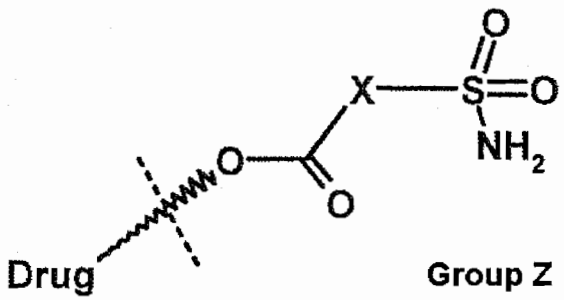
Heteroaromatic Sulfonamide Prodrugs

The invention relates to sulfonamide prodrugs of general formula (I),



(I),

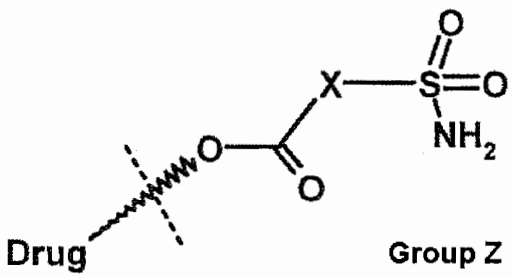
in which X is a heteroaromatic compound, a process for the production of these prodrugs, pharmaceutical compositions that contain these compounds, and their use for the production of orally available pharmaceutical agents.

From **WO 01/91797**, steroidal compounds are known that are bonded to erythrocytes via a group $-SO_2NR^1R^2$ and accumulate there. The concentration ratio of the compounds between erythrocytes and plasma is 10-1000:1, preferably 30-1000:1, such that a depot formation in the erythrocytes can be mentioned. Owing to the strong binding of the compounds to the erythrocytes, metabolization while passing through the liver is avoided. Disadvantageously, despite reduced metabolization with the indicated dosages, therapy-relevant active ingredient levels are not provided. The reasons for this are to be sought in excessively strong binding to erythrocytes, cleavage induced by enzymes and in low solubilities.

The object of the invention is to make available new prodrugs that are orally available and, in comparison to the prior art, guarantee a therapy-relevant active ingredient level even at a low dosage.

This object is achieved by heterocyclic sulfonamide prodrugs of general formula (I), in which a sulfamoyl radical is bonded to the drug to be released via a heteroaromatic spacer X by means of a carboxylic acid ester bond,

in which



(I)

X is an unsubstituted or substituted heteroaromatic radical or an alkylheteroaromatic compound, and

Drug is a pharmaceutical active ingredient that can form a carboxylic acid ester by means of an OH group, such as steroids, anti-malarial agents, nucleosides, or isoflavanoids, which optionally can be substituted.

The sulfonamide prodrugs according to the invention with a heteroaromatic linker X bind to erythrocytes, are readily water-soluble and are cleaved hydrolytically without the involvement of enzymes.

In terms of the invention, a heteroaromatic radical means, for example, thiophene, pyridine, pyrrole, furan or else thiophene, pyridine, pyrrole or furan that is substituted by C_{1-4}-alkyl or halogen. For substituted heteroaromatic compounds,

2-bromothiophene, 2-ethylthiophene, N-methylpyrrole and 2-bromopyridine can be mentioned.

C_{1-4}-Alkyl means a methyl, ethyl, propyl, butyl or isopropyl group.

The term "halogen atom" is understood within the context of this invention as a fluorine, chlorine, bromine or iodine atom; a fluorine, chlorine and bromine atom are preferred.

The above term "alkylheteroaromatic compound" means a heteroaromatic compound that is bonded to the ester group via a C_{1-3}-alkyl radical. Heteroaromatic compounds mean the groups that are named under heteroaromatic radical.

C_{1-3}-Alkyl radical means a methylene, ethylene or propylene bridge.

Preferred heteroaromatic compounds are pyridine and thiophene.

Preferred compounds are listed below:

1) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 6'-sulfamoyl nicotinate (1),
2) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoyl nicotinate (2),
3) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate (3),
4) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-bromo-5'-sulfamoyl-thiophene-3'-carboxylate (4),
5) 3-Oxoandrost-4-en-17β-yl 6'-sulfamoyl nicotinate (5),
6) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoyl nicotinate (6),
7) 3-Oxoandrost-4-en-17β-yl 2'-ethyl-5'-sulfamoyl-thiophene-3'-carboxylate,
8) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,
9) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

10) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

11) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

12) 3-Oxo-7α-methylandrost-4-en-17β-yl 5'-sulfamoyl nicotinate,

13) 3-Oxo-7α-methylandrost-4-en-17β-yl 6'-sulfamoyl nicotinate,

14) 3-Oxo-7α-methylandrost-4-en-17β-yl N-ethyl-5'-sulfamoylthiophene-3'-carboxylate,

15) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl N-methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylate.

The therapeutically relevant drug compound is released from the compounds according to the invention by hydrolysis.

In Vitro Tests:

a) Carboanhydrase Inhibition

Test principle:

Photometric determination of the inhibition of human carboanhydrase I or II by sulfonamides or sulfamates on microtiter plates with the aid of the enzymatic conversion of nitrophenyl acetate with a color change from colorless to yellow.

Table 1: IC_{50} Inhibitory Values of Human Carboanhydrase I

Inhibitor	CA II IC_{50} (nM)	CA I IC_{50} (nM)
Estradiol 3-sulfamate	34	157 ± 10.6
3-Hydroxyestra-1,3,5(10)-trien-17β-yl 6'-Sulfamoyl Nicotinate (1)	31	2900

Inhibitor	CA II IC_{50} (nM)	CA I IC_{50} (nM)
3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-Sulfamoyl Nicotinate (2)	**160**	**2100**
3-Oxoandrost-4-en-17β-yl 5'-Sulfamoyl Nicotinate (6)	**250**	**2900**
3-Oxoandrost-4-en-17β-yl 6'-Sulfamoyl Nicotinate (5)	**41**	**3200**
3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate (3)	**42**	**3400**
3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-Bromo-5'-sulfamoylthiophene-3'-carboxylate (4)	**47**	**3300**
Acetazolamide (Known CA Inhibitor)	**61**	**1200 1900[1)]**

Literature: [1]) C. Landolfi, M. Marchetti, G. Ciocci, and C. Milanese, Journal of Pharmacological and Toxicological Methods 38, 169-172 (1997).

It was found that the sulfamoyl prodrugs of general formula (I) according to the invention inhibit carboanhydrase II surprisingly well. From this, a concentration of the prodrugs according to the invention in the erythrocytes can be derived.

b) Blood-Plasma Concentration Ratio - Test Principle and Experimental Description:

The SO_2-NH_2 group of the substances according to the invention can lead to a concentration in erythrocytes owing to binding to carboanhydrases.

Test Principle:

Freshly obtained, heparinized blood from a rat is mixed with a defined amount of active ingredient. The active ingredient concentration in the plasma obtained therefrom is measured against a calibration curve of plasma that is spiked (with a known active ingredient concentration). The blood-plasma ratio is calculated from the measured concentration and the theoretical concentration.

Table 2: Blood/Plasma Ratio of Selected Prodrugs.

Prodrug	Blood/Plasma Ratio
Estradiol 3-sulfamate	**About 50**
3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-Sulfamoyl Nicotinate (2)	**2**
3-Oxoandrost-4-en-17β-yl 5'-Sulfamoyl Nicotinate (6)	**5.7**
3-Oxoandrost-4-en-17β-yl 6'-Sulfamoyl Nicotinate (5)	**3.6**
3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate (3)	**1.8**
3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-Bromo-5'-sulfamoylthiophene-3'-carboxylate (4)	**9.5**

In contrast to the results published in WO 01/91797, the concentration ratios of the compounds according to the invention between erythrocytes and plasma are not in a range from 10-1000:1, but rather in the range <10:1. This has shown itself as a decisive disadvantage for achieving therapy-relevant active

ingredient levels. By the selection of suitable linkers, it is possible to adjust the optimum blood/plasma ratio for a prodrug compound.

These test results open up to the compounds of general formula (I) according to the invention, depending on the definition of "drug", various possibilities for the treatment and/or prophylaxis of different clinical pictures. For example, for the case where "drug" is a steroid such as an androgen or estrogen, the compounds of general formula (I) can be used in hormone replacement therapy (HRT) in women and in men or in the treatment of hormonally induced diseases in men (prostate cancer, breast cancer, hypogonadism) and women (endometriosis, breast cancer). In addition, the compounds of general formula (I) according to the invention, in which "drug," for example, stands for an androgen or estrogen, are used for birth control in men or women.

The use of additional active ingredients mentioned for "drug," such as quinine, cinchonidine, hydroxychloroquine, primaquine or mefloquine, relates to the treatment of malaria.

Compounds of general formula (I) according to the invention in which "drug" means a cortisol derivative can be used for the treatment and prophylaxis of inflammatory and/or allergic diseases that are influenced by immunosuppressive agents and/or antiproliferative agents.

Prodrugs according to the invention in which "drug" means a nucleoside (zidovudine, brivudine, indinavir, nelfinavir) can be used for the treatment of viral diseases (herpes, HIV).

In addition, subjects of the invention are the pharmaceutical compositions that contain the compounds of general formula (I) according to the invention and optionally additional active ingredients, for example gestagens (norethisterone,

dienogest, drospirenone, levonorgestrel), antigestagens (mifepristone, onapristone) and/or progesterone receptor modulators (mesoprogestins such as asoprisnil).

These pharmaceutical compositions and pharmaceutical agents are preferably administered orally. In addition to the usual vehicles and/or diluents, they contain at least one compound of general formula I.

Dosage

The prodrugs according to the invention can be administered orally.

In general, satisfactory results are to be expected both for the treatment and/or prophylaxis of the above-mentioned indications or for birth control if the dosage is carried out such that, after administration of the prodrugs, an amount of corresponding active ingredient ("drug") is released that corresponds to a maximum of the highest dose of the respective "drug" substance administered pharmaceutically.

The pharmaceutical agents of the invention are produced in a known way with a suitable dosage with the usual solid or liquid vehicles or diluents and the pharmaceutical-technical adjuvants that are usually used corresponding to the desired type of administration. The preferred preparations consist in a dispensing form that is suitable for oral administration. Such dispensing forms are, for example, tablets, film-coated tablets, coated tablets, capsules, pills, powders, solutions or suspensions or else depot forms.

Corresponding tablets can be obtained by, for example, mixing the active ingredient with known adjuvants, for example inert diluents such as dextrose, sugar, sorbitol, mannitol, polyvinylpyrrolidone, explosive agents such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as

magnesium stearate or talc and/or agents for achieving a depot effect such as carboxylpolymethylene, carboxylmethyl cellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets can also consist of multiple layers.

Correspondingly, coated tablets can be produced by coating cores that are produced analogously to the tablets with agents that are usually used in tablet coatings, for example polyvinylpyrrolidone or shellac, gum arabic, talc, titanium oxide or sugar. Here, the coated tablet shell can also consist of several layers, whereby the adjuvants mentioned above in the case of the tablets can be used.

Solutions or suspensions with the compounds of general formula I according to the invention can additionally contain taste-enhancing agents such as saccharin, cyclamate or sugar as well as, e.g., flavoring substances such as vanilla or orange extract. In addition, they can contain suspending adjuvants such as sodium carboxymethyl cellulose or preservatives such as p-hydroxybenzoates.

The capsules that contain compounds of general formula I can, for example, be produced by mixing the compound(s) of general formula I with an inert vehicle such as lactose or sorbitol and encapsulating it (them) in gelatine capsules.

The prodrugs according to the invention can be synthesized according to the following examples, whereby the latter are used for a more detailed explanation, without limiting the invention.

The corresponding sulfamoylheteroarylcarboxylic acids are commercially available or can be produced from sulfonic acids or their derivatives by means of methods that are known to one skilled in the art. Linkers that are not commercially available can be synthesized as described by way of example below.

6-Sulfamoylnicotinic Acid

5 g of 6-thionicotinic acid is dissolved in 41 ml of concentrated hydrochloric acid and 9 ml of water. The solution is cooled to 0-5°C, and chlorine is introduced for 4 hours. Subsequently, the reaction solution is added to 100 g of ice, and the precipitated substance is filtered off and added to 100 ml of cold concentrated NH_3 solution. After 1 hour, it is concentrated by evaporation to 1/3 and acidified with HCl to pH = 3. The precipitated substance is suctioned off, washed with water and dried. Subsequently, purification is carried out by column chromatography. 6-Sulfamoylnicotinic acid is obtained.

^{1}H-NMR (DMSO-d_6): 7.62 (s, 2 H, NH_2); 8.03 (m, 1 H, CH); 8.50 (m, 1 H, CH); 9.08 (m, 1 H, CH).

5-Sulfamoylnicotinic Acid

1.) β-Picoline-5-sulfonic Acid

200 ml of oleum (25%) is introduced. 97 ml of β-picoline is added in drops while being cooled. 3.12 g of $HgSO_4$ is added at 40°C and then heated for 16 hours to 225-235°C. Then, about 100 ml of H_2SO_4 is distilled off (160°C, 2 mbar). Then, it is added to 400 g of ice and diluted with 2 l of water. It is subsequently neutralized with $CaCO_3$. Inorganic components are filtered out, and the residue is washed with 2 l of boiling water. The aqueous solution is concentrated by evaporation, and the residue is chromatographed on silica gel. β-Picoline-5-sulfonic acid is obtained.

^{1}H-NMR (DMSO-d_6): 2.31 (s, 3 H, CH_3); 7.75 (s, 1 H, CH); 8.36 (s, 1 H, CH); 8.57 (s, 1 H, CH).

2.) 5-Sulfamoyl-β-picoline

3.5 g of β-picoline-5-sulfonic acid is added together with 6.5 g of PCl_5 and 2.5 ml of $POCl_3$ under a protective gas, and it is heated at 120°C for 3 hours. The $POCl_3$ is distilled off in a vacuum, and 3 ml of ice water is added while being cooled. The mixture is stirred into 150 ml of NH_3 solution, and the solution is evaporated to the dry state. It is extracted with MeOH, and the product that is obtained after concentration by evaporation is purified by column chromatography on silica gel. 5-Sulfamoyl-β-picoline is obtained.

^{1}H-NMR (DMSO-d_6): 2.39 (s, 3 H, CH_3); 7.56 (s, 2 H, NH_2); 8.00 (s, 1 H, CH); 8.62 (s, 1 H, CH); 8.77 (s, 1 H, CH).

3.) 5-Sulfamoylnicotinic Acid

8.0 g of 5-sulfamoyl-β-picoline in introduced into 250 ml of water. After 12.5 g of $KMnO_4$ is added, it is heated to 70°C. After decolorization, 12.5 g of $KMnO_4$ is added again, and it is heated to 70°C for 12 hours. It is hot-filtered and concentrated by evaporation to about 20 ml. It is acidified (pH ~ 2) with 10% HCl. The substance that is crystallized under cold conditions is suctioned off, washed with water and dried. 5-Sulfamoylnicotinic acid is obtained.

^{1}H-NMR (DMSO-d_6): 7.76 (s, 2 H, NH_2); 8.62 (m, 1 H, CH); 9.15 (m, 1 H, CH); 9.23 (m, 1 H, CH).

Synthesis Examples

Example 1

3-tert-Butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 6'-Sulfamoyl Nicotinate

0.5 g of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-ol and 0.5 g of 6-sulfamoylnicotinic acid are dissolved in 7 ml of pyridine under argon. Subsequently, 0.1 g of p-Tos-OH and, finally, at 0°C, 0.5 g of DCC are added. After 48 hours, the reaction mixture is stirred at room temperature. For working-up, 40 ml of water is added, and it is adjusted to pH ~ 6 with 10% HCl. The precipitated substance is filtered off, washed with water and dried. It is purified by chromatography on silica gel. 3-tert-Butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 6'-sulfamoyl nicotinate is obtained.

^{1}H-NMR (DMSO-d_6): 0.16 (s, 6 H, SiMe), 0.938 (s, 9 H, t-Bu), 0.944 (s, 3 H, 18-Me), 4.90 (t, 1 H, 17-H), 6.50-7.15 (3 m, 3 H, CH_{Ar}), 7.69 (s, 2H, NH_2), 8.06, 8.55, 9.16 (3 m, 3 H, CH_{Py}).

Example 2

3-Hydroxyestra-1,3,5(10)-trien-17β-yl 6'-Sulfamoyl Nicotinate (1)

300 mg of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 6'-sulfamoyl nicotinate is dissolved in 20 ml of THF. 250 mg of TBAF is added at room temperature while being stirred. After 1 hour, 20 ml of water is stirred in. The substance is extracted with ethyl acetate. The organic phase is washed with saturated NaCl solution, dried on $MgSO_4$, filtered, concentrated by evaporation,

and chromatographed on silica gel. 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 6'-sulfamoyl nicotinate is obtained.

^{1}H-NMR (DMSO-d_6): 0.94 (s, 3 H, 18-Me), 4.90 (t, 1 H, 17-H), 6.40-7.15 (3 m, 3 H, CH_{Ar}), 7.69 (s, 2 H, NH_2); 8.06, 8.55 (2 m, 2 H, CH_{Py}), 9.02 (s, 1 H, 3-OH), 9.17 (1 s, 1 H, CH_{Py}).

Example 3

3-tert-Butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 5'-Sulfamoyl Nicotinate

0.55 g of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-ol and 0.55 g of 5-sulfamoylnicotinic acid are dissolved in 7 ml of pyridine under argon. Subsequently, 0.12 g of p-Tos-OH and, finally, at 0°C, 0.55 g of DCC are added. After 48 hours, the reaction mixture is stirred at room temperature. For working-up, 40 ml of water is added, and it is adjusted to pH ~ 6 with 10% HCl. The precipitated substance is filtered off, washed with water and dried. It is purified by chromatography on silica gel. 3-tert-Butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoyl nicotinate is obtained.

^{1}H-NMR (DMSO-d_6): 0.16 (s, 6 H, SiMe), 0.94 (s, 9 H, t-Bu), 0.95 (s, 3 H, 18-Me), 4.92 (t, 1 H, 17-H), 6.5-7.2 (3 m, 3 H, CH_{Ar}), 7.79 (s, 2 H, NH_2), 8.6-9.3 (3 s, 3 H, CH_{Py}).

Example 4

3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-Sulfamoyl Nicotinate (2)

250 mg of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoyl nicotinate is dissolved in 20 ml of THF. 220 mg of TBAF is added at

room temperature while being stirred. After 1 hour, 15 ml of water is stirred in. The substance is extracted with ethyl acetate. The organic phase is washed with saturated NaCl solution, dried on $MgSO_4$, filtered, concentrated by evaporation and chromatographed on silica gel. 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoyl nicotinate is obtained.

^{1}H-NMR (DMSO-d_6): 0.94 (s, 3 H, 18-Me), 4.91 (t, 1 H, 17-H), 6.4-7.1 (3 m, 3 H, CH_{Ar}), 7.92 (s, 2 H, NH_2); 8.61 (s, 1 H, CH_{Py}), 9.00 (s, 1 H, 3-OH), 9.17, 9.26 (2 s, 2 H, CH_{Py}).

Example 5

3-tert-Butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate

0.75 g of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-ol and 0.8 g of 5-(aminosulfonyl)-2-ethyl-3-thiophenecarboxylic acid are dissolved in 10 ml of pyridine under argon. Subsequently, 0.2 g of p-Tos-OH and, finally, at 0°C, 0.75 g of DCC are added. After 48 hours, the reaction mixture is stirred at room temperature. For working-up, 60 ml of water is added, and it is adjusted to pH ~ 6 with 10% HCl. The precipitated substance is filtered off, washed with water and dried. It is purified by chromatography on silica gel. 3-tert-Butyldimethyl-silyloxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate is obtained.

^{1}H-NMR ($CDCl_3$): 0.19 (s, 6 H, SiMe), 0.92 (s, 3 H, 18-Me), 0.97 (s, 9 H, t-Bu), 1.34 (t, 3 H, Et), 3.26 (q, 2 H, Et), 4.86 (t, 1 H, 17-H), 5.12 (s, 2 H, NH_2), 6.50-7.15 (3 m, 3 H, CH_{Ar}), 7.92 (s, 1 H, CH_{Th}).

Example 6

3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate (3)

440 mg of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate is dissolved in 20 ml of THF. 400 mg of TBAF is added at room temperature while being stirred. After 1 hour, 20 ml of water is stirred in. The reaction mixture is concentrated by evaporation, and the precipitated substance is suctioned off, washed with water and chromatographed on silica gel. 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoyl-thiophene-3'-carboxylate (3) is obtained.

^{1}H-NMR (DMSO-d_6): 0.89 (s, 3 H, 18-Me), 1.27 (t, 3 H, Et), 3.20 (q, 2 H, Et), 4.79 (t, 1 H, 17-H), 6.35-7.05 (3 m, 3 H, CH_{Ar}), 7.72 (s, 1 H, CH_{Th}), 7.76 (s, 2 H, NH_2), 9.01 (s, 1H, 3-OH).

Example 7

3-tert-Butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 2'-Bromo-5'-sulfamoylthiophene-3'-carboxylate

0.75 g of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-ol and 0.8 g of 5-(aminosulfonyl)-2-bromo-3-thiophenecarboxylic acid are dissolved in 10 ml of pyridine under argon. Subsequently, 0.2 g of p-Tos-OH and, finally, at 0°C, 0.75 g of DCC are added. After 48 hours, the reaction mixture is stirred at room temperature. For working-up, 70 ml of water is added, and if is adjusted to pH ~ 6 with 10% HCl. The precipitated substance is filtered off, washed with water and dried. It is purified by chromatography on silica gel. 3-tert-Butyldimethylsilyl-

oxyestra-1,3,5(10)-trien-17β-yl 2'-bromo-5'-sulfamoylthiophene-3'-carboxylate is obtained.

^{1}H-NMR ($CDCl_3$): 0.19 (s, 6 H, SiMe), 0.94 (s, 3 H, 18-Me), 0.97 (s, 9 H, t-Bu), 4.88 (t, 1 H, 17-H), 5.22 (s, 2H, NH_2), 6.50-7.10 (3 m, 3 H, CH_{Ar}), 7.85 (s, 1 H, CH_{Th}).

Example 8

3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-Bromo-5'-sulfamoylthiophene-3'-carboxylate (4)

330 mg of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl 2'-bromo-5'-sulfamoylthiophene-3'-carboxylate is dissolved in 30 ml of THF. 300 mg of TBAF is added at room temperature while being stirred. After 1 hour, 30 ml of water is stirred in. The reaction mixture is concentrated by evaporation, and the precipitated substance is suctioned off, washed with water, and chromatographed on silica gel. 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-bromo-5'-sulfamoyl-thiophene-3'-carboxylate (4) is obtained.

^{1}H-NMR (DMSO-d_6): 0.96 (s, 3 H, 18-Me), 4.84 (t, 1 H, 17-H), 6.40-7.15 (3 m, 3 H, CH_{Ar}), 7.75 (s, 1 H, CH_{Th}), 8.05 (s, 2 H, NH_2), 9.01 (s, 1H, 3-OH).

Example 9

3-Oxoandrost-4-en-17β-yl 6'-Sulfamoyl Nicotinate (5)

0.4 g of testosterone is dissolved in 2 ml of pyridine. After 0.4 g of 6-sulfamoylnicotinic acid, 50 mg of p-toluenesulfonic acid and 0.4 g of di-cyclohexylcarbodiimide (DCC) are added, it is stirred at room temperature for 72 hours. Subsequently, 10 ml of water is added. It is acidified slightly (pH = 5) with

10% HCl. The precipitate is filtered off and washed 2× with saturated $NaHCO_3$ solution and water. The dried residue is extracted with ethyl acetate. The organic phase is washed with 10% $NaHCO_3$ solution and saturated NaCl solution, dried on $MgSO_4$, filtered, concentrated by evaporation, and chromatographed on silica gel. 3-Oxoandrost-4-en-17β-yl 6'-sulfamoyl nicotinate (5) is obtained.

^{1}H-NMR (DMSO-D_6): 0.95 (s, 3 H, Me); 1.17 (s, 3 H, Me); 5.64 (s, 1 H, 4-H); 7.68 (s, 2 H, NH_2); 8.06, 8.53, 9.15 (3 m, 3 H, CH_{Ar}).

Example 10

3-Oxoandrost-4-en-17β-yl 5'-Sulfamoyl Nicotinate (6)

0.4 g of testosterone is dissolved in 2 ml of pyridine. After 0.4 g of 5-sulfamoylnicotinic acid, 50 mg of p-toluenesulfonic acid and 0.4 g of di-cyclohexylcarbodiimide (DCC) are added, it is stirred at room temperature for 72 hours. Subsequently, 10 ml of water is added. It is slightly acidified (pH = 5) with 10% HCl. The precipitate is filtered off and washed 2× with saturated $NaHCO_3$ solution and water. The dried residue is extracted with ethyl acetate. The organic phase is washed with 10% $NaHCO_3$ solution and saturated NaCl solution, dried on $MgSO_4$, filtered, concentrated by evaporation, and chromatographed on silica gel. 3-Oxoandrost-4-en-17β-yl 5'-sulfamoyl nicotinate (6) is obtained.

^{1}H-NMR (DMSO-D_6): 0.96 (s, 3 H, Me); 1.17 (s, 3 H, Me); 5.64 (s, 1 H, 4-H); 7.76 (s, 2 H, NH_2); 8.59, 9.17, 9.24 (3 s, 3 H, CH_{Ar}).

Example 11

3-tert-Butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl N-Methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylate

0.50 g of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-ol and 0.50 g of N-methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylic acid are dissolved in 7 ml of pyridine under argon. Subsequently, 0.12 g of p-Tos-OH and, finally, at 0°C, 0.5 g of DCC are added. After 48 hours, the reaction mixture is stirred at room temperature. For working-up, 40 ml of water is added, and it is adjusted to pH ~ 6 with 10% HCl. The precipitated substance is filtered off, washed with water and dried. It is purified by chromatography on silica gel. 3-tert-Butyldimethyl-silyloxyestra-1,3,5(10)-trien-17β-yl N-methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylate is obtained.

^{1}H-NMR ($CDCl_3$): 0.18 (s, 6 H, SiMe), 0.92 (s, 3 H, 18-Me), 0.97 (s, 9 H, t-Bu), 3.95 (s, 3 H, NMe), 4.83 (t, 1 H, 17-H), 4.95 (s, 2 H, NH_2), 6.5-7.3 (5 m, 5 H, CH_{Ar}).

Example 12

3-Hydroxyestra-1,3,5(10)-trien-17β-yl N-Methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylate

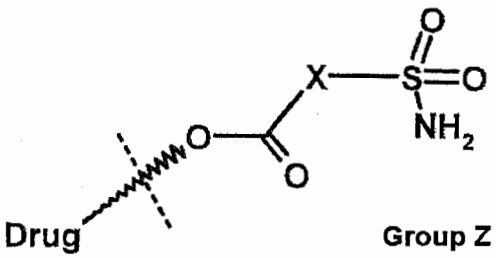
300 mg of 3-tert-butyldimethylsilyloxyestra-1,3,5(10)-trien-17β-yl N-methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylate is dissolved in 20 ml of THF. 250 mg of TBAF is added at room temperature while being stirred. After 1 hour, 20 ml of water is stirred in. The reaction mixture is concentrated by evaporation, and the precipitated substance is suctioned off, washed with water, and chromatographed

on silica gel. 3-Hydroxyestra-1,3,5(10)-trien-17β-yl N-methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylate is obtained.

^{1}H-NMR (DMSO-d_6): 0.89 (s, 3 H, 18-Me), 3.88 (s, 3 H, NMe), 4.76 (t, 1 H, 17-H), 7.12 (s, 2 H, NH_2), 8.99 (s, 1H, 3-OH).

Claims

1. Sulfonamide prodrugs of general formula I



(I),

in which

X is an unsubstituted or substituted heteroaromatic radical or an alkylheteroaromatic compound, and,

Drug is a pharmaceutical active ingredient that can form a carboxylic acid ester by means of an OH group, such as steroids, anti-malarial agents, nucleosides, or isoflavanoids, which optionally can be substituted.

2. Sulfonamide prodrugs according to Claim 1, whereby X is a pyridine or a thiophene radical.

3. Sulfamoylsulfonate prodrugs according to Claim 1, whereby

Drug means steroids such as estrogens, for example estradiol or estriol or androgens, for example testosterone, MENT (7α-methyl-19-nor-testosterone), eF-MENT (11-fluoro-7α-methyl-19-nortestosterone), nandrolone, DHT (dihydrotestosterone) or

gestagens, for example norethisterone, dienogest or levonorgestrel

corticoids, for example cortisol

anti-malarial agents, for example quinine, cinchonidine,

hydroxychloroquine, primaquine, mefloquine or

nucleosides consisting of a sugar such as ribose or deoxyribose and of a base such as adenine, guanine, cytosine, thymine or uracil, in addition zidovudine, brivudine, indinavir, nelfinavir

isoflavanoids, for example genistein.

4. Sulfamoylsulfonate prodrugs according to Claims 1 and 2, namely

1) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 6'-sulfamoyl nicotinate (1),

2) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoyl nicotinate (2),

3) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate (3),

4) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-bromo-5'-sulfamoylthiophene-3'-carboxylate (4),

5) 3-Oxoandrost-4-en-17β-yl 6'-sulfamoyl nicotinate (5),

6) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoyl nicotinate (6),

7) 3-Oxoandrost-4-en-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate,

8) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

9) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

10) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

11) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

12) 3-Oxo-7α-methylandrost-4-en-17β-yl 5'-sulfamoyl nicotinate,

13) 3-Oxo-7α-methylandrost-4-en-17β-yl 6'-sulfamoyl nicotinate,

14) 3-Oxo-7α-methylandrost-4-en-17β-yl N-ethyl-5'-sulfamoylthiophene-

3'-carboxylate,

15) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl N-methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylate.

5. Compounds according to one of Claims 1, 2 or 4, whereby the active ingredient is an anti-malarial agent such as arteether, artemether, artesunate, chloroquine, pamaquine, primaquine, pyrethamine, mefloquine, proguanil, cinchonidine, cinchonine, hydroxychloroquine, pamaquine, primaquine, pyrimethamine, quinine or a quinine derivative, such as quinine bisulfate, quinine carbonate, quinine dihydrobromide, quinine dihydrochloride, quinine ethyl carbonate, quinine formate, quinine gluconate, quinine hydroiodide, quinine hydrochloride, quinine salicylate or quinine sulfate.

6. Use of the compounds according to Claim 5 for the prevention of a parasitic infestation of erythrocytes.

7. Compounds according to one of Claims 1-6, whereby the therapeutically desired action takes place by release, in particular hydrolytic cleavage, of the active ingredient contained in the prodrug or its metabolites.

8. Pharmaceutical composition that contains at least one compound of general formula I according to one of Claims 1 to 4 and optionally at least one additional active ingredient together with pharmaceutically compatible adjuvants and/or vehicles.

9. Pharmaceutical composition according to Claim 8, whereby the additional active ingredient is a steroidal compound.

10. Pharmaceutical composition according to Claim 9, whereby the additional steroidal compound is a gestagen, antigestagen or a progesterone receptor modulator.

11. Pharmaceutical composition according to Claim 10, in which the gestagens that are contained are norethisterone, dienogest, drospirenone, levonorgestrel, the antigestagens mifepristone, onapristone and progesterone receptor modulators, for example mesoprogestins such as asoprisnil.

12. Use of compounds according to one of Claims 1 to 7 for the production of a pharmaceutical agent.

13. Use according to Claim 12 for the production of a pharmaceutical agent for hormone replacement therapy.

14. Use of compounds according to Claims 1-7 for female birth control.

15. Use according to Claim 12 for the production of a pharmaceutical agent for the therapy and/or prophylaxis of hormonally induced diseases in men and women.

16. Use according to Claim 12 for the production of a pharmaceutical agent for the therapy and prophylaxis of endometriosis, breast cancer, prostate cancer, or hypogonadism.

17. Use according to Claim 12 for the production of a pharmaceutical agent for the therapy and/or prophylaxis of diseases that can be positively influenced by the inhibition of the carboanhydrase activity.

18. Use according to Claim 12 for the production of a pharmaceutical agent for the therapy and/or prophylaxis of inflammatory and/or allergic diseases.

19. Process for the production of the sulfonamide prodrugs of general formula (I) according to Claim 1 by reaction of a carboxylic acid NH_2SO_2-X-COOH of the corresponding heteroaromatic linker in the presence of dicyclohexylcarbodiimide or EDC (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide) optionally with a catalyst, with the corresponding active

ingredient or by coupling of a sulfamoylcarboxylic acid chloride of the corresponding heteroaromatic linker to the corresponding active ingredient in the presence of a base, preferably pyridine.

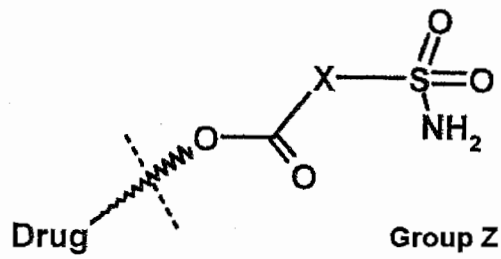
20. Process according to Claim 19, whereby the base is pyridine.

21. Process according to Claim 20, whereby the catalyst is p-toluenesulfonic acid.

AMENDED CLAIMS

Submitted to the International Office on May 29, 2007 (5/29/2007)

1. Sulfonamide prodrugs of general formula I



(I),

in which

X is an unsubstituted or substituted heteroaromatic radical or an alkylheteroaromatic compound, and,

Drug is a pharmaceutical active ingredient that can form a carboxylic acid ester by means of an OH group, such as steroids that optionally can be substituted.

2. Sulfonamide prodrugs according to Claim 1, whereby X is a pyridine or a thiophene radical.

3. Sulfamoylsulfonate prodrugs according to Claim 1, whereby

Drug means steroids such as estrogens, for example estradiol or estriol or androgens, for example testosterone, MENT (7α-methyl-19-nor-

testosterone), eF-MENT (11-fluoro-7α-methyl-19-nortestosterone), nandrolone, DHT (dihydrotestosterone) or

gestagens, for example norethisterone, dienogest or levonorgestrel

corticoids, for example cortisol.

4. Sulfamoylsulfonate prodrugs according to Claims 1 and 2, namely

1) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 6'-sulfamoyl nicotinate (1),

2) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoyl nicotinate (2),

3) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate (3),

4) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 2'-bromo-5'-sulfamoylthiophene-3'-carboxylate (4),

5) 3-Oxoandrost-4-en-17β-yl 6'-sulfamoyl nicotinate (5),

6) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoyl nicotinate (6),

7) 3-Oxoandrost-4-en-17β-yl 2'-ethyl-5'-sulfamoylthiophene-3'-carboxylate,

8) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

9) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

10) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl 5'-sulfamoylthiophene-3'-carboxylate,

11) 3-Oxoandrost-4-en-17β-yl 5'-sulfamoyl-thiophene-3'-carboxylate,

12) 3-Oxo-7α-methylandrost-4-en-17β-yl 5'-sulfamoyl nicotinate,

13) 3-Oxo-7α-methylandrost-4-en-17β-yl 6'-sulfamoyl nicotinate,

14) 3-Oxo-7α-methylandrost-4-en-17β-yl N-ethyl-5'-sulfamoylthiophene-3'-carboxylate,

15) 3-Hydroxyestra-1,3,5(10)-trien-17β-yl N-methyl-5'-sulfamoyl-1H-pyrrole-2'-carboxylate.

5. Compounds according to one of Claims 1-6, whereby the therapeutically desired action takes place by release, in particular hydrolytic cleavage, of the active ingredient that is contained in the prodrug or its metabolites.

6. Pharmaceutical composition that contains at least one compound of general formula I according to one of Claims 1 to 4 and optionally at least one additional active ingredient together with pharmaceutically compatible adjuvants and/or vehicles.

7. Pharmaceutical composition according to Claim 8, whereby the additional active ingredient is a steroidal compound.

8. Pharmaceutical composition according to Claim 9, whereby the additional steroidal compound is a gestagen, antigestagen or a progesterone receptor modulator.

9. Pharmaceutical composition according to Claim 10, in which the gestagens that are contained are norethisterone, dienogest, drospirenone, levonorgestrel, the antigestagens mifepristone, onapristone and progesterone receptor modulators, for example mesoprogestins such as asoprisnil.

10. Use of compounds according to one of Claims 1 to 7 for the production of a pharmaceutical agent.

11. Use according to Claim 12 for the production of a pharmaceutical agent for hormone replacement therapy.

AMENDED PAGE (ARTICLE 19)

12. Use of compounds according to Claims 1-7 for female birth control.

13. Use according to Claim 12 for the production of a pharmaceutical agent for the therapy and/or prophylaxis of hormonally induced diseases in men and women.

14. Use according to Claim 12 for the production of a pharmaceutical agent for the therapy and prophylaxis of endometriosis, breast cancer, prostate cancer, or hypogonadism.

15. Use according to Claim 12 for the production of a pharmaceutical agent for the therapy and/or prophylaxis of diseases that can be positively influenced by the inhibition of the carboanhydrase activity.

16. Use according to Claim 12 for the production of a pharmaceutical agent for the therapy and/or prophylaxis of inflammatory and/or allergic diseases.

17. Process for the production of the sulfonamide prodrugs of general formula (I) according to Claim 1 by reaction of a carboxylic acid NH_2SO_2-X-COOH of the corresponding heteroaromatic linker in the presence of dicyclohexylcarbodiimide or EDC (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide) optionally with a catalyst, with the corresponding active ingredient or by coupling of a sulfamoylcarboxylic acid chloride of the corresponding heteroaromatic linker to the corresponding active ingredient in the presence of a base, preferably pyridine.

18. Process according to Claim 19, whereby the base is pyridine.

19. Process according to Claim 20, whereby the catalyst is p-toluenesulfonic acid.

AMENDED PAGE (ARTICLE 19)