Title: IMIDAZO[1,2-B]PYRIDAZIN-6-AMINE DERIVATIVES AS KINASE JAK-2 INHIBITORS

Abstract: A compound represented by the general formula (I) wherein R represents H or Ci-C4 alkyl; R represents phenyl substituted with one or two substituents selected from the group consisting of halogen atom and OC-Cl alkyl; R represents phenyl or 5 to 10-membered monocyclic or bicyclic heteroaryl having from 1 to 4 ring heteroatoms selected from the group consisting of N, S, and O, which can be unsubstituted or substituted with a substituent selected from halogen atom, Ci-C4 alkyl, and -CO(0)G-C4 alkyl, and X represents -CH2 group or carbonyl-C(O)-group and their acid addition salts with the exclusion of 3-(4-chloro-2-fluorobenzyl)-2-methyl-IV-(5-methyl-4-[(4-pyrazol-3-yl)-5-(mopholinomethyl)-imidazo[1,2-f]pyridazine-6-amine, and its salts. The compounds are JAK2 inhibitors and are useful as medicaments, especially for treating proliferative disorders and cancer diseases.
as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

— of inventorship (Rule 4.17(iv))

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The present invention related to novel heterocyclic compounds, imidazo[1,2-b]-pyridazin-6-amine derivatives showing the activity of kinase JAK-2 inhibitors, pharmaceutical compositions containing these compounds, and their use as medicaments. The compounds can be useful, in particular, in the treatment of myeloproliferative and neoplastic diseases.

Tyrosine kinases JAK1, JAK2, JAK3, and TYK2 from the JAK kinases family are involved in intracellular signal transduction in the signaling pathway JAK-STAT, and play significant role in the activation of STAT proteins and initiation of transcription. Activation of JAK kinases is believed to be one of the factors of the proliferation of neoplastic cells. The activity of transcriptional factor STAT in a cell depends on its phosphorylation level. High STAT phosphorylation levels lead to pathological myeloproliferative disorders and leukemias. Phosphorylation level, in turn, is dependent on activity of JAK2 kinase - inhibition of JAK2 kinase causes lowering of the phosphorylation level and transcriptional activity of STAT. Kinase JAK2 is also activated in the range of solid tumors and leukemias. Therefore, kinase JAK2 inhibitors block specific signaling pathway which can lead to excessive proliferation of cells and neoplasm development, and can find use in the treatment of myeloproliferative and neoplastic diseases.

WO2008/030579 discloses very broad group of imidazo[1,2-b]pyridazine derivatives as modulators of interleukine-1 receptors associated kinase (IRAK), potentially useful in the treatment of inflammatory diseases, cell proliferation disorders and immunological diseases mediated by IRAK. Neither groups of compounds substituted with methylmorpholinyl group in the position 8 of the imidazo[1,2-b]pyridazine moiety and/or compounds substituted in the position 6 of the imidazo[1,2-b]pyridazine moiety with phenyl or unsaturated heterocyclic group having at least one nitrogen atom bonded via -NH- bridge, nor specific compounds falling into such groups are disclosed.

WO2010/074947 discloses single compound 3-(4-chloro-2-fluorobenzyl)-2-methyl-N-(5-methyl-1 H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine as a selective JAK-2 inhibitor, of potential utility in the treatment myeloproliferative and neoplastic diseases. This compound, known now under code designation LY-2784544, shows selectivity with respect to JAK2 receptor against JAK3 and is currently in the second phase of clinical trials. There is no suggestion as to the possibility and the type of modification of the structure of the disclosed compound required to obtain further JAK-2 inhibitors.
There is still a need for new highly effective compounds showing the ability to inhibit JAK2 kinase with high potency and/or high selectivity and potential use in the treatment of myeloproliferative and neoplastic diseases.

The invention relates to new compounds represented by the general formula (I)

![Chemical Structure]

wherein:
- $R^1$ represents H or C1-C4 alkyl;
- $R^2$ represents phenyl substituted with one or two substituents selected from the group consisting of halogen atom and -OC1-C4 alkyl;
- $R^3$ represents phenyl or 5- to 10-membered monocyclic or bicyclic heteroaryl with 1 to 4 ring heteroatoms selected from the group consisting of N, S, and O, which is unsubstituted or substituted with a substituent selected from halogen atom, Cl-C4-alkyl, and C(0)-C1-C4-alkyl; and
- $X$ represents -CH$_2$- group or -C(0)- group;

and their acid addition salts;

with the exclusion of 3-(4-chloro-2-fluorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine and its salts.

It has been found that new imidazo[1,2-b]pyridazin-6-amine compounds of the invention show potent ability of selective inhibition of the enzyme kinase JAK2 and advantageous pharmacokinetic properties.

Accordingly, the object of the invention is the compound of formula (I) as defined above for use as a medicament.

The object of the invention is also a pharmaceutical composition, comprising as an active ingredient a compound of the general formula (I) as defined above in combination with pharmaceutically acceptable excipients.

As kinase JAK2 inhibitors, the compounds of formula (I) as defined above can find use in the treatment of myeloproliferative and neoplastic diseases.
Accordingly, the object of the invention is the compound of formula (I) as defined above for use in a method of treatment of myeloproliferative disorders and neoplastic diseases.

The object of the invention is also a use of the compound of formula (I) as defined above for the preparation of a medicament for the treatment of myeloproliferative disorders and neoplastic diseases.

The object of the invention is also a method of treatment of myeloproliferative disorders and neoplastic diseases in a mammal subject, including humans, which comprises administration to the subject in need thereof a therapeutically effective amount of a compound of the general formula (I) or a pharmaceutical composition as defined above.

One embodiment of the invention is the compound of the above formula (I), wherein X represents \(-\text{CH}_2\)- group (i.e. methylene group).

Another embodiment of the invention is the compound of the above formula (I), wherein X represents \(-\text{C(O)}\)- group (i.e. carbonyl group).

Another embodiment of the invention is the compound of the above formula (I), wherein \(R^1\) represents H.

Another specific embodiment of the invention is the compound of the above formula (I), wherein \(R^1\) represents \(\text{CH}_3\).

Further specific embodiment of the invention is the compound of the above formula (I), wherein \(R^2\) represents phenyl substituted with fluorine atom.

Further specific embodiment of the invention is the compound of the above formula (I), wherein \(R^2\) represents phenyl substituted with one fluorine atom and one chlorine atom.

Further specific embodiment of the invention is the compound of the above formula (I), wherein \(R^2\) represents phenyl substituted with two chlorine atoms.

Further specific embodiment of the invention is the compound of the above formula (I), wherein \(R^2\) represents phenyl substituted with two fluorine atoms.

Further specific embodiment of the invention is the compound of the above formula (I), wherein \(R^2\) represents phenyl substituted with halogen atom, especially fluorine atom, and \(-\text{OCI}_2\)-C\(_4\)-alkyl, especially \(-\text{OCH}_3\).

Another specific embodiment of the invention is the compound of the above formula (I), wherein \(R^2\) represents phenyl.

Another specific embodiment of the invention is the compound of the above formula (I), wherein \(R^3\) represents 6-membered heteroaryl, which is
unsubstituted or substituted with a substituent as specified above, in particular halogen atom, especially fluorine or chlorine atom, or C1-C4-alkyl, especially methyl, or -C(0)0-C1-C4-alkyl, especially -C(0)0-CH2-CH3.

In particular, 6-membered heteroaryl can be a pyridinyl, such as 2-pyridinyl, 3-pyridinyl or 4-pyridinyl, unsubstituted or substituted with a substituent such as specified above, in particular halogen atom, especially fluorine atom, or C1-C4-alkyl, especially methyl, or -C(0)0-C1-C4-alkyl, especially -C(0)0-CH2-CH3.

6-Membered heteroaryl can also be a heteroaryl containing 2 nitrogen atoms, in particular pyridazinyl or pyrimidinyl, unsubstituted or substituted with a substituent such as specified above, in particular halogen atom, especially chlorine atom.

Another specific embodiment of the invention is the compound of the above formula (I), wherein R6 represents 5-membered heteroaryl containing 2 nitrogen atoms, such as pyrazolyl or imidazolyl, 5-membered heteroaryl containing 2 nitrogen atoms and one sulphur atom, such as thiadiazolyl, or 5-membered heteroaryl containing one nitrogen atom and one sulphur atom, such as thiazolyl, which are unsubstituted or substituted with a substituent such as specified above, in particular halogen atom, especially fluorine atom, C1-C4-alkyl, especially methyl, or -C(0)0-C1-C4-alkyl, especially -C(0)0-CH3.

Specific embodiments of the invention are the compounds selected from the group consisting of the following:

1. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-phenyl-imidazo[1,2-b]pyridazin-6-amine;
2. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(pyridin-2-yl)imidazo[1,2-b]pyridazin-6-amine;
3. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-A/-[5-fluoropyridin-2-yl]-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
4. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(6-methylpyridin-2-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
5. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-/V-(3-methylpyridin-2-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
6. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(pyridazin-3-yl)imidazo[1,2-b]pyridazin-6-amine;
7. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(pyridazin-3-yl)imidazo[1,2-fc]pyridazin-6-amine;
8. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(5-chloropyrimidin-4-yl)imidazo[1,2-b]pyridazin-6-amine;
9. 3-(4-Chloro-2-fluorobenzyl)-N-(5-chloropyrimidin-2-yl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
10. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
11. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
12. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-A/-1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
13. Ethyl 3-(3-(4-chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-imidazo[1,2-b]pyridazin-6-ylamino)-1H-pyrazole-4-carboxylate;
14. 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(1H-1,2,4-triazol-3-yl)imidazo[1,2-b]pyridazin-6-amine;
15. N-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-yl)-5-methylthiazol-2-amine;
16. N-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-yl)-4-methylthiazol-2-amine;
17. Methyl 2-(3-(4-chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-imidazo[1,2-b]pyridazin-6-ylamino)thiazole-5-carboxylate;
18. N-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-yl)-1,3,4-thiadiazol-2-amine;
19. 3-(4-Fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
20. 3-(4-Fluorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
21. 3-(2,4-Difluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
22. 3-(2,4-Difluorobenzyl)-2-methyl-A/-5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
23. (2,4-Difluorophenyl)(2-methyl-6-(5-methyl-1H-pyrazol-3-ylamino)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)methanone;
24. 3-(2,4-Dichlorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
25. 3-(2,4-Dichlorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
26. 3-(2-Fluoro-4-methoxybenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
27. 3-(4-Fluorobenzyl)-W-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
28. 3-(2,4-Difluorobenzyl)-2-methyl-A/-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
29. 3-(2,4-Dichlorobenzyl)-2-methyl-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine;
and their acid addition salts.

In the present description and claims the term "-C₄-alkyl" encompasses -CH₃ (methyl), -CH₂CH₃ (ethyl), -CH₂CH₂CH₃ (n-propyl), -CH(CH₃)₂ (isopropyl), -CH₂CH₂CH₂CH₃ (n-butyl), -CH₂CH(CH₃)₂ (isobutyl), -CH(CH₃)CH₂CH₃ (sec-butyl) and -C(CH₃)₃ (tert-butyl) groups.

The term "halogen" encompasses fluorine (F), chlorine (Cl), bromine (Br) and iodine (I) atoms.

The term "5- to 10-membered monocyclic or bicyclic heteroaryl containing 1 to 4 ring heteroatoms selected from the group consisting of N, S, and O" encompasses 5-membered and 6-membered monocyclic heteroaryls as well as 9-membered and 10-membered bicyclic heteroaryls.

In particular, one can mention 5-membered monocyclic heteroaryls, including heteroaryls containing 1 nitrogen atom, such as pyrrolyl, 2 nitrogen atoms, such as pyrazolyl and imidazolyl, 3 nitrogen atoms, such as triazolyl, such as 1,2,4-triazole, and 4 nitrogen atoms, such as 1H-tetrazolyl. Among 5-membered monocyclic heteroaryls one can also mention heteroaryls containing 1 nitrogen atom and 1 sulphur atom, such as thiazolyl and isothiazolyl, and heteroaryls containing 2 nitrogen atoms and 1 sulphur atom, such as thiadiazolyl.

In particular one can also mention 6-membered monocyclic heteroaryls, including heteroaryls containing 1 nitrogen atom, such as pyridinyl, and heteroaryls containing 2 nitrogen atom (diazines), such as pyridazinyl, pyrimidinyl and pirazynyl.

One can also mention, in particular, 9-membered bicyclic heteroaryls, including heteroaryls containing 1 nitrogen atom, such as indolyl, isoindolyl and
indolizynyl, heteroaryls containing 2 nitrogen atoms, such as benzimidazolyl and indazolyl, as well as heteroaryls containing 4 nitrogen atoms, such as purinyl.

One can also mention, in particular, 10-membered bicyclic heteroaryls, including heteroaryls containing 1 nitrogen atom, such as quinolinyl and isoquinolinyl, and heteroaryls containing 2 nitrogen atoms, such as quinazolinyl, quinoxalinyl and cinnolinyl.

It should be understood that when the compound of formula (I) of the invention contains chiral center, such compound can exist in the form of optical isomers or their mixtures. Such optical isomers and their mixtures at different ratios, including racemic mixtures, are included in the scope of the invention.

Acid addition salts of the compounds of formula (I) of the invention include salts with inorganic or organic acids. Preferred are salts that are pharmaceutically acceptable. Inorganic and organic acids that can form pharmaceutically acceptable salts with compounds having basic nitrogen atom are well known in the art. Salts with inorganic acids especially comprise those of hydrochloric, hydrobromic, sulfuric, and phosphoric acids. Salts with organic acids especially comprise those of methanesulfonic, ethanesulfonic, toluenesulfonic, benzenesulfonic, naphthalenedisulfonic, formic, acetic, propionic, lactic, tartaric, malic, citric, fumaric, maleic, and benzoic acids.

The compounds of formula (I) of the invention can be prepared by reaction of a compound of formula (II), wherein R¹, R² and X have the meanings as given above for formula (I), with an amine compound of formula (III), wherein R³ has the meaning as given above for formula (I), in accordance with Scheme 1.

Scheme 1

The reaction between compound (II) and amine compound (III) can be carried out as Buchwald-Hartwig coupling reaction, in a solvent, in the presence of a palladium catalyst, a phosphine ligand and an inorganic or organic base. Solvents used in the reaction can be aprotic solvents such as benzene, toluene, xylene, tetrahydrofuran, dioxane, dimethoxyethane, diethoxyethane, or protic solvents such as butanol, water or a mixture of these solvents. Amine R³-NH₂ is used in
the amount of 1 to 3 molar equivalents per 1 equivalent of the compound of formula (II). Palladium catalyst can be tris(dibenzyldieneacetone)dipalladium(0) (a preferred one), bis(dibenzyldieneacetone)palladium(0), palladium(II) acetate or 1,1'-bis(diphenylphosphino)ferrocene. Palladium catalyst is used in the amount of 0.05 to 0.10 molar equivalents per 1 equivalent of the compound of formula (II). Phosphine ligands used in the reaction can be Xantphos - 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene or BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl. Phosphine ligand is used in the amount of 0.10 to 0.20 molar equivalents per 1 equivalent of the compound of formula (II). As inorganic or organic base sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, or potassium tert-butanolate, in the amount of 1.05 to 1.5 molar equivalents per 1 equivalent of the compound of formula (II) can be used. The reaction is carried out in strictly oxygen-free conditions in the atmosphere of inert gas such as argon or nitrogen. The reaction is carried out at the solvent reflux temperature.

In the case when \( R \) in formula (III) is a heteroaryl group containing nitrogen atom substituted with hydrogen (-NH-) as a member of the ring, which may compete in the coupling reaction leading to undesired side product, it is recommended to protect such nitrogen atom in order to maximise yield. Therefore, in such a case coupling reaction is carried out using a compound of formula (III) with \( R \) as a heteroaryl group containing protected nitrogen atom. After completion of the coupling reaction protecting group is removed to obtain corresponding unprotected compound of formula (I). This relates among others to compounds wherein \( R \) group is derived from pyrrol, pyrazol, imidazol, triazol and tetrazol, and is selected from 1H-pyrol, 1H-pyrazol, 1H-imidazol, 1H-1,2,3-triazol, 4H-1,2,4-triazol, 1H-1,2,4-triazol, 1H-tetrazol, and 2H-tetrazol.

Typical nitrogen atom protecting groups chosen from tert-butil, tert-butoxy carbonyl, benzyl, \( \text{p}{\text{a}} \)-methoxybenzyl or dimethoxybenzyl groups can be used.

Protecting groups are introduced in accordance with methods of protecting nitrogen functional groups commonly known in the literature, that is by introducing tert-butoxy carbonyl group (Boc) in the reaction with tert-butoxy carbonyl anhydride, introducing benzyl group (Bz) in the reaction with halide such as benzyl chloride or bromide, introducing para-methoxybenzyl group (Pmb) in the reaction with para-methoxybenzyl halide such as para-methoxybenzyl chloride or bromide, introducing dimethoxybenzyl group (Dmb) in the reaction with dimethoxybenzyl halide such as dimethoxybenzyl chloride or bromide. Product of protection reaction is purified by column chromatography on silicagel stationary phase.
In the case when R³ represents 1H-pyrazolyl group, advantageous protecting group is tert-butyl (t-Bu). In such a case the compound with -N-t-Bu group can be obtained directly in the reaction of synthesis of amine (III). For example, 1-tert-butyl-3-methyl-1H-pyrazol-5-amine is prepared in accordance with the procedure described in Org. Process. Res. Rev. 2012, 16, 70-81 by reacting tert-butylhydrazine hydrochloride and 3-aminobut-2-enenitrile in the presence of aqueous solution of sodium hydroxide. Analogously other 1H-pyrazol-5-amines functionalized in the position 3 and/or position 4 can be obtained.

Removal of the -NH- group protecting group from substituent R³ in the compound of formula (I) is also carried out in a known, conventional manner. Conditions of deprotection step depend on the type of protecting group.

tert-Butyl group can be removed in the reaction with trifluoroacetic acid with the addition of water. In this reaction it is possible, although not necessary, to use a solvent such as dichloromethane or chloroform. It is advantageous to use the mixture of trifluoroacetic acid and water at the volume ratio from 1 : 4 to 1 : 5 using from 15 to 40 molar equivalents of trifluoroacetic acid per 1 equivalent of deprotected compound. The reaction is carried out in the temperature range 0 to 120°C. Advantageously, the reaction is carried out in the temperature range 80 to 100°C.

tert-Butoxycarbonyl group can be removed in the reaction with an acid, such as acetic, trifluoroacetic, hydrochloric or sulfuric acid with or without the addition of water.
Benzyl, para-methoxybenzyl, and dimethoxybenzyl groups can be removed in the reaction with trifluoroacetic acid with or without the addition of water.

Amines R³-NH₂ of formula (III) are commercially available. Alternatively, amines (III) can be prepared from commercially available corresponding nitro derivatives by reduction of nitro group to amine group using reductive conditions, such as Pd/C catalyzed hydrogenation, tin(II) chloride SnCl₂ in aqueous medium, or iron in aqueous medium.

Starting compounds of formula (II) can be prepared in accordance with Scheme 2.
In accordance with Scheme 2, to obtain the compound of formula (VI), 6-chloropyridazin-3-amine of formula (IV) is condensed with acetal of formula (V), wherein R' represent C1-C4 alkyl such as methyl, ethyl, propyl, isopropyl, butyl, or both R' groups can be joined with each other to form aliphatic C2-C4 chain such as ethylene, propylene, or butylene, forming with neighbouring oxygen atoms and bridging carbon atom a heterocycle such as 1,3-dioxolane, 1,3-dioxane or 1,3-dioxepane, R" represent methyl or ethyl, and R'1 has the meaning such as given above for the compounds of formula (I). Advantageous R' group is methyl, and advantageous R" group is methyl. It is advantageous to use the excess of the compound of formula (V) with respect to the compound of formula (IV) in the range from 1.2 to 3 molar equivalents. The reaction is carried out in an aprotic solvent such as benzene, toluene, xylene, alkyl (C2-C4) ether, tetrahydrofuran, 1,4-dioxane. Preferred solvent is toluene. The reaction is carried out in the temperature range 60 - 120°C, preferably 80 - 90°C.

Subsequently, thus obtained compound of formula (VI) is cyclized with 2-chloroethanone of formula (VII) to form a compound of formula (VIII). Cyclization is carried out in a solvent with the addition of a bromide salt. The
solvent can be dimethylformamide, N-methylpyrrolidone, acetonitrile, acetone, preferably dimethylformamide. The bromide salt can be lithium bromide, sodium bromide, or potassium bromide, preferably sodium bromide. The amount of the bromide salt is in the range 0.9 to 1.0 molar equivalents per 1 equivalent of the compound of formula (VI). The amount of the compound of formula (VII) is in the range 0.9 to 1.1 molar equivalents per 1 equivalent of the compound of formula (VI). The reaction is carried out under the inert gas atmosphere such as nitrogen or argon, in the temperature range 0 to 120°C. Preferred temperature is in the range 25 to 40°C.

Subsequently, the addition of A/-methylmorpholine moiety to the imidazo[1,2-t]-pyridazine ring is performed by the reaction of thus obtained compound of formula (VIII) with N-methylmorpholine N-oxide carried out in a solvent with the use of a catalyst. It is advantageous to use an excess of A/-methylmorpholine N-oxide with respect to the compound of formula (VIII) in the amount of 5 to 15 molar equivalents per 1 equivalent of the compound of formula (VIII). Advantageous is 7- to 10-fold excess. The solvent can be an alcohol, such as methanol, ethanol, propanol, isopropanol, or dichloromethane or chloroform. Preferred solvent is ethanol. Vanadyl acetylacetonate can be used as the catalyst, in the amount 0.05 to 0.25 molar equivalents per 1 equivalent of the compound of formula (VIII). Preferably, the amount of the catalyst is 0.20 molar equivalents per 1 equivalent of the compound of formula (VIII). The reaction is carried out under inert gas atmosphere, such as nitrogen or argon, in the temperature range 0 to 100°C. Preferred temperature is in the range 35 to 45°C.

In this manner the compounds of formula (II) wherein X represents carbonyl group -C(O)- can be obtained.

The compounds of formula (II) wherein X represents methylene group -CH₂- can be obtained from corresponding compound of formula (II) wherein X represents carbonyl group -C(O)- by reduction of carbonyl group.

Reduction of carbonyl group in the compound of formula (II) to the group -CH₂- is carried out using triethylsilane in trifluoroacetic acid as a solvent. Triethylsilane is used in the amount of 5 to 10 molar equivalents per 1 equivalent of the compound of formula (II). Preferably, trifluoroacetic acid is used in the excess with respect to the compound of formula (II) of 10 to 12 molar equivalents per 1 equivalent of the compound of formula (II). The reaction is carried out under inert gas atmosphere, such as nitrogen or argon. The reaction is carried out at the solvent reflux temperature.

Alternatively, reduction of carbonyl group in the compound of formula (II) to -CH₂- group can be carried out in two steps. In the first step, carbonyl group in the compound of formula (II) is reduced to hydroxyl group using sodium borohydride (preferably) or lithium borohydride as a reducing agent, in methanol
(preferably) or ethanol as a solvent. In the second step, hydroxyl group is reduced to methylene group with triethylsilane as the reducing agent in trifluoroacetic acid as a solvent.

Starting 2-chloroethanones of formula (VII) wherein R² has the meaning as defined above for the compounds of formula (I) are commercially available or can be obtained by chlorination of the corresponding ethanone (IX) in accordance with Scheme 3. Chlorination of the compound of formula (IX) can be carried out using sulfuryl chloride, preferably in the excess of 1.1 to 1.5 molar equivalents per 1 equivalent of the compound of formula (IX). Methanol is used in the reaction, and can be also replaced with another alcohol such as ethanol, propanol or isopropanol. Alcohol is used in the amount of 1 to 2 molar equivalents per 1 equivalents of the compound of formula (IX). Chlorination is carried out in a solvent such as dichloromethane, chloroform, hexane or heptane (preferably dichloromethane). The reaction is carried out in the temperature range -10°C to 0°C.

Scheme 3

The compounds of formula (I) can be administered in the treatment in the form of a pharmaceutical composition or preparation containing them.

The object of the invention is therefore also a pharmaceutical composition comprising as an active ingredient a compound or compounds of formula (I) as defined above in the mixture with pharmaceutically acceptable excipients.

The invention relates also to a method for treating myeloproliferative and neoplastic diseases in a mammal subject, including humans, which comprises administration to the subject in need thereof of a therapeutically effective amount of the compound of the above formula (I) or a pharmaceutical composition comprising said compound of the above formula (I) as an active ingredient.

In the treatment of diseases mentioned above the compounds of formula (I) of the invention can be administered as a chemical compound, but usually will be used in the form of pharmaceutical compositions comprising the compound of the invention or its pharmaceutically acceptable salt such as defined above as the active ingredient, in combination with pharmaceutically acceptable carriers and excipients.
In the treatment of diseases mentioned above the compositions of the invention will be administered by any route, preferably by oral route or parenteral route and will have the form of a preparation destined for use in medicine, depending on the intended route of administration.

Compositions for oral administration can have a form of solid or liquid preparations. Solid preparations can have the form of, for example, tablets or capsules produced in a conventional manner from pharmaceutically acceptable inactive excipients such as binders (for example, pregelatinised corn starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (for example lactose, saccharose or calcium hydrogenphosphate), lubricants (for example magnesium stearate, talc or silica), wetting agents (for example sodium laurylsulfate). Tablets can be coated with simple coatings, delayed/controlled-release coatings or enteral coatings well known in the art. Liquid preparations for oral administration can be in the form of, for example, solutions, syrups or suspensions, or can have the form of a dry solid product for reconstitution with water or other suitable vehicles before use. Such liquid preparations can be prepared using conventional means from pharmaceutically acceptable excipients, such as suspending agents (for example sorbitol syrup, cellulose derivatives or hydrogenated edible oils), emulsifiers (for example lecithine or acacia gum), nonaqueous vehicles (for example mandelic oil, oil esters, ethyl alcohol or fractionated vegetable oils), and preservatives (for example methyl or propyl p-hydroxybenzoate or sorbic acid). Preparations can also include suitable buffering agents, flavoring agents and sweeteners.

Preparations for oral administration can be formulated so as to obtain controlled release of the active compound using methods known for a person skilled in the art.

Parenteral route of administration includes administration by intramuscular and intravenous injections, as well as intravenous infusions. Compositions for parenteral administration can, for example, have the form of unit dosage form, such as ampoules, or multidosage containers, with the addition of a preservative. Compositions can have the form such as suspensions, solutions or emulsions in oily or aqueous vehicles, and can include excipients such as suspending agents, stabilizers, and/or dispersing agents. Alternatively, the active ingredient can have the form of a powder for reconstitution before use in a suitable carrier, for example sterile, pyrogen-free water.

The method of treatment with the use of the compounds of the present invention will comprise administration of a therapeutically effective amount of the compound of the invention, preferably in the form of a pharmaceutical composition, to the subject in need of such treatment.
Proposed dosage of the compounds of the invention is from 0.1 to about 1000 mg per day, in a single dose or in divided doses. It will be apparent for a person skilled in the art that the selection of a dosage required for obtaining desirable biological effect will depend on many factors, for example specific compound, the application, the manner of administration, the age and condition of a patient and that exact dosage will be ultimately found by a responsible physician.

Examples

Intermediates

Intermediate \( P_1 \): 1-tert-Butyl-3-methyl-1H-pyrazol-5-amine

\[
\begin{align*}
\text{tert-Butylhydrazine hydrochloride (15.2 g, 122 mmol) was added to the aqueous solution of sodium hydroxide (60 mL, 2M, 122 mmol) and stirred until dissolution of a solid. To the mixture 3-aminobut-2-enenitrile (10 g, 122 mmol) was added. The reaction mixture was stirred while heating at 90°C for 18 hours, then cooled to room temperature and extracted with dichloromethane (3 \times 50 mL). Organic layers were combined, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to obtain title product as a white, amorphous solid with the yield of 92\% (17.2 g, 112 mmol).} 
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.25 (t, \( J=8.3 \) Hz, 1H), 6.50 (d, \( J=8.3 \) Hz, 2H), 3.88 (s, 6H).

Intermediate \( P_2 \): 1-Methyl-4-nitro-1H-imidazole

\[
\begin{align*}
\text{To the mixture of 4-nitro-1H-imidazole (3.00 g, 17.7 mmol), potassium carbonate (3.67 g, 26.5 mmol) and acetonitrile (20 mL) iodomethane (1.32 mL, 21.2 mmol) was added during 10 minutes. The reaction mixture was stirred while heating at 65°C for 20 hours, cooled to room temperature and filtered through the sintered glass funnel. Filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: chloroform/methanol 98:2 to 90:10, v/v) to obtain an amorphous, creamy solid. The solid was hot-crystallized from isopropanol to obtain after filtration and}
\end{align*}
\]
drying title product in the form of light-creamy crystals with the yield of 70% (1.58 g, 12.4 mmol). Melting point 134.7-135.3°C.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.79 (d, J=1.4 Hz, 1H), 7.44 (s, 1H), 3.84 (s, 3H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 148.1, 136.7, 120.3, 34.60.

**Intermediate P3:** 1-Methyl-4-nitro-1H-pyrazole

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{N} \\
\text{O}
\end{array}
\]

To the solution of 4-nitro-1H-pyrazole (200 mg, 1.77 mol) in acetonitrile (2 mL) at 0°C, under argon atmosphere, sodium hydride (106 mg, 2.65 mmol, 60% solution in mineral oil) was added. Reaction mixture was stirred at room temperature for 1 hour. To the reaction mixture methyl iodide (121 \(\mu\)l, 1.95 mmol) was added during 5 minutes. After 10 minutes water (10 mL) was added. The mixture was poured onto sodium thiosulfate solution (10 mL, 5%). The mixture was extracted with ethyl acetate (3 x 15 mL). Organic layers were combined, washed with brine, dried (Na\(_2\)SO\(_4\)) and evaporated under reduced pressure. Remaining solid was purified by column chromatography (silica gel, eluent: heptane/diethyl ether 100:0 to 20:80, v/v). Resulted creamy solid was dissolved in boiling isopropanol and then cooled to 0°C. Crystallized light-yellow crystals were filtered and dried to obtain title product with the yield of 95% (214 mg, 1.68 mmol).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.18 (s, 1H), 8.05 (s, 1H), 3.99 (s, 3H).

**Intermediate P4:** (Z)-N’-(6-Chloropyridazin-3-yl)-N,N-dimethylformimidamide

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{N} \\
\text{Cl}
\end{array}
\]

To the solution of 6-chloropyridazin-3-amine (15.0 g, 116 mmol) in toluene (150 mL) N,N-dimethylformamide dimethyl acetal (27.8 mL, 208 mmol) was added. The reaction mixture was stirred while heating at 80°C for 20 hours, then concentrated under reduced pressure to the volume of 50 mL, added with heptane and cooled to 0°C. Precipitated white crystals were filtered, washed with heptane and dried, to obtain title product with the yield of 91% (19.4 g, 105 mmol).

MS-ESI: (m/z) calculated for C\(_7\)H\(_{10}\)ClN\(_4\) [M+H]\(^+\): 185.1, found 185.0.

\(^1\)H NMR (300 MHz, DMSO-d\(_6\)) 8.49 (s, 1H), 7.59 (d, J=9.0 Hz, 1H), 7.17 (d, .7=9.0 Hz, 1H). 3.15 (s, 3H), 3.03 (s, 3H).

\(^13\)C NMR (75 MHz, DMSO-cck) 163.4, 155.6, 149.8, 129.4, 125.5, 40.2, 34.3.

**Intermediate P5:** (Z)-N’-(6-Chloropyridazin-3-yl)-N,N-dimethylacetimidoamide
Title product was obtained according to the method described above for Intermediate P4, using 6-chloropyridazin-3-amine (10.0 g, 77 mmol), N,N-dimethylacetamide dimethyl acetal (20.7 mL, 106 mmol) and toluene (100 mL). Product was obtained in the form of white crystals with the yield of 97% (13.9 g, 75 mmol).

MS-ESI: (m/z) calculated for C₈H₂₇N₂Cl [M+H]⁺: 199.1, found 199.1.

1H NMR (300 MHz, DMSO-d₆) 7.55 (d, J=8.8 Hz, 1H), 7.01 (d, J=8.8 Hz, 1H), 3.05 (s, 6H), 2.01 (s, 3H).

Intermediate P6: 2-Chloro-1-(4-chloro-2-fluorophenyl)ethanone

To the mixture of 1-(4-chloro-2-fluorophenyl)ethanone (4.00 g, 23.2 mmol), dichloromethane (12 mL) and methanol (1.6 mL) cooled to 0°C under argon atmosphere sulfuryl chloride (2.35 mL, 29.0 mmol) solution in dichloromethane (5 mL) was added during 10 minutes. The reaction mixture was stirred for 24 hours at room temperature. Then, the reaction mixture was cooled to 0°C and 14% aqueous solution of sodium hydroxide (20 mL) was added. The mixture was extracted with dichloromethane (2 × 20 mL). Organic layers were combined, washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. Remaining solid was dissolved in boiling ethyl acetate and heptane was added to crystallize crystals. White crystals were filtered and washed with heptane to obtain title product with the yield of 57% (2.74 g, 13.2 mmol).

1H NMR (500 MHz, CDCl₃) δ 7.93 (t, J=8.1 Hz, 1H), 7.29 (dd, J=9.0 Hz, 1.2 Hz, 1H), 7.23 (dd, J=10.8 Hz, 1.9 Hz, 1H), 4.70 (d, J=2.9 Hz, 2H).

13C NMR (125 MHz, CDCl₃) δ 188.1, 162.6, 141.5, 132.2 (d, J=3.7 Hz), 125.6 (d, J=3.2 Hz), 121.1, 117.3 (d, J=27.2 Hz), 49.8 (d, J=11.5 Hz).

Intermediate P7: (6-Chloroimidazo[1,2-b]pyridazin-3-yl)(4-fluorophenyl)methanone

The mixture of (Z)-A'--(6-chloropyridazin-3-yl)-N,N-dimethylformimidoamide (Intermediate P4) (2.00 g, 10.8 mmol), 2-chloro-1-(4-fluorophenyl)ethanone
(1.78 g, 10.3 mmol) and dimethylformamide (10 mL) was stirred at room temperature under argon atmosphere for 15 minutes. Sodium bromide (1.10 g, 10.7 mmol) was added and the reaction mixture was heated at 35°C for 24 hours. The reaction mixture was cooled to room temperature, methanol/water mixture (4.4 mL, 1:1, v/v) was added and stirred for 2 hours. Precipitated white solid was filtered, washed with methanol/water mixture (30 mL, 1:1, v/v) and dried to obtain title product with the yield of 58% (1.74 g, 6.3 mmol).

MS-ESI: (m/z) calculated for C₁₃H₈N₃OClF [M+H]⁺: 276.0, found 275.8.

Intermediate P8: (6-Chloro-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(4-fluorophenyl)methanone

To the mixture of (6-chloroimidazo[1,2-b]pyridazin-3-yl)(4-fluorophenyl)methanone (Intermediate P7) (1.72 g, 6.25 mmol), vanadyl acetylacetonate (0.331 g, 1.25 mmol) and ethanol (10 mL) at 30°C under argon atmosphere the solution of N-methylmorpholine N-oxide (8.44 g, 62.5 mmol) in ethanol (10 mL) was added during 10 minutes. The reaction mixture was stirred while heating at 40°C for 20 hours, then cooled to room temperature, water (30 mL) was added and extracted with ethyl acetate (3 x 30 mL). Organic layers were combined, washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: heptane/AcOEt 80:20 to 0:100, v/v) to obtain amorphous, white solid. The solid was hot-crystallized from AcOEt/heptane. Crystallized white crystals were filtered and dried to obtain title product with the yield of 62% (1.45 g, 3.87 mmol).

MS-ESI: (m/z) calculated for C₁₈H₁₇ClFN₂O₂ [M+H]⁺: 375.1, found 375.0.

Intermediate P9: 4-((6-Chloro-3-(4-fluorobenzyl)imidazo[1,2-b]pyridazin-8-yl)methyl)morpholine

The mixture of (6-chloro-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(4-fluoropheny) methanone (Intermediate P8) (1.00 g, 2.67 mmol), trifluoroacetic
acid (2.25 mL, 29.4 mmol) and triethylsilane (3.84 mL, 24.0 mmol) was stirred while heating at 80-90 °C under argon atmosphere for 20 hours. Reaction mixture was cooled to room temperature, then water (10 mL) and ethanol (5 mL) were added. To the mixture ethyl acetate (30 mL) and 30% aqueous solution of sodium hydroxide (10 mL) were added and the mixture was stirred for 30 minutes. The mixture was extracted with ethyl acetate (3 x 30 mL), organic layers were combined, washed with brine, dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: heptane/AcOEt 6:4, v/v, to AcOEt 100%). After evaporation and drying title product was obtained in the form of amorphous, white solid with the yield of 89% (0.858 g, 2.38 mmol).

MS-ESI: (m/z) calculated for C$_{18}$H$_{16}$N$_4$OCIFNa [M+Na]+: 383.1, found 383.1.

Intermediates P10: N-(1-tert-Butyl-3-methyl-1H-pyrazol-5-yl)-3-(4-fluoro-benzyl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazyn-6-amine

The mixture of 4-((6-chloro-3-(4-fluorobenzyl)imidazo[1,2-b]pyridazin-8-yl)-methyl)morpholine (Intermediate P9) (200 mg, 0.55 mmol), 1-tert-butyl-3-methyl-1H-pyrazol-5-amine (Intermediate P1) (89 mg, 0.58 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (64 mg, 0.11 mmol), tris(dibenzylideneacetono)dipalladium(0) (50 mg, 0.56 mmol) and sodium carbonate (70 mg, 0.67 mmol) was suspended in degassed toluene (5 mL). Reaction mixture was degassed, purged with argon stream for 30 minutes, and then stirred at 100°C for 44 hours. Reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), filtered through celite layer and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, eluent: heptane/AcOEt 20:80, AcOEt 100% to AcOEt/methanol 98:2, v/v). After evaporation and drying title product was obtained in the form of amorphous white solid with the yield of 96% (253 mg, 0.53 mmol).

MS-ESI: (m/z) calculated for C$_{26}$H$_{33}$N$_7$OF [M+H]+: 478.3, found 478.3.

$^1$H NMR (500 MHz, DMSO-$_d_6$) δ 8.47 (s, 1H), 7.28 (d, J=5.7 Hz, 1H), 7.19 (m, 2H), 7.01 (m, 2H), 6.84 (s, 1H), 5.94 (s, 1H), 4.02 (d, J=4.2 Hz, 2H), 3.78 (d, J=1.0 Hz, 2H), 3.66-3.58 (m, 4H), 2.55-2.45 (m, 4H), 2.18 (s, 3H), 1.50 (s, 9H).


**C NMR (125 MHz, DMSO-\text{d}_6)** \(\delta\) 160.7 (d, \(J=241.3\) Hz), 152.9, 143.8, 137.0, 136.8, 136.1, 134.3 (x2), 130.5 (d, \(J=7.9\) Hz), 128.8, 127.3, 114.7 (d, \(J=21.3\) Hz), 107.2, 103.7, 66.2 (x2), 58.7, 55.3 (x2), 53.4, 29.7 (x3), 28.3, 14.1.

**Intermediate P11:** (6-Chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)(4-fluorophenyl)methanone

![Chemical Structure](image)

Title product was obtained in accordance with the method described above for Intermediate P7, using (Z)-A’-(6-chloropyridazin-3-yl)-N,N’-dimethylacetimidamide (Intermediate P5) (2.00 g, 10.1 mmol), 2-chloro-(4-fluorophenyl)-ethanone (1.65 g, 9.6 mmol), sodium bromide (1.03 g, 10.0 mmol) and dimethylformamide (10 mL). Product was obtained in the form of a white solid with the yield of 61% (1.79 g, 6.2 mmol).

**MS-ESI:** (m/z) calculated for C\(_{14}\)H\(_8\)N\(_2\)OClFNa [M+Na]\(^+\): 312.1, found 312.0.

**Intermediate P12:** (6-Chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(4-fluorophenyl)methanone

![Chemical Structure](image)

Title product was obtained in accordance with the method described above for Intermediate P8, using (6-chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)(4-fluorophenyl)methanone (Intermediate P11) (1.78 g, 6.13 mmol), vanadyl acetyl-acetonate (0.325 g, 1.23 mmol), N-methylmorpholine N-oxide (8.28 g, 61.3 mmol) and ethanol (20 mL). Product was obtained in the form of white crystals with the yield of 61% (1.45 g, 3.74 mmol).

**MS-ESI:** (m/z) calculated for C\(_{19}\)H\(_{19}\)N\(_4\)O\(_2\)ClF [M+H]\(^+\): 389.1, found 389.1.

**Intermediate P13:** 4-((6-Chloro-3-(4-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine

![Chemical Structure](image)
Title product was obtained in accordance with the method described above for Intermediate P9, using (6-chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-t]-pyridazin-3-yl)(4-fluorophenyl) methanone (Intermediate P12) (1.00 g, 2.57 mmol), trifluoroacetic acid (2.17 ml, 28.3 mmol) and triethylsilane (3.70 ml, 23.1 mmol). Product was obtained in the form of white crystals with the yield of 83% (0.80 g, 2.13 mmol).

MS-ESI: (m/z) calculated for C_{19}H_{24}N_{4}OClF [M+H]^+: 375.1, found 375.1.

^1^H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.26-7.22 (m, 2H), 7.19 (t, \(J=1.0\) Hz, 1H), 7.13-7.05 (m, 2H), 4.28 (s, 2H), 3.89 (d, \(J=1.0\) Hz, 2H), 3.68-3.58 (m, 4H), 2.55-2.45 (m, 4H), 2.40 (s, 3H).

^13^C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 160.9 (d, \(J=240.8\) Hz), 157.9, 145.4, 141.0, 138.0, 135.9, 134.1, 129.9 (x2), 124.2, 115.3 (d, \(J=21.4\) Hz), 114.7, 66.2 (x2), 55.3, 53.4 (x2), 27.0, 13.6.

Intermediate P14: A/-(1-(tert-Butyl)-3-methyl-1H-pyrazol-5-yl)-3-(4-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-t]pyrazin-6-amine

Title product was obtained in accordance with the method described above for Intermediate P10, using 4-((6-chloro-3-(4-fluorobenzyl)-2-methylimidazo[1,2-t]pyridazin-8-yl)methyl)morpholine (Intermediate P13) (200 mg, 0.534 mmol) and 1-tert-butyl-3-methyl-1H-pyrazol-5-amine (Intermediate P1) (86 mg, 0.56 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 34% (90 mg, 0.183 mmol).

MS-ESI: (m/z) calculated for C_{27}H_{35}N_{7}O_{3}F [M+H]^+: 492.3, found 492.3.

Intermediate P15: (6-Chloroimidazo[1,2-\(\Xi\)]pyridazin-3-yl)(2,4-difluorophenyl)methanone
Title product was obtained in accordance with the method described above for Intermediate P7, using (Z)-A\textsuperscript{-}N-(6-chloropyridazin-3-yl)-A\textsuperscript{-},N-dimethylformimidoamide (Intermediate P4) (0.50 g, 2.71 mmol), 2-chloro-1-(2,4-difluorophenyl)-ethanone (0.49 g, 2.57 mmol), sodium bromide (0.28 g, 2.68 mmol) and dimethylformamide (2.5 mL). Product was obtained in the form of an amorphous, creamy solid with the yield of 55% (0.43 g, 1.48 mmol).

MS-ESI: (m/z) calculated for C\textsubscript{13}H\textsubscript{6}N\textsubscript{3}OClF\textsubscript{2} [M+Na]\textsuperscript{+}: 316.0, found 316.0.

Intermediate P16: (6-Chloro-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-3-yl)(2,4-difluorophenyl)methanone

Title product was obtained in accordance with the method described above for Intermediate P8, using (6-chloroimidazo[1,2-t]pyridazin-3-yl)(2,4-difluorophenyl)methanone (Intermediate P15) (0.500 g, 1.70 mmol), vanadyl acetylacetonate (0.090 g, 0.34 mmol), N-methylmorpholine N-oxide (2.30 g, 17.0 mmol), and ethanol (15 mL). Product was obtained in the form of white crystals with the yield of 67% (0.445 g, 1.13 mmol).

MS-ESI: (m/z) calculated for C\textsubscript{18}H\textsubscript{19}N\textsubscript{3}OClF\textsubscript{2} [M+H]\textsuperscript{+}: 393.1, found 393.1.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 8.15 (d, \( J=1.3 \) Hz, 1H), 7.72 (dd, \( J=14.7 \) Hz, 8.1 Hz, 1H), 7.50 (s, 1H), 7.04 (m, 1H), 6.93 (m, 1H), 4.03 (s, 2H), 3.80 (m, 4H), 2.63 (m, 4H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 178.3, 165.3 (dd, \( J=254.4 \), \( J=12.0 \) Hz), 160.9 (dd, \( J=254.4 \) Hz, \( J=\text{M.I} \) Hz), 148.9, 142.2 (d, \( J=3.0 \) Hz), 141.1, 139.9, 132.3 (dd, \( J=10.4 \) Hz, 4.0 Hz), 128.2, 120.1, 112.1 (dd, \( J=21.7 \) Hz, 3.6 Hz), 104.7 (t, \( J=25.6 \) Hz), 66.9 (x2), 56.0, 53.8 (x2).

Intermediate P17: 4-((6-Chloro-3-(2,4-difluorobenzyl)imidazo[1,2-t]pyridazin-8-yl)methyl)morpholine
Title product was obtained in accordance with the method described above for Intermediate P9, using (6-chloro-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(2,4-difluorophenyl)methanone (Intermediate P16) (0.440 g, 1.12 mmol), trifluoroacetic acid (0.944 ml, 12.3 mmol), and triethylsilane (1.07 ml, 6.72 mmol). Product was obtained in the form of white crystals with the yield of 94% (0.397 g, 1.05 mmol).

MS-ESI: (m/z) calculated for C_{18}H_{14}F_{2}N_{2}O{H}[M+H]^{+}: 379.1, found 379.1.

1H NMR (500 MHz, CDCl₃) δ 7.47 (s, 1H), 7.27 (m, 2H), 6.83 (m, 2H), 4.29 (s, 2H), 3.97 (d, J=1.1 Hz, 2H), 3.78 (m, 4H), 2.60 (m, 4H).

Intermediate P18: N-(1-(tert-Butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2,4-difluoro-benzyl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for Intermediate P10, using 4-((6-chloro-3-(2,4-difluorobenzyl)imidazo[1,2-b]-pyridazin-8-yl)methyl)morpholine (Intermediate P17) (200 mg, 0.528 mmol) and 1-(tert-butyl)-3-methyl-1H-pyrazol-5-amine (Intermediate P1) (85 mg, 0.55 mmol). Product was obtained in the form of an amorphous, white solid with the yield of 92% (240 mg, 0.484 mmol).

MS-ESI: (m/z) calculated for C_{26}H_{32}N_{2}O{C}_{2}F_{2}[M+H]^{+}: 496.3, found 496.3.

1H NMR (500 MHz, CDCl₃) δ 7.33 (m, 1H), 7.14 (td, J=8.6 Hz, 6.5 Hz, 1H), 6.78 (m, 2H), 6.69 (t, J=1.1 Hz, 1H), 5.93 (s, 1H), 5.87 (s, 1H), 4.18 (s, 2H), 3.87 (d, J=1.2 Hz, 2H), 3.70 (m, 4H), 2.53 (m, 4H), 2.28 (s, 3H), 1.63 (s, 9H).

13C NMR (125 MHz, CDCl₃) δ 161.4 (ddd, J=246.0 Hz, J=108.6 Hz, J=11.8 Hz), 152.6, 145.6, 137.9, 137.2, 131.6 (d, J=5.3 Hz), 131.5 (d, J=5.8 Hz), 130.4, 126.2, 120.7 (dd, J=15.3 Hz, J=3.9 Hz), 111.0 (d, J=3.7 Hz), 110.8 (d, J=3.7 Hz),
106.4, 103.9 (d, J=25.3 Hz), 103.5 (d, J=13.1 Hz), 66.8 (x2), 59.4, 56.0, 53.8 (x2), 30.0 (x3), 22.5, 14.2.

**Intermediate P19**: (6-Chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)(2,4-difluorophenyl)methanone

Title product was obtained in accordance with the method described above for Intermediate P7, using (Z)-N’-(6-chloropyridazin-3-yl)-N,N-dimethylacetimidoamide (Intermediate P5) (2.00 g, 10.1 mmol), 2-chloro-1-(2,4-difluorophenyl)ethanone (1.82 g, 9.57 mmol), sodium bromide (1.03 g, 9.97 mmol) and dimethylformamide (10 mL). Product was obtained in the form of an amorphous light-yellow solid with the yield of 68% (2.12 g, 6.89 mmol).

**Intermediate P20**: (6-Chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(2,4-difluorophenyl)methanone

Title product was obtained in accordance with the method described above for Intermediate P8, using (6-chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)(2,4-difluorophenyl)methanone (Intermediate P19) (2.055 g, 6.68 mmol), vanadyl acetylacetonate (0.354 g, 1.34 mmol), N-methylmorpholine N-oxide (9.03 g, 66.8 mmol), and ethanol (60 mL). Product was obtained in the form of white crystals with the yield of 56% (1.51 g, 3.71 mmol).

**Intermediate P21**: (6-((1-(tert-Butyl)-3-methyl-1H-pyrazol-5-yl)amino)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(2,4-difluorophenyl)methanone

**MS-ESI**: (m/z) calculated for C_{14}H_{9}ClF_{2}N_{3}O [M+H]^+ 308.0, found 308.0.

**1H NMR** (500 MHz, CDCl$_3$) $\delta$ 7.71 (dt, $J=8.2$ Hz, $J=6.6$ Hz, 1H), 7.38 (s, 1H), 7.04 (dt, $J=8.3$ Hz, $J=2.3$ Hz, 1H), 6.83 (dt, $J=8.9$ Hz, $J=2.3$ Hz, 1H), 4.00 (d, $J=1.1$ Hz, 2H), 3.82-3.77 (m, 4H), 2.68 (s, 3H), 2.64-2.60 (m, 4H).
Title product was obtained in accordance with the method described above for Intermediate P10, using (6-chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]-pyridazin-3-yl)(2,4-difluorophenyl)methanone (Intermediate P20) (200 mg, 0.492 mmol) and 1-tert-butyl-3-methyl-1H-pyrazol-5-amine (Intermediate P1) (79 mg, 0.516 mmol). Product was obtained in the form of a yellow oil with the yield of 47% (121 mg, 0.231 mmol). MS-ESI: (m/z) calculated for C_{27}H_{33}N_{7}O_{2}F_{2}Na [M+Na]^+: 546.2, found 546.2.

Intermediate P22: 4-((6-Chloro-3-(2,4-difluorobenzyl)-2-methylimidazo[1,2-b]-pyridazin-8-yl)methyl)morpholine

Title product was obtained in accordance with the method described above for Intermediate P9, using (6-chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]-pyridazin-3-yl)(2,4-difluorophenyl)methanone (Intermediate P20) (1.00 g, 2.46 mmol), trifluoroacetic acid (2.07 ml, 27.0 mmol) and triethylsilane (2.36 mL, 14.7 mmol). Product was obtained in the form of white crystals with the yield of 92% (0.892 g, 2.27 mmol). MS-ESI: (m/z) calculated for C_{19}H_{20}N_{5}OClF_{2} [M+H]^+: 393.1, found 393.1.

Intermediate P23: N-((1-tert-Butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2,4-difluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine
Title product was obtained in accordance with the method described above for Intermediate P10, using 4-((6-chloro-3-(2,4-difluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P22) (200 mg, 0.509 mmol) and 1-terti-butyl-3-methyl-1H-pyrrozol-5-amine (Intermediate P1) (82 mg, 0.535 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 56% (145 mg, 0.285 mmol).

MS-ESI: (m/z) calculated for C_{27}H_{34}N_{7}O_{2} [M+H]+: 510.3, found 510.2.

Intermediate P24: (4-Chloro-2-fluorophenyl)(6-chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)methanone

Title product was obtained in accordance with the method described above for Intermediate P7, using (Z)-A'-(6-chloropyridazin-3-yl)-N,A'-dimethylacetimidoamide (Intermediate P5) (2.01 g, 10.1 mmol), 2-chloro-1-(4-chloro-2-fluorophenyl)ethanone (2.00 g, 9.66 mmol), sodium bromide (1.03 g, 9.97 mmol), and dimethylformamide (10 ml). Product was obtained in the form of a white solid with the yield of 72% (2.25 g, 6.95 mmol).

MS-ESI: (m/z) calculated for C_{14}H_{9}Cl_{2}FN_{3}O [M+H]+: 324.0, found 324.0.

\[^{1}\text{H} \text{NMR (500 MHz, DMSO-}d_{6})\delta 8.29 (d, J=9.1 \text{ Hz, 1H}), 7.67 (t, J=8.1 \text{ Hz, 1H}), 7.60 (d, J=9.6 \text{ Hz, 1H}), 7.59 (dd, J=10.2 \text{ Hz, J=2.1 Hz, 1H}), 7.47 (ddd, J=8.4 \text{ Hz, J=2.4 Hz, J=0.8 Hz, 1H}), 2.54 (s, 3H). \]

\[^{13}\text{C} \text{NMR (125 MHz, DMSO-}d_{6})\delta 179.2, 159.5 (d, J=254.4 \text{ Hz}), 152.1, 146.3, 138.7, 137.4 (d, J=10.4 Hz), 131.2 (d, J=4.8 Hz), 127.4, 126.2 (d, J=13.6 Hz), 125.2 (d, J=13.3 Hz), 124.3, 122.6, 116.4 (d, J=22.6 Hz), 16.0. \]

Intermediate P25: (4-Chloro-2-fluorophenyl)(6-chloro-2-methyl-8-(morpholino-methyl)imidazo[1,2-b]pyrazin-3-yl)methanone

Title product was obtained in accordance with the method described above for Intermediate P8, using (4-chloro-2-fluorophenyl)(6-chloro-2-methylimidazo[1,2-b]pyrazin-3-yl)methanone (Intermediate P24) (2.12 g, 6.54 mmol), vanadyl
acetylacetonate (0.347 g, 1.31 mmol), A/-methylmorpholine N-oxide (8.84 g, 65.4 mmol), and ethanol (60 ml). Product was obtained in the form of white crystals with the yield of 66% (1.83 g, 4.32 mmol).

Title product was obtained in accordance with the method described above for Intermediate P9, using (4-chloro-2-fluorophenyl)(6-chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)methanone (Intermediate P25) (2.00 g, 4.73 mmol), trifluoroacetic acid (3.98 ml, 52.0 mmol), and triethylsilane (4.53 ml, 28.4 mmol). Product was obtained in the form of white crystals with the yield of 91% (1.76 g, 4.30 mmol).

MS-ESI: (m/z) calculated for C_{19}H_{20}Cl_2FN_4O_2 [M+H]^+ : 423.1, found 423.0.

$^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 7.67 (t, J=8.0 Hz, 1H), 7.58 (dd, J=10.4 Hz, J=2.0 Hz, 1H), 7.45 (dd, J=8.6 Hz, J=2.0 Hz, 1H), 7.42 (s, 1H), 3.94 (s, 2H), 3.65 (t, J=4.4 Hz, 4H), 2.55 (s, 3H), 2.52 (t, J=4.6 Hz, 4H).

Intermediate P26: 4-((6-Chloro-3-(4-chloro-2-fluorobenzyl)-2-methylidyimidazo-1,2-t)pyridazin-8-yl)methyl)morpholine

![Structure of Intermediate P26](image)

Title product was obtained in accordance with the method described above for Intermediate P7, using (Z)-A/-A-(6-chloropyridazin-3-yl)-A/,N-dimethylformimidoamide (Intermediate P4) (1.60 g, 8.67 mmol), 2-chloro-1-(2,4-dichlorophenyl)-ethanone (1.57 g, 8.23 mmol), sodium bromide (0.88 g, 8.58 mmol), and dimethylformamide (7.0 ml). Product was obtained in the form of a white solid with the yield of 70% (1.98 g, 6.06 mmol).

MS-ESI: (m/z) calculated for C_{13}H_{7}N_3OCI_3 [M+H]^+ : 326.0, found 326.1.
Title product was obtained in accordance with the method described above for Intermediate P8, using (6-chloroimidazo[1,2-b]pyridazin-3-yl)(2,4-dichlorophenyl)methanone (Intermediate P27) (0.318 g, 1.20 mmol), A/-methylmorpholine N-oxide (8.11 g, 60.0 mmol), and ethanol (60 mL). Product was obtained in the form of white crystals with the yield of 31% (0.80 g, 1.88 mmol).

MS-ESI: (m/z) calculated for C_{31}H_{24}N_{4}O_{3}Cl [M+H]^+: 425.0, found 425.0.

Title product was obtained in accordance with the method described above for Intermediate P9, using (6-chloro-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(2,4-dichlorophenyl)methanone (Intermediate P28) (0.795 g, 1.87 mmol), trifluoroacetic acid (1.57 mL, 20.5 mmol), and triethylsilane (2.69 mL, 16.8 mmol). Product was obtained in the form of white crystals with the yield of 49% (0.360 g, 0.91 mmol).

MS-ESI: (m/z) calculated for C_{19}H_{17}N_{4}O_{3}Cl_{3}Na [M+Na]^+: 433.0, found 433.0.

^{1}H NMR (500 MHz, DMSO-d_{6}) δ 7.64 (s, 1H), 7.53 (s, 1H), 7.37 (s, 1H), 7.28 (s, 2H), 4.36 (s, 2H), 3.92 (s, 2H), 3.63 (s, 4H), 2.51 (s, 4H).

^{13}C NMR (125 MHz, DMSO-d_{6}) δ 146.5, 139.4, 137.4, 134.2, 133.9, 132.6, 132.4, 132.2, 128.9, 127.6, 126.3, 115.6, 66.2 (x2), 55.3, 53.4 (x2), 26.6.

Intermediate P30: N-{(1-(teri-Butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2,4-dichlorobenzyl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Intermediate P28: (6-Chloro-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(2,4-dichlorophenyl)methanone

Intermediate P29: 4-((6-Chloro-3-(2,4-dichlorobenzyl)imidazo[1,2-b]pyridazin-8-yl)methyl)morpholine
Title product was obtained in accordance with the method described above for Intermediate P10, using 4-((6-chloro-3-(2,4-dichlorobenzyl)imidazo[1,2-b]-pyridazin-8-yl)methyl)morpholine (Intermediate P29) (200 mg, 0.486 mmol) and 1-tert-butyl-3-methyl-1H-pyrazol-5-amine (Intermediate P1) (78 mg, 0.510 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 96% (247 mg, 0.467 mmol).

MS-ESI: (m/z) calculated for C_{26}H_{32}N_{7}O_{2} [M+H]^+: 528.2, found 528.2.

1H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1 H), 7.53 (d, J=2.2 Hz, 1 H), 7.29 (s, 1 H), 7.19 (dd, J=8.3 Hz, J=2.2 Hz, 1 H), 7.10 (d, J=8.3 Hz, 1 H), 6.86 (s, 1 H), 5.93 (s, 1 H), 4.11 (s, 2 H), 3.79 (d, J=1.0 Hz, 2 H), 3.66-3.58 (m, 4 H), 2.55-2.45 (m, 4 H), 2.17 (s, 3 H), 1.48 (s, 9 H).

13C NMR (125 MHz, DMSO-d_6) δ 153.4, 144.3, 137.4, 137.3, 136.6, 134.8, 134.5, 133.0, 132.2, 130.2, 129.0, 127.3, 125.1, 107.9, 104.3, 66.7 (x2), 59.2, 55.8, 53.9 (x2), 30.1 (x3), 22.5, 14.5.

**Intermediate P31**: (6-Chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)(2,4-dichlorophenyl)methanone

Title product was obtained in accordance with the method described above for Intermediate P7, using (Z)-N’-(6-chloropyridazin-3-yl)-N,N-dimethylacetimidamide (Intermediate P5) (3.00 g, 15.1 mmol), 2-chloro-1-(2,4-dichlorophenyl)ethanone (2.73 g, 14.3 mmol), sodium bromide (1.54 g, 15.0 mmol), and dimethylformamide (10 mL). Product was obtained in the form of a white solid with the yield of 70% (3.59 g, 10.5 mmol).

MS-ESI: (m/z) calculated for C_{14}H_{9}Cl_{3}N_{3}O [M+H]^+: 340.0, found 340.0.

**Intermediate P32**: (6-Chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]-pyridazin-3-yl)(2,4-dichlorophenyl)methanone
Title product was obtained in accordance with the method described above for Intermediate P8, using (6-chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)(2,4-dichlorophenyl)methanone (Intermediate P31) (2.59 g, 7.60 mmol), vanadyl acetylacetonate (0.403 g, 1.52 mmol), N-methylmorpholine N-oxide (10.3 g, 76.0 mmol), and ethanol (70 ml.). Product was obtained in the form of white crystals with the yield of 66% (2.20 g, 5.00 mmol).

MS-ESI: (m/z) calculated for C_{19}H_{18}Cl_{3}N_{4}O_{2} [M+H]^+ : 439.0, found 439.0.

**Intermediate P33**: 4-((6-Chloro-3-(2,4-dichlorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine

Title product was obtained in accordance with the method described above for Intermediate P9, using (6-chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(2,4-dichlorophenyl)methanone (Intermediate P32) (1.50 g, 3.41 mmol), trifluoroacetic acid (2.87 ml, 37.5 mmol), and triethylsilane (3.27 ml, 20.5 mmol). Product was obtained in the form of white crystals with the yield of 69% (1.01 g, 2.37 mmol).

MS-ESI: (m/z) calculated for C_{19}H_{20}N_{4}O_{3}Cl [M+H]^+ : 425.1 , found 425.0.

**Intermediate P34**: N-(1-(tert-Butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2,4-dichlorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine
Title product was obtained in accordance with the method described above for Intermediate P10, using 4-((6-chloro-3-(2,4-dichlorobenzyl)-2-methylimidazo-[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P33) (200 mg, 0.470 mmol) and 1-teri-butyl-3-methyl-1H-pyrazol-5-amine (Intermediate P1) (76 mg, 0.493 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 72% (184 mg, 0.339 mmol).

MS-ESI: (m/z) calculated for C19H20N4OCI3 [M+H]+: 542.2 found 542.2.

Intermediate P35: (6-Chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)(2-fluoro-4-methoxyphenyl)methanone

Title product was obtained in accordance with the method described above for Intermediate P7, using (Z)-N'-(6-chloropyridazin-3-yl)-N,N-dimethylacetimidoamide (Intermediate P5) (1.70 g, 8.56 mmol), 2-chloro-1-(2-fluoro-4-methoxyphenyl)ethanone (1.55 g, 8.13 mmol), sodium bromide (0.872 g, 8.47 mmol), and dimethylformamide (5 mL). Product was obtained in the form of a white solid with the yield of 73% (2.00 g, 6.26 mmol).

MS-ESI: (m/z) calculated for C15H12ClFN302 [M+H]+: 320.1, found 320.0.

1H NMR (500 MHz, CDCl3) δ 7.89 (d, J=9.4 Hz, 1H), 7.72 (t, J=8.5 Hz, 1H), 7.16 (d, J=9.4 Hz, 1H), 6.83 (dd, J=8.7 Hz, J=2.4 Hz, 1H), 6.58 (dd, J=12.5 Hz, J=2.4 Hz, 1H), 3.89 (s, 3H), 2.65 (s, 3H).

13C NMR (125 MHz, CDCl3) δ 180.2, 164.7 (d, J=1.8 Hz), 162.3 (d, J=251.3 Hz), 151.40, 146.54, 140.0, 132.1 (d, J=4.2 Hz), 126.1 (x2), 121.2, 120.3 (d, J=12.9 Hz), 110.58 (d, J=2.5 Hz), 101.35 (d, J=25.9 Hz), 55.9, 15.9.

Intermediate P36: (6-Chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-3-yl)(2-fluoro-4-methoxyphenyl)methanone

Title product was obtained in accordance with the method described above for Intermediate P8, using (6-chloro-2-methylimidazo[1,2-b]pyridazin-3-yl)(2-fluoro-4-methoxyphenyl)methanone (Intermediate P35) (1.96 g, 6.12 mmol), vanadyl acetylacetonate (0.324 g, 1.22 mmol), N-methylmorpholine N-oxide (8.27 g, 61.1
mmol), and ethanol (45 mL). Product was obtained in the form of white crystals with the yield of 61% (1.51 g, 3.71 mmol).

MS-ESI: (m/z) calculated for C_{20}H_{23}ClF_N_{0.3}[M+H]^+: 419.1, found 419.1.

^1H NMR (500 MHz, CDCl_3) δ 7.71 (t, J=8.5 Hz, 1H), 7.36 (s, 1H), 6.83 (dd, J=8.7 Hz, J=2.3 Hz, 1H), 6.57 (dd, J=12.4 Hz, J=2.3 Hz, 1H), 4.00 (s, 2H), 3.89 (s, 3H), 3.81-3.77 (m, 4H), 2.66-2.59 (m, 7H).

^13C NMR (125 MHz, CDCl_3) δ 180.3, 164.6 (d, J=9.1 Hz), 162.9, 150.6, 146.9, 138.5, 138.0, 132.1 (d, J=4.2 Hz), 126.2, 120.4 (d, J=12.9 Hz), 118.5, 110.5 (d, J=2.4 Hz), 101.3 (d, J=25.0 Hz), 66.9 (x2), 55.9, 55.8, 53.8 (x2), 13.8.

Intermediate P37: 4-((6-Chloro-3-(2-fluoro-4-methoxybenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine

Title product was obtained in accordance with the method described above for Intermediate P9, using (6-chloro-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(2-fluoro-4-methoxyphenyl)methanone (Intermediate P36) (1.30 g, 3.10 mmol), trifluoroacetic acid (3.61 mL, 47.2 mmol), and triethylsilane (4.46 mL, 27.9 mmol). Product was obtained in the form of white crystals with the yield of 81% (1.01 g, 2.50 mmol).

MS-ESI: (m/z) calculated for C_{26}H_{26}ClF_N_{0.2}[M+H]^+: 405.2, found 405.1.

^1H NMR (300 MHz, CDCl_3) δ 7.22-7.11 (m, 2H), 6.64-6.54 (m, 2H), 4.25 (s, 2H), 3.96 (s, 2H), 3.78 (t, J=4.7 Hz, 4H), 3.75 (s, 3H), 2.59 (t, J=4.7 Hz, 4H), 2.46 (s, 3H).

^13C NMR (75 MHz, CDCl_3) δ 162.9, 159.6 (d, J=9.1 Hz), 146.2, 141.3, 137.5, 136.2, 131.0 (d, J=6.0 Hz), 123.8, 116.2 (d, 16.6 Hz), 114.7, 109.6, 101.5 (d, J=25.6 Hz), 66.9 (x2), 55.9, 55.5, 53.8 (x2), 21.5, 13.8.

Intermediate P38: N-(1-(tert-Butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-methoxybenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine
Title product was obtained in accordance with the method described above for Intermediate P10, using 4-((6-chloro-3-(2-fluoro-4-methoxybenzyl)-2-methyl-imidazo[1,2-t]pyridazin-8-yl)methyl)morpholine (Intermediate P37) (200 mg, 0.489 mmol) and 1-teri-butyl-3-methyl-1H-pyrazol-5-amine (Intermediate P1) (150 mg, 0.977 mmol). Product was obtained in the form of an amorphous, creamy solid with the yield of 64% (162 mg, 0.311 mmol).

MS-ESI: (m/z) calculated for C_{28}H_{37}FN_{7}O_{2} [M+H]^+: 522.3 found 522.2.

H NMR (500 MHz, DMSO-d_{6}) δ 8.38 (s, 1H), 6.93 (t, J=8.7 Hz, 1H), 6.79 (s, 1H), 6.72 (dd, J=n.O Hz, J=2.3 Hz, 1H), 6.53 (dd, J=8.4 Hz, J=2.3 Hz, 1H), 5.95 (s, 1H), 3.94 (s, 2H), 3.76 (s, 2H), 3.71 (s, 3H), 3.65-3.58 (m, 4H), 2.51-2.44 (m, 4H), 2.29 (s, 3H), 2.19 (s, 3H), 1.50 (s, 9H).

Compounds of the invention

Example 1: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-phenylimidazo[1,2-b]pyridazin-6-amine

The mixture of 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]-pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol), aniline (134 µL, 1.47 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxantheine (57 mg, 0.098 mmol), tris(dibenzylideneacetone)dipalladium(0) (45 mg, 0.049 mmol) and sodium carbonate (62 mg, 0.586 mmol) were suspended in degassed toluene (5 mL). The reaction mixture was degassed, purged with argon stream for 30 minutes, and then stirred while heating at 100°C for 44 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), filtered through a Celite bed and washed with ethyl acetate. Filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, eluent: heptane/AcOEt 20:80, AcOEt 100% to AcOEt/ methanol 98:2, v/v). Title product was obtained in the form of an amorphous, white solid with the yield of 59% (130 mg, 0.287 mmol).
MS-ESI: (m/z) calculated for C_{25}H_{26}N_{5}OClF [M+H]^+ : 466.2, found 466.2.

\[^{1}\text{H NMR} (500 \text{ MHz, DMSO-cf}) \delta 9.25 \text{ (s, 1H)}, 7.55 \text{ (dd, J=8.6 Hz, 0.9 Hz, 2H)}, 7.46 \text{ (dd, J=10.0 Hz, 2.1 Hz, 1H)}, 7.28-7.23 \text{ (m, 2H)}, 7.13 \text{ (dd, J=8.3 Hz, 2.0 Hz, 1H)}, 7.07 \text{ (t, J=8.3 Hz, 1H)}, 6.95-6.90 \text{ (m, 2H)}, 4.25 \text{ (s, 2H)}, 3.80 \text{ (s, 2H)}, 3.71-3.61 \text{ (m, 4H)}, 2.94-2.86 \text{ (m, 4H)}, 2.36 \text{ (s, 3H)}.

\[^{13}\text{C NMR} (125 \text{ MHz, DMSO-d6}) \delta 160.7 \text{ (d, J=246.6 Hz)}, 150.9, 141.2, 138.3, 136.2, 135.1, 132.0 \text{ (d, J=10.4 Hz)}, 131.8 \text{ (d, J=5.3 Hz)}, 129.62, 129.0 \text{ (x2)}, 125.0 \text{ (d, J=9.3 Hz)}, 124.9 \text{ (d, J=23 Hz)}, 121.5 \text{ (d, J=18.0 Hz)}, 118.2 \text{ (x2)}, 116.2 \text{ (d, J=25.6 Hz)}, 109.2, 66.7 \text{ (x2)}, 55.9, 54.0 \text{ (x2)}, 21.7, 13.9.

Example 2: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(pyridin-2-yl)imidazo[1,2-b]pyrazin-6-amine

The mixture of 4-[(4-chloro-3-[(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl]morpholine (Intermediate P26) (200 mg, 0.489 mmol), pyridin-2-amine (48 mg, 0.513 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (28 mg, 0.049 mmol), tris(dibenzylideneacetone)dipalladium(0) (22 mg, 0.024 mmol) and 7.4% aqueous sodium hydroxide solution (0.30 mL, 0.56 mmol) were suspended in degassed o-xylene (4 mL) in Schlenk's flask. The reaction mixture was degassed, purged with argon stream for 30 minutes, and then stirred while heating at 100°C for 44 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), filtered through a Celite bed and washed with ethyl acetate. Filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, eluent:heptane/AcOEt 20:80, AcOEt 100% to AcOEt/methanol 98:2, v/v). Title product was obtained in the form of an amorphous, white solid with the yield of 89% (204 mg, 0.437 mmol).

MS-ESI: (m/z) calculated for C_{26}H_{28}N_{5}OClF [M+H]^+: 467.2, found 467.2.

\[^{1}\text{H NMR} (300 \text{ MHz, DMSO-cf}) \delta 9.88 \text{ (s, 1H)}, 8.25 \text{ (d, J=3.6 Hz, 1H)}, 7.83 \text{ (d, J=8.4 Hz, 1H)}, 7.66 \text{ (dt, J=9.0 Hz, 1.8 Hz, 1H)}, 7.46 \text{ (dd, J=9.9 Hz, 1.5 Hz, 1H)}, 7.27 \text{ (s, 1H)}, 7.06-7.16 \text{ (m, 2H)}, 6.94 \text{ (dd, J=6.3 Hz, 4.8 Hz, 1H)}, 4.27 \text{ (s, 2H)}, 3.80 \text{ (s, 2H)}, 3.70-3.61 \text{ (m, 4H)}, 2.55-2.45 \text{ (m, 4H)}, 2.36 \text{ (s, 3H)}.

\[^{13}\text{C NMR} (75 \text{ MHz, DMSO-d6}) \delta 160.3 \text{ (d, J=246.3 Hz)}, 153.1, 149.6, 147.9, 138.3, 137.7, 135.9, 134.9, 131.6 \text{ (d, J=10.5 Hz)}, 131.4 \text{ (d, J=5.5 Hz)}, 124.6, 124.4, 121.1, 117.0, 115.9 \text{ (d, J=25.6 Hz)}, 111.5, 109.1, 66.3 \text{ (x2)}, 55.4, 53.5 \text{ (x2)}, 21.3, 13.4.
Example 3: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(5-fluoropyridin-2-yl)-8-
(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for
Example 2, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-
b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol)
and 5-fluoropyridin-2-amine (58 mg, 0.513 mmol). Product was obtained in the
form of an amorphous, white solid with the yield of 91% (215 mg, 0.443 mmol).
MS-ESI: (m/z) calculated for C_{24}H_{14}N_5OClF_2 [M+H]^+: 485.2, found 485.2.

1H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.27 (d, J=3.0 Hz, 1H), 7.92 (dd,
J=9.3 Hz, 4.2 Hz, 1H), 7.64 (dt, J=8.1 Hz, 3.0 Hz, 1H), 7.51 (dd, J=9.9 Hz, 1.8
Hz, 1H), 7.15 (s, 1H), 7.09-7.19 (m, 2H), 4.27 (s, 2H), 3.80 (s, 2H), 3.70-3.60
(4H), 2.55-2.46 (m, 4H), 2.37 (s, 3H).

13C NMR (75 MHz, DMSO-d_6) δ 160.3 (d, J=246.8 Hz), 156.1, 152.8, 149.7, 149.4,
138.3, 136.0, 135.3, 134.9 (d, J=7.5 Hz), 131.7 (d, J=10.5 Hz), 131.5 (d, J=5.0
Hz), 124.9, 124.7, 124.5 (d, J=15.0 Hz), 121.2, 115.9 (d, J=25.5 Hz), 112.3,
108.8, 66.3 (x2), 55.4, 53.5 (x2), 21.3, 13.4.

Example 4: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(6-methylpyridin-2-yl)-8-
(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for
Example 2, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-
b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol)
and 6-methylpyridin-2-amine (55 mg, 0.513 mmol). Product was obtained in the
form of an amorphous, white solid with the yield of 69% (162 mg, 0.336 mmol).
MS-ESI: (m/z) calculated for C_{25}H_{27}N_6OClF [M+H]^+: 481.2, found 481.2.
1H NMR (500 MHz, DMSO-d$_6$) δ 9.80 (s, 1H), 7.62 (d, J=8.3 Hz, 1H), 7.54 (t, J=7.8 Hz, 1H), 7.45 (dd, J=10.0 Hz, J=1.9 Hz, 1H), 7.29 (s, 1H), 7.08 (dd, J=6.4 Hz, J=1.9 Hz, 1H), 7.07 (t, J=8.3 Hz, 1H), 6.80 (d, J=7.3 Hz, 1H), 4.25 (s, 2H), 3.78 (s, 2H), 3.65 (s, 2H), 2.54-2.46 (m, 4H), 2.37 (s, 3H), 2.34 (s, 3H).

13C NMR (125 MHz, DMSO-d$_6$) δ 160.2 (d, J=246.3 Hz), 156.2, 152.5, 149.6, 138.2, 138.1, 135.7, 134.8, 131.6 (d, J=11.3 Hz), 131.4 (d, J=5.0 Hz), 124.6 (d, J=3.8 Hz), 124.5 (d, J=15.0 Hz), 121.0, 116.2, 115.8 (d, J=26.3 Hz), 109.1, 108.5, 66.3 (x2), 55.3, 53.4 (x2), 23.7, 21.2, 13.4.

Example 5: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(3-methylpyridin-2-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyrazin-6-amine

Title product was obtained in accordance with the method described above for Example 2, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and 3-methylpyridin-2-amine (55 mg, 0.513 mmol). Product was obtained in the form of an amorphous, white solid with the yield of 72% (170 mg, 0.353 mmol). MS-ESI: (m/z) calculated for C$_{26}$H$_{27}$N$_4$OCl [M+H]: 481.2, found 481.2.

1H NMR (500 MHz, DMSO-d$_6$) δ 8.87 (s, 1H), 8.09 (d, J=3.7 Hz, 1H), 7.59 (d, J=6.7 Hz, 1H), 7.34-7.37 (m, 1H), 7.25 (s, 1H), 7.05-7.10 (m, 2H), 7.03 (dd, J=7.3 Hz, 4.8 Hz, 1H), 4.15 (s, 2H), 3.80 (s, 2H), 3.64-3.54 (m, 4H), 2.55-2.45 (m, 4H), 2.30 (s, 3H), 2.18 (s, 3H).

13C NMR (125 MHz, DMSO-d$_6$) δ 160.1 (d, J=246.3 Hz), 152.5, 150.7, 144.9, 138.8, 138.0, 135.4, 134.8, 131.7 (d, J=5.0 Hz), 131.6 (d, J=10.0 Hz), 124.5, 124.4, 124.3, 123.9, 120.7, 118.7, 115.7 (d, J=25.0 Hz), 110.2, 66.2 (x2), 55.4, 53.4 (x2), 17.4, 13.4.

Example 6: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(pyridin-3-yl)imidazo[1,2-b]pyrazin-6-amine
Title product was obtained in accordance with the method described above for Example 2, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-t]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and pyridin-3-amine (48 mg, 0.513 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 84% (192 mg, 0.411 mmol).

MS-ESI: (m/z) calculated for C_{24}H_{25}N_{6}O_{7}ClF [M+H]^+: 466.2, found 466.2.

$^1$H NMR (300 MHz, DMSO-d$_6$) δ 9.52 (s, 1H), 8.70 (d, J=2.4 Hz, 1H), 8.16 (d, J=4.2 Hz, 1H), 8.05 (d, J=9.3 Hz, 1H), 7.45 (d, J=10.2 Hz, 1H), 7.28 (dd, J=8.4 Hz, J=4.5 Hz, 1H), 7.20-7.00 (m, 2H), 6.96 (s, 1H), 4.26 (s, 2H), 3.82 (s, 2H), 3.68 (t, J=4.4 Hz, 4H), 2.55-2.49 (m, 4H), 2.36 (s, 3H).

$^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 161.4, 150.3, 141.8, 139.8, 138.1, 137.4, 136.2, 134.7, 131.4 (d, J=10.5), 131.2 (d, J=5.0 Hz), 128.2, 124.5, 124.3, 123.6 (d, J=47.1 Hz), 121.2, 115.9 (d, J=25.6 Hz), 108.4, 66.3 (x2), 55.4, 53.5 (x2), 21.3, 13.4.

Example 7: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(pyridazin-3-yl)imidazo[1,2-t]pyridazin-6-amine

Title product was obtained in accordance with the method described above for Example 2, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and pyridazin-3-amine (49 mg, 0.513 mmol). Product was obtained in the form of a light-orange, amorphous solid with the yield of 63% (144 mg, 0.308 mmol).

MS-ESI: (m/z) calculated for C_{24}H_{25}N_{6}O_{7}ClF [M+H]^+: 467.2, found 467.2.

$^1$H NMR (300 MHz, DMSO-d$_6$) δ 10.47 (s, 1H), 8.84 (d, J=4.5 Hz, 1H), 8.41 (d, J=4.5 Hz, 1H), 8.09 (d, J=9.3 Hz, 1H), 7.57 (dd, J=9.2 Hz, J=4.7 Hz, 1H), 7.47 (d, J=9.9 Hz, 1H), 7.28-7.10 (m, 2H), 4.29 (s, 2H), 3.84 (s, 2H), 3.68 (t, J=4.5 Hz, 4H), 2.55-2.46 (m, 4H), 2.38 (s, 3H).

Example 8: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(pyrimidin-4-yl)imidazo[1,2-b]pyridazin-6-amine
Title product was obtained in accordance with the method described above for Example 1, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and pyrimidin-4-amine (49 mg, 0.513 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 79% (204 mg, 0.386 mmol).

MS-ESI: (m/z) calculated for C_{23}H_{24}N_7OClF [M+H]^+: 468.2, found 468.2.

^1H NMR (300 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.80 (d, J=4.5 Hz, 1H), 8.42 (d, J=4.5 Hz, 1H), 7.60 (dd, J=9.2 Hz, J=4.5 Hz, 1H), 7.43 (d, J=9.7 Hz, 1H), 7.26-7.14 (m, 2H), 4.26 (s, 2H), 3.80 (s, 2H), 3.72-3.64 (m, 4H), 2.55-2.46 (m, 4H), 2.34 (s, 3H).

Example 9: 3-(4-Chloro-2-fluorobenzyl)-A/(5-chloropyrimidin-2-yl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for Example 2, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and 5-chloropyrimidin-2-amine (66 mg, 0.513 mmol). Product was obtained in the form of a light-orange, amorphous solid with the yield of 23% (54 mg, 0.11 mmol).

MS-ESI: (m/z) calculated for C_{23}H_{25}N_7OClF_2 [M+H]^+: 502.1, found 502.1.

^1H NMR (500 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.64-8.62 (m, 2H), 7.76-7.73 (m, 1H), 7.54-7.67 (m, 1H), 7.37 (dd, J=10.0 Hz, J=2.0 Hz, 1H), 7.16 (dd, J=8.3 Hz, J=2.0 Hz, 1H), 4.21 (s, 2H), 3.83 (s, 2H), 3.62 (t, J=4.5 Hz, 4H), 2.55-2.47 (m, 4H), 2.34 (s, 3H).

^13C NMR (125 MHz, DMSO-d_6) δ 158.7 (d, J=246.4 Hz), 156.4, 148.3, 139.0, 135.6, 135.4, 132.5, 124.5, 124.2, 121.6, 121.4, 115.7 (d, J=25.6 Hz), 108.3, 66.2 (x2), 55.4, 53.4 (x2), 21.2, 13.4.

Example 10: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-A-(1-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine
Title product was obtained in accordance with the method described above for Example 2, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and 1-methyl-1H-pyrazol-3-amine (50 mg, 0.513 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 96% (221 mg, 0.470 mmol).

MS-ESI: (m/z) calculated for C23H26N7OClF [M+H]+: 470.2, found 470.2.

1H NMR (500 MHz, DMSO-d6) δ 9.57 (s, 1H), 7.52 (d, J=2.1 Hz, 1H), 7.40 (dd, J=10.0 Hz, J=2.0 Hz, 1H), 7.13 (dd, J=8.3 Hz, J=2.0 Hz, 1H), 7.08 (t, J=8.2 Hz, 1H), 7.02 (s, 1H), 6.36 (d, J=2.2 Hz, 1H), 4.23 (s, 2H), 3.76 (s, 2H), 3.74 (s, 3H), 3.65 (t, J=4.4 Hz, 4H), 2.54-2.46 (m, 4H), 2.29 (s, 1H).

13C NMR (125 MHz, DMSO-d6) δ 160.1 (d, J=246.3 Hz), 149.9, 148.1, 137.5, 135.4, 134.7, 131.5 (d, J=1 1.3 Hz), 131.3 (x2), 130.6, 124.7, 124.6, 120.8, 115.8, 108.3, 95.6, 66.2 (x2 ), 55.4, 53.5 (x2), 38.2, 21.0, 13.4.

Example 11: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

To the solution of 1-methyl-4-nitro-1H-pyrazole (Intermediate P3) (124 mg, 0.98 mmol) in ethanol (10 mL) 5% palladium on active carbon (52 mg, 0.024 mmol) was added. The reaction mixture was stirred under hydrogen atmosphere under atmospheric pressure at room temperature for 3 hours. The reaction mixture was filtered through a Celite bed, washed with ethanol, and filtrate was concentrated under reduced pressure in Schlenk’s flask to obtain 1-methyl-1H-pyrazol-4-amine in the form of a yellow oil, which was used for further reaction without purification. To the Schlenk’s flask with 1-methyl-1H-pyrazol-4-amine, 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol), 4,5-bis(diphenyl-
phosphino)-9,9-dimethylxanthene (28 mg, 0.049 mmol), tris(dibenzylidene-acetone)dipalladium(O) (22 mg, 0.024 mmol) and sodium carbonate (104 mg, 0.977 mmol) were added. The mixture was suspended in degassed toluene (5 ml). The reaction mixture was degassed, purged with argon stream for 30 minutes, and then stirred while heating at 100°C for 20 hours. The reaction mixture was cooled to room temperature, filtered through a Celite of and washed with ethyl acetate. Filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, eluent: AcOEt 100% to AcOEt/ methanol 97:3, v/v). Fractions were concentrated to obtain yellow oil, which was dissolved in ethyl acetate and added with heptane until precipitation of crystals. Title product was obtained in the form of creamy crystals with the yield of 41% (93 mg, 0.198 mmol).

MS-ESI: (m/z) calculated for C23H26N7OCIF [M+H]⁺: 470.2, found 470.2.

\[^1\text{H} \text{NMR} \ (500 \text{ MHz, DMSO-}d_6) \delta \ 9.21 \ (s, 1\text{H}), \ 7.71 \ (s, 1\text{H}), \ 7.47 \ (dd, J=1.0 \text{ Hz}, J=2.0 \text{ Hz}, 1\text{H}), \ 7.36 \ (s, 1\text{H}), \ 7.13 \ (dd, J=8.5 \text{ Hz}, J=2.0 \text{ Hz}, 1\text{H}), \ 7.01 \ (t, J=8.4 \text{ Hz}, 1\text{H}), \ 6.79 \ (s, 1\text{H}), \ 4.27 \ (s, 2\text{H}), \ 3.79 \ (s, 3\text{H}), \ 3.77 \ (s, 2\text{H}), \ 3.65 \ (t, J=4.4 \text{ Hz}, 4\text{H}), \ 2.55-2.45 \ (m, 4\text{H}), \ 2.32 \ (s, 3\text{H}).\]

\[^{13}\text{C} \text{NMR} \ (125 \text{ MHz, DMSO-}d_6) \delta \ 160.6 \ (d, J=246.0 \text{ Hz}), \ 150.2, \ 137.8, \ 135.7, \ 135.0, \ 134.9, \ 132.0 \ (d, J=10.3 \text{ Hz}), \ 131.6 \ (d, J=5A \text{ Hz}), \ 129.5, \ 125.3, \ 125.1, \ 123.8, \ 121.3, \ 120.1, \ 116.2 \ (d, J=25.9 \text{ Hz}), \ 108.4, \ 66.8 \ (x2), \ 55.8, \ 54.0 \ (x2), \ 21.5, \ 13.8.\]

**Example 12**: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-V-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

![Chemical Structure](attachment:image)

Title product was obtained in accordance with the method described above for Example 11, using 1-methyl-4-nitro-1H-imidazole (Intermediate P3) (310 mg, 2.45 mmol) and 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (500 mg, 1.22 mmol). Product was obtained in the form of light-creamy crystals with the yield of 38% (221 mg, 0.467 mmol).

MS-ESI: (m/z) calculated for C23H26N7OCIF [M+H]⁺: 470.2, found 470.2.

\[^1\text{H} \text{NMR} \ (500 \text{ MHz, DMSO-}d_6) \delta \ 9.57 \ (s, 1\text{H}), \ 7.50 \ (dd, J=9.9 \text{ Hz}, J=2.1 \text{ Hz}, 1\text{H}), \ 7.40-7.34 \ (m, 1\text{H}), \ 7.14 \ (dd, J=8.4 \text{ Hz}, J=2A \text{ Hz}, 1\text{H}), \ 7.04-6.90 \ (m, 3\text{H}), \ 4.28 \ (s, 2\text{H}), \ 3.75 \ (s, 2\text{H}), \ 3.65 \ (t, J=4.2 \text{ Hz}, 4\text{H}), \ 3.60 \ (s, 3\text{H}), \ 2.55-2.45 \ (m, 4\text{H}), \ 2.33 \ (s, 3\text{H}).\]
\[^{13}\text{C}\] NMR (125 MHz, DMSO-d\textsubscript{6}) \(\delta\) 160.2 (d, \(J=246.8\) Hz), 149.0, 139.3, 134.4, 134.8, 134.6, 133.9, 131.6 (d, \(J=11.3\) Hz), 131.1 (d, \(J=44\) Hz), 124.9, 124.7, 120.6, 116.0, 115.6, 108.4, 105.3, 66.3 (x2 ), 55.4, 53.5 (x2), 39.1, 33.1, 21.0, 13.4.

Example 13: Ethyl 3-(3-(4-chloro-2-fluorobenzyl)-2-methyl-8-(morpholino-methyl)imidazo[1,2-b]pyridazin-6-ylamino)-1H-pyrazole-4-carboxylate

\[\text{Title product was obtained in accordance with the method described above for Example 1, using } 4-((6\text{-}chloro\text{-}3\text{-}((4\text{-}chloro\text{-}2\text{-}fluorobenzyl})\text{-}2\text{-}methyl\text{-}imidazo[1,2-b]pyridazin-8\text{-}yl)methyl)\text{morpholine (Intermediate P26) (200 mg, 0.489 mmol) and ethyl 3\text{-}amino\text{-}1H\text{-}pyrazole\text{-}4\text{-}carboxylate (80 mg, 0.513 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 12\% (30 mg, 0.057 mmol). MS-ESI: (m/z) calculated for } C_{28}H_{27}N_{8}O_{3}ClF [M+H]^+: 528.2, found 528.2.\]

\[^{1}\text{H}\] NMR (500 MHz, DMSO-d\textsubscript{6}) \(\delta\) 7.87 (s, 1H), 7.76 (s, 1H), 7.42 (dd, \(J=10.1\) Hz, 2.0 Hz, 1H), 7.22 (m, 2H), 7.15 (s, 2H), 4.39 (s, 2H), 4.24 (q, \(J=7\) Hz, 2H), 3.94 (s, 2H), 3.63 (m, 4H), 2.50 (m, 4H), 2.41 (s, 4H), 1.29 (t, \(J=7.1\) Hz, 3H).

Example 14: 3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(1H-1,2,4-triazol-3-yl)imidazo[1,2-b]pyridazin-6-amine

\[\text{Title product was obtained in accordance with the method described above for Example 1, using } 4-((6\text{-}chloro\text{-}3\text{-}((4\text{-}chloro\text{-}2\text{-}fluorobenzyl})\text{-}2\text{-}methyl\text{-}imidazo[1,2-b]pyridazin-8\text{-}yl)methyl)\text{morpholine (Intermediate P26) (200 mg, 0.489 mmol) and 1H-1,2,4-triazol-3-amine (45 mg, 0.513 mmol). Product was obtained in the form of an amorphous, yellow solid with the yield of 35\% (79 mg, 0.173 mmol). MS-ESI: (m/z) calculated for } C_{21}H_{23}N_{8}OClF [M+H]^+: 457.2, found 457.2.\]

\[^{1}\text{H}\] NMR (500 MHz, DMSO-d\textsubscript{6}) \(\delta\) 10.97 (s, 1H), 8.84 (s, 1H), 8.83 (s, 1H), 7.79 (s, 1H), 7.48 (t, \(J=8.5\) Hz, 1H), 7.38 (dd, \(J=10.0\) Hz, \(J=2.0\) Hz, 1H), 7.17 (dd, \(J=8.5\) Hz, 1H).
Hz, J=2.0 Hz, 1H), 4.25 (s, 2H), 3.87 (s, 2H), 3.64 (t, J=4.5 Hz, 4H), 2.54-2.46 (m, 4H), 2.37 (s,3H).

**Example 15:** N-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-imidazo[1,2-£]pyridazin-6-yl)-5-methylthiazol-2-amine

Title product was obtained in accordance with the method described above for Example 1, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and 5-methylthiazol-2-amine (59 mg, 0.513 mmol). Product was obtained in the form of an amorphous, light-yellow solid with the yield of 31% (72 mg, 0.152 mmol).

**^{1}H NMR** (500 MHz, DMSO-d6) δ 11.25 (s, 1H), 7.45 (dd, J=10.0, J=2.0, 1H), 7.15-7.05 (m, 3H), 6.94 (t, J=8.3 Hz, 1H), 4.35 (s, 2H), 3.83 (s, 2H), 3.65 (t, J=4.4 Hz, 4H), 2.54-2.46 (m, 4H), 2.32 (s, 3H), 2.31 (s, 3H).

**^{13}C NMR** (125 MHz, DMSO-d6) δ 160.1 (d, J=246. 1 Hz), 149.6, 148.9, 138.7, 138.6, 136.6, 134.9, 131.6 (d, J=11.1 Hz), 130.9 (d, J=4.0 Hz), 124.7, 124.5, 120.9, 115.7 (d, J=25.6 Hz), 108.4, 92.6, 66.3 (x2 ), 55.3, 53.4 (x2 ), 21.1, 13.4, 11.0.

**Example 16:** N-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-imidazo[1,2-t]pyridazin-6-yl)-4-methylthiazol-2-amine

Title product was obtained in accordance with the method described above for Example 1, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-t]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and 4-methylthiazol-2-amine (59 mg, 0.513 mmol). Product was obtained in the form of an amorphous, grey solid with the yield of 45% (115 mg, 0.218 mmol).

**MS-ESI:** (m/z) calculated for C_{23}H_{25}N_{6}O_{SCIF} [M+H]^{+}: 487.1, found 487.1.
\[ ^1 \text{H NMR (500 MHz, DMSO-d}_6 \] \( \delta \) 11.44 (s, 1H), 7.42 (dd, J=9.9 Hz, 1.8 Hz, 1H), 7.12 (m, 2H), 7.04 (t, J=8.3 Hz, 1H), 6.65 (s, 1H), 4.36 (s, 2H), 3.82 (s, 2H), 3.66 (m, 4H), 2.51 (s, 4H), 2.28 (s, 3H), 2.25 (s, 3H).

**Example 17:** Methyl 2-(3-(4-chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-ylamino)thiazole-5-carboxylate

![Methyl 2-(3-(4-chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-ylamino)thiazole-5-carboxylate](image)

Title product was obtained in accordance with the method described above for Example 1, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and methyl 2-aminothiazole-5-carboxylate (51 mg, 0.513 mmol). Product was obtained in the form of an amorphous, beige solid with the yield of 20% (52 mg, 0.098 mmol).

MS-ESI: (m/z) calculated for C24H25N6O3SCIF [M+H]+: 532.0, found 532.0.

**Example 18:** N-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-yl)-1,3,4-thiadiazol-2-amine

![N-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-yl)-1,3,4-thiadiazol-2-amine](image)

Title product was obtained in accordance with the method described above for Example 2, using 4-((6-chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P26) (200 mg, 0.489 mmol) and 1,3,4-thiadiazol-2-amine (52 mg, 0.513 mmol). Product was obtained in the form of an amorphous, beige solid with the yield of 97% (229 mg, 0.476 mmol).

MS-ESI: (m/z) calculated for C21H22N7O3SCIF [M+H]+: 474.9, found 474.9.
**Example 19**: 3-(4-Fluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

N-(1-(tert-Butyl)-3-methyl-1H-pyrazol-5-yl)-3-(fluorobenzyl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (Intermediate P10) (230 mg, 0.482 mmol) was dissolved in trifluoroacetic acid (1.00 mL, 13.1 mmol) and then water (4.0 mL) was added. The reaction mixture was stirred while heating at 100°C for 20 hours. The reaction mixture was cooled to room temperature, neutralized with 10% aqueous sodium hydroxide solution (10 mL) and extracted with ethyl acetate (3 x 20 mL). Organic layers were combined, washed with brine (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: AcOEt 100% to AcOEt/methanol 80:20, v/v). Fractions with the product were concentrated under reduced pressure. Remaining yellow solid was dissolved in hot ethyl acetate and heptane was added. Title product crystallized in the form of white crystals, which were filtered and dried to obtain the product with the yield of 75% (153 mg, 0.363 mmol).

**MS-ESI**: (m/z) calculated for C₉₂H₇₅N₃OF [M+H]⁺: 422.2, found 422.2.

**1H NMR** (500 MHz, DMSO-d₆) δ 11.87 (s, 1H), 9.52 (s, 1H), 7.30 (dd, J=8.5 Hz, J=5.6 Hz, 2H), 7.27 (s, 1H), 7.11 (t, J=8.9 Hz, 2H), 7.05 (s, 1H), 6.20 (s, 1H), 4.23 (s, 2H), 3.78 (s, 2H), 3.68-3.60 (m, 4H), 2.55-2.46 (m, 4H), 2.21 (s, 3H).

**13C NMR** (125 MHz, DMSO-d₆) δ 161.3 (d, J=240.3 Hz), 159.2, 159.1, 150.6, 148.8, 138.6 (x2), 138.5, 136.5, 135.0, 130.5 (d, J=8.1 Hz), 129.4, 127.4, 115.5 (d, J=21.3 Hz), 109.4, 95.5, 66.7 (x2), 55.8, 53.9 (x2), 28.9, 11.3.

**Example 20**: 3-(4-Fluorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine
Title product was obtained in accordance with the method described above for Example 19, using W-(1-(tert-butyl)-3-methyl-1H-pyrazol-5-yl)-3-(4-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (Intermediate P14) (90 mg, 0.183 mmol), trifluoroacetic acid (0.50 mL, 6.53 mmol), and water (2.0 mL). Product was obtained in the form of white crystals with the yield of 28% (22 mg, 0.051 mmol).

MS-ESI: (m/z) calculated for C_{235}H_{27}N_{7}O_{5} [M+H]^+: 436.2, found 436.2.

$^{1}$H NMR (500 MHz, DMSO-d$_6$) δ 11.84 (s, 1H), 9.41 (s, 1H), 7.24 (dd, $J$=8.2 Hz, $J$=5.6 Hz, 2H), 7.08 (t, $J$=8.8 Hz, 2H), 6.99 (s, 1H), 6.16 (s, 1H), 4.22 (s, 2H), 3.75 (s, 2H), 3.68-3.60 (m, 4H), 2.54-2.46 (m, 4H), 2.32 (s, 3H), 2.19 (s, 3H).

$^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 160.8 (d, $J$=240.8 Hz), 157.9 (d, $J$=31.1 Hz), 149.8, 136.9, 135.2, 135.1 (d, $J$=2.95 Hz), 129.7, 129.6, 122.8, 118.4, 116.0, 115.2 (d, $J$=21.4 Hz), 114.9, 108.2, 94.9, 66.2 (x2), 55.4, 53.5 (x2), 27.5, 13.4, 10.8.

**Example 21:** 3-(2,4-Difluorobenzyl)-A-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for Example 19, using N-(1-(tert-butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2,4-difluorobenzyl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (Intermediate P18) (200 mg, 0.404 mmol), trifluoroacetic acid (0.50 mL, 6.53 mmol), and water (2.5 mL). Product was obtained in the form of white crystals with the yield of 36% (72 mg, 0.145 mmol).

MS-ESI: (m/z) calculated for C_{22}H_{24}N_{6}OF [M+H]^+: 440.2, found 440.2.

$^{1}$H NMR (500 MHz, CDCl$_3$) δ 7.86 (s, 1H), 7.33 (s, 1H), 7.26 (s, 1H), 7.13 (dd, $J$=15.1 Hz, $J$=8.5 Hz, 1H), 6.87 (m, 2H), 6.77 (m, 1H), 6.30 (s, 1H), 4.28 (s, 2H), 3.91 (s, 2H), 3.73 (m, 4H), 2.59 (m, 4H), 2.33 (s, 3H).
Example 22: 3-(2,4-Difluorobenzyl)-2-methyl-8-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for Example 19, using N-(1-(tert-butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2,4-difluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (Intermediate P23) (90 mg, 0.177 mmol), trifluoroacetic acid (0.50 mL, 6.53 mmol), and water (2.0 mL). Product was obtained in the form of creamy crystals with the yield of 89% (71 mg, 0.157 mmol). MS-ESI: (m/z) calculated for C23H26N7OF2 [M+H]+: 454.2, found 454.2.

1H NMR (500 MHz, DMSO-d6) δ 11.85 (s, 1H), 9.42 (s, 1H), 7.24 (ddd, J=10.4 Hz, J=9.4, J=2.6 Hz, 1H), 7.12 - 7.02 (m, 1H), 7.00 (s, 1H), 6.92 (td, J=8.5, J=1.4 Hz, 1H), 6.13 (s, 1H), 4.22 (s, 2H), 3.76 (d, J=0.8 Hz, 2H), 3.70 - 3.58 (m, 4H), 2.57 - 2.44 (m, 4H), 2.31 (s, 3H), 2.19 (s, 3H).

13C NMR (125 MHz, DMSO-d6) δ 160.5 (ddd, J=243.3 Hz, J=77.9 Hz, J=12.1 Hz), 149.9, 137.9, 137.4, 135.2, 134.7, 130.9 (dd, J=9.6, J=6.0 Hz), 121.6 (dd, J=15.5, J=3.6 Hz), 120.9, 111.3 (dd, J=21.0, J=3.5 Hz), 108.3, 103.8, 103.6, 103.4, 94.8, 66.2 (x2), 55.4, 53.5 (x2). 20.9 (d, J=3.0 Hz), 13.3, 10.8.

Example 23: (2,4-Difluorophenyl)(2-methyl-6-(5-methyl-1H-pyrazol-3-ylamino)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)methanone

Title product was obtained in accordance with the method described above for Example 19, using (6-((1-(tert-butyl)-3-methyl-1H-pyrazol-5-yl)amino)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-3-yl)(2,4-difluorophenyl)methanone (Intermediate P21) (121 mg, 0.231 mmol), trifluoroacetic acid (0.50 mL, 6.53
mmol), and water (2.0 mL). Product was obtained in the form of white crystals with the yield of 44% (47 mg, 0.100 mmol).

MS-ESI: (m/z) calculated for C_{22}H_{24}N_{7}O_{2}F_{2} [M+H]: 468.2, found 468.1.

$^1$H NMR (500 MHz, DMSO-\(d_6\)) $\delta$ 11.83 (s, 1H), 9.69 (s, 1H), 7.81 (dd, \(J=15.1\) Hz, \(J=8.4\) Hz, 1H), 7.34-7.26 (m, 2H), 7.22 (s, 1H), 5.02 (s, 1H), 3.81 (s, 2H), 3.70-3.62 (m, 4H), 2.55-2.47 (m, 4H), 2.47 (s, 3H), 2.07 (s, 3H).

$^{13}$C NMR (125 MHz, DMSO-\(d_6\)) $\delta$ 150.1, 148.0, 137.6, 136.9, 135.8, 132.4 (d, \(J=12.5\) Hz), 132.3 (d, \(J=3.3\) Hz), 125.4, 124.9 (d, \(J=16.7\) Hz), 112.8, 112.4 (d, \(J=2^\prime\) Hz), 104.7 (t, \(J=26.1\) Hz), 93.6, 66.2 (x2), 55.3, 53.4 (x2), 21.2, 14.5, 11.2.

Example 24: 3-(2,4-Dichlorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for Example 19, using N-(1-(tert-butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2,4-dichlorobenzyl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (Intermediate P30) (220 mg, 0.416 mmol), trifluoroacetic acid (1.0 mL, 13.1 mmol), and water (4.0 mL). Product was obtained in the form of creamy crystals with the yield of 72% (141 mg, 0.298 mmol).

MS-ESI: (m/z) calculated for C_{22}H_{25}N_{7}O_{2}Cl [M+H]: 472.1, found 472.2.

$^1$H NMR (500 MHz, DMSO-\(d_6\)) $\delta$ 11.86 (s, 1H), 9.53 (s, 1H), 7.67 (d, \(J=2.2\) Hz, 1H), 7.29 (m, 2H), 7.06 (d, \(J=8.2\) Hz, 2H), 6.06 (s, 1H), 4.31 (s, 2H), 3.79 (d, \(J=0.8\) Hz, 2H), 3.68-3.60 (m, 4H), 2.50 (dt, \(J=3.6\) Hz, \(J=1.7\) Hz, 4H), 2.18 (s, 3H).

$^{13}$C NMR (125 MHz, DMSO-\(d_6\)) $\delta$ 150.6, 136.7, 136.6, 135.3, 134.4, 132.2, 131.7, 130.0, 129.1, 127.9, 125.0, 109.6, 95.4, 66.7, 60.2, 55.8, 53.9, 27.0, 21.2, 14.5, 11.2.

Example 25: 3-(2,4-Dichlorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine
Title product was obtained in accordance with the method described above for Example 19, using N-(1-(tert-butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2,4-dichlorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (Intermediate P34) (184 mg, 0.339 mmol), trifluoroacetic acid (0.50 mL, 6.53 mmol), and water (2.0 mL). Product was obtained in the form of creamy crystals with the yield of 67% (103 mg, 0.227 mmol).

MS-ESI: (m/z) calculated for C_{23}H_{25}N_7OCl_2Na [M+Na]^+: 508.2, found 508.1.

^1H NMR (500 MHz, DMSO-d_6) δ 11.82 (s, 1H), 9.42 (s, 1H), 7.67 (d, J=2.2 Hz, 1H), 7.24 (dd, J=8.4 Hz, J=2.2 Hz, 1H), 7.00 (s, 1H), 6.81 (d, J=8.4 Hz, 1H), 5.94 (s, 1H), 4.29 (s, 2H), 3.77 (s, 2H), 3.68-3.60 (m, 4H), 2.54-2.48 (m, 4H), 2.29 (s, 3H), 2.15 (s, 3H).

^13C NMR (125 MHz, DMSO-d_6) δ 149.8, 148.6, 137.9, 137.7, 135.2, 135.0, 134.9, 133.7, 131.5, 130.5, 128.5, 127.4, 120.3, 108.4, 94.8, 66.2 (x2), 55.4, 53.5 (x2), 25.7, 13.4, 10.6.

Example 26: 3-(2-Fluoro-4-methoxybenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for Example 19, using N-(1-(tert-butyl)-3-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-methoxybenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (Intermediate P38) (130 mg, 0.262 mmol), trifluoroacetic acid (0.40 mL, 5.22 mmol), and water (3.0 mL). Product was obtained in the form of creamy crystals with the yield of 67% (103 mg, 0.227 mmol).

MS-ESI: (m/z) calculated for C_{24}H_{26}FN_7O_2 [M+H]^+: 466.2, found 466.2.

Example 27: 3-(4-Fluorobenzyl)-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine
Title product was obtained in accordance with the method described above for Example 11, using 1-methyl-4-nitro-1H-imidazole (Intermediate P2) (194 mg, 1.53 mmol) and 4-((6-chloro-3-(4-fluorobenzyl)imidazo[1,2-b]pyridazin-8-yl)-methyl)morpholine (Intermediate P9) (184 mg, 0.51 mmol). Product was obtained in the form of light-creamy crystals with the yield of 60% (129 mg, 0.306 mmol).

MS-ESI: (m/z) calculated for C_{22}H_{25}N_{7}OF [M+H]^+: 422.2, found 422.2.

^1H NMR (500 MHz, DMSO-<sub>cf</sub>) δ 9.59 (s, 1H), 7.46 - 7.21 (m, 4H), 7.20-7.10 (m, 2H), 7.10-6.90 (m, 2H), 4.28 (s, 2H), 3.77 (s, 2H), 3.70-3.55 (m, 7H), 2.60-2.40 (m, 4H).

^13C NMR (125 MHz, DMSO-<sub>cf</sub>) δ 160.8 (d, J=240.0 Hz), 149.1, 139.1, 135.9, 135.6, 134.6, 133.8, 129.9 (x2), 128.9, 126.8, 115.1 (d, J=21.3 Hz), 108.9, 105.8, 66.2 (x2), 55.4, 53.4 (x2), 33.1, 28.4.

**Example 28:** 3-(2,4-Difluorobenzyl)-2-methyl-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

Title product was obtained in accordance with the method described above for Example 11, using 1-methyl-4-nitro-1H-imidazole (Intermediate P2) (124 mg, 1.53 mmol) and 4-((6-chloro-3-(2,4-difluorobenzyl)-2-methylimidazo[1,2-b]pyridazin-8-yl)methyl)morpholine (Intermediate P22) (200 mg, 0.51 mmol). Product was obtained in the form of light-creamy crystals with the yield of 7% (17 mg, 0.037 mmol).

MS-ESI: (m/z) calculated for C_{23}H_{26}N_{7}OF_{2} [M+H]^+: 454.2, found 454.2.

^1H NMR (500 MHz, DMSO-<sub>cf</sub>) δ 9.53 (s, 1H), 7.36 (s, 1H), 7.34-7.25 (m, 1H), 7.07-7.00 (m, 1H), 7.00-6.97 (m, 2H), 6.94 (td, J=8.6 Hz, J=2.3 Hz, 1H), 4.26 (s, 2H), 3.75 (s, 2H), 3.64 (t, J=4.5 Hz, 4H), 3.60 (s, 3H), 2.57-2.44 (m, 4H), 2.32 (s, 3H).
Example 29: 3-(2,4-Dichlorobenzyl)-2-methyl-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine

![Chemical Structure](image)

Title product was obtained in accordance with the method described above for Example 11, using 1-methyl-4-nitro-1H-imidazole (Intermediate P2) (134 mg, 1.66 mmol) and 4-((6-chloro-3-(2,4-dichlorobenzyl)-2-methylimidazo[1,2-b]-pyridazin-8-yl)methyl)morpholine (Intermediate P33) (217 mg, 0.51 mmol).

Product was obtained in the form of light-creamy crystals with the yield of 50% (127 mg, 0.256 mmol).

MS-ESI: (m/z) calculated for C23H26N7OCl2 [M+H]+: 486.2, found 486.1.

1H NMR (500 MHz, DMSO-d6) δ 9.54 (s, 1H), 7.74 (s, 1H), 7.33 (s, 1H), 7.25 (d, J=8.1 Hz, 1H), 6.99 (s, 1H), 6.78 (d, J=8.2 Hz, 1H), 6.71 (s, 1H), 4.33 (s, 2H), 3.77 (s, 2H), 3.65 (s, 4H), 3.55 (s, 3H), 2.51 (s, 4H), 2.30 (s, 3H).

13C NMR (125 MHz, DMSO-d6) δ 148.9, 139.3, 137.8, 135.1, 134.8, 134.7, 133.9, 133.6, 131.5, 130.4, 128.6, 127.5, 120.2, 108.4, 105.1, 66.2 (x2), 55.4, 53.5 (x2), 33.0, 25.7, 13.4.

Biological activity of the compounds of the invention

Test of JAK2 kinase inhibition in vitro

The effect of the compounds of the invention was analyzed using the test of JAK2 kinase inhibition as described below.

The compounds were dissolved in 100% DMSO, and obtained solutions were serially diluted in reaction buffer (50 mM Tris pH 7.5, 10 mM MgCl₂, 0.25 mM EGTA, 0.1 mM Na₃VO₄, 0.01% Triton X-100, 2.5 mM DTT). Recombinant JAK2 kinase (Carna Biosciences) was diluted to final concentration of 0.1 ng/μL in the dilution buffer (50 mM Tris-HCl pH 7.5, 150 mM NaCl, 10% glycerol, 0.05% Triton X-100, 1 mM DTT). 5 μL of prepared solutions of the compounds along with 5 μL of JAK2 kinase solution was added to each well of a 96-well plate. The plate was incubated for 10 minutes at 25°C in plate shaker-thermostat with orbital shaking at 400 rpm. To negative control wells all reagents were added except compounds and kinase, while to positive control wells - all reagents except tested compounds. Enzymatic reaction was initiated by adding 15 μL of solution consisting of: 5x concentrated reaction buffer (50 mM Tris pH 7.5, 10 mM MgCl₂, 0.25 mM EGTA, 0.1 mM Na₃VO₄, 0.01% Triton X-100, 2.5 mM DTT), water, 50 μM
ATP, and 16.67 µM IGF-1 Rtide peptide (MULpore). Than the plate was incubated for 1 hour at 25°C in plate shaker-thermostat with orbital shaking at 400 rpm. Detection of ADP obtained in enzymatic reaction was performed with ADP-Glo Kinase Assay (Promega). 25 µL of ADP-Glo Reagent was added to each well of 96-well plate and the plate was incubated for 40 minutes at 25°C in plate shaker-thermostat with orbital shaking at 400 rpm. Then 50 µL of Kinase Detection Reagent was added to each well of 96-well plate and the plate was incubated for 30 minutes at 25°C in plate shaker-thermostat with orbital shaking at 400 rpm. Finally, the intensity of luminescence was measured using Victor Light luminometer (Perkin Elmer, Inc.). The IC50 value was determined based on the intensity of luminescence in wells containing different concentrations of compounds and control wells. IC50 values were computed by fitting each point to the curve in non-linear regression model in Graph Pad software (ver. 5.03). Each compound was analyzed at least 6 times (in 6 wells) on two 96-well plates with at least three wells of each control.

The mean results of JAK2 inhibition of selected compounds of the invention is presented in the following table.

<table>
<thead>
<tr>
<th>Example</th>
<th>JAK2 IC50 [nM]</th>
</tr>
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<tbody>
<tr>
<td>Example 2</td>
<td>735.6</td>
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<tr>
<td>Example 18</td>
<td>2.2</td>
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<tr>
<td>Example 21</td>
<td>1.1</td>
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<td>Example 22</td>
<td>1.7</td>
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<tr>
<td>Example 23</td>
<td>5.5</td>
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<tr>
<td>Example 29</td>
<td>6.7</td>
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</tbody>
</table>

Western blot analysis of STAT3 protein phosphorylation

The level of phosphorylation of STAT3 transcription factor in a cell depends on the activity of JAK2 kinase - inhibition of JAK2 kinase by an inhibitor (tested compound) causes decrease of STAT3 phosphorylation, what is observed in Western blot assay as a decline of a band immunodetected with anti-pSTAT3 antibody. The inhibition of JAK2 kinase should not interfere with total amount of STAT3 protein - based on the immunodetection of STAT3. The loading control in this assay includes the immunodetection of beta-tubulin - a protein which is present at stable level in the cells.

The phosphorylation of STAT3 protein was evaluated in HEL-92.1.7 (ATCC) erythroleukemia cell line model harboring JAK2 kinase mutation [V617F],
entailing constant kinase activation in these cells. This cell line is the accepted model to study biological activity of JAK2 kinase inhibitors (H. Quentmeier et al., Leukemia 2006, 20, 471-476).

The cells were seeded into 6-well plates with the density of 0.5x10⁶/ml in the medium without the inhibitor. After 24 hours, cells were treated with the compound in the final concentration of 500 nM, for 2 hours. Then the cells were lysed with RIPA buffer (Sigma-Aldrich) containing proteases inhibitors (Halt Protease Inhibitor Cocktail, Thermo) and phosphatase inhibitors (PhosSTOP, Roche). The protein concentration in cell lysates were measured with BCA assay (Pierce) according to manufacturer's instruction. Cell lysates were separated with SDS-PAGE through 2 hours at 100 V in Mini Protean III system (BioRad). Electrophoretically-fractionated proteins were subsequently electrotransferred onto the nitrocellulose membrane through 1 hour at 100 V in Mini Protean III system. Western blot analysis of selected proteins was performed according to antibodies manufacturers’ instructions. In this analysis, the following primary antibodies were used: anti-pSTAT3, anti-STAT3 (Cell Signaling Technology) and anti-β-tubulin (Millipore). To detect primary antibodies immobilized onto the membrane, the secondary horseradish peroxidase-conjugated antibodies were used (Sigma-Aldrich). Immobilized proteins were visualized with LumiLight substrate (Roche) and subsequently exposed to Light Film BioMax (Kodak) which was developed.

Fig. 1 presents the results of the analysis of STAT phosphorylation in HEL cells treated with selected compounds of invention in concentration of 500 nM for 2 hours: A) pSTAT3 and B) STAT3. Abbreviation used: C - control; 21 - compound from example 21; 22 - compound from example 22.

Test of pharmacokinetics in vivo

The pharmacokinetic features including bioavailability of compounds of the invention were evaluated in a rat model as follows.

The study was conducted on 12-week old Wistar rats, weight 250-300 g, in groups of 5 animals each. Tested compound was administered orally at a dose of 10 mg per kg of body weight. After 10 min, 30 min, 1 h, 2 h, 4 h, 7 h and 12 h from compound administration, the blood was collected from each animal to K₂EDTA containing tube and subsequently centrifuged for 15 min, at 2000 x g at room temperature in order to obtain a serum. Acquired serum samples were stored at -20°C until analysis.

The compound concentration in serum was analyzed by spectrometry. Time to peak concentration (Tmax), peak concentration (Cmax) and area under the curve (AUC) were determined for every compound.
Fig. 2 shows the example of pharmacokinetic analysis result for the compound of the invention (Example 12) in reference to JAK2 kinase inhibitor LY-2784544 known from WO2010/074947. The compound of invention showed greater AUC than reference inhibitor (373.5 and 268.0, respectively). Moreover the Cmax for compound from Example 12 was higher (81.43 ng/mL) than for LY-2784544 (37.43 ng/mL).

This study demonstrated that compound of invention was more bioavailable and reached higher Cmax than reference drug in this class.
Claims

1. A compound represented by the general formula (I)

wherein:

\[ R^1 \text{ represents } \text{H or C}_1-\text{C}_4 \text{ alkyl; } \]
\[ R^2 \text{ represents phenyl substituted with one or two substituents selected from the group consisting of halogen atom and } \text{OC}_1-\text{C}_4 \text{ alkyl; } \]
\[ R^3 \text{ represents phenyl or 5 to 10-membered monocyclic or bicyclic heteroaryl having from 1 to 4 ring heteroatoms selected from the group consisting of N, S, and 0, which is unsubstituted or substituted with a substituent selected from halogen atom, C}_1-\text{C}_4 \text{ alkyl, and } -\text{C}(0)-\text{C}_1-\text{C}_4 \text{ alkyl; and } \]
\[ X \text{ represents } -\text{CH}_2- \text{ group or } -\text{C}(0)- \text{ group; } \]

and their acid addition salts;

with the exclusion of 3-(4-chloro-2-fluorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine and its salts.

2. The compound according to claim 1, wherein \( X \text{ represents } -\text{CH}_2- \text{ group.} \)

3. The compound according to claim 1, wherein \( X \text{ represents } -\text{C}(0)- \text{ group.} \)

4. The compound according to any one of claims 1 to 3, wherein \( R^1 \text{ represents } \text{H.} \)

5. The compound according to any one of claims 1 to 3, wherein \( R^1 \text{ represents } \text{C}_1-\text{C}_4 \text{ alkyl.} \)

6. The compound according to claim 5, wherein \( R^1 \text{ represents } \text{methyl.} \)

7. The compound according to any one of claims 1 to 6, wherein \( R^3 \text{ represents } 5\text{-membered monocyclic heteroaryl having 1 to 4 ring heteroatoms selected from the group consisting of N, S, and 0, which is unsubstituted or } \)
substituted with a substituent selected from halogen atom, -Ci-C4-alkyl, and
-C(0)0-CrC 4 -alkyL

8. The compound according to claim 7, wherein R^3 is selected from the group
of pyrazolyl, imidazolyl, thia diazolyl, and thiazolyl.

9. The compound according to any one of claims 1 to 6, wherein R^3 represents
6-membered monocyclic heteroaryl having 1 to 4 ring heteroatoms selected
from the group consisting of N, S, and O, which is unsubstituted or
substituted with a substituent selected from halogen atom, -Ci-C4-alkyl
group, and -C(0)0-Ci-C 4 -alkyl.

10. The compound according to claim 9, R^3 is selected from the group consisting
of pyridyl, pyrimidinyl, and pyrazinyl.

11. The compound according to claim 1, selected from the group consisting of
the following compounds and their acid addition salts:

3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-phenylimidazo-
[1,2-t]pyridazin-6-amine;

3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-A-(pyridin-2-yl)-
imidazo[1,2-b]pyridazin-6-amine;

3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(5-fluoropyridin-2-yl)-
imidazo[1,2-b]pyridazin-6-amine;

3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(6-methylpyridin-2-yl)-
imidazo[1,2-b]pyridazin-6-amine;

3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(3-methylpyridin-2-yl)-
imidazo[1,2-b]pyridazin-6-amine;

3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(5-chloropyridin-2-yl)-
imidazo[1,2-b]pyridazin-6-amine;

3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-
imidazo[1,2-b]pyridazin-6-amine;

3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-
imidazo[1,2-b]pyridazin-6-amine;

3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(pirymidyn-4-yl)-
imidazo[1,2-t]pyridazin-6-amine;
3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
3-(4-Chloro-2-fluorobenzyl)-2-methyl-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
Ethyl 3-(3-(4-chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-ylamino)-1H-pyrazole-4-carboxylate;
3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)-N-(1H-1,2,4-triazol-3-yl)imidazo[1,2-t]pyridazin-6-amine;
W-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]-pyridazin-6-yl)-5-methylthiazol-2-amine;
W-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]-pyridazin-6-yl)-4-methylthiazol-2-amine;
Methyl 2-(3-(4-chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]-pyridazin-6-ylamino)thiazole-5-carboxylate;
W-(3-(4-Chloro-2-fluorobenzyl)-2-methyl-8-(morpholinomethyl)imidazo[1,2-b]-pyridazin-6-yl)-1,3,4-thiadiazol-2-amine;
3-(4-Fluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
3-(4-Fluorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
3-(2,4-Difluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
3-(2,4-Difluorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-6-amine;
(2,4-Difluorophenyl)(2-methyl-6-(5-methyl-1H-pyrazol-3-ylamino)-8-(morpholinomethyl)imidazo[1,2-t]pyridazin-3-yl)methanone;
3-(2,4-Dichlorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholino)methyl)imidazo[1,2-t]pyridazin-6-amine;
3-(2,4-Dichlorobenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholino)methyl)imidazo[1,2-b]pyridazin-6-amine;
3-(2-Fluoro-4-metoksybenzyl)-2-methyl-N-(5-methyl-1H-pyrazol-3-yl)-8-(morpholino)methyl)imidazo[1,2-b]pyridazin-6-amine;
3-(4-Fluorobenzyl)-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholino)methyl)imidazo[1,2-b]pyridazin-6-amine;
3-(2,4-Difluorobenzyl)-2-methyl-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholino)methyl)imidazo[1,2-b]pyridazin-6-amine; and
3-(2,4-Dichlorobenzyl)-2-methyl-N-(1-methyl-1H-imidazol-4-yl)-8-(morpholino)methyl)imidazo[1,2-b]pyridazin-6-amine.

12. A pharmaceutical composition, comprising as an active ingredient a compound of the general formula (I) as defined in any one of claims 1 to 11, in combination with pharmaceutically acceptable excipients.

13. A compound of the general formula (I) as defined in any one of claims 1 to 11 for use as a medicament.

14. A use of a compound of the general formula (I) as defined in any one of claims 1 to 11 for the preparation of a medicament for treating myeloproliferative disorders and cancer diseases.

15. A method of treating of proliferative disorders and cancer diseases in a mammal subject, including humans, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of the general formula (I) as defined in any one of claims 1 to 11 or a pharmaceutical composition as defined in claim 12.
**INTERNATIONAL SEARCH REPORT**

**PCT/IB2013/056241**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D487/04 A61P35/00 A61K31/5025 A61K31/506

ADD.

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. See patent family annex.

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**Date of the actual completion of the international search**

18 October 2013

**Date of mailing of the international search report**

29/10/2013

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Brandstetter, T

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