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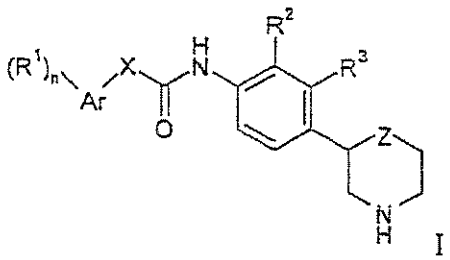
Objects of the ~~present invention~~embodiments disclosed herein are new compounds of formula I and their pharmaceutically acceptable salts, their use for the manufacture of medicaments for the treatment of diseases related to the biological function of the trace amine associated receptors, their manufacture and medicaments based on a compound in accordance with the invention in the control or prevention of illnesses such as depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders such as schizophrenia, neurological diseases such as Parkinson's disease, neurodegenerative disorders such as Alzheimer's disease, epilepsy, migraine, substance abuse and metabolic disorders such as eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy

consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

The preferred indications using the compounds of the present ~~invention~~disclosure are depression, psychosis, Parkinson's disease, anxiety, attention deficit hyperactivity disorder (ADHD) and diabetes.

In a first aspect, there is provided a compound of formula



I

wherein

R^1 is hydrogen, halogen, cyano, C_{1-7}-alkyl, C_{1-7}-alkyl substituted by halogen, C_{1-7}-alkoxy, C_{1-7}-alkoxy substituted by halogen or $C(O)NH_2$, or is phenyl optionally substituted by halogen, cyano or C_{1-7}-alkoxy substituted by halogen, or is 2,2-difluorobenzo[d][1,3]dioxol-5-yl, or is 6-(trifluoromethyl)pyrazin-2-yl or 5-(trifluoromethyl)pyrazin-2-yl or is 6-(trifluoromethyl)pyrimidin-4-yl, or is 6-(trifluoromethyl)pyridin-3-yl, or is 5-cyanopyrazin-2-yl or is 2-(trifluoromethyl)pyrimidin-4-yl;

n is 1 or 2

R^2 is halogen, C_{1-7}-alkyl or cyano and R^3 is hydrogen, or

R^2 is hydrogen and R^3 is halogen, C_{1-7}-alkyl or cyano;

X is a bond, -NR'-, $-CH_2NH-$ or –CHR'-;

R' is hydrogen or C_{1-7}-alkyl;

Z is a bond, $-CH_2-$ or –O-;

Ar is phenyl or is heteroaryl, selected from the group consisting of 1H-indazole-3yl, pyridine-2-yl, pyridine-3-yl, pyridine-4-yl, pyrimidine-5-yl, 1H-pyrazole-3-yl, 1H-pyrazole-4-yl or 1H-pyrazole-5-yl;

and the compound

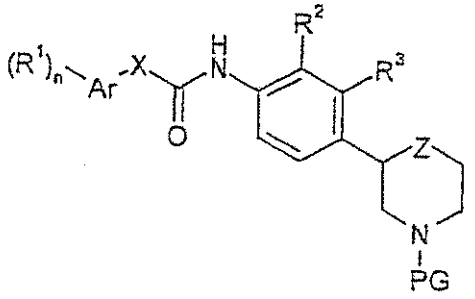
(S)-N-(3-fluoro-4-(morpholin-2-yl)phenyl)-5-(trifluoromethyl)pyrazine-2 carboxamide or

a pharmaceutically suitable acid addition salt thereof.

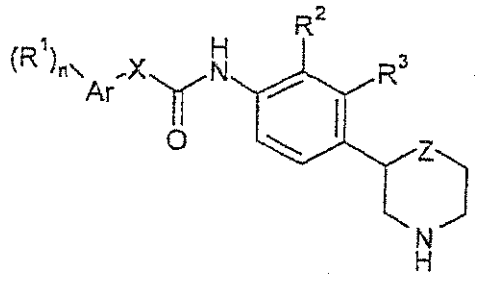
In a second aspect, there is provided the compound (S)-N-(3-fluoro-4-(morpholin-2-yl)phenyl)-5-(trifluoromethyl)pyrazine-2 carboxamide.

In a third aspect, there is provided a process for the manufacture of a compound of formula I as defined above, which process comprises

a) cleaving off the N-protecting group from compounds of formula



to a compound of formula



I

wherein PG is a N-protecting group selected from –C(O)O-tert-butyl and the other definitions are as described above and,

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

In a fourth aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutical acceptable carrier and/or adjuvant.

In a fifth aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutical acceptable carrier and/or adjuvant for use in the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder (ADHD), stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse, metabolic disorders, eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

In a sixth aspect, there is provided compounds as defined above for use as therapeutic active substances.

In a seventh aspect, there is provided compounds as defined above for use as therapeutic active substances in the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder (ADHD), stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse, metabolic disorders, eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

In an eighth aspect, there is provided the use of a compound as defined above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder (ADHD), stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse, metabolic disorders, eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon atoms.

As used herein, the term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above and which is attached via an oxygen atom.

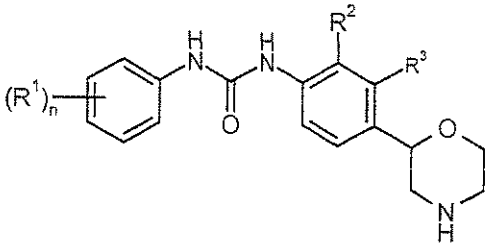
The term "halogen" denotes chlorine, iodine, fluorine and bromine.

As used herein, the term "lower alkyl substituted by halogen" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms as defined for the term "lower alkyl", wherein at least one hydrogen atom is replaced by a halogen atom. A preferred halogen atom is fluoro. Examples of such groups are CF_3, CHF_2, CH_2F, CH_2CF_3 or CH_2CHF_2 .

As used herein, the term "lower alkoxy substituted by halogen" denotes an alkoxy group as defined above and wherein on or more hydrogen atoms are replaced by halogen, for example OCH_3, $OCHF_2$, OCH_2F, OCH_2CF_3 or OCH_2CHF_2.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

One embodiment of the invention are compounds of formula IA



IA

R^1 is hydrogen, halogen, cyano, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, lower alkoxy substituted by halogen or $C(O)NH_2$,
or is phenyl optionally substituted by halogen, cyano or lower alkoxy substituted by halogen, or is 2,2-difluorobenzo[d][1,3]dioxol-5-yl, or is 6-(trifluoromethyl)pyrazin-2-yl