Abstract: The invention provides novel enol carbamate derivatives of formula (I) for inhibiting Fatty Acid Amide Hydrolase (FAAH), compositions that include such compounds as well as methods of treating diseases of energy metabolism, central nervous system disorders, cardiovascular and respiratory disorders, retinopathy, cancer, gastrointestinal and liver disorders and/or musculoskeletal disorders. The compounds of the present invention proved particularly efficacious in animal models of anxiety and pain.
Enol carbamate derivatives as modulators of fatty Acid Amide Hydrolase

The present invention relates to enol carbamate derivatives, processes for their preparation, and to pharmaceutical compositions containing them for the treatment of neurological disorders, such as Parkinson, pain and anxiety.

Background of the invention

Anandamide and other fatty acid amides are known to be chemical messengers that modulate a number of physiological processes (Hanus, L.O. Chem. Biodivers. 2007, 4, 1828-41). Anandamide activates through binding both the central-type (CBl) and peripheral type (CB2) cannabinoid receptors (Devane, W. A., et al. Science, 1992, 258, 1946-1949). Anandamide has been reported to be implicated in the modulation of nociception, feeding, emesis, anxiety, cell proliferation, inflammation, and memory (Labar, G., et al. C. Chem. Biodivers., 2007, 4, 1882-1902).


FAAH is also responsible of the catabolism of many other lipid signaling fatty acid amides (i.e. oleamide, Αf-oleoylethanolamine, arachidonylglycerol...
and palmitoylethanolamide). Modulating the activity of the endocannabinoid system by restoring the levels of endogenous signaling lipids turned out to hold therapeutic promise in a wide range of disparate diseases and pathological conditions such as diseases of energy metabolism (cachexia and anorexia), pain and inflammation, central nervous system disorders (stroke, multiple sclerosis, Parkinson's disease, Huntington disease, Alzheimer disease, epilepsy, schizophrenia, anxiety, depression and insomnia), cardiovascular and respiratory disorders (hypertension, circulatory shock, myocardial reperfusion injury, atherosclerosis and asthma), retinopathy, cancer, gastrointestinal and liver disorders (inflammatory bowel disease and hepatitis), musculoskeletal disorders (arthritis and osteoporosis) as nicely reviewed lately (Pasher P. et al, *Pharmacol. Rev.*, 2006, 58, 389 and references therein).


In particular URB-597, a carbamate-based inhibitor, was reported to be efficacious in the zero plus maze animal model of anxiety as well as to have
analgesic efficacy in the rat hot plate and formalin tests (Kathuria S., *et al*, *Nat. Med.*, 2003, 9, 1, 76).

Recently, oxadiazole and difluoroketone derivatives of the general formula R-X-Y were reported to be potent FAAH inhibitors (WO08013963). However, no mention about the selectivity profile of such inhibitors is reported.

The potential therapeutic relevance of inhibiting FAAH has stimulated interest in developing selective and potent inhibitors. Such a strategy potentially represents a safer alternative to the use of exogenous cannabinoid agonists, which have been found to give variable effects.

Inhibiting FAAH seems an ideal way of elevating the levels of the endogenous amidated lipids that activate CBI receptors. Therefore, the desire of potent and selective FAAH inhibitors remains an interesting and promising goal.

Certain enol carbamates have been described in the literature. For example, US 6284,911 describes ways of synthesis of enol carbamate derivatives for use in making vinyl carbamates by reacting vinyl carbonate with primary or secondary amines as depicted underneath.

\[
\begin{align*}
\text{O} & \quad \text{X} = \text{O}_1, \text{S} \\
\text{R}^1 & + \quad \text{HNR}^3 \text{R}^4 \\
\text{R}^3 \text{R}^4 & \quad \text{O} \quad \text{N} \\
\end{align*}
\]

In "*Tetrahedron Lett.*, 2006, 47, 6, 953", Jiang J.L. studies the ReBr(CO)\textsubscript{5}-catalyzed addition of Et2NH and CO2 to terminal alkynes to afford anti-Markovnikov adducts of alkenyl carbamates with a high regioselectivity.


Summary of the invention

The invention provides novel compounds for inhibiting Fatty Acid Amide Hydrolase (FAAH), compositions that include such compounds as well as methods of treating diseases of energy metabolism, pain and inflammation, central nervous system disorders, cardiovascular and respiratory disorders, retinopathy, cancer, gastrointestinal and liver disorders and musculoskeletal disorders by administering FAAH inhibitors to a patient.

The invention comprises compounds of general formula (I)

\[
\begin{align*}
R^1 & \text{"H", halogen or } G^1; \\
G^1 & \text{aryl, or heteroaryl, each being substituted with at least one radical chosen among halogen, hydroxy, lower alkoxy, cyano, aminocarbonyl, aryl or heteroaryl;}
\end{align*}
\]
$R^2$ is H or halogen;

$R^3$ and $R^4$ are independently H, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, arylkyl, alkylaryl, alkoxyaryl or haloaryl;

or $R^3$ and $R^4$ taken together with the nitrogen atom to which they are attached form a heterocycle;

$R^5$ is the group $[D-B-(A)_{n}]$- wherein

A is $(R^6)C=C(R^7)$, wherein $R^6$ and $R^7$ are the same or different and are H, alkyl, aryl, or halogen;

$n = 0, 1, 2$;

B is aryl or heteroaryl, each being optionally substituted with one or more radicals chosen among alkyl, cycloalkyl, aryl, hydroxy, alkoxy, alkylcarbonyloxy, sulfonyloxy, amino, aminoalkylamino, alkylcarbonylamino, cyano, halogen, $R^8SC^\wedge NH$, $R^9NHSC^\wedge$, aminocarbonyl or aminocarbonyloxy;

D is aryl or heteroaryl, each being optionally substituted with one or more radicals chosen among alkyl, cycloalkyl, aryl, hydroxy, alkoxy, alkylcarbonyloxy, sulfonyloxy, amino, aminoalkylamino, alkylcarbonylamino, cyano, halogen, $R^8SC^\wedge NH$, $R^9NHSC^\wedge$, aminocarbonyl or aminocarbonyloxy;

Rs and $R_g$ are alkyl, aryl or heteroaryl, both optionally substituted with one or more radicals chosen among alkyl, hydroxy, alkoxy and alkylcarbonyloxy; its tautomers, its geometrical isomers, its optically active forms such as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof.

with the following proviso:
when \( G_1 \) is para-ethoxy phenyl or para-methyl phenyl, \( R^3 \) and \( R^4 \) are not both ethyl at the same time.

An embodiment of this invention is that of compounds of formula (I), for use as medicaments.

In a further embodiment, said medicament is used for treating a neurological disorder, diseases of energy metabolism, cardiovascular and respiratory disorders, gastrointestinal and liver disorders, retinopathy, cancer and musculoskeletal disorders.

In a preferred embodiment, said medicament is used for treating a neurological disorder.

In a more preferred embodiment, said medicament is used for treating anxiety and pain.

**Detailed description of the invention**

The term "alkyl" refers to linear or branched alkyl groups having from 1 to 20 carbon atoms, or preferably, 1 to 12 carbon atoms, or even more preferably 1 to about 6 carbon atoms. Lower alkyl group is exemplified by \( \text{C}_1-\text{C}_{10} \)-alkyl groups such as methyl, ethyl, \( n \)-propyl, isopropyl, \( n \)-butyl, isobutyl, \( n \)-pentyl, isopentyl, \( n \)-hexyl and the like. Where specified, said alkyl can optionally be substituted with one or more alkyl, lower alkoxy, amino, aminocarbonyl, alkylcarbonyl or alkoxy carbonyl.

The term "cycloalkyl" refers to a saturated or unsaturated (but not aromatic) carbocyclic group of 3 to 10 carbon atoms having a single ring or multiple condensed rings. Examples of "C3-Cio-cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like. Where specified, said cycloalkyl can optionally be substituted with
one or more alkyl, lower alkoxy, amino, aminocarbonyl, alkylcarbonyl or alkoxy carbonyl.

The terms "heterocycloalkyl" and heterocycle refers to a saturated or unsaturated (but not aromatic) five-, six- or seven-membered ring containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings, where specified, may be substituted with amino, alkyl, heterocycloalkyl, alkoxy carbonyl, carboxy or aryl. Preferred heterocycloalkyl include pyrrolidine, piperidine, piperezine, ketopiperazine, 2,5-diketopiperazine, morpholine, thiomorpholine, dihydropyranyl, tetrahydropyranyl, tetrahydrofurane, dihydropyrrole, imidazolidine, dihydropyrazole, pyrazolidine and the like.

The term "aryl" refers to an aromatic carbocyclic group of 6 to 14 carbon atoms having a single ring (e. g., phenyl) or multiple rings, which may be attached in a pendent manner or may be fused. Preferred aryl include phenyl, naphthyl, phenantrenyl, biphenyl, indane and the like.

The term "arylkyl" refers to alkyl groups having one or more aryl substituent, including benzyl, phenethyl, diphenyl methyl and the like.

The term "heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or pyrazolyl.

The term "carboxy" refers to the group -C(O)OH.

The terms "alkoxy" or "lower alkoxy" refer to the group -OR where R includes "Ci-Ce-alkyl".
The term "alkylcarbonyloxy" refers to the group -OC(O)R where R includes H, "Ci-Ce-alkyl", "C₂-C₆-alkenyl", "C₂-C₆-alkynyl", "Cs-Cio-cycloalkyl", "heterocycloalkyl" or "heteroaryl".

The term "amino" refers to the group -NRR' where each R, R' is independently H, "alkyl", "alkenyl", "alkynyl", "cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl" or where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3 to 8-membered heterocycloalkyl ring.

The term "aminocarbonyl" refers to the group -C(O)NRR' where each R, R' includes independently H, "Ci-Ce-alkyl", "(VCe-alkenyl", "(VCe-alkynyl", "Cs-Cio-cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl"; or R and R' taken together with the nitrogen atom to which they are attached form a heterocycloalkyl.

The term "aminocarbonyloxy" refers to the group -OC(O)NRR' where each R, R' includes independently H, "Ci-Ce-alkyl", "C₂-C₆-alkenyl", "C₂-C₆-alkynyl", "Cs-Cio-cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl"; or R and R' taken together with the nitrogen atom to which they are attached form a heterocycloalkyl.

The term "sulfonyloxy" refers to a group -OSO₂-R where R is selected from H, "Ci-C₆-alkyl", substituted with halogens, e.g., an -OSO₂-CF₃ group, "alkenyl", "alkynyl", "cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl".

The term "alkoxycarbonyl" refers to the group -C(O)OR where R includes "alkyl" and "cycloalkyl".

The term "alkylcarbonylamino" refers to an amino group substituted by an alkylcarbonyl residue.
"Pharmaceutically acceptable salts" refers to salts of the below identified compounds of formula (I), that retain the desired biological activity. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfoic acid, toluene sulfoic acid, naphthalene disulfoic acid, methanesulfoic acid and poly-galacturonic acid. When the salt is of a mono acid (for example, the hydrochloride, the hydrobromide, the p-toluenesulphonate, or the acetate), the hydrogen form of a di-acid (for example, the hydrogen sulphate, or the succinate), or the dihydrogen form of a tri-acid (for example, the dihydrogen phosphate, or the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However, when such salts as the sulphate, the hemisuccinate, the hydrogen phosphate, or the phosphate are desired, the appropriate and exact chemical equivalents of acid are generally used. Suitable pharmaceutically acceptable base addition salts for the compound of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, Λf-.ZV'-dibenzylethlenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (Λf-methylglucamine) and procaine. Sodium salts are particularly preferred.

"Enantiomers" refers to the products that are obtained by an asymmetric synthesis, i.e. a synthesis involving non-racemic starting materials and/or
reagents or a synthesis comprising at least one enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% enantiomeric excess is yielded.

The compounds of the present invention can be prepared by conventional synthetic methods and are described underneath.

Compounds of formula (I), where \( n = 0 \), and \( R^1 \) and \( R^2 \) are H, may be prepared by reacting a ketone of formula (II)

\[
\begin{align*}
\text{R}^5 & \text{O} \\
\text{Formula II}
\end{align*}
\]

wherein \( \text{R}^5 \) has the meaning as described above, with a suitable base, usually NaH or LiH, to obtain the corresponding enolate, in an appropriate solvent, at a temperature ranging from -78°C to reflux of the solvent and by subsequently adding a suitable carbamoyl chloride. The solvent should preferably be an aprotic polar solvent, such as tetrahydrofuran, dioxane, or dimethylsulfoxide and the reaction is preferentially conducted at room temperature, for example like as reported by Panella L., et al., *Org. Lett.*, 2005, 7, 4177.

Alternatively, such compounds may also be prepared by reacting a ketone of formula (II) with a suitable carbamoyl chloride of formula (III)

\[
\begin{align*}
\text{Cl} & \text{N}^\text{R}_3 \text{R}_4 \\
\text{N} & \text{O} \\
\text{R}^4 & \text{R}^3 \\
\text{Formula III}
\end{align*}
\]
in the presence of a base under microwaves irradiation, for example as described by Seijas J.A., *et al.* *Synlett*, 2007, 2420.

Alternatively, such compounds may also be prepared by reacting an enol silyl ether of a ketone of Formula (II) with a carbamoyl fluoride or chloride, for example as reported by Olofson R.A., *et al.*, *Tetrahedron Lett.*, 1980, 21, 819.

Compounds of formula (I), where \( n = 1 \) or 2 and \( R^1 \) and \( R^2 \) are H, may be prepared by reacting a ketone of formula D-B-(A)_n-CO-CHs with a suitable base, usually NaH or LiH, in an appropriate solvent, usually an aprotic polar solvent, such as tetrahydrofuran, dioxane, or dimethylsulf oxide, to form the corresponding enolate, and by subsequently adding a carbamoyl chloride, for example as reported by Panella L., *et al.*, *Org. Lett.*, 2005, 7, 4177.

Alternatively, such compounds may also be prepared by reacting the enol silyl ether of a ketone of formula D-B-(A)_n-CO-CHs with a carbamoyl fluoride or chloride, for example as reported by Olofson R.A., *et al.*, *Tetrahedron Lett.*, 1980, 21, 819.

Compounds of formula (I), where \( n = 1 \), \( R^1 \) and \( R^2 \) are F, may be prepared by reacting an appropriate aryl- or heteroaryl boronic acid with a iododifluorovinylenolcarbamate, for example like as described by DeBoos G.A., *et al.*, *Synlett*, 2000, 963.

Alternatively, such compounds can be prepared by reaction of an appropriate iodoaryl or iodo heteroaryl compound with a metallated (Li or BusSn) difluoro enolcarbamate, for example like as described by DeBoos G.A., *et al.* *Synlett*, 2000, 963.
Compounds of formula (I), where $R_1$ is $G_1$, $R_2$ is H, may be prepared by reacting an appropriate aryl or heteroaryl ethyne with CO2 and an appropriate amine, in the presence of a ruthenium catalyst, for example like as described by Bruneau C., et al., *J. Mol. Catalysis*, 1992, 74, 97, or by Hofer J., et al, *Tetrahedron Lett.*, 1991, 32, 50, 7409.

In all said transformations, any interfering reactive group can be protected and then deprotected according to well-established procedures described in organic chemistry (see for example: Greene T. W. and P.G.M. Wuts "Protective Groups in Organic Synthesis", J. Wiley & Sons, Inc., 3rd Ed., 1999) and well known to those skilled in the art.

All said transformations are only examples of well-established procedures described in organic chemistry (see for example: March J., "Advanced Organic Chemistry", J. Wiley & Sons, Inc., 4th Ed., 1992) and well known to those skilled in the art.

We have found that the derivatives (I) and their pharmaceutically acceptable salts, prepared according to the invention, are useful agents for the treatment disease states, disorders and pathological conditions mediated by fatty acid amide hydrolase; in particular for the treatment of anxiety and pain.

The pharmaceutical compositions will contain at least one compound of Formula (I) as an active ingredient, in an amount such as to produce a significant therapeutic effect. The compositions covered by the present invention are entirely conventional and are obtained with methods which are common practice in the pharmaceutical industry, such as, for example, those illustrated in *Remington's Pharmaceutical Science Handbook, Mack*
According to the administration route chosen, the compositions will be in solid or liquid form, suitable for oral, parenteral or topical administration. The compositions according to the present invention contain, along with the active ingredient, at least one pharmaceutically acceptable vehicle or excipient. These may be particularly useful formulation coadjuvants, e.g. solubilising agents, dispersing agents, suspension agents, and emulsifying agents.

Generally, the compounds of this invention are administered in a "pharmaceutically effective amount". The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, drug combination, the age, body weight, and response of the individual patient, the severity of the patient's symptoms, and the like. Generally, an effective dose will be from 0.01 mg/kg to 100 mg/kg, preferably 0.05 mg/kg to 50 mg/kg. For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays or in animal models, usually mice, rats, guinea pigs, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. In calculating the Human Equivalent Dose (HED) it is recommended to use the conversion table provided by the FDA in Guidance for Industry and Reviewers document available from FDA. The precise effective dose for a human subject will depend upon the severity of the disease state, general health of the subject,
age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. This amount can be determined by routine experimentation and is within the judgement of the clinician.

Compositions may be administered individually to a patient or may be administered in combination with other agents, drugs or hormones. The medicament may also contain a pharmaceutically acceptable carrier, for administration of a therapeutic agent. Such carriers include antibodies and other polypeptides, genes and other therapeutic agents such as liposomes, provided that the carrier does not itself induce the production of antibodies harmful to the individual receiving the composition, and which may be administered without undue toxicity.

Suitable carriers may be large, slowly metabolised macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers and inactive virus particles.


Pharmaceutically acceptable carriers in therapeutic compositions may additionally contain liquids such as water, saline, glycerol and ethanol.

Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such compositions. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.
Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals; in particular, human subjects can be treated. The medicament of this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intrarterial, intramedullary, intrathecal, intraventricular, transdermal or transcutaneous applications, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, intravaginal or rectal means. The compositions for oral administration may take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include refilled, pre-measured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound of the invention is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form. Dosage treatment may be a single dose schedule or a multiple dose schedule. As above disclosed, the compounds of the present invention are useful as medicaments due to their FAAH inhibiting properties for the treatment of
disorders where such inhibition result in improving the health of the patient. In particular, patients suffering from: cachexia, anorexia, pain, inflammation, stroke, multiple sclerosis, Parkinson's disease, Huntington disease, Alzheimer disease, epilepsy, schizophrenia, anxiety, depression, insomnia, hypertension, circulatory shock, myocardial reperfusion injury, atherosclerosis, asthma, retinopathy, cancer, inflammatory bowel disease, hepatitis, arthritis and osteoporosis can be treated.

An object of the present invention are pharmaceutical compositions containing one or more of the compounds of formula (I) described earlier, in combination with excipients and/or pharmacologically acceptable diluents.

The compositions in question may, together with the compounds of formula (I), contain known active principles.

A further object of the invention is a process for the preparation of pharmaceutical compositions characterised by mixing one or more compounds of formula (I) with suitable excipients, stabilizers and/or pharmaceutically acceptable diluents.

An embodiment of this invention is that of compounds of formula (I), where R is a group [D-B-(A)n].

A preferred embodiment of this invention is that of compounds of formula (I), where R is a group [D-B-(A)n] and R and R are H.

A more preferred embodiment of this invention is that of compounds of formula (I), where R is a group [D-B-(A)n], R and R are H and B and D are optionally substituted aryl.

An even more preferred embodiment of this invention is that of compounds of formula (I), where R is a group [D-B-(A)n], R and R are H, B and D are
optionally substituted aryl and where R\textsuperscript{3} and R\textsuperscript{4} taken together form an
optionally substituted heterocycle.

**EXAMPLES**

**Abbreviations:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>arachidonic acid</td>
</tr>
<tr>
<td>AcOEt</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>AnNH</td>
<td>arachidonoylthanolamide (anandamide)</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>Et\textsubscript{2}O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>HMPT</td>
<td>hexamethyl phosphorous triamide</td>
</tr>
<tr>
<td>NaH</td>
<td>sodium hydride</td>
</tr>
<tr>
<td>RP-HPLC</td>
<td>reversed phase-high-performance liquid chromatography</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
</tbody>
</table>

**General Remarks:** \( ^1 \text{H} \) spectra were recorded in CDCl\textsubscript{3} solution as indicated, at 300 MHz with a Bruker instrument. The chemical shift values are given in ppm and the coupling constants in Hz. Flash column chromatography was carried out using silica gel (Merck 230-400 mesh).

**Example 1**

Dimethyl-carbamic acid l-biphenyl-4-yl-vinyl ester (ST 3714)
A solution of NaH (60% in oil, 0.22 g, 5.50 mmol) in 50 ml of dry DMSO was stirred for 2 h at 50°C and allowed to return to room temperature. 4-acetylbiphenyl (1 g, 5.1 mmol) in 15 ml of DMSO was added dropwise and the resulting solution was stirred for 30 min prior to addition of N,N-dimethylcarbamoyl chloride (0.52 ml, 5.61 mmol) in 10 ml of DMSO. The reaction mixture was stirred for 45 min. The latter was diluted by addition of hexane and washed with brine. After removal of the solvent under vacuo and purification through flash chromatography (hexane:AcOEt=3:1), dimethyl-carbamic acid l-biphenyl-4-yl-vinyl ester was obtained (0.48 g, 35%).

$^1$H NMR CDCl$_3$ $\delta$: 2.99 (s, 3H); 3.14 (s, 3H); 5.05 (d, IH, J = 1.12 Hz); 5.46 (d, IH, J = 1.12 Hz); 7.30-7.65 (m, 9H).

**Example 2**

Dimethylcarbamic acid l-biphenyl-3-yl-vinyl ester (ST 3851)

A solution of NaH (60% in oil, 0.22 g, 5.50 mmol) in 50 ml of dry DMSO was stirred for 2 h at 50°C and allowed to return to room temperature. 3-acetylbiphenyl (0.7 g, 3.6 mmol) in 15 ml of DMSO was added dropwise and the resulting solution was stirred for 30 min prior to addition of N,N-dimethylcarbamoyl chloride (0.43 g, 3.92 mmol) in 10 ml of DMSO. The reaction mixture was stirred for 45 min. The latter was diluted by addition of hexane and washed with brine. After removal of the solvent under vacuo
and purification through flash chromatography (hexane:AcOEt = 3:1),
dimethylcarbamic acid l-biphenyl-3-yl- vinyl ester was obtained (0.54 g, 57%).

$^1$H NMR CDCl$_3$ $\delta$: 2.98 (s, 3H); 3.13 (s, 3H); 5.07 (d, IH, $J = 1.49$ Hz); 5.48 (d, IH, $J = 1.49$ Hz); 7.30-7.63 (m, 8H); 7.69 (s, IH).

**Example 3**

Piperidine-1-carboxylic acid l-biphenyl-3-yl- vinyl ester (ST 3830)

A solution of NaH (60% in oil, 0.22 g, 5.50 mmol) in 50 ml of dry DMSO was stirred for 2 h at 50°C and allowed to return to room temperature. 3-acetylbiphenyl (1 g, 5.1 mmol) in 15 ml of DMSO was added dropwise and the resulting solution was stirred for 30 min prior to addition of piperidine-1-carbonyl chloride (0.61 g, 5.61 mmol) in 10 ml of DMSO. The reaction mixture was stirred for 45 min. The latter was diluted by addition of hexane and washed with water. After removal of the solvent under vacuo and purification through flash chromatography (hexane:AcOEt = 4:1), piperidine-1-carboxylic acid l-biphenyl-3-yl- vinyl ester was obtained (0.35 g, 23%).

$^1$H NMR CDCl$_3$ $\delta$: 1.48-1.62 (m, 6H); 3.44-3.49 (m, 2H); 3.60-3.67 (m, 2H); 5.06 (d, IH, $J = 1.86$ Hz); 5.47 (d, IH, $J = 1.86$ Hz); 7.29-7.62 (m, 8H); 7.68 (s, IH).
Example 4

Piperidine-1-carboxylic acid l-(3-piperidinecarboxybiphenyl)-3-yl-vinyl ester
(ST 3899)

A solution of NaH (60% in oil, 0.24 g, 6.0 mmol) in 50 ml of dry DMSO was stirred for 2 h at 50°C and allowed to return to room temperature. 1-(3'-hydroxybiphenyl-3-yl)ethanone (1 g, 2.83 mmol) in 15 ml of DMSO was added dropwise and the resulting solution was stirred for 30 min prior to addition of piperidine-1-carbonyl chloride (0.47 g, 3.11 mmol) in 10 ml of DMSO. The reaction mixture was stirred for 45 min. The latter was diluted by addition of hexane and washed with water. After removal of the solvent under vacuo and purification through flash chromatography (hexane:AcOEt = 4:1), piperidine-1-carboxylic acid l-(3-piperidinecarboxybiphenyl)-3-yl-vinyl ester was obtained (80 mg, 7%).

1H NMR CDCl$_3$ δ: 1.50-1.75 (m, 12H); 3.40-3.73 (m, 8H); 5.06 (d, IH, J = 2.23 Hz); 5.47 (d, IH, J = 2.23 Hz); 7.10 (d, IH, J = 6.70 Hz); 7.30-7.47 (m, 5H); 7.50 (d, IH, J = 7.44 Hz); 7.66 (s, IH).

Example 5

Piperidine-1-carboxylic acid l-(3-cyanobiphenyl)-3-yl-vinyl ester (ST 4019)
A solution of NaH (60% in oil, 20 mg, 0.50 mmol) in 2 ml of dry DMSO was stirred for 30 min at 50°C and allowed to return to room temperature. l-(3'-cyanobiphenyl-3-yl)ethanone (100 mg, 0.45 mmol) in 1.5 ml of DMSO was added dropwise and the resulting solution was stirred for 15 min prior to addition of piperidine-1-carbonyl chloride (74 mg, 0.50 mmol) in 0.10 ml of DMSO. The reaction mixture was stirred for 45 min. The latter was diluted by addition of Et2O and washed with water. After removal of the solvent under vacuo and purification through flash chromatography (hexane:CH2Cl2:Et2O = 5:5:0.1), piperidine-1-carboxylic acid l-(3-cyanobiphenyl)-3-yl-vinyl ester was obtained (35 mg, 23%).

1H NMR CDCl3 δ: 1.53-1.71 (m, 6H); 3.44-3.52 (m, 2H); 3.60-3.67 (m, 2H); 5.09 (d, IH, J = 1.91 Hz); 5.48 (d, IH, J = 1.91 Hz); 7.42-7.66 (m, 6H); 7.78 (d, IH, J = 8.01 Hz); 7.84 (s, IH).

Example 6

N-Methyl-N-phenylcarbamic acid l-biphenyl-3-yl-vinyl ester (ST 4071)

A solution of NaH (60% in oil, 34 mg, 0.85 mmol) in 2 ml of dry DMSO was stirred for 2 h at 50°C and allowed to return to room temperature. Biphenyl-3-yl)ethanone (0.15 g, 0.76 mmol) in 1 ml of DMSO was added dropwise and the resulting solution was stirred for 1 h prior to addition of N-methyl, N-phenyl carbamoyl chloride (142 mg, 0.84 mmol) in 0.15 ml of DMSO. The reaction mixture was stirred for 2 h. The latter was diluted by addition of
AcOEt and washed with water. After removal of the solvent under vacuo and purification through flash chromatography (hexane:CH2Cl2:Et2θ = 5:5:0.1), N-methyl-N-phenylcarbamic acid 1-biphenyl-3-yl-vinyl ester was obtained (100 mg, 40%).

1H NMR CDCl3 δ: 3.38 (s, 3H); 5.14 (d, IH, J = 1.81 Hz); 5.46 (d, IH, J = 1.81 Hz); 7.13-7.74 (m, 9H).

Example 7

Piperidine-1-carboxylic acid l-(3-thiophen-2-yl-phenyl)-vinyl ester (ST 4093)

A solution of NaH (60% in oil, 32 mg, 0.80 mmol) in 2 ml of dry DMSO was stirred for 2 h at 50°C and allowed to return to room temperature. 3-(2-thienyl)acetophenone (150 mg, 0.74 mmol) in 1 ml of DMSO was added dropwise and the resulting solution was stirred for 1 h prior to addition of piperidine-1-carbonyl chloride (120 mg, 0.81 mmol) in 0.15 ml of DMSO. The reaction mixture was stirred for 3 h. The latter was diluted by addition of AcOEt and washed with water. After removal of the solvent under vacuo and purification through flash chromatography (hexane:CH2Cl2:Et2θ = 5:5:0.1), piperidine-1-carboxylic acid 1-(3-thiophen-2-yl-phenyl)-vinyl ester was obtained (27 mg, 12%).

1H NMR (CDCl3) δ: 1.60 (m, 6H); 3.45 (s, 2H); 3.63 (s, 2H); 5.05 (s, IH); 5.45 (s, IH); 7.05 (t, IH); 7.20-7.40 (m, 4H); 7.55 (d, IH); 7.70 (s, IH).
Example 8

Morpholine-4-carboxylic acid 1-biphenyl-3-yl-vinyl ester (ST 4092)

A solution of NaH (60% in oil, 61 mg, 0.50 mmol) in 4 ml of dry DMSO was stirred for 2 h at 50°C and allowed to return to room temperature. 1-biphenyl-3-yl-ethanone (100 mg, 0.45 mmol) in 1.5 ml of DMSO was added dropwise and the resulting solution was stirred for 1 h prior to addition of morpholine-1-carbonyl chloride (74 mg, 0.50 mmol) in 0.5 ml of DMSO. The reaction mixture was stirred for 3 h. The latter was diluted by addition of AcOEt and washed with water. After removal of the solvent under vacuo and purification through flash chromatography (hexane:CH2Cl2:Et2O = 4:6:0.1), morpholine-4-carboxylic acid 1-biphenyl-3-yl-vinyl ester was obtained (68 mg, 29%).

\[ ^1H \text{NMR (CDCl}_3\text{)} \delta: 3.5 \text{ (m, 2H); 3.7 \text{ (m, 6H); 5.10 \text{ (m, IH); 5.48 \text{ (m, IH); 7.4-7.5 \text{ (m, 5H); 7.55-7.6 \text{ (m, 3H); 7.70 \text{ (s, IH)}})} } \]

Example 9

Piperidine-1-carboxylic acid 1-biphenyl-4-yl-vinyl ester (ST 4070)

A solution of NaH (60% in oil, 56 mg, 14 mmol) in 3 ml of dry DMSO was stirred for 2 h at 50°C and allowed to return to room temperature.
(Biphenyl-3-yl)ethanone (2.5 g, 13 mmol) in 1.5 ml of DMSO was added dropwise and the resulting solution was stirred for 1 h prior to addition of piperidine-1-carbonyl chloride (2.07 g, 14 mmol) in 0.5 ml of DMSO. The reaction mixture was stirred for 3 h. The latter was diluted by addition of AcOEt and washed with water. After removal of the solvent under vacuo and purification through flash chromatography (hexane/CHbC6 = 1:1), piperidine-1-carboxylic acid 1-biphenyl-4-yl-vinyl ester was obtained (1 g, 26%).

1H NMR CDCl3 δ: 1.50-1.75 (m, 6H); 3.45-3.50 (m, 2H); 3.57-3.66 (m, 2H); 5.04 (d, IH, J = 1.84 Hz); 5.46 (d, IH, J = 1.84 Hz); 7.27-7.78 (m, 9H).

Example 10

Morpholine-1-carboxylic acid 1-biphenyl-4-yl-vinyl ester (ST 5528)

A solution of NaH (60% in oil, 61 mg, 1.5 mmol) in 4 ml of dry DMSO was stirred for 30 min at 50°C and allowed to return to room temperature. (Biphenyl-4-yl)ethanone (150 mg, 0.75 mmol) in 0.75 ml of warm DMSO was added and the resulting solution was stirred for 1 h prior to addition of morpholinecarbonyl chloride (0.18 ml, 1.5 mmol) in 0.5 ml of DMSO. The reaction mixture was stirred for 3 h, poured in ice and extracted 3 times with AcOEt. After washing with brine, drying over Na2SO4, evaporation of the solvent under vacuo and purification through flash chromatography
(Et$_2$O/CH$_2$Cl$_2$ = 5:95), morpholine-1-carboxylic acid l-biphenyl-4-yl- vinyl ester was obtained (80 mg, 34%). mp 124-126°C

$^1$H NMR (CDCl$_3$) $\delta$: 3.5 (m, 2H); 3.7 (m, 6H); 5.08 (d, IH); 5.50 (d, IH); 7.35 (m, IH), 7.42 (t, 2H), 7.58 (m, 6H).

**Example 1**

N-methyl-N-phenylcarbamic acid l-biphenyl-4-yl-vinyl ester (ST 5529)

\[
\begin{array}{c}
\text{N-} \ \text{O} \\
\text{CH} \quad \text{CH} \\
\text{Ph} \quad \text{Ph}
\end{array}
\]

A solution of NaH (60% in oil, 61 mg, 1.5 mmol) in 4 ml of dry DMSO was stirred for 30 min at 50°C and allowed to return to room temperature. (Biphenyl-4-yl)ethanone (150 mg, 0.75 mmol) in 0.75 ml of warm DMSO was added and the resulting solution was stirred for 1 h prior to addition of iV-methyl-iV-phenylcarbonyl chloride (258 mg, 1.5 mmol) in 0.6 ml of DMSO. The reaction mixture was stirred for 2 h, poured in ice and extracted 3 times with AcOEt. After washing with brine, drying over Na$_2$SO$_4$, evaporation of the solvent under vacuo and purification through flash chromatography (hexane/acetone = 7:3) then again with CH$_2$Cl$_2$/hexane/Et$_2$O, N-methyl-N-phenylcarbamic acid l-biphenyl-4-yl-vinyl ester was obtained.

$^1$H NMR (CDCl$_3$) $\delta$: 3.42 (m, 3H); 5.10 (d, IH); 5.47 (d, IH); 7.3-7.6 (m, 14H).

**Example 12**

Piperidine-1-carboxylic acid l-(4-thiophen-2-yl-phenyl)-vinyl ester (ST 5584)
**STEP 1:** l-(4-thiophen-2-yl-phenyl)-ethanone

3-bromo-thiophene (0.24 ml, 2.45 mmol), Pd-tetrakis (50 mg, 0.04 mmol) and 3.12 ml of Na2CO3 (IM) were added under nitrogen atmosphere to a solution of 4-acetyl-benzene-boronic acid (512 mg, 3.12 mmol) in 4 ml of 1,4-dioxane. The resulting mixture was refluxed for 4 hours before returning to RT. It was then poured into water, extracted with AcOEt and washed with brine. After removal of the solvent under vacuo and purification through flash chromatography (AcOEt:hexane = 2:8), 418 mg of the desired adduct were obtained as a white solid (84%).

$^1$H NMR (CDCl$_3$) $\delta$: 2.65 (s, 3H); 7.12 (t, 1H); 7.40 (d, 1H); 7.45 (d, 1H); 7.70 (d, 2H); 8.00 (d, 2H).

**STEP 2:** A solution of NaH (60% in oil, 58 mg, 1.46 mmol) in 4 ml of dry DMSO was stirred for 2 h at 50°C, then allowed to return to RT. l-(4-Thiophen-2-yl-phenyl)-ethanone (150 mg, 0.74 mmol) in 1 ml of DMSO was added dropwise and the resulting solution was stirred for 1 h prior to addition of 1-piperidinocarbonyl chloride (0.185 ml, 1.48 mmol) in 0.5 ml of DMSO. The reaction mixture was stirred overnight. The mixture was poured into ice water, extracted with AcOEt and washed with brine. After removal of the solvent under vacuo and purification through flash chromatography (CH2Cl2:hexane:Et2θ =5:5:0.1), 62 mg of piperidine-1-carboxylic acid l-(4-thiophen-2-yl-phenyl)-vinyl ester was obtained (27%).
$^1$H NMR (CDCl$_3$) $\delta$: 1.60 (m, 6H); 3.50 (m, 2H); 3.70 (m, 2H); 5.06 (d, IH); 5.54 (d, IH); 7.05 (t, IH); 7.23-7.36 (m, 2H); 7.48 (d, 2H); 7.59 (d, 2H)

**Example 13**

(E)-dimethylcarbamic acid 3-biphenyl-4-yl-l-methylene-allyl ester

**STEP 1:** (3-biphenyl-4-yl-l-methylene-allyloxy)-trimethylsilane

0.32 ml of triethylamine was added dropwise to a solution of 4-biphenyl-4-yl-but-3-en-2-one (200 mg, 0.9 mmol) in THF (2.1 ml) at 0°C followed by dropwise addition of 0.18 ml of trimethylsilyl triflate. The mixture was stirred for 2 hrs at 0°C, then poured into a saturated solution of NH$_4$Cl, and extracted with Et$_2$O (3 x 15 ml). The resulting solution was dried over sodium sulfate and the solvent was removed under reduced pressure to afford 210 mg of the expected adduct which was used in the next step without any further purification.

$^1$H NMR (CDCl$_3$) $\delta$: 0.29 (s, 9H), 4.46 (d, 2H), 6.61 (d, IH), 6.82 (d, IH), 7.2-7.6 (m, 9H).

**STEP 2:** (E)-dimethylcarbamic acid 3-biphenyl-4-yl-l-methylene-allyl ester

0.23 ml of tert-butyllithium (2M, THF) was added to a solution of (3-biphenyl-4-yl-l-methylene-allyloxy)-trimethylsilane (150 mg) in 1.2 ml of dry THF at -40°C under nitrogen atmospher. The reaction mixture was
allowed to return to RT and 1.6 ml of dry HMPT were added together with 67 mg of N,N-dimethylcarbamoyl chloride. Stirring was maintained for 6 hrs. The reaction mixture was poured into a solution of 10% citric acid at pH 4, and was extracted with AcOEt. The solvent were removed under reduced pressure and the crude reaction mixture was purified by flash chromatography (hexane / AcOEt) to afford the title product.

Yield: 15%.

IH NMR CDCl₃ 2.97 (s, 3H), 3.12 (s, 3H), 4.95 (d, IH, J = 1.1 Hz), 5.04 (d, IH, J = 1.1 Hz), 6.60 (d, IH, J = 16 Hz), 6.68 (d, IH, J = 16 Hz), 7.15-7.65 (m, 9H).
BIOLOGICAL RESULTS

FAAH assay

The compounds of the present invention show affinity and inhibit the enzymatic activity of the fatty acid amide hydrolase enzyme.

The assay of FAAH (EC 3.5.1.4) was performed by measuring the release of \[^{1-14}\text{C}]\text{AA}\) from \[^{1-14}\text{C}]\text{AnNH}\ (52 \text{ mCi/mmole}), using RP-HPLC. Also \[^{3}\text{H}]\text{AnNH}\ (205 \text{ Ci/mmole}) could be used as substrate, measuring the release of \[^{3}\text{H}]\text{AA}\ under the same experimental conditions described below for \[^{1-14}\text{C}]\text{AnNH}\. Compounds of the invention, at various concentrations, were added in 200 µl hydrolase assay buffer (50 mM Tris-HCl, pH 9.0), in 2-ml Eppendorf tubes, 20 min before adding \[^{1-14}\text{C}]\text{AnNH}\, up to a concentration of 10 µM. The reaction was initiated by the addition of mouse brain homogenate (40 µg), and after incubation at 37°C for 15 min it was stopped by the addition of 800 µl ice-cold methanol/chloroform (2:1, v/v) with vortexing. This mixture was allowed to stand at room temperature for 30 min, then 240 µl chloroform and 240 µl water were added with vortexing. After 10 min at room temperature, the mixture was centrifuged at 3000g for 5 min, the upper aqueous layer was removed by suction and the lower organic phase was dried by spinning the samples in a DNA MINI speedvac (Heto-Holten, Denmark), at 100 mbar and 30°C for 30 min. The residue was dissolved into 50 µl methanol and subjected to RP-HPLC analysis for AA quantitation, as detailed below. FAAH specific activity was expressed as pmol AA released/min/mg protein. Kinetic studies were performed by Lineweaver-Burk analysis, using \[^{1-14}\text{C}]\text{AnNH}, \[^{1-14}\text{C}]\text{ODNHEtOH}, \text{ or }[^{1-14}\text{C}]\text{ODNH2}\ in the concentration range 0—12 µM. Fitting of the experimental
points by a linear regression programme (Kaleidagraph 3.0) yielded straight lines with \( r \) values > 0.97.

**Table 1**

<table>
<thead>
<tr>
<th>Examples</th>
<th>ST Number</th>
<th>IC(_{50}) (nM)</th>
<th>Ki (nM)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>ST3714</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>ST3851</td>
<td>+</td>
<td>++</td>
</tr>
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<td>3</td>
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</tr>
<tr>
<td>4</td>
<td>ST3899</td>
<td>+++</td>
<td>++++</td>
</tr>
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<td>5</td>
<td>ST4019</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>ST4071</td>
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<td>+</td>
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<td>+</td>
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<td>9</td>
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<td>++++</td>
</tr>
<tr>
<td>12</td>
<td>ST5584</td>
<td>+++</td>
<td>++++</td>
</tr>
</tbody>
</table>

[+++] \([\text{IC}_{50}] < 10 \text{ nM and/or } [\text{Ki}] < 10 \text{ nM}\)

[++] \(10 \text{ nM} < [\text{IC}_{50}] < 100 \text{ nM and/or } 10 \text{ nM} < [\text{Ki}] < 100 \text{ nM}\)

[+] \(100 < [\text{IC}_{50}] < 500 \text{ nM and/or } 100 < [\text{Ki}] < 500 \text{ nM}\)

[+] \(500 < [\text{IC}_{50}] < 5000 \text{ nM and/or } 500 < [\text{Ki}] < 5000 \text{ nM}\)

ND: not determined

Selectivity profile

Table 2

<table>
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<tr>
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<th>ST3830 a</th>
<th>ST3899</th>
<th>ST3851 a</th>
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<tr>
<td>CB1R</td>
<td>-</td>
<td>----</td>
<td>-</td>
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<tr>
<td>CB2R</td>
<td>-</td>
<td>60% @ 1 μM</td>
<td>-</td>
</tr>
<tr>
<td>TRPV1</td>
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<td>----</td>
<td>-</td>
</tr>
<tr>
<td>NAPE-PLD</td>
<td>-</td>
<td>----</td>
<td>-</td>
</tr>
<tr>
<td>AMT</td>
<td>-</td>
<td>60% @ 1 μM</td>
<td>-</td>
</tr>
<tr>
<td>DAGL</td>
<td>-</td>
<td>----</td>
<td>-</td>
</tr>
<tr>
<td>MAGL</td>
<td>-</td>
<td>----</td>
<td>-</td>
</tr>
</tbody>
</table>

a: the maximum concentration tested corresponds to 5 times those of the IC₅₀ on FAAH

[---] 1000 times [IC₅₀] with an inhibitory activity on the target < 60%
[---] 100 times [IC₅₀] with an inhibitory activity on the target < 60%
[-] 10 times [IC₅₀] with an inhibitory activity on the target < 60%
[-] 5 times [IC₅₀] with an inhibitory activity on the target < 60%

ST3830, ST3851 and ST3899 were shown to be selective against the above targets. Among those targets, only ST3899 was interfering with AMT and CB2.

Reversibility

Reversibility was ascertained by incubating FAAH with an excess (i.e., concentrations well above the IC₅₀ values) of the compounds of the present invention for 20 min (as in the enzymatic assay conditions). Subsequently, the FAAH/compound mixtures (in 1 ml volume) were dialyzed overnight against 2 litres of 10 mM Tris-HCl buffer (pH 7.4). The FAAH/compound
mixtures were subjected to activity assays as described above, both before and after dialysis. All compounds from the present invention demonstrated to be reversible, contrarily to URB-597, which was found to be irreversible.

5 Anxiety animal model

Many animal models of anxiety are based on the principle of innate general avoidance behaviors. Among them is the elevated plus maze (EPM) (Hogg S., Pharmacol. Biochem. Behav., 1996, 54, 21; Masse F., et al., Behav. Brain Res., 2007, 177, 2, 214) which is based on the natural aversion of rodents for open spaces that uses the conflict between exploration and aversion of elevated open space; the provoked behavior profiles in the EPM appear to include elements of neophobia, exploration and approach/avoidance conflict. EPM is able to demonstrate the anxiolytic effects of drugs. The purpose of the present study was to set up an animal model of anxiety EPM using the anxiolytic effects of benzodiazepine Diazepam in mice and evaluate the effect of FAAH inhibitors ST3108 (URB597) and ST4070.

Twelve male CDI mice (Charles River) of about 30 g (2 months old) per group were used. The Elevated Plus Maze apparatus was of grey Plexiglas and consisted of two open and two closed arms linked by a common central platform. The maze was elevated 40 cm above floor level and dimly lit. Animals were individually placed on the central platform of the maze facing an open arm. A standard five-min test was employed. The amount of time spent by each animal in either open or closed arm was recorded, as well as the number of entries by each animal into either arm.
Experiment: ST3108 and ST4070 were tested at a dose of 10 mg/10 ml/kg and Diazepam at a dose of 0.5 mg/5 ml/kg. ST3108 and ST4070, dispersed in a solution of 5% Tween 80 and 0.5% carboxymethylcellulose, were given orally 60 min before test; Diazepam, dispersed in a solution of 3% Tween 80, was given intraperitoneal 30 min before test.

**Table 3**

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose level (mg/kg)</th>
<th>Time spent in open arms (s)</th>
<th>Nb of entrances into open arms</th>
<th>Nb of entrances into closed arms</th>
<th>Nb of total entrances</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td></td>
<td>3.08±1.24</td>
<td>0.75±0.30</td>
<td>12.67±1.00</td>
<td>13.42±1.12</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.5</td>
<td>36.00±3.47</td>
<td>7.75±0.74</td>
<td>11.75±1.32</td>
<td>19.50±1.84</td>
</tr>
<tr>
<td>ST3108</td>
<td>10</td>
<td>24.67±3.59</td>
<td>4.25±0.88</td>
<td>10.75±1.17</td>
<td>15.00±1.23</td>
</tr>
<tr>
<td>ST4070</td>
<td>10</td>
<td>31.92±4.48</td>
<td>5.33±1.33</td>
<td>11.17±1.06</td>
<td>16.50±1.78</td>
</tr>
</tbody>
</table>

ST3108 and ST4070 reduced anxiety and did not affect the locomotor activity evaluated in elevated plus maze.

**Analgesia animal model**

The paw withdrawal test was used to assess mechanical hyperalgesia. The nociceptive threshold, expressed in grams, was measured by applying increasing pressure to the left and right hind paws using an Randall-Selitto analgesimeter (Ugo Basile, Varese, Italy). The parameter used to quantify the nociceptive threshold was defined as the pressure (grams) at which the rat withdrew its paw. Rats were habituated to the testing procedures and handling by the investigator in the week prior to the experiment. Acute oral treatment with ST3108 (50 mg/kg) did not exert analgesic activity, while ST4070 (50 mg/kg) showed significant analgesic activity after one hour (P<0.001) as demonstrated in figure 1.
A dose response experiment was also conducted with ST4070 at 25 and 50 mg/kg, demonstrating the increased activity at the higher dose with respect to the 25 mg/kg dose (figure 2).
1. A compound having the general formula (I)

\[
\begin{align*}
\text{Formula I} \\
& \text{wherein:} \\
& \text{R}^1 \text{ is H, halogen or } \text{G}^1; \\
& \text{G}^1 \text{ is aryl, or heteroaryl, each being substituted with at least one radical chosen among halogen, hydroxy, alkoxy, cyano, aminocarbonyl, aryl or heteroaryl;} \\
& \text{R}^2 \text{ is H or halogen;} \\
& \text{R}^3 \text{ and } \text{R}^4 \text{ are independently H, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, arylkyl, alkylaryl, alkoxyaryl or haloaryl;} \\
& \text{or R}^3 \text{ and R}^4 \text{ taken together form a heterocycle optionally substituted with alkyl, carboxy or heterocycloalkyl;} \\
& \text{R}^5 \text{ is the group [D-B-(A)\text{n]}} \text{- wherein} \\
& \text{A is (R}^6\text{C=C(R}^7\text{), wherein R}^6 \text{ and R}^7 \text{ are the same or different and are H, alkyl, aryl, or halogen;} \\
& \text{n} = 0, 1, 2; \\
& \text{B is aryl or heteroaryl, each being optionally substituted with one or more radicals chosen among alkyl, cycloalkyl, aryl, hydroxy, alkoxy, alkylcarbonyloxy, sulfonyloxy, amino, aminoalkylamino,}
\end{align*}
\]
alkylcarbonylamino, cyano, halogen, R^8SC^NH, R^9NHSC^, aminocarbonyl or aminocarbonyloxy;
D is aryl or heteroaryl, each being optionally substituted with alkyl, cycloalkyl, aryl, hydroxy, alkoxy, alkylcarbonyloxy, sulfonyloxy, amino, aminoalkylamino, alkylcarbonylamino, cyano, halogen, R^8SC^NH, R^9NHSθ₂, aminocarbonyl or aminocarbonyloxy;
Rs and R_g alkyl, aryl or heteroaryl, both optionally substituted with alkyl, hydroxy, alkoxy, alkylcarbonyloxy;
it its tautomers, its geometrical isomers, its optically active forms such as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof;
with the following proviso:
when G^1 is para-ethoxy phenyl or para-methyl phenyl, R^3 and R^4 are not both ethyl at the same time.

2. Compounds according to claim 1, wherein R^1 and R^2 are H.
3. Compounds according to any of claims 1-2, wherein R^3 and R^4 taken together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with alkyl, carboxy or heterocycloalkyl.
4. Compounds according to any of claims 1-3, wherein R^5 is represented by the group [D-B-(A)_n]- wherein D, B and A have the meaning as described above and n is 0.
5. A process for preparing compounds according to claim 1, which comprises reacting a compound of general formula (II)
wherein R⁵ has the meaning as described above, with a carbamoyl chloride of formula (III)

wherein R³ and R⁴ have the meaning as described above.

6. A pharmaceutical composition containing at least one compound according to claims 1-4 as the active ingredient in mixtures with at least one pharmaceutically acceptable vehicle and/or excipient.

7. A process for preparing the pharmaceutical composition according to claim 6, comprising mixing at least one of the compounds according to claims 1-4 with at least one pharmaceutically acceptable vehicle and/or excipient.

8. Use of compounds according to any one of claims 1-4 for the preparation of a medicine for treating a pathological state for which the modulation of FAAH activity would result at improving the health of the patient.

9. Use according to claim 8, wherein said pathological state is a central nervous system disorder, disease of energy metabolism, cardiovascular and respiratory disorder, gastrointestinal and liver disorders, retinopathy, cancer and musculoskeletal disorder.
10. Use according to claim 9 where the disorder is a central nervous system disorder.

11. Use according to claim 10 where the disorder is pain.

12. Use according to claim 10 where the disorder is anxiety.

13. Use according to claim 10 where the disorder is Parkinson's disease.

14. A method for inhibiting FAAH comprising the step of administering to a mammal afflicted with a pathological state for which the modulation of FAAH activity would result at improving the health of the patient, an effective amount of a compound of claims 1-4.
Figure 1: Analgesic effect of ST4070 and ST3108 at 50 mg/kg
Figure 2: Dose-response effect of the analgesic properties of ST4070
### INTERNATIONAL SEARCH REPORT

**International application No**

PCT/EP2009/052258

### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C271/12 C07C271/24 C07C271/28 A61K31/27

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)
C07C  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, CHEM ABS Data, BEILSTEIN Data, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document with Indication where appropriate, of the relevant passages</th>
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<td>A</td>
<td>FR 2 866 884 A (SANOFI SYNTHELABO [FR]) 2 September 2005 (2005-09-02) the whole document</td>
<td>1-14</td>
</tr>
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</table>

Further documents are listed in the continuation of Box C

See patent family 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 date(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
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**Date of the actual completion of the international search**

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