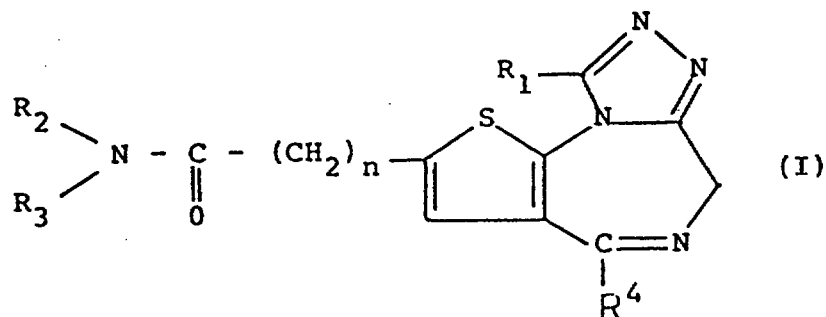


- 2 -

The invention relates to new thieno-triazolo-1,4-diazepino-2-carboxylic acid amides of general formula



In this formula:

- R_1 represents hydrogen, a straight-chained or branched alkyl group having 1 to 4 carbon atoms optionally substituted by halogen, preferably Cl or Br, or by hydroxy, cyclopropyl, alkoxy having 1 to 3 carbon atoms, preferably methoxy, halogen, preferably chlorine or bromine;
- R_2 and R_3 , which may be identical or different, represent hydrogen, a straight-chained or branched alkyl or hydroxyalkyl group having 1 to 4 carbon atoms or the two groups R_2 and R_3 together with the nitrogen atom represent a 5-, 6- or 7-membered ring which optionally contains a nitrogen, oxygen or sulphur atom as a further heteroatom, the second nitrogen atom optionally being substituted by an alkyl group having 1 to 4 carbon atoms, preferably a methyl group;
- R_4 represents phenyl, whilst the phenyl ring may be substituted preferably in the 2-position by methyl, halogen, preferably chlorine or bromine, nitro or trifluoromethyl, or R_4

may represent α -pyridyl; and
n represents one of the numbers 0, 1, 2, 3,
4, 5, 6, 7 or 8.

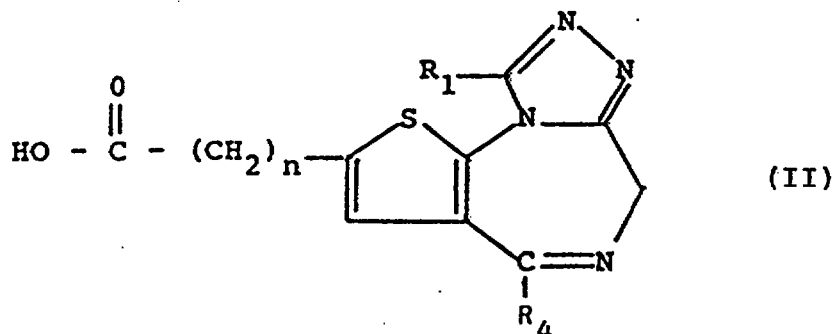
Unless otherwise stated, halogen represents one of the halogen atoms fluorine, chlorine, bromine or iodine.

Compounds of general formula I wherein n represents one of the numbers 0, 1 or 2, and particularly those wherein n = 2, are preferred.

Preferred alkyl groups are the methyl, ethyl, propyl, isopropyl, butyl and tert.butyl groups.

The invention further relates to processes for preparing the new compounds and pharmaceutical compositions which contain these compounds as active substances.

The new compounds may be obtained in conventional manner from the corresponding 2-carboxylic acids of general formula II



wherein the groups R_1 and R_4 are as hereinbefore defined, e.g.

- a) by reaction with a corresponding amine in the presence of a carbodiimide or carbonyldiimidazole,
- b) by converting the free acid into an acid halide or acid anhydride and subsequently reacting with a corresponding amine.

The reaction of the free acid with the amine is carried out in the presence of a carbodiimide, for example cyclohexylcarbodiimide or carbonyldiimidazole in an inert

solvent such as dimethylformamide, tetrahydrofuran or dioxan, at temperatures of between 0° C and the boiling point of the reaction mixture.

When the amine is reacted with an acid halide or acid anhydride, the amine is reacted with the acid halide or acid anhydride in an inert solvent, for example dimethylformamide, tetrahydrofuran, dioxan or a suitable hydrocarbon such as benzene or toluene at temperatures of between ambient temperature and the boiling point of the reaction mixture, optionally with the addition of an acid binding agent such as sodium carbonate, sodium bicarbonate or a tertiary organic base, e.g. pyridine or triethylamine.

If the amine is a liquid, the reaction may also be carried out in an excess of the amine without any added solvent.

The acid halide or anhydride is obtained from the free acid in conventional manner, e.g. by reacting the acid with a thionyl halide or by reacting an alkali metal salt of the acid with acetyl chloride or chloroformic acid chloride.

Using the processes described hereinbefore, the following end products may be obtained, for example:

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid morpholide

2-[4-(2-Chlorophenyl)-9-cyclopropyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid morpholide

[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]diazepin-2-yl]-carboxylic acid morpholide.

[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-carboxylic acid
amide

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid diethylamide

8-[4-(2-Chlorophenyl)-9-cyclopropyl-6H-thieno[3,2-f]-
[1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-n-octane-
1-carboxylic acid morpholide

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid N,N-di-(2-hydroxyethyl) amide]

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid methylamide

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid isopropylamide

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid dimethylamide

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid N'-methyl-piperazide

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid pyrrolidide

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid piperidide

2-[4-(2-Chlorophenyl)-9-cyclopropyl-6H-thieno[3,2-f]-
[1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-
1-carboxylic acid diethylamide

2-[4-(2-Chlorophenyl)-6H-thieno[3,2-f][1,2,4]triazolo-
[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid morpholide

2-[4-(2-Chlorophenyl)-9-bromo-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid morpholide

2-[4-(2-Chlorophenyl)-9-methoxy-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid morpholide

2-[4-Phenyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo-
[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid morpholide

2-[4-(2-nitrophenyl)-9-methyl-6H-thieno-[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid morpholide

2-[4-(2-methylphenyl)-9-methyl-6H-thieno-[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid morpholide

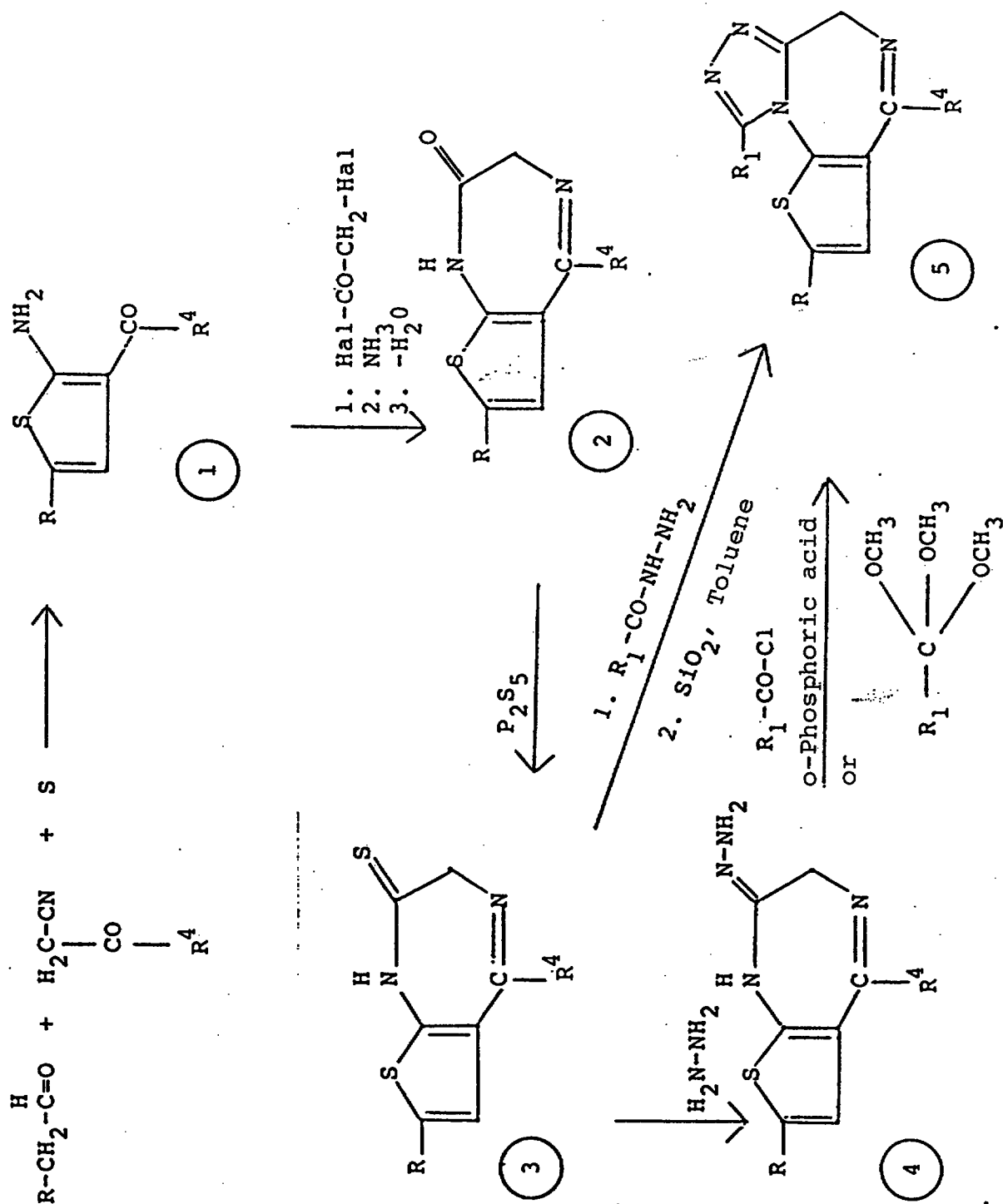
2-[4-(2-trifluoromethylphenyl)-9-methyl-6H-thieno-
[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-
ethane-1-carboxylic acid morpholide

2-[4-(2-Chlorophenyl)-9-methoxy-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid diethylamide

2-[4-(2-Chlorophenyl)-9-methoxy-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid piperidide

2-[4-(2-Chlorophenyl)-9-methoxy-6H-thieno[3,2-f][1,2,4]-
triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic
acid N'-methylpiperazide

The starting materials of general formula
II are for the most part new compounds. They are
obtained, starting from the corresponding aldehydes,
according to the following reaction scheme.



R = methyl or ethyl alkylcarboxylate or methyl or ethyl alkyldicarboxylate with 1 to 8 carbon atoms in the alkyl chain

If a dicarboxylic acid ester has been used, one of the carboxyl groups is split off at the stage of the aminoketone after saponification.

To obtain R_1 = hydrogen, either one uses as starting material a compound (3) which is reacted with formic acid hydrazide to produce compound (5) or a compound (4) is reacted with an o-formic acid ester.

To obtain R_1 = chlorine or bromine, first of all a compound wherein R_1 = hydrogen is prepared and then this is reacted with chlorine or bromine in pyridine.

The l-methoxy compound is obtained from a chlorine or bromine compound as mentioned above by reacting with a sodium alkoxide.

Compounds wherein n represents 0 are obtained from compounds with a carboxyl group in the 1 position as described in DOS 2503235; the free acid is reacted further as mentioned above.

The compounds according to the invention have a PAF-antagonistic activity.

As is known, PAF (platelet activating factor) is the phospholipid acetyl-glycerol-ether-phosphorylcholine (AGEPC) which is known as a potent lipid mediator released by animal and human proinflammatory cells. These cells include mainly basophilic and neutrophilic granulocytes, macrophages (from blood and tissue) and thrombocytes which are involved in inflammatory reactions.

In pharmacological tests, PAF exhibits bronchoconstriction, a lowering of blood pressure, the triggering of thrombocyte aggregation and a proinflammatory activity.

These experimentally demonstrable effects of PAF provide direct or indirect indications of possible functions of this mediator in anaphylaxis, in the pathophysiology of bronchial asthma and

in inflammation in general.

PAF antagonists are required on the one hand in order to clarify further pathophysiological functions of this mediator in animals and humans and on the other hand to treat pathological conditions and diseases in which PAF is implicated. Examples of indications of a PAF antagonist are inflammatory processes of the tracheobronchial tree (acute and chronic bronchitis, bronchial asthma) or of the kidneys (glomerulonephritis), anaphylactic conditions, allergies and inflammation in the mucous membranes and skin (e.g. psoriasis) and states of shock induced by sepsis, endotoxins or burns. Other important indications of a PAF antagonist are lesions and inflammation in the mucous membranes of the stomach and intestines, e.g. gastritis, peptic ulcers generally, but especially ventricular and duodenal ulcers.

The PAF-antagonistic effect of individual benzodiazepines is known, cf., E. Kornecki et al, Science 226, 1454 - 1456 (1984). These compounds which are commercially available and have proved themselves as tranquillizers and hypnotics are, however, unsuitable for use as PAF antagonists in therapy in many instances because of their marked CNS activity.

The compounds according to the invention, on the other hand, lack any CNS activity, whilst the PAF-antagonistic activity is up to fifty times greater than that of the known benzodiazepines.

Pharmacological test results will now be given:

Pharmacological test results

The PAF-antagonistic activity of some compounds of general formula I was investigated in terms of the restriction of blood platelet aggregation in vitro and antagonisation of the PAF-induced bronchoconstriction in anaesthetised guinea pigs, lowering of blood pressure in anaesthetised rats and skin weals in rats. Furthermore, these compounds were tested for possible side effects on the central nervous system. The LD₅₀ was also

determined as a guide to acute toxicity.

1. Tests in vitro: inhibition of blood platelet aggregation

In order to determine the PAF-antagonistic effect of substances the PAF-induced aggregation of human thrombocytes in vitro was used. To obtain thrombocyte-rich plasma (TRP) blood was taken from an uncongested vein using a plastic syringe containing a 3.8% sodium citrate solution. The ratio of sodium citrate solution to blood was 1:9. After careful mixing the citrated blood was centrifuged for 20 minutes at 150 x g (1200 rpm). The thrombocyte aggregation was measured using the method developed by Born and Cross (G. V. R. Born and M. J. Cross, J. Physiol. 168, 178 (1963)), PAF being added to the TRP with constant stirring to initiate aggregation.

The test substance is added 2 to 3 minutes before the aggregation is induced in a volume of 10 μ l. The solvent used is either distilled water, ethanol and/or dimethylsulphoxide. Control mixtures are given corresponding volumes of these solvents. After the initial absorption has been recorded (2 to 3 minutes) aggregation is induced with PAF (5×10^{-8} M).

To assess the effects of substances the maximum of the first aggregation wave is used. The maximum absorption rate induced by PAF (= maximum aggregation x 100%) is tested simultaneously in a parallel mixture (= control mixture in one of the channels of the 2-channel aggregometer) with each test mixture (second channel) and used as the 100% value.

The aggregation value achieved under the influence of the test substance is given as 100% -.

Each test substance is investigated at concentrations of 10^{-3} to 10^{-8} M with a random test scope of $n = 4$ for any inhibiting effect on the PAF-induced thrombocyte aggregation. Then a concentration-activity curve is drawn up using 3 concentrations and the IC_{50} is determined (concentration at 50% inhibition of aggregation). The IC values of compounds of general formula I vary between 0.17 and 1.5 μ M. 2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid diethylamide and 2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepino-2-yl]-ethane-1-carboxylic acid morpholide, having IC_{50} values of 0.7 and 0.17, respectively, proved particularly potent compounds.

2. Test in vivo

2.1. Antagonising of the PAF-induced bronchoconstriction in anaesthetised guinea pigs

Spontaneously breathing male guinea pigs weighing 300 to 450 g were treated orally 1 hour before intravenous infusion of PAF (30 ng/(kg x min)) with the test substance or a control vehicle. The test animals were then anaesthetised by intraperitoneal route with 2 mg/kg of urethane, whereupon the jugular vein, carotid artery and trachea were cannulated. PAF infusion induces in the control animals a powerful and long-lasting bronchoconstriction which is measured by means of the volume of respiration, compliance and resistance, and also a lowering

of blood pressure. After about 7 to 10 minutes death occurs. Using the PAF antagonists described, these effects on breathing and blood pressure and the onset of death can be prevented. The doses required range from 0.5 to 5 mg/kg p.o. and from 0.5 to 1.0 mg/kg i.v.

2.2. Antagonising of PAF-induced lowering of blood pressure in anaesthetised rats

Normotonic male Wistar rats weighing 200 to 250 g are anaesthetised by intraperitoneal route with 2 mg/kg of urethane. The carotid artery and jugular vein are cannulated. In the control animals, intravenous PAF infusion (30 ng/(kg x min)) induces a powerful and long-lasting lowering of blood pressure. This can be reversed, depending on dosage, by intravenous injections (cumulative administration) of the compounds described in a dosage range of from 0.01 to 0.5 mg/kg. Oral or intravenous administration of the compound before the start of the PAF infusion can also prevent the hypotensive activity of the above-mentioned PAF infusion, depending on the dosage.

2.3. Antagonising of PAF-induced skin weals in rats (modified according to P.P. Koelzer and K.H. Wehr, *Arzneim.-Forsch.* 8, 181 (1958))

Intracutaneous injection of PAF induces skin weals which indicate a PAF-induced increase in the permeability of the blood vessels.

Male Wistar rats with a body weight of 250 ± 20 g are shaved over their abdominal walls. Then 1 ml/kg of a 1% trypan blue solution is injected into the animals through a vein in the tail. Symmetrically with respect to the central line (linear alba) at three points about 1.5 cm apart, intracutaneous injections of physiological saline solution or PAF solution (12.5 to 25.0 mg/site in 0.1 ml) are administered. Whereas there is no reaction at the point of injection of the saline solution, PAF induces a skin reaction (weals) which is made visible by blue colouration of varying intensity, depending on the dosage of PAF. By simultaneously administering the compounds described by intracutaneous route in doses of from 0.5 to 5 μ g/site (in 0.1 ml) or by intravenous pre-treatment in doses of 0.2 to 3 mg/kg this PAF-induced skin reaction can be prevented.

3. Effects on the central nervous system

It is generally known that substances of this type of structure cause central nervous effects which are undesirable for a compound with a PAF-antagonistic effect. Therefore, the compounds described were tested for their hypnotic and anticonvulsive activities and for their effects on locomotion. Possible hypnotic effects were tested on guinea pigs weighing 400 to 450 g. Dosages of up to 200 mg/kg p.o. of these substances were unable to produce any hypnotic or sedative effects in these animals. Anticonvulsive activities can be tested using the pentetrazole antagonism in mice (body weight 20 to 25 g) (M. I. Gluckmann, Current Therapeutic Research 7:721, 1965).

Doses of up to 100 mg/kg p.o. of these compounds (1 hour before pentetrazole) showed no effect on the mortality caused by pentetrazole (125 mg/kg i.p., LD 100) in this test.

The effects on night motility (locomotion) in mice (body weight 20 to 25 g) can be investigated in a light beam cage. The number of times the light beam is broken is measured. Doses of up to 300 mg/kg p.o. of the compounds mentioned above showed no activity.

4. Acute toxicity in mice

The average lethal dose (LD₅₀) after oral administration was between 3 and 4 g/kg for the compounds tested. The LD₅₀ values after intravenous administration ranged from 400 to 700 mg/kg.

The new compounds of general formula I may be administered to warm-blooded animals topically, orally, parenterally or by inhalation. The compounds are presented as active substances in conventional preparations, e.g. in compositions consisting essentially of an inert pharmaceutical vehicle and an effective dose of the active substance, such as plain or coated tablets, capsules, lozenges, powders, solutions, suspensions, aerosols for inhalation, ointments, emulsions, syrups, suppositories, etc. An effective dose of the compounds according to the invention is between 1 and 50, preferably between 3 and 20 mg/dose for oral use, between 0.01 and 50, preferably between 0.1 and 10 mg/dose for intravenous or intramuscular use. For inhalation, solutions should be used containing 0.01 to 1.0, preferably 0.1 to 0.5% of active substance.

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The following Examples serve to illustrate the invention:

Example 1

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid morpholide

5.3 g (0.014 mol) of 2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid, 1.8 g of N-hydroxybenzotriazole (HOBt) and 60 ml of absolute dimethylformamide are mixed with 1.2 g (0.014 mol) of morpholine with stirring at ambient temperature, to form a clear solution. Then, at 0 to 5°C, over a period of 5 to 10 minutes, 3.5 g of dicyclohexylcarbodiimide in solid form are added and the temperature is maintained at 0 to 10°C for a further 6 to 8 hours. The dicyclohexylurea precipitated is suction filtered, washed with a little cold dimethylformamide and the filtrate is concentrated by evaporation in vacuo. The residue is dissolved in methylene chloride, washed with 5% soda solution and ice water, the organic phase is evaporated and the residue is crystallised using ethyl acetate. Yield: 5.2 g (83.2% of theory) colourless crystals, m.p. 189 - 190°C.

¹NMR (CDCl₃), δ = 2.64 (2t, -CH₂-CO-), 2.71 (3s, CH₃), 3.17 (2t, CH₂), 3.33-3.81 (8m, morpholine), 4.96 (2s, CH₂), 6.48 (1s, thiophene), 7.28-7.60 (4m, aryl).

The starting material is obtained as follows; it is new:

a) 2-Amino-3-o-chlorobenzoyl-5-(2,2-dicarbethoxyethyl)-thiophene

53.9 g (0.3 mol) of o-Chlorocynoacetophenone, 9.6 g of sulphur, 30.4 g (0.3 mol) of triethylamine and 120 ml of dimethylformamide are mixed with 64.8 g (0.3 mol) of dicarbethoxybutyraldehyde (D. T. Warner, J. Am. Chem. Soc.

70, 3470 (1948); Bp. 97°C/0.1 mbar) with stirring, initially at ambient temperature, but with the temperature rising to 45 - 50°C. The mixture is stirred for 2 to 3 hours at 60 to 70°C, cooled to ambient temperature and 400 ml of water are added. The thiophene derivative formed is extracted three times with 200 ml of methyl-tert.butylketone. After washing with water and drying of the organic phase it is evaporated and the crystalline residue is recrystallised from isopropanol/water 7:3. Yield: 90 g (74% of theory), m.p. 96 - 98°C.

b) 2-Amino-o-chlorobenzoyl-5-(2-carbomethoxyethyl)-thiophene

63 g (0.15 mol) of the above compound are refluxed for 2 hours with 120 ml of ethanol and 32.5 g of caustic potash in 50 ml of water. The mixture is concentrated in vacuo, diluted with 50 ml of water and acidified with HCl. The greasy acid precipitate is extracted several times with ethyl acetate. The extracts are dried and concentrated by evaporation and the residue is refluxed for 2 hours with 300 ml of toluene and 30 ml of dimethylformamide. After evaporation to about 50 ml, crystals of the monocarboxylic acid are obtained.

Yield: 20.5 g. The purified acid melts at 171 - 173°C.

The crude acid is stirred for 18 hours at ambient temperature together with 400 ml of absolute methanol and 0.4 ml of concentrated sulphuric acid. After evaporation of the methanol the residue is poured onto ice, extracted with methylene chloride and, after re-evaporation from isopropylether, 15 g of ester are obtained, m.p. 89 - 90°C.

c) 2-Bromoacetyl-amino-3-o-chlorobenzoyl-5-(2-carbomethoxy-ethyl)-thiophene

27.8 g (0.09 mol) of the above ester are suspended in 700 ml of toluene and mixed with 10 g of sodium bicarbonate in 57 ml of water. 7.9 ml of bromoacetyl bromide are gradually added at 40 to 50°C with stirring and the mixture is stirred for a further 30 minutes. It is washed with water, the toluene is dried, evaporated in vacuo and brought to crystallisation with isopropylether.

Yield: 35 - 37 g, m.p. 104 - 106°C.

d) 2-Aminoacetyl-amino-3-o-chlorobenzoyl-5-(2-carbomethoxy-ethyl)-thiophene

35.8 g (0.08 mol) of the above bromoacetyl compound are dissolved in 700 ml of ethyl acetate and dry ammonia is introduced at ambient temperature with stirring over a period of 2 to 3 hours. The mixture is left to stand overnight, washed with iced water, dried, evaporated and 22 - 25 g of oily amino compound are obtained.

e) 7-(2-Carbomethoxyethyl)-5-o-chlorophenyl-thieno-1,4-diazepinone

21.3 g (0.056 mol) of the above compound are dissolved in 500 ml of toluene and refluxed for 2 hours with 75 g of silica gel using a water separator. The SiO_2 is removed by suction filtering and the diazepine is extracted with hot methanol. After evaporation of the methanol, 12 - 15 g of diazepine are obtained, m.p. 160 - 162°C.

f) 7-(2-Carbomethoxyethyl)-5-o-chlorophenyl-thieno-1,4-diazepin-2-thione

10 g (0.03 mol) of the above diazepinone are stirred in 100 ml of diglyme with 6.8 g of phosphorus

pentasulphide and 5 g of sodium hydrogen carbonate for 3 hours at 70 - 80°C. The suspension is poured onto ice, stirred for 30 to 45 minutes and the crystals are suction filtered. After drying, 10 g of thione are obtained, m.p. 185 - 186°C.

g) Methyl 2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]ethane-1-carboxylate

6.1 g (0.016 mol) of the above sulphur compound are dissolved in 100 ml of tetrahydrofuran and, after the addition of 1 g of hydrazine hydrate, stirred for 30 minutes at 45 - 50°C. Then the mixture is evaporated in vacuo. 5 to 5.2 g of oil remain, which crystallises from isopropylether (m.p. 175 - 177°C).

On being heated in 35 ml of ortho-acetic acid ester to 80°C and evaporation from methylene chloride/ether, the hydrazino compound yields 3 g of the triazolodiazepine, m.p. 114 - 115°C.

The same compound can be obtained from the thione with acetic acid hydrazide.

After saponification in alcoholic-aqueous potassium hydroxide solution, 6.1 g of the methylester yield 5.7 - 5.8 g of the free carboxylic acid, m.p. 196 - 198°C.

Example 2

2-[4-(2-Chlorophenyl)-9-cyclopropyl-6H-thieno[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid morpholide

Starting from 15 g of 2-[4-(2-chlorophenyl)-9-cyclopropyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid, m.p.

227-230°C, the title compound is obtained with the aid of dicyclohexylcarbodiimide and morpholine using the method described in Example 1.

Yield: 15.0 g (86.5% of theory), m.p. 159 - 160°C.

$^1\text{H-NMR}$ (CDCl_3); δ = 0.96-1.40 (4m, cyclopropyl $-\text{CH}_2-$), 1.93-2.28 (1m, cyclopropyl), 2.64 (2t, $\text{CH}_2-\text{CO}-$), 3.15 (2t, CH_2), 3.31-3.77 (8m, morpholine), 4.91 (2s, CH_2 - 7-ring) 6.44 (1s, thiophene), 7.22-7.60 (4m, aryl)

The starting compound is obtained as follows:

38 g (0.1 mol) of 7-(2-Carbomethoxyethyl)-5-o-chlorophenyl-thieno-1,4-diazepin-2-thione (cf. Example 1), m.p. 185 - 186°C, are refluxed for 1 hour with 11 g of cyclopropylcarboxylic acid hydrazide in 50 ml of dioxan for 1 hour. After evaporation, on trituration with ether, 30 g of red crystals remain, m.p. 148 - 150°C, which are heated in 1 litre of toluene in the presence of 140 g of silica gel for 4 hours using a water separator. The mixture is then cooled, suction filtered and the triazolo compound is extracted with hot methanol. 24 g of viscous oil remain as the residue from the extraction and this oil is saponified by boiling for 1 hour in 250 ml of 2 N alcoholic potassium hydroxide solution. After working up in the usual way, 15 - 18 g of the carboxylic acid are obtained which can be converted directly into the amide.

Example 3

[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]diazepin-2-yl]-carboxylic acid morpholide

36 g (0.1 mol) of the corresponding carboxylic acid (K.H. Weber et al DE-A- 2503235, 29.7.1976,

p. 14) with a melting point of 302°C are reacted with 10 g of morpholine in the presence of dicyclohexylcarbodiimide in dimethylformamide as described in Example 1. 38 g (89% of theory) of viscous oil are obtained.

$^1\text{H-NMR}$ (CDCl_3); δ = 2.75 (3s, CH_3), 3.71 (8s, morpholine), 4.97 (2s CH_2 - 7 - ring) 6.83 (1s, thiophene) 7.26-7.64 (4m, aryl)

Starting from 2-amino-3-(2-chlorobenzoyl)-thiophene-5-carboxylic acid (O. Hromatka, Monatsh. Chem. 164, 973 (1973)) the morpholide, m.p. 206 - 208°C, is obtained via the corresponding acid chloride. This morpholide can also be converted into the title compound in the manner described in Example 1.

Example 4

[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]diazepin-2-yl]-carboxylic acid amide

3.7 g (0.01 mol) of the corresponding methyl carboxylate (K.H. Weber et al, DE-A- 2503235, 29.7.1976, p. 14), m.p. 230 - 232°C, are dissolved in 100 ml of methanol and ammonia is introduced with stirring at ambient temperature until saturation is reached. The mixture is then stirred for a further 2 days at 20 - 25°C, the solvent is evaporated off and chromatographed over SiO_2 (elution with methylene chloride/methanol 9:1)

Yield: 3.5 g (98% of theory), m.p. 300°C (decomp).

$^1\text{H-NMR}$ (CDCl_3); δ = 2.66 (3s, CH_3), 4.85 (2s, CH_2), 7.50 (1s, thiophene), 7.52 (4H, aryl), 7.65 and 8.25 (2s, NH_2)

Example 5

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid diethylamide

3.87 g (0.01 mol) of the corresponding carboxylic acid (see Example 1) are stirred in 50 ml of methylene chloride with 1 ml of pure thionylchloride for 2 hours at 30 - 35°C. Then 8 ml of diethylamine are added whilst cooling with ice and the mixture is stirred for a further 30 minutes. The salts are washed out with water, the methylene chloride phase is dried, partly evaporated and chromatographed over SiO₂ for final purification (eluant: methylene chloride containing 4% added methanol). 1.8 - 2.0 g of viscous oil are obtained.

¹H-NMR (CDCl₃); δ = 1.09 and 1.12 (2 x 3 t, C₂H₅)
2.52 (2t CH₂-CO), 2.72 (3s, CH₃), 3.03 - 3.56 (6m, C₂H₅ and CH₂), 4.90 (2s, CH₂ - 7 - ring), 6.44 (1s, thiophene), 7.25 - 7.55 (4m aryl)

Example 6

[4-(2-Chlorophenyl)-9-methyl-6-H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]-diazepin-2-yl]-methane carboxylic acid morpholide

20 g (0.054 mol) of [4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-methane carboxylic acid, 500 ml of tetrahydrofuran and 10 g of 1,1'-carbonyldiimidazole are stirred for 1 hour at ambient temperature and the solution, now clear, is mixed with 0.06 mol (5.2 g) of morpholine. After stirring overnight at ambient temperature, evaporation, taking up in methylene chloride, washing with sodium bicarbonate solution and filtering through a column of SiO₂, 9.4 g of the title compound, m.p. 143-144°C, are obtained by recrystallisation from ethyl acetate.

$^1\text{H-NMR}$ (CDCl_3): δ = 2.74 (3s, CH_3), 3.36 - 3.82 (8 m, morpholine), 3.88 (2s, $\text{CH}_2\text{-CO}$), 4.97 (2s, $\text{CH}_2\text{-7-ring}$), 6.51 (1s, thiophene), 7.25 - 7.60 (4m, aryl).

The carboxylic acid can be obtained as follows:

Diethyl malonate and bromoacetaldehyde acetal yield the dicarbethoxypropionaldehyde ($\text{Bp}_{0.01}$: 92 - 95°C) according to methods known from the literature, and this latter can be converted analogously to Example 1 with chlorocyanoacetophenone and sulphur into the corresponding 2-aminobenzoylthiophene. Saponification, decarboxylation and esterification with methanol/sulphuric acid yield the 2-amino-3-(o-chlorobenzoyl)-5-(carbomethoxy-methyl)-thiophene, bromoacetylation, amination and cyclising yield the corresponding diazepinone of m.p. 180 - 182°C. The thione obtained from this melts at 184 - 185°C. Treatment of the thione with hydrazine and subsequent reaction with orthoacetic acid ester yields the methyl triazolothienocarboxylate, m.p. 139 - 141°C; subsequent saponification with alcoholic-aqueous potassium hydroxide solution yields the free carboxylic acid, m.p. 257-259°C.

Example 7

3-[4-(2-Chlorophenyl)-9-methyl-6-H-thieno[3,2-f][1,2,4]-triazolo-[4,3-a][1,4]-diazepin-2-yl]-propane-1-carboxylic acid morpholide

Analogously to Example 6, 10 g (0.025 mol) of 3-[4-(2-chlorophenyl)-9-methyl-6-H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepin-2-yl]-propane-1-carboxylic acid are reacted in tetrahydrofuran with morpholine and 1,1'-carbonyldiimidazole and, after chromatographic working up, yield 10.5 g (89% of theory) of a viscous, almost colourless

oil.

$^1\text{H-NMR}$ (CDCl_3): δ 2.00 (2m, CH_2), 2.37 (2m, CH_2CO), 2.71 (3s, CH_3), 2.87 (2m, CH_2), 3.26 - 3.83 (8m, morpholine), 4.94 (2s, CH_2 -7-ring), 6.41 (1s, thiophene), 7.24 - 7.61 (4m, aryl).

The starting material was obtained as follows:

Starting from cyclohexanone, using methods known from the literature (L. Claisen, Ber.dtsch. chem. Ges. 40, 3907), the enoether can be obtained which is then subjected to ozonolysis (V. Schmid, P. Grafen, Liebigs Ann. Chem. 656, 97 (1962)). Methyl 5-formylvalerate is obtained, which is reacted as already described to form the 2-amino-benzoyl-thiophene-2-propane carboxylic acid ester. The thiophenediazepinone obtained from this melts at 152 - 153°C. Further reaction with phosphorus-pentasulphide analogously to Example 1 f yields the thione, m.p. 176 - 178°C. Reaction with hydrazine and with orthoacetic acid ester according to Example 1 g result in the corresponding ester, which is saponified with alcoholic potassium hydroxide solution to yield the carboxylic acid with a melting point of 257-259°C.

Example 8

4-[4-(2-Chlorophenyl-9-methyl-6-H-thieno[3,2-f][1,2,4]-triazolo[4,3-a][1,4]-diazepin-2-yl]-butane-1-carboxylic acid morpholide

15 g (0.036 mol) of 4-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]-triazolo-[4,3-a][1,4]-diazepin-2-yl]-butane-1-carboxylic acid yield the title compound as a bright yellow viscous oil (yield 13 g = 75% of theory) when reacted analogously to Example 1 with morpholine and dicyclohexylcarbodiimide

in dimethylformamide as the solvent.

$^1\text{H-NMR}$ (CDCl_3); δ 1.72 (4m, $-\text{CH}_2-\text{CH}_2-$), 2.87 (2m, CH_2CO), 2.71 (3s, CH_3), 2.83 (2m, CH_2), 3.30 - 3.77 (8m, morpholine), 4.93 (2s, CH_2 -7-ring), 6.41 (1s, thiophene), 7.21 - 7.58 (4m, aryl).

The carboxylic acid is obtained starting from commercial cycloheptanone analogously to Example 7 via the corresponding aldehyde, bp_{15} : 115 - 120°C, the methyl thienotriazolo-1,4-diazepin-2-butane-carboxylate, m.p. 119 - 121°C, is obtained after saponification of the latter and melts at 133 - 134°C.

Example 9

2-[9-Bromo-4-(2-chlorophenyl-6-H-thieno[3,2-f][1,2,4]-triazolo-[4,3-a][1,4]-diazepin-2-yl]-ethane-1-carboxylic acid morpholide

4.4 g (0.001 mol) of 2-[4-(2-chlorophenyl)-6-H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]-diazepin-2-yl]-ethane-1-carboxylic acid morpholide, m.p. 188 - 189°C (cf. Example 19) is dissolved in 44 ml of chloroform, then 2 ml of pyridine and 0.7 ml of bromine are added and the mixture is stirred overnight at ambient temperature. The light brown reaction solution is washed with sodium bicarbonate/water, the organic phase is dried and the solvent is evaporated. When ether is added, 3.1 g (60% of theory) of the title compound are obtained as bright greyish-brown crystals which melt at 181 - 182°C.

$^1\text{H-NMR}$ (CDCl_3): δ = 2.66 (2t, CH_2CO), 3.17 (2t, CH_2), 3.31 - 3.75 (8m, morpholine), 4.95 (2s, CH_2), 6.46 (1s, thiophene), 7.30 - 7.55 (4m, aryl)

Example 10

2-[4-(2-Chlorophenyl)-9-methoxy-6H-thieno[3,2-f]-[1,2,4]triazolo-[4,3-a][1,4]-diazepin-2-yl]-ethane-1-carboxylic acid morpholide

2.6 g (0.5 mmol) of the 9-Bromo compound of Example 9 are stirred with a solution of 3.7 g of caustic potash in 400 ml of methanol for 1 hour at 50 - 60°C. After evaporation of the methanol, the residue is mixed with ice water and extracted with methylene chloride. The organic phase is dried and the solvent is evaporated in vacuo. The residue remaining is recrystallised from ethyl acetate, to produce 1.8 g (76% of theory) of the title compound, m.p. 163 - 164°C.

$^1\text{H-NMR}$ (CDCl_3): δ = 2.62 (2t, CH_2), 3.11 (2t, CH_2), 3.32 - 3.77 (8m, morpholino), 4.27 (3s, CH_3), 4.88 (2s, CH_2), 6.36 (1s, thiophene), 7.36 (4s, aryl).

Example 11

8-[4-(2-Chlorophenyl)-9-cyclopropyl-6H-thieno[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-n-octane-1-carboxylic acid morpholide

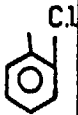
4.63 g (0.01 mol) of the corresponding carboxylic acid are converted into the amide by means of cyclohexylcarbodiimide analogously to the process described in Example 1. 4.4 g (84.6% of theory) of viscous oil are obtained.

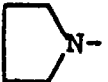
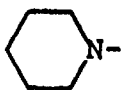
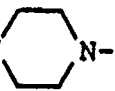
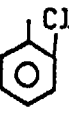
$^1\text{H-NMR}$ (CDCl_3): δ = 1.12-1.14 (12m, $(\text{CH}_2)_6$), 2.72 (3s, CH_3), 2.68 (2t, $\text{CH}_2\text{-CO}$), 3.15 (2t, CH_2), 3.31-3.78 (8m, morpholine), 4.90 (2s, CH_2), 6.42 (1s, thiophene), 7.25-7.60 (4m, aryl)

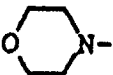
The starting compound for the carboxylic acid is methyl 9-formyl-nonanecarboxylate, b.p. 005 101 - 104°C, which is obtained according to R.A.

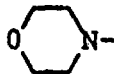
Volkman et al., J. Org. Chem. 48, 1767 (1983).

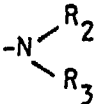
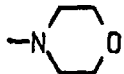
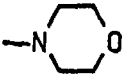
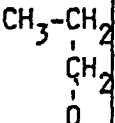
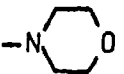
The following compounds were also obtained using the methods described hereinbefore:

Example No.	R ₁	$\begin{array}{c} \text{R}_2 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}_3 \end{array}$	R ₄	n	Mp. °C	Spectrum
12	CH ₃	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{H} \end{array}$		2	166-167	¹ H-NMR (CDCl ₃); δ = 2,50 (2t, CH ₂ -CO), 2,70 (3s, CH ₃), 2,79 (3d, CH ₃ N), 3,31 (2t, CH ₂), 4,85 (2s, CH ₂), 5,85 (1q, NH), 6,45 (1s, Thiophene), 7,25 - 7,57 (4m, Aryl)
13	CH ₃	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{HC} \\ \diagdown \\ \text{CH}_3 \end{array} \begin{array}{c} \diagdown \\ \text{N} \\ \diagup \\ \text{H} \end{array}$	"	2	Oil	¹ H-NMR (CDCl ₃); δ = 1,11 (6d (CH ₃)-Isoprop.), 2,45 (2t, CH ₂ CO), 2,68 (3s, CH ₃), 3,12 (2t, CH ₂), 4,08 (1m CH-Isoprop.), 4,91 (2s, CH ₂), 5,48 (1d, NHCO), 6,45 (1s, Thiophene), 7,22 - 7,57 (4m, Aryl)
14	CH ₃	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{CH}_3 \end{array}$	"	2	157-158	¹ H-NMR (CDCl ₃); δ = 2,63 (2t, CH ₂ -CO), 2,71 (3s, CH ₃), 2,97 (6s, N(CH ₃) ₂), 3,13 (2t, CH ₂), 4,14 (2s, CH ₂), 6,44 (1s, Thiophene), 7,28 - 7,57 (4m, Aryl)

Example No.	R ₁	$\begin{array}{c} R_2 \\ \diagup \\ -N- \\ \diagdown \\ R_3 \end{array}$	R ₄	n	Mp. °C	Spectrum
15	CH ₃			2	167-168	¹ H-NMR (CDCl ₃); δ = 1,64 - 2,20 (4m, Pyrrolazole), 2,57 (2t, CH ₂ -CO), 2,70 (3s, CH ₃), 3,14 (2t, CH ₂), 3,24 - 3,57 (4m, Pyrrolazole), 4,41 (2s, CH ₂), 6,42 (1s, Thiophene), 7,26 - 7,52 (4m, Aryl)
16	CH ₃			2	143-145	¹ H-NMR (CDCl ₃); δ = 1,33 - 1,77 (6m, Piperidine), 2,62 (2t, CH ₂ -CO), 2,71 (3s, CH ₃), 3,13 (2t, CH ₂), 3,35, 3,55 (4m, Piperidine), 4,93 (2s, CH ₂), 6,42 (1s, Thiophene), 7,24 - 7,57 (4m, Aryl)
17	CH ₃	CH ₃ -N  N-		2	Oil	¹ H-NMR (CDCl ₃); δ = 2,32 (3s, NCH ₃), 2,39 (4t, Piperazine), 2,65 (2t, CH ₂ -CO), 2,73 (3s, CH ₃), 3,16, 3,46 (4t, Piperazine), 3,65 (2t, CH ₂), 4,95 (2s, CH ₂), 6,45 (1s, Thiophene), 7,29 - 7,58 (4m, Aryl)

Example No.	R ₁	-N $\begin{matrix} R_2 \\ R_3 \end{matrix}$	R ₄	n	Mp. °C	Spectrum
18		$\begin{matrix} H_5C_2 \\ H_5C_2 \end{matrix} N-$		2	Oil	¹ H-NMR (CDCl ₃); δ = 0,93 - 1,35 (10m, Cyclopropyl, C ₂ H ₅), 1,93 - 2,26 (1m, CH-Cyclopropyl), 2,62 (2t, CH ₂ CO), 3,00 - 3,53 (6m, C ₂ H ₅ und CH ₂), 4,91 (2s, CH ₂), 6,46 (1s, Thiophene), 7,24 - 7,57 (4m, Aryl)
19	H			2	188-190	¹ H-NMR (CDCl ₃); δ = 2,63 (2t, CH ₂ -CO), 3,14 (2t, CH ₂), 3,32 - 3,67 (8m, Morpholine), 5,03 (2s, CH ₂), 6,42 (1s, Thiophene), 7,25 - 7,42 (4m, Aryl), 8,46 (1s, Triazole)
20	CH ₃	NH ₂		1	202-204	¹ H-NMR (CDCl ₃); δ = 2,70 (3s, CH ₃), 3,75 (2s, CH ₂ -NH ₂), 4,90 (2s, CH ₂ -7-Ring), 5,54 - 6,48 (2m, NH ₂), 6,53 (1s, Thiophene), 7,18 - 7,56 (4m, Aryl).

Example No	R ₁	$\begin{array}{c} R_2 \\ \diagup \\ -N \\ \diagdown \\ R_3 \end{array}$	R ₄	n	Mp. °C	Spectrum
21	CH ₃	$\begin{array}{c} \text{CH}_2\text{CH}_2\text{OH} \\ \diagup \\ N \\ \diagdown \\ \text{CH}_2\text{CH}_2\text{OH} \end{array}$		2	Oil	¹ H-NMR (CDCl ₃); δ = 2,16 (2s, OH), 2,69 (3s, CH ₃), 2,79 (2t, CH ₂ CO), 3,15 (2t, CH ₂), 3,53 - 3,77 (8m, <u>CH</u> ₂ - <u>CH</u> ₂ -OH), 4,90 (2s, CH ₂ -7-Ring), 6,45 (1s, Thiophene), 7,22 - 7,63 (4m, Aryl).
22	CH ₃	 N-		2	180-181	¹ H-NMR (CDCl ₃); δ = 2,70 (2t, CH ₂), 2,70 (3s, CH ₃), 3,22 (2t, CH ₂), 3,36 - 3,80 (8m, Morpholine), 4,85 (2s, CH ₂), 6,73 (1s, Thiophene), 7,24 - 7,72 (5m, Aryl)
23	CH ₃	HO(CH ₂) ₂ -N-		2	Oil	¹ H-NMR (CDCl ₃); δ = 3,50 (1s, OH), 2,54 (2t, CH ₂ CO), 2,65 (3s, CH ₃), 3,11 (2t, CH ₂), 3,38 (2m, NCH ₂), 3,65 (2t, OCH ₂), 4,86 (2s, CH ₂), 6,44 (1s, Thiophene), 6,88 (1t, NH-CO), 7,25 - 7,55 (4m, Aryl)

Example No.	R ₁		R ₄	n	Mp. °C	Spectrum
24	CH ₂ Cl			2	163-165	¹ H-NMR (CDCl ₃): δ = 2,64 (2t, CH ₂ CO), 3,16 (2t, CH ₂), 3,28 - 3,78 (8m, Morpholine), 4,94 (4s, CH ₂ Cl, CH ₂ -7-Ring) 6,41 (1s, Thiophene), 7,17 - 7,53 (4m, Aryl).
25	CH ₂ Br			2	Oil	¹ H-NMR (CDCl ₃): δ = 2,58 (2t, CH ₂ CO), 3,11 (2t, CH ₂), 3,22 - 3,74 (8m, Morpholine), (2s, CH ₂ Br), 4,98 (2s, CH ₂ -7-Ring), (1s, Thiophene), 7,21 - 7,71 (4m, Aryl)
26						¹ H-NMR (CDCl ₃): δ = 1.09 (3t, J=7Hz, CH ₃), 1.95 (2m, CH ₂ -CH ₃), 2.63 (2t, J=7Hz, CH ₂ CO), 3.15 (2t, J=7Hz, CH ₂ -thiophene), 3.31-3.74 (8m, morpholine), 4.60 (2t, J=6Hz, O-CH ₂), 4.90 (2s, CH ₂ -7-ring), 6.39 (1s, thiophene), 7.39 (4s, aryl)

Examples of some pharmaceutical compositions using compounds of general formula I as active ingredient will now be given. Unless otherwise expressly stated, the parts are parts by weight.

1. Tablets

The tablets contain the following ingredients:

Active substance of general formula I	0.020 parts
Stearic acid	0.010 parts
Dextrose	<u>1.890 parts</u>
	total 1.920 parts

Preparation

The substances are mixed together in known manner and the mixture is compressed to form tablets each weighing 1.92 g and containing 20 mg of active substance.

2. Ointment

The ointment consists of the following ingredients:

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno- [3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin- 2-yl]-ethane-1-carboxylic acid morpholide	50 mg
Neribas ointment (commercial product Scherax)	ad 10 g

Preparation:

The active substance is triturated with 0.5 g of ointment base and the remaining base is added in batches of 1.0 g gradually and intimately mixed to form an ointment. A 0.5% ointment is obtained. The distribution of the active substance in the base is monitored optically under a microscope.

3. Cream

Composition:

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno-

[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-
2-yl]-ethane-1-carboxylic acid morpholide 50 mg
Neribas ointment (commercial product
Scherax) ad 10 g

Preparation

The active substance is triturated with 0.5 g of cream base and the remaining base is gradually incorporated in amounts of 1.0 g with a pestle. A 0.5% cream is obtained. The distribution of the active substance in the base is monitored optically under a microscope.

4. Ampoule solution

Composition:

- a) 2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno-
[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-
2-yl]-ethane-1-carboxylic acid morpholide 1.0 mg
Sodium chloride 45.0 mg
Water for injection ad 5.0 ml
- b) 2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno-
[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-
2-yl]-ethane-1-carboxylic acid morpholide 5.0 mg
Sodium chloride 45.0 mg
Water for injection ad 5.0 ml
- c) 2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno-
[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-
2-yl]-ethane-1-carboxylic acid morpholide 1.0 mg
Sodium chloride 9.0 mg
Water for injection ad 1.0 ml

Preparation

The active substance is dissolved in water at its own pH and sodium chloride is added as an isotonic substance. The resulting solution is

filtered to remove pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 1 mg, 5 mg and 1 mg of active substance.

5. Suppositories

Each suppository contains:

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno- [3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]- ethane-1-carboxylic acid morpholide	1.0 parts
Cocoa butter (m.p. 36 - 37°C)	1200.0 parts
Carnauba wax	5.0 parts

Preparation:

The cocoa butter and carnauba wax are melted together. At 45°C the active substance is added and the mixture is stirred until a complete dispersion is formed. The mixture is poured into moulds of suitable sizes and the suppositories are appropriately packaged.

6. Solutions for inhalation

Composition:

a)

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno- [3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin- 2-yl]-ethane-1-carboxylic acid morpholide	500 mg
Na-EDTA	50 mg
Benzalkonium chloride	25 mg
Sodium chloride	880 mg
Distilled water	ad 100 ml

Preparation:

96% of the quantity of water is put in first, then the Na-EDTA, benzalkonium chloride, sodium chloride and active substance are dissolved successively

therein until a clear solution is formed and the remainder of the water is added. The solution is poured into drop vials with a capacity of 20 ml. One dose (20 drops, 1 ml) contains 5 mg of active substance.

b)

2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno- [3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin- 2-yl]-ethane-1-carboxylic acid morpholide	500 mg
Sodium chloride	820 mg
Distilled water	ad 100 ml

Preparation:

96% of the quantity of water is put in first, then the active substance and sodium chloride are successively dissolved therein, the remaining water is added and the solution is transferred into single dose containers (4 ml). The solution contains 20 mg of active substance.

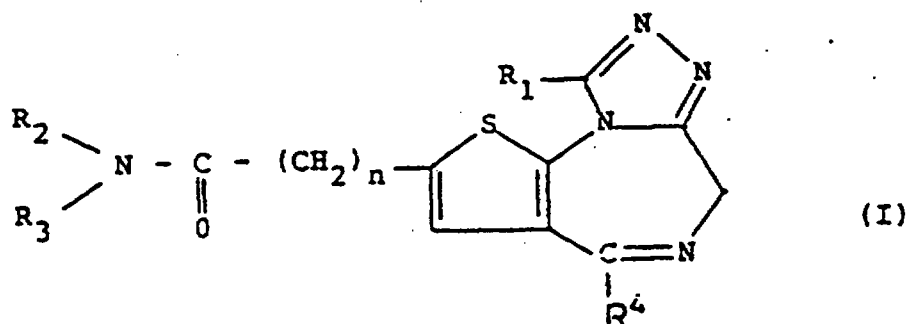


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Patent Claims

1. Thieno-triazolo-1,4-diazepino-2-carboxylic acid amides of general formula



wherein

- R_1 represents hydrogen, a straight-chained or branched alkyl group having 1 to 4 carbon atoms, optionally substituted by halogen or hydroxy, cyclopropyl, alkoxy with 1-3 carbon atoms or halogen;
- R_2 and R_3 , which may be identical or different, represent hydrogen, a straight-chained or branched alkyl or hydroxyalkyl group with 1 to 4 carbon atoms or both groups R_2 and R_3 together with the nitrogen atom represent a 5-, 6- or 7-membered ring which optionally contains a nitrogen, oxygen or sulphur atom as a further heteroatom, the second nitrogen atom optionally being substituted by an alkyl group with 1-4 carbon atoms;
- R_4 represents phenyl, wherein the phenyl ring may be mono- or polysubstituted by methyl, halogen, nitro or trifluoromethyl, or α -pyridyl and
- n represents one of the numbers 0, 1, 2, 3, 4, 5, 6, 7 or 8.



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2. Thieno-triazolo-1,4-diazepino-2-carboxylic acid amides of general formula I as claimed in claim 1, wherein

R_1 , R_2 and R_3 are defined as hereinbefore,

R_4 represents phenyl, 2-chlorophenyl or 2-bromophenyl and

n represents the number 1, 2 or 3.

3. Thieno-triazolo-1,4-diazepino-2-carboxylic acid amides of general formula I as claimed in claim 1 wherein

R_1 represents hydrogen, a straight-chained or branched alkyl group with 1 to 4 carbon atoms, cyclopropyl, methoxy, chlorine or bromine;

R_2 and R_3 represent hydrogen, methyl, ethyl, hydroxy-

ethyl or together with a nitrogen atom they represent morpholine;

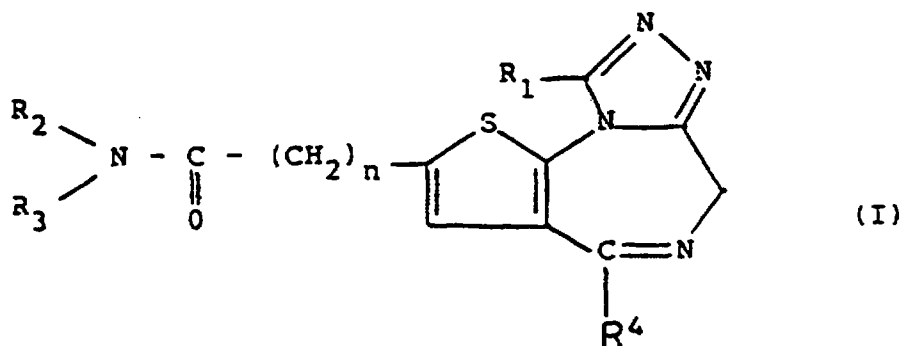
R_4 represents 2-chlorophenyl or 2-bromophenyl and

n represents the number 2.

4. 2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid morpholide).

5. 2-[4-(2-Chlorophenyl)-9-methyl-6H-thieno[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-ethane-1-carboxylic acid diethylamide).

6. Process for preparing thieno-triazolo-1,4-diazepino-2-carboxylic acid amides of general formula I





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wherein

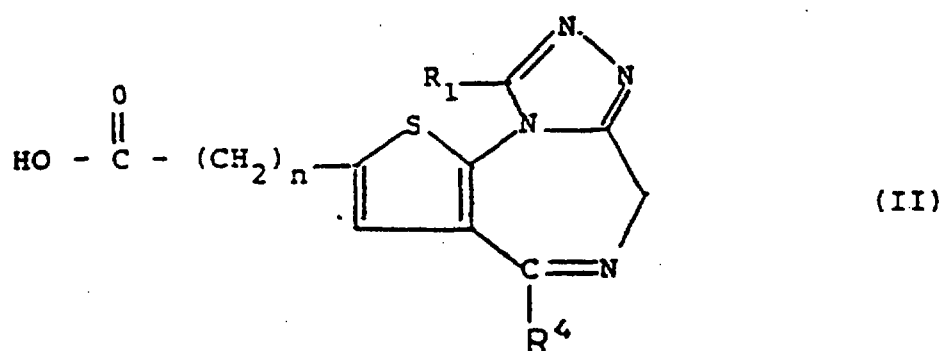
R_1 represents hydrogen, a straight-chained or branched alkyl group having 1 to 4 carbon atoms, optionally substituted by halogen or hydroxy, cyclopropyl, alkoxy with 1-3 carbon atoms, halogen;

R_2 and R_3 , which may be identical or different, represent hydrogen, a straight-chained or branched alkyl or hydroxyalkyl group with 1 to 4 carbon atoms or both groups R_2 and R_3 together with the nitrogen atom represent a 5-, 6- or 7-membered ring which optionally contains a nitrogen, oxygen or sulphur atom as a further heteroatom, the second nitrogen atom optionally being substituted by an alkyl group with 1-4 carbon atoms;

R_4 represents phenyl, the phenyl ring optionally being mono- or polysubstituted by methyl, halogen, nitro or trifluoromethyl, or a pyridyl;

and

n represents one of the numbers 0, 1, 2, 3, 4, 5, 6, 7 or 8, characterised in that a corresponding 2-carboxylic acid of general formula II

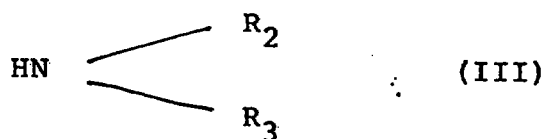


wherein the groups R_1 and R_4 are as hereinbefore defined,

a) is reacted with an amine of general formula III

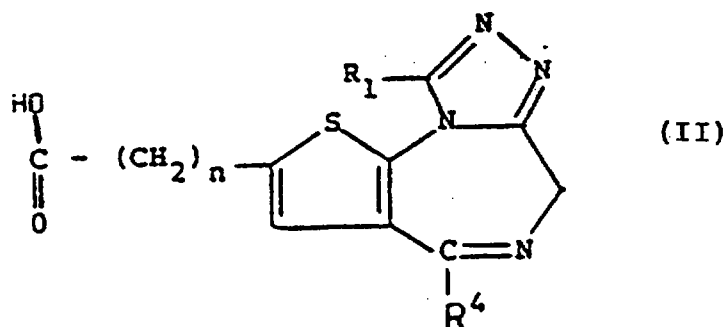


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wherein the groups R_2 and R_3 are as hereinbefore defined, or

- b) the carboxylic acid of general formula II is converted in the usual way into an acid halide or an acid anhydride and this is then reacted with a corresponding amine of general formula III.
7. Pharmaceutical preparations containing as active substances compounds of general formula I together with conventional excipients and/or carriers.
8. Process for preparing pharmaceutical preparations as claimed in claim 7, characterised in that compounds of general formula I are processed with conventional galenic excipients and/or carriers to form conventional pharmaceutical forms for administration.
9. Compounds of general formula I as claimed in claim 1 for use in the preparation of pharmaceutical compositions having a PAF antagonistic activity.
10. Compounds of general formula I as claimed in claim 1 for use in the preparation of pharmaceutical compositions for the treatment of bronchial asthma.
- 10.[sic] Thieno-triazolo-1,4-diazepino-2-carboxylic acids of general formula II



wherein



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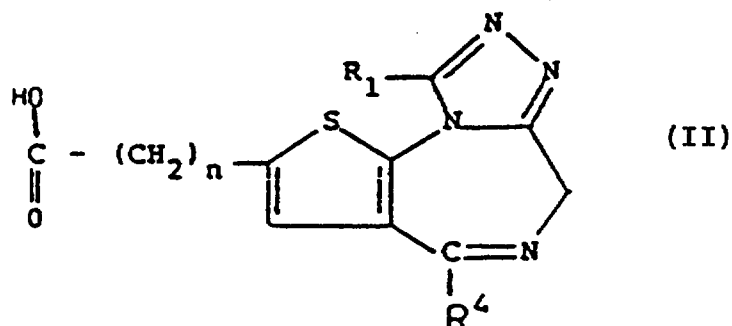
R_1 represents hydrogen, a straight-chained or branched alkyl group with 1-4 carbon atoms optionally substituted by halogen or hydroxy, or cyclopropyl, alkoxy with 1-3 carbon atoms, halogen,

and

R_4 represents phenyl, the phenyl ring optionally being mono- or polysubstituted by methyl, halogen, nitro or trifluoromethyl, or α -pyridyl, and

n represents one of the numbers 1, 2, 3, 4, 5, 6, 7 and 8.

11. Process for preparing thieno-triazolo-1,4-diazepino-2-carboxylic acids of general formula II



wherein

R_1 represents hydrogen, a straight-chained or branched alkyl group with 1-4 carbon atoms optionally substituted by halogen or hydroxy, or cyclopropyl, alkoxy with 1-3 carbon atoms, halogen, and

R_4 represents phenyl, in which the phenyl ring may be mono- or polysubstituted by methyl, halogen, nitro or trifluoromethyl, or α -pyridyl, and

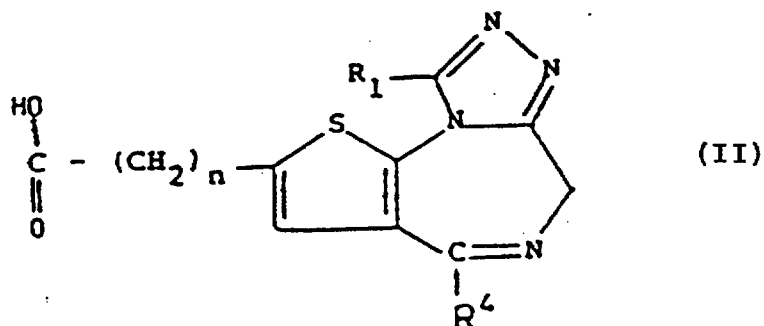
n represents one of the numbers 1, 2, 3, 4, 5, 6, 7 and 8,

characterised in that

a) a compound of general formula



12. Process for preparing thieno-triazolo-1,4-diazepino-2-carboxylic acids of general formula II



wherein

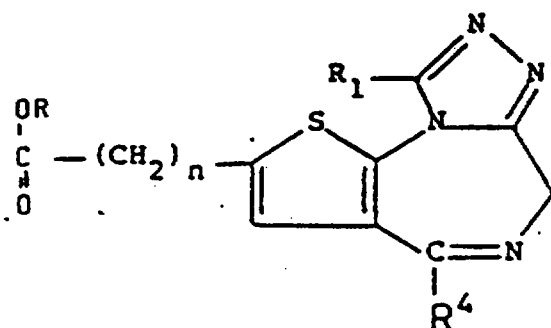
R_1 represents hydrogen, a straight-chained or branched alkyl group with 1-4 carbon atoms optionally substituted by halogen or hydroxy, or cyclopropyl, alkoxy with 1-3 carbon atoms, halogen,

and

R_4 represents phenyl, the phenyl ring optionally being mono- or polysubstituted by methyl, halogen, nitro or trifluoromethyl, or α -pyridyl, and

n represents one of the numbers 1, 2, 3, 4, 5, 6, 7 and 8,

characterised in that a compound of general formula



wherein R_1 , R_4 and n are defined as hereinbefore and R represents a lower alkyl group, is saponified.