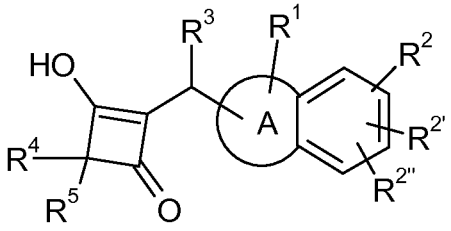
Case 23895

VINYLOGOUS ACIDS DERIVATIVES AS CHYMASE INHIBITORS

The invention is concerned with novel vinylogous acids derivatives of formula (I),



(I)

wherein

A is phenyl ring, or

heteroaryl ring, which is a monocyclic aromatic ring of 5 or 6 ring atoms, containing one or two ring heteroatoms selected from N, O and S, the remaining ring atoms being C, or

heterocyclyl ring, which is non-aromatic mono-cyclic ring of 5 or 6 ring atoms, containing one or two ring heteroatoms selected from N and $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C, one of the ring carbon atom of the heterocyclyl ring being optionally replaced with a carbonyl group;

R^1 is hydrogen, halogen, nitro, cyano, amino, C_{1-6} alkyl, heteroalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy,

–NR'R", –(C_{0-6} alkylene)–NR'R", in which R' and R" are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, heteroalkyl, formyl, C_{1-6} alkylcarbonyl, optionally substituted C_{3-7} cycloalkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted heterocyclylcarbonyl, C_{1-6} alkylsulfonyl, optionally substituted C_{3-7} cycloalkylsulfonyl, optionally substituted arylsulfonyl, optionally substituted heteroarylsulfonyl and optionally substituted heterocyclylsulfonyl, or

–(C_{0-6} alkylene)–OR', in which R' is hydrogen, C_{1-6} alkyl, heteroalkyl, formyl or C_{1-6} alkylcarbonyl;

R^2, $R^{2'}$ and $R^{2''}$ are independently hydrogen, halogen, cyano, nitro, amino, mono- or di-C_{1-6} alkyl substituted amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroalkyl, hydroxy or C_{1-6} alkoxy;

R^3 is hydrogen, halogen, cyano, nitro, amino, mono- or di- C_{1-6} alkyl substituted amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroalkyl, hydroxy, C_{1-6} alkoxy, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted C_{3-7} cycloalkyl C_{1-6} alkyl, optionally substituted aryl C_{1-6} alkyl, optionally substituted heteroaryl C_{1-6} alkyl or optionally substituted heterocyclyl C_{1-6} alkyl;

R^4 is hydrogen, halogen, cyano, nitro, amino, mono- or di- C_{1-6} alkyl substituted amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroalkyl, hydroxy, C_{1-6} alkoxy, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted C_{3-7} cycloalkyl C_{1-6} alkyl, optionally substituted aryl C_{1-6} alkyl, optionally substituted heteroaryl C_{1-6} alkyl or optionally substituted heterocyclyl C_{1-6} alkyl;

R^5 is hydrogen, halogen or C_{1-6} alkyl; or

R^4 and R^5, together with the carbon atom to which they are attached, form optionally substituted C_{3-7} cycloalkyl ring or optionally substituted heterocyclyl ring;

and prodrugs and pharmaceutically acceptable salts thereof.

Further, the invention is concerned with a process and an intermediate for the manufacture of the above compounds, pharmaceutical preparations which contain such compounds, the use of these compounds for the production of pharmaceutical preparations as well as a process for the manufacture of the intermediate.

The compounds of formula (I) inhibit Chymase. Chymase is a serine proteinase with an expression pattern striktly limited to a sub-population of mast cells (M_{CT} mast cell). Chymase is activated only upon mast cell activation and degranulation which restricts the enzyme activity to M_{CT} positive tissues. Chymase is specifically cleaving a number of pathologically relevant substrates (Raymond, W. W., S. W. Ruggles, et al.; JBC 2003 **278**(36): 34517-34524) whereby it can activate Angiotensin II, Endothelin, TGFb, Il1, SCF, collagenase and degrade proteins like Thrombin, FN, APO A1,2. This pattern renders chymase an attractive target for allergic, inflammatory and fibrotic diseases. Indeed a number of successful animal studies with chymase inhibitors have demonstrated efficacy in atopic animals, vascualr injury and atheroslerosis (Doggrell SA, Wanstall JC Can J Physiol Pharmacol. 2005 Feb;83(2):123-30; Lindstedt KA, Kovanen PT. Curr Opin Lipidol. 2004 Oct;15(5):567-73; Reed CE, Kita H.J Allergy Clin Immunol. 2004 Nov;114(5):997-1008; Takai S, et al, .Eur J Pharmacol. 2004 Oct 6;501(1-3):1-8; Takai S, et al, Trends Pharmacol Sci. 2004 Oct;25(10):518-22; Takai S, Miyazaki M. Curr Vasc Pharmacol. 2003 Jun;1(2):217-24).

Thus inhibition of chymase appears a useful modality in Allergy, Asthma, peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crons disease, wound healing (burns/ulcers in Diabetes/CLI).

The present invention provides the novel compounds of formula (I) which are chymase inhibitors.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term “halogen” or “halo” means fluorine, chlorine, bromine and iodine, with chlorine and fluorine being preferred.

The term "C_{1-6} alkyl", alone or in combination with other groups, means a branched or straight-chain monovalent alkyl radical, having one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl. C_{1-4} alkyl is more preferred.

The term "heteroalkyl" means C_{1-6} alkyl substituted by one or more substituents selected independently from the group consisting of nitro, hydroxy, halogen, cyano, C_{1-6} alkoxy, formyl, C_{1-6} alkylcarbonyl, carboxyl, C_{1-6} alkylthio, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl, amino and mono- or di- C_{1-6} alkyl substituted amino. This term is further exemplified by such radicals as 2-hydroxyethyl, perfluoromethyl. C_{1-6} alkyl substituted by one hydroxy group or one to three same or different halogen atoms are preferred.

The term "C_{3-7} cycloalkyl", alone or in combination with other groups, means a saturated monovalent cyclic hydrocarbon radical of three to seven ring carbons, e.g., cyclopropyl, cyclobutyl, cyclohexyl.

The term "C_{1-6} alkoxy", alone or in combination with other groups, means the group R'-O-, wherein R' is a C_{1-6} alkyl.

The term "C_{2-6} alkenyl", alone or in combination with other groups, means a straight-chain or branched hydrocarbon residue comprising an olefinic bond, having two to six carbon atoms, such as e.g. ethenyl, 2-propenyl.

The term "C_{2-6}-alkynyl", alone or in combination with other groups, means a straight-chain or branched hydrocarbon residue comprising a tripple bond, having two to six carbon atoms, such as e.g. ethynyl, 2-propynyl.

The term "C_{0-6} alkylene" means a bond or a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 6 carbon atoms. C_0 alkylene means a bond.

The term "aryl", alone or in combination with other groups, means a phenyl or a naphthyl group, preferably a phenyl group.

The term "heterocyclyl", alone or combination with other groups, means non-aromatic mono- or bi-cyclic radicals of three to eight ring atoms in which one or two ring atoms are heteroatoms

selected from N, O, or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C.

The term "heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C. Preferably, the attachment point of the heteroaryl radical will be on an aromatic ring.

The term "optionally substituted aryl", "optionally substituted heteroaryl", "optionally substituted heterocyclyl" and "optionally substituted C_{3-7} cycloalkyl" means, respectively aryl, heteroaryl, heterocyclyl and C_{3-7} cycloalkyl optionally substituted by one or more substituents independently selected from the group consisting of halogen, nitro, cyano, amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, mono- or di- C_{1-6} alkyl substituted amino and heteroalkyl.

Preferred radicals for the chemical groups whose definitions are given above are those specifically exemplified in Examples.

Compounds of formula (I) can form pharmaceutically acceptable acid addition salts. Examples of such pharmaceutically acceptable salts are salts of compounds of formula (I) with physiologically compatible mineral acids, such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The term "pharmaceutically acceptable salts" refers to such salts. Compounds of formula (I) in which a COOH group is present can further form salts with bases. Examples of such salts are alkaline, earth-alkaline and ammonium salts such as e.g. Na-, K-, Ca- and Trimethylammoniumsalt. The term "pharmaceutically acceptable salts" also refers to such salts. Acid addition salts as described above are preferred.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "aryl group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the aryl group is substituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

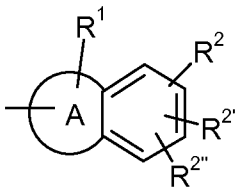
"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

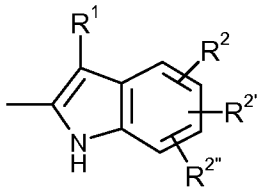
Compounds that have the same molecular Formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, if a carbon atom is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn, Ingold and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

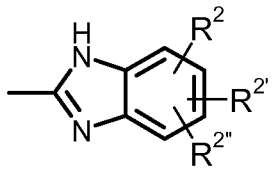
The compounds of formula (I) can possess one or more asymmetric centers. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof, as well as individual epimers and mixture thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

While the broadest definition of this invention is described before, the compounds of formula (I) having certain radicals are preferred.

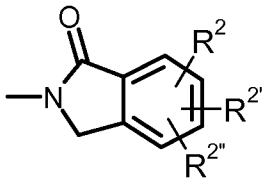
In the compounds of formula (I),

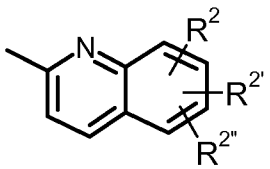


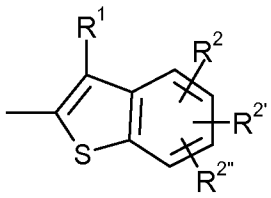
is preferably 

(a) , 

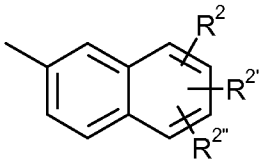
(b)



(c) , 

(d) , 

(e) or



(f) , more preferably (a), (d), (e) or (f), further more preferably (a), (e) or (f), and especially (a) is preferred.

In the compounds of formula (I), R^3 is preferably C_{1-6} alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl C_{1-6} alkyl or optionally substituted heteroaryl C_{1-6} alkyl, more preferably R^3 is C_{1-6} alkyl, phenyl optionally substituted by one to three fluorine atoms, heteroaryl optionally substituted by one to three fluorine atoms, in which heteroaryl is a monocyclic aromatic radical of 5 or 6 ring atoms, containing one or two ring nitrogen atoms or phenyl C_{1-6} alkyl, and R^3 is especially phenyl.

In the compounds of formula (I), R^1 is preferably hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, –(C_{0-6} alkylene)–NR'R", in which R' and R" are independently selected from the group consisting of hydrogen, formyl, C_{1-6} alkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted arylsulfonyl and optionally substituted heteroarylsulfonyl or –(C_{0-6} alkylene)–OR', in which R' is hydrogen or C_{1-6} alkylcarbonyl. More preferably R^1 is C_{1-6} alkyl, –(C_{2-6} alkylene)–NR'R", in which R' and R" are independently selected from the group consisting of hydrogen, formyl, acetyl, arylcarbonyl, in which aryl is optionally substituted by one or two perfluoro methyl and arylsulfonyl or –(C_{2-6} alkylene)–OR', in which R' is hydrogen or acetyl. Further more preferably R^1 is 2-aminoethyl, 2-acetylaminoethyl, 2-(N-

formyl-N-methylamino)ethyl, 2-acetylamino-2,2-dimethylethyl, methyl, isopropyl or 2-hydroxyethyl. Especially R^1 is methyl, 2-acetylaminoethyl, 2-acetylamino-2,2-dimethylethyl or 2-(N-formyl-N-methylamino)ethyl.

In the compounds of formula (I), R^2, $R^{2'}$ and $R^{2''}$ are preferably independently hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy. More preferably two of R^2, $R^{2'}$ and $R^{2''}$ are hydrogen, and the other is hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy. Further more preferably two of R^2, $R^{2'}$ and $R^{2''}$ are hydrogen, and the other is hydrogen, chloro, fluoro, methyl, ethyl or methoxy. Especially two of R^2, $R^{2'}$ and $R^{2''}$ are hydrogen, and the other is hydrogen, fluoro or methyl.

In the compounds of formula (I), R^4 is preferably hydrogen, C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted C_{3-7} cycloalkyl C_{1-6} alkyl or optionally substituted aryl C_{1-6} alkyl; or R^4 and R^5, together with the carbon atom to which they are attached, form optionally substituted C_{3-7} cycloalkyl ring. More preferably R^4 is C_{1-6} alkyl, optionally substituted aryl or optionally substituted aryl C_{1-6} alkyl, and R^5 is halogen or C_{1-6} alkyl. Especially R^4 is phenyl or 4-methylphenyl, and R^5 is methyl.

Preferred compound of the invention is a compound of formula (I), which is

N-(2-{2-[(2-Hydroxy-3-methyl-4-oxo-3-phenyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-yl}-1,1-dimethyl-ethyl)-acetamide,

3-Hydroxy-4-methyl-2-[(3-methyl-1H-indol-2-yl)-phenyl-methyl]-4-phenyl-cyclobut-2-enone,

2-[(3,5-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone,

2-[(3,6-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone,

2-[(5-Fluoro-3-methyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone,

N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-phenyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-acetamide,

3-Hydroxy-4-methyl-2-[(3-methyl-1H-indol-2-yl)-phenyl-methyl]-4-p-tolyl-cyclobut-2-enone,

2-[(3,5-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone,

2-[(3,6-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone,

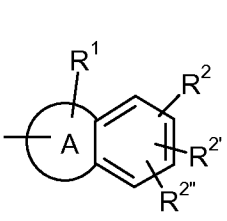
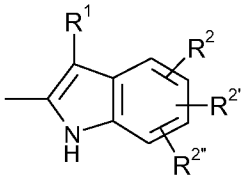
2-[(5-Fluoro-3-methyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone,

N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-acetamide or

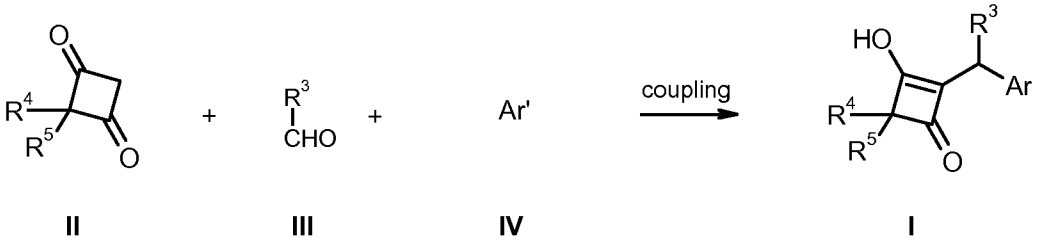
N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-N-methyl-formamide.

The compounds of the present invention can be prepared, for example, by the general synthetic procedures described below.

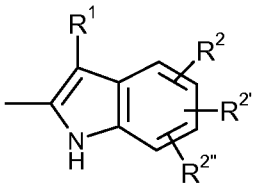
General Synthetic Procedures

I) The compounds of formula (I), wherein  is  (a) (, in which R^1, R^2, $R^{2'}$ and $R^{2''}$ are as defined before,) can be prepared in accordance with the following scheme 1:

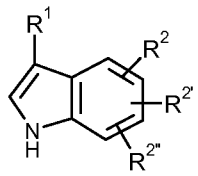
Scheme 1



II III IV I

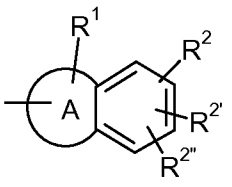


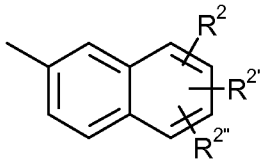
(a)



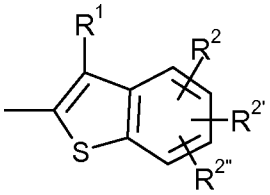
R^3, R^4 and R^5 as defined before. Ar is , and Ar' is , wherein R^1, R^2, $R^{2'}$ and $R^{2"}$ are as defined before.

The coupling of a diketone **II** (exists as an equilibrium of the keto and enol form), an aldehyde **III** and an aromatic compound **IV** to the vinylogous acid **I** can be effected in a solvent such as CH_3CN or an acid such as a carbonic acid, e.g. formic acid or preferably acetic acid at a temperature in the range of 22 °C – 100 °C, preferably at 22 °C for 1 – 20 h.

II) The compounds of formula (I), wherein 

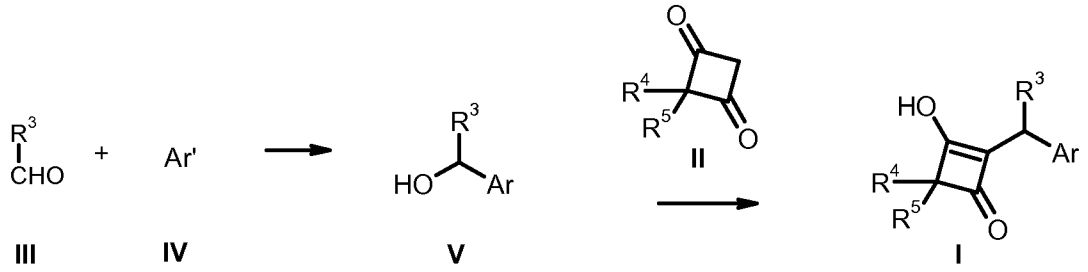
is 

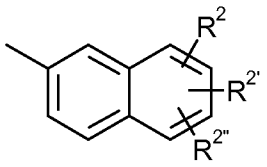
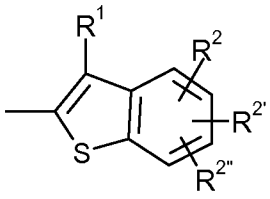
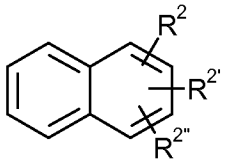
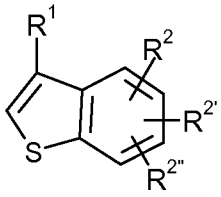
(f) or



(e) (, in which R^1, R^2, $R^{2'}$ and $R^{2"}$ are as defined before,) can be prepared in accordance with the following scheme 2:

Scheme 2



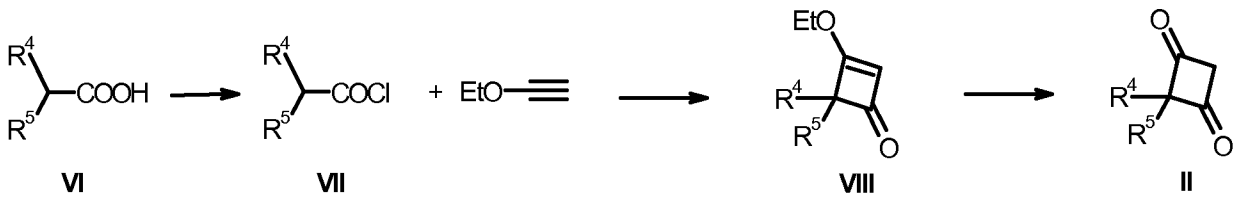
R^3, R^4 and R^5 are as defined before. Ar is  (f) or  (e), and Ar' is  or , wherein R^1, R^2, $R^{2'}$ and $R^{2''}$ are as defined before.

An aromatic compound Ar **IV** such as 2-halogen substituted naphthyl derivatives or benzothiophene derivatives can be lithiated at position 2 with an alkyl lithium reagent such as n-butyl lithium in a solvent like e.g. ethyl ether or preferably tetrahydrofurane at -100 °C to 60 °C, preferably at -80 °C. The lithiated intermediate obtained can be reacted with an aldehyde **III** at -80 °C to 22 °C to give the alcohol **V**.

The alcohol **V** may be reacted with the diketone **II** in the presence of a carbonic acid, e.g. acetic acid or preferably trifluoroacetic acid in a solvent such as an ether or preferably dichloromethane at a temperature in the range of 22 °C – 50 °C, preferably at 22 °C for 1 – 20 h to afford the vinylogous acid **I**.

III) The starting materials of formula **II** may be prepared in accordance with the following scheme 3:

Scheme 3



R^4 and R^5 are as defined before.

An acid **VI** may be converted to an acid chloride by standard methods using oxalyl chloride or preferably thionylchloride to give the acid chloride **VII**. The acid chloride can be reacted with ethoxy acetylene in the presence of a base, such as an alkyl amine, preferably triethylamine in a solvent like an ether, preferably diethyl ether at 0 °C – 40 °C, preferably at 40 °C to give the ethylester **VIII**. Hydrolysis of the ethylester **VIII** can be effected with a strong mineral acid, preferably hydrochloric acid in a solvent such as an ether, preferably tetrahydrofurane at 0 °C – 60 °C, preferably at 22 °C to give the diketone **II**.

The starting material of formula **II** can be prepared according to the following literature reference:

1) Brand, Stephen et al., Organic Letters (2003), 5(13), 2343-2346.

IV) The starting materials of formula **III** are all commercially available.

V) Most of the aromatic compounds of formula **IV** are commercially available, or can be prepared by a skilled person, using his/her common general knowledge. The compounds of formula IV can also be prepared, according to the following literature references:

2) Kreighbaum, William E. et al., J. Med. Chem. (1980), 23(3), 285-9.

3) Yang, Shyh-Chyun et al., Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (1999), 38B(8), 897-904.

4) Tsuchiya, Michihiro et al., international patent application, WO8200032 (1982).

5) Hengartner, Urs et al., Journal of Organic Chemistry (1979), 44(22), 3741-7.

6) Somei, Masanori et al., Heterocycles (1992), 33(1), 77-80.

VI) The starting materials of formula **VI** are all commercially available.

As described above, the compounds of formula (I) are active compounds and inhibit chymase. These compounds consequently prevent the activation of Angiotensin II, Endothelin, TGFb, Il1, SCF, collagenase and degradation of proteins like Thrombin, FN, APO A1,2. They therefore can be used for the treatment and/or prevention of allergic, inflammatory and/or fibrotic diseases, such as allergy, asthma, peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, atherothrombosis and/or burns/ulcers in Diabetes/CLI.

Prevention and/or treatment of allergic, inflammatory or fibrotic diseases, particularly atherothrombosis or asthma, is the preferred indication.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable excipient.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of allergic, inflammatory and/or fibrotic diseases, particularly as therapeutically active substances for the treatment and/or prophylaxis of allergy, asthma, peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, atherothrombosis and/or burns/ulcers in Diabetes/CLI.

The invention also relates to the use of compounds as described above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of allergic, inflammatory and/or fibrotic diseases, particularly for the therapeutic and/or prophylactic treatment of allergy, asthma, peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic

nephropathy, irritable Bowel Disease, Crohns' disease, atherothrombosis and/or burns/ulcers in Diabetes/CLI. Such medicaments comprise a compound as described above.

The invention also relates to the process and the intermediates for manufacturing the compounds of formula (I) as well as the process for manufacturing the intermediates.

The inhibition of chymase by the compounds of the present invention can be demonstrated by the peptide substrate assay as described hereinafter.

For the chymase a substrate was chosen containing the 4 amino acid peptide AAPF as a standard substrate for chymotrypsin like compounds (succinyl-Ala-Ala-Pro-Phe-[7-amino-4-methylcoumarin]; Lockhart BE, et al., "Recombinant human mast-cell chymase: an improved procedure for expression in Pichia pastoris and purification of the highly active enzyme." *Biotechnol Appl Biochem.* published as immediate publication 26 May 2004 as manuscript BA20040074)). The peptide was synthesized with a purity of 95% from Bachem, Bubendorf, Switzerland). Chymase purified form human skin mast cells was obtained from Calbiochem (Merck Biosciences, San Diego, California, USA). The assay buffer was 0.15 M NaCl, 0.05M, Tris HCl , 0.05% CHAPS (3-[(3-Cholamidopropyl)-dimethylammonio]-1-propane sulphonate), 0.1mg/ml Heparin (Heparin sodium, Sigma, porcine intestinal mucosa), 0.02mM AAPF-substrate, 1nM Chymase at pH 7.4. The assay was performed in 96-well plates (Packard Optiplate), with a 0.05ml volume at room temperature. Chymase activity was indicated by the initial rate of increase in fluorescence at 340/440nm (excitation / emission) from free 7-amino-4-methylcoumarin released from the substrate. Inhibition of the activity by inhibitory compounds was read after 30 min pre-incubation with the chymase at room temperature in assay buffer without AAPF-substrate. The assay was then started by addition of the indicated concentration of AAPF-substrate.
The IC50 values of the active compounds of the present invention preferably amount to about 1000 to 1 nM, especially about 50 to 1 nM.

Example	IC50(nM)
Example 3	27

Example 6	34
Example 10	25
Example 13	8

The compounds of formula (I) and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or suspensions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils,

liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 300 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula (I).

Examples

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

General procedure A: Preparation of the diketone **II**

A1. A mixture of the acid **VI** (30 mmole) in toluene (10 ml) was treated with thionyl chloride (90 mmole) and heated to reflux for ca. 1 h until gas evolution ceased. The mixture was evaporated to dryness to give the acid chloride **VII** which was used without further purification.

A2. To a stirred solution of the acid chloride **VII** (30 mmole) and ethoxy acetylene (40% in hexane, 60 mmole) in diethyl ether (70 ml) was added at 22 °C triethylamine (50 mmole) and stirring was continued at reflux temperature for 20 h. The suspension was filtered, the filtrate evaporated and the residue chromatographed on silica to give the ethylester **VIII**.

A3. A mixture of the ethylester **VIII** (2 mmole) and aqueous hydrochloric acid (25%, 1.5 ml) in tetrahydrofurane (2 ml) was stirred at 22 °C for 16 h. The mixture was evaporated and the residue partitioned between aqueous hydrochloric acid (1 N) and ethyl acetate. The organic layer was dried evaporated and chromatographed on silica to give the diketone **II**.

General procedure B: Preparation of the alcohols V

To a solution of a 2-bromonaphthalene derivative (10 mmole) or a benzothiophene derivative (10 mmole) in tetrahydrofurane (150 ml) was added at -78 °C n-butyllithium (1.6 M in n-hexane, 11 mmole) and stirring was continued at -78 °C for 1 h (in case of the benzothiophene derivatives stirring was continued at 22 °C followed by cooling to -78 °C). The mixture was treated with a solution of the aldehyde **III** (10 mmole) in tetrahydrofurane (20 ml) and stirring was continued for 30 min. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was dried evaporated and the residue chromatographed on silica to give the alcohols **V**.

General Procedure C: Coupling of a diketone II an aldehyde III and an aromatic compound such as an indole IV

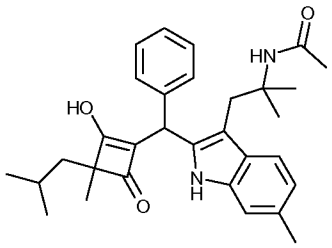
A solution of the diketone **II** (1 mmole), the aldehyde **III** (1.3 mmole) and the indole **IV** (1 mmole) in acetic acid (4 ml) was stirred at 22 °C for 16 h. The suspension was filtered and the residue washed with pentane. If no precipitaions occurred, the solution was purified on preparative HPLC (RP-18, CH_3CN/H_2O, gradient) to give the vinylogous acids **I**.

General Procedure D: Coupling of a diketone **II** and an alcohol **V**

A solution of the diketone **II** (0.2 mmole) and the alcohol **V** (0.2 mmole) in dichloromethane (2 ml) was added trifluoroacetic acid (0.4 mmole) and stirring was continued at 22°C for 6 h. The suspension was evaporated and the residue washed with n-pentane. If no precipitation occurred, the solution was purified on preparative HPLC (RP-18, CH_3CN/H_2O, gradient) to give the vinylogous acids **I**.

Example 1

N-(2-{2-[(2-Hydroxy-3-isobutyl-3-methyl-4-oxo-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-yl}-1,1-dimethyl-ethyl)-acetamide



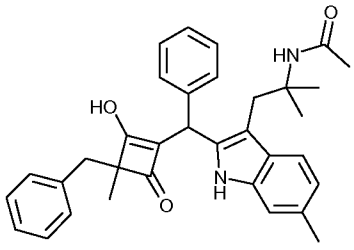
1.1. Using general procedure A, 2,4-dimethyl-pentanoic acid was converted to 2-isobutyl-2-methyl-cyclobutane-1,3-dione, obtained as a brown oil. MS: 153.4 ([M-H]$^-$).

1.2. A solution of 1,1-dimethyl-2-(6-methyl-1H-indol-3-yl)-ethylamine (2 mmole, prepared according to Lit. 2) and acetic anhydride (2.2 mmole) in dichloromethane (3 ml) was treated with triethylamine (6 mmole) and the mixture was stirred at 22 °C for 18 h. The mixture was washed with aqueous hydrochloric acid (1N), the organic layer was dried and evaporated to give N-[1,1-dimethyl-2-(6-methyl-1H-indol-3-yl)-ethyl]-acetamide as a brownish solid. MS: 243.2 ([M-H]$^-$).

1.3. Using general procedure C, 2-isobutyl-2-methyl-cyclobutane-1,3-dione was reacted with benzaldehyde and N-[1,1-dimethyl-2-(6-methyl-1H-indol-3-yl)-ethyl]-acetamide to give N-(2-{2-[(2-hydroxy-3-isobutyl-3-methyl-4-oxo-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-yl}-1,1-dimethyl-ethyl)-acetamide as a pale brown solid. MS: 485.6 ([M-H]$^-$).

Example 2

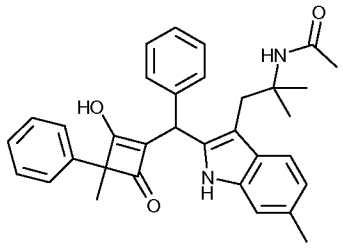
N-(2-{2-[(3-Benzyl-2-hydroxy-3-methyl-4-oxo-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-yl}-1,1-dimethyl-ethyl)-acetamide



Using general procedure C, 2-benzyl-2-methyl-cyclobutane-1,3-dione (Lit. 1) was reacted with benzaldehyde and N-[1,1-dimethyl-2-(6-methyl-1H-indol-3-yl)-ethyl]-acetamide (from Example 1.2) to give the title compound as a red solid. MS: 519.5 ([M-H]$^-$).

Example 3

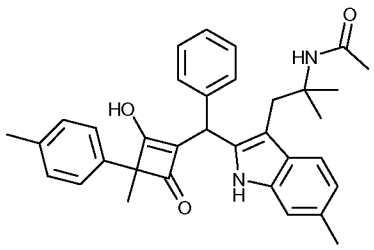
N-(2-{2-[(2-Hydroxy-3-methyl-4-oxo-3-phenyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-yl}-1,1-dimethyl-ethyl)-acetamide



Using general procedure C, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with benzaldehyde and N-[1,1-dimethyl-2-(6-methyl-1H-indol-3-yl)-ethyl]-acetamide (from Example 1.2) to give the title compound as a pale yellow solid. MS: 505.5 ([M-H]$^-$).

Example 4

N-(2-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-yl}-1,1-dimethyl-ethyl)-acetamide



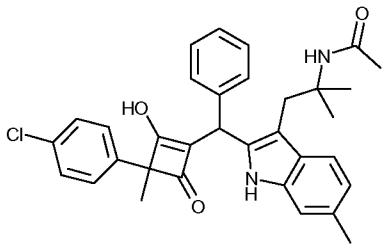
4.1. Using general procedure A, 2-p-tolyl-propionic acid was converted to 2-methyl-2-p-tolyl-cyclobutane-1,3-dione, obtained as a brown oil. MS: 187.4 ([M-H]$^-$).

4.2. Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione was reacted with benzaldehyde and N-[1,1-dimethyl-2-(6-methyl-1H-indol-3-yl)-ethyl]-acetamide (from Example 1.2) to give N-(2-{2-[(2-hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-

methyl]-6-methyl-1H-indol-3-yl}-1,1-dimethyl-ethyl)-acetamide as a pale yellow solid. MS: 519.5 ([M-H]$^-$).

Example 5

N-[2-(2-{[3-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-cyclobut-1-enyl]-phenyl-methyl}-6-methyl-1H-indol-3-yl)-1,1-dimethyl-ethyl]-acetamide

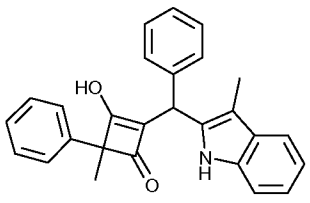


5.1. Using general procedure A, 2-(4-chloro-phenyl)-propionic acid was converted to 2-(4-chloro-phenyl)-2-methyl-cyclobutane-1,3-dione, obtained as a brown oil. MS: 206.9 ([M-H]-).

5.2. Using general procedure C, 2-(4-chloro-phenyl)-2-methyl-cyclobutane-1,3-dione was reacted with benzaldehyde and N-[1,1-dimethyl-2-(6-methyl-1H-indol-3-yl)-ethyl]-acetamide (from Example 1.2) to give N-[2-(2-{[3-(4-chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-cyclobut-1-enyl]-phenyl-methyl}-6-methyl-1H-indol-3-yl)-1,1-dimethyl-ethyl]-acetamide as a pale yellow solid. MS: 539.5 ([M-H]$^-$).

Example 6

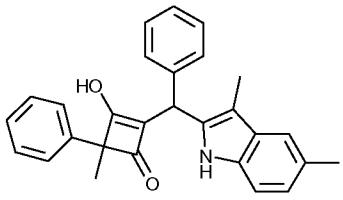
3-Hydroxy-4-methyl-2-[(3-methyl-1H-indol-2-yl)-phenyl-methyl]-4-phenyl-cyclobut-2-enone



Using general procedure C, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with benzaldehyde and 3-methyl-1H-indole to give the title compound as a colorless solid. MS: 392.3 ([M-H]$^-$).

Example 7

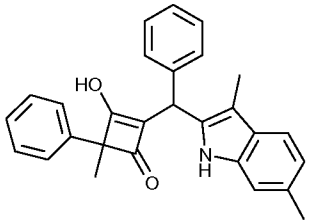
2-[(3,5-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone



Using general procedure C, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with benzaldehyde and 3,5-dimethyl-1H-indole (Lit. 3) to give the title compound as a colorless solid. MS: 406.5 ($[M-H]^-$).

Example 8

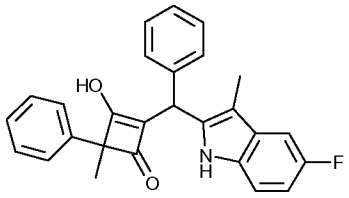
2-[(3,6-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone



Using general procedure C, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with benzaldehyde and 3,6-dimethyl-1H-indole (Lit. 4) to give the title compound as a colorless solid. MS: 406.4 ($[M-H]^-$).

Example 9

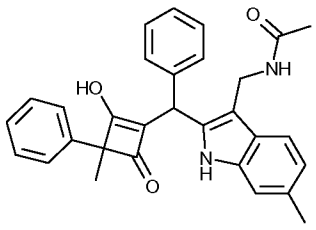
2-[(5-Fluoro-3-methyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone



Using general procedure C, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with benzaldehyde and 5-fluoro-3-methyl-1H-indole to give the title compound as a colorless solid. MS: 410.3 ([M-H]$^-$).

Example 10

N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-phenyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-acetamide



10.1. To a solution of 6-methyl-1H-indole-3-carbaldehyde (0.96 g, Lit. 5) in ethanol (30 ml) was added at 22°C hydroxylamine hydrochloride (0.46 g) and sodium acetate (0.54 g) and the mixture was stirred for 3 h. The mixture was evaporated and the residue triturated with water and dichloromethane/n-heptane (1:1) and dried to give 6-methyl-1H-indole-3-carbaldehyde oxime (0.96 g) as a pink solid. MS: 175.3 ([M+H]+).

10.2. To a mixture of 6-methyl-1H-indole-3-carbaldehyde oxime (0.66 g) and $NiCl_2 \cdot 6\ H_2O$ (0.97 g) in methanol (60 ml) was added at 22 °C sodium borohydride (3.04 g) in portions. The suspension was filtered and the filtrate evaporated. The residue was partitioned between aqueous NH3 (1%) and ethyl acetate, the organic layer was dried and evaporated to the give crude C-(6-methyl-1H-indol-3-yl)-methylamine as a yellow semi solid (0.68 g).

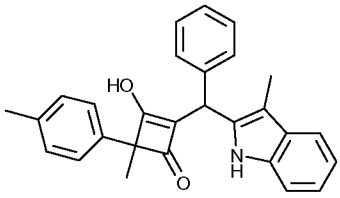
10.3. To a solution of C-(6-methyl-1H-indol-3-yl)-methylamine (0.24 g) in dichloromethane (4 ml) was added acetic anhydride (0.14 ml) and pyridine (0.13 ml) and stirring was continued at 22 °C for 20 min. The mixture was washed with aqueous HCl (1N), the organic layere was dried and

evaporated. The residue was chromatographed on silica using dichloromethane/methanol (70:1) to give N-(6-methyl-1H-indol-3-ylmethyl)-acetamide as colorless foam (0.15 g). MS: 203.1 ([M+H]+).

10.4. Using general procedure C, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with benzaldehyde and N-(6-methyl-1H-indol-3-ylmethyl)-acetamide to give N-{2-[(2-hydroxy-3-methyl-4-oxo-3-phenyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-acetamide as a pale red solid. MS: 463.4 ($[M-H]^-$).

Example 11

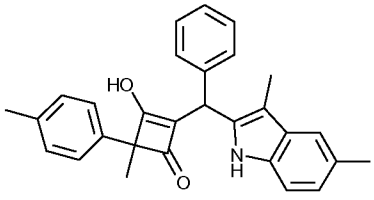
3-Hydroxy-4-methyl-2-[(3-methyl-1H-indol-2-yl)-phenyl-methyl]-4-p-tolyl-cyclobut-2-enone



Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and 3-methyl-1H-indole to give the title compound as a colorless solid. MS: 406.6 ($[M-H]^-$).

Example 12

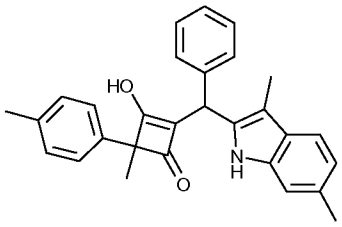
2-[(3,5-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone



Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and 3,5-dimethyl-1H-indole (Lit. 3) to give the title compound as a colorless solid. MS: 420.5 ([M-H]$^-$).

Example 13

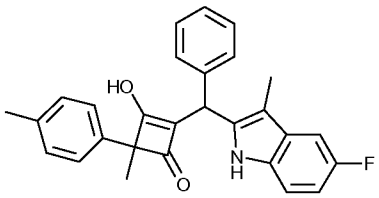
2-[(3,6-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone



Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and 3,6-dimethyl-1H-indole (Lit. 4) to give the title compound as a colorless solid. MS: 420.5 ([M-H]$^-$).

Example 14

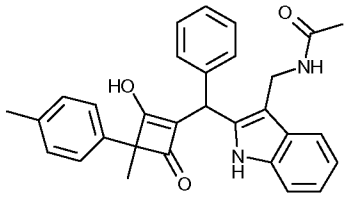
2-[(5-Fluoro-3-methyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone



Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and 5-fluoro-3-methyl-1H-indole to give the title compound as a red solid. MS: 424.5 ([M-H]$^-$).

Example 15

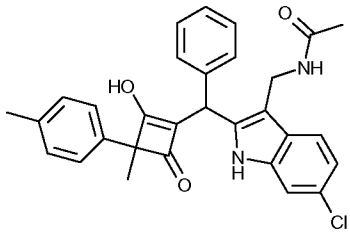
N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-1H-indol-3-ylmethyl}-acetamide



Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and N-(1H-indol-3-ylmethyl)-acetamide (Lit. 6) to give the title compound as an off-white solid. MS: 463.4 ([M-H]$^-$).

Example 16

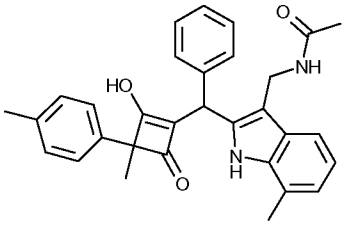
N-{6-Chloro-2-[(2-hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-1H-indol-3-ylmethyl}-acetamide



Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and N-(6-chloro-1H-indol-3-ylmethyl)-acetamide (prepared from C-(6-chloro-1H-indol-3-yl)-methylamine by acylation according to Example 1.2) to give the title compound as an off-white solid. MS: 497.3 ([M-H]$^-$).

Example 17

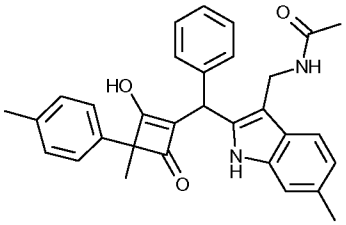
N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-7-methyl-1H-indol-3-ylmethyl}-acetamide



Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and N-(7-methyl-1H-indol-3-ylmethyl)-acetamide (prepared from 7-methyl-1H-indole-3-carbaldehyde according to Example 10.1-10.3) to give the title compound as an off-white solid. MS: 477.4 ($[M-H]^-$).

Example 18

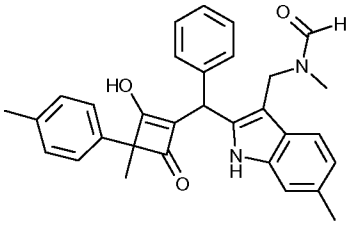
N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-acetamide



Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and N-(6-methyl-1H-indol-3-ylmethyl)-acetamide (from Example 10.3) to give the title compound as a pale red solid. MS: 477.3 ($[M-H]^-$).

Example 19

N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-N-methyl-formamide



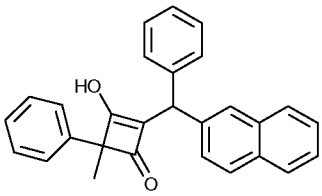
19.1. To a suspension of 6-methyl-1H-indole-3-carbaldehyde (0.96 g, Lit. 5) in methanol (15 ml) was added at 22 °C acetic acid (1.7 ml) and a solution of methylamine in tetrahydrofurane (2 M, 12.0 ml). After stirring for 1 h, sodium cyanoborohydride (0.76 g) was added in 5 portions and stirring was continued for 2 h. The mixture was evaporated and the residue partitioned between aqueous hydrochloric acid (1 N) and dichloromethane. The pH of the aqueous layer was adjusted to 14 using sodium hydroxide followed by extraction with dichloromethane. The organic layer was dried and evaporated to give crude methyl-(6-methyl-1H-indol-3-ylmethyl)-amine.

19.2. To a solution of crude methyl-(6-methyl-1H-indol-3-ylmethyl)-amine (87 mg) in acetonitrile (1 ml) was added diisopropylethyl amine (0.25 ml) and 4-nitrophenyl formate (90 mg) and stirring was continued for 3 h. The mixture was diluted with methanol and acetic acid evaporated and the residue was chromatographed on silica using n-heptane/AcOEt (1:1) to give N-methyl-N-(6-methyl-1H-indol-3-ylmethyl)-formamide as a colorless oil. MS: 202.9 ($[M]^+$).

19.3. Using general procedure C, 2-methyl-2-p-tolyl-cyclobutane-1,3-dione (from Example 4.1) was reacted with benzaldehyde and N-methyl-N-(6-methyl-1H-indol-3-ylmethyl)-formamide to give the title compound as a red solid. MS: 476.6 ($[M-H]^-$).

Example 20

3-Hydroxy-4-methyl-2-(naphthalen-2-yl-phenyl-methyl)-4-phenyl-cyclobut-2-enone

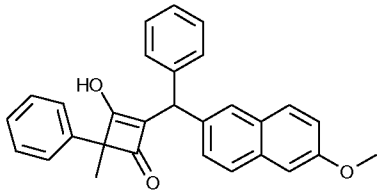


20.1. Using general procedure B, 2-bromonaphthalene was reacted with benzaldehyde to give naphthalen-2-yl-phenyl-methanol as a colorless solid.

20.2. Using general procedure D, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with naphthalen-2-yl-phenyl-methanol to give the title compound as a colorless solid. MS: 389.5 ([M-H]$^-$).

Example 21

3-Hydroxy-2-[(6-methoxy-naphthalen-2-yl)-phenyl-methyl]-4-methyl-4-phenyl-cyclobut-2-enone

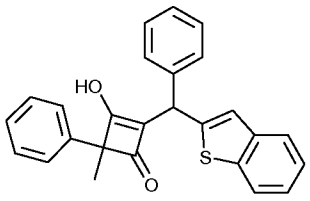


21.1. Using general procedure B, 2-bromo-6-methoxy-naphthalene was reacted with benzaldehyde to give (6-methoxy-naphthalen-2-yl)-phenyl-methanol as a colorless solid.

21.2. Using general procedure D, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with (6-methoxy-naphthalen-2-yl)-phenyl-methanol to give the title compound as a colorless solid. MS: 419.3 ([M-H]$^-$).

Example 22

2-(Benzo[b]thiophen-2-yl-phenyl-methyl)-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone

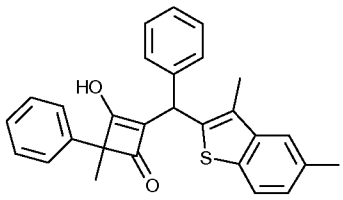


22.1. Using general procedure B, benzo[b]thiophene was reacted with benzaldehyde to give benzo[b]thiophen-2-yl-phenyl-methanol as a colorless solid. MS: 223.1 ($[M+H-H_2O]^+$).

22.2. Using general procedure D, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with benzo[b]thiophen-2-yl-phenyl-methanol to give the title compound as a colorless solid. MS: 395.3 ($[M-H]^-$).

Example 23

2-[(3,5-Dimethyl-benzo[b]thiophen-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone

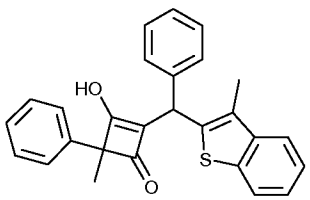


23.1. Using general procedure B, 3,5-dimethyl-benzo[b]thiophene was reacted with benzaldehyde to give (3,5-dimethyl-benzo[b]thiophen-2-yl)-phenyl-methanol as a colorless oil. MS: 251.4 ($[M+H-H_2O]^+$).

23.2. Using general procedure D, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with (3,5-dimethyl-benzo[b]thiophen-2-yl)-phenyl-methanol to give the title compound as a colorless solid. MS: 423.5 ($[M-H]^-$).

Example 24

3-Hydroxy-4-methyl-2-[(3-methyl-benzo[b]thiophen-2-yl)-phenyl-methyl]-4-phenyl-cyclobut-2-enone

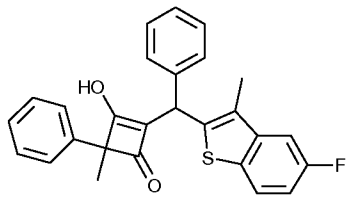


24.1. Using general procedure B, 3-methyl-benzo[b]thiophene was reacted with benzaldehyde to give (3-methyl-benzo[b]thiophen-2-yl)-phenyl-methanol as a pale yellow soild. MS: 236.8 ($[M+H-H_2O]^+$).

24.2. Using general procedure D, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with (3-methyl-benzo[b]thiophen-2-yl)-phenyl-methanol to give the title compound as a colorless solid. MS: 409.5 ($[M-H]^-$).

Example 25

2-[(5-Fluoro-3-methyl-benzo[b]thiophen-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone

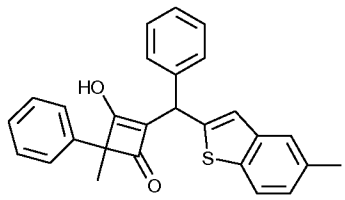


25.1. Using general procedure B, 5-fluoro-3-methyl-benzo[b]thiophene was reacted with benzaldehyde to give (5-fluoro-3-methyl-benzo[b]thiophen-2-yl)-phenyl-methanol as a pale yellow oil. MS: 255.3 ($[M+H-H_2O]^+$).

25.2. Using general procedure D, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with (5-fluoro-3-methyl-benzo[b]thiophen-2-yl)-phenyl-methanol to give the title compound as a colorless solid. MS: 427.5 ($[M-H]^-$).

Example 26

3-Hydroxy-4-methyl-2-[(5-methyl-benzo[b]thiophen-2-yl)-phenyl-methyl]-4-phenyl-cyclobut-2-enone

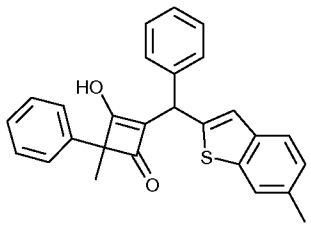


26.1. Using general procedure B, 5-methyl-benzo[b]thiophene was reacted with benzaldehyde to give (5-methyl-benzo[b]thiophen-2-yl)-phenyl-methanol as a colorless solid. MS: 237.1 ($[M+H-H_2O]^+$).

26.2. Using general procedure D, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with (5-methyl-benzo[b]thiophen-2-yl)-phenyl-methanol to give the title compound as a colorless solid. MS: 409.3 ($[M-H]^-$).

Example 27

3-Hydroxy-4-methyl-2-[(6-methyl-benzo[b]thiophen-2-yl)-phenyl-methyl]-4-phenyl-cyclobut-2-enone



27.1. Using general procedure B, 6-methyl-benzo[b]thiophene was reacted with benzaldehyde to give (6-methyl-benzo[b]thiophen-2-yl)-phenyl-methanol as an off-white solid. MS: 236.9 ($[M+H-H_2O]^+$).

27.2. Using general procedure D, 2-methyl-2-phenyl-cyclobutane-1,3-dione (Lit. 1) was reacted with (6-methyl-benzo[b]thiophen-2-yl)-phenyl-methanol to give the title compound as a pale yellow solid. MS: 409.3 ($[M-H]^-$).

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg

Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcristalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidon in water. The granulate is mixed with sodium starch glycolate and magesiumstearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	Ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents	
Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg

Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

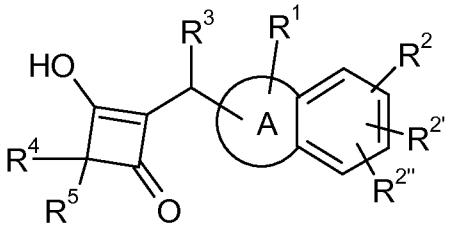
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcristalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcristalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesiumstearate and the flavouring additives and filled into sachets.

Claims:

1. Compounds of formula (I)



(I)

wherein

A is phenyl ring, or

heteroaryl ring, which is a monocyclic aromatic ring of 5 or 6 ring atoms, containing one or two ring heteroatoms selected from N, O and S, the remaining ring atoms being C, or

heterocyclyl ring, which is non-aromatic mono-cyclic ring of 5 or 6 ring atoms, containing one or two ring heteroatoms selected from N and $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C, one of the ring carbon atom of the heterocyclyl ring being optionally replaced with a carbonyl group;

R^1 is hydrogen, halogen, nitro, cyano, amino, C_{1-6} alkyl, heteroalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy,

–NR'R", –(C_{0-6} alkylene)–NR'R", in which R' and R" are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, heteroalkyl, formyl, C_{1-6} alkylcarbonyl, optionally substituted C_{3-7} cycloalkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted heterocyclylcarbonyl, C_{1-6} alkylsulfonyl, optionally substituted C_{3-7} cycloalkylsulfonyl, optionally substituted arylsulfonyl, optionally substituted heteroarylsulfonyl and optionally substituted heterocyclylsulfonyl, or

–(C_{0-6} alkylene)–OR', in which R' is hydrogen, C_{1-6} alkyl, heteroalkyl, formyl or C_{1-6} alkylcarbonyl;

R^2, $R^{2'}$ and $R^{2''}$ are independently hydrogen, halogen, cyano, nitro, amino, mono- or di-C_{1-6} alkyl substituted amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroalkyl, hydroxy or C_{1-6} alkoxy;

R^3 is hydrogen, halogen, cyano, nitro, amino, mono- or di- C_{1-6} alkyl substituted amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroalkyl, hydroxy, C_{1-6} alkoxy, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted C_{3-7} cycloalkyl C_{1-6} alkyl, optionally substituted aryl C_{1-6} alkyl, optionally substituted heteroaryl C_{1-6} alkyl or optionally substituted heterocyclyl C_{1-6} alkyl;

R^4 is hydrogen, halogen, cyano, nitro, amino, mono- or di- C_{1-6} alkyl substituted amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroalkyl, hydroxy, C_{1-6} alkoxy, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted C_{3-7} cycloalkyl C_{1-6} alkyl, optionally substituted aryl C_{1-6} alkyl, optionally substituted heteroaryl C_{1-6} alkyl or optionally substituted heterocyclyl C_{1-6} alkyl;

R^5 is hydrogen, halogen or C_{1-6} alkyl; or

R^4 and R^5, together with the carbon atom to which they are attached, form optionally substituted C_{3-7} cycloalkyl ring or optionally substituted heterocyclyl ring;

and prodrugs and pharmaceutically acceptable salts thereof;

wherein, unless otherwise defined,

the term "heteroalkyl" means C_{1-6} alkyl substituted by one or more substituents selected independently from the group consisting of nitro, hydroxy, halogen, cyano, C_{1-6} alkoxy, formyl, C_{1-6} alkylcarbonyl, carboxyl, C_{1-6} alkylthio, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl, amino and mono- or di-C_{1-6} alkyl amino.

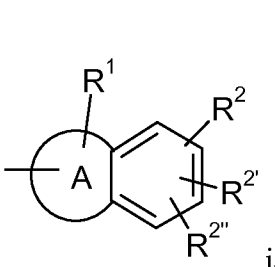
the term "aryl" means phenyl or naphthyl;

the term "heteroaryl" means a monocyclic or bicyclic ring of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring;

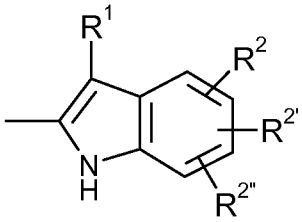
the term "heterocyclyl" means non-aromatic mono- or bi-cyclic radicals of three to eight ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C;

the term "optionally substituted aryl", "optionally substituted heteroaryl", "optionally substituted heterocyclyl" and "optionally substituted C_{3-7} cycloalkyl" means, respectively aryl, heteroaryl, heterocyclyl and C_{3-7} cycloalkyl optionally substituted by one or more substituents independently selected from the group consisting of halogen, nitro, cyano, amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxy, C_{1-6} alkoxy, mono- or di- C_{1-6} alkyl substituted amino and heteroalkyl.

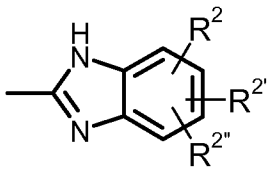
2. The compounds according to claim 1, wherein



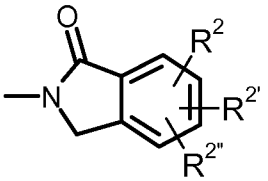
is



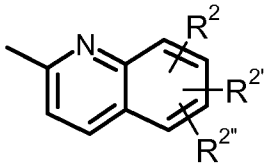
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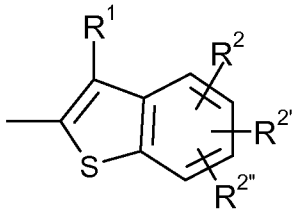
(b) ,



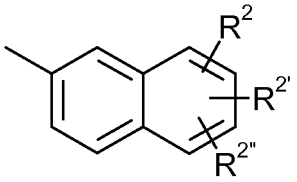
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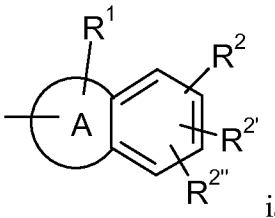


(e) or

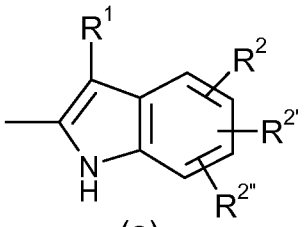


(f) .

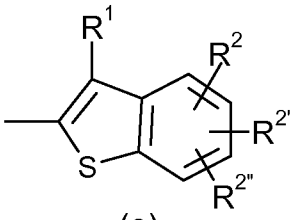
3. The compounds according to any one of claims 1 and 2, wherein



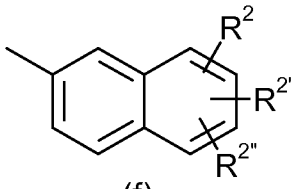
is



(a) ,

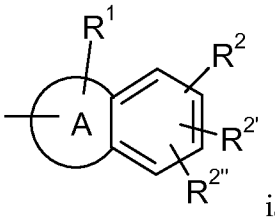


(e) or

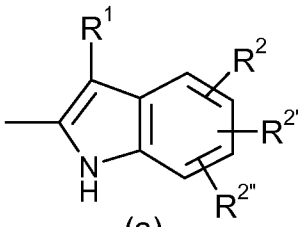


(f) .

4. The compounds according to any one of claims 1 to 3, wherein



is



(a) .

5. The compounds according to any one of claims 1 to 4, wherein R^3 is C_{1-6} alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl C_{1-6} alkyl or optionally substituted heteroaryl C_{1-6} alkyl.

6. The compounds according to any one of claims 1 to 5, wherein R^3 is C_{1-6} alkyl, phenyl optionally substituted by one to three fluorine atoms, heteroaryl optionally substituted by

one to three fluorine atoms, in which heteroaryl is a monocyclic aromatic radical of 5 or 6 ring atoms, containing one or two ring nitrogen atoms or phenyl C_{1-6} alkyl.

7. The compounds according to any one of claims 1 to 6, wherein R^3 is phenyl.

8. The compounds according to any one of claims 1 to 7, wherein R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, –(C_{0-6} alkylene)–NR'R", in which R' and R" are independently selected from the group consisting of hydrogen, formyl, C_{1-6} alkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroarylcarbonyl, optionally substituted arylsulfonyl and optionally substituted heteroarylsulfonyl or –(C_{0-6} alkylene)–OR', in which R' is hydrogen or C_{1-6} alkylcarbonyl.

9. The compounds according to any one of claims 1 to 8, wherein R^1 is C_{1-6} alkyl, –(C_{2-6} alkylene)–NR'R", in which R' and R" are independently selected from the group consisting of hydrogen, formyl, acetyl, arylcarbonyl, in which aryl is optionally substituted by one or two perfluoro methyl and arylsulfonyl or –(C_{2-6} alkylene)–OR', in which R' is hydrogen or acetyl.

10. The compounds according to any one of claims 1 to 9, wherein R^1 is 2-aminoethyl, 2-acetylaminoethyl, 2-(N-formyl-N-methylamino)ethyl, 2-acetylamino-2,2-dimethylethyl, methyl, isopropyl or 2-hydroxyethyl.

11. The compounds according to any one of claims 1 to 10, wherein R^1 is methyl, 2-acetylaminoethyl, 2-acetylamino-2,2-dimethylethyl or 2-(N-formyl-N-methylamino)ethyl.

12. The compounds according to any one of claims 1 to 11, wherein R^2, $R^{2'}$ and $R^{2''}$ are independently hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy.

13. The compounds according to any one of claims 1 to 12, wherein two of R^2, $R^{2'}$ and $R^{2''}$ are hydrogen, and the other is hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy.

14. The compounds according to any one of claims 1 to 13, wherein two of R^2, $R^{2'}$ and $R^{2''}$ are hydrogen, and the other is hydrogen, chloro, fluoro, methyl, ethyl or methoxy.

15. The compounds according to any one of claims 1 to 14, wherein two of R^2, $R^{2'}$ and $R^{2''}$ are hydrogen, and the other is hydrogen, fluoro or methyl.

16. The compounds according to any one of claims 1 to 15, wherein

R^4 is hydrogen, C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted C_{3-7} cycloalkyl C_{1-6} alkyl or optionally substituted aryl C_{1-6} alkyl; or

R^4 and R^5, together with the carbon atom to which they are attached, form optionally substituted C_{3-7} cycloalkyl ring.

17. The compounds according to any one of claims 1 to 16, wherein

R^4 is C_{1-6} alkyl, optionally substituted aryl or optionally substituted aryl C_{1-6} alkyl, and

R^5 is halogen or C_{1-6} alkyl.

18. The compounds according to any one of claims 1 to 17, wherein

R^4 is phenyl or 4-methylphenyl, and

R^5 is methyl.

19. The compounds according to claim 1, which is

N-(2-{2-[(2-Hydroxy-3-methyl-4-oxo-3-phenyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-yl}-1,1-dimethyl-ethyl)-acetamide,

3-Hydroxy-4-methyl-2-[(3-methyl-1H-indol-2-yl)-phenyl-methyl]-4-phenyl-cyclobut-2-enone,

2-[(3,5-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone,

2-[(3,6-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone,

2-[(5-Fluoro-3-methyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-phenyl-cyclobut-2-enone,

N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-phenyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-acetamide,

3-Hydroxy-4-methyl-2-[(3-methyl-1H-indol-2-yl)-phenyl-methyl]-4-p-tolyl-cyclobut-2-enone,

2-[(3,5-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone,

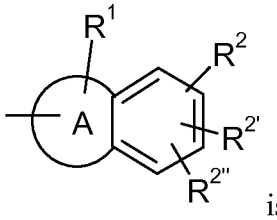
2-[(3,6-Dimethyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone,

2-[(5-Fluoro-3-methyl-1H-indol-2-yl)-phenyl-methyl]-3-hydroxy-4-methyl-4-p-tolyl-cyclobut-2-enone,

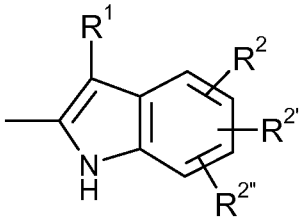
N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-acetamide or

N-{2-[(2-Hydroxy-3-methyl-4-oxo-3-p-tolyl-cyclobut-1-enyl)-phenyl-methyl]-6-methyl-1H-indol-3-ylmethyl}-N-methyl-formamide.

20. A process for the manifacture of the compounds of formula (I) according to claim 1,

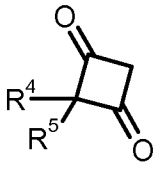


wherein is



(a)

, comprising a step of coupling compounds of formula (II),



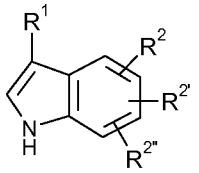
(II) ,

compounds of formula (III),



(III)

and compouds of formula (IV),



(IV) ,

wherein R^1, R^2, $R^{2'}$ and $R^{2''}$, R^3, R^4 and R^5 are as defined in claim 1.

21. Pharmaceutical compositions comprising a compound according to any one of claims 1 to 19 and a pharmaceutically acceptable excipient.

22. The compounds according to any one of claims 1 to 19 for use as therapeutic active substances.

23. The compounds according to any one of claims 1 to 19 for use as therapeutic active substances for the treatment and/or prophylaxis of atherotrombosis or asthma.

24. Use of compounds according to any of claims 1 to 19 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are associated with chymase.

25. The use according to claim 23, the disease is atherotrombosis or asthma.

26. The invention as hereinbefore defined, particularly with reference to the new compounds, intermediates, medicaments, uses and processes.

* * *