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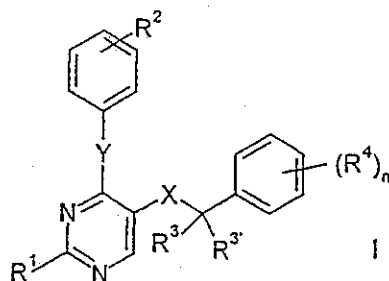
(54) Title: PYRIMIDINE DERIVATIVES

(57) Abstract: The invention relates to compounds of the general formula (I) wherein R<sup>1</sup> is lower alkyl, lower alkoxy, pyridinyl, pyrimidinyl, phenyl, -S-lower alkyl, -S(O)<sub>2</sub>-lower alkyl, -N(R)-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -N(R)<sub>2</sub>, or a cyclic tertiary amine of the group which may contain one additional heteroatom, selected from N, O or S, and wherein this group may be connected with the pyrimidine ring via the linker -O(CH<sub>2</sub>)<sub>n</sub>-; R<sup>2</sup> is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl; R<sup>3</sup>/R<sup>3'</sup> is, independently from each other, hydrogen or lower alkyl; R<sup>4</sup> is independently from each other halogen, trifluoromethyl or lower alkoxy; R<sup>5</sup> is hydrogen or lower alkyl; R is, independently from each other, hydrogen or lower alkyl; X is -C(O)N(R)- or -N(R)C(O)-; Y is -O-, -S-, -SO<sub>2</sub>-, - or -N(R)-; n is 1,2,3 or 4; and m is 0,1 or 2; and to pharmaceutically acceptable acid addition salts thereof. They have a good affinity to the NK1 receptor and they are therefore suitable in the treatment of diseases, related to this receptor.

WO 02/42280 A2

Pyrimidine derivatives

The present invention relates to compounds of the general formula



wherein

- 5  $R^1$  is lower alkyl, lower alkoxy, pyridinyl, pyrimidinyl, phenyl, -S-lower alkyl, -S(O)<sub>2</sub>-lower alkyl, -N(R)-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -N(R)<sub>2</sub>, or a cyclic tertiary amine of the group



- 10 which may contain one additional heteroatom, selected from N, O or S, and wherein this group may be connected with the pyrimidine ring via the linker -O(CH<sub>2</sub>)<sub>n</sub>-;

$R^2$  is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

$R^3/R^3'$  is, independently from each other, hydrogen or lower alkyl;

$R^4$  is independently from each other halogen, trifluoromethyl or lower alkoxy;

$R^5$  is hydrogen or lower alkyl;

15  $R$  is, independently from each other, hydrogen or lower alkyl;

$X$  is -C(O)N(R)- or -N(R)C(O)-;

$Y$  is -O-, -S-, -SO<sub>2</sub>-, - or -N(R)-;

$n$  is 1, 2, 3 or 4; and

m is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

The compounds of formula I and their salts are characterized by valuable therapeutic properties. It has been surprisingly found that the compounds of the present invention are  
5 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.

10 The neuropeptide receptor for substance P (NK-1) is 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  
15 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).

20 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  
25 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  
30 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.

The usefulness of neurokinin 1 receptor antagonists for the treatment of certain forms of urinary incontinence is further described in "Neuropeptides, 32(1), 1-49, (1998)" and "Eur. J. Pharmacol., 383(3), 297-303, (1999)".

Life Sci., (2000), 67(9), 985-1001 describes, that astrocytes express functional receptors to numerous neurotransmitters including substance P, which is an important stimulus for reactive astrocytes in CNS development, infection and injury. In brain tumors malignant glial cells originating from astrocytes are triggered by tachykinins via NK-1 receptors to release soluble mediators and to increase their proliferative rate. Therefore, selective NK-1 receptor antagonists may be useful as a therapeutic approach to treat malignant gliomas in the treatment of cancer.

In Nature (London) (2000), 405(6783), 180-183 is described that mice with a genetic disruption of NK-1 receptor show a loss of the rewarding properties of morphine. Consequently NK-1 receptor antagonists may be useful in the treatment of withdrawal symptoms of addictive drugs such as opiates and nicotine and reduction of their abuse/craving.

NK1 receptor antagonists have been reported to have also a beneficial effect in the therapy of traumatic brain injury (oral disclosure by Prof. Nimmo at the International Tachykinin Conference 2000 in La Grande Motte, France, October 17-20, 2000 with the title "Neurokinin 1 (NK-1) Receptor Antagonists Improve the Neurological Outcome Following Traumatic Brain Injury" (Authors: A.J. Nimmo, C.J. Bennett, X.Hu, I. Cernak, R. Vink).

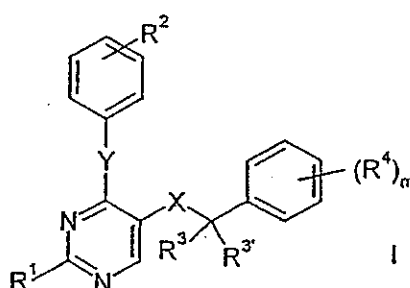
The compounds of the present invention are further useful for the treatment of benign prostatic hyperplasia (BPH), which is common in older men. BPH can be progressive and lead to urinary retention, infections, bladder calculi and renal failure. This indication has been reported in EP 01109853.0.

The compounds of formula I can also be used in the form of their prodrugs, for example in form of their N-oxides. The prodrugs may add to the value of the present

compounds advantages in adsorption, pharmacokinetics in distribution and transport to the brain.

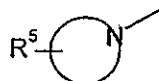
Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts thereof, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses,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

In a first aspect, the present invention provides compounds of the general formula



wherein

$R^1$  is lower alkyl, lower alkoxy, pyridinyl, pyrimidinyl, phenyl, -S-lower alkyl, -S(O)<sub>2</sub>-lower alkyl, -N(R)-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -N(R)<sub>2</sub>, or a cyclic tertiary amine of the group



which may contain one additional heteroatom, selected from N, O or S, and wherein this group may be connected with the pyrimidine ring via the linker -O(CH<sub>2</sub>)<sub>n</sub>-;

$R^2$  is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

$R^3/R^{3'}$  is, independently from each other, hydrogen or lower alkyl;

$R^4$  is independently from each other halogen, trifluoromethyl or lower alkoxy;

$R^5$  is hydrogen or lower alkyl;

R is, independently from each other, hydrogen or lower alkyl;

X is -C(O)N(R)- or -N(R)C(O)-;

- 4a -

Y is -O-, -S-, -SO<sub>2</sub>-, - or -N(R)-;

n is 1, 2, 3 or 4; and

m is 0, 1 or 2;

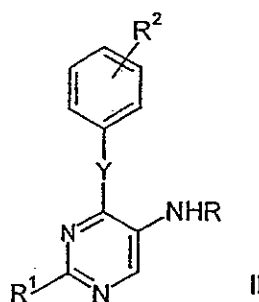
and pharmaceutically acceptable acid addition salts thereof.

In a second aspect, the present invention provides a medicament containing one or more compounds according to the first aspect and pharmaceutically acceptable excipients.

In a third aspect, the present invention provides a medicament according to the second aspect for the treatment of diseases related to NK-1 receptor antagonists.

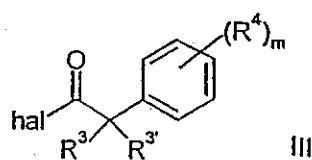
In a fourth aspect, the present invention provides a process for preparing a compound of formula I as defined in the first aspect, which process comprises

a) reacting a compound of formula

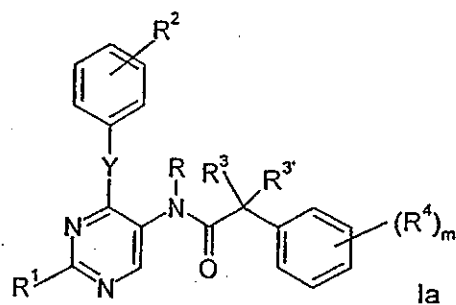


with a compound of formula

- 4b -



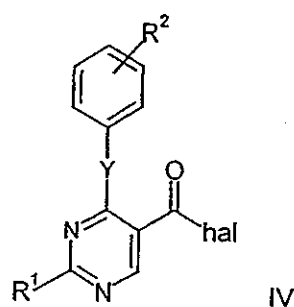
to a compound of formula



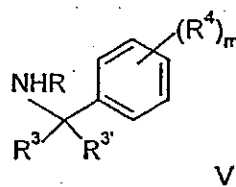
wherein Y, R¹, R², R³, R³', R⁴, R and m have the significances given above,

or

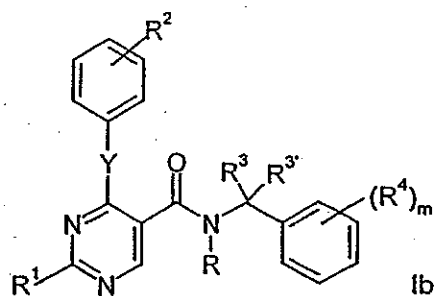
b) reacting a compound of formula



with a compound of formula



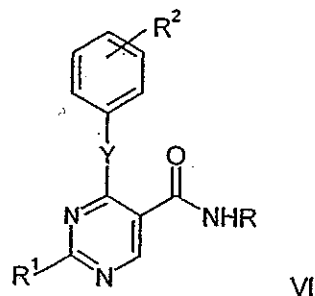
to give a compound of formula



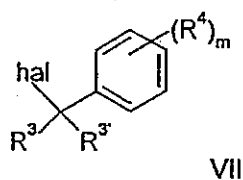
- 4c -

wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

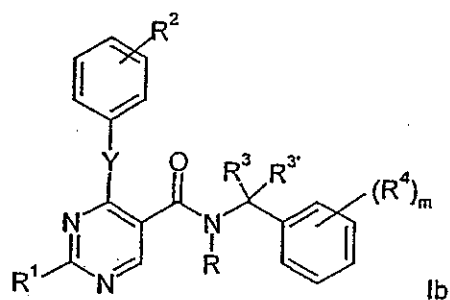
c) reacting a compound of formula



with a compound of formula

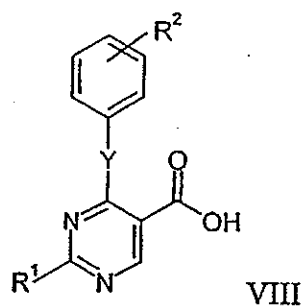


to a compound of formula



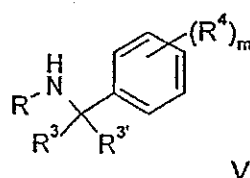
wherein hal is Cl, Br or I, and Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

d) reacting a compound of formula

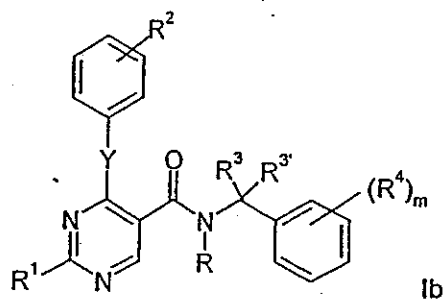


with a compound of formula

- 4d -

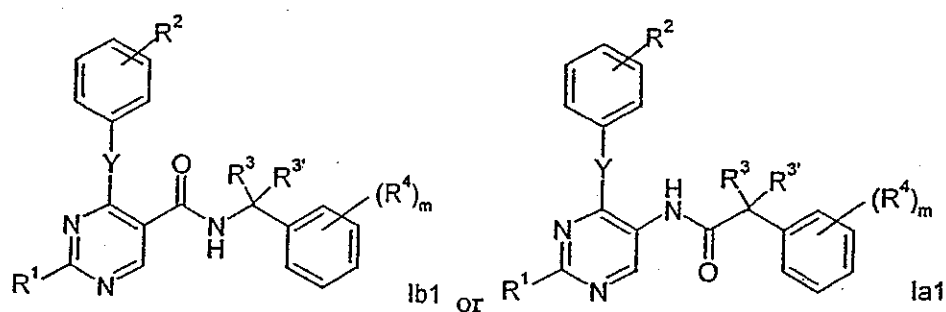


to a compound of formula

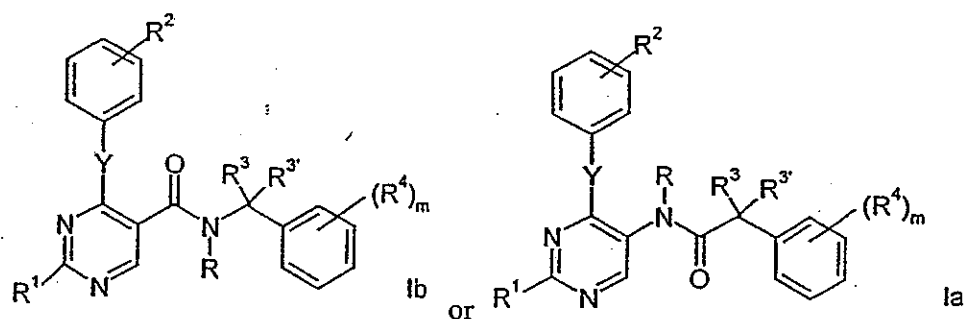


wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

e) alkylating a compound of formula



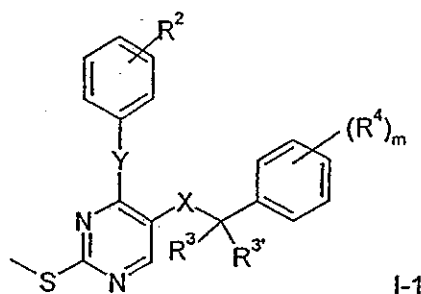
to a compound of formula



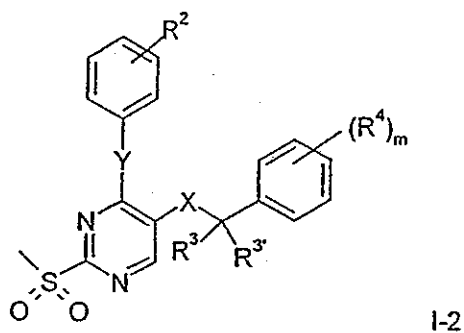
wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

f) transforming a compound of formula

- 4e -

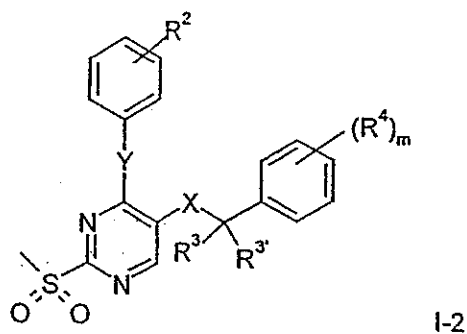


to a compound of formula

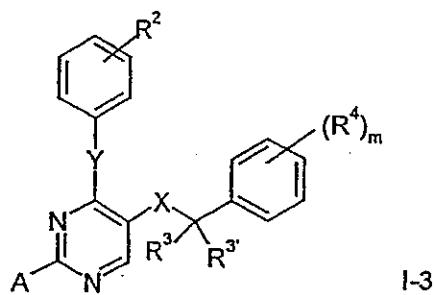


wherein X, Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> and m have the significances given above, or

g) reacting a compound of formula

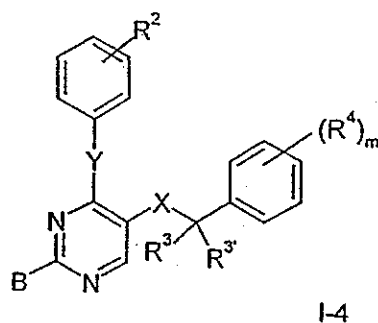


with a corresponding cyclic or non cyclic amine to a compound of formula

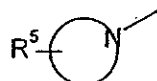


or with a corresponding alcohol to a compound of formula

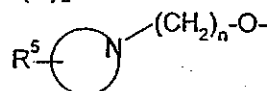
- 4 f -



wherein Y, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> and m have the significances given above, A is -N(R)-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -N(R)<sub>2</sub> or a cyclic tertiary amine of the formula



and B is lower alkoxy, -O-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub> or



and R<sup>5</sup> is described as above, or

h) modifying one or more substituents R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> or R within the definitions given above, and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

In a fifth aspect, the present invention provides a compound according to the first aspect, whenever prepared by a process according to the fourth aspect or by an equivalent method.

In a sixth aspect, the present invention provides the use of a compound in the first aspect for the treatment of diseases.

In a seventh aspect, the present invention provides the use of a compound in the first aspect for the manufacture of medicaments containing one or more compounds of formula I for the treatment of diseases related to NK-1 receptor antagonists.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl 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 lower alkyl groups are groups with 1 - 4 carbon atoms.

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

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 "cyclic tertiary amine" denotes a five or six membered heterocycle, wherein one N atom is always connected to the pyrimidine ring and which may further contain N, O or S atoms, for example pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiomorpholin-1,1-dioxo or thiomorpholin-1-oxo.

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.

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.

Preferred are compounds of formula I, in which X is  $-\text{C}(\text{O})\text{N}(\text{CH}_3)-$  and Y is  $-\text{O}-$ . Exemplary preferred compounds of this group are those, wherein  $\text{R}^1$  is a cyclic tertiary amine, for example the following compounds:

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

2-piperazin-1-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide or

- 5 4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

Further preferred compounds of the above mentioned group are those, wherein  $R^1$  is  $-O-(CH_2)_n$ -cyclic tertiary amine or the group  $-O-(CH_2)-NR_2$ . Such compounds are

- 2-(2-morpholin-4-yl-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide or  
 10 2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

Further preferred are compounds of formula I, in which X is  $-N(CH_3)C(O)-$  and Y is  $-O-$ . Exemplary preferred compounds of this group are those, wherein  $R^1$  is

- 15  $-S$ -lower alkyl, for example the following compounds:

2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide or

- 20 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide.

Further preferred compounds of the above group are those, wherein  $R^1$  is a cyclic tertiary amine, for example the following compounds:

2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-morpholin-4-yl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide,

- 25 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidin-5-yl]-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-piperazin-1-yl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide,

- 30 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-N-methyl-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-piperazin-1-yl-pyrimidin-5-yl]-N-methyl-isobutyramide,

- 35 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-morpholin-4-yl-pyrimidin-5-yl]-N-methyl-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-N-methyl-isobutyramide or

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-piperazin-1-yl-pyrimidin-5-yl]-N-methyl-isobutyramide.

Preferred compounds of this group are further those, wherein  $R^1$  is  $-N(R)(CH_2)_nNR_2$ , for example the following compounds:

- 5 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethylamino)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide or  
2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethylamino)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide.

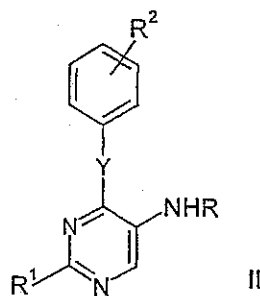
- Further preferred compounds of this group are those, wherein  $R^1$  is  
10  $-O(CH_2)_n$ -cyclic tertiary amine or the group  $-O(CH_2)_nNR_2$ , for example the following compounds:

- 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[2-(2-morpholin-4-yl-ethoxy)-4-o-tolyloxy-pyrimidin-5-yl]-isobutyramide,  
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-(2-morpholin-4-yl-ethoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide,  
15 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide,  
2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide,  
20 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide,  
2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide,  
2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(2-chloro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide or  
25 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-(2-chloro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide.

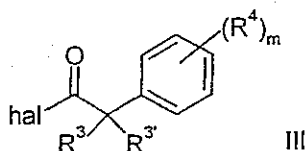
- The present compounds of formula I and their pharmaceutically acceptable salts can  
30 be prepared by methods known in the art, for example, by processes described below, which process comprises

- a) reacting a compound of formula

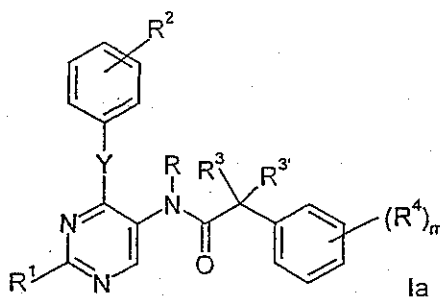
- 7 -



with a compound of formula



to a compound of formula

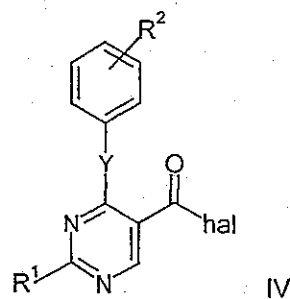


5

wherein Y, R¹, R², R³, R⁴, R and m have the significances given above,

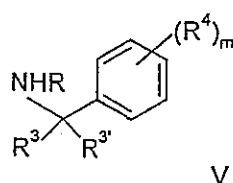
or

b) reacting a compound of formula

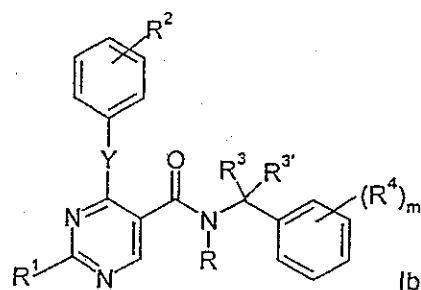


10 with a compound of formula

- 8 -

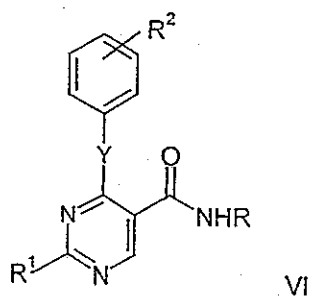


to give a compound of formula

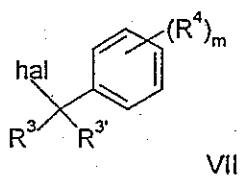


wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

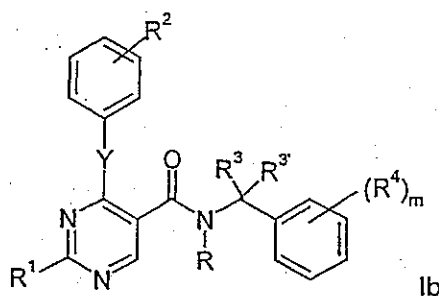
5 c) reacting a compound of formula



with a compound of formula

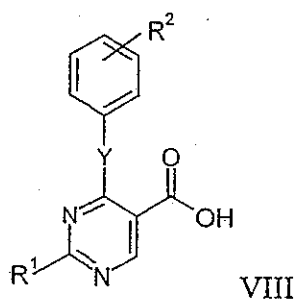


to a compound of formula

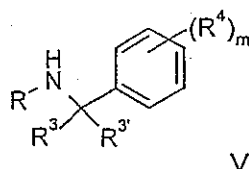


wherein hal is Cl, Br or I, and Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

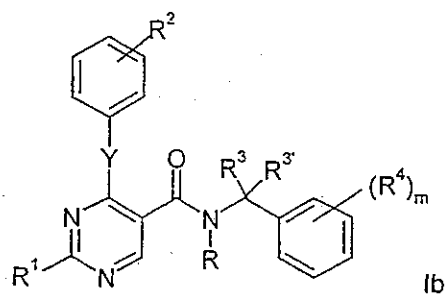
d) reacting a compound of formula



5 with a compound of formula

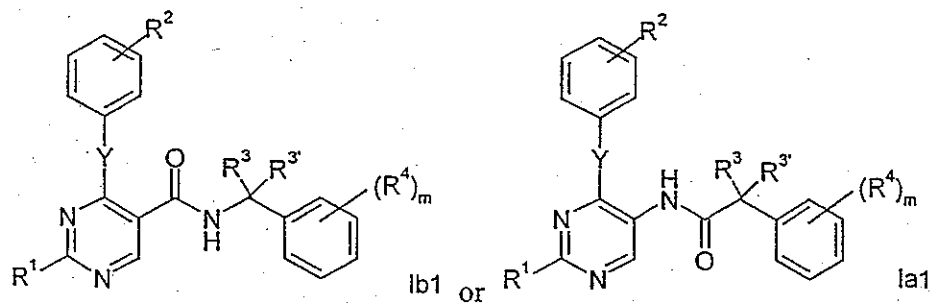


to a compound of formula

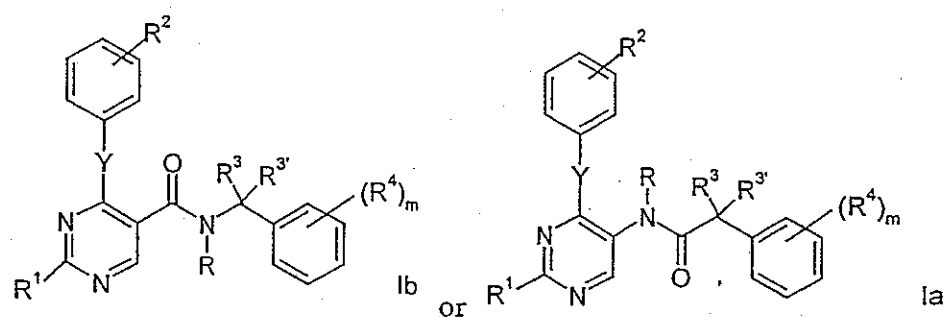


wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

10 e) alkylating a compound of formula

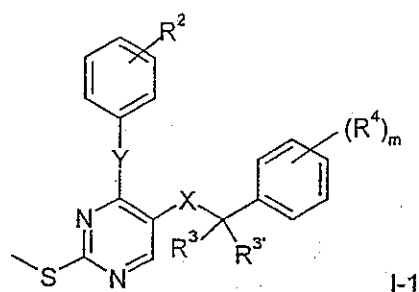


to a compound of formula

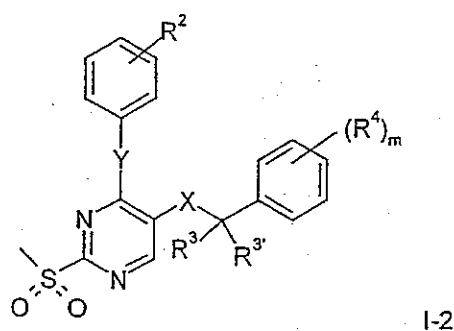


wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

f) transforming a compound of formula

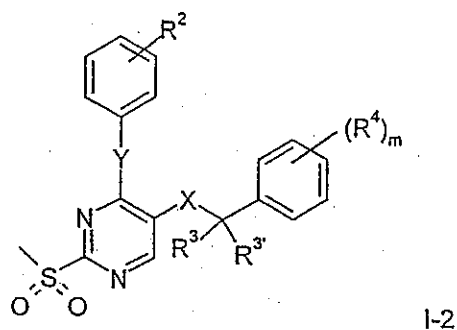


5 to a compound of formula

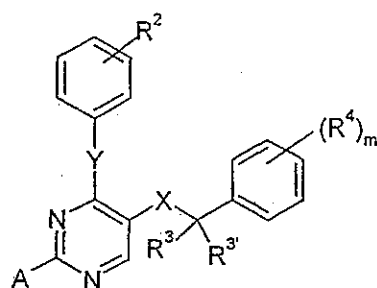


wherein X, Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> and m have the significances given above, or

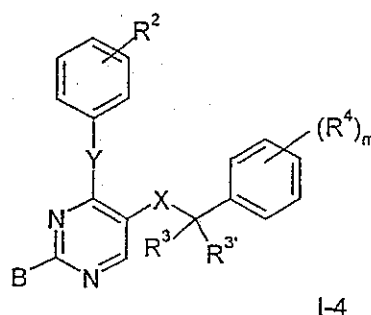
g) reacting a compound of formula



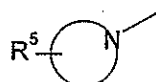
10 with a corresponding cyclic or non cyclic amine to a compound of formula



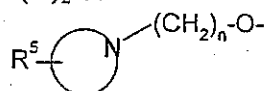
or with a corresponding alcohol to a compound of formula



wherein Y, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> and m have the significances given above, A is  
 5 -N(R)-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -N(R)<sub>2</sub> or a cyclic tertiary amine of the formula



and B is lower alkoxy, -O-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub> or



and R<sup>5</sup> is described as above, or

- 10 h) modifying one or more substituents R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> or R within the definitions given above, and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

In accordance with process variant a) DIPEA (N-ethyldiisopropyl-amine) is added to  
 15 a mixture of a compound of formula II and of a compound of formula III in dichloromethane and the mixture is stirred at temperatures between 25-40°C. The desired compound of formula Ia is isolated after purification in good yields.

Process variant b) describes the reaction of a compound of formula IV with a compound of formula V to a compound of formula Ib. The reaction is carried out in

conventional manner, for example in a solvent like toluene in the presence of triethylamine. The mixture is refluxed for about 1 hour.

In accordance with process variant c) a compound of formula Ib is prepared. This reaction is carried out with DIPEA (N-ethyl-diisopropyl-amine) which is added to a  
5 mixture of a compound of formula VI and of a compound of formula VII in dichloromethane.

A further method for the preparation of a compound of formula Ib is described in process variant d). A compound of formula VIII is treated with a compound of formula V in the presence of EDCI (1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide and  
10 HOBT (1-hydroxybenzotriazole hydrate) and triethylamine in conventional manner.

Compounds of formulas Ia or Ib may be prepared by alkylating the -NH-linking group with a corresponding lower alkyl iodine in the presence of NaH in DMF in accordance with process variant e) in conventional manner.

In accordance with process variant f) a compound of formula I-1 is treated with m-  
15 CPBA in dichloromethane to give a compound of formula I-2. Furthermore, this compound may then be treated with a corresponding cyclic amine, such as morpholine, piperazine or methyl-piperazine to a corresponding compound of formula I-3 or with a corresponding alcohol, such as 2-dimethylaminoethanol or N-(2-hydroxyethyl)morpholine, to a corresponding compound of formula I-4 in accordance  
20 with process variant g).

The salt formation is effected at room temperature in accordance with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates,  
25 methan-sulphonates, p-toluenesulphonates and the like are examples of such salts.

The following schemes 1-4 describe the processes for preparation of compounds of formula I in more detail. The starting materials are known compounds or may be prepared according to methods known in the art.

In the schemes the following abbreviations have been used:

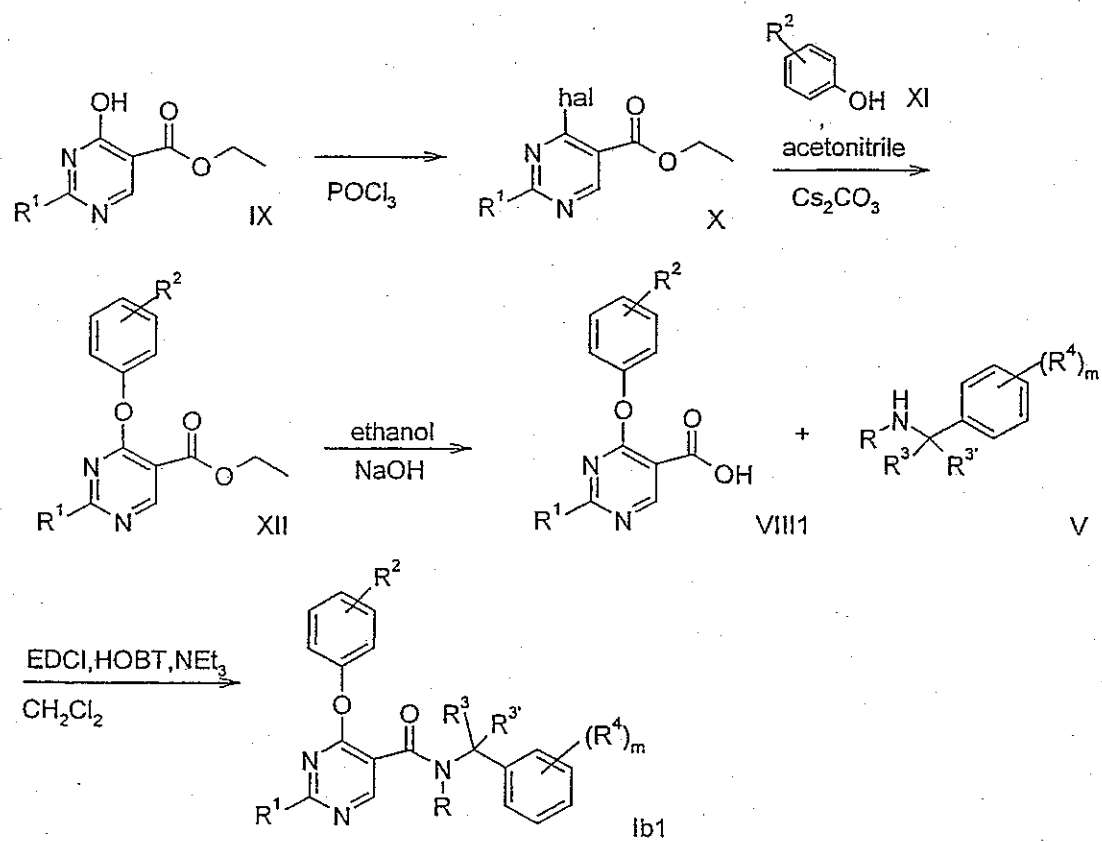
|    |        |                                                |
|----|--------|------------------------------------------------|
| 30 | DIPEA  | N-ethyl-diisopropyl-amine                      |
|    | EDCI   | 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide |
|    | HOBT   | 1-hydroxybenzotriazole hydrate                 |
|    | DMF    | dimethylformamid                               |
|    | m-CPBA | m-chloroperbenzoic acid                        |

- 13 -

DPPA

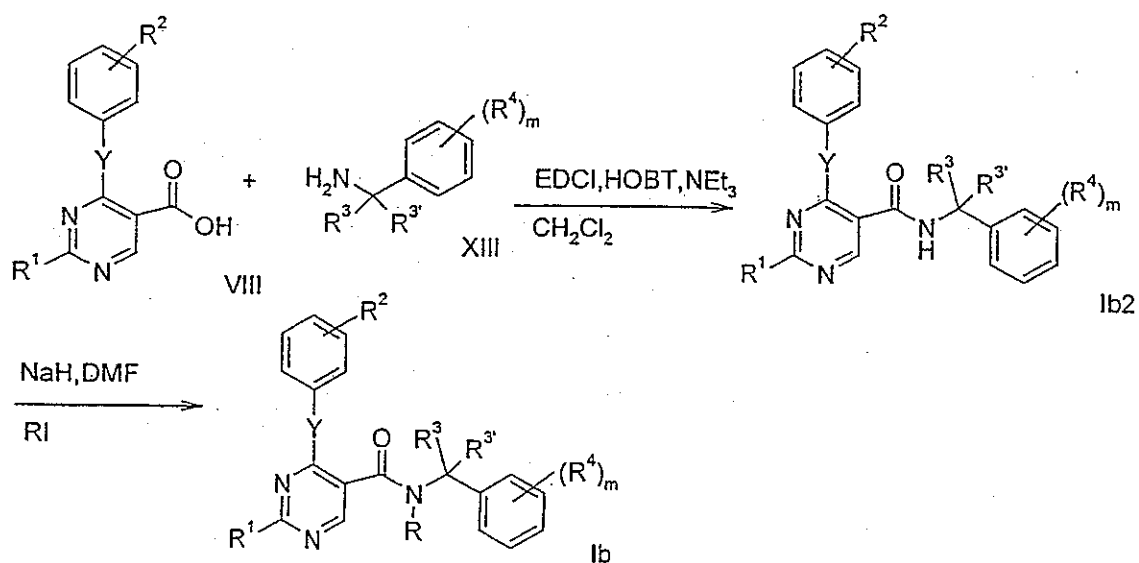
diphenylphosphoryl azide

Scheme 1



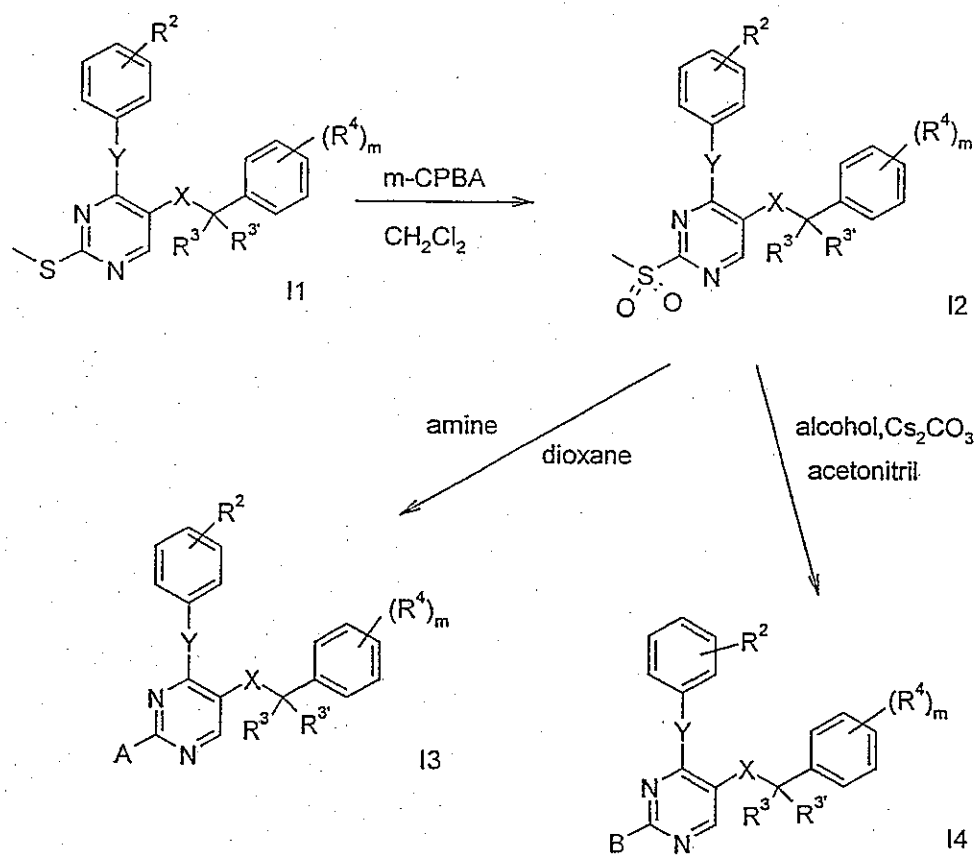
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup> and R<sup>4</sup> have the significances given above and R is lower alkyl.

Scheme 2



$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^3', \text{R}^4$  and Y have the significances given above and R is lower alkyl.

Scheme 3

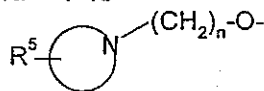


- 15 -

$R^2, R^3, R^{3'}, R^4, X, Y$  and  $m$  have the significances given above,  $A$  is  $-N(R)-(CH_2)_n-N(R)_2$ ,  $-N(R)_2$  or a cyclic tertiary amine of the formula



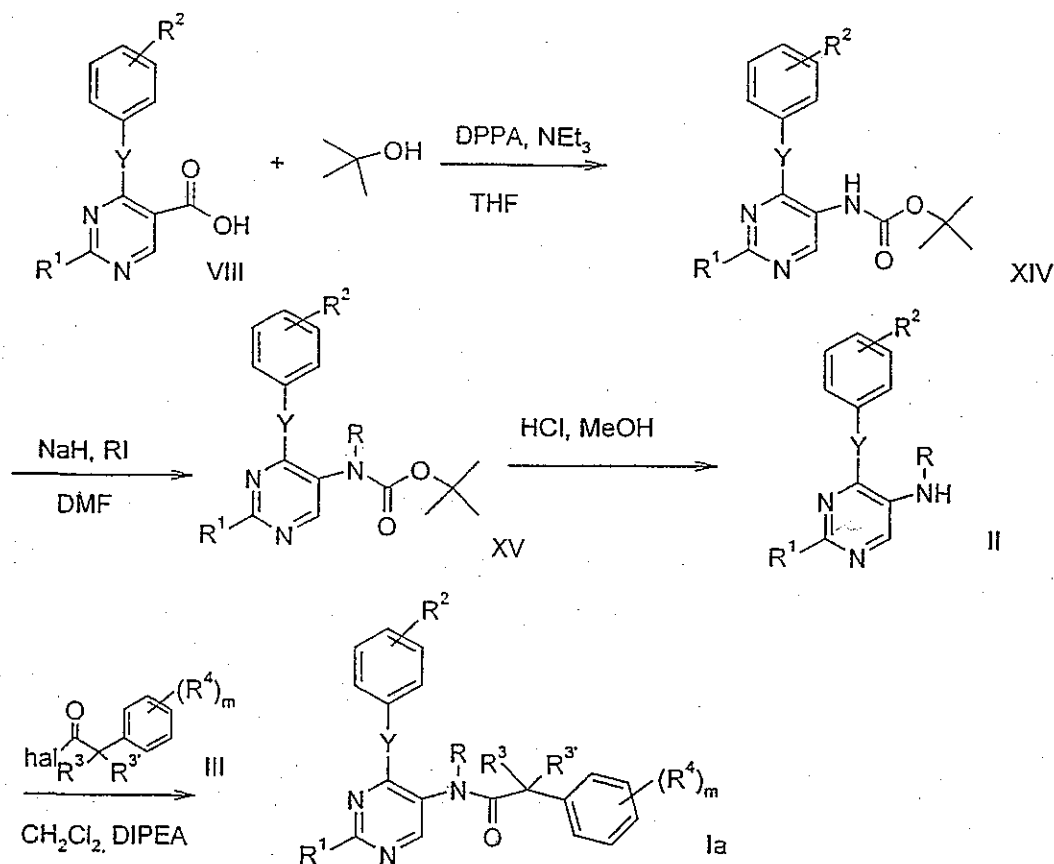
and  $B$  is lower alkoxy,  $-O-(CH_2)_n-N(R)_2$  or



5

and  $R^5$  is described as above.

Scheme 4



$R, R^1, R^2, R^3, R^{3'}, R^4, Y$  and  $m$  have the significances given above.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor.

The compounds were investigated in accordance with the tests given hereinafter.

The affinity of test compounds for the NK<sub>1</sub> receptor was evaluated at human NK<sub>1</sub> receptors in CHO cells infected with the human NK<sub>1</sub> receptor (using the Semliki virus expression system) and radiolabelled with [<sup>3</sup>H]substance P (final concentration 0.6 nM). Binding assays were performed in HEPES buffer (50 mM, pH 7.4) containing BSA (0.04 %) leupeptin (8 µg / ml), MnCl<sub>2</sub> (3mM) and phosphoramidon (2 µM). Binding assays consisted of 250 µl of membrane suspension (1.25x10<sup>5</sup> cells / assay tube), 0.125 µl of buffer of displacing agent and 125 µl of [<sup>3</sup>H]substance P. Displacement curves were determined with at least seven concentrations of the compound. The assay tubes were incubated for 60 min at room temperature after which time the tube contents were rapidly filtered under vacuum through GF/C filters presoaked for 60 min with PEI (0.3%) with 2 x 2 ml washes of HEPES buffer (50 mM, pH 7.4). The radioactivity retained on the filters was measured by scintillation counting. All assays were performed in triplicate in at least 2 separate experiments.

The affinity to the NK-1 receptor, given as pK<sub>i</sub>, is in the scope of 6.00 - 9.38 for the described compounds.

Examples of the pK<sub>i</sub> data for such compounds are described in the table below:

| Example No. | pK <sub>i</sub> |
|-------------|-----------------|
| 1           | 7.38            |
| 4           | 8.54            |
| 7           | 8.33            |
| 11          | 6.77            |
| 15          | 7.55            |
| 19          | 6.71            |
| 23          | 7.01            |
| 29          | 6.50            |
| 39          | 7.79            |
| 44          | 7.70            |
| 49          | 9.04            |

|    |      |
|----|------|
| 52 | 9.10 |
| 63 | 8.02 |
| 73 | 7.49 |

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragées and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily

dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

The following Examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

5

### Example 1

2-Methylsulfanyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

#### a) 2-Methylsulfanyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester

To a solution of 5.40 g (23.31 mmol) 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester in 150 ml acetonitrile 3.26 g (30.17 mmol) o-cresol and 30.25 g (92.83 mmol) Cs<sub>2</sub>CO<sub>3</sub> were added and the reaction mixture was stirred for 14 h at RT. The suspension was poured into ice-water and extracted two times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to give 7.0 g (99 %) 2-methylsulfanyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester, which was directly used for the next step

15

#### b) 2-Methansulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid

To a solution of 7.0 g (23.0 mmol) 2-methylsulfanyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester in 50 ml ethanol a solution of 1.37 g (34.50 mmol) sodiumhydroxide in 30 ml water was added and the resulting mixture was stirred 1 h at RT. The pH of the solution was adjusted to 1 with 25% HCl. The mixture was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The resulting solid was triturated twice with 10 ml diisopropylether, filtered off and dried to give 3.00 g (47 %) 2-methylsulfanyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid as a colorless solid, MS (ISN): 257.1 (M-H)<sup>+</sup>.

20

#### c) 2-Methylsulfanyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 1.0 g (3.62 mmol) 2-methylsulfanyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid in 60 ml CH<sub>2</sub>Cl<sub>2</sub> 1.0 ml (7.24 mmol) triethylamine, 0.554 g (3.62 mmol) 1-hydroxy-benzotriazole and 0.69 g (3.62 mmol) N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride 1.11 g (4.34 mmol) (3,5-bis-trifluoromethyl-benzyl)-methyl-amin were added. The reaction mixture was stirred for 16 hrs. The reaction mixture was diluted with 20 ml CH<sub>2</sub>Cl<sub>2</sub>, washed with 50 ml 0.5N HCl and 50 ml H<sub>2</sub>O. The aqueous layers were backextracted with 50 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 40:1) to give 1.80 g (96 %) 2-methylsulfanyl-4-o-tolyloxy-pyrimidine-5-

35

carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (EI): 515 ( $M^+$ ).

#### Example 2

2-Methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 1.70 g (3.30 mmol) 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 70 ml  $CH_2Cl_2$  2.03 g (8.24 mmol) 3-chloroperbenzoic acid (70 %) was added at 5 ° and the reaction mixture stirred for 2 hrs. at RT. After addition of 150 ml sat.  $NaHCO_3$ -solution, the layers were separated, the organic phase washed with sat.  $NaHCO_3$ -solution, dried ( $Na_2SO_4$ ), filtered and evaporated. The residue was purified by chromatography ( $SiO_2$ ,  $CH_2Cl_2$ /ethyl acetate 9:1) to give 1.50 g (83 %) 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 548.1 ( $M+H$ )<sup>+</sup>.

15

#### Example 3

2-Morpholin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.2 g (0.37 mmol) 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 10 ml dioxane 0.08 ml (0.91 mmol) morpholine was added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml  $CH_2Cl_2$  and 50 ml  $H_2O$ . The aqueous layer was extracted with 50 ml  $CH_2Cl_2$ , the combined organic layers dried ( $MgSO_4$ ), filtered and evaporated. The residue was purified by chromatography ( $SiO_2$ ,  $CH_2Cl_2$ /MeOH 40:1) to give 0.18 g (88 %) 2-morpholin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless oil, MS (ISP): 555.2 ( $M+H$ )<sup>+</sup>.

25

#### Example 4

2-(4-Methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.25 g (0.46 mmol) 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 10 ml dioxane 0.12 ml (1.14 mmol) 1-methylpiperazine was added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml  $CH_2Cl_2$  and 50 ml  $H_2O$ . The aqueous layer was extracted with 50 ml  $CH_2Cl_2$ , the combined organic

35

layers dried ( $\text{MgSO}_4$ ), filtered and evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  140:10:1) to give 0.2 g (77 %) 2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 563.3 ( $\text{M}+\text{H}$ )<sup>+</sup>.

5

## Example 5

2-Piperazin-1-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.32 g (0.58 mmol) 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 10 ml dioxane 0.125 g (1.46 mmol) piperazine was added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml  $\text{CH}_2\text{Cl}_2$  and 50 ml  $\text{H}_2\text{O}$ . The aqueous layer was extracted with 50 ml  $\text{CH}_2\text{Cl}_2$ , the combined organic layers dried ( $\text{MgSO}_4$ ), filtered and evaporated. The residue was purified by chromatography (10  $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  110:10:1) to give 0.25 g (77 %) 2-piperazin-1-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 554.2 ( $\text{M}+\text{H}$ )<sup>+</sup>.

15

## Example 6

20 2-(2-Dimethylamino-ethylamino)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.25 g (0.46 mmol) 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 10 ml dioxane 0.125 ml (1.14 mmol) 2-dimethylaminoethylamine was added. The reaction mixture was stirred for 25 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml  $\text{CH}_2\text{Cl}_2$  and 50 ml  $\text{H}_2\text{O}$ . The aqueous layer was extracted with 50 ml  $\text{CH}_2\text{Cl}_2$ , the combined organic layers dried ( $\text{MgSO}_4$ ), filtered and evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  140:10:1) to give 0.15 g (59 %) 2-(2-dimethylamino-ethylamino)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 556.2 ( $\text{M}+\text{H}$ )<sup>+</sup>.

30

## Example 7

2-(2-Morpholin-4-yl-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

35 To a solution of 0.2 g (0.37 mmol) 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 10 ml acetonitrile 0.066

ml (0.55 mmol) N-(2-hydroxyethyl)morpholine and 0.595 g (1.83 mmol)  $\text{Cs}_2\text{CO}_3$  were added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml  $\text{CH}_2\text{Cl}_2$  and 50 ml  $\text{H}_2\text{O}$ . The aqueous layer was extracted with 50 ml  $\text{CH}_2\text{Cl}_2$ , the combined organic layers dried ( $\text{MgSO}_4$ ), filtered and  
5 evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  140:10:1) to give 0.12 g (54 %) 2-(2-morpholin-4-yl-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 599.1 ( $\text{M}+\text{H}$ )<sup>+</sup>.

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## Example 8

2-(2-Dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.25 g (0.46 mmol) 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 10 ml acetonitrile 0.069  
15 ml (0.68 mmol) 2-dimethylaminoethanol and 0.743 g (2.28 mmol)  $\text{Cs}_2\text{CO}_3$  were added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml  $\text{CH}_2\text{Cl}_2$  and 50 ml  $\text{H}_2\text{O}$ . The aqueous layer was extracted with 50 ml  $\text{CH}_2\text{Cl}_2$ , the combined organic layers dried ( $\text{MgSO}_4$ ), filtered and evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  140:10:1) to  
20 give 0.15 g (59 %) 2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a light yellow oil, MS (ISP): 557.3 ( $\text{M}+\text{H}$ )<sup>+</sup>.

## Example 9

25 2-Methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide

In an analogous manner to that described in Example 1c) there was obtained from 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid and (3,5-dimethoxy-benzyl)-methyl-amine 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-  
30 dimethoxy-benzyl)-methyl-amide as a colorless oil, MS (EI): 439.1 ( $\text{M}^+$ ).

## Example 10

2-Methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide

35 In an analogous manner to that described in Example 2 there was obtained from 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-

methyl-amide and 3-chloroperbenzoic acid 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide as a colorless foam, MS (ISP): 472.1 (M+H)<sup>+</sup>.

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## Example 11

2-(4-Methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide

In analogous manner to that described in Example 4 there was obtained from 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide and 1-methylpiperazine 2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide as a colorless foam, MS (ISP): 492.3 (M+H)<sup>+</sup>.

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## Example 12

2-(2-Dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide

In analogous manner to that described in Example 8 there was obtained from 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide and 2-dimethylaminoethanol 2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethoxy-benzyl)-methyl-amide as a colorless oil, MS (ISP): 481.4 (M+H)<sup>+</sup>.

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## Example 13

2-Methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide

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In an analogous manner to that described in Example 1c there was obtained from 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid and (3,5-dimethyl-benzyl)-methyl-amine 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide as a colorless oil, MS (ISP): 408.3 (M+H)<sup>+</sup>.

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## Example 14

2-Methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 2 there was obtained from 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide and 3-chloroperbenzoic acid 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-

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carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 440.4 (M+H)<sup>+</sup>.

#### Example 15

2-(4-Methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 4 there was obtained from 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide and 1-methylpiperazine 2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide as a white foam, MS (ISP): 460.5 (M+H)<sup>+</sup>.

#### Example 16

2-(2-Dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 8 there was obtained from 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide and 2-dimethylaminoethanol 2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dimethyl-benzyl)-methyl-amide as a colorless oil, MS (ISP): 449.5 (M+H)<sup>+</sup>.

#### Example 17

2-Methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide

In an analogous manner to that described in Example 1c) there was obtained from 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid and 3,5-dichlorobenzylamine 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide as a light yellow oil, MS (EI): 433 (M<sup>+</sup>).

#### Example 18

2-Methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide

In an analogous manner to that described in Example 2 there was obtained from 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide and 3-chloroperbenzoic acid 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide as a colorless solid, MS (ISP): 466.2 (M+H)<sup>+</sup>.

## Example 19

2-(4-Methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide

In an analogous manner to that described in Example 4 there was obtained from 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide and 1-methylpiperazine 2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide as a colorless solid, MS (ISP): 486.3 (M+H)<sup>+</sup>.

## Example 20

2-Methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dichloro-benzyl)-methyl-amide

To a solution of 0.6 g (1.8 mmol) 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid 3,5-dichloro-benzylamide in 20 ml N,N-dimethylformamide 0.096 g (2.4 mmol) sodiumhydride (60 % dispersion in mineraloil) was added and the mixture stirred for 1 h. After the addition of 0.18 ml (2.9 mmol) methyl iodide at 0°, the reaction mixture was stirred for 3 hrs. at RT. The reaction mixture was distributed between 50 ml H<sub>2</sub>O, 50 ml brine and 50 ml CH<sub>2</sub>Cl<sub>2</sub>. The phases were separated, and the aqueous layer extracted twice with 50 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate 19:1) to give 0.5 g (61%) 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dichloro-benzyl)-methyl-amide as a light yellow oil, MS (EI): 447.1 (M<sup>+</sup>).

## Example 21

2-Methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dichloro-benzyl)-methyl-amide

In an analogous manner to that described in Example 2 there was obtained from 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dichloro-benzyl)-methyl-amide and 3-chloroperbenzoic acid 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dichloro-benzyl)-methyl-amide as a colorless foam, MS (ISP): 480.2 (M+H)<sup>+</sup>.

## Example 22

2-(4-Methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dichloro-benzyl)-methyl-amide

In an analogous manner to that described in Example 4 there was obtained from 2-methanesulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dichloro-benzyl)-methyl-

amide and 1-methylpiperazine 2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-dichloro-benzyl)-methyl-amide as a colorless foam, MS (ISP): 500.2 (M+H)<sup>+</sup>.

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## Example 23

2-Methylsulfanyl-4-phenoxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 1a) there was obtained from 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester and phenol 2-methylsulfanyl-4-phenoxy-pyrimidine-5-carboxylic acid ethyl ester, which was saponified as described in Example 1b) and reacted with (3,5-bis-trifluoromethyl-benzyl)-methylamine to give as described in Example 1c) 2-methylsulfanyl-4-phenoxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (TSP): 501 (M<sup>+</sup>).

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## Example 24

2-Methanesulfonyl-4-phenoxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 2 there was obtained from 2-methylsulfanyl-4-phenoxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 3-chloroperbenzoic acid 2-methanesulfonyl-4-phenoxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (TSP): 533 (M<sup>+</sup>).

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## Example 25

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

In an analogous manner to that described in Example 4 there was obtained from 2-methanesulfonyl-4-phenoxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 1-methylpiperazine 2-(4-methyl-piperazin-1-yl)-4-phenoxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 554.2 (M+H)<sup>+</sup>.

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## Example 26

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

In an analogous manner to that described in Example 1a) there was obtained from 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester and 2-chloro phenol 4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester which was saponified as described in Example 1b) and reacted with (3,5-bis-trifluoromethyl-benzyl)-methyl-amine to give as described in Example 1c) 4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 536.2 (M+H)<sup>+</sup>.

#### Example 27

10 4-(2-Chloro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 2 there was obtained from 4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 3-chloroperbenzoic acid 4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 560.0 (M+H)<sup>+</sup>.

#### Example 28

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

In an analogous manner to that described in Example 4 there was obtained from 4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 1-methylpiperazine 4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 588.2 (M+H)<sup>+</sup>.

#### Example 29

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

30 In an analogous manner to that described in Example 1a) there was obtained from 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester and 2-methoxyphenol 4-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester which was saponified as described in Example 1b) and reacted with (3,5-bis-trifluoromethyl-benzyl)-methyl-amine to give as described in Example 1c) 4-(2-methoxy-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 532.1 (M+H)<sup>+</sup>.

## Example 30

4-(2-Methoxy-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

- 5 In an analogous manner to that described in Example 2 there was obtained from 4-(2-methoxy-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 3-chloroperbenzoic acid 4-(2-methoxy-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 564.2 (M+H)<sup>+</sup>.

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## Example 31

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

- 15 In an analogous manner to that described in Example 4 there was obtained from 4-(2-methoxy-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 1-methylpiperazine 4-(2-methoxy-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 584.1 (M+H)<sup>+</sup>.

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## Example 32

2-(2-Dimethylamino-ethylamino)-4-(2-methoxy-phenoxy)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

- 25 In an analogous manner to that described in Example 6 there was obtained from 4-(2-methoxy-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 2-dimethylaminoethylamine 2-(2-dimethylamino-ethylamino)-4-(2-methoxy-phenoxy)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 572.1 (M+H)<sup>+</sup>.

## Example 33

- 30 4-(2-Fluor-phenoxy)-2-methansulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

- In an analogous manner to that described in Example 1a) there was obtained from 4-chloro-2-methylsulfonyl-pyrimidine-5-carboxylic acid ethyl ester and 4-fluoro-phenol 4-(4-fluoro-phenoxy)-2-methylsulfonyl-pyrimidine-5-carboxylic acid ethyl ester which was  
35 saponified as described in Example 1b) and reacted with (3,5-bis-trifluormethyl-benzyl)-methyl-amine to give as described in Example 1c) 4-(4-fluoro-phenoxy)-2-

methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 520.1 ( $M+H^+$ ).

#### Example 34

5 4-(4-Fluoro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 2 there was obtained from 4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 3-chloroperbenzoic acid 4-(4-fluoro-phenoxy)-2-

10 methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 552.0 ( $M+H^+$ ).

#### Example 35

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

In an analogous manner to that described in Example 4 there was obtained from 4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 1-methylpiperazine 4-(4-fluoro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-

20 methyl-amide as a white foam, MS (EI): 571 ( $M^+$ ).

#### Example 36

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

25 In an analogous manner to that described in Example 5 there was obtained from 4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and piperazine 4-(4-fluoro-phenoxy)-2-piperazin-1-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 558.2 ( $M+H^+$ ).

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#### Example 37

2-(2-Dimethylamino-ethylamino)-4-(4-fluoro-phenoxy)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 6 there was obtained from 4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and dimethylaminoethylamine 2-(2-

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dimethylamino-ethylamino)-4-(4-fluoro-phenoxy)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 560.2 (M+H)<sup>+</sup>.

#### Example 38

- 5 2-(2-Dimethylamino-ethoxy)-4-(4-fluoro-phenoxy)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 8 there was obtained from 4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide and 2-dimethylaminoethanol 2-(2-dimethylamino-ethoxy)-4-(4-fluoro-phenoxy)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 561.3 (M+H)<sup>+</sup>.

#### Example 39

- 15 2-Pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

##### a) 4-Chloro-2-pyridin-4-yl-pyrimidine-5-carboxylic acid ethyl ester

A suspension of 4.78 g (19.5 mmol) 4-hydroxy-2-pyridin-4-yl-pyrimidine-5-carboxylic acid ethyl ester in 20 ml POCl<sub>3</sub> was heated at reflux for 1 h. The solution was cooled to RT and poured into 100 ml ice-water. The pH of the solution was adjusted to 8 with  
20 sat. NaHCO<sub>3</sub>-solution. The water-phase was extracted three times with 80 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 40:1) to give 4.34 g (84 %) 4-chloro-2-pyridin-4-yl-pyrimidine-5-carboxylic acid ethyl ester as a yellow solid, MS (EI): 263.1 (M<sup>+</sup>).

- 25 b) 2-Pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester

A suspension of 0.6 g (2.28 mmol) 4-chloro-2-pyridin-4-yl-pyrimidine-5-carboxylic acid ethyl ester, 0.27 g (2.50 mmol) o-cresol and 2.97 g (9.10 mmol) Cs<sub>2</sub>CO<sub>3</sub> in 15 ml acetonitrile was stirred for 17 h at RT. The suspension was poured into 150 ml H<sub>2</sub>O and extracted three times with 90 ml ethyl acetate. The combined organic phases were dried  
30 (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, ethyl acetate/MeOH 100:1) to give 0.74 g (97 %) 2-pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester as a yellow solid, MS (EI): 335.1 (M<sup>+</sup>).

##### c) 2-Pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid

To a solution of 0.70 g (2.08 mmol) 2-pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester in 20 ml ethanol a solution of 0.12 g (3.12 mmol) sodiumhydroxide in 10  
35 ml water was added and the resulting mixture was stirred 2 h at RT. The pH of the solution

was adjusted to 3 with 25% HCl. The mixture was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The resulting solid was triturated twice with 10 ml ethanol, filtered off and dried to give 0.60 g (94 %) 2-pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid as a colorless solid, MS (EI): 307.1 (M<sup>+</sup>).

d) 2-Pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.35 g (1.14 mmol) 2-pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid in 20 ml CH<sub>2</sub>Cl<sub>2</sub> 0.32 ml (2.28 mmol) triethylamine, 0.15 g (1.14 mmol) 1-hydroxy-benzotriazole and 0.22 g (1.14 mmol) N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride 0.33 g (1.37 mmol) (3,5-bis-trifluoromethyl-benzyl)-methyl-amine were added. The reaction mixture was stirred for 16 hrs. The reaction mixture was diluted with 20 ml CH<sub>2</sub>Cl<sub>2</sub> and washed 50 ml H<sub>2</sub>O. The organic layer was dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 19:1) to give 0.33 g (53 %) 2-pyridin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 547.1 (M+H)<sup>+</sup>.

Example 40

4-(4-Fluoro-phenoxy)-2-pyridin-4-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 39 b) there was obtained from 4-chloro-2-pyridin-4-yl-pyrimidine-5-carboxylic acid ethyl ester and 4-fluorophenol 4-(4-fluoro-phenoxy)-2-pyridin-4-yl-pyrimidine-5-carboxylic acid ethyl ester, which was saponified as described in Example 39 c) and reacted with (3,5-bis-trifluoromethyl-benzyl)-methyl-amine to give as described in Example 39 d) 4-(4-fluoro-phenoxy)-2-pyridin-4-yl-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 551.0 (M+H)<sup>+</sup>.

Example 41

2-Methyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 39 b) there was obtained from 4-chloro-2-methyl-pyrimidine-5-carboxylic acid ethyl ester and o-cresol 2-methyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester, which was saponified as described in Example 39 c) and reacted with (3,5-bis-trifluoromethyl-benzyl)-methyl-amine to give as

described in Example 39 d) 2-methyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (EI): 483 ( $M^+$ ).

#### Example 42

- 5 2-Phenyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

In an analogous manner to that described in Example 39 b) there was obtained from 4-chloro-2-phenyl-pyrimidine-5-carboxylic acid ethyl ester and o-cresol 2-phenyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester, which was saponified as described in

- 10 Example 39 c) and reacted with (3,5-bis-trifluoromethyl-benzyl)-methyl-amine to give as described in Example 39 d) 2-phenyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless foam, MS (ISP): 546.1 ( $M+H$ )<sup>+</sup>.

#### Example 43

- 15 4-o-Tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

a) 4-Hydroxy-[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester

To a fresh prepared solution of sodiummethanolate in ethanol (prepared from 0.44 g (18.92 mmol) Na in 20 ml Ethanol) 1.50 g (9.46 mmol) pyrimidine-2-carboxamide

- 20 hydrochloride was added. After 10 min. 1.89 ml (9.46 mmol) diethyl ethoxymethylenemalonate was added at 0 ° and the resulting suspension was stirred for 12 hrs. After addition of 20 ml H<sub>2</sub>O, the pH was adjusted to 5 and the aqueous phase was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was triturated with 5 ml diisopropylether, filtered off
- 25 and dried to give 1.62 g (70 %) 4-hydroxy-[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester as a light yellow powder, MS (EI): 246.1 ( $M^+$ ).

b) 4-Chloro-[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester

A suspension of 1.62 g (6.5 mmol) 4-hydroxy-[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester in 16 ml POCl<sub>3</sub> was heated at reflux for 1h. The solution was cooled to RT and poured

30 into 100 ml ice-water. The pH of the solution was adjusted to 8 with sat. NaHCO<sub>3</sub>-solution. The water phase was extracted three times with 80 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5) to give 1.43 g (82 %) 4-chloro-

[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester as a light brown solid, MS (EI): 264.1 ( $M^+$ ).

c) 4-o-Tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester

To a solution of 1.43 g (5.4 mmol) 4-chloro-[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester in 35 ml acetonitrile 0.5 g (7.0 mmol) o-cresol and 7.0 g (21.6 mmol)  $CS_2CO_3$  were added and the reaction mixture stirred for 14 hrs at RT. The suspension was poured into ice-water and extracted two times with  $CH_2Cl_2$ . The combined organic phases were dried ( $Na_2SO_4$ ), filtered and evaporated. The residue was purified by chromatography ( $SiO_2$ ,  $CH_2Cl_2/MeOH$  19:1) to give 0.96 g (53 %) 4-o-tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester as a light yellow solid, MS (ISP): 337.2 ( $M+H$ )<sup>+</sup>.

d) 4-o-Tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid

To a solution of 0.33 g (0.98 mmol) 4-o-tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid ethyl ester in 15 ml ethanol 3.68 ml 0.4 N NaOH was added and the resulting solution was stirred for 2 hrs at RT. The pH of the solution was adjusted to 4 with 1N HCl. The aqueous solution was extracted three times with  $CH_2Cl_2$ . The combined organic phases were dried ( $Na_2SO_4$ ), filtered and evaporated. The resulting solid was triturated twice with diethyl ether, filtered off and dried to give 0.26 g (85 %) 4-o-tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid as a light yellow solid, MS (ISN): 307.3 ( $M-H$ )<sup>-</sup>.

e) 4-o-Tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.25 g (0.83 mmol) 4-o-tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid in 15 ml  $CH_2Cl_2$ , 0.23 ml (1.6 mmol) triethylamine, 0.13 g (0.83 mmol) 1-hydroxy-benzotriazole and 0.16 g (0.83 mmol) N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride 0.25 g (1 mmol) (3,5-bis-trifluoromethyl-benzyl)methyl-amin were added. The reaction mixture was stirred for 16 hrs. The reaction mixture was diluted with 20 ml  $CH_2Cl_2$ , washed with 50 ml 0.5N HCl and 50 ml  $CH_2Cl_2$ . The combined organic layers were dried ( $MgSO_4$ ), filtered and evaporated. The residue was purified by chromatography ( $SiO_2$ ,  $CH_2Cl_2/MeOH$  19:1) to give 0.39 g (86 %) 4-o-tolyloxy-[2,2']bipyrimidinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a light yellow foam, MS (ISP): 548.1 ( $M+H$ )<sup>+</sup>.

## Example 44

2-Thiomorpholin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.79 g (1.44 mmol) 2-methansulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 40 ml dioxane 0.34 ml (3.6 mmol) thiomorpholine was added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml CH<sub>2</sub>Cl<sub>2</sub> and 50 ml H<sub>2</sub>O. The aqueous layer was extracted with 50 ml CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layers dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 40:1) to give 0.48 g (59 %) 2-thiomorpholin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 571.1 (M+H)<sup>+</sup>.

## Example 45

2-(1,1-Dioxo-1λ<sup>6</sup>-thiomorpholin-4-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 0.44 g (0.77 mmol) 2-thiomorpholin-4-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 25 ml CH<sub>2</sub>Cl<sub>2</sub> 0.48 g (1.93 mmol) 3-chloroperbenzoic acid (70 %) was added at 5 ° and the reaction mixture was stirred for 1 h at RT. After addition of 50 ml sat. NaHCO<sub>3</sub>-solution, the layers were separated, the organic phase washed with NaHCO<sub>3</sub>-solution, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate 4:1) to give 0.42 g (91 %) 2-(1,1-dioxo-1λ<sup>6</sup>-thiomorpholin-4-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a colorless solid, MS (ISP): 602.9 (M+H)<sup>+</sup>.

## Example 46

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methylsulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide

a) (2-Methylsulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester

To a solution of 1.90 g (6.88 mmol) 2-methylsulfonyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid, 0.95 ml triethylamine (6.88 mmol) and 1.29 ml (1.37 mmol) t-butanol in 25 ml THF, 1.47 ml (6.88 mmol) diphenylphosphoryl azide were added and the resulting solution heated at reflux for 12 hrs. After evaporation of the solvent, the residue was distributed between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The aqueous phase was extracted twice with 80 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, ethyl acetate 40:1) to give 1.70 g

(71 %) (2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester as a colorless solid, MS (ISP): 348.2 (M+H)<sup>+</sup>.

b) Methyl-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert-butyl ester

To a solution of 1.60 g (4.61 mmol) (2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester in 20 ml N,N-dimethylformamide 0.25 g (6.4 mmol) sodiumhydride (60% dispersion in mineraloil) was added and the reaction mixture stirred for 1 h. After the addition of 0.48 ml ( 7.83 mmol) methyl iodide at 0°, the reaction mixture was stirred for 3 hrs. The reaction mixture was poured into 100 ml ice-water and three times extracted with 80 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate 19:1) to give 1.60 g (98 %) methyl-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert-butyl ester as a colorless oil, MS (EI): 361 (M<sup>+</sup>)

c) Methyl-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-amine

To a solution of 1.60 g (4.43 mmol) methyl-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester in 20 ml CH<sub>2</sub>Cl<sub>2</sub> 2 ml trifluoroacetic acid was added and the reaction mixture stirred for 2 hrs. at 40°. The reaction mixture was poured into ice-water and the pH of the solution adjusted to 10 with 1N NaOH solution. The aqueous phase was extracted three times with 80 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to give 1.10 g (95 %) methyl-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-amine as a white solid, MS (EI): 261 (M<sup>+</sup>).

d) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide

To a solution of 1.10 g (4.21 mol) methyl-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-amine and 1.44 ml (8.42 mmol) N-ethyl-diisopropylamine in 30 ml CH<sub>2</sub>Cl<sub>2</sub> a solution of 1.87 g (5.89 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 5 ml CH<sub>2</sub>Cl<sub>2</sub> was added and the reaction mixture stirred for 12 hrs at RT. The reaction mixture was poured into 50 ml 0.5 N NaOH-solution. The phases were separated and the aqueous phase three times extracted with 80 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, hexane/ ethyl acetate 2:1) to give 2.10 g (92 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide as a white foam, MS (ISP): 544.2 (M+H)<sup>+</sup>.

Example 47

2-(3,5-Bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide

To a solution of 2.00 g (3.68 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide in 80 ml CH<sub>2</sub>Cl<sub>2</sub> 2.26 g (9.20 mmol) 3-chloroperbenzoic acid (70 %) was added at 5 ° and the reaction mixture stirred for 2 hrs. at RT. After addition of 150 ml sat. NaHCO<sub>3</sub>-solution, the layers were separated, the organic phase washed with sat. NaHCO<sub>3</sub>-solution, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate 19:1) to give 1.90 g (83 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide as a white foam, MS (EI): 575 (M<sup>+</sup>).

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## Example 48

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(2-morpholin-4-yl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide

To a solution of 0.2 g (0.35 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide in 10 ml dioxane 0.076 ml (0.87 mmol) morpholine was added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml CH<sub>2</sub>Cl<sub>2</sub> and 50 ml sat. NaHCO<sub>3</sub>-solution. The aqueous layer was extracted with 50 ml CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layers dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/methanol 50:1) to give 0.17 g (84 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-morpholin-4-yl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide as a white foam, MS (ISP): 583.2 (M+H)<sup>+</sup>.

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## Example 49

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidin-5-yl]-isobutyramide

To a solution of 0.22 g (0.38 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide in 10 ml dioxane 0.106 ml (0.96 mmol) 1-methylpiperazine was added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml CH<sub>2</sub>Cl<sub>2</sub> and 50 ml sat. NaHCO<sub>3</sub>-solution. The aqueous layer was extracted with 50 ml CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layers dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH 110:10:1) to give 0.11 g (48 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidin-5-yl]-isobutyramide as a white foam, MS (ISP): 596.2 (M+H)<sup>+</sup>.

30

## Example 50

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(2-piperazin-1-yl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide

To a solution of 0.30 g (0.52 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide in 10 ml dioxane  
5 0.112 g (1.3 mmol) piperazine was added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml CH<sub>2</sub>Cl<sub>2</sub> and 50 ml sat. NaHCO<sub>3</sub>-solution. The aqueous layer was extracted with 50 ml CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layers dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified  
10 by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH 140:10:1 ) to give 0.20 g (66 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-piperazin-1-yl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide as a white foam, MS (ISP): 582.2 (M+H)<sup>+</sup>.

## Example 51

15 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethylamino)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide

To a solution of 0.25 g (0.43 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide in 10 ml dioxane  
20 0.119 ml (1.09 mmol) 2-dimethylaminoethylamine was added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml CH<sub>2</sub>Cl<sub>2</sub> and 50 ml sat. NaHCO<sub>3</sub>-solution. The aqueous layer was extracted with 50 ml CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layers dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/methanol/NH<sub>4</sub>OH 140:10:1 ) to give 0.20 g  
(79 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethylamino)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide as a white foam, MS (ISP): 584.2  
25 (M+H)<sup>+</sup>.

## Example 52

30 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[2-(2-morpholin-4-yl-ethoxy)-4-o-tolyloxy-pyrimidin-5-yl]-isobutyramide

To a solution of 0.4 g (0.7 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide in 20 ml acetonitrile 0.126 ml (1.04 mmol) N-(2-hydroxyethyl)morpholine and 1.13 g (3.48 mmol) Cs<sub>2</sub>CO<sub>3</sub> were added. The reaction mixture was stirred for 16 hrs. After evaporation of the  
35 solvent, the residue was distributed between 50 ml CH<sub>2</sub>Cl<sub>2</sub> and 50 ml H<sub>2</sub>O. The aqueous layer was extracted with 50 ml CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layers dried (MgSO<sub>4</sub>),

filtered and evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  40:1) to give 0.30 g (69 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[2-(2-morpholin-4-yl-ethoxy)-4-o-tolyloxy-pyrimidin-5-yl]-isobutyramide as a colorless foam, MS (ISP): 627.2 (M+H)<sup>+</sup>.

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## Example 53

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide

To a solution of 0.25 g (0.43 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide in 10 ml acetonitrile 0.066 ml (0.65 mmol) 2-dimethylaminoethanol and 0.70 g (2.14 mmol)  $\text{Cs}_2\text{CO}_3$  were added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml  $\text{CH}_2\text{Cl}_2$  and 50 ml  $\text{H}_2\text{O}$ . The aqueous layer was extracted with 50 ml  $\text{CH}_2\text{Cl}_2$ , the combined organic layers dried ( $\text{MgSO}_4$ ),  
15 filtered and evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  110:10:1) to give 0.18 g (71 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 585.2 (M+H)<sup>+</sup>.

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## Example 54

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide

To a solution of 0.30 g (0.52 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-(2-methanesulfonyl-4-o-tolyloxy-pyrimidin-5-yl)-N-methyl-isobutyramide in 20 ml  
25 acetonitrile 0.061 ml (0.78 mmol) 2-dimethylaminopropanol and 0.85 g (2.61 mmol)  $\text{Cs}_2\text{CO}_3$  were added. The reaction mixture was stirred for 16 hrs. After evaporation of the solvent, the residue was distributed between 50 ml  $\text{CH}_2\text{Cl}_2$  and 50 ml  $\text{H}_2\text{O}$ . The aqueous layer was extracted with 50 ml  $\text{CH}_2\text{Cl}_2$ , the combined organic layers dried ( $\text{MgSO}_4$ ), filtered and evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  
30  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  140:10:1) to give 0.20 g (64 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-propoxy)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless oil, MS (ISP): 599.2 (M+H)<sup>+</sup>.

## Example 55

35 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methylsulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 46 a) there was obtained from 4-(4-fluoro-phenoxy)-2-methylsulfanyl-pyrimidine-5-carboxylic acid, diphenylphosphorylazide and t-butanol [4-(4-fluoro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-carbamic acid tert.-butyl ester, which was methylated with methyl iodide and then deprotected with trifluoroacetic acid according to Example 43 b) c). The resulting [4-(4-fluoro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-methyl-amine was treated with 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as described in Example 43 e) to give 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide as a white foam, MS (EI): 547 (M<sup>+</sup>).

#### Example 56

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 47 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 3-chloroperbenzoic acid 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide as a white foam, MS (ISP): 580.2 (M+H)<sup>+</sup>.

#### Example 57

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-morpholin-4-yl-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 48 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and morpholine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-morpholin-4-yl-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 587.2 (M+H)<sup>+</sup>.

#### Example 58

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 49 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 1-methylpiperazine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 600.1 (M+H)<sup>+</sup>.

## Example 59

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-piperazin-1-yl-pyrimidin-5-yl]-N-methyl-isobutyramide

- 5 In an analogous manner to that described in Example 50 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and piperazine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-piperazin-1-yl-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 586.2 (M+H)<sup>+</sup>.

10

## Example 60

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethylamino)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide

- 15 In an analogous manner to that described in Example 51 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 2-dimethylaminoethylamine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethylamino)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 588.3 (M+H)<sup>+</sup>.

20

## Example 61

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-(2-morpholin-4-yl-ethoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide

- 25 In an analogous manner to that described in Example 52 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and N-(2-hydroxyethyl)morpholine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-(2-morpholin-4-yl-ethoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 631.1 (M+H)<sup>+</sup>.

30

## Example 62

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide

- 35 In an analogous manner to that described in Example 53 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 2-dimethylaminoethanol 2-(3,5-bis-trifluoromethyl-

phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 589.2 (M+H)<sup>+</sup>.

#### Example 63

- 5 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 54 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 2-dimethylaminopropanol 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 603.1 (M+H)<sup>+</sup>.

#### Example 64

- 15 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 46 a) there was obtained from 4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidine-5-carboxylic acid, diphenylphosphorylazide and t-butanol [4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-carbamic acid tert.-butyl ester, which was methylated with methyl iodide and then deprotected with trifluoroacetic acid according to Example 43 b) c). The resulting [4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-methyl-amine was treated with 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as described in Example 43 e) to give 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide as a white foam, MS (ISP): 564.2 (M+H)<sup>+</sup>.

25

#### Example 65

- 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 47 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 3-chloroperbenzoic acid 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide as a white foam, MS (ISP): 596.1 (M+H)<sup>+</sup>.

35

## Example 66

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-morpholin-4-yl-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 48 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and morpholine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-morpholin-4-yl-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 603.0 (M+H)<sup>+</sup>.

## Example 67

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 49 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 1-methylpiperazine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 616.1 (M+H)<sup>+</sup>.

## Example 68

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-piperazin-1-yl-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 50 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and piperazine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-piperazin-1-yl-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 602.1 (M+H)<sup>+</sup>.

## Example 69

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-(2-morpholin-4-yl-ethoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 52 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and N-(2-hydroxyethyl)morpholine 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-(2-morpholin-4-yl-ethoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 647.1 (M+H)<sup>+</sup>.

## Example 70

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(2-chloro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 53 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 2-dimethylaminoethanol 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(2-chloro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 605.0 (M+H)<sup>+</sup>.

## Example 71

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-(2-chloro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide

In an analogous manner to that described in Example 54 there was obtained from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methanesulfonyl-pyrimidin-5-yl]-N-methyl-isobutyramide and 2-dimethylaminopropanol 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(2-chloro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide as a colorless foam, MS (ISP): 619.1 (M+H)<sup>+</sup>.

## Example 72

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide

a) (2-Methyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester

To a solution of 2.50 g (10.24 mmol) 2-methyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid, 1.43 ml triethylamine (10.24 mmol) and 1.9 ml (20.4 mmol) t-butanol in 50 ml THF, 2.2 ml (10.24 mmol) diphenylphosphorylazide were added and the resulting solution heated at reflux for 12 hrs. After evaporation of the solvent, the residue was distributed between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The aqueous phase was extracted twice with 80 ml CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/ MeOH 40:1) to give 1.83 g (56 %) (2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester as a colorless solid, MS (ISP): 316.3 (M+H)<sup>+</sup>.

b) Methyl-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester

To a solution of 1.83 g (5.80 mmol) (2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester in 25 ml N,N-dimethylformamide 0.35 g (68.7 mmol) sodiumhydride (60% dispersion in mineraloil) was added and the reaction mixture stirred for 1 h. After the addition of 0.65 ml (10.4 mmol) methyl iodide at 0°, the reaction mixture was stirred

for 2 hrs. The reaction mixture was poured into 100 ml ice-water and three times extracted with 80 ml  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ /ethyl acetate 40:1) to give 1.90 g (99 %) methyl-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester as a colorless oil, MS (ISP): 330.4 ( $\text{M}+\text{H}$ )<sup>+</sup>.

c) Methyl-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-amine

To a solution of 1.90 g (5.77 mmol) methyl-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester in 25 ml  $\text{CH}_2\text{Cl}_2$  2 ml trifluoroacetic acid was added and the reaction mixture stirred for 2 hrs. at 40°. The reaction mixture was poured into ice-water and the pH of the solution adjusted to 10 with 1N NaOH solution. The aqueous phase was extracted three times with 80 ml  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to give 0.95 g (72 %) methyl-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-amine as a light yellow solid, MS (EI): 229.2 ( $\text{M}^+$ ).

d) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide

To a solution of 0.4 g (1.74 mol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide and 0.6 ml (3.49 mmol) N-ethyl-diisopropylamine in 15 ml  $\text{CH}_2\text{Cl}_2$  a solution of 0.78 g (2.44 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 5 ml  $\text{CH}_2\text{Cl}_2$  was added and the reaction mixture stirred for 12 hrs at RT. The reaction mixture was poured into 50 ml 0.5 N NaOH-solution. The phases were separated and the aqueous phase three times extracted with 80 ml  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ /MeOH 40:1) to give 0.82 g (94 %) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide as a white foam, MS (ISP): 511.1 ( $\text{M}+\text{H}$ )<sup>+</sup>.

### Example 73

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(2-phenyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide

In an analogous manner to that described in Example 72 a) there was obtained from 2-phenyl-4-o-tolyloxy-pyrimidine-5-carboxylic acid, diphenylphosphorylazide and t-butanol (2-phenyl-4-o-tolyloxy-pyrimidin-5-yl)-carbamic acid tert.-butyl ester, which was methylated with methyl iodide and then deprotected with trifluoroacetic acid according to Example 72 b) c). The resulting methyl-(2-phenyl-4-o-tolyloxy-pyrimidin-5-yl)-amine was treated with 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as described in Example 72 e) to give 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-phenyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide as a white foam, MS (ISP): 574.1 ( $\text{M}+\text{H}$ )<sup>+</sup>.

Example A

Tablets of the following composition are manufactured in the usual manner:

|                            | <u>mg/tablet</u> |
|----------------------------|------------------|
| Active substance           | 5                |
| 5 Lactose                  | 45               |
| Corn starch                | 15               |
| Microcrystalline cellulose | 34               |
| Magnesium stearate         | 1                |
| Tablet weight              | 100              |

10

Example B

Capsules of the following composition are manufactured:

|                     | <u>mg/capsule</u> |
|---------------------|-------------------|
| Active substance    | 10                |
| Lactose             | 155               |
| 15 Corn starch      | 30                |
| Talc                | 5                 |
| Capsule fill weight | 200               |

The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

20

Example C

Suppositories of the following composition are manufactured:

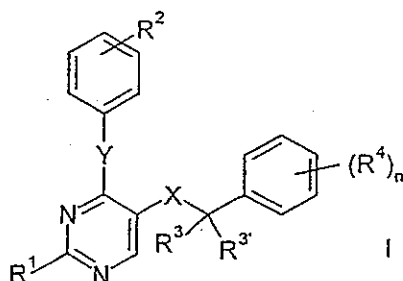
|                     | <u>mg/supp.</u> |
|---------------------|-----------------|
| Active substance    | 15              |
| 25 Suppository mass | 1285            |
| Total               | 1300            |

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and

stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

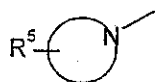
Claims

## 1. Compounds of the general formula



5 wherein

$R^1$  is lower alkyl, lower alkoxy, pyridinyl, pyrimidinyl, phenyl, -S-lower alkyl, -S(O)<sub>2</sub>-lower alkyl, -N(R)-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -N(R)<sub>2</sub>, or a cyclic tertiary amine of the group



10 which may contain one additional heteroatom, selected from N, O or S, and wherein this group may be connected with the pyrimidine ring via the linker -O(CH<sub>2</sub>)<sub>n</sub>-;

$R^2$  is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

$R^3/R^{3'}$  is, independently from each other, hydrogen or lower alkyl;

15  $R^4$  is independently from each other halogen, trifluoromethyl or lower alkoxy;

$R^5$  is hydrogen or lower alkyl;

R is, independently from each other, hydrogen or lower alkyl;

X is -C(O)N(R)- or -N(R)C(O)-;

Y is -O-, -S-, -SO<sub>2</sub>-, - or -N(R)-;

20 n is 1, 2, 3 or 4; and

m is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

2. A compound of formula I according to claim 1, wherein X is  $-\text{C}(\text{O})\text{N}(\text{CH}_3)-$  and Y is  $-\text{O}-$ .

3. A compound of formula I according to claim 2, wherein  $\text{R}^1$  is a cyclic tertiary amine.

4. A compound of formula I according to claim 3, which is  
2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,  
2-piperazin-1-yl-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide or  
4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

5. A compound of formula I according to claim 2, wherein  $\text{R}^1$  is  $-\text{O}-(\text{CH}_2)_n$ -cyclic tertiary amine.

6. A compound of formula I according to claim 5, which is  
2-(2-morpholin-4-yl-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

7. A compound of formula I according to claim 2, wherein  $\text{R}^1$  is the group  $-\text{O}-(\text{CH}_2)-\text{NR}_2$ .

8. A compound according to claim 7, which is  
2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidine-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

9. A compound of formula I according to claim 1, wherein X is  $-\text{N}(\text{CH}_3)\text{C}(\text{O})-$  and Y is  $-\text{O}-$ .

10. A compound of formula I according to claim 9, wherein  $\text{R}^1$  is  $-\text{S}$ -lower alkyl.

11. A compound of formula I according to claim 9, which is  
2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-methylsulfanyl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide or

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-methylsulfanyl-pyrimidin-5-yl]-N-methyl-isobutyramide.

5 12. A compound of formula I according to claim 9, wherein R<sup>1</sup> is a cyclic tertiary amine.

13. A compound of formula I according to claim 12, which is

2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-morpholin-4-yl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide,

10 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[2-(4-methyl-piperazin-1-yl)-4-o-tolyloxy-pyrimidin-5-yl]-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(2-piperazin-1-yl-4-o-tolyloxy-pyrimidin-5-yl)-isobutyramide,

15 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-N-methyl-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(4-fluoro-phenoxy)-2-piperazin-1-yl-pyrimidin-5-yl]-N-methyl-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-morpholin-4-yl-pyrimidin-5-yl]-N-methyl-isobutyramide,

20 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-N-methyl-isobutyramide or

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-piperazin-1-yl-pyrimidin-5-yl]-N-methyl-isobutyramide.

14. A compound of formula I according to claim 9, wherein R<sup>1</sup> is  
25 -N(R)(CH<sub>2</sub>)<sub>n</sub>NR<sub>2</sub>.

15. A compound of formula I according to claim 14, which is

2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethylamino)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide or

30 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethylamino)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide.

16. A compound of formula I according to claim 9, wherein R<sup>1</sup> is a  
-O-(CH<sub>2</sub>)<sub>n</sub>-cyclic tertiary amine.

17. A compound of formula I according to claim 16, which is

2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[2-(2-morpholin-4-yl-ethoxy)-4-o-tolyloxy-pyrimidin-5-yl]-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenoxy)-2-(2-morpholin-4-yl-ethoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide,

5 18. A compound of formula I according to claim 9, wherein  $R^1$  is  $-O-(CH_2)_nNR_2$ .

19. A compound of formula I according to claim 18, which is

2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-o-tolyloxy-pyrimidin-5-yl]-N-methyl-isobutyramide,

10 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide,

2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-(4-fluoro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide,

15 2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(2-dimethylamino-ethoxy)-4-(2-chloro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide or

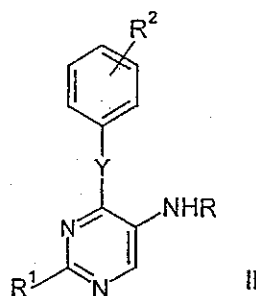
2-(3,5-bis-trifluoromethyl-phenyl)-N-[2-(3-dimethylamino-propoxy)-4-(2-chloro-phenoxy)-pyrimidin-5-yl]-N-methyl-isobutyramide.

20. A medicament containing one or more compounds as claimed in any one of claims 1-19 and pharmaceutically acceptable excipients.

21. A medicament according to claim 20 for the treatment of diseases related to NK-1 receptor antagonists.

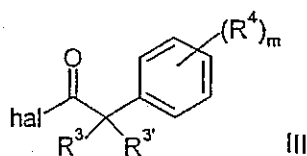
22. A process for preparing a compound of formula I as defined in claim 1, which process comprises

25 a) reacting a compound of formula

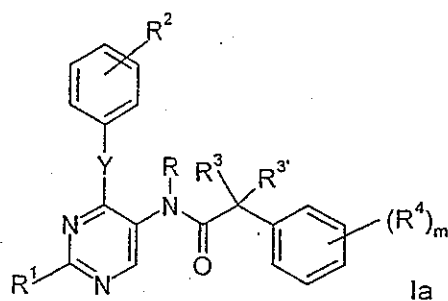


with a compound of formula

- 50 -



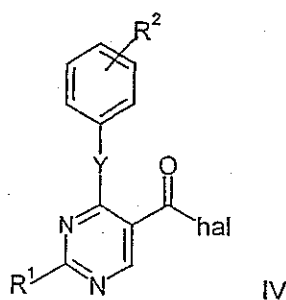
to a compound of formula



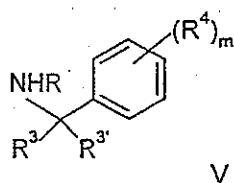
wherein Y, R¹, R², R³, R³', R⁴, R and m have the significances given above,

5 or

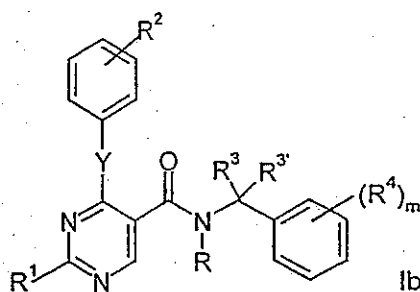
b) reacting a compound of formula



with a compound of formula

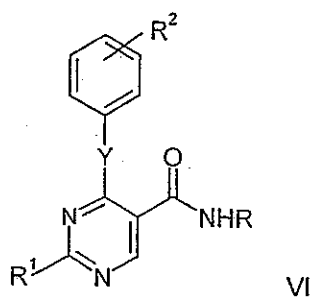


10 to give a compound of formula

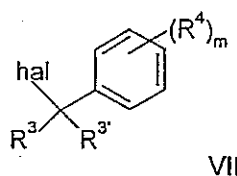


wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

c) reacting a compound of formula

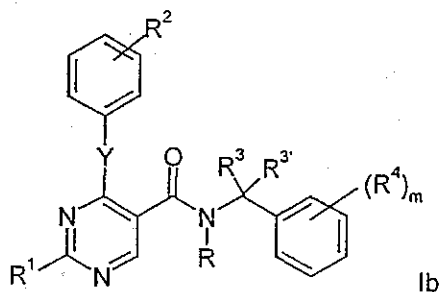


with a compound of formula



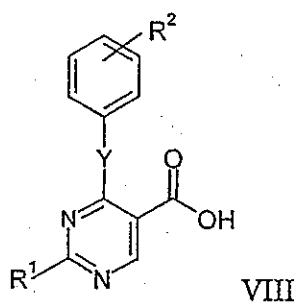
5

to a compound of formula

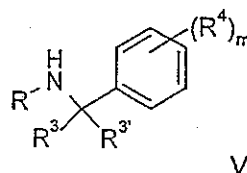


wherein hal is Cl, Br or I, and Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

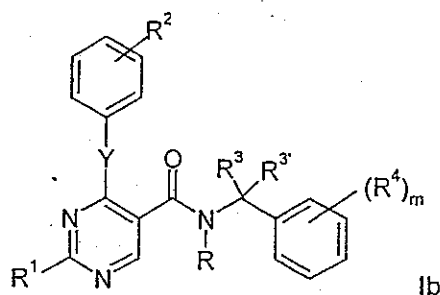
10 d) reacting a compound of formula



with a compound of formula

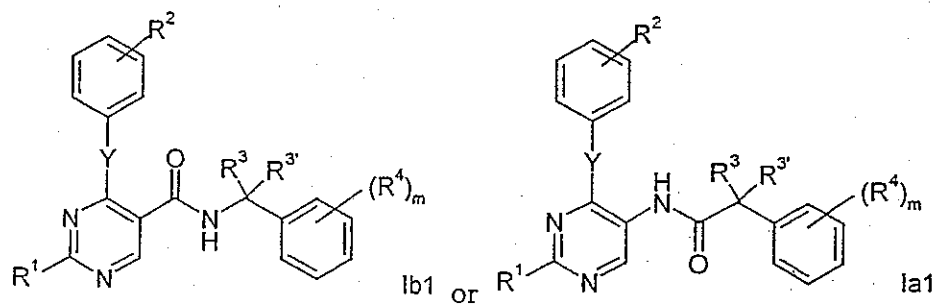


to a compound of formula

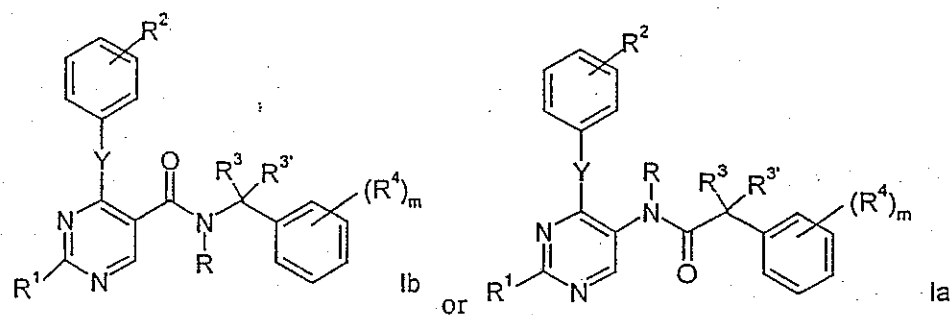


wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

5 e) alkylating a compound of formula

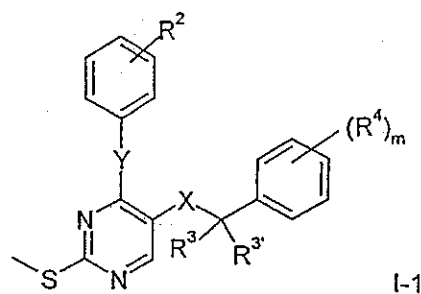


to a compound of formula

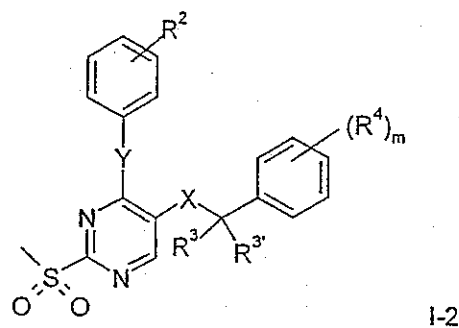


wherein Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup>, R and m have the significances given above, or

10 f) transforming a compound of formula

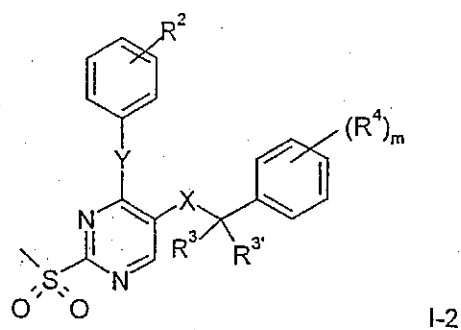


to a compound of formula

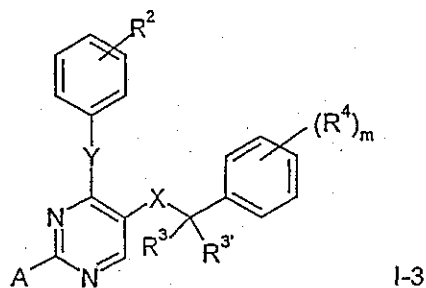


wherein X, Y, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> and m have the significances given above, or

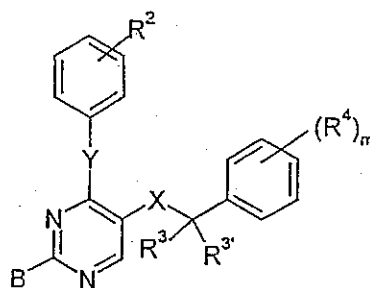
5 g) reacting a compound of formula



with a corresponding cyclic or non cyclic amine to a compound of formula

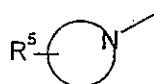


or with a corresponding alcohol to a compound of formula

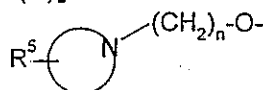


I-4

wherein Y, X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> and m have the significances given above, A is -N(R)-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub>, -N(R)<sub>2</sub> or a cyclic tertiary amine of the formula



- 5 and B is lower alkoxy, -O-(CH<sub>2</sub>)<sub>n</sub>-N(R)<sub>2</sub> or



and R<sup>5</sup> is described as above, or

- h) modifying one or more substituents R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> or R within the definitions given above, and

- 10 if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

23. A compound according to any one of claims 1-19, whenever prepared by a process as claimed in claim 22 or by an equivalent method.

24. The use of a compound in any one of claims 1-19 for the treatment of diseases.

- 15 25. The use of a compound in any one of claims 1-19 for the manufacture of medicaments containing one or more compounds of formula I for the treatment of diseases related to NK-1 receptor antagonists.

26. The invention as hereinbefore described.

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