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CDK inhibitorok

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

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(56) References cited:
WO-A1-2010/020675 WO-A1-2013/148748
WO-A2-2005/052147

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Description**Field of the Invention**

5 [0001] The invention relates to compounds useful for inhibiting cyclin-dependent kinase ("CDK").

Background

10 [0002] Cancer continues to be a challenge for modern medicine. At a basic level, cancer occurs when there is uncontrollable cell division. The uncontrollable cell division is an effect of a break down in the natural life cycle of cells. CDK is a family of kinases involved in the cell life cycle. Abnormally high CDK activity is one characteristic of several cancers. There are naturally occurring CDK-inhibiting proteins and the abnormally high CDK activity maybe due to a malfunction of the naturally occurring CDK inhibitors or due to an overabundance of CDK. CDK inhibitors are known in the art but there remains a need for additional CDK inhibitors.

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Summary

[0003] The invention is directed to compounds as defined in the claims wherein R, R¹, R², X, and y are as defined herein and to pharmaceutically acceptable salts thereof.

20 [0004] The disclosed compounds are useful as CDK inhibitors and could be useful in the treatment of diseases and disorders mediated by CDK such as cancer. Pharmaceutical compositions comprising the compounds and pharmaceutically acceptable salts of the compounds are also disclosed.

Brief Description of the Drawings

25

[0005]

FIGS. 1-3 illustrate embodiments of R² of the compounds of the invention.

30 FIGS. 4-6 illustrate embodiments of the core structure of the compounds of the invention.

Detailed Description

[0006] In one embodiment, compounds are provided wherein:

35 each X is independently CH or N;
R is H, C₁-C₃ alkyl or haloalkyl;
each R¹ is independently aryl, alkyl, cycloalkyl or haloalkyl, wherein each of said alkyl, cycloalkyl and haloalkyl groups optionally includes O or N heteroatoms in place of a carbon in the chain and two R¹'s on adjacent ring atoms
40 or on the same ring atom together with the ring atom(s) to which they are attached optionally form a 3-8-membered cycle;
y is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

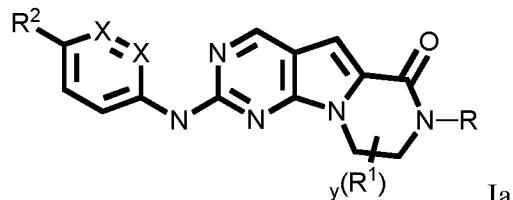
45 [0007] In some aspects, R is hydrogen or C₁-C₃ alkyl.

[0008] In some aspects, R² is selected from the structures depicted in FIGS. 1-3.

[0009] In some aspects, the compound has one of the general structures in FIGS. 4-6 wherein the variables are as previously defined.

[0010] In some aspects, the compound has general formula Ia:

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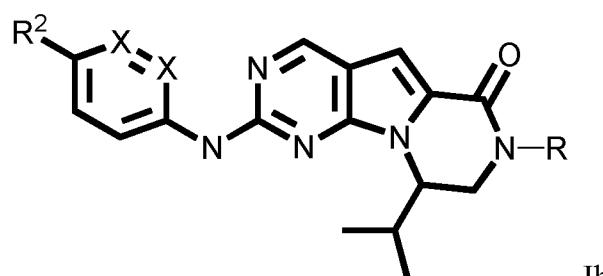


wherein R¹, R², R and y are as previously defined.

- [0011] In some embodiments, the compound has formula Ia and R is alkyl.
- [0012] In some embodiments, the compound has formula Ia and R is H.
- [0013] In some embodiments, the compound has formula Ib:

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Ib

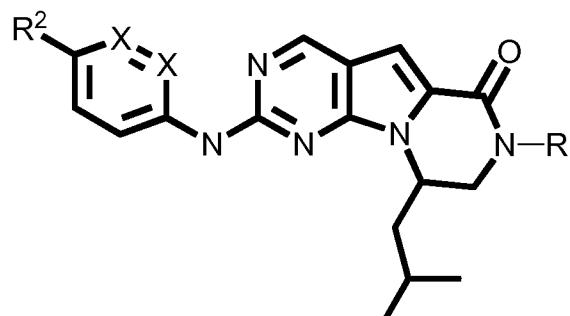
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wherein R² and R are as previously defined.

- [0014] In some embodiments, the compound has formula Ib and R is alkyl.
- [0015] In some embodiments, the compound has formula Ib and R is H.
- 20 [0016] In some embodiments, the compound has formula Ic:

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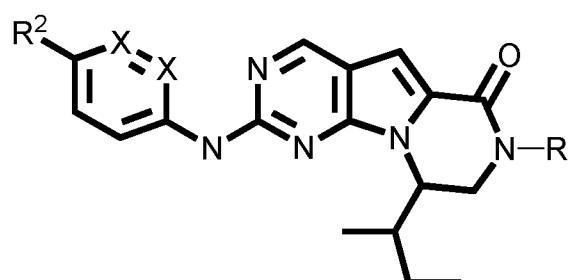
Ic

wherein R² and R are as previously defined.

- 35 [0017] In some embodiments, the compound has formula Ic and R is alkyl.
- [0018] In some embodiments, the compound has formula Ic and R is H.
- [0019] In some embodiments, the compound has formula Id:

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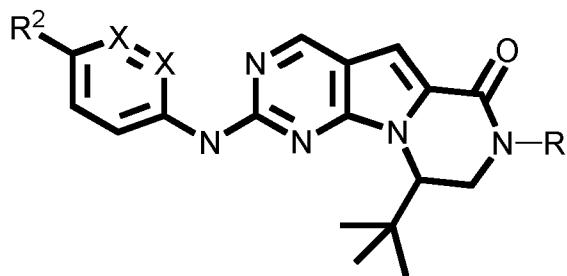


Id

50 wherein R² and R are as previously defined.

- [0020] In some embodiments, the compound has formula Id and R is alkyl.
- [0021] In some embodiments, the compound has formula Id and R is H.
- [0022] In some embodiments, the compound has formula Ie:

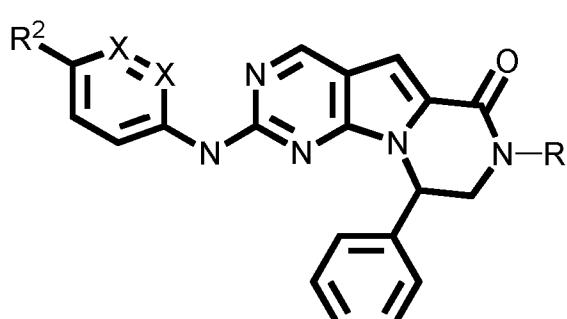
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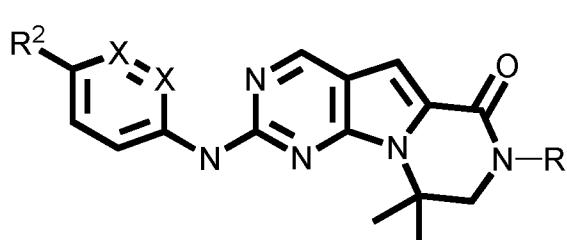
- [0023] In some embodiments, the compound has formula Ie and R is alkyl.
- [0024] In some embodiments, the compound has formula Ie and R is H.
- [0025] In some embodiments, the compound has formula If:



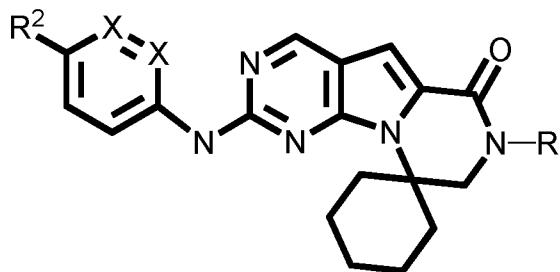
- [0026] In some embodiments, the compound has formula If and R is alkyl.
- [0027] In some embodiments, the compound has formula If and R is H.
- [0028] In some embodiments, the compound has formula Ig:



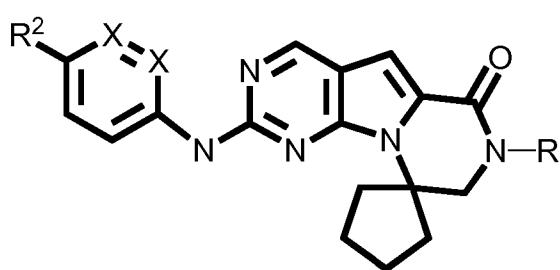
- [0029] In some embodiments, the compound has formula Ig and R is alkyl.
- [0030] In some embodiments, the compound has formula Ig and R is H.
- [0031] In some embodiments, the compound has formula Ih:



- [0032] In some embodiments, the compound has formula Ih and R is alkyl.
- [0033] In some embodiments, the compound has formula Ih and R is H.
- [0034] In some embodiments, the compound has formula Ii:

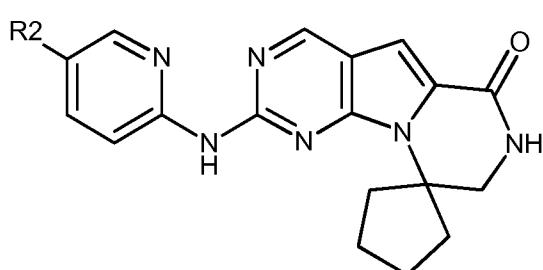


[0035] In some embodiments, the compound has formula Ii and R is alkyl.
 [0036] In some embodiments, the compound has formula Ii and R is H.
 [0037] In some embodiments, the compound has formula Ij:



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[0038] In some embodiments, the compound has formula Ij and R is alkyl.
 [0039] In some embodiments, the compound has formula Ij and R is H.
 [0040] In some embodiments, the compound has formula Ij and R is H, and both X are N.
 [0041] In some embodiments, the compound has formula Ik:



40 Definitions

[0042] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg (2007) Advanced Organic Chemistry 5th Ed. Vols. A and B, Springer Science+Business Media LLC, New York. The practice of the present invention will employ, unless otherwise indicated, conventional methods of synthetic organic chemistry, mass spectroscopy, preparative and analytical methods of chromatography, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology. Conventional methods of organic chemistry include those included in March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th Edition, M.B. Smith and J. March, John Wiley & Sons, Inc., Hoboken, NJ, 2007.

[0043] The term "alkyl," either alone or within other terms such as "haloalkyl" and "alkylamino," embraces linear or branched radicals having one to about twelve carbon atoms.

[0044] "Lower alkyl" radicals have one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. The term "alkylene" embraces bridging divalent linear and branched alkyl radicals. Examples include methylene, ethylene, propylene, isopropylene and the like.

[0045] The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. "Lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl,"

embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0046] The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. "Lower alkynyl" radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

5 [0047] Alkyl, alkenyl, and alkynyl radicals may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

[0048] The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. "Lower alkylamino" radicals have one or two alkyl radicals of one to six carbon atoms attached to a nitrogen atom. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

10 [0049] The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

[0050] The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo as defined above. Examples include monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical.

15 Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means an alkyl radical having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

20 [0051] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said "aryl" group may have 1 or more substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy, lower alkylamino, and the like.

25 [0052] An aryl group may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

30 [0053] The term "heterocyclyl" (or "heterocyclo") embraces saturated, and partially saturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Heterocyclic rings comprise monocyclic 6-8 membered rings, as well as 5-16 membered bicyclic ring systems (which can include bridged fused and spiro-fused bicyclic ring systems). It does not include rings containing -O-O-,-O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino, lower alkylamino, and the like.

35 [0054] Examples of saturated heterocyclo groups include saturated 3- to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl, dihydrothiazolyl, and the like.

40 [0055] Particular examples of partially saturated and saturated heterocyclo groups include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydrobenzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ⁴-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

45 [0056] Heterocyclo groups also includes radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl].

50 [0057] The term "heteroaryl" denotes aryl ring systems that contain one or more heteroatoms selected from the group O, N and S, wherein the ring nitrogen and sulfur atom(s) are optionally oxidized, and nitrogen atom(s) are optionally quaternized. Examples include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group

containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5- oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

5 [0057] The term "heteroarylalkyl" denotes alkyl radicals substituted with a heteroaryl group. Examples include pyridylmethyl and thienylethyl.

[0058] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals -SO_2^- .

10 [0059] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -C(O)-OH .

[0060] The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -C(O)- .

[0061] The term "aminocarbonyl" denotes an amide group of the formula -C(O)-NH_2 .

15 [0062] The terms "heterocycloalkyl" embrace heterocyclic-substituted alkyl radicals. Examples include piperidylmethyl and morpholinylethyl.

[0063] The term "arylalkyl" embraces aryl-substituted alkyl radicals. Examples include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

20 [0064] The term "cycloalkyl" includes saturated carbocyclic groups of 3 to 10 carbons. Lower cycloalkyl groups include $\text{C}_3\text{-C}_6$ rings. Examples include cyclopentyl, cyclopropyl, and cyclohexyl. Cycloalkyl groups may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

[0065] The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. "Lower cycloalkylalkyl" radicals are cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Examples of include cyclohexylmethyl. The cycloalkyl in said radicals may be additionally substituted with halo, alkyl, alkoxy and hydroxy.

25 [0066] The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Examples include cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

[0067] The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

[0068] The term "oxo" as used herein contemplates an oxygen atom attached with a double bond.

30 [0069] The term "nitro" as used herein contemplates -NO_2 .

[0070] The term "cyano" as used herein contemplates -CN .

Synthesis

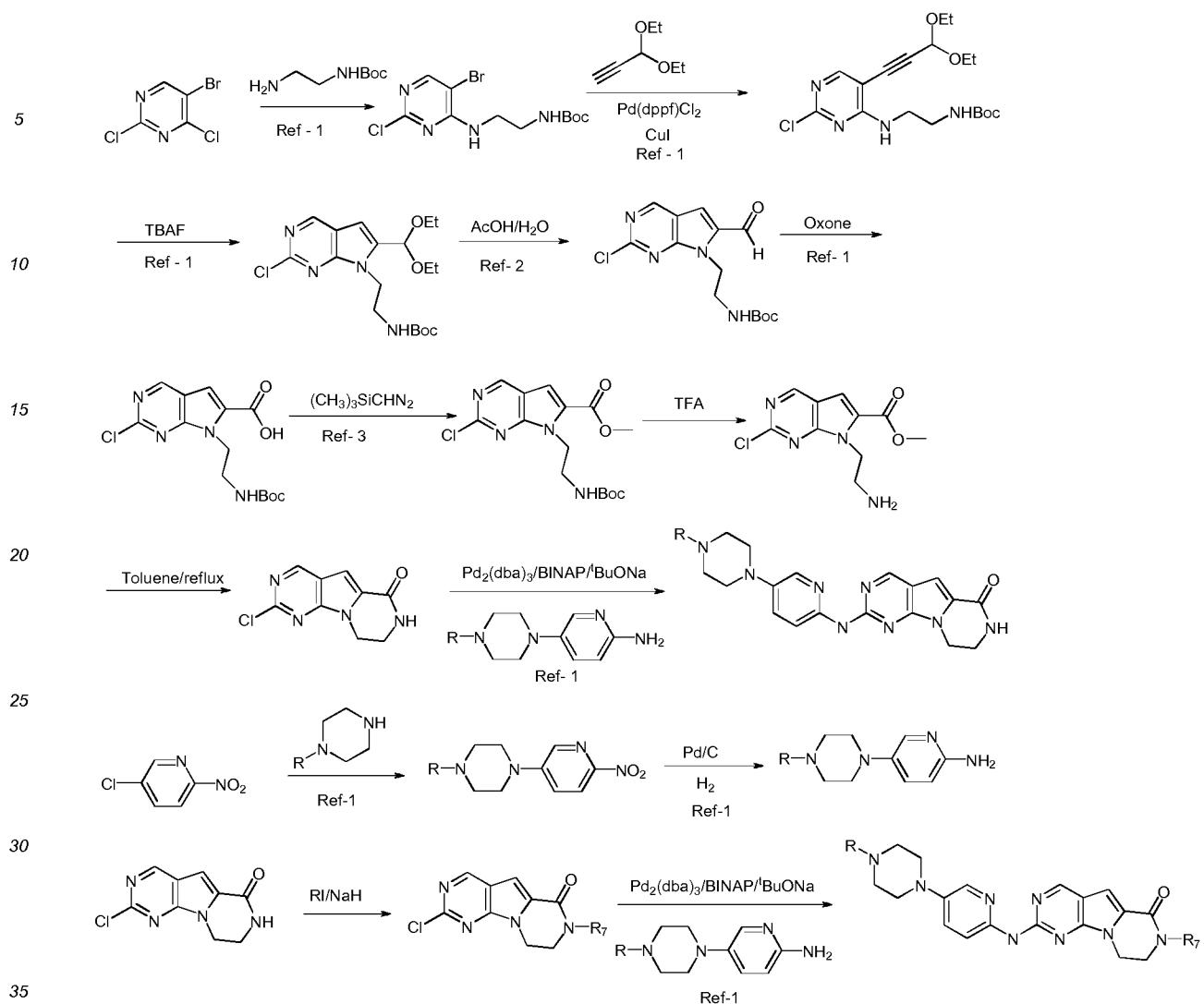
35 [0071] The disclosed compounds can be made by the following general schemes:

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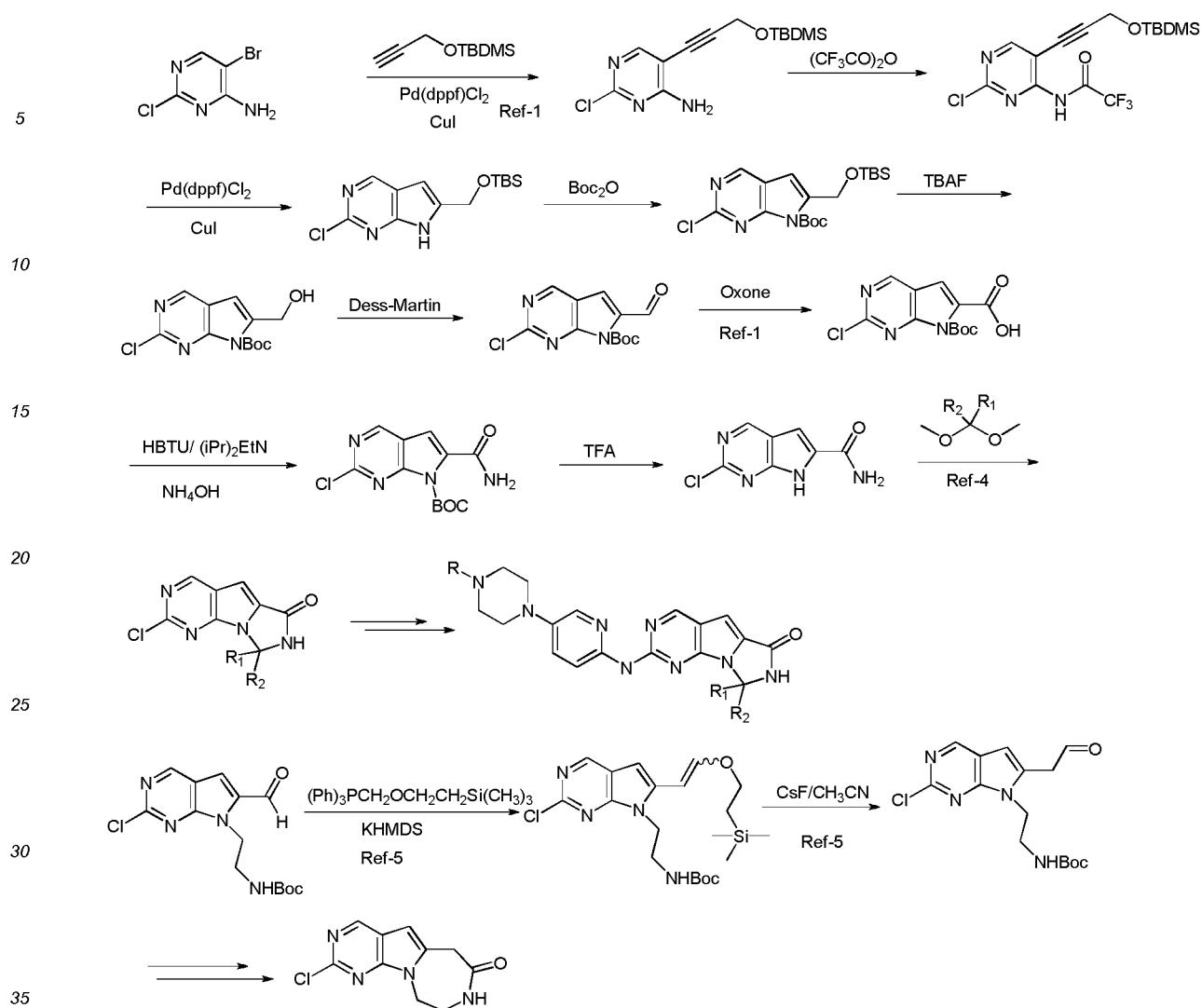
Scheme 1

[0072] In Scheme 1, Ref-1 is WO 2010/020675 A1; Ref-2 is White, J. D.; et al J. Org. Chem. 1995, 60, 3600; and Ref-3 Presser, A. and Hufner, A. Monatshefte fur Chemie 2004, 135, 1015.

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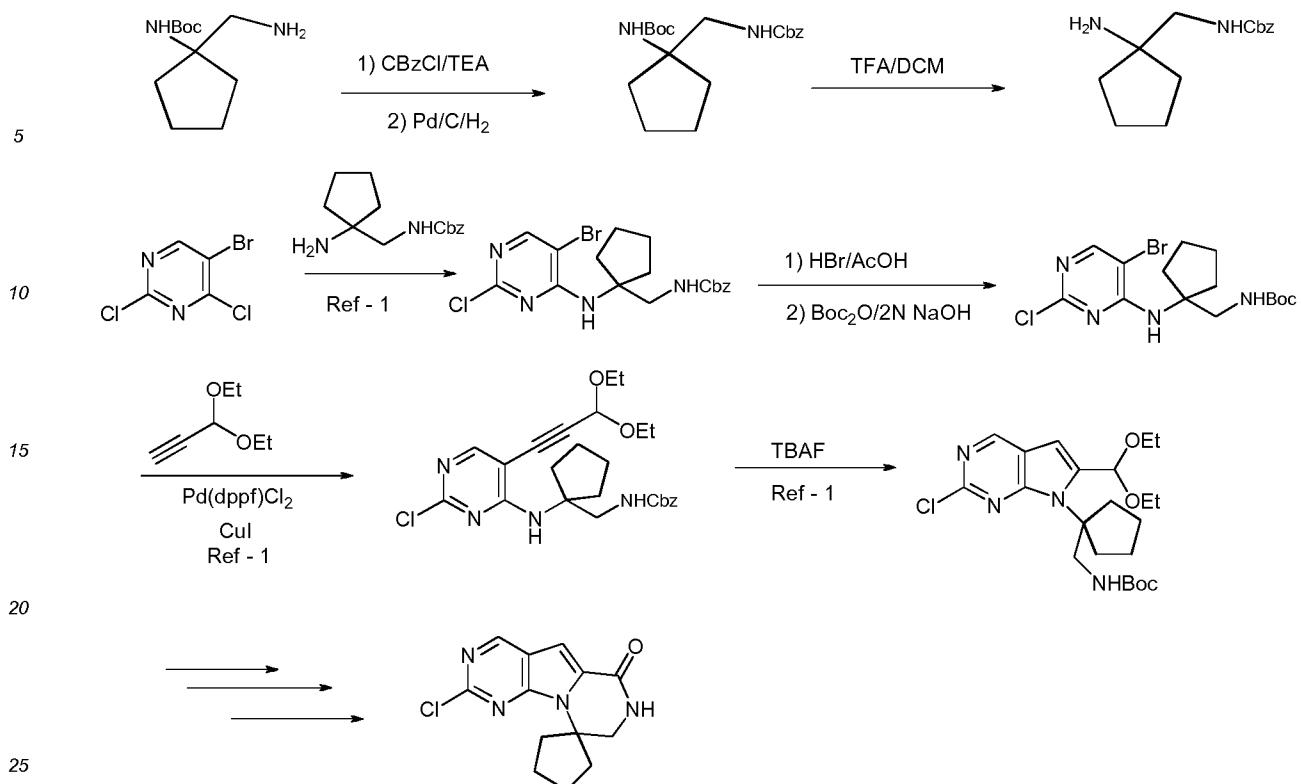
Scheme 2

[0073] In Scheme 2, Ref-1 is WO 2010/020675 A1; Ref-4 is WO 2005/040166 A1; and Ref-5 is Schoenauer, K and Zbiral, E. *Tetrahedron Letters* 1983, 24, 573.

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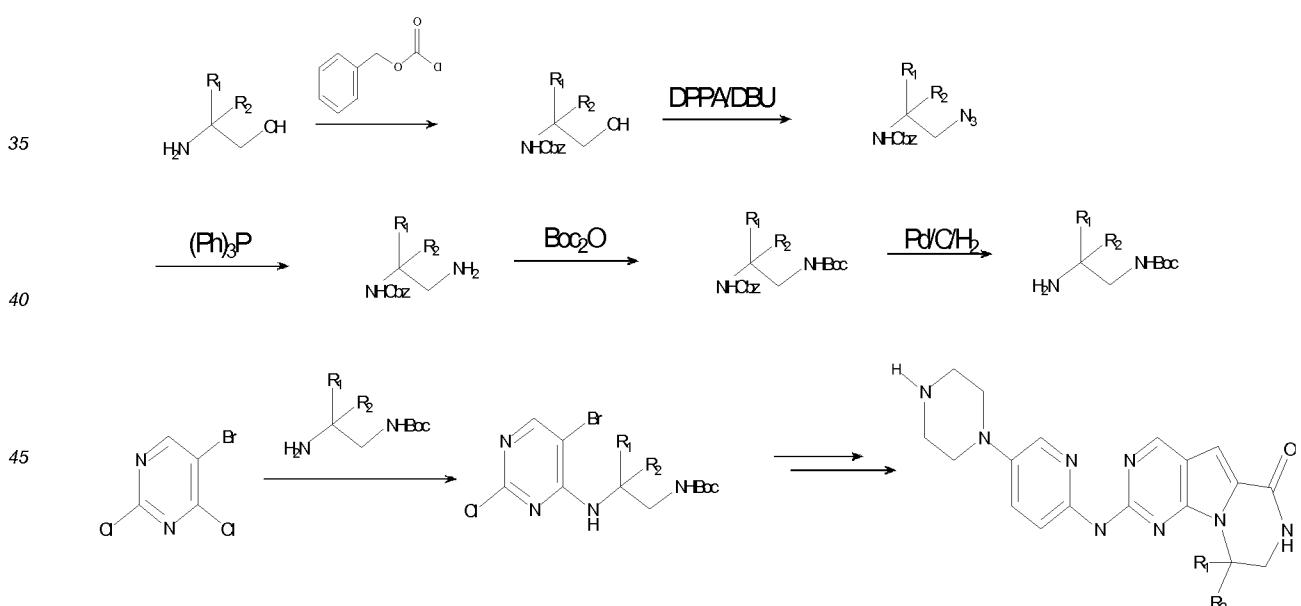
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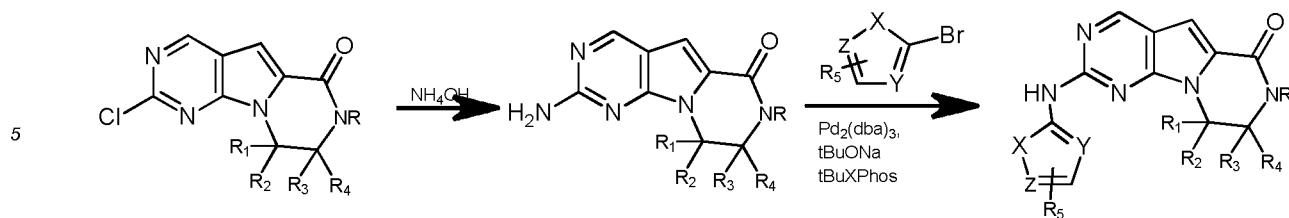


Scheme 3

[0074] In Scheme 3, Ref - 1 is WO 2010/020675 A1.



Scheme 4



Scheme 5

10 [0075] Scheme 5 illustrates a scheme useful for the synthesis of compounds of formula II.

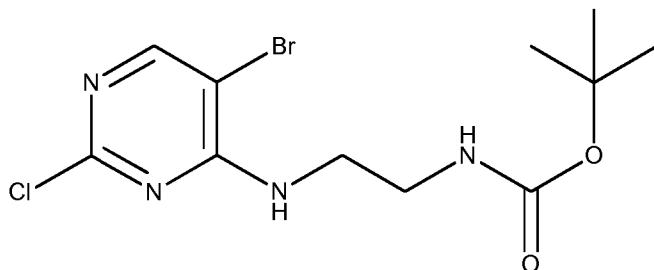
15 **EXAMPLES**

15 **Example 1**

20 **tert-butyl N- [2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino] ethyl] carbamate**

20 [0076]

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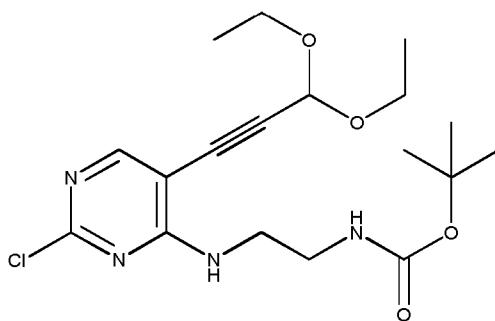


30 [0077] To a solution of 5-bromo-2,4-dichloropyrimidine 3.2 g (0.0135 mole) in ethanol 80 mL was added Hunig's base 3.0 mL followed by the addition of a solution of N-(*tert*-butoxycarbonyl)-1,2-diaminoethane 2.5 g (0.0156 mole) in 20 mL ethanol. The contents were stirred overnight for 20 hrs. The solvent was evaporated under vacuum. Ethyl acetate (200 mL) and water (100 mL) was added and the layers separated. The organic layer was dried with magnesium sulfate and then concentrated under vacuum. Column chromatography on silica gel using hexane/ethyl acetate (0- 60%) afforded *tert*-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate. ¹HNMR (d6-DMSO) 8.21 (s, 1H), 7.62 (brs, 1H), 7.27 (brs, 1H), 3.39 (m, 2H), 3.12 (m, 2H), 1.34 (s, 9H). LCMS (ESI) 351 (M + H)

40 **tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl] amino] ethyl] carbamate**

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45 [0078]

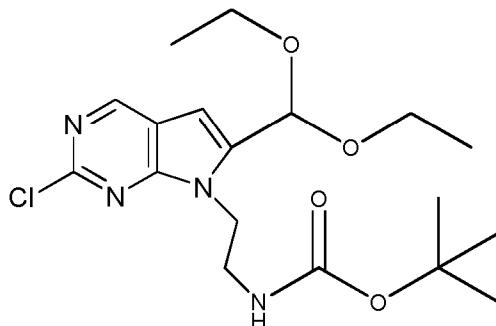


55 [0079] To 3.6 mmole (1.265 g) of *tert*-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate in THF (10 mL) was added 0.778 mL of the acetal (5.43 mmol), 148 mg of Pd(dppf)CH₂Cl₂, triethylamine 0.757 mL (5.43 mmol). The contents were degassed and then purged with nitrogen. To this was then added 29 mg of CuI. The reaction mixture was heated under reflux for 48 hrs. After cooling, the contents were filtered over CELITE™ and concentrated. Column

chromatography of the resulting residue using hexane/ethyl acetate (0- 30%) afforded *tert*-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate. ^1H NMR (d6-DMSO) 8.18 (s, 1H), 7.63 (brs, 1H), 7.40 (brs, 1H), 5.55 (s, 1H), 3.70 (m, 2H), 3.60 (m, 2H), 3.42 (m, 2H), 3.15 (m, 2H), 1.19 - 1.16 (m, 15H). LCMS (ESI) 399 (M + H)

5 ***tert*-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl] ethyl] carbamate**

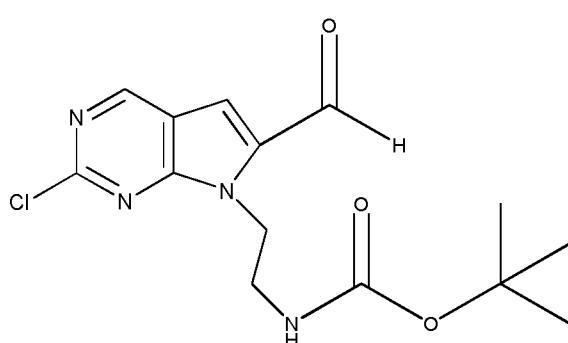
[0080]



[0081] To a solution of the coupled product 2.1 g (0.00526 mole) in THF (30 mL) was added 7.0 g of TBAF solid. The contents were heated to 65 degrees for 2 hrs. Concentration followed by column chromatography using ethyl acetate/hexane (0-50%) afforded *tert*-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate as a pale brown liquid (1.1 g). ^1H NMR (d6-DMSO) 8.88 (s, 1H), 6.95 (brs, 1H), 6.69 (s, 1H), 5.79 (s, 1H), 4.29 (m, 2H), 3.59 (m, 4H), 3.34 (m, 1H), 3.18 (m, 1H), 1.19 (m, 9H), 1.17 (m, 6H). LCMS (ESI) 399 (M + H).

***tert*-butyl N-[2-(2-chloro-6-formyl-pyrrolo[2,3-d]pyrimidin-7-yl)ethyl]carbamate**

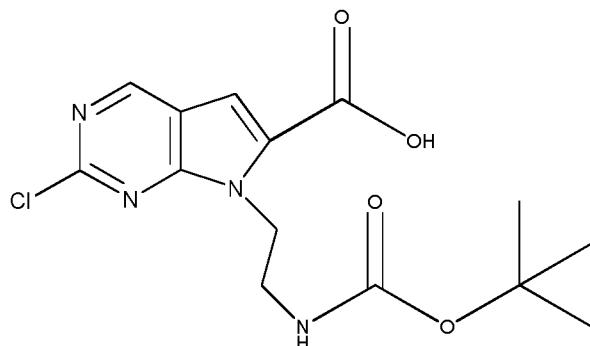
[0082]



[0083] To 900 mg of the acetal was added 8.0 mL AcOH and 1.0 mL water. This was stirred at room temperature for 16 hrs. Conc. and column ethyl acetate/hexanes (0- 60%) afforded 0.510 g of *tert*-butyl N-[2-(2-chloro-6-formyl-pyrrolo[2,3-d]pyrimidin-7-yl)ethyl]carbamate as a foam. ^1H NMR (d6-DMSO) 9.98 (s, 1H), 9.18 (s, 1H), 7.66 (s, 1H), 6.80 (brs, 1H), 4.52 (m, 2H), 4.36 (m, 2H), 1.14 (s, 9H). LCMS (ESI) 325 (M + H)

7-[2-(*tert*-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid

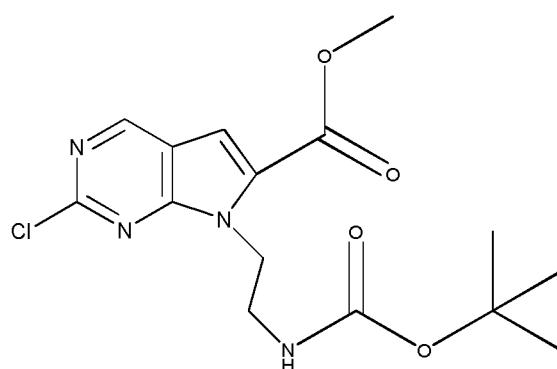
[0084]



15 [0085] To the aldehyde 0.940 g in DMF (4 mL) was added oxone (1.95 g, 1.1 eq). The contents were stirred at room temp for 7 hrs. Column hexane/ethyl acetate (0- 100%) afforded 0.545 g of 7-[2-(*tert*-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (d6-DMSO) 9.11 (s, 1H), 7.39 (s, 1H), 4.38 (m, 2H), 4.15 (m, 2H), 1.48 (m, 9H). LCMS (ESI) 341(M + H)

20 **methyl 7-[2-(*tert*-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylate**

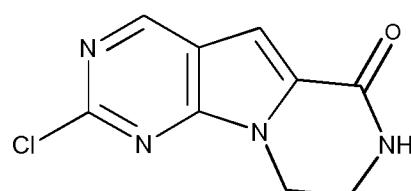
25 [0086]



35 [0087] To a solution of 2-chloro-7-propyl-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid 0.545 g (0.00156 mole) in toluene (3.5 mL) and MeOH (1 mL) was added TMS-diazomethane (1.2 mL). After stirring overnight at room temperature excess of TMS-diazomethane was quenched with acetic acid (3 mL) and then concentrated under vacuum. The residue was columned with hexane/ethyl acetate (0- 70%) to afford methyl 7-[2-(*tert*-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylate as a off white solid (0.52 g). ¹HNMR (d6-DMSO) 9.10 (s, 1H), 7.45 (s, 1H), 6.81 (brs, 1H) 4.60 (m, 2H), 3.91 (s, 3H), 3.29 (m, 2H), 1.18 (m, 9H) LCMS (ESI) 355 (M + H)

40 **Chloro tricyclic amide**

45 [0088]



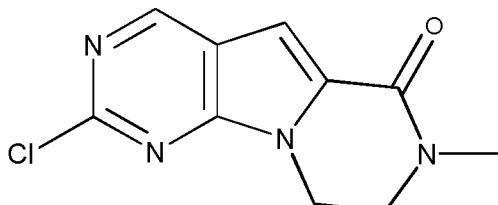
55 [0089] To methyl 7-[2-(*tert*-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylate 0.50 g (0.0014 mole) in dichloromethane (2.0 mL) was added TFA 0.830 mL. The contents were stirred at room temperature for 1 hr. Concentration under vacuum afforded the crude amino ester which was suspended in toluene (5 mL) and Hunig's base (0.5 mL). The contents were heated under reflux for 2 hrs. Concentration followed by column chromatog-

raphy using hexane/ethyl acetate (0- 50%) afforded the desired chloro tricyclic amide (0.260 g). ^1H NMR (d6-DMSO) 9.08 (s, 1H), 8.48 (brs, 1H), 7.21 (s, 1H) 4.33 (m, 2H), 3.64 (m, 2H). LCMS (ESI) 223 (M + H)

chloro-N-methyltricyclic amide

5

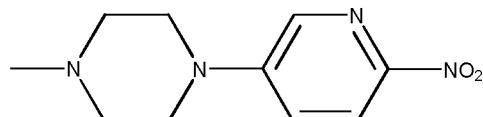
[0090]



[0091] To a solution of the chloro tricycliclactam (185 mg, 0.00083 mole) in DMF (2.0 mL) was added sodium hydride (55% dispersion in oil, 52 mg). After stirring for 15 mins, methyl iodide (62 μL , 1.2 eq). The contents were stirred at room temperature for 30 mins. After the addition of methanol (5 mL), sat NaHCO_3 was added followed by the addition of ethyl acetate. Separation of the organic layer followed by drying with magnesium sulfate and concentration under vacuum afforded the N-methylated amide in quantitative yield. ^1H NMR (d6-DMSO) 9.05 (s, 1H), 7.17 (s, 1H) 4.38 (m, 2H), 3.80 (m, 2H), 3.05 (s, 3H). LCMS (ESI) 237 (M + H)

1-methyl-4-(6-nitro-3-pyridyl)piperazine

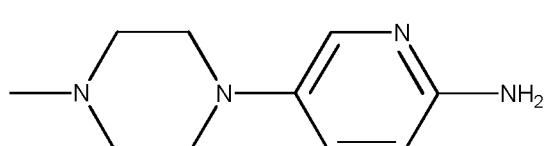
25 [0092]



[0093] To 5-bromo-2-nitropyridine (4.93 g, 24.3 mmole) in DMF (20 mL) was added N-methylpiperazine (2.96 g, 1.1 eq) followed by the addition of DIPEA (4.65 mL, 26.7 mmole). The contents were heated at 90 degrees for 24 hrs. After addition of ethyl acetate (200 mL) water 100 mL was added and the layers separated. Drying followed by concentration afforded the crude product which was columned using (0-10%) DCM/Methanol. ^1H NMR (δ 6-DMSO) 8.26 (s, 1H), 8.15 (1H, d, J = 9.3 Hz), 7.49 (1H, d, J = 9.4 Hz), 3.50 (m, 4H), 2.49 (m, 4H), 2.22 (s, 3H).

5-(4-methylpiperazin-1-yl)pyridin-2-amine

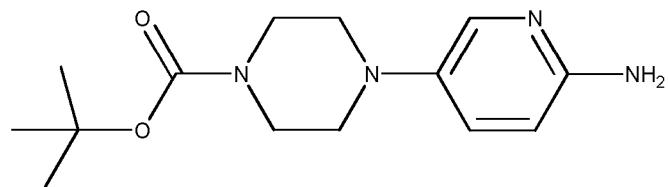
40 [0094]



[0095] To 1-methyl-4-(6-nitro-3-pyridyl)piperazine 3.4 g in ethyl acetate (100 mL) and ethanol (100 mL) was added 10% Pd/c (400 mg) and then contents stirred under hydrogen (10 psi) overnight. After filtration through CELITETM, the solvents were evaporated and the crude product was purified over silica gel using DCM/ 7N Ammonia in MeOH (0- 5%) to afford 5-(4-methylpiperazin-1-yl)pyridin-2-amine (2.2 g). ^1H NMR (d6-DMSO) 7.56 (1H, d, J = 3 Hz), 7.13 (1H, m), 6.36 (1H, d, J = 8.8 Hz), 5.33 (brs, 2H), 2.88 (m, 4H), 2.47 (m, 4H), 2.16 (s, 3H).

55 **tert-butyl 4-(6-amino-3-pyridyl)piperazine-1-carboxylate**

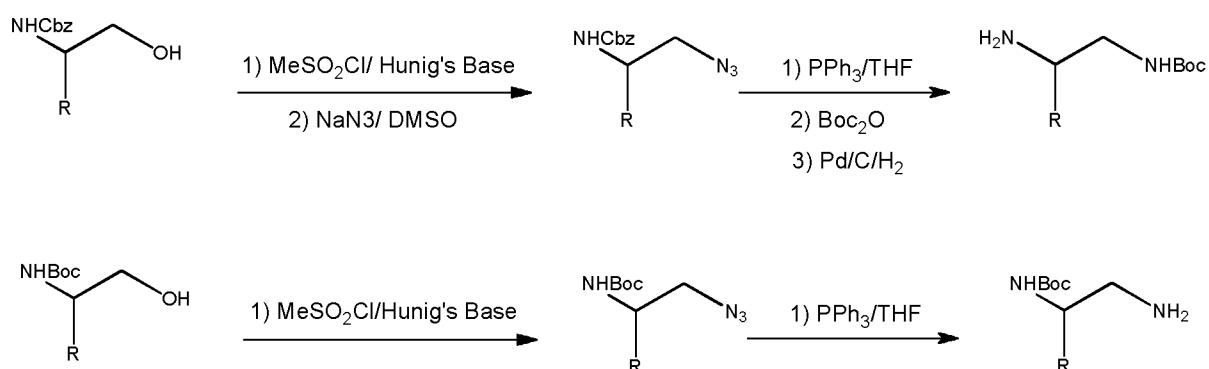
[0096]



[0097] This compound was prepared as described in WO 2010/020675 A1.

10 **Example 2 - Synthesis of Additional Intermediates**

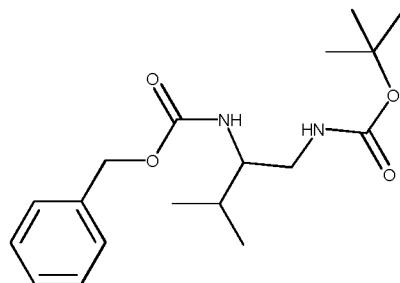
[0098]



Scheme 4

30 **Intermediate A: *tert*-butyl N-[2-(benzyloxycarbonylamino)-3-methyl-butyl] carbamate**

[0099]



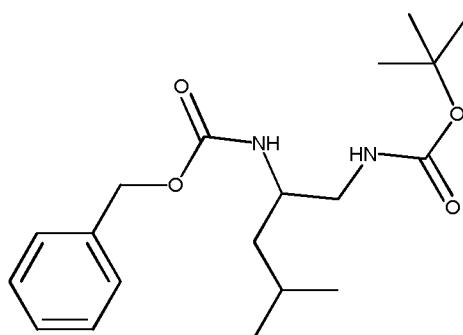
45 [0100] To 11.0 g (0.0464 mole) of benzyl N-[1-(hydroxymethyl)-2-methyl-propyl]carbamate in dioxane (100 mL) cooled to 0°C was added diphenylphosphoryl azide 10.99 mL (1.1 eq) followed by the addition of DBU 8.32 mL (1.2 eq). The contents were allowed to warm to room temperature and stirred for 16 hrs. After the addition of ethyl acetate (300 mL) and water (100 mL), the organic layer was separated and then washed with satd. NaHCO_3 (100 mL). The organic layer was then dried (magnesium sulfate) and then concentrated under vacuum. To this intermediate in DMSO (100 mL) was added sodium azide 7.54 g and the contents then heated to 90 degrees for 2 hrs. After addition of ethyl acetate and water the layers were separated. The organic layer was dried with magnesium sulfate followed by concentration under vacuum to afford an oil that was columned using hexane/ethyl acetate (0- 70%) to afford benzyl N-[1-(azidomethyl)-2-methyl-propyl] carbamate 6.9 g as a colorless oil.

50 [0101] To benzyl N-[1-(azidomethyl)-2-methyl-propyl] carbamate 6.9 g (0.0263 mole) in THF (100 mL) was added triphenyl phosphine 7.59 g (1.1 eq). The contents were stirred for 20 hrs. After addition of water (10 mL), and stirring for an additional 6 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was columned using DCM/MeOH (0 - 10%) to afford benzyl N-[1-(aminomethyl)-2-methyl-propyl] carbamate as a yellow oil.

[0102] To benzyl N-[1-(aminomethyl)-2-methyl-propyl] carbamate 4.65 g (0.019 mole) in THF (70 mL) was added 2N NaOH (20 mL) followed by the addition of di-*tert*-butyl dicarbonate 5.15 g (1.2 eq). After stirring for 16 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was purified using hexane/ethyl acetate (0- 40%) over a silica gel column to afford intermediate A, *tert*-butyl N-[2-(benzyloxycarbonylamino)-3-methyl-butyl] carbamate, (6.1 g). 1H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 0.89 (d, *J*=6.73 Hz, 3 H) 0.92 (d, *J*=6.73 Hz, 3 H) 1.38 (s, 9 H) 1.70 - 1.81 (m, 1 H) 3.18 (d, *J*=5.56 Hz, 2 H) 3.47 - 3.60 (m, 1 H) 4.76 (s, 1 H) 4.89 (d, *J*=7.90 Hz, 1 H) 5.07 (s, 2 H) 7.25 - 7.36 (m, 5 H). LCMS (ESI) 337 (M + H).

10 **Intermediate B: *tert*-butyl N-[2-(benzyloxycarbonylamino)-4-methyl-penty] carbamate**

[0103]



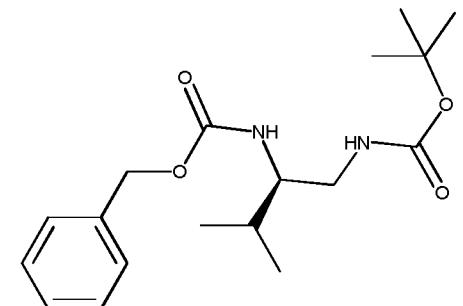
25 [0104] To a solution of benzyl N-[1-(hydroxymethyl)-3-methyl-butyl]carbamate 6.3 g (0.025 mole) in DCM (100 mL) was added diisopropylethyl amine 5.25 mL (1.2 eq) followed by the addition of methane sulfonylchloride 2.13 mL (1.1 eq) at 0 degrees. After stirring for 3 hrs, water (100 mL) was added and the organic layer separated. After drying with magnesium sulfate and concentration under vacuum, the crude [2-(benzyloxycarbonylamino)-4-methyl-penty] methanesulfonate which was taken directly to the next step.

30 [0105] To the crude [2-(benzyloxycarbonylamino)-4-methyl-penty] methanesulfonate from the above reaction in DMF (50 mL), was added sodium azide 2.43 g. The reaction mixture was then heated to 85 degrees for 3 hrs. After cooling, ethyl acetate (300 mL) and water was added. The organic layer was separated, dried with magnesium sulfate and then concentrated under vacuum to afford the crude benzyl N-[1-(azidomethyl)-3-methyl-butyl] carbamate. To this crude intermediate was added THF (100 mL) followed by triphenylphosphine 7.21 g and stirred under nitrogen for 16 hrs. After addition of water (10 mL), and stirring for an additional 6 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was columned using DCM/MeOH (0 - 10%) to afford benzyl N-[1-(aminomethyl)-3-methyl-butyl] carbamate (4.5 g).

35 [0106] To benzyl N-[1-(aminomethyl)-3-methyl-butyl] carbamate 4.5 g (0.018 mole) in THF (60 mL) was added 2N NaOH (18 mL) followed by the addition of di-*tert*-butyl dicarbonate 4.19 g (1.07 eq). After stirring for 16 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was taken to the next step. 1H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 0.89 (d, *J*=6.73 Hz, 6 H) 1.25 - 1.34 (m, 1 H) 1.39 (s, 9 H) 1.57 - 1.71 (m, 2 H) 3.04 - 3.26 (m, 2 H) 3.68 - 3.80 (m, 1 H) 4.72 - 4.89 (m, 2 H) 5.06 (s, 2 H) 7.25 - 7.38 (m, 5 H). LCMS (ESI) 351 (M + H).

45 **Intermediate C: *tert*-butyl N-[(2*R*)-2-(benzyloxycarbonylamino)-3-methyl-butyl] carbamate**

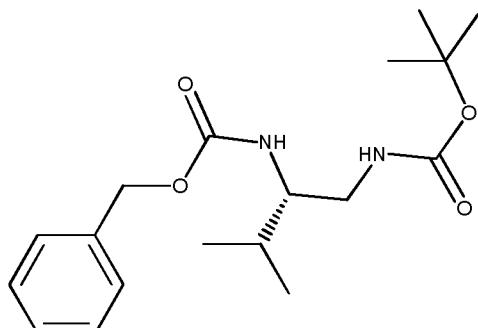
[0107]



[0108] Intermediate C was synthesized from benzyl N-[(1R)-1-(hydroxymethyl)-2-methyl-propyl] carbamate using similar synthetic steps as that described for intermediate B. The analytical data (NMR and mass spec) was consistent with that for intermediate A.

5 **Intermediate D: - *tert*-butyl N-[(2S)-2-(benzyloxycarbonylamino)-3-methyl-butyl] carbamate**

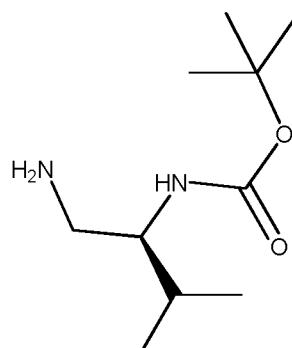
[0109]



[0110] Intermediate D was synthesized from benzyl N-[(1S)-1-(hydroxymethyl)-2-methyl-propyl] carbamate using similar synthetic steps as that described for intermediate B. The analytical data (NMR and mass spec) was consistent with that for intermediate A.

Intermediate E: *tert*-butyl N-[(1S)-1-(aminomethyl)-2-methyl-propyl]carbamate

[0111]



[0112] To a solution of *tert*-butyl N-[(1S)-1-(hydroxymethyl)-2-methyl-propyl]carbamate 6.3 g (0.025 mole) in THF (100 mL) was added diisopropylethyl amine 5.25 mL (1.2 eq) followed by the addition of methane sulfonylchloride 2.13 mL (1.1 eq) at 0 degrees. After stirring for 3 hrs, water (100 mL) was added and the organic layer separated. After 45 drying with magnesium sulfate and concentration under vacuum, the crude [(2S)-2-(*tert*-butoxycarbonylamino)-3-methyl-butyl] methanesulfonate which was taken directly to the next step.

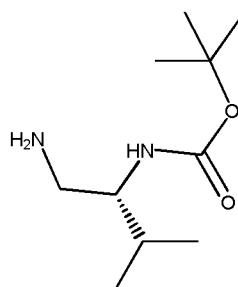
[0113] To the crude [(2S)-2-(*tert*-butoxycarbonylamino)-3-methyl-butyl] methanesulfonate from the above reaction in DMSO (50 mL), was added sodium azide 2.43 g. The reaction mixture was then heated to 85 degrees for 3 hrs. After 50 cooling, ethyl acetate (300 mL) and water was added. The organic layer was separated, dried with magnesium sulfate and then concentrated under vacuum to afford the crude benzyl N-[1-(azidomethyl)-3-methyl-butyl] carbamate. To this crude intermediate was added THF (100 mL) followed by triphenylphosphine 7.21 g and stirred under nitrogen for 16 hrs. After addition of water (10 mL), and stirring for an additional 6 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was columned using DCM/MeOH (0 - 10%) to afford benzyl N-[1-(aminomethyl)-3-methyl-butyl] carbamate (4.5 g). LCMS (ESI) 203 (M + H).

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Intermediate F: *tert*-butyl N-[(1R)-1-(aminomethyl)-2-methyl-propyl]carbamate

[0114]

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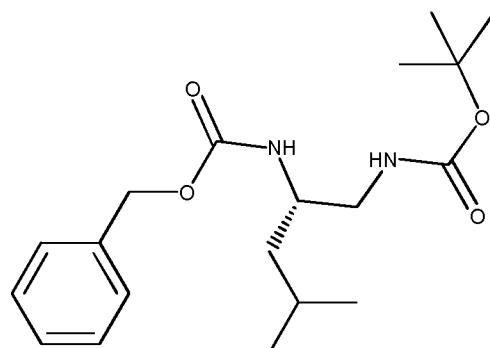
[0115] Intermediate F was synthesized from *tert*-butyl N-[(1*R*)-1-(hydroxymethyl)-2-methyl-propyl] carbamate using a similar synthetic sequence as described for intermediate E. The analytical data (NMR and mass spec) was consistent with intermediate E.

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Intermediate G: *tert*-butyl N-[(2*S*)-2-(benzyloxycarbonylamino)-4-methyl-pentyl] carbamate

[0116]

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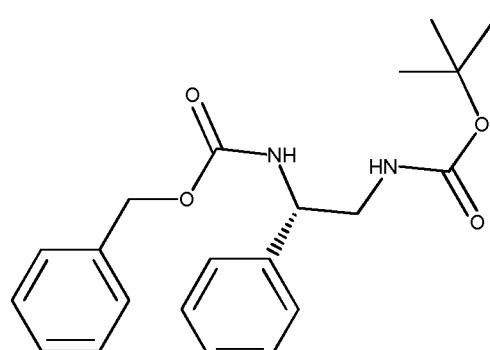
30

[0117] Intermediate G was synthesized from benzyl N-[(1*S*)-1-(hydroxymethyl)-3-methyl-butyl]carbamate using a similar synthetic sequence as described for intermediate B. The analytical data (NMR and mass spec) was consistent with intermediate B.

Intermediate H: *tert*-butyl N-[(2*S*)-2-(benzyloxycarbonylamino)-2-phenyl-ethyl] carbamate

[0118]

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[0119] Intermediate H was synthesized from benzyl N-[(1*S*)-2-hydroxy-1-phenyl-ethyl] carbamate using a similar synthetic sequence as described for intermediate B. ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.20 - 1.33 (m, 9 H) 3.11 (t, *J*=6.29 Hz, 2 H) 4.59 - 4.68 (m, 1 H) 4.88 - 5.01 (m, 2 H) 6.81 (t, *J*=5.42 Hz, 1 H) 7.14 - 7.35 (m, 10 H) 7.69 (d, *J*=8.49 Hz, 1 H). LCMS (ESI) 371 (M + H).

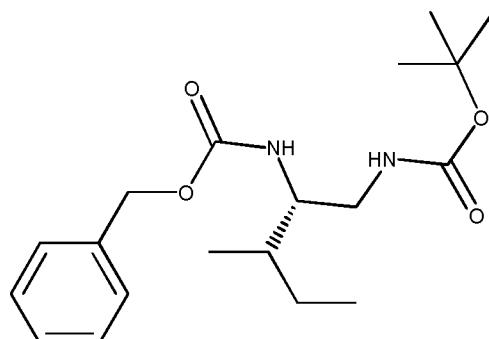
Intermediate I: *tert*-butyl N-[(2*S*)-2-(benzyloxycarbonylamino)-3-methyl-pentyl] carbamate

[0120]

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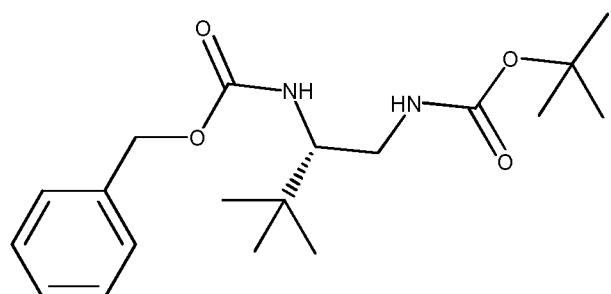
[0121] Intermediate I was synthesized from benzyl N-[(1*S*)-1-(hydroxymethyl)-2-methyl-butyl] carbamate using a similar synthetic sequence as described for intermediate B. ^1H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 0.85 - 0.92 (m, 6 H) 1.05 - 1.15 (m, 1 H) 1.35 - 1.41 (m, 9 H) 1.45 - 1.56 (m, 2 H) 3.14 - 3.24 (m, 2 H) 3.54 - 3.64 (m, 1 H) 4.78 (s, 1 H) 4.96 (d, J =7.91 Hz, 1 H) 5.06 (s, 2 H) 7.27 - 7.37 (m, 5 H). LCMS (ESI) 351 (M + H).

Intermediate J: *tert*-butyl N-[(2*S*)-2-(benzyloxycarbonylamino)-3,3-dimethyl-butyl] carbamate

[0122]

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[0123] Intermediate J was synthesized from benzyl N-[(1*S*)-1-(hydroxymethyl)-2,2-dimethyl-propyl]carbamate using a similar synthetic sequence as described for intermediate B. LCMS (ESI) 351.

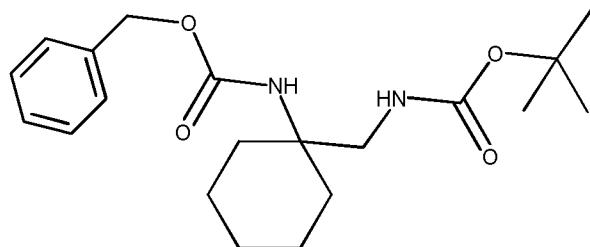
40

Intermediate K: *tert*-butyl N-[[1-(benzyloxycarbonylamino)cyclohexyl]methyl] carbamate

[0124]

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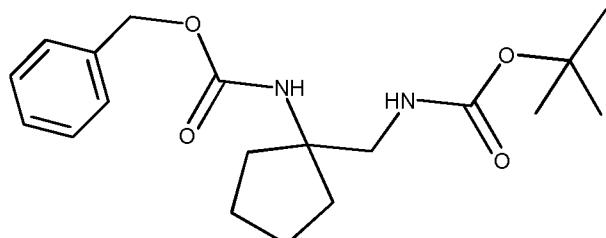
[0125] To a solution of benzyl N-[1-(aminomethyl)cyclohexyl]carbamate 10.0 g (0.0381 mole) in THF (150 mL) was added di-*tert*-butyl dicarbonate (9.15 g, 1.1 eq) and the contents stirred at room temperature for 16 hrs. Ethyl acetate and water was then added. The organic layer was separated, dried over magnesium sulfate and then concentrated under vacuum to afford *tert*-butyl N-[[1-(benzyloxycarbonylamino)cyclohexyl]methyl] carbamate (13.1 g). ^1H NMR (600

MHz, DMSO-*d*₆) δ ppm 0.92 - 1.54 (m, 17 H) 1.76 - 2.06 (m, 2 H) 3.09 (d, *J*=6.15 Hz, 2 H) 4.92 (s, 2 H) 6.63 (d, *J*=17.27 Hz, 1 H) 7.16 - 7.49 (m, 6 H). LCMS (ESI) 363 (M + H).

Intermediate L: *tert*-butyl N-[[1-(benzyloxycarbonylamino)cyclopentyl]methyl] carbamate

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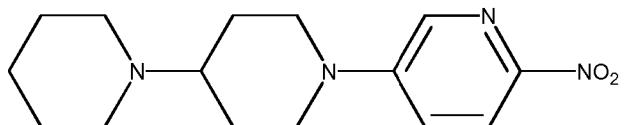
[0126]



[0127] *tert*-butyl N-[[1-(benzyloxycarbonylamino)cyclopentyl]methyl] carbamate was synthesized in an analogous manner to *tert*-butyl N-[[1-(benzyloxycarbonylamino) cyclohexyl]methyl] carbamate. LCMS (ESI) 349 (M + H).

20 Example 3 - Synthesis of Substituted 2-aminopyridines

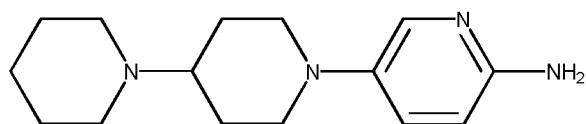
[0128]



30 [0129] To 5-bromo-2-nitropyridine (1.2 g, 5.9 mmol) in DMSO (4 mL) was added 1-(4-piperidyl)piperidine (1.0 g, 5.9 mmole) and triethyl amine (0.99 mL, 7.1 mmole). The contents were heated to 120 degrees in a CEM Discovery microwave system for 3 hours. The crude reaction was then loaded over a silica gel column and eluted with DCM/methanol (0-20%) to afford 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine as an oil (457 mg). 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.26 - 1.36 (m, 2 H) 1.43 (m, 6 H) 1.76 (m, 2 H) 2.37 (m, 5 H) 2.94 (t, *J*=12.74 Hz, 2 H) 4.06 (d, *J*=13.47 Hz, 2 H) 7.41 (dd, *J*=9.37, 2.64 Hz, 1 H) 8.08 (d, *J*=9.37 Hz, 1 H) 8.20 (d, *J*=2.64 Hz, 1 H).

35 .5-[4-(1-piperidyl)-1-piperidyl] pyridin-2-amine

[0130]



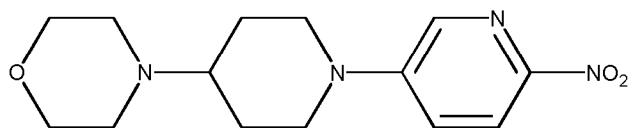
[0131] 5-[4-(1-piperidyl)-1-piperidyl]pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.13 - 1.37 (m, 6 H) 1.40 - 1.63 (m, 6 H) 1.71 (m, 2 H), 2.24 (m, 1H) 2.43 (m, 2 H) 3.33 (d, *J*=12.30 Hz, 2 H) 5.31 (s, 2 H) 6.33 (d, *J*=8.78 Hz, 1 H) 7.10 (dd, *J*=8.78, 2.93 Hz, 1 H) 7.55 (d, *J*=2.64 Hz, 1 H). LCMS (ESI) 261 (M + H).

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4-[1-(6-nitro-3-pyridyl)-4-piperidyl] morpholine

[0132]

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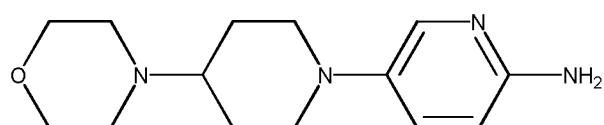
[0133] 4-[1-(6-nitro-3-pyridyl)-4-piperidyl]morpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.41 (m, 2 H) 1.82 (m, 2 H) 2.42 (m, 5 H) 2.98 (t, *J*=12.44 Hz, 2 H) 3.52 (s, 4 H) 4.04 (d, *J*=12.88 Hz, 2 H) 7.42 (d, *J*=9.37 Hz, 1 H) 8.08 (d, *J*=9.08 Hz, 1 H) 8.21 (s, 1 H).

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5-(4-morpholino-1-piperidyl) pyridin-2-amine

[0134]



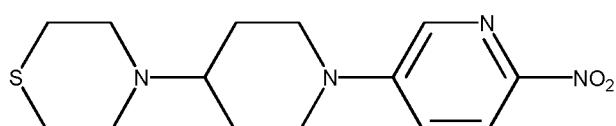
[0135] 5-(4-morpholino-1-piperidyl)pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.34 - 1.52 (m, 2 H) 1.78 (m, 2 H) 2.14 (m, 1 H) 2.43 (m, 4 H) 3.32 (d, *J*=12.30 Hz, 4 H) 3.47 - 3.59 (m, 4 H) 5.32 (s, 2 H) 6.34 (d, *J*=8.78 Hz, 1 H) 7.11 (dd, *J*=8.93, 2.78 Hz, 1 H) 7.47 - 7.62 (m, 1 H). LCMS (ESI) 263 (M + H).

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4-[1-(6-nitro-3-pyridyl)-4-piperidyl] thiomorpholine

[0136]



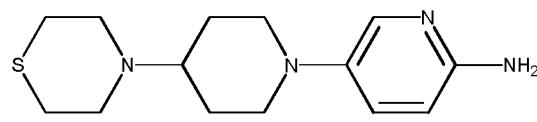
[0137] 4-[1-(6-nitro-3-pyridyl)-4-piperidyl] thiomorpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.40 - 1.52 (m, 2 H) 1.71 (m, 2 H) 2.49 - 2.55 (m, 4 H) 2.56 - 2.63 (m, 1 H) 2.68 - 2.75 (m, 4 H) 2.88 - 2.98 (m, 2 H) 4.09 (d, *J*=13.18 Hz, 2 H) 7.42 (dd, *J*=9.22, 3.07 Hz, 1 H) 8.08 (d, *J*=9.37 Hz, 1 H) 8.20 (d, *J*=3.22 Hz, 1 H).

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5-(4-thiomorpholino-1-piperidyl) pyridin-2-amine

[0138]

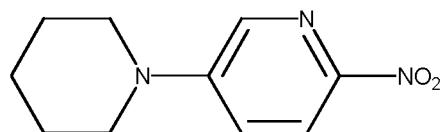


[0139] 5-(4-thiomorpholino-1-piperidyl) pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.47 - 1.59 (m, 2 H) 1.65 (m, 2 H) 2.22 - 2.38 (m, 1 H) 2.50 - 2.59 (m, 6 H) 2.68 - 2.82 (m, 4 H) 3.33 (d, *J*=12.00 Hz, 2 H) 5.31 (s, 2 H) 6.33 (d, *J*=9.08 Hz, 1 H) 7.10 (dd, *J*=8.78, 2.93 Hz, 1 H) 7.55 (d, *J*=2.64 Hz, 1 H). LCMS (ESI) 279 (M + H).

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2-nitro-5-(1-piperidyl)pyridine

[0140]

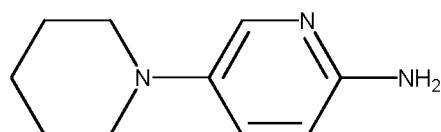


[0141] 2-nitro-5-(1-piperidyl) pyridine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.56 (m, 6 H) 3.49 (d, *J*=4.39 Hz, 4 H) 7.30 - 7.47 (m, 1 H) 8.02 - 8.12 (m, 1 H) 8.15 - 8.26 (m, 1 H).

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5-(1-piperidyl)pyridin-2-amine

[0142]



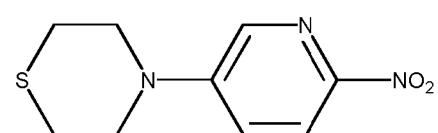
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[0143] 5-(1-piperidyl) pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.39 - 1.46 (m, 2 H) 1.51 - 1.62 (m, 4 H) 2.75 - 2.92 (m, 4 H) 5.30 (s, 2 H) 6.34 (d, *J*=8.78 Hz, 1 H) 7.09 (dd, *J*=8.78, 2.93 Hz, 1 H) 7.54 (d, *J*=2.93 Hz, 1 H). LCMS (ESI) 178 (M + H).

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4-(6-nitro-3-pyridyl) thiomorpholine

[0144]



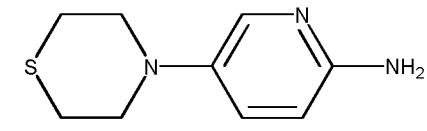
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[0145] 4-(6-nitro-3-pyridyl) thiomorpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 2.56 - 2.69 (m, 4 H) 3.79 - 3.92 (m, 4 H) 7.43 (dd, *J*=9.22, 3.07 Hz, 1 H) 8.10 (d, *J*=9.37 Hz, 1 H) 8.20 (d, *J*=2.93 Hz, 1 H).

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5-thiomorpholinopyridin-2-amine

[0146]



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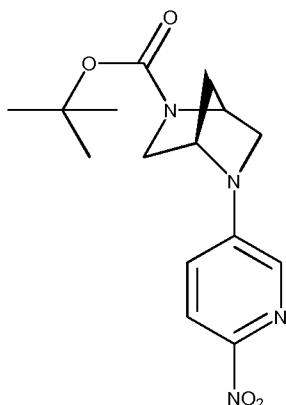
[0147] 5-thiomorpholinopyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl) pyridin-2-amine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 2.59 - 2.73 (m, 4 H) 3.04 - 3.20 (m, 4 H) 5.41 (s, 2 H) 6.35 (d, *J*=8.78 Hz, 1 H) 7.10 (dd, *J*=8.78, 2.93 Hz, 1 H) 7.57 (d, *J*=2.64 Hz, 1 H). LCMS (ESI) 196 (M + H).

tert-butyl (4R)-5-(6-nitro-3-pyridyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

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[0148]

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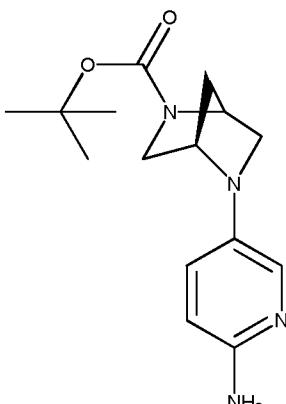
[0149] *tert*-butyl (4*R*)-5-(6-nitro-3-pyridyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.33 (d, *J*=32.21 Hz, 11 H) 1.91 (m, 2 H) 3.15 (d, *J*=10.25 Hz, 1 H) 3.58 (m, 1 H) 4.46 (m, 1 H) 4.83 (s, 1 H) 7.16 (s, 1 H) 7.94 (s, 1 H) 8.05 - 8.16 (m, 1 H).

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tert-butyl (4*R*)-5-(6-amino-3-pyridyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

[0150]

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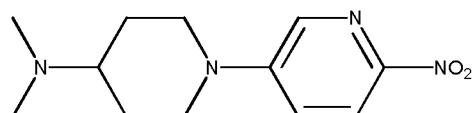
[0151] *tert*-butyl (4*R*)-5-(6-amino-3-pyridyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.31 (d, *J*=31.91 Hz, 11 H) 1.83 (m, 2 H) 2.71 - 2.82 (m, 1 H) 3.44 (m, 1 H) 4.30 (d, 2H) 5.08 (s, 2 H) 6.35 (d, *J*=8.78 Hz, 1 H) 6.77 - 6.91 (m, 1 H) 7.33 (s, 1 H). LCMS (ESI) 291 (M + H).

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N,N-dimethyl-1-(6-nitro-3-pyridyl) piperidin-4-amine

[0152]

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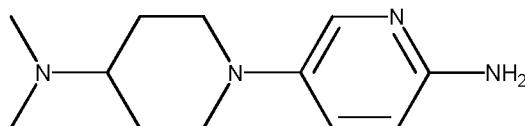


[0153] N,N-dimethyl-1-(6-nitro-3-pyridyl)piperidin-4-amine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.30 - 1.45 (m, 2 H) 1.79 (m, 2 H) 2.14 (s, 6 H) 2.33 (m, 1 H) 2.92 - 3.04 (m, 2 H) 4.03 (d, *J*=13.76 Hz, 2 H) 7.42 (dd, *J*=9.22, 3.07 Hz, 1 H) 8.04 - 8.11 (m, 1 H) 8.21 (d, *J*=2.93 Hz, 1 H).

5-[4-(dimethylamino)-1-piperidyl] pyridin-2-amine

[0154]

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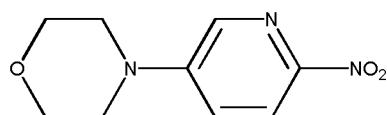
[0155] 5-[4-(dimethylamino)-1-piperidyl]pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.35 - 1.50 (m, 2 H) 1.69 - 1.81 (m, 2 H) 2.00 - 2.10 (m, 1 H) 2.11 - 2.22 (s, 6 H) 3.17 - 3.36 (m, 4 H) 5.19 - 5.38 (s, 2 H) 6.34 (d, $J=8.78$ Hz, 1 H) 7.10 (dd, $J=8.78, 2.93$ Hz, 1 H) 7.55 (d, $J=2.63$ Hz, 1 H). LCMS (ESI) 221 (M + H).

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4-(6-nitro-3-pyridyl) morpholine

[0156]

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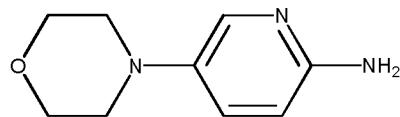
[0157] 4-(6-nitro-3-pyridyl) morpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl] pyridine.

5-morpholinopyridin-2-amine

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[0158]

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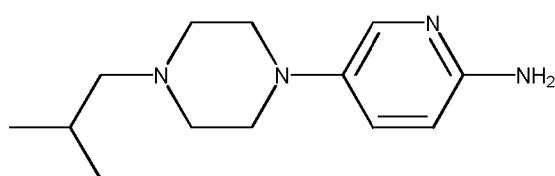
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[0159] 5-morpholinopyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl) pyridin-2-amine. ^1H NMR (600 MHz, $\text{CHLOROFORM}-d$) δ ppm 2.91 - 3.00 (m, 4 H) 3.76 - 3.84 (m, 4 H) 4.19 (br. s., 2 H) 6.45 (d, $J=8.78$ Hz, 1 H) 7.12 (dd, $J=8.78, 2.93$ Hz, 1 H) 7.72 (d, $J=2.93$ Hz, 1 H).

5-(4-isobutylpiperazin-1-yl) pyridin-2-amine

[0160]

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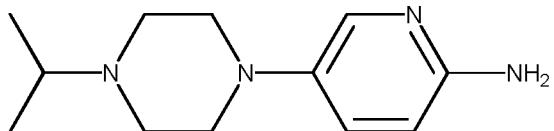
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[0161] 1-isobutyl-4-(6-nitro-3-pyridyl)piperazine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine which was then converted 5-(4-isobutylpiperazin-1-yl)pyridin-2-amine in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ^1H NMR (600 MHz, $\text{CHLOROFORM}-d$) δ ppm 0.88 (d, $J=6.73$ Hz, 6 H) 1.71 - 1.84 (m, 1 H) 2.10 (d, $J=7.32$ Hz, 2 H) 2.46 - 2.58 (m, 4 H) 2.97 - 3.07 (m, 4 H) 4.12 (s, 2 H) 6.45 (d, $J=8.78$ Hz, 1 H) 7.14 (dd, $J=8.78, 2.93$ Hz, 1 H) 7.75 (d, $J=2.93$ Hz, 1 H). LCMS (ESI) 235 (M + H).

5-(4-isopropylpiperazin-1-yl) pyridin-2-amine

[0162]

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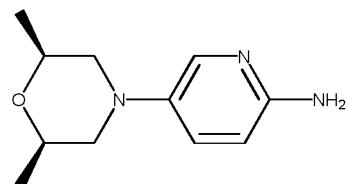
[0163] 1-isopropyl-4-(6-nitro-3-pyridyl)piperazine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine which was then converted to 5-(4-isopropylpiperazin-1-yl)pyridin-2-amine in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ^1H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 1.06 (d, *J*=6.44 Hz, 6 H) 2.59 - 2.75 (m, 5 H) 2.97 - 3.10 (m, 4 H) 4.13 (s, 2 H) 6.45 (d, *J*=8.78 Hz, 1 H) 7.15 (dd, *J*=9.08, 2.93 Hz, 1 H) 7.76 (d, *J*=2.93 Hz, 1 H). LCMS (ESI) 221 (M + H).

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5-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]pyridin-2-amine

[0164]

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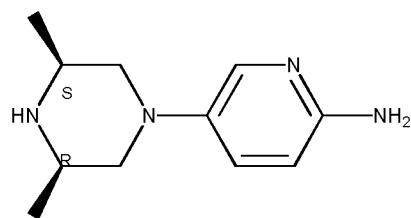
[0165] (2*S*,6*R*)-2,6-dimethyl-4-(6-nitro-3-pyridyl)morpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine which was then converted to 5-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]pyridin-2-amine in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ^1H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 1.20 (d, *J*=6.44 Hz, 6 H) 2.27 - 2.39 (m, 2 H) 3.11 - 3.21 (m, 2 H) 3.70 - 3.84 (m, 2 H) 4.15 (s, 2 H) 6.45 (d, *J*=8.78 Hz, 1 H) 7.12 (dd, *J*=8.78, 2.93 Hz, 1 H) 7.72 (d, *J*=2.63 Hz, 1 H). LCMS (ESI) 208 (M + H).

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5-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]pyridin-2-amine

[0166]

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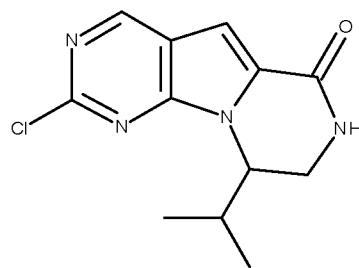
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[0167] (3*S*,5*R*)-3,5-dimethyl-1-(6-nitro-3-pyridyl)piperazine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine which was then converted to 5-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]pyridin-2-amine in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ^1H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 1.09 (d, *J*=6.44 Hz, 6 H) 2.20 (t, *J*=10.83 Hz, 2 H) 2.95 - 3.08 (m, 2 H) 3.23 (dd, *J*=11.71, 2.05 Hz, 2 H) 4.13 (s, 2 H) 6.45 (d, *J*=8.78 Hz, 1 H) 7.14 (dd, *J*=8.78, 2.93 Hz, 1 H) 7.73 (d, *J*=2.63 Hz, 1 H). LCMS (ESI) 207 (M + H).

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Intermediate 1A:

[0168]

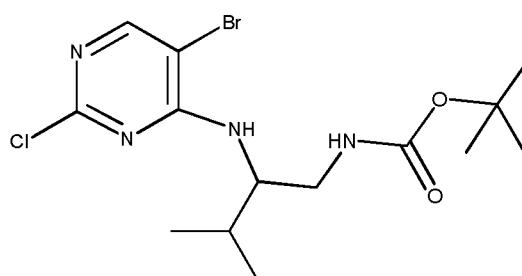


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tert-butyl N-[2-[(5-bromo-2-chloro-4-pyrimidinyl)amino]-3-methylbutyl] carbamate

[0169]

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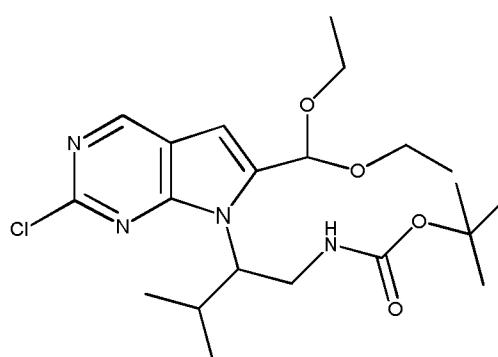
[0170] A solution of intermediate A in ethanol (100 mL) was hydrogenated under 30 psi of hydrogen using 10% Pd/C (0.7 g) in a pressure bomb for 7 hrs. After filtration of the reaction mixture through CELITE™, the organic layer was concentrated under vacuum to afford *tert*-butyl N-(2-amino-3-methyl-butyl) carbamate (3.8 g).

[0171] To a solution of 5-bromo-2,4-dichloro-pyrimidine 7.11 g (0.0312 mole) in ethanol (100 mL) was added diisopropylethyl amine 5.45 mL (1.0 eq) and *tert*-butyl N-(2-amino-3-methyl-butyl) carbamate 6.31 g (0.0312 mole). The reaction mixture was stirred at room temperature for 20 hrs. After concentration under vacuum, ethyl acetate and water was added. The organic layer was separated, dried with magnesium sulfate and then concentrated under vacuum. The crude product was purified by column chromatography using hexane/ethyl acetate (0- 30%) over silica gel to afford *tert*-butyl N-[2-[(5-bromo-2-chloropyrimidin-4-yl)amino]-3-methyl-butyl] carbamate. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 0.77 - 0.85 (d, *J*=6.5 Hz, 3 H) 0.87 (d, *J*=6.73 Hz, 3 H) 1.31 - 1.39 (m, 9 H) 1.82 - 1.93 (m, 1 H) 2.94 (d, *J*=5.56 Hz, 1 H) 3.08 - 3.22 (m, 2 H) 3.98 (d, *J*=8.20 Hz, 1 H) 6.96 (d, *J*=8.78 Hz, 1 H) 8.21 (s, 1 H). LCMS (ESI) 393 (M + H).

tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]-3-methyl-butyl]carbamate

[0172]

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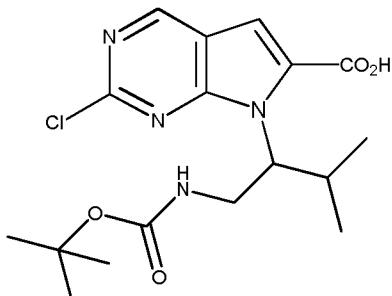
[0173] *tert*-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]-3-methyl-butyl]carbamate was synthesized by subjecting *tert*-butyl N-[2-[(5-bromo-2-chloropyrimidin-4-yl)amino]-3-methyl-butyl]carbamate to Sonogashira conditions as described for *tert*-butyl N-[2-[(2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl)amino]ethyl]carbamate followed by subsequent treatment with TBAF as described in the synthesis of *tert*-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.11 (d, *J*=6.44 Hz, 3 H) 1.18

(t, $J=7.03$ Hz, 6 H) 1.21 - 1.26 (m, 12 H) 2.88 (br. s., 1 H) 3.43 - 3.78 (m, 6 H) 3.97 - 4.08 (m, 1 H) 5.61 (s, 1 H) 6.65 (s, 1 H) 6.71 - 6.78 (m, 1 H) 8.87 (s, 1 H). LCMS (ESI) 441 (M + H).

7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[23-d]pyrimidine-6-carboxylic acid

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[0174]



20 **[0175]** To a solution *tert*-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate in THF was added TBAF and the contents refluxed for 3 hrs. Ethyl acetate and water was then added and the organic layer separated, dried with magnesium sulfate and then concentrated under vacuum. To this crude reaction was added acetic acid/water (9:1) and then contents stirred for 12 hrs at room temperature. After concentration under vacuum, sat NaHCO₃ and ethyl acetate was then added. The organic layer was separated, dried and then concentrated under vacuum. The crude reaction product thus obtained was dissolved in DMF, oxone was then added and the contents stirred for 3 hrs. After addition of ethyl acetate, the reaction mixture was filtered through CELITE™ and concentrated under vacuum. Column chromatography of the crude product over silica gel using hexane/ethyl acetate (0- 100%) afforded 7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 0.85 (d, $J=7.03$ Hz, 3 H) 0.97 (d, $J=6.73$ Hz, 3 H) 1.52 (s, 9 H) 1.99 - 2.23 (m, 1 H) 3.98 (dd, $J=14.05$, 3.51 Hz, 1 H) 4.47 - 4.71 (m, 2 H) 7.47 (s, 1 H) 9.17 (s, 1 H). LCMS (ESI) 383 (M + H).

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Intermediate 1A

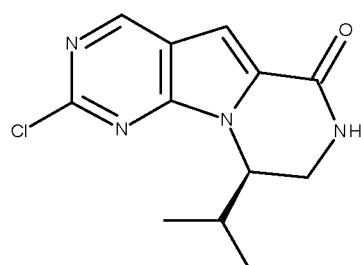
35 **[0176]** To 7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloropyrrolo[2,3-d]pyrimidine-6-carboxylic acid 0.050 g (0.00013 mole) in DCM (1.5 mL) was added DIC (32.7 mg) and DMAP (10 mg). The contents were stirred for 2 hrs. Trifluoroacetic acid (0.4 mL) was then added and stirring continued for an additional 30 minutes. After addition of satd NaHCO₃ to neutralize the excess acid, ethyl acetate was then added and the organic layer separated, dried using magnesium sulfate and then concentrated under vacuum. The crude product was column chromatographed over silica gel using hexane/ethyl acetate (0- 100%) to afford Intermediate 1A. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 0.72 (d, $J=6.73$ Hz, 3 H) 0.97 (d, $J=6.73$ Hz, 3 H) 2.09 - 2.22 (m, 1 H) 3.57 (dd, $J=13.18$, 4.98 Hz, 1 H) 3.72 (dd, $J=13.61$, 4.25 Hz, 1 H) 4.53 (dd, $J=8.05$, 3.95 Hz, 1 H) 7.20 (s, 1 H) 8.34 (d, $J=4.98$ Hz, 1 H) 9.08 (s, 1 H). LCMS (ESI) 265 (M + H).

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Intermediate 1B:

[0177]

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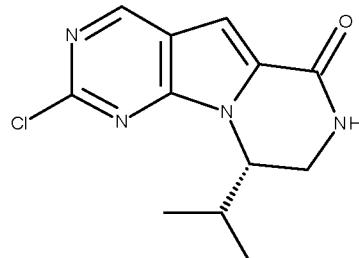
[0178] Intermediate C was hydrogenated with 10% Pd/C to afford the intermediate *tert*-butyl N-[(2R)-2-amino-3-methylbutyl] carbamate, which was then treated with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for Intermediate 1A to afford intermediate 1B. The analytical data is consistent with that reported for the

racemate (Intermediate 1A).

Intermediate 1C:

5 [0179]

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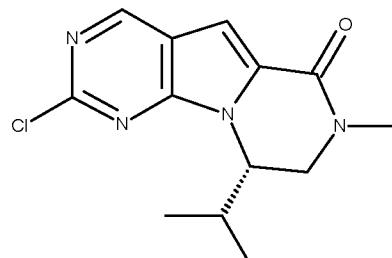
15

[0180] Intermediate D was hydrogenated with 10% Pd/C to afford the intermediate *tert*-butyl N-[(2*S*)-2-amino-3-methylbutyl]carbamate, which was then treated with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for Intermediate 1A to afford intermediate 1C. The analytical data (NMR and LCMS) was consistent with that reported for the racemate (intermediate 1A).

Intermediate 1CA:

25 [0181]

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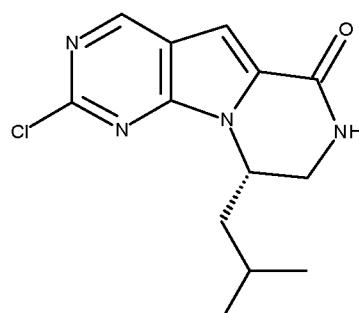
35

[0182] To a solution of Intermediate 1A (80 mg, 0.00030 mole) in DMF (3 mL) was added a 60% dispersion of sodium hydride in oil (40 mg). After stirring for 15 minutes, methyl iodide (37 μ L, 2eq) was added. The contents were stirred at room temperature for 30 minutes. Satd NaHCO₃ was then added followed by ethyl acetate. The organic layer was dried with magnesium sulfate and then concentrated under vacuum to afford intermediate 1AA. ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 0.74 (d, *J*=6.73 Hz, 3 H) 0.91 (d, *J*=6.73 Hz, 3 H) 2.04 - 2.20 (m, 1 H) 3.04 (s, 3 H) 3.69 (dd, *J*=13.76, 1.17 Hz, 1 H) 3.96 (dd, *J*=13.76, 4.68 Hz, 1 H) 4.58 (dd, *J*=7.32, 3.51 Hz, 1 H) 7.16 (s, 1 H) 9.05 (s, 1 H). LCMS (ESI) 279 (M + H).

Intermediate 1D

45 [0183]

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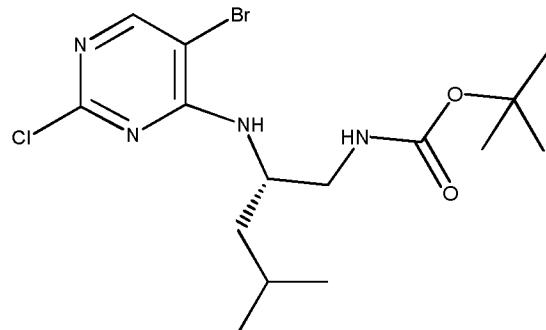


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tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-4-methyl-pentyl]carbamate

[0184]

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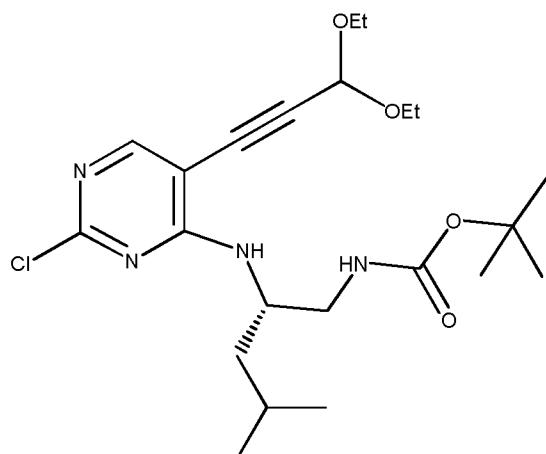
[0185] Intermediate G was hydrogenated with 10% Pd/C in ethanol under a blanket of hydrogen at 50 psi in a pressure bomb to afford *tert*-butyl N-[(2*S*)-2-amino-4-methylpentyl]carbamate which was then reacted with 5-bromo-2,4-dichloropyrimidine using analogous reaction conditions as described for *tert*-butyl N-[(2*S*)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate to afford *tert*-butyl N-[(2*S*)-2-[(5-bromo-2-chloropyrimidin-4-yl)amino]-4-methyl-pentyl]carbamate. ¹H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 0.91 (d, *J*=6.44 Hz, 3 H) 0.94 (d, *J*=6.44 Hz, 3 H) 1.32 - 1.51 (m, 11 H) 1.55 - 1.67 (m, 1 H) 3.28 (t, *J*=5.86 Hz, 2 H) 4.21 - 4.42 (m, 1 H) 4.84 (s, 1 H) 5.84 (d, *J*=7.32 Hz, 1 H) 8.07 (s, 1 H). LCMS (ESI) 407 (M + H).

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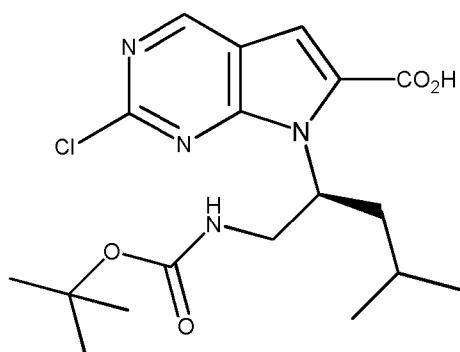
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[0186] To a solution of *tert*-butyl N-[(2*S*)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-4-methyl-pentyl]carbamate 5.0 g (12.3 mmole) in toluene (36 mL) and triethyl amine (7.2 mL) was added under nitrogen, 3,3-diethoxyprop-1-yne 2.8 mL (19.7 mmole), Pd₂(dba)₃ 1.1g (1.23 mmole), and triphenylarsine 3.8 g (12.3 mmole). The contents were heated to 70 degrees for 24 hrs. After cooling to room temperature, the reaction mixture was filtered through CELITETM and then concentrated under vacuum. The crude product was columned over silica gel using hexane/ethyl acetate (0- 30%) to afford (2*S*)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. LCMS (ESI) 455 (M + H).

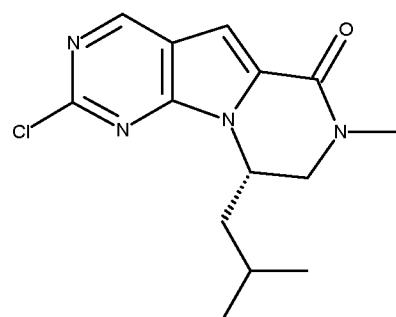


15 [0187] 7-[(1S)-1-[(tert-butoxycarbonyl)amino]methyl]-3-methylbutyl]-2-chloropyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(1-[(tert-butoxycarbonyl)amino]methyl)-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.88 (d, $J=6.44$ Hz, 3 H) 0.97 (d, $J=6.44$ Hz, 3 H) 1.47 (s, 9 H) 1.49 - 1.54 (m, 1 H) 1.56 (t, $J=7.17$ Hz, 2 H) 3.98 (dd, $J=13.91$, 3.07 Hz, 1 H) 3.76 (dd, $J=13.31$, 4.13 Hz, 1 H) 4.38 (d, $J=14.05$ Hz, 1 H) 4.90 (t, $J=7.17$ Hz, 1 H) 7.41 (s, 1 H) 9.11 (s, 1 H). LCMS (M + H) 397.

20 [0188] Intermediate 1D was synthesized using an analogous synthetic sequence as that described for intermediate 1A. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.82 (d, $J=6.73$ Hz, 3 H) 0.97 (d, $J=6.44$ Hz, 3 H) 1.34 - 1.46 (m, 1 H) 1.48 - 1.65 (m, 2 H) 3.40 (dd, $J=13.32$, 5.42 Hz, 1 H) 3.76 (dd, $J=13.47$, 4.10 Hz, 1 H) 4.76 - 4.92 (m, 1 H) 7.17 (s, 1 H) 8.34 (d, $J=5.27$ Hz, 1 H) 9.04 (s, 1 H). LCMS (ESI) 279 (M + H).

25 **Intermediate 1DA:**

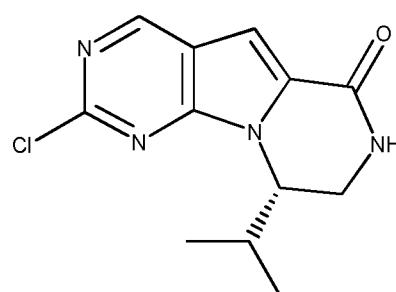
[0189]



[0190] Intermediate 1DA was synthesized in a manner similar to that described for 1CA. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.82 (d, $J=6.44$ Hz, 3 H) 0.97 (d, $J=6.44$ Hz, 3 H) 1.37 - 1.68 (m, 3 H) 3.04 (s, 3 H) 3.56 (d, $J=13.47$ Hz, 1 H) 4.00 (dd, $J=13.32$, 4.25 Hz, 1 H) 4.82 - 4.94 (m, 1 H) 7.16 (s, 1 H) 9.03 (s, 1 H). LCMS (ESI) 293 (M + H)

45 **Intermediate 1E:**

[0191]

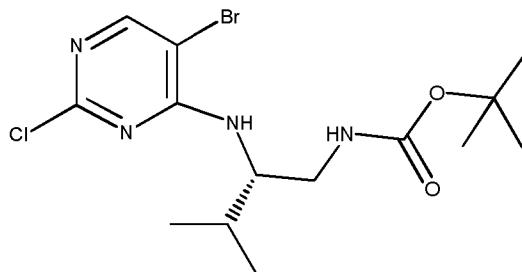


tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-pentyl]carbamate

[0192]

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15 [0193] Intermediate I was hydrogenated using 10% Pd/C under hydrogen at 50 psi in a pressure vessel to afford *tert*-butyl N-[(2*S*)-2-amino-3-methyl-pentyl]carbamate which was reacted with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for *tert*-butyl N-[(2*S*)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-pentyl]carbamate to afford *tert*-butyl N-[(2*S*)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-pentyl]carbamate. 1H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 0.88 - 0.95 (m, 6 H) 1.11 - 1.20 (m, 1 H) 1.34 (s, 9 H) 1.44 - 1.54 (m, 1 H) 1.64 - 1.72 (m, 1 H) 3.17 - 3.27 (m, 1 H) 3.33 - 3.43 (m, 1 H) 4.11 - 4.21 (m, 1 H) 4.81 (s, 1 H) 5.92 (d, *J*=8.20 Hz, 1 H) 8.05 (s, 1 H). LCMS (ESI) 407.

tert-butyl N-[(2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-3-methylpentyl]carbamate

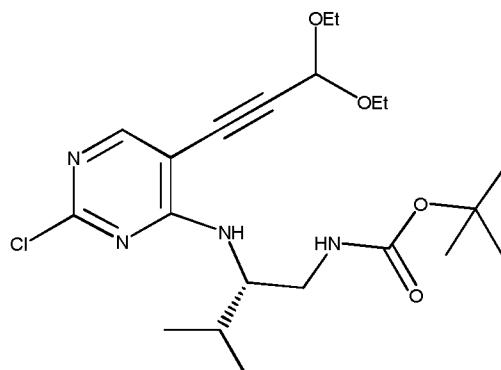
[0194]

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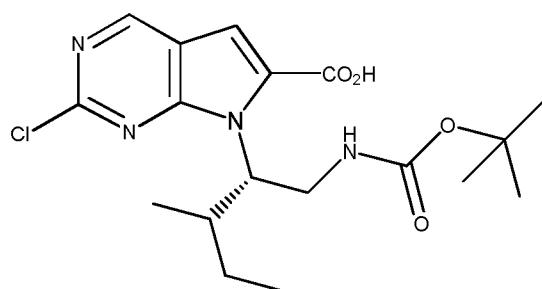
45 [0195] *tert*-butyl N-[(2*S*)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-3-methyl-pentyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2*S*)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 0.76 - 0.89 (m, 6 H) 1.03 (q, *J*=7.22 Hz, 3 H) 1.10 - 1.17 (m, 3 H) 1.25 - 1.42 (m, 11 H) 1.59 - 1.73 (m, 1 H) 3.35 - 3.47 (m, 4 H) 3.51 - 3.73 (m, 2 H) 3.99 - 4.11 (m, 1 H) 5.52 - 5.56 (m, 1 H) 6.76 - 7.03 (m, 2 H) 8.12 - 8.23 (m, 1 H). LCMS (ESI) 455 (M + H).

7-[(1*S*)-1-[(*tert*-butoxycarbonylamino)methyl]-2-methyl-butyl]-2-chloro-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic acid

[0196]

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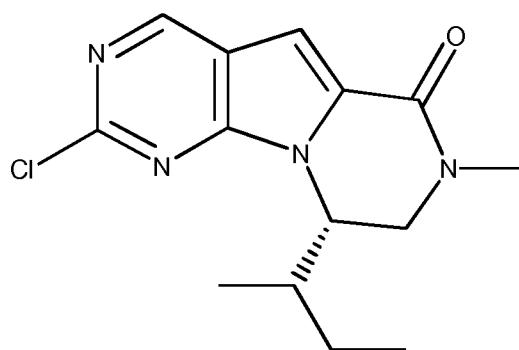
[0197] 7-[(1S)-1-[(tert-butoxycarbonyl)amino]methyl]-2-methyl-butyl]-2-chloropyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(1S)-1-[(tert-butoxycarbonyl)amino]methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.80 (t, $J=7.47$ Hz, 3 H) 0.86 (d, $J=7.03$ Hz, 3 H) 1.06 - 1.30 (m, 2 H) 1.48 (s, 9 H) 1.79 - 1.96 (m, 1 H) 3.95 (dd, $J=14.05, 3.22$ Hz, 1 H) 4.52 (d, $J=14.35$ Hz, 1 H) 4.61 - 4.73 (m, 1 H) 7.43 (s, 1 H) 9.13 (s, 1 H). LCMS (ESI) 397 ($M + H$).

[0198] Intermediate 1E was synthesized using an analogous synthetic sequence as that described for intermediate 1A. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.74 (t, $J=7.32$ Hz, 3 H) 0.89 (d, $J=6.73$ Hz, 3 H) 1.00 - 1.12 (m, 2 H) 1.82 - 1.94 (m, 1 H) 3.55 (dd, $J=13.91, 4.83$ Hz, 1 H) 3.70 (dd, $J=13.61, 4.25$ Hz, 1 H) 4.57 (dd, $J=7.91, 4.10$ Hz, 1 H) 7.17 (s, 1 H) 8.31 (d, $J=5.27$ Hz, 1 H) 9.05 (s, 1 H). LCMS (ESI) 279 ($M + H$).

Intermediate 1EA:

[0199]

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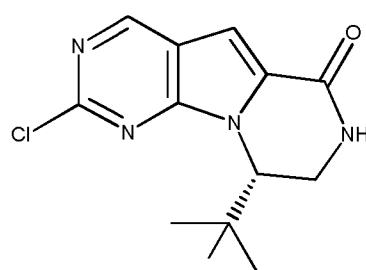


[0200] Intermediate 1EA was synthesized in a manner similar to Intermediate 1CA. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.77 (t, $J=7.47$ Hz, 3 H) 0.84 (d, $J=6.73$ Hz, 3 H) 1.07 - 1.16 (m, 2 H) 1.82 - 1.95 (m, 1 H) 3.03 (s, 3 H) 3.68 (d, $J=13.76$ Hz, 1 H) 3.96 (dd, $J=13.76, 4.39$ Hz, 1 H) 4.59 - 4.70 (m, 1 H) 7.16 (s, 1 H) 9.04 (s, 1 H). LCMS (ESI) 293 ($M + H$).

Intermediate 1F

[0201]

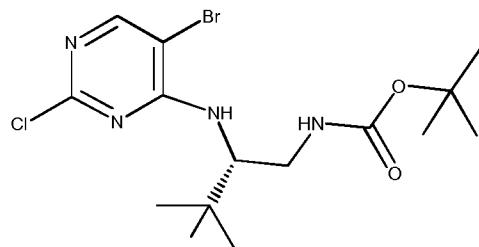
45



tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3,3-dimethyl-butyl] carbamate

[0202]

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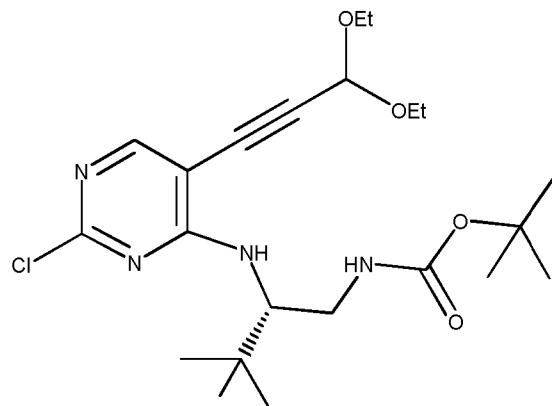
15 [0203] Intermediate J was hydrogenated using 10% Pd/C under hydrogen at 50 psi in a pressure vessel to afford *tert*-butyl N-[(2*S*)-2-amino-3,3-dimethyl-butyl]carbamate which was then reacted with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described using analogous reaction conditions as described for *tert*-butyl N-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate to afford *tert*-butyl N-[(2*S*)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3,3-dimethyl-butyl]carbamate. LCMS (ESI) 407 (M + H).

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tert-butyl N-[(2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-3,3-dimethyl-butyl] carbamate

[0204]

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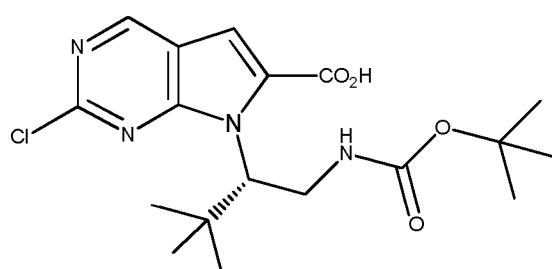
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40 [0205] *tert*-butyl N-[(2*S*)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-3,3-dimethyl-butyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2*S*)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. LCMS (ESI) 455 (M + H).

45

[0206]

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56 [0207] 7-[(1*S*)-1-[(tert-butoxycarbonylamino)methyl]-2,2-dimethyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-car-

boxylic acid was synthesized using analogous synthetic sequence as that described for 7-[1-[(*tert*-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 397 (M + H).

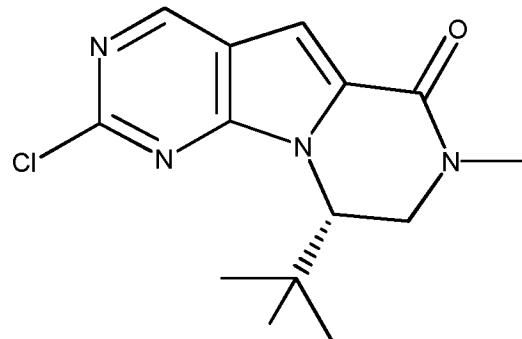
[0208] Intermediate 1F was synthesized using an analogous synthetic sequence as that described for intermediate 1A. LCMS (ESI) 279 (M + H).

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Intermediate 1FA

[0209]

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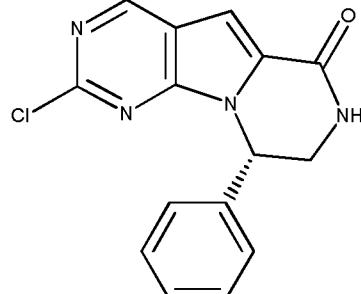
[0210] Intermediate 1FA was synthesized in a manner similar to that described for Intermediate 1CA. LCMS (ESI) 293 (M + H).

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Intermediate 1G

[0211]

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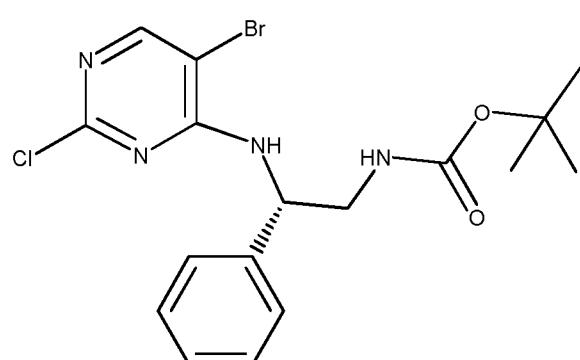
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tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-phenyl-ethyl] carbamate

45

[0212]

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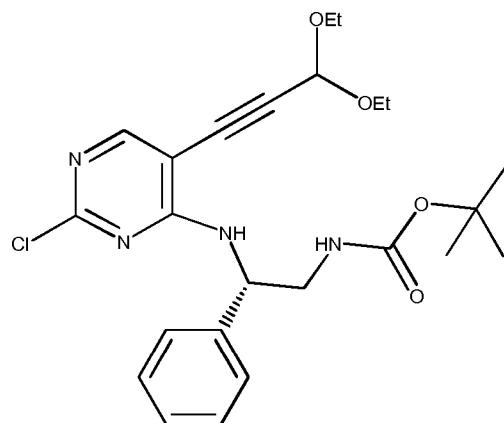
55

[0213] Intermediate J was hydrogenated using 10% Pd/C under hydrogen at 50 psi in a pressure vessel to afford

5 *tert*-butyl N-[(2*S*)-2-amino-2-phenyl-ethyl]carbamate which was then reacted with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described using analogous reaction conditions as described for *tert*-butyl N-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate to afford *tert*-butyl N-[(2*S*)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-phenyl-ethyl]carbamate. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.32 (s, 9 H) 3.29 - 3.50 (m, 2 H) 5.12 - 5.24 (m, 1 H) 7.10 (t, *J*=5.27 Hz, 1 H) 7.21 (t, *J*=6.88 Hz, 1 H) 7.26 - 7.34 (m, 4 H) 7.89 (d, *J*=7.32 Hz, 1 H) 8.24 (s, 1 H). LCMS (ESI) 427 (M + H).

tert-butyl N-[(2*S*)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-phenyl-ethyl]carbamate

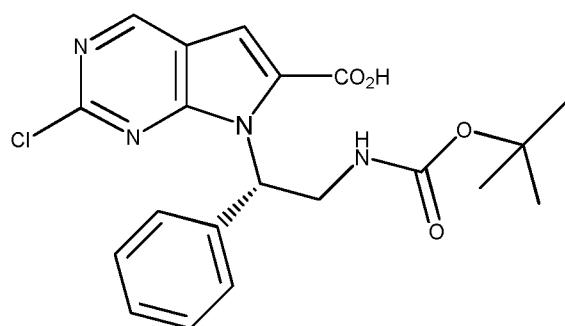
10 [0214]



30 [0215] *tert*-butyl N-[(2*S*)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-phenyl-ethyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2*S*)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.14 (t, *J*=7.03 Hz, 6 H) 1.32 (s, 9 H) 3.39 (s, 2 H) 3.52 - 3.61 (m, 2 H) 3.64 - 3.73 (m, 2 H) 5.17 - 5.26 (m, 1 H) 5.57 (s, 1 H) 7.07 - 7.14 (m, 1 H) 7.20 - 7.25 (m, 1 H) 7.26 - 7.33 (m, 4 H) 7.90 (d, *J*=7.61 Hz, 1 H) 8.19 (s, 1 H). LCMS (ESI) 475 (M + H).

7-[(1*S*)-2-(*tert*-butoxycarbonylamino)-1-phenyl-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid

35 [0216]



50 [0217] 7-[(1*S*)-2-(*tert*-butoxycarbonylamino)-1-phenyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(1-[(*tert*-butoxycarbonylamino)methyl]-2-methyl-propyl)-2-chloropyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 417 (M + H).

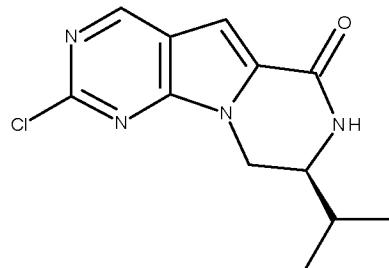
Intermediate 1G

55 [0218] Intermediate 1G was synthesized using an analogous synthetic sequence as that described for intermediate 1A. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 3.58 - 3.69 (m, 1 H) 4.13 (dd, *J*=13.47, 4.39 Hz, 1 H) 6.07 (d, *J*=3.81 Hz, 1 H) 6.85 (d, *J*=7.32 Hz, 2 H) 7.19-7.31 (m, 3 H) 7.34 (s, 1 H) 8.27 (d, *J*=5.27 Hz, 1 H) 9.13 (s, 1 H). LCMS (ESI) 299 (M + H).

Intermediate 1H

[0219]

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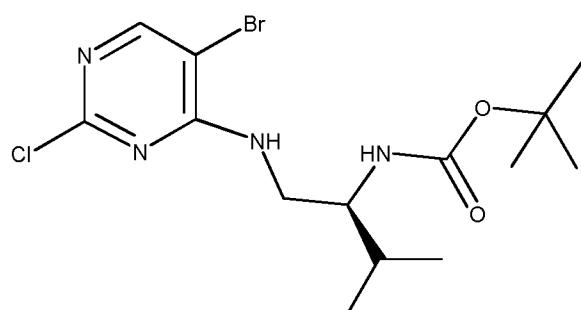


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15 tert-butyl N-[(1S)-1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]methyl]-2-methyl-propyl carbamate

[0220]

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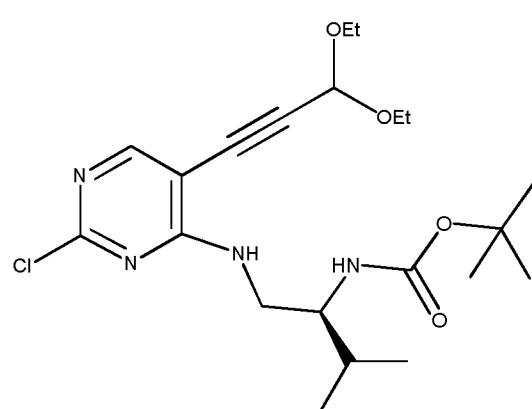
30 **[0221]** *tert-butyl N-[(1S)-1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]methyl]-2-methyl-propyl carbamate* was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate E using analogous reaction conditions as described for *tert-butyl N-[(1S)-1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]methyl]-2-methyl-propyl carbamate*. ¹H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 0.95 - 1.02 (m, 6 H) 1.35 - 1.45 (m, 9 H) 1.75 - 1.90 (m, 1 H) 3.35 - 3.48 (m, 1 H) 3.52 - 3.61 (m, 1 H) 3.64 - 3.76 (m, 1 H) 4.56 (d, *J*=8.49 Hz, 1 H) 6.47 (s, 1 H) 8.07 (s, 1 H). LCMS (ESI) 393 (M + H).
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36 tert-butyl N-[(1S)-1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]-2-methyl-propyl carbamate

[0222]

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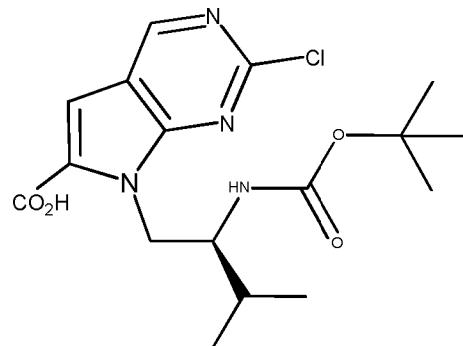
50

55 **[0223]** *tert-butyl N-[(1S)-1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]-2-methyl-propyl carbamate* was synthesized using similar experimental conditions to that used in the synthesis (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. ¹H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 0.90 - 1.00 (m, 6 H) 1.18 - 1.25 (m, 6 H) 1.34 - 1.36 (m, 9 H) 1.69 - 1.90 (m, 1 H) 3.34 - 3.82 (m, 6 H) 4.53 - 4.77 (m, 1 H) 5.45 - 5.55 (m, 1 H) 6.37 (dd, *J*=15.37, 6.59 Hz, 1 H) 6.56 (s, 1 H) 8.05 (s, 1 H). LCMS (ESI) 441 (M + H).
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7-[(2S)-2-(*tert*-butoxycarbonylamino)-3-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid

[0224]

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[0225] 7-[(2S)-2-(*tert*-butoxycarbonylamino)-3-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(2S)-2-(*tert*-butoxycarbonylamino)-3-methyl-butyl]-2-chloropyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 0.90 (d, *J*=6.73 Hz, 3 H) 0.96 (d, *J*=7.03 Hz, 3 H) 1.55 - 1.66 (m, 10 H) 4.14 (dd, *J*=13.61, 3.95 Hz, 1 H) 4.52 - 4.63 (m, 1 H) 4.84 (dd, *J*=13.61, 1.32 Hz, 1 H) 7.37 (s, 1 H) 8.95 (s, 1 H). LCMS (ESI) 383 (M + H).

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Intermediate H

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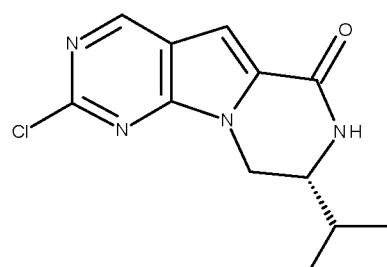
[0226] Intermediate 1H was synthesized using an analogous synthetic sequence as that described for intermediate 1A. LCMS (ESI) 265 (M + H).

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[0227]

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[0228] Intermediate 1I was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate F as starting materials, and following a similar sequence of synthetic steps as for intermediate 1H. The analytical data was consistent with that described for its antipode (intermediate 1H). ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 0.88 (d, *J*=6.44 Hz, 6 H) 1.73-1.86 (m, 1 H) 3.67 - 3.76 (m, 2 H) 4.11 - 4.21 (m, 1 H) 7.13 - 7.19 (m, 1 H) 8.56 (s, 1 H) 9.05 (s, 1 H). LCMS (ESI) 265 (M + H).

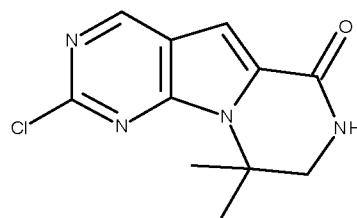
Intermediate 1J

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[0229]

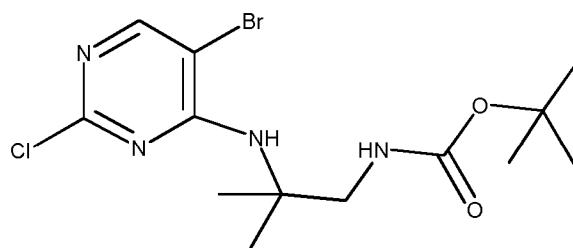
55

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10 tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-methyl-propyl]carbamate

[0230]

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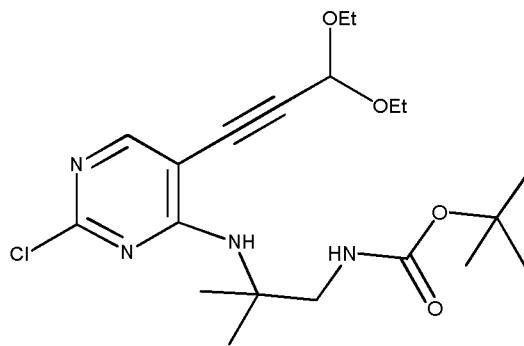
25 [0231] *tert*-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-methyl-propyl]carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and *tert*-butyl N-(2-amino-2-methyl-propyl)carbamate using analogous reaction conditions as described for *tert*-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate. LCMS (ESI) 379 (M + H).

tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methylpropyl]carbamate

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[0232]

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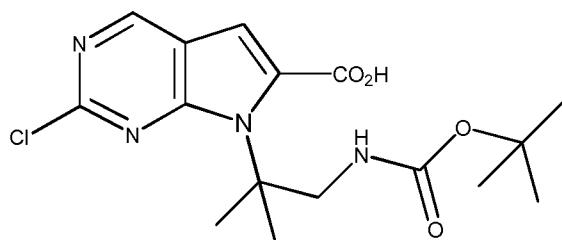
45 [0233] *tert*-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methyl-propyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2*S*)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methylpentane-1,2-diamine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.11 - 1.22 (m, 6 H) 1.31-1.45 (m, 15 H) 3.10 - 3.24 (m, 2 H) 3.51 - 3.76 (m, 4 H) 5.60 (s, 1 H) 6.94 (s, 1 H) 7.33 (t, *J*=6.44 Hz, 1 H) 8.18 (s, 1 H). LCMS (ESI) 427 (M + H).

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7-[2-(*tert*-butoxycarbonylamino)-1,1-dimethyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid

[0234]

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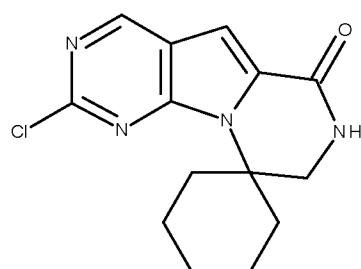
10 [0235] 7-[2-(*tert*-butoxycarbonylamino)-1,1-dimethyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid using analogous synthetic sequence as that described for 7-[1-[(*tert*-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.43 (s, 9H) 1.73 (s, 6H) 4.06 (s, 2H) 7.46 (s, 1H) 9.23 (s, 1H). LCMS (ESI) 369 ($M + H$).

15 Intermediate 1J

[0236] Intermediate 1J was synthesized using an analogous synthetic sequence as that described for intermediate 1A. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.73 (s, 6H) 3.50 (d, $J=2.93$ Hz, 2H) 7.25 (s, 1H) 8.46 - 8.55 (m, 1H) 9.07 (s, 1H). LCMS (ESI) 251 ($M + H$).

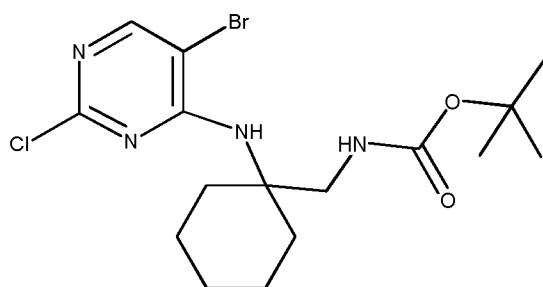
20 Intermediate 1K

[0237]



35 *tert*-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclohexyl]methyl]carbamate

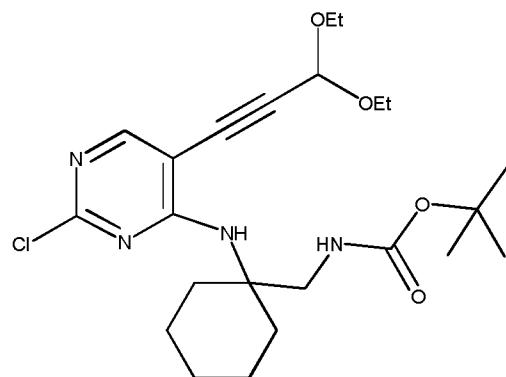
[0238]



50 [0239] *tert*-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclohexyl]methyl] carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate K using analogous reaction conditions as described for *tert*-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl] carbamate. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.18 - 1.54 (m, 17H) 2.23 (d, $J=14.35$ Hz, 2H) 3.36 (d, $J=6.44$ Hz, 2H) 5.82 (s, 1H) 6.93 (s, 1H) 8.22 (s, 1H). LCMS (ESI) 419 ($M + H$).

55 *tert*-butyl N-[[1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclohexyl]methyl]carbamate

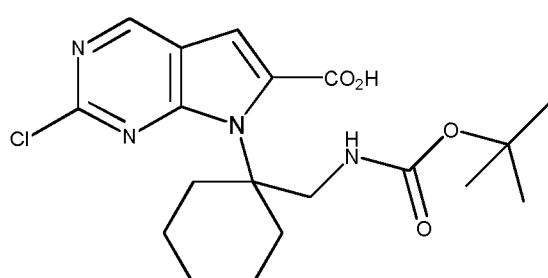
[0240]



15 **[0241]** *tert*-butyl N-[(1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclohexyl)methyl] carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2*S*)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.08 - 1.16 (m, 6 H) 1.17 - 1.54 (m, 17 H) 2.13 (br. s., 2 H) 3.36 (d, *J*=6.73 Hz, 2 H) 3.50-3.69 (m, 4 H) 5.72 (s, 1 H) 6.94 (s, 1 H) 5.72 (br. s., 1H) 8.17 (s, 1 H). LCMS (ESI) 467 (M + H).

20 7-[(tert-butoxycarbonylamino)methyl]cyclohexyl-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid

25 **[0242]**



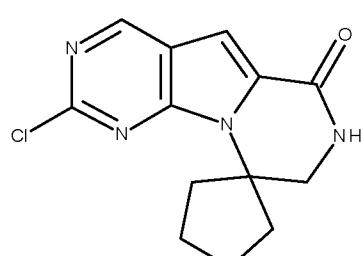
35 **[0243]** 7-[(tert-butoxycarbonylamino)methyl]cyclohexyl-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl-2-chloropyrrolo[2,3-d]pyrimidine-6-carboxylic acid. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.37-1.54 (m, 13 H) 1.75 (br. s., 4 H) 2.74 (br. s., 2 H) 3.78 - 3.84 (m, 2 H) 7.44 - 7.51 (m, 1 H) 8.23 (s, 1 H) 9.11 (s, 1 H). LCMS (ESI) 409 (M + H).

40 Intermediate K

[0244] Intermediate 1K was synthesized using an analogous synthetic sequence as that described for intermediate 1A. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.28 (br. s., 2 H) 1.42 (br. s., 2 H) 1.70 (br. s., 4 H) 1.85 - 1.95 (m, 2 H) 2.69 (m, 2 H) 7.16 - 7.25 (m, 1 H) 8.41 (br. s., 1 H) 9.04 (s, 1 H). LCMS 291 (M + H).

45 Intermediate 1L

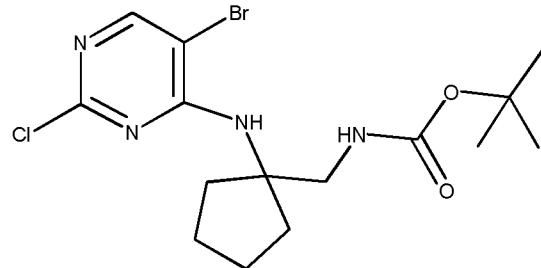
50 **[0245]**



tert-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]methyl]carbamate

[0246]

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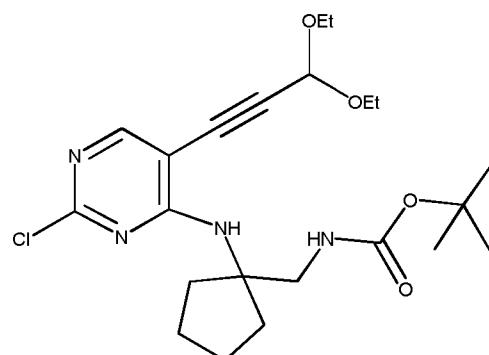
15 [0247] *tert*-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]methyl] carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate L using analogous reaction conditions as described for *tert*-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]3-methyl-butyl]carbamate. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.34 (s, 9 H) 1.50 - 1.58 (m, 2 H) 1.63 - 1.78 (m, 4 H) 1.96 - 2.06 (m, 2 H) 3.25 (d, *J*=6.15 Hz, 2 H) 6.71 (s, 1 H) 7.18 (t, *J*=6.29 Hz, 1 H) 8.20 (s, 1 H). LCMS (ESI) 405 (M + H).

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tert-butyl N-[[1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclopentyl] methyl]carbamate

[0248]

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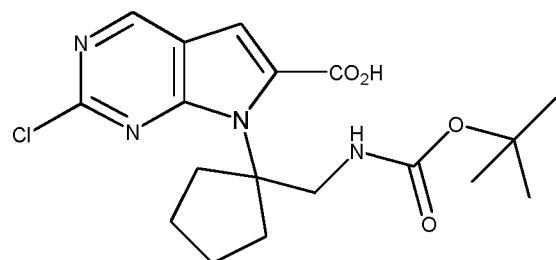
35

40 [0249] *tert*-butyl N-[[1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclopentyl]methyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2*S*)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. LCMS (ESI) 453 (M + H).

7-[1-[(*tert*-butoxycarbonylamino)methyl]cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid

[0250]

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[0251] 7-[1-[(*tert*-butoxycarbonylamino)methyl]cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[1-[(*tert*-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloropyrrolo[2,3-d]pyrimidine-6-carboxylic acid. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.47 (s, 9 H) 1.74 (br.

s., 2 H) 1.88 (br. s., 2 H) 2.04 (br. s., 2 H) 2.41 - 2.45 (m, 2 H) 4.06 (s, 2 H) 7.45 (s, 1 H) 9.11 (s, 1 H). LCMS (ESI) 395 (M + H).

Intermediate 1L

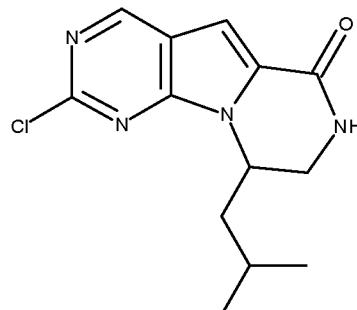
5 [0252] Intermediate 1L was synthesized using an analogous synthetic sequence as that described for intermediate 1A. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.72 (br. s., 2 H) 1.86 - 1.93 (m, 2 H) 1.99 (d, *J*=3.81 Hz, 2 H) 2.40 (br. s., 2 H) 3.48 (d, *J*=2.34 Hz, 2 H) 7.22 (s, 1 H) 8.53 (br. s., 1 H) 9.05 (s, 1 H). LCMS (ESI) 277 (M + H).

Intermediate 1M

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[0253]

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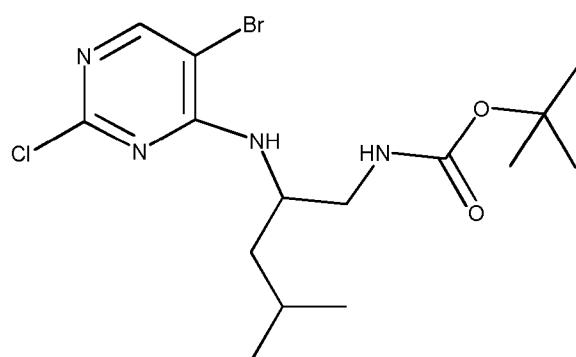


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25 tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-4-methyl-pentyl]carbamate

[0254]

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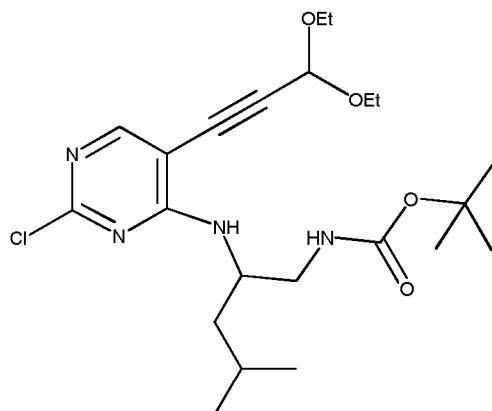
[0255] *tert*-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-4-methylpentyl]carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate B using analogous reaction conditions as described for *tert*-butyl N-[2-[(5-bromo-2-chloropyrimidin-4-yl)amino]-3-methyl-butyl]carbamate. The analytical data is consistent with that described for the L-enantiomer.

tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-4-methyl-pentyl]carbamate

[0256]

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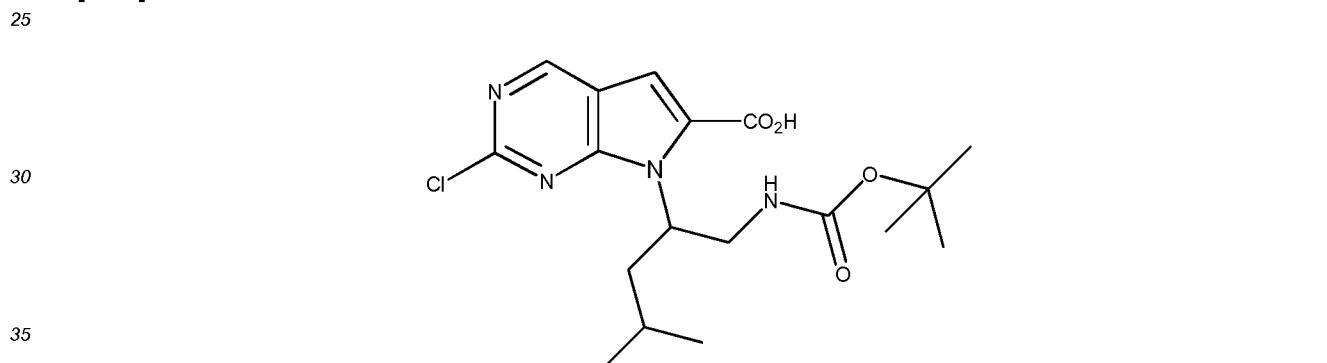
55



[0257] *tert*-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-4-methyl-pentyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of *tert*-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate. 1H NMR (600 MHz, CHLOROFORM-*d*) δ ppm 1.21 - 1.31 (m, 12 H) 1.38 - 1.46 (m, 11 H) 1.70 (m, 1H) 3.24 (m, 2 H) 3.65 - 3.82 (m, 4 H) 4.86 (br s., 1H), 5.65 (s, 1 H) 5.85 (br s., 1H) 6.94 (s, 1 H) 8.21 (s, 1 H). LCMS (ESI) 455 (M + H).

7-[1-[(*tert*-butoxycarbonylamino)methyl]-3-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid

[0258]



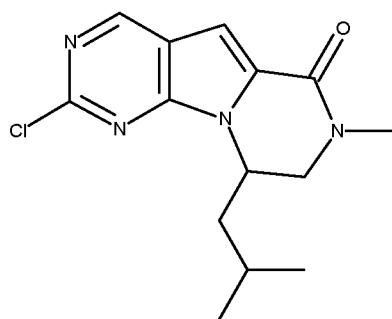
[0259] 7-[(*tert*-butoxycarbonylamino)methyl]-3-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(*tert*-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloropyrrolo[2,3-d]pyrimidine-6-carboxylic acid. The analytical data was consistent with that described for the L-isomer.

Intermediate 1M

[0260] Intermediate 1M was synthesized using an analogous synthetic sequence as that described for intermediate 1A. The analytical data was consistent with that described for the L-isomer.

Intermediate 1MA

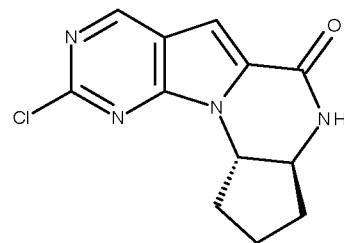
[0261]



15 [0262] To a solution of Intermediate 1M (100 mg, 0.00024 mole) in DMF (3.0 mL) was added sodium hydride (60 % dispersion in oil), (27.6 mg, 3 eq). After stirring for 15 mins, methyl iodide (30, 2 eq) was added. The contents were stirred at room temperature for 30 mins. After the addition of sat NaHCO₃, ethyl acetate was added. Separation of the organic layer followed by drying with magnesium sulfate and concentration under vacuum afforded the intermediate 1MA. Analytical data was similar to the Intermediate 1DA.

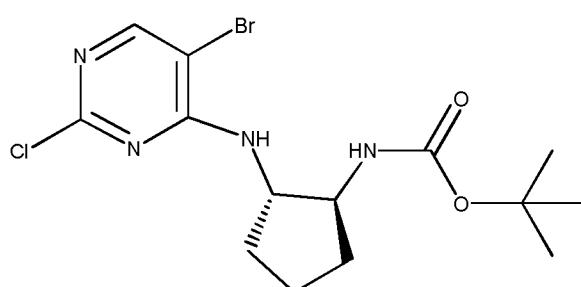
20 **Intermediate 1N**

[0263]



tert-butyl N-[(1S,2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]carbamate

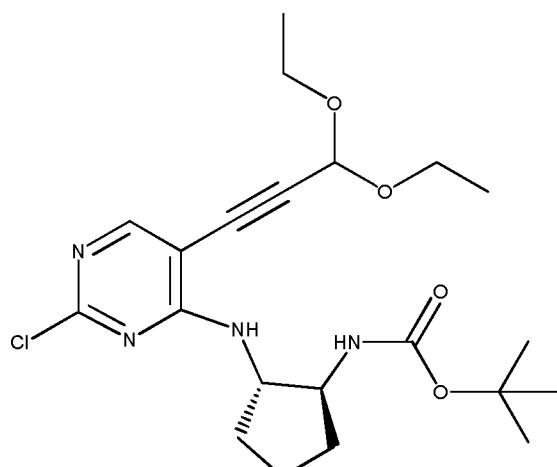
35 [0264]



50 [0265] *tert-butyl N-[(1S,2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]carbamate* was synthesized by treating *tert-butyl N-[(1S,2S)-2-aminocyclopentyl]carbamate* with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for *tert-butyl N-[(1S,2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]carbamate*. 1H NMR (600 MHz, DMSO-d₆) δ ppm 1.27 (s, 9 H) 1.42 - 1.54 (m, 2 H) 1.56 - 1.65 (m, 2 H) 1.80 - 1.88 (m, 1 H) 1.96 - 2.01 (m, 1 H) 3.88 - 3.96 (m, 1 H) 4.03 - 4.09 (m, 1 H) 6.91 (d, J=8.20 Hz, 1 H) 7.41 (d, J=7.32 Hz, 1 H) 8.18 (s, 1 H). LCMS (ESI) 391 (M + H).

55 tert-butyl N-[(1S,2S)-2-[(2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl)amino]cyclopentyl]carbamate

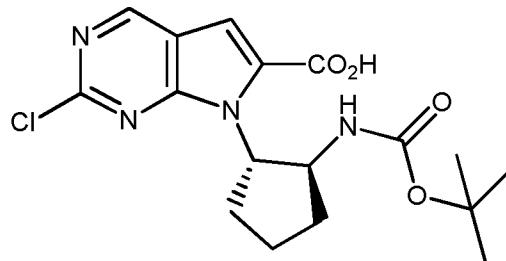
[0266]



[0267] *tert*-butylN-[(1*S*,2*S*)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclopentyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2*S*)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.13 (t, 6 H) 1.28 (s, 9 H) 1.42 - 1.52 (m, 2 H) 1.58 - 1.65 (m, 2 H) 1.81 - 1.90 (m, 1 H) 1.99 - 2.08 (m, 1 H) 3.49 - 3.60 (m, 2 H) 3.63 - 3.71 (m, 2 H) 3.84 - 3.93 (m, 1 H) 3.96 - 4.04 (m, 1 H) 5.53 (s, 1 H) 6.96 (d, *J*=7.90 Hz, 1 H) 7.34 (d, *J*=7.03 Hz, 1 H) 8.14 (s, 1 H). LCMS (ESI) 439 (M + H).

25 7-[(1*S*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid

[0268]



[0269] 7-[(1*S*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(1*S*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.41 - 1.52 (m, 9 H) 1.55 - 1.68 (m, 1 H) 1.88 - 2.00 (m, 2 H) 2.05 - 2.15 (m, 1 H) 2.26 - 2.35 (m, 1 H) 2.71 - 2.89 (m, 1 H) 4.01 - 4.16 (m, 1 H) 4.28 - 4.45 (m, 1 H) 7.41 (s, 1 H) 9.11 (s, 1 H). LCMS (ESI) 381 (M + H).

45 Intermediate 1N

[0270] Intermediate 1N was synthesized using an analogous synthetic sequence as that described for intermediate 1A. 1H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.48 - 1.60 (m, 1 H) 1.88 - 1.98 (m, 3 H) 1.99 - 2.08 (m, 1 H) 2.66 - 2.75 (m, 1 H) 3.63 - 3.74 (m, 1 H) 3.99 - 4.12 (m, 1 H) 7.21 (s, 1 H) 8.89 (s, 1 H) 9.04 (s, 1 H). LCMS (ESI) 263 (M + H).

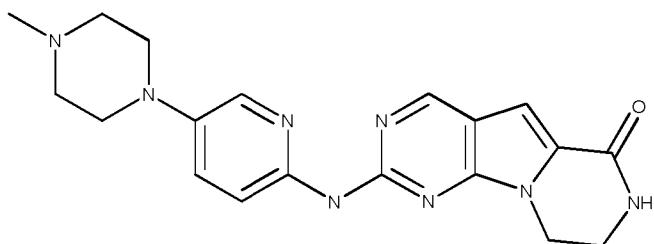
50

Example 3 - Example Compounds

Compound 1

55 **[0271]**

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10 [0272] To 0.050 g (0.225 mmole) chloro tricyclilactam in dioxane (2.0 mL) under nitrogen was added 5-(4-methylpiperazin-1-yl)pyridin-2-amine 0.052 g (1.2 eq, 0.270 mmole) followed by the addition of $Pd_2(dba)_3$ (18.5 mg), BINAP (25 mg) and sodium-*tert*-butoxide (31 mg, 0.324 mmole). The contents of the flask are degassed for 10 minutes and then heated to 100 degrees for 12 hours. The crude reaction was loaded on a silica gel column and eluted with DCM/MeOH (0- 15%) to afford the desired product (26 mg). To this compound dissolved in DCM/MeOH (10%) was added 3N HCl in iso-propanol (2 eq) and stirred overnight. Concentration under vacuum afforded the hydrochloride salt. 1H NMR (d6-DMSO) 11.13 (brs, 1H), 9.07 (s, 1H), 8.42 (s, 1H), 8.03 (br m 1H), 7.99 (s, 1H), 7.67 (brm, 1H), 7.18 (s, 1H), 4.33 (m, 2H), 3.79 (m, 2H), 3.64 (m, 2H), 3.50 (m, 2H), 3.16 (m, 4H), 2.79 (s, 3H). LCMS (ESI) 379 (M + H)

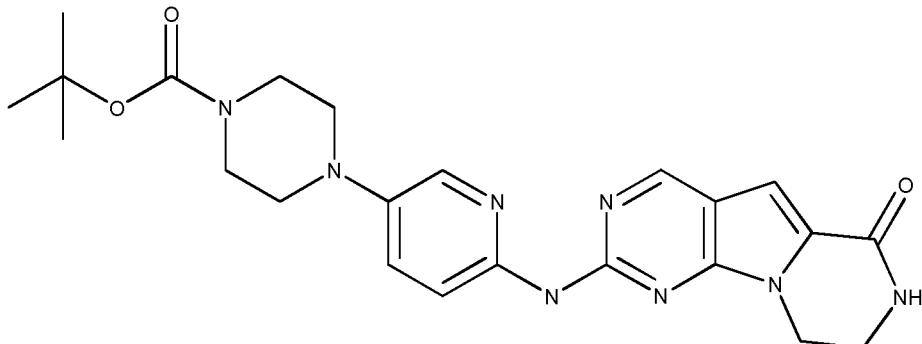
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Compound 2

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[0273]

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[0274] To chloro tricyclilactam 0.075 g (0.338 mmole) in dioxane 3.5 mL under nitrogen was added *tert*-butyl 4-(6-amino-3-pyridyl)piperazine-1-carboxylate 0.098 g (1.05 eq) followed by the addition of $Pd_2(dba)_3$ (27 mg) and BINAP (36 mg) and sodium-*tert*-butoxide (45 mg). The contents were refluxed for 11 hrs. The crude reaction was loaded on a silica gel column and eluted with DCM/MeOH (0- 10 %) to afford the desired product (32 mg). 1H NMR (d6-DMSO) 9.48 (s, 1H), 8.84 (s, 1H), 8.29 (s, 1H), 8.18 (s, 1H), 7.99 (s, 1H), 7.42 (m, 1H), 6.98 (s, 1H), 4.23 (m, 2H), 3.59 (m, 2H), 3.45 (m, 4H), 3.50 (m, 2H), 3.05 (m, 4H). LCMS (ESI) 465 (M + H)

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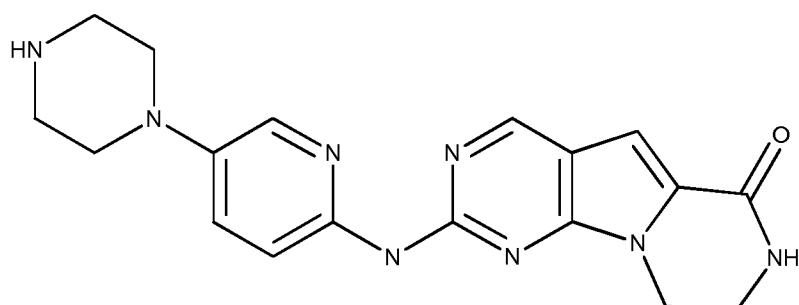
Compound 3

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[0275]

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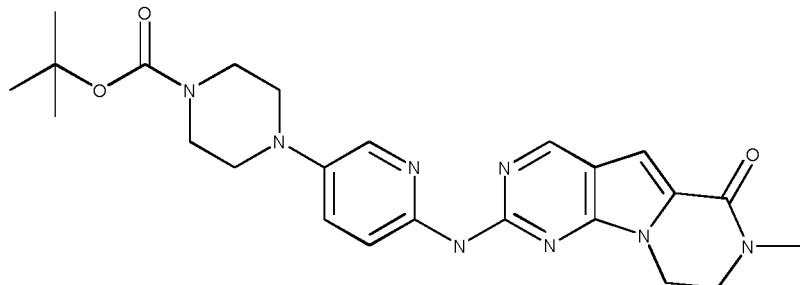


[0276] To a solution of Compound 2 (23 mg) in 10% DCM/MeOH was added 10 mL of a 3M solution of HCl in iso-

propanol. The contents were stirred overnight for 16 hrs. Concentration of the reaction mixture afforded the hydrochloride salt. ^1H NMR (d6-DMSO) 9.01 (s, 1H), 7.94 (m, 1H), 7.86 (m, 1H), 7.23 (s, 1H), 4.30 (m, 2H), 3.64 (m, 2H), 3.36 (m, 4H), 3.25 (m, 4H). LCMS (ESI) 465 (M + H)

5 **Compound 4**

[0277]

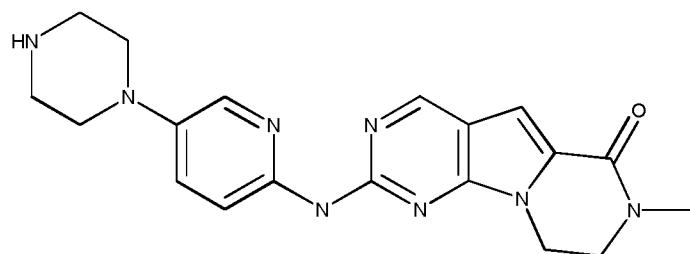


20 **[0278]** To chloro-N-methyltricyclic amide 0.080 g (0.338 mmole) in dioxane 3.5 mL under nitrogen was added *tert*-butyl 4-(6-amino-3-pyridyl)piperazine-1-carboxylate 0.102 g (1.1 eq) followed by the addition of $\text{Pd}_2(\text{dba})_3$ (27 mg), BINAP (36 mg) and sodium- *tert*-butoxide (45 mg). The contents were refluxed for 11 hrs. The crude product was purified using column chromatography with an eluent of dichloromethane/methanol (0- 5%) to afford the desired product (44 mg). ^1H NMR (d6-DMSO) 9.49 (s, 1H), 8.85 (s, 1H), 8.32 (m, 1H), 8.02 (s, 1H), 7.44 (m, 1H), 7.00 (s, 1H), 4.33 (m, 2H), 3.80 (m, 2H), 3.48 (m, 4H), 3.07 (m, 4H), 3.05 (s, 3H), 1.42 (s, 9H). LCMS (ESI) 479 (M + H)

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Compound 5

[0279]



40 **[0280]** To 32 mg of Compound 4 was added 10 mL 3N HCl in isopropanol and the contents stirred at room temperature overnight for 16 hrs. Concentration afforded the hydrochloride salt. ^1H NMR (d6-DMSO) 9.13 (m, 2H), 8.11 (m, 1H), 8.10 (s, 1H), 7.62 (m, 1H), 7.21 (s, 1H), 4.43 (m, 2H), 3.85 (m, 2H), 3.41 (m, 4H), 3.28 (m, 4H), 3.08 (s, 3H). LCMS (ESI) 379 (M + H)

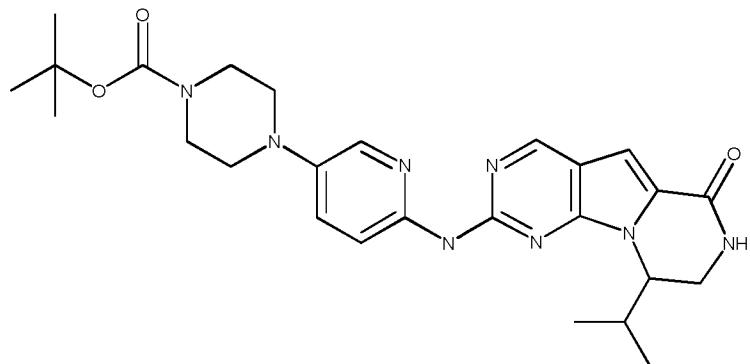
45

Compound 6

[0281]

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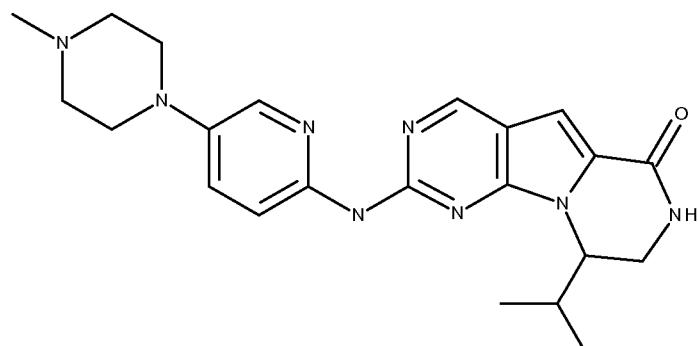
55



15 Compound 6 was synthesized using similar experimental conditions to that described for compound 2. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.79 (d, $J=7.03$ Hz, 3 H) 1.01 (d, $J=6.73$ Hz, 3 H) 1.35 - 1.48 (m, 9 H) 2.16 (dd, $J=14.64, 6.73$ Hz, 1 H) 3.00 - 3.14 (m, 4 H) 3.40 - 3.51 (m, 4 H) 3.51 - 3.60 (m, 1 H) 3.63 - 3.74 (m, 1 H) 4.44 (dd, $J=7.90, 3.81$ Hz, 1 H) 6.99 (s, 1 H) 7.46 (dd, $J=8.93, 2.78$ Hz, 1 H) 7.94 - 8.09 (m, 2 H) 8.31 (dd, $J=9.08, 1.46$ Hz, 1 H) 8.85 (s, 1 H) 9.46 (s, 1 H). LCMS (ESI) 507 ($M + H$).

20 **Compound 7**

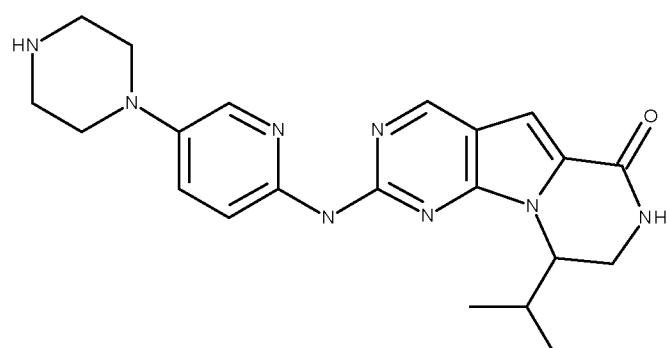
[0282]



40 **[0283]** Compound 7 was synthesized using similar experimental conditions to that described for compound 1 and was recovered as an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.77 - 0.86 (m, 3 H) 0.96 (d, $J=7.03$ Hz, 3 H) 2.10 - 2.24 (m, 1 H) 3.07 (s, 3 H) 3.37 - 3.79 (m, 8 H) 4.00 (dd, $J=13.61, 4.54$ Hz, 2 H) 4.63 - 4.73 (m, 1 H) 7.20 (s, 1 H) 7.58 - 7.71 (m, 1 H) 7.99 (d, $J=2.34$ Hz, 1 H) 8.12 (d, $J=9.37$ Hz, 1 H) 9.11 (s, 1 H) 9.41 (br. s., 2 H) 11.76 (br. s., 1 H). LCMS (ESI) 421 ($M + H$).

Compound 8

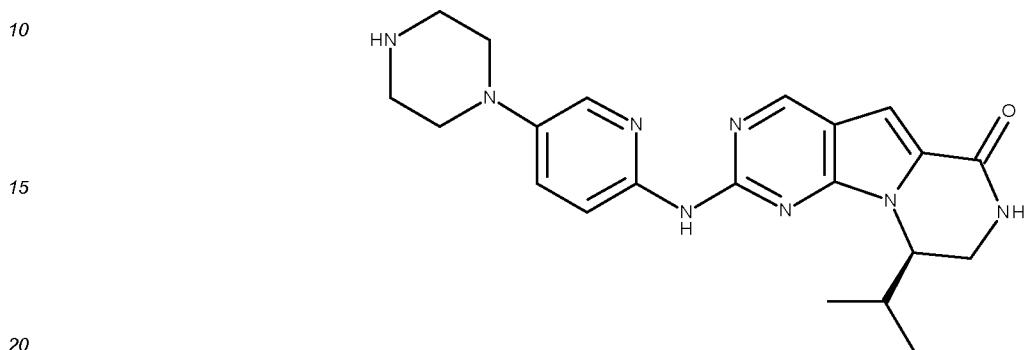
45 **[0284]**



[0285] Compound 8 was synthesized using similar experimental conditions to that described for compounds 2 and 3 and was recovered as an HCl salt. The characterization data (NMR and LCMS) was consistent with that reported for compound 9.

5 **Compound 9**

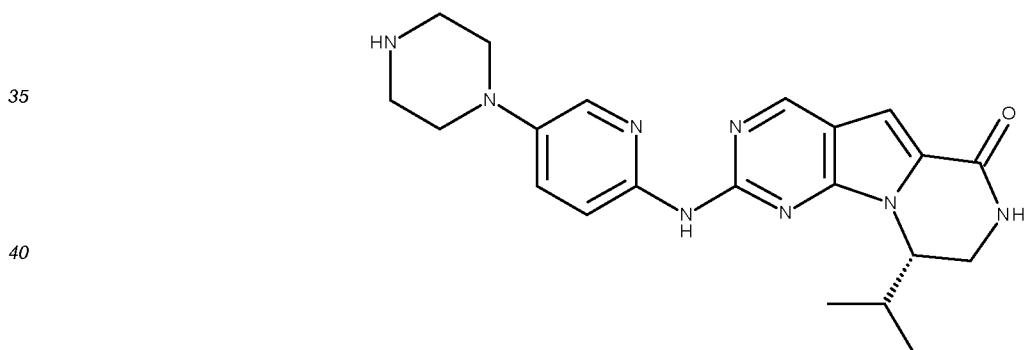
[0286]



[0287] Compound 9 was synthesized using similar experimental conditions to that described for compounds 2 and 3 and was recovered as an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.79 (d, $J=6.73$ Hz, 3 H) 1.01 (d, $J=6.73$ Hz, 3 H) 2.18 (dd, $J=14.49, 7.17$ Hz, 1 H) 3.18 - 3.84 (m, 10 H) 4.53 - 4.71 (m, 1 H) 7.24 (s, 1 H) 7.65 (d, $J=9.37$ Hz, 1 H) 8.01 (d, $J=2.64$ Hz, 1 H) 8.14 (d, $J=1.46$ Hz, 1 H) 8.35 (d, $J=5.27$ Hz, 1 H) 9.14 (s, 1 H) 9.46 (s, 2 H) 11.80 (s, 1 H) LCMS (ESI) 407 (M+H).
25

30 **Compound 10**

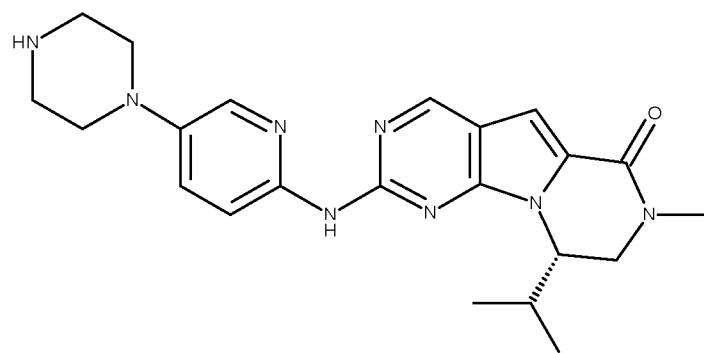
[0288]



45 [0289] Compound 10 was synthesized using similar experimental conditions to that described for compounds 2 and 3 and was recovered as an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.77 (d, $J=7.03$ Hz, 3 H) 0.99 (d, $J=6.73$ Hz, 3 H) 2.10 - 2.24 (m, 1 H) 3.18 - 3.81 (m, 10 H) 4.54 - 4.69 (m, 1 H) 7.22 (s, 1 H) 7.63 (d, $J=9.08$ Hz, 1 H) 7.99 (d, $J=2.63$ Hz, 1 H) 8.11 (s, 1 H) 8.33 (d, $J=5.27$ Hz, 1 H) 9.12 (s, 1 H) 9.43 (s, 2 H) 11.77 (s, 1 H). LCMS (ESI) 407 (M+H).
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Compound 11

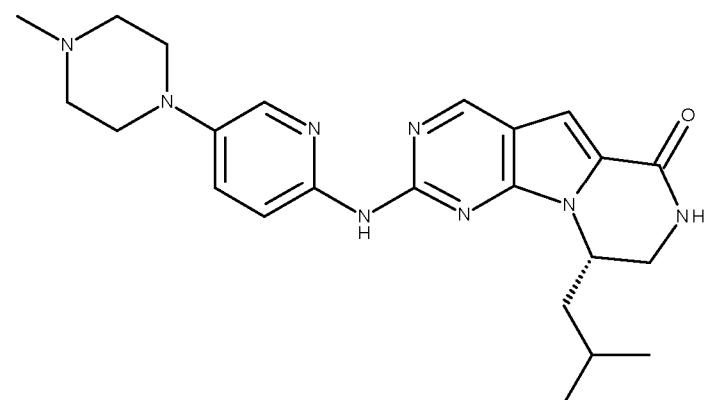
[0290]



15 [0291] Compound 11 was synthesized using similar experimental conditions to that described for compounds 2 and 3 and was recovered as an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.84 (d, $J=6.73$ Hz, 3 H) 0.98 (d, $J=6.73$ Hz, 3 H) 2.12 - 2.26 (m, 1 H) 3.09 (s, 3 H) 3.22 - 3.81 (m, 8 H) 4.01 (dd, $J=13.61, 4.25$ Hz, 2 H) 4.59 - 4.72 (m, 1 H) 7.19 (s, 1 H) 7.74 (s, 1 H) 7.96 - 8.10 (m, 2 H) 9.08 (s, 1 H) 9.22 (s, 2 H). LCMS (ESI) 421 ($M+\text{H}$).

20 **Compound 12**

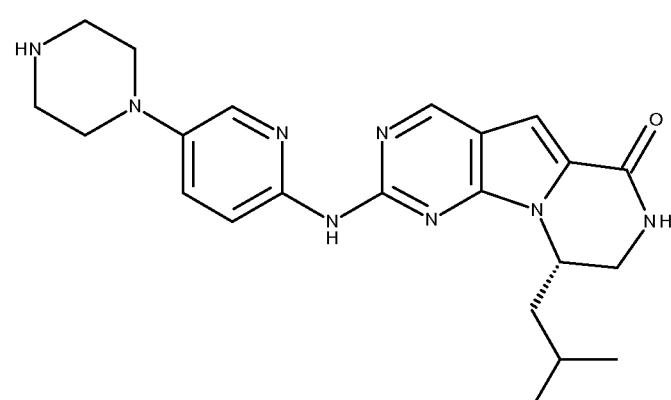
20 [0292]



40 [0293] Compound 12 was synthesized using similar experimental conditions to that described for compound 1 and was recovered as an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.85 (d, $J=4.98$ Hz, 3 H) 0.95 (d, $J=4.98$ Hz, 3 H) 1.42 - 1.70 (m, 3 H) 2.77 (d, $J=2.93$ Hz, 3 H) 3.07 - 4.14 (m, 10 H) 4.95 (s, 1 H) 7.20 (s, 1 H) 7.66 (d, $J=9.66$ Hz, 1 H) 7.94 (s, 1 H) 8.08 - 8.16 (m, 1 H) 8.33 (d, $J=4.68$ Hz, 1 H) 9.09 (s, 1 H) 11.38 (s, 1 H) 11.71 (s, 1 H). LCMS (ESI) 435 ($M+\text{H}$).

45 **Compound 13**

45 [0294]



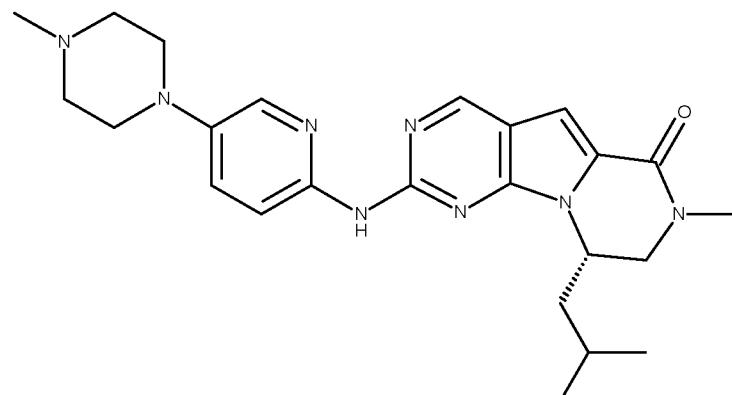
[0295] Compound 13 was synthesized using similar experimental conditions to that described for compounds 2 and 3 and was recovered as an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.87 (d, $J=6.15$ Hz, 3 H) 0.94 (d, $J=6.15$ Hz, 3 H) 1.57 (d, $J=84.61$ Hz, 3 H) 3.05 (s, 3 H) 3.13 - 3.55 (m, 8 H) 3.69 (d, $J=78.17$ Hz, 2 H) 4.90 (s, 1 H) 7.15 (s, 1 H) 7.63 - 7.85 (m, 1 H) 7.93 (s, 1 H) 8.26 (s, 1 H) 9.03 (s, 1 H) 9.20 (s, 2 H). LCMS (ESI) 421 (M+H).

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Compound 14

[0296]

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[0297] Compound 14 was synthesized using similar experimental conditions to that described for compound 1 and was recovered as an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.85 (d, $J=6.44$ Hz, 3 H) 0.95 (d, $J=6.44$ Hz, 3 H) 1.43 - 1.70 (m, 3 H) 2.78 (d, $J=2.93$ Hz, 3 H) 3.05 (s, 3 H) 3.24 - 3.84 (m, 8 H) 4.01 (d, $J=9.66$ Hz, 2 H) 4.89 - 5.01 (m, 1 H) 7.15 (s, 1 H) 7.77 (s, 1 H) 7.91 - 8.05 (m, 2 H) 9.03 (s, 1 H) 10.96 - 11.55 (m, 2 H). LCMS (ESI) 449 (M+H).

25

Compound 15

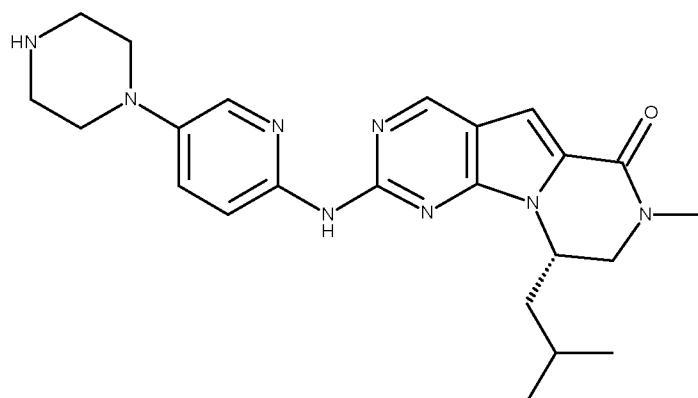
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[0298]

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[0299] Compound 15 was synthesized using similar experimental conditions to that described for compounds 2 and 3 and was recovered as an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.83 - 0.88 (d, $J=6.15$ Hz, 3 H) 0.95 (d, $J=6.15$ Hz, 3 H) 1.40 - 1.71 (m, 3 H) 3.28 - 3.83 (m, 8 H) 4.00 (d, $J=3.22$ Hz, 2 H) 4.91 - 5.08 (m, 1 H) 7.17 (s, 1 H) 7.68 (d, $J=9.66$ Hz, 1 H) 7.93 (s, 1 H) 8.07 (s, 1 H) 9.06 (s, 1 H) 9.40 (s, 2 H) 11.59 (s, 1 H). LCMS (ESI) 435 (M+H).

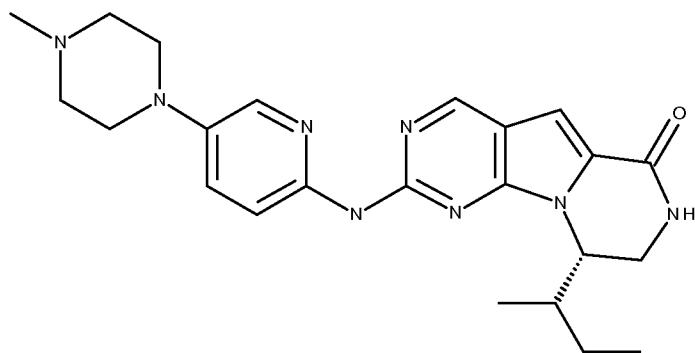
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Compound 16

[0300]

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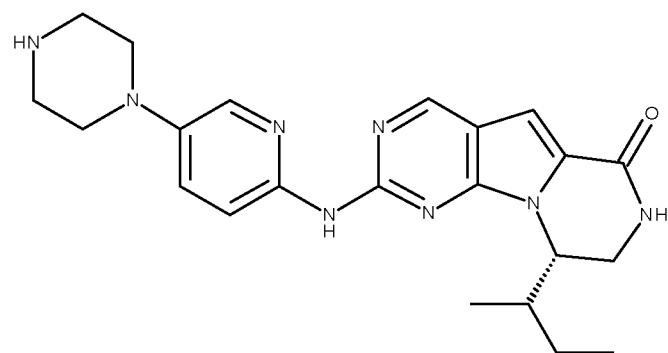
[0301] To intermediate IE 0.060 g (0.205 mmole) was added 5-(4-methylpiperazin-1-yl)pyridin-2-amine 35.42 mg (0.9 eq) followed by the addition of 1,4-dioxane (3 mL). After degassing with nitrogen, Pd_2dba_3 (12 mg), BINAP (16 mg) and sodium *tert*-butoxide (24 mg) were added. The contents were then heated at 90 degrees in a CEM Discovery microwave for 3 hrs. The reaction is then loaded over a silica gel column and purified by eluting with DCM/MeOH (0- 15%) to afford compound 16. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.75 (t, $J=7.47$ Hz, 3 H) 0.91 (d, $J=6.73$ Hz, 3 H) 1.04 - 1.20 (m, 2 H) 1.80 - 1.98 (m, 1 H) 2.77 (d, $J=3.81$ Hz, 3 H) 2.94 - 3.90 (m, 10 H) 4.54 - 4.68 (m, 1 H) 7.06 - 7.23 (m, 2 H) 7.56 - 7.75 (m, 1 H) 7.90 - 8.12 (m, 2 H) 8.29 (s, 1 H) 9.07 (s, 1 H) 10.98 - 11.74 (m, 2 H). LCMS (ESI) 435 ($\text{M} + \text{H}$).

Compound 17

[0302]

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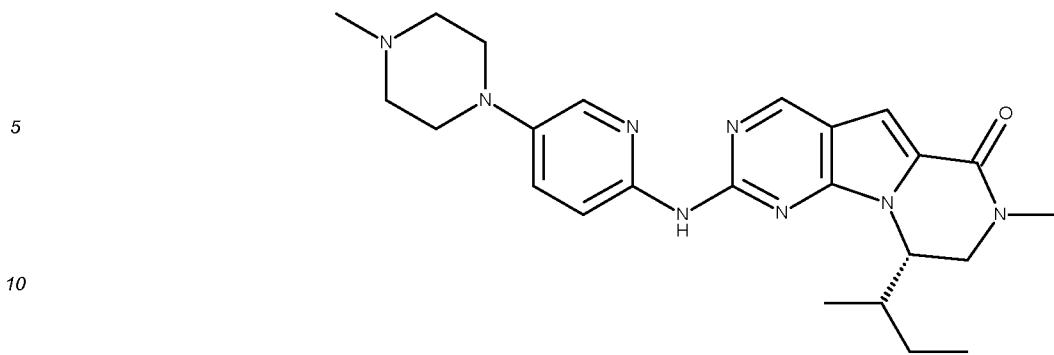
[0303] Compound 17 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.75 (t, $J=7.32$ Hz, 3 H) 0.90 (d, $J=6.73$ Hz, 3 H) 1.07 - 1.15 (m, 2 H) 1.85 - 1.94 (m, 1 H) 3.17 - 3.75 (m, 10 H) 4.58 - 4.67 (m, 1 H) 7.17 (s, 1 H) 7.71 (s, 1 H) 7.96 (s, 1 H) 7.98 - 8.05 (m, 1 H) 8.28 (d, $J=4.10$ Hz, 1 H) 9.06 (s, 1 H) 9.39 (s, 2 H). LCMS (ESI) 421 ($\text{M} + \text{H}$).

Compound 18

[0304]

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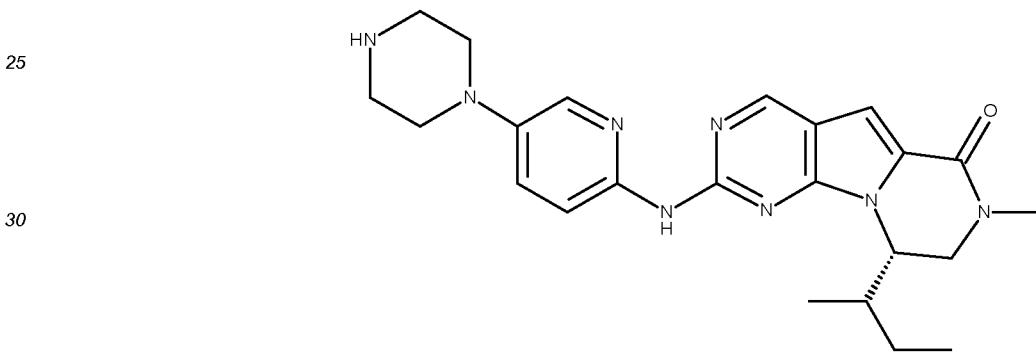
55



15 [0305] Compound 18 was synthesized in a similar manner to that described for compound 16. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.78 (t, $J=7.32$ Hz, 3 H) 0.86 (d, $J=6.73$ Hz, 3 H) 1.13 - 1.21 (m, 2 H) 1.84 - 1.96 (m, 1 H) 2.77 (d, $J=4.39$ Hz, 3 H) 3.04 (s, 3 H) 3.11 - 3.84 (m, 8 H) 3.98 (dd, $J=13.61, 4.25$ Hz, 2 H) 4.66 - 4.74 (m, 1 H) 7.17 (s, 1 H) 7.64 (s, 1 H) 7.96 (d, $J=2.34$ Hz, 1 H) 8.03 - 8.13 (m, 1 H) 9.08 (s, 1 H) 11.26 (s, 1 H) 11.66 (s, 1 H). LCMS (ESI) 449 (M+H).

20 Compound 19

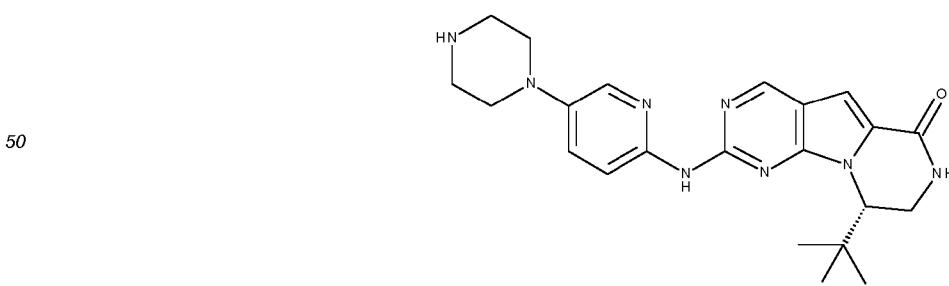
20 [0306]



40 [0307] Compound 19 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.78 (t, $J=7.32$ Hz, 3 H) 0.85 (d, $J=6.73$ Hz, 3 H) 1.10 - 1.27 (m, 2 H) 1.82 - 1.99 (m, 1 H) 3.04 (s, 3 H) 3.28 - 3.77 (m, 8 H) 3.97 (dd, $J=13.91, 4.54$ Hz, 2 H) 4.62 - 4.75 (m, 1 H) 7.07 - 7.24 (m, 1 H) 7.62 - 7.75 (m, 1 H) 7.94 (d, $J=2.34$ Hz, 1 H) 7.97 - 8.08 (m, 1 H) 9.05 (s, 1 H) 9.29 (s, 2 H). LCMS (ESI) 435 (M+H).

Compound 20

45 [0308]

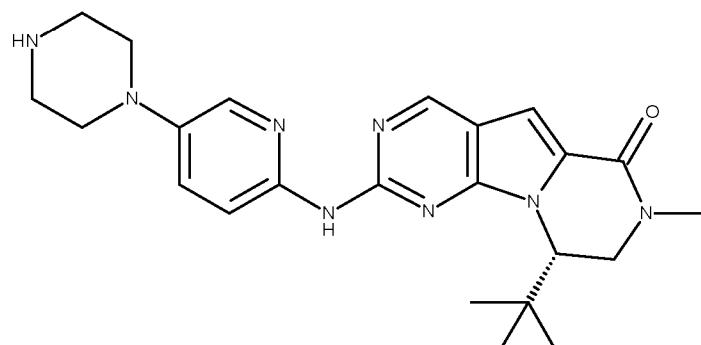


55 [0309] Compound 20 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.96 (s, 9 H) 3.15 - 3.87 (m, 10 H) 4.42 - 4.53 (m, 1 H) 6.99 (s, 1 H) 7.24 (s, 1 H) 8.06 (s, 1 H) 8.11 - 8.21 (m, 1 H) 8.79 - 8.98 (m, 2 H).

H) 9.25 (s, 2 H) 9.88 (s, 1 H). LCMS (ESI) 421 (M+H).

Compound 21

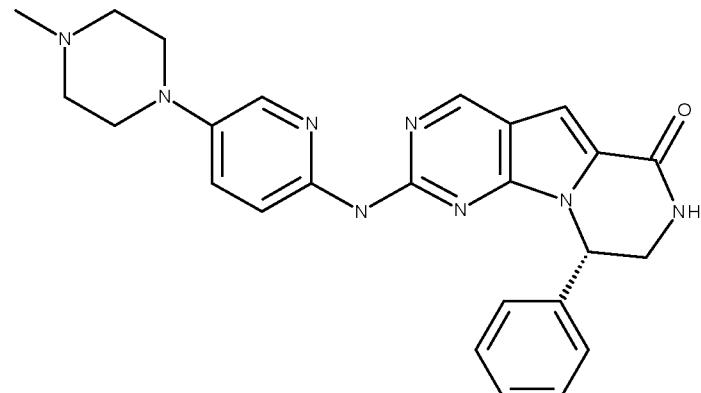
5 [0310]



20 [0311] Compound 21 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.95 (s, 9 H) 2.79 (d, $J=4.10$ Hz, 3 H) 3.06 - 3.86 (m, 10 H) 4.56 - 4.67 (m, 1 H) 7.17 (s, 1 H) 7.70 (s, 1 H) 7.96 (d, $J=2.63$ Hz, 1 H) 7.99 - 8.08 (m, 1 H) 8.26 (s, 1 H) 9.06 (s, 1 H) 10.80 (s, 1 H). LCMS (ESI) 435 (M+H).

25 **Compound 22**

[0312]



30 [0313] Compound 22 was synthesized in a similar manner to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 2.75 - 2.81 (m, 3 H) 3.12 - 3.16 (m, 2 H) 3.46 - 3.54 (m, 4 H) 3.60 - 3.69 (m, 2 H) 3.72 - 3.79 (m, 1 H) 4.07 - 4.18 (m, 2 H) 6.06 - 6.09 (m, 1 H) 6.90 (d, $J=7.61$ Hz, 2 H) 7.20 - 7.31 (m, 3 H) 7.33 (s, 1 H) 7.49 - 7.55 (m, 1 H) 7.62 - 7.70 (m, 1 H) 7.92 (d, $J=2.93$ Hz, 1 H) 8.22 (s, 1 H) 9.14 (s, 1 H). LCMS (ESI) 455 (M + H).

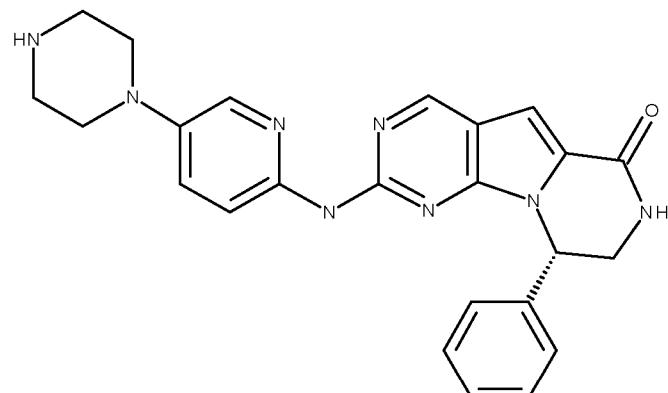
35 **Compound 23**

45 50

[0314]

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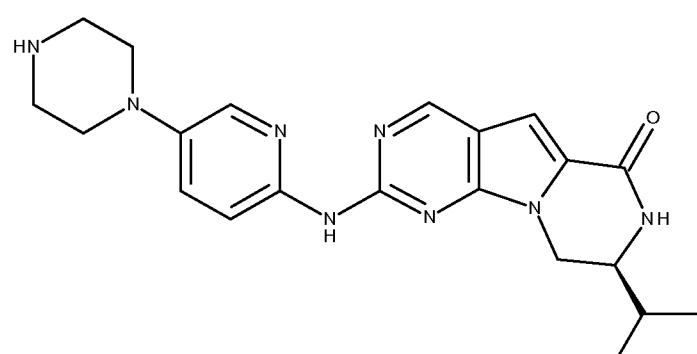
15 [0315] Compound 23 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 3.21 (s, 4 H) 3.35 - 3.67 (m, 5 H) 4.07 - 4.20 (m, 2 H) 6.13 (s, 1 H) 6.90 (d, J =7.32 Hz, 2 H) 7.22 - 7.31 (m, 3 H) 7.36 (s, 1 H) 7.48 (d, J =9.37 Hz, 1 H) 7.93 (d, J =2.34 Hz, 1 H) 8.04 - 8.11 (m, 1 H) 8.25 (d, J =4.98 Hz, 1 H) 9.17 (s, 1 H) 11.77 (br, s., 1H). LCMS (ESI) 441 (M + H).

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Compound 24

[0316]

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40 [0317] Compound 24 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.90 (d, J =6.15 Hz, 6 H) 1.72 - 1.89 (m, 1 H) 3.15 - 3.92 (m, 9 H) 4.10 - 4.46 (m, 2 H) 7.18 (s, 1 H) 7.59 (d, J =8.78 Hz, 1 H) 8.00 (s, 1 H) 8.13 (d, J =9.37 Hz, 1 H) 8.55 (s, 1 H) 9.09 (s, 1 H) 9.67 (s, 2 H) 11.91 (s, 1 H). LCMS (ESI) 407 (ESI).

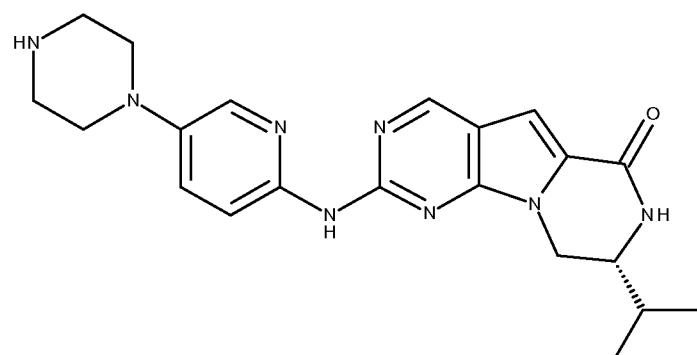
Compound 25

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[0318]

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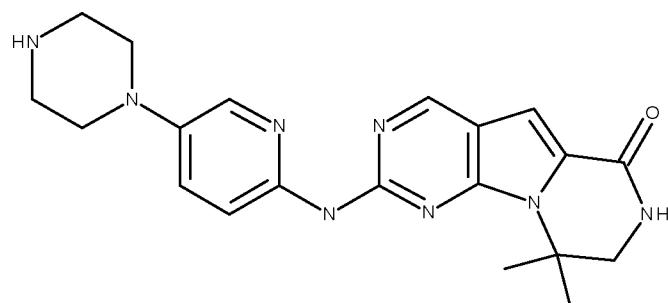
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[0319] Compound 25 was synthesized in a manner similar to compound 24 and was converted to an HCl salt. The characterization data (NMR and LCMS) was similar to that obtained for the antipode compound 24.

5 **Compound 26**

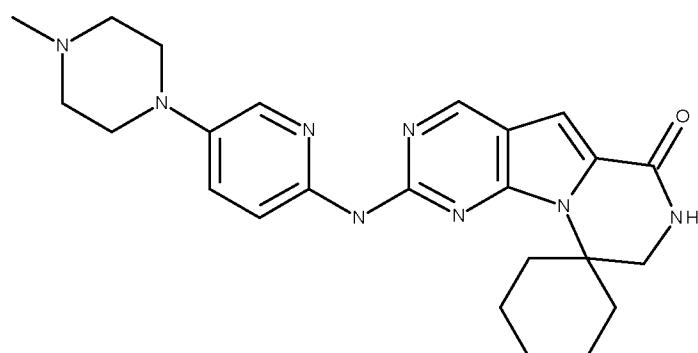
[0320]



20 [0321] Compound 26 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.78 (s, 6 H) 3.40 - 3.53 (m, 6 H) 3.64 - 3.73 (m, 4 H) 7.27 (s, 1 H) 7.66 (d, $J=9.37$ Hz, 1 H) 7.98 (d, $J=2.34$ Hz, 1 H) 8.12 (br. s., 1 H) 8.47 (br. s., 1 H) 9.11 (s, 1 H) 9.45 (br. s., 2 H) 11.62 (br. s., 1 H). LCMS (ESI) 393 ($\text{M} + \text{H}$).

25 **Compound 27**

[0322]



40 [0323] Compound 27 was synthesized in a similar manner to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.47 (br. s., 6 H) 1.72 (br. s., 2 H) 1.92 (br. s., 2 H) 2.77 (br. s., 3 H) 3.18 (br. s., 2 H) 3.46 (br. s., 2 H) 3.63 (br. s., 2 H) 3.66 (d, $J=6.15$ Hz, 2 H) 3.80 (br. s., 2 H) 7.25 (s, 1 H) 7.63 (br. s., 2 H) 7.94 (br. s., 1 H) 8.10 (br. s., 1 H) 8.39 (br. s., 1 H) 9.08 (br. s., 1 H) 11.59 (br. s., 1 H). LCMS (ESI) 447 ($\text{M} + \text{H}$).

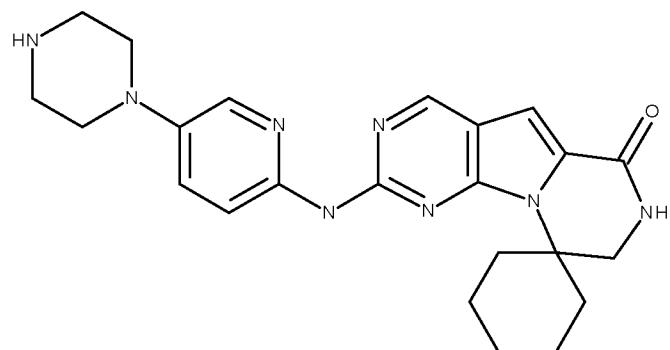
45 **Compound 28**

[0324]

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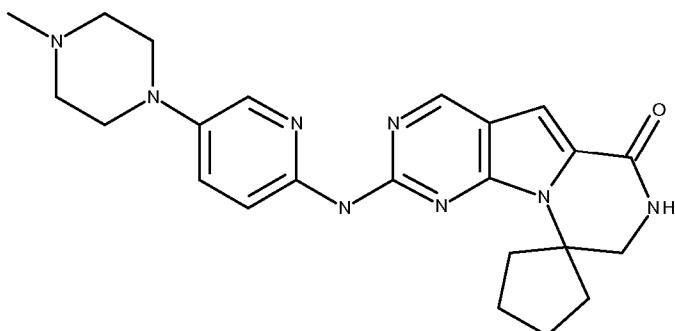
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[0325] Compound 28 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.27 - 1.64 (m, 6 H) 1.71 (br. s., 2 H) 1.91 (br. s., 2 H) 2.80 (br. s., 1 H) 3.17 - 3.24 (m, 2 H) 3.41 (br. s., 4 H) 3.65 (br. s., 4 H) 7.26 (br. s., 1 H) 7.63 (br. s., 1 H) 7.94 (br. s., 1 H) 8.13 (br. s., 1 H) 8.40 (br. s., 1 H) 9.09 (br. s., 1 H) 9.62 (br. s., 1 H) 11.71 (br. s., 1 H). LCMS (ESI) 433 ($M + H$).

20 Compound 29

[0326]

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[0327] Compound 29 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.64 - 1.75 (m, 2 H) 1.83 - 1.92 (m, 2 H) 1.96 - 2.06 (m, 2 H) 2.49 - 2.58 (m, 2 H) 2.79 (d, $J=3.81$ Hz, 3 H) 3.06 - 3.18 (m, 4 H) 3.59 - 3.69 (m, 2 H) 3.73 - 3.83 (m, 2 H) 4.04 - 4.12 (m, 2 H) 7.17 (br. s., 1 H) 7.60 - 7.70 (m, 2 H) 7.70 - 7.92 (m, 2 H) 7.96 (br. s., 1 H) 8.41 (br. s., 1 H) 8.98 (br. s., 1 H) 10.77 (br. s., 1 H). LCMS (ESI) 433 ($M + H$).

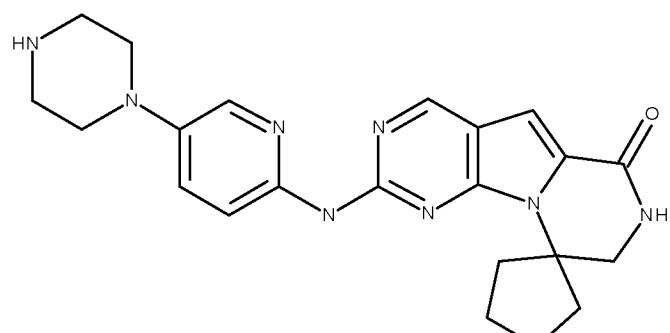
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Compound 30

[0328]

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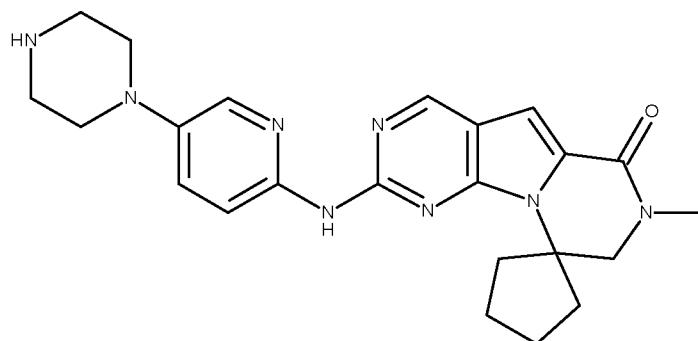
[0329] Compound 30 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.64 - 1.75 (m, 2 H) 1.84 - 1.92 (m, 2 H) 1.96 - 2.05 (m, 2 H) 2.48 - 2.56 (m, 2 H) 3.22 (br. s., 4 H) 3.42 - 3.48 (m, 4 H) 3.60 - 3.69 (m, 2 H) 4.05 - 4.13 (m, 1 H) 7.18 (s, 1 H) 7.65 (d, $J=13.47$ Hz, 1 H) 7.70 - 7.77 (m, 1 H) 7.94 (d, $J=1.76$ Hz, 1 H) 8.42 (br. s., 1 H) 9.00 (s, 1 H) 9.15 (br. s., 2 H). LCMS (ESI) 419 (M + H).

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Compound 31

[0330]

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[0331] Compound 31 was synthesized in a similar manner to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.76 (br. s., 2 H) 1.89 (br. s., 2 H) 2.03 (br. s., 2 H) 2.47 - 2.58 (m, 2 H) 3.04 (s, 3 H) 3.22 (br. s., 4 H) 3.39 (br. s., 4 H) 3.66 (s, 2 H) 7.21 (s, 1 H) 7.67 (d, $J=9.37$ Hz, 1 H) 7.93 (br. s., 1 H) 7.98 - 8.09 (m, 1 H) 9.04 (s, 1 H) 9.34 (br. s., 2 H) 11.31 (br. s., 1 H). LCMS (ESI) 433 (M + H).

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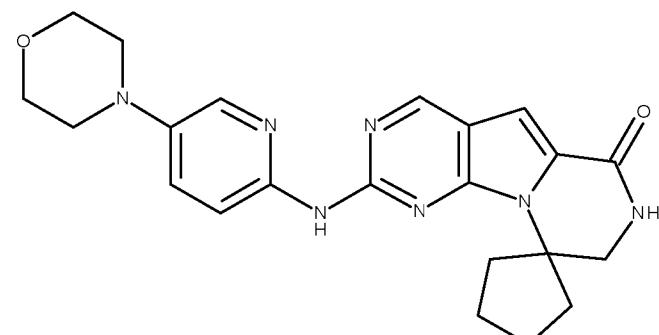
Compound 32

[0332]

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[0333] Compound 32 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.66 - 1.77 (m, 2 H) 1.84 - 1.94 (m, 2 H) 1.96 - 2.08 (m, 2 H) 2.48 - 2.57 (m, 2 H) 3.36 - 3.52 (m, 4 H) 3.60 - 3.80 (m, 6 H) 7.21 (s, 1 H) 7.53 - 7.74 (m, 2 H) 7.86 (s, 1 H) 8.02 (s, 1 H) 8.45 (s, 1 H) 9.03 (s, 1 H) 11.19 (br. s., 1 H). LCMS (ESI) 420 (M+H).

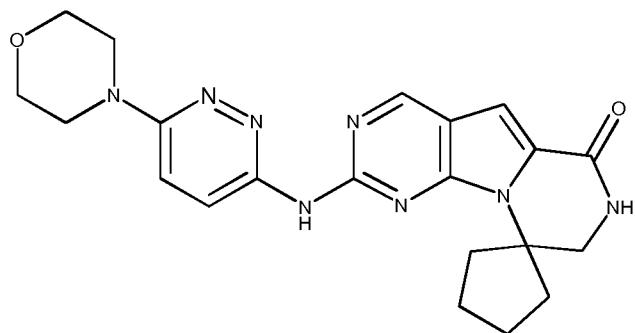
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Compound 33

[0334]

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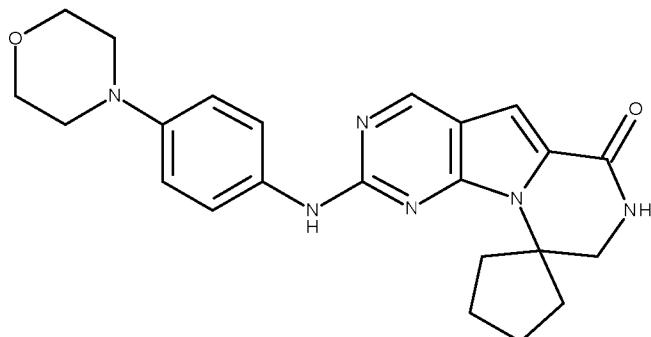
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[0335] Compound 33 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.65 - 1.79 (m, 2 H) 1.85 - 1.95 (m, 2 H) 1.97 - 2.08 (m, 2 H) 2.47 - 2.54 (m, 2 H) 3.40 - 3.58 (m, 5 H) 3.65 (dd, J =21.67, 5.56 Hz, 1 H) 3.69 - 3.78 (m, 4 H) 7.24 (s, 1 H) 7.97 - 8.17 (m, 2 H) 8.48 (s, 1 H) 9.08 (s, 1 H) 11.81 (s, 1 H). LCMS (ESI) 421 (M+H).

Compound 34

20 **[0336]**

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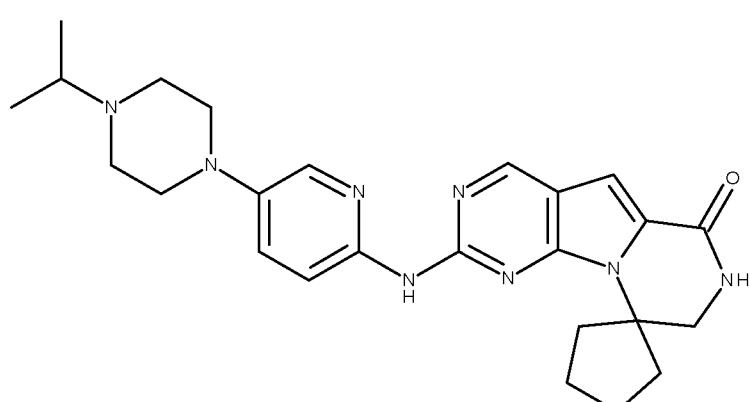
30

[0337] Compound 34 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.55 - 1.74 (m, 2 H) 1.80 - 1.98 (m, 4 H) 2.48 - 2.60 (m, 2 H) 3.40 - 3.50 (m, 4 H) 3.57 - 3.72 (m, 2 H) 3.90 - 4.20 (m, 4 H) 7.08 (s, 1 H) 7.37 - 7.57 (m, 2 H) 7.70 (m, 2 H) 8.32 (s, 1 H) 8.88 (s, 1 H) 9.98 (s, 1 H). LCMS (ESI) 419 (M+H).

Compound 35

[0338]

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[0339] Compound 35 was synthesized using similar conditions to that described for compound 16 and was converted

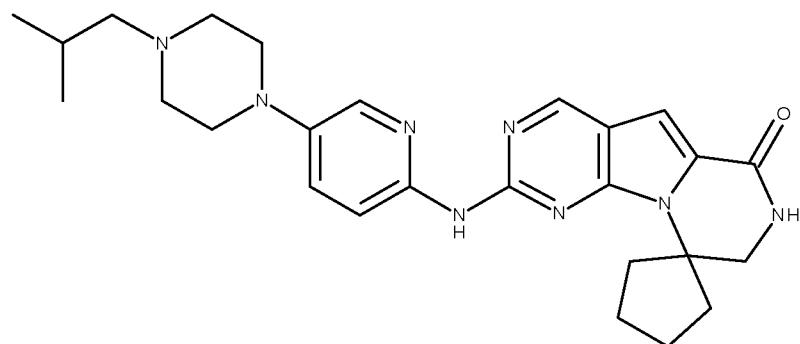
to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.30 (d, $J=5.27$ Hz, 6 H) 1.65 - 1.78 (m, 2 H) 1.83 - 1.95 (m, 2 H) 1.97 - 2.10 (m, 2 H) 2.45 - 2.55 (m, 2 H) 3.25 - 3.36 (m, 1 H) 3.39 - 3.48 (m, 4 H) 3.60 - 3.70 (m, 4 H) 3.75 - 4.15 (m, 2 H) 7.24 (s, 1 H) 7.54 - 7.75 (m, 2 H) 7.95 (s, 1 H) 8.10 (s, 1 H) 8.49 (s, 1 H) 9.07 (s, 1 H) 11.25 (s, 1 H) 11.48 (s, 1 H). LCMS (ESI) 461 (M+H).

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Compound 36

[0340]

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[0341] Compound 36 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 0.99 (d, $J=6.15$ Hz, 6 H) 1.65 - 1.78 (m, 2 H) 1.90 (m, 2 H) 1.97 - 2.08 (m, 2 H) 2.08 - 2.17 (m, 1 H) 2.45 - 2.55 (m, 2 H) 2.88 - 3.02 (m, 2 H) 3.33 - 3.48 (m, 4 H) 3.50 - 3.90 (m, 6 H) 7.24 (s, 1 H) 7.67 (s, 2 H) 7.94 (s, 1 H) 8.12 (s, 1 H) 8.49 (s, 1 H) 9.07 (s, 1 H) 10.77 (s, 1 H) 11.51 (s, 1 H). LCMS (ESI) 475 (M+H).

Compound 37

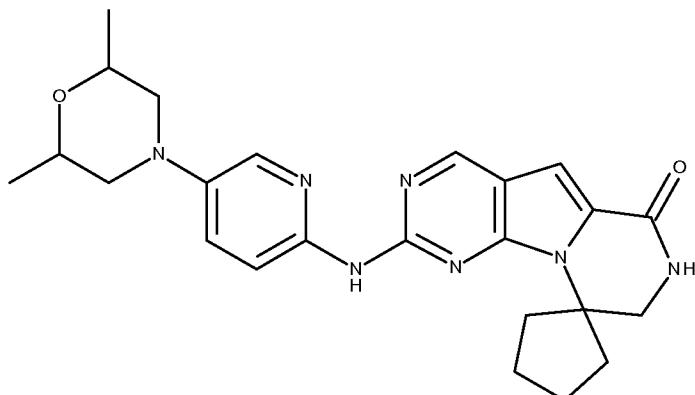
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[0342]

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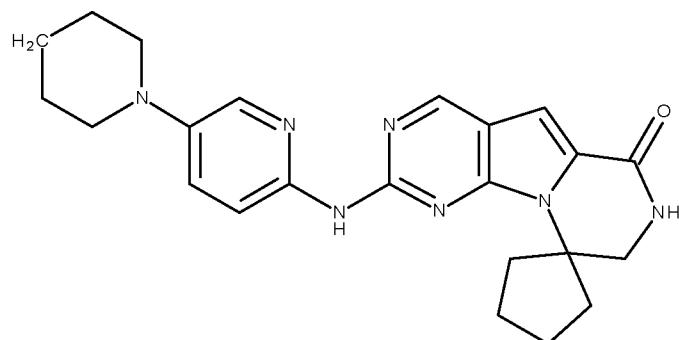


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Compound 38

[0344]

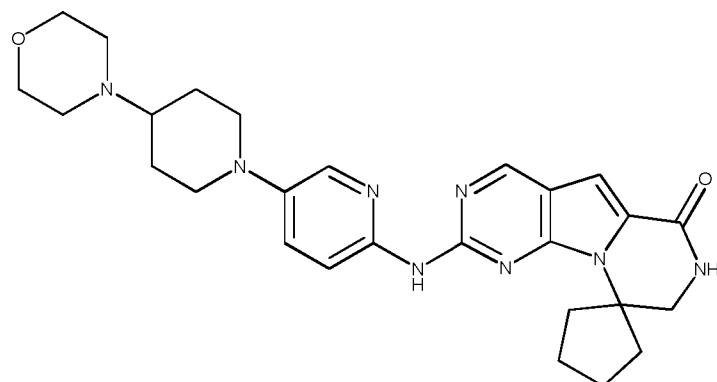
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[0345] Compound 38 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.50 - 1.57 (m, 2 H) 1.62 - 1.68 (m, 3 H) 1.68 - 1.75 (m, 2 H) 1.84 - 1.92 (m, 2 H) 1.97 - 2.08 (m, 2 H) 2.48 - 2.53 (m, 2 H) 3.14 - 3.23 (m, 4 H) 3.43 - 3.47 (m, 2 H) 3.58 - 3.70 (m, 2 H) 7.22 (s, 1 H) 7.58 - 7.70 (m, 2 H) 7.85 - 8.00 (m, 1 H) 8.16 (d, 1 H) 8.46 (s, 1 H) 9.04 (s, 1 H) 11.37 (br s., 1H). LCMS (ESI) 418 ($\text{M} + \text{H}$).

20 Compound 39

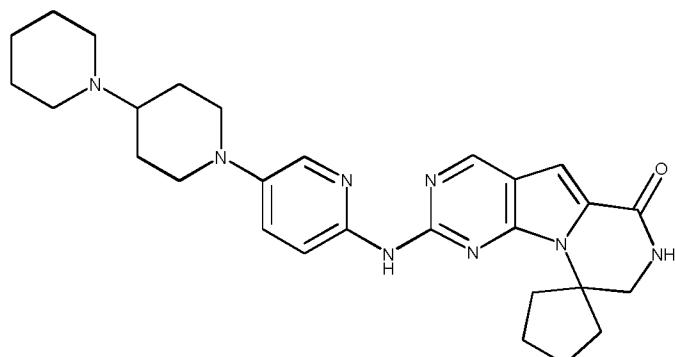
[0346]



[0347] Compound 39 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, DMSO- d_6) δ ppm 1.72 (s, 2 H) 1.90 (s, 4 H) 2.03 (s, 2 H) 2.21 (s, 2 H) 2.48 - 2.54 (m, 2 H) 2.73 (s, 2 H) 3.03 (s, 2 H) 3.25 - 3.35 (m, 1 H) 3.38 - 3.48 (m, 4 H) 3.65 - 3.99 (m, 5 H) 7.23 (s, 1 H) 7.63 (d, J =9.66 Hz, 1 H) 7.90 (s, 1 H) 8.13 (s, 1 H) 8.47 (s, 1 H) 9.06 (s, 1 H) 10.50 (br s, 1H). LCMS (ESI) 503 (M + H).

Compound 40

45 [0348]



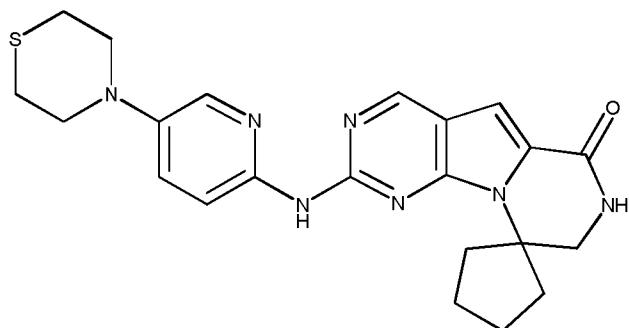
[0349] Compound 40 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.63 - 1.85 (m, 6 H) 1.87 - 1.92 (m, 2 H) 1.99 - 2.06 (m, 2 H) 2.15 - 2.23 (m, 2 H) 2.47 - 2.53 (m, 1 H) 2.69 - 2.79 (m, 2 H) 2.81 - 2.91 (m, 2 H) 2.98 - 3.08 (m, 2 H) 3.32 - 3.48 (m, 4 H) 3.57 - 3.72 (m, 4 H) 3.77 - 3.85 (m, 2 H) 7.22 (s, 1 H) 7.60 - 7.68 (m, 2 H) 7.90 (s, 1 H) 8.07 (s, 1 H) 8.46 (s, 1 H) 9.04 (s, 1 H). 11.41 (br s., 1H). LCMS (ESI) 501 (M + H).

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Compound 41

[0350]

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[0351] Compound 41 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.64 - 1.76 (m, 2 H) 1.87 - 1.93 (m, 2 H) 2.00 - 2.07 (m, 2 H) 2.48 - 2.53 (m, 2 H) 2.67 - 2.72 (m, 4 H) 3.44 - 3.47 (m, 2 H) 3.50 - 3.55 (m, 4 H) 7.24 (s, 1 H) 7.61 (d, $J=9.37$ Hz, 2 H) 7.86 (d, $J=2.63$ Hz, 1 H) 8.09 (d, $J=12.88$ Hz, 1 H) 8.48 (s, 1 H) 9.06 (s, 1 H) 11.41 (br s., 1H). LCMS (ESI) 436 (M + H).

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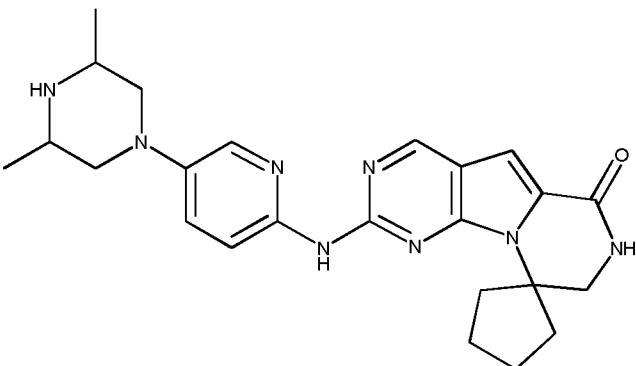
Compound 42

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[0352]

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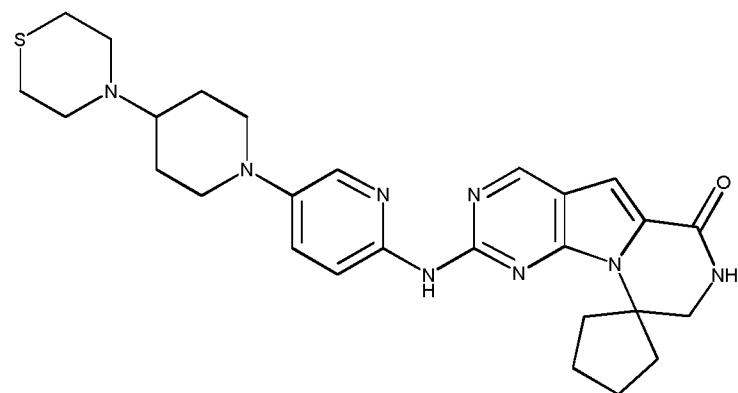
[0353] Compound 42 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.29 (d, $J=6.73$ Hz, 6 H) 1.66 - 1.79 (m, 2 H) 1.84 - 1.95 (m, 2 H) 1.98 - 2.09 (m, 2 H) 2.46 - 2.55 (m, 2 H) 3.29 - 3.39 (m, 2H) 3.58 - 3.70 (m, 4H) 3.77 - 3.86 (m, 4H) 7.24 (s, 1 H) 7.66 (d, $J=9.37$ Hz, 1 H) 7.96 (d, $J=2.93$ Hz, 1 H) 8.08 (s, 1 H) 8.48 (s, 1 H) 9.06 (s, 1 H) 9.28 (s, 1 H) 9.67 (s, 1 H) 11.36 (s, 1H). LCMS (ESI) 447 (M + H).

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Compound 43

[0354]

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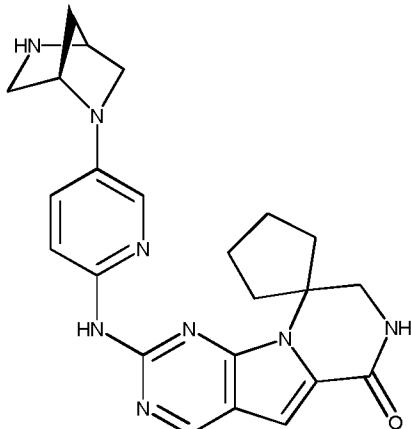
[0355] Compound 43 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.73 (s, 2 H) 1.76 - 1.85 (m, 2 H) 1.85 - 1.94 (m, 2 H) 1.98 - 2.07 (m, 2 H) 2.19 - 2.26 (m, 2 H) 2.48 - 2.52 (m, 1 H) 2.70 - 2.81 (m, 4 H) 3.13 - 3.20 (m, 1 H) 3.30 - 3.48 (m, 3 H) 3.58 - 3.71 (m, 4 H) 3.78 - 3.84 (m, 4 H) 7.24 (s, 1 H) 7.62 (d, $J=9.37$ Hz, 2 H) 7.89 (d, $J=1.17$ Hz, 1 H) 8.09 - 8.18 (m, 1 H) 8.48 (s, 1 H) 9.06 (s, 1 H) 11.46 (br s, 1 H). LCMS (ESI) 519 ($M + H$).

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Compound 44

[0356]

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[0357] Compound 44 was synthesized using similar conditions to that described for compound 16 followed by the deblocking step described for compound 3 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.65 - 1.75 (m, 2 H) 1.85 - 1.93 (m, 2 H) 1.93 - 1.99 (m, 1 H) 2.00 - 2.06 (m, 2 H) 2.08 - 2.14 (m, 1 H) 2.47 - 2.55 (m, 2 H) 3.07 - 3.25 (m, 2 H) 3.25 - 3.69 (m, 5 H) 4.46 (s, 1 H) 4.67 (s, 1 H) 7.22 (s, 1 H) 7.58 - 7.69 (m, 2 H) 8.46 (s, 1 H)

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9.02 (s, 1 H) 9.34 (s, 1 H) 9.65 (s, 1 H). LCMS (ESI) 431 ($M + H$).

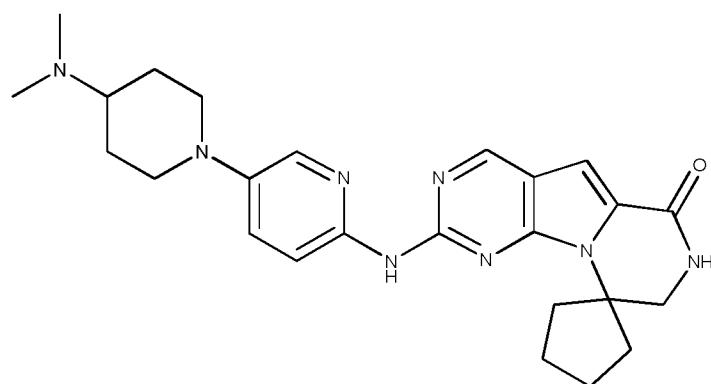
Compound 45

[0358]

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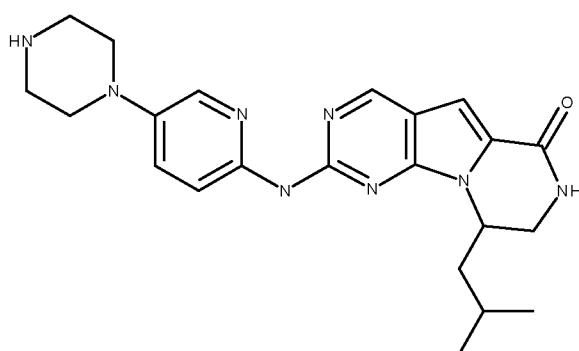
15 [0359] Compound 45 was synthesized using similar conditions to that described for compound 16 and was converted to an HCl salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.65 - 1.82 (m, 3 H) 1.89 (br. s., 2 H) 1.98 - 2.08 (m, 2 H) 2.13 (br. s., 2 H) 2.47 - 2.55 (m, 2 H) 2.68 (d, $J=4.98$ Hz, 6 H) 2.71 - 2.80 (m, 2 H) 3.29 - 3.71 (m, 10 H) 7.16 - 7.26 (m, 1 H) 7.67 (d, $J=9.66$ Hz, 2 H) 7.91 (d, $J=2.05$ Hz, 1 H) 8.14 (br. s., 1 H) 8.48 (br. s., 1 H) 9.05 (s, 1 H) 11.14 (br. s., 1 H) 11.43 (br. s., 1 H). LCMS (ESI) 461 (M + H).

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Compound 46

[0360]

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40 [0361] Compound 46 was synthesized in a manner similar to that described for compounds 2 and 3 and was recovered as an HCl salt. The analytical data was consistent with that described for the antipode compound 13.

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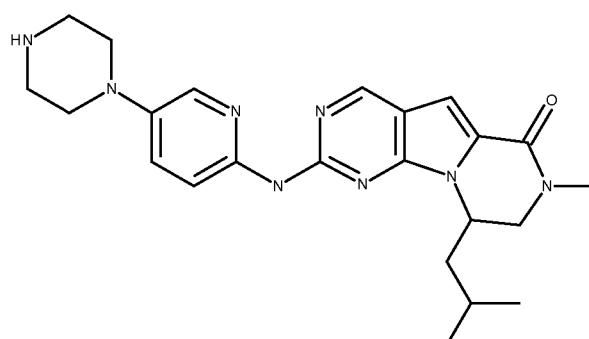
Compound 47

[0362]

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40 [0363] Compound 47 was synthesized in a manner similar to that described for compounds 2 and 3 and was recovered as an HCl salt. The analytical data was consistent with that described for the antipode compound 15.

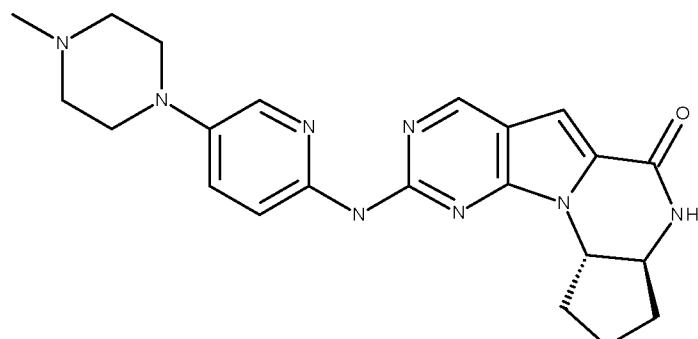
Compound 48

[0364]

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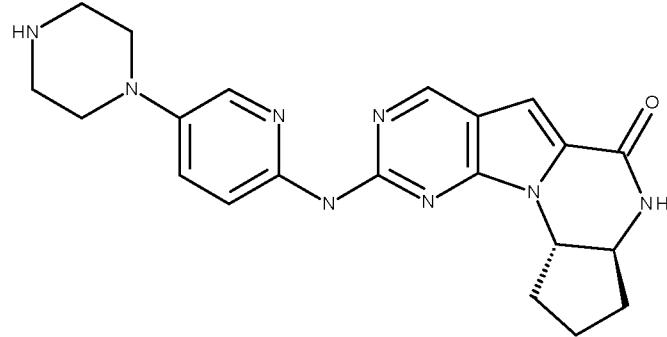
[0365] Compound 48 was synthesized in a similar manner to that described for compound 16 and then converted to its hydrochloride salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.50 - 1.65 (m, 1 H) 1.92 - 2.02 (m, 3 H) 2.06 - 2.15 (m, 1 H) 2.78 (d, $J=3.81$ Hz, 4 H) 3.10 - 3.20 (m, 4 H) 3.47 - 3.51 (m, 2 H) 3.64 - 3.71 (m, 1 H) 3.76 - 3.83 (m, 2 H) 3.98 - 4.14 (m, 1 H) 7.20 (s, 2 H) 7.77 (s, 1 H) 7.97 (s, 2 H) 8.81 (s, 1 H) 9.03 (s, 1 H) 10.97 (br s., 1 H). LCMS (ESI) 419 (M + H).

Compound 49

[0366]

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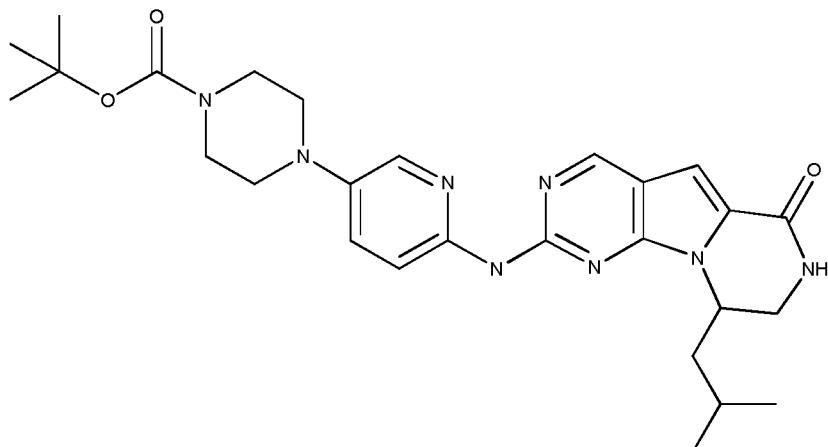
[0366] Compound 49 was synthesized in a similar manner to that described for compound 16 and then converted to its hydrochloride salt. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ ppm 1.54 - 1.59 (m, 1 H) 1.92 - 2.01 (m, 3 H) 2.06 - 2.15 (m, 1 H) 2.76 - 2.84 (m, 1 H) 3.17 - 3.24 (m, 6 H) 3.64 - 3.71 (m, 2 H) 4.02 - 4.11 (m, 2 H) 7.22 (s, 2 H) 7.64 (s, 1 H) 7.97 (s, 2 H) 8.75 (s, 1 H) 8.97 (s, 1 H) 9.21 (s, 1 H). LCMS (ESI) 405 (M + H).

Compound 50

[0367]

50

55



Biological Activity

20 [0368] Kinase enzymatic reactions were performed in 384-well microplates using a 12-channel Caliper LabChip instrument as a detection device. The enzymatic phosphorylation of a peptide results in a change in net charge, enabling electrophoretic separation of product from substrate. As substrate and product are separated, two peaks of fluorescence are observed. Change in the relative fluorescence intensity of the substrate and product peaks is the parameter measured, reflecting enzyme activity. In the presence of an inhibitor, the ratio between product and substrate is altered. The signal of the product decreases, while the signal of the substrate increases.

25 [0369] For the measurement of CDK2/cyclinE activity, enzyme (0.22 nM) was incubated with 100 mM ATP and the phosphoacceptor substrate peptide (1 mM) for one hour. For the measurement of CDK4/CyclinD activity, enzyme (0.85 nM) was incubated with 200 mM ATP and the phosphoacceptor substrate peptide (1 mM) for three hours. Potential inhibitor compounds (as HCl salts) were tested using 12-point dose response curves in single point at the K_m for ATP. The IC_{50} of each compound was determined using GraphPad Prism. Results from the IC_{50} values demonstrate 200 and 100 fold selectivity for compounds Compound 1 and Compound 3 for Cdk4/CycD1 over Cdk2/CycE respectively. Results are provided in Table 1.

Table 1.

Compound	CDK2/cyclinE		CDK4/cyclinD	
	IC_{50} (μ M)	Confidence Interval 95%	IC_{50} (μ M)	Confidence Interval 95%
staurosporine	0.00393	0.000706	0.0375	0.99
Compound 1	>100		0.453	0.85
Compound 3	>100		1.05	0.78

35 [0370] Additional CDK2/cyclinE data is provided in Table 2. IC_{50} data is as follows: A - 0.001-0.010 μ M; B - 0.010-0.100 μ M; C - 0.100-1 μ M; D - 1-100 μ M; and E - >100 μ M. Data is also shown for known CDK4/6 inhibitor, PD0332991.

Table 2.

Compound #	CDK2/CycE IC50(μ M)	Compound #	CDK2/CycE IC50(μ M)
PD0332991	D	34	B
28	D	36	D
27	D	35	D
33	D	39	D

	Compound #	CDK2/CycE
		IC50(µM)
5	40	D
	17	D
	41	D
10	46	D
	29	D
	30	D
15	16	D
	48	E
	32	D
20	12	D
	10	D
	13	D
25	38	D
	23	C
	49	D
30	26	D
	8	D
	37	D

	Compound #	CDK2/CycE
		IC50(µM)
	20	C
	19	E
	9	D
	22	D
	18	E
	47	E
	6	E
	21	D
	25	D
	31	E
	24	D
	11	E
	15	E
	7	E
	14	E
	1	E
	3	E
	5	E

35

Pharmaceutical Compositions

40 [0371] In one embodiment a pharmaceutical composition comprising compounds of the invention is provided. In a first aspect, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients or vehicles, and optionally other therapeutic and/or prophylactic ingredients. Such excipients are known to those of skill in the art. The compounds of the present invention include, without limitation, basic compounds such as free bases. A thorough discussion of pharmaceutically acceptable excipients and salts is available in Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990).

45 [0372] Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include an effective amount of the selected drug in combination with a pharmaceutically acceptable carrier and, in addition, may include other pharmaceutical agents, adjuvants, diluents, buffers, etc.

50 [0373] The invention includes a pharmaceutical composition comprising a compound of the present invention including isomers, racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof together with one or more pharmaceutically acceptable carriers and optionally other therapeutic and/or prophylactic ingredients.

55 [0374] For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate and the like.

[0375] For oral administration, the composition will generally take the form of a tablet, capsule, a softgel capsule nonaqueous solution, suspension or syrup. Tablets and capsules are preferred oral administration forms. Tablets and capsules for oral use will generally include one or more commonly used carriers such as lactose and corn starch.

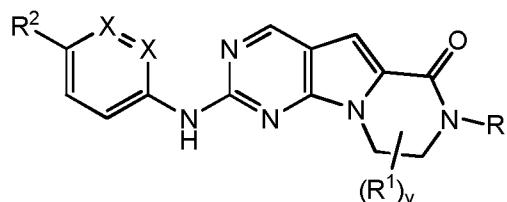
Lubricating agents, such as magnesium stearate, are also typically added. When liquid suspensions are used, the active agent may be combined with emulsifying and suspending agents. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional components for incorporation into an oral formulation herein include, but are not limited to, preservatives, suspending agents, thickening agents and the like.

5 [0376] The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or 10 veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

Claims

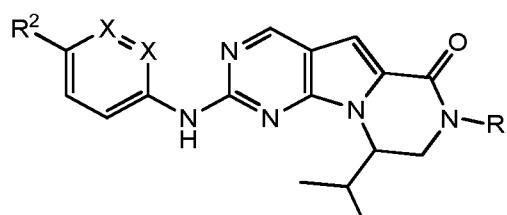
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1. A compound having formula Ia:



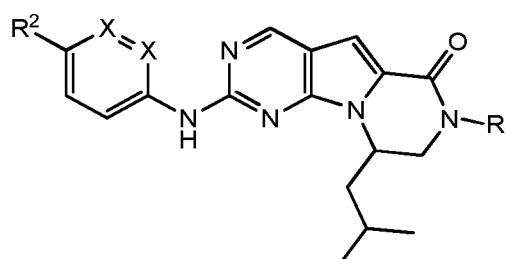
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or having formula Ib:



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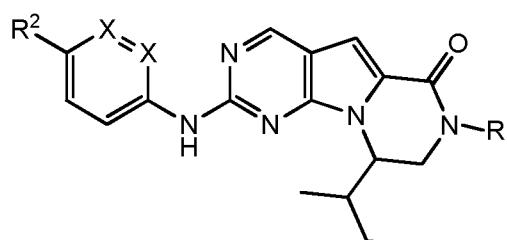
or having formula Ic:



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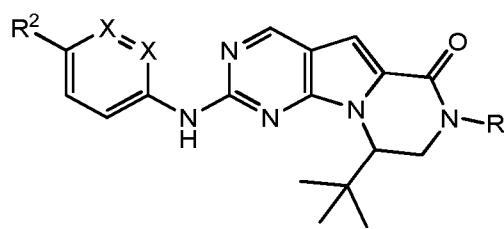
or having formula Id:

50



or having formula Ie:

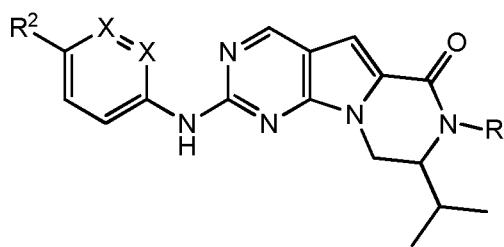
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or having formula If:

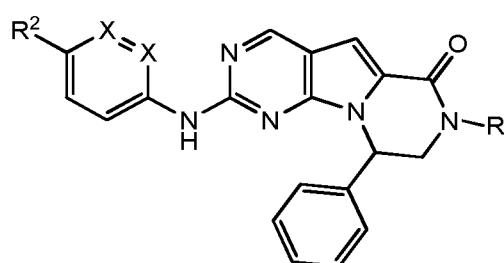
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or having formula Ig:

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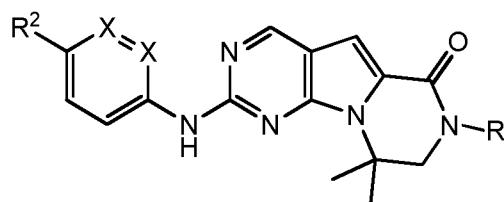


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or having formula Ih:

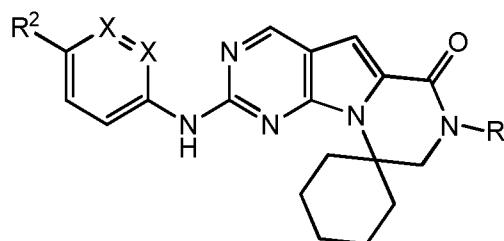
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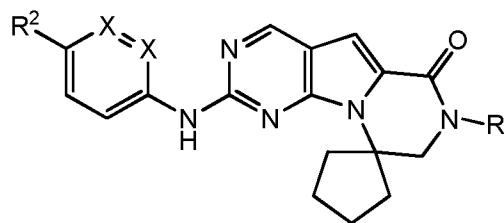
or having formula II:

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or having formula Ij:



10 or a pharmaceutically acceptable salt thereof

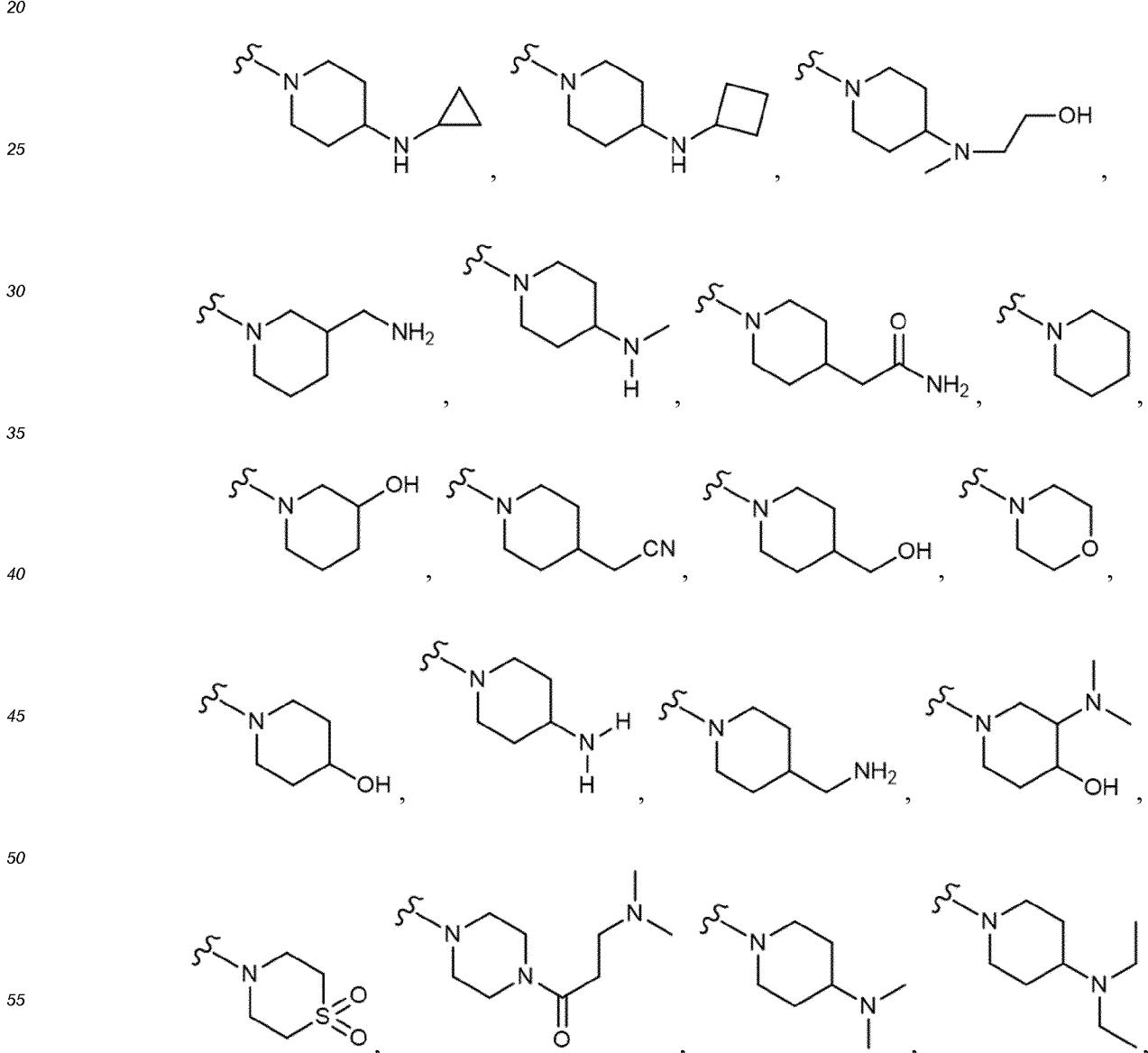
wherein R is H, C₁-C₃ alkyl or haloalkyl;

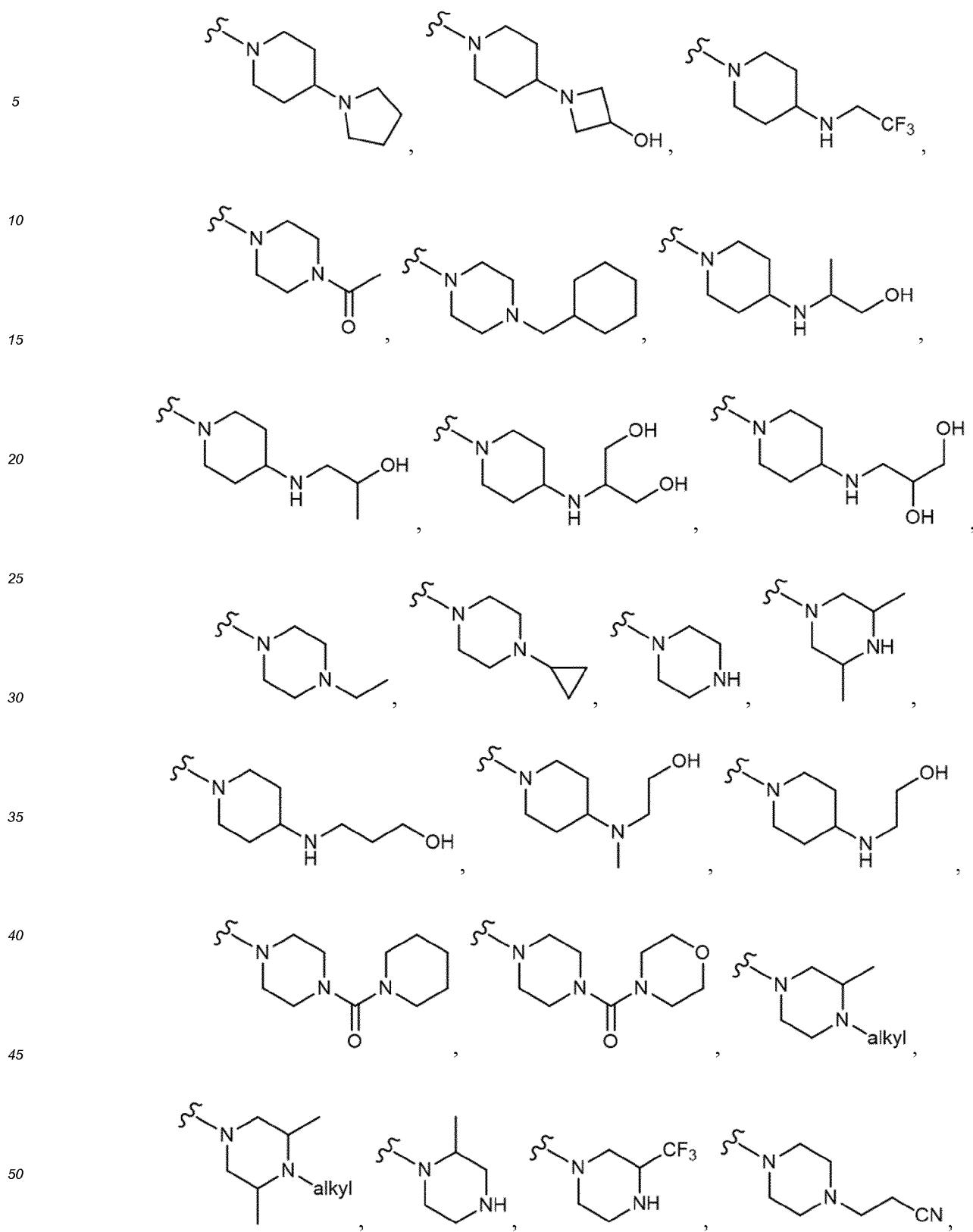
15 each R¹ is independently aryl, alkyl, cycloalkyl or haloalkyl, wherein each of said alkyl, cycloalkyl and haloalkyl groups optionally includes O or N heteroatoms in place of a carbon in the chain and two R¹'s on adjacent ring atoms or on the same ring atom together with the ring atom(s) to which they are attached optionally form a 3-8-membered cycle;

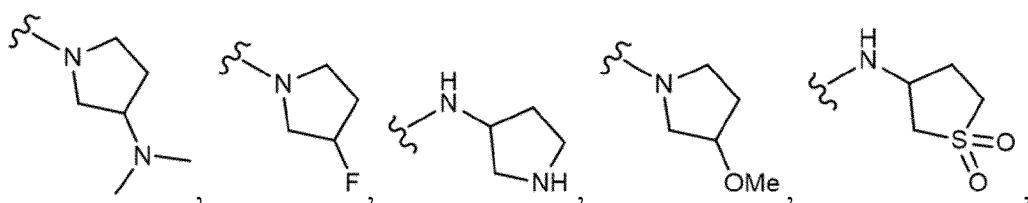
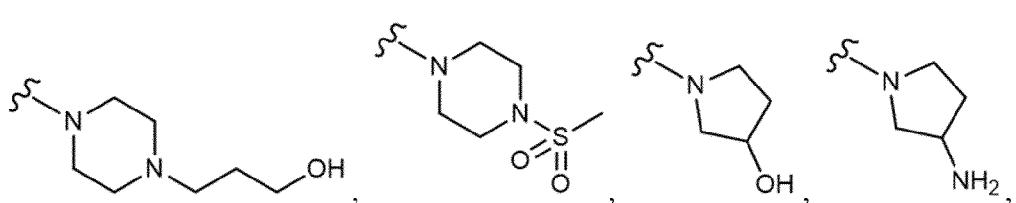
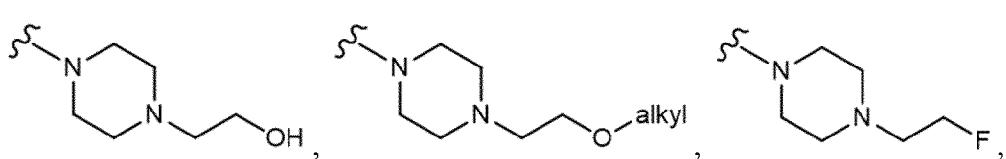
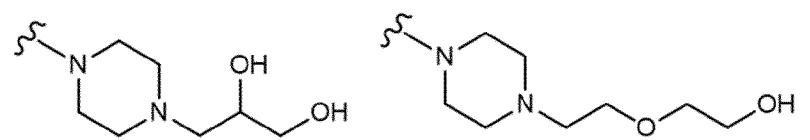
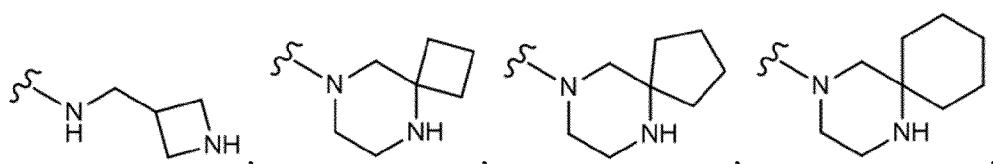
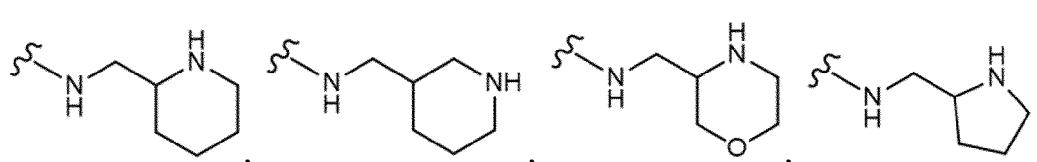
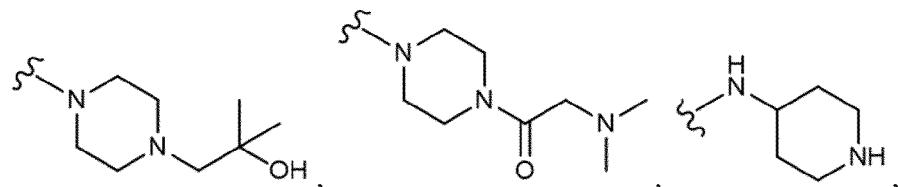
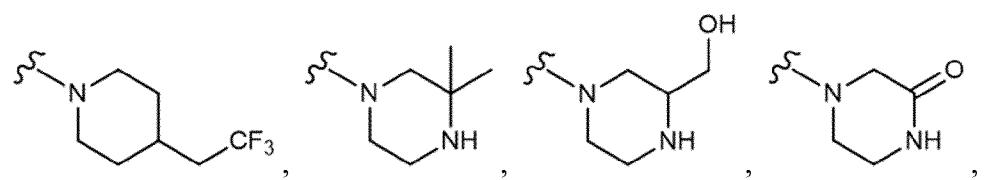
y is 0, 1, 2, 3 or 4;

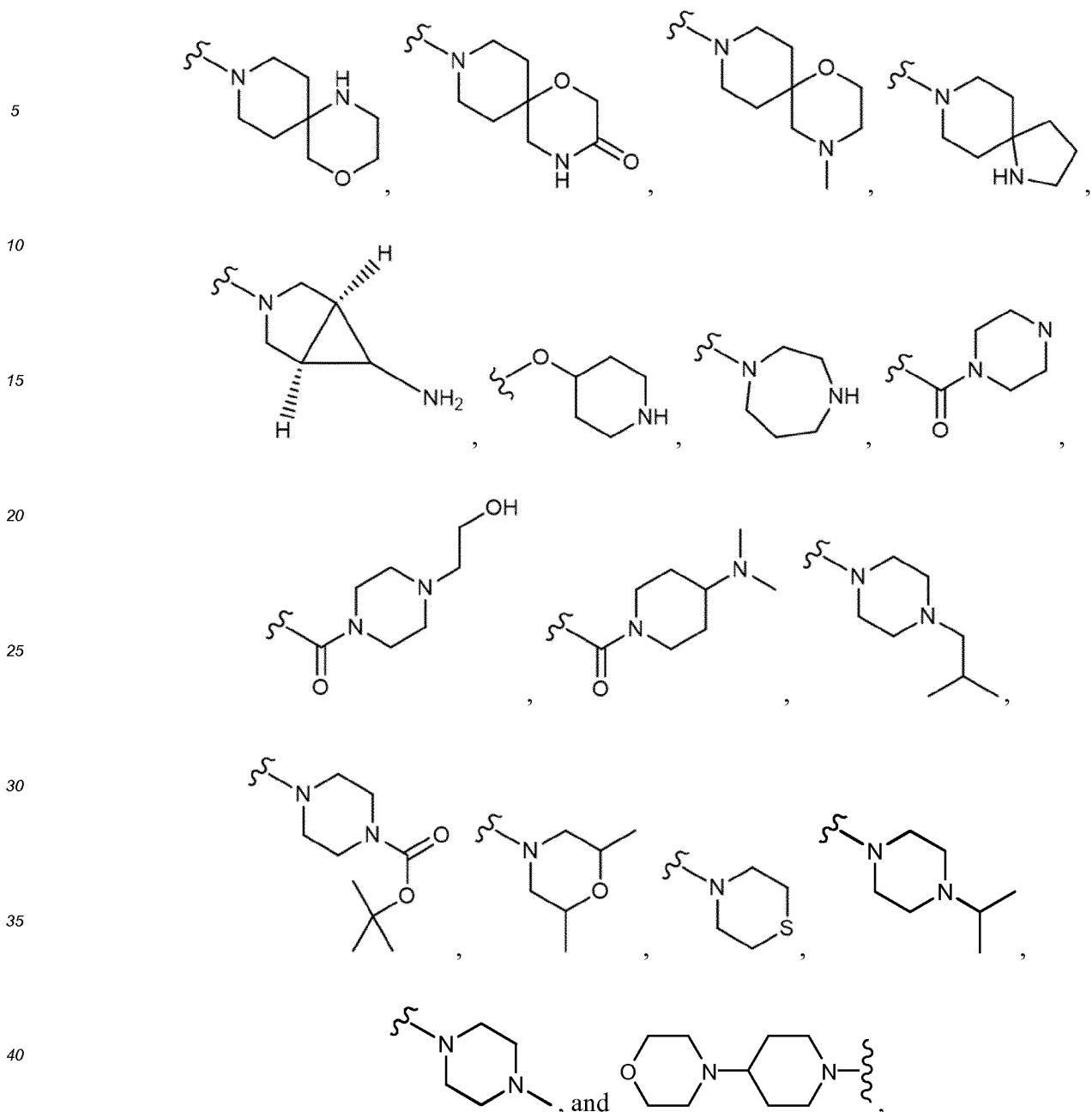
each X is independently CH or N; and

20 R² is selected from the structures:



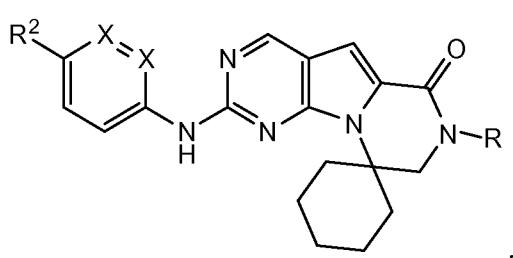






wherein the term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings
 45 wherein such rings may be attached together in a fused manner and wherein any aryl may have 1 or more substituents independently selected from C₁-C₆ alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and C₁-C₆ alkylamino.

2. The compound of claim 1 having the formula II:



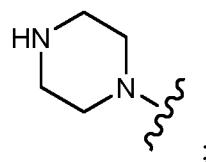
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or 2 wherein both of X are N.

5 4. The compound of any previous claim wherein R is hydrogen or C₁-C₃ alkyl.

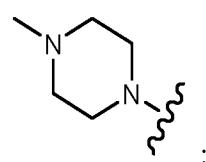
5. The compound of any one of claims 1 to 4 wherein R² is:

10 (a)



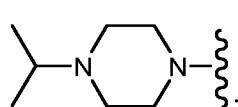
20 or

(b)



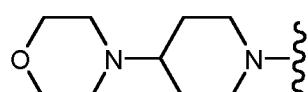
30 or

(c)

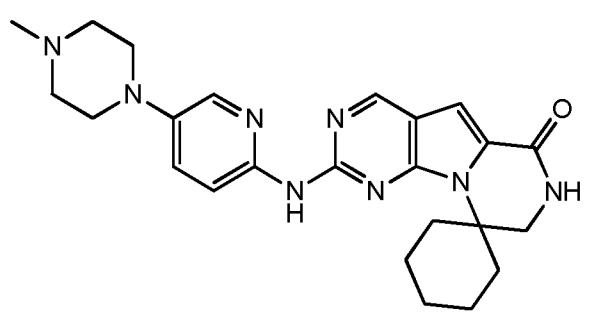


40 or

(d)



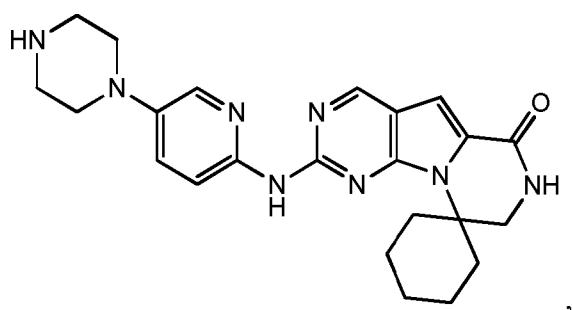
6. The compound of claims 1 or 2 having the formula:



or a pharmaceutically acceptable salt thereof

7. The compound of claims 1 or 2 having the formula:

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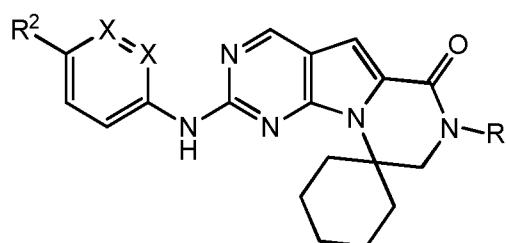
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or a pharmaceutically acceptable salt thereof.

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8. The compound of claims 1 or 2 having formula II:

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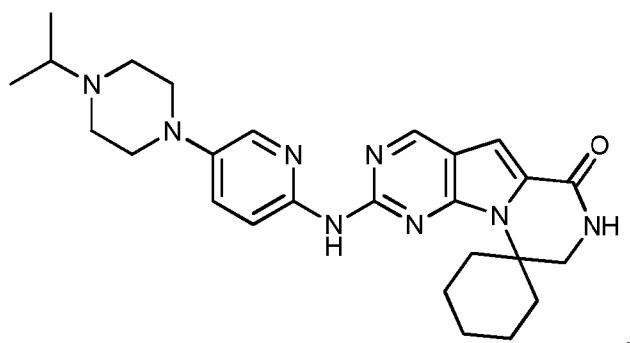
wherein R is H

or a pharmaceutically acceptable salt thereof

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9. The compound of claim 8 having the formula:

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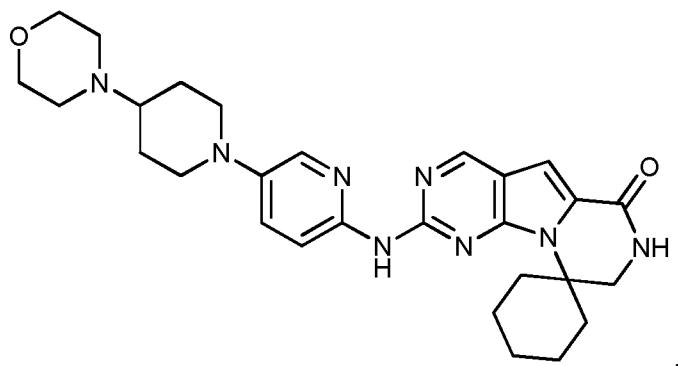
or a pharmaceutically acceptable salt thereof

10. The compound of claim 8 having the formula:

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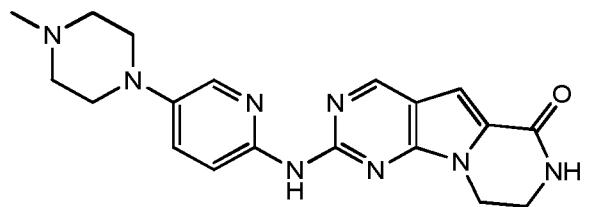
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or a pharmaceutically acceptable salt thereof.

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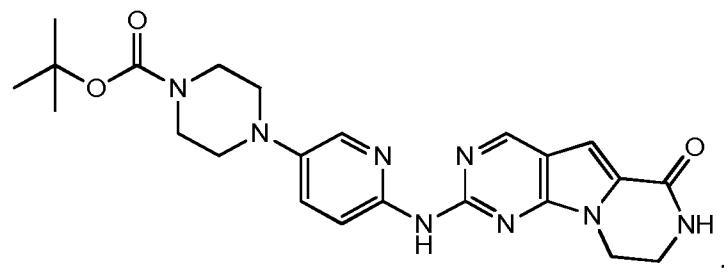
11. The compound of claim 1 selected from the structures:

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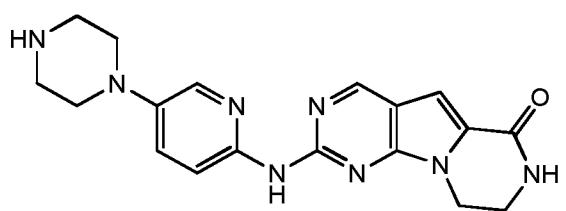
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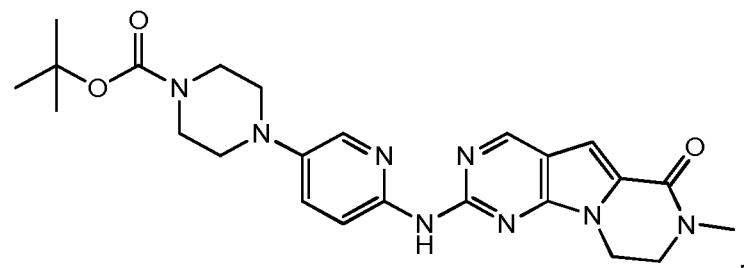
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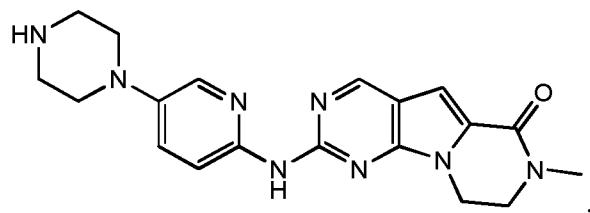
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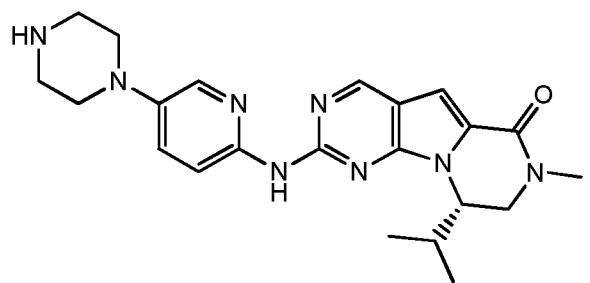
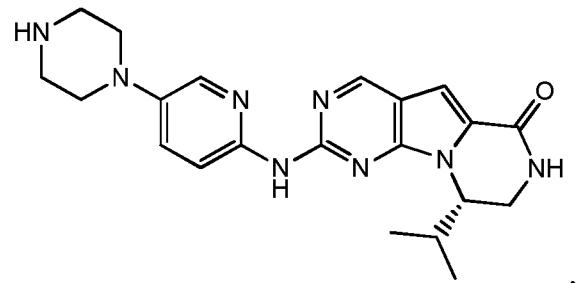
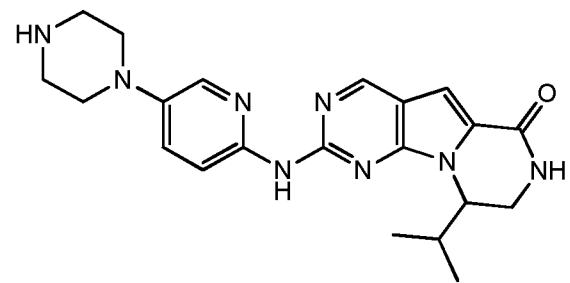
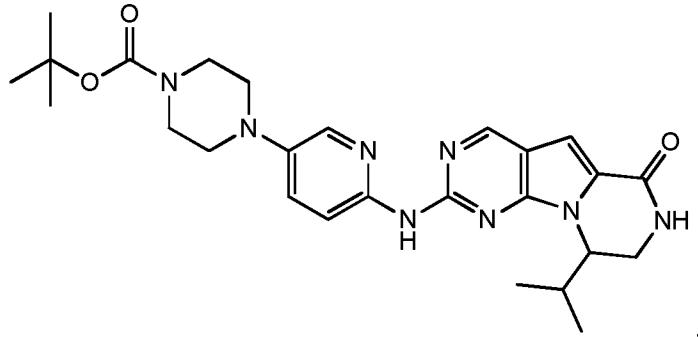
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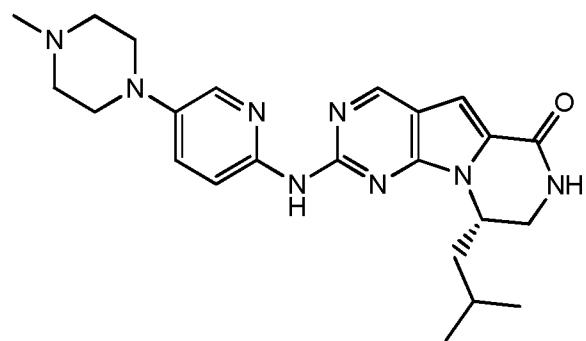
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and

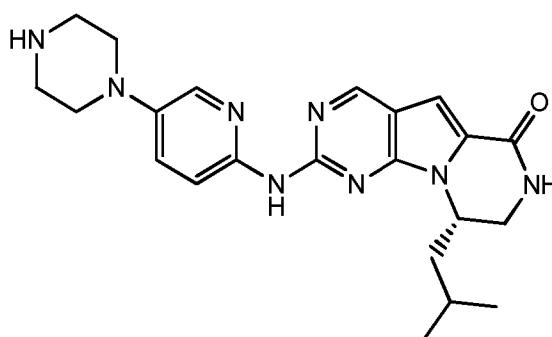
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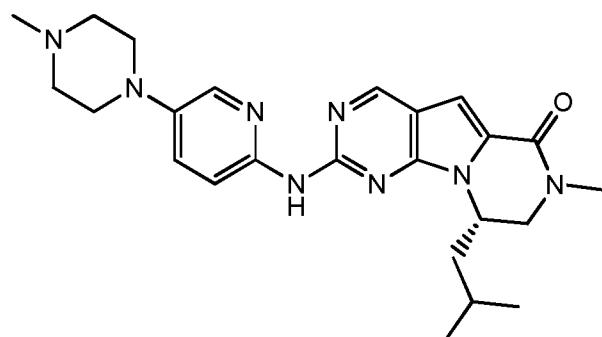
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12. The compound of claim 1 selected from the structures:

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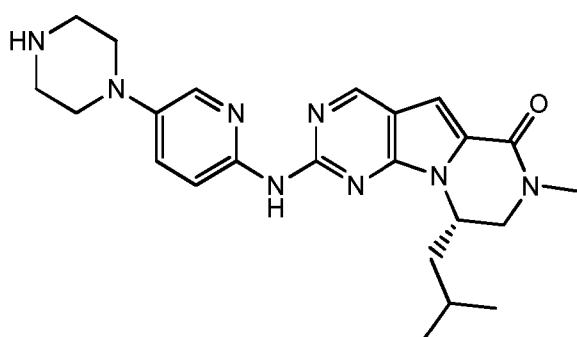


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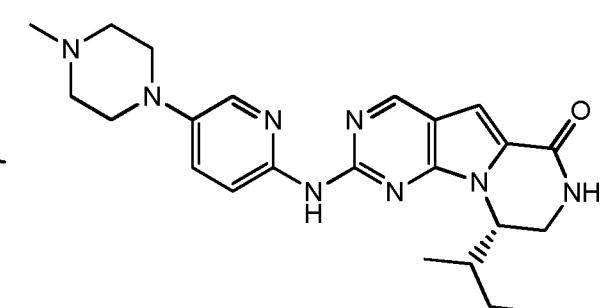


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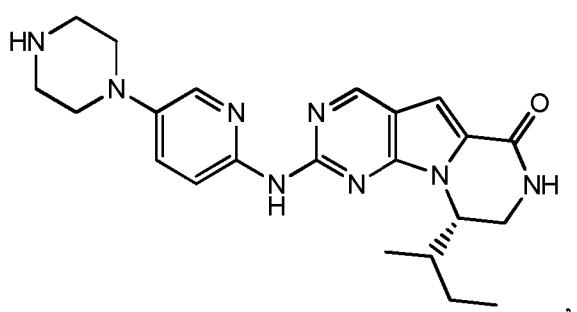


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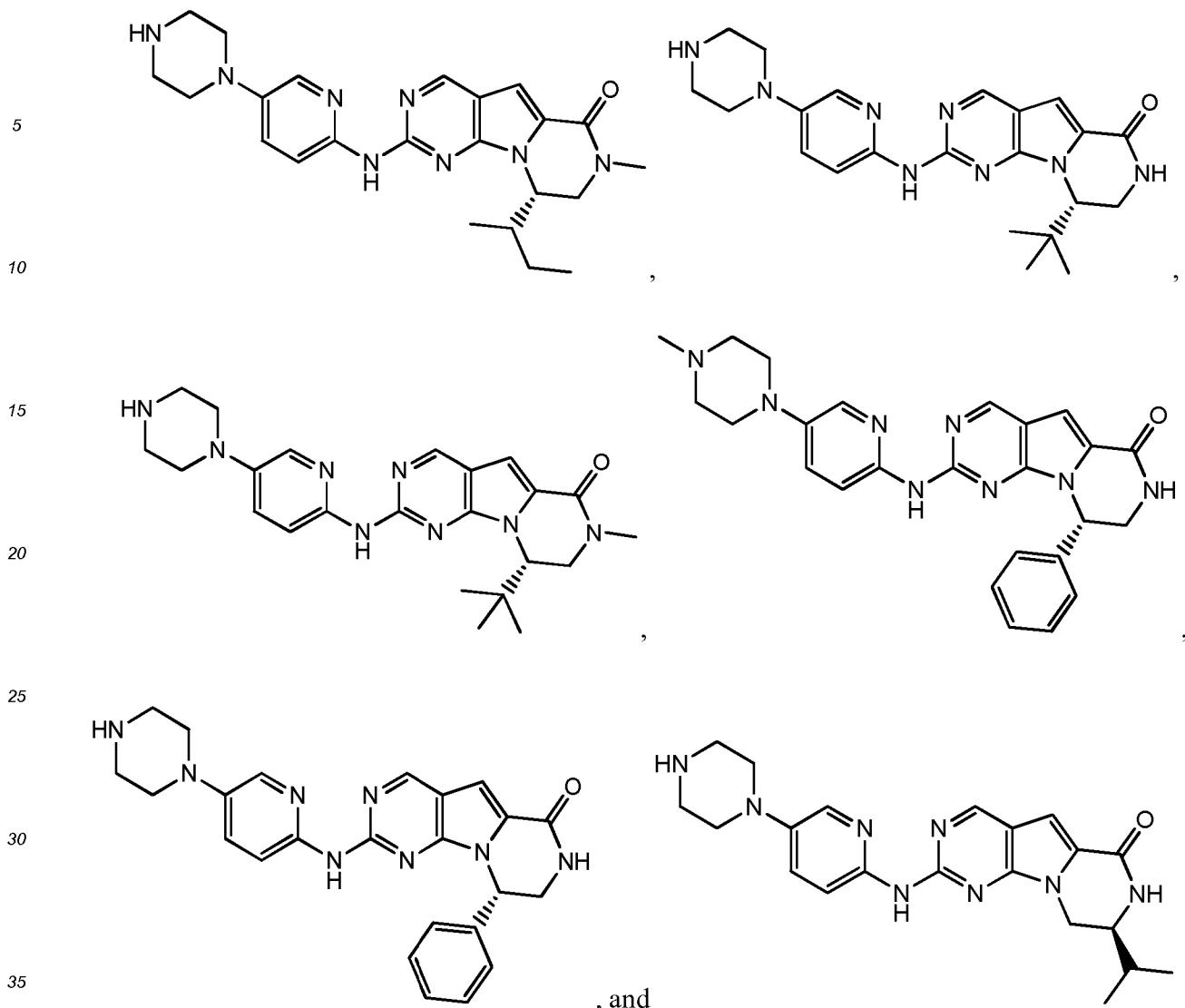
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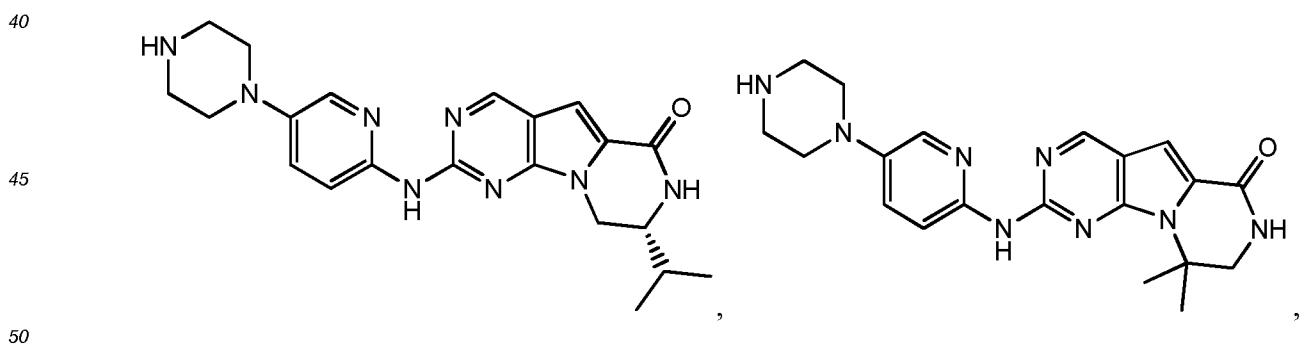


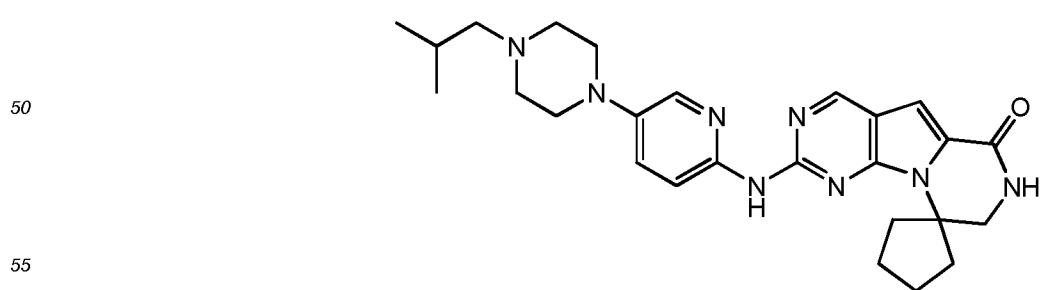
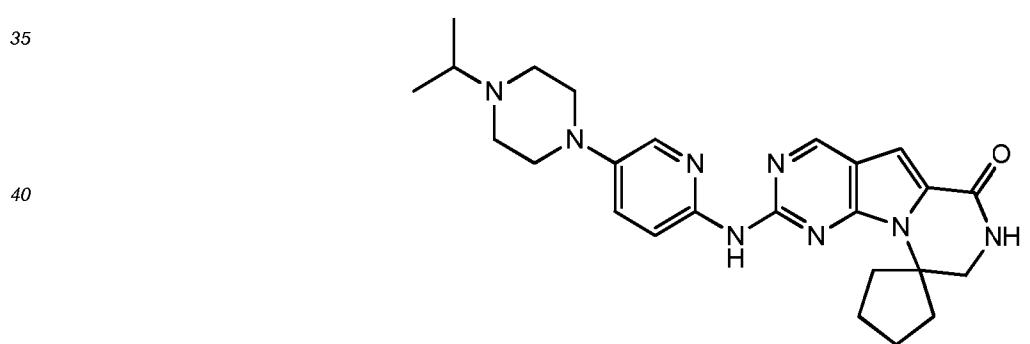
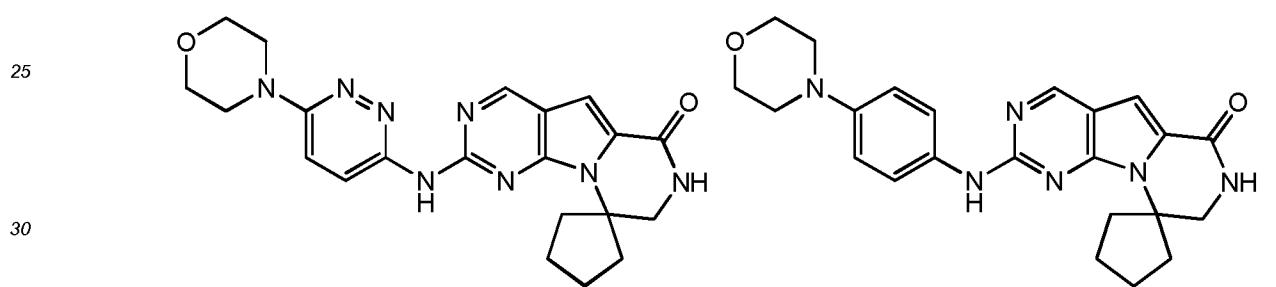
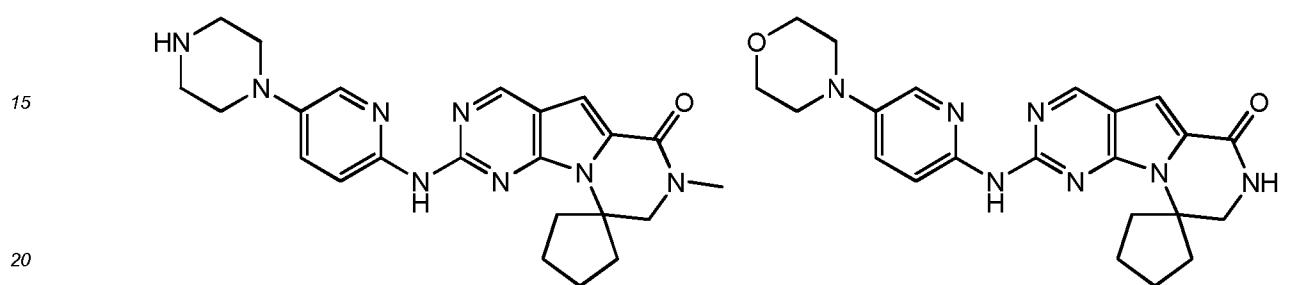
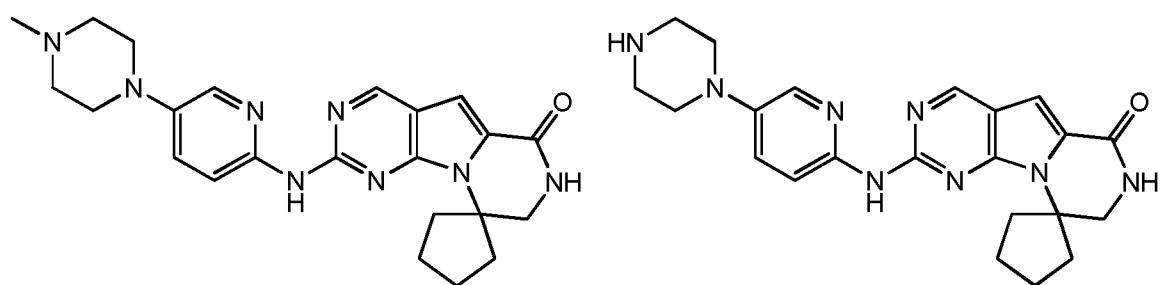
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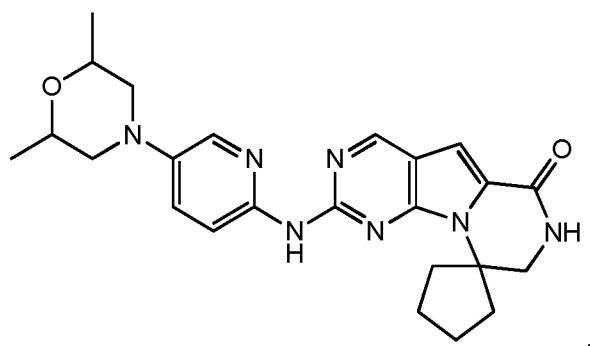


13. The compound of claim 1 selected from the structures:





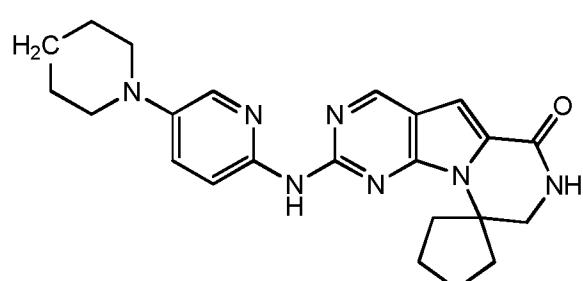
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and

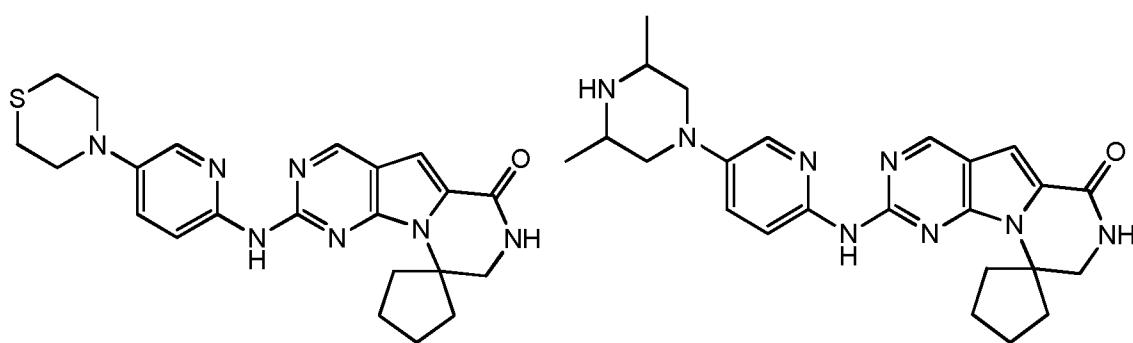
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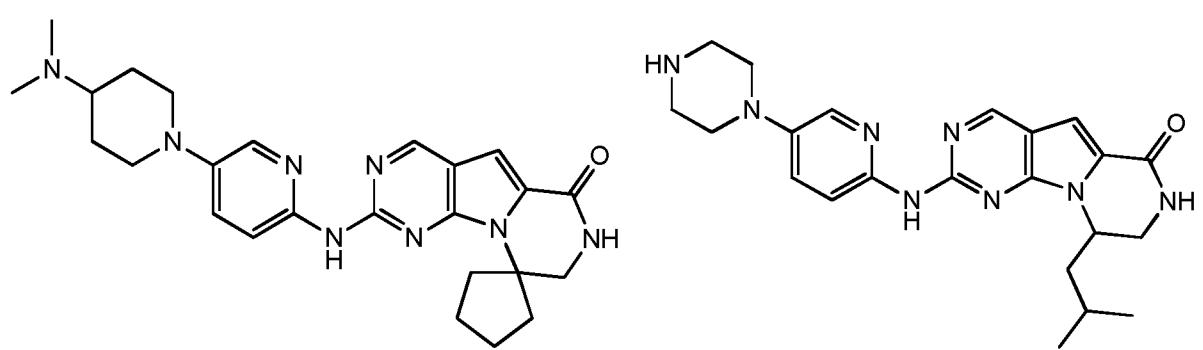
14. The compound of claim 1 selected from the structures:

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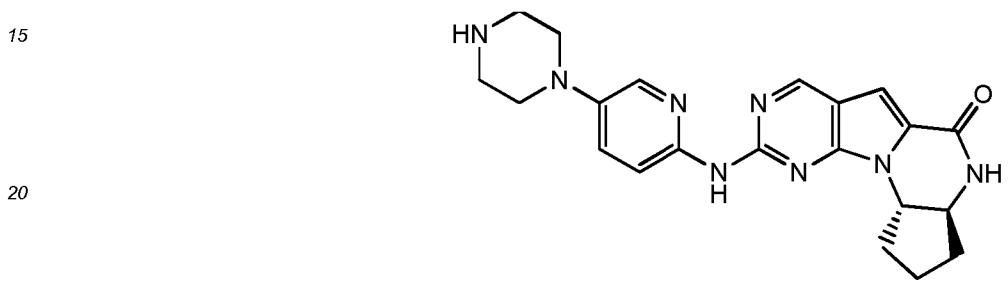
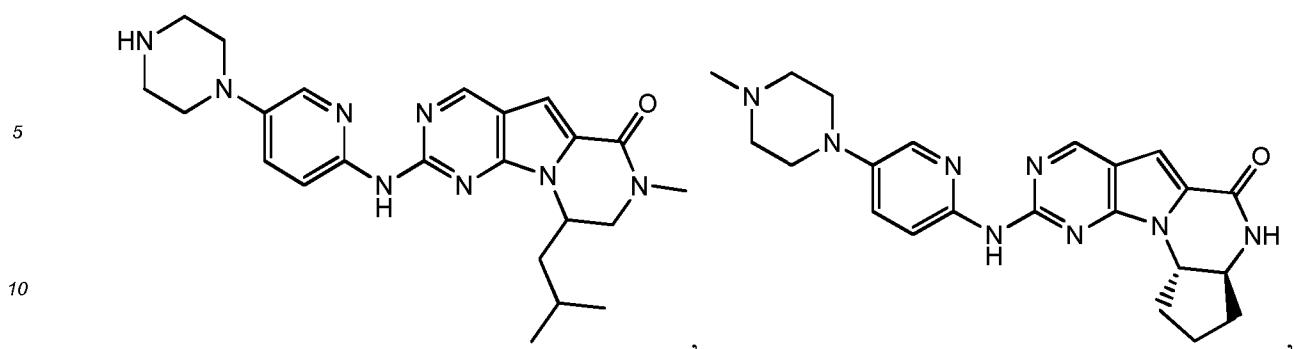
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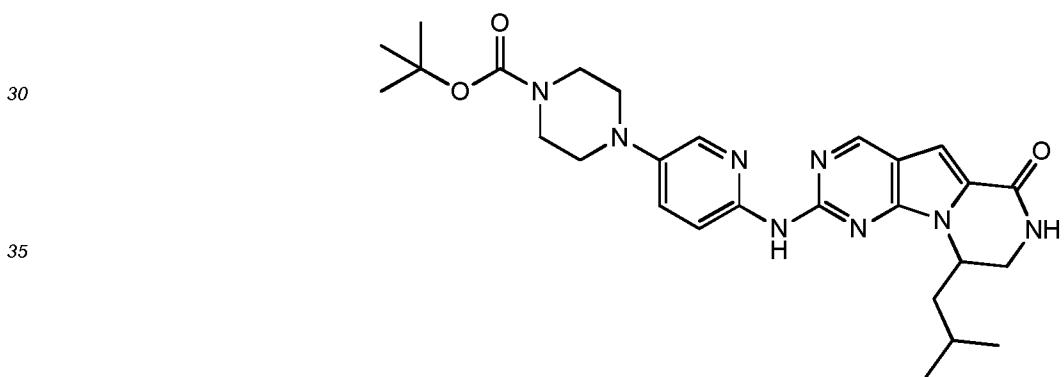
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25 and

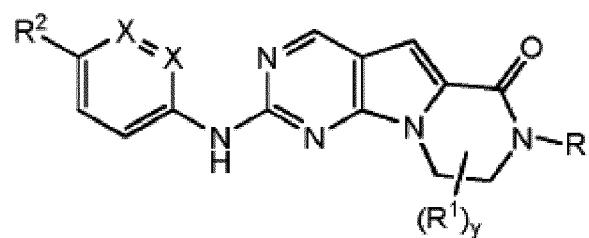


45 15. A compound of any one of claims 1 to 14, wherein the compound or pharmaceutically acceptable salt thereof is in the form of a solid, semi-solid, or liquid dosage form.

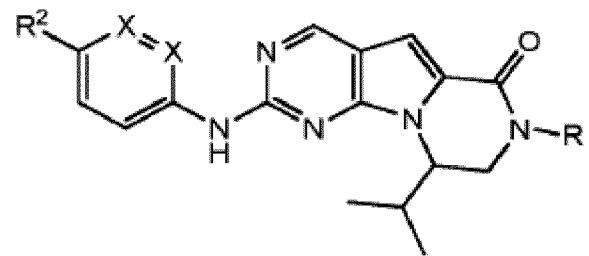
16. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

Patentansprüche

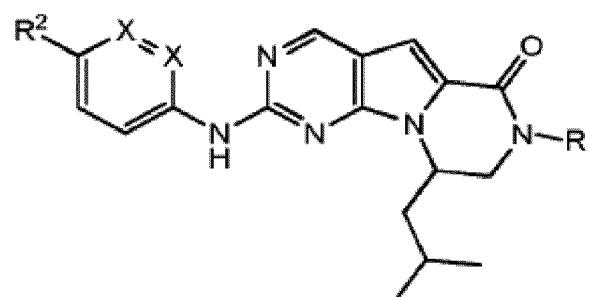
50 1. Verbindung der Formel Ia:



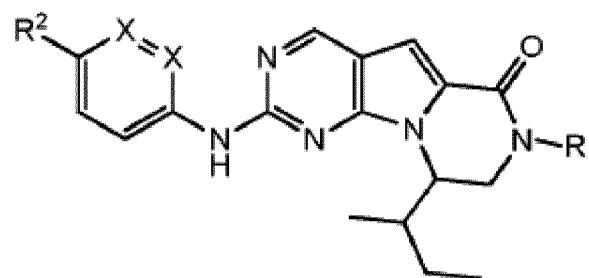
10 oder der Formel Ib:



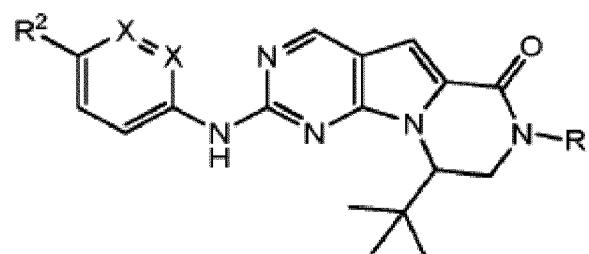
oder der Formel Ic:



35 oder der Formel Id:

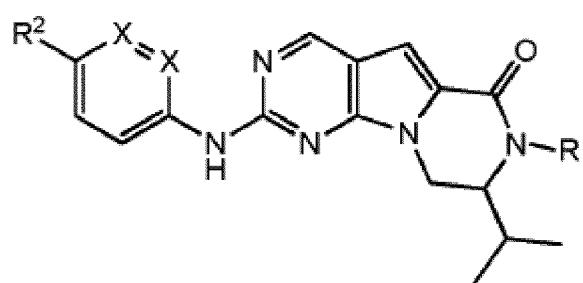


oder der Formel Ie:



oder der Formel If:

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oder der Formel Ig:

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oder der Formel Ih:

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oder der Formel II:

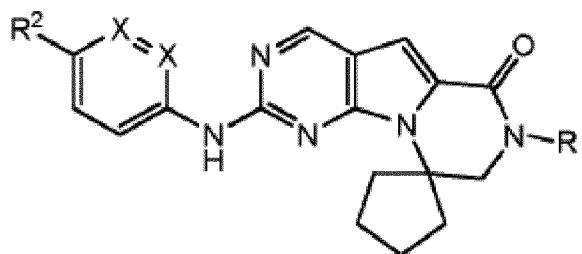
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oder der Formel Ij:

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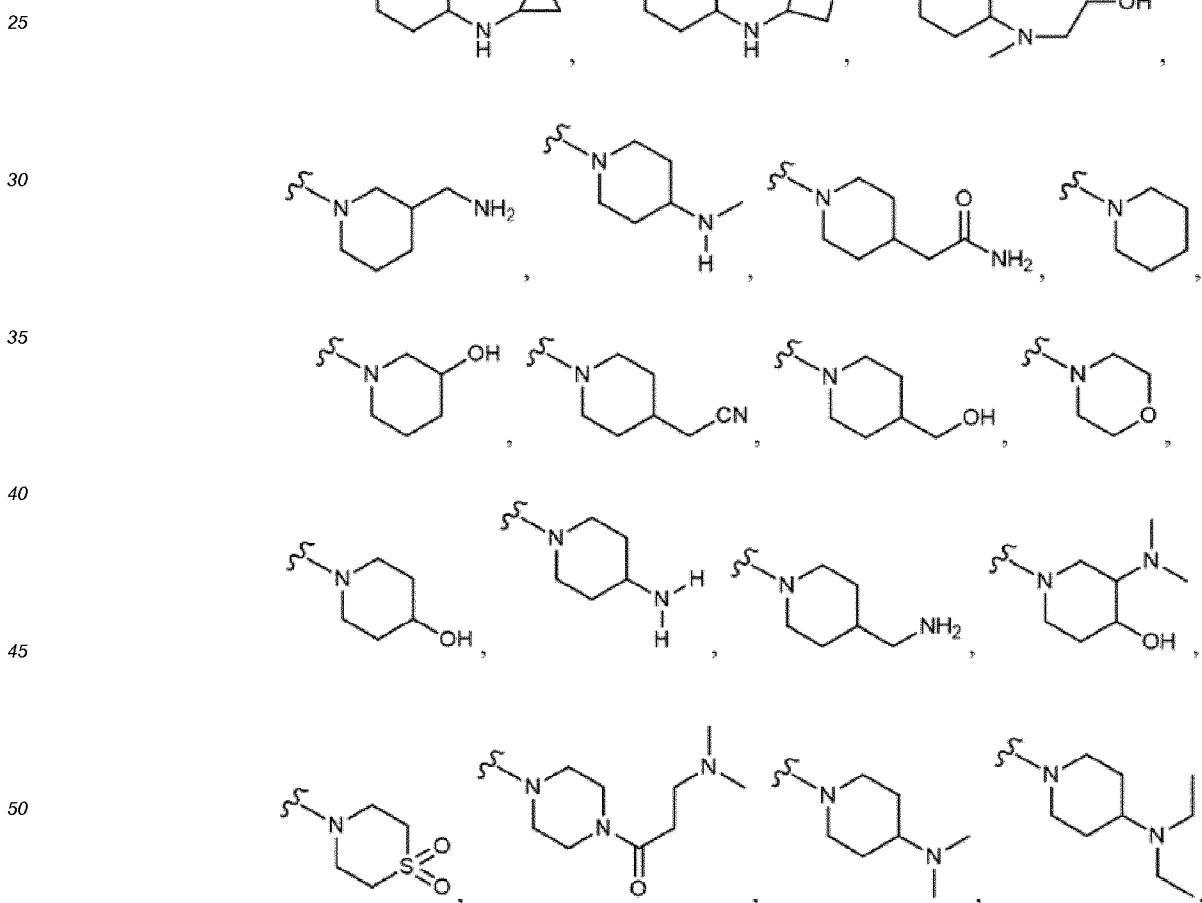
10

oder ein pharmazeutisch unbedenkliches Salz davon,

wobei R für H, C₁-C₃-Alkyl oder Halogenalkyl steht,

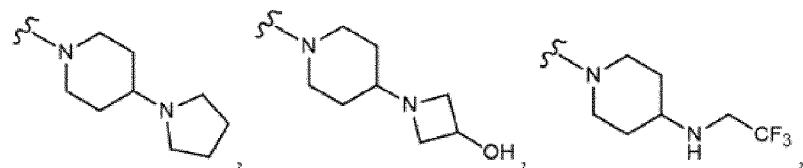
15 R¹ jeweils unabhängig für Aryl, Alkyl, Cycloalkyl oder Halogenalkyl steht, wobei die Alkyl-, Cycloalkyl- und Halogenalkylgruppen gegebenenfalls O- oder N-Heteroatome anstelle eines Kohlenstoffs in der Kette enthalten und zwei R¹-Reste an benachbarten Ringatomen oder am gleichen Ringatom zusammen mit den Ringatomen/dem Ringatom, an die/das sie gebunden sind, einen 3- bis 8-gliedrigen Cyclus bilden, y für 0, 1, 2, 3 oder 4 steht,

20 X jeweils unabhängig für CH oder N steht und
R² aus den folgenden Strukturen ausgewählt ist:

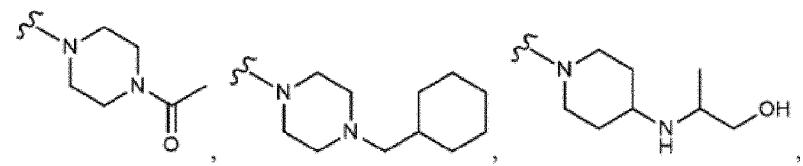


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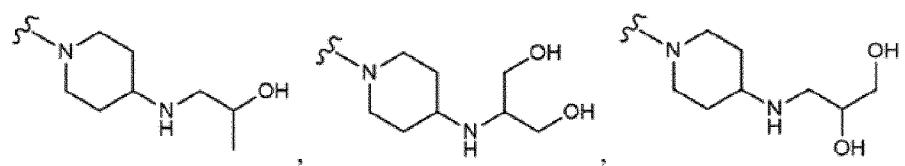
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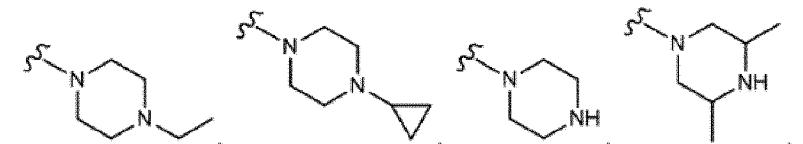


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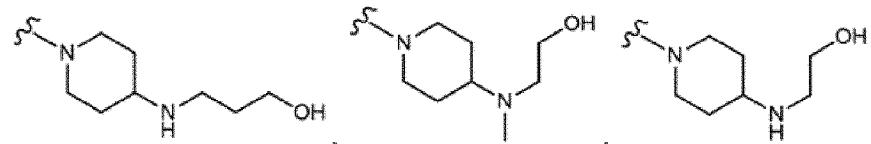


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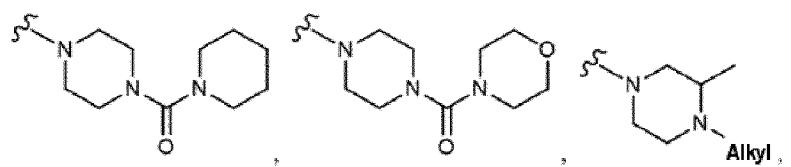
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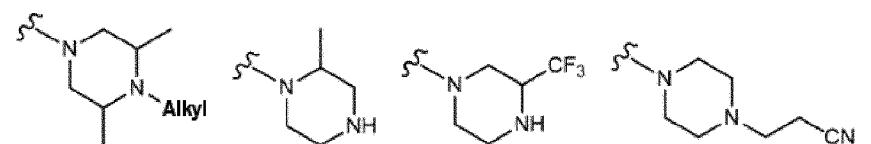


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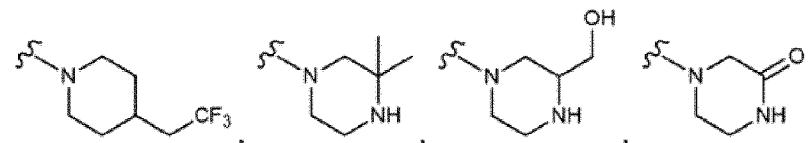


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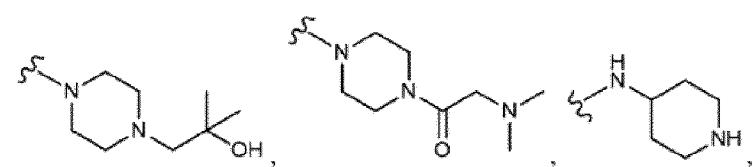
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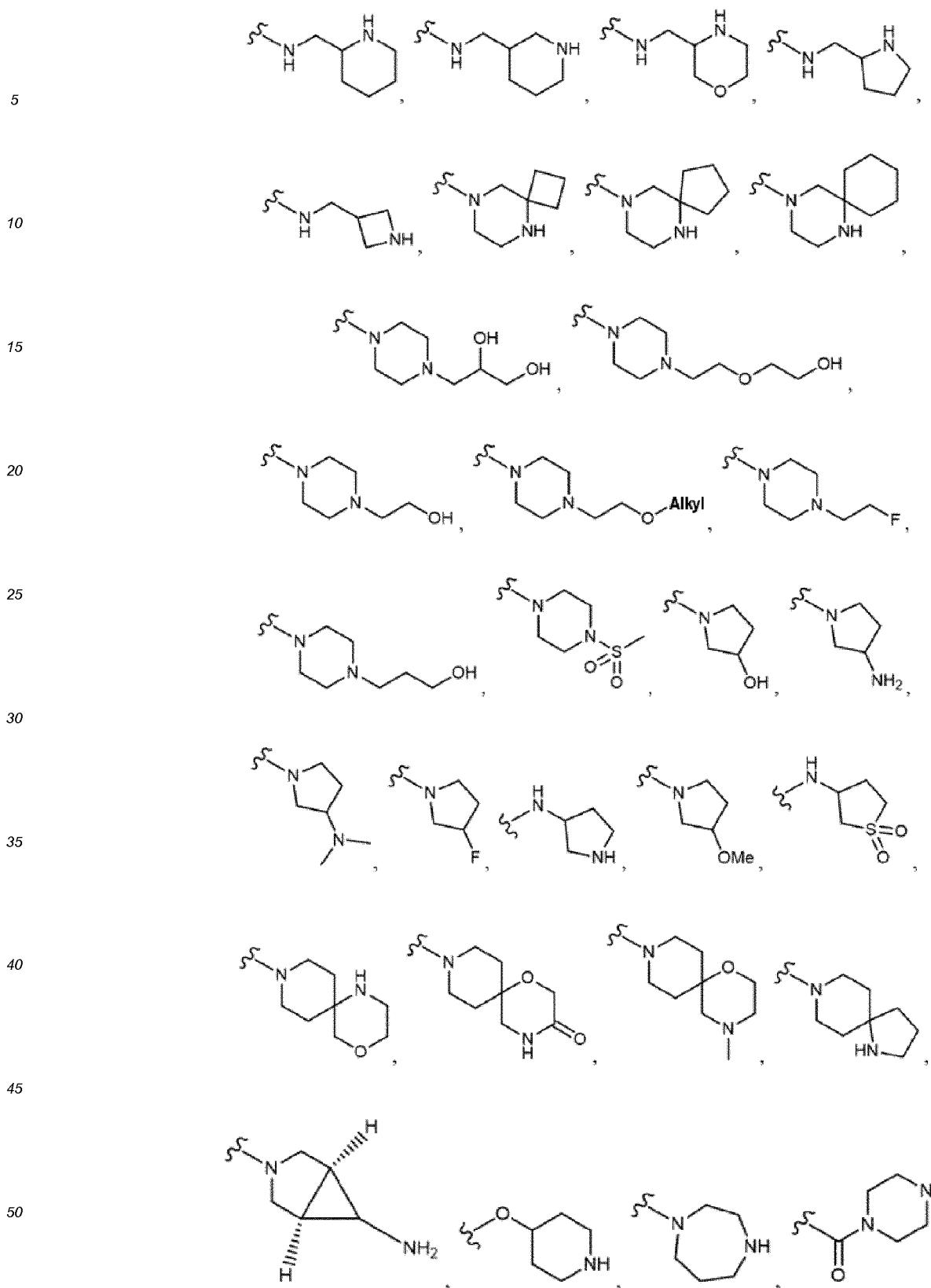


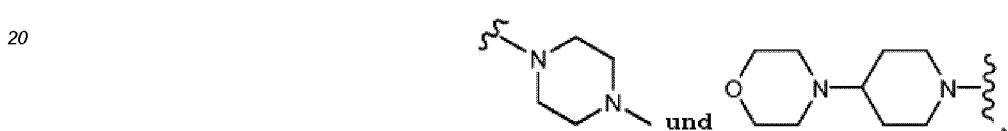
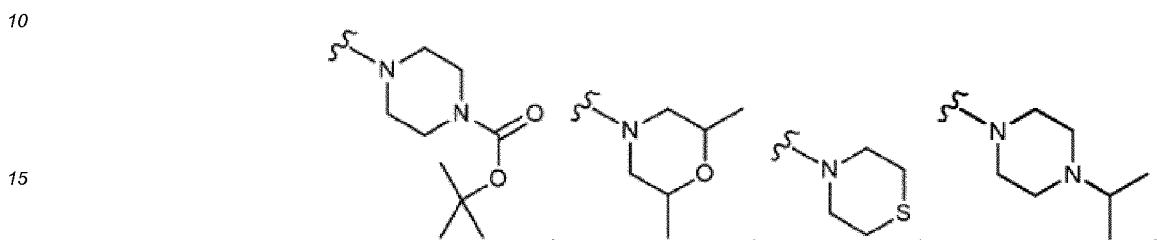
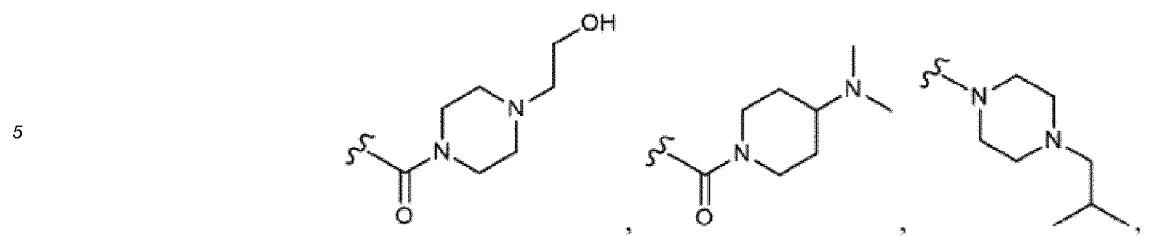
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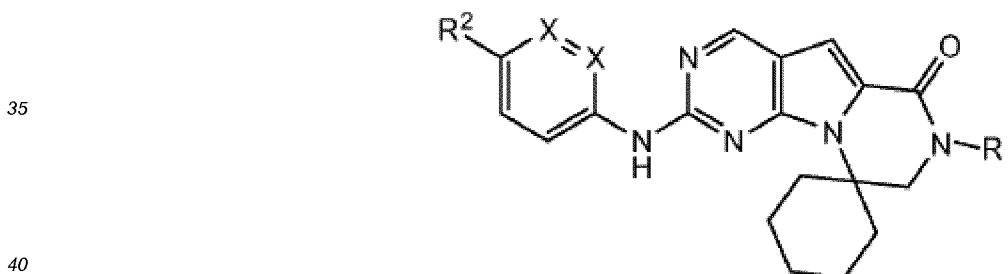






25 wobei der Begriff "Aryl" alleine oder in Kombination ein carbocyclisches aromatisches System mit einem oder zwei Ringen bedeutet, wobei solche Ringe miteinander kondensiert sein können und wobei Aryl jeweils einen oder mehrere unabhängig voneinander aus C₁-C₆-Alkyl, Hydroxy, Halogen, Halogenalkyl, Nitro, Cyano, Alkoxy und C₁-C₆-Alkylamino ausgewählte Substituenten aufweisen kann.

30 2. Verbindung nach Anspruch 1 mit der Formel II:



oder ein pharmazeutisch unbedenkliches Salz davon.

45

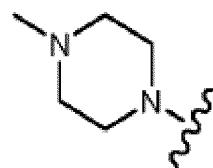
3. Verbindung nach Anspruch 1 oder 2, wobei beide X für N stehen.
4. Verbindung nach einem der vorhergehenden Ansprüche, wobei R für Wasserstoff oder C₁-C₃-Alkyl steht.
5. Verbindung nach einem der Ansprüche 1 bis 4, wobei R² für:

50 (a)



oder
(b)

5



10

oder
(c)

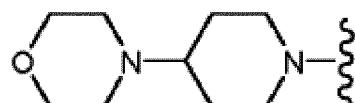
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oder
(d)

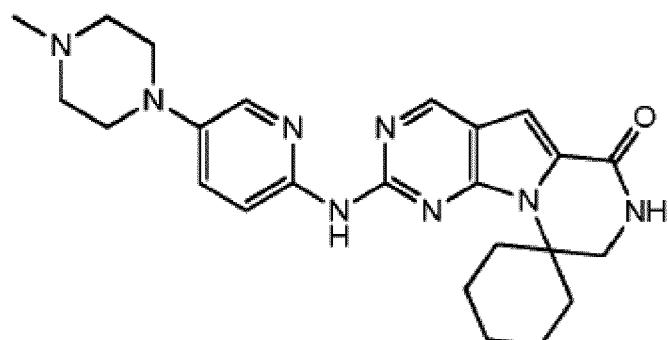
25



steht.

6. Verbindung nach Anspruch 1 oder 2 mit der Formel:

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oder ein pharmazeutisch unbedenkliches Salz davon.

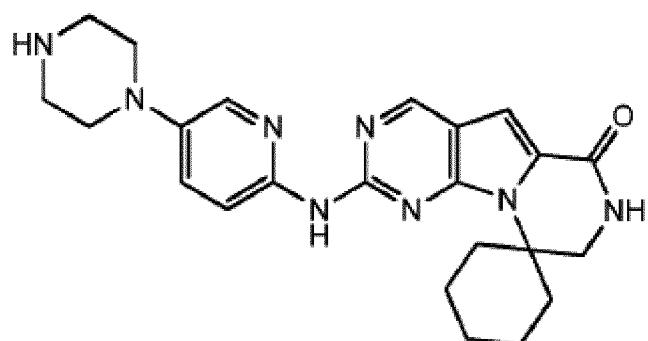
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7. Verbindung nach Anspruch 1 oder 2 mit der Formel:

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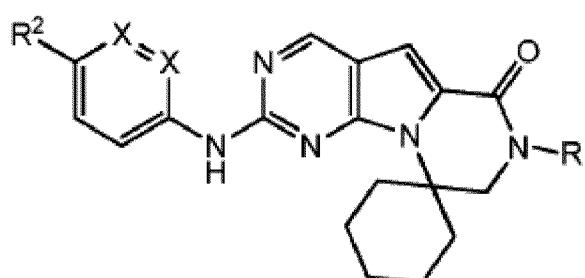
10

oder ein pharmazeutisch unbedenkliches Salz davon.

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8. Verbindung nach Anspruch 1 oder 2 mit der Formel II:

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wobei R für H steht,

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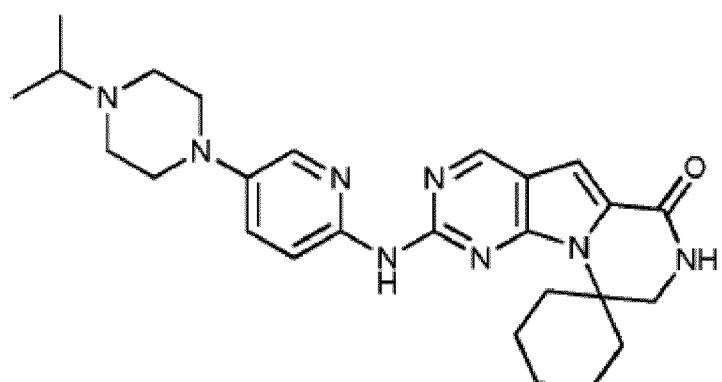
oder ein pharmazeutisch unbedenkliches Salz davon.

9. Verbindung nach Anspruch 8 mit der Formel:

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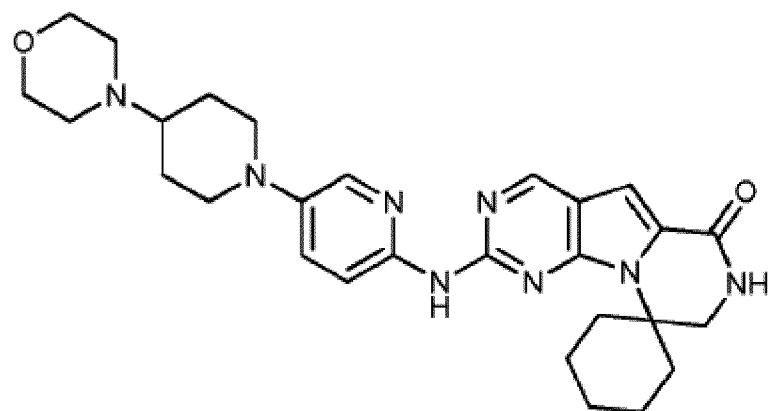


oder ein pharmazeutisch unbedenkliches Salz davon.

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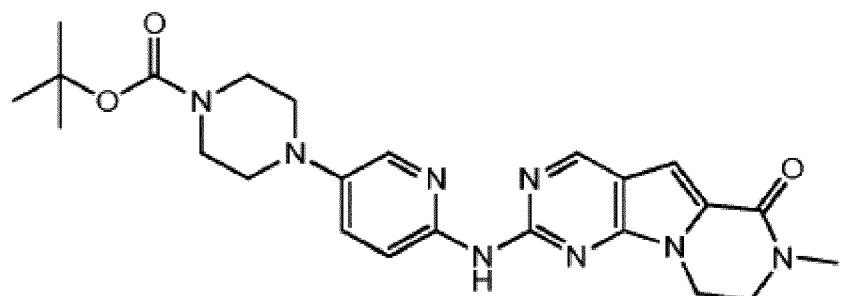
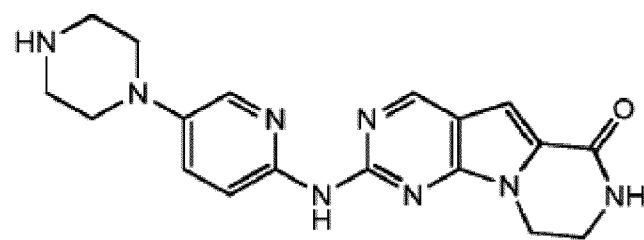
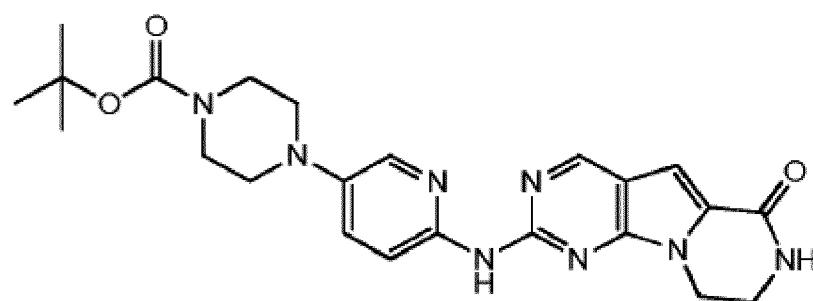
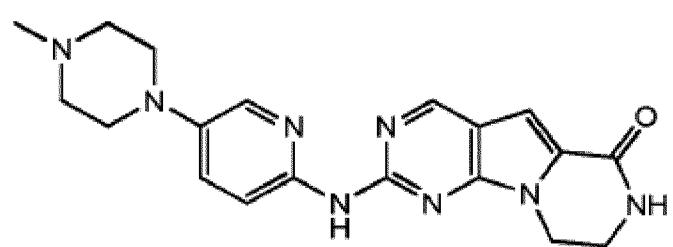
10. Verbindung nach Anspruch 8 mit der Formel:

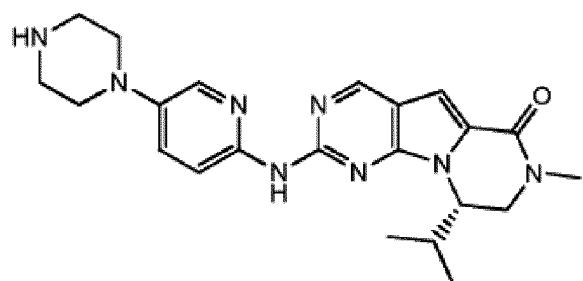
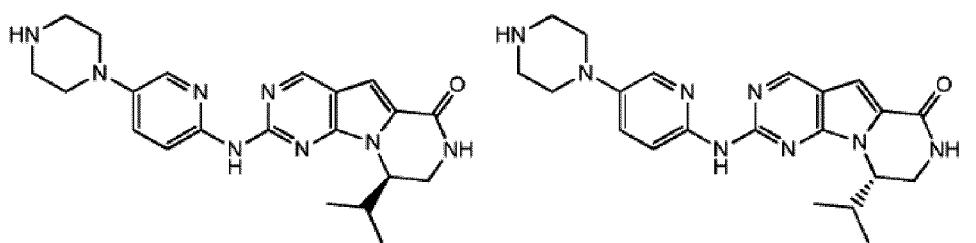
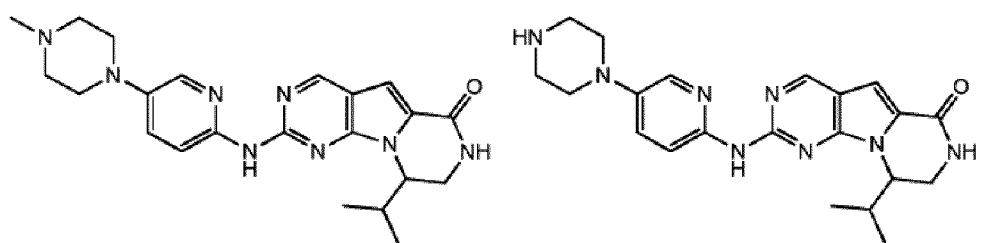
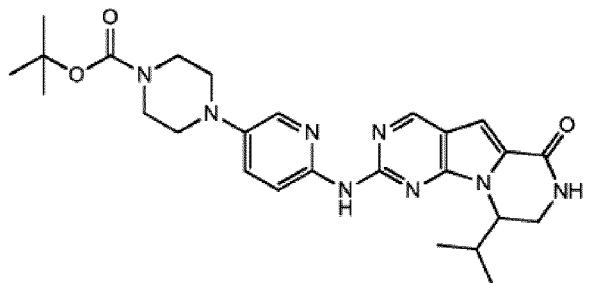
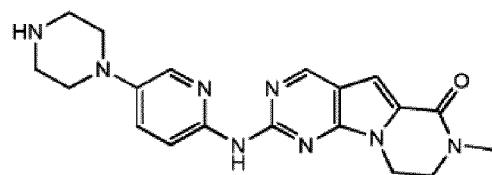
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oder ein pharmazeutisch unbedenkliches Salz davon.

11. Verbindung nach Anspruch 1, ausgewählt aus den Strukturen:



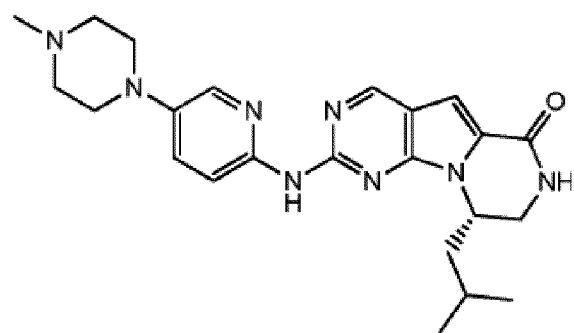


und

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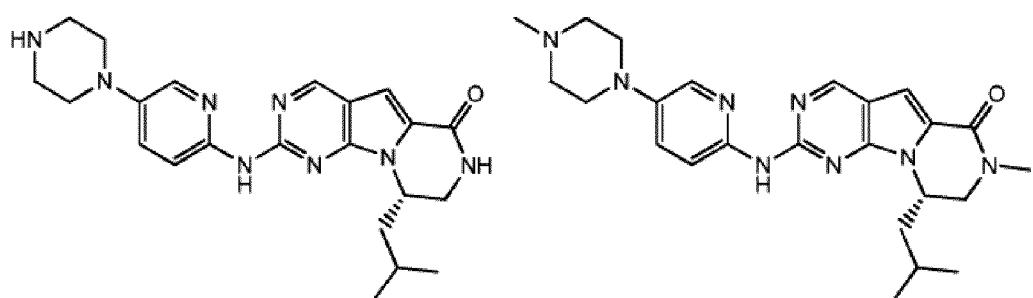
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12. Verbindung nach Anspruch 1, ausgewählt aus den Strukturen:

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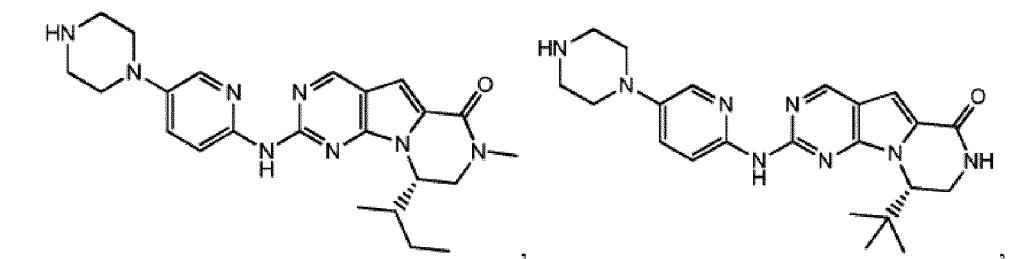
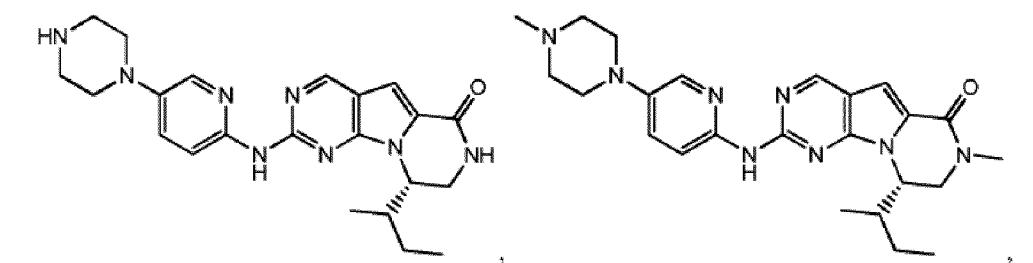
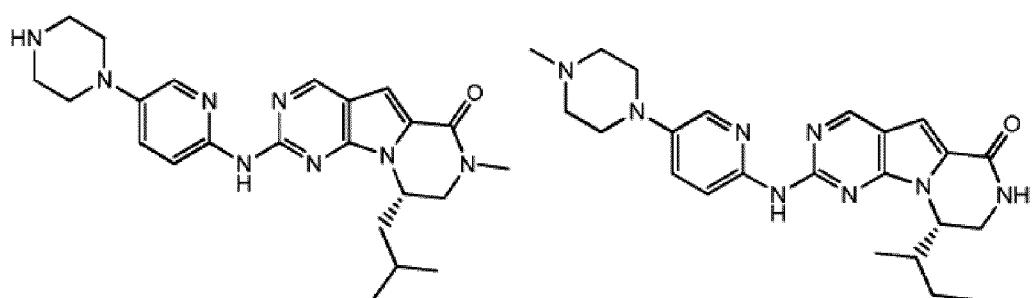
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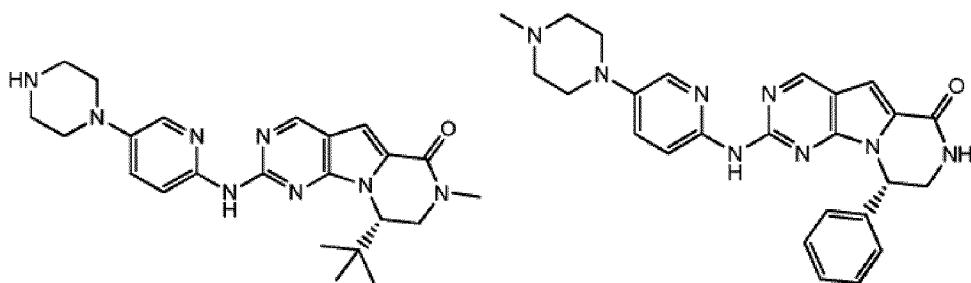
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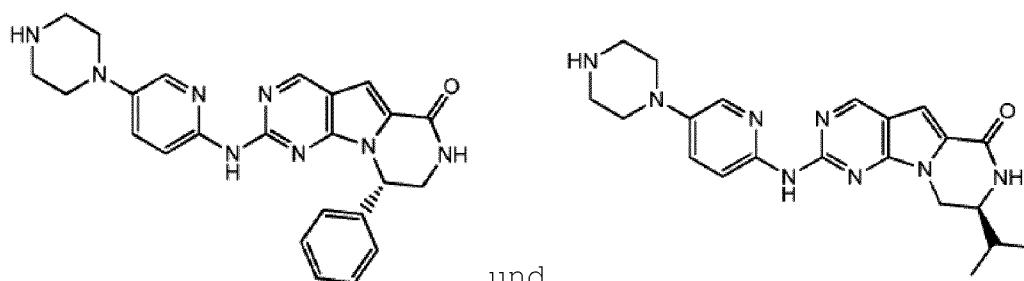


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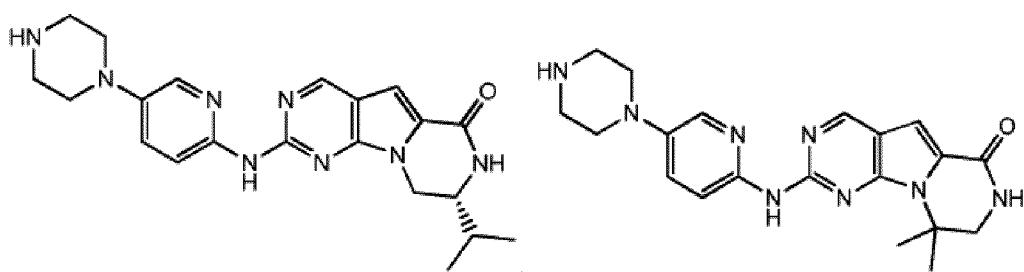


20

und

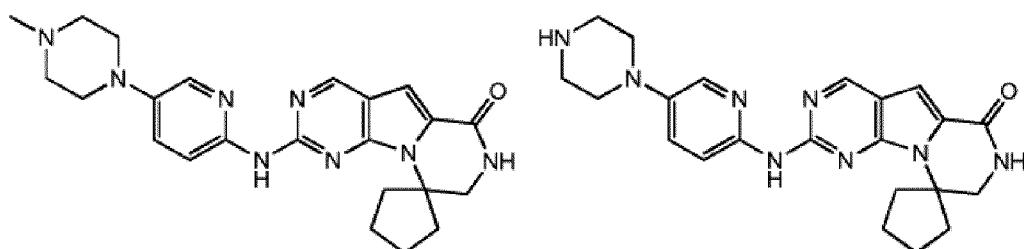
13. Verbindung nach Anspruch 1, ausgewählt aus den Strukturen:

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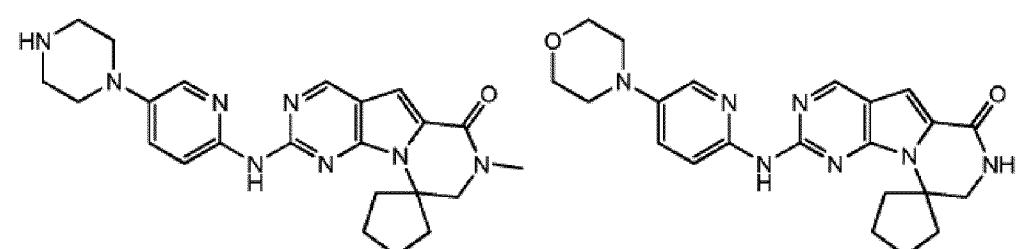
35



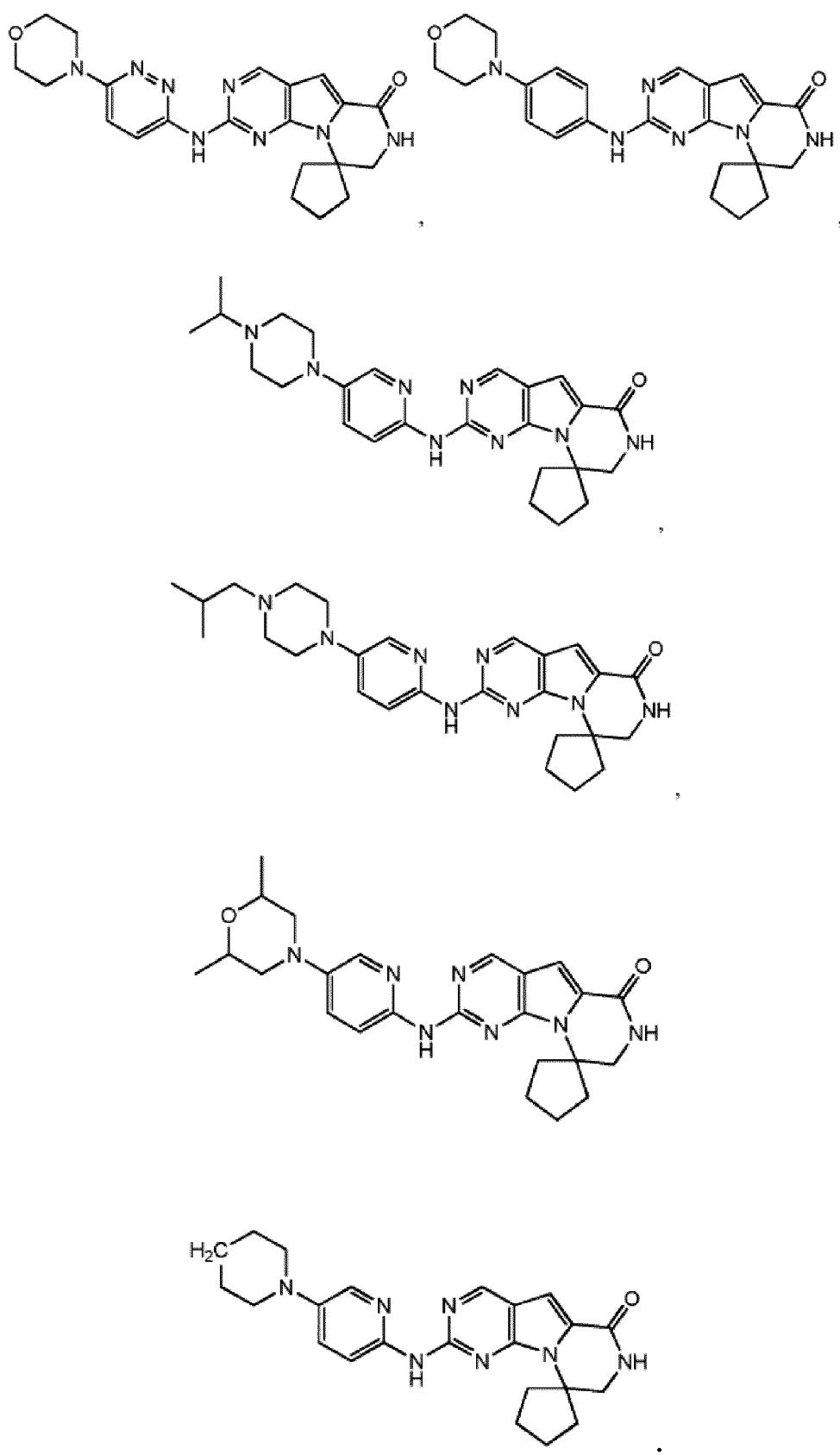
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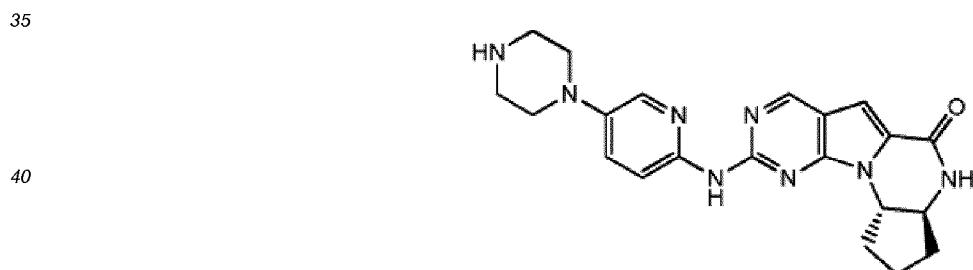
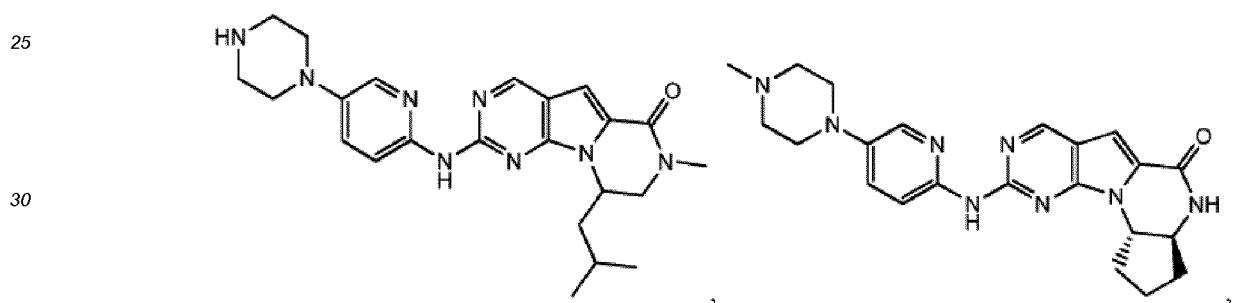
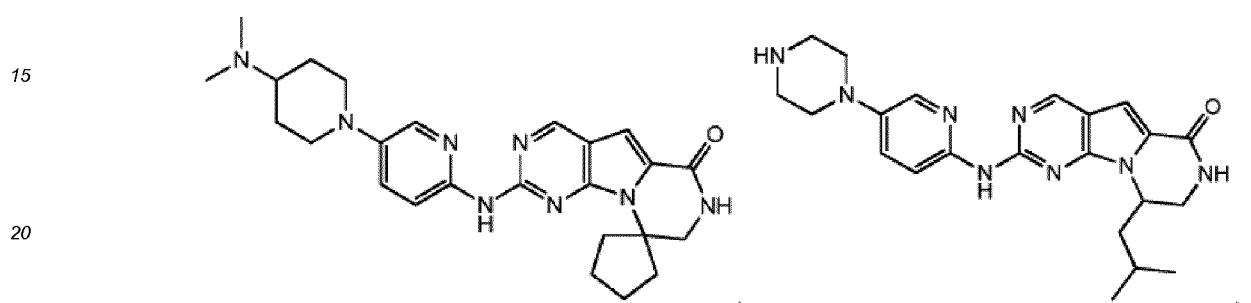
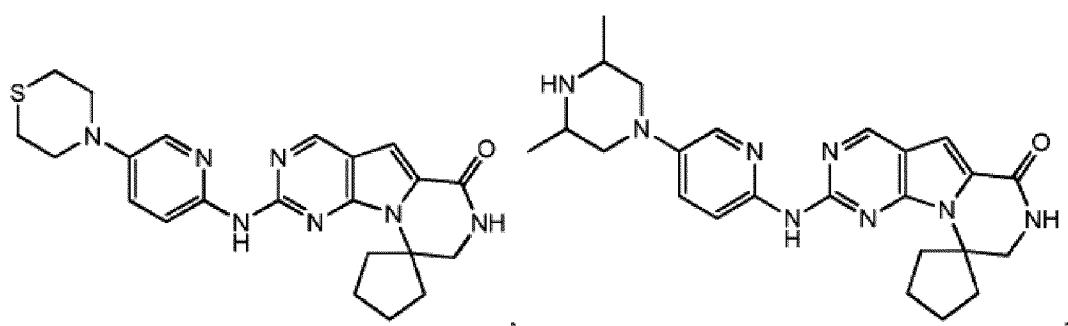
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14. Verbindung nach Anspruch 1, ausgewählt aus den Strukturen:

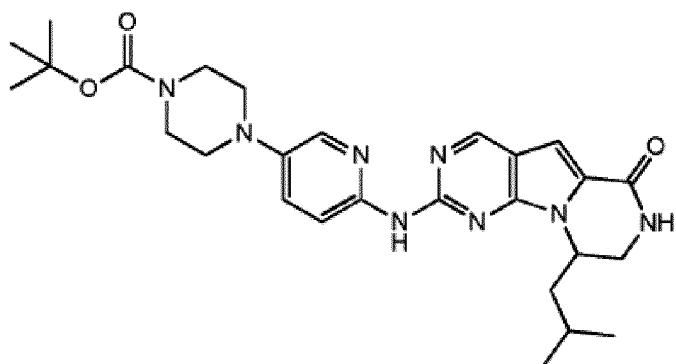


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15 15. Verbindung nach einem der Ansprüche 1 bis 14, wobei die Verbindung oder das pharmazeutisch unbedenkliche Salz davon in Form einer festen, halbfesten oder flüssigen Dosierungsform vorliegt.

16. Pharmazeutische Zusammensetzung, umfassend eine wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 14 oder ein pharmazeutisch unbedenkliches Salz davon.

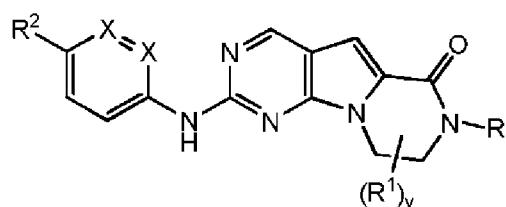
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Revendications

1. Composé ayant la formule Ia :

25

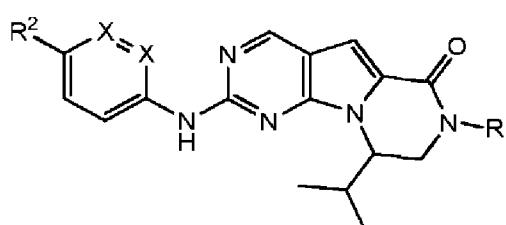
30



ou ayant la formule Ib :

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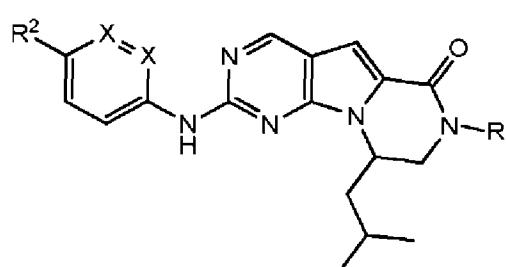


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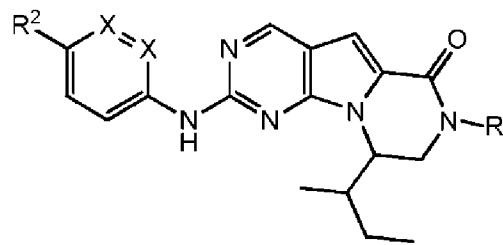
ou ayant la formule Ic :

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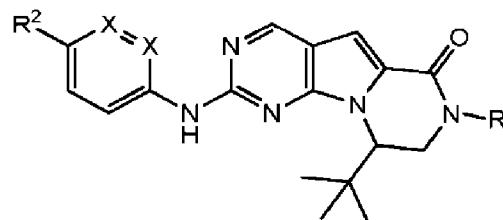
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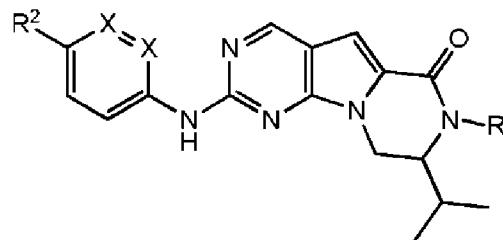
ou ayant la formule Id :



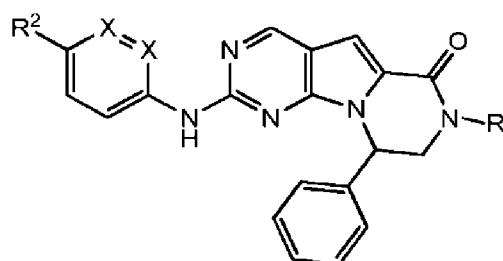
10 ou ayant la formule le :



20 ou ayant la formule lf :

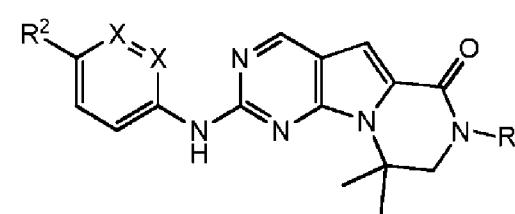


30 ou ayant la formule lg :

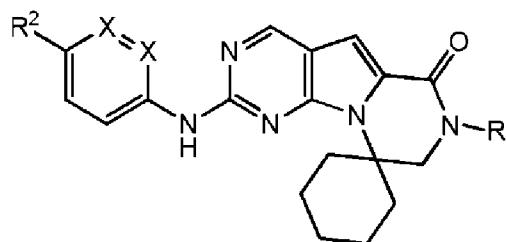


40 ou ayant la formule lh :

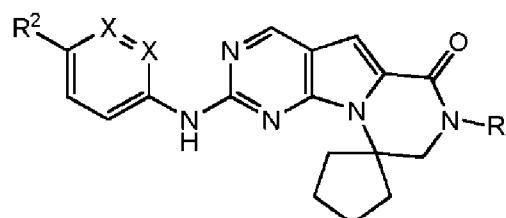
45



55 ou ayant la formule li :



10 ou ayant la formule Ij :



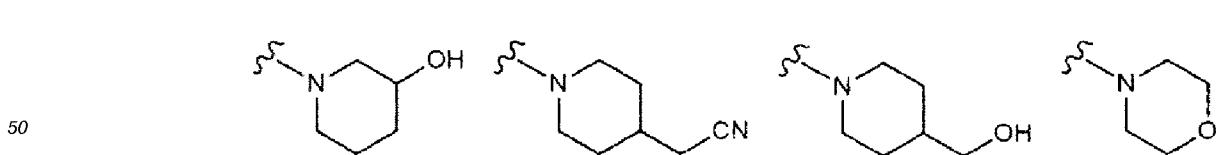
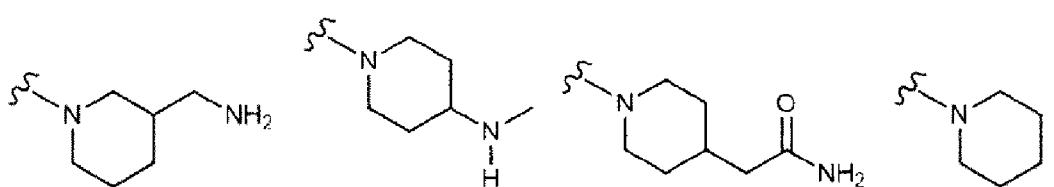
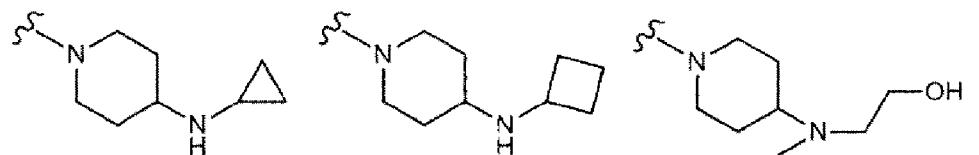
20 ou un sel pharmaceutiquement acceptable de celui-ci

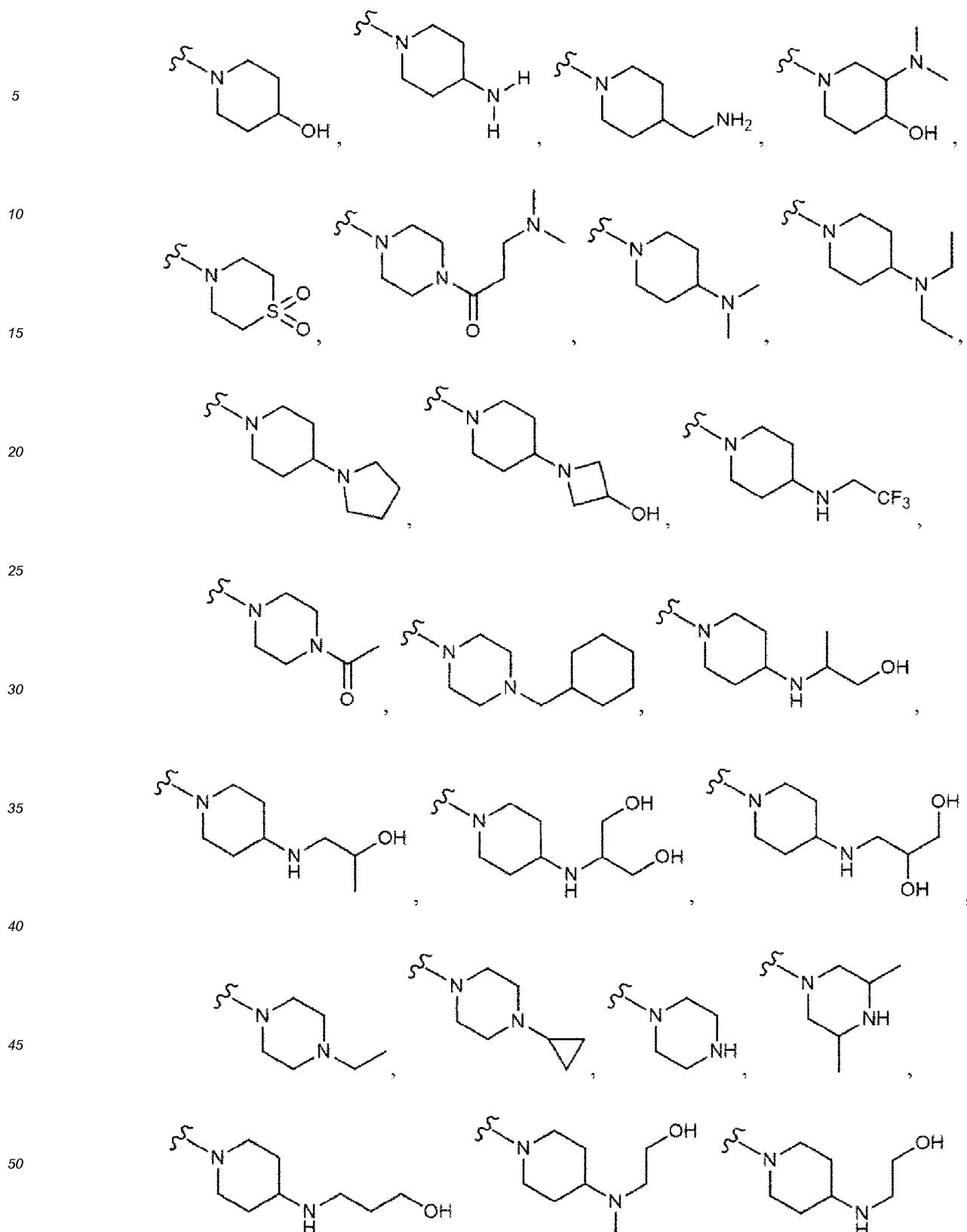
25 dans lequel R est H, alkyle ou halogénoalkyle en C₁-C₃ ; chaque R¹ est indépendamment aryle, alkyle, cycloalkyle ou halogénoalkyle, où chacun desdits groupes alkyle, cycloalkyle et halogénoalkyle comprend facultativement des hétéroatomes O ou N à la place d'un carbone dans la chaîne et deux R¹ sur des atomes cycliques adjacents ou sur le même atome cyclique conjointement avec le(s) atome(s) cyclique(s) auxquels ils sont liés forment facultativement un cycle de 3 à 8 chaînons ;

30 y est 0, 1, 2, 3 ou 4 ;

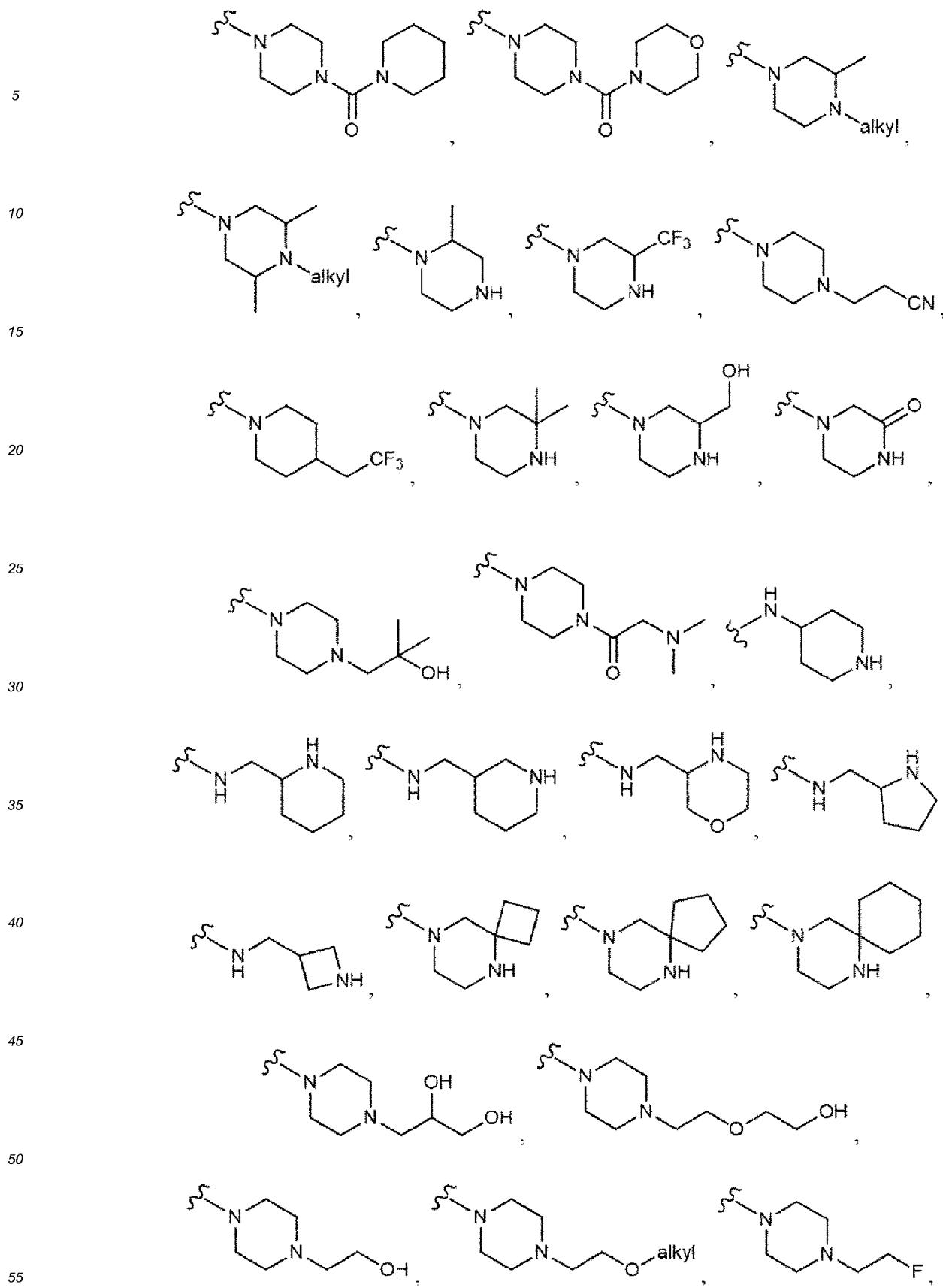
chaque X est indépendamment CH ou N ; et

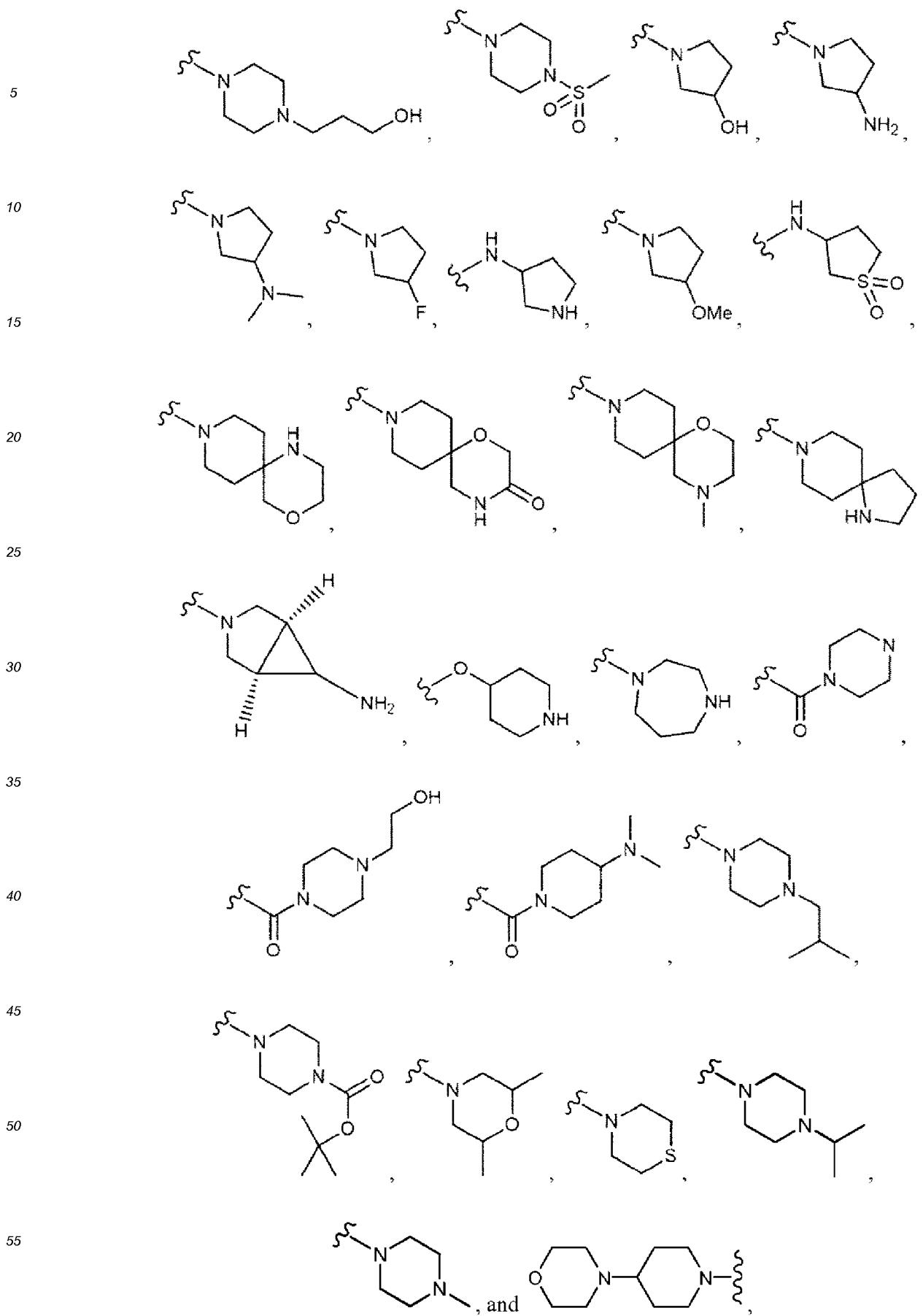
R² est choisi parmi les structures :





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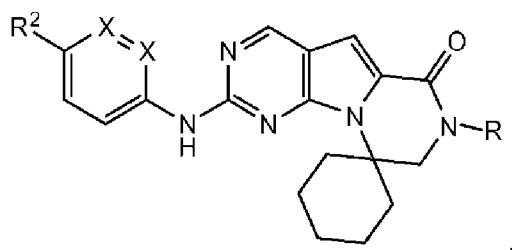


où le terme « aryle », seul ou en combinaison, désigne un système aromatique carbocyclique contenant un ou deux cycles où de tels cycles peuvent être liés conjointement d'une manière condensée et où un aryle quelconque peut avoir 1 ou plusieurs substituants indépendamment choisis parmi alkyle en C₁-C₆, hydroxyle, halogéno, halogénoalkyle, nitro, cyano, alcoxy et (alkyle en C₁-C₆)amino.

5

2. Composé de la revendication 1 ayant la formule li :

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15

ou un sel pharmaceutiquement acceptable de celui-ci.

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3. Composé de la revendication 1 ou 2 dans lequel X sont tous deux N.

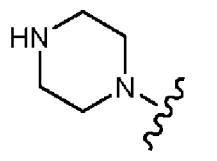
4. Composé de l'une quelconque des revendications précédentes dans lequel R est hydrogène ou alkyle en C₁-C₃.

5. Composé de l'une quelconque des revendications 1 à 4 dans lequel R² est :

25

(a)

30

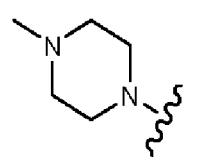


35

ou

(b)

40

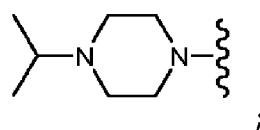


45

ou

(c)

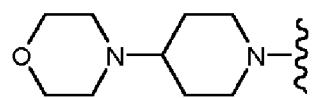
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55

ou

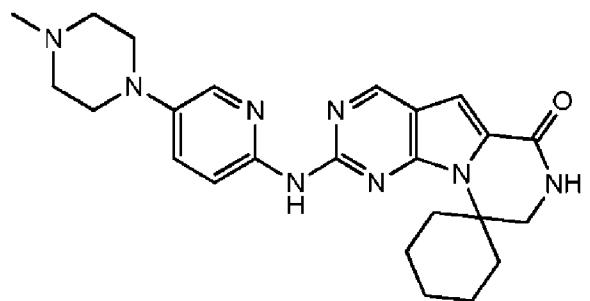
(d)



5

6. Composé des revendications 1 ou 2 ayant la formule :

10



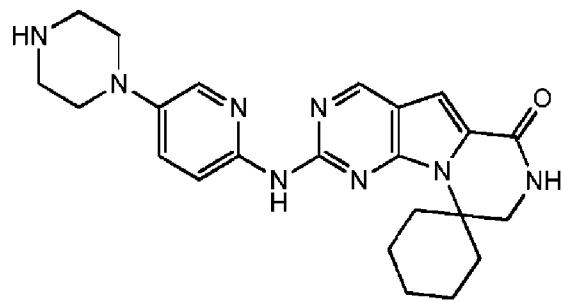
15

ou un sel pharmaceutiquement acceptable de celui-ci.

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7. Composé des revendications 1 ou 2 ayant la formule :

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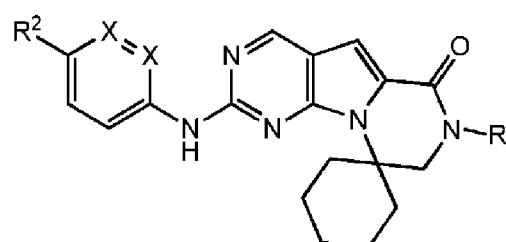
30

ou un sel pharmaceutiquement acceptable de celui-ci.

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8. Composé des revendications 1 ou 2 ayant la formule li :

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dans laquelle R est H

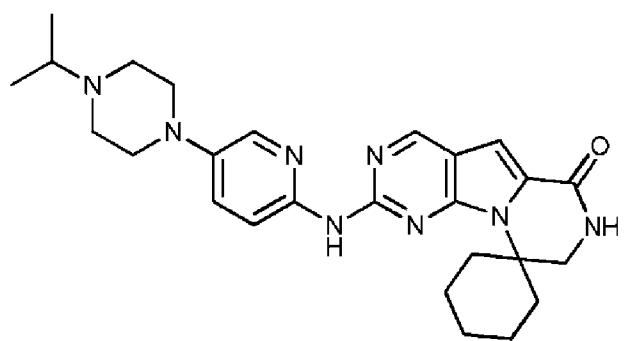
ou un sel pharmaceutiquement acceptable de celui-ci

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9. Composé de la revendication 8 ayant la formule :

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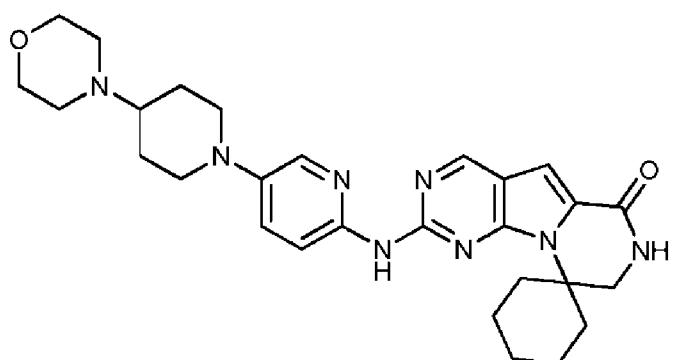
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ou un sel pharmaceutiquement acceptable de celui-ci.

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10. Composé de la revendication 8 ayant la formule :

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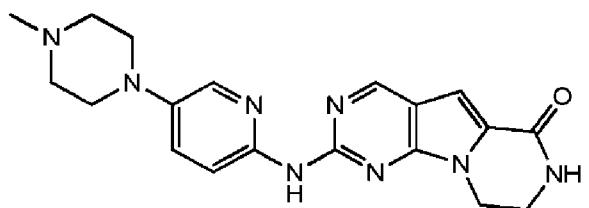
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ou un sel pharmaceutiquement acceptable de celui-ci.

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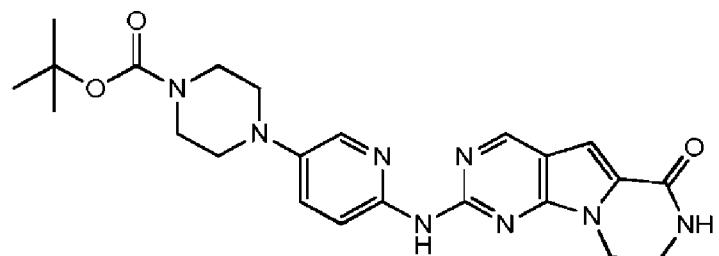
11. Composé de la revendication 1 choisi parmi les structures :

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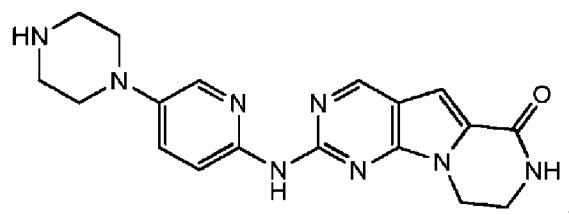
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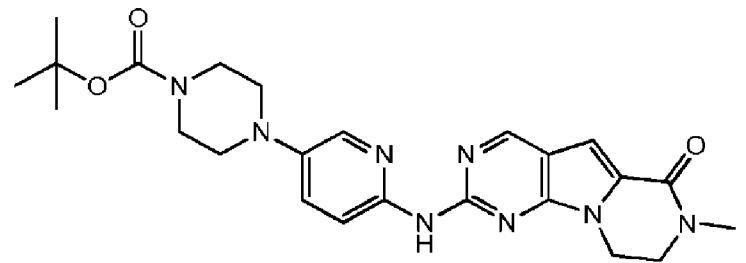
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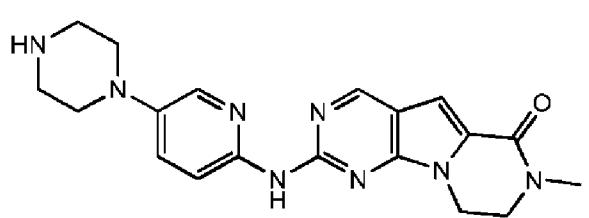
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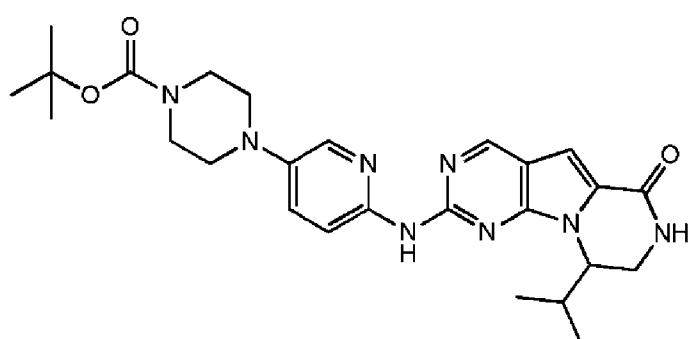
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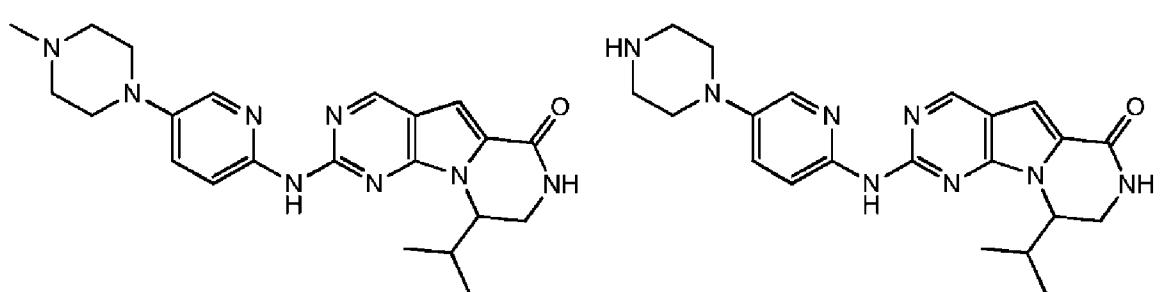
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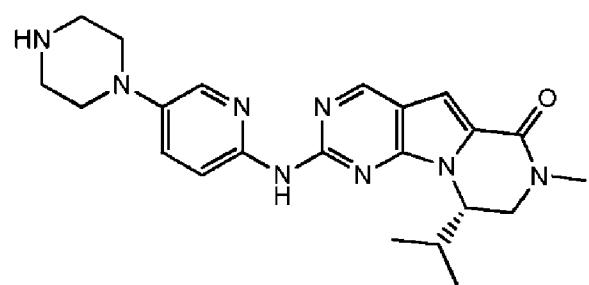
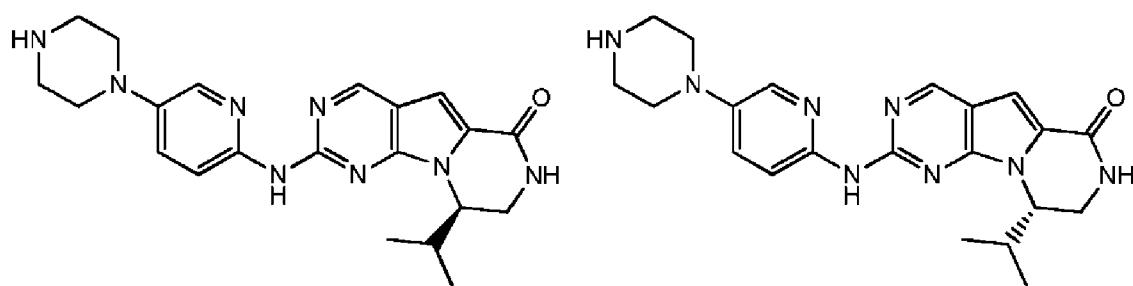
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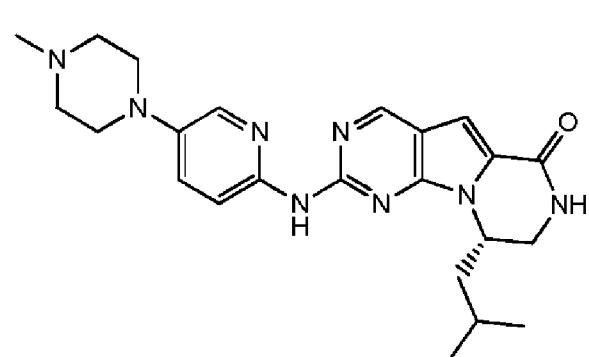


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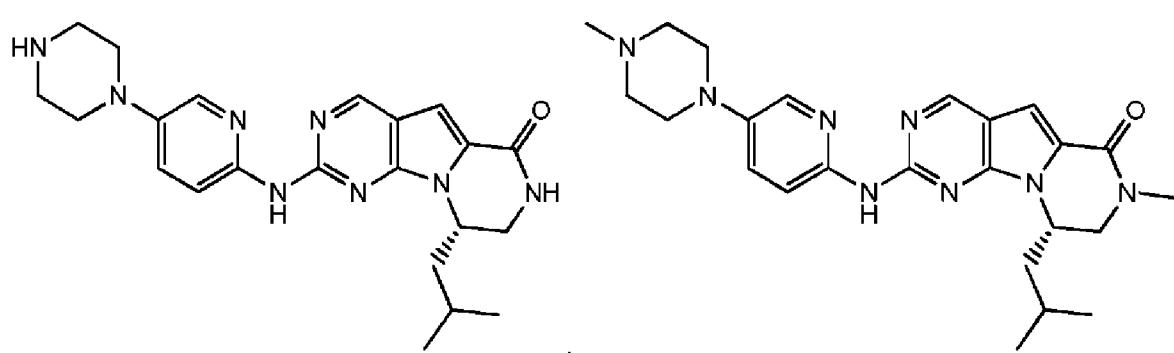
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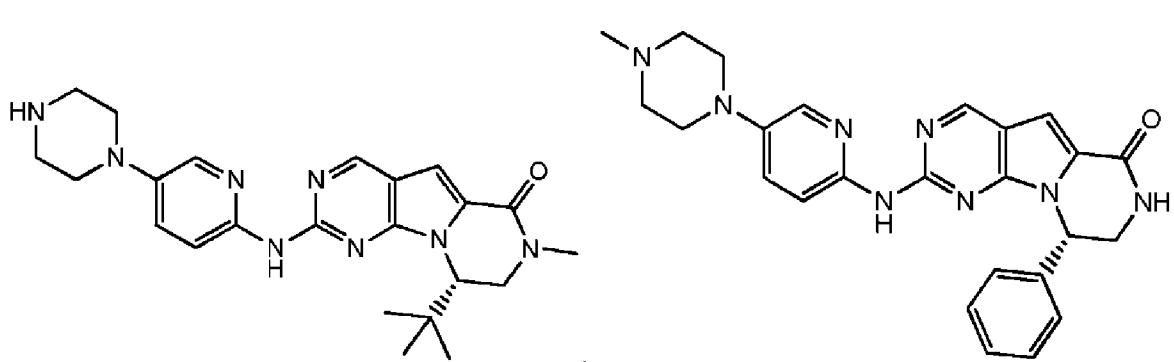
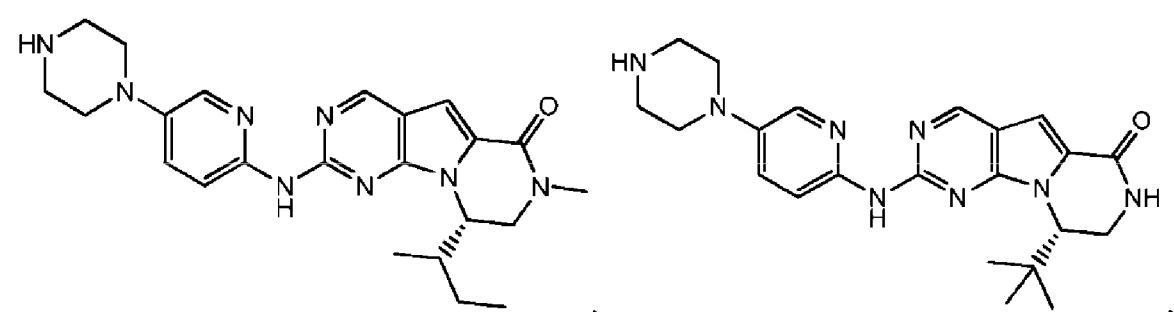
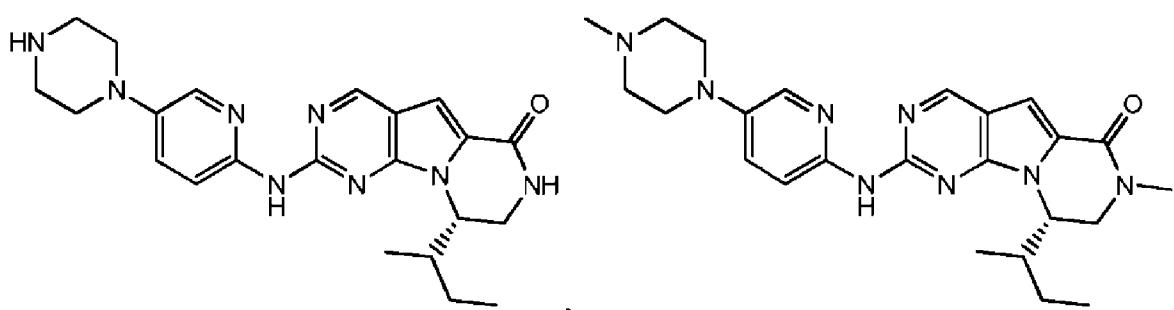
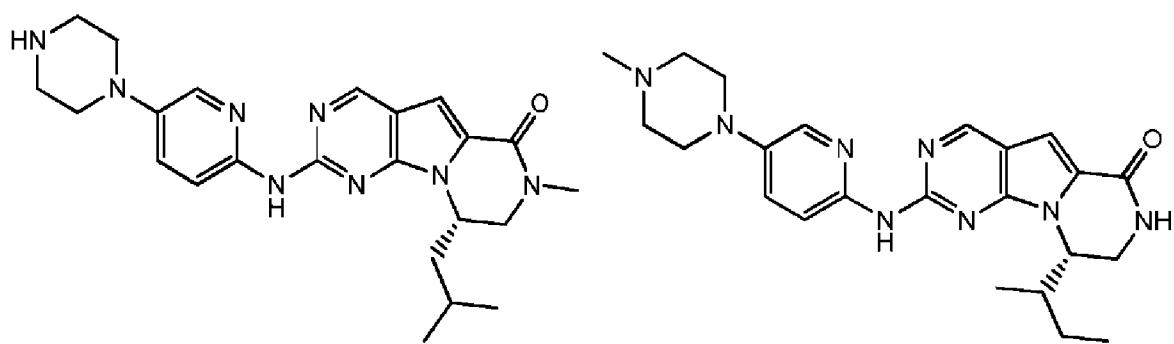
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12. Composé de la revendication 1 choisi parmi les structures :

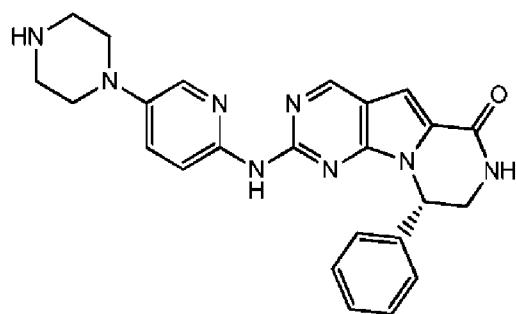


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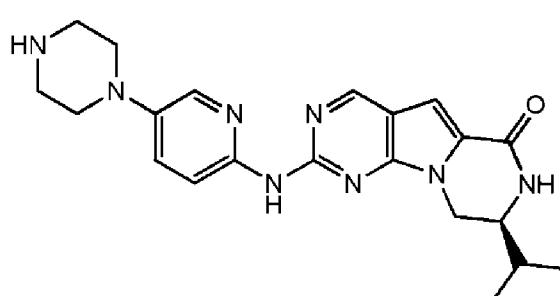


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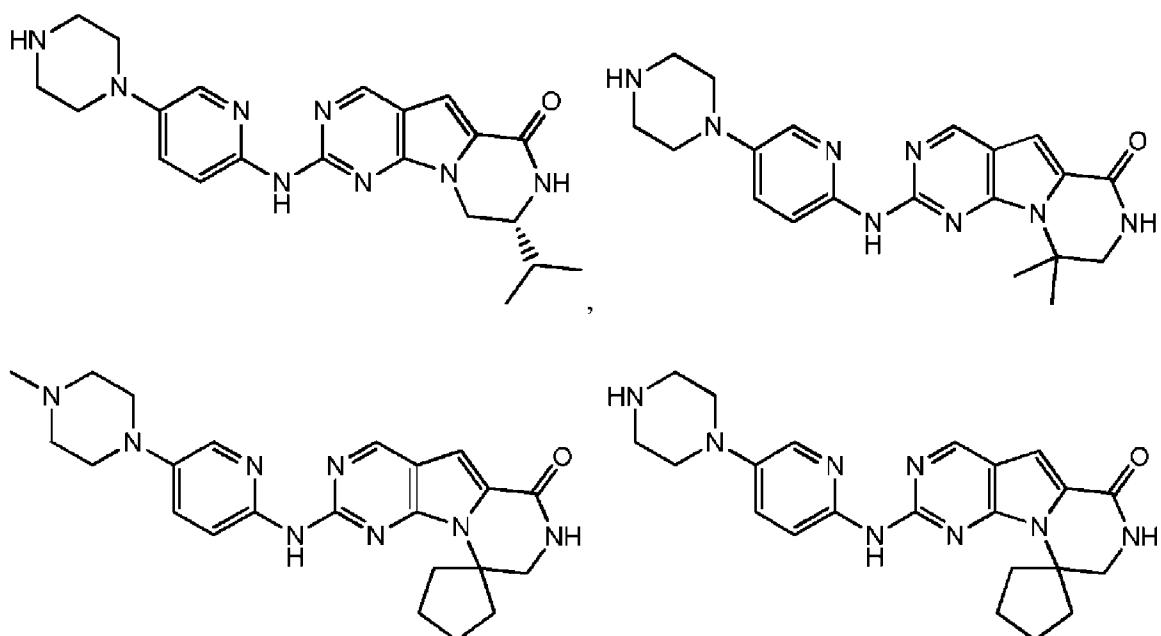
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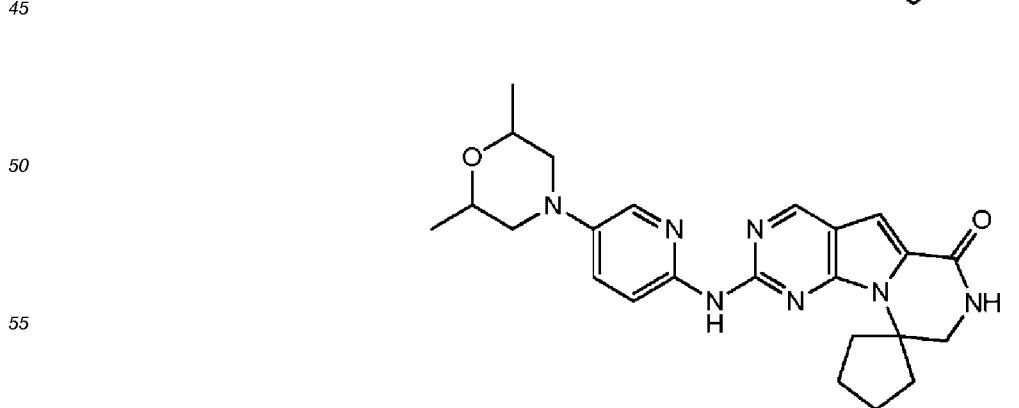
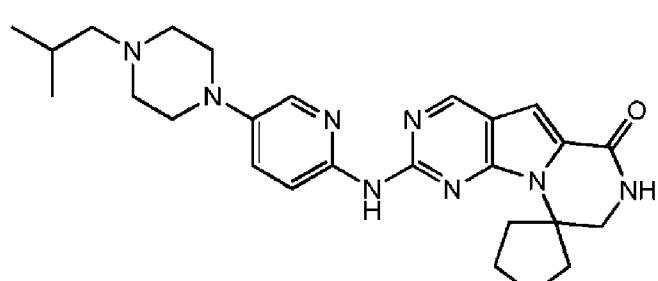
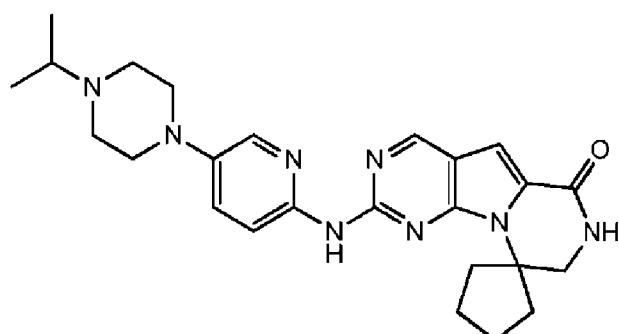
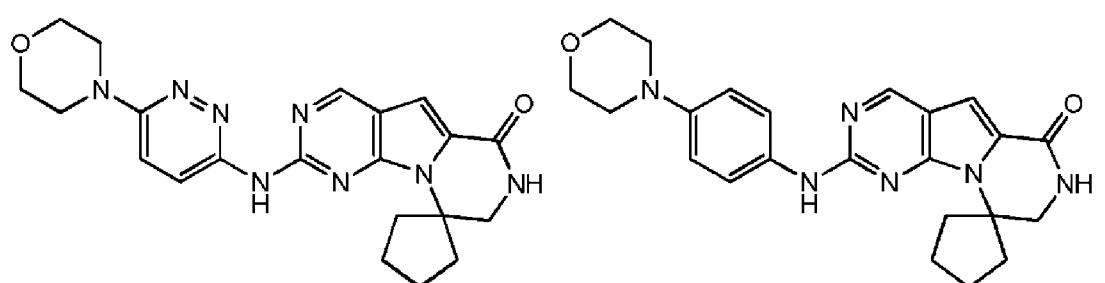
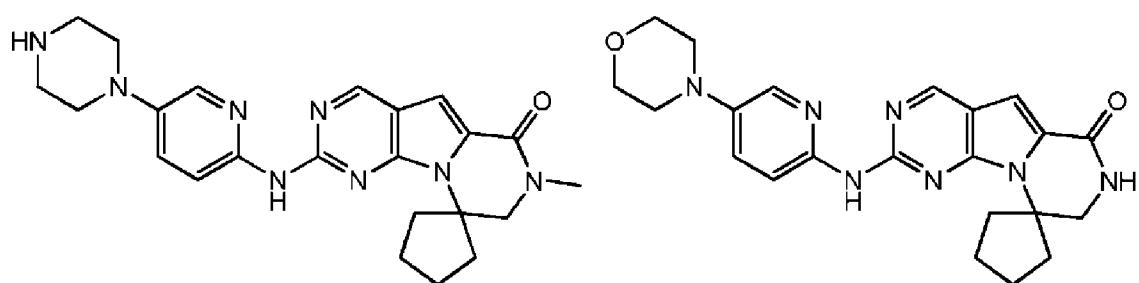


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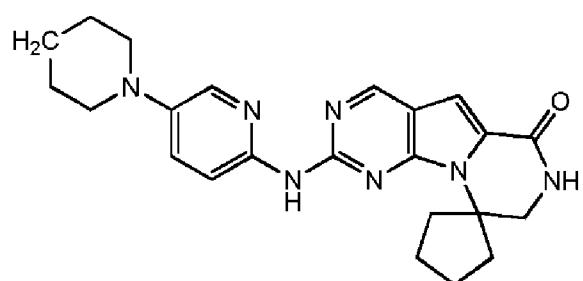
13. Composé de la revendication 1 choisi parmi les structures :





et

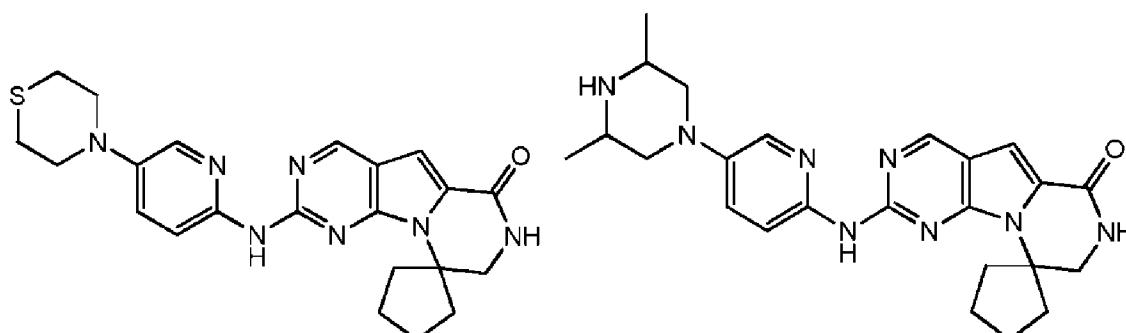
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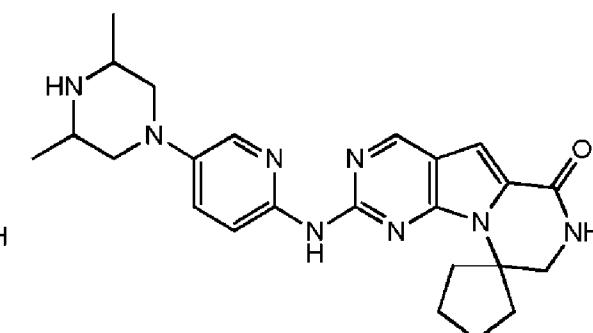
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14. Composé de la revendication 1 choisi parmi les structures :

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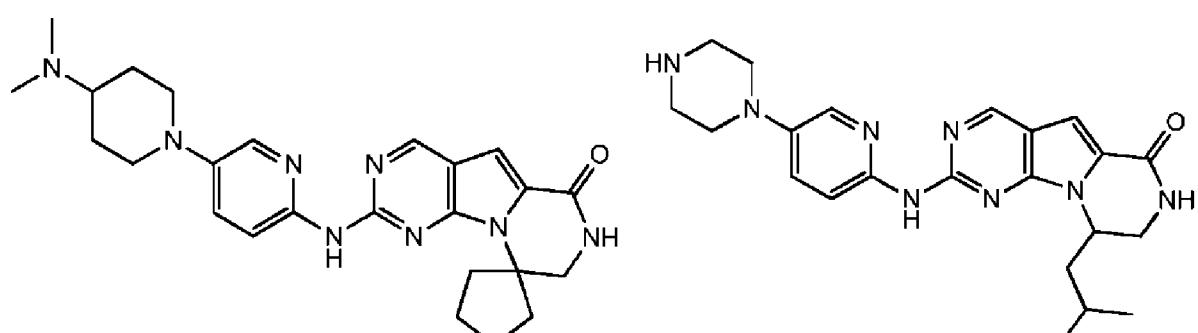
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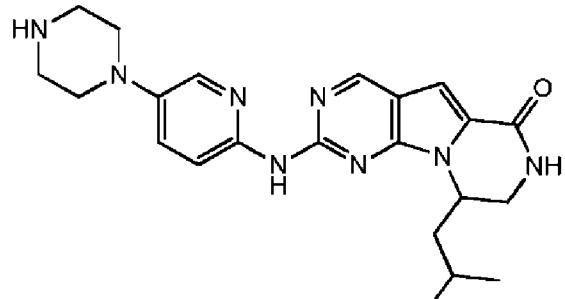
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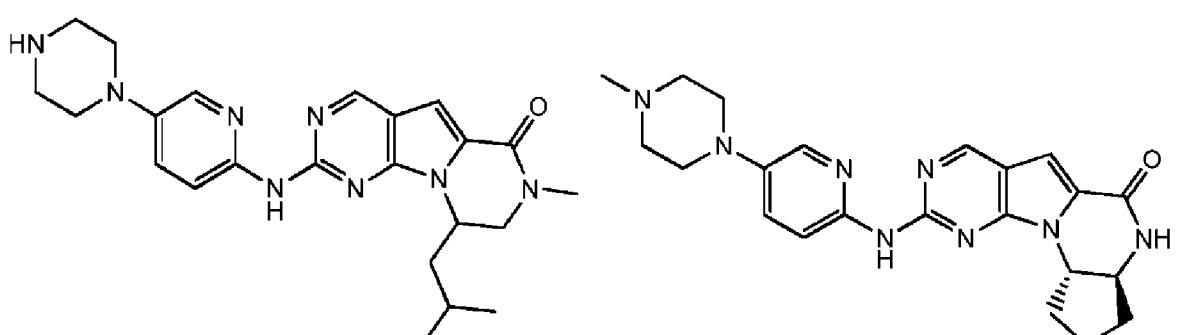
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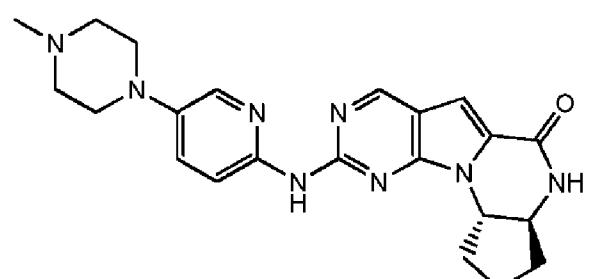
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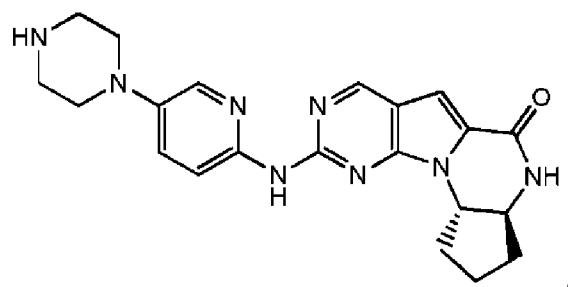


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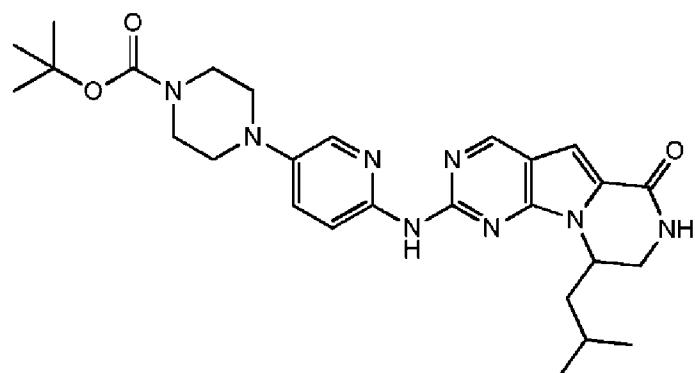
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et

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15. Composé de l'une quelconque des revendications 1 à 14, **caractérisé en ce que** le composé ou sel pharmaceutiquement acceptable de celui-ci est sous la forme d'une forme pharmaceutique solide, semi-solide ou liquide.

30 16. Composition pharmaceutique comprenant une quantité efficace d'un composé de l'une quelconque des revendications 1 à 14 ou un sel pharmaceutiquement acceptable de celui-ci.

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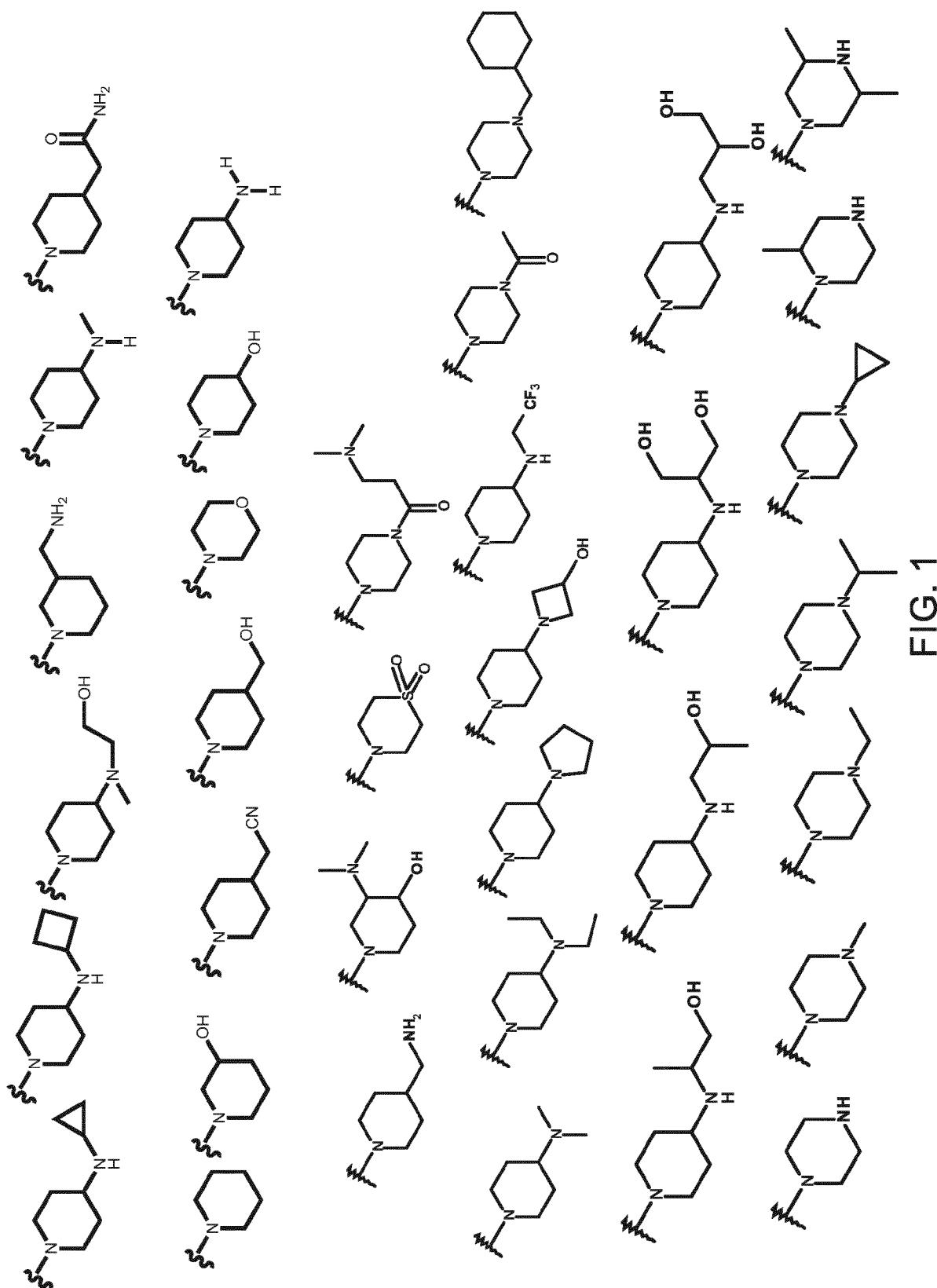


FIG. 1

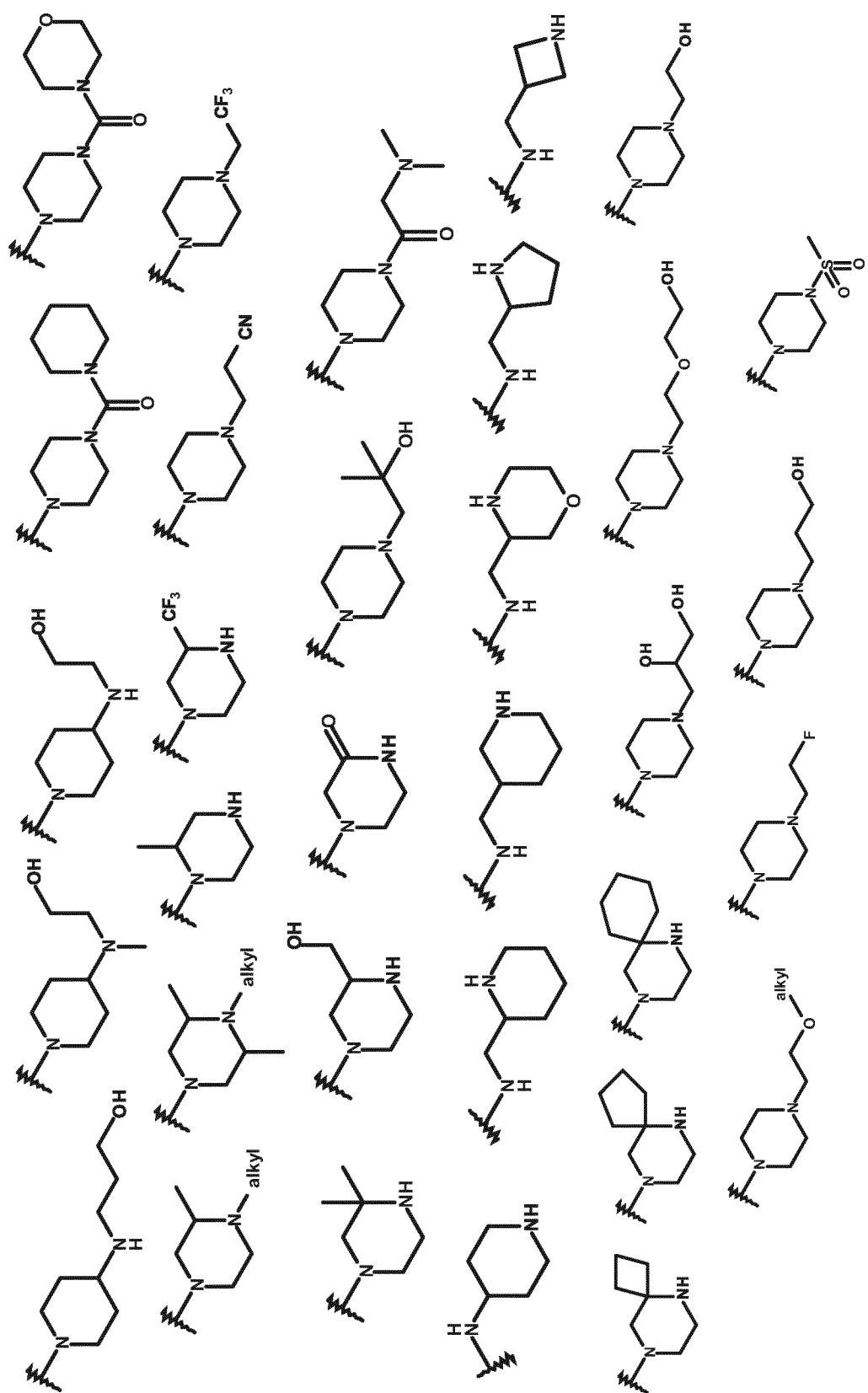


FIG. 2

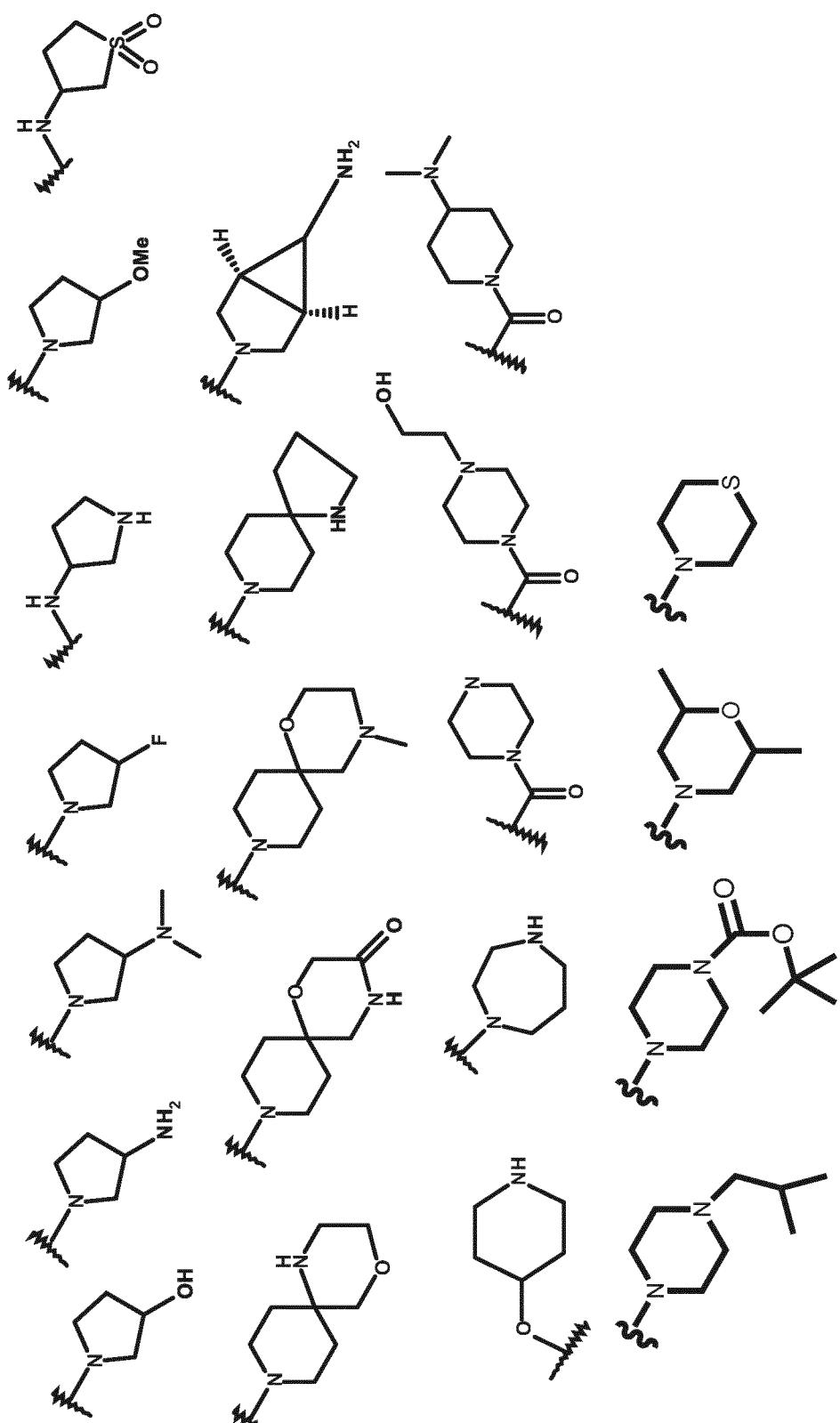


FIG. 3

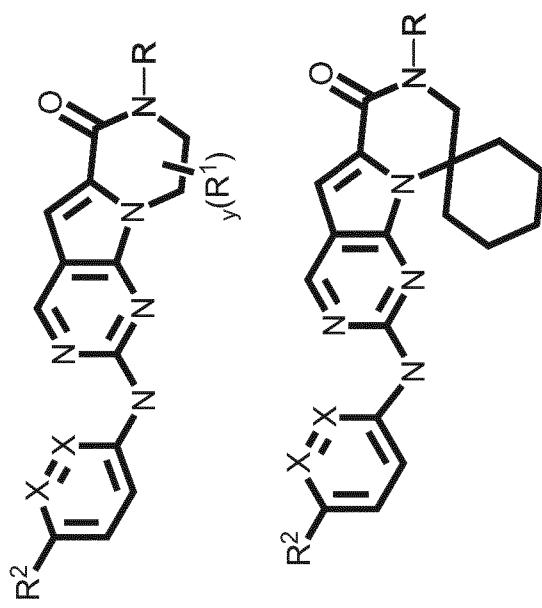
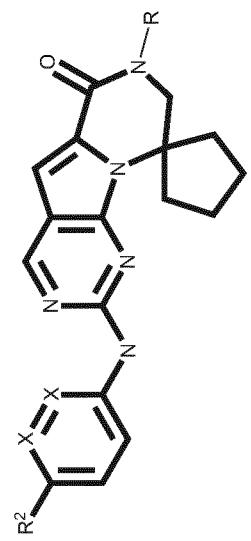


FIG. 4

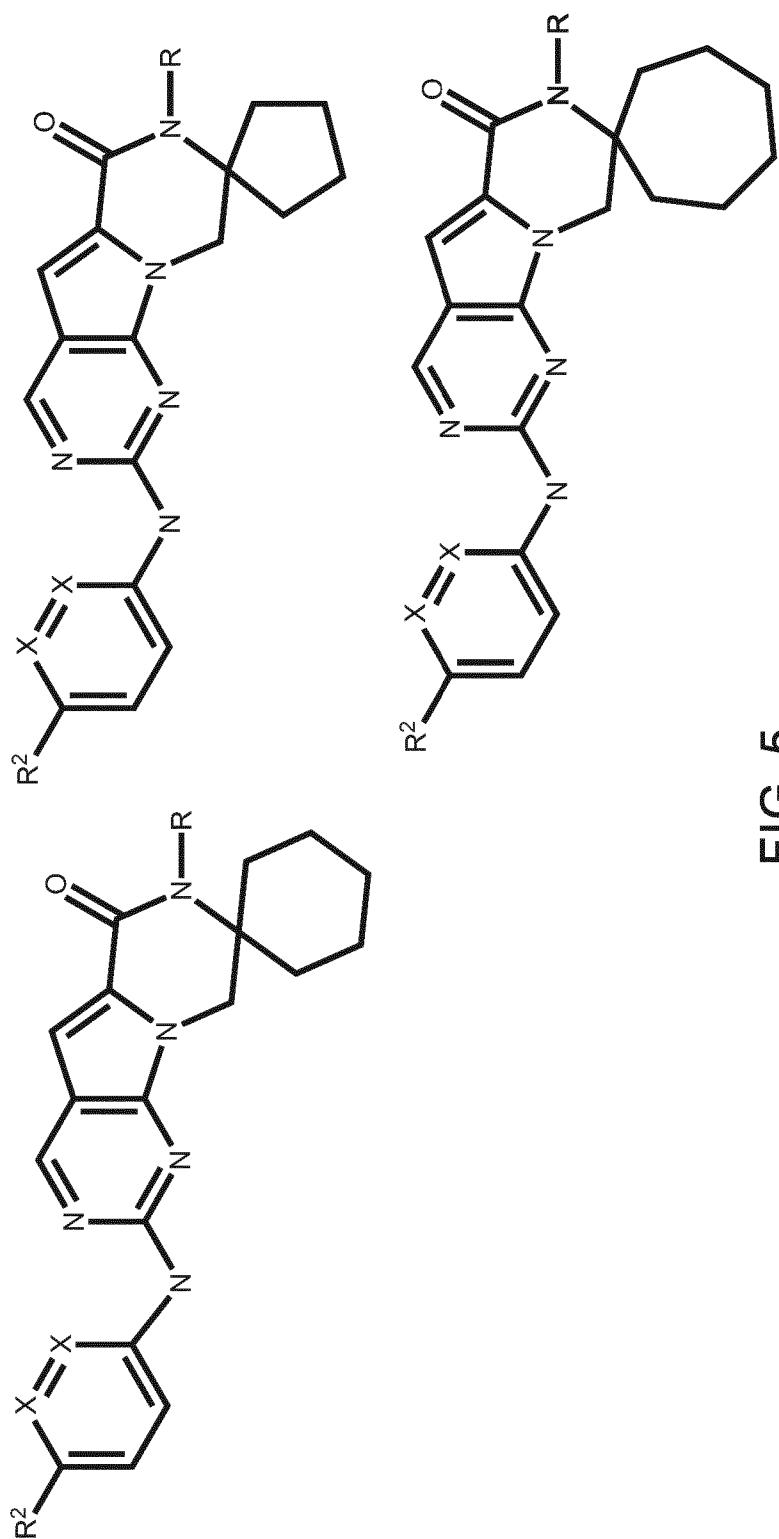


FIG. 5

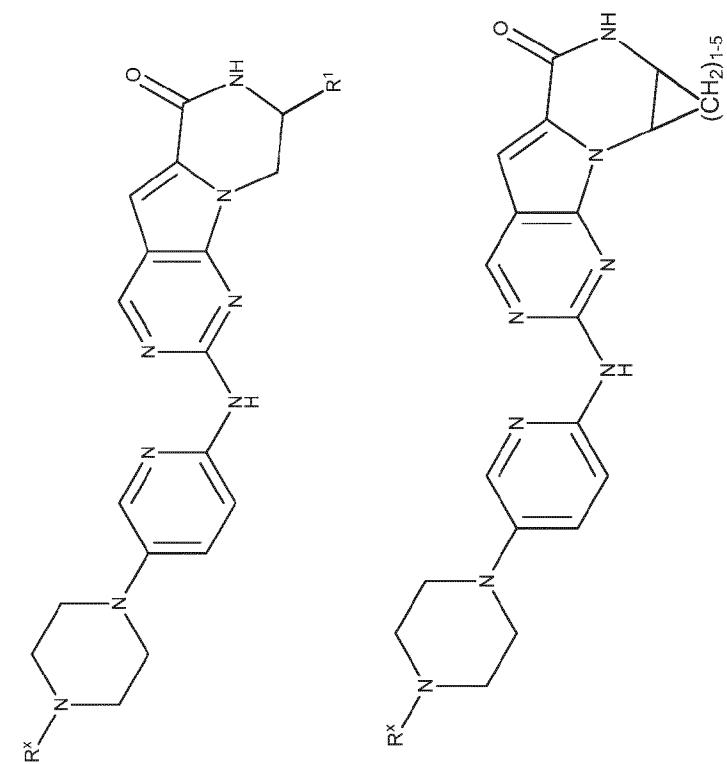
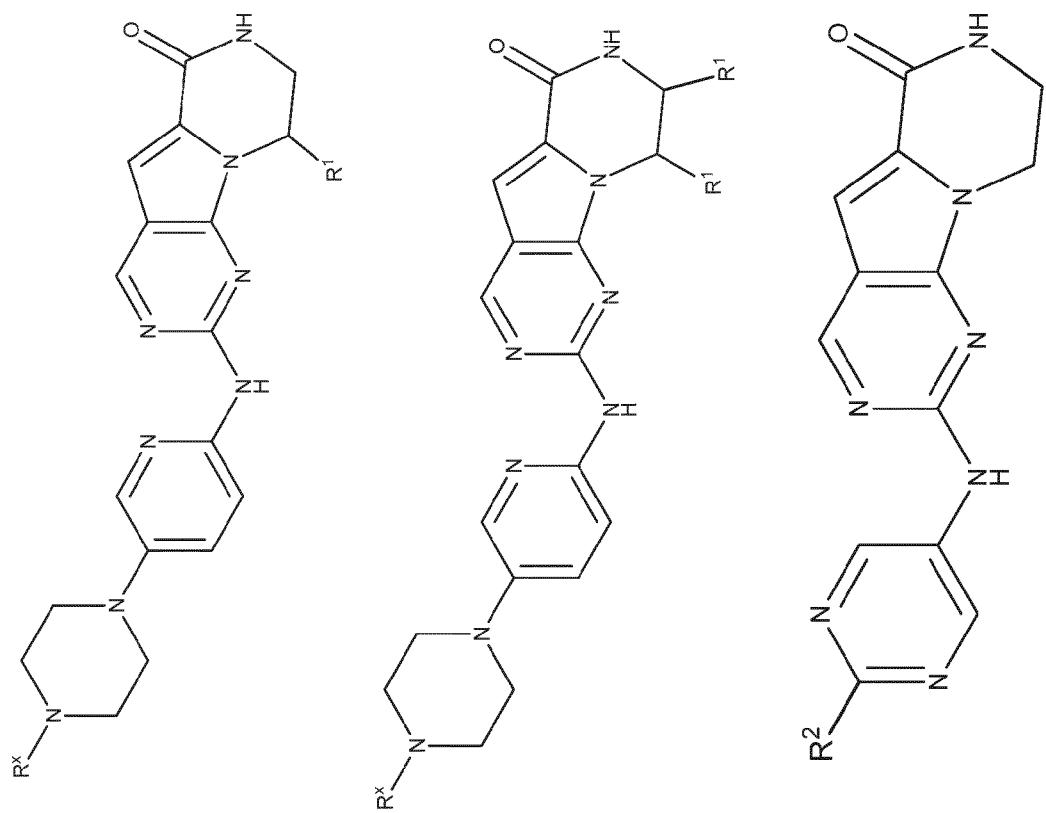


FIG. 6



REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

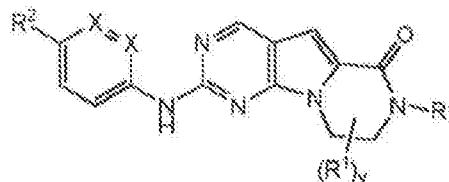
- WO 2010020675 A1 [0072] [0073] [0074] [0097]
- WO 2005040166 A1 [0073]

Non-patent literature cited in the description

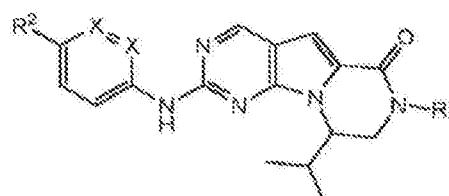
- **CAREY ; SUNDBERG.** Advanced Organic Chemistry. Springer Science+Business Media LLC, 2007, vol. A and B [0042]
- **M.B. SMITH ; J. MARCH.** March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. John Wiley & Sons, Inc, 2007 [0042]
- **WHITE, J. D. et al.** *J. Org. Chem.*, 1995, vol. 60, 3600 [0072]
- **PRESSER, A. ; HUFNER, A.** *Monatshefte für Chemie*, 2004, vol. 135, 1015 [0072]
- **SCHOENAUER, K ; ZBIRAL, E.** *Tetrahedron Letters*, 1983, vol. 24, 573 [0073]

Szabadalmi igényelvonalak

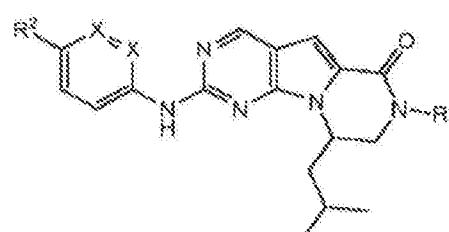
1. Ia képletű vegyület



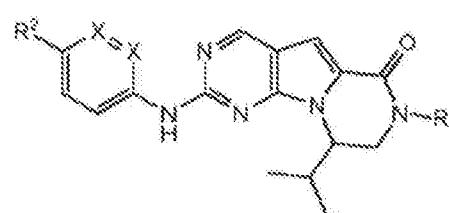
vagy Ib képletű vegyület



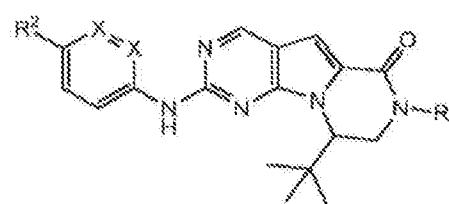
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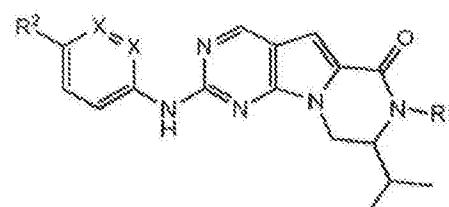
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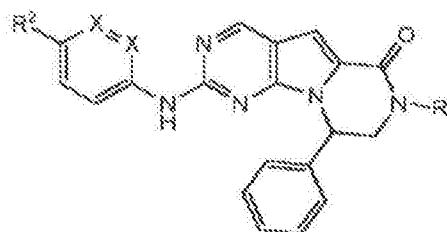
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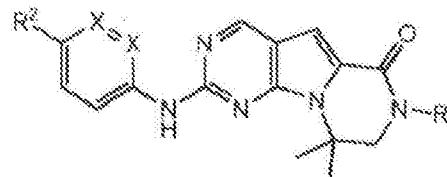
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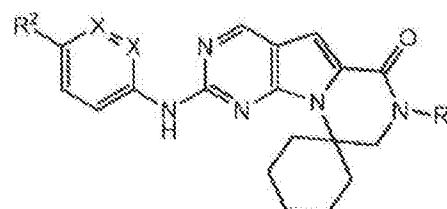
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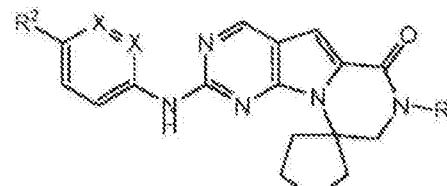
vagy Ia képletei vegyület



vagy Ib képletei vegyület



vagy Ic képletei vegyület



- ahol a képletekben:

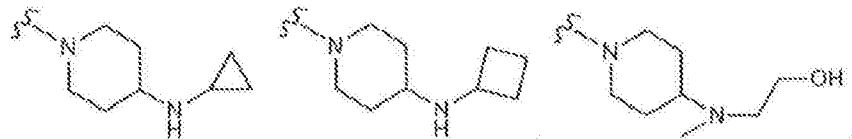
R jelentése H, C₁-C₃ alkil vagy halogénalkil;

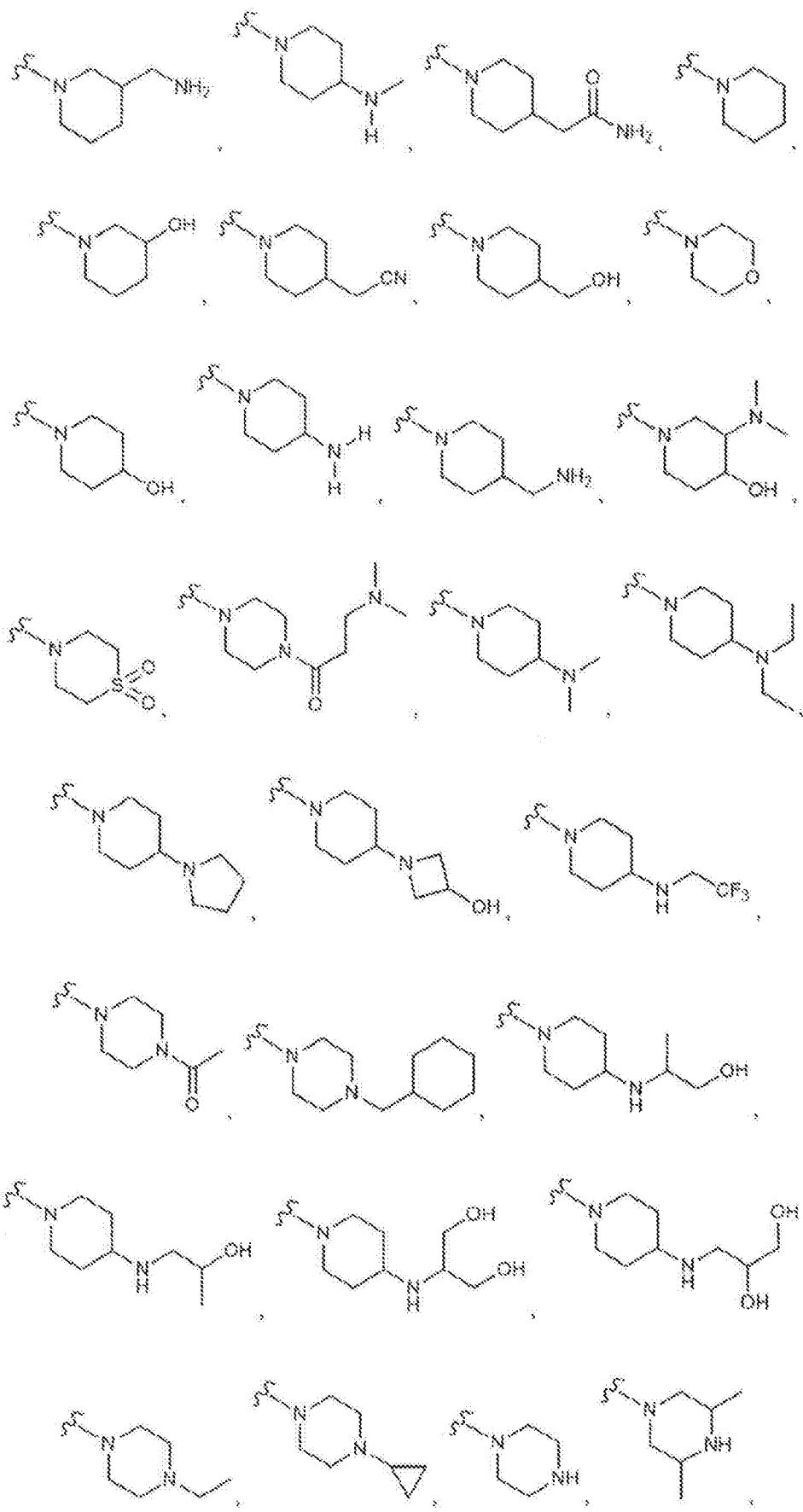
mindegyik R¹ jelentése egymástól függetlenül aril, alkil, cikloalkil vagy halogénalkil, ahol az említett alkil, cikloalkil és halogénalkil csoportok mindegyike adott esetben O vagy N heteroatomokat foglal magában a láncban egy szénatom helyett és szomszédos gyűrűbeli atomokhoz vagy ugyanazon gyűrűbeli atomhoz kapcsolódó kettő R¹ adott esetben 3 ~ 8-tagú gyűrűt képez együtt azzal a gyűrűbeli atommal vagy azokkal a gyűrűbeli atomokkal, amely(ek)hez kapcsolódnak;

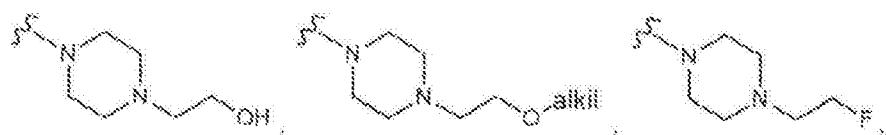
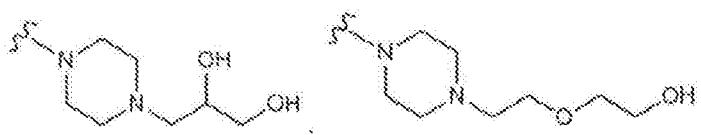
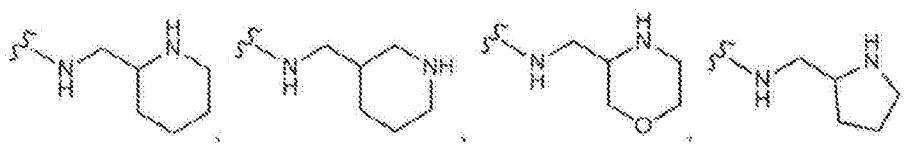
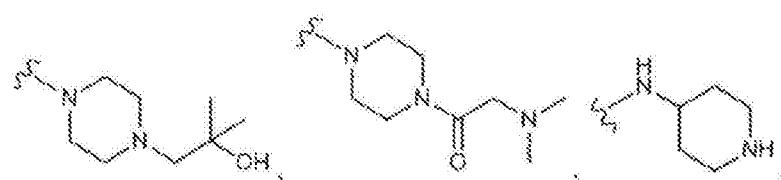
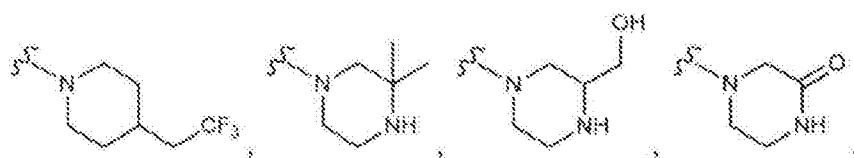
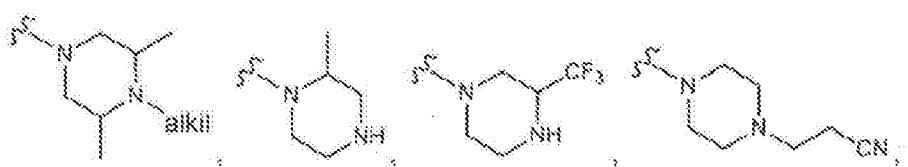
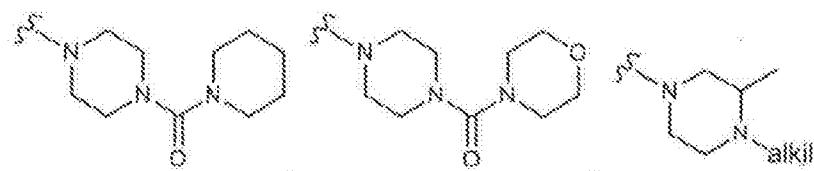
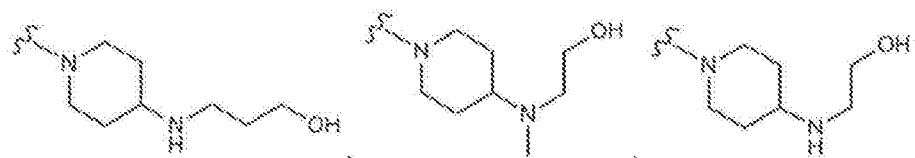
y értéke 0, 1, 2, 3 vagy 4;

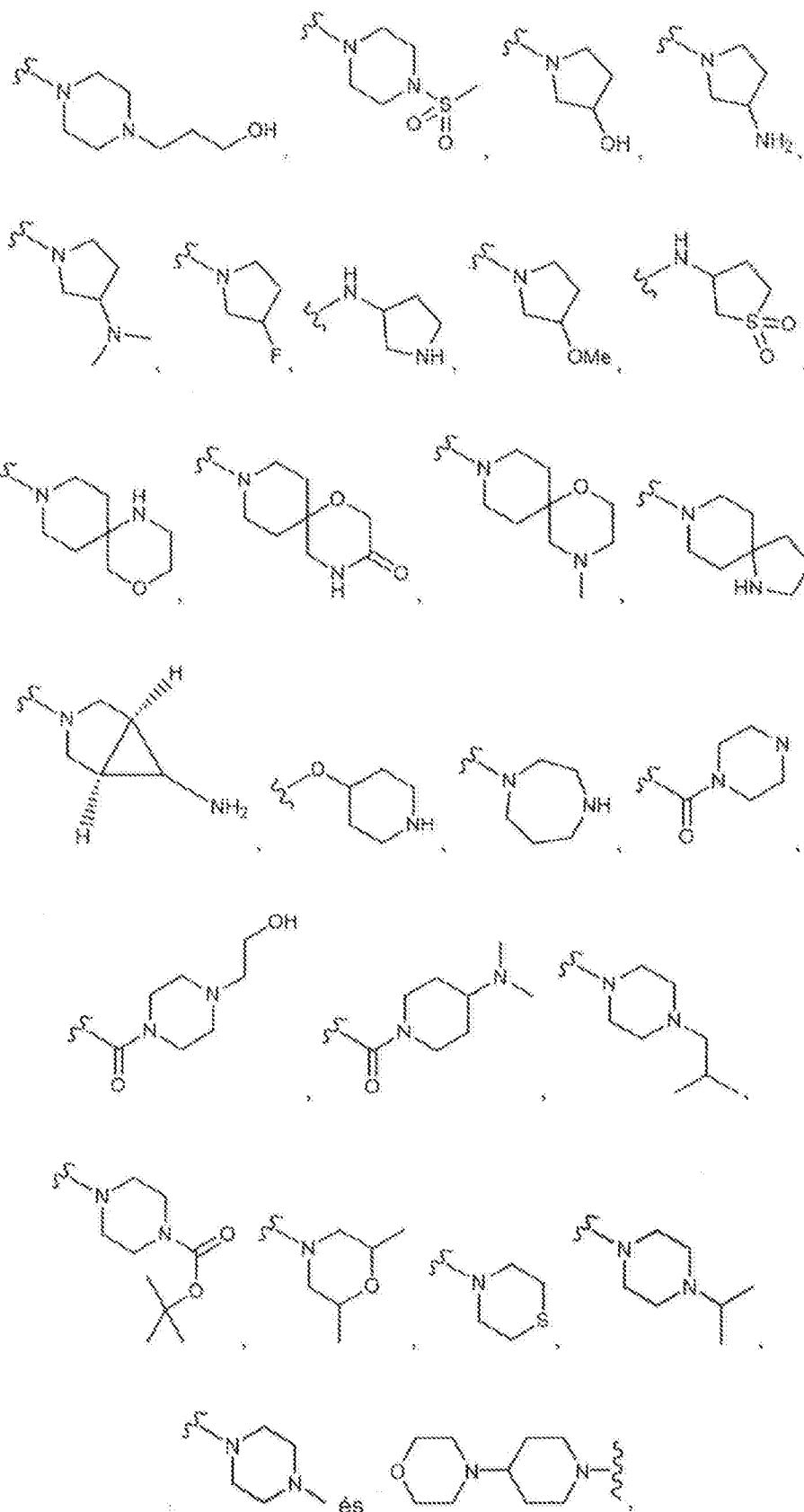
mindegyik X jelentése egymástól függetlenül CH vagy N; és

R² jelentése az alábbi szerkezetekből van megválasztva:





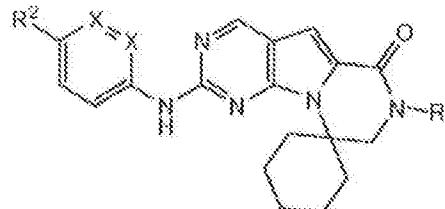




ahol az "aril" kifejezés – önmagában vagy kombinációban – egy vagy kettő gyűrűből álló karbociklusos aromás rendszert jelent, míg mellett ezek a gyűrűk kapcsolódhatnak egymáshoz kondenzált módon és bár-

mely aril csoport C_1 - C_6 alkil, hidroxil, halogén, halogénalkil, nitro, ciano, alkoxi és C_1 - C_6 alkilamino közül egymástól függetlenül megválasztott 1 vagy több helyettesítővel helyettesített lehet – vagy ezek valamelyikének egy gyógyászatilag elfogadható sója.

2. Az 1. igénypont szerinti vegyület, amely II képletű



vagy egy gyógyászatilag elfogadható sója.

3. Az 1. vagy 2. igénypont szerinti vegyület, ahol minden X jelentése N.

4. Az előző igénypontok bármelyike szerinti vegyület, ahol R jelentése hidrogén vagy C_1 - C_3 alkil.

5. Az 1 – 4. igénypontok bármelyike szerinti vegyület, ahol R^2 jelentése

(a)



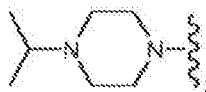
vagy

(b)



vagy

(c)

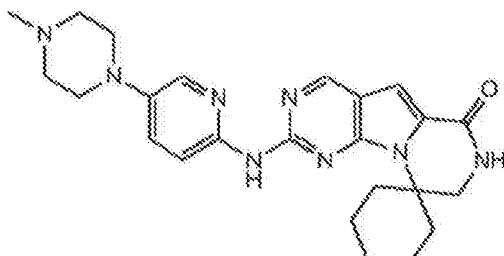


vagy

(d)

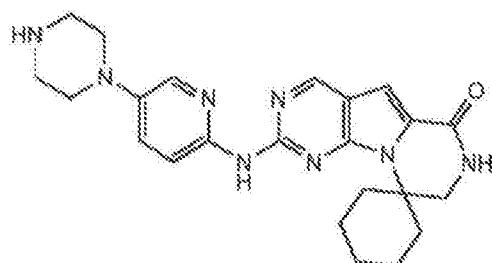


6. Az 1. vagy 2. igénypont szerinti vegyület, amely az alábbi képletű:



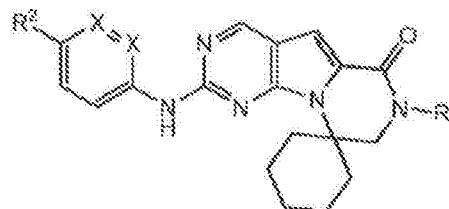
vagy egy gyógyászatilag elfogadható sója.

7. Az 1. vagy 2. igénypont szerinti vegyület, amely az alábbi képletű:



vagy egy gyógyászatilag elfogadható sója.

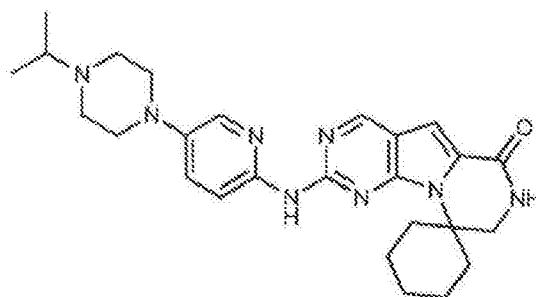
8. Az 1. vagy 2. igénypont szerinti vegyület, amely az alábbi képletű:



- ahol R jelentse H -

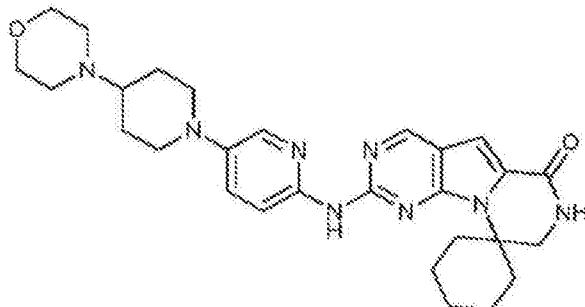
vagy egy gyógyászatilag elfogadható sója.

9. A 8. igénypont szerinti vegyület, amely az alábbi képletű:



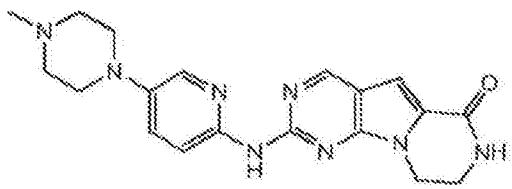
vagy egy gyógyászatilag elfogadható sója.

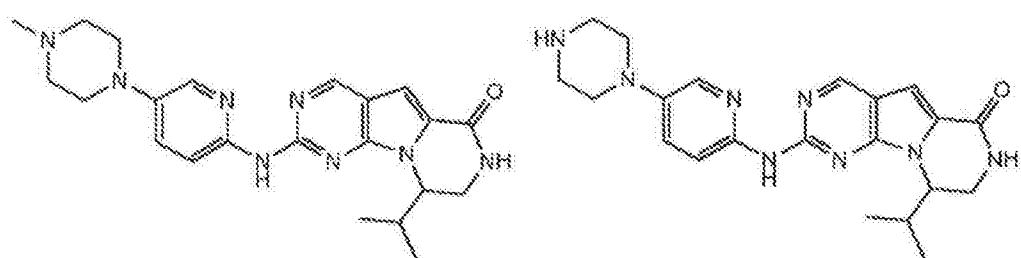
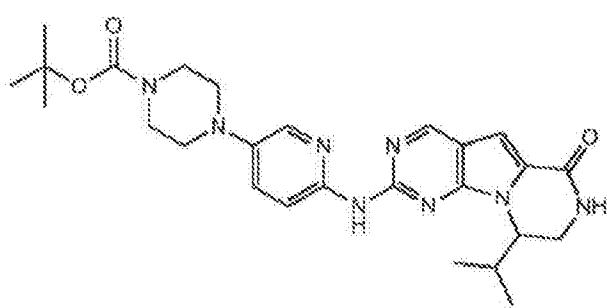
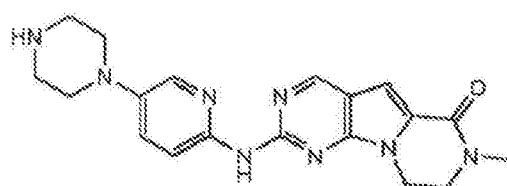
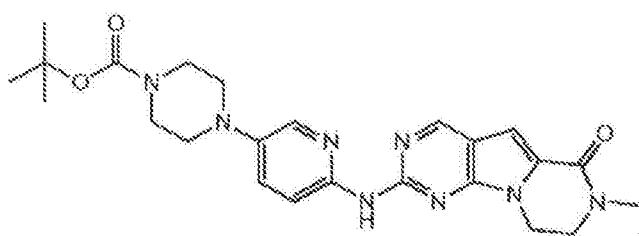
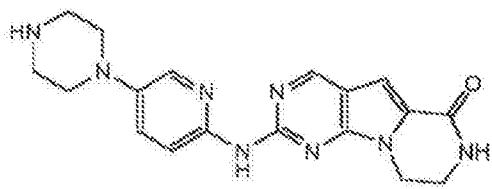
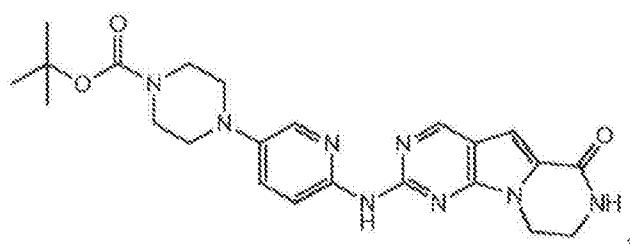
10. A 8. igénypont szerinti vegyület, amely az alábbi képletű:

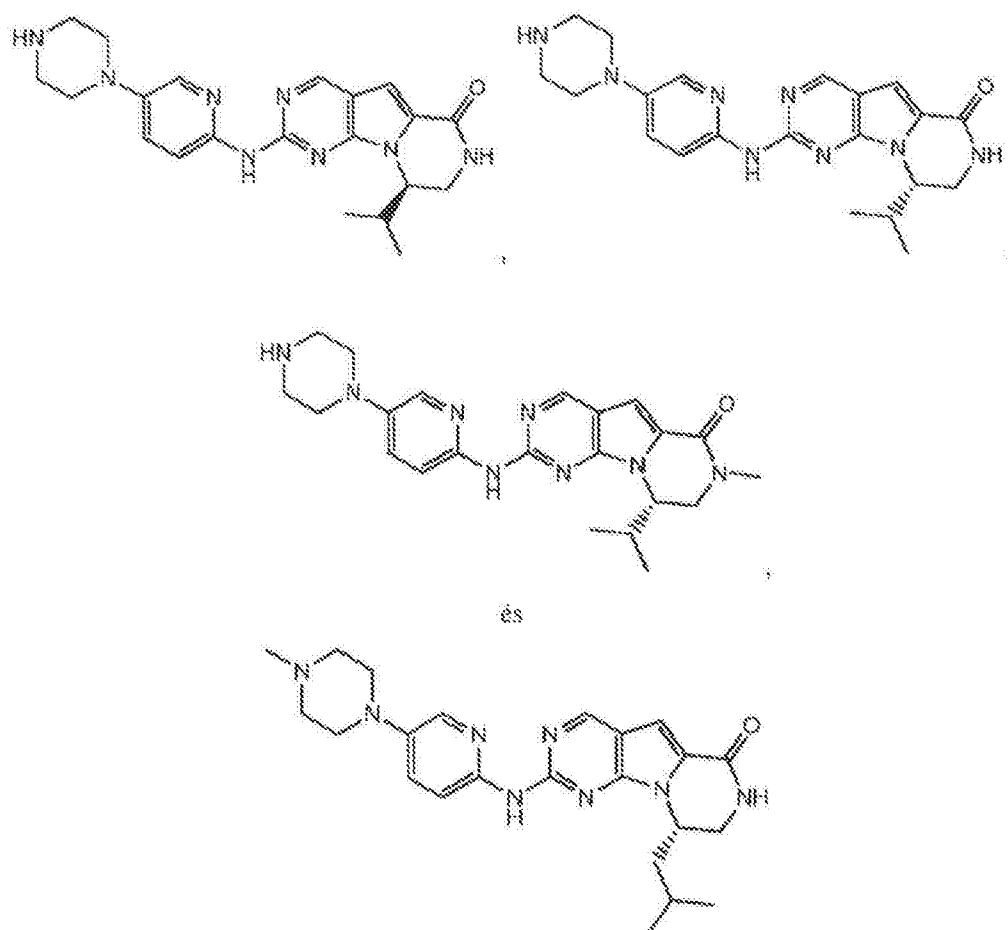


vagy egy gyógyászatilag elfogadható sója.

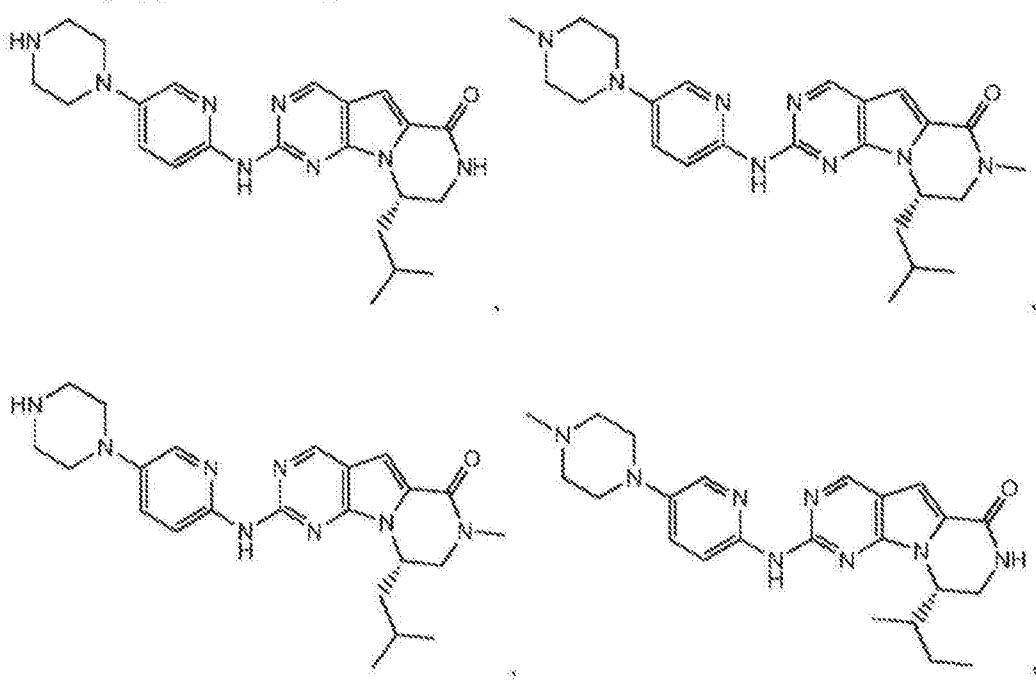
11. Az 1. igénypont szerinti vegyület az alábbi szerkezetűek közül megyálasztva:

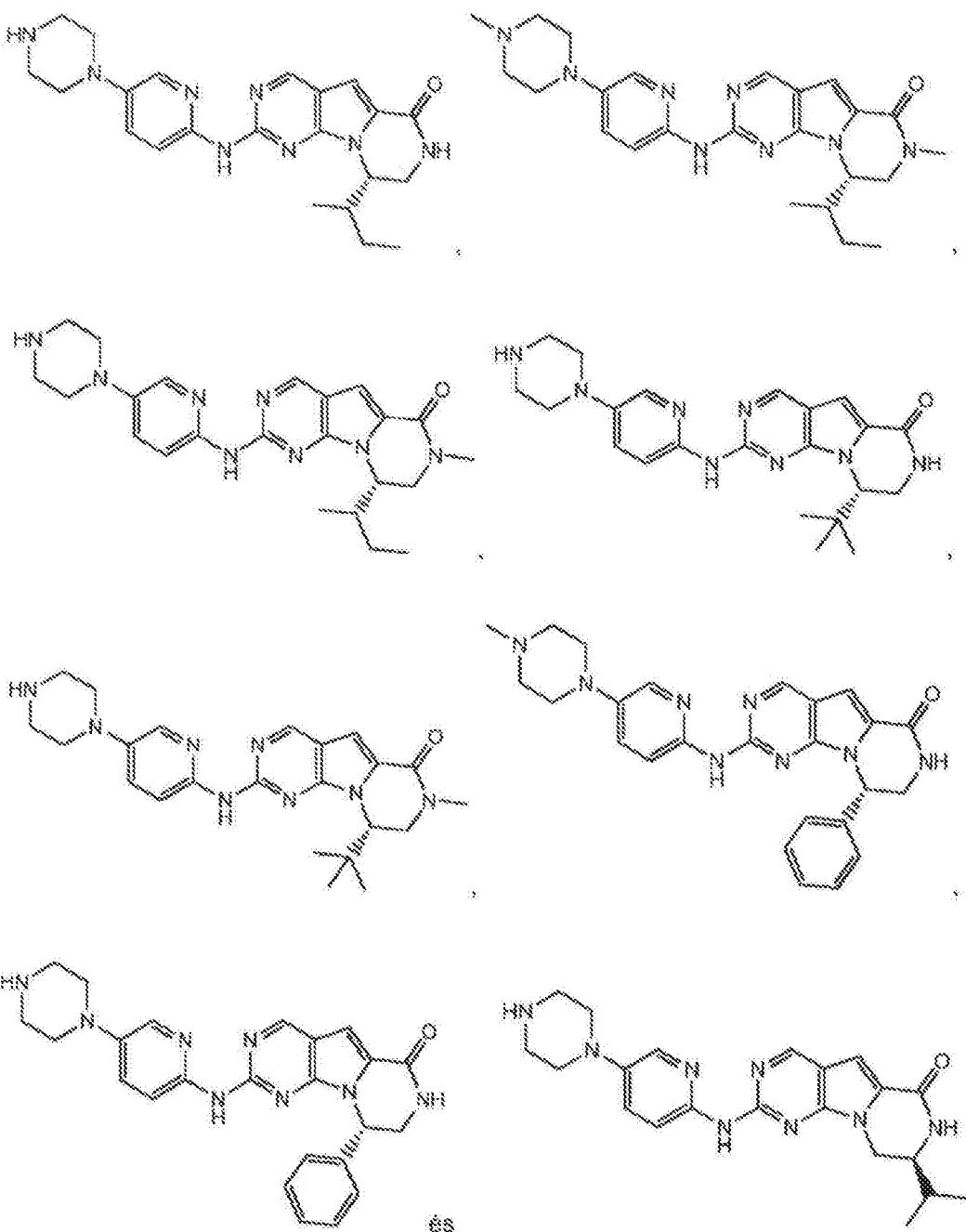




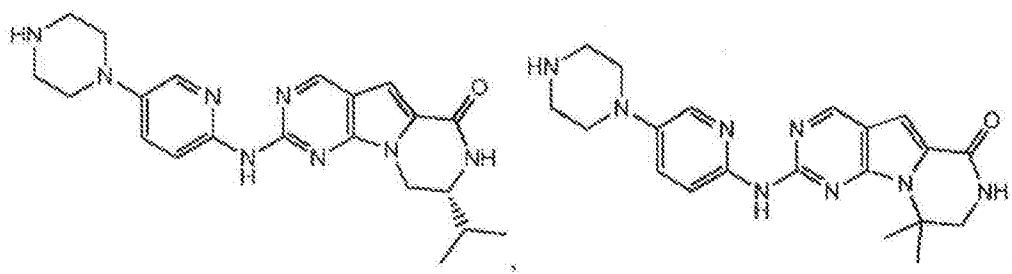


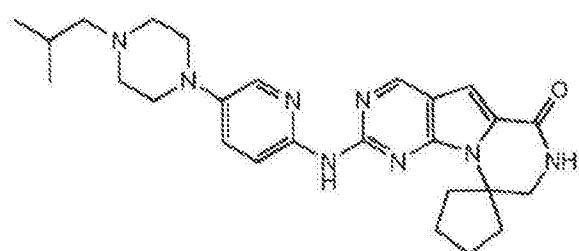
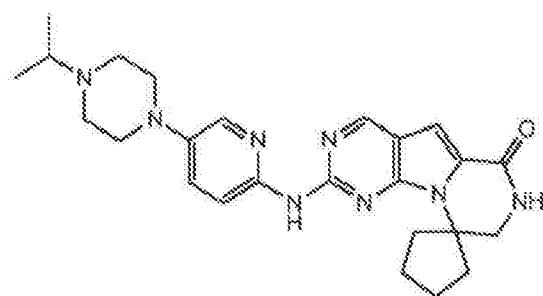
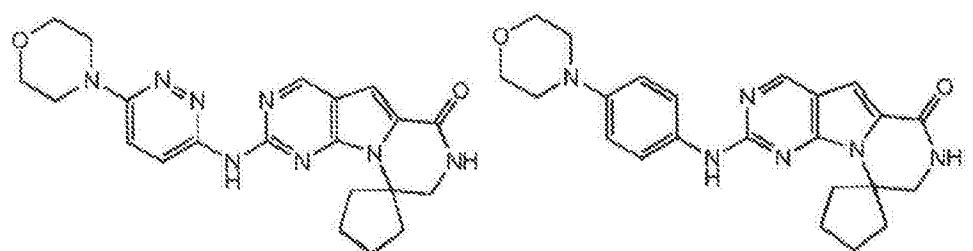
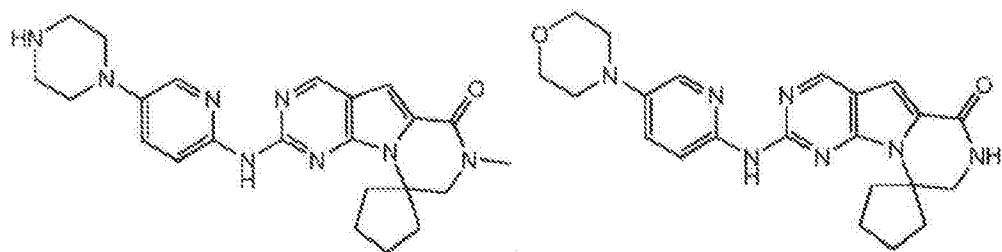
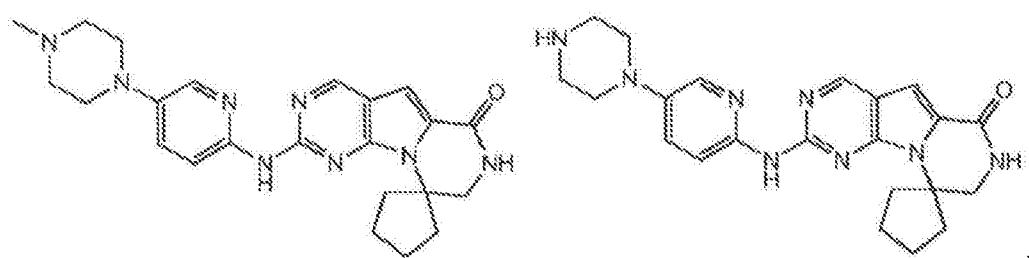
12. Az 1. igénypont szerinti vegyület az alábbi szerkezetek közül megválasztva:

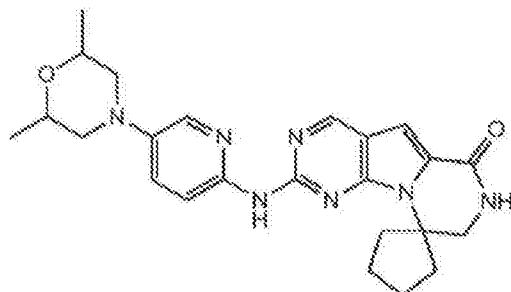




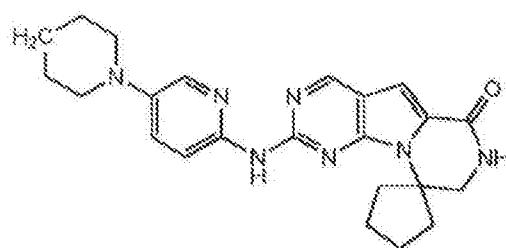
13. Az 1. igénypont szerinti vegyületet az alábbi szerkezetűek közül megválaszíva:



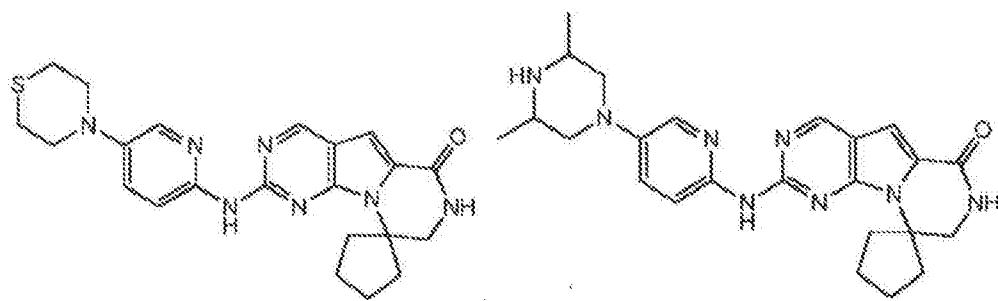




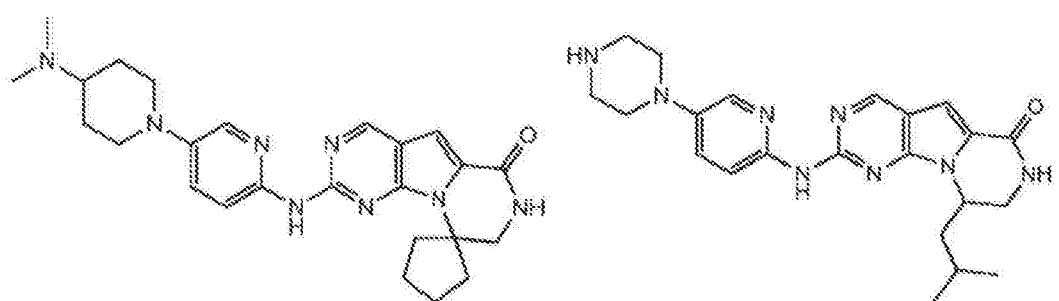
és



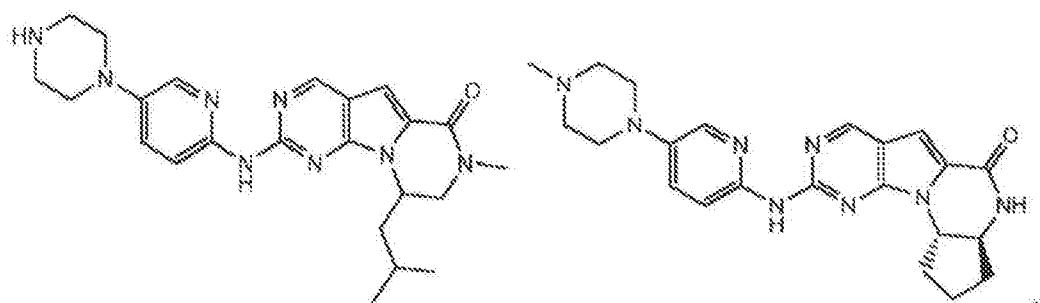
14. Az 1. igénypont szerinti vegyület az alábbi szerkezetek közül megválasztva:



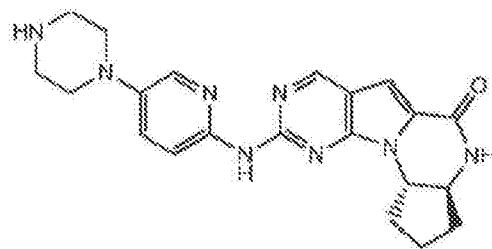
XXX



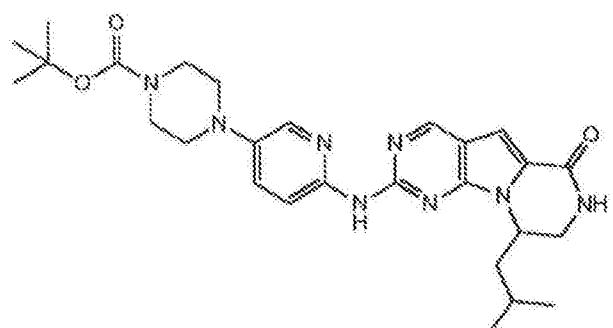
XXX



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15. Az 1 - 14. igénypontok bármelyike szerinti vegyület, ahol a vegyület vagy gyógyászatilag elfogadható sója szilárd, félgy szilárd vagy folyékony dózisformában van.

16. Gyógyászati készítmény, amely az 1 - 14. igénypontok bármelyike szerinti vegyület vagy gyógyászatilag elfogadható sója hatásos memóriáségét tartalmazza.