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(54) Title: METHODS OF TREATING COPD AND PULMONARY HYPERTENSION

(57) Abstract: Disclosed are methods of treating COPD and Pulmonary Hypertension using p38 Map Kinase inhibitors in combination with one or more other active ingredients.



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Methods of Treating COPD and Pulmonary Hypertension

APPLICATION DATA

- 5 This application claims benefit to US provisional application no. 60/497,376 filed August 22, 2003.

TECHNICAL FIELD OF THE INVENTION

- 10 The present invention relates to p38 kinase inhibitors in combination with other active ingredients, their pharmaceutical compositions, processes for preparing them and their use in the treatment of chronic obstructive pulmonary disease (COPD) and pulmonary hypertension.

15

BACKGROUND OF THE INVENTION

- Tumor necrosis factor (TNF), interleukin-1 (IL-1) IL-8 and GM-CSF are important biological entities collectively referred to as proinflammatory cytokines. These,
20 along with several other related molecules, mediate the inflammatory response associated with the immunological recognition of infectious agents. The inflammatory response plays an important role in limiting and controlling pathogenic infections.

- 25 TNF α and IL-8 levels are elevated in airways of patients with chronic obstructive pulmonary disease and it may contribute to the pathogenesis of this disease (Patel IS et al. Airway epithelial inflammatory responses and clinical parameters in COPD. *Eur Respir J.* 2003 Jul;22(1):94-9). Circulating TNF α may also contribute to

weight loss associated with this disease (N. Takabatake *et al.*, 2000, *Amer. J. Resp. & Crit. Care Med.*, 161 (4 Pt 1), 1179).

In PCT publications WO 00/43384, WO 00/55139 and PCT application
5 PCT/US02/28615 there are described aromatic heterocyclic compounds useful in
treating certain cytokine mediated diseases. US publication no. 20030130309
discloses novel uses of the compounds described in WO 00/43384 for treating
additional cytokine mediated diseases including COPD. US publication no.
20030118575 describes novel methods of treating these diseases using 1-[3-tert-
10 butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalen-1-yl]-
urea at particular dosages.

Corticosteroids, anticholinergics, theophyllines, beta2-agonists, mucolytics, are
among the most common respiratory drugs prescribed in COPD.

15
Naeije, R. et al, report that pulmonary hypertension is a common complication of
COPD. Robert Naeije, R. et al, Crit Care. 2001; 5 (6): 286–289, November 3, 2001.
It is further reported that pharmacological treatment of pulmonary hypertension may
be possible in selected patients with advanced COPD and right-sided heart failure.
20 Several drug candidates suggested were prostacyclin derivatives, endothelin
antagonists and inhaled nitric oxide. These drugs were alleged to obtain a clinical
benefit in primary pulmonary hypertension. Strange et al. report that treatments
including endothelin receptor antagonists, nitric oxide (NO), PDE inhibitors and
gene therapy may be useful in treating pulmonary hypertension. Strange et al.,
25 *Clinical Science* (2002), I 02, 253-268.

There are several major groups of medicines used to treat hypertension: diuretics,
alpha-adrenergic blockers, beta-adrenergic blockers, angiotensin-converting enzyme
(ACE) inhibitors, vasopeptidase inhibitors, angiotension II receptor antagonists

(AIIRA) and calcium channel blockers. Recently, it has been reported by Kroetz et al. in US patent no. 6,531,506 that epoxide hydrolase inhibitors may also be useful in treating hypertension. Examples of soluble epoxide hydrolase (sEH) inhibitors are found in Ingraham, R. et al. WO 03/002555, US application serial
5 no. 10/172,457.

The work cited above supports the principle that inhibition of cytokine production by small molecule inhibitors such as those which inhibit p38 MAP kinase, in combination with one or more second active ingredients as described above, will be
10 beneficial in the treatment of chronic obstructive pulmonary disease and/or pulmonary hypertension.

BRIEF SUMMARY OF THE INVENTION

15 It is therefore an object of the invention to provide of method of treating chronic obstructive pulmonary disease (COPD) and/or pulmonary hypertension using p38 MAP kinase inhibitors and one or more second active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

20 A beneficial therapeutic effect, particularly an additive or over-additive effect or an overall reduction of side effects of therapy, is desirable in the treatment of cytokine mediated diseases, particularly in the treatment of COPD and pulmonary hypertension, if one or more, preferably one of the active ingredients (hereafter
25 referred to as A) described herein is or are used together with one or more, preferably one, p38 kinase inhibitor (hereafter referred to as B). An additive or over-additive effect of the pharmaceutical combinations according to the invention provides for dose reduction side-effect reduction and/or interval extension when compared to the individual compounds of and A and B used in monotherapy in the

usual way. The effects mentioned above are observed both when the two active substances are administered simultaneously in a single active substance formulation and when they are administered successively in separate formulations. In the case of A being an injectable, especially a biological agent, other benefits of adding B may
5 be seen. For example, cost reduction by way of interval and/or dose reduction.

Active Ingredient A:

Within the scope of the invention for active ingredient A are one or more:
10

Anti-hypertensives include those known in the art, such as but not limited to: diuretics, alpha-adrenergic blockers, beta-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers, vasopeptidase inhibitors, angiotension II receptor antagonists (AIIRA) and epoxide hydrolase
15 inhibitors such as those described in US patent no. 6,531,506 and WO 03/002555; particularly preferred are ibesartan and olmesartan;

Prostacyclin derivatives, endothelin antagonists and inhaled nitric oxide, PDE inhibitors and gene therapy;
20

Inhaled EGFR tyr kin inhibitors;

PI-3 kinase γ inhibitors, PDE4 inhibitors, FPRL-1/Genomics, TGF β r inhibitors, hCLCA1 blockers, MEK-1 inhibitors, JNK inhibitors, PAI-1 inhibitors, RAR γ
25 modulators and antioxidants;

Non-steroid anti-inflammatory drugs (NSAIDs) which are widely used for the treatment of inflammation, pain and fever. These include acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal,

- etodolac, fenoprofen calcium, flurbiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, rofecoxib, celecoxib, etoricoxib, valdecoxib, nabumetone, naproxen, 5 lornoxicam, nimesulide, remifenzone, salsalate, tiaprofenic acid, flosulide, and the like; Arofylline, NIK-616 and AWD 123-281.

Also within the scope of active ingredient A are one or more

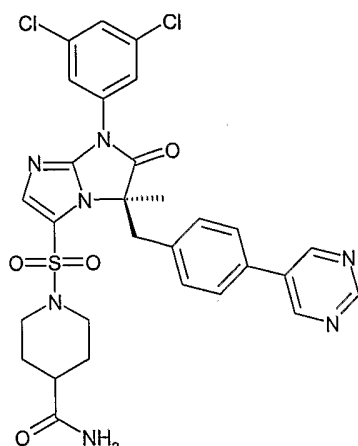
- 10 As oral route :
ROFLUMILAST any pharmaceutically acceptable salts
CILOMILAST any pharmaceutically acceptable salts

As inhaled route :

- 15 Fluticasone propionate
Salmeterol xinafoate
Budesonide
Triamcinolone acetonide
Formoterol fumarate
20 ipratropium bromide and salbutamol.

Preferred embodiment of ipratropium bromide can be found in US Pat. No. 6,739,333, and US application no. 10/804,710.

- 25 Another preferred combination for treating COPD and/or pulmonary hypertension is a p38 inhibitor compound with any of the compounds disclosed in US Pat. No. 6,492,408, more preferably:



- Inhibitors of Cathepsin S, L, K and B are also within the scope of the invention such as those described in WO/0170232, WO/0119796, WO/0119808,
- 5 WO/0170232, US publication no. 20010016207, US application no. 10/790,549, US patent nos. 5,501,969, 5,736,357, 5,830,850, 5,861,298, 5,948,669, 6,030,946, 6,506,733, 6,353,017, 6,395,897 and 6,420,364.

Active ingredient B:

10

- The p38 kinase inhibitors within the scope of the present invention the are compounds chosen from those disclosed in US Patents 6,319,921, 6,358,945, 5,716,972, US 5,686,455, US 5,656,644, US 5,593,992, US 5,593,991, US 5,663,334, US 5,670,527, US 5,559,137, 5,658,903, US 5,739,143, US
- 15 5,756,499, US 6,277,989, US 6,340,685, and US 5,716,955; and PCT applications WO 92/12154, WO 94/19350, WO 95/09853, WO 95/09851, WO 95/09847, WO 95/09852, WO 97/25048, WO 97/25047, WO 97/33883, WO 97/35856, WO 97/35855, WO 97/36587, WO 97/47618, WO 97/16442, WO 97/16441, WO 97/12876, WO 98/25619, WO 98/06715, WO 98/07425, WO 98/28292, WO
- 20 98/56377, WO 98/07966, WO 98/56377, WO 98/22109, WO 98/24782, WO 98/24780, WO 98/22457, WO 98/52558, WO 98/52559, WO 98/52941, WO

98/52937, WO 98/52940, WO 98/56788, WO 98/27098, WO 98/47892, WO 98/47899, WO 98/50356, WO 98/32733, WO 99/58523, WO 99/01452, WO 99/01131, WO 99/01130, WO 99/01136, WO 99/17776, WO 99/32121, WO 99/58502, WO 99/58523, WO 99/57101, WO 99/61426, WO 99/59960, WO 99/59959, WO 99/00357, WO 99/03837, WO 99/01441, WO 99/01449, WO 99/03484, WO 99/15164, WO 99/32110, WO 99/32111, WO 99/32463, WO 99/64400, WO 99/43680, WO 99/17204, WO 99/25717, WO 99/50238, WO 99/61437, WO 99/61440, WO 00/26209, WO 00/18738, WO 00/17175, WO 00/20402, WO 00/01688, WO 00/07980, WO 00/07991, WO 00/06563, WO 00/12074, WO 00/12497, WO 00/31072, WO 00/31063, WO 00/23072, WO 00/31065, WO 00/35911, WO 00/39116, WO 00/43384, WO 00/41698, WO 00/69848, WO 00/26209, WO 00/63204, WO 00/07985, WO 00/59904, WO 00/71535, WO 00/10563, WO 00/25791, WO 00/55152, WO 00/55139, WO 00/17204, WO 00/36096, WO 00/55120, WO 00/55153, WO 00/56738, WO 01/21591, WO 01/29041, WO 01/29042, WO 01/62731, WO 01/05744, WO 01/05745, WO 01/05746, WO 01/05749, WO 01/05751, WO 01/27315, WO 01/42189, WO 01/00208, WO 01/42241, WO 01/34605, WO 01/47897, WO 01/64676, WO 01/37837, WO 01/38312, WO 01/38313, WO 01/36403, WO 01/38314, WO 01/47921, WO 01/27089, DE 19842833, and JP 2000 86657 whose disclosures are all incorporated herein by reference in their entirety. Within the scope of the invention are any of the aforementioned B compounds in combination with component A in a single pharmaceutical composition or administered separately.

Of particular interest for the pharmaceutical compositions according to the invention are those p38 inhibitors disclosed in 6,319,921, 6,358,945, US 6,277,989, US 6,340,685, WO 00/12074, WO 00/12497, WO 00/59904, WO 00/71535, WO 01/64676, WO 99/61426, WO 00/10563, WO 00/25791, WO 01/37837, WO 01/38312, WO 01/38313, WO 01/38314, WO 01/47921, WO 99/61437, WO

99/61440, WO 00/17175, WO 00/17204, WO 00/36096, WO 98/27098, WO 99/00357, WO 99/58502, WO 99/64400, WO 99/01131, WO 00/43384, WO 00/55152, WO 00/55139 and WO 01/36403.

5

In another preferred embodiment the invention relates to pharmaceutical combinations comprising A and p38 kinase inhibitor B chosen from the compounds disclosed in WO 00/43384 and corresponding US patent 6,319,921.

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In another preferred embodiment the invention relates pharmaceutical combinations comprising compounds A and B, wherein the p38 kinase inhibitor B is selected from the compounds disclosed in WO 00/55139 and corresponding US patent no. 6,358,945.

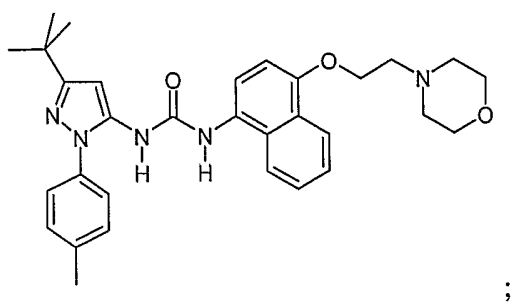
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In another preferred embodiment the invention relates pharmaceutical combinations comprising compounds A and B, wherein the p38 kinase inhibitor B is selected from the compounds disclosed in US provisional application no. 60/401,921.

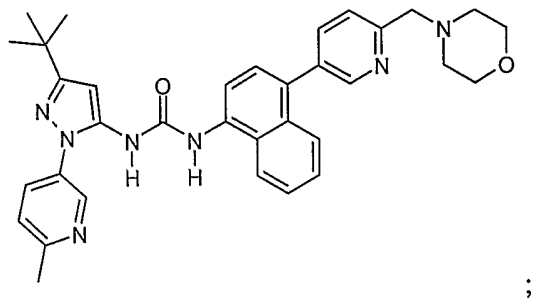
20 Each of the above-identified patent applications and patents are incorporated by reference herein in their entirety.

Particularly preferred the invention relates to pharmaceutical combinations comprising A and B, wherein the p38 kinase inhibitor B is:

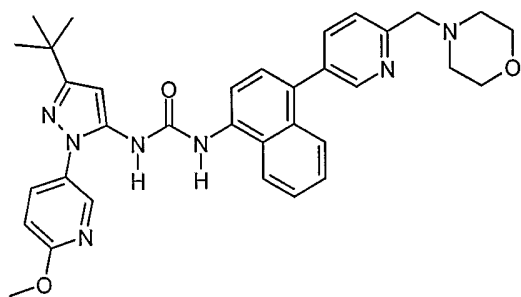
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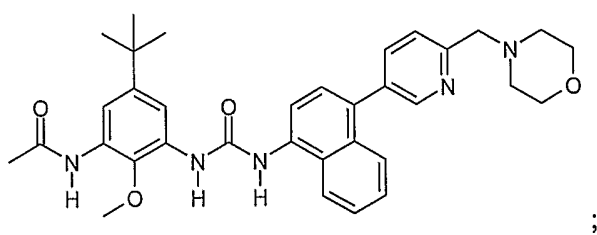


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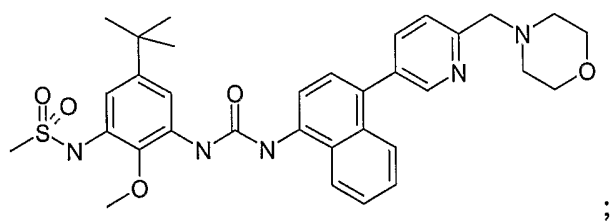
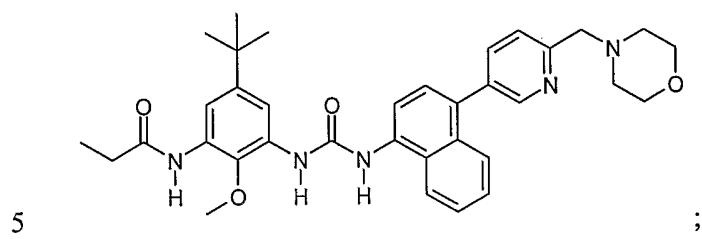
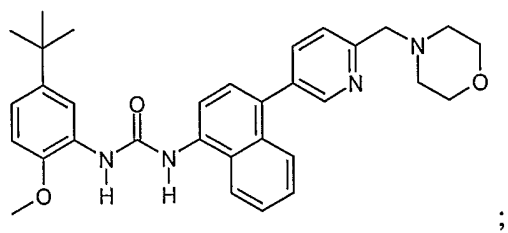
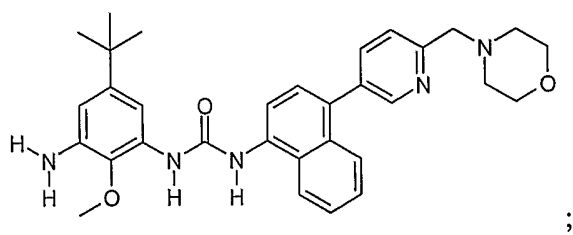


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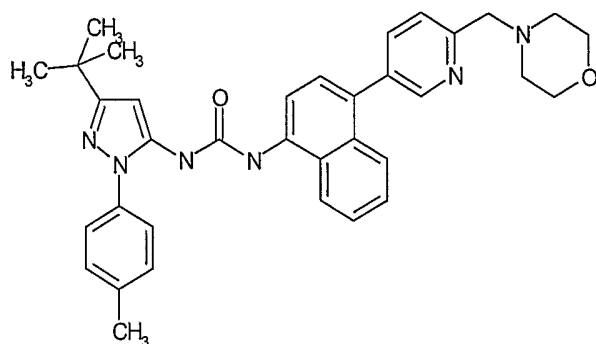
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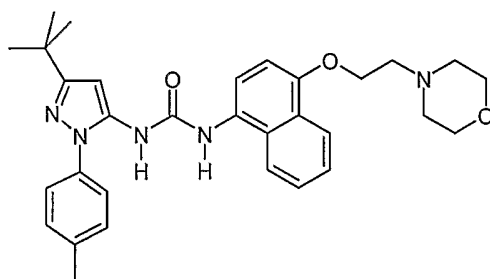


and



or the pharmaceutically acceptable salts thereof.

- 5 More particularly preferred the invention relates to pharmaceutical combinations comprising A and B, wherein the p38 kinase inhibitor B is:



- 10 and the pharmaceutically acceptable salts thereof.

Of particular importance according to the invention are the abovementioned pharmaceutical combinations comprising A and B, for use as pharmaceutical compositions with an anti-cytokine activity and one or more active ingredients with
 15 anti-hypertensive activity and those useful for treating respiratory diseases such as COPD and pulmonary hypertension.

The invention also relates combinations comprising A and B, for preparing a pharmaceutical composition for the treatment and/or prevention of COPD and pulmonary hypertension.

- 5 The invention also relates to pharmaceutical preparations, containing as active substance one or more compounds combinations comprising A and B, or the pharmaceutically acceptable derivatives thereof, optionally combined with conventional excipients and/or carriers.
- 10 Any reference to the abovementioned p38 kinase inhibitors B and compounds A include "pharmaceutically acceptable derivative" thereof which refers to any pharmaceutically acceptable salt or ester of a compound of this invention, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound B of this invention, a pharmacologically active
- 15 metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound B of the invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative p 38 compounds.
- 20 Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic,
- 25 malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of this invention and their pharmaceutically acceptable acid addition salts. Salts derived

from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C1-C4 alkyl)₄⁺ salts.

In addition, the compounds of this invention include prodrugs of p38 compounds.

- 5 Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug of this invention is administered to a patient, the prodrug may be transformed into a compound B of the invention, thereby imparting the desired pharmacological
10 effect.

- For therapeutic use, the pharmaceutical combinations of A and B according to the invention may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously,
15 intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally or by inhalation.

The preferred modes of administration are inhalable, oral or intravenous.

- 20 The the pharmaceutical combinations of A and B according to the invention may be administered separately, or in a combination formulation with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like,
25 including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Pharmaceutical combinations of A and B may therefore be physically combined with the conventional therapeutics or other adjuvants into a

single pharmaceutical composition. Reference in this regard may be made to Cappola et al.: US patent application no. 09/902,822, PCT/US 01/21860 and US provisional application no. 60/313,527, each incorporated by reference herein in their entirety. The optimum percentage (w/w) of a compound of the invention may vary and is within the purview of those skilled in the art.

As mentioned above, dosage forms of the compositions described herein include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovich, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. Regarding p38 component B, in some embodiments, dosage levels range from about 1-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. Reference in this regard may also be made to US publication 20030118575. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

In another aspect the present invention relates to a pharmaceutical composition suitable for inhalation which contains one or more salts A and one or more

compounds B, optionally in the form of their salts, solvates or hydrates. The active substances may either be combined in a single preparation or contained in two separate formulations. Pharmaceutical compositions which contain the active substances A and B in a single preparation are preferred according to the invention.

5

The present invention also relates to the use of A and B for preparing a pharmaceutical combinations containing therapeutically effective quantities of A and B for treating COPD and pulmonary hypertension, provided that treatment with p38 kinase inhibitors is not contraindicated from a therapeutic point of view, by simultaneous or successive administration.

10

In the active substance combinations of A and B according to the invention, ingredients A and B may be present in the form of their enantiomers, mixtures of enantiomers or in the form of racemates.

15

The proportions in which the two active substances A and B may be used in the active substance combinations according to the invention are variable. Active substances A and B may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds A and B, the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various compounds and their different potencies. Determination of ratios by weight is dependent on particular active ingredients of A and B, and within the skill in the art.

20

25 The active substance combinations of A and B according to the invention may be administered by inhalation or by nasal application. For this purpose, ingredients A and B have to be made available in inhalable forms. Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable solutions or suspensions. Inhalable powders according to the invention

containing the combination of active substances A and B may consist of the active substances on their own or of a mixture of the active substances with physiologically acceptable excipients. Within the scope of the present invention, the term propellant-free inhalable solutions or suspensions also includes

5 concentrates or sterile inhalable solutions ready for use. The preparations according to the invention may contain the combination of active substances A and B either together in one formulation or in two separate formulations. These formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

10

There are currently four devices to administer active substance combinations of A and B according to the invention to the lung:

Respimat - (Aqueous, ethanolic (or any mixture thereof) solution or suspension)
Metered Dose Inhaler , MDI (Suspension or Solution)

15 Dry Powder Inhaler, DPI (e.g. Spiriva)

Conventional nebulizers usually with unit dose vials (UDV)

The propellant-free inhalable solutions or suspensions according to the invention are administered in particular using inhalers of the kind which are capable of aerolising

20 a small amount of a liquid formulation in the therapeutic dose within a few seconds to produce an aerosol suitable for therapeutic inhalation. Within the scope of the present invention, preferred inhalers are those in which a quantity of less than 100 μ L active substance solution can be nebulised in preferably one spray action to form an aerosol with an average particle size of less than 20 μ m, in such a way that

25 the inhalable part of the aerosol corresponds to the therapeutically effective quantity.

An apparatus of this kind for propellant-free delivery of a metered quantity of a liquid pharmaceutical composition for inhalation is described for example in International Patent Application WO 91/14468 and also in WO 97/12687.

- 5 In a further aspect, the invention relates to pharmaceutical formulations in the form of propellant-free inhalable solutions or suspensions as described above combined with a device suitable for administering these formulations, preferably in conjunction with the Respimat®. Preferably, the invention relates to propellant-free inhalable solutions or suspensions characterised by the combination of active
- 10 substances A and B according to the invention in conjunction with the device known by the name Respimat®. In addition, the present invention relates to the above-mentioned devices for inhalation, preferably the Respimat®, characterised in that they contain the propellant-free inhalable solutions or suspensions according to the invention as described hereinbefore.
- 15 Inhalable solutions or suspensions which contain the active substances A and B in a single preparation are preferred according to the invention. The term preparation also includes those which contain both ingredients A and B in two-chamber cartridges as disclosed for example in WO 00/23037. Reference is hereby made to this publication in its entirety.

- 20 The propellant-free inhalable solutions or suspensions according to the invention may take the form of concentrates or sterile inhalable solutions or suspensions ready for use, as well as the above-mentioned solutions and suspensions designed for use in a Respimat®. Formulations ready for use may be produced from the
- 25 concentrates, for example, by the addition of isotonic saline solutions. Sterile formulations ready for use may be administered using energy-operated fixed or portable nebulisers which produce inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other principles.

Accordingly, in another aspect, the present invention relates to pharmaceutical compositions in the form of propellant-free inhalable solutions or suspensions as described hereinbefore which take the form of concentrates or sterile formulations ready for use, combined with a device suitable for administering these solutions,
5 characterised in that the device is an energy-operated free-standing or portable nebuliser which produces inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other methods.

Respimat® solutions and UDV require that the drug substance be both soluble and
10 stable in either an aqueous or an ethanolic media. Solution MDI require that the drug substance be both soluble and stable in either a propellant or in a mixture of propellants or in a mixture of propellants with co-solvents (e. g. ethanol, water). Suspension MDI, suspensions for Respimat® and DPI require that the drug substance be easily micronized to a respirable range (less than 5 microns). Ideally,
15 these micronized materials should have stable physical-chemical properties such that there is no water uptake, no aggregation and no chemical decomposition. For suspension MDI, the drug substance should not be soluble in the propellants (e. g. HFA 134a or HFA 227).

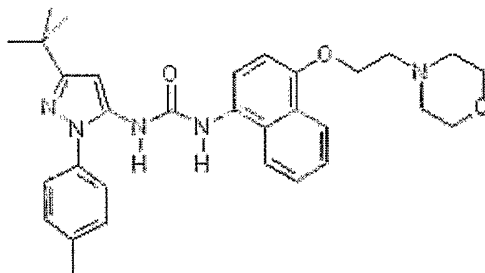
20 For combinations with preferred p38 compounds, the MDI device with a formulation of MDI suspensions using high-pressure homogenization techniques known in the art are preferred. Also preferred is the DPI device.

The Examples which follow serve to illustrate the present invention in more detail
25 without restricting the scope of the invention to the following embodiments by way of example.

Starting materials

Component B, p38 inhibitor: BIRB 796 BS

1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalen-1-yl]-urea.



5

The above p38 component B used in the following examples, may be obtained as described in US patent nos. 6,319,921 or 6,583,282.

10 FORMULATIONS:

In order to prepare the oral dosage formulations for use in tablets, the formulation described in US patent no. 6,565,880 or PCT/US 01/21860 may be used; for parental administration formulations, see US application no. 10/214,782.

15

Table 1

Core Tablet Formulas for 20, 25, 50, 100 and 200 mg Core Tablets

20

BIRB 796 BS Tablets	5 mg	20mg	25mg	50mg	100mg	200mg
Ingredients	Mg	mg	mg	mg	mg	mg
BIRB 796 BS (milled)	5.000	20.000	25.000	50.000	100.000	200.000
Lactose Monohydrate	55.000	40.000	50.000	100.000	200.000	400.000
Povidone K30	3.1600	3.158	3.9475	7.8950	15.790	31.580
Microcrystallin e Cellulose	30.000	30.000	37.500	75.000	150.000	300.000
Pregelatinized Starch	3.590	3.592	4.490	8.980	17.960	35.920
Sodium Starch Glycolate	2.000	2.000	2.500	5.000	10.000	20.000
Colloidal Silicon Dioxide	0.500	0.500	0.625	1.250	2.500	5.000
Magnesium Stearate	0.750	0.750	0.9375	1.875	3.750	7.500
Total Tablet Weight	100.00	100.00	125.00	250.00	500.00	1000.00

5

Examples of Pharmaceutical Combinations :

1)

Ingredients	dosage
component A:	CILOMILAST 15 mg BID
component B (BIRB 796 BS)	5 – 150 mg BID

5

2)

Ingredients	dosage
component A:	ROFLUMILAST 250-1000 mcg QD
component B (BIRB 796 BS)	5 – 150 mg BID

3)

Ingredients	dosage
component A:	SALMETEROL 25-50 mcg BID
component B (BIRB 796 BS)	5 – 150 mg BID

10 4)

Ingredients	dosage
component A:	FORMOTEROL 12-24 mcg bid
component B (BIRB 796 BS)	5 – 150 mg BID

5)

Ingredients	dose
component A:	FLUTICASONE 250-500 mcg BID
component B (BIRB 796 BS)	5 – 150 mg BID

6)

Ingredients	dose
component A:	BUDESONIDE 200-800 mcg BID
component B (BIRB 796 BS)	5 – 150 mg BID

5

Other formulations comprising particular active ingredients of A and B can be obtained based on the teachings and the examples provided herein, and from materials and methods known in the art without undue experimentation. These variations are within the scope of the invention.

10

Any of the above mentioned combinations within the scope of the invention may be tested by animal models known in the art. Reference in this regard may be made to: Shapiro SD: animals models for COPD. Chest 2000; 117 223S-227S.

Dawkins PA, et al. Animal models of chronic obstructive pulmonary disease.

15 Thorax 2001; 56:972-977.

Mahadeva R, Shapiro SD. Chronic obstructive pulmonary disease. 3. Experimental animal models of pulmonary emphysema. Thorax 2002; 57:908-914.

Wright JL, Churg A. Animal models of cigarette smoke-induced COPD. Chest 2002; 122 : 301S-306S.

20 Takeyama, K. et al. Activation of epidermal growth factor receptors is responsible for mucin synthesis induced by cigarette smoke. Am J. Physiol. Lung Cell Mol. Physiol 280: L165-L172, 2001.

Animal Model: Smoke-induced Goblet Cell Metaplasia in a Subchronic Rat

25 **Smoke Model**

- Subchronic exposure to cigarette smoke produces a significant increase in the number of goblet cells in the airway epithelium and subsequently an increase in mucus production. Studies suggest that p38 MAP kinase signalling may be involved in this pathway. The study described below can be used to evaluate the potential of
- 5 p38 MAP kinase inhibitors plus one or more other active ingredients as described herein to counteract the cigarette smoke-induced changes in the lungs.

Experimental procedures:

Smoke exposure

- 10 Male Sprague-Dawley rats weighing 250-300 g are used for the study. Animals should be housed in a temperature- and humidity-controlled room and have free access to water and standard laboratory food. Animals are assigned at random to the nonsmoking control group or to the smoke-exposed control and treatment groups with each group consisting of 6 animals. Rats in the smoking groups are to be
- 15 exposed to 16 regular, nonfilter cigarettes (1.2 mg nicotine, 12 mg condensate) a day for 5 days.

- On each day of exposure, 12 animals are placed individually in wire-mesh cages inside a Plexiglas cabinet (40 × 50 × 20 cm). Cigarette smoke is delivered into the
- 20 cabinet by passing air at a flow rate of 0.3 ml/s through a burning cigarette in a chamber. The combustion time of the cigarette is ~3 min. A ventilator inside the cabinet ensures a rapid and equal distribution of the smoke. Fresh air at a flow rate of 2 l/min is delivered into the cabinet to remove the smoke. At intervals of 20 min, the smoke of a new cigarette is conducted into the cabinet. During the exposure to
- 25 cigarette smoke, no animal, including control animals, receives food or water. At other times, the animals can have free access to food and water.

Treatment with combination of active ingredient A and p38 MAP kinase inhibitor B.

- 30 To evaluate the effect of combinations of A and B according to the invention on goblet cell metaplasia and mucus production, the animals are treated at least once daily with vehicle or the combination of A and B as described above. Preferably the p38 MAP kinase inhibitors is at doses of 10 or 30 mg/kg orally 1 h before and after the daily exposure to cigarette smoke. Treatment of the animals with vehicle or

combinations start on day 1 and continue for 5 days during exposure to cigarette smoke. The oral administration is performed via gavage in a volume of 3 ml/kg.

Tissue preparation and quantification of goblet cell production.

- 5 The lungs are dissected and fixed in 4% buffered Formalin and embedded in paraffin. The left main stem bronchus is used for immunohistochemical staining. Lung sections are cut to include the full length of the main intrapulmonary airway and stained sequentially with hematoxylin and eosin or with Alcian blue (AB)-periodic acid-Schiff (PAS) to evaluate the total epithelial area and the area stained
10 for intracellular mucous glycoconjugates, respectively. Goblet cell production is determined by the volume density of AB-PAS-stained mucous glycoconjugates on the epithelial mucosal surface using an image analysis system (Soft Imaging System, Münster, Germany). The AB-PAS-positive stained area, the number of goblet cells, and the total epithelial area are measured over a length of 2 mm of the basal lamina.

15

Statistics

- All data are expressed as means $\pm$ SEM. One-way analysis of variance (ANOVA) is used to determine statistically significant differences between groups. Scheffé's *F*-test is used to correct for multiple comparisons when statistical significances are
20 identified in the ANOVA. $P < 0.05$ for the null hypothesis is accepted as indicating a statistically significant difference.

Inhibition of smoke-induced goblet cell metaplasia

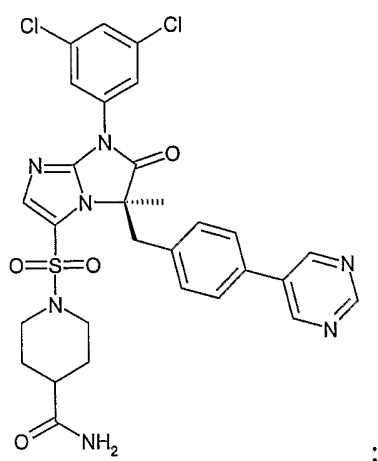
- 25 In solvent control animals, the airway epithelium should contain very few goblet cells. Inhalation of cigarette smoke (16 cigarettes/day for 5 days) typically results in at least 3 fold increase in the number of goblet cells. Treatment with preferred combinations of A and B will inhibit this increase dose-dependently.

30

All literature references, patents and publications cited in this application are incorporated herein by reference in their entirety.

WHAT IS CLAIMED IS:

1. A method of treating COPD or pulmonary hypertension comprising administering to a patient a therapeutically effective amount of one or more active ingredients A together with a therapeutically effective amount of one or more p38 kinase inhibitors;
- 5 wherein the active ingredients A is chosen from:
- diuretics, alpha-adrenergic blockers, beta-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, vasopeptidase inhibitors, angiotension II receptor antagonists (AIIRA), epoxide hydrolase inhibitors;
- 10 prostacyclin derivatives, endothelin antagonists, inhaled nitric oxide, PDE inhibitors;
- inhaled EGFR tyr kin inhibitors;
- 15 PI-3 kinase γ inhibitors, PDE4 inhibitors, FPRL-1/Genomics, TGF β r inhibitors, hCLCA1 blockers, MEK-1 inhibitors, JNK inhibitors, PAI-1 inhibitors, RAR γ modulators, antioxidants;
- Non-steroid anti-inflammatory drugs (NSAIDs);
- Arofylline, NIK-616, AWD 123-281;
- 20 ROFLUMILAST, CILOMILAST, FLUTICASONE PROPIONATE, SALMETEROL XINAFOATE, BUDESONIDE, TRIAMCINOLONE ACETONIDE, FORMOTEROL FUMARATE ;



and inhibitors of Cathepsin S, L, K and B.

- 5 2. The method according to claim 1 where the p38 kinase inhibitor is a compound chosen from:
 - 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl)phenyl)naphthalen-1-yl]urea;
 - 10 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-ylmethyl)phenyl)naphthalen-1-yl]urea;
 - 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(2-(morpholin-4-yl)ethyl)phenyl)naphthalen-1-yl]urea;
 - 15 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-dimethylaminophenyl)naphthalen-1-yl]urea;
 - 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl)phenyl)naphthalen-1-yl]urea;
 - 20 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-ylmethyl)phenyl)naphthalen-1-yl]urea;
 - 25 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;

- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(5-morpholin-4-ylmethyl-pyridin-2-yl)naphthalen-1-yl]urea;
- 5 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(5-morpholin-4-ylmethyl-fur-2-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;
- 10 1-[5-*tert*-butyl-2-methyl-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-phenyl-2H-pyrazol-3-yl]-3-[4-(4-piperdin-1-ylmethyl-phenyl)naphthalen-1-yl]urea;
- 15 1-[5-*tert*-butyl-2-phenyl-2H-pyrazol-3-yl]-3-[4-(4-(4-methylpiperazin-1-yl)methylphenyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3,4-di(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]urea;
- 20 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-pyridin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 25 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 30 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-tetrahydropyran-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-tetrahydrothiophen-3-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 35 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(imidazol-1-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(imidazol-1-ylmethyl)pyridin-3-yl)naphthalen-1-yl]urea;
- 40 1-[2-(3-dimethylaminomethylphenyl)-5-(1-methyl-cyclohexyl)-2H-pyrazol-3-yl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;

- 1-[2-(5-(1-methyl-cyclohexyl)-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]urea;
- 5 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-methoxy-5-(2-morpholin-4-yl-ethoxy)phenyl)naphthalen-1-yl]urea;
- 10 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-morpholin-4-yl-ethoxy)phenyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-3-(dimethylamino)phenyl)naphthalen-1-yl]urea;
- 15 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-3-(methylsulfonyl)phenyl)naphthalen-1-yl]urea;
- 5-*tert*-butyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}thiophene-2-carboxylic acid methyl ester;
- 20 5-*tert*-butyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}thiophene-2-carboxylic acid methylamide;
- 5-*tert*-butyl-1-methyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}-1H-pyrrole-2-carboxylic acid methyl ester;
- 25 5-*tert*-butyl-1-methyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}-1H-pyrrole-2-carboxylic acid methylamide;
- 30 2-acetylamino N-(5-*tert*-butyl-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)naphthalen-1-yl]ureido}thiophen-2-ylmethyl)acetamide;
- 35 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-morpholin-4-yl-cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-morpholin-4-yl-cyclohept-1-enyl)naphthalen-1-yl]urea;
- 40 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(2-morpholin-4-yl-ethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;

- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(3-morpholin-4-yl-cyclohept-1-enyl)naphthalen-1-yl]urea;
- 5 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(pyridin-4-yl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(dimethylaminoethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 10 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(pyridin-3-yl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(phenyl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 15 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-phenylethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(furan-2-yl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 20 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-pyridin-2-ylethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 25 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-piperdin-1-ylethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-imidazol-4-ylethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 30 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(pyridin-2-yl-methylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-(4-methoxyphenyl)ethylamino)cyclohex-1-enyl)naphthalen-1-yl]urea;
- 35 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-morpholin-4-ylmethyl-3-oxo-cyclohex-1-enyl)naphthalen-1-yl]urea;
- 40 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(1-oxo-tetrahydrothiophen-3-ylmethyl)-3-oxo-cyclohex-1-enyl)naphthalen-1-yl]urea;

- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(1-oxo-thiomorpholin-4-ylmethyl)-3-oxo-cyclohex-1-enyl)naphthalen-1-yl]urea;
- 5 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-methylpiperazin-1-ylmethyl)-3-oxo-cyclohex-1-enyl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-{6-oxo-1-(tetrahydro-pyran-4-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl}naphthalen-1-yl]urea;
- 10 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(2-oxo-1-pyridin-4-ylmethyl-piperdin-4-yl)naphthalen-1-yl]urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]urea;
- 15 1-[5-*tert*-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]urea;
- 5-*tert*-butyl-3-{3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]ureido}thiophene-2-carboxylic acid methyl ester;
- 20 5-*tert*-butyl-1-methyl-3-{3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]ureido}pyrrole-2-carboxylic acid methyl ester;
- 5-*tert*-butyl-1-methyl-3-{3-[4-(6-oxo-1-pyridin-4-yl-1,2,3,6-tetrahydro-pyridin-4-yl)naphthalen-1-yl]ureido}pyrrole-2-carboxylic acid methyl amide;
- 25 5-*tert*-butyl-3-{3-[4-(3-morpholin-4-yl-cyclohex-1-enyl)naphthalen-1-yl]ureido}thiophene-2-carboxylic acid methyl ester;
- 30 5-*tert*-butyl-1-methyl-3-{3-[4-(3-morpholin-4-yl-cyclohex-1-enyl)naphthalen-1-yl]ureido}pyrrole-2-carboxylic acid methyl ester;
- 5-*tert*-butyl-1-methyl-3-{3-[4-(3-morpholin-4-yl-cyclohex-1-enyl)naphthalen-1-yl]ureido}pyrrole-2-carboxylic acid methyl amide;
- 35 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(4-morpholin-4-yl-methylphenyl)-naphthalen-1-yl]-urea;
- 40 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[3-(4-morpholin-4-yl-methylphenyl)-naphthalen-1-yl]-urea;
- 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(5-morpholin-4-yl-methylfuran-2-yl)-

- naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl-methyl)cyclohexenyl)-naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(4-morpholin-4-yl)ethylphenyl)-naphthalen-1-yl]-urea;
- 10 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-dimethylaminomethylphenyl)-naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-methyl)pyridin-2-yl)-naphthalen-1-yl]-urea;
- 20 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(2-(morpholin-4-yl)ethylamino)cyclohexenyl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3,4-(morpholin-4-yl-methyl)phenyl)-naphthalen-1-yl]-urea;
- 30 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-methylpiperzin-1-yl-methyl)phenyl)-naphthalen-1-yl]-urea;
- 35 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(piperdin-1-yl-methyl)phenyl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(2-(pyridin-2-yl)ethylamino)cyclohexenyl)-naphthalen-1-yl]-urea;
- 40 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(2-(pyridin-4-yl)ethylaminomethyl)phenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(pyridin-3-yl-methylaminomethyl)phenyl)naphthalen-1-yl]-urea;

- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(3,4-dimethoxyphenylmethyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;
- 10 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)imidazol-1-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)imidazol-1-yl)naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(furan-3-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;
- 20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(4-hydroxybutylamino)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(pyridin-3-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;
- 25 1-[5-tert-butyl-2-(4-methyl-3-carbamylphenyl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(imidazol-2-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;
- 30 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(3-hydroxymorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;
- 35 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-2-methoxyethy-N-methylaminomethyl)phenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(4-hydroxymorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;
- 40 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl-methyl)cyclohexenyl)-naphthalen-1-yl]-urea;

- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(tetrahydrofuran-3-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N,N-di-(2-methoxyethyl)aminomethyl)phenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(3-cyanopropoxy)pyridin-3-yl)naphthalen-1-yl]-urea;
- 10 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-morpholin-4-yl-methyl-piperdinylnaphthalen-1-yl)-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N,N-di-(2-cyanoethyl)aminomethyl)phenyl)naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(1-morpholin-4-yl-indan-5-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(furan-2-yl-methyl)-3-hydroxyphenyl)naphthalen-1-yl]-urea;
- 20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(thiomorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;
- 25 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(3-carboxamidomorpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(2-methyl-3-oxo-piperzin-1-yl-methyl)phenyl)naphthalen-1-yl]-urea;
- 30 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(4-hydroxybutyloxy)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 35 1-[3-tert-butyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 40 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(furan-2-yl-methyl)-3-methoxyphenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-

- 4-carbonyl)pyrazin-2-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-(2-cyanoethyl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 10 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(2,6-dimethylmorpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(2-methoxypyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-(2-aminopyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-oxo-1,6-dihydropyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-4-carbonyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(3-carbamylphenyl)naphthalen-1-yl)-urea];
- 30 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-(2-cyanoethyl)-N-(pyridin-3-yl-methyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-(2-cyanoethyl)-N-(pyridin-2-yl-methyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;
- 35 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-(2-cyanoethyl)-N-(tetrahydrofuran-2-yl-methyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;
- 40 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)-4-methoxypyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-morpholin-4-

- yl-propyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(N-(3-methoxypropyl)amino)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(N-(3-methoxypropyl)-N-methylamino)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 10 1-[3-tert-butyl-1'-methyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-benzyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(4-(N-N-di-(2-cyanoethyl)aminomethyl)phenyl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(4-(4-carbamylphenyl)naphthalen-1-yl)-urea;
- 20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydropyran-4-yl-amino)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-[3-tert-butyl-1'-(3-cyanopropyl)-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 30 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-methanesulfinylphenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-methanesulfonylphenyl)naphthalen-1-yl]-urea;
- 35 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-sulfonamidophenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-(morpholin-4-yl)carbonylphenyl)naphthalen-1-yl]-urea;
- 40 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(5-(tetrahydrothiopyran-4-yl-amino)pyrazin-2-yl)-naphthalen-1-yl]-urea;

- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(methylcarbonylamino)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-4-carbonyl)phenyl)-naphthalen-1-yl]-urea;
- 1-[3-tert-butyl-1'-(3-methylsulfanylpropyl)-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 10 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-carbonyl)pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-methyl)pyrazin-2-yl)-naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-aminopyridin-3-yl)naphthalen-1-yl]-urea;
- 20 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-methylpiperdin-4-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(2-methyl-3-oxo-piperzin-1-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 25 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-carbonyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(N,N-di-(2-methoxyethyl)aminomethyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 30 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(tetrahydropyran-4-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;
- 35 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(5-(morpholin-4-yl-methyl)pyrazin-2-yl)naphthalen-1-yl]-urea;
- 40 1-[5-tert-butyl-2-(2-methylthiopyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;

- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(2-methyl-3-oxo-piperzin-1-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-oxy)pyridin-3-yl)naphthalen-1-yl]-urea
1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;
- 10 1-[5-tert-butyl-2-(2-methoxypyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(5-carbamylpyridin-3-yl)naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-(2-aminopyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(4-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;
- 20 1-[3-tert-butyl-1'-methyl-1'H-[1,4']bipyrazol-5-yl]-3-[4-(6-(morpholin-4-yl-methyl)phenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(2-cyclopropylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(6-(morpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 25 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(pyridin-3-yl-amino)pyrimidin-5-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-tetrahydrothiopyran-4-yl-amino)pyridin-3-yl)naphthalen-1-yl]-urea;
- 30 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 35 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-benzyl-3H-imidazo[4,5-b]pyridin-6-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-(6-methyl-pyridin-3-yl)-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 40 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-carbonyl)pyrimidin-5-yl)naphthalen-1-yl]-urea;

- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-methyl)pyrimidin-5-yl)naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(3-amino-4-carbamylphenyl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(1-oxo-thiomorpholin-4-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 10 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(pyridin-3-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(6-(hydroxy-pyridin-3-yl-methyl)pyridin-3-yl)naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-(2-methylpyrimidin-5-yl)-2H-pyrazol-3-yl]-3-[4-(2-(morpholin-4-yl-methyl)pyrimidin-5-yl)naphthalen-1-yl]-urea;
- 20 1-(3-Cyano-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(3-Fluoro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-(4-Chloro-2-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 30 1-(3,4-Dimethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 35 1-(3-Iodo-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-m-tolyl-urea;
- 1-(4-Methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 40 1-(3-Chloro-4-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 1-(4-Chloro-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 1-(2,5-Dichloro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-naphthalen-2-yl-urea;
- 10 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-phenyl-urea;
- 1-(3-Chloro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 15 1-(4-Chloro-3-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(2,4,6-trichloro-phenyl)-urea;
- 20 1-(2-Methyl-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-(4-Methyl-2-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(2,3-Dichloro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 30 1-(2-Methoxy-5-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(2-Chloro-6-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 35 1-(2,4-Dichloro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 40 1-(4-Methyl-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 1-(2,4-Dimethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 1-(2,3-Dimethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(4-Cyano-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 10 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3,4,5-trimethoxy-phenyl)-urea;
- 1-Biphenyl-4-yl-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 15 1-(2,5-Difluoro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(3-Chloro-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 20 1-(2-Fluoro-3-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(4-Benzoyloxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-(2-Methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(2-Fluoro-6-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 30 1-(4-Fluoro-3-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 35 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(2,4,5-trimethyl-phenyl)-urea;
- 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethyl-phenyl)-urea;
- 40 1-(3-Methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 1-(2-Methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(4-Methoxy-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 10 1-(2-Fluoro-5-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(4-Ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 15 1-(2,5-Dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 20 1-(4,5-Dimethyl-2-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(5-Chloro-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 25 1-(2-Isopropyl-6-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(2-Difluoromethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 30 1-(4-Isopropyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(4-Methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 35 1-(3-Ethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 40 1-(2-Ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea

- 1-(4-Butoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 5 4-{3-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzoic acid ethyl ester
- 1-(4-Butyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 10 1-(2,6-Dibromo-4-isopropyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(3-Methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 15 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethylsulfanyl-phenyl)-urea
- 5-{3-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-isophthalic acid dimethyl ester
- 20 1-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 25 3-{3-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzoic acid ethyl ester
- 1-(5-tert-Butyl-2-hydroxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 30 1-(2-Hydroxymethyl-4-phenyl-cyclohexyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(2-Methylsulfanyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 35 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-pentyloxy-biphenyl-3-yl)-urea
- 40 4-Methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzoic acid methyl ester

- 1-(2,5-Diethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 5 1-Benzothiazol-6-yl-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- N-(2,5-Diethoxy-4-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-benzamide
- 10 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-phenoxy-phenyl)-urea
- 15 1-(5-Ethanesulfonyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 4-Methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-N-phenyl-benzamide
- 20 1-(2-Methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(2,3-Dimethyl-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 25 N-Butyl-4-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-benzenesulfonamide
- 1-[3-(2-Methyl-[1,3]dioxolan-2-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 30 1-(3-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 35 1-(2,4-Dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(2-Methyl-4-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 40 1-(2-Methoxy-4-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea

- 1-(4-Chloro-2-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 5 1-(5-Chloro-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(3,5-Dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 10 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethoxy-phenyl)-urea
- 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethylsulfanyl-phenyl)-urea
- 15 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(2-phenoxy-phenyl)-urea
- 1-(2-Methoxy-5-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 20 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(3,5-Bis-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 25 1-(2-tert-Butyl-5-methyl-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 30 1-(3-Methyl-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(3-tert-Butyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 35 1-(4-Methyl-biphenyl-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 40 1-(4-tert-Butyl-biphenyl-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea

- 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 5 1-(5-Isopropyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(5-sec-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 10 1-(5-tert-Butyl-2-methoxy-3-propyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(5-tert-Butyl-2-methoxymethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 15 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 20 1-(5-tert-Butyl-2-methyl-phenyl)-3-(4-{6-[(3-methoxy-propyl)-methyl-amino]-pyridin-3-yl})-naphthalen-1-yl)-urea
- 1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(4-morpholin-4-ylmethyl-imidazol-1-yl)-naphthalen-1-yl]-urea
- 25 1-(5-tert-Butyl-2-methyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(5-tert-Butyl-2-methyl-phenyl)-3-{4-[6-(3-methoxy-propylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea
- 30 1-(5-tert-Butyl-2-methyl-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-(5-tert-Butyl-2-morpholin-4-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 35 1-(6-tert-Butyl-2-chloro-3-methyl-pyridin-4-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 40 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethyl-phenyl)-urea

- 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(4-trifluoromethoxy-phenyl)-urea
- 5 1-[5-(1,1-Dimethyl-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-[5-tert-Butyl-2-(1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 10 1-[5-tert-Butyl-2-(2-methyl-pyrimidin-5-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-[5-tert-Butyl-2-(3-hydroxy-propyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 15 1-[5-tert-Butyl-2-(3-morpholin-4-yl-3-oxo-propyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 1-[5-tert-Butyl-2-(morpholine-4-carbonyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea
- 20 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide
- 25 1-(3-Methyl-naphthalen-2-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;
- 30 1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-hydroxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(2,3-Dimethyl-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 35 1-{5-tert-Butyl-2-methyl-3-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-phenyl}-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 40 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-(2,2-Dimethyl-propionyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-

- pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-tert-Butyl-3-(3-hydroxy-prop-1-ynyl)-2-methyl-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 1-[5-tert-Butyl-2-(3-hydroxy-prop-1-ynyl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 10 1-[5-tert-Butyl-3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 15 1-[5-tert-Butyl-3-(2,3-dihydroxy-propyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 20 1-(5-tert-Butoxy-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[5-(1-Cyano-cyclopropyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-[5-tert-Butyl-3-(2-diethylamino-ethyl)-2-methoxy-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-[1,3]dioxolan-2-yl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 30 1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(5-tert-Butyl-2-dimethylamino-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 35 1-(5-tert-Butyl-2-propoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-hydroxymethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 40 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 1-(5-Cyclohexyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;

- 1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 1-(5-tert-Butyl-2-methoxy-3-nitro-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-methyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 10 N-Acetyl-N-(5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-acetamide;
- 15 1-(6-tert-Butyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(5-tert-Butyl-2-ethoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 20 1-(5-tert-Butyl-2-isopropoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(5-tert-Butyl-2-imidazol-1-yl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-(5-tert-Butyl-3-ethylamino-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 30 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-bis(methanesulfon)amide;
- 1-[5-tert-Butyl-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 35 1-(2-Methanesulfinyl-5-trifluoromethyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-[4-(6-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;
- 40 N-[1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-pyrrolidin-3-yl]-acetamide;

- 1-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 5 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-propionamide;
- 1-(5-tert-Butyl-2-methyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 10 1-[4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-3-(3-trifluoromethanesulfonyl-phenyl)-urea;
- N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-isobutyramide;
- 15 2-(4-tert-Butyl-2-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenoxy)-acetamide;
- 1-(5-tert-Butyl-2-oxo-2,3-dihydro-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 20 1-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(5-tert-Butyl-benzooxazol-7-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-benzenesulfonamide;
- 30 Ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-ylmethyl-pyrimidin-5-yl)-naphthalen-1-yl]-urea;
- 35 1-(5-tert-Butyl-2-methylsulfanyl-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 40 1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 2,2,2-Trifluoro-ethanesulfonic acid (5-tert-butyl-2-methoxy-3-{3-[4-(6-morpholin-4-

- ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-amide;
- N-(5-{4-[3-(5-tert-Butyl-2-methyl-phenyl)-ureido]-naphthalen-1-yl}-pyrazin-2-yl)-methanesulfonamide;
- 5 1-[4-(6-{[Bis-(2-cyano-ethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-phenyl)-urea;
- 10 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-thiomorpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 15 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-piperidin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-tetrahydro-thiopyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(tetrahydro-pyran-4-ylamino)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-{[(2-cyano-ethyl)-(tetrahydro-furan-2-ylmethyl)-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methoxymethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 30 1-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-ylmethyl)-piperidine-3-carboxylic acid amide;
- 35 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(1-oxo-114-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 1-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 40 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;

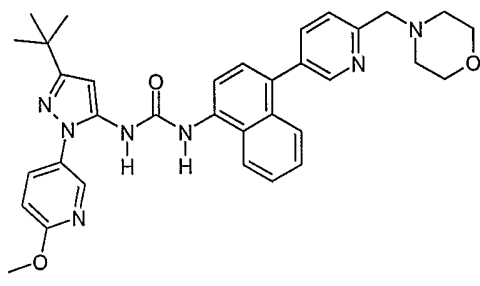
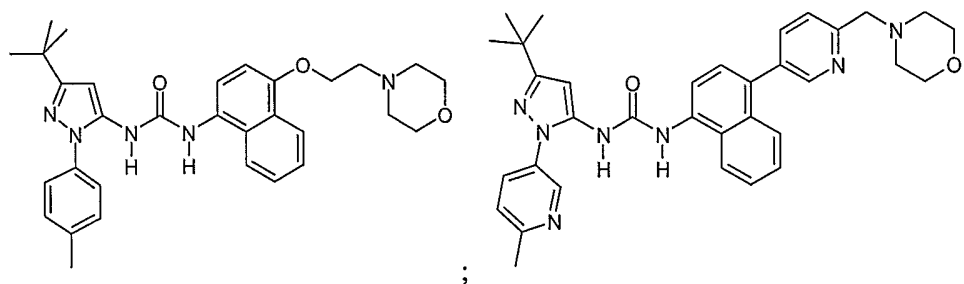
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[(tetrahydro-furan-3-ylamino)-methyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;
- 5 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(6-{[(2-cyano-ethyl)-pyridin-3-ylmethyl-amino]-methyl}-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 10 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(2,6-dimethyl-morpholin-4-ylmethyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-(4-{6-[4-(3-methoxy-phenyl)-piperazin-1-ylmethyl]-pyridin-3-yl}-naphthalen-1-yl)-urea;
- 15 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(morpholine-4-carbonyl)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 20 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(5-morpholin-4-ylmethyl-pyrazin-2-yl)-naphthalen-1-yl]-urea;
- 1-(6-tert-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- 25 1-(3-Amino-5-tert-butyl-2-methoxy-phenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-urea;
- N-(5-{4-[3-(5-tert-Butyl-2-methoxy-phenyl)-ureido]-naphthalen-1-yl}-pyridin-2-yl)-acetamide;
- 30 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-N-methyl-acetamide;
- 35 N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-2,2,2-trifluoro-acetamide;
- 1-(5-tert-Butyl-2-methoxy-phenyl)-3-{4-[6-(pyridin-3-yloxy)-pyridin-3-yl]-naphthalen-1-yl}-urea;
- 40 [4-(6-Morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-carbamic acid 3-tert-butyl-phenyl ester and

N-(5-tert-Butyl-2-methoxy-3-{3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]-ureido}-phenyl)-methanesulfonamide

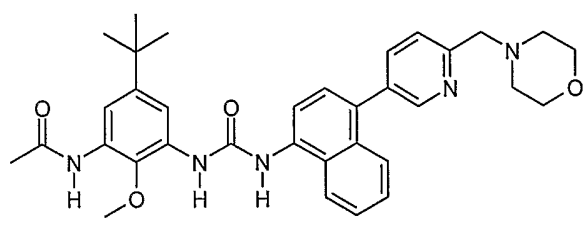
or the pharmaceutically acceptable salts thereof.

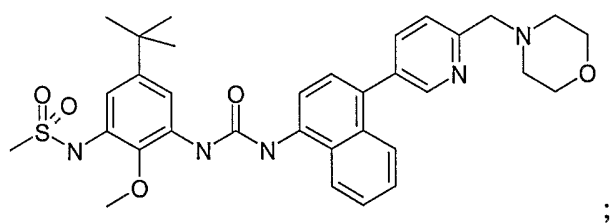
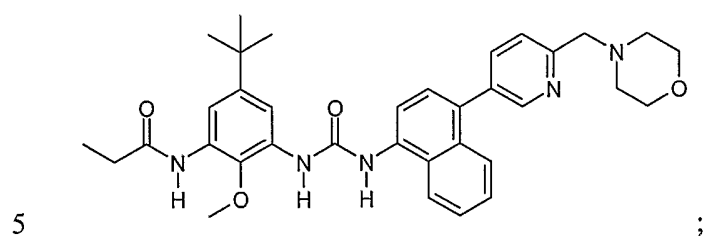
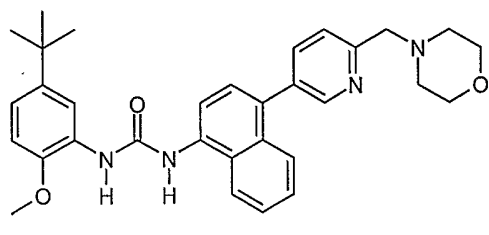
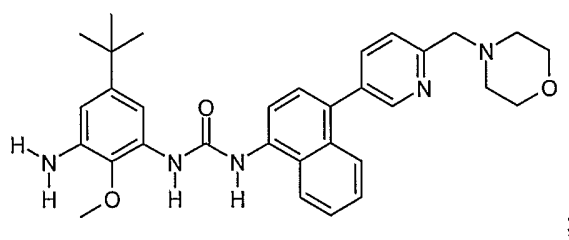
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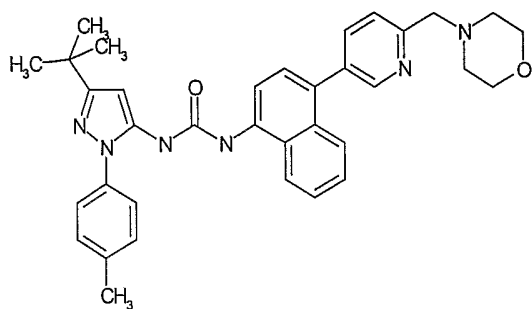
3. The method according to claim 1 where the p38 kinase inhibitor is a compound chosen from:



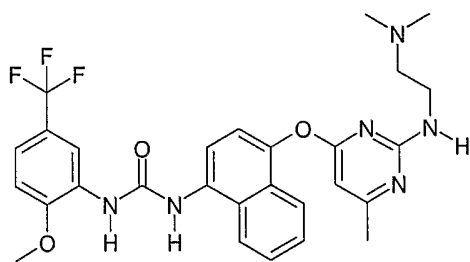
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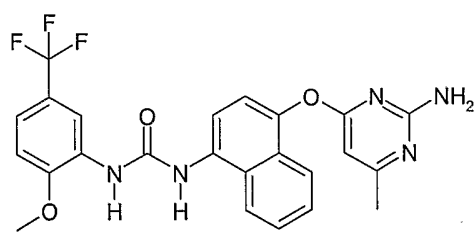




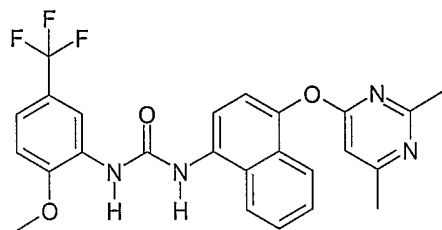
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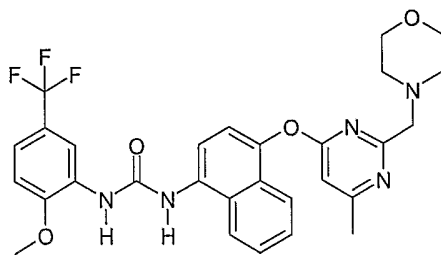
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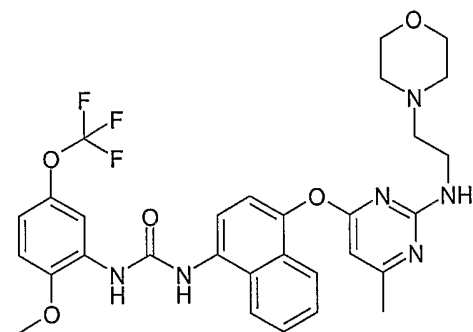
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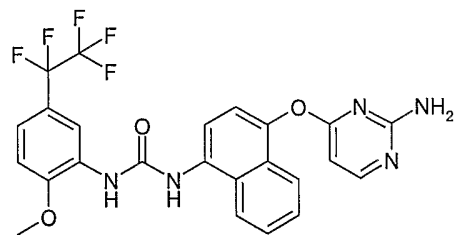


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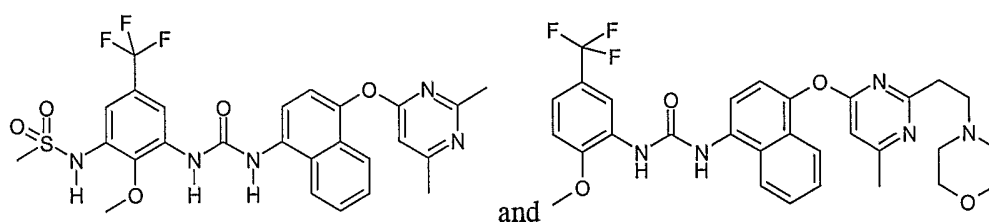


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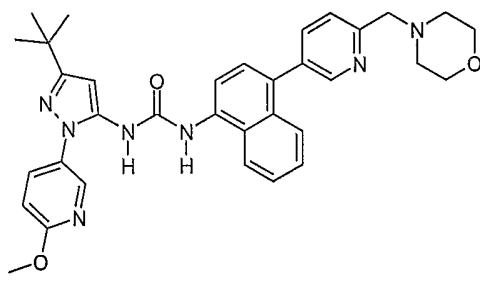
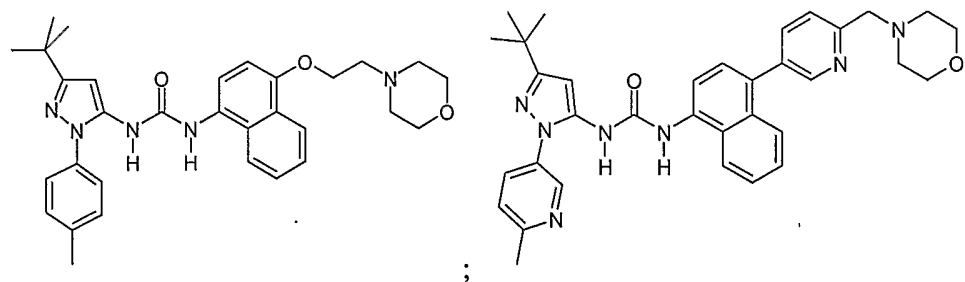
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- 5 or the pharmaceutically acceptable salts thereof.
4. The method according to any of claims 1-3 wherein active ingredient A is
ibesartan or olmesartan.
- 10 5. The method according to any of claims 1-3 wherein active ingredient A is
acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate,
diclofenac, diflunisal, etodolac, fenoprofen calcium, flurbiprofen, indomethacin,
ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate,
meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate,
15 sulindac, tolmetin, meloxicam, rofecoxib, celecoxib, etoricoxib, valdecoxib,
nabumetone, naproxen, lornoxicam, nimesulide, remifenzone, salsalate, tiaprofenic
acid or flosulide.
6. The method according to any of claims 1-3 wherein active ingredient A is
20 Fluticasone propionate, Salmeterol xinafoate, Budesonide, Triamcinolone acetonide
or Formoterol fumarate.
7. A method of treating COPD or pulmonary hypertension comprising
25 administering to a patient a therapeutically effective amount of one or more active

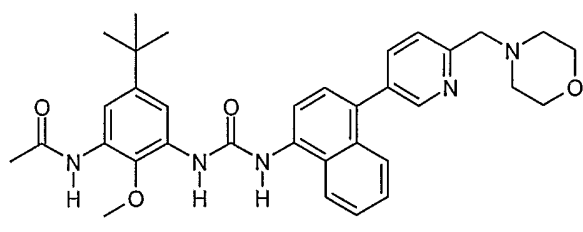
ingredients **A** together with a therapeutically effective amount of one or more p38 kinase inhibitors;
 wherein the active ingredients **A** is chosen from ipratropium bromide and salbutamol.

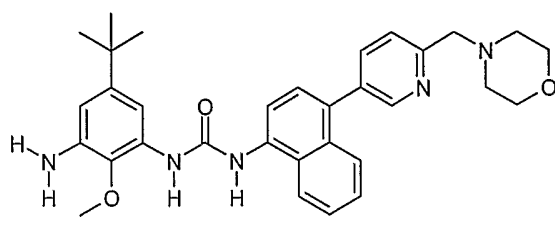
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8. The method according to claim 7 where the p38 kinase inhibitor is a compound chosen from:

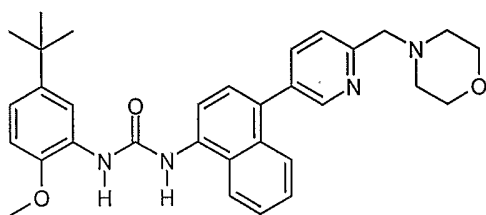


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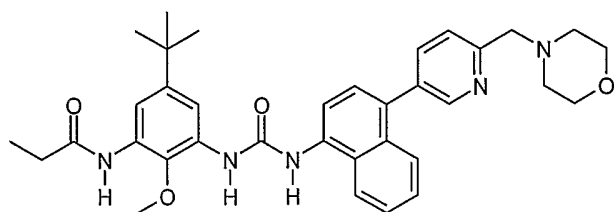




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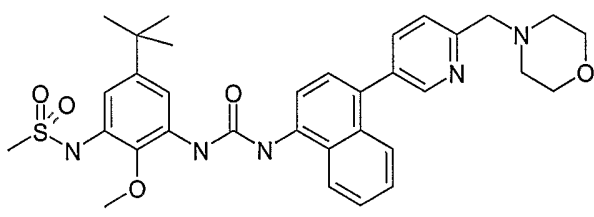


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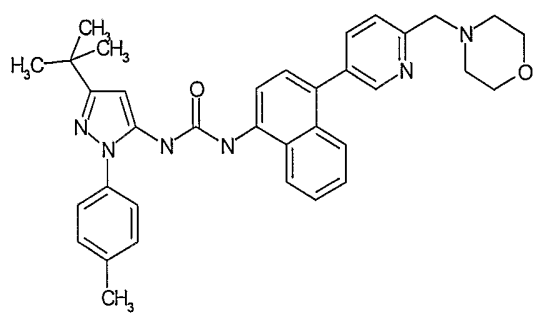


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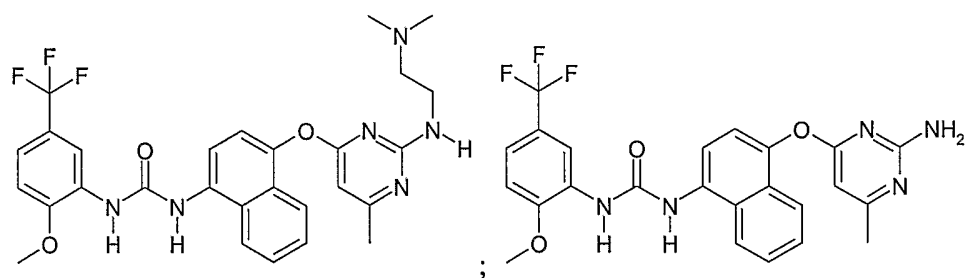
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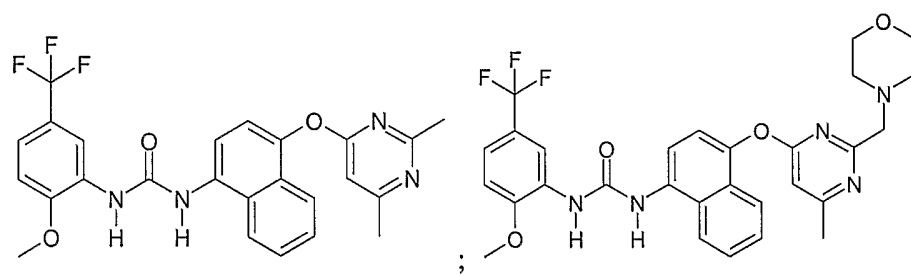


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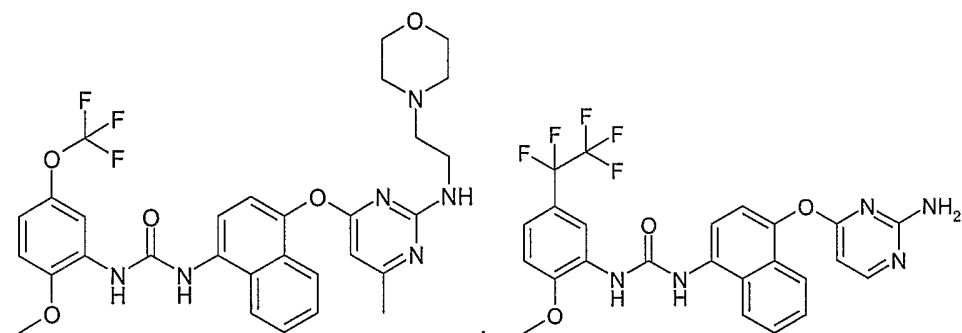
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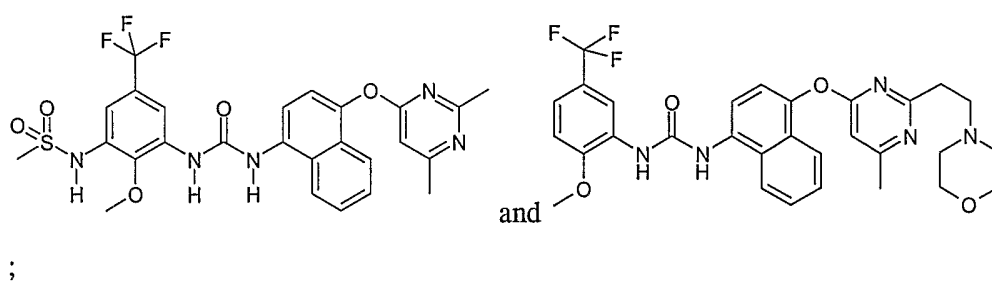
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5 or the pharmaceutically acceptable salts thereof.