

(19) AUSTRALIAN PATENT OFFICE

- (54) Title
Aralkyl-tetrahydro-pyridines, their preparation and pharmaceutical compositions containing same
- (51)⁶ International Patent Classification(s)
C07D 211/70 9/10
 (2006.01) 20060101ALI2005122
A61K 31/4409 OBMJP **A61P**
 (2006.01) 11/06
A61K 31/4418 20060101ALI2005122
 (2006.01) OBMJP **A61P**
A61K 31/444 13/12
 (2006.01) 20060101ALI2005122
A61P 1/04 (2006.01) OBMJP **A61P**
A61P 1/10 (2006.01) 17/00
A61P 9/10 (2006.01) 20060101ALI2005122
A61P 11/06 (2006.01) OBMJP **A61P**
A61P 13/12 (2006.01) 17/06
A61P 17/00 (2006.01) 20060101ALI2005122
A61P 17/06 (2006.01) OBMJP **A61P**
A61P 19/02 (2006.01) 19/02
A61P 19/06 (2006.01) 20060101ALI2005122
A61P 19/08 (2006.01) OBMJP **A61P**
A61P 25/00 (2006.01) 19/06
A61P 25/16 (2006.01) 20060101ALI2005122
A61P 25/28 (2006.01) OBMJP **A61P**
A61P 27/02 (2006.01) 19/08
A61P 29/00 (2006.01) 20060101ALI2005122
A61P 31/02 (2006.01) OBMJP **A61P**
A61P 31/04 (2006.01) 25/00
A61P 31/06 (2006.01) 20060101ALI2005122
A61P 31/08 (2006.01) OBMJP **A61P**
A61P 31/08 (2006.01) 25/16
A61P 35/00 (2006.01) 20060101ALI2005122
A61P 37/00 (2006.01) OBMJP **A61P**
A61P 37/06 (2006.01) 25/28
A61P 37/08 (2006.01) 20060101ALI2005122
C07C 57/50 (2006.01) OBMJP **A61P**
C07D 211/72 27/02
 (2006.01) 20060101ALI2005122
C07D 211/80 OBMJP **A61P**
 (2006.01) 29/00
C07D 401/04 20060101ALI2006112
 (2006.01) 5BMEP **A61P**
C07D 211/70 31/02
 20060101AFI2007072 20060101ALI2005122
1BMEP **A61K** OBMJP **A61P**
 31/4409 31/04
 20060101ALI2005122 20060101ALI2005122
OBMJP **A61K** OBMJP **A61P**
 31/4418 31/06
 20060101ALI2007022 20060101ALI2005122
4BMEP **A61K** OBMJP **A61P**
 31/444 31/08
 20060101ALI2005122 20060101ALI2005122
OBMJP **A61P** OBMJP **A61P**
 1/04 35/00
 20060101ALI2005122 20060101ALI2005122
OBMJP **A61P** OBMJP **A61P**
 1/10 37/00
 20060101ALI2005122 20060101ALI2005122
OBMJP **A61P** OBMJP **A61P**

37/06	20060101ALI2007022
20060101ALI2005122	4BMEP C07D
0BMJP A61P	211/80
37/08	20060101ALI2007022
20060101ALI2005122	4BMEP C07D
0BMJP C07C	401/04
57/50	20060101ALI2007072
20060101ALI2007022	1BMEP
4BMEP C07D	PCT/FR02/03508
211/72	

(21) Application No: 2002360117

(22) Application Date: 2002 .10 .14

(87) WIPO No: W003/033466

(30) Priority Data

(31) Number	(32) Date	(33) Country
01/13469	2001 .10 .18	FR

(43) Publication Date : 2003 .04 .28

(43) Publication Journal Date : 2003 .07 .03

(71) Applicant(s)
Sanofi-Aventis

(72) Inventor(s)
Cardamone, Rosanna, Baroni, Marco, Casellas, Pierre, Bourrie, Bernard

(74) Agent/Attorney
Davies Collison Cave, Level 15 1 Nicholson Street, Melbourne, VIC, 3000

(56) Related Art
US 5 281 606 A

(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION
EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété
Intellectuelle
Bureau international



(43) Date de la publication internationale
24 avril 2003 (24.04.2003)

PCT

(10) Numéro de publication internationale
WO 03/033466 A1

(51) Classification internationale des brevets⁷ :
C07D 211/70, 401/04, A61K 31/444, A61P 29/00

(74) Mandataire : VARADY, Peter; Sanofi-Synthelabo, 174,
avenue de France, F-75013 Paris (FR).

(21) Numéro de la demande internationale :
PCT/TR02/03508

(81) États désignés (national) : AE, AG, AL, AM, AI, AU, AZ,
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GI, GM,
HK, 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, NO, NZ, OM, PI, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
VN, YU, ZA, ZM, ZW.

(22) Date de dépôt international :
14 octobre 2002 (14.10.2002)

(25) Langue de dépôt : français

(26) Langue de publication : français

(84) États désignés (régional) : brevet ARIPO (GH, GM, KE,
LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), brevet
eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet
européen (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), brevet
OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG).

(30) Données relatives à la priorité :
01/13469 18 octobre 2001 (18.10.2001) FR

(71) Déposant (pour tous les États désignés sauf US) :
SANOFI-SYNTHELABO [FR/FR]; 174, avenue de
France, F-75013 Paris (FR).

Publiée :

- avec rapport de recherche internationale
- avant l'expiration du délai prévu pour la modification des
revendications, sera republiée si des modifications sont
requises

En ce qui concerne les codes à deux lettres et autres abrévia-
tions, se référer aux "Notes explicatives relatives aux codes et
abréviations" figurant au début de chaque numéro ordinaire de
la Gazette du PCT.

(54) Title: ARALKYL-TETRAHYDRO-PYRIDINES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS
CONTAINING SAME

(54) Titre : ARALKYL-TETRAHYDRO-PYRIDINES, LEUR PREPARATION ET COMPOSITIONS PHARMACEUTIQUES
LES CONTENANT

(57) Abstract: The invention concerns compounds of formula (I), wherein: X represents N or CH; R₁ represents a hydrogen or
halogen atom of a CF₃ group; n is an integer from 1 to 5; A represents a partly saturated bicyclic or tricyclic carbon compound,
as well as their salts or solvates, their N-oxides, pharmaceutical compositions containing them, a method for preparing them and
synthesis intermediates in said method.

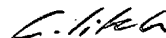
(57) Abrégé : La présente invention concerne des composés de formule (I), dans laquelle X représente N ou CH; R₁ représente un
atome d'hydrogène ou d'halogène ou un groupe CF₃; n est un entier de 1 à 5; A représente un bi- ou tri-cycle carbonné partiel-
lement saturé, ainsi que leurs sels ou solvates, leurs N-oxides, les compositions pharmaceutiques les contenant, un procédé pour leur
préparation et des intermédiaires de synthèse dans ce procédé.

WO 03/033466 A1

IN THE MATTER OF an Australian
Application corresponding to
PCT Application PCT/FR02/03508

RWS Group plc, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England, hereby solemnly and sincerely declares that, to the best of its knowledge and belief, the following document, prepared by one of its translators competent in the art and conversant with the English and French languages, is a true and correct translation of the PCT Application as published under No. PCT/FR02/03508.

Date: 16 February 2004



C. E. SITCH

Deputy Managing Director - UK Translation Division
For and on behalf of RWS Group plc

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

(19) World Intellectual Property Organization
International Bureau



(43) International publication date
24 April 2003 (24.04.2003)

PCT

(10) International publication number
WO 03/033466 A1

- (51) International patent classification⁷:
C07D 211/70, 401/04, A61K 31/444, A61P 29/00
- (21) International application number: PCT/FR02/03508
- (22) International filing date: 14 October 2002 (14.10.2002)
- (25) Language of filing: French
- (26) Language of publication: French
- (30) Data relating to the priority:
01/13,469 18 October 2001 (18.10.2001) FR
- (71) Applicant (for all designated States except US): SANOFI-SYNTHELABO [FR/FR]; 174, avenue de France, F-75013 Paris (FR).
- (72) Inventors; and
(75) Inventors/Applicants (US only): BARONI, Marco [IT/IT]; Via Umberto I n°9, I-20010 Vanzago (IT). BOURRIE, Bernard [FR/FR]; 138, rue des Kermes, F-34980 Saint Gely du Fesc (FR). CARDAMONE, Rosanna [IT/IT]; Via al Roccolo, 5C, I-22100 Como (IT). CASELLAS, Pierre [FR/FR]; 10, rue Carl-van-Linné, F-34000 Montpellier (FR).
- (74) Representative: VARADY, Peter; Sanofi-Synthelabo, 174, avenue de France, F-75013 (FR).
- (81) Designated states (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated states (regional): ARIPO Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- With the International Search Report.
- Before expiry of the period provided for amending the claims, will be republished if such amendments are received.

For an explanation of the two-letter codes and the other abbreviations, reference is made to the explanations ("Guidance Notes on Codes and Abbreviations") at the beginning of each regular edition of the PCT Gazette.

As printed

(54) Title: ARALKYL-TETRAHYDRO-PYRIDINES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

(54) Titre : ARALKYL-TETRAHYDRO-PYRIDINES, LEUR PREPARATION ET COMPOSITIONS PHARMACEUTIQUES LES CONTENANT

(57) Abstract: The invention concerns compounds of formula (I), wherein: X represents N or CH; R₁ represents a hydrogen or halogen atom of a CF₃ group; n is an integer from 1 to 5; A represents a partly saturated bicyclic or tricyclic carbon compound, as well as their salts or solvates, their N-oxides, pharmaceutical compositions containing them, a method for preparing them and synthesis intermediates in said method.

(57) Abrégé : La présente invention concerne des composés de formule (I), dans laquelle X représente N ou CH; R₁ représente un atome d'hydrogène ou d'halogène ou un groupe CF₃; n est un entier de 1 à 5; A représente un bi- ou tri-cycle carbonné partiellement saturé, ainsi que leurs sels ou solvates, leurs N-oxydes, les compositions pharmaceutiques les contenant, un procédé pour leur préparation et des intermédiaires de synthèse dans ce procédé.

WO 03/033466 A1

"Aralkyltetrahydropyridines, their preparation and pharmaceutical compositions containing same"

The present invention relates to novel aralkyltetrahydropyridines, the pharmaceutical
5 compositions containing them, a method for their preparation and synthesis intermediates in this method.

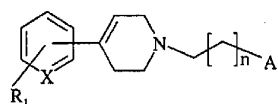
EP 0 458 697 describes naphthylalkyltetrahydropyridine derivatives having an intestinal motility modulating activity.

10 Bourrié et al. (Proc. Natl. Acad. Sci. 1999, 96(22):12855-12859) have described the activity of a compound called SR 57746 (1-(2-naphth-2-ylethyl)-4-(3-trifluoromethyl)-1,2,3,6-tetrahydropyridine) in an experimental autoimmune encephalomyelitis (EAE) model
15 and in the modulation of TNF-alpha (Tumor Necrosis Factor).

It has now been found that some tetrahydropyridines, substituted with a partially saturated aralkyl radical, possess a potent activity on
20 the modulation of TNF-alpha.

TNF-alpha is a cytokine which has recently aroused interest as a mediator of immunity, of inflammation, of cell proliferation, of fibrosis, etc. This mediator is present in abundance in inflamed
25 synovial tissue and exercises an important role in the pathogenesis of autoimmunity (Annu. Rep. Med. Chem., 1997, 32:241-250).

Thus, the present invention relates,
according to one of its aspects, to
aralkyltetrahydropyridines of formula (I):



(I)

5

in which

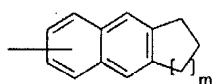
X represents N or CH;

R₁ represents a hydrogen or halogen atom or a CF₃
group;

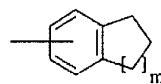
10

n is an integer from 1 to 5;

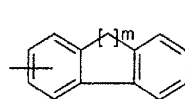
A represents a group of formula (a) to (d):



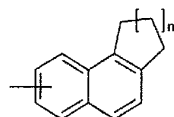
(a)



(b)



(c)



(d)

15

in which m is 1 or 2;

and their salts or solvates and their N-
oxides.

In the present description, the term "halogen" denotes an atom chosen from chlorine, bromine, iodine and fluorine.

Preferred compounds are those where n is 1.

5 Other preferred compounds are those where R_1 is a CF_3 group.

Other preferred compounds are those where X is CH and R_1 is at the 3-position of the benzene.

10 Other preferred compounds are those where X is CH and R_1 is a CF_3 group.

Other preferred compounds are those where X is N and pyridine is substituted at the 2,6-positions.

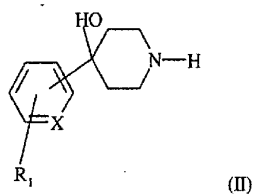
The salts of the compounds of formula (I) according to the present invention comprise both the
15 addition salts with pharmaceutically acceptable inorganic or organic acids such as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, dihydrogen phosphate, citrate, maleate, tartrate, fumarate, gluconate, methanesulfonate, 2-naphthalenesulfonate,
20 etc., and the addition salts which allow a suitable separation or crystallization of the compounds of formula (I), such as the picrate or oxalate, or the addition salts with optically active acids, for example camphorsulfonic acids and mandelic acids or substituted
25 mandelic acids.

According to the present invention, the compounds of formula (I) may exist as N-oxide

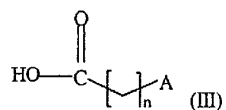
derivatives, in particular they may bear an N-oxide group on the tetrahydropyridine.

The compounds of formula (I) can be synthesized by a method which involves

- 5 (a) reacting the compound of formula (II):

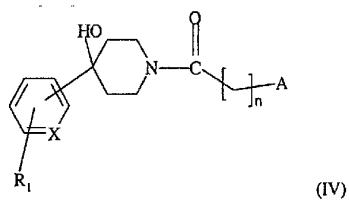


in which R_1 is as defined above, with the acid of
10 formula (III) or one of its functional derivatives:

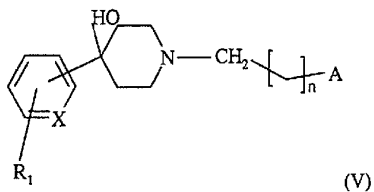


in which n and A are as defined above,

- 15 (b) reducing the carbonyl group of the compound of formula (IV) thus obtained:



(c) dehydrating the intermediate piperidinol of formula (V) thus obtained



(d) isolating the compound of formula (I) thus obtained and optionally converting it to one of its salts or solvates or to its N-oxide derivatives.

10 The reaction of step (a) can be suitably carried out in an organic solvent at a temperature of between -10°C and the reflux temperature of the reaction mixture.

15 It may be preferable to carry out the reaction at cold temperature when it is exothermic, as in the case where the chloride is used as functional derivative of the acid of formula (III).

20 As compound of formula (III), it is possible to use either the free acid, optionally activated (for example with BOP, namely tri(dimethylamino)benzotriazol-1-yloxyphosphonium hexafluorophosphate), or one of its functional derivatives such as, for example, an anhydride, a mixed anhydride, an active ester or an acid halide,

preferably the bromide. Among the active esters, p-nitrophenyl ester is particularly preferred, but methoxyphenyl, trityl and benzhydryl esters, and the like, are also suitable.

5 As reaction solvent, a halogenated solvent such as methylene chloride, dichloroethane, 1,1,1-trichloroethane, chloroform or the like, is preferably used, but other organic solvents compatible with the reagents used, for example dioxane, tetrahydrofuran or
10 a hydrocarbon such as hexane, may also be used.

The reaction may be suitably carried out in the presence of a proton acceptor, for example an alkali metal carbonate or a tertiary amine such as triethylamine.

15 The reduction of step (b) may be suitably carried out by appropriate reducing agents such as borane complexes, for example borane-dimethyl sulfide ($[\text{CH}_3]_2\text{S-BH}_3$), aluminum hydrides or a lithium aluminum hydride complex in an inert organic solvent, at a
20 temperature of between 0°C and the reflux temperature of the reaction mixture, according to the customary techniques.

The expression "inert organic solvent" is understood to mean a solvent which does not interfere
25 with the reaction. Such solvents are for example ethers, such as diethyl ether, tetrahydrofuran (THF), dioxane or 1,2-dimethoxyethane.

According to a preferred mode of operation, the procedure is carried out with the borane-dimethyl sulfide used in excess in relation to the starting compound (II), at the reflux temperature, optionally
5 under an inert atmosphere. The reduction is normally complete after a few hours.

The dehydration of step (c) is easily carried out, for example, using an acetic acid/sulfuric acid mixture, at a temperature of between room temperature
10 and the reflux temperature of the solvent used.

According to a preferred method, the reaction of step (c) is carried out in an acetic acid/sulfuric acid mixture in a 3/1 ratio by volume, by heating at the temperature of about 80-100°C for 1 to 3 hours.

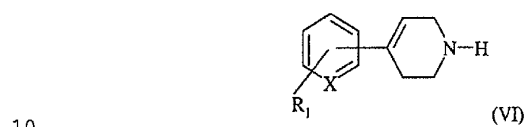
15 The desired compound is isolated according to conventional techniques in the form of a free base or of one of its salts. The free base may be converted to one of its salts by mere salification in an organic solvent such as an alcohol, preferably ethanol or
20 2-propanol, an ether such as 1,2-dimethoxyethane, ethyl acetate, acetone or a hydrocarbon such as hexane.

The compound of formula (I) obtained is optionally converted to one of its N-oxide derivatives.

The compounds of formula (I) bearing an N-
25 oxide group on the nitrogen atom of the tetrahydropyridine can be prepared by oxidation of the corresponding compound of formula (I). In this case, the compound of formula (I) is subjected to an

oxidation reaction according to conventional methods,
 for example to a reaction with m-chloroperbenzoic acid
 in a suitable solvent, and isolated according to the
 usual techniques well known to persons skilled in the
 5 art.

The compounds of formula (I) can also be
 prepared by a condensation reaction from a
 tetrahydropyridine of formula (VI):



in which X and R₁ are as defined above, with a compound
 of formula (VII):



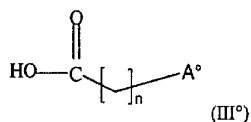
in which n and A are as defined above, and L is a
 leaving group, isolation of the compound of formula (I)
 thus obtained and optional conversion to one of its
 20 salts or solvates.

As leaving group "L", it is possible for
 example to use a halogen group, or any other group
 suitable for condensation with the compound of
 formula (VI).

The condensation reaction is carried out by mixing the starting compounds (VI) and (VII) in an organic solvent such as an alcohol such as for example methanol or butanol, in the presence of a base such as
 5 for example alkali metal carbonates, at a temperature of between room temperature and the reflux temperature of the chosen solvent, according to conventional methods.

The starting compounds of formula (II) are
 10 known or they can be prepared in a similar manner to the known compounds.

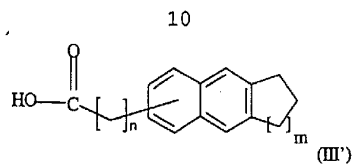
The compounds of formula (III°)



15

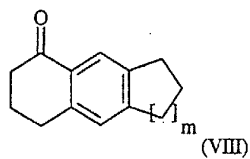
in which A° is a group of formula (a), (c) or (d) as defined above, n is an integer from 1 to 5 and m is 1 or 2, and their salts or solvates are novel compounds and constitute a subsequent aspect of the present
 20 invention.

When A is a group (a), these novel compounds are represented by formula (III')

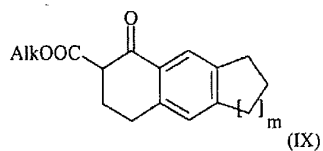


where n and m are as defined above, and may be synthesized by a method which involves:

- 5 (i) reacting compound (VIII) below



where m is 1 or 2, with a dialkyl carbonate in the presence of a strong base such as an alkali metal hydride, reacting the compound of formula (IX) thus obtained

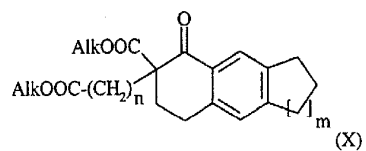


with a Hal-(CH₂)_n-COOAlk derivative in which n is as defined above, Alk is an alkyl group and Hal is a halogen atom,

in the presence of a strong base such as
an alkali metal hydride,

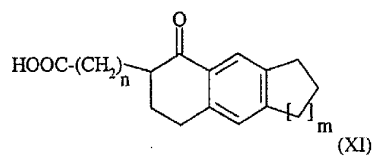
- (iii) hydrolyzing and decarboxylating the
compound (X) thus obtained

5

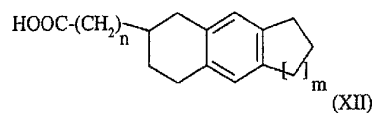


by heating in the presence of a base,
such as sodium hydroxide,

- 10 (iv) reducing the ketone of formula (XI) thus
obtained



- 15 (v) aromatizing the compound of formula
(XII) thus obtained

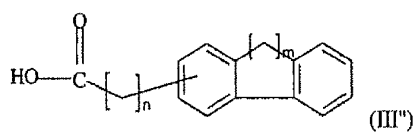


- 20 for example by oxidation with Pd/C at
high temperature, in a solvent such as

Decalin, obtaining the compound of
formula (III') which is isolated
according to conventional methods and
optionally converted to one of its
salts.

5

When A is a group (c), these novel compounds
are represented by formula (III'')

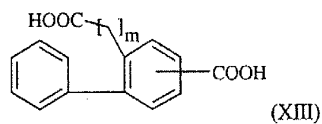


10

where n and m are as defined above.

When n is 0, these compounds may be
synthesized according to a method which involves:

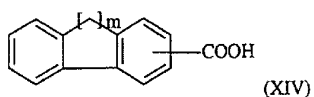
15 (vi) reacting the compound of formula (XIII)



20

with polyphosphoric acid (PPA) and
reducing the 9-oxofluorene derivative
thus obtained, obtaining the compound of
formula (III'') where n is 0; and when n
is 1,

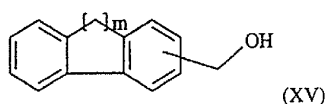
- (vii) esterifying and reducing the fluorenecarboxylic acid (XIV) thus obtained:



5

for example by reaction with methanol in the presence of hydrochloric acid followed by reduction with LiAlH_4

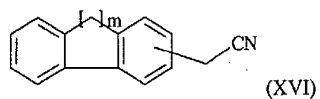
- 10 (viii) converting the alcohol of formula (XV) thus obtained



15

to a cyano derivative, for example by preparation of the corresponding chloride and reaction with KCN ;

- (ix) and hydrolyzing this cyano derivative of formula (XVI)



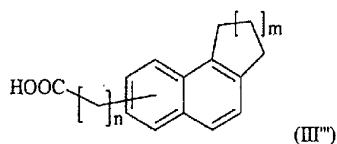
for example in an acid medium, obtaining the compound of formula (III'') where n is 1, which is isolated according to conventional methods and optionally converted to one of its salts.

5

If it is desired to prepare the compounds of formula (III'') where n is > 1, it is sufficient to repeat the passages (vii)-(ix), although other known methods of synthesis may be used to extend the alkyl chain.

10

When A is a group (d), these novel compounds are represented by formula (III''')



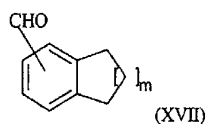
15

where n and m are as defined above.

The compounds of formula (III''') where n is 0 or 1, may be synthesized according to a method which involves:

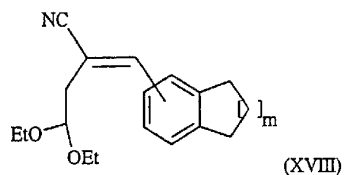
20

(x) reacting the compound of formula (XVII)

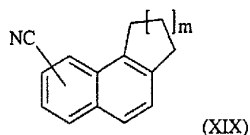


with (1-cyano-3,3-diethoxypropyl)diethyl phosphonate;

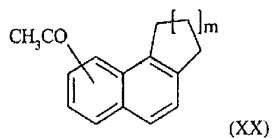
- (xi) cyclizing the compound of formula (XVIII) thus obtained:



- for example in the presence of SnCl_4 , and
 (xii) either hydrolyzing the cyano derivative
 of formula (XIX)
- 10



- obtaining the compound of formula
 (III'') where n is 0,
 (xiii) or, when n is 1, converting the
 derivative of formula (XIX) to a ketone
 of formula (XX)
- 15



for example by a Grignard reaction with CH_3MgI ; and

- (xiv) converting the ketone (XX) to the
5 corresponding acid of formula (III''')
where n is 1.

If it is desired to prepare the compounds of
formula (III''') where n is > 1 , it is sufficient to
repeat the passages (vii)-(ix) above starting with the
10 acid of formula (III''') as obtained in the passage
(xiv), or to use other methods of synthesis known to
extend the alkyl chain.

When the cyclization of the passage (xi) is
carried out starting with a beta-aldehyde, it is
15 possible to obtain two derivatives of formula (XIX),
because the formation of the aromatic ring may be
achieved by cyclization on one of the two adjacent
positions. In this case, the isomers thus formed should
be separated, for example by means of chromatography on
20 a silica gel column, and proceeding using the desired
isomer.

The reactions described above are in general
well known to persons skilled in the art. Detailed
examples of such methods are in any case reported in
25 the experimental section.

The compounds of the invention have
advantageous properties with respect to the inhibition
of $\text{TNF-}\alpha$.

These properties were demonstrated with the aid of a test aimed at measuring the effect of molecules on the synthesis of TNF- α induced in Balb/c mice by lipopolysaccharide (LPS) from Escherichia Coli (055:B5, Sigma, St. Louis, Mo).

The test products are administered orally to groups of 5 female 7- to 8-week old Balb/c mice (Charles River, France). One hour later, the LPS is administered intravenously (10 μ g/mouse). The blood of each animal is taken 1.5 hours after the administration of the LPS. The samples are centrifuged and the plasma is recovered and frozen at -80°C. The TNF- α is measured using commercial kits (R and D, Abingdon, UK).

In this test, representative compounds of the invention were found to be very active, by inhibiting the synthesis of TNF- α even at very low doses.

By virtue of this activity and their low toxicity, the compounds of formula (I) and their salts or solvates can be used in the treatment of diseases linked to immune and inflammatory disorders or as analgesics. In particular, the compounds of formula (I) can be used for treating atherosclerosis, autoimmune diseases, diseases entailing demyelination of the neurons (such as multiple sclerosis), asthma, rheumatoid arthritis, fibrotic diseases, pulmonary idiopathic fibrosis, cystic fibrosis, glomerulonephritis, rheumatoid spondylitis, osteoarthritis, gout, bone and cartilage resorption,

osteoporosis, Paget's disease, multiple myeloma,
uveoretinitis, septic shock, septicemia, endotoxic
shock, graft-versus-host reaction, graft rejection,
adult respiratory distress syndrome, silicosis,
5 asbestosis, pulmonary sarcoidosis, Crohn's disease,
ulcerative colitis, amyotrophic lateral sclerosis,
Alzheimer's disease, Parkinson's disease, disseminated
lupus erythematosus, hemodynamic shock, ischemic
pathologies (myocardial infarction, myocardial
10 ischemia, coronary vasospasm, angina pectoris, cardiac
insufficiency, heart attack), post-ischemic reinfusion
attacks, malaria, mycobacterial infections, meningitis,
leprosy, viral infections (HIV, cytomegalovirus,
herpesvirus), opportunistic infections associated with
15 AIDS, tuberculosis, psoriasis, atopic dermatitis and
contact dermatitis, diabetes, cachexia, cancer and
radiation-mediated damage.

The compounds of formula (I) and the
pharmaceutically acceptable salts and solvates thereof
20 are preferably administered orally.

In the pharmaceutical compositions of the
present invention for oral use, the active principle
can be administered in unit administration forms, as a
mixture with conventional pharmaceutical supports, to
25 animals and human beings for the treatment of the
abovementioned complaints. The appropriate unit
administration forms comprise, for example, tablets,

which may be splittable, gel capsules, powders, granules and oral solutions or suspensions.

When a solid composition in the form of tablets is prepared, the main active ingredient is
5 mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose or other suitable materials or alternatively they can be treated such that they have sustained or delayed
10 activity and such that they release a predetermined amount of active principle continuously.

A preparation in the form of gel capsules is obtained by mixing the active ingredient with a diluent and pouring the mixture obtained into soft or hard gel
15 capsules.

A preparation in the form of syrup or elixir can contain the active ingredient together with a sweetener, preferably a calorie-free sweetener, methylparaben and propyl paraben as antiseptic agents,
20 as well as a flavoring and a suitable colorant.

The water-dispersible powders or granules can contain the active ingredient as a mixture with dispersants or wetting agents, or suspending agents, such as polyvinylpyrrolidone, as well as with
25 sweeteners or flavour enhancers.

The active principle can also be formulated in the form of microcapsules, optionally with one or more supports or additives.

In the pharmaceutical compositions according to the present invention, the active principle can also be in the form of an inclusion complex in cyclodextrins, or ethers or esters thereof.

5 The amount of active principle to be administered depends, as always, on the degree of progress of the disease as well as the age and weight of the patient. Nevertheless, the unit doses generally comprise from 0.001 mg to 100 mg, better still from
10 0.01 mg to 50 mg and preferably from 0.1 mg to 20 mg of active principle, advantageously from 0.5 mg to 10 mg.

According to another of its aspects, the present invention relates to a combination comprising a compound of formula (I) or one of its pharmaceutically
15 acceptable salts or solvates, and at least one compound chosen from immunosuppressants, such as interferon beta-1b; adrenocorticotrophic hormone; glucocorticoids such as prednisone or methylprednisolone; interleukin-1 inhibitors.

20 More particularly, the invention relates to a combination comprising a compound of formula (I), or one of its pharmaceutically acceptable salts or solvates, and at least one compound chosen from roquinimex (1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-3-
25 quinolinecarboxanilide), myloran (product from the company Autoimmune containing bovine myelin), antegren (monoclonal human antibody from the companies

Elan/Athena Neurosciences) and recombinant interferon beta-1b.

Other possible combinations are those consisting of a compound of formula (I), or one of its
5 pharmaceutically acceptable salts or solvates, and a potassium-channel blocker such as, for example, fampridine (4-aminopyridine).

According to another of its aspects, the invention relates to a method for treating diseases
10 linked to immune and inflammatory disorders and/or in the treatment of pain, in particular atherosclerosis, autoimmune diseases, diseases entailing demyelination of the neurons (such as multiple sclerosis), asthma, rheumatoid arthritis,
15 fibrotic diseases, pulmonary idiopathic fibrosis, cystic fibrosis, glomerulonephritis, rheumatoid spondylitis, osteoarthritis, gout, bone and cartilage resorption, osteoporosis, Paget's disease, multiple myeloma, uveoretinitis, septic shock, septicemia,
20 endotoxic shock, graft-versus-host reaction, graft rejection, adult respiratory distress syndrome, silicosis, asbestosis, pulmonary sarcoidosis, Crohn's disease, ulcerative colitis, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease,
25 disseminated lupus erythematosus, hemodynamic shock, ischemic pathologies (myocardial infarction, myocardial ischemia, coronary vasospasm, angina pectoris, cardiac insufficiency, heart attack), post-ischemic reinfusion

2002360117 02 Jul 2008

22

attacks, malaria, mycobacterial infections, meningitis, leprosy, viral infections (HIV, cytomegalovirus, herpesvirus), opportunistic infections associated with AIDS, tuberculosis, psoriasis, atopic dermatitis and contact
 5 dermatitis, diabetes, cachexia, cancer and radiation-mediated damage, comprising the administration of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, alone or in combination with other active principles.

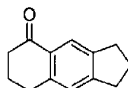
10 The invention further provides the use of a compound of formula (I) or of one of its pharmaceutically acceptable salts, solvates or N-oxides for the preparation of analgesic medicaments and/or medicaments intended for the treated of diseases linked to immune and inflammatory
 15 disorders.

The examples which follow illustrate the invention.

PREPARATION 1

1,2,3,6,7,8-Hexahydro-5H-cyclopenta [b]naphthalene-5-one

20



A suspension of 61 g (0.457 mol) of anhydrous $AlCl_3$
 25 in 188 ml of a dichloromethane/nitromethane=8/1 mixture is cooled to 0-5°C and 22.15 g of indan and, in portions, 22.5 g (0.225 mol) of succinic anhydride are added thereto. After one hour at 0°C, the medium is poured into a water/ice mixture, hydrochloric acid at 37% is added until a clear

2002360117 02 Jul 2008

22A

solution is obtained. The medium is extracted with ethyl acetate, washed with water, the organic phase is dried and the solvent is

evaporated off under reduced pressure. A white solid is obtained which is dissolved in 500 ml of dioxane.

4.6 ml of sulfuric acid at 98% in 50 ml of ethanol and 3.6 g of 10% Pd/C are added thereto. After 5 hours

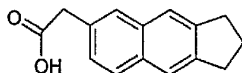
5 under a hydrogen atmosphere, the catalyst is filtered off, the solvent is evaporated off, the residue is taken up in water and the medium is extracted with ethyl acetate. The product obtained is dissolved in 20 ml of methanol and 8 ml of a 1 N aqueous sodium

10 hydroxide solution are added thereto and the medium is stirred at room temperature for 2 hours. The solvent is evaporated off, water is added, the medium is brought to an acidic pH, it is extracted and a white solid is isolated. 38.7 g of this product are dissolved in

15 1000 ml of anhydrous methylene chloride under a nitrogen atmosphere; the medium is cooled to 0°C and 47 g (0.225 mol) of PCl₃ are carefully added thereto, the medium is stirred at 0°C for two hours and 121.8 g (0.467 mol) of SnCl₄ are slowly added thereto and,

20 after 10 minutes, the medium is allowed to heat up to room temperature. After two hours at room temperature, the medium is poured into a water/ice mixture, extracted with methylene chloride and an oil is isolated which is then purified by chromatography on a

25 silica gel column, eluting with a cyclohexane/ethyl acetate=8/2 mixture. 6.0 g of the title compound are obtained.

PREPARATION 2**2,3-Dihydro-1H-cyclopenta[b]naphthalen-6-ylacetic acid**

5

The procedure being carried out under a nitrogen stream, 3 g of sodium hydride at 80% (0.075 mol) are mixed in 845 ml of tetrahydrofuran and 0.7 g (0.0375 mol) of the product of Preparation 1, dissolved in 45 ml of tetrahydrofuran, is added thereto. After 1 hour under reflux, 9 ml (0.075 mol) of diethyl carbonate in 45 ml of tetrahydrofuran are added and the medium is kept stirring under reflux for 5 hours. The mixture is cooled and a saturated aqueous ammonium chloride solution and water are added thereto until complete dissolution is obtained and the medium is extracted with ethyl acetate. The medium is washed with water, the organic phase is dried and the solvent is evaporated off under reduced pressure. The oil obtained is dissolved in 60 ml of tetrahydrofuran and this solution is added, at room temperature and under a nitrogen atmosphere, to a suspension of sodium hydride at 80% (1.6 g; 0.41 mol) in 30 ml of tetrahydrofuran. The medium is stirred for 30 minutes and 8.8 ml of ethyl bromoacetate (0.08 mol) are added thereto, and the medium is stirred at room temperature for 5 hours. Ammonium chloride is added and the medium is extracted

10

15

20

25

with methylene chloride. The medium is washed with water, the organic phase is dried and the solvent is evaporated off under reduced pressure. The oil thus obtained is dissolved in 600 ml of a 0.5 N aqueous-
5 alcoholic solution of sodium hydroxide (EtOH/H₂O ratio = 2/1). The medium is heated at about 40°C until complete conversion of the product to its sodium salt is obtained (formation of a product with the base in the thin-layer chromatography trial, eluting with an
10 ethyl acetate/hexane = 3/7 mixture. After about 8 hours, half of the solvent is evaporated off under reduced pressure, the medium is acidified with 15 ml of 1 N hydrochloric acid and heated at 50°C for about 45 minutes. The medium is extracted with ethyl acetate,
15 the organic phase is dried and the solvent is evaporated off under reduced pressure. The product obtained is dissolved in 60 ml of acetic acid and 4.5 ml of sulfuric acid at 98%, diluted in 9 ml of acetic acid, and 1 g of 10% Pd/C are added thereto; the
20 medium is then hydrogenated for 8 hours. Half of the solvent is evaporated off, the catalyst is filtered off, water is added and the medium is extracted with ethyl acetate, the organic phase is dried and the solvent is evaporated off. The product thus obtained is
25 dissolved in 100 ml of methanol, 200 mg of para-toluenesulfonic acid are added thereto and the medium is heated under reflux for 4 hours. The solvent is partially evaporated off and 50 ml of a 5% aqueous

sodium bicarbonate solution are added thereto and the medium is extracted with diethyl ether, the medium is washed with water and with brine. The organic phase is dried, and the solvent is evaporated off under reduced pressure. The product thus obtained is dissolved in Decalin (20 ml), 1.4 g of 10% Pd/C are added thereto and the medium is heated at 200°C for 48 hours. The catalyst is filtered off, the solvent is evaporated off and the crude reaction product is purified by chromatography on a silica gel column, eluting with a cyclohexane/ethyl acetate = 9/1 mixture. 750 mg of the product thus obtained are dissolved in 30 ml of ethanol, 20 ml of 1 N NaOH are added thereto and the medium is heated at 50°C for 4 hours. The ethanol is evaporated off and the medium is acidified with 1 N HCl. A white solid is obtained.

m.p. 185-188°C

PREPARATION 3

5-(2-Bromoethyl)indan

2 ml (0.016 mol) of indan in 33 ml of methylene chloride and 1.6 ml (0.019 mol) of bromoacetyl bromide are mixed at 0°C. 2.27 g (0.017 mol) of AlCl₃ are slowly added and the medium is allowed to return to room temperature and stirred for 2 hours. The mixture is poured into water/ice and extracted with methylene chloride. The organic phase is dried, filtered and the solvent is evaporated off under reduced pressure. The crude reaction product is

crystallized from hexane. A white solid is separated (m.p. 57.8-58.1°C) corresponding to the acylation product. 1.67 g (7 mmol) of this product are dissolved in 3.9 ml of triethylsilane and 3.9 ml of

- 5 trifluoroacetic acid and the medium is heated at 80°C for two hours. The medium is poured into an ice/NaOH mixture and extracted with ethyl acetate. The title compound is obtained.

PREPARATION 4

- 10 **2-(2-Bromoethyl)-5,6,7,8-tetrahydronaphthalene**

By carrying out the procedure as described in Preparation 3, but using Tetralin instead of indan, the title compound is obtained.

PREPARATION 5

- 15 **5-(3-Bromopropyl)indan**

By carrying out the procedure as described in Preparation 3 but using bromopropionyl bromide instead of bromoacetyl bromide, the title compound is obtained.

PREPARATION 6

- 20 **5-(3-Bromobutyl)indan**

By carrying out the procedure as described in Preparation 3 but using bromobutanoyl bromide instead of bromoacetyl bromide, the title compound is obtained.

PREPARATION 7

- 25 **2-(2-Bromoethyl)fluorene**

By carrying out the procedure as described in Preparation 3 but using fluorine instead of indan, the title compound is obtained.

PREPARATION 8**2-(2-Bromoethyl)-9,10-dihydrophenanthrene**

By carrying out the procedure as described in Preparation 3 but using 9,10-dihydrophenanthrene instead of indan, the title compound is obtained.

PREPARATION 9**3-Fluorenylacetic acid****9a) 9-Oxofluoren-3-ylcarboxylic acid**

A mixture of 0.45 g (0.00186 mol) of 2,5-biphenyldicarboxylic acid and 13.9 g of polyphosphoric acid (PPA) is heated to 200°C. After one hour, the medium is cooled to 100°C and ice is added thereto until a volume of about 100 ml is obtained. The medium is filtered and a solution of 0.5 g of NaOH in 90 ml of water is added to the precipitate and the medium is stirred for one hour at 60°C. The medium is acidified with hydrochloric acid and extracted with ethyl acetate. The organic phase is dried, filtered and the solvent is evaporated off under reduced pressure. 0.31 g of the title product is obtained in the form of a light brown solid.

9b) Fluoren-3-ylcarboxylic acid

0.27 g (0.0012 mol) of the product of the preceding step is dissolved in 2.5 ml of ethylene glycol and 0.1 g of NaOH and 0.25 ml of hydrazine at 98% (d=1.03) are added thereto. The medium is heated under reflux for 1.5 hours, it is allowed to return to room temperature, 70 ml of water are added and the

medium is acidified to pH = 6 with hydrochloric acid. The medium is extracted with ethyl acetate, the organic phase is dried, filtered and the solvent is evaporated off under reduced pressure. 0.4 g of the title product is thus obtained in the form of a yellow solid.

9c) Methyl ester of fluoren-3-ylcarboxylic acid

The ester of the product of the preceding step is prepared with the aid of methanol in hydrochloric acid. The solution is brought to a basic pH and extracted with ethyl acetate, thus obtaining the title product in the form of an oil.

9d) 3-Hydroxymethylfluorene

A mixture of 0.68 g of LiAlH_4 in 7 ml of anhydrous ethyl ether is cooled to 0°C and under a nitrogen stream, and a solution of 3.4 g (0.0152) of the product of the preceding step in 27 ml of anhydrous ethyl ether are added thereto dropwise and the medium is stirred overnight. A water/ice mixture is then added, the medium is extracted with ethyl acetate, the organic phase is dried, filtered and the solvent is evaporated off under reduced pressure. 3 g of the crude product are thus obtained, which product is purified by chromatography on a silica gel column, eluting with a cyclohexane/ethyl acetate 7/3 mixture. 1.33 g of the title product are thus obtained in the form of a white solid.

9e) 3-Chloromethylfluorene

A solution of 35 mg (0.178 mmol) of the product of the preceding step in 0.5 ml of methylene chloride is cooled to 0°C and 0.13 ml of thionyl chloride (1.178 mmol) is added thereto dropwise. The mixture is stirred for three hours at room temperature and a mixture of water and sodium bicarbonate is added thereto to pH 8. The medium is extracted with methylene chloride, the organic phase is dried, filtered and the solvent is evaporated off under reduced pressure. 20 mg of the title product are thus obtained in the form of a yellow oil.

9f) 3-Cyanomethylfluorene

1.3 g (0.00605 g) of the product of the preceding step are dissolved in 32 ml of DMSO and 0.44 g (0.00666 mol) of KCN is added thereto. The medium is heated at 80°C for 3 hours, a water/ice mixture is added thereto and the medium is extracted with ethyl acetate. The organic phase is dried, filtered and the solvent is evaporated off under reduced pressure. The crude product is purified by flash chromatography, eluting with a cyclohexane/ethyl acetate 8/2 mixture. 250 mg of the title product are thus obtained.

9g) 3-Fluorenylacetic acid

The cyano derivative of the preceding step is hydrolyzed with the aid of 6 N hydrochloric acid while heating under reflux. A water/ice mixture is added and the medium is extracted with ethyl acetate. The organic

phase is dried, filtered and the solvent evaporated off under reduced pressure. 0.22 g of the title product is thus obtained in the form of a solid.

m.p.: 166-168°C

5 PREPARATION 10

**2,3-Dihydro-1H-cyclopenta[a]naphthalen-8-ylacetic acid
10a) 4,4-Diethoxy-2-indan-4-ylmethylenbutyronitrile**

0.23 g (0.0092 mol) of NaH at 60% in 20 ml of anhydrous THF is cooled at 0°C under a nitrogen stream and a solution of 2.26 g (0.0085 mol) of a diethyl ester of (1-cyano-3,3-diethoxypropyl)phosphonic acid in 16 ml of THF is added thereto. After 30 minutes, the mixture becomes clear and a solution of 1.1 g (0.0075 mol) of 2,3-dihydro-1H-inden-8-ylbenzaldehyde in 16 ml of THF is then added thereto dropwise. The medium is stirred for one hour at 0°C and a water/ice mixture is added. The medium is extracted with methylene chloride, the organic phase is washed with an NaOH/water solution, the organic phase is dried, filtered and the solvent is evaporated off under reduced pressure. 2.49 g of the crude product are thus obtained in the form of an orange-colored oil which is purified by flash chromatography, eluting with a cyclohexane/ethyl acetate 95/5 mixture. The title product is thus obtained.

10b) 8-Cyano-2,3-dihydro-1H-cyclopenta[a]naphthalene

A mixture of 0.56 g (0.0021 mol) of the product of the preceding step in 14 ml of methylene

chloride is cooled to 0°C and 152 ml (0.0013 mol) of SnCl₄ (d = 2.226) are added thereto dropwise. The medium is stirred at room temperature for 4 hours, sodium bicarbonate at 10% is then added thereto and the medium is extracted with methylene chloride. The organic phase is dried, filtered and the solvent is evaporated off under reduced pressure. 0.43 g of the title product is thus obtained in the form of a light yellow solid.

10 **10c) 8-Methylcarbonyl-2,3-dihydro-1H-cyclopenta[a]naphthalene**

0.5 g (0.0025 mol) of the product of the preceding step is dissolved in 20 ml of anhydrous toluene and 1.6 ml (0.005 mol) of 3 M methylmagnesium iodide are added thereto dropwise and under a nitrogen stream. The medium is stirred overnight at room temperature, and water and hydrochloric acid are then added thereto. The medium is stirred for 15 minutes, brought to a basic pH with a 5 M NaOH solution and extracted with ethyl acetate. The organic phase is washed, it is dried, filtered and the solvent is evaporated off under reduced pressure. 0.69 g of the crude product is thus obtained, which product is purified by flash chromatography, eluting with a hexane/diethyl ether 95/5 mixture. 0.35 g of the title product is thus obtained.

10d) 8-(Morpholinothiocarbonyl)-2,3-dihydro-1H-cyclopenta[a]naphthalene

0.35 g (0.0016 mol) of the product of the preceding step is dissolved in 0.35 ml (0.0016 mmol) of morpholine ($d = 0.999$) and 0.54 g (0.0020) of sulfur and a crystal of para-toluenesulfonic acid (PTSA) are added thereto. The medium is heated under reflux for 6 hours and methanol is then added. The medium is stirred at room temperature overnight. The solvent is removed under reduced pressure and 2.5 g of the crude product are thus obtained, which product is purified by flash chromatography, eluting with a cyclohexane/ethyl acetate 9/1 mixture. 0.16 g of the title product is thus obtained.

10e) 2,3-Dihydro-1H-cyclopenta[a]naphthalen-8-ylacetic acid

0.16 g (0.0005 mol) of the product of the preceding step is dissolved in 7.6 ml of a 1:1 methanol/water solution and 0.02 g of solid NaH is added thereto. The medium is heated under reflux for 6 hours, the solvent is then removed under reduced pressure, the residue is taken up in a water and ethyl acetate mixture, the organic phase is removed, the aqueous phase is acidified and extracted with methylene chloride. The organic phase is dried, filtered and the solvent evaporated off under reduced pressure. 20 mg of the title product are thus obtained.

PREPARATION 11**5,6,7,8-Tetrahydrophenanthren-3-ylacetic acid**

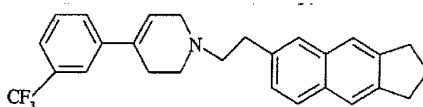
By following the procedure described in Preparation 10 but using 5,6,7,8-tetrahydronaphthalen-1-ylbenzaldehyde instead of 2,3-dihydro-1H-inden-7-ylbenzaldehyde, the title product is obtained.

PREPARATION 12**5,6,7,8-Tetrahydroanthren-2-ylacetic acid**

By following the procedure described in Preparation 10 but using 5,6,7,8-tetrahydronaphthalen-2-ylbenzaldehyde instead of 2,3-dihydro-1H-inden-7-ylbenzaldehyde, the title product is obtained.

EXAMPLE 1

1-[2-(2,3-Dihydro-1H-cyclopenta[b]naphthalen-6-yl)ethyl]-4-[3-trifluoromethylphenyl]-1,2,3,6-tetrahydropyridine and its hydrochloride



1a) 1-[4-Hydroxy-4-(3-trifluoromethylphenyl)-1-piperidinyl]-2-(2,3-dihydro-1H-cyclopenta[b]naphthalen-6-yl)-1-ethanone

400 mg (1.76 mol) of the product of Preparation 2 are dissolved under a nitrogen atmosphere in 10 ml of anhydrous methylene chloride and 430 mg (1.76 mol) of 4-hydroxy-4-(3-

trifluoromethylphenyl)piperidine, 0.79 g (1.76 mol) of BOP and 0.73 ml of triethylamine are added thereto and the medium is stirred at room temperature for 3 hours. 40 ml of ethyl acetate are added, the medium is washed
5 with a 1 N hydrochloric acid solution, then with a 1 N sodium hydroxide solution, and then with water. The organic phase is dried over sodium sulfate and the solvent is evaporated off. 0.8 g of the title compound is obtained in the form of an oil.

10 **1b) 1-[2-(2,3-Dihydro-1H-cyclopenta[b]naphthalen-6-yl)ethyl]-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine**

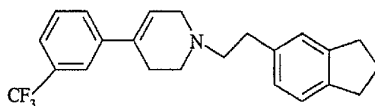
The product obtained in Example 1a is dissolved in 7 ml of anhydrous THF, the medium is
15 heated under reflux and 0.5 ml of borane-dimethyl sulfide is added thereto and the medium is heated under reflux for 4 hours. The medium is cooled to 0-5°C and 7 ml of methanol are carefully added thereto. After 5 minutes, the medium is heated under reflux for 30
20 minutes, the solvent is evaporated off, the residue is taken up in the water/ammonia=1/1 mixture, the medium is extracted with ethyl acetate, the two phases are separated and the organic phase is washed with water. The medium is dried over sodium sulfate and the solvent
25 is evaporated off under reduced pressure. The crude crystallization product is purified in 2-propyl ether. 0.37 g of the title product is obtained.
m.p. 154-156°C.

1c) 1-[2-(2,3-Dihydro-1H-cyclopenta[b]naphthalen-6-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

350 mg (0.8 mmol) of the product of the preceding step are dissolved in 10 ml of acetic acid, 1 ml of sulfuric acid at 96% is added thereto and the medium is heated at 80°C for 2 hours. The medium is cooled, concentrated NH₄OH is added thereto and the medium is extracted with ethyl acetate. The medium is washed with water, dried and evaporated under reduced pressure. The title compound is obtained. The hydrochloride is prepared with the aid of a solution of 2-propanol saturated with hydrochloric acid. m.p. (hydrochloride) 264-266°C.

15 EXAMPLE 2

1-[2-(2,3-Dihydro-1H-inden-5-yl)ethyl]-4-[3-trifluoromethylphenyl]-1,2,3,6-tetrahydropyridine and its hydrochloride



20

The product obtained in Preparation 3 is dissolved in 17 ml of butanol. 0.84 g (3.2 mol) of 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and 0.9 g (6.5 mmol) of potassium carbonate are added thereto and the medium is heated under reflux for 5

hours. The solvent is evaporated off and the residue is washed with water. It is extracted with methylene chloride, the organic phase is dried and the solvent is evaporated off under reduced pressure. The residue is

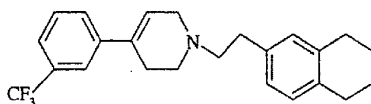
5 purified on a silica gel column, eluting with a cyclohexane/ethyl acetate = 8/2 mixture. The title compound is obtained. The hydrochloride is prepared with the aid of 2-propanol saturated with hydrochloric acid.

10 m.p. (hydrochloride) 252-255°C.

EXAMPLE 3

1-[2-(5,6,7,8-Tetrahydronaphthalen-2-yl)ethyl]-4-[3-trifluoromethylphenyl]-1,2,3,6-tetrahydropyridine and its hydrochloride

15



By carrying out the procedure as described in Example 2 but using the product of Preparation 4

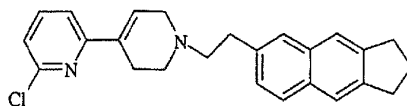
20 instead of the product of Preparation 3, the title compounds are obtained.

m.p. (hydrochloride): 263-267°C.

EXAMPLE 4

1-[2-(2,3-Dihydro-1H-cyclopenta[b]naphthalen-6-yl)ethyl]-4-(6-chloropyrid-2-yl)-1,2,3,6-tetrahydropyridine and its hydrochloride

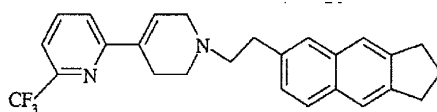
25



By carrying out the procedure as described in
 5 Example 1 but using 4-(6-chloropyrid-2-yl)-1,2,3,6-
 tetrahydropyridine instead of 4-(3-
 trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine, the
 title compounds are obtained.
 m.p. (hydrochloride): 254-258°C.

10 EXAMPLE 5

1-[2-(2,3-Dihydro-1H-cyclopenta[b]naphthalen-6-
 yl)ethyl]-4-(6-trifluoromethylpyrid-2-yl)-1,2,3,6-
 tetrahydropyridine and its hydrochloride

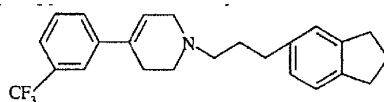


15

By carrying out the procedure as described in
 Example 1 but using 4-(6-trifluoromethylpyrid-2-yl)-
 1,2,3,6-tetrahydropyridine instead of 4-(3-
 20 trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine, the
 title compounds are obtained.
 m.p. (hydrochloride): 264 - 267°C.

EXAMPLE 6

1-[3-(2,3-Dihydro-1H-inden-5-yl)propyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride



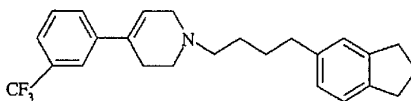
5

By carrying out the procedure as described in Example 2 but using the product of Preparation 5 instead of the product of Preparation 3, the title compounds are obtained.

m.p. (hydrochloride): 192 - 195°C.

EXAMPLE 7

1-[4-(2,3-Dihydro-1H-inden-5-yl)butyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

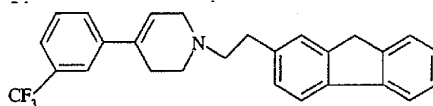


By carrying out the procedure as described in Example 2 but using the product of Preparation 6 instead of the product of Preparation 3, the title compounds are obtained.

m.p. (hydrochloride): 198-200°C

EXAMPLE 8

**1-[2-(Fluoren-2-yl)ethyl]-4-(3-trifluoromethylphenyl)-
1,2,3,6-tetrahydropyridine and its hydrochloride**



5

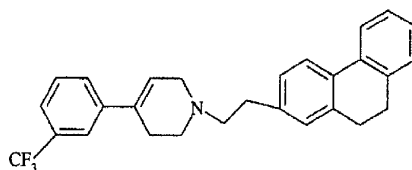
By carrying out the procedure as described in Example 2 but using the product of Preparation 7 instead of the product of Preparation 3, the title compounds are obtained.

10 m.p. (hydrochloride): 285-287°C

EXAMPLE 9

**1-[2-(9,10-Dihydrophenanthren-2-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and
its hydrochloride**

15



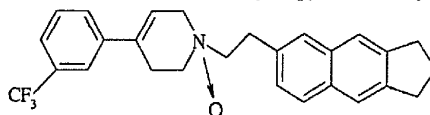
By carrying out the procedure as described in Example 2 but using the product of Preparation 8 instead of the product of Preparation 3, the title compounds are obtained.

20 m.p. (hydrochloride): 256-258°C

EXAMPLE 10

1-[2-(2,3-Dihydro-1H-cyclopenta[b]naphthalen-6-yl)ethyl]-(4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine 1-oxide

5



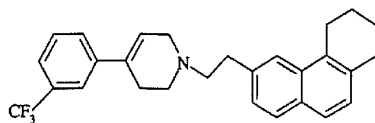
0.27 g of m-chloroperbenzoic acid is added to a solution of 0.47 g (1.1 mmol) of 1-[2-(2,3-dihydro-1H-cyclopenta[b]naphthalen-6-yl)ethyl]-4-(6-trifluoromethylpyrid-2-yl)-1,2,3,6-tetrahydropyridine in 40 ml of methylene chloride at the temperature of 0-5°C. The medium is kept stirring at 0-5°C for two hours, washed with a saturated aqueous sodium bicarbonate solution and the two phases are separated. The organic phase is dried, filtered and evaporated under reduced pressure. The medium is purified by chromatography, eluting with a methanol/ethyl acetate = 1/1 mixture and the title product is obtained.

m.p.: 116-117°C

EXAMPLE 11

1-[2-(Fluoren-3-yl)ethyl]-(4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride

43

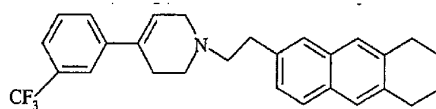


By carrying out the procedure as described in Example 1 but using the product of Preparation 11 instead of the product of Preparation 2, the title compounds are obtained.

m.p. (hydrochloride): 222-224°C

EXAMPLE 14

1- [2-(5,6,7,8-Tetrahydroanthracen-2-yl)ethyl]-(4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine and its hydrochloride



By carrying out the procedure as described in Example 1 but using the product of Preparation 12 instead of the product of Preparation 2, the title compounds are obtained.

m.p. (hydrochloride): 252-253°C

2002360117 02 Jul 2008

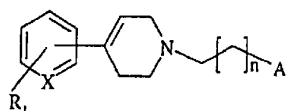
43A

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a
5 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
10 matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that 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 of formula (I):



(I)

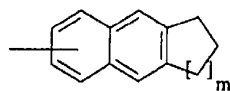
in which

X represents N or CH;

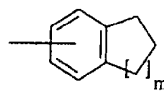
R_1 represents a hydrogen or halogen atom or a CF_3 group;

n is an integer from 1 to 5;

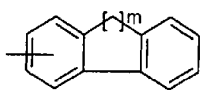
A represents a group of formula (a) to (d):



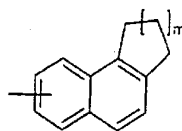
(a)



(b)



(c)



(d)

15

in which m is 1 or 2;

and its salts or solvates and its N-oxides.

2. The compound as claimed in claim 1,
where n is 1.

3. The compound as claimed in claim 1 or 2,
where R₁ is a CF₃ group.

5 4. The compound as claimed in claims 1 to
3, where X is CH and R₁ is at the 3-position of the
benzene.

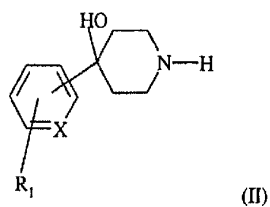
5. The compound as claimed in claims 1 to
3, where X is N and the pyridine is substituted at the
10 2,6-positions.

6. The compound as claimed in claim 1,
chosen from the following compounds:

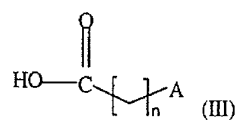
1-[2-(2,3-dihydro-1H-cyclopenta[b]naphthalen-6-
yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-
15 tetrahydropyridine,
1-[2-(2,3-dihydro-1H-inden-5-yl)ethyl]-4-[3-
trifluoromethylphenyl]-1,2,3,6-tetrahydropyridine,
1-[2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]-4-[3-
trifluoromethylphenyl]-1,2,3,6-tetrahydropyridine,
20 1-[2-(2,3-dihydro-1H-cyclopenta[b]naphthalen-6-
yl)ethyl]-4-(6-chloropyrid-2-yl)-1,2,3,6-
tetrahydropyridine,
1-[2-(2,3-dihydro-1H-cyclopenta[b]naphthalen-6-
yl)ethyl]-4-(6-trifluoromethylpyrid-2-yl)-1,2,3,6-
25 tetrahydropyridine,
1-[3-(2,3-dihydro-1H-inden-5-yl)propyl]-4-(3-
trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,

- 1-[4-(2,3-dihydro-1H-inden-5-yl)butyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,
 1-[2-(fluoren-2-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,
- 5 1-[2-(9,10-dihydrophenanthren-2-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,
 1-[2-(2,3-dihydro-1H-cyclopenta[b]naphthalen-6-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,
- 10 1-[2-(fluoren-3-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,
 1-[2-(2,3-dihydro-1H-cyclopenta[a]naphthalen-8-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,
- 15 1-[2-(5,6,7,8-tetrahydrophenanthren-3-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,
 1-[2-(5,6,7,8-tetrahydroanthracen-2-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine,
 their salts and solvates and their N-oxides.
- 20 7. A method for preparing a compound (I) of claim 1, characterized in that
- (a) the compound of formula (II):

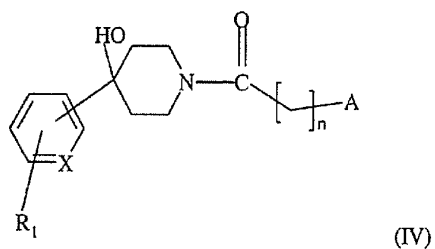
47



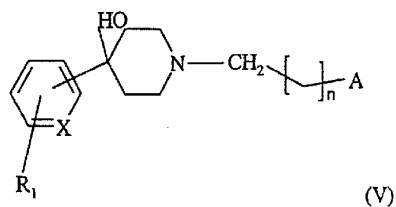
in which R_1 is as defined in claim 1, is reacted with
the acid of formula (III) or one of its functional
5 derivatives:



in which n and A are as defined in claim 1,
10 (b) the carbonyl group of the compound of formula (IV)
thus obtained:



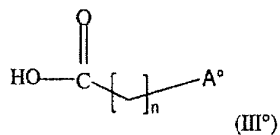
15 is reduced
(c) the piperidinol intermediate of formula (V):



is dehydrated

- 5 (d) the compound of formula (I) thus obtained is isolated and it is optionally converted to one of its salts or solvates or their N-oxides.

8. A compound of formula (III°)



10

in which A° is a group of formula (a), (c) or (d) as defined in claim 1, n is an integer from 1 to 5 and m is 1 or 2, and its salts or solvates.

- 15 9. A pharmaceutical composition comprising, as active ingredient, a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates or N-oxides as claimed in one of claims 1 to 6.

2002360117 02 Jul 2008

49

10. The composition as claimed in claim 9, characterized in that it contains from 0.001 to 100 mg of active ingredient.

11. The use of a compound of formula (I) or of one of its pharmaceutically acceptable salts, solvates or N-oxides as claimed in one of claims 1 to 6 for the preparation of analgesic medicaments and/or medicaments intended for the treatment of diseases linked to immune and inflammatory disorders.

12. A medicament, characterized in that it consists of one of the compounds of formula (I) or one of its salts, solvates or N-oxides as claimed in one of claims 1 to 6.

13. A compound prepared by the method of claim 7.

14. A method for the treatment of pain and/or diseases linked to immune and inflammatory disorders comprising the administration of a compound of Formula (I) or one of its pharmaceutically acceptable salts, solvates or N-oxides as claimed in any one of claims 1 to 6 to a subject in need thereof.

15. A compound according to claim 1, 8 or 13; or a method according to claim 7 or 14; or a composition according to claim 9; or a use according to claim 11; or a medicament according to claim 12 substantially as hereinbefore described and/or exemplified.