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DESCRIPTION

[0001] Our invention relates to the use of novel 8-hydroxy-quinoline-derivatives according to the invention in the treatment and prevention of different diseases, primarily those diseases that are associated with neurological and/or oxidative stress.

[0002] Our invention discloses cytoprotective and metal chelate forming agents and their medical use. Furthermore, the object of our invention are compounds for use in the treatment of ischemia, reperfusion injury, cardiovascular disorders, neurodegenerative disorders (including Alzheimer's disease and Huntington's disease) and trauma. Furthermore, the object of our invention are compounds for use in the treatment of depression and other neuropsychiatric disorders, including anxiety disorders. Another object of our invention is the treatment of liver, kidney or lung injuries. The compounds according to the invention can be used as neuroprotective and cardioprotective agents, and for the treatment of neuropsychiatric disorders.

[0003] The various etiological cell injuries and cell deaths are the main characteristics of many cardiovascular, neurological and inflammatory disorders. Cell injuries may occur as the results of cellular hypoxia or ischemia, formation of various kinds of oxidants or free radicals and/or overproduction of various biological mediators (cytokines, chemokines, lipid mediators). These processes are often interdependent; so those occur as parts of self-amplifying ("suicidal") intracellular cycles and form the determining basis of many human diseases. Though cell death is typically qualified as apoptosis or necrosis, these two forms only represent the two ends of the spectrum of the forms of cell injuries. The intercellular mechanisms taking part in the above cell death processes are complex, but often activate the cell death effector family called caspases and mitochondrial dysfunction, mitochondrial depolarisation, generation of reactive oxygen species and release of mitochondrial components into the cytosol (comprehensive literature: Szabó, 2005; Duprez et al., 2009; Degterev es Yuan, 2008; Wang et al., 2009). The pathway of cell death includes activation of poly(ADP-ribose) polymerase (PARP). The latter enzyme is expressed in the nuclei (comprehensive literature: Jagtap and Szabó, 2005) .

[0004] The compounds preventing cell injury and cell death are usually called "cytoprotective" compounds. Cytoprotection may be achieved by many pharmacological and biochemical methods. The following examples of them are mentioned here: scavengers of oxidants and free radicals, inhibitors of certain "death effector pathways", stabilisation of cell membranes, etc. In the course of ischemia or several related disease processes, iron and copper cations are released from the tissues which catalyse hydroxy-free radical formation in the Haber-Weiss pathway in a known manner causing cell injuries. Inactivation or chelate formation of these metal cations may result in a cytoprotective effect. Thus experiments were conducted to mitigate the catalytic efficiency of iron and copper cations in such a way that iron-chelate forming siderophores (e.g. deferoxamine) were administered (Lewen et al., 2000; Britton et al., 2002).

[0005] It is known that glutamate is released along with zinc cations from the synaptosomes of the nervous system cells using glutamate as a chemical messenger. Usually, the zinc released in the nervous synapsis is quickly built again in the synaptosomes. As a result of ischemia, lasting attacks and cerebral lesion, the zinc released from the synaptosomes is accumulated in the extracellular liquid surrounding the neurons. When an excessive amount of zinc enters the cell body, zinc may trigger cell death via apoptosis and necrosis. Zinc-chelate forming through that mechanism may result in neuroprotection and influence the outcome of various neuropsychiatric diseases. (Regland et al., 2001; Koh et al., 1996).

[0006] Therefore the zinc-chelating agents may also be useful in treatment of the Alzhemier's disease by binding zinc occurring in the plaques thus weakening the structure of the plaques (Frederickson et al., 2005; Schafer et al., 2007). The zinc-chelating agents may also be useful in the treatment of Huntington's disease (Nguyen et al., 2005).

[0007] According to another way of cytoprotection, the intracellular pathways mediating protective effects are

induced. A prototype of this approach is the so-called "ischemic preconditioning" where the cells or organs are subjected to ischemia for a short time in order to induce over-regulation of the cytoprotectives genes (e.g. genes of antioxidant enzymes, heat shock proteins and others). Heme oxygenase expression of the enzyme (HO-1) has demonstrated cytoprotection in several experimental systems (e.g. Li et al., 2007; Idris et al., 2008).

[0008] The previous patent applications relating to the cytoprotective approach pertain to the following: inhibitors of various apoptotic pathways or effectors (e.g. US 6,949,516; US 6,737,511; US 6,544,972; US 6,521,617; US 6,495,522; US 7,604,989; US 7,601,846; US 7,533,852); maintaining the mitochondrial function during the cell injury (e.g. US 6,552,076; US 6,511,966; US 7,550,439; US 7,528;174); direct inhibition of the catalytic activity of PARP enzyme (e.g. US 6,476,048; US 6,531,464; US 7,601,719; US 7,595,406; US 7,550,603; US 7,449,464; US 7,217,709; US 6,956,053; US 6,534,651); over-regulation of cytoprotective genes (including heme oxygenase) (e.g. US 7,524,819; US 7,364,757).

[0009] WO 2008/014602 A1 discloses quinoline compounds which are useful for the treatment of disorders caused by oxidative stress and neurodegenerative disorders, including ischemia/reperfusion injury and Alzheimer's disease.

[0010] Compounds used for inhibition of endoplasmatic reticulum stress have been described in the American patent application publication no. 2008/293699.

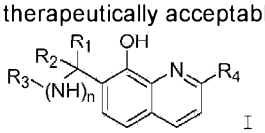
[0011] Cell-based screening tests have recently been performed for systematic identification of cytoprotective compounds. In this test a certain form of cell injury was simulated and a chemical library was screened in order to identify compounds preventing or retarding the cell injury. (e.g. Gero et al., 2007). The screening tests do not identify the mechanism of the effect, however, it can be identified by means of secondary tests.

[0012] By means of the cell-based screening method, we have found and identified novel hydroxy-quinoline derivatives. These compounds protect the cells from injuries induced by oxidative stress therefore these can potentially be used in the treatment of many diseases. The compounds according to the invention exert various cellular effects e.g. iron-chelating, inhibition of PARP-activation, inhibition of mitochondrial dysfunction, activation of heme oxigenase and chelate forming with iron ions. In the course of implementation of our invention the chelators are added in a form free of iron, zinc and copper cations therefore these compounds form complexes with the above cations when in contact with the physiological system.

[0013] The pharmaceutical compositions according to our invention contain chelators as the active agent, which are not in a complex bond with iron, copper or zinc cations.

[0014] The further object of our invention is a neuroprotective and/or cardioprotective procedure for patients suffering from conditions associated with cell death. Neuroprotection and/or cardioprotection is achieved in accordance with our invention in such a way that a compound according to our invention, capable of protecting the cells from cytotoxic attacks is administered to the patient in need of treatment.

[0015] The object of our invention on the one hand is compounds with the general formula (I) and their therapeutically acceptable salts



I

in which formula R_1, R_2, R_3, R_4 and n are defined as in claim 1,

for use in the prophylaxis or treatment of ischemia, reperfusion injury, cardiovascular disorders, neurodegenerative disorders (including especially Alzheimer's disease and Huntington's disease), trauma, neuropsychiatric diseases (including especially depression and anxiety disorders), and liver, kidney and lung injuries.

[0016] Described herein, but not part of the invention, is the group of the compounds with the general formula (I) in which

R_1
: represents a group substituted with an electron withdrawing group in para position, or a group substituted with an electron withdrawing group in meta position, or the above group substituted with an electron donating group in ortho, meta or para position; or R_1 represents a group double-substituted with electron withdrawing groups in meta and para positions; or R_1 represents a group double-substituted with electron withdrawing groups in ortho and para position; or R_1 represents a substituted or unsubstituted heterocyclic group;

R_3
: represents an aromatic group substituted with an electron withdrawing group in para position; or R_3 represents a heteroaromatic or alicyclic group unsubstituted or substituted with an alkyl group and/or electron withdrawing groups in ortho, meta or para position;

R_2 and R_4
: represent hydrogen atom; and

n
: is 1. Described herein, but not part of the invention, is the group of the compounds with the general formula (I) in which

R_1
: represents a phenyl group optionally single or double substituted with a nitro group, trifluoromethyl group, hydroxy group, fluorine atom or isopropoxy group, or pyridyl group

R_2
: represents a hydrogen atom;

R_3
: represents a phenyl group optionally single or double substituted with a trifluoromethyl group or methoxy-carbonyl group or a pyridyl group optionally single or double substituted with a methyl group, fluorine atom, nitro group or a pyrimidyl, pyrrolidinyl, oxazolidinyl group or pyrazolyl group;

R_4
: represents a hydrogen atom; and

n
: is 1.

[0017] Especially preferred are the 8-hydroxy-quinoline derivatives mentioned as title compounds of the examples.

Brief description of the figures:

[0018]

Fig. 1a, 1b and 1c
: illustrate the reperfusion injury reducing effect of the compound according to Example 1 after heart transplantation;

Fig. 2
: illustrates the effect of several compounds according to the invention on cell death caused by hydrogen peroxide in vitro on liver cells;

Fig. 3
: illustrates the effect of several compounds according to the invention on cell death caused by hydrogen

peroxide in vitro on mixed neurons and astrocytes;

Fig. **4**

illustrates the effect of the compound according to Example 1 in elevated plus-maze tests; and

Fig. 5.

illustrates the effect of the compound according to Example 1 in forced swimming tests.

[0019] The terms used in the description should be interpreted as follows:
A "lower alkyl group" means a branched or unbranched alkyl group with 1-**4** carbon atoms (e.g. methyl, ethyl, isopropyl etc. group).

[0020] The term "lower alkenyl group" means a branched or unbranched alkenyl group with 2-**4** carbon atoms (e.g. allyl or propenyl group).

[0021] The term "cycloalkyl group" means cyclic groups containing 3-8 carbon atoms (e.g. cyclopropyl, cyclobutyl, cyclohexyl, etc. group).

[0022] The term "aryl group" means monocyclic or bicyclic aromatic hydrocarbon groups (e.g. phenyl, naphthyl etc. group).

[0023] The term "aralkyl group" means alkyl groups single or double substituted with above aryl groups meeting the above definition (e.g. benzyl, beta phenylethyl etc. group).

[0024] The term "heterocyclic group" means aromatic groups with 3 to 7, preferably 5 or 6 members containing one or more oxygen, nitrogen and/or sulphur atoms (e.g. pyridyl, pyrimidyl, pyrrolyl, oxazolyl etc. group).

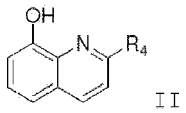
[0025] The term "halogen atom" means bromine, fluorine, chlorine or iodine atom; fluorine and chlorine atoms are preferred. The "electron withdrawing group" substituents are preferably halogen atoms, trifluoromethyl or nitro groups.

[0026] Of the "electron donating" substituents, the lower alkyl groups (e.g. methyl group) are mentioned.

[0027] The "acid functional group" may be any ester group (lower alkoxycarbonyl group, preferably methoxycarbonyl group) or nitrile or acid amide group.

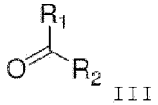
[0028] The compounds having the general formula (I) form salts with bases on the hydroxyl groups or with acids on the nitrogen atom. For salt formation, pharmaceutically acceptable bases (e.g. alkali metal hydroxides, like e.g. sodium or potassium hydroxide) or pharmaceutically acceptable inorganic or organic acids (e.g. hydrochloric acid, hydrogen bromide, acetic acid, fumaric acid, maleic acid, malic acid, succinic acid, tartaric acid, benzene sulphonic acid, p-toluene sulphonic acid, methane sulphonic acid, etc.) can be used.

[0029] The process for preparation of compounds with the general formula (I) and of their pharmaceutically acceptable salts is characterised in that an 8-hydroxyquinoline derivative with the general formula (II)



II

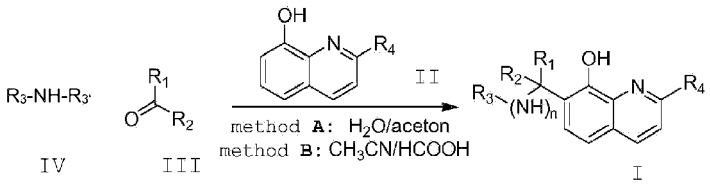
is reacted with an oxo-compound with the general formula (III)



III

and an amine with the general formula (IV)

R_3-NH-$R_{3'}$ IV



(in which formulas the substituents are as defined above and $R_{3'}$ can be independently selected from the possible meanings of R_3, and $R_{3'}$ may be a hydrogen atom as well; and R_3 and $R_{3'}$ may be connected with each other forming a cyclic secondary amine) then the compound with the formula (I) obtained is optionally transformed to its pharmaceutically acceptable salt or released from its salt.

[0030] The reaction is carried out using the modified Betti reaction, which is a method known (Betti, 1900; Betti, 1903; Phillips et al., 1954; Phillips et al., 1956; Phillips, 1956).

[0031] The reaction is carried out in a solvent. Water or organic solvents (e.g. acetonitrile) can be used as a reaction medium. Optionally the reaction is conducted in the presence of an acidic catalyst (e.g. formic acid).

[0032] For preparation of the compounds according to the invention - depending on the starting materials- the following method A or B were used:

Method A:

[0033] Suspend or dissolve 1 mmol of aldehyde in 2x volume of water and add 1.1 equivalent of primary amine to the reaction mixture. Keep at 60 °C for 1 hour and, to the hot mixture, add dropwise a solution of 0.6 equivalent of 8-hydroxy-quinoline dissolved in a volume of acetonitrile or acetone which is double the volume of water. Subsequently cool the reaction mixture to room temperature and stir until precipitation occurs. Monitor the reaction by means of HPLC and TLC. Filter the precipitate, wash with acetonitrile and dry.

Method B:

[0034] Dissolve 1 mmol of aldehyde in 3x volume of acetonitrile and add 1 equivalent of amine, 0.6 equivalent of 8-hydroxy-quinoline and 1V/V% formic acid to the reaction mixture. Stir the mixture until precipitation occurs or the starting quinoline spot disappears. Process the mixture by filtering, washing with acetonitrile, execute chromatography with a mixture of hexane (isomer mixture) /ethyl acetate and recrystallize from alcohol or acetonitrile.

[0035] Having completed the reaction, isolate the desired product from the reaction mixture using the usual methods (e.g. filtering or centrifuging) and purify by known methods (recrystallization or chromatography) if required.

[0036] Also described herein is a pharmaceutical composition containing a compound of the general formula (I) or its pharmaceutically acceptable salt as the active agent and an inert solid or liquid pharmaceutical carrier and/or excipient.

[0037] The pharmaceutical compositions described herein may be solid (e.g. tablet, capsule) semi-solid (e.g. suppository) or liquid (e.g. injectable solution) preparations. The preparations can be administered orally, rectally or parenterally. The compositions described herein may contain common therapeutically suitable carriers and/or

excipients (e.g. starch, cellulose or cellulose-derivatives, lactose, mannitol, sodium chloride, sodium carbonate, saccharose, maltose, calcium carbonate, etc.) .

[0038] The pharmaceutical compositions described herein can be used for treatment of neurological and/or oxidative stress-related diseases during which a therapeutically efficient amount of a compound with the general formula (I) or its pharmaceutically acceptable salt is administered to the patient in need of treatment. The neurological or oxidative stress-related diseases are selected from the following diseases: ischemia, reperfusion injury, cardiovascular disorders, neurodegenerative disorders (including especially Alzheimer's disease and Huntington's disease), trauma, neuropsychiatric diseases (including especially depression and anxiety disorders) and liver, kidney and lung injuries.

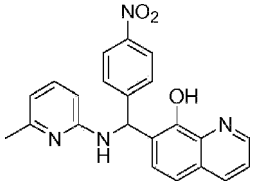
[0039] According to the above, the pharmaceutical compositions described herein can be used as neuroprotective and cardioprotective agents, in the case of liver, kidney and lung injuries and for the treatment or prevention of depression, anxiety disorders, Alzheimer's disease and Huntington's disease.

[0040] Further details of our invention are described in the examples below without limiting the scope of protection to the examples.

CHEMICAL EXAMPLES

Example 1: 7-((6-methylpyridin-2-ylamino)(4-nitrophenyl)methyl)quinolin-8-ol

[0041]



Method A:

[0042] To 10.1 g (18.5 mmol, Sigma) of **4**-nitro-benzaldehyde water (20 ml) was added dropwise then 2-amino-6-picoline (7.95 g, 1.1 equivalent, Aldrich) was added to the lemon yellow suspension under intensive stirring. After a change of colour (from lemon yellow to orange yellow), a solution of 5.82 g of 8-hydroxy-quinoline (0.6 equivalent, Sigma) with 20 mL of acetone (Molar) was added to the suspension and the reaction vessel was heated at 60 °C for **4** hours then the solution was cooled to room temperature. The yellow powder precipitated was filtered (7.87 g 50.8%), washed with a small amount of acetone; its purity was checked by HPLC (≥99.5%).

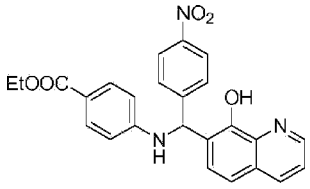
Method B:

[0043] **4**-nitro-benzaldehyde (2.8 g, 18.5 mmol, Sigma) was dissolved in absolute acetonitrile (15 ml, Molar) and 2-amino-6-picoline (2 g, 1 equivalent, Aldrich) was added to the lemon yellow solution under stirring. 1.61 g of 8-hydroxy-quinoline (0.6 equivalent, Sigma) was added to the mixture and it was stirred at room temperature for four days. The product precipitated (**4**.2 g, 27.1 %) was filtered, the molecular weight of the product was verified by mass spectroscopy, its structure was demonstrated by NMR (MW: 386.1), and the purity was checked by HPLC (≥99.6%).

$C_{22}H_{18}N_4O_3$ (MW: 386.1); m.p.: 157-160 °C; HPLC (CH_3CN/H_20 70:30 Phenomenex C18 282 nm) : T_r = 7.14 min ^1H NMR **1** (DMSO) δ 2.2 (3H, s, CH_3), 6.37 (1H, d, J = 7.0 Hz), 6.49 (1H, d, J = 7.9 Hz), 6.98 (1H, d, J = 8.8 Hz, NHCH), 7.28 (1H, t, J = 7.9 Hz), 7.40 (2H, t, J = 7.9 and 8.8 Hz), 7.50-7.55 (1H, m),7.59-7.66 (3H, m), 8.16 (2H, d, J = 8.8 Hz), 8.28 (1H, d, J = 7.9 Hz), 10.1 (1H, wide s, OH) ^{13}C NMR **1** (DMSO) δ 24.2 (CH3), 51.5 (CH), 105.6 (CH), 111.6 (CH), 117.7 (CH), 121.9 (CH), 123.5 (2xCH), 124.5 (Cq), 126.7 (CH), 127.7 (Cq), 128.2 (2xCH), 136.1 (CH), 137.3 (CH), 138.2 (Cq), 146.2 (Cq), 148.4 (CH), 149.8 (Cq), 152.0, 155.7 and 157.3 (Cq).

Example 2 (not according to the invention): Ethyl 4-((8-hydroxyquinolin-7-yl)(4-nitrophenyl) methylamino)benzoate

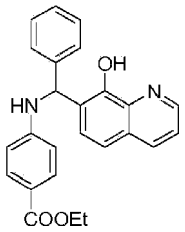
[0044]



[0045] The title compound was prepared by both method A and method B presented for the compound of Example 1 with the change that benzocaine (Sigma), 4-nitro-benzaldehyde (Sigma) and 8-hydroxy quinoline were used as starting materials. Product purified by column chromatography: $C_{25}H_{21}N_3O_5$; (MW: 443.2); yield: 50 mg (30.9%, Method A). HPLC (CH_3CN/H_2O 70:30 Phenomenex C-18 254 nm): T_r = 8.82 min.

Example 3 (not according to the invention): 4-{[(8-hydroxyquinolin-7-yl)-phenyl-methyl]-amino}-benzoic acid ethyl ester

[0046]

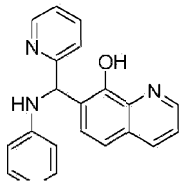


[0047] $C_{25}H_{22}N_2O_3$; (MW: 398.1)

[0048] It was prepared by method A of Example 1.

Example 4: 7-(phenylamino-pyridin-2-yl-methyl)-quinolin-8-ol

[0049]

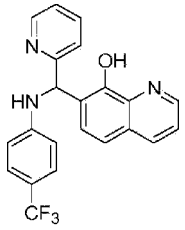


[0050] $C_{21}H_{17}N_3O$; (MW: 327.1)

[0051] It was prepared by method A of Example 1.

Example 5: 7-[pyridin-2-yl-(4-trifluoromethyl-phenylamino)-methyl]-quinolin-8-ol

[0052]

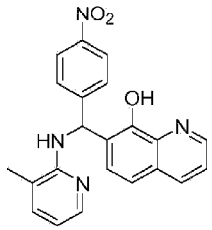


[0053] The title compound according to Example 5 was prepared by both method A and method B presented for the compound of Example 1 with the change that pyridine-2-carboxaldehyde (Molar) was used as starting aldehyde and 4-trifluoromethyl-aniline (Sigma) was used as primary amine. Product purified by column chromatography: $C_{22}H_{16}F_3N_3O$ (MW: 395.1); yield: 151 mg, (42.1%, method B) ; m.p.: 158-161°C; HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 254 nm) : T_r = 10.39 min.

^1H NMR 5 (DMSO) δ 6.31 (1H, d, J = 7.1 Hz), 6.79 (1H, d, J = 7.6 Hz), 7.27 (1H, t, J = 5.1 Hz), 7.29-7.37 (4H, m), 7.47-7.54 (3H, m), 7.75 (1H, t, J = 7.2 Hz), 7.74 (1H, d, J = 8.5 Hz), 8.24 (1H, d, J = 8.3 Hz), 8.55 (1H, d, J = 4.1 Hz), 8.85 (1H, d, J = 3.2 Hz), 10.24 (1H, wide s).

Example 6: 7-[(3-methyl-pyridin-2-ylamino)-(4-nitrophenyl)-methyl]-quinolin-8-ol

[0054]

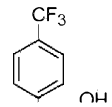


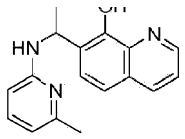
[0055] $C_{22}H_{18}N_4O_3$; (MW+1: 386, 1)

[0056] It was prepared using method A of Example 1.

Example 7: 7-[(6-methyl-pyridin-2-ylamino)-(4-trifluoromethyl-phenyl)-methyl]-quinolin-8-ol

[0057]

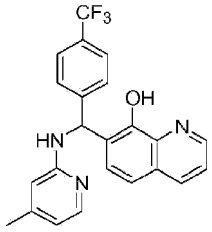




[0058] The title compound was prepared by both method A and method B presented for the compound of Example 1 with the change that **4**-trifluoromethyl benzaldehyde (Sigma), 2-amino-6-picoline and 8-hydroxy-quinoline were used as starting materials. Product obtained (method B): $C_{23}H_{18}F_3N_3O$ (MW: **409**.1); (229 mg, 32.5 %); m.p.: 136-138°C; HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 **254** nm) : T_r = 10.18 min.

Example 8: 7-[(4-methyl-pyridin-2-ylamino)-(4-trifluoromethylphenyl)-methyl]-quinolin-8-ol

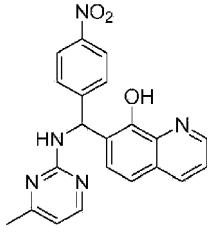
[0059]



[0060] The title compound was prepared by method B presented for the compound of Example 1 with the change that 2-amino-**4**-methyl-pyridine (Molar), **4**-trifluoromethyl-benzaldehyde (Sigma) and 8-hydroxy-quinoline (Sigma) were used as starting materials. Product obtained: $C_{23}H_{18}F_3N_3O$; (MW: **409**.1); yield: 230 mg, (29.6%) m.p.: 104-107°C; HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm) : T_r = 7.61 min. ^{1}H NMR **8** (DMSO) δ 2.18 (3H, s, C<u>H</u>$_3$), 6.41 (1H, d, J = 5.1 Hz), 6.44 (1H, s, N<u>H</u>), 6.49 (1H, d, J = 4.9 Hz), 7.07 (1H, d, J = 9.2 Hz), 7.39 (1H, d, J = 8.9 Hz), 7.49-7.54 (1H, m), 7.58 (2H, d, J = 7.9 Hz), 7.63 (2H, d, J = 8.3 Hz), 7.73 (1H, d, J = 7.9 Hz), 7.85 (2H, d, J = 7.9 Hz), 8.03- 8.08 (1H, m), 8.12 (2H, d, J = 8.5 Hz), 8.27 (1H, d, J = 8.2 Hz), 8.81-8.86 (1H, m); 13C-NMR **8** (DMSO) δ 23.5 (CH3), 51.8 (NHCH), 109.5 (CH), 117.6 (CH), 121.8 (CH), 124.5 (Cq), 125.1 (CH), 125.6 (2xCH), 126.8 (CH), 127.7 (2xCH), 127.8 (Cq), 130.1 (CH), 134.7 (Cq), 136.1 (CH), 138.1 (Cq), 148.2 (Cq), 148.5 (CH), 149.6 (Cq), 157.7 (CH), 161.6 (Cq), 166.3 (Cq) .

Example 9: 2-((4-methylpyrimidin-2-ylamino)(4-nitrophenyl) methyl)phenol

[0061]

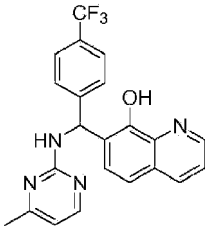


[0062] The title compound was prepared by method B presented for the compound of Example 1 with the change that 2-amino-**4**-methyl-pyrimidine (Sigma), **4**-nitro-benzaldehyde and 8-hydroxy-quinoline were used as starting materials. Product obtained: $C_{21}H_{17}N_5O_3$, (MW: 387.1); yield: **344** mg, (**49**.6%); m.p.: 136-**145**°C; HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm) : T_r = 5.21 min. ^{1}H NMR **9** (DMSO) δ 2.14 (3H, s, CH_3), 6.35 (1H,

d, J = 5.8 Hz), 6.55 (1H, s), 7.00 (1H, d, J = 8.0 Hz), 7.36-7.43 (2H, m], 7.50-7.55 (1H, m), 7.56 (1H, d, J = 7.5 Hz), 7.60 (1H, d, J = 8.5 Hz), 7.79 (1H, d, J = 5.5 Hz), 8.15 (2H, d, J = 8.5 Hz), 8.28 (1H, d, J = 8.5 Hz), 8.84 (s, 1H), 10.1 (s, 1H); ^{13}C NMR **9** (DMSO) δ 20.6 (CH3), 51.6 (NHCH), 109.0 (CH), 114.2 (CH), 117.7 (CH), 121.9 (CH), 123.5 (2xCH), 124.6 (Cq), 126.7 (CH), 127.7 (Cq), 128.2 (2xCH), 136.1 (CH), 138.2 (Cq), 146.2 (Cq), 147.1 (Cq), 147.2 (CH), 148.5 (CH), 149.8, 152.0 and 157.9 (3 Cq).

Example 10: 7-((4-methylpyrimidin-2-ylamino)(4-(trifluoromethyl)phenyl)methyl)quinolin-8-ol

[0063]

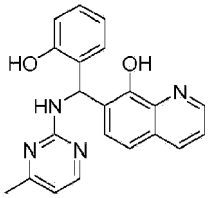


[0064] The title compound was prepared by both method A and method B presented for the compound of Example 1 with the change that **4**-trifluoromethyl-benzaldehyde and 2-amino-**4**-methyl-pyrimidine were used as aldehyde and amine sources (Molar). Product obtained (method B), yield: 1.7 g, (34.8%); $C_{22}H_{17}F_3N_4O$; (MW: 410.1), m.p.: 144-147°C; HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 254 nm): T_r = 7.75 min. ^{1}H NMR **10** (DMSO) δ 2.24 (3H, s, CH_3), 6.49 (1H, d, J = 5.1 Hz), 7.07 (1H, d, J = 9.0 Hz, NHCH)), 7.39 (1H, d, J = 8.5 Hz), 7.49-7.55 (1H, m), 7.58 (2H, d, J = 7.7 Hz), 7.64 (2H, d, J = 7.9 Hz), 7.74 (1H, d, J = 8.5 Hz), 8.07 (1H, d, J = 8.9 Hz), 8.14 (1H, d, J = 4.9 Hz), 8.28 (1H, d, J = 7.7 Hz), 8.83 (1H, s), 10.08 (1H, wide s).

^{13}C NMR **10** (DMSO) δ 23.6 (CH3), 51.7 (NHCH), 110.4 (CH), 117.6 (CH), 121.8 (CH), 124.6 (Cq), 125.2 (2xCH), 126.8 (CH), 127.2 (Cq), 127.4 (Cq), 127.7 (Cq), 127.8 (2xCH), 136.1 (CH), 138.1 (Cq), 148.2 (Cq), 148.4 (CH), 149.8, 149.6, 161.6 and 167.6 (4 Cq).

Example 11 (not according to the invention) : 7-[(2-hydroxyphenyl)-(4-methyl-pyrimidin-2-ylamino)-methyl]-quinolin-8-ol

[0065]

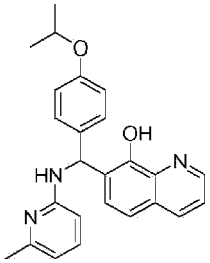


[0066] The title compound was prepared by method B presented for the compound of Example 1 with the change that 2-hydroxy-benzaldehyde (Molar) and 2-amino-**4**-methylpyrimidine (Sigma) were used as starting materials. The product precipitated, yield: 45 mg; $C_{21}H_{18}N_4O_2$; (MW: 358.1) .

^{1}H NMR **11** (DMSO) δ 2.21 (3H, s, CH_3), 6.39-6.46 (2H, m), 6.69 (1H, t, J = 6.4 Hz), 6.75 (1H, d, J = 7.7 Hz), 7.23 (1H, d, J = 7.0 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.44-7.51 (2H, m), 7.57 (2H, d, J = 8.0 Hz), 8.09 (1H, d, J = 5.4 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.79 (1H, wide s), 9.47 (1H, wide s, OH), 9.80 (1H, wide s, OH).

Example 12 (not according to the invention) : 7-[(4-isopropoxyphenyl)-(6-methyl-pyridin-2-ylamino)-methyl]-quinolin-8-ol

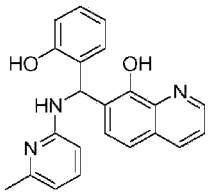
[0067]



[0068] The title compound was prepared by method B presented for the compound of Example 1 with the change that **4**-isopropyl-oxy-benzaldehyde (Molar) was used as aldehyde component. Product purified by column chromatography, $C_{25}H_{25}N_3O_2$; (MW+1: 399.2), yield 135 mg, (63.1%), m.p.: 132-134°C; HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm): T_r = 9.23 min.

Example 13 (not according to the invention) : 7-[(2-hydroxyphenyl)-(6-methyl-pyridin-2-ylamino)-methyl]-quinolin-8-ol

[0069]



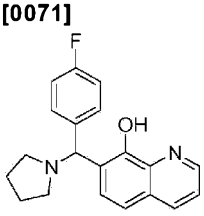
[0070] The title compound was prepared by method B presented for the compound of Example 1 with the change that the reaction was conducted with salicylaldehyde (Molar), 2-amino-6-picoline (1 equivalent) and 8-hydroxy-quinoline (0.6 equivalent) as starting materials. Product precipitation; $C_{22}H_{19}N_3O_2$; (MW: 357.1), yield 1.6 g, (50.9%); m.p.: 189-191°C; HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm): T_r = 5.05 min.

^{1}H NMR **13** (DMSO) δ 2.23 (3H, s), 6.34 (1H, d, J = 6.0 Hz), 6.38 (1H, d, J = 7.1 Hz), 6.69 (1H, t, J = 7.2 Hz), 6.80 (2H, m), 7.02 (2H, m), 7.18 (1H, d, J = 6.2 Hz), 7.25 (1H, d, J = 6.8 Hz), 7.36 (1H, d, J = 7.4 Hz), 7.42-7.54 (1H, m), 7.64 (1H, d, J = 7.9 Hz), 8.25 (1H, d, J = 7.1 Hz), 8.80 (1H, s), 9.85 (1H, s)

^{13}C NMR **13** (DMSO) δ 23.9 (CH3), 47.8 (CHNH), 111.1 (CH), 115.7 (CH), 116.7 (CH), 118.7 (CH), 121.5 (CH), 125.3 (Cq), 127.2 (CH), 127.4 (Cq), 127.8 (CH), 128.3 (CH), 129.2 (Cq), 135.9 (CH), 137.5 (CH), 138.2 (Cq), 148.1 (CH), 149.7, 155.1, 155.6 and 157.6 (4 x Cq).

Example 14 (not according to the invention) : 7-[(4-fluorophenyl)-(pyrrolidin-1-yl)-methyl]-quinolin-8-ol

[0071]

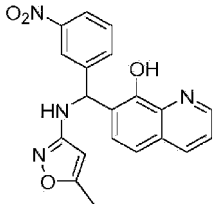


[0072] $C_{20}H_{19}FN_2O$; (MW: 322.2)

[0073] The title compound was prepared by method A of Example 1.

Example 15: 7 {[(5-methyl-1,2-oxazol-3-yl)amino](3-nitrophenyl)methyl}quinolin-8-ol

[0074]

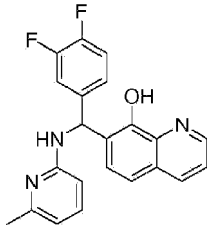


[0075] $C_{20}H_{16}N_4O_4$; (MW: 376.1)

[0076] The title compound was prepared by method A of Example 1.

Example 16: 7-((6-methylpyridin-2-ylamino)(3,4-difluorophenyl)methyl)quinolin-8-ol

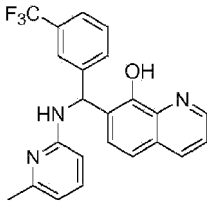
[0077]



[0078] The title compound was prepared by method B presented for the compound of Example 1 with the change that 3,4-difluorobenzaldehyde was reacted with 2-amino-6-picoline and 8-hydroxy-quinoline. White powder precipitated, $C_{22}H^{17}F_2N_3O$, (MW: 377.1); yield: 275 mg (53.3%). m.p.: 162-165°C; HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm): 7.97 min.

Example 17: 7-((6-methylpyridin-2-ylamino)(3-(trifluoromethylphenyl)methyl)quinolin-8-ol

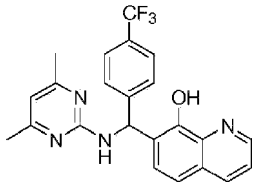
[0079]



[0080] The title compound was prepared by method B presented for the compound of Example 1 with a higher yield. White powder precipitated, $C_{23}H_{18}F_3N_3O$ (MW: 409.1); yield: 356 mg, 57.3 %. m.p.: 140-143°C, HPLC (MeOH/H_2O 80:20 Phenomenex C18 254 nm): 10.21 min.

Example 18: 7-[(4,6-dimethyl-pyrimidin-2-ylamino)-(4-trifluoromethyl-phenyl)-methyl]-quinolin-8-ol

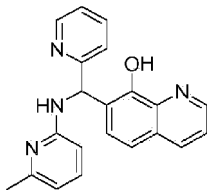
[0081]



[0082] The title compound was prepared by method B presented for the compound of Example 1 with a higher yield. White powder precipitated; $C_{23}H_{19}F_3N_4O$; (MW: 424.2); yield: 255 mg, (54.6 %).

Example 19: 7-[(6-methyl-pyridin-2-ylamino)-pyridin-2-yl-methyl]-quinolin-8-ol

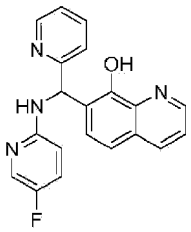
[0083]



[0084] The title compound was prepared by method B presented for the compound of Example 1. Yellowish-white powder precipitated, $C_{21}H_{18}N_4O$ (MW: 342.2); yield: 1.2 g, (70.5%). m.p.: 155-157°C.

Example 20: 7-[(5-fluoro-pyridin-2-ylamino)-pyridin-2-yl-methyl]-quinolin-8-ol

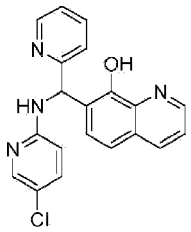
[0085]



[0086] The title compound was prepared by method B presented for the compound of Example 1. Bone-coloured powder, purified by column chromatography. $C_{20}H_{15}FN_4O$; (MS: 346,1), yield 45 mg, (18.4 %). m.p.: 165-168°C, HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm): 4.44 min.

Example 21: 7-[(5-chloro-pyridin-2-ylamino)-pyridin-2-yl-methyl]-quinolin-8-ol

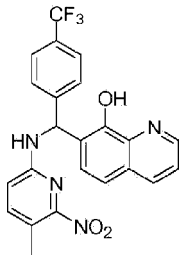
[0087]



[0088] The title compound was prepared by method B presented for the compound of Example 1; 2-amino-5-chloropyridine, 2-pyridine-carboxaldehyde and 8-hydroxy-quinoline were used in the reaction; the reaction mixture was heated at 60°C for 3 days. Greyish-white powder, product purified by column chromatography. $C_{20}H_{15}ClN_4O$; (MW: 362.1) ; yield: 55 mg, (23.7 %). m.p. : 160-162°C, HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm) : 5.69 min.

Example 22: 7-[(5-methyl-6-nitro-pyridin-2-ylamino)-(4-trifluoromethyl-phenyl)-methyl]-quinolin-8-ol

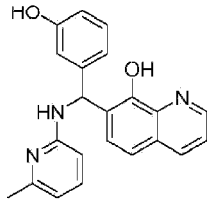
[0089]



[0090] The title compound was prepared by method B presented for the compound of Example 1 with the change that 2-amino-5-methyl-6-nitro-pyridine, **4**-trifluoromethyl-benzaldehyde and 8-hydroxy-quinoline were used and the reaction mixture was heated at 60°C for 7 days. Yellowish white powder. $C_{23}H_{17}F_3N_4O_3$; (MW: **454**.1), yield: 26 mg, (10 %). m.p. ≥ 300°C, HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm): T_r = 5.60 min.

Example 23 (not according to the invention) : 7-[(3-hydroxy-phenyl)-(6-methyl-pyridin-2-ylamino)-methyl]-quinolin-8-ol

[0091]



[0092] The title compound was prepared by method B presented for the compound of Example 1 with the change that 3-hydroxy-benzaldehyde was reacted with 2-methyl-6-picoline and 8-hydroxy-quinoline. White powder, purified by column chromatography. $C_{22}H_{19}N_3O_2$; (MW: 357.2), yield: 211 mg, (80.2 %). m.p.: 187-189°C, HPLC (CH_3CN/H_2O 70:30 Phenomenex C18 282 nm): T_r = 3.97 min.

BIOLOGICAL EXAMPLES

Example 24: Inhibition of activities of Matrix metalloproteinase 2 (MMP-2, 72 kDa gelatinase) and Matrix metalloproteinase 9 (MMP-9, 92 kDa gelatinase) by 7-((6-methylpyridin-2-ylamino) (4-nitrophenyl)methyl)quinolin-8-ol

[0093] H9c2 rat embryonic myocardial cells (from ATCC, Rockville, MD, USA) were grown in Dulbecco's modified Eagle's medium containing 10 % cattle serum, 4 mM L-glutamine (Sigma-Aldrich, Hungary), 100 IU/ml penicillin and 100 ug/ml streptomycin. To the H9c2 supernatant sample, 30 uM of the compound according to Example 1 (7-((6-methylpyridin-2-ylamino)(4-nitrophenyl)methyl)quinolin-8-ol) from a stock solution containing 30 mM of DMSO (1000-fold dilution) was added before electrophoresis. To the control, DMSO not containing the compound according to Example 1 was added. After electrophoresis, the gel was cut in two halves following renaturation; one half was incubated in such a way that 30 uM of the compound according to Example 1 was added to it at the final concentration, while the second half (control) was incubated without it. The compound according to Example 1 completely inhibited the 72 kDa gelatinase (MMP-2) if the substance was present during incubation. It inhibited the 92 kDa gelatinase (MMP-9) as well, but to a less extent than the 72 kDa gelatinase.

[0094] MMP-9 and MMP-2 contribute to caspase-mediated endothelium cell death, after hypoxia reoxygenation via destruction of the cell-matrix interactions and the homeostatic integrin signal. The MMP-2 and MMP-9 inhibitors reduce the caspase-3 activity significantly and decrease the endothelial cell death (Lee et al., 2004).

Example 25: the compound according to Example 1 (7-((6-methylpyridin-2-ylamino)(4-nitrophenyl)methyl)quinolin-8-ol) reduces reperfusion injury after heart transplantation.

[0095] A heterotropic heart transplant experiment model was performed in a way described earlier (Poly(ADP-Ribose); inhibition of polymerase reduces the reperfusion injury occurring after heart transplantation (Szabó et al. 2002). Briefly: the donor hearts were transplanted from Lewis rats. After ischemic protection performed at 4°C for 1 hour, the hearts were implanted intraabdominally via anastomising the aorta and the pulmonary artery of the donor heart with the abdominal aorta or vena cava of the recipient rat. Care of all animals was performed by people in line with the requirements of "Principles of Laboratory Animal Care"; National Society of Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences; publisher: National Institutes of Health (NIH Publication No. 86-23, revised 1996).

[0096] The functional measurements of the transplant were carried out as follows: the left ventricular systolic pressure (LVSP), left ventricular end diastolic pressure (LVEDP), rate of the change of blood pressure (dP/dt) and relaxation time constant (TE) were measured by means of a Millar micromanometer (Millar Instruments, Inc.), with different LV, using an intraventricular ballon. The total coronary blood flow (CBF) was measured on the donor aorta with perivascular ultrasonic flow sample. After determination of the baseline, the endothelium-dependent vasodilator acetylcholine (ACH, 1 nmol/l, 0.2 ml) and bradykinin (BK 0.1 nmol/l, 0.2 ml), and the endothelium-independent vasodilator sodium nitroprussid (SNP, 10 nmol/l, 0.2 ml) were added directly into the coronary arteries of the transplant through the donor aorta. Between the infusions, CBF was allowed to return to the baseline level. The vasodilator response was expressed as the maximum percentage change of CBF from the baseline.

[0097] Two transplant groups were studied (n=6/in each group). Just before loosening the aorta clamp, slow injection of common salt solution (control group) or the compound according to Example 1 (3 mg/kg) was started and it was continued during the first 5 minutes of the reperfusion period.

[0098] Measurement of the systolic and diastolic function and CBF in group A (control) and group B (compound according to Example 1) was performed 1 hour after reperfusion.

[0099] The hemodynamic parameters and myocardial blood flow were determined after 60 minute reperfusion. The heart frequency and aorta pressure of the recipient were the same in every group. The systolic functional recovery was significantly better in the group treated with the compound according to Example 1 than the control values. The LVSP and the peak positive dP/dt were significantly (P=0.05) higher in the group treated with the compound according to Example 1.

[0100] The systolic heart function curves in the group treated with the compound according to Example 1 showed a significant drift to the left compared with the group treated with the carrier (Fig. 1a and Fig. 1b). The LVEDP did not show changing values between the groups. The diastolic cooperation curves (end diastolic pressure - volume relationship) were similar in every group (Fig. 1c).

Example 26: treatment with compounds having the general formula (I) prevented cell death caused by hydrogen peroxide in vitro in heart, neuronal and liver cells

[0101] H9c2 rat embryonic myocardial cells (ATCC, Rockville, MD, USA) were grown in Dulbecco's modified Eagle's medium containing 10 % cattle serum, 4 mM L-glutamine (Sigma-Aldrich, Hungary), 100 IU/ml penicillin and 100 ug/ml streptomycin. The cells were placed into 96-well microtitration plates (10 000 cell/well) and after 24 hours, treated with 1 % H_2O_2 (Sigma) solution (0.2 mM final concentration). 30 minutes after the treatment various compounds with the general formula (I) in various concentrations were put on them and after 3 and 24 hours viability of the cells was determined by means of MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) test.

[0102] 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT, Serva) was added to the cells in 0.5 mg/ml final concentration and incubated at 37°C for 1 hour. The cells were washed with PBS and the formazan dye was dissolved in isopropanol. The amount of the formazan dye transformed was measured by means of a Powerwave reader (Biotek, Winooski, VT) at 570 nm; background measurement 690 nm. The calibration curve was obtained in such a way that the capacity of the serial dilutions of the cells to transform MTT was measured and the viable cell count was calculated using Gen5 software. The measurements were executed 3 hours and 24 hours after the exposure of each series of the experiments to the effect of H_2O_2.

Example 27: treatment with various compounds having the general formula (I) prevented cell death caused by hydrogen peroxide in vitro in liver cells

[0103] Hep3B human hematoma cells (ATCC, Rockville, MD, USA) 10 % were grown in Dulbecco's modified Eagle's medium containing 10 % cattle serum, 4 mM L-glutamine (Sigma-Aldrich, Hungary), 100 IU/ml penicillin and 100 ug/ml streptomycin. The cells were kept in 100 mm TC dishes (Orange Scientific, Belgium) in an incubator in a 37 °C space containing moistened air and 5 % CO_2.

[0104] The cells were placed in 96-well E-plate (Roche) microtitration plates pre-treated with gelatine (10 000 cells/well) and grown for 16 hours. 30 minutes after the treatment, various compounds with the general formula (I) in various concentrations were put on them and the viability of the cells was measured with an Excelligence instrument by RT-CES method (Roche) continuously by determining the cell index measured in every 2 minutes. The results are shown in Fig 2. Curve "A" represents the untreated control, curve "I" represents the compound PJ34, a known PARP inhibitor, while curve "J" represents the control treated with peroxide.

[0105] In this experiment the following compounds according to the general formula (I) were tested (indicating which curve in Fig 2 represents the effect of the given compound on the normalized cell index):

7-((4-nitrophenylamino)(phenyl)methyl)quinolin-8-ol (curve "B"),

4-{ [(8-hydroxyquinolin-7-yl)-phenyl-methyl]-amino}-benzoic acid ethyl ester (curve "C", Example 3),

7-((4-phenylpiperazin-1-yl)(thiophen-2-yl)methyl)quinolin-8-ol (curve "D"),

7-((6-methylpyridin-2-ylamino)(4-(trifluoromethyl)phenyl)methyl) quinolin-8-ol (curve "E"),

7-((4-fluorophenyl)(thiazol-2-ylamino)methyl)quinolin-8-ol (curve "F"),

7-(phenylamino-pyridin-2-yl-methyl)-quinolin-8-ol (curve "G", Example 4) and

7-[(4-fluorophenyl)-(pyrrolidin-1-yl)-methyl]-quinolin-8-ol (curve "H", 14).

[0106] The tests were executed in order to determine the cytoprotective effect on Hep3B human hematoma cells 30 minutes after treating with H_2O_2. 250 uM of hydrogen peroxide was used in these cells. Cell growth is linear during the application of hydrogen peroxide. 30 minutes after the treatment with various compounds with the general formula (I) according to our invention the slopes of the cell index curves changed significantly based on which different cytoprotective effects of the compounds according to our invention can be established.

Example 28: treatment with various compounds having the general formula (I) prevented cell death caused by hydrogen peroxide in vitro on mixed primary neurons and astrocytes

[0107] The cells were kept in 100 mm TC dishes (Orange Scientific, Belgium) in an incubator in a 37 °C space containing moistened air and 5 % carbon dioxide. A combined culture of cerebral neurons and astrocytes was prepared following the method of Griffin S et al (Griffin et al., 2005). The cell cultures were kept in an Eagle's minimal essential medium containing 10 % foetal cattle serum and 1 % non-essential amino acid solution (Sigma-Aldrich, Hungary). The results are shown in Fig 3. Curve "K" represents the untreated control, curve "P" represents the control treated with PJ34 and curve "Q" represents the control treated with hydrogen peroxide.

[0108] The cells were placed in 96-well E-plate (Roche) microtitration plates (10 000 cells/well) pre-treated with gelatine , and grown for 16 hours. 5 minutes before the treatment the following compounds with the general formula (I) according to our invention in 5 um concentration were put on them:

7-((6-methylpyridin-2-ylamino)(4-nitrophenyl)methyl)quinolin-8-ol (curve "L", Example 1),

7-[(6-methyl-pyridin-2-ylamino)-(4-trifluoromethyl-phenyl)-methyl]-quinolin-8-ol (curve "M", Example 7),
ethyl 4-((8-hydroxyquinolin-7-yl)(4-nitrophenyl)methylamino)benzoate (curve "N", Example 2) and

7-((4-methylpyrimidin-2-ylamino) (4-(trifluoromethyl)phenyl)methyl) quinolin-8-ol (curve "O", Example 10).

[0109] Then the viability of the cells was measured with an Excelligence instrument by RT-CES method (Roche) continuously by determining the cell index measured in every 2 minutes. The treatment started with adding 100 uM H_2O_2 causing destruction of 90 % of the total cells in the control well not containing a compound with the general formula (I).

Example 29: Effect of the compound according to Example 1

(7-((6-methylpyridin-2-ylamino)(4-nitrophenyl)methyl)quinolin-8-ol) on the behaviour of rats

Test animals

[0110] Wistar rats received from Charles River Laboratories (Budapest, Hungary) were used as test animals. App. 2 month rats were used (200-300 g body weight). The animals were conditioned for app. 1 week. The animals received standard laboratory food (Charles River Laboratories, Budapest, Hungary) and tap water ad libitum. The temperature and humidity were kept at 22 ± 2°C and 60 ± 10 %, respectively. The rats were kept in groups of 5 in 45x35x25 cm Makrolon cages. Day/night cycles of 12 hours were used; the light was switched off at 19:00. The experiments were conducted in the daylight period. The experiments were conducted in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC, according to the control and approval of the Animal Welfare Committee of the Institute of Experimental Medicine).

Example 29.1 : verification of anxiety-inhibiting effect of the compound according to Example 1 by elevated plus-maze test

Elevated plus-maze test

[0111] A black metal box was used for the elevated plus-maze test. The sizes of the equipment are as follows: arm length: 40 cm, arm width: 12 cm, wall height: 30 cm and platform height: 70 cm. The open arms are surrounded by 0.5 cm ledges. The test was conducted according to the following publication: Pellow et al., 1985.

[0112] In the early hours of the light phase, the rats were treated with the carrier, the compound according to Example 1 (2 mg/kg), the compound according to Example 1 (8 mg/kg) and chlordiazepoxide (8 mg/kg) (n=10 in each group). This chlordiazepoxide dose reliably reduced anxiety in this test earlier. 2 hours after the treatment the animals were placed in the centre of the equipment with their heads directed towards the closed arm. The exposure time was 5 minutes. Entries to the closed arms are indicators of locomotive activity while the use of the open arms is the indicator of the degree of anxiety. Use of the open arm was characterised by two variables: percentage share of time spent in open arms and percentage frequency of entries to open arms (100 x entries to open arms/ total entries to arms) (Pellow et al., 1985; Hogg, 1996).

[0113] The results are shown in Fig. 4. In the figure, "Example 1" refers to the compound according to Example 1, CDP refers to chlordiazepoxide.

Example 29.2: effect of the compound according to Example 1 on depression

Forced swimming test

[0114] Rats were forced to swim twice as described in the following publication: Porsolt et al., 1978. On the first day every rat was placed in a 15 cm wide, 35 cm high glass cylinder filled with water to 30 cm. At that water depth the tails of the rats did not touch the bottom of the cylinder. Water temperature was 24±0.5 °C. On the following day the animals were treated with the carrier, 2 mg/kg of the compound according to Example 1, 8 mg/kg of the compound according to Example 1 and 30 mg/kg imipramine. This dose of impipramine reliably

reduced floating in previous experiments; in this test it is the main characteristic of depression-like behaviour. After a rest period of 2 hours the rats were forced to swim again for 5 min. Behaviour of the animals was recorded by a video camera located 2 meters from the cylinders. The following behaviour factors were recorded: struggling (the animal tries to leave the cylinder by climbing on the walls); swimming (swimming round in the cylinder) and floating (the animal makes only the movements necessary to keep its head above the water). The time of floating indicates the degree of depression-like behaviour in this test.

[0115] The results are shown in Fig. 5. In the figure, "Fig. 1" refers to the compound according to Example 1.

Example 30: cytotoxic effect of the compounds according to the invention on various tumour cell lines

[0116] In our experiment, HepG2 and Hep3B (human hepatocellular carcinoma), SUM149PT (human breast tumour), K562 (human erythroblastic leukaemia, U87 (human glioma), CCRF-CEM (human leukaemia) cell cultures were used; these were grown in the following medium: U87, CCRF-CEM: Dulbecco's Modified Eagle Medium (D-MEM) (high glucose) (Gibco BRL, Carlsbad, CA, USA), penicillin (50 IU/ml -streptomycin (50 mg/ml), 10 % foetal cattle serum.

[0117] 1:1 mixture of HepG2, Hep3B, SUM149PT: Dulbecco's Modified Eagle Medium (D-MEM) (high glucose) (Gibco BRL, Carlsbad, CA, USA) and Nutrient Mixture F-12 Ham (Sigma, St. Louis, MO, USA), penicillin (50 IU/ml)-streptomycin (50 mg/ml), 10 % foetal cattle serum.

[0118] CCRF-CEM: RPMI Media 1640 (Gibco BRL, Carlsbad, CA, USA), penicillin (50 IU/ml -streptomycin (50 mg/ml), 10 % foetal cattle serum.

[0119] The cells were placed into 96-well microtitration plates (10 000 cells/well), and after 24 hours the cells were incubated with the various substances. After incubation MTS test (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium) (Promega, Madison, Wi, USA) was conducted adding it in a final concentration of 0.5 mg/ml to the cells, which were then incubated at 37°C for 1 hour. The cells were washed with PBS and the formazan dye was dissolved in isopropanol. The amount of the formazan dye transformed was measured by means of a Powerwave reader (Biotek, Winooski, VT) at 570 nm; background measurement 690 nm. The calibration curve was obtained in such a way that the capacity of the serial dilutions of the cells to transform MTS was measured and the viable cell count was calculated using Gen5 software.

[0120] The results of the experiment with the various cells are shown in Table 1. In the table the EC50 values of each substance is presented (the concentration where half of the cells died based on the results of the MTS test).

[0121] It can be seen well that the compounds according to the present invention exhibited cytotoxic effect on the various tumour cell lines.

Table 1: Cytostatic effect of various quinoline derivatives on various human tumour cell lines

Compound's name (Example no.)	Cell line (type)					
	CCRF-CEM (leukaemia)	Hep3B (liver)	HepG2 (liver)	K562 (leukaemia)	SUM149PT (breast)	U87 (glioma)
7-((6-methylpyridin-2-ylamino)(4-nitrophenyl)me thyl)quinolin-8-ol (Example 1)	1.0		0.5	1.0	10.0	2.5
7-[(6-Methyl-pyridin-2-ylamino)-(4-trifluoromethyl-phenyl)-methyl]-quinolin-8-ol (Example 7)	0.3	5.0	0.5	15.0		
Ethyl 4-((8-hydroxyquinolin-7-yl)						

Compound's name (Example no.)	Cell line (type)					
	CCRF-CEM (leukaemia)	Hep3B (liver)	HepG2 (liver)	K562 (leukaemia)	SUM149PT (breast)	U87 (glioma)
(4-nitrophenyl)methylamino)benzoate (Example 2)	1.0	5.0	2.5			4.0
7-[Pyridin-2-yl-(4-trifluoromethyl-phenylamino)-methyl]-quinolin-8-ol (Example 5)	0.1	2.0	2.0			3.5
7-((4-methylpyrimidin-2-ylamino) (4-(trifluorometh yl)phenyl)methyl)quinolin-8-ol (Example 10)			1.0	7.0	5.0	5.0
7-[(2-Hydroxyphenyl) -(4-methylpyrimidin-2-ylamino)-methyl]-quinolin-8-ol (Example 11)			1.0	5.0		
7-[(4-Methylpyridin-2-ylamino)-(4-trifluoromethylphenyl)-methyl]-quinolin-8-ol (Example 8)				8.0	10.0	
7-((6-methylpyridin-2-ylamino) (3,4-difluorophenyl)methyl)quinolin-8-ol (Example 16)			5.0	1.5		2.5
7-((6-methylpyridin-2-ylamino)(2-fluoro-4-(trifluorometh yl)phenyl)methyl)quinolin-8-ol			1.0	1.5		2.5

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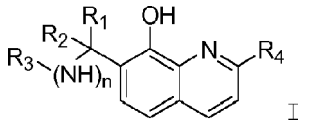
PATENTKRAV

1. Forbindelse i overensstemmelse med den almene formel I



I

i hvilken formel

R_1 repræsenterer et hydrogenatom, lavere alkylgruppe, som er en forgrenet eller ikke-forgrenet alkylgruppe med 1-4 carbonatomer, lavere alkenylgruppe, som er en forgrenet eller ikke-forgrenet alkenylgruppe med 2-4 carbonatomer, arylgruppe, aralkylgruppe eller heterocyclisk gruppe, hvor de ovennævnte aryl-, aralkyl- og heterocycliske grupper eventuelt er substituerede i ortho-, meta- og/eller para-positionen med 1, 2, 3 eller 4 elektron-modtagende grupper valgt blandt halogenatomer, trifluormethyl eller nitrogrupper, eller elektron-afgivende grupper valgt blandt lavere alkylgrupper, som er forgrenede eller ikke-forgrenede alkylgrupper med 1-4 carbonatomer;

R_2 repræsenterer et hydrogenatom, lavere alkylgruppe, som er en forgrenet eller ikke-forgrenet alkylgruppe med 1-4 carbonatomer, arylgruppe, aralkylgruppe eller heterocyclisk gruppe, hvor de ovennævnte grupper eventuelt er substituerede med ét eller flere halogenatomer;

R_3 repræsenterer en arylgruppe, aralkylgruppe eller heterocyclisk gruppe, hvor de ovennævnte grupper eventuelt er substituerede i ortho-, meta- eller para-positionen med 1, 2, 3 eller 4 elektron-modtagende grupper valgt blandt halogenatomer, trifluormethyl eller nitrogrupper, eller elektron-afgivende grupper, valgt blandt lavere alkylgrupper, som er forgrenede eller ikke-forgrenede alkylgrupper med 1-4 carbonatomer;

R_4 repræsenterer et hydrogenatom, lavere alkylgruppe, som er en forgrenet eller ikke-forgrenet alkylgruppe med 1-4 carbonatomer, eller en syrefunktionel gruppe valgt blandt methoxycarbonylgruppe, nitril eller syreamidgruppe;

n er 1 eller 2; og deres farmaceutisk acceptable salt, til anvendelse ved en fremgangsmåde til forebyggelse eller behandling af iskæmi, reperfusionsskade, kardiovaskulære lidelser, neurodegenerative lidelser (inkl. især Alzheimer's sygdom og Huntington's sygdom), trauma, neuropsykiatriske lidelser (inkl. især depression og angstlidelser), og lever-, nyre- og lungeskader.

DRAWINGS

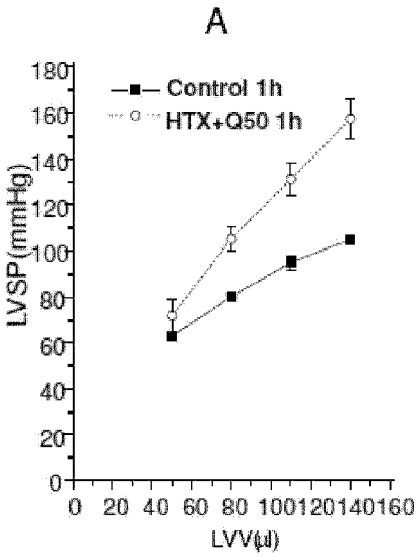


Fig. 1a

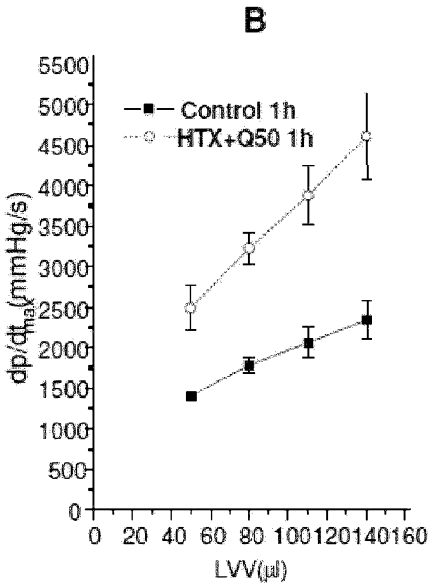


Fig. 1b

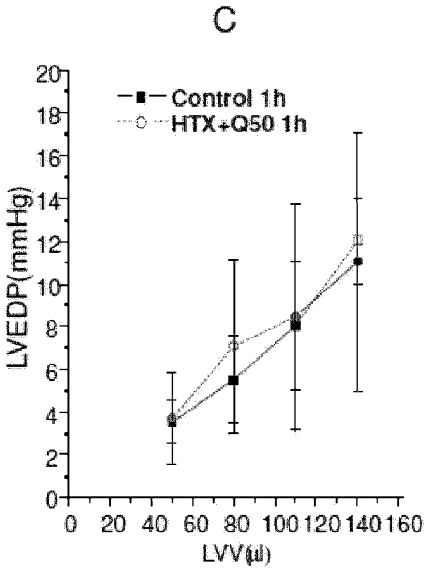


Fig. 1c

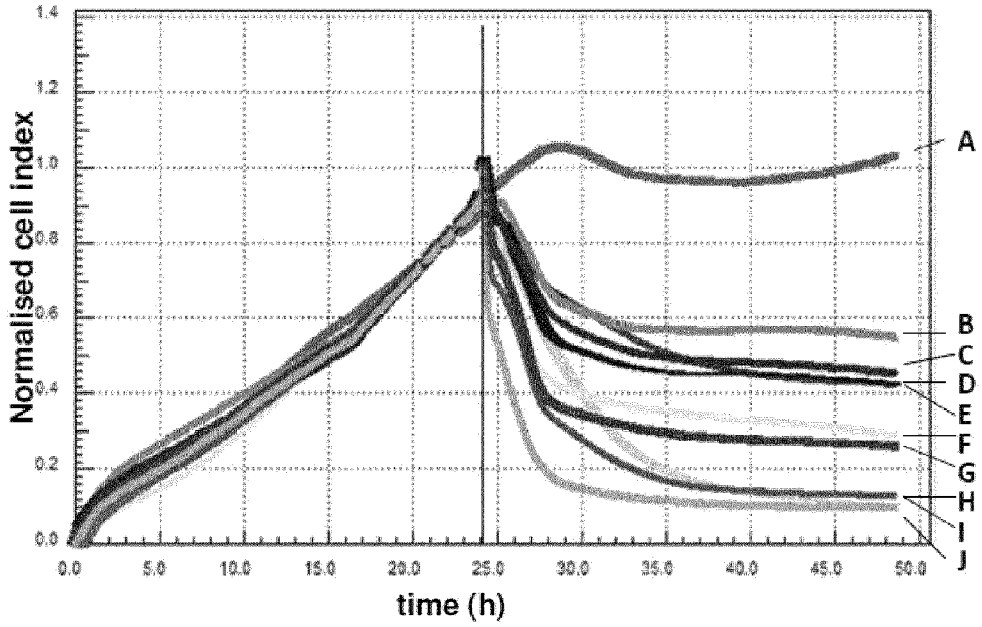

Normalised cell index
time (h)
A
B
C
D
E
F
G
H
I
J

Fig. 2

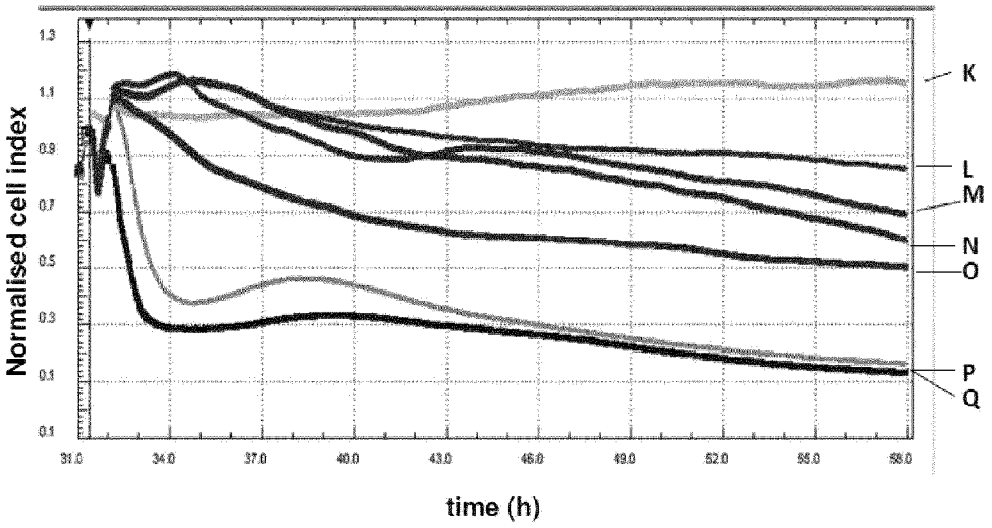

Normalised cell index
time (h)
K
L
M
N
O
P
Q

Fig. 3

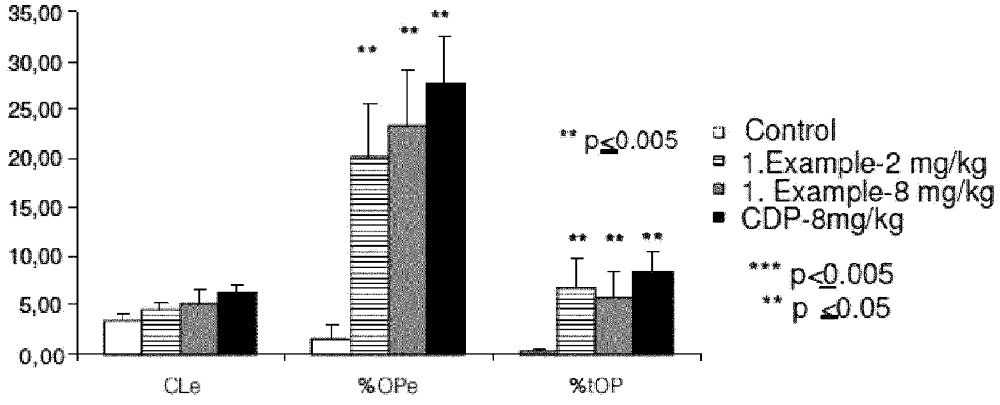

35,00
30,00
25,00
20,00
15,00
10,00
5,00
0,00
CLe
%OPe
%tOP
** p≤0.005
Control
1.Example-2 mg/kg
1. Example-8 mg/kg
CDP-8mg/kg
*** p≤0.005
** p ≤0.05

Fig. 4

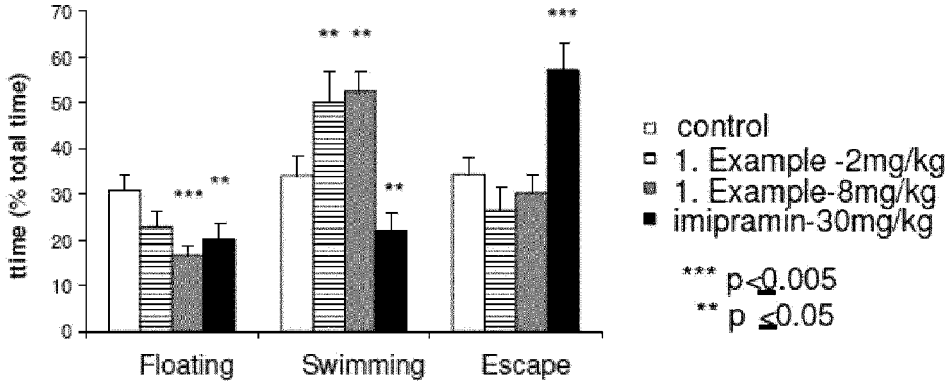

ttime (% total time)
70
60
50
40
30
20
10
0
Floating
Swimming
Escape
control
1. Example -2mg/kg
1. Example-8mg/kg
imipramin-30mg/kg
*** p≤0.005
** p ≤0.05

Fig. 5