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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 August 2005 (11.08.2005)

PCT

(10) International Publication Number
WO 2005/072719 A1

(51) International Patent Classification[7]: A61K 31/192, 35/78

(21) International Application Number: PCT/NL2005/000075

(22) International Filing Date: 2 February 2005 (02.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04075300.6 2 February 2004 (02.02.2004) EP

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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, 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, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(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, MC, 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*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MEDICINAL ACIDIC CANNABINOIDS

(57) Abstract: The invention relates to an acidic cannabinoid for medical use and to a cannabis extract comprising an acidic cannabinoid. The extract may comprise one or more compounds selected from the group consisting of cannabidiolic acid (CBD-A), cannabidiol (CBD), cannabigerolic acid (CBGA), cannabigerol (CBG), cannabinolic acid (CBN-A) and cannabinol. The invention further relates to a method for preparing a preparation comprising extracting an acidic cannabinoid from cannabis.

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Title: Medicinal acidic cannabinoids

The invention relates to an acidic cannabinoid for medical use and to a cannabis extract comprising an acidic cannabinoid.

Δ^9-Tetrahydrocannabinol (THC) is naturally found in cannabis. THC has been reported to have use as an analgesic, for instance for patients suffering from rheumatoid arthritis. A side effect of THC is its psychoactive activity. Further, conventionally THC is administered by smoking, which may be detrimental to general health, in particular to the lungs and the coronary system.

WO 89/01332 describes an acidic metabolite of THC, wherein the methyl group at the 9-position, a major metabolite formed in humans and other mammals, is substituted by a carboxyl group. This metabolite is reported to be non-psychoactive. Its use as a therapeutic agent for such purposes as the treatment of chronic pain and tissue inflammation often associated with illnesses such as rheumatoid arthritis is suggested. The Examples show a mouse hot plate test for analgesia, which indicates that, in mice, the metabolite shows about the same analgesic activity as THC and a somewhat lower activity than Naproxen. The Examples further indicate that the metabolite does not induce the formation of gastric lesions in an animal test under conditions wherein aspirin does.

In a review by Bhargava (Gen. Pharmac. Vol 9 (1978), No 4, pages 195-213), potential uses of cannabinoids are mentioned in rather general terms. Bhargava mentions that several cannabinoids have been pharmacologically tested, without disclosing in any detail, a specific medical activity for carboxylated THCs (THC acids), such as Δ^9-tetrahydrocannabinolic acid or the like. In addition, reference is made to the analgesic activity of THC and several other cannabinoids compared to morphine. THC is reported to

perform equi-analgesic with morphine, but other tested cannabinoids are reported to be much less potent or even inactive.

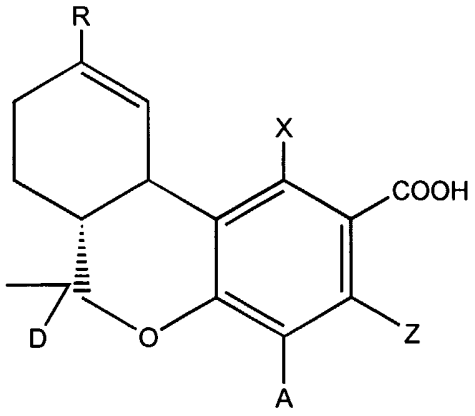
Williamson and Evans (Drugs 2000, Dec. 60(6):1303-1314 discuss in general terms a potential clinical use of cannabis. The specific use of THC acids, such as Δ^9-tetrahydrocannabinolic acid or the like, as the active pharmaceutical ingredient, is not disclosed.

GB-A 2 384 707 relates to the use of a cannobinoid acid, in particular cannabidiol (CBD) and cannabidiol acid (CBDA) for use as an active pharmaceutical substance in the treatment of nausea, vomiting, emisis and motion sickness. The compounds may be obtained by extraction from cannabis. As a result of the extraction, relatively small amounts of THC-acids may be present in the extract, but the use of a THC-acid as an active pharmaceutical substance is not mentioned.

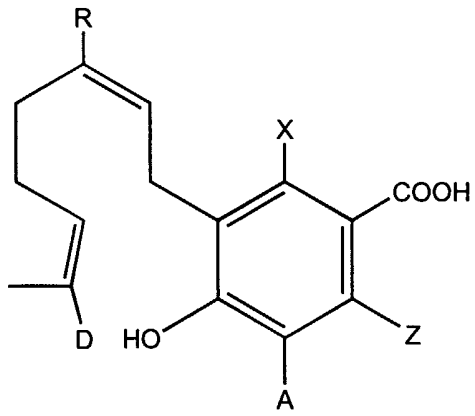
There remains a continuing desire for alternative therapeutics. It is therefore an object of the invention to provide such a therapeutic.

Surprisingly, it has now been found that a specific precursor of THC has properties which are of interest to medical use, such as analgesic and/or anti-inflammatory properties. Accordingly, the present invention relates to an acidic THC precursor for medical use.

More in particular, the present invention relates to an acidic cannabinoid represented by formula Ia or Ib for use as a medicament



Formula Ia



Formula Ib

In these formulae X, Z and A each represent a different group selected from the groups –OH, hydrogen and a first alkyl; accordingly, each of these four groups are present in the compound. The first alkyl is preferably a C1-C10 linear or branched alkyl, more preferably a C4-C7 linear or branched alkyl, even more preferably n-pentyl. The first alkyl is preferably Z.

D represents –OH or alkyl, preferably a C1-C3 linear or branched alkyl, in particular a methyl.

R represents a hydrogen, a C_nH_{2n}-OH, a C_nH_{2n}-COOH or a second alkyl; The n in these groups is an integer, preferably 0, 1 or 2. R is preferably a C1-C3 linear or branched alkyl, more preferably -CH_3.

Figure 1 shows a cannabinoid biosynthetic pathway.

Figure 2A and 2B show the effect of treatment with a cannabis extract comprising THC-A on the release of TNF-α in an ELISA assay.

Figures 3A and 3B show respectively the inhibitory effect on TNF-α release and the stimulatory effect on interleukin-10 release of an unheated cannabis extract comprising THC-A

Figure 4 shows the effect of treatment with (an extract comprising) THC-A in mice suffering from autoimmune encephalomyelitis.

Within the context of the invention, the term "acidic" is used to describe a compound having a carboxyl group, unless specified otherwise. In general, an acidic precursor of THC is transformable into THC by decarboxylation, optionally in combination with one or more other reactions, such as a cyclisation of a precursor having two of the rings forming the core of the THC to form the third ring, (de)alkylation, (de)hydroxylation and the like. Besides the compounds of formula Ia and of Ib, examples of acidic THC precursors are cannabidiolic acid (CBDA), cannabichromenic acid (CBCA), cannabinorolic acid (CBNRA), cannabigerolic acid (CBGA), cannabinolic acid (CBNA) and functional and structural analogues thereof. A number of these compounds are shown in the pathway displayed in Figure 1.

A compound according to the present invention has been found to have analgesic and/or anti-inflammatory activity. This is surprising, as this finding is contrary from what may be concluded from a standard receptor binding test wherein the dissociation constants (K_d) were determined for binding of the compounds to the cannabinoid receptors CB1 and CB2 and compared with the binding of THC (See Examples).

In particular, an acidic compound according to the invention may be used for relieving pain and/or for suppression of an inflammatory response, preferably for modulating the release of one or more inflammatory mediators, in particular cytokine(s), in an animal, preferably in a human.

In a highly preferred embodiment the acidic compound is used to suppress the release of one or more pro-inflammatory cytokines, in particular TNF-α (tumour necrosis factor α), and/or to stimulate the release of anti-inflammatory cytokines, in particular interleukins, more in particular interleukin-10 (IL-10). A compound or composition that can both suppress the release of a pro-inflammatory cytokine and stimulate the release of an anti-inflammatory cytokine, as is provided by the present invention, is of considerable interest to the pharmaceutical industry, and medical science.

An acidic compound according to the invention may for instance be used for (prophylactic or therapeutic) treatment of an animal, preferably a human, against an inflammation, an auto-immune disease or an infection. It may also be used to alleviate symptoms, such as pain or nausea, accompanied with a disease.

In particular, a compound may be used in accordance with the invention for the treatment of a disease selected from the group consisting of multiple sclerosis, arthritis, arthrosis and other inflammatory diseases of bone and/or joint, encephalomyelitis (in particular autoimmune encephalomyelitis), AIDS, inflammatory bowel disease, Crohn's disease, inflammatory skin diseases (dermatitis, Psoriasis) and alleviated symptoms associated with cancer, anorexia, AIDS, spasticity, glaucoma and chronic pain.

Further, it has been found that a compound according to the invention is only lowly psychoactive or even non-psychoactive. Besides, it is expected that the risk for gastro-intestinal damage as a result of using a compound according to the invention is low, and in particular less than for at least some commercially very successful drugs, *e.g.* aspirin.

Particularly good results have been achieved with an acidic cannabinoid according to Formula Ia or Ib, more in particular a compound according to Formula Ia, wherein Z represents the alkyl and X represents the OH and with an acidic cannabinoid according to Formula Ia or Ib, more in particular a compound according to Formula Ia ,wherein A the hydrogen. In the presence of such a compound it has been found that the suppression of an inflammatory response, as indicated by its capacity for suppressing TNF-α release, is high in comparison to THC, whilst having no noticeable detrimental psycho-active side effect. Of these compounds Δ^9-tetrahydrocannabinolic acid (THC-A), is particularly preferred. This compound is represented by Formula Ia, wherein Z represents n-pentyl, X is -OH, A is hydrogen, D is methyl and R is methyl. Of this compound in particular, it has surprisingly been found that

it is capable of both suppressing a pro-inflammatory cytokine, such as TNF-α, and stimulating an anti-inflammatory cytokine, such as interleukin 10.

In principle, it is possible to synthesise a compound according to the invention (bio)chemically. The skilled person will know how to perform such synthesis based upon common general knowledge and the present disclosure.

It is however an advantage of the invention that an acidic cannabinoid – in particular a compound wherein the first alkyl at the aromatic ring is n-pentyl (such as Z in formula Ia or Ib, or in the equivalent position in an acidic precursor of THC in general) - may be derived from a natural source, such as cannabis. An acidic cannabinoid can be used (to treat a medical indication) directly without further chemical modifications, such as decarboxylising the compound into THC and subsequently metabolising the THC.

A compound according to the invention may be used in isolated form or in an extract from a natural source, in particular from flower tops of cannabis. Particular suitable is a plant or a part thereof, comprising at least 5 wt. % of acidic cannabinoids, *e.g.* 5-15 wt. %. Very good results have been achieved with *Cannabis sativa, Cannabis indica.* . Suitable methods to extract an acidic compound according to the invention are known in the art and include liquid extraction, *e.g.* with a apolar phase, such as chloroform and a polar phase, in particular an aliphatic alcohol, such as methanol or ethanol. In such an extraction the acidic cannabinoid typically is found in the apolar phase, especially if the extraction procedure is carried out at pH lower than 7. The skilled person will know how to carry out a suitable extraction and further process the acidic cannabinoid, based on common general knowledge and the information disclosed herein. It has been found that an extract according to the invention, comprising an acidic cannabinoid is effective in reducing TNF-α excretion in human macrophages, demonstrating an inhibitory effect of the acidic cannabinoid. In an embodiment, it has further surprisingly been found to be effective in increasing interleukin release too (see Examples).

The preparation of the extract in accordance with the invention is generally carried out under essentially non-decarboxylising conditions to avoid an excessive formation of THC, which may be undesired for its psycho-active side effects and/or for legal reasons, THC at present being illicit in many states. In practice, it is therefore preferred to perform the extraction at a temperature not exceeding 95 °C, more preferably at a temperature of less then about 50 °C, even more preferably of less than about 25 °C. Very good results have been achieved with extraction at a temperature not exceeding about 4 °C. The lower limit for the temperature is not particularly critical, as long as the extraction medium remains fluid.

The extract may then be further processed in any way, without excessive exposure to heat to maintain essentially non-decarboxylising conditions and thus avoid excessive formation of THC. In particular such conditions are met if the extract is not excessively exposed to temperatures of about 200 °C or more. Preferably the extract is processed at a temperature not exceeding about 50 °C. More preferably any further processing of the extract takes place at a temperature of about 25 °C or less. Accordingly, the solvent of the extract is preferably removed by lyophilisation.

In practice, conditions are considered to be essentially non-decarboxylising heat treatment is considered to be non-excessive when the amount of THC as a percentage of the total dry weight of the extract is less than 5 wt. %, preferably less than 2 wt. %, even more preferably less than 0.5 wt. %. For practical reasons the amount of THC is preferably less than the maximum allowable amount to allow use as a non-prescription medicament, as determined by law. In this respect it is interesting to note that the present invention allows for the preparation of extracts with less than about 0.15 wt. % as a percentage of the dry weight without a need for selective removal of THC from the extract.

THC may be totally absent (*i.e.* non-determinable by a conventional analytical technique) in an extract or other composition according to the

invention. For practical reasons some THC may be present, such as about 0.01 wt. % as a percentage of the dry weight or more.

Good results with respect to its pharmaceutical properties and low side effects have been achieved with an extract or other composition according to the invention wherein the amount of THC as a weight percentage of the amount of the at least one acidic cannabinoid is 0- 2 wt. %, preferably less than about 1 wt. %. As indicated above, THC may be absent, although some THC may be present; as such, for practical reasons a preferred lower limit for the amount of THC as a weight percentage of the amount of the at least one acidic cannabinoid is about 0.01 wt. %, more in particular about 0.1 wt. %.

Good results have *inter alia* been achieved with an extract - in particular a cannabis extract - comprising at least about 10 mg/ g based upon the dry weight, preferably at least about 15 mg/g based upon the dry weight, of the acidic cannabinoid. Very good results have been achieved with an extract comprising at least about 20 mg/g based upon the dry weight of the acidic cannabinoid. The upper limit is not particularly critical. For practical reasons the upper limit is preferably about 500 mg/g, more preferably 250 mg/g dry weight.

Preferably, a composition according to the invention, such as a (cannabis) extract, comprises at least one compound selected from the group consisting of cannabidiolic acid (CBD-A), cannabidiol (CBD), cannabigerolic acid (CBGA), cannabigerol (CBG), cannabinolic acid (CBN-A) and cannabinol (CBN), Cannabichromenic acid(CBC-A) and cannabichromene (CBC). In particular in such a composition also comprising a cannabinoid according to formula Ia or Ib, preferably formula Ia, has been found very effective as an anti-inflammatory preparation. The amount of the compounds of this group may be chosen within wide limits. Good results have *inter alia* been achieved with a composition, in particular an extract, wherein the total amount of CBD and CBD-A is in the range of about 0.01-200 %, more in particular about 1-100

wt. % based upon the amount of the at least one acidic cannabinoid. In particular in this range indications exist that synergy occurs.

An extract according to the invention may be employed in any form. It may for instance very suitably be in a dry form or in a liquid form, in particular solubilised in ethanol, water, a vegetable oil or a liquid comprising any of these compounds alone or in a combination.

An extract may very suitably be present in the form of a paste, cream or ointment. Such form is in particular attractive for topical applications, *e.g.* for treating a dermal inflammation.

An acidic compound or extract according to the invention may very suitably be present in a pharmaceutical preparation, further comprising a pharmaceutically acceptable carrier. A preparation may for instance have the form of a tincture, an ointment, a spray, an inhalant, a powder, a granulate, a suppository, a tablet or a capsule.

Of particular interest is administration as a liquid preparation for oral use or dermal application as a cream or ointment. Applications via the nasal or inhalatory route are in particular attractive for purified acids.

The skilled person will know how to determine a particular dosage regime, depending upon the medical indication, the patients condition and the type of administration.

The invention further relates to a method of treating an animal, preferably a human, with an acidic cannabinoid, which treatment comprises administering the acidic cannabonoid in acidic form. This means in particular that the cannabinoid is administered under essentially non-decarboxylising conditions, in contrast to conventional ways of administering cannabinoids, *i.e.* by smoking (heating and inhaling) dried flower tops of cannabis plants. Besides avoiding the psycho-active side-effects (as a result of the formation of THC during heating), the present form of administration does not impose any health risks normally associated with smoking. Suitable forms of

administration include oral administration (such as ingestion or inhalation) and any other conventional medical ways of administering a medicament.

Accordingly, the invention further relates to the use of an acidic cannabinoid, optionally in the form of an extract or a pharmaceutical preparation as described herein, in the manufacture of a medicament for administration of the cannabinoid in acidic form.

The invention will now be illustrated by the following examples.

Examples

Example 1: Preparation of the extracts

Flower tops of three cannabis varieties belonging to *C. sativa* or *C. indica* and hybrids. were used to make extracts. The flower tops were deep-frozen immediately after harvesting and thereafter lyophilised, shortly before extraction.

700 mg dried flower tops were extracted twice with 20 mL chloroform / methanol (1:9), according to the following procedure:

- 700 mg flower tops were mixed with 18 ml Methanol and sonicated for 5 minutes. 2 mL chloroform were added after which the mixture was sonicated again for 5 minutes. Extraction was then performed (60 minutes 4°C, shaking 250 rpm). Supernatant was removed and the extraction was repeated with the remaining plant-pellet. Both supernatants were pooled and stored at -20°C until measurements started.

Composition of the unheated extracts

The concentration of THC-A, CBD (the total of cannabidiolic acid and cannabidiol) CBN and THC was determined with LC/MS-MS.

The results are shown in Table 1.

Table 1

Extract	THC-A	THC	CBD	CBN
	all concentrations in mg per gram dry weight.			
cultivar 1	202	1.43	0.21	<0.00005
cultivar 2	184	1.14	0.16	<0.00005
cultivar 3	16.0	0.11	14.86	<0.00005

Example 2: Receptor binding studies

The affinity of the three extracts for binding to the cannabinoid receptors CB1 and CB2 was determined in a receptor binding study. Herein a competitive assay was used between the components of the extracts and tritium labelled ligand CP55,940. The receptors were recombinant human CB1 and CB2 co-expressed with Gαiβ1γ proteins in Sf9 cells

In the binding studies, unheated extracts were compared with extracts heat at 200 C to decarboxylate the THC-A. The affinity constants (K_d) are shown in Table 2.

Table 2

Extract	K_d CB1 [μM]	K_d CB2 [μM]
Cultivar 1unheated	>1	>1
Cultivar 2 unheated	>1	>1
Cultivar 3 unheated	>1	>1
Cultivar 1 heated	0.0062	0.019
Cultivar 2heated	0.0079	0.021
Cultivar 3 heated	0.017	0.023

A compound with a low K_d is generally considered as a potential anti-inflammatory agent or as a potential analgesic.. From the much higher K_d values from the unheated (undecarboxylated) extract, one would expect that

the acidic cannabinoids would not be promising agents for pain relieve or anti-inflammatory activity.

To confirm that the difference in affinity can be assigned to the cannabinoids the experiments were repeated with the purified components (obtained by fractionation on a Hypersil 10 C18 column, 250 x 10mm, 10 micron with 50x10 mm precolumn, Phenomenex)

The results are shown in Table 3.

Table 3

Extract	K_d CB1 [μM]	K_d CB2 [μM]
THC-A	>1	>1
THC	0.0038	0.0032
CBD	0.66	0.28
CBN*	(0.036)	(0.017)

* the CBN was found to be contaminated with THC

Thus, based upon the binding studies it appeared that the precursors of THC, in particular acidic cannabinoids such as THC-A, were not a promising compound for medical use.

Example 3: Biological immuno-system based assay

U937 monocytes (described *e.g.* in Izeboud et al., J. Rec. Sign. Tr. Research (1999), 19 (1-4): 191-202) were differentiated into macrophages by treating the monocytes for 16 hours with phorbol myristate acetate (PMA)

After 48 hours storage of the macrophages in RPMI-1640 culture medium wherein the medium was replaced every 24 hours. The macrophages were allowed to recover from PMA treatment for 48 hours, during which culture medium was replaced every 24 hours. At day three after PMA treatment, the macrophages were exposed to lipopolysacharide (LPS) (Sigma-

Aldrich, L-2630) The macrophages were exposed to LPS in the presence or absence of the cannabis extracts described above (in methanol). The extracts were tested undiluted and in 2.5-fold, 5-fold, 7.5-fold and 10-fold dilution). In the culture medium the TNF-α level was determined a by specific ELISA test (TNFα Cytoset, Biosource CHC1754). Further, the toxicity of the cannabis extracts was determined with a MTT test (Sigma-Aldrich, M-2128) (also described in Mosmann, J. Immunol.Meth 1983, 55-63).

The results of the TNF-α ELISA indicated that the TNF-α release after treatment with unheated extract was considerably reduced, compared to the control treatment (with an almost complete inhibition of the release for undiluted unheated extract). With the heated extract (wherein the THC-A is decarboxylated), no clear effect on the TNF-α release was seen. This demonstrates that the unheated extracts are generally more potent or at least as potent in suppressing the TNFα as the heated extracts. This is an indication that an acidic precursor such as THC-A is a suitable alternative to THC as an anti-inflammatory agent and potentially more potent than THF and/or carboxylated THF metabolites, reported previously.

The MTT tests further demonstrated that none of the tested extracts were toxic (data not shown.)

The experiment was repeated with extracts from two cannabis cultivars, obtained by the method as described in Example 1. Part of the extracts was heated (typically 7 min. at 200 °C), the remainder was not exposed to a temperature exceeding 25 °C (typically kept refrigerated. Heated and unheated extracts were administered in diluted form (100-fold to 1000-fold dilution) to cultures of U937 cells after induction with LPS (as described above).

THC and THC-A concentrations were as shown in Table 4:

Table 4

	THC (mg/mL)	THC-acid (mg/mL)
Cultivar 1 heated	4.81	0.12
Cultivar 1 unheated	0.04	5.05
Cultivar 2 heated	4.37	0.09
Cultivar 2 unheated	0.03	4.60

Figures 2A and 2B show that a considerable reduction in TNF-α was achieved with all unheated extracts (rich in THC-A), with an (almost) complete inhibition at the 100-fold dilution. In contrast, the treatment with the heated extracts (rich in THC) did not result in a reduction of the TNF-α release. This demonstrates the potency of an extract according to the invention for the treatment of an inflammation, in particular an extract obtainable by extraction under conditions at which decarboxylation is avoided, such as by extraction at a temperature below 25 °C, more in particular at a temperature of about 4 °C or less.

Example 4: effect of acidic cannabinoid on pro-inflammatory and anti-inflammatory cytokines

THC-acid was able to decrease the mRNA levels coding for TNF-alpha in isolated and cultured Peripheral Blood Mononuclear Cells (PBMC) that were stimulated by PHA (phytohemagglutinin). By stimulation with PHA, a response is induced that resembles an inflammatory reaction. TNF-alpha is known as a pro-inflammatory cytokine that is released during the initial stages of inflammation.

In the same study, the levels of mRNA coding for interleukin-10 (IL-10) were increased. IL-10 is known as an anti-inflammatory cytokine. The experimental design of the study was as follows:

PBMC were prepared as described by Visser *et al.* (J. Investigative Medicine, 49 (2), 2001). In 6-wells plates, each well was filled with 2.5 mL

PBMC's (2 x 10^6 cells in IMDM (Isocoves modified Dulbecco's medium + glutamax, containing 5 x 10^{-5}M 2-mercaptoethanol, 100 U/mL penicillin, 100 U/mL streptomycin and 10% fetal calf serum)) together with 500 µL THC-acid (or medium as control) and 500 µL PHA (or medium as control) After incubation for 4 days (at 37°C), total RNA was isolated by using Trizol ™ according manufactures protocol. From isolated RNA, cDNA was synthesized by using *Promega Reverse Transcription System* according to manufactures protocol.

The levels of cDNA were determined by means of Real Time (RT)-PCR using Taqman ® Gene Expression assay (Applied Biosystems) according to manufactures protocol. From the levels of cDNA, the amount of mRNA-copies as original present in the PBMC's was calculated as compared to the housekeeping gene β-actine.The presence of THC-acid during incubation resulted in both a decrease in the level of the pro-inflammatory cytokine TNFα and an increase in the level of the anti-inflammatory cytokine IL-10 (see figures 3A and 3B).These results further support the potential of THC-acid to inhibit inflammation.

Example 5: *in vivo* study of use of acidic cannabinoid in the treatment of encephalomyelitis.

The effect of purified THC-acid and unheated cannabis extracts were tested *in vivo* in a mouse model for Experimental Autoimmune Encephalomyelitis.

In a randomized study (10 mice for each treatment) the disease was induced in 9 weeks old female SJL mice (Harlan) after immunization with the proteolipid-protein as described by Nagelkerken et al. (Interactions Do Not Play a Major Role in Inhibition of Experimental Autoimmune Encephalomyelitis by Anti-CD154 Monoclonal Antibodies. J Immunol, 173, 993-999, 2004). Between day 0 and day 20 after onset of the disease the mice

were treated daily with a specified oral dose of THC-acid or unheated extract according to the following scheme:

Group 1: vehicle (0.2 mL olive oil/day);

Group 2: 1 mg purified THC-acid in 0.2 mL olive oil/day;

Group 3: unheated cannabis extract in 0.2 mL olive oil containing 1 mg THC-acid/day.

The severity of the disease was followed during 42 days after onset of the disease by means of clinical behaviour and body weight (as described by Nagelkerken *et al.* (Interactions Do Not Play a Major Role in Inhibition of Experimental Autoimmune Encephalomyelitis by Anti-CD154 Monoclonal Antibodies. J Immunol, 173, 993-999, 2004). After 42 days, the mice were sacrificed and the effect on the brainstem was studied. Treatment with 1 mg purified THC-acid or the unheated cannabis extract containing 1 mg THC-acid reduced the number of inflammatory cells in the brain stem significantly as compared to vehicle.

Moreover, as shown in Figure 4, treatment with 1 mg THC-acid or unheated cannabis extract improved the clinical score significantly. The scores as shown in Figure 4 are defined as:

0: no infiltrates

1: mild perivascular accumulation

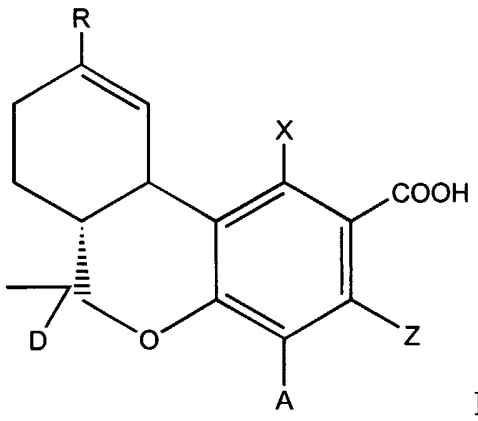
2: mild perivascular accumulation, multi-focal

3: perivascular accumulation, multiple cell layers, multi-focal.

The results in this experiment further indicate that the unheated extract tends to be more effective than the purified THC-A (the median score of the experiments with the extract being 0). Based upon this indication a multivariant analysis was performed, to verify whether other components in the extract are likely to positively contribute to the treatment. From the results of the multivariant analysis, it was apparent that this indeed was the case (results not shown).

Claims

1. Acidic Cannabinoid represented by formula Ia or Ib for use as a medicament



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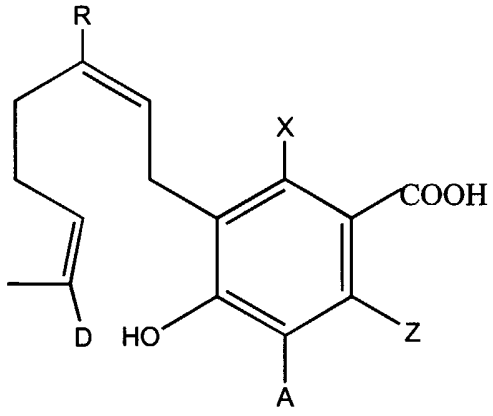


Formula Ib

wherein X, Z and A each represent a different group selected from the groups –OH , hydrogen and a first alkyl;

wherein R represents a hydrogen, a C_nH_{2n}-OH, a C_nH_{2n}-COOH or a second alkyl;

and wherein D represents hydroxyl or a third alkyl.

2. Acidic Cannabinoid according to claim 1, wherein Z represents the first alkyl, X represents the OH and A represents the hydrogen.

3. Acidic Cannabinoid according to claim 1or 2, wherein the first alkyl is a C4-C7 linear or branched alkyl.

4. Acidic Cannabinoid according to claim 3, wherein the first alkyl is n-pentyl.

5. Acidic Cannabinoid according to any one of the preceding claims, wherein R is a C1-C3 linear or branched alkyl, preferably $-CH_3$.

6. Plant extract comprising at least one acidic cannabinoid as defined in any one of the preceding claims, wherein the amount of Δ^9-tetrahydrocannabinol (THC) as a weight percentage of the total dry weight of the extract is 0-5 wt. %.

7. Extract according to claim 6, wherein the amount of THC is less than 1 wt. %, preferably less than 0.5 wt. %.

8. Extract according to any one of the claims 7 or 8, comprising at least about 10 mg/ g based upon the dry weight of extract, preferably about 15-500 mg/g based upon the dry weight, of the acidic cannabinoid.

9. Extract according to any one of the claims 6-8, comprising at least one compound selected from the group consisting of cannabidiolic acid (CBD-A), cannabidiol (CBD), cannabigerolic acid (CBGA), cannabigerol (CBG), cannabinolic acid (CBN-A) and cannabinol.

10. Extract according to claim 9, wherein the total amount of CBD and CBD-A is in the range of 0.01-200 wt. % based upon the amount of the at least one acidic cannabinoid represented by formula I.

11. Extract according to any one of the claims 6-10, wherein the extract is a liquid extract comprising ethanol and/or methanol.

12. Extract according to any one of the claim 6-11, for use as a medicament.

13. Pharmaceutical preparation comprising at least one compound according to any one of the claims 1-5 and a pharmaceutically acceptable carrier.

14. Pharmaceutical preparation according to claim 13, wherein the preparation is selected from the group consisting of tinctures, ointments,

sprays, inhalants, powders, granules, suppositories, creams, tablets and capsules.

15. Use of an acidic cannobinoid according to any one of the claims 1-5, an extract according to any one of the claims 6-11 or a preparation according to claim 13 or 14 in the manufacture of a medicament for administration of the cannabinoid in acidic form to an animal, preferably a human.

16. Use of an acidic cannabinoid according to any one of the claims 1-5, an extract according to any one of the claims 6-11 or a preparation according to claim 13 or 14 – the use preferably being according to claim 15 - in the manufacture of a medicament for relieving pain.

17. Use of a acidic cannabinoid according to any one of the claims 1-5, an extract according to any one of the claims 6-11 or a preparation according to claim 13 or 14 – the use preferably being according to claim 15 - in the manufacture of a medicament for suppression of an inflammatory response, preferably for suppressing release of a pro-inflammatory cytokine, in particular TNF-α and/or stimulating release of an anti-inflammotory cytokine, in particular interleukin-10.

18. Use of an acidic cannabinoid according to any one of the claims 1-5, an extract according to any one of the claims 6-11 or a preparation according to claim 13 or 14 – the use optionally being according to any one of the claims 15-17 - in the manufacture of a medicament for treating a medical indication (disease) selected from the group consisting of infections, inflammations, autoimmune diseases and symptoms associated with a disease, preferably selected from the group consisting of multiple sclerosis, arthritis, AIDS, inflammatory bowel disease, Crohn's disease, inflammatory skin diseases (such as dermatitis, Psoriasis), encephalomyelitis and alleviated symptoms associated with cancer, anorexia, AIDS, spasticity, glaucoma and chronic pain.

19. Method of treating an animal with an acidic cannabinoid according to any one of the claims 1-5, an extract according to any one of the claims 6-11

or a preparation according to claim 13 or, which treatment comprises administering the acidic cannabonoid in acidic form.

20. Method according to claim 19, wherein the cannabinoid is used to treat an animal, preferably a human, suffering from a disease selected from the group consisting of multiple sclerosis, arthritis, AIDS, inflammatory bowel disease and Crohn's disease.

21. Method for manufacturing an preparation comprising an acidic cannabinoid as defined in any one of the claims 1-5 - optionally in the form of an extract according to any one of the claims 6-12 or a pharmaceutical preparation according to claim 13 or 14 - comprising extracting the acidic cannabinoid from harvested parts of a plant, preferably cannabis, under conditions at which decarboxilation of the acidic cannabinoid is avoided.

22. Method according to claim 21, wherein said conditions involve extraction at a temperature of less than 95 °C, preferably a temperature not exceeding about 25 °C.

23. Method according to claim 22, wherein said conditions involve extraction at a temperature not exceeding about 4 °C.

24. Extract obtainable by a method according to any one of the claims 21-23.

Figure 1

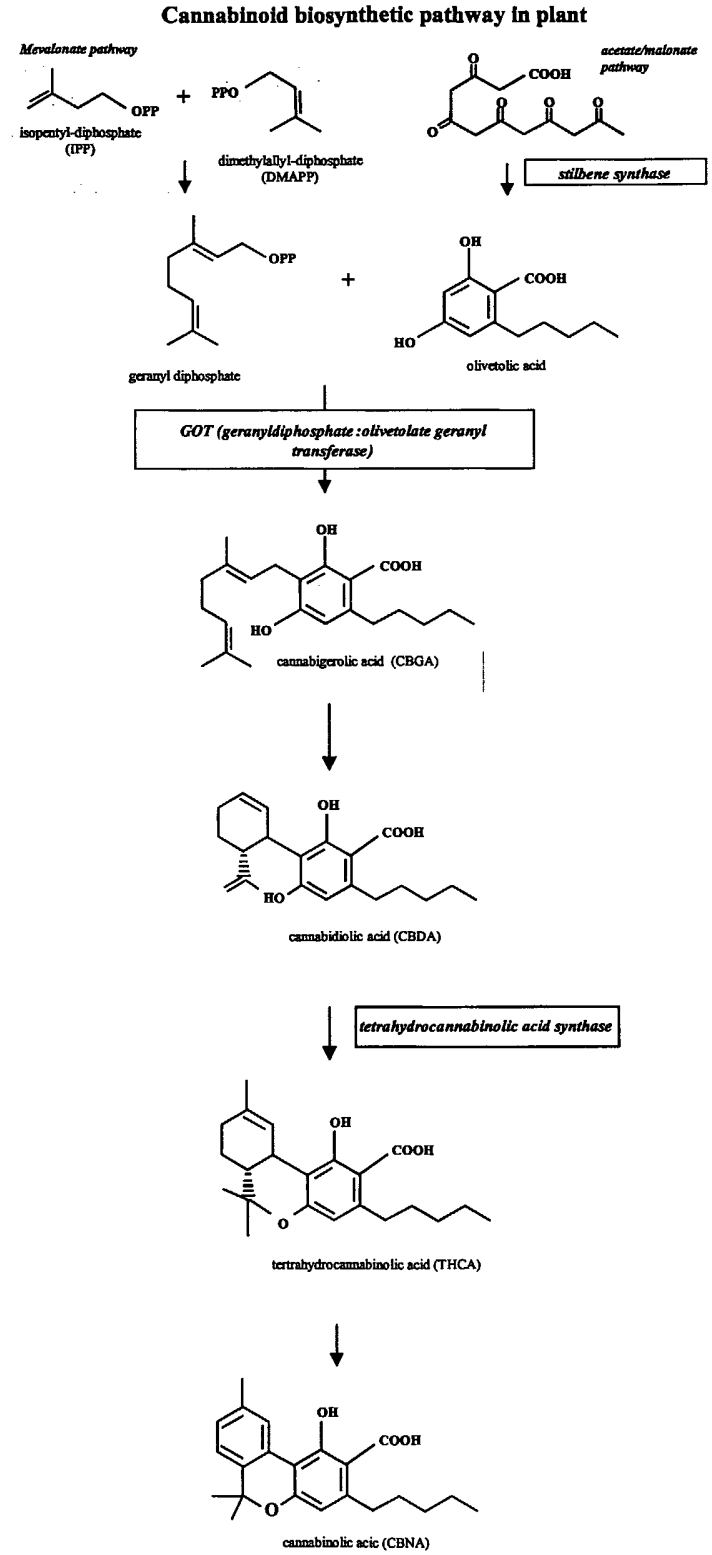

Cannabinoid biosynthetic pathway in plant
Mevalonate pathway
OPP
isopentyl-diphosphate (IPP)
PPO
dimethylallyl-diphosphate (DMAPP)
acetate/malonate pathway
COOH
stilbene synthase
OPP
geranyl diphosphate
OH
COOH
HO
olivetolic acid
GOT (geranyldiphosphate:olivetolate geranyl transferase)
cannabigerolic acid (CBGA)
cannabidiolic acid (CBDA)
tetrahydrocannabinolic acid synthase
tertrahydrocannabinolic acid (THCA)
cannabinolic acic (CBNA)

Figure 2A

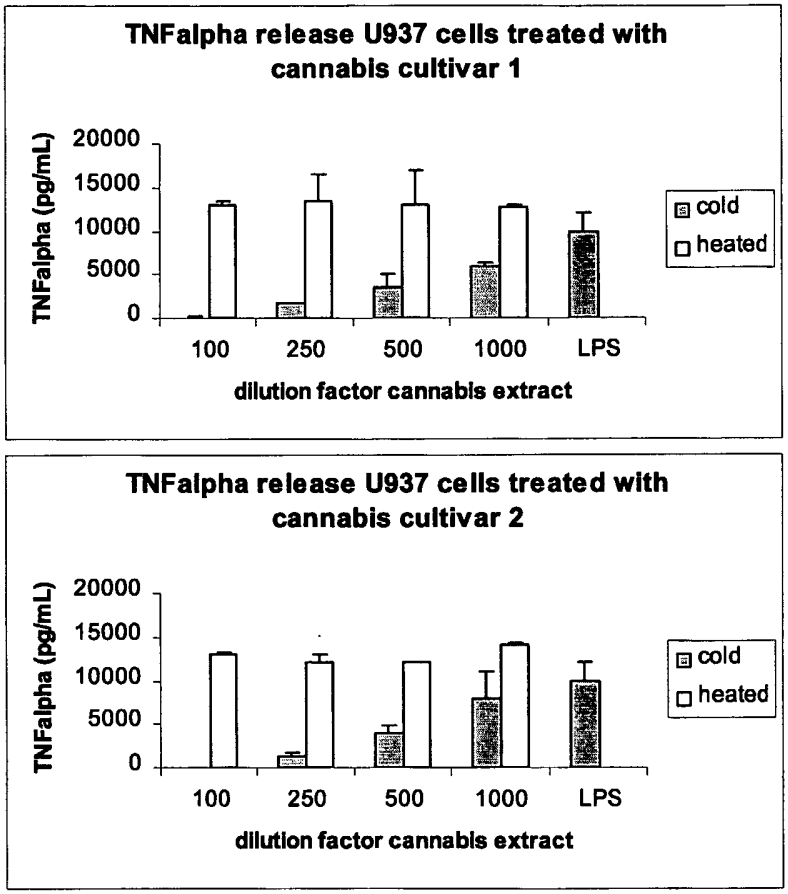


Figure 2B

Figure 3A

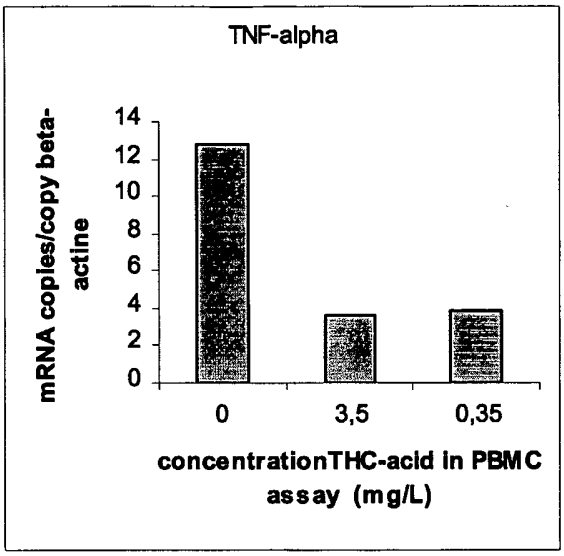


Figure 3B

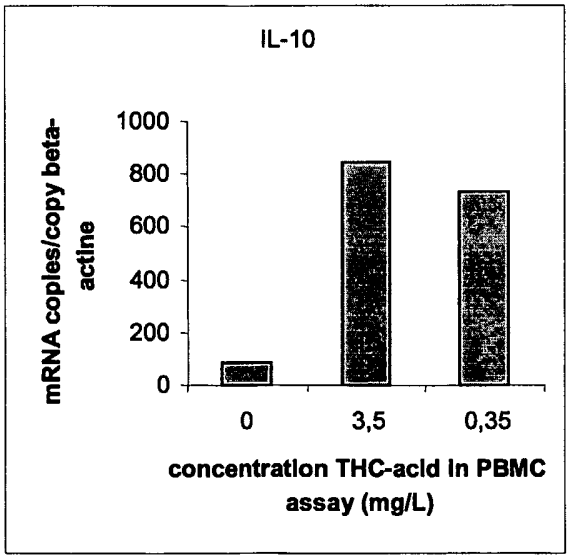
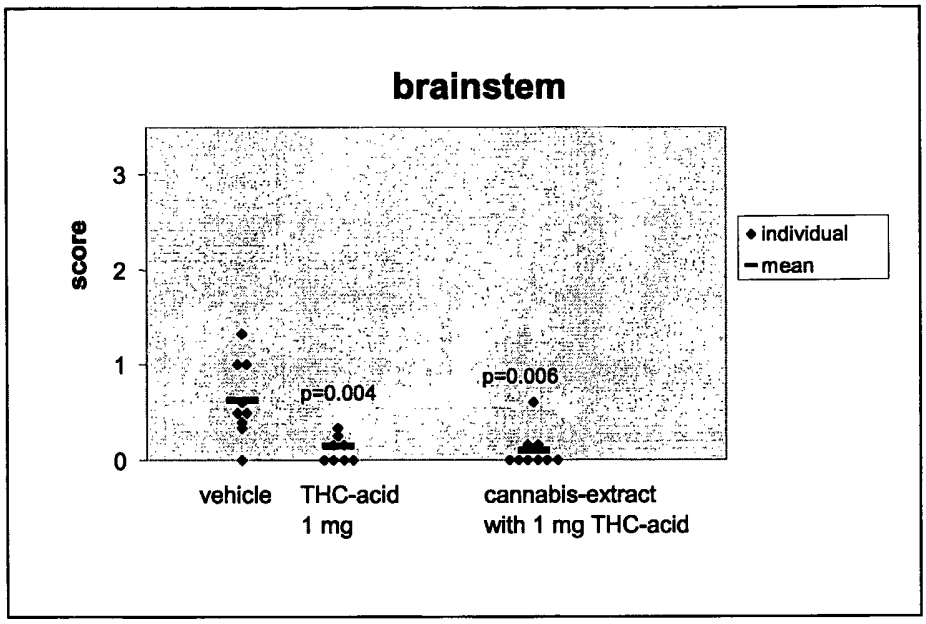


Figure 4


brainstem
score
3
2
1
0
p=0.004
p=0.006
vehicle
THC-acid 1 mg
cannabis-extract with 1 mg THC-acid
individual
mean

INTERNATIONAL SEARCH REPORT

PCT/NL2005/000075

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/192 A61K35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, MEDLINE, CHEM ABS Data, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BHARGAVA H N: "POTENTIAL THERAPEUTIC APPLICATIONS OF NATURALLY OCCURRING AND SYNTHETIC CANNABINOIDS" GENERAL PHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 9, no. 4, 1978, pages 195-213, XP000981417 ISSN: 0306-3623 cited in the application *page 196, right-hand column, last two sentences* abstract; figure 1a	1-24

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2005	18/04/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beyss-Kahana, E

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL2005/000075

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WILLIAMSON E M ET AL: "CANNABINOIDS IN CLINICAL PRACTICE" DRUGS, ADIS INTERNATIONAL LTD, AT, vol. 60, no. 6, December 2000 (2000-12), pages 1303-1314, XP001025657 ISSN: 0012-6667 *page 1305, left-hand column, first paragraph* abstract	1-24
X	GB 2 384 707 A (GW PHARMA LTD) 6 August 2003 (2003-08-06) cited in the application page 8, line 33 - page 9, line 1; claims 1,8	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL2005/000075

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15, 19, 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL2005/000075

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2384707 A	06-08-2003	EP 1482917 A1	08-12-2004
		WO 03063847 A1	07-08-2003