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(54) **2-MERCAPTO-4,5-DIARYLIMIDAZOLE DERIVATIVES AND THE USE THEREOF AS CYCLOOXYGENASE INHIBITORS**

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(57) **ABSTRACT**

The invention relates to the 2-mercapto-4,5-diarylimidazole derivatives of formula (I), wherein R^1, R^2, R^3 and R^4 are defined as in the description. The inventive compounds have an immunomodulatory and cyclooxygenase-inhibiting activity and are therefore suitable for the treatment of disease that are associated with a disturbed immune system.

2-MERCAPTO-4,5-DIARYLIMIDAZOLE DERIVATIVES AND THE USE THEREOF AS CYCLOOXYGENASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is a continuation application of U.S. patent application Ser. No. 10/672,613, filed Sep. 26, 2003, which is a continuation application of PCT/EP02/03264, filed Mar. 22, 2002, which are incorporated herein by reference in their entirety, and also claims the benefit of German Priority Application No. 101 14 775.9, filed Mar. 26, 2001.

FIELD OF THE INVENTION

[0002] The present invention relates to 2-mercapto-4,5-diarylimidazole derivatives having immunomodulating and cyclooxygenase-inhibiting action, pharmaceutical compositions which contain the compound, and their use in pharmacy.

BACKGROUND OF THE INVENTION

[0003] The action of conventional nonsteroidal antiinflammatories, such as acetylsalicylic acid, is essentially based on the inhibition of cyclooxygenase, an enzyme of the arachidonic acid cascade, which is also known as prostaglandin G/H synthase. Meanwhile, two different forms of cyclooxygenase have been found, which are designated as COX-1 and COX-2. Despite numerous investigations, the biochemical mode of action of the two enzymes is not yet completely elucidated. Various studies have shown, however, that they play an essential role in numerous diseases and inflammatory processes.

[0004] Pharmacologically active imidazole compounds which inhibit cyclooxygenase-1 and -2 are already known. In J. Med. Chem. 1996, 39, 3927-37, for example, imidazole derivatives having 5-lipoxygenase- and cyclooxygenase-inhibiting action are described, 2-(4-methylsulfinylphenyl)-4-(4-fluorophenyl-5-(pyrid-4-yl)imidazole also having a cytokine-inhibiting action.

[0005] WO 95/00501 describes further phenylheterocycles which have a cyclooxygenase-inhibiting action, among these also 4,5-diaryl-substituted imidazoles, for the treatment of diseases which are connected with cyclooxygenase.

[0006] Pharmaceutically active imidazole derivatives are further known which contain 4,5-di-(hetero)arylimidazole elements and are substituted in the 2-position. U.S. Pat. No. 4,585,771 discloses, for example, 4,5-diphenylimidazole derivatives which are substituted in the 2-position by a pyrrolyl, indolyl, imidazolyl or thiazolyl radical and have an antiinflammatory and antiallergic activity. U.S. Pat. Nos. 4,528,298 and 4,402,960 furthermore describe 4,5-di(hetero)arylimidazole derivatives, which are substituted in the 2-position with a phenyl, pyridyl, N-oxypyridyl, pyrimidyl, thiazolyl or thienyl radical, and have an antiinflammatory and antiallergic activity.

[0007] DE 198 42 833 relates to 4-heteroaryl-5-phenylimidazole derivatives which are substituted in the 2-position by a phenylalkylthio group. These compounds act as antiinflammatories and inhibitors of cytokine release. WO 99/03837, WO 93/14081 and DE 198 42 833 describe 2-substituted imidazoles which inhibit the synthesis of a number of inflammatory cytokines. These compounds alternatively have a further substituent on the nitrogen atom in the 1-position.

[0008] Further pharmacologically active imidazole derivatives are known from U.S. Pat. Nos. 4,461,770, 4,584,310, JP 0140467, DE 28 23 197, EP 372445, WO 91/10662, Acta Chim. 1969, 61, 69-77 and J. Prakt. Chem. 1972, 314, 785-792.

[0009] It is known that the conventional nonsteroidal antiinflammatories have a number of undesired side effects, in particular gastrointestinal side effects, nephrotoxicity and allergic reactions. It was further found that the known compounds are not stable and are difficult to process or have a low activity.

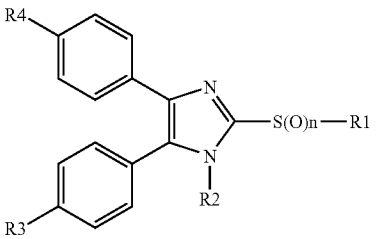
[0010] In spite of the numerous known compounds, there is therefore furthermore a need for compounds having antiinflammatory, antipyretic and analgesic action, which inhibit the release of various cytokines and serve as inhibitors of the mediators of the arachidonic acid cascade. In particular there is a need for compounds which act not only on the parameters which are decisive in acute diseases, but which also can intervene in the immunological processes crucial for the chronic course (cytokine release, expression of cell-surface antigens). In particular, owing to the importance of the COX enzymes for a number of further pathological processes, e.g.: colon carcinoma, overshooting angiogenesis, excitatory neuronal processes, wound healing etc, the development of COX inhibitors has a novel and additional importance.

SUMMARY OF THE INVENTION

[0011] The object of the invention is the provision of such compounds.

[0012] Surprisingly, it has now been found that certain 2-mercapto-4,5-diarylimidazole derivatives are stable compounds which are easy to process, and which have a high cyclooxygenase-inhibiting action with a variable COX-1/COX-2 selectivity.

[0013] The present invention therefore relates to the 2-mercapto-4,5-diarylimidazole derivatives of the formula:



in which

[0014] R^1 has the following meanings:

[0015] $CONR^5R^6$, in which R^5 and R^6 independently of one another are H or C_1-C_6-alkyl or, together with the nitrogen atom to which they are bonded, form a saturated heterocyclic radical having 5 or 6 ring atoms and

one or two heteroatoms which independently of one another are selected from N and O,

[0016] A-$CONR^5R^6$, in which A is C_1-C_6-alkylene which is optionally substituted by C_1-C_3-alkyl-CO, and R^5 and R^6 independently of one another are H, C_1-C_6-alkyl or phenyl which is optionally substituted by one or 2 halogen atoms,

[0017] C_1-C_6-alkylene-R^7, where R^7 is NR^5R^6, an aromatic heterocyclic radical having 5 or 6 ring atoms and one or two heteroatoms, which independently of one another are selected from N, S and O, where the heterocyclic radical can optionally be fused to a benzene ring, or is $COOR^8$, R^5 and R^6 independently of one another are H or C_1-C_6-alkyl and R^8 is H or C_1-C_6-alkyl,

[0018] C_1-C_6-alkylene-CO—R^9, where R^9 is phenyl which is optionally substituted by halogen,

[0019] C_1-C_6-alkylene-NR^{10}—CO—R^{11}, or

[0020] C_1-C_6-alkylene-NR^{10}—SO^2—R^{12};

[0021] R^{10} is H or C_1-C_6-alkyl;

[0022] R^{11} is

[0023] phenyl which is optionally substituted by 1, 2 or 3 substituents, which independently of one another are selected from halogen, CN, NO_2, CF_3, OC_1—C_6-alkyl and C_1-C_6-alkyl,

[0024] naphthyl,

[0025] C_1-C_6-alkyl which is optionally substituted by 1 or 2 phenyl groups,

[0026] C_2-C_6-alkenyl,

[0027] CH═CH-phenyl,

[0028] an aromatic, heterocyclic radical having 5 or 6 ring atoms and 1 or 2 heteroatoms, which independently of one another are selected from N, O and S, or

[0029] NR^5R^6, where R^5 and R^6 independently of one another are H or C_1-C_6-alkyl;

[0030] R^{12} is

[0031] phenyl which optionally has 1, 2 or 3 substituents which independently of one another are selected from halogen, NO_2, CF_3, OC_1—C_6-alkyl, C_1-C_6-alkyl, NH_2 and $NHCOC_1$—C_3-alkyl,

[0032] C_1-C_6-alkyl which is optionally substituted by one or two phenyl groups, or

[0033] naphthyl;

[0034] R^2 is H, C_1-C_6-alkyl or $(CH_2)_oCOOH$;

[0035] R^3 and R^4, which can be identical or different, are H, OH, OC_1—C_6-alkyl, halogen or C_1-C_6-alkyl which is substituted by 1, 2 or 3 halogen atoms;

[0036] n is 0, 1 or 2; and

[0037] o is0, 1,2,3, or4;

[0038] and the optical isomers and physiologically tolerable salts thereof

[0039] If the compounds according to the invention contain asymmetric centers, racemates and optical isomers (enantiomers, diastereomers) are included.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0040] The expression "alkyl" (also in combinations with other groups, such as aminoalkyl, alkylsulfonyl etc.) includes straight-chain and branched alkyl groups preferably having 1 to 6 and in particular 1 to 4 C atoms, such as methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, sec-butyl, n-pentyl and n-hexyl.

[0041] If alkyl is substituted by halogen, preferably 1, 2 or 3 halogen substituents are present. Preferred examples of halogen-substituted alkyl are chloromethyl, CHF_2 and in particular CF_3.

[0042] The expression "alkylene" preferably represents a straight-chain or branched alkylene group having 1 to 6, preferably 1 to 4, C atoms, such as methylene, ethylene, ethylidene, 1,2- or 1,3-propylene, 1,4-butylene or 1,6-hexylene.

[0043] The expression "alkenyl" represents a straight-chain or branched alkenyl group having 2 to 6 and in particular 2 to 4 C atoms, such as —CH═CH_2, —CH═$CHCH_3$ or —CH_2—CH═CH_2.

[0044] The expression "halogen" represents a fluorine, chlorine, bromine or iodine atom, in particular a fluorine or chlorine atom.

[0045] Nonaromatic heterocyclic radicals are preferably piperidinyl, pyranyl, morpholinyl or pyrrolidinyl.

[0046] Preferred aromatic heterocyclic radicals are pyridyl, in particular 2-, 3- or 4-pyridyl, furyl, in particular 2-furyl, thienyl, in particular 2-thienyl, pyrimidinyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl or thiazolyl. Furyl and thienyl are preferred.

[0047] If R^7 represents a radical fused to a benzene ring, it is preferably quinolyl, in particular 2-quinolyl, or benzimidazole, in particular 2-benzimidazole.

[0048] Compounds of the formula I are preferred where one of the radicals R^3 and R^4 is an OH group or C_1-C_6-alkoxy group, preferably a methoxy group. Additionally preferably, both radicals R^3 and R^4 are an OH group or C_1-C_6-alkoxy group, preferably a methoxy group. Particularly preferably, one or both radicals R^3 and R^4 are a C_1-C_6-alkoxy group, in particular OCH_3.

[0049] Compounds of the formula I are furthermore preferred where R^2 is hydrogen or methyl, preferably hydrogen.

[0050] Preferred embodiments are as follows:

[0051] a) R^1 is $CONR^5R^6$, where R^5 and R^6 independently of one another are H or C_1-C_6-alkyl or, together with the nitrogen atom to which they are bonded, are morpholino, piperidino or pyrrolidino;

[0052] R^2 is H or C_1-C_6-alkyl and

[0053] at least one of the radicals R^3 and R^4 is OC_1—C_6-alkyl;

[0054] b) R^1 is A-$CONR^5R^6$,

[0055] A is methylene, ethylene, ethylidene or —$CH(COCH_3)$—

[0056] R^2 is H or C_1-C_6-alkyl,

[0057] at least one of the radicals R^3 and R^4 is OC_1—C_6-alkyl and R^5 and R^6 independently of one another are H, C_1-C_6-alkyl, phenyl or halogen-substituted phenyl, in particular chlorine-substituted phenyl.

[0058] The substituent is particularly preferably situated in the H-position.

[0059] c) R^1 is C_1-C_6-alkylene-R^7,

[0060] R^7 is NR^5R^6,

[0061] R^5 and R^6 independently of one another are H or C_1-C_6-alkyl,

[0062] R^2 is H or C_1-C_6-alkyl and

[0063] at least one of the radicals R^3 and R^4 is OC_1—C_6-alkyl;

[0064] d) R^1 is C_1-C_6-alkylene-R^7,

[0065] R^7 is 2-pyridyl, 3-pyridyl, 4-pyridyl, quinolyl or benzymidazolyl,

[0066] R^2 is H or C_1-C_6-alkyl,

[0067] at least one of the radicals R^3 and R^4 is OC_1—C_6-alkyl and

[0068] C_1-C_6-alkylene is methylene.

[0069] e) R^1 is C_1-C_6-alkylene-R^7,

[0070] R^7 is an aromatic heterocyclic radical having 5 or 6 ring atoms and one or two heteroatoms which independently of one another are selected from N, S and O,

[0071] R^2 is $(CH_2)_oCOOH$,

[0072] o is 0, 1, 2, 3or4,

[0073] at least one of the radicals R^3 and R^4 is OC_1—C_6-alkyl.

[0074] The heterocyclic radical is preferably pyridyl.

[0075] f) R^1 is C_1-C_6-alkylene-CO—R^9,

[0076] R^9 is phenyl or phenyl which is substituted by halogen, in particular chlorine, where substitution in the 4-position is particularly preferred,

[0077] R^2 is H or C_1-C_6-alkyl, and

[0078] at least one of the radicals R^3 and R^4 is OC_1—C_6-alkyl.

[0079] g) R^1 is C_1-C_6-alkylene-NR^{10}—CO—R^{11},

[0080] R^2 is H or C_1-C_6-alkyl,

[0081] at least one of the radicals R^3 and R^4 is OC_1—C_6-alkyl,

[0082] R^{10} is H or C_1-C_6-alkyl,

[0083] R^{11} is phenyl which optionally has one or two substituents which independently of one another are selected from halogen, CN, NO_2 and CF_3, where the substituents are preferably situated in the 2- and/or 4-position.

[0084] C_1-C_6-alkylene is particularly preferably ethylene.

[0085] h) R^1 is C_1-C_6-alkylene-NR^{10}—CO—R^{11}, where R^2, R^3, R^4, R^{10} and C_1-C_6-alkylene have the meanings indicated above under g) and R^1 is C_1-C_6-alkyl, benzyl, phenylethyl, CH═CHPh or $CH(Ph)_2$.

[0086] i) R^1 is C_1-C_6-alkylene-NR^{10}—SO_2—R^{12}, where R^2, R^3, R^4, R_{10} and C_1-C_6-alkylene have the meanings indicated above under g) and R^{12} is furyl, thienyl or naphthyl.

[0087] j) R^1 is C_1-C_6-alkylene-NR^{10}—CO—R^{11}, where R^2, R^3, R^4, R^{10} and C_1-C_6-alkylene have the meanings indicated above under g) and R^{11} is phenyl, which optionally has one, two or three substituents which independently of one another are selected from halogen, NO_2, CF_3, C_1-C_6-alkyl and $NHCOC_1$—C_3-alkyl, or C_1-C_6-alkyl, benzyl or naphthyl.

[0088] k) R^1 is —CH_2—R^7,

[0089] R^7 is $COOR^8$,

[0090] R^8 is H or C_1-C_6-alkyl,

[0091] R^2 is H or C_1-C_6-alkyl and

[0092] at least one of the radicals R^3 and R^4 is OC_1—C_6-alkyl.

[0093] Particularly preferably, in the above embodiments a) to k) both radicals R^3 and R^4 are OC_1—C_6-alkyl.

[0094] The physiologically tolerable salts can in the present case be acid addition or base addition salts. For acid addition salts, inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid are employed or organic acids such as tartaric acid, citric acid, maleic acid, fumaric acid, malic acid, mandelic acid, ascorbic acid, gluconic acid and the like.

[0095] The compounds according to the invention are prepared in a 2-stage process. First, the synthesis of a 4,5-diaryl-1H-imidazole-2-thiol is carried out. This is then reacted in the second step such that the desired substituents are introduced. The substituents are preferably introduced into the positions 1 and 2 on the nitrogen or sulfur atom.

[0096] The preparation of the compounds according to the invention is illustrated by way of example of compounds in which R^3 and R^4 are both a methoxy group. Compounds having other radicals R^3 and R^4 can be prepared in a corresponding manner.

1) Preparation of the 4,5-diaryl-1H-imidazole-2-thiols

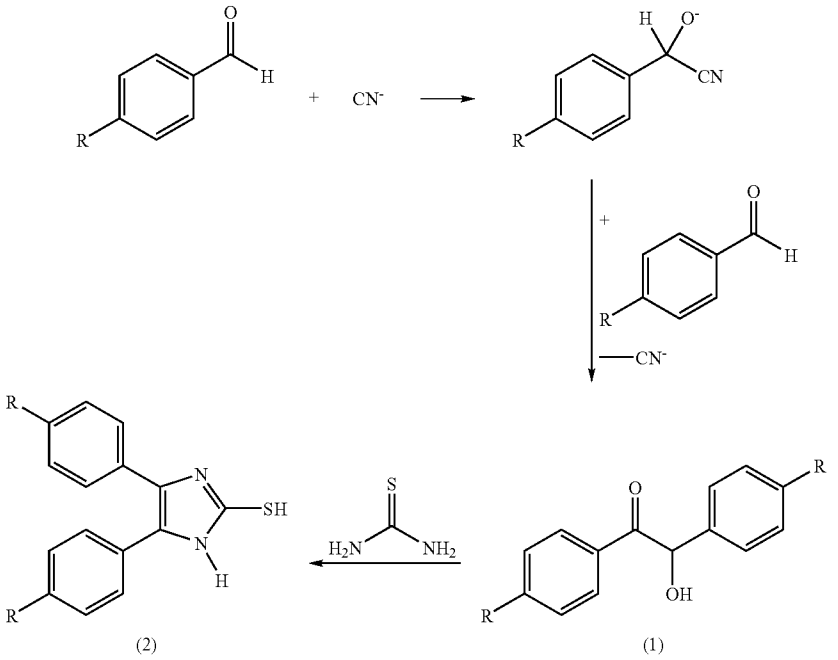
a) Symmetrically substituted 4,5-diaryl-1H-imidazole-2-thiols

[0097] By reacting the corresponding benzoins (compounds 1), which are obtainable by benzoin condensation, e.g., according to Houben-Weyl, Methoden der organischen Chemie (Methods of organic chemistry), volume 7/2a, Thieme-Verlag, Stuttgart, 1973, 653-671, with thiourea, symmetrically substituted 4,5-diaryl-1H-imidazole-2-thiols (compounds 2) are synthesized by the process from scheme I. The process is described in Liebigs Ann. Chem. 1895, 284, 24-29.

Scheme 1

Synthesis of Symmetrically Substituted 4,5-diaryl-1H-imidazole-2-thiols

[0098]



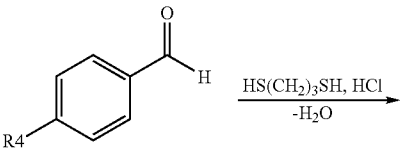
b) Unsymmetrically substituted 4,5-diaryl-1H-imidazole-2-thiols

[0099] Unsymmetrically substituted 4,5-diaryl-1H-imidazole-2-thiols are, however, preferably synthesized according to the process from scheme II. In this process, an aldehyde is reacted with 1,3-propanedithiol in the presence of an acid, the polarity of the electrophilic carbon of the carbonyl group being reversed by conversion to the cyclic dithioacetal. The methyl group between the two sulfur atoms can be deprotonated using a strong base such as n-butyllithium, which makes possible the addition of another aldehyde, see J. Org. Chem. 1966, 31, 4303-4304. The thioacetal function is then converted into the corresponding carbonyl compound by addition of a mercury salt, see Liebigs Ann. Chem. 1981, 10-19. The benzoins thus obtained are then reacted with thiourea according to the condensation already described, the unsymmetrically substituted 4,5-diaryl-1H-imidazole-2-thiols of the formula 2 in scheme 2 being formed.

Scheme 2

Synthesis of Unsymmetrically Substituted 4,5-diaryl-1H-imidazole-2-thiols

[0100]



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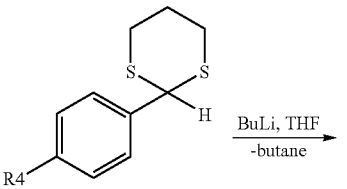

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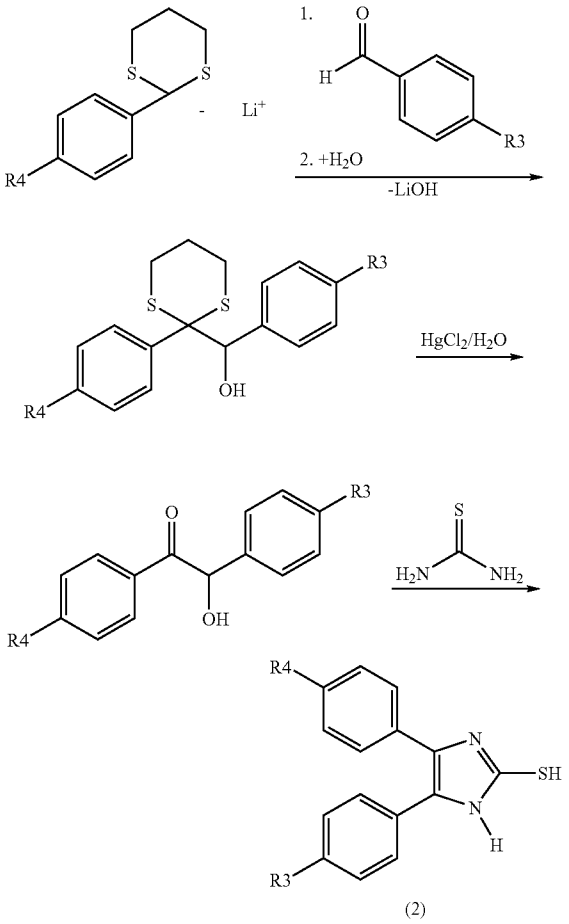


(2)

Introduction of the Desired Substituents

[0101] The substitutions of the 4,5-diaryl-1H-imidazole-2-thiols can be carried out by customary processes. These include reactions for the substitution of the sulfur in position 2 of the imidazole ring by nucleophilic substitution for the introduction of a group having an alkyl, amine, aryl ketone, acetic acid ethyl ester, carbonyl and substituted carbonyl function.

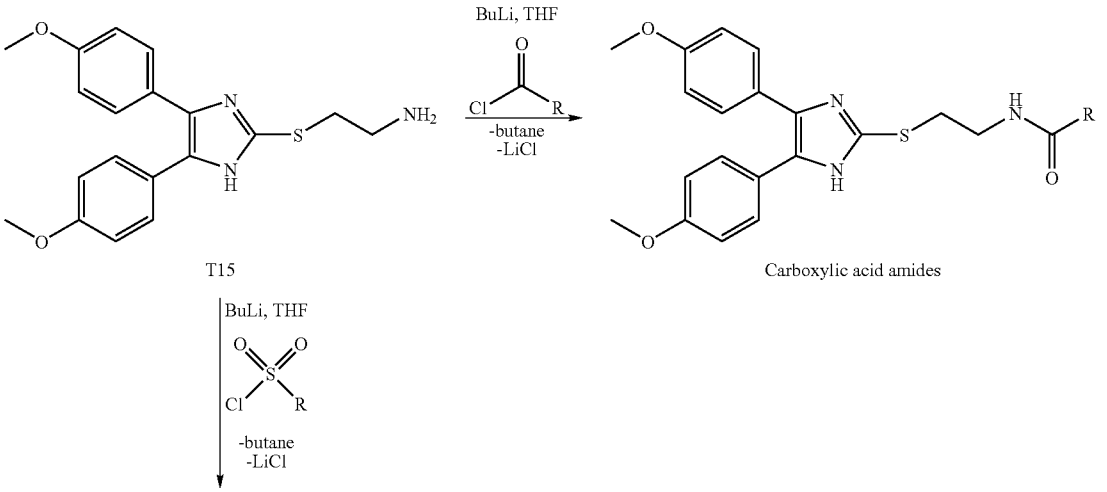
[0102] The nucleophilic substitution of the thiols is carried out by reaction with the side chain to be introduced, which has a suitable leaving group, eg. a halogen atom, in particular a bromine or iodine atom, the methanesulfonyl or toluenesulfonyl group. The reaction is customarily carried out in the presence of a base, such as sodium carbonate or potassium carbonate or the sodium or potassium salt of the thiol is employed, which is generated by reaction of the thiol with a base, such as a sodium or potassium alkoxide. The substitution is in general carried out in a polar organic solvent, such as methanol, ethanol, dimethylformamide etc, and at a temperature in the range from room temperature up to the boiling point of the reaction mixture.

[0103] The introduction of a side chain using a carboxylic acid amide or sulfonamide group is expediently carried out according to scheme 3 below:

Scheme 3

Synthesis of Compounds of the Formula I Having Carboxylic Acid Amide or Sulfonamide Side Chains

[0104]



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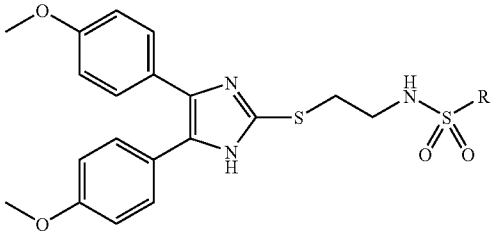


sulfonamides

R = alkyl, aryl

[0105] The compound T15 is prepared by nucleophilic substitution as described above. The reaction of T15 is then carried out in a polar, aprotic organic solvent, such as tetrahydrofuran (THF), dioxane etc. at a temperature in the range from −60° C. to approximately ambient temperature.

[0106] The preparation of the compounds of the formula I having a urea group in the side chain is carried out in a customary manner.

[0107] The oxidation of the sulfur in the 2-position of the imidazole to the corresponding sulfinyl or sulfonyl compound is carried out according to customary processes using a suitable oxidant, e.g., m-chloroperbenzoic acid, hydrogen peroxide, benzoyl peroxide etc.

[0108] The compounds according to the invention are potent selective inhibitors of cyclooxygenase. Cyclooxygenase is an enzyme of the arachidonic acid cascade, in which prostaglandins, for example the prostaglandins G_2 and H_2, and thromboxanes are formed from the C_{20}-carboxylic acid arachidonic acid.

[0109] The compounds according to the invention are suitable on account of their cyclooxygenase-inhibiting action as antiallergic, antipyretic and analgesic active compounds for the treatment of diseases which are connected with a disturbance of the immune system. They are suitable, for example, for the inhibition of prematurely commencing labor, for the treatment of cancer, for example colon carcinoma, and Alzheimer's disease. Further possibilities of use are offered in the treatment of autoimmune diseases, rheumatoid arthritis, gout, septic shock, osteoporosis, neuropathic pain, alopecia, psoriasis, acute pancreatitis, rejection reactions in allogenic transplants, allergically caused pneumonia, arteriosclerosis, multiple sclerosis, cachexia and inflammatory bowel disease (IBD), adenomatous polyposis (Gardner's syndrome), and colon carcinoma, for the inhibition of angiogenesis in connection with oncoses. Moreover, the compounds are utilizable for the topical treatment of inflammations of differing origin (contact eczema, erythema, such as UV erythema).

[0110] The compounds according to the invention can be administered either as individual active compounds or as mixtures with other therapeutic active compounds. The compounds can be administered systemically or as topical active compounds. The compounds can be administered on their own, but in general they are dosed and administered in the form of pharmaceutical compositions, i.e., as mixtures of the active compounds with suitable pharmaceutical carriers or diluents. For systemic action, the compounds or compositions can be administered orally or parenterally, preferably they are given in oral dosage forms.

[0111] The nature of the pharmaceutical composition or carrier or of the diluent depends on the desired administration form. Oral compositions can be present, for example, as tablets or capsules and can contain customary excipients such as binders (e.g., syrup, acacia, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone), fillers (e.g., lactose, sugar, cornstarch, calcium phosphate, sorbitol or glycine), lubricants (e.g., magnesium stearate, talc, polyethylene glycol or silicon dioxide), disintegrants (e.g., starch) or wetting agents (e.g., sodium laurylsulfate). Liquid oral preparations can be in the form of aqueous or oily suspensions, solutions, emulsions, syrups, elixirs or sprays and the like. They can also be present as a dry powder, which is prepared for reconstitution with water or another suitable carrier. Liquid preparations of this type can contain customary additives, for example suspending agents, flavorings, diluents or emulsifiers. For parenteral administration, solutions or suspensions with customary pharmaceutical carriers can be employed.

[0112] The compounds or compositions according to the invention can be administered to mammals (human or animal) in a dose of approximately 0.5 to 100 mg per kg of body weight per day. They can be given in an individual dose or in a number of doses. The spectrum of action of the compounds as inhibitors of cyclooxygenases (COX-1 and COX-2) was investigated with the aid of the test systems below.

[0113] The compounds according to the invention can also be present as pharmaceutical or cosmetic preparations for topical administration, for example in the form of emulsions, pastes, ointments, gels, creams, lotions, powders or sprays. In addition to the active compound(s), these preparations can contain customary vehicles. The preparations in the form of ointments, pastes, creams or gels can contain, for example, animal and/or vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures thereof. In addition to the active compounds, powders and sprays can contain, for example, lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide powder. Emulsions and lotions can contain customary solvents, diluents and emulsifiers.

In-Vitro Test Procedure for the Determination of COX-1 Inhibition

[0114] The inhibition of the cyclooxygenase pathway is carried out by fluorimetric quantification of malonaldehyde

(MA). This condenses in the acidic medium with twice the molar amount of thiobarbituric acid to give a red pigment dye, which has a fluorescence at $\lambda_{Excitation}$:533 nm, $\lambda_{Emission}$:550 nm.

[0115] A platelet suspension obtained from pig's blood is preincubated with the test substance for 10 min at 37° C. The concentration of the suspension should be 8×10^8 cells/ml. The arachidonic acid cascade is then activated by addition of the antibiotic calcium ionophore A23187 (5 mol/l). After a further 10 min at 37° C., the reaction is stopped using a trichloroacetic acid solution. The samples are centrifuged and the supernatant is incubated with thiobarbituric acid for 30 min at 70° C. After cooling (30 min at room temperature), the samples are measured fluorimetrically at 533/550 nm and the IC_{50} values of the test compounds are determined therefrom by means of a calibration curve.

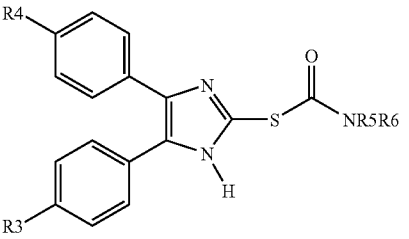
In-Vitro Test Procedure for the Determination of COX-2 Inhibition

[0116] The procedure is carried out on LPS-stimulated human monocytes which have been obtained by Ficoll extraction. The measurement variable used is the PGE_2 formed, which is determined by means of ELISA.

[0117] The results of the in-vitro test for COX-1 inhibition are shown in tables 1 to 17 below.

TABLE 1

Inhibitory activities of the carbamic acid thioesters of the formula:

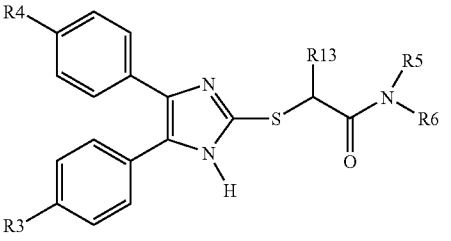


Example	Compound	NR^5R^6	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
42	T1	$N(CH_3)_2$	OCH_3	OCH_3	7.1×10^{-8}	7.15
43	T2	$N(C_2H_5)_2$	OCH_3	OCH_3	4.8×10^{-9}	8.32
44	T3	$N(I—C_3H_7)_2$	OCH_3	OCH_3	1.2×10^{-8}	7.92
45	T4	morpholino	OCH_3	OCH_3	2.8×10^{-8}	7.55
68	T103	$N(CH_3)_2$	Cl	H	7.3×10^{-6}	5.14
69	T104	$N(C_2H_5)_2$	Cl	H	4.2×10^{-6}	5.38
72	T108	$N(C_2H_5)_2$	Cl	OCH_3	1.6×10^{-7}	6.80

[0118]

TABLE 2

Inhibitory activities of the sulfanylacetamides of the formula:

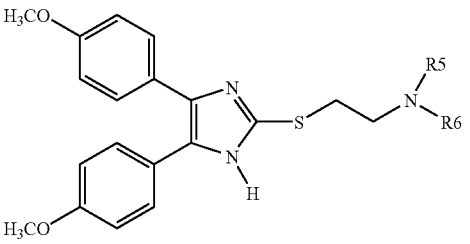


Example	Compound	R^6	R^5	R^3, R^4	R^{13}	MDA IC_{50} [M]	MDA pIC_{50} [M]
23	T5	H	H	OCH_3	H	4.5×10^{-7}	6.35
24	T6	CH_3	CH_3	OCH_3	H	1.0×10^{-8}	8.00
46	T7	CH_3	CH_3	OCH_3	$COCH_3$	3.3×10^{-8}	7.48
47	T9	C_6H_5	H	OCH_3	H	3.5×10^{-8}	7.46
48	T10	4-ClC_6H_4	H	OCH_3	H	2.1×10^{-7}	6.68

[0119]

TABLE 3

Inhibitory activities of the amines of the formula:

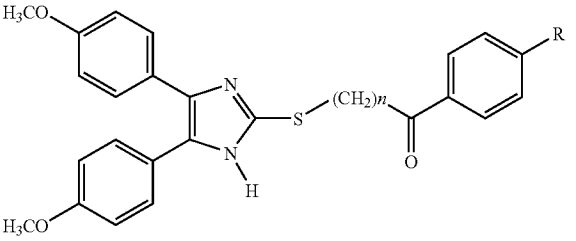


Example	Compound	R^5	R^6	MDA IC_{50} [M]	MDA pIC_{50} [M]
27	T14	CH_3	CH_3	3.2×10^{-6}	5.49
28	T15	H	H	7.8×10^{-8}	6.11

[0120]

TABLE 4

Inhibitory activities of the aryl ketones of the formula:

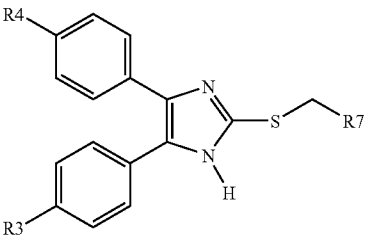


Example	Compound	R	n	MDA IC_{50} [M]	MDA pIC_{50} [M]
25	T11	H	1	9.5×10^{-9}	8.02
26	T12	Cl	1	4.6×10^{-8}	7.34
49	T13	H	2	2.1×10^{-8}	7.68

[0121]

TABLE 5

Inhibitory activities of the heteroarylmethyl sulfides of the formula:

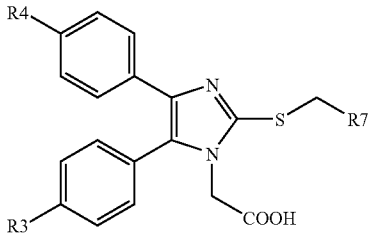


Example	Compound	R^7	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
30	T69	2-pyridyl	OCH_3	OCH_3	1.0×10^{-7}	7.00
31	T70	3-pyridyl	OCH_3	OCH_3	3.0×10^{-9}	8.52
32	T71	4-pyridyl	OCH_3	OCH_3	3.0×10^{-9}	8.52
33	T72	2-quinolyl	OCH_3	OCH_3	9.0×10^{-8}	7.05
34	T73	2-benzimidazolyl	OCH_3	OCH_3	3.9×10^{-7}	6.41
36	T83	2-pyridyl	Cl	Cl	3.3×10^{-7}	6.48
38	T91	2-pyridyl	H	H	7.0×10^{-7}	6.15

[0122]

TABLE 6

Inhibitory activities of the N^1-acetic acid derivatives of the formula:

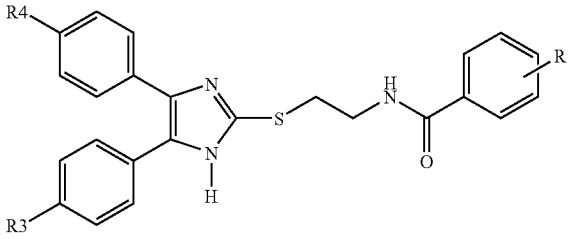


Example	Compound	R^7	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
130	T77	4-pyridyl	OCH_3	OCH_3	7.2×10^{-7}	6.14
133	T109	2-pyridyl	Cl	OCH_3	4.9×10^{-7}	6.31

[0123]

TABLE 7

Inhibitory activities of the arylamides of the formula:

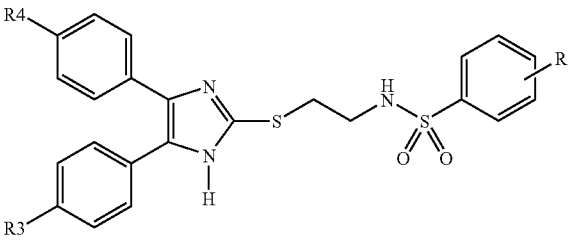


Example	Compound	R	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
29	T28	H	OCH_3	OCH_3	5.4×10^{-7}	6.27
86	T32	4-Cl	OCH_3	OCH_3	2.5×10^{-7}	6.60
87	T33	3-Cl	OCH_3	OCH_3	9.3×10^{-7}	6.03
88	T34	2-Cl	OCH_3	OCH_3	6.2×10^{-8}	7.21
89	T35	2,4-diCl	OCH_3	OCH_3	1.5×10^{-7}	6.82
90	T36	2,6-diCl	OCH_3	OCH_3	1.1×10^{-7}	6.96
91	T37	3,5-diCl	OCH_3	OCH_3	5.2×10^{-7}	6.28
92	T38	4-F	OCH_3	OCH_3	2.5×10^{-7}	6.60
93	T39	4-CN	OCH_3	OCH_3	1.4×10^{-7}	6.85
94	T40	4-NO_2	OCH_3	OCH_3	8.1×10^{-8}	7.09
95	T41	2-NO_2	OCH_3	OCH_3	1.7×10^{-7}	6.77
96	T42	4-CF_3	OCH_3	OCH_3	3.2×10^{-7}	6.49
97	T43	3-CF_3	OCH_3	OCH_3	1.0×10^{-7}	7.00
98	T44	3,5-diCF_3	OCH_3	OCH_3	5.2×10^{-7}	6.28
99	T45	4-OCH_3	OCH_3	OCH_3	1.0×10^{-6}	6.00
100	T46	3,4,5-triOCH_3	OCH_3	OCH_3	6.4×10^{-7}	6.22
101	T47	4-CH_3	OCH_3	OCH_3	1.4×10^{-7}	6.85
102	T48	4-tertC_4H_9	OCH_3	OCH_3	8.2×10^{-8}	7.09
56	T85	H	Cl	Cl	4.5×10^{-7}	6.35
61	T94	H	H	H	2.1×10^{-6}	5.68
64	T98	H	F	F	1.0×10^{-6}	6.00
70	T106	H	Cl	H	9.0×10^{-7}	6.05
73	T110	H	Cl	OCH_3	3.3×10^{-6}	5.48

[0124]

TABLE 8

Inhibitory activities of the arylsulfonamides of the formula:

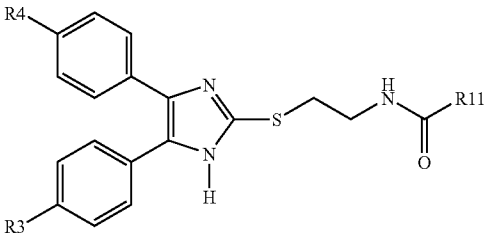


Example	Compound	R	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
76	T17	H	OCH_3	OCH_3	5.0×10^{-8}	7.30
50/77	T18	4-Cl	OCH_3	OCH_3	2.8×10^{-7}	6.55
78	T20	4-F	OCH_3	OCH_3	6.0×10^{-8}	7.22
79	T21	2-NO_2	OCH_3	OCH_3	1.1×10^{-7}	6.96
80	T22	3,5-diCF_3	OCH_3	OCH_3	4.1×10^{-7}	6.39
82	T24	4-CH_3	OCH_3	OCH_3	4.8×10^{-8}	7.32
83	T25	2,4,6-triCH_3	OCH_3	OCH_3	3.2×10^{-7}	6.49
84	T26	4-tertC_4H_9	OCH_3	OCH_3	4.9×10^{-7}	6.31
85	T27	4-$NHCOCH_3$	OCH_3	OCH_3	1.8×10^{-8}	7.74
74	T111	4-Cl	Cl	OCH_3	1.3×10^{-7}	6.89

[0125]

TABLE 9

Inhibitory activities of the alkylamides of the formula:

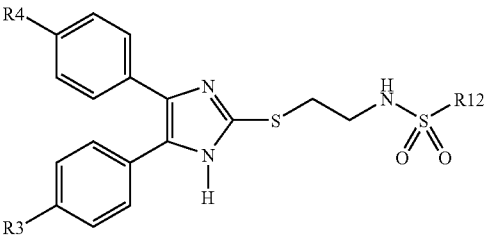


Example	Compound	R^{11}	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
52	T49	CH_3	OCH_3	OCH_3	1.0×10^{-8}	8.00
103	T50	CH_2CH_3	OCH_3	OCH_3	4.7×10^{-8}	7.33
104	T51	$CH(CH_3)_2$	OCH_3	OCH_3	8.8×10^{-9}	8.06
105	T52	$C(CH_3)_3$	OCH_3	OCH_3	4.2×10^{-7}	6.38
112	T59	CH_2Ph	OCH_3	OCH_3	5.4×10^{-8}	7.27
113	T60	$(CH_2)_2Ph$	OCH_3	OCH_3	1.5×10^{-7}	8.82
114	T61	CH=CHPh	OCH_3	OCH_3	1.8×10^{-7}	6.74
115	T62	$CH(Ph)_2$	OCH_3	OCH_3	1.3×10^{-7}	6.89
55	T84	CH_3	Cl	Cl	1.1×10^{-8}	5.96

[0126]

TABLE 10

Inhibitory activities of the alkylsulfonamides of the formula:

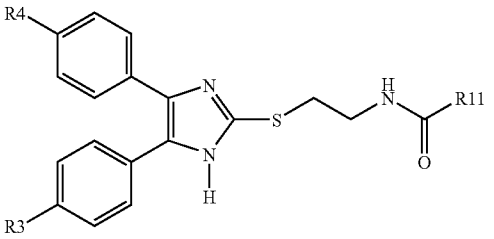


Example	Compound	R^{12}	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
116	T63	CH_3	OCH_3	OCH_3	7.6×10^{-8}	7.12
117	T64	CH_2CH_3	OCH_3	OCH_3	3.9×10^{-8}	7.41
118	T65	$CH(CH_3)_2$	OCH_3	OCH_3	1.0×10^{-8}	8.00
119	T66	CH_2Ph	OCH_3	OCH_3	1.0×10^{-7}	7.00

[0127]

TABLE 11

Inhibitory activities of the heteroaryl- and naphthylamides of the formula:

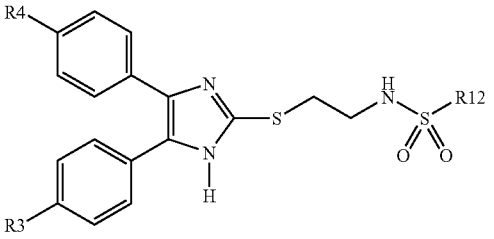


Example	Compound	R^{11}	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
106	T53	2-furyl	OCH_3	OCH_3	3.5×10^{-7}	6.46
107	T54	2-thienyl	OCH_3	OCH_3	1.0×10^{-7}	7.00
108	T55	1-naphthyl	OCH_3	OCH_3	5.6×10^{-7}	6.25
109	T56	2-naphthyl	OCH_3	OCH_3	4.0×10^{-8}	7.40

[0128]

TABLE 12

Inhibitory activities of the naphthylsulfonamides of the formula:

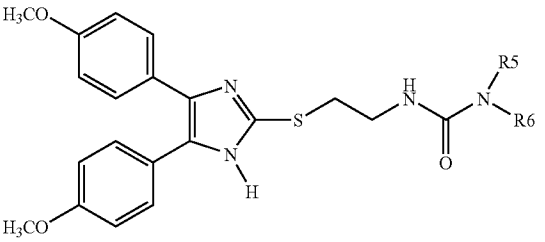


Example	Compound	R^{12}	R^4	R^3	MDA IC_{50} [M]	MDA pIC_{50} [M]
120	T67	1-naphthyl	OCH_3	OCH_3	3.8×10^{-7}	6.42
121	T68	2-naphthyl	OCH_3	OCH_3	1.3×10^{-7}	6.89

[0129]

TABLE 13

Inhibitory activities of the urea derivatives of the formula:

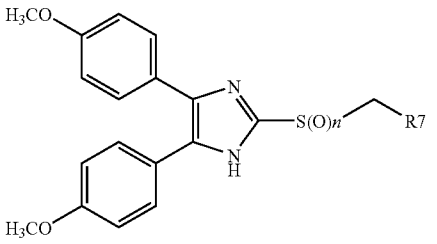


Example	Compound	R^5, R^6	MDA IC_{50} [M]	MDA pIC_{50} [M]
110	T57	CH_3	7.8×10^{-8}	7.11
111	T58	C_2H_3	5.0×10^{-8}	7.30

[0130]

TABLE 14

Inhibitory activities of the sulfones and their sulfide analogs of the formula:

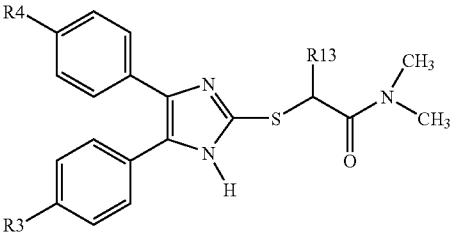


Example	Compound	R^7	n	MDA IC_{50} [M]	MDA pIC_{50} [M]
	T69	2-pyridyl	0	1.0×10^{-7}	7.00
134	T74	2-pyridyl	2	8.1×10^{-8}	7.09
30	T79	$COOC_2H_5$	0	1.2×10^{-8}	7.92
135	T80	$COOC_2H_5$	2	7.5×10^{-9}	8.12

[0131]

TABLE 15

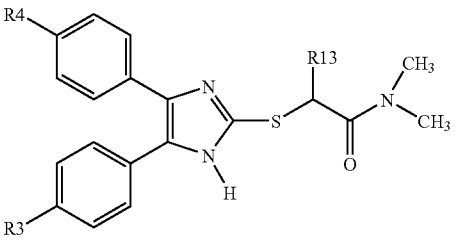
Inhibitory activities of the N,N-acetamides of the formula:



Example	Compound	R^{13}	R^3, R^4	MDA IC_{50} [M]	MDA pIC_{50} [M]
24	T6	H	OCH_3	1.0×10^{-8}	8.00
135	T8	CH_3	OCH_3	4.2×10^{-7}	6.38

TABLE 15-continued

Inhibitory activities of the N,N-acetamides of the formula:

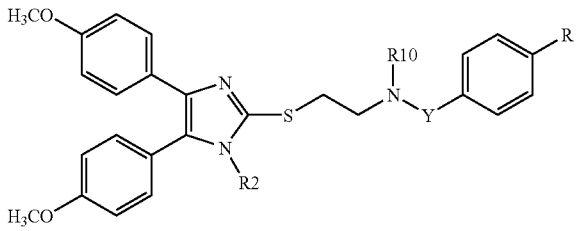


Example	Compound	R^{13}	R^3, R^4	MDA IC_{50} [M]	MDA pIC_{50} [M]
37	T87	H	Cl	1.5×10^{-6}	5.82
139	T88	CH_3	Cl	5.2×10^{-7}	5.28

[0132]

TABLE 16

Inhibitory activities of the dimethyl compounds of the formula:

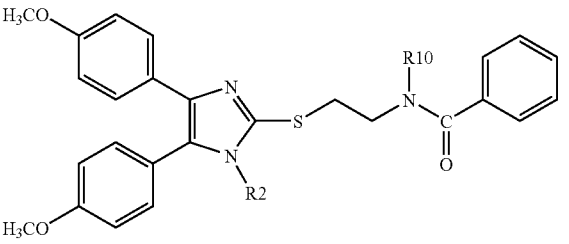


Example	Compound	R^2, R^{10}	R	Y	MDA IC_{50} [M]	MDA pIC_{50} [M]
138	T31	CH_3	H	C=O	8.4×10^{-7}	7.08
137	T19	CH_3	Cl	SO_2	6.9×10^{-7}	7.16

[0133]

TABLE 17

Inhibitory activities of the methyl derivatives of the formula:



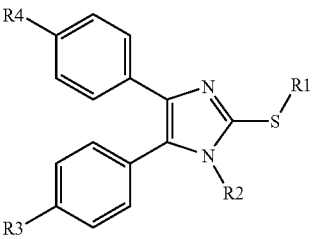
Example	Compound	R^{10}	R^2	MDA IC_{50} [M]	MDA pIC_{50} [M]
140	T29	CH_3	H	2.1×10^{-8}	7.68
51	T30	H	CH_3	4.2×10^{-8}	7.38

[0134] Particularly suitable compounds according to the invention are the compounds T2, T11, T51, T70, T71 and T80 having IC_{50} values in the molar region of 10^{-9}. These compounds show a particularly high activity for the inhibition of cyclooxygenase-1.

[0135] The results of the in-vitro tests for COX-2 inhibition are shown in table 18 below.

TABLE 18

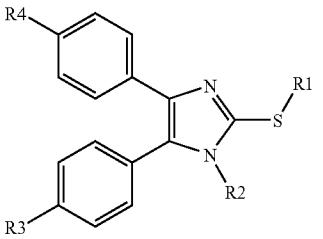
COX-2 inhibition by compounds of the formula:



Example	No.	R^4	R^3	R^1	R^2	IC_{50} [M]	pIC_{50} [M]
43	T2	OCH_3	OCH_3	$CON(C_2H_5)_2$	H	2.4×10^{-6}	5.62
24	T6	OCH_3	OCH_3	$CH_2CON(CH_3)_2$	H	2.3×10^{-6}	5.64
46	T7	OCH_3	OCH_3	$CH(COCH_3)CON(CH_3)_2$	H	5.0×10^{-7}	6.30
25	T11	OCH_3	OCH_3	CH_2COPh	H	2.6×10^{-7}	6.59
50/77	T18	OCH_3	OCH_3	$CH_2CH_2NHSO_2Ph$-4Cl	H	3.0×10^{-6}	5.52

TABLE 18-continued

COX-2 inhibition by compounds of the formula:



Example	No.	R^4	R^3	R^1	R^2	IC_{50} [M]	pIC_{50} [M]
80	T22	OCH_3	OCH_3	$CH_2CH_2NHSO_2Ph$-3,5-diCF_3	H	1.5×10^{-6}	5.82
85	T27	OCH_3	OCH_3	$CH_2CH_2NHSO_2Ph$-4$NHCOCH_3$	H	1.2×10^{-6}	5.92
140	T29	OCH_3	OCH_3	$CH_2CH_2N(CH_3)COPh$	H	1.0×10^{-8}	8.00
138	T31	OCH_3	OCH_3	$CH_2CH_2N(CH_3)COPh$	CH_3	9.1×10^{-7}	6.04
52	T49	OCH_3	OCH_3	$CH_2CH_2NHCOCH_3$	H	2.7×10^{-6}	5.57
110	T57	OCH_3	OCH_3	$CH_2CH_2NHCON(CH_3)_2$	H	2.1×10^{-7}	6.68
30	T69	OCH_3	OCH_3	2-pyridylmethyl	H	2.4×10^{-7}	6.62
55	T84	Cl	Cl	$CH_2CH_2NHCOCH_3$	H	2.7×10^{-6}	5.57
72	T108	Cl	OCH_3	$CON(C_2H_5)_2$	H	1.0×10^{-6}	6.00
133	T109	Cl	OCH_3	2-pyridylmethyl	CH_2COOH	1.0×10^{-6}	6.00
74	T111	Cl	OCH_3	$CH_2CH_2NHSO_2Ph$-4Cl	H	8.0×10^{-7}	6.10

[0136] It has been found that the compound T29 according to the invention inhibits both isoenzymes, COX-1 and COX-2, with approximately equally high potency. A medium-strong inhibition for both enzymes was observed with the compound T 109.

[0137] The compounds according to the invention and the processes for their preparation are now described in greater detail by examples below, which do not restrict the invention in any manner.

EXAMPLES

[0138] In the examples, the syntheses of the intermediate compounds Z1 to Z22 named by Z, from which the compounds T1 to T111 according to the invention were obtained, are described first.

[0139] a) Synthesis of Symmetrical Benzoins

Example 1

Synthesis of 1,2-bis(4-chlorophenyl)-2-hydroxy-ethanone (4,4'-dichloro-benzoin) (Z1)

[0140] 42.2 g of 4-chlorobenzaldehyde and 5 g of KCN were heated under reflux in 300 ml of a 1:1 mixture of ethanol and water for 6 hours. After cooling, the ethanol was stripped off, the residue was cooled in an ice bath and the supernatant aqueous phase was decanted off. The product was recrystallized from ethanol/petroleum ether and dried. 22 g of the compound Z1 mentioned in the title were obtained.

Example 2

Synthesis of 1,2-bis(4-fluorophenyl)-2-hydroxyethanone (4,4'-dichloro-benzoin) (Z2)

[0141] 50 g of 4-fluorobenzaldehyde were reacted by the same process as in example 1. 29 g were obtained.

Example 3

Synthesis of 1,2-bis[4-(trifluoromethyl)phenyl]-2-hydroxyethanone (4,4'-trifluoromethylbenzoin) (Z3)

[0142] 50 g of 4-fluorobenzaldehyde were reacted by the same process as in example 1. The yield was 28 g.

[0143] b) Synthesis of Unsymmetrical Benzoins

Example 4

Synthesis of 2-phenyl-1,3-dithiane (Z4)

[0144] 26.5 g (0.25 mol) of benzaldehyde and 27.1 g (0.25 mol) of propanedithiol were dissolved in chloroform and cooled in an ice bath. HCl gas was then passed in for approximately 5 min until saturation and the solution was allowed to stand at RT (room temperature). The reaction mixture was washed twice with 100 ml of water, three times with 100 ml of 10% strength KOH solution and twice again with 100 ml of water. The organic phases were dried using Na_2SO_4, evaporated in a rotary evaporator and recrystallized from methanol. The yield was 34.9 g.

Example 5

Synthesis of 2-(4-chlorophenyl)-1,3-dithiane (Z5)

[0145] 34 g (0.24 mol) of 4-chlorobenzaldehyde were reacted with the same molar amount of propanedithiol by the process as described in example 4. The yield was 48.64 g.

Example 6

Synthesis of 2-chlorophenyl-(2-phenyl-1,3-dithian-2-yl)methanol (Z6)

[0146] 33.0 g (0.169 mol) of the compound Z4 from example 4 were dissolved in dry THF and cooled to −60° C.

112 ml (0.178 mol) of n-butyllithium (BuLi) were then added under nitrogen and the reaction mixture was stirred in the cold for 15-30 min. 24.0 g (0.169 mol) of 4-chlorobenzaldehyde were added and the mixture was stirred at RT for 1 hour. The THF (tetrahydrofuran) was then stripped off, the residue was treated with water and the mixture was extracted four times with CH_2Cl_2. The organic phase was washed twice each with water, 7% strength KOH and again with water, dried using Na_2SO_4 and evaporated in a rotary evaporator. The yield was 48.5 g.

Example 7

Synthesis of 2-(4-chlorophenyl)-1,3-dithian-2-yl-4-methoxyphenyl-methanol (Z7)

[0147] 47 g (0.204 mol) of the compound Z 5 from example 5 and the same molar amount of 4-methoxybenzaldehyde were reacted together with 112 ml (0.178 mol) of BuLi as in example 6. The yield of the compound named in the title was 64.2 g.

Example 8

Synthesis of 2-(4-chlorophenyl)-2-hydroxy-1-phenylethan-1-one (Z8)

[0148] 46.6 g (0.138 mol) of the compound Z6 was heated under reflux for 5 hours with 80.0 g (0.295 mol) of $HgCl_2$ and 40.0 g (0.185 mol) of HgO in 600 ml of 90% strength methanol. The solids were filtered off and washed with CH_2Cl_2 and diethyl ether. The filtrate was evaporated, the residue was treated with water and the mixture was extracted four times with diethyl ether. The combined organic phases were washed successively with water, 5% strength NH_4Cl solution and again with water, dried over Na_2SO_4, evaporated in a rotary evaporator and recrystallized from petroleum ether. The yield was 24.8 g.

Example 9

Synthesis of 2-(4-chlorophenyl)-2-hydroxy-(4-methoxyphenyl)ethan-1-one (Z9)

[0149] 64.2 g (0.175 mol) of the compound Z7 were reacted as in example 8. The yield was 35.89 g.

[0150] c) Synthesis of the 4,5-diaryl-1H-imidazole-2-thiols

Example 10

Synthesis of 4,5-diphenyl-1H-imidazole-2-thiol (Z10)

[0151] 21.2 g (0.10 mol) of benzoin were dissolved in DMF (dimethylformamide) with 10.8 g (0.15 mol) of thiourea with warming and the mixture was heated under reflux for 15 hours. After cooling, the DMF was stripped off and the residue was treated with ethanol. The precipitate resulting in the course of this was filtered off with suction, washed with cold ethanol, dried and reused without further purification. The yield was 18.4 g.

Example 11

Synthesis of 4,5-bis(4-methoxyphenyl)-1H-imidazole-2-thiol (Z11)

[0152] 27.23 g (0.1 mol) of p-anisoin and 10.8 g (0.15 mol) of thiourea were reacted as in example 10. The yield was 20 g.

Example 12

Synthesis of 4,5-bis(4-chlorophenyl)-1H-imidazole-2-thiol (Z12)

[0153] 22 g (78.5 mol) of the compound Z1 from example 1 and 12 g (157 mol) of thiourea were reacted as in example 10. The yield was 15.7 g.

Example 13

Synthesis of 4,5-bis(4-fluorophenyl)-1H-imidazole-2-thiol (Z13)

[0154] 29 g (0.12 mol) of the compound Z2 from example 2 and 18 g (0.24 mol) of thiourea were reacted as in example 10. The yield was 17.9 g.

Example 14

Synthesis of 4,5-bis[4-(trifluoromethyl)phenyl)-1H-imidazole-2-thiol (Z14)

[0155] 28 g (0.08 mol) of the compound Z3 from example 3 and 12 g (0.16 mol) of thiourea were reacted as in example 10. The yield was 7.4 g.

Example 15

Synthesis of 4,5-bis(4-methoxyphenyl)-1-methyl-1H-imidazole-2-thiol (Z15)

[0156] 13.6 g (50 mmol) of p-anisoin and 6.8 g (75 mmol) of N-methylthiourea were reacted as in example 10. The yield was 7.4 g.

Example 16

Synthesis of 4-(4-chlorophenyl)-5-phenyl-1H-imidazole-2-thiol (Z16)

[0157] 24.8 g (0.10 mol) of the compound Z8 from example 8 and 10.8 g (0.15 mol) of thiourea were reacted as in example 10. The yield was 11.3 g.

Example 17

Synthesis of 4-(4-chlorophenyl)-5-(4-methoxyphenyl)-1H-imidazole-2-thiol (Z17)

[0158] 35.9 g (0.13 mol) of the compound Z9 from example 9 and 15.2 g (0.20 mol) of thiourea were reacted as in example 10. The yield was 17 g.

[0159] d) Synthesis of N^1-(4-chlorophenyl)-2-chloroacetamide

Example 18

Synthesis of N^1-(4-chlorophenyl)-2-chloroacetamide (Z18)

[0160] 3.4 g (30 mol) of 2-chloroacetyl chloride were dissolved in anhydrous dioxane and a solution containing 3.8 g (30 mol) of 4-chloroaniline was added dropwise. After an hour, the batch was poured into ice water, acidified using dilute hydrochloric acid, the supernatant was removed by

suction and the residue was washed with water until neutral. The reaction product was recrystallized from ethanol. The yield was 3.2 g.

[0161] e) Synthesis of N^1-(2-halophenyl)-4-chlorobenzenesulphonamides

Example 19

Synthesis of N^1-(2-chloroethyl)-4-chlorobenzenesulfonamide (Z19)

[0162] 11.6 g (100 mmol) of 2-chloroethylamine HCl were suspended in dichloromethane. 13.8 g (175 mmol) of pyridine were added, the mixture was stirred for 10 minutes and then 15.8 g (75 mmol) of 4-chlorobenzenesulfonyl chloride, dissolved in dichloro-methane, were added dropwise. The reaction mixture was heated under reflux for 8-10 hours, then treated with water and adjusted to a pH of 1-2 using HCl. The organic phase was washed three times with 3% strength HCl and the aqueous phase was extracted by shaking 3-4 times with dichloromethane. The combined organic phases were dried using Na_2SO_4, evaporated in the and recrystallized from ethanol. The yield was 11 g.

Example 20

Synthesis of N^1-(2-bromoethyl)-4-chlorobenzenesulfonamide (Z20)

[0163] 15.4 g (75 mmol) of 2-bromoethylamine HBr, 11.8 g (150 mmol) of pyridine and 10.6 g (50 mmol) of 4-chlorobenzenesulfonyl chloride were reacted as in example 19. The yield was 6.5 g.

[0164] f) Compounds which were obtained by nucleophilic substitution of the 4,5-diaryl-1H-imidazole-2-thiols in the 2-position with the aid of a sodium methoxide solution

Example 21

Synthesis of 2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]-propanamine (Z21)

[0165] Dry methanol was slowly added dropwise to 1.0 g (42 mmol) of initially introduced Na^0 such that the solution boiled moderately. 5.0 g (16 mmol) of the compound Z11 from example 11 were added and the reaction mixture was stirred at RT for 10 min. 3.5 g (16 mmol) of 3-bromopropylamine HBr, dissolved in methanol, were then added and the mixture was heated under reflux for 2 h. After cooling, the product was worked up by stripping of the methanol, treating the residue with dichloromethane and washing it with 1 N NaOH and water. The organic phase was dried over Na_2SO_4 and evaporated. The yield was 3.5 g.

Example 22

Synthesis of 2-[4-(4-chlorophenyl)-5-(4-methoxyphenyl)-1H-imidazol-2-ylsulfanylmethyl]pyridine (Z22)

[0166] 387 mg (16.8 mmol) of Na^0, 2.5 g (7.89 mmol) of the compound Z17 from example 17 and 1.3 g (7.89 mmol) of 2-chloromethylpyridine HCl were reacted as in example 21. Working-up was carried out by means of column chromatography on silica gel, eluting with ethyl acetate. The yield was 1.77 g.

Example 23

Synthesis of 2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]-acetamide (T5)

[0167] 213 mg (10 mmol) of Na^0, 2.5 g (8 mmol) of the compound Z11 from example 11 and 748 g (8 mmol) of 2-chloroacetamide were reacted as in example 21. Working-up was carried out by means of column chromatography on silica gel, eluting with ethyl acetate. 0.8 g of the compound named in the title was obtained.

[0168] IR (KBr): $1/\lambda$ (cm^{-1})=1670, 1610, 1500, 1440, 1240

[0169] In an analogous manner to that described in example 23, the compounds below were prepared from the starting materials mentioned:

Example 24

N^1N^1-Dimethyl-2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]-acetamide (T6)

[0170] Starting substances: 3.0 g (9.6 mmol) of Z11; 1.2 g (9.6 mmol) of 2-chloro-N,N-di-methylacetamide; 230 mg (10 mmol) of Na^0

[0171] Yield: 1.8 g

[0172] IR (KBr): $1/\lambda$ (cm^{-1})=2820, 1620, 1500, 1455, 1240, 830

Example 25

2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]-1-phenylethan-1-one (T11)

[0173] Starting substances: 2.5 g (8 mmol) of Z11; 748 mg (8 mmol) of ω-bromo-acetophenone; 230 mg (10 mmol) of Na^0

[0174] Eluent: ethyl acetate/dichloromethane 1:3

[0175] Yield: 0.9 g

[0176] IR (KBr): $1/\lambda$ (cm^{-1})=1680, 1610, 1590, 1500, 1445, 1245, 830, 750, 690

Example 26

2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]-1-(4-chloro-phenyl)ethan-1-one (T12)

[0177] Starting substances: 3.0 g (9.6 mmol) of Z11; 2.2 g (9.6 mmol) of ω-bromo-4-chloro-acetophenone; 0.3 g (13 mmol) of Na^0

[0178] Eluent: ethyl acetate/dichloromethane 1:3

[0179] Yield: 2.3 g

[0180] IR (KBr): $1/\lambda$ (cm^{-1})=1680, 1610, 1585, 1500, 1460, 1245, 835

Example 27

N,N-Dimethyl-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]-ethanamine (T14)

[0181] Starting substances: 5.0 g (16 mmol) of Z11; 2.3 g (16 mmol) of N,N-dimethyl-2-chloroethanamine HCl; 0.8 g (35 mmol) of Na^0

[0182] Work-up: the precipitate was filtered off with suction and discarded. The filtrate was evaporated and purified on a silica gel column, eluting with NH_3/methanol/acetone/toluene.

[0183] Yield: 1.8 g

[0184] IR (KBr): 1/λ (cm^{-1})=2820, 1610, 1570, 1500, 1465, 1240, 830

Example 28

2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethanamine (T15)

[0185] Starting substances: 10.0 g (32 mmol) of Z11; 7.71 g (32 mmol) of 2-chloroethylamine HCl; 1.91 g (83 mmol) of Na^0

[0186] Work-up: the precipitate was filtered off with suction and discarded. The filtrate was evaporated, the residue was treated with 10% strength HCl and washed a number of times with dichloromethane. The aqueous phase was rendered alkaline using 10% strength KOH and extracted by shaking a number of times with diethyl ether and dichloromethane. The combined organic phases were dried using Na_2SO_4 and evaporated. The product was crystallized from diethyl ether.

[0187] Yield: 5.9 g

[0188] IR (KBr): 1/λ (cm^{-1})=1610, 1570, 1500, 1455, 1240, 830

Example 29

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}benzamide (T28)

[0189] Starting substances: 3.0 g (9.6 mmol) of Z11; 1.8 g (9.6 mmol) of N-(2-chloroethyl)-benzamide; 230 mg (10 mmol) of Na^0

[0190] Eluent: ethyl acetate/dichloromethane 5:1

[0191] Yield: 0.44 g

[0192] IR (KBr): 1/λ (cm^{-1})=1635, 1610, 1500, 1460, 1240, 830, 710, 690

Example 30

2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanylmethyl]pyridine (T69)

[0193] Starting substances: 2.9 g (9.1 mmol) of Z11; 1.5 g (9.1 mmol) of 2-chloromethylpyridine HCl; 460 mg (20 mmol) of Na^0

[0194] Work-up: the precipitate was filtered off with suction, washed using methanol and discarded. The filtrate was evaporated and the residue was purified on a silica gel column, eluting with ethyl acetate.

[0195] Yield: 2.2 g

[0196] IR (KBr): 1/λ (cm^{-1})=1610, 1590, 1500, 1440, 1250, 840, 800, 750

Example 31

3-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanylmethyl]pyridine (T70)

[0197] Starting substances: 2.9 g (9.1 mmol) of Z11; 1.5 g (9.1 mmol) of 2-chloromethylpyridine HCl; 460 mg (20 mmol) of Na^0

[0198] Work-up: the precipitate was filtered off with suction, washed using methanol and discarded. The filtrate was evaporated and the residue was purified on a silica gel column, eluting with ethyl acetate.

[0199] Yield: 1.95 g

[0200] IR (KBr): 1/λ (cm^{-1})=1610, 1575, 1500, 1460, 1250, 830, 800, 710

Example 32

4-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanylmethyl]pyridine (T71)

[0201] Starting substances: 2.9 g (9.1 mmol) of Z11; 1.5 g (9.1 mmol) of 2-chloromethylpyridine HCl; 460 mg (20 mmol) of Na^0

[0202] Work-up: the precipitate was filtered off with suction, washed using methanol and discarded. The filtrate was evaporated and the residue was purified on a silica gel column, eluting with ethyl acetate.

[0203] Yield: 2.06 g

[0204] IR (KBr): 1/λ (cm^{-1})=1610, 1555, 1490, 1440, 1210, 840, 760, 670

Example 33

2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanylmethyl]quinoline (T72)

[0205] Starting substances: 1.5 g (4.8 mmol) of Z11; 1.0 g (4.8 mmol) of 2-chloromethyl-quinoline HCl; 176 mg (12 mmol) of Na^0

[0206] Work-up: the methanol was stripped off, the residue was washed using water and the product was recrystallized from ethyl acetate.

[0207] Yield: 1 g

[0208] IR (KBr): 1/λ (cm^{-1})=1610, 1590, 1500, 1440, 1240, 830, 800, 775

Example 34

2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanylmethyl]-1H-indole (T73)

[0209] Starting substances: 1.5 g (4.8 mmol) of Z11; 0.8 g (4.8 mmol) of 2-chloromethylindole HCl; 176 mg (12 mmol) of Na^0

[0210] Work-up: the precipitate was filtered off with suction, washed using methanol and discarded. The filtrate was evaporated, treated with water and extracted by shaking with CH_2Cl_2 and ethyl acetate. The organic phase was dried over Na_2SO_4, evaporated and the residue was crystallized from CH_2Cl_2.

[0211] Yield: 166 mg

[0212] IR (KBr): 1/λ (cm^{-1})=1615, 1525, 1505, 1250, 840

Example 35

Ethyl 2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]acetate (T79)

[0213] Starting substances: 2.5 g (8.1 mmol) of Z11; 1.4 G. (8.1 mmol) of ethyl bromoacetate; 230 mg (10 mmol) of Na^0

[0214] Eluent: ethyl acetate/dichloromethane 1:3

[0215] Yield: 2.2 g

[0216] IR (KBr): 1/λ (cm^{-1})=2950, 1740, 1610, 1570, 1500, 1460, 1250, 830

Example 36

2-[4,5-Bis(4-chlorophenyl)-1H-imidazol-2-ylsulfanylmethyl]pyridine (T83)

[0217] Starting substances: 3.0 g (9.3 mmol) of Z12; 11.5 g (9.3 mmol) of 2-chloromethylpyridine HCl; 460 mg (20 mmol) of Na

[0218] Eluent: ethyl acetate

[0219] Yield: 1.8 g

[0220] IR (KBr): 1/λ (cm^{-1})=1590, 1500, 1435, 820, 775, 745

Example 37

N^1N^1-Dimethyl-2-[4,5-bis(4-chlorophenyl)-1H-imidazol-2-ylsulfanyl]-acetamide (T87)

[0221] Starting substances: 2.5 g (7.8 mmol) of Z12; 1.0 g (7.8 mmol) of 2-chloro-N,N-di-methylacetamide; 230 mg (10 mmol) of Na^0

[0222] Work-up : recrystallization from methanol

[0223] Yield: 1.7 g

[0224] IR (KBr): 1/λ (cm^{-1})=1630, 1500, 1480, 825

Example 38

2-[4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl] pyridine (T91)

[0225] Starting substances: 3.0 g (12 mmol) of Z10; 2.0 g (12 mmol) of 2-chloromethylpyridine HCl; 598 mg (26 mmol) of Na^0

[0226] Eluent: ethyl acetate/dichloromethane 1:3

[0227] Yield: 2.4 g

[0228] IR (KBr): 1/λ (cm^{-1})=3060, 2940, 1600, 1590, 1490, 1435, 765, 700, 750, 670

Example 39

2-[4,5 -Bis(4-fluorophenyl)-1H-imidazol-2-ylsulfanylmethyl]pyridine (T97)

[0229] Starting substances: 5.0 g (17.3 mmol) of Z13; 2.8 g (17.3 mmol) of 2-chloromethylpyridine HCl; 830 mg (36 mmol) of Na

[0230] Eluent: ethyl acetate

[0231] Yield: 4.1 g

[0232] IR (KBr): 1/λ (cm^{-1})=1580, 1495, 1430, 830, 780, 740

Example 40

2-[4,5-Bis(4-trifluoromethylphenyl)-1H-imidazol-2-ylsulfanylmethyl]-pyridine (T100)

[0233] Starting substances: 2.9 g (7.7 mmol) of Z14; 1.5 g (7.7 mmol) of 2-chloromethylpyridine HCl; 414 mg (18 mmol) of Na

[0234] Eluent: ethyl acetate

[0235] Yield: 1.82 g

[0236] IR (KBr): 1/λ (cm^{-1})=3060, 2940, 1620, 1590, 1510, 1440, 1240, 850, 750, 690

Example 41

2-[4-(4-Chlorophenyl)-5-phenyl-1H-imidazol-2-ylsulfanylmethyl]pyridine (T105)

[0237] Starting substances: 2.0 g (6.97 mmol) of Z16; 1.2 g (6.97 mmol) of 2-chloromethylpyridine HCl; 350 mg (15.2 mmol) of Na

[0238] Eluent: ethyl acetate

[0239] Yield: 734 mg

[0240] IR (KBr): 1/λ (cm^{-1})=1590, 1500, 1430, 830, 770, 700, 740

[0241] g) Compounds which were obtained by nucleophilic substitution of the 4,5-diaryl-1H-imidazole-2-thiols in the 2-position with the aid of n-butyllithium

Example 42

[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-yl]-N,N-dimethylcarbamic acid thioester (T1)

[0242] 1.0 g (3.2 mmol) of the compound Z11 from example 11 was suspended in absolute THF, cooled to −50° C. and 2.5 ml (4 mmol) of BuLi were injected under nitrogen. The mixture was stirred in the cold for 5 min and 0.4 g (3.2 mmol) of N,N-dimethylcarbamoyl chloride, which was dissolved in THF, was then added dropwise. The reaction mixture was stirred overnight at RT. The work-up was carried out by means of column chromatography on silica gel, eluting with ethyl acetate. 740 mg of the compound mentioned in the title were obtained.

[0243] IR(KBr): 1/λ (cm^{-1})=1660, 1615, 1525, 1505, 1460, 1250, 840

Example 43

[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-yl]-N,N-diethylcarbamic acid thioester (T2)

[0244] The synthesis was carried out as described in example 42, except that in the after addition of the BuLi, N,N-diethylcarbamoyl chloride was added. 841 mg of the compound mentioned in the title were obtained.

[0245] IR (KBr): 1/λ (cm^{-1})=2970, 1650, 1610, 1570, 1500, 1455, 1240, 830

[0246] In an analogous manner to that described in the example 42, the compounds below were prepared from the starting substances mentioned:

Example 44

[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-yl]-N,N-diisopropylcarbamic acid thioester (T3)

[0247] Starting substances: 2.5 g (8 mmol) of Z11; 1.3 g (8 mmol) of diisopropylcarbamoyl chloride; 6.5 ml (10 mmol) of BuLi

[0248] Eluent: ethyl acetate/dichloromethane 1:10

[0249] Yield: 840 mg

[0250] IR (KBr): 1/λ (cm^{-1})=2830, 1665, 1610, 1500, 1460, 1420, 1245, 830

Example 45

[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-yl]-morpholine-4-carbamic acid thioester (T4)

[0251] Starting substances: 2.5 g (8.1 mmol) of Z11; 1.2 g (8.1 mmol) of morpholine-4-carbamoyl chloride; 6.1 ml (9.8 mmol) of BuLi

[0252] Eluent: ethyl acetate

[0253] Yield: 2.1 g

[0254] IR (KBr): 1/λ (cm^{-1})=2960, 2815, 1650, 1605, 1570, 1500, 1450, 1240, 1210, 830

Example 46

N^1,N^1-Dimethyl-2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]-3-oxobutanamide (T7)

[0255] Starting substances: 1.0 g (3.2 mmol) of Z11; 10.5 g (3.2 mmol) of 2-chloro-N,N-di-methylacetoacetamide; 3 ml (4.8 mmol) of BuLi

[0256] Eluent: ethyl acetate

[0257] Yield: 281 mg

[0258] IR (KBr): 1/λ (cm^{-1})=2960, 2820, 1750, 1715, 1635, 1610, 1570, 1500, 1460, 1245, 830

Example 47

N^1-Phenyl-2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]acetamide (T9)

[0259] Starting substances: 1.0 g (3.2 mmol) of Z11; 0.6 g (3.2 mmol) of N-(2-chloroacetyl)-aniline; 2.1 ml (3.4 mmol) of BuLi

[0260] Eluent: ethyl acetate/dichloromethane 1:3

[0261] Yield: 687 mg

[0262] IR (KBr): 1/λ (cm^{-1})=1670, 1610, 1560, 1500, 1440, 1245, 830, 750, 690

Example 48

N^1-(4-Chlorophenyl)-2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-yl -sulfanyl]acetamide (T10)

[0263] Starting substances: 1.0 g (3.2 mmol) of Z11; 0.7 g (3.2 mmol) of Z18; 2.1 ml (3.4 mmol) of BuLi

[0264] Eluent: ethyl acetate/dichloromethane 1:3

[0265] Yield: 430 mg

[0266] IR (KBr): 1/λ (cm^{-1})=1660, 1600, 1500, 1450, 1250, 830

Example 49

3-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]-1-phenylpropan-1-one (T13)

[0267] Starting substances: 660 mg (1.9 mmol) of Z11; 324 mg (1.9 mmol) of β-chloro-propiophenone; 1.4 ml (2.1 mmol) of BuLi

[0268] Eluent: ethyl acetate/dichloromethane 1:5

[0269] Yield: 100 mg

[0270] IR (KBr): 1/λ(cm^{-1})=1680, 1610, 1580, 1510, 1470, 1255, 840, 750, 700

Example 50

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-chlorobenzenesulfonamide (T18)

[0271] Starting substances: 6.76 g (21.6 mmol) of Z11; 5.50 g (21.6 mmol) of Z19; 14.0 ml (22.4 mmol) of BuLi

[0272] Eluent: ethyl acetate/dichloromethane 1:10

[0273] Yield: 5.6 g

[0274] IR (KBr): 1/λ (cm^{-1})=2840, 1610, 1580, 1500, 1460, 1320, 1250, 1160, 835

Example 51

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1-methyl-1H-imidazol-2-ylsulfanyl]-ethyl}benzamide (T30)

[0275] Starting substances: 457 mg (1.4 mmol) of Z15; 257 mg (1.4 mmol) of N-(2-chloro-ethyl)benzamide; 1.0 ml (1.6 mmol) of BuLi

[0276] Eluent: ethyl acetate/dichloromethane 1:3

[0277] Yield: 350 mg

[0278] IR (KBr): 1/λ (cm^{-1})=1655, 1615, 1580, 1500, 1460, 1250, 840, 760, 710

Example 52

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl}acetamide (T49)

[0279] Starting substances: 2.5 g (8 mmol) of Z11; 1.0 g (8 mmol) of N-(2-chloroethyl)-acetamide; 5.7 ml (9 mmol) of BuLi

[0280] Eluent: ethyl acetate

[0281] Yield: 1.7 g

[0282] IR (KBr): 1/λ (cm^{-1})=2960, 1630, 1610, 1550, 1500, 1450, 1240, 830

Example 53

[4,5-Bis(4-chlorophenyl)-1H-imidazol-2-yl]-N,N-dimethylcarbamic acid thioester (T81)

[0283] Starting substances: 2.5 g (7.8 mmol) of Z12; 0.8 g (7.8 mmol) of N,N-dimethyl-carbamoyl chloride; 5.1 ml (8.2 mmol) of BuLi

[0284] Eluent: ethyl acetate

[0285] Yield: 2.25 g

[0286] IR (KBr): 1/λ (cm^{-1})=1660, 1600, 1500, 1485, 830

Example 54

[4,5-Bis(4-chlorophenyl)-1H-imidazol-2-yl]-N,N-diethylcarbamic acid thioester (T82)

[0287] Starting substances: 2.5 g (7.78 mmol) of Z12; 0.93 g (7.78 mmol) of N,N-diethylcarbamoyl chloride; 5.1 ml (8.16 mmol) of BuLi

[0288] Eluent: dichloromethane

[0289] Yield: 2.2 g

[0290] IR (KBr): 1/λ (cm-$^{-1}$)=2960, 1670, 1500, 1405, 830

Example 55

N^1-{2-[4,5-Bis(4-chlorophenyl)-1H-imidazol-2-yl-sulfanl]ethyl}acetamide (T84)

[0291] Starting substances: 1.0 g (3.1 mmol) of Z12; 0.4 g (3.1 mmol) of N-(2-chloroethyl)-acetamide; 2.1 ml (3.4 mmol) of BuLi

[0292] Eluent: ethyl acetate

[0293] Yield: 0.97 g

[0294] IR (KBr): 1/λ (cm^{-1})=1635, 1550, 1500, 1410, 830

Example 56

N^1-{2-[4,5-Bis(4-chlorophenyl)-1H-imidazol-2-yl-sulfanyl]ethyl}benzamide (T85)

[0295] Starting substances: 0.8 g (2.5 mmol) of Z12; 0.5 g (2.5 mmol) of N-(2-chloroethyl)-benzamide; 1.7 ml (2.7 mmol) of BuLi

[0296] Eluent: ethyl acetate/dichloromethane 1:3

[0297] Yield: 71 mg

[0298] IR (KBr): 1/λ (cm^{-1})=2900, 1630, 1500, 1400, 830

Example 57

N^1-{2-[4,5-Bis(4-chlorophenyl)-1H-imidazol-2-yl-sulfanyl]ethyl}-4-chloro-benzenesulfonamide (T86)

[0299] Starting substances: 500 mg (1.6 mmol) of Z12; 464 mg (1.6 mmol) of Z20; 1.2 ml (1.9 mmol) of BuLi

[0300] Eluent: ethyl acetate/petroleum ether 1:2

[0301] Yield: 167 mg

[0302] IR (KBr): 1/λ (cm^{-1})=3290, 3060, 2840, 1580, 1500, 1480, 1320, 1150, 825

Example 58

2-(4,5-Diphenyl)-1H-imidazol-2-yl)-N,N-dimethyl-carbamic acid thioester (T89)

[0303] Starting substances: 2.0 g (7.95 mmol) of Z10; 0.9 g (7.97 mmol) of N,N-dimethylcarbamoyl chloride; 5.6 ml (9 mmol) of BuLi

[0304] Eluent: ethyl acetate

[0305] Yield: 1.6 g

[0306] IR (KBr): 1/λ (cm^{-1})=1660, 1480, 1430, 760, 695

Example 59

2-(4,5-Diphenyl)-1H-imidazol-2-yl)-N,N-diethylcar-bamic acid thioester (T90)

[0307] Starting substances: 808 mg (3.2 mmol) of Z10; 434 mg (3.2 mmol) of N,N-diethylcarbamoyl chloride; 2.1 ml (3.4 mmol) of BuLi

[0308] Eluent: ethyl acetate/petroleum ether 1:1

[0309] Yield: 295 mg

[0310] IR (KBr): 1/λ (cm^{-1})=1650, 1600, 1570, 1500, 1445, 1245, 760, 695

Example 60

N^1-[2-(4,5-Diphenyl)-1H-imidazol-2-ylsulfanyl] ethyl]acetamide (T93)

[0311] Starting substances: 1.0 g (4.0 mmol) of Z10; 0.5 g (4.0 mmol) of N-(2-chloroethyl)-acetamide; 2.6 ml (4.2 mmol) of BuLi

[0312] Eluent: ethyl acetate

[0313] Yield: 755 mg

[0314] IR (KBr): 1/λ (cm^{-1})=1650, 1600, 1570, 1510, 1440, 770, 700

Example 61

N^1-[2-(4,5-Diphenyl)-1H-imidazol-2-ylsulfanyl] ethyl]benzamide (T94)

[0315] Starting substances: 1.0 g (4.0 mmol) of Z10; 0.7 g (4.0 mmol) of N-(2-chloroethyl)-benzamide; 2.6 ml (4.2 mmol) of BuLi

[0316] Eluent: ethyl acetate/dichloromethane 1:3

[0317] Yield: 700 mg

[0318] IR (KBr): 1/λ (cm^{-1})=3070, 2940, 1640, 1600, 1550, 1490, 1450, 770, 700

Example 62

[4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl]-N,N-dimethylcarbamic acid thioester (T95)

[0319] Starting substances: 2.5 g (8.7 mmol) of Z13; 0.9 g (8.7 mmol) of N,N-dimethylcarbamoyl chloride; 6 ml (9.6 mmol) of BuLi

[0320] Eluent: ethyl acetate

[0321] Yield: 1.5 g

[0322] IR (KBr): 1/λ (cm^{-1})=1675, 1605, 1500, 835

Example 63

[4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl]-N,N-diethylcarbamic acid thioester (T96)

[0323] Starting substances: 2.5 g (8.67 mmol) of Z13; 1.2 g (8.67 mmol) of N,N-diethylcarbamoyl chloride; 6.5 ml (10.4 mmol) of BuLi

[0324] Eluent: ethyl acetate/dichloromethane 1:6

[0325] Yield: 2.2 g

[0326] IR (KBr): 1/λ (cm^{-1})=1670, 1610, 1590, 1500, 1460, 840

Example 64

N^1-{2-[4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl-sulfanyl]ethyl}benzamide (T98)

[0327] Starting substances: 1.0 g (3.5 mmol) of Z13; 0.7 g (3.5 mmol) of N-(2-chloroethyl)-benzamide; 2.3 ml (3.7 mmol) of BuLi

[0328] Eluent: ethyl acetate/dichloromethane 1:1

[0329] Yield: 541 mg

[0330] IR (KBr): 1/λ (cm^{-1})=1630, 1600, 1545, 1500, 1400, 835

Example 65

[4,5-Bis(4-trifluoromethylphenyl)-1H-imidazol-2-yl]-N,N-diethylcarbamic acid thioester (T99)

[0331] Starting substances: 1.0 g (2.57 mmol) of Z14; 0.3 g (2.57 mmol) of N,N-dimethylcarbamoyl chloride; 1.8 ml (2.88 mmol) of BuLi

[0332] Eluent: ethyl acetate/dichloromethane 1:3

[0333] Yield: 583 mg

[0334] IR (KBr): 1/λ (cm^{-1})=2940, 1650, 1610, 1580, 1500, 1450, 1255, 840

Example 66

N^1-{2-[4,5-Bis(4-trifluoromethylphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-acetamide (T101)

[0335] Starting substances: 1.0 g (2.6 mmol) of Z14; 0.3 g (2.6 mmol) of N-(2-chloroethyl)-acetamide; 1.7 ml (2.7 mmol) of BuLi

[0336] Eluent: ethyl acetate

[0337] Yield: 677 mg

[0338] IR (KBr): 1/λ (cm^{-1})=1650, 1610, 1560, 1460, 845

Example 67

N^1-{2-[4,5-Bis(4-trifluoromethylphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-benzamide (T102)

[0339] Starting substances: 1.0 g (2.6 mmol) of Z14; 0.3 g (2.5 mmol) of N-(2-chloroethyl)-benzamide; 1.7 ml (2.7 mmol) of BuLi

[0340] Eluent: ethyl acetate/dichloromethane 1:3

[0341] Yield: 630 mg

[0342] IR (KBr): 1/λ (cm^{-1})=3060, 2930, 1620, 1575, 1490, 1420, 845, 710

Example 68

[4-(4-Chlorophenyl)-5-phenyl-1H-imidazol-2-yl]-N,N-dimethylcarbamic acid thioester (T103)

[0343] Starting substances: 2.0 g (7.0 mmol) of Z16; 0.8 g (7.0 mmol) of N,N-dimethylcarbamoyl chloride; 5.3 ml (8.4 mmol) of BuLi

[0344] Eluent: ethyl acetate

[0345] Yield: 1.45 g

[0346] IR (KBr): 1/λ (cm^{-1})=1650, 1600, 1500, 1480, 830, 765, 695

Example 69

[4-(4-Chlorophenyl)-5-phenyl-1H-imidazol-2-yl]-N,N-diethylcarbamic acid thioester (T104)

[0347] Starting substances: 2.0 g (7.0 mmol) of Z16; 1.0 g (7.0 mmol) of N,N-diethylcarbamoyl chloride; 5.3 ml (8.4 mmol) of BuLi

[0348] Eluent: ethyl acetate/dichloromethane 1:3

[0349] Yield: 1.6 g

[0350] IR (KBr): 1/λ (cm^{-1})=1670, 1500, 1485, 830, 770, 700

Example 70

N^1-{2-[4-(4-Chlorophenyl)-5-phenyl-1H-imidazol-2-ylsulfanyl]ethyl}benzamide (T106)

[0351] Starting substances: 1.0 g (3.5 mmol) of Z16; 0.6 g (3.5 mmol) of N-(2-chloroethyl)-benzamide; 2.3 ml (3.7 mmol) of BuLi

[0352] Eluent: ethyl acetate/dichloromethane 1:3

[0353] Yield: 538 mg

[0354] IR (KBr): 1/λ (cm^{-1})=3060, 2920, 1640, 1600, 1540, 1500, 1475, 830, 770, 700

Example 71

[4-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1H-imidazol-2-yl]-N,N-dimethylcarbamic acid thioester (T 107)

[0355] Starting substances: 2.5 g (7.9 mmol) of Z17; 0.9 g (7.9 mmol) of N,N-dimethylcarbamoyl chloride; 6.0 ml (9.5 mmol) of BuLi

[0356] Eluent: ethyl acetate

[0357] Yield: 1.2 g

[0358] IR (KBr): 1/λ (cm^{-1})=2960, 1650, 1600, 1500, 1480, 1240, 820

Example 72

[4-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1H-imidazol-2-yl]-N,N-diethylcarbamic acid thioester (T108)

[0359] Starting substances: 2.5 g (7.9 mmol) of Z17; 0.9 g (7.9 mmol) of N,N-diethyl-carbamoyl chloride; 6.0 ml (9.5 mmol) of BuLi

[0360] Eluent: ethyl acetate/dichloromethane 1:10

[0361] Yield: 1.2 g

[0362] IR (KBr): 1/λ (cm^{-1})=2960, 1640, 1600, 1500, 1480, 1240, 825

Example 73

N^1-{2-[4-(4-Chlorophenyl)-5-(4-methoxypheny)-1H-imidazol-2-yl-sulfanyl]ethyl}benzamide (T110)

[0363] Starting substances: 0.5 g (1.6 mmol) of Z17; 0.3 g (1.6 mmol) of N-(2-chloroethyl)-benzamide; 1.2 ml (1.9 mmol) of BuLi

[0364] Eluent: ethyl acetate/dichloromethane 1:3

[0365] Yield: 130mg

[0366] IR (KBr): 1/λ (cm^{-1})=3060, 2940, 1640, 1615, 1560, 1490, 1460, 1250, 835, 740, 710

Example 74

N^1-{2-[4-(4-Chlorophenyl)-5-(4-methoxypheny)-1H-imidazol-2-yl-sulfanyl]ethyl}-4-chlorobenzene-sulfonamide (T111)

[0367] Starting substances: 0.5 g (1.6 mmol) of Z17; 471 mg (1.6 mmol) of Z20; 1.2 ml (1.9 mmol) of BuLi

[0368] Eluent: ethyl acetate/petroleum ether 1:2

[0369] Yield: 226 mg

[0370] IR(KBr): $1/\lambda$ (cm^{-1})=1610, 1565, 1505, 1455, 1310, 1240, 1150, 825

[0371] h) Compounds which were obtained by reaction of 4,5-diaryl-IH-imidazol-2-yl-sulfanylalkylamines with carboxylic acid or sulfonic acid halides

Example 75

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]propyl}benzamide (T16)

[0372] 500 mg (1.4 mmol) of the compound Z 21 from Example 21 were suspended in dry THF, cooled to −50° C. and 1.0 ml (1.6 mmol) of BuLi was injected under nitrogen. After stirring for 5 minutes, 190 mg (1.4 mmol) of benzoyl chloride, which were dissolved in dry THF, were added dropwise. The reaction mixture was stirred overnight. The product was purified on a silica gel column, eluting with ethyl acetate. 234 mg of the compound named in the title were obtained.

[0373] IR (KBr): $1/\lambda$ (cm^{-1})=1635, 1610, 1575, 1500, 1465, 1250, 835, 710, 710

[0374] In an analogous manner to that described in the example 75, the compounds below were prepared from the starting substances mentioned:

Example 76

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}benzene-sulfonamide (T17)

[0375] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 250 mg (1.4 mmol) of benzoylsulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0376] Eluent: ethyl acetate/dichloromethane 1:5

[0377] Yield: 200 mg

[0378] IR (KBr): $1/\lambda$ (cm^{-1})=1610, 1500, 1450, 1320, 1250, 1150, 830, 750, 690

Example 77

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-chlorobenzenesulfonamide (T18)

[0379] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 300 mg (1.4 mmol) of 4-chlorobenzoyl-sulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0380] Eluent: ethyl acetate/dichloromethane 1:10

[0381] Yield: 446 mg

[0382] IR (KBr): $1/\lambda$ (cm^{-1})=2840, 1610, 1580, 1500, 1460, 1320, 1250, 1160, 835

Example 78

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-fluorobenzenesulfonamide (T20)

[0383] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 272 mg (1.4 mmol) of 4-fluorobenzoyl-sulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0384] Eluent: ethyl acetate/petroleum ether 1:1

[0385] Yield: 347 mg

[0386] IR (KBr): $1/\lambda$ (cm^{-1})=2840, 1610, 1590, 1500, 1460, 1320, 1250, 1160, 830

Example 79

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-nitro-benzenesulfonamide (T21)

[0387] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 313 mg (1.4 mmol) of 4-nitrobenzoyl-sulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0388] Eluent: ethyl acetate/dichloromethane 1:10

[0389] Yield: 455 mg

[0390] IR (KBr): $1/\lambda$ (cm^{-1})=2840, 1610, 1525, 1500, 1460, 1440, 1350, 1250, 1160, 835

Example 80

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-3,5-bis-(trifluoromethyl)benzene-sulfonamide (T22)

[0391] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 438 mg (1.4 mmol) of 4-bis(trifluorom-ethyl)benzoylsulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0392] Eluent: ethyl acetate/petroleum ether 1:2

[0393] Yield: 405 mg

[0394] IR(KBr): $1/\lambda$ (cm^{-1})=1600, 1510, 1490, 1455, 1350, 1240, 1155, 825

Example 81

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl}-4-methoxybenzenesulfonamide (T23)

[0395] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 289 mg (1.4 mmol) of 4-methoxyben-zoylsulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0396] Eluent: ethyl acetate/dichloromethane 1:5

[0397] Yield: 387 mg

[0398] IR (KBr): $1/\lambda$ (cm^{-1})=1610, 1590, 1500, 1455, 1330, 1240, 1155, 825

Example 82

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-methylbenzenesulfonamide (T24)

[0399] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 250 mg (1.4 mmol) of p-toluenesulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0400] Eluent: ethyl acetate/dichloromethane 1:5

[0401] Yield: 430 mg

[0402] IR (KBr): 1/λ (cm^{-1})=1610, 1570, 1500, 1450, 1320, 1240, 1150, 830

Example 83

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl}-2,4,6-trimethylbenzenesulfonamide (T25)

[0403] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 306 mg (1.4 mmol) of mesetylenesulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0404] Eluent: ethyl acetate/petroleum ether 1:1

[0405] Yield: 430 mg

[0406] IR (KBr): 1/λ (cm^{-1})=1615, 1520, 1505, 1465, 1325, 1250, 1160, 840

Example 84

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyllethyl}-4-(tert-butyl)benzenesulfonamide (T26)

[0407] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 326 mg (1.4 mmol) of 4-tert-butylbenzoylsulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0408] Eluent: ethyl acetate/petroleum ether 1:1

[0409] Yield: 368 mg

[0410] IR (KBr): 1/λ (cm^{-1})=1615, 1525, 1465, 1330, 1255, 1170, 840

Example 85

N^1-(4-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl-sulfamoyl}phenyl)acetamide (T27)

[0411] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 327 mg (1.4 mmol) of 4-acetamidobenzenesulfonyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0412] Eluent: ethyl acetate

[0413] Yield: 360 mg

[0414] IR (KBr): 1/λ (cm^{-1})=1680, 1610, 1590, 1500, 1460, 1320, 1250, 1150, 835

Example 86

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-chlorobenzamide (T32)

[0415] Starting substances: 840 mg (2.4 mmol) of T15 from Example 28; 420 mg (2.4 mmol) of 4-chlorobenzoyl chloride; 1.6 ml (2.6 mmol) of BuLi

[0416] Eluent: ethyl acetate/dichloromethane 2:1

[0417] Yield: 636 mg

[0418] IR(KBr): 1/λ (cm^{-1})=1630, 1590, 1560, 1500, 1455, 1240, 830

Example 87

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-3-chlorobenzamide (T33)

[0419] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 327 mg (1.4 mmol) of 4-chlorobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0420] Eluent: ethyl acetate/dichloromethane 1:3

[0421] Yield: 344 mg

[0422] IR (KBr): 1/λ (cm^{-1})=2840, 1640, 1615, 1570, 1500, 1465, 1250, 840, 805

Example 88

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-2-chlorobenzamide (T34)

[0423] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 247 mg (1.4 mmol) of 2-chlorobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0424] Eluent: ethyl acetate/dichloromethane 1:3

[0425] Yield: 300 mg

[0426] IR (KBr): 1/λ (cm^{-1})=1645, 1615, 1600, 1500, 1465, 1250, 840, 750

Example 89

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-2,4-di-chlorobenzamide (T35)

[0427] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 295 mg (1.4 mmol) of 2,4-dichlorobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0428] Eluent: ethyl acetate/dichloromethane 1:3

[0429] Yield: 120 mg

[0430] IR (KBr): 1/λ (cm^{-1})=2960, 2840, 1640, 1610, 1585, 1500, 1460, 1250, 835

Example 90

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-2,6-di-chlorobenzamide (T36)

[0431] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 295 mg (1.4 mmol) of 2,6-dichlorobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0432] Eluent: ethyl acetate/dichloromethane 1:6

[0433] Yield: 470 mg

[0434] IR (KBr): 1/λ (cm^{-1})=2840, 1650, 1615, 1580, 1500, 1460, 1430, 1250, 840, 780

Example 91

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl-3,5-di-chlorobenzamide (T37)

[0435] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 293 mg (1.4 mmol) of 3,5-dichlorobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0436] Eluent: ethyl acetate/dichloromethane 1:3

[0437] Yield: 527 mg

[0438] IR (KBr): 1/λ (cm^{-1})=1650, 1620, 1570, 1510, 1470, 1255, 840

Example 92

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-fluorobenzamide (T38)

[0439] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 223 mg (1.4 mmol) of 4-fluorobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0440] Eluent: ethyl acetate/dichloromethane 1:3

[0441] Yield: 95 mg

[0442] IR (KBr): 1/λ (cm^{-1})=1630, 1600, 1550, 1500, 1455, 1240, 830

Example 93

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl}-4-cyanobenzamide (T39)

[0443] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 234 mg (1.4 mmol) of 4-cyanobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0444] Eluent: ethyl acetate

[0445] Yield: 384mg

[0446] IR (KBr): 1/λ (cm^{-1})=1650, 1615, 1560, 1505, 1440, 1250, 840

Example 94

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-nitro-benzamide (T40)

[0447] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 262 mg (1.4 mmol) of 4-nitrobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0448] Eluent: ethyl acetate/dichloromethane 1:3

[0449] Yield: 523 mg

[0450] IR (KBr): 1/λ (cm^{-1})=1640, 1600, 1560, 1500, 1440, 1345, 1250, 835

Example 95

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-2-nitro-benzamide (T41)

[0451] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 262 mg (1.4 mmol) of 2-nitrobenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0452] Eluent: ethyl acetate/dichloromethane 1:3

[0453] Yield: 523 mg

[0454] IR (KBr): 1/λ (cm^{-1})=2840, 1645, 1610, 1560, 1500, 1440, 1350, 1250, 840, 730

Example 96

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-(tri-fluoromethyl)benzamide (T42)

[0455] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 294 mg (1.4 mmol) of 4-trifluoromethylbenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0456] Eluent: ethyl acetate/dichloromethane 1:3

[0457] Yield: 400 mg

[0458] IR (KBr): 1/λ (cm^{-1})=1640, 1610, 1570, 1500, 1460, 1250, 830

Example 97

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-3-(tri-fluoromethyl)benzamide (T43)

[0459] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 294 mg (1.4 mmol) of 3-trifluoromethylbenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0460] Eluent: ethyl acetate/dichloromethane 1:3

[0461] Yield: 400 mg

[0462] IR (KBr): 1/λ (cm^{-1})=1640, 1610, 1590, 1500, 1430, 1250, 840, 760

Example 98

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-3,5-bis-(trifluoromethyl)benzamide (T44)

[0463] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 391 mg (1.4 mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0464] Eluent: ethyl acetate/dichloromethane 1:3

[0465] Yield: 400 mg

[0466] IR (KBr): 1/λ (cm^{-1})=1655, 1620, 1580, 1510, 1465, 1250, 840

Example 99

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl}-4-methoxybenzamide (T46)

[0467] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 240 mg (1.4 mmol) of p-anisoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0468] Eluent: ethyl acetate/dichloromethane 1:1

[0469] Yield: 384 mg

[0470] IR (KBr): 1/λ (cm^{-1})=1620, 1580, 1500, 1460, 1255, 840

Example 100

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl}-3,4,5-trimethoxybenzamide (T46)

[0471] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 323 mg (1.4 mmol) of 3,4,5-trimethoxybenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0472] Eluent: ethyl acetate

[0473] Yield: 200 mg

[0474] IR (KBr): 1/λ (cm^{-1})=2930, 2820, 1620, 1605, 1570, 1495, 1450, 1240, 830

Example 101

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl}4-methylbenzamide (T47)

[0475] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 218 mg (1.4 mmol) of p-toluoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0476] Eluent: ethyl acetate/dichloromethane 1:3

[0477] Yield: 357 mg

[0478] IR (KBr): $1/\lambda$ (cm^{-1})=1615, 1555, 1460, 1250, 830

Example 102

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanl]ethyl}-4-(tert-butyl)benzamide (T48)

[0479] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 277 mg (1.4 mmol) of 4-tert-butylbenzoyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0480] Eluent: ethyl acetate/dichloromethane 1:3

[0481] Yield: 390 mg

[0482] IR (KBr): $1/\lambda$ (cm^{-1})=2860, 1630, 1610, 1585, 1500, 1460, 1250, 835

Example 103

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-4-(tert-butyl)benzamide (T50)

[0483] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 130 mg (1.4 mmol) of propionyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0484] Eluent: ethyl acetate

[0485] Yield: 317 mg

[0486] IR (KBr): $1/\lambda$ (cm^{-1})=1730, 1605, 1510, 1495, 1450, 1240, 825

Example 104

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-2-methylpropanamide (T51)

[0487] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 150 mg (1.4 mmol) of isobutyryl chloride; 1.0 ml (1.6 mmol) of BuLi

[0488] Eluent: ethyl acetate

[0489] Yield: 217 mg

[0490] IR (KBr): $1/\lambda$ (cm^{-1})=2960, 1635, 1605, 1515, 1495, 1455, 1240, 830

Example 105

N^{1-}2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyllethyl-2,2-di-methylpropanamide (T52)

[0491] Starting substances: 500 mg (1.4 mmol) of T15 from Example 28; 170 mg (1.4 mmol) of pivaloyl chloride; 1.0 ml (1.6 mmol) of BuLi

[0492] Eluent: ethyl acetate/dichloromethane 1:3

[0493] Yield: 219 mg

[0494] IR (KBr): $1/\lambda$ (cm^{-1})=2970, 1620, 1580, 1525, 1505, 1465, 1250, 840

[0495] The compounds below were prepared in an analogous manner to examples 104 and 105:

Example 106

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}furan-2-carboxamide (T53)

Example 107

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}thiophene -2-carboxamide (T54)

Example 108

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-1-naphthamide (T55)

Example 109

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1 H-imidazol-2-ylsulfanyl]ethyl}-2-naphthamide (T56)

Example 110

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-N',N'-dimethylurea (T57)

Example 111

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-N',N'-diethylurea (T58)

Example 112

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-2-phenylacetamide (T59)

Example 113

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-3-phenylpropanamide (T60)

Example 114

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-3-phenylprop-2-enamide (T61)

Example 115

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-2,2-di-phenylacetamide (T62)

Example 116

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-methanesulfonamide (T63)

Example 117

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-ethanesulfonamide (T64)

Example 118

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-propane -2-sulfonamide (T65)

Example 119

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-phenylmethanesulfonamide (T66)

Example 120

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-naphthalene -1-sulfonamide (T67)

Example 121

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-naphthalene -2-sulfonamide (T68)

[0496] i) Synthesis of the ethyl 2-(4,5-diaryl-IH-imidazolyl)acetates

Example 122

Ethyl 2-[4,5-bis(4-methoxyphenyl)-2-(2-pyridylmethylsulfanyl)-1H-imidazol-1-yl]acetate (Z23)

[0497] 1.3 g (3.3 mmol) of the compound T69 from Example 30 were dissolved in absolute THF and 120 mg (5 mmol) of NaH were added in small portions with stirring. The reaction mixture was stirred at RT for 10 min. 0.5 g (3.3 mmol) of ethyl bromoacetate, dissolved in dry DMF, was then added dropwise. The reaction mixture was then stirred at RT for 2 h. For the work-up, the DMF was evaporated and the residue by means of column chromatography on silica gel, eluting with ethyl acetate. 1.37 g of the compound mentioned in the title were obtained.

[0498] The compounds below were prepared from the starting substances mentioned in an analogous manner to that described in example 122:

Example 123

Ethyl 2-[4,5-bis(4-methoxyphenyl)-2-(3-pyridylmethylsulfanyl)-1H-imidazol-1-yl]acetate (Z24)

[0499] Starting substances: 500 mg (1.2 mmol) of T70 from Example 31; 270 mg (1.6 mmol) of ethyl bromoacetate; 72 mg (3 mmol) of NaH Yield: 587 mg

Example 124

Ethyl 2-[4,5-bis(4-methoxyphenyl)-2-(4-pyridylmethylsulfanyl)-1H-imidazol-1-yl]acetate (Z25)

[0500] Starting substances: 500 mg (1.2 mmol) of T71 from Example 32; 270 mg (1.6 mmol) of ethyl bromoacetate; 72 mg (3 mmol) of NaH

[0501] Yield: 584 mg

Example 125

Ethyl 2-[4,5-bis(4-methoxyphenyl)-2-(2-quinolylmethylsulfanyl)-1H-imidazol-1-yl]acetate (Z26)

[0502] Starting substances: 400 mg (0.9 mmol) of T72 from Example 33; 150 mg (0.9 mmol) of ethyl bromoacetate; 30 mg (1.2 mmol) of NaH

[0503] Yield: 423 mg

Example 126

Ethyl 2-[4,5-diphenyl-2-(2-pyridylmethylsulfanyl)-1H-imidazol-1-yl]-acetate (Z27)

[0504] Starting substances: 1.2 g (3.5 mmol) of T91 from Example 38; 0.4 g (3.5 mmol) of ethyl bromoacetate; 101 mg (4.2 mmol) of NaH

[0505] Yield: 1.0 g

Example 127

Ethyl 2-[4-(4-chlorophenyl)-5-(4-methoxyphenyl)-2-(2-pyridylmethyl-sulfanyl) -1H-imidazol-1-yl]acetate (Z28)

[0506] Starting substances: 0.85 g (2.1 mmol) of Z22 from Example 22; 0.35 g (2.1 mmol) of ethyl bromoacetate; 0.60 g (2.5 mmol) of NaH

[0507] Yield: 788 mg

[0508] k) Synthesis of the carboxylic acids by ester hydrolysis

Example 128

2-[4,5-Bis(4-methoxyphenyl)-2-(2-pyridylmethylsulfanyl)-1H-imidazol-1-yl]acetic acid (T75)

[0509] 1.37 g (2.8 mmol) of the compound Z23 from Example 23 were dissolved in ethanol, treated with 5 ml (10 mmol) of 2 N NaOH and refluxed for 2 h. After cooling, the ethanol was stripped off, the residue was treated with water and washed a number of times with dichloromethane. The aqueous phase was acidified to a pH of 6-7 using 10% strength H3PO4 and again extracted by shaking with dichloromethane. The organic phase was dried using Na_2SO_4, evaporated and the residue was recrystallized from ethanol. 865 mg of the compound mentioned in the title were obtained.

[0510] IR (KBr): $1/\lambda$ (cm^{-1})=3400, 1720, 1600, 1510, 1430, 1240, 830, 790, 740

[0511] The compounds below were prepared from the starting substances mentioned in an analogous manner to that described in example 128:

Example 129

2-[4,5-Bis(4-methoxyphenyl)-2-(3-pyridylmethylsulfanyl)-1H-imidazol-1-yl]-acetic acid (T76)

[0512] Starting substances: 587 mg (1.2 mmol) of Z24 from Example 123; 5 ml (10 mmol) of 2 N NaOH

[0513] Yield: 445 mg

[0514] IR (KBr): $1/\lambda$ (cm^{-1})=3450, 2965, 1710, 1600, 1560, 1500, 1410, 1235, 825, 775, 700

Example 130

2-[4,5-Bis(4-methoxyphenyl)-2-(4-pyridylmethylsulfanyl)-1H-imidazol-1-yl]-acetic acid (T77)

[0515] Starting substances: 584 mg (1.2 mmol) of Z25 from Example 124; 5 ml (10 mmol) of 2 N NaOH

[0516] Yield: 308 mg

[0517] IR (KBr): 1/λ (cm^{-1})=3450, 2960, 1710, 1600, 1575, 1485, 1410, 1230, 830, 740, 680

Example 131

2-[4,5-Bis(4-methoxyphenyl)-2-(2-quinolylmethylsulfanyl)-1H-imidazol-1-yl]acetic acid (T78)

[0518] Starting substances: 423 mg (0.8 mmol) of Z26 from Example 125; 2 ml (4 mmol) of 2 N NaOH

[0519] Yield: 305 mg

[0520] IR (KBr): 1/λ (cm^{-1})=3450, 1720, 1610, 1500, 1420, 1250, 835, 780, 760

Example 132

2-[4,5-Diphenyl-2-(2-pyridylmethylsulfanyl)-1H-imidazol-1-yl]-acetic acid (T92)

[0521] Starting substances: 1.0 g (2.3 mmol) of Z27 from Example 126; 7.5 ml (15 mmol) of 2 N NaOH

[0522] Yield: 3444 mg

[0523] IR (KBr): 1/λ (cm^{-1})=3440, 3050, 1720, 1600, 1570, 1500, 1430, 1235, 770, 700, 750, 675

Example 133

2-[4-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2-(2-pyridylmethylsulfanyl)-1H-imidazol-1-yl]acetic acid (Z109)

[0524] Starting substances: 788 mg (1.6 mmol) of Z28 from Example 127; 5 ml (10 mmol) of 2 N NaOH

[0525] Yield: 242 mg

[0526] IR (KBr): 1/λ (cm^{-1})=3400, 1715, 1615, 1570, 1510, 1430, 1250, 830, 740, 695

[0527] 1) Oxidation of Thio Ethers to Sulfones

Example 134

2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfonylmethyl]pyridine (T74)

[0528] 0.2 g (0.5 mmol) of the compound T69 from Example 30 was dissolved in 30 ml of THF/methanol (1:1) and cooled to 0° C. 2.3 g (3.7 mmol) of Oxone® (potassium monopersulfate triple salt=$2KHSO_5 \times KHSO_4 \times K_2SO_4$) dissolved in 30 ml of water were then added dropwise. The reaction mixture was stirred overnight. The Oxone® was then filtered off, the organic solvents were stripped off and the aqueous phase was extracted by shaking with ethyl acetate and dichloromethane. The combined organic phases were dried using Na_2SO_4 and evaporated. The residue was recrystallized from ethyl acetate (alternatively, CH_2Cl_2/n-hexane can also be used). 140 mg of the compound mentioned in the title were obtained.

[0529] IR (KBr): 1/λ (cm^{-1})=1610, 1520, 1500, 1430, 1330, 1245, 1140, 830, 770, 705

Example 135

Ethyl 2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfonyl]acetate (T80)

[0530] 1.0 g (2.5 mmol) of the compound T79 from Example 35 was reacted with 6.1 g (10 mmol) of Oxone® as described in Example 134. 0.9 g of the compound mentioned in the title was obtained.

[0531] IR (KBr): 1/λ (cm^{-1})=2940, 1740, 1610, 1570, 1500, 1450, 1335, 1250, 1140, 830

[0532] m) Alkylation using methyl iodide and NaH

Example 136

2-[4,5-Bis(4-methoxyphenyl)-1-methyl-1H-imidazol-2-ylsulfanyl]-1-(di-methylamino)propan -1-one (T8)

[0533] 500 mg (1.26 mmol) of the compound T6 from Example 24 were dissolved in DMF. 48 mg (2.0 mmol) of NaH were then added in portions. The mixture was stirred for 10 min and then 358 mg (2.52 mmol) of methyl iodide were added dropwise. The reaction was carried out for 2 h at RT. For the inactivation of the excess NaH, the reaction mixture was then treated with 10 ml of methanol. After evolution of gas had ended, the solvents were stripped off and the residue was purified on a silica gel column using ethyl acetate.

[0534] IR (KBr): 1/λ (cm^{-1})=2940, 1640, 1620, 1620, 1585, 1500, 1455, 1255, 845

[0535] The compounds below were prepared analogously to the process described in example 136:

Example 137

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1-methyl-1H-imidazol-2-ylsulfanyl]-ethyl}-N^1-1-methyl-4-chlorobenzenesulfonamide (T19)

[0536] Starting substances: 400 mg (0.8 mmol) of T18 from Example 50; 284 mg (2.0 mmol) of methyl iodide; 96 mg (4.0 mmol) of NaH

[0537] Yield: 30 mg

[0538] IR (KBr): 1/λ (cm^{-1})=1620, 1590, 1500, 1465, 1350, 1255, 1170, 840

Example 138

N^1-{2-[4,5-Bis(4-methoxyphenyl)-1-methyl-1H-imidazol-2-ylsulfanyl]-ethyl}-N^1-1-methylbenzamide-4-chlorobenzenesulfonamide (T31)

[0539] Starting substances: 340 mg (0.7 mmol) of T28 from Example 29; 213 mg (1.5 mmol) of methyl iodide; 96 mg (4.0 mmol) of NaH

[0540] Yield: 234 mg

[0541] IR (KBr): 1/λ (cm^{-1})=2940, 2820, 1625, 1570, 1490, 1450, 1240, 830, 770, 710

Example 139

2-[4,5-Bis(4-chlorophenyl)-1-methyl-1H-imidazol-2-ylsulfanyl]-1-(di-methylamino)propan -1-one (T88)

[0542] Starting substances: 500 mg (1.23 mmol) of T87 from Example 37; 350 mg (2.46 mmol) of methyl iodide; 48 mg (2.0 mmol) of NaH

[0543] Yield: 410 mg

[0544] IR (KBr): 1/λ (cm^{-1})=2920, 1640, 1490, 1470, 830

[0545] n) Synthesis of N^1-{2-[4,5-bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-N^1-1-methylbenzamide

Example 140

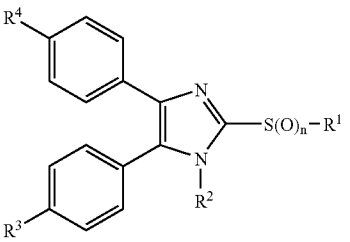
N^1-{2-[4,5-Bis(4-methoxyphenyl)-1H-imidazol-2-ylsulfanyl]ethyl}-N^1-1-methylbenzamide (T29)

[0546] 2.0 g (6.4 mmol) of the compound Z11 from Example 11 were suspended in dry THF and cooled to −50° C. 4.2 ml (6.7 mmol) of n-butyllithium were then injected under nitrogen. After stirring at the low temperature for 5 min, 0.9 g (6.4 mmol) of 1-bromo-2-chloroethane was added dropwise. The cooling bath was removed and the reaction mixture was stirred at RT for 3 h. The mixture was then again cooled to −50° C. and 0.9 g (6.4 mmol) of N-methylbenzamide was added. A further 4.2 ml (6.7 mmol) of n-butyllithium were injected and the reaction mixture was stirred at RT overnight. The product was chromatographed on a silica gel column, eluting with ethyl acetate/petroleum ether (3:1). 200 mg of the compound mentioned in the title were obtained.

[0547] IR (KBR): 1/λ (cm^{-1})=1600, 1570, 1510, 1450, 1240, 830

That which is claimed:

1. A compound of the formula I



(I)

in which

R^1 is selected from:

a) $CONR^5R^6$, in which R^5 and R^6, together with the nitrogen atom to which they are bonded, form a saturated heterocyclic radical having 5 or 6 ring atoms and one or two heteroatoms which independently of one another are selected from N and O,

b) C_1-C_6-alkylene-R^7, where R^7 is an aromatic heterocyclic radical having 5 or 6 ring atoms and one or two heteroatoms, which independently of one another are selected from N, S and O, where the heterocyclic radical can optionally be fused to a benzene ring, or

c) C_1-C_6-alkylene-NR^{10}-CO-R^{11};

R^{10} is H or C_1-C_6-alkyl;

R^{11} is

a) CH═CH-phenyl, or

b) an aromatic, heterocyclic radical having 5 or 6 ring atoms and 1 or 2 heteroatoms, which independently of one another are selected from N, O or S;

R^2 is H, C_1-C_6-alkyl or $(CH_2)_oCOOH$;

R^3 and R^4, which can be identical or different, are H, OH, OC_1-C_6-alkyl, halogen or C_1-C_6-alkyl which is substituted by 1, 2 or 3 halogen atoms, where at least one of the radicals R^3 and R^4 is OH or OC_1-C_6-alkyl;

n is 0, 1 or 2; and

o is 0, 1, 2, 3 or 4;

and the optical isomers and physiologically tolerable salts thereof.

2. A compound as claimed in claim 1, where R^1 is selected from:

a) $CONR^5R^6$, in which R^5 and R^6, together with the nitrogen atom to which they are bonded, form a saturated heterocyclic radical having 5 or 6 ring atoms and one or two heteroatoms which independently of one another are selected from N and O, or

b) C_1-C_6-alkylene-NR^{10}-CO-R^{11};

R^{11} is CH═CH-phenyl or an aromatic, heterocyclic radical having 5 ring atoms and 1 or 2 heteroatoms, which independently of one another are selected from N, O or S;

and R^2, R^3, R^4, and R^{10} have the meaning as indicated in claim 1.

3. A compound as claimed in claim 1, where both radicals R^3 and R^4 are a C_1-C_6-alkoxy group.

4. A compound as claimed in claim 1, where RI is $CONR^5R^6$ and R^5 and R^6 have the meaning indicated in claim 1.

5. A compound as claimed in claim 1, where R^1 is C_1-C_6-alkylene-R^7, in which R^7 is pyridyl, quinolyl, or benzimidazolyl.

6. A compound as claimed in claim 5, in which R^7 is 3-pyridyl or 4-pyridyl.

7. A compound as claimed in claim 1, where R^1 is C_1-C_6-alkylene-R^7, in which R^7 is an aromatic heterocyclic radical having 5 or 6 ring atoms and one or two heteroatoms, which independently of one another are selected from N, S and O.

8. A compound as claimed in claim 7, in which R^2 is $(CH_2)_oCOOH$ and o is 1, 2, 3, or 4.

9. A compound as claimed in claim 1, where R^1 is C_1-C_6-alkylene-NR^{10}—CO—R^{11}, in which R^{10} is H or C_1-C_4-alkyl and R^{11} is —CH═CH-phenyl.

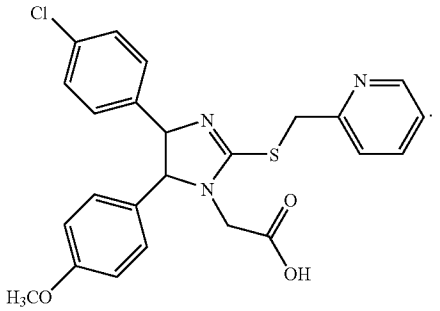
10. A compound as claimed in claim 9, where R^1 is C_1-, C_2- or C_3-alkylene-NR^{10}—CO—R^{11}, in which R^{10} and R^{11} have the meanings indicated in claim 9.

11. A compound as claimed in claim 1, where R^1 is C_1-C_6-alkylene-NR^{10}—CO—R^{11}, in which R^{11} is an aromatic, heterocyclic radical having 5 ring atoms and 1 or 2 heteroatoms, which independently of one another are selected from N, O or S, and R^{10} is H or C_1-C_6-alkyl.

12. A compound as claimed in claim 11, where R^{11} is a furyl or thienyl radical.

13. A compound as claimed in claim 1, where R^1 is C_1-C_6-alkylene-R^7, in which R^7 is 2-pyridyl.

14. A compound 2-[4-(4-chlorophenyl)-5-(4-methoxyphenyl)-2-(pyridylmethylsulfanyl) -1H-imidazol-1-yl]acetic acid of the following formula



15. A pharmaceutical or cosmetic composition comprising at least one compound as claimed in claim 1, together with one or more pharmaceutically acceptable vehicles or additives.

16. A method for treating a disease that is connected with an immune system disorder, comprising administering a pharmaceutical composition comprising at least one compound as claimed in claim 1.

17. A method for treating inflammation, comprising topically applying a pharmaceutical composition comprising at least one compound as claimed in claim 1.

18. A procedure for the treatment of diseases which are connected with a disorder of the immune system, where an amount of a compound as claimed in claim 1 having an immunomodulating or cyclooxygenase-inhibiting action is administered to a person in need of such treatment.

19. A method for treating a disease that is connected with an immune system disorder, comprising administering a pharmaceutical composition comprising at least one compound as claimed in claim 1, wherein said disease is selected from the group consisting of premature labor, colon carcinoma, Alzheimer's disease, rheumatoid arthritis, gout, septic shock, osteoporosis, neuropathic pain, alopecia, psoriasis, acute pancreatitis, rejection reactions in allogenic transplants, allergically caused pneumonia, arteriosclerosis, multiple sclerosis, cachexia, inflammatory bowel disease, adenomatous polyposis, inhibition of angiogenesis in connection with oncoses, contact eczema, and erythema.

20. A procedure for the treatment of diseases which are connected with a disorder of the immune system, where an amount of a compound as claimed in claim 1 having an immunomodulating or cyclooxygenase-inhibiting action is administered to a person who need treatment of this type, and wherein said disease is selected from the group consisting of premature labor, colon carcinoma, Alzheimer's disease, rheumatoid arthritis, gout, septic shock, osteoporosis, neuropathic pain, alopecia, psoriasis, acute pancreatitis, rejection reactions in allogenic transplants, allergically caused pneumonia, arteriosclerosis, multiple sclerosis, cachexia, inflammatory bowel disease, adenomatous polyposis, inhibition of angiogenesis in connection with oncoses, contact eczema, and erythema.

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