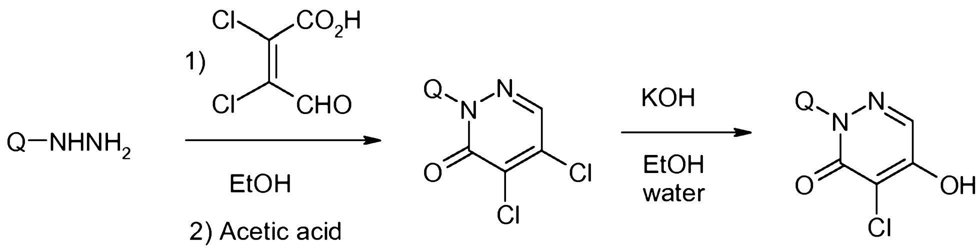
^1H NMR DMSOd6 δ 8.35 (s, 1H), 7.75 (m, 1H), 7.7 (m, 2H), 4.15 (s, 3H)

Also prepared in a similar manner

4-Bromo-2-(2,5-dichlorophenyl)-5-methoxypyridazin-3-one

^1H NMR DMSOd6 δ 8.35 (s, 1H), 7.8 (d, 1H, J = 2.5Hz), 7.7 (d, 1H, J = 8.5Hz), 7.65 (d of d, 1H, J = 2.5, 8Hz), 4.15 (s, 3H)

Scheme



Example 33

4-Chloro-2-phenyl-5-hydroxypyridazin-3-one

4,5-Dichloro-2-phenylpyridazin-3-one (2.4g, 0.01moles) was suspended in ethanol (50ml) and potassium hydroxide (2.0g, 0.03moles) was added in water (20ml). Refluxed for 4 hours. Evaporated to dryness and added water. Acidified to pH2 with c. hydrochloric acid. Filtered off the product as a buff solid and dried in a desiccator. (2.1g) Took 0.5g and dissolved in methanol, filtered and evaporated. Triturated with ether to give the product as a cream solid. (0.4g, 76%)

^{1}H NMR DMSOd6 δ 7.9, (s, 1H), 7.5 (m, 4H), 7.4 (m, 1H)

Example 34

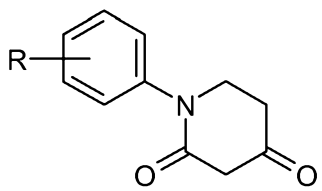
4,5-Dichloro-2-phenylpyridazin-3-one

Mucochloric acid (9.3g, 0.055moles) was dissolved in ethanol (60ml) and phenyl hydrazine (5.4g, 0.05moles) was added. The reaction mixture was stirred at room temperature for 2 hours. Evaporated to a low bulk and the residue was suspended in glacial acetic acid (60ml). Refluxed with stirring for 3hours.

Evaporated to dryness and triturated with methanol to give the required product as a pale brown solid. (11.0g, 91%)

^{1}H NMR DMSOd6 δ 7.95 (s, 1H), 7.5 (m, 4H), 7.4 (m, 1H)

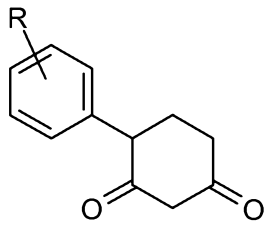
The following compounds have also been found to be effective in treating glaucoma or ocular hypertension according to the method of the present invention.



R = H; 2-CO_2H, 5-Cl

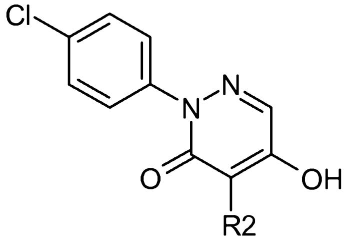
H Nishino et al. Tetrahedron, 2005, 11107-11124
H Nishino et al. Heterocyclic Comm. 2005, 11, 379-384
Bekhli et al. Chem. Heterocyclic Compds. Engl. Trans. 1970, 6, 814

Cyclohexane-1,3-diones



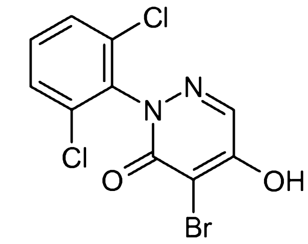
R = H, 4-OMe	See EP 291114 (R = H, 4-OMe), US 4546104, US 4795488 (R = 2-F)
	Bergmann et al. J. Am. Chem. Soc. 1953, 3226
R = 3,4-DiOMe	See Synthesis 1980, 394-397
R =4-Cl	See J. Med. Chem. 1981, 1006-1010

Pyridazin-3-ones

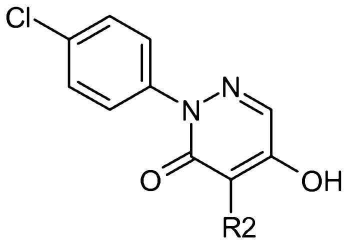


Nissan, EP 210647

R2 = H, Cl

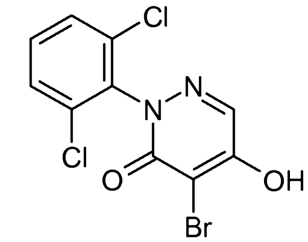


Pharmacia, WO2005007632

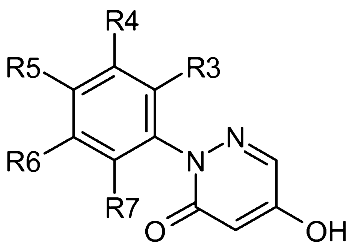


Nissan, EP 210647

R2 = H, Cl



Pharmacia, WO2005007632



i) R3, R4, R5, R6, R7 = H

ii) R3 = CF_3, R4-R7 = H

iii) R4 = CF_3, R3, R5-R7 = H

iv) R5 = Cl, R3, R4, R6, R7 = H

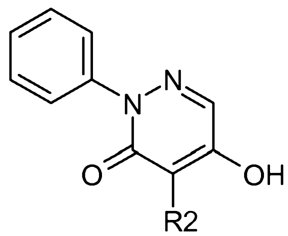
i) Maier et al. Helv. Chim. Acta. 1954, 37, 523

ii),iii),iv) J. Het. Chem. 1989, 26, 169-176; J. Het. Chem. 1990, 27, 471-477

i) R3, R4, R5, R6, R7 = H

iii) R4 = CF_3, R3, R5-R7 = H

ii) R4 = CF_3, R3, R5-R7 = H; iv) R5 = Cl, R3, R4, R6, R7 = H



R2 = OMe Chem. Pharm. Bull. 1971, 1635
1972, 747

R2 = SEt Collect. Czech. Chem. Comm. 1980, 45,
127

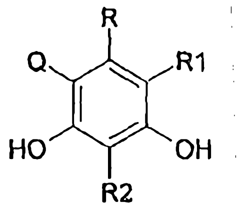
It is apparent to one of ordinary skill in the art that different pharmaceutical compositions may be prepared and used with substantially the same results. That is, other Abnormal Cannabidiols will effectively lower intraocular pressure in animals and are within the scope of the present invention. Also, the novel compounds of the present invention may be used in a method of providing neuroprotection to the eye of a mammal in a similar manner to the abnormal Cannabidiols of Published U.S. Patent Application 2005/0282912.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "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.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that the prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

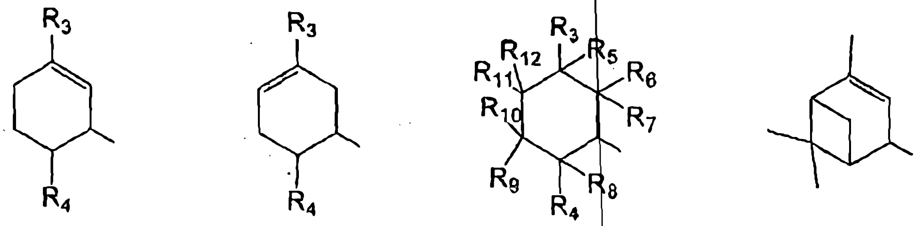
The claims defining the invention are as follows:

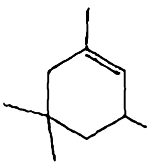
1. A compound for treating glaucoma or ocular hypertension having the formula II:



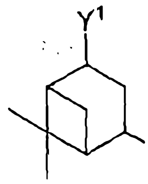
(II)

wherein Q is selected from the group consisting of:





and



wherein Y^1 is R^3 and R^5, or =O, or OH

R is a halogen;

R^1 is selected from the group consisting of H and halogen;

R^2 is independently selected from the group consisting of H, C_{1-5} alkyl, halogen, XC_{1-5} alkyl, C_{1-5} alkylOR^{13}, C_{1-5} alkylN(R^{13})$_2$, N(R^{13})$_2$, XC $_{1-5}$ alkylN(R^{13})$_2$ and XC $_{1-5}$ alkylOR^{13}; wherein X is O or S(O)$_n$; and n is 0 or an integer of from 1 to 2;

R^3 is selected from the group consisting of H, hydroxyl C_{1-5} alkyl, C_{1-5} alkylOR^{13} and C_{1-5} alkylN(R^{13})$_2$;

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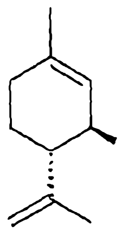
R^4 is selected from the group consisting of H, C_{1-5} alkenyl, C_{2-5} alkyl, C_{1-5} alkylOR^{13} and C_{1-5} alkyl$N(R^{13})_2$;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} are independently selected from the group consisting of H, C_{1-5} alkyl, C_{1-5} alkylOR^{13} and OR^{13}; and

R^{13} is selected from the group consisting of H, C_{1-5} alkyl and C_{3-8} cyclic alkyl.

2. The compound of claim 1, wherein R is selected from the group consisting of bromo and chloro and R^2 is selected from the group consisting of hydrogen, methyl and chloro.

3. The compound of claim 1 or claim 2, wherein Q is:

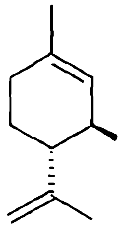


4. The compound of claim 1, wherein R is selected from the group consisting of bromo and chloro, R^1 is selected from the group consisting of hydrogen and chloro, R^2 is hydrogen, R^3 is methyl, R^5 R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are hydrogen and R^4 is isopropenyl.

5. The compound of claim 1, wherein the compound is 5-Chloro-4-(6-Isopropenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol.

6. The compound of claim 1, wherein the compound is 5-Chloro-4-cyclohexylbenzene-1,3-diol.

7. The compound of claim 1, wherein R is chloro, R_1 is halogen, R_2 is hydrogen, and wherein Q is:



8. The compound of claim 1, wherein said compound is 5-Chloro-4-(4,6,6-trimethyl-bicyclo [3.1.1]hept-3-en-2-yl)benzene-1,3-diol.

9. A pharmaceutical composition which is an ophthalmic solution comprising a therapeutically effective amount of a compound according to any one of claims 1 to 8.

10. A pharmaceutical product comprising a container adapted to dispense the contents in metered form, and an ophthalmic solution therein according to claim 9.

11. A method of treating glaucoma or ocular hypertension comprising applying to the eye of a subject in need thereof a sufficient amount of a compound according to any one of claims 1 to 8.

12. A method for treating glaucoma or intraocular pressure comprising applying to the eye of a subject in need thereof a sufficient amount of a combination of a compound according to any one of claims 1 to 8, and a drug selected from the group consisting of a β-blocker, an adrenergic agonist, a carbonic anhydrase inhibitor, a cholinergic agonist, a chlolinesterase inhibitor, a glutamate antagonist, a prostamide and a prostaglandin.

13. Use of a compound according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension.

14. Use of a compound according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of glaucoma or intraocular pressure, wherein the compound is intended for administration with a drug selected from the group consisting of a β-blocker, an adrenergic agonist, a carbonic anhydrase inhibitor, a cholinergic

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agonist, a cholinesterase inhibitor, a glutamate antagonist, a prostamide and a prostaglandin.

15. A compound as defined in claim 1, substantially as hereinbefore described with reference to the Examples.

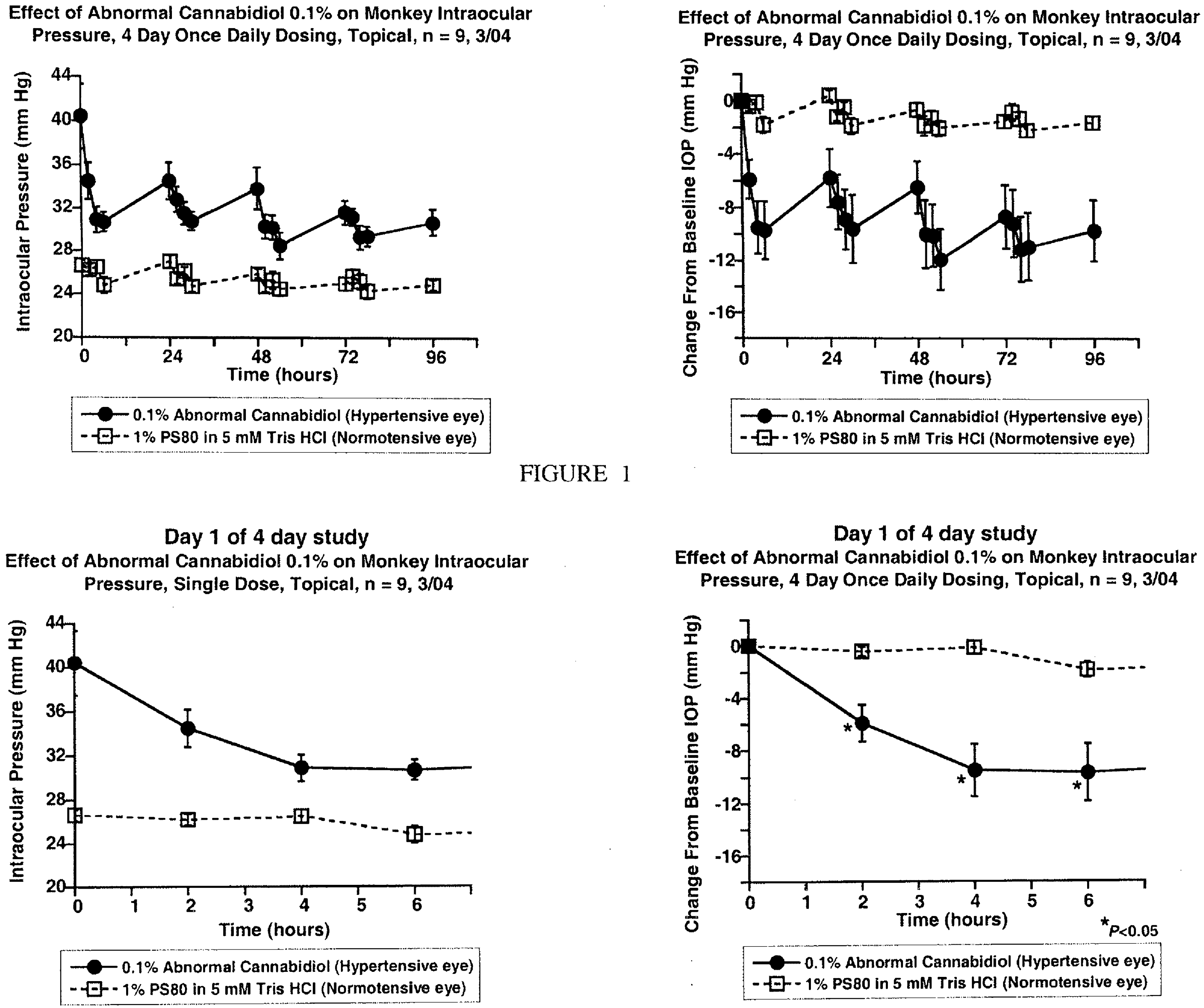

Effect of Abnormal Cannabidiol 0.1% on Monkey Intraocular Pressure, 4 Day Once Daily Dosing, Topical, n = 9, 3/04
Intraocular Pressure (mm Hg)
44
40
36
32
28
24
20
0
24
48
72
96
Time (hours)
0.1% Abnormal Cannabidiol (Hypertensive eye)
1% PS80 in 5 mM Tris HCl (Normotensive eye)
Effect of Abnormal Cannabidiol 0.1% on Monkey Intraocular Pressure, 4 Day Once Daily Dosing, Topical, n = 9, 3/04
Change From Baseline IOP (mm Hg)
0
-4
-8
-12
-16
0
24
48
72
96
Time (hours)
0.1% Abnormal Cannabidiol (Hypertensive eye)
1% PS80 in 5 mM Tris HCl (Normotensive eye)
Day 1 of 4 day study
Effect of Abnormal Cannabidiol 0.1% on Monkey Intraocular Pressure, Single Dose, Topical, n = 9, 3/04
Intraocular Pressure (mm Hg)
44
40
36
32
28
24
20
0
1
2
3
4
5
6
Time (hours)
0.1% Abnormal Cannabidiol (Hypertensive eye)
1% PS80 in 5 mM Tris HCl (Normotensive eye)
Day 1 of 4 day study
Effect of Abnormal Cannabidiol 0.1% on Monkey Intraocular Pressure, 4 Day Once Daily Dosing, Topical, n = 9, 3/04
Change From Baseline IOP (mm Hg)
0
-4
-8
-12
-16
0
1
2
3
4
5
6
Time (hours)
*P<0.05
0.1% Abnormal Cannabidiol (Hypertensive eye)
1% PS80 in 5 mM Tris HCl (Normotensive eye)

FIGURE 1

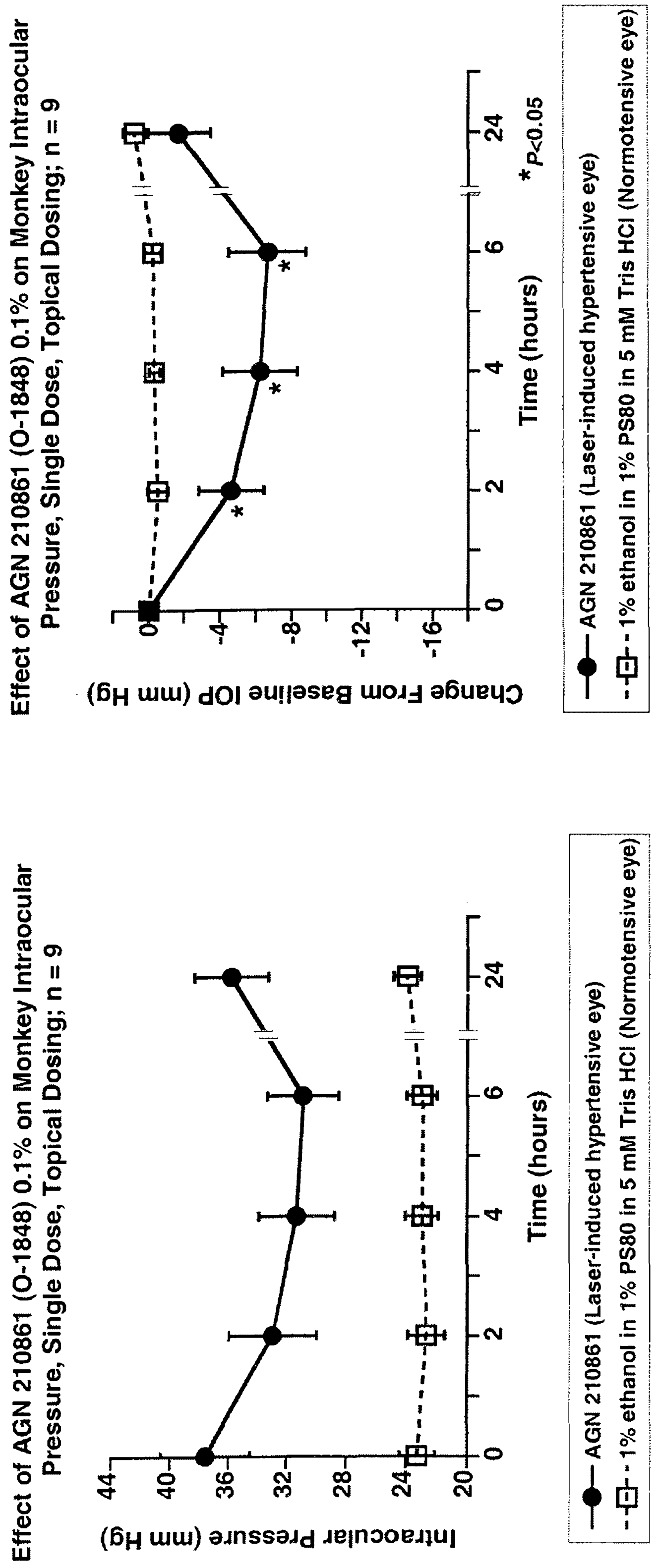
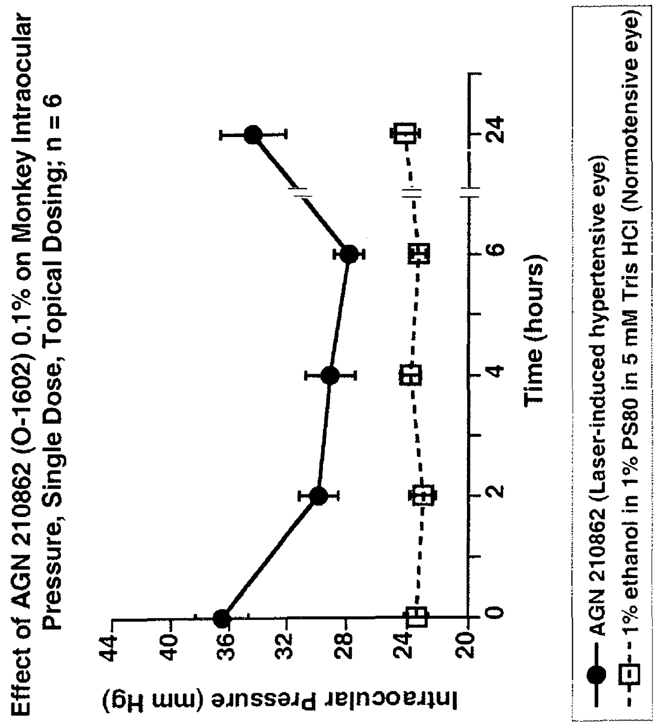

Effect of AGN 210861 (O-1848) 0.1% on Monkey Intraocular Pressure, Single Dose, Topical Dosing; n = 9
Change From Baseline IOP (mm Hg)
0
-4
-8
-12
-16
0
2
4
6
24
Time (hours)
*
*P<0.05
AGN 210861 (Laser-induced hypertensive eye)
1% ethanol in 1% PS80 in 5 mM Tris HCl (Normotensive eye)
Effect of AGN 210861 (O-1848) 0.1% on Monkey Intraocular Pressure, Single Dose, Topical Dosing; n = 9
Intraocular Pressure (mm Hg)
44
40
36
32
28
24
20
0
2
4
6
24
Time (hours)
AGN 210861 (Laser-induced hypertensive eye)
1% ethanol in 1% PS80 in 5 mM Tris HCl (Normotensive eye)

FIGURE 2


Effect of AGN 210862 (O-1602) 0.1% on Monkey Intraocular Pressure, Single Dose, Topical Dosing; n = 6
Intraocular Pressure (mm Hg)
44
40
36
32
28
24
20
0
2
4
6
24
Time (hours)
AGN 210862 (Laser-induced hypertensive eye)
1% ethanol in 1% PS80 in 5 mM Tris HCl (Normotensive eye)

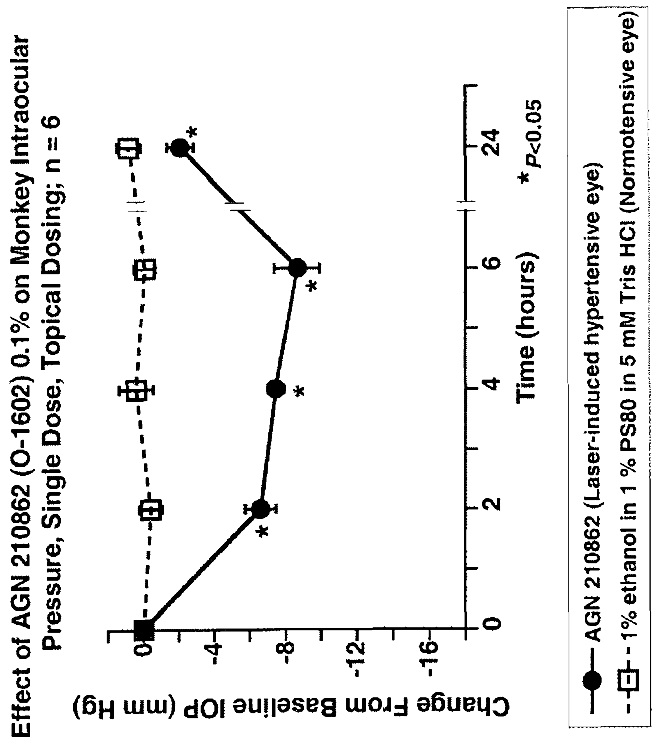

Effect of AGN 210862 (O-1602) 0.1% on Monkey Intraocular Pressure, Single Dose, Topical Dosing; n = 6
Change From Baseline IOP (mm Hg)
0
-4
-8
-12
-16
0
2
4
6
24
Time (hours)
*P<0.05
AGN 210862 (Laser-induced hypertensive eye)
1% ethanol in 1 % PS80 in 5 mM Tris HCl (Normotensive eye)

FIGURE 3

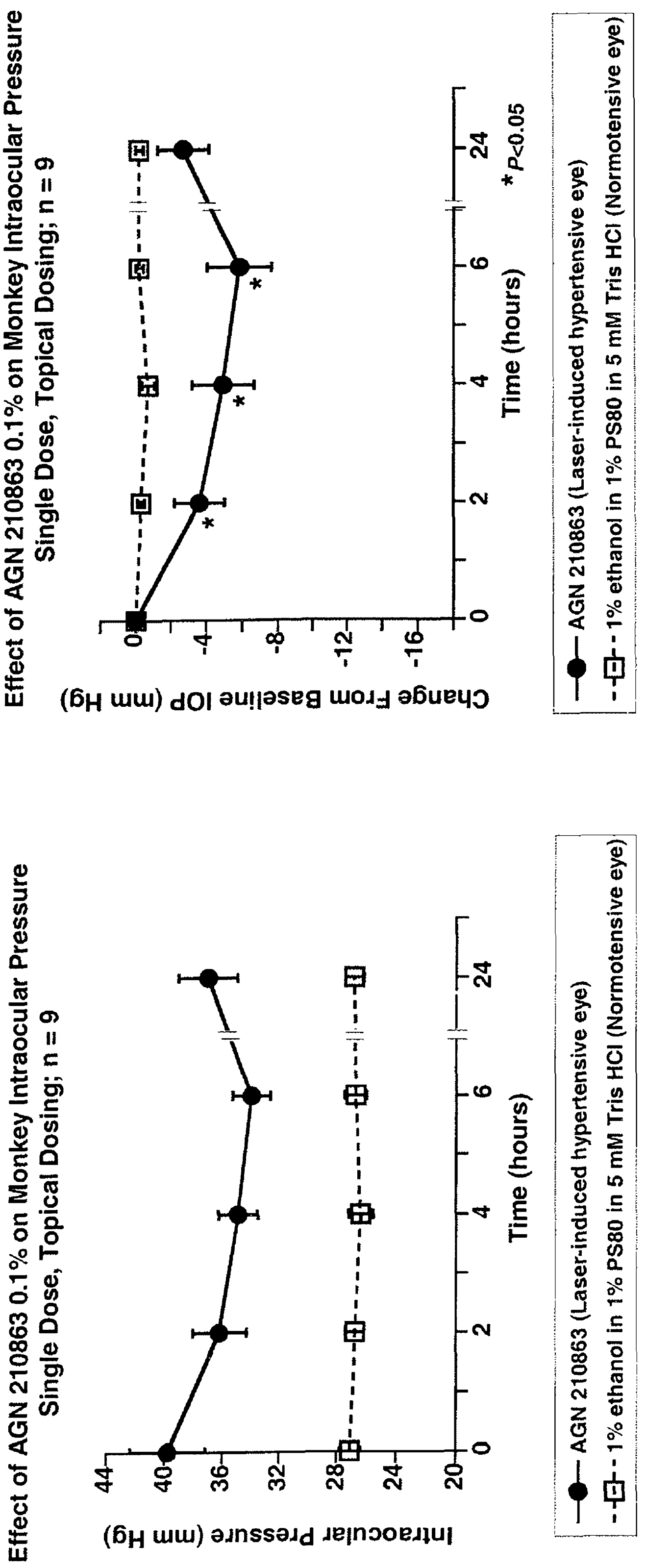

Effect of AGN 210863 0.1% on Monkey Intraocular Pressure
Single Dose, Topical Dosing; n = 9
Change From Baseline IOP (mm Hg)
0
-4
-8
-12
-16
0
2
4
6
24
Time (hours)
*P<0.05
AGN 210863 (Laser-induced hypertensive eye)
1% ethanol in 1% PS80 in 5 mM Tris HCl (Normotensive eye)
Effect of AGN 210863 0.1% on Monkey Intraocular Pressure
Single Dose, Topical Dosing; n = 9
Intraocular Pressure (mm Hg)
44
40
36
32
28
24
20
0
2
4
6
24
Time (hours)
AGN 210863 (Laser-induced hypertensive eye)
1% ethanol in 1% PS80 in 5 mM Tris HCl (Normotensive eye)

FIGURE 4

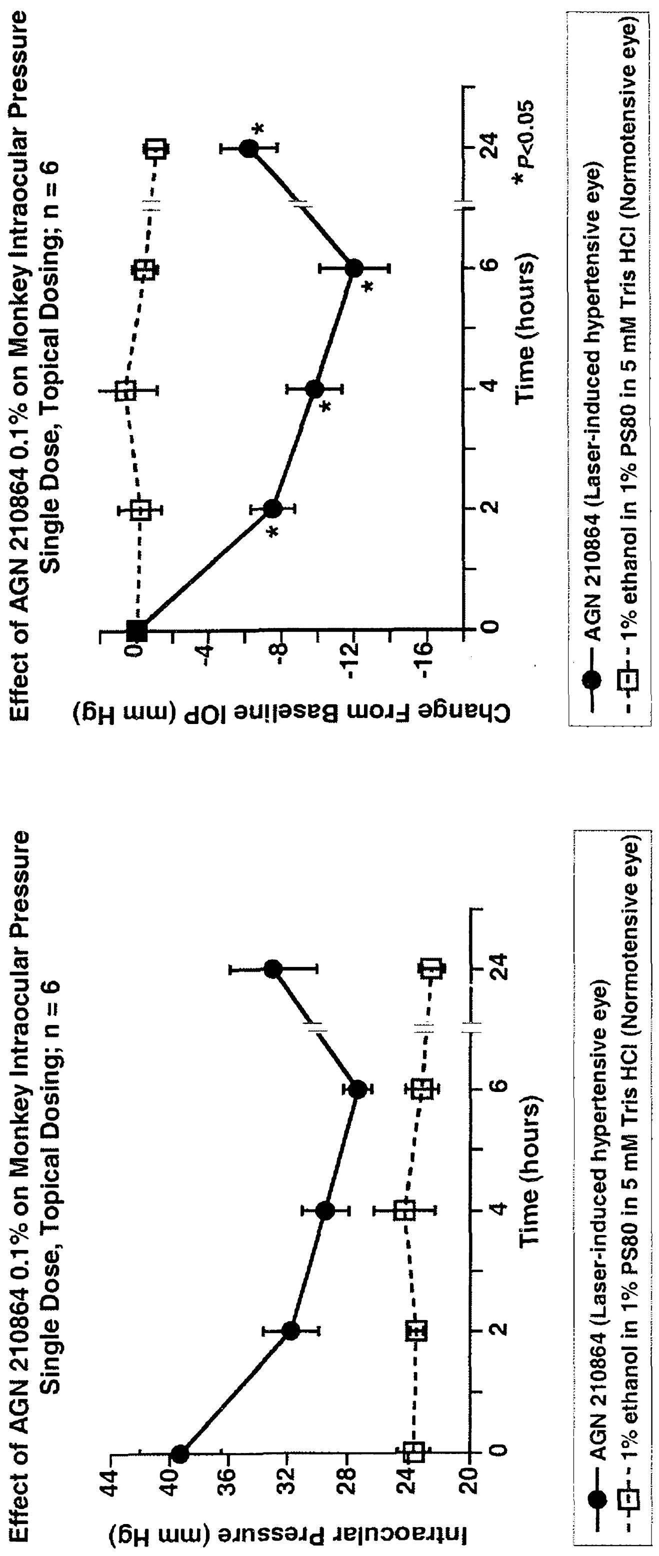

Effect of AGN 210864 0.1% on Monkey Intraocular Pressure
Single Dose, Topical Dosing; n = 6
Intraocular Pressure (mm Hg)
44
40
36
32
28
24
20
0
2
4
6
24
Time (hours)
AGN 210864 (Laser-induced hypertensive eye)
1% ethanol in 1% PS80 in 5 mM Tris HCl (Normotensive eye)
Effect of AGN 210864 0.1% on Monkey Intraocular Pressure
Single Dose, Topical Dosing; n = 6
Change From Baseline IOP (mm Hg)
0
-4
-8
-12
-16
0
2
4
6
24
Time (hours)
*P<0.05
AGN 210864 (Laser-induced hypertensive eye)
1% ethanol in 1% PS80 in 5 mM Tris HCl (Normotensive eye)

FIGURE 5