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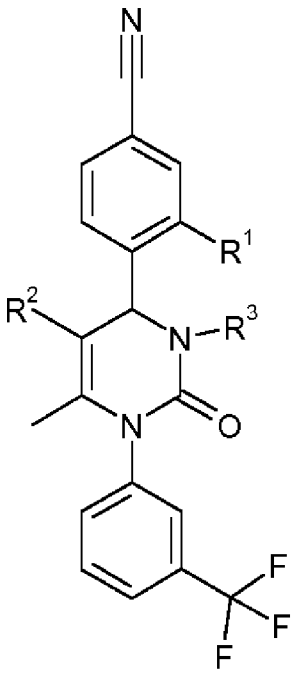
(54) Title: SUBSTITUTED DIHYDROPYRIMIDINONES AND THEIR USE AS INHIBITORS OF NEUTROPHIL ELASTASE ACTIVITY



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(57) Abstract: This invention relates to substituted dihydropyrimidinones of formula 1 and their use as inhibitors of neutrophil elastase activity, pharmaceutical compositions containing the same, and methods of using the same as agents for treatment and/or prevention of pulmonary, gastrointestinal and genitourinary diseases, inflammatory diseases of the skin and the eye and other autoimmune and allergic disorders, allograft rejection, and oncological diseases.

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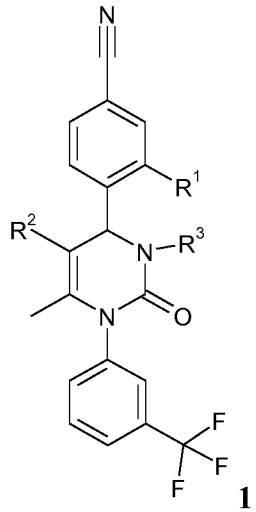
SUBSTITUTED DIHYDROPYRIMIDINONES AND THEIR USE AS INHIBITORS OF NEUTROPHIL ELASTASE ACTIVITY

This invention relates to substituted dihydropyrimidinones of formula **1**



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and their use as inhibitors of neutrophil elastase activity, pharmaceutical compositions containing the same, and methods of using the same as agents for treatment and/or prevention of pulmonary, gastrointestinal and genitourinary diseases, inflammatory diseases of the skin and the eye and other autoimmune and allergic disorders, allograft rejection, and oncological diseases.

BACKGROUND INFORMATION

- The following references describe neutrophil elastase inhibitors with a monocyclic dihydro-pyrimidinone core: GB2392910, WO04024700, WO05082864, WO05082863, DE102006031314, US100010024, WO10115548, WO09080199, DE102007061766, WO06136857, WO06082412, WO12002502.
- The following references describe neutrophil elastase inhibitors with a bicyclic tetra-hydropyrrolopyrimidinedione core: WO07129060, WO08135537, US090093477, WO09013444, WO09060206, WO09060203, WO09060158, US110034433.

- The following references describe neutrophil elastase inhibitors with core structures other than those herein before mentioned: WO04020412, WO04020410, WO03053930, WO10078953, WO09135599, DE102009004197, WO11110858, WO11110859, WO09060158, WO09037413, WO04024701, US130065913, WO13018804, WO12002502, WO2014029831,. WO2014029832 and WO2014029830.
- For a review on various inhibitors of neutrophil elastase see: P. Sjö (*Future Med. Chem.* **2012**, *4*, 651-660).

BRIEF SUMMARY OF THE INVENTION

Neutrophil elastase (NE) is a 29 kDa serine protease. It is expressed in bone marrow precursor cells, stored in the granula of peripheral blood granulocytes at high concentrations and it is released upon cellular activation. To the substrates of NE belong major elements of the extracellular matrix: elastin, fibronectin, laminin, collagen and proteoglycans. Neutrophil elastase activity leads to ECM degradation, increases migration and chemotaxis of monocytes and vascular smooth muscle cells and directly affects components of the coagulation and fibrinolytic pathways (PAI-1 and TFPI). Increased activity of neutrophil elastase is associated with chronic inflammatory and fibrotic diseases of several organs. The potential of neutrophil elastase inhibitors as anti-inflammatory therapies has been reviewed by P. A. Henriksen in *Current Opinion in Hematology* 2014, *21*, 23-28. Inhibitors of neutrophil elastase will therefore have an important role for the treatment of different diseases like COPD, idiopathic pulmonary fibrosis and other fibrotic diseases, cancer, acute lung injury, acute respiratory distress syndrome, bronchiectasis, cystic fibrosis, alpha1-antitrypsin deficiency and others.

The problem of the present invention is to prepare new compounds which on the basis of their pharmaceutical effectiveness as inhibitors of neutrophil elastase activity, may be used therapeutically, that is for the treatment of pathophysiological processes caused by increased activity of neutrophil elastase.

It has surprisingly been found that the compounds of the present invention have the following properties which are advantageous in view of the indications of the current invention.

The compounds according to the present invention, including the physiologically acceptable salts, are effective as inhibitors of neutrophil elastase and exhibit favourable inhibitory potency, as determined by the half maximal inhibitory concentration (IC_{50}), in an enzymatic inhibition assay.

Some compounds according to the present invention, including the physiologically acceptable salts, are additionally effective as inhibitors of neutrophil serin protease proteinase 3 and exhibit favourable inhibitory potency, as determined by the half maximal inhibitory concentration (IC_{50}), in an enzymatic inhibition assay. This inhibitory activity on a second neutrophil serin protease may be benificial for pharmacological efficacy.

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable inhibitory potency, as determined by the half maximal effective concentration (EC_{50}), in a plasma or whole-blood assay, for instance as described in T. Stevens et al. (*J. Pharm. Exp. Ther.* **2011**, *339*, 313-320).

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable in vivo potency, as determined, for example, by the half maximal effective dose (ED_{50}), in models of human neutrophil elastase-induced lung injury in mouse or rat, for instance as described in Tremblay et al. (*Chest* **2002**, *121*, 582-588) or T. Stevens et al. (*J. Pharm. Exp. Ther.* **2011**, *339*, 313-320).

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable metabolic stability in an in vitro microsomal assay for metabolic stability as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, **2008**), chapter 29 and references therein.

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable metabolic stability in an in vitro hepatocytes assay for metabolic stability as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, **2008**), chapter 29 and references therein.

An improved metabolic stability in an in vitro test system is expected to translate into a reduced in vivo clearance (CL), because the metabolic conversion in the liver is reduced. Based on the pharmacokinetic equation CL/F_{oral} = Dose / AUC (F_{oral}: oral bioavailability, AUC: area under the curve), a reduced in vivo clearance is expected to lead to higher dose-normalized systemic exposure (AUC) of the drug.

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable permeability in an in vitro Caco-2 cell layer method for permeability as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, **2008**), chapter 26 and references therein. For an oral drug, improved permeability is expected to translate into a higher fraction of the drug absorbed in the intestinal tract, thus, resulting in higher dose-normalized systemic exposure (AUC).

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit a favourable, that is low efflux ratio (permeability in the efflux direction divided by the permeability in the influx direction) in an in vitro Caco-2 or MDCK cell layer method as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, **2008**), chapter 26 and 27 and references therein. For an oral drug, an improved, that is reduced efflux ratio is expected to translate into a higher fraction of the drug absorbed in the intestinal tract, thus, resulting in higher dose-normalized systemic exposure (AUC).

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable aqueous solubility in a kinetic or thermodynamic solubility method as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, **2008**), chapter 25 and references therein. For an oral drug, improved aqueous solubility is expected to translate into a higher fraction of the drug absorbed in the intestinal tract resulting in higher dose-normalized systemic exposure (AUC) and/or oral bioavailability (F_{oral}) and/or peak plasma concentration after administration (C_{max}) . Furthermore, improved aqueous solubility is expected to reduce development challenges, such as expensive formulations, increased development time, high drug load.

Comparatively higher dose-normalized systemic exposure (AUC) can be advantageous in several ways: (1) If a certain systemic exposure (AUC) needs to be achieved for efficacy, the drug can be dosed in a lower amount. Lower dosages have the advantages of lower drug load (parent drug and metabolites thereof) for the patient causing potentially less side effects, and lower production costs for the drug product. (2) Comparatively higher dose-normalized systemic exposure (AUC) can lead to increased efficacy or prolonged duration of action of the drug when the same dose is applied.

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable metabolic stability, favourable permeability and favourable aqueous solubility. Accordingly, some compounds of the present invention are expected to exhibit favourable pharmacokinetic (PK) properties after oral dosing, in particular favourable systemic exposure (area under the curve, AUC), thus, leading to favourable efficacy in vivo.

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable pharmacokinetic (PK) properties. The PK properties can be determined in pre-clinical animal species, for example mouse, rat, hamster, dog, guinea pig, mini pig, cynomolgus monkey, rhesus monkey. The PK properties of a compound can be described, for example, by the following parameters: Mean residence

time (MRT), elimination half-live ($t_{1/2}$), volume-of-distribution (V_D), area under the curve (AUC), clearance (CL) and bioavailability after oral administration (F_{oral}), peak plasma concentration after administration (C_{max}), time to reach Cmax (T_{max}).

Some compounds according to the present invention and metabolites thereof are devoid of the hydrazine substructure that causes structural alerts for mutagenicity and carcinogenicity as described in Benigni et al. (*Chem. Rev.* **2011**, *11*, 2507-2536). Thus, compounds of the invention may bear the advantage of reduced genotoxic potential.

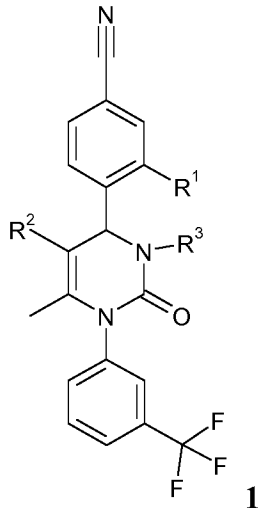
Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable inhibition of cytochrome P450 (CYP) isozymes in corresponding in vitro assays for CYP isozyme inhibition as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, **2008**), chapter 32 and references therein. Reduced inhibition of CYP isozymes is expected to translate into a reduced risk for undesirable drug-drug interactions which is the interference of one drug with the normal metabolic or pharmaco-kinetic behaviour of a co-administered drug.

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable, that is low, CYP induction potential. Cytochrome P450 (CYP) induction can affect the pharmacokinetics of a drug molecule upon multiple dosing, which can result in pharmacokinetic drug-drug interactions with co-administered drugs. CYP induction can lead to decreased exposure of the inducing compound (e.g. autoinduction) or decreased exposure of a co-administered compound metabolized by the induced enzyme. CYP induction can also lead to an increase in the metabolism of a drug causing changes in pharmacological (active metabolite) and toxicological (toxic metabolite) outcomes. The primary mechanism by which drugs cause enzyme induction is by the activation of gene transcription. The nuclear receptor that are most commonly involved in the activation of transcription of drug-metabolizing enzyme CYP3A4 and transporters is the pregnane X receptor (PXR).

Some compounds according to the present invention, including the physiologically acceptable salts, exhibit favourable, that is low, inhibition of the hERG channel in a patch clamp assay as described in E. Kerns & L. Di (*Drug-like properties: concepts, structure design and methods: from ADME to toxicity optimization*, Elsevier, 1st ed, **2008**), chapter 34 and references cited therein.

DETAILED DESCRIPTION OF THE INVENTION

1. A compound of formula **1**



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wherein

R^1 is selected from the group consisting of

$-CO-R^{1.1}$, $-CONH-R^{1.2}$, $R^{1.10}$,

$-CO-NH_2$, $-COOH$, $-CON(CH_3)_2$, $-CONH-C(CH_3)_2-CN$,

$-CONH-C_{1-3}$-alkyl, $-CONH-CH_2-R^{1.7}$, $-CONH-CH_2CH_2-R^{1.3}$,

$-CONH-CH_2CH_2CH_2-R^{1.5}$,

$-CONH-CH(CH_3)R^{1.9}$, $-CON(CH_3)-CH_2-R^{1.6}$, $-CON(CH_3)-CH_2CH_2-R^{1.4}$ and

$-CON(CH_3)-CH_2CH_2CH_2-R^{1.8}$,

$R^{1.1}$ denotes a 4-to 10-membered heterocyclic or 5-to 10-membered N-containing heteroaryl ring, containing one to four heteroatoms independently selected from among N, O and S, each of the rings optionally substituted with a group independently selected from among morpholinyl, -$NHCOCH_3$, $N(CH_3)COCH_3$, $-COCH_3$, -OH, $-NH_2$,$-N(CH_3)_2$ and C_{1-3} alkyl $-N(CH_3)_2$, cyclopropyl and $-CH(CH_3)_2$,
wherein the N-atom of each ring is bound to the core structure;

$R^{1.2}$ denotes a C_{3-6}-cycloalkyl or
a 4-to 10-membered heterocyclic ring containing one to four heteroatoms independently selected from among N, O and S, each of the rings optionally substituted with one or two C_{1-3} alkyl, $-NH_2$, -OH, -CN or =O,

$R^{1.3}$, $R^{1.4}$, $R^{1.5}$ independently from each other are selected from the group consisting of morpholinyl, F, $-N(CH_3)_2$, $-SO_2CH_3$, $-OCH_3$, , -OH and CH_3,

$R^{1.6}$, $R^{1.7}$ independently from each other denote a group selected from among -CO-morpholinyl, $-C(CH_3)_2CN$, $-C(CH_3)_2$-OH, $-CF_3$, -CN, CHF_2 and -CH≡CH,
or
a 4-to 10-membered aromatic or 5-to 10-membered heteroaryl ring, containing one to four heteroatoms independently selected from among N, O and S, each of the rings optionally substituted with C_{1-3} alkyl or CN,

$R^{1.8}$ $-OCH_3$,

$R^{1.9}$ denotes furanyl,

$R^{1.10}$ denotes a 4-to 10-membered heterocyclic or 5-to 10-membered heteroaryl ring, containing one to four heteroatoms independently selected from among N, O and S, each of the rings substituted with $R^{1.11}$and $R^{1.12}$.

$R^{1.11}$, $R^{1.12}$ are independently selected from among hydrogen, =O, C_{1-4}-alkyl ,and -COO-C_{1-4}-alkyl, C_{1-3}-cycloalkyl, OH, -O-C_{1-3}-alkyl, -O-C_{1-3}-cycloalkyl, -CN, halogen, -CO-C_{1-3}-alkyl, -CO-C_{1-3}-cycloalkyl and -$N(CH_3)_2$,

R^2 is selected from the group consisting of -$COCH_3$ and -$COOCH_2CH_3$,

R^3 is selected from the group consisting of H, $R^{3.1}$, $R^{3.1}$-CO-, $R^{3.1}$-O-CO-, $R^{3.1}SO_2$- and $R^{3.1}R^{3.2}$N-CO-,

$R^{3.1}$ is selected from the group consisting of H, -C_{1-4} alkyl, -C_{3-6} cycloalkyl, -C_{1-4}-haloalkyl and -C_{3-6}-halocycloalkyl,
each optionally substituted with one substituent independently selected from the group consisting of OH, CN and NH_2,

$R^{3.2}$ is selected from the group consisting of H and Me,

or optical and geometrical isomers, solvates, hydrates or salts, preferably pharmaceutically acceptable salts, thereof.

USED TERMS AND DEFINITIONS

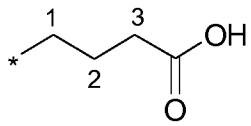
Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or radical having 1 to 6 carbon atoms.

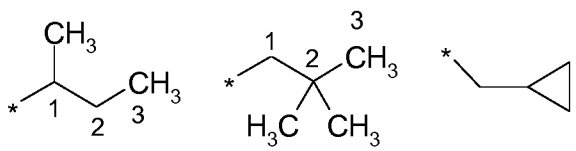
In general in single groups like HO, H_2N, S(O), $S(O)_2$, NC (cyano), HOOC, F_3C or the like, the skilled artisan can see the radical attachment point(s) to the molecule from the free valences of the group itself. For combined groups comprising two or more subgroups, the first or last named subgroup, where the free valence is indicated, is the radical attachment point, for example, the substituent "aryl-C_{1-3}-alkyl-" means an aryl group which is bound to a C_{1-3}-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail. An asterisk or a broken line may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

For example, the term "3-carboxypropyl-group" represents the following substituent:



wherein the carboxy group is attached to the third carbon atom of the propyl group. The terms "1-methylpropyl-", "2,2-dimethylpropyl-" or "cyclopropylmethyl-" group represent the following groups:



The asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

Many of the followings terms may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

The term "substituted" as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound.

The expressions "prevention", "prophylaxis", "prophylactic treatment" or "preventive treatment" used herein should be understood synonymous and in the sense that the risk to develop a condition mentioned hereinbefore is reduced, especially in a patient having elevated risk for said conditions or a corresponding anamnesis, e.g. elevated risk of developing metabolic disorder such as diabetes or obesity or another disorder mentioned herein. Thus the expression "prevention of a disease" as used herein means the management and care of an individual at risk of developing the disease prior to the clinical onset of the disease. The purpose of prevention is to combat the development of the disease, condition or disorder, and includes the administration of the active compounds to prevent or delay the onset of the symptoms or complications and to prevent or delay the development of related diseases, conditions or disorders. Success of said preventive treatment is reflected statistically by reduced incidence of said condition within a patient population at risk for this condition in comparison to an equivalent patient population without preventive treatment.

The expression "treatment" or "therapy" means therapeutic treatment of patients having already developed one or more of said conditions in manifest, acute or chronic form, including symptomatic treatment in order to relieve symptoms of the specific indication or causal treatment in order to reverse or partially reverse the condition or to delay the

progression of the indication as far as this may be possible, depending on the condition and the severity thereof. Thus the expression "treatment of a disease" as used herein means the management and care of a patient having developed the disease, condition or disorder. The purpose of treatment is to combat the disease, condition or disorder. Treatment includes the administration of the active compounds to eliminate or control the disease, condition or disorder as well as to alleviate the symptoms or complications associated with the disease, condition or disorder.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc…) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

All isomeric forms (especially all stereoisomeric forms, e.g. all chiral, enantiomeric, diastereomeric and racemic forms, all tautomeric and all geometric isomeric forms) of a compound of the present invention are intended with this invention, unless the specific isomer is specifically indicated. Obviously, the isomer which is pharmacologically more potent and/or more efficacious is preferred.

It will be appreciated that the compounds of the present invention contain at least one asymmetrically substituted carbon atom, and may therefore be isolated as pure enantiomers or as a racemic or non-racemic mixture of both enantiomers. It will be appreciated that some of the compounds of the present invention contain more than one stereogenic center, that is more than one asymmetrically substituted carbon or sulfur atom, and may therefore be isolated as pure diastereomers or as diastereomeric mixtures, both in optically active or racemic forms.

The invention contemplates all conceivable stereoisomers, particularly the diastereomers and enantiomers mentioned herein, e.g. in substantially pure form, in enriched form (e.g. substantially free of any or all other undesired enantiomers and/or diastereomers and/or in any mixing ratio, including the racemic forms, as well as the salts thereof.

In general, substantially pure stereoisomers can be obtained according to synthetic principles known to a person skilled in the field, e.g. by separation of corresponding mixtures, by using stereochemically pure starting materials and/or by stereoselective synthesis. It is known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, e.g. starting from optically active starting materials and/or by using chiral reagents.

Enantiomerically pure compounds of this invention or intermediates may be prepared via asymmetric synthesis, for example by preparation and subsequent separation of appropriate diastereomeric compounds or intermediates which can be separated by known methods (e.g. by chromatographic separation or crystallization) and/or by using chiral reagents, such as chiral starting materials, chiral catalysts or chiral auxiliaries.

Further, it is known to the person skilled in the art how to prepare enantiomerically pure compounds from the corresponding racemic mixtures, such as by chromatographic separation of the corresponding racemic mixtures on chiral stationary phases; or by resolution of a racemic mixture using an appropriate resolving agent, e.g. by means of diastereomeric salt formation of the racemic compound with optically active acids or bases, subsequent resolution of the salts and release of the desired compound from the salt; or by derivatization of the corresponding racemic compounds with optically active chiral auxiliary reagents, subsequent diastereomer separation and removal of the chiral auxiliary group; or by kinetic resolution of a racemate (e.g. by enzymatic resolution); by enantioselective crystallization from a conglomerate of enantiomorphous crystals under suitable conditions; or by (fractional) crystallization from a suitable solvent in the presence of an optically active chiral auxiliary.

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

As used herein the term "prodrug" refers to (i) an inactive form of a drug that exerts its effects after metabolic processes within the body converting it to a usable or active form, or (ii) a substance that gives rise to a pharmacologically active metabolite, although not itself active (that is an inactive precursor).

The terms "prodrug" or "prodrug derivative" mean a covalently-bonded derivative, carrier or precursor of the parent compound or active drug substance which undergoes at least some biotransformation prior to exhibiting its pharmacological effect(s). Such prodrugs either have metabolically cleavable or otherwise convertible groups and are rapidly transformed in vivo to yield the parent compound, for example, by hydrolysis in blood or by activation via oxidation as in case of thioether groups. Most common prodrugs include esters and amide analogs of the parent compounds. The prodrug is formulated with the objectives of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity, improved formulation (e.g., increased hydrosolubility), and/or decreased side effects (e.g., toxicity). In general, prodrugs themselves have weak or no biological activity and are stable under ordinary conditions. Prodrugs can be readily prepared from the parent compounds using methods known in the art, such as those described in A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard (eds.), Gordon & Breach, 1991, particularly Chapter 5: "Design and Applications of Prodrugs"; Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Prodrugs: Topical and Ocular Drug Delivery, K.B. Sloan (ed.), Marcel Dekker, 1998; Methods in Enzymology, K. Widder *et al.* (eds.), Vol. 42, Academic Press, 1985, particularly pp. 309-396; Burger's Medicinal Chemistry and Drug Discovery, 5th Ed., M. Wolff (ed.), John Wiley & Sons, 1995, particularly Vol. 1 and pp. 172-178 and pp. 949-982; Pro-Drugs as Novel Delivery Systems, T. Higuchi and V. Stella (eds.), Am. Chem. Soc., 1975; Bioreversible Carriers in Drug Design, E.B. Roche (ed.), Elsevier, 1987, each of which is incorporated herein by reference in their entireties.

The term "pharmaceutically acceptable prodrug" as used herein means a prodrug of a compound of the invention which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2',2"-nitrilotris-(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2.2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethane-sulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid,

lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts) also comprise a part of the invention.

The term "C_{1-n}-alkyl", wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C_{1-5}-alkyl embraces the radicals H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2-, H_3C-$CH(CH_3)$-, H_3C-CH_2-CH_2-CH_2-, H_3C-CH_2-$CH(CH_3)$-, H_3C-$CH(CH_3)$-CH_2-, H_3C-$C(CH_3)_2$-, H_3C-CH_2-CH_2-CH_2-CH_2-, H_3C-CH_2-CH_2-$CH(CH_3)$-, H_3C-CH_2-$CH(CH_3)$-CH_2-, H_3C-$CH(CH_3)$-CH_2-CH_2-, H_3C-CH_2-$C(CH_3)_2$-, H_3C-$C(CH_3)_2$-CH_2-, H_3C-$CH(CH_3)$-$CH(CH_3)$- and H_3C-CH_2-$CH(CH_2CH_3)$-.

The term "C_{1-n}-alkylene" wherein n is an integer 2 to n, either alone or in combination with another radical, denotes an acyclic, straight or branched chain divalent alkyl radical containing from 1 to n carbon atoms. For example the term C_{1-4}-alkylene includes $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-C(CH_3)_2-$, $-CH(CH_2CH_3)-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-CH_2-$, $-CH_2-CH(CH_3)-CH_2-$, $-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$, $-CH(CH_3)-CH(CH_3)-$, $-CH_2-CH(CH_2CH_3)-$, $-CH(CH_2CH_3)-CH_2-$, $-CH(CH_2CH_2CH_3)-$, $-CH(CH(CH_3))_2-$ and $-C(CH_3)(CH_2CH_3)-$.

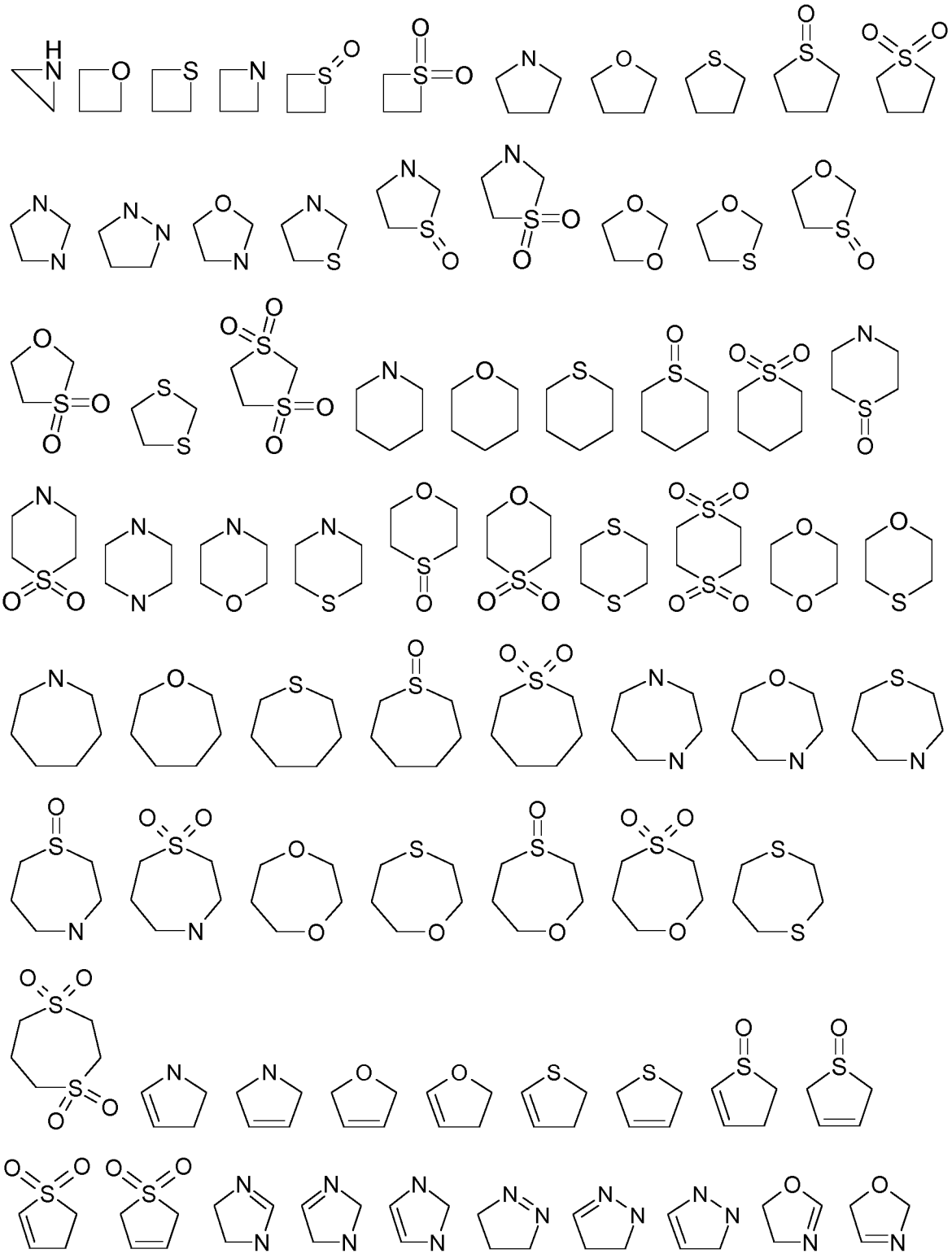
The term "C_{3-n}-cycloalkyl", wherein n is an integer from 4 to n, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C atoms. For example the term C_{3-7}-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

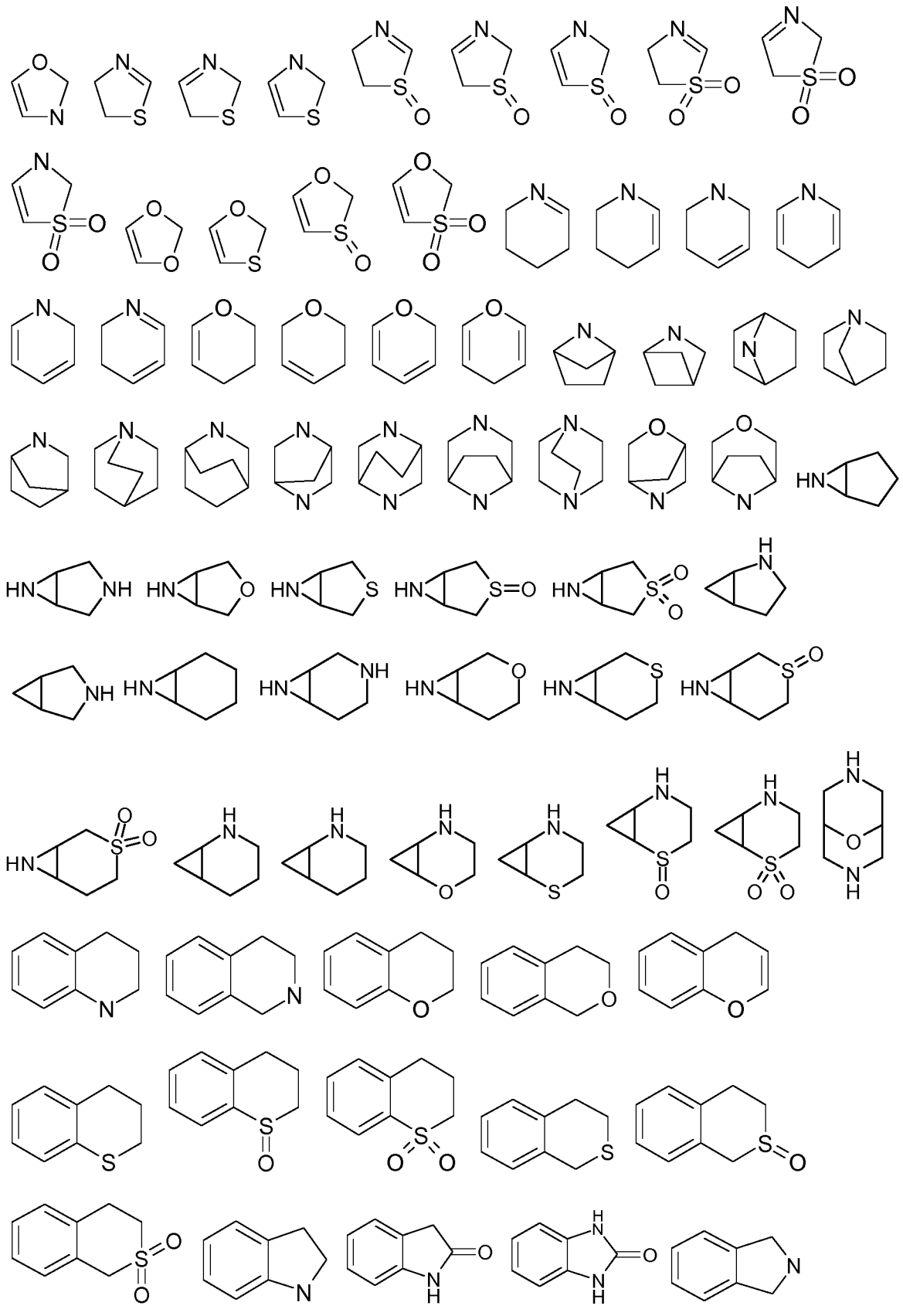
By the term "halo" added to a "alkyl", "alkylene" or "cycloalkyl" group (saturated or unsaturated) is such a alkyl or cycloalkyl group wherein one or more hydrogen atoms are replaced by a halogen atom selected from among fluorine, chlorine or bromine, preferably fluorine and chlorine, particularly preferred is fluorine. Examples include: H_2FC-, HF_2C-, F_3C-.

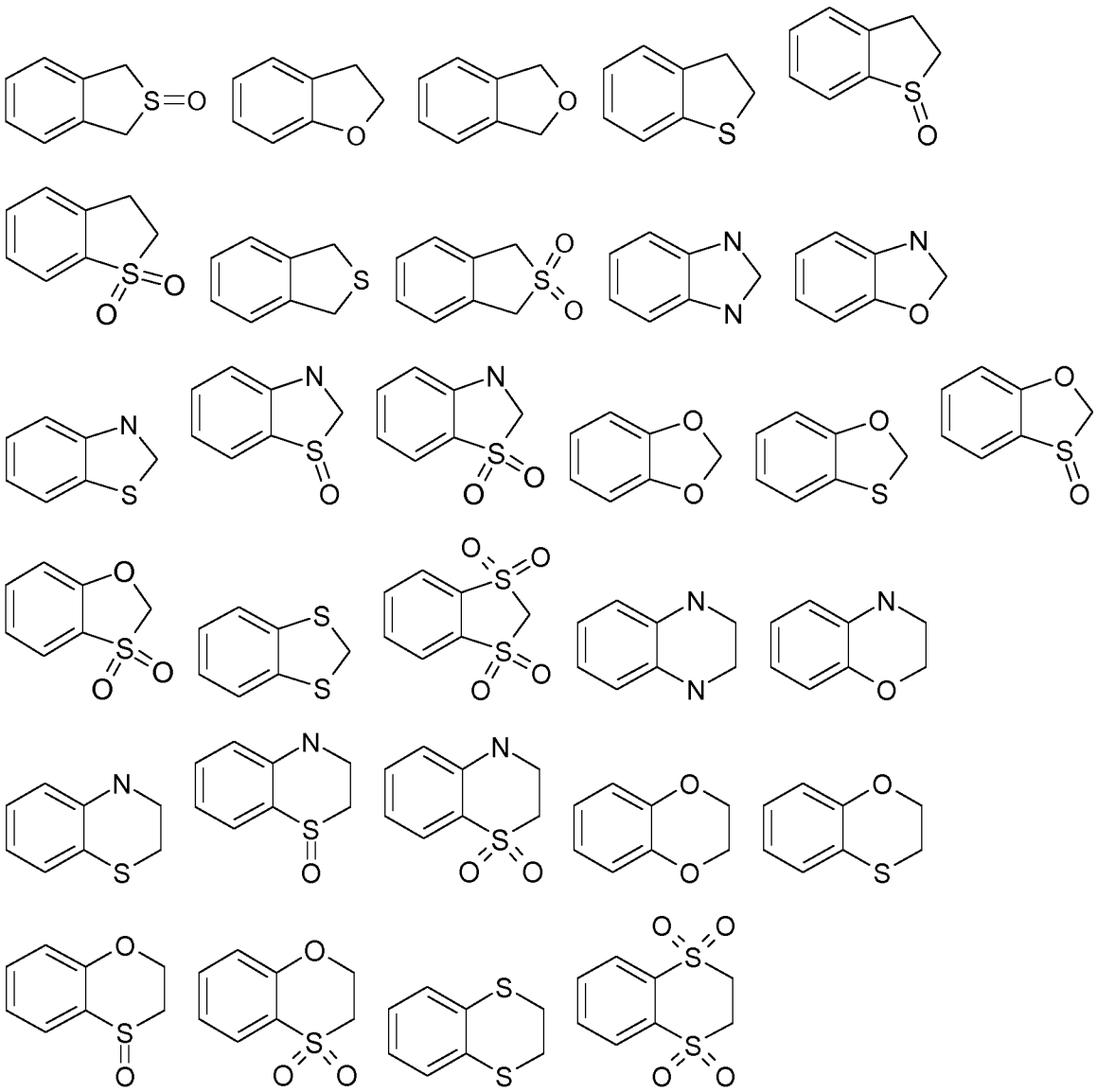
The term "aryl" as used herein, either alone or in combination with another radical, denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second five- or six-membered, carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl.

The term "heterocyclyl" means a saturated or unsaturated mono- or polycyclic-ring system including aromatic ring system containing one or more elements selected from N, O, S, S(O) or $S(O)_2$, consisting of 3 to 14 ring atoms wherein none of the heteroatoms is part of the aromatic ring. The term "heterocyclyl" is intended to include all the possible isomeric forms; thus, the term "heterocyclyl" includes the following exemplary structures which are

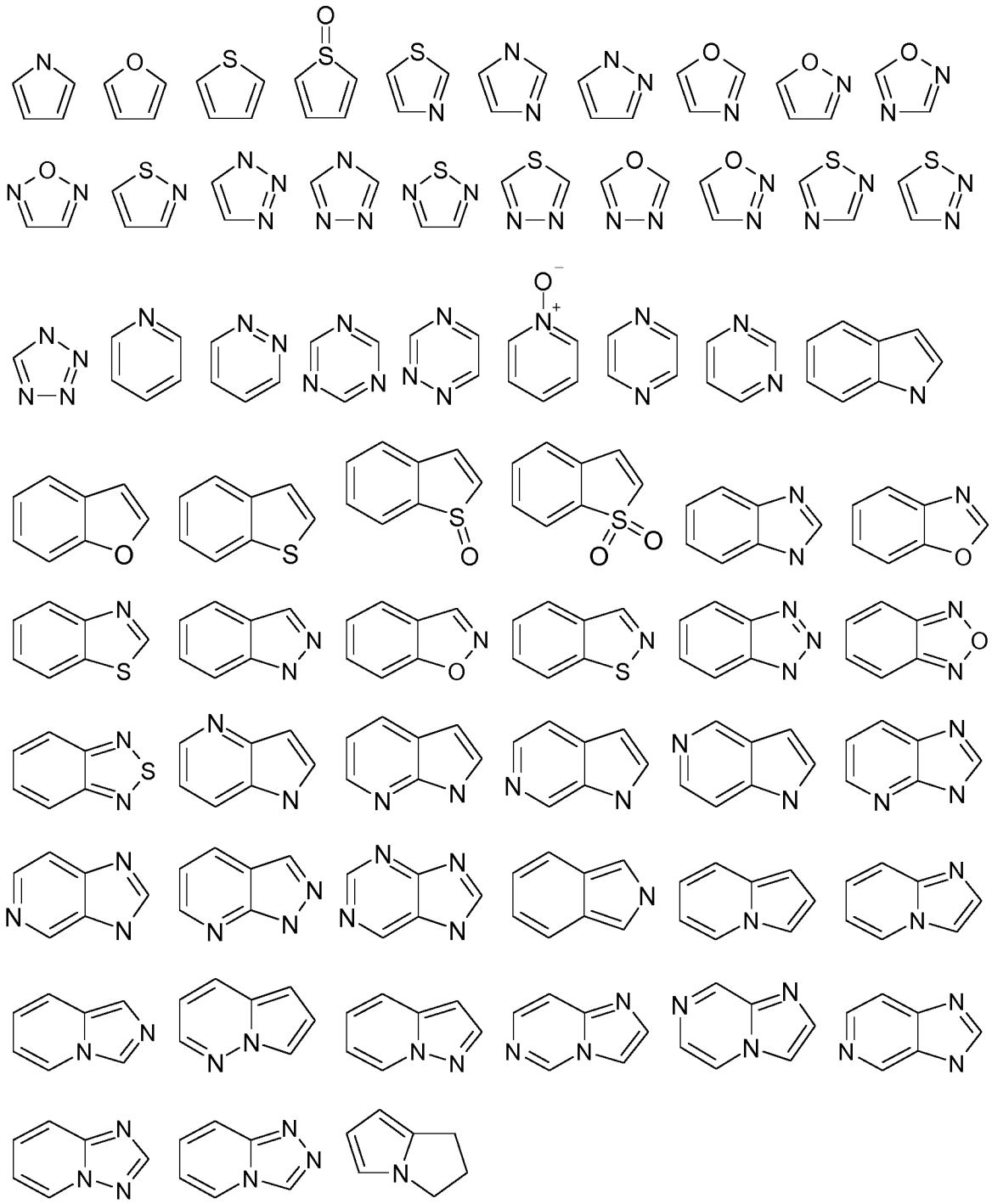
not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:







The term "heteroaryl" means a mono- or polycyclic-ring systems containing one or more elements selected from N, O, S, S(O) or $S(O)_2$, consisting of 5 to 14 ring atoms wherein at least one of the heteroatoms is part of aromatic ring. The term "heteroaryl" is intended to include all the possible isomeric forms; Thus, the term "heteroaryl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:



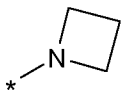
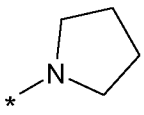
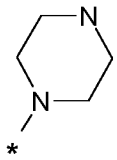
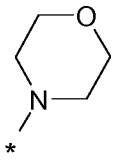
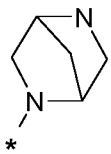
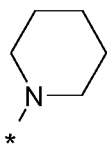
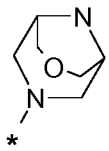
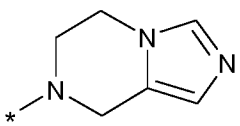
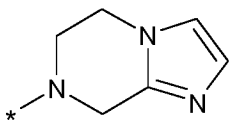
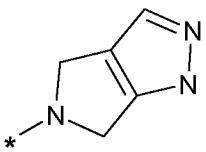
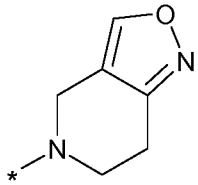
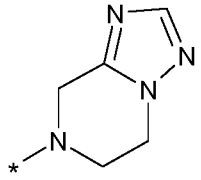
FURTHER EMBODIMENTS

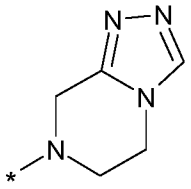
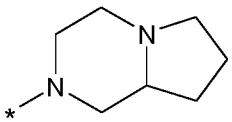
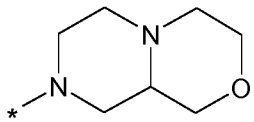
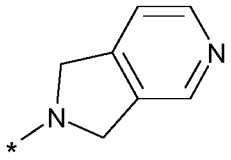
Embodied are the above compounds of formula **1**, wherein

R^1 is selected from the group consisting of

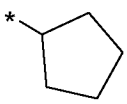
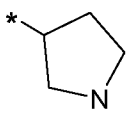
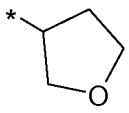
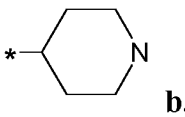
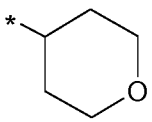
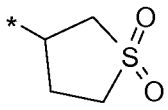
-CO-$R^{1.1}$, -CONH-$R^{1.2}$,
-$CONH_2$, -COOH, -$COOCH_3$, -$CON(CH_3)_2$, -CONH-$C(CH_3)_2$-CN,
-CONH-C_{1-2}-alkyl, -CONH-CH_2-$R^{1.7}$, -CONH-CH_2CH_2-$R^{1.3}$,
-CONH-$CH_2CH_2CH_2$-$R^{1.5}$,
-CONH-$CH(CH_3)R^{1.9}$, -$CON(CH_3)$-CH_2-$R^{1.6}$, -$CON(CH_3)$-CH_2CH_2-$R^{1.4}$ and
-$CON(CH_3)$-$CH_2CH_2CH_2$-$R^{1.8}$,

$R^{1.1}$ is selected from the group consisting of
formulas **a.1** to **a.16,**
each optionally substituted with a group selected from among –OH, -NH_2, C_{1-2}-alkyl, -$NHCH_3$, -$N(CH_3)_2$, cyclopropyl, -$CH(CH_3)_2$, morpholine, -$COCH_3$, -$NHCOCH_3$ and -$N(CH_3)CO$-CH_3

 **a.1**	 **a.2**	 **a.3**	 **a.4**
 **a.5**	 **a.6**	 **a.7**	 **a.8**
 **a.9**	 **a.10**	 **a.11**	 **a.12**

 a.13	 a.14	 a.15	 a.16

$R^{1.2}$ is selected from the group consisting of formulas **b.1** to **b.9,** each optionally substituted with a group selected from among NH_2, OH, -CN, CH_3 and $-CH(CH_3)_2$,

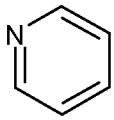
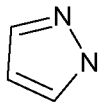
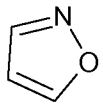
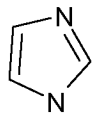
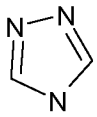
 b.1	 b.2	 b.3	 b.4
 b.5	 b.6	 b.7	 b.8
 b.9			

$R^{1.3}$ is selected from the group consisting of $-NH_2$, -OH, F, $-NHCH_3$, $-N(CH_3)_2$, $-SO_2CH_3$ and-OCH_3,

$R^{1.4}$ is selected from the group consisting of $-NH_2$, -OH, $-OCH_3$, $-NHCH_3$ and $-N(CH_3)_2$,

$R^{1.5}$ is selected from the group consisting of OH, $-N(CH_3)_2$ and $-OCH_3$,

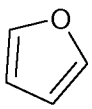
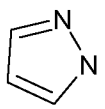
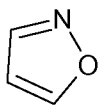
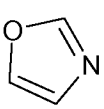
$R^{1.6}$ is selected from the group consisting of formulas **c.1** to **c.5,** each optionally substituted with CH_3,

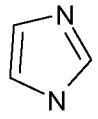
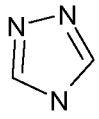
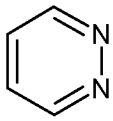
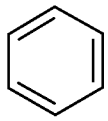
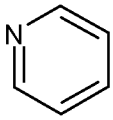
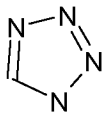
 **c.1**	 **c.2**	 **c.3**	 **c.4**
 **c.5**			

$R^{1.7}$ is selected from the group consisting of - $-C(CH_3)_2$-OH, $-C(CH_3)_2-NH_2$, CF_3, -CN, CHF_2 and -CH≡CH,

or

$R^{1.7}$ is selected from the group consisting of formulas **d.1** to **d.10,** each optionally substituted with CH_3 or -CN

 **d.1**	 **d.2**	 **d.3**	 **d.4**

 **d.5**	 **d.6**	 **d.7**	 **d.8**
 **d.9**	 **d.10**		

$R^{1.8}$ denotes $-OCH_3$,

$R^{1.9}$ denotes a group of formula **d.1,**

R^2 is selected from the group consisting of $-COCH_3$ and $-COOCH_2CH_3$,

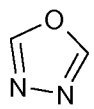
R^3 is H or methyl,

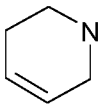
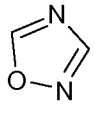
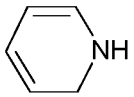
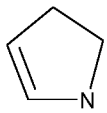
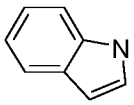
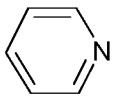
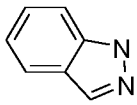
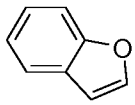
or a pharmaceutically acceptable salt thereof.

Embodied are the above compounds of formula **1**, wherein

R^1 is $R^{1.10}$,

$R^{1.10}$ is selected from the group consisting of formulas **a.1** to **a.12,** each of the rings substituted with $R^{1.11}$ and $R^{1.12}$,

 **a.1**	 **a.2**	 **a.3**	 **a.4**

 a.5	 a.6	 a.7	 a.8
 a.9	 a.10	 a.11	 a.12

$R^{1.11}$, $R^{1.12}$ are independently selected from among hydrogen, F,-CN, $-OCH_3$, =O, $-CH_3$ and $-COO-C(CH_3)_3$.

R^3 is H or methyl

or a pharmaceutically acceptable salt thereof.

Embodied are the above compounds of formula **1**, wherein

R^1 is selected from the group consisting of

$-CONH-R^{1.2}$, $-CONH_2$, $-COOCH_3$, $-CONH-C(CH_3)_2-CN$, $-CONH-C_{1-2}$-alkyl, $-CONH-CH_2-R^{1.7}$, $-CONH-CH_2CH_2-R^{1.3}$, $-CONH-CH_2CH_2CH_2-R^{1.5}$ and $-CON(CH_3)-CH_2CH_2-R^{1.4}$,

$R^{1.2}$ is selected from the group consisting of formulas **b.1** and **b.4,** each optionally substituted with a group selected from among $-NH_2$, -OH, CN, CH_3 and $-CH(CH_3)_2$,

b.1

$R^{1.3}$ is selected from the group consisting of $-NH_2$, F and $-NHCH_3$,

$R^{1.4}$ denotes $-NH_2$ or -OH,

$R^{1.5}$ denotes OH,

$R^{1.7}$ is selected from the group consisting of –CN, $-C(CH_3)_2$-OH, $-C(CH_3)_2$-NH_2 and -CH≡CH,

or a pharmaceutically acceptable salt thereof.

Embodied are the above compounds of formula **1**, wherein

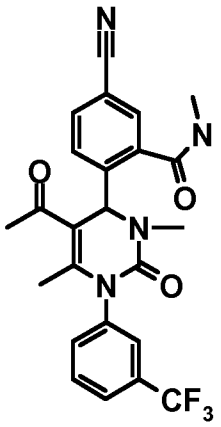
R^2 denotes $-COCH_3$.

Embodied are the above compounds of formula **1**, wherein

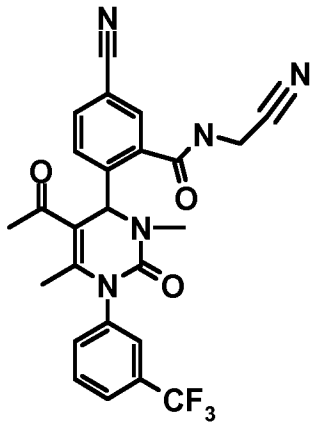
R^2 denotes $-COOCH_2CH_3$.

Embodied are the above compounds of formula **1**, wherein

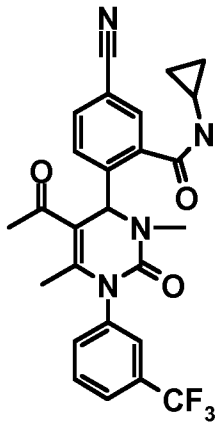
formula **1** is selected from the group consisting of formulas **1.a** to **1.h.**



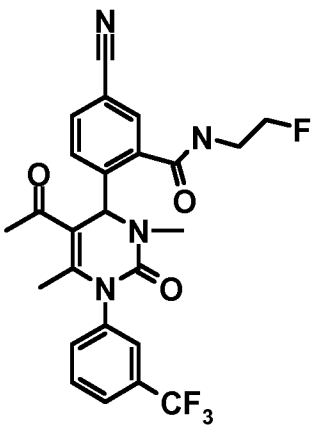
1.a

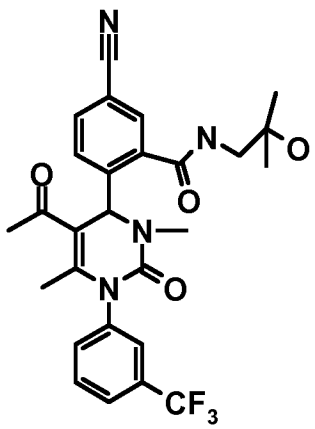


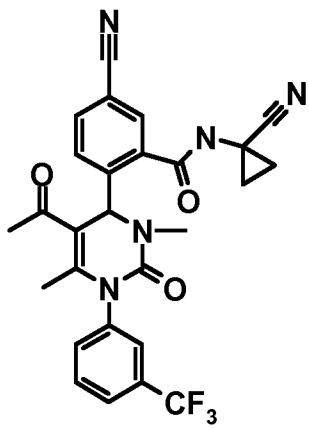
1.b



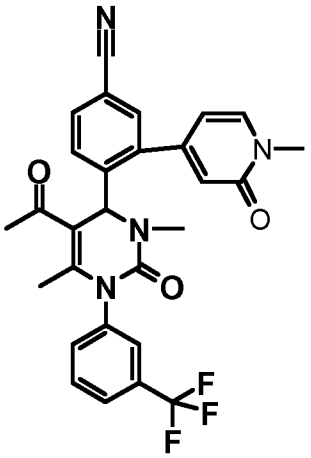
1.c



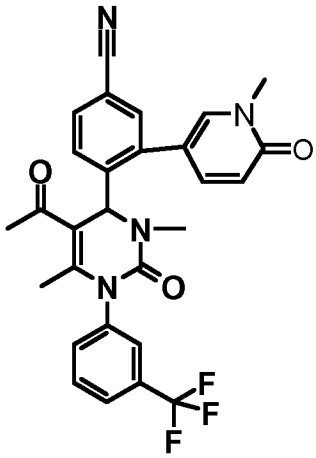




1.d



1.e



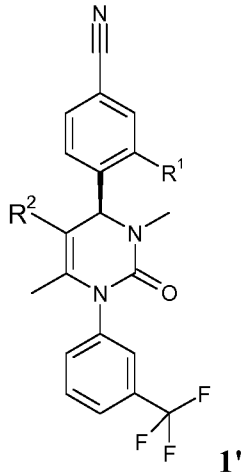
1.f

1.g

1.h

or a pharmaceutically acceptable salt thereof.

Embodied are the above compounds of formula **1**, wherein the configuration of formula **1** is formula **1'**,



1'

or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention are the above compounds of formula **1** for use as a medicament.

A further embodiment of the invention are above compounds of formula **1** for use as a medicament for the treatment of asthma and allergic diseases, gastrointestinal inflammatory diseases, glomerulonephritis, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes, rheumatoid arthritis, neutrophilic diseases, cystic fibrosis (CF), non-cystic fibrosis, idiopathic pulmonary fibrosis, bronchiectasis, ANCA-associated vasculitis, lung cancer, non-cyctic fibrosis bronchiectasis, emphysema, chronic bronchitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary arterial hypertension (PAH) and Alpha-1-antitrypsin deficiency (AATD), obesity and related inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.

A further embodiment of the invention is a compound of formula **1**, for use as a medicament for the treatment of traumatic brain injury, abdominal aortic aneurism and Graft vs. Host Disease (GvHD).

A further embodiment of the invention is a pharmaceutical composition, characterised in that it contains one or more compounds of formula **1** or a pharmaceutically active salt thereof.

A further embodiment of the invention is a method of treatment or prevention of diseases in which neutrophil elastase inhibitors have a therapeutic benefit, which method comprises administration of a therapeutically or preventively effective amount of a compounds of formula **1** to a patient in need thereof.

A further embodiment of the invention is a pharmaceutical composition comprising additionally to a compound of formula **1**, a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, Cathepsin C inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists and SYK-inhibitors, but also combinations of two or three active substances.

Embodied are the above compounds of formula **1**, wherein

R^1 is selected from the group consisting of

$-CO-R^{1.1}$, $-CONH-R^{1.2}$, $R^{1.10}$,

$-CO-NH_2$, -COOH, $-CON(CH_3)_2$, $-CONH-C(CH_3)_2-CN$,

-CONH-C_{1-3}-alkyl, -CONH-CH_2-$R^{1.7}$, -CONH-CH_2CH_2-$R^{1.3}$,
-CONH-$CH_2CH_2CH_2$-$R^{1.5}$,
-CONH-$CH(CH_3)R^{1.9}$, -CON(CH_3)-CH_2-$R^{1.6}$, -CON(CH_3)-CH_2CH_2-$R^{1.4}$ and
-CON(CH_3)-$CH_2CH_2CH_2$-$R^{1.8}$.

Embodied are the above compounds of formula **1**, wherein

R^1 is $R^{1.10}$.

Embodied are the above compounds of formula **1**, wherein

R^1 is -CO-$R^{1.1}$.

Embodied are the above compounds of formula **1**, wherein

R^1 is -CONH-$R^{1.2}$.

Embodied are the above compounds of formula **1**, wherein

R^1 is selected from the group consisting of
-CONH-$R^{1.2}$, -$CONH_2$, -$COOCH_3$, -CONH-$C(CH_3)_2$-CN, -CONH-C_{1-2}-alkyl,
-CONH-CH_2-$R^{1.7}$, -CONH-CH_2CH_2-$R^{1.3}$, -CONH-$CH_2CH_2CH_2$-$R^{1.5}$ and
-CON(CH_3)-CH_2CH_2-$R^{1.4}$.

Embodied are the above compounds of formula **1**, wherein

-CO-NH_2, -CONH-$C(CH_3)_2$-CN and -CONH-C_{1-3}-alkyl.

Embodied are the above compounds of formula **1**, wherein

$R^{1.1}$ is selected from the group consisting of
formulas **a.1** to **a.16,**
each optionally substituted with a group selected from among –OH, -NH_2,
C_{1-2}-alkyl, -$NHCH_3$, -$N(CH_3)_2$, cyclopropyl, -$CH(CH_3)_2$, morpholine, -$COCH_3$, -
$NHCOCH_3$ and -$N(CH_3)CO$-CH_3.

Embodied are the above compounds of formula **1**, wherein

$R^{1.2}$ is selected from the group consisting of formulas **b.1** to **b.9,** each
optionally substituted with a group selected from among -NH_2, -OH, -CN, -CH_3 and
-$CH(CH_3)_2$.

Embodied are the above compounds of formula **1**, wherein

$R^{1.2}$ is formula **b.1,** optionally substituted with -NH_2, -OH, CN, CH_3, -$CH(CH_3)_2$

Embodied are the above compounds of formula **1**, wherein

$R^{1.3}$, $R^{1.4}$, $R^{1.5}$ independently from each other are selected from the group consisting of morpholinyl, F, $-N(CH_3)_2$, $-SO_2CH_3$, $-OCH_3$, , -OH and CH_3, particularly preferred OH.

Embodied are the above compounds of formula **1**, wherein

$R^{1.3}$ is selected from the group consisting of $-NH_2$, -OH, F, $-NHCH_3$, $-N(CH_3)_2$, $-SO_2CH_3$ and $-OCH_3$.

Embodied are the above compounds of formula **1**, wherein

$R^{1.3}$ is selected from the group consisting of $-NH_2$, F and $-NHCH_3$, particularly preferred F.

Embodied are the above compounds of formula **1**, wherein

$R^{1.4}$ is selected from the group consisting of $-NH_2$, -OH, $-OCH_3$, $-NHCH_3$ and $-N(CH_3)_2$, particularly preferred $-NH_2$ and –OH.

Embodied are the above compounds of formula **1**, wherein

$R^{1.5}$ is selected from the group consisting of OH, $-N(CH_3)_2$ and $-OCH_3$, particularly preferred OH.

Embodied are the above compounds of formula **1**, wherein

$R^{1.6}$, $R^{1.7}$ independently from each other denote a group selected from among -CO-morpholinyl, $-C(CH_3)_2CN$, $-C(CH_3)_2$-OH, $-CF_3$, -CN, CHF_2 and -CH≡CH, particularly preferred $-C(CH_3)_2$-OH and –CN,

or

a 4-to 10-membered aromatic or 5-to 10-membered heteroaryl ring, containing one to four heteroatoms independently selected from among N, O and S, each of the rings optionally substituted with C_{1-3} alkyl or CN.

Embodied are the above compounds of formula **1**, wherein

$R^{1.6}$ is selected from the group consisting of formulas **c.1** to **c.5,** each optionally substituted with - CH_3.

Embodied are the above compounds of formula **1**, wherein

$R^{1.7}$ is selected from the group consisting of $-C(CH_3)_2$-OH, $-C(CH_3)_2-NH_2$,$-CF_3$, -CN, $-CHF_2$ and-CH≡CH, particularly preferred CN and $C(CH_3)_2$-OH.

Embodied are the above compounds of formula **1**, wherein

$R^{1.7}$ is selected from the group consisting of formulas **d.1** to **d.10,** each optionally substituted with - CH_3 or –CN.

Embodied are the above compounds of formula **1**, wherein

$R^{1.8}$ -OCH_3 and

$R^{1.9}$ denotes furanyl.

Embodied are the above compounds of formula **1**, wherein

$R^{1.10}$ denotes a 4-to 10-membered heterocyclic or 5-to 10-membered heteroaryl ring, containing one to four heteroatoms independently selected from among N, O and S, each of the rings substituted with $R^{1.11}$and $R^{1.12}$.

Embodied are the above compounds of formula **1**, wherein

$R^{1.10}$ is selected from the group consisting of formulas **a.1** to **a.12,** each of the rings substituted with $R^{1.11}$ and $R^{1.12}$.

Embodied are the above compounds of formula **1**, wherein

$R^{1.11}$, $R^{1.12}$ are independently selected from among hydrogen, =O, C_{1-4}-alkyl ,and -COO-C_{1-4}-alkyl, C_{1-3}-cycloalkyl, OH, -O-C_{1-3}-alkyl, -O-C_{1-3}-cycloalkyl, -CN, halogen, -CO-C_{1-3}-alkyl, -CO-C_{1-3}-cycloalkyl and -$N(CH_3)_2$., particularly preferred , =O and C_{1-4}-alkyl.

Embodied are the above compounds of formula **1**, wherein

$R^{1.11}$, $R^{1.12}$ are independently selected from among hydrogen,,F,-CN, -OCH_3, =O, -CH_3 and -COO-$C(CH_3)_3$.

Embodied are the above compounds of formula **1**, wherein

$R^{1.11}$ denotes hydrogen or =O.

Embodied are the above compounds of formula **1**, wherein

R^2 is selected from the group consisting of -$COCH_3$ and -$COOCH_2CH_3$.

Embodied are the above compounds of formula **1**, wherein

R^3 is selected from the group consisting of H, $R^{3.1}$, $R^{3.1}$-CO-, $R^{3.1}$-O-CO- , $R^{3.1}SO_2$- and $R^{3.1}R^{3.2}$N-CO-.

Embodied are the above compounds of formula **1**, wherein

R^3 is H or methyl.

Embodied are the above compounds of formula **1**, wherein

R^3 is H.

Embodied are the above compounds of formula **1**, wherein

R^3 is methyl.

Embodied are the above compounds of formula **1**, wherein

$R^{3.1}$ is selected from the group consisting of H, -C_{1-4} alkyl, -C_{3-6} cycloalkyl, -C_{1-4}-haloalkyl and -C_{3-6}-halocycloalkyl,
each optionally substituted with one substituent independently selected from the group consisting of OH, CN and NH_2.

Embodied are the above compounds of formula **1**, wherein

$R^{3.1}$ is CH_3.

Embodied are the above compounds of formula **1**, wherein

$R^{3.2}$ is selected from the group consisting of H and Me.

Embodied are the compounds of formula **1**, wherein the compounds are selected from the group consisting of examples 1.6, 1.8, 1.10, 1.22, 1.73, 13.1, 8, 16 and 17.

Embodied are the compounds of formula **1**, wherein the compounds are selected from the group consisting of examples 1.6, 1.8, 1.10, 1.22, 1.73, 13.1, 16 and 17.

Any and each other of the definitions of **R^1**, **$R^{1.1}$**, **$R^{1.2}$**, **$R^{1.3}$**, **$R^{1.4}$**, **$R^{1.5}$**, **$R^{1.6}$**, **$R^{1.7}$**, **$R^{1.8}$**, **$R^{1.9}$**, **$R^{1.10}$**, **$R^{1.11}$**, **$R^{1.12}$**, **R^2**, **R^3**, **$R^{3.1}$** and **$R^{3.2}$** may be combined with each other.

PREPARATION

The compounds according to the present invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis. Preferably, the compounds are obtained in analogous fashion to the methods of preparation explained more fully hereinafter, in particular as described in the experimental section. In some cases, the order in carrying out the reaction

steps may be varied. Variants of the reaction methods that are known to the one skilled in the art but not described in detail here may also be used. The general processes for preparing the compounds according to the invention will become apparent to the one skilled in the art studying the following schemes. Starting materials are commercially available or may be prepared by methods that are described in the literature or herein, or may be prepared in an analogous or similar manner. Any functional groups in the starting materials or intermediates may be protected using conventional protecting groups. These protecting groups may be cleaved again at a suitable stage within the reaction sequence using methods familiar to the one skilled in the art.

Compounds of the invention **V** are accessible using the synthetic route illustrated in Scheme 1; $R^{1.10}$, R^2 and R^3 have the meanings as defined hereinbefore and hereinafter.

Intermediate **IV** (Step A) can be prepared by the Biginelli reaction (C.O.Kappe, *Tetrahedron*, **1993**, 32, 6937-6963) by reacting intermediates **I, II** and **III** in presence of a Brønsted acid or Lewis acid in an organic solvent at temperatures between 0 °C and 120 °C. Preferred Lewis acid is polyphosphoric acid, preferred solvent is tetrahydrofurane and preferred temperature is between room temperature and 60 °C.

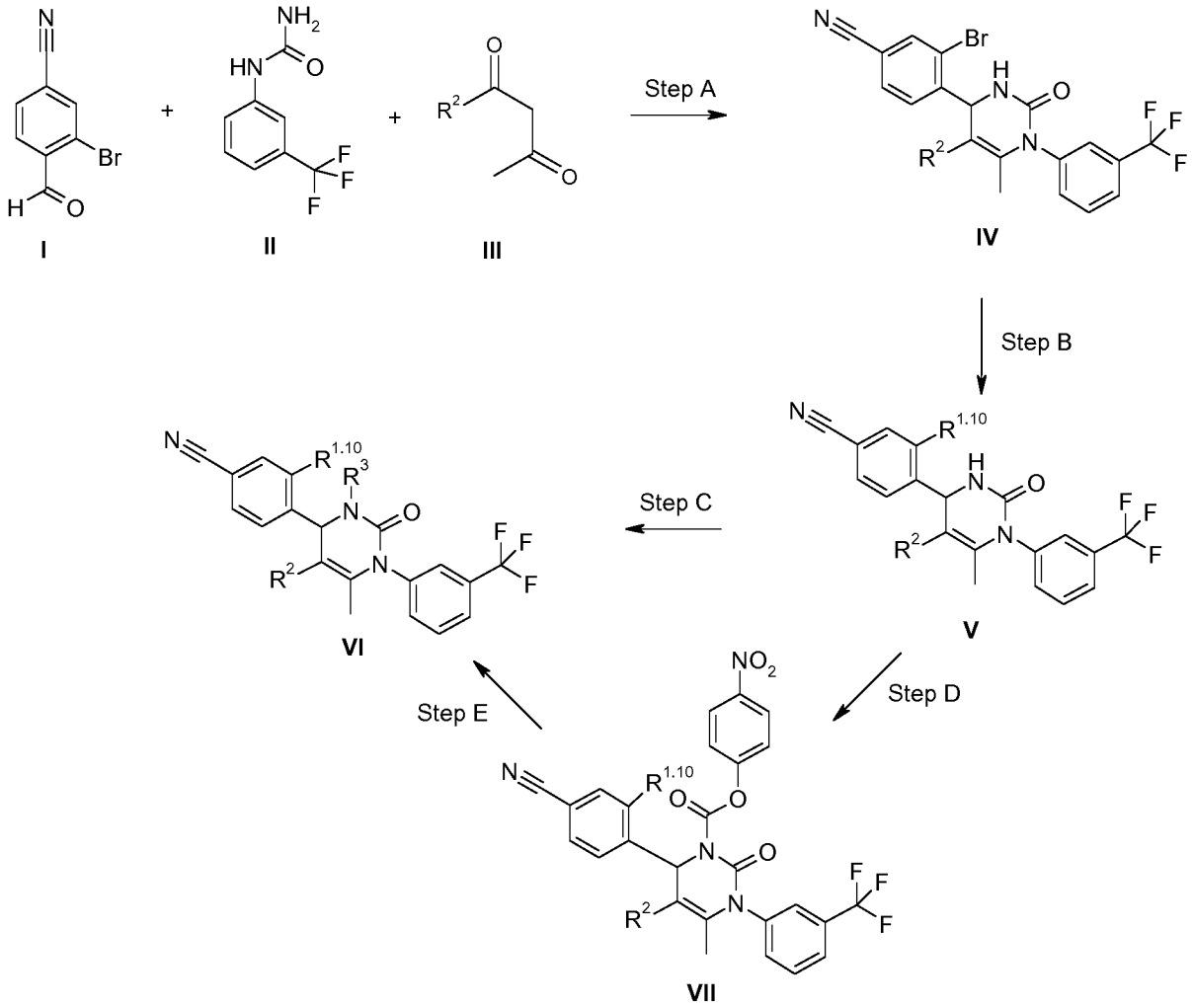
Compounds of the invention **V** (Step B) can be prepared by reacting intermediates **IV** with a boronic acid derivative (acid or ester, e.g. pinacol ester) in the presence of a suitable catalyst such as 1,1'-Bis(di-tert-butylphosphino)ferrocene palladium dichloride or [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) as a 1:1 complex with dichloromethane, and in the presence of a base, for example alkali carbonates, hydrogencarbonates, phosphates, hydrogenphosphates or acetates, especially cesium carbonate, in an organic solvent, for example tetrahydrofurane, *N*,*N*-dimethylformamide, acetonitrile, 1,4-dioxane or dichloromethane. The reaction takes place within 1-72 hours. Preferred reaction temperatures are between 0 °C and the boiling point of the solvent, for example 80 °C.

Compounds of the invention **VI** (R^3 = $R^{3.1}$-SO_2-) can be prepared as described in WO07137874, by reacting compounds of the invention **V** with a sulfonylating agent (step C), for example methanesulfonyl chloride or *para*-toluenesulfonyl chloride in the presence of a base, for example sodium hydride, lithium diisopropylamide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, an organolithium reagent, for example *tert*-butyllithium or a Grignard reagent, for example *iso*-propylmagnesiumchloride, in an organic solvent, for example tetrahydrofurane, *N*,*N*-dimethylformamide, acetonitrile, 1,4-dioxane or dichloromethane. The reaction takes place within 1-72 hours. Preferred reaction temperatures are between 0 °C and room temperature.

Intermediates **VII** (Step D) can be prepared as described in WO09080199, by reacting compounds of the invention **V** with 4-nitrophenyl chloroformate in the presence of a base, for example triethylamine, *N*,*N*-diisopropylethylamine or *N*-methylmorpholine, optionally in the presence of a catalyst, for example 4-dimethylaminopyridine, in an organic solvent, for example dichloromethane, tetrahydrofurane, acetonitrile or *N*,*N*-dimethylformamide. The reaction takes place within 1-24 hours. Preferred reaction temperatures are between 0 °C and 50 °C, most preferred room temperature.

Compounds of the invention **VI** (R^3 = $R^{3.1}R^{3.2}$N-CO -) can be prepared as described in WO09080199, by reacting intermediates **VII** with an amine $R^{3.1}R^{3.2}NH_2$ (step E) in an organic solvent, for example dichloromethane, acetonitrile, tetrahydrofurane, 1,4-dioxane, toluene or *N*,*N*-dimethylformamide. The reaction takes place within 1-72 hours. Preferred reaction temperatures are between 0 °C and 50 °C, most preferred room temperature. Alternatively, the Suzuki reaction can also be performed on intermediates **VIII** ($R^{3.1}$ = Alkyl, in particular Methyl) to provide examples of the invention.

Scheme 1



Compounds of the invention **XI** are accessible using the synthetic route illustrated in Scheme 2; R^I, $R^{2,}$ $R^{3.1}$ have the meanings as defined hereinbefore and hereinafter, E^{R1} has the meaning -CO-$R^{1.1}$, -CONH-$R^{1.2}$.

Intermediates **VIII** (Step F) can be prepared as described in WO04024700 by reacting intermediates **IV** with an alkylating agent, for example a dialkyl sulfate, for example dimethyl sulfate, an alkyl halide, for example methyl iodide or an alkyl sulfonylate, for example benzyl tosylate, in the presence of a suitable base, for example sodium hydride, sodium hydroxide, cesium carbonate, lithium diisopropylamide, potassium hexamethyl-disilazide, lithium hexamethyldisilazide, an organolithium reagent, for example *tert*-butyllithium or a Grignard reagent, for example isopropylmagnesiumchloride, in an organic

solvent, for example tetrahydrofurane, *N*,*N*-dimethylformamide, acetonitrile, 1,4-dioxane, dichloromethane or toluene. The reaction takes place within 1-72 hours. Preferred reaction temperatures are between 0 °C and 100 °C. Alternatively, the alkylation reaction can also be performed on compounds **V** ($R^{1.10}$ = aryl or hetaryl) to provide examples of the invention.

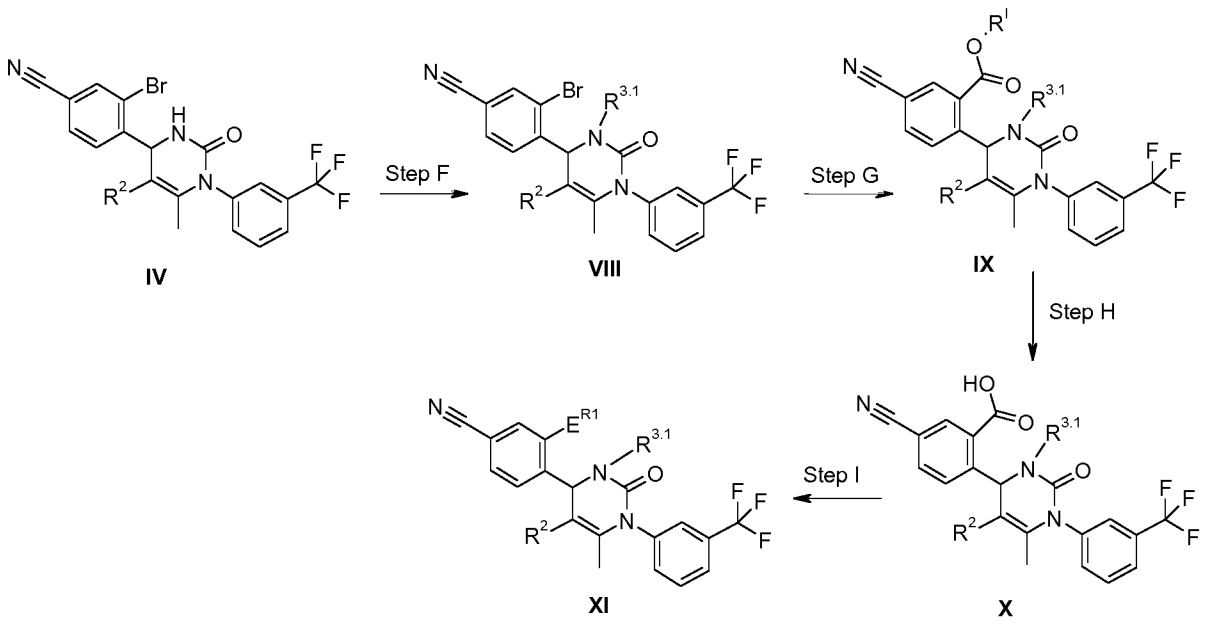
Compounds of the invention **IX** (Step G) can be prepared by reacting intermediates **VIII** with carbon monoxide in the presence of a suitable catalyst such as 1,1-bis(diphenylphosphino)-ferrocen with palladium(II)-acetate, 1,1'-Bis(di-tert-butyl-phosphino)ferrocene palladium dichloride or [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) as a 1:1 complex with dichloromethane, and in the presence of a base, for example alkali carbonates, hydrogencarbonates, phosphates, hydrogenphosphates or acetates, especially sodium acetate, in an alcohol, preferred a primary alcohol, most preferred methanol or ethanol (R^I= Me or Et). The reaction takes place within 1h-6 days. Preferred reaction temperatures are between r.t. and 150 °C, for example 100 °C. The reaction is performed in an autoclave under elevated pressure, preferably between 2 and 10 bar, most preferred 5 bar.

Compounds of the invention **X** (Step H) can be prepared by basic hydrolysis of compounds of the invention **IX** using e.g. alkali hydroxides like lithium hydroxide in a mixture of water and a polar organic solvent like THF, dioxane, DMF, DMSO or acetonitrile, preferably dioxane. The reaction takes place within 10 min to 24 h. Preferred reaction temperatures are between 0 °C and 100 °C, for example r.t.. The reaction has to be monitored by TLC or HPLC to minimize decomposition of the molecule.

Compounds of the invention **XI** (Step I) can be prepared by reaction of compounds of the invention **X** with an appropriate amine or ammonium salt in the presence of a sufficient amount of a base like N-N-diisopropylethyl amine (DIPEA) in a polar solvent like DMF, THF or dioxane using standard literature procedures. The carboxylic acids **X** has to be activated in advance by reaction with an activating agent such as O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or O-(Benzotriazol-1-yl)-

N,N,N',N'-tetramethyluroniumtetrafluoroborate (TBTU) and *N*,*N*-diisopropylethyl amine (DIPEA). The reaction takes place within 10 min to 24 h. Preferred reaction temperatures are between -20 °C and 80 °C, preferably at r.t.

Scheme 2



Compounds of the invention **XIII, XV and XVII** are accessible using the synthetic routes illustrated in Scheme 3; R^{II}, R^2 and $R^{3.1}$ have the meanings as defined hereinbefore and hereinafter.

Intermediate **XII** (Step J) can be prepared by reaction of compounds of the invention **X** with propagyl amine in the presence of a sufficient amount of a base like N-N-diisopropylethyl amine (DIPEA) in a polar solvent like DMF, THF or dioxane using standard literature procedures. The carboxylic acids **X** has to be activated in advance by reaction with an activating agent such as O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or O-(Benzotriazol-1-yl)- N,N,N',N'-tetramethyluroniumtetrafluoroborate (TBTU) and *N*,*N*-diisopropylethyl amine (DIPEA). The reaction takes place within 10 min to 24 h. Preferred reaction temperatures are between -20 °C and 80 °C, preferably at r.t.

Compounds of the invention **XIII** (Step K) can be prepared by reaction of intermediates **XII** with gold(III)-chloride (A.S.K. Hashmi, *Gold Bull.* **2003**, 36, 3) in an organic solvent, preferably dichloromethane. Preferred reaction temperatures are between r.t and 80 °C, preferably at r.t.

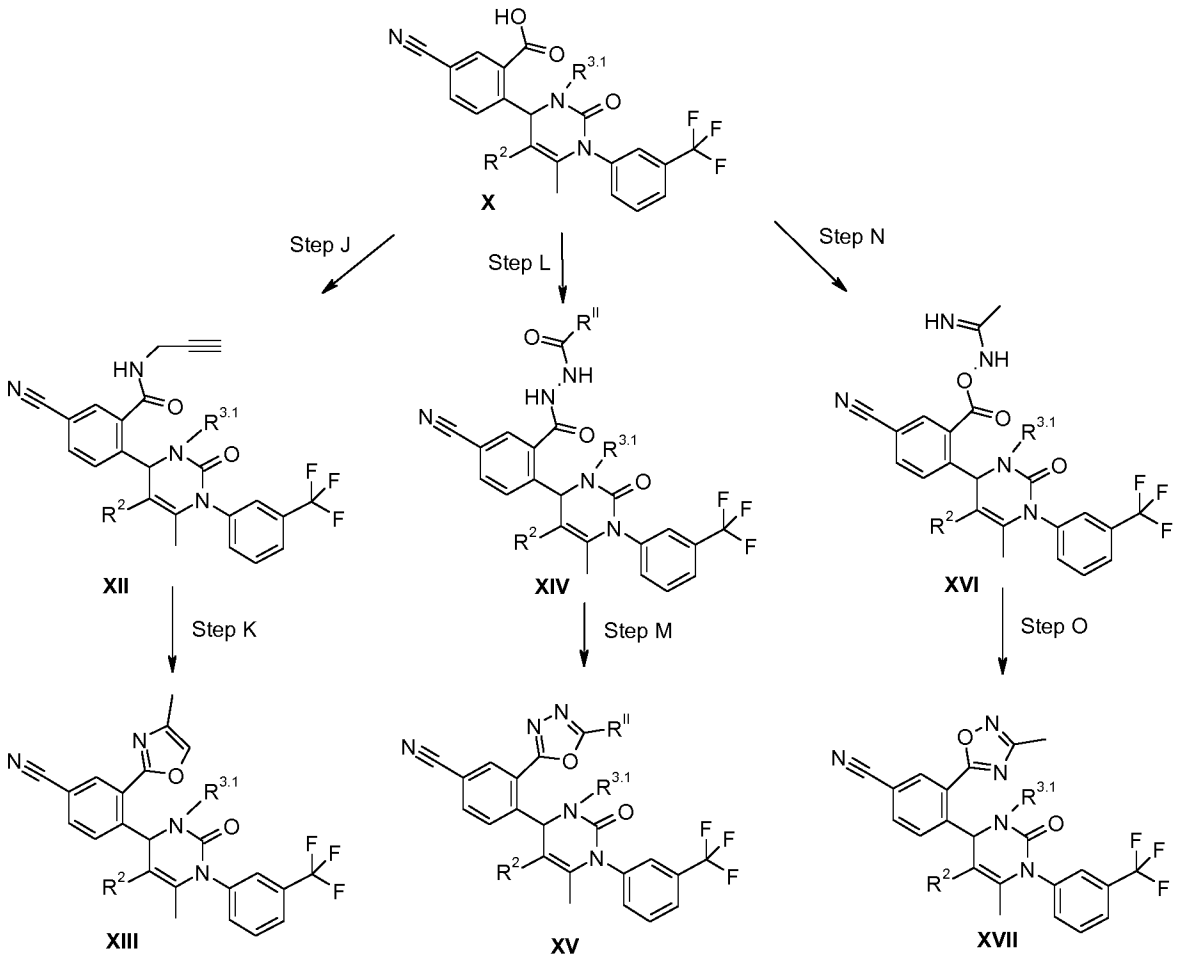
Intermediate **XIV** (Step L) can be prepared by reaction of compounds of the invention **X** with acylhydrazides (R^{II} = H, alkyl) in the presence of a sufficient amount of a base like N-N-diisopropylethyl amine (DIPEA) in a polar solvent like DMF, THF or dioxane using standard literature procedures. The carboxylic acids **X** has to be activated in advance by reaction with an activating agent such as O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or O-(Benzotriazol-1-yl)- N,N,N',N'-tetramethyluroniumtetrafluoroborate (TBTU) and *N,N*-diisopropylethyl amine (DIPEA). The reaction takes place within 10 min to 24 h. Preferred reaction temperatures are between -20 °C and 80 °C, preferably at r.t.

Compounds of the invention **XV** (Step M) can be prepared by reaction of intermediates **XIV** with a dehydrating reagent, preferably Burgess Reagent (C.T. Brain, *Tetrahedron Lett.* **40** (1999), 3275-78) in an organic solvent, preferably dichloromethane. Preferred reaction temperatures are between r.t and 80 °C, preferably at 40 °C.

Intermediate **XVI** (Step N) can be prepared by reaction of compounds of the invention **X** with N-hydroxyacetamidine in the presence of a sufficient amount of a base like N-N-diisopropylethyl amine (DIPEA) in a polar solvent like DMF, THF or dioxane using standard literature procedures. The carboxylic acids **X** has to be activated in advance by reaction with an activating agent such as O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or O-(Benzotriazol-1-yl)- N,N,N',N'-tetramethyluroniumtetrafluoroborate (TBTU) and *N,N*-diisopropylethyl amine (DIPEA). The reaction takes place within 10 min to 24 h. Preferred reaction temperatures are between -20 °C and 80 °C, preferably at r.t.

Compounds of the invention **XVII** (Step O) can be prepared by reaction of intermediates **XVI** with a dehydrating reagent, preferably Burgess Reagent in an organic solvent, preferably dichloromethane. Preferred reaction temperatures are between r.t and 80 °C, preferably at 40 °C.

Scheme 3



PRELIMINARY REMARKS

The term room temperature denotes a temperature of about 20 °C. As a rule, ^{1}H NMR spectra and/or mass spectra have been obtained of the compounds prepared. Compounds given with a specific configuration at a stereocenter are isolated as pure isomers.

The retention times given are measured under the following conditions (TFA: trifluoroacetic acid, DEA: diethylamine, $scCO_2$: supercritical carbon dioxide):

Method Name:		**V011_S01**		
Column:		XBridge C18, 4.6 x 30 mm, 3.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1% NH_3]	% Solvent [acetonitrile]	Flow [ml/min]	Temp [°C]
0.0	97	3	5	60
0.2	97	3	5	60
1.6	0	100	5	60
1.7	0	100	5	60

Method Name:		**X012_S01**		
Column:		XBridge BEH C18, 2.1 x 30 mm, 1.7 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%TFA]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0.0	99	1	1.6	60
0.02	99	1	1.6	60
1.00	0	100	1.6	60
1.10	0	100	1.6	60

Method Name:		**X012_S02**		
Column:		XBridge BEH C18, 2.1 x 30 mm, 1.7 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%TFA]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0.0	99	1	1.3	60
0.02	99	1	1.3	60
1.00	0	100	1.3	60
1.10	0	100	1.3	60

Method Name:		**Z011_S03**		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%NH_3]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

Method Name:		**Z018_S04**		
Column:		Sunfire, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%TFA]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

Method Name:		**003_CA03**		
Column:		Sunfire, 3 x 30 mm, 3.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%TFA]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0.00	98	2	2.0	60
0.30	98	2	2.0	60
1.50	0	100	2.0	60
1.60	0	100	2.0	60

Method Name:		**003_CA04**		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%NH_3]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0.0	98	2	2.0	60
1.2	0	100	2.0	60
1.4	0	100	2.0	60

Method Name:		**004_CA05**		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%NH_3]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0.0	98	2	2.0	60
1.2	0	100	2.0	60
1.4	0	100	2.0	60

Method Name:		**005_CA01**		
Column:		SunFire C18, 3.0 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%TFA]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0.0	98	2	2.0	60.0
1.2	0	100	2.0	60.0
1.4	0	100	2.0	60.0

Method Name:		**005_CA07**		
Column:		Sunfire C18_3.0x30mm, 2.5µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H_2O, 0.1%TFA]	% Solvent [acetonitrile]	Flow [ml/min]	Temperature [°C]
0	95	5	1.5	60
1.3	0	100	1.5	60
1.5	0	100	1.5	60

Method Name:		**I_IC_25_MeOH_NH_3**			
Column:		Chiralpak IC 4.6 x 250 mm, 5 µm			
Column Supplier:		Daicel			
Gradient/ Solvent Time [min]	% Solvent [MeOH, 0.2% NH_3]	% Solvent [$scCO_2$]	Flow [ml/min]	Temperature [°C]	Back Pressure [bar]
0	25	75	4	40	150
10	25	75	4	40	150

Method Name:		**I_IC_30_MeOH_NH_3**			
Column:		Chiralpak IC 4.6 x 250 mm, 5 µm			
Column Supplier:		Daicel			
Gradient/ Solvent Time [min]	% Solvent [MeOH, 0.2% NH_3]	% Solvent [$scCO_2$]	Flow [ml/min]	Temperature [°C]	Back Pressure [bar]
0	30	70	4	40	150
10	30	70	4	40	150

Method Name:			**I_IC_20_MeOH_NH$_3$**		
Column:			Chiralpak IC 4.6 x 250 mm, 5 µm		
Column Supplier:			Daicel		
Gradient/ Solvent Time [min]	% Solvent [MeOH, 20 mM NH_3]	% Solvent [$scCO_2$]	Flow [ml/min]	Temperature [°C]	Back Pressure [bar]
0	20	80	4	40	150
10	20	80	4	40	150

Method Name:			**I_IB_15_MeOH_NH3**		
Column:			Chiralpak IB 4.6 x 250 mm, 5 µm		
Column Supplier:			Daicel		
Gradient/ Solvent Time [min]	% Solvent [MeOH, 20mM NH_3]	% Solvent [$scCO_2$]	Flow [ml/min]	Temperature [°C]	Back Pressure [bar]
0	15	85	4	40	150
10	15	85	4	40	150

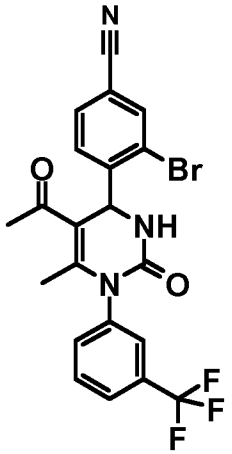
Method Name:			I_IA_20_MeOH_NH3		
Device-Description			Agilent 1260 SFC with DAD and MS		
Column			Daicel Chiralpak® IA		
Column Dimension			4.6 x 250 mm		
Particle Size			5 µm		
Solvent Gradient time [min]	% Sol [$scCO_2$]	% Sol [MeOH], 20mM ammonia]	Flow [ml/min]	Temp [°C]	Backpressure [bar]
0.00	80	20	4	40	150
10.00	80	20	4	40	150

SYNTHESES OF STARTING MATERIALS

The following starting material is prepared as described in the literature cited:

3-(3-(trifluoromethyl)phenylamino)cyclopent-2-enone: *Aust. J. Chem.* **2005**, *58*, 870-876.

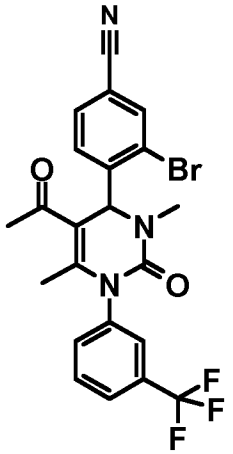
INTERMEDIATE 3



4-[5-Acetyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-bromo-benzonitrile

3-Bromo-4-formyl-benzonitrile (intermediate 2, 1.09 g, 4.92 mmol) is stirred with acetylacetone (0.60 mL, 5.88 mmol), 3-(trifluoromethyl)phenylurea (1.00 g, 4.90 mmol) and polyphosphoric acid (3.02 g, 7.90 mmol) in tetrahydrofurane (40.0 mL) at 50 °C overnight. The reaction mixture is concentrated in vacuo, ethyl acetate and water is added and the phases are separated. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over $MgSO_4$ and concentrated. Yield: 2.38 g; ESI mass spectrum: $[(^{79}Br)\text{-}M+H]^+ = 478$, $[(^{81}Br)\text{-}M+H]^+ = 480$; Retention time HPLC: 1.06 min (HPLC method Z018_S04).

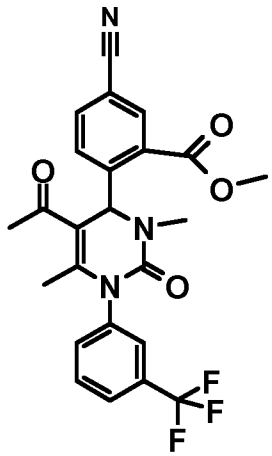
INTERMEDIATE 4



4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-bromo-benzonitrile

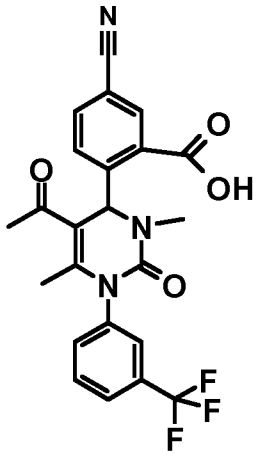
Methyliodide (c = 2 mol/L, 3.24 mL, 6.48 mmol) is added to a suspension of 4-[5-acetyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-bromo-benzonitrile (intermediate 3) (2.48 g, 5.18 mmol) and cesium carbonate (2.20 g, 6.74 mmol) in *N,N*-dimethylformamide (50.0 mL). The reaction mixture is stirred at room temperature overnight. Water and ethyl acetate are added and the phases are separated. The aqueous phase is extracted twice with ethyl acetate and the combined organic phases are washed with saturated sodium chloride solution, dried over $MgSO_4$ and concentrated. The residue is purified by reversed phase HPLC. Yield: 2.64 g. ESI mass spectrum: $[(^{79}Br)\text{-}M+H]^+ = 492$, $[(^{81}Br)\text{-}M+H]^+ = 494$; Retention time HPLC: 1.06 min (HPLC method Z018_S04).

INTERMEDIATE 5



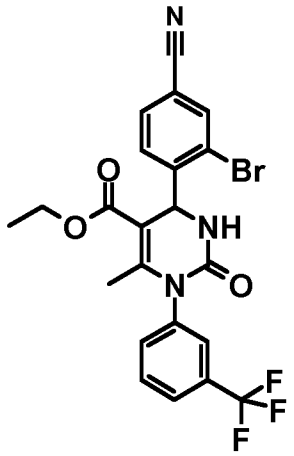
2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid methyl ester 4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-bromo-benzonitrile (intermediate 4)(643.0 mg, 1.31 mmol), 1.1-bis(diphenyl-phosphino)-ferrocendichloropalladium(II), complex with dichloromethane (1:1) (51.5 mg, 0.06 mmol) and sodium acetate (327.5 mg, 4.0 mmol) are suspended in methanol (21 mL) and treated with carbon monoxide at 5 bar and 100 °C for 19 h. The reaction mixture is concentrated, water and ethyl acetate are added and the phases are separated. The organic phase is washed twice with water, dried over $MgSO_4$ and concentrated. Yield: 671 mg. ESI mass spectrum: $[M+H]^+$ = 472; Retention time HPLC: 1.12 min (HPLC method Z018_S04).

INTERMEDIATE 6



2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid 2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid methyl ester (intermediate 5)(612 mg, 1.30 mmol) and lithium hydroxide (93.3 mg, 3.90 mmol) are stirred in 1,4-dioxane (12.0 ml) and water (6.0 mL) at room temperature for 20 min. Water (200 mL) is added and the mixture is acidified with hydrochloric acid (1.0 M, 44 mL) to a pH value of 3. The aqueous phase is extracted with ethyl acetate. The organic phase is washed twice with water, dried over $MgSO_4$ and concentrated. Yield: 665 mg. ESI mass spectrum: $[M+H]^+$ = 472; Retention time HPLC: 1.09 min (HPLC method Z018_S04).

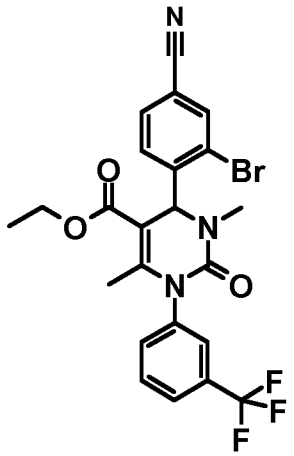
INTERMEDIATE 7



4-(2-Bromo-4-cyano-phenyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

3-Bromo-4-formyl-benzonitrile (intermediate 2, 3.25 g, 14.7 mmol) is stirred with acetylacetone (2.42 mL, 19.1 mmol), 3-(trifluoromethyl)phenylurea (3 g, 14.7 mmol) and polyphosphoric acid (3.02 g, 7.90 mmol) in tetrahydrofurane (80.0 mL) at 60 °C for 48 h. The reaction mixture is concentrated in vacuo and ethyl acetate and water is added and the phases are separated. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over $MgSO_4$ and concentrated. Yield: 7.66 g; ESI mass spectrum: $[M+ H]^+ = 508$; Retention time HPLC: 1.14 min (HPLC method Z018_S04)

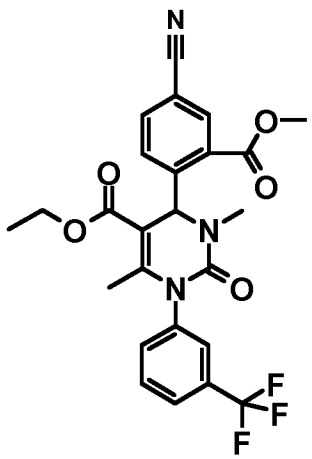
INTERMEDIATE 8



4-(2-Bromo-4-cyano-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

Methyliodide (c = 2 mol/L, 1.1 mL, 17.7 mmol) is added to a solution 4-(2-Bromo-4-cyano-phenyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (intermediate 7. 47 g, 14.7 mmol) and cesium carbonate (7.9 g, 24.3 mmol) in *N,N*-dimethylformamide (80 mL). The mixture is stirred at room temperature overnight. Additional methyliodide (c = 2 mol/L, 1.1 mL, 17.7 mmol) and cesium carbonate (5.0 g, 15.4 mmol) are added and the reaction is continued for 5 h. Water and ethyl acetate are added and the phases are separated. The aqueous phase is extracted twice with ethyl acetate and the combined organic phases are washed with saturated sodium chloride solution, dried over $MgSO_4$ and concentrated. The residue is purified by reversed phase HPLC. Yield: 7.61 g. ESI mass spectrum: $[M+H]^+$ = 522; Retention time HPLC: 1.20 min (HPLC method Z018_S04).

INTERMEDIATE 9

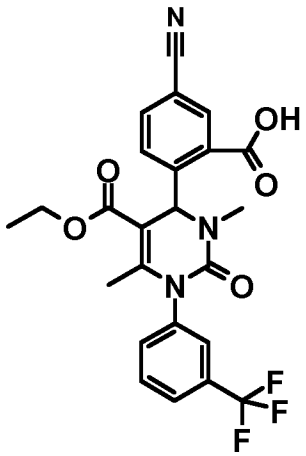


4-(4-Cyano-2-methoxycarbonyl-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

4-(2-Bromo-4-cyano-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (intermediate 8, 7.16 g, 13.7 mmol), 1.1-bis(diphenylphosphino)-ferrocendichloropalladium(II), complex with dichloromethane (1:1) (559.3 mg, 0.69 mmol) and sodium acetate (3.37 g, 41.1 mmol) are suspended in

methanol (120 mL) and treated with carbon monoxide at 8 bar and 100 °C for 19 h. A small amount of 1.1-bis(diphenylphosphino)-ferrocendichloropalladium(II), complex with dichloromethane (1:1) is added and the reaction under carbon monoxide is continued at 8 bar and 100 °C for 19 h. The reaction mixture is concentrated and purified by reversed phase HPLC. Yield: 3.70 g. ESI mass spectrum: $[M+H]^+$ = 502; Retention time HPLC: 1.20 min (HPLC method Z018_S04)

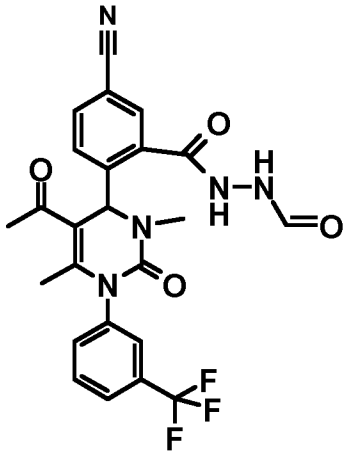
INTERMEDIATE 10



4-(2-Carboxy-4-cyano-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

4-(4-Cyano-2-methoxycarbonyl-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (intermediate 9)(3.39 g, 6.76 mmol) and lithium hydroxide (194.4 mg, 8.11 mmol) are stirred in 1,4-dioxane (84ml) and water (6.0 mL) at room temperature for 100 h. Water is added and the mixture is acidified with hydrochloric acid (4.0 mol/L) to a pH value of 3. The aqueous phase is extracted with dichloromethane three times. The combined organic phase is dried over $MgSO_4$, concentrated and purified by reversed phase HPLC. Yield: 1.34 g. ESI mass spectrum: $[M+H]^+$ = 488; Retention time HPLC: 1.08 min (HPLC method Z018_S04).

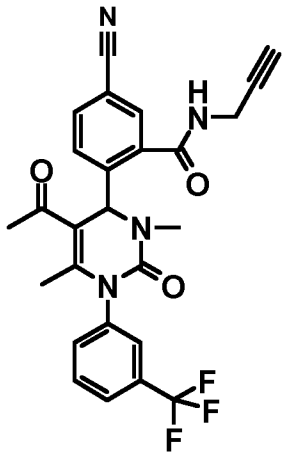
INTERMEDIATE 11



2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid formyl hydrazide

2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid (intermediate 6) (75.0 mg, 0.16 mmol)) and triethylamine (57.1 µL, 0.41 mmol) are suspended in *N,N*-dimethylformamide (2 mL), stirred for 5 min and *N,N,N',N'*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (63.2 mg, 0.20 mmol) is added. The mixture is stirred for 10 min and formic acid hydrazide (10.8 mg, 0.18 mmol) is added. The mixture is stirred overnight at room temperature. Another equivalent of formic acid hydrazide is added to bring the reaction to completion. The crude product is purified by reversed phase HPLC. Yield 30 mg; ESI mass spectrum $[M+H]^+ = 500$; Retention time HPLC: 0.94 min (HPLC method Z018_S04).

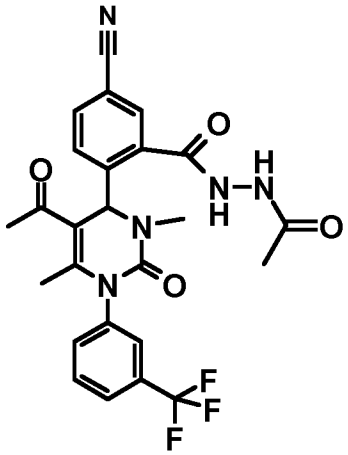
INTERMEDIATE 12



2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-N-prop-2-ynyl-benzamide

2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid (intermediate 6) (70 mg, 0.15 mmol) and triethylamine (35 µL, 0.25 mmol) are suspended in *N,N*-dimethylformamide (1.5 mL) and the mixture is shaken for 5 min. A solution of O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (61.1 mg, 0.16 mmol) in *N,N*-dimethylformamide (0.5 mL) and triethylamine (35 µL, 0.25 mmol) is added and the reaction mixture is shaken for 1.5 h at room temperature. The product is purified by reversed phase HPLC. Yield 48 mg; ESI mass spectrum $[M+H]^+$ = 495; Retention time HPLC: 0.99 min (HPLC method Z011_S03).

INTERMEDIATE 13

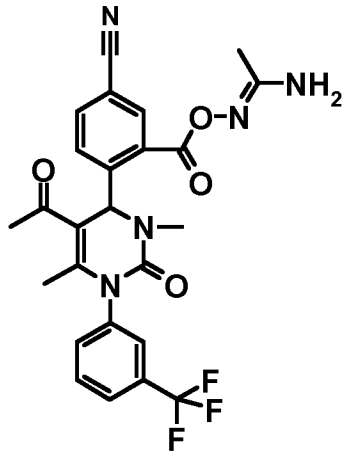


2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid acetyl hydrazide

2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid (intermediate 6) (47.0 mg, 0.10 mmol)) and triethylamine (35.8 µL, 0.26 mmol) are suspended in *N,N*-dimethylformamide (2 mL), stirred for 5 min and O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (41.0 mg, 0.11 mmol) is added. The mixture is stirred for 10 min and acetic acid hydrazide (12.2 mg, 0.16 mmol) is added. The mixture is stirred overnight at room temperature. Another equivalent of acetic acid hydrazide is added to bring the reaction to completion. The crude

product is purified by reversed phase HPLC. Yield 15 mg; ESI mass spectrum $[M+H]^+$ = 514; Retention time HPLC: 0.95 min (HPLC method Z018_S04).

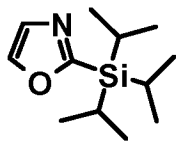
INTERMEDIATE 14



[1-Aminoethylideneamino]2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoate

2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid (example 6)(70 mg, 0.15 mmol) and diisopropylethylamine (125.1 µL, 0.73 mmol) are suspended in *N,N*-dimethylformamide (3 mL), stirred for 10 min and *N,N,N',N'*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (49 mg, 0.15 mmol) is added. The mixture is stirred for 10 min and N-hydroxyacetamidine (17.2 mg, 0.23 mmol) is added. The mixture is stirred overnight at room temperature. The crude product is purified by reversed phase HPLC. Yield 16 mg; ESI mass spectrum $[M+H]^+$ = 513; Retention time HPLC: 0.96 min (HPLC method Z011_S03).

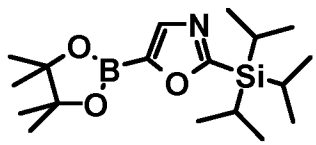
INTERMEDIATE 15



2-Triisopropylsilanyl-oxazole (see *Tetrahedron* **2009**, *65*, 6348-6353).

Oxazole (10 g, 144.797 mmol) is dissolved in 400 mL abs. diethylether under argon. The solution is cooled to -78°C and n-butyllithium (1.6 M solution in hexane, 100 mL, 160 mmol) is added slowly at that temperature. After stirring for 1 h triisopropylsilyl trifluoromethanesulfonate (40.265 mL, 144.797 mmol) in 100 mL abs. diethylether is added slowly. The mixture is warmed to r.t. within 12 h, and the solvent is evaporated in vacuo. The residue is treated with cyclohexane, filtered over silica gel, washed with cylcohexane/ethyl acetate 8:1, and the solvent is evaporated in vacuo. Yield: 33 g; ESI mass spectrum: $[M+H]^+$ = 226; retention time HPLC: 1.428 min (HPLC method Z001_002).

INTERMEDIATE 16

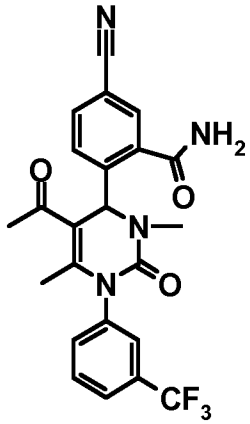


5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilanyl-oxazole (see *Tetrahedron* **2009**, *65*, 6348-6353).

2-Triisopropylsilanyl-oxazole (intermediate 16, 10 g, 44.365 mmol) is dissolved in 40 mL abs. diethylether under argon. The solution is cooled to -78°C and n-butyllithium (1.6 M solution in hexane, 100 mL, 160 mmol) is added slowly at that temperature. After stirring for 1 h boronic acid triispropylester (12 mL, 52.193 mmol) 20 mL abs. THF is added slowly. The mixture is stirred for 2 h, and is warmed to r.t.. The mixture is quenched with methanol. 2,3-Dihydroxy-2,3-dimethylbutane (pinacole, 5.243 g, 44.365 mmol) is dissolved in 10 mL THF and injected to the mixture at 18°C within 3 min. The mixture is acidified to pH 5 with acetic acid and stirred for 12 h. After addition of 150 mL diethylether and filtration over silica gel, the solvent is evaporated in vacuo. Yield: 15.2 g; ESI mass spectrum: $[M+H]^+$ = 352; retention time HPLC: 1.334 min (HPLC method Z001_002).

SYNTHESES OF EXAMPLES

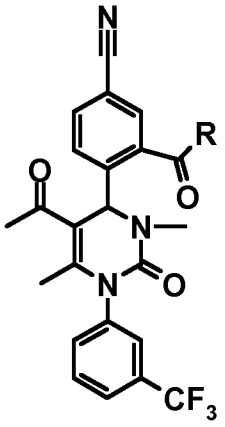
EXAMPLE 1

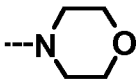
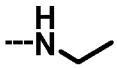
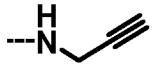
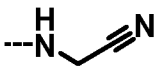
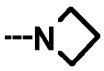
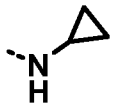
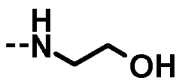
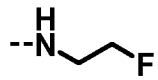
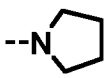


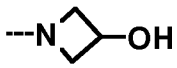
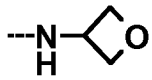
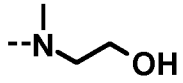
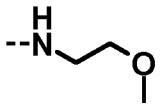
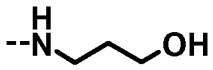
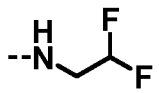
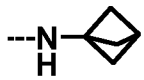
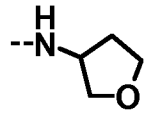
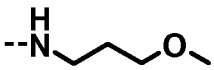
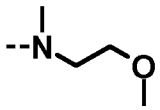
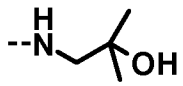
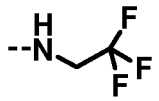
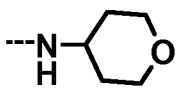
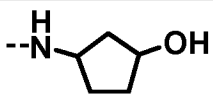
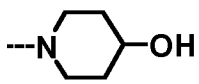
2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzamide

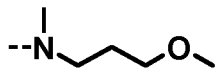
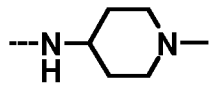
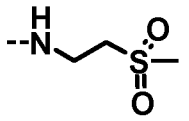
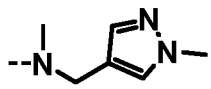
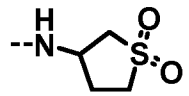
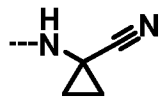
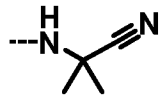
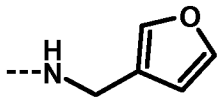
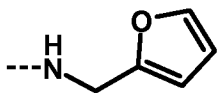
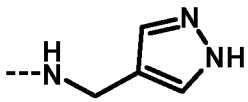
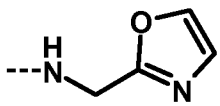
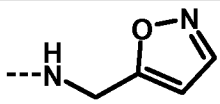
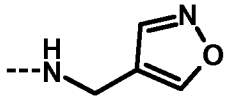
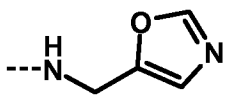
To a solution of 2-[5-acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid (intermediate 6, 20.0 mg, 0.04 mmol) in *N,N*-dimethylformamide (1 mL) triethylamine (15.0 µL, 0.11 mmol) is added and stirred at room temperature for 5 min. O-(7-azabonzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (17.5 mg, 0.05 mmol) is added and stirred for 15 min. A solution of ammonia (0.5 mol/L, 600.0 µL, 0.30 mmol) and triethylamine (15.0 µL, 0.11 mmol) in *N,N*-dimethylformamide (1 mL) is added and stirred at room temperature overnight. The reaction mixture is purified by reversed phase HPLC. Yield: 10.0 mg; ESI mass spectrum $[M+H]^+$ = 457; Retention time HPLC: 0.94 min (HPLC method Z011_S03).

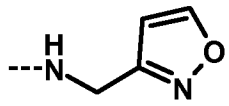
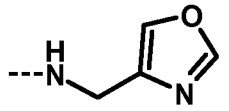
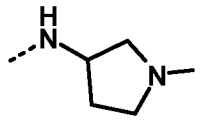
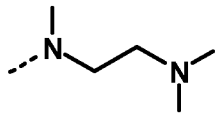
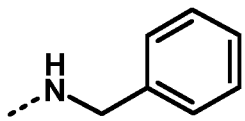
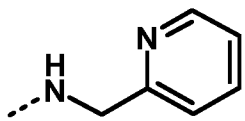
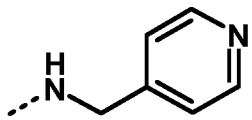
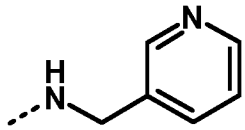
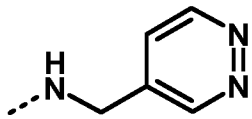
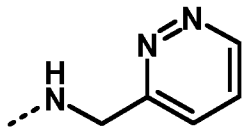
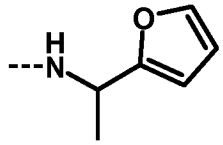
The following examples are prepared in analogy of 2-[5-acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-Pyrimidin-4-yl]-5-cyano-benzamide (example 1), using the appropriate amine as starting material. Example 1.3 is using morpholine as base.

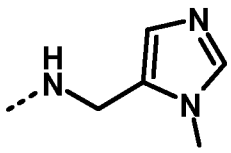
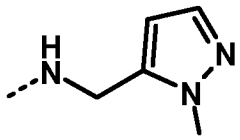
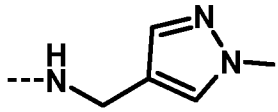
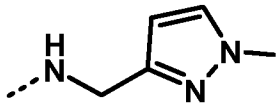
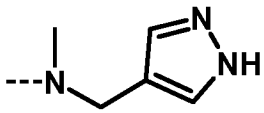
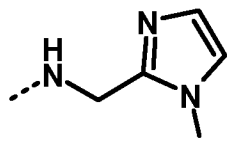
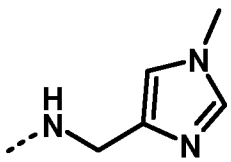
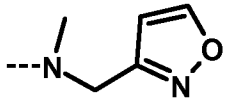
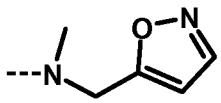
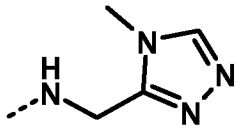
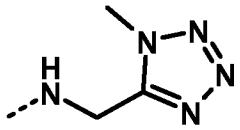


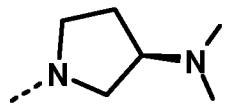
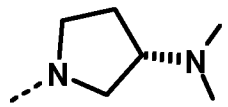
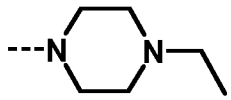
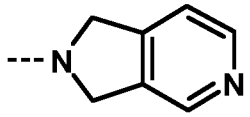
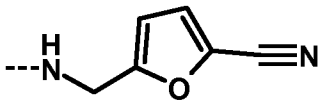
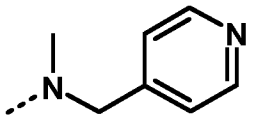
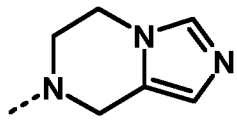
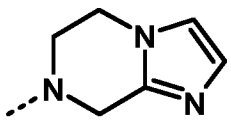
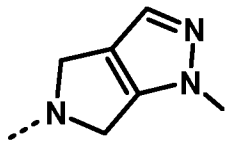
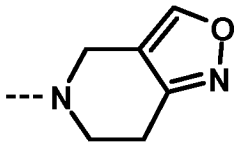
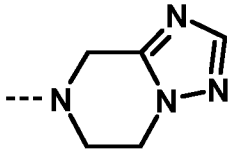
Example	R	MS $[M+H]^+$	Retention time [min]	HPLC-Method
1.1		471	0.97	Z011_S03
1.2		485	0.97	Z011_S03
1.3		527	0.97	Z011_S03
1.4		485	0.83	003_CA04
1.5		495	0.83	003_CA04
1.6		496	0.78	003_CA04
1.7		497	0.84	003_CA04
1.8		497	0.83	003_CA04
1.9		501	0.73	003_CA04
1.10		503	0.82	003_CA04
1.11		511	0.87	003_CA04

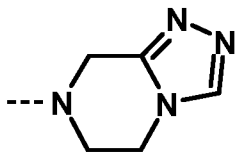
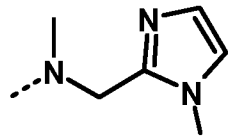
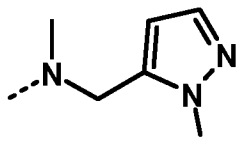
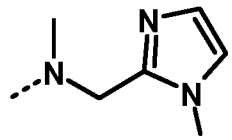
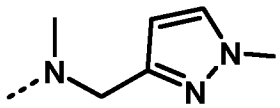
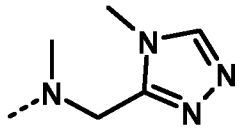
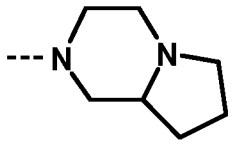
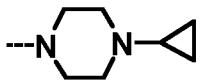
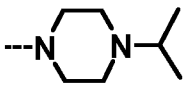
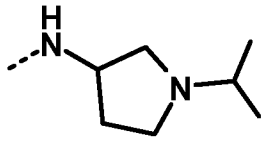
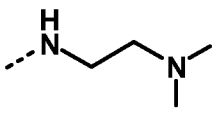
1.12		513	0.74	003_CA04
1.13		513	0.77	003_CA04
1.14		515	0.75	003_CA04
1.15		515	0.82	003_CA04
1.16		515	0.74	003_CA04
1.17		521	0.85	003_CA04
1.18		523	0.93	003_CA04
1.19		527	0.80	003_CA04
1.20		529	0.83	003_CA04
1.21		529	0.84	003_CA04
1.22		529	0.79	003_CA04
1.23		539	0.89	003_CA04
1.24		541	0.81	003_CA04
1.25		541	0.77	003_CA04
1.26		541	0.76	003_CA04

1.27		543	0.86	003_CA04
1.28		554	0.81	003_CA04
1.29		563	0.76	003_CA04
1.30		565	0.80	003_CA04
1.31		575	0.77	003_CA04
1.32		522	0.83	005_CA01
1.33		524	1.02	Z018_S04
1.34		537	0.88	005_CA01
1.35		537	0.89	005_CA01
1.36		537	0.72	005_CA01
1.37		538	0.79	005_CA01
1.38		538	0.82	005_CA01
1.39		538	0.82	005_CA01
1.40		538	0.78	005_CA01

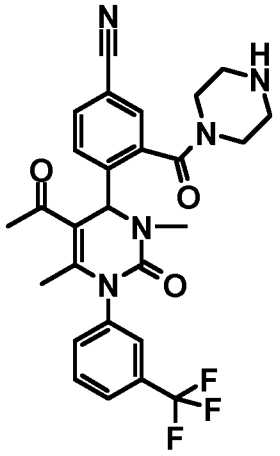
1.41		538	0.82	005_CA01
1.42		538	0.79	005_CA01
1.43		540	0.59	005_CA01
1.44		542	0.63	005_CA01
1.45		547	0.94	005_CA01
1.46		548	0.63	005_CA01
1.47		546	0.69	005_CA01
1.48		548	0.60	005_CA01
1.49		549	0.70	005_CA01
1.50		549	0.72	005_CA01
1.51		551	0.93	005_CA01

1.52		551	0.59	005_CA01
1.53		551	0.78	005_CA01
1.54		551	0.77	005_CA01
1.55		551	0.79	005_CA01
1.56		551	0.74	005_CA01
1.57		551	0.60	005_CA01
1.58		551	0.85	Z018_S04
1.59		552	0.85	005_CA01
1.60		552	0.85	005_CA01
1.61		552	0.64	005_CA01
1.62		553	0.77	005_CA01

1.63		554	0.59	005_CA01
1.64		554	0.59	005_CA01
1.65		554	0.86	Z018_S04
1.66		560	0.60	005_CA01
1.67		562	0.89	005_CA01
1.68		562	0.61	005_CA01
1.69		563	0.60	005_CA01
1.70		563	0.60	005_CA01
1.71		563	0.79	005_CA01
1.72		564	0.84	005_CA01
1.73		564	0.76	005_CA01

1.74		564	0.67	005_CA01
1.75		565	0.60	005_CA01
1.76		565	0.82	005_CA01
1.77		565	0.62	005_CA01
1.78		565	0.83	005_CA01
1.79		566	0.67	005_CA01
1.80		566	0.60	005_CA01
1.81		566	0.61	005_CA01
1.82		568	0.61	005_CA01
1.83		568	0.62	005_CA01
1.84		528	0.59	005_CA01

EXAMPLE 2



4-(5-Acetyl-3,6-dimethyl-2-oxo-1-m-tolyl-1,2,3,4-tetrahydro-pyrimidin-4-yl)-3-(piperazine-1-carbonyl)-benzonitrile

Step1:

4-{2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoylamino}-piperidine-1-carboxylic acid *tert*-butyl ester

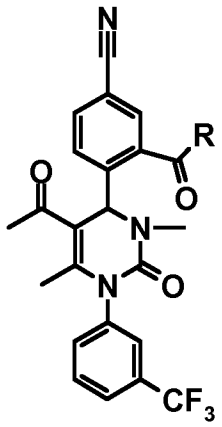
To a solution of 2-[5-acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid (intermediate 6, 40.0 mg, 0.09 mmol) in *N,N*-dimethylformamide (1 mL) triethylamine (25.0 µL, 0.18 mmol) is added and stirred at room temperature for 5 min. Then O-(7-azabonzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (34.9 mg, 0.09 mmol) is added and stirred for 15 min. A solution of *tert*-butyl 1-piperazinecarboxylate (24.4 mg, 0.13 mmol) and triethylamine (25.0 µL, 0.18 mmol) in *N,N*-dimethylformamide (1 mL) is added and stirred at room temperature for 72 h. The reaction mixture is purified by reversed phase HPLC. ESI mass spectrum $[M\text{-}Boc+H]^+ = 526$; Retention time HPLC: 1.16 min (HPLC method Z018_S04).

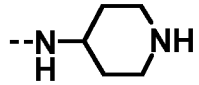
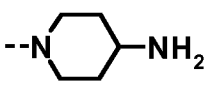
Step 2:

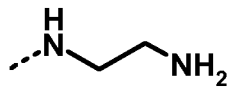
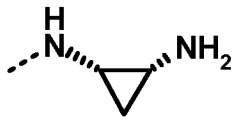
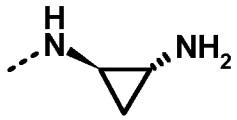
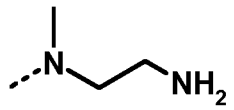
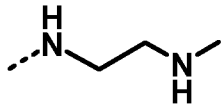
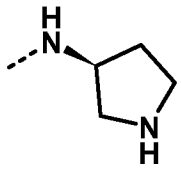
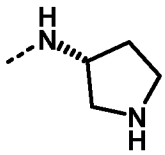
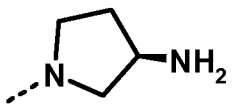
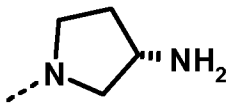
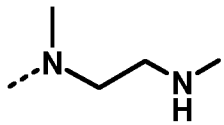
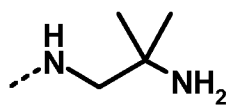
4-(5-Acetyl-3,6-dimethyl-2-oxo-1-m-tolyl-1,2,3,4-tetrahydro-pyrimidin-4-yl)-3-(piperazine-1-carbonyl)-benzonitrile

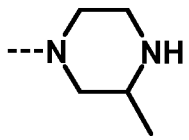
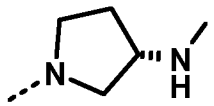
To a solution of 4-{2-[5-acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoylamino}-piperidine-1-carboxylic acid *tert*-butyl ester (step 1) in dichloromethane (1.0 mL), 95% aqueous trifluoroacetic acid (1 mL, 6.5 mmol) is added and stirred at room temperature for 2 h. The reaction mixture is concentrated and purified by reversed phase HPLC. Yield: 21.0 mg; ESI mass spectrum $[M+H]^+$ = 526; Retention time HPLC: 0.84 min (HPLC method Z018_S04).

The following examples are prepared in analogy of 2-[5-acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-N-piperidin-4-yl-benzamide (example 2), using the appropriate amine as starting material. The Boc-protected intermediate from step 1 is not purified and after evaporation of the solvent the residue is treated with trifluoroacetic acid as described in step 2.

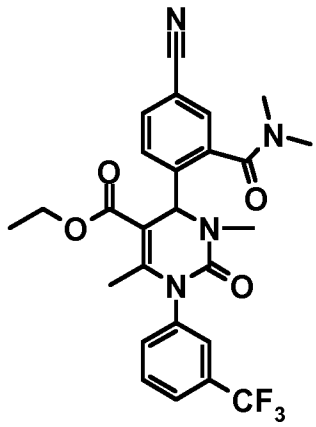


Example	R	MS $[M+H]^+$	Retention time [min]	HPLC-Method
2.1		540	0.84	Z018_S04
2.2		540	0.84	Z018_S04

2.3		500	0.58	005_CA01
2.4		512	0.58	005_CA01
2.5		512	0.58	005_CA01
2.6		514	0.59	005_CA01
2.7		514	0.59	005_CA01
2.8		526	0.59	005_CA01
2.9		525	0.59	005_CA01
2.10		526	0.58	005_CA01
2.11		526	0.58	005_CA01
2.12		528	0.60	005_CA01
2.13		528	0.60	005_CA01
2.14		538	0.85	Z018_S04

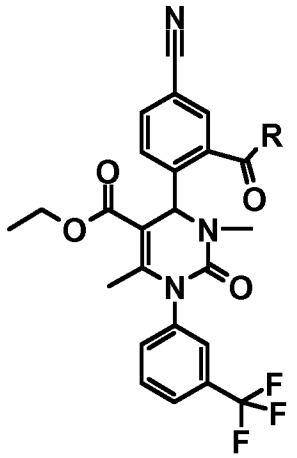
2.15		540	0.59	005_CA01
2.16		540	0.59	005_CA01

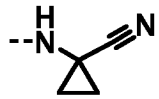
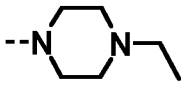
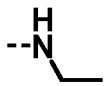
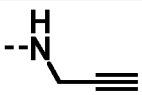
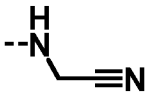
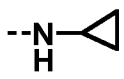
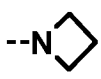
EXAMPLE 3

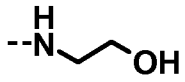
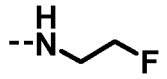
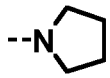
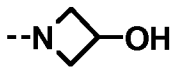
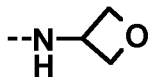
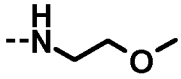
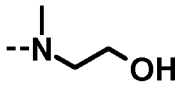
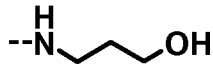
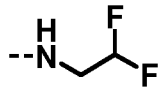
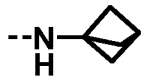
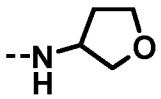
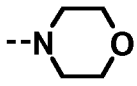
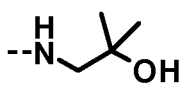
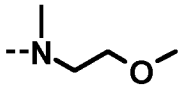
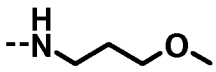


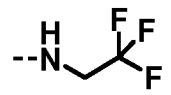
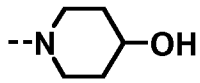
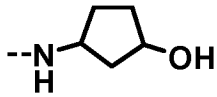
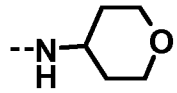
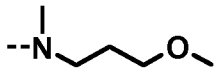
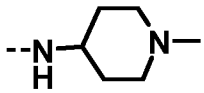
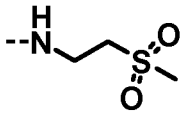
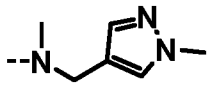
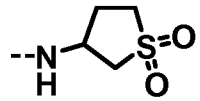
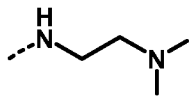
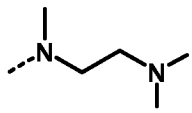
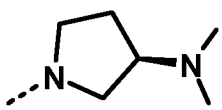
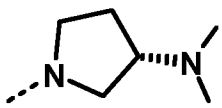
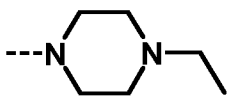
4-(4-Cyano-2-dimethylcarbamoyl-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester To a solution of 4-(2-carboxy-4-cyano-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (intermediate 10)(27.0 mg, 0.06 mmol) is suspended in *N,N*-dimethylformamide (1.0 mL) and triethylamine (20.0 µL, 0.14 mmol) is added. The mixture is stirred at room temperature for 10 min and O-(7-azabonzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (21.9 mg, 0.06 mmol) is added and the mixture is stirred for 15 min. A solution of dimethyl amine in tetrahydrofurane (c = 2 mol/L, 138.5 µL, 0.28 mmol) and triethylamine (20.0 µL, 0.14 mmol) in *N,N*-dimethylformamide (1.0 mL) is added and the reaction mixture stirred at room temperature for 3 days. The crude product is purified by reversed phase HPLC. Yield 16.1 mg; ESI mass spectrum $[M+H]^+$ = 515; Retention time HPLC: 1.04 min (HPLC method Z011_S03).

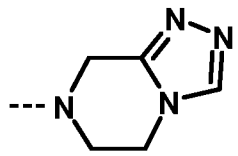
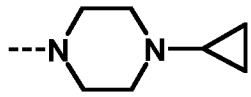
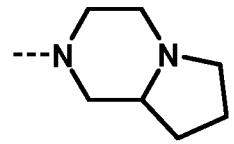
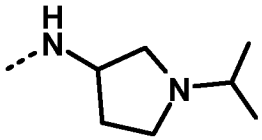
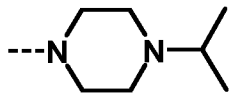
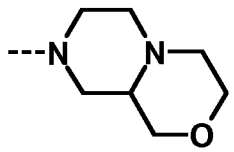
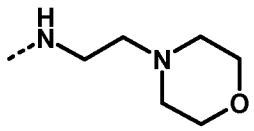
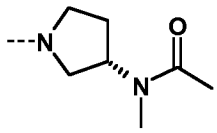
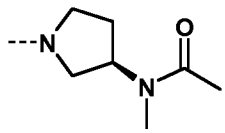
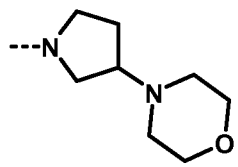
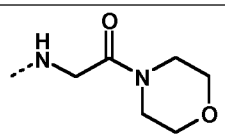
The following examples are prepared in analogy of 4-(4-cyano-2-dimethylcarbamoyl-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (example 3), using the appropriate amine as starting material.

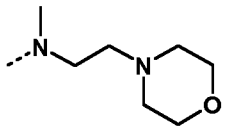
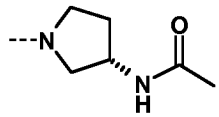
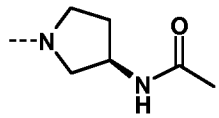
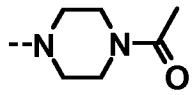
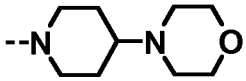


Example	R	MS $[M+H]^+$	Retention time [min]	HPLC-Method
3.1		552	1.10	Z018_S04
3.2		584	0.91	Z018_S04
3.3		487	0.83	003_CA04
3.4		501	0.88	003_CA04
3.5		515	0.93	003_CA04
3.6		525	0.91	003_CA04
3.7		526	0.87	003_CA04
3.8		527	0.93	003_CA04
3.9		527	0.93	003_CA04

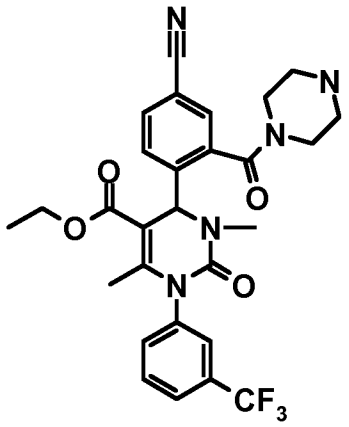
3.10		531	0.82	003_CA04
3.11		533	0.91	003_CA04
3.12		541	0.97	003_CA04
3.13		543	0.83	003_CA04
3.14		543	0.86	003_CA04
3.15		455	0.91	003_CA04
3.16		455	0.85	003_CA04
3.17		455	0.83	003_CA04
3.18		551	0.93	003_CA04
3.19		553	1.02	003_CA04
3.20		554	0.95	003_CA04
3.21		557	0.89	003_CA04
3.22		557	0.91	003_CA04
3.23		559	0.88	003_CA04
3.24		559	0.94	003_CA04
3.25		559	0.93	003_CA04

3.26		569	0.97	003_CA04
3.27		571	0.82	003_CA04
3.28		571	0.86	003_CA04
3.29		571	0.91	003_CA04
3.30		573	0.95	003_CA04
3.31		584	0.91	003_CA04
3.32		593	0.84	003_CA04
3.33		595	0.89	003_CA04
3.34		605	0.86	003_CA04
3.35		558	0.66	005_CA01
3.36		572	0.68	005_CA01
3.37		584	0.66	005_CA01
3.38		584	0.66	005_CA01
3.40		584	0.91	Z018_S04

3.41		594	0.76	005_CA01
3.42		596	0.68	005_CA01
3.43		596	0.68	005_CA01
3.44		598	0.69	005_CA01
3.45		598	0.68	005_CA01
3.46		612	0.68	005_CA01
3.47		570	0.77	004_CA05
3.48		582	0.96	Z011_S03
3.49		582	0.76	004_CA05
3.50		596	0.85	Z018_S04
3.51		583	0.94	Z011_S03

3.52		584	0.79	004_CA05
3.53		568	0.99	Z018_S04
3.54		568	0.73	004_CA05
3.55		568	0.74	004_CA05
3.56		610	0.78	004_CA05

EXAMPLE 4



Step1:

4-[2-(4-*tert*-Butoxycarbonyl-piperazine-1-carbonyl)-4-cyano-phenyl]-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

4-(2-carboxy-4-cyano-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (intermediate 10)(30.0 mg, 0.06 mmol) is suspended in *N,N*-dimethylformamide (0.5 mL) and triethylamine (20.0 µL, 0.14 mmol) is added. The mixture is stirred at room temperature for 5 min and O-(7-azabonzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (24.6 mg, 0.065 mmol) is added

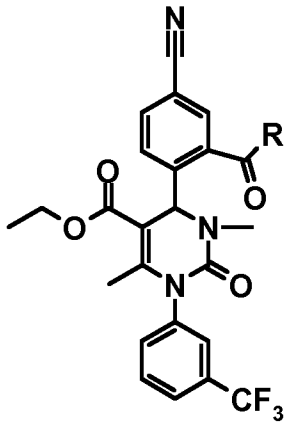
and the mixture is stirred for 15 min. A solution of *tert*-butyl 1-piperazinecaboxylate (17.2 mg, 0.09 mmol) in *N,N*-dimethylformamide (0.5 mL) and triethylamine (20.0 µL, 0.14 mmol) is added and the reaction mixture stirred at room temperature for 2 h. The crude product is purified by reversed phase HPLC. ESI mass spectrum $[M\text{-}tBu+H]^+ = 600$; Retention time HPLC: 1.21 min (HPLC method Z018_S08).

Step 2:

4-[4-Cyano-2-(piperazine-1-carbonyl)-phenyl]-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

To a solution of 4-[2-(4-*tert*-butoxycarbonyl-piperazine-1-carbonyl)-4-cyano-phenyl]-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (step 1) in dichloromethane (1.0 mL) trifluoroacetic acid (0.75 mL) is added and stirred at room temperature for 2 h. The reaction mixture is concentrated and purified by reversed phase HPLC. Yield: 12.5 mg; ESI mass spectrum $[M+H]^+ = 556$; Retention time HPLC: 0.88 min (HPLC method Z018_S04).

The following examples are prepared in analogy of 4-[4-Cyano-2-(piperazine-1-carbonyl)-phenyl]-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (example 4), using the appropriate amine as starting material. The Boc-protected intermediate from step 1 is not purified and after evaporation of the solvent the residue is treated with trifluoroacetic acid as described in step 2



Example	R	MS $[M+H]^+$	Retention time [min]	HPLC-Method
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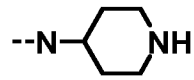
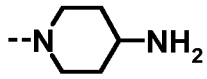
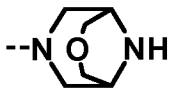
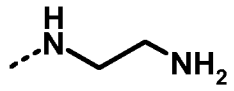
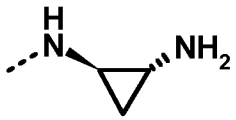
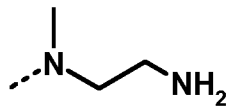
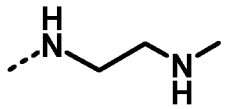
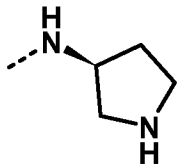
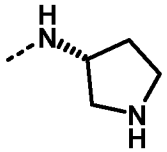
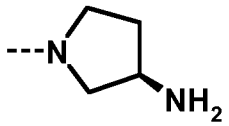
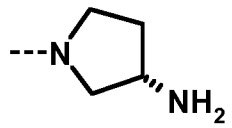
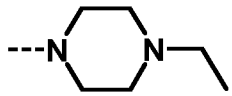
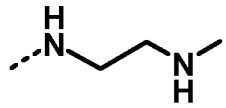
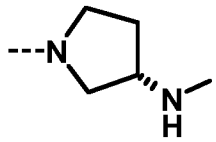
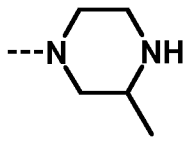
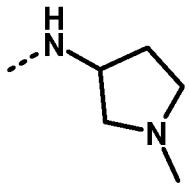
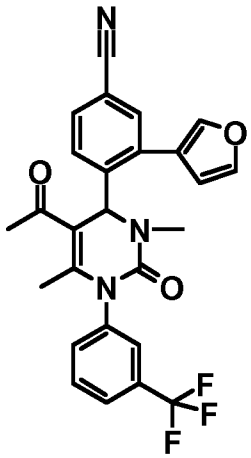
4.2		570	0.89	Z018_S04
4.3		570	0.88	Z018_S04
4.4		598	0.89	Z018_S04
4.5		530	0.65	005_CA01
4.6		542	0.65	005_CA01
4.7		542	0.65	005_CA01
4.8		544	0.66	005_CA01
4.9		544	0.67	005_CA01
4.10		556	0.66	005_CA01
4.11		556	0.66	005_CA01
4.12		556	0.65	005_CA01

4.13		556	0.65	005_CA01
4.14		584	0.91	Z018_S04
4.15		558	0.68	005_CA01
4.16		570	0.66	005_CA01
4.17		570	0.66	005_CA01
4.18		570	0.67	005_CA01

EXAMPLE 5



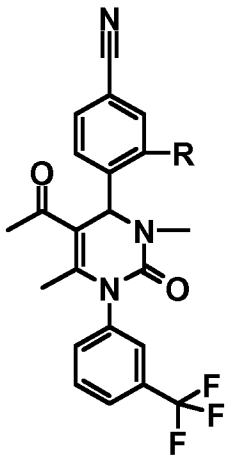
4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-furan-3-yl-benzonitrile

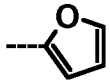
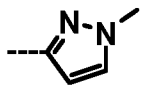
4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-bromo-benzonitrile (intermediate 4)(30.0 mg, 0.06 mmol) and furane-3 boronic acid

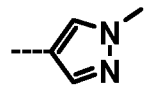
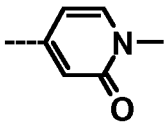
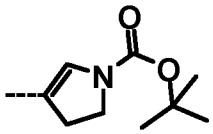
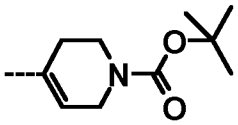
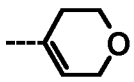
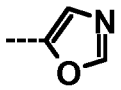
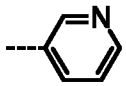
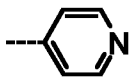
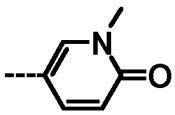
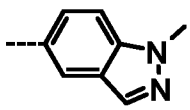
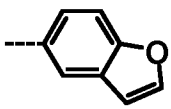
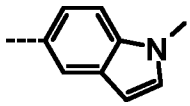
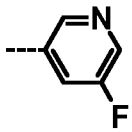
(10.3 mg, 0.09 mmol) are suspended in *N,N*-dimethylformamide (1 mL) and are degassed with a stream of argon. Caesium carbonate solution (2 mol/L, 64 µL, 0.13 mmol) and 1.1-bis(diphenylphosphino)-ferrocendichloropalladium(II), complex with dichloromethane (1:1) (3.97 mg, 0.005 mmol) are added and the reaction is stirred at 80 °C overnight. The reaction mixture is filtrated over a layer of silica gel and basic aluminum oxide 1:1and purified by reversed phase HPLC. Yield: 7.2 mg; ESI mass spectrum $[M+H]^+$ = 480; Retention time HPLC: 1.13 min (HPLC method Z018_S04).

The following examples are prepared in analogy 4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-furan-3-yl-benzonitrile (example 5), using the appropriate boronic acid or boronic acid ester as starting material. For examples 5.2, 5.3, 5.4, 5.5,5.6, 5.13-5.15 potassium carbonate is used as base and acetonitrile as solvent.

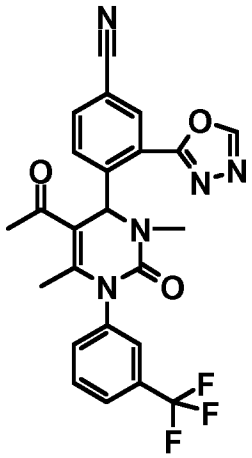
Example 5.8 is synthesized as described for example 5 using 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilanyl-oxazole (intermediate 16) as reagent. The silylgroup is deprotected with trifluoroacetic acid/water 1:1.



Example	R	MS $[M+H]^+$	Retention time [min]	HPLC-Method
5.1		480	1.13	Z018_S04
5.2		494	0.75	X018_S01

5.3		494	1.05	Z018_S04
5.4		521	0.83	005_CA07
5.5		581	1.20	Z018_S04
5.6		595	1.20	Z018_S04
5.7		496	1.09	Z018_S04
5.8		481	1.04	Z018_S04
5.9		491	0.56	X018_S01
5.10		491	0.53	X018_S01
5.11		521	0.64	X018_S01
5.12		544	1.06	Z018_S04
5.13		530	0.91	004_CA05
5.14		543	0.91	004_CA05
5.15		509	1.08	Z018_S04

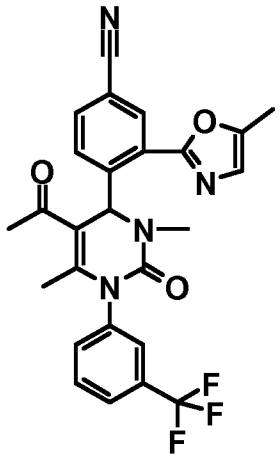
EXAMPLE 6



4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-[1,3,4]oxadiazol-2-yl-benzonitrile

2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid formyl hydrazide (intermediate 11) (30.0 mg, 0.06 mmol)) is suspended in dichloromethane (1 mL) and (methoxycarbonylsulfamoyl)triethyl-ammonium hydroxide (Burgess reagent)(35.8 mg,0.15 mmol) is added.The mixture is stirred at room temperature for 3 days. Additional (methoxycarbonylsulfamoyl)triethyl-ammonium hydroxide (Burgess reagent)(35.8 mg,0.15 mmol) is added and the reaction is continued for 2 h at 40 °C. The solvent is removed under reduced pressure and purification is performed by reversed phase HPLC. Yield: 4 mg; ESI mass spectrum $[M+H]^+$ = 482; Retention time HPLC: 1.02 min (HPLC method Z018_S04).

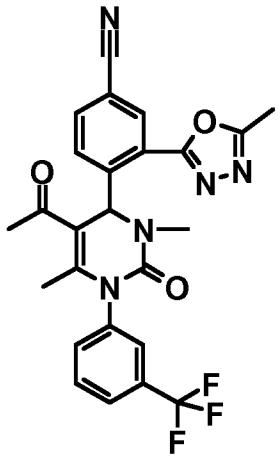
EXAMPLE 7



4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-(5-methyl-oxazol-2-yl)-benzonitrile

2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-N-prop-2-ynyl-benzamide (intermediate 12) (48 mg, 0.097 mmol) is suspended in dichloromethane (2 mL) and degassed with a stream of argon. gold(III)-chloride (1.2 mg, 0.004 mmol) is added and the reaction is shaken at room temperature for 2 h. The solvent is evaporated and the residue is purified by reversed phase HPLC. Yield: 17 mg; ESI mass spectrum $[M+H]^+$ = 495; Retention time HPLC: 1.09 min (HPLC method Z011_S03).

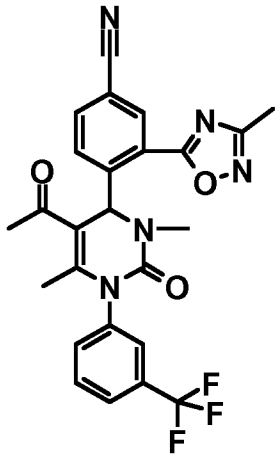
EXAMPLE 8



4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-(5-methyl-[1,3,4]oxadiazol-2-yl)-benzonitrile 2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-

benzoic acid acetyl hydrazide (intermediate 13) (15 mg, 0.03 mmol) is suspended in dichloromethane (1 mL) and (methoxycarbonylsulfamoyl)triethyl-ammonium hydroxide (Burgess reagent)(17.4 mg, 0.07 mmol) is added. The mixture is stirred at room temperature for 3 days. The solvent is removed under reduced pressure and purification is performed by reversed phase HPLC. Yield: 6.4 mg; ESI mass spectrum $[M+H]^+ = 496$; Retention time HPLC: 1.04 min (HPLC method Z018_S04).

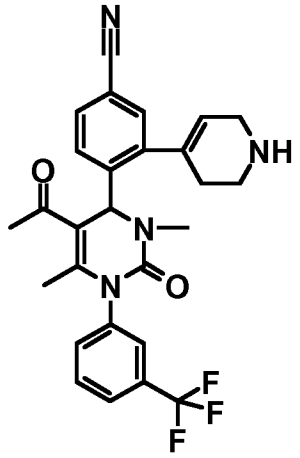
EXAMPLE 9



4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-(5-methyl-[1,3,4]oxadiazol-2-yl)-

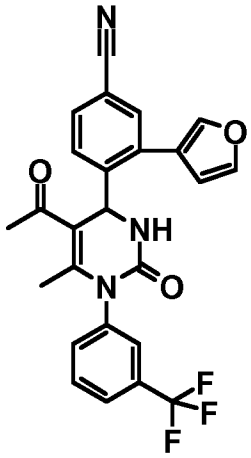
[1-Aminoethylideneamino]2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoate (intermediate 14)(16.0 mg, 0.03 mmol) is suspended in dichloromethane (1 mL) and (methoxycarbonylsulfamoyl)triethyl-ammonium hydroxide (Burgess reagent)(18.6 mg, 0.08 mmol) is added. The mixture is stirred at room temperature overnight. The temperature is raised to 40 °C and additional (methoxycarbonyl-sulfamoyl)triethyl-ammonium hydroxide (Burgess reagent)(9 mg, 0.04 mmol) is added. After 3 h the reaction is complete and the solvent is removed under reduced pressure. Purification is performed by reversed phase HPLC. Yield: 6.0 mg; ESI mass spectrum $[M+H]^+ = 496$; Retention time HPLC: 1.06 min (HPLC method Z011_S03).

EXAMPLE 10



4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-benzonitrile 4-{2-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-phenyl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (example 5.6) (35 mg, 0.06 mmol) is suspended wit aqueous trifluoroacetic acid (95%, 2 mL). The reaction mixture is shaken for 15 min, evaporated and the product is purified by reversed phase HPLC. Yield: 25 mg; ESI mass spectrum $[M+H]^+$ = 495; Retention time HPLC: 1.20 min (HPLC method Z018_S04).

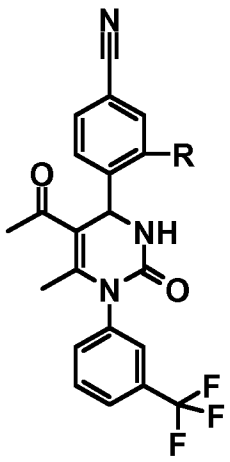
EXAMPLE 11

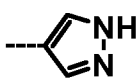
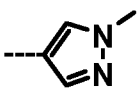


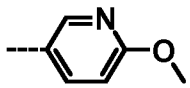
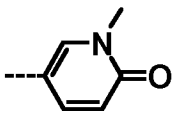
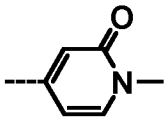
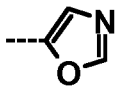
4-[5-Acetyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-furan-3-yl-benzonitrile 4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-

trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-bromo-benzonitrile (intermediate 4) (50 mg, 0.11 mmol) and furane-3 boronic acid (17.6 mg, 0.16 mmol) are suspended in acetonitrile (1.5 mL) and are degassed with a stream of argon. Potassium carbonate solution (2 mol/L, 162 µL, 0.32 mmol) and 1.1-bis(diphenylphosphino)-ferrocendichloropalladium(II), complex with dichloromethane (1:1) (4.3 mg, 0.005 mmol) are added and the reaction is shaken at 80 °C overnight. The reaction mixture is filtrated over a layer of silica gel and basic aluminum oxide 1:1and purified by reversed phase HPLC. Yield: 28.8 mg; ESI mass spectrum $[M+H]^+$ = 466; Retention time HPLC: 1.03 min (HPLC method Z011_S03).

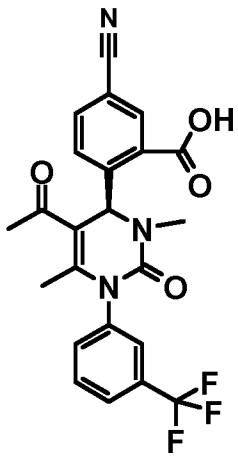
The following examples are prepared in analogy 4-[5-Acetyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-furan-3-yl-benzonitrile (example 11), using the appropriate boronic acid or boronic acid ester as starting material. Example 11.6 is synthesized using cesium carbonate as base, dioxane as solvent and 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilanyl-oxazole (intermediate 16) as reagent. The silylgroup is deprotected with trifluoroacetic acid/water 1:1.



Example	R	MS $[M+H]^+$	Retention time [min]	HPLC-Method
11.1		466	0.98	Z018_S04
11.2		480	0.96	Z011_S03

11.3		507	1.03	Z011_S03
11.4		507	0.98	Z018_S04
11.5		507	0.93	Z011_S03
11.6		467	1.0	Z018_S04

EXAMPLE 12

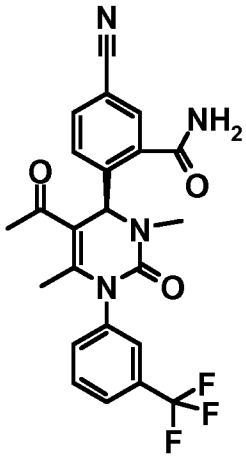


2-[(R)-5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid

The racemate is prepared as described for intermediate 6, yield 2.23g. The enantiomers are separated by preparative chromatography on a chiral phase (Lux C4, 20 x 250 mm, 5 µm, eluent heptane/ethanol and trifluoroacetic acid as modifier. Yield: 877 mg; ESI mass spectrum $[M+H]^+$ = 458; Retention time: 2.77 min (early eluting R-enantiomer) (method I_IC_20_MeOH_NH3).

The configuration of example 12 is assigned based on X-ray structure of example 12 in complex with neutrophil elastase.

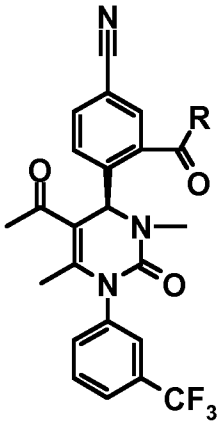
EXAMPLE 13

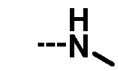
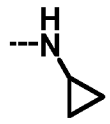
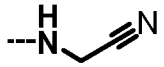


2-[(R)-5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzamide

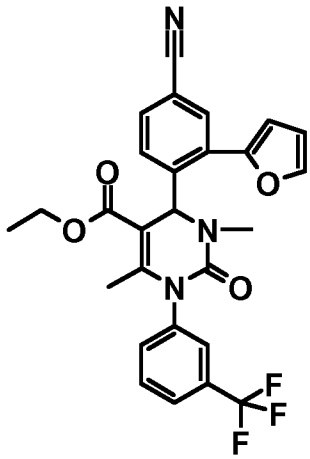
2-[(R)-5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzoic acid (example 12)(110.0 mg, 0.24 mmol) is suspended in *N,N*-dimethylformamide (1 mL) and triethylamine (100.0 µL, 714 µmol) is added. The mixture is stirred at room temperature for 10 min and O-(7-azabonzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (92.4 mg, 0.24 mmol) is added and the mixture is stirred for 15 min. A solution of ammonia in dioxane (0.5 mol/L, 2 mL, 1.0 mmol) in *N,N*-dimethylformamide (1 mL) is added and the reaction mixture stirred at room temperature overnight. The crude product is purified by reversed phase HPLC. Yield 33.7 mg; ESI mass spectrum $[M+H]^+$ = 457; Retention time HPLC: 0.92 min (HPLC method Z011_S03).

The following examples are prepared in analogy of 2-[(R)-5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-5-cyano-benzamide (example 13), using the appropriate amine as starting material.



Example	R	MS $[M+H]^+$	Retention time [min]	HPLC-Method
13.1		471	0.95	Z011_S03
13.2		497	1.0	Z011_S03
13.3		496	0.96	Z011_S03

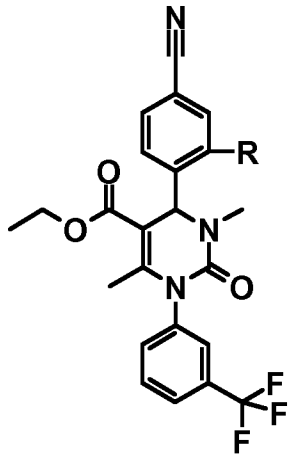
EXAMPLE 14

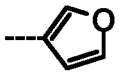
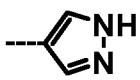
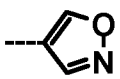
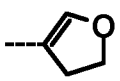


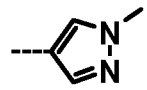
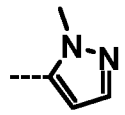
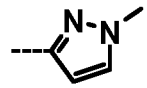
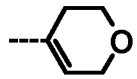
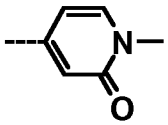
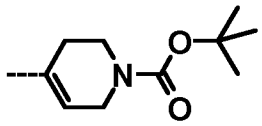
4-(4-Cyano-2-furan-2-yl-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester 4-(2-Bromo-4-cyano-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (intermediate 8) (50 mg, 0.1 mmol) and furane-2 boronic acid

(13.9 mg, 0.12 mmol) are suspended in acetonitrile (2.0 mL) and are degassed with a stream of argon. Potassium carbonate solution (2 mol/L, 144 µL, 0.29 mmol) and 1.1-bis(diphenylphosphino)-ferrocendichloropalladium(II), complex with dichloromethane (1:1) (2.35 mg, 0.003 mmol) are added and the reaction is shaken at 80 °C for 7 hours. The reaction mixture is filtrated over a layer of silica gel and basic aluminum oxide 1:1and purified by reversed phase HPLC. Yield: 18.3 mg; ESI mass spectrum $[M+H]^+$ = 510; Retention time HPLC: 1.20 min (HPLC method Z018_S04).

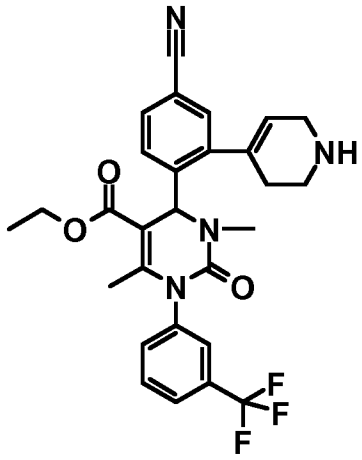
The following examples are prepared in analogy 4-(4-Cyano-2-furan-2-yl-phenyl)-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (example 14), using the appropriate boronic acid or boronic acid ester as starting material.



Example	R	MS $[M+H]^+$	Retention time [min]	HPLC-Method
14.1		510	1.09	Z018_S04
14.2		510	1.07	Z018_S04
14.3		511	1.14	Z018_S04
14.4		512	1.13	Z011_S03

14.5		524	1.11	Z018_S04
14.6		524	1.12	Z018_S04
14.7		524	1.15	Z018_S04
14.8		525	1.16	Z018_S04
14.9		551	1.06	Z018_S04
14.10		525 (-Boc)	1.25	Z018_S04

EXAMPLE 15

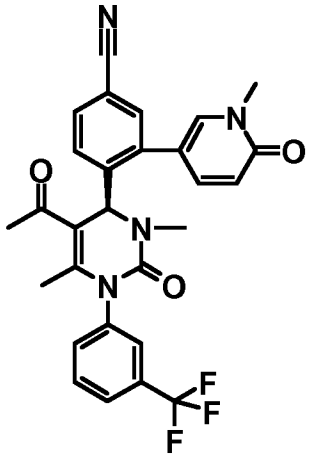


4-[4-Cyano-2-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester

4-[2-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-cyano-phenyl]-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (example 15.10) (35 mg, 0.06 mmol) is suspended wit aqueous trifluoroacetic acid (95%, 2 mL). The reaction mixture is shaken for 15 min, evaporated and

the product is purified by reversed phase HPLC. Yield: 7.2 mg; ESI mass spectrum $[M+H]^+$ = 525; Retention time HPLC: 0.56 min (HPLC method X018_S01).

EXAMPLE 16



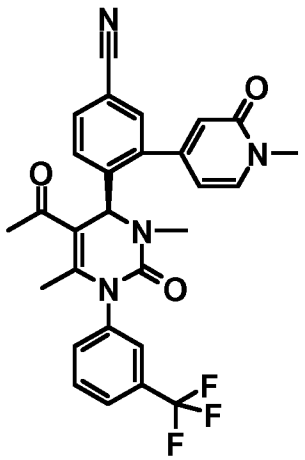
4-[(R)-5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-benzonitrile.

4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-bromo-benzonitrile (intermediate 4)(400 mg, 0.81 mmol) and N-methyl-1H-pyridin-2-one-5-boronic acid pinacol ester (248 mg, 1.06 mmol) are suspended in acetonitrile (15 mL) and are degassed with a stream of argon. Potassium carbonate solution (2 mol/L, 1.22 mL, 2.44 mmol) and 1.1-bis(diphenylphosphino)-ferrocendichloro-palladium(II), complex with dichloromethane (1:1) (6.34 mg, 0.008 mmol) are added and the reaction is stirred at 100 °C overnight. Additional N-methyl-1H-pyridin-2-one-5-boronic acid pinacol ester (100 mg, 0.4 mmol) and 1.1-bis(diphenylphosphino)-ferrocendichloropalladium(II), complex with dichloromethane (1:1) (2 mg, 0.002 mmol) are added and the reaction is continued at 120 °C for 60 min under microwave irradiation. The reaction mixture is filtrated over a layer of silica gel and basic aluminum oxide 1:1and purified by reversed phase HPLC. Yield: 125 mg; ESI mass spectrum $[M+H]^+$ = 521; Retention time HPLC: 1.01 min (HPLC method Z018_S04).

The enantiomer separation is performed by preparative supercritical fluid chromatography on a chiral phase (Daicel Chiralpak IA, 10 x 250 mm, 5 µm, 20% methanol and 20 mM NH_3 in supercritical CO_2, 40 °C, flow 10 ml/min, 120 bar back pressure).Yield 55 mg;

retention time: 1.6 min (early eluting enantiomer) (method: I_IA_20_MEOH_NH3). The configuration of example 16 is assigned based on the X-Ray structure of example 16 in complex with neutrophil elastase.

EXAMPLE 17



4-[(R)-5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-(1-methyl-2-oxo-1,2-dihydro-pyridin-4-yl)-benzonitrile.

4-[5-Acetyl-3,6-dimethyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-4-yl]-3-bromo-benzonitrile (intermediate 4)(300 mg, 0.61 mmol) and (1-methyl-2-oxo-4-pyridyl)boronic acid (121 mg, 0.79 mmol) are suspended in acetonitrile (9 mL) and are degassed with a stream of argon. Potassium carbonate solution (2 mol/L, 914 µL, 1.83 mmol) and 1.1-bis(diphenylphosphino)-ferrocendichloropalladium(II), complex with dichloromethane (1:1) (9.95 mg, 0.012 mmol) are added and the reaction is shaken at 75 °C overnight. The reaction mixture is filtrated over a layer of silica gel and basic aluminum oxide 1:1and purified by reversed phase HPLC. Yield: 142 mg; ESI mass spectrum $[M+H]^+$ = 521; Retention time HPLC: 0.99 min (HPLC method Z018_S04).

The enantiomer separation is performed by preparative supercritical fluid chromatography on a chiral phase (Daicel Chiralpak IB, 20 x 250 mm, 5 µm, 10% methanol in supercritical CO_2, 40 °C, flow 60 ml/min, 150 bar back pressure).Yield 57.9 mg; retention time: 3.38 min (late eluting enantiomer) (method: I_IB_15_MeOH_NH3). The configuration of

example 17 is assigned based on the X-Ray structure of example 17 in complex with neutrophil elastase

PHARMACOLOGICAL DATA

Other features and advantages of the present invention will become apparent from the following more detailed examples which illustrate, by way of example, the principles of the invention.

HUMAN NEUTROPHIL ELASTASE ASSAY

Materials: Human neutrophil elastase was purchased from Calbiochem (Cat.No.: 324681) and the elastase substrate MeOSuc-Ala-Ala-Pro-Val-AMC from Bachem (Cat.No.: I-1270). All other materials were of the highest grade commercially available.

The following buffers were used: Compound buffer: 100mM Tris, 500mM NaCl, adjusted to pH 7.5; Assay buffer: 100mM Tris, 500mM NaCl, adjusted to pH 7.5, containing 0.01%BSA.

Assay conditions: Test compounds were prediluted in DMSO and subsequently in compound buffer (5% DMSO final). 5 µL of these compound dilutions were mixed with 10 µl Neutrophil elastase (9 ng/ml in assay buffer) in a black 384 well OptiPlate (Perkin Elmer, Cat No.: 6007270) and incubated for 15 min at room temperature. Subsequently 10 µL substrate solution in assay buffer were added (250 µM final concentration) and the plates were incubated for 60 min at room temperature. After inactivation of the enzyme, fluorescence intensities were measured at 380 nm excitation and 460 nm emission wavelengths.

Each plate contains wells with a high value control (DMSO+enzyme+substrate) and wells with a low value control (DMSO+inactivated enzyme+substrate). IC_{50} values were estimated using a sigmoidal concentration response curve with variable slope. Means of

low values were taken as 0%, means of high values as 100%. The IC_{50} values of selected compounds in the Neutrophil Elastase assay are listed in Table 1.

Table 1

Compound	IC_{50} [nM]	Compound	IC_{50} [nM]	Compound	IC_{50} [nM]
Intermediate 5	<1	Example 1.27	<1	Example 1.56	0.3
Intermediate 6	3.93	Example 1.28	<1	Example 1.57	<1
Example 1	<1	Example 1.29	<1	Example 1.58	<1.
Example 1.1	<1	Example 1.30	<1	Example 1.59	<1.
Example 1.2	<1	Example 1.31	<1	Example 1.60	<1
Example 1.3	2.25	Example 1.32	<1	Example 1.61	<1.3
Example 1.4	<1	Example 1.33	1.8	Example 1.62	<1
Example 1.5	<1	Example 1.34	<1	Example 1.63	1.8
Example 1.6	<1	Example 1.35	<1	Example 1.64	<1
Example 1.7	<1	Example 1.36	<1	Example 1.65	4.1
Example 1.8	<1	Example 1.37	<1	Example 1.66	1.7
Example 1.9	<1	Example 1.38	<1	Example 1.67	1.3
Example 1.10	<1	Example 1.39	<1	Example 1.68	<1
Example 1.11	<1	Example 1.40	<1	Example 1.69	<1
Example 1.12	<1	Example 1.41	<1	Example 1.70	<1
Example 1.13	<1	Example 1.42	<1	Example 1.71	<1
Example 1.14	<1	Example 1.43	<1	Example 1.72	2.8
Example 1.15	<1	Example 1.44	<1	Example 1.73	<1
Example 1.16	<1	Example 1.45	1.0	Example 1.74	<1
Example 1.17	<1	Example 1.46	<1	Example 1.75	<1
Example 1.18	1	Example 1.47	<1	Example 1.76	<1
Example 1.19	<1	Example 1.48	<1	Example 1.77	<1
Example 1.20	<1	Example 1.49	<1	Example 1.78	<1

Compound	IC_{50} [nM]
Example 1.21	<1
Example 1.22	1.4
Example 1.23	<1
Example 1.24	<1
Example 1.25	1.1
Example 1.26	4.7
Example 2.10	<1
Example 2.11	<1
Example 2.12	<1
Example 2.13	<1
Example 2.14	5.4
Example 2.15	4.5
Example 2.16	1.2
Example 3	<1
Example 3.1	<1
Example 3.2	3.0
Example 3.3	3.0
Example 3.4	3.0
Example 3.5	3.0
Example 3.6	3.0
Example 3.7	3.0
Example 3.8	3.0
Example 3.9	3.0
Example 3.10	3.0
Example 3.11	<1
Example 3.12	<1
Example 3.13	<1

Compound	IC_{50} [nM]
Example 1.50	<1
Example 1.51	1.4
Example 1.52	<1
Example 1.53	<1
Example 1.54	<1
Example 1.55	<1
Example 3.22	2.0
Example 3.23	1.3
Example 3.24	1.0
Example 3.25	1.2
Example 3.26	1.6
Example 3.27	2.2
Example 3.28	1.3
Example 3.29	1.4
Example 3.30	1.1
Example 3.31	1.0
Example 3.32	1.1
Example 3.33	<1
Example 3.34	1.0
Example 3.35	<1
Example 3.36	<1
Example 3.37	2.8
Example 3.38	1.0
Example 3.40	3.0
Example 3.41	<1
Example 3.42	2.9
Example 3.43	2.8

Compound	IC_{50} [nM]
Example 1.79	<1
Example 1.80	6.3
Example 1.81	8.8
Example 1.82	2.7
Example 1.83	1.2
Example 1.84	<1
Example 3.52	<1
Example 3.53	<1
Example 3.54	<1
Example 3.55	1.3
Example 3.56	1.9
Example 4	1.4
Example 4.1	2.4
Example 4.2	1.7
Example 4.3	4.8
Example 4.4	11.4
Example 4.5	<1
Example 4.6	<1
Example 4.7	<1
Example 4.8	<1
Example 4.9	<1
Example 4.10	1.2
Example 4.11	1.1
Example 4.12	<1
Example 4.13	<1
Example 4.14	3.0
Example 4.15	<1

Compound	IC_{50} [nM]
Example 3.14	<1
Example 3.15	<1
Example 3.16	<1
Example 3.17	<1
Example 3.18	<1
Example 3.19	<1
Example 3.20	1.6
Example 3.21	1.4
Example 5.5	5.3
Example 5.6	4.8
Example 5.7	<1
Example 5.8	<1
Example 5.9	1.4
Example 5.10	1.3
Example 5.11	<1
Example 5.12	3.0
Example 5.13	22.6
Example 5.14	5.7
Example 6	<1
Example 7	<1
Example 8	<1
Example 9	<1

Compound	IC_{50} [nM]
Example 3.44	1.1
Example 3.45	1.8
Example 3.46	3.8
Example 3.47	<1
Example 3.48	<1
Example 3.49	<1
Example 3.50	1.1
Example 3.51	1.0
Example 10	<1
Example 11	4.6
Example 11.1	1.6
Example 11.2	2.3
Example 11.3	1.6
Example 11.4	1.3
Example 11.5	<1
Example 11.6	1.3
Example 13	<1
Example 13.1	<1
Example 13.2	<1
Example 13.3	<1
Example 14	3.7
Example 14.1	3.2

Compound	IC_{50} [nM]
Example 4.16	<1
Example 4.17	2.0
Example 4.18	1.3
Example 5	2.6
Example 5.1	1.9
Example 5.2	1.4
Example 5.3	1.1
Example 5.4	<1
Example 14.2	1.9
Example 14.3	<1
Example 14.4	1.9
Example 14.5	<1
Example 14.6	3.1
Example 14.7	2.4
Example 14.8	1.2
Example 14.9	<1
Example 14.10	3.0
Example 15	3.0
Example 5.15	<1
Example 16	<1
Example 17	<1

ASSAY FOR THE DETERMINATION OF NEUTROPHIL ELASTASE INHIBITORY ACTIVITY IN HUMAN PLASMA

Citrated blood from human healthy donors is mixed with zymosan suspension and incubated at room temperature. This leads to the stimulation of neutrophils and the release of neutrophil elastase into the plasma. The stimulated blood is centrifuged to generate the neutrophil elastase enriched plasma.

Preparation of zymosan working solution:
Zymosan (100 mg) is mixed with saline (0.9%, 10 mL) and stored at 4 °C for up to one week (note: zymosan does not dissolve in the saline and is used as a suspension).

Whole blood stimulation:

- A single 45 ml blood sample is taken into a 50 ml tube containing citrate (3.13%, 5 mL) and the tube is gently inverted 4 times.
- Immediately after blood sampling, zymosan working solution (5 mL) is added.
- After the addition of zymosan working solution, the tubes are capped, mixed gently and incubated at 22 °C for 15 min on a shaker at 20 rpm.
- Make 10 ml aliquots after the incubation time.
- Centrifuge the 15 ml tubes at 800g for 15 min at 4°C in a Jouan centrifuge.
- Harvest the plasma and make 1-5 ml aliquots.
- Store the plasma at -80 °C.

Various concentrations of the neutrophil elastase inhibitor are incubated with plasma. Subsequently, the enzyme activity is measured using the fluorogenic substrate MeOSuc-Ala-Ala-Pro-Val-AMC (Bachem Cat. No. I-1270, substrate concentration: 250 μM, pH 7.5, 25 mM TRIS buffer, 250 mM NaCl) in analogous fashion as described for the human neutrophil assay. A dose response curve is generated to calculate the EC_{50} of the inhibitor. The analysis of the data is performed by the calculation of the percentage of fluorescence in the presence of the test compound compared to the fluorescence of the vehicle control after subtracting the background fluorescence: An inhibitor of the neutrophil elastase enzyme will give values between 100 %control (no inhibition) and 0 %control (complete inhibition).

The EC_{50} values of selected compounds in the human plasma assay described above are listed in Table 2.

Table 2

Example	EC_{50} [µM]
1.6	0.001
1.8	0.001
1.10	0.001
1.22	0.002
1.73	0.002
13.1	0.001
8	0.006
16	0.001
17	0.005

ASSAY FOR THE DETERMINATION OF METABOLIC STABILITY WITH HUMAN LIVER MICROSOMES

The metabolic degradation of the test compound is assayed at 37 °C with pooled human liver microsomes. The final incubation volume of 100 µl per time point contains TRIS buffer pH 7.6 (0.1 M), magnesium chloride (5 mM), microsomal protein (1 mg/ml) and the test compound at a final concentration of 1 µM. Following a short preincubation period at 37 °C, the reactions are initiated by addition of beta-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM) and terminated by transfering an aliquot into acetonitrile after different time points. Additionally, the NADPH-independent degradation is monitored in incubations without NADPH, terminated at the last time point. The [%] remaining test compound after NADPH independent incubation is reflected by the parameter c(control) (metabolic stability). The quenched incubations are pelleted by centrifugation (10'000 g, 5 min). An aliquot of the supernatant is assayed by LC-MS/MS for the amount of parent compound.

The half-life ($t_{1/2}$ INVITRO) is determined by the slope of the semilogarithmic plot of the concentration-time profile. The intrinsic clearance (CL_INTRINSIC) is calculated by considering the amount of protein in the incubation:

CL_INTRINSIC [µl/min/mg protein] = (ln 2 / (half-life [min] * protein content [mg/ml])) *1'000.

The half-life ($t_{1/2}$ INVITRO) values of selected compounds in the metabolic stability assay human liver microsomes described above are listed in Table 3.

Table 3

Example	$t_{1/2}$ INVITRO [min]
1.6	130
1.8	110
1.10	>130
1.22	>130
1.73	120
8	>130
13.1	>130
16	>130
17	>130

ASSAY FOR THE DETERMINATION OF METABOLIC STABILITY WITH HUMAN HEPATOCYTES

The metabolic degradation of the test compound is assayed in a human hepatocyte suspension. Human hepatocytes (typically cryopreserved) are incubated in an appropriate buffer system (e.g. Dulbecco´s modified eagle medium plus 3.5 µg glucagon / 500 mL, 2.5 mg insulin / 500 mL and 3.75 mg / 500 mL hydrocortison) containing 5% species serum. Following a (typically) 30 min preincubation in an incubator (37 °C, 10% CO_2),

5 µl of test compound solution (80 µM; from 2 mM stock solution in DMSO diluted 1:25 with medium) are added into 395 µl hepatocyte suspension (cell density in the range 0.25-5*10^6 cells/mL, typically 1*10^6 cells/mL; final concentration of test compound 1µM, final DMSO concentration 0.05%). The cells are incubated for six hours (incubator, orbital shaker) and samples (25 µl) are taken at 0, 0.5, 1, 2, 4 and 6 hours. Samples are transferred into acetonitrile and pelleted by centrifugation (5 min). The supernatant is transferred to a new 96-deepwell plate, evaporated under nitrogen and resuspended. The decline of parent compound is analyzed by LC-MS/MS.

The intrinsic clearance CL_INTRINSIC is calculated as follows:

$$CL\_INTRINSIC = Dose / AUC = (C_0/CD) / (AUD + c_{last}/k) * 1'000/60$$

(C_0: initial concentration in the incubation [µM], CD: cell density of vital cells [10^6 cells/mL], AUD: area under the data [µM * h], c_{last}: concentration of last data point [µM], k: slope of the regression line for parent decline [h^{-1}])

The calculated in vitro hepatic intrinsic clearance Q_h can be scaled up to the intrinsic in vivo hepatic clearance and used to predict hepatic in vivo blood clearance (CL) by the use of a liver model (well stirred model):

CL_INTRINSIC_INVIVO [ml/min/kg] = (CL_INTRINSIC [µL/min/10^6 cells] * hepatocellularity [10^6 cells/g liver] * liver factor [g/kg bodyweight]) / 1'000

CL [ml/min/kg] = CL_INTRINSIC_INVIVO [ml/min/kg] * hepatic blood flow [ml/min/kg] / (CL_INTRINSIC_INVIVO [ml/min/kg] + hepatic blood flow [ml/min/kg])

Q_h [%] = CL [ml/min/kg] / hepatic blood flow [ml/min/kg])

(Hepatocellularity, human: 120*10^6 cells / g liver; liver factor, human: 25.7 g / kg bodyweight; blood flow, human: 21 ml/(min * kg))

Based on this assay.

The calculated in vitro hepatic intrinsic clearance values of selected compounds in the metabolic stability assay with human hepatocytes described above are listed in Table 4.

Table 4

Example	Q_h [%]
1.6	25
1.8	22
1.10	27
1.22	15
1.73	19
13.1	16
16	5
17	6

ASSAY FOR DETERMINATION OF DRUG TRANSPORT ACROSS HUMAN CACO-2 CELLS

The assay provides information on the potential of a compound to pass the cell membrane, on the extent of oral absorption as well as on whether the compound is actively transported by uptake and/or efflux transporters. For the measurement of permeability across polarized, confluent human cancer colon carcinoma cells 2 (Caco-2) cell monolayers grown on permeable filter supports are used as the in vitro absorption model.
Apparent permeability coefficients (PE) of the compounds across the Caco-2 monolayers are measured (pH 7.2, 37 °C) in apical-to-basal (AB) (absorptive) and basal-to-apical (BA) (secretory) transport direction. AB permeability (PEAB) represents drug absorption from the intestine into the blood and BA permeability (PEBA) drug secretion from the blood back into the intestine via both passive permeability as well as active transport mechanisms mediated by efflux and uptake transporters that are expressed on the Caco-2 cells. The

compounds are assigned to permeability/absorption classes by comparison of the AB permeabilities with the AB permeabilities of reference compounds with known in vitro permeability and oral absorption in the human. Identical or similar permeabilities in both transport directions indicate passive permeation, vectorial permeability points to additional active transport mechanisms. Higher PEBA than PEAB suggests the involvement of an apical efflux transporter (like P-gp) and/or basolateral uptake transporter; higher PEAB than PEBA permeability suggests involvement of an apical uptake transporter (like PepT1) and/or basolateral efflux transporter (like MRP3). Active transport is concentration-dependently saturable.

Caco-2 cells (1-2 * 10^5 cells/cm^2 area) are seeded on filter inserts (Costar transwell polycarbonate or PET filters, 0.4 µm pore size) and cultured (DMEM) for 10 to 25 days. Compounds are dissolved in appropriate solvent (like DMSO, 1-20 mM stock solutions). Stock solutions are diluted with HTP-4 buffer (128.13 mM NaCl, 5.36 mM KCl, 1 mM $MgSO_4$, 1.8 mM $CaCl_2$, 4.17 mM $NaHCO_3$, 1.19 mM $Na_2HPO_4x7H_2O$, 0.41 mM $NaH_2PO_4xH_2O$, 15 mM HEPES, 20 mM glucose, pH 7.2) to prepare the transport solutions (typically 10 µM compound, final DMSO <= 0.5 %). The transport solution (TL) is applied to the apical or basolateral donor side for measuring A-B or B-A permeability (3 filter replicates), respectively. The receiver side contains HTP-4 buffer supplemented with 2% BSA. Samples are collected at the start and end of experiment from the donor and at various time intervals for up to 2 hours also from the receiver side for concentration measurement by LC-MS/MS or scintillation counting. Sampled receiver volumes are replaced with fresh receiver solution.

The apparent permeability coefficients (PEAB and PEBA) of selected compounds in the Caco-2 drug transport assay described above are listed in Table 5.

TABLE 5

Example	PEAB [cm/s]	PEBA [cm/s]
1.6	10 x 10^{-6}	81 x 10^{-6}
1.8	44 x 10^{-6}	74 x 10^{-6}

1.10	39×10^{-6}	78×10^{-6}
1.22	7.8×10^{-6}	81×10^{-6}
1.73	5.1×10^{-6}	92×10^{-6}
8	77×10^{-6}	63×10^{-6}
13.1	33×10^{-6}	80×10^{-6}
16	12×10^{-6}	120×10^{-6}
17	11×10^{-6}	114×10^{-6}

ASSAY FOR DETERMINATION OF AQUEOUS SOLUBILITY

The aqueous solubility of a compound is determined by comparing the amount dissolved in aqueous buffer (containing 2.5% DMSO) to the amount dissolved in an acetonitrile/water (1/1) solution. Starting from a 10 mM DMSO stock solution, aliquots are diluted with acetonitrile/water (1/1) and McIlvaine buffer pH 6.8, respectively. After 24 h of shaking, the solutions or suspensions are filtered and analyzed by LC-UV. The amount dissolved in buffer is compared to the amount dissolved in the acetonitrile/water (1/1) solution. Solubility is measured from 0.001 to 0.125 mg/ml at a DMSO concentration of 2.5%. If more than 90 % of the compound is dissolved in buffer, the value is marked with ">".

The aqueous solubility of selected compounds in the solubility assay described above is listed in Table 6.

TABLE 6

Example	**Aqueous solubility [mg/mL]**
1.6	0.070
1.8	0.076
1.10	0.066
1.22	0.065
1.73	0.073

8	0.03
13.1	0.051
16	0.073
17	0.062

ASSAY FOR DETERMINATION OF CYTOCHROME P450 2C9 INHIBITION

The inhibition of cytochrome P450 2C9-isoenzyme catalysed hydroxylation of Diclofenac by the test compound is assayed at 37°C with human liver microsomes. All assays are carried out on a robotic system in 96 well plates. The final incubation volume contains TRIS buffer (0.1 M), $MgCl_2$ (5 mM), human liver microsomes (0.1 mg/ml), Diclofenac (10 µM) and the test compound at five different concentrations or no compound (high control) in duplicate (e.g. highest concentration 10-50 µM with subsequent serial 1:4 dilutions). Following a short preincubation period, reactions are started with the cofactor (NADPH, 1 mM) and stopped by cooling the incubation down to 8 °C and subsequently by addition of one volume of acetonitrile. An internal standard solution - usually the stable isotope of the formed metabolite - is added after quenching of incubations. Peak area analyte (=metabolite formed) and internal standard is determined by LC-MS/MS. The resulting peak area ratio analyte to internal standard in these incubations is compared to a control activity containing no test compound. Within each of the assay runs, the IC_{50} of a positive control inhibitor (sulfaphenazole) is determined. Experimental IC_{50} values are calculated by least square regression according to the following equation:

$$\% \text{ control activity} = (100 \% \text{ control activity}/(1+(I/IC_{50})*S))-B$$

(I = inhibitor concentration, S = slope factor, B = background activity)

If the inhibition of the reaction is already >50% at the lowest concentration of the test compound, the IC_{50} is assigned "< lowest concentration tested" (usually <0.4 µM). If the inhibition of the reaction is still <50% at the highest concentration of the test compound,

the IC_{50} is assigned "> highest concentration tested" (usually >50 µM). Example 13.1 and Example 16 exhibit an IC_{50} value > 50 µM in this assay.

ASSAY FOR DETERMINATION OF CYTOCHROME P450 2C19 INHIBITION

The inhibition of cytochrome P450 2C19-isoenzyme catalysed hydroxylation of Mephenytoin by the test compound is assayed at 37 °C with human liver microsomes. All assays are carried out on a robotic system in 96 well plates. The final incubation volume contains TRIS buffer (0.1 M), $MgCl_2$ (5 mM), human liver microsomes (0.5 mg/ml), (*S*)-Mephenytoin (70 µM) and the test compound at five different concentrations or no compound (high control) in duplicate (e.g. highest concentration 10-50 µM with subsequent serial 1:4 dilutions). Following a short preincubation period, reactions are started with the cofactor (NADPH, 1 mM) and stopped by cooling the incubation down to 8 °C and subsequently by addition of one volume of acetonitrile. An internal standard solution - usually the stable isotope of the formed metabolite - is added after quenching of incubations. Peak area analyte (= metabolite formed) and internal standard is determined by LC-MS/MS. The resulting peak area ratio analyte to internal standard in these incubations is compared to a control activity containing no test compound. Within each of the assay runs, the IC_{50} of a positive control inhibitor (tranylcypromine) is determined. Experimental IC_{50} values are calculated by least square regression according to the following equation:

$$\% \text{ control activity} = (100 \% \text{ control activity}/(1+(I/IC_{50})*S))-B$$

(I = inhibitor concentration, S = slope factor, B = background activity)

If the inhibition of the reaction is already >50% at the lowest concentration of the test compound, the IC_{50} is assigned "< lowest concentration tested" (usually <0.4 µM). If the inhibition of the reaction is still <50% at the highest concentration of the test compound, the IC_{50} is assigned "> highest concentration tested" (usually >50 µM). Example 13.1 and Example 16 exhibit an IC_{50} value > 50 µM in this assay.

ASSAY FOR DETERMINATION OF CYTOCHROME P450 2C8 INHIBITION

The inhibition of cytochrome P450 2C8-isoenzyme catalysed deethylation of Amodiaquine by the test compound is assayed at 37°C with human liver microsomes. All assays are carried out on a robotic system in 96 well plates. The final incubation volume contains TRIS buffer (0.1 M), $MgCl_2$ (5 mM), human liver microsomes (0.05 mg/ml), Amodiaquine (1 µM) and the test compound at five different concentrations or no compound (high control) in duplicate (e.g. highest concentration 10-50 µM with subsequent serial 1:4 dilutions). Following a short preincubation period, reactions are started with the cofactor (NADPH, 1mM) and stopped by cooling the incubation down to 8°C and subsequently by addition of one volume of acetonitrile. An internal standard solution - usually the stable isotope of the formed metabolite - is added after quenching of incubations. Peak area analyte (=metabolite formed) and internal standard is determined by LC-MS/MS. The resulting peak area ratio analyte to internal standard in these incubations is compared to a control activity containing no test compound. Within each of the assay runs, the IC_{50} of a positive control inhibitor (Montelukast) is determined. Experimental IC_{50} values are calculated by least square regression according to the following equation:

$$\% \text{ control activity} = (100 \% \text{ control activity}/(1+(I/IC_{50})*S))-B$$

(I = inhibitor concentration, S = slope factor, B = background activity)

If the inhibition of the reaction is already >50% at the lowest concentration of the test compound, the IC_{50} is assigned "< lowest concentration tested" (usually <0.4 µM). If the inhibition of the reaction is still <50% at the highest concentration of the test compound, the IC_{50} is assigned "> highest concentration tested" (usually >50 µM). Example 13.1 and Example 16 exhibit an IC_{50} value > 50 µM in this assay.

ASSAY FOR DETERMINATION OF CYTOCHROME P450 INDUCTION

To assess induction of metabolizing enzyme CYP3A4, cryopreserved HepaRG® cells are seeded at a density of 1.0 x 105 per 96 well. Cells are allowed to equilibrate for 72 hours prior to exposure of 10 µM test article for 48 hours with renewal of test article every 24 hours. Known prototypical CYP3A4 inducers Rifampicin is used as a positive control at a concentration of 25 µM. After 48 hours of exposure, medium containing the test article is removed and cells were washed with phosphate buffered saline (PBS) prior to mRNA isolation.

Calculations:

Fold induction = (Enzyme mRNA Compound)/(Enzyme mRNA Solvent Control)

Inducer Potency = (Fold Compound)/(Fold Rifampicin)*100

ASSAY FOR DETERMINATION OF hERG INHIBITION

The inhibition of the hERG (human ether-a-go-go-related gene) potassium channel can be determined as described in Rast, G., & Guth, B.D., Journal of Pharmacological and ToxicologicalMethods (2014), http://dx.doi.org/10.1016/j.vascn.2014.08.001.
The hERG inhibition of selected compounds in this patch clamp assay is listed in Table 7.

TABLE 7

Example	hERG inhibition
13.1	IC_{50} >30 µM (7% @ 10 µM)
16	IC_{50} >30 µM (8% @ 10 µM)

COMBINATIONS

The compounds of general formula **1** may be used on their own or combined with other active substances of formula **1** according to the invention. The compounds of general formula **1** may optionally also be combined with other pharmacologically active substances. These include, ß2-adrenoceptor-agonists (short and long-acting), anti-cholinergics (short and long-acting), anti-inflammatory steroids (oral and topical corticosteroids), cromoglycate, methylxanthine, dissociated-glucocorticoidmimetics, PDE3 inhibitors, PDE4- inhibitors, PDE7- inhibitors, LTD4 antagonists, EGFR- inhibitors, Dopamine agonists, PAF antagonists, Lipoxin A4 derivatives, FPRL1 modulators, LTB4-receptor (BLT1, BLT2) antagonists, Histamine H1 receptor antagonists, Histamine H4 receptor antagonists, dual Histamine H1/H3-receptor antagonists, PI3-kinase inhibitors, inhibitors of non-receptor tyrosine kinases as for example LYN, LCK, SYK, ZAP-70, FYN, BTK or ITK, inhibitors of MAP kinases as for example p38, ERK1, ERK2, JNK1, JNK2, JNK3 or SAP, inhibitors of the NF-κB signalling pathway as for example IKK2 kinase inhibitors, iNOS inhibitors, MRP4 inhibitors, leukotriene biosynthese inhibitors as for example 5-Lipoxygenase (5-LO) inhibitors, cPLA2 inhibitors, Leukotriene A4 Hydrolase inhibitors or FLAP inhibitors, MMP9-inhibitors, MMP12-inhibitors, non-steroidale anti-inflammatory agents (NSAIDs), Cathepsin C (or DPPI / Dipeptidylaminopeptidase I) inhibitors, CRTH2 antagonists, DP1-receptor modulators, Thromboxane receptor antagonists, CCR3 antagonists, CCR4 antagonists, CCR1 antagonists, CCR5antagonists, CCR6 antagonists, CCR7 antagonists, CCR8 antagonists, CCR9 antagonists, CCR30 antagonists, CXCR3 antagonists, CXCR4 antagonists, CXCR2 antagonists, CXCR1 antagonists, CXCR5 antagonists, CXCR6 antagonists, CX3CR3 antagonists, Neurokinin (NK1, NK2) antagonists, Sphingosine 1-Phosphate receptor modulators, Sphingosine 1 phosphate lyase inhibitors, Adenosine receptor modulators as for example A2a-agonists, modulators of purinergicreceptors as for example P2X7 inhibitors, Histone Deacetylase (HDAC) activators, Bradykinin (BK1, BK2) antagonists, TACE inhibitors, PPAR gamma modulators, Rho-kinase inhibitors, interleukin 1-beta converting enzyme (ICE) inhibitors,

Toll-Like receptor (TLR) modulators, HMG-CoA reductase inhibitors, VLA-4 antagonists, ICAM-1 inhibitors, SHIP agonists, GABAa receptor antagonist, ENaC-inhibitors, Prostasin-inhibitors, Melanocortin receptor (MC1R, MC2R, MC3R, MC4R, MC5R) modulators, CGRP antagonists, Endothelin antagonists, TNFα antagonists, anti-TNF antibodies, anti-GM-CSF antibodies, anti-CD46 antibodies, anti-IL-1 antibodies, anti-IL-2 antibodies, anti-IL-4 antibodies, anti-IL-5 antibodies, anti-IL-13 antibodies, anti-IL-4/IL-13 antibodies, anti-TSLP antibodies, anti-OX40 antibodies, mucoregulators, immuno-therapeutic agents, compounds against swelling of the airways, compounds against cough, VEGF inhibitors, but also combinations of two or three active substances.

Preferred are betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, Cathepsin C inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists and SYK-inhibitors, especially Cathepsin C inhibitors, but also combinations of two or three active substances, that is:

- Betamimetics with corticosteroids, PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists,
- Anticholinergics with betamimetics, corticosteroids, PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists,
- Corticosteroids with PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists
- PDE4-inhibitors with CRTH2-inhibitors or LTD4-antagonists
- CRTH2-inhibitors with LTD4-antagonists.

PHARMACEUTICAL COMPOSITIONS

Suitable preparations for administering the compounds of formula will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders etc. Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula I with known excipients, for example inert diluents, carriers,

disintegrants, adjuvants, surfactants, binders and/or lubricants . The tablets may also consist of several layers.

INDICATIONS

The compounds of the invention and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as inhibitors of neutrophil elastase, and thus may be used in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; alpha1-antitrypsin deficiency; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus; acute lung injury; acute respiratory distress syndrome;

2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid,

epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial;

4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

5. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome andSazary syndrome;

7. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes;

8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, Candida, aspergillus, cryptococcal meningitis, Pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis and,

9. other diseases: traumatic brain injury, abdominal aortic aneurism.

The present invention is directed to compounds of general formula **1** which are useful in the prevention and/or treatment of a disease and/or condition wherein the activity of inhibitors of neutrophil elastase is of therapeutic benefit, including but not limited to the treatment and/or prevention of asthma and allergic diseases, gastrointestinal inflammatory diseases, glomerulonephritis, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes, rheumatoid arthritis,
neutrophilic diseases, cystic fibrosis (CF), non-cystic fibrosis, idiopathic pulmonary fibrosis, non-cyctic fibrosis bronchiectasis, ANCA-associated vasculitis, lung cancer, bronchiectasis, emphysema, chronic bronchitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary arterial hypertension (PAH), Alpha-1-antitrypsin deficiency (AATD.),
obesity and related inflammation, e.g. chronic adipose tissue inflammation, adipose inflammation and high-fat diet induced inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.
A correlation between the biological activity and the medical indications is described in the literature e.g. “Henriksen, P. A. Current Opinion in Hematology (2014), 21(1), 23-28”
Accordingly, the present invention relates to a compound of general formula **1** as a medicament.

In a further aspect of the present invention the present invention relates to methods for the treatment or prevention of above mentioned diseases and conditions, which method comprises the administration of an effective amount of a compound of general formula **1** to a human being.

For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 20mg/kg of body weight per dosage. For Example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

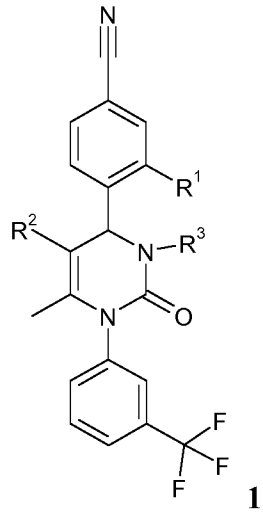
The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the active ingredient will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

LIST OF ABBREVIATIONS

ACN	acetonitrile
aq.	aqueous
BOC	tert. butyloxycarbonyle-
d	day
DCM	dichloromethane
DEA	diethylamine
DIPEA	n,n-diisopropylethylamine
DIPE	diisopropyl ether
DMAP	4-dimethylaminopyridine
DMF	n,n-dimethylformamide
DMSO	dimethyl sulfoxide
EA	ethyl acetate
FA	formic acid
h	hour
HATU	o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate
LiOH	lithium hydroxide
MeOH	methanol
MeTHF	methyl tetrahydrofuran
NaH	sodium hydride
PE	petrol ether
RT, r.t.	room temperature
rt	retention time
TBME	tert-butyl methyl ether
TBTU	o-(1H-benzo-1,2,3-triazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TSA	toluene sulfonic acid

WHAT WE CLAIM

1. A compound of formula **1**



1

wherein

R^1 is selected from the group consisting of

$-CO-R^{1.1}$, $-CONH-R^{1.2}$, $R^{1.10}$,

$-CO-NH_2$, $-COOH$, $-CON(CH_3)_2$, $-CONH-C(CH_3)_2-CN$,

$-CONH-C_{1-3}$-alkyl, $-CONH-CH_2-R^{1.7}$, $-CONH-CH_2CH_2-R^{1.3}$,

$-CONH-CH_2CH_2CH_2-R^{1.5}$,

$-CONH-CH(CH_3)R^{1.9}$, $-CON(CH_3)-CH_2-R^{1.6}$, $-CON(CH_3)-CH_2CH_2-R^{1.4}$ and

$-CON(CH_3)-CH_2CH_2CH_2-R^{1.8}$,

$R^{1.1}$ denotes a 4- to 10-membered heterocyclic or 5- to 10-membered N-containing heteroaryl ring, containing one to four heteroatoms independently selected from among N, O and S, each of the rings optionally substituted with a group independently selected from among morpholinyl, $-NHCOCH_3$, $N(CH_3)COCH_3$, $-COCH_3$, -OH, $-NH_2$,$-N(CH_3)_2$ and C_{1-3} alkyl $-N(CH_3)_2$, cyclopropyl and $-CH(CH_3)_2$,

wherein the N-atom of each ring is bound to the core structure;

$R^{1.2}$ denotes a C_{3-6}-cycloalkyl or
a 4-to 10-membered heterocyclic ring containing one to four heteroatoms independently selected from among N, O and S, each of the rings optionally substituted with one or two C_{1-3} alkyl, $-NH_2$, -OH, -CN or =O,

$R^{1.3}$, $R^{1.4}$, $R^{1.5}$ independently from each other are selected from the group consisting of morpholinyl, F, $-N(CH_3)_2$, $-SO_2CH_3$, $-OCH_3$, , -OH and CH_3,

$R^{1.6}$, $R^{1.7}$ independently from each other denote a group selected from among -CO-morpholinyl, $-C(CH_3)_2CN$, $-C(CH_3)_2$-OH, $-CF_3$, -CN, CHF_2 and -CH≡CH,
or
a 4-to 10-membered aromatic or 5-to 10-membered heteroaryl ring, containing one to four heteroatoms independently selected from among N, O and S, each of the rings optionally substituted with C_{1-3} alkyl or CN,

$R^{1.8}$ denotes $-OCH_3$,

$R^{1.9}$ denotes furanyl,

$R^{1.10}$ denotes a 4-to 10-membered heterocyclic or 5- to 10-membered heteroaryl ring, containing one to four heteroatoms independently selected from among N, O and S, each of the rings substituted with $R^{1.11}$and $R^{1.12}$,

$R^{1.11}$, $R^{1.12}$ are independently selected from among hydrogen, =O, C_{1-4}-alkyl , -COO-C_{1-4}-alkyl, C_{1-3}-cycloalkyl, OH, -O-C_{1-3}-alkyl, -O-C_{1-3}-cycloalkyl, -CN, halogen, -CO-C_{1-3}-alkyl, -CO-C_{1-3}-cycloalkyl and $-N(CH_3)_2$,

R^2 is selected from the group consisting of

-$COCH_3$ and -$COOCH_2CH_3$,

R^3 is selected from the group consisting of H, $R^{3.1}$, $R^{3.1}$-CO-, $R^{3.1}$-O-CO- ,$R^{3.1}SO_2$- and $R^{3.1}R^{3.2}N$-CO-,

$R^{3.1}$ is selected from the group consisting of H, -C_{1-4} alkyl, -C_{3-6} cycloalkyl, -C_{1-4}-haloalkyl and -C_{3-6}-halocycloalkyl,
each optionally substituted with one substituent independently selected from the group consisting of OH, CN and NH_2,

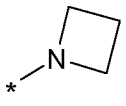
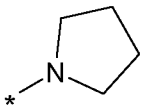
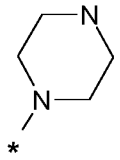
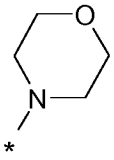
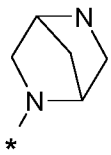
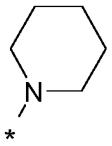
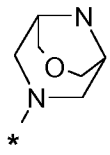
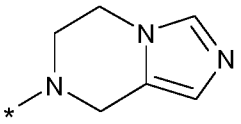
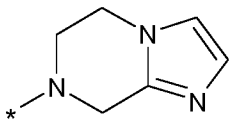
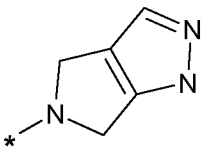
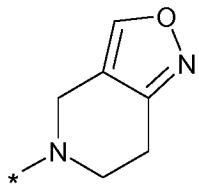
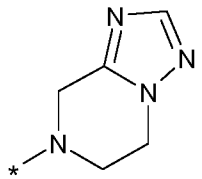
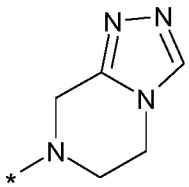
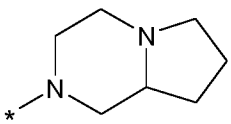
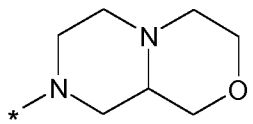
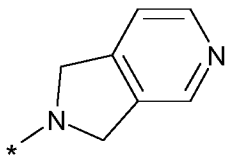
$R^{3.2}$ is selected from the group consisting of H and Me,

or a pharmaceutically acceptable salt thereof.

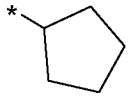
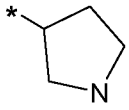
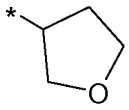
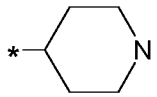
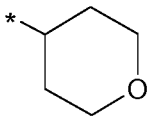
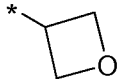
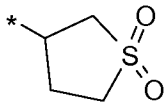
2. A compound of formula **1** according to claim 1, wherein

R^1 is selected from the group consisting of
-CO-$R^{1.1}$, -CONH-$R^{1.2}$,
-$CONH_2$, -COOH, -$COOCH_3$, -$CON(CH_3)_2$, -CONH-$C(CH_3)_2$-CN,
-CONH-C_{1-2}-alkyl, -CONH-CH_2-$R^{1.7}$, -CONH-CH_2CH_2-$R^{1.3}$,
-CONH-$CH_2CH_2CH_2$-$R^{1.5}$,
-CONH-$CH(CH_3)R^{1.9}$, -$CON(CH_3)$-CH_2-$R^{1.6}$, -$CON(CH_3)$-CH_2CH_2-$R^{1.4}$ and
-$CON(CH_3)$-$CH_2CH_2CH_2$-$R^{1.8}$,

$R^{1.1}$ is selected from the group consisting of
formulas **a.1** to **a.16,**
each optionally substituted with a group selected from among –OH, -NH_2, C_{1-2}-alkyl, -$NHCH_3$, -$N(CH_3)_2$, cyclopropyl, -$CH(CH_3)_2$, morpholine, -$COCH_3$, -$NHCOCH_3$ and -$N(CH_3)CO$-CH_3,

 a.1	 a.2	 a.3	 a.4
 a.5	 a.6	 a.7	 a.8
 a.9	 a.10	 a.11	 a.12
 a.13	 a.14	 a.15	 a.16

$R^{1.2}$ is selected from the group consisting of formulas **b.1** to **b.9,** each optionally substituted with a group selected from among $-NH_2$, -OH, -CN, CH_3 and $-CH(CH_3)_2$,

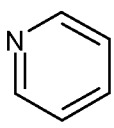
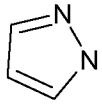
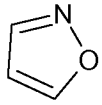
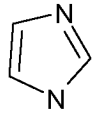
 **b.1**	 **b.2**	 **b.3**	 **b.4**
 **b.5**	 **b.6**	 **b.7**	 **b.8**
 **b.9**			

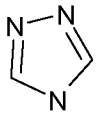
$R^{1.3}$ is selected from the group consisting of -NH_2, -OH, F, -$NHCH_3$, -$N(CH_3)_2$, -SO_2CH_3 and-OCH_3,

$R^{1.4}$ is selected from the group consisting of -NH_2, -OH, -OCH_3, -$NHCH_3$ and -$N(CH_3)_2$,

$R^{1.5}$ is selected from the group consisting of OH, -$N(CH_3)_2$ and -OCH_3,

$R^{1.6}$ is selected from the group consisting of formulas **c.1** to **c.5,** each optionally substituted with CH_3,

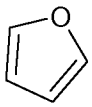
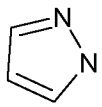
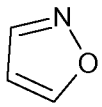
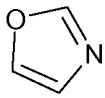
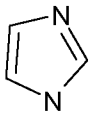
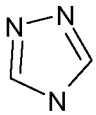
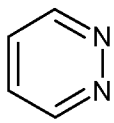
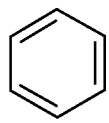
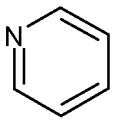
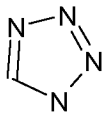
 **c.1**	 **c.2**	 **c.3**	 **c.4**

 **c.5**			

$R^{1.7}$ is selected from the group consisting of $-C(CH_3)_2-OH$, $-C(CH_3)_2-NH_2$, $-CF_3$, -CN, $-CHF_2$ and $-CH\equiv CH$,

or

$R^{1.7}$ is selected from the group consisting of formulas **d.1** to **d.10,** each optionally substituted with $-CH_3$ or –CN,

 **d.1**	 **d.2**	 **d.3**	 **d.4**
 **d.5**	 **d.6**	 **d.7**	 **d.8**
 **d.9**	 **d.10**		

$R^{1.8}$ denotes $-OCH_3$,

$R^{1.9}$ denotes a group of formula **d.1**

R^2 is selected from the group consisting of $-COCH_3$ and $-COOCH_2CH_3$,

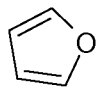
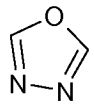
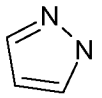
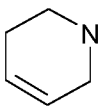
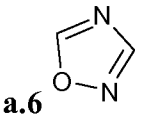
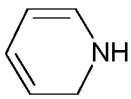
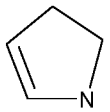
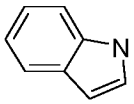
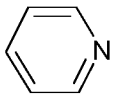
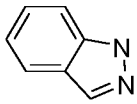
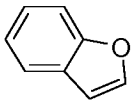
R^3 is H or methyl,

or a pharmaceutically acceptable salt thereof.

3. A compound of formula **1** according to claim 1, wherein

R^1 is $R^{1.10}$,

$R^{1.10}$ is selected from the group consisting of formulas **a.1** to **a.12,** each of the rings substituted with $R^{1.11}$ and $R^{1.12}$,

 **a.1**	 **a.2**	 **a.3**	 **a.4**
 **a.5**	 **a.6**	 **a.7**	 **a.8**
 **a.9**	 **a.10**	 **a.11**	 **a.12**

$R^{1.11}$, $R^{1.12}$ are independently selected from among hydrogen,F,-CN, $-OCH_3$, =O, $-CH_3$ and $-COO-C(CH_3)_3$.

R^3 is H or methyl,

or a pharmaceutically acceptable salt thereof.

4. A compound of formula **1** according to claim 1 or 2, wherein

R^1 is selected from the group consisting of
-CONH-$R^{1.2}$, -$CONH_2$, -$COOCH_3$, -CONH-$C(CH_3)_2$-CN, -CONH-C_{1-2}-alkyl,
-CONH-CH_2-$R^{1.7}$, -CONH-CH_2CH_2-$R^{1.3}$, -CONH-$CH_2CH_2CH_2$-$R^{1.5}$ and
-CON(CH_3)-CH_2CH_2-$R^{1.4}$,

$R^{1.2}$ is selected from the group consisting of formulas **b.1,** each optionally substituted with a group selected from among -NH_2, -OH, CN, CH_3 and -$CH(CH_3)_2$,

b.1

$R^{1.3}$ is selected from the group consisting of -NH_2, F and -$NHCH_3$,

$R^{1.4}$ denotes -NH_2 or -OH,

$R^{1.5}$ OH,

$R^{1.7}$ is selected from the group consisting of –CN, -$C(CH_3)_2$-OH, -$C(CH_3)_2$-NH_2 and -CH≡CH,

or a pharmaceutically acceptable salt thereof.

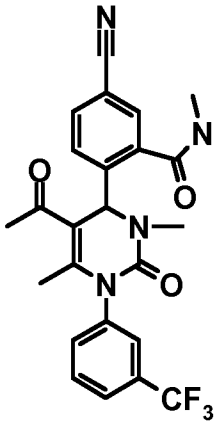
5. A compound of formula **1** according to any of claims 1 to 4, wherein

R^2 denotes -$COCH_3$.

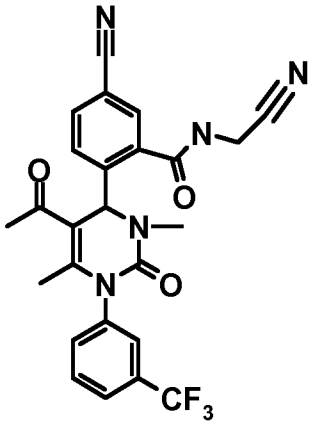
6. A compound of formula **1** according to any of claims 1 to 4, wherein

R^2 denotes -$COOCH_2CH_3$.

7. A compound of formula **1** according to claim 1, selected from the group consisting of compounds **1.a** to **1.h.**



1.a



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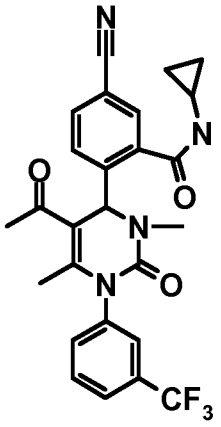
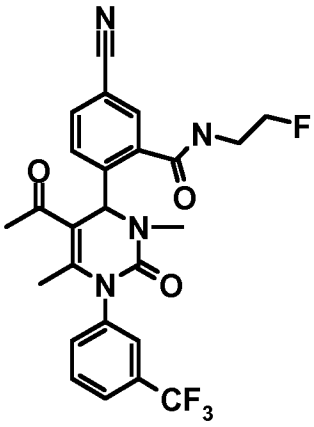
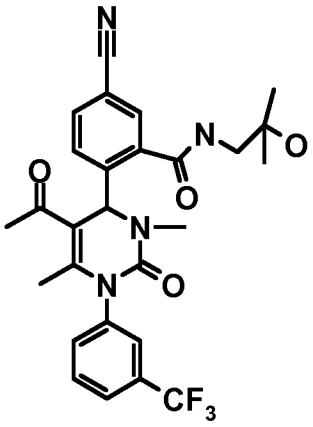


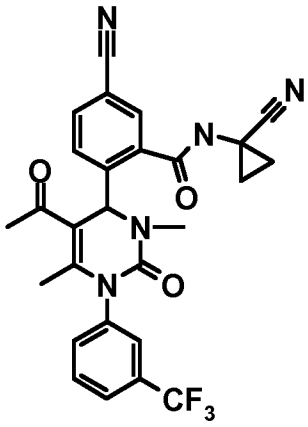
1.c



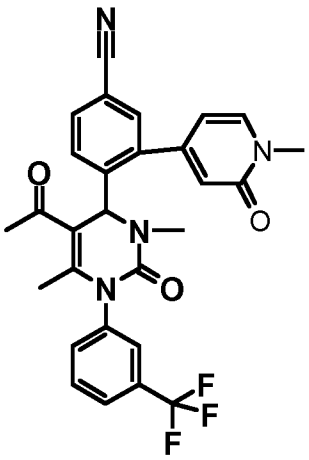
1.d



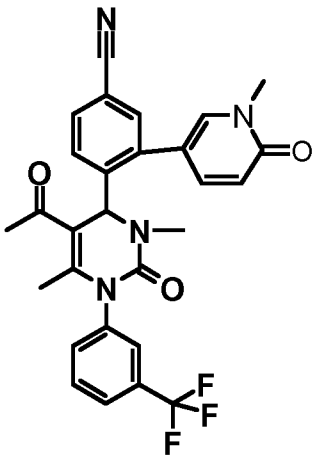
1.e



1.f



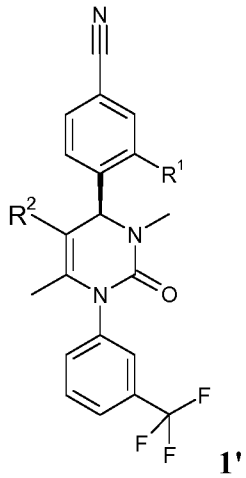
1.g



1.h

or a pharmaceutically acceptable salt thereof.

8. A compound of formula **1** according to any of claims 1 to 7, wherein the configuration of formula **1** is formula **1'**,



1'

or a pharmaceutically acceptable salt thereof.

9. A compound of formula **1** according to any one of claims 1 to 8 for use as a medicament.

10. A compound of formula **1** according to any one of claims 1 to 8 for use as a medicament for the treatment of asthma and allergic diseases, gastrointestinal inflammatory diseases, glomerulonephritis, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes, rheumatoid arthritis, neutrophilic diseases, cystic fibrosis (CF), non-cystic fibrosis, idiopathic pulmonary fibrosis, bronchiectasis, ANCA-associated vasculitis, lung cancer, non-cyctic fibrosis bronchiectasis, emphysema, chronic bronchitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary arterial hypertension (PAH) and Alpha-1-antitrypsin deficiency (AATD.), obesity and related inflammation, insulin resistence, diabetes, fatty liver and liver steatosis.

11. A compound of formula **1** according to any one of claims 1 to 6 for use as a medicament for the treatment of traumatic brain injury, abdominal aortic aneurism and Graft vs. Host Disease (GvHD).

12. Pharmaceutical composition, characterised in that it contains one or more compounds of formula **1** according to any one of claims 1 to 8 or a pharmaceutically active salt thereof.

13. Method of treatment or prevention of diseases in which neutrophil elastase inhibitors have a therapeutic benefit, which method comprises administration of a therapeutically or preventively effective amount of a compounds of formula **1** according to one of claims 1 to 8 to a patient in need thereof.

14. A pharmaceutical composition comprising additionally to a compound of formula **1**, according to any one of claims 1 to 8, a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, Cathepsin C inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists and SYK-inhibitors, but also combinations of two or three active substances.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067504

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/22 A61K31/513 A61P29/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/080199 A1 (BAYER SCHERING PHARMA AG [DE]; NUSSBAUM FRANZ [DE]; KARTHAUS DAGMAR [D) 2 July 2009 (2009-07-02) cited in the application claim 1 and pages 210-212	1-14
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A	GB 2 392 910 A (BAYER AG [DE]) 17 March 2004 (2004-03-17) cited in the application claims 1 and 21	1-14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2015	30/09/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sahagún Krause, H

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067504

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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