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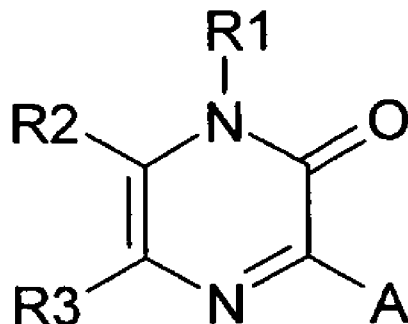
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(54) Title: ARYLPYRAZINONE DERIVATIVES INSULIN SECRETION STIMULATORS, METHODS FOR OBTAINING THEM AND USE THEREOF FOR THE TREATMENT OF DIABETES



(I)

(57) Abstract: The present invention relates to arylpyrazinone derivatives of formula (I), wherein R1, R2, R3 and A are as defined in claim 1, as insulin secretion stimulators. The invention also relates to the preparation and use of these pyrazinone derivatives for the prophylaxis and/or treatment of diabetes and pathologies associated.

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**Arylpyrazinone derivatives insulin secretion stimulators, methods for obtaining them and use thereof for the treatment of diabetes**

Field of the invention

5 The present invention relates to arylpyrazinone derivatives of formula (I) as insulin secretion stimulators. The invention also relates to the preparation and use of these pyrazinone derivatives for the prophylaxis and/or treatment of diabetes and pathologies associated.

10 Background of the invention

Type 2 diabetes mellitus is one of the most common worldwide diseases. In 2007, its prevalence was estimated at 5.9 % (246 million people) of the adult population and is in continuous increase. This disease is even more serious since it could lead to severe micro- and macro-complications, which could become disabling or lethal, as diabetes is a major risk factor for cardiovascular disease and stroke.

Type 2 diabetes is characterized by a fasted and post-prandial hyperglycemia, consequence of two main defects: an insulin resistance at the level of target tissues and an altered insulin secretion from the pancreatic beta cells. This latter anomaly seems to appear very early as it is present at the Impaired Glucose Tolerance (IGT) stage (Mitrakou et al., N. Engl. J. Med. 326: 22-29, 1992). It has been observed in UK Prospective Diabetes Study (UKPDS) that 50% of the beta cell function is already lost when diabetes is diagnosed, suggesting that deterioration in beta cell function may begin 10-12 years before diabetes diagnosis (*Holman, Diabetes Res. Clin. Pract. 40 : S21, 1998 or UKPDS Group, Diabetes 44: 1249-58, 1995*).

The defective insulin secretion is due to a quantitative and a qualitative defect of the beta cell, i.e. a decreased beta cell mass and a specific defect of insulin release in response to glucose, especially the first phase of secretion, since the response to non-glucose secretagogues is preserved

1A

(Pfeifer et al., Am. J. Med. 70: 579-88, 1981). The importance of restoring a normal profile of insulin release in response to glucose to maintain the glycemic control within a normal range was supported by studies in non

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diabetic volunteers showing that delaying the first phase of insulin secretion in response to glucose led to glucose intolerance (Calles-Escandon et al., Diabetes 36: 1167-72,1987).

5 Oral antidiabetics available for treatment of type 2 diabetic patients, such as sulfonylureas or glinides, are known to induce insulin secretion, by binding to sulfonylurea receptor on the K-ATP channels of the beta cell, leading to increase in intracellular calcium and insulin exocytosis. This insulin release is thus totally independent of the plasma glucose level and treatment with these  
10 molecules usually induces sustained hyperinsulinemia, which could lead to several side-effects, such as severe hypoglycaemia, body weight gain, and aggravation of cardiovascular risk. In addition, the prolonged hyperinsulinemia observed with sulfonylurea treatment, with no preservative effect of the beta cell mass, could lead to secondary failure due to beta cell  
15 exhaustion, another deleterious side effect of these compounds.

New treatment of type 2 diabetes should restore a normal profile of insulin release specifically in response to glucose, while preserving or increasing the beta cell mass. This is observed with GLP-1 analogs, such as exenatide or  
20 liraglutide, but these molecules are peptides and must be administered by parenteral route.

Such characteristics for a new oral small molecule would be a great advantage over the other antidiabetic drugs.

25 According to the present invention, the compounds of the formula (I) are insulin secretion stimulators, useful for treatment of diabetes and pathologies associated. They lower blood glucose levels by restoring the defective glucose-induced insulin secretion in type 2 diabetics.

30 The patent application US 2007082913 describes piperidinylpiperazine compounds for treating chemokine mediated diseases, such as, inflammatory diseases, autoimmune diseases, graft rejection, infectious diseases (e.g,

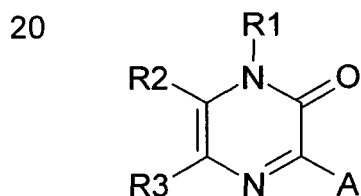
tuberculoid leprosy), fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, type I diabetes, viral meningitis and tumors.

5 The patent application WO 2004099161 describes pyrazinones as corticotropin releasing factor (CRF1) receptor antagonists for the treatment of CNS and other disorders, particularly anxiety-related disorders and mood disorders.

10 The patent JP 63301874 describes quinoxalines that exhibit aldose reductase inhibiting activity and are effective to remedy for diabetes complication, such as corneal wound healing defect, cataract, nervous disease, cell membrane disease or renal disease.

#### Summary of the invention

15 The present invention is directed towards arylpyrazinone derivatives of formula (I). Said derivatives are useful for treating diabetes and pathologies associated therewith. Arylpyrazinone derivatives according to the invention have the following formula (I):



(I)

25 wherein:

**R1** is selected from Z;

**R2** is selected from hydrogen, alkyl, cycloalkyl;

**R3** is selected from hydrogen, halogen, alkyl, cycloalkyl;

**A** is selected from aryl, heteroaryl, arylalkyl,

30 wherein alkyl, aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

Z is:

alkyl, alkenyl, alkynyl, alkoxyalkyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl,  
arylthioalkyl, arylalkylthioalkyl, heteroarylalkyl, heteroaryloxyalkyl,  
heteroarylalkoxyalkyl, heteroarylthioalkyl, heteroarylalkylthioalkyl,  
5 heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkyloxyalkyl,  
heterocycloalkylalkoxyalkyl, heterocycloalkylthioalkyl,  
heterocycloalkylalkylthioalkyl, arylalkenyl, arylalkynyl, cycloalkyl,  
cycloalkylalkyl, cycloalkyloxyalkyl, cycloalkylalkoxyalkyl, cycloalkylthioalkyl,  
cycloalkylalkylthioalkyl,  
10 each of these groups can be optionally substituted by one or more  
substituents selected from Y;

Y is:

hydroxy, thio, halogen, cyano, trifluoromethoxy, trifluoromethyl, carboxy,  
15 carboxymethyl, carboxyethyl, alkyl, alkoxy, alkylamino, aryl, aryl sulfonylalkyl,  
aryloxy, arylalkoxy, amino, NR<sub>5</sub>R<sub>6</sub>, azido, nitro, guanidino, amidino,  
phosphono, oxo, carbamoyl, alkylsulfonyl, alkylsulfinyl, alkylthio, SF<sub>5</sub>, two Y  
groups can form a methylenedioxy;

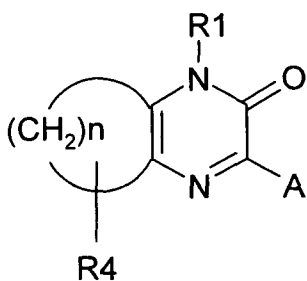
20 **R<sub>5</sub>** and **R<sub>6</sub>** are independently selected from hydrogen, alkyl, aryl, arylalkyl,  
heteroaryl, heteroarylalkyl,  
wherein alkyl, aryl and heteroaryl groups can be optionally substituted by one  
or more substituents selected from Y,

**R<sub>5</sub>** and **R<sub>6</sub>** together can constitute a heterocycle;

25

**R<sub>2</sub>** and **R<sub>3</sub>** can constitute a cycle which corresponds to the general formula  
(II)

30



5

(II)

wherein:

**R1** and **A** are defined as above;

10

**n** = 3, 4, 5;**R4** represents one or more substituents selected from hydrogen, alkyl, alkoxy, cycloalkyl, aryl,

wherein alkyl, cycloalkyl and aryl groups can be optionally substituted by one or more substituents, selected from hydroxy, halogen, alkyl, alkoxy,

15

trifluoromethoxy, trifluoromethyl, alkylsulfonyl, NR<sub>7</sub>R<sub>8</sub>;**R7** and **R8** are independently selected from hydrogen, alkyl, cycloalkyl;

as well as its racemic forms, tautomers, enantiomers, diastereomers,

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epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof;

In another preferred embodiment, the invention provides arylpyrazinone derivatives of formula (I), wherein:

25

**R1** is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkyl,

each of these groups can be optionally substituted by one or more substituents selected from Y;

30

**R2** is selected from hydrogen, alkyl, cycloalkyl;**R3** is selected from hydrogen, halogen, alkyl, cycloalkyl;**A** is selected from aryl, heteroaryl,

wherein aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

Y is:

5 hydroxy, thio, halogen, cyano, trifluoromethoxy, trifluoromethyl, carboxy, carboxymethyl, carboxyethyl, alkyl, alkoxy, alkylamino, aryl, aryl sulfonylalkyl, aryloxy, arylalkoxy, amino, NR<sub>5</sub>R<sub>6</sub>, azido, nitro, guanidino, amidino, phosphono, oxo, carbamoyl, alkylsulfonyl, alkylsulfinyl, alkylthio, SF<sub>5</sub>, two Y groups can form a methylenedioxy;

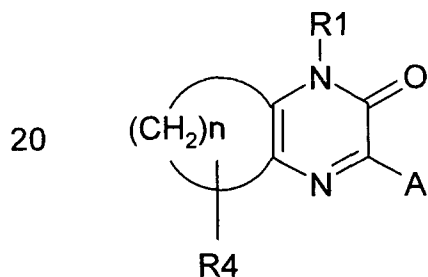
10 **R<sub>5</sub>** and **R<sub>6</sub>** are independently selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl;

wherein alkyl, aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

**R<sub>5</sub>** and **R<sub>6</sub>** together can constitute a heterocycle;

15

**R<sub>2</sub>** and **R<sub>3</sub>** can constitute a cycle which corresponds to the general formula (II),



(II)

25

wherein:

**R<sub>1</sub>** and **A** are defined as above;

**n** = 3, 4, 5;

**R<sub>4</sub>** represents one or more substituents selected from hydrogen, alkyl, alkoxy, cycloalkyl, aryl;

30

wherein alkyl, cycloalkyl and aryl groups can be optionally substituted by one or more substituents, selected from hydroxy, halogen, alkyl, alkoxy, trifluoromethoxy, trifluoromethyl, alkylsulfonyl;

as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

5

In another preferred embodiment, the invention provides pyrazinone derivatives of formula (I), wherein:

**R1** is selected from alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl;

each of these groups can be optionally substituted by one or more

10

substituents selected from halogen, hydroxy;

preferably, **R1** is: ethyl, propyl, isopropyl, butyl; sec-butyl, tert-butyl, cyclopropyl, cyclopropylmethyl;

**R2** is selected from hydrogen, alkyl, cycloalkyl;

**R3** is hydrogen, alkyl, cycloalkyl, halogen;

15

preferably **R2** and **R3** are selected independently from hydrogen, alkyl; more preferably **R2** and **R3** are hydrogen;

**A** is selected from aryl, heteroaryl;

wherein aryl and heteroaryl groups can be optionally substituted by one or

20

more substituents selected from Y; preferably, **A** is: phenyl, indolyl, quinoliny; each of these groups can be optionally substituted by one or more groups selected from Y;

**Y** is:

25

hydroxy, thio, halogen, cyano, trifluoromethoxy, trifluoromethyl, carboxy, carboxymethyl, carboxyethyl, alkyl, alkoxy, alkylamino, aryl, aryl sulfonylalkyl, aryloxy, arylalkoxy, amino, NR<sup>5</sup>R<sup>6</sup>, azido, nitro, guanidino, amidino, phosphono, oxo, carbamoyl, alkylsulfonyl, alkylsulfinyl, alkylthio, SF<sub>5</sub>, two Y groups can form a methylenedioxy

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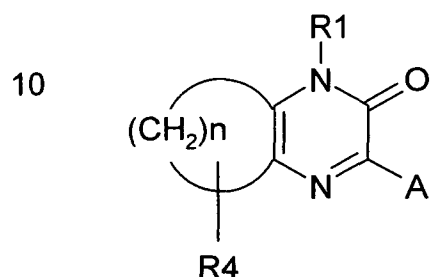
preferably, **Y** is: halogen, trifluoromethoxy, trifluoromethyl, carboxy, alkyl, alkoxy, alkylsulfonyl, two Y groups can form a methylenedioxy;

**R5** and **R6** are independently selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl;

wherein alkyl, aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

5 **R5** and **R6** together can constitute a heterocycle;

**R2** and **R3** can constitute a cycle which corresponds to the general formula (II),



15 (II)

wherein:

**R1** and **A** are defined as above;

$n = 3, 4, 5$ ;

20 **R4** represents one or more substituents selected from hydrogen, alkyl, alkoxy, cycloalkyl, aryl;

wherein alkyl, cycloalkyl and aryl groups can be optionally substituted by one or more substituents, selected from hydroxy, halogen, alkyl, alkoxy, trifluoromethoxy, trifluoromethyl, alkylsulfonyl;

25 preferably, **R2** and **R3** constitute a cycle, which corresponds to tetrahydroquinoxalin-2(1*H*)-one;

other preferred compounds are compounds of general formula (I) wherein, when A is a phenyl group, the phenyl group is not substituted in meta position with a phenyl group optionally substituted;

30

other preferred compounds are compounds of general formula (I) wherein, when R1 is a methyl, A is not 4-substituted-piperidinemethyl;

as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

5 The compounds of the formula (I) may be chosen from the following compounds:

- 1-cyclopropyl-3-phenylpyrazin-2(1*H*)-one;
- 1-(cyclopropylmethyl)-3-phenylpyrazin-2(1*H*)-one;
- 1-ethyl-3-(4-fluorophenyl)pyrazin-2(1*H*)-one;
- 10 1-ethyl-3-(4-methoxyphenyl)pyrazin-2(1*H*)-one;
- 1-ethyl-3-(4-methylphenyl)pyrazin-2(1*H*)-one;
- 1-ethyl-3-(5-fluoro-2-methoxyphenyl)pyrazin-2(1*H*)-one;
- 1-ethyl-3-[4-(methylsulfonyl)phenyl]pyrazin-2(1*H*)-one;
- 1-ethyl-3-[4-(trifluoromethoxy)phenyl]pyrazin-2(1*H*)-one;
- 15 1-ethyl-3-[4-(trifluoromethyl)phenyl]pyrazin-2(1*H*)-one;
- 1-ethyl-3-phenylpyrazin-2(1*H*)-one;
- 1-ethyl-3-(1*H*-indol-5-yl)pyrazin-2(1*H*)-one;
- 1-ethyl-3-(1*H*-indol-6-yl)pyrazin-2(1*H*)-one;
- 1-ethyl-3-quinolin-6-ylpyrazin-2(1*H*)-one;
- 20 1-isopropyl-3-phenylpyrazin-2(1*H*)-one;
- 1-butyl-3-phenylpyrazin-2(1*H*)-one;
- 1-isobutyl-3-phenylpyrazin-2(1*H*)-one;
- 3-(1,3-benzodioxol-5-yl)-1-ethylpyrazin-2(1*H*)-one;
- 3-(2-ethoxyphenyl)-1-ethylpyrazin-2(1*H*)-one;
- 25 3-(4-chlorophenyl)-1-(cyclopropylmethyl)pyrazin-2(1*H*)-one;
- 3-(4-chlorophenyl)-1-ethyl-5,6,7,8-tetrahydroquinoxalin-2(1*H*)-one;
- 3-(4-chlorophenyl)-1-ethylpyrazin-2(1*H*)-one;
- 3-(4-chlorophenyl)-1-isobutylpyrazin-2(1*H*)-one;
- 3-(4-tert-butylphenyl)-1-ethylpyrazin-2(1*H*)-one;
- 30 3-phenyl-1-propylpyrazin-2(1*H*)-one;
- 4-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)benzoic acid;

as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

5 More preferably, the compounds of the formula (I) according to the invention may be chosen from:

3-(1,3-benzodioxol-5-yl)-1-ethylpyrazin-2(1*H*)-one;

3-(4-chlorophenyl)-1-(cyclopropylmethyl)pyrazin-2(1*H*)-one;

3-(4-chlorophenyl)-1-ethyl-5,6,7,8-tetrahydroquinoxalin-2(1*H*)-one;

10 3-(4-chlorophenyl)-1-isobutylpyrazin-2(1*H*)-one;

3-phenyl-1-propylpyrazin-2(1*H*)-one;

as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

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The invention also relates to the racemic forms, tautomeric forms, enantiomers, diastereoisomers, epimers and organic or mineral salts of the compounds of the general formula (I), as well as their crystalline forms, including their polymorphic forms and the polymorphic forms of the

20 compounds of formula (I).

The present invention is directed not only to racemic mixtures of these compounds, but also to individual stereoisomers and/or diastereoisomers thereof, as well or as mixtures of these in all proportions.

The compounds of the invention of the formula (I), as defined above,

25 containing a sufficiently acidic function or a sufficiently basic function, or both, may include the corresponding pharmaceutically acceptable salts of an organic or mineral acid, or of an organic or mineral base.

The expression "pharmaceutically acceptable salts" refers to the relatively non-toxic mineral and organic acid-addition salts, and the base-addition salts,

30 of the compounds of the present invention. These salts may be prepared in situ during the final isolation and purification of the compounds.

In particular, the acid-addition salts may be prepared by separately reacting the purified compound in its purified form with an organic or mineral acid and isolating the salt thus formed. The resulting salts are, for example, hydrochlorides, hydrobromides, sulfates, hydrogenosulfates, dihydrogenophosphates, citrates, maleates, fumarates, trifluoroacetates, 2-naphthalenesulfonates, para-toluenesulfonates.

The invention also relates to pharmaceutically acceptable salts with organic or inorganic bases. In particular, the basic-addition salts may be prepared by separately reacting the purified compound in its purified form with an organic or inorganic base and isolating the salt thus formed. The resulting salts are, for example, metal salts, particularly alkali metal salts, alkaline-earth metal salts and transition metal salts (such as sodium, potassium, calcium, magnesium, aluminum), or salts obtained with bases, such as ammonia or secondary or tertiary amines (such as diethylamine, triethylamine, piperidine, piperazine, morpholine), or with basic amino-acids, or with osamines (such as meglumine), or with aminoalcohols (such as 3-aminobutanol and 2-aminoethanol).

The invention also relates to the salts used for chiral resolution of the racemates.

As examples, the following chiral acids can be used : (+)-D-di-O-benzoyltartaric acid, (-)-L-di-O-benzoyltartaric acid, (-)-L-di-O,O'-p-toluyl-L-tartaric acid, (+)-D-di-O,O'-p-toluyl-L-tartaric acid, (R)-(+)-malic acid, (S)-(-)-malic acid, (+)-camphoric acid, (-)-camphoric acid, R-(-)1,1'-binaphtalen-2,2'-diyl hydrogenophosphonic, (+)-camphanic acid, (-)-camphanic acid, (S)-(+)-2-phenylpropionic acid, (R)-(+)-2-phenylpropionic acid, D-(-)-mandelic acid, L-(+)-mandelic acid, D-tartaric acid, L-tartaric acid, or any mixture of them.

As examples, the following chiral amines can be used: quinine, brucine, (S)-1-(benzyloxymethyl)propylamine (III), (-)-ephedrine, (4S,5R)-(+)-1,2,2,3,4-tetramethyl-5-phenyl-1,3-oxazolidine, (R)-1-phenyl-2-p-tolyethylamine, (S)-phenylglycinol, (-)-N-methylephedrine, (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol, (S)-phenylglycinol, (S)- $\alpha$ -methylbenzylamine or any mixture of them.

Also included in the scope of the present invention are prodrugs of the compounds of formula (I).

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the "drug" substance (a biologically active compound) as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), and/or metabolic chemical reaction(s).

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "aryl" refers to aromatic groups which have 5-14 ring atoms and at least one ring having a conjugated pi ( $\pi$ ) electron system and includes biaryl groups, all of which may be optionally substituted. Suitable aryl groups include phenyl, naphthyl, biphenyl, anthryl, phenanthryl, indenyl and the like.

The term "heteroaryl" refers to 5-14 ring atom aromatic heterocycles containing 1 to 4 heteroatoms, as ring atoms in the aromatic ring and the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include O, S, N. Suitable heteroaryl groups include furanyl, benzofuranyl, thienyl, pyridyl, pyridyl-N-oxide, pyrimidinyl, pyrazinyl, oxazolyl, thiazolyl, isoxazolyl, quinolinyl, triazolyl, pyridazinyl, pyrrolyl, imidazolyl, indazolyl, isothiazolyl, indolyl, oxadiazolyl and the like.

The term "cycloalkyl" means saturated carbocyclic rings, optionally substituted, and includes mono-, bi- and tri-cyclic compounds with 3 to 10 carbon atoms. Suitable cycloalkyl groups are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, adamantyl and the like.

The term "heterocycloalkyl" refers to optionally substituted monocyclic, bicyclic or tricyclic radicals, comprising one or more heteroatoms, preferably chosen from among O, S and N, optionally in the oxidized state (for S and N), and optionally one or more double bonds. At least one of the rings preferably  
5 comprises from 1 to 4 endocyclic heteroatoms, more preferably from 1 to 3 heteroatoms. Most preferably, the heterocycloalkyl (or simply "heterocyclic" or "heterocycle") radical comprises one or more rings, each having from 5 to 8 nodes. Examples of heterocyclic radicals are: morpholinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, tetrahydrothienyl, dihydrofuranyl,  
10 tetrahydrofuranyl, pyrazolidinyl, 1,3-dioxolanyl, pyrrolidinyl, pyranyl, dihydropyranyl, isoxazolidinyl, imidazolyl, imidazolidinyl and the like.

The term "alkyl" refers to a saturated aliphatic groups, including straight chain and branched chain groups. Suitable alkyl groups, having 1 to 20 carbon  
15 atoms, include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, hexyl, octyl, decanoyl, dodecanoyl, hexadecyl, octadecyl groups and the like.

The term "alkenyl" refers to unsaturated groups comprising at least one  
20 carbon-carbon double bond, and includes straight chain, branched chain and cyclic groups. Suitable alkenyl groups, having 2 to 20 carbon atoms, include ethenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl and the like.

25 The term "alkynyl" refers to unsaturated groups comprising at least one carbon-carbon triple bond and includes straight chain, branched chain and cyclic groups; and optionally includes at least one carbon-carbon double bond. Suitable alkynyl groups, having 2 to 20 carbon atoms, include ethynyl, 2-propynyl, 2-butyne, 3-butyne, 2-pentyne, 3-pentyne, 4-pentyne and the  
30 like.

The term "arylalkyl" refers to an alkyl group, preferably an alkyl group having 1 to 20 carbon atoms, substituted with an aryl group. Suitable arylalkyl groups include benzyl, picolyl, and the like.

- 5 The term "arylalkenyl" refers to an alkenyl group, preferably an alkenyl group having 1 to 20 carbon atoms, substituted with an aryl group.

The term "arylalkynyl" refers to an alkynyl group, preferably an alkynyl group having 1 to 20 carbon atoms, substituted with an aryl group.

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The term "alkoxy" refers to the group alk-O- wherein "alk" is an alkyl group.

The term "aryloxy" refers to the group aryl-O-.

- 15 The term "aryloxyalkyl" refers to an alkyl group substituted with an aryloxy group.

The term "arylalkoxyalkyl" refers to an alkyl group substituted with an arylalkoxy group.

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The term "arylalkoxy" refers to the group aryl-Alk-O-, wherein "Alk" is an alkyl group.

- 25 The term "arylthioalkyl" refers to an alkyl group substituted with an arylthio group.

The term "alkylsulfinyl" refers to an alkyl-SO- group.

The term "alkylsulfonyl" refers to an alkyl-SO<sub>2</sub>- group.

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The term "aryl sulfonylalkyl" refers to an alkyl group substituted with an arylsulfonyl (aryl-SO<sub>2</sub>-) group.

The term "arylalkylthioalkyl" refers to an alkyl group substituted with an arylalkylthio.

5 The term "heteroarylalkyl" refers to an alkyl group substituted with a heteroaryl group.

The term "heteroaryloxyalkyl" refers to an alkyl group substituted with a heteroaryloxy group.

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The term "heteroarylalkoxyalkyl" refers to an alkyl group substituted with a heteroarylalkoxy group.

15 The term "heteroarylthioalkyl" refers to an alkyl group substituted with a heteroarylthio group.

The term "heteroarylalkylthioalkyl" refers to an alkyl group substituted with a heteroarylalkylthio group.

20 The term "heterocycloalkylalkyl" refers to an alkyl group substituted with a heterocycloalkyl group.

The term "heterocycloalkyloxyalkyl" refers to an alkyl group substituted with a heterocycloalkyloxy group.

25

The term "heterocycloalkylalkoxyalkyl" refers to an alkyl group substituted with a heterocycloalkylalkoxy group.

30 The term "heterocycloalkylthioalkyl" refers to an alkyl group substituted with a heterocycloalkylthio group.

The term "heterocycloalkylalkylthioalkyl" refers to an alkyl group substituted with a heterocycloalkylalkylthio group.

5 The term "cycloalkylalkyl" refers to an alkyl group substituted with a cycloalkyl group.

The term "cycloalkyloxyalkyl" refers to an alkyl group substituted with a cycloalkyloxy group.

10 The term "cycloalkylalkoxyalkyl" refers to an alkyl group substituted with a cycloalkylalkoxy group.

The terms "alkylthio" refers to the group alkyl-S-.

15 The term "cycloalkylthio" refers to the group cycloalkyl-S-.

The term "cycloalkylthioalkyl" refers to an alkyl group substituted with a cycloalkylthio group.

20 The term "cycloalkylalkylthioalkyl" refers to an alkyl group substituted with a cycloalkylalkylthio group.

The term "halogen" refers to a fluorine, bromine or chlorine atom.

25 The term "amidino" refers to  $-C(NR_5)-NR_5R_6$  where  $R_5R_6$  are as defined above, all, except hydrogen, are optionally substituted.

The term "carbamoyl" refers to an unsubstituted aminocarbonyl group.

30 The invention's compounds according to formula (I) exhibit an hypoglycemic activity, and are useful in the treatment of pathologies associated with the syndrome of insulin resistance.

Insulin resistance is characterised by a reduction in the action of insulin (cf. "Presse Medicale", (1997), 26(14), 671-677) and is involved in many pathological conditions, such as diabetes and more particularly non-insulin-dependent diabetes (type II diabetes or NIDDM), dyslipidaemia, obesity, arterial hypertension, and also certain cardiac, microvascular and macrovascular complications, for instance atherosclerosis, retinopathy and neuropathy. In this respect, reference will be made, for Example, to *Diabetes*, 37, (1988), 1595-1607; *Journal of Diabetes and its complications*, 12, (1998), 110-119; *Horm. Res.*, 38, (1992), 28-32.

10

The invention also relates to pharmaceutical composition containing as active ingredient at least one compound of formula (I), as defined above, and/or a pharmaceutically acceptable salt thereof, in combination with one or several pharmaceutically acceptable carrier, adjuvant, diluent or excipient. A person skilled in the art is aware of a whole variety of such carrier, adjuvant, diluent or excipient compounds suitable to formulate a pharmaceutical composition. The pharmaceutical compositions of the present invention can be administered by a variety of routes including oral, parenteral, intravenous, intramuscular, rectal, permucous or percutaneous.

20

They will thus be presented in the form of injectable solutions or suspensions or multi-dose bottles, in the form of plain or coated tablets, sugar-coated tablets, wafer capsules, gel capsules, pills, sachets, powders, suppositories or rectal capsules, solutions or suspensions, for percutaneous use in a polar solvent, or for permucous use.

25

The excipients that are suitable for such administrations are pharmaceutically acceptable excipients, such as cellulose or microcrystalline cellulose derivatives, alkaline-earth metal carbonates, magnesium phosphate, starches, modified starches, lactose and the like for solid forms.

30

For rectal use, cocoa butter or polyethylene glycol stearates are the preferred excipients.

For parenteral use, water, aqueous solutions, physiological saline and isotonic solutions are the vehicles most appropriately used.

For example, in the case of an oral administration, for example in the form of granules, tablets or coated tablets, pills, capsules, gel capsules, gels, cachets or powders, a suitable posology of the compounds is between about 0.1 mg/kg and about 100 mg/kg, preferably between about 0.5 mg/kg and about 50 mg/kg, more preferably between about 1 mg/kg and about 10 mg/kg and most preferably between about 2 mg/kg and about 5 mg/kg of body weight per day.

If representative body weights of 10 kg and 100 kg are considered, in order to illustrate the daily oral dosage range that can be used and as described above, suitable dosages of the compounds of the formula (I) will be between about 1-10 mg/per day and 1000-10000 mg/per day, preferably between about 5-50 mg/per day and 500-5000 mg/per day, more preferably between 10-100 mg and 100-1000 mg/per day and most preferably between 20-200 mg and 50-500 mg/per day.

It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those skilled in the art.

As noted above, formulations of the present invention suitable for oral administration may be presented as discrete units, such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

In the non-insulin-dependent diabetes, for the man, the hyperglycemia is the results of two main defects: an alteration of the insulin secretion and a reduction in the effectiveness of insulin at level of three sites to knowing the liver, the muscles and adipose tissue.

The present invention also relates to compound of general formula (I) as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof, for the preparation of a medicament for the prevention and/or treatment of pathologies associated with hyperglycaemia; for the preparation of a medicament that induces insulin secretion in response of glucose concentration, preferably for the treatment of diabetes, more preferably for the prevention and/or treatment of type II diabetes and pathologies associated to metabolic disorders, hypercholesteremia, hyperlipidemia, which are increased by hyperinsulinemia and hyperglycemia; for the treatment of diseases chosen from diabetes related microvascular and macrovascular complications, such as arterial hypertension, inflammatory processes, microangiopathy, macroangiopathy, retinopathy and neuropathy; for reducing hyperglycaemia, for the treatment of dyslipidaemia and obesity; or diseases such as cardiovascular diseases, comprising atherosclerosis, myocardial ischemia.

The present invention also relates to the use of at least a compound of the general formula (I), as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts, and pro-drugs thereof, for the preparation of a medicament for the prevention and/or treatment of pathologies associated with hyperglycaemia, preferably for the treatment of diabetes, more preferably for the prevention and/or treatment of type II diabetes and pathologies associated to metabolic disorders, hypercholesteremia, hyperlipidemia, which are increased by hyperinsulinemia and hyperglycemia; for the treatment of diseases chosen from diabetes related microvascular and macrovascular complications, such as arterial hypertension, inflammatory processes, microangiopathy, macroangiopathy, retinopathy and neuropathy; for reducing hyperglycaemia, for the treatment of dyslipidaemia and obesity;

or diseases such as cardiovascular diseases, comprising atherosclerosis, myocardial ischemia.

5 The present invention also relates to manufacturing process of compounds of formula (I), as defined above, according to the following representative methods shown in Scheme 1 (Preparation of the intermediates); Scheme 2 (Preparation of arylpyrazinone derivatives, Method A) or Scheme 3 (Preparation of arylpyrazinone derivatives, Method B).

10 The following schemes are given for representative purposes, and solely for the purpose of facilitating the representation. Needless to say, depending on the nature of the compounds of the formula (I) to be obtained, the methodologies presented may be adapted by a person skilled in the art by selecting the appropriate starting materials, in which the nature of the  
15 substituents R1, R2 and R3 may be modified, especially as a function of the nature and length of the desired chain.

The compounds useful according to the invention may be prepared, unless specifically specified, by the application or adaptation of known methods, by which are meant methods used heretofore or described in the literature,  
20 patents or patent applications, the Chemical Abstracts and on the Internet.

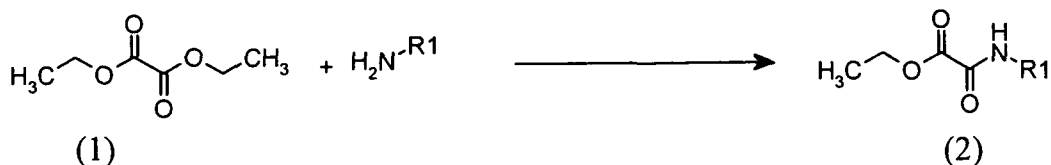
### **Preparation of the intermediates**

#### **Scheme 1:**

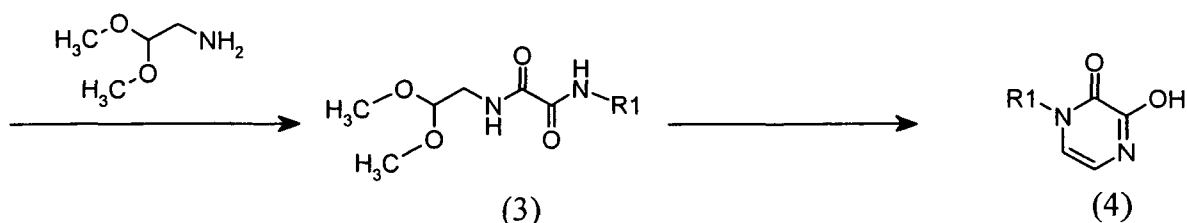
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5



10

wherein R1 is as above defined in formula (I).

Compounds (2) are prepared by reacting diethyl oxalate (1) with an amine in the presence of a quaternary ammonium salt, such as aliquat 336, in an inert solvent, such as chloroform, toluene or dichloromethane, at a temperature between 20°C and the reflux for 24 to 100h.

15

Intermediates (3), with a side chain containing a protected aldehyde in the form of an acetal, are prepared by reacting compounds of formula (2) with a protected aminoacetaldehyde dialkyl-acetate, such as (2,2-dimethoxyethyl)amine. The reaction is carried out in a solvent, such as an alcohol, for example 2-propanol, at a temperature between 20°C and the reflux, for 1 to 24h.

20

Pyrazinones (4) can be prepared by cyclization of compound (3) under acidic conditions, for example in a solvent, such as acetic acid, and catalytic amount of concentrated hydrochloric acid, at a temperature between 20°C and the reflux for 1 to 24h.

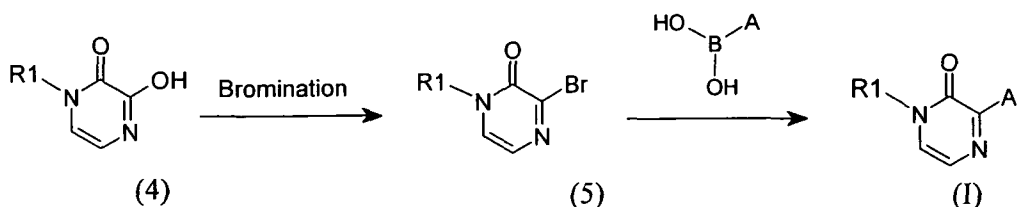
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### Preparation of arylpyrazinone derivatives.

30

### Scheme 2: Method A

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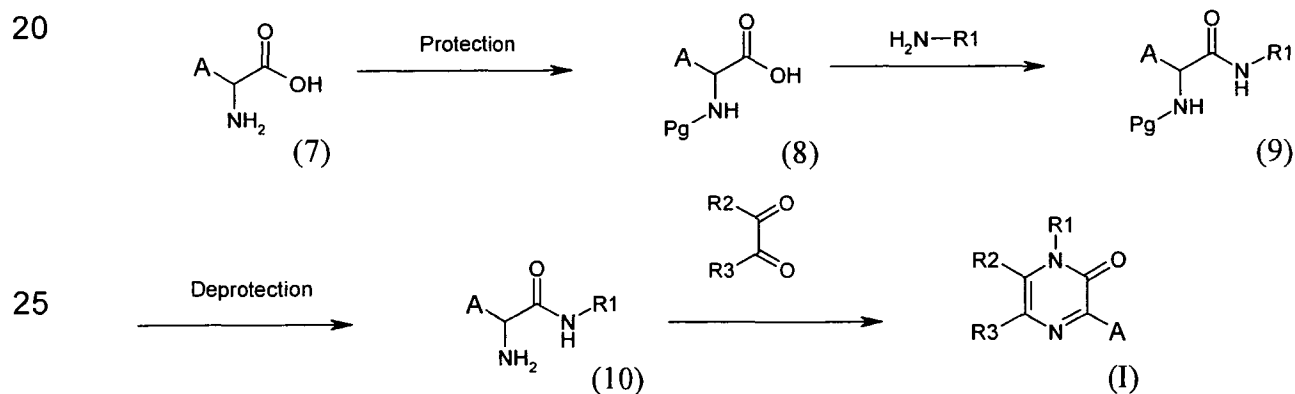


5 wherein R1 and A are as above defined in formula (I).

3-bromo pyrazinones (5) are prepared by bromination of the corresponding 3-hydroxypyrazinones (4), using a brominating agent, such as POBr<sub>3</sub>, in an inert solvent, such as 1,2-dichloroethane, at a temperature between 20°C and the reflux, more preferably reflux, for 1 to 24h.

10 Aryl pyrazinones (I) are prepared in reacting the 3-bromopyrazinones (5) with suitable boronic acids or esters (cyclic or not) of boronic acids in the presence of a base, such as sodium carbonate or potassium carbonate, and a catalyst, such as bis(triphenylphosphine) palladium(II)chloride, in an inert solvent, such as dimethylformamide or toluene, at a temperature between 20°C and the reflux, more preferably reflux, for 1 to 24h.

### Scheme 3: Method B:



wherein R1, R2, R3 and A are as above defined in formula (I).

30 Amino acid derivative is protected using the methods known.

Pg are known protecting groups used for the protection of amines.

Amino function of amino acid derivatives (7) is protected using the methods known in the art. In these formula Pg is a protecting group of the amine function, such as those described by T. W. Greene, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991), preferably a tert-butoxycarbonyl radical or a benzyloxycarbonyl (Cbz) radical.

5

For example, aminoacid (7) can be protected using di-tert-butylidicarbonate to give compounds (8) in which Pg is a tert-butoxycarbonyl radical.

Amides (9) are prepared in reacting compounds (8) with selected amines. In order to activate the carboxylic acids, coupling agents, such as 1-hydroxybenzotriazole (HOBt) or benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluoro phosphate (PyBOP) can be used.

10

Carbonyldiimidazole (CDI) or dicyclohexylcarbodiimide (DCC) can also be used as coupling agents.

15

Amides (9) can also be prepared directly from corresponding carboxylic acids (8) by in situ generation of mixed anhydride. The coupling reaction is usually carried out in the presence of a tertiary amine, such as N-methylmorpholine (NMM), triethylamine (TEA) or diisopropylethylamine (DIPEA), in an organic solvent chosen from those generally used for amide preparation. Preferred solvents for the coupling reaction are ethylacetate (AcOEt), dimethylformamide (DMF), N-methylpyrrolidone (NMP) or tetrahydrofurane (THF). The mixed anhydride prepared, for example, by treating compounds (8) with isobutyl chloroformate in the presence of 4-methylmorpholine on reaction with amines give compound (9). The reaction can be carried out in a solvent, such as tetrahydrofurane, at a temperature between  $-50^{\circ}\text{C}$  to  $0^{\circ}\text{C}$ , for 1 to 6h.

20

25

Compound (10) is prepared from compound (9) using the methods of deprotection known by those skilled in the art and particularly those described by T. W. Greene, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991). Deprotection of BOC-protected amines can

30

be achieved by using organic acid, such as trifluoroacetic acid (CF<sub>3</sub>COOH), or mineral acid, such as hydrochloric acid (HCl).

5 For example amino function of (9) can be deprotected in using hydrochloric acid in dioxane, at a temperature of 0°C to reflux, preferably at room temperature.

Deprotection reactions can also be carried out by means of catalytic hydrogenation.

10 Compounds (I) are prepared by reacting compounds (10) with 1,2-dicarbonyl derivatives, such as oxaldehyde, or cyclic 1,2-dione derivatives, such as cyclohexane-1,2-dione or cyclopentane-1,2-dione, optionally substituted. Cyclization can be carried out in a solvent, such as methanol, in the presence of a mineral base, such as sodium hydroxide, at a temperature between –  
15 50°C to 0°C, for 1 to 10h, preferably between –40°C and –20°C.

The examples that follow illustrate the invention without, however, limiting it. The starting materials used are known products or products prepared according to known procedures. The percentages are expressed on a weight  
20 basis, unless otherwise mentioned.

The compounds were characterised especially via the following analytical techniques.

The NMR spectra were acquired using a Bruker Avance DPX 300 MHz NMR spectrometer.

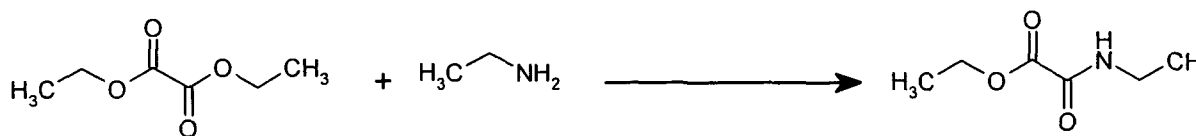
25 The masses were determined by HPLC coupled to an Agilent Series 1100 mass detector. The melting points (m.p.) were measured on a Stuart Scientific block.

### **Examples:**

30

**Example 1: ethyl(ethylamino)(oxo)acetate**

25

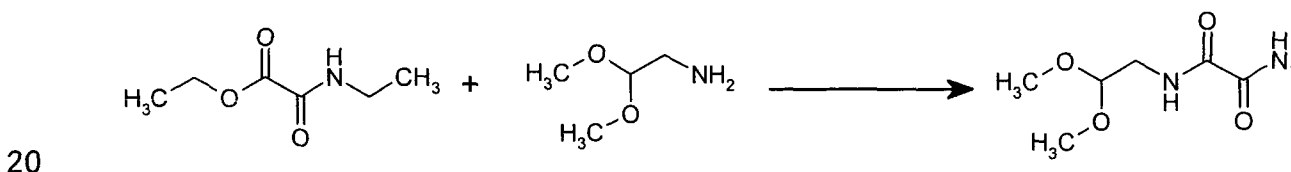


5 To 135,8 ml (1000 mM) of diethyl oxalate and 1g of aliquat 336, in 1000 ml of dichloromethane, were added 64 ml (1000 mM) of ethylamine at 70% in water. The reaction mixture was stirred at room temperature for 72h. The reaction mixture was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give an oil, which was further purified by silica gel column chromatography, using dichloromethane/dimethylketone (95/5) as eluant, to give 59.9g of ethyl(ethylamino)(oxo)acetate as an oil.

10 Yield: 41.3%.

15 NMR <sup>1</sup>H (300 MHz / DMSO-d<sub>6</sub>) δ (ppm): 1.06(t, 3H), 1.28(t, 3H), 3.17(m, 2H), 4.22(q, 2H), 8.92(s, 1H)

### Example 2: N-(2,2-dimethoxyethyl)-N'-ethylethanedi-*amide*



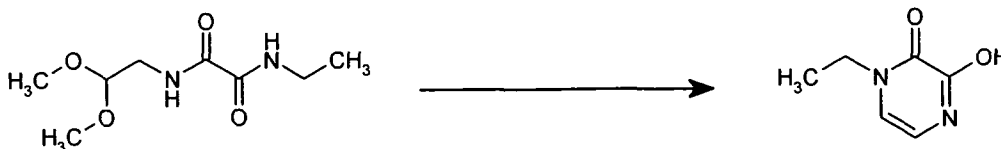
20 59.9 g (412.6 mM) of ethyl(ethylamino)(oxo)acetate and 45 ml (412.6 mM) of (2,2-dimethoxyethyl)amine, in 480 ml of 2-propanol, were stirred at room temperature for 16 h. A white precipitate was filtered, washed with 2-propanol and dried under vacuum to give 67.8 g of N-(2,2-dimethoxyethyl)-N'-ethylethanedi-*amide*.

25 Yield: 80.5%.

30 NMR <sup>1</sup>H (300 MHz / DMSO-d<sub>6</sub>) δ (ppm): 1.07(t, 3H), 3.15(m, 2H), 3.27(m, 8H), 4.51(m, 1H), 8.62(m, 1H), 8.81(m, 1H)

### Example 3: 1-ethyl-3-hydroxypyrazine-2(1*H*)-one

26



5 67.5 g (330 mM) of N-(2,2-dimethoxyethyl)-N'-ethylethanedi- amide and 2 ml of concentrated hydrochloric acid, in 390 ml of acetic acid, were refluxed under stirring for 1 h. The solvent was removed under vacuum to give an oil, which was further purified by silica gel column chromatography, using dichloromethane/methanol (95/5) as eluant to give 37 g of 1-ethyl-3-hydroxypyrazine-2(1H)-one as an oil.

10 Yield: 79.5%.

NMR <sup>1</sup>H (300 MHz / DMSO-d<sub>6</sub>) δ (ppm): 1.20(t, 3H), 3.73(q, 2H), 6.34(d, 1H), 6.56(d, 1H), 11.22(s, 1H)

15

#### Method A:

#### Example 4: 3-bromo-1-ethylpyrazin-2(1H)-one



20

10.5 g (75 mM) of 1-ethyl-3-hydroxypyrazine-2(1H)-one and 23.1 g (80.5 mM) of phosphorous oxybromide in 75 ml of dichloroethane were refluxed under stirring for 2h. The reaction mixture was then neutralized to pH 7-8 with a saturated aqueous solution of sodium carbonate, while maintaining the temperature at 10°C. The reaction mixture was then stirred at room temperature for 1h. Water was added and the organic phase was extracted with dichloromethane. The combined organic layer was washed with water, dried on anhydrous sodium sulfate and the solvent was removed under vacuum. The compound was further purified by silica gel column chromatography using dichloromethane as eluant to give 6.1 g of 3-bromo-1-ethylpyrazin-2(1H)-one as a solid.

25

30

Yield: 40.2 %.

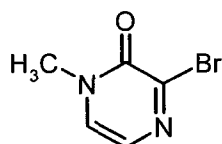
NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 1.18(t, 3H), 3.87(q, 2H), 7.13(d, 1H), 7.75(d, 1H)

5

The following compounds were obtained using the same procedure as in Example 4:

**Example 4-2: 3-bromo-1-methylpyrazin-2(1H)-one**

10

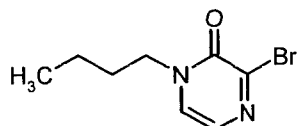


15

NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 3.51(s, 3H), 7.18(d, 1H), 7.80(d, 1H)

**Example 4-3: 3-bromo-1-butylpyrazin-2(1H)-one**

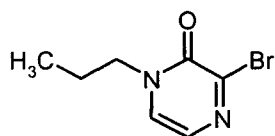
20



NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 0.90(t, 3H), 1.30(m, 2H), 1.65(m, 2H), 3.93(t, 2H), 7.20(d, 1H), 7.79(d, 1H)

25

**Example 4-4: 3-bromo-1-propylpyrazin-2(1H)-one**

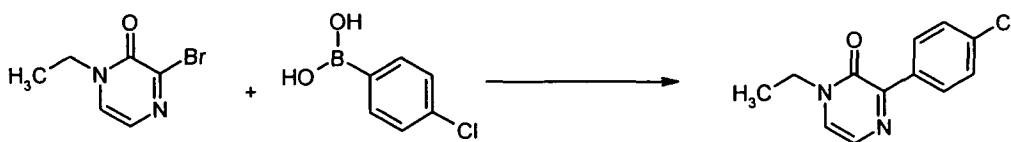


30

$\text{C}_7\text{H}_9\text{BrN}_2\text{O}$  = 217.06    Mass 218.0 (M+1)

**Example 5: 3-(4-chlorophenyl)-1-ethylpyrazin-2(1H)-one**

28



5 To 200 mg (0.98 mM) of 3-bromo-1-ethylpyrazin-2(1H)-one and 57 mg (0.05 mM) of palladium tetrakis triphenylphosphine in 4 ml of toluene were added, under nitrogen, 231.0 mg (1.48 mM) of 4-chlorophenylboronic acid and 2.9 ml of 2M sodium carbonate aqueous solution. The mixture was stirred for 3h at reflux under nitrogen atmosphere, and then at room temperature

10 overnight. Water was added and the mixture was extracted with ethyl acetate. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated. The compound was purified through a silica plug, eluting with dichloromethane, which afforded 110 mg of 3-(4-chlorophenyl)-1-ethylpyrazin-2(1H)-one as a solid.

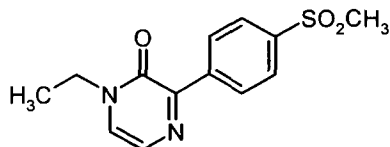
15 Yield: 56%.

NMR <sup>1</sup>H (300 MHz / DMSO-d<sub>6</sub>) δ (ppm): 1.31(t, 3H), 4.03(q, 2H), 7.50(m, 3H), 7.81(d, 1H), 8.30(m, 2H)

C<sub>12</sub>H<sub>11</sub>ClN<sub>2</sub>O = 234.68 Mass 235.0 (M+1)

20

**Example 5-2: 1-ethyl-3-[4-(methylsulfonyl)phenyl]pyrazin-2(1H)-one**



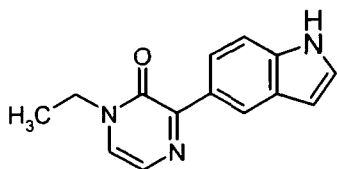
25

NMR <sup>1</sup>H (300 MHz / DMSO-d<sub>6</sub>) δ (ppm): 1.31(t, 3H), 3.01(s, 3H), 4.03(q, 2H), 6.52(d, 1H), 7.94(d, 2H), 8.06(d, 2H), 8.38(d, 1H)

m.p.: 108-110°C

30

**Example 5-3: 1-ethyl-3-(1H-indol-5-yl)pyrazin-2(1H)-one**

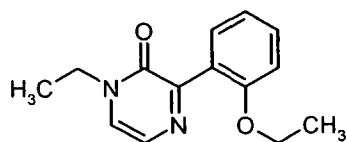


5

$C_{14}H_{13}N_3O = 239.27$  Mass 240.1 (M+1)

**Example 5-4: 3-(2-ethoxyphenyl)-1-ethylpyrazin-2(1H)-one**

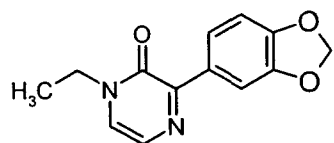
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$C_{14}H_{16}N_2O_2 = 244.29$  Mass 245.1 (M+1)

15

**Example 5-5: 3-(1,3-benzodioxol-5-yl)-1-ethylpyrazin-2(1H)-one**

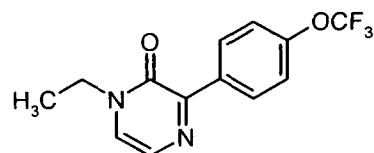


20

$C_{13}H_{12}N_2O_3 = 244.25$  Mass 245.1 (M+1)

**Example 5-6: 1-ethyl-3-[4-(trifluoromethoxy)phenyl]pyrazin-2(1H)-one**

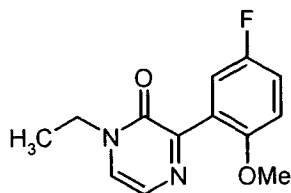
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$C_{13}H_{11}F_3N_2O_2 = 284.23$  Mass 285.1 (M+1)

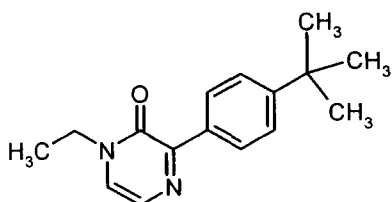
**Example 5-7: 1-ethyl-3-(5-fluoro-2-methoxyphenyl)pyrazin-2(1H)-one**

30



5

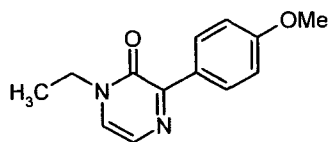
 $C_{13}H_{13}FN_2O_2 = 248.25$  Mass 249.1 (M+1)

**Example 5-8: 3-(4-tert-butylphenyl)-1-ethylpyrazin-2(1H)-one**


10

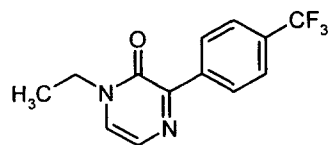
 $C_{16}H_{20}N_2O = 256.34$  Mass 257.1 (M+1)

15

**Example 5-9: 1-ethyl-3-(4-methoxyphenyl)pyrazin-2(1H)-one**


20

 $C_{13}H_{14}N_2O_2 = 230.26$  Mass 231.1 (M+1)

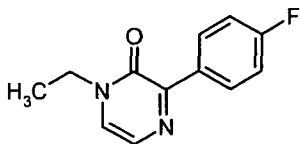
**Example 5-10: 1-ethyl-3-[4-(trifluoromethyl)phenyl]pyrazin-2(1H)-one**


25

 $C_{13}H_{11}F_3N_2O = 268.23$  Mass 269.0 (M+1)

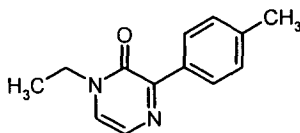
30

**Example 5-11: 1-ethyl-3-(4-fluorophenyl)pyrazin-2(1H)-one**



5  $C_{12}H_{11}FN_2O = 218.23$  Mass 219.0 (M+1)

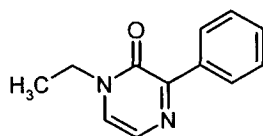
**Example 5-12: 1-ethyl-3-(4-methylphenyl)pyrazin-2(1H)-one**



10

$C_{13}H_{14}N_2O = 214.26$  Mass 215.1 (M+1)

**Example 5-13: 1-ethyl-3-phenylpyrazin-2(1H)-one**

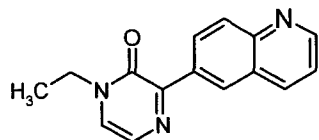


15

$C_{12}H_{12}N_2O = 200.24$  Mass 201.1 (M+1)

20

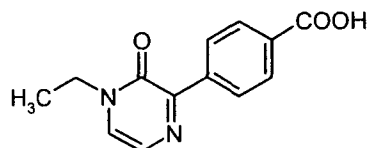
**Example 5-14: 1-ethyl-3-quinolin-6-ylpyrazin-2(1H)-one**



25

$C_{15}H_{13}N_3O = 251.28$  Mass 252.1 (M+1)

**Example 5-15: 4-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)benzoic acid**

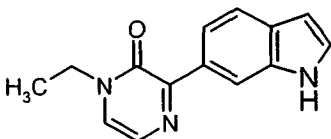


30

NMR  $^1\text{H}$  (300 MHz /  $\text{CDCl}_3$ )  $\delta$  (ppm): 1.38(t, 3H), 3.99(q, 2H), 7.18(d, 1H), 7.47(d, 1H), 8.10(m, 2H), 8.39(m, 2H)

m.p.: 170°C

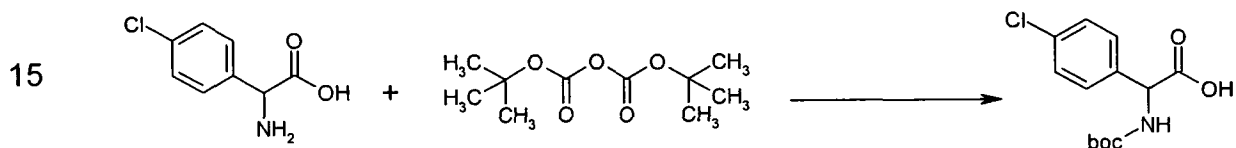
5 **Example 5-16: 1-ethyl-3-(1H-indol-6-yl)pyrazin-2(1H)-one**



10  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O} = 239.27$  Mass 240.1 (M+1)

m.p.: 170°C

15 **Example 6: [(tert-butoxycarbonyl)amino](4-chlorophenyl)acetic acid**



20 To 25g (134.6 mM) of amino(4-chlorophenyl)acetic in 270ml of a 1N aqueous solution of sodium hydroxide were added 34 g (156 mM) of di-tert-butyl dicarbonate. The mixture was stirred at room temperature for 16h. The reaction mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give 34.3 g of [(tert-butoxycarbonyl)amino](4-chlorophenyl)acetic acid as a yellow oily compound.  
25 Yield: 89.2%.

NMR  $^1\text{H}$  (300 MHz /  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 1.40(s, 9H), 5.14(d, 1H), 7.42(m, 4H), 7.62(d, 1H)

30

**Example 7: tert-butyl 1-(4-chlorophenyl)-2-(ethylamino)-2-oxoethylcarbamate**

33



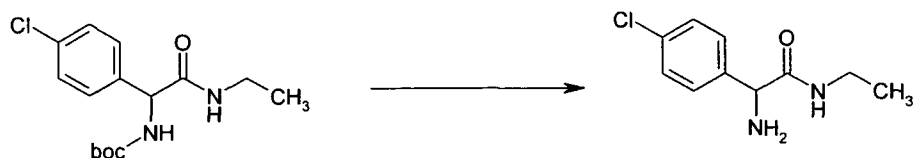
5 To 1.1g (3.85 mM) of [(tert-butoxycarbonyl)amino](4-chlorophenyl)acetic acid in 10 ml of tetrahydrofuran were added, under stirring at  $-25^{\circ}\text{C}$ , 0.5 ml (4.6 mM) of 4-methyl morpholine and 0.52 ml (4.0 mM) of isobutyl chloroformate. After 10 mn were then added, at  $-25^{\circ}\text{C}$  under stirring, 1.9 ml (3.85 mM) of ethylamine 2M in tetrahydrofurane. The reaction mixture was stirred at  $-25^{\circ}\text{C}$

10 for 1h, and at room temperature for 16h. The reaction mixture was filtered and the filtrate was concentrated under vacuum to give an oil, which was further purified by silica gel column chromatography, using dichloromethane/cyclohexane (75/25) as eluant, to give 520 mg of tert-butyl 1-(4-chlorophenyl)-2-(ethylamino)-2-oxoethylcarbamate as a white solid.

15 Yield: 43%.

NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 0.99(t, 3H), 1.39(s, 9H), 3.08(m, 2H), 5.14(d, 1H), 7.35(d, 1H), 7.42(s, 4H), 8.19(t, 1H)

20 **Example 8: 2-amino-2-(4-chlorophenyl)-N-ethylacetamide**



25 A solution of 516 mg (1.65 mM) of tert-butyl 1-(4-chlorophenyl)-2-(ethylamino)-2-oxoethylcarbamate in 2 ml of 4N hydrochloric acid-dioxane solution were stirred at room temperature for 2 h. The reaction mixture was neutralized with an aqueous solution of sodium hydrogenocarbonate and was extracted twice with ethyle acetate. The combined organic layer was washed

30 with water and dried over anhydrous sodium sulfate. The solvent was

removed under vacuum to give 350 mg of 2-amino-2-(4-chlorophenyl)-N-ethylacetamide as an oil.

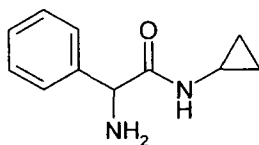
Yield: 99.8%.

5 NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 1.01(t, 3H), 2.27,(s, 2H), 3.08(m, 2H), 4.32(s, 1H), 4.32(s, 1H), 7.39(m, 4H), 8.09(m, 1H)

The following compounds were obtained using the same procedure as in Example 8

10

**Example 8-2: 2-amino-N-cyclopropyl-2-phenylacetamide, hydrochloride**

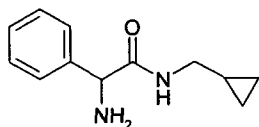


15

NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 0.24(m, 4H), 2.46(m, 1H), 4.72(s, 1H), 7.22(m, 3H), 7.39(m, 2H), 8.62(s, 3H), 8.85(d, 1H)

20

**Example 8-3: 2-amino-N-(cyclopropylmethyl)-2-phenylacetamide, hydrochloride**

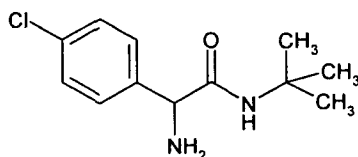


25

NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 0.10(m, 2H), 0.35(m, 2H), 0.83(m, 1H), 2.95(m, 2H), 4.99(s, 1H), 7.39(m, 3H), 7.49(m, 2H), 8.72(m, 4H)

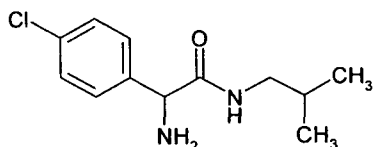
30

**Example 8-4: 2-amino-N-(tert-butyl)-2-(4-chlorophenyl)acetamide, hydrochloride**



NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 1.24(s, 9H), 4.97(s, 1H), 7.56(s, 4H), 8.40(s, 1H), 8.72(s, 3H)

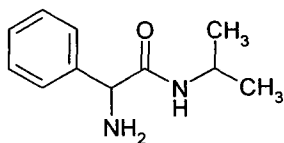
5 **Example 8-5: 2-amino-2-(4-chlorophenyl)-N-isobutylacetamide, hydrochloride**



10

NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 0.75(dd, 6H), 1.68(m, 1H), 2.94(m, 2H), 3.59(s, 1H), 7.57(s, 4H), 8.60(m, 1H), 8.70(s, 3H)

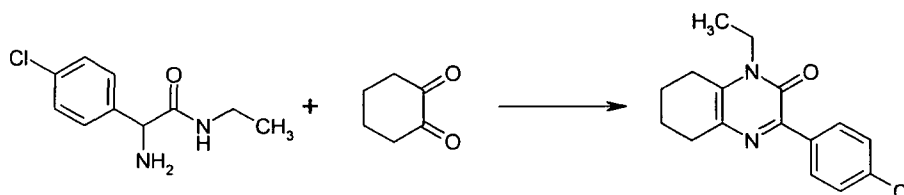
15 **Example 8-6: 2-amino-N-isopropyl-2-phenylacetamide, hydrochloride**



20

NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 0.96(d, 3H), 1.13(d, 3H), 3.85(m, 1H), 4.95(m, 1H), 7.42(m, 3H), 7.57(m, 2H), 8.82(m, 4H)

25 **Example 9: 3-(4-chlorophenyl)-1-ethyl-5,6,7,8-tetrahydroquinoxalin-2(1H)-one**



30

To 330 mg (1.55 mM) of 2-amino-2-(4-chlorophenyl)-N-ethylacetamide in 3.5 ml of methanol at  $-35^\circ\text{C}$  were added 174.1 mg (1.55 mM) of cyclohexane-1,2-dione and 310  $\mu\text{l}$  of a 10N aqueous solution of sodium hydroxide. After stirring at  $-35^\circ\text{C}$  for one hour, the reaction mixture was then stirred at  $5^\circ\text{C}$  for

3 h and at room temperature for 16h. After addition of water, the reaction mixture was acidified with hydrochloric acid and extracted twice with dichloromethane. The combined organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and the solvent was then removed under vacuum to give a brown solid, which was further purified by silica gel column chromatography, using dichloromethane/cyclohexane (75/25) as eluant, to give 192 mg of 3-(4-chlorophenyl)-1-ethyl-5,6,7,8-tetrahydroquinoxalin-2(1H)-one as a yellow solid. Yield: 42.8%.

10 NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 1.24(t, 3H), 1.78(m, 4H), 2.70(t, 2H), 2.83(t, 2H), 4.08(q, 2H), 7.48(d, 2H), 8.37(d, 2H)

$\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{O} = 288.77$  Mass 289.1 (M+1)

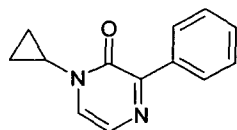
m.p.: 110-113°C

15

The following compounds were obtained using the same procedure as in Example 9:

**Example 9-2: 1-cyclopropyl-3-phenylpyrazin-2(1H)-one**

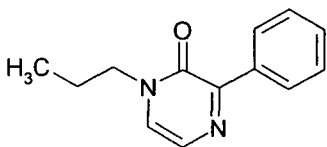
20



$\text{C}_{13}\text{H}_{12}\text{N}_2\text{O} = 212.25$  Mass 213.1 (M+1)

**Example 9-3: 3-phenyl-1-propylpyrazin-2(1H)-one**

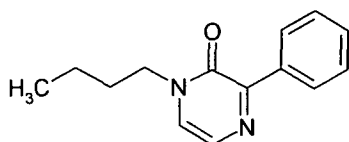
25



30

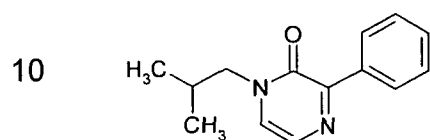
$\text{C}_{13}\text{H}_{14}\text{N}_2\text{O} = 214.26$  Mass 215.1 (M+1)

**Example 9-4: 1-butyl-3-phenylpyrazin-2(1H)-one**



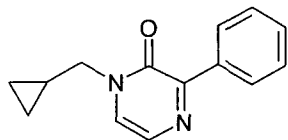
- 5 NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 0.86(t, 3H), 1.42(m, 2H), 1.82(m, 2H), 4.97(m, 2H), 7.49(m, 3H), 7.60(d, 1H), 7.79(d, 1H), 8.31(m, 2H)

**Example 9-5: 1-isobutyl-3-phenylpyrazin-2(1H)-one**



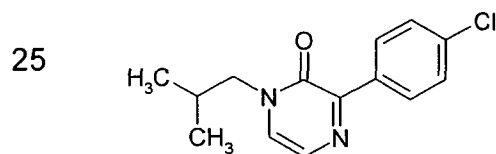
$\text{C}_{14}\text{H}_{16}\text{N}_2\text{O} = 228.29$  Mass 229.1 (M+1)

15 **Example 9-6: 1-(cyclopropylmethyl)-3-phenylpyrazin-2(1H)-one**



- 20 NMR  $^1\text{H}$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 0.21(m, 2H), 0.30(m, 2H), 1.,04(m, 1H), 3.62(d, 2H), 7.21(m, 3H), 7.28(d, 1H), 7.58(d, 1H), 8.05(m, 2H)

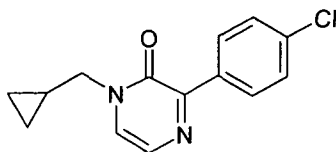
**Example 9-7: 3-(4-chlorophenyl)-1-isobutylpyrazin-2(1H)-one**



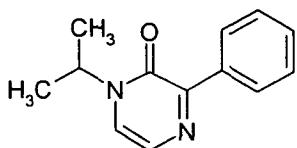
$\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O} = 262.73$  Mass 263.1 (M+1)

**Example 9-8: 3-(4-chlorophenyl)-1-(cyclopropylmethyl)pyrazin-2(1H)-one**

5

 $C_{14}H_{13}Cl N_2O = 260.72$  Mass 261.1 (M+1)

10

**Example 9-9: 1-isopropyl-3-phenylpyrazin-2(1H)-one**

15

NMR  $^1H$  (300 MHz / DMSO- $d_6$ )  $\delta$  (ppm): 1.43(d, 6H), 5.15(m, 1H), 7.49(m, 3H), 7.59(d, 1H), 7.84(d, 1H), 8.30(m, 2H)

**BIOLOGICAL ASSAYS**

20

The INS-1 cells were selected to evaluate our compounds for their superior response to glucose and other physiological and pharmacological insulin secretagogues.

**Culture of pancreatic INS-1 cells**

25

INS-1 cells were cultured in complete medium, RPMI1640 containing 1mM sodium pyruvate, 50 $\mu$ M 2-mercaptoethanol, 2mM glutamine, 10mM HEPES, 100IU/mL penicillin, and 100 $\mu$ g/mL streptomycin (CM), supplemented with 10mM glucose, and 10% (vol/vol) heat-inactivated fetal calf serum (FCS), as described by Asfari et al. (Endocrinology 130: 167-178, 1992).

30

## Insulin secretion assay

INS-1 cells were plated and cultured in 48-well plates. After 2 days of culture, the medium was removed and cells were cultured for 24h with a medium change to 5mM glucose, 1% FCS. The cells were then washed with Krebs-Ringer Bicarbonate HEPES buffer (KRBH; 135mM NaCl; 3.6mM KCl; 5mM NaHCO<sub>3</sub>; 0.5mM NaH<sub>2</sub>PO<sub>4</sub>; 0.5mM MgCl<sub>2</sub>; 1.5mM CaCl<sub>2</sub> and 10mM HEPES; pH 7.4) 0,1% BSA containing 2.8 mM glucose and preincubated for 30min at 37°C in the same buffer. The cells were then washed twice and incubated for 1h in KRBH 0.1% BSA containing 4.2mM glucose and different concentrations of the tested molecule. Insulin concentration in the collected supernatants was measured with ELISA using rat insulin antibody (Insulin Rat Elit PLUS, cat. ref 10-1145-01).

Insulin secretion results are expressed in % of control (glucose 4.2mM).

15

**Insulin secretion in INS-1 cells (glucose at 4.2 mM)**

20

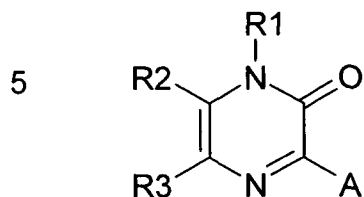
<i>Example</i>	<i>% of ctrl at 10µM of cpd</i>	<i>% of ctrl at 50µM of cpd</i>
<b>9</b>	343	371
<b>9-3</b>	145	182
<b>9-7</b>	140	338
<b>9-8</b>	172	333
<b>5-5</b>	158	204

25

30

## Claims

1. A compound of the general formula (I)



(I)

wherein:

10 **R1** is selected from Z;

**R2** is selected from hydrogen, alkyl, cycloalkyl;

**R3** is selected from hydrogen, halogen, alkyl, cycloalkyl;

**A** is selected from aryl, heteroaryl, arylalkyl,

15 wherein alkyl, aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

**Z** is:

alkyl, alkenyl, alkynyl, alkoxyalkyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl,  
 arylthioalkyl, arylalkylthioalkyl, heteroarylalkyl, heteroaryloxyalkyl,  
 20 heteroarylalkoxyalkyl, heteroarylthioalkyl, heteroarylalkylthioalkyl,  
 heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkyloxyalkyl,  
 heterocycloalkylalkoxyalkyl, heterocycloalkylthioalkyl,  
 heterocycloalkylalkylthioalkyl, arylalkenyl, arylalkynyl, cycloalkyl,  
 cycloalkylalkyl, cycloalkyloxyalkyl, cycloalkylalkoxyalkyl, cycloalkylthioalkyl,  
 25 cycloalkylalkylthioalkyl,

each of these groups can be optionally substituted by one or more substituents selected from Y;

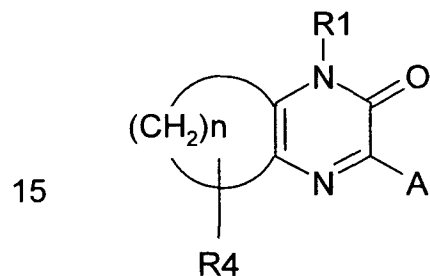
**Y** is:

30 hydroxy, thio, halogen, cyano, trifluoromethoxy, trifluoromethyl, carboxy,  
 carboxymethyl, carboxyethyl, alkyl, alkoxy, alkylamino, aryl, aryl sulfonylalkyl,  
 aryloxy, arylalkoxy, amino, NR<sub>5</sub>R<sub>6</sub>, azido, nitro, guanidino, amidino,

phosphono, oxo, carbamoyl, alkylsulfonyl, alkylsulfinyl, alkylthio, SF<sub>5</sub>, two Y groups can form a methylenedioxy;

**R5** and **R6** are independently selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, wherein alkyl, aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y, **R5** and **R6** together can constitute a heterocycle;

**R2** and **R3** can constitute a cycle which corresponds to the general formula (II)



(II)

wherein:

**R1** and **A** are defined as above;

$n = 3, 4, 5$ ;

**R4** represents one or more substituents selected from hydrogen, alkyl, alkoxy, cycloalkyl, aryl,

wherein alkyl, cycloalkyl and aryl groups can be optionally substituted by one or more substituents, selected from hydroxy, halogen, alkyl, alkoxy, trifluoromethoxy, trifluoromethyl, alkylsulfonyl, NR<sub>7</sub>R<sub>8</sub>;

**R7** and **R8** are independently selected from hydrogen, alkyl, cycloalkyl;

as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein:

**R1** is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkyl, each of these groups can be optionally substituted by one or more substituents selected from Y;

**R2** is selected from hydrogen, alkyl, cycloalkyl;

**R3** is selected from hydrogen, halogen, alkyl, cycloalkyl;

**A** is selected from aryl, heteroaryl,

wherein aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

**Y** is:

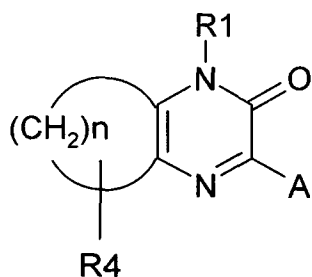
hydroxy, thio, halogen, cyano, trifluoromethoxy, trifluoromethyl, carboxy, carboxymethyl, carboxyethyl, alkyl, alkoxy, alkylamino, aryl, aryl sulfonylalkyl, aryloxy, arylalkoxy, amino, NR<sub>5</sub>R<sub>6</sub>, azido, nitro, guanidino, amidino, phosphono, oxo, carbamoyl, alkylsulfonyl, alkylsulfinyl, alkylthio, SF<sub>5</sub>, two Y groups can form a methylenedioxy;

**R5** and **R6** are independently selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl;

wherein alkyl, aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

**R5** and **R6** together can constitute a heterocycle;

**R2** and **R3** can constitute a cycle which corresponds to the general formula (II),



(II)

wherein:

**R1** and **A** are defined as above;

**n** = 3, 4, 5;

5 **R4** represents one or more substituents selected from hydrogen, alkyl, alkoxy, cycloalkyl, aryl;

wherein alkyl, cycloalkyl and aryl groups can be optionally substituted by one or more substituents, selected from hydroxy, halogen, alkyl, alkoxy, trifluoromethoxy, trifluoromethyl, alkylsulfonyl;

10

as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

15

3. A compound according to claims 1 or 2, wherein:

**R1** is selected from alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl;

each of these groups can be optionally substituted by one or more substituents selected from halogen, hydroxy;

**R2** is selected from hydrogen, alkyl, cycloalkyl;

20

**R3** is hydrogen, alkyl, cycloalkyl, halogen;

**A** is selected from aryl, heteroaryl;

wherein aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

25

**Y** is:

hydroxy, thio, halogen, cyano, trifluoromethoxy, trifluoromethyl, carboxy, carboxymethyl, carboxyethyl, alkyl, alkoxy, alkylamino, aryl, aryl sulfonylalkyl, aryloxy, arylalkoxy, amino, NR<sub>5</sub>R<sub>6</sub>, azido, nitro, guanidino, amidino, phosphono, oxo, carbamoyl, alkylsulfonyl, alkylsulfinyl, alkylthio, SF<sub>5</sub>, two Y groups can form a methylenedioxy

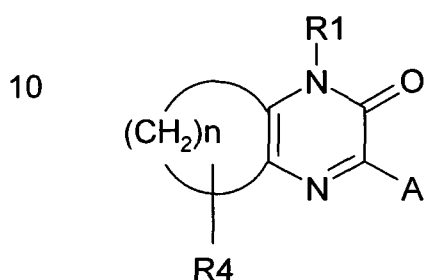
30

**R5** and **R6** are independently selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl;

wherein alkyl, aryl and heteroaryl groups can be optionally substituted by one or more substituents selected from Y;

5 **R5** and **R6** together can constitute a heterocycle;

**R2** and **R3** can constitute a cycle which corresponds to the general formula (II),



15 (II)

wherein:

**R1** and **A** are defined as above;

$n = 3, 4, 5$ ;

20 **R4** represents one or more substituents selected from hydrogen, alkyl, alkoxy, cycloalkyl, aryl;

wherein alkyl, cycloalkyl and aryl groups can be optionally substituted by one or more substituents, selected from hydroxy, halogen, alkyl, alkoxy, trifluoromethoxy, trifluoromethyl, alkylsulfonyl;

25 as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

30 4. A compound according to claim 3, wherein **R1** is: ethyl, propyl, isopropyl, butyl; sec-butyl, tert-butyl, cyclopropyl, cyclopropylmethyl.

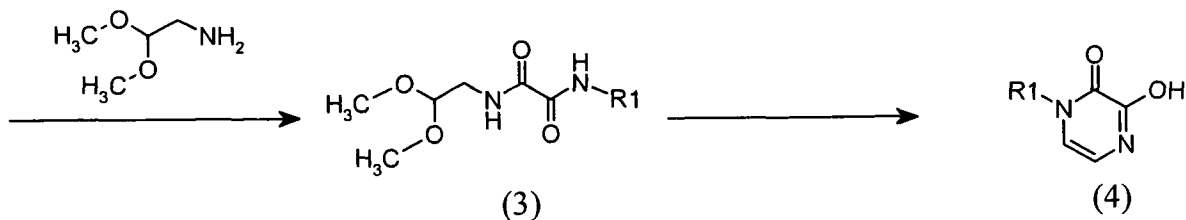
5. A compound according to claim 3, wherein **R2** and **R3** are selected independently from hydrogen, alkyl or constitute a cycle, which corresponds to tetrahydroquinoxalin-2(1*H*)-one.
- 5 6. A compound according to claim 3, wherein **R2** and **R3** are hydrogen, or constitute a cycle, which corresponds to tetrahydroquinoxalin-2(1*H*)-one.
7. A compound according to claim 3, wherein **A** is: phenyl, indolyl, quinolinyl; each of these groups can be optionally substituted by one or more  
10 groups selected from **Y**, as defined in claim 1.
8. A compound according to claim 3, wherein **Y** is: halogen, trifluoromethoxy, trifluoromethyl, carboxy, alkyl, alkoxy, alkylsulfonyl, two **Y** groups can form a methylenedioxy.
- 15 9. A compound according to any of the preceding claims, selected from the following compounds:
- 1-cyclopropyl-3-phenylpyrazin-2(1*H*)-one;  
1-(cyclopropylmethyl)-3-phenylpyrazin-2(1*H*)-one;  
20 1-ethyl-3-(4-fluorophenyl)pyrazin-2(1*H*)-one;  
1-ethyl-3-(4-methoxyphenyl)pyrazin-2(1*H*)-one;  
1-ethyl-3-(4-methylphenyl)pyrazin-2(1*H*)-one;  
1-ethyl-3-(5-fluoro-2-methoxyphenyl)pyrazin-2(1*H*)-one;  
1-ethyl-3-[4-(methylsulfonyl)phenyl]pyrazin-2(1*H*)-one;  
25 1-ethyl-3-[4-(trifluoromethoxy)phenyl]pyrazin-2(1*H*)-one;  
1-ethyl-3-[4-(trifluoromethyl)phenyl]pyrazin-2(1*H*)-one;  
1-ethyl-3-phenylpyrazin-2(1*H*)-one;  
1-ethyl-3-(1*H*-indol-5-yl)pyrazin-2(1*H*)-one;  
1-ethyl-3-(1*H*-indol-6-yl)pyrazin-2(1*H*)-one;  
30 1-ethyl-3-quinolin-6-ylpyrazin-2(1*H*)-one;  
1-isopropyl-3-phenylpyrazin-2(1*H*)-one;  
1-butyl-3-phenylpyrazin-2(1*H*)-one;

- 1-isobutyl-3-phenylpyrazin-2(1*H*)-one;  
3-(1,3-benzodioxol-5-yl)-1-ethylpyrazin-2(1*H*)-one;  
3-(2-ethoxyphenyl)-1-ethylpyrazin-2(1*H*)-one;  
3-(4-chlorophenyl)-1-(cyclopropylmethyl)pyrazin-2(1*H*)-one;  
5 3-(4-chlorophenyl)-1-ethyl-5,6,7,8-tetrahydroquinoxalin-2(1*H*)-one;  
3-(4-chlorophenyl)-1-ethylpyrazin-2(1*H*)-one;  
3-(4-chlorophenyl)-1-isobutylpyrazin-2(1*H*)-one;  
3-(4-tert-butylphenyl)-1-ethylpyrazin-2(1*H*)-one;  
3-phenyl-1-propylpyrazin-2(1*H*)-one;  
10 4-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)benzoic acid;  
as well as its racemic forms, tautomers, enantiomers, diastereomers,  
epimers and polymorphs, and mixtures thereof, and the pharmaceutically  
acceptable salts thereof.
- 15 10. A compound according to claim 9, selected from the following  
compounds:  
3-(1,3-benzodioxol-5-yl)-1-ethylpyrazin-2(1*H*)-one;  
3-(4-chlorophenyl)-1-(cyclopropylmethyl)pyrazin-2(1*H*)-one;  
3-(4-chlorophenyl)-1-ethyl-5,6,7,8-tetrahydroquinoxalin-2(1*H*)-one;  
20 3-(4-chlorophenyl)-1-isobutylpyrazin-2(1*H*)-one;  
3-phenyl-1-propylpyrazin-2(1*H*)-one;  
as well as its racemic forms, tautomers, enantiomers, diastereomers,  
epimers and polymorphs, and mixtures thereof, and the pharmaceutically  
acceptable salts thereof.
- 25 11. Process for the preparation of the compounds of general formula (I)  
according to any one of the preceding claims, the process comprising:  
a) reacting a compound of formula (1)

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with an amine  $\text{R}_1-\text{NH}_2$ , wherein  $\text{R}_1$  is as defined in claim 1, in the presence of a quaternary ammonium salt, such as aliquat 336, in an inert solvent, to give a compound of formula (2);

reacting a compound of formula (2) with a protected aminoacetaldehyde dialkylacetate, such as (2,2-dimethoxyethyl)amine, in an alcohol such as 2-propanol, to give a compound of formula (3);

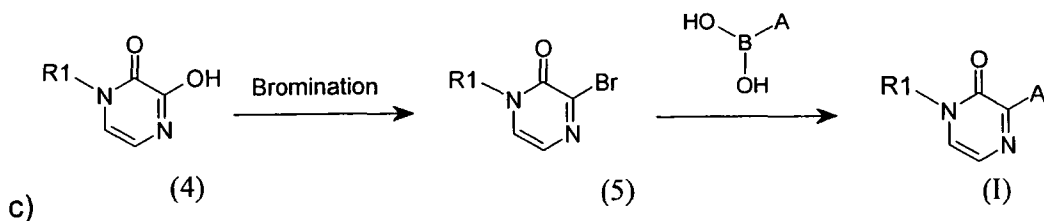
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cyclizing a compound of formula (3) under acidic conditions, in a solvent, such as acetic acid, and catalytic amount of concentrated hydrochloric acid, to give a compound of formula (4);

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b) brominating the compound of formula (4), wherein  $\text{R}_1$  is as defined in claim 1, using a brominating agent, such as  $\text{POBr}_3$ , in an inert solvent to give a compound of formula (5);

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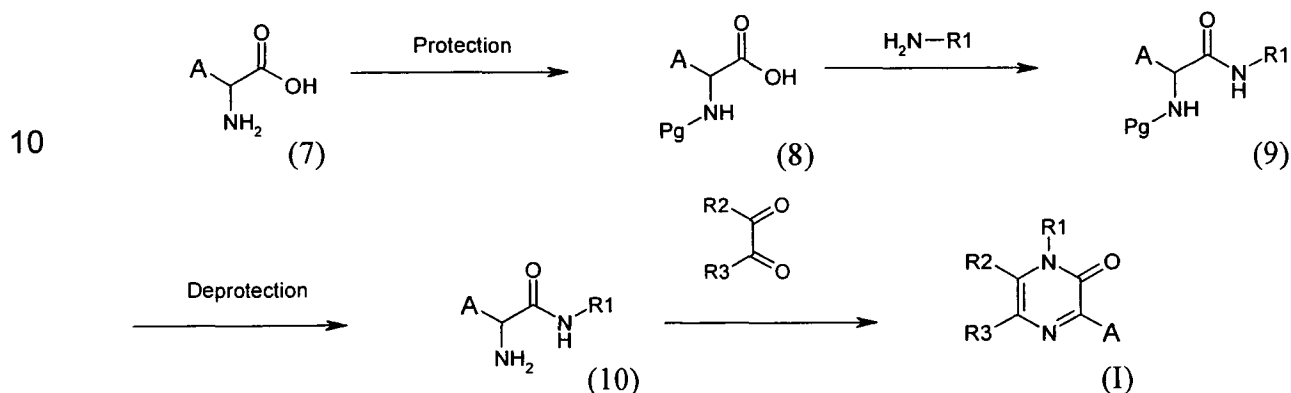


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reacting a compound of formula (5) with boronic acids or esters of boronic acids, wherein  $\text{A}$  is as defined in claim 1, in the presence of a base, such as sodium carbonate or potassium carbonate, and a catalyst, such as bis(triphenylphosphine) palladium(II)chloride, in an inert solvent, to give compounds of formula (I) as well as its racemic forms, tautomers,

enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

12. Process for the preparation of the compounds of general formula (I) according to any one of the preceding claims, the process comprising:  
 5 protecting the amino function of amino acid derivatives of formula (7),  
 wherein A is as defined in claim 1,



with a protecting group of the amine function, Pg, preferably a tert-butoxycarbonyl group or a benzyloxycarbonyl group, to give a compound of formula (8);

18 reacting a compound of formula (8) with an amine R1-NH<sub>2</sub>, wherein R1 is as defined in claim 1, in the presence of coupling agents, such as 1-hydroxybenzotriazole, benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluoro phosphate, carbonyldiimidazole or dicyclohexylcarbodiimide, or by  
 20 in situ generation of mixed anhydride, by reaction e.g. with isobutyl chloroformate, in the presence of a tertiary amine, such as N-methylmorpholine, triethylamine or diisopropylethylamine, in an organic  
 25 solvent, to give an amide of formula (9);

deprotecting the amino function of compounds of formula (9), by using organic acid, such as trifluoroacetic acid, or mineral acid, such as hydrochloric acid, or by catalytic hydrogenation, in a solvent, to give a  
 30 compound of formula (10);

cyclizing a compound of formula (10) with 1,2-dicarbonyl derivatives, such as oxaldehyde, or cyclic 1,2-dione derivatives, such as cyclohexane-1,2-

dione or cyclopentane-1,2-dione, optionally substituted, wherein R2 and R3 are as defined in claim 1, in a solvent, in the presence of a mineral base, such as sodium hydroxide, to give compounds of formula (I) as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition containing at least a compound of general formula (I), and/or a pharmaceutically acceptable salt thereof, according to claims 1 to 10 and a pharmaceutically acceptable excipient.

14. A compound of general formula (I), wherein **R1**, **R2**, **R3** and **A** are as defined in claim 1, as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof, for the preparation of a medicament for the prevention and/or treatment of pathologies associated with hyperglycaemia.

15. A compound according to claim 14, for the preparation of a medicament that induces insulin secretion in response of glucose concentration.

16. A compound according to claims 14 or 15, for the preparation of a medicament suitable for the treatment of diabetes.

17. A compound according to claim 16, for the preparation of a medicament suitable for the treatment of type II diabetes.

18. A compound according to claims 14 or 15, for the preparation of a medicament suitable for the treatment of diseases chosen from dyslipidaemia and obesity.

19. A compound according to claims 14 to 17, for the preparation of a medicament suitable for the treatment of diseases chosen from diabetes related microvascular and macrovascular complications.

5 20. A compound according to claim 19, for which the said complications include arterial hypertension, atherosclerosis, inflammatory processes, microangiopathy, macroangiopathy, retinopathy and neuropathy.

10 21. A compound according to claim 14, for the preparation of a medicament suitable for reducing hyperglycaemia.

15 22. Use of a compound of general formula (I) according to any one of claims 1 to 10, wherein **R1**, **R2**, **R3** and **A** are as defined in claim 1, as well as its racemic forms, tautomers, enantiomers, diastereomers, epimers and polymorphs, and mixtures thereof, and the pharmaceutically acceptable salts thereof, for the preparation of a medicament, for the prevention and/or treatment of pathologies associated with hyperglycaemia

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# INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/002328

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D241/18 C07D241/38 C07D401/04 C07D403/04 C07D405/04  
 A61K31/4965 A61K31/497 A61K31/498 A61P16/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NISHIO, TAKEHIKO ET AL: "Photochemical reactions of tetrahydroquinoxalin-2(1H)-ones and related compounds" HELVETICA CHIMICA ACTA , 74(1), 225-31 CODEN: HCACAV; ISSN: 0018-019X, 1991, XP002533409 page 227; compounds 1A,1D -----	1-8
X	AZZAM, RASHA ET AL: "Expanding the substitution pattern of 2(1H)-pyrazinones via Suzuki and Heck reactions" TETRAHEDRON , 61(16), 3953-3962 CODEN: TETRAB; ISSN: 0040-4020, 2005, XP025383160 page 3954; compound 7A ----- -/--	1-8

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

23 June 2009

Date of mailing of the international search report

14/07/2009

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/002328

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROMBOUTS, FREDERIK J. R. ET AL: "Synthesis and conformational analysis of Substance P antagonist analogues based on a 1,7-naphthyridine scaffold" TETRAHEDRON , 59(26), 4721-4731 CODEN: TETRAB; ISSN: 0040-4020, 2003, XP004431645 page 4723; compound 11 -----	1-8
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X	HABIB, M. S. ET AL: "Mechanism and scope of an N-oxide rearrangement" JOURNAL OF THE CHEMICAL SOCIETY 3371-83 CODEN: JCSOA9; ISSN: 0368-1769, 1960, XP000615499 page 3372; compound VI -----	1-8
X	CHEESEMAN ET AL: "Pyrazines. IV. 2,6-Dihydroxy-3,5-diphenylpyrazine and related compounds" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL SOCIETY, LETCHWORTH., GB, vol. 18, 1 January 1971 (1971-01-01), pages 2977-2979, XP002077515 ISSN: 0368-1769 page 2978; compound 10B -----	1-8
X	NISHIO T: "[4+2]Cycloaddition of 2(1H)-pyrazinones and 1,2,4-triazoline-3,5-diones" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 35, 1 January 1998 (1998-01-01), pages 655-658, XP002290218 ISSN: 0022-152X page 655; compound 1H -----	1-8
X	BUYSSENS K J ET AL: "Synthesis of New Pyrrolo[3,4-b]- and [3,4-c]pyridin(on)es and Related 1,7-Naphthyridinones and 2,7-Naphthyridines via Intramolecular Diels-Alder Reactions of 2(1H)-Pyrazinones" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 52, no. 27, 1 July 1996 (1996-07-01), pages 9161-9178, XP004104003 ISSN: 0040-4020 page 9162; compounds 2C,2D,3C,3D ----- -/--	1-8

## INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BUYSENS K J ET AL: "GENERATION OF 6-ALKYLIDENE/BENZYLIDENE-3,6-2(1H)-ONES Y REACTION OF 6-BROMOMETHYLPYRAZIN-2(1H)-ONES WITH METHOXIDE AND FURTHER CONVERSION INTO SPECIFIC PIPERAZINE-2,5-DIONES AND PYRAZIN-2(1H)-ONES"</p> <p>JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY, LETCHWORTH, GB, vol. 3, 1 January 1996 (1996-01-01), pages 231-238, XP009034546 ISSN: 0300-922X page 231; compounds 5C,5E</p>	1-8
X	<p>DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOCEVAR, M. ET AL: "Syntheses and transformations of some 1,2,4-oxadiazolylpyrazines"</p> <p>XP002533411 retrieved from STN Database accession no. 1983:143377 abstract RN=85124-07-8 &amp; JOURNAL OF HETEROCYCLIC CHEMISTRY , 19(6), 1397-402 CODEN: JHTCAD; ISSN: 0022-152X, 1982,</p>	1-8
X	<p>DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HABIB, M. S. ET AL: "Rearrangement of certain quinoxalinecarboxanilides. Isolation of an intermediate in a related N-oxido rearrangement"</p> <p>XP002533412 retrieved from STN Database accession no. 1962:46026 abstract RN= 88614-00-0 &amp; PROCEEDINGS OF THE CHEMICAL SOCIETY, LONDON 167-8 CODEN: PCSLAW; ISSN: 0369-8718, 1961,</p>	1-8
X	<p>EP 0 242 957 A (TOYO JOZO KK [JP]) 28 October 1987 (1987-10-28) page 3, line 1 - page 8, line 12 compounds 110,291-297,374-387,467-480</p>	1-8,13

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International application No  
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 2004/009586 A (BIOVITRUM AB [SE]; NILSSON BJOERN [SE]; THOR MARKUS [SE]; CERNERUD MAG) 29 January 2004 (2004-01-29) claims 1,16 -----	1-22
A	WO 2005/097136 A (MERCK & CO INC [US]; LIANG JUN [US]; CHAKRAVARTY PRASUN K [US]; PAN DE) 20 October 2005 (2005-10-20) claims 1,27 -----	1-22
A	WO 2007/071646 A (JANSSEN PHARMACEUTICA NV [BE]; ANDRES-GIL JOSE IGNACIO [ES]; ALCAZAR-V) 28 June 2007 (2007-06-28) claims 1,24 -----	1-22

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Information on patent family members

International application No

PCT/EP2009/002328

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