

Azepinoindole derivatives, their preparation and use

The present invention relates to novel azepinoindole derivatives,
5 their preparation and use as inhibitors of the enzyme
poly(ADP-ribose) polymerase or PARP (EC 2.4.2.30) for the
production of pharmaceuticals.

Poly(ADP-ribose) polymerase (PARP) or, as it is also called,
10 poly(ADP-ribose) synthase (PARS) is a regulatory enzyme which is
found in cell nuclei (K. Ikai et al., J. Histochem. Cytochem.
1983, 31, 1261-1264). It is assumed that PARP plays a role in the
repair of DNA breaks (M.S. Satoh et al., Nature 1992, 356,
356-358). Damage to or breaks in the DNA strands activate the
15 enzyme PARP, which, when it is activated, catalyzes the transfer
of ADP-ribose from NAD (S. Shaw, Adv. Radiat. Biol., 1984, 11,
1-69). In this process, nicotinamide is released from NAD.
Nicotinamide is converted again into NAD by other enzymes using
the energy carrier ATP. Overactivation of PARP would accordingly
20 have resulted in a nonphysiologically high consumption of ATP and
in the extreme case this leads to cell damage and cell death.

It is known that free radicals such as the superoxide anion, NO
and hydrogen peroxide can lead to DNA damage in cells and thus
25 activate PARP. The formation of large amounts of free radicals is
observed in a number of pathophysiological conditions and it is
assumed that this accumulation of free radicals leads or
contributes to the observed cell or organ damage. This counts,
for example, ischemic conditions of organs such as in stroke,
30 cardiac infarct (C. Thiernemann et al., Proc. Natl. Acad. Sci.
USA, 1997, 94, 679-683) or ischemia of the kidneys, but also
reperfusion damage such as occurs after the lysis of cardiac
infarct (see above: C. Thiernemann et al.). The inhibition of the
enzyme PARP could accordingly be a means of preventing or
35 alleviating this damage at least partially. PARP inhibitors could
thus be a novel therapy principle for the treatment of a number
of diseases.

The enzyme PARP influences the repair of DNA damage and could
40 thus also play a role in the therapy of carcinomatous diseases,
as a higher potential of action against tumor tissue has been
observed in combination with cytostatically active substances (G.
Chen et al. Cancer Chemo. Pharmacol. 1988, 22, 303).

Nonlimiting examples of tumors are leukemia, glioblastoma,
45 lymphoma, melanoma, mammary and cervical carcinoma.

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Moreover, it has been found that PARP inhibitors can show immunosuppressant action (D. Weltin et al. *Int. J. Immunopharmacol.* 1995, 17, 265-271).

- 5 It has likewise been discovered that PARP is involved in immunological disorders or diseases in which the immune system plays an important role, such as rheumatoid arthritis and septic shock, and that PARP inhibitors can show a favorable effect on the course of the disease (H. Kröger et al. *Inflammation* 1996, 20, 203-215; W. Ehrlich et al. *Rheumatol. Int.* 1995, 15, 171-172; C. Szabo et al., *Proc. Natl. Acad. Sci. USA* 1998, 95, 3867-3872; S. Cuzzocrea et al. *Eur. J. Pharmacol.* 1998, 342, 67-76).

PARP within the meaning of this invention is also understood as meaning isoenzymes of the PARP enzyme described above.

The PARP inhibitor 3-aminobenzamide furthermore showed protective effects in a model of circulatory shock (S. Cuzzocrea et al., *Br. J. Pharmacol.* 1997, 121, 1065-1074).

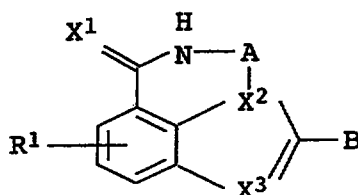
- 20 There are likewise experimental indications that inhibitors of the enzyme PARP could be useful as a means for the treatment of diabetes mellitus (V. Burkart et al. *Nature Med.* 1999, 5, 314-319).
- 25 WO 00/42040 mentions azepinoindoles which inhibit the PARP enzyme. In particular, derivatives are described there as active which carry a phenyl ring in the 2 position, which can additionally be substituted by simple substituents.
- 30 The compounds of the general formula I according to the invention here have not been described until now and are accordingly novel.

In the present invention, novel azepinoindole derivatives of the general formula I are described which are potent PARP inhibitors.

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The present invention relates to substituted azepinoindole derivatives of the general formula I

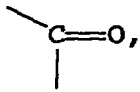
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I

45 in which

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- A can be a C₁-C₃ chain, where each carbon atom can additionally carry one or two of the following substituents: C₁-C₄-alkyl, OH, O-C₁-C₄-alkyl, COOH, COO-C₁-C₄-alkyl and phenyl or a C atom can also carry an =O group and
- 5 X¹ can be S, O or NH and
- X² can be a carbon atom which can additionally carry a C₁-C₄ chain, and N and
- 10 X³ can be N or C-R², where
- R² can be hydrogen, branched or unbranched C₁-C₆-alkyl, C₁-C₄-alkylphenyl, phenyl and
- 15 X² and X³ cannot simultaneously be N, and
- R¹ can be hydrogen, chlorine, fluorine, bromine, iodine, branched or unbranched C₁-C₆-alkyl, OH, nitro, CF₃, CN, NR¹¹R¹², NH-CO-R¹³, O-C₁-C₄-alkyl, where R¹¹ and R¹² independently of one another are hydrogen or C₁-C₄-alkyl and R¹³ is hydrogen, C₁-C₄-alkyl, C₁-C₄-alkylphenyl or phenyl, and
- 20 B can be an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 14 carbon atoms and 0 to 5 nitrogen atoms, 0 to 2 oxygen atoms and 0 to 2 sulfur atoms, which in each case are additionally substituted by one R⁴ and at most 3 different or identical radicals R⁵, and can carry one or two carbon or sulfur atoms and also one or two =O groups such as keto groups, sulfones or sulfoxides,
- 30 R⁴ is -(D)_p-(E)_s-(F¹)_q-G¹-(F²)_r-(G²)-G³, where G¹, G² and G³ cannot simultaneously be hydrogen or a bond and if p = s = 0 and q or r = 1 or p, q and r = 0, then two radicals G¹, G² and G³ cannot simultaneously be a bond or hydrogen, and
- 35 D can be S, NR⁴³ or O
- 40 E can be phenyl,
- 
- SO₂-, -SO₂NH-, -NHCO-, -CONH-, NHSO₂-,
-NHCOCH₂X⁴,
- 45 and

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X⁴ can be S, O or NH, and

F¹ can be a straight-chain or branched saturated or unsaturated carbon chain of 1 to 8 C atoms and

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F² independently of F¹ has the same meaning as F¹,

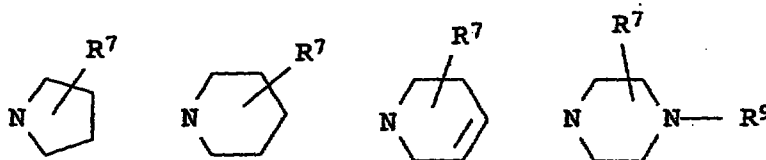
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G¹ is a bond or can be an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 14 carbon atoms and 0 to 5 nitrogen atoms, 0 to 2 oxygen atoms and 0 to 2 sulfur atoms, which in each case are additionally substituted by at most 3 different or identical radicals R⁵ and can carry one or two carbon or sulfur atoms and one or two =O groups, and

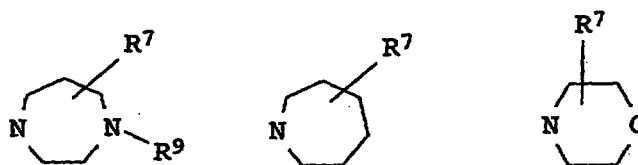
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G² is NR⁴¹R⁴² or

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25



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or a bond and

G³ can be an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 14 carbon atoms and 0 to 5 nitrogen atoms, 0 to 2 oxygen atoms or 0 to 2 sulfur atoms, which in each case are additionally substituted by at most 3 different or identical radicals R⁵, and one or two carbon or sulfur atoms can also carry one or two =O groups, or hydrogen, and

35

40

p can be 0 or 1 and

s can be 0 or 1 and

45

q can be 0 or 1 and

5

r can be 0 or 1 and

5 R⁴¹ can be hydrogen, C₁-C₆-alkyl, where each carbon atom can additionally carry up to two radicals R⁶, phenyl which can additionally carry at most two radicals R⁶, and (CH₂)_t-K and

R⁴² can be hydrogen, C₁-C₆-alkyl, -CO-R⁸, CO₂-R⁸, SO₂NH₂, SO₂-R⁸, -(C=N)-R⁸ and -(C=N)-NHR⁸ and

10 R⁴³ can be hydrogen or C₁-C₄-alkyl and

t can be 1, 2, 3 or 4 and

15 K can be NR¹¹R¹², NR¹¹-C₁-C₄-alkylphenyl, pyrrolidine, piperidine, 1,2,5,6-tetrahydropyridine, morpholine, homopiperidine, piperazine, which can additionally be substituted by an alkyl radical C₁-C₆-alkyl, and homopiperazine which can additionally be substituted by an alkyl radical C₁-C₆-alkyl, and

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R⁵ can be hydrogen, chlorine, fluorine, bromine, iodine, OH, nitro, CF₃, CN, NR¹¹R¹², NH-CO-R¹³, C₁-C₄-alkyl-CO-NH-R¹³, COR⁸, C₀-C₄-alkyl-O-CO-R¹³, C₁-C₄-alkylphenyl, phenyl, CO₂-C₁-C₄-alkyl, and branched or unbranched C₁-C₆-alkyl,

25 O-C₁-C₄-alkyl, S-C₁-C₄-alkyl, where each C atom of the alkyl chains can carry up to two radicals R⁶ and the alkyl chains can also be unsaturated, and

30 R⁶ can be hydrogen, chlorine, fluorine, bromine, iodine, branched or unbranched C₁-C₆-alkyl, OH, nitro, CF₃, CN, NR¹¹R¹², NH-CO-R¹³, O-C₁-C₄-alkyl

35 R⁷ can be hydrogen, C₁-C₆-alkyl, phenyl, where the ring can additionally be substituted by up to two radicals R⁷¹, and one amine NR¹¹R¹² or a cyclic saturated amine having 3 to 7 members, which can additionally be substituted by an alkyl radical C₁-C₆-alkyl, and homopiperazine which can additionally be substituted by an alkyl radical C₁-C₆-alkyl, and

40 where the radicals R¹¹, R¹² and R¹³ in K, R⁵, R⁶ and R⁷ independently of one another can assume the same meaning as R¹, and

45 R⁷¹ can be OH, C₁-C₆-alkyl, O-C₁-C₄-alkyl, chlorine, bromine, iodine, fluorine, CF₃, nitro, NH₂, and

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R⁸ can be C₁-C₆-alkyl, CF₃, phenyl, C₁-C₄-alkylphenyl, where the ring can additionally be substituted by up to two radicals R⁸¹, and

5 R⁸¹ can be OH, C₁-C₆-alkyl, O-C₁-C₄-alkyl, chlorine, bromine, iodine, fluorine, CF₃, nitro, NH₂, and

R⁹ can be hydrogen, C₁-C₆-alkyl, C₁-C₄-alkylphenyl, CO₂-C₁-C₄-alkylphenyl, CO₂-C₁-C₄-alkyl, SO₂-phenyl, COR⁸ and
10 phenyl, where the phenyl rings can additionally be substituted by up to two radicals R⁹¹, and

R⁹¹ can be OH, C₁-C₆-alkyl, O-C₁-C₄-alkyl, chlorine, bromine, iodine, fluorine, CF₃, nitro, NH₂,

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and their tautomeric forms, possible enantiomeric and diastereomeric forms, and their prodrugs.

Preferred compounds of the formula I are those where

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A is a C₂ chain which can be substituted, and

X¹ is O and

25 R¹ is hydrogen.

Preferred compounds of the formula I are those as indicated above, in which

30 B can be an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 14 carbon atoms and 0 to 5
35 nitrogen atoms, 0 to 2 oxygen atoms or 0 to 2 sulfur atoms, which in each case are additionally substituted by an R⁴ and at most 3 different or identical radicals R⁵, and can carry one or two carbon or sulfur atoms and also one or two =O groups.

40 Particularly preferred radicals for B are the following:

B is phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiophene, furan, oxazole, naphthalene, piperazine, quinoline, pyrazine, which can additionally be
45 substituted by one R⁴ or at most 2 R⁵.

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Very particularly preferred compounds of the formula I are those where

R^4 is $D-F^{10,1}-G^2-G^3$ where G^3 is hydrogen and

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D is O or NR^{43} , where R^{43} is hydrogen or C_1-C_3 -alkyl and

F^1 is C_2-C_4 -alkyl.

- 10 The compounds of the formula I can be employed as racemates, as enantiomerically pure compounds or as diastereomers. If enantiomerically pure compounds are desired, these can be obtained, for example, by carrying out a classical resolution with the compounds of the formula I or their intermediates using
- 15 a suitable optically active base or acid.

Alkyl chains can in each case be branched or unbranched. Unbranched alkyl chains are preferred.

- 20 The invention also relates to compounds which are mesomeric or tautomeric to compounds of the formula I.

The invention further relates to the physiologically tolerable salts of the compounds I, which can be obtained by conversion of

25 compounds I using a suitable acid or base. Suitable acids and bases are listed, for example, in Fortschritte der Arzneimittelforschung, 1966, Birkhäuser Verlag, Vol. 10, pp. 224-285. These include, for example, hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid,

30 methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid etc. or sodium hydroxide, lithium hydroxide, potassium hydroxide and tris.

Prodrugs are understood as meaning those compounds which are

35 metabolized in vivo to compounds of the general formula I. Typical prodrugs are phosphates, carbamates of amino acids, esters and others.

The azepinoindole derivatives I according to the invention can be

40 prepared in various ways, such as described in WO 00/42040.

The substituted azepinoindole derivatives I obtained in the present invention are inhibitors of the enzyme poly(ADP-ribose)polymerase or PARP (EC 2.4.2.30).

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The inhibitory action of the substituted azepinoindole derivatives I can be determined using an enzyme test which is already known in the literature, the measure of activity determined being a K_i value. The azepinoindole derivatives I were
5 measured in this way for inhibitory action of the enzyme poly(ADP-ribose)polymerase or PARP (EC 2.4.2.30).

The substituted azepinoindole derivatives of the general formula I are inhibitors of poly(ADP-ribose)polymerase (PARP) or, as it
10 is also called, poly(ADP-ribose)synthase (PARS) and can thus be used for the treatment and prophylaxis of diseases which are connected with an increased enzyme activity of these enzymes.

The compounds of the formula I can be employed for the production
15 of pharmaceuticals for the treatment of damage after ischemia and for prophylaxis in the case of expected ischemia of various organs.

The present azepinoindole derivatives of the general formula I
20 can accordingly be used for the treatment and prophylaxis of neurodegenerative diseases which occur after ischemia, trauma (craniocerebral trauma), mass hemorrhages, subarachnoid hemorrhages and stroke, and of neurodegenerative diseases such as multiple infarct dementia, Alzheimer's disease, Huntington's
25 disease and of epilepsy, in particular of generalized epileptic attacks, such as petit mal and tonic-clonic attacks and partially epileptic attacks, such as temporal lobe, and complex/partial attacks, and furthermore for the treatment and prophylaxis of damage to the heart after cardiac ischemia and damage to the
30 kidneys after renal ischemia, for example of acute renal insufficiency caused by medicinal therapies such as in the case of cyclosporin treatment, of acute kidney failure or of damage which occurs during and after a kidney transplantation.

Furthermore, the compounds of the general formula I can be used
35 for the treatment of acute myocardial infarct and damage which occurs during and after medicinal lysis thereof (for example using TPA, reteplase, streptokinase or mechanically using a laser or rotator) and of microinfarcts during and after heart valve replacement, aneurysm resection and heart transplantation.

40 Likewise, the present azepinoindole derivatives I can be used for the treatment of a revascularization of critically constricted coronary arteries, for example in PCTA and bypass operations, and critically constricted peripheral arteries, for example leg arteries. Moreover, the azepinoindole derivatives I can be useful
45 for the treatment of tumors and metastasis thereof and for the treatment of inflammation and rheumatic disorders, such as rheumatoid arthritis and also for the treatment of diabetes

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mellitus, for the treatment of multiorgan failure, e.g. in septic shock and for the treatment of ARDS (acute respiratory distress syndrome, shock lung).

- 5 In addition to the customary pharmaceutical excipients, the pharmaceutical preparations according to the invention contain a therapeutically active amount of the compound I.

For local external application, for example in powders, ointments
10 or sprays, the active compounds can be present in the customary concentrations. As a rule, the active compounds are present in an amount from 0.001 to 1% by weight, preferably 0.001 to 0.1% by weight.

- 15 In the case of internal administration, the preparations are administered in individual doses. In an individual dose, 0.1 to 100 mg are given per kg of body weight. The preparations can be administered daily in one or more doses, depending on the nature and severity of the disorders.

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Corresponding to the desired manner of administration, the pharmaceutical preparations according to the invention contain the customary vehicles and diluents in addition to the active compound. For local external application, pharmaceutical
25 excipients, such as ethanol, isopropanol, ethoxylated castor oil, ethoxylated hydrogenated castor oil, polyacrylic acid, polyethylene glycol, polyethylene glycol stearate, ethoxylated fatty alcohols, liquid paraffin, petroleum jelly and wool fat can be used. For internal administration, for example, lactose,
30 propylene glycol, ethanol, starch, talc and polyvinylpyrrolidone are suitable.

- Antioxidants such as tocopherol and butylated hydroxyanisole and also butylated hydroxytoluene, flavor-improving additives,
35 stabilizers, emulsifiers and lubricants can furthermore be present.

The substances contained in the preparation in addition to the active compound and the substances used in the production of the
40 pharmaceutical preparations are toxicologically innocuous and compatible with the respective active compound. The pharmaceutical preparations are produced in a customary manner, for example by mixing the active compound with other customary vehicles and diluents.

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The pharmaceutical preparations can be administered in various modes of administration, for example perorally, parenterally, such as intravenously, by infusion, subcutaneously, intraperitoneally and topically. Thus, preparation forms such as
5 tablets, emulsions, infusion and injection solutions, pastes, ointments, gels, creams, lotions, powders and sprays are possible.

Pharmacological Example:

10 Inhibition of the enzyme poly(ADP-ribose)polymerase or PARP
(EC 2.4.2.30)

A 96-well microtiter plate (Flacon) is coated with histones (type II-AS; SIGMA H7755). For this purpose, histones are dissolved in
15 carbonate buffer (0.05 M NaHCO_3 ; pH 9.4) to give a concentration of 50 $\mu\text{g/ml}$. The individual wells of the microtiter plates are incubated overnight with 100 μl each of this histone solution. The histone solution is then removed and the individual wells are incubated at room temperature for 2 hours with 200 μl of a 1%
20 strength BSA (bovine serum albumin) solution in carbonate buffer. The wells are then washed three times with wash buffer (0.05% Tween 10 in PBS). For the enzyme reaction, 50 μl of the enzyme reaction solution (5 μl of reaction buffer (1 M tris HCl pH 8.0, 100 mM MgCl_2 , 10 mM DTT), 0.5 μl of PARP ($c = 0.22 \mu\text{g}/\mu\text{l}$), 4 μl of
25 activated DNA (SIGMA D-4522, 1 mg/ml in water), 40.5 μl of H_2O) are preincubated with 10 μl of an inhibitor solution per well for 10 minutes. The enzyme reaction is started by addition of 40 μl of a substrate solution (4 μl of reaction buffer (see above), 8 μl of NAD solution (100 μM in H_2O), 28 μl of H_2O). The reaction
30 time is 20 minutes at room temperature. The reaction is stopped by washing three times with wash buffer (see above). A one-hour incubation at room temperature with a specific anti-poly-ADP-ribose antibody then follows. The antibodies used were monoclonal anti-poly-(ADP-ribose) antibodies "10H"
35 (Kawamatsu H et al. (1984) Monoclonal antibodies to poly (adenosine diphosphate ribose) recognize different structures. Biochemistry 23, 3771-3777). Polyclonal antibodies can also be used.

40 The antibodies were employed in a 1:5 000 dilution in antibody buffer (1% BSA in PBS; 0.05% Tween 20). After washing three times with wash buffer, a one-hour incubation at room temperature with secondary antibody follows. Here, for the monoclonal antibody, an anti-mouse IgG coupled to peroxidase (Boehringer Mannheim) and,
45 for the rabbit antibody, an anti-rabbit IgG coupled to peroxidase (SIGMA A-6154), in each case in a 1:10 000 dilution in antibody buffer, were used. After washing three times with wash buffer,

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the color reaction was carried out using 100 µl/well of color reagent (SIGMA, TMB ready-to-use mix, T8540) for about 15 min at room temperature. The color reaction is stopped by addition of 100 µl of 2 M H₂SO₄. The color is then immediately measured

5 (450 nm against 620 nm; ELISA "Easy Reader" EAR340AT plate reader, SLT-Labinstruments, Austria). The IC₅₀ value of an inhibitor to be measured is the inhibitor concentration where a half-maximal color concentration change occurs.

10 The following compounds according to the invention can be prepared analogously to the methods described above:

1. 2-(4-(4-*n*-Propylpiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
- 15 2. 2-(4-Piperazin-1-ylphenyl)-1,3,4,5-tetrahydro-6H-azepino-[5,4,3-*c,d*]indol-6-one
3. 2-(4-(4-Isopropylpiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
- 20 4. 2-(4-(4-Benzylpiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
- 25 5. 2-(4-(4-*n*-Butylpiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
6. 2-(4-(4-Ethylpiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
- 30 7. 2-(4-(2-*N,N*-Dimethylaminoeth-1-yloxy)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
8. 2-(4-(2-Pyrrolidinyleth-1-yloxy)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
- 35 9. 2-(4-(2-Piperidin-1-yleth-1-yloxy)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
- 40 10. 2-(4-(2-Piperazin-1-yleth-1-yloxy)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one
11. 2-(4-(2-(4-Methylpiperazin-1-yl)eth-1-yloxy)phenyl)-1,3,4,5-tetrahydro-6H-azepino[5,4,3-*c,d*]indol-6-one

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12. 2-(4-(2-(4-Propyl-piperazin-1-yl)eth-1-yloxy)phenyl)-
1,3,4,5-tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one
13. 2-(4-(2-(4-Ethyl-piperazin-1-yl)eth-1-yloxy)phenyl)-
5 1,3,4,5-tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one
14. 2-(4-(2-(4-Benzylpiperazin-1-yl)eth-1-yloxy)phenyl)-
1,3,4,5-tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one
- 10 15. 2-(4-(2-(4-Acetamidopiperazin-1-yl)eth-1-yloxy)phenyl)-
1,3,4,5-tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one
16. 2-(4-(2-(4-Benzamidopiperazin-1-yl)eth-1-yloxy)phenyl)-
1,3,4,5-tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one
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17. 2-(4-Homopiperazin-1-yl-phenyl)-1,3,4,5-tetrahydro-6H-
azepino[5,4,3-c,d]indol-6-one
18. 2-(4-(4-Methylhomopiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-
20 6H-azepino[5,4,3-c,d]indol-6-one
19. 2-(4-(4-Benzylhomopiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-
6H-azepino[5,4,3-c,d]indol-6-one
- 25 20. 2-(4-(4-n-Butylhomopiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-
6H-azepino[5,4,3-c,d]indol-6-one
21. 2-(4-(4-Ethylhomopiperazin-1-yl)phenyl)-1,3,4,5-tetrahydro-
6H-azepino[5,4,3-c,d]indol-6-one
30
22. 2-Piperidin-4-yl-1,3,4,5-tetrahydro-6H-azepino[5,4,3-c,d]-
indol-6-one
23. 2-(1-Methylpiperidin-4-yl)-1,3,4,5-tetrahydro-6H-azepino-
35 [5,4,3-c,d]indol-6-one
24. 2-(1-n-Propylpiperidin-4-yl)-1,3,4,5-tetrahydro-6H-azepino-
[5,4,3-c,d]indol-6-one
- 40 25. 2-(1-Benzylpiperidin-4-yl)-1,3,4,5-tetrahydro-6H-azepino-
[5,4,3-c,d]indol-6-one
26. 2-(1-n-Butylpiperidin-4-yl)-1,3,4,5-tetrahydro-6H-azepino-
[5,4,3-c,d]indol-6-one
45

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27. 2-(1-Isopropylpiperidin-4-yl)-1,3,4,5-tetrahydro-6H-azepino-
[5,4,3-c,d]indol-6-one

28. 2-(2-(N,N-Dimethylamino)eth-1-ylamino)phenyl)-1,3,4,5-
5 tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one

29. 2-(2-(N,N-Diethylamino)eth-1-ylamino)phenyl)-1,3,4,5-
tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one

10 30. 2-(2-Piperidin-1-yleth-1-ylamino)phenyl)-1,3,4,5-tetrahydro-
6H-azepino[5,4,3-c,d]indol-6-one

31. 2-(2-Pyrrolidin-1-yleth-1-ylamino)phenyl)-1,3,4,5-tetrahydro-
6H-azepino[5,4,3-c,d]indol-6-one

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32. 2-(3-(N,N-Dimethylamino)prop-1-ylamino)phenyl)-1,3,4,5-
tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one

33. 2-(3-(N,N-Diethylamino)prop-1-ylamino)phenyl)-1,3,4,5-
20 tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one

34. 2-(3-Piperidin-1-yl-prop-1-ylamino)phenyl)-1,3,4,5-
tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one

25 35. 2-(3-Pyrrolidin-1-yl-prop-1-ylamino)phenyl)-1,3,4,5-
tetrahydro-6H-azepino[5,4,3-c,d]indol-6-one

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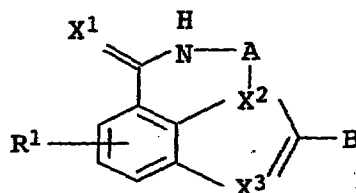


We claim:

1. A compound of the formula I

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I

in which

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A can be a C₁-C₃ chain, where each carbon atom can additionally carry one or two of the following substituents: C₁-C₄-alkyl, OH, O-C₁-C₄-alkyl, COOH, COO-C₁-C₄-alkyl and phenyl or a C atom can also carry an =O group and

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X¹ can be S, O or NH and

X² can be a carbon atom which can additionally carry a C₁-C₄ chain, and N and

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X³ can be N or C-R², where

R² can be hydrogen, branched or unbranched C₁-C₆-alkyl, C₁-C₄-alkylphenyl, phenyl and

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X² and X³ cannot simultaneously be N, and

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R¹ can be hydrogen, chlorine, fluorine, bromine, iodine, branched or unbranched C₁-C₆-alkyl, OH, nitro, CF₃, CN, NR¹¹R¹², NH-CO-R¹³, O-C₁-C₄-alkyl, where R¹¹ and R¹² independently of one another are hydrogen or C₁-C₄-alkyl and R¹³ is hydrogen, C₁-C₄-alkyl, C₁-C₄-alkylphenyl or phenyl, and

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B can be an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 14 carbon atoms and 0 to 5 nitrogen atoms, 0 to 2 oxygen atoms and 0 to 2 sulfur atoms, which in each case are additionally substituted by one R⁴ and at most 3 different or

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identical radicals R^5 , and can carry one or two carbon or sulfur atoms and also one or two $=O$ groups,

5 R^4 is $-(D)_p-(E)_s-(F^1)_q-G^1-(F^2)_r-(G^2)-G^3$, where G^1 , G^2 and G^3 cannot simultaneously be hydrogen or a bond and if $p = s = 0$ and q or $r = 1$ or p , q and $r = 0$, then two radicals G^1 , G^2 and G^3 cannot simultaneously be a bond or hydrogen, and

10 D can be S, NR^{43} or O

E can be phenyl,

15 $\begin{array}{c} \diagup \\ C=O, \\ | \end{array}$ $-SO_2-$, $-SO_2NH-$, $-NHCO-$, $-CONH-$, $NHSO_2-$,
 $-NHCOCH_2X^4$,
 and

X^4 can be S, O or NH, and

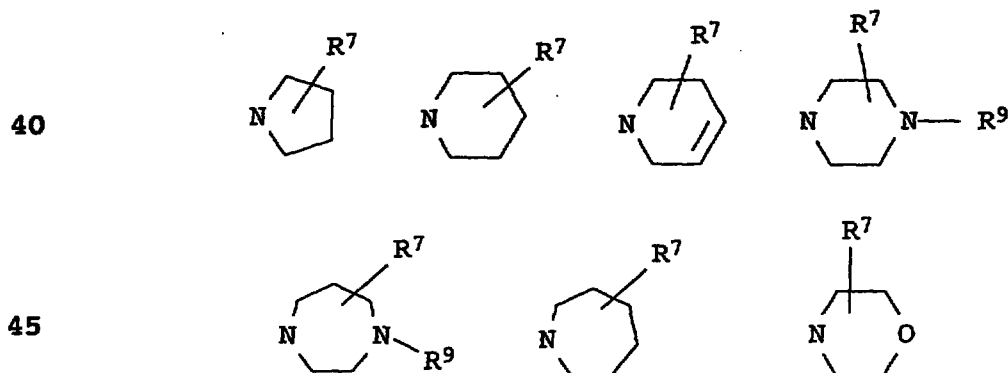
20 F^1 can be a straight-chain or branched saturated or unsaturated carbon chain of 1 to 8 C atoms and

F^2 independently of F^1 has the same meaning as F^1 ,

25 G^1 is a bond or can be an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 14 carbon atoms and 0
 30 to 5 nitrogen atoms, 0 to 2 oxygen atoms and 0 to 2 sulfur atoms, which in each case are additionally substituted by at most 3 different or identical radicals R^5 and can carry one or two carbon or sulfur atoms and one or two $=O$ groups, and

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G^2 is $NR^{41}R^{42}$ or





or a bond and

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G^3 can be an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 14 carbon atoms and 0 to 5 nitrogen atoms, 0 to 2 oxygen atoms or 0 to 2 sulfur atoms, which in each case are additionally substituted by at most 3 different or identical radicals R^5 , and one or two carbon or sulfur atoms can also carry one or two =O groups, or hydrogen, and

p can be 0 or 1 and

s can be 0 or 1 and

q can be 0 or 1 and

r can be 0 or 1 and

R^{41} can be hydrogen, C_1 - C_6 -alkyl, where each carbon atom can additionally carry up to two radicals R^6 , phenyl which can additionally carry at most two radicals R^6 , and $(CH_2)_t$ -K and

R^{42} can be hydrogen, C_1 - C_6 -alkyl, $-CO-R^8$, CO_2-R^8 , SO_2NH_2 , SO_2-R^8 , $-(C=N)-R^8$ and $-(C=N)-NHR^8$ and

R^{43} can be hydrogen or C_1 - C_4 -alkyl and

t can be 1, 2, 3 or 4 and

K can be $NR^{11}R^{12}$, NR^{11} - C_1 - C_4 -alkylphenyl, pyrrolidine, piperidine, 1,2,5,6-tetrahydropyridine, morpholine, homopiperidine, piperazine, which can additionally be substituted by an alkyl radical C_1 - C_6 -alkyl, and homopiperazine which can additionally be substituted by an alkyl radical C_1 - C_6 -alkyl, and

R^5 can be hydrogen, chlorine, fluorine, bromine, iodine, OH, nitro, CF_3 , CN, $NR^{11}R^{12}$, $NH-CO-R^{13}$, C_1 - C_4 -alkyl-CO-NH- R^{13} , COR^8 , C_0 - C_4 -alkyl-O-CO- R^{13} , C_1 - C_4 -alkylphenyl, phenyl, CO_2 - C_1 - C_4 -alkyl, and branched or unbranched C_1 - C_6 -alkyl, O- C_1 - C_4 -alkyl, S- C_1 - C_4 -alkyl, where each C atom of the

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alkyl chains can carry up to two radicals R^6 and the alkyl chains can also be unsaturated, and

5 R^6 can be hydrogen, chlorine, fluorine, bromine, iodine, branched or unbranched C_1 - C_6 -alkyl, OH, nitro, CF_3 , CN, $NR^{11}R^{12}$, $NH-CO-R^{13}$, $O-C_1-C_4$ -alkyl

10 R^7 can be hydrogen, C_1 - C_6 -alkyl, phenyl, where the ring can additionally be substituted by up to two radicals R^{71} , and one amine $NR^{11}R^{12}$ or a cyclic saturated amine having 3 to 7 members, which can additionally be substituted by an alkyl radical C_1 - C_6 -alkyl, and homopiperazine which can additionally be substituted by an alkyl radical C_1 - C_6 -alkyl, and

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where the radicals R^{11} , R^{12} and R^{13} in K, R^5 , R^6 and R^7 independently of one another can assume the same meaning as R^1 , and

20 R^{71} can be OH, C_1 - C_6 -alkyl, $O-C_1-C_4$ -alkyl, chlorine, bromine, iodine, fluorine, CF_3 , nitro, NH_2 , and

25 R^8 can be C_1 - C_6 -alkyl, CF_3 , phenyl, C_1 - C_4 -alkylphenyl, where the ring can additionally be substituted by up to two radicals R^{81} , and

R^{81} can be OH, C_1 - C_6 -alkyl, $O-C_1-C_4$ -alkyl, chlorine, bromine, iodine, fluorine, CF_3 , nitro, NH_2 , and

30 R^9 can be hydrogen, C_1 - C_6 -alkyl, C_1 - C_4 -alkylphenyl, CO_2 - C_1 - C_4 -alkylphenyl, CO_2 - C_1 - C_4 -alkyl, SO_2 -phenyl, COR^8 and phenyl, where the phenyl rings can additionally be substituted by up to two radicals R^{91} , and

35 R^{91} can be OH, C_1 - C_6 -alkyl, $O-C_1-C_4$ -alkyl, chlorine, bromine, iodine, fluorine, CF_3 , nitro, NH_2 ,

or its tautomeric forms, possible enantiomeric and diastereomeric forms, and its prodrugs.

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2. A compound of the formula I as claimed in claim 1, where

A is a C₂ chain which can be substituted, and

5 X¹ is O and

R¹ is hydrogen.

10 3. A compound of the formula I as claimed in one of claims 1 and 2, in which

15 B can be an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tricyclic ring having at most 14 carbon atoms and 0 to 5 nitrogen atoms, 0 to 2 oxygen atoms or 0 to 2 sulfur atoms, which in each case are additionally substituted by an R⁴ and at most 3 different or identical radicals R⁵, and can carry one or two carbon or sulfur atoms and also one or two =O groups.

4. A compound of the formula I as claimed in claim 3, where

25 B is phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiophene, furan, oxazole, naphthalene, piperazine, quinoline, pyrazine, which can additionally be substituted by one R⁴ or at most 2 R⁵.

30 5. A compound of the formula I as claimed in claim 4, where

R⁴ is D-F¹_{0,1}-G²-G³ where G³ is hydrogen and

D is O or NR⁴³, where R⁴³ is hydrogen or C₁-C₃-alkyl and

35 F¹ is C₂-C₄-alkyl.

40 6. A pharmaceutical comprising, in addition to customary carriers and excipients, compounds of the formula I as claimed in one of claims 1 to 5.

7. The use of compounds of the general formula I as claimed in one of claims 1 to 5 for the production of pharmaceuticals having PARP-inhibitory action.

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8. The use of compounds of the formula I as claimed in claim 7 for the production of pharmaceuticals for the treatment of neurodegenerative diseases and neuronal damage.
- 5 9. The use as claimed in claim 7 for the treatment of those neurodegenerative diseases and that neuronal damage which are/is caused by ischemia, trauma or mass hemorrhages.
- 10 10. The use as claimed in claim 7 for the treatment of stroke and of craniocerebral trauma.
11. The use as claimed in claim 7 for the treatment of Alzheimer's disease, Parkinson's disease and Huntington's disease.
- 15 12. The use of compounds of the formula I as claimed in claim 7 for the production of pharmaceuticals for the treatment or prophylaxis of damage due to ischemias.
- 20 13. The use of compounds of the formula I as claimed in claim 7 for the production of pharmaceuticals for the treatment of epilepsy, in particular of generalized epileptic attacks, such as, for example, petit mal and tonic/clonic attacks and partially epileptic attacks, such as temporal lobe and
- 25 complex/partial attacks.
14. The use of compounds of the formula I as claimed in claim 7 for the production of pharmaceuticals for the treatment of damage to the kidneys after renal ischemia, damage which is
- 30 caused by medicinal therapy, such as during cyclosporin therapy, and for treatment during and after kidney transplantation.
15. The use of compounds of the formula I as claimed in claim 7
- 35 for the production of pharmaceuticals for the treatment of damage to the heart after cardiac ischemia.
16. The use of compounds of the formula I as claimed in claim 7 for the production of pharmaceuticals for the treatment of
- 40 microinfarcts such as during and after heart valve replacement, aneurysm resection and heart transplantation.
17. The use of compounds of the formula I as claimed in claim 7 for the production of pharmaceuticals for treatment during
- 45 revascularization of critically constricted coronary arteries



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such as in PTCA and bypass operations or critically constricted peripheral arteries, in particular leg arteries.

18. The use of compounds of the formula I as claimed in claim 7
5 for the production of pharmaceuticals for the treatment of acute myocardial infarct and of damage during and after its medicinal or mechanical lysis.
19. The use of compounds of the formula I as claimed in claim 7
10 for the production of pharmaceuticals for the treatment of tumors and metastases thereof.
20. The use of compounds of the formula I as claimed in claim 7
15 for the production of pharmaceuticals for the treatment of multiorgan failure sepsis such as during septic shock and acute respiratory distress syndrome.
21. The use of compounds of the formula I as claimed in claim 7
20 for the production of pharmaceuticals for the treatment of immunological diseases such as inflammation and rheumatic disorders, such as rheumatoid arthritis.
22. The use of compounds of the formula I as claimed in claim 7
25 for the production of pharmaceuticals for the treatment of diabetes mellitus.

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