(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2021 (14.10.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/204626 A1

(51) International Patent Classification:
C07D 401/12 (2006.01) *A61K 31/444* (2006.01)
C07D 213/82 (2006.01) *A61K 31/4965* (2006.01)
C07D 237/24 (2006.01) *A61P 17/00* (2006.01)
C07D 401/14 (2006.01) *A61P 17/06* (2006.01)
C07D 403/12 (2006.01) *A61P 35/00* (2006.01)
C07D 471/04 (2006.01) *A61P 37/00* (2006.01)
A61K 31/437 (2006.01) *A61P 37/08* (2006.01)
A61K 31/44 (2006.01)

(21) International Application Number:
PCT/EP2021/058465

(22) International Filing Date:
31 March 2021 (31.03.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
20382271.3 06 April 2020 (06.04.2020) EP

(71) Applicant: **ALMIRALL, S.A.** [ES/ES]; Ronda del General Mitre 151, 08022 Barcelona (ES).

(72) Inventors: **PUIG DURAN, Carlos**; C/Laureà Miró, 408-410 Sant Feliu de Llobregat, 08980 Barcelona (ES). **GOMEZ CASTILLO, Elena**; C/Laureà Miró, 408-410 Sant Feliu de Llobregat, 08980 Barcelona (ES). **CATURLA JAVALOYES, Juan Francisco**; C/Laureà Miró, 408-410 Sant Feliu de Llobregat, 08980 Barcelona (ES). **PAGES SANTACANA, Lluis Miquel**; C/Laureà Miró, 408-410 Sant Feliu de Llobregat, 08980 Barcelona (ES). **ERRA SOLA, Montserrat**; C/Laureà Miró, 408-410 Sant Feliu de Llobregat, 08980 Barcelona (ES).

(74) Agent: **J A KEMP LLP**; 80 Turnmill Street, London EC1M 5QU (GB).

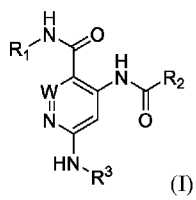
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2021/204626 A1

(54) Title: ARYL AND HETEROARYL-CARBOXAMIDE SUBSTITUTED HETEROARYL COMPOUNDS AS TYK2 INHIBITORS



(I)

(57) Abstract: Novel carboxamide substituted compounds of Formula (I) are disclosed; as well as processes for their preparation, pharmaceutical compositions comprising them and their use in therapy as inhibitors of Tyrosine Kinase 2 (Tyk2).

ARYL AND HETEROARYL-CARBOXAMIDE SUBSTITUTED HETEROARYL COMPOUNDS AS TYK2 INHIBITORS

FIELD OF THE INVENTION

The present invention deals with compounds and methods able to inhibit the TYK2 receptor by binding to its pseudokinase domain and with pharmaceutical formulations of such compounds useful in the treatment of related disorders.

BACKGROUND OF THE INVENTION

Protein kinases constitute a very relevant and large family of enzymes responsible for several transduction processes within the cells. The main function of such enzymes is to transfer phosphate groups from ATP to specific substrates of very broad nature: carbohydrates, proteins or lipids. Protein kinases direct phosphorylation processes towards threonine, serine, tyrosine and other amino acid residues present in the structure of the proteins. Such phosphorylation results in a functional change of the target protein giving rise to a modification of enzymatic activity, cellular location or modification of its signalling pathway. A huge sub-family of the protein kinases includes tyrosine kinases, those kinases able to phosphorylate tyrosine residues of different proteins. The receptor-associated tyrosine kinases include a tyrosine-kinase domain recruited to a receptor and are involved in a number of signalling cascades (cytokine signalling, growth hormone and others). The Janus kinase (JAK) family belongs to the later family and catalyses the phosphorylation of STAT proteins through a complex structure known as the JAK-STAT signalling pathway. This structure includes the cytokine receptor, the associated JAK proteins and the STAT protein able, once activated by phosphorylation/dimerization, to translocate into the cell nucleus and to induce transcription of target genes. The JAK family members are JAK1, JAK2, JAK3 and TYK2, which are associated to different cytokine receptors and catalyse the phosphorylation of the different STAT family members. Seven different STAT members (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6) have been described (Shuai, 2006). The binding of cytokines (such as interleukins or interferons) to its corresponding receptors causes the receptors dimerization and further

phosphorylation through the JAK proteins. STAT then binds to the phosphorylated receptors and are in turn phosphorylated by JAKs.

Different interactions of JAK isoforms are used by many cytokine-receptor complexes. TYK2 pairs with JAK2 and interact with IL-12 and IL-23 cytokine receptors that are associated with Th1 and Th17 differentiation, respectively (Minegishi, 2006) and with JAK1 for type I interferons. Considering the relevant but narrow spectrum of cytokines that signal through TYK2, inhibitors for this kinase may exert selective inhibitory effects on the mentioned cytokines signaling without broad-based immunosuppression. Interestingly, a single nucleotide polymorphism (P1104A; substitution of a highly conserved proline with an alanine at position 1104 in the kinase domain of the TYK2 protein) has been identified which is protective across different autoimmune diseases including among others psoriasis, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease and ulcerative colitis. Homozygous individuals show impaired responses to type I IFN, IL-12 and IL-23 and was not associated with increased viral or mycobacterium infections (Dendrou, 2016).

The structure of the JAK family includes several homology regions being the most significant the JH1 or kinase domain, which accommodates the ATP substrate and catalyses the phosphate transferences. There is also a JH2 or pseudokinase domain, structurally similar to the JH1 domain and essential for normal kinase activity, but lacking enzymatic activity. The pseudokinase domain is involved in the regulation of the kinase or catalytic domain and presents lower sequence homology among the different JAK proteins.

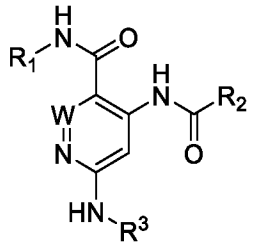
The nuclear role of the IL12/IL17 immune axis on the pathogenesis of psoriasis has been well established in recent years with the introduction of biological therapies against different cytokines like TNFa, IL17 or IL23. TYK2 has a key role on the activation of this axis by transduction of the signals of IL12, IL23 and IFNa. The inhibition of TYK2 shows thus a great potential in the management of psoriasis and other autoimmune diseases like Crohn's disease, Rheumatoid Arthritis or Lupus Erythematosus.

Several JAK inhibitors have been introduced as therapeutic agents but most of them lack isoform selectivity and, in addition to TYK2, inhibit other family kinases as JAK1. Such promiscuity could give raise to unwanted side effects that could be potentially avoided by use of TYK2 selective inhibitors.

Given the much lower sequence homology of the pseudokinase domains compared to the catalytic ones, the use of TYK2 JH2 binders shows advantages in terms of selectivity (both isoform and general kinome selectivities).

SUMMARY OF THE INVENTION

Thus, the present invention is directed to new compounds that possess Tyk2 inhibitory activity. Accordingly, there is provided a carboxamide substituted derivative, which carboxamide substituted derivative is a compound of Formula (I), or a pharmaceutically acceptable salt, or a solvate, or a *N*-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



Formula (I)

wherein:

- R^1 is selected from the group consisting of a hydrogen atom, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} deuterioalkyl group and a monocyclic C_{3-6} cycloalkyl group,
- R^2 is selected from the group consisting of a phenyl group, a monocyclic C_{5-7} cycloalkyl group or a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one heteroatom selected from O, N and S, wherein the phenyl, cycloalkyl and heteroaryl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} deuterio alkyl group, a linear or branched C_{1-4} alkoxy group, a cyano group, a $-S(O)_nCH_3$ group, a linear or branched C_{1-4} haloalkyl group, a -P(O)(C_{1-4} alkyl) group, a linear or branched C_{1-3} haloalkoxy group, a linear or branched C_{1-4} hydroxyalkyl group, a linear or branched C_{1-4} alkylamino group, a linear or branched (C_{1-6} alkoxy)-(C_{1-6} alkyl)- group, a $-(CH_2)_{0-1}O-(CH_2)_{1-2}-R^a$ group, a $-NR^bSO_2CH_3$ group, a monocyclic C_{3-6} cycloalkyl group, a $-(CH_2)_{0-1}-$ monocyclic 5- to 6- membered heterocyclyl group containing at least one heteroatom selected from O, N and S and a monocyclic 5- to 6- membered heteroaryl group containing at least one heteroatom selected from O, N and S optionally substituted by a methyl group,

- R^3 represents a –C(O)-R^4 group or a G^1 group,
- R^4 is selected from the group consisting of a linear or branched C_{1-4} alkyl group, linear or branched C_{1-4} hydroxyalkyl group, a phenyl group, a -$(CH_2)_{0-1}$-monocyclic C_{3-6} cycloalkyl group and a -$(CH_2)_{0-1}$- monocyclic 5- to 6- membered heterocyclyl group containing at least one heteroatom selected from the group consisting of O, N and S, wherein the phenyl, cycloalkyl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from a halogen atom, a linear or branched C_{1-4} alkyl group, a hydroxyl group and a –$(CH_2)_{0-1}$-monocyclic or bicyclic 5- to 6-membered heteroaryl group containing at least one heteroatom selected from the group consisting of O, N and S,
- G^1 represents a phenyl group, a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one heteroatom selected from the group consisting of O, N and S or a monocyclic 5-to 6-membered heterocyclyl group containing one heteroatom selected from O, N and S, wherein the phenyl, heteroaryl and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from a linear or branched C_{1-4} alkyl group, a halogen atom, a cyano group, a hydroxyl group, an oxo group, a linear or branched C_{1-4} alkoxy group, a linear or branched C_{1-3} haloalkyl group, a linear or branched C_{1-3} haloalkoxy group, a linear or branched (C_{1-4} alkoxy)-(C_{1-4} alkyl)- group, a –$(CH_2)_{0-1}C(O)NHCH_3$ group, a linear or branched C_{1-4} hydroxyalkyl group, a linear or branched C_{1-4} alkylamino group, a $–NHSO_2CH_3$ group, a $–SO_2NH_2$ group, a –NH-$(CH_2)_2OR^c$ group, -O-$(CH_2)_{1-2}$-R^d group, a –$(CH_2)_{0-1}$-monocyclic or bicyclic 5- to 6- membered heteroaryl group containing at least one heteroatom selected from the group consisting of O, N and S, a -NH-(CH_2)-C(O)-monocyclic 5- to 6-membered heterocyclyl group containing at least one heteroatom selected from the group consisting of O, N and S or a –$(CH_2)_{0-1}$-monocyclic or bicyclic 5- to 7-membered heterocyclyl group containing at least one heteroatom selected from the group consisting of N, O and S, wherein the heterocyclyl group is optionally substituted by one or more substituents selected from a linear or branched C_{1-4} alkyl group, a hydroxyl group, a linear or branched C_{1-2} hydroxyalkyl group and a linear or branched (C_{1-4} alkoxy)-(C_{1-4} alkyl)- group,
- W represents a nitrogen atom or a CH group,

- R^a and R^d each independently represent a hydroxyl group, a linear or branched C_{1-3} alkoxy group and a 5- to 6- membered heterocyclyl group containing at least one heteroatom selected from N, O and S,
- R^b and R^c each independently represent a hydrogen atom or a linear or branched C_{1-4} alkyl group, and
- n represents an integrer selected from 0, 1 and 2.

The invention further provides synthetic processes and intermediates described herein, which are useful for preparing said carboxamide substituted derivatives.

The invention is also directed to a carboxamide substituted derivative of the invention as described herein for use in the treatment of the human or animal body by therapy.

The invention also provides a pharmaceutical composition comprising the carboxamide substituted derivatives of the invention and a pharmaceutically-acceptable diluent or carrier.

The invention is also directed to the carboxamide substituted derivatives of the invention as described herein, for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibiton of Tyrosine kinase 2 (Tyk2), in particular wherein the pathological condition or disease is selected from a dermatological disease, an inflammatory or autoimmune-mediated disease and a metabolism/endocrine function disorder. More in particular, wherein the pathological condition or disease is selected from plaque psoriasis, scalp psoriasis, genital psoriasis, pustular psoriasis, psoriatic erythroderma, acrodermatitis continua, pityriasis rubra pilaris, lichen planus, hidradenitis suppurativa, bullous pemphigoid, pyoderma gangrenousm (PASH), ichthyosis, atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, primary biliary cholangitis, asthma and human multiple myeloma.

The invention is also directed to use of the carboxamide substituted derivatives of the invention as described herein, in the manufacture of a medicament for treatment of a pathological condition or disease susceptible to amelioration by inhibiton of Tyrosine Kinase 2 (Tyk2), in particular wherein the pathological condition or disease is selected from a dermatological disease, an inflammatory or autoimmune-mediated disease and a metabolism/endocrine function disorder. More in particular, wherein the pathological condition or disease is selected from plaque psoriasis, scalp psoriasis, genital psoriasis, pustular psoriasis, psoriatic

erythroderma, acrodermatitis continua, pityriasis rubra pilaris, lichen planus, hidradenitis suppurativa, bullous pemphigoid, pyoderma gangrenousm (PASH), ichthyosis, atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, primary biliary cholangitis, asthma and human multiple myeloma.

The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibiton of Tyrosine Kinase 2 (Tyk2), in particular wherein the pathological condition or disease is selected from a dermatological disease, an inflammatory or autoimmune-mediated disease and a metabolism/endocrine function disorder. More in particular wherein the pathological condition or disease is selected from plaque psoriasis, scalp psoriasis, genital psoriasis, pustular psoriasis, psoriatic erythroderma, acrodermatitis continua, pityriasis rubra pilaris, lichen planus, hidradenitis suppurativa, bullous pemphigoid, pyoderma gangrenousm (PASH), ichthyosis, atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, primary biliary cholangitis, asthma and human multiple myeloma.

The invention also provides a combination product comprising (i) the carboxamide substituted derivatives of the invention as described herein; and (ii) one or more additional active substances.

DETAILED DESCRIPTION OF THE INVENTION

When describing carboxamide substituted derivatives, compositions, combinations and methods of the invention the following terms have the following meaning, unless otherwise indicated.

As used herein, the term C_{1-4} alkyl embraces linear or branched radicals having 1 to 4 carbon atoms. Analogously the term C_{1-2} alkyl embraces unsubstituted linear or branched radicals having 1 to 2 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl and t-butyl.

As used herein, the term C_{1-4} deuterioalkyl embraces linear or branched radicals having 1 to 4 carbon atoms. Analogously, the term C_{1-2} deuterioalkyl embraces linear or branched radicals

having 1 to 2 carbon atoms. Examples of such radicals include monodeuteriomethyl, dideuteriomethyl, trideuteriomethyl, trideuterioethyl, pentadeuteriopropyl and trideuteriobutyl.

As used herein, the term C_{3-6} cycloalkyl embraces saturated monocyclic carbocyclic radicals having from 3 to 6 carbon atoms. Examples of monocyclic cycloalkyl groups include cyclopropyl, cycobutyl, cyclopentyl and cyclohexyl.

As used herein, a monocyclic C_{5-7} cycloalkyl group is a saturated monocyclic carbocyclic group having from 5 to 7 carbon atoms. Examples of monocyclic C_{5-7} cycloalkyl groups include cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term monocyclic or bicyclic 5- to 9-membered heteroaryl group is a 5- to 9- membered ring system, comprising at least one heteoaromatic ring and containing at least one heteroatom selected from O, N and S. A 5- to 9- membered heteroaryl radical may be a single ring (i.e monocyclic) or two fused rings wherein at least one ring contains a heteroatom. Analogously, a 5- to 6-membered heteroaryl group is a 5 to 6 membered heteroaromatic ring and containing at least one heteroatom selected from O, S and N. Examples of such radicals include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, oxadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrrolyl, benzimidazolyl, indazolyl, indolyl, benzotriazolyl, pyrrolopyridinyl, pyrazoloxazinyl, benzothiophenyl or benzofuranyl. Such heteroaryl radical is typically unsubstituted or substituted by 1, 2 or 3 substituents which may be the same or different.

As used herein, a bicyclic group can contain one or two fused rings that form a fused bicyclic ring structure, whereby the two rings are linked by two adjacent atoms. Alternatively, a bicyclic group can contain a bridged bicyclic ring structure, whereby the two rings are linked by two non-adjacent atomsAlternatively, a bicyclic group can contain a spirocyclic bicyclic ring structure, whereby the two rings are connected through a single common atom.

As used herein, the term C_{1-4} alkoxy (or alkyloxy) embraces a linear or branched oxy-containing radicals each having alkyl portions of 1 to 4 carbon atoms. Examples of alkoxy radicals include methoxy, ethoxy, n-propxy, i-propoxy, n-butoxy, sec-butoxy or t-butoxy.

As used herein, the term C_{1-3} alkoxy (or alkyloxy) embraces a linear or branched oxy-containing radicals each having alkyl portions of 1 to 3 carbon atoms. Analogously, the term

C_{1-2} alkoxy embraces a linear or branched oxy-containing radicals having alkyl portion of 1 to 2 carbon atoms. Examples of alkoxy radicals include methoxy, ethoxy, n-propxy or i-propoxy.

As used herein, the term C_{1-4} haloalkyl embraces a linear or branched alkyl group, which is substituted by one or more, preferably 1, 2 or 3 halogen atoms. Examples of haloalkyl groups include CCl_3, CF_3, CHF_2, CH_2CF_3, CH_2CHF_2, CH_2CHFCH_3, $CH_2CH_2CH_2Cl$ or $CH_2CH_2CH_2CHF_2$.

As used herein, the term C_{1-3} haloalkyl embraces linear or branched alkyl groups, which are substituted by one or more, preferably 1, 2 or 3 halogen atoms. Analogously, the term C_{1-2} haloalkyl embraces linear or branched alkyl groups, which are substituted by one or more, preferably 1, 2 or 3 halogen atoms Examples of haloalkyl groups include CCl_3, CF_3, CHF_2, CH_2CF_3, CH_2CHF_2, CH_2CHFCH_3 or $CH_2CH_2CH_2Cl$.

As used herein, the term C_{1-3} haloalkoxy embraces linear or branched alkoxyl groups in which one or more hydrogen radicals are replaced by a halo group. Examples of haloalkoxy groups include trifluoromethoxy, bromomethoxy, 1,2-dichloroethoxy and 3-iodopropoxy.

As used herein, the term C_{1-4} hydroxyalkyl embraces linear or branched alkyl radicals having 1 to 4 carbon atoms, any one of which may be substituted with one or more hydroxyl radicals. Analogously, the term C_{1-3} hydroxyakyl embraces linear or branched alkyl radicals having 1 to 3 carbon atoms, any one of which may be substituted with one or more hydroxyl radicals and the term C_{1-2} hydroxyalkyl embraces linear or branched alkyl radicals having 1 to 2 carbon atoms, any one of which may be substituted with one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, 2,3-dihydroxypropyl and 1,3-dihydroxypropan-2-yl.

As used herein, the term C_{1-4} alkylamino embraces amino groups which are substituted by one or more alkyl groups having 1 to 4 carbon atoms. Analogously, the term C_{1-2} alkylamino embraces amino groups which are substituted by one or more alkyl groups having 1 to 2 carbon atoms. Examples of such radicals include methylamine, dimethylamino, ethylamine, propylamine, methylpropylamine and butylamine.

As used herein the term (C_{1-6} alkoxy)-(C_{1-6} alkyl)- embraces linear or branched radicals having 1 to 6 carbon atoms substituted with a C_{1-6} alkoxy group. Analogously, the term (C_{1-4} alkoxy)-(C_{1-4} alkyl)- embraces linear or branched radicals having 1 to 4 carbon atoms substituted with

a C_{1-4} alkoxy group and the term (C_{1-2} alkoxy)-(C_{1-2} alkyl)- embraces linear or branched radicals having 1 to 2 carbon atoms substituted with a C_{1-2} alkoxy group. Examples of such radicals include methoxy-methyl, ethoxy-methyl, methoxy-ethyl, ethoxy-ethyl, methoxy-propyl, propoxy-methyl, ethoxy-propyl, propoxy-ethyl, propoxy-propyl, methoxy-butyl, ethoxy-butyl, methoxy-pentyl, ethoxy-pentyl and methoxy-hexyl.

As used herein, the term monocyclic 5- to 7- membered heterocyclyl radical embraces typically a non-aromatic, saturated or unsaturated C_{5-7} carbocyclic ring system in which one or more, for example, 1, 2, 3 or 4 of the carbon atoms preferably 1 or 2 of the carbon atoms are replaced by a heteroatom selected from N, O and S. Examples of such radicals include piperinyl, pyrroldyl, pyrrolinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolinyl, pirazolidinyl, triazolyl, pyrazolyl, tetrazolyl, imidazolidinyl, 4,5-dihydro-oxazolyl, 1,3-dioxol-2-one, tetrahydrofuranyl, 3-aza-tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,4-azathianyl, azepanyl, 2-oxa-6-azaspiro[3.3]heptanyl or oxepanyl.

Analogously, the term monocyclic 5- to 6- membered heterocyclic radical embraces typically a non-aromatic, saturated or unsaturated C_{5-6} carbocylic ring system in which one or more, for example, 1, 2, 3 or 4 of the carbon atoms preferably 1 or 2 of the carbon atoms are replaced by a heteroatom selected from N, O and S. Examples of 5- to 6- membered heterocyclyl radicals include piperinyl, pyrroldyl, pyrrolinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolinyl, pirazolidinyl, triazolyl, pyrazolyl, tetrazolyl, imidazolidinyl, 4,5-dihydro-oxazolyl, 1,3-dioxol-2-one, tetrahydrofuranyl, 3-aza-tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,4-azathianyl.

As used herein, the term halogen atom embraces fluorine, chlorine, bromine and iodine. A halogen atom is typically a fluorine, chlorine or bromine atom. The term halo when used as a prefix has the same meaning.

As used herein, some of the atoms, radicals, moieties, chains and cycles present in the general structures of the invention are “unsubstituted or substituted”. This means that these atoms, radicals, moieties, chains and cycles can be either unsubstituted or substituted in any position by one or more, for example 1, 2, 3 or 4, substituents, whereby the hydrogen atoms bound to the unsubstituted atoms, radicals, moieties, chains and cycles are replaced by chemically acceptable atoms, radicals, moieties, chains and cycles.

Compounds containing one or more chiral centers may be used in enantiomerically or diastereomerically pure form, in the form of a racemic mixtures and in the form of mixtures enriched in one or more stereoisomer. The scope of the invention as described and claimed encompasses the racemic forms of the compounds as well as the individual enantiomers, diastereomers and stereoisomer-enriched mixtures.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to one skilled in the art. Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20% and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Stereoisomer conglomerates may be separated by conventional techniques known to those skilled in the art. See, e.g. “Stereochemistry of Organic Compounds” by Ernest L. Eliel (Wiley, New York, 1994).

The term "therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "treatment" as used herein refers to the treatment of a disease or medical condition in a human patient which includes:

(a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;

(b) ameliorating the disease or medical condition, i.e., causing regression of the disease or medical condition in a patient;

(c) suppressing the disease or medical condition, i.e., slowing the development of the disease or medical condition in a patient; or

(d) alleviating the symptoms of the disease or medical condition in a patient.

The phrase "pathological condition or disease susceptible to amelioration by inhibiton of Tyk2 includes all disease states and/or conditions that are acknowledged now, or that are found in the future, to be associated with an increased Tyk2 activity. Such disease states include, but are not limited to, dermatological diseases, inflammatory or autoimmune-mediated diseases and a metabolism/endocrine function disorders.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt prepared from a base or acid which is acceptable for administration to a patient, such as a mammal. Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids.

As used herein, a N-oxide is formed from the tertiary basic amines or imines present in the molecule, using a convenient oxidising agent.

The carboxamide substituted derivatives of the invention may exist in both unsolvated and solvated forms. The term solvate is used herein to describe a molecular complex comprising a compound of the invention and an amount of one or more pharmaceutically acceptable solvent molecules. The term hydrate is employed when said solvent is water. Examples of solvate forms include, but are not limited to, compounds of the invention in association with water, acetone, dichloromethane, 2-propanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof.

The invention also includes isotopically-labelled carboxamide substituted derivatives of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}CI, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S. Preferred isotopically-labelled compounds include deuterated derivatives of the compounds of the invention. As used herein, the term deuterated derivative embraces compounds of the invention where in a particular position at least one hydrogen atom is replaced by deuterium. Deuterium

(D or ^{2}H) is a stable isotope of hydrogen which is present at a natural abundance of 0.015 molar %.

Isotopically-labelled carboxamide substituted derivatives of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labelled reagent in place of the non-labelled reagent otherwise employed.

As used in the present invention, the term tautomer means two or more forms or isomers of an organic compound that readily could be interconverted into each other via a common chemical reaction called tautomerization. This reaction commonly results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. The concept of tautomerizations is called tautomerism. Because of the rapid interconversion, tautomers are generally considered to be the same chemical compound. In solutions in which tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH.

As used herein, the term deuterated derivatives embraces compounds of the invention where in a particular position at least one hydrogen atom is replaced by deuterium. Deuterium (D or ^{2}H) is a stable isotope of hydrogen which is present at a natural abundance of 0.015% molar.

Hydrogen deuterium exchange (deuterium incorporation)- is a chemical reaction in which a covalently bonded hydrogen atom is replaced by a deuterium atom. Said exchange (incorporation) reaction can be total or partial.

Prodrugs of the carboxamide substituted derivatives described herein are also within the scope of the invention. Thus certain derivatives of the carboxamide substituted derivatives of the present invention, which derivatives may have little or no pharmacological activity themselves, when administered into or onto the body may be converted into compounds of the present invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of the present invention with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

In the case of carboxamide substituted derivatives that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystalline or polymorphic forms, or in an amorphous form, all of which are intented to be within the scope of the present invention.

Typically, R^1 is selected from the group consisting of a hydrogen atom, a methyl group or a trideuteriomethyl group.

Preferably, R^1 represents a methyl group or a trideuteriomethyl group.

Typically, R^2 represents a phenyl group or a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one N atom, wherein the phenyl and heteroaryl groups are unsubstituted or substituted by one or more substituents selected from a linear C_{1-2} alkyl group, a linear C_{1-2} deuterioalkyl group, a linear C_{1-2} haloalkyl group, a linear C_{1-2} alkoxy group, a $-S(O)_{1-2}CH_3$ group, a halogen atom, a hydroxyl group, a linear C_{1-2} alkylamino group, a linear C_{1-2} hydroxyalkyl group, a cyano group, a $NHSO_2CH_3$ group and a 5-membered heteroaryl group containing at least one N atom, said heteroaryl group being optionally substituted by a methyl group.

Preferably, R^2 represents a phenyl group or an indolyl group wherein the phenyl and indolyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a fluorine atom, a chlorine atom, a methyl group, a methoxy group, a hydroxyl group, a linear C_{1-2} hydroxyalkyl group and a triazolyl group optionally substituted by a methyl group.

Typically, n is an integer selected from 0, 1 and 2.

Preferably, n represents 1 or 2.

Typically, R^3 represents a $-C(O)-R^4$ group.

Typically, R^4 is selected from the group consisting of a linear or branched C_{1-4} hydroxyalkyl group and a C_{3-6} cycloalkyl group, wherein the cycloalkyl group is unsubstituted or substituted by one or more substituents selected from a halogen atom and a hydroxyl group.

Preferably, R^4 represents a cyclopropyl group unsubstituted or substituted by a fluorine atom.

Typically, R^3 represents a G^1 group.

Typically, G^1 represents a monocyclic 5- to 6- membered heteroaryl group containing at least one N atom, wherein the heteroaryl group is unsubstituted or substituted by one or more substituents selected from the group consisting of a linear C_{1-2} alkyl group, a cyano group, a linear or branched C_{1-3} hydroxyalkyl group, a linear or branched (C_{1-2} alkoxy)-(C_{1-2} alkyl)- group and a 6- membered heterocyclyl group containing at least one heteroatom selected from the group consisting of N and O, wherein the heterocyclyl group is optionally substituted by one or more substituents selected from a linear or branched (C_{1-2} alkoxy)-(C_{1-2} alkyl)- group, a linear C_{1-2} hydroxyalkyl group and a linear C_{1-2} alkyl group.

Preferably, G^1 represents a pyridine, a pyrimidine or a pyrazolyl group, wherein the pyridine, pyrimidine and pyrazolyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a methyl group, a linear or branched C_{1-3} hydroxyalkyl group and a 6-membered heterocyclyl containing at least one heteroatom selected from the group consisting of N and O group, said heterocyclyl group being optionally substituted by one or more substituents selected from a methyl group, a hydroxyethyl group and a methoxyethyl group.

Preferably, W is a CH group.

In one embodiment,

- R^1 represents a hydrogen atom, a methyl group or a trideuteriomethyl group, preferably a methyl group or a trideuteriomethyl group,
- R^2 represents a phenyl group or a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one N atom, wherein the phenyl and heteroaryl groups are unsubstituted or substituted by one or more substituents selected from a linear C_{1-2} alkyl group, a linear C_{1-2} deuterioalkyl group, a linear C_{1-2} haloalkyl group, a linear C_{1-2} alkoxy group, a $-S(O)_{1-2}CH_3$ group, a halogen atom, a hydroxyl group, a linear C_{1-2}

alkylamino group, a linear C_{1-2} hydroxyalkyl group, a cyano group, a $NHSO_2CH_3$ group and a 5-membered heteroaryl group containing at least one N atom, said heteroaryl group being optionally substituted by a methyl group,

- R^3 represents a $-C(O)-R^4$ group,
- R^4 is selected from the group consisting of a linear or branched C_{1-4} hydroxyalkyl group and a C_{3-6} cycloalkyl group, wherein the cycloalkyl group is unsubstituted or substituted by one or more substituents selected from a halogen atom and a hydroxyl group, and
- W represents a CH group.

In another embodiment:

- R^1 represents a hydrogen atom, a methyl group or a trideuteriomethyl group, preferably a methyl group or a trideuteriomethyl group,
- R^2 represents a phenyl group or a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one N atom, wherein the phenyl and heteroaryl groups are unsubstituted or substituted by one or more substituents selected from a linear C_{1-2} alkyl group, a linear C_{1-2} deuterioalkyl group, a linear C_{1-2} haloalkyl group, a linear C_{1-2} alkoxy group, a $-S(O)_{1-2}CH_3$ group, a halogen atom, a hydroxyl group, a linear C_{1-2} alkylamino group, a linear C_{1-2} hydroxyalkyl group, a cyano group, a $NHSO_2CH_3$ group and a 5-membered heteroaryl group containing at least one N atom, said heteroaryl group being optionally substituted by a methyl group,
- R^3 represents a G^1 group,
- G^1 represents a monocyclic 5- to 6- membered heteroaryl group containing at least one N atom, wherein the heteroaryl group is unsubstituted or substituted by one or more substituents selected from the group consisting of a linear C_{1-2} alkyl group, a cyano group, a linear or branched C_{1-3} hydroxyalkyl group, a linear or branched (C_{1-2} alkoxy)-(C_{1-2} alkyl)- group and a 6- membered heterocyclyl group containing at least one heteroatom selected from the group consisting of N and O, wherein the heterocyclyl group is optionally substituted by one or more substituents selected from a linear or branched (C_{1-2} alkoxy)-(C_{1-2} alkyl)- group, a linear C_{1-2} hydroxyalkyl group and a linear C_{1-2} alkyl group, and
- W represents a CH group.

In a preferred embodiment,

- R^2 represents a phenyl group or an indolyl group, wherein the phenyl and indolyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a fluorine atom, a chlorine atom, a methyl group, a methoxy group, a hydroxyl group, a linear C_{1-2} hydroxyalkyl group and a triazolyl group optionally substituted by a methyl group,
- R^4 represents a cyclopropyl group unsubstituted or substituted by a fluorine atom, and
- G^1 represents a pyridine, pyrimidine or a pyrazolyl group, wherein the pyridine, pyrimidine and pyrazolyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a methyl group, a linear or branched C_{1-3} hydroxyalkyl group or a 6-membered heterocyclyl containing at least one heteroatom selected from the group consisting of N and O group, optionally substituted by one or more substituents selected from a methyl group, a hydroxyethyl group and a methoxyethyl group.

In another preferred embodiment,

- R^1 represents a hydrogen atom, a methyl group, a trideuteriomethyl group or a cyclopropyl group,
- R^2 is selected from the group consisting of a phenyl group, a cyclohexyl group, a pyridinyl group, a benzimidazolyl group, an imidazolpyridinyl group, an indolyl group, a pyrrolopyridinyl group, a benzotriazolyl group, a pyrazolyl group and an indazolyl group, wherein the phenyl, pyridinyl, indolyl, pyrrolopyridinyl, benzotriazolyl, pyrazolyl, imidazolpyridinyl and benzimidazolyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of a methyl group, a fluorine atom, a chlorine atom, a methoxy group, a cyano group, a $–S(O)_{1-2}CH_3$ group, a trifluoromethyl group, a trifluoromethoxy group, a trideuteriomethyl group, a CF_3CH_2- group, a hydroxyl group, a hydroxymethyl group, a hydroxyethyl group, a trideuteriomethyl group, a $-NHCH_3$ group, an imidazole group, a $-NHSO_2CH_3$ group, a methyl-triazole group, a cyclopropyl, a triazole group, an imidazole group, a methyl-imidazole group, a methoxyethyl group, a methoxymethyl group, an $–(CH_2)_{0-1}-O(CH_2)_2OCH_3$ group, an $-O(CH_2)_2OH$ group, a $-(CH_2)O(CH_2)_2OH$ group, a $–(CH_2)$-morpholinyl and a $-CH(CH_3)CH_2OCH_3$ group,

- R^3 represents a –C(O)-R^4 group or a G^1 group,
- R^4 is selected from the group consisting of a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, phenyl group, a –$CH(CH_3)_2$ group, a –$C(CH_3)_3$ group, a –$C(CH_3)_2OH$ group, a –(CH_2)-morpholinyl group, a –(CH_2)-cyclohexyl group and a –$(CH_2)_{1-2}$-OH group, wherein the cyclopropyl, cyclobutyl, phenyl and cyclohexyl groups are unsubstituted or substituted by one or more substituents selected from a fluorine atom, a methyl group, a hydroxyl group and a –(CH_2)-triazole group,
- G^1 is selected from the group consisting of a phenyl group, pyrazolyl group, pyridinyl group, a pyrimidinyl group, a pyridazinyl group, a indazolyl group, an imidazolyl group, a pyrazyl group, a triazolyl group, a tetrahydropyranyl group and a pyrazoloxazinyl group, wherein the phenyl, pyrazolyl, pyridinyl, pyrimidinyl, imidazolyl, pyrazyl and triazolyl groups are unsubstituted or substituted by one or more substituents selected from a fluorine atom, methyl group, a methoxy group, a trifluoromethyl group, a –CH_2CF_3 group, a –OCH_2CF_3 group, a cyano group, an oxo group, a hydroxyl group, a methoxymethyl group, a –$C(CH_3)_2OH$ group, a –$CH_2C(O)NHCH_3$ group, a -$NHCH_3$ group, a –$NHCH_2C(O)$-morpholinyl group, a –$N(CH_3)_2$ group, a -$NHSO_2CH_3$ group, -$NH(CH_2)_2OCH_3$ group, -$NH(CH_2)_2OH$ group, a –SO_2NH_2 group, an –O-$(CH_2)_2$-morpholinyl group, a methoxyethyl group, a hydroxyethyl group, a hydroxymethyl group, a –(CH_2)-triazolyl group, a –$(CH_2)_{0-1}$-morpholinyl group, a –$CH(CH_3)OH$ group, a –$O(CH_2)_2OCH_3$ group, a –$O(CH_2)_2OH$ group, a –$(CH_2)_{0-1}$-tetrahydropyranyl group, an oxa-5-azabicyclo[2.2.1]heptyl group, a hydroxyethyl substituted piperazinyl group, a methoxyethyl substituted piperazinyl group, a dimethyl substituted morpholinyl group, a methyl substituted piperazinyl group and a hydroxyl substituted piperidinyl group, and
- W represents a nitrogen atom or a –CH group.

In one embodiment, the R^2 and R^3 groups of formula I are unsubstituted or substituted by one, two, three or four substituents. In another embodiment, the substituents are the same. In another embodiment, the substituents are different. The substituents can be present at the ortho, meta or para positions, preferably the ortho and meta positions.

Particular individual compounds of the invention include:

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(2-pyridylamino)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[(2,4,6-trimethylbenzoyl) amino]pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(4-pyridylamino)pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[(5-cyano-2-pyridyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-cyclopropyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(pyrimidin-4-ylamino)pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-[(1-methylpyrazol-3-yl)amino]pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[[4-(methoxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-4-cyano-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

4-[(2-chloro-6-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

6-[(5-cyano-2-pyridyl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[(2-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[1-[2-(methylamino)-2-oxo-ethyl]pyrazol-4-yl]amino]pyridine-3-carboxamide

4-(2-fluoro-6-methoxybenzamido)-6-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-N-methylnicotinamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[1-(2-hydroxyethyl)pyrazol-4-yl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[4-(1,2,4-triazol-1-ylmethyl)benzoyl]amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(1,2,4-triazol-1-ylmethyl)-2-pyridyl]amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(morpholinomethyl)-2-pyridyl]amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(6-methyl-2-pyridyl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(2-pyridylamino)pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-(hydroxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-(1H-indazol-6-ylamino)-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(4-cyano-2-fluoro-6-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[4-(methoxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[3-(1-hydroxyethyl)anilino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,4-difluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(tetrahydropyran-4-ylamino)pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(pyrimidin-2-ylamino)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[[4-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(methylamino)-2-pyridyl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[[3-(trifluoromethyl)benzoyl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-4-(trifluoromethoxy)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-5-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-(hydroxymethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(hydroxymethyl)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[[6-(methylamino)pyridine-3-carbonyl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[[2-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-2-methoxy-6-(methylamino)pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(4-hydroxy-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[(2,4,5-trifluoro-3-methoxy-benzoyl)amino]pyridine-3-carboxamide

4-[[3,5-bis(trifluoromethyl)benzoyl]amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

4-[(4-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridazine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[5-(tetrahydropyran-3-ylmethyl)-2-pyridyl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2,6-difluorobenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-5-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-fluoro-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(3-chloro-5-fluoro-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(5-hydroxy-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-(2,4-difluoro-5-methoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-[(5-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

4-[(3,5-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(1H-imidazol-2-yl)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxypyridine-3-carbonyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-6-[[1-[2-(methylamino)-2-oxo-ethyl]pyrazol-4-yl]amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[3-(methanesulfonamido)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3H-benzimidazole-5-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(1H-1,2,4-triazol-5-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(1H-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(6-methyl-2-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(pyridazin-3-ylamino)pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-6-[(5-morpholino-2-pyridyl)amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(1-methylimidazol-2-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(2-morpholinoacetyl)amino]pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-indazole-6-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(6-fluoro-2,3-dimethoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(4-methyl-6-oxo-1H-pyrimidin-2-yl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-6-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[2-(4-hydroxycyclohexyl)acetyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-indole-5-carboxamide

4-[(3-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(methanesulphonamido)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[2-methyl-6-(methylamino)pyrimidin-4-yl]amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(2-methyl-6-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[(5-fluoro-2-pyridyl)amino]-N-methyl-pyridine-3-carboxamide

6-[[5-(2,2-dimethylmorpholin-4-yl)-2-pyridyl]amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[5-(2-hydroxyethoxy)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[(3-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(4-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(3-cyano-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-6-methoxy-3H-benzotriazole-5-carboxamide

6-[[6-(dimethylamino)-2-methyl-pyrimidin-4-yl]amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(methanesulfonamido)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3H-benzimidazole-5-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(5-sulfamoyl-2-pyridyl)amino]pyridine-3-carboxamide

4-[(3-cyclopropyl-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1H-indole-2-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(2-methoxyethoxy)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(5,6-dimethylpyrazin-2-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-4-methoxy-indole-2-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-6-[(6-methyl-2-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[[2-[4-(2-methoxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(3-chloro-2-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-3-methoxy-indole-2-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-6-[[6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl) benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(3,5-difluoro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-methyl-indole-6-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxamide

N-[2-(cyclopropanecarbonylamino)-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-3-methoxy-indole-2-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-methyl-indole-2-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-methyl-benzimidazole-5-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-methyl-benzimidazole-5-carboxamide

6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(3-fluoro-2-methoxy-benzoyl)amino]-6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

4-[(3-chloro-2-methoxy-benzoyl)amino]-6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridazine-3-carboxamide

N-[2-(cyclopropanecarbonylamino)-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-methoxy-1-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-methoxy-2-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1H-indole-5-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-methoxypyridine-2-carbonyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridazine-3-carboxamide

4-[(3,6-difluoro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-(2-fluoro-6-methoxybenzamido)-6-((6-((2-methoxyethyl)amino)-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((4-(trifluoromethyl)pyridin-2-yl)amino)nicotinamide

4-(2,5-dimethoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-((6-((2-hydroxyethyl)amino)-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(morpholinomethyl)benzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-((6-methoxy-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((4-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

6-((6-cyano-2-methylpyrimidin-4-yl)amino)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(3-hydroxypropanamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-5-(methoxymethyl)benzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-((6-(2-hydroxyethoxy)pyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(3-hydroxycyclobutane-1-carboxamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(2-hydroxyacetamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-(2-methoxyethoxy)-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-isobutyramido-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-(1-methylcyclopropane-1-carboxamido)nicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((6-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

6-(3,3-difluorocyclobutane-1-carboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-pivalamidonicotinamide

6-(cyclopentanecarboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-indazole-6-carboxamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-(2-hydroxyethoxy)-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-((2-hydroxyethoxy)methyl)-2-methoxybenzamido)-N-methylnicotinamide

6-(cyclobutanecarboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(2-hydroxy-2-methylpropanamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(3-fluorocyclobutane-1-carboxamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-((4-(1-hydroxyethyl)pyridin-2-yl)amino)-N-methylnicotinamide

4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methyl-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidin-4-yl)amino)nicotinamide

4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methyl-2-(2-morpholinoethoxy)pyrimidin-4-yl)amino)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(1-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-2-carboxamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-ethyl-2-methoxybenzamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1-methyl-1H-pyrrolo[3,2-c]pyridine-3-carboxamide

4-(2-methoxy-3-(trifluoromethyl)benzamido)-N-methyl-6-((6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)nicotinamide

4-(3-chloro-2-methoxybenzamido)-N-methyl-6-((6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)nicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-fluoro-1-(2-hydroxyethyl)-3-methoxy-1H-indole-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2,2,2-trifluoroethyl)-1H-indole-2-carboxamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-((2-methoxyethoxy)methyl)benzamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1H-indole-2-carboxamide

4-(3-chloro-2-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-methoxyisonicotinamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1H-pyrrolo[3,2-c]pyridine-3-carboxamide

4-(3,4-difluoro-2-methoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(3-chloro-2-methoxybenzamido)-6-((2-(2-methoxyethoxy)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-fluoro-2-methoxybenzamido)-N-methylpyridazine-3-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-2-(methoxymethyl)-1H-benzo[d]imidazole-5-carboxamide

6-(cyclopropanecarboxamido)-4-(3-fluoro-2-methoxybenzamido)-N-methylnicotinamide

4-(3-chloro-2-methoxybenzamido)-N-methyl-6-((6-methyl-2-((2-morpholino-2-oxoethyl)amino)pyrimidin-4-yl)amino)nicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(3-fluoro-2-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(3-chloro-2-methoxybenzamido)-6-((2-fluoro-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-indole-6-carboxamide

N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(2-fluoro-6-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2,3-dimethoxybenzamido)-6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-benzo[d][1,2,3]triazole-6-carboxamide

N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-indole-2-carboxamide

4-(2,3-dimethoxybenzamido)-N-methyl-6-((2-methylpyrimidin-4-yl)amino)nicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-3H-imidazo[4,5-b]pyridine-6-carboxamide

N-(2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3,4-dimethoxypicolinamide

N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3,4-dimethoxypicolinamide

6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-4-(2-methoxynicotinamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(2-methoxyethoxy)benzamido)-N-(methyl-d3)nicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3-fluoro-7-methoxy-1H-indole-6-carboxamide

N-(2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

4-(2,3-dimethoxybenzamido)-N-methyl-6-((6-methylpyrimidin-4-yl)amino)nicotinamide

6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-4-(2-methoxy-3-(methyl-d3)benzamido)-N-methylnicotinamide

N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

4-(3-cyano-2-methoxybenzamido)-6-(cyclopropanecarboxamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-(2-hydroxyethoxy)-2-methoxybenzamido)-N-(methyl-d3)nicotinamide

N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(2,3-dimethoxybenzamido)-N-methyl-6-((1-methyl-1H-pyrazol-3-yl)amino)nicotinamide

N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1-methyl-1H-pyrazole-5-carboxamido)-N-(methyl-d3)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1-methyl-1H-pyrazole-3-carboxamido)-N-(methyl-d3)nicotinamide

4-(2,3-dimethoxybenzamido)-6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-N-methylpyridazine-3-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-fluoro-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(2-methoxy-3-(methyl-d3)benzamido)-6-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-N-methylnicotinamide

N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

4-(2,3-dimethoxybenzamido)-N-methyl-6-((1-methyl-1H-1,2,4-triazol-3-yl)amino)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)benzamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(methylsulfinyl)benzamido)-N-(methyl-d3)nicotinamide

6-(2,2-difluorocyclopropane-1-carboxamido)-4-(2,3-dimethoxybenzamido)-N-methylnicotinamide

6-((6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl)amino)-4-(2,3-dimethoxybenzamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine-6-carboxamide

6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-4-(2-methoxy-3-(methyl-d3)benzamido)-N-methylnicotinamide

3-methoxy-N-(2-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(2,3-dimethoxybenzamido)-6-((1,5-dimethyl-1H-pyrazol-3-yl)amino)-N-methylnicotinamide

4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)nicotinamide

4-(2,3-dimethoxybenzamido)-6-((5-fluoropyridin-2-yl)amino)-N-methylnicotinamide

4-(2-methoxy-3-methylbenzamido)-6-((1-(2-methoxyethyl)-1H-imidazol-4-yl)amino)-N-methylnicotinamide

4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methylpyrimidin-4-yl)amino)nicotinamide

4-(2,3-dimethoxybenzamido)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1,3-dimethyl-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-3-(methyl-d3)-1H-indole-5-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(1-methoxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

N-(2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methyl-4-(2-(N-methylmethylsulfonamido)benzamido)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxycyclohexane-1-carboxamido)-N-methylnicotinamide

or a pharmaceutically acceptable salt, or solvate, or N-oxide, or stereoisomer, or tautomer, or isotopically labelled derivatives thereof.

Of particular interest are the compounds

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

or a pharmaceutically acceptable salt, or solvate, or N-oxide, or stereoisomer, or tautomer, or isotopically labelled derivatives thereof.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be prepared using the methods and procedures described herein, or using similar methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Starting compounds are commercially available or may be obtained following the conventional synthetic methods already known in the art.

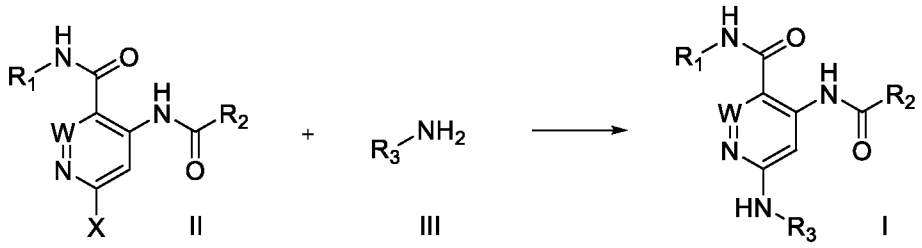
Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group, as well as suitable conditions for protection and deprotection, are well known in the art. For example, numerous

protecting groups, and their introduction and removal are described in T. W. Greene and G. M. Wuts, Protecting Groups in Organic Synthesis, Third Edition, Wiley, New York, 1999, and references cited therein.

Processes for preparing compounds of the invention are provided as further embodiments of the invention and are illustrated by the procedures below.

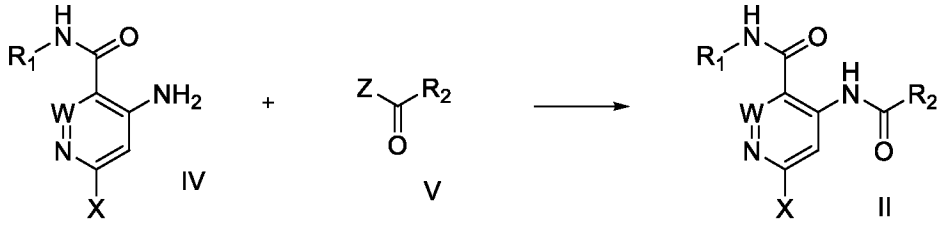
The methods presented below are not meant to limit the synthetic pathways in order to obtain the compounds of the invention. All examples of the present application are prepared by the methods disclosed herein.

Method A



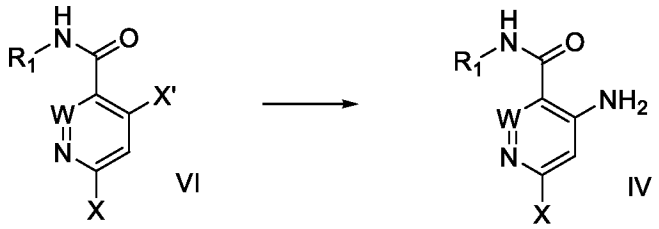
Scheme 1

Scheme 1 depicts the synthesis of compounds I from haloderivatives II (X=Cl, Br, I) by reaction with amines III. This transformation is carried on preferently in the presence of derivatives of transition metals like palladium which catalyse the process.



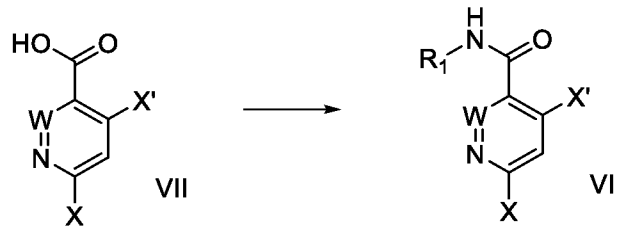
Scheme 2

The preparation of intermediates II from amines IV is depicted in Scheme 2 and involves the acylation of IV with an acid chloride (Z=Cl) in the presence of a proton scavenger such as sodium hydride or with an acid (Z=OH) in the presence of an activating agent such as HATU.



Scheme 3

The intermediate amine IV can be in turn obtained from haloderivatives VI directly by carefully controlled reaction with ammonia or by reaction with a benzylic amine and a further de-benzylation process by well-known methods such as hydrogenation in the presence of a metal catalyst as palladium.

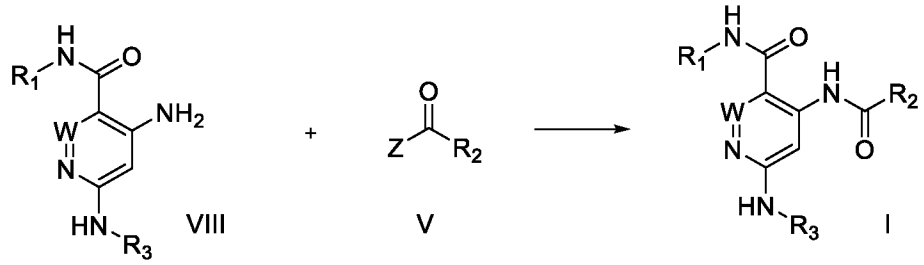


Scheme 4

The amide haloderivatives VI can be obtained from well-known carboxylic derivatives VII through the corresponding acyl halides obtained by conventional methods such as treatment with oxalyl chloride and further reaction with an amine R1-NH2 in the presence of an acid scavenger as a tertiary amine.

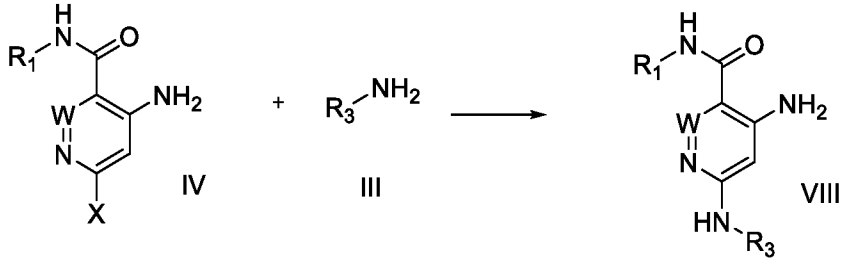
Alternatively, method B can also be used to reach the target structures

Method B



Scheme 5

Scheme 5 depicts the synthesis of compounds I by acylation of amines VIII with an acid chloride V (Z=Cl) in the presence of a proton scavenger such as sodium hydride or with an acid V (Z=OH) in the presence of an activating agent such as HATU.



Scheme 6

Amine intermediates VIII can be prepared from haloderivatives IV (X=Cl, Br, I) by reaction with amines III. This transformation, as showed in Scheme 6, is carried on preferently in the presence of derivatives of transition metals like palladium which catalyse the process.

EXAMPLES

The syntheses of the compounds of the invention are illustrated by the following Examples (1 to 261) including Intermediates (1 to 240) which do not limit the scope of the invention in any way.

General

Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. Commercial intermediates are referred to in the experimental section by their IUPAC name. Ether refers to diethyl ether, unless otherwise specified. Concentration or evaporation refer to evaporation under vacuum using a Büchi rotatory evaporator.

Reaction products were purified, when necessary, by flash chromatography on silica gel (40-63 μm) with the solvent system indicated. Purifications in reverse phase were made in a Biotage Isolera® automated purification system equipped with a C18 column and using a gradient, unless otherwise stated, of water-acetonitrile/MeOH (1:1) (0.1% v/v ammonium formate both phases) from 0% to 100% acetonitrile/MeOH (1:1) in 40 column volumes. The conditions "formic acid buffer" refer to the use of 0.1% v/v formic acid in both phases. The appropriate fractions were collected and the solvents evaporated under reduced pressure and/or liofilized.

Purifications in reverse phase were also made in a Biotage SP1® automated purification system equipped with a C18 column and using a gradient of, unless otherwise stated, water-acetonitrile/MeOH (1:1) (0.1% v/v ammonium formate both phases) from 0% to 100% acetonitrile/MeOH (1:1) in 80 column volumes. The conditions "formic acid buffer" refer to the use of 0.1% v/v formic acid in both phases. The appropriate fractions were collected and freeze dried.

Preparative HPLC-MS were performed on a Waters instrument equipped with a 2767 injector/collector, a 2525 binary gradient pump, a 2996 PDA detector, a 515 pump as a make-up pump and a ZQ4000 Mass spectrometer detector or on a Agilent 1200 Series coupled to an Agilent 6120 Mass spectrometer detector. Both systems were equipped with a Symmetry Prep C18 (19 x 300 mm, 7 μm) column or a XBridge Prep C18 (19 x 100 mm, 5 μm) column. The mobile phase was formic acid (0.4 mL), ammonia (0.1 mL), methanol (500 mL) and acetonitrile (500 mL) (B) and formic acid (0.5 mL), ammonia (0.125 mL) and water (1000 mL) (A), the specific gradients used are specified in each particular case. The flow rate was 20 ml/min.

The UPLC chromatographic separations were obtained using a Waters Acquity UPLC system coupled to a SQD mass spectrometer detector. The system was equipped with an ACQUITY UPLC BEH C-18 (2.1x50 mm, 1.7 mm) column. The mobile phase was formic acid (0.4 mL), ammonia (0.1 mL), methanol (500 mL) and acetonitrile (500 mL) (B) and formic acid (0.5 mL), ammonia (0.125 mL) and water (1000 mL) (A). A gradient between 0 to 95% of B was used. The run time was 3 or 6 minutes. The injection volume was 0.5 microliter. Chromatograms were processed at 210 nM or 254 nM. Mass spectra of the chromatograms were acquired using positive and negative electrospray ionization.

The HPLC chromatographic separations were obtained using a Waters Alliance HT HPLC system coupled to a ZQ mass spectrometer detector. The system was equipped with an YMC-Pack ODS-AQ C-18 (4-6x50 mm, 3 μM) column. The mobile phase was formic acid (1.0 mL) and acetonitrile (1000 mL) (B), formic acid (1.0 mL) and water (1000 mL) (A). A gradient between 5 to 100% of B was used. The run time was 3.5 minutes. The injection volume was 5 microliter. Chromatograms were processed from 210 nM to 400 nM. Mass spectra of the chromatograms were acquired using positive electrospray ionization.

1H Nuclear Magnetic Resonance Spectra were recorded on a Varian Mercury plus operating at a frequency of 400MHz or a Varian VNMRS operating at 600MHz and equipped with a cold

probe for the 1H spectra. Samples were dissolved in the specified deuterated solvent. Tetramethylsilane was used as reference.

Abbreviations:

$Pd_2(dba)_3$: tris(dibenzylidineacetone)dipalladium(0)

Xantphos: (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine)

DIPEA: Diisopropylethylamine

DMF: N,N-dimethylformamide

DMSO: dimethylsulfoxyde

THF: Tetrahydrofuran

AcOEt: Ethyl acetate

DCM: Dichloromethane

HATU: 1-(bis(dimethylamino)methylene)-1H-[1,2,3]triazolo[4,5-b]pyridine-1-ium 3-oxide hexafluorophosphate(V)

Preparation 1: Synthesis of 4,6-dichloro-N-methyl-pyridine-3-carboxamide

To a stirred solution of 4,6-dichloropyridine-3-carboxylic acid (5000mg, 26.04mmol) in 130 mL of anh. DCM one drop of DMF was added and the temperature was lowered to 0 ºC. Oxalyl chloride (6.7mL, 78.12mmol) was added dropwise and the mixture was stirred at room temperature for 4 hr. The solvent was evaporated (co-evaporated with AcOEt) and the crude was redissolved in DCM (66 mL) and cooled to -20 ºC. Methylamine (2 M in THF, 32 mL, 64 mmol) was added dropwise and the mixture was stirred at 0 ºC for 45 min. Excess water was added followed by NaHCO3 sat. solution. The phases were separated and the aqueous phase was extracted with DCM (x 1). The combined organic extracts were dried over anh. MgSO4, filtered and evaporated to have the title compound (5.11g, 96%) as a white solid.
HPLC/MS tR=1.65min (100%). LRMS (m/z): 205,207,209 (2 Cl).

^{1}H-RMN (400 MHz, CDCl3) δ ppm 3.05 (d, J = 4.9 Hz, 3H), 6.22 (brs, 1H), 7.42 (s, 1H), 8.66 (s, 1H).

Preparation 2: Synthesis of 4,6-dichloro-N-(trideuteriomethyl)pyridine-3-carboxamide

To a stirred solution of 1050 mg (5.46 mmol) of 4,6-dichloropyridine-3-carboxylic acid in 28 mL of anh. DCM 4 drops of DMF were added and the temperature was lowered to 0 ºC. Oxalyl chloride (0.5 mL, 5.83 mmol) was added dropwise and the mixture was stirred for 30 min. at room temperature and for 1h 30min at reflux. The volatiles were removed under reduced pressure and the residue redissolved in DCM (14 mL) and cooled to -20 ºC. Trideuteriomethylamine hydrochloride (600 mg, 8.50 mmol) was added in one portion and then DIEA (4.8 ml, 27.55 mol) was added dropwise. The mixture was stirred at 0 ºC for 1 h. By UPLC-control the desired product was observed together with some starting carboxylic acid from the hydrolysis of the acid chloride. The reaction was then finished. Water was added followed by NaHCO3 sat. The phases were separated and the aqueous was extracted again with DCM. The combined organic extracts were washed with NaHCO3 sat. dried with phase separator and evaporated to have the title product as a yellow solid (997 mg).

HPLC/MS tr = 1.00 min (96%). LRMS (m/z): 208,210,212 (2 Cl)

Preparation 3: Synthesis of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide

To a solution of 4,6-dichloro-N-methyl-pyridine-3-carboxamide (Preparation 1; 451 mg, 2.19 mmol) in 4 mL of anh. ACN was added ammonia (25 % in water, 4 mL, 52.85 mmol) and the mixture was heated at 120 ºC. After 6 h of reaction the conversion is 83 % by HPLC-MS. The mixture was left to stir at 120 ºC for 4 additional hours. The mixture was cooled down to room temperature and the volatiles were partially removed under reduced pressure. The white solid was filtered, rinsed with water and dried in the vacuum oven at 40 ºC. The title compound was obtained as a white solid (305 mg, 75 %).

HPLC-MS: tr = 1.27 min.(99 %). LRMS (m/z): 186/188 (1 Cl).

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.86 (s, 3H), 6.68 (s, 1H), 8.20 (s, 1H).

Preparation 4: 4-amino-6-chloro-N-(trideuteriomethyl)pyridine-3-carboxamide

To a solution of 997 mg (4. 79 mmol) of 4,6-dichloro-N-(trideuteriomethyl)pyridine-3-carboxamide (Preparation 2) in 6 mL of ACN was added ammonia (32 % in water, 6 mL) and the mixture was stirred carefully at 120 ºC.overnight. The next day the reaction is 60 % of

desired compound and 40% of starting material. Then, further ammonia (6 mL) was added and the mixture heated again at 120ºC for 24 additional hours. The mixture was carefully cooled down to room temperature and the solid formed filtered and washed with a little quantity of water. The white solid was dried in the vacuum oven at 45 ºC (660 mg, 100%).

UPLC-MS: tr = 0.60 min.(99 %). LRMS (m/z): 189/191.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 6.68 (s, 1H), 7.30-7.40 (bs, 2H), 8.22 (s, 1H), 8.42 (s 1H).

Preparation 5: Synthesis of 4,6-dichloro-N-methyl-pyridazine-3-carboxamide

4,6-dihydroxypyridazine-3-carboxylic acid (250 mg, 1.6 mmol) and TEA (225 µL, 1.61 mmol) were placed in a pressure tube, then phosphorus oxychloride (2 ml, 21.4 mmol) was added and the mixture was heated at 80ºC first and then the temperature was raised to 110ºC and the reaction run for 120 minutes. The heating was stopped and the reaction allowed to cool a bit. Then anhydrous DCE was added and the crude was concentrated. After two co-evaporations with DCE the residual black solid was taken up in DCM (10 ml) and methylamine (2M in THF, 0.96 ml) was added at 0ºC and the mixture allowed to stir for 5 min. HPLC showed still the presence of starting material (as the methyl ester), so more methylamine was added (0.6 ml) at 0ºC and the mixture stirred at 0ºC. After 20 minutes at 0ºC, water and more DCM were added. The phases were separated and the aqueous phase was extracted with dichlomethane (x 2). The combined organic extracts were dried over anh. MgSO4, filtered and evaporated to have a dark solid that was purified by flash chromatography (Biotage, SNAP 12g) using DCM/DCM-MeOH (2%), 200 mg (60% yield) of a grey solid were obtained.

HPLC-MS tr = 1.48 min (90%) ES+ 206/208

^{1}H-NMR (400 MHz, CDCl3) δ ppm 3.07 (d, J = 5 Hz, 3H), 7.71 (s, 1H).

Preparation 6: Synthesis of 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide

To a solution of 4,6-dichloro-N-methyl-pyridazine-3-carboxamide (Preparation 5; 246 mg, 1.19 mmol) in 2.5 mL of anh. MeCN was added ammonia (29 % in water, 2.5 mL, 132.12 mmol) and the mixture was stirred at 100 ºC. After 2h 30m the reaction is complete and the mixture was left to cool down to room temperature. Water was added and the mixture was

filtered and washed with water. The solid was dried in the vacuum oven for one night at 50 ºC to have the title compound as a brown solid (168 mg, 75 %).

HPLC-MS: tr = 1.55 min.(99 %). LRMS (m/z): 187/189 (M+1, Cl).

Preparation 7: 4,6-dichloro-N-cyclopropyl-pyridine-3-carboxamide

To a stirred solution of 4,6-dichloropyridine-3-carboxylic acid (250 mg, 1.3 mmol) in 6 mL of anh. DCM oxalyl chloride (0.335 mL, 3.9 mmol) was added dropwise and then DMF (1 drop) and the mixture was stirred for 10 min. at room temperature and for 30 min. at reflux. The volatiles were removed under reduced pressure and the residue redissolved in DCM (14 mL) and cooled to -10 ºC. Cyclopropanamine (225 µL, 13 mmol) was added dropwise and the mixture was stirred at -10 ºC for 30 min. Excess water was added followed by NaHCO3 sat. solution and DCM. The phases were separated and the aqueous phase was extracted with dichlomethane (x 1). The combined organic extracts were dried over anh. MgSO4, filtered and evaporated to have the title compound as a white solid (262 mg, 87%).

HPLC-MS tr = 2.00 min (98%). LRMS (m/z): 227/229/231/233 (2 Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.65-0.66 (m 2H), 0.89-0.91 (m 2H), 2.90-2.95 (m 1H), 6.28 (bs 1H), 7.40 (s 1H), 8.63 (s 1H).

Preparation 8: 4-amino-6-chloro-N-cyclopropyl-pyridine-3-carboxamide

To a solution of 4,6-dichloro-N-cyclopropyl-pyridine-3-carboxamide (Preparation 7; 262 mg, 1.13 mmol) in 2 mL of ACN was added ammonia (29 % in water, 2 mL, 105.7 mmol) and the mixture was stirred at 130ºC for 20 h. The crude was concentrated and additional NH4OH was added (4 ml) and ACN (2ml), the suspension was heated again at 130ºC for 3 h. The solution was cooled down to room temperature, more water was added and the white solid was filtrated, washed with water and dried in an oven under vacuum. 163 mg of title compound were obtained as a white solid

HPLC-MS tr =1.57 min (73%). LRMS (m/z): 212/214 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.54-0.55 (m 2H), 0.67-0.68 (m 2H), 2.76-2.81 (m 1H), 6.65 (s 1H), 7.35 (bs 1H), 8.24 (s 1H), 8.43 (bs 1H).

Intermediate 1: 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)-amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 50 mg, 0.27 mmol) in 1 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 22 mg, 0.55 mg) at 0 ºC. The mixture was stirred at room temperature for 15 min. Then, the temperature was lowered to 0 ºC and a solution of 2-chloro-6-fluoro-benzoyl chloride (77 mg, 0.39 mmol) in 0.5 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature overnight. Water was added followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 2). The combined organic extracts were washed with water, dried over anh. MgSO4, filtered and evaporated. The final oil was purified via flash chromatography in Hx/AcOEt to have a white solid (100 mg, 59 %).

HPLC-MS: tr = 2.88 min. (96 %). LRMS (m/z): 342/344/346 (2 Cl).

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.00 (d, J = 4.8 Hz, 3H), 6.62 (s, 1H), 7.11 (td, J = 8.7, 1.0 Hz, 1H), 7.26 – 7.29 (m, 1H), 7.35 – 7.42 (m, 1H), 8.58 (s, 1H), 8.87 (s, 1H), 12.00 (s, 1H).

Intermediate 2: 6-chloro-N-methyl-4-[(2,4,6-trimethylbenzoyl)amino]-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 125 mg, 0.67 mmol) in 2 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 54 mg, 1.35 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (orange dispersion). Then, the temperature was lowered to 0 ºC and a solution of 2,4,6-trimethylbenzoyl chloride (181 mg, 0.99 mmol) in 1 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature (yellow dispersion). After 16 h the reaction is finished and water was added followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 2). The combined organic extracts were washed with water, dried over anh. MgSO4, filtered and evaporated. The final white solid was purified via flash chromatography in Hexane/AcOEt to have the title compound as a white solid (121 mg, 54 %).

HPLC-MS: tr = 3.18 min.(99 %). LRMS (m/z): 332 (M+1).

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.29 (s, 3H), 2.33 (s, 6H), 2.97 (d, J = 4.7 Hz, 3H), 6.88 (s, 2H), 8.52 (s, 1H), 8.93 (s, 1H), 11.47 (s, 1H).

Intermediate 3: 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 380 mg, 2.05 mmol) in 9 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 164 mg, 4.10 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (orange dispersion). Then, the temperature was lowered to 0 ºC and a solution of 2-fluoro-4-methoxy-benzoyl chloride (558 mg, 2.96 mmol) in 3 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature (yellow dispersion). After 16 h the reaction is finished and water was added followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 1). The combined organic extracts were washed with water (x 3), LiCl (5%, x 2), dried over anh. MgSO4, filtered and evaporated. The final white solid was purified via flash chromatography in DCM/DCM with 5 % MeOH to have the title compound as a white solid (441 mg, 57 %).

HPLC-MS: tr = 2.67 min.(90 %). LRMS (m/z): 338/340 (M+1, Cl).

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.89 (s, 3H), 3.93 (s, 3H), 6.82 – 6.88 (m, 1H), 6.99 (d, J = 8.6 Hz, 1H), 7.47 – 7.55 (m, 1H), 8.63 (s, 1H), 8.71 (s, 1H).

Intermediate 4: 6-chloro-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 125 mg, 0.67 mmol) in 2 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 54 mg, 1.35 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (orange dispersion). Then, the temperature was lowered to 0 ºC and a solution of 2-methoxy-benzoyl chloride (169 mg, 0.99 mmol) in 1 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature (yellow dispersion) for 16 hr. Water was added and the mixture was extracted with AcOEt (x 3). The combined organic extracts were washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a residue which was purified by reverse phase.

HPLC-MS: tr = 2.80 min.(99 %). LRMS (m/z): 320/322 (M+1, Cl).

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.05 (d, J = 4.8 Hz, 3H), 4.12 (s, 3H), 6.33 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 7.26 (s, 1H), 7.52 (t, J = 7.8 Hz, 1H), 8.18 (d, J = 9.6 Hz, 1H), 8.43 (s, 1H), 8.89 (s, 1H), 12.18 (s, 1H).

Intermediate 5: 4-[(4-bromo-2-chloro-6-fluoro-benzoyl)amino]-6-chloro-N-methyl-pyridazine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 168 mg, 0.90 mmol) in 4 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 72 mg, 1.80 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (orange solution). Then, the temperature was lowered to 0 ºC and a solution of 4-bromo-2-chloro-6-fluoro-benzoyl chloride (268 mg, 0.98 mmol) in 2 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature (brown dispersion). After 1h 30min the reaction is complete. Water was added and the mixture was extracted with AcOEt (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a purple solid which was purified by flash chromatography giving 166 mg (white solid, 44%).

HPLC-MS: tr = 3.38 min. LRMS (m/z): 421/423/425 (M+1, 2 Cl, 1 Br).

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.04 (d, J = 5.1 Hz, 3H), 7.33 (d, J = 10.1 Hz, 1H), 7.49 (t, J = 1.5 Hz, 1H), 8.40 (s, 1H), 9.02 (s, 1H), 12.77 (s, 1H).

Intermediate 6: 6-chloro-4-[(2-chloro-4-cyano-6-fluoro-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

In a small sized reactor the starting material (Intermediate 5; 90 mg, 0.21 mmol) was suspended in 2 mL of anh. DMA. Under an Ar flushing the reactants were added, zinc cyanide (11.3 mg, 0.096 mmol), Tris(dibenzylideneacetone)dipalladium(0) (1.95 mg, 0.02 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (2.47 mg, 0.04 mmol). The mixture was heated at 130 ºC. After 30 min. the proportion of starting material is 45 % (55 % of final product). The reaction was left for 1 h 30 min. in total (75 % of purity, 10 % of bis-cyano derivative and 15 % of starting material). Water was added and the mixture extracted with AcOEt (x 3). The combined organic extracts were washed with water (x 3) and brine (x 1); dried over anh. MgSO4, filtered and evaporated to have a yellow solid which was purified via flash chromatography in Hx/Hx with AcOEt (50 %), but all the intermediates eluted together. The purification was repeated in reverse phase but the separation was not optimal. Finally it was decided to use the crude for the next step after all the attempts failed (white solid, 50 mg, 64 %).

HPLC-MS: tr = 2.95 min. (81 %). LRMS (m/z): 369/371 (M+1)

Intermediate 7: 6-chloro-N-methyl-4-[(2-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 175 mg, 0.94 mmol) in 2 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 75 mg, 1.87 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow-green dispersion). Then, the temperature was lowered to 0 ºC and a solution of 2-methylsulfonylbenzoyl chloride (303 mg, 1.38 mmol) in 2 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature (orange dispersion) overnight. The next day the reaction is finished (35 % of final product). Water was added and the mixture was extracted with AcOEt (x 2). The combined organic extracts were washed with water (x 3), LiCl 5 % (x 2) and brine; dried over anh. MgSO4, filtered and evaporated to have a pink semisolid which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have the title compound as a white solid (109 mg, 32 %).

HPLC-MS: tr = 2.32 min. (98 %). LRMS (m/z): 368/370 (M+1, Cl).

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.87 (s, 3H), 3.40 (s, 3H), 7.78 – 7.83 (m, 2H), 7.85 – 7.91 (m, 1H), 8.15 (d, J = 9.3 Hz, 1H), 8.66 (d, J = 1.5 Hz, 2H).

Intermediate 8: 6-chloro-4-[(4-cyano-2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 30 mg, 0.16 mmol) in 0.5 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 13 mg, 0.32 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow solution). Then, the temperature was lowered to 0 ºC and a solution of 4-cyano-2-fluoro-6-methoxy-benzoyl chloride (55 mg, 0.26 mmol) in 0.5 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature (orange solution). After 2h the reaction is finished and water and AcOEt were added. Phases separated and the organic fraction was washed with LiCl (5 % solution, x 2) and water (x 2); dried over anh. MgSO4, filtered and evaporated. The residue was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid (19 mg, 32 %).

HPLC-MS: tr = 2.68 min. (96 %). LRMS (m/z): 363/365 (M+1, Cl).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.77 (d, J = 4.6 Hz, 3H), 3.93 (s, 3H), 7.61 – 7.69 (m, 2H), 8.53 (s, 1H), 8.76 (s, 1H), 9.05 (d, J = 3.7 Hz, 1H), 12.36 (s, 1H).

Intermediate 9: 6-chloro-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.54 mmol) in 4 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 54 mg, 1.35 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow solution). Then, the temperature was lowered to 0 ºC and was added 5-fluoro-2-methoxy-benzoyl chloride (150 mg, 0.79 mmol) in one portion. The mixture was stirred at room temperature. The next day the reaction is finished. Water and AcOEt were added and the phases separated. The organic was washed with LiCl (5 %, x 2), and brine, dried over anh. MgSO4, filtered and evaporated to have a solid which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid (52 mg, 28 %).

HPLC-MS: tr = 2.87 min. LRMS (m/z): 338/340 (M+1, Cl).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.84 (d, J = 4.6 Hz, 3H), 4.05 (s, 3H), 7.29 (dd, J = 9.2, 4.3 Hz, 1H), 7.45 – 7.53 (m, 1H), 7.73 (dd, J = 9.4, 3.3 Hz, 1H), 8.63 (s, 1H), 8.69 (s, 1H), 8.94 (d, J = 8.8 Hz, 1H), 12.46 (s, 1H).

Intermediate 10: 6-chloro-N-methyl-4-[[4-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.54 mmol) in 4 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 54 mg, 1.35 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow solution). Then, the temperature was lowered to 0 ºC and was added 5-fluoro-2-methoxy-benzoyl chloride (150 mg, 0.79 mmol) in one portion. The mixture was stirred at room temperature overnight. Water and AcOEt were added and the phases separated. The organic was washed with LiCl (5 %, x 2), and brine, dried over anh. MgSO4, filtered and evaporated to have a solid which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid (58 mg, 29 %).

HPLC-MS: tr = 3.23 min. (96 %). LRMS (m/z): 374/376 (M+1, Cl).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.85 (d, J = 4.5 Hz, 3H), 7.65 (d, J = 8.8 Hz, 2H), 8.00 – 8.10 (m, 2H), 8.64 (s, 1H), 8.82 (s, 1H), 9.16 (d, J = 4.4 Hz, 1H), 13.07 (s, 1H).

Intermediate 11: 6-chloro-N-methyl-4-[[3-(trifluoromethyl)benzoyl]amino]pyridine-3-carboxamide

4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100mg, 0.54mmol) in 4mL of anh. DMF was cooled at 0ºC and sodium hydride (60 % in mineral oil dispersion, 43mg, 1.07 mmol). The mixture was stirred at room temperature for 15 min. The temperature

was lowered to 0 ºC and a solution of 3-(trifluoromethyl)benzoyl chloride (236mg, 0.79mmol) in 1mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature overnight. As significant amounts of starting material were still present the solution was cooled at 0ºC and 0.2eq NaH added. The stirring at room temperature was resumed for 15min. Then the system was cooled at 0ºC, 0.2 additional equivalents of 3-(trifluoromethyl)benzoyl chloride were added and the reaction stirred at room temperature for 30 min. Water was added followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt. The combined organic extracts were washed with water (x 3), LiCl (5%, x 2), dried over anh. MgSO4, filtered and evaporated. The residue was purified by flash chromatography (Biotage Telos12g) using hexane/ DCM and DCM/MeOH (225nm) to give the title compound. HPLC/MS tR=3.18min (78%, mz358,360). Repurification was carried on by eluting with hexane/diethyl ether (225nm) to give the title compound (67mg, 35%) as a white solid.
HPLC/MS tR=3.18min (96%). LRMS (m/z): 358, 360 (M+1, Cl).
^{1}H NMR (400 MHz, CDCl3) δ ppm 3.08 (d, 3H), 6.41 (s, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.34 (s, 1H), 8.54 (s, 1H), 8.86 (s, 1H), 12.76 (s, 1H).

Intermediate 12: 6-chloro-4-[[2-methoxy-4-(trifluoromethoxy)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.54 mmol) in 3 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 54 mg, 1.35 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow solution). Then, the temperature was lowered to 0 ºC and was added 2-methoxy-4-(trifluoromethoxy)benzoyl chloride (201 mg, 0.79 mmol) in one portion. The mixture was stirred at room temperature overnight. The next day the reaction is finished (tr = 3.26 min., 56 %, 404/406 m/z). Water and AcOEt were added and the phase separated. The organic fraction was washed with LiCl (5 % solution, x 2) and brine, dried over anh. MgSO4, filtered and evaporated to have a residue which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid as the title product (72 mg, 33 %).
HPLC-MS: tr = 3.27 min. (97 %). LRMS (m/z): 404/406 (M+1, Cl).
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.84 (d, J = 4.6 Hz, 3H), 4.08 (s, 3H), 7.14 (d, J = 8.6 Hz, 1H), 7.24 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 8.64 (s, 1H), 8.70 (s, 1H), 8.94 (d, J = 4.5 Hz, 1H), 12.42 (s, 1H).

Intermediate 13: 2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoic acid

To a solution of 2-(hydroxymethyl)-benzoic acid (400 mg, 2.63 mmol) in 6.5 mL of pyridine was added tert-butyldimethylsilylchloride (900 uL, 6.31 mmol). The mixture was stirred overnight at room temperature. After completion of reaction, the mixture was diluted with saturated solution of NaHCO3 and extracted with DCM. The organic fraction was washed with water (x 2), LiCl (5 % solution, x 2) and brine; dried over anh. MgSO4, filtered and evaporated to give a colorless oil. This oil was dissolved in 26 mL of MeOH and THF (9 mL) and treated with an aqueous solution of K2CO3 (910 mg, 9 mL) and the mixture stirred at room temperature for 3 h and left in the freezer.The next day the volatiles are removed partially under reduced pressure (one-quarter volume) and brine (30 mL) was added. The pH was lowered to 4-5 with KHSO4 1M, extracted with Et2O (x 3) and dried over magnesium sulfate. After evaporation the colorless oil was purified via flash chromatography in Hx/Hx with 50 % Et2O (2nd peak) to have a white solid (276 mg, 27 %).

HPLC-MS: tr = 3.83 min. (99 %). LRMS (m/z): 391 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.11 (s, 9H), 5.11 (s, 2H), 7.34 – 7.45 (m, 7H), 7.59 (td, J = 7.6, 1.4 Hz, 1H), 7.65 – 7.70 (m, 4H), 7.76 (d, J = 8.3 Hz, 1H), 8.05 (dd, J = 7.8, 1.2 Hz, 1H).

Intermediate 14: 2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoyl chloride

To a solution of 2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoic acid (Intermediate 13; 100 mg, 0.25 mmol) in 2 mL of anh. toluene was added oxalyl chloride (55 uL, 0.64 mmol) dropwise and the mixture was stirred at 50 ºC for one hour (reaction finished). Phthalide is observed (a part of the starting material is deprotected, 30 % by HPLC-MS). The volatiles were removed under reduced pressure and the crude (colorless oil) was used for the next step without further purification (108 mg, quant. yield).

Intermediate 15: 4-[[2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoyl]amino]-6-chloro-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 25 mg, 0.13 mmol) in 1 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 14 mg, 0.35 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow solution). Then, the temperature was lowered to 0 ºC and was added 2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoyl chloride (Intermediate 14; 81 mg, 0.19 mmol) in 0.5

mL of anh. DMF one portion. The mixture was stirred overnight at room temperature. Water and AcOEt were added. The organic phase was washed with LiCl (5 % solution, x 2) and brine; dried over anh. MgSO4, filtered and evaporated. The residue was purified via flash chromatography in DCM/DCM with 10 % MeOH to have a colorless oil (49 mg, 85 % purity, 55 %).

HPLC-MS: tr = 2.12 min. (85 %). LRMS (m/): 558/560 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.05 (s, 9H), 2.99 (d, J = 4.8 Hz, 3H), 5.12 (s, 2H), 7.30 – 7.46 (m, 6H), 7.56 (t, J = 9.5 Hz, 2H), 7.62 – 7.70 (m, 4H), 7.79 – 7.84 (m, 1H), 7.99 – 8.07 (m, 1H), 8.46 (s, 1H), 8.72 (s, 1H).

Intermediate 16: 4-[[2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoyl]amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-[[2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoyl]amino]-6-chloro-N-methyl-pyridine-3-carboxamide (Intermediate 15; 34 mg, 0.060 mmol) in 1 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (8.2 mg, 0.066 mmol), Pd2(dba)3 (5.5 mg, 0.006 mmol), Xantphos (7 mg, 0.012 mmol) and cesium carbonate (60 mg, 0.25 mmol) and heated at 100 ºC. After 3 h the reaction is finished. Water and AcOEt were added and the phases separated. The aqueous phase was extracted with AcOEt (x 1) and the combined organic fractions were washed with brine, dried over anh. MgSO4, filtered and evaporated. The crude was purified via flash chromatography in DCM/DCM with 10 % MeOH to have a white solid (20 mg, 51 %).

HPLC-MS: tr = 3.08 min. (99 %). LRMS (m/z): 645 (M+1)

Intermediate 18: methyl 4-(acetoxymethyl)-2-methoxy-benzoate

To a solution of methyl 4-(bromomethyl)-2-methoxy-benzoate (750 mg, 2.89 mmol) in 15 mL of anh. DMF was added potassium acetate (1420 mg, 14.5 mmol) and the mixture was heated at 80 ºC. After 1 h the reaction is complete and the mixture was cooled down to room temperature and poured into ice-water and extracted with DCM (x 2). The combined organic fractions were washed with LiCl (5 %, x 2), water (x 3) and brine (x 1); dried over anh. MgSO4, filtered and evaporated to have a residue which was purified via flash chromatography in Hx/Hx with 50 % AcOEt to have a colorless oil (518 mg, 75 %).

HPLC-MS: tr = 2.33 min. (99 %). LRMS (m/z): 239 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.13 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 5.12 (s, 2H), 6.96 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.5 Hz, 1H).

Intermediate 19: 4-(hydroxymethyl)-2-methoxy-benzoic acid

To a solution of methyl 4-(acetoxymethyl)-2-methoxy-benzoate (Interemdiate 18; 515 mg, 2.16 mmol) in 15 mL of methanol was added NaOH (1 M, 4,4 mL, 4,4 mmol) and the mixture was stirred at room temperature. After 4 h the reaction is complete in 37 % by HPLC-MS (63 % of methyl ester). The mixture was stirred overnight at rt. The next day the proportion is 68:32 (final product:ester). The mixture was left stirring for one additional day. After 48 h is remaining a 20 % of ester. More NaOH 1M (1 mL) was added and the mixture was stirred for 12 additional hours. The reaction was stopped with a 17 % of Me ester. The volatiles were removed under reduced pressure and water was added and washed with Et2O (x 2, only Me ester). The pH of the aqueous phase was acidified with HCl 6M to pH 4 and the water removed under reduced pressure. EtOH was added and the solid precipitated was filtered and washed with a little quantity of EtOH. The filtrate was removed under reduced pressure to have the title compound as a white solid (480 mg, mass higher than expected, possible salts in the solid).
HPLC-MS: tr = 1.37 min. (99 %) . LRMS (m/z): 183 (M+1)
^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 3.71 (s, 3H), 4.45 (s, 2H), 6.75 (d, J = 8.9 Hz, 1H), 6.86 (s, 1H), 7.27 (d, J = 7.6 Hz, 1H).

Interemdiate 20: 4-[[tert-butyl(diphenyl)silyl]oxymethyl]-2-methoxy-benzoic acid

To a suspension of 4-(hydroxymethyl)-2-methoxy-benzoic acid (Interemdiate 19; 350 mg, 1.92 mmol) in 6 mL of pyridine was added tert-butyldimethylsilylchloride (657 uL, 4.60 mmol). After 15 min. the solution becomes clear. The mixture was stirred at room temperature for all the night. Reaction mixture was diluted with NaHCO3 and extracted with DCM (x 1). The organic fraction was washed with water (x 2), LiCl (5 % solution, x 2) and brine; dried over anh. MgSO4, filtered and evaporated to have a slightly yellow oil (HPCL cru1; Iso gradient). This oil was dissolved in 19 mL of MeOH and THF (7 mL) and treated with an aqueous solution of K2CO3 (669 mg, 7 mL) and the mixture stirred at room temperature for 1h. The volatiles are removed partially under reduced pressure (one-quarter volume) and brine (23 mL) was added. The pH was lowered to 4-5 with KHSO4 1M and extracted with DCM (x 3) and dried over magnesium sulfate. After evaporation the colorless oil was purified via flash chromatography in Hx/Et2O to have a colorless oil (110 mg, 14 %).

HPLC-MS: tr = 3.80 min. (99 %). LRMS (m/z): 421 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.12 (s, 9H), 4.04 (s, 3H), 4.82 (s, 2H), 7.02 (d, J = 7.3 Hz, 1H), 7.15 (s, 1H), 7.36 – 7.48 (m, 6H), 7.67 (dd, J = 7.9, 1.4 Hz, 4H), 8.12 (d, J = 8.1 Hz, 1H).

Interemdiate 21: 4-[[tert-butyl(diphenyl)silyl]oxymethyl]-2-methoxy-benzoyl chloride

To a solution of 4-[[tert-butyl(diphenyl)silyl]oxymethyl]-2-methoxy-benzoic acid (Intermediate 20; 110 mg, 0.26 mmol) in 2 mL of anh. toluene was added one drop of DMF and oxalyl chloride (56 uL, 0.65 mmol) dropwise and the mixture was stirred at room temperature (gas evolution). After 15 min. the reaction is finished (quenching with MeOH, Me ester observed by HPLC-MS). Volatiles were removed under reduced pressure and the yellow oil obtained was used for the next step without further purification. (118 mg, quant. yield).

HPLC-MS: tr = 4.05 min. (96 %). LRMS (m/z): 435 (M+1, Me ester)

Intermediate 22: 4-[[4-[[tert-butyl(diphenyl)silyl]oxymethyl]-2-methoxy-benzoyl]amino]-6-chloro-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 40 mg, 0.21 mmol) in 1.2 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 22 mg, 0.55 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow solution). Then, the temperature was lowered to 0 ºC and was added 2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoyl chloride (Intermediate 21; 114 mg, 0.26 mmol) in 0.5 mL of anh. DMF one portion. The mixture was stirred at room temperature overnight (yellow dispersion). The next day the major product is the desired one. Water and AcOEt were added. Phases separated and the organic phase was washed with LiCl (5 % solution, x 2) and brine; dried over anh. MgSO4, filtered and evaporated. The residue was purified via flash chromatography in DCM/DCM with 10 % MeOH to have a colorless oil (38 mg, 30 %).

HPLC-MS: tr = 2.27 min. (80 %). LRMS (m/): 558/560 (M+1, Cl)

Intermediate 23: 4-[[4-[[tert-butyl(diphenyl)silyl]oxymethyl]-2-methoxy-benzoyl]amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-[[4-[[tert-butyl(diphenyl)silyl]oxymethyl]-2-methoxy-benzoyl]amino]-6-chloro-N-methyl-pyridine-3-carboxamide (Intermediate 22; 38 mg, 0.064 mmol) in 1 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (9 mg, 0.073 mmol), Pd2(dba)3 (6

mg, 0.006 mmol), Xantphos (7.5 mg, 0.012 mmol) and cesium carbonate (63 mg, 0.19 mmol) and heated at 100 ºC. After 3 h the reaction is finished and water was added. The mixture was extracted with AcOEt, and the organic phase was washed with brine (x 1), dried ova rnh. MgSO4, filtered and evaporated to have yellow oil which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid.

HPLC-MS: tr = 3.38 min. (99 %). LRMS (m/z): 676 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.08 (s, 9H), 2.33 (s, 3H), 2.78 – 2.84 (m, 3H), 3.98 (s, 3H), 4.87 (s, 2H), 7.13 (d, J = 9.5 Hz, 1H), 7.18 (s, 1H), 7.41 – 7.53 (m, 7H), 7.67 (dd, J = 7.6, 1.7 Hz, 4H), 7.96 (d, J = 8.0 Hz, 1H), 8.57 (s, 1H), 8.66 (d, J = 4.9 Hz, 1H), 9.18 (s, 1H), 10.31 (s, 1H), 12.37 (s, 1H).

Intermediate 24: 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 2g, 10.77mmol) in anh dioxane (65mL) was added, under nitrogen, 2,6-dimethylpyrimidin-4-amine (3.32g, 26.96mmol), Pd2(dba)3 (987mg, 1.08mmol), Xantphos (1.25g, 2.16mmol) and K2CO3 (4.47g, 32.34 mmol). The mixture was heated at 140 ºC for 24 hr. AcOEt was added and the solid residues filtered and washed with AcOEt. The filtrates were evaporated to dryness and suspended in toluene and again filtered and the solid washed with toluene. The crude was purified by flash chromatography (Biotage Telos120g) using diethyl ether/MeOH (up to 10%) (220nm) to give the title compound (1.68g, 57%) as a pale yellow solid.

HPLC/MS rt=1.20 min (100%), LRMS (m/z): 273

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.27 (s, 3H), 2.45 (s, 3H), 2.72 (d, J = 4.5 Hz, 3H), 7.06 (s, 1H), 7.18 (s, 2H), 7.28 (s, 1H), 8.20 (d, J = 4.5 Hz, 1H), 8.31 (s, 1H), 9.76 (s, 1H).

Intermediate 25: 6-chloropyridine-3-carbonyl chloride, hydrochloride

A dispersion of 6-chloropyridine-3-carboxylic acid (500 mg, 3.17 mmol) in 1 mL of thionyl chloride was heated at reflux. After 3 h the proportion is 30:70 (SM:Final product, quenching with MeOH). The mixture was left heating all the night.The next day the reaction is finished. The volatiles were removed under reduced pressure, adding toluene in order to remove all the thionyl chloride traces. The crude was used for the next step without further purification.

Intermediate 26: 4-[(6-chloropyridine-3-carbonyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 24; 50 mg, 0.18 mmol) in 1.5 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 26 mg, 0.65 mmol) at 0 ºC. The mixture was stirred at 0 ºC (yellow solution). Then, was added 6-chloropyridine-3-carbonyl chloride hydrochloride (Intermediate 25; 47 mg, 0.22 mmol). The mixture was stirred at room temperature (orange dispersion). After 3 h the reaction is complete. Water was added and the mixture extracted with AcOEt (x 1). The organic fraction was washed with LiCl (5 % solution, x 2) and brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a white solid which was precipitated in EtOH to have a white solid which is 80 % by HPLC-MS. The solid was washed with acetonitrile (x 2) to have the final product as a slightly yellow solid (25 mg, 33 %).

HPLC-MS: tr = 1.92 min. (92 %). LRMS (m/z): 412/414 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.84 (d, J = 4.8 Hz, 3H), 7.38 (s, 1H), 7.81 (d, J = 9.1 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.77 (s, 1H), 8.89 – 8.97 (m, 2H), 9.22 (s, 1H), 10.43 (s, 1H), 13.28 (d, J = 2.3 Hz, 1H).

Intermediate 27: 6-chloro-N-methyl-4-[[2-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide

4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Intermediate 3; 123mg, 0.66mmol) in 1mL of anh. DMF was cooled at 0ºC and sodium hydride (60 % in mineral oil dispersion, 53mg, 1.32mmol). The mixture was stirred at room temperature for 15 min. The temperature was lowered to 0 ºC and a solution of 2-(trifluoromethoxy)benzoyl chloride (0.97mmol) in 1mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature overnight. Water was added followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 1). The combined organic extracts were washed with water (x 3), LiCl (5%, x 2), dried over anh. MgSO4, filtered and evaporated. The crude was purified by flash chromatography (Biotage Telos12g) using dihcloromethane/MeOH (up to 5%) (225nm) and repurified eluting with hexane/diethyl ether (225nm), to give the title compound (41mg, 17%) as a white solid.

HPLC/MS rt=2.95min (99%). LRMS (m/z): 374,376

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.02 (s, 3H), 6.50 (s, 1H), 7.38 (dd, J = 9.5, 1.2 Hz, 1H), 7.42 – 7.50 (m, 1H), 7.55 – 7.62 (m, 1H), 7.89 (dd, J = 7.7, 1.8 Hz, 1H), 8.56 (s, 1H), 8.86 (s, 1H), 12.08 (s, 1H).

Intermediate 28: 6-chloro-2-methoxy-pyridine-3-carboxylic acid

To a solution of methanol (1000 uL, 24.7 mmol) in anh. THF (52 mL) at 0 ºC was added slowly NaH (60 % dispersion in mineral oil, 1.04 g, 26 mmol) and the mixture was stirred at 0 ºC for 30 min. Then 2,6-dichloropyridine-3-carboxylic acid (1000 mg, 5.2 mmol) was added gradually and the mixture was stirred at 60 ºC overnight (compact mass difficult to shake).The next day the reaction is finished (tr = 2.02 min., 188/190 and 205/207 m/z; 87 %). The mixture was partitioned between Et2O and NaOH 1M. The aqueous phase was separated and acidified with concentrated HCl to pH 1 and a white solid precipitated which was filtered and dried under vacuum (white solid, 695 mg, 71 %). The product was used in the next step without further purification.

HPLC-MS: tr = 2.05 min. (91 %). LRMS (m/z): 188/190 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.92 (s, 3H), 7.18 (d, J = 7.9 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H).

Intermediate 29: 6-chloro-2-methoxy-pyridine-3-carbonyl chloride

A dispersion of 6-chloro-2-methoxy-pyridine-3-carboxylic acid (Intermediate 28; 205 mg, 1.09 mmol) in 4 mL of thionyl chloride was heated at 80 ºC. After 2 h the reaction is complete. The volatiles were removed under reduced pressure and toluene was added and removed (x 3) to eliminate all the traces of thionyl chloride. The slightly brown solid was used for the next step without further purification (235 mg, quant.).

Intermediate 30: 6-chloro-N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-2-methoxy-pyridine-3-carboxamide

To a solution of 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 24; 163 mg, 0.59 mmol) in 4 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 84 mg, 2.1 mmol) at 0 ºC. The mixture was stirred at 0 ºC (yellow solution). Then, was added 6-chloro-2-methoxy-pyridine-3-carbonyl chloride hydrochloride (Intermediate 29; 174 mg, 0.72 mmol) in portions. The mixture was stirred at 0 ºC (brown dispersion). After 2h 15 min. the proportion of final product is 58 %. Water was added and extracted with AcOEt (x 1). The organic fraction was washed with LiCl (5 % solution, x 2), water (x 1) and brine (x 1); dried over anh. MgSO4, filtered and evaporated to

have a brown solid which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid (35 mg, 13 %) which it is 80 % of purity by HPLC-MS. The material was used per se in the next synthetic step.

HPLC-MS: tr = 2.17 min. (80 %). LRMS (m/z): 442/444 (M+1, Cl)

Intermediate 31: 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Preparation 3; 400 mg, 2.15 mmol) in 25 mL of anh. THF (under N2, at 0 ºC were added LiHMDS (1M in THF, 5.4 mL, 5.4 mmol) dropwise (white dispersion). The mixture was stirred at room temperature for 15 min. and the temperature was lowered again to 0 ºC and was added 2,3-dimethoxybenzoyl chloride (821 mg, 4.1 mmol) in 5 mL of anh. THF dropwise. The mixture was stirred at room temperature. After 30 min. a solid appeared. After 1 h 30 min the conversion is about 84 % of final product (5 % of starting material and 8 % of diacylated). The temperature was lowered to 0 ºC and NH4Cl sat. was added. A little of water was added (in order to improve the solubility of the aqueous phase) and the mixture was extracted with AcOEt (x 1) and was washed with NaHCO3 sat. (x 1); dried over anh. MgSO4, filtered and evaporated to have a beige solid, to which was added Et2O, filtrated and washed with MeOH (x 1). The white solid was used for the next step after drying in the vacuum oven (510 mg, 68 %).

HPLC-MS: tr = 2.70 min. (99 %). LRMS (m/z): 350/352 (M+1, Cl)

Intermediate 32: 4-benzyloxy-2-methoxy-benzaldehyde

To a solution of 4-hydroxy-2-methoxy-benzaldehyde (700 mg, 4.6 mmol) in 19 mL of ethanol was added potassium carbonate (1908 mg, 13.8 mmol) and benzyl chloride (795 uL, 6.91 mmol). The mixture was heated at reflux overnight.The next day the reaction is finished. The reaction was filtered and the filtrate removed under reduced pressure. AcOEt was added and the solution washed with water (x 2), NaOH 2N (x 2), HCl 1N (x 2) and brine (x2); dried over anh. MgSO4, filtered and evaporated to have a yellow solid as the final product (912 mg, 82 %).

HPLC-MS: tr = 3.00 min. (94 %). LRMS (m/z): 243 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.90 (s, 3H), 5.23 (s, 2H), 6.70 – 6.82 (m, 2H), 7.34 – 7.51 (m, 5H), 7.67 (d, J = 8.6 Hz, 1H), 10.17 (s, 1H).

Intermediate 33: 4-benzyloxy-2-methoxy-benzoic acid

To a solution of 4-benzyloxy-2-methoxy-benzaldehyde (Intermediate 32; 905 mg, 3.73 mmol) in 15 mL of THF and 5 mL of water was added sodium dihydrogenphosphate hydrate (310 mg, 2.24 mmol) and the mixture was stirred at room temperature for 20 min. Then, sodium chlorite (1115 mg, 12.33 mmol) and hydrogen peroxide 30 % (839 uL, 8.21 mmol) in 5 mL of water were added and the mixture was stirred at room temperature. After 3h the conversion is about 40 % by HPLC-MS. The mixture was left stirring overnight at room temperature. The next day the reaction is finished. THF was removed under reduced pressure and the aqueous suspension extracted with AcOEt (x 3). The combined organic were washed with water (x 2) and extracted with NaOH 2M (x 3). The aqueous phase was acidified with HCl conc. to have a white solid which was filtered and dried in the vacuum oven (786 mg, 81 %).

HPLC-MS: tr = 2.67 min. (98 %). RMS (m/z): 259 (M+1)

Intermediate 34: 4-benzyloxy-2-methoxy-benzoyl chloride

To a solution of 4-benzyloxy-2-methoxy-benzoic acid (Intermediate 33; 500 mg, 1.93 mmol) in 10 mL of anh. DCM a few drops of DMF and oxalyl chloride (200 uL, 2.33 mmol) were added dropwise at room temperature under nitrogen. The reaction was left stirring at room temperature overnight. The next day the reaction is finished. The volatiles were removed under reduced pressure and the crude was used for the next step without further purification (yellow oil, 540 mg, quant.)

Intermediate 35: 4-[(4-benzyloxy-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)-amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 24; 50 mg, 0.18 mmol) in 1.3 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 26 mg, 0.65 mmol) at 0 ºC. The mixture was stirred at 0 ºC (yellow solution). Then, was added 4-benzyloxy-2-methoxy-benzoyl chloride (Intermediate 34; 61 mg, 0.22 mmol) in 0.2 mL of anh. DMF. The mixture was stirred at room temperature (orange dispersion). After 1h 20 min. the starting material was the major product, and final product is the next major product. More NaH (20 mg) and 4-benzyloxy-2-methoxy-benzoyl chloride (40 mg) were added at 0 ºC and the mixture was stirred at room temperature. After additional 1h 40 min. the proportion of final product is 60 %. Water and AcOEt were

added and the phases separated. The organic phase was washed with LiCl (5 % solution, x 2) and brine (x 1). The organic phase was dried over anh. MgSO4, filtered and evaporated to have a yellow solid which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid (29 mg, 31 %).

HPLC-MS: tr = 2.48 min. (75 %). LRMS (m/z): 513 (M+1)

Intermediate 36: 6-chloro-4-[(4-chloro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-chloro-2-methoxy-benzoic acid (121 mg, 0.64 mmol) and HATU (369 mg, 0.97 mmol) in DMF (2 ml) was added DIPEA (169 µL, 0.97 mmol) and the mixture was stirred at room temperature for 60 min. HPLC-MS showed the total conversion into the activated acid (2.87 min., m/z 305/307 (M+1)). Water was added and a sticky solid did appear which was isolated by the addition-separation of AcOEt. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have a brown solid. In a 25 mL round bottomed flask vial 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 60 mg, 0.32 mmol) was soolved in DMF (2 ml) at 0ºC. NaH (60%, 39 mg, 0.97 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling again to 0ºC the activated acid in DMF (0.4 mL) was added dropwise and the mixture was stirred at rt. After 1h 15 min. the reaction is finished and water was added. The mixture extracted with AcOEt (x1) and the organic washed with brine (x1), dried over anh. MgSO4, filtered and evaporated to have a white semisolid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 5 % MeOH to have a white solid (75 mg, 65 %).

HPLC-MS: tr = 3.10 min. (99 %). LRMS (m/z): 354/356/358 (M+1, 2 Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.84 (d, J = 4.6 Hz, 3H), 4.09 (s, 3H), 7.21 (d, J = 10.4 Hz, 1H), 7.37 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 8.63 (s, 1H), 8.70 (s, 1H), 8.94 (s, 1H), 12.41 (s, 1H).HPLC-MS: tr = 1.58 min. (53 %). LRMS (m/): 348/350 (M+1, Cl)

Intermediate 37: 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 70 mg, 0.375 mmol) in 5 mL of anh. THF was added LiHMDS (1M in THF, 0.75 mL, 0.75 mmol) dropwise at rt. The mixture was stirred for 15 min. The temperature was lowered to 0 ºC and a solution of 2,3-dimethoxybenzoyl chloride (113 mg, 0.563 mmol) in THF (2 ml) was added

dropwise and the reaction was left to stir for 1 h at rt. NH4Cl aqueous saturated solution and EtOAc were added and phases separated. The aqueous phase was further extracted with EtOAc. The organic phases were dried (MgSO4), filtered and solvent removed to yield and orange solid that was purified by flash chromatography (Biotage, SNAP 12g) using DCM/DCM-MeOH (2%). 66 mg (50%) of title compound were obtained as a white solid

HPLC-MS: rt = 2.93' (99%). LRMS (m/z): 351/353

^{1}H-NMR 1H (CDCl3, 400 MHz) δ ppm 3.02 (d, J = 5 Hz, 3H), 3.91 (s, 3H), 4.05 (s, 3H), 7.12 (dd, J = 8 and 1.7 Hz , 1H), 7.17 (t, J = 8 Hz, 1H), 7.60 (dd, J = 8 and 1.7 Hz, 1H), 8.28 (br s, 1H), 9.21 (s, 1H), 13.2 (br s, 1H).

Intermediate 38: 6-chloro-4-[(2,6-difluorobenzoyl)amino]-N-methyl-pyridine-3-carboxamide

LiHMDS (1M in THF, 0.97 mL, 0.97 mmol) was added dropwise under N2 at 0 ºC to a solution of 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.54 mmol) in 6.5 mL of anh. THF. The mixture was stirred at room temperature for 15 min. and the temperature was lowered again to 0 ºC. 2,6-difluorobenzoyl chloride (167 mg, 0.945 mmol) in 1.5 mL of anh. THF was added dropwise. The mixture was stirred at room temperature. After 30 min. a solid appeared. After 3 h, the conversion was about 50%. The temperature was lowered to 0 ºC and excess NH4Cl sat. solution was added. The mixture was extracted with AcOEt (x 2) and the organic phase was washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a yellowish crude. Solid was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid (92 mg, 52 %).

HPLC-MS: tr = 2.68 min. LRMS (m/z): 326/328 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.56 (s, 1H), 9.08 (m, 1H), 8.79 (s, 1H), 8.56 (s, 1H), 7.74 – 7.64 (m, 1H), 7.33 (t, J = 8.5 Hz, 2H), 2.78 (d, J = 4.5 Hz, 3H).

Intermediate 39: 6-chloro-4-[(2-fluoro-5-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Preparation 3; 50 mg, 0.27 mmol) in 3 mL of anh. THF (under N2, at 0 ºC was added LiHMDS (1M in THF, 539 uL, 0.54 mmol) dropwise. The mixture was stirred at room temperature for 15 min. and the temperature was lowered again to 0 ºC. 2-fluoro-5-methoxy-benzoyl chloride (81 mg, 0.43 mmol) in 1 mL of anh. THF was added dropwise and the mixture

was stirred at room temperature (clear brown solution). After 1h 30 min. the reaction is complete and the temperature was lowered to 0 ºC and NH4Cl sat. was added. A little of water was added (in order to improve the solubility of the aqueous phase) and the mixture was extracted with AcOEt (x 1) and was washed with NaHCO3 sat. (x 1) and brine; dried over anh. MgSO4, filtered and evaporated to have a white solid which was precipitated in Et2O and washed with a little of MeOH to have a white solid which was dried in the vacuum oven (51 mg, 56 %).

HPLC-MS: tr = 2.77 min (95 %). LRMS (m/z): 338/340 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.77 – 2.85 (m, 3H), 3.81 (s, 3H), 7.25 (d, J = 8.4 Hz, 1H), 7.39 (t, J = 9.7 Hz, 2H), 8.64 (s, 1H), 8.76 (s, 1H), 9.05 (s, 1H), 12.57 (d, J = 3.9 Hz, 1H).

Intermediate 40: 6-chloro-4-[[2-fluoro-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100mg, 0.54 mmol) was solved in DMF (1.5mL) and cooled at 0ºC. NaH (75mg, 1.87mmol) was added and stirred at room temperature for 15min. After cooling again at 0ºC 2-fluoro-4-(trifluoromethyl)benzoyl chloride (160mg, 0.70mmol) was added and the mixture stirred overnight at room temperature. Water was added followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 1). The combined organic extracts were washed with water (x 3), LiCl (5%, x 2), dried over anh. MgSO4, filtered and evaporated. The crude was purified by flash chromatography (Biotage Telos12g) using hexane/diethyl ether (220nm) to give the title compound (58mg, 29%) as a white solid.

HPLC-MS tr=3.12min (100%). LRMS (m/z) 376/378

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.06 (s, 3H), 7.51 (d, J = 9.7 Hz, 1H), 7.56 – 7.72 (m, 1H), 8.16 (t, J = 7.7 Hz, 1H), 8.74 (s, 1H), 8.91 (s, 1H), 12.58 (d, J = 5.3 Hz, 1H).

Intermediate 41: 6-chloro-4-[(3-chloro-5-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100mg, 0.54mmol) was solved in DMF (1.5mL) and cooled at 0ºC. NaH (75mg, 1.87mmol) was added and stirred at room temperature for 15min. The solution was again cooled at 0ºC and 2-fluoro-4-(trifluoromethyl)benzoyl chloride (187 mg, 0.97mmol) was added and stirred at room temperature overnight. Water was added followed by AcOEt. The phases were separated and

the aqueous was extracted with AcOEt (x 1). The combined organic extracts were washed with water (x 3), LiCl (5%, x 2), dried over anh. $MgSO_4$, filtered and evaporated. The crude was purified by flash chromatography (Reveleris Telos12g) using hexane/diethyl ether (220nm) to give the title compound impure. It was repurified using Biotage Telos12g (hexane/diethyl ether), to obtain the desired product (50mg, 22%) as a white solid.

HPLC-MS tR=3.27min (100%). LRMS (m/z): 342/344

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.85 (d, J = 4.5 Hz, 3H), 7.67 (dt, J = 8.9, 2.2 Hz, 1H), 7.72 – 7.80 (m, 1H), 7.83 (dt, J = 8.5, 2.1 Hz, 1H), 8.56 (s, 1H), 8.82 (s, 1H), 9.17 (t, J = 3.9 Hz, 1H), 13.03 (s, 1H).

Intermediate 42: 4-(5-(benzyloxy)-2-methoxybenzamido)-6-chloro-N-methylnicotinamide

To a suspension of NaH (60 % in mineral oil dispersion, 26 mg, 0.55 mg) in DMF (0.5 ml) at 0ºC was added 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 50 mg, 0.27 mmol). The mixture was stirred at room temperature for 15 min. Then, the temperature was lowered to 0 ºC and a solution of 5-benzyloxy-2-methoxy-benzoyl chloride (0.795 mmol) in 1 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature overnight. Water and EtOAc were added and the layers separated, the aqueous phase was further extracted with more EtOAc and then the organic phases were washed with brine (2x), dried (MgSO4), filtered and solvent removed to yield a white solid that was purified via flash chromatography in DCM/DCM-MeOH (2%) to have a white solid (68 mg, 30%), then DCM-MeOH (5%) was passed through in order to obtained the SM (B, 40 mg as a white solid). Final product: 68 mg as a white solid.

HPLC-MS tr = 3.30 min (97%). LRMS (m/z): 426/428

NMR 1H (400 MHz, DMSO-d6) δ ppm 2.85 (d, J = 4.5 Hz, 3H), 3.97 (s, 3H), 5.10 (s 2H), 7.12 (s, 1H), 7.24-7.51 (cs 8H), 8.83 (s 1H), 12.36 (bs, 1H)

Intermediate 43: 4-[(5-benzyloxy-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-

carboxamide (Intermediate 42; 300mg, 0.88mmol), 2,6-dimethylpyrimidin-4-amine (131mg, 1.06mmol), Pd2(dba)3 (81mg, 0.088mmol), Xantphos (103mg, 0.17mmol) and cesium carbonate (868mg, 2.66mmol) were added and the mixture was heated in dioxane (10mL) at 100ºC. After 2h the mixture was filtrated and the solid washed with EtOAc. Since a solid remained on the filter, DCM-MeOH was added and collected apart, After analysing both organic phases by HPLC, it was observed that the EtOAc fraction was dirtier and after concentration it was taken up in few EtOAc and the solution was discarded since almost no desired product was detected. The solid was joined to the DCM fraction and was purified by flash chromatography (Biotage Telos12g) using dichloroemthane/DCM-MeOH (5%) (220nm) to give the title compound (45 mg, 58%) as an off white solid.

HPLC-MS tr = 2.42' (99%). LRMS (m/z): 513

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm 2.30 (s, 3H), under DMSO (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 3.95 (s, 3H), 5.10 (s, 2H), 7.15 (d, J = 9 Hz, 1H), 7.24 (dd, J = 9 and 3.2 Hz, 1H), 7.28-7.34 (m, 1H), 7.35-7.40 (m, 2H), 7.41-7.46 (m, 3H), 7.53 (d, J = 7.5 Hz, 1H), 8.54 (s, 1H), 8.60-8.65 (m, 1H), 9.14 (s, 1H), 10.26 (s, 1H), 12.35 (s, 1H).

Intermediate 44: 6-chloro-4-[(2,4-difluoro-5-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 50 mg, 0.27 mmol) in 3 mL of anh. THF LiHMDS (1M in THF, 539 uL, 0.54 mmol) was added dropwise under N2, at 0 ºC. The mixture was stirred at room temperature for 15 min. and the temperature was lowered again to 0 ºC. 2,4-difluoro-5-methoxy-benzoyl chloride (89 mg, 0.43 mmol) in 1 mL of anh. THF was added dropwise and the mixture was stirred at room temperature (clear yellow solution). After 45 min. the reaction is complete and the temperature was lowered to 0 ºC and NH4Cl sat. was added. A little of water was added (in order to improve the solubility of the aqueous phase) and the mixture was extracted with AcOEt (x 1) and was washed with NaHCO3 sat. (x 1) and brine; dried over anh. MgSO4, filtered and evaporated to have a white solid which was precipitated in Et2O and washed with a little of MeOH to have a white solid which was dried in the vacuum oven (49 mg, 51 %).

HPLC-MS: tr = 2.68 min. (99 %). LRMS (m/z): 356/358 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.81 (d, J = 4.5 Hz, 3H), 3.91 (s, 3H), 7.57 – 7.60 (m, 1H), 7.60 – 7.63 (m, 1H), 8.64 (s, 1H), 8.76 (s, 1H), 9.05 (d, J = 4.8 Hz, 1H), 12.57 (d, J = 6.2

Hz, 1H).

Intermediate 45: 6-chloro-4-[(5-chloro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 50 mg, 0.27 mmol) in 3 mL of anh. THF LiHMDS (1M in THF, 539 uL, 0.54 mmol) was added dropwise under N2, at 0 ºC. The mixture was stirred at room temperature for 15 min. and the temperature was lowered again to 0 ºC. 5-chloro-2-methoxy-benzoyl chloride (89 mg, 0.43 mmol) in 1 mL of anh. THF was added dropwise and the mixture was stirred at room temperature (clear yellow solution). After 45 min. the conversion was 65 %. The temperature was lowered to 0 ºC and NH4Cl sat. was added. A little of water was added (in order to improve the solubility of the aqueous phase) and the mixture was extracted with AcOEt (x 1) and was washed with NaHCO3 sat. (x 1) and brine; dried over anh. MgSO4, filtered and evaporated to have a white solid which was precipitated in Et2O and washed with a little of MeOH to have a white solid which was dried in the vacuum oven (40 mg, 42 %).
HPLC-MS: tr = 3.10 min.(87 %). LRMS (m/z): 354/356/358 (M+1, 2Cl)
Staring material is present in 13 % by HPLC-MS, however the solid was used for the next step without further purification.
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.85 (d, J = 4.6 Hz, 3H), 4.07 (s, 3H), 7.31 (d, J = 9.0 Hz, 1H), 7.69 (dd, J = 8.9, 2.8 Hz, 1H), 7.94 – 7.97 (m, 1H), 8.65 (s, 1H), 8.70 (s, 1H), 8.95 (d, J = 4.8 Hz, 1H), 12.46 (s, 1H).

Intermediate 46: 6-chloro-4-[(3,5-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.58 mmol) in 6.5 mL of anh. THF under N2, at 0 ºC was added LiHMDS (1M in THF, 0.97 mL, 1.05 mmol) dropwise. The mixture was stirred at room temperature for 15 min. The temperature was lowered again to 0 ºC and 2,3-dimethoxybenzoyl chloride (220 mgl) in 2 mL THF was added dropwise. The mixture was stirred at room temperature. After 30 min, the conversion was about 40%. After 2.5 h, the reaction did not evolved, so the mixture was cooled to 0 ºC and additional LiHMDS (0.97 mL more) was added. After 4 h, the reaction showed a

46% of conversion. The temperature was lowered to 0 ºC and NH4Cl sat. was added. The crude was extracted with AcOEt, washed with brine and dried over MgSO4. Solid which was purified via flash chromatography in DCM/DCM with 5 % MeOH to get a white solid (41 mg 22%).

HPLC-MS: tr = 2.87 min. LRMS (m/z): 338/340 (M+1, Cl)
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.97 (s, 1H), 9.14 (bs, 1H), 8.80 (s, 1H), 8.64 (s, 1H), 7.06 (s, 1H), 7.06 (s, 1H), 6.83 (s, 1H), 3.84 (s, 6H), 2.85 (d, J = 4.5 Hz, 3H).

Intermediate 47: 2-[(2-iodoimidazol-1-yl)methoxy]ethyl-trimethyl-silane

60% Sodium hydride (269 mg, 6.72 mmol) was added in portions to a solution of 2-iodo-1H-imidazole (1085 mg, 6.78 mmol) in 28 mL of anh. THF at 0 ºC. The mixture stirred at 0 ºC for 30 min. Then SEM-Cl (1.2 mL, 6.72 mmol) was added at 0 ºC and the mixture was stirred at room temperature. After 1 h the reaction is complete and the mixture was cooled in an ice bath and quenched with aq. solution of ammonium chloride, diluted with EA. The layers were separated and the organic layer dried (sodium sulfate), concentrated and absorbed onto silica to purify via FCC in Hx/Hx with 50 % AcOEt to have a brown oil (1487 mg, 82 %).
HPLC-MS: tr = 2.65 min. (99 %). LRMS (m/z): 325 (M+1)

Intermediate 48: methyl 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoate

To a solution of 2-[(2-iodoimidazol-1-yl)methoxy]ethyl-trimethyl-silane (Intermediate 47; 1487 mg, 4.58 mmol) in 30 mL of anh. DMF and 6 mL of water was added dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) (336 mg, 0.46 mmol) and potassium carbonate (1267 mg, 9.16 mmol), and the mixture was heated under Ar at 110 ºC. After 3h 15 min. the reaction is finished and water and AcOEt were added. Phases separated and the organic phase was washed with LiCl (5 % solution, x 2), water and brine; dried over anh. MgSO4, filtered and evaporated to have a reddish oil which was purified via flash chromatography in Hx/AcOEt to have a brown-red oil (824 mg, 49 %).
HPLC-MS: tr = 2.42 min. (99 %). LRMS (m/z): 363 (M+1)

Intermediate 49: 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoic

acid

To a solution of methyl 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoate (Intermediate 48; 500 mg, 0.25 mmol) in 7 mL of THF anh 1.4 mL of water was added LiOH·H2O (174 mg, 4.14 mmol) and the solution was stirred at room temperature. The next day the reaction is finished and the volatiles were removed under reduced pressure. More water was added and the solution was acidified with HCl 1N to pH 3-4, extracted with AcOEt (x 3), washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a brown solid (75 %, 361 mg).

HPLC-MS: tr = 2.17 min.(99 %). LRMS (m/z): 349 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.04 (s, 9H), 0.84 – 0.92 (m, 2H), 3.57 – 3.65 (m, 2H), 3.86 (s, 3H), 5.41 (s, 2H), 7.07 (s, 1H), 7.42 (d, J = 9.4 Hz, 1H), 7.53 (d, J = 4.8 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H).

Intermediate 50: 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoyl chloride

To a solution of 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoic acid (Intermediate 49; 361 mg, 1.03 mmol) in 7 mL of anh. DCM at 0 ºC were added two drops of DMF and oxalyl chloride (150 uL, 1.93 mmol) added dropwise and the mixture was stirred at room temperature. After 30 min. the reaction is complete and the volatiles were removed under reduced pressure (adding toluene and evaporating it in order to remove all the oxalyl chloride traces) to have a brown solid as a final product. The compound was used per se in the next synthetic step.

HPLC-MS: tr = 2.45 min. (99 %). LRMS (m/z): 364 (M+1, Me ester)

Intermediate 51: 6-chloro-4-[[2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 50; 120 mg, 0.65 mmol) in 8 mL of anh. THF at 0ºC LiHMDS (1M in THF, 1,29 mL, 1.29 mmol) ºC was added dropwise under N2. The mixture was stirred at room temperature for 30 min. and the temperature was lowered again to 0 ºC and 2-methoxy-

4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoyl chloride (380 mg, 1.03 mmol) in 4 mL of anh. THF was added (partially soluble, heating with a gun improves the solubility) dropwise (during the addition the crude is clear but at the end, a brown suspension is observed). The mixture was stirred at room temperature (brown suspension) After 40 min. the conversion is about 50 %.The temperature was lowered to 0 ºC and NH4Cl sat. was added. A little of water was added (in order to improve the solubility of the aqueous phase) and the mixture was extracted with AcOEt (x 1) and was washed with NaHCO3 sat. (x 1) and brine; dried over anh. MgSO4, filtered and evaporated to have a brown semisolid which was precipitated in MeOH to have a white solid (HPLC-MS: tr = 1.03 min., 95 %, no ionization observed, possibly starting material) and a dark brown solution as a filtrate (HPLC-MS: tr = 2.43 min., 25 %, 516/518 m/z ok) which was cocentrated under reduced pressure and purified via flash chromatography in Et2O/Et2O with 10 % MeOH to have a colorless oil (tr = 2.72 min., 45 %). This material was repurified thorugh reverse phase to have a white solid (34 mg, 10 %).

HPLC-MS: tr = 2.45 min. (99 %). LRMS (m/z): 516/518 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.04 (s, 9H), 0.85 – 0.95 (m, 2H), 2.85 (d, J = 4.5 Hz, 3H), 3.56 – 3.69 (m, 2H), 4.11 (s, 3H), 5.45 (s, 2H), 7.10 (s, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.68 (s, 1H), 8.09 (d, J = 8.2 Hz, 1H), 8.14 (s, 1H), 8.64 (s, 1H), 8.74 (s, 1H), 8.94 (d, J = 4.7 Hz, 1H), 12.47 (s, 1H).

Intermediate 52: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[[2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 51; 33 mg, 0.063 mmol), 2,6-dimethylpyrimidin-4-amine (12 mg, 0.097 mmol), Pd2(dba)3 (6 mg, 0.006 mmol), Xantphos (7.5 mg, 0.012 mmol) and cesium carbonate (62 mg, 0.19 mmol) in dioxane (1 mL) was heated at 100ºC. After 1h 30min. the reaction shows a 45 % of final product and a 31 % of proportion of starting material. Reduction of Cl is observed in a 14 %. The mixture was heated again after adding more quantities of reactants (3 mg Pd, 4 mg Xantphos, 30 mg of cesium carbonate and 6 mg of dimethylpyrimidine) and the mixture was heated again. After two additional hours the expected product is around 75 % and starting material is 5 % (reduction of chlorine is 15 % and seems stable with the time). The reaction was left heating

for one more hour and left cool down to room temperature (4 h 30 min total). The mixture was cooled down to room temperature and NH4Cl sat. was added. AcOEt was added and water in order to improve the separation of phases. The organic phase was washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified in DCM/DCM with 10 % MeOH to have a white solid (21 mg), which is impurified with 2,6-dimethylpyrimidin-4-amine. Water was added and sonicated, the slightly yellow solid was filtered and washed with water to have the final product (16.3 mg, 42 %).

HPLC-MS: tr = 2.13 min.(99 %). LRMS (m/z): 603 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.04 (s, 9H), 0.85 – 0.97 (m, 2H), 2.33 (s, 3H), 2.77 – 2.87 (m, 3H), 3.58 – 3.65 (m, 2H), 4.08 (s, 3H), 5.45 (s, 2H), 7.10 (s, 1H), 7.45 (s, 1H), 7.53 – 7.58 (m, 2H), 7.65 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H), 8.58 (s, 1H), 8.68 (d, J = 5.1 Hz, 1H), 9.22 (s, 1H), 10.31 (s, 1H), 12.46 (s, 1H).

Intermediate 53: 3-[tert-butoxycarbonyl(methylsulfonyl)amino]benzoic acid

The title compound was prepared from methyl 3-(methanesulfonamido)benzoate via methyl 3-[tert-butoxycarbonyl(methylsulfonyl)amino]benzoate according to the method described in J.Med:Chem. 57 (3), 793 (2014).

HPLC-MS: tr = 2.35 min.(86 %). LRMS (m/z): 316 (M+1)/333 (M+17)

^{1}H NMR (400 MHz, CDCl3): δ ppm 1.47 (s, 9H), 3.47 (s, 3H), 7.51 – 7.58 (m, 2H), 7.94 – 7.97 (m, 1H), 8.12 – 8.17 (m, 1H).

Intermediate 54: tert-butyl N-[3-[[2-chloro-5-(methylcarbamoyl)-4-pyridyl]carbamoyl]phenyl]-N-methylsulfonyl-carbamate

To a solution of 3-[tert-butoxycarbonyl(methylsulfonyl)amino]benzoic acid (Intermediate 53; 68mg, 0.37mmol) and HATU (280mg, 0.74mmol) in DMF (1mL) was added DIPEA (128uL, 0.73mmol) and the mixture was stirred at room temperature for 1h. Water was added and extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness (activated carboxylic acid stored in freezer). 2-amino-4-chloro-N-methyl-benzamide (Preparation 3; 68mg, 0.37mmol) was solved in DMF (0.5mL) and cooled at 0ºC. Then NaH (60%, 44mg, 1.10mmol) was added and stirred for 30min at room temperature. Again cooled at 0ºC and activated acid was added dropwise solved in DMF (1mL) and stirred at room temperature for 1hr. NH4Cl was added and compound was extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and

evaporated to dryness.The crude was purified by flash chromatography (Reveleris Telos12g) using hexane/AcOEt (220nm) to give the title compound (87mg, 42%) as a colourles oil.
HPLC/MS tr=2.92 min. (86%). LCMS (m/z): 483,485
^{1}H NMR (400 MHz, CDCl3) δ ppm 1.48 (s, 9H), 3.05 (d, J = 4.8 Hz, 3H), 3.50 (s, 3H), 6.46 (d, J = 5.4 Hz, 1H

Intermediate 55: tert-butyl N-[3-[[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]carbamoyl]phenyl]-N-methylsulfonyl-carbamate

Tert-butyl 2-[3-[[2-chloro-5-(methylcarbamoyl)-4-pyridyl]carbamoyl]phenyl]-2-methylsulfonyl-acetate (Intermediate 54; 85mg, 0.15mmol), 2,6-dimethylpyrimidin-4-amine (28mg, 0.23mmol), Pd2(dba)3 (14mg, 0.015mmol), xantphos (18mg, 0.031mmol) and cesium carbonate (148mg, 0.44mmol) were heated in dioxane (2mL) at 100ºC for 3hr. Saturated bicarbonate and AcOEt were added and extracted with AcOEt (x2), then washed with brine. The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Gold12g) using DCM /MeOH (up to 5%) (220nm) to give the title compound (27mg, 31%) as a white solid.
HPLC/MS tr=2.20 min (100%). LRMS (m/z): 570
^{1}H NMR (400 MHz, CDCl3) δ ppm 1.48 (s, 9H), 2.47 (s, 3H), 2.65 (s, 3H), 3.02 (s, 3H), 3.51 (s, 3H), 6.52 (s, 1H), 7.46 – 7.55 (m, 2H), 7.60 (t, J = 7.9 Hz, 1H), 7.92 (t, J = 1.9 Hz, 1H), 8.03 – 8.11 (m, 1H), 8.24 (s, 1H), 8.54 (s, 1H), 8.89 (s, 1H), 12.81 (s, 1H).

Intermediate 56: methyl 4-cyano-2-methoxy-benzoate

500 mg (2.82 mmol) of 4-cyano-2-methoxy-benzoic acid were dissolved in 14 mL of methanol and p-toluensulfonic acid (139 mg, 0.73 mmol) was added. The mixture was heated to reflux for all the night. The solvent was removed and the reaction residue was extracted with EtOAc, and washed with saturated sodium carbonate, water, and saturated NaCl, and dried over Na2SO4. 4-Cyano-2-methoxy-benzoic acid methyl ester as a white solid (530 mg, 98 %).
HPLC-MS: tr = 2.30 min. (99 %). LRMS (m/z): 192 (M+1)
^{1}H NMR (400 MHz, CDCl3) δ ppm 3.92 (s, 3H), 3.94 (s, 3H), 7.22 (d, J = 1.4 Hz, 1H), 7.29 (dd, J = 7.9, 1.4 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H).

Intermediate 57: methyl 4-carbamoyl-2-methoxy-benzoate

To a solution of methyl 4-cyano-2-methoxy-benzoate (Intermediate 56; 527 mg, 2.75 mmol) in 10 mL of DMSO was added potassium carbonate (57 mg, 0.41 mmol) and the temperature was lowered to 0 ºC. Hydrogen peroxide (310 uL, 3.03 mmol) was added dropwise and the mixture was stirred at room temperature overnight.The next day the reaction is finished. Water was added but no precipitate appeared. The mixture was extracted with DCM (x 3) and washed with water (there is product in the aqueous phase). The organic was dried over anh. MgSO4, filtered and evaporated to give 543 mg 94% yield) of a white solid.

HPLC-MS: tr = 1.60 min. (93 %). LRMS (m/z): 210 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.80 (s, 3H), 3.87 (s, 3H), 7.49 (d, J = 9.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 7.9 Hz, 1H), 8.12 (s, 1H).

Intermediate 58: methyl 4-[(E)-1-(dimethylamino)ethylidenecarbamoyl]-2-methoxy-benzoate

542 mg (2.59 mmol) of methyl 4-carbamoyl-2-methoxy-benzoate (Intermediate 57) were suspended in 2 mL of 1,1-dimethoxy-N,N-dimethyl-ethanamine (13 mmol, 5 eq.) and the mixture was stirred at 90 ºC. After 30 min. the reaction is complete and the volatiles were removed under high vacuum to have a brown oil which used for the next step without further purification (612 mg, 85 %).

HPLC-MS: tr = 1.90 min. (92 %). LRMS (m/z): 279 (M+1)

Intermediate 59: methyl 2-methoxy-4-(5-methyl-4H-1,2,4-triazol-3-yl)benzoate

methyl 4-[(E)-1-(dimethylamino)ethylidenecarbamoyl]-2-methoxy-benzoate (Intermediate 58; 605 mg, 2.17 mmol, crude) was dissolved in 4 mL of glacial acetic acid. Under nitrogen atmosphere was added, over syringe, anhydrous hydrazine (1M in THF, 4.3 mL, 4.3 mmol) and the mixture was heated at 90 ºC for 30 min. The reaction is finished and the mixture was cooled down to room temperature. The crude was evaporated to dryness, methanol was added and the mixture neutralized with saturated aqueous sodium bicarbonate. The mixture was extracted with DCM and AcOEt, the extracts were combined and dried over anh. MgSO4, filtered and evaporated to have a white solid which was precipitated with Et2O, filtered and dried in the vacuum oven (white solid, 315 mg, 59 %).

HPLC-MS: tr = 1.85 min. (99 %). LRMS (m/z): 248 (M+1)

Intermediate 60: methyl 2-methoxy-4-[5-methyl-4-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoate

Sodium hydride (60 mg, 1.50 mmol) was added to a solution of methyl 2-methoxy-4-(5-methyl-4H-1,2,4-triazol-3-yl)benzoate (Intermediate 59; 310 mg, 1.25 mmol) in 7 mL of anh. DMF at 0 ºC. The mixture was stirred at 0 ºC for 30 min, then SEM-Cl (266 uL, 1.50 mmol) was added at 0 ºC and the mixture was stirred at room temperature for 1hr. The mixture was cooled in an ice bath, quenched with aq. solution of ammonium chloride and diluted with AcOEt. The layers were separated and the organic layer dried (sodium sulfate), concentrated and absorbed onto silica to purify via FCC in Hx/AcOEt. Two isomers observed by NMR.

HPLC-MS: tr = 3.22 min. (99 %). LRMS (m/z): 378 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.01 (s 9H), 0.93 (t 2H, J = 8.4 Hz), 2.60 (s 3H), 3.69 (t 2H J = 8.3 Hz), 3.90 (s 3H), 4.01 (s 3H), 5.48 (s 2H), 7.55 (m 1H), 7.70 (m 1H), 7.89 (m 1H).

Intermediate 61: 2-methoxy-4-[5-methyl-4-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoic acid

To a solution of methyl 2-methoxy-4-[5-methyl-4-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoate (Intermediate 60; 487 mg, 1.29 mmol) in 3 mL of THF and 1.5 mL of water was added LiOH·H2O (162 mg, 3.86 mmol) and the solution was stirred overnight at room temperature. The volatiles were removed under reduced pressure. More water was added and the solution was acidified with HCl 1N to pH 3-4, extracted with AcOEt (x 3), washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a white solid (406 mg, 74 %).

HPLC-MS: tr = 2.88 min. (99 %). LRMS (m/z): 364 (M+1)

Intermediate 62: 6-chloro-4-[[2-methoxy-4-[5-methyl-4-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-4-[5-methyl-4-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoic acid (Intermediate 61; 196 mg, 0.54 mmol) and HATU (307 mg, 0.80 mmol) in DMF (2 ml) was added DIPEA (141 µL, 0.8 mmol) and the mixture was stirred at room temperature for 60 min. After 60 min, HPLC-MS showed the total conversion of benzotriazolyl derivative (3.32 min, m/z 482 (M+1)). Water was added but a precipitate did not appear (sticky solid). AcOEt was added and extracted (x 2). The combined organic extracts were washed with water (x 2) and sat. NaCl (x 1), dried over anh. MgSO4 and evaporated to have a brown oil. (tr = 3.38 min., 95 %). In a 25 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 50 mg, 0.27 mmol) in DMF (2 ml) at 0ºC. NaH (60%, 32 mg, 0.8 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was

cooled to 0ºC again, the activated acid in DMF (0.4 mL) was added dropwise and the mixture was stirred at rt. After 1 h 30 min. the reaction is complete (starting material is not observed and the conversion is almost 100 %). NH4Cl sat. was added (precipitated) followed by water and AcOEt. Phases separated and the organic phase was washed with water (x 3) and brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a white semisolid. MeOH was added and a white solid precipitated after sonication, filtered and dried in the vacuum oven for one night (72 mg, 50 %).

HPLC-MS: tr = 3.48 min. (99 %). LRMS (m/z): 531/533 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.04 (s, 9H), 0.79 – 0.94 (m, 2H), 2.54 (s, 3H), 2.83 – 2.90 (m, 3H), 3.57 – 3.72 (m, 2H), 4.05 – 4.16 (m, 3H), 5.55 (s, 2H), 7.74 (s, 2H), 8.11 (d, J = 8.3 Hz, 1H), 8.63 (s, 1H), 8.74 (s, 1H), 8.94 (d, J = 5.2 Hz, 1H), 12.46 (s, 1H).

Intermediate 63: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-[5-methyl-4-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[[2-methoxy-4-[5-methyl-4-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 62; 75 mg, 0.14 mmol), 2,6-dimethylpyrimidin-4-amine (24 mg, 0.19 mmol), Pd2(dba)3 (13 mg, 0.014 mmol), Xantphos (15 mg, 0.025 mmol) and cesium carbonate (138 mg, 0.42 mmol) were heated in dioxane (1.5 mL) at 100ºC. After 3h 30min. the reaction is complete and NH4Cl sat. was added followed by AcOEt. Phases were separated and the aqueous phase extracted with AcOEt, the organics (a little solid in suspension) were combined and washed with NaCl sat., dried over anh. MgSO4, filtered and evaporated to have yellow solid which was purified via flash chromatography in DCM/DCM with 10 % MeOH to have a yellow solid (49 mg, 55 %).

HPLC-MS: tr = 3.37 min. (95 %). LRMS (m/z): 618 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.04 (s, 9H), 0.85 – 0.92 (m, 2H), 2.33 (s, 3H), 2.54 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 3.60 – 3.68 (m, 2H), 4.11 (s, 3H), 5.56 (s, 2H), 7.43 (s, 1H), 7.71 – 7.75 (m, 2H), 8.07 (d, J = 8.4 Hz, 1H), 8.58 (s, 1H), 8.67 (d, J = 4.7 Hz, 1H), 9.22 (s, 1H), 10.31 (s, 1H), 12.46 (s, 1H).

Intermediate 64: methyl 3H-benzimidazole-5-carboxylate

Thionyl chloride (1.1 ml, 15.1 mmol) was added dropwise to a suspension of 3H-benzimidazole-5-carboxylic acid (500mg, 3.08 mmol) in MeOH cooled to 0ºC. The reaction

mixture was heated at reflux for 7 hr.The so0lvent was removed and the grey solid was taken up in MeOH and concentrated again. The residue was treated with aqueous saturated solution of NaHCO3, extracted with EtOAc (2x), then the organic phase was dried (MgSO4), filtered and solvent removed to yield a pale brown solid (489 mg).

HPLC-MS rt: 1.25 min (99%) LRMS (m/z): 177 (M+1)

Intermediate 65: methyl 1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylate and methyl 3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylate

To the solution of methyl 3H-benzimidazole-5-carboxylate (Intermediate 64; 439 mg, 2.49 mmol) in DMF (10 ml) at 0°C, NaH (60% in mineral oil, 110 mg, 2.75 mmol) was added. After 5minutes SEMCl (575 µL, 3.25 mmol) was added and the mixture was stirred at rt overnight. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAc. Then the organic phase was washed with brine (2x), dried (MgSO4), filtered and solvent removed. The residue was purified by flash chromatography (Biotage, SNAP 40g) using DCM/DCM-MeOH (2%) from 0 to 100%.

Final product (both regioisomers): 645 mg as a pale brown solid

HPLC-MS rt: 2.98' (100%). LRMS (m/z): 307

Intermediate 66: 1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylic acid and 3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylic acid

To a solution of methyl 1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylate and methyl 3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylate (Intermediate 65; 640 mg, 2.1 mmol) in MeOH/H2O (10/2 ml) NaOH (163 mg, 4.07 mmol) was added and the mixture was heated at 80°C for 1hr. Solvent was removed and water was added. The pH was adjusted to 6 and the product extracted with EtOAc (2x), dried (MgSO4), filtered and solvent removed.

Final product: 457 mg (84%) of an orange foam mixture of 2 isomers.

HPLC-MS rt: 2.43' (45%) and 2.53' (54%). LRMS (m/z): 293

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.08 (s 9H), 0.83 (t 2H J = 8 Hz), 3.50 (t 2H, J=8Hz), 5.67 and 5.71 (s 2H), 7.72 (d 1H J = 2.4 Hz), 7.85 and 7.90 (d 1H J=1.2 Hz), 8.24 and 8.25 (s 1H), 8.26 and 8.27 (s 1H).

Intermediate 67: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide and N-[2-chloro-5-

(methylcarbamoyl)-4-pyridyl]-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide

To a solution of 1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylic acid and 3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylic acid (Intermediate 66; 445 mg, 1.52 mmol) and HATU (573 mg, 1.51 mmol) in DMF (5 ml) DIPEA (262 µL, 1.50 mmol) was added and the mixture was stirred at room temperature for 60 min. Water was added and a precipitate appeared that was filtered off and taken up in EtOAc, dried (MgSO4), filtered and solvent removed. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 140 mg, 0.135 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 60 mg, 1.50 mmol) was added and the mixture was stirred at rt for 30 minute. After cooling to 0ºC again the activated acid in DMF was added dropwise and the mixture was stirred at rt for 2 hr. Water and EtOAc were added and the phases separated. The aqueous phase was further extracted with EtOAc, then the organic phases were washed with brine (2x), dried, filtered and solvent removed. The crude was purified by flash chromatography (biotage, SNAP 40g) by using DCM/DCM-MeOH (10%). A second purification was requiered (Biotage, SNAP 12g GOLD) using DCM/DCM-MeOH (5%). There were obtained 72 (20%) mg of a stereoisomeric mixture (93/7).

HPLC-MS rt: 2.43' (7%); 3.18' (93%). LRMS (m/z): 460/462

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.06 (s 9H), 0.987 (t 2H J=8.4 Hz), 3.02 (d 3H J=4.8 Hz), 3.51 (t 2H J=8.4 Hz), 5.56 and 5.62 (s 2H), 7.65 (d 1H J=8.4 Hz), 7.91-8.03 (cs 1H), 8.09 (s 1H), 8.48 (cs 2H), 8.85 (s 1H)

Intermediate 68: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide

The mixture of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide (Intermediate 67; 70 mg, 0.152 mmol), 2,6-dimethylpyrimidin-4-amine (23 mg, 0.186 mmol), Pd2(dba)3 (14 mg, 0.015 mmol), Xantphos (18 mg, 0.031 mmol) and cesium carbonate (119 mg, 0.365 mmol) were heated in dioxane (5 mL) at 100ºC for 22 hr. The reaction was cooled down and filtered. The residue obtained after concentration was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (10%). 37 mg (21%) of title compound were obtained.

HPLC-MS rt = 2.43' (32%). LRMS (m/z): 547 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.04 (s 9H), 0.92 (t 2H J=10 Hz), 2.33 (s 3H), 2.50 (s 6H), 2.52 (t 2H J 10 Hz), 5.58 (s 2H), 6.13 (s 1H), 7.66 (d 1H J= 8.8 Hz), 8.05-8.10 (cs 2H), 8.55 (cs 2H).

Intermediate 69: methyl 4-[(E)-dimethylaminomethylenecarbamoyl]-2-methoxy-benzoate

Methyl 4-carbamoyl-2-methoxy-benzoate (Intermediate 57; 545 mg) was suspended in 2 mL of 1,1-dimethoxy-N,N-dimethyl-methanamine (DMF-DMA) and the reaction was heated at 90 ºC under argon gas in a sealed flask. After 60 min, the starting material has disappeared and the volatiles were removed, co-evaporated with toluene, to give a yellowish solid (625 mg). The product was used in the next step without further purification.

Intermediate 70: methyl 2-methoxy-4-(4H-1,2,4-triazol-3-yl)benzoate

Methyl 4-[(E)-1-(dimethylamino)ethylidenecarbamoyl]-2-methoxy-benzoate (Intermediate 69; 605 mg, 2.17 mmol, crude) was dissolved in 4 mL of glacial acetic acid under nitrogen atmosphere and anhydrous hydrazine (1M in THF, 4.3 mL, 4.3 mmol) was added, over syringe, and the mixture was heated at 90 ºC for 30 min. The reaction was finished and the mixture was cooled down to room temperature. The crude was evaporated to dryness, methanol was added and the mixture neutralized with saturated aqueous sodium bicarbonate. The mixture was extracted with DCM and AcOEt, the extracts were combined and dried over anh. MgSO4, filtered and evaporated to have a white solid which was precipitated with Et2O, filtered and dried in the vacuum oven (white solid, 525 mg, 95%).

HPLC-MS: tr = 1.78 min. (95 %). LRMS (m/z): 234 (M+1)

Intermediate 71: methyl 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoate

Sodium hydride (51 mg, 1.28 mmol) was added to a solution of methyl 2-methoxy-4-(1H-1,2,4-triazol-3-yl)benzoate (Intermediate 70; 200 mg, 0.86 mmol) in 4.3 mL of anh. DMF at 0 ºC. The mixture stirred at 0 ºC for 30 min. Then SEM-Cl (70 µL, 0.395 mmol) was added at 0 ºC and the mixture was stirred at room temperature. After 45 min, the reaction is not finished (85% conversion) so it was let to stir overnight at room temperature. After overnight, the reaction was not finished; 20 mg NaH (0.5 mmol) were added at 0 ºC, and after 10 min, additional 0.1 mL of SEMCl were added to the mixture, and the reaction was stirred at room

temperature. After 30 min, the reaction was completed. The mixture was cooled in an ice bath and quenched with aq. solution of ammonium chloride, diluted with AcOEt. The layers were separated and the organic layer washed with brine (2x), dried (magnesium sulfate), filtrated and concentrated. The crude was purified by flash chromatography (5% Methanol in DCM) to afford a colorless oil (281 mg).

HPLC-MS: rt: 3.15 min. LRMS (m/z): 364 (M+1)

Intermediate 72: 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoic acid

To a solution of methyl methyl 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoate (Intermediate 71; 281 mg, 0.77 mmol) in 3.9 mL of THF anh 0.68 mL of water was added LiOH·H2O (98 mg, 2.33 mmol) and the solution was stirred at room temperature overnight. The HPLC showed total conversion. The volatiles were removed under reduced pressure. More water was added and the solution was acidified with HCl 1N to pH 3-4 at 0 ºC, extracted with AcOEt (x 3), washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to obtain a white solid (198 mg 73%) that was used per se in the next step.

HPLC-MS: rt: 2.80 min (98%). LRMS (m/z): 350 (M+1).

Intermediate 73: 6-chloro-4-[[2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoic acid (Intermediate 72; 198 mg, 0.566 mmol) and HATU (430 mg, 1.13 mmol) in DMF (3 ml) was added DIPEA (0.2 mL, 1.14 mmol) and the mixture was stirred at room temperature for 60 min. After 60 min, HPLC-MS showed the total conversion to benzotriazolyl derivative (3.32 min, m/z 468 (M+1)). Water was added and a precipitate appeared that was filtered off and taken up in EtOAc, dried (MgSO4), filtered and solvent removed. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 70 mg, 0.377 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 45 mg, 1.13 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again, the activated acid in DMF (0.4 mL) was added dropwise and the mixture was stirred at rt. After overnight reaction, HPLC-MS showed total conversion to product. The reaction was quenched with ammonium chloride at 0 ºC and diluted with AcOEt. The organic phase was washed with brine, dried over magnesium sulphate, filtered and concentrated. The product was quite insoluble so it was precipitated with methanol

and filtered. The yellowish solid (160 mg; 82%) was checked by HPLC-MS (purity 93%) and used per se in the next step.

HPLC-MS tr: 3.42 min. LRMS (m/z) 517/519 (M+1, Cl)

Intermediate 74: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide

A solution of methyl 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxylate (Intermediate 73;108 mg, 0.044 mmol), 2,6-dimethylpyrimidin-4-amine (59 mg, 0.479 mmol), Pd2(dba)3 (29 mg, 0.10 mmol), Xantphos (37 mg, 0.2 mmol) and cesium carbonate (312 mg, 0,96 mmol) was heated in dioxane (3,2 mL) at 100 ºC. The reaction was finished after 45 min. It was sotred at -20 ºC.The reaction was quenched with water after 3 h, extracted with AcOEt, washed with brine and dried over MgSO4. The crude was purified by flash chromatography (100% DCM to 10 % MeOH in DCM gradient) to obtain a yellowish solid (200 mg 60%). The 1H-NMR spectrum shows the presence of regioisomers.

HPLC-MS tr: 2.53 min. LRMS (m/z): 604 (m+1))

^{1}H NMR (400 MHz, d6-DMSO) δ ppm 0.04 (s 9H), 0.88 (t 2H J= 8 Hz), 2.13 (s 3H), 2.25 (s 3H), 2.33 (s 3H), 3.65 (t 2H J = 8 Hz), 4.11 (s 3H), 5.62 (s 2H), 6.06 (s 1H), 6.55-6.65 (bs, 1H), 7.44 (s 1H), 7.70 (m 1H), 8.58 (cs 1H), 8.60 (m 1H), 8.87 (s 1H), 9.22 (s 1H), 10.30 (s 1H), 12.49 (s 1H).

Intermediate 75: 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-3-methyl-benzoic acid (107 mg, 0.64 mmol) and HATU (369 mg, 0.97 mmol) in DMF (2 ml) was added DIPEA (169 µL, 0.97 mmol) and the mixture was stirred at room temperature for 60 min. After 60 min, HPLC-MS showed the total conversion of activated derivative. Water was added and a sticky solid appeared which was isolated by the addition-separation of AcOEt. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have a brown solid. In a 25 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 60 mg, 0.32 mmol) in DMF (2 ml) at 0ºC, NaH (60%, 39 mg, 0.97 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF

(0.4 mL) was added dropwise and the mixture was stirred at rt. After 1h 15 min. the reaction is finished and water was added. The mixture extracted with AcOEt (x1) and the organic washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a yellow semisolid which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid.

HPLC-MS: tr = 2.83 min. (98 %). LRMS (m/z): 334/336 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.81 (d, J = 4.6 Hz, 3H), 3.76 (s, 3H), 7.22 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 6.3 Hz, 1H), 7.70 (dd, J = 8.0, 1.5 Hz, 1H), 8.67 (s, 1H), 8.70 (s, 1H), 8.91 – 8.99 (m, 1H), 12.34 (s, 1H).

Intermediate 76: 2-methoxybenzene-1,3-dicarboxylic acid

A suspension of 2-methoxy-1,3-dimethyl-benzene (2g, 14.7 mmol), potassium permanganate (15.3 g, 96.82 mmol) and KOH (2.64g, 47 mmol) in water (72 ml) was heated at 80ºC for 5hr.The suspension was filtrated through Celite and washed with water. Then pH of the filtrate was ajusted to 2-3 and the product was extracted with EtOAc, dried over MgSO4 an concentrated to give 2.28 g (79%) of title compound as a brown solid.

HPLC-MS rt = 1.43 min (95%). LRMS (m/z): ES+ 197 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.78 (s, 3H), 7.24 (t, J = 7.7 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H).

Intermediate 77: dimethyl 2-methoxybenzene-1,3-dicarboxylate

SOCl2 (5 ml, 68.5 mmol) was added dropwise to a solution of 2-methoxybenzene-1,3-dicarboxylic acid (Intermediate 76; 1.35g, 6.88 mmol) in anhydrous MeOH (25 ml) at 0ºC under argon. The reaction was stirred overnight at rt. The solution was concentrated and the residue was taken up in EtOAc and washed with saturated NaHCO3 aqueous solution (2x). The organic phase was dried, filtered and solvent removed giving 1.6 g (quantitative) of an orange oil

HPLC-MS rt = 2.40 min (97%). LRMS (m/z): 225 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.93 (s, 6H), 3.93 (s, 3H), 7.20 (t, J = 7.8 Hz, 1H), 7.92 (d, J = 7.8 Hz, 2H).

Intermediate 78: 2-methoxy-3-methoxycarbonyl-benzoic acid

To a solution of dimethyl 2-methoxybenzene-1,3-dicarboxylate (Intermediate 77; 1.5 g; 6.88 mmol) in 15 mL of MeOH was added KOH (386 mg, 6.88 mmol) and the solution was stirred at 65ºC. After 3h the reaction was stopped because diacid was observed. Solvent was removed, water and EtOAc were added, phases separated, the organic phase contained compound A. The aqueous phase was acidified to pH 2-3 and was extracted with EtOAc (2x), then it was dried, filtered and solvent removed giving 890 mg (60%) of title compound as an off white solid
HPLC-MS rt = 1.88 min (95%). LRMS (m/z): 211 (M+1)

Intermediate 79: methyl 3-carbamoyl-2-methoxy-benzoate

To a stirred solution of 2-methoxy-3-methoxycarbonyl-benzoic acid (Intermediate 78; 2 g, 9.5 mmol) in 50 mL of anh. DCM one drop of DMF was added and the temperature was lowered to 0 ºC. Oxalyl chloride (2.5 mL, 29.15 mmol) was added dropwise and the mixture was stirred at room temperature during 1 hr. The reaction mixture was then concentrated. Then an aqueous solution of NH4OH (25%, 15 ml) was cooled to -10ºC and the acyl chloride obtained was added dropwise in solution (DCM, 15 ml). Phases were separated and the organic phase was further extracted with H2O, then it was dried (MgSO4), filtered and solvent removed. 1.5 g of title compound were obtained as an white solid.
HPLC-MS rt = 1.68 min (95%). LRMS (m/z): 210 (M+1).

Intermediate 80: methyl 2-methoxy-3-(4H-1,2,4-triazol-3-yl)benzoate

Methyl 3-carbamoyl-2-methoxy-benzoate (Intermediate 79; 1.5 g, 7.17 mmol) was slurred in DMF-DMA (9.5 ml, 71.75 mmol) and the mixture was heated at 95ºC for 1h. Then the reaction was concentrated and to the resulting yellow oil was added toluene and concentrated again. It was repeated twice. The crude oil thus obtained was dissolved in EtOH (5 ml) and used immediately in the following step. In a separate flask was prepared a mixture of EtOH (20 ml) and AcOH (6.7 ml) and the resulting solution was cooled in an ice bath. Once cooled, hydrazine hydrate (3.6 ml, 71.9 mmol) was added dropwise. At this time the solution containing the crude DMF-DMA adduct as prepared above was transferred dropwise to the ice-cold mixture containing the hydrazine. After the addition was complete, the resulting cloudy white mixture was allowed to warm to rt and stir for 2h. The reaction mixture was concentrated, diluted with water and EtOAc, the suspension was filtered. The solid was discarded and the two phases of the filtrate were separated. The organic phase was dried (MgSO4), filtered and solvent removed under vacuum. 993 mg (59%) of title compound were obtained and used per se in the next step.

HPLC-MS rt = 1.80 min (92%). LRMS (m/z): 234 (M+1)

Intermediate 81: methyl 2-methoxy-3-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoate

Sodium hydride (103 mg, 2.57 mmol) was added to a solution of methyl 2-methoxy-3-(1H-1,2,4-triazol-3-yl)benzoate (Intermediate 80; 400 mg, 1.71 mmol) in 9 mL of anh. DMF at 0 ºC. The mixture was stirred at 0 ºC for 30 min. Then SEM-Cl (364 µL, 2.06 mmol) was added at 0 ºC and the mixture was stirred at room temperature. After 1 h the reaction is complete and the mixture was cooled in an ice bath and quenched with aq. solution of ammonium chloride, diluted with EA. The layers were separated and the organic layer washed with brine (2x), dried (magnesium sulfate), filtrated and concentrated. The residue was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (5%). Title compound was obtained as a clear oil (580 mg, 93%). ^{1}H NMR spectrum shows the presence of 2 regioisomers.
HPLC-MS rt = 3.12 min (91%). LRMS (m/z): 364 (M+1)
^{1}H NMR (400 MHz, d6-DMSO) δ ppm 0.04 (s 9H), 0.69 and 0.86 (t 2H, J=8 Hz), 3.55 and 3.75 (s 3H), 3.65 (t 2H J=8Hz), 3.86 (s 3H), 5.37 and 5.57 (s 2H), 7.32 and 7.39 (t 1H J=7.6 Hz), 7.66 and 7.68 (d 1H J=7.6 Hz), 7.91 and 8.02 (d 1H J=7.6 Hz).

Intermediate 82: 2-methoxy-3-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoic acid

To a solution of methyl 2-methoxy-3-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoate (Intermediate 81; 575 mg, 1.58 mmol) in 8 mL of THF and 2 mL of water was added LiOH·H2O (200 mg, 4.78 mmol) and the solution was stirred at room temperature. The next day the reaction is finished and the volatiles were removed under reduced pressure. More water was added and the solution was acidified with HCl 1N to pH 3-4, extracted with AcOEt (x 3), washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to obtain 550 mg (99%) of a regioisomeric mixture.
HPLC-MS rt = 2.72 min (99%). LRMS (m/z): 350 (M+1)
^{1}H NMR (400 MHz, d6-DMSO) δ ppm 0.04 (s 9H), 0.70 and 0.87 (t 2H, J=8 Hz), 3.40 and 3.66 (t 2H J=8 Hz), 3.56 and 3.76 (s 3H), 5.37 and 5.57 (s 2H), 7.28 and 7.34 (t 1H J=7.6 Hz), 7.59 and 7.71 (d 1H J=7.6 Hz), 7.86 and 7.95 (d 1H J=7.6 Hz), 8.16 (s 1H), 8.80 (s 1H).

Intermediate 83: 6-chloro-4-[[2-methoxy-3-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-3-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoic acid (Intermediate 82; 527 mg, 1.51 mmol) and HATU (574 mg, 1.51 mmol) in DMF (5 ml) was added DIPEA (263 µL, 1.51 mmol) and the mixture was stirred at room temperature for 2h. Water was added and a precipitate appeared that was extracted with EtOAc, dried (MgSO4), filtered and concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 140 mg, 0.135 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 60 mg, 1.50 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling again to 0ºC the activated acid in DMF was added dropwise and the mixture was stirred at rt. After 2h there was no evolution so water and EtOAc were added and phases separated. The aqueous phase was further extracted with EtOAc, then the organic phases were washed with brine (2x), dried, filtered and solvent removed. The crude was purified by flash chromatography (biotage, SNAP 40g) by using DCM/DCM-MeOH (5%). 272 mg (70%) of title compound as isomeric mixture were obtained.

HPLC-MS tr = 3.27 min (90%). LRMS (m/z): 517/519 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm -0.06 (s 9H), 0.81 and 0.96 (t 2H J=8 Hz), 3.01 (d 3H J=4.8 Hz), 3,54 and 3.73 (t 2H J=8Hz), 3.65 and 3.89 (s 3H), 5.52 and 5.58 (s 2H), 6.49-6.51 (bs 1H), 7.33-7.40 (m 1H), 7.69 (s 1H), 8.07-8.20 (m 1H), 8.41 and 8.45 (s 2H), 8.84 and 8.87 (s 1H), 12.18 and 12.21 (s 1H).

Intermediate 84: 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide

The mixture of 6-chloro-4-[[2-methoxy-3-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 83; 130 mg, 0.251 mmol), cyclopropanecarboxamide (26 mg, 0.305 mmol), Pd2(dba)3 (23 mg, 0.025 mmol), Xantphos (29 mg, 0.050 mmol) and cesium carbonate (197 mg, 0.604 mmol) were heated in dioxane (4 mL) at 100ºC. After 18h the reaction was cooled down and filtered. The residue obtained after concentration was purified by flash chromatography (Biotage, SNAP Gold 12g) by using DCM/DCM-MeOH (5%). 50 mg (35%) of title product (as regioisomeric mixture) were obtained.

HPLC-MS rt = 2.97 min (89%). LRMS (m/z): 566 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm -0.07 (s 9H), 0.81 and 0.93 (t 2H J=8 Hz), 0.84 and 1.15 (cs 4H), 2.98 (s 3H), 3.54 and 3.71 (t 2H J=8 Hz), 3.64 and 3.88 (s 3H), 5.53 and 5,57 (s 2H), 7.33 (m 1H), 7.65 (m 1H), 8.06 (s 1H), 8.12 (m 1H), 8.20 (m 1H), 8.30 and 8.34 (s 1H), 9.54 (bs 1H), 12.09 and 12.16 (bs 1H).

Intermediate 85: methyl 2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)benzoate and methyl 2-methoxy-3-(2-methyl-1,2,4-triazol-3-yl)benzoate

A suspension of methyl 2-methoxy-3-(1H-1,2,4-triazol-3-yl)benzoate (Intermediate 80; 593 mg, 2.54 mmol) in DMF (5 ml) was treated with potassium carbonate (1,05 g, 7.6 mmol). After cooling the mixture in an ice bath, a solution of iodomethane (206 µL, 3.31 mmol) was slowly added. After the addition was complete, the ice bath was removed and the reaction mixture was allowed to warm to room temperature. After 1hr, since no SM was observed the reaction was cooled in an ice bath and was diluted with water. A precipitate appeared and the suspension was filtered, the solid was discarded. The filtrated was extracted with EtOAc (3x). The organic phases were washed with brine (3x), dried, filtered and concentrated to yield a clear oil. The crude was purified by flash chromatography (Biotage, SNAP 40g) using DCM/DCM-MeOH (2%) isocratic.Two fractions were collected (total yield: 414 mg; 66%)

Fraction 1: 155 mg being compound 2

HPLC-MS rt = 1.92 min (97%). LRMS (m/z): 248 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.57 (s, 3H), 3.80 (s, 3H), 3.95 (s, 3H), 7.31 (t, J = 8 Hz, 1H), 7.67 (dd, J = 8 and 1.8 Hz, 1H), 7.98 (dd, J = 8 and 1.8 Hz, 1H), 7.99 (s, 1H).

Fraction 2: 259 mg being compound 1

HPLC-MS rt = 1.95 min (97%). LRMS (m/z): 248 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.86 (s, 3H), 3.93 (s, 3H), 4.00 (s, 3H), 7.23 (t, J = 8 Hz, 1H), 7.81 (dd, J = 8 and 1.8 Hz, 1H), 8.09 (dd, J = 8 and 1.8 Hz, 1H), 8.10 (s, 1H).

Intermediate 86: 2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)benzoic acid

To a solution of methyl 2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)benzoate (Intermediate 85, compound 2; 259 mg, 1.05 mmol) in 5 mL of THF and 1 mL of water was added LiOH·H2O (132 mg, 3.15 mmol) and the solution was stirred overnight at room temperature. The next day the reaction is finished and the volatiles were removed under reduced pressure. More water was added and the solution was acidified with HCl 1N to pH 3-4, extracted with AcOEt (x 3),

washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated giving 193 mg (79%) of title product.

HPLC-MS rt =1.55 min (99%). LRMS (m/z): 234 (M+1)

NMR 1H (400 MHz, CDCl3) δ ppm 3.91 (s, 3H), 4.04 (s, 3H), 7.38 (t, J = 7.8 Hz, 1H), 8.17 (s, 1H), 8.23 (d, J = 7.8 Hz, 2H).

Intermediate 87: 6-chloro-4-[[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl) benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)benzoic acid (Intermediate 86; 188 mg, 0.806 mmol) and HATU (307 mg, 0.807 mmol) in DMF (2 ml) was added DIPEA (141 µL, 0.809 mmol) and the mixture was stirred at room temperature for 2h. Water was added and a precipitate appeared that was extracted with EtOAc, dried (MgSO4), filtered and concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.539 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 26 mg, 0.65 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF was added dropwise and the mixture was stirred at rt for 1hr. Since no activated acid was observed a saturated solution of NH4Cl and EtOAc were added and the phases separated. The aqueous phase was further extracted with EtOAc, then the organic phases were washed with brine (2x), dried, filtered and solvent removed. The crude was purified by flash chromatography (biotage, SNAP Gold 12g) by using DCM/DCM-MeOH (5%). 128 g (59%) of title compound were thus obtained.

HPLC-MS tr = 2.37 min (88%). LRMS (m/z): 401/403

Intermediate 88: (3-methoxy-4-methoxycarbonyl-phenyl)boronic acid

To a solution of 4-borono-2-methoxy-benzoic acid (250 mg, 1.27 mmol) in 3 mL of anh. MeOH was added H2SO4 (100 uL) and the mixture was heated to reflux under nitrogen overnight.The next day the reaction is finished and the volatiles were removed under reduced pressure and water was added and extracted with AcOEt (x 3) and the combined organic extracts were washed with water and brine; dried over anh. MgSO4, filtered and evaporated to have an oil which was precipitated in Et2O to have a yellow solid which was used for the next step without further purification (225 mg, 84 %).

HPLC-MS: tr = 1.72 min. (95 %). LRMS (m/z): 211 (M+1)

^{1}H NMR (400 MHz, d6-DMSO) δ ppm 3.78 (s, 3H), 3.82 (s, 3H), 7.40 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 8.27 (s, 2H).

Intermediate 89: methyl 2-methoxy-4-(1-methylimidazol-2-yl)benzoate

To a solution of (3-methoxy-4-methoxycarbonyl-phenyl)boronic acid (Intermediate 88; 424 mg, 2.02 mmol) in 8 mL of anh. DMF was added 2-iodo-1-methyl-imidazole (350 mg, 1.68 mmol), potassium carbonate (465 mg, 3.36 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (123 mg, 0.17 mmol) under a stream of Ar. The mixture was heated at 110 ºC. After 3h 30 min. the reaction (no SM, final product is the major product). The reaction mixture was cooled down to room temperature and filtered over a pad with Celite and anh. MgSO4, washing with AcOEt. The filtrate was removed under reduced pressure to have a black residue which was purified to have via flash chromatography in DCM/DCM with 5 % MeOH to have a slightly brown oil (152 mg, 37 %).

HPLC-MS: tr = 1.33 min. (86 %). LRMS (m/z): 247 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 3.83 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 7.09 (s, 1H), 7.19 – 7.29 (m, 2H), 7.38 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H).

Intermediate 90: 2-methoxy-4-(1-methylimidazol-2-yl)benzoic acid

To a solution of methyl 2-methoxy-4-(1-methylimidazol-2-yl)benzoate (Intermediate 89; 145 mg, 0.59 mmol) in 1.2 mL of THF anf 0.6 mL of water was added LiOH·H2O (74 mg, 1.76 mmol) and the solution was stirred at room temperature for all the night. The next day the reaction is finished and the volatiles were removed under reduced pressure. More water was added and the solution was acidified with HCl 1N to pH 3-4, extracted with AcOEt (x 3), but the product was in the aqueous phase (organic phase free of final product) which was removed under reduced pressure to have a white solid (256 mg, overweight). Assuming that the final solid has salts from the work-up.

HPLC-MS: tr = 0.87 min. (98 %). LRMS (m/z): 233 (M+1)

Intermediate 91: 6-chloro-4-[[2-methoxy-4-(1-methylimidazol-2-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-4-(1-methylimidazol-2-yl)benzoic acid (Intermediate 90; 130 mg, 0.56 mmol) and HATU (307 mg, 0.80 mmol) in DMF (2 ml) was added DIPEA (141 µL, 0.8 mmol) and the mixture was stirred at room temperature for 60 min (yellow clear solution). After 60 min, HPLC-MS showed the total conversion of imidazolyl derivative. Water was added but a precipitate did not appear (clear solution). AcOEt was added and phases separated. The organic extract were dried over anh. MgSO4 and evaporated to have a DMF solution (1.5

mL) of the activated acid. In a 10 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 50 mg, 0.27 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 32 mg, 0.8 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (1.5 mL) was added dropwise and the mixture was stirred at rt. After 2h the major product is the final product but starting material and activated acid are present. The mixture was stirred for all the night. The next day the proportion of final product is 60 % and starting material is 40 %. Activated acid is not present. Sat. NH4Cl solution is added followed by AcOEt. Water was added improving the solubility of the aqueous phase. The aqueous phase was extracted again with AcOEt. The combined organic extracts were washed with water and brine and a white precipitate did appear in the aqueous fraction. The aqueous phase was filtered to have a white solid (tr = 1.78 min, 99 %, 400/402 m/z). The organic phase was removed under reduced pressure and MeOH was added over the crude and a white solid precipitates, which was filtered off (tr = 1.80 min., 99 %, 400/402 m/z), the mother liquor was 18 % of final product. Both solids were dried under vacuum for all the night (28 mg, 26 %).

HPLC-MS: tr = 1.80 min. (99 %). LRMS (m/z): 400/402 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) □ ppm 2.85 (d, J = 4.3 Hz, 3H), 3.85 (s, 3H), 4.12 (s, 3H), 7.06 (d, J = 9.3 Hz, 1H), 7.35 (s, 1H), 7.45 – 7.50 (m, 1H), 7.53 (s, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.63 (s, 1H), 8.74 (s, 1H), 8.94 (s, 1H), 12.45 (s, 1H).

Intermediate 92: methyl 1-(2-trimethylsilylethoxymethyl)indazole-6-carboxylate and methyl 2-(2-trimethylsilylethoxymethyl)indazole-6-carboxylate

To a suspension of methyl 1H-indole-6-carboxylate (500 mg, 2.84 mmol) and K2CO3 (981 mg, 7.1 mmol) in DMF (8 ml) was added SEMCl (754 µL, 4.3 mmol) and the mixture was stirred at rt. For 1.5 hr. Water and EtOAc were added, phases separated and the organic phase was further washed with brine (2x), dried, filtered and solvent removed. The residue was purified by flash chromatography (Biotage, SNAP 40g) by using hexane/DCM from 50 to 100% then DCM-MeOH (1%) 100% and finally DCM-MeOH (2%). Two fractions corresponding to two regioisomers were isolated:

Fraction 1: 181 mg as a yellow oil

HPLC-MS tr = 3.42 min (92%). LRMS (m/z): 307

^{1}H NMR (400 MHz, CDCl3) δ ppm -0.07 (s, 9H), 0.86-0.91 (m, 2H), 3.53-3.58 (m, 2H), 3.97 (s, 3), 5.80 (s, 2H), 7.78 (dd, J= 8.5 and 0.8 Hz, 1H), 7.87 (dd, J = 8.5 and 1.3 Hz, 1H), 8.07 (d, J = 1 Hz, 1H), 8.34 (q, J = 1 Hz, 1H).

Fraction 2: 170 mg as a yellow oil

HPLC-MS tr = 3.28 min (86%). LRMS (m/z): 307

^{1}H NMR (400 MHz, CDCl3) δ ppm -0.03 (s, 9H), 0.92-0.97 (m, 2H), 3.62-3.97 (m, 2H), 3.96 (s, 3H), 5.76 (s, 2H), 7.73 (s, 2H), 8.15 (s, 1H), 8.53 (s, 1H).

Both fractions were mixed and used in the next synthetic step.

Intermediate 93: 1-(2-trimethylsilylethoxymethyl)indazole-6-carboxylic acid and 2-(2-trimethylsilylethoxymethyl)indazole-6-carboxylic acid

To a solution of methyl 1-(2-trimethylsilylethoxymethyl)indazole-6-carboxylate and methyl 2-(2-trimethylsilylethoxymethyl)indazole-6-carboxylate (Intermediate 92; 345 mg, 1.126 mmol) in MeOH (8 ml) was added a solution of NaOH (90 mg, 2.25 mmol) in H2O (2 ml) and the mixture was stirred at rt overnight. MeOH was removed and more water was added. The pH was adjusted to 3-4 by the addition of 1N HCl. The product was extracted with EtOAc (2x), the organic phases were dried, filtered and solvent removed to yield a yellow oil (241 mg) that solidifies overtime. The crude containing two regioisomers was used in the next step without further purification.

HPLC-MS tr = 2.83 min (55%); 2.93' (40%). LRMS (m/z): +293 (M+1)

Intermediate 94: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)indazole-6-carboxamide and N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-2-(2-trimethylsilylethoxymethyl)indazole-6-carboxamide

To a solution of 1-(2-trimethylsilylethoxymethyl)indazole-6-carboxylic acid and 2-(2-trimethylsilylethoxymethyl)indazole-6-carboxylic acid (Intermediate 93; 236 mg, 0.807 mmol) in DMF (5 ml) was added HATU (307 mg, 0.807 mmol) and DIPEA (141 µL, 0.809 mmol) and the mixture was stirred at room temperature for 60 min. Water was added and a precipitate appeared that was filtered off and taken up in EtOAc, dried (MgSO4), filtered and solvent removed. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.539 mmol) in DMF (3 ml) at 0ºC and NaH (60%, 43 mg, 1.07 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF was added dropwise and the mixture was stirred at rt. After 2h there

was no evolution so water and EtOAc were added and phases separated. The aqueous phase was further extracted with EtOAc, then the organic phases were washed with brine (2x), dried, filtered and solvent removed. The crude was purified by flash chromatography (Biotage, SNAP 12g) using DCM/DCM-MeOH (2%). 203 mg of a regioisomeric mixture were obtained HPLC-MS tr = 3.43 min and 3.55 min (50% and 42%). LRMS (m/z): 460/462 (M+1, 1Cl)

Intermediate 95: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)indazole-6-carboxamide and N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-2-(2-trimethylsilylethoxymethyl)indazole-6-carboxamide

The mixture of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-1 and 2-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide (Intermediate 94; 70 mg, 0.152 mmol), 2,6-dimethylpyrimidin-4-amine (23 mg, 0.186 mmol), Pd2(dba)3 (14 mg, 0.015 mmol), Xantphos (18 mg, 0.031 mmol) and cesium carbonate (119 mg, 0.365 mmol) were heated in dioxane (5 mL) at 100ºC for 2 hr. Since no SM was detected the reaction was cooled down and filtered. The residue obtained after concentration was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (5%). 93 mg of a regioisomeric mixture were obtained as a yellow solid.

HPLC-MS tr = 2.50 min (99%) LRMS (m/z): 547 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm -0.12 and -0.05 (s 9H), 0.83 and 0.87 (t J=8 Hz 2H), 2.33 and 2.52 (s 6H), 2.84 and 2.85 (d J=4.5 Hz 3H), 3.56 and 3.64 (t J=8 Hz 2H), 5.80 and 5.87 (s 2H), 7.38 and 7.41 (s 1H), 7.64 and 7.74 (m 1H), 7.96 and 8.03 (m 1H), 8.31 (m 1H), 8.75 (s 1H), 8.88 (s 1H), 9.24 and 9.27 (s 1H), 10.36 and 10.39 (s 1H), 13.21 and 13.23 (s 1H)

Intermediate 96: 6-chloro-4-[(6-fluoro-2,3-dimethoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-fluoro-2,3-dimethoxy-benzoic acid (147mg, 0.73mmol) and HATU (279mg, 0.73mmol) in DMF (1mL) was added DIPEA (128uL, 0.73mmol) and the mixture was stirred at room temperature for 1h. Excess water was added and the mixture extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. 2-amino-4-chloro-N-methyl-benzamide (Preparation 3; 68mg, 0.37mmol) was solved in DMF (0.5mL) and cooled at 0ºC. Then NaH (60%, 44mg, 1.10mmol) was added and the mixture stirred for 30min at room temperature. The system was again cooled at 0ºC and the activated acid was

added dropwise solved in DMF (1mL) and stirred at room temperature for 1 hr. Water was added and extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos12g) using hexane/diethyl ether (220nm) to give the title compound (115mg, 85%) as a white solid.

HPLC/MS tr = 2.70min (99%). LRMS: m/z 368,370 M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.98 – 3.02 (m, 3H), 3.87 (s, 3H), 3.95 (s, 3H), 6.35 (s, 1H), 6.86 (t, J = 9.5 Hz, 1H), 6.91 – 7.02 (m, 1H), 8.48 (s, 1H), 8.87 (s, 1H), 11.75 (s, 1H).

Intermediate 97: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[(4-methoxy-6-methyl-pyrimidin-2-yl)amino]-N-methyl-pyridine-3-carboxamide

In a closed pressure tube, a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 80 mg, 0.23 mmol), 4-methoxy-6-methyl-pyrimidin-2-amine (40 mg, 0.28 mmol), and K2CO3 (100 nmg, 0.72 mmol) in 2.5 mL anh. dioxane was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (25 mg, 0.027 mmol) and 9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine (30 mg, 0.052 mmol) were added and the mixture was degassed again and heated at 140 ºC overnight. uPLC-control showed the formation of the desired compound as a minor product. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated to afford 102 mg of crude. This crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH from 0% to 5% in 40 CV. Collection of the fractions containing the product yielded 8mg (7%).

HPLC/MS tr = 1.54min (90%). LRMS: m/z 441 M+1)

Intermediate 98: 6-chloro-4-[(2-methoxy-6-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-6-methyl-benzoic acid (122mg, 0.73mmol) and HATU (279mg, 0.73mmol) in DMF (1mL) was added DIPEA (128uL, 0.73mmol) and the mixture was stirred at room temperature for 1 hr. Excess water was added and the mixture was extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. 2-amino-4-chloro-N-methyl-benzamide (Preparation 3; 68mg, 0.37mmol) was solved in DMF (0.5mL) and cooled at 0ºC. Then NaH (60%, 44mg, 1.10mmol) was added and stirred for 30min at room temperature. Again cooled at 0ºC and activated acid was added dropwise solved

in DMF (1mL) and stirred at room temperature for 1 hr. Water was added and the mixture was extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. The resulting residue was purified by flash chromatography (Biotage Telos12g) using hexane/diethyl ether (220nm) to give the title compound (117mg, 96%) as a white solid.

HPLC/MS tr = 2.77min (98%). LRMS (m/z): 334,336 M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.38 (s, 3H), 2.98 (d, J = 4.8 Hz, 3H), 3.84 (s, 3H), 6.39 (s, 1H), 6.82 (dd, J = 14.1, 8.0 Hz, 1H), 7.23 – 7.31 (m, 1H), 8.47 (s, 1H), 8.90 (s, 1H), 11.48 (s, 1H).

Intermediate 99: 6-chloro-4-[[2-methoxy-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-4-(trifluoromethyl)benzoic acid (161mg, 0.73mmol) and HATU (279mg, 0.73mmol) in DMF (1mL) was added DIPEA (128uL, 0.73mmol) and the mixture was stirred at room temperature for 1 hr. Excess water was added and the mixture was extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. 2-amino-4-chloro-N-methyl-benzamide (Preparation 3; 68mg, 0.37mmol) was solved in DMF (0.5mL) and cooled at 0ºC. Then NaH (60%, 44mg, 1.10mmol) was added and the system was stirred for 30min at room temperature. Again cooled at 0ºC and activated acid was added dropwise solved in DMF (1mL) and stirred at room temperature for 1 hr. Excess water was added and the mixture was extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. The resulting crude was purified by flash chromatography (Biotage Telos12g) using hexane/diethyl ether (220nm) to give the title compound (112mg, 79%) as a white solid.

HPLC/MS tr =3.18 min 99%). LRMS (m/z: 388,390 M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.99 – 3.14 (m, 3H), 4.18 (s, 3H), 6.24 (s, 1H), 7.25 – 7.26 (m, 1H), 7.36 (d, J = 9.0 Hz, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.46 (s, 1H), 8.87 (s, 1H), 12.29 (s, 1H).

Intermediate 100: 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 2-methoxy-3-methyl-benzoic acid (200 mg, 1.2 mmol) and HATU (460 mg, 1.2 mmol) in DMF (2 ml) was added DIPEA (210 µL, 1.2 mmol) and the mixture was stirred

at room temperature for 1h. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAC, then the organic phases were washed with brine (3x), dried (MgSO4), filtered and solvent removed. In another vial there was placed 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 150 mg, 0.804 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 65 mg, 1.6 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling to 0ºC again the activated acid in 2 ml DMF was added dropwise and the mixture was stirred at 0ºC for 30 min. Excess water and EtOAc were added and phases separated. The aqueous phase was further extracted with EtOAc, then the organic phases were washed with brine (2x), dried, filtered and the solvent was removed. The crude was treated with diethylether and the suspension was filtered, the solid was washed with more Et2O. The filtrate also contained some final product but was discarded. 225 mg (84%) of title compound were obtained.

HPLC-MS tr = 3.02 min (97%). LRMS (m/z): 335/337 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), 2.84 (d, J = 4.8 Hz, 3H), 3.76 (s, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 8.98 (s, 1H), 9.48-9.51 (m, 1H), 13.0 (s, 1H).

Intermediate 101: methyl 1-(2-trimethylsilylethoxymethyl)indole-5-carboxylate

To a solution of methyl 1H-indole-5-carboxylate (200 mg, 1.14 mmol) in 3.8 mL of DMF at 0 ºC was added sodium hydride (60%, 50 mg, 1,25 mmol) and the mixture was stirred 15 min. at 0 ºC and 15 min. at room temperature. The temperature was lowered again to 0 ºC and 2-(chloromethoxy)ethyl-trimethyl-silane (0.25 mL,1.41 mmol) was added dropwise and left stirring at room temperature overnight. The reaction was quenched with ammonium chloride and extracted with AcOEt, washed with brine, dried with MgSO4, filtered and concentrated. Flash chromatography (hexanes to 30% AcOEt in hexanes gradient) gave a colorless oil (220 mg 63%).

HPLC-MS: tr = 3.55 min. LRMS (m/z): 306 (M+1).

^{1}H NMR (400 MHz, CDCl3) δ ppm 8.39 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.23 (s, 1H), 6.62 (s, 1H), 5.50 (s, 2H), 3.93 (s, 3H), 3.51 – 3.42 (m, 2H), 0.92 – 0.83 (m, 2H), -0.08 (s, 9H).

Intermediate 102: 1-(2-trimethylsilylethoxymethyl)indole-5-carboxylic acid

220 mg (0.72 mmol) of methyl 1-(2-trimethylsilylethoxymethyl)indole-5-carboxylate (Intermediate 101) were dissolved in THF (3.6 mL) and water (0.6mL), and LiOH monohydrate (91mg) were added. The reaction was stirred 60 h at 66 ºC. The mixture was diluted with excess water and acidified to pH 4, the aqueous phase was extracted with AcOEt. The organic phases were dried, filtered and concentrated in vacuum. The white solid (209 mg, quantitative yield) was used in the next step without further purification.

HPLC-MS: tr = 3.07 min (100%). LRMS (m/z): 292 (M+1).

Intermediate 103: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)indole-5-carboxamide

To a solution of 1-(2-trimethylsilylethoxymethyl)indole-5-carboxylic acid (Intermediate 102; 209 mg, 0.72 mmol) and HATU (545 mg, 1.43 mmol) in DMF (4 ml) was added DIPEA (0.38 mL, 2.15 mmol) and the mixture was stirred at room temperature for 60 min. Water was added and a precipitate appeared that was filtered off and taken up in EtOAc, dried (MgSO4), filtered and solvent removed. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 70 mg, 0.377 mmol) in DMF (2 ml) at 0ºC, NaH (60%, 45 mg, 1.13 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling again to 0ºC the activated acid in DMF (0.4 mL) was added dropwise and the mixture was stirred at rt. Overnight. The reaction was quenched with NH4Cl and extracted with AcOEt. The organic phase was washed with brine, dried over magnesium sulphate, filtered and concentrated. The crude was purified by flash chromatography (100% DCM to 5 % MeOH in DCM gradient) to obtain an oil. The oil has DMF, so it was treated with water/AcOEt. The organic phase was dried and concentrated to afford a white solid (308 mg 93%).

HPLC-MS tr = 3.65 min. LRMS (m/z): 459/461 (M+1, Cl)

Intermediate 104: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)indole-5-carboxamide

A solution of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)indole-5-carboxamide (Intermediate 103; 308 mg, 0.67 mmol), 2,6-dimethylpyrimidin-4-amine (132 mg, 1.07 mmol), Pd2(dba)3 (66 mg, 0.072 mmol), Xantphos (82.5 mg, 0.14 mmol) and cesium carbonate (697 mg, 2.14 mmol) was heated in dioxane (7 mL) at 100 ºC for 4 hr. The mixture was diluted with excess water and extracted with AcOEt. The organic phase was washed with brine, dried, filtered and concentrated. The

crude was purified by flash chromatography (telos 12g, gradient up to 10% methanol in DCM). The title compound was obtained as a yellowish solid (195 mg 53%).

HPLC-MS tr = 2.68 min (93%). LRMS (m/z): 546 (M+1)

Intermediate 105: 6-chloro-4-[(3-chloro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 3-chloro-2-methoxy-benzoic acid (201 mg, 1.08 mmol) and HATU (615 mg, 1.61 mmol) in DMF (2.2 mL) was added DIPEA (0.28 mL) and the mixture was stirred at room temperature for 60 min. Water was added and a precipitate appeared that was filtered off and taken up in EtOAc, dried (MgSO4), filtered and solvent removed. In another vial 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.54 mmol) was dissolved in DMF (4 ml), cooled at 0ºC, NaH (60%, 65 mg, 1.63 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling again to 0ºC the activated acid in DMF (4.2 mL) was added dropwise and the mixture was stirred at rt overnight. The reaction was quenched with NH4Cl and extracted with AcOEt. The organic phase was washed with brine, dried over magnesium sulphate, filtered and concentrated. The crude was purified by precipitation, due to the low solubility, to get 156 mg (81%) of a white/yellowish solid.

HPLC-MS tr = 2.95 min (99%). LRMS (m/z): 354/356/358 (M+1, 2Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.39 (s, 1H), 8.98 (s, 1H), 8.68 (s, 1H), 8.65 (d, J = 3.0 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 3.86 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H)

Intermediate 106: 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-amino-6-chloro-N-(trideuteriomethyl)pyridine-3-carboxamide (Preparation 4; 150 mg, 0795 mmol) in 5mL of anh. DMF was cooled at 0ºC and sodium hydride was added. The mixture was stirred at room temperature for 30 min. Then, the temperature was lowered to 0 ºC and a solution of 2-fluoro-4-methoxy-benzoyl chloride in 1 mL of anh. DMF was added dropwise and the reaction was left to stir overnight at room temperature. Water was added (200 ml) followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 3). The combined organic extracts were washed with water (x 3), and brine, dried over anh. MgSO4, filtered and evaporated. The residue was treated with Et2O and the solid was filtered and washed with Et2O to give the title compound (121 mg, 36%) as an off- white solid.

HPLC-MS tr = 1.47 min (82%). LRMS (m/z): 340/341 (M+1, Cl)

^{1}H NMR (400 MHz, CD3OD) δ ppm 3.91 (s 3H), 6.83 (m 2H), 6.98 (d J=8 Hz 1H), 7.5 (m 1H), 8.63 (s 1H), 8.72 (s 1H)

Intermediate 107: methyl 6-chloro-4-[(4-methoxyphenyl)methylamino]pyridine-3-carboxylate

Methyl 4,6-dichloropyridine-3-carboxylate (2g, 9.70mmol) was solved in DMF (25mL) and (4-methoxyphenyl)methanamine (1.4mL, 10.71mmol) and triethylamine (4mL, 28.70mmol) were added and stirred at room temperature overnight. Excess water was added and the mixture was extracted with AcOEt (x2). The organic phase was washed with water and brine. The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos40g) using hexane/AcOEt (up to 10%) (254nm) to give the title compound (2.36g, 79%) as a white solid.

HPLC/MS tr = 3.08 min (100%). LRMS (m/z): 307/309 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.81 (s, 3H), 3.88 (s, 3H), 4.35 (d, J = 5.4 Hz, 2H), 6.56 (s, 1H), 6.88 – 6.94 (m, 2H), 7.21 – 7.26 (m, 2H), 8.35 – 8.49 (m, 1H), 8.68 (s, 1H)

Intrermediate 108: methyl 4-amino-6-chloro-pyridine-3-carboxylate

A solution of methyl 6-chloro-4-[(4-methoxyphenyl)methylamino]pyridine-3-carboxylate (Intermediate 107; 2.36g, 7.69mmol) in TFA (16mL) was heated at 50ºC for 22 hr. The solvent was evaporated and saturated solution of NaHCO3 was added and the mixture extracted with AcOEt (x2). The organic phase was washed with water. The organic phase was dried over MgSO4, filtered and evaporated to dryness. The residue was solved in AcOEt and washed with aqueous Na2CO3 (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. 2.10 g of title compound were obtained (overweight). The crude was purified by flash chromatography (Biotage Telos80g) using hexane/DCM (224nm) to give the title compound (1.14g, 79%) as a pale yellow solid.

HPLC/MS tr = 1.90 min (98%). LRMS (m/z): 187,189 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.90 (s, 3H), 6.57 (s, 1H), 8.69 (s, 1H)

Intermediate 109: methyl 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxylate

To a solution of 2-fluoro-6-methoxy-benzoic acid (182 mg, 1.07 mmol) and HATU (611 mg, 1.61 mmol) in DMF (2 ml) was added DIPEA (0.3 mL, 1.72 mmol) and the mixture was stirred at room temperature for 60 min.Water was added and a precipitate appeared that was filtered off and taken up in EtOAc, dried (MgSO4), filtered and solvent removed. In another vial was placed 4-amino-6-chloro-pyridine-3-carboxylate (Intermediate 108; 10 mg, 0.054 mmol) in DMF (0.4 ml) at 0ºC, NaH (60%, 7 mg, 0.175 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (0.4 mL) was added dropwise and the mixture was stirred at rt. for 30 min. The reaction was then quenched with NH4Cl and extracted with AcOEt. The organic phase was washed with brine, dried over magnesium sulphate, filtered and concentrated. The crude was purified by flash chromatography (100% DCM to 1 % MeOH in DCM gradient) to obtain 108 mg (58%) a white solid.

HPLC/MS tr = 3.08 min (100%). LRMS (m/z): 339,341 (M+1, Cl)

Intermediate 110: Methyl 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxylate

A solution of methyl 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxylate (Intermediate 109; 108 mg, 0.318 mmol), 2,6-dimethylpyrimidin-4-amine (59 mg, 0.479 mmol), Pd2(dba)3 (29 mg, 0.10 mmol), Xantphos (37 mg, 0.2 mmol) and cesium carbonate (312 mg, 0,96 mmol) was heated in dioxane (3,2 mL) at 100 ºC. The reaction was quenched with water after 3 h, extracted with AcOEt, washed with brine and dried over MgSO4. The crude was purified by flash chromatography (100% DCM to 5 % MeOH in DCM gradient) to obtain a yellowish solid (96 mg 71%).

HPLC-MS tr = 2.17 min (100%). LRMS (m/z): 426 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.39 (s, 1H), 10.56 (s, 1H), 9.31 (s, 1H), 8.84 (s, 1H), 7.55 (td, J = 8.5, 7.0 Hz, 1H), 7.33 (s, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.97 (t, J = 8.9 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.34 (s, 3H)

Intermediate 111: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxylic acid

methyl 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxylate (Intermediate 110; 158 mg, 0.37 mmol) was suspended in THF (1.9 mL) and water (0.33 mL) and LiOH monohydrate (47 mg, 1.12 mmol) was added.

The reaction was stirred overnight at room temperature. The HPLC-MS showed total conversion to the product. The mixture was acidified and extracted with AcOEt, but the carboxylic acid is too polar and remains in the aqueous phase. The aqueous phase was concentrated and the solid was filtered and washed with methanol. The methanolic filtrates were concentrated and purified by flash chromatography (reverse phase, water 0.1% formic acid to acetonitrile 0.1% formic acid) to get a white solid (31 mg, 20%).

HPLC-MS tr = 1.80 min (100%). LRMS (m/z) 412 (M+1)

Intermediate 112: 6-chloro-4-[(2-methoxy-4-nitro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-4-nitro-benzoic acid (122mg, 0.73mmol) and HATU (144mg, 0.73mmol) in DMF (1mL) was added DIPEA (128uL, 0.73mmol) and the mixture was stirred at room temperature for 90 min. Excess water was added and the mixture was extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. 2-amino-4-chloro-N-methyl-benzamide (Preparation 3; 68mg, 0.37mmol) was solved in DMF (0.5mL) and cooled at 0ºC. Then NaH (60%, 44mg, 1.10mmol) was added and the mixture was stirred for 30min at room temperature. After cooling again at 0ºC the activated acid was added dropwise solved in DMF (1mL) and stirred at room temperature for 1 hr. Excess water was added and the mixture was extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness.The crude was purified by flash chromatography (Biotage Telos12g) using DCM/methanol (up to 5%) to give the title compound (65 mg, 48%)

HPLC/MS tr = 2.88 min (100%). LRMS (m/z): 365,367 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.93 (s, 3H), 4.17 (s, 3H), 7.74 (s, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.88 (dd, J = 8.6, 2.1 Hz, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.54 (s, 1H), 8.79 (s, 1H), 12.48 (s, 1H)

Intermediate 113: 4-[(4-amino-2-methoxy-benzoyl)amino]-6-chloro-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-methoxy-4-nitro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 112; 60mg, 0.16mmol), iron (6mg, 0.82mmol) and ammonium chloride (9mg, 0.17mmol) were heated in EtOH/THF/water (0.9mL, 4:4:1) at 80ºC for 2 hr. The mixture was

filtered and washed with EtOH, then evaporated. The solid was washed with water and filtered. The precipitate was dried in oven overnight (45 mg, 82%) as a white solid.

HPLC/MS tr = 2.23 min (100%). LRMS (m/z): 335,337 (M+1, Cl)

Intermediate 114: 6-chloro-4-[[4-(methanesulphonamido)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(4-amino-2-methoxy-benzoyl)amino]-6-chloro-N-methyl-pyridine-3-carboxamide (Intermediate 113; 43mg, 0.13mmol) was solved in pyridine (2mL) and methanesulfonyl chloride (13uL, 0.17mmol) was added and stirred under N2 at room temperature for 3.5 hr. HPLC analysis shows around 10% of title compound and 90% os starting material. Additional 1.3 equivalents of methanesulphonyl chloride were added and stirring was prosecuted for 18 h at rt. As the amount of final compound is still around 20% 10 additional equivalents of mesyl chloride were added and the mixture stirred for 4 h (HPLC analysis shows ca 90% conversion). The solvent was evaporated and water and sodium bicarbonate were added and the mixture was extracted with DCM (x4). The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos12g) using Et2O/MeOH (up to 5%) (225nm) to give the title compound (26mg, 49%) as a white solid.

HPLC/MS tr = 2.33 min (96%). LRMS (m/z): 413,415 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.92 (d, J = 4.7 Hz, 3H), 2.98 (s, 3H), 4.05 (s, 3H), 6.88 (dd, J = 8.6, 2.0 Hz, 1H), 6.99 (d, J = 1.9 Hz, 1H), 7.58 (d, J = 6.3 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 8.46 (s, 1H), 8.80 (s, 1H), 9.65 (s, 1H), 12.16 (s, 1H)

Intermediate 115: 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-amino-6-chloro-N-(trideuteriomethyl)pyridine-3-carboxamide (Preparation 4; 100 mg, 0.53 mmol) was solved in 4mL of anh. DMF. After cooling at 0ºC 60% sodium hydride (25 mg, 1.04 mmol) was added. The mixture was stirred at room temperature for 30 min. After lowering again the temperature to 0 ºC a solution of 2-fluoro-4-methoxy-benzoyl chloride in 1 mL of anh. DMF was added dropwise and the reaction was left to stir overnight at room temperature. Water was added (200 ml) followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 3). The combined organic extracts were washed with water (x 3), and brine, dried over anh. MgSO4, filtered and evaporated. The resulting white solid was

treated with Et2O (15 mL) and the solid was filtered and washed with Et2O to give the title compound (78 mg, 70% purity) as an off- white solid. The compound was used per se in the next synthetic step.

HPLC/MS tr = 1.55 MIN (70%). LRMS (m/z): 353,355 (M+1, Cl)

Intermediate 116: 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-amino-6-chloro-N-(trideuteriomethyl)pyridine-3-carboxamide (Preparation 4; 100 mg, 0.53 mmol) was solved in 4mL of anh. DMF. After cooling at 0ºC 60% sodium hydride (25 mg, 1.04 mmol) was added. The mixture was stirred at room temperature for 30 min. After lowering again the temperature to 0 ºC a solution of 2-fluoro-4-methoxy-benzoyl chloride in 1 mL of anh. DMF was added dropwise and the reaction was left to stir overnight at room temperature. Water was added (200 ml) followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 3). The combined organic extracts were washed with water (x 3), and brine, dried over anh. MgSO4, filtered and evaporated. The white solid residue was treated with Et2O (15 mL) and the solid was filtered and washed with Et2O (x 1), to give the title compound (59 mg, 85% purity) as an off- white solid.

HPLC/MS Tr = 1.65 min (70%). LRMS (m/z): 337,339 (M+1, Cl)

Intermediate 117: 6-chloro-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-6-methyl-benzoic acid (122mg, 0.73mmol) and HATU (279mg, 0.73mmol) in DMF (1mL) was added DIPEA (128uL, 0.73mmol) and the mixture was stirred at room temperature for 1 hr. Excess water was added and the mixture was extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. 2-amino-4-chloro-N-methyl-benzamide (Preparation 3, 68mg, 0.37mmol) was solved in DMF (0.5mL) and cooled at 0ºC. 60% NaH (44mg, 1.10mmol) was added and stirred for 30min at room temperature. After cooling again at 0ºC activated acid was added dropwise solved in DMF (1mL) and stirred at room temperature for 1 hr. Water was added and the mixture was extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos12g) using hexane/diethyl ether (220nm) to give the title compound (100mg, 81%) as a white solid.

HPLC/MS tr = 2.82 min (99%). LRMS (m/z): 338,340 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.82 (d, J = 4.6 Hz, 3H), 4.07 (s, 3H), 7.23 – 7.30 (m, 1H), 7.54 – 7.61 (m, 1H), 7.73 – 7.77 (m, 1H), 8.67 (s, 2H), 8.94 – 9.03 (m, 1H), 12.32 (s, 1H)

Intermediate 118: 2-methyl-6-morpholino-pyrimidin-4-amine

A suspension of 6-chloro-2-methyl-pyrimidin-4-amine (250 mg, 1.74 mmol) and morpholine (300 uL, 3.48 mmol) in 2.5 mL of toluene was heated to 115ºC overnight. A crystalline solid that was filttered-off and dried in the oven affording 455 mg of title compound (overweight) that was used per se in the next step.

HPLC/MS tr = 0.52 min (100%). LRMS (m/z): 195 (M+1)

Intermediate 119: 2-[4-(6-amino-2-methyl-pyrimidin-4-yl)piperazin-1-yl]ethanol

A suspension of 6-chloro-2-methyl-pyrimidin-4-amine (250 mg, 1.74 mmol) and 2-piperazin-1-ylethanol (430 uL, 3.50 mmol) in 2.8 mL of toluene was heated to 115ºC overnight. A crystalline solid that was filtered-off and dried in the oven affording 561 mg of title compound (overweight) that was used per se in the next step.

HPLC/MS tr = 0.20 min (100%). LRMS (m/z): 238 (M+1)

Intermediate 120: 2,2-dimethyl-4-(6-nitro-3-pyridyl)morpholine

A mixture of 5-bromo-2-nitropyridine (600 mg, 295 mmol), 2,2-dimethylmorpholine hydrochloride (500 mg, 329 mmol), 3.1 ml (17.8 mmol) of diisopropylethyl amine and 5 mL of DMF were stirred at 90ºC for three days. 200 ml of water were added and the mixture is extracted (x3) with EtOAc. The organic phase was dried with magnesium sulphate, filtered and concentrated. The residue was purified by flash chromatography (Biotage) using DCM to DCM/methanol 5% to give the title compound (346 mg, 50%) as a red low melting point solid.

HPLC/MS tr = 1.17 min (95%). LRMS (m/z): 238 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 8.17 (d, J = 9.1 Hz, 1H), 8.10 (d, J = 3.0 Hz, 1H), 7.17 (dd, J = 9.2, 3.1 Hz, 1H), 3.96 – 3.87 (m, 2H), 3.41 (dd, J = 5.9, 4.3 Hz, 2H), 3.25 (s, 2H), 1.33 (s, 6H)

Intermediate 121: 5-(2,2-dimethylmorpholin-4-yl)pyridin-2-amine

A mixture of 2,2-dimethyl-4-(6-nitro-3-pyridyl)morpholine (Intermediate 120; 346 mg, 1.45 mmol) and palladium 10% on charcoal (160 mg, 0.15 mmol) in 20 ml of methanol was

hydrogenated at 10 Psi at room temperature for 5 hr. After filtering the catalyst and concentrating the title compound (301 mg) was obtained as a yellowish solid and used per se in the next synthetic step.

HPLC/MS tr = 0.66 min (63%). LRMS (m/z): 208 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.58 (d, J = 2.8 Hz, 1H), 7.14 (dd, J = 8.8, 3.0 Hz, 1H), 6.40 (d, J = 8.9 Hz, 1H), 5.40 (s, 2H), 3.71 (dd, J = 5.7, 4.2 Hz, 2H), 2.87 – 2.77 (m, 2H), 2.69 (s, 2H), 1.22 (s, 6H)

Intermediate 122: 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 70 mg, 0.375 mmol) in 1 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 30 mg, 0.750 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. Then, the temperature was lowered to 0 ºC and a solution of 2-chloro-6-fluoro-benzoyl chloride (75 µL, 0.568 mmol) was added dropwise and the reaction was left to stir at 0ºC for 30 min and 1 h at rt. Excess water was added followed by Et_2O. The phases were separated and the aqueous was extracted with Et2O (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated. The final orange oil was purified via flash chromatography (BIotage, SNAP 12g) using Hexane/Hexane-EtOAc (1-1) to obtain a white solid (50 mg, 39 %).

HPLC-MS tr = 3.02 min . LRMS (m/z): 343/345 (2Cl)

^{1}H-NMR (CDCl3, 400 MHz) δ ppm 3.02 (d, J = 5 Hz, 3H), 7.13 (td, J = 8.7 and 1 Hz, 1H), 7.29 (dt, J = 8 and 1 Hz, 1H), 7.41 (td, J = 8 and 6 Hz, 1H), 8.42 (br s, 1H), 9.06 (s, 1H), 12.70 (br s, 1H)

Intermediate 123: 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-cyclopropyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-cyclopropyl-pyridine-3-carboxamide (Preparation 8; 83 mg, 0.392 mmol) in 2 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 20 mg, 0.833 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. Then, the temperature was lowered to 0 ºC and a solution of 2-chloro-6-fluoro-benzoyl chloride (78 µL, 0.595 mmol) was added dropwise and the reaction was left to stir at 0ºC for 10 min. and 30 min at rt. Escess water was added followed by Et2O. The phases were separated

and the aqueous was extracted with Et2O (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated. The final yellow oil was purified via flash chromatography (Biotage, SNAP 12g) using DCM/DCM-MeOH (2%) to obtain a clear oil (79 mg 38%).

HPLC-MS tr = 3.03 min (70%). LRMS (m/z): 368/370 (2Cl)

Intermediate 124: 6-chloro-4-[(2-chloro-6-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 120 mg, 0.64 mmol) in 3 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 51 mg, 1.27 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (orange solution). The temperature was lowered to 0 ºC and a solution of 2-chloro-6-methoxy-benzoyl chloride (145 mg, 0.71 mmol) in 1 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature overnight. Excess water was added and the mixture was extracted with AcOEt (x 2). Organic phase was washed with LiCl 5 % and brine, dried over anh. MgSO4, filtered and evaporated to have a grey solid which was purified via flash chromatography in Hx/AcOEt to have a white solid (141 mg, 62 %).

HPLC-MS: tr =2.98 min. (90 %). LRMS (m/z): 355/357 (M+1, 2 Cl)

^{1}H NMR (400 MHz, Chloroform-d) δ ppm 3.02 (d, J = 5.1 Hz, 3H), 3.85 (s, 3H), 6.89 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 7.34 (t, J = 8.3 Hz, 1H), 8.37 (s, 1H), 9.11 (s, 1H), 12.40 (s, 1H).

Intermediate 125: 2-(4-nitropyrazol-1-yl)ethanol

To a solution of 4-nitro-1H-pyrazole (1000 mg, 8.84 mmol) in 8 mL of acetonitrile were added 2-bromoethanol (628 uL, 8.85 mmol) and potassium carbonate (1467 mg, 10.61 mmol) and stirred to 82 ºC overnight. The mixture was cooled down to room temperature and was filtered and washed with AcOEt. The filtrate was removed under reduced pressure to have a white solid as the title compound (1350 mg, 97 %).

HPLC-MS: tr = 1.23 min. (95 %). LRMS (m/z): 158 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.76 (q, J = 5.0 Hz, 2H), 4.20 – 4.23 (m, 2H), 4.94 – 5.02 (m, 1H), 8.26 (s, 1H), 8.81 (s, 1H).

Intermediate 126: 4-nitro-1-(2-tetrahydropyran-2-yloxyethyl)pyrazole

A solution of 2-(4-nitropyrazol-1-yl)ethanol (Intermediate 125; 1350 mg, 8.59 mmol) in 14 mL of anh. THF, 3,4-dihydro-2H-pyran (1.17 mL, 12.82 mmol) and p-toluenesulfonic acid (60 mg, 0.38 mmol) was stirred at room temperature for 5 hr. The mixture was diluted with AcOEt, washed with sat. aqueous sodium carbonate and water. The organic phase was dried over MgSO4, filtered and evaporated to have a colorless oil as a crude (2200 mg, quant.) which was used for the next step without further purification.

HPLC-MS: tr = 2.42 min. (82 %). LRMS (m/z): 242 (M+1)

Intermediate 127: 1-(2-tetrahydropyran-2-yloxyethyl)pyrazol-4-amine

To a solution of 1-(2-methoxyethyl)-4-nitro-pyrazole (Intermediate 126; 2200 mg, 9.11 mmol) in 20 mL of methanol was added palladium on carbon (291 mg, 0.273 mmol) and replaced three times with hydrogen. The mixture was stirred at room temperature overnight. The crude was filtered off over Celite and washed with MeOH several times. The filtrate was removed and purified via flash chromatography in DCM/DCM with 5 % MeOH to have a purple oil as a final product (939 mg, 49 %).

HPLC-MS: tr = 0.95 and 1.08 min. (98 %). LRMS (m/z): 212 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 1.43 – 1.57 (m, 6H), 1.61 – 1.69 (m, 1H), 1.74 – 1.83 (m, 1H), 3.43 (dt, J = 10.9, 4.7 Hz, 1H), 3.60 – 3.72 (m, 2H), 3.96 (ddd, J = 10.7, 5.9, 4.7 Hz, 1H), 4.19 (t, J = 5.8 Hz, 2H), 4.52 (t, J = 3.3 Hz, 1H), 7.12 – 7.18 (m, 1H), 7.27 (d, J = 0.8 Hz, 2H).

Intermediate 128: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[1-(2-tetrahydropyran-2-yloxyethyl)pyrazol-4-yl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 155 mg, 0.46 mmol) in 4 mL of anh. dioxane was added 1-(2-tetrahydropyran-2-yloxyethyl)pyrazol-4-amine (Intermediate 127; 146 mg, 0.69 mmol), Pd2(dba)3 (42 mg, 0.045 mmol), Xantphos (53 mg, 0.091 mmol) and cesium carbonate (449 mg, 1.38 mmol) and heated at 100 ºC. After 4 h the mixture was cooled down. Water and AcOEt were added, the phases separated and the aqueous phase extracted twice with AcOEt. The combined organic fractions were dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified via flash chromatography in AcOEt/AcOEt with 10 % MeOH to have the title product as a pink oil (52 mg, 22 %).

HPLC-MS. tr = 2.32 min. (94 %). LRMS (m /z): 513 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.44 – 1.62 (m, 4H), 1.61 – 1.72 (m, 1H), 1.73 – 1.83 (m, 1H), 2.94 (d, J = 4.6 Hz, 3H), 3.43 – 3.52 (m, 1H), 3.65 – 3.84 (m, 2H), 3.88 (s, 3H), 4.05 – 4.14 (m, 1H), 4.30 – 4.36 (m, 2H), 4.51 – 4.60 (m, 1H), 6.76 (dt, J = 8.5, 4.3 Hz, 2H), 7.31 – 7.43 (m, 1H), 7.55 (s, 1H), 7.75 (s, 1H), 8.30 (s, 1H), 8.79 (s, 1H), 12.38 (s, 1H).

Intermediate 129: 4-(bromomethyl)benzamide

To a solution of 4-(bromomethyl)benzoic acid (1000 mg, 4.65 mmol) in 15 mL of AcOEt was added thionyl chloride under Ar and the mixture was stirred at 75 ºC overnight. The solvent was removed under reduced pressure and the residue was dissolved in 15 mL of anh. DCM. The temperature was lowered to 0 ºC and NH4OH (25 % aq., 1.4 mL, 18.5 mmol) was added dropwise and the mixture was stirred at low temperature for 1h 45 minutes. The reaction is finished and water (10 mL) was added. The white precipitate was filtered off and washed with DCM and dried in the vacuum oven for two days at 45 ºC (943 mg, 95 %).

HPLC-MS: tr = 1.93 min. (99 %). LRMS (m/z): 214/216 (M+1, Br)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 4.72 (s, 2H), 7.38 (s, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.99 (s, 1H).

Intermediate 130: 4-(1,2,4-triazol-1-ylmethyl)benzamide

To a solution of 4-(bromomethyl)benzamide (Intermediate 129; 635 mg, 2.96 mmol) in 9 mL of DMF was added potassium hydroxide (666 mg, 11.87 mmol) followed by 1,2,4-triazole (205 mg, 2.97 mmol) and the mixture was stirred at room temperature overnight having added 2 mL of water to improve the solubility of KOH. The DMF and water are removed under reduced pressure. Water was added (minimum quantity) and the pH adjusted to 4-5 (first with HCl 6N, and at the end with HCl 1N) and extracted with AcOEt (x 3). The combined organic fractions were dried over anh. MgSO4, filtered and evaporated well (DMF traces) to have a white solid (356 mg, 59 %).

HPLC-MS: tr = 1.20 min. (96 %). LRMS (m/z): 203 (M+1)

Intermediate 131: tert-butyl N-(6-methyl-2-pyridyl)carbamate

A solution of 6-methylpyridin-2-amine (3000 mg, 27.74 mmol) in 200 mL of anh. THF was added tert-butoxycarbonyl tert-butyl carbonate (6.66 g, 30.5 mmol) and TEA (4.25 mL, 30.5 mmol) at 0 ºC. The reaction mixture was warmed to room temperature and added DMAP (334 mg, 2.73 mmol). After 3 h 30 min. the reaction is complete and water and AcOEt were added.

Phase separated and the organic fraction was washed with NH4Cl sat. (x 1), water (x 3) and brine (x 2); dried over anh. MgSO4, filtered and evaporated to have a yellow-orange oil (5141 mg, 89 %) which was used for the next step without further purification.

HPLC-MS: tr = 1.90 min. (91 %). LRMS (m/z): 209 m/z (poor), 153 (-56)

Intermediate 132: tert-butyl N-[6-(bromomethyl)-2-pyridyl]carbamate

To a solution of tert-butyl N-(6-methyl-2-pyridyl)carbamate (Intermediate 131; 500 mg, 2.40 mmol) in 24 mL of carbon tetrachloride was added NBS (427 mg, 2.40 mmol) followed by 2,2'-Azobis(2-methylpropionitrile) (23 mg, 0.14 mmol) and the mixture was heated to reflux (77 ºC) overnight. More AIBN (23 mg) was added and the mixture was heated again to reflux. After 6 h the proportion had raised to 22 %. More AIBN (23 mg again) was added and the mixture was heated for 24 h at reflux. The proportion of final product is 33 %. The solvent was removed under reduced pressure and the final brown semisolid was purified via flash chromatography in Hx/Hx with 50 % AcOEt to have a sligthly yellow oil (170 mg, 25 %).

HPLC-MS: tr = 3.07 min. (99 %). LRMS (m/z): 287/289 (M+1, Br)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.52 (s, 9H), 4.43 (s, 2H), 7.09 (d, J = 7.1 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H).

Intermediate 133: tert-butyl N-[6-(1,2,4-triazol-1-ylmethyl)-2-pyridyl]carbamate

To a solution of tert-butyl N-[[4-(bromomethyl)phenyl]methyl]carbamate (Intermediate 132; 85 mg, 0.29 mmol) in 1.5 mL of anh. acetonitrile was added 1H-1,2,4-triazole (23 mg, 0.33 mmol), potassium carbonate (53 mg, 0.38 mmol), potassium iodide (3 mg, 0.018 mmol) and the mixture was stirred at room temperature overnight.The volatiles were removed under reduced pressure. Water and AcOEt were added and the phases separated. The aqueous was extracted once more with AcOEt and the combined organic fractions were washed with brine and dried over anh. MgSO4, filtered and evaporated. The crude was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a yellow oil which solidifies upon standing (61 mg, 75 %).

HPLC-MS: tr = 2.33 min. (97 %). LRMS (m/z): 276 (M+1)

Intermediate 134: 6-(1,2,4-triazol-1-ylmethyl)pyridin-2-amine

To a solution of tert-butyl N-[6-(1,2,4-triazol-1-ylmethyl)-2-pyridyl]carbamate (Intermediate 133; 99 mg, 0.36 mmol) in 2 mL of anh. dioxane was added HCl (4 M in dioxane, 450 uL, 1.8

mmol) dropwise and the mixture was stirred at room temperature overnight. More HCl 4N (500 uL) was added and the mixture was heated at 80 ºC for 1 h and at 100ºC for 2 hr. The volatiles were removed under reduced pressure and 4 mL of methanol were added. The residue was dissolved and passed through a resin of NaHCO3 washing with methanol. The solvent was removed to have a brown solid (54 mg, 86 %) as the title product.

HPLC-MS: tr = 0.48 min. and 0.70 min. (99 %). LRMS (m/z): 189 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 5.29 (s, 2H), 6.42 (d, J = 7.2 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 7.38 – 7.44 (m, 1H), 7.99 (s, 1H), 8.55 (s, 1H).

Intermediate 135: 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 70 mg, 0.375 mmol) in 1 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 30 mg, 0.750 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. The temperature was lowered to 0 ºC and a solution of 2-chloro-6-methoxy-benzoyl chloride (106 mg, 0.562 mmol) was added dropwise and the reaction was left to stir at 0ºC for 30 min. Water was added and a precipitate appeared, it was filtered and washed with water. The solid was taken up in EtOAc and purified by flash chromatography (Biotage, SNAP 12g) using Hexane/Hexane-EtOAc (1-1) to obtain a white solid (50 mg, 39 %).

HPLC-MS tr = 2.80 min (99%). LRMS (m/z): 339/341 (M+1, Cl)

^{1}H NMR (CDCl3, 400 MHz) δ ppm 3.02 (d, J = 5 Hz, 3H), 3.93 (s, 3H), 6.77-6.83 (m, 2H), 7.41 (td, J = 8.5 and 6.5 Hz, 1H), 8.36 (br s, 1H), 9.11 (s, 1H), 12.61 (br s, 1H).

Intermediate 136: 2-chloro-4-(methoxymethyl)pyridine

To a solution of (2-chloro-4-pyridyl)methanol (830 mg, 5.78 mmol) in 17 mL of anh. DMF was added at 0 ºC NaH (60 %, 243 mg, 6.07 mmol) followed by the addition of methyl iodide (486 µL, 7.80 mmol) dropwise. The mixture was left stirring at 0 ºC. By HPLC-MS is observed that the reaction does not progress once achieved 80 % of conversion. NH4Cl sat. was added (at 0 ºC) and the solution extracted twice with AcOEt. The organic fractions were washed with water (x 2), LiCl (5 % aq., x 2) and brine; dried over anh. MgSO4, filtered and evaporated to have an orange oil which was purified by flash chromatography in Hx/Hx with 50 % Et2O to have a colorless oil (663 mg, 73 %).

HPLC-MS: tr = 2.17 min. (99 %). LRMs (m/z): 158/160 (M+1, 1 Cl)

^{1}H NMR 1H (CDCl3, 400 MHz) δ ppm 3.44 (s 3H), 4.46 (s 2H), 7.16 (d J=5 Hz 1H), 7.31 (s 1H), 8.33 (d J=5 Hz 1H).

Intermediate 137: N-[4-(methoxymethyl)-2-pyridyl]-1,1-diphenyl-methanimine

To a solution of 2-chloro-4-(methoxymethyl)pyridine (Intermediate 136; 830 mg, 5.26 mmol) in 17 mL of anh. dioxane was added, under Ar flushing, benzophenone imine (882 µL, 5.26 mmol), palladium (II) acetate (53.5 mg, 0.24 mmol), BINAP (302 mg, 0.48 mmol) and cesium carbonate (2325 mg, 7.13 mmol). The mixture was heated at 80 ºC. After 3 h the reaction is complete and the mixture was cooled down to room temperature (by HPLC-MS it is observed the acidic hydrolysis of the imine during the analysis). Water was added at 0 ºC and the mixture was extracted twice with AcOEt. The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a brown oil which was used for the next step without further purification.

HPLC-MS: tr = 2.50 min. (35 %). LRMS (m/z): 303 (M+1)

Intermediate 138: 4-(methoxymethyl)pyridin-2-amine

To a solution of crude N-[4-(methoxymethyl)-2-pyridyl]-1,1-diphenyl-methanimine (Intermediate 137; 1400 mg, 4.63 mmol) in 12 mL of anh. THF was added hydrochloric acid 6 M (12 mL, 72 mmol) and the mixture was stirred at room temperature. After 1 h the reaction is complete and water was added (white dispersion appeared). The aqueous fraction was washed with AcOEt (x 1) and the organic phase was discarded. The aqueous solution was basified with NaOH 6M and extracted with AcOEt (x 3). The combined organic fractions were dried over anh. MgSO4, filtered and evaporated to have a yellow oil. DCM was added and the solvent removed under reduced pressure to have a yellow solid which was triturated in Et2O to have a white solid which was filtered, rinsed with Et2O and dried in the vacuum oven for one night to have the title compound (223 mg, 35 %).

HPLC-MS: tr = 0.70 min. (95 %). LRMS (m/z): 139 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.28 (s, 3H), 4.27 (s, 2H), 5.84 (s, 2H), 6.35 – 6.42 (m, 2H), 7.82 (d, J = 5.8 Hz, 1H).

Intermediate 139: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[(6-fluoro-2-pyridyl)amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 177 mg, 0.52 mmol) was dissolved in dioxane (5.3 mL). 6-fluoropyridin-2-amine (89 mg, 0.79 mmol), Tris(dibenzylideneacetone)dipalladium(0) (48 mg, 0.052 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (61 mg, 0.10 mmol) and cesium carbonate (513 mg, 1.57 mmol) were added and the mixture was stirred overnight at 100 ºC under nitrogen atmosphere. EtOAc and water were added and the product was extracted with EtOAc (2x). The organic phase was washed with brine, dried over anh. Na2SO4, filtered and concentrated.The crude was purified by Isolera using a Merck Si column (10 g) and eluting with DCM/MeOH from 0% to 5% in 40 CV, affording 33 mg (15%) of pure product.

HPLC-MS: tr = 1.45 min. (85 %). LRMS (m/z): 414 (M+1)

Intermediate 140: 2-methoxy-5-(trifluoromethyl)benzoyl chloride

250 mg (1.13 mmol) of 2-methoxy-5-(trifluoromethyl)benzoic acid is solved in 3.5 mL (5.73 g, 48 mmol) of thionyl chloride and the mixture was heated to reflux for 2 hr. The volatiles were removed under reduced pressure and co-evaporated with toluene (x 3) to have a brown oil as the final product. The product was used for the next step without further purification.

Intermediate 141: 6-chloro-4-[[2-methoxy-5-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.54 mmol) in 3 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion, 54 mg, 1.35 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow solution). Then, the temperature was lowered to 0 ºC and was added 2-methoxy-5-(trifluoromethyl)benzoyl chloride (Intermediate 140; 189 mg, 0.79 mmol) in one portion. The mixture was stirred at room temperature for overnight. Water and AcOEt were added and the phases separated. The organic fraction was washed with LiCl (5 % solution, x 2) and brine, dried over anh. MgSO4, filtered and evaporated to have a residue which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a white solid as the title product (31 mg, 15 %).

HPLC-MS: tr = 3.17 min. (97 %). LRMS (m/z): 388/390 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.80 – 2.90 (m, 3H), 4.15 (s, 3H), 7.48 (d, J = 8.7 Hz, 1H), 7.95 – 8.02 (m, 1H), 8.25 – 8.28 (m, 1H), 8.66 (s, 1H), 8.71 (s, 1H), 8.97 (d, J = 6.4 Hz, 1H), 12.53 (s, 1H).

Intermediate 142: 2-nitro-5-(tetrahydropyran-3-ylmethyl)pyridine

Zinc (242 mg, 3.7 mmol) was added to a vial equipped with a stir bar, the vial was heated at 80ºC under high vacuum for 1h. After back-filling with nitrogen, iodine chips (31 mg, 0.122 mmol) were added to the vial. DMA (2 ml) was added to the vial and the mixture was stirred at room temperature for 30min. Next, 3-(bromomethyl)tetrahydropyran (441 mg, 2.46 mmol) was added and the mixture was was stirred at 80ºC overnight. In a separate vial were placed 5-bromo-2-nitro-pyridine (100mg, 0.492 mmol), S-Phos (40.4 mg, 0.098 mmol) and Palladium acetate (11 mg, 0.049 mmol) in DMF (0.5 ml). That solution was purged with argon. After cooling to rt the bromozinc intermediate, the mixture was filtered through a syringe filter (0.45 um) and was added dropwise to the solution that contained the bromopyridine, at that mixture was heated to reflux overnight. A saturated aqueous NH4Cl solution and EtOAc were added, phases separated. The aqueous phase was further extracted with more EtOAc, then the organic phase was washed with brine (2x), dried (MgSO4), filtered and solvent removed to give a dark oil. The residue was purified by flash chromatography (Biotage, SNAP 12g) by using hexane/EtOAc from 0 to 75%. 45 mg (41%) of the title compound were obtained as a yellow oil.

HPLC-MS tr = 2.27 min (42%). LRMS (m/z): 223 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.25-1.28 (cs 1H), 1.55-1.64 (cs 3H), 1.73-1.76 (cs 1H), 1.87-1.98 (cs 1H), 2.56-2.74 (cs 2H), 3.16-3.21 (cs 1H), 3.42-3.43 (cs 1H), 3.79-3.88 (cs 2H), 7.80 (d J=8 Hz 1H), 8.20 (d J=8 Hz 1H), 8.4 (s 1H).

Intermediate 143: 5-(tetrahydropyran-3-ylmethyl)pyridin-2-amine

In a 50 mL round bottomed flask 2-nitro-5-(tetrahydropyran-3-ylmethyl)pyridine (Intermediate 142; 43 mg, 0.193 mmol) was dissolved in MeOH and purgued with N2 (x 3). Pd over carbon (20 mg, 0.019 mmol) was added, the atmosphere was replaced with hydrogen (balloon) and the reaction was stirred at room temperature for 30 min.The reaction mixture was filtered through a syringe filter and solvent was removed under vacuum. The crude was used in the next step without further purification.

HPLC-MS tr -= 1.30 min (81%). LRMS (m/z): 193 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.10-1.28 (cs 1H), 1.43-1.80 (cs 3H), 2.20-2.45 (cs 1H), 2.56-2.74 (cs 1H), 3.12 (m 1H), 3.30-3.80 (cs 4H), 6.90 (d J=8 Hz 1H), 7.47 (d J=8 Hz 1H), 7.60 (s 1H).

Intermediate 144: N-methyl-2-(4-nitropyrazol-1-yl)acetamide

A suspension of 4-nitro-1H-pyrazole (1g, 8.84 mmol), 2-chloro-N-methyl-acetamide (1.4 g, 13.0 mmol) and K2CO3 (1.83 g, 13.2 mmol) in acetone (25 ml) was heated at 60ºC. for 1.5 hr. The mixture was filtrated and concentrated. The residue was purified by flash chromatography (Biotage, SNAP 120g) using DCM/DCM-MeOH (5%) from 0 to 100%. 1.5 g (92%) of title compound were obtained as a white solid.

HPLC-MS tr = 1.20 min (94%). LRMS (m/z): 185 (M+1)

^{1}H NMR 1H (400 MHz, DMSO-d6) δ ppm 2.61 (d, J = 4 Hz, 3H), 4.85 (s, 2H), 8.15 (br s, 1H), 8.23 (d, J = 0.7 Hz, 1H), 8.80 (d, J = 0.7 Hz, 1H).

Intermediate 145: 2-(4-aminopyrazol-1-yl)-N-methyl-acetamide

Pd/C (5%, 61.5 mg, 0.029 mmol) was added to the solution of N-methyl-2-(4-nitropyrazol-1-yl)acetamide (Intermediate 144; 615 mg, 3.34 mmol) in MeOH (100 ml). The mixture was stirred under a hydrogen atmosphere for 4.5 hr. The mixture was filtered and concentrated to give 371 mg (72%) of the title compound as a red oily solid.

HPLC-MS tr = 0.45 min (95%): LRMS (m/z): 155 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.73 (s, 3H), 4.68 (s, 2H), 7.20 (s, 1H), 7.24 (s, 1H).

Intermediate 146: 4-(6-nitro-3-pyridyl)morpholine

To a solution of 5-bromo-2-nitro-pyridine (400 mg, 1.97 mmol) in 2 mL of anh. DMF was added morpholine (187 uL, 2.17 mmol) followed by DIPEA (377 uL, 2.16 mmol) and the mixture was heated at 90 ºC overnight. AcOEt and water were added. The organic phase was dried over anh. MgSO4, filtered and evaporated to give a yellow oil which was purified in DCM/DCM with 5 % MeOH to afford title compound as a yellow solid (279 mg, 68 %).

HPLC-MS: tr = 1.85 min. (99 %). LRMS (m/z): 210 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.35 – 3.48 (m, 4H), 3.83 – 3.95 (m, 4H), 7.22 (dd, J = 9.1, 3.1 Hz, 1H), 8.14 (d, J = 3.0 Hz, 1H), 8.18 (d, J = 9.1 Hz, 1H).

Intermediate 147: 5-morpholinopyridin-2-amine

To a solution of 4-(6-nitro-3-pyridyl)morpholine (Intermediate 146; 270 mg, 1.3 mmol) in 7 mL of anh. MeOH and 5 mL of AcOEt (partially soluble) was added palladium (137 mg, 0.13 mmol) and the reaction was purgued with hydrogen (x 3) and stirred at room temperature. After

3h the reaction is complete and the crude was filtrated over a Celite pad, washing with MeOH. The filtrate was removed under reduced pressure to afford a white solid (188 mg, 81 %).

HPLC-MS: tr = 0.97 min. (99 %). LRMS (m/z): 180 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.98 (dd, J = 5.4, 4.0 Hz, 4H), 3.81 (dd, J = 5.6, 3.8 Hz, 4H), 6.59 (dd, J = 8.9, 0.7 Hz, 1H), 7.31 (dd, J = 9.0, 2.9 Hz, 1H), 7.60 (d, J = 2.9 Hz, 1H).

Intermediate 148: ethyl 2-(4-hydroxycyclohexyl)acetate

To a solution of ethyl 2-(4-oxocyclohexyl)acetate (250 mg, 1.36 mmol) in MeOH at 0ºC was added NaBH4 (103 mg, 2.72 mmol) and the mixture was stirred at 0ºC for 1h. and at rt for additional 2h. A saturated aqueous solution of NH4Cl was added and the methanol was removed. Then the aqueous phase was extracted with EtOAc, dried, filtered and solvent removed to yield an oil (250 mg; 98%) that was used in the next step without further purification.

HPLC-MS: tr = 2.09 min (93%). LRMS (m/z): 187 (M+1).

Intermediate 149: 2-(4-hydroxycyclohexyl)acetamide

The mixture of ethyl 2-(4-hydroxycyclohexyl)acetate (Intermediate 148; 250 mg, 1.345 mmol) and aqueous NH3 (32%, 2 ml) in ACN (2 ml) was heated at 150ºC for 20hr. The crude was concentrated. Et2O was added and a solid appeared, solvent was removed and the solid was washed again with more Et2O, then it was dried in an oven and used without further purification.

HPLC-MS: rt = 0.87 min / 0.98 min (85% both isomers). LRMS (m/z): 158 (M+1)

Intermediate 150: 6-chloro-2-methyl-pyrimidin-4-amine

4,6-dichloro-2-methyl-pyrimidine (297 mg, 1.82 mmol) were dissolved in a solution of ammonia (7 N in methanol, 3.3 mL, 23.1 mmol) and the solution was stirred in a sealed flask at 110 ºC overnight.The solvent was removed and the crude was re-crystallized from a small volume of water to get a white solid, 190 mg (73%).

HPLC-MS: tr = 1.20 min (100%). LRMS (m/z): 144/146 (M+1, Cl).

Intermediate 151: N-6,2-dimethylpyrimidine-4,6-diamine

6-chloro-2-methyl-pyrimidin-4-amine (Intermediate 150; 190 mg, 1.32 mmol) was dissolved in 2-propanol (14 mL) and methylamine in ethanol (33%, 500 uL, 3.04 mmol) were added. The

mixture was heated at 160 ºC in a sealed flask for 3 h. After 3 h, the hplc-ms showed a 60% of conversion, so further 500 uL methylamine in ethanol were added and the reaction was heated at 160 ºC overnight.The solution was let to cool down, thus precipitating a white solid. The solid was filtered to give 112 mg (61%) of title compound.

HPLC-MS: tr = 0.73 min (85%). LRMS (m/z): 139 (M+1).

Intermediate 152: methyl 5-(2-benzyloxyethoxy)-2-methoxy-benzoate

To a suspension of methyl 5-hydroxy-2-methoxy-benzoate (Prepared as described in J. Med. Chem. 2015, 58, 3757−3766; 400mg, 2.2 mmol) and Cs2CO3 (1 g, 3.07 mmol) in DMF (8 ml) was added 2-bromoethoxymethylbenzene (382 µL, 2.42 mmol) and the mixture was stirred at rt for 3 hr. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAc. The organic phase was washed with brine (2x), dried (MgSO4), filtered and concentrated to give 578 mg (83%) of title compound as a clear oil

HPLC-MS: tr = 2.98 min (97%): LRMS (m/z): 317 (M+1)

Intermediate 153: 5-(2-benzyloxyethoxy)-2-methoxy-benzoic acid

To a solution of methyl 5-(2-benzyloxyethoxy)-2-methoxy-benzoate (Intermediate 152; 570 mg, 1.8 mmol) in 9 mL of THF and 2 mL of water was added LiOH·H2O (227 mg, 5.41 mmol) and the solution was stirred at room temperature for 20 hr. THF was eliminated and more water was added, the pH was ajusted to 2-3 and the acid was extracted with EtOAc (2x), dried (MgSO4), filtered and concentrated to give 542 mg (99%) of title compound as a clear oil

HPLC-MS: tr = 2.67 min (94%). LRMS (m/z): 303 (M+1)

Intermediate 154: 4-[[5-(2-benzyloxyethoxy)-2-methoxy-benzoyl]amino]-6-chloro-N-methyl-pyridine-3-carboxamide

To a solution of 5-(2-benzyloxyethoxy)-2-methoxy-benzoic acid (Intermediate 153; 326 mg, 1.08 mmol) and HATU (410 mg, 1.08 mmol) in DMF (2 ml) was added DIPEA (188 µL, 1.08 mmol) and the mixture was stirred at room temperature for 30min. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAC, then the organic phases were washed with brine (3x), dried (MgSO4), filtered and solvent removed. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.539 mmol) in DMF (2 ml) at 0ºC, NaH (60%, 43 mg, 1.07 mmol) was added and the mixture was stirred at rt for 30 minutes.It was cooled again to 0ºC and the activated acid in

DMF was added dropwise and the mixture was stirred at rt for 1.5 hr. Water was added and a white solid appeared that was filtered and washed with more water.The solid was dried in an oven to give 200 mg (79%) of title compound as a white solid.

HPLC-MS: tr = 3.23 min (98%). LRMS (m/z): 470/472 (M+1, Cl)

Intermediate 155: 4-[[5-(2-benzyloxyethoxy)-2-methoxy-benzoyl]amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To the solution of 4-[[5-(2-benzyloxyethoxy)-2-methoxy-benzoyl]amino]-6-chloro-N-methyl-pyridine-3-carboxamide (Intermediate 154; 100 mg, 0.213 mmol) in anh dioxane (4 ml) was added 2,6-dimethylpyrimidin-4-amine (31 mg, 0.252 mmol) and Cs2CO3 (166 mg, 0.509 mmol). Reaction mixture was degassed under argon gas for 5 minutes, then Pd2(dba)3 (19.5 mg, 0.021 mmol) and Xantphos (25 mg, 0.043 mmol) were added and the mixture was degassed for an additional 2 minutes. Finally, reaction mixture was heated at 100ºC for 1.5 hr.The reaction was cooled down and filtered. The residue was purified by flash chromatography (Biotage, SNAP 12g) DCM/DCM-MeOH (5%) from 0 to 100% in 40CV affording 80 mg 67%) of title compound as an off white solid

HPLC-MS: tr = 2.32 min (98%). LRMS (m/z): 557 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.38 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 3.77-3.77 (m, 2H), 3.95 (s, 3H), 4.12-4.16 (m, 2H), 4.54 (s, 2H), 7.14 (d; J= 9 hz, 1H), 7.19 (dd, J = 9 and 3 Hz, 1H), 7.24-7.30 (m, 1H), 7.32 (s, 1H), 7.34 (s, 1H), 7.44 (s, 1H), 7.48 (d, J = 3 Hz, 1H), 8.55 (s, 1H), 8.63 (q, J = 4.5 Hz, 1H), 9.14 (s, 1H),10.27 (s, 1H), 12.36 (s, 1H).

Intermediate 156: 6-chloro-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-fluoro-2-methoxy-3-methyl-benzoic acid (135mg, 0.73mmol) and HATU (279mg, 0.73mmol) in DMF (1mL) was added DIPEA (128uL, 0.73mmol) and the mixture was stirred at room temperature for 1hr. Water was added and extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and concentrated. 2-amino-4-chloro-N-methyl-benzamide (Preparation 3; 100mg, 0.54mmol) was solved in DMF (1.5mL) and cooled at 0ºC. NaH (60%, 65mg, 1.63mmol) was added and stirred for 30min at room temperature. After cooling at 0ºC the activated acid was added dropwise solved in DMF (1mL) and stirred at room temperature for 1 hr. Water was added and the mixture extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and concentrated.

The crude was purified by flash chromatography (Biotage Telos12g) using hexane/diethyl ether (also up to 5% MeOH needed) (220nm) to give the title compound (167mg, 88%) as a white solid.

HPLC/MS: tr = 2.85 min (100%). LRMS (m/z): 352,354 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.25 (s, 3H), 2.76 (d, J = 4.5 Hz, 3H), 3.75 (s, 3H), 7.08 (t, J = 8.9 Hz, 1H), 7.40 – 7.46 (m, 1H), 8.60 (s, 1H), 8.77 (s, 1H), 9.01 – 9.12 (m, 1H), 12.34 (s, 1H).

Intermediate 157: 6-chloro-N-methyl-4-[(3-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide

To a solution of 3-methylsulfonylbenzoic acid (215 mg, 1.07 mmol) and HATU (615 mg, 1.61 mmol) in DMF (2.2 mL) was added DIPEA (0.28 mL) and the mixture was stirred at room temperature for 60 min. Water was added and a precipitate appeared that was filtered off and taken up in EtOAc, dried (MgSO4), filtered and concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 100 mg, 0.54 mmol) in DMF (4 ml) at 0ºC and NaH (60%, 65 mg, 1.63 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (4.2 mL) was added dropwise. After 2h stirring at rt the reaction was quenched with NH4Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulphate, filtered and concentrated. The crude was purified by flash chromatography (100% DCM to 5 % MeOH in DCM gradient) to obtain the title compound as a yellowish solid (87 mg; 44%).

HPLC-MS: tr = 2.33 min (96%). LRMS (m/z): 368/370 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 13.12 (s, 1H), 9.19 – 9.13 (m, 1H), 8.83 (s, 1H), 8.63 (s, 1H), 8.44 (t, J = 1.8 Hz, 1H), 8.24 (ddd, J = 8.0, 3.0, 1.4 Hz, 2H), 7.94 (t, J = 7.8 Hz, 1H), 3.31 (s, 3H), 2.86 (d, J = 4.5 Hz, 3H).

Intermediate 158: 6-chloro-4-[(4-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-fluoro-2-methoxy-3-methyl-benzoic acid (150 mg, 1.08 mmol) and HATU (307 mg, 0.807 mmol) in DMF (2 ml) was added DIPEA (141 µL, 0.809 mmol) and the mixture was stirred at room temperature for 30min. Water and AcOEt were added, phases separated and the aqueous phase was further extracted with more AcOEt, then the organic phases were washed with brine (3x), dried (MgSO4), filtered and concentrated. In another vial was placed

4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 75 mg, 0.404 mmol) in DMF (1.5 ml) at 0ºC. NaH (60%, 32 mg, 0.8 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again, the activated acid in DMF was added dropwise and the mixture was stirred at rt for 30 min. Water and AcOEt were added, phases separated and the organic phase was further washed with binre (2x), dried (MgSO4), filtered and solvent removed. The white solid was purified by flash chromatography (Biotage, SNAP 12g) by using DCM//DCM-MeOH (2%) to afford 140 mg (99%) as a white solid.

HPLC-MS: tr = 3.23 min (98%). LRMS (m/z): 470/472 (M+1, Cl)

Intermediate 159: 3-cyano-2-methoxy-benzoyl chloride

To a suspension of 3-cyano-2-methoxy-benzoic acid (prepared as described in US20180215730 example 2 step 1; 286 mg, 1.61 mmol) in 2 mL of anh. DCM was added 1 drop of DMF and oxalyl chloride (0.21 mL, 2.45 mmol) dropwise at room temperature under nitrogen. The reaction was stirred overnight at room temperature. The mixture was concentrated and the residue was re-evaporated several times with dichloromethane to have a yellow liquid (316 mg, quant. yield) of title compound used per se in the next synthetic step.

UPLC-MS: tr = 1.22 min. LRMS (m/z): 192 (M+1, Me ester)

Intermediate 160: 6-chloro-4-[(3-cyano-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 190 mg, 1.02 mmol) in 5 mL of anh. DMF was cooled at 0ºC and sodium hydride (60 % in mineral oil dispersion, 80 mg, 2 mmol) was added. The mixture was stirred at room temperature for 30 min. Then, the temperature was lowered again to 0 ºC and a solution of 2-fluoro-4-methoxy-benzoyl chloride (Intermediate 159; 315 mg, 1.6 mmol) in 2 mL of anh. DMF was added dropwise and the reaction was stirred overnight at room temperature. Water was added (100 ml) followed by AcOEt. The phases were separated and the aqueous was extracted with AcOEt (x 3). The combined organic extracts were washed with water (x 3), dried over anh. MgSO4, filtered and evaporated. Weight: 1.43g. The white solid was ground with in Et2O and the solid was filtered and washed with Et2O, to give the title compound (100 mg) as an off-white solid. The aqueous phase was filtered and the solid dried to afford 72 additional mg of title compound Total weight 172 mg, 48%).

UPLC-MS tr = 1.49 min (100%). LRMS (m/z): 345 (M+1).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.43 (s, 1H), 9.01 (s, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 6.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 4.10 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H).

Intermediate 161: 6-chloro-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-3-(trifluoromethyl)benzoic acid (142 mg, 0.645 mmol) and HATU (246 mg, 0.647 mmol) in DMF (2 ml) was added DIPEA (113 µL, 0.809 mmol) and the mixture was stirred at room temperature for 30min. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more AcOEt. The organic phases were washed with brine (3x), dried (MgSO4), filtered and concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preperation 3; 60 mg, 0.323 mmol) in DMF (1.5 ml) at 0ºC and NaH (60%, 26 mg, 0.65 mmol) was added. The mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF was added dropwise and the mixture was stirred at rt. for 1 hr. Water and AcOEt were added, phases separated and the organic phase was further washed with binre (2x), dried (MgSO4), filtered and solvent removed. The white solid was purified by flash chromatography (Biotage, SNAP 12g) by using DCM//DCM-MeOH (5%) to afford the title compound (83 mg, 66%) as a white solid.

HPLC-MS: tr = 3.03 min (98%). LRMS (m/z): 388/390 (M+1, Cl)

^{1}H NMR (DMSO, 400 MHz) δ ppm 2.77 (d, J = 4.6 Hz, 3H), 3.81 (s, 3H), 7.48 (t, J = 8 Hz, 1H), 7.92 (dd, J = 8 and 1.4 Hz, 1H), 8.04 (dd, J = 8 and 1.6 Hz, 1H), 8.62 (s, 1H), 8.71 (s, 1H), 8.95-9.02 (m, 1H), 12.42 (s, 1H).

Intermediate 162: 6-methyl-2-morpholino-pyrimidin-4-amine

A mixture of 2-chloro-6-methyl-pyrimidin-4-amine (150 mg, 1.04 mmol), morpholine (180 uL, 2.08 mmol) and 1.7 mL of toluene was heated to 115ºC overnight. Next day a crystalline solid was filtered-off and dried in the oven affording 134 mg 66%) of title compound as a hydrochloride salt. The compound is used per se in the next synthetic step.

HPLC-MS: tr = 0.42 min (100%). LRMS (m/z): 195 (M+1)

Intermediate 163: methyl 4,5-diamino-2-methoxy-benzoate

Methyl 4-amino-2-methoxy-5-nitro-benzoate (405 mg, 1.79 mmol) was dissoved in a mixture of MeOH (40 ml) and EtOAc (30 ml). Then Pd/C (40 mg, 0.038 mmol) was added and the suspension was stirred under a hydrogen atmosphere (balloon) for 18hr. The mixture was filtrated and concentrated. The final brown foam (350 mg, 99%) was used without further purification.

HPLC-MS: tr = 0.95 min (95%). LRMS (m/z): 197 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.61 (s, 3H), 3.62 (s, 3H), 4.23 (br s, 2H), 5.32 (br s, 2H), 6.22 (s, 1H), 7.00 (s, 1H).

Intermediate 164: methyl 6-methoxy-1H-benzotriazole-5-carboxylate

To the solution of methyl 4,5-diamino-2-methoxy-benzoate (Intermediate 163; 350 mg, 1.78 mmol) in AcOH (2.6 ml) at 5ºC was added dropwise a solution of sodium nitrite (136 mg, 1.97 mmol) in water (0.5 ml). After few minutes a precipitate appeared. The mixture was filtrated and the solid washed with Et2O. Both the solid and the filtrate contained target compound, so the solid was dried in an oven (207 mg of a light orange solid) and the filtrate was concentrated and purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (5%) from 0 to 100%, 62 mg of a light orange solid were obtained. Total weight of title compound: 162 mg (72%)

HPLC-MS: tr = 1.70 min (99%). LRMS (m/z): 208 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.80 (s, 3H), 3.87 (s, 3H), 7.30 (s, 1H), 8.20 (s, 1H).

Intermediate 165: methyl 6-methoxy-3-(2-trimethylsilylethoxymethyl)benzotriazole-5-carboxylate

To the solution of methyl 6-methoxy-1H-benzotriazole-5-carboxylate (Intermediate 164; 265 mg, 1.28 mmol) in DMF (5 ml) at 0ºC was added NaH (60% in mineral oil, 92 mg, 2.3 mmol) and the mixture was stirred for 1h. SEMCl (275 µL, 1.55 mmol) was added and the mixture was stirred at rt for 1 hr. Water and EtOAc were added, phases separated and the organic phase was further washed with brine (2x), dried, filtered and solvent removed. The residue was purified by flash chromatography (Biotage, SNAP 12g) by using hexane/DCM from 50 to 100% to afford 205 mg (71%) of title compounds as a clear oil containing both 2 regioisomers.

HPLC-MS: tr = 2.75 min (67%). LRMS (m/z): 324 (M+1) and tr: 2.90' (32%). LRMS (m/z): 324 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.122 (s 9H), 0.77-0.87 (cs 2H), 3.84 (s 3H), 3.91 (s 3H), 5.94 and 6.03 (s 2H), 7.42 and 7.51 (s 1H), 8.20 and 8.31 (s 1H)

The aqueous phase contained the corresponding carboxylic acid, so it was acidified and extracted with EtOAc, then the organic phase was dried, filtered and solvent removed to give 100 mg of solid that were joined to the product of next step (Intermediate 166).

Intermediate 166: 6-methoxy-3-(2-trimethylsilylethoxymethyl)benzotriazole-5-carboxylic acid

To a solution of methyl 6-methoxy-3-(2-trimethylsilylethoxymethyl)benzotriazole-5-carboxylate (Intermediate 165; 200 mg, 0.593 mmol) in MeOH/THF (2/4 ml) was added LiOH·H2O (75 mg, 1.79 mmol) in water (2 ml) and the mixture was stirred at rt for 1 hr. THF was removed and more water was added. The pH was ajusted to 4 by the addition of 1N HCl, and the precipitate was extracted with EtOAc, the organic phase was then dried (MgSO4), filtered and concentrated. 189 mg (98%) of a regioisomeric mixture of 2 compounds was obtained as a white solid.

HPLC-MS: tr = 2.75 min (61%) & 2.90' (33%). LRMS (m/z): 324 (M+1)

Intermediate 167: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-6-methoxy-3-(2-trimethylsilylethoxymethyl)benzotriazole-5-carboxamide

To a solution of 6-methoxy-3-(2-trimethylsilylethoxymethyl)benzotriazole-5-carboxylic acid (mixture of isomers; Intermediate 166; 279 mg, 0.862 mmol) and HATU (328 mg, 0.862 mmol) in DMF (4 ml) was added DIPEA (150 µL, 0.861 mmol) and the mixture was stirred at room temperature for 30min. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAC, then the organic phases were washed with brine (3x), dried (MgSO4), filtered and solvent removed. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 80 mg, 0.431 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 35 mg, 0.875 mmol) was added. The mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again, the activated acid in DMF was added dropwise and the mixture was stirred at rt for 1hr. Water and EtOAc were added, phases separated and the organic phase was further washed with binre (2x), dried (MgSO4), filtered and solvent removed. The white solid was purified by flash chromatography (Biotage, SNAP 12g) by using DCM//DCM-MeOH (2%), from 0 to 100% to afford 163 mg (77%) of title compound (regioisomeric mixture) as a white solid.

HPLC-MS: tr = 3.37 min (61%) and 3.53 min (25%). LRMS (m/z): 491/493 (M+1, Cl)

Intermediate 168: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-6-methoxy-3-(2-trimethylsilylethoxymethyl)benzotriazole-5-carboxamide

N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-6-methoxy-3-(2-trimethylsilylethoxymethyl)benzotriazole-5-carboxamide (Intermediate 167; 80 mg, 0.163 mmol), 2,6-dimethylpyrimidin-4-amine (32 mg, 0.260 mmol), Pd2(dba)3 (15 mg, 0.016 mmol), Xantphos (19 mg, 0.033 mmol) and cesium carbonate (106 mg, 0.325 mmol) were heated in dioxane (5 mL) at 100ºC. After 1.5 h the crude was filtered and purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (5%) from 0 to 100% in 40CV to afford 95 mg (97%) of a regioisomeric mixture as an off-white solid

HPLC-MS: tr = 2.53 min (69%) and 2.63 min (31%). LRMS (m/z): 578 (M+1)

Intermediate 169: N-(6-nitro-3-pyridyl)methanesulfonamide

Acetamide (591 mg, 10.00 mmol) was heated at 90 ºC and treated with a mixture of 5-bromo-2-nitropyridine (500 mg, 2.46 mmol), methanesulfonamide (702 mg, 7.38 mmol), and potassium carbonate (851 mg, 6.16 mmol), and the resulting mixture was brought to 145 ºC, for 30 min. The mixture was diluted in water, and the pH was adjusted to 8 with 1 M HCl. A solid wich precipitates was removed by filtration. The aqueous phase was adjusted to pH 1 with 1 M HCl, but the expected solid (157 mg) does precipitate (0 ºC), so the water was concentrated in vacuo and stored at -20 ºC (some solid precipitates again, 99 mg). The resulting solid was filtered and the aqueous phase was concentrated and purified by flash chromatography, reverse phase, to get the yellowish solid (22 mg).The combined amounts of solid were used for the following reaction (284 mg).

HPLC-MS tr = 1.60 min. LRMS (m/z): 218 (M+1).

Intermediate 170: N-(6-amino-3-pyridyl)methanesulfonamide

A solution of N-(6-nitro-3-pyridyl)methanesulfonamide (Intermediate 169; 130 mg, 0.59 mmol) in methanol (3,6 mL) was treated with a soution of ammonium chloride (37 mg) in water (436 uL). This solution was stirred at room temperature for 5 min. Zinc (dust) (840 mg, 12.82 mmol) was added to the reaction and the mixture was heated at 75 ºC in a sealed flask for 3 h. The reaction was cooled to room temperature and filtered through a pad of celite with

methanol. The filtrate was concentrated and purified by flash chromatography (10% methanol in DCM) to obtain a reddish solid (143 mg, 58%).

HPLC-MS: tr = 0.45 and 0.62 min, LRMS (m/z) 188 (M+1)

Intermediate 171: methyl 3,4-diamino-2-methoxy-benzoate

A solution of methyl 4-amino-5-chloro-2-methoxy-3-nitro-benzoate (1347 mg, 5.17 mmol) in 70 mL was degassed with Ar followed by the addition of Pd/C (1252 mg, 1.17 mmol) and triethylamine (8.5 mL, 60.9 mmol). The mixture was then stirred under an hydrogen atmosphere overnight. The reaction mixture was filtered over a Celite pad washing with MeOH. Evaporation of the crude yielded the crude diamine (brown gum) with residual triethylamine (1700 mg, overweight).

HPLC-MS tr = 1.43 min (98 %). LRMS (m/z): 197 (M+1).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.65 (s, 3H), 3.70 (s, 3H), 4.38 (s, 2H), 5.35 (s, 2H), 6.32 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H).

Intermediate 172: methyl 4-methoxy-1H-benzimidazole-5-carboxylate

A solution of methyl 3,4-diamino-2-methoxy-benzoate (Intermediate 171; 1700 mg, crude, 8.66 mmol) in 50 mL of formic acid was heated at 100 ºC. After 2 h the reaction is complete and the volatiles were removed under reduced pressure and water was added. The pH was basified with NaHCO3 sat. to pH 7-8. A clear brown solid precipitated after sonication. After filtering and drying in the vacuum oven 621 mg (99 %) of title compound were obtained.

HPLC-MS: tr = 1.40 min (!00%). LRMS (m/z): 207 (M+1)

Intermediate 173: methyl 4-methoxy-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylate and methyl 4-methoxy-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylate

To a solution of methyl 4-methoxy-3H-benzimidazole-5-carboxylate (Intermediate 172; 300 mg, 1.45 mmol) in 14 mL of anh. DMF at 0 ºC was added sodium hydride (60 % in oil mineral dispersion, 70 mg, 1.75 mmol)) and the mixture was stirred 10 min. at 0 ºC. 2-(chloromethoxy)ethyl-trimethyl-silane (283 uL, 1.6 mmol) was added dropwise and left to stir at 0 ºC for 1h. The reaction is complete and NH4Cl sat. was added. Phases separated and the organic was washed with water (x 3) and brine (x 1), dried over anh MgSO4, filtered and

evaporated to have a brown oil which was purified via flash chromatography in Hx/AcOEt to have a light brown oil (378 mg, 77 %).

HPLC-MS: tr = 3.03 min. (99 %). LRMS (m/z): 337 (M+1)

Both isomers present by NMR:

1H NMR: (400 MHz, CDCl3) δ ppm -0.02 and -0.05 s (9H), 0.90 and 0.92 (t J=8 Hz, 2H), 3.52 and 3.58 (t J = 8 Hz, 2H), 3.93 and 3.96 (s 3H), 4.03 (s 3H), 5.51 and 5.75 (s 2H), 7.17 and 7.55 (d J = 8 Hz, 1H), 7.79 (d J = 8 Hz, 1H), 7.93 and 8.02 (s 1H)

Intermediate 174: 4-methoxy-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylic acid and 4-methoxy-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylic acid

To the solution of methyl 4-methoxy-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylate (Intermediate 173; 375 mg, 1.11 mmol) in MeOH/H2O (4/1 ml) was added NaOH (89 mg, 2.22 mmol) and the mixture was heated at 50ºC. After 1 h, two peaks with the mass of final product were found (tr = 2.52 and 2.75 min., 323 m/z, 45 %), the two substituted nitrogens with SEM, and starting material (tr = 3.03 min, 55 %). After 3 h the starting material is 35 %. The temperature was raised to 80 ºC. After two hours the proportion does not improve at all. Additional NaOH (45 mg) was added and the heating was initiated again and after 1h 30 min. the reaction was finished. The volatiles were removed under reduced pressure (cooling previously the reaction). Water was added and the pH adjusted to 5, extracted with EtOAc (x 3), dried over anh. MgSO4, filtered and evaporated to have a slightly brown oil (310 mg, 86 %) of the title mixture.

HPLC-MS: tr = 2.52 min. (40 %, 323 m/z) and 2.73 min. (60 %, 323 m/z)

1H NMR (400 MHz, DMSO-d6) δ ppm -0.07 and -0.08 (s 9H), 0.83 (t J = 8 Hz, 2H), 3.50 and 3.53 (t J = 8 Hz, 2H), 3.93 and 4.29 (s 3H), 5.63 and 5.71 (s 2H), 7.32 and 7.34 (t J = 8 Hz 1H), 7.62 and 7.63 (t J = 8 Hz, 1H), 8.40 and 8.46 (s 1H)

Intermediate 175: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide and N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide

To a solution of 4-methoxy-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylic acid and 4-methoxy-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxylic acid

(Intermediate 174; 208 mg, 0.64 mmol) and HATU (369 mg, 0.97 mmol) in DMF (2 ml) was added DIPEA (169 µL, 0.97 mmol) and the mixture was stirred at room temperature for 60 min. After 60 min, HPLC-MS showed the total conversion into the activated acid (1.70 min., iso 5_95). Water was added and appeared a sticky solid which was isolated by the extraction with EtOAc. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have a brown oil which was kept under refrigeration until the next day. In a 25 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 60 mg, 0.32 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 39 mg, 0.97 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (0.4 mL) was added dropwise. The mixture was stirred at rt. After 1h 15 min. the reaction is finished (two peaks corresponding the two isomers) and water was added. The mixture extracted with EtOAc and the organic washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a white semisolid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 5 % MeOH to have a white solid (131 mg, 83 %).

HPLC-MS: tr = 3.10 min. and 3.35 min. (95 %). LRMS (m/z): 490/492 (M+1, Cl)

Both isomers present by NMR.

1H NMR (400 MHz, d6-DMSO) δ ppm -0.07 and 0.08 (s 9H), 0.83 and 0.85 (t J= 8Hz, 2H), 2.84 (s 3H), 3.92 (s 3H), 5.65 and 5.75 (s 2H), 7.40 (d J = 8 Hz, 1H), 7.59 and 7.70 (d, J = 8 Hz, 1H), 7.94 (d J = 8 Hz 1H), 8.46 (s 1H), 8.55 and 8.60 (s 1H), 8.69 (d J = 8 Hz 1H)

Intermediate 176: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide and N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide

To a solution of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide and N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide (Intermediate 175; 128 mg, 0.26 mmol) in 3 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (48 mg, 0.39 mmol), Pd2(dba)3 (24 mg, 0.026 mmol), Xantphos (30 mg, 0.051 mmol) and cesium carbonate (255 mg, 0.78 mmol) and the mixture was heated at 100ºC. After 3h 45 min. the reaction is finished and the mixture was cooled down to room temperature. The reaction mixture was diluted with EtOAc and washed with water and brine;

dried over anh. MgSO4, filtered and evaporated to have a brown semisolid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 10 % MeOH to have a white solid (88 mg, 58 %).

HPLC-MS: tr = 2.28 min. and 2.43 min. (99 %). LRMS (m/z): 577 (M+1)

Both isomers present by NMR

Intermediate 177: ethyl 1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridine-2-carboxylate and 2-trimethylsilylethoxymethyl 1-(2-trimethylsilylethoxymethyl) pyrrolo[2,3-b]pyridine-2-carboxylate

To a dispersion of 60% sodium hydride (44 mg, 1.1 mmol) in 3 mL of anh. DMF was added ethyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (150 mg, 0.79 mmol) in 2 mL of anh. DMF dropwise under Ar. The mixture was stirred at room temperature for 45 min (orange dispersion). Then the temperature was lowered to 0 ºC and 2-(chloromethoxy)ethyl-trimethyl-silane (195 uL, 1.1 mmol) was added (yellow dispersion). The mixture was stirred at room temperature. After 3h 30 min. the reaction is finished (tr = 3.67 min., 321 m/z) and surprisingly tr = 4.10 min. (423 m/z) shows the transesterification of final product into the SEM derivative. Water was added, the mixture extracted with EtOAc (x 1) and the organic washed with water (x 3) and brine (x1), dried over anh. MgSO4, filtered and evaporated to have a green-yellow oil (223 mg, crude, mixture of products) which was used for the next step without further purification.

Intermediate 178: 1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid

To the solution of ethyl 1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridine-2-carboxylate (Intermediate 177; 220 mg, 0.68 mmol, mixture of two products) in MeOH/H2O (3 mL/0.6 uL) was added NaOH (55 mg, 1.37 mmol) and the mixture was stirred at room temperature. After 1 h, the major product is the expected (73 %), and methyl ester (18 %) was also observed. After 3 h 30 min. the reaction is finished and the volatiles were removed under reduced pressure. Water was added and washed with EtOAc (x 1), then acidified with HCl 1N to pH 4-5 and extracted with EtOAc (x3). The organic fractions were combined, dried over anh. MgSO4, filtered and evaporated to have a slightly brown oil which solidifies upon standing (148 mg, 74 %).

HPLC-MS. tr = 2.97 min. (98 %). LRMS (m/z): 293 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.16 (s, 9H), 0.69 – 0.83 (m, 2H), 3.42 – 3.48 (m, 2H), 6.03 (s, 2H), 7.22 – 7.26 (m, 1H), 7.30 (s, 1H), 8.15 (d, J = 9.5 Hz, 1H), 8.47 (d, J = 6.2 Hz, 1H).

Intermediate 179: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridine-2-carboxamide

To a solution of 1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (Intermediate 178; 142 mg, 0.48 mmol) and HATU (369 mg, 0.97 mmol) in DMF (2 ml) was added DIPEA (169 µL, 0.97 mmol) and the mixture was stirred at room temperature. After 60 min, HPLC-MS showed the total conversion into the activated acid (1.80 min., m/z 411 (M+1)). Water was added and a sticky solid appeared. Water and AcOEt were added. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have a brown oil. In a 25 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 45 mg, 0.24 mmol) in DMF (1 ml) at 0ºC and NaH (60%, 29 mg, 0.72 mmol) was added. The mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again, the activated acid in DMF (0.4 mL) was added dropwise and the mixture was stirred at rt. After 1h 30 min. the reaction is finished and water was added. The mixture was extracted with EtOAc (x1) and the phases separated. The organic phase was washed with water (x 3) and brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a semisolid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 5 % MeOH to have the title compound as a white solid (52 mg, 47 %).

HPLC-MS: tr = 3.63 min. (95 %). LRMS (m/z): 460/462 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.20 (s, 9H), 0.74 (t, J = 7.8 Hz, 2H), 2.84 – 2.89 (m, 3H), 3.43 (dd, J = 15.0, 7.1 Hz, 2H), 6.08 (s, 2H), 7.31 (dd, J = 7.9, 4.6 Hz, 1H), 7.35 (s, 1H), 8.31 (dd, J = 7.9, 1.6 Hz, 1H), 8.52 (d, J = 6.2 Hz, 1H), 8.61 (s, 1H), 8.83 (s, 1H), 9.18 (d, J = 6.6 Hz, 1H), 13.10 (s, 1H).

Intermediate 180: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridine-2-carboxamide

To a solution of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridine-2-carboxamide (Intermediate 179; 50 mg, 0.108 mmol) in 2 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (20 mg, 0.16 mmol), Pd2(dba)3 (10 mg, 0.010 mmol), Xantphos (13 mg, 0.022 mmol) and cesium carbonate

(106 mg, 0.32 mmol) and the mixture was heated at 100ºC under Ar atmosphere. After 2h 45 min. the reaction is finished and the mixture was cooled down to room temperature.The reaction mixture was diluted with EtOAc and washed with water and brine; dried over anh. MgSO4, filtered and evaporated to have a brown semisolid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 10 % MeOH to afford the title compound as a yellow solid (41 mg, 69 %).

HPLC-MS: tr = 2.62 min. (99 %). LRMS (m/z): 547 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.20 (s, 9H), 0.75 (t, J = 7.9 Hz, 2H), 2.34 (s, 3H), 2.79 – 2.89 (m, 3H), 3.46 (t, J = 7.9 Hz, 2H), 6.13 (s, 2H), 7.29 (d, J = 4.7 Hz, 1H), 7.32 (s, 1H), 7.35 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.50 (d, J = 6.1 Hz, 1H), 8.76 (s, 1H), 8.89 (d, J = 4.5 Hz, 1H), 9.28 (s, 1H), 10.41 (s, 1H), 13.21 (s, 1H).

Intermediate 181: 6-chloro-4-[(3-cyclopropyl-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 3-cyclopropyl-2-methoxy-benzoic acid (124 mg, 0.64 mmol) and HATU (369 mg, 0.97 mmol) in DMF (2 ml) was added DIPEA (169 µL, 0.97 mmol) and the mixture was stirred at room temperature for 60 min. After 60 min, HPLC-MS showed the total conversion into the activated acid (1.80 min, m/z 411 (M+1)). Water was added and a sticky solid appeared which was isolated by the addition-separation of AcOEt. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have a brown oil. In a 25 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Intermediate 3; 60 mg, 0.33 mmol) in DMF (1 ml) at 0ºC and NaH (60%, 39 mg, 0.0.97 mmol) was added. The mixture was stirred at rt for 30 minutes and, after cooling again to 0ºC the activated acid in DMF (0.4 mL) was added dropwise and the mixture was stirred at rt. After 1h the reaction is finished and water was added. The mixture extracted with EtOAc (x1) and the phases separated. The organic was washed with water (x 3) and brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a semisolid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 5 % MeOH to afford the title compound as a white solid (91 mg, 78 %).

HPLC-MS: tr = 3.03 min. (99 %). LRMS (m/z): 360/362 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.71 – 0.78 (m, 2H), 1.01 – 1.08 (m, 2H), 2.18 – 2.25 (m, 1H), 2.81 (d, J = 4.6 Hz, 3H), 3.84 (s, 3H), 7.10 – 7.14 (m, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.63 – 7.67 (m, 1H), 8.66 (s, 1H), 8.69 (s, 1H), 8.95 (d, J = 4.8 Hz, 1H), 12.36 (s, 1H).

Intermediate 182: methyl 7-methoxy-1H-indole-2-carboxylate

Methyl 7-methoxy-1H-indole-2-carboxylate (159 mg, 0.83 mmol) was dissolved in anhydrous methanol (3.87 mL) and sulfuric acid (64 uL) was added. The reaction was heated at 65 ºC in a sealed flask overnight.The mixture was diluted in dichloromethane and washed with sodium bicarbonate solution and the organic phase was washed with brine, dried over MgSO4, filtered and concentrated. The slightly brown solid was used in the following step without further purification.

HPLC-MS: tr = 2.63 min (100%). LRMS (m/z): 206 (M+1)

Intermediate 183: methyl 7-methoxy-1-(2-trimethylsilylethoxymethyl)indole-2-carboxylate

60% sodium hydride (51 mg, 1.28 mmol) was added to a solution of methyl 7-methoxy-1H-indole-2-carboxylate (Intermediate 182; 150 mg, 0.73 mmol) in 3.6 mL of anh. DMF at 0 ºC. The mixture was stirred at 0 ºC for 30 min. Then SEM-Cl (155 µL, 0.875 mmol) was added at 0 ºC and the mixture was stirred at room temperature overnight. The crude was extracted with ethyl acetate and washed with water/brine, dried over magnesium sulphate, filtered and concentrated. The crude was purified by flash chromatography (50% ethyl acetate in hexanes gradient) to get two fractions:

F1: oil, 173 mg HPLC-MS tr = 3.77 min (100%)

F2: colorless solid, 68 mg HPLC-MS tr = 3.23 min (100%)

None of the MS matched with the expected mass. The 1H-NMR spectra shows that F1 is the expected compound whilst F2 the corresponding carboxylic acid from saponification.

^{1}H-NMR (400 MHz, CDCl3) δ ppm -0.12 (s 9H), 2.09 (t J=8 Hz, 2H), 2.21 (t J=8Hz, 2H), 3.90 (s 3H), 3.97 (s 3H), 6.29 (s 2H), 6.26 (d J=8Hz 1H), 7.10 (t J=8Hz 1H), 7.25 (s 1H), 7.27 (s 1H).

Intermediate 184: 7-methoxy-1-(2-trimethylsilylethoxymethyl)indole-2-carboxylic acid

Methyl 7-methoxy-1-(2-trimethylsilylethoxymethyl)indole-2-carboxylate (Intermediate 183; 173 mg, 0.515 mmol) was dissolved in THF (2,58 mL) and water (430 uL), and LiOH monohydrate (65 mg) was added. The reaction was stirred overnight at room temperature. As the reaction is not finished yet, LiOH monohydrate (65 mg) was added and the reaction was warmed to 55 ºC for 4 h. The mixture was acidified with HCl 1 M to pH 7 and extracted with

ethyl acetate. The organic phase was dried, filtered and concentrated to afford 114 mg of the desired carboxylic acid.

HPLC-MS: tr = 3.25 min. LRMS (m/z): 204 (M+1)

Intermediate 185: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-(2-trimethylsilylethoxymethyl)indole-2-carboxamide

To a solution of 7-methoxy-1-(2-trimethylsilylethoxymethyl)indole-2-carboxylic acid (Intermediate 184; 187 mg, 0.582 mmol) and HATU (553 mg, 1.45 mmol) in DMF (2 mL) was added DIPEA (250 uL) and the mixture was stirred at room temperature for 60 min.The mixture was diluted in water and extracted with ethyl acetate, dried, filtered and concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 90 mg, 0.484 mmol) in DMF (3 ml) at 0ºC. NaH (60%, 58 mg, 0.16 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (1 mL) was added dropwise. The mixture was stirred at rt. for 1 h. The crude was then quenched with NH4Cl and extracted with ethyl acetate to get an oil. The crude was purified by flash chromatography (50% ethyl acetate in hexanes gradient) to afford the title compound as a white solid (182 mg; 76%).

HPLC-MS: tr = 3.85 min, LRMS (m/z): 489/491 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 12.42 (s, 1H), 8.85 (s, 1H), 8.50 (s, 1H), 7.35 – 7.31 (m, 2H), 7.10 (t, J = 7.9 Hz, 1H), 6.84 – 6.77 (m, 1H), 6.36 (s, 2H), 3.98 (s, 3H), 3.53 – 3.46 (m, 2H), 3.08 (d, J = 4.8 Hz, 3H), 0.87 – 0.79 (m, 2H), -0.14 (s, 7H).

Intermediate 186: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-(2-trimethylsilylethoxymethyl)indole-2-carboxamide

A solution of [2-chloro-5-(methylcarbamoyl)-4-pyridyl]carbamoyl 7-methoxy-1-(2-trimethylsilylethoxymethyl)indole-2-carboxylate (Intermediate 185; 182 mg, 0.34 mmol), 2,6-dimethylpyrimidin-4-amine (63 mg, 0.511 mmol), Pd2(dba)3 (31 mg, 0.034 mmol), Xantphos (40 mg, 0.069 mmol) and cesium carbonate (334 mg, 0.68 mmol) was heated in dioxane (3,4 mL) at 100 ºC for 4 h. The crude was extracted with ethyl acetate and washed with brine, dried, filtered and concentrated. The residue was purified by flash chromatography (100% DCM to 5 % MeOH in DCM gradient) to obtain 115 mg (54%) of the title compound as a yellowish solid

HPLC-MS: tr = 2.78 min, LRMS (m/z): 576 (M+1)

Intermediate 187: methyl 4-methoxy-1H-indole-2-carboxylate

Sodium (metal, 175 mg, 7.6 mmol) was added to anhydrous methanol (2,5 mL) and the solution was cooled to 0 ºC. 3-methoxybenzaldehyde (250 mg, 1.84 mmol) and methyl 2-azidoacetate (0.72 mL, 7.4 mmol) was dissolved in methanol (1 mL + 0.5 mL wash) and the solution was added dropwise to the previous sodium methoxide solution at 0 ºC. The mixture was stirred for 90 min at 0 ºC. A yellow, slurry solution was observed. The solution was diluted in diethyl ether and extracted, washed with brine, dried, filtered and concentrated.The crude was dissolved in xylene (9.2 mL) and heated at 138 ºC for 1 h. One peak was observed by hplc. The solution was concentrated to get a yellow solid which was purified by flash chromatography (80:20, hexanes/ethyl acetate) to get 134 mg (35%) of title compound as a yellowish solid.

HPLC-MS: tr = 2.53 min. LRMS (m/z): 206 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 8.84 (bs, 1H), 7.34 (dd, J = 2.2, 1.0 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.01 (dt, J = 8.3, 0.7 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H)

Intermediate 188: acid 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-methoxy-indole-2-carboxylic

Sodium hydride (32 mg, 60%, 0.8 mmol) was added to a solution of methyl 4-methoxy-1H-indole-2-carboxylate (Intermediate 187; 109 mg, 0.53 mmol) in DMF (5.3 mL) at 0 ºC. 2-Bromoethoxy-tert-butyl-dimethyl-silane (137 uL, 0.64 mmol) was added to the mixture and the reaction was stirred at this temperature for 1 h. The reaction was stirred overnight at room temperature. As the reaction is not finished yet, additional quantities of sodium hydride (16 mg, 0-4 mmol) and 2-Bromoethoxy-tert-butyl-dimethyl-silane (68 uL, 0.32 mmol) were added to the reaction. Water and AcOEt were added, the organic phase being dried and concentrated. The crude was purified by flash chromatography (70:20, hexanes/ethyl acetate) to afford 110 mg (57%) of title compound as a solid.

HPLC-MS: tr = 3.50 min. LRMS (m/z): 350 (M+1)

Intermediate 189: 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-indole-2-carboxamide

To a solution of 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-4-methoxy-indole-2-carboxylic acid (Intermediate 188; 151 mg, 0.477 mmol) and HATU (384 mg, 1.01 mmol) in DMF (3 mL) was added DIPEA (175 uL, 0.69 mmol) and the mixture was stirred at room temperature for 60

min. The mixture was diluted in water and extracted with ethyl acetate, dried, filtered and concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 55 mg, 0.296 mmol) in DMF (2 ml) at 0ºC, NaH (60%, 32 mg, 0.800 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling again to 0ºC the activated acid in DMF (1 mL) was added dropwise and the mixture was stirred at rt. 1 h later, the reaction is completed. The crude was purified by flash chromatography (5% methanol in DCM gradient) to get 115 mg (75%) of title compound as a solid.

HPLC tr = 4.12 min. LRMS (m/z): 517/519 (M+1, Cl)

Intermediate 190: 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-indole-2-carboxamide

A solution of 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-N-(2-chloro-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-2-carboxamide (Intermediate 189; 115 mg, 0.22 mmol), 2,6-dimethylpyrimidin-4-amine (41 mg, 0.341 mmol), Pd2(dba)3 (20 mg, 0.022 mmol), Xantphos (26 mg, 0.045 mmol) and cesium carbonate (217 mg, 0.68 mmol) was heated in dioxane (2.2 mL) at 100 ºC. After 3h the crude was extracted with ethyl acetate and washed with brine, dried, filtered and concentrated. The residue was purified by flash chromatography (100% DCM to 10 % MeOH in DCM gradient) to obtain 97 mg (72%) of title compound as a yellowish solid.

HPLC-MS: tr = 3.02 min. LRMS (m/z): 604 (M+1)

Intermediate 191: methyl 3-bromo-2-methoxy-benzoate

To a solution of 3-bromo-2-methoxy-benzoic acid (250 mg, 1.08 mmol) in 6 mL of methanol was added dropwise sulphuric acid (500 uL) and the mixture was stirred at reflux overnight. The reaction is quenched in a saturated NaHCO3 saturated solution and the aqueous phase was extracted with CH2Cl2 (x 3). The combined organic solutions were washed with NaCl sat. solution and dried over anh. MgSO4, filtered and evaporated to afford the title compound as a colorless oil (244 mg, 92 %).

HPLC-MS: tr = 2.82 min. (99 %). LRMS (m/z): 245/247 (M+1, Br)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.93 (s, 6H), 7.04 (t, J = 7.9 Hz, 1H), 7.70 – 7.77 (m, 2H).

Intermediate 192: methyl 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)benzoate

A mixture of methyl 3-bromo-2-methoxy-benzoate (Intermediate 191, 925 mg, 0.377 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1450 mg, 5.71 mmol), PdCl2dppf (155 mg, 0.19 mmol), potassium acetate (1100 mg, 11.2 mmol) in 30 ml of dioxane was stirred at 110ºC overnight. Once at room temperature the mixture was filtered through a pad of Celite that was washed with AcOEt. The filtrates were concentrated and the residue was purified by flash chromatography through a Merck column (40 g) eluting with DCM to obtain 710 mg (64%) of title compound as a colourless oil.

UPLC-EM tr =1.77 min (76%). LRMS (m/z): 293 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 7.85 (d, J = 7.6 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.36 (s, 12H).

Intermediate 193: methyl 2-methoxy-3-(trideuteriomethyl)benzoate

In a pressure vessel a mixture of methyl 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (Intermediate 192; 167 mg, 0.91 mmol), potassium tert-butylate (272 mg, 2.42 mmol) and 20 mL of tert-amyl alcohol were placed. After bubbling argon for 1 minute palladium (II) acetate (25 mg, 0.111 mmol), tri-o-phenylphosphine (62 mg, 0.20 mmol) and trideuterio(iodo)methane (0.25 mL, 4.02 mmol) were added and the mixture was heated at 65ºC overnight.After cooling to room temperature the mixture was filtered through a pad of Celite that was washed with AcOEt. The filtrates are concentrated and the residue is partitioned in AcOEt/4% sodium hydrogen carbonate solution. The aqueous phase is re-extrated with AcOEt (x3). The combined organic phases are dried and concentrated. The residue (386 mg) is purified through Isolera (Merck column 10 g) eluting with hexane from 0% to 5% AcOEt to afford 167 mg (45%) of title compound as a colorless oil.

UPLC-EM tr =1.43 min (98%).

^{1}H NMR (400 MHz, CDCl3) δ ppm 7.64 (dd, J = 7.8, 1.8 Hz, 1H), 7.34 (dd, J = 7.5, 1.8 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 3.92 (s, 3H), 3.83 (s, 3H).

Intermediate 194: 2-methoxy-3-(trideuteriomethyl)benzoic acid

A mixture of methyl 2-methoxy-3-(trideuteriomethyl)benzoate (Intermdiate 193; 167 mg, 0.91 mmol), LiOH·H2O (115 mg, 2.74 mmol), 2 mL of MeOH, 4 mL of THF and 2 mL of water is stirred at room temperature overnight. After evaporating and adding some water to the residue

the pH is adjusted to 2 with 2N HCl and the mixture is extracted with AcOEt. The organic phase is dried and concentrated to give 147 mg (95%) of title compound as a white solid.

uPLC-EM tr =1.16 min (100%). LRMS (m/z): 168 (M-1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.50 (dd, J = 7.7, 1.8 Hz, 1H), 7.38 (dd, J = 7.5, 1.8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 3.73 (s, 3H).

Intermediate 195: 6-chloro-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 2-methoxy-3-(trideuteriomethyl)-benzoic acid (Intermediate 194; 145 mg, 0.86 mmol) and HATU (492 mg, 1.30 mmol) in DMF (3 ml) was added DIPEA (0.23 mL, 1.32 mmol) and the mixture was stirred at room temperature for 60 min. After 90 min water (75 ml) was added and the intermediate activated ester was extracted with AcOEt. The organic fraction was washed with brine (x 2), dried and evaporated to afford 309 mg of a brown solid. In a 5 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 80 mg, 0.43 mmol) in DMF (2 ml) at 0ºC. NaH (60%, 55 mg, 1.32 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling again to 0ºC the activated acid in DMF (1 mL) was added dropwise and the mixture was stirred overnight at rt. Water was added, the mixture extracted with AcOEt (x3) and the organic washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a yellow semisolid which weights 188 mg. It is suspended in ethyl ether and the solid filtered to afford 128 mg (88%) of title compound which is used without purification in the next synthetic step.

uPLC-MS tr = 1.64 min (100 %). LRMS (m/z): 337/339 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.34 (s, 1H), 9.03 – 8.89 (m, 1H), 8.70 (s, 1H), 8.67 (s, 1H), 7.71 (dd, J = 7.8, 1.7 Hz, 1H), 7.50 (dd, J = 7.5, 1.7 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 3.76 (s, 3H), 2.81 (d, J = 4.6 Hz, 3H).

Intermediate 196: 6-methyl-2-morpholino-pyrimidin-4-amine

A suspension of 2-chloro-6-methyl-pyrimidin-4-amine (150 mg, 1.04 mmol), morpholine (180 uL, 2.08 mmol) and 1.7 mL of toluene was heated to 115ºC overnight. Next day, there is a crystalline solid that was filttered-off and dried in vacuo affording 134 mg (66%) of title compound (hygroscopic).

uPLC-MS tr = 0.42 min (100 %). LRMS (m/z): 195 (M+1)

Intermediate 197: 2-[4-(4-amino-6-methyl-pyrimidin-2-yl)piperazin-1-yl]ethanol

A suspension of 2-chloro-6-methyl-pyrimidin-4-amine (150 mg, 1.04 mmol), 2-piperazin-1-ylethanol (256 uL, 2.08 mmol) and 1.7 mL of toluene was heated to 115ºC overnight. Next day there is still starting material so 1 extra eq of amine was added and the heating prosecuted for 6 hr. A brown solid appeared and was filtered off and washed with toluene to afford 303 mg (overweight) of title compound.

uPLC-MS tr = 0.18 min (80 %). LRMS (m/z): 238 (M+1)

Intermediate 198: 2-[4-(2-methoxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-amine

A suspension of 2-chloro-6-methyl-pyrimidin-4-amine (150 mg, 1.04 mmol), 1-(2-methoxyethyl)piperazine (311 uL, 2.09 mmol) and 1.7 mL of toluene was heated to 115ºC overnight. Next day a viscous brown oil was isolated and used per se in the next synthetic step.

UPLC-MS tr = 0.20 min (98 %). LRMS (m/z): 252 (M+1)

Intermediate 199: 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-methoxy-indole-2-carboxylic acid

Sodium hydride (60% in mineral oil, 102 mg, 2.55 mmol) was added to a solution of methyl 3-methoxy-1H-indole-2-carboxylate (350 mg, 1.71 mmol) in DMF (9 mL) at rt. 2-Bromoethoxy-tert-butyl-dimethyl-silane (439 µL, 2.05 mmol) was added to the mixture and the reaction was stirred at rt. overnight. Equivalent amounts of bromosilane and sodium hydride were added and let the reaction stir 24h additional hours. The reaction was quenched by the addition of aqueous saturated NH4Cl solution. The product was extracted with EtOAc (2x), then the organic phase was dried (MgSO4), filtered and solvent removed. The orange oil obtained was purified by flash chromatography (Biotage, SNAP 40g) by using DCM/DCM-MeOH (5%). 236 mg (42%) of title compound as an orange oil was thus isolated.

HPLC-MS tr = 3.55 min (80%). LRMS (m/z): 350 (M+1)

Intermediate 200: 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-indole-2-carboxamide

To a solution of 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-methoxy-indole-2-carboxylic acid (Intermediate 199; 240 mg, 0.687 mmol) and HATU (261 mg, 0.687 mmol) in DMF (2 ml) was added DIPEA (120 µL, 0.69 mmol) and the mixture was stirred at room temperature. Since acid was still present after 1h of reaction, more HATU (66mg) and DIPEA (30 µL) were added

and the mixture was stirred for 30 additional minutes. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAc then the organic phases were washed with brine (3x), dried (MgSO4), filtered and concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 75 mg, 0.404 mmol) in DMF (2 ml) at 0ºC. NaH (60%, 32 mg, 0.8 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling again to 0ºC the activated acid in DMF was added dropwise and the mixture was stirred at 0ºC for 15 min. Water and EtOAc were added, phases separated and the organic phase was further washed with brine (2x), dried (MgSO4), filtered and solvent removed. The white solid was purified by flash chromatography (Biotage, SNAP 12g) by using DCM//DCM-MeOH (2%) to afford the title compound (182 mg, 87%) as an off white solid.

HPLC-MS tr = 4.07 min (99%). LRMS (m/z): 517/519 (M+1; Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.28 (s, 6H), 0.63 (s, 9H), 2.84 (d, J = 4.6 Hz, 3H), 3.83 (t, J = 5 Hz, 2H), 4.24 (s, 3H), 4.69 (t, J = 5 Hz, 2H), 7.08-7.13 (m, 1H), 7.33 (ddd, J = 8, 7 and 1 Hz, 1H), 7.58 (d, J= 8 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 8.59 (s, 1H), 8.66 (s, 1H), 8.87-8.92 (m, 1H), 12.01 (s, 1H).

Intermediate 201: 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-indole-2-carboxamide

1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-indole-2-carboxamide (Intermediate 200; 100 mg, 0.193 mmol), 2,6-dimethylpyrimidin-4-amine (38 mg, 0.309 mmol), Pd2(dba)3 (18 mg, 0.02 mmol), Xantphos (22 mg, 0.038 mmol) and cesium carbonate (126 mg, 0.387 mmol) were heated in dioxane (4 mL) at 100ºC for 2 hr. Water and EtOAc were added and the phases separated. The organic phase was dried, filtered and solvent removed. The residue obtained was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (5%) to afford 72 mg (61%) of title compound.

HPLC-MS tr = 2.95 min (95%). LRMS (m/z): 604 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm -0.28 (s, 6H), 0.62 (s, 9H), 2.32 (s, 3H), under dmso (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 3.89 (t, J = 5 Hz, 2H), 4.22 (s, 3H), 4.68 (t, J = 5 Hz, 2H), 7.10 (ddd, J = 8, 7 and 1 Hz, 1H), 7.31-7.35 (m, 2H), 7.57 (d, J= 8.7 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 8.56 (s, 1H), 8.61-8.65 (m, 1H), 9.30 (s, 1H), 10.25 (s, 1H), 12.12 (s, 1H), 12.01 (s, 1H).

Intermediate 202: 6-chloro-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

To a solution of 2-methoxy-3-(trideuteriummethyl)-benzoic acid (Intermediate 194; 150 mg, 0.80 mmol) and HATU (910 mg, 2.4 mmol) in DMF (5 ml) was added DIPEA (0.42 mL, 2.41 mmol) and the mixture was stirred at room temperature for 90 min. Water (75 ml) was added and the sticky solid was extracted with AcOEt. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have 660 mg of a brown solid corresponding to the activated ester especies. In a 5 mL round bottomed flask vial was placed 4-amino-6-chloro-N-trideuteratedmethyl-pyridine-3-carboxamide (Preparation 4; 150 mg, 0.795 mmol) in DMF (5 ml) at 0ºC and NaH (60%, 100 mg, 1.32 mmol) was added. The mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (1 mL) was added dropwise. The mixture was stirred overnight at rt. Water was added. The mixture extracted with AcOEt (x1) and the organic washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a yellow semisolid which weights 434 mg. This crude is suspended in ethyl ether and the solid filtered, to obtain 227 mg (84%) of a pale cream solid that was used without purification in the next synthetic step.

UPLC-MS tr = 1.63 min (100%). LRMS (m/z): 340/342 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 12.15 (s, 1H), 8.88 (s, 1H), 8.46 (s, 1H), 7.86 (dd, J = 7.8, 1.8 Hz, 1H), 7.38 (dd, J = 7.5, 1.8 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 6.27 (bs, 1H), 3.86 (s, 3H).

Intermediate 203: 6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-amine

A suspension of 2-chloro-6-methyl-pyrimidin-4-amine (150 mg, 1.04 mmol) and 1-methylpiperazine (464 uL, 4.18 mmol) in 1.7 mL of toluene was heated to 110ºC for 3 hr. The mixture was cooled down and a solid appeared

uPLC-MS tr = min (98 %). LRMS (m/z): (M+1)

Intermediate 204: 6-chloro-4-[(3,5-difluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 3,5-difluoro-2-methoxy-benzoic acid (81 mg, 0.43 mmol) and HATU (246 mg, 0.65 mmol) in DMF (2 ml) was added DIPEA (113 µL, 0.65 mmol) and the mixture was stirred at room temperature for 60 min. Water was added and the sticky solid that appeared was isolated by the addition-separation of AcOEt. The organic fraction was washed with brine (x

2), dried over anh. MgSO4, filtered and evaporated to have a brown oil. In a 25 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 40 mg, 0.21 mmol) in DMF (1.5 ml) at 0ºC. NaH (60%, 25 mg, 0.62 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (1 mL) was added dropwise. The mixture was stirred at rt. for 30 min. NH4Cl sat. was added followed by water and EtOAc and the phases separated. The organic was washed with brine (x 3), dried over anh. MgSO4, filtered and evaporated to have a slightly yellow solid which was precipitated with MeOH to afford the title compound as a white solid (59 mg, 77 %).

HPLC-MS: tr = 2.95 min. (99 %). LRMS (m/z): 356/358 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.79 – 2.85 (m, 3H), 4.03 (s, 3H), 7.56 (dd, J = 9.1, 5.1 Hz, 1H), 7.63 – 7.76 (m, 1H), 8.64 (s, 1H), 8.68 (s, 1H), 8.99 (d, J = 8.0 Hz, 1H), 12.38 (s, 1H).

Intermediate 205: 7-methoxy-1-methyl-indole-6-carboxylic acid

A mixture of methyl 7-methoxy-1-methyl-indole-6-carboxylate (prepared according to WO2010084185; 213mg, 0.97mmol), MeOH/water (5:1, 1.8mL) and NaOH (78mg, 1.95mmol) was stirred at room temperature overnight and then at 50ºC for 24 hr. The solvent was evaporated, water was added and pH adjusted to 4-5. After extracting with AcOEt (x2) the organic phase was dried over MgSO4, filtered and evaporated to dryness to give the title compound (80mg, 40%) as a pale blue solid.

HPLC/MS tr = 2.18 min (96%). LRMS (m/z): 206 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 4.05 (s, 3H), 4.08 (s, 3H), 6.52 (d, J = 3.0 Hz, 1H), 7.15 (d, J = 3.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H).

Intermediate 206: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-methyl-indole-6-carboxamide

To a solution of 7-methoxy-1-methyl-indole-6-carboxylic acid (Intermediate 205; 66mg, 0.32mmol) and HATU (123mg, 0.32mmol) in DMF (1mL) was added DIPEA (56.3uL, 0.32mmol) and the mixture was stirred at room temperature. Water was added and the intermediate extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. 2-amino-4-chloro-N-methyl-benzamide (Preparation 3; 40mg, 0.21mmol) was solved in DMF (1mL) and cooled at 0ºC. Then NaH (60%, 26mg, 0.65mmol) was added and stirred for 30min at room temperature. After cooling again to 0ºC the activated

acid was added dropwise solved in DMF (1mL) and stirred at room temperature for 1 hr. Water was added and the mixture was extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos12g) using dichloromethane/MeOH (up to 5%) (220nm) to give the title compound (57mg, 71%) as a white solid-

HPLC/MS tr =2.83 min (98%). LRMS (m/z): 373,375 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.02 – 3.05 (m, 3H), 3.98 (s, 3H), 4.13 (s, 3H), 6.50 (d, J = 3.0 Hz, 1H), 7.13 (d, J = 3.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 8.63 (s, 1H), 8.97 (s, 1H), 12.21 (s, 1H).

Intermediate 207: methyl 7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxylate

Methyl 7-methoxy-1H-indole-6-carboxylate (Prepared according to J.Med.Chem 2012, 55(19) 8524; 200 mg, 0.97 mmol) was solved in DMF (2mL). Cesium carbonate (952 mg, 2.92 mmol) was added and stirred at room temperature for 10min. Then 2,2,2-Trifluoroethyl trifluoromethanesulphonate (241uL, 1.67mmol) was added and the mixture was stirred at room temperature for 2 hr. Water and AcOEt were added and the organic phase was washed with water (x2), brine (x2) and was dried over MgSO4, filtered and concentrated. The crude was purified by flash chromatography (Biotage Telos12g) using hexane/dichloromethane (227nm) to give the title compound (252mg, 90%) as a white solid

HPLC/MS tr = 2.92 min (96%). LRMS (m/z): 288 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.95 (s, 3H), 3.98 (s, 3H), 5.09 (q, J = 8.7 Hz, 2H), 6.59 (d, J = 3.2 Hz, 1H), 7.18 (dd, J = 3.2, 1.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H).

Intermediate 208: 7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxylic acid

A mixture of methyl 7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxylate (Intermediate 207; 252mg, 0.88mmol), MeOH/water (5:1, 1.8mL) and NaOH (70mg, 1.75mmol) was stirred at 50ºC overnight. The solvent evaporated, water was added and pH adjusted to 4-5. After extracting with AcOEt (x2), the organic phase was dried over MgSO4, filtered and concentrated to give the title compound (195mg, 81%) as a white solid.

HPLC/MS tr = 2.47 min (97%). LRMS (m/z): 274 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.90 (s, 3H), 5.28 (q, J = 9.1 Hz, 2H), 6.62 (d, J = 3.2 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 3.2 Hz, 1H).

Intermediate 209: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxamide

To a solution of 7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxylic acid (Intermediate 208; 88mg, 0.32mmol) and HATU (123mg, 0.32mmol) in DMF (1mL) was added DIPEA (56.3uL, 0.32mmol) and the mixture was stirred at room temperature for 30 min. Water was added and the mixture was extracted with AcOEt (x2). The organic phase was dried over MgSO4, filtered and evaporated to dryness. 2-amino-4-chloro-N-methyl-benzamide (Preparation 3; 40mg, 0.21mmol) was solved in DMF (1mL) and cooled at 0ºC. Then NaH (60%, 26mg, 0.65mmol) was added and stirred for 30min at room temperature. After cooling again to 0ºC the activated acid was added dropwise solved in DMF (1mL) and stirred at room temperature for 1 hr. Water was added and the mixture was extracted with AcOEt, washed with water (x2) and brine (x2). The organic phase was dried over MgSO4, filtered and concentrated. The crude was purified by flash chromatography (Biotage Telos12g) using dichloromethane/MeOH (up to 5%) (220nm) to give the title compound (56mg, 59%) as a colourless oil-

HPLC/MS tr = 3.00 min (100%). LRMS (m/z): 441,443 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3) δ ppm 3.02 (d, J = 4.5 Hz, 3H), 3.99 (s, 3H), 5.13 (q, J = 8.6 Hz, 2H), 6.64 (d, J = 3.3 Hz, 1H), 7.26 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 8.74 (s, 1H), 9.00 (s, 1H), 12.26 (s, 1H).

Intermediate 210: 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-(cyclopropanecarbonylamino)-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-indole-2-carboxamide

A mixture of 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-indole-2-carboxamide (Intermediate 200; 100 mg, 0.193 mmol), cyclopropanecarboxamide (38 mg, 0.309 mmol), Pd2(dba)3 (18 mg, 0.02 mmol), Xantphos (22 mg, 0.038 mmol) and cesium carbonate (126 mg, 0.387 mmol) was heated in dioxane (4 mL) at 100ºC for 3.5 hr. Water and EtOAc were added and phases separated. The organic phase was dried, filtered and concentrated. The residue obtained was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (5%) to afford 25 mg (30%) of title compound.

HPLC/MS tr = 1.88 min (99%). LRMS (m/z): 567 (M+1)

^{1}H NMR (DMSO-d6, 400 MHz) δ ppm -0.29 (s, 6H), 0.63 (s, 9H), 0.80-0.88 (m, 4H), 1.99-2.05 (m, 1H), 2.82 (d, J = 4.5 Hz, 3H), 3.84 (t, J = 5 Hz, 2H), 4.20 (s, 3H), 4.68 (t, J = 5 Hz, 2H), 7.09 (ddd, J = 8, 7 and 1 Hz, 1H), 7.31 (ddd, J = 8, 7 and 1 Hz, 1H), 7.58 (d, J= 8.7 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 8.55 (s, 1H), 8.67-8.71 (m, 1H), 9.38 (s, 1H), 10.89 (s, 1H), 12.05 (s, 1H).

Intermediate 211: Ethyl 2-[(2-ethoxy-2-oxo-ethyl)amino]benzoate

To a stirred solution of ethyl 2-aminobenzoate (1g, 6.05 mmol) in DMF (5 ml) was added ethyl 2-bromoacetate (680 µL, 6.13 mmol) at rt, then it was heated at 80ºC for 16h. The reaction mixture was allowed to cool to rt and then was poured into ice water (25ml), the resulting solution being extracted with EtOAc (2x). The combined extracts were washed with saturated aqueous NaHCO3 (2x), water (3x) and brine, dried (over MgSO4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (Biotage, SNAP 40g) by using hexane/hexane-EtOAc (95-5) from 0 to 100% to give 971 mg (64%) of the title compound as white solid.

HPLC-MS tr = 3.13 min (86%). LRMS (m/z): 252 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.30 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 4.00 (d, J = 5.4 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 6.53 (dd, J = 8.4 and 1 Hz, 1H), 6.65 (ddd, J = 8, 7 and 1 Hz, 1H), 7.33-7.38 (m, 1H), 7.95 (dd, J = 8 and 2 Hz, 1H), 8.19 (t, J = 5.4 Hz, 1H).

Intermediate 212: ethyl 3-hydroxy-1H-indole-2-carboxylate

To a solution of ethyl 2-[(2-ethoxy-2-oxo-ethyl)amino]benzoate (Intermediate 211; 955 mg, 3.8 mmol) in anhydrous toluene (10 ml) was added sodium ethoxide (388 mg, 5.7 mmol) at 110ºC. After 2h the reaction was cooled down, and the solid was filtrated and washed with more toluene. Then it was washed with cold MeOH but the solid was solubilized. So the filtrate was concentrated and water was added. The aqueous solution was neutralised by the addition of 1N HCl, and it was extracted with EtOAc and concentrated. The green solid residue was purified by flash chromatography (Biotage, SNAP 40g) by using hexane/DCM from 0 to 100% to give 490 mg (63%) of title compound as a white solid.

HPLC-MS tr = 2.50 min (94%). LRMS (m/z): 206, 224 (M+1, M+1+18)

NMR 1H (400 MHz, CDCl3) δ ppm 1.43 (t, J = 7.1 Hz, 3H), 4.44 (q, J = 7.1 Hz, 2H), 7.10 (ddd, J = 8, 7 and 1 Hz, 1H), 7.27 (dm, J = 8.3 Hz, 1H), 7.34 (ddd, J = 8.3, 7 and 1 Hz, 1H), 7.74 (dm, J = 8 Hz, 1H), 7.79+ (br s, 1H).

Intermediate 213: ethyl 3-methoxy-1H-indole-2-carboxylate

To a solution of ethyl 3-hydroxy-1H-indole-2-carboxylate (Intermediate 212; 1 g, 4.87 mmol) in THF (20 ml) was added (trimethylsilyl)diazomethane solution (2M in hexane, 10 ml, 20 mmol) and MeOH (10 ml) and the mixture was stirred at rt for 24h. Solvent was removed and water was added. The product was extracted with DCM (2x), the organic phase was dried (MgSO4), filtered and solvent removed. The residue was purified by flash chromatography (Biotage, SNAP 40g) by using Hexane/Hexane-EtOAc (7/3) from 0 to 100% to afford 912 mg (85%) of title compound as a white solid

HPLC-MS tr = 2.65 min (92%). LRMS (m/z): 220 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.43 (t, J = 7.1 Hz, 3H), 4.13 (s, 3H), 4.43 (q, J = 7.1 Hz, 2H), 7.11 (ddd, J = 8, 4.4 and 3.5 Hz, 1H), 7.31 (t, J = 1 Hz, 1H), 7.32 (d, J = 1 Hz, 1H), 7.76 (dm, J = 8 Hz, 1H), 8.31 (br s, 1H).

Intermediate 214: 3-methoxy-1-(2-methoxyethyl)indole-2-carboxylic acid

Sodium hydride (68 mg, 60%, 1.70 mmol) was added to a solution of ethyl 3-methoxy-1H-indole-2-carboxylate (Intermediate 213; 250 mg, 1.14 mmol) in DMF (30 mL) at 0 ºC. 1-bromo-2-methoxy-ethane (129 uL, 1.37 mmol) was added to the mixture and the reaction was stirred at rt. for 1 hr. Additional 100 µL of 1-chloro-2-methoxyethane were added and the mixture was stirred for 1 hr. An additional equivalent of NaH was then added and the stirring prosected for 72 hr. Water and EtOAc were added and the phases separated, being the organic phase discarded. The aqueous phase was acidified to pH 4 by the addition of 1N HCl and then it was extracted with EtOAc (2x). The organic phase was washed with brine (3x), dried (MgSO4), filtered and solvent removed. The residue obtained (183 mg; 64%) as a pale orange oil that solidifies overtime was used in the next step without further purification.

HPLC-MS tr = 2.38 min (97%). LRMS (m/z): 250 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.16 (s, 3H), 3.57 (t, J = 5.5 Hz, 2H), 3.94 (s, 3H), 4.61 (t, J = 5.5 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 7.30 (ddd, J = 8.5, 7 and 1.02 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8 Hz, 1H).

Intermediate 215: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide

To a solution of 3-methoxy-1-(2-methoxyethyl)indole-2-carboxylic acid (Intermediate 214; 171 mg, 0.686 mmol) and HATU (261 mg, 0.686 mmol) in DMF (4 ml) was added DIPEA (120 µL, 0.69 mmol) and the mixture was stirred at room temperature for 30 min. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAc. The organic phases were then washed with brine (3x), dried (MgSO4), filtered and solvent removed. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 75 mg, 0.404 mmol) in DMF (2 ml) at 0ºC. NaH (60%, 32 mg, 0.8 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling to 0ºC again the activated acid in DMF was added dropwise and the mixture was stirred at 0ºC for 30 min. Water and EtOAc were added, phases separated and the organic phase was further washed with brine (2x), dried (MgSO4), filtered and solvent removed. The white solid was purified by flash chromatography (Biotage, SNAP 12g) by using DCM//DCM-MeOH (2%) to afford 69 mg (40%) of title compound as an off white solid.

HPLC-MS tr = 3.13 min (98%). LRMS (m/z): 417/419 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.85 (d, J = 4.6 Hz, 3H), 3.16 (s, 3H), 3.62 (t, J = 5.4 Hz, 2H), 4.27 (s, 3H), 4.71 (t, J = 5.4 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.35 (ddd, J = 8, 7 and 1 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8 Hz, 1H), 8.61 (s, 1H), 8.68 (s, 1H), 8.89-8.92 (m, 1H), 12.04 (s, 1H).

Intermediate 216: ethyl 3-methoxy-1-methyl-indole-2-carboxylate

Sodium hydride (69 mg, 60%, 1.73 mmol) was added to a solution of ethyl 3-methoxy-1H-indole-2-carboxylate (Intermediate 213; 250 mg, 1.14 mmol) in DMF (5 mL) at 0 ºC. 1-bromo-2-methoxy-ethane (86 µL, 1.38 mmol) was added to the mixture and the reaction was stirred at rt for 1 hr. Since no SM was detected a saturated aqueous NH4Cl and EtOAc were added, phases were separated and the organic phase was washed with brine (2x), dried (MgSO4), filtered and concentrated. The residue was purified by flash chromatography (Biotage, SNAP 12g) by using Hexane/Hexane-EtOAc (7/3) from 0 to 100% to afford 184 mg (69%) of title compound as a white solid.

HPLC-MS tr)= 3.03 min (99%). LRMS (m/z): 234 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.35 (t, J = 7.1 Hz, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.34 (q, J = 7.1 Hz, 2H), 7.10 (ddd, J = 8, 7 and 1 Hz, 1H), 7.35 (ddd, J = 8, 7 and 1 Hz, 1H), 7.55 (dt, J = 8 and 1 Hz, 1H), 7.71 (dt, J = 8 and 1 Hz, 1H).

Intermediate 217: 3-methoxy-1-methyl-indole-2-carboxylic acid

The mixture of ethyl 3-methoxy-1-methyl-indole-2-carboxylate (Intermediate 216; 180 mg, 0.772 mmol) and NaOH (186 mg, 4.65 mmol) in MeOH/H2O (3/2.5 ml) was stirred at 55ºC for 2 hr. MeOH was removed and more water was added, the pH was ajusted to 4 by the addition of 1N HCl. The suspension was extracted with EtOAc (2x). The organic phases were dried (MgSO4), filtered and solvent removed to yield 140 mg (88%) of title compound as a white solid.

HPLC-MS tr = 2.37 min (99%). LRMS (m/z): 206 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.89 (s, 3H), 3.93 (s, 3H), 7.07 (ddd J = 8, 7 and 1 Hz, 1H), 7.31 (ddd J = 8,7 and 1 Hz, 1H), 7.51 (dt, J = 8 and 1 Hz, 1H), 7.68 (dt, J = 8 and 1 Hz, 1H).

Intermediate 218: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-methyl-indole-2-carboxamide

To a solution of 3-methoxy-1-methyl-indole-2-carboxylic acid (132 mg, 0.643 mmol) and HATU (246 mg, 0.647 mmol) in DMF (4 ml) was added DIPEA (113 µL, 0.649 mmol) and the mixture was stirred at room temperature for 30 min. Water and EtOAc were added, the organic phase after separation and drying was concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Prepàratrion 3; 75 mg, 0.404 mmol) in DMF (2 ml) at 0ºC. NaH (60%, 32 mg, 0.8 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (5 ml) as a suspension was added dropwise and the mixture was stirred at 0ºC. Water and EtOAc were added, a solid was filtered to give 65 mg 43%) of title compound as a pale yellow solid.

HPLC-MS tr = 3.17 min (98%). LRMS (m/z): 373/375 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.85 (d, J = 4.2, 3H), 3.98 (s, 3H), 4.25 (s, 3H), 7.12 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.60 (s, 1H), 8.69 (s, 1H), 8.91 (br s, 1H), 12.01 (s, 1H).

Intermediate 220: Methyl 4-methoxy-1-methyl-benzimidazole-5-carboxylate and methyl 4-methoxy-3-methyl-benzimidazole-5-carboxylate

To a solution of methyl 4-methoxy-1H-benzimidazole-5-carboxylate (Intermediate 172; 350 mg, 1.69 mmol) in 17 mL of anh. DMF at 0 ºC was added sodium hydride (60 % in oil mineral dispersion, 81 mg, 2.02 mmol)) and the mixture was stirred 10 min. at 0 ºC. Methyl iodide (116 uL, 1.86 mmol) was added dropwise and left to stir at 0 ºC for 1h. After 40 min. the two isomers are present at different proportion (2:1) and starting material is present (12 %). After 2 h the proportion is more or less the same and another impurities are observed. NH4Cl sat. followed by water. The mixture was extracted once with EtOAc and the organic fraction dried over anh. MgSO4, filtered and evaporated to have a brown oil (with DMF) which was removed with the high vacuum pump to have a brown residue which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 5 % MeOH to have both isomers as a brown oil (230 mg, 61 %).
HPLC-MS: tr = 1.48 min. (36 %) and tr = 1.67 min. (62 %). LRMS (m/z): 221 (M+1)

Intermediate 221: 4-methoxy-1-methyl-benzimidazole-5-carboxylic acid and 4-methoxy-3-methyl-benzimidazole-5-carboxylic acid

To the solution of methyl 4-methoxy-1-methyl-benzimidazole-5-carboxylate and methyl 4-methoxy-3-methyl-benzimidazole-5-carboxylate (Intermediate 220; 230 mg, 1.04 mmol) in MeOH/H2O (5/1) was added NaOH (84 mg, 2.10 mmol) and the mixture was heated at 80ºC. After 5h the reaction is complete and the volatiles were removed under reduced pressure. A little quantity of water was added and the pH was lowered to 2-3 with HCl 1N. The volume was reduced in the vacuum to have a brown semisolid which was used for the next step due to the difficulty of isolation.
HPLC-MS: tr = 0.55, 0.92 and 1.25 min. (96 %). LRMS (m/z): 207 (M+1).

Intermediate 222: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-methyl-benzimidazole-5-carboxamide and N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-methyl-benzimidazole-5-carboxamide

To a solution of 4-methoxy-1-methyl-benzimidazole-5-carboxylic acid and 4-methoxy-3-methyl-benzimidazole-5-carboxylic acid (Intermediate 221; 205 mg, 0.99 mmol) and HATU (553 mg, 1.45 mmol) in DMF (2.5 ml) was added DIPEA (253 µL, 1.45 mmol) and the mixture was stirred at room temperature for 60 min. Water was added and the sticky solid which was extracted with AcOEt. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have a brown oil. In a 25 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 90 mg, 0.48

mmol) in DMF (2 ml) at 0ºC. NaH (60%, 58 mg, 1.45 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (1 mL) was added dropwise and the mixture was stirred at rt. After 1h NH4Cl sat. was added followed by water and EtOAc and the phases separated. The organic was washed with water (x 3) and brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a white solid. MeOH was added and a white solid precipitated (mixture of final products, 53 mg, 29 %). HPLC-MS: tr = 1.93 and 2.32 min. (99 %). LRMS (m/z): 374/376 (M+1, Cl)

Intermediate 223: 6-chloro-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 2-methoxy-3-(trideuteriomethyl)benzoic acid (Intermediate 194; 155 mg, 0.92 mmol) and HATU (520 mg, 1.35 mmol) in DMF (3 ml) was added DIPEA (0.25 mL, 1.43 mmol) and the mixture was stirred at room temperature for 2h. uPLC-MS showed total conversion to activated acid. Water (75 ml) was added and the mixture was extracted with AcOEt. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have 302 mg of a brown solid. In a 5 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 85 mg, 0.46 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 60 mg, 1.5 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling again to 0ºC the activated acid in DMF (1 mL) was added dropwise and the mixture was stirred overnight at rt. Water was added. The mixture extracted with AcOEt (x3) and the organic washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have 208 mg of a yellow semisolid. It was suspended in ethyl ether and the solid filtered to afford 146 mg (94%) of title compound that was used per se in the next synthetic step.

UPLC-MS: Rt = 1.71 min (97 %). LRMS (m/z): 336/338 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 13.02 (s, 1H), 9.52 (s, 1H), 9.01 (s, 1H), 7.73 (d, J = 6.6 Hz, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 3.78 (s, 3H), 2.86 (d, J = 4.2 Hz, 3H).

Intermediate 224: 6-chloro-4-[(2,4-difluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 125 mg, 0.67 mmol) in 4 mL of anh. DMF was added sodium hydride (60 % in mineral oil dispersion,

54 mg, 1.35 mmol) at 0 ºC. The mixture was stirred at room temperature for 15 min. (yellow solution). Then, the temperature was lowered to 0 ºC and a solution of 2,4-difluoro-6-methoxy-benzoyl chloride (205 mg, 0.99 mmol) in 1 mL of anh. DMF was added dropwise and the reaction was left to stir at room temperature (orange solution). After 4h major product is observed but accompanied by other mass (366/368 m/z) in the same retention time. More NaH (30 mg) was added and the mixture stirred at room temperature overnight. The next day the chromatogram shows a better conversion (the mass of 366/368 m/z is not so intense), although starting material is present too. Water and AcOEt were added and the phases separated. The aqueous phase is extracted with AcOEt (x 1) and the combined organic extracts were washed with LiCl (5 % solution, x 1), water and brine; dried over anh. MgSO4, filtered and evaporated to have a white solid which was purified via flash chromatography (Biotage) in DCM/DCM with 5 % MeOH to have a white solid (101 mg, 42 %).

HPLC-MS: tr = 2.75 min. (97 %). LRMS (m/z): 356/358 (M+1).

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.90 (s, 3H), 3.94 (s, 3H), 6.67 – 6.75 (m, 1H), 6.86 (dt, J = 10.9, 2.0 Hz, 1H), 8.62 (s, 1H), 8.69 (s, 1H).

Intermediate 225: methyl 4-bromo-1H-pyrazole-5-carboxylate

To a solution of 4-bromo-1H-pyrazole-5-carboxylic acid (500 mg, 2.62 mmol) in 12 mL of methanol was added dropwise sulfuric acid (1 mL) and the mixture was stirred at reflux overnight. The next day the reaction is completed. The reaction is quenched in a saturated NaHCO3 saturated solution and the aqueous phase was extracted with CH2Cl2 (x 3, partially soluble) and the combined organic solutions were joined and washed with NaCl sat. solution and dried over anh. MgSO4, filtered and evaporated to have the crude which was sonicated with Et2O and filtrated to have a white solid (1120 mg, 52 %).

HPLC-MS: tr = 1.77 min. (99 %)

LRMS (m/z): 205/207 (M+1, Br)

Intermediates 226a: methyl 4-bromo-2-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylate and 226b: methyl 4-bromo-1-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylate

To a solution of methyl 4-bromo-1H-pyrazole-5-carboxylate (500 mg, 2.43 mmol) in 24 mL of anh. DMF at 0 ºC was added sodium hydride (60 % in oil mineral dispersion, 117 mg, 2.92 mmol)) and the mixture was stirred 10 min. at 0 ºC. 2-(chloromethoxy)ethyl-trimethyl-silane

(474 uL, 2.67 mmol) was added dropwise and left to stir at 0 ºC for 1h. The reaction is complete (two peaks with the same mass, 3:1 proportion) and NH4Cl sat. was added. The organic phase was washed with water (x 3) and brine (x 1), dried over anh MgSO4, filtered and evaporated to have a brown oil which was purified via flash chromatography in Hx/Hx with 50 % Et2O to have both colorless oils:

226a 236 mg (29%)

HPLC-MS: tr = 3.22 min. (97%). LRMS (m/z): 335/337 (M+1, Br)

226b 459 mg (56%)

HPLC-MS: tr = 3.48 min. (98 %). LRMS (m/z): 335/337 (M+1, Br)

Intermdiate 227: 4-methoxy-2-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylic acid

A mixture of methyl 4-bromo-1-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylate (Intermediate 226b; 213 mg, 0.63 mmol), methanol (3 mL), CuI (6 mg, 0.031 mmol) and lithium tert-butoxide (156 mg, 1.94 mmol) was heated over Ar atmosphere to 120 ºC for 3 h. under microwave conditions. NaHCO3 sat. was added and the mixture washed with EtOAc. The aqueous phase was acidified with HCl 1N to pH 3-4 and extracted with EtOAc (x 3). The combined organic extracts were dried over anh. MgSO4, filtered and evaporated to have a yellowish oil which was purified by flash chromatography in CH2Cl2/CH2Cl2 with 10 % MeOH to afford the title compound as a white solid (131 mg, 76 %).

HPLC-MS: tr = 2.60 min. (85%). LRMS (m/z): 273 (M+1)

Intermediate 228: 6-chloro-4-[[4-methoxy-2-(2-trimethylsilylethoxymethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-methoxy-2-(2-trimethylsilylethoxymethyl)pyrazole-3-carboxylic acid (Intermediate 227; 132 mg, 0.48 mmol) and HATU (369 mg, 0.97 mmol) in DMF (2.5 ml) was added DIPEA (169 µL, 0.97 mmol) and the mixture was stirred at room temperature for 60 min. Water was added and the a sticky solid extracted with AcOEt. The organic fraction was washed with brine (x 2), dried over anh. MgSO4, filtered and evaporated to have a brown oil. In a 25 mL round bottomed flask vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 60 mg, 0.32 mmol) in DMF (1.5 ml) at 0ºC and NaH (60%, 39 mg, 0.97 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (0.5 mL) was added dropwise and the mixture was stirred at rt. After 1h the reaction is finished and water was added. The mixture was extracted

with EtOAc (x1), washed with water (x 3) and brine (x 1), dried over anh. MgSO4, filtered and evaporated. The residue was purified via flash chromatography in CH2Cl2/CH2Cl2 with 5 % MeOH to have a white solid (112 mg, 79 %).

HPLC-MS: tr = 3.32 min. (99 %). LRMS (m/z): 440/442 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ -0.10 (s, 9H), 0.68 – 0.86 (m, 2H), 2.80 – 2.88 (m, 3H), 3.47 – 3.54 (m, 2H), 3.98 (s, 3H), 5.74 (s, 2H), 7.74 (s, 1H), 8.59 (s, 1H), 8.63 (s, 1H), 8.91 (d, J = 5.1 Hz, 1H), 11.85 (s, 1H).

Intermediate 229: 6-chloro-4-[(4-methoxy-1H-pyrazole-5-carbonyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[[4-methoxy-2-(2-trimethylsilylethoxymethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 228; 100 mg, 0.23 mmol) in 2 mL of CH2Cl2 was added trifluoroacetic acid (2 mL) and the mixture was stirred at room temperature. After 1 h the reaction is finished and the volatiles were removed under reduced pressure. NH3 (7N in MeOH, 3 mL) was added and the mixture was stirred at room temperature. After 1 h the reaction is over and the volatiles were removed under reduced pressure, evaporating with MeOH several times to have a white solid. Water was added and solid filtered off, washed with MeOH (x 1) and dried in the vacuum oven to have the title compound as a white solid (55 mg, 78 %).

HPLC-MS: tr = 1.92 min. (99 %). LRMS (m/z): 310/312 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ 2.74 – 2.90 (m, 3H), 3.76 (s, 3H), 7.73 (s, 1H), 8.67 (s, 2H), 8.91 (s, 1H), 12.44 (s, 1H), 13.24 (s, 1H).

Intermediates 230a: 6-chloro-4-[[4-methoxy-1-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide and 230b: 6-chloro-4-[[4-methoxy-2-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide

To a dispersion of 6-chloro-4-[(4-methoxy-1H-pyrazole-5-carbonyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 229; 40 mg, 0.13 mmol) in 1.3 mL of DMF and under Ar, was added cesium carbonate (84 mg, 0.26 mmol) (solubility improves) and 1-bromo-2-methoxy-ethane (13 uL, 0.14 mmol). The mixture was stirred at room temperature. After 40 h 23 %, more cesium carbonate (20 mg) and 1-bromo-2-methoxy-ethane (5 uL) were added and the mixture was left stirring at room temperature for additional 24 hr. Water was added and the mixture extracted with EtOAc (x 2), washed with brine (x 2), dried over anh. MgSO4, filtered

and evaporated to have a crude which was purified via flash chromatography in Et2O/Et2O with 5 % MeOH to have both white solids:

Intermediate 230a: 15 mg (31%)

HPLC-MS: tr = 2.38 min. (93 %). LRMS (m/z): 368/370 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ 2.83 (d, J = 4.6 Hz, 3H), 3.19 (s, 3H), 3.66 (t, J = 5.6 Hz, 2H), 3.96 (s, 3H), 4.64 (t, J = 5.6 Hz, 2H), 7.61 (s, 1H), 8.59 (s, 1H), 8.62 (s, 1H), 8.89 (d, J = 4.6 Hz, 1H), 11.77 (s, 1H).

Intermediate 230b: 28 mg (59%)

HPLC-MS: tr = 2.13 min. (99 %). LRMS (m/z): 368/370 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ 2.82 (d, J = 4.6 Hz, 3H), 3.26 (s, 3H), 3.74 (d, J = 4.8 Hz, 2H), 3.77 (s, 3H), 4.28 (t, J = 5.2 Hz, 2H), 7.75 (s, 1H), 8.64 (s, 1H), 8.67 (s, 1H), 8.91 (d, J = 4.5 Hz, 1H), 12.26 (s, 1H).

Intermediate 231: methyl 4-methoxy-1H-indole-5-carboxylate

The mixture of methyl 7-chloro-4-methoxy-1H-indole-5-carboxylate (205 mg, 0.855 mmol; see preparation in European Journal of Medicinal Chemistry 2019 pag 234), ammonium formate (540 mg, 8.56 mmol) and Pd (0) (91 mg, 0.086 mmol) in MeOH (12 ml) was heated at reflux overnight. The reaction mixture was filtered through Celite and concentrated to give 154 mg (87%) of title compound as a white solid.

HPLC-MS tr: 2.15 min (98%). LRMS (m/z): 206 (M+1)

Intermediate 232: methyl 4-methoxy-1-(2-trimethylsilylethoxymethyl)indole-5-carboxylate

Sodium hydride (60% in mineral oil, 44 mg, 1.1 mmol) was added to a solution of methyl 4-methoxy-1H-indole-5-carboxylate (Intermediate 231; 150 mg, 0.731 mmol) in DMF (4 mL) at 0ºC. After 15 minutes, 2-(chloromethoxy)ethyl-trimethyl-silane (154 µL, 0.878 mmol) was added to the mixture and the reaction was stirred at rt for 4 days.

Since no SM was detected water and EtOAc were added and phases separated, the aqueous phase was further extracted with EtOAc. The organic phases were washed with brine (3x), dried (MgSO4), filtered and concentrated. The residue was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (2%) to afford 170 mg (69%) of title compound.

HPLC-MS tr: 3.42 min. (97%). LRMS (m/z): 336 (M+1)

^{1}H (DMSO, 400 MHz) δ -0.1 (s, 9H), 0.78-0.83 (m, 2H), 3.43-3.48 (m, 2H), 3.81 (s, 3H), 3.98 (s, 3H), 5.55 (s, 2H), 6.71 (dd, J = 4 and 0.8 Hz, 1H), 7.34 (dd, J = 9 and 0.8 Hz, 1H), 7.51-7.55 (m, 2H).

Intermediate 233: 4-methoxy-1-(2-trimethylsilylethoxymethyl)indole-5-carboxylic acid

To the solution of methyl 4-methoxy-1-(2-trimethylsilylethoxymethyl)indole-5-carboxylate (Intermediate 232; 166 mg, 0.495 mmol) in a mixture of MeOH/THF/H2O (3/3/2.5 ml) was added NaOH (147 mg, 3.67 mmol) and the reaction mixture was stirred at rt overnight and at 50ºC for 8 hr. The organic solvent was removed, the pH adjusted to pH 4 and the aqueous phase extracted with EtOAc (3x). The organic phases were dried (MgSO4), filtered and concentrated, the crude acid being used in the next step without further purification. 145 mg (91%) of title compound were thus obtained.

HPLC-MS tr: 3.07 min (92%). LRMS (m/z): 322 (M+1)

^{1}H NMR (DMSO, 400 MHz) δ ppm -0.09 (s, 9H), 0.78-0.83 (m, 2H), 3.43-3.48 (m, 2H), 3.98 (s, 3H), 5.54 (s, 2H), 6.69 (dd, J = 3.2 and 0.4 Hz, 1H), 7.32 (dd, J = 8.8 and 0.4 Hz, 1H), 7.51 (d, J = 3.3 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 12.3 (br s, 1H).

Intermediate 234: N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-(2-trimethylsilylethoxymethyl)indole-5-carboxamide

To a solution of 4-methoxy-1-(2-trimethylsilylethoxymethyl)indole-5-carboxylic acid (Intermediate 233; 166 mg, 0.436 mmol) and HATU (166 mg, 0.436 mmol) in DMF (4 ml) was added DIPEA (76 µL, 0.436 mmol) and the mixture was stirred at room temperature for 30 min. Water and EtOAc were added, the organic phase was washed with water, dried and concentrated. In another vial was placed 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 75 mg, 0.404 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 32 mg, 0.8 mmol) was added and the mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (5 ml) as a suspension was added dropwise and the mixture was stirred at 0ºC for 30 min. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAc, then the organic phases were washed with brine, dried (MgSO4), filtered and solvent removed. The residue was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (2%) to afford 143 mg 81%) of title compound as pale yellow solid.

HPLC-MS tr: 3.55' (99%). LRMS (m/z): 489/491 (M+1; Cl)

^{1}H NMR (DMSO, 400 MHz) δ -0.09 (s, 9H), 0.79-0.84 (m, 2H), 2.85 (d, J = 4.5 Hz, 3H), 3.45-3.50 (m, 2H), 4.30 (s, 3H), 5.57 (s, 2H), 6.93 (d, J = 3 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 3.3 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 8.59 (s, 1H), 8.75 (s, 1H), 8.88-8.93 (m, 1H), 12.33 (s, 1H).

Intermediate 235: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-(2-trimethylsilylethoxymethyl)indole-5-carboxamide

To a solution of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-(2-trimethylsilylethoxymethyl)indole-5-carboxamide (Intermediate 234; 140 mg, 0.286 mmol) in 4 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (56 mg, 0.455 mmol), Pd2(dba)3 (26 mg, 0.028 mmol), Xantphos (33 mg, 0.057 mmol) and cesium carbonate (187 mg, 0.574 mmol) and the mixture was heated at 100ºC for 2.5 hr. After cooling down to room temperature water and EtOAc were added, the organic phase was washed with water and brine (x 1 both), dried over anh. MgSO4, filtered and evaporated. The residue was purified via flash chromatography in CH2Cl2/CH2Cl2 with 5 % MeOH to afford 130 mg (79%) of title compound as a white solid

HPLC-MS tr: 2.62' (97%). LRMS (m/z): 576 (M+1)

^{1}H NMR (DMSO, 400 MHz) δ ppm -0.08 (s, 9H), 0.80-0.85 (m, 2H), 2.33 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 3.45-3.50 (m, 2H), 4.26 (s, 3H), 5.57 (s, 2H), 6.90 (d, J = 3.3 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.47 (s, 1H), 7.56 (d, J = 3.3 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 8.56 (s, 1H), 8.62-8.67 (m, 1H), 9.16 (s, 1H), 10.26 (s, 1H), 12.32 (s, 1H).

Intermediate 236: 6-chloro-4-[(3-methoxypyridine-2-carbonyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 3-methoxypyridine-2-carboxylic acid (506 mg, 3.31 mmol) and HATU (1878 mg, 4.94 mmol) in DMF (12 ml) was added DIPEA (859 µL, 4.93 mmol) and the mixture was stirred at room temperature for 60 min. Water and EtOAc were added, the organic phase was washed with water, dried and concentrated. In another vial NaH (60%, 83.5 mg, 3.48 mmol) was added over a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 331 mg, 1.785 mmol) in DMF (17 ml) at 0ºC. The mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (5 ml) was added dropwise and the mixture was stirred at 0ºC for 30 min. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAc, then the organic

phases were washed with brine, dried (MgSO4), filtered and solvent removed. The residue was slurried with ethyl ether and the solid filtered to afford 104 mg (18%) of title compound as an off-white solid.

UPLC tr: 1.16 min. (97%). LRMS (m/z): 321 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ 12.95 (s, 1H), 8.95 (s, 1H), 8.71 (s, 2H), 8.31 (d, J = 4.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 8.5, 4.4 Hz, 1H), 5.76 (s, 0H), 3.92 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H).

Intermediate 237: 6-chloro-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

This compound was prepared with 86% yield in a similar way as Intermediate 117 but replacing the 2-amino-4-chloro-N-methyl-benzamide (Preparation 3) by 4-amino-6-chloro-N-(trideuteriomethyl)pyridine-3-carboxamide (Preparation 4).

HPLC/MS tr = 1.63 min (99%). LRMS (m/z): 341,343 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 4.07 (s, 3H), 7.20 – 7.30 (m, 1H), 7.50 – 7.59 (m, 1H), 7.73 – 7.75 (m, 1H), 8.69 (s, 2H), 8.91 – 9.02 (m, 1H), 12.30 (s, 1H)

Intermediate 238: 6-chloro-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 3-fluoro-2-methoxy-benzoic acid (123 mg, 0.72 mmol) and HATU (550 mg, 1.4 mmol) in DMF (4 ml) was added DIPEA (250 µL, 1.4 mmol) and the mixture was stirred at room temperature for 1h. Water and EtOAc were added, phases separated and the aqueous phase was further extracted with more EtOAC, then the organic phases were washed with brine (3x), dried (MgSO4), filtered and concentrated. In another vial there was placed 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 90 mg, 0.482 mmol) in DMF (2 ml) at 0ºC and NaH (60%, 60 mg, 1.5 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling to 0ºC again the activated acid in 2 ml DMF was added dropwise and the mixture was stirred at 0ºC for 30 min. Excess water and EtOAc were added and phases separated. The aqueous phase was further extracted with EtOAc, then the organic phases were washed with brine (2x), dried, filtered and concentrated. The solid obtained 108 mg (66%) was used per se in the next synthetic step.

UPLC-MS tr = 1.72 min (90%). LRMS (m/z): 339/341 (M+1, Cl)

Intermediate 239: 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 2,3-dimethoxybenzoic acid (90 mg, 0.49 mmol) and HATU (250 mg, 0.657 mmol) in DMF (2 ml) was added DIPEA (120 µL, 0.689 mmol) and the mixture was stirred at room temperature for 1h. Water and EtOAc were added, the phases separated and the aqueous phase was further extracted with more EtOAC, then the organic phases were washed with brine (3x), dried (MgSO4), filtered and concentrated. In another vial there was placed 4-amino-6-chloro-N-methyl-pyridazine-3-carboxamide (Preparation 6; 40 mg, 0.214 mmol) in DMF (2 ml) at 0ºC, NaH (60%, 25 mg, 0.625 mmol) was added and the mixture was stirred at rt for 30 minutes. After cooling to 0ºC again the activated acid in 1 ml DMF was added dropwise and the mixture was stirred at 0ºC for 30 min. and at room temperature overnight. Excess water and EtOAc were added and phases separated. The aqueous phase was further extracted with EtOAc, then the organic phases were washed with brine (2x), dried, filtered and concentrated. The residue was purified with Isolera through a Merck 10g column eluting with DCM/MeOH from 100% DCM to 5% MeOH to afford the title compound (54 mg; 72%) as a pale brown solid.
UPLC-MS tr = 1.66 min (90%). LRMS (m/z): 351/353 (M+1, Cl)
^{1}H NMR (400 MHz, CDCl3) δ 13.19 (s, 1H), 8.02 (s, 1H), 7.72 (dd, J = 7.9, 1.7 Hz, 1H), 7.60 (dd, J = 7.8, 1.8 Hz, 1H), 7.22 – 7.03 (m, 2H), 3.93 (s, 3H), 3.91 (d, J = 1.1 Hz, 3H), 3.06 (d, J = 5.1 Hz, 3H)

Intermediate 240: 6-chloro-4-[(3,6-difluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 3,6-difluoro-2-methoxy-benzoic acid (152 mg, 0.808 mmol) and HATU (310 mg, 0.815 mmol) in DMF (4 ml) was added DIPEA (137 µL, 0.844 mmol) and the mixture was stirred at room temperature for 30 min. Water and EtOAc were added, the organic phase was washed with water, dried and concentrated. In another vial NaH (60%, 43 mg, 1.075 mmol) was added over a solution of 4-amino-6-chloro-N-methyl-pyridine-3-carboxamide (Preparation 3; 103 mg, 0.555 mmol) in DMF (2 ml) at 0ºC. The mixture was stirred at rt for 30 minutes, then it was cooled to 0ºC again and the activated acid in DMF (0.5 ml) was added dropwise and the mixture was stirred at rt for 3 hr. Water and EtOAc were added, phases were separated and the aqueous phase was further extracted with more EtOAc, then the organic phases were washed with brine, dried (MgSO4), filtered and concentrated. The residue was

purified via flash chromatography in CH2Cl2/ CH2Cl2-MeOH(9:1) to afford 192 mg (97%) of title compound as an off-white solid.

HPLC tr: 2.77 min. (97%). LRMS (m/z): 355/357 (M+1; Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ 12.32 (s, 1H), 9.05 (d, J = 4.7 Hz, 1H), 8.75 (d, J = 0.4 Hz, 1H), 8.53 (s, 1H), 7.52 (ddd, J = 11.4, 9.3, 5.3 Hz, 1H), 7.14 (ddd, J = 9.3, 8.7, 3.4 Hz, 1H), 3.93 (d, J = 2.2 Hz, 4H), 2.75 (d, J = 4.5 Hz, 4H)

Example 1: 4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1, 15 mg, 0.04 mmol) in 0.5 mL of anh. dioxane was added cyclopropanecarboxamide (4 mg, 0.04 mmol), Pd2(dba)3 (4 mg, 0.004 mmol), Xantphos (5 mg, 0.008 mmol) and cesium carbonate (43 mg, 0.19 mmol) and heated at 100 ºC. After 2h 30 min. the reaction is complete and the mixture was cooled down and diluted with DCM and water. Phases were separated and the aqueous fraction was extracted with DCM (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified by flash chromatography in DCM/DCM with 10 % MeOH. The product is the repurified by precipitation in Et2O with a few drops of MeOH. A white solid was thus obtained.

HPLC-MS: tr = 2.57 min (98 %). LRMS (m/z): 391/393 (M+1, Cl)

^{1}H NMR (400 MHz, CD3OD) δ ppm 0.92 (dq, J = 7.4, 4.4, 3.9 Hz, 2H), 1.02 (p, J = 3.9, 3.4 Hz, 2H), 1.90 (dt, J = 7.9, 4.4 Hz, 1H), 2.86 (s, 3H), 7.22 – 7.29 (m, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.52 (td, J = 8.3, 6.1 Hz, 1H), 8.62 (s, 1H), 9.36 (s, 1H)

Example 2: 4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

To the solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 122; 47 mg, 0.139 mmol) in anh dioxane (1.5 ml) was added cyclopropanecarboxamide (35.5 mg, 0.417 mmol) and K2CO3 (58 mg, 0.419 mmol). Reaction mixture was degassed under argon gas for 5 minutes, then Pd2(dba)3 (12.5 mg, 0.013 mmol) and Xantphos (16 mg, 0.027 mmol) were added and the mixture was degassed for an additional 2 minutes. Finally, reaction mixture was heated at 100ºC overnight. The crude was filtered and

solvent removed. The residue was purified by flash chromatography (Biotage, SNAP 12g) EtOAc/EtOAc-MeOH (10%) from 0 to 100% in 30CV. 27 mg (50% yield) of title compound were obtained as a white solid

HPLC-MS tr = 2.77 min (98%). LRMS (m/z): 392/394 (M+1, Cl)

^{1}H NMR (400 MHz, CDCl3+ drop of CD3OD) δ ppm 0.95-1.01 (m, 2H), 1.19-1.23 (m, 2H), 1.72 (tt, J = 7.6 and 4.4 Hz, 1H), 2.98-3.01 (m, 3H), 7.09 (td, J = 8.5 and 1 Hz, 1H), 7.24-7.27 (m 1H), 7.37 (td, J = 8.5 and 6 Hz, 1H), 8.29 (br s, 1H), 9.85 (s, 1H), 12.58 (br s, 1H)

Example 3: 4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1; 100 mg, 0.29 mmol) in 3 mL of anh. dioxane was added (1R,2R)-2-fluorocyclopropanecarboxamide (33,5 mg, 0.04 mmol), Pd2(dba)3 (27 mg, 0.029 mmol), Xantphos (34 mg, 0.058 mmol) and cesium carbonate (286 mg, 0.88 mmol) and heated at 100 ºC. After 2h 30 min. the reaction is complete and the mixture was cooled down and diluted with DCM and water. Phases were separated and the aqueous fraction was extracted with DCM (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified by flash chromatography in DCM/DCM with 10 % MeOH to have a slightly yellow solid (59 mg, 49 %).

HPLC-MS: tr = 2.48 min. (95 %). LRMS (m/z): 409/411 (M+1, Cl)

^{1}H NMR (400 MHz, CD3OD) δ ppm 1.14 – 1.25 (m, 1H), 1.75 – 1.88 (m, 1H), 2.08 – 2.16 (m, 1H), 2.86 (s, 3H), 4.75 – 4.81 (m, 0,5H), 4.95 (td, J = 6.0, 3.8 Hz, 0,5H), 7.22 – 7.29 (m, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.52 (td, J = 8.3, 6.1 Hz, 1H), 8.62 (s, 1H), 9.37 (s, 1H)

Example 4: 4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(2-pyridylamino)pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1; 100 mg, 0.29 mmol) in 2.5 mL of anh. DMF was added pyridin-2-amine (42 mg, 0.44 mmol) and potassium triphosphate (124 mg, 0.58 mmol) and the mixture was degassed for 15 min. using Ar. [(2-di-tertbutylphosphino-2',4',6'-triisopropyl-l, 1 '-biphenyl)-Z-(2'-amino-l, 1 '-biphenyl)] palladium (II) methanesulfonate (23.2 mg, 0.029 mmol) was added and the mixture was degassed for 5 min. The mixture was heated at 50 ºC overnight. The mixture was cooled down to room temperature and water was added. The aqueous fraction was extracted with AcOEt (x 2) and the combined organic extracts were washed with water (x

2), LiCl (5 % aq., x 1) and brine (x 1); dried over anh. MgSO4, filtered and evaporated to have a brown solid which was purified via flash chromatography in Hx/Hx with 50 % AcOEt to have a yellow solid (43 mg). By NMR was observed 2-aminopyridine together with our final product. The yellow solid was precipitated in Et2O and filtered, rinsed with Et2O (x 2) and dried to have the final product as a white solid (25 mg, 21 %).

HPLC-MS: tr = 1.95 min (97 %). LRMS (m/z): 400/402 (M+1, Cl)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.85 (s, 3H), 6.96 – 7.00 (m, 1H), 7.27 (t, J = 9.0 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.53 (td, J = 8.3, 6.1 Hz, 1H), 7.73 (dd, J = 8.9, 2.1 Hz, 2H), 8.29 (dd, J = 5.0, 1.3 Hz, 1H), 8.58 (s, 1H), 8.82 (s, 1H)

Example 5: 6-(cyclopropanecarbonylamino)-N-methyl-4-[(2,4,6-trimethylbenzoyl)amino]pyridine-3-carboxamide

To a solution of 6-chloro-N-methyl-4-[(2,4,6-trimethylbenzoyl)amino]pyridine-3-carboxamide (Intermediate 2; 121 mg, 0.36 mmol) in 3.5 mL of anh. dioxane was added cyclopropanecarboxamide (34 mg, 0.39 mmol), Pd2(dba)3 (34 mg, 0.037 mmol), Xantphos (42 mg, 0.072 mmol) and cesium carbonate (356 mg, 1.09 mmol) and heated at 100 ºC. After 4 h the reaction is complete and the mixture was cooled down and diluted with DCM and water. Phases were separated and the aqueous fraction was extracted with DCM (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified by flash chromatography in DCM/DCM with 5 % MeOH to have a yellow oil which was precipitated in Et2O to have a white solid which was rinsed with Et2O (x 1) and dried to have the title compound (75 mg, 54 %).

HPLC-MS: tr = 2.83 min. (99 %). LRMS (m/z): 381 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 0.92 (dt, J = 7.9, 3.2 Hz, 2H), 0.98 – 1.05 (m, 2H), 1.87 – 1.96 (m, 1H), 2.30 (s, 9H), 2.84 (s, 3H), 6.93 (s, 2H), 8.59 (s, 1H), 9.40 (s, 1H)

Example 6: 4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1; 150 mg, 0.44 mmol) in 4.5 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (81 mg, 0.66 mmol), Pd2(dba)3 (40 mg, 0.43 mmol), Xantphos (51 mg, 0.88 mmol) and cesium carbonate (428 mg, 1.32 mmol) and heated at 100 ºC. After 3 h the reaction is complete and the mixture was cooled down and diluted with DCM and water.

Phases were separated and the aqueous fraction was extracted with DCM (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified by flash chromatography in DCM/DCM with 10 % MeOH to have a yellow oil which was precipitated (trituration with sonication) in Et2O to have a slightly yellow solid as the title product (73 mg, 39 %)

HPLC-MS: tr = 2.27 min. (99 %). LRMS: 429/431 (M+1, Cl)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.41 (s, 3H), 2.59 (s, 3H), 2.86 (s, 3H), 7.24 – 7.30 (m, 1H), 7.35 – 7.42 (m, 2H), 7.54 (td, J = 8.3, 6.1 Hz, 1H), 8.64 (s, 1H), 9.22 (s, 1H).

Example 7: 4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(4-pyridylamino)pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1; 150 mg, 0.44 mmol) in 4.5 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (81 mg, 0.66 mmol), Pd2(dba)3 (40 mg, 0.43 mmol), Xantphos (51 mg, 0.88 mmol) and cesium carbonate (428 mg, 1.32 mmol) and the mixture was heated at 100 ºC. After 3 h the reaction is complete and the mixture was cooled down and diluted with DCM and water. Phases were separated and the aqueous fraction was extracted with DCM (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified by flash chromatography in DCM/DCM with 10 % MeOH to have a slightly green solid which was triturated in Et2O to have the title compound (65 mg, 37 %).

HPLC-MS: tr = 1.90 (96 %). LRMS (m/z): 400/402 (M+1, Cl)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.86 (s, 3H), 7.23 – 7.31 (m, 1H), 7.40 (dd, J = 8.2, 1.0 Hz, 1H), 7.54 (td, J = 8.3, 6.1 Hz, 1H), 7.77 – 7.85 (m, 2H), 8.23 – 8.32 (m, 3H), 8.66 (s, 1H).

Example 8: 4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[(5-cyano-2-pyridyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1; 150 mg, 0.44 mmol) in 4.5 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (81 mg, 0.66 mmol), Pd2(dba)3 (40 mg, 0.43 mmol), Xantphos (51 mg, 0.88 mmol) and cesium carbonate (428 mg, 1.32 mmol) and heated at 100 ºC. After 3 h the reaction is complete and the mixture was cooled down and diluted with AcOEt and water. Phases were separated and the aqueous fraction was extracted with AcOEt (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to

have an orange solid which was triturated with Et2O, filtered, rinsed (x 3) and dried to have a slightly orange solid. The solid was washed with MeOH (x 2) to have the title compound as a white solid (120 mg, 64 %).

HPLC-MS: tr = 2.60 min. (96 %). LRMS (m/z): 425/427 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.73 – 2.76 (m, 3H), 7.39 – 7.53 (m, 2H), 7.62 (q, J = 8.0 Hz, 1H), 7.94 (d, J = 8.9 Hz, 1H), 8.12 (dd, J = 8.9, 2.3 Hz, 1H), 8.70 (s, 1H), 8.75 (s, 1H), 8.87 (d, J = 6.4 Hz, 1H), 8.97 (s, 1H), 10.73 (s, 1H), 12.71 (s, 1H).

Example 9: 4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-cyclopropyl-pyridine-3-carboxamide

To the solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-cyclopropyl-pyridine-3-carboxamide (Intermediate 123; 79 mg, 0.214 mmol) in anh dioxane (2 ml) was added cyclopropanecarboxamide (55 mg, 0.646 mmol) and K2CO3 (89 mg, 0.644 mmol). Reaction mixture was degassed under argon gas for 5 minutes, then Pd2(dba)3 (20 mg, 0.0022 mmol) and Xantphos (25 mg, 0.043 mmol) were added and the mixture was degassed for an additional 2 minutes. Finally, reaction mixture was heated at 120ºC overnight. Once at room temperature the crude was filtered and the solvent removed. The residue was purified by flash chromatography (Biotage, SNAP 12g) DCM/DCM-MeOH (5%) from 0 to 80% in 30CV. And repurified by flash chromatography (biotage, SNAp 4g) using DCM/DCM-MeOH (2%) from 0 to 100% in 36 CV. The solid obtained was washed with Et2O (3x) to give 22 mg (24%) of title compound

HPLC-MS tr = 2.73 min (97%). LRMS (m/z): 419/421 (M+1, Cl)

^{1}H-NMR (400 MHz, CD3OD) δ ppm 0.60-0.64 (m, 2H), 0.74-0.80 (m, 2H), 0.88-0.93 (m, 2H), 0.99-1.04 (m, 2H), 1.87-0.93 (m, 1H), 2.73-2.79 (m, 1H), 7.23-7.28 (m, 1H), 7.38 (d, J = 8 Hz, 1H), 7.52 (dt, J = 8 and 6 Hz, 1H), 8.58 (s, 1H), 9.34 (s, 1H).

Example 10: 4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(pyrimidin-4-ylamino)pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1; 150 mg, 0.44 mmol) in 4.5 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (81 mg, 0.66 mmol), Pd2(dba)3 (40 mg, 0.43 mmol), Xantphos (51 mg, 0.88 mmol) and cesium carbonate (428 mg, 1.32 mmol) and heated at 100 ºC. After 3 h the reaction is complete and the mixture was cooled down and diluted with DCM and water.

Phases were separated and the aqueous fraction was extracted with DCM (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have an orange solid. The residue was triturated in Et2O to have a yellow solid which was filtered and washed with Et2O (x 2) and MeOH (x 3) to have the title compound as a white solid (69 mg, 39 %).

HPLC-MS: tr = 2.05 min. (96 %). LRMS (m/z): 401/403 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.75 (d, J = 4.4 Hz, 3H), 7.41 – 7.54 (m, 2H), 7.59 – 7.67 (m, 1H), 7.79 – 7.83 (m, 1H), 8.47 – 8.52 (m, 1H), 8.77 (d, J = 7.3 Hz, 2H), 8.89 (d, J = 8.9 Hz, 1H), 8.99 (s, 1H), 10.59 (s, 1H), 12.71 (s, 1H).

Example 11: 4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-[(1-methylpyrazol-3-yl)amino]pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1; 150 mg, 0.44 mmol) in 4.5 mL of anh. dioxane was added 1-methylpyrazol-3-amine (64 mg, 0.66 mmol), Pd2(dba)3 (40 mg, 0.43 mmol), Xantphos (51 mg, 0.88 mmol) and cesium carbonate (428 mg, 1.32 mmol) and heated at 100 ºC. After 3 h the reaction is complete and the mixture was cooled down and diluted with AcOEt and water. Phases were separated and the aqueous fraction was extracted with AcOEt (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified by flash chromatography in DCM/DCM with 10 % MeOH to have a slightly yellow solid which was triturated with Et2O to have a white solid which was rinsed with Et2O (x 2). By HPLC-MS the purity is 92 % and the product was purified again in reverse phase to have the title compound as a white solid.

HPLC-MS: tr = 2.10 min. (99 %). LRMS (m/z): 403/405 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.71 (d, J = 4.5 Hz, 3H), 3.75 (s, 3H), 6.35 (s, 1H), 7.40 – 7.51 (m, 2H), 7.54 – 7.66 (m, 2H), 8.36 (s, 1H), 8.59 (s, 1H), 8.67 (d, J = 4.5 Hz, 1H), 9.72 (s, 1H), 12.76 (s, 1H).

Example 12: 4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[[4-(methoxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 1; 125 mg, 0.36 mmol) in 4 mL of anh. dioxane was added 5-(methoxymethyl)pyridin-2-amine (76 mg, 0.55 mmol), Pd2(dba)3 (34 mg, 0.037 mmol),

Xantphos (42 mg, 0.072 mmol) and cesium carbonate (357 mg, 1.09 mmol) and heated at 100 ºC. After 3 h the reaction is complete and the mixture was cooled down and diluted with AcOEt and water. The phases separated and the aqueous phase extracted with AcOEt (x 1). The combined organic extracts were washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have an orange solid which was triturated in Et2O, filtered and washed with Et2O (x 2). The yellow solid was washed with MeOH (x 2) to have the title compound as a yellowish solid (88 mg, 54 %).

HPLC-MS: tr = 2.27 min. (99 %). LRMS: 429/431 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.73 (d, J = 4.5 Hz, 3H), 3.35 (s, 3H), 4.44 (s, 2H), 6.88 (d, J = 5.1 Hz, 1H), 7.40 – 7.55 (m, 2H), 7.56 – 7.67 (m, 1H), 7.72 (s, 1H), 8.23 (d, J = 5.1 Hz, 1H), 8.71 (s, 1H), 8.78 (d, J = 7.8 Hz, 1H), 8.96 (s, 1H), 10.12 (s, 1H), 12.75 (s, 1H).

Example 13: 6-(cyclopropanecarbonylamino)-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 66 mg, 0.19 mmol) in 2 mL of anh. dioxane was added cyclopropanecarboxamide (19 mg, 0.22 mmol), Pd2(dba)3 (18 mg, 0.019 mmol), Xantphos (23 mg, 0.039 mmol) and cesium carbonate (194 mg, 0.59 mmol) and heated at 100 ºC. After 3 h the reaction is finished and AcOEt and water were added. Phases separated and the aqueous phase extracted with AcOEt (x 1). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have an orange solid which was triturated with Et2O, filtered and washed with Et2O (x 3) and MeOH (x 2). The final yellow solid was dried in the vacuum oven. By NMR it is not pure enough and the solid was purified again by reverse phase to have a slightly yellow solid as the title compound (102 mg, 30 %).

HPLC-MS: tr = 2.38 min. (98 %). LRMS (m/z): 387 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.81 – 0.88 (m, 4H), 1.99 – 2.07 (m, 1H), 2.74 (d, J = 4.5 Hz, 3H), 3.84 (s, 3H), 6.94 (t, J = 8.8 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.45 – 7.60 (m, 1H), 8.69 (s, 1H), 8.80 – 8.88 (m, 1H), 9.32 (s, 1H), 10.98 (s, 1H), 12.31 (s, 1H).

Example 14: 6-(cyclopropanecarbonylamino)-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 4; 33 mg, 0.10 mmol) in 1,5 mL of anh. dioxane was added

cyclopropanecarboxamide (9.7 mg, 0.11 mmol), Pd2(dba)3 (9.5 mg, 0.01 mmol), Xantphos (12 mg, 0.02 mmol) and cesium carbonate (101 mg, 0.30 mmol) and heated at 100 ºC. After 2 h 30 min. the reaction is finished. The mixture was cooled down to room temperature and filtered over a Celite pad washing with AcOEt. The filtrate was removed under reduced pressure and the final orange solid was purified by flash chromatography in DCM/DCM with 10 % MeOH to have a white solid (29 mg) which is not pure enough by NMR. The solid was triturated in Et2O and washed several times to have a white solid (19 mg, 50 %).

HPLC-MS: tr = 2.33 min. (99 %). LRMS (m/z): 369 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.79 – 0.88 (m, 4H), 1.97 – 2.06 (m, 1H), 2.76 – 2.84 (m, 3H), 4.02 (s, 3H), 7.11 (t, J = 7.1 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.54 – 7.62 (m, 1H), 7.94 (dd, J = 7.8, 1.8 Hz, 1H), 8.56 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 9.42 (s, 1H), 10.89 (s, 1H), 12.35 (s, 1H).

Example 15: 4-[(2-chloro-4-cyano-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-4-cyano-6-fluoro-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 6; 50 mg, 81 %, 0.13 mmol) in 1.5 mL of anh. dioxane was added cyclopropanecarboxamide (13 mg, 0.15 mmol), Pd2(dba)3 (13 mg, 0.014 mmol), Xantphos (16 mg, 0.027 mmol) and cesium carbonate (133 mg, 0.41 mmol) and heated at 130 ºC. After 3 h the reaction is complete. The mixture was cooled down and water was added and extracted with AcOEt (x 3). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified by flash chromatography in DCM/DCM with 5 % MeOH to have a white solid (12 mg, 21 %).

HPLC-MS: tr = 2.75 min. (90 %). LRMS (m/z): 417/419 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.91 (d, J = 6.8 Hz, 4H), 2.09 – 2.18 (m, 1H), 2.78 – 2.83 (m, 3H), 8.14 – 8.23 (m, 2H), 9.49 (s, 1H), 9.56 (s, 1H), 11.70 (s, 1H), 12.95 (s, 1H).

Example 16: 4-[(2-chloro-6-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

To a solution of 6-chloro-4-[(2-chloro-6-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 124; 135 mg, 0.38 mmol) in 4 mL of anh. dioxane was added cyclopropanecarboxamide (36 mg, 0.42 mmol), Pd2(dba)3 (35 mg, 0.04 mmol), Xantphos (44 mg, 0.07 mmol) and cesium carbonate (371 mg, 1.13 mmol) and heated at 100 ºC overnight.

The mixture was then heated at 130ºC for 5 additional hours. The mixture was cooled down and water was added and extracted with AcOEt (x 3). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil. The residue was triturated with Et2O to have a brown solid which was filtered off and rinsed with Et2O (x 3). The solid was no pure enough by HPLC (85 %) and was purified by flash chromatography in DCM/DCM with 5 % MeOH. Purification was not successful and the product was purified again in reverse phase to have the title product as a white solid (10 mg, 7 %)

HPLC-MS: tr = 2.73 min. (97 %). LRMS (m/z): 404/406 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.87 – 0.93 (m, 4H), 2.09 – 2.18 (m, 1H), 2.78 (d, J = 4.9 Hz, 3H), 3.82 (s, 3H), 7.18 (t, J = 9.2 Hz, 2H), 7.45 – 7.54 (m, 1H), 9.38 – 9.44 (m, 1H), 9.59 (s, 1H), 11.62 (s, 1H), 12.55 (s, 1H).

Example 17: 6-[(5-cyano-2-pyridyl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 157 mg, 0.46 mmol) in 4.5 mL of anh. dioxane was added 6-aminopyridine-3-carbonitrile (83 mg, 0.69 mmol), Pd2(dba)3 (42 mg, 0.045 mmol), Xantphos (54 mg, 0.093 mmol) and cesium carbonate (454 mg, 1.39 mmol) and heated at 100 ºC. After 2h 30 min. the mixture was cooled down to room temperature and diluted with AcOEt and water. Phases were separated and the aqueous fraction was extracted with AcOEt (x 2). The combined organic extracts were washed with brine, dried over anh. MgSO4, filtered and evaporated to have an orange solid which was triturated with Et2O, filtered, rinsed (x 3) and dried to have a slightly orange solid. The solid was washed with MeOH (x 2) to have the title compound as a white solid (101 mg, 52 %).

HPLC-MS: tr = 2.32 min. (100 %). LRMS (m/z): 421 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.74 (d, J = 4.5 Hz, 3H), 3.85 (s, 3H), 6.95 (t, J = 8.8 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.48 – 7.58 (m, 1H), 7.93 (d, J = 9.0 Hz, 1H), 8.11 (d, J = 8.9 Hz, 1H), 8.69 (s, 2H), 8.81 (s, 1H), 8.94 (s, 1H), 10.67 (s, 1H), 12.37 (s, 1H).

Example 18: 6-(cyclopropanecarbonylamino)-N-methyl-4-[(2-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide

To a solution of 6-chloro-N-methyl-4-[(2-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide (Intermediate 7; 157 mg, 0.46 mmol) in 4.5 mL of anh. dioxane was added 6-aminopyridine-3-carbonitrile (83 mg, 0.69 mmol), Pd2(dba)3 (42 mg, 0.045 mmol), Xantphos (54 mg, 0.093 mmol) and cesium carbonate (454 mg, 1.39 mmol) and heated at 100 ºC. After 3 h it is observed a 25 % of starting material and the major product is the expected product. The mixture was left heating for 2 additional hours. Water and AcOEt were added. The organic phase separated and the aqueous phase was extracted with AcOEt (x 1). The combined organic fractions were dried over anh. MgSO4, filtered and evaporated to have a yellow solid which was triturated with Et2O, filtered and washed with Et2O (x 3) and MeOH (x 1). The slightly yellow solid was purified by flash chromatography in DCM/DCM with 10 % MeOH to have the title compound as a white solid (40 mg, 32 %).

HPLC-MS: tr = 2.15 min. (95 %). LRMS (m/z): 417 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.81 – 0.90 (m, 4H), 2.00 – 2.08 (m, 1H), 2.73 (d, J = 4.5 Hz, 3H), 3.39 (s, 3H), 7.82 (q, J = 10.7, 7.7 Hz, 2H), 7.90 (t, J = 7.5 Hz, 1H), 8.06 (d, J = 9.3 Hz, 1H), 8.74 (s, 1H), 8.85 – 8.92 (m, 1H), 9.30 (s, 1H), 11.02 (s, 1H), 12.56 (s, 1H).

Example 19: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[1-[2-(methylamino)-2-oxo-ethyl]pyrazol-4-yl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 74 mg, 0.22 mmol) in 2.5 mL of DMA was added 2-(4-aminopyrazol-1-yl)-N-methyl-acetamide (51 mg, 0.33 mmol), Pd2(dba)3 (20 mg, 0.021 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (214 mg, 0.65 mmol) and heated at 130 ºC overnight. The mixture was cooled down and water and AcOEt were added. Phases separated and the aqueous phase was extracted with AcOEt (x 1). The combined organic fractions were washed with water, LiCl (5 %) and brine; dried over anh. MgSO4, filtered and evaporated to have a yellow semisolid which was purified via flash chromatography in DCM/DCM with 5 % MeOH to have a slightly yellow solid (32 mg, 31%)

HPLC-MS: tr = 1.87 min. (96 %). LRMS (m/z): 456 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.62 (d, J = 4.6 Hz, 3H), 2.71 (d, J = 4.5 Hz, 3H), 3.84 (s, 3H), 4.73 (s, 2H), 6.94 (t, J = 8.8 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.52 (q, J = 5.3, 3.5 Hz, 2H), 7.89 – 7.99 (m, 3H), 8.59 (d, J = 11.8 Hz, 2H), 9.48 (s, 1H), 12.42 (s, 1H).

Example 20: 4-(2-fluoro-6-methoxybenzamido)-6-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-N-methylnicotinamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 150 mg, 0.44 mmol) in 4.5 mL of anh. dioxane was added 1-(2-methoxyethyl)pyrazol-4-amine (94 mg, 0.66 mmol), Pd2(dba)3 (41 mg, 0.044 mmol), Xantphos (52 mg, 0.089 mmol) and cesium carbonate (434 mg, 1.33 mmol) and heated at 100 ºC overnight. Water and AcOEt were added. The aqueous phase was extracted with AcOEt (x 1). The combined organic fractions were dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified by flash chromatography in DCM/DCM with 10 % MeOH to have a brown oil which is not pure enough to send as a final product. The product was purified again via reverse phase to have a white solid as the title product (24 mg, 12 %).

HPLC-MS: tr = 2.05 min. (95 %). LRMS (m/z): 443 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.70 (d, J = 4.5 Hz, 3H), 3.23 (s, 3H), 3.66 (t, J = 5.3 Hz, 2H), 3.84 (s, 3H), 4.22 (t, J = 5.3 Hz, 2H), 6.94 (t, J = 9.1 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 7.45 – 7.58 (m, 2H), 7.92 (s, 1H), 8.13 (s, 1H), 8.57 (d, J = 5.1 Hz, 2H), 9.40 (s, 1H), 12.42 (s, 1H).

Example 21: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[1-(2-hydroxyethyl)pyrazol-4-yl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[1-(2-tetrahydropyran-2-yloxyethyl)pyrazol-4-yl]amino]pyridine-3-carboxamide (Intermediate 128; 60 mg, 0.12 mmol) in 2 mL of methanol was added dropwise HCl 4N in dioxane (200 uL, 0.8 mmol) and the mixture was stirred at room temperature. After 50 min. the reaction is finished. The volatiles were removed under reduced pressure and the solid is purified via flash chromatography in reverse phase to have a white solid (20 mg, 40 %) as the title product.

HPLC-MS: tr = 1.82 min. (99 %). LRMS (m/z): 429 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.64 – 2.75 (m, 3H), 3.71 (q, J = 5.5 Hz, 2H), 3.84 (s, 3H), 4.10 (t, J = 5.6 Hz, 2H), 4.92 (t, J = 5.3 Hz, 1H), 6.94 (t, J = 8.8 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.46 – 7.55 (m, 2H), 7.93 (d, J = 5.1 Hz, 2H), 8.57 (d, J = 3.9 Hz, 2H), 9.41 (s, 1H), 12.41 (s, 1H).

Example 22: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[4-(1,2,4-triazol-1-ylmethyl)benzoyl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 85 mg, 0.25 mmol) in 2.5 mL of anh. dioxane was added, under Ar, 4-(1,2,4-triazol-1-ylmethyl)benzamide (Intermediate 130; 65 mg, 0.32 mmol), Pd2(dba)3

(23 mg, 0.025 mmol), Xantphos (29 mg, 0.050 mmol) and cesium carbonate (246 mg, 0.75 mmol). 0.5 mL of DMA was added in order to improve the solubility of the amide. The mixture was heated at 110 ºC in a microwaves oven for 2 hr. The crude was filtered over Celite washing with AcOEt. The organic filtrate was washed with LiCl (5 % solution, x 1), and brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified to have a white solid (9 mg, 7 %).

HPLC-MS: tr = 2.33 min. (94 %). LRMS (m/z): 504 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.76 (d, J = 4.5 Hz, 3H), 3.86 (s, 3H), 5.53 (s, 2H), 6.96 (t, J = 8.8 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.49 – 7.57 (m, 1H), 8.00 – 8.05 (m, 3H), 8.71 (s, 1H), 8.76 (s, 1H), 8.90 (d, J = 4.6 Hz, 1H), 9.46 (s, 1H), 10.98 (s, 1H), 12.36 (s, 1H).

Example 23: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(1,2,4-triazol-1-ylmethyl)-2-pyridyl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 70 mg, 0.21 mmol) in 2 mL of anh. dioxane was added 6-(1,2,4-triazol-1-ylmethyl)pyridin-2-amine (Intermediate 134; 54 mg, 0.31 mmol), Pd2(dba)3 (19 mg, 0.021 mmol), Xantphos (24 mg, 0.041 mmol) and cesium carbonate (203 mg, 0.62 mmol) and heated at 100 ºC overnight. Water and AcOEt were added and the phases separated. The aqueous phase was extracted with AcOEt (x 2) and the combined organic fractions were dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified via flash chromatography in DCM/DCM with 5 % in MeOH. 15 mg of final product (slightly yellow solid) pure were obtained. Starting material was recovered (20 mg).

HPLC-MS: tr = 1.92 min. (98 %). LRMS (m/z): 477 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.87 (s, 3H), 3.94 (s, 3H), 5.52 (s, 2H), 6.83 – 6.90 (m, 1H), 6.95 (d, J = 7.4 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.63 – 7.71 (m, 1H), 7.96 (s, 1H), 8.53 (s, 1H), 8.89 (s, 1H), 9.63 (s, 1H).

Example 24: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(morpholinomethyl)-2-pyridyl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 100 mg, 0.29 mmol) in 3 mL of anh. dioxane was added 6-(morpholinomethyl)pyridin-2-amine (obtained according to WO2003070727 preparation N;

143 mg, 0.44 mmol), Pd2(dba)3 (27 mg, 0.029 mmol), Xantphos (34 mg, 0.058 mmol) and cesium carbonate (290 mg, 0.89 mmol) and heated at 100 °C overnight. Water and AcOEt were added and the phases separated. The aqueous phase was extracted with AcOEt (x 2) and the combined organic extracts were washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified via flash chromatography in DCM/DCM with 10 % MeOH and purified again in reverse phase to have a white solid (12 mg, 8 %).

HPLC-MS: tr = 1.78 min. (94 %). LRMS (m/z): 495 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.43 – 2.47 (m, 4H), 2.73 (d, J = 4.5 Hz, 3H), 3.51 – 3.65 (m, 4H), 3.85 (s, 2H), 6.89 – 7.07 (m, 3H), 7.45 – 7.57 (m, 2H), 7.63 – 7.70 (m, 1H), 8.63 (s, 1H), 8.68 – 8.74 (m, 1H), 9.17 (s, 1H), 10.07 (s, 1H), 12.38 (s, 1H).

Example 25: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 161; 80 mg, 0.206 mmol), 2,6-dimethylpyrimidin-4-amine (41 mg, 0.333 mmol), Pd2(dba)3 (19 mg, 0.021 mmol), Xantphos (24 mg, 0.041 mmol) and cesium carbonate (134 mg, 0.411 mmol) was heated in dioxane (5 mL) at 100°C. for 2 hr. The crude was filtered and purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (10%) from 0 to 100% in 40CV. The title compound (50 mg, 50%) was isolated as a pale yellow solid.

HPLC-MS tr = 2.15 min (98%). LRMS (m/z): 475 (M+1)

^{1}H NMR (DMSO, 400 MHz) δ ppm 2.31 (s, 3H), 2.75 (d, J = 4 Hz, 3H), 3.82 (s, 3H), 7.32 (s, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 7.3 Hz, 1H), 8.67 (s, 1H), 8.71-8.77 (m, 1H), 9.28 (s, 1H), 10.36 (s, 1H), 12.58 (s, 1H).

Example 26: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(6-methyl-2-pyridyl)amino]pyridine-3-carboxamide

6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 75 mg, 0.22 mmol) was dissolved in Dioxane (2.3 mL). 6-methylpyridin-2-amine (36 mg, 0.33 mmol). Tris(dibenzylideneacetone) dipalladium(0) (21 mg, 0.023 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (26 mg, 0.045 mmol) and cesium carbonate (217 mg, 0.66 mmol) were added and the mixture was stirred at 100 °C under nitrogen atmosphere overnight. EtOAc and water were added and the product was extracted with EtOAc

(2x). The organic phase was washed with brine, dried over anh. Na2SO4, filtered and concentrated. The crude was purified by flash chromatography (Isolera) using a Merck Si column (5 g) and eluting with DCM/MeOH from 0% to 5% in 30 CV, affording 23 mg of impure product which was repurified using a reverse phase column (5 g) and eluting with water/MeOH from 0% to 100% in 20 CV, affording 6 mg of pure product.

HPLC-MS: tr = 1.13 min. (95 %). LRMS (m/z): 410 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.50 (s 3H), 2.85 (s 3H), 3.93 (s 3H), 6.70 – 6.80 (m, 4H), 7.63 – 7.71 (m, 1H), 7.5 (bs, 2H), 8.53 (s, 1H), 8.92 (bs, 1H), 11.92 (bs, 1H).

Example 27: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(2-pyridylamino)pyridine-3-carboxamide

6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 75 mg, 0.22 mmol) was dissolved in dioxane (2.3 mL). pyridin-2-amine (32 mg, 0.34 mmol), Tris(dibenzylideneacetone)dipalladium(0) (21 mg, 0.023 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (26 mg, 0.045 mmol) and cesium carbonate (217 mg, 0.66 mmol) were added and the mixture was stirred overnight at 100 ºC under nitrogen atmosphere. EtOAc and water were added and the product was extracted with EtOAc (2x). The organic phase was washed with brine, dried over anh. Na2SO4, filtered and concentrated.The crude was purified by Isolera using a Merck Si column (5 g) and eluting with DCM/MeOH from 0% to 5% in 30 CV, affording 27 mg of impure product that was repurified by Isolera using a reverse phase column (5 g) and eluting with water/MeOH from 0% to 100% in 40 CV, affording 6 mg of pure product.

HPLC-MS: tr = 1.06 min. (96 %). LRMS (m/z): 396 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.82 (s 3H), 3.88 (s 3H), 6.75 (t J= 8Hz 2H), 6.83 (t, J= 4 Hz 1H), 7.17 (bs, 1H), 7.33 (c J=8 Hz 1H), 7.57 (m, 1H), 7.72-7.80 (bs 1H), 8.37 (m 1H), 8.59 (s 1H), 8.80-8.85 (bs 1H), 9.90-10.3 (bs, 1H), 12.02-12-20 (bs 1H).

Example 28: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-(hydroxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 90 mg, 0.26 mmol) was dissolved in dioxane (3 mL). (6-amino-2-pyridyl)methanol (50 mg, 0.40 mmol), Tris(dibenzylideneacetone)dipalladium(0) (25 mg, 0.027 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (31 mg, 0.053 mmol) and

cesium carbonate (260 mg, 0.80 mmol) were added and the mixture was stirred overnight at 100 ºC under nitrogen atmosphere. EtOAc and water were added and the product was extracted with EtOAc (2x). The organic phase was washed with brine, dried over anh. Na2SO4, filtered and concentrated. The crude was purified by Isolera using a Merck Si column (5 g) and eluting with DCM/MeOH from 0% to 5% in 30 CV, affording 5 mg of title compound.

HPLC-MS: tr = 1.06 min. (94 %). LRMS (m/z): 426 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.86 (s 3H), 3.94 (s 3H), 4.72 (s 2H), 6.80 (t J=8 Hz 1H), 6.93 (d J=8 Hz 1H), 7.15 (d J=8 Hz 1H), 7.40 (m 1H), 7.48 (c J=5 Hz 1H), 7.70-7.80 (bs, 1H), 8.58 (bs, 1H), 9.2 (bs 1H).

Example 29: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-(1H-indazol-6-ylamino)-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 93 mg, 0.27 mmol) was dissolved in dioxane (3 mL). 1H-indazol-6-amine (55 mg, 0.41 mmol), Tris(dibenzylideneacetone)dipalladium(0) (25 mg, 0.027 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (32 mg, 0.055 mmol) and cesium carbonate (270 mg, 0.83 mmol) were added and the mixture was stirred overnight at 100 ºC under nitrogen atmosphere. EtOAc and water were added and the product was extracted with EtOAc (2x). The organic phase was washed with brine, dried over anh. Na2SO4, filtered and concentrated. The crude was purified by Isolera using a Merck Si column (5 g) eluting with DCM/MeOH from 0% to 5% and repurified by Isolera using a Merck Si column (5 g) eluting with DCM/EtOAc from 0% to 100% affording 5 mg of title compound.

HPLC-MS: tr = 1.50 min. (96 %). LRMS (m/z): 435 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.84 (s 3H), 3.94 (s 3H), 6.75 (m 1H), 6.82 (m 1H), 7.01 (m 1H), 7.40 (m 1H), 7.51 (cs 2H), 8.11 (s 2H), 8.60 (s 3H), 8.77 (s 1H), 9.23 (s 1H).

Example 30: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 1200mg, 0.35mmol), 2,6-dimethylpyrimidin-4-amine (53mg, 0.43mmol), Pd2(dba)3 (33mg, 0.036mmol), Xantphos (41mg, 0.071mmol) and cesium carbonate (347mg, 1.06mmol) in dioxane (2mL) was stirred at 100ºC for 24 hr. Water and AcOEt were added and the compound was extracted with AcOEt and washed with water and

brine. The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos12g) using DCM/MeOH (up to 10%) (220nm) to give the title compound (81 mg 52%)

HPLC/MS tR=1.85min (98%). LRMS (m/z): 425 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.31 (s, 3H), 2.49 (s, 3H), 2.72 (d, J = 4.4 Hz, 3H), 3.83 (s, 3H), 6.93 (t, J = 8.8 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.32 (s, 1H), 7.42 – 7.57 (m, 1H), 8.67 (s, 1H), 8.76 (d, J = 4.6 Hz, 1H), 9.21 (s, 1H), 10.35 (s, 1H), 12.35 (s, 1H).

Example 31: 4-[(4-cyano-2-fluoro-6-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(4-cyano-2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 8; 17 mg, 0.046 mmol) in 0.5 mL of anh. dioxane was added cyclopropanecarboxamide (4.3 mg, 0.050 mmol), Pd2(dba)3 (4.3 mg, 0.004 mmol), Xantphos (5.4 mg, 0.009 mmol) and cesium carbonate (46 mg, 0.14 mmol) and the mixture was heated at 100 ºC. After 1h 30 min. the reaction is finished and the volatiles were removed under reduced pressure. The orange residue was purified via flash chromatography in reverse phase to have a white solid which was dissolved in 1 mL of NH3 7N in MeOH and stirred 2 h at room temperature, evaporated and dried in the vacuum oven.

HPLC-MS: tr = 2.42 min. (98 %). LRMS (m/z): 412 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.82 – 0.88 (m, 4H), 1.98 – 2.07 (m, 1H), 2.74 (d, J = 4.5 Hz, 3H), 3.91 (s, 3H), 7.57 – 7.68 (m, 2H), 8.72 (s, 1H), 8.87 (d, J = 9.0 Hz, 1H), 9.30 (s, 1H), 11.03 (s, 1H), 12.48 (s, 1H).

Example 32: 6-(cyclopropanecarbonylamino)-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

To the solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 135; 45 mg, 0.133 mmol) in anh dioxane (2 ml) was added cyclopropanecarboxamide (34 mg, 0.4 mmol) and K2CO3 (55 mg, 0.398 mmol). Reaction mixture was degassed under argon gas for 5 minutes, then Pd2(dba)3 (12 mg, 0.013 mmol) and Xantphos (15 mg, 0.026 mmol) were added and the mixture was degassed for an additional 2 minutes. Finally, reaction mixture was heated at 100ºC overnight.The crude was filtered and the solvent removed. The residue was purified by flash chromatography (Biotage, SNAP 12g) EtOAc/EtOAc-MeOH (10%) from 0 to 100% in 30CV. A second purification was required by

RP (Biotege, 10g) using H2O/ACN both containing 0.1% HCOOH) to give 13.7 mg (39%) of title product

HPLC-MS tr = 2.60 min (98%). LRMS (m/z): 388 (M+1)

^{1}H NMR 1H (CDCl3, 400 MHz) δ ppm 0.95-1.01 (m, 2H), 1.19-1.23 (m, 2H), 1.72 (tt, J = 7.6 and 4.4 Hz, 1H), 2.98-3.01 (m, 3H), 7.09 (td, J = 8.5 and 1 Hz, 1H), 7.24-7.27 (m 1H), 7.37 (td, J = 8.5 and 6 Hz, 1H), 8.29 (br s, 1H), 9.85 (s, 1H), 12.58 (br s, 1H).

Example 33: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[4-(methoxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 90 mg, 0.26 mmol) was dissolved in dioxane (27 mL). 4-(methoxymethyl)pyridin-2-amine (Intermediate 138; 56 mg, 0.40 mmol), Tris(dibenzylideneacetone)dipalladium(0) (25 mg, 0.027 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (31 mg, 0.05 mmol) and cesium carbonate (261 mg, 0.80 mmol) were added and the mixture was stirred overnight at 100 ºC under nitrogen atmosphere. EtOAc and water were added and the product was extracted with EtOAc (2x). The organic phase was washed with brine, dried over anh. Na2SO4, filtered and concentrated.The crude was purified by Isolera using a Merck Si column (5 g) and eluting with DCM/MeOH from 0% to 5% in 40 CV, affording 20 mg (17%) of pure product.

HPLC-MS: tr = 1.14 min. (96 %). LRMS (m/z): 440 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.84 (s 3H), 3.40 (s 3H), 3.86 (s 3H), 3.45 (s 2H), 6.47-6.56 (cs 1H), 6.70-6.77 (cs 2H), 6.85-6.87 (cs 1H) 7.30-7.47 (cs 2H), 7.74 (s 1H), 8.01 (d J=5 Hz 1H), 8.38 (s 1H), 8.65 (s 1H), 8.88 (s 1H), 10.22 (bs 1H), 12.090 (bs 1H).

Example 34: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[3-(1-hydroxyethyl)anilino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 90 mg, 0.26 mmol) was dissolved in dioxane (27 mL). 1-(3-aminophenyl)ethanol (55 mg, 0,40 mmol), Tris(dibenzylideneacetone)dipalladium(0) (25 mg, 0.027 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (31 mg, 0.054 mmol) and cesium carbonate (261 mg, 0.80 mmol) were added and the mixture was stirred overnight at 100 ºC under nitrogen atmosphere. EtOAc and water were added and the product was extracted with EtOAc (2x). The organic phase was washed with brine, dried over anh. Na2SO4, filtered

and concentrated. The crude was purified by Isolera using a Merck Si column (5 g) and eluting with DCM/MeOH from 0% to 5% in 40 CV, affording 8.5 mg (7%) of pure product.

HPLC-MS: tr = 1.41 min. (95 %). LRMS (m/z): 439 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.46 (d J= 8Hz 3H), 2.84 (d J=5 Hz 3H), 3.85 (s 3H), 3.85 (q J= 8Hz 1H), 6.70-6.77 (cs 3H), 6.98 (s 1H), 7.23-7.35 (cs 3H), 7.47 (s 1H), 7.90 (s 1H), 7.38 (d J= 8Hz 2H), 12.02 (s 1H).

Example 35: 6-(cyclopropanecarbonylamino)-4-[(2,4-difluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2,4-difluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 224; 50 mg, 0.14 mmol) in 1.5 mL of anh. dioxane was added cyclopropanecarboxamide (13 mg, 0.15 mmol), Pd2(dba)3 (13 mg, 0.014 mmol), Xantphos (16.2 mg, 0.027 mmol) and cesium carbonate (137 mg, 0.42 mmol) and heated at 100 ºC overnight. Water and AcOEt were added and the phases separated. The aqueous was extracted with AcOEt (x 1) and the combined organic fractions were washed with water and brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified via flash chromatography in DCM/DCM with 5 % MeOH. The title compound was obtained as a white solid (29 mg, 51 %).

HPLC-MS: tr = 2.47 min. (99 %). LRMS (m/z): 405 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.81 – 0.88 (m, 4H), 2.03 (p, J = 5.2 Hz, 1H), 2.71 – 2.78 (m, 3H), 3.86 (s, 3H), 6.95 – 7.05 (m, 2H), 8.69 (s, 1H), 8.84 (d, J = 4.5 Hz, 1H), 9.31 (s, 1H), 10.99 (s, 1H), 12.34 (s, 1H).

Example 36: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(tetrahydropyran-4-ylamino)pyridine-3-carboxamide

A solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 70 mg, 0.21 mmol) in 0.7 mL of tetrahydropyran-4-amine was heated at 125 ºC. After 1h 30 min. the proportion of final product is 25 % by HPLC-MS (major product is the amine instead the F) and is observed bis-aminated product. The crude was directly purified by reverse phase to have a white solid (10 mg, 12 %).

HPLC-MS: tr = 1.92 min. (98 %). LRMS (m/z): 403 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.45 (qd, J = 12.6, 11.5, 4.3 Hz, 2H), 1.80 – 1.87 (m, 2H), 2.68 (d, J = 4.4 Hz, 3H), 3.38 – 3.47 (m, 2H), 3.83 (s, 3H), 3.84 – 3.90 (m, 2H), 4.01 (d,

J = 0.4 Hz, 1H), 6.93 (t, J = 8.8 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.45 – 7.54 (m, 1H), 7.71 (s, 1H), 8.45 (d, J = 14.4 Hz, 2H), 12.38 (s, 1H).

Example 37: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(pyrimidin-2-ylamino)pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 50 mg, 0.15 mmol) in 1.5 mL of anh. dioxane was added, under nitrogen, pyrimidin-2-amine (16 mg, 0.17 mmol), Tris(dibenzylideneacetone)dipalladium(0) (14 mg, 0.015 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (17 mg, 0.029 mmol) and cesium carbonate (145 mg, 0.44 mmol). The mixture was heated at 100 ºC overnight. After cooling down to room temperature water and AcOEt were added and the phases separated. The aqueous phase was extracted once more with AcOEt. The combined organic extracts were dried over anh. MgSO4, filtered and evaporated. The crude was purified via flash chromatography in DCM/DCM with MeOH (10 %) to have a white solid (20 mg, 34 %).

HPLC-MS: tr = 1.95 min. (99 %). LRMS (m/z): 397 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.74 (s 3H), 3.85 (s 3H), 6.95 (t J= 8Hz 1H), 7.04 (cs 1H), 7.51 (cs 1H), 8.61 (cs 2H), 8.68 (s 1H), 8.78 (bs 1H), 9.54 (s 1H), 10.15 (s 1H), 12.44 (s 1H).

Example 38: 6-(cyclopropanecarbonylamino)-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 9; 50 mg, 0.15 mmol) in 1.5 mL of anh. dioxane was added cyclopropanecarboxamide (14 mg, 0.16 mmol), Pd2(dba)3 (14 mg, 0.015 mmol), Xantphos (17 mg, 0.029 mmol) and cesium carbonate (145 mg, 0.45 mmol) and heated at 100 ºC. After 3h 30 min. the reaction is finished and water and AcOEt were added and the phases separated. The aqueous phase was extracted once more with AcOEt. The combined organic extracts were dried over anh. MgSO4, filtered and evaporated. The crude was purified via flash chromatography in DCM/DCM with MeOH (10 %) to have a white solid (12 mg, 21 %).

HPLC-MS: tr = 2.47 min. (99 %). LRMS (m/z): 387 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.81 – 0.87 (m, 4H), 1.99 – 2.06 (m, 1H), 2.81 (d, J = 4.5 Hz, 3H), 4.02 (s, 3H), 7.27 (dd, J = 9.2, 4.3 Hz, 1H), 7.46 (ddd, J = 9.0, 7.8, 3.4 Hz, 1H),

7.69 (dd, J = 9.4, 3.3 Hz, 1H), 8.58 (s, 1H), 8.73 (d, J = 8.1 Hz, 1H), 9.42 (s, 1H), 10.92 (s, 1H), 12.44 (s, 1H).

Example 39: 6-(cyclopropanecarbonylamino)-N-methyl-4-[[4-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-N-methyl-4-[[4-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide (Intermediate 10; 55 mg, 0.15 mmol) in 1.5 mL of anh. dioxane was added cyclopropanecarboxamide (14 mg, 0.16 mmol), Pd2(dba)3 (13 mg, 0.014 mmol), Xantphos (17 mg, 0.029 mmol) and cesium carbonate (144 mg, 0.44 mmol) and heated at 100 ºC. After 3h 30 min. the reaction is finished and water and AcOEt were added and the phases separated. The aqueous phase was extracted once more with AcOEt. The combined organic extracts were dried over anh. MgSO4, filtered and evaporated. The crude was purified via flash chromatography in DCM/DCM with MeOH (10 %) to have a white solid (22 mg, 35 %).

HPLC-MS: tr = 2.92 min. (96 %). LRMS (m/z): 423 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.82 – 0.88 (m, 4H), 1.98 – 2.08 (m, 1H), 2.83 (d, J = 4.5 Hz, 3H), 7.63 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.9 Hz, 2H), 8.76 (s, 1H), 8.95 (d, J = 4.7 Hz, 1H), 9.40 (s, 1H), 11.00 (s, 1H), 13.16 (s, 1H).

Example 40: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(methylamino)-2-pyridyl]amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[(6-fluoro-2-pyridyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 139; 33 mg, 0.079 mmol) was dissolved in 1-methylpyrrolidin-2-one (1 mL). Methyl amine 2M in THF (60 µL, 0.12 mmol) and N-ethyl-N-isopropylpropan-2-amine (28 µL, 0.160 mmol) were added and the mixture was heated at 100 ºC overnight. The volatiles were removed under reduced pressure. The crude was purified by Isolera using a Merck Si column(5 g) and eluting with DCM/MeOH from 0% to 5% in 30 CV, and repurified eluting with DCM/MeOH from 0% to 5% in 40 CV, affording 2 mg (6%) of title compound.

HPLC-MS: tr = 1.57 min. (92 %). LRMS (m/z): 425 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 2.85 (s 3H), 2.97 (s 3H), 4.00 (s 3H), 6.07-6.17 (bs 1H), 6.22 (d J= 6 Hz 1H), 6.30 (d J=6 Hz 1H), 6.50 (d J= 4Hz 1H), 7.70 (cs 1H), 7.81 (bs 1H), 8.09 (bs 1H), 8.35 (s 1H), 8.62 (s 1H), 12.07 (s 1H).

Example 41: 6-(cyclopropanecarbonylamino)-N-methyl-4-[[3-(trifluoromethyl)benzoyl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-N-methyl-4-[[3-(trifluoromethyl)benzoyl]amino]pyridine-3-carboxamide (Intermediate 11; 30 mg, 0.084mmol) in 1mL of anh. dioxane was added cyclopropanecarboxamide (8mg, 0.094mmol), Pd2(dba)3 (8mg, 0.0087mmol), xantphos (10mg, 0.017mmol) and cesium carbonate (82mg, 0.25mmol) and the mixture heated at 100 ºC overnight. The mixture was filtered and concentrated. The crude was purified by flash chromatography (Biotage Telos12g) using DCM/MeOH (up to 5%) (225nm) to give the title compound (16mg 29%) as a white solid.

HPLC/MS tr = 2.87min (100%). LRMS (m/z): 407 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δppm 0.85 (t, J = 5.7 Hz, 4H), 1.93 – 2.09 (m, 1H), 2.83 (s, 3H), 7.89 (t, J = 8.1 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 8.17 – 8.23 (m, 2H), 8.76 (s, 1H), 8.92 – 9.00 (m, 1H), 9.39 (s, 1H), 10.99 (s, 1H), 13.23 (s, 1H).

Example 42: 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-4-(trifluoromethoxy)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[[2-methoxy-4-(trifluoromethoxy)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 12; 69 mg, 0.17 mmol) in 2 mL of anh. dioxane was added cyclopropanecarboxamide (16 mg, 0.19 mmol), Pd2(dba)3 (16 mg, 0.017 mmol), Xantphos (20 mg, 0.034 mmol) and cesium carbonate (167 mg, 0.51 mmol) and heated at 100 ºC. After 4h the reaction is finished and water and AcOEt were added and the phases separated. The aqueous phase was extracted once more with AcOEt. The combined organic extracts were dried over anh. MgSO4, filtered and evaporated. The crude was purified via flash chromatography in DCM/DCM with MeOH (5 %) to have a white solid (32 mg, 41 %).

HPLC-MS: tr = 2.87 min. (96 %). LRMS (m/z): 453 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.81 – 0.87 (m, 4H), 1.98 – 2.06 (m, 1H), 2.81 (d, J = 4.5 Hz, 3H), 4.06 (s, 3H), 7.12 (dd, J = 9.3, 2.9 Hz, 1H), 7.17 – 7.25 (m, 1H), 8.06 (d, J = 8.7 Hz, 1H), 8.58 (s, 1H), 8.74 (d, J = 4.6 Hz, 1H), 9.42 (s, 1H), 10.92 (s, 1H), 12.41 (s, 1H).

Example 43: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-5-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[[2-methoxy-5-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 141; 28 mg, 0.069 mmol) in 1 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (9,5 mg, 0.077 mmol), Pd2(dba)3 (6,3 mg, 0.007 mmol), Xantphos (8 mg, 0.014 mmol) and cesium carbonate (68 mg, 0.21 mmol) and heated

at 100 ºC. After 2h 30 min. the reaction is finished and water was added. The solid was filtered and washed with water (x 2) and with with Et2O (x 3) to have a white solid. The solid was purified via flash chromatography in DCM/DCM with 10 % MeOH to have the title compound as a white solid (25 mg, 73 %).

HPLC-MS: tr = 2.20 min. (95 %). LRMS (m/z): 475 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 4.12 (s, 3H), 7.41 – 7.49 (m, 2H), 7.97 (dd, J = 8.8, 2.5 Hz, 1H), 8.21 – 8.25 (m, 1H), 8.60 (s, 1H), 8.70 (d, J = 4.7 Hz, 1H), 9.20 (s, 1H), 10.35 (s, 1H), 12.56 (s, 1H).

Example 44: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-(hydroxymethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-[[2-[[tert-butyl(diphenyl)silyl]oxymethyl]benzoyl]amino]-6-[(2,4-dimethylpyrimidin-5-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 16; 20 mg, 0.031 mmol) in 0.4 mL of anh. THF was added TBAF (1 M, 31 uL, 0.031 mmol) and the mixture was stirred at room temperature. After 1 h the reaction is finished and water was added followed by AcOEt. Phases separated and the aqueous phase was extracted with AcOEt. The combined organic phases were dried over anh. MgSO4, filtered and concentrated to low volume, precipitating a white solid. The solid was filtered, washed with MeOH (x 2) and water (x 2) and dried in the vacuum oven overnight.

HPLC-MS: tr = 1.68 min. (99 %). LRMS (m/z): 407 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.76 (d, J = 4.3 Hz, 3H), 4.75 (d, J = 5.5 Hz, 2H), 5.24 (t, J = 6.2 Hz, 1H), 7.36 (s, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.62 – 7.70 (m, 2H), 8.70 (s, 1H), 8.79 (d, J = 6.3 Hz, 1H), 9.23 (s, 1H), 10.35 (s, 1H), 12.52 (s, 1H).

Example 45: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(hydroxymethyl)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 4-[[4-[[tert-butyl(diphenyl)silyl]oxymethyl]-2-methoxy-benzoyl]amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 23; 14 mg, 0.021 mmol) in 0.2 mL of anh. THF was added TBAF (1 M, 21 uL, 0.021 mmol) and the mixture was stirred at room temperature. After 1 h the reaction is complete and the volatiles were removed under reduced pressure. MeOH and acetonitrile were added and a white solid

precipitated. The solid was filtered and washed with MeOH and ACN and dried in the vacuum oven (4.5 mg, 48 %).

HPLC-MS: tr = 1.67 min. (96 %). LRMS (m/z): 437 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.79 – 2.83 (m, 3H), 4.03 (s, 3H), 4.59 (d, J = 5.6 Hz, 2H), 5.39 (t, J = 5.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 7.45 (s, 1H), 7.91 – 7.96 (m, 1H), 8.56 (s, 1H), 8.65 (d, J = 6.0 Hz, 1H), 9.17 (s, 1H), 10.28 (s, 1H), 12.36 (s, 1H).

Example 46: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[[6-(methylamino)pyridine-3-carbonyl]amino]pyridine-3-carboxamide

4-[(6-chloropyridine-3-carbonyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 26; 14 mg, 0.034 mmol) was suspended in 800 uL of NMP. Methylamine solution (40 % in water, 450 uL, 12.99 mmol) was added and the mixture was heated at 140 ºC. After 25 min. of heating the reaction is complete. The mixture is purified directly by reverse phase together with to have a white solid which was dissolved in 1 mL of NH3 7N in MeOH and stirred for 2 h at room temperature. The volatiles were removed and the solid was dried in the vacuum oven for one night (7 mg, 51 %).

HPLC-MS: tr = 1.43 min. (98 %). LRMS (m/z): 407 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), 2.83 (d, J = 4.5 Hz, 3H), 2.86 (d, J = 4.8 Hz, 3H), 6.57 (d, J = 8.9 Hz, 1H), 7.35 (d, J = 4.6 Hz, 1H), 7.41 (s, 1H), 7.87 (d, J = 9.1 Hz, 1H), 8.63 – 8.65 (m, 1H), 8.70 (s, 1H), 8.84 (d, J = 2.3 Hz, 1H), 9.12 (s, 1H), 10.30 (s, 1H), 12.86 (s, 1H).

Example 47: 6-(cyclopropanecarbonylamino)-N-methyl-4-[[2-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-N-methyl-4-[[2-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide (Intermediate 27; 41 mg, 0.11mmol) in 1mL of anh. dioxane was added cyclopropanecarboxamide (10mg, 0.11mmol), Pd2(dba)3 (10mg, 0.011mmol), xantphos (13mg, 0.022mmol) and cesium carbonate (107mg, 0.33mmol) and was heated at 100 ºC for 24 hr.The mixture was then filtered and evaporated. The crude was purified by flash chromatography (Biotage Telos12g) using DCM/MeOH (up to 5%) (225nm) and repurified by reverse phase water/ACN (both 0.1% HCOOH), 225nm, to give (after neutralization with ammonia 7M in MeOH and evaporation) the title compound (8 mg 17%).

HPLC/MS tr =2.67 min (96%). LRMS (m/z): 423 (M+1)

^{1}H NMR (400 MHz, Chloroform-d) δ ppm 0.88 – 0.97 (m, 2H), 1.14 – 1.21 (m, 2H), 1.65 – 1.75 (m, 1H), 3.00 (s, 3H), 6.96 (s, 1H), 7.29 – 7.45 (m, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.87 (d, J = 7.3 Hz, 1H), 8.52 (s, 1H), 9.22 (s, 1H), 9.47 (s, 1H), 12.12 (s, 1H).

Example 48: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-2-methoxy-6-(methylamino)pyridine-3-carboxamide

6-chloro-N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-2-methoxy-pyridine-3-carboxamide (Intermediate 30; 25 mg, 0.056 mmol) was suspended in 1 mL of NMP. Methylamine solution (40 % in water, 600 uL, 17.32 mmol) was added and the mixture was heated at 140 ºC for 30 min. The crude was purified directly by reverse phase to have 7.5 mg (30%) of the title compound as a white solid.

HPLC-MS: tr = 1.97 min. (99 %). LRMS (m/z): 437 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.31 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 2.87 (d, J = 4.5 Hz, 3H), 4.06 (s, 3H), 6.17 (d, J = 8.6 Hz, 1H), 7.37 (s, 1H), 7.47 (s, 1H), 8.00 (d, J = 7.4 Hz, 1H), 8.49 (s, 1H), 8.58 (d, J = 4.9 Hz, 1H), 9.08 (s, 1H), 10.18 (s, 1H), 12.09 (s, 1H).

Example 49: 4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of of 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 31; 137 mg, 0.39 mmol), 2,6-dimethylpyrimidin-4-amine (58 mg, 0.47 mmol), Pd2(dba)3 (36 mg, 0.039mmol), Xantphos (45 mg, 0.077 mmol) and cesium carbonate (383 mg, 1.17 mmol) in dioxane (10mL) was heated at 100ºC. After 1h 30min. the reaction is finished and the mixture was cooled down to room temperature and water was added. AcOEt was added and NaCl sat. in order to improve the separation of phases. The organic phase was washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified in DCM/DCM with 5 % MeOH to have a white solid which was dried in the vacuum oven (91 mg, 53 %)

HPLC-MS: tr = 1.93 min. (99 %). LRMS (m/z): 437 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 7.19 – 7.24 (m, 1H), 7.27 – 7.30 (m, 1H), 7.35 (d, J = 9.3 Hz, 1H), 7.39 (s, 1H), 8.60 (s, 1H), 8.69 (d, J = 6.0 Hz, 1H), 9.20 (s, 1H), 10.31 (s, 1H), 12.29 (s, 1H).

Example 50: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(4-hydroxy-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(4-benzyloxy-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)-amino]-N-methyl-pyridine-3-carboxamide (Intermediate 35; 29 mg, 0.056 mmol) was dissolved in a mixture of DCM/MeOH/drops of DMF (partially soluble) and purgued with N2 (x 3). Pd over carbon (12 mg, 0.011 mmol) was added, the atmosphere was replaced with hydrogen (balloon) and the reaction was stirred at room temperature overnight. The crude was filtrated over a Celite pad washing with MeOH (x 3). The filtrate was removed under reduced pressure and directly purified by reverse phase to have a white solid (10 mg, 42 %).

HPLC-MS: tr = 1.70 min. (99 %). LRMS (m/z): 423 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), 2.81 (d, J = 4.5 Hz, 3H), 3.98 (s, 3H), 6.48 – 6.56 (m, 2H), 7.46 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 8.51 (s, 1H), 8.61 (d, J = 4.5 Hz, 1H), 9.12 (s, 1H), 10.22 (s, 1H), 10.39 (s, 1H), 12.16 (s, 1H).

Example 51: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[(2,4,5-trifluoro-3-methoxy-benzoyl)amino]pyridine-3-carboxamide

HATU (245 mg, 0.64 mmol) was added to a solution of 2,4,5-trifluoro-3-methoxy-benzoic acid (132 mg, 0.091 mmol) in DMF (1 mL) containing DIPEA (157 µL, 0.9 mmol), and the reaction mixture was stirred for 30 min. Consequently, 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 24; 35 mg, 0.13 mmol) was added, and the resulting solution was stirred at 50ºC. After 2h 30 min. the reaction is stopped (45 % final product) and NH4Cl sat. was added. Phases separated and the organic fraction was washed with LiCl (5 % solution, x 2) and brine; dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified in DCM/DCM with 10 % MeOH to have a brown solid (88 % purity) which was purified again by reverse phase to have a white solid (11 mg, 19 %).

HPLC-MS: tr = 2.17 min. (96 %). LRMS (m/z): 461 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.79 (d, J = 4.4 Hz, 3H), 4.06 (s, 3H), 7.36 (s, 1H), 7.59 – 7.72 (m, 1H), 8.72 (s, 1H), 8.81 (d, J = 4.7 Hz, 1H), 9.21 (s, 1H), 10.40 (s, 1H), 12.77 (s, 1H).

Example 52: 4-[[3,5-bis(trifluoromethyl)benzoyl]amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

HATU (350 mg, 0.92 mmol) was added to a solution of 3,5-bis(trifluoromethyl)benzoic acid (237 mg, 0.92 mmol) in DMF (3 mL) containing DIPEA (224 µL, 1.29 mmol), and the reaction mixture was stirred for 30 min. Consequently, 4-amino-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 24; 50 mg, 0.18 mmol) was added, and the resulting solution was stirred at 50ºC. After 1h 30 min. the reaction is stopped (45 % final product) and NH4Cl sat. was added. Phases separated and the organic fraction was washed with LiCl (5 % solution, x 2) and brine; dried over anh. MgSO4, filtered and evaporated to have a brown oil which was purified in DCM/DCM with 5 % MeOH. The product was purified again by reverse phase to have a white solid (5 mg, 5 %)

HPLC-MS: tr = 2.57 min. (96 %). LRMS (m/z): 513 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.77 – 2.87 (m, 3H), 7.36 (s, 1H), 8.47 (s, 1H), 8.50 (s, 1H), 8.77 (s, 1H), 8.90 (d, J = 4.7 Hz, 1H), 9.21 (s, 1H), 10.43 (s, 1H), 13.38 (s, 1H).

Example 53: 4-[(4-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(4-chloro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermnediate 36; 75 mg, 0.21 mmol), 2,6-dimethylpyrimidin-4-amine (39 mg, 0.32 mmol), Pd2(dba)3 (19 mg, 0.020 mmol), Xantphos (24 mg, 0.041 mmol) and cesium carbonate (207 mg, 0.63 mmol) in dioxane (2.5 mL) was heated at 100ºC. After 3h 30 min. NH4Cl sat. was added followed by AcOEt. Phases were separated and the aqueous phase extracted with AcOEt, the organics were combined and washed with NaCl sat., dried over anh. MgSO4, filtered and evaporated to have a yellow semisolid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 10 % MeOH affording a slightly green solid (95 % purity) which was precipitated in Et2O (partially soluble) to give a white solid (25 mg, 27 %).

HPLC-MS: tr = 2.15 min. (99 %). LRMS (m/z): 441/443 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.81 (d, J = 4.5 Hz, 3H), 4.06 (s, 3H), 7.19 (d, J = 10.3 Hz, 1H), 7.34 (d, J = 1.9 Hz, 1H), 7.43 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.58 (s, 1H), 8.67 (d, J = 4.5 Hz, 1H), 9.20 (s, 1H), 10.32 (s, 1H), 12.42 (s, 1H).

Example 54: 4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridazine-3-carboxamide

To a solution of 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 37; 63 mg, 0.179 mmol), 2,6-dimethylpyrimidin-4-amine (33 mg, 0.268 mmol), Pd2(dba)3 (16 mg, 0.017 mmol), Xantphos (21 mg, 0.036 mmol) and cesium carbonate (175 mg, 0.537 mmol) were heated in dioxane (2.5 mL) at 100ºC for 2 hr. The mixture was cooled down and EtOAc and water were added, no dissolution was observed so the crude was filtrated and toluene was added to the solid. Then the residue was dissolved in DCM/MeOH and purified by flash chromatography (Biotage, SNAP 12g) using Hexane-EtOAc/EtOAc from 0 to 100%B. 38 mg (48%) of title compound as a white solid were obtained.

HPLC-MS tr = 1.70 min (99%). LRMS (m/z): 438 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.34 (s, 3H), 2.51 (s, 3H), 2.82 (d, J = 4.8 Hz, 3H), 3.87 (s, 6H), 7.21 (t, J = 8 Hz, 1H), 7.30 (dd, J = 8 and 1.5Hz, 1H), 7.38 (dd, J = 8 and 1.5 Hz, 1H), 7.40 (s, 1H), 9.28 (q, J = 4.5 Hz, 1H), 9.62 (s, 1H), 10.73 (s, 1H), 12.79 (s, 1H).

Example 55: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[5-(tetrahydropyran-3-ylmethyl)-2-pyridyl]amino]pyridine-3-carboxamide

The mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 143; 70 mg, 0.207 mmol), 5-(tetrahydropyran-3-ylmethyl)pyridin-2-amine (Intermediate 143; 40 mg, 0.208 mmol), Pd2(dba)3 (19 mg, 0.021 mmol), Xantphos (24 mg, 0.041 mmol) and cesium carbonate (136 mg, 0.417 mmol) were heated in dioxane (2 mL) at 100ºC overbight. After concentration the crude was purified by flash chromatography (Biotage Telos12g) using DCM/DCM-MeOH(5%) (220nm) and the compound repurified in RP (Biotage, SNAP 5g) using H2O/ACN both containing 0.1% HCOOH from 5 to 100%B. The residue was treated with NH3 (7N in MeOH), then it was concentrated and dried in an oven to give 14 mg (13%) of title compound.

HPLC-MS tr = 2.15 min (96%). LRMS (m/z): 494 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.14-1.57 (cs 4H), 1.71 (m 1H), 2.35-2.43 (m 2H), 2.72 (d J=4 Hz 3H), 3.05 (cs 2H), 3.71 (cs 1H), 3.84 (s 3H), 6.95 (t J=8 Hz 1H), 7.04 (d, J= 8Hz 1H), 7.54 (m 2H), 7.64 (d J= 8Hz 1H), 8.07 (s 1H), 8.61 (s 1H), 8.70 (bs 1H), 8.92 (s 1H), 9.95 (bs 1H), 12.39 (bs 1H).

Example 56: 6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 31; 20 mg, 0.057 mmol), cyclopropanecarboxamide (7 mg, 0.082 mmol), Pd2(dba)3 (5 mg, 0.005mmol), Xantphos (7 mg, 0.012 mmol) and cesium carbonate (56 mg, 0.17 mmol) was heated in dioxane (800 uL) at 100ºC for 3.5 hr. The mixture was cooled down to room temperature and NH4Cl sat. was added. AcOEt was added and NaCl sat. in order to improve the separation of phases. The organic phase was washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified in DCM/DCM with 10 % MeOH to have a white solid (10 mg, 44 %).

HPLC-MS: tr = 2.18 min. (99 %). LRMS (m/z): 399 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.81 – 0.87 (m, 4H), 1.99 – 2.07 (m, 1H), 2.78 (d, J = 4.5 Hz, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 7.19 – 7.23 (m, 1H), 7.29 (dd, J = 8.2, 1.6 Hz, 1H), 7.34 – 7.37 (m, 1H), 8.60 (s, 1H), 8.74 (d, J = 4.5 Hz, 1H), 9.38 (s, 1H), 10.93 (s, 1H), 12.27 (s, 1H).

Example 57: 4-[(2,6-difluorobenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[(2,6-difluorobenzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 38; 92mg, 0.282 mmol), 2,6-dimethylpyrimidin-4-amine (44.4 mg, 0.36 mmol), Pd2(dba)3 (25.9 mg, 0.028 mmol), Xantphos (32.7 mg, 0.056 mmol) and cesium carbonate (276 mg, 0.85 mmol) was heated in dioxane (3 mL) at 100 ºC. for1 h. Water and AcOEt were added and the organic phase washed with water and brine, dried over MgSO4, filtered and concentrated. The crude was purified by flash chromatography (Biotage Telos12g) using dichloroemthane/MeOH (up to 10%) (220nm) to give the title compound (21 mg, 18%)

HPLC-MS tr = 1.90 min (100%). LRMS (m/z): 413 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.76 (s, 1H), 10.43 (bs, 1H), 9.25 (s, 1H), 8.83 (m, 1H), 8.74 (s, 1H), 7.67 (m, 1H), 7.37 – 7.27 (m, 3H), 2.75 (d, J = 4.4 Hz, 3H), 2.33 (m, 6H).

Example 58: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-5-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-5-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 39; 49 mg, 0.14 mmol), 2,6-dimethylpyrimidin-4-amine (22 mg, 0.18 mmol), Pd2(dba)3 (13 mg, 0.014mmol), Xantphos (17 mg, 0.029 mmol) and cesium carbonate (142 mg, 0.43 mmol) was heated in dioxane (1.5 mL) at 100ºC for 3 hr. The mixture was cooled down to room temperature and water was added. AcOEt was added and NaCl sat.

in order to improve the separation of phases. The organic phase was washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow solid which was purified in DCM/DCM with 10 % MeOH to afford a white solid which was dried in the vacuum oven for one night (25 mg, 41 %).

HPLC-MS: tr = 1.62 min. (99 %). LRMS (m/z): 425 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.73 – 2.83 (m, 3H), 3.82 (s, 3H), 7.22 (dd, J = 9.0, 3.7 Hz, 1H), 7.35 (dd, J = 9.5, 3.2 Hz, 2H), 7.40 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.78 (d, J = 4.8 Hz, 1H), 9.20 (s, 1H), 10.40 (s, 1H), 12.67 (d, J = 4.1 Hz, 1H).

Example 59: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-fluoro-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[[2-fluoro-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 40; 58mg, 0.15mmol), 2,6-dimethylpyrimidin-4-amine (29mg, 0.23mmol), Pd2(dba)3 (14mg, 0.015mmol), xantphos (18mg, 0.031mmol) and cesium carbonate (151mg, 0.46mmol) were heated in dioxane (2mL) at 100ºC for 4 hr. Water and AcOEt were added and extracted with AcOEt (x2), then washed with brine. The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos12g) using dichlormethane/methanol (up to 10%) (220nm) to give the title compound (43mg, 60%) as a white solid

HPLC/MS tr = 1.88 min (100%) LRMS (m/z): 463 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.50 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 7.36 (s, 1H), 7.77 – 7.85 (m, 1H), 7.97 (d, J = 10.4 Hz, 1H), 8.06 – 8.16 (m, 1H), 8.73 (s, 1H), 8.81 (d, J = 4.4 Hz, 1H), 9.26 (s, 1H), 10.41 (s, 1H), 12.87 (d, J = 3.3 Hz, 1H).

Example 60: 4-[(3-chloro-5-fluoro-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(3-chloro-5-fluoro-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 41, 50mg, 0.14mmol), 2,6-dimethylpyrimidin-4-amine (27mg, 0.22mmol), Pd2(dba)3 (13mg, 0.014mmol), xantphos (17mg, 0.029mmol) and cesium carbonate (143mg, 0.44mmol) was heated in dioxane (2mL) at 100ºC for 2.5 hr. Water and AcOEt were added and extracted with AcOEt (x2), then washed with brine. The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash

chromatography (Biotage Telos12g) using DCM/methanol (up to 10%) (220nm) to give the title compound (40mg, 64%) as a white solid

HPLC/MS tr = 1.93 min (100%). LRMS (m/z): 429,431 (M+1 Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.51 (s, 3H), 2.84 (d, J = 4.5 Hz, 3H), 7.37 (s, 1H), 7.66 – 7.73 (m, 1H), 7.76 – 7.84 (m, 2H), 8.76 (s, 1H), 8.89 (d, J = 4.6 Hz, 1H), 9.19 (s, 1H), 10.41 (s, 1H), 13.22 (s, 1H).

Example 61: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 9; 83 mg, 0.246 mmol), 2,6-dimethylpyrimidin-4-amine (36 mg mg, 0.36 mmol), Pd2(dba)3 (22.5 mg, 0.02 mmol), Xantphos (28.4 mg, 0.049 mmol) and cesium carbonate (276 mg, 0.86 mmol) was heated in dioxane (2.5 mL) at 100 ºC. After 4 h, water and AcOEt were added and extracted with AcOEt and washed with water and brine. The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos12g) using DCM/MeOH (up to 5%) to give a white solid (23.56 mg, 22%).

HPLC-MS tr = 1.65 min (100%). LRMS (m/z): 425 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.48 (s, 1H), 10.32 (s, 1H), 9.18 (s, 1H), 8.68 (m, 1H), 8.58 (s, 1H), 7.70 (dd, J = 9.3, 3.3 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.27 (dd, J = 9.2, 4.3 Hz, 1H), 4.02 (s, 3H), 3.17 (d, J = 5.3 Hz, 1H), 2.81 (d, J = 4.5 Hz, 3H), 2.33 (s, 3H).

Example 62: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(5-hydroxy-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

In a 100 mL round bottomed flask 4-[(5-benzyloxy-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 43; 40 mg, 0.078 mmol) was suspended in EtOH (10 ml) and purgued with N2 (x 3). Pd over carbon (10 mg, 0.010 mmol) was added and the atmosphere was replaced with hydrogen (balloon) and the reaction was stirred at room temperature for 44 hr. The reaction was filtered through a syringe filter and solvent was removed under vacuum. The residue was purified by RP chromatography (Biotage, SNAP 10g) by using H2O/ACN both containing 0.1% HCOOH. Fractions that contained the product were collected and concentrated. The residue was treated with NH3 (7N in MeOH). Title product was obtained (5.3 mg 15%) as an off white solid

HPLC-MS tr = 1.40 min (95%). LRMS (m/z): 423 (M+1=

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), under dmso (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 3.91 (s, 3H), 6.95 (dd, J = 8.8 and 3 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 3 Hz, 1H), 7.40 (s, 1H), 8.51 (s, 1H), 8.58-8.64 (m, 1H), 9.15 (s, 1H), 9.35 (s, 1H), 10.23 (s, 1H), 12.28 (s, 1H).

Example 63: 4-(2,4-difluoro-5-methoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

A mixture of 6-chloro-4-[(2,4-difluoro-5-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 44; 48 mg, 0.13 mmol), 2,6-dimethylpyrimidin-4-amine (25 mg, 0.2 mmol), Pd2(dba)3 (12 mg, 0.013 mmol), Xantphos (16 mg, 0.027 mmol) and cesium carbonate (132 mg, 0.40 mmol) in dioxane (1.3 mL) was heated at 100ºC. for 2 h 30 min. The mixture was cooled down to room temperature and water was added. AcOEt was added and NaCl sat. in order to improve the separation of phases. The organic phase was washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow solid which was purified in DCM/DCM with 10 % MeOH to give the title compound as a white solid which was dried in the vacuum oven for one night (28 mg, 47 %).

HPLC-MS: tr = 2.05 min. (99 %). LRMS (m/z): 443 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 3.91 (s, 3H), 7.39 (s, 1H), 7.52 – 7.63 (m, 2H), 8.69 (s, 1H), 8.78 (d, J = 4.6 Hz, 1H), 9.18 (s, 1H), 10.40 (s, 1H), 12.69 (d, J = 5.1 Hz, 1H).

Example 64: 4-[(5-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of of 6-chloro-4-[(5-chloro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 45; 36 mg, 0.10 mmol), 2,6-dimethylpyrimidin-4-amine (19 mg, 0.15 mmol), Pd2(dba)3 (9.5 mg, 0.010 mmol), Xantphos (12 mg, 0.020 mmol) and cesium carbonate (99 mg, 0.30 mmol) was heated in dioxane (1 mL) at 100ºC. for 2 h 30 min. The mixture was cooled down to room temperature and water was added. AcOEt was added and NaCl sat. in order to improve the separation of phases. The organic phase was washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow solid which was purified in DCM/DCM with 10 % MeOH to have a white solid which was dried in the vacuum oven for one night (19 mg, 42 %).

HPLC-MS: tr = 2.23 min. (99 %). LRMS (m/z): 441/443 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.26 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H), 3.97 (s, 3H), 7.22 (d, J = 9.0 Hz, 1H), 7.36 (s, 1H), 7.58 (dd, J = 8.9, 2.8 Hz, 1H), 7.84 (d, J = 2.8 Hz, 1H), 8.52 (s, 1H), 8.61 (d, J = 4.6 Hz, 1H), 9.12 (s, 1H), 10.26 (s, 1H), 12.41 (s, 1H).

Example 65: 4-[(3,5-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[(3,5-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 46; 15 mg, 0.044 mmol), 2,6-dimethylpyrimidin-4-amine (6.6 mg mg, 0.054 mmol), Pd2(dba)3 (4 mg, 0.02mmol), Xantphos (5 mg, 0.049 mmol) and cesium carbonate (44 mg, 0,135 mmol) in dioxane (0.5 mL) was heated at 100 ºC. The reaction was quenched with water after 3 h, extracted with AcOEt, washed with brine and dried over MgSO4. The concentrated crude was purified by flash chromatography (5% methanol in DCM gradient) to obtain a yellowish solid (16 mg 32%).

HPLC-MS rt = 2.12 min (98%). LRMS (m/z): 437 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 13.06 (s, 1H), 10.38 (s, 1H), 9.16 (s, 1H), 8.86 (m, 1H), 8.74 (s, 1H), 7.41 (s, 1H), 7.08 (s, 1H), 7.08 (s, 1H), 6.80 (m, 1H), 3.85 (s, 6H), 2.83 (d, J = 4.5 Hz, 3H), 2.33 (s, 3H).

Example 66: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(1H-imidazol-2-yl)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 52; 15 mg, 0.025 mmol) in 500 uL of anh. DCM 150 uL of TFA were added and the reaction mixture was stirred at room temperature overnight. The next day more TFA (100 uL) was added. After 14 h of stirring the volatiles were removed under reduced pressure and Et2O was added and removed (x 2) to have a white solid as the reaction crude.The crude was purified through semipreparative HPLC to obtain 4 mg (30%) of title compound.

HPLC-MS rt = 0.74 min (90%). LRMS (m/z): 473 (M+1)

^{1}H NMR (DMSO, 400 MHz) δ ppm 2.32 (s, 3H), under dmso (s, 3H), 2.80 (d, J = 4.5 Hz, 3H), 4.11 (s, 3H), 7.10 (m 1H), 7.36 (m 1H), 7.43 (s, 1H), 7.67 (m 1H), 7.78 (s 1H), 8.02 (m 1H), 8.56 (m, 1H), 8.66 (m 1H), 9.19 (s, 1H), 10.30 (s, 1H), 12.42 (s, 1H), 12.81 (s 1H).

Example 67: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxypyridine-3-carbonyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-2-methoxy-pyridine-3-carboxamide (Intermediate 30; 15 mg, 0.033 mmol) in 0.6 mL of NMP was added 3,3-difluorocyclohexanamine (46 mg, 0.34 mmol) and the mixture was stirred at 140 ºC (yellow clear solution). After 25 min. of heating the major product corresponds to the reduction of Cl atom. The crude was purified directly via reverse phase to have a white solid (7 mg, 51 %).

HPLC-MS: tr = 1.87 min. (96 %). LRMS (m/z): 408 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.82 (d, J = 4.4 Hz, 3H), 4.12 (s, 3H), 7.23 (dd, J = 7.6, 5.0 Hz, 1H), 7.43 (s, 1H), 8.35 – 8.45 (m, 2H), 8.60 (s, 1H), 8.66 – 8.72 (m, 1H), 9.21 (s, 1H), 10.32 (s, 1H), 12.57 (s, 1H).

Example 68: 4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-6-[[1-[2-(methylamino)-2-oxo-ethyl]pyrazol-4-yl]amino]pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 31; 85 mg, 0.24 mmol) in 2 mL of DMA was added 2-(4-aminopyrazol-1-yl)-N-methyl-acetamide (Intermediate 145; 57 mg, 0.37 mmol), Pd2(dba)3 (25 mg, 0.027 mmol), Xantphos (30 mg, 0.051 mmol) and cesium carbonate (238 mg, 0.73 mmol) and heated at 110 ºC under microwave conditions for 1h 30 min. The crude was filtered over a Celite pad washing with AcOEt and the filtrate was removed under reduced pressure was purified via flash chromatography in DCM/DCM with 10 % MeOH to have a pink oil which was purified again (70 % purity, 25 mg) by reverse phase to give 8 mg (7 %) of title compound.

HPLC-MS: tr = 1.90 min. (99 %). LRMS (m/z): 468 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.62 (d, J = 4.6 Hz, 3H), 2.74 (d, J = 4.5 Hz, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.72 (s, 2H), 7.17 – 7.22 (m, 1H), 7.24 – 7.34 (m, 2H), 7.50 (s, 1H), 7.91 (d, J = 1.9 Hz, 1H), 7.97 (s, 1H), 8.05 (s, 1H), 8.51 (d, J = 5.9 Hz, 2H), 9.41 (s, 1H), 12.37 (s, 1H).

Example 69: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[3-(methanesulfonamido)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

Tert-butyl N-[3-[[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]carbamoyl]phenyl]-N-methylsulfonyl-carbamate (Intermediate 55; 27mg, 0.047mmol) was solved in DCM and 4M HCl (in dioxane) was added and stirred at room temperature for 1 hr. The solvent was evaporated and the residue Neutralized with a NaHCO3 saturated solution and extracted with dichoromethane (x3). The organic phase was dried over MgSO4, filtered and concentrated. The crude was purified by flash chromatography (Biotage Gold12g) using DCM DCM/MeOH (up to 10%) (220nm) to give the title compound (12mg, 54%) as a white solid.

HPLC/MS tr = 1.78 min (100%). LRMS (m/z):470 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.51 (s, 3H), 2.83 (d, J = 4.5 Hz, 3H), 3.08 (s, 3H), 7.39 (s, 1H), 7.45 – 7.50 (m, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.65 (dt, J = 7.7, 1.3 Hz, 1H), 7.81 – 7.84 (m, 1H), 8.74 (s, 1H), 8.80 – 8.92 (m, 1H), 9.21 (s, 1H), 10.09 (s, 1H), 10.38 (s, 1H), 13.10 (s, 1H).

Example 70: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a dispersion of 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-[5-methyl-4-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 63; 47 mg, 0.076 mmol) in 1 mL of DCM was added TFA (500 uL) and the mixture was stirred at room temperature (yellow clear solution). After 3 h the proportion of final product is 70 % and SM is 30 %. More TFA (400 uL) was added and the stirring was kept for longer time. After 5h the reaction is finished. The volatiles were removed under reduced pressure, adding more DCM and removing it to eliminate the traces of TFA. Water was added and the solution basified to pH 8 with sat. NaHCO3 and extracted with AcOEt (x 3), but the final product remains in the aqueous phase. The volume was reduced to the middle and pH adjusted to 6-7 and cold was applied but the product did not precipitate. The aqueous fraction was directly used for the Biotage in reverse phase to remove the salts but the product elutes at the beginning of the program and it has salts (54 mg). The purification was carried on by preparative HPLC, affording 6 mg (16%) of the title compound as a white solid.

HPLC-MS: tr = 1.75 min. (99 %). LRMS (m/z): 488 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), 2.43 (s, 3H), 2.81 (s 3H), 4.10 (s 3H), 7.41 (s, 1H), 7.73 (m, 1H), 8.07 (m 1H), 8.57 (m 1H), 9.21 (s, 1H), 10.31 (s, 1H), 12.45 (s, 1H), 13.09 (bs, 1H).

Example 71: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3H-benzimidazole-5-carboxamide

To the solution of N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide (Intermediate 68; 37 mg, 0.068 mmol) in DCM (2 ml) was added TFA (2 ml) and the mixture was stirred at rt for 18 hr. Solvent was removed, NH3 (7N in MeOH) was added and then removed under vacuum. The residue was purified by RP chromatography (Biotage, SNAP 10g) by using H2O/ACN both containing 0.1% HCOOH. Fractions collected were concentrated and the residue was treated with NH3 (7N in MeOH) and solvent removed, affording 10 mg (33%) of title compound.

HPLC-MS tr = 1.4 min' (95%). LRMS (m/z): 417 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.52 (s, 3H), 2.84 (d, J = 4 Hz, 3H), 7.43 (s, 1H), 7.77 (d, J = 8 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 8.24 (s, 1H), 8.42 (s, 1H), 8.74 (s, 1H), 8.87 (s, 1H), 9.24 (s, 1H), 1.047 (s, 1H), 13.14 (s, 1H).

Example 72: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(1H-1,2,4-triazol-5-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 74; 200 mg, 0.33 mmol) in DCM (3.3 mL) was added TFA (2.1 mL, 27.4 mmol) dropwise and the reaction was stirred at room temperature. After 4h, the reaction was complete. TFA and solvent were removed and co-evaporated with 7 N ammonia in methanol.The crude was purified by flash chromatography (DCM to 15% methanol in DCM) and repurified through reverse phase to give 30 mg (19%) of the title compound.

HPLC-MS tr = 1.70 min (95%). LRMS (m/z): 474 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.46 (s, 1H), 10.31 (s, 1H), 9.22 (s, 1H), 8.69 (brs, 1H), 8.58 (s, 1H), 8.16 – 8.04 (m, 1H), 7.92 – 7.71 (m, 2H), 7.45 (s, 1H), 4.12 (s, 3H), 2.83 (d, J = 4.4 Hz, 3H), 2.33 (s, 3H).

Example 73: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (80mg, 0.24mmol), 2,6-dimethylpyrimidin-4-amine (Intermediate 75; 44mg, 0.36mmol), Pd2(dba)3 (22mg, 0.024mmol), xantphos (28mg, 0.048mmol) and cesium carbonate (234mg, 0.72mmol) were heated in dioxane (2mL) at 100ºC for 18 hr. Saturated bicarbonate and AcOEt were added and the mixture was extracted with AcOEt (x2), then washed with brine. The organic phase was dried over MgSO4, filtered and concentrated. The crude was purified by flash chromatography (Biotage Telos12g) using DCM/MeOH (up to 5%) (220nm) to give the title compound (65mg, 65%) as a white solid.

HPLC/MS tr = 2.02 min (100%). LRMS (m/z): 421 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.30 – 2.35 (m, 6H), 2.77 (d, J = 4.5 Hz, 3H), 3.75 (s, 3H), 7.19 (t, J = 7.6 Hz, 1H), 7.40 (s, 1H), 7.42 – 7.49 (m, 1H), 7.54 – 7.66 (m, 1H), 8.63 (s, 1H), 8.68 – 8.79 (m, 1H), 9.24 (s, 1H), 10.33 (s, 1H), 12.38 (s, 1H).

Example 74: 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(1H-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To the solution of 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-[1-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 84; 48 mg, 0.085 mmol) in DCM (2 ml) was added TFA (2 ml) and the mixture was stirred at rt for 2 hr. Solvent was removed, NH3 (7N in MeOH) was added and then removed under vacuum. The residue was tried to purify by RP chromatography but no solubilization was accomplished so the suspension was filtrated to give 17.4 mg (47%) of the title compound.

HPLC-MS tr = 2.03 min (99%). LRMS (m/z): 436 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.81-0.87 (m, 4H), 2.00-2.07 (m, 1H), 2.76 (d, J = 4.4 Hz, 3H), 3.75 (s, 3H), 7.40 (br s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 8.06 (br s, 1H), 8.65 (br s, 1H), 8.78 (br s, 1H), 9.42 (s, 1H), 10.98 (s, 1H), 12.45 (s, 1H).

Example 75: 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To the solution of 6-chloro-4-[[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 87; 117 mg, 0.292 mmol) in anh dioxane (5 ml) was added cyclopropanecarboxamide (50 mg, 0.587 mmol) and Cs2CO3 (190 mg, 0.583 mmol). Reaction mixture was degassed under argon gas for 5 minutes, then Pd2(dba)3 (27 mg, 0.029 mmol) and Xantphos (34 mg, 0.059 mmol) were added and the mixture was degassed

for an additional 2 minutes. Finally, reaction mixture was heated at 100ºC for 2.5 hr. The reaction was cooled down and filtered. The product was present in the filtrated but also in the solid, so water and EtOAc-MeOH were added and phases separated, the aqueous phase was further extracted with more EtOAc-MeOH. The first filtrate was dirtier than the EtOAc extract but both fractions were joined and purified together by flash chromatography (Biotage, SNAP 12g) DCM/DCM-MeOH (10%) from 0 to 100% in 40CV to afford title compound (54 mg, 40%) as a white solid

HPLC-MS tr = 2.08 min (98%). LRMS (m/z): 450 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.82-0.88 (m, 4H), 2.01-2.07 (m, 1H), 2.76 (d, J = 4.5 Hz, 3H), 3.77 (s, 3H), 3.97 (s, 3H), 7.37 (t, J = 7.7 Hz, 1H), 7.85 (dd, J = 7.7 and 1.8 Hz, 1H), 8.01 (dd, J = 7.7 and 1.8 Hz, 1H), 8.60 (s, 1H), 8.64 (s, 1H), 8.76 (q, J = 4 Hz, 1H), 9.43 (s, 1H), 10.96 (s, 1H), 12.42 (s, 1H).

Example 76: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(6-methyl-2-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 60 mg, 0.17 mmol), 6-methyl-2-morpholino-pyrimidin-4-amine (Intermediate 162; 70 mg, 0.36 mmol), Pd2(dba)3 (33 mg, 0.036 mmol), Xantphos (41 mg, 0.071 mmol) and potassium carbonate (74, 0.535 mmol) in 2 mL dioxane was heated at 110 ºC overnight. Water was added and the mixture extracted with AcOEt (x2). The organic phase was washed with water and brine, dried and concentrated to afford 144 mg of a crude. After purification through flash chromatography in DCM/DCM with 15 % MeOH to afford the title compound (13 mg, 11 %).

HPLC-MS tr = 1.25 min (98%). LRMS (m/z): 496 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.25 (s 3H); 2.86 (s 3H), 2.72 (m 4H), 2.86 (m 4H), 3.90 (s 3H), 6.31 (s 1H), 6.83 (t J= 8Hz 1H), 6.96 (t J=8 Hz 1H), 7.47 (cs 1H), 8.51 (s 1H), 9.32 (s 1H), 12.10 (s 1H)

Example 77: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(pyridazin-3-ylamino)pyridine-3-carboxamide

In a schlenk tube, a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 40 mg, 0.12 mmol), pyridazin-3-amine (13 mg, 0-13 mmol) and K2CO3 (50 mg, 0.36 mmol) in anh. dioxane (1.2 mL) was degassed with 3 vacuum-

nitrogen cycles. Pd2(dba)3 (11 mg, 0.012 mmol) and Xantphos (14 mg, 0.024 mmol) were added and the mixture degassed once again. The mixture was heated at 140 ºC overnight. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated to afford 58 mg of crude. This crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 5% in 40 CV to give 9mg (19%) of title compound.

HPLC-MS: tr = 1.07 min. (96 %). LRMS (m/z): 397 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.85 (s 3H), 3.90 (s 3H), 6.82 (t J= 8 Hz 1H), 6.97 (d, J = 8 Hz 1H), 7.43 – 7.50 (m 1H), 7.59 (m 1H), 8.47 (d, J= 8 Hz 1H), 8.58 (d J= 4Hz 1H), 8.74 (d J= 4 Hz 1H).

Example 78: 4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-6-[(5-morpholino-2-pyridyl)amino]pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 31; 75 mg, 0.21 mmol), 5-morpholinopyridin-2-amine (Intermediate 147; 57 mg, 0.32 mmol), Pd2(dba)3 (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (210 mg, 0.64 mmol) in dioxane (1.5 mL) was heated at 100ºC. After 4 h the reaction was cooled down to room temperature and NH4Cl sat. was added. Water was added and extracted with AcOEt (x 1); the organic was washed with brine (x 1), dried over anh. MgSO4, filtered and evaporated to have a yellow semisolid which was purified via flash chromatography in DCM/DCM with 10 % MeOH to have a yellowish solid which was purified again (80 % purity) in reverse phase to have a yellow solid (20 mg, 19%) which was dried in high vacuum overnight.

HPLC-MS: tr = 2.10 min. (99 %). LRMS (m/z): 493 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.75 (d, J = 4.4 Hz, 3H), 3.06 – 3.10 (m, 4H), 3.73 – 3.77 (m, 4H), 3.85 (s, 3H), 3.88 (s, 3H), 7.20 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.32 (dd, J = 7.7, 1.6 Hz, 1H), 7.42 (dd, J = 9.1, 3.0 Hz, 1H), 7.66 – 7.71 (m, 1H), 7.95 – 7.99 (m, 1H), 8.51 (s, 1H), 8.58 (d, J = 4.2 Hz, 1H), 8.77 (s, 1H), 9.73 (s, 1H), 12.32 (s, 1H).

Example 79: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(1-methylimidazol-2-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[[2-methoxy-4-(1-methylimidazol-2-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 91; 28 mg, 0.0.07 mmol), 2,6-dimethylpyrimidin-4-

amine (13 mg, 0.1 mmol), Pd2(dba)3 (6.5 mg, 0.007 mmol), Xantphos (8.1 mg, 0.014 mmol) and cesium carbonate (68 mg, 0.21 mmol) in dioxane (1.0 mL) was heated at 100ºC for 2.5 hr. After cooling down to room temperature AcOEt was added. A solid precipitated and was filtered, washed with water and dried to afford the title compound as a greenish solid (16 mg, 49%).

HPLC-MS: tr = 1.43 min. (95 %). LRMS (m/z): 487 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.83 (d, J = 4 Hz, 3H), 3.85 (s, 3H), 4.09 (s 3H), 7.05 (s 1H), 7.34 (m 1H), 7.44 – 7.53 (m 2H), 8.05 (m 1H), 8.58 (m 1H) 8.68 (m 1H), 9.22 (m 1H), 10.33 (m 1H), 12.46 (s 1H).

Example 80: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(2-morpholinoacetyl)amino]pyridine-3-carboxamide

To the solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 30 mg, 0.088 mmol) in anh dioxane (1 ml) was added 2-(4-morpholino)acetamide (26 mg, 0.180 mmol) and Cs2CO3 (58 mg, 0.178 mmol). Reaction mixture was degassed under argon gas for 5 minutes, then Pd2(dba)3 (8 mg, 0.009 mmol) and Xantphos (10 mg, 0.017 mmol) were added and the mixture was degassed for an additional 2 minutes. Finally, reaction mixture was heated at 100ºC for 2 hr. The reaction was cooled down and filtered. The residue was purified by flash chromatography (Biotage, SNAP 12g) DCM/DCM-MeOH (5%) from 0 to 100% in 40CV. Title compound was obtained (15 mg, 54%) as an off-white solid.

HPLC-MS tr = 1.78 min (99%). LRMS (m/z): 446 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.49-2.54 (m, 4), 2.72 (d, J = 4.5 Hz, 3H), 3.21 (s, 3H), 3.58-3.64 (m, 4H), 3.82 (s, 3H), 6.93 (t, J = 8.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.50 (q, J = 8.5 Hz, 1H), 8.67 (s, 1H), 8.84 (d, J = 5 Hz, 1H), 9.32 (s, 1H), 10.15 (s, 1H), 12.32 (s, 1H).

Example 81: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-indazole-6-carboxamide

To the suspension of N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)indazole-6-carboxamide (Intermediate 95; 80 mg, 0.020 mmol) in DCM (5 ml) was added TFA (2.5 ml) and the mixture was stirred at rt for 75 min. Solvent was removed, NH3 (7N in MeOH) was added and the mixture stirred for 30min, then removed under vacuum. EtOAc and NaHCO3 saturated solution were added, but no

solubilization was accomplished. The mixture was filtered and the solid obtained was treated twice with Et2O and then dried in an oven to afford 54 mg (87%) of the title compound as a pale yellow solid.

HPLC-MS tr = 1.78 min (99%). LRMS (m/z): 417 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.31 (s 3H), 2.83 (s 3H), 7.40 (m 1H), 7.70 (m 1H), 7.95 (m 1H), 8.16 (m 2H), 8.74 (s 1H), 8.90 (m 1H), 9.26 (m 1H), 10.36 (bs 1H), 13.19 (bs 1H).

Example 82: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(6-fluoro-2,3-dimethoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(6-fluoro-2,3-dimethoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 96; 57mg, 0.15mmol), 2,6-dimethylpyrimidin-4-amine (Intermediate 96; 29mg, 0.23mmol), Pd2(dba)3 (14mg, 0.015mmol), xantphos (18mg, 0.031mmol) and cesium carbonate (151mg, 0.46mmol) were heated in dioxane (2mL) at 100ºC for 2.5 hr. Saturated sodium bicarbonate and AcOEt were added and the aqueous phase was extracted with AcOEt (x2), then washed with brine. The organic phase was dried over MgSO4, filtered and concentrated. The crude was purified by flash chromatography (Biotage Telos12g) using diethyl ether/MeOH (up to 5%) (220nm) to give the title compound (38mg, 54%) as a white solid.

HPLC/MS tr = 1.95min (100%). LRMS (m/z): 455 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.50 (s, 3H), 2.73 (d, J = 4.5 Hz, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 7.10 (t, J = 8.9 Hz, 1H), 7.18 – 7.27 (m, 1H), 7.33 (s, 1H), 8.71 (s, 1H), 8.80 (q, J = 4.2 Hz, 1H), 9.26 (s, 1H), 10.38 (s, 1H), 12.43 (s, 1H).

Example 83: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(4-methyl-6-oxo-1H-pyrimidin-2-yl)amino]pyridine-3-carboxamide

NaI (9 mg, 0.06 mmol) followed by TMSCl (7 uL, 0.055 mmol) were added to a solution of 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[(4-methoxy-6-methyl-pyrimidin-2-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 97; 8 mg, 0.018 mmol) in AcCN (0,5 mL). A precipitate appeared (NaCl). The mixture was shaken at 70ºC for 1 hr. The mixture was treated with aq. sodium thiosulphate solution and extracted with DCM (2x). The DCM layer was dried and evaporated to afford 4 mg of crude. This crude was purified using Isolera with a Merck

silica 5g column eluting with DCM/MeOH from 0% to 10 in 20 CV. Affording 3 mg (38%) of the title compound.

HPLC/MS tr = 1.49 min (96%). LRMS (m/z): 427 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.23 (s 3H), 2.87 (s 3H), 3.91 (s 3H), 5.90 (s 1H), 6.83 (t J= 8 Hz 1H), 6.93 (d J= 8Hz 1H), 7.43 (cs 1H), 8.41 (s 1H), 8.60 (s 1H).

Example 84: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 50 mg, 0.148 mmol) in 2 mL of anh. dioxane were added, under nitrogen, 2-(6-amino-3-pyridyl)propan-2-ol (Prepared as in US2009143420, example 13 section b; 30 mg, 0.148 mmol), Pd2(dba)3 (15 mg, 0.016 mmol), Xantphos (18 mg, 0.031 mmol) and K2CO3 (65 mg, 0.470 mmol). The mixture was heated at 120 ºC overnight. The mixture was cooled down to room temperature, poured into a separation funnel with water and AcOEt and the two phases separated. The aqueous phase was extracted twice with EtOAc. The joint organic phases were dried over magnesium sulfate, filtered and concentrated. The crude was purified at Isolera through a 10g Merck reverse phase column, eluting from 100% water to 100% MeCN/MeOH 1:1 in 40CV and repurified at Isolera with a 2.5g Merck column eluting with DCM/MeOH from 0 to 5% MeOH in 10CV + 5CV at 5% MeOH + from 5 to 10% MeOH in 10CV. 3 mg (4%) of title compound were obtained.

HPLC/MS tr = 1.08 min (99%). LRMS (m/z): 454 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 8.78 (s, 1H), 8.53 (s, 1H), 8.45 – 8.39 (m, 1H), 7.84 (dd, J = 8.7, 2.3 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.48 (td, J = 8.5, 6.6 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.89 – 6.79 (m, 1H), 4.58 (s, 1H), 3.91 (s, 3H), 2.86 (s, 3H), 2.27 (bs, 1H), 1.56 (s, 6H).

Example 85: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-6-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-methoxy-6-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 98; 57mg, 0.15mmol), 2,6-dimethylpyrimidin-4-amine (32mg, 0.26mmol), Pd2(dba)3 (16mg, 0.017mmol), xantphos (20mg, 0.035mmol) and cesium carbonate (167mg, 0.51mmol) were heated in dioxane (2mL) at 100ºC for 2 hr. Saturated sodium bicarbonate and AcOEt were added and the aqueous phase was extracted with AcOEt (x2), then washed with brine. The organic phase was dried over MgSO4, filtered and concentrated. The crude was

purified by flash chromatography (Biotage Telos12g) using diethyl ether/MeOH (up to 10%) (220nm) to give the title compound (35mg, 49%) as a yellow solid.

HPLC/MS tr = 1.95 min (98%). LRMS (m/z): 421 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.26 (s, 3H), 2.33 (s, 3H), 2.49 (s, 3H), 2.72 (d, J = 4.4 Hz, 3H), 3.77 (s, 3H), 6.90 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.29 – 7.40 (m, 2H), 8.67 (s, 1H), 8.70 – 8.77 (m, 1H), 9.25 (s, 1H), 10.33 (s, 1H), 12.08 (s, 1H).

Example 86: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[[2-methoxy-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 99; 57mg, 0.15mmol), 2,6-dimethylpyrimidin-4-amine (27mg, 0.22mmol), Pd2(dba)3 (14mg, 0.015mmol), xantphos (17mg, 0.029mmol) and cesium carbonate (144mg, 0.44mmol) were heated in dioxane (2mL) at 100ºC for 1 hr. Saturated sodium bicarbonate and AcOEt were added and extracted with AcOEt (x2), then washed with brine. The organic phase was dried over MgSO4, filtered and concentrated.The crude was purified by flash chromatography (Biotage Telos12g) using diethyl ether/MeOH (up to 10%) (220nm) to give the title compound (14mg, 20%) as a white solid.

HPLC/MS tr = 2.30 min (100%). LRMS (m/z): 475 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.81 (d, J = 4.5 Hz, 3H), 3.30 (s, 3H), 4.10 (s, 3H), 7.38 – 7.59 (m, 3H), 8.12 (d, J = 8.1 Hz, 1H), 8.61 (s, 1H), 8.71 (d, J = 4.1 Hz, 1H), 9.23 (s, 1H), 10.34 (s, 1H), 12.55 (s, 1H).

Example 87: 6-(cyclopropanecarbonylamino)-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 75; 84 mg, 0.25 mmol), cyclopropanecarboxamide (32 mg, 0.37 mmol), Pd2(dba)3 (23 mg, 0.025 mmol), Xantphos (29 mg, 0.05 mmol) and cesium carbonate (246 mg, 0.75 mmol) in dioxane (1.7) mL was heated at 100ºC. for 3.5 hr. The mixture was cooled down to room temperature and NH4Cl sat., AcOEt and NaCl sat. were added. The organic phase was washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified in DCM/DCM with 10 % MeOH in GOLD column to have a white solid which was dried in the vacuum oven for one night to afford 59 mg (61 %) of title compound.

HPLC-MS: tr = 2.47 min. (99 %). LRMS (m/z): 383 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.82 – 0.87 (m, 4H), 2.02 (q, J = 6.2, 5.0 Hz, 1H), 2.31 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 3.73 (s, 3H), 7.19 (t, J = 7.6 Hz, 1H), 7.41 – 7.48 (m, 1H), 7.60 (dd, J = 7.7, 1.7 Hz, 1H), 8.62 (s, 1H), 8.75 (d, J = 4.6 Hz, 1H), 9.40 (s, 1H), 10.94 (s, 1H), 12.33 (s, 1H).

Example 88: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

A mixture of 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 100; 60 mg, 0.179 mmol), 2,6-dimethylpyrimidin-4-amine (33 mg, 0.268 mmol), Pd2(dba)3 (16 mg, 0.017 mmol), Xantphos (21 mg, 0.036 mmol) and cesium carbonate (175 mg, 0.537 mmol) in dioxane (2.5 mL) was heated at 100ºC for 20 hr. The mixture was cooled down, the crude was filtered and the filtrates concentrated. The residue was purified by flash chromatography (Biotage, SNAP 12g) using DCM/DCM-MeOH (5%) from 0 to 100%B to afford 15 mg (19%) of title compound as a white solid.

HPLC-MS: tr = 2.12 min. (98 %). LRMS (m/z): 422 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.36 (s, 3H), 2.53 (s, 3H), 2.83 (d, J = 4.8 Hz, 3H), 3.76 (s, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.41 (s, 1H), 7.48 (d, J = 8 Hz, 1H), 7.66 (dd, J = 8 and 1.2 Hz, 1H), 9.31 (q, J = 4.5 Hz, 1H), 9.68 (s, 1H), 10.77 (s, 1H), 12.85 (s, 1H).

Example 89: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[2-(4-hydroxycyclohexyl)acetyl]amino]-N-methyl-pyridine-3-carboxamide

To the solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 30 mg, 0.088 mmol) in anh dioxane (1 ml) was added 2-(4-hydroxycyclohexyl)acetamide (Intermediate 149; 28 mg, 0.178 mmol) and Cs2CO3 (58 mg, 0.178 mmol). Reaction mixture was degassed under argon gas for 5 minutes, then Pd2(dba)3 (8 mg, 0.009 mmol) and Xantphos (10 mg, 0.017 mmol) were added and the mixture was degassed for an additional 2 minutes. Finally, reaction mixture was heated at 100ºC for 3hr. The reaction was cooled down, filtered and concentrated. The residue was purified by RP flash chromatography (Biotage, SNAP 10g) using H2O/ACN from 0 to 100% in 80CV to afford 15 mg (36%) of the title compound as a white solid.

HPLC-MS tr = 2.20 min and 2.26 min (98%). LRMS (m/z): 459 (M+1)

^{1}H NMR (400 MHz, CDCl3) δ ppm 1.00-1.94 (cs 9H), 2.25 (d J=5 Hz 2H), 2.86 (s 3H), 3.48 (cs 1H), 3.83 (s 3H), 6.71 (t J=8 Hz 2H), 7.30 (cs 2H), 8.36 (s 1H), 9.32 (s 1H).

Example 90: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 50 mg, 0.148 mmol), 2-(5-amino-2-pyridyl)propan-2-ol (prepared according to US2016096823 preparation 4; 70 mg, 0.46 mmol), Pd(dba)3 (15 mg, 0.016 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (18 mg, 0.031 mmol), potassium carbonate (65 mg, 0.47 mmol) in 4 ml of dioxane was stirred at 110ºC overnight. Additional 15 mg of Pd(dba)3, 18 mg of (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) and 2 mL of dioxane were added and the heating at 110ºC was prosected for 18 hr. The mixture is cooled down at rt and water/AcOEt are added. The aqueous phase is extracted with AcOEt (x2). The combined organic phases are dried and concentrated. The crude was purified at Isolera through a 10g Merck reverse phase column, eluting from 100 DCM to 10% MeOH in DCM in 30 CV and repurified at Isolera (reverse phase) with a 5 g Merck column eluting from 100% water to 100% MeCN/MeOH 1:1 in 80CV. 2.2 mg (3%) of title compound were obtained.

HPLC-MS: tr = 1.17 min. (98 %). LRMS (m/z): 454 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 8.85 (s, 1H), 8.52 (s, 1H), 8.17 (s, 2H), 7.64 (d, J = 8.6 Hz, 1H), 7.48 (td, J = 8.5, 6.6 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.84 (t, J = 8.9 Hz, 1H), 4,58 (bs, 1H), 3.91 (s, 3H), 2.85 (s, 3H), 1.56 (s, 6H).

Example 91: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-indole-5-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)indole-5-carboxamide (Intermediate 104; 195 mg, 0.357 mmol) was suspended in ethanol (92 uL) and HCl (37%, 30 uL) was added. The reaction was stirred at 85 ºC for 10 min., then at 55 ºC for 2 hr. The crude was concentrated and treated with ammonia in methanol at 55 ºC overnight. The mixture was concentrated and purified by flash chromatography (100% DCM to 5 % MeOH in DCM gradient) and repurified by flash chromatography (100% diethyl ether to 10% MeOH in Et2O gradient) to obtain the title compound as a white solid (17 mg; 11%).

HPLC-MS tr = 1.90 min (95%). LRMS (m/z): 416 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 13.01 (s, 1H), 11.50 (s, 1H), 10.34 (s, 1H), 9.24 (s, 1H), 8.84 (d, J = 4.7 Hz, 1H), 8.73 (s, 1H), 8.25 (d, J = 1.7 Hz, 1H), 7.75 (dd, J = 8.6, 1.8 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.51 (t, 1H), 7.43 (s, 1H), 6.65 (d, J = 2.7 Hz, 1H), 2.85 (d, J = 4.4 Hz, 3H), 2.52 (s, 3H), 2.33 (s, 3H).

Example 92: 4-[(3-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[(3-chloro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 105; 156 mg, 0.44 mmol), 2,6-dimethylpyrimidin-4-amine (82 mg, 0.67 mmol), Pd2(dba)3 (40 mg, 0.044 mmol), Xantphos (51 mg, 0.20 mmol) and cesium carbonate (430 mg, 1.32 mmol) was heated in dioxane (4.4 mL) at 100 ºC for 5hr. The mixture was diluted in water and extracted with AcOEt. The organic phase was washed with brine, dried over magnesium sulphate, filtered and concentrated. The crude was purified by flash chromatography (100% DCM to 5 % MeOH in DCM gradient) to obtain the title compound a yellowish solid (108 mg; 55%).

HPLC-MS tr: 2.07 min (98%). LRMS (m/z): 441/443 (M+1, Cl))

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.50 (s, 1H), 10.36 (s, 1H), 9.26 (s, 1H), 8.74 (d, J = 4.9 Hz, 1H), 8.66 (s, 1H), 7.75 (m, 2H), 7.38 (s, 1H), 7.33 (t, J = 7.9 Hz, 1H), 3.87 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.33 (s, 3H).

Example 93: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide (Intermediate 106; 40 mg, 0.12 mmol), 2,6-dimethylpyrimidin-4-amine (17 mg, 0.14 mmol) and K2CO3 (50 mg, 0.36 mmol) in anh. Dioxane (1.5 mL) was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (11 mg, 0.012 mmol) and Xantphos (14 mg, 0.024 mmol) were added and the mixture degassed once again. The mixture was heated at 100 ºC overnight. Same additional amounts of pyrimidine, xanthphos and palladium catalyst were added and the reaction was heated for another night at 110ºC. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentraed. The crude was purified by Isolera with a Merck

silica column 5g eluting with DCM/MeOH fromn 0% to 5% in 20 CV to yield 6 mg (12%) of title compound.

HPLC-MS tr: 1.07 min (98%). LRMS (m/z): 428 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.40 (s 3H), 2.47 (s 3H), 3.90 (s 3H), 6.82 (t J= 8Hz 1H), 6.97 (d J= 8Hz 1H), 7.39 (s 1H), 7.46 (cs 1H), 8.57 (s 1H), 9.12 (s 1H).

Example 94: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxamide

To a solution of 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxylic acid (Intermediate 111; 31 mg, 0.068 mmol) in 0.75 mL of anh. DCM wasadded oxalyl chloride (75 uL, 0.87 mmol) at 0 ºC, dropwise and a drop of DMF, the mixture was stirred at 0 ºC under argon gas for 2 h. Ammonia (32% in water, 1 mL) was added at 0 ºC, the reaction was stirred for 2 hr. Additional ammonia (32% in water, 1 mL) was added to the mixture and the reaction was stirred for 30 min at room temperature. The solvent was removed affording 18 mg of a residue (mixture of final and starting compounds) that was purified by way of HPLC (water buffered at pH 8 with ammonia/ammonium bicarbonate to acetonitrile 5% to 100% in 4.5 min) giving 9 mg (29%) of title compound as a white solid.

HPLC-MS tr = 1.77 min (100%). LRMS (m/z): 412 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.39 (s 3H), 2.56 (s 3H), 3.90 (s 3H), 6.82 (t J= 8Hz 1H), 6.96 (d J= 8Hz 1H), 7.42 (s 1H), 7.47 (cs 1H), 8.70 (s 1H), 9.19 (s 1H).

Example 95: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(methanesulphonamido)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[[4-(methanesulphonamido)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 114; 26mg, 0.062mmol), 2,6-dimethylpyrimidin-4-amine (12mg, 0.097mmol), Pd2(dba)3 (6mg, 0.006mmol), xantphos (7mg, 0.012mmol) and cesium carbonate (62mg, 0.19mmol) were heated in dioxane (2mL) at 100ºC for 3.5 hr. Water and AcOEt were added and extracted with AcOEt (x7), then washed with brine. The organic phase was dried over MgSO4, filtered and concentrated. The residue was purified by flash chromatography (Biotage Telos12g) using diethyl ether/MeOH (up to 10%) (220nm) to give the title compound (11mg, 35%) as a white solid.

HPLC/MS tr = 1.75 min (100%). LRMS (m/z):500 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 0H), 2.50 (s, 3H), 2.75 – 2.89 (m, 3H), 3.14 (s, 3H), 4.01 (s, 3H), 6.93 (dd, J = 8.8, 1.5 Hz, 1H), 6.99 (s, 1H), 7.46 (s, 1H), 7.90 – 8.03 (m, 1H), 8.55 (s, 1H), 8.64 (d, J = 4.6 Hz, 1H), 9.14 (s, 1H), 10.23 – 10.36 (m, 2H), 12.30 (s, 1H).

Example 96: 4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide (Intermediate 115; 78 mg, 0.22 mmol), 2,6-dimethylpyrimidin-4-amine (54 mg, 0.44 mmol) and K2CO3 (92 mg, 0.66 mmol) in anh. Dioxane (2.5 mL) was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (40 mg, 0.043 mmol) and Xantphos (51 mg, 0.088 mmol) were added and the mixture degassed once again. The mixture was heated at 100 ºC overnight. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated. The crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 5% in 20 CV to yield 28 mg (28%) of title compound.

HPLC-MS tr = 1.09 min (100%). LRMS (m/z): 440 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.39 (s 3H), 2.53 (s 3H), 3.90 (s 3H), 3.96 (s 3H), 7.15-7.26 (cs 2H), 7.42 (s 1H), 7.51 (cs 1H), 8.51 (s 1H), 9.21 (s 1H).

Example 97: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide (Intermediate 116; 59 mg, 0.17 mmol), 2,6-dimethylpyrimidin-4-amine (43 mg, 0.35 mmol) and K2CO3 (73 mg, 0.52 mmol) in anh. Dioxane (2 mL) was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (32 mg, 0.035 mmol) and Xantphos (41 mg, 0.071 mmol) were added and the mixture degassed once again. The mixture was heated at 100 ºC overnight. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated. The crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 5% in 20 CV to yield 15 mg (20%) of title compound.

HPLC-MS tr = 1.18 min (100%). LRMS (m/z): 424 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.36 (s 3H), 2.38 (s 3H), 2.57 (s 3H), 3.81 (s 3H), 7.17 (t J= 8 Hz 1H), 7.42 (cs 2H), 7.71 (d J= 8 Hz 1H), 8.52 (s 1H), 9.17 (s 1H).

Example 98: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[2-methyl-6-(methylamino)pyrimidin-4-yl]amino]pyridine-3-carboxamide

A solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 50 mgl, 0.15 mmol), N6,2-dimethylpyrimidine-4,6-diamine (Intermediate 151; 31 mg, 0.22 mmol), Pd2(dba)3 (14 mg, 0.015 mmol), Xantphos (17 mg, 0.029 mmol) and cesium carbonate (143 mg, 0.445 mmol) was heated in dioxane (1.5 mL) at 100 ºC for 1hr. Crude was extracted as usual with ethyl acetate and the organic phase was washed with brine x3, dried over magnesium sulphate, filtered and concentrated. The crude was purified by flash chromatography (100% DCM to 10 % MeOH in DCM gradient) to obtain a greenish solid (30 mg) which was re-purified by flash chromatography (reverse phase, water to acetonitrile gradient without formic acid) to obtain a white solid (14 mg, 21%).

HPLC-MS tr = 2.02 min (100%). LRMS (m/z): 440 (M+1).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.35 (s, 1H), 9.89 (s, 1H), 8.96 (s, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 7.55 – 7.48 (m, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.67 (s, 1H), 3.85 (s, 3H), 2.75 (d, J = 4.8 Hz, 3H), 2.73 (d, J = 4.4 Hz, 3H), 2.31 (s, 3H).

Example 99: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 117; 95mg, 0.28mmol), 2,6-dimethylpyrimidin-4-amine (Intermediate 117; 52mg, 0.42mmol), Pd2(dba)3 (26mg, 0.028mmol), xantphos (33mg, 0.057mmol) and cesium carbonate (275mg, 0.84mmol) were heated in dioxane (2mL) at 100ºC for 2 hr. Saturated sodium bicarbonate and AcOEt were added and extracted with AcOEt (x7), then washed with brine. The organic phase was dried over MgSO4, filtered and concentrated. The crude was purified by flash chromatography (Biotage Telos12g) using diethyl ether/MeOH (up to 5%) (220nm) to give the title compound as a white solid (68 mg; 57%)

HPLC/MS tr = 2.00 min (100%). LRMS (m/z): 425 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.50 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 4.03 (d, J = 2.4 Hz, 3H), 7.22 – 7.30 (m, 1H), 7.39 (s, 1H), 7.53 (ddd, J = 11.9, 8.2, 1.6 Hz, 1H), 7.64 – 7.68 (m, 1H), 8.63 (s, 1H), 8.70 – 8.76 (m, 1H), 9.22 (s, 1H), 10.33 (s, 1H), 12.40 (s, 1H).

Example 100: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(2-methyl-6-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 60 mg, 0.17 mmol), 2-methyl-6-morpholino-pyrimidin-4-amine (Intermediate 118; 86 mg, 0.35 mmol) and Cs2CO3 (174 mg, 0.53 mmol) in anh. Dioxane (2 mL) was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (17 mg, 0.018 mmol) and Xantphos) (21 mg, 0.036 mmol) were added and the mixture degassed once again. The mixture was heated at 100 ºC overnight. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated. The crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 5% in 30 CV. The resulting material was re-purified through reverse phase (Isolera with 5g Merck C-18 column) eluting from 0 to 100% water to MeOH/MeCN 1:1 in 40 CV to yield 6 mg (6%) of title compound.

HPLC-MS tr = 1.21 min (97%). LRMS (m/z): 496 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.48 (s 3H), 2.86 (s 3H), 3.21 (m 2H), 3.75 (cs 6H), 3.91 (s 3H), 6.82 (t J= 8 Hz 1H), 6.91 (d J= 8 Hz 1H), 7.47 (cs 1H), 7.70 (bs 1H), 8.59 (s 1H), 8.77 (s 1H),10.70 (s 1H).

Example 101: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 60 mg, 0.17 mmol), 2-[4-(6-amino-2-methyl-pyrimidin-4-yl)piperazin-1-yl]ethanol (Intermediate 119; 84 mg, 0.35 mmol) and K2CO3 (74 mg, 0.53 mmol) in anh. Dioxane (2 mL) was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (33 mg, 0.036 mmol) and Xantphos (41 mg, 0.070 mmol) were added and the mixture degassed once again. The mixture was heated at 100 ºC overnight. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated. The crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH from 0% to 5% in 20 CV to yield 13 mg (13%) of title compound.

HPLC-MS tr = 0.84 min (100%). LRMS (m/z): 539 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.41 (s 3H), 6.60 (cs 6H), 2.84 (s 3H), 3-63-3.75 (cs 6H), 3.90 (s 3H), 6.81 (t J= 8 Hz 1H), 6.92 (s 1H), 6.97 (d J= 8 Hz 1H), 7.48 (cs 1H), 8.56 (s 1H), 8.82 (s 1H),12.10 (s 1H).

Example 102: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[(5-fluoro-2-pyridyl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 100 mg, 0.29 mmol), 5-fluoropyridin-2-amine (134 mg, 1.18 mmol) and Cs2CO3 (285 mg, 0.87 mmol) in anh. DMF (5 mL) was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (54 mg, 0.058 mmol) and Xantphos (68 mg, 0.116 mmol) were added and the mixture degassed once again. The mixture was heated at 100 ºC overnight. Water was added and the mixture extracted with EtAcO (3x). The organic phase was washed with brine, dried and concentrated. The crude was purified through reverse phase (Isolera with 20 g Merck C-18 column) eluting from 0 to 100% water to MeOH/MeCN 1:1 in 40 CV to yield 5 mg (4%) of title compound.

HPLC-MS tr = 1.22 min (90%). LRMS (m/z): 414 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 8.75 (s, 1H), 8.53 (s, 1H), 8.18 (d, J = 3.0 Hz, 1H), 7.82 (dd, J =9.1, 3.9 Hz, 1H), 7.58 – 7.43 (m, 3H), 6.98 (d, J = 8.5 Hz, 1H), 6.90 – 6.80 (m, 1H), 3.91 (s, 3H), 2.86 (s, 3H).

Example 103: 6-[[5-(2,2-dimethylmorpholin-4-yl)-2-pyridyl]amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 100 mg, 0.29 mmol), 5-(2,2-dimethylmorpholin-4-yl)pyridin-2-amine (Intermediate 121; 123 mg, 0.59 mmol) and K2CO3 (123 mg, 0.89 mmol) in anh. Dioxane (3 mL) was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (54 mg, 0.059 mmol) and Xantphos (69 mg, 0.12 mmol) were added and the mixture degassed once again. The mixture was heated at 110 ºC overnight. Water was added and the mixture extracted with EtAcO (3x). The organic phase was washed with brine, dried and concentrated. The crude was purified by reverse phase (Isolera with 20 g Merck C-18 column) eluting from 0 to 100% water to MeOH/MeCN 1:1 in 40 CV to yield 12.6 mg (8%) of title compound as a yellowish solid.

HPLC-MS tr = 1.29 min (91%). LRMS (m/z): 509 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.41 (s, 1H), 9.81 (s, 1H), 8.79 (s, 1H), 8.66 (d, J = 4.4 Hz, 1H), 8.60 (s, 1H), 7.96 (d, J = 2.8 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.57 – 7.45 (m, 1H), 7.41 (dd, J = 9.1, 3.0 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.95 (t, J = 8.8 Hz, 1H), 3.85 (s, 3H), 3.80 – 3.73 (m, 2H), 3.05 – 2.98 (m, 2H), 2.91 (s, 2H), 2.72 (d, J = 4.3 Hz, 3H), 1.25 (s, 6H).

Example 104: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[5-(2-hydroxyethoxy)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To the suspension of 4-[[5-(2-benzyloxyethoxy)-2-methoxy-benzoyl]amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 155; 75 mg, 0.134 mmol) in EtOH (40 ml) was added Pd/C (20 mg) and the mixture was hydrogenated at rt under H2 pressure of 5 bar overnight. 20 additional mg of Pd/C were added and the mixture was stirred again under a H2 atmosphere (5 bar) for 20h. The crude was filtered and concentrated. The residue was purified by RP chromatography (Biotage, SNAP 10g) by using H2O/ACN-MeO (1-1) to give 8 mg 12%) of title compound as a white solid.

HPLC-MS tr = 1.75 min (96%). LRMS (m/z): 467 (M+1)

^{1}H NMR (DMSO-d6, 400 MHz) δ ppm 2.31 (s 3H), 2.78 (s 3H), 3.69 (t J = 6Hz 2H), 3.95-4.00 (cs 5H), 7.13-7.17 (cs 2H), 7.43-7.47 (cs 2H), 8.54 (s 1H), 9.14 (s 1H), 10.28 (s 1H), 12.35 (s 1H).

Example 105: 6-(cyclopropanecarbonylamino)-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

A mixture of 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 100; 45 mg, 0.135 mmol), cyclopropanecarboxamide (34 mg, 0.405 mmol), Pd2(dba)3 (12 mg, 0.0135 mmol), Xantphos (15 mg, 0.025 mmol) and cesium carbonate (175 mg, 0.538 mmol) was heated in dioxane (2.5 mL) at 140ºC for 1 hr. The crude was filtered and purified through flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (2%) from 0 to 100% in 40CVand re-purified through reverse phase (Biotage, SNAP 10g) by using H2O/ACN-MeOH (1-1) from 5 to 100%. 17 mg (48%) of title compound as an off white solid were thus obtained.

HPLC-MS tr = 2.77 min (97%). LRMS (m/z): 384 (M+1)

^{1}H NMR (DMSO-d6, 400 MHz) δ ppm 0.82-0.95 (m, 4H), 2.07-2.16 (m, 1H), 2.31 (s, 3H), 2.82 (d, J = 5 Hz, 3H), 3.73 (s, 3H), 7.19 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 7 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 9.25-9.31 (m, 1H), 9.71 (s, 1H), 11.53 (s, 1H), 12.84 (s, 1H).

Example 106: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 156; 80 mg, 0.23 mmol), 2,6-dimethylpyrimidin-4-amine (42 mg, 0.341 mmol), Pd2(dba)3 (21 mg, 0.023 mmol), Xantphos (26 mg, 0.045 mmol) and cesium carbonate (222 mg, 0.68 mmol) was heated in dioxane (2.3 mL) at 100 ºC overnight. The crude was extracted with ethyl acetate and washed with brine, dried, filtered and concentrated. The crude was purified by flash chromatography (100% DCM to 10 % MeOH in DCM gradient) to obtain the title compound as a yellowish solid (89 mg; 89%).

HPLC-MS tr = 2.02 min (100%). LRMS (m/z): 439 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.47 (s, 1H), 10.39 (s, 1H), 9.29 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 7.46 – 7.36 (m, 1H), 7.33 (s, 1H), 7.07 (t, J = 8.8 Hz, 1H), 3.78 (s, 3H), 2.73 (d, J = 4.4 Hz, 3H), 2.33 (s, 4H), 2.26 (s, 3H).

Example 107: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[(3-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide

A solution of 6-chloro-N-methyl-4-[(3-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide (Intermediate 157; 79 mgl, 0.21 mmol), 2,6-dimethylpyrimidin-4-amine (44 mg, 0.357 mmol), Pd2(dba)3 (22 mg, 0.024 mmol), Xantphos (27 mg, 0.047 mmol) and cesium carbonate (231 mg, 0.71 mmol) was heated in dioxane (2.4 mL) at 100 ºC for 2 hr. Excess water was added and the mixture was extracted with ethyl acetate and washed with brine, dried, filtered and concentrated. The crude was purified by flash chromatography (100% DCM to 10 % MeOH in DCM gradient) to obtain the title compound as a yellowish solid (40 mg; 41%).

HPLC-MS tr = 1.73 min (100%). LRMS (m/z): 455 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 13.31 (s, 1H), 10.43 (s, 1H), 9.26 (s, 1H), 8.90 (d, J = 4.8 Hz, 1H), 8.77 (s, 1H), 8.46 (t, J = 1.8 Hz, 1H), 8.30 – 8.18 (m, 2H), 7.94 (t, J = 7.8 Hz, 1H), 7.37 (s, 1H), 2.84 (d, J = 4.5 Hz, 3H), 2.53 (s, 3H), 2.34 (s, 3H).

Example 108: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(4-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(4-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 158; 75 mg, 0.213 mmol), 2,6-dimethylpyrimidin-4-amine (42 mg, 0.341 mmol), Pd2(dba)3 (19 mg, 0.021 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (139 mg, 0.427 mmol) were heated in dioxane (2 mL) at 100ºC for 1.5 hr. The crude was filtered and purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (5%) from 0 to 100% in 40CV to afford 64 mg (67%) of title compound as a pale yellow solid

HPLC-MS tr = 2.08 min (99%). LRMS (m/z): 439 (m+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.20 (s 3H), 2.30 (s 3H), 2.76 (d J=4.5 Hz 3H), 3.76 (s 3H), 7.13 (t J= 8Hz 1H), 7.36 (s 1H), 7.71 (m 1H), 8.60 (s 1H), 8.68 (d J=5 Hz) 1H), 9.21 (s 1H), 10.29 (s 1H), 12.37 (s 1H).

Example 109: 4-[(3-cyano-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(3-cyano-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 160; 172 mg, 0.498 mmol), 2,6-dimethylpyrimidin-4-amine (123 mg, 0.998 mmol), Pd2(dba)3 (29 mg, 0.050 mmol), Xantphos (58 mg, 0.100 mmol) and potassium carbonate (207 mg, 1.497 mmol) were heated in dioxane (8 mL) at 140ºC overnight. The crude was filtered, washed with MeOH and the filtrate concentrated. The residue was partitioned between AcOEt and water. The organic phase was washed with water, dried and concentrated. The residue was rinsed with AcOEt and filtered to give 62 mg (29%) of title compound.

UPLC-MS tr = 1.05 min (100%). LRMS (m/z): 432 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.56 (s, 1H), 10.38 (s, 1H), 9.27 (s, 1H), 8.76 (d, J = 4.6 Hz, 1H), 8.67 (s, 1H), 8.13 (dd, J = 7.8, 1.6 Hz, 1H), 8.05 (dd, J = 7.7, 1.6 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.37 (s, 1H), 4.07 (s, 3H), 3.30 (s, 3H), 2.79 (d, J = 4.4 Hz, 3H), 2.33 (s, 3H).

Example 110: 6-(cyclopropanecarbonylamino)-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 156; 80 mg, 0.23 mmol), cyclopropanecarboxamide (29 mg, 0.34 mmol), Pd2(dba)3 (21 mg, 0.023 mmol), xantphos (26 mg, 0.045 mmol) and potassium carbonate (94 mg, 0.68 mmol) were heated in dioxane (2mL) at 100ºC. After 2h same quantites of cyclopropanecarboxamide, Pd2(dba)3, xantphos and K2CO3 were added and heated again

at 100ºC overnight. Saturated bicarbonate and AcOEt were added and extracted with AcOEt (x2), then washed with brine. The organic phase was dried over MgSO4, filtered and concentrated. The crude was purified by flash chromatography (Biotage Telos12g) using diethyl ether/MeOH (225nm) to give the title compound (46mg, 51%) as a yellow solid.

HPLC/MS tr = 2.58 min (99%). LRMS (m/z): 401 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) □ ppm 0.79 – 0.95 (m, 4H), 2.01 – 2.09 (m, 1H), 2.25 (s, 3H), 2.73 (d, J = 4.5 Hz, 3H), 3.75 (s, 3H), 7.06 (t, J = 8.8 Hz, 1H), 7.34 – 7.48 (m, 1H), 8.73 (s, 1H), 8.80 – 8.98 (m, 1H), 9.37 (s, 1H), 11.02 (s, 1H), 12.44 (s, 1H).

Example 111: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-6-methoxy-3H-benzotriazole-5-carboxamide

To the solution of N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-6-methoxy-3-(2-trimethylsilylethoxymethyl)benzotriazole-5-carboxamide (Intermediate 168; 90 mg, 0.156 mmol) in DCM (2 ml) was added TFA (2 ml) and the mixture was stirred at room temperature for 3.5 hr.Solvent was removed and the residue was treated with NH3 (7N in MeOH) for 30min and then concentrated. The residue was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (10%) from 0 to 100% in 40CV to afford 34.3 mg (49%) of title compound as an off white solid

HPLC-MS tr = 1.63 min (99%). LRMS (m/z): 448 (M+1)

1H NMR (DMSO-d6, 400 MHz) δ ppm 2.31 (s 3H), 2.78 (d J = 4 Hz 3H), 4.06 (s 3H), 7.40 (s 1H), 8.57 (m 1H), 8.68 (cs 1H), 9.21 (s 1H), 10.28 (s 1H), 12.47 (s 1H).

Example 112: 6-[[6-(dimethylamino)-2-methyl-pyrimidin-4-yl]amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 60 mg, 0.177 mmol), N4,N4,2-trimethylpyrimidine-4,6-diamine (54 mg, 0.354 mmol), Pd2(dba)3 (33 mg, 0.036 mmol), Xantphos (41 mg, 0.07 mmol) and potassium carbonate (74 mg, 0.535 mmol) were heated in dioxane (2 mL) at 110ºC overnight. Excess water was added and the mixture was extracted with ethyl acetate and washed with brine, dried, filtered and concentrated to afford 144 mg of material. The crude was purified by flash chromatography (100% DCM to 15 % MeOH in DCM gradient) to obtain the title compound (13 mg; 30%).

UPLC-MS tr = 1.21 min (90%). LRMS (m/z): 454 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.41 (s 3H), 2.84 (s 3H), 3.12 (s 6H), 3.91 (s 3H), 6.82 (t J = 5 Hz 2H), 6.97 (d J=5 Hz 1H), 6.44-6-50 (cs 1H), 8.56 (s 1H), 8.81 (s 1H)

Example 113: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(methanesulfonamido)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 50 mg, 0.15 mmol), N-(6-amino-3-pyridyl)methanesulfonamide (Intermediate 170; 42 mg, 0.224 mmol), Pd2(dba)3 (14 mg, 0.015 mmol), Xantphos (17 mg, 0.029 mmol) and cesium carbonate (143 mg, 0.445 mmol) was heated in dioxane (1.5 mL) at 90 ºC for 1 hr. Ethyl acetate and brine were added and the organic phase dried, filtered and concentrated. The crude was purified by flash chromatography (100% DCM to 10 % MeOH in DCM gradient) to obtain a brown solid. As this solid showed two peaks by hplc it was repurified by reverse phase chromatography and again by reverse phase in acidic conditions (1% formic acid) to obtain the title compound as a white solid (12 mg).

HPLC-MS tr = 1.93 min (97%). LRMS (m/z): 489 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.86 (d, J= 4 Hz, 3H), 2.97 (s, 3H), 3.92 (s, 3H), 6.87 (m, 1H), 6.98 (m, 1H), 7.49 (m, 1H), 7.71 (dd, J = 7.9, 0.8 Hz, 1H), 8.21 (s, 1H), 8.54 (s, 1H), 8.80 (s, 1H)

Example 114: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3H-benzimidazole-5-carboxamide

To a solution of N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide and N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-(2-trimethylsilylethoxymethyl)benzimidazole-5-carboxamide (Intermediate 176; 88 mg, 0.15 mmol) in 2 mL of CH2Cl2 (partially soluble) was added TFA (2 mL) and the mixture was stirred at room temperature. After 2h 30 min. the conversion is about 80 % and after 6 h the reaction is complete. The volatiles were removed under reduced pressure and NH3 in MeOH was added and evaporated in order to neutralize the TFA. The brown residue was purified directly via flash chromatography (CH2Cl2/CH2Cl2 with 20 % MeOH) to have a white solid which was in turn repurified by reverse phase to give 35 mg (51 %) of title compound.

HPLC-MS: tr = 1.53 min. (96 %). LRMS (m/z): 447 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 4.61 (s, 3H), 7.27 (d, J = 8.7 Hz, 1H), 7.46 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H), 8.29 (s, 1H), 8.55 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 9.17 (s, 1H), 10.27 (s, 1H), 12.32 (s, 1H), 12.80 (s, 1H).

Example 115: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

To a solution of N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridine-2-carboxamide (Intermediate 181; 39 mg, 0.071 mmol) in 1 mL of CH2Cl2 was added 1 mL of TFA and the mixture was stirred at room temperature. After 2h the reaction is complete (CH2OH intermediate). The volatiles were removed under reduced pressure to have an orange oil which was treated with 2 mL of NH3 7N in MeOH at room temperature. After 1 h the reaction is complete and the volatiles were removed under reduced pressure to have a brown solid. MeOH and DMF were added and the precipitated solid was filtered and washed with water (x 1) to afford the title compound as a grey solid (13 mg, 44 %).

HPLC-MS: tr = 1.87 min. (99 %). LRMS (m/z): 417 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.34 (s, 3H), 2.87 (d, J = 4.3 Hz, 3H), 7.14 – 7.21 (m, 2H), 7.46 (s, 1H), 8.20 – 8.26 (m, 1H), 8.42 (s, 1H), 8.77 (s, 1H), 8.90 (d, J = 5.8 Hz, 1H), 9.10 (s, 1H), 10.44 (s, 1H), 12.55 (s, 1H), 13.24 (s, 1H).

Example 116: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(5-sulfamoyl-2-pyridyl)amino]pyridine-3-carboxamide

A solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 60 mg, 0.167 mmol), N-(6-amino-3-pyridyl)methanesulfonamide (61mg, 0.352 mmol), Pd2(dba)3 (33 mg, 0.036 mmol), Xantphos (41 mg, 0.071 mmol) and potassium carbonate (74 mg, 0.535 mmol) was heated in dioxane (2 mL) under argon atmosphere at 110 ºC overnight. Ethyl acetate and brine were added and the organic phase dried, filtered and concentrated. This crude (97 mg) was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 5% in 20 CV. The obtained solid (12 mg) was repurified by preparative HPLC to afford the title compound as a white solid (2 mg; 2%).

HPLC-MS tr = 1.13 min (100%). LRMS (m/z): 475 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.86 (s, 3H), 2.97 (s, 3H), 3.92 (s, 3H), 6.82 (m, 1H), 6.98 (m, 1H), 7.21 (m, 1H), 7.41-7.50 (bs, 2H), 7.91 (m, 1H), 8.08 (m, 1H), 8.57 (s, 1H), 8.75 (s, 1H), 8.92 (s, 1H).

Example 117: 4-[(3-cyclopropyl-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(3-cyclopropyl-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 181; 88 mg, 0.24 mmol) in 3 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (45 mg, 0.36 mmol), Pd2(dba)3 (22 mg, 0.024 mmol), Xantphos (28 mg, 0.048 mmol) and cesium carbonate (239 mg, 0.73 mmol) and the mixture was heated at 100ºC. After 2h 30 min. the reaction is finished and the mixture was cooled down to room temperature. The reaction mixture was diluted with EtOAc and washed with water and brine; dried over anh. MgSO4, filtered and evaporated to have a brown semisolid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 10 % MeOH to afford the title compound as a white solid (52 mg, 48 %).

HPLC-MS: tr = 2.17 min. (99 %). LRMS (m/z): 447 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.74 (p, J = 4.3 Hz, 2H), 1.01 – 1.08 (m, 2H), 2.16 – 2.25 (m, 1H), 2.33 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 3.83 (s, 3H), 7.08 (dd, J = 7.8, 1.7 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.39 (s, 1H), 7.52 – 7.59 (m, 1H), 8.63 (s, 1H), 8.70 (d, J = 4.9 Hz, 1H), 9.24 (s, 1H), 10.32 (s, 1H), 12.39 (s, 1H).

Example 118: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1H-indole-2-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-(2-trimethylsilylethoxymethyl)indole-2-carboxamide (Intermediate 186; 101 mg, 0.175 mmol) were suspended in ethanol (90 uL) and HCl (37%, 260 uL) was added. Additional water (0.5 mL) was added in order to ease the hydrolisis. The reaction was stirred at 55 ºC for 3 h. After being concentrated, the crude was treated with ammonia 8 M in methanol. The residue was purified by flash chromatography (5% methanol in dichloromethane gradient) to afford the title compound as a yellow solid (44 mg; 56%).

HPLC-MS tr = 2.18 min. LRMS (m/z): 446 (M+1).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 13.05 (s, 1H), 11.86 (s, 1H), 10.38 (s, 1H), 9.12 (s, 1H), 8.86 (d, J = 4.2 Hz, 2H), 8.75 (s, 1H), 7.44 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.13 (d, J =

2.2 Hz, 1H), 7.04 (t, J = 7.9 Hz, 1H), 6.81 (dd, J = 7.9, 0.8 Hz, 1H), 3.93 (s, 3H), 2.86 (d, J = 4.4 Hz, 3H), 2.52 (s, 3H), 2.34 (s, 3H).

Example 119: 4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(2-methoxyethoxy)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 40 mg, 0.12 mmol) in 2.5 mL of anh. dioxane was added 5-(2-methoxyethoxy)pyridin-2-amine (WO2010009155; 30 mg, 0.18 mmol), Pd2(dba)3 (11 mg, 0.012 mmol), Xantphos (14 mg, 0.024 mmol) and cesium carbonate (115 mg, 0.35 mmol).The mixture was heated at 100ºC in a microwave oven for 80 min under Ar. Water and AcOEt were added and the organic phase was washed with brine, dried and concentrated. The residue was purified by flash chromatography (5% methanol in dichloromethane gradient) to afford the title compound (13 mg; 22%).

HPLC-MS tr = 1.17 min (93%). LRMS (m/z): 470 (M+1).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.89 (d J=6Hz 3H), 3.47 (s 3H), 3.74 (t J=8Hz 2H), 3.87 (s 3H), 4.14 (t J=8Hz 2H), 6.75 (cs 2H), 7.34 (cs 2H), 7.79 (d J=6Hz 1H), 8.1 (bs 1H), 8.49 (s 2H), 8.69 (s 1H), 12.0 (s 1H)

Example 120: 6-[(5,6-dimethylpyrazin-2-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

In a 2ml MW tube, a solution of 6-chloro-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 3; 50 mg, 0.15 mmol), 5,6-dimethylpyrazin-2-amine (30 mg, 0.24 mmol), and Cs2CO3 (145 mg, 0.445 mmol) in 1.5 ml of anh. dioxane was degassed with 3 vacuum-nitrogen cycles. Pd2dba3 (14 mg, 0.015 mmol) and xantphos (17 mg, 0.029 mmol) were added and the mixture was again degassed and heated at 100 ºC for 1,5 h. (Absorption: Water was added and the mixture extracted with AcOEt (2x). The organic phase was washed with brine, dried and concentrated to afford 87 mg of crude. This crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH from 0% to 5% in 30 CV. Collection of the fractions containing the product yielded 22 mg (35%) of title compound.

HPLC-MS: tr = 1.40' (98 %). LRMS (m/z): 425 (M+1, Cl)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.47 (s 3H), 2.51 (s 3H), 2.84 (s 3H), 6.81 (dd, J = 7.9, 0.8 Hz, 1H), 6.98 (d J=8Hz 1H), 7.40.7.51 (cs 2H), 8.55 (s 1H), 8.76 (s 1H), 8.94 (s 1H)

Example 121: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-4-methoxy-indole-2-carboxamide

To a solution of 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-indole-2-carboxamide (Intermediate 190; 95 mg, 0.157 mmol) in methanol (3.1 uL) and THF (3.1 uL) was added HCl (37%, 60 uL) and the reaction was stirred at room temperature for 15 min. The crude was purified by flash chromatography (100% DCM to 10 % MeOH in DCM gradient) to get 60 mg (75%) of title compound as a white solid.

HPLC-MS tr = 2.12 min. LRMS (m/z): 490 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 13.04 (bs, 1H), 10.36 (bs, 1H), 9.25 (s, 1H), 8.87 (d, J = 4.8 Hz, 1H), 8.75 (s, 1H), 7.38 (s, 1H), 7.31 – 7.18 (m, 3H), 6.63 (d, J = 7.6 Hz, 1H), 4.80 (t, J = 5.5 Hz, 1H), 4.65 (t, J = 5.8 Hz, 2H), 3.94 (s, 3H), 3.73 (q, J = 5.5 Hz, 3H), 2.86 (d, J = 4.5 Hz, 3H), 2.34 (s, 3H)

Example 122: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 195; 70 mg, 0.21 mmol) in 5 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (40 mg, 0.32 mmol), Pd2(dba)3 (40 mg, 0.043 mmol), Xantphos (50 mg, 0.086 mmol) and cesium carbonate (205 mg, 0.63 mmol) and the mixture was heated at 100ºC overnight. The mixture was cooled down to room temperature, diluted with EtOAc and washed with water and brine; dried over anh. MgSO4, filtered and evaporated to have 192 mg of residue which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 5 % MeOH to afford the title compound as a white solid (10 mg, 11 %).

HPLC-MS tr = 1.17 min (92%). LRMS (m/z): 424 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.39 (s, 1H), 10.33 (s, 1H), 9.24 (s, 1H), 8.70 (d, J = 4.6 Hz, 1H), 8.64 (s, 1H), 7.62 (dd, J = 7.7, 1.8 Hz, 1H), 7.45 (dd, J = 7.5, 1.8 Hz, 1H), 7.40 (s, 1H), 7.20 (t, J = 7.6 Hz, 1H), 3.75 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.33 (s, 3H).

Example 123: 4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-6-[(6-methyl-2-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

In a 0,5-2ml MW tube, a solution of 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 75; 60 mg, 180 mmol), 6-methyl-2-morpholino-

pyrimidin-4-amine (Intermediate 196; 52 mg, 0.267 mmol and cessium carbonate (175, 0.537 mmol) in 1.8 mL of anh. dioxane was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (16 mg, 0.017 mmol) and Xantphos (21 mg, 0.036 mmol) were added and the mixture degassed again. The mixture was heated at 100 ºC for 5,5 h. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated to afford 193 mg of crude. This crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 5% in 30 CV. Collection of the fractions containing the product yielded 18 mg (20%) of title compound.

HPLC-MS: tr = 1.34 min (100 %). LRMS (m/z): 492 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.25 (s 3H), 2.38 (s 3H), 2.90 (s 3H), 3.77 (m 4H), 3.80 (s 3H), 3.86 (m 4H), 6.32 (s, 1H), 7.18 (m 1H), 7.41 (d J=8Hz 1H), 7.51 (d J=8Hz 1H), 8.47 (s 1H), 9.40 (s 1H), 12.21 (s 1H)

Example 124: 6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

In a 0,5-2ml MW tube, a solution of 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 75; 60 mg, 180 mmol), 2-[4-(4-amino-6-methyl-pyrimidin-2-yl)piperazin-1-yl]ethanol (Intermediate 197; 64 mg, 0.269 mmol and cessium carbonate (175, 0.537 mmol) in 1.8 mL of anh. dioxane was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (33 mg, 0.036 mmol) and Xantphos (41 mg, 0.070 mmol) were added and the mixture degassed again. The mixture was heated at 100 ºC for 6 h. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated to afford 139 mg of crude. This crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 15% in 30 CV. Collection of the fractions containing the product yielded 28 mg (29%) of title compound.

HPLC-MS: tr = 1.04 min (100 %). LRMS (m/z): 535 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.25 (s 3H), 2.36 (s 3H), 2.57 (t J=8Hz 2H), 2.89 (s 3H), 3.71 (t J=8Hz 2H), 3.80 (s 3H), 3.91 (m 4H), 6.31 (s, 1H), 7.15 (m 1H), 7.41 (d J=8Hz 1H), 7.72 (d J=8Hz 1H), 8.47 (s 1H), 9.38 (s 1H), 12.20 (s 1H)

Example 125: 6-[[2-[4-(2-methoxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

In a 0,5-2ml MW tube, a solution of 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 75; 60 mg, 180 mmol), 2-[4-(2-methoxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-amine (Intermediate 197; 70 mg, 0.278 mmol and cessium carbonate (175, 0.537 mmol) in 1.8 mL of anh. dioxane was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (33 mg, 0.036 mmol) and Xantphos (41 mg, 0.070 mmol) were added and the mixture degassed again. The mixture was heated at 100 ºC for 6 h. Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated to afford 158 mg of crude. This crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 10% in 20 CV. Collection of the fractions containing the product yielded 19 mg (19%) of title compound.

HPLC-MS: tr = 1.13 min (92 %). LRMS (m/z): 549 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.25 (s 3H), 2.36 (s 3H), 2.51 (t J=8Hz 2H), 2.82 (s 3H), 3.32 (s 3H), 3.52 (t J=8Hz 2H), 3.71 (m 2H), 3.80 (s 3H), 3.92 (m 4H), 6.31 (s, 1H), 7.25 (m 1H), 7.42 (d J=8Hz 1H), 7.72 (d J=8Hz 1H), 8.43 (s 1H), 9.39 (s 1H), 12.20 (s 1H).

Example 126: 4-[(3-chloro-2-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[(3-chloro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 105; 100 mg, 0.28 mmol), cyclopropanecarboxamide (36 mg, 0.423 mmol), Pd2(dba)3 (26 mg, 0.028 mmol), Xantphos (33 mg, 0.057 mmol) and cesium carbonate (276 mg, 0.85 mmol) was heated in dioxane (2.8 mL) at 100 ºC for 6 h. The mixture was directly purified by flash chromatography (DCM to MeOH 10% in DCM) to obtain 69 mg of material. As some amount of cyclopropanecarboxamide was detected by NMR, the sample was dissolved in ethyl acetate and washed with water (x3) in order to remove the impurities. The organic phase was dried and concentrated to get 48.17 mg (41%) of title compound-

HPLC-MS: tr = 2.60 min. LRMS (m/z) 403/405 (M+1, Cl)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.45 (s, 1H), 10.98 (s, 1H), 9.40 (s, 1H), 8.79 (q, J = 4.8 Hz, 1H), 8.66 (s, 1H), 7.79 – 7.70 (m, 2H), 7.33 (t, J = 7.9 Hz, 1H), 3.85 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.08 – 2.00 (m, 1H), 0.90 – 0.79 (m, 4H).

Example 127: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-3-methoxy-indole-2-carboxamide

To a solution of 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-indole-2-carboxamide (Intermediate

201; 65 mg, 0.107 mmol) in methanol (1.5 mL) and THF (1.5 mL) was added HCl (37%, 60 µL) and the reaction was stirred at room temperature for 15 min. Solvent was removed and more MeOH was added and removed again. Then NH3 (7N in MeOH) was added and the yellow solid turned white. After 30 minutes the mixture was concentrated and the residue was suspended in ACN and filtered. The solid was purified by RP (Biotage, SNAP 40g) using H2O/ACN-MeOH (1-1) to afford 30 mg (56%) of title compound as a white solid

HPLC-MS tr = 1.98 min (99%). LRMS (m/z): 490 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.3 (s, 3H), under dmso (s, 3H), 2.80 (d, J = 4.5 Hz, 3H), 3.69 (q, J = 5.6 Hz, 2H), 4.20 (s, 3H), 4.57 (t, J = 5.6 Hz, 2H), 4.78 (t, J = 5.4 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.27-7.34 (m, 2H), 7.59 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 8.53 (s, 1H), 8.59-8.64 (m, 1H), 9.26 (s, 1H), 10.2 (s, 1H), 12.07 (S, 1h).

Example 128: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

In a 0,5-2ml MW tube a mixture of 6-chloro-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide (Intermediate 202; 113 mg, 0.332 mmol), 2,6-dimethylpyrimidin-4-amine (65 mg, 0.527 mmol) and cesium carbonate (325 mg, 0.997 mmol) and 3.5 mL of anh. dioxane was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (61 mg, 0.066 mmol) and Xantphos (77 mg, 0.133 mmol) were added and the mixture degassed again. The mixture was heated at 100 ºC for 5 h. Water was added and the mixture extracted with EtAcO (3x). The organic phase was washed with brine, dried and concentrated to afford 321 mg of crude. This crude was purified by Isolera with a Merck silica column 10g eluting with DCM/MeOH from 0% to 5% in 30 CV. Collection of the fractions containing the product yielded 66 mg (46%) of title compound as an off-white solid.

HPLC-MS: tr = 1.17 min. (99 %). LRMS (m/z): 427 (M+1)

^{1}H NMR (400 MHz, DMSOd6) δ ppm 12.39 (s, 1H), 10.33 (s, 1H), 9.24 (s, 1H), 8.67 (s, 1H), 8.64 (s, 1H), 7.62 (dd, J = 7.7, 1.8 Hz, 1H), 7.45 (dd, J = 7.5, 1.8 Hz, 1H), 7.40 (s, 1H), 7.20 (t, J = 7.6 Hz, 1H), 3.75 (s, 3H), 2.33 (s, 3H)

Example 129: 4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-6-[[6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]amino]pyridine-3-carboxamide

In a 0,5-2ml MW tube a mixture of 6-chloro-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 75; 60 mg, 0.180 mmol), 6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-amine (56 mg, 0.27 mmol) and cesium carbonate (175 mg, 0.537 mmol) and 1.8 mL of anh. dioxane was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (17 mg, 0.018 mmol) and Xantphos (21 mg, 0.036 mmol) were added and the mixture degassed again. The mixture was heated at 100 ºC for 6 h. Water was added and the mixture extracted with EtAcO (3x). The organic phase was washed with brine, dried and concentrated to afford 151 mg of crude. This crude was purified by Isolera with a Merck silica column 5 g eluting with DCM/MeOH from 0% to 15% in 40 CV. Collection of the fractions containing the product yielded 38 mg (42%) of title compound as an off-white solid.

HPLC-MS: tr = 1.03 min. (97 %). LRMS (m/z): 505 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.22 (s, 3H), 2.30-233 (cs, 5H), 2.37 (s, 3H), 2.45 (m, 2H), 2.74 (m, 4H), 2.90 (s, 3H), 3.82 (s, 3H), 6.32 (s, 1H), 7.15 (t, J=8Hz, 1H), 7.41 (d, J=8Hz, 1H), 7.71 (d, J=8Hz, 1H), 7.48 (s, 1H), 9.38 (s, 1H), 12.22 (s, 1H)

Example 130: 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl) benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

A solution of 6-chloro-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide (Intermediate 202; 55 mg, 0.16 mmol), cyclopropanecarboxamide (21 mg, 0.24 mmol), Pd2(dba)3 (30 mg, 0.032 mmol), Xantphos (38 mg, 0.065 mmol) and cesium carbonate (160 mg, 0.49 mmol) was heated in dioxane (3 mL) at 100 ºC overnight. As there is still a relevant amount of starting material one additional equivalent of cyclopropylamide and catalysts is added and the heating at 100ºC prosecuted for 48 hr. Water and AcOEt were added, the organic phase was washed with brine, dried and concentrated to afford 115 mg of crude material. This residue was purified by flash chromatography (DCM to MeOH 10% in DCM) to obtain 11 mg (17%) of title compound-

HPLC-MS tr = 1.45 min. (85%). LRMS (m/z) 389 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.34 (s, 1H), 10.95 (s, 1H), 9.41 (s, 1H), 7.61 (dd, J = 7.7, 1.8 Hz, 1H), 7.50 (s, 1H), 7.45 (dd, J = 7.5, 1.8 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 6.74 (bs, 1H), 3.30 (s, 3H), 1.50 (tt, J = 7.3, 5.2 Hz, 1H), 0.73 – 0.51 (m, 4H)

Example 131: 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 195; 100 mg, 0.296 mmol), cyclopropanecarboxamide (50 mg, 0.587 mmol), Pd2(dba)3 (60 mg, 0.065 mmol), Xantphos (70 mg, 0.121 mmol) and cesium carbonate (300 mg, 0.92 mmol) was heated in dioxane (5 mL) at 100 ºC overnight under argon atmosphere. As there is still a relevant amount of starting material one additional equivalent of cyclopropylamide and catalysts is added and the heating at 100ºC prosecuted for 6 hr. Water and AcOEt were added, the organic phase was washed with brine, dried and concentrated to afford 274 mg of crude material. This residue was purified by flash chromatography (DCM to MeOH 10% in DCM) to obtain 30 mg (26%) of title compound.

HPLC-MS tr = 1.45 min. (100%). LRMS (m/z) 386 (M+1)

1H NMR (400 MHz, DMSO-d6) δ ppm 12.34 (s, 1H), 10.95 (s, 1H), 9.41 (s, 1H), 8.75 (d, J = 4.6 Hz, 1H), 8.63 (s, 1H), 7.61 (dd, J = 7.7, 1.8 Hz, 1H), 7.45 (dd, J = 7.5, 1.8 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 3.73 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 2.03 (ddd, J = 12.5, 7.6, 5.2 Hz, 1H), 0.89 – 0.79 (m, 4H).

Example 132: 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 161; 84 mg, 0.25 mmol), cyclopropanecarboxamide (32 mg, 0.37 mmol), Pd2(dba)3 (23 mg, 0.025 mmol), Xantphos (29 mg, 0.05 mmol) and cesium carbonate (246 mg, 0.75 mmol) was heated in dioxane (1.7 mL) at 100ºC. After 3h 30 min. the mixture was cooled down to room temperature and NH4Cl sat. was added. AcOEt was added and NaCl sat. in order to improve the separation of phases. The organic phase was washed with brine, dried over anh. MgSO4, filtered and evaporated to have a yellow oil which was purified by flash chromatography (DCM to MeOH 10% in DCM) to obtain 41 mg (45%) of title compound.

HPLC-MS: tr = 2.47 min. (99 %). LRMS (m/z): 383 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 9.42 (s, 1H), 8.56 (s, 1H), 8.05 (dd, J = 7.8, 1.4 Hz, 1H), 7.84 (dd, J = 7.8, 1.3 Hz, 1H), 7.45 – 7.33 (m, 1H), 3.89 (s, 3H), 2.90 (s, 3H), 1.90 (tq, J = 8.7, 4.3 Hz, 1H), 1.06 – 0.71 (m, 5H).

Example 133: 4-[(3,5-difluoro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

To a suspension of 6-chloro-4-[(3,5-difluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 204; 57 mg, 0.16 mmol) in 2 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (30 mg, 0.24 mmol), Pd2(dba)3 (15 mg, 0.016 mmol), Xantphos (18 mg, 0.031 mmol) and cesium carbonate (157 mg, 0.48 mmol) and the mixture was heated at 100 ºC. After 3 h the reaction is complete and it was filtered. The solid was washed with water (x3), Et2O (x3) and MeOH (x 2) to afford the title compound as a grey solid which was dried in the vacuum oven for one night (45 mg, 63 %).

HPLC-MS: tr = 2.07 min. (99 %). LRMS (m/z): 443 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 3.93 – 4.04 (m, 3H), 7.37 (s, 1H), 7.46 – 7.53 (m, 1H), 7.60 – 7.70 (m, 1H), 8.63 (s, 1H), 8.73 (d, J = 2.8 Hz, 1H), 9.21 (s, 1H), 10.34 (s, 1H), 12.45 (s, 1H).

Example 134: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-methyl-indole-6-carboxamide

A mixture of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-methyl-indole-6-carboxamide (Intermediate 206; 53mg, 0.14mmol), 2,6-dimethylpyrimidin-4-amine (53mg, 0.43mmol), Pd2(dba)3 (13mg, 0.014mmol), xantphos (17mg, 0.029mmol) and cesium carbonate (139mg, 0.42mmol) was heated in dioxane (2mL) at 100ºC for 4 hr. Saturated bicarbonate and AcOEt were added and the mixture was extracted with AcOEt (x3), then washed with brine. The organic phase was dried over MgSO4, filtered and evaporated to dryness. The crude was purified by flash chromatography (Biotage Telos12g) using dichloromethane/MeOH (up to 10%) (225nm) to give the title compound (40mg, 61%) as a pale brown solid

HPLC/MS tr = 2.02 min (98%). LRMS (m/z): 460 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.51 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 3.89 (s, 3H), 4.06 (s, 3H), 6.51 (d, J = 3.0 Hz, 1H), 7.42 (d, J = 6.6 Hz, 3H), 7.47 (d, J = 3.0 Hz, 1H), 8.63 (s, 1H), 8.66 – 8.75 (m, 1H), 9.23 (s, 1H), 10.33 (s, 1H), 12.36 (s, 1H).

Example 135: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxamide

A mixture of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxamide (Intermediate 209; 53mg, 0.12mmol), 2,6-dimethylpyrimidin-4-amine (45mg, 0.36mmol), Pd2(dba)3 (11mg, 0.012mmol), xantphos (14mg, 0.024mmol) and cesium carbonate (118mg, 0.36mmol) was heated in dioxane (2mL)

at 100ºC for 4 hr. Saturated bicarbonate and AcOEt were added and the mixture was extracted with AcOEt (x3), then washed with brine. The organic phase was dried over MgSO4, filtered and evaporated to dryness.The crude was purified by flash chromatography (Biotage Telos12g) using dichloromethane/MeOH (up to 5%) (225nm) to give the title compound (37mg, 58%) as a pale yellow solid.

HPLC/MS tr = 2.22 min (100%). LRMS (m/z): 528 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.33 (s, 3H), 2.50 (d, J = 3.7 Hz, 3H), 2.76 (d, J = 4.5 Hz, 3H), 3.90 (s, 3H), 5.31 (q, J = 9.1 Hz, 2H), 6.68 (d, J = 3.2 Hz, 1H), 7.38 – 7.42 (m, 2H), 7.46 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 3.2 Hz, 1H), 8.67 (s, 1H), 8.72 (q, J = 3.9 Hz, 1H), 9.25 (s, 1H), 10.35 (s, 1H), 12.42 (s, 1H).

Example 136: N-[2-(cyclopropanecarbonylamino)-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-3-methoxy-indole-2-carboxamide

To a solution of 1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-[2-(cyclopropanecarbonylamino)-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-indole-2-carboxamide (Intermediate 210; 48 mg, 0.085 mmol) in methanol (1.5 mL) and THF (1.5 ml) was added HCl (37%, 42 µL) and the reaction was stirred at room temperature for 30 min. Solvent was removed and more MeOH was added and concentrated again. Then NH3 (7N in MeOH) was added and the yellow solid turned white. After 30 minutes the solvent was concentrated. The residue was taken up in DCM/MeOH and purified by flash chromatography (Biotage, SNAP 12g) using DCM/DCM-MeOH (10%) from 0 to 75% to afford 25 mg (64%) of title compound.

HPLC-MS tr = 2.35 min (99%). LRMS (m/z): 452 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.80-0.89 (m, 4H), 2.00-2.06 (m, 1H), 2.82 (d, J = 4.5 Hz, 3H), 3.66 (q, J = 5.8 Hz, 2H), 4.21 (s, 3H), 4.58 (t, J = 5.8 Hz, 2H), 4.77 (t, J = 5.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 8.52 (s, 1H), 8.67-8.72 (m, 1H), 9.39 (s, 1H), 10.90 (s, 1H), 12.04 (s, 1H).

Example 137: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide

A mixture of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide (Intermediate 215; 65 mg, 0.156 mmol), 2,6-dimethylpyrimidin-4-amine (31 mg, 0.252 mmol), Pd2(dba)3 (14 mg, 0.015 mmol), Xantphos

(18 mg, 0.031 mmol) and cesium carbonate (102 mg, 0.313 mmol) was heated in dioxane (4 mL) at 100ºC for 2h 15 min. EtOAc was added and the suspension was filtered, the solid was washed with more EtOAc and water, then it was dried in an oven under vacuum to give 66 mg (84%) of title compound as an off white solid.

HPLC-MS tr = 2.23 min (100%). LRMS (m(z): 504 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), under dmso (s, 3H), 2.82 (d, J = 4.4 Hz, 3H), 3.65 (t, J = 5.4 Hz, 2H), 4.23 (s, 3H), 4.72 (t, J = 5.4 Hz, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.31-7.36 (m, 2H), 7.60 (d, J= 8.6 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 8.56 (s, 1H), 8.62-8.66 (m, 1H), 9.30 (s, 1H), 10.26 (s, 1H), 12.12 (s, 1H).

Example 138: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-methyl-indole-2-carboxamide

A mixture of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-methyl-indole-2-carboxamide (Intermediate 218; 100 mg, 0.193 mmol), 2,6-dimethylpyrimidin-4-amine (38 mg, 0.309 mmol), Pd2(dba)3 (18 mg, 0.02 mmol), Xantphos (22 mg, 0.038 mmol) and cesium carbonate (126 mg, 0.387 mmol) was heated in dioxane (4 mL) at 100ºC for 2.5 hr. Water and EtOAc were added and the suspension was filtered, the solid was washed with more EtOAc and water, then it was dried in an oven under vacuum to afford 31 mg (39%) of title compound.

HPLC-MS tr = 2.20 min (96%). LRMS (m/z): 460 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.32 (s, 3H), under dmso (s, 3H), 2.82 (d, J = 4 Hz, 3H), 4.00 (s, 3H), 4.22 (s, 3H), 7.12 (t, J = 8 Hz, 1H), 7.32-7.42 (m, 2H), 7.57 (d, J= 8 Hz, 1H), 7.89 (d, J = 7.2 Hz, 1H), 8.55(s, 1H), 8.63 (br s, 1H), 9.22 (s, 1H), 10.25 (s, 1H), 12.09 (s, 1H).

Examples 139 and 140: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-methyl-benzimidazole-5-carboxamide and N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-methyl-benzimidazole-5-carboxamide

To a solution of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-methyl-benzimidazole-5-carboxamide and N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-methyl-benzimidazole-5-carboxamide (Intermediate 222; 60 mg, 0.14 mmol) in 2 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (25 mg, 0.20 mmol), Pd2(dba)3 (13 mg, 0.014 mmol), Xantphos (16 mg, 0.027 mmol) and cesium carbonate (133 mg, 0.41 mmol) and the mixture was heated at 100ºC. After 3.5 h. EtOAc was added and the mixture was washed

with water (x 1). A solid is present in the organic phase (insoluble), which was dried and filtered to have a white-yellow solid which was purified via flash chromatography in CH2Cl2/CH2Cl2 with 10 % MeOH to have the corresponding title compounds:

FRACTION 1 (compound 139): 5 mg

HPLC-MS: tr = 1.70 min. (90 %). LRMS (m/z): 461 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.25 (s, 3H), under dmso (s, 3H), 2.80 (s, 3H), 3.89 (s, 3H), 4.58 (s, 3H), 7.24 (m, 1H), 7.32 (s, 1H), 7.83 (m, 1H), 8.21 (s, 1H), 8.56 (s, 1H), 8.62 (m, 1H), 9.15 (s, 1H), 10.21 (s, 1H), 12.35 (s, 1H)

FRACTION 2 (compound 140): 10 mg

HPLC-MS: tr = 1.48 min. (85 %). LRMS (m/z): 461 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.25 (s, 3H), under dmso (s, 3H), 2.75 (s, 3H), 3.91 (s, 3H), 4.05 (s, 3H), 7.39 (s, 1H), 7.51 (m, 1H), 7.59 (m, 1H), 8.24 (s, 1H), 8.61 (s, 1H), 8.64 (m, 1H), 9.21 (s, 1H), 10.32 (s, 1H), 12.41 (s, 1H)

Example 141: 6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

In a 0,5-2ml MW tube, a mixture of 6-chloro-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 161; 80 mg, 0.206 mmol), 2-[4-(4-amino-6-methyl-pyrimidin-2-yl)piperazin-1-yl]ethanol (Intermediate 197; 75 mg, 0.316 mmol), and Cs2CO3 (202 mg, 0.62 mmol) in anh. Dioxane (2 mL) was degassed with 3 vacuum-nitrogen cycles. Pd2(dba)3 (38 mg, 0.041 mmol) and Xantphos (48 mg, 0.043 mmol) were added and the mixture was degassed again. The mixture was heated at 100 ºC for 6 h. (Absorption: Normal) Water was added and the mixture extracted with EtAcO (2x). The organic phase was washed with brine, dried and concentrated to afford 139 mg of crude. This crude was purified by Isolera with a Merck silica column 5g eluting with DCM/MeOH fromn 0% to 15% in 30 CV. Collection of the fractions containing the product yielded 28 mg (30%) of title compound.

HPLC-MS: tr = 1.17 min. (100 %). LRMS (m/z): 589 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ ppm 9.39 (s, 1H), 8.52 (s, 1H), 8.04 (dd, J = 7.8, 1.4 Hz, 1H), 7.84 (dd, J = 7.8, 1.3 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 6.32 (s, 1H), 4.88 (s, 5H), 3.94 (q, J = 8.9, 6.7 Hz, 4H), 3.89 (s, 3H), 3.72 (t, J = 5.9 Hz, 2H), 2.89 (s, 3H), 2.63 (dt, J = 22.6, 5.4 Hz, 6H), 2.25 (s, 3H).

Example 142: 4-[(3-fluoro-2-methoxy-benzoyl)amino]-6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

6-chloro-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 117; 30mg, 0.089mmol), 2-[4-(4-amino-6-methyl-pyrimidin-2-yl)piperazin-1-yl]ethanol (Intermediate 197; 63mg, 0.26mmol), Pd2(dba)3 (8mg, 0.008mmol), xantphos (10mg, 0.017mmol) and cesium carbonate (87mg, 0.26mmol) were heated in dioxane (2mL) and three drops of NMP at 100ºC in a microwave reactor for 5h. Water and dichloromethane were added and extracted with dichloromethane (x4). The organic phase was dried over MgSO4, filtered and evaporated to dryness.The crude was purified by flash chromatography (Biotage Telos12g) using dichloromethane/MeOH (up to 10%) (225nm) to give the title compound (20mg) as a solid. As this material contained a remaining 5% of Xantphos the solid was repurified by reverse phase water/ACN (225nm), [water has formic acid, so the product was neutralized with 7M NH3 in methanol and evaporated], to give the title compound (11mg, 23%) as a pale brown solid.

HPLC/MS tR = 1.78min (100%). LRMS (m/z): 539 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.17 (s, 3H), 2.38 – 2.47 (m, 2H), 2.79 (d, J = 4.5 Hz, 3H), 3.44 – 3.49 (m, 8H), 3.79 (s, 2H), 4.03 (d, J = 2.4 Hz, 3H), 6.41 (s, 1H), 7.21 – 7.39 (m, 1H), 7.43 – 7.59 (m, 1H), 7.66 (d, J = 6.7 Hz, 1H), 8.59 (s, 1H), 8.67 – 8.80 (m, 1H), 9.29 (s, 1H), 9.96 (s, 1H), 12.42 (s, 1H).

Example 143: 4-[(3-chloro-2-methoxy-benzoyl)amino]-6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

In a similar way to that described for Example 142 the title compound was obtained in 35% yield starting from 6-chloro-4-[(3-chloro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 105) and 2-[4-(4-amino-6-methyl-pyrimidin-2-yl)piperazin-1-yl]ethanol (Intermediate 197).

HPLC/MS tR = 1.08min (100%). LRMS (m/z): 555 (M+1; Cl)

^{1}H NMR (400 MHz, CD3OD) δ ppm 2.22 (s, 3H), 2.58 (t J = 8Hz, 2H), 2.58-2.65 (m 4H), 2.89 (s, 2H), 2.71 (t J = 8Hz, 2H), 3.92 (s, 3H), 6.31 (s, 1H), 7.22 – 7.28 (m, 1H), 7.62 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 8.49 (s, 1H), 9.38 (s, 1H), 12.30 (s, 1H).

Example 144: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

A solution of 6-chloro-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 4; 150 mg, 0.469 mmol), 2,6-dimethylpyrimidin-4-amine (87 mg, 0.706 mmol), Pd2(dba)3 (43 mg, 0.047 mmol), Xantphos (54 mg, 0.093 mmol) and cesium carbonate (459 mg, 1.41 mmol) was heated in dioxane (1.2 mL) at 100 ºC for 3hr. After cooling, water and AcOEt were added and the organic phase extracted, washed with brine, dried, filtered and concentrated. The residue was purified by flash chromatography (10% methanol in DCM gradient) to get 39 mg of title compound as a yellowish solid.

HPLC-MS tr = 1.92 min (97%). LRMS (m/z): 407 (M+1).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.39 (s, 1H), 10.29 (s, 1H), 9.19 (s, 1H), 8.66 (d, J = 4.7 Hz, 1H), 8.57 (s, 1H), 7.95 (dd, J = 7.7, 1.8 Hz, 1H), 7.59 (ddd, J = 8.4, 7.3, 1.9 Hz, 1H), 7.45 (s, 1H), 7.23 (dd, J = 8.5, 1.0 Hz, 1H), 7.12 (td, J = 7.5, 1.0 Hz, 1H), 4.02 (s, 3H), 2.81 (d, J = 4.6 Hz, 3H), 2.33 (s, 3H).

Example 145: 6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridazine-3-carboxamide

A mixture of 6-chloro-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 223; 146 mg, 0.432 mmol), cyclopropanecarboxamide (75 mg, 0.88 mmol), Pd2(dba)3 (80 mg, 0.087 mmol), Xantphos (100 mg, 0.173 mmol), cesium carbonate (425 mg, 1.30 mmol) in 10 mL dioxane were heated in a MW oven at 110ºC for 3 hr. Water and AcOEt were added and the aqueous fraction was further extracted with more AcOEt (x2). The organic fraction was washed with brine, dried and concentrated to give 283 mg of residue that was purified through flash chromatography (10% methanol in DCM gradient) to afford 116 mg of title compound. As the material was contaminated it was repurified through reverse phase chromatography (Merck C-18, 10 g) eluting from H2O to MeCN/MeOH 1:1 to afford 17 mg (10%) of the title compound.

UPLC-EM: tR=1.58 min (89%). LRMS (m/z): 387 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.86 (s, 1H), 11.56 (s, 1H), 9.73 (s, 1H), 9.31 (d, J = 4.8 Hz, 1H), 7.65 (dd, J = 7.8, 1.8 Hz, 1H), 7.48 (dd, J = 7.5, 1.8 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 3.75 (s, 3H), 2.84 (d, J = 4.8 Hz, 3H), 2.14 (m, 1H). 0.91 – 0.86 (m, 4H).

Example 146: N-[2-(cyclopropanecarbonylamino)-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide

A mixture of N-[2-chloro-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide (Intermediate 215; 80 mg, 0.192 mmol), cyclopropanecarboxamide (26 mg, 0.305 mmol), Pd2(dba)3 (18 mg, 0.020 mmol), Xantphos (22 mg, 0.038 mmol) and cesium carbonate (125 mg, 0.384 mmol) was heated in dioxane (4 mL) at 100ºC for 3.5 hr. EtOAc was added and the crude was filtered and concentrated. The residue was purified by flash chromatography (Biotage, SNAP 12g) by using DCM/DCM-MeOH (5%) to afford 60 mg of title compound.

HPLC-MS: 2.72' (99%). LRMS (m/z): 466 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.80-0.90 (m, 4H), 2.00-2.07 (m, 1H), 2.83 (d, J = 4.5 Hz, 3H), 3.15 (s, 3H), 3.61 (t, J = 5.4 Hz, 2H), 4.22 (s, 3H), 4.70 (t, J = 5.4 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.30-7.36 (m, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 8.56 (s, 1H), 8.67-8.73 (m, 1H), 9.38 (s, 1H), 10.90 (s, 1H), 12.05 (s, 1H)

Example 147: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-methoxy-1-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[[4-methoxy-1-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 230a; 13 mg, 0.035 mmol) in 400 uL of anh. dioxane, was added 2,6-dimethylpyrimidin-4-amine (6.5 mg, 0.052 mmol), $Pd_2(dba)_3$ (3 mg, 0.003 mmol), Xantphos (4.1 mg, 0.007 mmol) and cesium carbonate (34 mg, 0.104 mmol) and the mixture was heated at 100 ºC. After 3h 30 m the reaction is finished. Water was added followed by EtOAc. A solid appeared and was filtered off and washed with water, Et2O and CH2Cl2 to have the final product as a grey solid (3 mg). The organic phase also contains product so it was dried over an. MgSO4, filtered, evaporated and purified in CH2Cl2/CH2Cl2 with 10 % MeOH to have a white solid (2 mg). Total: 5 mg (31%) of title compound as a greyish solid.

HPLC-MS: tr = 1.70 min. (99 %). LRMS (m/z): 455 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ 2.32 (s, 3H), 2.80 (d, J = 4.3 Hz, 3H), 3.20 (s, 3H), 3.64 – 3.70 (m, 2H), 3.94 (s, 3H), 4.65 (t, J = 4.0 Hz, 2H), 7.34 (s, 1H), 7.58 (s, 1H), 8.56 (s, 1H), 8.63 (d, J = 7.0 Hz, 1H), 9.19 (s, 1H), 10.26 (s, 1H), 11.85 (s, 1H).

Example 148: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-methoxy-2-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[[4-methoxy-2-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide (Intermediate 230b; 21 mg, 0.057 mmol) in 700 uL of anh. dioxane, was added 2,6-dimethylpyrimidin-4-amine (10.5 mg, 0.085 mmol), $Pd_2(dba)_3$ (5.2 mg, 0.005 mmol), Xantphos (7 mg, 0.012 mmol) and cesium carbonate (56 mg, 0.17 mmol) and the mixture was heated at 100 ºC. After 3h 30 min. the proportion of final product is 43 % (56 % of starting material left). A second equivalent of reactants was added and the heating was kept for 3 more hours. Once cooled, the crude was filtered off and washed with water. The final solid (final product and starting material mostly) was picked-up in dioxane, all reactants were added again and all the mixture was heated again at 130 ºC. After 45 min. the reaction is complete. The mixture was cooled down to room temperature, filtered and washed with Et2O (x 2). The residue was purified via HPLC through a symmetry prep C18 7µm 19X300mm column eluting from MeCN/MeOH 1:1 to water to afford 4 mg (15%) of pure title compound. uPLC-MS: tr = 0.90 min. (100 %). LRMS (m/z): 455 (M+1)

^{1}H NMR (400 MHz, CD3OD) δ 2.39 (s, 3H), 2.56 (s, 3H), 2.92 (d, J = 4 Hz, 3H), 3.36 (s, 3H), 3.81 (t, J= 8 Hz, 2H), 4.32 (t, J= 8 Hz, 2H), 7.48 (s, 1H), 7.56 (s, 1H), 8.52 (s, 1H), 9.01 (s, 1H).

Example 149: N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1H-indole-5-carboxamide

To a suspension of N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-(2-trimethylsilylethoxymethyl)indole-5-carboxamide (Intermediate 235; 40 mg, 0.069 mmol) in water/dioxane (1/2 ml) was added HCl (35%, 0.5 ml) and the mixture was heated at 75 ºC for 1 hr. NH4OH (32%, 1 ml) was added and the reaction mixture was heated again at 75ºC for 2 h and stirred at room temperature overnight. The pH was ajusted to 7 by the addition of 1N HCl, and the mixture was filtered. The solid was taken up in DCM and MeOH and was purified by flash chromatography (biotage, SNAP 12g) by using DCM/DCM-MeOH (10%) to afford 7 mg (22%) of title compound as an off-white solid.
HPLC-MS tr: 1.83' (99%). LRMS (m/z): 446 (M+1)

^{1}H NMR (DMSO, 400 MHz) δ ppm 2.33 (s, 3H), under DMSO (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 4.27 (s, 3H), 6.83 (ddd, J = 3, 2 and 1 Hz, 1H), 7.20 (dd, J = 8.6 and 1 Hz, 1H), 7.40-7.43 (m, 1H), 7.47 (s, 1H), 7.71 (d, J = 8.6 Hz, 1H), 8.54 (s, 1H), 8.60-8.67 (m, 1H), 9.15 (s, 1H), 10.24 (s, 1H), 11.52 (s, 1H), 12.28 (s, 1H).

Example 150: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-methoxypyridine-2-carbonyl)amino]-N-methyl-pyridine-3-carboxamide

To a solution of 6-chloro-4-[(3-methoxypyridine-2-carbonyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 236; 104 mg, 0.324 mmol) in 4 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine (64 mg, 0.521 mmol), Pd2(dba)3 (63 mg, 0.069 mmol), Xantphos (58 mg, 0.10 mmol) and cesium carbonate (323 mg, 0.992 mmol) and the mixture was heated in a MW oven at 110ºC for 3 hr. After cooling down to room temperature water and EtOAc were added, the organic phase was washed with water and brine (x 1 both), dried over anh. MgSO4, filtered and evaporated. The residue was purified via reverse-phase chromatography eluting with H2O to MeOH/MeCN 1:1 afford 18 mg (13%) of title compound as a white solid.
UPLC tr: 0.88 min. (96%). LRMS (m/z): 408 (M+1)
^{1}H NMR (400 MHz, DMSO-d6) δ 12.82 (s, 1H), 10.32 (s, 1H), 9.15 (s, 1H), 8.67 (d, J = 13.7 Hz, 2H), 8.29 (d, J = 3.3 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.64 (dd, J = 8.5, 4.5 Hz, 1H), 7.46 (s, 1H), 3.91 (s, 3H), 2.78 (d, J = 4.4 Hz, 3H), 2.33 (s, 3H).

Example 151: 6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

By starting with Intermediate 237 and following the same methodology as in Example 99 the title compound was obtained as a white solid in 50% yield
UPLC/MS tr = 1.17 min (100%). LRMS (m/z): 428 (M+1)
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.34 (s, 3H), 2.50 (s, 3H), 4.03 (s, 3H), 7.25 – 7.30 (m, 1H), 7.33 (s, 1H), 7.59 (ddd, J = 11.9, 8.2, 1.6 Hz, 1H), 7.66 – 7.70 (m, 1H), 8.65 (s, 1H), 8.72 (s, 1H), 9.22 (s, 1H), 10.34 (s, 1H), 12.40 (s, 1H).

Example 152: 6-(cyclopropanecarbonylamino)-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

A mixture of 6-chloro-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 238; 50 mg; 0.147 mmol), cyclopropanecarboxamide (20 mg; 0.235 mmol), Pd2(dba)3 (27 mg; 0.029 mmol), Xantphos (34 mg; 0.058 mmol) and cesium carbonate (144 mg; 0.442 mmol) in dioxane (1 mL) was heated at 100ºC under MW irradiation. After 1h 30 min. the mixture was cooled down to room temperature and water/AcOEt were added. A solid appeared between phases that was filtered-off. This solid corresponds to the

final product and was added to final crude for purification. The organic phase was washed with NaCl sat., dried over anh. MgSO4, filtered and evaporated to have a crude of 100 mg which was purified in CH2Cl2/MeOH with a Merck SI 5g column from 0% to 5% of MeOH. Collection of the fractions containing the product afforded 28 mg of product with some impurities. This solid was triturated with EtAcO and filtered to produce 18 mg of pure product.
UPLC/MS tr = 1.59 min (100%). LRMS (m/z): 388 (M+1)
^{1}H NMR (400 MHz, DMSO-d6) δ 12.89 (s, 1H), 11.58 (s, 1H), 9.71 (s, 1H), 9.33 (m, 1H), 7.69 (d, J = 4 Hz, 1H), 7.57 (m, 1H), 7.27 (m, 1H), 4.06 (s, 3H), 2.85 (d, J = 4.4 Hz, 3H), 2.13 (m, 1H), 0.90 (s, 4H).

Example 153: 6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridazine-3-carboxamide

A mixture of 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridazine-3-carboxamide (Intermediate 239; 54 mg; 0.154 mmol), cyclopropanecarboxamide (25 mg; 0.293 mmol), Pd2(dba)3 (30 mg; 0.032 mmol), Xantphos (37 mg; 0.064 mmol) and cesium carbonate (150 mg; 0.460 mmol) in dioxane (3 mL) was heated at 100ºC under MW irradiation. After 3h the mixture was cooled down to room temperature and water/AcOEt were added. A solid appeared between phases that was filtered-off. This solid corresponds to the final product and was added to final crude for purification. The organic phase was washed with NaCl sat., dried over anh. MgSO4, filtered and evaporated to have a crude of 312 mg which was purified in CH2Cl2/MeOH with a Merck SI 10 g column from 0% to 10% of MeOH. Collection of the fractions containing the product afforded 10 mg (16%) of title product as a white solid.
UPLC/MS tr = 1.51 min (90%). LRMS (m/z): 400 (M+1)
^{1}H NMR (400 MHz, DMSO-d6) δ 12.82 (s, 1H), 11.55 (s, 1H), 9.71 (s, 1H), 9.29 (d, J = 4.8 Hz, 1H), 7.39 (dd, J = 7.8, 1.6 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.28 – 7.18 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.84 (d, J = 4.8 Hz, 3H), 2.13 (p, J = 6.3, 5.9 Hz, 1H), 0.93 – 0.84 (m, 4H)

Example 154: 4-[(3,6-difluoro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

A mixture of 6-chloro-4-[(3,6-difluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide (Intermediate 240; 85.3 mg, 0.239 mmol) , Pd2(dba)3 (22 mg, 0.024 mmol), Xantphos (27 mg, 0.046 mmol) and cesium carbonate (233 mg, 0.715 mmol) in 4 mL of anh. dioxane was added 2,6-dimethylpyrimidin-4-amine(61 mg, 0.495 mmol) and heated at 100ºC

for 2.5 hr. The reaction mixture was cooled down to room temperature and diluted with water and EtOAc, the organic phase washed with brine (x 3), dried over anh. MgSO4, filtered and evaporated. The residue was purified via flash chromatography in Et2O/Et2O- MeOH (80:20) and re-purified via 5.5g C18 gold column, H2O-ACN:MeOH (1:1) without any additive to afford 6.8 mg (6%) of the title compound as a white solid.

HPLC-MS tr: 1,97 min (99.6%). LRMS (m/z): 443 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ 12.54 (s, 1H), 10.39 (s, 1H), 9.24 (s, 1H), 8.80 (q, J = 4.5 Hz, 1H), 8.71 (s, 1H), 7.51 (ddd, J = 11.3, 9.2, 5.3 Hz, 1H), 7.31 (s, 1H), 7.15 (td, J = 8.9, 3.4 Hz, 1H), 3.94 (d, J = 1.9 Hz, 3H), 2.73 (d, J = 4.4 Hz, 3H), 2.34 (s, 1H), 2.31 (s, 3H).

Example 155: 6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

A mixture of 6-chloro-4-[(2,3-dimethoxybenzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide (Intermediate 115; 280 mg, 0.794 mmol), cyclopropanecarboxamide (101 mg, 1,187 mmol), Pd2(dba)3 (145 mg, 0.158 mmol), Xantphos (184 mg, 0.318 mmol) and cesium carbonate (776 mg, 2.382 mmol) in 6 mL of anh. dioxane was heated at 100ºC under MW irradiation for 3 hr. After cooling to room temperature water and AcOEt were added and the organic phase was washed with brine, dried and concentrated. The residue was purified in CH2Cl2/MeOH with a Merck SI 20g column from 0% to 10% of MeOH in 40 CV to afford 161 mg of title compound (45%) as a white powder.

UPLC-MS: tr = 1.36 min. (98 %). LRMS (m/z): 402 (M+1)

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.78 – 0.97 (m, 4H), 2.01 – 2.05 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 7.19 – 7.23 (m, 1H), 7.25-7.29 (m, 1H), 7.34 – 7.37 (m, 1H), 8.61 (s, 1H), 8.70-8.73 (bs, 1H), 9.38 (s, 1H), 10.92 (s, 1H), 12.28 (s, 1H).

The following compounds were prepared using methods identical or similar to those described above, unless stated otherwise.

Example 156: 4-(2-fluoro-6-methoxybenzamido)-6-((6-((2-methoxyethyl)amino)-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC/MS tr = 1.14 min (100%). LRMS (m/z): 484 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 8.76 (s, 1H), 8.55 (s, 1H), 7.48 (td, J = 8.5, 6.6 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.88 – 6.79 (m, 2H), 3.91 (s, 3H), 3.61 – 3.45 (m, 4H), 3.38 (s, 3H), 2.86 (s, 3H), 2.39 (s, 3H).

Example 157: 4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((4-(trifluoromethyl)pyridin-2-yl)amino)nicotinamide

Example 158: 4-(2,5-dimethoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC/MS tr = 1.97 min (99%). LRMS (m/z): 437 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.33 (s, 3H), 2.50 (s, 3H), 2.81 (d, J = 4.5 Hz, 3H), 3.77 (s, 3H), 3.97 (s, 3H), 7.18 (d, J = 1.8 Hz, 1H), 7.39 – 7.53 (m, 2H), 8.56 (s, 1H), 8.61 – 8.77 (m, 1H), 9.14 (s, 1H), 10.30 (s, 1H), 12.37 (s, 1H).

Example 159 4-(2-fluoro-6-methoxybenzamido)-6-((6-((2-hydroxyethyl)amino)-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC/MS tr = 1.06 min (96%). LRMS (m/z): 470 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.35 (s, 1H), 9.89 (s, 1H), 8.95 (s, 1H), 8.75 (d, J = 4.5 Hz, 1H), 8.63 (s, 1H), 7.52 (td, J = 8.4, 6.9 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.95 (t, J = 8.8 Hz, 2H), 6.72 (s, 1H), 4.75 (t, J = 5.5 Hz, 1H), 3.85 (s, 2H), 3.52 (q, J = 5.8 Hz, 2H), 3.30 – 3.23 (m, 3H), 2.73 (d, J = 4.5 Hz, 2H), 2.30 (s, 2H), 1.37 – 1.21 (m, 2H).

Example 160 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(morpholinomethyl)benzamido)-N-methylnicotinamide

HPLC/MS tr = 1.35 min (98%). LRMS (m/z): 506 (M+1)

1H NMR (400 MHz, Chloroform-d) δ 12.23 (s, 1H), 8.98 (s, 1H), 8.75 (s, 1H), 8.54 (s, 1H), 7.84 (dd, J = 7.8, 1.8 Hz, 1H), 7.58 (dd, J = 7.6, 1.8 Hz, 1H), 7.45 (s, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.58 (d, J = 5.1 Hz, 1H), 3.91 (s, 3H), 3.71 (t, J = 4.7 Hz, 4H), 3.63 (s, 3H), 2.99 (d, J = 4.7 Hz, 3H), 2.65 (s, 3H), 2.52 (t, J = 4.2 Hz, 4H), 2.46 (s, 3H).

Exemple 161 4-(2-fluoro-6-methoxybenzamido)-6-((6-methoxy-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC/MS tr = 1.43 min (92%). LRMS (m/z): 441 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 8.85 (s, 1H), 8.58 (s, 1H), 7.48 (td, J = 8.5, 6.6 Hz, 1H), 7.12 (s, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.88 – 6.79 (m, 1H), 3.92 (d, J = 5.9 Hz, 6H), 3.83 (s, 1H), 2.86 (s, 3H), 2.50 (s, 3H), 2.32 (s, 1H), 2.26 (s, 0H).

Exemple 162 4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((4-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

HPLC/MS tr = 2.22 min (98%). LRMS (m/z): 494 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.73 (d, J = 4.5 Hz, 3H), 3.85 (s, 3H), 4.86 (q, J = 8.8 Hz, 2H), 6.74 (dd, J = 5.9, 2.4 Hz, 1H), 6.91 – 7.00 (m, 1H), 7.04 (d, J = 8.6 Hz, 1H), 7.46 – 7.61 (m, 2H), 8.18 (d, J = 5.9 Hz, 1H), 8.66 (s, 1H), 8.73 (d, J = 4.7 Hz, 1H), 8.85 (s, 1H), 10.08 (s, 1H), 12.38 (s, 1H).

Example 163 6-((6-cyano-2-methylpyrimidin-4-yl)amino)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

HPLC/MS tr = 1.54 min (100%). LRMS (m/z): 436 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 11.04 (s, 1H), 9.21 (s, 1H), 8.85 (s, 1H), 8.76 (s, 1H), 8.01 (s, 1H), 7.63 – 7.43 (m, 1H), 7.05 (d, J = 8.5 Hz, 1H), 7.00 – 6.87 (m, 1H), 3.86 (s, 1H), 3.30 (s, 3H), 2.75 (d, J = 4.3 Hz, 1H).

Example 164 4-(2-fluoro-6-methoxybenzamido)-6-(3-hydroxypropanamido)-N-methylnicotinamide

HPLC/MS tr =1.98 min (96%). LRMS (m/z): 391 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.55 (t, J = 6 Hz, 2H), 2.72 (d, J = 4.5 Hz, 3H), 3.70 (q, J = 6 Hz, 2H), 3.83 (s, 3H), 4.71 (t, J = 5.2 Hz, 1H), 6.93 (d, J = 9 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 7.50 (td, J = 8.5 and 7 Hz, 1H), 8.67 (s, 1H), 8.80-8.84 (m, 1H), 9.34 (s, 1H), 10.60 (s, 1H), 12.32 (s, 1H).

Example 165 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-5-(methoxymethyl)benzamido)-N-methylnicotinamide

HPLC/MS tr = 1.93 min (94%). LRMS (m/z): 451 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.30 (s, 3H), under DMSO (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 3.26 (s, 3H), 3.99 (s, 3H), 4.39 (s, 2H), 7.19 (d, J = 8.5 Hz, 1H), 7.41 (s, 1H), 7.51 (dd, J = 8.5 and 2.3 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 8.53 (s, 1H), 8.61-8.65 (m, 1H), 9.14 (s, 1H), 10.26 (s, 1H), 12.34 (s, 1H).

Example 166 4-(2-fluoro-6-methoxybenzamido)-6-((6-(2-hydroxyethoxy)pyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC/MS tr = 1.21 min (99%). LRMS (m/z): 457 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 8.66 (s, 1H), 8.61 (s, 1H), 8.40 (d, J = 0.8 Hz, 1H), 7.53 – 7.43 (m, 2H), 6.98 (d, J = 8.5 Hz, 1H), 6.85 (t, J = 8.9 Hz, 1H), 4.44 – 4.37 (m, 2H), 3.94 – 3.84 (m, 4H), 2.87 (s, 2H), 1.36 – 1.26 (m, 1H).

Example 167 4-(2-fluoro-6-methoxybenzamido)-6-(3-hydroxycyclobutane-1-carboxamido)-N-methylnicotinamide

HPLC/MS tr = 1.17 min (96%). LRMS (m/z): 417 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 9.38 (d, J = 4.9 Hz, 1H), 8.56 (s, 1H), 7.48 (td, J = 8.5, 6.6 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.83 (t, J = 8.9 Hz, 1H), 4.55 – 4.38 (m, 1H), 4.20 – 4.01 (m, 1H), 3.91 (s, 2H), 3.23 (qd, J = 10.9, 9.6, 6.1 Hz, 1H), 2.86 (s, 2H), 2.64 – 2.39 (m, 2H), 2.31 – 2.01 (m, 2H), 1.40 – 1.20 (m, 1H).

Example 168 4-(2-fluoro-6-methoxybenzamido)-6-(2-hydroxyacetamido)-N-methylnicotinamide

UPLC/MS tr = 1.13 min (95%). LRMS (m/z): 377 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 9.46 (s, 1H), 8.59 (s, 1H), 7.48 (td, J = 8.5, 6.6 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.84 (t, J = 8.9 Hz, 1H), 4.17 (s, 2H), 3.91 (s, 3H), 2.87 (s, 3H), 2.65 (s, 1H).

Example 169 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-(2-methoxyethoxy)-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

Example 170 4-(2-fluoro-6-methoxybenzamido)-6-isobutyramido-N-methylnicotinamide

HPLC/MS tr = 2.42 min (99%). LRMS (m/z): 389 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 1.09 (s, 3H), 1.11 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H), 2.76 – 2.82 (m, 1H), 3.85 (s, 3H), 6.95 (t, J = 9.1 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.47 – 7.57 (m, 1H), 8.70 (s, 1H), 8.84 (d, J = 4.7 Hz, 1H), 9.36 (s, 1H), 10.63 (s, 1H), 12.34 (s, 1H).

Example 171 4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-(1-methylcyclopropane-1-carboxamido)nicotinamide

HPLC/MS tr = 2.52 min (99%). LRMS (m/z): 401 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 0.67 (q, J = 4 Hz, 2H), 1.14 (q, J = 4 Hz, 2H), 1.14 (s, 3H), 2.73 (d, J = 4.5 Hz, 3H), 3.82 (s, 3H), 6.93 (t, J = 8.8 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.50 (td, J = 8.5 and 7 Hz, 1H), 8.69 (s, 1H), 8.81-8.86 (m, 1H), 9.25 (s, 1H), 9.66 (s, 1H), 12.31 (s, 1H).

Example 172 4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((6-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

HPLC/MS tr = 3.00 min (100%). LRMS (m/z): 494 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.74 (d, J = 4.5 Hz, 3H), 3.84 (s, 3H), 5.09 (q, J = 9.1 Hz, 2H), 6.49 (d, J = 7.9 Hz, 1H), 6.95 (t, J = 8.8 Hz, 1H), 7.00 – 7.24 (m, 2H), 7.44 – 7.64 (m, 1H), 7.69 (t, J = 8.0 Hz, 1H), 8.67 (s, 1H), 8.72 – 8.81 (m, 1H), 9.13 (s, 1H), 10.16 (s, 1H), 12.50 (s, 1H).

Example 173 6-(3,3-difluorocyclobutane-1-carboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

HPLC/MS tr = 2.58 min (98%). LRMS (m/z): 437 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.72 (d, J = 4.5 Hz, 3H), 2.72-2.84 (m, 4H), 3.18-3.30 (m, 1H), 3.82 (s, 3H), 6.93 (t, J = 8.8 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.50 (td, J = 8.5 and 7 Hz, 1H), 8.67 (s, 1H), 8.80-8.85 (m, 1H), 9.36 (s, 1H), 10.84 (s, 1H), 12.31 (s, 1H).

Example 174 4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-pivalamidonicotinamide

HPLC/MS tr = 2.62 min (100%). LRMS (m/z): 403 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 1.25 (s, 9H), 2.75 (d, J = 4.5 Hz, 3H), 3.85 (s, 3H), 6.95 (t, J = 8.8 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.52 (td, J = 8.5, 7.0 Hz, 1H), 8.72 (s, 1H), 8.83 – 8.93 (m, 1H), 9.34 (s, 1H), 10.00 (s, 1H), 12.36 (s, 1H).

Example 175 6-(cyclopentanecarboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

UPLC/MS tr = 1.53 min (96%). LRMS (m/z): 415 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 9.37 (s, 1H), 8.57 (s, 1H), 7.48 (td, J = 8.5, 6.6 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.83 (t, J = 8.9 Hz, 1H), 3.91 (s, 2H), 2.96 – 2.88 (m, 1H), 2.86 (s, 2H), 2.69 – 2.61 (m, 1H), 1.96 (d, J = 8.1 Hz, 1H), 1.90 – 1.71 (m, 5H), 1.71 – 1.57 (m, 3H).

Example 176 N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-indazole-6-carboxamide

HPLC/MS tR = 1.73min (96%). LRMS (m/z): 447 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.33 (s, 3H), 2.50 (s, 3H), 2.79 (s, 3H), 4.18 (s, 3H), 7.44 (s, 2H), 7.49 – 7.69 (m, 2H), 8.21 (s, 1H), 8.62 (s, 1H), 9.20 (s, 1H), 10.27 (s, 1H), 12.47 (s, 1H).

Example 177: 4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

HPLC-MS tr = 2.32 min (99%). LRMS (m/z): 494 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, 1H), 10.00 (s, 1H), 8.81 (s, 1H), 8.69 (d, J = 4.6 Hz, 1H), 8.62 (s, 1H), 8.11 (dd, J = 3.1, 0.7 Hz, 1H), 7.76 (d, J = 9.1 Hz, 1H), 7.59 – 7.47 (m, 2H), 7.04 (d, J = 8.5 Hz, 1H), 6.95 (ddd, J = 9.2, 8.4, 0.8 Hz, 1H), 4.81 (q, J = 8.9 Hz, 2H), 3.85 (s, 3H), 2.73 (d, J = 4.5 Hz, 3H).

Example 178: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-(2-hydroxyethoxy)-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

UPLC-MS tr = 0.80 min (91%). LRMS (m/z): 427 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 9.14 (s, 1H), 8.55 (d, J = 13.8 Hz, 1H), 7.54 (s, 1H), 7.43 (d, J = 16.8 Hz, 1H), 4.16 (s, 1H), 4.00 (s, 1H), 2.93 (d, J = 8.1 Hz, 3H), 2.58 (d, J = 4.2 Hz, 3H), 2.39 (s, 3H), 1.89 (s, 1H), 1.28 (s, 2H).

Example 179: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-((2-hydroxyethoxy)methyl)-2-methoxybenzamido)-N-methylnicotinamide

HPLC-MS tr = 1.68 min (97%). LRMS (m/z): 481 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.42 (s, 1H), 10.35 (s, 1H), 9.25 (s, 1H), 8.71 (d, J = 4.7 Hz, 1H), 8.65 (s, 1H), 7.73 (dd, J = 7.7, 1.8 Hz, 1H), 7.65 (dd, J = 7.6, 1.8 Hz, 1H), 7.40 (s,

1H), 7.30 (t, J = 7.6 Hz, 1H), 4.67 (t, J = 5.2 Hz, 1H), 4.61 (s, 2H), 3.79 (s, 3H), 3.62 – 3.50 (m, 4H), 2.77 (d, J = 4.5 Hz, 3H), 2.33 (s, 3H).

Example 180: 6-(cyclobutanecarboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

HPLC-MS tr = 2.50 min (99%). LRMS (m/z): 401 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 1.75-1.85 (m, 1H), 1.88-1.98 (m, 1H), 2.05-2.14 (m, 2H), 2.16-2.26 (m, 2H), 2.72 (d, J = 4.5 Hz, 3H), 3.31-3.41 (m, 1H), 3.83 (s, 3H), 6.94 (t, J = 8.7 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.51 (td, J = 8.5 and 7 Hz, 1H), 8.67 (s, 1H), 8.78-8.84 (m, 1H), 9.36 (s, 1H), 10.49 (s, 1H), 12.33 (s, 1H).

Example 181: 4-(2-fluoro-6-methoxybenzamido)-6-(2-hydroxy-2-methylpropanamido)-N-methylnicotinamide

HPLC-MS tr: 2.28' (97%). LRMS (m/z): 405 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 1.36 (s, 9H), 2.72 (d, J = 4.5 Hz, 3H), 3.83 (s, 3H), 6.10 (s, 1H), 6.93 (t, J = 8.8 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.50 (q, J = 8.5, 1H), 8.68 (s, 1H), 8.81-8.89 (m, 1H), 9.36 (s, 1H), 9.52 (s, 1H), 12.34 (s, 1H).

Example 182: 4-(2-fluoro-6-methoxybenzamido)-6-(3-fluorocyclobutane-1-carboxamido)-N-methylnicotinamide

HPLC-MS tr: 2.43' (100%). LRMS (m/z): 419 (M+1)

Example 183: 4-(2-fluoro-6-methoxybenzamido)-6-((4-(1-hydroxyethyl)pyridin-2-yl)amino)-N-methylnicotinamide

HPLC/MS tr =1.92min (100%). LRMS (m/z): 440 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 1.33 (d, J = 6.5 Hz, 3H), 2.73 (d, J = 4.5 Hz, 3H), 3.85 (s, 3H), 4.50 – 4.80 (m, 1H), 5.37 (d, J = 4.1 Hz, 1H), 6.82 – 7.01 (m, 2H), 7.04 (d, J = 8.5 Hz, 1H), 7.44 – 7.64 (m, 1H), 7.71 (s, 1H), 8.10 – 8.24 (m, 1H), 8.65 (s, 1H), 8.69 – 8.79 (m, 1H), 8.96 (s, 1H), 10.00 (s, 1H), 12.41 (s, 1H).

Example 184 4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methyl-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidin-4-yl)amino)nicotinamide

UPLC/MS tr =1.20min (92%). LRMS (m/z): 504 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.43 (s, 1H), 10.03 (s, 1H), 9.41 (s, 1H), 8.70 (d, J = 4.7 Hz, 1H), 8.61 (s, 1H), 7.62 (dd, J = 7.7, 1.3 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.22 (t, J = 7.6 Hz, 1H), 6.51 (s, 1H), 4.70 (s, 4H), 4.27 (s, 3H), 3.80 (s, 3H), 2.77 (d, J = 4.4 Hz, 3H), 2.33 (s, 3H), 2.18 (s, 3H).

Example 185 4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methyl-2-(2-morpholinoethoxy)pyrimidin-4-yl)amino)nicotinamide

UPLC/MS tr =1.14min (97%). LRMS (m/z): 536 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 9.36 (s, 1H), 8.52 (s, 1H), 7.73 (dd, J = 7.8, 1.4 Hz, 1H), 7.44 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.86 (s, 1H), 4.71 (t, J = 5.6 Hz, 2H), 4.43 (t, J = 5.7 Hz, 1H), 3.82 (s, 3H), 3.73 – 3.62 (m, 2H), 3.62 – 3.56 (m, 3H), 2.89 (d, J = 19.4 Hz, 5H), 2.80 (t, J = 5.7 Hz, 1H), 2.63 (s, 5H), 2.38 (s, 3H), 2.33 (s, 3H).

Example 186 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

HPLC/MS tr =1.53min (92%). LRMS (m/z): 397 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.32 (s, 3H), 2.74 – 2.84 (m, 3H), 3.76 (s, 3H), 7.44 (s, 1H), 7.70 (s, 1H), 8.60 (s, 1H), 8.62 – 8.66 (m, 1H), 9.05 (s, 1H), 10.26 (s, 1H), 12.46 (s, 1H), 13.15 (s, 1H).

Example 187 4-(2-fluoro-6-methoxybenzamido)-6-(1-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

HPLC/MS tr = 2.55 min (98%). LRMS (m/z): 405 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 1.32-1.40 (m, 2H), 1.40-1.44 (m, 1H), 1.44-1.50 (m, 1H), 2.74 (d, J = 4.5 Hz, 3H), 3.83 (s, 3H), 6.93 (t, J = 8.8 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.51 (td, J = 8.5 and 7 Hz, 1H), 8.73 (s, 1H), 8.87-8.91 (m, 1H), 9.29 (s, 1H), 10.42 (s, 1H), 12.32 (s, 1H).

Example 188 N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-2-carboxamide

HPLC/MS tr = 2.20 min (99%). LRMS (m/z): 446 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 13.18 (s, 1H), 11.99 (s, 1H), 10.38 (s, 1H), 9.20 (s, 1H), 8.88 (d, J = 4.7 Hz, 1H), 8.75 (s, 1H), 7.37 (s, 1H), 7.23 – 7.14 (m, 2H), 7.08 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 7.6 Hz, 1H), 3.93 (s, 3H), 2.88 (d, J = 4.5 Hz, 3H), 2.53 (s, 3H), 2.33 (s, 3H).

Example 189: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-ethyl-2-methoxybenzamido)-N-methylnicotinamide

HPLC-MS: tr = 2.15 min. (99 %). LRMS (m/z): 435 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 1.21 (t, J = 7.5 Hz, 3H), 2.69 (q, J = 7.4 Hz, 2H), 2.76 (d, J = 4.5 Hz, 3H), 3.74 (s, 3H), 7.23 (t, J = 7.6 Hz, 1H), 7.37 (s, 1H), 7.46 – 7.50 (m, 1H), 7.56 – 7.62 (m, 1H), 8.63 (s, 1H), 8.70 (d, J = 5.1 Hz, 1H), 9.25 (s, 1H), 10.31 (s, 1H), 12.37 (s, 1H).

Example 190: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1-methyl-1H-pyrrolo[3,2-c]pyridine-3-carboxamide

HPLC-MS: tr = 1.38 min. (97 %). LRMS (m/z): 431 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.70 (s, 1H), 10.31 (s, 1H), 9.44 (s, 1H), 9.21 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.73 (s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 8.09 (s, 1H), 7.64 (d, J = 5.7 Hz, 1H), 7.42 (s, 1H), 3.95 (s, 3H), 2.86 (d, J = 4.4 Hz, 3H), 2.53 (s, 3H), 2.33 (s, 3H).

Example 191: 4-(2-methoxy-3-(trifluoromethyl)benzamido)-N-methyl-6-((6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)nicotinamide

uPLC-MS: tr = 1.23 min. (82 %). LRMS (m/z): 559 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 9.38 (s, 1H), 8.53 (s, 1H), 8.03 (dd, J = 7.8, 1.4 Hz, 1H), 7.85 (dd, J = 7.9, 1.3 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 6.34 (s, 1H), 4.58 (s, 1H), 3.96 (s, 3H), 3.89 (s, 4H), 2.89 (s, 3H), 2.57 (t, J = 4.9 Hz, 4H), 2.35 (s, 3H), 2.25 (s, 3H).

Example 192: 4-(3-chloro-2-methoxybenzamido)-N-methyl-6-((6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)nicotinamide

uPLC-MS: tr = 1.12 min. (99 %). LRMS (m/z): 525, 527 (M+1, Cl)

Example 193: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-fluoro-1-(2-hydroxyethyl)-3-methoxy-1H-indole-2-carboxamide

HPLC-MS: tr = 2.07 min. (99 %). LRMS (m/z): 508 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.30 (s, 3H), under dmso (s, 3H), 2.80 (d, J = 4.2 Hz, 3H), 3.69 (q, J = 5.4 Hz, 2H), 4.16 (s, 3H), 4.57 (t, J = 5 Hz, 2H), 4.74 (t, J = 5.4 Hz, 1H), 7.20 (td, J = 9 and 2 Hz, 1H), 7.33 (s, 1H), 7.61-7.66 (m, 2H), 8.55 (s, 1H), 8.60-8.65 (m, 1H), 9.27 (s, 1H), 10.24 (s, 1H), 12.14 (s, 1H).

Example 194: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2,2,2-trifluoroethyl)-1H-indole-2-carboxamide

HPLC-MS: tr = 2.30 min. (99 %). LRMS (m/z): 528 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.30 (s, 3H), under dmso (s, 3H), 2.81 (d, J = 4.5 Hz, 3H), 4.28 (s, 3H), 5.67 (q, J = 8 Hz, 2H), 7.19 (t, J = 8 Hz, 1H), 7.26 (s, 1H), 7.42 (t, J = 8 Hz, 1H), 7.72 (d, J= 8.7 Hz, 1H), 7.96 (d, J = 8 Hz, 1H), 8.55(s, 1H), 8.61-8.67 (m, 1H), 9.32 (s, 1H), 10.24 (s, 1H), 12.19 (s, 1H).

Example 195: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-((2-methoxyethoxy)methyl)benzamido)-N-methylnicotinamide

HPLC-MS: tr = 1.88 min. (99 %). LRMS (m/z): 495 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.33 (s, 3H), 2.49 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 3.27 (s, 3H), 3.49 – 3.57 (m, 2H), 3.62 – 3.72 (m, 2H), 3.78 (s, 3H), 4.60 (s, 2H), 7.30 (t, J = 7.7 Hz, 1H), 7.39 (s, 1H), 7.62 (d, J = 5.8 Hz, 1H), 7.73 (dd, J = 7.7, 1.8 Hz, 1H), 8.64 (s, 1H), 8.67 – 8.78 (m, 1H), 9.25 (s, 1H), 10.33 (s, 1H), 12.41 (s, 1H).

Example 196 N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1H-indole-2-carboxamide

HPLC-MS: tr = 2.10 min. (98 %). LRMS (m/z): 446 (M+1)

NMR 1H (DMSO, 400 MHz) δ 2.31 (s, 3H), under DMSO (3H), 2.82 (d, J = 4.4 Hz, 3H), 4.24 (s, 3H), 7.03 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.84 (d, J = 8 Hz, 1H), 8.55 (s, 1H), 8.60-8.63 (m, 1H), 9.11 (s, 1H), 10.28 (s, 1H), 11.3 (s, 1H), 12.06 (s, 1H).

Example 197: 4-(3-chloro-2-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

uPLC-MS: tr = 1.22 min. (94 %). LRMS (m/z): 526, 528 (M+1, Cl)

1H NMR (400 MHz, Methanol-d4) δ 9.35 (s, 1H), 8.50 (s, 1H), 7.87 (dd, J = 7.9, 1.6 Hz, 1H), 7.65 (dd, J = 8.0, 1.6 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 6.33 (s, 1H), 3.95 (s, 3H), 3.84 (tt, J = 8.7, 3.9 Hz, 1H), 3.30 – 3.22 (m, 4H), 2.91 (s, 3H), 2.26 (s, 3H), 2.03 – 1.89 (m, 2H), 1.58 – 1.44 (m, 2H).

Example 198: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-methoxyisonicotinamido)-N-methylnicotinamide

uPLC-MS: tr = 0.85 min. (99 %). LRMS (m/z): 408 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 10.36 (s, 1H), 9.23 (s, 1H), 8.81 – 8.54 (m, 2H), 8.41 (s, 1H), 7.82 (s, 1H), 7.41 (s, 1H), 4.14 (s, 3H), 2.82 (s, 3H), 2.33 (s, 3H).

Example 199: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1H-pyrrolo[3,2-c]pyridine-3-carboxamide

HPLC-MS: tr = 1.35 min. (98 %). LRMS (m/z): 417 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.84 (s, 1H), 12.43 (s, 1H), 10.36 (s, 1H), 9.46 (s, 1H), 9.21 (s, 1H), 8.86 (d, J = 4.8 Hz, 1H), 8.74 (s, 1H), 8.38 (s, 1H), 8.19 (s, 1H), 7.68 (s, 1H), 7.42 (s, 1H), 2.85 (d, J = 4.4 Hz, 3H), 2.54 (s, 3H), 2.34 (s, 3H).

Example 200: 4-(3,4-difluoro-2-methoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC-MS: tr = 2.05 min. (100 %). LRMS (m/z): 443 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, 1H), 10.34 (s, 1H), 9.21 (s, 1H), 8.72 (d, J = 4.7 Hz, 1H), 8.63 (s, 1H), 7.76 (ddd, J = 8.8, 6.2, 2.2 Hz, 1H), 7.33 (td, J = 9.3, 7.2 Hz, 1H), 4.13 (d, J = 2.9 Hz, 3H), 2.80 (d, J = 4.6 Hz, 3H), 2.33 (s, 3H).

Example 201: 4-(3-chloro-2-methoxybenzamido)-6-((2-(2-methoxyethoxy)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC-MS: tr = 2.37 min. (96 %). LRMS (m/z): 501 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.54 (s, 1H), 10.39 (s, 1H), 9.17 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 7.76 (ddd, J = 8.3, 6.7, 1.7 Hz, 2H), 7.34 (t, J = 7.9 Hz, 1H), 7.03 (s, 1H), 4.56 – 4.49 (m, 2H), 3.87 (s, 3H), 3.69 – 3.59 (m, 2H), 3.28 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.28 (s, 3H).

Example 202: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-fluoro-2-methoxybenzamido)-N-methylpyridazine-3-carboxamide

uPLC-MS: tr = 1.30 min. (92 %). LRMS (m/z): 426 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 9.89 (s, 1H), 8.54 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.42 (ddd, J = 11.9, 8.2, 1.6 Hz, 1H), 7.27 – 7.17 (m, 1H), 3.65 (s, 3H) , 2.99 (s, 3H), 2.63 (s, 3H), 2.43 (s, 3H)

Example 203: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-2-(methoxymethyl)-1H-benzo[d]imidazole-5-carboxamide

HPLC-MS: tr = 1.62 min. (99 %). LRMS (m/z): 491 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.31 (s, 3H), under DMSO (s, 3H), 2.80 (d, J = 4.5 Hz, 3H), 4.57 (s, 3H), 4.65 (s, 2H), 7.18 (t, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.80 (d, J = 8.6 Hz, 1H), 8.53 (s, 1H), 8.60-8.65 (m, 1H), 9.14 (s, 1H), 10.25 (s, 1H), 12.28 (s, 1H), 12.87 (s, 1H).

Example 204: 6-(cyclopropanecarboxamido)-4-(3-fluoro-2-methoxybenzamido)-N-methylnicotinamide

HPLC-MS: tr = 2.47 min. (99 %). LRMS (m/z): 387 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 0.80 – 0.87 (m, 4H), 1.98 – 2.07 (m, 1H), 2.79 (d, J = 4.5 Hz, 3H), 4.02 (d, 3H), 7.21 – 7.30 (m, 1H), 7.49 – 7.56 (m, 1H), 7.62 – 7.69 (m, 1H), 8.62 (s, 1H), 8.77 (d, J = 4.8 Hz, 1H), 9.38 (s, 1H), 10.95 (s, 1H), 12.34 (s, 1H).

Example 205: 4-(3-chloro-2-methoxybenzamido)-N-methyl-6-((6-methyl-2-((2-morpholino-2-oxoethyl)amino)pyrimidin-4-yl)amino)nicotinamide

uPLC-MS: tr = 1.22 min. (92 %). LRMS (m/z): 569, 571 (M+1, Cl)

1H NMR (400 MHz, Methanol-d4) δ 9.48 (s, 1H), 8.48 (s, 1H), 7.81 (dd, J = 7.8, 1.6 Hz, 1H), 7.65 (dd, J = 8.0, 1.6 Hz, 1H), 7.27 (t, J = 7.9 Hz, 2H), 6.35 (s, 1H), 4.45 (s, 4H), 3.99 (d, J = 9.6 Hz, 1H), 3.95 (s, 3H), 3.54 (dd, J = 16.7, 4.6 Hz, 4H), 3.45 (d, J = 4.4 Hz, 2H), 2.96 (s, 1H), 2.89 (s, 3H), 2.23 (s, 3H).

Example 206: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC-MS: tr = 2.00 min. (95 %). LRMS (m/z): 505 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.32 (s, 3H), 2.83 (d, J = 3.9 Hz, 3H), 3.19 (s, 3H), 3.61 – 3.66 (m, 2H), 4.30 (s, 3H), 4.83 – 4.91 (m, 2H), 7.20 (d, J = 7.3 Hz, 1H), 7.34 (s, 1H), 8.42 (d, J = 6.3 Hz, 1H), 8.47 (d, J = 3.1 Hz, 1H), 8.57 (s, 1H), 8.66 (d, J = 4.5 Hz, 1H), 9.31 (s, 1H), 10.27 (s, 1H), 12.21 (s, 1H).

Example 207: 4-(3-fluoro-2-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC-MS: tr = 1.98 min. (96 %). LRMS (m/z): 510 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, 1H), 9.92 (s, 1H), 9.23 (s, 1H), 8.69 (d, J = 4.7 Hz, 1H), 8.58 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.25 (td, J = 8.1, 4.8 Hz, 1H), 6.40 (s, 1H), 4.01 (s, 3H), 3.67 (m, 1H), 3.43 (m, 4H), 2.77 (d, J = 4.4 Hz, 3H), 2.16 (s, 3H), 1.75 (d, J = 12.2 Hz, 2H), 1.31 (d, J = 9.6 Hz, 2H).

Example 208: 4-(3-chloro-2-methoxybenzamido)-6-((2-fluoro-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

uPLC-MS: tr = 1.64 min. (100 %). LRMS (m/z): 445, 447 (M+1, Cl)

1H NMR (400 MHz, Methanol-d4) δ 8.85 (s, 1H), 8.60 (s, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.77 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 3.96 (s, 3H), 2.93 (s, 3H), 2.44 (s, 3H).

Example 209: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

HPLC-MS: tr = 1.88 min. (96 %). LRMS (m/z): 505 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.32 (s, 3H), 2.83 (d, J = 4.5 Hz, 3H), 3.15 (s, 3H), 3.64 (t, J = 6.2 Hz, 2H), 4.49 (s, 3H), 4.73 (t, J = 5.4 Hz, 2H), 7.32 – 7.36 (m, 2H), 8.05 (dd, J = 8.7, 1.2 Hz, 1H), 8.46 (d, J = 4.2 Hz, 1H), 8.57 (s, 1H), 8.64 – 8.68 (m, 1H), 9.31 (s, 1H), 10.27 (s, 1H), 12.23 (s, 1H).

Example 210: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-indole-6-carboxamide

HPLC-MS: tr = 1.88 min. (100 %). LRMS (m/z): 446 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.36 (s, 1H), 11.70 (s, 1H), 10.28 (s, 1H), 9.20 (s, 1H), 8.66 (q, J = 4.7 Hz, 1H), 8.58 (s, 1H), 7.57 – 7.53 (m, 2H), 7.46 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 6.55 (dd, J = 2.9, 1.8 Hz, 1H), 4.03 (s, 3H), 2.80 (d, J = 4.5 Hz, 3H), 2.33 (s, 3H)

Example 211: N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC-MS: tr = 2.40 min. (94 %). LRMS (m/z): 467 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 0.85 (dd, J = 10.9, 6.0 Hz, 4H), 1.99 – 2.05 (m, 1H), 2.82 (d, J = 4.5 Hz, 3H), 3.16 (s, 3H), 3.59 (t, J = 5.9 Hz, 2H), 4.29 (s, 3H), 4.85 (t, J = 5.8 Hz, 2H), 7.19 (dd, J = 8.1, 4.6 Hz, 1H), 8.37 – 8.43 (m, 1H), 8.45 – 8.49 (m, 1H), 8.57 (s, 1H), 8.72 (d, J = 6.4 Hz, 1H), 9.38 (s, 1H), 10.91 (s, 1H), 12.13 (s, 1H).

Example 212: 4-(2-fluoro-6-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

HPLC-MS: tr = 1.08 min. (100%). LRMS (m/z): 510 (M+1)

Example 213: 4-(2,3-dimethoxybenzamido)-6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

uPLC-MS: tr = 1.31 min. (100%). LRMS (m/z): 417 (M+1)

1H NMR (400 MHz, Methanol-d4) δ 9.32 (s, 1H), 8.40 (s, 1H), 7.42 (dd, J = 7.8, 1.7 Hz, 1H), 7.16 (dd, J = 8.2, 1.7 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 4.48 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 2.82 (s, 3H), 2.07 – 1.95 (m, 1H), 1.71 (dtd, J = 23.0, 7.1, 3.7 Hz, 2H), 1.10 (ddt, J = 12.8, 9.1, 6.5 Hz, 1H).

Example 214: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-benzo[d][1,2,3]triazole-6-carboxamide

Example 215: N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-indole-2-carboxamide

HPLC-MS: tr = 2.70 min. (98%). LRMS (m/z): 422 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 0.80-0.90 (m, 4H), 1.98-2.08 (m, 1H), 2.82 (d, J = 4.2 Hz, 3H), 3.98 (s, 3H), 4.22 (s, 3H), 7.12 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.58 (d, J= 8.5 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 8.55 (s, 1H), 8.67-8.72 (m, 1H), 9.41 (s, 1H), 10.89 (s, 1H), 12.04 (s, 1H).

Example 216: 4-(2,3-dimethoxybenzamido)-N-methyl-6-((2-methylpyrimidin-4-yl)amino)nicotinamide

uPLC-MS: tr = 1.07 min. (92%). LRMS (m/z): 423 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.32 (s, 1H), 10.42 (s, 1H), 9.23 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.61 (s, 1H), 8.47 – 8.30 (m, 2H), 7.53 (d, J = 5.9 Hz, 1H), 7.36 (dd, J = 7.7, 1.6 Hz, 1H), 7.32 – 7.19 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.54 (s, 3H).

Example 217: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-3H-imidazo[4,5-b]pyridine-6-carboxamide

uPLC-MS: tr = 0.91 min. (98%). LRMS (m/z): 448 (M+1)

Example 218: N-(2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC-MS: tr = 2.38 min. (95%). LRMS (m/z): 426 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 0.81 – 0.88 (m, 4H), 1.98 – 2.06 (m, 1H), 4.04 (s, 3H), 4.29 (s, 3H), 7.18 (dd, J = 8.2, 4.5 Hz, 1H), 8.42 (dd, J = 8.1, 1.5 Hz, 1H), 8.48 (dd, J = 4.5, 1.5 Hz, 1H), 8.57 (s, 1H), 8.67 – 8.71 (m, 1H), 9.42 (s, 1H), 10.92 (s, 1H), 12.14 (s, 1H).

Example 219: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3,4-dimethoxypicolinamide

uPLC-MS: tr = 0.88 min. (93%). LRMS (m/z): 441 (M+1)

Example 220: N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3,4-dimethoxypicolinamide

uPLC-MS: tr = 1.04 min. (89%). LRMS (m/z): 421 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 11.00 (s, 1H), 9.44 (s, 1H), 8.73 (s, 1H), 8.68 (s, 1H), 8.36 (d, J = 5.4 Hz, 1H), 7.36 (d, J = 5.5 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 2.30 – 2.19 (m, 1H), 1.68 (dtd, J = 23.3, 6.8, 3.8 Hz, 1H), 1.30 – 1.13 (m, 2H).

Example 221: 6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-4-(2-methoxynicotinamido)-N-methylnicotinamide

uPLC-MS: tr = 1.27 min. (90%). LRMS (m/z): 388 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.54 (s, 1H), 10.98 (s, 1H), 9.45 (s, 1H), 8.76 (d, J = 4.5 Hz, 1H), 8.61 (s, 1H), 8.42 (dd, J = 4.9, 2.0 Hz, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 7.6, 4.9 Hz, 1H), 4.94 (ddd, J = 66.1, 10.2, 6.4 Hz, 1H), 4.12 (s, 3H), 2.83 (d, J = 4.5 Hz, 3H), 1.67 (ddd, J = 23.7, 10.5, 6.8 Hz, 1H), 1.27 – 1.13 (m, 2H).

Example 222: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(2-methoxyethoxy)benzamido)-N-(methyl-d3)nicotinamide

uPLC-MS: tr = 1.08 min. (96%). LRMS (m/z): 484 (M+1)

Example 223: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3-fluoro-7-methoxy-1H-indole-6-carboxamide

HPLC-MS: tr = 2.00 min. (91%). LRMS (m/z): 467 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.33 (s, 3H), under DMSO (s, 3H), 4.02 (s, 3H), 7.40 (d, J = 8.4 Hz, 1H), 7.43 (br s, 1H), 7.54-7.57 (m, 2H), 8.59 (s, 1H), 8.65 (s, 1H), 9.22 (s, 1H), 10.30 (s, 1H), 11.51 (s, 1H), 12.40 (s, 1H)

Example 224:N-(2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

HPLC-MS: tr = 2.10 min. (99%). LRMS (m/z): 411 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 0.80-0.87 (m, 4H), 1.99-2.06 (m, 1H), 4.26 (s, 3H), 6.83 (ddd, J = 3, 2 and 1 Hz, 1H), 7.19 (dd, J = 8.6 and 1 Hz, 1H), 7.40-7.43 (m, 1H), 7.47 (s, 1H), 7.70 (d, J = 8.6 Hz, 1H), 8.53 (s, 1H), 8.66 (s, 1H), 9.42 (s, 1H), 10.86 (s, 1H), 11.52 (s, 1H), 12.25 (s, 1H).

Example 225: 4-(2,3-dimethoxybenzamido)-N-methyl-6-((6-methylpyrimidin-4-yl)amino)nicotinamide

uPLC-MS: tr = 1.11 min. (100%). LRMS (m/z): 423 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.32 (s, 1H), 10.38 (s, 1H), 8.96 (s, 1H), 8.71 (d, J = 4.5 Hz, 1H), 8.67 – 8.59 (m, 2H), 7.71 (s, 1H), 7.38 (dd, J = 7.7, 1.6 Hz, 1H), 7.30 (dd, J = 8.2, 1.6 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.38 (s, 3H).

Example 226 6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-4-(2-methoxy-3-(methyl-d3)benzamido)-N-methylnicotinamide

uPLC- MS: tr = 1.41 min. (97%). LRMS (m/z): 404 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.36 (s, 1H), 11.00 (s, 1H), 9.42 (s, 1H), 8.77 (d, J = 4.6 Hz, 1H), 8.64 (s, 1H), 7.62 (dd, J = 7.7, 1.8 Hz, 1H), 7.46 (dd, J = 7.5, 1.8 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 5.03 (td, J = 6.2, 3.8 Hz, 1H), 4.86 (td, J = 6.1, 3.7 Hz, 1H), 3.74 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.29 – 2.18 (m, 1H), 1.67 (dtd, J = 23.3, 6.8, 3.7 Hz, 1H), 1.19 (ddt, J = 12.5, 9.0, 6.3 Hz, 1H).

Example 227 N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC- MS: tr = 2.38 min. (97%). LRMS (m/z): 423 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 0.81 – 0.88 (m, 4H), 1.99 – 2.06 (m, 1H), 2.82 (d, J = 4.5 Hz, 3H), 4.03 (s, 3H), 4.28 (s, 3H), 7.18 (dd, J = 8.1, 4.6 Hz, 1H), 8.41 (dd, J = 8.1, 1.5 Hz, 1H), 8.47 (dd, J = 4.5, 1.5 Hz, 1H), 8.56 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 9.41 (s, 1H), 10.90 (s, 1H), 12.12 (s, 1H).

Example 228 N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC- MS: tr = 1.15 min. (94%). LRMS (m/z): 461 (M+1)

Example 229 N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

HPLC-MS: tr = 1.40 min. (99 %). LRMS (m/z): 447 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 2.33 (s, 3H), 2.84 (d, J = 4.5 Hz, 3H), 4.29 (s, 3H), 7.45 (s, 1H), 7.87 (s, 1H), 8.13 (s, 1H), 8.60 (d, J = 3.6 Hz, 1H), 8.69 (s, 1H), 8.81 (d, J = 1.7 Hz, 1H), 9.18 (s, 1H), 10.37 (s, 1H), 11.89 (s, 1H), 12.27 (s, 1H).

Example 230 4-(3-cyano-2-methoxybenzamido)-6-(cyclopropanecarboxamido)-N-methylnicotinamide

uPLC-MS: tr = 1.34 min. (93 %). LRMS (m/z):394 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.50 (s, 1H), 10.99 (s, 1H), 9.39 (s, 1H), 8.88 – 8.75 (m, 1H), 8.67 (s, 1H), 8.12 (dd, J = 7.8, 1.7 Hz, 1H), 8.05 (dd, J = 7.7, 1.7 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 4.06 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 2.03 (ddd, J = 12.4, 7.3, 5.0 Hz, 1H), 0.85 (t, J = 5.9 Hz, 2H), 0.67 – 0.57 (m, 2H).

Example 231 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-(2-hydroxyethoxy)-2-methoxybenzamido)-N-(methyl-d3)nicotinamide

uPLC-MS: tr = 1.29min. (93 %). LRMS (m/z):470 (M+1)

Example 232 N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC-MS: tr = 2.37 min. (99 %). LRMS (m/z): 441 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 1.14 – 1.26 (m, 1H), 1.61 – 1.75 (m, 1H), 2.18 – 2.28 (m, 1H), 2.83 (d, J = 4.5 Hz, 3H), 4.05 (s, 3H), 4.29 (s, 3H), 4.83 – 5.07 (m, 1H), 7.18 (dd, J = 8.1, 4.5 Hz, 1H), 8.39 – 8.45 (m, 1H), 8.46 – 8.50 (m, 1H), 8.58 (s, 1H), 8.71 – 8.76 (m, 1H), 9.43 (s, 1H), 10.96 (s, 1H), 12.15 (s, 1H).

Example 233 4-(2,3-dimethoxybenzamido)-N-methyl-6-((1-methyl-1H-pyrazol-3-yl)amino)nicotinamide

uPLC-MS: tr = 1.12 min. (100 %). LRMS (m/z): 412 (M+1)

Example 234 N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

HPLC-MS: tr = 2.10 min. (98 %). LRMS (m/z): 408 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 0.80-0.87 (m, 4H), 1.98-2.07 (m, 1H), 2.82 (d, J = 4.5 Hz, 3H), 4.26 (s, 3H), 6.83 (br s, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.41 (t, J = 2.7 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 8.52 (s, 1H), 8.65-8.71 (m, 1H), 9.41 (s, 1H), 10.85 (s, 1H), 11.52 (s, 1H), 12.24 (s, 1H).

Example 235 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1-methyl-1H-pyrazole-5-carboxamido)-N-(methyl-d3)nicotinamide

Example 236 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1-methyl-1H-pyrazole-3-carboxamido)-N-(methyl-d3)nicotinamide

Example 237 4-(2,3-dimethoxybenzamido)-6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-N-methylpyridazine-3-carboxamide

uPLC-MS: tr = 1.45 min. (96 %). LRMS (m/z): 448 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.86 (s, 1H), 11.61 (s, 1H), 9.73 (s, 1H), 9.31 (d, J = 4.8 Hz, 1H), 7.41 (dd, J = 7.8, 1.6 Hz, 1H), 7.33 (dd, J = 8.2, 1.5 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 5.00 (ddd, J = 66.2, 10.1, 6.3 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 2.85 (d, J = 4.8 Hz, 3H), 1.79 – 1.64 (m, 1H), 1.32 – 1.18 (m, 1H).

Example 238 N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-fluoro-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC-MS: tr = 2.22 min. (99 %). LRMS (m/z): 479 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.32 (s, 3H), under dmso (s, 3H), 2.82 (d, J = 3.3 Hz, 3H), 4.06 (s, 3H), 4.26 (s, 3H), 7.39 (s, 1H), 8.36 (d, J = 10.3 Hz, 1H), 8.50 (s, 1H), 8.58 (s, 1H), 8.66 (br s, 1H), 9.26 (s, 1H), 10.28 (s, 1H), 12.23 (s, 1H).

Example 239 4-(2-methoxy-3-(methyl-d3)benzamido)-6-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-N-methylnicotinamide

uPLC-MS: tr = 1.30 min. (100 %). LRMS (m/z): 442 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 9.36 (s, 1H), 8.52 (d, J = 3.9 Hz, 2H), 8.05 (s, 1H), 7.93 (s, 1H), 7.56 (dd, J = 7.7, 1.8 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.43 (dd, J = 7.5, 1.8 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 4.22 (t, J = 5.3 Hz, 2H), 3.74 (s, 3H), 3.67 (t, J = 5.3 Hz, 2H), 3.24 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H).

Example 240 N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

HPLC-MS: tr = 2.23 min. (99 %). LRMS (m/z): 426 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 1.23-1.32 (m, 1H), 1.47-1.60 (m, 1H), under DMSO (1H), 2.82 (d, J = 4.5 Hz, 3H), 4.26 (s, 3H), 4.81–5.02 (m, 1H), 6.82-6.84 (m, 1H), 7.19 (dd, J = 8.7

and 1 Hz, 1H), 7.40-7.43 (m, 1H), 7.70 (d, J = 8.7 Hz, 1H), 8.54 (s, 1H), 8.69 – 8.72 (m, 1H), 9.40 (s, 1H), 11.02 (s, 1H), 11.53 (s, 1H), 12.25 (s, 1H).

Example 241 4-(2,3-dimethoxybenzamido)-N-methyl-6-((1-methyl-1H-1,2,4-triazol-3-yl)amino)nicotinamide

HPLC-MS: tr = 1.95 min. (97 %). LRMS (m/z): 412 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.33 (s, 1H), 9.80 (s, 1H), 9.01 (d, J = 1.0 Hz, 1H), 8.57 (d, J = 4.9 Hz, 1H), 8.48 (s, 1H), 8.28 (q, J = 1.2 Hz, 1H), 7.27 (m, 2H), 7.18 (m, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 2.74 (d, J = 4.5, 3H).

Example 242 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)benzamido)-N-methylnicotinamide

HPLC-MS: tr = 1.78 min. (95 %). LRMS (m/z): 488 (M+1)

Example 243: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(methylsulfinyl)benzamido)-N-(methyl-d3)nicotinamide

uPLC-MS: tr = 0.83 min. (92 %). LRMS (m/z): 472 (M+1)

Example 244: 6-(2,2-difluorocyclopropane-1-carboxamido)-4-(2,3-dimethoxybenzamido)-N-methylnicotinamide

uPLC-MS: tr = 1.44 min. (100 %). LRMS (m/z): 435 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.30 (s, 1H), 11.15 (s, 1H), 9.39 (s, 1H), 8.77 (d, J = 4.5 Hz, 1H), 8.63 (s, 1H), 7.40 – 7.17 (m, 3H), 3.87 (d, J = 7.7 Hz, 6H), 3.07 – 2.95 (m, 1H), 2.78 (d, J = 4.5 Hz, 3H), 2.11 – 1.96 (m, 2H).

Example 245: 6-((6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl)amino)-4-(2,3-dimethoxybenzamido)-N-methylnicotinamide

uPLC-MS: tr = 1.16 min. (100 %). LRMS (m/z): 453 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 9.65 (s, 1H), 8.57 – 8.50 (m, 1H), 8.47 (s, 1H), 8.39 (s, 1H), 7.33 – 7.16 (m, 3H), 6.26 (s, 1H), 4.76 (s, 2H), 4.10 – 4.03 (m, 2H), 4.02 – 3.96 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H).

Example 246: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine-6-carboxamide

uPLC-MS: tr = 1.82min. (98%). LRMS (m/z): 447 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.33 (s, 3H), under dmso (s, 3H), 2.8 (s, 3H), 4.13 (s, 3H), 6.50 (s, 3H), 7.44 (s, 1H), 7.78 (s, 1H), 8.48 (s, 1H), 8.55 (s, 1H), 8.58 (s, 1H), 8.65 (br s, 1H), 9.25 (s, 1H), 10.28 (s, 1H), 11.52 (s, 1H), 12.52 (s, 1H).

Example 247: 6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-4-(2-methoxy-3-(methyl-d3)benzamido)-N-methylnicotinamide

uPLC-MS: tr = 1.17min. (100%). LRMS (m/z): 420 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 9.36 (s, 1H), 8.53 (s, 1H), 8.05 (s, 1H), 7.95 (s, 1H), 7.56 (dd, J = 7.7, 1.8 Hz, 1H), 7.48 (d, J = 0.6 Hz, 1H), 7.43 (dd, J = 7.5, 1.8 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 5.76 (s, 0H), 4.88 (t, J = 5.3 Hz, 1H), 4.11 (t, J = 5.6 Hz, 2H), 3.74 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H).

Example 248: 3-methoxy-N-(2-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

uPLC-MS: tr = 1.25min. (99%). LRMS (m/z): 479 (M+1)

Example 249: 4-(2,3-dimethoxybenzamido)-6-((1,5-dimethyl-1H-pyrazol-3-yl)amino)-N-methylnicotinamide

uPLC-MS: tr = 1.19 min. (100%). LRMS (m/z): 425 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.33 (s, 1H), 9.48 (s, 1H), 8.55 – 8.48 (m, 1H), 8.46 (s, 1H), 8.37 (s, 1H), 7.32 – 7.25 (m, 2H), 7.23 – 7.17 (m, 1H), 6.20 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.63 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H), 2.23 (s, 3H).

Example 250: 4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)nicotinamide

uPLC-MS: tr = 1.36 min. (100%). LRMS (m/z): 465 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 9.36 (s, 1H), 8.56 – 8.48 (m, 2H), 8.06 (s, 1H), 7.97 (s, 1H), 7.56 (dd, J = 7.7, 1.4 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.22 – 7.12 (m, 1H), 4.44 – 4.30 (m, 1H), 4.01 – 3.92 (m, 2H), 3.74 (s, 3H), 3.51 – 3.42 (m, 2H), 2.74 (d, J = 4.5 Hz, 3H), 2.31 (s, 3H), 2.02 – 1.86 (m, 4H).

Example 251: 4-(2,3-dimethoxybenzamido)-6-((5-fluoropyridin-2-yl)amino)-N-methylnicotinamide

uPLC-MS: tr = 1.21 min. (80%). LRMS (m/z): 426 (M+1)

Example 252: 4-(2-methoxy-3-methylbenzamido)-6-((1-(2-methoxyethyl)-1H-imidazol-4-yl)amino)-N-methylnicotinamide

HPLC-MS: tr = 2.03 min. (99%). LRMS (m/z): 439 (M+1)

NMR 1H (DMSO, 400 MHz) δ ppm 2.31 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H), 3.26 (s, 3H), 3.60 (t, J = 5 Hz, 2H), 3.73 (s, 3H), 4.10 (t, J = 5 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.30 (br s, 1H), 7.40-7.44 (m, 2H), 7.56 (dd, J = 7.6 and 1.6 Hz, 1H), 8.17 (s, 1H), 8.51 (s, 1H), 9.57 (s, 1H), 12.36 (s, 1H).

Example 253: 4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methylpyrimidin-4-yl)amino)nicotinamide

uPLC-MS: tr = 1.22 min. (97%). LRMS (m/z): 407 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 10.39 (s, 1H), 8.99 (s, 1H), 8.72 (q, J = 4.0 Hz, 1H), 8.65 (s, 1H), 8.64 (d, J = 1.0 Hz, 1H), 7.71 (s, 1H), 7.64 (dd, J = 7.8, 1.3 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.20 (t, J = 7.6 Hz, 1H), 3.75 (s, 3H), 3.17 (d, J = 5.3 Hz, 3H), 2.38 (s, 3H), 2.33 (s, 3H). Senyals no assignables a 4.10 (q, 1H) i a 2.79 (d, 3H).

Example 254: 4-(2,3-dimethoxybenzamido)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

uPLC-MS: tr = 1.31 min. (100%). LRMS (m/z): 417 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.39 (s, 1H), 8.78 – 8.72 (m, 1H), 8.61 (s, 1H), 7.36 (dd, J = 7.7, 1.7 Hz, 1H), 7.29 (dd, J = 8.2, 1.7 Hz, 1H), 7.24 – 7.19 (m, 1H), 5.06 – 4.83 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H), 2.28 – 2.19 (m, 1H), 1.73 – 1.60 (m, 1H), 1.22 – 1.14 (m, 1H).

Example 255: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1,3-dimethyl-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

HPLC-MS: tr = 1.78 min. (97%). LRMS (m/z): 425 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 11.90 (s, 1H), 10.26 (s, 1H), 9.18 (s, 1H), 8.63 (d, J = 4.8 Hz, 1H), 8.56 (s, 1H), 7.37 (s, 1H), 3.97 (d, J = 1.4 Hz, 3H), 3.89 (d, J = 1.5 Hz, 3H), 3.27 (d, J = 1.4 Hz, 1H), 2.78 (d, J = 4.4 Hz, 3H), 2.30 (s, 3H), 2.23 (s, 3H).

Example 256: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-3-(methyl-d3)-1H-indole-5-carboxamide

HPLC-MS: tr = 1.93 min. (88%). LRMS (m/z): 463 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 12.25 (s, 1H), 11.17 (s, 1H), 10.26 (s, 1H), 9.16 (s, 1H), 8.63 (d, J = 4.9 Hz, 1H), 8.56 (s, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.44 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 3.84 (s, 3H), 2.77 (d, J = 4.5 Hz, 3H), 2.31 (s, 3H).

Example 257: N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(1-methoxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC-MS: tr = 2.20 min. (99 %). LRMS (m/z): 519 (M+1)

1H NMR (400 MHz, DMSO-d6) δ 1.61 (d, J = 7.0 Hz, 3H), 2.33 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 3.15 (s, 3H), 3.80 (dd, J = 9.9, 6.1 Hz, 1H), 4.17 (dd, J = 9.8, 8.2 Hz, 1H), 4.24 (s, 3H), 5.69 – 5.78 (m, 1H), 7.18 (dd, J = 8.1, 4.6 Hz, 1H), 7.37 (s, 1H), 8.36 – 8.46 (m, 2H), 8.59 (s, 1H), 8.66 – 8.71 (m, 1H), 9.28 (s, 1H), 10.28 (s, 1H), 12.26 (s, 1H).

Example 258: N-(2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

HPLC-MS: tr = 1.88 min. (90 %). LRMS (m/z): 465 (M+1)

Example 259: 6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methyl-4-(2-(N-methylmethylsulfonamido)benzamido)nicotinamide

uPLC-MS: tr = 0.92 min. (97 %). LRMS (m/z): 484 (M+1)

Example 260: 6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxycyclohexane-1-carboxamido)-N-methylnicotinamide

uPLC-MS: tr = 1.11 min. (20 %). LRMS (m/z): 413 (M+1); tr = 1.13 min. (80 %). LRMS (m/z): 413 (M+1). Diastereomeric mixture

1H NMR (400 MHz, DMSO-d6) δ 11.91 (s, 1H), 10.25 (s, 1H), 9.05 (s, 1H), 8.71 (dd, J = 9.1, 4.9 Hz, 1H), 8.63 (s, 1H), 7.40 (s, 1H), 3.85 (s, 1H), 3.22 (s, 1H), 3.20 (s, 3H), 2.80 (d, J = 4.5 Hz, 4H), 2.60 – 2.52 (m, 1H), 2.47 (s, 4H), 2.32 (s, 4H), 2.24 – 2.13 (m, 1H), 2.04 (d, J = 10.6 Hz, 1H), 1.75 (s, 3H), 1.48 – 1.19 (m, 5H). Diastereomeric mixture

PHARMACOLOGICAL ACTIVITY

TYK2 JH2 domain binding assay

TYK2 (JH2domain-pseudokinase) KINOMEscan assay. For the assay, TYK2 (JH2domain-pseudokinase)-tagged T7 phage strains were prepared in an E. coli host derived from the BL21 strain.E. coli were grown to log-phase and infected with T7 phage and incubated with shaking at 32°C until lysis. The lysates were centrifuged and filtered to remove cell debris. The remaining TYK2 (JH2domain-pseudokinase) were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining TYK2 (JH2domain-pseudokinase), liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock, 0.17x PBS, 0.05% Tween 20, 6 mM DTT). Test compounds were prepared as 111X stocks in 100% DMSO. Kds were determined using an 11-point 3-fold compound dilution series with three DMSO control points. All compounds for Kd measurements are distributed by acoustic transfer (non-contact dispensing) in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.9%. All reactions performed in polypropylene 384-well plate. Each was a final volume of 0.02 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 μM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR. Confidential SDZ179-01-s-00001 11/1/2019 2 of 6

Compound Handling

An 11-point 3-fold serial dilution of each test compound was prepared in 100% DMSO at 100x final test concentration and subsequently diluted to 1x in the assay (final DMSO concentration = 1%). Most Kds were determined using a compound top concentration = 30,000 nM. If the initial Kd determined was < 0.5 nM (the lowest concentration tested), the measurement was

repeated with a serial dilution starting at a lower top concentration. A Kd value reported as 40,000 nM indicates that the Kd was determined to be >30,000 nM.

Binding Constants (Kds)

Binding constants (Kds) were calculated with a standard dose-response curve using the Hill equation: Response = Background + Signal – Background

1 + (KdHill Slope / DoseHill Slope)

The Hill Slope was set to -1.

Curves were fitted using a non-linear least square fit with the Levenberg-Marquardt algorithm.

Affinities for TykZ JHZ Domain Binding Assay are presented in Table 1. Compounds denoted as "A" had a Kd lower than 200 pM; compounds denoted as "B" had a Kd between 200 pM and 1 nM; compounds denoted as "C" had a Kd between 1 nM and 10 nM, and compounds denoted as "D" had a Kd greater than 10 nM.

TABLE 1: Kd Affinities for TykZ JH2 Domain Binding Assay

Compound Example	TYK2 JH2 Kd
1	C
2	C
3	D
4	D
5	D
6	C
7	D
8	D
9	D
10	D
11	D
12	C
13	B
14	B
15	C
16	B

17	B
18	D
19	C
20	C
21	C
22	D
23	C
24	B
25	D
26	B
27	B
28	A
29	D
30	A
31	D
32	A
33	B
34	D
35	C
36	D
37	D
38	B
39	D
40	C
41	D
42	D
43	C
44	C
45	B
46	D
47	D
48	B

49	A
50	B
51	D
52	D
53	C
54	A
55	B
56	A
57	B
58	C
59	D
60	D
61	B
62	B
63	D
64	C
65	D
66	C
67	B
68	A
69	D
70	C
71	C
72	B
73	A
74	A
75	A
76	D
77	B
78	A
79	C
80	D

81	B
82	A
83	D
84	B
85	B
86	D
87	A
88	A
89	C
90	D
91	C
92	A
93	A
84	A
95	B
96	A
97	A
98	B
99	A
100	C
101	B
102	B
103	B
104	C
105	A
106	A
107	C
108	A
109	A
110	A
111	D
112	D

113	A
114	A
115	C
116	B
117	A
118	D
119	B
120	A
121	D
122	A
123	A
124	A
125	A
126	A
127	A
128	A
129	A
130	A
131	A
132	A
133	A
134	A
135	C
136	A
137	A
138	A
139	C
140	C
141	A
142	A
143	A
144	B

145	A
146	A
147	A
148	D
149	A
150	C
151	A
152	B
153	A
154	B
155	A

IFNa induced STAT phosphorylation in HEK293 cells

Stimulation of HEK293T-sie-bla cells with interferon alpha (INFa) activates the signaling pathway of STAT1/3 through TYK2/JAK1. In this assay, measurement of the activity of the reporter gene β-lactamase expression was used as the readout.

CellSensorTM SIE-bla HEK293T cell line were purchased from Thermo Fisher Scientific (ref. #K1649B) and cultured as specified by the provider. A number of 30.000 cells per well (40 µl) were plated in a 384-well plate (Corning ref.# 3712) and cultured overnight at 37ºC with 5% CO2 in a complete Optimem media (ThermoFisher ref. #11058-021) containing 0.5% (v/v) heat inactivated dialyzed FBS (Life Technologies ref. #26400044), 10 µM non-essential aminoacids NEAA (Sigma ref. #M7145), 100 µM Sodium Pyruvate (Gibco ref. #11360-039) and 100 U/mL Penicillin (Sigma ref. #P0781). Compounds were initially dissolved in 100% DMSO. Compound curves were then prepared using a 1/5 serial dilution (10 dilutions). The dilutions were directly diluted in complete Optimem media at 40-fold their final concentration in 20% DMSO. IFNa initial solution (R&D systems ref. #11100-1) was prepared at 10-fold its EC80 in complete Optimem media. Compounds and IFNa were added simultaneously to the wells with cells and incubated during 4 hours at 37ºC (the final DMSO was 0.1%). The □-lactamase substrate (LifeTechnologies ref.#K1138) was prepared at 6-fold its final concentration as specified by the provider. Then 10 µL of the mixture was added to the wells to stop the stimulation. Plate was left in the dark over-night. Then a FRET reading was performed on an appropriate plate reader.

All experiments were analysed using an ExcelFit template and the four-parameter log equation. Inhibitions of IFNa induced STAT phosphorylation in HEK293 cells are presented in Table 2. Compounds denoted as 'A" had a IC50 lower than 10 nM; compounds denoted as "B" had a IC50 between 10 nM and 100 nM; compounds denoted as 'C" had a IC50 between 100 nM and 1 uM, and compounds denoted as "D" had a IC50 greater than 1 uM.

TABLE 2: IC50 Inhibitions of IFNa induced STAT phosphorylation in HEK293 cells

Compound Example	Inhibition of IFNa induced STAT phosphorylation HEK293 cells IC50
1	D
2	C
3	D
4	C
5	D
6	C
7	D
8	D
9	D
10	D
11	D
12	D
13	C
14	C
15	C
16	C
17	C
18	D
19	D
20	D
21	D

22	D
23	C
24	C
25	D
26	B
27	C
28	B
29	D
30	B
31	D
32	B
33	B
34	D
35	C
36	D
37	D
38	D
39	D
40	C
41	D
42	D
43	D
44	D
45	D
46	D
47	D
48	B
49	A
50	B
51	D
52	D
53	D

54	A
55	B
56	A
57	C
58	D
59	D
60	D
61	C
62	C
63	D
64	D
65	D
66	D
67	C
68	C
69	D
70	D
71	D
72	D
73	A
74	C
75	B
76	D
77	C
78	A
79	D
80	D
81	D
82	B
83	D
84	B
85	C

86	D
87	A
88	A
89	D
90	D
91	D
92	A
93	B
94	A
95	D
96	B
97	B
98	D
99	B
100	D
101	D
102	B
103	B
104	D
105	A
106	A
107	D
108	A
109	A
110	B
111	D
112	D
113	C
114	B
115	D
116	C
117	A

118	D
119	B
120	B
121	D
122	A
123	A
124	A
125	A
126	A
127	A
128	A
129	A
130	A
131	A
132	A
133	A
134	B
135	B
136	A
137	A
138	A
139	D
140	D
141	A
142	A
143	A
144	B
145	A
146	A
147	A
148	D
149	A

150	C
151	A
152	B
153	A
154	C
155	A

IL4 induced STAT phosphorylation in Ramos cells

Stimulation of RAMOS cells with interleukine IL-4 activates the signaling pathway of STAT6 through JAK1/JAK3. In this assay, measurement of the activity of the reporter gene β-lactamase expression was used as the readout.

Ramos STAT6-bla RA-1 cell line were purchased from Life Technologies (ref. #K1243) and cultured as specified by the provider. A number of 30.000 cells per well (35 µl) were plated in a 384-well plate (Corning ref.# 3712) and cultured overnight at 37ºC with 5% CO2 in a complete Optimem media (Life Technologies ref. #11058-021) containing 556 µg/mL CD40 (Life Technologies ref. #PHP0025), 0.5% (v/v) heat inactivated FBS (Life Technologies ref. #10082-147), 10 µM non-essential aminoacids NEAA (Sigma ref. #M7145), 100 µM Sodium Pyruvate (Gibco ref. #11360-039) and 100 U/mL Penicillin (Sigma ref. #P0781). Compounds were initially dissolved in 100% DMSO. Compound curves were then prepared using a 1/5 serial dilution (10 dilutions). The dilutions were directly diluted in complete Optimem media without CD40 at 40-fold their final concentration in 20% DMSO. IL-4 initial solution (Prepotech ref. #200-04) was prepared at 10-fold its EC80 in complete Optimem media without CD40. Compounds and IL-4 were added simultaneously to the wells with cells and incubated during 4 hours at 37ºC (the final DMSO was 0.1%). The □-lactamase substrate (LifeTechnologies ref.#K1138) was prepared at 6-fold its final concentration as specified by the provider. Then 10 µL of the mixture was added to the wells to stop the stimulation. Plate was left in the dark over-night. Then a FRET reading was performed on an appropriate plate reader.

All experiments were analysed using an ExcelFit template and the four-parameter log equation. Inhibitions of IL4 induced STAT phosphorylation in Ramos cells are presented in Table 3. Compounds denoted as “A" had a inhibitory effect at 5 uM higher than 40%; compounds

denoted as "B" had a inhibitory effect at 5 uM between 20% and 40% and compounds denoted as "C" had a inhibitory effect at 5 uM lesser than 20%.

TABLE 3: IC50 Inhibition of IL4 induced STAT phosphorylation in Ramos cells

Compound Example	% Inhibition of IL4 induced STAT phosphorylation Ramos cells at 5 uM
2	A
8	C
13	A
26	C
27	C
28	C
30	B
32	B
33	C
40	A
48	C
49	C
50	B
54	C
56	C
73	B
78	B
87	B
88	A
92	B
97	C
99	C
105	A
117	A
122	B

123	A
124	B
125	B
126	C
127	C
128	C
129	A
130	C
131	C
132	A
133	C
137	C
138	C
151	C

COMBINATIONS

The carboxamide substituted derivatives of the present invention may also be combined with other active compounds in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Tyrosine kinase 2 (Tyk2).

The combination of the invention can optionally comprise one or more additional active substances which are known to be useful in the treatment of a dermatological disease, an inflammatory or autoimmune-mediated disease and a metabolism/endocrine function disorder; more in particular wherein the pathological condition or disease is selected from plaque psoriasis, scalp psoriasis, genital psoriasis, pustular psoriasis, psoriatic erythroderma, acrodermatitis continua, pityriasis rubra pilaris, lichen planus, hidradenitis suppurativa, bullous pemphigoid, pyoderma gangrenousm (PASH), ichthyosis, atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, primary biliary cholangitis, asthma and human multiple myeloma, such as,

a) Corticosteroids, such as prednisone, methylprednisolone or beta-methasone;

b) Immunosuppressants, such as cyclosporine, tacrolimus methotrexate, hydroxyurea, mycophenolate mofetil, mycophenolic acid, sulfasalazine, 6-thioguanine or azathioprine;

c) Fumaric acid esters, such as dimethyl fumarate or tepilamide fumarate;

d) Dihydroorotate dehydrogenase (DHODH) inhibitors such as leflunomide;

e) Retinoids, such as acitretin or isotretinoin;

f) Anti-inflammatories such as apremilast, crisaborole, celecoxib, diclofenac, aceclofenac, aspirin or naproxen;

g) Antibiotics such as gentamicin;

h) Antivirals such as aciclovir, efavirenz or ribavirin

i) Anti-cancer agents such as lenalidomide, pomalidomide, pembrolizumab, nivolumab, daratumumab, bortezomib, carfilzomib, ixazomib, bendamustine or ventoclast;

j) T-cell blockers such as alefacept or efalizumab;

k) Tumor necrosis factor-alpha (TNF-alpha) blockers such as etanercept, adalimumab, infliximab, golimumab, certolizumab pegol;

l) anti-IL4/IL13 antagonist such as dupilumab, lebrikizumab or tralokinumab;

o) IL-1b blockers such as canakinumab;

p) IL-alpha blockers such as bermekimab;

q) CD6 blockers such as itolizumab;

r) IL-36R blockers such as BI-655130 orANB019;

s) IL-6 antagonist such as tocilizumab;

t) Calcineurin inhibitors such as pimecrolimus, tacrolimus or cyclosporine;

u) Phototherapy agents commonly employed in phototherapy such as psoralen, methoxypsoralen or 5-methoxypsoralen + UVA (PUVA) or treatment with UVB (with or without tar);

v) Fixed combinations of corticosteroids and vitamin D derivatives;

w) Fixed combinations of corticosteroids and retinoids;

x) Corticosteroid tapes;

y) Other combinable agents may include piclidenoson, LYC-30937, LEO-32731, BI-730357, PRCL-02, LNP-1955, GSK-2982772, CBP-307, KD-025, MP-1032, petesicatib, JTE-451, Hemay-005, SM-04755, EDP-1815, BI-730460, GLPG3970, SFA-002 ER, JNJ-3534, SAR-441169, BOS-172767, SCD-044, CUDC-305. ABBV-157, BAY-1834845, AUR-101, R-835,

PBF-1650, IMU-935, RTA-1701, AZD-0284, CD20 antagonist, salicylic acid, coal tar, Mical-1, DUR-928, AM-001, BMX-010, TA-102, SNA-125, KP-470, pegcantratinib, pefcalcitol, ESR-114, tapinarof, NP-000888, SM-04755, BOS-475, SB-414, LEO-134310, CBS-3595, PF-06763809, XCUR-17 or BTX-1308, MGC topical cream,. RIST4721, aminopterin Na.

PHARMACEUTICAL COMPOSITIONS

Pharmaceutical compositions according to the present invention comprise the carboxamide substituted derivatives of the invention in association with a pharmaceutically acceptable diluent or carrier.

As used herein, the term pharmaceutical composition refers to a mixture of one or more of the carboxamide substituted derivatives of the invention or prodrugs thereof, with other chemical components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

As used herein, a physiologically/pharmaceutically acceptable diluent or carrier refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

The invention further provides pharmaceutical compositions comprising the carboxamide substituted derivatives of the invention in association with a pharmaceutically acceptable diluent or carrier together with one or more other therapeutic agents for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibiton of Tyk2, such as the ones previously described.

The invention also encompasses the use of a pharmaceutical composition of the invention for the manufacture of a medicament for treating a pathological condition or disease susceptible to amelioration by inhibiton of Tyk2, such as the ones previously described.

The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibiton of Tyk2, such as the ones previously described, the

method comprising administering a therapeutically effective amount of a pharmaceutical composition of the invention.

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a carboxamide substituted derivative of the invention in association with a pharmaceutically acceptable excipient such as a carrier or a diluent. Preferably the pharmaceutical compositions of the invention are made up in a form suitable for oral, topical, nasal, rectal, percutaneous or injectable administration.

Pharmaceutical compositions suitable for the delivery of triamide derivatives of the invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation can be found, for example, in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins, Philadelphia, Pa., 2001.

i) Topical Administration

The carboxamide substituted derivatives of the invention may be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

ii) Oral Administration

The carboxamide substituted derivatives of the invention may be administered orally (peroral administration; *per os* (latin)). Oral administration involve swallowing, so that the compound is absorbed from the gut and delivered to the liver via the portal circulation (hepatic first pass metabolism) and finally enters the gastrointestinal (GI) tract.

Compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules, inhalation aerosols, inhalation solutions, dry powder inhalation, or liquid preparations, such as mixtures, solutions, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art. The active ingredient may also be presented as a bolus, electuary or paste.

iii) Oral mucosal administration

The carboxamide substituted derivatives of the invention can also be administered via the oral mucosal. Within the oral mucosal cavity, delivery of drugs is classified into three categories: (a) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, (b) buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and (c) local delivery, which is drug delivery into the oral cavity.

Pharmaceutical products to be administered via the oral mucosal can be designed using mucoadhesive, quick dissolve tablets and solid lozenge formulations, which are formulated with one or more mucoadhesive (bioadhesive) polymers and/or oral mucosal permeation enhancers.

iv) Inhaled administration

The carboxamide substituted derivatives of the invention can also be administered by inhalation, typically in the form of a dry powder from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant.

v) Nasal mucosal administration

The carboxamide substituted derivatives of the invention may also be administered via the nasal mucosal.

Typical compositions for nasal mucosa administration are typically applied by a metering, atomizing spray pump and are in the form of a solution or suspension in an inert vehicle such

as water optionally in combination with conventional excipients such as buffers, anti-microbials, tonicity modifying agents and viscosity modifying agents

vi) Parenteral Administration

The carboxamide substituted derivatives of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art. The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

vii) Rectal/Intravaginal Administration

The carboxamide substituted derivatives of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate. Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

viii) Ocular Administration

The carboxamide substituted derivatives of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic,

pH- adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable {e.g. absorbable gel sponges, collagen) and nonbiodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. Such formulations may also be delivered by iontophoresis.

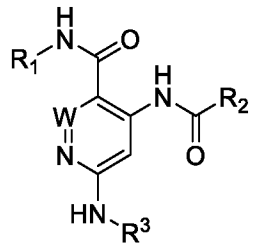
Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The amount of the carboxamide substituted derivative of the invention administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is typically in the range of 0.01-3000 mg, more preferably 0.5-1000 mg of active ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof per day.
Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

The amount of each active which is required to achieve a therapeutic effect will, of course, vary with the particular active, the route of administration, the subject under treatment, and the particular disorder or disease being treated.

CLAIMS

1. A carboxamide substituted derivative, which carboxamide substituted derivative is a compound of Formula (I), or a pharmaceutically acceptable salt, or a solvate, or a N-oxide, or a tautomer, or a stereoisomer, or an isotopically-labelled derivative thereof:



Formula (I)

wherein:

- R^1 is selected from the group consisting of a hydrogen atom, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} deuterio alkyl group and a monocyclic C_{3-6} cycloalkyl group,
- R^2 is selected from the group consisting of a phenyl group, a monocyclic C_{5-7} cycloalkyl group or a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one heteroatom selected from O, N and S, wherein the phenyl, cycloalkyl and heteroaryl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a halogen atom, a hydroxyl group, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} deuterioalkyl group, a linear or branched C_{1-4} alkoxy group, a cyano group, a $–S(O)_nCH_3$ group, a linear or branched C_{1-4} haloalkyl group, a -P(O)(C_{1-4} alkyl) group, a linear or branched C_{1-3} haloalkoxy group, a linear or branched C_{1-4} hydroxyalkyl group, a linear or branched C_{1-4} alkylamino group, a linear or branched (C_{1-6} alkoxy)-(C_{1-6} alkyl)- group, a $-(CH_2)_{0-1}O-(CH_2)_{1-2}-R^a$ group, a $–NR^bSO_2CH_3$ group, a monocyclic C_{3-6} cycloalkyl group, a $-(CH_2)_{0-1}-$ monocyclic 5- to 6- membered heterocyclyl group containing at least one heteroatom selected from O, N and S and a monocyclic 5- to 6- membered heteroaryl group containing at least one heteroatom selected from O, N and S optionally substituted by a methyl group,
- R^3 represents a $–C(O)-R^4$ group or a G^1 group,

- R^4 is selected from the group consisting of a linear or branched C_{1-4} alkyl group, linear or branched C_{1-4} hydroxyalkyl group, a phenyl group, a -$(CH_2)_{0-1}$-monocyclic C_{3-6} cycloalkyl group and a -$(CH_2)_{0-1}$- monocyclic 5- to 6- membered heterocyclyl group containing at least one heteroatom selected from the group consisting of O, N and S, wherein the phenyl, cycloalkyl and heterocyclyl groups are unsubstituted or substituted by one or more substituents selected from a halogen atom, a linear or branched C_{1-4} alkyl group, a hydroxyl group and a –$(CH_2)_{0-1}$-monocyclic or bicyclic 5- to 6-membered heteroaryl group containing at least one heteroatom selected from the group consisting of O, N and S,
- G^1 represents a phenyl group, a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one heteroatom selected from the group consisting of O, N and S or a monocyclic 5-to 6-membered heterocyclyl group containing one heteroatom selected from O, N and S, wherein the phenyl, heteroaryl and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from a linear or branched C_{1-4} alkyl group, a halogen atom, a cyano group, a hydroxyl group, an oxo group, a linear or branched C_{1-4} alkoxy group, a linear or branched C_{1-3} haloalkyl group, a linear or branched C_{1-3} haloalkoxy group, a linear or branched (C_{1-4} alkoxy)-(C_{1-4} alkyl)- group, a –$(CH_2)_{0-1}C(O)NHCH_3$ group, a linear or branched C_{1-4} hydroxyalkyl group, a linear or branched C_{1-4} alkylamino group, a $–NHSO_2CH_3$ group, a $–SO_2NH_2$ group, a –NH-$(CH_2)_2OR^c$ group, -O-$(CH_2)_{1-2}$-R^d group, a –$(CH_2)_{0-1}$-monocyclic or bicyclic 5- to 6- membered heteroaryl group containing at least one heteroatom selected from the group consisting of O, N and S, a -NH-(CH_2)-C(O)-monocyclic 5- to 6-membered heterocyclyl group containing at least one heteroatom selected from the group consisting of O, N and S or a –$(CH_2)_{0-1}$-monocyclic or bicyclic 5- to 7-membered heterocyclyl group containing at least one heteroatom selected from the group consisting of N, O and S, wherein the heterocyclyl group is optionally substituted by one or more substituents selected from a linear or branched C_{1-4} alkyl group, a hydroxyl group, a linear or branched C_{1-2} hydroxyalkyl group and a linear or branched (C_{1-4} alkoxy)-(C_{1-4} alkyl)- group,
- W represents a nitrogen atom or a CH group,
- R^a and R^d each independently represent a hydroxyl group, a linear or branched C_{1-3} alkoxy group and a 5- to 6- membered heterocyclyl group containing at least one heteroatom selected from N, O and S,

- R^b and R^c each independently represent a hydrogen atom or a linear or branched C_{1-4} alkyl group, and
- n represents an integrer selected from 0, 1 and 2.

2. A compound according to claim 1 wherein R^1 represents a hydrogen atom, a methyl group or a trideuteriomethyl group, preferably a methyl group or a trideuteriomethyl group.

3. A compound according to claims 1 or 2, wherein R^2 represents a phenyl group or a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one N atom, wherein the phenyl and heteroaryl groups are unsubstituted or substituted by one or more substituents selected from a linear C_{1-2} alkyl group, a linear C_{1-2} deuterioalkyl group, a linear C_{1-2} haloalkyl group, a linear C_{1-2} alkoxy group, a $-S(O)_{1-2}CH_3$ group, a halogen atom, a hydroxyl group, a linear C_{1-2} alkylamino group, a linear C_{1-2} hydroxyalkyl group, a cyano group, a $NHSO_2CH_3$ group and a 5-membered heteroaryl group containing at least one N atom, said heteroaryl group being optionally substituted by a methyl group.

4. A compound according to claim 3, wherein R^2 represents a phenyl group or an indolyl group wherein the phenyl and indolyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a fluorine atom, a chlorine atom, a methyl group, a methoxy group, a hydroxyl group, a linear C_{1-2} hydroxyalkyl group and a triazolyl group optionally substituted by a methyl group.

5. A compound according to claims 1 to 4, wherein R^3 represents a $-C(O)-R^4$ group.

6. A compound according to claim 5, wherein R^4 is selected from the group consisting of a linear or branched C_{1-4} hydroxyalkyl group and a C_{3-6} cycloalkyl group, wherein the cycloalkyl group is unsubstituted or substituted by one or more substituents selected from a halogen atom and a hydroxyl group.

7. A compound according to claims 5 or 6 wherein, R^4 represents a cyclopropyl group unsubstituted or substituted by a fluorine atom.

8. A compound according to claim 1, wherein R^3 represents a G^1 group.

9. A compound according to claim 8, wherein G^1 represents a monocyclic 5- to 6- membered heteroaryl group containing at least one N atom, wherein the heteroaryl group is unsubstituted or substituted by one or more substituents selected from the group consisting of a linear C_{1-2} alkyl group, a cyano group, a linear or branched C_{1-3} hydroxyalkyl group, a linear or branched (C_{1-2} alkoxy)-(C_{1-2} alkyl)- group and a 6- membered heterocyclyl group containing at least one heteroatom selected from the group consisting of N and O, wherein the heterocyclyl group is optionally substituted by one or more substituents selected from a linear or branched (C_{1-2} alkoxy)-(C_{1-2} alkyl)- group, a linear C_{1-2} hydroxyalkyl group and a linear C_{1-2} alkyl group.

10. A compound according to claims 8 or 9, wherein G^1 represents a pyridine, a pyrimidine or a pyrazolyl group, wherein the pyridine, pyrimidine and pyrazolyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a methyl group, a linear or branched C_{1-3} hydroxyalkyl group and a 6-membered heterocyclyl containing at least one heteroatom selected from the group consisting of N and O group, said heterocyclyl group being optionally substituted by one or more substituents selected from a methyl group, a hydroxyethyl group and a methoxyethyl group.

11. A compound according to claims 1 to 10, wherein W represents a CH group.

12. A compound according to claim 1 wherein:

- R^1 represents a hydrogen atom, a methyl group or a trideuteriomethyl group, preferably a methyl group or a trideuteriomethyl group,
- R^2 represents a phenyl group or a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one N atom, wherein the phenyl and heteroaryl groups are unsubstituted or substituted by one or more substituents selected from a linear C_{1-2} alkyl group, a linear C_{1-2} deuterioalkyl group, a linear C_{1-2} haloalkyl group, a linear C_{1-2} alkoxy group, a $-S(O)_{1-2}CH_3$ group, a halogen atom, a hydroxyl group, a linear C_{1-2} alkylamino group, a linear C_{1-2} hydroxyalkyl group, a cyano group, a $NHSO_2CH_3$ group and a 5-membered heteroaryl group containing at least one N atom, said heteroaryl group being optionally substituted by a methyl group,
- R^3 represents a $-C(O)-R^4$ group,

- R^4 is selected from the group consisting of a linear or branched C_{1-4} hydroxyalkyl group and a C_{3-6} cycloalkyl group, wherein the cycloalkyl group is unsubstituted or substituted by one or more substituents selected from a halogen atom and a hydroxyl group, and
- W represents a CH group.

13. A compound according to claim 1 wherein:

- R^1 represents a hydrogen atom, a methyl group or a trideuteriomethyl group, preferably a methyl group or a trideuteriomethyl group,
- R^2 represents a phenyl group or a monocyclic or bicyclic 5- to 9- membered heteroaryl group containing at least one N atom, wherein the phenyl and heteroaryl groups are unsubstituted or substituted by one or more substituents selected from a linear C_{1-2} alkyl group, a linear C_{1-2} deuterioalkyl group, a linear C_{1-2} haloalkyl group, a linear C_{1-2} alkoxy group, a $-S(O)_{1-2}CH_3$ group, a halogen atom, a hydroxyl group, a linear C_{1-2} alkylamino group, a linear C_{1-2} hydroxyalkyl group, a cyano group, a $NHSO_2CH_3$ group and a 5-membered heteroaryl group containing at least one N atom, said heteroaryl group being optionally substituted by a methyl group,
- R^3 represents a G^1 group,
- G^1 represents a monocyclic 5- to 6- membered heteroaryl group containing at least one N atom, wherein the heteroaryl group is unsubstituted or substituted by one or more substituents selected from the group consisting of a linear C_{1-2} alkyl group, a cyano group, a linear or branched C_{1-3} hydroxyalkyl group, a linear or branched (C_{1-2} alkoxy)-(C_{1-2} alkyl)- group and a 6- membered heterocyclyl group containing at least one heteroatom selected from the group consisting of N and O, wherein the heterocyclyl group is optionally substituted by one or more substituents selected from a linear or branched (C_{1-2} alkoxy)-(C_{1-2} alkyl)- group, a linear C_{1-2} hydroxyalkyl group and a linear C_{1-2} alkyl group, and
- W represents a CH group.

14. A compound according to claims 1 to 13, wherein:

- R^2 represents a phenyl group or an indolyl group, wherein the phenyl and indolyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a fluorine atom, a chlorine atom, a methyl group, a methoxy group, a

hydroxyl group, a linear C_{1-2} hydroxyalkyl group and a triazolyl group optionally substituted by a methyl group,

- R^4 represents a cyclopropyl group unsubstituted or substituted by a fluorine atom, and
- G^1 represents a pyridine, pyrimidine or a pyrazolyl group, wherein the pyridine, pyrimidine and pyrazolyl groups are unsubstituted or substituted by one or more substituents selected from the group consisting of a methyl group, a linear or branched C_{1-3} hydroxyalkyl group or a 6-membered heterocyclyl containing at least one heteroatom selected from the group consisting of N and O group, optionally substituted by one or more substituents selected from a methyl group, a hydroxyethyl group and a methoxyethyl group.

15. A compound according to claim 1, wherein:

- R^1 represents a hydrogen atom, a methyl group, a trideuteriomethyl group or a cyclopropyl group,
- R^2 is selected from the group consisting of a phenyl group, a cyclohexyl group, a pyridinyl group, a benzimidazolyl group, an imidazolpyridinyl group, an indolyl group, a pyrrolopyridinyl group, a benzotriazolyl group, a pyrazolyl group and an indazolyl group, wherein the phenyl, pyridinyl, indolyl, pyrrolopyridinyl, benzotriazolyl, pyrazolyl, imidazolpyridinyl and benzimidazolyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of a methyl group, a fluorine atom, a chlorine atom, a methoxy group, a cyano group, a $-S(O)_{1-2}CH_3$ group, a trifluoromethyl group, a trifluoromethoxy group, a trideuteriomethyl group, a CF_3CH_2- group, a hydroxyl group, a hydroxymethyl group, a hydroxyethyl group, a trideuteriomethyl group, a $-NHCH_3$ group, an imidazole group, a $-NHSO_2CH_3$ group, a methyl-triazole group, a cyclopropyl, a triazole group, an imidazole group, a methyl-imidazole group, a methoxyethyl group, a methoxymethyl group, an $-(CH_2)_{0-1}-O(CH_2)_2OCH_3$ group, an $-O(CH_2)_2OH$ group, a $-(CH_2)O(CH_2)_2OH$ group, a $-(CH_2)$-morpholinyl and a $-CH(CH_3)CH_2OCH_3$ group,
- R^3 represents a $-C(O)-R^4$ group or a G^1 group,
- R^4 is selected from the group consisting of a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, phenyl group, a $-CH(CH_3)_2$ group, a $-C(CH_3)_3$ group, a $-C(CH_3)_2OH$ group, a $-(CH_2)$-morpholinyl group, a $-(CH_2)$-cyclohexyl group and a $-(CH_2)_{1-2}$-OH group, wherein the cyclopropyl, cyclobutyl, phenyl and cyclohexyl groups

are unsubstituted or substituted by one or more substituents selected from a fluorine atom, a methyl group, a hydroxyl group and a –(CH_2)-triazole group,

- G^1 is selected from the group consisting of a phenyl group, pyrazolyl group, pyridinyl group, a pyrimidinyl group, a pyridazinyl group, a indazolyl group, an imidazolyl group, a pyrazyl group, a triazolyl group, a tetrahydropyranyl group and a pyrazoloxazinyl group, wherein the phenyl, pyrazolyl, pyridinyl, pyrimidinyl, imidazolyl, pyrazyl and triazolyl groups are unsubstituted or substituted by one or more substituents selected from a fluorine atom, methyl group, a methoxy group, a trifluoromethyl group, a $–CH_2CF_3$ group, a $–OCH_2CF_3$ group, a cyano group, an oxo group, a hydroxyl group, a methoxymethyl group, a $–C(CH_3)_2OH$ group, a $–CH_2C(O)NHCH_3$ group, a $-NHCH_3$ group, a $–NHCH_2C(O)$-morpholinyl group, a $–N(CH_3)_2$ group, a $-NHSO_2CH_3$ group, $-NH(CH_2)_2OCH_3$ group, $-NH(CH_2)_2OH$ group, a $–SO_2NH_2$ group, an –O-$(CH_2)_2$-morpholinyl group, a methoxyethyl group, a hydroxyethyl group, a hydroxymethyl group, a –(CH_2)-triazolyl group, a $–(CH_2)_{0\text{-}1}$-morpholinyl group, a $–CH(CH_3)OH$ group, a $–O(CH_2)_2OCH_3$ group, a $–O(CH_2)_2OH$ group, a $–(CH_2)_{0\text{-}1}$-tetrahydropyranyl group, an oxa-5-azabicyclo[2.2.1]heptyl group, a hydroxyethyl substituted piperazinyl group, a methoxyethyl substituted piperazinyl group, a dimethyl substituted morpholinyl group, a methyl substituted piperazinyl group and a hydroxyl substituted piperidinyl group, and
- W represents a nitrogen atom or a –CH group.

16. A carboxamide derivative according to claim 1, wherein the compound of Formula (I) is one of:

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(2-pyridylamino)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[(2,4,6-trimethylbenzoyl) amino]pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(4-pyridylamino)pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[(5-cyano-2-pyridyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-cyclopropyl-pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-(pyrimidin-4-ylamino)pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-N-methyl-6-[(1-methylpyrazol-3-yl)amino]pyridine-3-carboxamide

4-[(2-chloro-6-fluoro-benzoyl)amino]-6-[[4-(methoxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-chloro-4-cyano-6-fluoro-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

4-[(2-chloro-6-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridazine-3-carboxamide

6-[(5-cyano-2-pyridyl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[(2-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[1-[2-(methylamino)-2-oxo-ethyl]pyrazol-4-yl]amino]pyridine-3-carboxamide

4-(2-fluoro-6-methoxybenzamido)-6-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-N-methylnicotinamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[1-(2-hydroxyethyl)pyrazol-4-yl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[4-(1,2,4-triazol-1-ylmethyl)benzoyl]amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(1,2,4-triazol-1-ylmethyl)-2-pyridyl]amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(morpholinomethyl)-2-pyridyl]amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(6-methyl-2-pyridyl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(2-pyridylamino)pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-(hydroxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-(1H-indazol-6-ylamino)-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(4-cyano-2-fluoro-6-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[4-(methoxymethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[3-(1-hydroxyethyl)anilino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,4-difluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(tetrahydropyran-4-ylamino)pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(pyrimidin-2-ylamino)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[[4-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[6-(methylamino)-2-pyridyl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[[3-(trifluoromethyl)benzoyl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-4-(trifluoromethoxy)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-5-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-(hydroxymethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(hydroxymethyl)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[[6-(methylamino)pyridine-3-carbonyl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-N-methyl-4-[[2-(trifluoromethoxy)benzoyl]amino]pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-2-methoxy-6-(methylamino)pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(4-hydroxy-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[(2,4,5-trifluoro-3-methoxy-benzoyl)amino]pyridine-3-carboxamide

4-[[3,5-bis(trifluoromethyl)benzoyl]amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

4-[(4-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridazine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[5-(tetrahydropyran-3-ylmethyl)-2-pyridyl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2,6-difluorobenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-5-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-fluoro-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(3-chloro-5-fluoro-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(5-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(5-hydroxy-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-(2,4-difluoro-5-methoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-[(5-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

4-[(3,5-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(1H-imidazol-2-yl)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxypyridine-3-carbonyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-6-[[1-[2-(methylamino)-2-oxo-ethyl]pyrazol-4-yl]amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[3-(methanesulfonamido)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(5-methyl-4H-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3H-benzimidazole-5-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(1H-1,2,4-triazol-5-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(1H-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(6-methyl-2-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-(pyridazin-3-ylamino)pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-6-[(5-morpholino-2-pyridyl)amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(1-methylimidazol-2-yl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(2-morpholinoacetyl)amino]pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-indazole-6-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(6-fluoro-2,3-dimethoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(4-methyl-6-oxo-1H-pyrimidin-2-yl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-6-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-4-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[2-(4-hydroxycyclohexyl)acetyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-(1-hydroxy-1-methyl-ethyl)-3-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-indole-5-carboxamide

4-[(3-chloro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-(methanesulphonamido)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2,3-dimethoxybenzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[[2-methyl-6-(methylamino)pyrimidin-4-yl]amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(2-methyl-6-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[(5-fluoro-2-pyridyl)amino]-N-methyl-pyridine-3-carboxamide

6-[[5-(2,2-dimethylmorpholin-4-yl)-2-pyridyl]amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[5-(2-hydroxyethoxy)-2-methoxy-benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-4-[(3-methylsulfonylbenzoyl)amino]pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(4-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(3-cyano-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(6-fluoro-2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-6-methoxy-3H-benzotriazole-5-carboxamide

6-[[6-(dimethylamino)-2-methyl-pyrimidin-4-yl]amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(methanesulfonamido)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3H-benzimidazole-5-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-6-[(5-sulfamoyl-2-pyridyl)amino]pyridine-3-carboxamide

4-[(3-cyclopropyl-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1H-indole-2-carboxamide

4-[(2-fluoro-6-methoxy-benzoyl)amino]-6-[[5-(2-methoxyethoxy)-2-pyridyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(5,6-dimethylpyrazin-2-yl)amino]-4-[(2-fluoro-6-methoxy-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-4-methoxy-indole-2-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-6-[(6-methyl-2-morpholino-pyrimidin-4-yl)amino]pyridine-3-carboxamide

6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-[[2-[4-(2-methoxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-pyridine-3-carboxamide

4-[(3-chloro-2-methoxy-benzoyl)amino]-6-(cyclopropanecarbonylamino)-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-3-methoxy-indole-2-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-[(2-methoxy-3-methyl-benzoyl)amino]-N-methyl-6-[[6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl]amino]pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl) benzoyl]amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(3,5-difluoro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-methyl-indole-6-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-7-methoxy-1-(2,2,2-trifluoroethyl)indole-6-carboxamide

N-[2-(cyclopropanecarbonylamino)-5-(methylcarbamoyl)-4-pyridyl]-1-(2-hydroxyethyl)-3-methoxy-indole-2-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-methyl-indole-2-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1-methyl-benzimidazole-5-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-3-methyl-benzimidazole-5-carboxamide

6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-4-[[2-methoxy-3-(trifluoromethyl)benzoyl]amino]-N-methyl-pyridine-3-carboxamide

4-[(3-fluoro-2-methoxy-benzoyl)amino]-6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

4-[(3-chloro-2-methoxy-benzoyl)amino]-6-[[2-[4-(2-hydroxyethyl)piperazin-1-yl]-6-methyl-pyrimidin-4-yl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(2-methoxybenzoyl)amino]-N-methyl-pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[[2-methoxy-3-(trideuteriomethyl)benzoyl]amino]-N-methyl-pyridazine-3-carboxamide

N-[2-(cyclopropanecarbonylamino)-5-(methylcarbamoyl)-4-pyridyl]-3-methoxy-1-(2-methoxyethyl)indole-2-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-methoxy-1-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[[4-methoxy-2-(2-methoxyethyl)pyrazole-3-carbonyl]amino]-N-methyl-pyridine-3-carboxamide

N-[2-[(2,6-dimethylpyrimidin-4-yl)amino]-5-(methylcarbamoyl)-4-pyridyl]-4-methoxy-1H-indole-5-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-methoxypyridine-2-carbonyl)amino]-N-methyl-pyridine-3-carboxamide

6-[(2,6-dimethylpyrimidin-4-yl)amino]-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(3-fluoro-2-methoxy-benzoyl)amino]-N-methyl-pyridazine-3-carboxamide

6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-methyl-pyridazine-3-carboxamide

4-[(3,6-difluoro-2-methoxy-benzoyl)amino]-6-[(2,6-dimethylpyrimidin-4-yl)amino]-N-methyl-pyridine-3-carboxamide,

6-(cyclopropanecarbonylamino)-4-[(2,3-dimethoxybenzoyl)amino]-N-(trideuteriomethyl)pyridine-3-carboxamide

4-(2-fluoro-6-methoxybenzamido)-6-((6-((2-methoxyethyl)amino)-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((4-(trifluoromethyl)pyridin-2-yl)amino)nicotinamide

4-(2,5-dimethoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-((6-((2-hydroxyethyl)amino)-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(morpholinomethyl)benzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-((6-methoxy-2-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((4-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

6-((6-cyano-2-methylpyrimidin-4-yl)amino)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(3-hydroxypropanamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-5-(methoxymethyl)benzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-((6-(2-hydroxyethoxy)pyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(3-hydroxycyclobutane-1-carboxamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(2-hydroxyacetamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-(2-methoxyethoxy)-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-isobutyramido-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-(1-methylcyclopropane-1-carboxamido)nicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((6-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

6-(3,3-difluorocyclobutane-1-carboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-pivalamidonicotinamide

6-(cyclopentanecarboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-indazole-6-carboxamide

4-(2-fluoro-6-methoxybenzamido)-N-methyl-6-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)amino)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-(2-hydroxyethoxy)-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-((2-hydroxyethoxy)methyl)-2-methoxybenzamido)-N-methylnicotinamide

6-(cyclobutanecarboxamido)-4-(2-fluoro-6-methoxybenzamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(2-hydroxy-2-methylpropanamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(3-fluorocyclobutane-1-carboxamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-((4-(1-hydroxyethyl)pyridin-2-yl)amino)-N-methylnicotinamide

4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methyl-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrimidin-4-yl)amino)nicotinamide

4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methyl-2-(2-morpholinoethoxy)pyrimidin-4-yl)amino)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

4-(2-fluoro-6-methoxybenzamido)-6-(1-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-2-carboxamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-ethyl-2-methoxybenzamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1-methyl-1H-pyrrolo[3,2-c]pyridine-3-carboxamide

4-(2-methoxy-3-(trifluoromethyl)benzamido)-N-methyl-6-((6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)nicotinamide

4-(3-chloro-2-methoxybenzamido)-N-methyl-6-((6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)nicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-fluoro-1-(2-hydroxyethyl)-3-methoxy-1H-indole-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2,2,2-trifluoroethyl)-1H-indole-2-carboxamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-((2-methoxyethoxy)methyl)benzamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1H-indole-2-carboxamide

4-(3-chloro-2-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-methoxyisonicotinamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1H-pyrrolo[3,2-c]pyridine-3-carboxamide

4-(3,4-difluoro-2-methoxybenzamido)-6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(3-chloro-2-methoxybenzamido)-6-((2-(2-methoxyethoxy)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-fluoro-2-methoxybenzamido)-N-methylpyridazine-3-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-2-(methoxymethyl)-1H-benzo[d]imidazole-5-carboxamide

6-(cyclopropanecarboxamido)-4-(3-fluoro-2-methoxybenzamido)-N-methylnicotinamide

4-(3-chloro-2-methoxybenzamido)-N-methyl-6-((6-methyl-2-((2-morpholino-2-oxoethyl)amino)pyrimidin-4-yl)amino)nicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(3-fluoro-2-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(3-chloro-2-methoxybenzamido)-6-((2-fluoro-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-indole-6-carboxamide

N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(2-methoxyethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(2-fluoro-6-methoxybenzamido)-6-((2-(4-hydroxypiperidin-1-yl)-6-methylpyrimidin-4-yl)amino)-N-methylnicotinamide

4-(2,3-dimethoxybenzamido)-6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-1H-benzo[d][1,2,3]triazole-6-carboxamide

N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-indole-2-carboxamide

4-(2,3-dimethoxybenzamido)-N-methyl-6-((2-methylpyrimidin-4-yl)amino)nicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-7-methoxy-3H-imidazo[4,5-b]pyridine-6-carboxamide

N-(2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3,4-dimethoxypicolinamide

N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3,4-dimethoxypicolinamide

6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-4-(2-methoxynicotinamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(2-methoxyethoxy)benzamido)-N-(methyl-d3)nicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-3-fluoro-7-methoxy-1H-indole-6-carboxamide

N-(2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

4-(2,3-dimethoxybenzamido)-N-methyl-6-((6-methylpyrimidin-4-yl)amino)nicotinamide

6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-4-(2-methoxy-3-(methyl-d3)benzamido)-N-methylnicotinamide

N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

4-(3-cyano-2-methoxybenzamido)-6-(cyclopropanecarboxamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(3-(2-hydroxyethoxy)-2-methoxybenzamido)-N-(methyl-d3)nicotinamide

N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(2,3-dimethoxybenzamido)-N-methyl-6-((1-methyl-1H-pyrazol-3-yl)amino)nicotinamide

N-(2-(cyclopropanecarboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1-methyl-1H-pyrazole-5-carboxamido)-N-(methyl-d3)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1-methyl-1H-pyrazole-3-carboxamido)-N-(methyl-d3)nicotinamide

4-(2,3-dimethoxybenzamido)-6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-N-methylpyridazine-3-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-fluoro-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(2-methoxy-3-(methyl-d3)benzamido)-6-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-N-methylnicotinamide

N-(2-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-1H-indole-5-carboxamide

4-(2,3-dimethoxybenzamido)-N-methyl-6-((1-methyl-1H-1,2,4-triazol-3-yl)amino)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)benzamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxy-3-(methylsulfinyl)benzamido)-N-(methyl-d3)nicotinamide

6-(2,2-difluorocyclopropane-1-carboxamido)-4-(2,3-dimethoxybenzamido)-N-methylnicotinamide

6-((6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl)amino)-4-(2,3-dimethoxybenzamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine-6-carboxamide

6-((1-(2-hydroxyethyl)-1H-pyrazol-3-yl)amino)-4-(2-methoxy-3-(methyl-d3)benzamido)-N-methylnicotinamide

3-methoxy-N-(2-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

4-(2,3-dimethoxybenzamido)-6-((1,5-dimethyl-1H-pyrazol-3-yl)amino)-N-methylnicotinamide

4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)nicotinamide

4-(2,3-dimethoxybenzamido)-6-((5-fluoropyridin-2-yl)amino)-N-methylnicotinamide

4-(2-methoxy-3-methylbenzamido)-6-((1-(2-methoxyethyl)-1H-imidazol-4-yl)amino)-N-methylnicotinamide

4-(2-methoxy-3-methylbenzamido)-N-methyl-6-((6-methylpyrimidin-4-yl)amino)nicotinamide

4-(2,3-dimethoxybenzamido)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-methylnicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(4-methoxy-1,3-dimethyl-1H-pyrazole-5-carboxamido)-N-methylnicotinamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-4-methoxy-3-(methyl-d3)-1H-indole-5-carboxamide

N-(2-((2,6-dimethylpyrimidin-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-(1-methoxypropan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

N-(2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-5-(methylcarbamoyl)pyridin-4-yl)-3-methoxy-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-N-methyl-4-(2-(N-methylmethylsulfonamido)benzamido)nicotinamide

6-((2,6-dimethylpyrimidin-4-yl)amino)-4-(2-methoxycyclohexane-1-carboxamido)-N-methylnicotinamide

or a pharmaceutically acceptable salt, or solvate, or N-oxide, or stereoisomer, or tautomer, or isotopically labelled derivatives thereof.

17. A carboxamide substituted compound as defined in any one of claims 1 to 16, for use in the treatment of the human or animal body by therapy.

18. A carboxamide substituted compound as defined in any one of claims 1 to 16, for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Tyk2.

19. A carboxamide substituted compound according to any one of claims 1 to 16, for use according to claim 18, wherein the treatment is of a pathological condition or disease selected plaque psoriasis, scalp psoriasis, genital psoriasis, pustular psoriasis, psoriatic erythroderma, acrodermatitis continua, pityriasis rubra pilaris, lichen planus, hidradenitis suppurativa, bullous pemphigoid, pyoderma gangrenousm (PASH), ichthyosis, atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, primary biliary cholangitis, asthma and human multiple myeloma.

20. A pharmaceutical composition comprising a carboxamide substituted compound as defined in any one of claims 1 to 16 in association with a pharmaceutically acceptable diluent or carrier.

21. Use of a carboxamide substituted compound derivative as defined in any one of claims 1 to 16, for the manufacture of a medicament for the treatment of a pathological condition or disease as defined in claim 18 and 19.

22. A method for treating a subject afflicted with a pathological condition or disease as defined in claims 18 and 19, which comprises administering to said subject a therapeutically effective amount of a carboxamide substituted compound as defined in any one of claims 1 to 16, or a pharmaceutical composition as defined in claim 20.

23. A combination product comprising (i) at least one carboxamide substituted derivative as defined in any one of claims 1 to 16, and (ii) one or more active ingredients selected from:

a) Corticosteroids, such as prednisone, methylprednisolone or beta-methasone;

b) Immunosuppressants, such as cyclosporine, tacrolimus methotrexate, hydroxyurea, mycophenolate mofetil, mycophenolic acid, sulfasalazine, 6-thioguanine or azathioprine;

c) Fumaric acid esters, such as dimethyl fumarate or tepilamide fumarate;

d) Dihydroorotate dehydrogenase (DHODH) inhibitors such as leflunomide;

e) Retinoids, such as acitretin or isotretinoin;

f) Anti-inflammatories such as apremilast, crisaborole, celecoxib, diclofenac, aceclofenac, aspirin or naproxen;

g) Antibiotics such as gentamicin;

h) Antivirals such as aciclovir, efavirenz or ribavirin

i) Anti-cancer agents such as lenalidomide, pomalidomide, pembrolizumab, nivolumab, daratumumab, bortezomib, carfilzomib, ixazomib, bendamustine or ventoclast;

j) T-cell blockers such as alefacept or efalizumab;

k) Tumor necrosis factor-alpha (TNF-alpha) blockers such as etanercept, adalimumab, infliximab, golimumab, certolizumab pegol;

l) anti-IL4/IL13 antagonist such as dupilumab, lebrikizumab or tralokinumab;

o) IL-1b blockers such as canakinumab;

p) IL-alpha blockers such as bermekimab;

q) CD6 blockers such as itolizumab;

r) IL-36R blockers such as BI-655130 orANB019;

s) IL-6 antagonist such as tocilizumab;

t) Calcineurin inhibitors such as pimecrolimus, tacrolimus or cyclosporine;

u) Phototherapy agents commonly employed in phototherapy such as psoralen, methoxypsoralen or 5-methoxypsoralen + UVA (PUVA) or treatment with UVB (with or without tar);

v) Fixed combinations of corticosteroids and vitamin D derivatives;

w) Fixed combinations of corticosteroids and retinoids;

x) Corticosteroid tapes; and

y) Other combinable agents may include piclidenoson, LYC-30937, LEO-32731, BI-730357, PRCL-02, LNP-1955, GSK-2982772, CBP-307, KD-025, MP-1032, petesicatib, JTE-451, Hemay-005, SM-04755, EDP-1815, BI-730460, GLPG3970, SFA-002 ER, JNJ-3534, SAR-441169, BOS-172767, SCD-044, CUDC-305. ABBV-157, BAY-1834845, AUR-101, R-835, PBF-1650, IMU-935, RTA-1701, AZD-0284, CD20 antagonist, salicylic acid, coal tar, Mical-1, DUR-928, AM-001, BMX-010, TA-102, SNA-125, KP-470, pegcantratinib, pefcalcitol, ESR-114, tapinarof, NP-000888, SM-04755, BOS-475, SB-414, LEO-134310, CBS-3595, PF-06763809, XCUR-17 or BTX-1308, MGC topical cream,. RIST4721, aminopterin Na.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/058465

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D213/82 C07D237/24 C07D401/14 C07D403/12
C07D471/04 A61K31/437 A61K31/44 A61K31/444 A61K31/4965
A61P17/00 A61P17/06 A61P35/00 A61P37/00 A61P37/08

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.
X	WO 2014/074661 A1 (SQUIBB BRISTOL MYERS CO [US]) 15 May 2014 (2014-05-15) page 82 - page 86; claim 1 page 108 - page 125 -----	1-23
X	WO 2015/069310 A1 (SQUIBB BRISTOL MYERS CO [US]) 14 May 2015 (2015-05-14) page 64 - page 66; claim 1 -----	1-23

☐ Further documents are listed in the continuation of Box C.

☒ 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2021	16/06/2021

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	Lewis, Sara

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/058465

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014074661 A1	15-05-2014	AR 094452 A1	05-08-2015
		AU 2013341186 A1	02-07-2015
		AU 2017201076 A1	09-03-2017
		AU 2018267545 A1	13-12-2018
		AU 2020203967 A1	16-07-2020
		BR 112015010102 A2	11-07-2017
		CA 2890981 A1	15-05-2014
		CL 2015001231 A1	28-08-2015
		CN 104884454 A	02-09-2015
		CY 1121188 T1	29-05-2020
		DK 2922846 T3	21-01-2019
		EA 201590917 A1	30-09-2015
		EP 2922846 A1	30-09-2015
		EP 3495358 A1	12-06-2019
		ES 2702148 T3	27-02-2019
		HK 1215255 A1	19-08-2016
		HR P20181937 T1	25-01-2019
		HU E041750 T2	28-05-2019
		JP 6407159 B2	17-10-2018
		JP 6585231 B2	02-10-2019
		JP 2016506369 A	03-03-2016
		JP 2018154636 A	04-10-2018
		JP 2020002157 A	09-01-2020
		KR 20150081339 A	13-07-2015
		LT 2922846 T	10-12-2018
		MA 38072 A1	29-07-2016
		NZ 708859 A	30-11-2018
		PE 20150944 A1	20-06-2015
		PH 12015501004 A1	27-07-2015
		PL 2922846 T3	29-03-2019
		PT 2922846 T	19-12-2018
		SG 10201706897T A	28-09-2017
		SG 10201706985U A	30-10-2017
		SG 11201503399X A	28-05-2015
		SI 2922846 T1	30-04-2019
		TR 201820824 T4	21-01-2019
		TW 201422593 A	16-06-2014
		US RE47929 E	07-04-2020
		US 2015299183 A1	22-10-2015
		US 2017022192 A1	26-01-2017
		US 2018265504 A1	20-09-2018
		US 2020071315 A1	05-03-2020
		UY 35126 A	30-05-2014
		WO 2014074661 A1	15-05-2014
		ZA 201504052 B	29-11-2017
WO 2015069310 A1	14-05-2015	AR 094537 A1	12-08-2015
		AU 2014347275 A1	23-06-2016
		BR 112016010172 A2	08-08-2017
		CA 2930060 A1	14-05-2015
		CL 2016001101 A1	16-12-2016
		CN 106660960 A	10-05-2017
		DK 3066078 T3	26-08-2019
		EA 201690865 A1	30-01-2017
		EP 3066078 A1	14-09-2016
		EP 3590926 A1	08-01-2020
		ES 2738826 T3	27-01-2020
		HK 1226400 A1	29-09-2017

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/058465

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		HR P20191368 T1	29-11-2019
		HU E046052 T2	28-02-2020
		IL 245448 A	29-08-2019
		JP 6312823 B2	18-04-2018
		JP 2017512749 A	25-05-2017
		KR 20160071475 A	21-06-2016
		LT 3066078 T	25-07-2019
		MA 39001 A1	31-10-2017
		MX 369394 B	07-11-2019
		NZ 720710 A	20-12-2019
		PE 20160961 A1	08-10-2016
		PH 12016500779 A1	30-05-2016
		PL 3066078 T3	31-10-2019
		PT 3066078 T	01-08-2019
		SI 3066078 T1	30-08-2019
		TN 2016000153 A1	06-10-2017
		TW 201420572 A	01-06-2014
		US 2016280649 A1	29-09-2016
		US 2017209426 A1	27-07-2017
		WO 2015069310 A1	14-05-2015