antagonists of the Neurokinin 1 (NK-1, substance P) receptor. Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue.

The receptor for substance P is a member of the superfamily of G protein-coupled receptors.

The neuropeptide receptors for substance P (NK-1) are widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes.

The central and peripheral actions of the mammalian tachykinin substance P have been associated with numerous inflammatory conditions including migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease as well as mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 1996, 7, 187-214), anxiety (Can. J. Phys., 1997, 75, 612-621) and depression (Science, 1998, 281, 1640-1645).

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases reviewed in "Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13, 23-93, 1993.

Furthermore, Neurokinin 1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinin, in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (WO 95/16679, WO 95/18124 and WO 95/23798).

The neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting.

In addition, in The New England Journal of Medicine, Vol. 340, No. 3 190-195, 1999 has been described the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.

Furthermore, US 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as NK-1 receptor antagonist.

Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts thereof, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier or in the manufacture of corresponding medicaments.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders or emesis by the administration of NK-1 receptor antagonists. A major depressive episode has been defined as being a period of at least two weeks during which, for most of the day and nearly every day, there is either depressed mood or the loss of interest or pleasure in all, or nearly all activities.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1-7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, t-butyl and the like.
Preferred lower alkyl groups are groups with 1-4 carbon atoms.

The term "lower alkoxy" denotes a group wherein the alkyl residues are as defined above, and which is attached via an oxygen atom.

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

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.

Exemplary preferred are compounds, in which X is $-C(O)N(R^{4''})-$, wherein $R^{4''}$ is methyl, and R^5 is piperazinyl, optionally substituted by one or two methyl groups, for example the following compounds:

4-(2-bromo-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,

(3R,5S)-4-(2-bromo-phenyl)-2-(3,5-dimethyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-bromo-phenyl)-2-piperazin-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-chloro-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
(3R,5S)-4-(2-chloro-phenyl)-2-(3,5-dimethyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-chloro-phenyl)-2-piperazin-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
2-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
(3R,5S)-2-(3,5-dimethyl-piperazin-1-yl)-4-o-tolyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
2-piperazin-1-yl-4-o-tolyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-methoxy-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
(3R,5S)-2-(3,5-dimethyl-piperazin-1-yl)-4-(2-methoxy-phenyl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-methoxy-phenyl)-2-piperazin-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(4-fluoro-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-fluoro-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
(3R,5S)-2-(3,5-dimethyl-piperazin-1-yl)-4-(2-fluoro-phenyl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(4-fluor-phenyl)-2-piperazin-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(4-fluoro-2-methyl-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
(3R,5S)-2-(3,5-dimethyl-piperazin-1-yl)-4-(4-fluoro-2-methyl-phenyl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(4-fluor-2-methyl-phenyl)-2-piperazin-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,

2-(4-methyl-piperazin-1-yl)-4-naphthalen-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
(3R,5S)-2-(3,5-dimethyl-piperazin-1-yl)-4-naphthalen-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-naphthalen-1-yl-2-piperazin-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-chloro-4-fluoro-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and
4-(2-chloro-4-fluoro-phenyl)-2-piperazin-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

Further preferred are compounds, in which X is $-C(O)N(R^{4''})-$, wherein $R^{4''}$ is methyl and R^5 is morpholinyl or $-O(CH_2)_2$ -morpholinyl .

Examples of such compounds are:

4-(2-bromo-phenyl)-2-morpholin-4-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-chloro-phenyl)-2-morpholin-4-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-chloro-phenyl)-2-(2-morpholin-4-yl-ethoxy)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
2-morpholin-4-yl-4-o-tolyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-methoxy-phenyl)-2-morpholin-4-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(4-fluoro-2-methyl-phenyl)-2-morpholin-4-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
2-morpholin-4-yl-4-naphthalen-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and
4-(2-chloro-4-fluoro-phenyl)-2-morpholin-4-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

Preferred are further compounds, in which X is $-C(O)N(R^{4''})-$, $R^{4''}$ is methyl and R^5 is $-NH(CH_2)_2N(CH_3)_2$, $-O(CH_2)_2N(CH_3)_2$ or $-O(CH_2)_3N(CH_3)_2$, for example the following compounds:

4-(2-chloro-phenyl)-2-(2-dimethylamino-ethylamino)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide