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(54) BENZOXAZOLE AND BENZOTHAZOLYL SULFAMATES AND THEIR USE AS STEROID SULFATASE INHIBITORS

**BENZOXAZOLE- UND BENZOTHAZOLYLSULFAMATE SOWIE IHRE VERWENDUNG ALS
STEROID-SULFATASEINHIBITOREN**

**SULFAMATES DE BENZOXAZOLE ET BENZOTHAZOLE ET LEUR UTILISATION COMME
INHIBITEURS DE SULFATASE**

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CHEMISTRY, vol. 41, no. 7, 26 March 1998
(1998-03-26), pages 1068-1083, XP002162181**

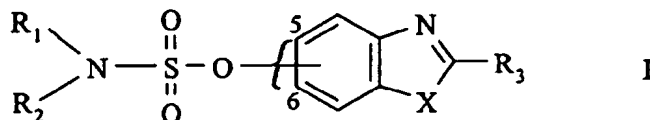
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Description

[0001] The invention relates to benzoxa- and benzthiazole derivatives. It concerns a benzoxa- or benzthiazole substituted at the 2 position and carrying a sulfamic acid ester group bound via oxygen to the phenyl part of the ring structure, hereinafter briefly named "a compound of the invention".

[0002] More specifically, it concerns a compound of formula I



wherein

X is O or S;

R₁ and R₂ either independently are hydrogen or alkyl, or one is hydrogen and the other is acyl or alkoxycarbonyl; and R₃ is alkyl; alkenyl; alkynyl; cycloalkyl selected from adamantyl and hexahydro-2,5-methanopentalenyl; cycloalkenyl; aryl; cycloalkylalkyl selected from adamantylalkyl of 1 to 4 carbon atoms in the alkylene part thereof and dicyclohexylmethyl; cycloalkylalkenyl (including cycloalkanylidenealkyl) selected from adamantanylidene(C₁₋₄)alkyl, (C₄₋₁₂)cycloalkylenyl(C₁₋₄)alkyl, bicyclo[3.3.1]nonylidenemethyl, dimethylcyclohexylidenemethyl, (C₁₋₄)alkoxycyclohexylidenemethyl, (C₁₋₄)alkylcyclohexylidenemethyl, tetra(C₁₋₄)alkylcyclohexylidenemethyl, 1,4-dioxaspiro[4.5]dec-8-ylidenemethyl, 3,3-dimethyl-1,5-dioxaspiro[5.5]undec-9-ylidenemethyl and octahydronaphthalylidenemethyl; cycloalkenylalkyl; arylalkyl; arylalkenyl; arylalkynyl; alkoxycarbonylaminoalkyl; hydroxycycloalkylalkyl; cycloalkanylidenealkyl; cycloalkanylidenealkyl; heteroaryl; or heteroarylalkyl;

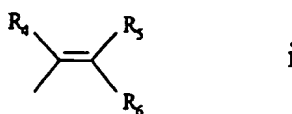
in free form or salt form.

[0003] The sulfamoyloxy moiety in formula I is bound to the ring system in position 5 or 6, preferably 6.

[0004] Alkyl as a group R₁ or R₂ preferably is of 1 to 4 carbon atoms, it especially is methyl. Acyl as a group R₁ or R₂ preferably is formyl or alkylcarbonyl of altogether 2 to 5 carbon atoms, it especially is acetyl. Alkoxycarbonyl as a group R₁ or R₂ preferably is of altogether 2 to 5 carbon atoms, it especially is methoxycarbonyl.

[0005] In significance R₃:

- alkyl as such or as part of a substituent such as cycloalkylalkyl includes (C₁₋₂₂)alkyl, e.g. (C₁₋₁₆)alkyl and (C₁₋₄)alkyl;
- alkenyl as such or as part of a substituent such as cycloalkylalkenyl includes (C₂₋₂₂)alkenyl, e.g. (C₂₋₁₆)alkenyl and (C₂₋₄)alkenyl; when it is part of cycloalkanylidenealkyl the double bond is attached directly to the cycloalkyl moiety and thus the alkenyl part of such a cycloalkylalkenyl group is to be viewed as consisting of just one carbon atom;
- alkynyl as such or as part of a substituent such as arylalkynyl includes (C₂₋₂₂)alkynyl;
- cycloalkenyl as such or as part of cycloalkenylalkyl includes (C₄₋₁₂)cycloalkenyl, such as cyclohexenyl; it may be polycyclic, as in e.g. decahydrophenanthrenyl, and may be substituted, e.g. with 1 to 3 (C₁₋₄)alkyl;
- aryl as such or as part of arylalkyl, arylalkenyl or arylalkynyl includes (C₅₋₁₈)aryl, e.g. (C₅₋₁₂)aryl, e.g. phenyl or tetrahydronaphthalenyl, and may be substituted by e.g. alkyl; there may be up to 3, preferably 1 aryl moiety when aryl is part of a substituent, as in di- or triphenylmethyl;
- acyl includes the residue of a carboxylic acid, in particular an alkyl, aralkyl or aryl carboxylic acid, e.g. an alkyl, aralkyl or aryl carbocyclic acid;
- cycloalkylalkenyl includes e.g. a cycloalkanylidenealkyl group of formula i



wherein

R_4 is hydrogen or alkyl, e.g. (C_{1-4})alkyl, especially methyl, and
 R_5 and R_6 together with the carbon atom to which they are attached form cycloalkyl;

- **cycloalkenylalkyl** is e.g. cyclohexenylmethyl;
- **alkoxycarbonylaminoalkyl** is e.g. tert-butoxycarbonylamino-2,2-dimethylpropyl;
- in **hydroxycycloalkylalkyl** the hydroxy group preferably is bound to the cycloalkyl part at the same carbon atom that is bound to the alkylene part of the hydroxycycloalkylalkyl moiety;
- **cycloalkanylidencycloalkanylidenealkyl** is e.g. bicyclobutylidenemethyl;
- **heteroaryl** as such or as part of **heteroarylalkyl** preferably is pyridyl or thienyl.

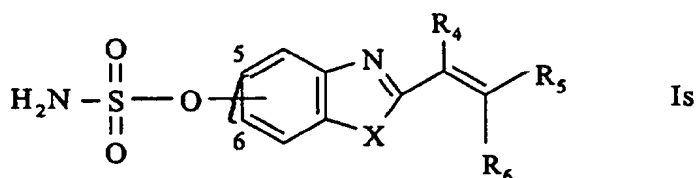
[0006] X preferably is oxygen. R_1 and R_2 preferably are hydrogen. R_3 preferably is alkyl; cycloalkylalkyl; cycloalkenylalkyl; alkoxycarbonylaminoalkyl; or cycloalkylalkenyl, e.g. a group of formula i as defined above.

A subgroup of compounds of the invention is the compounds of formula I wherein X is as defined above;

R_1 and R_2 are hydrogen; and
 R_3 is alkyl, alkenyl, cycloalkyl as defined above or cycloalkenyl,

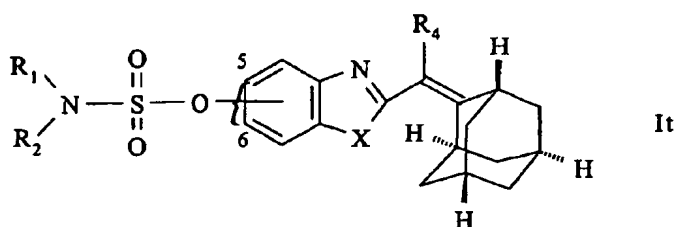
in free form or salt form.

[0007] A further subgroup of compounds of the invention is the compounds of formula Is



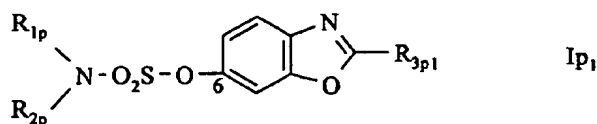
wherein X, R_4 , R_5 and R_6 are as defined above; in free form or salt form.

[0008] A further subgroup of compounds of the invention is the compounds of formula It



wherein X, R_1 , R_2 and R_4 are as defined above; in free form or salt form; e.g. sulfamic acid 2-(adamantan-2-ylidenemethyl)benzoxazol-6-yl ester in free form or salt form.

[0009] A further subgroup of compounds of the invention is the compounds of formula Ip₁



wherein

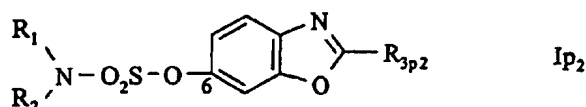
either R_{1p} and R_{2p} have the significances indicated above for R_1 and R_2 ; and

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R_{3p1} is alkyl; alkenyl; alkynyl; cycloalkyl as defined above; cycloalkylalkyl as defined above; arylalkyl; arylalkenyl; arylalkynyl; heteroaryl; or heteroarylalkyl; ,
 or R_{1p} and R_{2p} are hydrogen; and
 R_{3p1} is adamantan-2-ylidenemethyl;

in free form or salt form.

[0010] A further subgroup is the compounds of formula Ip₂

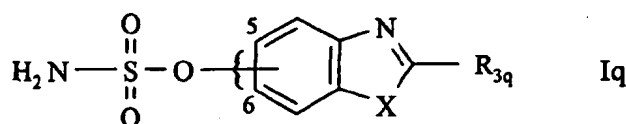


wherein

R_1 and R_2 are as defined above; and
 R_{3p2} is alkyl; alkenyl; alkynyl; cycloalkyl as defined above; cycloalkylalkyl as defined above; adamantylalkenyl, including adamantanylidenealkyl; arylalkyl; arylalkenyl; arylalkynyl; heteroaryl; or heteroarylalkyl;

in free form or salt form.

[0011] A further subgroup is the compounds of formula Iq



wherein X is as defined above and

R_{3q} is:

- (C₁₋₁₃)alkyl;
- (C₁₀₋₁₆)alkenyl;
- cycloalkyl selected from adamantyl and hexahydro-2-5-methano-pentalenyl;
- the cycloalkenyl moiety 7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthren-1-yl;
- an aryl moiety 5,6,7,8-tetrahydronaphthalenyl;
- cycloalkylalkyl selected from adamantylalkyl of 1 to 4 carbon atoms in the alkylene part thereof and dicyclohexylmethyl;
- cycloalkylalkenyl (including cycloalkanylidenealkyl) selected from:

adamantanylidene(C₁₋₄)alkyl; (C₄₋₁₂)cycloalkylidene(C₁₋₄)alkyl;
 bicyclo[3.3.1]nonylidenealkyl; dimethylcyclohexylidenealkyl;
 (C₁₋₄)alkoxycyclohexylidenealkyl; (C₁₋₄)alkylcyclohexylidenealkyl;
 tetra(C₁₋₄)alkylcyclohexylidenealkyl; 1,4-dioxaspiro[4.5]dec-8-ylidenealkyl;
 3,3-dimethyl-1,5-dioxaspiro[5.5]undec-9-ylidenealkyl; and
 octahydronaphthalylidenealkyl;

- cyclohexenyl(C₁₋₄)alkyl;
- arylalkyl selected from di- or triphenyl(C₁₋₄)alkyl;
- (C₁₋₄)alkoxycarbonylamino(C₁₋₆)alkyl;
- hydroxycycloalkylalkyl selected from: (2-hydroxyadamant-2-yl)(C₁₋₆)alkyl;
 (9-hydroxybicyclo[3.3.1]non-9-yl)(C₁₋₄)alkyl; and
 1-hydroxy-2,2-dimethylcyclohexyl(C₁₋₄)alkyl; or
- a cycloalkanylidenealkyl moiety bicyclobutylidenealkyl;

in free form or salt form.

[0012] A compound of the invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a solvated salt.

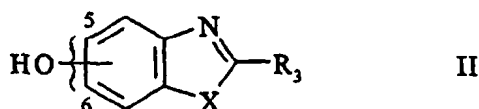
[0013] A salt of a compound of the invention includes a pharmaceutically acceptable salt, e.g. an acid addition salt. A compound of the invention in free form may be converted into a corresponding compound in the form of a salt and vice versa. A compound of the invention in the form of a solvate in free form or salt form may be converted into a corresponding compound in free form or salt form in unsolvated form and vice versa.

[0014] A compound of the invention may exist in the form of isomers and mixtures thereof; e.g. a compound of the invention may contain substituents exhibiting geometric isomerism and/or asymmetrically substituted carbon atoms and may thus exist in the form of isomers and/or diastereoisomers and mixtures thereof. Isomeric mixtures may be separated in conventional manner to obtain pure isomers or diastereoisomers, respectively. The invention includes a compound of the present invention in any isomeric and/or diastereoisomeric pure form and in the form of any isomeric and/or diastereoisomeric mixture.

[0015] The invention further includes a process for the preparation of a compound of the invention as defined above, comprising sulfamoylating a corresponding benzoxa- or benzthiazole substituted in the 2 position and carrying a hydroxy group on the phenyl part of the ring structure.

[0016] More specifically, it concerns a process for the preparation of a compound of formula I as defined above, in free form or salt form, comprising

- a) when R_1 and R_2 are both hydrogen,
sulfamoylating a compound of formula II



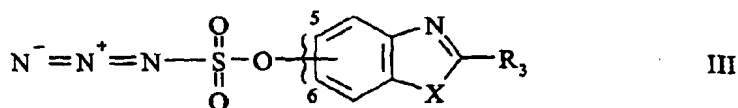
- wherein X and R_3 are as defined above, or
b) when one or both of R_1 and R_2 are other than hydrogen,
appropriately N-substituting a compound of formula I wherein R_1 and R_2 are both hydrogen,

and recovering the resultant compound of formula I in free form or salt form.

[0017] The process of the invention may be effected in conventional manner.

[0018] Process variant a) may be carried out e.g. by reacting a compound of formula II

- a1) with sulfonyl chloride and sodium- or potassium azide, and reducing the azide group to an amino group $-NH_2$ in a resultant compound of formula III



- wherein X and R_3 are as defined above; or
a2) with $Cl-SO_2-NCO$ and submitting the product obtained to aqueous hydrolysis; or
a3) with a compound of formula IV



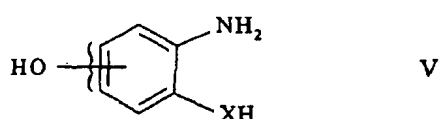
wherein R_1 and R_2 are both hydrogen and L is a leaving group, e.g. halogen, preferably chloro; such as H_2N-SO_2Cl ; e.g. in an inert solvent, e.g. dimethylformamide or dimethylacetamide, with or without addition of an organic base, such as an organic tertiary amine, or an inorganic base, e.g. an alkali(hydrogen)carbonate or alkali hydride, preferably sodium hydride.

[0019] Process variant b) may be effected by N-alkylating, N-acylating or N-alkoxycarbonylating using e.g. for N-alkylation activated alkyl, e.g. alkyl halogenides, such as alkyl iodides, alkyl sulfates or alkyl mesy(tosy)lates; for N-acylation acyl halogenides; and for N-alkoxycarbonylation alkoxycarbonyl halides, preferably chlorides. The reaction is effected conveniently in the presence of a suitable base, preferably an alkali metal carbonate or alkali metal hydride, preferably in an inert, preferably polar solvent such as acetone or dimethylformamide, at temperatures between about -20° and about +120°C, preferably between room temperature and about 60°C.

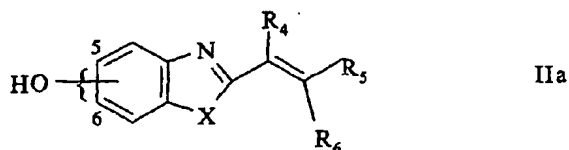
[0020] A resultant compound of the invention may be recovered from the reaction mixture and isolated and purified in conventional manner. Isomers, such as geometric isomers or enantiomers or diastereoisomers, may be obtained in conventional manner, e.g. by fractional crystallization or asymmetric synthesis from corresponding asymmetrically substituted, e.g. optically active starting materials.

[0021] The starting materials may also be prepared in conventional manner. A compound of formula II may e.g. be obtained by

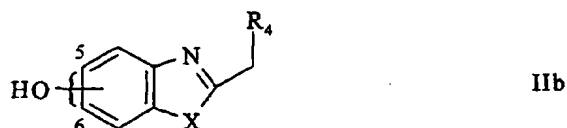
α) reacting a compound of formula V



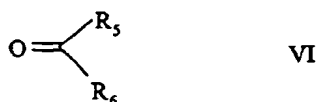
wherein X is as defined above, with a compound of formula $R_3\text{-COHal}$, wherein Hal is halogen, e.g. chloro, and R_3 is as defined above and, if desired, further reacting a resultant compound of formula II with sulfonyl chloride and sodium- or potassium azide to obtain a compound of formula III; or
β) for the production of a compound of formula IIa



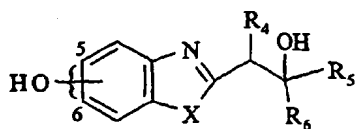
wherein X, R_4 , R_5 and R_6 are as defined above, reacting a compound of formula IIb



wherein R_4 and X are as defined above, with a compound of formula VI



wherein R_5 and R_6 are as defined above, e.g. in the presence of trimethylsilyl chloride (TMSCl), N-ethyldiisopropylamine and sodium bis(trimethylsilyl)amide in an inert solvent, e.g. tetrahydrofuran, at low temperatures, e.g. around -70°C, and dehydrating a resultant compound of formula IIc

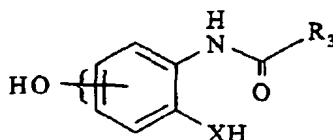


IIc

wherein X, R₄, R₅ and R₆ are as defined above, e.g. by treatment with trifluoroacetic acid in an inert solvent such as toluene.

[0022] Process variant a3) above is also indicated for the preparation of a compound of formula I wherein R₁ and R₂ are hydrogen, X is as defined above and R₃ is a group of formula I as defined above, starting from a corresponding compound of formula IIc and dehydrating a resultant compound of formula I wherein R₃ is hydroxycycloalkylalkyl as described under β) above.

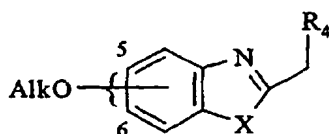
[0023] Alternatively a compound of formula II may be obtained by reaction of a compound of formula V with a compound of formula R₃COOH, conveniently in the presence of propylphosphonic acid anhydride and N-ethyl-diisopropylamine; or 2,2'-dithiopyridine and triphenylphosphane; preferably in an inert solvent, e.g. methylene chloride, and cyclizing a resultant compound of formula VII



VII

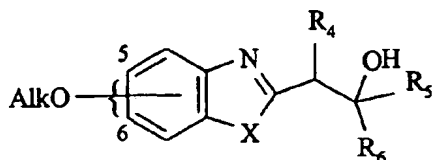
wherein X and R₃ are as defined above, e.g. in the presence of diethylazodicarboxylate and triphenylphosphine in an inert solvent, e.g. tetrahydrofuran, at e.g. room temperature.

[0024] Alternatively a compound of formula IIa may be obtained by reaction of a compound of formula VIII



VIII

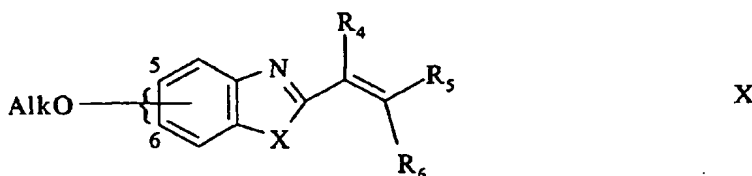
wherein X and R₄ are as defined above and Alk is alkyl, preferably methyl, with a compound of formula VI, e.g. in the presence of butyl lithium in an inert solvent, e.g. tetrahydrofuran, conveniently at low temperatures, such as around -70°C, to obtain a compound of formula IX



IX

wherein Alk, X, R₄, R₅ and R₆ are as defined above; and either

- dealkylating to obtain a compound of formula IIc and then dehydrating, e.g. as described under β) above, to obtain a corresponding compound of formula IIa; or
- dehydrating first, e.g. as described under β) above, to obtain a compound of formula X



10 wherein Alk, X, R₄, R₅ and R₆ are as defined above; and then dealkylating to obtain a corresponding compound of formula IIa, e.g. in the presence of pyridine and HCl, conveniently at high temperatures, such as above about 100°C, e.g. around 200°C.

[0025] Many starting materials and intermediates are either known or can be prepared according to known methods or analogously as described in the Examples.

15 [0026] The compounds of formula IIa, IIc, IX and X in free form or salt form are novel and also form part of the invention.

[0027] The following documents have been cited as background art:

D1: US-A-4'472'418 (Woltersdorf); disclosing 2-sulfamoylbenzothiazol-5,6-sulfamates prepared from corresponding hydroxy derivatives, for treatment of elevated intraocular pressure;

20 D2: WO 99/027935 (Imperial College); disclosing steroid 3-O-sulfamate derivatives as inhibitors of oestrone sulphatase; and

D3: L. Woo et al., *J. Med. Chem.* 41 (1998) 1068-1083; disclosing synthetic routes to various steroidal and non-steroidal inhibitors of steroid sulfatase, e.g. coumarin, tetralone and indanone sulfamates.

25 [0028] The following Examples illustrate the invention. Temperatures are in degrees Celsius. NMR values are for ¹³C-NMR spectra at 62.9 MHz in CDCl₃ unless indicated otherwise. The following abbreviations are used:

DMA = dimethylamide

DMSO = dimethylsulfoxide

30 Ex. = Example

m.p. = melting point.

Example 1: Sulfamic acid 2-(adamantan-1-ylmethyl)benzoxazol-6-yl ester

35 [X = O; R₁ = R₂ = H; R₃ = adamantan-1-ylmethyl; sulfamoyloxy moiety in position 6] [process variant a)]

40 [0029] 74 mg 2,6-di-tert-butyl-4-methylpyridine and 83 mg **amidosulfonyl chloride** are added to a solution of 50 mg **2-(adamantan-1-ylmethyl)benzoxazol-6-ol** (formula II) in 5 ml of a mixture of dichloromethane and dimethylformamide and the mixture obtained is stirred at room temperature for about 2 hours. The solvent is evaporated off and the residue obtained is purified by chromatography on silica gel (cyclohexane/ethyl acetate 2/1). The title compound is obtained (crystals; m.p. 147-150°); ¹³C-NMR: 166.556, 150.344, 147.020, 139.886, 119.423, 118.873, 105.526, 42.977, 42.300, 36.477, 33.977, 28.441.

45 **Examples 1a and 1b: Sulfamic acid 2-[1-(2-hydroxyadamantan-2-yl)pentyl]benzoxazol-6-yl ester and, respectively, sulfamic acid 2-[1-(adamantan-2-ylidene)pentyl]benzoxazol-6-yl ester**

[X = O; R₁ = R₂ = H; R₃ = 1-(2-hydroxyadamantan-2-yl)pentyl and, respectively, 1-(adamantan-2-ylidene)pentyl; sulfamoyloxy moiety in position 6] [process variant a)]

50 [0030] To a solution of 100 mg **2-[1-(2-hydroxyadamantan-2-yl)pentyl]benzoxazol-6-ol** (formula II) in 2 ml of dry DMA is added 100 mg **sulfamoyl chloride** and the reaction mixture is stirred at about 60° for about 30 minutes. To the resultant mixture are added 6 ml of an aqueous sodium acetate solution (13.1 g in 60 ml) and 10 ml of ethyl acetate at room temperature and the mixture is stirred for a few minutes. The two phases formed are separated, the organic phase is washed with sodium acetate solution and brine and dried. From the dried solution the solvent is evaporated off and the residue obtained is purified by chromatography (silica gel; ethylacetate/cyclohexane 1/2). The title **compound of Example 1a, and the title compound of Example 1b**, are obtained as oil; ¹³C-NMR:

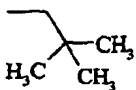
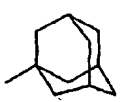
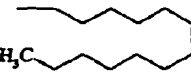
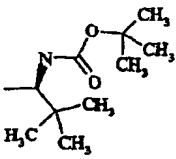
- Example 1a: 170.909, 149.692, 146.899, 139.651, 119.899, 118.934, 105.730, 76.199, 44.068, 38.109, 37.509,


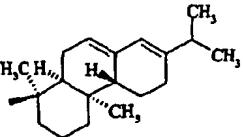
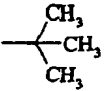
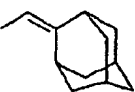

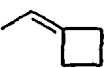




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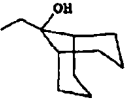
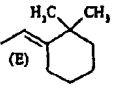
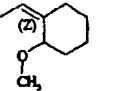
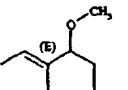
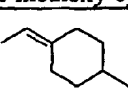
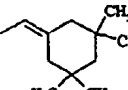
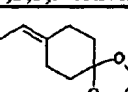
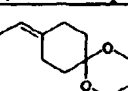
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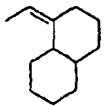
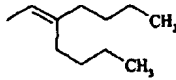
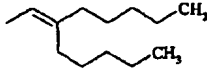

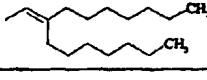
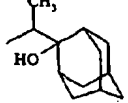
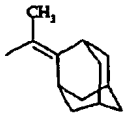
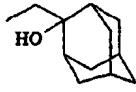
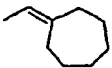

- Example 1b: (125.8 MHz, d_6 -DMSO) 166.091, 158.038, 149.590, 147.630, 119.957, 119.610, 116.214, 105.746, 39.393, 36.636, 35.022, 34.091, 31.971, 29.783, 27.643, 26.799, 22.203.

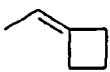
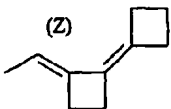
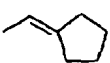
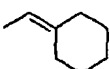




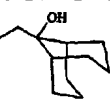
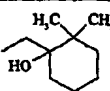
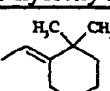
5 [0031] The following compounds of formula I are obtained in analogous manner using appropriate starting materials of formula II:

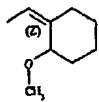
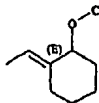
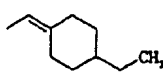
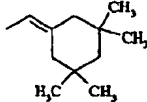
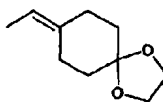
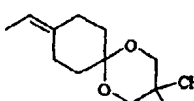
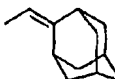
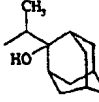
Ex. No.	X	R ₁	R ₂	R ₃	Sulfamoyl-oxy moiety at position	m.p.
2	O	H	H	 2,2-dimethylpropyl	6	140-143°
3	O	H	H	 adamantan-1-yl	6	97-100°
4	O	H	H	 tridecyl	6	99-101°
5	O	H	H	-CH ₂ CH(C ₆ H ₅) ₂ 2,2-diphenylethyl	6	145-148°
6	O	H	H	-CH ₂ C(C ₆ H ₅) ₃ 2,2,2-triphenylethyl	6	160-180°
7	O	H	H	-CH(C ₆ H ₁₁) ₂ dicyclohexylmethyl	6	66-72°
8	O	H	H	 1-tert-butoxycarbonylamino-2,2-dimethylpropyl	6	oil; NMR*

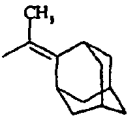
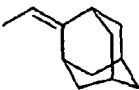
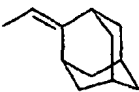
Ex. No.	X	R ₁	R ₂	R ₃	Sulfamoyl-oxy moiety at position	m.p.
9	O	H	H	 hexahydro-2,5-methanopentalen-3a-yl	6	164-166°
10	O	H	H	 7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,5,6,10,10a-decahydrophenanthren-1-yl	6	92-99°
11	O	H	H	 tert-butyl	6	172-174°
12	O	H	H	 adamantan-2-ylidenemethyl	6	170-172°; NMR*
13	O	H	H	 cyclohexylidenemethyl	6	149-152°
14	O	H	H	 cyclobutylidenemethyl	6	129-131°
15	O	H	H	 cyclopentylidenemethyl	6	110-117°
16	O	H	H	 cycloheptylidenemethyl	6	159-161°
17	O	H	H	 cyclododecanylidene-methyl	6	161-174°
18	O	H	H	 bicyclo[3.3.1]non-9-ylidenemethyl	6	161-163°

Ex. No.	X	R ₁	R ₂	R ₃	Sulfamoyl-oxy moiety at position	m.p.
19	O	H	H		6	oil
20	O	H	H		6	oil
21	O	H	H		6	115-117°
22	O	H	H		6	156-159°
23	O	H	H		6	151-153°
24	O	H	H		6	130-135°
25	O	H	H		6	195-199°
26	O	H	H		6	169-172°

Ex. No.	X	R ₁	R ₂	R ₃	Sulfamoyl-oxy moiety at position	m.p.
27	O	H	H	 octahydro-naphthal-1-ylidenemethyl	6	194-195°
28	O	H	H	 2-butylhex-1-ylidene	6	oil; NMR*
29	O	H	H	 2-pentylhept-1-ylidene	6	oil; NMR*
30	O	H	H	 2-hexyloct-1-ylidene	6	oil; NMR*
31	O	H	H	 2-heptylnon-1-ylidene	6	oil; NMR*
32	O	H	H	 1-(2-hydroxy-adamantan-2-yl)ethyl	6	oil
33	O	H	H	 1-(adamantan-2-ylidene)ethyl	6	178-180°
34	O	H	H	 2-hydroxyadamantan-2-ylmethyl	6	oil
35	S	H	H	 cycloheptylidenemethyl	5	oil; NMR*
36	O	H	H	 5,6,7,8-tetrahydronaphthalen-1-yl	6	161-163°

Ex. No.	X	R ₁	R ₂	R ₃	Sulfamoyl-oxy moiety at position	m.p.
37	O	H	H	 cyclobutylidenemethyl	5	180-185°
38	O	H	H	 bicyclobutylidene-(2Z)-ylidenemethyl	5	200°
39	O	H	H	 cyclopentylidenemethyl	5	166-169°
40	O	H	H	 cyclohexylidenemethyl	5	173-176°
41	O	H	H	 cyclohex-1-enylmethyl	5	174-176°
42	O	H	H	 cycloheptylidenemethyl	5	156-159°
43	O	H	H	 cyclododecanylidene-methyl	5	148-152°
44	O	H	H	 bicyclo[3.3.1]non-9-ylidenemethyl	5	175-178°
45	O	H	H	 9-hydroxy-bicyclo[3.3.1]non-9-ylmethyl	5	oil
46	O	H	H	 1-hydroxy-2,2-dimethylcyclohexylmethyl	5	oil
47	O	H	H	 2,2-dimethylcyclohexylidenemethyl	5	163-166°

Ex. No.	X	R ₁	R ₂	R ₃	Sulfamoyl-oxy moiety at position	m.p.
48	O	H	H	 2-methoxycyclohex-(Z)-ylidenemethyl	5	147-150°
49	O	H	H	 2-methoxycyclohex-(E)-ylidenemethyl	5	146-148°
50	O	H	H	 4-ethylcyclohexylidenemethyl	5	161-164°
51	O	H	H	 3,3,5,5-tetramethyl-cyclohexylidenemethyl	5	178-181°
52	O	H	H	 1,4-dioxa-spiro[4.5]dec-8-ylidenemethyl	5	168-170°
53	O	H	H	 3,3-dimethyl-1,5-dioxaspiro[5.5]undec-9-ylidenemethyl	5	145-150°
54	O	H	H	 adamantan-2-ylidenemethyl	5	138-139°
55	O	H	H	 1-(2-hydroxyadamantan-2-yl)ethyl	5	oil

Ex. No.	X	R ₁	R ₂	R ₃	Sulfamoyl-oxy moiety at position	m.p.
56	O	H	H	 1-(adamantan-2-ylidene)ethyl	5	188-190°
57	S	H	H	 adamantan-2-ylidenemethyl	6	oil; NMR*
58	S	H	H	 adamantan-2-ylidenemethyl	5	200-205°

* ¹³C-NMR:

Example 8: 166.745, 155.558, 150.600, 149.648, 147.269, 120.358, 119.394, 105.693, 64.292, 57.866, 35.634, 28.333, 26.318, 14.102.

Example 12: 168.446, 146.658, 140.656, 119.420, 118.622, 105.099, 103.659, 41.770, 40.197, 39.233, 36.789, 33.951, 27.851.

Example 28: (125.8 MHz) 164.389, 160.842, 149.534, 146.796, 140.860, 119.638, 118.531, 110.406, 105.023, 38.294, 32.437, 30.581, 30.030, 22.869, 22.406, 13.866, 13.835.

Example 29: (125.8 MHz) 160.874, 146.784, 140.909, 119.643, 118.522, 110.396, 105.037, 38.574, 32.674, 31.955, 31.506, 28.017, 27.538, 22.460, 22.277, 13.919.

Example 30: (125.8 MHz) 160.924, 146.798, 140.770, 119.592, 118.590, 110.348, 105.036, 38.639, 32.736, 31.575, 29.427, 29.003, 28.333, 27.849, 22.529, 22.496, 14.006, 13.976.

Example 31: (125.8 MHz) 160.870, 146.764, 140.969, 119.653, 118.499, 110.392, 105.021, 38.609, 32.702, 31.736, 29.733, 29.298, 29.050, 28.378, 27.886, 22.614, 14.008.

Example 35: (125.8 MHz, d₆-DMSO) 167.336, 157.635, 154.176, 149.395, 132.640, 130.962, 123.041, 120.036, 118.927, 115.893.

Example 57: (d₆-DMSO) 165.887, 162.639, 151.553, 147.166, 134.719, 122.842, 121.308, 115.533, 110.953, 40.749, 38.615, 36.358, 33.594, 27.502.

[0032] Starting materials and intermediates may be obtained as follows:

A) 2-(Adamantan-1-ylmethyl)benzoxazol-6-ol (formula II)

[0033] To a mixture of 424 mg 2-(adamantan-1-yl)-N-(2,4-dihydroxyphenyl)acetamide (formula VII) and 1.18 g triphenylphosphane in 15 ml of dry tetrahydrofuran, 0.7 ml of diethyl azodicarboxylate (DEAD) are added dropwise.

The mixture is stirred overnight at room temperature, the solvent evaporated off and the residue purified by chromatography. The **title compound** is obtained (m.p. 247-251°).

B) 2-tert-Butyl-benzoxazol-6-ol (formula II)

[0034] A mixture of 1.01 ml of **pivaloyl chloride**, 808 mg **2,4-dihydroxyaniline** hydrochloride (formula V) and 0.4 ml of pyridine is heated at about 210° for about 18 hours. The mixture obtained is dispersed in a mixture of cyclohexane and ethyl acetate and purified by chromatography. The **title compound** is obtained (m.p. 204-210°).

C) 2-(Adamantan-2-ylidenemethyl)benzoxazol-6-ol (formula IIa) and 2-(2-hydroxyadamantan-2-ylmethyl)benzoxazol-6-ol (formula IIc)

[0035] To a solution of 6.6 g **2-methyl-benzoxazol-6-ol** (formula IIb) in 100 ml of dry tetrahydrofuran, cooled to 0°, N-ethyl-diisopropylamine and trimethylsilyl chloride are added. The mixture is stirred at room temperature for about 2 hours, cooled to -78°, and **sodium bis(trimethylsilyl)amide** solution is added in portions. To the mixture obtained solid **2-adamantanone** (formula VI) is added and the mixture is kept at -78° for about one hour. The reaction mixture is allowed to warm up to room temperature and is poured into 300 ml of 1 M NaHSO₄ solution. The mixture is extracted with ethyl acetate and the organic layer is dried over sodium sulfate. The solvent is evaporated off and the residue is purified by chromatography. The above **title compounds** are obtained (m.p., respectively, 248-253° and 238-240°).

[0036] Alternatively, in order to maximize the yield of the first title compound above, the evaporation residue obtained is treated with 240 ml of toluene, 3.1 ml of trifluoroacetic acid are added, and the reaction mixture is heated at about 115° for about 7 hours and cooled. Crystallization occurs. The first title compound above is obtained in the form of a crystalline salt with trifluoroacetic acid. This is recrystallized in ethanol. The compound in free form is obtained (m.p. 248-253°).

D) 2-(Adamantan-2-ylidenemethyl)benzothiazol-5-ol (formula IIa)

[0037] 300 mg **2-(5-methoxy-benzothiazol-2-ylmethyl)adamantan-2-ol** (formula IX) and 527 mg pyridine hydrochloride are heated at about 200° for about 30 minutes. The melt obtained is dissolved in 100 ml of ethyl acetate, the mixture is extracted with water, 2.5 M sodium acetate solution and brine, the organic phase dried and the solvent evaporated off. The evaporation residue obtained is subjected to chromatography. The **title compound** is obtained (m.p. 156-158 °).

E) 2-(Cycloheptylidenemethyl)benzothiazol-5-ol (formula IIa)

[0038] By reacting 120 mg **2-(cycloheptylidenemethyl)-5-methoxybenzothiazole** (formula X) as described under D) above, the title compound is obtained (m.p. 105-120°).

[0039] Analogously as described under A) to E) above and using appropriate starting materials, the following compounds of formula II are obtained:

- **2-(2,2-Dimethylpropyl)benzoxazol-6-ol** (m.p. 176-184°);
- **2-(Adamantan-1-yl)benzoxazol-6-ol** (m.p. 260-265°);
- **2-Tridecyl-benzoxazol-6-ol** (m.p. 72-73°);
- **2-(2,2-Diphenylethyl)benzoxazol-6-ol** (m.p. 182-206°);
- **2-(2,2,2-Triphenylethyl)benzoxazol-6-ol** (m.p. 150-155°);
- **2-Dicycloheptylmethyl-benzoxazol-6-ol** (m.p. 196-204°);
- **[1-(6-Hydroxy-benzoxazol-2-yl)-2,2-dimethylpropyl]carbamic acid tert-butyl ester** (m.p. 131-160°);
- **2-(Hexahydro-2,5-methano-pentalen-3a-yl)benzoxazol-6-ol** (m.p. 241-243°);
- **2-(7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthren-1-yl)benzoxazol-6-ol** (m.p. 90-95°);
- **2-(Cyclohexylidenemethyl)benzoxazol-6-ol** (m.p. 158-162°);
- **2-(Cyclobutylidenemethyl)benzoxazol-6-ol** (m.p. 200-203°);
- **2-(Cyclopentylidenemethyl)benzoxazol-6-ol** (m.p. 168-172°);
- **2-(Cycloheptylidenemethyl)benzoxazol-6-ol** (m.p. 141-142°);
- **2-(Cyclododecanylidenemethyl)benzoxazol-6-ol** (m.p. 155-157°);
- **2-(Bicyclo[3.3.1]non-9-ylidenemethyl)benzoxazol-6-ol** (m.p. 221-223°);
- **2-(9-Hydroxy-bicyclo[3.3.1]non-9-ylmethyl)benzoxazol-6-ol** (m.p. 221-223°);
- **2-(2,2-Dimethyl-cyclohexylidenemethyl)benzoxazol-6-ol** (¹³C-13-NMR [CDCl₃/CD₃OD]: 163.552, 162.497,

154.865, 150.599, 134.691, 119.197, 112.951, 106.621, 97.295, 41.928, 38.100, 27.979, 27.915, 26.931, 22.141);

- 2-(2-Methoxy-cyclohex-(Z)-ylidenemethyl)benzoxazol-6-ol (m.p. 157-160°);
- 2-(2-Methoxy-cyclohex-(E)-ylidenemethyl)benzoxazol-6-ol (m.p. 148-150°);
- 2-(4-Ethylcyclohexylidenemethyl)benzoxazol-6-ol (m.p. 137-139°);
- 5 - 2-(3,3,5,5-Tetramethylcyclohexylidenemethyl)benzoxazol-6-ol (m.p. 161-163°);
- 2-(1,4-Dioxo-spiro[4.5]dec-8-ylidenemethyl)benzoxazol-6-ol (m.p. 154-156°);
- 2-(3,3-Dimethyl-1,5-dioxo-spiro[5.5]undec-9-ylidenemethyl)benzoxazol-6-ol (m.p. 194-196°);
- 2-[Octahydronaphthal-1-ylidenemethyl]benzoxazol-6-ol (m.p. 160-162°);
- 2-(2-Butylhex-1-ylidene)benzoxazol-6-ol (m.p. 76-80°);
- 10 - 2-(2-Pentylhept-1-ylidene)benzoxazol-6-ol : (¹³C-NMR [CDCl₃/CD₃OD]: 162.626, 158.774, 156.116, 151.451, 134.282, 119.369, 113.678, 111.164, 97.619, 39.046, 32.974, 32.458, 32.018, 28.723, 28.150, 22.974, 22.857, 14.188);
- 2-(2-Hexyloct-1-ylidene)benzoxazol-6-ol (¹³C-NMR [CDCl₃/CD₃OD; 125.8 MHz]: 162.307, 158.269, 154.347, 150.785, 135.067, 119.352, 113.021, 110.771, 97.518, 38.504, 32.597, 31.645, 31.576, 29.409, 28.981, 28.410, 27.883, 22.511, 13.979);
- 15 - 2-(2-Heptylnon-1,2-ylidene)benzoxazol-6-ol (¹³C-NMR [CDCl₃/CD₃OD]: 162.640, 158.877, 156.143, 151.466, 134.266, 119.355, 113.694, 111.165, 97.638, 39.091, 33.033, 32.283, 30.194, 29.800, 29.643, 29.563, 29.475, 28.495, 23.106, 14.256);
- 2-[1-(2-Hydroxyadamantan-2-yl)ethyl]benzoxazol-6-ol: (¹³C-NMR [CDCl₃/CD₃OD]: 119.169, 112.873, 97.4021, 38.110, 37.333, 36.660, 34.264, 33.568, 33.126, 32.878, 32.681, 26.978, 12.195);
- 20 - 2-(1-Adamantan-2-ylidene-ethyl)benzoxazol-6-ol (oil);
- 2-[1-(2-Hydroxyadamantan-2-yl)pentyl]benzoxazol-6-ol (¹³C-NMR: 119.037, 113.029, 97.790, 31.204, 28.435, 26.423, 22.184, 13.797);
- 2-(1-Adamantan-2-ylidene-pentyl)benzoxazol-6-ol (oil);
- 25 - 2-(5,6,7,8-Tetrahydronaphthalin-1-yl)benzoxazol-6-ol (m.p. 120-122°);
- 2-(Cyclobutylidenemethyl)benzoxazol-5-ol (m.p. 169-170°);
- 2-(Bicyclobutylidene-(2E)-ylidenemethyl)benzoxazol-5-ol (oil);
- 2-(Cyclopentylidenemethyl)benzoxazol-5-ol (m.p. 174-175°);
- 2-(Cyclohexylidenemethyl)benzoxazol-5-ol (m.p. 144-145°);
- 30 - 2-(Cyclohex-1-enylmethyl)benzoxazol-5-ol (oil);
- 2-(Cycloheptylidenemethyl)benzoxazol-5-ol (m.p. 93-95°);
- 2-(Cyclododecanylidenemethyl)benzoxazol-5-ol (m.p. 170-172°);
- 2-(Bicyclo[3.3.1]non-9-ylidenemethyl)benzoxazol-5-ol (m.p. 177-178°);
- 2-(9-Hydroxy-bicyclo[3.3.1]non-9-ylmethyl)benzoxazol-5-ol (m.p. 218-219°);
- 35 - 2-(1-Hydroxy-2,2-dimethylcyclohexylmethyl)benzoxazol-5-ol (m.p. 166-168°);
- 2-(2,2-Dimethylcyclohexylidenemethyl)benzoxazol-5-ol (oil);
- 2-(2-Methoxycyclohex-(Z)-ylidenemethyl)benzoxazol-5-ol (¹³C-NMR; 125.8 MHz: 162.709, 155.743, 153.888, 144.335, 142.170, 113.849, 112.059, 110.422, 105.244, 73.709, 55.602, 33.297, 32.882, 28.577, 20.122);
- 2-(2-Methoxycyclohex-(E)-ylidenemethyl)benzoxazol-5-ol (m.p. 141-144°);
- 40 - 2-(4-Ethylcyclohexylidenemethyl)benzoxazol-5-ol (¹³C-NMR [CDCl₃/CD₃OD]: 165.203, 160.259, 155.998, 145.294, 142.867, 114.835, 111.739, 109.631, 105.497, 40.269, 38.948, 35.672, 34.921, 31.423, 30.305, 12.672);
- 2-(3,3,5,5-Tetramethylcyclohexylidenemethyl)benzoxazol-5-ol (m.p. 138-139°);
- 2-(1,4-Dioxo-spiro[4.5]dec-8-ylidenemethyl)benzoxazol-5-ol (m.p. 160-162°);
- 2-(3,3-Dimethyl-1,5-dioxo-spiro[5.5]undec-9-ylidenemethyl)benzoxazol-5-ol; (m.p. 137-140°);
- 45 - 2-(Adamantan-2-ylidenemethyl)benzoxazol-5-ol (m.p. 160-162°);
- 2-[1-(2-Hydroxyadamantan-2-yl)ethyl]benzoxazol-5-ol (m.p. 125-130°);
- 2-(1-Adamantan-2-ylidene-ethyl)benzoxazol-5-ol (oil); and
- 2-(Adamantan-2-ylidenemethyl)benzthiazol-6-ol (m.p. 289-293°).

50 F) 2-(Adamantan-1-yl)-N-(2,4-dihydroxy-phenyl)acetamide (formula VII)

[0040] 1.05 ml of N-ethyl-diisopropylamine is added to a solution of 323 mg **2,4-dihydroxyaniline** hydrochloride (formula V), 388 mg (adamantan-1-yl)acetic acid (formula R₃COOH) and 1.2 ml of propylphosphonic anhydride (50 % in ethyl acetate) in 20 ml of dry dichloromethane at 0°. The mixture obtained is stirred for about 18 hours at room temperature and the solvent is evaporated off. The residue is dissolved in 50 ml of ethyl acetate and extracted with 1 M aqueous hydrochloric acid, saturated aqueous NaHCO₃ solution and brine. The organic layer is dried and the solvent is evaporated off. The **title compound** is obtained (m.p. 195-197°).

G) 2-(Adamantan-2-ylidene)-N-(2,4-dihydroxyphenyl)acetamide (formula VII)

[0041] 3.0 g (adamantan-2-ylidene)acetic acid (formula R_3COOH), 5.91 g triphenylphosphane and 4.95 g dipyridyldisulfide, dissolved in 100 ml of dichloromethane, are stirred at room temperature overnight. To the mixture obtained, 5.13 ml of N-ethyl-diisopropylamine and 4.83 g 2,4-dihydroxyaniline hydrochloride (formula V) are added and the mixture is stirred for about 24 hours, the solvent is evaporated off, the evaporation residue is dissolved in ethyl acetate and extracted with a saturated aqueous NaH_2PO_4 solution and brine. The organic layer is dried, the solvent is evaporated off and the residue is purified by chromatography. The **title compound** is obtained (m.p. 166-169°).

[0042] The following compounds of formula VII are obtained in analogous manner as described under F) and G) above:

- N-(2,4-Dihydroxyphenyl)-3,3-dimethyl-butyramide: [1H -NMR ($CDCl_3$): 7.41 (s, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.49 (d, J = 2.7 Hz, 1H), 6.34 (dd, J = 2.7 + 8.5 Hz, 1H), 2.29 (s, 2H), 1.10 (s, 9H)];
- Adamantane-1-carboxylic acid (2,4-dihydroxyphenyl)amide (m.p. 108-110°);
- Tetradecanoic acid (2,4-dihydroxyphenyl)amide (m.p. 110-112°);
- N-(2,4-Dihydroxyphenyl)-3,3-diphenyl-propionamide (m.p. 206-208°);
- N-(2,4-Dihydroxyphenyl)-3,3,3-triphenyl-propionamide (m.p. 234-235°);
- 2,2-Dicyclohexyl-N-(2,4-dihydroxyphenyl)acetamide (m.p. 179-181°);
- [1-(2,4-Dihydroxy-phenylcarbonyl)-2,2-dimethylpropyl]carbamic acid tert.-butyl ester (m.p. 88-91°);
- Hexahydro-2,5-methano-pentalene-3a-carboxylic acid (2,4-dihydroxyphenyl)amide (m.p. 204-206°);
- 7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,5,6,10,10a-decahydrophenanthren-1-carboxylic acid (2,4-dihydroxyphenyl)amide (m.p. 200-207°);
- 2-Cyclohexylidene-N-(2,4-dihydroxyphenyl)acetamide [1H -NMR ($CDCl_3$): 6.85 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 2.7 Hz, 1H), 6.27 (dd, J = 2.7 + 8.6 Hz, 1H), 5.69 (s, 1H), 2.82 (bm, 2H), 2.16 (bm, 2H), 1.60 (s, 6H)]; and
- 5,6,7,8-Tetrahydronaphthalene-1-carboxylic acid (2,4-dihydroxyphenyl)-amide (m.p. 168-174°).

H) 2-(Cycloheptan-2-ylidenemethyl)-5-methoxy-benzothiazole (formula X)

[0043] 187 μ l of methansulfonyl chloride are added to a mixture of 350 mg of 2-(5-methoxybenzothiazol-2-ylmethyl)cycloheptan-2-ol (formula IX), 665 μ l of triethylamine and a catalytical amount of 4-N,N-dimethylaminopyridine in 12 ml of dry dichloromethane at about 0°. The mixture is stirred for about 12 hours at room temperature, 187 μ l of methansulfonyl chloride and 665 μ l of triethylamine are added and the resultant reaction mixture is stirred at about 40° for about 48 hours. The mixture is diluted with 100 ml of ethyl acetate and then extracted with 1 M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution and brine. The organic phase is dried and the solvent is evaporated off. The residue is subjected to chromatography. The **title compound** is obtained [^{13}C -NMR (125.8 MHz): 166.528, 158.978, 155.645, 154.597, 126.878, 121.337, 119.750, 114.743, 105.127, 55.561, 39.394, 33.143, 29.921, 29.344, 28.775, 26.435].

I) 2-(5-Methoxybenzothiazol-2-ylmethyl)adamantan-2-ol (formula IX)

[0044] 2.5 ml of a 1.6 M n-butyllithium solution in hexane are added dropwise to a solution of 358 mg of 5-methoxy-2-methylbenzothiazole (formula VIII) in 5 ml of dry THF, cooled to about -78° and the mixture obtained is stirred for about one hour. Solid 2-adamantanone (formula VI) is added and the mixture is kept at -78° for about one hour. The mixture is allowed to warm to room temperature and 400 μ l of acetic acid are added. The resultant mixture is diluted with 60 ml of ethyl acetate and extracted with saturated NaH_2PO_4 solution. The solvent of the organic phase is evaporated off and the residue obtained is subjected to chromatography. The **title compound** is obtained (m.p. 140-142°).

[0045] The following compounds of formula IX are obtained in analogous manner as described under I) above:

- 2-(5-Methoxy-benzothiazol-2-ylmethyl)cycloheptan-2-ol [^{13}C -NMR (125.8 MHz): 169.841, 159.007, 154.324, 121.540, 115.095, 105.275, 75.529, 55.605, 46.163, 41.063, 29.655, 22.300]; and
- 2-(6-Methoxy-benzothiazol-2-ylmethyl)adamantan-2-ol (m.p. 161-163°).

[0046] The compounds of the invention, in particular the compounds of formula I, in free form or pharmaceutically acceptable salt form, including as solvates, hereinafter briefly named "the agents of the invention", possess pharmacological activity. They are indicated for use as pharmaceuticals. In particular, they inhibit steroid sulfatase activity.

[0047] Steroidal hormones in particular tissues are associated with several diseases, such as tumors of the breast, endometrium and prostate. Important precursors for the local production of these steroid hormones are steroid 3-O-sulfates which are desulfated by the enzyme steroid sulfatase in the target tissues. Inhibition of this enzyme results in

therapeutically relevant, reduced local levels of the corresponding active steroidal hormones. Furthermore, steroid sulfatase inhibitors may also be immunosuppressive, and enhance memory when delivered to the brain.

[0048] The agents of the invention reduce endogenous levels of androgens and/or estrogens in skin and are thus particularly indicated for use in the prevention or treatment of androgen-dependent disorders of the pilosebaceous unit, such as acne, seborrhea, androgenic alopecia and hirsutism, and in the topical treatment of squamous cell carcinoma.

[0049] The agents of the invention are therefore indicated for use as steroid sulfatase inhibitors, particularly in the prevention and treatment of illnesses responsive to steroid sulfatase inhibition, such as illnesses in which the steroid products of sulfatase cleavage play a role, in particular in the prevention and treatment of the following specific conditions: androgen-dependent disorders of the pilosebaceous unit such as acne, seborrhea, androgenic alopecia and hirsutism; cancer, especially estrogen- and androgen-dependent tumors such as tumors of the breast, endometrium and prostate, and squamous cell carcinoma; inflammatory and autoimmune diseases such as rheumatoid arthritis, type I and II diabetes, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, thyroiditis, vasculitis, ulcerative colitis and Crohn's disease; skin disorders such as psoriasis, eczema and contact dermatitis; graft versus host disease; asthma; organ rejection following transplantation; and for enhancement of cognitive function, as in senile dementia, including Alzheimer's disease, by increasing DHEAS (dehydroepiandrosterone) levels in the central nervous system.

[0050] The above activities can be shown e.g. in the following assays:

1. Steroid sulfatase inhibition in vitro:

[0051] Human steroid sulfatase is obtained in pure form as described in WO 99/52890 and the assay is effected as follows:

[0052] Purified human steroid sulfatase not only is capable of cleaving steroid sulfates, but also readily cleaves aryl sulfates, such as p-nitrocatechol sulfate which is used herein. Assay mixtures are prepared by consecutively dispensing the following solutions into the wells of flat-bottom microtiter plates:

- 1) 50 μ l inhibitor dilution in buffer (= 0.1 M Tris-HCl, pH 7.5, 0.1 % Triton X-100);
- 2) 50 μ l substrate (= 20 mM p-nitrocatechol sulfate in buffer)
- 3) 50 μ l enzyme dilution to give a final concentration of 75 nM steroid sulfatase.

[0053] Plates are incubated at 37°C for 30 minutes. The assay is stopped by addition of 100 μ l of 1 N NaOH, and optical density measured in a microplate reader at 492 nm. Compounds are added from stock solutions in ethanol; the final ethanol concentration does not exceed 0.1 %. IC₅₀ values are calculated by nonlinear regression of the concentration/optical density data using the program Grafit (Erithacus Ltd.). Reported values are the result of three determinations.

[0054] From the fluorescence intensity data (I) obtained at different concentrations (c) of the test compound, the concentration inhibiting the enzymatic activity by 50 % (IC₅₀) is calculated using the equation

$$I = \frac{I_{100}}{1 + (c/IC_{50})^s}$$

wherein I₁₀₀ is the intensity observed in the absence of inhibitor and s is the slope factor.

[0055] Estrone-3-O-sulfamate serves as reference compound and its IC₅₀ value is determined in parallel to the test compounds and is about 60 nM. Relative IC₅₀ values (rel IC₅₀) are defined as follows:

$$\text{rel IC}_{50} = \frac{\text{IC}_{50} \text{ of test compound}}{\text{IC}_{50} \text{ of estrone sulfamate}}$$

[0056] The agents of the invention inhibit steroid sulfatase in this assay with rel IC₅₀ values in the range of about 0.1 to 30.

2. Steroid sulfatase inhibition in the CHO/STS assay:

[0057] CHO cells stably transfected with human steroid sulfatase (CHO/STS) are seeded into microtiter plates. After reaching approximately 90% confluency, they are incubated overnight with graded concentrations of test substances.

They are then fixed with 4 % paraformaldehyde for 10 minutes at room temperature and washed 4 times with PBS before incubation with 100 μ l/well 0.5 mM 4-methylumbelliferyl sulfate (MUS) dissolved in 0.1M Tris-HCl, pH 7.5. The enzyme reaction is carried out at 37°C for one hour. Then 50 μ l/well stop solution (1M Tris-HCl, pH 10.4) are added. The enzyme reaction solutions are transferred to white plates (Microfluor, Dynex, Chantilly, VA, USA) and read in a Fluoroskan II fluorescence microtiter plate reader. Reagent blanks are subtracted from all values. For drug testing, the fluorescence units (FU) are divided by the optical density readings after staining cellular protein with sulforhodamine B (OD₅₅₀) in order to correct for variations in cell number. IC₅₀ values are determined by linear interpolation between two bracketing points. In each assay with inhibitors, estrone 3-O-sulfamate is run as a reference compound, and the IC₅₀ values are normalized to estrone 3-O-sulfamate:

$$\text{relative IC}_{50} = \text{IC}_{50} \text{ compound} / \text{IC}_{50} \text{ estrone 3-O-sulfamate.}$$

[0058] In this assay the agents of the invention inhibit steroid sulfatase with rel IC₅₀ values in the range 0.8 - 165, corresponding to absolute IC₅₀ values in the range 32 nM to 7800 nM.

[0059] For the above use in steroid sulfatase inhibition the dosage to be used will vary, of course, depending e.g. on the particular agent employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the agents are administered at a daily dose of from about 0.1 mg/kg to about 100 mg/kg animal body weight, conveniently given in divided doses two to four times daily. For most large mammals the total daily dosage is from about 5 mg to about 5000 mg, conveniently administered, for example, in divided doses up to four times a day or in retarded form. Unit dosage forms comprise, e.g. from about 1.25 mg to about 2000 mg of the agents in admixture with at least one solid or liquid pharmaceutically acceptable carrier or diluent.

[0060] The agents of the invention may be administered in similar manner to known standards for use in such indications. The agents of the invention may be admixed with conventional, chemotherapeutically acceptable carriers and diluents and optionally further excipients, and administered e.g. orally e.g. in the form of formulations, e.g. in the form of tablets and capsules.

[0061] Alternatively, the agents may be administered topically, e.g. in the form of formulations, e.g. lotions, solutions, ointments or creams; or parenterally or intravenously. The concentration of active substance will of course vary, e.g. depending on the agent employed, the treatment desired and the nature of the form or formulation used. In general, satisfactory results are obtained in e.g. topical formulations at concentrations of from about 0.05 % to about 5 %, particularly from about 0.1 % to about 1 % by weight.

[0062] The invention therefore also provides:

- an agent of the invention for use as a pharmaceutical, especially as a steroid sulfatase inhibitor;
- a pharmaceutical composition comprising an agent of the invention together with at least one pharmaceutically acceptable carrier or diluent;
- a process for the preparation of a pharmaceutical composition having an agent of the invention together with at least one pharmaceutically acceptable carrier or diluent, comprising mixing an agent of the invention together with at least one pharmaceutically acceptable carrier or diluent; and
- the use of an agent of the invention in the preparation of a medicament for prevention or treatment of illnesses responsive to steroid sulfatase inhibition.

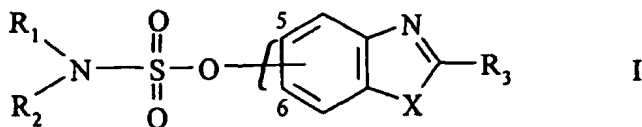
[0063] The invention includes the agents of the invention for use in particular in the prevention or treatment of androgen-dependent disorders of the pilosebaceous unit, such as acne, seborrhea, androgenic alopecia and hirsutism, and in the topical treatment of squamous cell carcinoma, as well as for use in enhancement of cognitive function.

[0064] The agents of the invention are particularly beneficial as regards side effect profile and chemical stability and thus well-suited for e.g. long term storage of topical galenical forms.

[0065] The compound of Example 12, namely sulfamic acid 2-(adamantan-2-ylidenemethyl)benzoxazol-6-yl ester, is the most preferred agent of the invention in the above indications. It has, for example, been determined that in the above assay 1., this agent has a rel IC₅₀ value of 4.6 and an absolute IC₅₀ value of about 0.97 μ M, and in the above assay 2., a rel IC₅₀ value of 1.25.

Claims

1. A compound of formula I

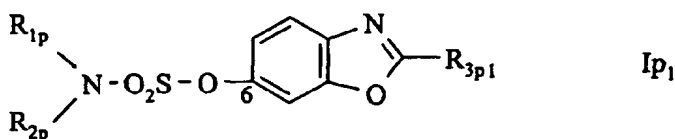


10 wherein

X is O or S;
 R₁ and R₂ either independently are hydrogen or alkyl, or one is hydrogen and the other is acyl or alkoxycarbonyl;
 and
 R₃ is alkyl; alkenyl; alkynyl; cycloalkyl selected from adamantyl and hexahydro-2,5-methanopentalenyl; cycloalkenyl; aryl; cycloalkylalkyl selected from adamantylalkyl of 1 to 4 carbon atoms in the alkylene part thereof and dicyclohexylmethyl; cycloalkylalkenyl (including cycloalkanylidenealkyl) selected from adamantanylidene(C₁₋₄)alkyl, (C₄₋₁₂)cycloalkylidene(C₁₋₄)alkyl, bicyclo[3.3.1]nonylidenemethyl, dimethylcyclohexylidenemethyl, (C₁₋₄)alkoxycyclohexylidenemethyl, (C₁₋₄)alkylcyclohexylidenemethyl, tetra(C₁₋₄)alkylcyclohexylidenemethyl, 1,4-dioxaspiro[4.5]dec-8-ylidenemethyl, 3,3-dimethyl-1,5-dioxaspiro[5.5]undec-9-ylidenemethyl and octahydronaphthalylidenemethyl; cycloalkenylalkyl; arylalkyl; arylalkenyl; arylalkynyl; alkoxycarbonylaminoalkyl; hydroxycycloalkylalkyl; cycloalkanylidenealkyl; heteroaryl; or heteroarylalkyl;

25 in free form or salt form.

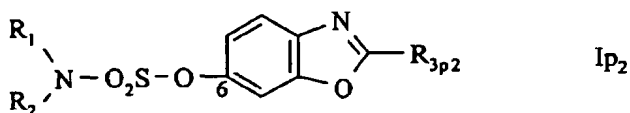
2. A compound according to claim 1 or 2 of formula Ip₁



35 wherein either

R_{1p} and R_{2p} have the significances indicated in claim 1 for R₁ and R₂; and
 R_{3p1} is alkyl; alkenyl; alkynyl; cycloalkyl as defined in claim 1; cycloalkylalkyl as defined in claim 1; arylalkyl; arylalkenyl; arylalkynyl; heteroaryl; or heteroarylalkyl; or
 R_{1p} and R_{2p} are hydrogen; and
 R_{3p1} is adamantan-2-ylidenemethyl; or

45 of formula Ip₂



wherein

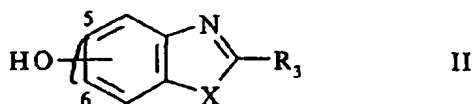
R₁ and R₂ are as defined in claim 1; and
 R_{3p2} is alkyl; alkenyl; alkynyl; cycloalkyl as defined in claim 1; cycloalkylalkyl as defined in claim 1; adamantylalkenyl, including adamantanylidenealkyl; arylalkyl; arylalkenyl; arylalkynyl; heteroaryl; or heteroarylalkyl;

in free form or salt form.

3. Sulfamic acid 2-(adamantan-2-ylidenemethyl)benzoxazol-6-yl ester in free form or salt form according to claim 1.

4. A process for the preparation of a compound according to claim 1 in free form or salt form, comprising

a) when R_1 and R_2 are both hydrogen,
sulfamoylating a compound a formula II

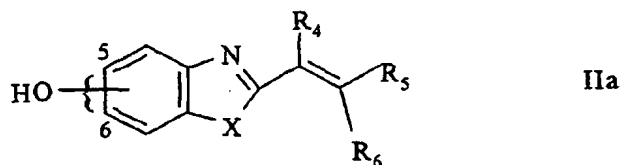


wherein X and R_3 are as defined in claim 1, or

b) when one or both of R_1 and R_2 are other than hydrogen,
appropriately N-substituting a compound of formula I wherein R_1 and R_2 are both hydrogen,

and recovering the resultant compound in free form or salt form.

5. A compound of formula IIa



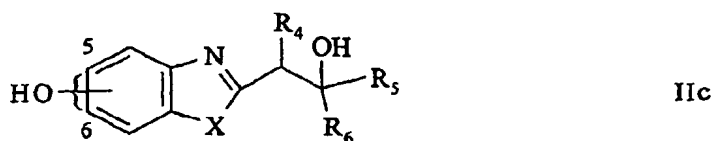
wherein

X is as defined in claim 1;

R_4 is hydrogen or alkyl; and

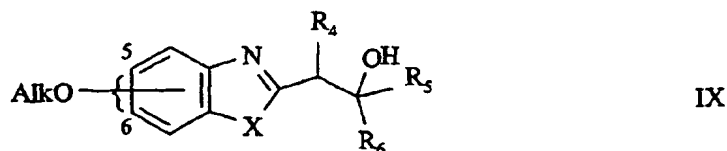
R_5 and R_6 together with the carbon atom to which they are attached form cycloalkyl;

or of formula IIc



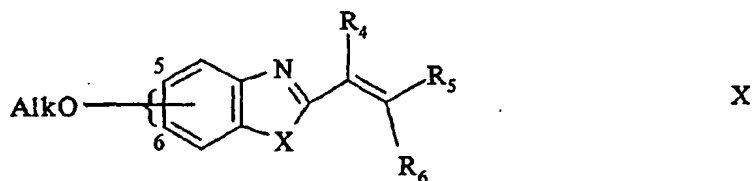
wherein X is as defined in claim 1 and R_4 , R_5 and R_6 are as defined in this claim;

or of formula IX



wherein X is as defined in claim 1, Alk is alkyl and R_4 , R_5 and R_6 are as defined in this claim;

or of formula X



10 wherein X is as defined in claim 1 and Alk, R₄, R₅ and R₆ are as defined in this claim;
in free form or salt form.

6. A compound according to claim 1 in free form or pharmaceutically acceptable salt form for use as a pharmaceutical.

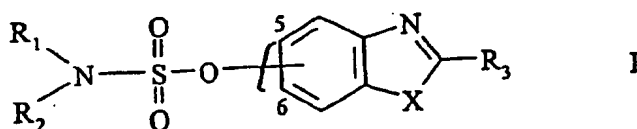
15 7. A pharmaceutical composition comprising a compound according to claim 1 in free form or pharmaceutically acceptable salt form together with at least one pharmaceutically acceptable carrier or diluent.

8. A process for the preparation of a pharmaceutical composition comprising mixing a compound according to claim 1 in free form or pharmaceutically acceptable salt form together with at least one pharmaceutically acceptable carrier or diluent.

20

Patentansprüche

25 1. Verbindung der Formel I



35 worin

X für O oder S steht,

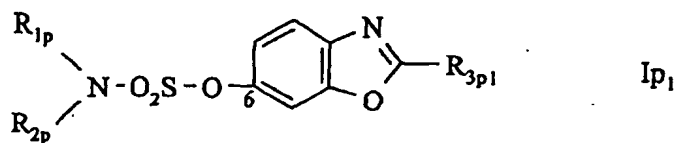
40 R₁ und R₂ entweder unabhängig für Wasserstoff oder Alkyl stehen oder einer dieser Reste für Wasserstoff steht und der andere für Acyl oder Alkoxycarbonyl steht, und

R₃ steht für Alkyl, Alkenyl, Alkynyl, Cycloalkyl ausgewählt aus Adamantyl und Hexahydro-2,5-methanopentalenyl, für Cycloalkenyl, Aryl, Cycloalkylalkyl ausgewählt aus Adamantylalkyl mit 1 bis 4 Kohlenstoffatomen im Alkylenteil hiervon und Dicyclohexylmethyl, für Cycloalkylalkenyl unter Einschluss von Cycloalkanylidenalkyl ausgewählt aus Adamantyliden(C₁-C₄)alkyl, (C₄-C₁₂)Cycloalkyliden(C₁-C₄)alkyl, Bicyclo[3.3.1]nonylidenmethyl, Dimethylcyclohexylidenmethyl, (C₁-C₄)Alkoxycyclohexylidenmethyl, (C₁-C₄)Alkylcyclohexylidenmethyl, Tetra(C₁-C₄)alkylcyclohexylidenmethyl, 1,4-Dioxaspiro[4.5]dec-8-ylidenmethyl, 3,3-Dimethyl-1,5-dioxaspiro[5.5]undec-9-ylidenmethyl und Octahydronaphthalylidenmethyl, für Cycloalkenylalkyl, Arylalkyl, Arylalkenyl, Arylalkynyl, Alkoxycarbonylaminoalkyl, Hydroxycycloalkylalkyl, Cycloalkanylidenalkyl, Heteroaryl oder Heteroarylalkyl,

50

in freier Form oder in Form eines Salzes.

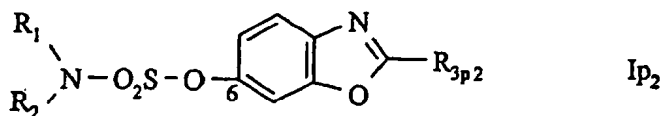
55 2. Verbindung nach Anspruch 1 oder 2 der Formel Ip₁



10 worin entweder

R_{1p} und R_{2p} p die im Anspruch 1 für R₁ oder R₂ angegebenen Bedeutungen haben und
 R_{3p1} steht für Alkyl, Alkenyl, Alkynyl, Cycloalkyl gemäß Definition von Anspruch 1, Cycloalkylalkyl gemäß
 Definition von Anspruch 1, Arylalkyl, Arylalkenyl, Arylalkynyl, Heteroaryl oder Heteroarylalkyl, oder
 R_{1p} und R_{2p} für Wasserstoff stehen und
 R_{3p1} für Adamantan-2-ylidenmethyl steht, oder

15 der Formel Ip₂

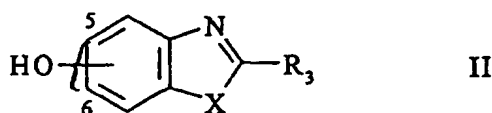


worin

R₁ und R₂ wie im Anspruch 1 definiert sind und
 R_{3p2} steht für Alkyl, Alkenyl, Alkynyl, Cycloalkyl gemäß Definition von Anspruch 1, Cycloalkylalkyl gemäß
 Definition von Anspruch 1, Adamantylalkenyl unter Einschluss von Adamantanylidenalkyl, für Aryl-
 alkyl, Arylalkenyl, Arylalkynyl, Heteroaryl oder Heteroarylalkyl,

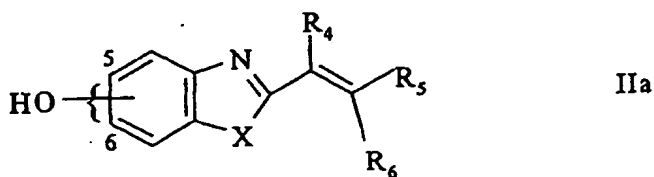
in freier Form oder in Form eines Salzes.

3. Sulfaminsäure-2-(adamantan-2-ylidenmethyl)benzoxazol-6-ylester in freier Form oder in Form eines Salzes nach
 Anspruch 1.
4. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 in freier Form oder in Form eines Salzes, umfassend
- a) falls R₁ und R₂ jeweils für Wasserstoff stehen,
 Sulfamoylierung einer Verbindung der Formel II



worin X und R₃ wie im Anspruch 1 definiert sind, oder
 b) falls einer oder beide Reste R₁ und R₂ etwas anderes als Wasserstoff sind,
 geeignete N-Substitution einer Verbindung der Formel I, worin R₁ und R₂ beide für Wasserstoff stehen,
 und Gewinnung der erhaltenen Verbindung in freier Form oder in Form eines Salzes.

5. Verbindung der Formel IIa



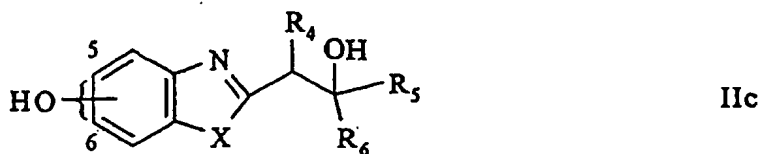
10 worin

X wie im Anspruch 1 definiert ist,

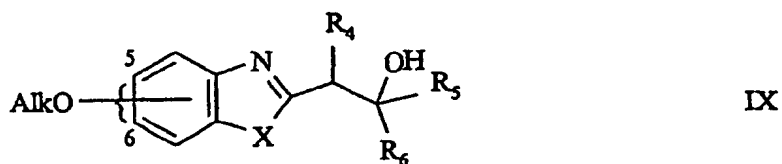
R₄ für Wasserstoff oder Alkyl steht, und

R₅ und R₆ zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, für Cycloalkyl stehen,

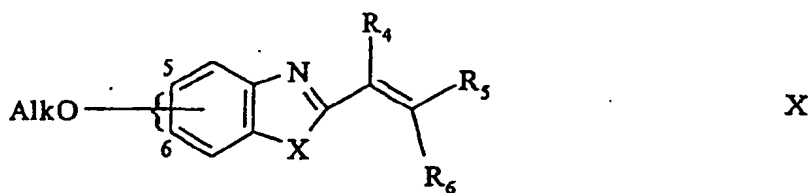
15 oder Verbindung der Formel IIc



25 worin X wie im Anspruch 1 definiert ist und R₄, R₅ und R₆ wie in diesem Anspruch definiert sind,
oder Verbindung der Formel IX



35 worin X wie im Anspruch 1 definiert ist, Alk für Alkyl steht und R₄, R₅ und R₆ wie in diesem Anspruch definiert sind,
oder Verbindung der Formel X



45 worin X wie im Anspruch 1 definiert ist und Alk, R₄, R₅ und R₆ wie in diesem Anspruch definiert sind,
in freier Form oder in Form eines Salzes.

50 6. Verbindung nach Anspruch 1 in freier Form oder in Form eines pharmazeutisch annehmbaren Salzes zur Verwendung als Pharmazeutikum.

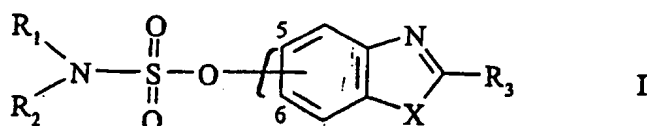
55 7. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung nach Anspruch 1 in freier Form oder in Form eines pharmazeutisch annehmbaren Salzes zusammen mit wenigstens einem pharmazeutisch annehmbaren Trä-

ger oder Verdünnungsmittel.

8. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung durch Vermischung einer Verbindung nach Anspruch 1 in freier Form oder in Form eines pharmazeutisch annehmbaren Salzes mit wenigstens einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.

Revendications

1. Composé de formule I



dans laquelle,

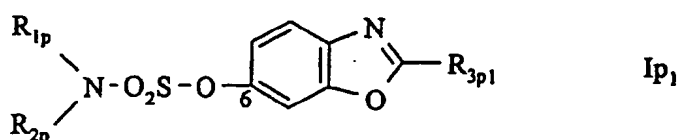
X est O ou S ;

R₁ et R₂ sont soit indépendamment l'un de l'autre hydrogène ou alkyle, soit l'un est hydrogène et l'autre acyle ou alcoxycarbonyle ; et

R₃ est alkyle ; alkényle ; alkinyle ; cycloalkyle sélectionné à partir d'adamantyle et d'hexahydro-2,5-méthanopentalényle ; cycloalkényle ; aryle ; cycloalkylalkyle sélectionné à partir d'adamantylalkyle ayant de 1 à 4 atomes de carbone dans sa partie alkylène et de dicyclohexylméthyle ; cycloalkylalkényle (y compris cycloalkanylidènealkyle) sélectionné à partir d'adamantanylidène(C₁₋₄)alkyle, (C₄₋₁₂)cycloalkylidène(C₁₋₄)alkyle, bicyclo[3.3.1]nonylidènealkyle, diméthylcyclohexylidènealkyle, (C₁₋₄)alcoxycyclohexylidènealkyle, (C₁₋₄)alkylcyclohexylidènealkyle, tétra(C₁₋₄)alkylcyclohexylidènealkyle, 1,4-dioxaspiro[4.5]dec-8-ylidènealkyle, 3,3-diméthyl-1,5-dioxa-spiro[5.5]undec-9-ylidènealkyle et octahydronaphtalylidènealkyle ; cycloalkénylalkyle ; arylalkyle ; arylalkényle ; arylalkinyle ; alcoxycarbonylaminoalkyle ; hydroxycycloalkylalkyle ; cycloalkanylidènealkyle ; cycloalkanylidènealkyle ; hétéroaryle ou hétéroarylalkyle ;

sous forme libre ou forme de sel.

2. Composé selon la revendication 1 ou 2 de formule Ip₁



dans laquelle, soit

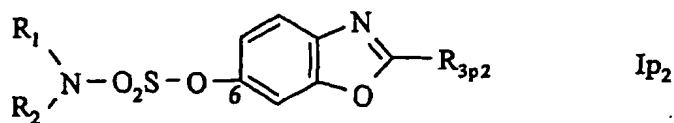
R_{1p} et R_{2p} ont la même signification que R₁ et R₂ à la revendication 1 ; et

R_{3p1} est alkyle ; alkényle ; alkinyle ; cycloalkyle tel que défini à la revendication 1 ; cycloalkylalkyle tel que défini à la revendication 1 ; arylalkyle ; arylalkényle ; arylalkinyle ; hétéroaryle ou hétéroarylalkyle ; ou, soit

R_{1p} et R_{2p} sont hydrogène ; et

R_{3p1} est adamantan-2-ylidènealkyle ; ou

de formule Ip₂



dans laquelle,

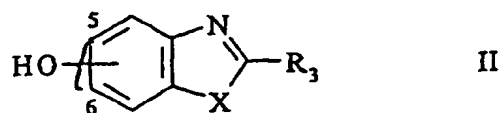
R₁ et R₂ sont tels que définis à la revendication 1 ; et
 R_{3p2} est alkyle ; alkényle ; alkinyle ; cycloalkyle tel que défini à la revendication 1 ; cycloalkylalkyle tel que défini à la revendication 1 ; adamantylalkényle, y compris adamantanylidénalkyle ; arylalkyle ; arylalkényle ; arylalkinyle ; hétéroaryle ou hétéroarylalkyle ;

sous forme libre ou forme de sel.

3. Ester 2-(adamantan-2-ylidénéméthyl)benzoxazol-6-yle de l'acide sulfamique sous forme libre ou sous forme de sel selon la revendication 1.

4. Procédé de préparation d'un composé selon la revendication 1 sous forme libre ou sous forme de sel comprenant,

a) quand soit R₁ soit R₂ sont tous deux hydrogène,
 la sulfamoylation d'un composé de formule II

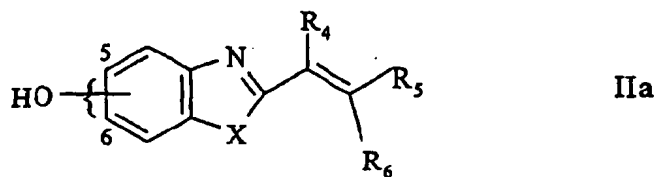


dans laquelle X et R₃ sont tels que définis à la revendication 1, ou

b) quand soit R₁ soit R₂ ou les deux sont autres qu'hydrogène,
 la N-substitution appropriée d'un composé de formule I dans laquelle R₁ ou R₂, sont tous deux hydrogène,

et la récupération du composé résultant sous forme libre ou sous forme de sel.

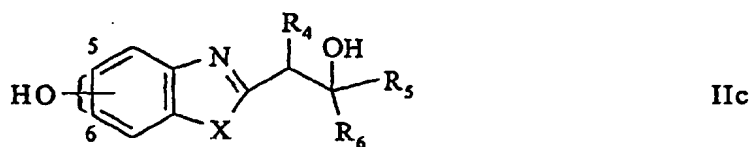
5. Composé de formule IIa



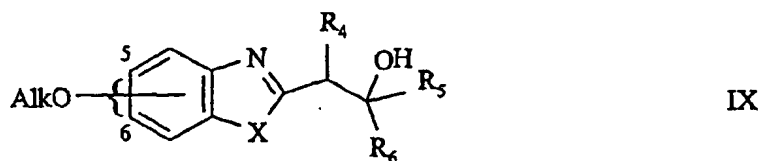
dans laquelle

X est tel que défini à la revendication 1 ;
 R₄ est hydrogène ou alkyle ; et
 R₅ et R₆ forment, de pair avec l'atome de carbone auquel ils sont attachés, cycloalkyle ;

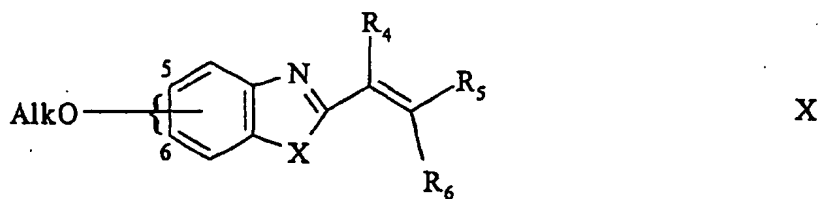
ou, de formule IIc



10 dans laquelle X est tel que défini à la revendication 1 et R₄, R₅ et R₆ sont tels que définis à la présente revendication ;
ou de formule IX



20 dans laquelle X est tel que défini à la revendication 1, Alk est alkyle et R₄, R₅ et R₆ sont tels que définis à la présente revendication ;
ou de formule X



30 dans laquelle, X est tel que défini à la revendication 1 et Alk, R₄, R₅ et R₆ sont tels que définis à la présente revendication ;
sous forme libre ou sous forme de sel.

- 35
6. Composé selon la revendication 1 sous forme libre ou sous forme de sel pharmaceutiquement acceptable destiné à être utilisé comme produit pharmaceutique.
 7. Composition pharmaceutique comprenant un composé selon la revendication 1 sous forme libre ou sous forme de sel pharmaceutiquement acceptable avec au moins un véhicule ou diluant pharmaceutiquement acceptable.
 8. Procédé de préparation d'une composition pharmaceutique comprenant le mélange d'un composé selon la revendication 1 sous forme libre ou sous forme de sel pharmaceutiquement acceptable avec au moins un véhicule ou diluant pharmaceutiquement acceptable.
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- 55