

4H-Pyrrolo[3,2-c]pyridin-4-one Compounds

Field of application of the invention

- 5 The invention relates to substituted 4H-pyrrolo[3,2-c]pyridin-4-one compounds, a process for their production and uses thereof.

BACKGROUND OF THE INVENTION

10 The Epidermal Growth Factor Receptor (EGFR or EGF-receptor) receptor tyrosine kinase family consists of 4 members: EGFR (ErbB1, Her1), ERBB2 (Her2), ERBB3 (Her3), and ERBB4 (Her4). EGFR mediates activation of MAPK and PI3K signaling pathways and thereby regulates cell proliferation, differentiation, migration and survival (Pao et al., 2010). EGFR gene amplification, overexpression, and mutations are frequently observed in various cancer indications and are associated with a poor prognosis (Gridelli et al., 2015).

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In lung adenocarcinoma, mutations of EGFR are prevalent in approximately 15% of Western patients and up to 50% of East Asian patients (Paez et al., 2004). These mutations typically occur in one of four exons, exons 18-21, in the kinase domain of EGFR (Paez et al., 2004). The most common activating mutations in EGFR are a point mutation in exon 21, substituting an arginine for a leucine (L858R), and a small in-frame deletion in exon 19 that removes four amino acids (del 19/del746-750) (Pao et al., 2010). The FDA-approved inhibitors gefitinib, erlotinib, and afatinib, targeting mutations in exons 18, 19, and 21 of EGFR, are effective in patients but the response is often not durable (Mok et al., 2009; Sequist et al., 2013). Resistance frequently occurs in these patients in response to acquisition of a second mutation, T790M (Pao et al., 2005). Second generation inhibitors, e.g. afatinib, irreversibly target this mutation but are still potent inhibitors of wild-type EGFR, leading to dose-limiting toxicity and lack of efficacy in patients. A third-generation irreversible inhibitor, osimertinib, that maximizes activity towards T790M while minimizing activity towards wild-type EGFR, is effective in T790M mutant patients and is currently the standard treatment for T790M positive patients (Mok et al., 2017). Osimertinib is also approved as a front-line therapy for patients with mutations of EGFR exons 19 or 21 (Soria et al., 2018).

20 However, patients also develop resistance to irreversible third-generation EGFR inhibitors, such as osimertinib. One of the major osimertinib resistance mechanisms identified is

mutation of the cysteine in position 797 to a serine, resulting in loss of the covalently interacting cysteine and loss of sensitivity to irreversible EGFR inhibitors, at which point progressing patients have currently only limited treatment options (Thress et al., 2015; Oxnard et al., 2018). Such C797S mutations can also occur when osimertinib is used as a first-line therapy, in the absence of the T790M mutation (Ramalingham et al., 2018a; Ramalingham et al., 2018b). A novel targeted therapy that is able to specifically address the EGFR-C797S acquired resistance mutation would be highly beneficial for those patients.

10 By contrast, and with the exception of A763_Y764insFQEA, small in-frame insertions of EGFR exon20 are resistant to all clinically-approved EGFR inhibitors at doses achievable in lung cancer patients and comprise an unmet medical need (Yasuda et. al., 2013).

Patients with EGFR exon20 insertions, such as V769_D770insASV, D770_N771insSVD, D770_N771insNPG, N771_P772insH, H773_V774insH, H773_V774insNPH, V774_C775insHV show particular low response rates to all currently approved EGFR-targeted therapies, resulting in significantly reduced progression-free survival as well as overall survival (Chen et al., 2016). This has been shown for the first-generation inhibitors erlotinib and gefitinib as well as for the second-generation inhibitor afatinib (Chen et al., 2016; Yang et al., 2015).

Therefore, the standard treatment for EGFR exon20 insertion patients is currently chemotherapy.

25 The same resistance profile has been observed for exon20 insertion mutations in ERBB2 (e.g. ERBB2 A775_G776insYVMA with the highest prevalence), another member of the EGF-receptor family (Arcila et al., 2012) and some of the uncommon EGFR mutations like L681Q (Chiu et al., 2015).

30 Several irreversible inhibitors are currently in clinical trials for the treatment of EGFR exon20 insertion patients: Osimertinib, initially approved for the treatment of T790M mutant NSCLC patients (Floc'h et al., 2018); poziotinib (HM-781-36B), a non-approved pan-Her inhibitor targeting EGFR, Her2/neu, and Her4 (Robichaux et al., 2018); as well as TAK-788 (AP32788) (Doebele et al., ASCO 2018). Of these, the first clinical data have been published for poziotinib and TAK-788. Both compounds clearly show clinical efficacy in

EGFR exon20 insertion patients. However, major adverse events, mediated by inhibition of wild-type EGFR, have been reported for both clinical trials and these adverse events may limit clinical utility.

- 5 More recently, new preclinical data has been published for two additional compounds showing activity on EGFR exon20 insertions: TAS6417 (TCP-064) and compound 1a (Hasako et al., 2018; Jang et al., 2018). No clinical results are yet available for these two compounds.
- 10 In summary, mutant EGFR is a promising drug target for cancer therapy. In particular, patients with primary resistance to approved anti-EGFR therapies, due to EGFR exon20 insertions, have only few treatment options to date and there is a great need for novel alternative and/or improved therapeutics to provide these patients with an efficacious, well-tolerable therapy (Oxnard et al., 2013). Therefore, potent inhibitors of mutant EGFR,
- 15 particularly of mutant EGFR with exon20 insertion mutations that show improved selectivity versus wild-type EGFR, represent valuable compounds that should complement therapeutic options either as single agents or in combination with other drugs.

SUMMARY OF THE INVENTION

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The invention provides compounds that inhibit a mutant EGFR; specifically, an EGFR comprising one or more exon 20 insertion mutations, an L858R mutation, or a small in-frame deletion of exon 19, in the presence or absence of a C797S mutation. These compounds furthermore have reduced activity towards the wild-type-EGFR.

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It has now been found that the compounds of the present invention have surprising and advantageous properties.

- In particular, said compounds of the present invention have surprisingly been found to
- 30 effectively inhibit mutant EGFR with exon 20 insertion mutations, particularly those harboring a D770_N771ins SVD exon 20 insertion with an IC₅₀ below 5 nM. Furthermore it has been found that these compounds additionally show cellular potency below 1 µM in EGFR V769_D770insASV, D770_N771insSVD, D770_N771insNPG, N771_P772insH, or H773_V774insNPH exon 20 insertion harboring BA/F3 cell lines. Furthermore, the here
- 35 described compounds are active in BA/F3 cell lines harboring D770_N771insSVD C797S.

In addition, the here described compounds potently inhibit proliferation of BA/F3 cell lines carrying EGFR activating mutations with or without C797S acquired resistance mutations (EGFR E746_A750del, L858R, E746_A750del C797S, L858R C797S), uncommon EGFR mutations (EGFR L681Q) or ERBB2 exon20 insertion A775_G776insYVMA.

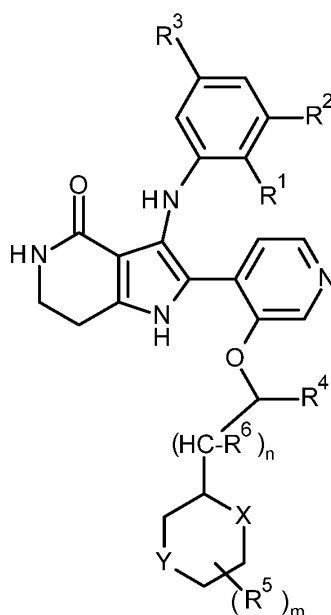
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Surprisingly these compounds additionally show at least 5-fold selectivity in an antiproliferative assay of EGFR D770_N771ins SVD exon 20 insertion harboring BA/F3 cell lines versus wild-type EGFR harboring BA/F3 cells and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses mediated by mutant EGFR with exon 20 insertion mutations and/or reduce (or block) proliferation in cells harboring EGFR exon 20 insertion mutations, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

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Description of the invention

25 In accordance with a first aspect, the invention relates to compounds of formula (I),



(I)

in which:

- 5 R¹ represents methyl, ethyl, trifluoromethyl, 2,2-difluoroethyl, cyano, chloro, bromo, methoxy or difluoromethoxy;
- R² represents hydrogen, methyl, ethyl, fluoro, chloro or bromo;
- R³ represents hydrogen or fluoro;
- R⁴ represents hydrogen or methyl;
- 10 R⁵ independently at each occurrence represents hydrogen, trifluoromethyl or C₁-C₃ alkyl, R⁵ being bound to any carbon atom of the ring;
- R⁶ independently at each occurrence represents hydrogen, C₁-C₃-alkyl or C₁-C₃-haloalkyl;
- R⁷ represents C₁-C₃-alkyl or C₂-C₃-haloalkyl;
- 15 R⁸ represents C₁-C₃-alkyl or C₂-C₃-haloalkyl;
- X represents NR⁷ or O;
- Y represents NR⁸ or O;

m represents 0, 1, 2 or 3;

n represents 0 or 1;

or an N-oxide, a salt or a tautomer of said compound, or a salt of said N-oxide or tautomer. In some embodiments at least two R⁵ groups are geminal groups (i.e., attached
5 to the same carbon atom).

In a second aspect, the invention relates to compounds of formula (I) as described *supra*, wherein:

R¹ represents methyl, ethyl, chloro, methoxy or difluoromethoxy;

10 R² represents methyl, ethyl, fluoro or chloro;

R³ represents hydrogen or fluoro;

R⁴ represents hydrogen or methyl;

R⁵ represents hydrogen, methyl or trifluoromethyl,
R⁵ being bound to any carbon atom of the ring;

15 R⁶ represents hydrogen, methyl or trifluoromethyl;

R⁷ represents C₁-C₂-alkyl or C₂-C₃-fluoroalkyl;

R⁸ represents C₁-C₂-alkyl or C₂-C₃-fluoroalkyl;

X represents NR⁷ or O;

Y represents NR⁸ or O;

20 m represents 0, 1 or 2;

n represents 0 or 1;

or an N-oxide, a salt or a tautomer of said compound, or a salt of said N-oxide or tautomer.

25 In a third aspect, the invention relates to compounds of formula (I) as described *supra*, wherein:

R¹ represents methyl, ethyl, chloro or methoxy;

- R² represents, fluoro or chloro;
- R³ represents hydrogen or fluoro;
- R⁴ represents hydrogen;
- R⁵ represents hydrogen or methyl,
 5 R⁵ being bound to any carbon atom of the ring;
- R⁶ represents hydrogen;
- R⁷ represents methyl;
- R⁸ represents methyl, 2,2,2-trifluoroethyl or 2,2-difluoroethyl;
- X represents NR⁷ or O;
- 10 Y represents NR⁸ or O;
- m represents 0, 1, or 2;
- n represents 0 or 1;

or an N-oxide, a salt or a tautomer of said compound, or a salt of said N-oxide or tautomer.

- 15 In a fourth aspect, the invention relates to compounds of formula (I) as described *supra*, which is selected from the group consisting of:

- 3-(3-chloro-2-methoxyanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 20 3-(3-chloro-2-methoxyanilino)-2-(3-[(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-[(2R)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 25 2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-[(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-[(2R)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

- 3-(2,3-dichloroanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(2,3-dichloroanilino)-2-(3-{[(2S)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 5 3-(2,3-dichloroanilino)-2-(3-{[(2R)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{[(3R)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 10 3-(3-fluoro-2-methoxyanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(2R)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 15 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(2S)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2R)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 20 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2S)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-{[4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 25 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-{[1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(3S)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{[(3S)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 30 2-(3-{[(2S)-4-(2,2-difluoroethyl)morpholin-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(2S)-4-(2,2,2-trifluoroethyl)morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

- 3-(3-chloro-2-methoxyanilino)-2-{3-[2-(4-dioxan-2-yl)ethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{2-[(2R)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 5 3-(3-chloro-2-methoxyanilino)-2-(3-{2-[(2S)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-{[(2S)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-{[(2S)-4-(2,2,2-trifluoroethyl)morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 10 3-(3-chloro-2-ethylanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 15 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2R)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-{[(2R)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 20 2-(3-{[(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-{2-[(2R)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 25 2-(3-{2-[(2S)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(3R)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methylanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 30 2-(3-{[(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methylanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

- 3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-2-(3-[(2S)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-(3-[(2S)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 5 3-(3-chloro-2-methylanilino)-2-(3-[(3R)-4-methylmorpholin-3-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-(3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-(3-[(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 10 3-(3-chloro-2-methylanilino)-2-(3-[(2R)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methylanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 15 2-(3-[(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(3-fluoro-2-methylanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-[(2R)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(3-fluoro-2-methylanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-(3-[(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 20 3-(3-chloro-2-methylanilino)-2-(3-[(2R)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-ethylanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 25 3-(3-chloro-2-ethylanilino)-2-(3-[(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-ethylanilino)-2-(3-[(2R)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-ethylanilino)-2-(3-[(2R)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 30 3-(3-chloro-2-ethylanilino)-2-(3-[(2S)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{1-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

- 3-(3-chloro-2-methoxyanilino)-2-(3-((1S)-1-[(2S)-1,4-dioxan-2-yl]ethoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-((1S)-1-[(2R)-1,4-dioxan-2-yl]ethoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 5 3-(3-chloro-2-methoxyanilino)-2-(3-((1R)-1-[(2S)-1,4-dioxan-2-yl]ethoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-((1R)-1-[(2R)-1,4-dioxan-2-yl]ethoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methylanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 10 3-(3-fluoro-2-methylanilino)-2-(3-[(2R)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methylanilino)-2-(3-[(2S)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 15 2-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-[(2R)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-[(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 20 2-(3-[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-[(2R)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 25 2-(3-[(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-[3-((1R)-1-[(2R)-4-methylmorpholin-2-yl]ethyl)oxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 30 4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-[3-((1S)-1-[(2S)-4-methylmorpholin-2-yl]ethyl)oxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-[3-((1R)-1-[(2S)-4-methylmorpholin-2-yl]ethyl)oxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

3-(3-chloro-2-methoxyanilino)-2-[3-({(1S)-1-[(2R)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

A further aspect of the invention relates to compounds of formula (I), which are present as
5 their salts.

It is to be understood that the present invention relates to any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I), supra.

10 More particularly still, the present invention covers compounds of general formula (I) which are disclosed in the Example section of this text, infra.

In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention, said methods comprising the steps as described in the
15 Experimental Section herein.

Another embodiment of the invention are compounds according as disclosed in the Claims section or disclosed analogs of the exemplified compounds and subcombinations thereof.

20 Definitions

It is to be understood that embodiments disclosed herein are not meant to be understood as individual embodiments which would not relate to one another. Features discussed with one embodiment or aspect of the invention are meant to be disclosed also in connection with other embodiments or aspects of the invention shown herein. If, in one case, a specific
25 feature is not disclosed with one embodiment or aspect of the invention, but with another, the skilled person would understand that does not necessarily mean that said feature is not meant to be disclosed with said other embodiment or aspect of the invention. The skilled person would understand that it is the gist of this application to disclose said feature also for the other embodiment or aspect of the invention, but that just for purposes of clarity and
30 to keep the length of this specification manageable. For example, it is to be understood that all aspects, embodiments, pharmaceutical compositions, combinations, uses and/or methods of the present invention defined herein for the compounds of formula (I) also relate to more specific embodiments of the compounds of formula (I), such as, but not limited to, the compounds of formula (Ia) and vice-versa, for example.

35

It is further to be understood that the content of the documents referred to herein is incorporated by reference in their entirety, e.g., for enablement purposes, namely when e.g. a method is discussed details of which are described in said document. This approach serves to keep the length of this specification manageable.

5

Constituents, which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently of one another at any possible position. When any variable occurs more than one time in any constituent, each definition is independent. For example, when R¹, R^{1a}, R^{1b}, R^{1c}, R², R³ and/or R⁴ occur more than one
10 time in any compound of formula (I) each definition of R¹, R^{1a}, R^{1b}, R^{1c}, R², R³ and R⁴ is independent.

Should a constituent be composed of more than one part, e.g. C₁-C₄-alkoxy-C₂-C₄-alkyl, the position of a possible substituent can be at any of these parts at any suitable position. A
15 hyphen at the beginning or at the end of the constituent marks the point of attachment to the rest of the molecule. Should a ring be substituted the substituent could be at any suitable position of the ring, also on a ring nitrogen atom, if suitable.

The term "comprising" when used in the specification includes "consisting of".

20

If it is referred to "as mentioned above" or "mentioned above", "*supra*" within the description it is referred to any of the disclosures made within the specification in any of the preceding pages.

25 If it is referred to "as mentioned herein", "described herein", "provided herein," or "as mentioned in the present text," or "stated herein" within the description it is referred to any of the disclosures made within the specification in any of the preceding or subsequent pages.

30 "Suitable" within the sense of the invention means chemically possible to be made by methods within the knowledge of a skilled person.

The terms as mentioned in the present text may have the following meanings:

The term “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a fluorine, chlorine, bromine or iodine atom.

The term “C₁-C₆-alkyl” is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5, or 6 carbon atoms, e.g. a methyl, ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms (“C₁-C₄-alkyl”), e.g. a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms (“C₁-C₃-alkyl”), e.g. a methyl, ethyl, n-propyl or iso-propyl group.

The term “C₁-C₄-haloalkyl” is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term “C₁-C₄-alkyl” is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, in identically or differently, *i.e.* one halogen atom being independent from another. Particularly, said halogen atom is F. Said C₁-C₄-haloalkyl group is, for example, -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, -CH₂CH₂CF₃, or -CH(CH₂F)₂.

The term “C₂-C₃-fluoroalkyl” is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term “C₂-C₃-alkyl” is defined *supra*, and in which one or more hydrogen atoms is replaced by a fluoro atom. Said C₂-C₃-fluoroalkyl group is, for example, -CF₂CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, -CH₂CH₂CF₃, or -CH(CH₂F)₂.

The term “C₁-C₄-alkoxy” is to be understood as meaning a linear or branched, saturated, monovalent, hydrocarbon group of formula -O-alkyl, in which the term “alkyl” is defined *supra*, e.g. a methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy or sec-butoxy group, or an isomer thereof.

Unless defined otherwise, the term “5- to 6-membered heterocycloalkyl” or “5- to 6-membered heterocyclic ring”, is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 4 or 5 carbon atoms, and one heteroatom-

containing group selected from O and NR, wherein R means a hydrogen atom, a C₁-C₃-alkyl or a C₁-C₃-haloalkyl group, it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms.

- 5 Particularly, without being limited thereto, said heterocycloalkyl can be a 5-membered ring, such as tetrahydrofuranyl, pyrazolidinyl, or a 6-membered ring, such as tetrahydropyranyl, piperidinyl, for example.

10 The term "C₁-C₆", as used throughout this text, *e.g.* in the context of the definition of "C₁-C₆-alkyl" or "C₁-C₆-haloalkyl" is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C₁-C₆" is to be interpreted as any sub-range comprised therein, *e.g.* C₁-C₆, C₂-C₆, C₃-C₆, C₁-C₂, C₁-C₃, particularly C₁-C₂, C₁-C₃, C₁-C₄.

- 15 The term "C₁-C₄", as used throughout this text, *e.g.* in the context of the definition of "C₁-C₄-alkyl", "C₁-C₄-haloalkyl", "C₁-C₄-alkoxy", or "C₁-C₄-haloalkoxy" is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 4, *i.e.* 1, 2, 3 or 4 carbon atoms. It is to be understood further that said term "C₁-C₄" is to be interpreted as any sub-range comprised therein, *e.g.* C₁-C₄, C₂-C₄, C₃-C₄, C₁-C₂, C₁-C₃, particularly C₁-C₂, C₁-C₃, C₁-C₄, in the case of "C₁-C₆-haloalkyl" or "C₁-C₄-haloalkoxy" even more particularly C₁-C₂.

- 25 Further, as used herein, the term "C₃-C₆", as used throughout this text, *e.g.* in the context of the definition of "C₃-C₆-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C₃-C₆" is to be interpreted as any sub-range comprised therein, *e.g.* C₃-C₆, C₄-C₆, C₃-C₅, C₃-C₄, C₄-C₆, C₅-C₆; particularly C₃-C₆.

- 30 The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

Ring system substituent means a substituent attached to an aromatic or nonaromatic ring system which, for example, replaces an available hydrogen on the ring system.

As used herein, the term "one or more", e.g. in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four, five, etc. particularly one, two, three or four, more particularly one, two or three, even more particularly one or two".

The compounds of general formula (I) may exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of general formula (I), particularly deuterium-containing compounds of general formula (I).

The term "isotopic variant" of a compound or a reagent is defined as a compound exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The term "isotopic variant of the compound of general formula (I)" is defined as a compound of general formula (I) exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The expression "unnatural proportion" is to be understood as meaning a proportion of such isotope which is higher than its natural abundance. The natural abundances of isotopes to be applied in this context are described in "Isotopic Compositions of the Elements 1997", Pure Appl. Chem., 70(1), 217-235, 1998. Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{125}I , ^{129}I and ^{131}I , respectively.

With respect to the treatment and/or prophylaxis of the disorders specified herein the isotopic variant(s) of the compounds of general formula (I) in one embodiment contain deuterium ("deuterium-containing compounds of general formula (I)"). Isotopic variants of the compounds of general formula (I) in which one or more radioactive isotopes, such as ^3H or ^{14}C , are incorporated are useful e.g. in drug and/or substrate tissue distribution studies. These isotopes are particularly preferred for the ease of their incorporation and

detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of general formula (I). These isotopic variants of the compounds of general formula (I) are useful for *in vivo* imaging applications. Deuterium-containing and ^{13}C -containing compounds of general formula (I) can be used in mass spectrometry analyses (H. J. Leis et al., Curr. Org. Chem., 1998, 2, 131) in the context of preclinical or clinical studies.

Isotopic variants of the compounds of general formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, in one embodiment for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds (Esaki et al., Tetrahedron, 2006, 62, 10954; Esaki et al., Chem. Eur. J., 2007, 13, 4052). Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds (H. J. Leis et al., Curr. Org. Chem., 1998, 2, 131; J. R. Morandi et al., J. Org. Chem., 1969, 34 (6), 1889) and acetylenic bonds (N. H. Khan, J. Am. Chem. Soc., 1952, 74 (12), 3018; S. Chandrasekhar et al., Tetrahedron, 2011, 52, 3865) is a rapid route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons (J. G. Atkinson et al., US Patent 3966781). A variety of deuterated reagents and synthetic building blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA. Further information on the state of the art with respect to deuterium-hydrogen exchange is given for example in Hanzlik et al., J. Org. Chem. 55, 3992-3997, 1990; R. P. Hanzlik et al., Biochem. Biophys. Res. Commun. 160, 844, 1989; P. J. Reider et al., J. Org. Chem. 52, 3326-3334, 1987; M. Jarman et al., Carcinogenesis 16(4), 683-688, 1993; J. Atzrodt et al., Angew. Chem., Int. Ed. 2007, 46, 7744; K. Matoishi et al., J. Chem. Soc, Chem. Commun. 2000, 1519-1520; K. Kassahun et al., WO2012/112363.

The term "deuterium-containing compound of general formula (I)" is defined as a compound of general formula (I), in which one or more hydrogen atom(s) is/are replaced by one or more deuterium atom(s) and in which the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than the natural abundance of

deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of general formula (I) the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, in one embodiment higher than 90%, 95%, 96% or 97%, in other embodiments higher than 98% or 99% at said position(s). It is understood that the abundance of deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of general formula (I) may alter the physicochemical properties (such as for example acidity [A. Streitwieser et al., *J. Am. Chem. Soc.*, 1963, 85, 2759; C. L. Perrin, et al., *J. Am. Chem. Soc.*, 2007, 129, 4490], basicity [C. L. Perrin, et al., *J. Am. Chem. Soc.*, 2003, 125, 15008; C. L. Perrin in *Advances in Physical Organic Chemistry*, 44, 144; C. L. Perrin et al., *J. Am. Chem. Soc.*, 2005, 127, 9641], lipophilicity [B. Testa et al., *Int. J. Pharm.*, 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (D. J. Kushner et al., *Can. J. Physiol. Pharmacol.*, 1999, 77, 79; A. E. Mutlib et al., *Toxicol. Appl. Pharmacol.*, 2000, 169, 102). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., *Chem. Res. Toxicol.*, 2013, 26, 410; Uetrecht et al., *Chemical Research in Toxicology*, 2008, 21, 9, 1862; Efavirenz: A. E. Mutlib et al., *Toxicol. Appl. Pharmacol.*, 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic relationship. Indiplon (A. J. Morales et al., Abstract 285, The 15th North American Meeting of the International Society of Xenobiotics, San Diego, CA, October 12-16, 2008), ML-337 (C. J. Wenthur et al., *J. Med. Chem.*, 2013, 56, 5208), and Odanacatib (K. Kassahun et al.,

WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., *Arzneim. Forsch. Drug. Res.*, 2006, 56, 295; Telaprevir: F. Maltais et al., *J. Med. Chem.*, 5 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

10 A compound of general formula (I) may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of general formula (I) having a certain pattern of one or more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium- containing compound(s) of general formula (I) is/are attached to a carbon atom and/or is/are located at those positions of the compound of 15 general formula (I), which are sites of attack for metabolizing enzymes such as e.g. cytochrome P₄₅₀.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, 20 isomer, hydrate, solvate or the like.

By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

25

The compounds of this invention may contain one or more asymmetric centre, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration, resulting in racemic mixtures in the case of a single asymmetric centre, and diastereomeric mixtures in the case of multiple asymmetric 30 centres. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention.

5 Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

10

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid.

15 Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with
20 or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Daicel, e.g., Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

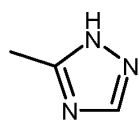
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In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

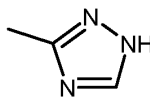
30 The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, e.g. R- or S-isomers, or E- or Z-isomers, in any ratio. Isolation of a single stereoisomer, e.g. a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

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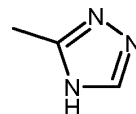
Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers, namely :



1H-tautomer



2H-tautomer



4H-tautomer.

10 The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

20 The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, e.g. a hydrate, hemi-, (semi-), 25 mono-, sesqui-, di-, tri-, tetra-, penta- etc. solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, e.g. as a free base, 30 or as a free acid, or as a zwitterion, or can exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," J. Pharm. Sci. **1977**, 66, 1-19.

5

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalenedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric or thiocyanic acid, for example.

20

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadiazine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

30

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the
5 compounds of the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

10 In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

15 Unless specified otherwise, suffixes to chemical names or structural formulae such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF₃COOH", "x Na⁺", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.

20 This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates with (if defined) unknown stoichiometric composition.

25 The salts include water-insoluble and, particularly, water-soluble salts.

Furthermore, derivatives of the compounds of formula (I) and the salts thereof which are converted into a compound of formula (I) or a salt thereof in a biological system
30 (bioprecursors or pro-drugs) are covered by the invention. Said biological system is *e.g.* a mammalian organism, particularly a human subject. The bioprecursor is, for example, converted into the compound of formula (I) or a salt thereof by metabolic processes.

As used herein, the term "*in vivo* hydrolysable ester" is understood as meaning an *in vivo*
35 hydrolysable ester of a compound of the present invention containing a carboxy or hydroxy

group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C₁-C₆ alkoxyethyl esters, e.g. methoxyethyl, C₁-C₆ alkanoyloxyethyl esters, e.g. pivaloyloxyethyl, phthalidyl esters, C₃-C₈ cycloalkoxy-carbonyloxy-C₁-C₆ alkyl esters, e.g. 1-cyclohexylcarbonyloxyethyl, 1,3-dioxolen-2-onylmethyl esters, e.g. 5-methyl-1,3-dioxolen-2-onylmethyl, and C₁-C₆-alkoxycarbonyloxyethyl esters, e.g. 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of this invention.

10

An *in vivo* hydrolysable ester of a compound of the present invention containing a hydroxy group includes inorganic esters such as phosphate esters and [alpha]-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of [alpha]-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxyacetoxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxyethyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

20

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorphs, in any ratio.

25 In the context of the properties of the compounds of the present invention the term "pharmacokinetic profile" means one single parameter or a combination thereof including permeability, bioavailability, exposure, and pharmacodynamic parameters such as duration, or magnitude of pharmacological effect, as measured in a suitable experiment. Compounds with improved pharmacokinetic profiles can, for example, be used in lower doses to achieve
30 the same effect, may achieve a longer duration of action, or may achieve a combination of both effects.

The term "combination" in the present invention is used as known to persons skilled in the art and may be present as a fixed combination, a non-fixed combination or kit-of-parts.

35

- A “fixed combination” in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a “fixed combination” is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical combination wherein the said first active ingredient and the said second active ingredient are present in one unit without being in admixture.
- A non-fixed combination or “kit-of-parts” in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the non-fixed combination or kit-of-parts may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered. Any such combination of a compound of formula (I) of the present invention with an anti-cancer agent as defined below is an embodiment of the invention.
- The term “(chemotherapeutic) anti-cancer agents” relates to any agent that reduces the survival or proliferation of a cancer cell, and includes but is not limited to 131I-chTNT, abarelix, abiraterone, aclarubicin, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alemtuzumab, Alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, Hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, axitinib, azacitidine, basiliximab, belotecan, bendamustine, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcium folinate, calcium levofolinate, capecitabine, capromab, carboplatin, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, docetaxel, dolasetron, doxifluridine,

doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, 5 fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, 10 lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, lanreotide, lapatinib, lasocholine, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, 15 lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, 20 molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, nedaplatin, nelarabine, neridronic acid, nivolumabpentetate, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orlitolmod, 25 osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, 30 pixantrone, plerixafor, plicamycin, poliglucosam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pozotinib, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, 35 refametinib, regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, romidepsin,

romiplostim, romurtide, roniciclib, samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-
 5 [Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex,
 10 valatinib, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

By "Epidermal Growth Factor Receptor (EGFR) Polypeptide" is meant a polypeptide having
 15 at least about 95% amino acid sequence identity to the sequence provided at UniProt Accession No. P00533-1 or a fragment thereof. In some embodiments, the EGFR fragment binds an EGFR ligand and/or has kinase activity. Mutant EGFR polypeptides include those having an insertion between, for example, amino acids V769 and D770 or between D770 and N771. In other embodiments, the amino acid sequence identity is 96, 97, 98, 99, or
 20 100% to UniProt Accession No. P00533-1.

An exemplary full length sequence of human EGFR, which indicates V769, D770, and N771 in bold, is provided at UniProt Accession No. P00533-1, which is reproduced below:

	10	20	30	40	50
25	MRPSGTAGAA	LLALLAALCP	ASRALEEKKV	CQGTSNKLTQ	LGT FEDHFLS
	60	70	80	90	100
	LQRMFN NCEV	VLGNLEITYV	QRNYDLSFLK	TIQEVAGYVL	IALNTVERIP
	110	120	130	140	150
	LENLQIIRGN	MYYENSYALA	VLSNYDANKT	GLKELPMRNL	QEILHGAVRF
30	160	170	180	190	200
	SNNPALCNVE	SIQWRDIVSS	DFLSNMSMDF	QNH LGSCQKC	DPSCPNGSCW
	210	220	230	240	250
	GAGEENCQKL	TKIICAQQCS	GRCRGKSPSD	CCHNQCAAGC	TGPRES DCLV
	260	270	280	290	300
35	CRKFRDEATC	KDTCPLMLY	NPTTYQMDVN	PEGKYSFGAT	CVKKCPRNYV

	310	320	330	340	350
	VTDHGSCVRA	CGADSYEMEE	DGVRKCKKCE	GPCRKVCNGI	GIGEFKDSLS
	360	370	380	390	400
	INATNIKHFK	NCTSISGDLH	ILPVAFRGDS	FTHTPPLDPQ	ELDILKTVKE
5	410	420	430	440	450
	ITGFLLIQAW	PENRTDLHAF	ENLEIIRGRT	KQHGQFSLAV	VSLNITSLGL
	460	470	480	490	500
	RSLKEISDGD	VIISGNKNLC	YANTINWKKL	FGTSGQKTKI	ISNRGENSCK
	510	520	530	540	550
10	ATGQVCHALC	SPEGCWGPEP	RDCVSCRNVS	RGRECVDKCN	LLEGEPRFV
	560	570	580	590	600
	ENSECIQCHP	ECLPQAMNIT	CTGRGPDNCI	QCAHYIDGPH	CVKTCPAGVM
	610	620	630	640	650
	GENNTLVWKY	ADAGHVCHLC	HPNCTYGCTG	PGLEGCPNG	PKIPSIATGM
15	660	670	680	690	700
	VGALLLLLVV	ALGIGLFMRR	RHIVRKRTL	RLLQERELVE	PLTPSGEAPN
	710	720	730	740	750
	QALLRILKET	EFKKIKVLGS	GAFGTVYKGL	WIPEGEKVKI	PVAIKELREA
	760	770	780	790	800
20	TSPKANKEIL	DEAYVMASVD	NPHVCRLGI	CLTSTVQLIT	QLMPFGCLLD
	810	820	830	840	850
	YVREHKDNIG	SQYLLNWCVQ	IAKGMNYLED	RRLVHRDLAA	RNVLVKTPQH
	860	870	880	890	900
	VKITDFGLAK	LLGAEEKEYH	AEGGKVPIKW	MALESILHRI	YTHQSDVWSY
25	910	920	930	940	950
	GVTWVWELMTF	GSKPYDGIPA	SEISSILEKG	ERLPQPPICT	IDVYMIMVKC
	960	970	980	990	1000
	WMIDADSRPK	FRELIIEFSK	MARDPQRYLV	IQGDERMHLP	SPTDSNFYRA
	1010	1020	1030	1040	1050
30	LMDEEDMDDV	VDADEYLIPQ	QGGFSSPSTS	RTPLLSSLSA	TSNNSTVACI
	1060	1070	1080	1090	1100
	DRNGLQSCPI	KEDSFLQSYS	SDPTGALTED	SIDDTFLPVP	EYINQSVPKR
	1110	1120	1130	1140	1150
	PAGSVQNPVY	HNQPLNPAPS	RDPHYQDPHS	TAVGNPEYLN	TVQPTCVNST
35	1160	1170	1180	1190	1200
	FDSPAHWQK	GSHQISLDNP	DYQQDFFPKE	AKPNGIFKGS	TAENAEYLRV

1210
APQSSEFIGA

An exemplary polynucleotide encoding EGFR is provided at NCBI Reference Sequence:

5 NM_001346897.1, which is reproduced below:

```
1  gtccgggcag cccccggcgc agcgcggccg cagcagcctc cccccccgc
   acggtgtgag
61  cgcccgacgc ggccgaggcg gccggagtcc cgagctagcc ccggcggccg
10  ccgccgcccc
   121  gaccggacga caggccacct cgtcggcgtc cgcccgagtc cccgcctcgc
      cgccaacgcc
   181  acaaccaccg cgcacggccc cctgactccg tccagtattg atcgggagag
      ccggagcgag
15  241  ctcttcgggg agcagcgatg cgaccctccg ggacggccgg ggcagcgctc
      ctggcgctgc
   301  tggctgcgct ctgcccggcg agtcgggctc tggaggaaaa gaaagtttgc
      caaggcacga
   361  gtaacaagct cagcgagttg ggcacttttg aagatcattt tctcagcctc
20  cagaggatgt
   421  tcaataactg tgagggtggtc cttgggaatt tggaaattac ctatgtgcag
      aggaattatg
   481  atctttcctt cttaaagacc atccaggagg tggctggtta tgtcctcatt
      gccctcaaca
25  541  cagtggagcg aattcctttg gaaaacctgc agatcatcag aggaaatatg
      tactacgaaa
   601  attcctatgc cttagcagtc ttatctaact atgatgcaaa taaaaccgga
      ctgaaggagc
   661  tgcccatgag aaatttacag ggccaaaagt gtgatccaag ctgtcccaat
30  gggagctgct
   721  ggggtgcagg agaggagaac tgccagaaac tgaccaaatt catctgtgcc
      cagcagtgct
   781  ccgggcgctg ccgtggcaag tccccagtg actgctgcca caaccagtgt
      gctgcaggct
35  841  gcacaggccc ccgggagagc gactgcctgg tctgccgcaa attccgagac
      gaagccacgt
```

901 gcaaggacac ctgcccccca ctcatgtctt acaaccccac cacgtaccag
atggatgtga
961 accccgaggg caaatacagc tttggtgcc cctgctgaa gaagtgtccc
cgtaattatg
5 1021 tgggtgacaga tcacggctcg tgcgtccgag cctgtggggc cgacagctat
gagatggagg
1081 aagacggcgt ccgcaagtgt aagaagtgcg aagggccttg ccgcaaagtg
tgtaacggaa
1141 taggtattgg tgaatttaaa gactcactct ccataaatgc tacgaatatt
10 aaacacttca
1201 aaaactgcac ctccatcagt ggcgatctcc acatcctgcc ggtggcatTT
aggggtgact
1261 ccttcacaca tactcctcct ctggatccac aggaactgga tattctgaaa
accgtaaagg
15 1321 aaatcacagg gtttttctg attcaggctt ggcctgaaaa caggacggac
ctccatgcct
1381 ttgagaacct agaaatcata cgcggcagga ccaagcaaca tggtcagttt
tctcttgag
1441 tcgtcagcct gaacataaca tccttgggat tacgctccct caaggagata
20 agtcatggag
1501 atgtgataat ttcaggaaac aaaaatttgt gctatgcaa tacaataaac
tggaaaaaac
1561 tgtttgggac ctccggtcag aaaacaaaa ttataagcaa cagaggtgaa
aacagctga
25 1621 aggccacagg ccaggctctgc catgccttgt gctccccga gggctgctgg
ggcccgagc
1681 ccagggactg cgtctcttgc cggaatgtca gccgaggcag ggaatgcgtg
gacaagtga
1741 accttctgga gggtgagcca agggagtttg tggagaactc tgagtgcata
30 cagtgccacc
1801 cagagtgcct gcctcaggcc atgaacatca cctgcacagg acggggacca
gacaactgta
1861 tccagtgtgc ccactacatt gacggcccc actgctcaa gacctgcccg
gcaggagtca
35 1921 tgggagaaaa caacaccctg gtctggaagt acgcagacgc cgccatgtg
tgccacctgt

1981 gccatccaaa ctgcacctac ggatgcactg ggccaggtct tgaaggctgt
ccaacgaatg
2041 ggccctaagat cccgtccatc gccactggga tgggtggggc cctcctcttg
ctgctggtgg
5 2101 tggccctggg gatcggcctc ttcattgcga ggccgccacat cgttcggaag
cgcacgctgc
2161 ggaggctgct gcaggagagg gagcttgtgg agcctcttac acccagtgga
gaagctccca
2221 accaagctct cttgaggatc ttgaaggaaa ctgaattcaa aaagatcaaa
10 gtgctgggct
2281 ccggtgcggt cggcacgggt tataaggagc tctggatccc agaaggtag
aaagttaaaa
2341 ttcccgctgc tatcaaggaa ttaagagaag caacatctcc gaaagccaac
aaggaaatcc
15 2401 tcgatgaagc ctacgtgatg gccagcgtgg acaacccccca cgtgtgccgc
ctgctgggca
2461 tctgcctcac ctccaccgtg cagctcatca cgcagctcat gcccttcggc
tgctcctgg
2521 actatgtccg ggaacacaaa gacaatattg gctcccagta cctgctcaac
20 tgggtgtgtgc
2581 agatcgcaaa gggcatgaac tacttggagg accgtcgctt ggtgcaccgc
gacctggcag
2641 ccaggaacgt actggtgaaa acaccgcagc atgtcaagat cacagatttt
gggctggcca
25 2701 aactgctggg tgcggaagag aaagaatacc atgcagaag aggcaaagtg
cctatcaagt
2761 ggatggcatt ggaatcaatt ttacacagaa tctataccca ccagagtgat
gtctggagct
2821 acggggtgac tgtttgggag ttgatgacct ttggatccaa gccatatgac
30 ggaatccctg
2881 ccagcgagat ctctccatc ctggagaaag gagaacgcct ccctcagcca
cccatatgta
2941 ccacgatgt ctacatgatc atgggtcaagt gctggatgat agacgcagat
agtcgccccaa
35 3001 agttccgtga gttgatcatc gaattctcca aaatggccc agacccccag
cgctaccttg

3061 tcattcaggg ggatgaaaga atgcatttgc caagtcctac agactccaac
ttctaccgtg
3121 ccctgatgga tgaagaagac atggacgacg tggatggatgc cgacgagtac
ctcatccac
5 3181 agcagggctt cttcagcagc ccctccacgt cacggactcc cctcctgagc
tctctgagtg
3241 caaccagcaa caattccacc gtggcttgca ttgatagaaa tgggctgcaa
agctgtccca
3301 tcaaggaaga cagcttcttg cagcgataca gctcagaccc cacaggcgcc
10 ttgactgagg
3361 acagcataga cgacaccttc ctcccagtgc ctggtgagtg gcttgtctgg
aaacagtcct
3421 gtcctcaac ctctcgacc cactcagcag cagccagtct ccagtgtcca
agccagggtgc
15 3481 tccctccagc atctccagag ggggaaacag tggcagattt gcagacacag
tgaagggcgt
3541 aaggagcaga taaacacatg accgagcctg cacaagctct ttgttgtgtc
tggttggttg
3601 ctgtacctct gttgtaagaa tgaatctgca aaatttctag cttatgaagc
20 aaatcacgga
3661 catacacatc tgtgtgtgtg agtggttcag atgtgtgtac atctgtgtat
gtgtgtgtgt
3721 gtatgtgtgt gtttgtgaca gatttgatcc ctgttctctc tgctggctct
atcttgacct
25 3781 gtgaaacgta tatttaacta attaaatatt agttaatatt aataaatttt
aagctttatc
3841 cagaaaaaaaa aaaaaaaaa

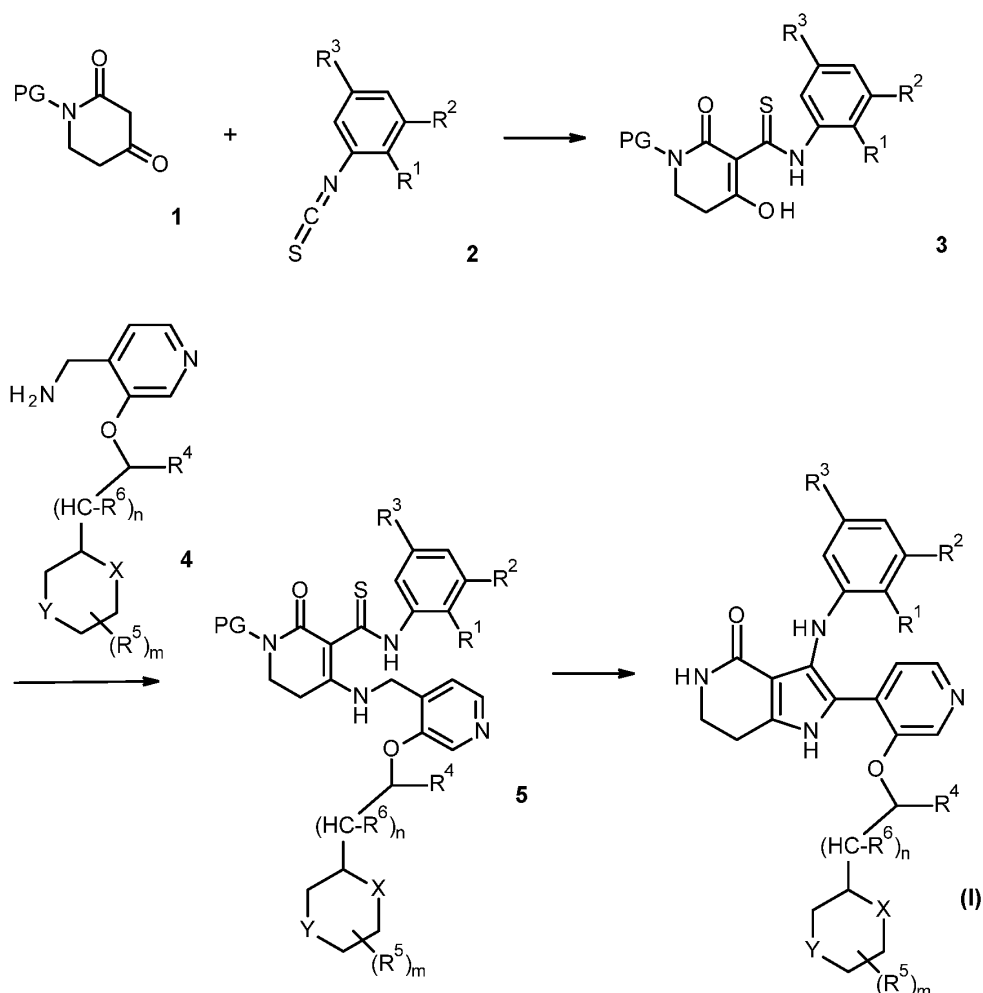
30 The intermediates used for the synthesis of the compounds of claims 1-4 as described below, as well as their use for the synthesis of the compounds of claims 1-4, are one further aspect of the present invention. Preferred intermediates are the Intermediate Examples as disclosed below.

General Procedures

The compounds according to the invention can be prepared according to the following schemes 1 – 4.

- 5 The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is obvious to the person skilled in the art that the order of transformations as exemplified in the schemes can be modified in various ways. The order of transformations exemplified in the schemes is therefore not intended to be limiting. In addition, interconversion of any of the substituents R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and PG can be achieved before and/or after the exemplified
- 10 transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and
- 15 cleavage are well-known to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

Scheme 1:



Scheme 1: Route for the preparation of compounds of general formula (I), wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , X, Y, m and n have the meaning as given for general formula (I) and PG can be hydrogen or optionally a suitable protecting group, e.g. tert-butoxycarbonyl (Boc).

Compound of formula 1, 2, and 4 are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

A suitably substituted piperidine-2,4-diones of general formula (Compound of formula 1), such as, for example, 2,4-piperidinedione, can be reacted with a suitably substituted isothiocyanate (Compound of formula 2), such as, for example, 3-fluorophenylisothiocyanate, in a suitable solvent system, such as, for example,

acetonitrile, in the presence of a suitable base, such as, for example, triethylamine or DBU, at temperatures ranging from -78°C to +100°C, in some embodiments the reaction is carried out at 0°C or +100°C, to furnish general formula (3). Similar reactions have been performed in the literature (D. E. Worrall, *J. Am. Chem. Soc.*, 1940, 62, 675).

- 5 Intermediates of general formula (3) can be converted to Intermediates of general formula (5) by reaction with a suitable amine (compounds of general formula 4), such as, for example 4-(aminomethyl)pyridine, in a suitable solvent system, such as, for example, ethanol and ethyl acetate, at a temperature between room temperature and the boiling point of the respective solvents, in some embodiments the reaction is carried out at the boiling point of the respective solvents, whereby the water formed in the reaction is removed from the reaction by methods known to those skilled in the art, such as, for example, azeotropic removal of water (Dean-Stark conditions) or with molecular sieves, to furnish general formula (5).

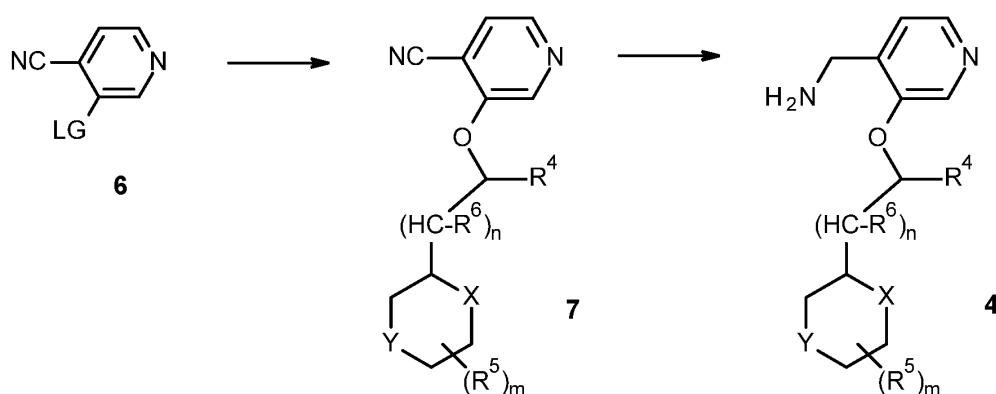
- 15 Intermediates of general formula (3) and intermediates of general formula (5) in which PG represents a protecting group can be converted to Intermediates in which PG represents a hydrogen atom using standard deprotection conditions known to those skilled in the art. When PG is a protecting group such as, for example, tert-butoxycarbonyl (Boc), the deprotection can be carried out using acids, such as, for example, hydrochloric acid and trifluoroacetic acid, in a suitable solvent system, such as, for example, dichloromethane and dioxane, at a temperature between 0°C and the boiling point of the respective solvents, in one embodiment the reaction is carried out at the room temperature, to furnish compounds of general formula (3) and intermediates of general formula (5) whereby PG is hydrogen atom.

- 25 Intermediates of general formula (5) are reacted with a base and/or oxidizing reagent, in one embodiment an oxidizing agent, such as, for example hydrogen peroxide or SIBX (stabilized iodoxybenzoic acid, in a suitable solvent system, such as, for example, methanol, in a temperature range from -30°C to the boiling point of the respective solvent, in one embodiment the reaction is carried out at the boiling point of the respective solvent, to furnish compounds of general formula (I). Optionally, these types of reactions can be carried on with an additive, such as, for example, an acid or base, such as, for example, acetic acid or trifluoroacetic acid (not-limiting), and triethylamine or diisopropylethylamine (not-limiting).

Intermediates of general formula (5) could be converted to compounds of general formula (I) by thermal heating them in a suitable solvent at elevated temperatures, which could be above the boiling point of the said solvent, such as, for example, RT to +250°C. These

reactions could optionally be carried out in vessel whereby the pressure can be increased, such as, for example, in an autoclave. Intermediates of general formula (5) can also be converted to compounds of general formula (I) by thermal heating in the presence of a metal catalyst, such as, for example, palladium on activated charcoal, in a suitable solvent, such as, for example, DMF, DMA, EtOH, MeOH, NMP (not-limiting) at elevated temperatures, such as, for example, RT to +150°C. Optionally, these types of reactions can be carried on with an additive, such as, for example, an acid or base, such as, for example, acetic acid or trifluoroacetic acid (not-limiting), and triethylamine or diisopropylethylamine (not-limiting), to furnish compounds of general formula (I).

10 **Scheme 2:**



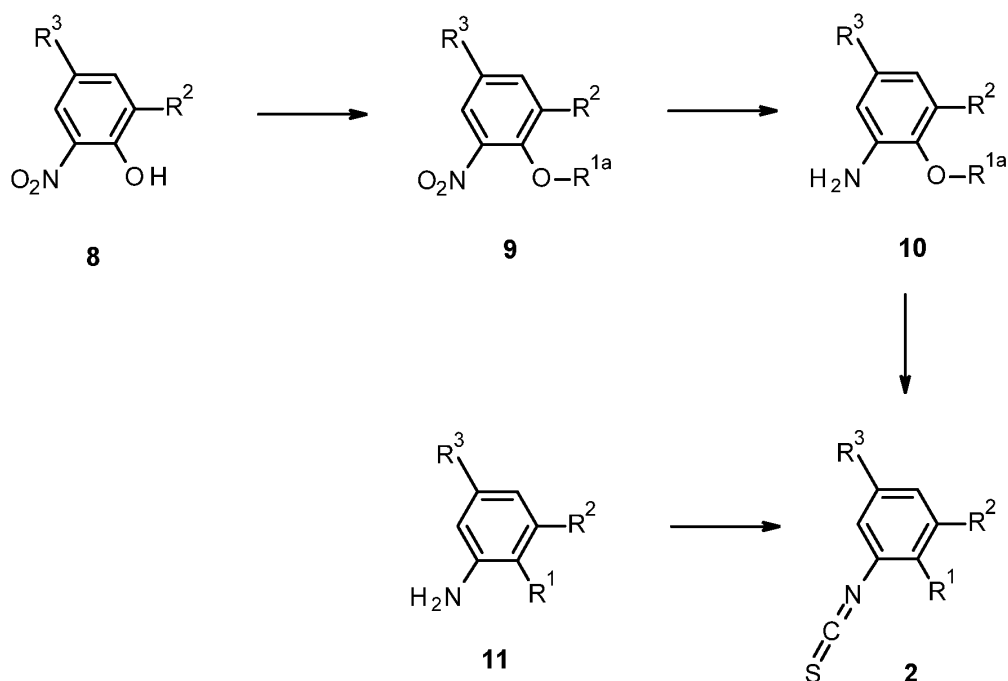
Scheme 2: Process for the preparation of compounds of general formula (4), wherein R⁴, R⁵, R⁶, X, Y, m and n have the meaning as given for general formula (I).

Compounds of general formula (6) can be converted to compounds of general formula (7) by treatment with a suitable nucleophile, such as for example, amines, alcohols, metal alkoxides, azides, thiols or metal thiolates, under either basic, neutral, acidic, catalytic conditions, in one embodiment basic conditions, in a suitable solvent or using the nucleophile as solvent, such as, for example, DMF, tetrahydrofuran (THF), in a temperature range from -78°C to the boiling point of the respective solvent, in one embodiment the reaction is carried out -10°C to the boiling point of the respective solvent, to furnish general formula (7). Such substitution reactions have been previously reported (Clark *et al.*, *J. Med. Chem.*, 2008, 51, 6631 – 6634; Guo *et al.*, *Tetrahedron Letts.*, 2013, 54, 3233 – 3237; Watterson *et al.*, *J. Med. Chem.*, 2007, 50, 3730 – 3742; Bellale *et al.*, *J. Med. Chem.*, 2014, 57, 6572 – 6582; Klimesova *et al.*, *Eur. J. Med. Chem.*, 1996, 31, 389 – 395; Leroy *et al.*,

Synth. Commun., 1997, 27, 2905 – 2916; LaMattina *et al.*, *J. Org. Chem.*, 1981, 46, 4179 – 4182; Beugelmans *et al.*, *Tetrahedron*, 1983, 39, 4153 - 4162).

Compounds of general formula (7) can be converted to compounds of general formula (4) by many reducing methods known to those skilled in the art, using numerous different reagents and reaction conditions; such methods and reagents can be carried out with metal hydrides, such as, for example, lithium aluminum hydride in THF (Bullock *et al.*, *J. Am. Chem. Soc.*, 1956, 78, 490, Wang *et al.*, *J. Org. Chem.*, 2006, 71, 4021 - 3160), or using zinc in acetic acid (Rabe, *Chem. Ber.*, 1913, 46, 1024), or using diborane (De Munno *et al.*, *Heterocycles*, 1996, 43, 1893 – 1900), or using catalytic hydrogenation methods, for example, hydrogen and palladium on carbon under acidic conditions (Stokker *et al.*, *J. Med. Chem.*, 1981, 24, 115 – 117; Bertini *et al.*, *J. Med. Chem.*, 2005, 48, 664 - 670), hydrogen and nickel under basic conditions (Walpole *et al.*, *J. Med. Chem.*, 1993, 36, 2362 – 2372, Kuramochi *et al.*, *Bioorg. Med. Chem.*, 2005, 13, 4022 – 4036.)

Scheme 3:



15

Scheme 3: Process for the preparation of compounds of general formula 2, wherein R^{1a} represents methyl or difluoromethyl corresponding to R^1 in the general formula (I) with the meaning of methoxy and difluoromethoxy. The synthesis of compounds 9 and 10 relates to alkoxy substitution of the phenyl ring. However, the isothiocyanate containing product 2 and

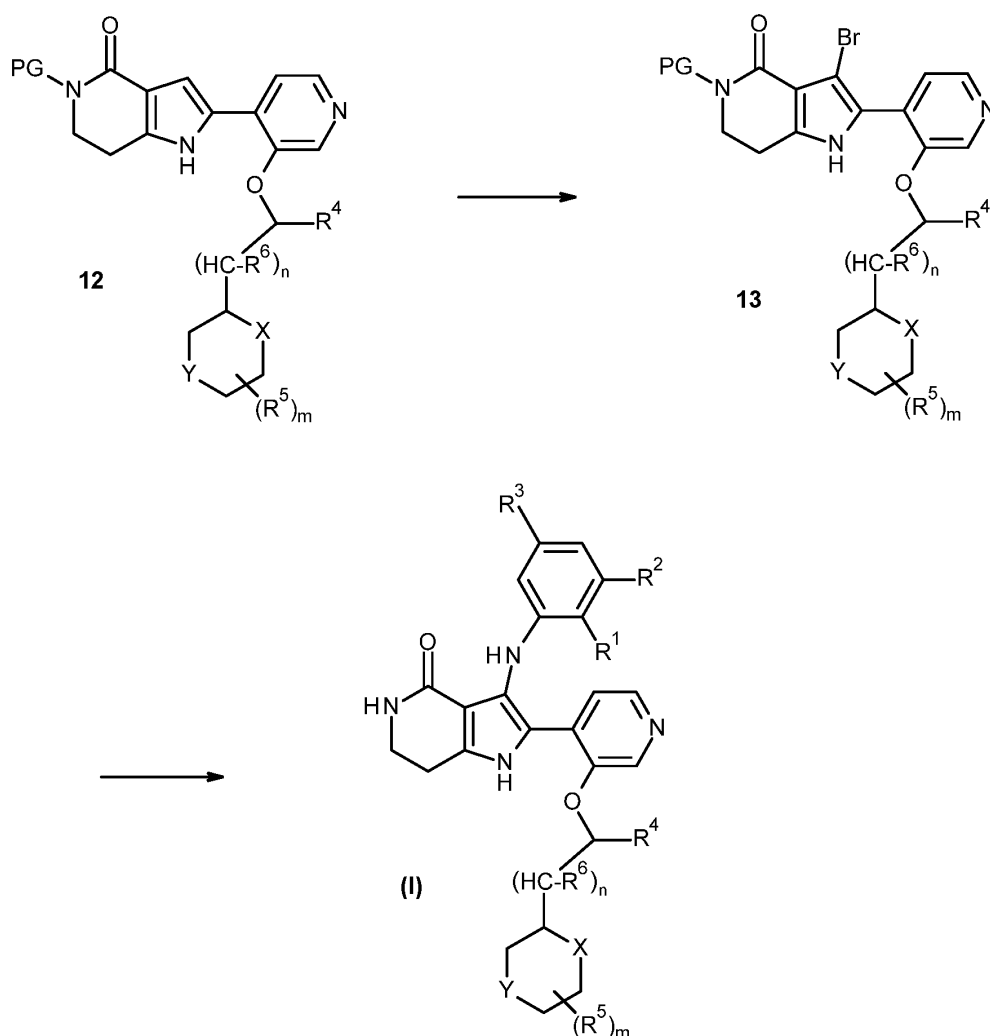
the synthesis thereof (*i.e.*, **10** $\rightarrow$ **2** or **11** $\rightarrow$ **2**) is general to R¹ groups according to general formula (I).

Compounds of general formula (**8**), can be converted to compounds of general formula (**9**), using various methods which are known to those skilled in the art. Such transformations could be, for example, to alkylate the phenolic alcohol with alkylating reagents, such as, for example, alkyl halides, alkyl sulfonates, in which these alkyl groups can optionally contain fluorides, alkoxy groups. These alkylation reactions are known to those skilled in the art using a variety of methods: i) K₂CO₃ in a solvent such as, DMF, acetone, DMFA (see the teachings of Muro *et al.*, J. Med. Chem., 2009, 52, 7974 and WO2009/20990 A1); ii) KOH in EtOH (see the teachings of Macias *et al.*, J. Agric. Food Chem., 2006, 54, 9843); iii) Mitsunobu reaction (see the teachings of US2006/122168 A1 and EP2151431 A1) to furnish intermediates of general formula (**9**).

Compounds of general formula (**9**) can be converted to compounds of general formula (**10**) by reduction methods and these methods are known to those skilled in the art. These reductions can be carried using: i) hydrogen gas and a catalyst (for Pd/C as catalyst see the teachings of Chan *et al.*, J. Am. Chem. Soc., 2011, 133, 2989; for platinum see the teachings of Niemann *et al.*, J. Am. Chem Soc., 1941, 63, 2204; for Raney-Nickel see the teachings of US2009/253767 A1); ii) iron and ammonium chloride (see the teachings of Sweeney *et al.*, Bioorg. Med. Chem. Lett., 2008, 18, 4348); iii) sodium dithionite (see the teachings of Chong *et al.*, J. Med. Chem., 2012, 55, 10601); iv) zinc and ammonium chloride (see the teachings of WO2010/42699 A1) to furnish intermediates of general formula (**10**).

Compounds of general formula (**10**) can be converted to compounds of general formula (**2**) by using reagents such as, for example, thiophosgene, carbon disulphide, 1,1"-thiocarbonyldi-2(1H)-pyridone or 1,1'-thiocarbonyldiimidazole, in one embodiment thiophosgene, under basic conditions, in a suitable solvent, such as, for example, dichloromethane, chloroform, acetone, or biphasic mixtures, such as, for example, dichloromethane, chloroform with aqueous basic solutions, in another embodiment, dichloromethane with an aqueous saturated solution of sodium hydrogen carbonate or sodium carbonate, in a temperature range from -78°C to the boiling point of the respective solvent, in another embodiment the reaction is carried out 0°C to room temperature, to furnish compounds of general formula (**2**). Such transformations reactions have been previously reported (Harris *et al.*, J. Med. Chem., 2005, 48, 1610; Degorce *et al.*, Tetrahedron Lett., 2011, 52, 6719; WO2016/91845 A1; Fairhurst *et al.*, Org. Lett., 2005, 7, 4697; Chaskar *et al.*, Synth. Commun., 2008, 38, 16940; US2004/122237 A1).

Scheme 4:



Scheme 4: Route for the preparation of compounds of general formula (I), wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , X, Y, m and n have the meaning as given for general formula (I) and PG represents hydrogen or a suitable protecting group, e.g. tert-butoxycarbonyl (Boc).

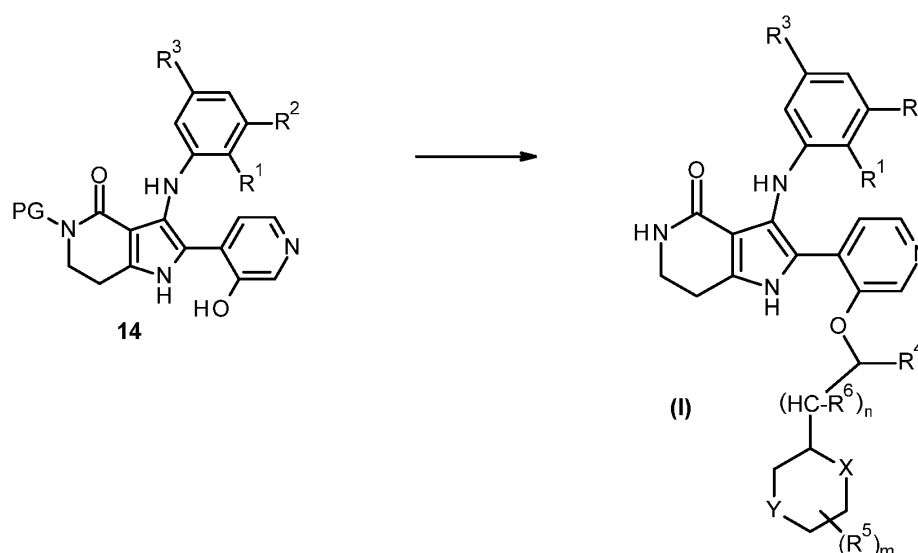
Compounds similar to those of general formula **12** are known to those skilled in the art and their syntheses have been reported in the literature (see the teachings of Voss et al., WO2015/22073 A1; Hart et al., WO2016/100166 A1; Anderson et al., J. Med. Chem., 2007, 50, 2647; Vanotti et al., J. Med. Chem., 2008, 51, 487).

Compounds of general formula (**12**) could be converted to compounds of general formula (**13**) using standard bromination methods which are known to those skilled in the art

(WO2016/100166 A1). Such brominations could be carried out using a brominating agent, such as, for example, N-bromosuccinimide, in a suitable solvent, such as, for example, DMF, in a temperature range from -78°C to the boiling point of said solvent, in one embodiment the temperature range is 0°C to RT.

- 5 Intermediates of general formula (13) can be reacted with suitable anilines, such as, for example, 2-difluoromethoxyaniline, in the presence of a base, such as, for example, lithium bis(trimethylsilyl)amide (LHMDS), in the presence of a catalyst, such as, for example a suitable ligand, in one embodiment 2-(di-tert-butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl (tBuBrettPhos) and in the presence of a pre-catalyst, such as, for
- 10 example a palladium pre-catalyst, in another embodiment chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) (BrettPhos-PreCat MTBE ether adduct) in a suitable solvent system, such as, for example, tetrahydrofuran (THF), at a temperature range of 0°C to 200°C. In one embodiment, the reaction is carried out at 80°C, to furnish compounds of
- 15 general formula (I). Similar transformations have been carried out and have been reported (WO2015/193339 A1).

Scheme 5:



- 20 *Scheme 5:* Route for the preparation of compounds of general formula (I), wherein R¹, R², R³, R⁴, R⁵, R⁶, X, Y, m and n have the meaning as given for general formula (I) and PG represents hydrogen or a suitable protecting group, e.g. tert-butoxycarbonyl (Boc).

Compounds similar to those of general formula (14) can be prepared according to the procedure described by Scheme 1 under the use of 4-(aminomethyl)-3-hydroxypyridine instead of intermediate (4). Intermediates of general formula (14) can be converted to compounds of general formula (I) by reaction with a suitable alcohol under Mitsunobu conditions (the teachings of Oyo Mitsunobu, *Synthesis*, 1981, 1-28 or Tsunoda *et al.*, *Tetrahedron Lett.*, 1994, 35, 5081) such as, for example oxetan-3-ylmethanol, in the presence of (tributylphosphoranylidene)acetonitrile or triphenylphosphin together with diisopropyl azodicarboxylate in a suitable solvent system, such as, for example, dioxane or THF, at a temperature between room temperature and the boiling point of the respective solvents.

It is known to the person skilled in the art that, if there are a number of reactive centers on a starting or intermediate compound, it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center.

The compounds according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent *in vacuo* and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as chromatography on a suitable support material. Furthermore, reverse phase preparative HPLC may be applied. The compounds of the present invention which possess a sufficiently basic or acidic functionality, may result as a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. Salts of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. Additionally, the drying process during the isolation of the compounds of the present invention may not fully remove traces of cosolvents, especially such as formic acid or trifluoroacetic acid, to give solvates or inclusion complexes. The person skilled in the art will recognise which solvates or inclusion complexes are acceptable to be used in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base, free acid, solvate, inclusion complex) of a compound of the present invention as isolated and described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Salts of the compounds of formula (I) according to the invention can be obtained by dissolving the free compound in a suitable solvent (for example a ketone such as acetone, methylethylketone or methylisobutylketone, an ether such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The acid or base can be employed in salt preparation, depending on whether a mono- or polybasic acid or base is concerned and depending on which salt is desired, in an equimolar ratio or one differing therefrom. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the salt or by evaporating the solvent. Salts obtained can be converted into the free compounds which, in turn, can be converted into salts. In this manner, pharmaceutically unacceptable salts, which can be obtained, for example, as process products in the manufacturing on an industrial scale, can be converted into pharmaceutically acceptable salts by processes known to the person skilled in the art. Especially preferred are hydrochlorides and the process used in the example section.

Pure diastereomers and pure enantiomers of the compounds and salts according to the invention can be obtained e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis or by splitting up enantiomeric and diasteriomer mixtures obtained in synthesis.

Enantiomeric and diastereomeric mixtures can be split up into the pure enantiomers and pure diastereomers by methods known to the person skilled in the art. In one embodiment, diastereomeric mixtures are separated by crystallization, in particular fractional crystallization, or chromatography. Enantiomeric mixtures can be separated e.g. by forming diastereomers with a chiral auxillary agent, resolving the diastereomers obtained and removing the chiral auxillary agent. As chiral auxillary agents, for example, chiral acids can be used to separate enantiomeric bases such as e.g. mandelic acid and chiral bases can be used to separate enantiomeric acids by formation of diastereomeric salts. Furthermore, diastereomeric derivatives such as diastereomeric esters can be formed from enantiomeric mixtures of alcohols or enantiomeric mixtures of acids, respectively, using chiral acids or chiral alcohols, respectively, as chiral auxillary agents. Additionally, diastereomeric complexes or diastereomeric clathrates may be used for separating enantiomeric mixtures. Alternatively, enantiomeric mixtures can be split up using chiral separating columns in

chromatography. Another suitable method for the isolation of enantiomers is the enzymatic separation.

One preferred aspect of the invention is the process for the preparation of the compounds
5 of claims 1-4 according to the examples as well as the intermediates used for their preparation.

Optionally, compounds of the formula (I) can be converted into their salts, or, optionally, salts of the compounds of the formula (I) can be converted into the free compounds.
10 Corresponding processes are customary for the skilled person.

Commercial utility

As mentioned supra, the compounds of the present invention have surprisingly been found
15 to effectively inhibit mutant EGFR in a cell (e.g., a cancer cell) contacted with the compound, thereby inducing cell death (e.g., apoptosis) and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or
20 survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by mutant EGFR, such as, for example, benign and malignant neoplasia, more specifically haematological tumours, solid tumours, and/or metastases thereof, e.g.
25 leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof, especially
30 haematological tumours, solid tumours, and/or metastases of breast, bladder, bone, brain, central and peripheral nervous system, cervix, colon, endocrine glands (e.g., thyroid and adrenal cortex), endocrine tumours, endometrium, esophagus, gastrointestinal tumours, germ cells, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, stomach, skin, testis, ureter, vagina and
35 vulva as well as malignant neoplasias including primary tumours in said organs and

corresponding secondary tumours in distant organs ("tumour metastases"). Haematological tumours can, e.g., be exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell
5 lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site, as well as AIDS related malignancies.

10 A further aspect of the invention is the use of the compounds according to formula (I) for the treatment of lung cancer, particularly lung cancer harboring mutant EGFR with exon 20 insertion mutations, more particularly lung cancer harboring V769_770ins ASV and/or D770_N771ins SVD exon 20 insertions, and/or metastases thereof, comprising administering an effective amount of a compound of formula (I).

15 A further aspect of the invention is the use of the compounds according to formula (I) for the treatment of lung cancer, particularly lung cancer harboring a mutant EGFR with in-frame deletions in exon 19 (such as EGFR E746_A750del) or point mutations in exon 21 (e.g. L858R), and/or metastases thereof.

20 A further aspect of the invention is the use of the compounds according to formula (I) for the treatment of lung cancer, particularly lung cancer harboring a mutant EGFR with a D770_N771insSVD C797S, E746_A750del C797S, or L858R C797S acquired resistance mutation, and/or metastases thereof.

25 A further aspect of the invention is the use of the compounds according to formula (I) for the treatment of lung cancer, particularly lung cancer harboring a mutant ERBB2 with exon 20 insertion mutations (such as ERBB2 A775_G776insYVMA), and/or metastases thereof. In accordance with an aspect of the present invention therefore the invention relates to a compound of general formula I, or an N-oxide, a salt, a tautomer or a stereoisomer of said
30 compound, or a salt of said N-oxide, tautomer or stereoisomer particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, especially for use in the treatment of a disease.

Another particular aspect of the present invention is therefore the use of a compound of general formula I, described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of hyperproliferative disorders or disorders responsive to induction of cell death, i.e., apoptosis.

By "hyperproliferative disease" is meant a disease, such as cancer, associated with inappropriately high levels of cell division, inappropriately low levels of apoptosis, or both. The term "inappropriate" within the context of the present invention, in particular in the context of "inappropriate cellular immune responses, or inappropriate cellular inflammatory responses", as used herein, is to be understood as generally meaning a response, which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said diseases.

In particular embodiments, the use is in the treatment or prophylaxis of diseases, especially the treatment, wherein the diseases are haematological tumours, solid tumours and/or metastases thereof.

Another aspect is the use of a compound of formula (I) for the prophylaxis and/or treatment of lung cancer, particularly lung cancer harboring mutant EGFR with exon 20 insertion mutations, more particularly lung cancer harboring V769_770ins ASV and/or D770_N771ins SVD exon 20 insertions, and/or metastases thereof, especially preferred for the treatment thereof.

Another aspect of the present invention is the use of a compound of formula (I) or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described herein, in the manufacture of a medicament for the treatment or prophylaxis of a disease, wherein such disease is a hyperproliferative disorder or a disorder responsive to induction of cell death e.g., apoptosis. In an embodiment the disease is a haematological tumour, a solid tumour and/or metastases thereof. In another embodiment the disease is lung cancer, particularly lung cancer harboring mutant EGFR with exon 20 insertion mutations, more particularly lung cancer harboring V769_770ins ASV and/or D770_N771ins SVD exon 20 insertions, and/or metastases thereof.

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce cell death e.g. apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumours, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukaemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma *in situ*.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypothalamic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

Tumours of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumours of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumours of the digestive tract include, but are not limited to anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumours of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

5

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

10 Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, inverted sinonasal papilloma, inverted sinonasal papilloma-associated sinonasal squamous cell carcinoma, Merkel cell skin cancer, and non-melanoma skin cancer.

15 Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, inverted sinonasal papilloma, inverted sinonasal papilloma-associated sinonasal squamous cell carcinoma, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease,
20 and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

25 Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar
30 etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, e.g., the management or care of a subject for the purpose of combating,

alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

5 The present invention relates to a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a compound of general formula (I) as defined herein.

10 The present invention relates to a method of treating cancer in a subject, wherein the cancer is or has acquired resistance to an anti-EGF receptor therapy, the method comprising administering to the subject an effective amount of a compound of general formula (I) as defined herein.

15 The present invention relates to a method of enhancing the efficacy of an anti-EGF-receptor therapy, the method comprising administering to the subject an anti-EGF receptor therapy in combination with a a compound of general formula (I) as defined herein.

20 In a further embodiment, the present invention relates to a method of treating cancer in a subject, wherein the cancer is selected from the group consisting of leukemia, myelodysplastic syndrome, malignant lymphoma, head and neck tumours, tumours of the thorax, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours, skin tumours, and sarcomas, the method comprising administering to the subject an effective amount of a compound of general formula (I) as defined herein.

25 In a further embodiment, the present invention relates to a method of treating cancer in a subject, wherein the cancer is selected from the group consisting of inverted sinonasal papilloma or inverted sinonasal papilloma associated sinanonasal squamous cell carcinoma, the method comprising administering to the subject an effective amount of a compound of general formula (I) as defined herein.

30

In a further embodiment, the present invention relates to a method of treating cancer in a subject, wherein the tumour of the thorax is non-small cell lung cancer, the method comprising administering to the subject an effective amount of a compound of general formula (I) as defined herein.

35

In a further embodiment, the present invention relates to a method of treating cancer in a subject, wherein the cancer is lung cancer, particularly lung cancer harboring a mutant EGFR with in-frame deletions in exon 19 (such as EGFR E746_A750del) or point mutations in exon 21 (e.g. L858R), and/or metastases thereof, the method comprising administering
5 to the subject an effective amount of a compound of general formula (I) as defined herein.

In a further embodiment, the present invention relates to a a method of treating cancer in a subject, wherein the cancer is lung cancer, particularly lung cancer harboring a mutant EGFR with a D770_N771insSVD C797S, E746_A750del C797S, or L858R C797S acquired
10 resistance mutation, and/or metastases thereof, the method comprising administering to the subject an effective amount of a compound of general formula (I) as defined herein.

In a further embodiment, the present invention relates to a a method of treating cancer in a subject, wherein the cancer is lung cancer, particularly lung cancer harboring a mutant
15 ERBB2 with exon 20 insertion mutations (such as ERBB2 A775_G776insYVMA), and/or metastases thereof, the method comprising administering to the subject an effective amount of a compound of general formula (I) as defined herein.

The present disclosure is also related to method of selecting a patient for cancer treatment
20 with a compound of general formula (I) comprising detecting the presence of a mutation in exon 20 of the gene encoding the EGF-receptor in a biological sample of the subject, thereby determining that the patient should be treated with said compound. In some embodiments, the EGFR comprises aD770_N771insSVD C797S, E746_A750del C797S, or L858R C797S acquired resistance mutation, and/or metastases thereof. In some
25 embodiments, the method of selecting a patient for cancer treatment with a compound of general formula (I) may comprise detecting the presence of in-frame deletions in exon 19 or point mutations in exon 21 of the gene encoding EGF-receptor in a biological sample of the subject, thereby determining that the patient should be treated with said compound. For example, the in-frame deletion in exon 19 may be EGFR E746_A750del or the point
30 mutation in exon 21 may be L858R. In some embodiments, the method of selecting a patient for cancer treatment with a compound of general formula (I) may comprise detecting the presence of a mutation in exon 20 of the gene encoding ERBB2 in a biological sample of the subject, thereby determining that the patient should be treated with said compound. In some embodiments, the ERBB2 comprises an ERBB2 A775 or_G776insYVMA insertion
35 mutation, and/or metastases thereof. Furthermore, methods of treating a patient with

cancer may comprise administering to the subject a compound of general formula (I) (e.g., in combination with anti-EGF receptor therapy), wherein the subject is selected for therapy by detecting the presence of a mutation in EGFR in a biological sample of the subject. Detection of the presence of a mutation in exon 20 is within the skill of one of the art.

5

In some embodiments, the detection of a mutation (e.g., in an EGFR or a mutation in exon 20 of the gene encoding EGFR) may be performed by sequencing (e.g., Sanger, Next Generation Sequencing) or a method selected from the group consisting of immunoblotting, mass spectrometry, immunoprecipitation quantitative PCR, Northern Blot, microarray, enzyme-linked immunosorbent assay (ELISA), in situ hybridization, and combinations thereof.

10

Methods of treating kinase disorders

15 The present invention also provides methods for the treatment of disorders associated with aberrant mitogen extracellular kinase activity, including, but not limited to stroke, heart failure, hepatomegaly, cardiomegaly, diabetes, Alzheimer's disease, cystic fibrosis, symptoms of xenograft rejections, septic shock or asthma.

20 Effective amounts of compounds of the present invention can be used to treat such disorders, including those diseases (e.g., cancer) mentioned in the Background section above. Nonetheless, such cancers and other diseases can be treated with compounds of the present invention, regardless of the mechanism of action and/or the relationship between the kinase and the disorder.

25

The phrase "aberrant kinase activity" or "aberrant tyrosine kinase activity," includes any abnormal expression or activity of the gene encoding the kinase or of the polypeptide it encodes. Examples of such aberrant activity, include, but are not limited to, over-expression of the gene or polypeptide; gene amplification; mutations which produce constitutively-active or hyperactive kinase activity; gene mutations, deletions, substitutions, additions, etc.

30

The present invention also provides for methods of inhibiting kinase activity, especially of mitogen extracellular kinase, comprising administering an effective amount of a compound of the present invention, including salts, polymorphs, metabolites, hydrates, solvates,

prodrugs (e.g.: esters) thereof, and diastereoisomeric forms thereof. Kinase activity can be inhibited in cells (e.g., *in vitro*), or in the cells of a mammalian subject, especially a human patient in need of treatment.

5 Methods of treating angiogenic disorders

The present invention also provides methods of treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. **1994**, 331, 1480; Peer et al. Lab. Invest. **1995**, 72, 638], age-related macular degeneration [AMD; see, Lopez et al. Invest. Ophthalmol. Vis. Sci. **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumour enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumour provides an escape route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, compounds of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death e.g. apoptosis of such cell types.

In various embodiments, the diseases of said method are haematological tumours, solid tumour and/or metastases thereof.

The compounds of the present invention can be used in particular in therapy and prevention i.e. prophylaxis, especially in therapy of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for
5 the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition, disorder, or disease.

Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier or auxiliary and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention.

10 Another aspect of the invention is a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula (I) and a pharmaceutically acceptable auxiliary for the treatment of a disease mentioned supra, especially for the treatment of haematological tumours, solid tumours and/or metastases thereof.

A pharmaceutically acceptable carrier or auxiliary may be a carrier that is non-toxic and
15 innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. Carriers and auxiliaries are all kinds of additives assisting to the composition to be suitable for administration.

20 A pharmaceutically effective amount of compound may be that amount which produces a result or exerts the intended influence on the particular condition being treated.

The compounds of the present invention can be administered with pharmaceutically-acceptable carriers or auxiliaries well known in the art using any effective conventional
25 dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations
30 such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatine type containing auxiliaries, for

example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional
5 tablet bases such as lactose, sucrose and cornstarch in combination with binders such as
acacia, corn starch or gelatine, disintegrating agents intended to assist the break-up and
dissolution of the tablet following administration, such as potato starch, alginic acid, corn
starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of
10 tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet
dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate,
dyes, colouring agents, and flavouring agents such as peppermint, oil of wintergreen, or
cherry flavouring, intended to enhance the aesthetic qualities of the tablets and make them
more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms
include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol,
15 benzyl alcohol, and polyethylene alcohols, either with or without the addition of a
pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various
other materials may be present as coatings or to otherwise modify the physical form of the
dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or
both.

20

Dispersible powders and granules are suitable for the preparation of an aqueous
suspension. They provide the active ingredient in admixture with a dispersing or wetting
agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting
agents and suspending agents are exemplified by those already mentioned above.
25 Additional excipients, for example those sweetening, flavouring and colouring agents
described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water
emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of
30 vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as
gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean
and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for
example, sorbitan monooleate, (4) condensation products of said partial esters with
ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also
35 contain sweetening and flavouring agents.

- Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more colouring agents; one or more flavouring agents; and one or more sweetening agents such as sucrose or saccharin.
- 5
- 10 Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavouring and colouring agents.
- 15 The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in, for example, a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent
- 20
- 25 such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.
- Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl,
- 30
- 35

olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimise or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) in one embodiment of from about 12 to about 17. The quantity of surfactant in such formulation in one embodiment ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be

employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be
5 used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at
10 the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

15

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for administration, for example, administering a drug directly to the brain usually involve
20 placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

25 The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

30 Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science &
35 Technology **1999**, 53(6), 324-349; and Nema, S. *et al.*, "Excipients and Their Use in

Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

- Commonly used pharmaceutical ingredients that can be used as appropriate to formulate
5 the composition for its intended route of administration include:

- acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);
- alkalinizing agents (examples include but are not limited to ammonia solution, ammonium
10 carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, triamine);
- adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);
- aerosol propellants (examples include but are not limited to carbon dioxide, CCl₂F₂, F₂CIC-
15 CCIF₂ and CCIF₃);
- air displacement agents (examples include but are not limited to nitrogen and argon);
- antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);
- antimicrobial preservatives (examples include but are not limited to benzalkonium chloride,
20 benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);
- antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde
25 sulfoxylate, sodium metabisulfite);
- binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);
- buffering agents (examples include but are not limited to potassium metaphosphate,
30 dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate);
- carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for
35 injection);

- chelating agents (examples include but are not limited to edetate disodium and edetic acid);
colourants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);
- 5 clarifying agents (examples include but are not limited to bentonite);
emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);
encapsulating agents (examples include but are not limited to gelatin and cellulose acetate
- 10 phthalate);
flavourants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);
humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);
levigating agents (examples include but are not limited to mineral oil and glycerin);
- 15 oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);
ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);
- 20 penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas);
- 25 plasticizers (examples include but are not limited to diethyl phthalate and glycerol);
solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);
stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax,
- 30 microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);
suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));
surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, octoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

- suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);
- sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol,
- 5 mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);
- tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);
- tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);
- 10 tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);
- tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose,
- 15 ethylcellulose, cellulose acetate phthalate and shellac);
- tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);
- tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-
- 20 linked polyvinylpyrrolidone, sodium alginate, sodium starch glycolate and starch);
- tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);
- tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);
- tablet/capsule opaquants (examples include but are not limited to titanium dioxide);
- 25 tablet polishing agents (examples include but are not limited to carnuba wax and white wax);
- thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin);
- tonicity agents (examples include but are not limited to dextrose and sodium chloride);
- viscosity increasing agents (examples include but are not limited to alginic acid, bentonite,
- 30 carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and
- wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile i.v. solution: A 5 mg/ml solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is
5 diluted for administration to 1 – 2 mg/ml with sterile 5% dextrose and is administered as an i.v. infusion over about 60 minutes.

Lyophilised powder for i.v. administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilised powder, (ii) 32- 327 mg/ml sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted
10 with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/ml, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/ml, and is administered either IV bolus or by IV infusion over 15 – 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

15 50 mg/ml of the desired, water-insoluble compound of this invention
5 mg/ml sodium carboxymethylcellulose
4 mg/ml TWEEN 80
9 mg/ml sodium chloride
9 mg/ml benzyl alcohol

20 Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement
25 pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the
30 dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

10 Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and in particular embodiments from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will in other embodiments be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will in particular embodiments be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will in other embodiments be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will in still other embodiments be from 0.1 to 200

mg administered between one to four times daily. The transdermal concentration will in other embodiments be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will in other embodiments be from 0.01 to 100 mg/kg of total body weight.

- 5 Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of
- 10 doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Combination Therapies

- The compounds of this invention can be administered as the sole pharmaceutical agent or
- 15 in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. Those combined pharmaceutical agents can be other agents having antiproliferative effects such as for example for the treatment of haematological tumours, solid tumours and/or metastases thereof and/or agents for the treatment of undesired side effects. The present invention relates also to such
- 20 combinations.

- Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 1225-1287,
- 25 (1996), which is hereby incorporated by reference, especially (chemotherapeutic) anti-cancer agents as defined supra. The combination can be a non-fixed combination or a fixed-dose combination as the case may be.

- Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.
- 30

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

As will be appreciated by persons skilled in the art, the invention is not limited to the particular embodiments described herein, but covers all modifications of said embodiments that are within the spirit and scope of the invention as defined by the appended claims.

5

The following examples illustrate the invention in greater detail, without restricting it. Further compounds according to the invention, of which the preparation is not explicitly described, can be prepared in an analogous way.

- 10 The compounds, which are mentioned in the examples and the salts thereof represent preferred embodiments of the invention as well as a claim covering all subcombinations of the residues of the compound of formula (I) as disclosed by the specific examples.

- 15 The term “according to” within the experimental section is used in the sense that the procedure referred to is to be used “analogously to”.

EXPERIMENTAL SECTION

- 20 Chemical names were generated using the ACD/Name software from ACD/Labs. In some cases generally accepted names of commercially available reagents were used in place of ACD/Name generated names.

The following table 1 lists the abbreviations used in this paragraph and in the Examples section as far as they are not explained within the text body. Other abbreviations have their meanings customary *per se* to the skilled person.

Table 1: Abbreviations

Abbreviation	Meaning
ACN	Acetonitrile
AcOH	Acetic acid
br	broad signal (NMR)
d	doublet (NMR)
DAD	Diode Array Detector
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene

Abbreviation	Meaning
DCM	Dichloromethane
dd	doublet of doublet (NMR)
DIPEA	Diisopropylethylamine
DMA	N,N-dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
EDC.HCl	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride salt
ESI	electrospray (ES) ionization
EtOAc	Ethyl acetate
EtOH	Ethanol
h, hr (hrs)	hour(s)
HCl	hydrogen chloride, hydrochloric acid
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography–mass spectrometry
m	multiplet (NMR)
MeCN	Acetonitrile
MeOH	Methanol
min	minute(s)
MS	mass spectrometry
MTBE	Methyl- <i>tert</i> -butylether
MWD	Multiple wavelength detector
NMR	Nuclear Magnetic Resonance spectroscopy : chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to 2.50 ppm using unless otherwise stated.
q	quartet (NMR)
Rt or RT	room temperature
R _t , Rt	retention time
s	singulet (NMR)
sat.	Saturated
SFC	Supercritical Fluid Chromatography
t	triplet (NMR)
td	triplet of doublet (NMR)

Abbreviation	Meaning
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
δ	chemical shift

Other abbreviations have their meanings customary *per se* to the skilled person.

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

- 5 The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

EXPERIMENTAL SECTION - GENERAL PART

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known
10 compounds by known methods by a person skilled in the art.

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no
15 purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be removed by trituration using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. Biotage SNAP cartridges KP-Sil® or KP-NH® in combination with a Biotage autopurifier
20 system (SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or DCM/methanol. In flash column chromatography, unmodified ("regular") silica gel may be used as well as aminophase functionalized silica gel. If reference is made to flash column chromatography or to flash chromatography in the experimental section without specification of a stationary phase, regular silica gel was used.

25

In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray

ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

- 5 In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this
10 type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base etc.) of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific
15 biological activity.

Analytical LC-MS Methods:

Method 1:

Instrument: Waters Acquity UPLCMS SingleQuad; Column: Acquity UPLC BEH C18 1.7 μ m, 50x2.1mm; eluent A: water + 0.1 vol. % formic acid (99 %), eluent B: acetonitrile;
20 gradient: 0-1.6 min. 1-99 % B, 1.6-2.0 min. 99 % B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Method 2:

Instrument: Waters Acquity UPLCMS SingleQuad; Column: Acquity UPLC BEH C18 1.7 μ m, 50x2.1mm; eluent A: water + 0.2 vol. % aqueous ammonia (32 %), eluent B: acetonitrile;
25 gradient: 0-1.6 min. 1-99 % B, 1.6-2.0 min. 99 % B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

Method 3:

Instrument: Waters Acquity UPLC H-Class system; Column: Acquity CSH C18 1.7 μ m 2.1x50 mm; eluent A: water + 0.1 vol. % formic acid, eluent B: acetonitrile, eluent C: 2 vol. % ammonia (28 %) in water, eluent D: 2 vol. % formic acid in water; gradient: 0-1.2 min 2-95 % B with A and 5 % D throughout, 1.2-1.4 min. 95 % B; flow 0.8 ml/min; temperature: 40 °C; PDA: 215-350 nm.

Method 4:

Instrument: Waters Acquity UPLC H-Class system; Column: XBridge BEH C18 2.5 μ m 2.1 x 50 mm; eluent A: water + 0.1 vol % formic acid, eluent B: acetonitrile, eluent C: 2 vol % ammonia (28%) in water, eluent D: 2 vol % formic acid in water; gradient: 0-1.2 min 2-95% B with A and 5% C throughout, 1.2-1.4 min 95% B; flow 0.8 ml/min; temperature: 40 °C; PDA: 215-350 nm.

Method 5:

MS instrument: SHIMADZU LCMS-2020; HPLC instrument: LabSolution Version 5.72; Column: Kinetex@5 μ m EVO C18 30 x 2.1mm; eluent A: 0.0375% TFA in water (v/v), eluent B: 0.01875% TFA in acetonitrile; gradient: 0.0 min 0% B $\rightarrow$ 3.00 min 60% B $\rightarrow$ 3.50 min 60% B $\rightarrow$ 3.51 min 0% B $\rightarrow$ 4.00 min 0% B; flow rate: 0.8 mL/min; oven temperature: 50 °C; UV detection: 220 nm & 254 nm.

Method 6:

Instrument: Agilent 1290 UPLCMS 6230 TOF; Säule: BEH C 18 1.7 μ m, 50x2.1mm; Eluent A: Wasser + 0.05 % Ameisensäure (99%); Eluent B: Acetonitril + 0.05 % Ameisensäure (99%); Gradient: 0-1.7 2-90% B, 1.7-2.0 90% B; Fluss 1.2 ml/min; Temperatur: 60°C; DAD scan: 190-400 nm.

Preparative LC-MS Methods:20 Method 7:

Instrument: Waters Autopurification MS SingleQuad; Column: Waters XBridge C18 5 μ 100x30mm; eluent A: water + 0.2 vol. % aqueous ammonia (32 %), eluent B: acetonitrile; gradient: 0-5.5 min. 5-100 % B; flow 70 ml/min; temperature: 25 °C; DAD scan: 210-400 nm

Method 8:

25 Instrument: Waters Autopurification MS SingleQuad; Column: Waters XBridge C18 5 μ 50x50mm; eluent A: water + 0.1 vol% formic acid, eluent B: methanol; gradient: 0-0.50 min. 20 % B; flow 50 to 100 ml/min, 0.50-8.00 min. 20 - 60% B; flow 100 ml/min, temperature: 25 °C; DAD scan: 210-400 nm

Method 9:

30 Instrument: Labomatic HD-5000, pump head HDK-280, gradient module NDB-1000, fraction collector Labomatic Labocol Vario 2000, Knauer UV detector Azura UVD 2.1S,

Prepcon 5 software. Column: Chromatorex C18 10 μ M 120x30 mm; Eluent A: water + 0.1% formic acid; Eluent B: acetonitrile; gradient: given for intermediates and examples, rate 150 mL/min, temperature 25°C.; UV 220 nm

Method 10:

- 5 Instrument: Labomatic HD-5000, pump head HDK-280, gradient module NDB-1000, fraction collector Labomatic Labocol Vario 2000, Knauer UV detector Azura UVD 2.1S, Prepcon 5 software. Column: Chromatorex C18 10 μ M 120x30 mm; Eluent A: 0.1% ammonia in water; Eluent B: acetonitrile; gradient: given for intermediates and examples, rate 150 mL/min, temperature 25°C.; UV 250 nm

10 Method 11:

- Instrument: Labomatic HD-5000, pump head HDK-280, gradient module NDB-1000, fraction collector Labomatic Labocol Vario 2000, Knauer UV detector Azura UVD 2.1S, Prepcon 5 software. Column: Chromatorex C18 10 μ M 300x50 mm; Eluent A: 0.1% ammonia in water; Eluent B: acetonitrile; gradient: given for intermediates and examples, rate 250 mL/min, temperature 25°C.; UV 250 nm

NMR Spectra:

- The multiplicities of proton signals in ^1H NMR spectra given in the following paragraphs reflect the observed signal form and do not take into account any higher-order signal phenomena. As a rule, the chemical shift data refers to the center of the signal in question. In the case of wide multiplets, a range is specified. Signals hidden by solvent or water were either assigned tentatively or are not listed. Strongly broadened signals - e.g. caused by rapid rotation of molecular moieties or by interchanging protons - have also been assigned tentatively (often referred to as a broad multiplet or broad singlet) or are not shown.

- 25 The ^1H -NMR data of selected compounds are listed in the form of ^1H -NMR peaklists. Therein, for each signal peak the δ value in ppm is given, followed by the signal intensity, reported in round brackets. The δ value-signal intensity pairs from different peaks are separated by commas. Therefore, a peaklist is described by the general form: δ_1 (intensity₁), δ_2 (intensity₂), ... , δ_i (intensity_i), ... , δ_n (intensity_n).

The intensity of a sharp signal correlates with the height (in cm) of the signal in a printed NMR spectrum. When compared with other signals, this data can be correlated to the real

ratios of the signal intensities. In the case of broad signals, more than one peak, or the center of the signal along with their relative intensity, compared to the most intense signal displayed in the spectrum, are shown. A ^1H -NMR peaklist is similar to a classical ^1H -NMR readout, and thus usually contains all the peaks listed in a classical NMR interpretation.

5 Moreover, similar to classical ^1H -NMR printouts, peaklists can show solvent signals, signals derived from stereoisomers of the particular target compound, peaks of impurities, ^{13}C satellite peaks, and/or spinning sidebands. The peaks of stereoisomers, and/or peaks of impurities are typically displayed with a lower intensity compared to the peaks of the target compound (e.g., with a purity of >90%). Such stereoisomers and/or impurities may be

10 typical for the particular manufacturing process, and therefore their peaks may help to identify a reproduction of the manufacturing process on the basis of "by-product fingerprints". An expert who calculates the peaks of the target compound by known methods (MestReC, ACD simulation, or by use of empirically evaluated expectation values), can isolate the peaks of the target compound as required, optionally using additional intensity

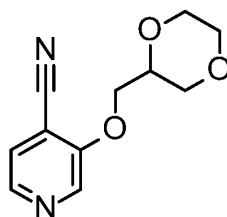
15 filters. Such an operation would be similar to peak-picking in classical ^1H -NMR interpretation. A detailed description of the reporting of NMR data in the form of peaklists can be found in the publication "Citation of NMR Peaklist Data within Patent Applications" (cf. <http://www.researchdisclosure.com/searching-disclosures>, Research Disclosure Database Number 605005, 2014, 01 Aug 2014). In the peak picking routine, as described

20 in the Research Disclosure Database Number 605005, the parameter "MinimumHeight" can be adjusted between 1% and 4%. However, depending on the chemical structure and/or depending on the concentration of the measured compound it may be reasonable to set the parameter "MinimumHeight" <1%.

25 Syntheses of Intermediate 1 Compounds

Intermediate 1-1

3-[(1,4-dioxan-2-yl)methoxy]pyridine-4-carbonitrile



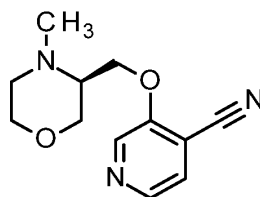
3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 1.40 g, 10.1 mmol) and (1,4-dioxan-2-yl)methanol (CAS 143669-41-4, 1.31 g, 11.1 mmol) were dissolved in THF (45 ml). Potassium tert-butoxide (1.03 g, 9.14 mmol) was added and the mixture was stirred for 1 h at 0°C. The reaction mixture was diluted slowly with sat. ammonium chloride solution and
5 extracted with EtOAc (3x). The organic phase was washed with brine and filtered over a water-repellent filter, concentrated under reduced pressure and purified by flash chromatography (silica, hexane / EtOAc gradient 0-100 %; EtOAc / EtOH gradient 0-35 %) to give 1.18 g of the title compound (53 % yield).

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 8.72 (s, 1H), 8.23 - 8.46 (m, 1H), 7.68 - 7.86 (m,
10 1H), 4.32 (d, 2H), 3.40 - 3.99 (m, 7H).

LC-MS (method 2): R_t = 0.77 min; MS (ESIpos): m/z = 221 [M+H]⁺

Intermediate 1-2

3-[(3*R*)-4-methylmorpholin-3-yl]methoxy}pyridine-4-carbonitrile



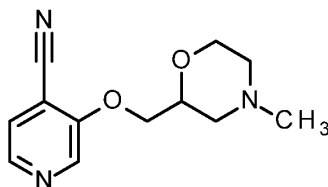
15 To a solution of [(3*S*)-4-methylmorpholin-3-yl]methanol (CAS 1620510-50-0, 1.00 g, 7.62 mmol) in THF (20 ml) at 0°C was slowly added sodium hydride (366 mg, 9.15 mmol, 60 % purity). The reaction mixture was stirred for 3 h at RT. 3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 1.06 g, 7.62 mmol) in THF (10 ml) was added and the mixture was stirred overnight. The reaction mixture was quenched with 1N HCl until pH = 7. The suspension
20 was filtered through a hydrophobic filter paper and the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (basic silica, hexane / EtOAc gradient 0-100 %) to give 355 mg of the title compound (20 % yield).

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 8.75 (s, 1H), 8.40 (d, 1H), 7.78 (d, 1H), 4.44 (dd,
25 1H), 4.23 (dd, 1H), 3.87 (dd, 1H), 3.71 (dt, 1H), 3.50 (td, 1H), 3.35 - 3.41 (m, 1H), 2.65 - 2.71 (m, 1H), 2.45 - 2.49 (m, 1H), 2.29 - 2.35 (m, 3H), 2.24 (ddd, 1H).

LC-MS (method 2): R_t = 0.72 min; MS (ESIpos): m/z = 234.2 [M+H]⁺

Intermediate 1-3

3-{{[4-methylmorpholin-2-yl]methoxy}pyridine-4-carbonitrile



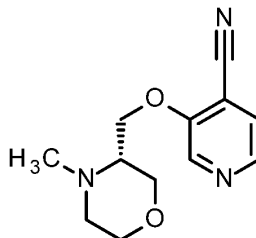
Using an analogous method as described for intermediate 1-1 with 3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 764 mg, 5.51 mmol) and [4-methylmorpholin-2-yl]methanol (CAS 40987-46-0, 940 mg, 7.17 mmol) as the starting materials; 836 mg (90 % purity, 59 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 1.893 (0.97), 1.920 (1.44), 1.947 (1.07), 1.954 (0.50), 1.962 (0.54), 1.983 (1.01), 1.991 (1.03), 2.011 (0.58), 2.019 (0.52), 2.197 (16.00), 2.518 (0.41), 2.589 (0.80), 2.593 (0.82), 2.617 (0.73), 2.621 (0.74), 2.766 (0.66), 2.770 (0.95), 2.794 (0.63), 2.798 (0.89), 3.513 (0.60), 3.520 (0.73), 3.541 (1.36), 3.547 (1.39), 3.570 (0.80), 3.575 (0.67), 3.793 (0.74), 3.796 (1.10), 3.801 (1.12), 3.805 (0.92), 3.808 (0.85), 3.814 (0.79), 3.821 (1.18), 3.826 (1.18), 3.833 (1.27), 3.839 (0.66), 4.316 (5.03), 4.329 (4.72), 7.772 (2.40), 7.774 (2.63), 7.785 (2.49), 8.381 (3.41), 8.393 (3.28), 8.714 (4.32).

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 234.2 [M+H]⁺

Intermediate 1-4

3-[[[(3S)-4-methylmorpholin-3-yl]methoxy]pyridine-4-carbonitrile



20

Using an analogous method as described for intermediate 1-2 with 3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 1.00 g, 7.24 mmol) and [(3R)-4-methylmorpholin-3-

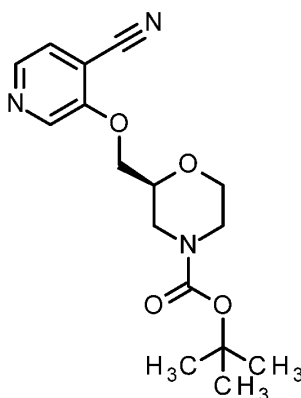
yl]methanol (1.00 g, 95 % purity, 7.24 mmol; CAS 1620510-51-1) as the starting materials; 823 mg (99 % purity, 48 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 2.211 (0.52), 2.219 (0.64), 2.236 (0.66), 2.240 (0.68), 2.245 (0.68), 2.249 (0.72), 2.266 (0.69), 2.274 (0.63), 2.306 (16.00), 2.472 (0.48),
5 2.475 (0.50), 2.518 (1.22), 2.522 (0.71), 2.658 (0.56), 2.664 (1.27), 2.671 (0.67), 2.687 (0.47), 2.694 (0.96), 2.701 (0.47), 3.356 (1.17), 3.378 (1.16), 3.384 (1.30), 3.406 (1.20), 3.472 (0.50), 3.478 (0.58), 3.499 (0.80), 3.506 (0.81), 3.525 (0.71), 3.532 (0.61), 3.685 (0.44), 3.692 (0.86), 3.698 (0.45), 3.720 (0.66), 3.856 (0.80), 3.864 (0.81), 3.884 (0.73), 3.892 (0.72), 4.209 (1.03), 4.223 (1.01), 4.234 (1.29), 4.249 (1.23), 4.417 (1.25), 4.429
10 (1.28), 4.443 (1.03), 4.454 (0.99), 7.778 (2.39), 7.780 (2.38), 7.790 (2.45), 7.792 (2.50), 8.391 (3.23), 8.403 (3.11), 8.745 (3.91).

LC-MS (method 2): Rt = 0.70 min; MS (ESIpos): m/z = 234 [M+H]⁺

Intermediate 1-5

tert-butyl (2S)-2-[[[4-cyanopyridin-3-yl]oxy]methyl]morpholine-4-carboxylate



15

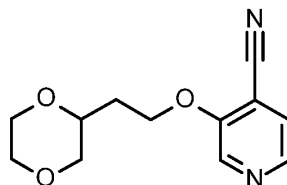
Using an analogous method as described for intermediate 1-1 with 3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 2.55 g, 18.4 mmol) and *tert*-butyl (2S)-2-(hydroxymethyl)morpholine-4-carboxylate (CAS 135065-76-8, 4.00 g, 18.4 mmol) as the starting materials; 4.82 g (90 % purity, 74 % yield) of the title compound were prepared.

20 ¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.41 (s, 9H), 2.72 - 3.05 (m, 2H), 3.46 (br d, 1H), 3.67 - 3.82 (m, 2H), 3.82 - 3.88 (m, 1H), 4.00 (s, 1H), 4.37 (br d, 2H), 7.79 (d, 1H), 8.40 (d, 1H), 8.73 (s, 1H).

LC-MS (method 2): R_t = 1.06 min; MS (ESIpos): m/z = 320 [M+H]⁺

Intermediate 1-6

3-[2-(1,4-dioxan-2-yl)ethoxy]pyridine-4-carbonitrile



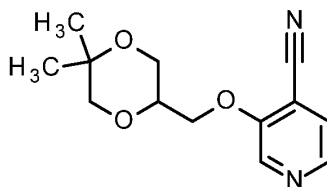
Using an analogous method as described for intermediate 1-2 with 3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 2.10 g, 15.1 mmol) and 2-(1,4-dioxan-2-yl)ethan-1-ol (CAS 151720-04-6, 2.00 g, 15.1 mmol) as the starting materials; 2.89 g (99 % purity, 81 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.754 (0.63), 1.768 (1.37), 1.774 (0.82), 1.781 (0.98), 1.790 (2.18), 1.803 (3.39), 1.810 (2.10), 1.817 (1.93), 1.824 (3.23), 1.838 (2.78), 1.855 (2.41), 1.867 (2.45), 1.869 (2.40), 1.874 (2.53), 1.886 (2.23), 1.902 (0.99), 1.910 (0.87), 1.922 (0.67), 2.326 (0.72), 2.668 (0.69), 3.223 (4.26), 3.247 (5.57), 3.250 (5.62), 3.276 (5.26), 3.428 (1.77), 3.434 (1.89), 3.455 (4.59), 3.462 (4.80), 3.483 (3.76), 3.489 (3.97), 3.530 (3.36), 3.535 (3.38), 3.558 (4.71), 3.564 (5.40), 3.585 (1.93), 3.592 (3.08), 3.626 (4.58), 3.631 (4.33), 3.654 (3.70), 3.659 (4.02), 3.668 (1.98), 3.673 (1.97), 3.680 (2.77), 3.687 (2.85), 3.693 (2.89), 3.706 (6.98), 3.712 (6.06), 3.724 (1.75), 3.735 (3.40), 3.759 (4.77), 3.766 (4.02), 3.788 (4.04), 3.794 (3.73), 4.315 (0.93), 4.329 (1.18), 4.339 (3.54), 4.354 (6.92), 4.359 (5.21), 4.370 (6.49), 4.384 (3.79), 4.392 (1.47), 4.408 (0.68), 7.778 (9.22), 7.790 (9.58), 8.380 (10.88), 8.392 (10.45), 8.698 (16.00).

LC-MS (method 6): Rt = 0.64 min; MS (ESIpos): m/z = 235 [M+H]⁺

Intermediate 1-7

3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridine-4-carbonitrile



Using an analogous method as described for intermediate 1-2 with 3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 948 mg, 6.84 mmol) and (5,5-dimethyl-1,4-dioxan-2-

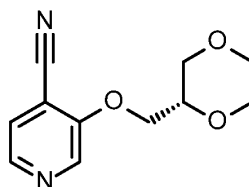
yl)methanol (1.00 g, 6.84 mmol; CAS 54321-57-2) as the starting materials; 1.31 g (95 % purity, 73 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 1.014 (0.69), 1.048 (16.00), 1.172 (0.55), 1.200 (0.51), 1.263 (13.01), 1.987 (0.92), 2.518 (0.62), 2.523 (0.43), 3.313 (1.67), 3.340 (2.27),
5 3.342 (2.21), 3.542 (2.95), 3.570 (2.39), 3.604 (1.50), 3.627 (1.97), 3.734 (1.24), 3.760 (3.08), 3.781 (2.25), 3.787 (2.73), 3.791 (1.58), 3.796 (0.77), 3.802 (0.63), 4.356 (3.63), 4.365 (4.41), 7.780 (3.42), 7.792 (3.63), 8.387 (4.49), 8.399 (4.29), 8.715 (5.54).

LC-MS (method 6): Rt = 0.75 min; MS (ESIpos): m/z = 249 [M+H]⁺

Intermediate 1-8

10 3-[[*(2S)*-1,4-dioxan-2-yl]methoxy]pyridine-4-carbonitrile



Using an analogous method as described for intermediate 1-1 with 3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 1.00 g, 7.22 mmol) and [(*2R*)-1,4-dioxan-2-yl]methanol (CAS406913-88-0, 938 mg, 7.94 mmol) as the starting materials; 490 mg (95% purity, 29%
15 yield) of the title compound were prepared.

Optical rotation: [α]_D = - 1.68° +/- 0.35° (c = 7 mg/ml, methanol)

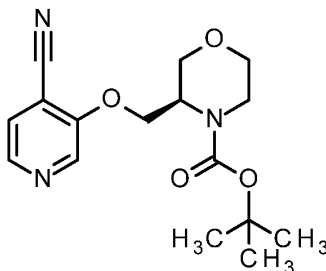
¹H-NMR (400 MHz, DMSO-d₆): δ ppm= 3.41 - 3.53 (m, 2 H), 3.59 - 3.72 (m, 2 H), 3.75 - 3.81 (m, 1 H), 3.82 - 3.87 (m, 1 H), 3.87 - 3.95 (m, 1 H), 4.27 - 4.37 (m, 2 H), 7.77 - 7.80 (m, 1 H), 8.38 - 8.41 (m, 1 H), 8.71 - 8.73 (m, 1 H).

20

25

Intermediate 1-9

tert-butyl (3*R*)-3-[[4-cyanopyridin-3-yl]oxy]methyl}morpholine-4-carboxylate

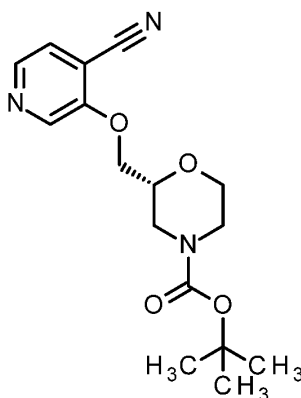


To a solution of *tert*-butyl (3*S*)-3-(hydroxymethyl)morpholine-4-carboxylate (4.30 g, 19.8
5 mmol) in THF (28 ml) at 0°C was slowly added sodium hydride (1.55 g, 55% purity, 35.6 mmol). The reaction mixture was stirred for 1 h. 3-fluoropyridine-4-carbonitrile (CAS 113770-88-0, 2.42 g, 19.8 mmol) in THF (14 ml) was added and the mixture was stirred for 4 h at 0°C. The reaction mixture was quenched with 2N HCl until pH = 6 – 7 and was extracted with EE. The organic layer was filtered through a water repellent filter paper and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, DCM / EtOH gradient 0-7%) to give 4 g of the title compound (70% yield).
10

LC-MS (method 6): R_t = 0.95 min; MS (ESIpos): m/z = 264 $[M+H]^+$

Intermediate 1-10

tert-butyl (2*R*)-2-[[4-cyanopyridin-3-yl]oxy]methyl}morpholine-4-carboxylate



15

Using an analogous method as described for intermediate 1-1 with 3-chloropyridine-4-carbonitrile (CAS 68325-15-5, 3.25 g, 23.5 mmol) and *tert*-butyl (2*R*)-2-

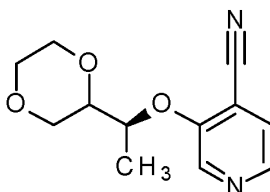
(hydroxymethyl)morpholine-4-carboxylate (CAS 135065-71-3, 5.10 g, 23.5 mmol) as the starting materials; 6.92 g (90% purity, 83% yield) of the title compound were prepared.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.41 (s, 9H), 2.73 - 3.00 (m, 2H), 3.39 - 3.50 (m, 1H), 3.75 (m, 2H), 3.82 - 3.89 (m, 1H), 3.95 - 4.00 (m, 1H), 4.37 (br d, 2H), 7.79 (d, 1H),
5 8.40 (d, 1H), 8.73 (s, 1H).

LC-MS (method 2): R_t = 1.04 min; MS (ESIpos): m/z = 320 [M+H]⁺

Intermediate 1-11

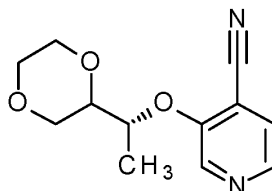
3-[(1S)-1-(1,4-dioxan-2-yl)ethoxy]pyridine-4-carbonitrile



10 Using an analogous method as described for intermediate 1-9 with 3-fluoropyridine-4-carbonitrile (878 mg, 7.19 mmol) and (1S)-1-[1,4-dioxan-2-yl]ethan-1-ol (CAS 1372875-59-6, 950 mg, 7.19 mmol) as the starting materials; 1.68 g (95 % purity, 95 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO- d₆): δ ppm= 0.988 (0.85), 1.004 (0.92), 1.056 (0.59), 1.071
15 (0.60), 1.154 (4.47), 1.166 (0.63), 1.172 (9.29), 1.189 (4.59), 1.276 (12.44), 1.292 (12.55), 1.325 (11.08), 1.341 (11.16), 1.987 (16.00), 2.518 (1.63), 2.522 (1.05), 3.300 (0.46), 3.396 (1.81), 3.421 (2.99), 3.424 (2.99), 3.429 (1.78), 3.450 (5.06), 3.457 (3.42), 3.472 (1.97), 3.478 (1.62), 3.485 (2.38), 3.497 (2.19), 3.500 (1.91), 3.525 (2.26), 3.552 (1.16), 3.559 (1.31), 3.582 (2.48), 3.588 (2.91), 3.611 (1.70), 3.616 (2.62), 3.638 (4.15), 3.642 (3.63),
20 3.664 (3.89), 3.671 (4.01), 3.676 (1.93), 3.683 (1.76), 3.685 (1.80), 3.689 (1.79), 3.695 (1.76), 3.701 (1.17), 3.704 (1.27), 3.707 (1.26), 3.710 (1.28), 3.744 (1.82), 3.750 (3.32), 3.757 (1.01), 3.778 (3.94), 3.784 (2.19), 3.807 (1.47), 3.813 (1.33), 3.906 (1.40), 3.912 (1.35), 3.935 (1.24), 3.941 (1.18), 3.999 (1.24), 4.016 (3.72), 4.034 (3.66), 4.052 (1.20), 4.804 (0.41), 4.821 (1.95), 4.836 (3.43), 4.852 (2.64), 4.864 (1.34), 7.755 (3.58), 7.757
25 (3.60), 7.769 (4.33), 7.771 (3.80), 7.783 (3.28), 7.785 (3.20), 8.351 (4.95), 8.363 (4.90), 8.368 (4.48), 8.380 (4.17), 8.749 (6.40), 8.772 (5.46).

LC-MS (method 6): R_t = 0.64 min; MS (ESIpos): m/z = 235 [M+H]⁺

Intermediate 1-123-{{(1*R*)-1-[1,4-dioxan-2-yl]ethoxy}pyridine-4-carbonitrile

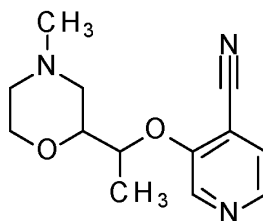
Using an analogous method as described for intermediate 1-9 with 3-fluoropyridine-4-carbonitrile (905 mg, 7.42 mmol) and (1*R*)-1-[1,4-dioxan-2-yl]ethan-1-ol (CAS 1372881-98-5, 980 mg, 7.42 mmol) as the starting materials; 1.39 g (95 % purity, 76 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO- *d*₆): δ ppm= 1.274 (0.82), 1.289 (0.87), 1.322 (16.00), 1.337 (15.97), 1.984 (0.48), 2.331 (0.56), 2.673 (0.57), 3.427 (2.95), 3.448 (3.45), 3.455 (3.30), 3.471 (3.27), 3.482 (2.59), 3.496 (3.79), 3.499 (3.36), 3.524 (3.41), 3.580 (1.59), 3.586 (1.80), 3.609 (2.32), 3.615 (2.92), 3.636 (5.12), 3.662 (3.60), 3.668 (3.70), 3.680 (2.08), 3.687 (1.49), 3.693 (1.53), 3.698 (1.52), 3.704 (1.41), 3.746 (3.19), 3.754 (1.74), 3.775 (2.26), 3.903 (2.52), 3.909 (2.44), 3.932 (2.24), 3.937 (2.13), 4.818 (0.65), 4.833 (2.08), 4.845 (2.30), 4.849 (2.22), 4.861 (2.00), 4.876 (0.57), 7.766 (5.15), 7.778 (5.29), 8.348 (0.42), 8.365 (6.23), 8.377 (6.01), 8.743 (0.51), 8.765 (9.13).

LC-MS (method 6): *R*_t = 0.67 min; MS (ESIpos): *m/z* = 235 [M+H]⁺

Intermediate 1-71

3-[1-(4-methylmorpholin-2-yl)ethoxy]isonicotinonitrile



20

Using an analogous method as described for intermediate 1-9 with 3-fluoropyridine-4-carbonitrile (824 mg, 6.75 mmol) and 1-(4-methylmorpholin-2-yl)ethanol (980 mg, 6.75 mmol, CAS 1540922-49-3) as the starting materials; 817 mg (99 % purity, 48 % yield) of the title compound were prepared after column chromatography using the Biotage Isolera.

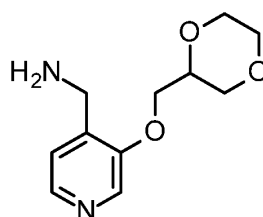
¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.285 (4.44), 1.300 (4.47), 1.318 (5.38), 1.333 (5.31), 1.848 (0.57), 1.874 (0.94), 1.901 (0.63), 1.927 (0.93), 1.933 (0.66), 1.953 (2.04), 1.961 (1.23), 1.981 (1.32), 1.990 (0.60), 2.188 (16.00), 2.518 (1.33), 2.522 (0.90), 2.572 (0.89), 2.600 (0.79), 2.718 (0.54), 2.746 (0.52), 2.839 (0.64), 2.867 (0.60), 3.485 (0.78),
5 3.488 (0.66), 3.491 (0.85), 3.516 (1.00), 3.522 (0.92), 3.544 (0.48), 3.550 (0.42), 3.562 (0.44), 3.568 (0.54), 3.573 (0.73), 3.578 (0.77), 3.587 (0.81), 3.593 (0.83), 3.598 (0.85), 3.604 (0.71), 3.772 (0.51), 3.777 (0.56), 3.781 (0.78), 3.786 (0.61), 3.789 (0.59), 3.794 (0.56), 3.800 (0.46), 3.805 (0.46), 3.809 (0.64), 3.814 (0.50), 3.817 (0.45), 4.818 (0.60), 4.833 (0.97), 4.848 (0.79), 4.858 (0.65), 4.862 (0.67), 4.874 (0.57), 7.746 (1.41), 7.760
10 (2.88), 7.772 (1.71), 8.341 (1.93), 8.355 (2.69), 8.368 (2.12), 8.745 (2.34), 8.766 (2.68).

LC-MS (method 6): R_t = 0.32 min; MS (ESIpos): m/z = 248 [M+H]⁺

Syntheses of Intermediate 2 Compounds

Intermediate 2-1

1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine



15

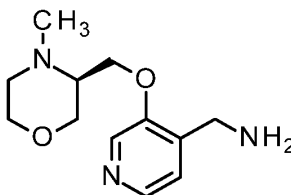
An autoclave was charged with 3-[(1,4-dioxan-2-yl)methoxy]pyridine-4-carbonitrile (intermediate 1-1, 1.17 g, 5.34 mmol), ammonia (19 ml, 7.0 M in methanol, 850 mmol) and Raney-Nickel (CAS 7440-02-0, 783 mg, 50 % wetted) and the mixture was stirred under 25 bar hydrogen atmosphere at RT for 22 h. The mixture was filtered through a pad of celite,
20 eluted with methanol and the combined filtrates were concentrated under reduced pressure. The residue was used directly in the next step without further purification (1.13 g, 94 % yield).

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 8.24 (s, 1H), 8.17 (d, 1H), 7.38 (d, 1H), 4.09 (d, 2H), 3.73 - 3.91 (m, 3H), 3.59 - 3.73 (m, 4H), 3.46 - 3.52 (m, 2H), 3.39 - 3.45 (m, 2H). 2.06
25 (br., 2H).

LC-MS (method 2): R_t = 0.54 min; MS (ESIpos): m/z = 225 [M+H]⁺

Intermediate 2-2

1-(3-[[[(3*R*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methanamine

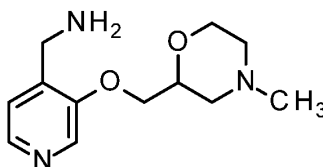


- Using an analogous method as described for intermediate 2-1 with 3-[[[(3*R*)-4-methylmorpholin-3-yl]methoxy]pyridine-4-carbonitrile (intermediate 1-2, 355 mg, 1.52 mmol) as the starting material; 350 mg of the title compound were prepared (89 % yield).

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 8.24 - 8.31 (m, 1H), 8.17 (d, 1H), 7.39 (d, 1H), 4.18 - 4.27 (m, 1H), 4.00 (dd, 1H), 3.86 (dd, 1H), 3.63 - 3.75 (m, 3H), 3.42 - 3.55 (m, 1H), 3.36 - 3.41 (m, 1H), 2.67 (dq, 1H), 2.40 - 2.47 (m, 1H), 2.19 - 2.31 (m, 4H), 1.63 - 2.19 (m, 2H).

10 **Intermediate 2-3**

1-(3-[[[4-methylmorpholin-2-yl]methoxy]pyridin-4-yl)methanamine



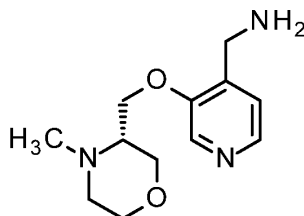
- Using an analogous method as described for intermediate 2-1 with 3-[[[4-methylmorpholin-2-yl]methoxy]pyridine-4-carbonitrile (intermediate 1-3, 836 mg, 3.58 mmol) as the starting material; 860 mg (90 % purity, 91 % yield) of the title compound were prepared.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 1.68 - 1.84 (br s, 2H), 1.85 - 1.94 (t, 1H), 1.94 - 2.05 (td, 1H), 2.19 (s, 3H), 2.57 - 2.64 (d, 1H), 2.73 - 2.83 (d, 1H), 3.46 - 3.63 (t, 1H), 3.63 - 3.73 (s, 2H), 3.73 - 3.86 (m, 3H), 4.10 (br d, 2H), 7.34 - 7.44 (d, 1H), 8.10 - 8.20 (d, 1H), 8.21 - 8.30 (s, 1H).

- 20 LC-MS (method 2): *R*_t = 0.56 min; MS (ESIpos): *m/z* = 238 [M+H]⁺

Intermediate 2-4

1-(3-(((3S)-4-methylmorpholin-3-yl)methoxy)pyridin-4-yl)methanamine

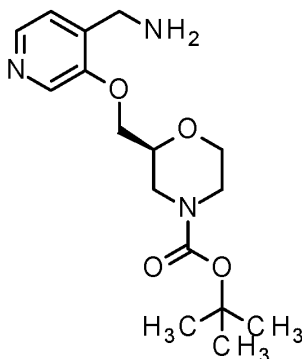


Using an analogous method as described for intermediate 2-1 with 3-(((3S)-4-methylmorpholin-3-yl)methoxy)pyridine-4-carbonitrile (intermediate 1-4, 823 mg, 3.53 mmol) as the starting material; 798 mg (90 % purity, 86 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 1.865 (0.49), 2.199 (0.64), 2.210 (1.08), 2.228 (0.99), 2.233 (0.96), 2.236 (0.96), 2.254 (0.85), 2.263 (0.81), 2.269 (0.55), 2.284 (16.00),
2.327 (0.53), 2.430 (0.78), 2.439 (0.81), 2.447 (0.65), 2.518 (2.11), 2.523 (1.42), 2.649 (0.75), 2.654 (1.38), 2.660 (0.91), 2.669 (0.65), 2.674 (0.60), 2.678 (0.83), 2.684 (1.22), 2.690 (0.66), 3.361 (1.52), 3.365 (1.53), 3.388 (1.10), 3.469 (0.59), 3.474 (0.65), 3.496 (1.15), 3.502 (1.16), 3.523 (0.75), 3.528 (0.68), 3.683 (2.49), 3.690 (2.42), 3.712 (0.79), 3.719 (1.11), 3.846 (1.01), 3.853 (1.04), 3.873 (0.94), 3.880 (0.91), 3.982 (0.79), 3.997 (0.86), 4.007 (1.03), 4.021 (0.96), 4.215 (1.01), 4.226 (1.09), 4.240 (0.86), 4.250 (0.84), 7.379 (0.99), 7.389 (1.01), 8.168 (1.06), 8.179 (1.11), 8.259 (1.53).

Intermediate 2-5

tert-butyl (2S)-2-({[4-(aminomethyl)pyridin-3-yl]oxy)methyl)morpholine-4-carboxylate



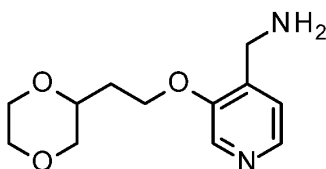
Using an analogous method as described for intermediate 2-1 with *tert*-butyl (2*S*)-2-[[[4-cyanopyridin-3-yl)oxy]methyl]morpholine-4-carboxylate (intermediate 1-5, 5.75 g, 18.0 mmol) as the starting material; 6.00 g (95 % purity, 98 % yield) of the title compound were prepared.

- 5 ¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 1.41 (s, 9H), 3.16 (s, 2H), 3.39 - 3.49 (m, 2H), 3.66 - 3.79 (m, 5H), 3.79 - 3.98 (m, 3H), 4.07 - 4.20 (m, 3H), 7.39 (d, 1H), 8.19 (d, 1H), 8.27 (s, 1H).

LC-MS (method 2): R_t = 0.84 min; MS (ESIpos): m/z = 324 [M+H]⁺

Intermediate 2-6

- 10 1-{3-[2-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}methanamine

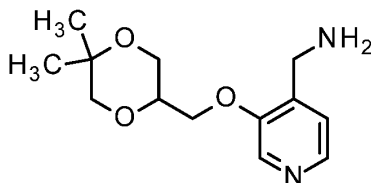


Using an analogous method as described for intermediate 2-1 with 3-[2-(1,4-dioxan-2-yl)ethoxy]pyridine-4-carbonitrile (intermediate 1-6, 2.89 g, 12.3 mmol) as the starting material; 2.22 g (90 % purity, 68 % yield) of the title compound were prepared.

- 15 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.536 (0.40), 1.729 (1.99), 1.751 (3.41), 1.765 (5.01), 1.785 (6.00), 1.804 (5.59), 1.817 (5.34), 1.834 (4.06), 1.852 (2.92), 1.870 (2.15), 2.326 (1.02), 2.669 (1.04), 3.159 (0.53), 3.208 (5.54), 3.235 (8.67), 3.261 (7.11), 3.424 (3.46), 3.430 (3.63), 3.451 (7.09), 3.457 (7.51), 3.479 (5.43), 3.485 (5.78), 3.528 (4.90), 3.534 (5.03), 3.557 (6.69), 3.563 (7.65), 3.584 (3.06), 3.590 (4.57), 3.622 (8.16), 3.653 (8.66), 3.688 (14.98), 3.697 (16.00), 3.731 (13.03), 3.759 (6.36), 4.136 (7.05), 4.152 (13.01), 4.167 (8.38), 7.385 (5.36), 7.394 (5.58), 8.163 (5.21), 8.172 (5.56), 8.224 (7.44).

Intermediate 2-7

- 1-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine

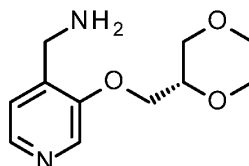


Using an analogous method as described for intermediate 2-1 with 3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridine-4-carbonitrile (intermediate 1-7, 1.30 g, 5.24 mmol) as the starting material; 1.26 g (90 % purity, 86 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.014 (0.96), 1.049 (16.00), 1.201 (0.72), 1.262 (13.58), 1.751 (0.48), 2.518 (2.17), 2.523 (1.47), 3.308 (2.76), 3.539 (2.43), 3.567 (1.99), 3.601 (1.13), 3.623 (1.75), 3.694 (1.97), 3.720 (2.07), 3.746 (2.38), 3.783 (0.46), 4.128 (3.01), 4.136 (2.80), 7.386 (0.85), 8.181 (0.83), 8.237 (0.96).

Intermediate 2-8

1-(3-[(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)methanamine



10

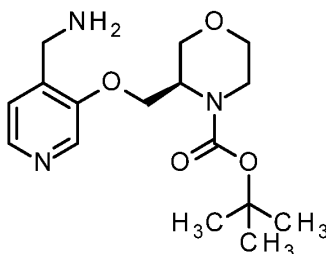
Using an analogous method as described for intermediate 2-1 with 3-[(2S)-1,4-dioxan-2-yl]methoxy]pyridine-4-carbonitrile (intermediate 1-8, 1.24 g, 5.63 mmol) as the starting material; 1.56 g (80% purity, 99% yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 1.232 (0.52), 1.845 (1.06), 2.518 (2.37), 2.523 (1.54), 3.159 (14.24), 3.171 (14.33), 3.376 (0.69), 3.379 (0.65), 3.404 (2.41), 3.419 (0.41), 3.428 (3.79), 3.431 (3.86), 3.439 (0.59), 3.447 (0.69), 3.455 (2.71), 3.465 (1.97), 3.474 (0.57), 3.486 (2.71), 3.493 (2.97), 3.508 (1.01), 3.520 (2.61), 3.592 (0.45), 3.601 (1.92), 3.608 (2.10), 3.630 (2.77), 3.636 (3.65), 3.659 (5.73), 3.661 (5.45), 3.683 (16.00), 3.700 (1.95), 3.754 (3.49), 3.762 (2.18), 3.784 (2.51), 3.794 (0.57), 3.812 (0.61), 3.823 (2.48), 3.829 (3.16), 3.842 (0.81), 3.849 (2.07), 3.856 (6.45), 3.868 (1.93), 3.874 (1.37), 3.880 (1.69), 3.887 (1.30), 3.892 (1.13), 3.899 (0.89), 4.087 (11.44), 4.099 (10.46), 4.111 (2.62), 4.125 (1.15), 7.380 (4.02), 7.391 (4.11), 7.411 (0.67), 7.423 (0.67), 8.168 (6.28), 8.179 (6.26), 8.184 (1.58), 8.196 (1.02), 8.230 (10.21), 8.274 (1.76).

25

Intermediate 2-9

tert-butyl (3*R*)-3-({[4-(aminomethyl)pyridin-3-yl]oxy)methyl)morpholine-4-carboxylate



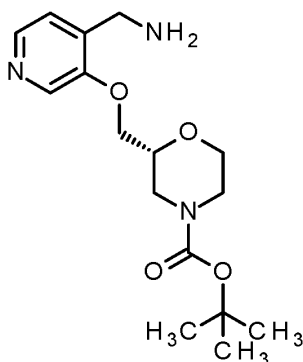
Using an analogous method as described for intermediate 2-1 with *tert*-butyl (3*R*)-3-[[4-cyanopyridin-3-yl]oxy]methyl)morpholine-4-carboxylate (intermediate 1-9, 4.00 g, 12.5 mmol) as the starting material; 3.65 g of the title compound were prepared (86% yield).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.038 (0.41), 1.055 (0.77), 1.073 (0.44), 1.363 (10.92), 1.754 (6.47), 2.200 (1.02), 2.325 (1.05), 2.330 (1.42), 2.334 (1.05), 2.521 (5.72), 2.526 (3.72), 2.667 (0.88), 2.672 (1.22), 2.676 (0.89), 3.057 (1.02), 3.068 (1.10), 3.087 (1.65), 3.090 (1.62), 3.097 (1.89), 3.101 (1.73), 3.120 (2.21), 3.130 (2.39), 3.168 (16.00), 3.210 (1.86), 3.235 (0.59), 3.240 (1.07), 3.258 (1.25), 3.265 (1.40), 3.286 (1.75), 3.294 (2.07), 3.316 (3.15), 3.365 (3.67), 3.372 (3.73), 3.395 (1.88), 3.402 (1.68), 3.462 (1.41), 3.470 (1.43), 3.503 (3.53), 3.534 (2.78), 3.682 (7.14), 3.764 (1.68), 3.774 (1.81), 3.792 (3.17), 3.802 (2.81), 3.820 (1.93), 3.855 (0.89), 3.859 (1.19), 3.865 (1.80), 3.869 (2.32), 3.873 (3.62), 3.882 (2.64), 3.886 (3.02), 3.889 (2.79), 3.893 (4.31), 3.899 (3.39), 3.902 (2.87), 3.927 (2.09), 4.111 (1.76), 4.227 (3.64), 4.303 (0.96), 4.315 (1.37), 4.329 (3.71), 4.331 (3.43), 4.338 (1.95), 4.345 (2.50), 7.401 (2.60), 8.192 (2.81), 8.337 (2.91).

LC-MS (method 1): *R*_t = 0.49 min; MS (ESIpos): *m/z* = 324 [M+H]⁺

Intermediate 2-10

tert-butyl (2R)-2-({[4-(aminomethyl)pyridin-3-yl]oxy}methyl)morpholine-4-carboxylate



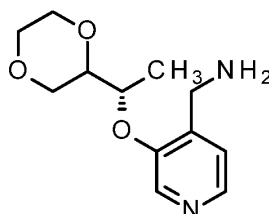
Using an analogous method as described for intermediate 2-1 with *tert*-butyl (2R)-2-[[4-cyanopyridin-3-yl]oxy]methyl]morpholine-4-carboxylate (intermediate 1-10, 6.92 g, 21.7 mmol) as the starting material; 6.95 g of the title compound were prepared (90% purity, 89% yield).

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.41 (s, 9H), 2.70 - 3.01 (m, 2H), 3.17 (d, 3H), 3.41 - 3.52 (m, 1H), 3.63 - 3.70 (m, 2H), 3.70 - 3.81 (m, 2H), 3.82 - 4.00 (m, 2H), 4.08 - 4.18 (m, 3H), 7.39 (d, 1H), 8.18 (d, 1H), 8.25 (s, 1H).

LC-MS (method 2): R_t = 0.84 min; MS (ESIpos): m/z = 324 [M+H]⁺

Intermediate 2-11

1-{3-[(1S)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}methanamine



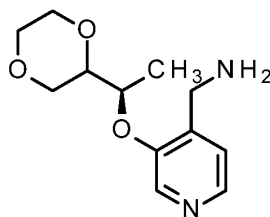
Using an analogous method as described for intermediate 2-1 with 3-[(1S)-1-(1,4-dioxan-2-yl)ethoxy]pyridine-4-carbonitrile (intermediate 1-11, 1.68 g, 7.17 mmol) as the starting material; 1.49 g (90% purity, 78% yield) of the title compound were prepared.

LC-MS (method 6): R_t = 0.2 min; MS (ESIpos): m/z = 239 [M+H]⁺

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.990 (0.87), 1.006 (0.89), 1.058 (0.73), 1.073 (0.73), 1.165 (0.76), 1.216 (15.68), 1.232 (16.00), 1.256 (14.15), 1.272 (13.96), 1.755 (9.46), 1.917 (0.88), 3.240 (0.43), 3.265 (0.46), 3.276 (0.41), 3.293 (0.54), 3.302 (0.81), 3.325 (0.68), 3.338 (0.50), 3.350 (0.56), 3.371 (0.56), 3.378 (0.58), 3.400 (2.78), 3.412 (2.79), 3.426 (5.84), 3.438 (5.24), 3.453 (6.52), 3.459 (6.28), 3.466 (5.96), 3.479 (2.46), 3.486 (3.26), 3.493 (2.78), 3.521 (0.49), 3.529 (0.67), 3.535 (0.58), 3.564 (2.05), 3.572 (2.72), 3.580 (2.41), 3.600 (6.11), 3.609 (5.52), 3.617 (4.09), 3.634 (11.25), 3.637 (11.05), 3.756 (8.08), 3.785 (6.75), 3.889 (2.49), 3.894 (2.48), 3.917 (2.26), 3.922 (2.16), 4.540 (1.04), 4.555 (3.05), 4.569 (4.27), 4.580 (2.83), 4.584 (2.84), 7.369 (3.21), 7.379 (4.91), 8.135 (3.33), 8.146 (5.23), 8.157 (3.20), 8.261 (4.69), 8.275 (4.23).

Intermediate 2-12

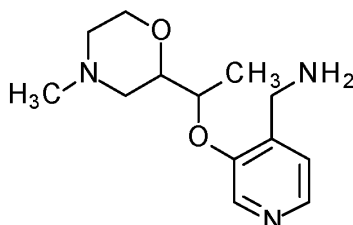
1-{3-[(1*R*)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}methanamine



Using an analogous method as described for intermediate 2-1 with 3-{[(1*R*)-1-[1,4-dioxan-2-yl]ethoxy}pyridine-4-carbonitrile (intermediate 1-12, 1.39 g, 5.93 mmol) as the starting material; 1.36 g (95 % purity, 91 % yield) of the title compound were prepared.

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.216 (0.81), 1.232 (0.99), 1.255 (15.91), 1.271 (16.00), 1.753 (0.71), 3.290 (0.44), 3.399 (0.54), 3.412 (2.42), 3.424 (0.71), 3.437 (3.81), 3.440 (3.42), 3.453 (0.77), 3.459 (2.72), 3.465 (5.00), 3.485 (1.48), 3.494 (2.02), 3.573 (1.45), 3.580 (1.70), 3.598 (2.00), 3.603 (3.43), 3.609 (3.84), 3.616 (2.24), 3.622 (2.04), 3.628 (1.97), 3.634 (4.41), 3.638 (4.68), 3.645 (2.04), 3.662 (5.32), 3.672 (6.05), 3.713 (0.63), 3.757 (2.28), 3.764 (2.39), 3.787 (1.75), 3.790 (1.84), 3.887 (2.14), 3.894 (2.12), 3.916 (1.94), 3.922 (1.85), 4.535 (0.53), 4.550 (1.85), 4.564 (2.15), 4.566 (2.17), 4.579 (1.80), 4.595 (0.50), 7.381 (3.18), 7.393 (3.14), 8.144 (4.36), 8.156 (4.13), 8.257 (0.50), 8.272 (6.58).

LC-MS (method 6): R_t = 0.21 min; MS (ESIpos): m/z = 239 [M+H]⁺

Intermediate 2-71**1-{3-[1-(4-methylmorpholin-2-yl)ethoxy]pyridin-4-yl}methanamine**

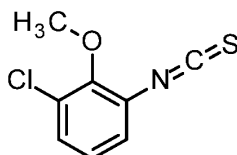
- 5 Using an analogous method as described for intermediate 2-1 with 3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridine-4-carbonitrile (intermediate 1-71, 815 mg, 3.30 mmol) as the starting material; 810 mg (99 % purity, 97 % yield) of the title compound were prepared.

- 1H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.227 (3.82), 1.242 (3.97), 1.254 (4.80), 1.270 (4.60), 1.850 (1.08), 1.862 (1.12), 1.876 (1.43), 1.888 (1.42), 1.903 (0.90), 1.915 (1.07), 1.928 (0.67), 1.937 (0.65), 1.945 (0.81), 1.957 (1.14), 1.965 (0.95), 1.973 (0.53), 1.985 (0.64), 1.993 (0.48), 2.152 (0.51), 2.183 (16.00), 2.332 (0.45), 2.518 (2.14), 2.522 (1.29), 2.575 (1.38), 2.602 (1.24), 2.673 (0.44), 2.692 (0.68), 2.720 (0.63), 2.834 (0.79), 2.862 (0.75), 3.475 (0.48), 3.480 (0.56), 3.487 (0.60), 3.504 (1.27), 3.508 (1.56), 3.514 (1.44), 3.536 (1.04), 3.542 (1.01), 3.563 (0.49), 3.568 (0.50), 3.575 (0.48), 3.588 (0.47), 3.667 (1.61), 3.793 (1.27), 3.821 (1.05), 4.561 (0.97), 7.374 (1.24), 8.138 (1.27), 8.267 (1.31).

LC-MS (method 6): R_t = 0.11 min; MS (ESIpos): m/z = 252 [M+H]⁺

Syntheses of Intermediate 3 Compounds**Intermediate 3-1**

- 20 1-chloro-3-isothiocyanato-2-methoxybenzene



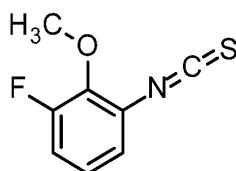
3-chloro-2-methoxyaniline (CAS 51114-68-2, 8.4 ml, 63 mmol) was solved in DCM (100 ml) and sat. sodium bicarbonate solution (100 ml) was added. To the ice cooled mixture was slowly added thiophosgene (5.4 ml, 70 mmol). The reaction was stirred at 0°C for 2 h. At

RT the DCM layer was separated and washed with sat. sodium bicarbonate solution, filtered through a hydrophobic filter and concentrated under reduced pressure to give the title compound (12.97 g, 100 % yield) which was used directly in the next step.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 7.51 (dd, 1H), 7.35 (dd, 1H), 7.20 (t, 1H), 3.85 - 3.91 (m, 3H).

Intermediate 3-4

1-fluoro-3-isothiocyanato-2-methoxybenzene

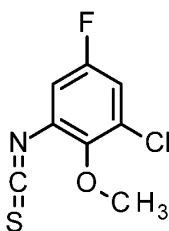


Using an analogous method as described for intermediate 3-1; 3-fluoro-2-methoxyaniline (CAS 437-83-2, 5.00 g, 35.4 mmol) as the starting material; 6.24 g of the title compound were prepared (96 % yield).

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 7.32 (m, 1H), 7.10 - 7.19 (m, 2H), 3.96 (d, 3H).

Intermediate 3-18

1-chloro-5-fluoro-3-isothiocyanato-2-methoxybenzene

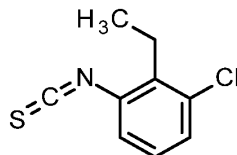


Using an analogous method as described for intermediate 3-1 with 3-chloro-5-fluoro-2-methoxyaniline (1.00 g, 5.70 mmol) as the starting material; 1.17 g of the title compound were prepared (95 % purity, 90 % yield).

¹H NMR (400 MHz, DMSO-d₆): δ [ppm]= 3.86 (s, 3 H) 7.38 (dd, 1H) 7.58 (dd, 1H).

Intermediate 3-29

1-chloro-2-ethyl-3-isothiocyanatobenzene



Using an analogous method as described for intermediate 3-1; 3-chloro-2-ethylaniline

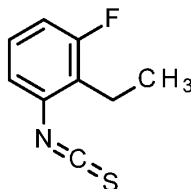
- 5 (5.00 g, 85 % purity, 27.3 mmol) as the starting material, the title compound was prepared 6.29 g (85 % purity, 99 % yield).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.009 (7.50), 1.027 (16.00), 1.046 (7.55), 1.090 (0.44), 1.109 (0.89), 1.128 (0.44), 2.590 (2.26), 2.608 (6.71), 2.627 (6.58), 2.646 (2.00), 5.199 (6.39), 6.533 (4.44), 6.539 (4.27), 6.553 (5.20), 6.559 (4.97), 6.821 (3.47), 6.841 (5.70), 6.861 (2.75), 7.056 (0.43), 7.060 (0.52).

10

Intermediate 3-65

2-ethyl-1-fluoro-3-isothiocyanatobenzene



- 15 Using an analogous method as described for intermediate 3-1; 2-ethyl-3-fluoroaniline (2.50 g, 18.0 mmol, CAS 1139437-61-8) as the starting material, the title compound was prepared 3.0 g (90 % purity, 83 % yield).

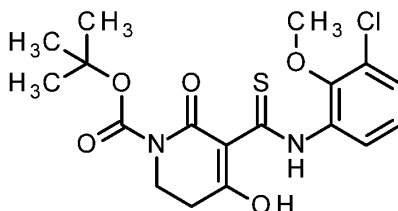
¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 1.108 (7.13), 1.127 (16.00), 1.146 (7.13), 2.462 (0.95), 2.483 (1.27), 2.517 (0.79), 2.522 (0.48), 2.637 (0.95), 2.641 (1.11), 2.655 (3.17), 2.659 (3.17), 2.674 (3.17), 2.678 (3.17), 2.693 (0.95), 2.697 (0.95), 3.461 (0.48), 3.477 (0.63), 3.484 (0.63), 3.506 (1.11), 3.528 (2.06), 3.537 (2.69), 3.625 (3.01), 3.648 (1.11), 3.663 (0.63), 3.669 (0.63), 7.185 (1.11), 7.189 (1.11), 7.205 (1.58), 7.209 (2.53), 7.212 (1.27), 7.229 (1.43), 7.233 (1.74), 7.243 (1.27), 7.246 (1.43), 7.263 (3.80), 7.266 (2.38), 7.282 (2.53), 7.296 (2.38), 7.301 (2.38), 7.317 (2.53), 7.322 (0.79), 7.337 (0.79).

20

Syntheses of Intermediate 4 Compounds

Intermediate 4-1

tert-butyl 5-[(3-chloro-2-methoxyphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate



5

To an ice-cooled solution of 1-chloro-3-isothiocyanato-2-methoxybenzene (intermediate 3-1, 4.00 g, 20.0 mmol) and *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 4.27 g, 20.0 mmol) in acetonitrile (92 ml) was added dropwise DBU (4.5 ml, 30 mmol). The reaction was stirred at RT overnight. To the reaction mixture was added ice-water (200 mL) and conc. HCl (2 mL). The mixture was stirred for 20 min. and extracted with DCM. The organic phase was filtered over a water-repellent filter, concentrated under reduced pressure and purified by flash chromatography (silica, hexane / EtOAc gradient 0-50 %) to give 6.54 g of the title compound (71 % yield).

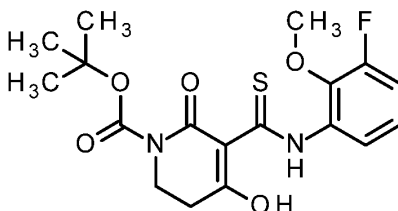
¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 13.36 (br s, 1H), 7.73 (d, 1H), 7.47 (dd, 1H), 7.22 (t, 1H), 3.76 - 3.82 (m, 5H), 2.88 (t, 2H), 1.48 (s, 9H).

15

LC-MS (method 1): *R*_t = 1.49 min; MS (ESIpos): *m/z* = 413.1 [M+H]⁺

Intermediate 4-4

tert-butyl 5-[(3-fluoro-2-methoxyphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate



20

Using an analogous method as described for Intermediate 4-1 with *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 7.26 g, 34.1 mmol) and 1-fluoro-3-

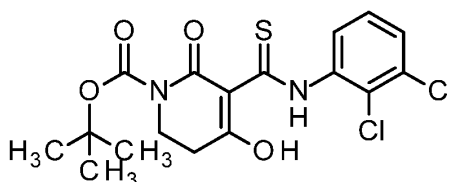
isothiocyanato-2-methoxybenzene (intermediate 3-4, 6.24 g, 34.1 mmol) as the starting materials; 9.49 g of the title compound were prepared (67 % yield) after stirring the product in MeOH, filtration and drying of the precipitate *in vacuo*.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 13.37 (br s, 1H), 7.58 (br d, 1H), 7.23 - 7.30 (m, 1H), 7.09 - 7.21 (m, 1H), 4.10 (br s, 1H), 3.78 (t, 2H), 3.17 (s, 3H), 2.88 (br t, 2H), 1.48 (s, 9H).

LC-MS (method 2): R_t = 0.66 min; MS (ESIpos): m/z = 397.3 [M+H]⁺

Intermediate 4-7

tert-butyl 5-[(2,3-dichlorophenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate



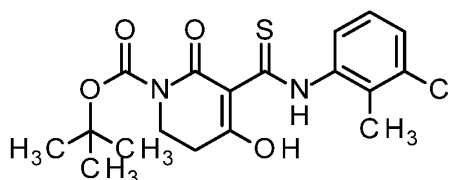
1,2-Dichloro-3-isothiocyanatobenzene (CAS 6590-97-2, 5.00 g, 24.5 mmol) and *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 5.22 g, 24.5 mmol) were solubilised in acetonitrile (55 ml), DBU (5.5 ml, 37 mmol) was added carefully at 0°C under argon atmosphere and the mixture was stirred overnight at RT. The reaction mixture was diluted with HCl (200 ml, 1N in water) and stirred for 30 min. at RT. The resulting solid was filtered off, the filter cake was washed with water and dried at 50°C in *vacuo* oven overnight to give 9.40 g of the title compound (92 % yield).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.467 (16.00), 1.484 (0.56), 1.622 (0.34), 1.644 (0.25), 1.661 (0.20), 1.674 (0.17), 1.898 (0.19), 1.913 (0.31), 1.927 (0.19), 2.075 (0.20), 2.327 (0.18), 2.518 (0.60), 2.523 (0.39), 2.621 (0.30), 2.647 (0.32), 2.665 (0.24), 2.669 (0.29), 2.673 (0.25), 3.249 (0.25), 3.459 (0.23), 3.473 (0.39), 3.487 (0.22), 3.538 (0.28), 3.561 (0.29), 3.727 (0.50), 7.357 (0.17), 7.377 (0.36), 7.383 (0.28), 7.397 (0.28), 7.544 (0.27), 7.547 (0.33), 7.560 (0.29), 7.564 (0.31), 7.568 (0.25), 7.580 (0.18).

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 416 [M-H]⁻

Intermediate 4-10

tert-butyl 5-[(3-chloro-2-methylphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate



- 5 According to the method described for intermediate 4-1; 1-chloro-3-isothiocyanato-2-methylbenzene (CAS 19241-35-1; 2.50 g, 13.6 mmol) and *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 2.9 g, 13.6 mmol) as the starting materials; 4.68 g of the title compound were prepared (78 % yield), after addition of HCl, filtration, and drying of the precipitate *in vacuo*.

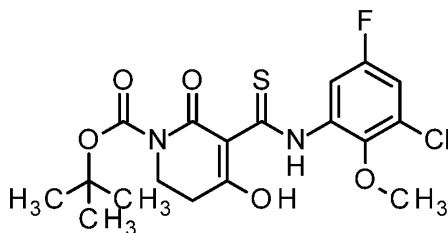
- 10 ¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 15.73 (s, 1H), 12.77 (br s, 1H), 7.45 (d, 1H), 7.30 (t, 1H), 7.19 (d, 1H), 3.78 (t, 2H), 2.85 (t, 2H), 2.20 (s, 3H), 1.48 (s, 9H).

LC-MS (method 2): R_t = 0.72 min; MS (ESIpos): m/z = 397.3 [M+H]⁺

Intermediate 4-18

tert-butyl 5-[(3-chloro-5-fluoro-2-methoxyphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-

- 15 dihydropyridine-1(2*H*)-carboxylate



- Using an analogous method as described for Intermediate 4-1 with *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 1.15 g, 5.38 mmol) and 1-chloro-5-fluoro-3-isothiocyanato-2-methoxybenzene (intermediate 3-18, 1.17 g, 5.38 mmol) as the starting materials; 1.42 g of the title compound were prepared (75 % purity, 46 % yield).

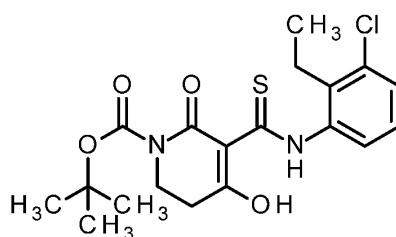
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.154 (0.88), 1.172 (1.70), 1.189 (0.80), 1.484 (16.00), 1.987 (3.28), 2.518 (0.89), 2.522 (0.61), 2.883 (0.73), 2.899 (0.40), 3.359 (0.69),

3.644 (4.46), 3.760 (7.94), 3.774 (0.44), 3.782 (1.03), 3.798 (0.53), 4.017 (0.69), 4.035 (0.69), 6.400 (0.60), 6.405 (0.53), 6.427 (1.00), 7.498 (0.41).

LC-MS (method 2): R_t = 0.73 min; MS (ESIpos): m/z = 431 $[M+H]^+$

Intermediate 4-29

- 5 *tert*-butyl 5-[(3-chloro-2-ethylphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate

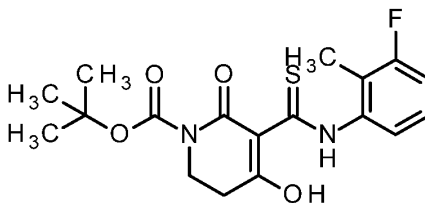


- Using an analogous method as described for Intermediate 4-1 with *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 5.77 g, 27.0 mmol) and 2-chloro-1-ethyl-3-isothiocyanatobenzene (intermediate 3-29, 6.29 g, 85 % purity, 27.0 mmol) as the starting materials; 6.35 g of the title compound were prepared (85 % purity, 49 % yield).

- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.063 (0.89), 1.082 (2.14), 1.100 (0.95), 1.362 (0.65), 1.478 (16.00), 1.486 (1.29), 2.518 (0.64), 2.523 (0.44), 2.631 (0.70), 2.650 (0.69), 2.850 (0.41), 2.866 (0.78), 2.883 (0.43), 3.775 (0.51), 3.791 (0.90), 3.807 (0.46), 7.212 (0.46), 7.214 (0.44), 7.232 (0.62), 7.234 (0.61), 7.293 (0.62), 7.313 (1.08), 7.332 (0.53), 7.440 (0.61), 7.443 (0.62), 7.460 (0.49), 7.463 (0.45).

Intermediate 4-38

tert-butyl 5-[(3-fluoro-2-methylphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate



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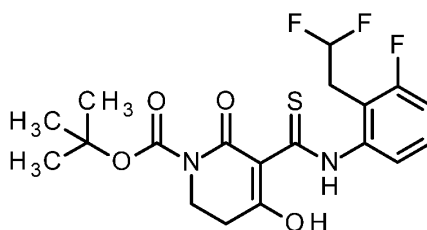
Using an analogous method as described for Intermediate 4-1 with *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 8.19 g, 38.4 mmol) and 1-fluoro-3-

isothiocyanato-2-methylbenzene (CAS 363179-58-2, 6.42 g, 38.4 mmol) as the starting materials; 11.1 g of the title compound were prepared (95% purity, 72% yield) after stirring the product in MeOH, filtration and drying of the precipitate *in vacuo*.

¹H-NMR (400 MHz, DMSO- d₆): δ [ppm]= 1.479 (16.00), 2.084 (2.80), 2.088 (2.74), 2.834 (0.58), 2.850 (1.12), 2.866 (0.61), 3.768 (0.64), 3.784 (1.16), 3.800 (0.59), 7.073 (0.61), 7.093 (0.71), 7.186 (0.59), 7.299 (0.45), 7.316 (0.42).

Intermediate 4-40

tert-butyl 5-[[2-(2,2-difluoroethyl)-3-fluorophenyl]carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate



10

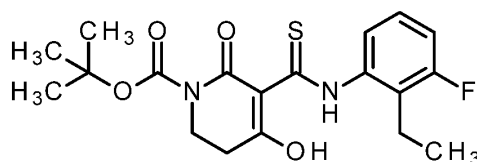
Using an analogous method as described for Intermediate 4-1 with *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 7.85 g, 36.8 mmol) and 2-(2,2-difluoroethyl)-1-fluoro-3-isothiocyanatobenzene (CAS 2311902-79-9, 8.00 g, 36.8 mmol) as the starting materials; 12.1 g of the title compound were prepared (95% purity, 72% yield).

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 1.471 (16.00), 2.518 (0.65), 2.523 (0.43), 2.788 (0.47), 2.804 (0.87), 2.820 (0.50), 3.166 (3.72), 3.754 (0.60), 3.770 (1.08), 3.786 (0.57), 7.149 (0.62), 7.169 (0.70), 7.271 (0.58), 7.446 (0.46), 7.462 (0.43).

Intermediate 4-65

tert-butyl 5-[(2-ethyl-3-fluorophenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate

20



Using an analogous method as described for Intermediate 4-1 with *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (CAS 845267-78-9, 7.85 g, 36.8 mmol) and 2-ethyl-1-fluoro-

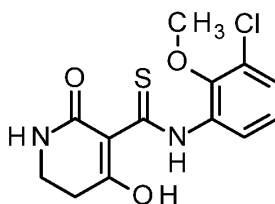
3-isothiocyanatobenzene (intermediate 3-65, 3.00 g, 16.6 mmol) as the starting materials; 5.46 g of the title compound were prepared (95% purity, 79% yield).

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.066 (1.02), 1.085 (2.41), 1.104 (1.06), 1.477 (16.00), 1.486 (1.04), 2.074 (0.65), 2.518 (1.12), 2.522 (0.92), 2.538 (0.61), 2.858 (0.69),
5 3.771 (0.55), 3.787 (0.98), 3.803 (0.50), 7.092 (0.50), 7.112 (0.55), 7.186 (0.45), 7.311 (0.44), 7.327 (0.41). LC-MS (method 2): R_t = 0.72 min; MS (ESIpos): m/z = 395 [M+H]⁺

Syntheses of Intermediate 5 Compounds

Intermediate 5-1

- 10 *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



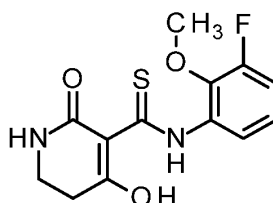
- To a solution of *tert*-butyl 5-[(3-chloro-2-methoxyphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (intermediate 4-1, 6.54 g, 15.8 mmol) in
15 dichloromethane (94 ml) was added TFA (12 ml, 160 mmol) and the mixture was stirred 1.5 h at RT. The reaction mixture was concentrated under reduced pressure and the residue was solved in EtOAc and washed with sat. sodium bicarbonate solution and brine. The organic layer was filtered through a hydrophobic filter and the filtrate was dried to dryness. The residue was purified by flash chromatography (silica, hexane / EtOAc gradient 20-100
20 %) to give 4.06 g of the title compound (78 % yield).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 16.45 (d, 1H), 14.69 (s, 1H), 14.33 (s, 1H), 9.37 (br s, 1H), 8.18 (br s, 1H), 7.76 - 7.87 (m, 1H), 7.37 - 7.45 (m, 1H), 7.15 - 7.23 (m, 1H), 3.73 - 3.76 (m, 3H), 3.43 (td, 1H), 3.27 - 3.32 (m, 1H), 2.79 (t, 1H), 2.59 - 2.69 (m, 1H).

LC-MS (method 1): R_t = 1.19 min; MS (ESIpos): m/z = 313 [M+H]⁺

Intermediate 5-4

N-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



5

Using an analogous method as described for intermediate 5-1 with *tert*-butyl 5-[(3-fluoro-2-methoxyphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (intermediate 4-4, 9.49 g, 23.9 mmol) as the starting material, 6.98 g of the title compound

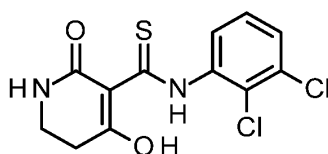
10 further purification.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 16.48 (d, 1H), 14.63 (s, 0.5H), 14.28 (s, 0.5H), 9.34 (br s, 0.5H), 8.16 (br s, 0.5H), 7.65 (t, 1H), 6.97 - 7.37 (m, 2H), 3.79 - 3.85 (m, 3H), 3.35 - 3.46 (m, 1H), 3.26 - 3.32 (m, 1H), 2.78 (t, 1H), 2.63 (t, 1H).

LC-MS (method 2): R_t = 0.46 min; MS (ESIpos): m/z = 297.1 [M+H]⁺

15 **Intermediate 5-7**

N-(2,3-dichlorophenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



Using an analogous method as described for intermediate 5-1 with *tert*-butyl 5-[(2,3-dichlorophenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate

20 (intermediate 4-7, 9.40 g, 22.5 mmol) as the starting material; 5.71 g of the title compound were prepared (62 % yield) after stirring overnight.

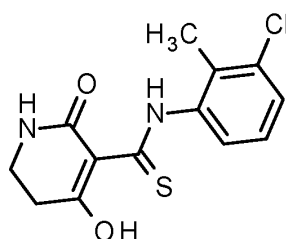
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.018 (1.18), 1.050 (1.33), 1.072 (0.81), 1.102 (0.59), 1.132 (0.81), 1.154 (1.84), 1.172 (3.17), 1.189 (1.84), 1.199 (0.88), 1.231 (1.92), 1.259 (1.40), 1.486 (0.66), 1.593 (1.33), 1.626 (1.18), 1.695 (1.25), 1.727 (1.18), 1.907

- (2.14), 1.987 (5.97), 2.322 (3.17), 2.326 (4.28), 2.331 (3.17), 2.518 (15.85), 2.522 (9.44), 2.638 (11.06), 2.664 (7.82), 2.669 (7.52), 2.673 (5.53), 2.798 (8.11), 3.436 (9.81), 4.017 (1.18), 4.035 (1.11), 5.560 (1.33), 5.579 (1.25), 7.392 (4.42), 7.410 (10.03), 7.430 (9.22), 7.565 (12.24), 7.585 (16.00), 7.605 (9.51), 8.134 (0.74), 8.197 (4.35), 9.418 (3.91), 14.273 (6.93), 14.665 (6.64), 16.114 (1.03), 16.295 (9.95), 16.352 (5.82), 16.503 (1.11).

LC-MS (method 2): R_t = 0.55 min; MS (ESIpos): m/z = 316 [M-H]⁻.

Intermediate 5-10

N-(3-chloro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



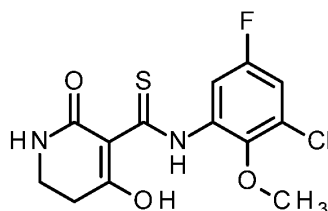
- 10 Using an analogous method as described for intermediate 5-1 with *tert*-butyl 5-[(3-chloro-2-methylphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (intermediate 4-10, 4.67 g, 11.8 mmol) as the starting material, 3.54 g of the title compound were prepared (91 % yield) after 3 h and used in the next steps without further purification.

- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 16.42 (d, 1H), 14.01 - 14.37 (m, 1H), 8.14 - 9.40 (m, 1H), 7.43 (br t, 1H), 7.16 - 7.32 (m, 2H), 3.42 - 3.48 (m, 1H), 3.26 - 3.34 (m, 1H), 2.78 (t, 1H), 2.60 - 2.68 (m, 1H), 2.12 - 2.21 (m, 3H).

LC-MS (method 2): R_t = 0.60 min; MS (ESIpos): m/z = 297.4 [M+H]⁺.

Intermediate 5-18

- 20 *N*-(3-chloro-5-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



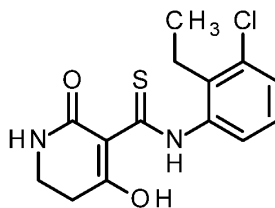
Using an analogous method as described for intermediate 5-1 with *tert*-butyl 5-[(3-chloro-5-fluoro-2-methoxyphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (intermediate 4-18, 1.42 g, 3.30 mmol) as the starting material; 690 mg of the title compound were prepared (95 % purity, 60 % yield).

- 5 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 2.61 - 2.70 (m, 1H), 2.80 (m, 1H), 3.25 - 3.32 (m, 1H), 3.38 - 3.47 (m, 1H), 3.74 (s, 3H), 7.39 - 7.62 (m, 1H), 7.83 - 8.02 (m, 1H), 8.20 - 8.33 (s, 0,5H), 9.33 - 9.57 (s, 0,5H), 14.53 (s, 0,5H), 14.93 (s, 0,5H), 16.29 (s, 0,5H), 16.36 (s, 0,5H).

LC-MS (method 2): R_t = 0.57 min; MS (ESI_{neg}): m/z = 329 [M-H]⁻.

10 Intermediate 5-29

N-(3-chloro-2-ethylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



Using an analogous method as described for intermediate 5-1 with *tert*-butyl 5-[(3-chloro-2-ethylphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate

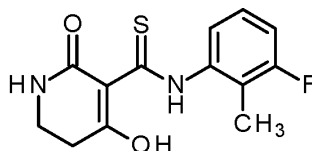
- 15 (intermediate 4-29, 2.35 g, 75 % purity, 4.29 mmol) as the starting material; 1.22 g of the title compound were prepared (95 % purity, 87 % yield).

- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.048 (7.06), 1.067 (16.00), 1.086 (7.43), 1.107 (1.58), 1.124 (1.32), 1.143 (0.50), 1.154 (1.34), 1.172 (2.43), 1.190 (1.24), 1.232 (0.50), 1.988 (4.56), 2.318 (0.47), 2.323 (1.05), 2.327 (1.56), 2.332 (1.11), 2.336 (0.47), 2.518 (5.61), 2.523 (4.03), 2.581 (2.03), 2.600 (6.41), 2.619 (6.62), 2.642 (4.59), 2.661 (2.69), 2.669 (1.90), 2.673 (1.27), 2.678 (0.58), 2.771 (2.35), 2.789 (4.82), 2.807 (2.58), 3.287 (1.61), 3.294 (1.79), 3.305 (3.11), 3.312 (3.14), 3.323 (2.06), 3.330 (2.35), 3.415 (1.53), 3.422 (1.66), 3.433 (2.56), 3.441 (2.45), 3.452 (1.40), 3.459 (1.24), 4.017 (1.03), 4.035 (1.00), 7.166 (0.95), 7.176 (0.58), 7.179 (0.58), 7.248 (0.71), 7.259 (6.30), 7.268 (3.58), 7.275 (4.43), 7.287 (7.20), 7.294 (3.90), 7.303 (3.56), 7.324 (0.87), 7.392 (1.85), 7.400 (1.37), 7.407 (1.85), 7.415 (1.74), 7.419 (2.40), 7.426 (1.77), 7.436 (1.77), 7.443 (1.45), 8.174 (1.77), 9.335 (1.42), 14.111 (2.98), 14.452 (2.74), 16.428 (7.88), 16.441 (7.38).

LC-MS (method 6): R_t = 1.28 min; MS (ESI_{pos}): m/z = 311 [M+H]⁺.

Intermediate 5-38

N-(3-fluoro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



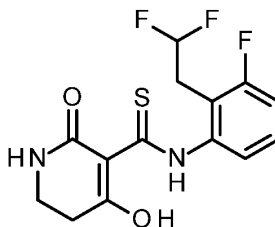
Using an analogous method as described for intermediate 5-1 with *tert*-butyl 5-[(3-fluoro-2-methylphenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (intermediate 4-38, 11.1 g, 29.1 mmol) as the starting material, 7.25 g of the title compound was prepared (84% yield) after 15 min of stirring and used in the next steps without further purification.

¹H-NMR (400 MHz, DMSO- *d*₆): δ [ppm]= 1.172 (0.55), 1.987 (1.05), 2.063 (16.00), 2.518 (1.49), 2.523 (1.01), 2.612 (1.94), 2.631 (3.67), 2.649 (2.11), 2.761 (1.99), 2.779 (4.22), 2.798 (2.26), 3.280 (1.36), 3.287 (1.47), 3.298 (2.58), 3.305 (2.57), 3.315 (1.39), 3.322 (1.33), 3.410 (1.40), 3.417 (1.48), 3.428 (2.27), 3.435 (2.22), 3.446 (1.27), 3.454 (1.15), 7.112 (1.56), 7.119 (0.96), 7.132 (2.25), 7.141 (3.30), 7.161 (2.66), 7.168 (2.15), 7.192 (1.12), 7.243 (0.73), 7.262 (1.15), 7.272 (0.99), 7.279 (1.25), 7.292 (1.27), 7.308 (1.21), 7.328 (0.45), 8.150 (1.43), 9.317 (1.16), 14.003 (2.32), 14.321 (2.05), 16.439 (5.35), 16.468 (4.62).

LC-MS (method 2): *R*_t = 0.47 min; MS (ESIpos): *m/z* = 281 [M+H]⁺.

Intermediate 5-40

N-[2-(2,2-difluoroethyl)-3-fluorophenyl]-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



Using an analogous method as described for intermediate 5-1 with *tert*-butyl 5-[[2-(2,2-difluoroethyl)-3-fluorophenyl]carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2H)-

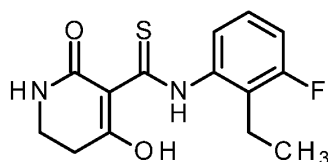
carboxylate (intermediate 4-40, 12.1 g, 28.0 mmol) as the starting material; 8.81 g of the title compound were prepared (95% purity, 90% yield).

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 1.145 (0.50), 1.154 (1.98), 1.172 (3.87), 1.190 (1.88), 1.441 (0.60), 1.987 (7.01), 2.323 (1.39), 2.327 (1.98), 2.332 (1.39), 2.518 (8.20),
5 2.523 (5.52), 2.617 (6.21), 2.635 (11.74), 2.653 (7.04), 2.665 (3.21), 2.669 (3.14), 2.673 (2.21), 2.769 (5.92), 2.786 (10.81), 2.803 (6.18), 3.059 (7.57), 3.067 (7.93), 3.104 (15.40), 3.111 (15.40), 3.148 (7.93), 3.307 (9.36), 3.434 (8.96), 4.000 (0.56), 4.017 (1.65), 4.035 (1.65), 4.053 (0.53), 6.057 (3.27), 6.067 (6.55), 6.077 (2.98), 6.198 (6.18), 6.208 (13.09), 6.217 (6.12), 6.339 (2.81), 6.348 (6.12), 6.358 (3.01), 7.165 (5.62), 7.185 (7.24), 7.207
10 (6.64), 7.227 (8.53), 7.242 (9.39), 7.265 (9.26), 7.288 (3.31), 7.393 (2.38), 7.413 (5.55), 7.430 (6.51), 7.459 (4.53), 7.479 (1.45), 8.152 (5.29), 9.352 (4.96), 14.013 (9.02), 14.389 (7.90), 16.346 (15.47), 16.353 (16.00).

LC-MS (method 2): R_t = 0.48 min; MS (ESIpos): m/z = 331.1 [M+H]⁺.

Intermediate 5-65

- 15 **N-(2-ethyl-3-fluorophenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide**



- 20 Using an analogous method as described for intermediate 5-1 with tert-butyl 5-[(2-ethyl-3-fluorophenyl)carbamothioyl]-4-hydroxy-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (intermediate 4-65, 5.46 g, 71 % purity, 9.83 mmol) as the starting material; 4.0 g of the title compound were prepared (70% purity, 97% yield).

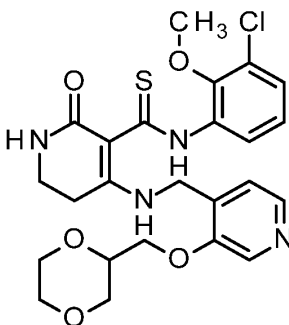
¹H-NMR (400 MHz, DMSO-d₆) delta [ppm]: 1.052 (6.61), 1.071 (16.00), 1.089 (6.75), 1.116 (0.56), 1.224 (4.60), 1.734 (1.58), 2.326 (0.43), 2.472 (1.56), 2.518 (2.10), 2.523 (1.69), 2.647 (0.85), 2.659 (0.85), 2.664 (0.98), 2.668 (1.03), 2.673 (0.80), 2.782 (0.89), 3.423
25 (0.82), 4.037 (0.62), 7.160 (2.35), 7.288 (0.98), 8.170 (0.48), 14.073 (0.46), 14.414 (0.52).

LC-MS (method 6): R_t = 1.18 min; MS (ESIpos): m/z = 295 [M+H]⁺.

Syntheses of Intermediate 6 Compounds

Intermediate 6-1

N-(3-chloro-2-methoxyphenyl)-4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



5

A mixture of *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 498 mg, 1.59 mmol) and 1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-1, 0.5 g, 2.23 mmol) was stirred for 4 h at 120°C. The reaction mixture was purified by flash chromatography (silica, DCM / EtOH gradient 0-30 %) to give 325 mg of the title compound (39 % yield).

10

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 14.79 (s, 1H), 13.69 (t, 1H), 8.39 (s, 1H), 8.24 (d, 1H), 7.81 (dd, 1H), 7.73 (s, 1H), 7.26 - 7.33 (m, 2H), 7.11 (t, 1H), 4.67 (d, 2H), 4.16 (t, 2H), 3.84 - 3.95 (m, 2H), 3.74 - 3.79 (m, 1H), 3.71 (s, 3H), 3.59 - 3.70 (m, 2H), 3.45 - 3.54 (m, 2H), 3.11 - 3.20 (m, 2H), 2.78 (t, 2H).

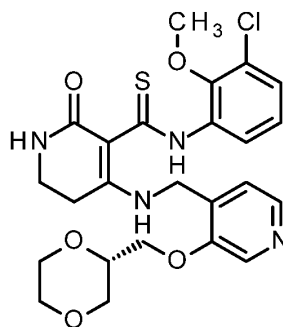
15

LC-MS (method 2): *R*_t = 1.07 min; MS (ESIpos): *m/z* = 519.2 [M+H]⁺.

20

Intermediate 6-2

N-(3-chloro-2-methoxyphenyl)-4-[(3-[(2*S*)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino}-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



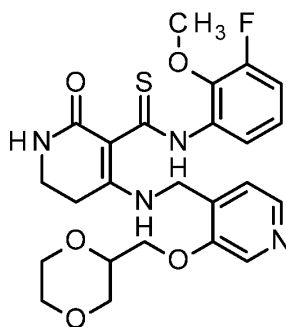
- 5 A mixture of *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 866 mg, 2.77 mmol) and 1-(3-[(2*S*)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methanamine (intermediate 2-8, 776 mg, 80% purity, 2.77 mmol) in ACN (22 ml) was treated with *N,O*-bis(trimethylsilyl)acetamide (2.05 ml, 8.6 mmol, CAS 10416-59-8) and stirred at 80°C for 4 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (silica, DCM / EtOH gradient 0-20%) to give 1.23 g (95% purity, 81% yield) of the title compound.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 2.78 (t, 2H), 3.16 (td, 2H), 3.40 - 3.54 (m, 3H), 3.59 - 3.69 (m, 2H), 3.71 (s, 3H), 3.73 - 3.79 (m, 1H), 3.83 - 3.95 (m, 2H), 4.16 (t, 2H), 4.67 (d, 2H), 7.11 (t, 1H), 7.27 - 7.33 (m, 2H), 7.73 (br s, 1H), 7.81 (dd, 1H), 8.24 (d, 1H), 8.39 (s, 1H), 13.69 (s, 1H), 14.79 (s, 1H).

LC-MS (method 2): *R*_t = 1.09 min; MS (ESIpos): *m/z* = 519 [M+H]⁺

Intermediate 6-4

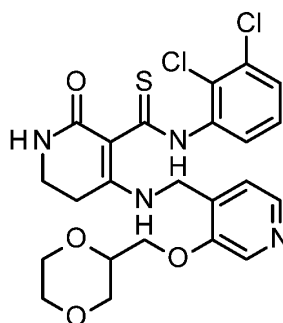
4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-*N*-(3-fluoro-2-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-4, 179 mg, 604 μ mol) and 1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-1, 190 mg, 845 μ mol) as the starting materials; 120 mg of the title compound were prepared (34 % yield) after heating for 2 h and purification by flash chromatography (amino phase silica, DCM / EtOH gradient 0-10 %).
- 10 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 14.74 (s, 1H), 13.70 (br t, 1H), 8.39 (s, 1H), 8.24 (d, 1H), 7.64 - 7.73 (m, 2H), 7.30 (d, 1H), 7.02 - 7.14 (m, 2H), 4.67 (d, 2H), 4.13 - 4.21 (m, 2H), 3.84 - 3.95 (m, 2H), 3.59 - 3.77 (m, 4H), 3.40 - 3.53 (m, 2H), 3.13 - 3.22 (m, 2H), 2.68 - 2.80 (m, 2H), 1.59 (br s, 1H), 0.93 - 1.39 (m, 1H).
- 15 LC-MS (method 2): R_t = 1.01 min; MS (ESIpos): m/z = 503 $[\text{M}+\text{H}]^+$.

Intermediate 6-7

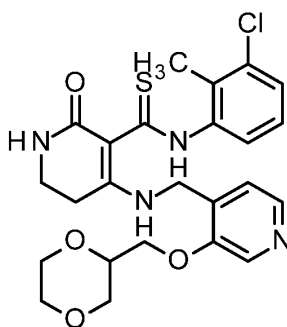
N-(2,3-dichlorophenyl)-4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-1 with *N*-(2,3-dichlorophenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-7, 160 mg, 504 μmol) and 1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-1, 158 mg, 706 μmol) as the starting materials; 110 mg of the title compound were prepared (35 % yield) after and heating for 2 h and purification by flash chromatography (amino phase
- 10 silica, DCM / EtOH gradient 0-10 %).
- $^1\text{H-NMR}$ (400MHz, $\text{DMSO}-d_6$): δ [ppm]= 14.90 (s, 1H), 13.66 (t, 1H), 8.39 (s, 1H), 8.24 (d, 1H), 7.75 (br s, 1H), 7.55 (dd, 1H), 7.51 (dd, 1H), 7.28 - 7.38 (m, 3H), 4.68 (d, 3H), 4.14 - 4.21 (m, 2H), 3.87 - 3.90 (m, 1H), 3.72 - 3.76 (m, 1H), 3.64 - 3.67 (m, 1H), 3.58 - 3.63 (m, 1H), 3.35 - 3.53 (m, 3H), 2.79 (t, 2H).
- 15 LC-MS (method 2): R_t = 1.08 min; MS (ESIpos): m/z = 523 $[\text{M}+\text{H}]^+$.

Intermediate 6-10

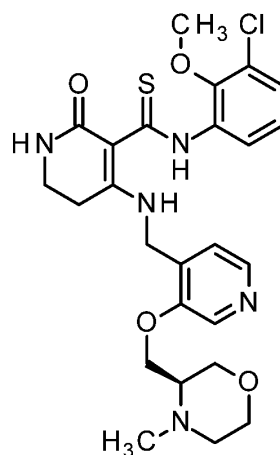
N-(3-chloro-2-methylphenyl)-4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-1; *N*-(3-chloro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-10, 189 mg, 637 μ mol) and 1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-1, 200 mg, 892 μ mol) as the starting materials; 180 mg of the title compound were prepared (56 % yield) after heating for 2 h and purification by flash chromatography
- 10 (amino phase silica, DCM / EtOH gradient 0-10 %).
- $^1\text{H-NMR}$ (400MHz, $\text{DMSO-}d_6$): δ [ppm]= 14.54 (s, 1H), 13.64 (br t, 1H), 8.38 (s, 1H), 8.24 (d, 1H), 7.69 (br s, 1H), 7.28 - 7.37 (m, 2H), 7.13 - 7.26 (m, 2H), 4.65 (d, 2H), 4.14 - 4.20 (m, 2H), 3.74 - 3.88 (m, 3H), 3.63 - 3.71 (m, 2H), 3.42 - 3.53 (m, 2H), 3.14 - 3.31 (m, 2H), 2.77 (t, 2H), 2.16 (s, 3H).
- 15 LC-MS (method 2): R_t = 1.09 min; MS (ESIpos): m/z = 501 $[\text{M}+\text{H}]^+$.

Intermediate 6-11

N-(3-chloro-2-methoxyphenyl)-4-[[3-[[3*R*]-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methyl]amino}-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 142 mg, 407 μ mol) and 1-(3-[[3*R*]-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methanamine (intermediate 2-2, 116 mg, 489 μ mol) as the starting materials; 85.6 mg of the title compound were prepared (36 % yield) after heating for 3 h
- 10 and purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 30% B, 0.50 – 6.00 min 30 – 70% B).

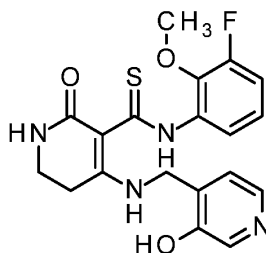
$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm]= 14.79 (s, 1H), 13.67 (br t, 1H), 8.41 (s, 1H), 8.24 (d, 1H), 7.81 (dd, 1H), 7.73 (br s, 1H), 7.28 - 7.33 (m, 2H), 7.11 (t, 1H), 4.67 (br d, 2H), 4.31 (dd, 1H), 4.05 (dd, 1H), 3.90 (dd, 1H), 3.67 - 3.73 (m, 4H), 3.50 (td, 1H), 3.34 - 3.40 (m, 1H),

15 3.13 - 3.21 (m, 2H), 2.79 (t, 2H), 2.63 - 2.70 (m, 1H), 2.19 - 2.33 (m, 4H), 1.46 - 1.76 (m, 1H).

LC-MS (method 2): R_t = 1.08 min; MS (ESIpos): m/z = 532.5 $[\text{M}+\text{H}]^+$

Intermediate 6-12

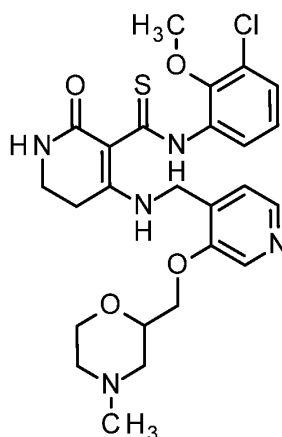
N-(3-fluoro-2-methoxyphenyl)-4-(((3-hydroxypyridin-4-yl)methyl)amino)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 A mixture of 4-(aminomethyl)pyridin-3-ol (CAS 20485-35-2, 75 g, 0.604 mol) and *N*-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-4, 150 g, 0.506 mol) in DMA (1.2 L) was stirred at 120°C for 2.5 h under nitrogen. The mixture was concentrated in vacuum to remove most of the solvent. The dark brown solution was slowly added to EtOAc (8 L) with stirring. The resulting mixture was
- 10 washed with water (2.5 L) and brine (2.5 L x 2). The organic phase was dried over sodium sulphate, filtered and concentrated in vacuum. The residue was slurried with EtOAc (300 mL) and filtered. The filter cake was dried in vacuum to afford the title compound (87 g, 47 % yield) as a yellow solid.
- ¹H NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 14.73 (s, 1H), 13.69 (t, 1H), 10.28 (s, 1H), 8.21-8.13 (m, 2H), 7.67-7.66 (m, 2H), 7.10 (br.s, 1H), 7.09-7.04 (m, 2H), 4.61 (d, 2H), 3.79 (s, 3H), 3.16 (t, 2H), 2.77 (t, 2H).
- 15

Intermediate 6-15

N-(3-chloro-2-methoxyphenyl)-4-[(3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-4, 100 mg, 320 μ mol) and 1-(3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl)methanamine (intermediate 2-3, 114 mg, 480 μ mol) as the starting materials; 74.3 mg (80 % purity, 35 % yield) of the title compound were prepared after heating for 4 h and
- 10 purification by flash chromatography (amino phase silica, DCM / EtOH gradient 0-10 %).

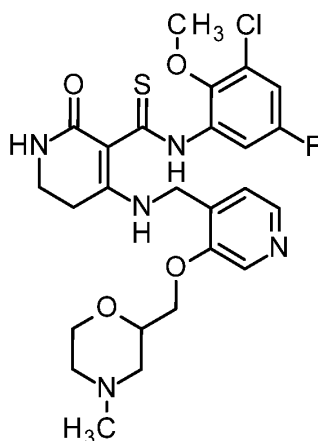
$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.880 (0.45), 2.176 (4.07), 2.186 (0.73), 2.191 (0.45), 2.518 (1.66), 2.523 (1.13), 2.787 (0.65), 2.799 (0.61), 3.162 (0.56), 3.169 (0.54), 3.533 (0.46), 3.539 (0.45), 3.711 (9.24), 3.819 (0.47), 3.823 (0.40), 4.149 (0.65), 4.161 (1.12), 4.176 (0.61), 4.655 (0.80), 4.670 (0.82), 5.759 (16.00), 7.086 (0.63), 7.107 (1.27),

15 7.127 (0.73), 7.283 (0.77), 7.287 (0.81), 7.302 (0.77), 7.306 (1.39), 7.318 (0.80), 7.723 (0.53), 7.803 (0.59), 7.806 (0.60), 7.823 (0.57), 7.827 (0.53), 8.234 (1.27), 8.246 (1.26), 8.392 (1.87), 14.791 (1.01).

LC-MS (method 2): R_t = 0.84 min; MS (ESIpos): m/z = 532 $[\text{M}+\text{H}]^+$

Intermediate 6-18

N-(3-chloro-5-fluoro-2-methoxyphenyl)-4-[(3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



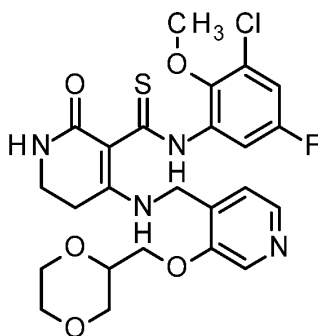
- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-5-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-18, 100 mg, 302 μ mol) and 1-(3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl)methanamine (intermediate 2-3, 108 mg, 453 μ mol) as the starting materials; 166 mg (70 % purity, 70 % yield) of the title compound were prepared after purification by flash chromatography (amino phase silica, DCM / EtOH gradient 0-10 %).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.881 (0.59), 1.908 (0.51), 1.984 (0.51), 1.991 (0.55), 2.174 (5.75), 2.185 (0.88), 2.191 (2.53), 2.518 (2.46), 2.523 (1.65), 2.581 (0.55), 2.609 (0.49), 2.785 (0.52), 2.798 (0.96), 2.815 (0.60), 3.096 (0.44), 3.161 (0.55), 3.168 (0.51), 3.387 (0.97), 3.535 (0.57), 3.542 (0.68), 3.700 (7.75), 3.786 (0.69), 3.791 (0.73), 3.795 (0.71), 3.810 (0.63), 3.815 (0.70), 3.823 (0.75), 4.115 (0.52), 4.119 (0.55), 4.128 (0.53), 4.154 (0.77), 4.166 (0.94), 4.181 (0.60), 4.672 (0.76), 4.687 (0.77), 5.759 (16.00), 7.267 (0.58), 7.275 (0.65), 7.287 (0.58), 7.295 (0.63), 7.313 (0.77), 7.325 (0.74), 7.792 (0.49), 8.046 (0.50), 8.053 (0.50), 8.073 (0.47), 8.080 (0.47), 8.238 (1.20), 8.250 (1.12), 8.267 (0.55), 8.279 (0.66), 8.399 (1.72), 15.080 (0.94).

20 LC-MS (method 2): R_t = 1.11 min; MS (ESIpos): m/z = 550 $[\text{M}+\text{H}]^+$

Intermediate 6-19

N-(3-chloro-5-fluoro-2-methoxyphenyl)-4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



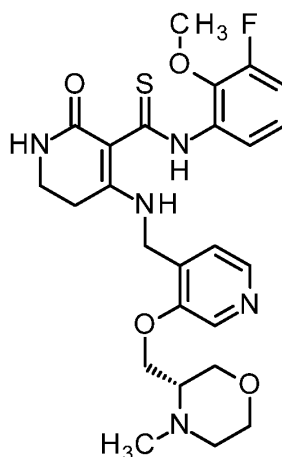
- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-5-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-18, 100 mg, 302 μ mol) and 1-(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methanamine (intermediate 2-1, 94.9 mg, 423 μ mol) as the starting materials, 160 mg (90 % purity, 89 % yield) of the title compound were prepared after purification by flash chromatography (silica, DCM / EtOH gradient 0-30 %).

¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 0.821 (0.41), 0.904 (0.45), 1.035 (8.84), 1.052 (16.00), 1.070 (9.56), 1.154 (1.90), 1.172 (3.66), 1.189 (1.72), 1.987 (6.85), 2.518 (1.36), 2.522 (0.92), 2.790 (0.61), 3.157 (0.42), 3.404 (1.39), 3.417 (1.49), 3.421 (4.01), 3.434 (4.35), 3.439 (4.40), 3.452 (4.43), 3.457 (1.21), 3.461 (0.53), 3.469 (1.28), 3.501 (0.40), 3.652 (0.66), 3.655 (0.65), 3.702 (7.42), 3.750 (0.43), 3.785 (0.67), 3.788 (0.43), 3.890 (0.58), 3.999 (0.46), 4.017 (1.36), 4.035 (1.39), 4.053 (0.47), 4.156 (0.56), 4.165 (0.77), 4.179 (0.54), 4.343 (2.52), 4.356 (4.91), 4.368 (2.35), 4.683 (0.68), 4.697 (0.68), 7.272 (0.48), 7.280 (0.60), 7.293 (0.51), 7.300 (0.64), 7.305 (0.63), 7.317 (0.62), 7.800 (0.42), 8.032 (0.40), 8.040 (0.42), 8.059 (0.41), 8.066 (0.40), 8.242 (0.98), 8.254 (0.94), 8.394 (1.43), 15.078 (0.82).

LC-MS (method 2): R_t = 1.14 min; MS (ESIpos): m/z = 537 [M+H]⁺

Intermediate 6-20

N-(3-fluoro-2-methoxyphenyl)-4-[[[3-[[[(3*S*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-4, 200 mg, 675 μ mol) and 1-(3-[[[(3*S*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methanamine (intermediate 2-4, 208 mg, 877 μ mol) as the starting materials, 105 mg (99 % purity, 30 % yield) of the title compound were prepared after
- 10 heating for 3 h and purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 2.195 (0.50), 2.203 (0.62), 2.221 (0.73), 2.224 (0.80), 2.229 (0.79), 2.232 (0.77), 2.250 (0.69), 2.258 (0.63), 2.287 (16.00), 2.322 (0.48), 2.326 (0.65), 2.331 (0.46), 2.518 (2.86), 2.522 (1.80), 2.645 (0.60), 2.651 (1.24), 2.658 (0.75), 2.664 (0.58), 2.668 (0.75), 2.673 (0.96), 2.680 (1.16), 2.687 (0.56), 2.760 (1.14), 2.776 (2.31), 2.793 (1.34), 3.134 (0.86), 3.142 (0.98), 3.152 (1.59), 3.158 (1.51), 3.167 (0.87), 3.175 (0.73), 3.347 (1.31), 3.371 (1.26), 3.375 (1.37), 3.398 (1.19), 3.473 (0.50), 3.480 (0.60), 3.501 (0.98), 3.507 (0.98), 3.527 (0.72), 3.533 (0.60), 3.677 (0.56), 3.683 (1.07), 3.690 (0.58), 3.704 (0.46), 3.711 (0.82), 3.718 (0.41), 3.780 (13.85), 3.783 (13.72), 3.884 (0.99), 3.892 (0.99), 3.912 (0.89), 3.920 (0.88), 4.029 (0.98), 4.044 (1.01), 4.054 (1.17), 4.070 (1.12), 4.291 (1.18), 4.302 (1.21), 4.317 (1.03), 4.327 (0.97), 4.658 (1.87), 4.674 (1.89), 7.044 (0.58), 7.049 (1.31), 7.065 (1.59), 7.069 (2.63), 7.075 (1.64), 7.085 (1.41), 7.090 (0.58), 7.096 (1.44), 7.101 (1.44), 7.117 (0.56), 7.122 (0.41), 7.296 (2.20), 7.308 (2.24), 7.653 (1.44), 7.658 (0.89), 7.670 (1.15), 7.676 (0.86), 7.704 (1.58), 8.236

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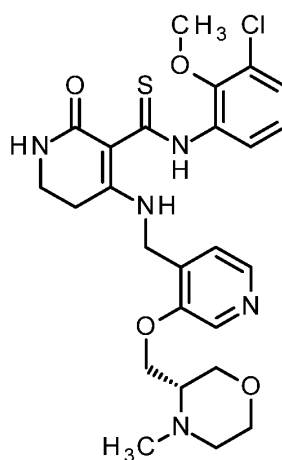
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(3.27), 8.247 (3.17), 8.411 (4.92), 13.661 (0.56), 13.676 (1.10), 13.690 (0.53), 14.736 (2.92).

LC-MS (method 6): Rt = 0.62 min; MS (ESIpos): m/z = 516 [M+H]⁺

Intermediate 6-21

- 5 *N*-(3-chloro-2-methoxyphenyl)-4-[[[3-[[[(3*S*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide

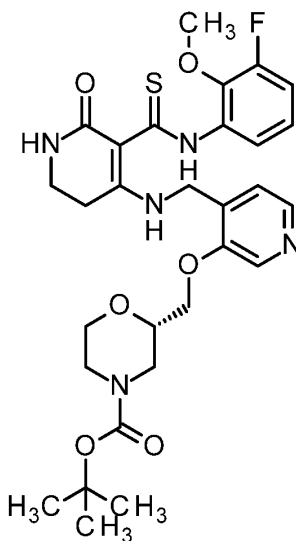
- 10 (intermediate 5-1, 200 mg, 639 μmol) and 1-(3-[[[(3*S*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methanamine (intermediate 2-4, 197 mg, 831 μmol) as the starting materials 102 mg (99 % purity, 30 % yield) of the title compound were prepared after heating for 3h at 120°C and purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).

- 15 ¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 2.288 (3.78), 2.327 (0.47), 2.518 (1.87), 2.523 (1.27), 2.651 (0.43), 2.665 (0.45), 2.669 (0.59), 2.673 (0.55), 2.679 (0.47), 2.769 (0.69), 2.786 (1.40), 2.803 (0.81), 3.141 (0.53), 3.148 (0.61), 3.157 (0.97), 3.164 (0.93), 3.174 (0.53), 3.181 (0.44), 3.346 (0.55), 3.372 (0.52), 3.506 (0.45), 3.684 (0.50), 3.712 (16.00), 3.883 (0.44), 3.891 (0.53), 3.912 (0.42), 4.293 (0.54), 4.304 (0.56), 4.319 (0.47), 4.329 (0.44), 4.663 (1.08), 4.679 (1.10), 7.088 (1.04), 7.108 (2.24), 7.128 (1.28), 7.285 (1.42), 7.289 (1.49), 7.301 (1.47), 7.305 (1.46), 7.309 (1.44), 7.312 (1.47), 7.726 (0.92), 7.794 (1.07), 7.797 (1.08), 7.814 (1.02), 7.818 (0.96), 8.238 (1.81), 8.250 (1.65), 8.413 (3.11), 13.667 (0.68), 14.787 (1.82).

LC-MS (method 6): $R_t = 0.68$ min; MS (ESIpos): $m/z = 532$ $[M+H]^+$

Intermediate 6-22

tert-butyl (2*S*)-2-[(4-[(5-[(3-fluoro-2-methoxyphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]amino)methyl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate



5

Using an analogous method as described for intermediate 6-1 with *N*-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-4, 1.00 g, 3.37 mmol) and *tert*-butyl (2*S*)-2-[(4-(aminomethyl)pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 2-5, 1.53 g, 4.72 mmol) as the starting materials; 1.43 g (70 % purity, 49 % yield) of the title compound were prepared after heating for 6 h and purification by flash chromatography (silica, DCM / EtOH gradient 0-20 %).

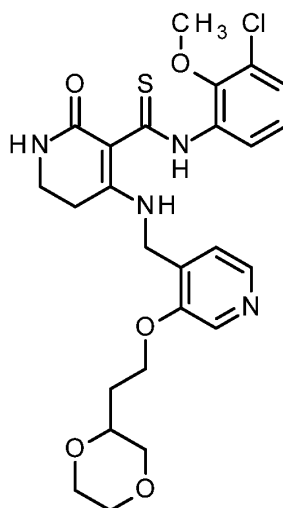
$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 1.035 (6.69), 1.052 (16.00), 1.070 (7.70), 1.394 (4.63), 1.401 (2.39), 1.405 (3.46), 2.331 (0.41), 2.518 (1.92), 2.523 (1.41), 2.673 (0.42), 3.404 (1.10), 3.417 (1.21), 3.422 (3.66), 3.435 (3.78), 3.440 (3.26), 3.452 (3.33), 3.457 (1.19), 3.469 (1.18), 3.780 (2.11), 3.782 (2.08), 3.797 (0.42), 3.857 (0.84), 3.860 (0.83), 4.219 (0.41), 4.231 (0.42), 4.344 (2.52), 4.356 (4.87), 4.369 (2.35), 8.241 (0.54), 8.253 (0.53), 8.402 (0.81), 14.735 (0.40).

LC-MS (method 2): $R_t = 1.19$ min; MS (ESIpos): $m/z = 602$ $[M+H]^+$

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Intermediate 6-24

N-(3-chloro-2-methoxyphenyl)-4-[(3-[2-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl)methyl]amino)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 200 mg, 639 μ mol) and 1-(3-[2-[1,4-dioxan-2-yl]ethoxy]pyridin-4-yl)methanamine (intermediate 2-6, 198 mg, 831 μ mol) as the starting materials, 110 mg (96 % purity, 31 % yield) of the title compound were prepared after heating for 3h at 130°C and
- 10 purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).

¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 1.792 (0.45), 1.812 (0.43), 1.838 (0.40), 1.850 (0.42), 2.518 (1.13), 2.523 (0.78), 2.763 (0.87), 2.771 (0.86), 2.780 (0.52), 2.786 (0.47), 3.140 (0.51), 3.148 (0.57), 3.156 (0.97), 3.164 (0.96), 3.173 (0.50), 3.181 (0.43), 3.197 (0.60), 3.224 (0.94), 3.227 (0.95), 3.253 (0.64), 3.445 (0.75), 3.452 (0.83), 3.471 (0.48), 3.480 (0.60), 3.545 (0.45), 3.551 (0.53), 3.573 (0.70), 3.580 (0.81), 3.605 (0.86), 3.611 (1.14), 3.617 (0.53), 3.638 (0.55), 3.644 (0.47), 3.689 (0.92), 3.697 (1.10), 3.712 (16.00), 3.718 (2.12), 3.744 (0.88), 3.749 (0.65), 4.203 (0.84), 4.219 (1.35), 4.232 (0.58), 4.238 (0.56), 4.656 (1.44), 4.670 (1.43), 7.089 (1.01), 7.110 (2.16), 7.130 (1.25), 7.286 (1.37), 7.289 (1.46), 7.306 (2.13), 7.310 (1.42), 7.317 (1.10), 7.726 (0.93), 7.802 (1.03), 7.806 (1.05), 7.823 (0.99), 7.826 (0.93), 8.225 (1.23), 8.237 (1.18), 8.373 (1.98), 13.695 (0.65), 14.792 (1.75).

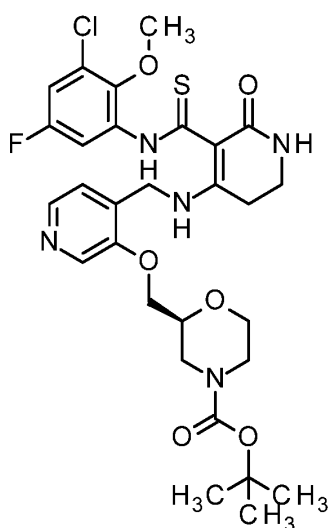
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LC-MS (method 6): $R_t = 0.90$ min; MS (ESIpos): $m/z = 533$ $[M+H]^+$

Intermediate 6-27

tert-butyl (2*S*)-2-[(4-[(5-[(3-chloro-5-fluoro-2-methoxyphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)amino)methyl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate



Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-5-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-18, 225 mg, 680 μ mol) and *tert*-butyl (2*S*)-2-[(4-(aminomethyl)pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 2-5, 308 mg, 952 μ mol) as the starting materials; 150 mg (80 % purity, 28 % yield) of the title compound were prepared after heating for 6 h and purification by flash chromatography (silica, DCM / EtOH gradient 0-20 %).

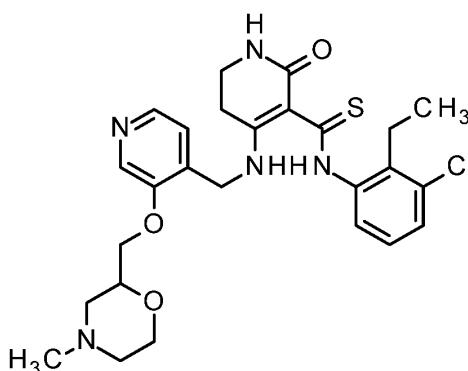
$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.035 (2.70), 1.052 (5.86), 1.070 (3.02), 1.232 (0.46), 1.389 (16.00), 1.405 (6.16), 1.419 (1.21), 2.331 (0.75), 2.430 (0.47), 2.447 (0.51), 2.518 (3.46), 2.523 (2.53), 2.673 (0.75), 2.772 (0.61), 2.789 (1.14), 2.805 (0.74), 3.137 (0.46), 3.145 (0.53), 3.154 (0.79), 3.161 (0.75), 3.405 (0.58), 3.417 (0.72), 3.422 (1.54), 3.435 (1.70), 3.440 (1.70), 3.445 (0.63), 3.452 (1.56), 3.457 (0.61), 3.469 (0.63), 3.655 (0.79), 3.699 (12.68), 3.719 (0.53), 3.732 (0.75), 3.738 (0.84), 3.757 (0.49), 3.764 (0.44), 3.787 (2.07), 3.821 (0.49), 3.842 (0.93), 3.870 (0.40), 4.225 (1.58), 4.237 (1.60), 4.344 (0.84), 4.357 (1.63), 4.370 (0.82), 4.681 (1.14), 4.696 (1.11), 5.759 (0.75), 7.267 (0.93), 7.275 (1.12), 7.287 (0.96), 7.295 (1.05), 7.311 (0.79), 7.323 (0.79), 7.799 (0.77), 8.031

(0.67), 8.038 (0.68), 8.057 (0.67), 8.065 (0.63), 8.245 (1.81), 8.257 (1.63), 8.290 (0.54), 8.410 (2.60), 13.671 (0.58), 15.074 (1.58).

LC-MS (method 2): $R_t = 1.30$ min; MS (ESIpos): $m/z = 636$ $[M+H]^+$

Intermediate 6-29

- 5 *N*-(3-chloro-2-ethylphenyl)-4-[(3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



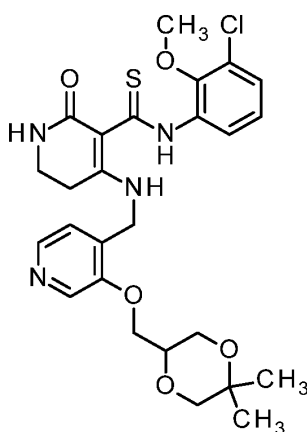
Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-2-ethylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-
 10 29, 300 mg, 965 μ mol) and 1-(3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl)methanamine (intermediate 2-3, 321 mg, 1.35 mmol) as the starting materials; 300 mg (80 % purity, 47 % yield) of the title compound were prepared after heating for 6 h and purification by flash chromatography (silica, DCM / EtOH gradient 0-20 %).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 0.798 (0.84), 0.814 (0.93), 0.821 (0.93), 0.840
 15 (0.43), 0.886 (0.53), 0.904 (1.07), 0.922 (0.50), 1.035 (9.51), 1.052 (16.00), 1.066 (1.09), 1.070 (9.08), 1.073 (1.50), 1.232 (0.45), 1.874 (0.59), 1.901 (0.47), 1.907 (0.59), 1.983 (0.41), 1.990 (0.52), 2.178 (5.56), 2.195 (1.38), 2.202 (0.47), 2.331 (0.74), 2.518 (3.86), 2.522 (2.50), 2.580 (0.57), 2.591 (1.05), 2.610 (1.21), 2.673 (0.95), 2.784 (0.95), 2.817 (0.50), 3.162 (0.41), 3.172 (0.69), 3.179 (0.65), 3.404 (1.33), 3.417 (1.38), 3.421 (3.41),
 20 3.434 (3.43), 3.439 (3.91), 3.452 (4.01), 3.457 (1.15), 3.469 (1.19), 3.529 (0.57), 3.535 (0.57), 3.735 (0.55), 3.784 (0.47), 3.788 (0.47), 3.792 (0.47), 3.812 (0.64), 3.816 (0.62), 4.111 (0.41), 4.123 (0.48), 4.138 (0.83), 4.149 (0.83), 4.154 (0.88), 4.168 (0.74), 4.343 (2.64), 4.356 (5.06), 4.368 (2.39), 4.636 (0.93), 4.651 (0.93), 7.205 (1.50), 7.208 (1.38), 7.218 (2.69), 7.296 (1.02), 7.305 (1.02), 7.308 (1.05), 7.315 (1.17), 7.327 (0.55), 7.701
 25 (0.64), 8.228 (1.50), 8.240 (1.38), 8.282 (0.47), 8.385 (2.07), 13.654 (0.43), 14.636 (1.17).

LC-MS (method 2): $R_t = 1.14$ min; MS (ESIpos): $m/z = 530$ $[M+H]^+$

Intermediate 6-30

N-(3-chloro-2-methoxyphenyl)-4-[(3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



5

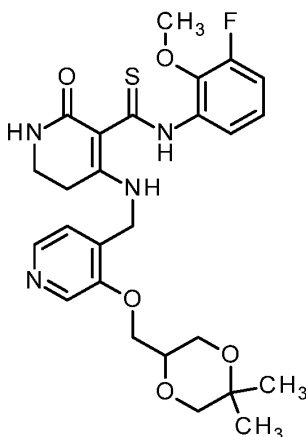
Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 200 mg, 639 μ mol) and 1-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-7, 210 mg, 831 μ mol) as the starting materials; 55.0 mg (98 % purity, 15 % yield) of the title compound were prepared after heating for 3h at 130°C and purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.042 (9.29), 1.249 (8.31), 2.518 (2.85), 2.523 (1.83), 2.752 (0.79), 2.768 (1.57), 2.785 (0.95), 3.147 (0.74), 3.156 (1.18), 3.164 (1.13), 3.299 (1.11), 3.533 (1.90), 3.562 (1.50), 3.628 (0.50), 3.648 (1.21), 3.658 (1.28), 3.667 (1.26), 3.691 (1.55), 3.713 (16.00), 3.720 (1.14), 3.795 (0.51), 3.806 (0.64), 3.817 (0.52), 4.154 (0.42), 4.164 (0.43), 4.180 (1.25), 4.191 (1.23), 4.198 (1.31), 4.212 (1.18), 4.225 (0.43), 4.663 (1.86), 4.678 (1.86), 7.088 (1.13), 7.108 (2.42), 7.128 (1.39), 7.286 (1.58), 7.290 (1.68), 7.305 (2.17), 7.310 (1.58), 7.316 (1.59), 7.729 (1.16), 7.799 (1.26), 7.803 (1.27), 7.819 (1.18), 7.823 (1.14), 8.241 (1.91), 8.253 (1.81), 8.397 (3.02), 13.669 (0.43), 13.683 (0.81), 14.792 (2.17).

LC-MS (method 6): $R_t = 1.04$ min; MS (ESIpos): $m/z = 547$ $[M+H]^+$

Intermediate 6-33

4-[(3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino)-N-(3-fluoro-2-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



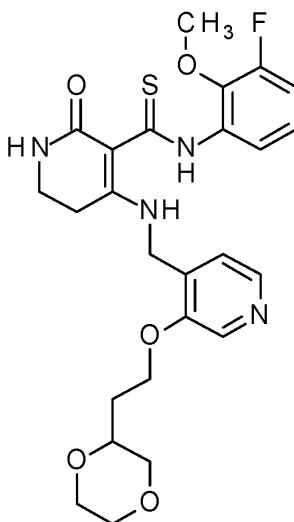
- 5 Using an analogous method as described for intermediate 6-1; N-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 200 mg, 675 μ mol) and 1-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-7, 221 mg, 877 μ mol) as the starting materials, 130 mg (96 % purity, 35 % yield) of the title compound were prepared after
- 10 heating for 2 h at 130°C and purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).

¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.043 (15.59), 1.251 (13.74), 2.518 (2.60), 2.523 (1.78), 2.742 (1.25), 2.759 (2.52), 2.775 (1.52), 3.134 (1.00), 3.142 (1.15), 3.152 (1.86), 3.158 (1.79), 3.167 (1.02), 3.175 (0.86), 3.300 (1.91), 3.535 (3.14), 3.563 (2.56), 3.622 (0.60), 3.630 (0.81), 3.650 (1.97), 3.659 (2.07), 3.668 (2.14), 3.692 (2.45), 3.722 (1.19), 3.782 (15.81), 3.785 (16.00), 3.796 (0.91), 3.808 (1.03), 3.819 (0.82), 3.832 (0.62), 4.155 (0.57), 4.165 (0.61), 4.181 (1.80), 4.192 (1.83), 4.198 (1.91), 4.212 (1.68), 4.225 (0.61), 4.238 (0.55), 4.658 (2.20), 4.672 (2.17), 7.029 (0.54), 7.045 (0.69), 7.050 (1.65), 7.065 (1.84), 7.069 (2.29), 7.071 (2.14), 7.077 (2.06), 7.085 (1.65), 7.093 (0.69), 7.098 (1.72), 7.103 (1.74), 7.119 (0.69), 7.124 (0.54), 7.307 (0.94), 7.317 (0.99), 7.657 (1.74), 7.662 (1.08), 7.676 (1.36), 7.681 (1.03), 7.708 (1.84), 8.254 (0.72), 8.404 (0.81), 13.678 (0.65), 13.693 (1.25), 13.707 (0.60), 14.741 (3.47).

LC-MS (method 6): Rt = 0.94 min; MS (ESIpos): m/z = 531 [M+H]⁺

Intermediate 6-35

4-[[3-{2-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)methyl]amino]-N-(3-fluoro-2-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide

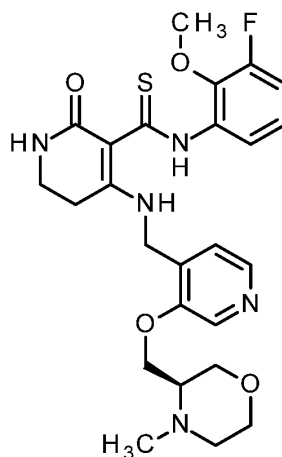


- 5 Using an analogous method as described for intermediate 6-1; N-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-4, 200 mg, 675 μ mol) and 1-(3-{2-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)methanamine (intermediate 2-6, 209 mg, 877 μ mol) as the starting materials, 137 mg (96 % purity, 38 % yield) of the title compound were prepared.
- 10 LC-MS (method 6): Rt = 0.83 min; MS (ESIpos): m/z = 517 [M+H]⁺
- ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.757 (0.42), 1.778 (0.61), 1.793 (0.89), 1.813 (0.86), 1.822 (0.55), 1.826 (0.49), 1.833 (0.54), 1.840 (0.80), 1.852 (0.85), 1.857 (0.64), 1.868 (0.60), 2.518 (2.52), 2.523 (1.61), 2.674 (0.45), 2.735 (0.74), 2.752 (1.68), 2.761 (1.69), 2.769 (1.02), 2.777 (0.89), 3.134 (1.00), 3.142 (1.11), 3.151 (1.92), 3.159 (1.89),
- 15 3.168 (0.98), 3.175 (0.85), 3.198 (1.19), 3.224 (1.91), 3.228 (1.91), 3.254 (1.24), 3.421 (0.47), 3.425 (0.68), 3.446 (1.52), 3.453 (1.67), 3.472 (0.99), 3.481 (1.19), 3.545 (0.92), 3.552 (1.09), 3.574 (1.39), 3.580 (1.60), 3.606 (1.73), 3.612 (2.26), 3.618 (1.04), 3.639 (1.07), 3.645 (0.93), 3.690 (1.77), 3.697 (2.11), 3.709 (0.79), 3.719 (3.54), 3.728 (1.41), 3.735 (0.73), 3.744 (1.71), 3.751 (1.33), 3.782 (15.79), 3.784 (16.00), 4.203 (1.78), 4.219
- 20 (2.73), 4.232 (1.20), 4.237 (1.18), 4.653 (2.89), 4.667 (2.88), 7.030 (0.49), 7.046 (0.68), 7.051 (1.63), 7.067 (1.82), 7.070 (3.31), 7.077 (2.11), 7.086 (1.65), 7.092 (0.71), 7.098 (1.72), 7.103 (1.73), 7.119 (0.68), 7.124 (0.52), 7.303 (1.99), 7.314 (2.03), 7.660 (1.68),

7.665 (1.06), 7.677 (1.35), 7.683 (1.07), 7.703 (1.84), 8.226 (1.84), 8.237 (1.79), 8.373 (2.98), 13.689 (0.64), 13.704 (1.28), 13.718 (0.60), 14.740 (3.42).

Intermediate 6-37

N-(3-fluoro-2-methoxyphenyl)-4-[[[(3*R*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methyl]amino}-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



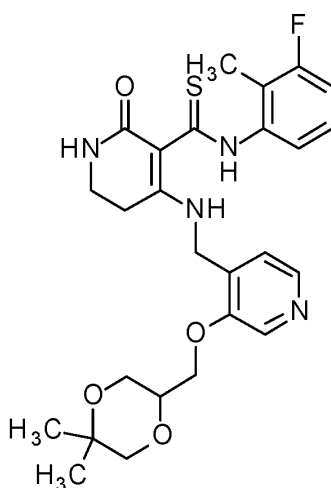
Using an analogous method as described for intermediate 6-1 with *N*-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-4, 200 mg, 675 μ mol) and 1-(3-[[[(3*R*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methanamine (intermediate 2-2, 224 mg, 945 μ mol) as the starting materials; 134 mg of the title compound were prepared (38% yield) after heating for 1 h at 124 °C and purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 2.205 (0.86), 2.226 (1.57), 2.254 (1.23), 2.290 (15.27), 2.327 (1.28), 2.654 (2.07), 2.681 (1.95), 2.762 (2.11), 2.779 (3.81), 2.795 (2.41), 3.155 (3.13), 3.374 (3.80), 3.401 (2.16), 3.482 (0.97), 3.504 (1.80), 3.531 (1.16), 3.686 (1.75), 3.714 (1.51), 3.784 (16.00), 3.888 (1.65), 3.916 (1.59), 4.031 (1.27), 4.047 (1.48), 4.057 (1.61), 4.073 (1.47), 4.294 (1.53), 4.304 (1.57), 4.320 (1.45), 4.328 (1.29), 4.661 (3.52), 4.675 (3.54), 7.031 (0.48), 7.052 (1.50), 7.070 (3.26), 7.087 (1.82), 7.099 (1.95), 7.122 (0.79), 7.299 (2.83), 7.311 (2.84), 7.655 (2.12), 7.672 (2.11), 7.706 (2.52), 8.239 (20 3.08), 8.250 (2.98), 8.414 (5.21), 13.678 (1.85), 14.738 (3.80).

LC-MS (method 6): *R*_t = 0.64 min; MS (ESIpos): *m/z* = 516 [M+H]⁺

Intermediate 6-38

4-[[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]methylamino]-*N*-(3-fluoro-2-methylphenyl)-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide



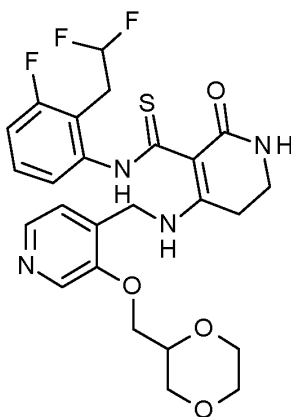
- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-fluoro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-38, 350 mg, 1.25 mmol) and 1-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-7, 315 mg, 1.25 mmol) as the starting materials; 192 mg of the title compound were prepared (27% yield) after heating for 3 h at 120 °C and purification
10 by preparative HPLC (method 11, gradient: 0.00 – 2.00 min 30% B, 2.00 – 14.00 min 30 – 70% B).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.046 (16.00), 1.253 (14.02), 2.045 (8.35), 2.050 (8.21), 2.063 (1.09), 2.521 (2.37), 2.525 (1.62), 2.741 (1.29), 2.757 (2.61), 2.774 (1.60), 3.145 (1.01), 3.152 (1.15), 3.161 (1.90), 3.168 (1.80), 3.178 (0.99), 3.185 (0.85), 3.298
15 (1.92), 3.534 (3.17), 3.562 (2.60), 3.617 (0.65), 3.626 (0.83), 3.647 (2.00), 3.656 (2.10), 3.666 (2.13), 3.690 (2.57), 3.719 (1.29), 3.780 (0.43), 3.793 (0.82), 3.803 (1.04), 3.814 (0.83), 3.828 (0.60), 4.148 (0.72), 4.159 (0.78), 4.174 (2.17), 4.186 (2.01), 4.194 (2.14), 4.208 (2.03), 4.220 (0.76), 4.234 (0.69), 4.647 (3.08), 4.662 (3.06), 7.040 (0.87), 7.061 (1.78), 7.074 (1.74), 7.085 (1.37), 7.094 (2.40), 7.189 (0.89), 7.208 (1.38), 7.225 (1.30),
20 7.244 (0.54), 7.295 (2.49), 7.307 (2.52), 7.686 (1.77), 8.237 (2.54), 8.249 (2.42), 8.393 (3.97), 13.662 (1.07), 14.520 (2.54).

LC-MS (method 6): *R*_t = 0.98 min; MS (ESIpos): *m/z* = 515 [M+H]⁺

Intermediate 6-40

N-[2-(2,2-difluoroethyl)-3-fluoro-phenyl]-4-[[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]methylamino]-6-oxo-2,3-dihydro-1H-pyridine-5-carbothioamide

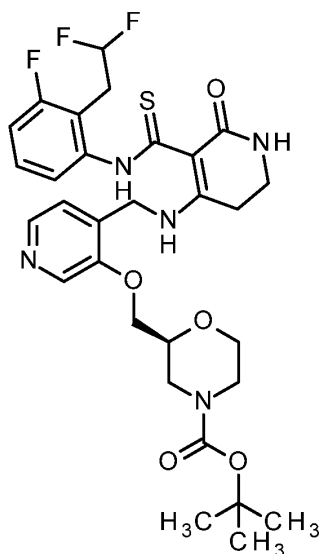


- 5 Using an analogous method as described for intermediate 6-1 with *N*-[2-(2,2-difluoroethyl)-3-fluorophenyl]-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-40, 100 mg, 303 μ mol) and 1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-1, 95.0 mg, 424 μ mol) as the starting materials; 19.5 mg of the title compound were prepared (10% yield) after purification by flash chromatography
- 10 (silica, DCM / EtOH gradient 0-10%).

LC-MS (method 2): R_t = 1.07 min; MS (ESIpos): m/z = 537 $[M+H]^+$

Intermediate 6-41

tert-butyl (2*S*)-2-[[[4-[[[5-[[2-(2,2-difluoroethyl)-3-fluorophenyl]carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]amino]methyl]pyridin-3-yl]oxy]methyl]morpholine-4-carboxylate



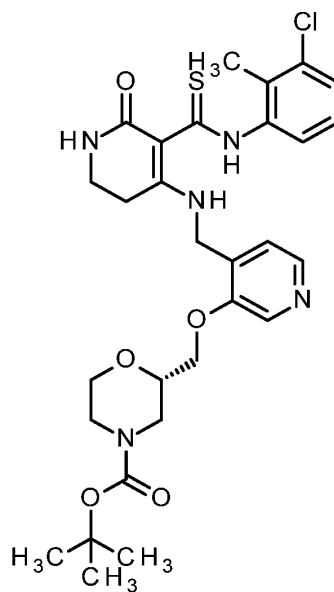
5

A mixture of *N*-[2-(2,2-difluoroethyl)-3-fluorophenyl]-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-40, 200 mg, 605 μ mol) and *tert*-butyl (2*S*)-2-[[[4-(aminomethyl)pyridin-3-yl]oxy]methyl]morpholine-4-carboxylate (intermediate 2-5, 274 mg, 848 μ mol) in ACN (2.5 ml) was treated with *N,O*-bis-(trimethylsilyl)acetamide (111 μ l, 0.6 mmol, CAS 10416-59-8) and stirred at 80°C for 5 h. The reaction was treated with another equivalent (111 μ l, 0.6 mmol) of *N,O*-bis-(trimethylsilyl)acetamide and stirred at 80°C overnight. The reaction mixture was diluted in DCM and purified by flash chromatography (silica, DCM / EtOH gradient 0-20%) to give 255 mg (45% yield) of the title compound.

15 LC-MS (method 2): R_t = 1.25 min; MS (ESIpos): m/z = 636 $[M+H]^+$

Intermediate 6-42

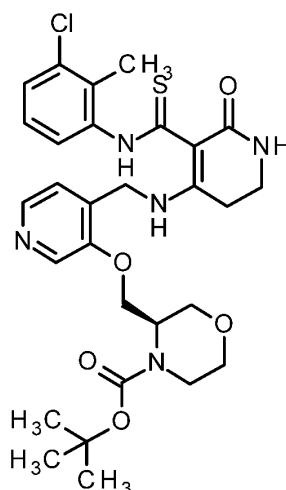
tert-butyl (2*S*)-2-[[[4-[[[5-[(3-chloro-2-methylphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]amino)methyl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate



- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-10, 350 mg, 1.18 mmol) and *tert*-butyl (2*S*)-2-[[[4-(aminomethyl)pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 2-5, 381 mg, 1.18 mmol) as the starting materials; 208 mg of the title compound were prepared (99% purity, 29% yield) after
- 10 heating for 3 h and purification by preparative HPLC (method 11, 0.00-1.00 min 30% B, 1.00-12.74 min 30-68.9% B, 12.74 – 14.19 min 68.9 B, 14.19 – 14.45 min 68.9 – 70% B)
- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.396 (16.00), 2.077 (0.96), 2.158 (7.73), 2.520 (2.53), 2.525 (1.63), 2.542 (0.50), 2.747 (0.68), 2.763 (1.35), 2.780 (0.85), 3.146 (0.53), 3.153 (0.62), 3.162 (0.99), 3.169 (0.96), 3.434 (0.57), 3.441 (0.60), 3.710 (0.46), 3.723 (0.54), 3.730 (0.70), 3.737 (0.68), 3.749 (0.56), 3.756 (0.45), 3.837 (0.42), 4.213 (1.89), 4.225 (1.86), 4.648 (1.39), 4.663 (1.40), 7.153 (0.57), 7.170 (1.15), 7.196 (0.92), 7.216 (1.36), 7.236 (0.59), 7.294 (0.89), 7.306 (0.92), 7.326 (1.13), 7.329 (1.10), 7.346 (0.85), 7.349 (0.79), 7.691 (0.91), 8.237 (2.11), 8.249 (1.94), 8.399 (3.05), 13.653 (0.59), 14.540 (1.38).
- 15
- 20 LC-MS (method 6): *R*_t = 1.17 min; MS (ESIpos): *m/z* = 602 [M+H]⁺

Intermediate 6-43

tert-butyl (3*R*)-3-[(4-[(5-[(3-chloro-2-methylphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)amino)methyl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate



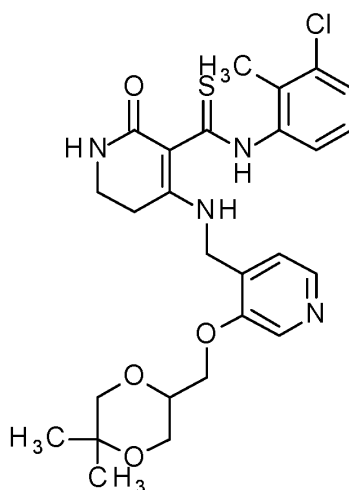
- 5 Using an analogous method as described for intermediate 6-1 with *N*-(3-chloro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-10, 350 mg, 1.18 mmol) and *tert*-butyl (3*R*)-3-([4-(aminomethyl)pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 2-9, 381 mg, 1.18 mmol) as the starting materials; 184 mg of the title compound were prepared (99% purity, 26% yield) after
- 10 heating for 3 h and by preparative HPLC (method 11, 0.00-1.00 min 30% B, 1.00-12.74 min 30-68.9% B, 12.74 – 14.19 min 68.9 B, 14.19 – 14.45 min 68.9 – 70% B)

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.339 (2.92), 2.087 (1.31), 2.161 (16.00), 2.521 (1.63), 2.525 (1.08), 2.676 (0.52), 2.708 (0.66), 2.725 (1.74), 2.742 (1.82), 2.757 (0.75), 3.140 (1.42), 3.147 (1.59), 3.156 (2.44), 3.163 (2.41), 3.319 (0.58), 3.365 (1.06), 3.372 (1.25), 3.395 (0.56), 3.402 (0.54), 3.478 (0.92), 3.507 (1.00), 3.651 (0.51), 3.797 (0.72), 3.821 (0.64), 3.957 (0.67), 3.985 (0.59), 4.236 (1.53), 4.415 (0.46), 4.441 (0.83), 4.625 (2.12), 4.639 (2.15), 7.160 (1.07), 7.178 (2.26), 7.200 (2.08), 7.220 (3.03), 7.239 (1.27), 7.291 (1.19), 7.301 (1.19), 7.329 (2.50), 7.332 (2.34), 7.349 (1.83), 7.352 (1.71), 7.691 (1.99), 8.240 (3.22), 8.252 (3.11), 8.489 (2.72), 13.669 (0.94), 14.536 (3.05).

20 LC-MS (method 6): *R*_t = 1.17 min; MS (ESIpos): *m/z* = 602 [M+H]⁺

Intermediate 6-44

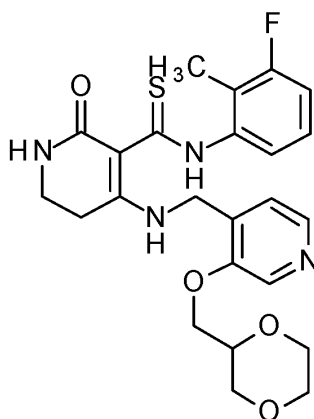
N-(3-chloro-2-methyl-phenyl)-4-[[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]methylanino]-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide



- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-chloro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-10, 200 mg, 674 μ mol) and 1-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-7, 200 mg, 85% purity, 674 μ mol) as the starting materials; 328 mg of the title compound were prepared (97% purity, 89% yield).
- 10 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm]= 1.047 (14.25), 1.253 (12.85), 2.077 (16.00), 2.162 (14.45), 2.520 (1.87), 2.525 (1.19), 2.742 (1.21), 2.759 (2.44), 2.775 (1.45), 3.147 (0.98), 3.154 (1.11), 3.163 (1.80), 3.170 (1.74), 3.180 (0.98), 3.186 (0.82), 3.297 (1.66), 3.327 (2.92), 3.533 (2.87), 3.561 (2.30), 3.617 (0.55), 3.626 (0.77), 3.646 (1.84), 3.655 (1.96), 3.664 (1.91), 3.689 (2.20), 3.718 (1.12), 3.791 (0.79), 3.802 (0.97), 3.812 (0.78), 3.826 (0.56), 4.147 (0.62), 4.158 (0.66), 4.173 (1.85), 4.184 (1.77), 4.193 (1.88), 4.206 (1.73), 4.220 (0.66), 4.233 (0.60), 4.644 (2.79), 4.659 (2.74), 7.158 (1.13), 7.175 (2.37), 7.200 (1.72), 7.220 (2.58), 7.239 (1.09), 7.298 (1.31), 7.310 (1.39), 7.328 (2.08), 7.332 (2.01), 7.348 (1.56), 7.351 (1.42), 7.689 (1.69), 8.245 (0.80), 8.399 (1.03), 13.621 (0.57), 13.635 (1.07), 14.542 (2.54).
- 15
- 20 LC-MS (method 6): R_t = 1.06 min; MS (ESIpos): m/z = 531 $[\text{M}+\text{H}]^+$

Intermediate 6-47

4-[[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]methylamino]-*N*-(3-fluoro-2-methyl-phenyl)-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide

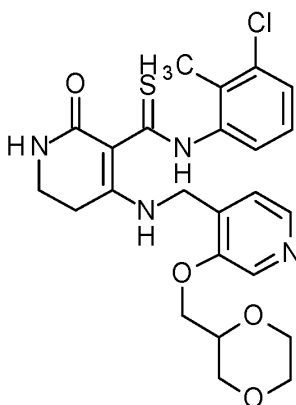


- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-fluoro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-38, 300 mg, 1.07 mmol) and 1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-1, 240 mg, 1.07 mmol) as the starting materials; 156.3 mg of the title compound were prepared (93% purity, 71% yield).
- 10 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 0.000 (0.70), 1.998 (0.55), 2.033 (16.00), 2.038 (15.45), 2.064 (3.23), 2.508 (3.78), 2.513 (2.36), 2.737 (2.61), 2.754 (5.23), 2.771 (2.96), 3.142 (2.39), 3.151 (3.71), 3.158 (3.53), 3.168 (2.07), 3.393 (2.34), 3.418 (3.51), 3.421 (3.41), 3.446 (3.16), 3.461 (1.34), 3.482 (2.56), 3.488 (2.76), 3.506 (1.42), 3.516 (2.71), 3.579 (1.64), 3.585 (1.94), 3.608 (2.49), 3.614 (2.79), 3.641 (5.03), 3.670 (1.97), 3.735 (2.71), 3.744 (2.66), 3.769 (2.09), 3.837 (2.39), 3.844 (2.81), 3.871 (4.35), 3.883 (1.72), 3.890 (1.32), 3.895 (1.57), 3.902 (1.32), 3.907 (1.44), 3.914 (1.14), 3.926 (0.62), 4.108 (0.85), 4.120 (0.95), 4.134 (3.73), 4.145 (6.69), 4.158 (3.48), 4.171 (0.87), 4.184 (0.75), 4.624 (4.75), 4.639 (4.68), 7.028 (1.64), 7.050 (3.46), 7.062 (3.48), 7.073 (2.79), 7.081 (4.60), 7.179 (1.62), 7.198 (2.71), 7.215 (2.51), 7.235 (1.00), 7.333 (1.12), 7.676 (3.41),
- 15 8.321 (0.42), 13.651 (2.04), 14.509 (4.80).
- 20

LC-MS (method 6): *R*_t = 0.85 min; MS (ESIpos): *m/z* = 487 [M+H]⁺

Intermediate 6-50

N-(3-chloro-2-methyl-phenyl)-4-[[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]methylamino]-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide

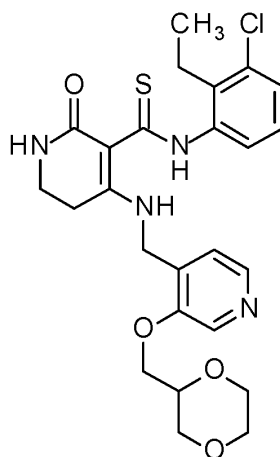


- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-chloro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-10, 200 mg, 674 μ mol) and 1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-1, 151 mg, 674 μ mol) as the starting materials; 150.0 mg of the title compound were prepared (96% purity, 42% yield).
- 10 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm]= 2.077 (1.64), 2.162 (16.00), 2.520 (2.60), 2.525 (1.64), 2.751 (1.41), 2.768 (2.82), 2.784 (1.63), 3.156 (1.22), 3.165 (1.94), 3.172 (1.87), 3.404 (1.32), 3.429 (1.94), 3.432 (1.93), 3.457 (1.81), 3.472 (0.72), 3.493 (1.40), 3.500 (1.50), 3.518 (0.79), 3.528 (1.45), 3.591 (0.91), 3.597 (1.05), 3.619 (1.35), 3.626 (1.54), 3.650 (2.14), 3.653 (2.65), 3.660 (0.95), 3.682 (1.04), 3.748 (1.44), 3.756 (1.54), 3.781 (1.16), 3.849 (1.30), 3.855 (1.59), 3.883 (2.54), 3.894 (0.99), 3.901 (0.68), 3.906 (0.89), 3.913 (0.76), 3.918 (0.79), 3.925 (0.62), 3.930 (0.51), 4.118 (0.55), 4.129 (0.59), 4.144 (2.26), 4.155 (4.42), 4.168 (2.30), 4.181 (0.52), 4.194 (0.48), 4.648 (3.19), 4.663 (3.19), 7.159 (1.24), 7.176 (2.55), 7.203 (1.84), 7.222 (2.83), 7.242 (1.22), 7.290 (2.72), 7.302 (2.78), 7.330 (2.22), 7.333 (2.19), 7.349 (1.69), 7.353 (1.54), 7.691 (1.83), 8.233 (4.07), 8.245 (3.96), 8.383 (6.40), 13.623 (0.61), 13.637 (1.14), 14.544 (2.74).
- 20

LC-MS (method 6): Rt = 0.94 min; MS (ESIpos): m/z = 503 [M+H]⁺

Intermediate 6-52

N-(3-chloro-2-ethyl-phenyl)-4-[[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]methylamino]-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide



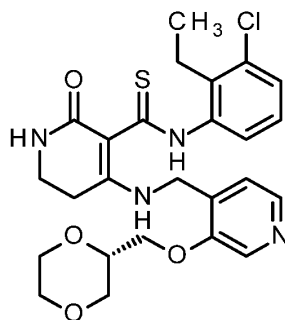
- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-chloro-2-ethylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-29, 150 mg, 483 μ mol) and 1-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}methanamine (intermediate 2-1, 108 mg, 483 μ mol) as the starting materials; 150.0 mg of the title compound were prepared (90% purity, 54% yield) by using flash chromatography (silica, 10 DCM / EtOH gradient 1-13%).

¹H-NMR (400 MHz, DMSO-d₆): δ ppm= 1.01 - 1.11 (m, 4 H), 2.56 - 2.65 (m, 2 H), 2.73 - 2.81 (m, 2 H), 3.12 - 3.22 (m, 2 H), 3.39 - 3.54 (m, 3 H), 3.58 - 3.69 (m, 2 H), 3.73 - 3.80 (m, 1 H), 3.88 (s, 2 H), 4.09 - 4.23 (m, 2 H), 4.11 - 4.15 (m, 1 H), 4.57 - 4.71 (m, 2 H), 7.16 - 7.25 (m, 2 H), 7.28 - 7.36 (m, 2 H), 7.32 (s, 1 H), 7.66 - 7.75 (m, 1 H), 8.07 - 8.11 (m, 1 H), 8.21 - 8.26 (m, 1 H), 8.33 - 8.43 (m, 1 H), 13.60 - 13.70 (m, 1 H), 14.59 - 14.67 (m, 1 H).

LC-MS (method 2): $R_t = 1.15$ min; MS (ESIpos): $m/z = 517$ $[M+H]^+$

Intermediate 6-53

N-(3-chloro-2-ethylphenyl)-4-[[[3-[[[(2*S*)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



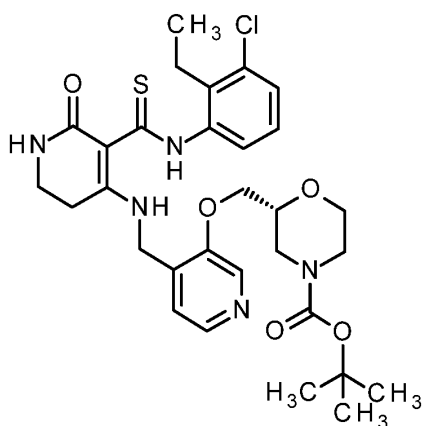
- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-chloro-2-ethylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-29, 210 mg, 676 μ mol) and 1-(3-[[[(2*S*)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methanamine (intermediate 2-8, 185 mg, 90% purity, 743 μ mol) as the starting materials; 320.0 mg of the title compound were prepared (86% yield) by using flash chromatography (silica, DCM /
10 EtOH gradient 1-15%).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.036 (8.39), 1.040 (4.03), 1.053 (16.00), 1.059 (9.01), 1.071 (8.71), 1.078 (3.84), 2.066 (0.41), 2.518 (1.19), 2.523 (0.81), 2.577 (0.95), 2.596 (2.98), 2.614 (2.87), 2.632 (0.86), 2.757 (1.69), 2.774 (3.38), 2.790 (1.92), 3.152 (1.31), 3.159 (1.49), 3.169 (2.36), 3.174 (2.23), 3.185 (1.26), 3.403 (1.67), 3.405 (1.77),
15 3.418 (1.45), 3.423 (4.19), 3.427 (2.48), 3.430 (2.54), 3.435 (4.26), 3.440 (3.60), 3.453 (4.76), 3.457 (2.12), 3.470 (1.96), 3.492 (1.59), 3.498 (1.73), 3.516 (0.85), 3.526 (1.70), 3.589 (1.03), 3.594 (1.21), 3.617 (1.57), 3.623 (1.85), 3.651 (3.24), 3.679 (1.31), 3.745 (1.75), 3.754 (1.70), 3.779 (2.03), 3.847 (1.59), 3.853 (1.84), 3.880 (2.81), 3.893 (1.13), 3.900 (0.84), 3.905 (1.04), 3.912 (0.89), 3.917 (0.95), 3.924 (0.75), 3.929 (0.59), 3.936
20 (0.44), 4.116 (0.64), 4.127 (0.69), 4.142 (2.65), 4.154 (5.01), 4.167 (2.53), 4.180 (0.60), 4.193 (0.55), 4.343 (2.64), 4.356 (5.10), 4.369 (2.52), 4.647 (3.70), 4.662 (3.66), 7.209 (5.05), 7.211 (4.85), 7.222 (8.23), 7.231 (0.55), 7.293 (2.86), 7.307 (4.24), 7.319 (3.43), 7.331 (1.67), 7.706 (2.31), 8.234 (3.16), 8.246 (3.01), 8.383 (5.19), 13.642 (0.84), 13.657 (1.55), 13.672 (0.72), 14.639 (4.11).

25 LC-MS (method 2): *R*_t = 1.17 min; MS (ESIpos): *m/z* = 517 [M+H]⁺

Intermediate 6-55

tert-butyl (2*R*)-2-[(4-[(5-[(3-chloro-2-ethylphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)amino)methyl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate



- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-chloro-2-ethylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-29, 300 mg, 965 μ mol) and *tert*-butyl (2*R*)-2-([4-(aminomethyl)pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 2-10, 312 mg, 965 μ mol) as the starting materials; 476.0 mg of the title compound were prepared (95% purity, 76% yield)
- 10 by using flash chromatography (silica, DCM / EtOH gradient 1-10%).

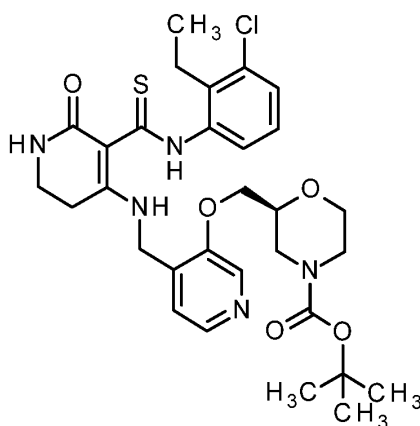
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.036 (1.51), 1.055 (3.57), 1.073 (1.55), 1.393 (16.00), 2.518 (1.71), 2.523 (1.10), 2.590 (1.19), 2.609 (1.16), 2.751 (0.68), 2.769 (1.33), 2.785 (0.84), 3.165 (0.96), 3.171 (0.92), 3.431 (0.55), 3.438 (0.59), 3.729 (0.71), 3.749 (0.48), 3.756 (0.41), 3.835 (0.41), 4.210 (1.81), 4.222 (1.76), 4.646 (1.35), 4.662 (1.35),

15 5.758 (7.84), 7.202 (2.06), 7.214 (2.99), 7.296 (1.00), 7.304 (1.58), 7.316 (1.60), 7.328 (0.75), 7.703 (0.94), 8.236 (1.90), 8.248 (1.81), 8.398 (2.84), 13.671 (0.64), 14.632 (1.67).

LC-MS (method 2): R_t = 1.32 min; MS (ESIpos): m/z = 616 [M+H]⁺

Intermediate 6-56

tert-butyl (2*S*)-2-[[[4-[[[5-[(3-chloro-2-ethylphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]amino)methyl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate



- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-chloro-2-ethylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-29, 300 mg, 965 μ mol) and *tert*-butyl(2*S*)-2-([4-(aminomethyl)pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 2-5, 312 mg, 965 μ mol) as the starting materials; 479.0 mg of the title compound were prepared (95% purity, 77% yield) after purification by
- 10 flash chromatography (silica, DCM / EtOH gradient 1-10%).

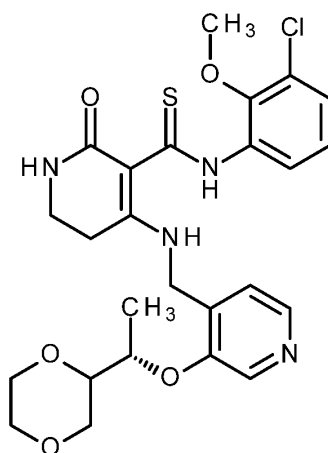
$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 14.55 - 14.67 (m, 1H), 13.60 - 13.72 (m, 1H), 8.40 (s, 1H), 8.24 (d, 1H), 7.70 (br s, 1H), 7.16 - 7.36 (m, 4H), 5.70 - 5.80 (m, 1H), 5.66 - 5.81 (m, 1H), 4.59 - 4.73 (m, 2H), 4.12 - 4.27 (m, 2H), 3.80 - 3.99 (m, 2H), 3.65 - 3.78 (m, 2H), 3.37 - 3.50 (m, 1H), 3.10 - 3.22 (m, 2H), 2.70 - 2.99 (m, 4H), 2.55 - 2.64 (m, 2H), 1.30 - 1.46

15 (m, 9H), 1.01 - 1.12 (m, 3H).

LC-MS (method 2): R_t = 1.32 min; MS (ESIpos): m/z = 616 $[\text{M}+\text{H}]^+$

Intermediate 6-57

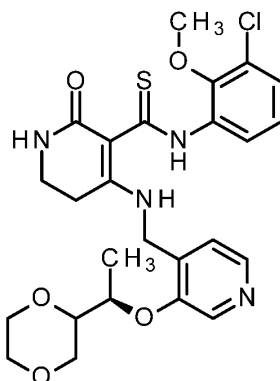
N-(3-chloro-2-methoxyphenyl)-4-([3-[(1*S*)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl)methylamino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 300 mg, 959 μ mol) and 1-{3-[(1*S*)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}methanamine (intermediate 2-11, 251 mg, 1.06 mmol) as the starting materials; 384 mg of the title compound were prepared (99% purity, 74% yield) as mixture of diastereomers.
- 10 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm]= 0.064 (0.95), 1.239 (2.82), 1.255 (2.83), 1.279 (2.06), 1.295 (2.09), 2.518 (1.11), 2.523 (0.82), 2.761 (0.76), 2.777 (0.86), 3.141 (0.52), 3.148 (0.60), 3.157 (1.00), 3.164 (0.99), 3.181 (0.43), 3.417 (0.87), 3.443 (0.88), 3.455 (0.44), 3.462 (0.47), 3.470 (0.68), 3.476 (0.41), 3.591 (0.40), 3.597 (0.65), 3.620 (0.88), 3.632 (0.76), 3.639 (0.41), 3.647 (0.54), 3.653 (0.56), 3.672 (0.40), 3.678 (0.44), 3.711 (16.00), 3.732 (0.56), 3.766 (0.89), 3.772 (0.52), 3.794 (0.57), 4.651 (1.27), 4.665 (1.31), 4.682 (0.58), 7.090 (0.70), 7.110 (1.53), 7.131 (0.88), 7.287 (1.67), 7.289 (1.87), 7.300 (1.26), 7.305 (1.12), 7.309 (1.02), 7.314 (0.67), 7.726 (0.98), 7.791 (0.95), 7.794 (0.96), 7.811 (0.90), 7.815 (0.85), 8.198 (1.34), 8.211 (1.99), 8.223 (0.91), 8.416 (1.88), 8.432 (1.35), 13.666 (0.43), 13.675 (0.50), 14.790 (1.61).
- 15
- 20 LC-MS (method 6): R_t = 0.96 min and R_t = 0.98 min; MS (ESIpos): m/z = 533.2 $[\text{M}+\text{H}]^+$

Intermediate 6-60

N-(3-chloro-2-methoxyphenyl)-4-{{[3-{{(1*R*)-1-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)methyl]amino}-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide

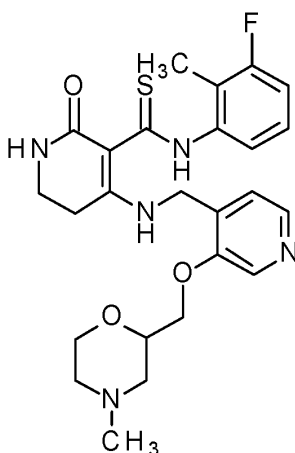


- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 300 mg, 959 μ mol) and 1-{3-[(1*R*)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}methanamine (intermediate 2-12, 251 mg, 1.06 mmol) as the starting materials; 346 mg (99% purity, 67% yield) of the title compound were prepared.
- 10 ¹H-NMR (400 MHz, DMSO- d_6): δ [ppm]= 1.278 (5.25), 1.294 (5.21), 2.073 (0.98), 2.331 (0.40), 2.518 (2.02), 2.522 (1.36), 2.673 (0.42), 2.749 (0.74), 2.765 (0.56), 2.775 (0.83), 2.792 (0.42), 3.140 (0.62), 3.147 (0.73), 3.156 (1.17), 3.164 (1.16), 3.417 (0.81), 3.441 (1.16), 3.445 (1.15), 3.469 (1.68), 3.475 (0.85), 3.503 (0.74), 3.570 (0.47), 3.576 (0.55), 3.598 (0.72), 3.604 (0.82), 3.631 (1.87), 3.638 (0.97), 3.646 (0.63), 3.652 (0.78), 3.657 (1.02), 3.663 (0.93), 3.670 (0.52), 3.677 (0.47), 3.710 (16.00), 3.758 (0.87), 3.767 (0.74), 3.790 (0.67), 3.920 (0.78), 3.926 (0.76), 3.949 (0.72), 3.955 (0.66), 4.646 (1.57), 4.653 (1.48), 4.662 (1.63), 4.682 (0.73), 7.092 (1.08), 7.112 (2.33), 7.133 (1.33), 7.287 (1.60), 7.290 (1.60), 7.302 (1.73), 7.306 (1.61), 7.310 (1.69), 7.314 (1.68), 7.725 (1.16), 7.791 (1.23), 7.794 (1.22), 7.811 (1.17), 7.814 (1.08), 8.210 (2.42), 8.222 (2.24), 8.430 (3.36),
- 15 13.651 (0.41), 13.665 (0.79), 14.786 (2.12).
- 20

LC-MS (method 6): R_t = 0.96 min; MS (ESIpos): m/z = 533 [M+H]⁺

Intermediate 6-62

N-(3-fluoro-2-methylphenyl)-4-[[[3-[[[(2*S*)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



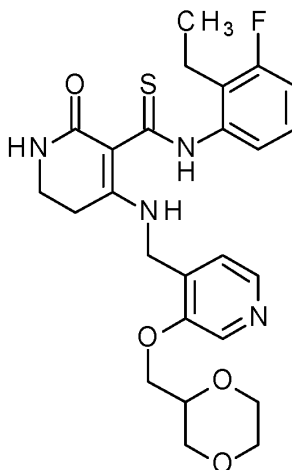
- 5 Using an analogous method as described for intermediate 6-41 with *N*-(3-fluoro-2-methylphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-38, 197 mg, 704 μ mol) and 1-(3-[[4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)methanamine (intermediate 2-3, 167 mg, 704 μ mol) as the starting materials; 170 mg of the title compound were prepared (93% purity, 45% yield) after purification by reversed
10 phase HPLC (basic).

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ [ppm]= 1.035 (0.65), 1.053 (1.08), 1.070 (0.68), 1.848 (1.00), 1.876 (1.47), 1.901 (1.11), 1.953 (0.45), 1.962 (0.59), 1.982 (1.04), 1.990 (1.08), 2.010 (0.69), 2.019 (0.57), 2.040 (7.36), 2.044 (6.91), 2.177 (16.00), 2.518 (1.64), 2.522 (1.10), 2.578 (0.88), 2.607 (0.81), 2.756 (0.84), 2.770 (1.72), 2.789 (2.10), 2.817 (1.02),
15 3.149 (0.83), 3.156 (0.97), 3.166 (1.67), 3.173 (1.63), 3.182 (0.94), 3.318 (0.50), 3.501 (0.55), 3.507 (0.70), 3.529 (1.25), 3.535 (1.29), 3.557 (0.76), 3.563 (0.62), 3.784 (0.93), 3.788 (0.90), 3.791 (0.76), 3.812 (1.29), 3.815 (1.26), 3.829 (0.63), 3.837 (0.57), 4.112 (0.53), 4.124 (0.56), 4.138 (1.82), 4.150 (1.97), 4.154 (2.08), 4.168 (1.68), 4.180 (0.56), 4.194 (0.52), 4.636 (2.30), 4.651 (2.34), 7.034 (0.71), 7.055 (1.49), 7.070 (1.47), 7.079
20 (1.12), 7.089 (1.98), 7.185 (0.72), 7.204 (1.19), 7.221 (1.13), 7.241 (0.44), 7.295 (2.26), 7.306 (2.30), 7.679 (1.46), 8.227 (3.76), 8.239 (3.55), 8.383 (5.45), 13.662 (0.88), 14.516 (2.06).

LC-MS (method 6): R_t = 0.62 min; MS (ESIpos): m/z = 500 $[\text{M}+\text{H}]^+$

Intermediate 6-65

4-[[[3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino]-N-(2-ethyl-3-fluorophenyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide

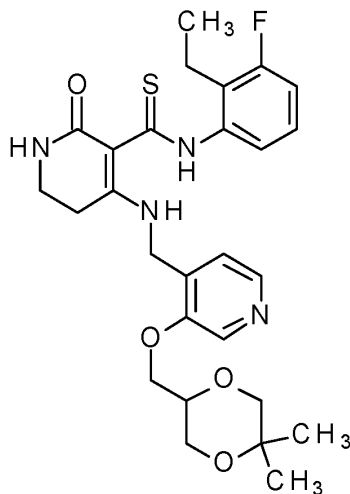


- 5 Using an analogous method as described for intermediate 6-41 with N-(2-ethyl-3-fluorophenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (300 mg, 1.02 mmol) and 1-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methanamine (229 mg, 1.02 mmol) as the starting materials; 218 mg of the title compound were prepared (90% purity, 38% yield) after evaporation of the solvent, filtration and washing of the solid with ACN.
- 10 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 0.057 (1.12), 1.042 (7.32), 1.061 (16.00), 1.080 (7.29), 1.231 (0.88), 1.751 (0.58), 2.074 (6.86), 2.522 (5.66), 2.753 (3.09), 2.770 (6.11), 2.787 (3.52), 3.156 (2.86), 3.166 (4.42), 3.172 (4.30), 3.181 (2.51), 3.402 (2.65), 3.427 (3.92), 3.430 (3.92), 3.455 (3.70), 3.471 (1.62), 3.491 (2.84), 3.498 (3.08), 3.516 (1.51), 3.526 (2.87), 3.589 (1.80), 3.594 (1.99), 3.617 (2.79), 3.623 (3.19), 3.650 (5.74), 3.679 (2.35), 3.745 (3.17), 3.754 (3.06), 3.778 (2.46), 3.846 (2.80), 3.853 (3.24), 3.881 (4.78), 3.893 (1.98), 3.900 (1.58), 3.905 (1.80), 3.911 (1.59), 3.918 (1.69), 3.925 (1.36), 3.936 (0.73), 4.117 (1.01), 4.129 (1.14), 4.143 (4.20), 4.155 (7.71), 4.168 (3.95), 4.181 (1.08), 4.194 (0.91), 4.632 (5.48), 4.646 (5.40), 7.029 (2.23), 7.051 (3.97), 7.074 (2.84), 7.091 (3.92), 7.110 (5.33), 7.191 (2.31), 7.207 (2.86), 7.211 (3.55), 7.228 (3.42), 7.248 (1.35), 7.351 (1.30), 7.701 (4.14), 8.329 (0.48), 8.476 (0.42), 13.662 (1.51), 13.676 (2.76), 13.691 (1.37), 14.588 (6.37).
- 20

LC-MS (method 6): R_t = 0.92 min; MS (ESIpos): m/z = 501 [M+H]⁺

Intermediate 6-68

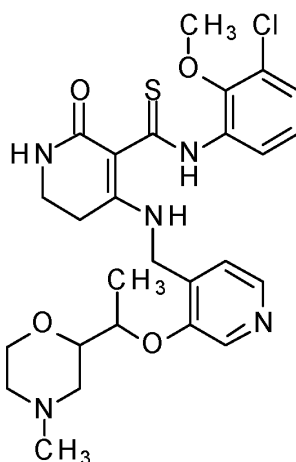
4-[[[3-[[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino]-N-(2-ethyl-3-fluorophenyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



- 5 Using an analogous method as described for intermediate 6-41 with N-(2-ethyl-3-fluorophenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (300 mg, 1.02 mmol) and 1-(3-[[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methanamine (257 mg, 1.02 mmol) as the starting materials; 360 mg of the title compound were prepared (93% purity, 62% yield) after purification by column chromatography.
- 10 ¹H-NMR (400 MHz, DMSO-d₆) δ [ppm]: 1.014 (0.69), 1.044 (16.00), 1.061 (7.08), 1.080 (3.30), 1.172 (0.52), 1.200 (0.60), 1.251 (13.22), 1.987 (0.87), 2.745 (1.36), 2.761 (2.65), 2.779 (1.61), 3.164 (2.11), 3.170 (2.09), 3.295 (1.79), 3.532 (2.73), 3.560 (2.19), 3.615 (0.59), 3.624 (0.79), 3.644 (1.91), 3.653 (2.05), 3.664 (1.79), 3.688 (2.07), 3.718 (1.01), 3.778 (0.45), 3.789 (0.91), 3.801 (1.07), 3.812 (0.86), 3.824 (0.63), 4.145 (0.65), 4.156 (0.71), 4.172 (1.96), 4.182 (1.95), 4.191 (2.02), 4.205 (1.76), 4.218 (0.69), 4.231 (0.59), 4.644 (3.11), 4.658 (3.10), 7.029 (0.86), 7.050 (1.63), 7.074 (1.12), 7.091 (1.71), 7.111 (2.37), 7.189 (0.89), 7.208 (1.52), 7.225 (1.39), 7.245 (0.52), 7.295 (2.40), 7.306 (2.41), 7.700 (1.92), 8.235 (3.11), 8.247 (2.98), 8.389 (5.24), 13.661 (0.71), 13.675 (1.32), 13.688 (0.68), 14.587 (3.04).
- 15
- 20 LC-MS (method 6): R_t = 1.03 min; MS (ESIpos): m/z = 529 [M+H]⁺

Intermediate 6-71

N-(3-chloro-2-methoxyphenyl)-4-({[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]methyl}amino)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide



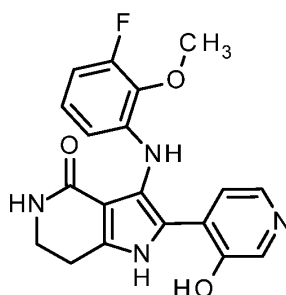
- 5 Using an analogous method as described for intermediate 6-41 with N-(3-chloro-2-methoxyphenyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 5-1, 300 mg, 959 μ mol) and 1-[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]methanamine (intermediate 2-71, 265 mg, 1.06 mmol) as the starting materials; 360 mg of the title compound were prepared (93% purity, 62% yield) after
10 purification by column chromatography.

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.014 (0.69), 1.044 (16.00), 1.061 (7.08), 1.080 (3.30), 1.172 (0.52), 1.200 (0.60), 1.251 (13.22), 1.987 (0.87), 2.745 (1.36), 2.761 (2.65), 2.779 (1.61), 3.164 (2.11), 3.170 (2.09), 3.295 (1.79), 3.532 (2.73), 3.560 (2.19), 3.615 (0.59), 3.624 (0.79), 3.644 (1.91), 3.653 (2.05), 3.664 (1.79), 3.688 (2.07), 3.718 (1.01),
15 3.778 (0.45), 3.789 (0.91), 3.801 (1.07), 3.812 (0.86), 3.824 (0.63), 4.145 (0.65), 4.156 (0.71), 4.172 (1.96), 4.182 (1.95), 4.191 (2.02), 4.205 (1.76), 4.218 (0.69), 4.231 (0.59), 4.644 (3.11), 4.658 (3.10), 7.029 (0.86), 7.050 (1.63), 7.074 (1.12), 7.091 (1.71), 7.111 (2.37), 7.189 (0.89), 7.208 (1.52), 7.225 (1.39), 7.245 (0.52), 7.295 (2.40), 7.306 (2.41), 7.700 (1.92), 8.235 (3.11), 8.247 (2.98), 8.389 (5.24), 13.661 (0.71), 13.675 (1.32), 13.688
20 (0.68), 14.587 (3.04).

LC-MS (method 6): R_t = 1.03 min; MS (ESIpos): m/z = 529 $[\text{M}+\text{H}]^+$

Intermediate 12

3-((3-fluoro-2-methoxyphenyl)amino)-2-(3-hydroxypyridin-4-yl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one



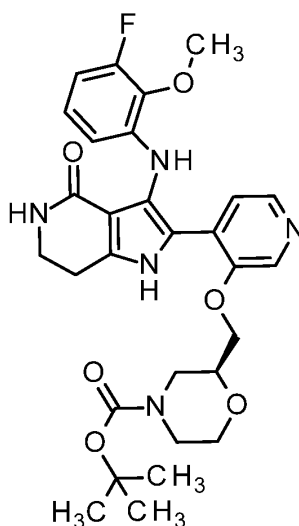
- 5 To a suspension of *N*-(3-fluoro-2-methoxyphenyl)-4-(((3-hydroxypyridin-4-yl)methyl)amino)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-12, 41 g, 101.88 mmol) in MeOH (410 mL) was added TFA (0.75 mL, 10.13 mmol), followed by hydrogen peroxide (18 mL, 30 % in water). The mixture was heated to 60°C and stirred for 16 h. Additional TFA (6.8 mL, 91.84 mmol) and hydrogen peroxide (1.5 mL, 30 % in water)
- 10 were added. The suspension was stirred at 60°C for further 3 h. The mixture was cooled to room temperature and stand overnight. The suspension was combined with a second batch that was generated identically. The combined suspension was filtered and the cake was washed with water (250 mL) and MeOH (150 mL), and then slurried in MeOH (150 mL). The suspension was filtered. The cake was washed with MeOH (75 mL) and dried in
- 15 vacuum to afford the title compound (25.4 g, 33.8 % yield) as a yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.45 (s, 1H), 8.18 (s, 1H), 7.98 (d, 1H), 7.39 (d, 1H), 7.18 (s, 1H), 6.67 (t, 1H), 6.54 (t, 1H), 6.04 (d, 1H), 3.92 (s, 3H), 3.40 (t, 2H), 2.90 (t, 2H).

LC-MS (method 5): *R*_t = 1.851 min; *m/z* = 369.0 (*M* + *H*)⁺

Intermediate 22-1

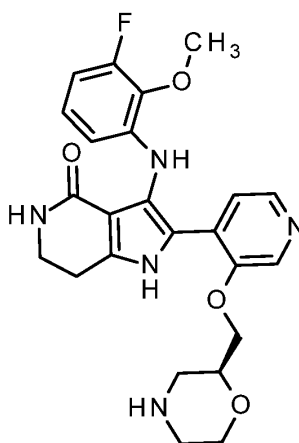
tert-butyl (2*S*)-2-[[{4-[3-(3-fluoro-2-methoxyanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl}oxy)methyl]morpholine-4-carboxylate



- 5 Using an analogous method as described for example 1 with *tert*-butyl (2*S*)-2-[[{4-[3-(3-fluoro-2-methoxyphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]amino)methyl]pyridin-3-yl}oxy)methyl]morpholine-4-carboxylate (intermediate 6-22, 1.43 g, 2.38 mmol) as the starting material; 572 mg (80 % purity, 34 % yield) of the title compound were prepared after purification by flash chromatography (silica, DCM / EtOH gradient 0-10 %).
- 10 ¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 1.035 (0.86), 1.053 (1.99), 1.071 (0.88), 1.380 (0.83), 1.401 (6.79), 1.409 (16.00), 2.518 (1.63), 2.523 (1.18), 2.842 (0.65), 2.859 (1.16), 2.877 (0.76), 3.178 (0.95), 3.301 (0.60), 3.398 (0.50), 3.404 (0.61), 3.415 (0.94), 3.418 (0.82), 3.422 (1.10), 3.435 (0.77), 3.440 (0.72), 3.452 (0.50), 3.553 (0.42), 3.560 (0.43), 3.750 (0.64), 3.760 (0.40), 3.851 (0.50), 3.858 (0.40), 3.873 (0.46), 3.906 (6.63), 3.936 (0.57), 3.939 (0.59), 3.950 (0.46), 4.343 (0.56), 4.356 (0.65), 5.759 (1.09), 5.993 (0.75), 6.013 (0.76), 6.485 (0.50), 6.489 (0.49), 6.492 (0.42), 6.513 (0.45), 6.516 (0.42), 6.627 (0.54), 6.642 (0.52), 7.147 (0.86), 7.280 (1.09), 7.293 (1.13), 7.509 (0.98), 8.025 (1.38), 8.038 (1.27), 8.401 (2.10), 11.020 (0.61).
- 15
- 20 LC-MS (method 2): *R*_t = 1.12 min; MS (ESIpos): *m/z* = 568 [M+H]⁺

Intermediate 22-2

3-(3-fluoro-2-methoxyanilino)-2-(3-[(2*S*)-morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-*c*]pyridin-4-one



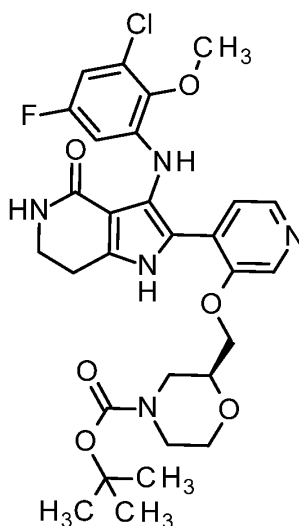
- 5 *Tert*-butyl (2*S*)-2-[(4-[3-(3-fluoro-2-methoxyanilino)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 22-1, 572 mg, 1.01 mmol) was solubilised in dichloromethane (7.2 ml) and TFA (780 μ l, 10 mmol) was added. The mixture was stirred for 2h at RT. The mixture was evaporated and purified by flash chromatography (amino phase silica, DCM / EtOH gradient 0-20 %) to give
- 10 352 mg (95 % purity, 71 % yield) of the title compound.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 2.53 - 2.78 (m, 4H), 2.80 - 2.90 (m, 3H), 3.38 - 3.47 (m, 3H), 3.55 - 3.66 (m, 1H), 3.83 - 3.90 (m, 1H), 3.91 - 3.95 (s, 3H), 4.07 - 4.16 (m, 1H), 4.29 - 4.39 (m, 1H), 6.01 (d, 1H), 6.44 - 6.56 (m, 1H), 6.65 (dt, 1H), 7.17 (s, 1H), 7.29 (d, 1H), 7.53 (s, 1H), 8.01 (d, 1H), 8.39 (s, 1H), 11.10 (s, 1H).

- 15 LC-MS (method 2): R_t = 0.84 min; MS (ESIpos): m/z = 468 $[\text{M}+\text{H}]^+$

Intermediate 27-1

tert-butyl (2*S*)-2-[[{4-[3-(3-chloro-5-fluoro-2-methoxyanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl}oxy)methyl]morpholine-4-carboxylate

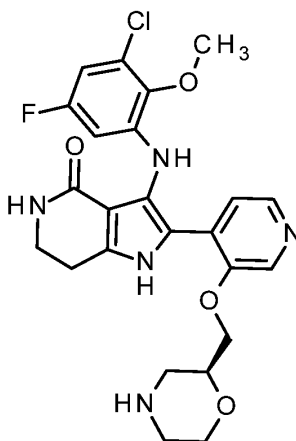


- 5 Using an analogous method as described for example 1 with *tert*-butyl (2*S*)-2-[[{4-[3-(3-chloro-5-fluoro-2-methoxyphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]amino)methyl]pyridin-3-yl}oxy)methyl]morpholine-4-carboxylate (intermediate 6-27, 150 mg, 236 μ mol) as the starting material, 73.5 mg (90 % purity, 47 % yield) of the title compound were prepared.
- 10 ¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 1.40 (s, 9H), 2.52 - 2.53 (m, 2H), 2.70 - 3.03 (m, 1H), 2.87 (br t, 2H), 3.42 (td, 2H), 3.46 - 3.61 (m, 1H), 3.71 - 3.79 (m, 1H), 3.82 (s, 4H), 3.93 (br d, 1H), 4.20 (m, 1H), 4.27 - 4.33 (dd, 1H), 5.85 (dd, 1H), 6.55 (dd, 1H), 7.11 (s, 1H), 7.32 (d, 1H), 7.60 (s, 1H), 8.10 (d, 1H), 8.44 (s, 1H), 11.17 (s, 1H).

LC-MS (method 2): R_t = 1.19 min; MS (ESIpos): m/z = 602 [M+H]⁺

Intermediate 27-2

3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-[(2*S*)-morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



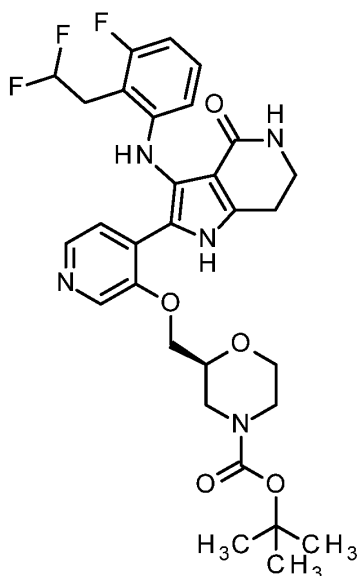
- 5 Using an analogous method as described for intermediate 22-2 with *tert*-butyl (2*S*)-2-[(4-[3-(3-chloro-5-fluoro-2-methoxyanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 27-1, 73.0 mg, 121 μ mol) as the starting material; 56.3 mg (95 % purity, 88 % yield) of the title compound were prepared after purification by flash chromatography (amino phase silica, DCM / EtOH
- 10 gradient 0-15 %).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 2.51 - 2.58 (m, 2H), 2.61 - 2.75 (m, 2H), 2.77 - 2.94 (m, 3H), 3.38 - 3.48 (m, 1H), 3.56 (td, 1H), 3.76 - 3.92 (m, 2H), 3.84 (s, 3H), 4.10 (dd, 1H), 4.29 (dd, 1H), 5.85 (dd, 1H), 6.57 (dd, 1H), 7.13 (s, 1H), 7.32 (d, 1H), 7.64 (d, 1H), 8.09 (d, 1H), 8.43 (s, 1H), 11.22 (s, 1H).

- 15 LC-MS (method 2): R_t = 0.93 min; MS (ESIpos): m/z = 502 $[\text{M}+\text{H}]^+$.

Intermediate 41-1

tert-butyl (2*S*)-2-[[[4-{3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl)oxy]methyl]morpholine-4-carboxylate

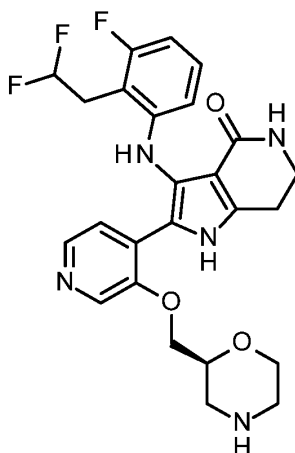


- 5 Using an analogous method as described for example 1 with *tert*-butyl (2*S*)-2-[[[4-{(5-{[2-(2,2-difluoroethyl)-3-fluorophenyl]carbamothioyl}-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)amino]methyl]pyridin-3-yl)oxy]methyl]morpholine-4-carboxylate (intermediate 6-41, 266 mg, 418 μ mol) as the starting material; 33.0 mg (65% purity, 9% yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00-0.50 min
- 10 30% B, 0.50–6.00 min 30-70% B).

LC-MS (method 2): R_t = 1.16 min; MS (ESI^{neg}): m/z = 600 [M-H]⁻

Intermediate 41-2

3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-2-(3-[[2*S*]-morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one

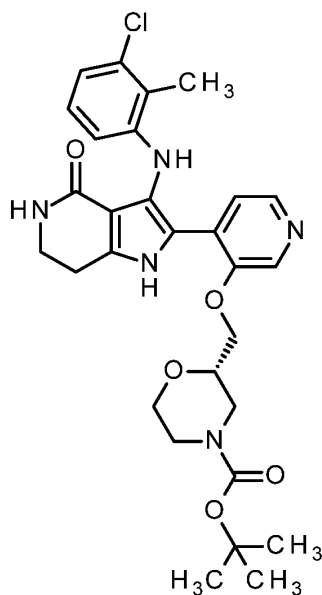


- 5 Using an analogous method as described for intermediate 22-2 with *tert*-butyl (2*S*)-2-[[4-{3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl}pyridin-3-yl]oxy]methyl]morpholine-4-carboxylate (intermediate 41-1, 33.0 mg, 54.9 μ mol) as the starting material; 22.0 mg (65% purity, 52% yield) of the title compound were prepared after purification by flash chromatography (amino phase silica, DCM / EtOH
- 10 gradient 0-10%).

LC-MS (method 2): R_t = 0.92 min; MS (ESI^{neg}): m/z = 500 [M-H]⁻

Intermediate 42-1

tert-butyl (2*S*)-2-[[{4-[3-(3-chloro-2-methylanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl}oxy)methyl]morpholine-4-carboxylate



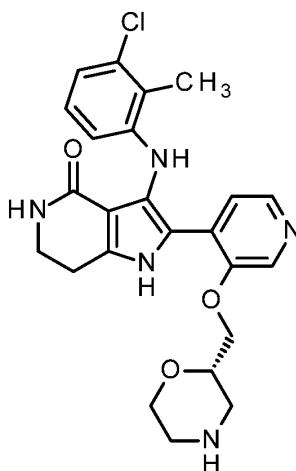
- 5 Using an analogous method as described for example 1 with *tert*-butyl (2*S*)-2-[[{4-[3-(3-chloro-2-methylphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]amino)methyl]pyridin-3-yl}oxy)methyl]morpholine-4-carboxylate (intermediate 6-42, 207 mg, 344 μ mol) as the starting material; 27.8 mg (90% purity, 13% yield) of the title compound were prepared after purification by preparative HPLC (method 9, gradient: 0.00-
10 0.50 min 15% B, 0.50–4.65 min 15–44.9% B, 4.65 – 5.94 min 44.9% B, 5.94 – 7.29 min 44.9 – 55% B).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.414 (16.00), 2.349 (5.99), 2.520 (0.82), 2.525 (0.50), 2.853 (0.68), 2.870 (1.29), 2.887 (0.75), 3.405 (0.49), 3.410 (0.53), 3.422 (0.95), 3.428 (0.93), 3.439 (0.48), 3.445 (0.43), 3.554 (0.43), 3.560 (0.45), 4.294 (0.43), 4.304 (0.45), 6.191 (0.69), 6.195 (0.66), 6.211 (0.71), 6.214 (0.69), 6.719 (0.48), 6.735 (1.31), 6.738 (1.11), 6.747 (0.85), 6.767 (0.82), 7.175 (0.83), 7.232 (0.92), 7.245 (0.92), 7.351 (0.48), 7.998 (1.24), 8.010 (1.16), 8.378 (1.84), 11.016 (0.78).

LC-MS (method 6): *R*_t = 0.92 min; MS (ESIpos): *m/z* = 568 [M+H]⁺

Intermediate 42-2

3-(3-chloro-2-methylanilino)-2-(3-[(2*S*)-morpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



- 5 Using an analogous method as described for intermediate 22-2 with *tert*-butyl (2*S*)-2-[(4-[3-(3-chloro-2-methylanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 42-1, 30.0 mg, 52.8 μ mol) as the starting material, 19.0 mg (92% purity, 71% yield) of the title compound were prepared after filtration through a SCX-2 column (MeOH wash followed by elution with 1M ammonia in
- 10 MeOH).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.235 (1.09), 2.334 (1.58), 2.338 (0.84), 2.362 (16.00), 2.520 (7.24), 2.525 (4.55), 2.545 (1.21), 2.570 (1.33), 2.575 (1.40), 2.601 (1.20), 2.676 (1.83), 2.680 (1.06), 2.705 (1.02), 2.713 (0.99), 2.732 (1.01), 2.740 (0.93), 2.758 (1.50), 2.787 (0.62), 2.846 (1.74), 2.863 (4.52), 2.880 (2.07), 2.894 (1.12), 3.300 (4.30),

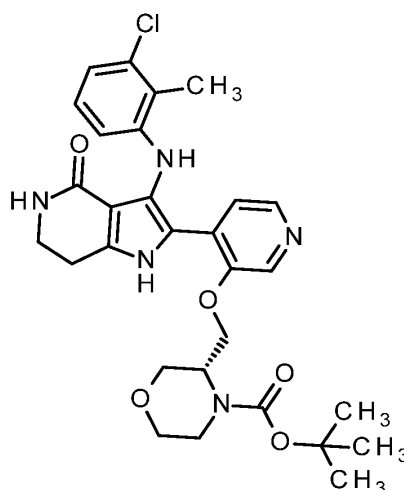
15 3.410 (1.44), 3.416 (1.55), 3.427 (2.54), 3.433 (2.52), 3.445 (1.29), 3.585 (0.65), 3.593 (0.77), 3.612 (1.20), 3.620 (1.22), 3.640 (0.69), 3.646 (0.62), 3.851 (0.59), 3.868 (0.92), 3.875 (0.91), 3.902 (1.40), 3.930 (1.00), 4.073 (1.20), 4.090 (1.18), 4.098 (1.63), 4.116 (1.39), 4.274 (1.41), 4.282 (1.45), 4.299 (1.18), 4.307 (1.08), 5.528 (0.41), 6.196 (1.85), 6.200 (1.81), 6.215 (2.00), 6.219 (1.86), 6.726 (1.04), 6.730 (1.33), 6.746 (3.44), 6.750

20 (2.92), 6.761 (2.53), 6.780 (2.58), 6.800 (0.88), 7.192 (2.31), 7.231 (3.82), 7.244 (3.92), 7.364 (4.42), 7.980 (4.81), 7.993 (4.51), 8.370 (6.73), 8.397 (0.45), 11.102 (2.40).

LC-MS (method 6): *R*_t = 0.52 min; MS (ESIpos): *m/z* = 468 [M+H]⁺

Intermediate 43-1

tert-butyl (3R)-3-[(4-{3-(3-chloro-2-methylanilino)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl}pyridin-3-yl)oxy)methyl]morpholine-4-carboxylate



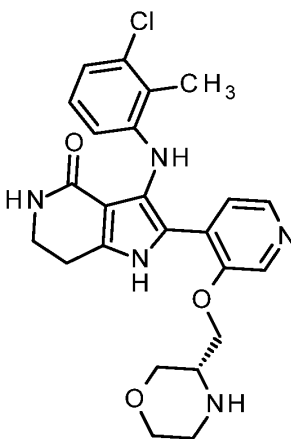
- 5 Using an analogous method as described for example 1 with *tert*-butyl (3R)-3-[(4-{3-(3-chloro-2-methylphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)amino)methyl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (180 mg, 299 μ mol) as the starting material; 35.1 mg (90% purity, 19% yield) of the title compound were prepared after purification by preparative HPLC (method 9, gradient: 0.00-0.50 min 15% B, 0.50-4.23 min 15-41.9% B, 4.23 – 5.60 min 41.9% B, 5.60 – 7.37 min 41.9 – 55% B).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.344 (16.00), 2.357 (14.22), 2.520 (2.49), 2.525 (1.70), 2.891 (0.42), 2.923 (1.43), 3.384 (1.03), 3.405 (2.12), 3.412 (2.73), 3.417 (2.74), 3.435 (1.48), 3.555 (0.76), 3.577 (0.85), 3.680 (1.24), 3.709 (1.06), 3.840 (1.02), 3.860 (0.92), 3.952 (1.42), 3.982 (1.23), 4.301 (0.62), 6.161 (1.64), 6.165 (1.44), 6.179 (1.77), 6.184 (1.67), 6.725 (0.94), 6.740 (3.11), 6.745 (3.77), 6.765 (1.40), 6.785 (0.46), 7.187 (1.94), 7.309 (2.75), 7.322 (2.75), 7.351 (4.78), 7.971 (1.97), 7.983 (1.88), 8.445 (5.01), 11.063 (1.60).

LC-MS (method 6): *R*_t = 0.92 min; MS (ESIpos): *m/z* = 568 [M+H]⁺

Intermediate 43-2

3-(3-chloro-2-methylanilino)-2-(3-[(3*R*)-morpholin-3-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



- 5 Using an analogous method as described for intermediate 22-2 with *tert*-butyl (3*R*)-3-[(4-[3-(3-chloro-2-methylanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 43-1, 30.0 mg, 52.8 μ mol) as the starting material 25.3 mg (97% purity, 99% yield) of the title compound were prepared after filtration through a SCX-2 column (MeOH wash followed by elution with 1M ammonia in
- 10 MeOH).

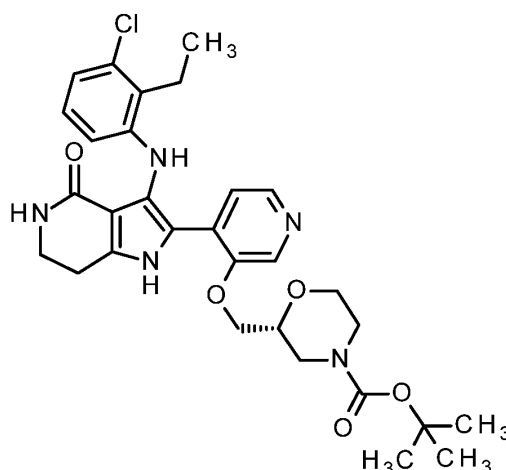
$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm]= 1.235 (0.47), 2.334 (1.10), 2.338 (0.53), 2.367 (16.00), 2.383 (0.45), 2.520 (5.15), 2.525 (3.36), 2.676 (1.09), 2.680 (0.50), 2.825 (1.81), 2.842 (3.79), 2.860 (2.41), 2.888 (0.56), 2.945 (0.90), 2.976 (0.54), 3.155 (0.67), 3.371 (1.08), 3.398 (1.36), 3.416 (2.04), 3.426 (3.16), 3.433 (2.75), 3.444 (2.06), 3.450 (1.95), 3.471 (0.57), 3.720 (1.01), 3.747 (0.86), 3.794 (1.03), 3.816 (0.90), 4.192 (0.59), 4.208 (0.66), 4.218 (1.25), 4.232 (1.21), 4.252 (1.38), 4.261 (1.46), 4.277 (0.69), 4.286 (0.59), 6.222 (1.82), 6.225 (1.83), 6.241 (1.98), 6.245 (1.89), 6.731 (1.15), 6.735 (1.43), 6.751 (3.26), 6.754 (2.74), 6.769 (2.24), 6.790 (2.51), 6.809 (0.87), 7.172 (2.36), 7.217 (2.75), 7.230 (2.77), 7.391 (4.55), 7.941 (1.75), 7.953 (1.66), 8.359 (2.93), 12.612 (0.40).

15

- 20 LC-MS (method 6): R_t = 0.53 min; MS (ESIpos): m/z = 468 $[\text{M}+\text{H}]^+$

Intermediate 55-1

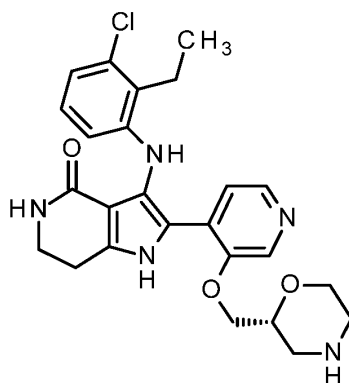
tert-butyl (2*R*)-2-[(4-{3-(3-chloro-2-ethylanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl}pyridin-3-yl)oxy)methyl]morpholine-4-carboxylate



- 5 Using an analogous method as described for example 1 with *tert*-butyl (2*R*)-2-[(4-{3-(3-chloro-2-ethylphenyl)carbamothioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)amino)methyl]pyridin-3-yl)oxy)methyl]morpholine-4-carboxylate (intermediate 6-55, 473 mg, 768 μ mol) as the starting material; 57.0 mg (95% purity, 12% yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00-10 0.50 min 10% B, 0.50–11.05 min 10–34.4% B, 11.05 – 12.46 min 34.4% B, 12.46 – 24.12 min 34.4 – 60% B) followed by flash chromatography (silica, DCM / EtOH gradient 0–12%).
- LC-MS (method 2): R_t = 1.26 min; MS (ESIpos): m/z = 582 $[M+H]^+$

Intermediate 55-2

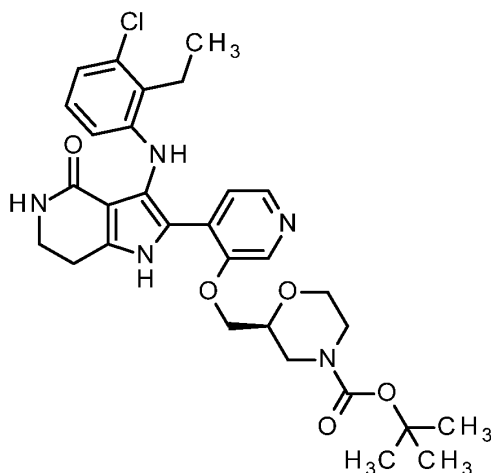
3-(3-chloro-2-ethylanilino)-2-(3-[(2R)-morpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



- 5 Using an analogous method as described for intermediate 22-2 with *tert*-butyl (2*R*)-2-[(4-[3-(3-chloro-2-ethylanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridin-2-yl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 55-1, 70.4 mg, 121 μ mol) as the starting material; 58.0 mg (95% purity, 95% yield) of the title compound were prepared after purification by flash chromatography (silica, DCM / EtOH + triethylamine gradient 1-40%).
- 10 $^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 10.96 - 11.17 (m, 1H), 8.36 (s, 1H), 7.69 - 8.02 (m, 1H), 7.37 - 7.51 (m, 1H), 7.19 (s, 2H), 6.65 - 6.86 (m, 2H), 6.15 - 6.24 (m, 1H), 6.12 - 6.31 (m, 1H), 4.26 - 4.36 (m, 1H), 4.06 - 4.14 (m, 1H), 3.85 - 3.96 (m, 2H), 3.58 - 3.67 (m, 1H), 3.40 - 3.46 (m, 2H), 3.35 - 3.39 (m, 1H), 2.69 - 2.96 (m, 7H), 2.56 - 2.64 (m, 1H), 1.19 - 1.27 (m, 6H).
- 15 LC-MS (method 2): R_t = 0.99 min; MS (ESI $^-$): m/z = 480 $[\text{M-H}]^-$

Intermediate 56-1

tert-butyl (2*S*)-2-[[{4-[3-(3-chloro-2-ethylanylino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl}oxy)methyl]morpholine-4-carboxylate

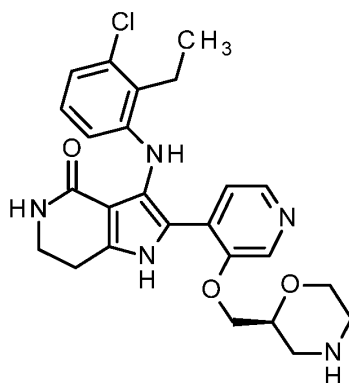


- 5 Using an analogous method as described for example 1 with *tert*-butyl (2*S*)-2-[[{4-[3-(3-chloro-2-ethylphenyl)carbamoethioyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-yl}amino)methyl]pyridin-3-yl}oxy)methyl]morpholine-4-carboxylate (intermediate 6-56, 476 mg, 772 μ mol) as the starting material; 68.0 mg (95% purity, 14% yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00-10 0.50 min 20% B, 0.50–12.99 min 20-40% B, 12.99 – 15.46 min 40% B, 15.46 – 24.12 min 40 – 55% B) followed by flash chromatography (silica, DCM / EtOH gradient 0-12%).

LC-MS (method 2): R_t = 1.26 min; MS (ESIpos): m/z = 582 $[M+H]^+$

Intermediate 56-2

3-(3-chloro-2-ethylanilino)-2-(3-[(2*S*)-morpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



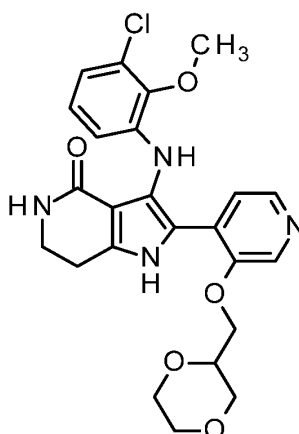
- 5 Using an analogous method as described for intermediate 22-2 with *tert*-butyl (2*S*)-2-[(4-[3-(3-chloro-2-ethylanilino)-4-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl]pyridin-3-yl]oxy)methyl]morpholine-4-carboxylate (intermediate 56-1, 70.4 mg, 121 μ mol) as the starting material; 46.9 mg (95% purity, 78% yield) of the title compound were prepared after purification by flash chromatography (amino phase silica, DCM / EtOH gradient 1-35%).
- 10 $^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 11.09 (s, 1H), 8.36 (s, 1H), 7.96 (d, 1H), 7.46 (s, 1H), 7.19 (d, 2H), 6.68 - 6.84 (m, 2H), 6.23 (dd, 1H), 4.24 - 4.34 (m, 1H), 4.03 - 4.16 (m, 1H), 3.82 - 3.96 (m, 2H), 3.57 - 3.65 (m, 1H), 3.39 - 3.48 (m, 2H), 2.82 - 2.94 (m, 5H), 2.64 - 2.79 (m, 2H), 2.54 - 2.60 (m, 1H), 1.23 (t, 3H).

LC-MS (method 2): R_t = 0.99 min; MS (ESI $^-$): m/z = 480 $[\text{M-H}]^-$

Examples

Example 1

3-(3-chloro-2-methoxyanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



5

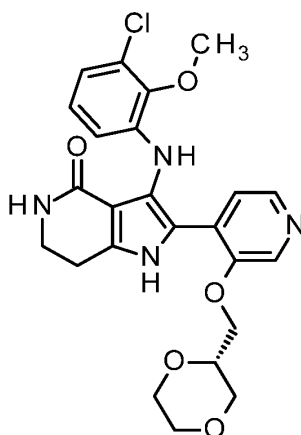
To a suspension of N-(3-chloro-2-methoxyphenyl)-4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-1, 140 mg, 240 μ mol) in MeOH (2.7 ml) was added TFA (42 μ l, 540 μ mol) followed by aqueous hydrogen peroxide (94 μ l, 35 % purity, 1.08 mmol) and the mixture was heated at 50°C for 17 h. The reaction mixture was allowed to cool down to RT and concentrated under reduced pressure. The residue was purified by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50–6.00 min 15-55% B) to give 70 mg of the title compound (51 % yield).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 2.86 (t, 2H), 3.37 - 3.57 (m, 4H), 3.70 - 3.90 (m, 4H), 3.88 (s, 3H), 3.92 - 4.08 (m, 1H), 4.10 - 4.20 (m, 1H), 4.28 (dd, 1H), 6.15 (t, 1H), 6.68 (d, 2H), 7.16 (br s, 1H), 7.28 (d, 1H), 7.52 (s, 1H), 8.04 (d, 1H), 8.39 (s, 1H), 11.07 (s, 1H).

LC-MS (method 2): *R*_t = 0.98 min; MS (ESIpos): *m/z* = 485 [M+H]⁺

Example 2

3-(3-chloro-2-methoxyanilino)-2-(3-[[[(2S)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (Stereoisomer 1)



- 5 The title compound from example 1 (140 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 27 mg at R_t = 14.0 – 17.0 min) and enantiomer 2 (25 mg at R_t = 20.0 – 24.8 min, see example 3).

Preparative chiral HPLC method:

- Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000;
 10 column: Cellulose SB 5 μ , 250x30 mm; eluent A: hexane + 0.1 vol. % diethylamine (99 %);
 eluent B: 2-propanol; isocratic: 50 % A + 50 % B; flow 50 ml/min; UV: 254 nm.

Analytical chiral HPLC method:

- Instrument: Agilent HPLC 1260; column: Cellulose SB 3 μ , 100x4.6 mm; eluent A: hexane +
 0.1 vol. % diethylamine (99 %); eluent B: 2-propanol; isocratic: 50 % A + 50 % B, flow 1.4
 15 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: R_t = 4.49 min.

Optical rotation: $[\alpha]_D = 1.7^\circ \pm 0.98^\circ$ (c = 3.6 mg/2 ml, methanol)

- Enantioselective synthesis confirmed the title compound as 3-(3-chloro-2-methoxyanilino)-
 2-(3-[[[(2S)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-
 20 c]pyridin-4-one. 872 mg (95% purity, 72% yield) of the title compound were prepared in
 analogy to example 1 using *N*-(3-chloro-2-methoxyphenyl)-4-[[[(3-[[[(2S)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide

(intermediate 6-2, 1.23 g, 2.36 mmol) as starting material, followed by purification with preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50–6.00 min 15-55% B).

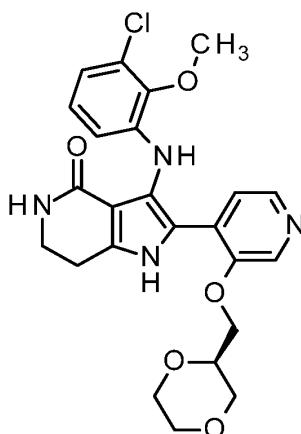
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.86 (t, 2H), 3.38 - 3.47 (m, 3H), 3.53 (td, 1H), 3.69 - 3.78 (m, 2H), 3.83 (dd, 1H), 3.88 (s, 3H), 3.90 (m, 1H), 3.98 - 4.08 (m, 1H), 4.12 - 4.18 (m, 1H), 4.28 (dd, 1H), 6.12 - 6.17 (quin, 1H), 6.66 - 6.71 (m, 2H), 7.16 (s, 1H), 7.28 (d, 1H), 7.52 (s, 1H), 8.04 (d, 1H), 8.39 (s, 1H), 11.07 (s, 1H).

Analytical chiral HPLC: R_t = 4.46 min.

Optical rotation:[α]_D = -12.5° +/- 0.52° (c = 5.6 mg/ml, chloroform)

Example 3

- 10 3-(3-chloro-2-methoxyanilino)-2-(3-[(2*R*)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (Stereoisomer 2)



- For the preparation of the racemic title compound see example 1. Separation of enantiomers by preparative chiral HPLC (method see example 2) gave 25 mg of the title compound (at R_t = 20.0 – 24.8 min).

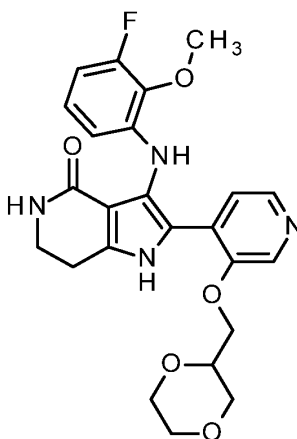
Analytical chiral HPLC (method see example 2): R_t = 6.56 min.

Optical rotation:[α]_D = -3.0° +/- 1.03° (c = 3.2 mg/2 ml, methanol)

Optical rotation:[α]_D = 22.8° +/- 6.1° (c = 6.3 mg/ml, chloroform)

Example 4

2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



5

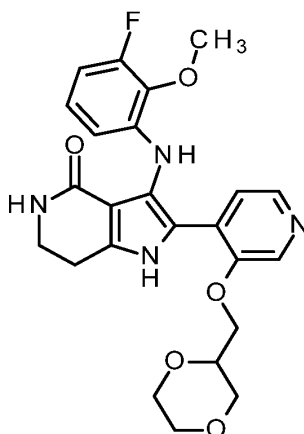
In analogy to example 1 4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-*N*-(3-fluoro-2-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-4, 120 mg, 239 μ mol) was used to prepare 25.7 mg of the title compound (21 % yield) after heating for 25 hours and purification by preparative HPLC (method 10, gradient: 0.00-10 0.50 min 15% B, 0.50–6.00 min 15-55% B).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 2.86 (t, 2H), 3.37 - 3.57 (m, 4H), 3.66 - 3.89 (m, 4H), 3.91 (s, 3H), 3.98 - 4.09 (m, 1H), 4.09 - 4.20 (m, 1H), 4.28 (dd, 1H), 6.00 (d, 1H), 6.45 - 6.54 (m, 1H), 6.64 (m, 1H), 7.16 (br s, 1H), 7.29 (d, 1H), 7.53 (s, 1H), 8.04 (d, 1H), 8.39 (s, 1H), 11.05 (s, 1H).

15 LC-MS (method 2): R_t = 0.92 min; MS (ESIpos): m/z = 469 $[\text{M}+\text{H}]^+$

Example 5

2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (stereoisomer 1)



5

The title compound from example 4 (26 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 11 mg, at $R_t = 8.2 - 9.1$ min, 10 % yield) and enantiomer 2 (12 mg, at $R_t = 9.7 - 10.7$ min, see example 6).

Preparative chiral HPLC method:

- 10 Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000; column: Cellulose SB 5 μ , 250x30 mm; eluent A: MTBE + 0.1 vol. % diethylamine (99 %); eluent B: acetonitrile; gradient: 2-60 % B in 20 min; flow 50 ml/min; UV: 280 nm

Analytical chiral HPLC method:

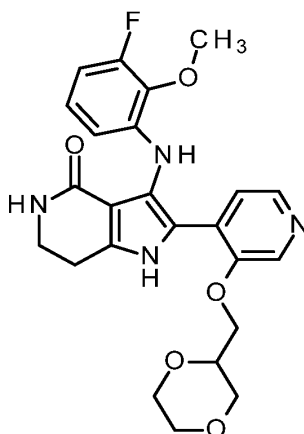
- 15 Instrument: Agilent HPLC 1260; column: Cellulose SB 3 μ , 100x4.6 mm; eluent A: MTBE + 0.1 vol. % diethylamine (99 %); eluent B: acetonitrile; gradient: 2-60 % B in 7 min, flow 1.4 ml/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC: $R_t = 4.34$ min.

Optical rotation: $[\alpha]_D = -0.5^\circ \pm 0.87^\circ$ ($c = 7.5$ mg/2 ml, methanol)

Example 6

2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (stereoisomer 2)



5

For the preparation of the racemic title compound see example 4. Separation of enantiomers by preparative chiral HPLC (method see example 5) to give 12 mg of the title compound (at $R_t = 9.7 - 10.7$ min, 11 % yield).

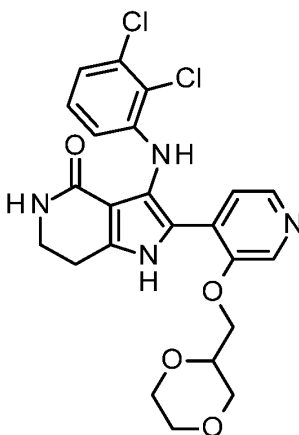
Analytical chiral HPLC (method see example 5): $R_t = 5.11$ min.

10 Optical rotation: $[\alpha]_D = -0.1^\circ \pm 0.89^\circ$ ($c = 6.3$ mg/3ml, methanol)

15

Example 7

3-(2,3-dichloroanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



5

In analogy to example 1 *N*-(2,3-dichlorophenyl)-4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-7, 110 mg, 210 μ mol) was used to prepare 34.6 mg of the title compound (32 % yield) after heating for 25 hours and purification by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50–6.00 min 15-55% B).

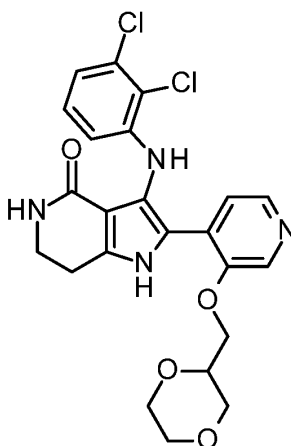
10

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 2.86 (br t, 2H), 3.35 - 3.45 (m, 3H), 3.47 - 3.56 (m, 1H), 3.65 - 3.75 (m, 2H), 3.75 - 3.88 (m, 2H), 3.93 - 4.04 (m, 1H), 4.06 - 4.20 (m, 2H), 6.27 (dd, 1H), 6.83 - 6.91 (m, 2H), 7.17 (br s, 1H), 7.26 (d, 1H), 7.66 (s, 1H), 8.08 (d, 1H), 8.38 (s, 1H), 11.21 (s, 1H).

15 LC-MS (method 2): R_t = 1.01 min; MS (ESIpos): m/z = 489 $[\text{M}+\text{H}]^+$

Example 8

3-(2,3-dichloroanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (stereoisomer 1)



5

The title compound from example 7 (27 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 10 mg) and enantiomer 2 (12 mg, see example 9).

Preparative chiral HPLC method:

- 10 Instrument: Labomatic HD5000, Labocord-5000; Gilson GX-241, Labcol Vario 4000; column: Cellulose SB 5 μ , 250x30 mm; eluent A: MTBE + 0.1 vol. % diethylamine (99 %); eluent B: acetonitrile; gradient: 2-60 % B in 20 min; flow 50 ml/min; UV: 280 nm

Analytical chiral HPLC method:

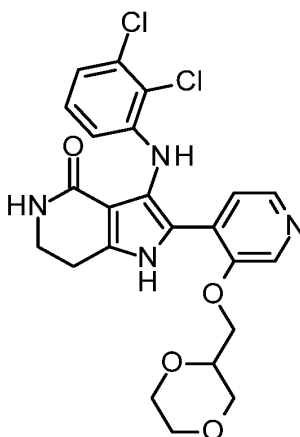
- 15 Instrument: Agilent HPLC 1260; column: Cellulose SB 3 μ , 100x4.6 mm; eluent A: MTBE + 0.1 vol. % diethylamine (99 %); eluent B: acetonitrile; gradient: 2-60 % B in 7 min, flow 1.4 ml/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC : R_t = 5.11 min.

Optical rotation: $[\alpha]_D = 1.4^\circ \pm 0.69^\circ$ ($c = 5.8$ mg/2 ml, methanol)

Example 9

3-(2,3-Dichloroanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (stereoisomer 2)



5

For the preparation of the racemic title compound see example 7. Separation of enantiomers by preparative chiral HPLC (method see example 8) to gave 12 mg of the title compound.

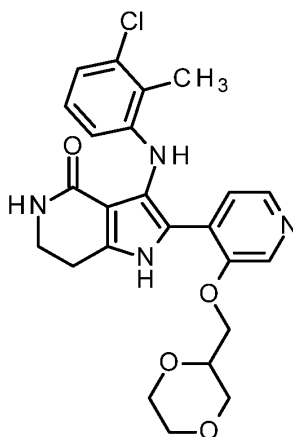
Analytical chiral HPLC (method see example 8): $R_t = 6.74$ min.

10 Optical rotation: $[\alpha]_D = -14.9^\circ \pm 3.16^\circ$ ($c = 5.6$ mg/ml, methanol)

15

Example 10

3-(3-chloro-2-methylanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



5 In analogy to example 1 *N*-(3-chloro-2-methylphenyl)-4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-10, 180 mg, 358 μ mol) was used to prepare 12.1 mg of the title compound (7 % yield) after heating for 25 hours and purification by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50–6.00 min 15-55% B).

10 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 2.35 (s, 3H), 2.86 (br t, 2H), 3.37 - 3.47 (m, 3H), 3.55 (br dd, 1H), 3.67 - 3.85 (m, 3H), 3.89 (br d, 1H), 4.01 (br dd, 1H), 4.08 - 4.18 (m, 1H), 4.24 (dd, 1H), 6.20 (d, 1H), 6.71 - 6.80 (m, 2H), 7.19 (br s, 1H), 7.24 (d, 1H), 7.37 (s, 1H), 8.01 (d, 1H), 8.37 (s, 1H), 11.05 (s, 1H).

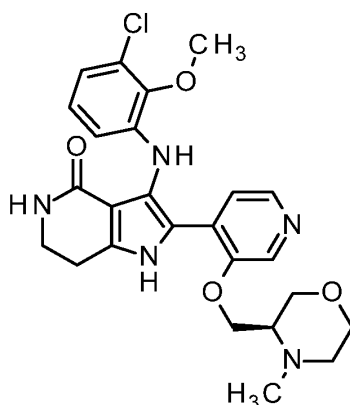
LC-MS (method 2): R_t = 1.02 min; MS (ESIpos): m/z = 469 $[\text{M}+\text{H}]^+$

15

20

Example 11

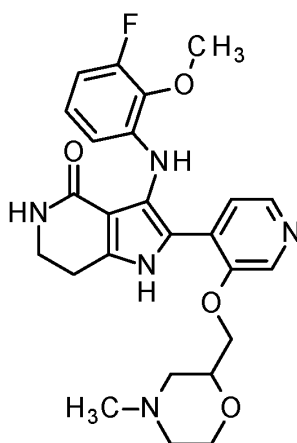
3-(3-chloro-2-methoxyanilino)-2-(3-[[[(3*R*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



- 5 In analogy to example 1 *N*-(3-chloro-2-methoxyphenyl)-4-[[[3-[[[(3*R*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-11, 82 mg, 139 μ mol) was used to prepare 11 mg of the title compound (15 % yield) after heating for 17 hours and purification by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50–6.00 min 15-55% B).
- 10 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 11.51 - 12.57 (m, 1H), 8.40 (br s, 1H), 8.04 (br s, 1H), 7.62 (br s, 1H), 7.32 (d, 1H), 7.19 (br s, 1H), 6.71 (br d, 2H), 6.15 (dd, 1H), 4.40 (br s, 2H), 3.90 (s, 4H), 3.85 (br s, 1H), 3.60 (br d, 3H), 3.40 - 3.51 (m, 3H), 3.01 (br s, 1H), 2.74 - 2.96 (m, 3H), 2.22 - 2.43 (m, 2H).
- LC-MS (method 6): R_t = 0.55 min; MS (ESIpos): m/z = 498.2 $[\text{M}+\text{H}]^+$
- 15 Optical rotation: $[\alpha]_D = -82.0^\circ \pm 0.41^\circ$ (c = 5.8 mg/ml, methanol)

Example 12

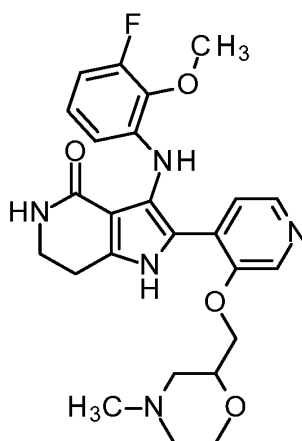
3-(3-fluoro-2-methoxyanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



- 5 3-(3-Fluoro-2-methoxyanilino)-2-(3-hydroxypyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (intermediate 12, 150 mg, 407 μ mol) was solved in dioxane (4.8 ml). The reaction mixture was degassed with argon. Then (tributylphosphanylidene)acetonitrile (384 μ l, 1.5 mmol, CAS 157141-27-0) and (4-methylmorpholin-2-yl)methanol (CAS 40987-46-0, 80.0 mg, 610 μ mol) were added and the mixture was stirred at 50°C for 30 h. The mixture
- 10 was concentrated under reduced pressure and sat. sodium bicarbonate solution was added. The mixture was extracted with DCM. The organic phase was filtered over a water-repellent filter, concentrated under reduced pressure and purified by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 1% B, 0.50 – 27.40 min 1 – 50% B) to give 16.2 mg of the title compound (8 % yield).
- 15 ¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 11.05 (s, 1H), 8.40 (s, 1H), 8.02 (d, 1H), 7.52 (s, 1H), 7.29 (d, 1H), 7.16 (s, 1H), 6.64 (td, 1H), 6.50 (ddd, 1H), 6.01 (d, 1H), 4.34 (dd, 1H), 4.15 (dd, 1H), 3.88 - 4.00 (m, 5H), 3.67 (td, 1H), 3.37 - 3.47 (m, 2H), 2.85 (t, 2H), 2.77 (br d, 1H), 2.66 - 2.70 (m, 1H), 2.20 (s, 3H), 2.04 (td, 1H), 1.91 (t, 1H).
- LC-MS (method 2): *R*_t = 0.92 min; MS (ESIpos): *m/z* = 482.3 [M+H]⁺

Example 13

3-(3-fluoro-2-methoxyanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (stereoisomer 1)



- 5 The title compound from example 12 (19 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 6 mg, at R_t = 6.7 – 8.7 min, 3 % yield) and enantiomer 2 (7 mg, at R_t = 8.9 – 11.9 min, see example 14).

Preparative chiral HPLC method:

- Instrument: PrepCon Labomatic HPLC; column: Chiralcel OD-H 5 μ , 250x20; eluent A: acetonitrile + 0.1 vol. % diethylamine (99 %); eluent B: ethanol; isocratic: 93 % A + 7 % B; flow 20 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC method:

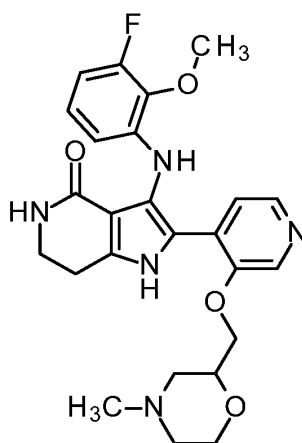
- Instrument: Waters Alliance 2695; column: Chiralcel OD-H 5 μ , 100x4.6; eluent A: ethanol + 0.1 vol. % diethylamine (99 %); eluent B: ethanol; isocratic: 90 % A + 10 % B, flow 1.4 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC : R_t = 2.91 min.

- $^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm]= 11.05 (s, 1H), 8.40 (s, 1H), 8.02 (d, 1H), 7.53 (s, 1H), 7.29 (d, 1H), 7.16 (s, 1H), 6.64 (td, 1H), 6.50 (t, 1H), 6.01 (d, 1H), 4.34 (dd, 1H), 4.15 (dd, 1H), 3.89 - 3.99 (m, 5H), 3.67 (td, 1H), 3.38 - 3.46 (m, 2H), 2.85 (t, 2H), 2.77 (br d, 1H), 2.61 - 2.71 (m, 1H), 2.20 (s, 3H), 1.98 - 2.16 (m, 1H), 1.91 (t, 1H).

Example 14

3-(3-fluoro-2-methoxyanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (stereoisomer 2)



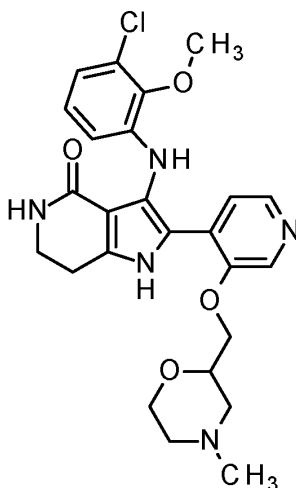
- 5 For the preparation of the racemic title compound see example 12. Separation of enantiomers by preparative chiral HPLC (method see example 13) to give 7 mg of the title compound (at $R_t = 8.9 - 11.9$ min, 3 % yield).

Analytical chiral HPLC (method see example 13): $R_t = 3.70$ min.

- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 11.05 (s, 1H), 8.40 (s, 1H), 8.02 (br d, 1H), 7.53 (s, 1H), 7.29 (d, 1H), 7.16 (br s, 1H), 6.59 - 6.70 (m, 1H), 6.50 (br t, 1H), 6.01 (br d, 1H), 4.34 (br dd, 1H), 4.15 (br dd, 1H), 3.86 - 4.00 (m, 5H), 3.60 - 3.74 (m, 1H), 3.40 - 3.48 (m, 2H), 2.85 (br t, 2H), 2.77 (br d, 1H), 2.63 - 2.70 (m, 1H), 2.20 (s, 3H), 1.99 - 2.09 (m, 1H), 1.91 (br t, 1H).
- 10

Example 15

3-(3-chloro-2-methoxyanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one

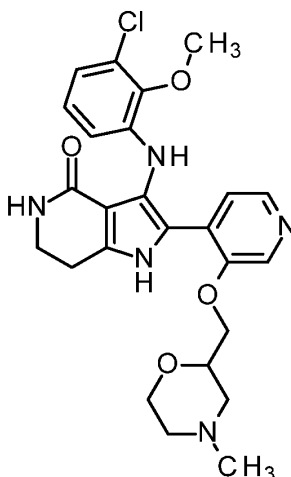


- 5 In analogy to example 1 *N*-(3-chloro-2-methoxyphenyl)-4-[(3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-15, 74.0 mg, 139 μ mol) was used to prepare 24.1 mg (90 % purity, 31 % yield) of the title compound after heating for 18 hours and purification by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50–6.00 min 15-55% B).
- 10 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.86 - 1.95 (t, 1H), 2.00 - 2.09 (td, 1H), 2.20 (s, 3H), 2.66 (br d, 1H), 2.73 - 2.81 (br d, 1H), 2.86 (t, 2H), 3.42 (td, 2H), 3.61 - 3.73 (td, 1H), 3.88 (s, 3H), 3.91 - 4.02 (m, 2H), 4.16 (dd, 1H), 4.33 (dd, 1H), 6.15 (t, 1H), 6.69 (d, 2H), 7.16 (s, 1H), 7.28 (d, 1H), 7.53 (s, 1H), 8.03 (d, 1H), 8.40 (s, 1H), 11.07 (s, 1H).

LC-MS (method 2): R_t = 0.97 min; MS (ESIpos): m/z = 498 $[\text{M}+\text{H}]^+$

Example 16

3-(3-chloro-2-methoxyanilino)-2-(3-[[4-methylmorpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 1)



- 5 The title compound from example 15 (24.1 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 8 mg, at $R_t = 17.4 - 21.8$, 11 % yield) and enantiomer 2 (7 mg, at $R_t = 12.5 - 14.5$ min, see example 17).

Preparative chiral HPLC method:

Instrument: PrepCon Labomatic HPLC; Column: Chiralpak IF 5 μ , 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 50%A+50%B; flow: 40 ml/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC method:

Instrument: Waters Alliance 2695; Column: Chiralpak IF 3 μ , 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 50%A+50%B; flow: 1.4 ml/min; temperature: 25°C; UV: 280 nm

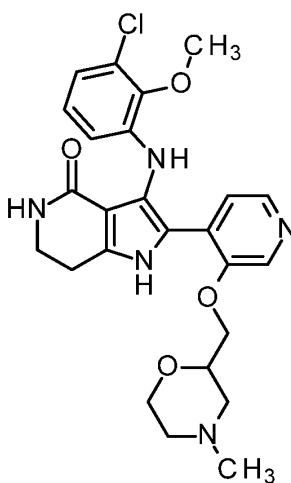
Analytical chiral HPLC : $R_t = 4.55$ min.

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ [ppm]= 1.232 (1.95), 1.259 (0.49), 1.888 (0.59), 1.914 (1.04), 1.941 (0.65), 2.016 (0.40), 2.037 (0.73), 2.045 (0.70), 2.065 (0.49), 2.206 (9.36), 2.327 (0.42), 2.518 (1.60), 2.523 (1.15), 2.540 (16.00), 2.646 (0.75), 2.670 (0.96), 2.673 (0.98), 2.758 (0.81), 2.787 (0.77), 2.841 (1.13), 2.858 (2.36), 2.876 (1.27), 3.405 (0.89), 3.410 (0.98), 3.422 (1.69), 3.428 (1.67), 3.439 (0.85), 3.445 (0.77), 3.638 (0.41), 3.644 (0.49), 3.666 (0.89), 3.672 (0.89), 3.694 (0.54), 3.700 (0.52), 3.883 (15.90), 3.933 (0.86),

3.952 (0.89), 3.960 (1.15), 3.976 (0.47), 3.983 (0.40), 4.137 (0.82), 4.154 (0.74), 4.163 (1.02), 4.179 (0.84), 4.315 (0.97), 4.324 (1.01), 4.341 (0.80), 4.349 (0.72), 6.139 (1.35), 6.151 (2.23), 6.163 (1.38), 6.681 (4.49), 6.692 (3.40), 6.694 (3.35), 7.163 (1.58), 7.274 (1.81), 7.287 (1.83), 7.533 (3.41), 8.021 (1.20), 8.034 (1.14), 8.402 (1.87), 11.066 (1.70).

5 **Example 17**

3-(3-chloro-2-methoxyanilino)-2-(3-[[4-methylmorpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 2)

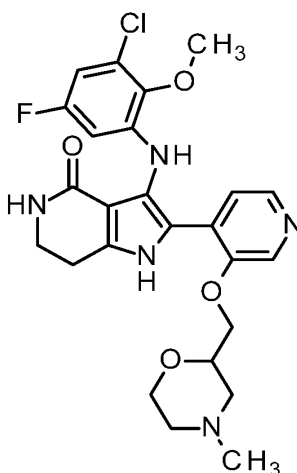


For the preparation of the racemic title compound see example 15. Separation of enantiomers by preparative chiral HPLC (method see example 16) to give 7 mg of the title compound (at $R_t = 12.5 - 14.5$ min).

Analytical chiral HPLC (method see example 16): $R_t = 2.93$ min.

Example 18

3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-([4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



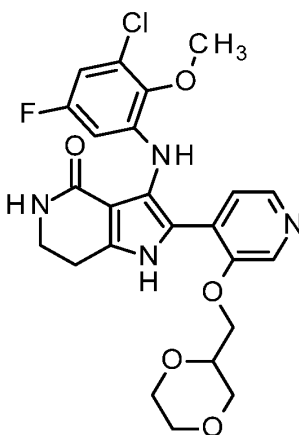
- 5 Using an analogous method as described for example 1 with *N*-(3-chloro-5-fluoro-2-methoxyphenyl)-4-[(3-([4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-18, 166 mg, 302 μ mol) as the starting material; 13.0 mg (95 % purity, 8 % yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.88 (t, 1H), 1.93 - 2.05 (dt, 1H), 2.19 (s, 3H), 2.60 - 2.66 (d, 1H), 2.70 - 2.77 (d, 1H), 2.86 (t, 2H), 3.37 - 3.48 (m, 2H), 3.56 - 3.68 (m, 1H), 3.83 (s, 3H), 3.90 (br d, 2H), 4.15 (m, 1H), 4.27 (dd, 1H), 5.85 (dd, 1H), 6.56 (dd, 1H), 7.13 (s, 1H), 7.33 (d, 1H), 7.64 (s, 1H), 8.10 (d, 1H), 8.43 (s, 1H), 11.18 (s, 1H).

- 15 LC-MS (method 2): R_t = 1.00 min; MS (ESIpos): m/z = 516 $[\text{M}+\text{H}]^+$

Example 19

3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



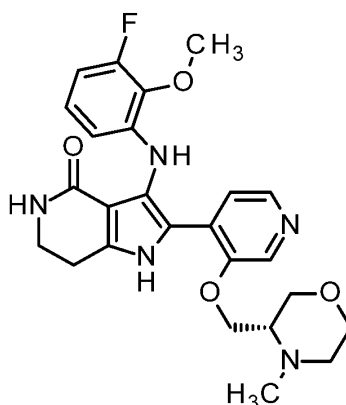
- 5 Using an analogous method as described for example 1 with *N*-(3-chloro-5-fluoro-2-methoxyphenyl)-4-[(3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-19, 160 mg, 298 μ mol) as the starting material; 3.90 mg (90 % purity, 2 % yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 2.86 (t, 2H), 3.37 - 3.45 (m, 3H), 3.47 - 3.61 (m, 1H), 3.62 - 3.77 (m, 3H), 3.77 - 3.87 (m, 6H), 3.94 - 4.01 (m, 1H), 4.07 - 4.20 (m, 1H), 4.24 (dd, 1H), 5.85 (dd, 1H), 6.56 (dd, 1H), 7.13 (s, 1H), 7.33 (d, 1H), 7.60 - 7.66 (d, 1H), 8.11 (br d, 1H), 8.42 (s, 1H), 11.19 (s, 1H).

- 15 LC-MS (method 2): R_t = 1.01 min; MS (ESIpos): m/z = 503 $[\text{M}+\text{H}]^+$

Example 20

3-(3-fluoro-2-methoxyanilino)-2-(3-[[[(3*S*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



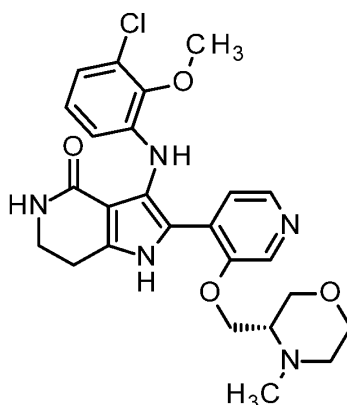
- 5 Using an analogous method as described for example 1 with *N*-(3-fluoro-2-methoxyphenyl)-4-[[[(3-[[[(3*S*)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-20, 102 mg, 197 μ mol) as the starting material; 27.9 mg (90 % purity, 26 % yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 10% B, 0.50 – 6.00 min 10 – 50% B).

LC-MS (method 6): R_t = 0.51 min; MS (ESIpos): m/z = 482 $[M+H]^+$

- ¹H-NMR (400 MHz, DMSO-*d*₆) δ [ppm]: 2.274 (13.29), 2.304 (1.76), 2.318 (0.55), 2.404 (0.46), 2.426 (0.88), 2.434 (0.91), 2.449 (0.43), 2.454 (0.88), 2.458 (1.03), 2.463 (1.43), 2.468 (1.37), 2.473 (1.55), 2.518 (5.99), 2.523 (4.32), 2.775 (0.40), 2.798 (0.70), 2.815 (1.49), 2.822 (0.88), 2.832 (0.91), 2.841 (1.16), 2.858 (0.79), 2.908 (1.13), 2.938 (1.00), 3.294 (0.43), 3.406 (0.64), 3.423 (1.46), 3.429 (1.19), 3.438 (1.37), 3.453 (0.58), 3.459 (0.55), 3.546 (1.13), 3.573 (1.76), 3.589 (1.13), 3.594 (1.22), 3.600 (1.28), 3.618 (0.61), 3.816 (0.94), 3.840 (1.83), 3.847 (1.95), 3.868 (1.06), 3.875 (0.97), 3.938 (16.00), 3.951 (2.07), 4.374 (1.67), 4.386 (2.71), 4.414 (0.46), 6.011 (1.89), 6.031 (1.89), 6.514 (1.03), 6.518 (0.97), 6.535 (1.28), 6.539 (1.34), 6.541 (1.19), 6.545 (0.94), 6.562 (1.19), 6.565 (1.06), 6.655 (0.97), 6.670 (1.03), 6.675 (1.70), 6.691 (1.55), 6.696 (0.82), 6.711 (0.67), 7.176 (2.07), 7.310 (3.71), 7.323 (3.68), 7.514 (0.43), 7.527 (0.52), 7.533 (0.58), 7.601 (4.56), 7.977 (5.29), 7.990 (4.50), 8.067 (0.61), 8.080 (0.55), 8.358 (6.27), 8.439 (0.73), 12.011 (2.13).

Example 21

3-(3-chloro-2-methoxyanilino)-2-(3-[[[(3S)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



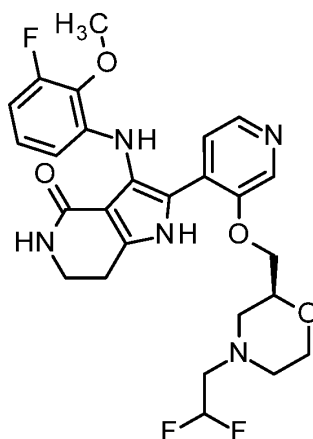
- 5 Using an analogous method as described for example 1 with *N*-(3-chloro-2-methoxyphenyl)-4-[[[(3-[[[(3S)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-21, 99.5 mg, 187 μ mol) as the starting material; 4.70 mg (98 % purity, 5 % yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 10%
10 B, 0.50 – 6.00 min 10 – 50% B).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.232 (0.45), 2.276 (9.36), 2.426 (0.63), 2.434 (0.67), 2.456 (0.51), 2.464 (0.76), 2.472 (0.79), 2.518 (1.95), 2.523 (1.26), 2.539 (9.95), 2.806 (0.54), 2.823 (1.37), 2.841 (1.19), 2.860 (0.60), 2.910 (0.85), 2.940 (0.76), 3.408 (0.49), 3.425 (1.12), 3.431 (0.95), 3.441 (1.04), 3.454 (0.49), 3.460 (0.44), 3.544 (0.71),
15 3.572 (1.31), 3.588 (0.84), 3.594 (0.92), 3.599 (0.96), 3.617 (0.47), 3.817 (0.72), 3.841 (1.23), 3.847 (1.34), 3.868 (0.69), 3.875 (0.63), 3.912 (16.00), 3.924 (0.49), 4.376 (1.24), 4.387 (2.11), 6.151 (1.35), 6.162 (2.22), 6.175 (1.39), 6.718 (3.50), 6.720 (3.93), 6.731 (4.23), 7.179 (1.54), 7.299 (2.18), 7.312 (2.21), 7.614 (3.34), 7.983 (1.76), 7.995 (1.68), 8.362 (2.68), 12.027 (1.61).

20 LC-MS (method 6): R_t = 0.54 min; MS (ESIpos): m/z = 498 $[\text{M}+\text{H}]^+$

Example 22

2-(3-[[*(2S)*-4-(2,2-difluoroethyl)morpholin-2-yl]methoxy]pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



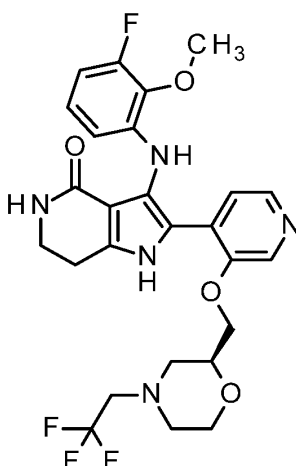
- 5 3-(3-Fluoro-2-methoxyanilino)-2-(3-[[*(2S)*-morpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (intermediate 22, 50.0 mg, 107 μ mol) was solubilized in DMF (1.6 ml), triethylamine (89 μ l, 640 μ mol) and 2,2-difluoroethyl trifluoromethanesulfonate (64 μ l, 480 μ mol) were added and the mixture was stirred for 1h at RT. The mixture was purified by preparative HPLC (method 10, gradient: 0.00 – 0.50 min
10 15% B, 0.50 – 6.00 min 15 – 55% B) to give 11.3 mg (90 % purity, 18 % yield) of the target compound.

$^1\text{H-NMR}$ (400MHz, $\text{DMSO-}d_6$): δ [ppm]= 2.24 (t, 1H), 2.34 - 2.40 (dd, 1H), 2.78 (m, 1H), 2.78 - 2.81 (m, 1H), 2.83 (m, 1H), 2.85 - 2.90 (t, 2H), 2.90 - 2.97 (d, 1H), 3.38 - 3.47 (m, 2H), 3.68 (dt, 1H), 3.89 - 3.92 (s, 3H), 3.92 - 4.03 (m, 2H), 4.17 (dd, 1H), 4.29 (dd, 1H), 5.97
15 - 6.02 (d, 1H), 6.02 - 6.34 (tt, 1H), 6.47 - 6.54 (m, 1H), 6.64 (td, 1H), 7.16 (s, 1H), 7.29 (d, 1H), 7.54 (s, 1H), 8.02 (d, 1H), 8.40 (s, 1H), 11.03 (s, 1H).

LC-MS (method 2): R_t = 1.04 min; MS (ESIpos): m/z = 532 $[\text{M}+\text{H}]^+$

Example 23

3-(3-fluoro-2-methoxyanilino)-2-(3-[(2S)-4-(2,2,2-trifluoroethyl)morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



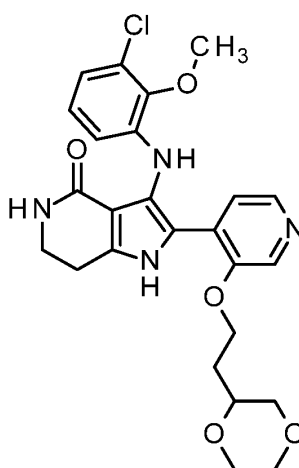
- 5 Using an analogous method as described for example 22 with 3-(3-fluoro-2-methoxyanilino)-2-(3-[(2S)-morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (intermediate 22, 35.0 mg, 74.9 μ mol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (CAS 6226-25-1, 16 μ l, 110 μ mol) as the starting materials; 11.9 mg (95 % purity, 27 % yield) of the title compound were prepared after preparative HPLC
10 (method 10, gradient: 0.00 – 0.50 min 30% B, 0.50 – 6.00 min 30 – 70% B).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.231 (0.47), 1.264 (0.47), 2.326 (2.22), 2.331 (1.58), 2.359 (0.93), 2.387 (1.69), 2.414 (1.15), 2.518 (7.61), 2.522 (5.31), 2.668 (2.30), 2.673 (1.58), 2.805 (1.18), 2.836 (2.55), 2.853 (3.44), 2.870 (1.79), 2.936 (1.26), 2.964 (1.11), 3.196 (0.54), 3.205 (0.61), 3.221 (1.54), 3.230 (1.58), 3.247 (1.51), 3.255 (1.47),
15 3.271 (0.61), 3.281 (0.54), 3.400 (1.26), 3.406 (1.33), 3.417 (2.37), 3.423 (2.26), 3.434 (1.15), 3.440 (1.08), 3.654 (0.54), 3.660 (0.65), 3.674 (0.72), 3.683 (1.18), 3.688 (1.15), 3.711 (0.68), 3.912 (16.00), 3.934 (1.11), 3.966 (1.11), 3.983 (0.72), 3.999 (0.75), 4.008 (0.65), 4.157 (1.04), 4.174 (1.00), 4.183 (1.51), 4.199 (1.22), 4.277 (1.40), 4.286 (1.36), 4.303 (1.04), 4.312 (0.86), 5.989 (1.94), 6.010 (1.97), 6.472 (0.86), 6.475 (0.86), 6.493
20 (1.26), 6.497 (1.26), 6.502 (0.93), 6.520 (1.18), 6.523 (1.04), 6.611 (0.90), 6.626 (1.04), 6.632 (1.54), 6.647 (1.51), 6.652 (0.75), 6.668 (0.65), 7.161 (2.22), 7.278 (3.52), 7.291 (3.55), 7.535 (4.77), 8.018 (4.38), 8.030 (4.02), 8.391 (6.17), 11.018 (2.48).

LC-MS (method 2): R_t = 1.09 min; MS (ESIpos): m/z = 550 $[\text{M}+\text{H}]^+$

Example 24

3-(3-chloro-2-methoxyanilino)-2-{3-[2-(4-dioxan-2-yl)ethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

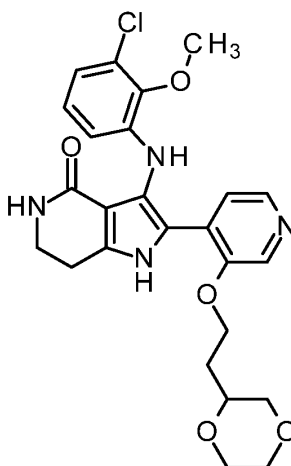


- 5 Using an analogous method as described for example 1 with *N*-(3-chloro-2-methoxyphenyl)-4-[(3-[2-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl)methyl]amino)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide(intermediate 6-24, 105 mg, 197 μ mol) as the starting material; 43.5 mg (95 % purity, 42 % yield) of the title compound were prepared after preparative HPLC (method 7).
- 10 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.817 (0.39), 1.834 (1.18), 1.849 (1.57), 1.861 (1.08), 1.876 (0.49), 2.518 (3.04), 2.522 (2.06), 2.673 (0.59), 2.833 (0.88), 2.846 (1.87), 2.863 (0.98), 3.204 (0.88), 3.231 (1.47), 3.260 (1.08), 3.312 (1.28), 3.396 (1.67), 3.408 (2.16), 3.413 (2.16), 3.426 (1.28), 3.456 (1.18), 3.462 (1.08), 3.484 (0.98), 3.490 (0.98), 3.521 (0.79), 3.525 (0.88), 3.549 (1.08), 3.554 (1.18), 3.582 (0.69), 3.625 (1.28), 3.648 (1.37), 3.668 (2.45), 3.678 (0.98), 3.693 (1.37), 3.716 (1.28), 3.745 (0.98), 3.858 (16.00), 4.226 (1.37), 4.241 (2.94), 4.257 (1.37), 6.103 (1.47), 6.115 (2.06), 6.127 (1.47), 6.640 (5.60), 6.650 (3.63), 7.108 (1.77), 7.287 (2.65), 7.299 (2.75), 7.458 (3.93), 8.020 (3.04), 8.033 (2.85), 8.350 (4.32), 11.191 (1.96).
- 15

LC-MS (method 6): R_t = 0.68 min; MS (ESIpos): m/z = 499 $[\text{M}+\text{H}]^+$

Example 25

3-(3-chloro-2-methoxyanilino)-2-{3-[2-(4-dioxan-2-yl)ethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (stereoisomer 1)



- 5 The title compound from example 24 (40 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 18.0 mg, at R_t = 18.8 – 21.3 min, 96 % purity) and enantiomer 2 (17 mg, at R_t = 21.7 – 24.5 min, see example 26).

Preparative chiral HPLC method:

- Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5 μ , 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile + 0.1 vol % diethylamine; gradient: 0-20 min 2-60% B; flow: 40 ml/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC method:

- Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3 μ , 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; gradient: 0-7 min 2-60% B; flow: 1.4 ml/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC: R_t = 4.94 min.

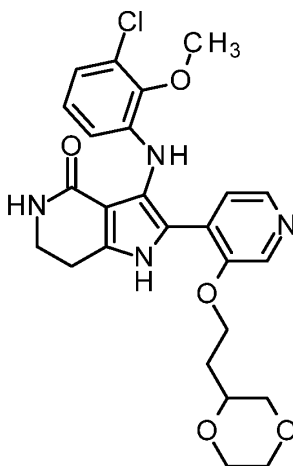
Optical rotation: $[\alpha]_D = -1.6^\circ \pm 1.63^\circ$ (c = 2,8 mg/ml in methanol)

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]= 1.835 (1.01), 1.851 (1.31), 1.862 (0.93), 1.877 (0.41), 2.518 (1.52), 2.522 (0.99), 2.834 (0.77), 2.846 (1.61), 2.852 (1.47), 2.864 (0.82), 2.869 (0.80), 3.205 (0.76), 3.231 (1.30), 3.235 (1.27), 3.261 (0.85), 3.391 (0.83), 3.397 (0.91), 3.408 (1.57), 3.415 (1.62), 3.430 (0.98), 3.457 (0.99), 3.463 (1.01), 3.485 (0.84), 3.491 (0.79), 3.522 (0.72), 3.527 (0.76), 3.551 (0.96), 3.556 (1.07), 3.584 (0.57), 3.624

- (1.00), 3.649 (1.11), 3.654 (1.11), 3.671 (1.96), 3.680 (0.81), 3.687 (0.53), 3.695 (1.23), 3.718 (1.09), 3.723 (1.01), 3.747 (0.79), 3.859 (16.00), 4.227 (1.22), 4.242 (2.58), 4.258 (1.21), 6.105 (1.40), 6.118 (1.81), 6.129 (1.46), 6.641 (5.45), 6.651 (3.33), 6.654 (3.12), 7.110 (1.60), 7.288 (2.35), 7.300 (2.36), 7.306 (0.49), 7.462 (3.57), 8.023 (2.38), 8.035 (2.27), 8.353 (3.43), 11.186 (1.77).

Example 26

3-(3-chloro-2-methoxyanilino)-2-{3-[2-(4-dioxan-2-yl)ethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (Stereoisomer 2)



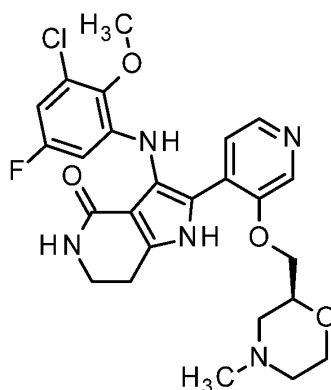
- 10 For the preparation of the racemic title compound see example 24. Separation of enantiomers by preparative chiral HPLC (method see example 25) to give 25 mg of the title compound (at $R_t = 21.7 - 24.5$ min, 19 % yield).

Analytical chiral HPLC (method see example 25): $R_t = 5.49$ min.

Optical rotation: $[\alpha]_D = 2.5^\circ \pm 1.93^\circ$ ($c = 2.7$ mg/ml in methanol)

Example 27

3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-[[2-(S)-4-methylmorpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



- 5 3-(3-Chloro-5-fluoro-2-methoxyanilino)-2-(3-[[2-(S)-morpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (intermediate 27, 24.0 mg, 47.8 μ mol) was solubilized in methanol (650 μ l), formaldehyde (7.2 μ l, 37 % purity, 96 μ mol) and acetic acid (2.7 μ l, 48 μ mol) were added and the mixture was stirred for 15 min at RT. Sodium triacetoxyborohydride (15.2 mg, 71.7 μ mol) was added and the mixture was stirred for 1h
- 10 at RT. The mixture was diluted with methanol, filtered through a SCX column and washed with methanol and ammonia (7 M in methanol). The filtrate was evaporated and purified by preparative HPLC (method 9, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B) to yield 17.3 mg (95 % purity, 61 % yield) of the title compound as its formate salt.

LC-MS (method 2): R_t = 1.01 min; MS (ESIpos): m/z = 516 $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ [ppm]: 2.189 (13.49), 2.330 (5.06), 2.729 (5.60), 2.861 (7.86), 3.348 (16.00), 3.419 (15.57), 3.624 (4.81), 3.830 (14.46), 3.908 (6.49), 7.633 (4.30), 8.098 (4.59), 8.146 (8.39).

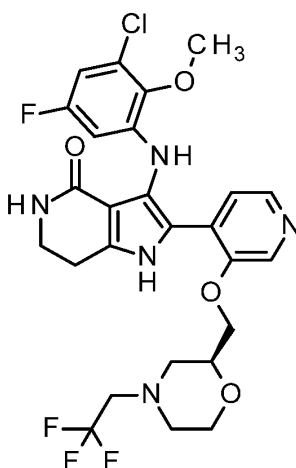
- 3-(3-chloro-5-fluoro-2-methoxy-anilino)-2-[3-[[2-(S)-4-methylmorpholin-4-ium-2-yl]methoxy]-4-pyridyl]-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one;formate were
- 20 solubilized in DCM and washed saturated aqueous NaHCO_3 and brine to yield 9.00 mg (90 % purity, 33 % yield) of the target compound as its free base.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.79 - 1.96 (t, 1H), 1.97 - 2.05 (td, 1H), 2.19 (s, 3H), 2.63 (br d, 1H), 2.71 - 2.82 (br d, 1H), 2.86 (t, 2H), 3.43 (td, 2H), 3.58 - 3.67 (m, 1H),

3.83 (s, 3H), 3.87 - 4.01 (m, 2H), 4.14 (dd, 1H), 4.29 (dd, 1H), 5.85 (dd, 1H), 6.56 (dd, 1H), 7.13 (s, 1H), 7.33 (d, 1H), 7.64 (d, 1H), 8.07 - 8.12 (d, 1H), 8.43 (s, 1H), 11.18 (s, 1H).

Example 28

3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-[[*(2S)*-4-(2,2,2-trifluoroethyl)morpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



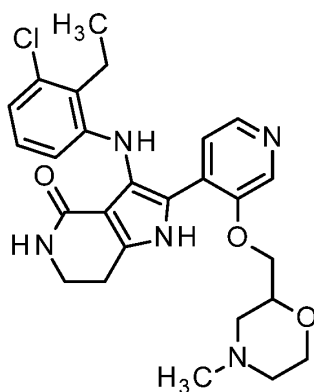
Using an analogous method as described for example 22 with 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-[[*(2S)*-morpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (intermediate 27, 25.0 mg, 49.8 μ mol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (CAS 6226-25-1, 11 μ l, 75 μ mol) as the starting materials; 15.1 mg (95 % purity, 49 % yield) of the title compound were prepared after preparative HPLC (method 10, gradient: 0.00 – 0.50 min 30% B, 0.50 – 6.00 min 30 – 70% B).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 2.35 (t, 1H), 2.77 - 2.95 (m, 4H), 3.21 (dd, 2H), 3.42 (td, 2H), 3.60 - 3.69 (m, 1H), 3.83 (s, 3H), 3.88 - 4.01 (m, 2H), 4.14 - 4.28 (m, 2H), 5.84 (dd, 1H), 6.56 (dd, 1H), 7.13 (s, 1H), 7.32 (d, 1H), 7.62 - 7.66 (m, 1H), 8.10 (d, 1H), 8.43 (s, 1H), 11.16 (s, 1H).

LC-MS (method 2): R_t = 1.19 min; MS (ESIpos): m/z = 584 [M+H]⁺

Example 29

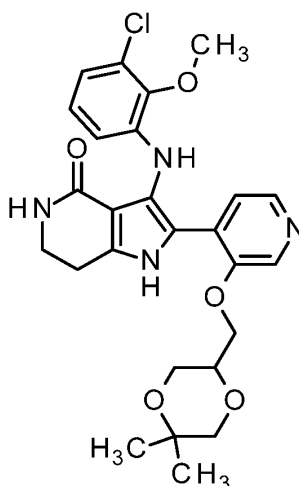
3-(3-chloro-2-ethylphenyl)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



- 5 Using an analogous method as described for example 1 with *N*-(3-chloro-2-ethylphenyl)-4-[[{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-29, 300 mg, 566 μ mol) as the starting material; 3.00 mg (85 % purity, 1 % yield) of the title compound were prepared after preparative HPLC (method 10, gradient: 0.00 – 0.50 min 30% B, 0.50 – 6.00 min 30 – 70% B).
- 10 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 0.851 (0.47), 1.210 (0.41), 1.230 (2.24), 1.352 (0.41), 2.206 (1.49), 2.331 (2.92), 2.336 (1.36), 2.518 (16.00), 2.522 (10.31), 2.539 (1.02), 2.673 (3.05), 2.678 (1.42), 2.864 (0.41), 6.728 (0.41), 6.735 (0.47), 7.188 (0.47), 7.201 (0.47), 7.962 (0.54), 7.975 (0.47), 8.365 (0.68).
- 15 LC-MS (method 2): R_t = 1.07 min; MS (ESIpos): m/z = 496 [M+H]⁺

Example 30

3-(3-chloro-2-methoxyanilino)-2-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-
1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



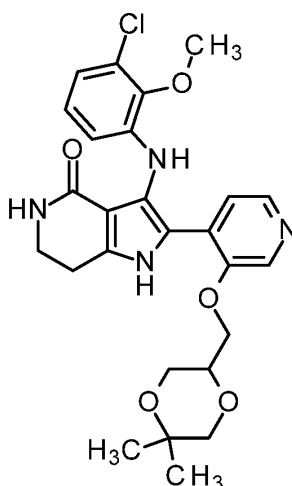
- 5 Using an analogous method as described for example 1 with *N*-(3-chloro-2-methoxyphenyl)-4-[(3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-30, 55.0 mg, 101 μ mol) as the starting material; 28.00 mg (98 % purity, 53 % yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 30%
10 B, 0.50 – 6.00 min 30 – 70% B).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.066 (9.57), 1.234 (8.81), 2.074 (0.42), 2.326 (1.06), 2.331 (0.74), 2.518 (3.90), 2.522 (2.65), 2.668 (1.04), 2.673 (0.76), 2.819 (1.08), 2.837 (2.21), 2.853 (1.18), 3.398 (1.96), 3.409 (1.62), 3.416 (1.61), 3.427 (2.05), 3.580 (0.57), 3.588 (0.65), 3.609 (1.17), 3.618 (1.13), 3.629 (1.85), 3.654 (1.43), 3.657 (1.70),
15 3.679 (1.32), 3.709 (0.74), 3.868 (16.00), 3.894 (0.49), 3.902 (0.53), 3.910 (0.64), 3.918 (0.58), 3.927 (0.42), 4.155 (0.76), 4.171 (0.72), 4.181 (1.01), 4.198 (0.88), 4.295 (0.97), 4.304 (0.99), 4.322 (0.76), 4.330 (0.67), 6.143 (1.40), 6.155 (1.71), 6.167 (1.40), 6.653 (0.46), 6.663 (5.26), 6.673 (3.14), 6.676 (2.88), 7.138 (1.48), 7.270 (2.51), 7.283 (2.51), 7.475 (3.39), 8.033 (3.36), 8.045 (2.98), 8.404 (4.26), 11.073 (1.66).

20 LC-MS (method 6): R_t = 0.80 min; MS (ESIpos): m/z = 513 $[\text{M}+\text{H}]^+$

Example 31

3-(3-chloro-2-methoxyanilino)-2-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (Stereoisomer 1)



- 5 The title compound from example 30 (26.3 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 11.00 mg, at R_t = 10.7 – 13.4 min) and enantiomer 2 (10 mg, at R_t = 14.0 – 19.9 min, see example 32).

Preparative chiral HPLC method:

- Instrument: PrepCon Labomatic HPLC; Column: Chiralcel OD-H 5 μ , 250x20; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 70%A+30%B; flow: 20 ml/min; temperature: 25°C; UV: 280 nm
- 10

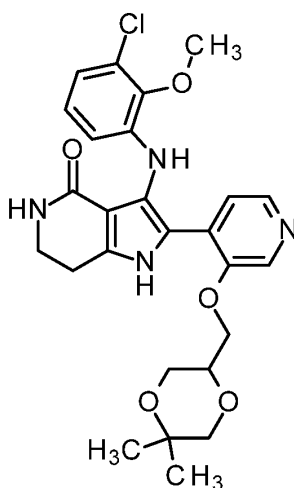
Analytical chiral HPLC method:

- Instrument: Waters Alliance 2695; Column: Chiralcel OD-H 5 μ , 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 1.4 ml/min; temperature: 25°C; UV: 280 nm
- 15

Analytical chiral HPLC: R_t = 6.72 min.

Example 32

3-(3-chloro-2-methoxyanilino)-2-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (Stereoisomer 2)

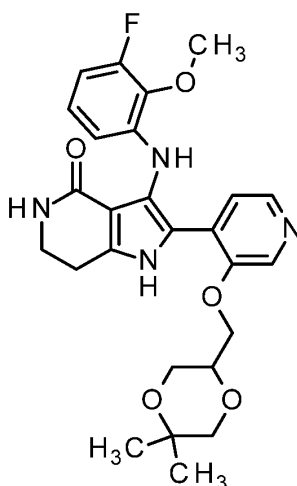


- 5 For the preparation of the racemic title compound see example 30. Separation of enantiomers by preparative chiral HPLC (method see example 31) to give 10 mg of the title compound (at $R_t = 14.0 - 19.9$ min).

Analytical chiral HPLC (method see example 31): $R_t = 10.04$ min.

Example 33

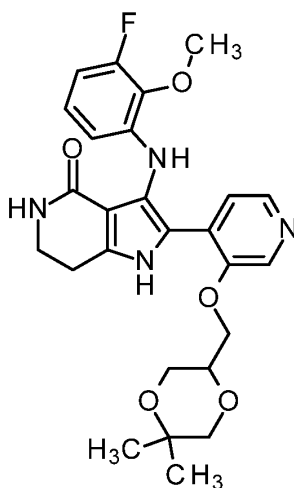
2-(3-[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



- 5 Using an analogous method as described for example 1; 4-[[3-[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino]-N-(3-fluoro-2-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-33, 125 mg, 236 μ mol) as the starting material, 15.00 mg (80 % purity, 10 % yield) of the title compound were prepared after preparative HPLC (method 7).
- 10 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.068 (15.53), 1.236 (15.37), 2.517 (2.98), 2.522 (2.00), 2.817 (1.52), 2.834 (3.10), 2.851 (1.65), 2.903 (0.47), 2.921 (0.89), 2.936 (0.48), 3.402 (2.87), 3.408 (2.55), 3.415 (2.29), 3.431 (3.39), 3.580 (0.97), 3.588 (1.12), 3.609 (2.52), 3.618 (2.17), 3.633 (3.03), 3.651 (2.10), 3.661 (2.34), 3.677 (2.32), 3.706 (1.26), 3.900 (16.00), 3.917 (5.39), 3.933 (0.80), 3.942 (0.71), 4.147 (1.18), 4.163 (1.12), 4.173 (1.56), 4.189 (1.34), 4.294 (1.63), 4.302 (1.37), 4.320 (1.26), 4.329 (0.93), 4.769 (0.55), 4.780 (0.55), 4.787 (0.58), 4.797 (0.52), 5.696 (0.85), 5.759 (1.92), 5.985 (0.55), 6.000 (1.88), 6.020 (1.84), 6.455 (0.97), 6.476 (1.43), 6.479 (1.49), 6.503 (1.30), 6.597 (0.86), 6.612 (1.11), 6.618 (1.49), 6.625 (0.60), 6.633 (1.47), 6.638 (0.71), 6.653 (0.62), 7.141 (2.11), 7.277 (3.15), 7.289 (3.21), 7.297 (1.00), 7.479 (4.43), 7.531 (1.26), 8.030 (3.74), 8.042 (3.54), 8.399 (6.35), 11.053 (2.30), 11.085 (0.73).
- 20

LC-MS (method 6): R_t = 0.71 min; MS (ESIpos): m/z = 497 $[\text{M}+\text{H}]^+$

2-(3-([5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (Stereoisomer 1)



The title compound from example 33 (15.0 mg) was separated into enantiomers by
5 preparative chiral HPLC to give title compound (enantiomer 1, 5.00 mg, at R_t = 10.9 – 13.1
min, 32 % yield) and enantiomer 2 (4 mg, at R_t = 13.5 – 18.3 min, see example 34).

Preparative chiral HPLC method:

Instrument: PrepCon Labomatic HPLC; Column: Chiralcel OD-H 5 μ , 250x20; eluent A:
hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 20 ml/min;
10 temperature: 25°C; UV: 280 nm

Analytical chiral HPLC method:

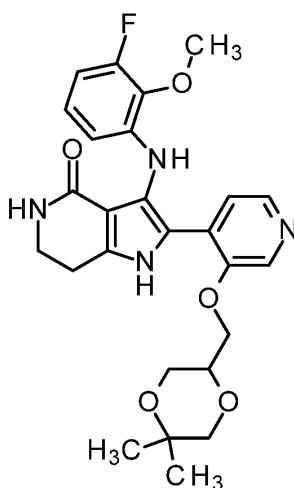
Instrument: Waters Alliance 2695; Column: Chiralcel OD-H 5 μ , 100x4.6; eluent A: hexane
+ 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 1.4 ml/min;
temperature: 25°C; UV: 280 nm

15 Analytical chiral HPLC: R_t = 6.58 min.

Optical rotation: $[\alpha]_D = 2.6^\circ \pm 1.66^\circ$ (c = 2,3 mg/ml in methanol)

Example 34

2-(3-[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 2)



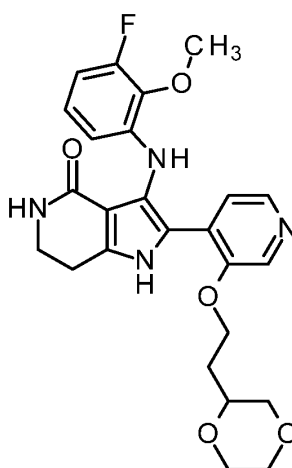
- 5 For the preparation of the racemic title compound see example 33. Separation of enantiomers by preparative chiral HPLC (method see example 33) to give 4 mg of the title compound (at $R_t = 13.5 - 18.3$ min, 24 % yield).

Analytical chiral HPLC (method see example 33): $R_t = 9.21$ min.

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.046 (0.67), 1.068 (13.52), 1.108 (0.86), 1.185 (0.55), 1.236 (13.07), 1.259 (0.64), 2.084 (0.44), 2.331 (0.49), 2.518 (2.88), 2.523 (1.93), 2.673 (0.47), 2.817 (1.52), 2.834 (3.11), 2.851 (1.67), 3.403 (2.57), 3.409 (2.57), 3.416 (2.39), 3.431 (2.89), 3.581 (0.83), 3.589 (0.95), 3.611 (1.68), 3.618 (1.66), 3.633 (2.61), 3.652 (1.72), 3.661 (2.23), 3.678 (1.86), 3.707 (1.00), 3.901 (16.00), 3.917 (1.07), 3.926 (0.91), 3.934 (0.65), 3.943 (0.58), 4.148 (1.01), 4.165 (0.96), 4.174 (1.36), 4.190 (1.18), 4.294 (1.36), 4.303 (1.36), 4.320 (1.03), 4.329 (0.91), 6.000 (1.83), 6.021 (1.91), 6.455 (0.83), 6.459 (0.87), 6.476 (1.19), 6.480 (1.27), 6.486 (0.94), 6.503 (1.10), 6.506 (1.01), 6.597 (0.86), 6.612 (1.01), 6.618 (1.47), 6.633 (1.44), 6.638 (0.75), 6.654 (0.61), 7.141 (2.15), 7.277 (2.70), 7.290 (2.68), 7.479 (4.53), 8.030 (2.67), 8.043 (2.48), 8.400 (4.07), 11.054 (2.33).

Example 35

2-(3-{2-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 1)



- 5 Using an analogous method as described for example 1 with 4-[[3-{2-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)methyl]amino]-N-(3-fluoro-2-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-35, 130 mg, 252 μ mol) as the starting material, 30.0 mg (90 % purity, 22 % yield) of the racemic title compound were prepared after preparative HPLC (method 7).
- 10 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm]= 1.229 (0.48), 1.827 (0.71), 1.843 (1.74), 1.859 (2.06), 1.869 (1.50), 1.885 (0.63), 2.331 (0.40), 2.517 (2.30), 2.522 (1.50), 2.539 (4.51), 2.669 (0.55), 2.673 (0.48), 2.831 (1.19), 2.842 (2.22), 2.848 (2.06), 2.858 (1.19), 2.865 (1.11), 3.162 (1.27), 3.174 (0.71), 3.207 (1.35), 3.233 (2.14), 3.236 (2.14), 3.262 (1.58), 3.406 (4.44), 3.412 (3.88), 3.428 (2.22), 3.456 (1.90), 3.462 (1.82), 3.484 (1.50), 3.490 (1.50), 3.522 (1.27), 3.527 (1.35), 3.550 (1.66), 3.556 (1.90), 3.578 (0.95), 3.583 (1.27), 3.624 (2.22), 3.651 (2.14), 3.671 (3.25), 3.681 (1.50), 3.695 (2.22), 3.700 (1.98), 3.716 (2.06), 3.721 (1.98), 3.728 (1.35), 3.745 (1.50), 3.780 (0.71), 3.862 (0.95), 3.889 (16.00), 3.906 (1.19), 4.074 (0.71), 4.222 (2.14), 4.238 (3.96), 4.253 (1.82), 4.754 (0.55), 5.960 (1.98), 5.981 (1.98), 6.430 (0.95), 6.433 (0.95), 6.451 (1.43), 6.455 (1.43), 6.461 (0.95), 6.478 (1.19), 6.482 (1.11), 6.572 (0.95), 6.587 (1.11), 6.593 (1.58), 6.608 (1.58), 6.613 (0.79), 6.628 (0.63), 7.108 (2.30), 7.292 (2.77), 7.305 (2.77), 7.455 (4.67), 8.017 (2.61), 8.030 (2.46), 8.344 (4.04), 11.175 (2.46).
- 20

LC-MS (method 6): R_t = 0.63 min; MS (ESIpos): m/z = 483 $[\text{M}+\text{H}]^+$

- Racemic 2-(3-{2-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (25.0 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 12.00 mg, at $R_t = 15.1 - 17.0$ min,) and enantiomer 2 (4 mg, at $R_t = 19.8 - 26.8$ min, see example 36).

Preparative chiral HPLC method:

Instrument: PrepCon Labomatic HPLC; Column: Chiralpak IF 5 μ , 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 70%A+30%B; flow: 50 ml/min; temperature: 25°C; UV: 280 nm

10 Analytical chiral HPLC method:

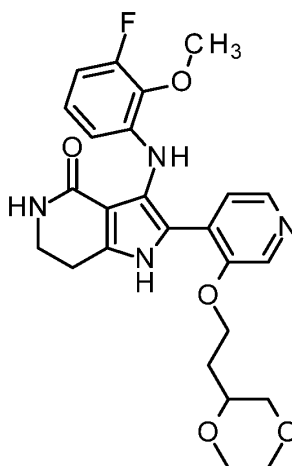
Instrument: Waters Alliance 2695; Column: Chiralpak IF 3 μ , 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 1.4 ml/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC: $R_t = 4.68$ min.

- 15 Optical rotation: $[\alpha]_D = -12.9^\circ \pm 1.72^\circ$ (c = 1,4 mg/ml in methanol)

Example 36

2-(3-{2-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (Stereoisomer 2)



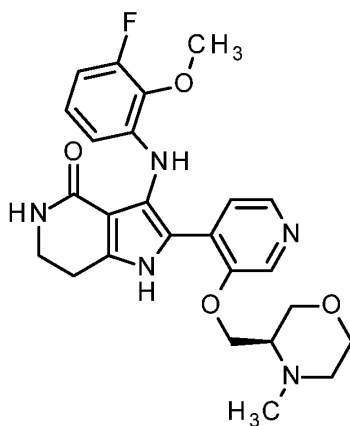
For the preparation of the racemic title compound see example 35. Separation of enantiomers by preparative chiral HPLC (method see example 35) gave 4 mg of the title compound (at $R_t = 19.8 - 26.8$ min).

Analytical chiral HPLC (method see example 35): $R_t = 6.58$ min.

- 5 Optical rotation: $[\alpha]_D = -21.4^\circ \pm 1.94^\circ$ ($c = 1,3$ mg/ml in methanol)

Example 37

3-(3-fluoro-2-methoxyanilino)-2-(3-[[[(3R)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



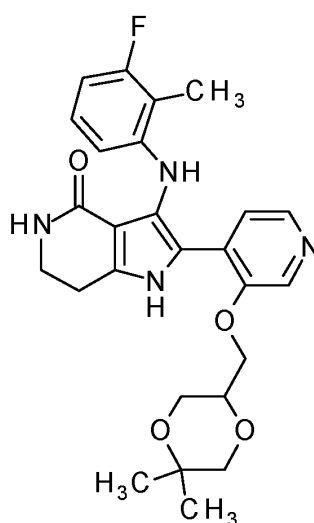
- 10 Using an analogous method as described for example 1; N-(3-fluoro-2-methoxyphenyl)-4-[[[3-[[[(3R)-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)methyl]amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-37, 130 mg, 252 μ mol) as the starting material, 35.00 mg (92% purity, 27% yield) of the title compound were prepared after preparative HPLC (method 7).
- 15 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm]= 2.277 (13.00), 2.292 (1.54), 2.307 (0.96), 2.324 (0.70), 2.329 (0.89), 2.334 (0.66), 2.407 (0.69), 2.428 (1.27), 2.435 (1.36), 2.520 (2.98), 2.525 (1.88), 2.667 (0.63), 2.671 (0.83), 2.676 (0.62), 2.777 (0.67), 2.801 (0.82), 2.818 (1.61), 2.825 (0.99), 2.835 (1.02), 2.844 (1.23), 2.860 (0.82), 2.911 (1.23), 2.940 (1.09), 3.388 (0.53), 3.408 (0.96), 3.425 (1.66), 3.431 (1.41), 3.441 (1.54), 3.455 (0.69), 3.548 (1.12), 3.576 (1.89), 3.592 (1.35), 3.597 (1.35), 3.602 (1.33), 3.621 (0.70), 3.626 (0.70), 3.783 (1.37), 3.785 (1.33), 3.818 (1.11), 3.843 (1.97), 3.849 (2.06), 3.870 (1.11), 3.878 (0.99), 3.941 (16.00), 3.954 (1.12), 4.078 (0.56), 4.349 (0.43), 4.358 (0.42), 4.376 (1.85), 4.388 (2.91), 4.416 (0.47), 6.013 (1.90), 6.034 (1.91), 6.516 (0.95), 6.520 (0.92), 6.537
- 20

(1.27), 6.541 (1.33), 6.547 (0.95), 6.564 (1.12), 6.568 (1.03), 6.657 (0.94), 6.672 (1.04), 6.678 (1.61), 6.693 (1.51), 6.698 (0.80), 6.714 (0.65), 7.180 (2.21), 7.313 (3.72), 7.325 (3.57), 7.605 (4.51), 7.980 (4.40), 7.993 (4.17), 8.360 (6.21), 8.414 (0.59), 12.014 (2.24).

LC-MS (method 6): R_t = 0.51 min; MS (ESIpos): m/z = 482 $[M+H]^+$

5 Example 38

2-[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]-3-(3-fluoro-2-methyl-anilino)-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one



Using an analogous method as described for example 1; 4-[[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]methylamino]-*N*-(3-fluoro-2-methyl-phenyl)-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide (intermediate 6-38, 190 mg, 369 μ mol) as the starting material, 30.2 mg (98% purity, 17% yield) of the title compound were prepared after preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 5.59 min 15 – 51.7% B, 5.59 – 5.88 min 51.7% B, 5.88 – 5.93 min 51.7 – 52.1% B, 5.93 – 5.95 min 52.1% B, 5.95 – 6.32 min 52.1-55% B)

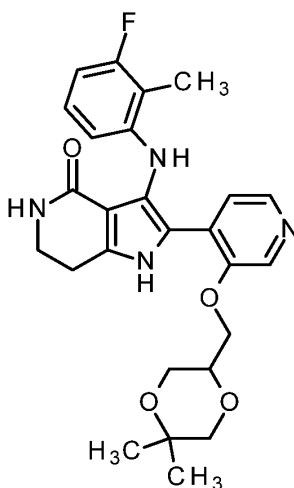
$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm] = 1.073 (16.00), 1.243 (14.37), 2.177 (9.43), 2.180 (9.37), 2.520 (3.20), 2.525 (2.30), 2.542 (0.63), 2.826 (1.74), 2.843 (3.73), 2.861 (2.01), 3.406 (3.15), 3.417 (2.63), 3.424 (2.71), 3.434 (3.36), 3.569 (0.91), 3.577 (1.10), 3.598 (1.87), 3.607 (1.84), 3.643 (4.40), 3.671 (4.37), 3.699 (1.24), 3.881 (0.69), 3.890 (0.81), 3.898 (1.03), 3.907 (0.94), 3.915 (0.67), 3.923 (0.65), 4.121 (1.26), 4.137 (1.17), 4.147 (1.71), 4.163 (1.45), 4.265 (1.62), 4.274 (1.65), 4.291 (1.24), 4.300 (1.11), 6.059 (2.34),

6.080 (2.42), 6.427 (1.06), 6.449 (1.94), 6.470 (1.21), 6.721 (0.73), 6.742 (1.51), 6.759 (1.47), 6.779 (0.63), 7.168 (2.42), 7.232 (4.19), 7.244 (4.24), 7.308 (4.82), 7.997 (5.22), 8.009 (4.80), 8.373 (6.80), 11.029 (2.61).

LC-MS (method 6): $R_t = 0.74$ min; MS (ESIpos): $m/z = 481$ $[M+H]^+$

5 **Example 39**

2-[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]-3-(3-fluoro-2-methyl-anilino)-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one (stereoisomer 1)



The title compound from example 38 (30.2 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 10.00 mg, $R_t = 30.4 - 36.0$ min, 5% yield) and enantiomer 2 (9 mg, $R_t = 45.9 - 51.7$ min).

Preparative chiral HPLC method: NPB

Instrument: PrepCon Labomatic HPLC; Column: Chiralpak IF 5 μ , 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 90%A+10%B; flow: 50 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC method: NPB

Instrument: Waters Alliance 2695; Column: Chiralpak IF 3 μ , 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 90%A+10%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

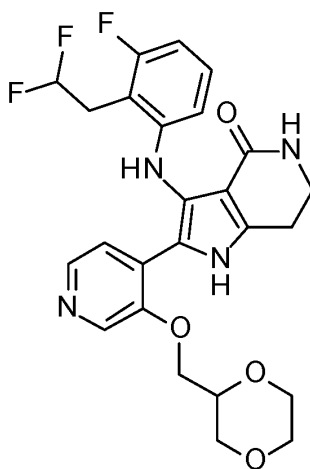
Analytical chiral HPLC: $R_t = 11.60$ min.

Optical rotation: $[\alpha]_D = -6.4^\circ \pm 0.47^\circ$ ($c = 6.2$ mg/ml in DMSO)

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 0.700 (5.10), 0.744 (1.84), 0.764 (1.85), 0.836 (0.93), 0.854 (1.20), 1.073 (15.11), 1.152 (5.69), 1.235 (8.54), 1.243 (16.00), 1.296 (2.78), 1.350 (0.95), 1.378 (0.62), 1.672 (0.88), 2.179 (9.59), 2.525 (2.28), 2.827 (1.75), 2.844 (3.61), 2.861 (1.95), 3.407 (3.22), 3.418 (2.68), 3.424 (2.72), 3.434 (3.38), 3.570 (0.86),
 5 3.578 (1.00), 3.599 (1.76), 3.607 (1.71), 3.644 (4.10), 3.671 (4.05), 3.700 (1.09), 3.882 (0.67), 3.890 (0.80), 3.899 (1.00), 3.907 (0.92), 3.915 (0.66), 3.924 (0.61), 4.121 (1.09), 4.138 (1.06), 4.147 (1.50), 4.164 (1.30), 4.267 (1.44), 4.275 (1.48), 4.292 (1.11), 4.301 (1.01), 6.060 (2.24), 6.080 (2.31), 6.428 (1.04), 6.450 (1.90), 6.472 (1.17), 6.722 (0.70), 6.742 (1.49), 6.759 (1.45), 6.780 (0.58), 6.959 (0.44), 7.170 (2.40), 7.201 (0.51), 7.222
 10 (0.55), 7.234 (1.95), 7.246 (1.95), 7.309 (4.47), 7.999 (1.12), 8.010 (1.08), 8.375 (1.57), 11.031 (2.61).

Example 40

3-[2-(2,2-difluoroethyl)-3-fluoro-anilino]-2-[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one



15

Using an analogous method as described for example 1 with N-[2-(2,2-difluoroethyl)-3-fluorophenyl]-4-[[3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino}-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-40, 19.5 mg, 36.3 μmol) as the starting material; 3.80 mg (92% purity, 19% yield) of the title compound were prepared after
 20 purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 30% B, 0.50 – 6.00 min 30 – 70% B).

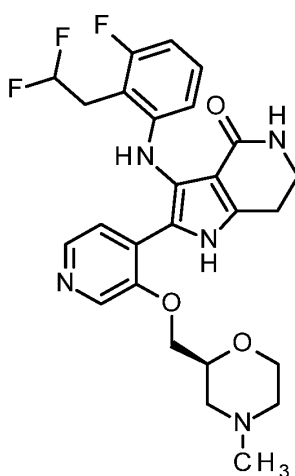
¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.86 (t, 2H), 3.22 - 3.30 (m, 1H), 3.39 - 3.48 (m, 3H), 3.50 - 3.58 (td, 1H), 3.67 - 3.93 (m, 5H), 3.97 - 4.06 (m, 1H), 4.09 - 4.18 (m, 1H), 4.25

- 4.31 (dd, 1H), 6.07 - 6.17 (d, 1H), 6.29 - 6.63 (q, 2H), 6.83 - 6.94 (m, 1H), 7.10 (s, 1H), 7.34 (s, 1H), 7.37 (d, 2H), 8.00 (d, 1H), 8.38 (s, 1H), 11.07 (s, 1H).

LC-MS (method 2): R_t = 0.99 min; MS (ESIpos): m/z = 503 $[M+H]^+$

Example 41

- 5 3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-2-(3-[[2-(2S)-4-methylmorpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



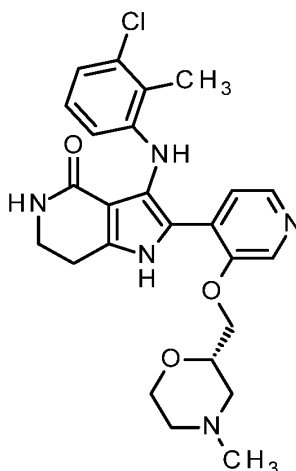
- 3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-2-(3-[[2-(2S)-morpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (intermediate 41, 22.0 mg, 43.9 μ mol) was suspended in MeOH, formaldehyde (6.6 μ l, 37% purity in water, 88 μ mol) and acetic acid (2.5 μ l, 44 μ mol) were added. The reaction mixture was stirred for 15 min at room temperature. Sodium triacetoxyborohydride (13.9 mg, 65.8 μ mol) was added the the mixture was stirred for 1h at room temperature. The mixture was filtered through a SCX column and washed with MeOH and ammonia (7M in MeOH). The ammonia filtrate was evaporated and purified by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50-6.00 min 15-55% B) to give 8.8 mg (90% purity, 35% yield) of the title compound.

- $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 2.07 (m, 3H), 2.22 (s, 3H), 2.63 - 2.83 (m, 2H), 2.86 (t, 2H), 3.27 - 3.31 (m, 1H), 3.35 - 3.38 (m, 1H), 3.42 (td, 2H), 3.68 (td, 1H), 3.91 - 4.00 (m, 2H), 4.12 - 4.19 (dd, 1H), 4.33 (dd, 1H), 6.13 (d, 1H), 6.29 - 6.64 (m, 1H), 6.89 (q, 1H), 7.07 - 7.14 (m, 1H), 7.33 - 7.40 (t, 2H), 7.99 (d, 1H), 8.39 (s, 1H), 11.07 (s, 1H).

LC-MS (method 2): R_t = 0.98 min; MS (ESIpos): m/z = 516 $[M+H]^+$

Example 42

3-(3-chloro-2-methylanilino)-2-(3-[(2*S*)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one

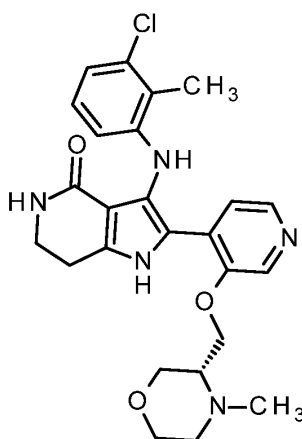


- 5 Using an analogous method as described for example 41 with 3-(3-chloro-2-methylanilino)-2-(3-[(2*S*)-morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (intermediate 42, 18.0 mg, 38.5 μ mol) as the starting material; 10.9 mg (94% purity, 55% yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).
- 10 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.234 (0.45), 1.874 (1.12), 1.901 (1.88), 1.928 (1.19), 2.006 (0.51), 2.015 (0.63), 2.035 (1.18), 2.043 (1.18), 2.064 (0.68), 2.072 (0.56), 2.207 (15.79), 2.324 (0.67), 2.329 (0.91), 2.334 (0.71), 2.338 (0.45), 2.357 (16.00), 2.374 (1.16), 2.520 (2.98), 2.525 (1.85), 2.647 (1.22), 2.671 (1.61), 2.676 (1.69), 2.736 (1.32), 2.764 (1.23), 2.847 (1.67), 2.865 (3.57), 2.882 (1.86), 3.411 (1.24), 3.417 (1.33), 3.428 (2.40), 3.434 (2.36), 3.445 (1.17), 3.451 (1.06), 3.639 (0.62), 3.645 (0.95), 3.667 (1.35), 3.672 (1.38), 3.695 (0.78), 3.701 (0.66), 3.937 (1.97), 3.960 (1.51), 4.111 (1.22), 4.128 (1.10), 4.137 (1.63), 4.153 (1.36), 4.253 (1.46), 4.262 (1.52), 4.279 (1.14), 4.287 (1.03), 6.190 (1.81), 6.194 (1.78), 6.209 (1.99), 6.213 (1.81), 6.722 (0.90), 6.726 (1.25), 6.742 (3.67), 6.746 (2.96), 6.753 (2.81), 6.773 (2.59), 6.792 (0.84), 7.190 (2.30), 7.232 (3.39), 7.244 (3.38), 7.377 (4.48), 7.990 (3.43), 8.003 (3.19), 8.370 (5.23), 11.051 (2.53).

LC-MS (method 6): R_t = 0.52 min; MS (ESIpos): m/z = 482 [M+H]⁺

Example 43

3-(3-chloro-2-methylanilino)-2-(3-[[*(3R)*-4-methylmorpholin-3-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one

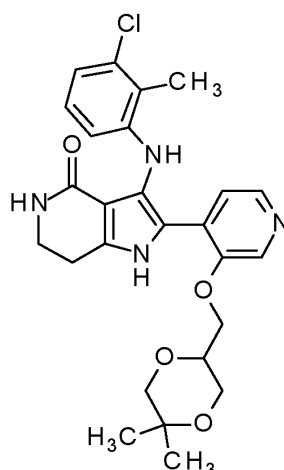


- 5 Using an analogous method as described for example 41 with 3-(3-chloro-2-methylanilino)-2-(3-[[*(3R)*-morpholin-3-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (30.0 mg, 64.1 μ mol) as the starting material; 7.0 mg (94% purity, 21% yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 15% B, 0.50 – 6.00 min 15 – 55% B).
- 10 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= -0.002 (3.00), 0.879 (0.57), 2.085 (5.27), 2.272 (14.21), 2.318 (0.47), 2.382 (16.00), 2.397 (1.43), 2.423 (1.05), 2.431 (1.10), 2.460 (1.63), 2.518 (5.17), 2.523 (3.38), 2.660 (0.46), 2.810 (0.81), 2.828 (2.27), 2.845 (1.96), 2.864 (0.87), 2.909 (1.32), 2.938 (1.16), 3.411 (0.70), 3.428 (1.64), 3.435 (1.37), 3.444 (1.50), 3.464 (0.63), 3.540 (1.08), 3.568 (2.41), 3.595 (2.18), 3.620 (0.70), 3.818 (1.11), 3.844 (2.09), 3.864 (1.06), 3.872 (0.93), 4.357 (1.94), 4.368 (3.51), 4.395 (0.46), 6.209 (1.79), 6.212 (1.85), 6.228 (1.98), 6.232 (1.91), 6.756 (1.10), 6.760 (1.40), 6.776 (3.46), 6.779 (2.93), 6.793 (2.52), 6.813 (2.75), 6.833 (0.95), 7.200 (2.25), 7.250 (3.55), 7.263 (3.70), 7.431 (4.31), 7.946 (3.93), 7.958 (3.66), 8.338 (5.51), 12.003 (2.32).
- 15

LC-MS (method 6): R_t = 0.57 min; MS (ESIpos): m/z = 512 [M+H]⁺

Example 44

3-(3-chloro-2-methyl-anilino)-2-[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one



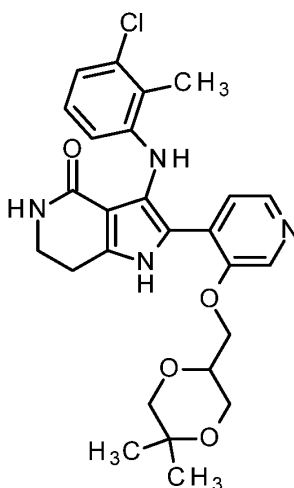
- 5 In analogy to example 1 *N*-(3-chloro-2-methyl-phenyl)-4-[[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]methylamino]-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide (intermediate 6-44, 320 mg, 603 μ mol) was used to prepare 32 mg of the title compound (98% purity, 10% yield) after stirring for 2 h at room temperature and purification by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50-5.92 min 15-54.2% B, 10 5.92 – 7.34 min 54.2% B, 7.34 – 7.42 min 54.2 – 55% B).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm]= 1.072 (14.59), 1.241 (13.05), 2.325 (0.47), 2.329 (0.73), 2.344 (16.00), 2.520 (1.82), 2.525 (1.27), 2.671 (0.54), 2.828 (1.59), 2.845 (3.40), 2.862 (1.80), 3.402 (2.68), 3.417 (2.39), 3.423 (2.57), 3.431 (2.75), 3.565 (0.87), 3.574 (1.01), 3.595 (1.70), 3.603 (1.65), 3.640 (3.45), 3.668 (4.15), 3.697 (1.17), 3.872 (0.64), 15 3.880 (0.75), 3.888 (0.95), 3.897 (0.88), 3.905 (0.63), 3.914 (0.58), 4.122 (1.12), 4.139 (1.05), 4.149 (1.54), 4.165 (1.34), 4.254 (1.47), 4.263 (1.52), 4.281 (1.10), 4.289 (0.98), 6.196 (1.81), 6.199 (1.76), 6.215 (1.97), 6.218 (1.81), 6.705 (0.97), 6.709 (1.30), 6.725 (3.57), 6.729 (2.82), 6.738 (2.56), 6.757 (2.50), 6.778 (0.82), 7.165 (2.26), 7.230 (3.85), 7.243 (3.87), 7.323 (4.45), 8.004 (5.13), 8.016 (4.69), 8.374 (6.56), 11.049 (2.45).

- 20 LC-MS (method 6): R_t = 0.79 min; MS (ESIpos): m/z = 497 $[\text{M}+\text{H}]^+$

Example 45

3-(3-chloro-2-methyl-anilino)-2-[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one (stereoisomer 1)



- 5 The title compound from example 44 (32.0 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 15.50 mg, $R_t = 12.1 - 14.2$ min) and enantiomer 2 (12.6 mg, $R_t = 14.5 - 19.0$ min, see example 46).

Preparative chiral HPLC method: POB

- Instrument: PrepCon Labomatic HPLC; Column: Chiralcel OD-H 5 μ , 250x20; eluent A: ethanol + 0.1 vol % diethylamine; eluent B: methanol; isocratic: 70%A+30%B; flow: 10 ml/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC method: POB

- Instrument: Waters Alliance 2695; Column: Chiralcel OD-H 5 μ , 100x4.6; eluent A: ethanol + 0.1 vol % diethylamine; eluent B: methanol; isocratic: 70%A+30%B; flow: 1.4 ml/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC: $R_t = 3.52$ min.

Optical rotation: $[\alpha]_D = 30.31^\circ \pm 1.05^\circ$ ($c = 2.7$ mg/ml in Chloroform)

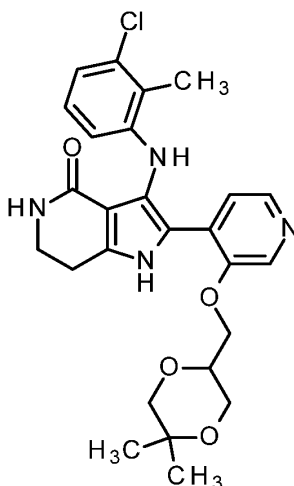
- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ [ppm] = 1.050 (0.51), 1.070 (14.54), 1.119 (0.40), 1.137 (0.77), 1.155 (0.80), 1.190 (0.47), 1.239 (13.63), 2.085 (0.73), 2.318 (0.77), 2.323 (1.71), 2.327 (2.48), 2.332 (2.11), 2.342 (16.00), 2.518 (7.25), 2.523 (5.03), 2.660 (0.73), 2.665 (1.64), 2.669 (2.30), 2.673 (1.60), 2.679 (0.73), 2.825 (1.60), 2.842 (3.43), 2.859 (1.86),

3.306 (0.95), 3.399 (2.77), 3.415 (2.44), 3.421 (2.59), 3.429 (2.84), 3.563 (0.87), 3.572 (1.02), 3.592 (1.71), 3.601 (1.68), 3.638 (3.46), 3.665 (4.15), 3.695 (1.17), 3.869 (0.77), 3.878 (0.77), 3.886 (0.95), 3.894 (0.87), 3.903 (0.62), 3.911 (0.58), 4.120 (1.13), 4.137 (1.06), 4.147 (1.53), 4.163 (1.31), 4.252 (1.46), 4.261 (1.53), 4.278 (1.09), 4.287 (0.98),
 5 6.193 (1.82), 6.197 (1.75), 6.212 (1.93), 6.216 (1.82), 6.703 (0.98), 6.707 (1.28), 6.723 (3.50), 6.727 (2.81), 6.736 (2.59), 6.756 (2.51), 6.775 (0.84), 7.162 (2.22), 7.228 (3.64), 7.241 (3.64), 7.321 (4.48), 8.002 (4.30), 8.014 (4.01), 8.372 (5.94), 11.046 (2.48).

LC-MS (method 6): $R_t = 0.80$ min; MS (ESIpos): $m/z = 497$ $[M+H]^+$

Example 46

- 10 3-(3-chloro-2-methyl-anilino)-2-[3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]-4-pyridyl]-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one (stereoisomer 2)



- For the preparation of the racemic title compound see example 44. Separation of enantiomers by preparative chiral HPLC (method see example 45) to give 12.6 mg of the
 15 title compound ($R_t = 14.5 - 19.0$ min).

Analytical chiral HPLC (method see example 45): $R_t = 4.43$ min.

Optical rotation: $[\alpha]_D = -26.44^\circ \pm 1.41^\circ$ ($c = 2.9$ mg/ml in Chloroform)

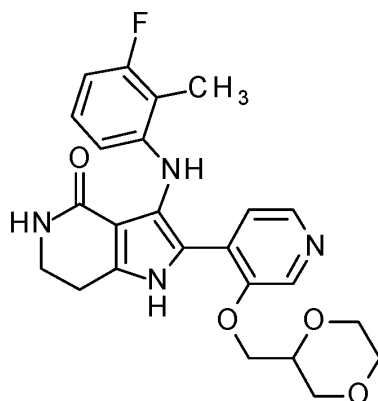
- $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm] = 0.748 (0.44), 0.764 (0.44), 1.053 (0.52), 1.070 (14.81), 1.154 (1.45), 1.239 (13.86), 2.085 (1.85), 2.318 (0.46), 2.323 (0.99), 2.327 (1.45),
 20 2.332 (1.39), 2.342 (16.00), 2.518 (4.03), 2.523 (2.82), 2.540 (0.54), 2.665 (0.89), 2.669 (1.25), 2.673 (0.85), 2.825 (1.61), 2.843 (3.39), 2.859 (1.81), 3.399 (2.78), 3.415 (2.48), 3.421 (2.64), 3.429 (2.88), 3.563 (0.83), 3.572 (0.99), 3.593 (1.69), 3.601 (1.67), 3.638

(3.49), 3.665 (4.15), 3.695 (1.15), 3.869 (0.83), 3.878 (0.77), 3.886 (0.95), 3.895 (0.89), 3.903 (0.64), 3.912 (0.58), 4.120 (1.09), 4.137 (1.03), 4.147 (1.53), 4.163 (1.33), 4.252 (1.45), 4.261 (1.51), 4.278 (1.09), 4.287 (0.97), 6.193 (1.77), 6.197 (1.75), 6.212 (1.97), 6.216 (1.85), 6.703 (0.95), 6.707 (1.27), 6.723 (3.51), 6.727 (2.82), 6.736 (2.58), 6.756 (2.54), 6.775 (0.85), 7.162 (2.26), 7.228 (3.10), 7.241 (3.12), 7.321 (4.45), 8.002 (2.54), 8.015 (2.36), 8.372 (3.89), 11.046 (2.46).

LC-MS (method 6): R_t = 0.80 min; MS (ESIpos): m/z = 497 $[M+H]^+$

Example 47

2-[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]-3-(3-fluoro-2-methyl-anilino)-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one



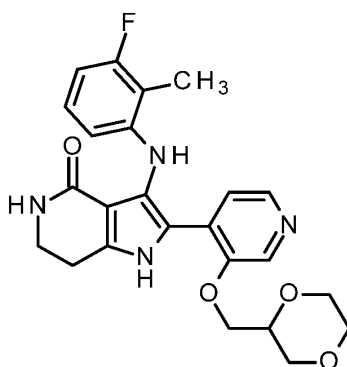
In analogy to example 1 4-[[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]methylamino]-*N*-(3-fluoro-2-methyl-phenyl)-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide (intermediate 6-47, 399 mg, 820 μ mol) was used to prepare 135 mg of the title compound (97% purity, 35% yield) after stirring for overnight at 60 °C and purification by preparative HPLC (method 9, gradient: 0.00-0.50 min 15% B, 0.50-6.00 min 15-55% B).

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.154 (4.20), 1.172 (8.22), 1.189 (3.94), 1.987 (16.00), 2.185 (2.36), 2.189 (2.36), 2.518 (0.75), 2.522 (0.47), 2.843 (0.44), 2.860 (0.94), 2.877 (0.50), 3.398 (0.42), 3.425 (1.01), 3.451 (0.56), 3.709 (0.44), 3.740 (0.57), 3.999 (1.26), 4.017 (3.61), 4.035 (3.57), 4.053 (1.15), 4.125 (0.48), 4.230 (0.43), 4.239 (0.42), 5.758 (0.88), 6.052 (0.58), 6.072 (0.60), 6.459 (0.48), 7.186 (0.59), 7.234 (1.00), 7.247 (1.01), 7.345 (1.17), 7.990 (1.32), 8.002 (1.20), 8.361 (1.76), 11.030 (0.60).

LC-MS (method 6): R_t = 0.65 min; MS (ESIpos): m/z = 453 $[M+H]^+$

Example 48

2-[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]-3-(3-fluoro-2-methyl-anilino)-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one (stereoisomer 1)



- 5 The title compound from example 47 (15.0 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 3.0 mg, R_t = 5.5 – 6.2 min) and enantiomer 2 (2.0 mg, R_t = 9.0 – 9.9 min, see example 49).

Preparative chiral HPLC method: MTBE

- Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5 μ , 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 55%B+45%A; flow: 80 ml/min; temperature: 25°C; UV: 280 nm;
- 10

Analytical chiral HPLC method: MTBE

- Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3 μ , 100x4.6; eluent A: methyl tert-butyl ether + 0.2 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 ml/min; temperature: 25°C; UV: 280 nm;
- 15

Analytical chiral HPLC: R_t = 2.90 min.

Optical rotation: $[\alpha]_D$ = - 19.1° +/- 1.65° (c = 2,19 mg/ml in Chloroform)

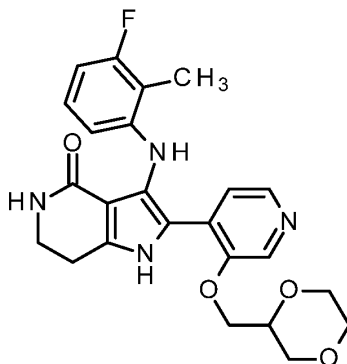
- ¹H-NMR (400 MHz, DMSO- d_6): δ [ppm]= -0.008 (0.55), 0.000 (16.00), 0.008 (0.53), 0.700 (0.57), 0.752 (0.76), 0.770 (0.76), 1.140 (1.18), 1.160 (2.36), 1.234 (1.64), 1.296 (0.42), 2.189 (11.55), 2.191 (11.53), 2.521 (2.85), 2.525 (1.90), 2.846 (2.15), 2.863 (4.59), 2.880 (2.42), 3.401 (1.96), 3.410 (1.71), 3.417 (1.88), 3.428 (4.95), 3.444 (1.64), 3.454 (2.68), 3.505 (0.67), 3.510 (0.82), 3.532 (1.56), 3.539 (1.58), 3.560 (1.14), 3.569 (1.03), 3.712 (2.13), 3.721 (1.35), 3.743 (2.76), 3.750 (1.24), 3.771 (1.14), 3.778 (0.84), 3.800 (1.69), 3.806 (1.85), 3.829 (1.52), 3.835 (1.54), 3.885 (1.66), 3.912 (1.22), 3.992 (0.42), 4.001
- 20

(0.68), 4.008 (1.01), 4.017 (1.14), 4.025 (1.10), 4.033 (0.93), 4.042 (0.78), 4.049 (0.53), 4.103 (1.71), 4.119 (1.24), 4.129 (2.26), 4.145 (1.73), 4.233 (2.09), 4.243 (2.05), 4.259 (1.54), 4.269 (1.33), 6.056 (2.82), 6.076 (2.91), 6.440 (1.29), 6.463 (2.36), 6.484 (1.46), 6.734 (0.89), 6.754 (1.85), 6.771 (1.77), 6.792 (0.72), 7.187 (2.91), 7.237 (3.80), 7.250 (3.82), 7.348 (5.65), 7.994 (2.64), 8.006 (2.47), 8.365 (4.17), 11.029 (3.12).

LC-MS (method 6): $R_t = 0.66$ min; MS (ESIpos): $m/z = 453$ $[M+H]^+$

Example 49

2-[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]-3-(3-fluoro-2-methyl-anilino)-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one (stereoisomer 2)



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For the preparation of the racemic title compound see example 47. Separation of enantiomers by preparative chiral HPLC (method see example 48) to give 2.0 mg of the title compound ($R_t = 9.0 - 9.9$ min).

Analytical chiral HPLC (method see example 48): $R_t = 4.67$ min.

15 Optical rotation: $[\alpha]_D = 24.3^\circ \pm 7.66^\circ$ ($c = 1.29$ mg/ml in Chloroform)

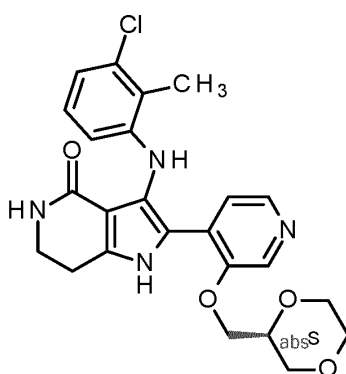
$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: -0.008 (0.54), 0.000 (16.00), 0.008 (0.54), 0.700 (0.74), 0.752 (0.54), 0.771 (0.57), 0.854 (0.52), 1.139 (0.91), 1.160 (1.70), 1.234 (2.19), 1.296 (0.52), 2.087 (0.66), 2.189 (11.26), 2.191 (11.28), 2.521 (4.55), 2.525 (3.00), 2.846 (2.09), 2.863 (4.47), 2.880 (2.36), 3.401 (1.99), 3.410 (1.67), 3.417 (1.87), 3.428 (4.87), 3.444 (1.65), 3.454 (2.65), 3.505 (0.69), 3.510 (0.84), 3.532 (1.52), 3.539 (1.55), 3.560 (1.13), 3.569 (1.03), 3.712 (2.09), 3.721 (1.35), 3.744 (2.70), 3.750 (1.23), 3.771 (1.16), 3.778 (0.81), 3.800 (1.67), 3.806 (1.77), 3.829 (1.50), 3.835 (1.52), 3.885 (1.62), 3.912 (1.20), 3.992 (0.42), 4.001 (0.66), 4.009 (0.98), 4.017 (1.11), 4.025 (1.08), 4.033 (0.91), 4.042 (0.76), 4.049 (0.54), 4.103 (1.70), 4.119 (1.20), 4.129 (2.19), 4.145 (1.72), 4.233

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(2.04), 4.243 (2.04), 4.259 (1.52), 4.269 (1.33), 6.055 (2.75), 6.076 (2.85), 6.440 (1.25), 6.463 (2.31), 6.484 (1.45), 6.734 (0.86), 6.754 (1.79), 6.772 (1.72), 6.792 (0.74), 7.187 (2.83), 7.237 (3.37), 7.250 (3.42), 7.349 (5.43), 7.994 (2.24), 8.007 (2.14), 8.365 (3.56), 11.030 (3.02).

5 **Example 50**

3-(3-chloro-2-methylanilino)-2-(3-[[[(2S)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



Using an analogous method as described for example 1 with *N*-(3-chloro-2-methyl-phenyl)-4-[[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]methylamino]-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide (intermediate 6-50, 150 mg, 298 μ mol) as the starting material, 35.0 mg (25% yield) of the racemic title compound were prepared after preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50–6.00 min 15-55% B).

LC-MS (method 6): R_t = 0.71 min; MS (ESIpos): m/z = 469 $[M+H]^+$

Racemic 3-(3-chloro-2-methyl-anilino)-2-[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one (35.0 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 12.5 mg, R_t = 14.3 – 16.6 min,) and enantiomer 2 (13.4 mg, R_t = 21.1 – 25.3 min, see example 51).

Preparative chiral HPLC method: MTBE

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5 μ , 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: ethanol; gradient:; flow: 40 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC method: MTBE

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3 μ , 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: ethanol; gradient:; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

- 5 Analytical chiral HPLC: $R_t = 3.23$ min.

Optical rotation: $[\alpha]_D = -20.5^\circ \pm 1.23^\circ$ (c = 2,7 mg/ml in Chloroform)

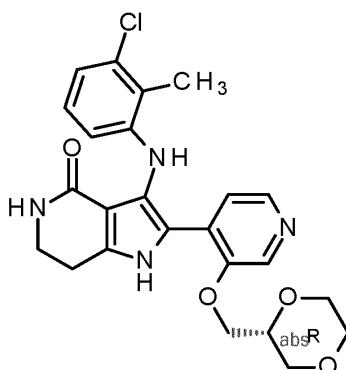
- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ [ppm] = 1.234 (0.41), 2.338 (0.44), 2.355 (16.00), 2.520 (2.76), 2.524 (1.87), 2.847 (1.60), 2.864 (3.40), 2.882 (1.80), 3.398 (1.50), 3.410 (1.20), 3.416 (1.35), 3.427 (3.93), 3.432 (2.41), 3.444 (1.16), 3.451 (2.30), 3.502 (0.46), 3.508 (0.60), 3.530 (1.13), 3.537 (1.16), 3.558 (0.85), 3.566 (0.78), 3.711 (1.87), 3.718 (1.04), 3.740 (2.36), 3.768 (0.89), 3.775 (0.60), 3.796 (1.27), 3.802 (1.36), 3.825 (1.15), 3.831 (1.16), 3.883 (1.23), 3.909 (0.88), 3.994 (0.48), 4.001 (0.77), 4.009 (0.80), 4.018 (0.79), 4.025 (0.69), 4.033 (0.55), 4.104 (1.32), 4.120 (0.96), 4.130 (1.76), 4.146 (1.34), 4.223 (1.59), 4.232 (1.56), 4.249 (1.15), 4.258 (1.00), 6.190 (1.73), 6.194 (1.69), 6.210 (2.01), 6.213 (1.79), 6.718 (0.97), 6.722 (1.27), 6.738 (3.59), 6.742 (2.81), 6.751 (2.54), 6.771 (2.47), 6.790 (0.80), 7.184 (2.17), 7.234 (3.49), 7.247 (3.51), 7.364 (4.36), 7.999 (3.35), 8.012 (3.08), 8.365 (4.78), 11.044 (2.32).

LC-MS (method 6): $R_t = 0.70$ min; MS (ESIpos): $m/z = 469$ $[\text{M}+\text{H}]^+$

- Enantioselective synthesis starting from 1-(3-([(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)methanamine (intermediate 2-8) confirmed the title compound as 3-(3-chloro-2-methylanilino)-2-(3-([(2S)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one.

Example 51

3-(3-chloro-2-methylanilino)-2-(3-[[*(2R)*-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



- 5 For the preparation of the racemic title compound see example 50. Separation of enantiomers by preparative chiral HPLC (method see example 50) gave 13.4 mg of the title compound ($R_t = 21.1 - 25.3$ min).

Analytical chiral HPLC (method see example 50): $R_t = 5.22$ min.

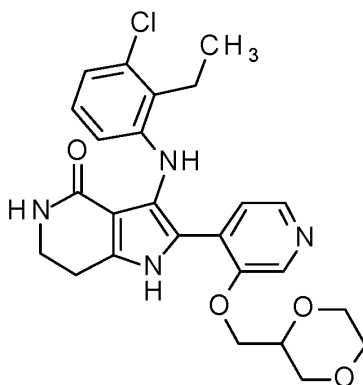
Optical rotation: $[\alpha]_D = 20.4^\circ \pm 1.23^\circ$ ($c = 2.69$ mg/ml in chloroform)

- 10 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm] = 1.173 (0.44), 1.234 (0.51), 2.355 (16.00), 2.521 (2.29), 2.525 (1.50), 2.848 (1.58), 2.865 (3.44), 2.882 (1.83), 3.346 (0.44), 3.399 (1.49), 3.410 (1.19), 3.416 (1.34), 3.428 (3.98), 3.432 (2.45), 3.444 (1.19), 3.452 (2.35), 3.503 (0.46), 3.508 (0.62), 3.531 (1.13), 3.538 (1.20), 3.558 (0.84), 3.567 (0.81), 3.711 (1.90), 3.718 (1.09), 3.740 (2.39), 3.768 (0.88), 3.775 (0.62), 3.797 (1.26), 3.803 (1.39), 3.825 (1.14), 3.832 (1.17), 3.883 (1.25), 3.910 (0.90), 3.995 (0.49), 4.001 (0.76), 4.010 (0.82), 4.018 (0.79), 4.026 (0.71), 4.035 (0.56), 4.042 (0.40), 4.104 (1.30), 4.121 (0.95), 4.130 (1.77), 4.147 (1.36), 4.224 (1.60), 4.233 (1.58), 4.250 (1.15), 4.259 (0.99), 6.191 (1.74), 6.195 (1.73), 6.210 (1.96), 6.214 (1.81), 6.719 (0.94), 6.723 (1.27), 6.738 (3.57), 6.743 (2.82), 6.752 (2.56), 6.771 (2.49), 6.791 (0.81), 7.185 (2.19), 7.235 (3.09), 7.248 (3.12),
- 15 7.365 (4.33), 8.000 (2.48), 8.013 (2.34), 8.366 (3.75), 11.045 (2.33).

LC-MS (method 6): $R_t = 0.70$ min; MS (ESIpos): $m/z = 469$ $[\text{M}+\text{H}]^+$

Example 52

3-(3-chloro-2-ethyl-anilino)-2-[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridin-4-one



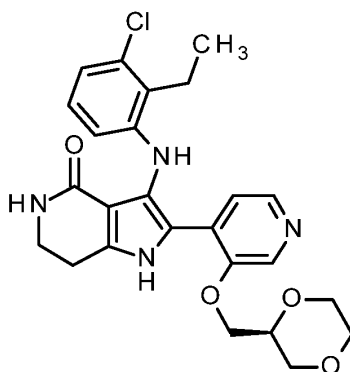
- 5 In analogy to example 1 *N*-(3-chloro-2-ethyl-phenyl)-4-[[3-(1,4-dioxan-2-ylmethoxy)-4-pyridyl]methylamino]-6-oxo-2,3-dihydro-1*H*-pyridine-5-carbothioamide (intermediate 6-52, 150 mg, 290 μ mol) was used to prepare 23.2 mg of the title compound (95% purity, 16% yield) after stirring for 4 h at 60 °C and purification by preparative HPLC (method 10, gradient: 0.00-0.50 min 10% B, 0.50–8.06 min 10-20% B, 8.06-9.02 min 20% B, 9.02-24.12 min 20-50% B, 24.12-27.44 min 50% B).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ ppm= 1.23 (t, 3 H), 2.86 (s, 4 H), 3.38 - 3.46 (m, 4 H), 3.49 - 3.58 (m, 1 H), 3.68 - 3.78 (m, 2 H), 3.78 - 3.85 (m, 1 H), 3.86 - 3.92 (m, 1 H), 3.98 - 4.06 (m, 1 H), 4.09 - 4.17 (m, 1 H), 4.21 - 4.28 (m, 1 H), 6.22 (dd, 1 H), 6.67 - 6.78 (m, 2 H), 7.20 (d, 2 H), 7.45 (s, 1 H), 7.98 (d, 1 H), 8.32 - 8.39 (m, 1 H).

- 15 LC-MS (method 2): R_t = 1.08 min; MS (ESIpos): m/z = 483 $[\text{M}+\text{H}]^+$

Example 53

3-(3-chloro-2-ethylanilino)-2-(3-[[[(2*S*)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



- 5 The title compound from example 52 (23.2 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (enantiomer 1, 6.0 mg, $R_t = 6.6 - 7.3$ min) and enantiomer 2 (5.0 mg, $R_t = 10.7 - 11.6$ min, see example 54).

Preparative chiral HPLC method: MTBE

- Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5 μ , 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 60 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC method: MTBE

- Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3 μ , 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: $R_t = 2.40$ min.

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ [ppm]= 1.23 (t, 3H), 2.81 - 2.91 (m, 4H), 3.40 - 3.45 (m, 3H), 3.53 (dt, 1H), 3.69 - 3.79 (m, 2H), 3.79 - 3.85 (m, 1H), 3.86 - 3.93 (m, 1H), 3.99 - 4.06 (m, 1H), 4.12 (dd, 1H), 4.24 (dd, 1H), 6.23 (dd, 1H), 6.69 - 6.78 (m, 2H), 7.15 - 7.23 (m, 2H), 7.43 - 7.47 (m, 1H), 7.98 (d, 1H) 8.36 (s, 1H), 11.03 (br s, 1H).

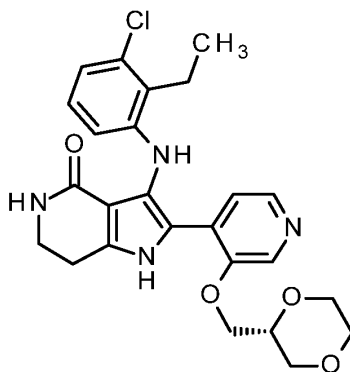
Enantioselective synthesis confirmed the title compound as 3-(3-chloro-2-ethylanilino)-2-(3-[[[(2*S*)-1,4-dioxan-2-yl]methoxy]pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one. In analogy to example 1 the title compound (25 mg, 7.6% yield) was prepared by using *N*-(3-chloro-2-ethylphenyl)-4-[[[3-[[[(2*S*)-1,4-dioxan-2-yl]methoxy]pyridin-4-

yl)methyl]amino}-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-53, 320 mg, 0.62 mmol) as starting material, followed by purification with preparative HPLC (method 10, gradient: 0.00-0.50 min 5% B, 0.50–7.99 min 5-60% B, 7.99-11.20 min 60% B).

- 5 ¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 11.03 (s, 1H), 8.36 (s, 1H), 7.98 (d, 1H), 7.43 - 7.49 (m, 1H), 7.15 - 7.24 (m, 2H), 6.68 - 6.80 (m, 2H), 6.14 - 6.28 (m, 1H), 4.21 - 4.33 (m, 1H), 4.10 - 4.17 (m, 1H), 4.00 - 4.05 (m, 1H), 3.70 - 3.92 (m, 4H), 3.51 - 3.59 (m, 1H), 3.39 - 3.47 (m, 3H), 2.81 - 2.90 (m, 4H), 1.23 (t, 3H).

Example 54

- 10 3-(3-chloro-2-ethylanilino)-2-(3-[(2*R*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



For the preparation of the racemic title compound see example 52. Separation of enantiomers by preparative chiral HPLC (method see example 53) gave 5.0 mg of the title compound (*R*_t = 10.7 – 11.6 min).

- 15

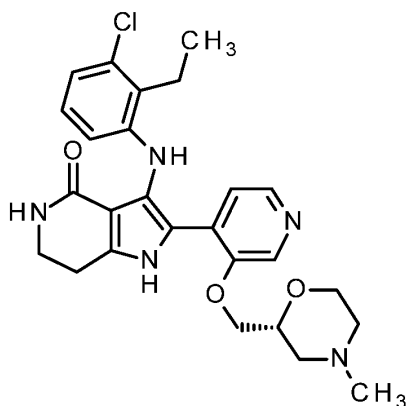
Analytical chiral HPLC (method see example 53): *R*_t = 3.22 min.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.14 - 1.34 (m, 6H), 2.81 - 2.91 (m, 4H), 3.38 - 3.48 (m, 3H), 3.55 (dd, 1H), 3.69 - 3.85 (m, 3H), 3.85 - 3.93 (m, 1H), 3.99 - 4.06 (m, 1H), 4.09 - 4.17 (m, 1H), 4.25 (dd, 1H), 6.23 (dd, 1H), 6.69 - 6.79 (m, 2H), 7.14 - 7.23 (m, 2H), 7.39 - 7.49 (m, 1H), 7.91 - 8.04 (m, 1H), 8.31 - 8.40 (m, 1H), 10.97 - 11.12 (m, 1H).

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Example 55

3-(3-chloro-2-ethyl-anilino)-2-(3-[(2*R*)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one

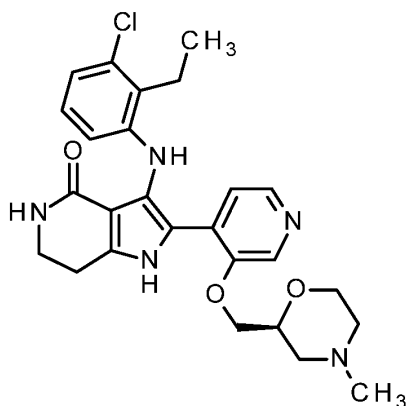


- 5 Using an analogous method as described for example 41 with 3-(3-chloro-2-ethyl-anilino)-2-(3-[(2*R*)-morpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (intermediate 55, 58.0 mg, 120 μ mol) as the starting material; 27.5 mg (95% purity, 44% yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 30% B, 0.50 – 7.00 min 30 – 70% B).
- 10 $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 1.23 (t, 3H), 1.90 (t, 1H), 1.99 - 2.09 (td, 1H), 2.21 (s, 3H), 2.63 - 2.71 (d, 1H), 2.73 - 2.78 (d, 1H), 2.78 - 2.89 (m, 4H), 3.40 - 3.47 (td, 2H), 3.67 (td, 1H), 3.92 - 3.98 (m, 2H), 4.14 (dd, 1H), 4.27 (dd, 1H), 6.23 (dd, 1H), 6.71 - 6.78 (m, 2H), 7.16 - 7.21 (m, 2H), 7.46 (s, 1H), 7.97 (d, 1H), 8.36 (s, 1H), 11.04 (s, 1H).

LC-MS (method 2): R_t = 1.10 min; MS (ESIpos): m/z = 496 $[\text{M}+\text{H}]^+$

Example 56

3-(3-chloro-2-ethyl-anilino)-2-(3-[(2*S*)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



- 5 Using an analogous method as described for example 41 with 3-(3-chloro-2-ethyl-anilino)-2-(3-[(2*S*)-morpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (intermediate 56, 68.0 mg, 141 μ mol) as the starting material; 37.8 mg (95% purity, 51% yield) of the title compound were prepared after purification by preparative HPLC (method 10, gradient: 0.00 – 0.50 min 30% B, 0.50 – 7.00 min 30 – 70% B).
- 10 $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ [ppm]= 1.23 (t, 3H), 1.90 (t, 1H), 2.00 - 2.08 (td, 1H), 2.21 (s, 3H), 2.63 - 2.72 (d, 1H), 2.72 - 2.81 (d, 1H), 2.81 - 2.90 (m, 4H), 3.44 (td, 2H), 3.67 (td, 1H), 3.91 - 3.99 (m, 2H), 4.13 (dd, 1H), 4.29 (dd, 1H), 6.23 (dd, 1H), 6.71 - 6.78 (m, 2H), 7.16 - 7.21 (m, 2H), 7.46 (s, 1H), 7.97 (d, 1H), 8.36 (s, 1H), 11.04 (s, 1H).

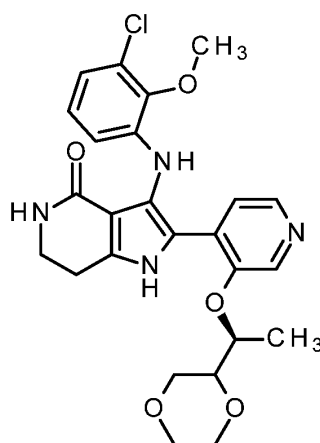
LC-MS (method 2): R_t = 1.10 min; MS (ESIpos): m/z = 496 $[\text{M}+\text{H}]^+$

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Example 57

3-(3-chloro-2-methoxyanilino)-2-{3-[(1*S*)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



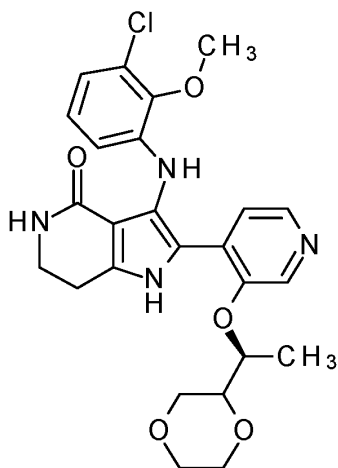
- 5 In a microwave tube, a solution of *N*-(3-chloro-2-methoxyphenyl)-4-([3-[(1*S*)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl]methyl)amino]-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-57, 380 mg, 713 μ mol) in methanol (1.5 ml) was treated with TFA (55 μ l, 710 μ mol) followed by hydrogen peroxide (9.2 μ l, 0.106 mmol), heated to 60°C and stirred for 16h. The reaction mixture was concentrated to dryness under
- 10 reduced pressure, dissolved in DMSO and purified by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50–5.00 min 15-50% B, 5.00-8.00 min 50% B) to give after freeze drying the desired product (174mg, 44% yield) as mixture of two stereoisomers.
- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.176 (0.47), 1.192 (0.46), 1.245 (3.61), 1.261 (3.63), 1.326 (5.41), 1.342 (5.34), 2.074 (0.90), 2.518 (2.00), 2.523 (1.30), 2.832 (0.58), 2.853 (1.78), 2.871 (2.29), 2.889 (1.20), 3.374 (0.58), 3.402 (1.93), 3.412 (1.77), 3.419 (2.47), 3.427 (2.74), 3.435 (1.67), 3.442 (1.31), 3.455 (1.30), 3.464 (0.88), 3.485 (1.04), 3.493 (0.81), 3.500 (0.81), 3.522 (0.58), 3.614 (0.42), 3.643 (1.28), 3.650 (1.69), 3.669 (0.97), 3.699 (1.00), 3.725 (1.81), 3.734 (0.89), 3.748 (1.07), 3.754 (0.91), 3.768 (0.44),
- 20 3.777 (0.54), 3.783 (0.42), 3.806 (1.65), 3.813 (2.16), 3.823 (1.17), 3.836 (1.62), 3.843 (1.75), 3.850 (1.00), 3.863 (9.50), 3.890 (16.00), 3.919 (0.92), 3.948 (0.61), 4.068 (2.33), 4.626 (0.70), 4.630 (0.86), 4.643 (1.15), 4.653 (0.66), 4.658 (0.86), 6.133 (0.95), 6.143 (2.18), 6.148 (0.96), 6.151 (1.32), 6.158 (1.98), 6.167 (1.48), 6.638 (1.70), 6.643 (2.02), 6.653 (3.46), 6.678 (0.58), 6.690 (6.05), 6.699 (2.71), 6.706 (2.31), 7.122 (0.98), 7.161

(1.50), 7.264 (0.72), 7.285 (0.52), 7.294 (1.80), 7.299 (2.64), 7.307 (1.85), 7.312 (2.64), 7.440 (2.17), 7.519 (3.36), 7.631 (0.44), 7.998 (3.33), 8.011 (3.08), 8.031 (2.20), 8.044 (1.98), 8.396 (4.10), 8.411 (2.66), 11.072 (1.20), 11.085 (1.69).

LC-MS (method 6): $R_t = 0.72$ min; MS (ESIpos): $m/z = 499$ $[M+H]^+$

5 Example 58

3-(3-chloro-2-methoxyanilino)-2-{3-[(1S)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (Stereoisomer 1)



The title compound from example 57 (170 mg) was separated into stereoisomers by preparative chiral HPLC to give title compound (stereoisomer 1, 58 mg, $R_t = 16.2$ -18.8 min) and stereoisomer 2 (35 mg, $R_t = 19.3$ -21.6 min, see example 60).

Preparative chiral HPLC method:

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 5 μ , 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; gradient: 0-15 min 20-30% B; flow: 40 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral analytical HPLC method:

Instrument: Waters Alliance 2695; Column: YMC Cellulose SC 3 μ , 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: $R_t = 5.19$ min.

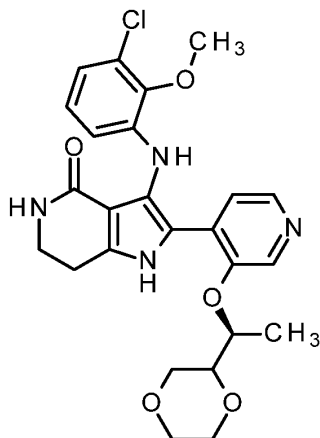
¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 1.157 (0.42), 1.326 (5.83), 1.342 (5.94), 2.518 (2.45), 2.523 (1.64), 2.854 (1.00), 2.872 (2.23), 2.889 (1.30), 3.159 (0.76), 3.172 (0.81), 3.403 (0.88), 3.409 (0.98), 3.420 (1.66), 3.427 (1.98), 3.435 (0.89), 3.456 (1.40), 3.469 (0.49), 3.485 (1.09), 3.493 (0.89), 3.500 (0.89), 3.522 (0.63), 3.530 (0.42), 3.699 (1.04),
 5 3.725 (1.77), 3.748 (1.00), 3.755 (0.79), 3.777 (0.55), 3.783 (0.42), 3.806 (1.16), 3.812 (1.76), 3.824 (0.88), 3.836 (1.39), 3.843 (1.20), 3.850 (0.51), 3.890 (16.00), 3.919 (1.02), 3.948 (0.70), 4.631 (0.81), 4.646 (0.95), 4.659 (0.80), 6.143 (1.46), 6.151 (1.29), 6.159 (1.42), 6.167 (1.47), 6.679 (0.61), 6.691 (6.25), 6.699 (2.81), 6.706 (2.43), 6.727 (0.42), 7.159 (1.65), 7.298 (2.69), 7.311 (2.69), 7.518 (3.71), 7.998 (3.52), 8.010 (3.22), 8.395
 10 (4.49), 11.084 (1.82).

Optical rotation: [α]_D = 30.21° +/- 0.60° (c = 1.0 g/100 ml chloroform)

LC-MS (method 6): R_t = 0.72 min; MS (ESIpos): m/z = 499 [M+H]⁺

Example 59

3-(3-chloro-2-methoxyanilino)-2-{3-[(1S)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (Stereoisomer 2)
 15



The title compound from example 57 (170 mg) was separated into stereoisomers by preparative chiral HPLC to give title compound stereoisomer 2 (35 mg, R_t = 19.3-21.6 min, see example 58 for method of separation).

20 Analytical chiral HPLC: R_t = 5.91 min.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 0.798 (0.48), 0.815 (0.56), 0.822 (0.55), 0.905 (0.48), 1.084 (0.46), 1.137 (0.84), 1.156 (0.69), 1.233 (1.00), 1.246 (6.21), 1.261 (6.32), 2.084 (0.60), 2.332 (0.57), 2.518 (3.49), 2.522 (2.23), 2.673 (0.60), 2.833 (1.01), 2.850

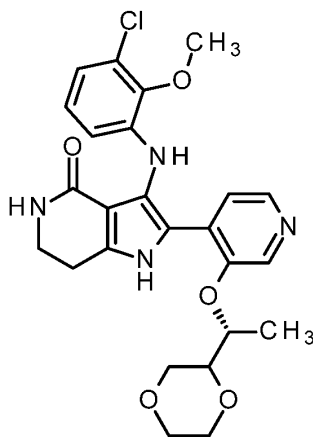
(2.05), 2.867 (1.22), 3.308 (0.48), 3.373 (0.98), 3.402 (2.29), 3.412 (2.05), 3.418 (2.16), 3.427 (2.02), 3.435 (1.84), 3.442 (1.19), 3.465 (0.79), 3.607 (0.46), 3.614 (0.62), 3.643 (2.17), 3.670 (1.14), 3.726 (0.62), 3.732 (0.73), 3.738 (0.65), 3.744 (0.72), 3.751 (0.57), 3.757 (0.63), 3.762 (0.57), 3.768 (0.57), 3.805 (1.25), 3.815 (1.51), 3.821 (1.12), 3.834 (1.01), 3.844 (1.36), 3.850 (1.08), 3.863 (16.00), 3.889 (0.74), 4.625 (0.83), 4.637 (0.87), 4.641 (0.90), 4.653 (0.81), 6.133 (1.40), 6.143 (1.44), 6.147 (1.32), 6.157 (1.50), 6.639 (2.71), 6.643 (3.20), 6.653 (5.57), 6.663 (0.45), 7.120 (1.71), 7.294 (2.55), 7.307 (2.61), 7.438 (3.73), 8.031 (2.89), 8.043 (2.69), 8.411 (4.05), 11.071 (1.88).

Optical rotation: $[\alpha]_D = 19.87^\circ \pm 0.91^\circ$ ($c = 1.0$ g/100 ml chloroform)

10 LC-MS (method 6): $R_t = 0.72$ min; MS (ESIpos): $m/z = 499$ $[M+H]^+$

Example 60

3-(3-chloro-2-methoxyanilino)-2-{3-[(1*R*)-1-(1,4-dioxan-2-yl)ethoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (Stereoisomer 1)



15 Using an analogous method as described for example 57 with *N*-(3-chloro-2-methoxyphenyl)-4-[(3-[(1*R*)-1-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)methyl]amino}-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-60, 340 mg, 638 μ mol) as the starting material; 76.0 mg (99% purity, 24% yield) of the title compound (stereoisomer 1, $R_t = 18.7$ -22.0 min) were prepared after purification by preparative HPLC (method 10, gradient: 0.00-0.50 min 15% B, 0.50-5.00 min 15-50% B, 5.00-8.00 min 50% B) followed by chiral prep. HPLC. Additionally 7mg of stereoisomer 2 (example 61) ($R_t = 16.5$ -17.9 min) was isolated.

Preparative chiral HPLC method:

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5 μ , 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 60 ml/min; temperature: 25°C; UV: 254 nm

5 Analytical chiral analytical HPLC method:

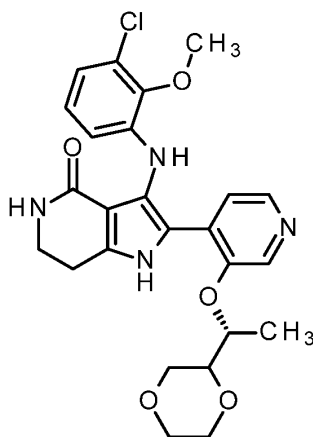
Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3 μ , 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: R_t = 6.96 min.

- 10 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm]= 1.245 (5.93), 1.261 (5.97), 2.518 (0.96), 2.522 (0.61), 2.833 (0.89), 2.850 (1.81), 2.868 (1.07), 3.374 (0.88), 3.398 (1.92), 3.402 (2.05), 3.412 (1.84), 3.418 (1.88), 3.427 (1.81), 3.435 (1.62), 3.442 (1.07), 3.465 (0.71), 3.608 (0.45), 3.614 (0.62), 3.643 (2.07), 3.669 (1.04), 3.726 (0.57), 3.733 (0.70), 3.736 (0.65), 3.744 (0.69), 3.751 (0.53), 3.757 (0.58), 3.762 (0.53), 3.768 (0.55), 3.805 (1.12), 3.815 (1.32), 3.821 (0.99), 3.834 (0.89), 3.844 (1.24), 3.850 (0.97), 3.864 (16.00), 3.890 (0.81), 4.068 (0.46), 4.626 (0.76), 4.637 (0.80), 4.641 (0.83), 4.653 (0.76), 6.133 (1.41), 6.143 (1.51), 6.148 (1.26), 6.158 (1.48), 6.638 (2.78), 6.643 (3.34), 6.653 (5.70), 6.663 (0.46), 7.122 (1.57), 7.294 (2.67), 7.307 (2.70), 7.440 (3.53), 8.031 (3.75), 8.044 (3.34), 8.411 (4.42), 11.072 (1.72).
- 15
- 20 LC-MS (method 6): R_t = 0.72 min; MS (ESIpos): m/z = 499 $[\text{M}+\text{H}]^+$

Example 61

3-(3-chloro-2-methoxyanilino)-2-(3-((1*R*)-1-[(1,4-dioxan-2-yl]ethoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (Stereoisomer 2)



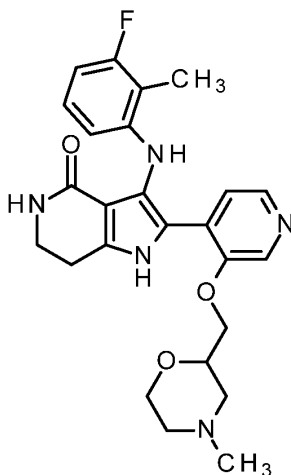
- 5 For the preparation of title compound as mixture of two diastereomeres see example 60. Separation of enantiomers by preparative chiral HPLC (method see example 60) gave 7.0 mg of the title compound ($R_t = 9.4 - 10.8$ min).

Analytical chiral HPLC (method see example 60): $R_t = 6.10$ min.

Optical rotation: $[\alpha]_D = -3.38^\circ \pm 0.78^\circ$ ($c = 3.7$ mg/ml, chloroform).

10 **Example 62**

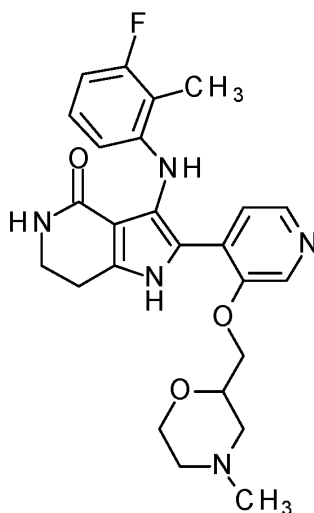
3-(3-fluoro-2-methylanilino)-2-(3-[[4-methylmorpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one



- To a solution of *N*-(3-fluoro-2-methylphenyl)-4-{{(3-{{[4-methylmorpholin-2-yl]methoxy}}pyridin-4-yl)methyl}amino}-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-62, 110 mg, 220 μ mol) in acetic acid (1.1 ml) was added aqueous hydrogen peroxide (45 μ l, 30% purity, 440 μ M) and the mixture was heated at 80°C for 2 h.
- 5 The reaction mixture was quenched with saturated sodium thiosulfate solution and pH 7 was adjusted by addition of aqueous 4M sodium hydroxide solution. After addition of DCM the mixture was stirred for 15 min at RT. The phases were separated and the aqueous phase extracted with DCM. The combined organic layers were dried by hydrophobic filter paper and concentrated under reduced pressure. The mixture was purified by prep. HPLC
- 10 (method 10) to give the title compound; 28 mg (97% purity, 26% yield).
- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm]= 1.877 (1.11), 1.904 (1.76), 1.931 (1.15), 2.007 (0.48), 2.016 (0.62), 2.036 (1.18), 2.044 (1.14), 2.064 (0.65), 2.074 (0.91), 2.188 (9.04), 2.191 (9.20), 2.204 (16.00), 2.326 (0.50), 2.518 (1.93), 2.522 (1.23), 2.647 (1.09), 2.669 (1.06), 2.673 (1.34), 2.743 (1.21), 2.770 (1.13), 2.844 (1.64), 2.861 (3.54), 2.878 (1.85),
- 15 3.410 (1.18), 3.415 (1.29), 3.426 (2.35), 3.432 (2.33), 3.443 (1.13), 3.449 (1.04), 3.642 (0.55), 3.648 (0.70), 3.670 (1.28), 3.675 (1.30), 3.698 (0.76), 3.703 (0.63), 3.935 (1.65), 3.942 (1.53), 3.951 (0.92), 3.962 (1.44), 3.967 (1.29), 4.109 (1.20), 4.126 (1.08), 4.135 (1.56), 4.151 (1.27), 4.276 (1.43), 4.285 (1.48), 4.301 (1.18), 4.310 (1.07), 6.056 (2.20), 6.076 (2.25), 6.442 (1.00), 6.464 (1.83), 6.486 (1.13), 6.735 (0.68), 6.755 (1.42), 6.772
- 20 (1.36), 6.793 (0.57), 7.188 (2.26), 7.230 (3.88), 7.242 (3.85), 7.346 (4.43), 7.979 (5.07), 7.991 (4.58), 8.368 (6.78), 11.029 (2.41).
- LC-MS (method 6): *R*_t = 0.46 min; MS (ESIpos): *m/z* = 466 [M+H]⁺

Example 63

3-(3-fluoro-2-methylanilino)-2-(3-{[4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one (stereoisomer 1)



- 5 The title compound from example 62 (21 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (stereoisomer 1, 7.0 mg, R_t = 7.1-8.1 min) and stereoisomer 2 (9.0 mg, R_t = 9.4 – 10.8 min, see example 64).

Preparative chiral HPLC method:

- Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5 μ , 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 60 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC method:

- Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3 μ , 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: R_t = 2.60 min.

Optical rotation: $[\alpha]_D = 21.60^\circ \pm 1.04^\circ$ (c = 1.0 g/100 ml chloroform)

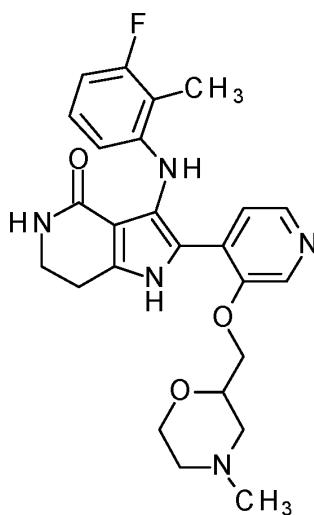
- ¹H-NMR (400 MHz, DMSO- d_6): δ [ppm] = 1.232 (0.89), 1.877 (1.15), 1.904 (1.74), 1.931 (1.14), 2.008 (0.48), 2.016 (0.62), 2.036 (1.17), 2.044 (1.15), 2.064 (0.65), 2.073 (0.56), 2.188 (9.17), 2.191 (9.34), 2.204 (16.00), 2.322 (0.45), 2.327 (0.62), 2.332 (0.45), 2.518 (2.49), 2.523 (1.54), 2.646 (1.12), 2.669 (1.21), 2.673 (1.46), 2.743 (1.23), 2.770 (1.15),

- 2.844 (1.60), 2.861 (3.42), 2.878 (1.82), 3.410 (1.23), 3.415 (1.32), 3.426 (2.40), 3.432 (2.38), 3.444 (1.15), 3.449 (1.07), 3.641 (0.56), 3.648 (0.70), 3.670 (1.28), 3.675 (1.31), 3.698 (0.76), 3.703 (0.61), 3.935 (1.67), 3.942 (1.57), 3.951 (0.95), 3.962 (1.45), 4.109 (1.14), 4.126 (1.03), 4.135 (1.51), 4.152 (1.21), 4.276 (1.39), 4.285 (1.43), 4.301 (1.14),
 5 4.310 (1.03), 6.056 (2.16), 6.076 (2.23), 6.442 (1.01), 6.464 (1.85), 6.486 (1.14), 6.735 (0.67), 6.755 (1.42), 6.772 (1.37), 6.793 (0.56), 7.188 (2.29), 7.230 (3.04), 7.243 (3.00), 7.345 (4.40), 7.979 (3.05), 7.991 (2.83), 8.368 (4.67), 11.030 (2.40).

LC-MS (method 6): $R_t = 0.46$ min; MS (ESIpos): $m/z = 466$ $[M+H]^+$

Example 64

- 10 3-(3-fluoro-2-methylanilino)-2-(3-[[4-methylmorpholin-2-yl]methoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 2)



- For the preparation of the racemic title compound see example 63. Separation of enantiomers by preparative chiral HPLC (method see example 63) to give 9.0 mg of the title
 15 compound ($R_t = 9.4 - 10.8$ min).

Analytical chiral HPLC (method see example 63): $R_t = 3.37$ min.

Optical rotation: $[\alpha]_D = -20.75^\circ \pm 1.29^\circ$ ($c = 1.0$ g/ 100ml in Chloroform)

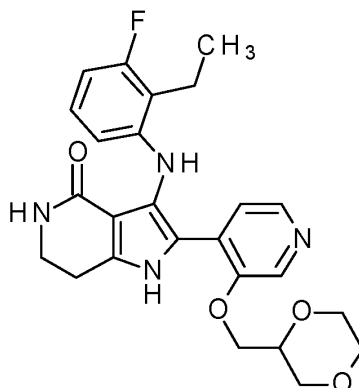
- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ [ppm]= 1.232 (0.99), 1.877 (1.12), 1.904 (1.80), 1.931 (1.15), 2.008 (0.49), 2.016 (0.64), 2.036 (1.17), 2.044 (1.15), 2.065 (0.66), 2.073 (0.57),
 20 2.188 (9.36), 2.191 (9.48), 2.204 (16.00), 2.323 (0.47), 2.327 (0.62), 2.332 (0.47), 2.518 (2.39), 2.522 (1.44), 2.647 (1.15), 2.669 (1.24), 2.673 (1.48), 2.743 (1.24), 2.770 (1.16),

2.844 (1.63), 2.861 (3.47), 2.878 (1.82), 3.410 (1.27), 3.415 (1.36), 3.426 (2.43), 3.432 (2.39), 3.443 (1.17), 3.449 (1.07), 3.642 (0.56), 3.648 (0.70), 3.670 (1.30), 3.675 (1.30), 3.698 (0.75), 3.703 (0.63), 3.935 (1.71), 3.942 (1.60), 3.962 (1.47), 4.109 (1.17), 4.126 (1.03), 4.135 (1.51), 4.152 (1.22), 4.276 (1.40), 4.285 (1.45), 4.301 (1.13), 4.310 (1.03),
 5 6.056 (2.19), 6.076 (2.26), 6.442 (1.05), 6.464 (1.87), 6.486 (1.15), 6.735 (0.70), 6.755 (1.43), 6.772 (1.38), 6.793 (0.56), 7.188 (2.30), 7.230 (3.03), 7.243 (3.07), 7.346 (4.46), 7.979 (3.01), 7.992 (2.84), 8.368 (4.73), 11.030 (2.43).

LC-MS (method 6): R_t = 0.46 min; MS (ESIpos): m/z = 466 $[M+H]^+$

Example 65

- 10 **2-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one**



- Using an analogous method as described for example 62 with 4-[[3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino}-N-(2-ethyl-3-fluorophenyl)-2-oxo-1,2,5,6-
 15 tetrahydropyridine-3-carbothioamide (intermediate 6-65, 215 mg, 429 μ mol) as the starting material; 76.0 mg (95% purity, 36% yield) of the title compound were prepared after purification by preparative HPLC (basic conditions).

- $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 1.097 (0.45), 1.206 (6.70), 1.225 (16.00), 1.244 (6.93), 2.322 (0.88), 2.327 (1.21), 2.332 (0.88), 2.518 (4.46), 2.522 (2.73), 2.664 (1.18),
 20 2.669 (1.70), 2.673 (2.02), 2.697 (3.88), 2.715 (3.73), 2.732 (1.31), 2.847 (3.66), 2.864 (7.84), 2.881 (4.11), 3.404 (3.38), 3.415 (2.84), 3.420 (3.17), 3.432 (8.74), 3.437 (5.90), 3.449 (2.86), 3.457 (4.93), 3.506 (1.16), 3.511 (1.46), 3.533 (2.58), 3.540 (2.78), 3.562 (2.02), 3.570 (1.77), 3.711 (3.25), 3.719 (1.53), 3.726 (2.41), 3.738 (2.86), 3.749 (3.64), 3.756 (2.33), 3.777 (2.11), 3.783 (1.59), 3.804 (2.97), 3.810 (3.25), 3.833 (2.65), 3.839
 25 (2.67), 3.887 (2.80), 3.915 (2.07), 4.005 (0.73), 4.013 (1.16), 4.021 (1.72), 4.029 (1.94), 4.036 (1.90), 4.045 (1.57), 4.054 (1.36), 4.061 (0.97), 4.106 (3.19), 4.123 (2.20), 4.132

(4.05), 4.149 (3.10), 4.246 (3.66), 4.255 (3.60), 4.272 (2.73), 4.281 (2.45), 6.084 (4.91), 6.104 (5.10), 6.433 (2.28), 6.454 (4.07), 6.476 (2.61), 6.720 (1.92), 6.741 (3.81), 6.758 (3.70), 6.778 (1.62), 7.180 (5.15), 7.199 (8.92), 7.212 (8.89), 7.427 (9.02), 7.964 (12.58), 7.976 (11.33), 8.358 (15.85), 11.012 (5.43).

- 5 LC-MS (method 6): R_t = 0.70 min; MS (ESIpos): m/z = 467 $[M+H]^+$

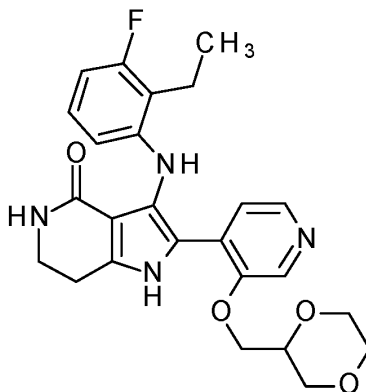
Example 66, example 67

2-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

- 2-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 10

Example 66

2-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 1)



- 15 The title compound from example 65 (74 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (stereoisomer 1, 30 mg, R_t = 4.5-5.3 min) and stereoisomer 2 (31 mg, R_t = 5.3-6.2 min, see example 67).

Preparative chiral HPLC method:

- Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10 μ , 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: methanol; isocratic: 90%A+10%B; flow: 150 ml/min; temperature: 25°C; UV: 254 nm
- 20

Analytical chiral HPLC method:

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3 μ , 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: methanol; isocratic: 90%A+10%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

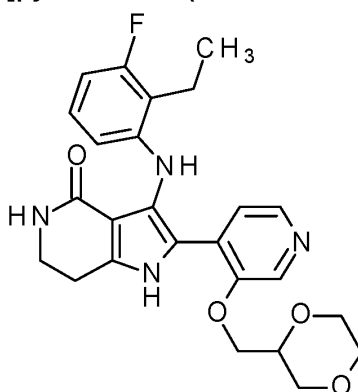
- 5 Analytical chiral HPLC: $R_t = 4.41$ min.

Optical rotation: $[\alpha]_D = -21.9^\circ \pm 0.60^\circ$ ($c = 1.0$ g/100 ml chloroform)

- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.097 (0.44), 1.104 (0.61), 1.206 (6.68), 1.225 (16.00), 1.243 (7.03), 2.074 (3.21), 2.322 (1.00), 2.326 (1.39), 2.332 (1.01), 2.518 (6.14), 2.522 (3.75), 2.664 (1.33), 2.669 (1.92), 2.673 (2.17), 2.696 (3.92), 2.715 (3.83), 2.732 (1.29), 2.846 (3.62), 2.864 (7.78), 2.881 (4.15), 3.404 (3.29), 3.414 (2.85), 3.420 (3.24), 3.431 (8.73), 3.437 (6.06), 3.448 (2.90), 3.457 (4.88), 3.505 (1.14), 3.511 (1.37), 3.533 (2.57), 3.540 (2.76), 3.562 (1.97), 3.570 (1.73), 3.711 (3.19), 3.719 (1.56), 3.726 (2.37), 3.738 (2.90), 3.749 (3.58), 3.755 (2.31), 3.777 (1.96), 3.783 (1.46), 3.804 (2.93), 3.810 (3.13), 3.833 (2.59), 3.839 (2.71), 3.887 (2.80), 3.914 (2.06), 4.013 (1.15), 4.020 (1.68), 4.029 (1.97), 4.036 (1.90), 4.045 (1.59), 4.053 (1.40), 4.060 (0.95), 4.106 (3.06), 4.122 (2.09), 4.132 (3.85), 4.148 (2.90), 4.245 (3.58), 4.255 (3.47), 4.271 (2.68), 4.280 (2.36), 6.083 (4.88), 6.104 (5.09), 6.433 (2.24), 6.454 (4.08), 6.476 (2.56), 6.720 (1.80), 6.741 (3.65), 6.758 (3.54), 6.778 (1.53), 7.179 (5.11), 7.199 (8.20), 7.211 (8.15), 7.426 (8.99), 7.963 (9.54), 7.976 (8.80), 8.357 (13.39), 11.012 (5.48).
- 10
- 15
- 20 LC-MS (method 6): $R_t = 0.70$ min; MS (ESIpos): $m/z = 467$ $[\text{M}+\text{H}]^+$

Example 67

2-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 2)



For the preparation of the racemic title compound see example 65. Separation of enantiomers by preparative chiral HPLC (method see example 66) to give 31 mg of the title compound.

Analytical chiral HPLC (method see example 63): $R_t = 4.49$ min.

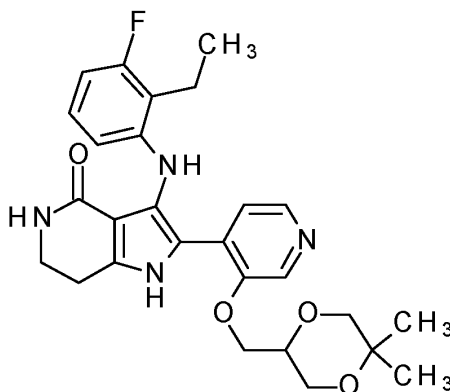
5 Optical rotation: $[\alpha]_D = 22.51^\circ \pm 0.86^\circ$ ($c = 1.0$ g/ 100ml in Chloroform)

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 1.104 (0.57), 1.164 (0.90), 1.206 (6.89), 1.225 (16.00), 1.244 (7.18), 2.322 (0.60), 2.326 (0.81), 2.332 (0.59), 2.518 (3.44), 2.522 (2.12), 2.665 (0.84), 2.669 (1.32), 2.677 (1.68), 2.696 (3.95), 2.715 (3.83), 2.732 (1.33), 2.847 (3.68), 2.864 (7.81), 2.881 (4.16), 3.404 (3.21), 3.415 (2.88), 3.421 (3.23), 3.432 (8.92),
 10 3.437 (6.02), 3.449 (2.91), 3.457 (4.87), 3.506 (1.11), 3.511 (1.37), 3.533 (2.61), 3.540 (2.72), 3.562 (2.00), 3.570 (1.74), 3.712 (3.25), 3.719 (1.51), 3.726 (2.32), 3.738 (2.93), 3.749 (3.59), 3.756 (2.31), 3.777 (1.96), 3.784 (1.44), 3.804 (2.94), 3.810 (3.18), 3.833 (2.64), 3.839 (2.70), 3.887 (2.87), 3.915 (2.12), 4.005 (0.70), 4.014 (1.17), 4.020 (1.70), 4.029 (2.01), 4.037 (1.92), 4.045 (1.57), 4.053 (1.42), 4.060 (0.95), 4.106 (3.05), 4.123 (2.12),
 15 (2.12), 4.132 (3.86), 4.148 (2.88), 4.246 (3.51), 4.255 (3.49), 4.271 (2.68), 4.281 (2.35), 6.084 (4.92), 6.105 (5.14), 6.433 (2.23), 6.454 (4.07), 6.476 (2.59), 6.720 (1.81), 6.741 (3.64), 6.758 (3.58), 6.778 (1.55), 7.180 (5.16), 7.199 (7.86), 7.212 (7.80), 7.426 (9.02), 7.963 (7.86), 7.976 (7.32), 8.358 (12.12), 11.012 (5.54).

LC-MS (method 6): $R_t = 0.70$ min; MS (ESIpos): $m/z = 467$ $[\text{M}+\text{H}]^+$

20 Example 68

2-(3-[[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl]-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



Using an analogous method as described for example 62 with 4-[[[3-[[[5,5-dimethyl-1,4-
 25 dioxan-2-yl]methoxy]pyridin-4-yl)methyl]amino]-N-(2-ethyl-3-fluorophenyl)-2-oxo-1,2,5,6-

tetrahydropyridine-3-carbothioamide (intermediate 6-68, 350 mg, 662 μmol) as the starting material; 82 mg (85% purity, 21% yield) of the title compound were prepared after purification by preparative HPLC (basic conditions).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ [ppm]: 1.051 (1.89), 1.073 (11.18), 1.171 (0.57), 1.182 (0.76), 1.197 (3.04), 1.216 (5.73), 1.234 (3.31), 1.243 (10.52), 2.326 (0.46), 2.518 (1.69), 2.522 (1.07), 2.539 (16.00), 2.669 (0.94), 2.673 (0.76), 2.688 (1.36), 2.706 (1.38), 2.828 (1.23), 2.845 (2.62), 2.862 (1.40), 3.412 (2.22), 3.422 (1.93), 3.428 (1.91), 3.440 (2.37), 3.574 (0.81), 3.582 (0.90), 3.604 (1.34), 3.612 (1.29), 3.629 (0.40), 3.646 (2.91), 3.674 (3.37), 3.703 (0.90), 3.896 (0.52), 3.903 (0.59), 3.912 (0.74), 3.920 (0.70), 3.929 (0.49), 3.938 (0.47), 4.129 (0.89), 4.146 (0.81), 4.155 (1.16), 4.172 (1.00), 4.284 (1.20), 4.292 (1.15), 4.310 (0.88), 4.319 (0.81), 5.758 (2.21), 6.089 (1.68), 6.110 (1.75), 6.420 (0.77), 6.443 (1.38), 6.464 (0.88), 6.709 (0.64), 6.729 (1.28), 6.746 (1.24), 6.767 (0.55), 7.165 (1.72), 7.200 (2.88), 7.213 (2.92), 7.249 (0.48), 7.369 (0.47), 7.382 (0.67), 7.392 (2.91), 7.972 (3.81), 7.985 (3.48), 8.067 (0.61), 8.080 (0.54), 8.372 (5.10), 8.439 (0.78), 11.018 (1.92).

LC-MS (method 6): $R_t = 0.79$ min; MS (ESIpos): $m/z = 495$ $[\text{M}+\text{H}]^+$

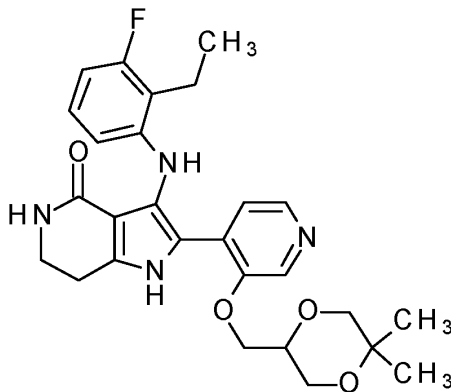
Example 69, example 70

2-(3-([(2R)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

20 2-(3-([(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

Example 69

2-(3-[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 1)



- 5 The title compound from example 68 (32 mg) was separated into enantiomers by preparative chiral HPLC to give title compound (stereoisomer 1, 13 mg, $R_t = 36.8$ -46.0 min) and stereoisomer 2 (10 mg, $R_t = 21.9$ -26.4 min., see example 70)

Preparative chiral HPLC method:

- Instrument: PrepCon Labomatic HPLC-4; Column: Chiralcel OD-H 5 μ , 250x20; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 10 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC method:

- Instrument: Thermo Fisher UltiMate 3000; Column: Chiralcel OD-H 5 μ , 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: $R_t = 7.38$ min.

Optical rotation: $[\alpha]_D = -24.42^\circ \pm 0.72^\circ$ ($c = 1.0$ g/100 ml chloroform)

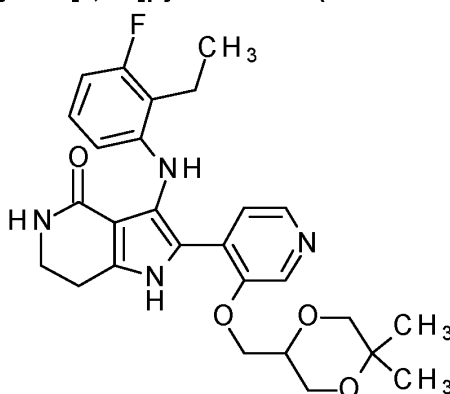
- $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 0.698 (1.11), 0.742 (0.61), 0.834 (0.47), 0.851 (0.63), 1.072 (16.00), 1.147 (1.48), 1.195 (4.00), 1.214 (8.27), 1.233 (6.80), 1.242 (15.37), 1.294 (0.70), 2.322 (0.63), 2.326 (0.85), 2.331 (0.63), 2.517 (3.89), 2.522 (2.40), 2.664 (1.17), 2.668 (1.54), 2.673 (1.19), 2.687 (1.95), 2.705 (1.86), 2.722 (0.66), 2.826 (1.78), 2.843 (3.74), 2.860 (2.02), 3.411 (3.06), 3.420 (2.79), 3.427 (2.73), 3.440 (3.33), 3.573 (0.89), 3.581 (1.05), 3.603 (1.84), 3.611 (1.82), 3.646 (3.73), 3.674 (4.44), 3.703 (1.16), 3.893 (0.70), 3.901 (0.84), 3.910 (1.06), 3.918 (0.98), 3.926 (0.71), 3.935 (0.66), 4.126 (1.20), 4.143 (1.14), 4.152 (1.62), 4.169 (1.39), 4.281 (1.52), 4.290 (1.61), 4.307 (1.22),

4.316 (1.10), 6.088 (2.37), 6.108 (2.47), 6.417 (1.08), 6.440 (1.96), 6.461 (1.24), 6.707 (0.87), 6.728 (1.74), 6.745 (1.70), 6.765 (0.75), 7.159 (2.50), 7.197 (3.08), 7.209 (3.08), 7.378 (4.32), 7.967 (2.35), 7.980 (2.25), 8.368 (3.77), 11.014 (2.75).

LC-MS (method 6): $R_t = 0.78$ min; MS (ESIpos): $m/z = 495$ $[M+H]^+$

5 Example 70

2-(3-[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 2)



For the preparation of the racemic title compound see example 68. Separation of enantiomers by preparative chiral HPLC (method see example 69) to give 10 mg of the title compound.

Analytical chiral HPLC (method see example 69): $R_t = 5.50$ min.

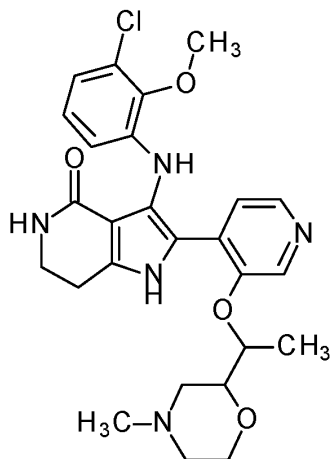
Optical rotation: $[\alpha]_D = 33.52^\circ \pm 1.07^\circ$ ($c = 1.0$ g/100ml in Chloroform)

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 0.852 (0.50), 1.072 (16.00), 1.147 (0.81), 1.195 (3.63), 1.214 (8.06), 1.233 (5.99), 1.242 (15.29), 2.322 (0.67), 2.326 (0.93), 2.331 (0.67), 2.518 (4.20), 2.522 (2.70), 2.664 (1.19), 2.668 (1.61), 2.673 (1.22), 2.687 (1.88), 2.705 (1.81), 2.722 (0.65), 2.826 (1.76), 2.843 (3.72), 2.860 (1.98), 3.411 (2.99), 3.420 (2.72), 3.427 (2.69), 3.440 (3.28), 3.573 (0.90), 3.582 (1.04), 3.603 (1.85), 3.611 (1.82), 3.646 (3.73), 3.674 (4.50), 3.703 (1.19), 3.893 (0.69), 3.901 (0.82), 3.910 (1.04), 3.918 (0.98), 3.927 (0.70), 3.935 (0.65), 4.126 (1.23), 4.143 (1.15), 4.152 (1.63), 4.169 (1.40), 4.281 (1.53), 4.290 (1.62), 4.307 (1.24), 4.316 (1.12), 6.088 (2.36), 6.108 (2.47), 6.419 (1.10), 6.440 (1.96), 6.461 (1.24), 6.707 (0.90), 6.728 (1.77), 6.744 (1.72), 6.765 (0.75), 7.159 (2.47), 7.196 (3.38), 7.209 (3.41), 7.378 (4.36), 7.967 (2.84), 7.980 (2.69), 8.368 (4.39), 11.014 (2.71).

LC-MS (method 6): $R_t = 0.78$ min; MS (ESIpos): $m/z = 495$ $[M+H]^+$

Example 71

3-(3-chloro-2-methoxyanilino)-2-[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one



- 5 Using an analogous method as described for example 62 with N-(3-chloro-2-methoxyphenyl)-4-({[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]methyl}amino)-2-oxo-1,2,5,6-tetrahydropyridine-3-carbothioamide (intermediate 6-71, 420 mg, 769 μ mol) as the starting material; 139 mg (95% purity, 33% yield) of the title compound were prepared after purification by preparative HPLC (basic conditions).
- 10 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.277 (4.27), 1.293 (4.32), 1.333 (0.47), 1.350 (0.67), 1.358 (4.99), 1.374 (4.94), 1.824 (0.55), 1.851 (0.91), 1.878 (0.61), 1.893 (0.74), 1.906 (0.40), 1.920 (1.17), 1.934 (0.70), 1.947 (0.76), 1.956 (0.54), 1.965 (0.55), 1.987 (0.64), 1.995 (0.65), 2.128 (0.82), 2.159 (7.74), 2.180 (8.74), 2.322 (0.51), 2.326 (0.68), 2.332 (0.49), 2.518 (2.39), 2.522 (1.49), 2.577 (0.56), 2.606 (0.54), 2.642 (0.72), 2.665 (0.85), 2.669 (1.29), 2.673 (1.01), 2.748 (1.31), 2.775 (1.22), 2.835 (0.82), 2.852 (2.10), 2.867 (2.15), 2.882 (1.06), 3.403 (1.26), 3.414 (1.72), 3.420 (2.29), 3.437 (1.06), 3.546 (0.63), 3.551 (0.64), 3.640 (0.42), 3.663 (1.06), 3.668 (1.07), 3.680 (0.51), 3.691 (0.88), 3.696 (0.73), 3.712 (0.46), 3.717 (0.51), 3.724 (0.46), 3.729 (0.51), 3.738 (0.48), 3.743 (0.44), 3.750 (0.47), 3.754 (0.43), 3.867 (12.16), 3.891 (16.00), 3.969 (0.62), 3.993 (0.54), 20 4.637 (0.80), 4.650 (1.17), 4.659 (0.74), 4.665 (1.09), 4.675 (0.61), 6.146 (2.23), 6.155 (2.15), 6.162 (1.69), 6.170 (2.32), 6.642 (2.11), 6.647 (2.51), 6.657 (4.69), 6.667 (0.52), 6.672 (0.41), 6.680 (0.65), 6.692 (5.88), 6.701 (2.71), 6.709 (2.25), 7.122 (1.19), 7.160 (1.40), 7.290 (2.01), 7.300 (2.69), 7.303 (2.35), 7.313 (2.45), 7.426 (0.41), 7.435 (2.71), 7.520 (3.23), 7.989 (3.33), 8.002 (3.13), 8.019 (2.70), 8.031 (2.40), 8.402 (3.96), 8.421 25 (3.26), 11.070 (1.28), 11.110 (1.54).

LC-MS (method 6): $R_t = 0.54$ min; MS (ESIpos): $m/z = 512$ $[M+H]^+$

Example 72, example 73, example 74, example 75

3-(3-chloro-2-methoxyanilino)-2-[3-({(1R)-1-[(2R)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

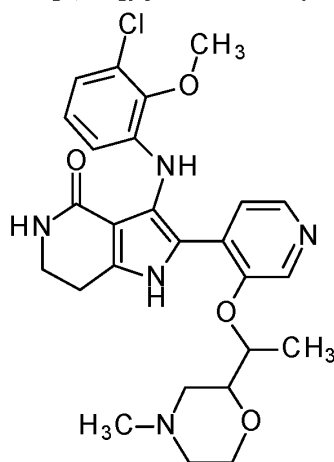
- 5 3-(3-chloro-2-methoxyanilino)-2-[3-({(1S)-1-[(2S)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

3-(3-chloro-2-methoxyanilino)-2-[3-({(1R)-1-[(2S)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

- 10 3-(3-chloro-2-methoxyanilino)-2-[3-({(1S)-1-[(2R)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

Example 72

3-(3-chloro-2-methoxyanilino)-2-[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 1)



- 15 The title compound from example 71 (135 mg) was separated into four stereoisomers by preparative chiral HPLC. The title compound stereoisomer 1, (20 mg, $R_t = 6.8$ -7.6 min) was obtained besides stereoisomer 2 (27 mg, $R_t = 9.6$ -10.9 min., see example 73), stereoisomer 3 (37 mg, see example 74) and stereoisomer 4 (37 mg, see example 75).

Preparative chiral HPLC method:

Instrument: PrepCon Labomatic HPLC 4; Column: YMC Cellulose SB 10 μ , 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm

5 Analytical chiral HPLC method:

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3 μ , 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: R_t = 3.85 min.

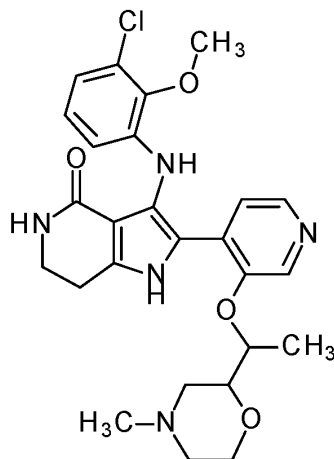
10 Optical rotation: $[\alpha]_D = 16.84^\circ \pm 0.40^\circ$ (c = 1.0 g/100 ml chloroform)

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.137 (0.95), 1.159 (0.63), 1.232 (0.54), 1.277 (5.83), 1.293 (5.97), 1.826 (0.63), 1.853 (1.16), 1.880 (0.71), 1.907 (0.46), 1.928 (0.77), 1.935 (0.78), 1.956 (0.45), 2.160 (9.53), 2.326 (0.58), 2.522 (2.28), 2.579 (0.94), 2.608 (0.86), 2.665 (0.41), 2.669 (0.54), 2.673 (0.40), 2.748 (0.95), 2.776 (0.90), 2.835 (1.17), 2.852 (2.46), 2.869 (1.37), 3.402 (1.17), 3.413 (1.92), 3.419 (1.92), 3.431 (0.97), 3.523 (0.52), 3.545 (0.95), 3.551 (0.92), 3.573 (0.56), 3.660 (0.71), 3.670 (0.67), 3.690 (0.73), 3.866 (16.00), 3.891 (0.61), 4.649 (0.83), 4.659 (0.85), 4.664 (0.85), 4.675 (0.80), 5.758 (1.51), 6.145 (1.46), 6.155 (1.45), 6.159 (1.36), 6.169 (1.48), 6.643 (2.83), 6.647 (3.21), 6.657 (5.61), 6.667 (0.55), 7.123 (1.81), 7.291 (2.03), 7.303 (2.10), 7.435 (3.81), 8.018 (1.65), 8.031 (1.59), 8.420 (2.63), 11.071 (2.01).

LC-MS (method 6): R_t = 0.53 min; MS (ESIpos): m/z = 512 $[\text{M}+\text{H}]^+$

Example 73

3-(3-chloro-2-methoxyanilino)-2-[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 2)



- 5 For the preparation of the racemic title compound see example 71. Separation of stereoisomers by preparative chiral HPLC (method see example 72) to give 27 mg of the title compound stereoisomer 2.

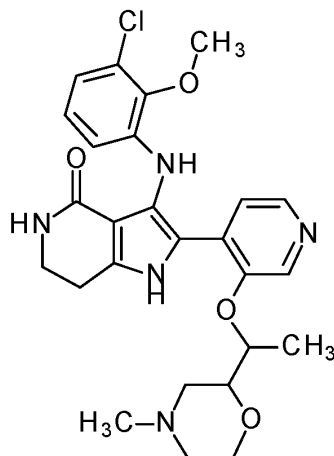
Analytical chiral HPLC (method see example 72): $R_t = 5.24$ min.

Optical rotation: $[\alpha]_D = 16.84^\circ \pm 0.40^\circ$ ($c = 1.0$ g/ 100ml in Chloroform)

- 10 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 1.137 (0.95), 1.159 (0.63), 1.232 (0.54), 1.277 (5.83), 1.293 (5.97), 1.826 (0.63), 1.853 (1.16), 1.880 (0.71), 1.907 (0.46), 1.928 (0.77), 1.935 (0.78), 1.956 (0.45), 2.160 (9.53), 2.326 (0.58), 2.522 (2.28), 2.579 (0.94), 2.608 (0.86), 2.665 (0.41), 2.669 (0.54), 2.673 (0.40), 2.748 (0.95), 2.776 (0.90), 2.835 (1.17), 2.852 (2.46), 2.869 (1.37), 3.402 (1.17), 3.413 (1.92), 3.419 (1.92), 3.431 (0.97), 3.523 (0.52), 3.545 (0.95), 3.551 (0.92), 3.573 (0.56), 3.660 (0.71), 3.670 (0.67), 3.690 (0.73), 3.866 (16.00), 3.891 (0.61), 4.649 (0.83), 4.659 (0.85), 4.664 (0.85), 4.675 (0.80), 5.758 (1.51), 6.145 (1.46), 6.155 (1.45), 6.159 (1.36), 6.169 (1.48), 6.643 (2.83), 6.647 (3.21), 6.657 (5.61), 6.667 (0.55), 7.123 (1.81), 7.291 (2.03), 7.303 (2.10), 7.435 (3.81), 8.018 (1.65), 8.031 (1.59), 8.420 (2.63), 11.071 (2.01).
- 15
- 20 LC-MS (method 6): $R_t = 0.53$ min; MS (ESIpos): $m/z = 512$ $[\text{M}+\text{H}]^+$

Example 74

3-(3-chloro-2-methoxyanilino)-2-[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 3)



- 5 For the preparation of the racemic title compound see example 71. For the separation of stereoisomers 3 and stereoisomer 4 (see example 75) first a preparative chiral HPLC was carried out using the method described in example 72. One fraction ($R_t = 5.5\text{--}6.5$ min.) was further separated by another preparative chiral HPLC using the following method to give 37 mg of the title compound stereoisomer 3.

10 Preparative chiral HPLC method:

Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IG 5 μ 250x30mm; eluent A: CO₂; eluent B: 2-propanol + 0.4 vol % diethylamin; isocratic: 40%B; flow: 100 ml/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

Analytical chiral HPLC method:

- 15 Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IG 5 μ 100x4.6mm; eluent A: CO₂; eluent B: 2-propanol + 0.4 vol % diethylamin; isocratic: 40%B; flow: 4 ml/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

Analytical chiral HPLC: $R_t = 3.98$ min.

Optical rotation: $[\alpha]_D = 30.08^\circ \pm 0.91^\circ$ ($c = 1.0$ g/ 100ml in Chloroform)

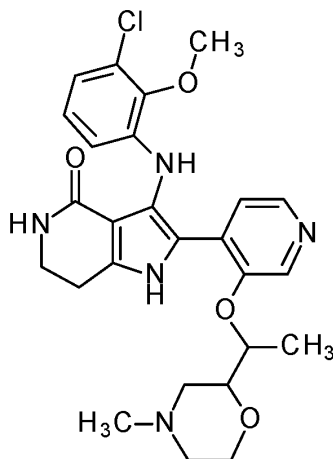
- 20 ¹H-NMR (400 MHz, DMSO-d₆) delta [ppm]: 0.697 (0.90), 1.026 (1.27), 1.042 (1.28), 1.088 (0.45), 1.137 (0.56), 1.232 (1.77), 1.293 (0.50), 1.358 (5.47), 1.374 (5.50), 1.893 (0.68), 1.920 (1.22), 1.947 (0.76), 1.959 (1.07), 1.966 (0.44), 1.987 (0.74), 1.995 (0.74), 2.016 (0.44), 2.180 (9.88), 2.327 (0.45), 2.523 (1.85), 2.643 (0.83), 2.669 (1.19), 2.749 (0.84),

- 2.776 (0.82), 2.847 (0.81), 2.865 (1.90), 2.882 (1.25), 3.409 (0.92), 3.419 (1.42), 3.425 (1.62), 3.439 (0.79), 3.640 (0.45), 3.663 (0.82), 3.668 (0.85), 3.691 (0.49), 3.712 (0.49), 3.718 (0.58), 3.724 (0.55), 3.730 (0.61), 3.738 (0.58), 3.744 (0.54), 3.750 (0.58), 3.755 (0.50), 3.891 (16.00), 3.970 (0.75), 3.993 (0.66), 4.638 (0.75), 4.653 (0.92), 4.666 (0.75),
- 5 6.146 (1.43), 6.154 (1.30), 6.162 (1.45), 6.170 (1.48), 6.681 (0.60), 6.693 (6.14), 6.701 (2.75), 6.709 (2.40), 6.729 (0.44), 7.162 (1.65), 7.301 (1.65), 7.313 (1.71), 7.521 (3.68), 7.990 (1.16), 8.002 (1.10), 8.403 (1.76), 11.111 (1.82).

LC-MS (method 6): $R_t = 0.53$ min; MS (ESIpos): $m/z = 512$ $[M+H]^+$

Example 75

- 10 3-(3-chloro-2-methoxyanilino)-2-[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (stereoisomer 4)



- For the preparation of the racemic title compound see example 71. For the separation of stereoisomers 3 (see example 74) and stereoisomer 4 (example 75) first a preparative chiral
- 15 HPLC was carried out using the method described in example 72. One fraction ($R_t = 5.5$ - 6.5 min.), was further separated by another preparative chiral HPLC (method see example 74) to give 37 mg of the title compound stereoisomer 4.

Analytical chiral HPLC: $R_t = 7.23$ min.

Optical rotation: $[\alpha]_D = -24.97^\circ \pm 0.50^\circ$ ($c = 1.0$ g/ 100ml in Chloroform)

- 20 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ [ppm]: 0.697 (2.05), 0.742 (1.32), 0.760 (1.30), 0.832 (0.55), 0.851 (0.74), 0.973 (0.66), 0.984 (0.67), 0.991 (0.96), 0.999 (0.64), 1.009 (0.72), 1.026 (0.75), 1.042 (0.77), 1.070 (0.82), 1.088 (1.27), 1.106 (1.27), 1.151 (4.27), 1.232 (4.01), 1.293 (1.22), 1.358 (5.91), 1.373 (6.07), 1.894 (0.71), 1.921 (1.28), 1.948 (0.80),

1.959 (1.52), 1.988 (0.82), 1.995 (0.85), 2.017 (0.51), 2.181 (10.00), 2.322 (0.74), 2.326 (0.99), 2.331 (0.74), 2.522 (4.96), 2.643 (0.98), 2.669 (1.77), 2.749 (0.99), 2.777 (0.93), 2.849 (0.99), 2.865 (2.18), 2.882 (1.43), 3.408 (1.14), 3.424 (1.91), 3.640 (0.51), 3.663 (0.93), 3.668 (0.95), 3.692 (0.56), 3.718 (0.67), 3.730 (0.69), 3.743 (0.64), 3.750 (0.64),
5 3.891 (16.00), 3.969 (0.87), 3.993 (0.79), 4.638 (0.82), 4.653 (1.03), 4.667 (0.80), 6.145 (1.44), 6.154 (1.38), 6.161 (1.41), 6.169 (1.51), 6.681 (0.63), 6.693 (5.87), 6.701 (2.92), 6.709 (2.49), 6.729 (0.47), 7.162 (1.85), 7.300 (1.91), 7.313 (1.96), 7.520 (3.80), 7.990 (1.46), 8.002 (1.40), 8.402 (2.29), 11.110 (1.99).

LC-MS (method 6): $R_t = 0.53$ min; MS (ESIpos): $m/z = 512$ [M+H]⁺

10

EXPERIMENTAL SECTION – BIOLOGICAL ASSAYS

The pharmacological activity of the compounds according to the invention can be assessed using *in vitro*- and/or *in vivo*-assays, as known to the person skilled in the art. The following
15 examples describe the biological activity of the compounds according to the invention, without the invention being limited to said examples.

Example compounds according to the invention were tested in selected biological assays one or more times. When tested more than once, data are reported as either average values
20 or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median
25 is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values or median values calculated utilizing data
30 sets obtained from testing of one or more synthetic batch.

The *in vitro* activity of the compounds of the present invention can be demonstrated in the following assays:

Expression and purification of the EGFR proteins used in the biochemical kinase assays

The different EGFR proteins used in the biochemical kinase activity inhibition assays were generated inhouse by expression in insect cells using Baculo Virus system and subsequent purification as described in the following paragraphs.

Expression constructs:

The cDNAs encoding the various protein sequences from human EGFR human (P00533) were optimized for expression in eukaryotic cells and synthesized by the GeneArt Technology at Life Technologies.

These DNA sequences encoded the following sequence:

Construct EGFR #1 amino acid R669 to A1210

Construct EGFR #2 amino acid R669 to A1210 and the insertion of the amino acids sequence ASV between V769 and D770

Construct EGFR #3 amino acid R669 to A1210 and the insertion of the amino acids sequence SVD between D770 and N771

Additionally all constructs EGFR #1 to #3 encoded: at the N-terminus a TEV (Tobacco etch virus) protease cleavage site (DYDIPTTENLYFQG), at the C-terminus two stop codons and additionally 5' and 3' att-DNA sequences for Gateway Cloning.

Each of the four EGFR constructs was subcloned using the Gateway Technology into the Destination vector pD-Ins1. The vector pD-Ins1 is a Baculovirus transfer vector (based on vector pVL1393, Pharmingen) which provides a N-terminal fusion of a GST-tag to the integrated gene construct. The respective transfer vectors were termed pD-Ins1_ EGFR #1, pD-Ins1_ EGFR #2, pD-Ins1_ EGFR #3.

EGFR amino acid sequences:

GST-EGFR #1 (Wild Type)

MSPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYID
 GDVKLTQSMIIRYIADKHNMMLGGCPKERAEISMLEGAVLDIRYGVSRAYSKDFETLKVD
 FLSKLP EMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFK
 KRIEAIPQIDKYLKSSKYIAWPLQGQWQATFGGGDHPPKSDPITSLYKKAGSDYDIPTTEN
 LYFQGRRRHIVRKRTLRLQLERELVEPLTPSGEAPNQALLRILKETEFKKIKVLGSGAFG
 TVYKGLWIPEGEKV KIPVAIKELREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTV
 QLITQLMPFGCLLDYVREHKDNIGSQYLLNWCVQIAKGMNYLEDRLVHRDLAARNVLV

KTPQHVKITDFGLAKLLGAEKEYHAEGGKVPKWMMALESILHRIYTHQSDVWSYGVTVW
ELMTFGSKPYDGIPASEISSILEKGERLPQPPICTIDVYMIMVKCWMIDADSRPKFRELIIEF
SKMARDPQRYLVIQGDERMHLPSPTDSNFYRALMDEEDMDDVVDADLEYLIPQQGFFSS
PSTSRTPLLSSLSATSNNSTVACIDRNLQSCPIKEDSFLQRYSSDPTGALTEDSIDDTFL
5 PVPEYINQSVPKRPAGSVQNPVYHNQPLNPAPSRDPHYQDPHSTAVGNPEYLNTVQPT
CVNSTFDSPAHWAKGSHQISLDNPDYQQDFFPKEAKPNGIFKGSTAENAEYLRVAPQS
SEFIGA

GST-EGFR #2 (ASV between V769 and D770)

MSPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYID
10 GDVKLTQSMAIIRYIADKHNMLGGCPKERAESMLEGAVLDIRYGVSRAYSQKDFETLKVD
FLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFK
KRIEAIQIDKYLKSSKYIAWPLQGQWQATFGGGDHPPKSDPITSLYKKAGSDYDIPTTEN
LYFQGRRRHIVRKRTLRRLLQERELVEPLTPSGEAPNQALLRILKETEFKKIKVLGSGAFG
TVYKGLWIPEGEKVKIPVAIKELREATSPKANKEILDEAYVMASVASVDNPHVCRLLGICLT
15 STVQLITQLMPFGCLLDYVREHKDNIGSQYLLNWCVQIAKGMNYLEDRLVHRDLAARN
VLVKTPQHVKITDFGLAKLLGAEKEYHAEGGKVPKWMMALESILHRIYTHQSDVWSYGV
TVWELMTFGSKPYDGIPASEISSILEKGERLPQPPICTIDVYMIMVKCWMIDADSRPKFRE
LIIEFSKMARDPQRYLVIQGDERMHLPSPTDSNFYRALMDEEDMDDVVDADLEYLIPQQGF
FSSPSTSRTPLLSSLSATSNNSTVACIDRNLQSCPIKEDSFLQRYSSDPTGALTEDSIDD
20 TFLPVPEYINQSVPKRPAGSVQNPVYHNQPLNPAPSRDPHYQDPHSTAVGNPEYLNTVQ
PTCVNSTFDSPAHWAKGSHQISLDNPDYQQDFFPKEAKPNGIFKGSTAENAEYLRVAP
QSSEFIGA

GST-EGFR #3 (SVD between D770 and N771)

MSPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYID
25 GDVKLTQSMAIIRYIADKHNMLGGCPKERAESMLEGAVLDIRYGVSRAYSQKDFETLKVD
FLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFK
KRIEAIQIDKYLKSSKYIAWPLQGQWQATFGGGDHPPKSDPITSLYKKAGSDYDIPTTEN
LYFQGRRRHIVRKRTLRRLLQERELVEPLTPSGEAPNQALLRILKETEFKKIKVLGSGAFG
TVYKGLWIPEGEKVKIPVAIKELREATSPKANKEILDEAYVMASVDSVDNPHVCRLLGICLT
30 STVQLITQLMPFGCLLDYVREHKDNIGSQYLLNWCVQIAKGMNYLEDRLVHRDLAARN
VLVKTPQHVKITDFGLAKLLGAEKEYHAEGGKVPKWMMALESILHRIYTHQSDVWSYGV
TVWELMTFGSKPYDGIPASEISSILEKGERLPQPPICTIDVYMIMVKCWMIDADSRPKFRE
LIIEFSKMARDPQRYLVIQGDERMHLPSPTDSNFYRALMDEEDMDDVVDADLEYLIPQQGF
FSSPSTSRTPLLSSLSATSNNSTVACIDRNLQSCPIKEDSFLQRYSSDPTGALTEDSIDD
35 TFLPVPEYINQSVPKRPAGSVQNPVYHNQPLNPAPSRDPHYQDPHSTAVGNPEYLNTVQ

PTCVNSTFDSPAHWAKGSHQISLDNPDYQQDFFPKEAKPNGIFKGSTAENAEYLRVAP
QSSEFIGA

Generation of recombinant Baculovirus:

- 5 In separate approaches each of the three transfer vectors was co-transfected in Sf9 cells with Baculovirus DNA (Flashbac Gold DNA, Oxford Expression Technologies) using Fugene HD (Roche). After 5 days the supernatant of the transfected cells containing the recombinant Baculovirus encoding the various EGFR proteins was used for further infection of Sf9 cells for virus amplification whereby the virus titer was monitored using qPCR.

10

EGFR expression in Sf9 cells using bioreactor:

Sf9 cells cultured (Insect-xpress medium, Lonza, 27 °C) in a Wave-bioreactor with a disposable culture bag were infected at a cell density of 10⁶ cells/ml with one of the recombinant baculovirus stocks at a multiplicity of infection of 1 and incubated for 48 h.

- 15 Subsequently the cells were harvested by centrifugation and the cell pellet frozen at -80 °C.

Purification of the GST-EGFR fusion proteins:

Purification of the GST-EGFR fusion proteins was achieved by affinity chromatography using Glutathion Sepharose 4B matrix (GE Healthcare Life Sciences).

20

The pelleted cells (from 4 l cell culture) were resuspended in Lysis-Buffer (50 mM HEPES pH 7.4, 150 mM NaCl, 5 % Glycerol, 1 mM MgCl₂, 1 mM MnCl₂, 0.5 mM Na₃VO₄) and lysed by a freeze-thaw cycle followed by an incubation on ice for 60 min. The supernatant was centrifuged at 4000 x g for 30 min. at 4 °C. The supernatant was then incubated with
25 Glutathion Sepharose 4B matrix (in a glass bottle rotating for 16 h, at 4 °C) for binding of the GST EGFR fusion protein, rinsed with Wash-Buffer and finally the bound protein was eluted using Elution-Buffer (Lysis Buffer plus 25 mM Glutathione) and shock frozen with liquid nitrogen.

30 WT-EGFR kinase assay

Inhibitory activity of compounds of the present invention against wild-type Epidermal Growth Factor Receptor (EGFR) was quantified employing the TR-FRET based EGFR assay as described in the following paragraphs.

35

Recombinant fusion protein of N-terminal Glutathion-S-Transferase (GST) and a fragment of human EGFR (amino acids R669 to A1210), expressed in Sf9 insect cells and purified via affinity chromatography using Glutathion Sepharose as described above, was used as a kinase. As substrate for the kinase reaction the biotinylated peptide biotin-Ahx-
5 AEEEEYFELVAKKK (C-terminus in amide form) was used, which can be purchased e.g. from the company Biosynthan GmbH (Berlin-Buch, Germany).

For the assay 50 nl of a 100 fold concentrated solution of the test compound in DMSO was pipetted into either a black low volume 384 well microtiter plate or a black 1536 well
10 microtiter plate (both Greiner Bio-One, Frickenhausen, Germany), 2 µl of a solution of EGFR in aqueous assay buffer [50 mM Hepes pH 7.0, 10 mM MgCl₂, 1mM dithiothreitol, 0.5 mM EGTA, 0.3 mM activated sodium ortho-vanadate, 0.005 % (w/v) bovine serum albumin, 0.005% (v/v) Tween-20] were added and the mixture was incubated for 15 min at 22°C to allow pre binding of the test compounds to the enzyme before the start of the kinase
15 reaction. Then the kinase reaction was started by the addition of 3 µL of a solution of adenosine tri phosphate (ATP, 3.33 mM => final conc. in the 5 µL assay volume is 2 mM) and substrate (1.67 µM => final conc. in the 5 µL assay volume is 1 µM) in assay buffer and the resulting mixture was incubated for a reaction time of 30 min at 22°C. The concentration of EGFR was adjusted depending of the activity of the enzyme lot and was chosen
20 appropriate to have the assay in the linear range, typical concentration was 7.6 pg/µl. The reaction was stopped by the addition of 3 µl of a solution of HTRF detection reagents (83.3 nM streptavidine-XL665 [Cisbio Bioassays, Codolet, France] and 1.67 nM PT66-Tb-Cryptate, an terbium-cryptate labelled anti-phospho-tyrosine antibody from Cisbio Bioassays [instead of the PT66 Tb cryptate PT66 Eu Chelate from Perkin Elmer can also
25 be used]) in an aqueous EDTA-solution (133.3 mM EDTA, 0.2 % (w/v) bovine serum albumin in 50 mM HEPES pH 7.5).

The resulting mixture was incubated 1 h at 22°C to allow the binding of the biotinylated phosphorylated peptide to the streptavidine-XL665 and the PT66-Tb-Cryptate.
30 Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the PT66-Tb-Cryptate to the streptavidine-XL665. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 337 nm were measured in a HTRF reader, e.g. a Pherastar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm
35 was taken as the measure for the amount of phosphorylated substrate. The data were

normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Usually the test compounds were tested on the same microtiterplate in 11 different concentrations in the range of 20 μ M to 0.07 nM (20 μ M, 5.7 μ M, 1.6 μ M, 0.47 μ M, 0.13 μ M, 38 nM, 11 nM, 3.1 nM, 0.9 nM, 0.25 nM and 0.07 nM, the
5 dilution series prepared separately before the assay on the level of the 100-fold concentrated solutions in DMSO by serial dilutions, exact concentrations may vary depending pipettors used) in duplicate values for each concentration and IC₅₀ values were calculated using Genedata Screener™ software.

10 Exon20-mutant-EGFR(D770_N771insSVD) kinase assay

Inhibitory activity of compounds of the present invention against an Epidermal Growth Factor Receptor (EGFR) with an insertion of the amino acids sequence SVD between D770 and N771 was quantified employing the TR-FRET based kinase activity assay as described
15 in the following paragraphs.

A recombinant fusion protein of N-terminal Glutathion-S-Transferase (GST) and a fragment of human EGFR variant (amino acids R669 to A1210 with insertion of the amino acids sequence SVD between D770 and N771 ("EGFR ins SVD"), expressed in Sf9
20 insect cells and purified via affinity chromatography using Glutathion Sepharose as described above, was used as a kinase. As substrate for the kinase reaction the biotinylated peptide biotin-Ahx-AEEEEYFELVAKKK (C-terminus in amide form) was used which can be purchased e.g. from the company Biosynthan GmbH (Berlin-Buch, Germany).

25 For the assay 50 nl of a 100-fold concentrated solution of the test compound in DMSO was pipetted into either a black low volume 384 well microtiter plate or a black 1536 well microtiter plate (both Greiner Bio-One, Frickenhausen, Germany), 2 μ l of a solution of EGFR in aqueous assay buffer [50 mM Hepes pH 7.0, 10 mM MgCl₂, 1 mM dithiothreitol, 0.5 mM EGTA, 0.3 mM activated sodium ortho-vanadate, 0.005 % (w/v) bovine serum albumin,
30 0.005% (v/v) Tween-20] were added and the mixture was incubated for 15 min at 22°C to allow pre binding of the test compounds to the enzyme before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 μ L of a solution of adenosine tri phosphate (ATP, 3.33 mM => final conc. in the 5 μ L assay volume is 2 mM)
35 and substrate (1.67 μ M => final conc. in the 5 μ L assay volume is 1 μ M) in assay buffer and

- the resulting mixture was incubated for a reaction time of 30 min at 22°C. The concentration of EGFR was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical concentration was 15 pg/μl. The reaction was stopped by the addition of 3 μl of a solution of HTRF detection reagents (83.3 nM streptavidine-XL665 [Cisbio Bioassays, Codolet, France] and 1.67 nM PT66-Tb-Cryptate, a terbium-cryptate labelled anti-phospho-tyrosine antibody from Cisbio Bioassays [instead of the PT66 Tb cryptate PT66 Eu Chelate from Perkin Elmer can also be used]) in an aqueous EDTA-solution (133.3 mM EDTA, 0.2 % (w/v) bovine serum albumin in 50 mM HEPES pH 7.5).
- 10 The resulting mixture was incubated 1 h at 22°C to allow the binding of the biotinylated phosphorylated peptide to the streptavidine-XL665 and the PT66-Tb-Cryptate. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the PT66-Tb-Cryptate to the streptavidine-XL665. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 337 nm
- 15 were measured in a HTRF reader, e.g. a Pherastar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Usually the test compounds were tested on the same
- 20 microtiterplate in 11 different concentrations in the range of 20 μM to 0.07 nM (20 μM, 5.7 μM, 1.6 μM, 0.47 μM, 0.13 μM, 38 nM, 11 nM, 3.1 nM, 0.9 nM, 0.25 nM and 0.07 nM, the dilution series prepared separately before the assay on the level of the 100fold concentrated solutions in DMSO by serial dilutions, exact concentrations may vary depending pipettors used) in duplicate values for each concentration and IC₅₀ values were calculated using
- 25 Genedata Screener™ software.

Exon20-mutant-EGFR(V769_D770insASV) kinase assay

- Inhibitory activity of compounds of the present invention against an Epidermal Growth
- 30 Factor Receptor (EGFR) with an insertion of the amino acids sequence ASV between V769 and D770 was quantified employing the TR-FRET based kinase activity assay as described in the following paragraphs.

- A recombinant fusion protein of N-terminal Glutathion-S-Transferase (GST) and a
- 35 fragment of human EGFR variant (amino acids R669 to A1210 with insertion of the amino

acids sequence ASV between V769 and D770; ("EGFR ins ASV"), expressed in Sf9 insect cells and purified via affinity chromatography using Glutathion Sepharose as described above, was used as kinase. As substrate for the kinase reaction the biotinylated peptide biotin-Ahx-AEEEEYFELVAKKK (C-terminus in amide form) was used which can
5 be purchased e.g. form the company Biosynthan GmbH (Berlin-Buch, Germany).

For the assay 50 nl of a 100-fold concentrated solution of the test compound in DMSO was pipetted into either a black low volume 384well microtiter plate or a black 1536 well microtiter plate (both Greiner Bio-One, Frickenhausen, Germany), 2 µl of a solution of EGFR in
10 aqueous assay buffer [50 mM Hepes pH 7.0, 10 mM MgCl₂, 1mM dithiothreitol, 0.5 mM EGTA, 0.3 mM activated sodium ortho-vanadate, 0.005 % (w/v) bovine serum albumin, 0.005% (v/v) Tween-20] were added and the mixture was incubated for 15 min at 22°C to allow pre binding of the test compounds to the enzyme before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 µL of a solution of
15 adenosine tri phosphate (ATP, 3.33 mM => final conc. in the 5 µL assay volume is 2 mM) and substrate (1.67 µM => final conc. in the 5 µL assay volume is 1 µM) in assay buffer and the resulting mixture was incubated for a reaction time of 30 min at 22°C. The concentration of EGFR was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical concentration was 2.5 pg/µl. The
20 reaction was stopped by the addition of 3 µl of a solution of HTRF detection reagents (83.3 nM streptavidine-XL665 [Cisbio Bioassays, Codolet, France] and 1.67 nM PT66-Tb-Cryptate, an terbium-cryptate labelled anti-phospho-tyrosine antibody from Cisbio Bioassays [instead of the PT66 Tb cryptate PT66 Eu Chelate from Perkin Elmer can also be used]) in an aqueous EDTA-solution (133.3 mM EDTA, 0.2 % (w/v) bovine serum
25 albumin in 50 mM HEPES pH 7.5).

The resulting mixture was incubated 1 h at 22°C to allow the binding of the biotinylated phosphorylated peptide to the streptavidine-XL665 and the PT66-Tb-Cryptate. Subsequently the amount of phosphorylated substrate was evaluated by measurement of
30 the resonance energy transfer from the PT66-Tb-Cryptate to the streptavidine-XL665. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 337 nm were measured in a HTRF reader, e.g. a Pherastar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were
35 normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components

- but no enzyme = 100 % inhibition). Usually the test compounds were tested on the same microtiterplate in 11 different concentrations in the range of 20 μ M to 0.07 nM (20 μ M, 5.7 μ M, 1.6 μ M, 0.47 μ M, 0.13 μ M, 38 nM, 11 nM, 3.1 nM, 0.9 nM, 0.25 nM and 0.07 nM, the dilution series prepared separately before the assay on the level of the 100-fold concentrated solutions in DMSO by serial dilutions, exact concentrations may vary depending pipettors used) in duplicate values for each concentration and IC₅₀ values were calculated using Genedata Screener™ software. Table 2 shows the results of the inhibition in mutant EGFR biochemical assay.

10 Table 2:

Example No.	mutEGFR (D770_N771insSVD) kinase assay IC ₅₀ [mol/l]
1	1.59 E-10
2	< 7.25 E-11 7.79 E-11 7.87 E-11 9.12 E-11 1.65 E-10 2.00 E-10
3	1.37 E-10
4	2.56 E-10
5	< 7.25 E-11 8.51 E-11 1.12 E-10 1.14 E-10 1.20 E-10 1.24 E-10 1.36 E-10
6	1.00 E-10
7	1.37 E-10
8	7.99 E-11

Example No.	mutEGFR (D770_N771insSVD) kinase assay IC ₅₀ [mol/l]
9	8.91 E-11
10	6.69 E-10
11	2.86 E-10
12	7.94 E-11
13	1.39 E-10
14	1.30 E-10
15	1.51 E-10
16	2.28 E-10
17	1.56 E-10
18	1.47 E-10
19	1.13 E-10
20	8.72 E-11
21	1.26 E-10
22	1.53 E-10
23	1.69 E-10
24	2.61 E-10
25	2.82 E-10
26	2.13 E-10
27	1.18 E-10
28	2.49 E-10
29	5.47 E-10
30	3.96 E-10
31	1.33 E-10
32	1.27 E-10
33	2.13 E-10
34	1.93 E-10
35	8.73 E-11

Example No.	mutEGFR (D770_N771insSVD) kinase assay IC ₅₀ [mol/l]
36	1.14 E-10
37	4.00 E-10
38	1.19 E-10
39	3.04 E-10
40	1.15 E-10
41	2.91 E-10
42	1.55 E-10
43	2.25 E-10
44	1.50 E-10
45	4.92 E-10
46	4.33 E-10
47	< 7.25 E-11 1.69 E-10 2.27 E-10 2.30 E-10
48	2.49 E-10
49	1.70 E-10
50	1.70 E-10
51	1.36 E-10
52	2.26 E-10
53	4.26 E-10
54	5.71 E-10
55	2.57 E-10
56	2.58 E-10
57	2.69 E-10
58	1.70 E-10 2.15 E-10

Example No.	mutEGFR (D770_N771insSVD) kinase assay IC ₅₀ [mol/l]
	< 2.54 E-10 3.64 E-10
59	2.35 E-10
60	3.05 E-10
61	9.35 E-10
62	2.37 E-10
63	2.65 E-10
64	1.87 E-10
65	1.36 E-10
66	1.82 E-10
67	2.17 E-10
68	2.67 E-10
69	2.33 E-10
70	1.68 E-10
71	4.05 E-10
72	1.41 E-9
73	1.12 E-9
74	6.61 E-10
75	4.99 E-9

Bub1 high ATP kinase assay

Bub1-inhibitory activity of compounds of the present invention at a high ATP concentration
 5 was quantified employing the Bub1 TR-FRET high ATP kinase assay as described in the
 following paragraphs.

N-terminally His₆-tagged recombinant catalytic domain of human Bub1 (amino acids 704-
 1085), expressed in insect cells (Hi5) and purified by Ni-NTA affinity chromatography and

subsequent size exclusion chromatography, was used as enzyme. As substrate for the kinase reaction the biotinylated peptide biotin-Ahx-VLLPKKSFAEPG – SEQ ID 5 (C-terminus in amid form) was used which can be purchased e.g. from the company Biosyntan (Berlin, Germany).

5

For the assay 50 nl of a 100-fold concentrated solution of the test compound in DMSO was pipetted into either a black low volume 384well microtiter plate or a black 1536well microtiter plate (both Greiner Bio-One, Frickenhausen, Germany), 3 µl of a solution of adenosine-tri-phosphate (ATP, 3.33 mM => final conc. in the 5 µl assay volume is 2 mM) and substrate
10 (1.67 µM => final conc. in the 5 µl assay volume is 1 µM) in aqueous assay buffer [50 mM Tris/HCl pH 7.5, 10 mM magnesium chloride (MgCl₂), 200 mM potassium chloride (KCl), 1.0 mM dithiothreitol (DTT), 0.1 mM sodium ortho-vanadate, 1% (v/v) glycerol, 0.01 % (w/v) bovine serum albumine (BSA), 0.005% (v/v) Triton X-100 (Sigma), 1x *Complete EDTA-free* protease inhibitor mixture (Roche)] were added. Then the kinase reaction was started by
15 the addition of 2 µl of a solution of Bub1 in assay buffer and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of Bub1 was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, a typical concentration is about 200 ng/ml. The reaction was stopped by the addition of 3 µl of a solution of TR-FRET detection reagents (0.167 µM streptavidine-
20 XL665 [Cisbio Bioassays, Codolet, France] and 1.67 nM anti-phospho-Serine antibody [Merck Millipore, cat. # 35-002] and 0.67 nM LANCE EU-W1024 labeled anti-mouse IgG antibody [Perkin-Elmer, product no. AD0077, as an alternative a Terbium-cryptate-labeled anti-mouse IgG antibody from Cisbio Bioassays can be used]) in an aqueous EDTA-solution (83.3 mM EDTA, 0.2 % (w/v) bovine serum albumin in 100 mM HEPES pH 7.5).

25

The resulting mixture was incubated 1 h at 22°C to allow the formation of complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Eu-chelate to the streptavidine-XL. Therefore, the fluorescence
30 emissions at 620 nm and 665 nm after excitation at 350 nm was measured in a TR-FRET reader, e.g. a Pherastar or Pherastar FS (both from BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and at 622 nm was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components
35 but no enzyme = 100 % inhibition). Usually the test compounds were tested on the same

- microtiterplate in 11 different concentrations in the range of 20 μM to 0.7 nM (20 μM , 5.7 μM , 1.6 μM , 0.47 μM , 0.13 μM , 38 nM, 11 nM, 3.1 nM, 0.9 nM, 0.25 nM and 0.07 nM, the dilution series prepared separately before the assay on the level of the 100fold concentrated solutions in DMSO by serial dilutions, exact concentrations may vary depending pipettors used) in duplicate values for each concentration and IC_{50} values were calculated by a 4 parameter fit. Table 3 shows the results of the inhibition in Bub1 high ATP kinase assay.

Table 3:

Example No.	Bub1 high ATP (2 mM) IC_{50} [mol/l]
1	3.36 E-6
2	6.04 E-6
3	3.33 E-6
4	1.13 E-5
5	1.29 E-5
6	6.31 E-6
7	1.06 E-5
8	7.88 E-6
9	4.23 E-6
10	1.78 E-6
11	4.33 E-6
12	> 2.00 E-5
13	> 2.00 E-5
14	> 2.00 E-5
15	> 2.00 E-5
16	> 2.00 E-5
17	> 2.00 E-5
18	> 2.00 E-5
19	1.14 E-5
20	9.53 E-6
21	3.79 E-6

22	> 2.00 E-5
23	> 2.00 E-5
24	1.94 E-6
25	> 2.00 E-5
26	1.08 E-6
27	> 2.00 E-5
28	> 2.00 E-5
29	1.72 E-5
30	> 2.00 E-5
33	> 2.00 E-5
34	> 2.00 E-5
35	> 2.00 E-5
36	2.82 E-6
37	1.90 E-5
38	> 5.71 E-6
39	> 2.00 E-5
40	8.62 E-6
41	> 2.00 E-5
42	> 2.00 E-5
43	2.41 E-6
45	> 5.71 E-6
46	1.30 E-5
47	5.01 E-6
48	1.22 E-5
49	3.93 E-6
50	3.54 E-6
51	1.52 E-6
52	7.29 E-7
53	1.36 E-6
54	9.94 E-7
55	7.59 E-6
56	1.65 E-5

57	1.40 E-5
58	1.39 E-5
59	1.22 E-5
60	1.64 E-5
62	> 2.00 E-5
63	> 2.00 E-5
64	> 2.00 E-5
65	3.58 E-6
66	5.04 E-6
67	2.08 E-6
68	> 2.00 E-5
69	> 2.00 E-5
70	> 2.00 E-5
71	> 2.00 E-5
72	> 2.00 E-5
73	> 2.00 E-5
74	> 2.00 E-5
75	> 2.00 E-5

Compounds of the present invention may show additional advantageous properties, such as, more potent inhibition of mutant EGFR with exon20 insertions than inhibition of wild-type EGFR, which may be useful to reduce potential toxicity arising from excessive inhibition of wild-type EGFR.

Cellular Data Description (WT, insSVD)

293T cells from ATCC were transfected with pBABEpuro expression constructs for WT EGFR or EGFR-insSVD and pCL-Eco packaging vector using Fugene-6 transfection reagent from Promega. Plates were incubated at at 37°C for 48 h. Retrovirus was harvested by filtering the media supernatant through a 0.45 µm filter.

Ba/F3 cells purchased from DSMZ were grown in RPMI + 10% FBS + 10 ng/mL IL-3 and infected with filtered retroviral supernatant at a 1:2 dilution. Polybrene was added to a concentration of 8 µg/mL, plates were spun for 90 min, and incubated overnight at 37°C. 2 µg/mL puromycin was added to the infected cells 24 h after infection and cells were

5 continually grown in the presence of puromycin and 10 ng/mL IL-3. Following stably expressing Ba/F3 cell lines were generated: Ba/F3-EGFR-WT, Ba/F3-EGFR-insSVD, (Ba/F3- vector-control).

For cell survival assays, Ba/F3 cells were grown to a density of 1-2 million cells per mL, spun down and resuspended in media without IL-3, and replated at a concentration

10 200,000-500,000 cells per mL. The cells ectopically expressing WT EGFR or EGFR-insSVD were plated with 10 ng/mL Millipore Culture grade EGF. The cells ectopically expressing pBABEpuro empty vector were plated with 10 ng/mL IL-3.

15 2 days later, cells were plated in 50 µL in a 384 well plate at a concentration of 4000 cells per well for cells assayed in the absence of IL-3 and 2000 cells per well for cells assayed in the presence of IL-3. 100 nL of compound was added to each well using a 100 nL pin head, and plates were incubated at 37°C for 48 h.

20 Cell viability was measured by adding 20 µL of Cell Titer-Glo Luminescent Cell Viability Reagent diluted 1:3 in PBS. Plates were sealed with Perkin Elmer Top-Seal, inverted several times to mix, and immediately centrifuged at 1000 rpm for 2 min. Plates were incubated in low light conditions for 8-10 min and luminescence was measured. The IC₅₀ values for the examples are shown in Table 4.

25

Table 4:

Example No.	BA/F3 (insSVD) IC ₅₀ [mol/l]	BA/F3 (wild type) IC ₅₀ [mol/l]
1	9.80 E-9	3.66 E-7
2	7.12 E-9	2.92 E-7
3	2.28 E-8	7.55 E-7
4	1.95 E-8	4.52 E-7
5	9.73 E-9	2.62 E-7

Example No.	BA/F3 (insSVD)	BA/F3 (wild type)
	IC ₅₀ [mol/l]	IC ₅₀ [mol/l]
6	5.03 E-8	7.85 E-7
7	1.80 E-8	2.92 E-7
8	8.18 E-9	1.21 E-7
9	3.27 E-8	3.03 E-7
10	1.11 E-8	4.96 E-7
11	1.87 E-8	7.01 E-7
12	2.28 E-8	5.74 E-7
13	1.57 E-7	1.52 E-6
14	1.05 E-8	3.87 E-7
15	1.53 E-8	4.26 E-7
16	1.26 E-7	1.05 E-6
17	9.53 E-9	2.31 E-7
18	2.79 E-8	5.79 E-7
19	2.91 E-8	5.32 E-7
20	8.25 E-9	3.13 E-7
21	8.49 E-9	3.41 E-7
22	4.19 E-8	5.44 E-7
23	7.10 E-8	6.48 E-7
24	3.46 E-8	4.44 E-7
25	1.83 E-8	3.49 E-7
26	8.99 E-8	8.39 E-7
27	1.69 E-8	5.02 E-7
28	1.26 E-7	1.24 E-6
29	3.36 E-8	6.21 E-7
30	1.93 E-8	4.07 E-7
33	1.02 E-7	5.57 E-7
34	1.20 E-8	2.04 E-7
35	2.15 E-8	2.61 E-7

Example No.	BA/F3 (insSVD)	BA/F3 (wild type)
	IC ₅₀ [mol/l]	IC ₅₀ [mol/l]
36	6.81 E-8	8.45 E-7
37	3.57 E-8	3.48 E-7
38	2.93 E-8	4.19 E-7
39	4.40 E-8	6.30 E-7
40	1.19 E-7	8.67 E-7
41	7.75 E-8	6.95 E-7
42	1.98 E-8	5.96 E-7
43	6.05 E-8	1.25 E-6
44	2.57 E-8	
45	1.11 E-7	1.64 E-6
46	1.01 E-8	3.76 E-7
47	4.16 E-8	7.15 E-7
48	1.88 E-8	3.79 E-7
49	5.36 E-8	7.85 E-7
50	8.82 E-9	3.61 E-7
51	4.67 E-8	7.42 E-7
52	1.34 E-8	5.47 E-7
53	2.13 E-8	4.08 E-7
54	8.09 E-8	9.17 E-7
55	1.24 E-7	1.31 E-6
56	1.19 E-8	4.35 E-7
57	2.80 E-8	5.39 E-7
58	2.98 E-8	5.19 E-7
59	1.86 E-8	3.36 E-7
60	5.27 E-8	9.46 E-7
61	3.00 E-7	3.77 E-6
62	2.67 E-8	6.97 E-7
63	1.47 E-7	1.37 E-6

Example No.	BA/F3 (insSVD) IC ₅₀ [mol/l]	BA/F3 (wild type) IC ₅₀ [mol/l]
64	7.58 E-9	2.71 E-7
65	1.34 E-8	2,87 E-7
66	7.52 E-9	2,52 E-7
67	2.90 E-8	1,98 E-7
68	3.73 E-8	6,44 E-7
69	7.17 E-9	3,12 E-7
70	6.79 E-8	7,14 E-7
71	1.32 E-7	1,42 E-6
72	6.73E-8	9.57 E-7
73	7.80 E-8	1.28 E-6
74	5.11 E-8	8.28 E-7
75	5.71 E-7	3,90 E-6

In contrast to the claimed compounds of this invention the compounds claimed in the closest prior art WO 2016/120196 do not show the advantageous combined properties described above. This can be seen in Table 5.

5

Table 5:

WO 2016/120196 Example No.	mutEGFR (D770_N771insSVD) kinase assay IC ₅₀ [mol/l]	BA/F3 (insSVD) IC ₅₀ [mol/l]	BA/F3 (wild type) IC ₅₀ [mol/l]
38	2,24 E-7	> 2,00 E-6	5,91 E-6
41	3,43 E-8	> 2,00 E-6	5,02 E-6
45	1,28 E-8	> 2,00 E-6	4,04 E-6

Cellular Data Description (Ba/F3 cells overexpressing mutant EGFR different from insSVD)

- 293T cells from ATCC were transfected with pBABEpuro expression constructs for mutant EGFR (V769_D770insASV, D770_N771insNPG, N771_P772insH, H773_V774insNPH, E746_A750del, L858R, D770_N771insSVD C797S, E746_A750del C797S, L858R C797S, L861Q) or mutant ERBB2 (A775_G776insYVMA) and pCL-Eco packaging vector using Fugene-6 transfection reagent from Promega. Plates were incubated at at 37°C for 48 h. Retrovirus was harvested by filtering the media supernatant through a 0.45 µm filter.
- 10 Ba/F3 cells purchased from DSMZ were grown in RPMI + 10% FBS + 10 ng/mL IL-3 and infected with filtered retroviral supernatant at a 1:2 dilution. Polybrene was added to a concentration of 8 µg/mL, plates were spun for 90 min, and incubated overnight at 37°C. 2 µg/mL puromycin was added to the infected cells 24 h after infection and cells were
- 15 continually grown in the presence of puromycin and 10 ng/mL IL-3. Following stably expressing Ba/F3 cell lines were generated: Ba/F3-EGFR-V769_D770insASV, Ba/F3-EGFR-D770_N771insNPG, Ba/F3-EGFR-N771_P772insH, Ba/F3-EGFR-H773_V774insNPH, Ba/F3-EGFR-E746_A750del, Ba/F3-EGFR-L858R, Ba/F3-EGFR-D770_N771insSVD C797S, Ba/F3-EGFR-E746_A750del C797S, Ba/F3-EGFR-L858R
- 20 C797S, Ba/F3-EGFR L861Q and Ba/F3-ERBB2-A775_G776insYVMA (Ba/F3-vector-control).
- For cell survival assays, Ba/F3 cells were grown to a density of 1-2 million cells per mL, spun down and resuspended in media without IL-3, and replated at a concentration
- 25 200,000-500,000 cells per mL. The cells ectopically expressing WT EGFR plated with 10 ng/mL Millipore Culture grade EGF and Ba/F3 cells containing mutant EGFR or Mutant ERBB2 were cultivated without EGF. The cells ectopically expressing pBABEpuro empty vector were plated with 10 ng/mL IL-3.
- 30 2 days later, cells were plated in 50 µL in a 384 well plate at a concentration of 4000 cells per well for cells assayed in the absence of IL-3 and 2000 cells per well for cells assayed in the presence of IL-3. 100 nL of compound was added to each well using a 100 nL pin head, and plates were incubated at 37°C for 48 h.
- 35 Cell viability was measured by adding 20 µL of Cell Titer-Glo Luminescent Cell Viability Reagent diluted 1:3 in PBS. Plates were sealed with Perkin Elmer Top-Seal, inverted

several times to mix, and immediately centrifuged at 1000 rpm for 2 min. Plates were incubated in low light conditions for 8-10 min and luminescence was measured. The IC₅₀ values for the examples are shown in Tables 6, 7, 8 and 9.

Cellular Data Description (PC9 cells, EGFRex19del)

5

PC9 cells were purchased from ATCC. 400 PC9 cells per well were seeded in growth medium (DMEM, 10% FCS) in a 384-well plate (CORNING #3571). Seed reference plate for time zero determination on the same day. All plates were incubated overnight at 37°C. After 24 hours, test compound were added in 7-step dilution using HP Compound printer and incubated at 37°C for 72h. After 3 days, 30 µL/well CTG solution (Promega Cell Titer Glo solution; catalog # G755B and G756B) were added to each well, incubated for 30 minutes and the plate were read on PheraStar. Proliferation is calculated after subtracting time zero luminescence values from day 4 values and comparing to untreated wells. The IC₅₀ values were determined using the four parameter fit. The IC₅₀ values for the examples are shown in Table 9.

15

Cellular Data Description (HCC-827 cells, EGFRex19del)

HCC-827 cells were purchased from ATCC. 400 HCC-829 cells per well were seeded in growth medium (RPMI1640, 10% FCS) in a 384-well plate (CORNING #3571). Seed reference plate for time zero determination on the same day. All plates were incubated overnight at 37°C. After 24 hours, test compound were added in 7-step dilution using HP Compound printer and incubated at 37°C for 72h. After 3 days, 30 µL/well CTG solution (Promega Cell Titer Glo solution; catalog # G755B and G756B) were added to each well, incubated for 30 minutes and the plate were read on PheraStar. Proliferation is calculated after subtracting time zero luminescence values from day 4 values and comparing to untreated wells.

25

The IC₅₀ values were determined using the four parameter fit. The IC₅₀ values for the examples are shown in Table 9.

30

Table 6: (EGFR Exon20 insertion mutations)

Example No.	BA/F3 (insNPG) IC ₅₀ [mol/l]	BA/F3 (ASV) IC ₅₀ [mol/l]	BA/F3 (EGFR N771_772 insH) IC ₅₀ [mol/l]	BA/F3 (EGFR 773_774insNPH) IC ₅₀ [mol/l]
2	4.44 E-9	4.66 E-9	7.48 E-9	2.82 E-8
5	2.63 E-8	2.87 E-8	1.15 E-8	7.93 E-8
8	1.16 E-8	9.62 E-9	4.91 E-9	2.31 E-8
14	1.25 E-8	1.64 E-8	7.60 E-9	6.58 E-8
20	1.47 E-8	1.17 E-8	6.59 E-9	5.67 E-8
21	5.65 E-9	7.78 E-9	4.22 E-9	2.76 E-8
32	9.38 E-9	1.32 E-8	1.10 E-8	4.73 E-8
42	1.20 E-8	1.41 E-8	6.01 E-9	4.85 E-8
46	1.43 E-8	1.17 E-8	5.77 E-9	3.89 E-8
48	4.24 E-8	4.18 E-8	1.76 E-8	1.42 E-7
50	1.13 E-8	1.04 E-8	7.42 E-9	4.03 E-8
56	6.96 E-9	1.41 E-8	7.36 E-9	4.89 E-8

Table 7: (classical activating and rare EGFR mutations)

Example No.	BA/F3 (EGFR E746_A750del) IC ₅₀ [mol/l]	BA/F3 (EGFR L858R) IC ₅₀ [mol/l]	BA/F3 (EGFR L861Q) IC ₅₀ [mol/l]
2	< 1.58 E-10	5.25 E-10	1.48 E-8
5	7.39 E-10	2.03 E-9	3.09 E-8
8	< 1.58 E-10	7.01 E-10	1.37 E-8
14	1.72 E-9	1.22 E-9	2.01 E-8
20	3.32 E-10	9.64 E-10	1.62 E-8

Example No.	BA/F3 (EGFR E746_A750del) IC ₅₀ [mol/l]	BA/F3 (EGFR L858R) IC ₅₀ [mol/l]	BA/F3 (EGFR L861Q) IC ₅₀ [mol/l]
21	2.03 E-10	6.44 E-10	7.34 E-9
32	2.89 E-9	1.06 E-9	1.74 E-8
42	4.86 E-10	1.51 E-9	1.88 E-8
46	1.05 E-9	9.57 E-10	1.58 E-8
48	1.43 E-9	2.36 E-9	3.97 E-8
50	1.10 E-9	1.07 E-9	2.40 E-8
56	8.92 E-10	1.34 E-9	2.95 E-8

Table 8: (aquired resistance space)

Example No.	BA/F3 (EGFR 0770_N771 insSVD C797S) IC ₅₀ [mol/l]	BA/F3 (EGFR E746_A750del C797S) IC ₅₀ [mol/l]	BA/F3 (EGFR L858R C797S) IC ₅₀ [mol/l]
2	8.22 E-9	2.20 E-10	6.03 E-10
5	3.70 E-8	6.68 E-10	2.67 E-9
8	1.46 E-8	2.47 E-10	1.20 E-9
14	2.49 E-8	3.79 E-10	1.91 E-9
20	1.22 E-8	3.49 E-10	7.91 E-10
21	7.84 E-9	2.59 E-10	4.44 E-10
32	1.58 E-8	5.11 E-10	1.12 E-9
42	1.93 E-8	4.94 E-10	1.63 E-9
46	1.85 E-8	4.00 E-10	1.13 E-9
48	5.66 E-8	7.76 E-10	2.56 E-9
50	2.07 E-8	3.48 E-10	1.60 E-9
56	1.40 E-8	4.23 E-10	1.31 E-9

Table 9: (ERBB2 mutants, PC9, HCC-827)

Example No.	BA/F3 (ERBB2 A775_G776 insYVMA) IC ₅₀ [mol/l]	PC9 IC ₅₀ [mol/l]	HCC-827 IC ₅₀ [mol/l]
2	8.31 E-9	6.73 E-10	< 3,00 E-9
5	3.18 E-8	1.94 E-9	< 3,00 E-9
8	1.31 E-8	7.38 E-10	< 3,00 E-9
14	1.36 E-8	2.12 E-9	< 3,00 E-9
20	2.35 E-8	2.68 E-9	< 3,00 E-9
21	1.34 E-8	1.16 E-9	< 3,00 E-9
32	1.67 E-8	1.70 E-9	< 3,00 E-9
42	1.32 E-8	4.03 E-9	< 3,00 E-9
46	1.10 E-8	2.89 E-9	< 3,00 E-9
48	3.98 E-8	3.40 E-9	< 3,00 E-9
50	1.03 E-8	6.82 E-9	< 3,00 E-9
56	1.35 E-8	1.74 E-9	< 3,00 E-9

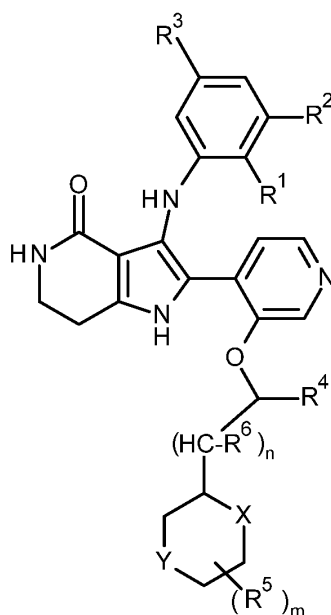
5 References:

- Arcila et al., 2012: Arcila et al., Clin Cancer Res. 2012 Sep 15;18(18):4910-8.
- Chen *et al.*, 2016: Chen et al., Onco Targets Ther. 2016 Jul 8;9:4181-6
- Chiu et al., 2015 : Chiu et al., J Thorac Oncol. 2015;10: 793–799
- 10 Doebele et al., 2018 : Doebele et al.. Poster 338, presented at the 54th Annual Meeting of the American Society of Clinical Oncology, June 1–5, 2018, Chicago, Illinois
- Floc'h et al., 2018 : Floc'h et al., Mol Cancer Ther. 2018 May 17(5) : 885-896
- Hasako et al., 2018: Hasako et al., Mol Cancer Ther. 2018 Aug ;17(8):1648-1658
- Jang et al., 2018: Jang et al., Angew Chem Int Ed Engl. 2018 Sep 3; 57(36): 11629–
- 15 11633

- Mok *et al.*, 2009 : Mok et al., N Engl J Med. 2009 Sep 3;361(10):947-57
Mok *et al.*, 2017: Mok et al., N Engl J Med. 2017 Feb 16;376(7):629-640
Oxnard *et al.*, 2013: Oxnard et al., J Thorac Oncol. 2013 Feb; 8(2): 179–184
Oxnard *et al.*, 2018: Oxnard et al., JAMA Oncol. 2018;4(11):1527-1534
- 5 Paez *et al.*, 2004 : Paez et al., Science. 2004 Jun 4;304(5676):1497-500
Pao *et al.*, 2005: Pao et al., PLoS Med. 2005 Mar;2(3):e73
Pao *et al.*, 2010: Pao and Chmielecki, Nat Rev Cancer. 2010 Nov;10(11):760-74
Ramalingam et al.,2018a: Ramalingam et al., J Clin Oncol. 2018 Mar 20;36(9):841-849.
Ramalingam et al., 2018b: Ramalingam et al., ESMO 2018; Annals Oncol. 2018 Oct : 29
- 10 (Suppl 8)
Robichaux et al., 2018 : Robichaux et al., Nat Med. 2018 May;24(5):638-646
Sequist *et al.*, 2013: Sequist et al., J Clin Oncol. 2013 Sep 20;31(27):3327-34
Soria et al., 2018: Soria et al., N Engl J Med. 2018 Jan 11;378(2):113-125.
Thress et al., 2015: Thress et al., Nat Med. 2015 Jun; 21(6): 560–562.
- 15 Yang *et al.*, 2015: Yang et al., Lancet Oncol. 2015 Jul;16(7):830-8
Yasuda, 2013: Yasuda, Sci Transl Med. 2013 Dec 18;5(216):216ra177.

Claims

1. A compound of formula (I)



5

(I)

in which:

- R¹ represents methyl, ethyl, trifluoromethyl, 2,2-difluoroethyl, cyano, chloro, bromo, methoxy or difluoromethoxy;
- R² represents hydrogen, methyl, ethyl, fluoro, chloro or bromo;
- 10 R³ represents hydrogen or fluoro;
- R⁴ represents hydrogen or methyl;
- R⁵ independently at each occurrence represents hydrogen, trifluoromethyl or C₁-C₃ alkyl,
R⁵ being bound to any carbon atom of the ring;
- 15 R⁶ independently at each occurrence represents hydrogen, C₁-C₃-alkyl or C₁-C₃-haloalkyl;
- R⁷ represents C₁-C₃-alkyl or C₂-C₃-haloalkyl;
- R⁸ represents C₁-C₃-alkyl or C₂-C₃-haloalkyl;

X represents NR⁷ or O;

Y represents NR⁸ or O;

m represents 0, 1, 2 or 3;

n represents 0 or 1;

5 or an N-oxide, a salt or a tautomer of said compound, or a salt of said N-oxide or tautomer.

2. The compound of formula (I) according to claim 1, wherein:

R¹ represents methyl, ethyl, chloro, methoxy or difluoromethoxy;

10 R² represents methyl, ethyl, fluoro or chloro;

R³ represents hydrogen or fluoro;

R⁴ represents hydrogen or methyl;

R⁵ represents hydrogen, methyl or trifluoromethyl,
R⁵ being bound to any carbon atom of the ring;

15 R⁶ represents hydrogen, methyl or trifluoromethyl;

R⁷ represents C₁-C₂-alkyl or C₂-C₃-fluoroalkyl;

R⁸ represents C₁-C₂-alkyl or C₂-C₃-fluoroalkyl;

X represents NR⁷ or O;

Y represents NR⁸ or O;

20 m represents 0, 1 or 2;

n represents 0 or 1;

or an N-oxide, a salt or a tautomer of said compound, or a salt of said N-oxide or tautomer.

25 3. The compound of formula (I) according to claim 1 or 2, wherein:

R¹ represents methyl, ethyl, chloro or methoxy;

- R^2 represents fluoro or chloro;
 R^3 represents hydrogen or fluoro;
 R^4 represents hydrogen;
 R^5 represents hydrogen or methyl,
 5 R^5 being bound to any carbon atom of the ring;
 R^6 represents hydrogen;
 R^7 represents methyl;
 R^8 represents methyl, 2,2,2-trifluoroethyl or 2,2-difluoroethyl;
 X represents NR^7 or O;
 10 Y represents NR^8 or O;
 m represents 0, 1, or 2;
 n represents 0 or 1;
- or an N-oxide, a salt or a tautomer of said compound, or a salt of said N-oxide or tautomer.
- 15
4. The compound of formula (I) according to any of claims 1 to 3, which is selected from the group consisting of:
- 3-(3-chloro-2-methoxyanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
 20 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2*S*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2*R*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
 25 2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
 2-(3-{[(2*S*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
 2-(3-{[(2*R*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one

- 3-(2,3-dichloroanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(2,3-dichloroanilino)-2-(3-{[(2S)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 5 3-(2,3-dichloroanilino)-2-(3-{[(2R)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{[(3R)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 10 3-(3-fluoro-2-methoxyanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(2R)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 15 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(2S)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2R)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 20 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2S)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-{[4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 25 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-{[1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(3S)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{[(3S)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 30 2-(3-{[(2S)-4-(2,2-difluoroethyl)morpholin-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(2S)-4-(2,2,2-trifluoroethyl)morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 35 3-(3-chloro-2-methoxyanilino)-2-(3-[2-(4-dioxan-2-yl)ethoxy]pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

- 3-(3-chloro-2-methoxyanilino)-2-(3-{2-[(2R)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{2-[(2S)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 5 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-{[(2S)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-5-fluoro-2-methoxyanilino)-2-(3-{[(2S)-4-(2,2,2-trifluoroethyl)morpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-ethylanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 10 3-(3-chloro-2-methoxyanilino)-2-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2R)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 15 3-(3-chloro-2-methoxyanilino)-2-(3-{[(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-{[(2R)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-{[(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 20 2-(3-{2-[(2R)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-{2-[(2S)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-3-(3-fluoro-2-methoxyanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one.
- 25 3-(3-fluoro-2-methoxyanilino)-2-(3-{[(3R)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methylanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 2-(3-{[(2S)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methylanilino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 30 3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 3-[2-(2,2-difluoroethyl)-3-fluoroanilino]-2-(3-{[(2S)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
- 35 3-(3-chloro-2-methylanilino)-2-(3-{[(2S)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one

- 3-(3-chloro-2-methylanilino)-2-(3-[(3*R*)-4-methylmorpholin-3-yl]methoxy}pyridin-4-yl)-
1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-{3-[(5,5-dimethyl-1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-
1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 5 3-(3-chloro-2-methylanilino)-2-(3-[(2*S*)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-
yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-(3-[(2*R*)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy}pyridin-4-
yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-3-(3-fluoro-2-methylanilino)-1,5,6,7-
10 tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 2-(3-[(2*S*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methylanilino)-1,5,6,7-
tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 2-(3-[(2*R*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-3-(3-fluoro-2-methylanilino)-1,5,6,7-
tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 15 3-(3-chloro-2-methylanilino)-2-(3-[(2*S*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-
tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methylanilino)-2-(3-[(2*R*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-
tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-ethylanilino)-2-{3-[(1,4-dioxan-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-
20 tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-ethylanilino)-2-(3-[(2*S*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-
tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-ethylanilino)-2-(3-[(2*R*)-1,4-dioxan-2-yl]methoxy}pyridin-4-yl)-1,5,6,7-
tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 25 3-(3-chloro-2-ethylanilino)-2-(3-[(2*R*)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-
1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-ethylanilino)-2-(3-[(2*S*)-4-methylmorpholin-2-yl]methoxy}pyridin-4-yl)-
1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{1-[1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-1,5,6,7-
30 tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{(1*S*)-1-[(2*S*)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-
1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-(3-{(1*S*)-1-[(2*R*)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-
1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 35 3-(3-chloro-2-methoxyanilino)-2-(3-{(1*R*)-1-[(2*S*)-1,4-dioxan-2-yl]ethoxy}pyridin-4-yl)-
1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one

- 3-(3-chloro-2-methoxyanilino)-2-(3-((1*R*)-1-[(2*R*)-1,4-dioxan-2-yl]ethoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-fluoro-2-methylanilino)-2-{3-[(4-methylmorpholin-2-yl)methoxy]pyridin-4-yl}-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 5 3-(3-fluoro-2-methylanilino)-2-(3-[(2*R*)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-fluoro-2-methylanilino)-2-(3-[(2*S*)-4-methylmorpholin-2-yl]methoxy)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 2-(3-[[1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 10 2-(3-[(2*R*)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 2-(3-[(2*S*)-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 15 2-(3-[[5,5-dimethyl-1,4-dioxan-2-yl]methoxy]pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 2-(3-[(2*R*)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 2-(3-[(2*S*)-5,5-dimethyl-1,4-dioxan-2-yl]methoxy)pyridin-4-yl)-3-(2-ethyl-3-fluoroanilino)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 20 3-(3-chloro-2-methoxyanilino)-2-[3-({1-[4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-[3-((1*R*)-1-[(2*R*)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 25 3-(3-chloro-2-methoxyanilino)-2-[3-((1*S*)-1-[(2*S*)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-[3-((1*R*)-1-[(2*S*)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 3-(3-chloro-2-methoxyanilino)-2-[3-((1*S*)-1-[(2*R*)-4-methylmorpholin-2-yl]ethyl}oxy)pyridin-4-yl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
- 30

5. Use of a compound of general formula (I) according to any of claims 1 to 4 for the treatment or prophylaxis of diseases.

- 35 6. Use of a compound of general formula (I) according to claim 5, wherein the diseases are hyperproliferative diseases and/or disorders responsive to induction of cell death.

7. Use of a compound of general formula (I) according to claim 6, wherein the hyperproliferative diseases and/or disorders responsive to induction of cell death are haematological tumours, solid tumours and/or metastases thereof.
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8. Use of a compound of formula (I) according to claim 7, wherein the tumour harbors a mutant EGFR and/or metastases thereof.
9. Use of a compound of formula (I) according to claim 7, wherein the tumour is lung cancer, particularly lung cancer harboring a mutant EGFR with exon 20 insertion mutation, and/or metastases thereof.
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10. Use of a compound of formula (I) according to claim 7, wherein the tumour is lung cancer, particularly lung cancer harboring a mutant EGFR with in-frame deletions in exon 19 (such as EGFR E746_A750del) or point mutations in exon 21 (e.g. L858R), and/or metastases thereof
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11. Use of a compound of formula (I) according to claim 7, wherein the tumour is lung cancer, particularly lung cancer harboring a mutant EGFR with a D770_N771insSVD C797S, E746_A750del C797S, or L858R C797S acquired resistance mutation, and/or metastases thereof
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12. Use of a compound of formula (I) according to claim 7, wherein the tumour is lung cancer, particularly lung cancer harboring a mutant ERBB2 with exon 20 insertion mutations (such as ERBB2 A775_G776insYVMA), and/or metastases thereof
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13. A pharmaceutical composition comprising at least one compound of general formula (I) according to any of claims 1 to 4, together with at least one pharmaceutically acceptable auxiliary.
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14. A composition according to claim 13 for the treatment of haematological tumours, solid tumours and/or metastases thereof.
15. A combination comprising one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 4, and one or more
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second active ingredients selected from chemotherapeutic anti-cancer agents and target-specific anti-cancer agents.

16. A method of inhibiting EGF-receptor kinase activity in a cancer cell, the method
5 comprising contacting the cancer cell with a compound of general formula (I) according to any of claims 1 to 4.

17. The method of claim 16, wherein the cancer cell is *in vitro* or *in vivo*.

10 18. A method of reducing the survival of a cancer cell or inducing death in a cancer cell, the method comprising contacting a cancer cell comprising a mutation in an EGF-receptor with a compound of general formula (I) according to any of claims 1 to 4.

15 19. The method of any one of claims 16 to 18, wherein the EGF-receptor comprises a mutation in exon 20.

20 20. The method of any one of claims 16 to 19, wherein the cancer cell is derived from a cancer selected from the group consisting of leukemia, myelodysplastic syndrome, malignant lymphoma, head and neck tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours, skin tumours, and sarcomas.

25 21. The method of claim 20, wherein the cancer cell is derived from a cancer selected from the group consisting of inverted sinonasal papilloma or inverted sinonasal papilloma associated sinonasal squamous cell carcinoma.

30 22. A method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a compound of general formula (I) according to any of claims 1 to 4.

23. A method of treating cancer in a subject, wherein the cancer is or has acquired resistance to an anti-EGF receptor therapy, the method comprising administering to the subject an effective amount of a compound of general formula (I) according to any of claims 1 to 4.

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24. A method of enhancing the efficacy of an anti-EGF-receptor therapy, the method comprising administering to the subject an anti-EGF receptor therapy in combination with a compound of general formula (I) according to any of claims 1 to 4.
- 5 25. The method of any one of claims 22 to 24, wherein the cancer is selected from the group consisting of leukemia, myelodysplastic syndrome, malignant lymphoma, head and neck tumours, tumours of the thorax, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours, skin tumours, and sarcomas.
- 10 26. The method of claim 25, wherein the cancer is selected from the group consisting of inverted sinonasal papilloma or inverted sinonasal papilloma associated sinanonasal squamous cell carcinoma.
- 15 27. The method of claim 25, wherein the tumour of the thorax is non-small cell lung cancer.
- 20 28. The method of any one of claims 16 to 27, wherein the EGF-receptor comprises a mutation.
- 25 29. The method of claim 28, wherein the EGF-receptor comprises a mutation in exon 20.
- 30 30. The method of claim 29, wherein the EGF-receptor comprises an insertion in exon 20.
- 35 31. The method of claim 30, wherein the EGF-receptor comprises an insertion between amino acids V769-D770 and/or between D770-N771.
- 30 32. The method of claim 31, wherein the insertion is an ASV and/or SVD insertion.
- 35 33. The method of claim 30, wherein the EGF-receptor comprising an ASV insertion between amino acids V769-D770 and/or a SVD insertion between amino acids D770-N771.
- 35 34. A method of selecting a patient for cancer treatment with a compound of general formula (I) according to any of claims 1 to 4, the method comprising detecting the

presence of a mutation in exon 20 of the EGF-receptor in a biological sample of the subject, thereby determining that the patient should be treated with said compound.

35. A method for treating a patient with cancer, the method comprising administering to
5 the subject an anti-EGF receptor therapy in combination with a compound of general formula (I) according to any of claims 1 to 4, wherein the subject is selected for therapy by detecting the presence of a mutation in exon 20 of the EGF-receptor in a biological sample of the subject.

10 36. The method of claim 34 or 35, wherein the EGF-receptor comprises an insertion in exon 20.

37. The method of claim 36, wherein the EGF-receptor comprises an insertion between amino acids V769-D770 and/or between amino acids D770-N771.

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38. The method of claim 37, wherein the insertion is an ASV and/or SVD insertion.

39. The method of claim 36, wherein the EGF-receptor comprising an ASV insertion between amino acids V769-D770 and/or a SVD insertion between amino acids D770-
20 N771.

40. The method of any one of claims 16, 18, 24, 34 and 35, wherein the cancer is lung cancer, particularly lung cancer harboring a mutant EGFR with in-frame deletions in exon 19 (such as EGFR E746_A750del) or point mutations in exon 21 (e.g. L858R), and/or
25 metastases thereof.

41. The method of any one of claims 16, 18, 24, 34 and 35, wherein the cancer is lung cancer, particularly lung cancer harboring a mutant EGFR with a D770_N771insSVD C797S, E746_A750del C797S, or L858R C797S acquired resistance mutation, and/or
30 metastases thereof

42. The method of any one of claims 16, 18, 24, 34 and 35, wherein the cancer is lung cancer, particularly lung cancer harboring a mutant ERBB2 with exon 20 insertion mutations (such as ERBB2 A775_G776insYVMA), and/or metastases thereof

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