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(54) Title: COMPOSITIONS AND METHODS FOR THE PRODUCTION OF PYRIMIDINE AND PYRIDINE COMPOUNDS WITH BTK INHIBITORY ACTIVITY

(57) Abstract: The present invention provides novel pyrimidine and pyridine compounds which are attached to a warhead, and the manufacture and use for the treatment of hyperproliferative diseases including, but not limited to, cancer, lupus, allergic disorders, Sjogren's disease and rheumatoid arthritis. The invention also describes kinase inhibitors including, but not limited to, inhibitors of Bruton's tyrosine kinase.



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Compositions and Methods for the Production of Pyrimidine and Pyridine Compounds with BTK Inhibitory Activity

5 *Related applications*

This application claims the benefit of U.S. provisional application USSN 61/735,186, filed on December 10, 2012, the entire contents of which are incorporated herein in its entirety.

10 *Field of the invention*

The invention relates to a series of pyrimidine and pyridine compounds that are useful as therapeutics in the treatment of a variety of pathological conditions including (but not limited to) cancer, auto-immune disease, inflammatory diseases and neurodegenerative diseases in
15 mammals. More particularly, embodiments of the present invention describe irreversible kinase inhibitors including, but not limited to, inhibitors of Bruton's tyrosine kinase (hereinafter referred to as: "BTK"). Methods for the preparation of the aforementioned compounds are disclosed in addition to the incorporation of these compounds into pharmaceutical compositions that include the same. Methods of using these BTK inhibitors
20 are disclosed, alone or in combination with other therapeutic agents, for the treatment of hyperproliferative diseases in mammals, especially humans, as well as pharmaceutical compositions which contain said inhibitors.

25 *Background*

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Book. I and II, Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate
30 (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., FASEB J., 9:576-596 (1995); Knighton, et al., Science, 253:407-414 (1991); Hiles, et al., Cell, 70:419-429 (1992); Kunz, et al., Cell, 73:585-596 (1993); Garcia-Bustos, et al., EMBO J., 13:2352-2361 (1994)). Protein kinases may be characterized by their
35 regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions,

and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, diseases and conditions of the immune system, diseases and conditions of the central nervous system, and angiogenesis.

BTK, a member of the Tec family of non-receptor tyrosine kinases, is a signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. BTK plays a well documented role in the B-cell signaling pathway linking cell surface B-cell receptor stimulation to downstream intracellular responses. BTK is also a regulator of B-cell development, activation, signaling, and survival (Kurosaki, Curr Op Imm, 2000, 276-281; Schaeffer and Schwartzberg, Curr Op Imm 2000, 282-288). In addition, BTK exerts a physiological effect through other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF- α production in macrophages, IgE receptor (Fc ϵ RI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation. BTK has an ATP-binding pocket with high similarity to Src-family kinases, such as lymphocyte-specific protein tyrosine kinase (Lck) and Lyn. Comparing BTK to other kinases one finds a conserved cysteine residue, Cys-481, in 11 of 491 kinases, specifically members of the Tec and EGFR (epidermal growth factor receptor) kinase families.

BTK plays important roles in the development, differentiation, activation and proliferation of B cells, as well as their antibody and cytokine generation. In addition, Btk plays a central role in other immunological processes such as cytokine production by neutrophils, mast cells and monocytes, degranulation of neutrophils and mast cells as well as differentiation/activation of osteoclasts. B-cell activation, break of tolerance and auto-antibody production, on one hand

and the proinflammatory milieu originated from exacerbated activation of monocytes, neutrophils and mast cells, on the other hand, are crucial in the etiology of autoimmune diseases, including (but not limited to) rheumatoid arthritis and systemic lupus erythematosus.

5

Reversible kinase inhibitors have been developed into therapeutic compounds. These reversible inhibitors, however, have decided disadvantages. Many reversible inhibitors of kinases interact with the ATP-binding site. Given the structure of the ATP-binding sites are highly conserved among kinases, it has been difficult to develop a reversible inhibitor that selectively inhibits a desired (*i.e.*, target) kinase. Moreover, given that many reversible kinase inhibitors readily dissociate from their target polypeptide(s), maintaining inhibition over extended periods of time can be difficult. When using reversible kinase inhibitors as therapeutics, therefore, often times near toxic dosages and/or frequent dosing is required to achieve the intended biological effect.

15

Generating potent, selective, oral BTK inhibitors is thus difficult using the reversible approach. Generating potent, selective, oral BTK inhibitors using a covalent, irreversible approach has been easier. However, the covalent approach comes with potential risks, such as potentially higher toxicity that might arise from indiscriminate covalent binding to off-targets. Electrophilic drug candidates have the potential to form covalent bonds not only with the target protein, but also with off-target macromolecules. The off-target reactivity is undesirable because covalent binding to off-target macromolecules can be toxic. For example, binding to liver proteins could inhibit their function; and binding to DNA can result in genotoxicity. The problem to be solved here is increasing the therapeutic window of electrophilic drug candidates.

25

What is needed, therefore, are irreversible kinase inhibitors that covalently bind to their target polypeptide(s) without (substantially) binding to off-target polypeptides and, thereby, exerting undesirable off-target effects.

30

Summary

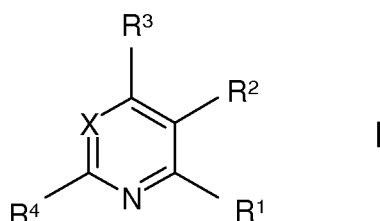
The present invention provides novel pyrimidine and pyridine BTK inhibitors attached to an electrophilic warhead comprising a Michael acceptor.

35

Description of the Invention

The present invention provides a series of novel pyrimidine and pyridine kinase inhibitors attached to a warhead. In some embodiments said kinase inhibitors are irreversible inhibitors of tyrosine kinases. In preferred embodiments, said irreversible kinase inhibitors inhibit BTK. While it is not intended that the compounds described by the present invention be limited to any specific mechanism of action, in some embodiments said irreversible kinase inhibitors exert a physiological effect by forming a covalent bond with Cys 481 in BTK. Significantly, this Cys 481 in BTK finds homologs in other kinases. Embodiments of the present invention also described methods for synthesizing said irreversible inhibitors, methods for using said irreversible inhibitors in the treatment of diseases (including, but not limited to, cancer, auto-immune / inflammatory diseases, and neurodegenerative diseases). Further described are pharmaceutical formulations that include an irreversible kinase inhibitor including pharmaceutically acceptable salts, solvates or prodrugs thereof, that are kinase inhibitors and useful in the treatment of the above mentioned diseases.

The kinase inhibitors of the present invention comprise (i) compounds of Formula (I):



in which:

X is CH or N;

R¹ is NR⁵[C(R⁵)₂]_nHet², NH₂, CONH₂ or H;

R² is Hal, Ar¹ or Het¹;

R³ is NH₂, NR⁵[C(R⁵)₂]_nHet², O[C(R⁵)₂]_nHet², NR⁵[C(R⁵)₂]_nCyc, O[C(R⁵)₂]_nCyc, NR⁵[C(R⁵)₂]_nAr², O[C(R⁵)₂]_nAr², NR⁵[C(R⁵)₂]_nHet¹, O[C(R⁵)₂]_nHet¹, NR⁵[C(R⁵)₂]_nA, O[C(R⁵)₂]_nA, NR⁵(CH₂)_pNR⁵R⁶, O(CH₂)_pNR⁵R⁶, NR⁵(CH₂)_pCR⁷R⁸NR⁵R⁶ or Het²;

R⁴ is H, CH₃ or NH₂;

R⁵ is H or alkyl having 1, 2, 3 or 4 C atoms;

R⁶ is N(R⁵)₂CH₂CH=CHCONH-, Het³CH₂CH=CHCONH-, CH₂=CHCONH(CH₂)_n-, Het⁴(CH₂)_nCOHet³-diyl-CH₂CH=CHCONH-, HC≡CCO-, CH₃C≡CCO-, CH₂=CH-CO-, CH₂=C(CH₃)CONH-, CH₃CH=CHCONH(CH₂)_n-, N≡CCR⁷R⁸CONH(CH₂)_n-, Het⁴NH(CH₂)_pCOHet³-diyl-CH₂CH=CHCONH-, Het⁴(CH₂)_pCONH(CH₂CH₂O)_p(CH₂)_pCOHet³-diyl-CH₂CH=CHCONH-,

CH₂=CHSO₂⁻, ACH=CHCO⁻, CH₃CH=CHCO⁻,
 Het⁴(CH₂)_pCONH(CH₂)_pHet³-diyl-CH₂CH=CHCONH⁻, Ar³CH=CHSO₂⁻,
 CH₂=CHSO₂NH⁻ or N(R⁵)CH₂CH=CHCO⁻;

R⁷, R⁸ are together alkylene having 2, 3, 4, or 5 C atoms;

Ar¹ is phenyl or naphthyl, each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, Hal, (CH₂)_nNH₂, CONHAr³, (CH₂)_nNHCOA, O(CH₂)_nAr³, OCyc, A, COHet³, OA and/or OHet³ (CH₂);

Ar² is phenyl, naphthyl or pyridyl each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, Hal, OH, OAr³, (CH₂)_nNH₂, (CH₂)_nNHCOA and/or Het³;

Ar³ is phenyl, which is unsubstituted or mono-, di- or trisubstituted by OH, OA, Hal, CN and/or A;

Het¹ is a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by R⁶, Hal, OH, O(CH₂)_nAr³ and/or (CH₂)_nAr³;

Het² is a mono- or bicyclic saturated heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by R⁶, Het³, CycSO₂, OH, Hal, COOH, OA, COA, COHet³, CycCO, SO₂ and/or =O;

Het³ is a monocyclic unsaturated, saturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by Hal, A and/or =O;

Het⁴ is a bi- or tricyclic unsaturated, saturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, NO₂, Hal and/or =O;

Cyc is cyclic alkyl having 3, 4, 5 or 6 C atoms, which is unsubstituted, monosubstituted or disubstituted by R⁶, Hal and/or OH and which may comprise a double bond;

A is unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl and/or in which one or two non-adjacent CH₂ and/or CH-groups may be replaced by O, NH and/or by N;

Hal is F, Cl, Br or I;

n is 0, 1, 2, 3 or 4; and

p is 1, 2, 3, 4, 5 or 6;

and (ii) an electrophilic warhead comprising a Michael acceptor,

wherein the warhead is coupled to the compound of Formula (I) at R¹, R² or R³;

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

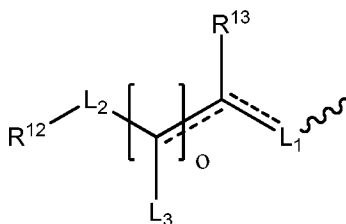
- 5 It has been surprisingly found by the inventors that said kinase inhibitors of the invention reduce the covalent binding to off-targets while maintaining the prolonged, durable inhibition of the target.

10 Reducing the covalent binding to off-targets can be achieved by using a warhead that results in a covalent macromolecule-drug that is not durable. With the right warhead structure, the covalent adduct that forms will quickly degrade via a retro-Michael addition reaction. Once the covalent bond is cleaved, the drug candidate will quickly dissociate from the off-target. This means that off-target binding will be reversible and transient in nature.

- 15 Prolonged inhibition of the kinase target can be achieved if the warhead is highly electrophilic and the reversible interactions with the target are selective and strong enough to keep the molecule from diffusing out of the ATP-binding pocket. Because the kinase inhibitor is anchored to the ATP-binding site via non-covalent interactions (hydrogen bonds, hydrophobic interactions, electrostatic interactions, etc.), it will stay docked in the ATP
20 binding site even if the Michael reaction and the retro-Michael reaction are rapidly taking place. In essence, the inhibition can be irreversible even if the covalent bond is not.

The warhead can be any electrophilic chemical structure that solves the problem of the invention if attached to an electrophilic drug candidate. It is preferred that the compounds
25 of Formula (I) are attached to a warhead as described in WO 2011/060440 A2 and/or WO 2012/158843 A2, which are incorporated in its entirety, including all the embodiments, by reference in the disclosure of the invention hereby. It is also preferred that the warhead is coupled to the compound of Formula (I) at R³.

- 30 In a more preferred aspect of the invention, the warhead is a compound of Formula (VI)



(VI)

in which

- R^{11} , R^{12} are, independently from one another, H, A, Cyc, Ar^1 , Ar^2 , Ar^3 , Het^1 , Het^2 , Het^3 or Het^4 , which have the meanings indicated above;
- R^{13} is an electron withdrawing group selected from nitrile and ester;
- L_1 is $-CO-$, $-CONH-$, $=CH-(CH_2)_m-$, $=CH-(CH_2)_mNH-$ or $-(CH_2)_m-$;
- L_2 is $CONR^{11}$ or absent;
- L_3 is absent or together with R^{12} forms a 4-8 membered carbocyclic, aryl, heterocyclic, or heteroaryl ring;
- m is 1, 2, 3 or 4; and
- o is 0 or 1.

In certain embodiments, the warhead comprises a cyano group.

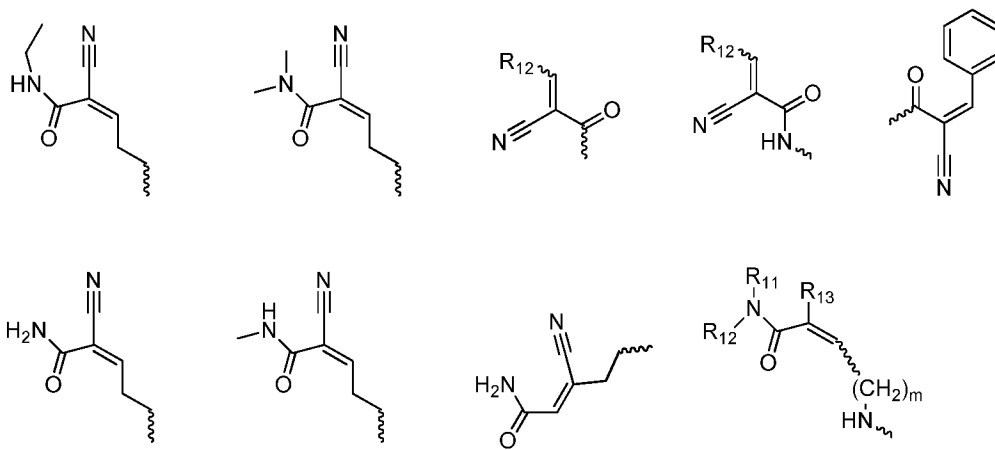
It is another more preferred aspect of the warhead that it comprises a cyanoacrylamide group.

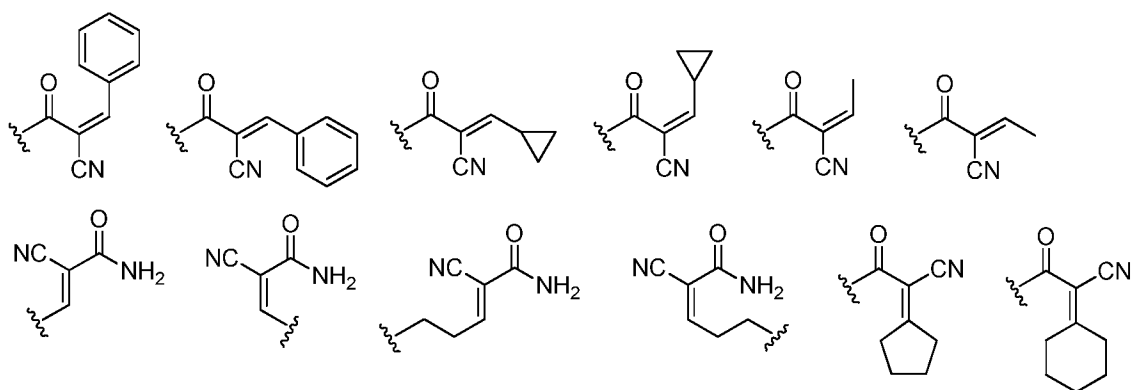
It is most preferred that the warhead is a compound of Formula (VI) as depicted above, in which

- R^{11} , R^{12} are, independently from one another, H, A or Ar^3 ;
- R^{13} is CN;
- L_1 is $-CO-$, $=CH-(CH_2)_m-$ or $-(CH_2)_m-$;
- L_2 is $CONR^{11}$ or absent;
- m is 1 or 2; and/or
- o is 0 or 1.

Highly preferred warheads of the invention are selected from the group found in Table 1:

Table 1





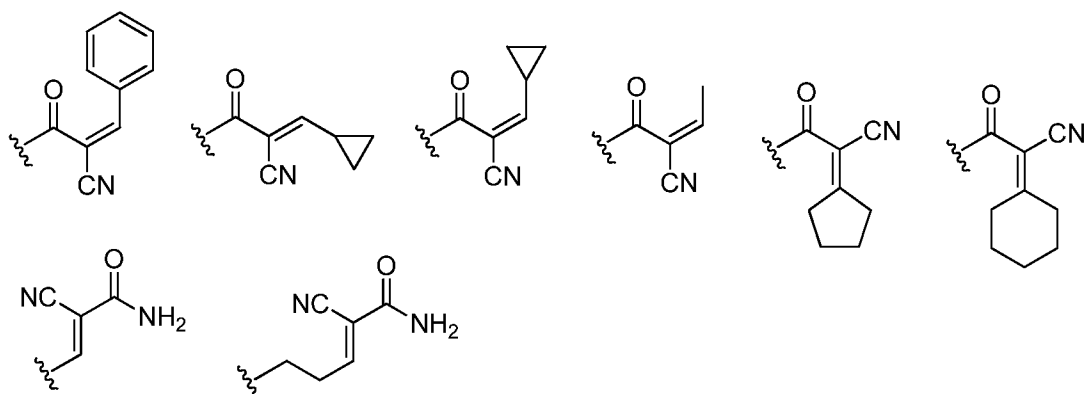
in which R^{11} - R^{13} have the meanings indicated above; and

wherein “~” denotes the bonding point of the warhead to R^1 , R^2 , or R^3 .

5

In certain embodiments, the warheads are selected from Table 2:

Table 2

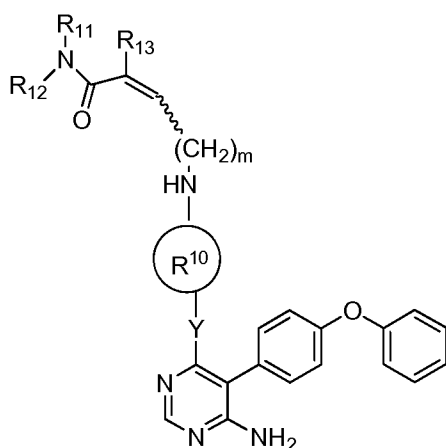


wherein “~” denotes the bonding point of the warhead to R^1 , R^2 , or R^3 .

10

In certain embodiments, each of X , R^1 , R^2 , R^3 , and R^4 is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

In certain embodiments, the invention provides a compound of formula **IA**.

**IA**

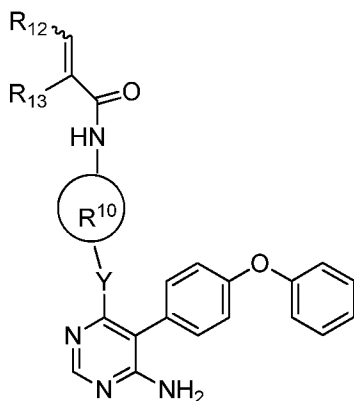
in which

each Y is independently NH, NHCH₂, or O;

5 each R¹⁰ is independently Het², Cyc, Ar², Het¹ or A; and

each of R¹¹-R¹³, Het², Cyc, Ar², Het¹ and A have the meanings indicated above.

In certain embodiments, the invention provides a compound of formula **IB**.

**IB**

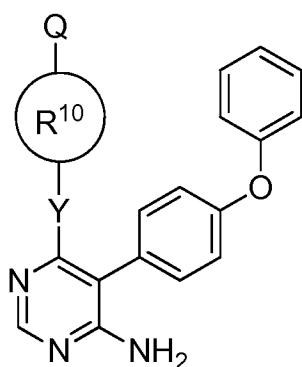
in which

each Y is independently NH, NHCH₂, or O;

each R¹⁰ is independently Het², Cyc, Ar², Het¹ or A; and

each of R¹¹-R¹³, Het², Cyc, Ar², Het¹ and A have the meanings indicated above.

In certain embodiments, the invention provides a compound of formula **IC**.

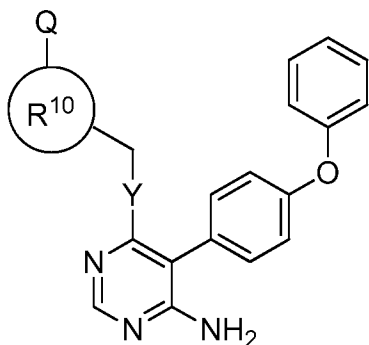
**IC**

in which

Y is NH, NHCH₂, or O;R¹⁰ is Het², Cyc, Ar², Het¹ or A; and

Q is a warhead selected from Table 1 or Table 2.

In certain embodiments, the invention provides a compound of formula **ID**.

**ID**

in which

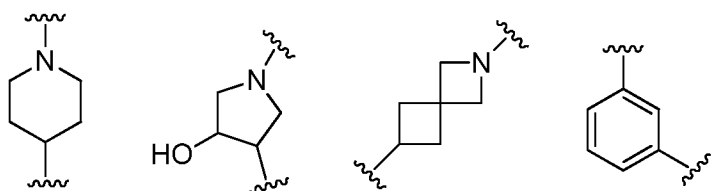
Y is NH, NHCH₂, or O;R¹⁰ is Het², Cyc, Ar², Het¹ or A; and

Q is a warhead selected from Table 1 or Table 2.

In certain embodiments, the invention provides a compound of any of formulae IA – ID, wherein R¹⁰ is piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, indazolyl, azabicyclo[3.2.1]octyl, azabicyclo[2.2.2]octyl, imidazolidinyl, azetidiny, azepanyl, benzo-2,1,3-thiadiazolyl, tetrahydrofuryl, dioxolanyl, tetrahydrothienyl, dihydropyrrolyl, tetrahydroimidazolyl, dihydropyrazolyl, tetrahydropyrazolyl, tetrahydropyridyl, dihydropyridyl, dihydrobenzodioxinyl, piperidinyl, piperazinyl, pyrrolidinyl,

morpholinyl, azabicyclo[3.2.1]octyl, azabicyclo[2.2.2]octyl, 2,7-diazaspiro[3.5]nonyl, 2,8-diazaspiro[4.5]decyl, 2,7-diazaspiro[4.4]nonyl, 3-azabicyclo[3.1.0]hexyl, 2-azaspiro[3.3]heptyl, 6-azaspiro[3.4]octyl, 7-azaspiro[3.5]nonyl, 5-azaspiro[3.5]nonyl, imidazolidinyl, azetidyl, azepanyl, tetrahydrofuryl, dioxolanyl, tetrahydrothienyl, tetrahydroimidazolyl, tetrahydropyrazolyl, tetrahydropyridyl, phenyl, naphthyl, pyridyl, cyclic alkyl having 3, 4, 5 or 6 C atoms, or unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl and/or in which one or two non-adjacent CH₂ and/or CH-groups may be replaced by O, NH and/or by N.

- 10 In certain embodiments, the invention provides a compound of any of formulae IA – ID, wherein R¹⁰ is



- In Subformula 1, Het¹ denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, indazolyl, azabicyclo[3.2.1]octyl, azabicyclo[2.2.2]octyl, imidazolidinyl, azetidyl, azepanyl, benzo-2,1,3-thiadiazolyl, tetrahydrofuryl, dioxolanyl, tetrahydrothienyl, dihydropyrrolyl, tetrahydroimidazolyl, dihydropyrazolyl, tetrahydropyrazolyl, tetrahydropyridyl, dihydropyridyl or dihydrobenzodioxinyl, each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, O(CH₂)_nAr³ and/or (CH₂)_nAr³.

- In Subformula 2, Het¹ denotes pyrazolyl, pyridyl, pyrimidinyl, dihydropyridyl or dihydrobenzodioxinyl, each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, O(CH₂)_nAr³ and/or (CH₂)_nAr³.

- In Subformula 3, Het² denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, azabicyclo[3.2.1]octyl, azabicyclo[2.2.2]octyl, 2,7-diazaspiro[3.5]nonyl, 2,8-diazaspiro[4.5]decyl, 2,7-diazaspiro[4.4]nonyl, 3-azabicyclo[3.1.0]hexyl, 2-azaspiro[3.3]heptyl, 6-azaspiro[3.4]octyl, 7-azaspiro[3.5]nonyl, 5-azaspiro[3.5]nonyl, imidazolidinyl, azetidyl, azepanyl, tetrahydrofuryl, dioxolanyl, tetrahydrothienyl, tetrahydroimidazolyl, tetrahydropyrazolyl, tetrahydropyridyl, each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, Het³, CycSO₂, OH, OA, COA, COHet³, CycCO, SO₂ and/or =O.

In Subformula 4, Het³ denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, imidazolidinyl, azetidyl, azepanyl, tetrahydrofuryl, dioxolanyl, tetrahydrothienyl, dihydropyrrolyl, tetrahydroimidazolyl, dihydropyrazolyl, tetrahydropyrazolyl, tetrahydropyridyl or dihydropyridyl, each of which may be unsubstituted or mono-, di- or trisubstituted by Hal, A and/or =O.

In Subformula 5, Het³ denotes piperidinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, dihydropyrrolyl, dihydropyrazolyl or dihydropyridyl, each of which may be unsubstituted or mono-, di- or trisubstituted by Hal, A and/or =O.

In Subformula 6, Het⁴ denotes hexahydrothieno[3,4-d]imidazolyl, benzo[c][1,2,5]oxadiazolyl or 5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-uidyl, each of which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, NO₂, Hal and/or =O.

In Subformula 7, selected substituents of Formula I are further defined such that:

	X	denotes CH or N,
	R ¹	denotes NH ₂ , CONH ₂ or H,
20	R ²	denotes Hal, Ar ¹ or Het ¹ ,
	R ³	denotes NR ⁵ [C(R ⁵) ₂] _n Het ² , NR ⁵ [C(R ⁵) ₂] _n Cyc, Het ² , O[C(R ⁵) ₂] _n Ar ² , NR ⁵ [C(R ⁵) ₂] _n Ar ² , O[C(R ⁵) ₂] _n Het ² , NR ⁵ (CH ₂) _p NR ⁵ R ⁶ , O(CH ₂) _p NR ⁵ R ⁶ or NR ⁵ (CH ₂) _p CR ⁷ R ⁸ NR ⁵ R ⁶ ,
	R ⁴	denotes H,
25	R ⁵	denotes H or alkyl having 1, 2, 3 or 4 C atoms,
	R ⁶	N(R ⁵) ₂ CH ₂ CH=CHCONH, Het ³ CH ₂ CH=CHCONH, CH ₂ =CHCONH(CH ₂) _n , Het ⁴ (CH ₂) _n COHet ³ -diyl-CH ₂ CH=CHCONH, HC≡CCO, CH ₃ C≡CCO, CH ₂ =CH-CO, CH ₂ =C(CH ₃)CONH, CH ₃ CH=CHCONH(CH ₂) _n , N≡CCR ⁷ R ⁸ CONH(CH ₂) _n , Het ⁴ NH(CH ₂) _p COHet ³ -diyl-CH ₂ CH=CHCONH, Het ⁴ (CH ₂) _p CONH(CH ₂ CH ₂ O) _p (CH ₂) _p COHet ³ -diyl-CH ₂ CH=CHCONH, CH ₂ =CHSO ₂ , ACH=CHCO, CH ₃ CH=CHCO, Het ⁴ (CH ₂) _p CONH(CH ₂) _p Het ³ -diyl-CH ₂ CH=CHCONH, Ar ³ CH=CHSO ₂ , CH ₂ =CHSO ₂ NH or N(R ⁵)CH ₂ CH=CHCO,
30		
35	R ⁷ , R ⁸	denote together alkylene having 2, 3, 4, or 5 C atoms,

	Ar ¹	denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di- or trisubstituted by R ⁶ , Hal, (CH ₂) _n NH ₂ , CONHAr ³ , (CH ₂) _n NHCOA, O(CH ₂) _n Ar ³ , OCyc, A, COHet ³ , OA and/or OHet ³ (CH ₂),
5	Ar ²	denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di- or trisubstituted by R ⁶ , Hal, OAr ³ , (CH ₂) _n NH ₂ , (CH ₂) _n NHCOA and/or Het ³ ,
	Ar ³	denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by OH, OA, Hal, CN and/or A,
10	Het ¹	denotes piperidiny, piperaziny, pyrrolidiny, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, benzimidazolyl, benzotriazolyl, indolyl, benzo-1,3-dioxolyl, indazolyl, azabicyclo[3.2.1]octyl, azabicyclo[2.2.2]octyl, imidazolidinyl, azetidiny, azepanyl, benzo-2,1,3-thiadiazolyl, tetrahydrofuryl, dioxolanyl, tetrahydrothienyl, dihydropyrrolyl,
15		tetrahydroimidazolyl, dihydropyrazolyl, tetrahydropyrazolyl, tetrahydropyridyl, dihydropyridyl or dihydrobenzodioxinyl, each of which is unsubstituted or mono-, di- or trisubstituted by R ⁶ , O(CH ₂) _n Ar ³ and/or (CH ₂) _n Ar ³ ,
20	Het ²	denotes piperidiny, piperaziny, pyrrolidiny, morpholinyl, azabicyclo[3.2.1]octyl, azabicyclo[2.2.2]octyl, 2,7-diazaspiro[3.5]nonyl, 2,8-diazaspiro[4.5]decyl, 2,7-diazaspiro[4.4]nonyl, 3-azabicyclo[3.1.0]hexyl, 2-azaspiro[3.3]heptyl, 6-azaspiro[3.4]octyl, 7-azaspiro[3.5]nonyl, 5-azaspiro[3.5]nonyl, imidazolidinyl, azetidiny, azepanyl, tetrahydrofuryl, dioxolanyl, tetrahydrothienyl,
25		tetrahydroimidazolyl, tetrahydropyrazolyl, tetrahydropyridyl, each of which is unsubstituted or mono-, di- or trisubstituted by R ⁶ , Het ³ , CycSO ₂ , OH, OA, COA, COHet ³ , CycCO, SO ₂ and/or =O,
30	Het ³	denotes piperidiny, piperaziny, pyrrolidiny, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, imidazolidinyl, azetidiny, azepanyl, tetrahydrofuryl, dioxolanyl, tetrahydrothienyl, dihydropyrrolyl, tetrahydroimidazolyl, dihydropyrazolyl, tetrahydropyrazolyl, tetrahydropyridyl or dihydropyridyl, each of which may be unsubstituted or
35		mono-, di- or trisubstituted by Hal, A and/or =O,
	Het ⁴	denotes hexahydrothieno[3,4-d]imidazolyl, benzo[c][1,2,5]oxadiazolyl or 5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-uidyl, each of which

may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, NO₂, Hal and/or =O,

Cyc denotes cyclic alkyl having 3, 4, 5 or 6 C atoms, which is unsubstituted or monosubstituted by R⁶ and which may comprise a double bond,

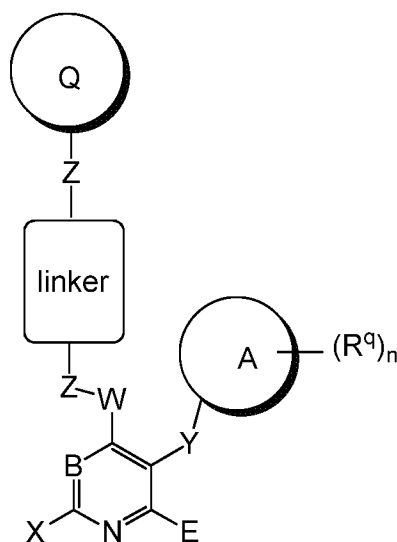
5 A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl and/or in which one or two non-adjacent CH₂ and/or CH-groups may be replaced by O, NH and/or by N,

Hal denotes F, Cl, Br or I,

10 n denotes 0, 1, 2, 3 or 4,

p denotes 1, 2, 3, 4, 5 or 6.

In some embodiments of the present invention, the kinase inhibitors of the present invention are also defined by Formula (II):



(II)

in which:

X is H or CH₃ or NH₂;

Y is absent;

20 B is N or CH;

E is NH₂ or H;

W is NR, O or cyclic amine;

Z is, independently, CH₂, CH₂-CH₂, =CH-CH₂, CH=CH, NH or absent;

Linker is -(CH₂)_n-; an optionally substituted group selected from phenyl, aryl,

25 heteroaryl, branched or unbranched alkyl, 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from

nitrogen or oxygen, a 4-7 membered saturated or partially unsaturated heterocycle having 1-3 heteroatoms independently selected from nitrogen or oxygen, a 7-10 membered bicyclic saturated or partially unsaturated heterocycle having 1-5 heteroatoms independently selected from nitrogen or oxygen, and a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms attached to a hetero saturated ring; a cycloalkane optionally substituted by heteroatoms independently selected from nitrogen or oxygen; a cycloalkane optionally substituted with -NH or OH; fused or bridged rings; or an optionally substituted spirocycle that optionally contains one or more heteroatoms;

A is a mono- or bicyclic aromatic carbocyclic or heterocycle having 0, 1, 2, 3 or 4 N and/or O atoms and 5, 6, 7, 8, 9 or 10 skeleton C atoms, which may be unsubstituted or, independently of one another, mono-, di- or trisubstituted by Hal, OH or OR;

Hal is F, Cl, Br or I;

R is, independently, hydrogen; oxygen; an optionally substituted group selected from C₁₋₆ linear or cyclic aliphatic, benzyl, phenyl, a 4-7 membered heterocycle having 1-2 heteroatoms independently selected from nitrogen or oxygen, and 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen or oxygen; a mono- or bicyclic aromatic homo- or heterocycle having 0, 1, 2, 3 or 4 N and/or O atoms and 5, 6, 7, or 8 C skeleton atoms, which may be unsubstituted or, independently of one another, mono-, di- or trisubstituted by Hal, A, OH, NH₂, nitrile and/or CH(Hal)₃; or unbranched or branched linear alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 C atoms in which one or two CH₂ groups may be replaced by O, -NH-, -CO-, -NHCOO-, -NHCONH-, -CONH-, -NHCO- or -CH=CH- and/or in which 1-3 H atoms may be replaced by Hal;

R^q is R, A, Hal, OR, O(CH₂)_rOR, NO₂, C(O)R, CO₂R, C(O)N(R)₂, NRC(O)R, NRC(O)NR₂, NRSO₂R or N(R)₂;

r is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4; and

Q is a warhead as defined in Table 1 or Table 2;

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

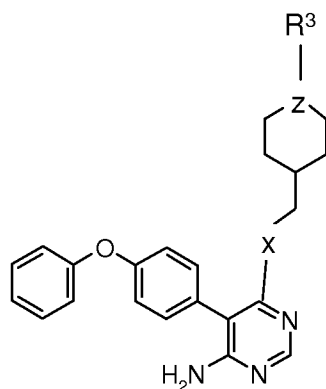
As used herein the term "warhead" refers to a part, functional group or substituent of the compounds as claimed in the present invention, wherein, said part, functional group or substituent covalently binds to an amino acid (such as cysteine, lysine, or any other amino acid, either native or modified, that can form said covalent bond) that is present, for example, in the binding region within a given ligand wherein said warhead binds with said ligand, wherein the covalent binding between said warhead and the binding region of said target protein occurs under conditions wherein a physiological function of said protein is irreversibly inhibited.

- 10 While it is not intended that the present invention be limited to a specific group for substituent Q, as set out in Formula (II) above, in certain embodiments substituent Q is selected from the groups set out in Table 1 or Table 2.

The prior teaching of the present specification concerning the compounds of Formula (I) attached to a warhead is valid and applicable without restrictions to the compounds according to Formula (II) attached to a warhead if expedient. Similarly, the teaching of the present specification concerning the compounds of Formulae (I) and (II) is valid and applicable without restrictions to the compounds according to Formulae (I) and (II) attached to a warhead in the meaning of the invention.

20

In some embodiments, the pyrimidine and pyridine kinase inhibitors of the present invention are also defined by Formula (IV):

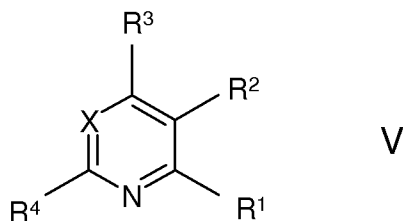


Formula (IV)

- 25 and pharmaceutically acceptable salts, solvates, solvates of salts, or prodrugs thereof, wherein:

Z is N or CH,
 X is O or NH, and
 R³ is selected from Table 1 or Table 2.

In some embodiments, the pyrimidine and pyridine kinase inhibitors of the present invention are also defined by (i) a compound of Formula (V):



5 and pharmaceutically acceptable salts, solvates, solvates of salts, or prodrugs thereof, in which:

X denotes CH or N,

R¹ denotes NR⁵[C(R⁵)₂]_nHet²,

R² denotes Hal, Ar¹ or Het¹,

10 R³ denotes NH₂,

R⁴ denotes H, CH₃ or NH₂,

R⁵ denotes H or alkyl having 1, 2, 3 or 4 C atoms,

R⁶ N(R⁵)₂CH₂CH=CHCONH, Het³CH₂CH=CHCONH,
CH₂=CHCONH(CH₂)_n, Het⁴(CH₂)_nCOHet³-diyl-CH₂CH=CHCONH,

15 HC≡CCO, CH₃C≡CCO, CH₂=CH-CO, CH₂=C(CH₃)CONH,

CH₃CH=CHCONH(CH₂)_n, N≡CCR⁷R⁸CONH(CH₂)_n,

Het⁴NH(CH₂)_pCOHet³-diyl-CH₂CH=CHCONH,

Het⁴(CH₂)_pCONH(CH₂CH₂O)_p(CH₂)_pCOHet³-diyl-CH₂CH=CHCONH,

CH₂=CHSO₂, ACH=CHCO, CH₃CH=CHCO,

20 Het⁴(CH₂)_pCONH(CH₂)_pHet³-diyl-CH₂CH=CHCONH, Ar³CH=CHSO₂,

CH₂=CHSO₂NH or N(R⁵)CH₂CH=CHCO,

R⁷, R⁸ denote together alkylene having 2, 3, 4, or 5 C atoms,

Ar¹ denotes phenyl or naphthyl, each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, Hal, (CH₂)_nNH₂, CONHAr³, (CH₂)_nNHCOA,
25 O(CH₂)_nAr³, OCyc, A, COHet³, OA and/or OHet³ (CH₂),

Ar² denotes phenyl, naphthyl or pyridyl each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, Hal, OAr³, (CH₂)_nNH₂, (CH₂)_nNHCOA and/or Het³,

Ar³ denotes phenyl, which is unsubstituted or mono-, di- or trisubstituted by
30 OH, OA, Hal, CN and/or A,

Het¹ denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be

unsubstituted or mono-, di- or trisubstituted by R^6 , $O(CH_2)_nAr^3$ and/or $(CH_2)_nAr^3$,

Het² denotes a mono- or bicyclic saturated heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by R^6 , Het³, CycSO₂, OH, Hal, COOH, OA, COA, COHet³, CycCO, SO₂ and/or =O,

Het³ denotes a monocyclic unsaturated, saturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by Hal, A and/or =O,

Het⁴ denotes a bi- or tricyclic unsaturated, saturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, NO₂, Hal and/or =O,

Cyc denotes cyclic alkyl having 3, 4, 5 or 6 C atoms, which is unsubstituted, monosubstituted or disubstituted by R^6 and/or OH and which may comprise a double bond,

A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl and/or in which one or two non-adjacent CH₂ and/or CH-groups may be replaced by O, NH and/or by N,

Hal denotes F, Cl, Br or I,

n denotes 0, 1, 2, 3 or 4,

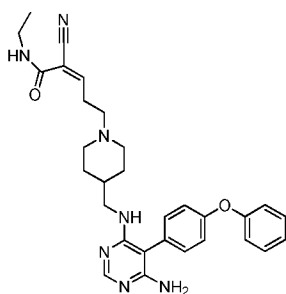
p denotes 1, 2, 3, 4, 5 or 6,

and (ii) an electrophilic warhead selected from Table 1 or Table 2,

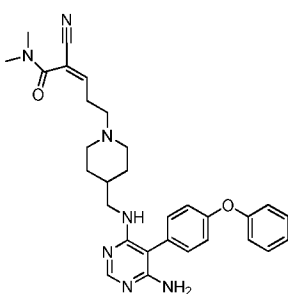
wherein the warhead is coupled to the compound of Formula (V) at R^1 , R^2 or R^3 ;

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

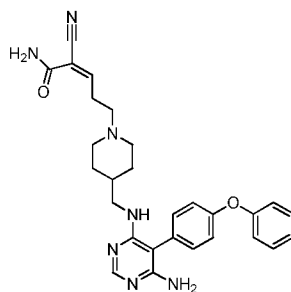
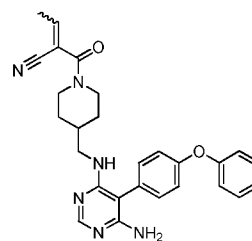
In certain embodiments, the invention provides a compound from below.



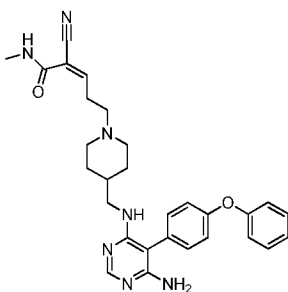
and the E isomer



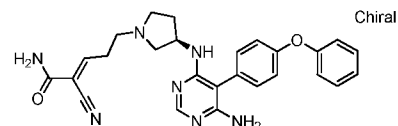
and the E isomer



and the E isomer

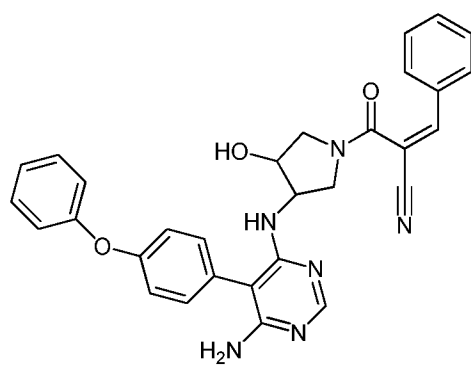


and the E isomer

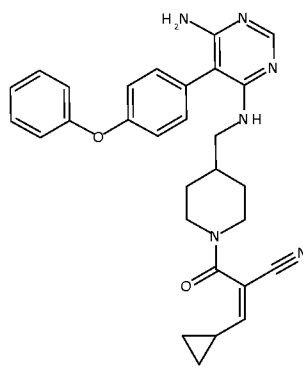


and the E isomer

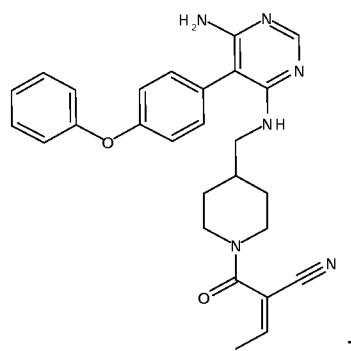
In certain embodiments, the invention provides a compound from below



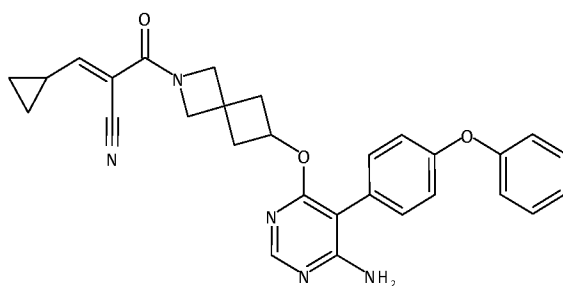
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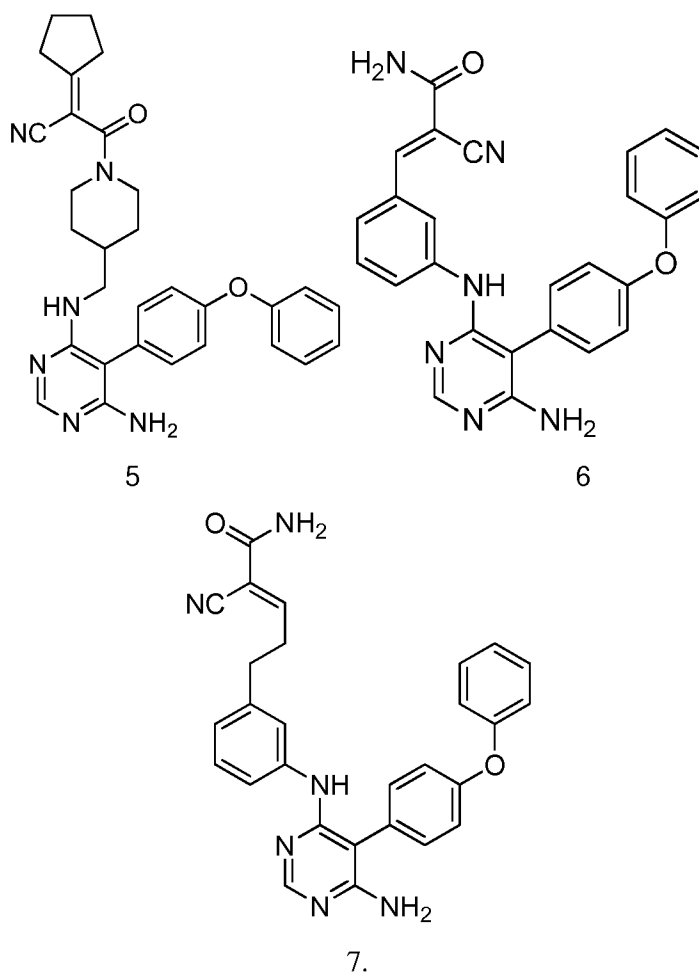


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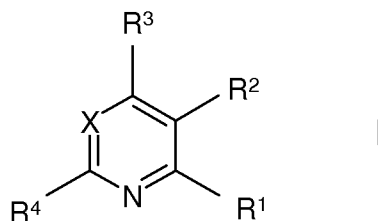
5

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

10

The kinase inhibitor of the invention can be prepared by a process comprising the steps of:

- a) reacting a compound of Formula (I)

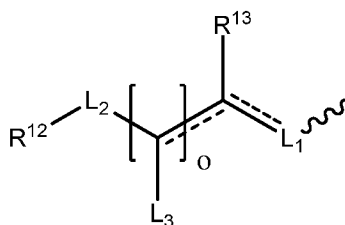


(I)

15

in which R^1 - R^4 and X have the meanings indicated above,

with a warhead of Formula (VI)



(VI)

in which L₁, L₂, L₃, R¹², R¹³ and o have the meanings indicated above,
to yield the kinase inhibitor in the meaning of the invention;

and optionally

(b) converting a base or an acid of the kinase inhibitor into one of its salts.

- 10 The invention also relates to a medicament comprising at least one inhibitor of the invention and/or a pharmaceutically usable salt, tautomer or stereoisomers thereof, including mixtures thereof in all ratios.

- 15 In another aspect the invention relates to a pharmaceutical composition comprising as active ingredient at least one inhibitor of the invention and/or a pharmaceutically usable salt, tautomer or stereoisomer thereof, including mixtures thereof in all ratios, together with pharmaceutically tolerable excipients and/or adjuvants, optionally in combination with one or more further active ingredients.

- 20 In general, all residues which occur more than once may be identical or different, i.e. are independent of one another. In other embodiments, the residues and parameters have the meanings indicated for the Formula (I), unless expressly indicated otherwise.

- 25 Further preferred are compounds of Subformulae 1 to 7 of Formula (I), in which the residues not designated in greater detail have the meaning indicated for the preferred group of compounds above, and pharmaceutically acceptable salts, solvates, solvates of salts, or prodrugs thereof.

- 30 In general, all residues which occur more than once may be identical or different, i.e. are independent of one another. Above and below, the residues and parameters have the meanings indicated for Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V) unless expressly indicated otherwise. Accordingly, the invention relates, in particular, to the compounds of Formula (I), Formula (IA), Formula (IB),

Formula (II), Formula (III), Formula (IV) and Formula (V) in which at least one of the said residues has one of the preferred meanings indicated below.

5 The term "substituted" preferably relates to the substitution by the above-mentioned substituents, where a plurality of different degrees of substitution are possible, unless indicated otherwise.

10 All physiologically acceptable salts, derivatives, solvates, solvates of salts, and stereoisomers of these compounds, including mixtures thereof in all ratios, are also in accordance with the invention.

The compounds of the Formula (I), (IA), (IB), (II), (III), (IV) and (V) may have one or more centres of chirality. They may accordingly occur in various enantiomeric forms and be in racemic or optically active form. The invention therefore also relates to the optically active
15 forms (stereoisomers), the enantiomers, the racemates, the diastereomers and hydrates and solvates of these compounds.

Since the pharmaceutical activity of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these
20 cases, the end product or even the intermediates can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with
25 an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitably N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline), or the various optically active camphorsulfonic acids. Also advantageous is chromatographic enantiomer resolution with the aid of an
30 optically active resolving agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel). Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/ acetonitrile, for example in the ratio 82:15:3. An elegant method for the resolution of racemates containing ester groups (for
35 example acetyl esters) is the use of enzymes, in particular esterases.

It is also contemplated that compounds of Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V) include isotope-labeled forms thereof. An isotope-labeled form of a compound of Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V) is identical to this compound apart from the fact that one or more atoms of the compound have been replaced by an atom or atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the atom which usually occurs naturally. Examples of isotopes which are readily commercially available and which can be incorporated into a compound of the Formula I by well-known methods include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. It is also contemplated that a compound of the Formula I, a prodrug, thereof or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other iso-topes of other atoms are embodiments of the present invention. An isotope-labeled compound of the Formula I can be used in a number of beneficial ways. For example, an isotope-labeled compound of the Formula I into which, for example, a radioisotope, such as ^3H or ^{14}C , has been incorporated, is suitable for medicament and/or substrate tissue distribution assays. These radioisotopes, i.e. tritium (^3H) and carbon-14 (^{14}C), are particularly preferred owing to their ease of preparation and excellent detectability. Incorporation of heavier isotopes, for example deuterium (^2H), into a compound of the Formula I may have therapeutic advantages owing to the higher metabolic stability of this isotope-labeled compound. Higher metabolic stability translates directly into an increased *in vivo* half-life or lower dosages, which under some circumstances would represent a preferred embodiment of the present invention. An isotope-labeled compound of the Formula I can adapted to the procedures disclosed in the synthesis schemes and the related description, in the example part and in the preparation part in the present text, replacing a non-isotope-labeled reactant by a readily available isotope-labeled reactant.

In other embodiments it is contemplated that deuterium (^2H) may be incorporated into a compound of Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V). Such deuterated compounds can modify the oxidative metabolism of said deuterated compound by means the primary kinetic isotope effect. The primary kinetic isotope effect is a change of the rate for a chemical reaction that results from exchange of isotopic nuclei, which in turn is caused by the change in ground state energies necessary for covalent bond formation after this isotopic exchange. Exchange of a heavier isotope usually results in a lowering of the ground state energy for a chemical bond and thus causes a reduction in the rate in rate-limiting bond breakage. If the bond breakage occurs in or in the vicinity of a saddle-point region along the coordinate of a multi-product reaction, the product

distribution ratios can be altered substantially. For explanation: if deuterium is bonded to a carbon atom at a non-exchangeable position, rate differences of $k_M/k_D = 2-7$ are typical. If this rate difference is observed in any compounds of Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V) susceptible to oxidation, the profile of this compound, *in vivo*, can be drastically modified and result in improved pharmacokinetic properties.

When discovering and developing therapeutic agents, the person skilled in the art attempts to optimize pharmacokinetic parameters while retaining desirable *in vitro* properties. It is reasonable to assume that many compounds with poor pharmacokinetic profiles are susceptible to oxidative metabolism. *In vitro* liver microsomal assays known in the art may provide valuable information on the course of oxidative metabolism of this type, which in turn permits the rational design of deuterated compounds of Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V) with improved stability through resistance to said oxidative metabolism. Significant improvements in the pharmacokinetic profiles of compounds of the Formula I may thereby be obtained, and can be expressed quantitatively in terms of increases in the *in vivo* half-life ($t_{1/2}$), concentration at maximum therapeutic effect (C_{max}), area under the dose response curve (AUC), and F; and in terms of reduced clearance, dose and materials costs.

While it is not intended that the present invention be limited to any deuterated motif, the following is an example. A compound of Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V) which has multiple potential sites of attack for oxidative metabolism, for example benzylic hydrogen atoms and hydrogen atoms bonded to a nitrogen atom, is prepared as a series of analogues in which various combinations of hydrogen atoms are replaced by deuterium atoms, so that some, most or all of these hydrogen atoms have been replaced by deuterium atoms. Half-life determinations enable favorable and accurate determination of the extent to which the improvement in resistance to oxidative metabolism has improved. In this way, it can be determined that the half-life of the parent compound may be extended by up to 100% as the result of deuterium-hydrogen exchange of this type.

Deuterium-hydrogen exchange in a compound of Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V) can also be used to achieve a favorable modification of the metabolite spectrum of the starting compound in order to diminish or eliminate undesired toxic metabolites. For example, if a toxic metabolite arises through oxidative carbon-hydrogen (C-H) bond cleavage, it can reasonably be assumed that

the deuterated analogue will greatly diminish or eliminate production of the unwanted metabolite, even if the particular oxidation is not a rate-determining step. Further information on the state of the art with respect to deuterium-hydrogen exchange may be found, for example in Hanzlik et al., J. Org. Chem. **55**, 3992-3997, 1990, Reider et al., J. Org. Chem. **52**, 3326-3334, 1987, Foster, Adv. Drug Res. **14**, 1-40, 1985, Gillette et al, Biochemistry **33**(10) 2927-2937, 1994, and Jarman et al. Carcinogenesis **16**(4), 683-688, 1993.

The compounds of the present invention can be in the form of a prodrug compound.

"Prodrug compound" means a derivative that is converted into a biologically active compound according to the present invention under physiological conditions in the living body, e.g., by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically, or without enzyme involvement. Examples of prodrugs are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated, or wherein a sulfhydryl group forms a disulfide bridge with a carrier molecule, e.g. a peptide, that delivers the drug selectively to a target and/or to the cytosol of a cell. These compounds can be produced from compounds of the present invention according to well-known methods. Other examples of prodrugs are compounds, wherein the carboxylate in a compound of the present invention is for example converted into an alkyl-, aryl-, choline-, amino, acyloxymethylester, linolenoyl-ester.

Metabolites of compounds of the present invention are also within the scope of the present invention.

Where tautomerism, e.g., keto-enol tautomerism, of compounds of the present invention or their prodrugs may occur, the individual forms, e.g., the keto or the enol form, are claimed separately and together as mixtures in any ratio. The same applies for stereoisomers, e.g., enantiomers, cis/trans isomers, conformers and the like. If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. The same applies for enantiomers, e.g., by using chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e., coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of the present invention may be obtained from stereoselective synthesis using optically pure starting materials

The compounds of the present invention can be in the form of a pharmaceutically acceptable salt or a solvate. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids. In cases where the compounds of the present invention contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the present invention which contain acidic groups can be present in salt form, and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the present invention which contain one or more basic groups, i.e. groups which can be protonated, can be present in salt form, and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples of suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the present invention simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods which are known to a person skilled in the art, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the present invention which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

Furthermore, the present invention relates to pharmaceutical compositions comprising a compound of the present invention, or a prodrug compound thereof, or a pharmaceutically acceptable salt or solvate thereof as an active ingredient together with a pharmaceutically acceptable carrier.

"Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the present invention may additionally comprise one or more other compounds as active ingredients, such as one or more additional compounds of the present invention, or a prodrug compound or other BTK inhibitors. The pharmaceutical compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

It is another object of the invention to provide an inhibitor according to invention above and below and/or a pharmaceutically usable salt, tautomer or stereoisomer thereof, including mixtures thereof in all ratios, for use in the prophylactic or therapeutic treatment and/or monitoring of a disease that is caused, mediated and/or propagated by BTK activity.

In still a further object, the invention relates to a method for treating a disease that is caused, mediated and/or propagated by BTK activity, wherein at least one inhibitor as described above and below and/or a pharmaceutically usable salt, tautomer or stereoisomer thereof, including mixtures thereof in all ratios, is administered to a mammal in need of such treatment. In a preferred embodiment of the method of treatment, the disease is a solid tumour, which is selected from the group of tumours of the squamous epithelium, bladder, stomach, kidneys, head, neck, oesophagus, cervix, thyroid, intestine, liver, brain, prostate, urogenital tract, lymphatic system, larynx, lung, blood and immune system. In a more preferred embodiment of the method of treatment, the disease is a tumour, which is selected from the group of lung adenocarcinoma, small-cell lung carcinoma, pancreatic cancer, glioblastoma, colon carcinoma, breast carcinoma, monocytic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphatic leukaemia and chronic lymphatic leukaemia.

Yet another object of the invention is directed to a method for inhibiting BTK, wherein a system expressing BTK is contacted with at least one inhibitor of the invention and/or a pharmaceutically usable salt, tautomer or stereoisomer thereof, including mixtures thereof in all ratios, under conditions such that BTK is inhibited, preferably irreversibly and/or in-vitro.

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In one embodiment, said compounds and pharmaceutical composition are for the treatment of cancer such as brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, uterine, rectal, oesophageal, testicular, gynecological, thyroid cancer, melanoma, hematologic malignancies such as acute myelogenous leukemia, multiple myeloma, chronic myelogenous leukemia, myeloid cell leukemia, glioma, Kaposi's sarcoma, or any other type of solid or liquid tumors. Preferably, the cancer to be treated is chosen from breast, colorectal, lung, prostate or pancreatic cancer or glioblastoma.

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The invention also relates to the use of compounds according to the invention for the preparation of a medicament for the treatment of hyperproliferative diseases related to the hyperactivity of BTK as well as diseases modulated by the BTK cascade in mammals, or disorders mediated by aberrant proliferation, such as cancer or hyperactivity of B cells, mast cells, neutrophils and monocytes such in inflammatory conditions.

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The invention also relates to a compound or pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.

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In one embodiment, said compound or pharmaceutical composition is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, Sjögren's Syndrome, atherosclerosis, skin and allergic diseases such as psoriatic arthritis, psoriasis, eczema, and sclerodema, asthma and atopic dermatitis or diseases such as diabetes, diabetic retinopathy, retinopathy of prematurity and age-related macular degeneration.

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In one embodiment the treatment of rheumatoid arthritis with BTK inhibitors is preferred given experimental validation which confirms the efficacy of BTK inhibitors in the treatment of collagen antibody induced arthritis and collagen induced arthritis. Pan, Z. et al., Discovery

of Selective Irreversible Inhibitors of Brunton's Tyrosine Kinase. ChemMedChem 2, 58-61 (2007). More specifically treatment with BTK inhibitors have been show to reduce the incidence and severity of collagen induced arthritis and K/BxN serum induced arthritis.

- 5 This invention also relates to a compound or pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate or prodrug thereof, in combination with an amount of another anti-cancer therapeutic, wherein the amounts of the compound, salt, solvate, or prodrug, and of the chemotherapeutic are together effective in inhibiting abnormal cell growth.
- 10 As used here, the term "anticancer agent" relates to any agent which is administered to a patient with cancer for the purposes of treating the cancer. The anti-cancer treatment defined above may be applied as a monotherapy or may involve, in addition to the herein disclosed compounds of formula I, conventional surgery or radiotherapy or medicinal therapy. Such medicinal therapy, e.g. a chemotherapy or a targeted therapy, may include one or more, but preferably one, of the
- 15 following anti-tumor agents: Alkylating agents such as altretamine, bendamustine, busulfan, carmustine, chlorambucil, chlormethine, cyclophosphamide, dacarbazine, ifosfamide, improsulfan, tosilate, lomustine, melphalan, mitobronitol, mitolactol, nimustine, ranimustine, temozolomide, thiotepa, treosulfan, mechlorethamine, carboquone; apaziquone, fotemustine, glufosfamide, palifosfamide, pipobroman, trofosfamide, uramustine, TH-302⁴, VAL-083⁴;
- 20 Platinum Compounds such as carboplatin, cisplatin, eptaplatin, miriplatine hydrate, oxaliplatin, lobaplatin, nedaplatin, picoplatin, satraplatin; lobaplatin, nedaplatin, picoplatin, satraplatin; DNA altering agents such as amrubicin, bisantrene, decitabine, mitoxantrone, procarbazine, trabectedin, clofarabine; amsacrine, brostallicin, pixantrone, laromustine^{1,3}; Topoisomerase Inhibitors such as etoposide, irinotecan, razoxane, sobuzoxane, teniposide, topotecan;
- 25 amonafide, belotecan, elliptinium acetate, voreloxin; Microtubule modifiers such as cabazitaxel, docetaxel, eribulin, ixabepilone, paclitaxel, vinblastine, vincristine, vinorelbine, vindesine, vinflunine; fosbretabulin, tesetaxel; Antimetabolites such as asparaginase³, azacitidine, calcium levofofinate, capecitabine, cladribine, cytarabine, enocitabine, floxuridine, fludarabine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, nelarabine, pemetrexed, pralatrexate,
- 30 azathioprine, thioguanine, carmofur; doxifluridine, elacytarabine, raltitrexed, sapacitabine, tegafur^{2,3}, trimetrexate; Anticancer antibiotics such as bleomycin, dactinomycin, doxorubicin, epirubicin, idarubicin, levamisole, miltefosine, mitomycin C, romidepsin, streptozocin, valrubicin, zinostatin, zorubicin, daunorubicin, plicamycin; aclarubicin, peplomycin, pirarubicin; Hormones/Antagonists such as abarelix, abiraterone, bicalutamide, buserelin, calusterone,
- 35 chlorotrianisene, degarelix, dexamethasone, estradiol, fluocortolone, fluoxymesterone, flutamide, fulvestrant, goserelin, histrelin, leuprorelin, megestrol, mitotane, nafarelin, nandrolone, nilutamide, octreotide, prednisolone, raloxifene, tamoxifen, thyrotropin alfa, toremifene,

trilostane, triptorelin, diethylstilbestrol; acolbifene, danazol, deslorelin, epitiostanol, orteronel, enzalutamide^{1,3}; Aromatase inhibitors such as aminoglutethimide, anastrozole, exemestane, fadrozole, letrozole, testolactone; formestane; Small molecule kinase inhibitors such as crizotinib, dasatinib, erlotinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib, vemurafenib, bosutinib, gefitinib, axitinib; afatinib, alisertib, dabrafenib, dacomitinib, dinaciclib, dovitinib, enzastaurin, nintedanib, lenvatinib, linifanib, linsitinib, masitinib, midostaurin, motesanib, neratinib, orantinib, perifosine, ponatinib, radotinib, rigosertib, tipifarnib, tivantinib, tivozanib, trametinib, pimasertib, brivanib alaninate, cediranib, apatinib⁴, cabozantinib S-malate^{1,3}, ibrutinib^{1,3}, icotinib⁴, buparlisib², ciplatinib⁴, cobimetinib^{1,3}, idelalisib^{1,3}, fedratinib¹, XL-647⁴; Photosensitizers such as methoxsalen³; porfimer sodium, talaporfin, temoporfin; Antibodies such as alemtuzumab, besilesomab, brentuximab vedotin, cetuximab, denosumab, ipilimumab, ofatumumab, panitumumab, rituximab, tositumomab, trastuzumab, bevacizumab, pertuzumab^{2,3}; catumaxomab, elotuzumab, epratuzumab, farletuzumab, mogamulizumab, necitumumab, nimotuzumab, obinutuzumab, ocaratuzumab, oregovomab, ramucirumab, rilotumumab, siltuximab, tocilizumab, zalutumumab, zanolimumab, matuzumab, dalotuzumab^{1,2,3}, onartuzumab^{1,3}, racotumomab¹, tabalumab^{1,3}, EMD-525797⁴, nivolumab^{1,3}; Cytokines such as aldesleukin, interferon alfa², interferon alfa2a³, interferon alfa2b^{2,3}; celmoleukin, tasonermin, teceleukin, oprelvekin^{1,3}, recombinant interferon beta-1a⁴; Drug Conjugates such as denileukin diftitox, ibritumomab tiuxetan, iobenguane I123, prednimustine, trastuzumab emtansine, estramustine, gemtuzumab, ozogamicin, aflibercept; cintredekin besudotox, edotreotide, inotuzumab ozogamicin, naptumomab estafenatox, oportuzumab monatox, technetium (99mTc) arcitumomab^{1,3}, vintafolide^{1,3}; Vaccines such as sipuleucel³; vitespen³, emepepimut-S³, oncoVAX⁴, rindopepimut³, troVax⁴, MGN-1601⁴, MGN-1703⁴; Miscellaneous alitretinoin, bexarotene, bortezomib, everolimus, ibandronic acid, imiquimod, lenalidomide, lentinan, metirosine, mifamurtide, pamidronic acid, pegaspargase, pentostatin, sipuleucel³, sizofiran, tamibarotene, temsirolimus, thalidomide, tretinoin, vismodegib, zoledronic acid, vorinostat; celecoxib, cilengitide, entinostat, etanidazole, ganetespib, idronoxil, iniparib, ixazomib, lonidamine, nimorazole, panobinostat, peretinoin, plitidepsin, pomalidomide, procodazol, ridaforolimus, tasquinimod, telotristat, thymalfasin, tirapazamine, tosedostat, trabedersen, ubenimex, valspodar, gendicine⁴, picibanil⁴, reolysin⁴, retaspimycin hydrochloride^{1,3}, trebananib^{2,3}, virulizin⁴, carfilzomib^{1,3}, endostatin⁴, immucothel⁴, belinostat³, MGN-1703⁴; (¹ Prop. INN (Proposed International Nonproprietary Name); ² Rec. INN (Recommended International Nonproprietary Names); ³ USAN (United States Adopted Name); ⁴ no INN).

In one embodiment, the anti-cancer therapeutic is a chemotherapeutic selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating

antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

In another embodiment the anti-cancer therapeutic is an antibody selected from the group consisting of bevacizumab, CD40-specific antibodies, chTNT-1/B, denosumab,

5 zanolimumab, IGF1R-specific antibodies, lintuzumab, edrecolomab, WX G250, rituximab, ticilimumab, trastuzumab and cetuximab. In yet another embodiment the anti-cancer therapeutic is an inhibitor of another protein kinase, such as Akt, Axl, Aurora A, Aurora B, dyrk2, epha2, fgfr3, igf1r, IKK2, JNK3, Vegfr1, Vegfr2, Vegfr3 (also known as Flt-4), KDR, MEK, MET, Plk1, RSK1, Src, TrkA, Zap70, cKit, bRaf, EGFR, Jak2, PI3K, NPM-Alk, c-Abl,
10 BTK, FAK, PDGFR, TAK1, LimK, Flt-3, PDK1 and Erk.

This invention further relates to a method for inhibiting abnormal cell growth in a mammal or treating a hyperproliferative disorder that comprises administering to the mammal an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate or
15 prodrug thereof, in combination with radiation therapy, wherein the amounts of the compound, salt, solvate, or prodrug, is in combination with the radiation therapy effective in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal.

Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of a compound
20 of the invention in this combination therapy can be determined as described herein. It is believed that the compounds of the present invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells.

25 Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of the present invention or pharmaceutically acceptable salt or solvate or prodrug thereof, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, or solvate in this method can be
30 determined according to the means for ascertaining effective amounts of such compounds described herein. The invention also relates to a method for inhibiting abnormal cell growth in a mammal that comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, a prodrug thereof, or an isotopically-labeled derivative thereof, and an amount of one or more substances selected from anti-
35 angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

In practical use, the compounds of the present invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like. In the case of oral liquid preparations, any of the usual pharmaceutical media may be employed, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. In the case of oral solid preparations the composition may take forms such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of the present invention may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of the present invention are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating or preventing a disease for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.01 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose. For most large mammals, the total daily dosage is from about 0.1 milligrams to about 1000 milligrams, preferably from about 0.2 milligram to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.2 milligrams to about 200 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The invention also relates to a set (kit) consisting of separate packs of

a) an effective amount of a compound according to the invention or a physiologically acceptable salt, solvate or prodrug thereof, and

b) an effective amount of a further medicament active ingredient.

- 5 The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules, each containing an effective amount of a compound according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and an effective amount of a further medicament active ingredient in dissolved or lyophilised
- 10 form.

Experimental Section

Some abbreviations that may appear in this application are as follows:

Abbreviations

<i>Designation</i>	
ACN	acetonitrile
ATP	Adenosine triphosphate
b	Broad peak
BOC	<i>tert</i> -butyloxycarbonyl
BOP-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
d	Doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
DMSO	dimethylsulfoxide
DIEA	N,N-Diisopropylethylamine
DIPEA	diisopropylethylamine
DMF	dimethylformamide
DTT	dithiothreitol
EDTA	Ethylenediaminetetraacetic acid
equiv.	equivalents

Et	ethyl
EtOAc	ethyl acetate
h	hour
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
¹ H-NMR	proton NMR
HPLC	High pressure /performance liquid chromatography
LC	Liquid chromatography
LC/MS	Liquid chromatography coupled to mass spectrometry
m	multiplet
M	Molecular ion
m/z	Mass-to-charge ratio
MHz	megahertz
Me	methyl
min	minutes
MeOH	methanol
MS	Mass spectrometry /spectrum
N	Normal (unit of concentration)
NMO	4-methylmorpholine <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
PG	Protecting group
psi	Pounds per square inch
q	Quartette (or quartet)
R _f	Retention factor
RT/rt	Room temperature
R _t /RT	Retention time
s	Singlet
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl triplet
t	triplet
Tert	Tertiary
TEA	Triethylamine
TFA	Trifluoroacetic acid
THAB	Tetrahexylammonium bromide

THF	Tetrahydrofuran
T3P	1-Propanephosphonic Acid Cyclic Anhydride
UV	ultraviolet
VIS	visible
x	times

The compounds of the present invention can be prepared according to the procedures of the following Schemes and Examples, using appropriate materials and are further exemplified by the following specific examples. Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present invention claimed herein can be readily prepared. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

The instant compounds are generally isolated in the form of their pharmaceutically acceptable salts, such as those described above. The amine-free bases corresponding to the isolated salts can be generated by neutralization with a suitable base, such as aqueous sodium hydrogencarbonate, sodium carbonate, sodium hydroxide and potassium hydroxide, and extraction of the liberated amine-free base into an organic solvent, followed by evaporation. The amine-free base, isolated in this manner, can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent, followed by addition of the appropriate acid and subsequent evaporation, precipitation or crystallization.

The invention will be illustrated, but not limited, by reference to the specific embodiments described in the following schemes and examples. Unless otherwise indicated in the schemes, the variables have the same meaning as described above.

Unless otherwise specified, all starting materials are obtained from commercial suppliers and used without further purifications. Unless otherwise specified, all temperatures are expressed in °C and all reactions are conducted at room temperature. Compounds were purified by either silica chromatography or preparative HPLC.

The present invention also relates to processes for manufacturing the compounds of Formula (I), Formula (IA), Formula (IB), Formula (II), Formula (III), Formula (IV) and Formula (V), as described above, according to the hereinafter described schemes and working examples.

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Analytical Methodology

Analytical LC/MS was performed using the following three methods:

- 10 Method 1: A Discovery C¹⁸, 5 μ m, 3 x 30 mm column was used at a flow rate of 400 μ L/min, sample loop 5 μ L, mobile phase: (A) water with 0.1% formic acid, mobile phase, (B) methanol with 0.1% formic acid; retention times are given in minutes. Method details: (I) runs on a Quaternary Pump G1311A (Agilent) with UV/VIS diode array detector G1315B (Agilent) and Finnigan LCQ Duo MS detector in ESI + modus with UV-detection at 254 and
15 280 nm with a gradient of 15-95% (B) in a 3.2 min linear gradient (II) hold for 1.4 min at 95% (B) (III) decrease from 95-15% (B) in a 0.1 min linear gradient (IV) hold for 2.3 min at 15% (B).

- Method 2: A Waters Symmetry C¹⁸, 3.5 μ m, 4.6 x 75 mm column at a flow rate of 1 mL /min, sample loop 10 μ L, mobile phase (A) is water with 0.05% TFA, mobile phase (B) is ACN with
20 0.05% TFA; retention times are given in minutes. Methods details: (I) runs on a Binary Pump G1312A (Agilent) with UV/Vis diode array detector G1315B (Agilent) and Agilent G1956B (SL) MS detector in ESI + mode with UV-detection at 254 and 280 nm with a gradient of 20-85% (B) in a 10 min linear gradient (II) hold for 1 min at 85% (B) (III)
25 decrease from 20-85% (B) in a 0.2 min linear gradient (IV) hold for 3.8 min at 20% (B).

- Method 3: Gradient: 4.2 min/ Flow: 2 ml/min 99:01 - 0:100 Water + 0.1%(Vol.) TFA; Acetonitril + 0.1%(Vol.) TFA; 0.0 to 0.2 min: 99:01; 0.2 to 3.8 min: 99:01 $\rightarrow$ 0:100; 3.8 to 4.2 min: 0:100; Column: Chromolith Performance RP18e; 100 mm long, 3 mm diameter;
30 Wavelength: 220nm.

HPLC method for purity determination

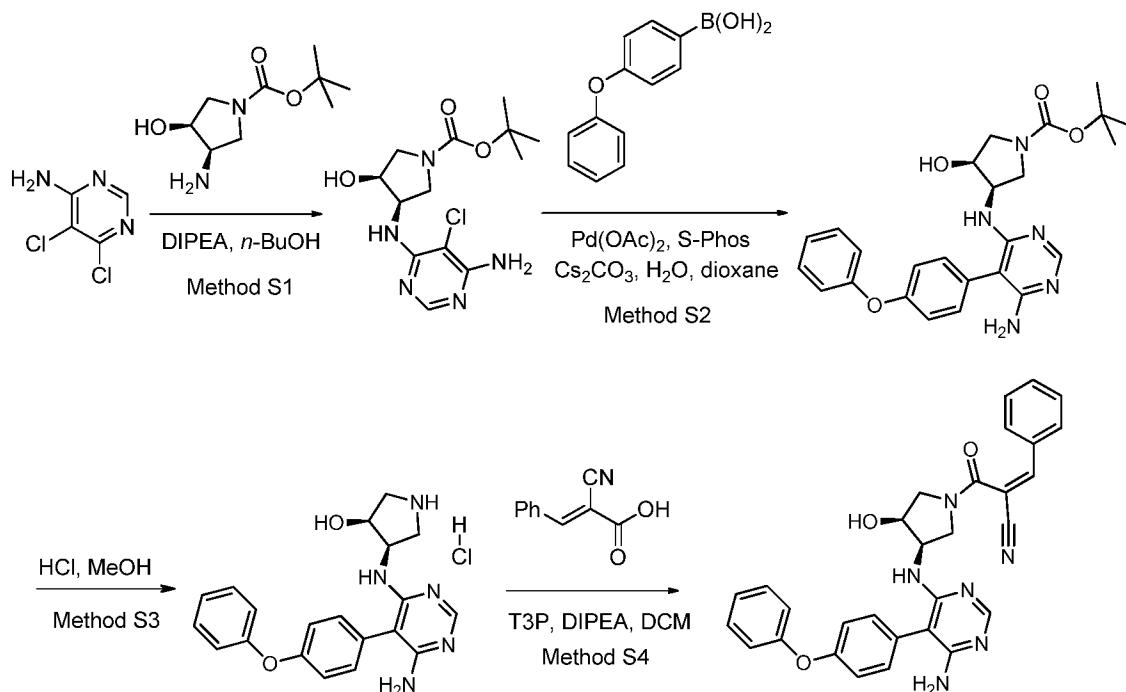
- Purity was determined on an Agilent HPLC using UV detection at 254 nm with a Waters Xbridge C8 column (5 μ m, 4.6 X 50 mm). Mobile Phase A: 0.1% TFA in water. Mobile
35 phase B: 0.1% TFA in acetonitrile. The method involved a gradient from 98% mobile phase A/2% mobile phase B to 100% mobile phase B over 8 minutes at a flow rate of 2 mL/min.

General method for preparative HPLC

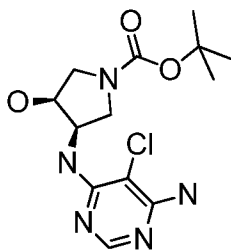
Preparative HPLC was carried out on a Waters preparative HPLC system using a Waters Sunfire C18 column (5 or 10 μ m). Mobile phase A: water with 0.1% TFA. Mobile phase B: acetonitrile. Crude compounds were loaded on the column using a minimum volume of methanol or DMSO. A typical gradient used for separation was 0-50% Mobile Phase B over 20-25 minutes with an optional wash step (100% Mobile Phase B).

Examples**Example 1**

Preparation of kinase inhibitors comprising a compound of formula (I) and a warhead as described above was carried out according to the following scheme:



Method S1: nucleophilic aromatic substitution

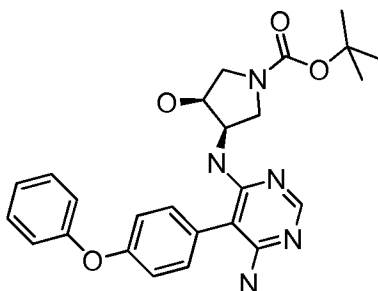


cis-3-(6-Amino-5-chloro-pyrimidin-4-ylamino)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

In a microwave vial containing 5,6-dichloro-pyrimidin-4-ylamine (200.00 mg; 1.22 mmol; 1.00 eq.) and *cis*-3-Amino-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (308.32 mg; 1.52 mmol; 1.25 eq.) in 2 mL *n*-BuOH was added DIPEA (606.24 μ l; 3.66 mmol; 3.00 eq.). The reaction mixture was stirred at 120°C for 100 h before it was concentrated.

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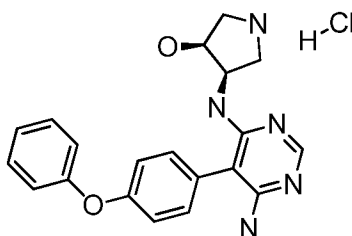
Method S2: Suzuki coupling



***cis*-3-[6-Amino-5-(4-phenoxy-phenyl)-pyrimidin-4-ylamino]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester**

- 10 In a microwave vial containing *cis*-3-(6-amino-5-chloro-pyrimidin-4-ylamino)-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (402.33 mg; 1.22 mmol; 1.00 eq.), 4-phenyloxyphenyl boronic acid (522.22 mg; 2.44 mmol; 2.00 eq.), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (100.17 mg; 0.24 mmol; 0.20 eq.) and cesium carbonate (874.52 mg; 2.68 mmol; 2.20 eq.) in dioxane (6.00 ml; 70.42 mmol; 57.72 eq.) and water (0.60 ml; 33.31 mmol; 27.30 eq.) was added palladium(ii) acetate (27.39 mg; 0.12 mmol; 0.10 eq.).
- 15 The reaction was stirred for 2 h at 105 °C before it was filtered, concentrated and carried to the next step.

Method S3: deprotection of *tert*-butoxycarbonyl-protected amine

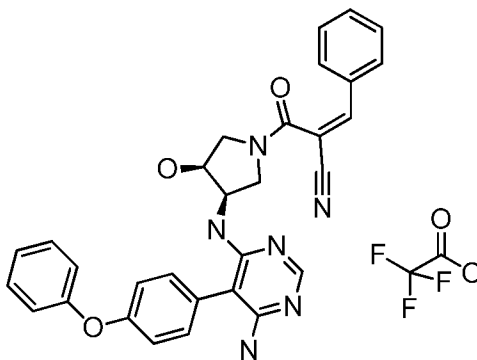


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***cis*-4-[6-Amino-5-(4-phenoxy-phenyl)-pyrimidin-4-ylamino]-pyrrolidin-3-ol hydrochloride**

- In a 25 mL rbf containing *cis*-3-[6-amino-5-(4-phenoxy-phenyl)-pyrimidin-4-ylamino]-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (565.51 mg; 1.22 mmol; 1.00 eq.) in
- 25 methanol (5.00 ml; 123.43 mmol; 101.17 eq.) was added hydrogen chloride (3.10 ml; 12.20 mmol; 10.00 eq.). The mixture was stirred at rt for 2 h before it was concentrated and carried to the next step.

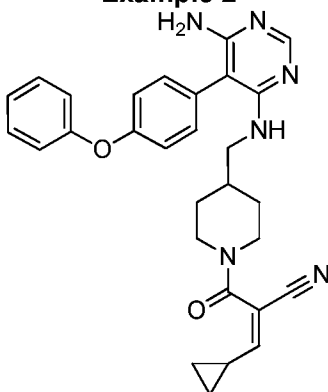
Method S4: Amide coupling



(Z)-2-((cis-3-(6-Amino-5-(4-phenoxy-phenyl)-pyrimidin-4-ylamino)-pyrrolidine-1-carbonyl)-3-phenyl-acrylonitrile trifluoroacetate (racemic mixture) (1)

In a rbf containing *cis*-4-[6-amino-5-(4-phenoxy-phenyl)-pyrimidin-4-ylamino]-pyrrolidin-3-ol hydrochloride (200.00 mg; 0.50 mmol; 1.00 eq.) and 2-cyano-3-phenyl-acrylic acid (86.61 mg; 0.50 mmol; 1.00 eq.) in 1,2-dichloroethane (4.00 ml; 25.26 mmol; 50.51 eq.) was added DIPEA (0.50 ml; 3.00 mmol; 6.00 eq.). The mixture was stirred for 5 min before 2,4,6-tripropyl-[1,3,5,2,4,6]trioxatriphosphinane 2,4,6-trioxide (237.00 μ l; 0.60 mmol; 1.20 eq.) was added. The reaction was stirred at rt for 1h before it was concentrated and purified with Waters pre-HPLC (acidic condition). The fractions containing the desired product were lyophilized to afford the title product as a white solid (29.7 mg, 8.5%). HPLC purity: 91%. MS: $m/z=519[M+H]^+$.

Example 2

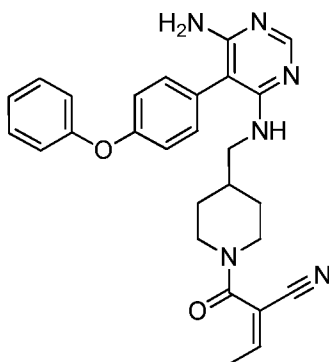


2-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile (2)

2-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile was synthesized from 5-(4-phenoxyphenyl)-*N*4-(piperidin-4-ylmethyl)pyrimidine-4,6-diamine and 2-cyano-3-cyclopropylacrylic acid using Method S4, described above. HPLC: 87.5 %, RT= 4.0 min. MS: $m/z = 495 [M+H]^+$, RT= 3.26 min. ^1H

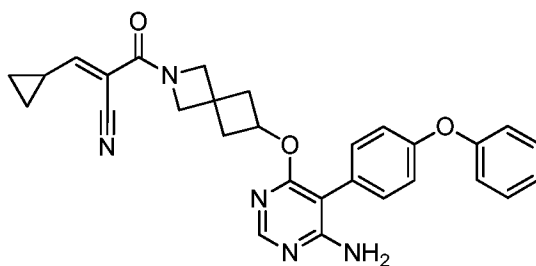
NMR (400 MHz, DMSO-d₆) δ 7.96 (s, 2H), 7.43 (dd, J = 8.4, 7.2 Hz, 2H), 7.28 – 7.08 (m, 7H), 6.56 (d, J = 11.0 Hz, 1H), 5.51 – 5.31 (m, 3H), 3.16 (t, J = 6.5 Hz, 2H), 1.87 (dtq, J = 12.8, 9.0, 4.7 Hz, 2H), 1.75 – 1.54 (m, 2H), 1.17 (dq, J = 7.0, 4.1 Hz, 1H), 0.99 (dd, J = 27.2, 10.2 Hz, 3H), 0.90 (m, 2H). The rest of the protons overlap with solvent peak.

5

Example 3

2-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)piperidine-1-carbonyl)but-2-enenitrile (3)

- 10 2-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)piperidine-1-carbonyl)but-2-enenitrile was synthesized from 5-(4-phenoxyphenyl)-N4-(piperidin-4-ylmethyl)pyrimidine-4,6-diamine and 2-cyanobut-2-enoic acid using Method S4, described above. HPLC: 96.9%, RT= 4.2 min. MS: m/z = 469 [M+H]⁺, RT= 3.21 min. ¹H NMR (400 MHz, DMSO-d₆) δ 8.22 (s, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.42 (t, J = 7.8 Hz, 3H), 7.28 – 7.05 (m, 7H), 5.56 – 5.26 (m, 3H), 3.16 (t, J = 6.3 Hz, 3H), 2.94 (p, J = 8.5, 8.0 Hz, 3H), 2.62 (q, J = 9.4, 6.7 Hz, 2H), 1.84 (s, 1H), 1.62 (d, J = 13.9 Hz, 2H). The rest of the protons overlap with solvent peak.
- 15

Example 4

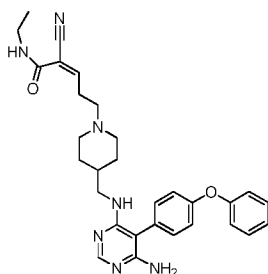
- 20 **2-{6-[6-Amino-5-(4-phenoxy-phenyl)-pyrimidin-4-yloxy]-2-aza-spiro[3.3]heptane-2-carbonyl}-3-cyclopropyl-acrylonitrile (4)**

2-{6-[6-Amino-5-(4-phenoxy-phenyl)-pyrimidin-4-yloxy]-2-aza-spiro[3.3]heptane-2-carbonyl}-3-cyclopropyl-acrylonitrile was synthesized from 6-(2-azaspiro[3.3]heptan-6-yloxy)-5-(4-phenoxyphenyl)pyrimidin-4-amine and 2-cyano-3-cyclopropylacrylic acid using Method S4, described above. HPLC: 96.6 %, RT= 4.27 min. MS: m/z = 494 [M+H]⁺, RT= 4.90 min. ¹H

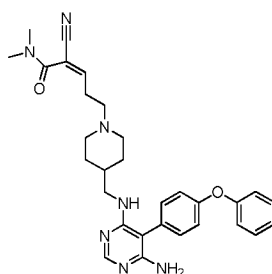
25

NMR (400 MHz, DMSO-d₆) δ 8.09 (d, J = 2.0 Hz, 1H), 7.42 (td, J = 8.0, 7.6, 2.1 Hz, 2H), 7.35 – 7.24 (m, 2H), 7.17 (t, J = 7.4 Hz, 1H), 7.08 (ddd, J = 21.5, 8.6, 2.1 Hz, 4H), 6.98 – 6.83 (m, 1H), 6.18 (s, 2H), 5.15 – 4.92 (m, 1H), 4.43 (s, 1H), 4.34 (s, 1H), 3.97 (d, J = 27.8 Hz, 1H), 3.89 (s, 1H), 2.73 – 2.54 (m, 2H), 2.22 – 2.02 (m, 2H), 2.01 – 1.79 (m, 1H), 1.28 – 1.14 (m, 2H), 1.04 – 0.90 (m, 2H).

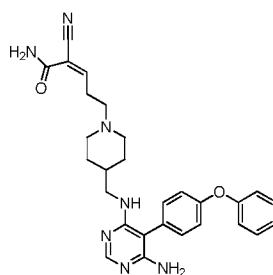
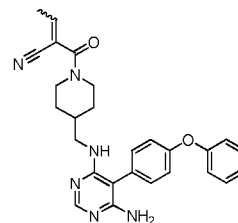
Other compounds contemplated by the invention, which may be made according to the methods provided above, include the following:



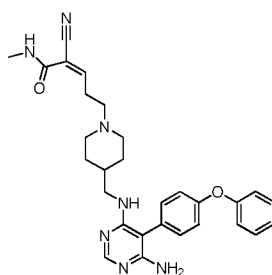
and the E isomer



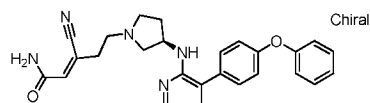
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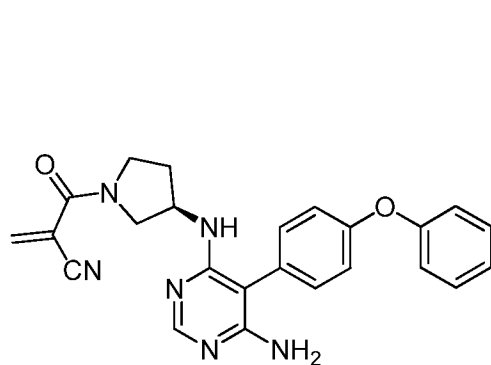
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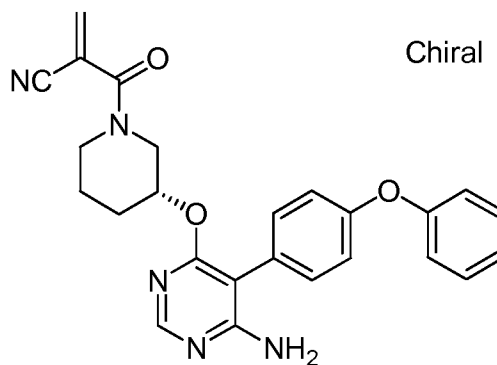
and the E isomer



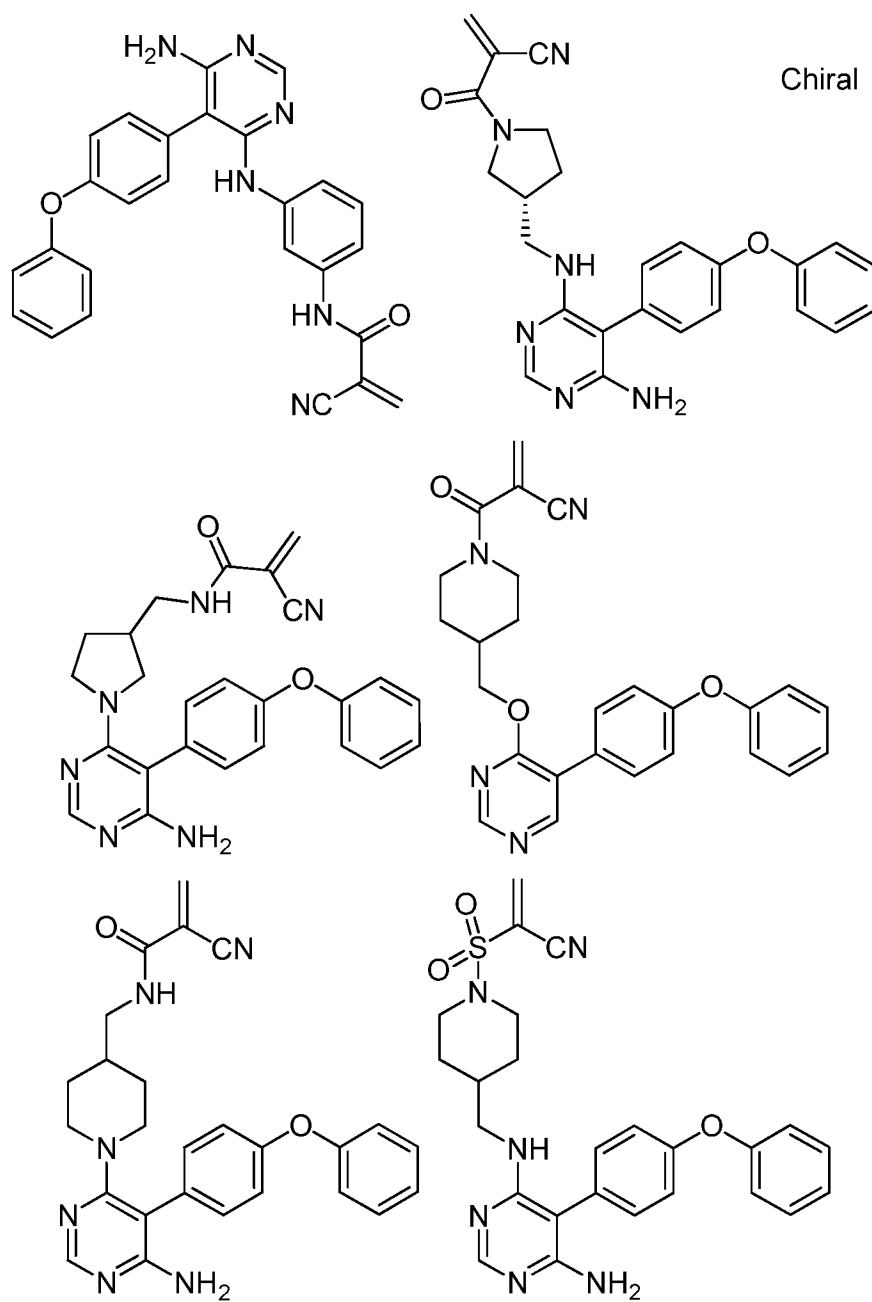
and the E isomer

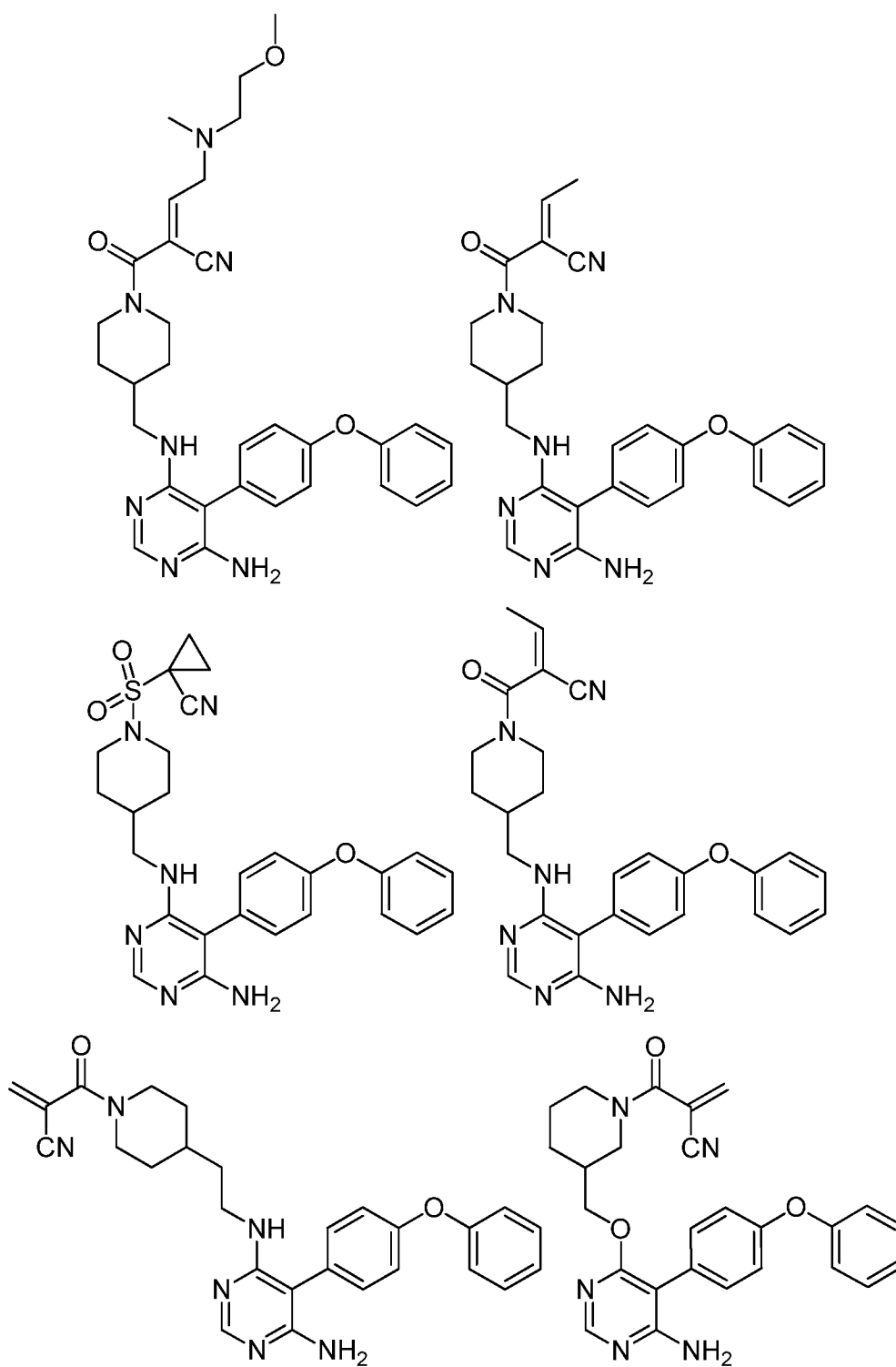


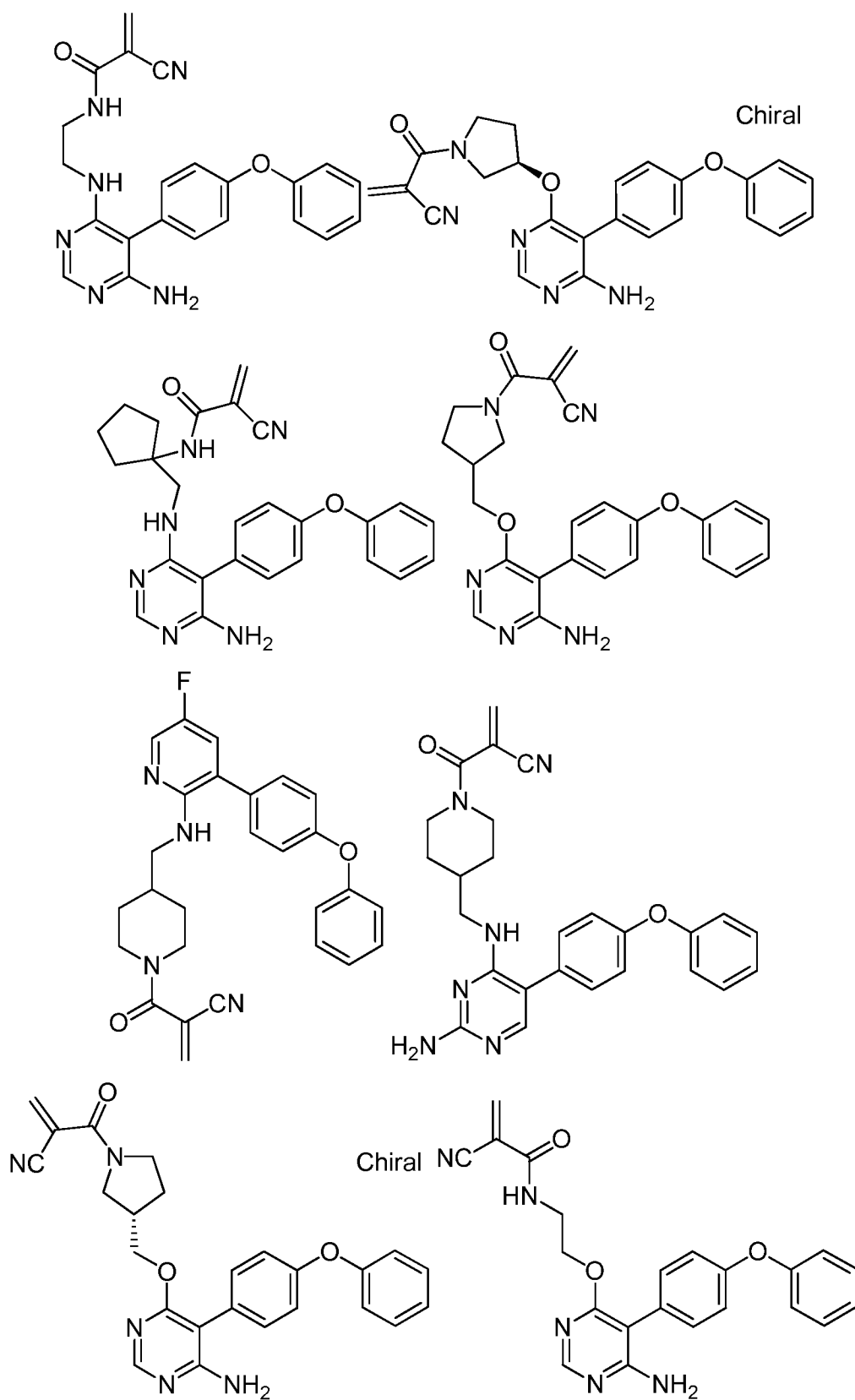
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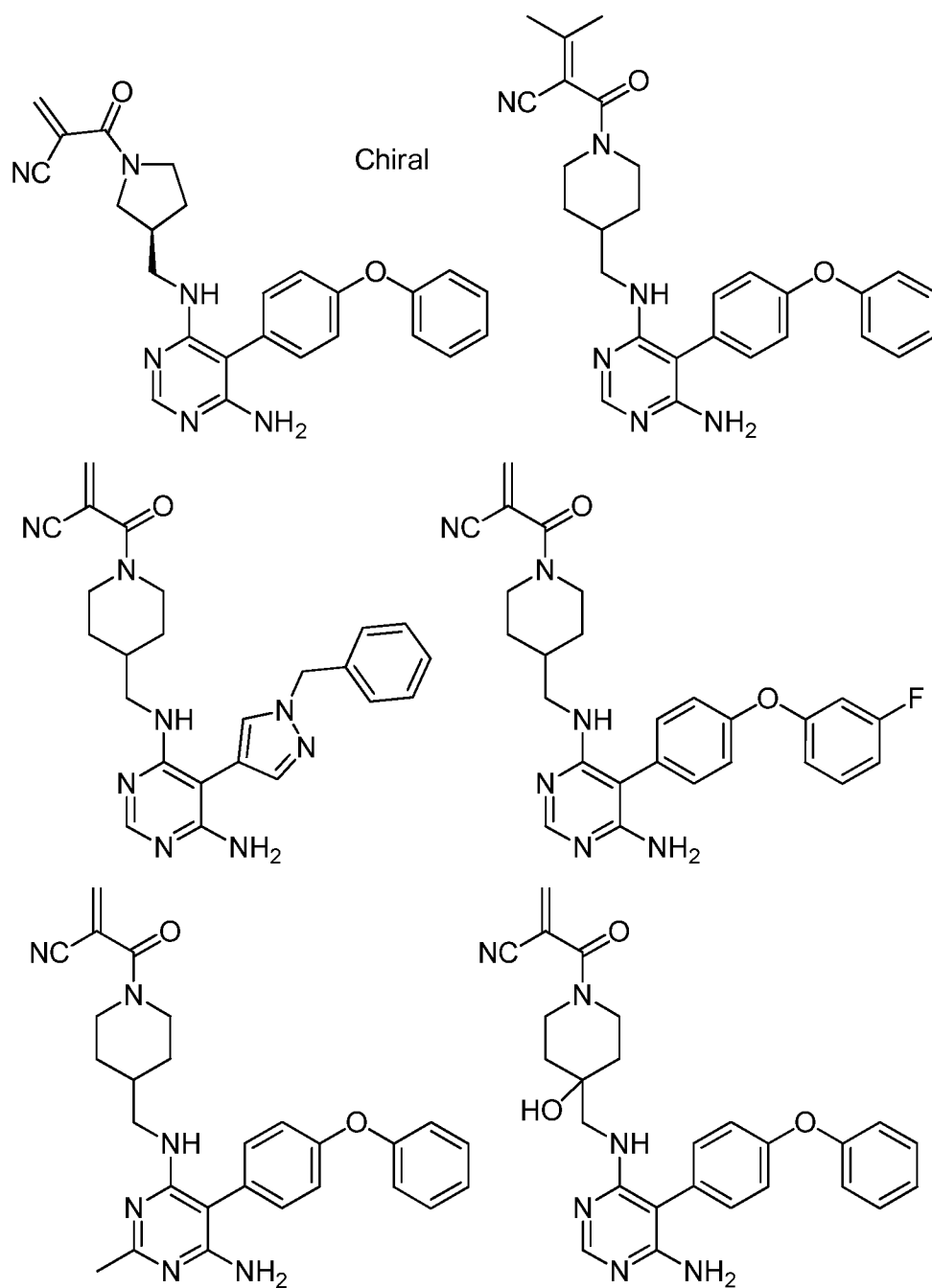


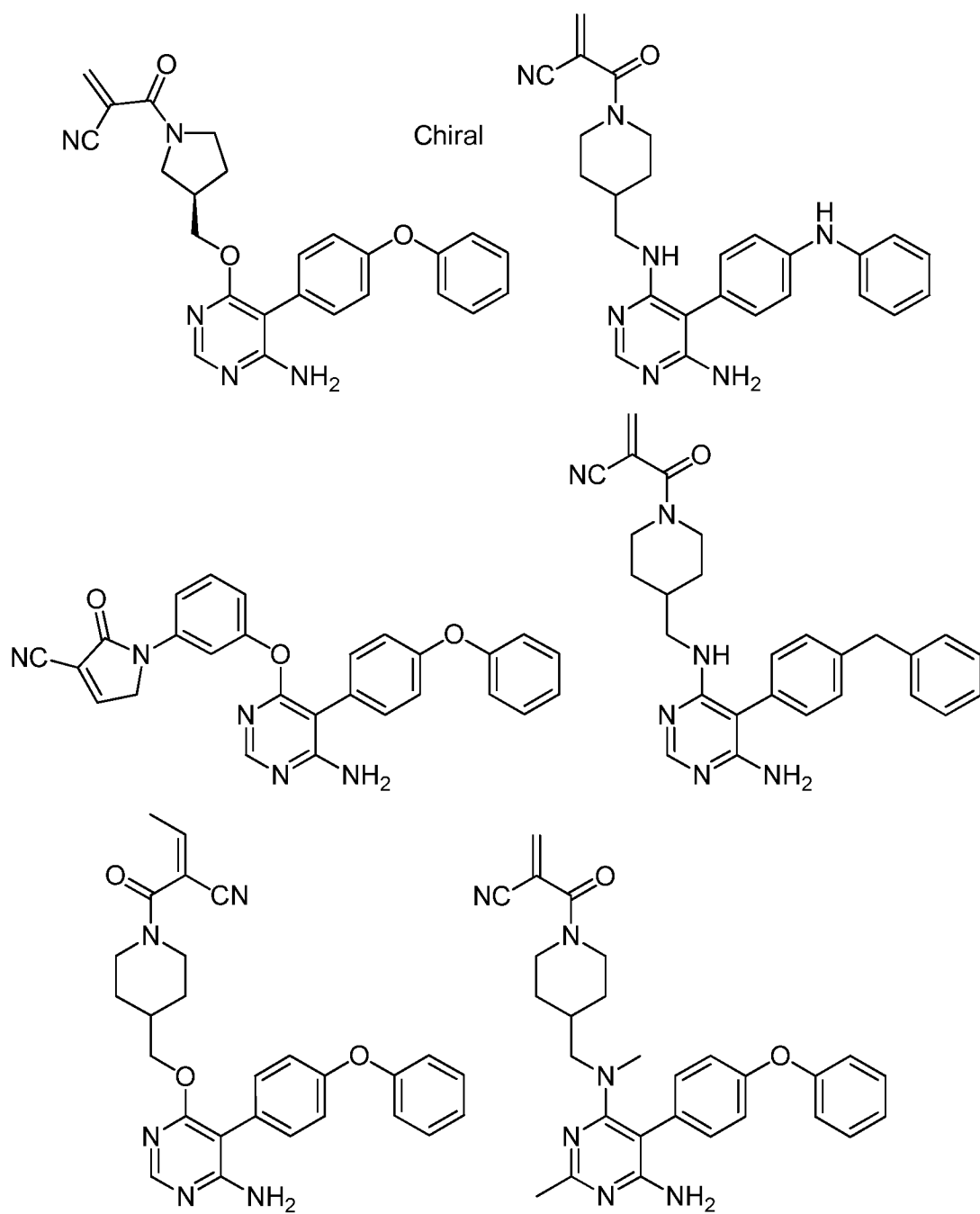
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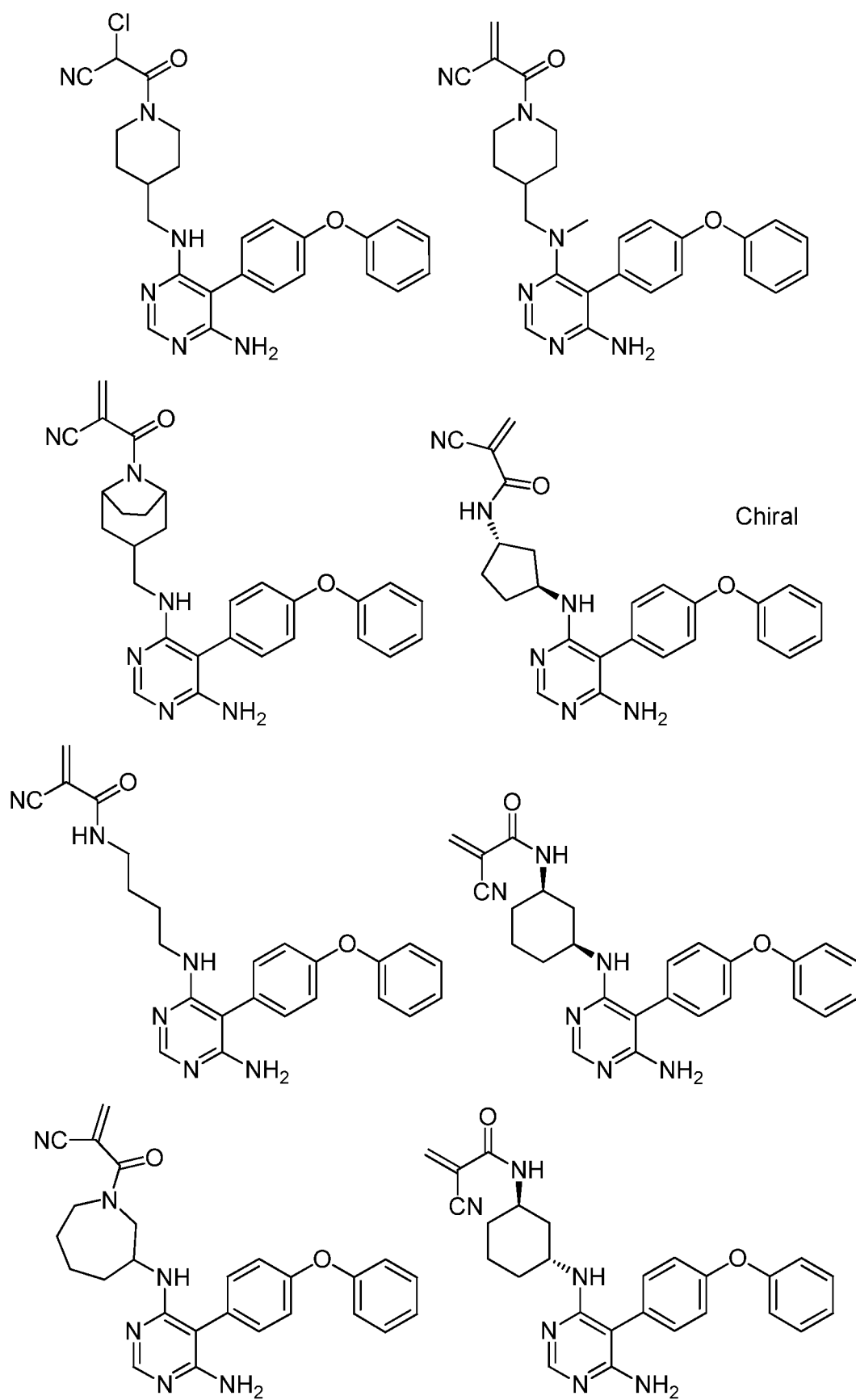


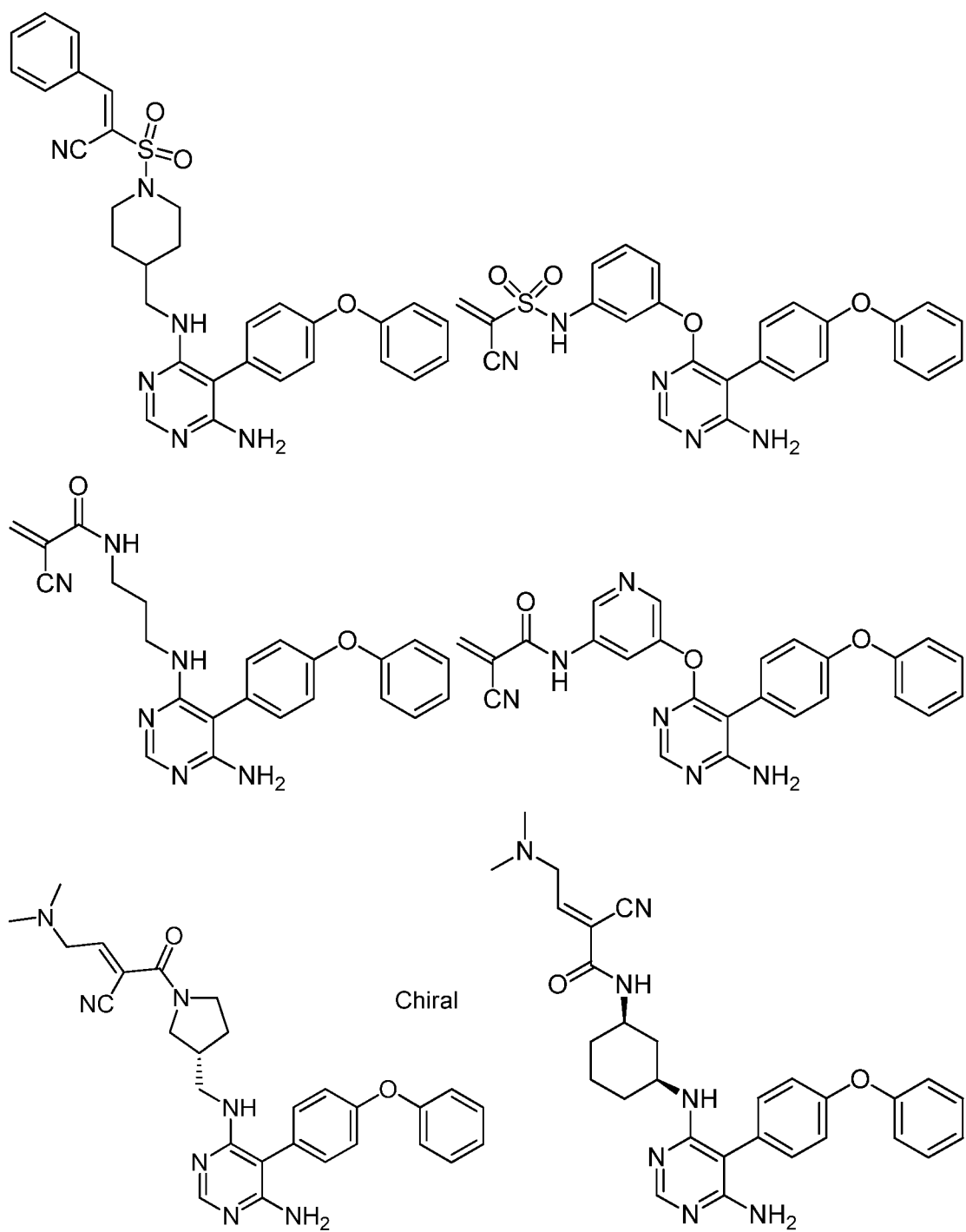


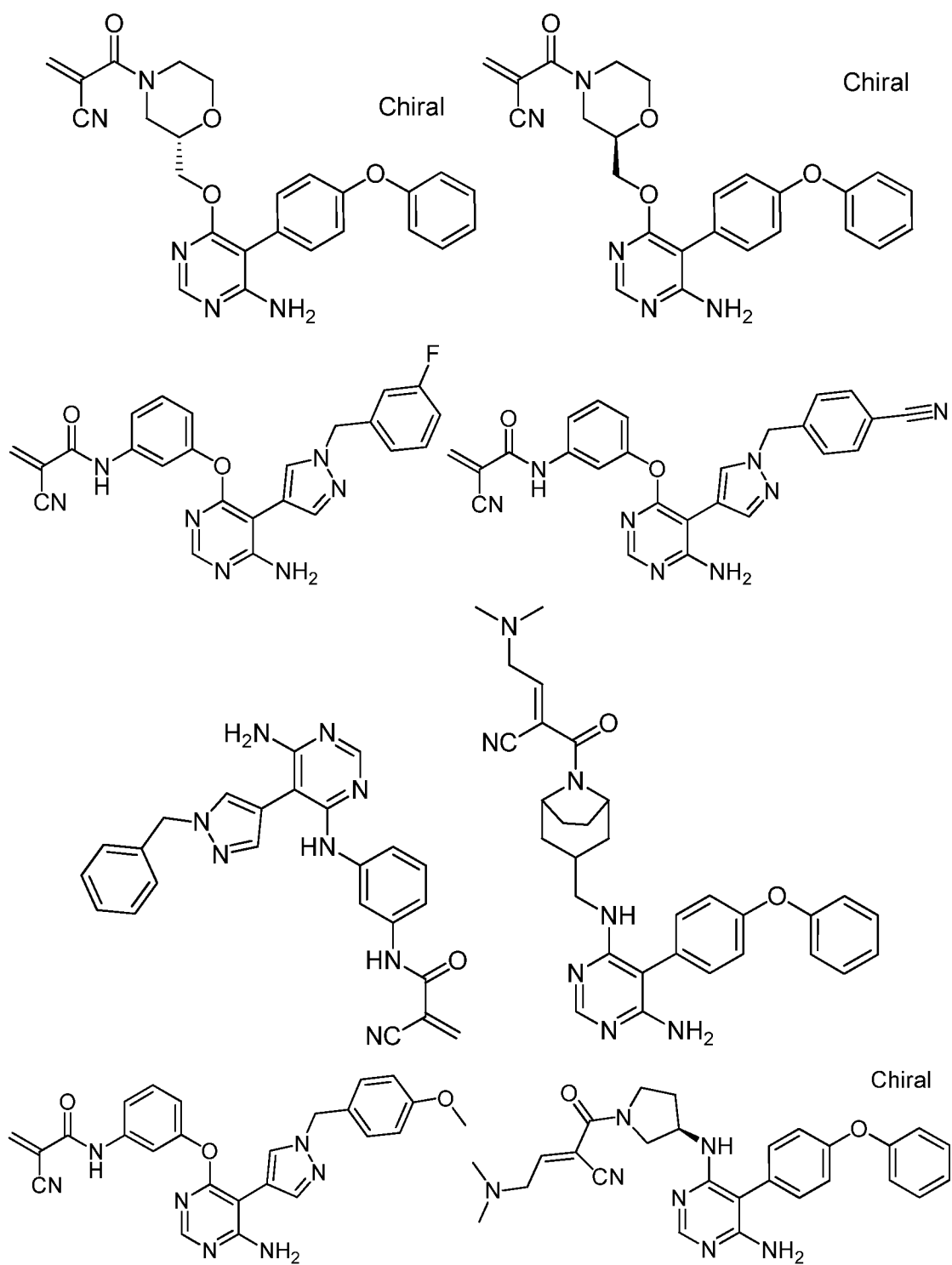


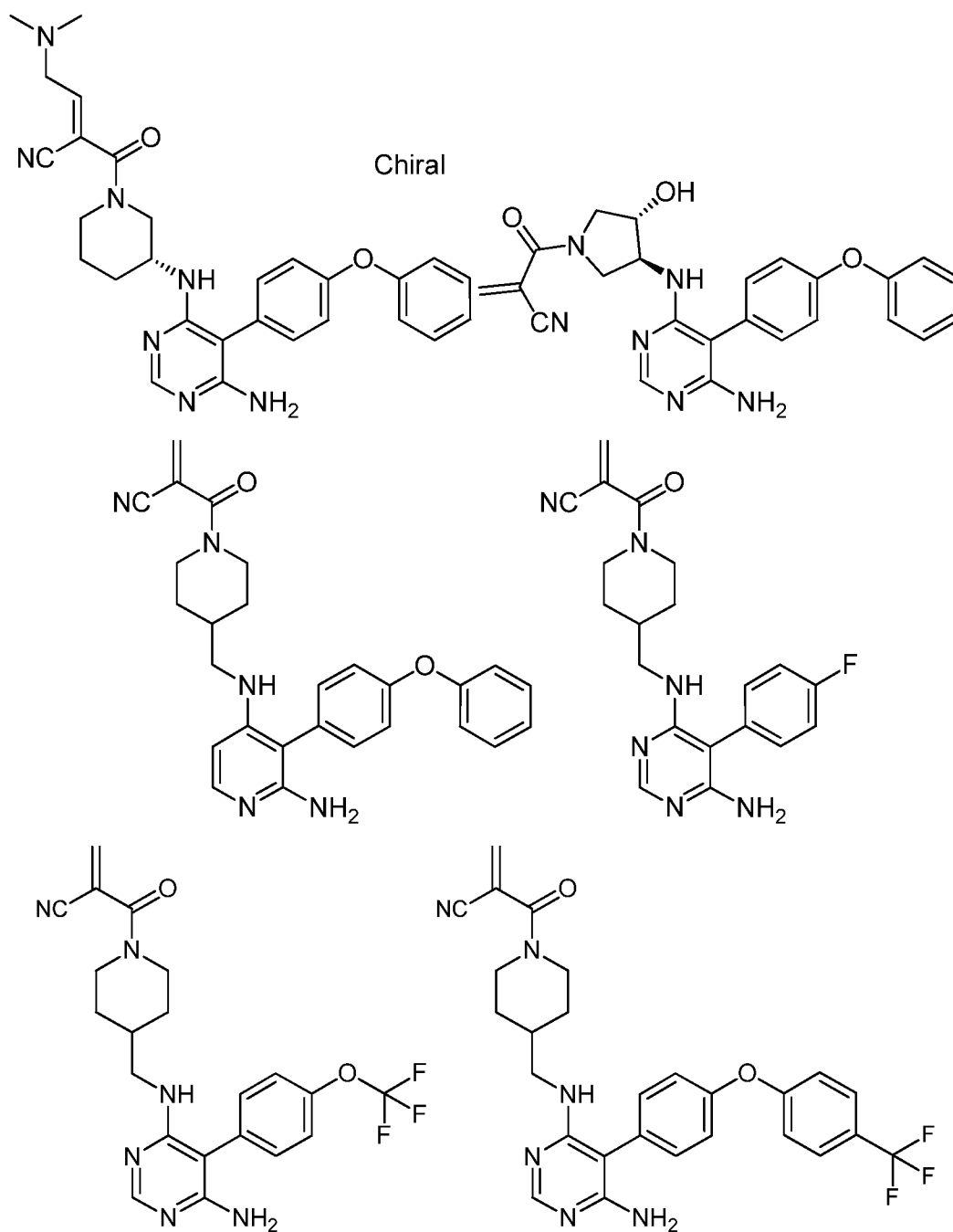


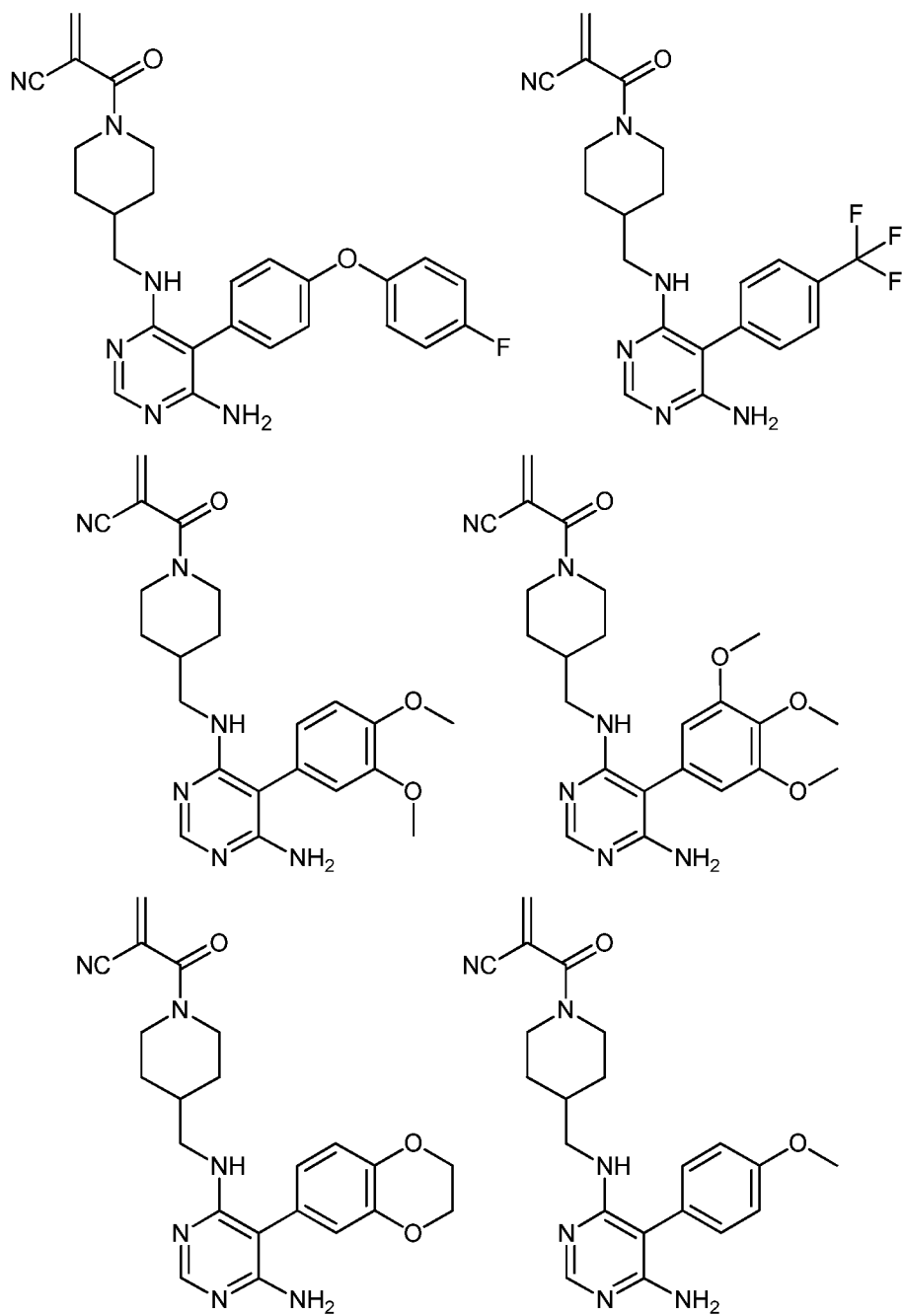


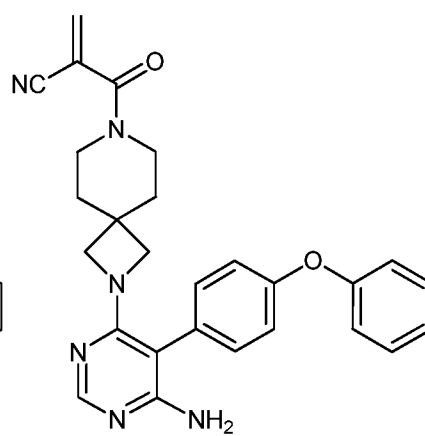
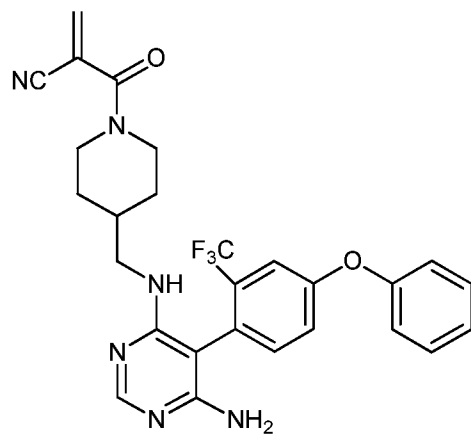
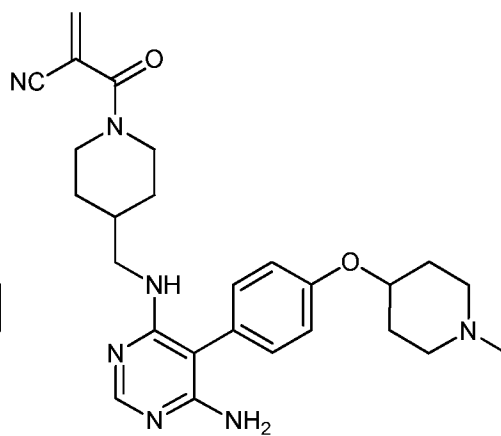
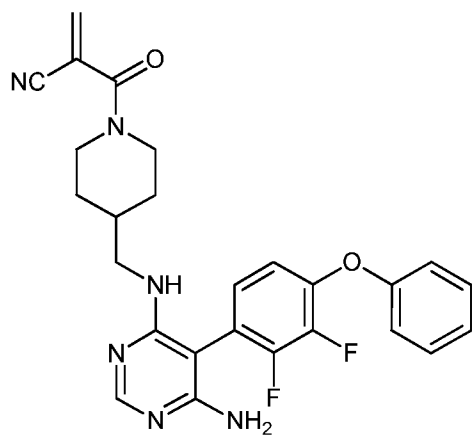
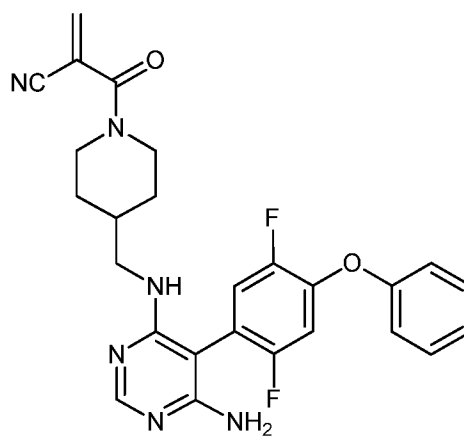
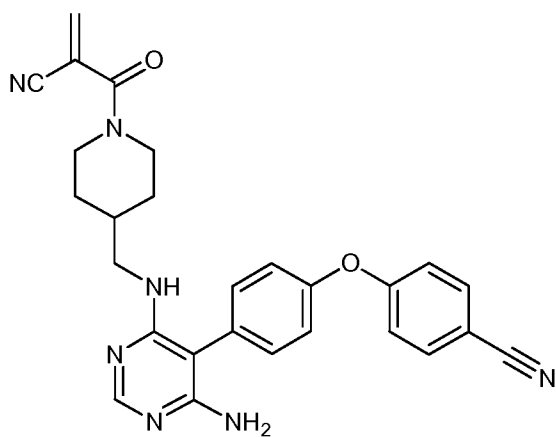


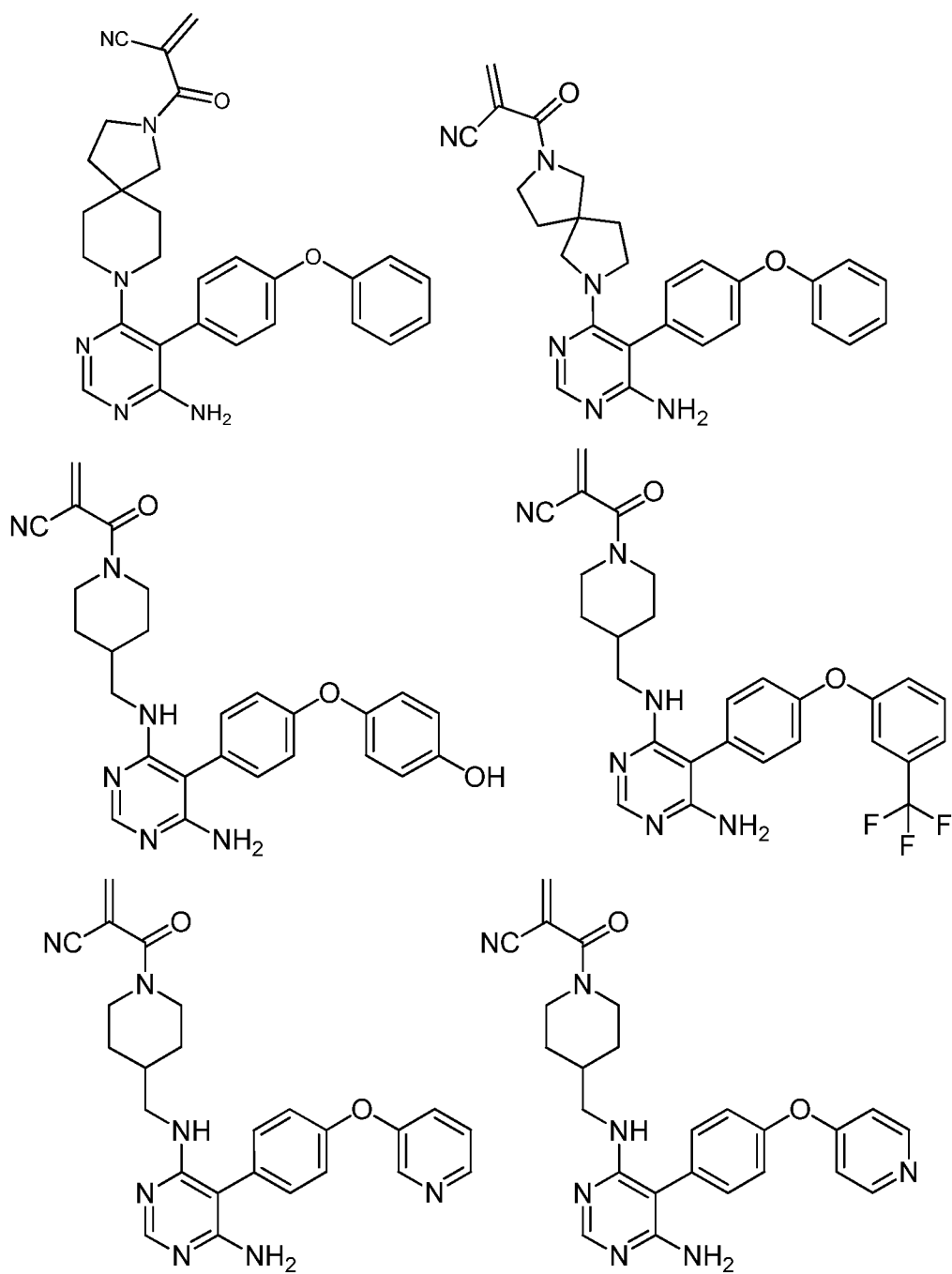


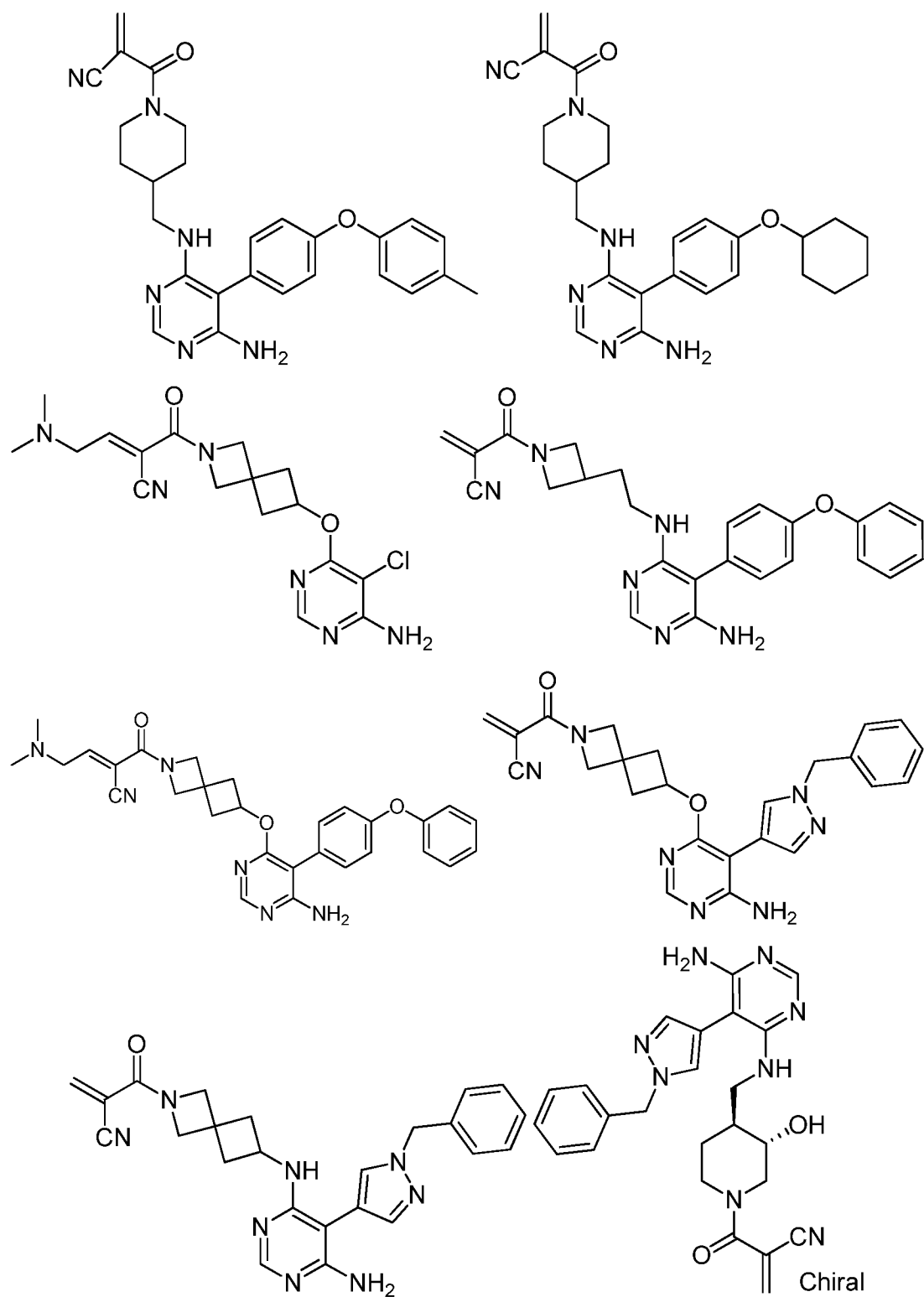


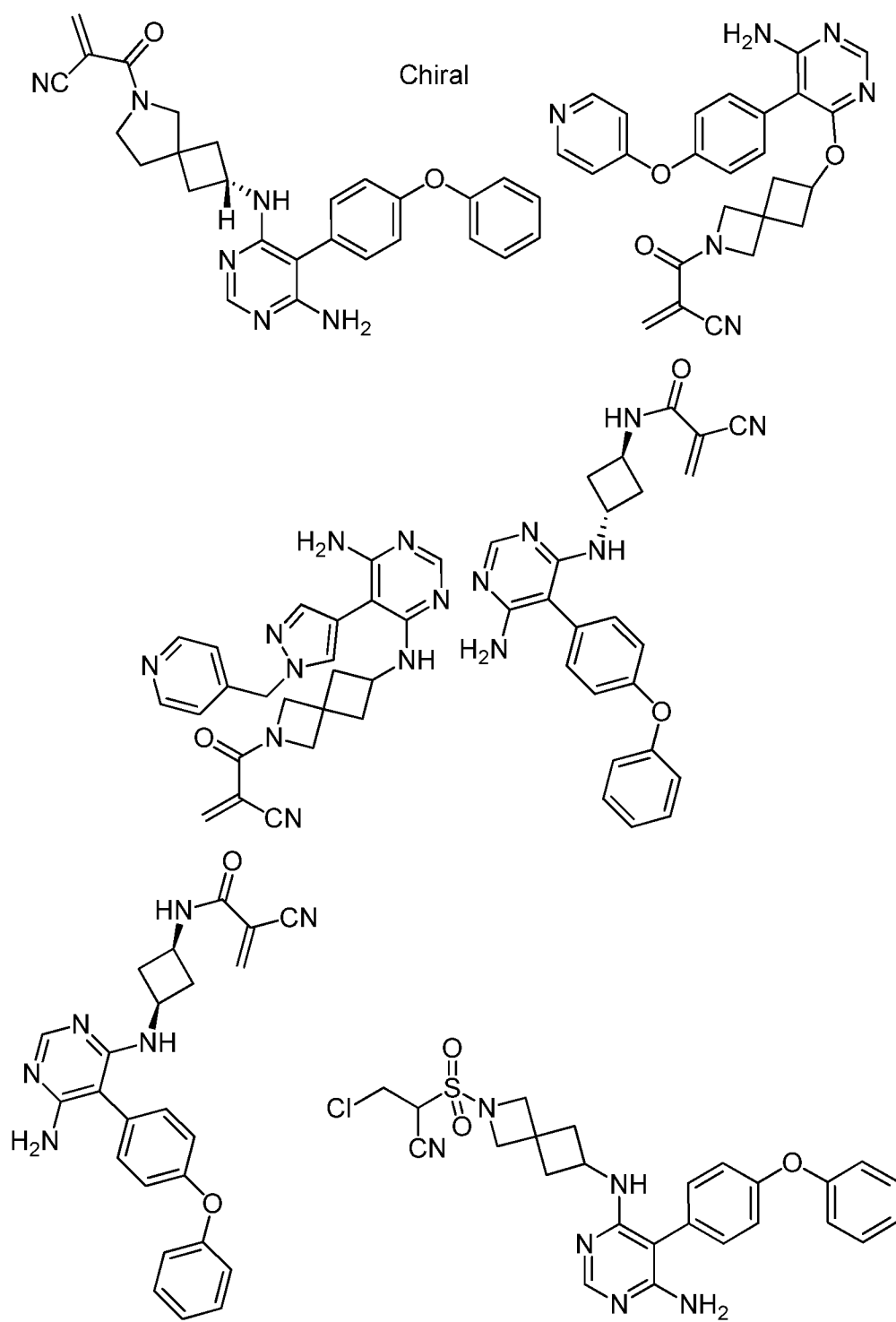


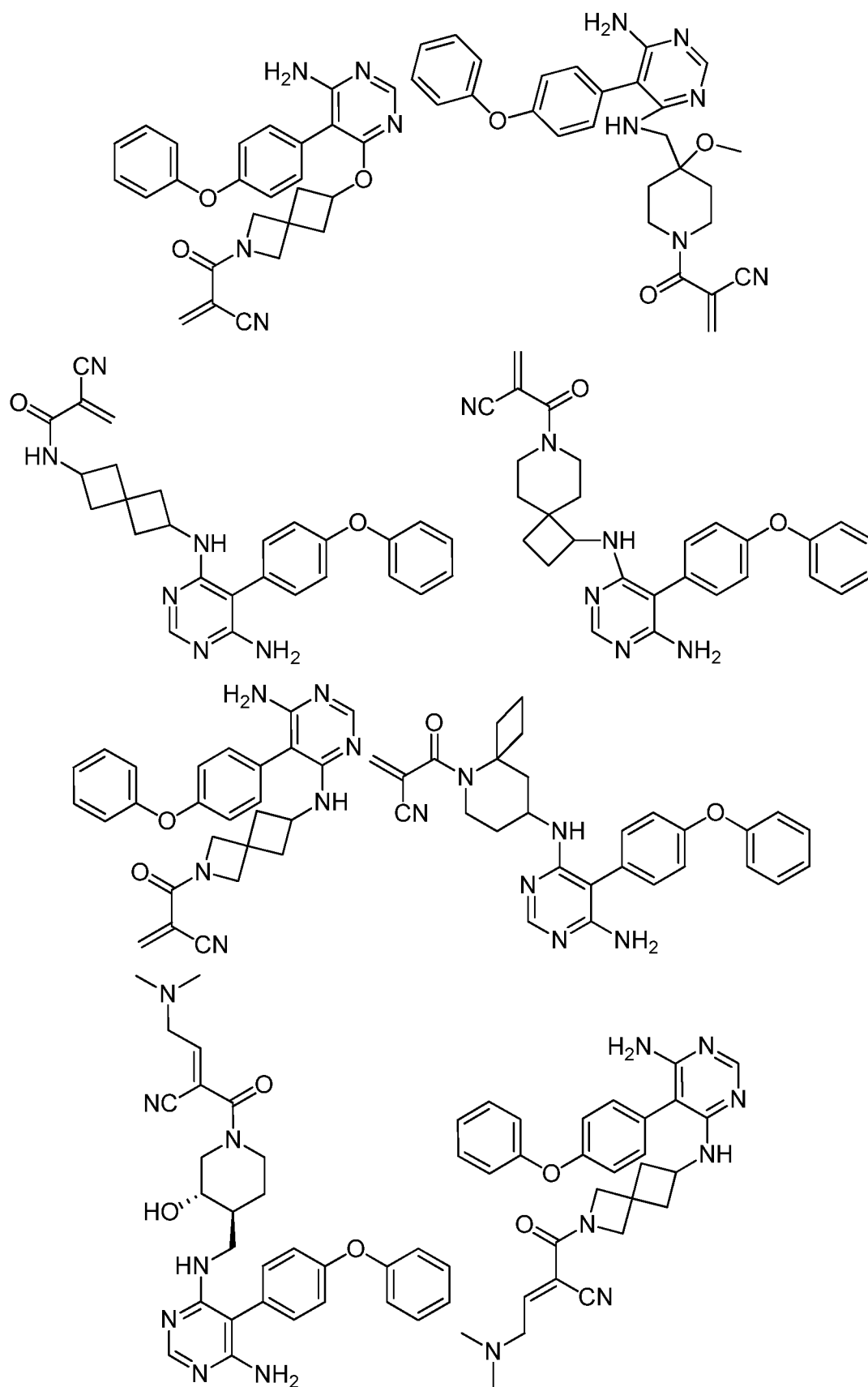


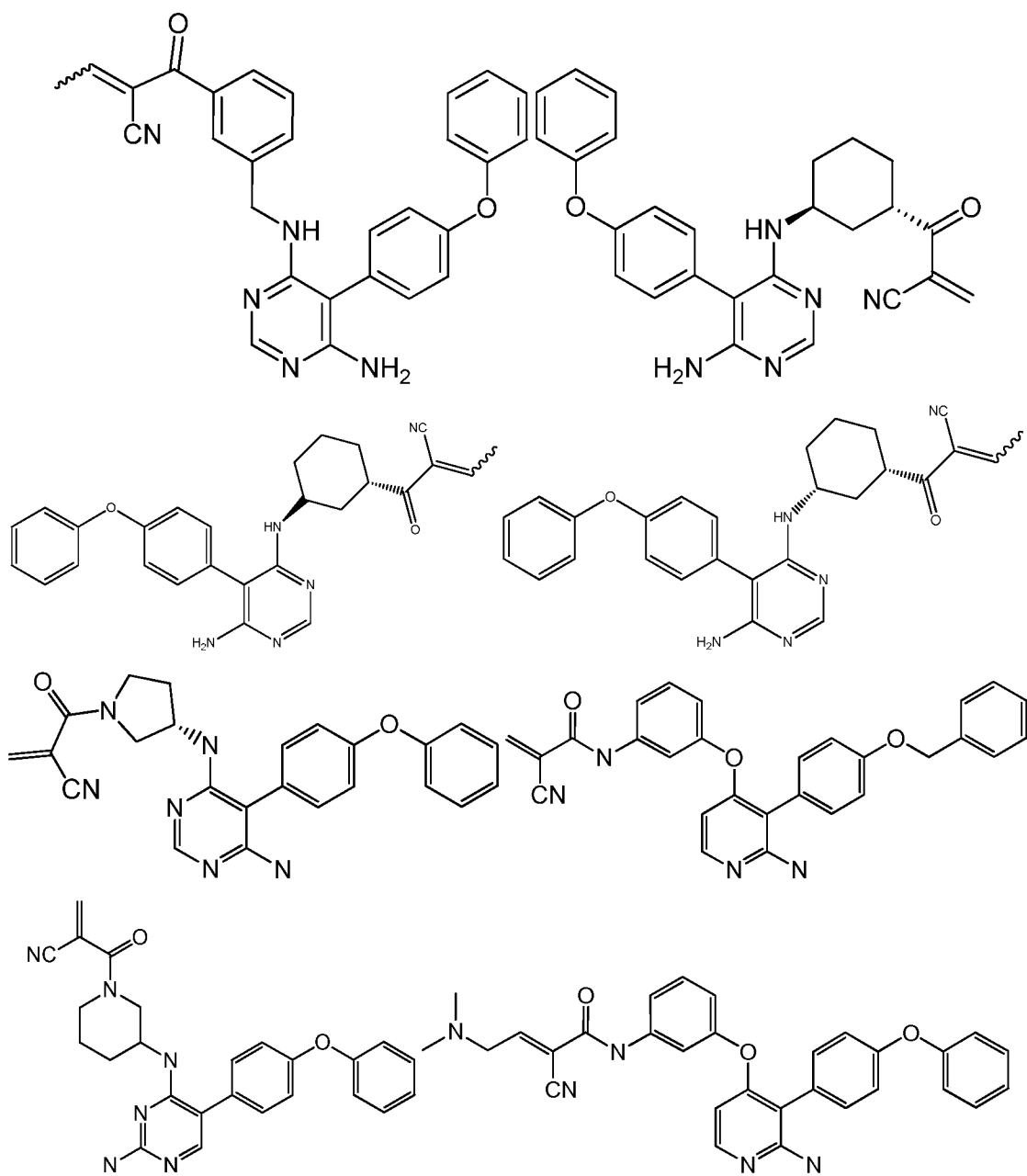


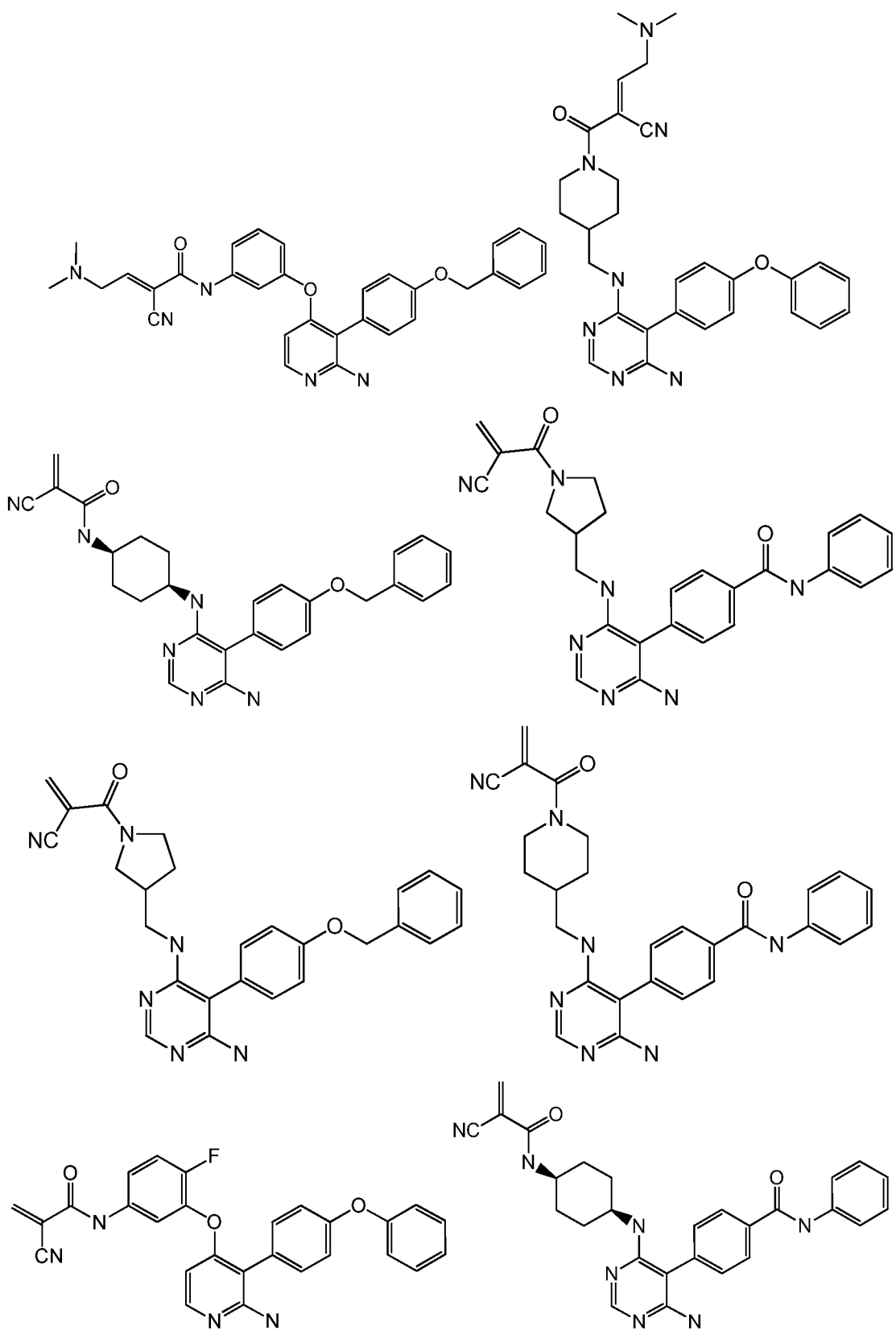


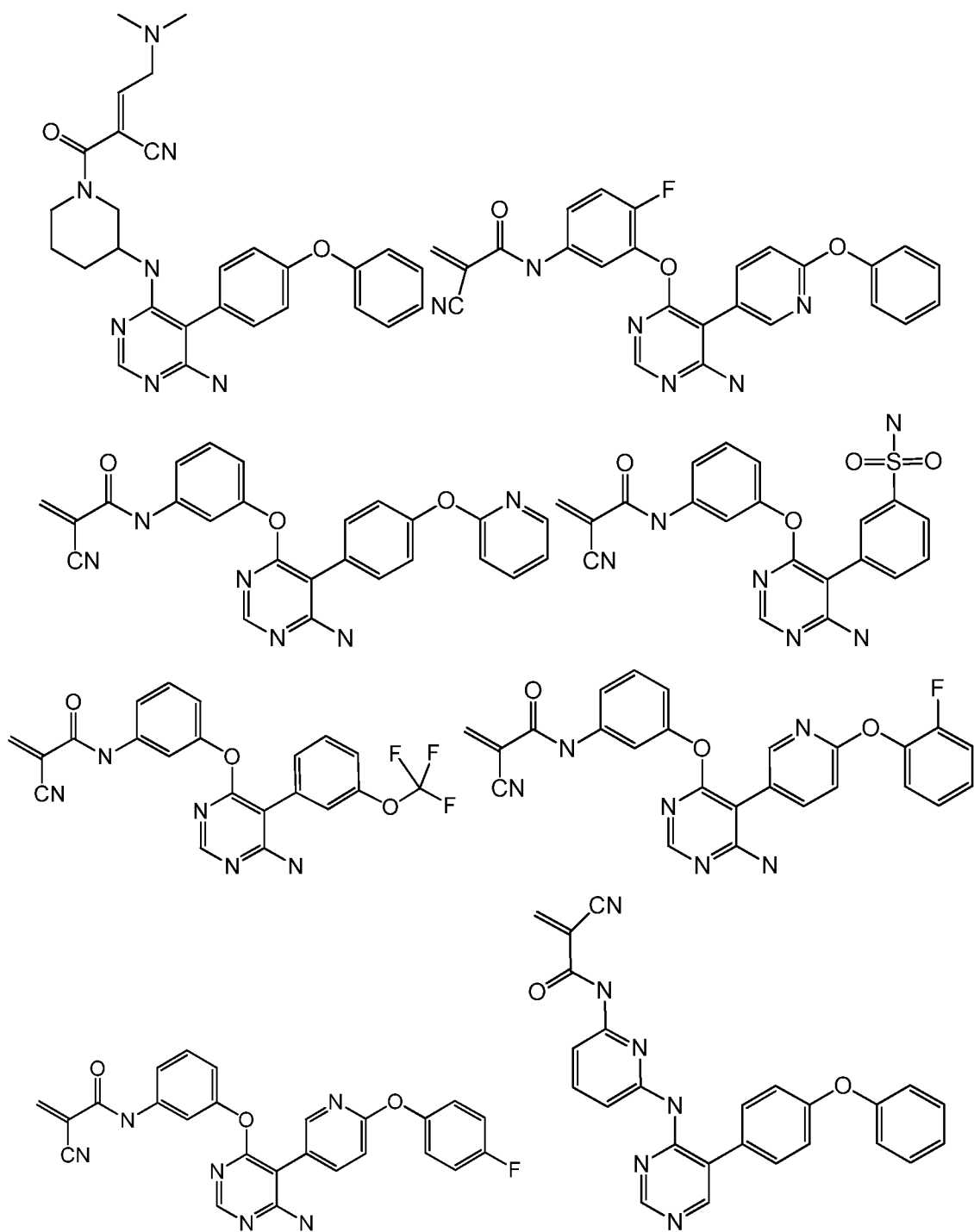


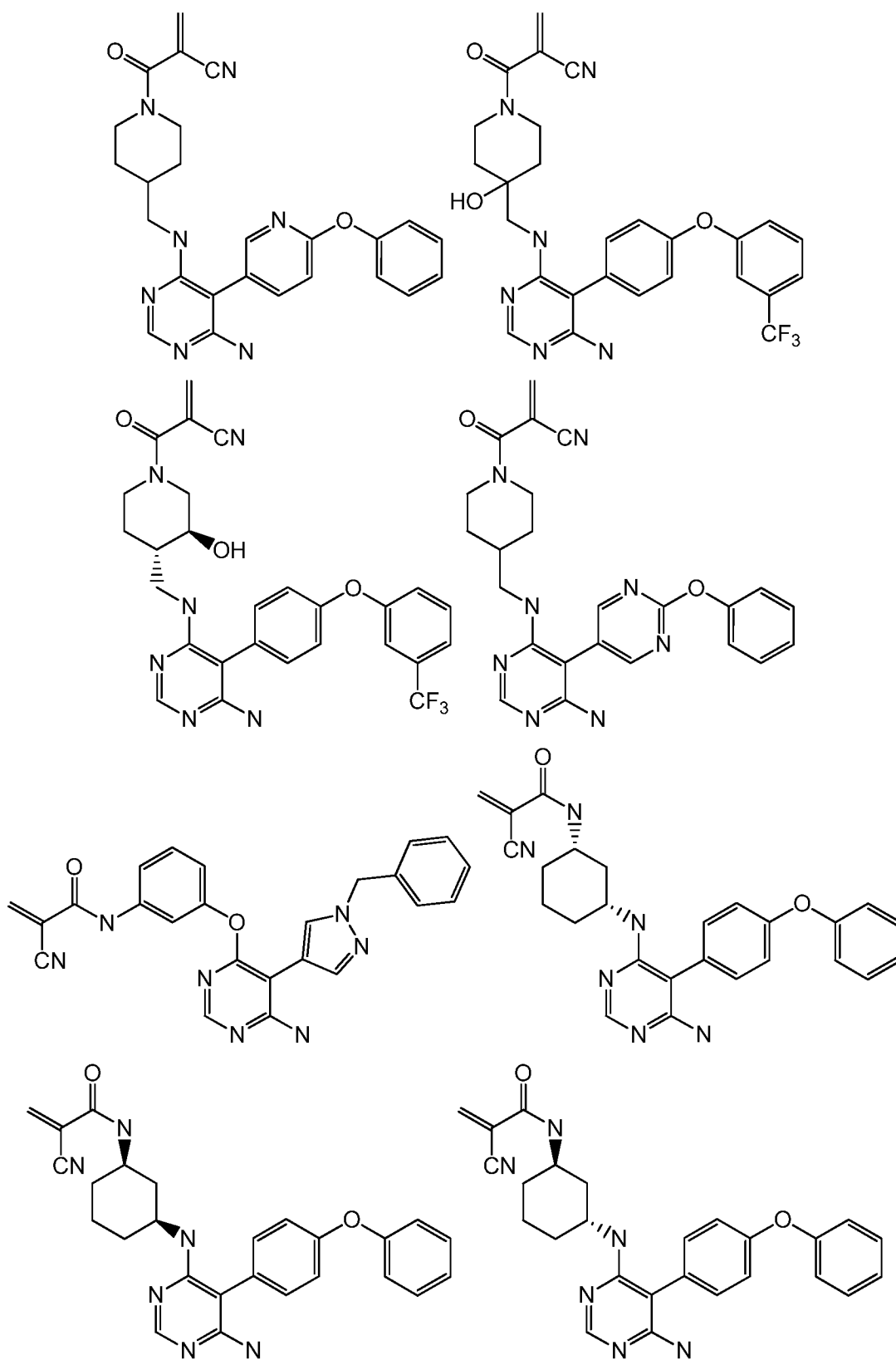


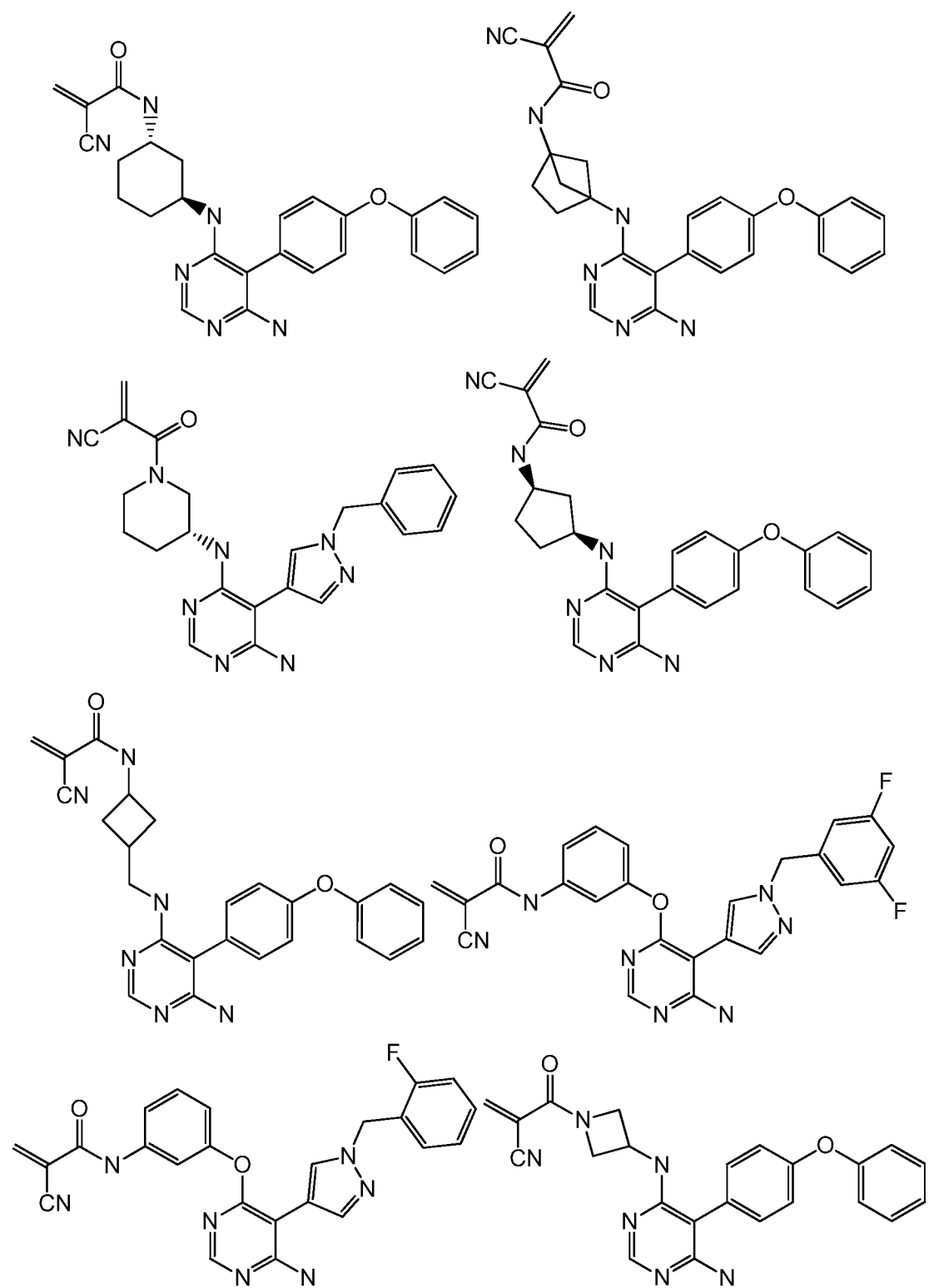


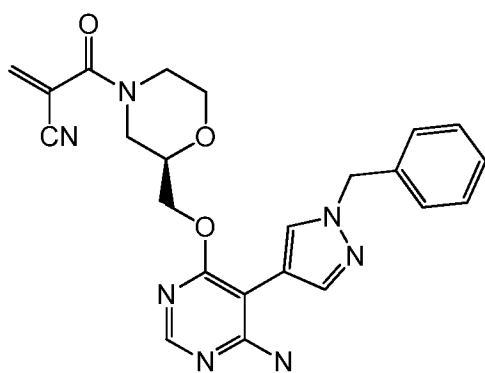
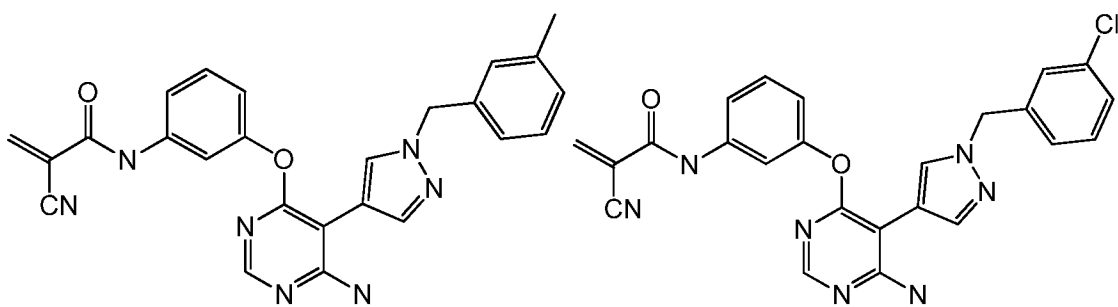
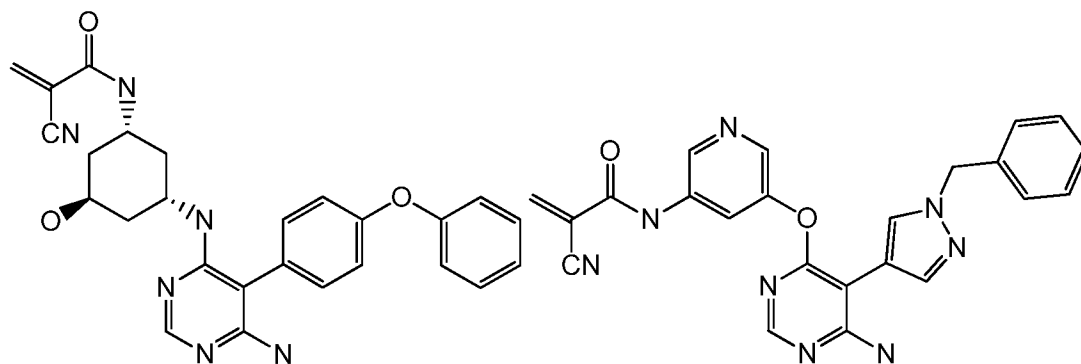
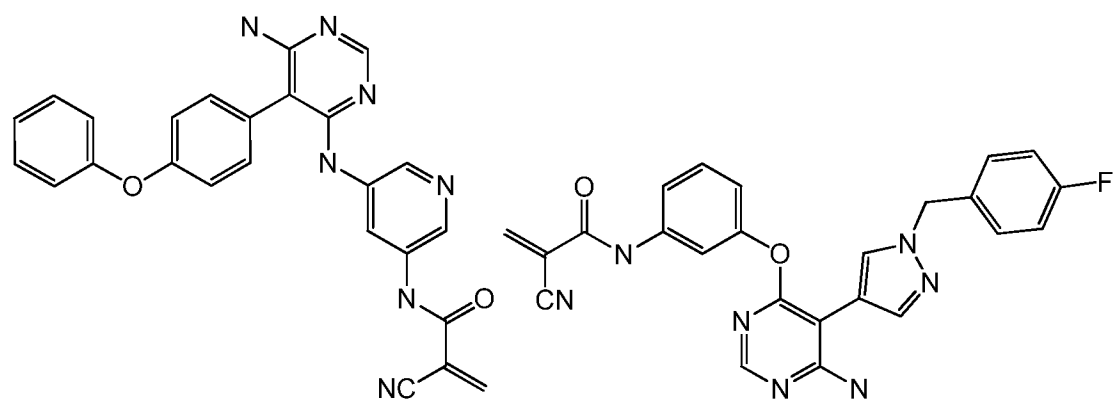




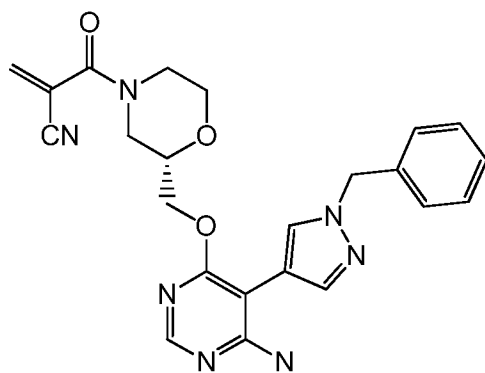




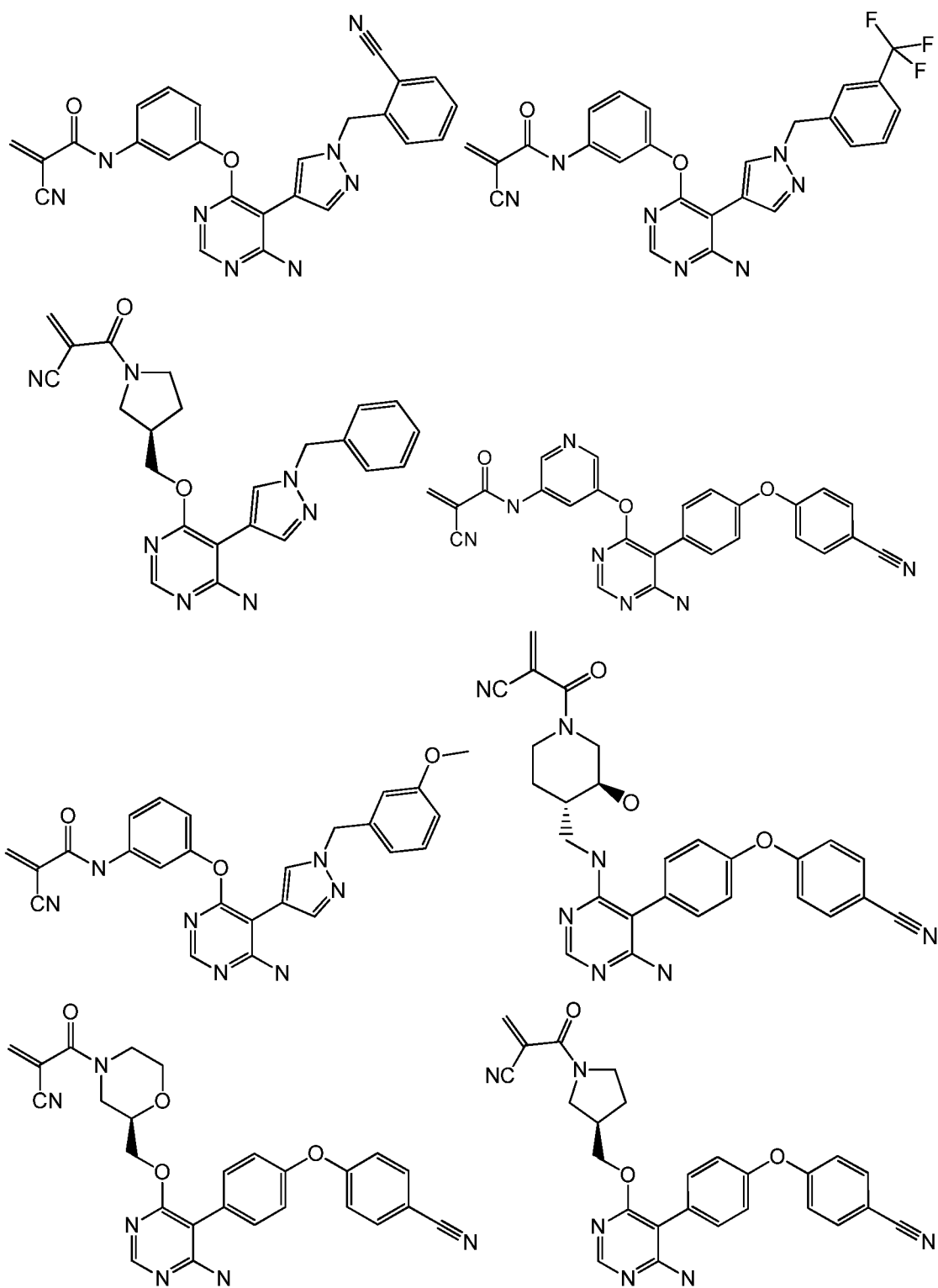


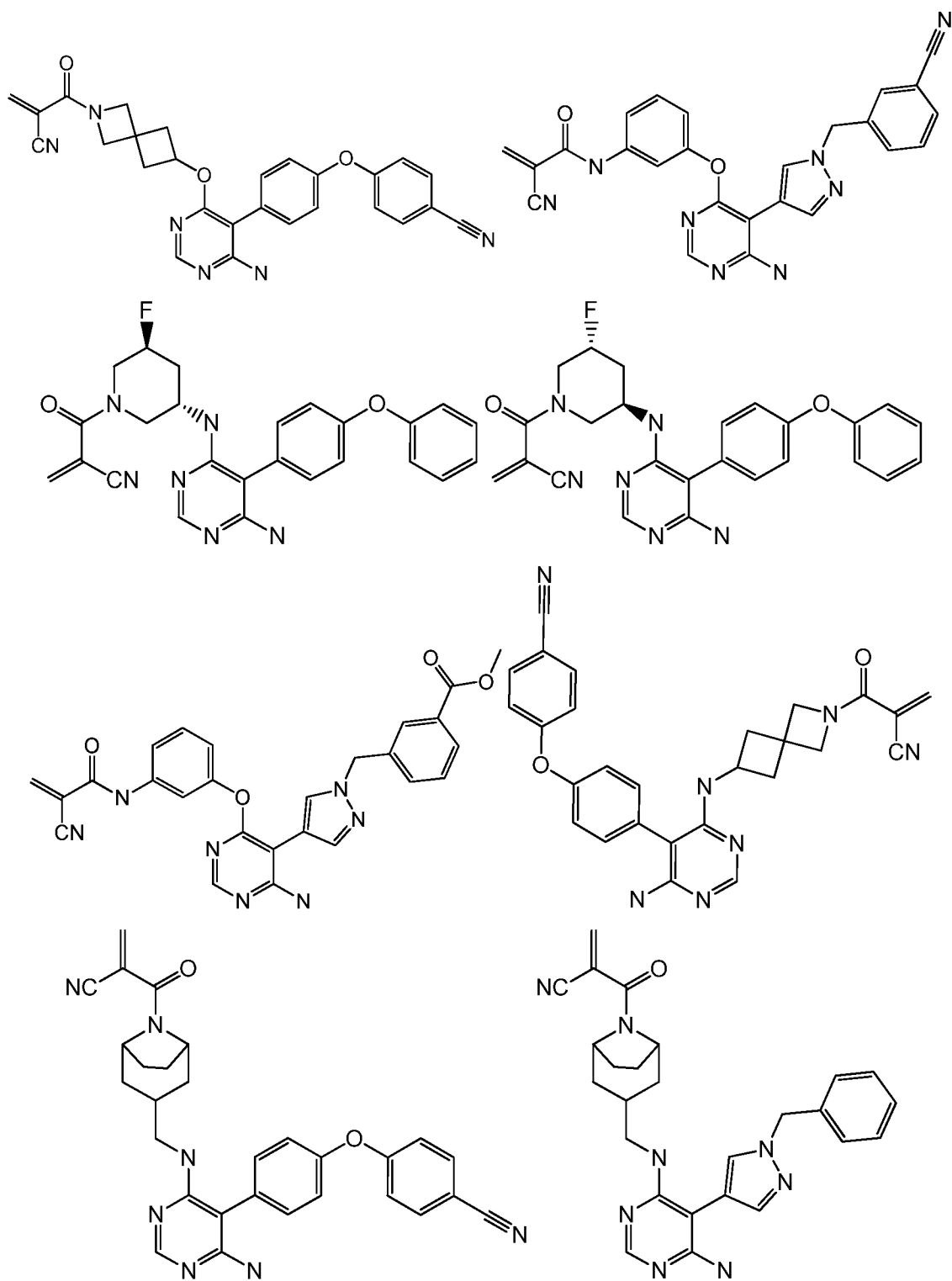


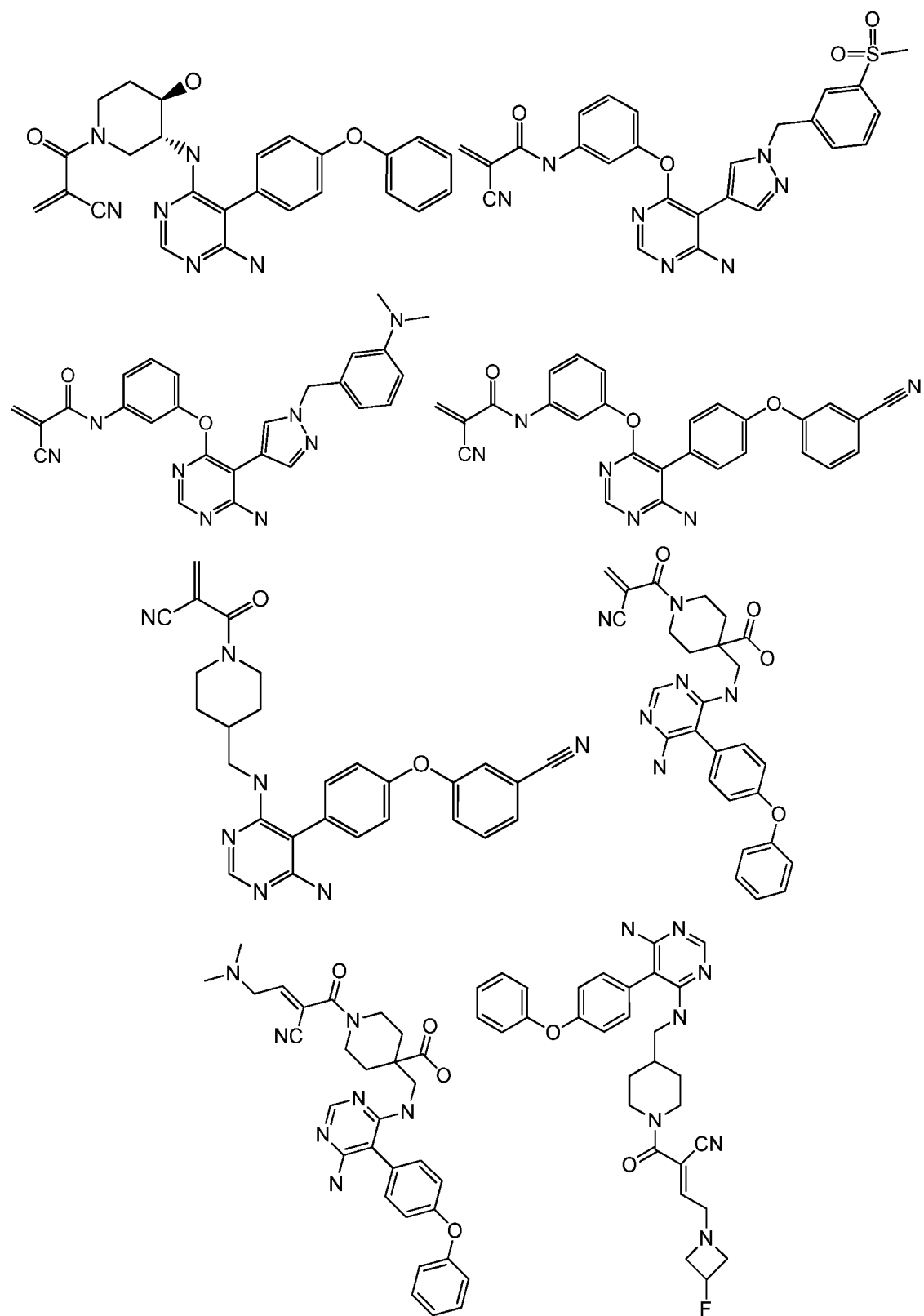
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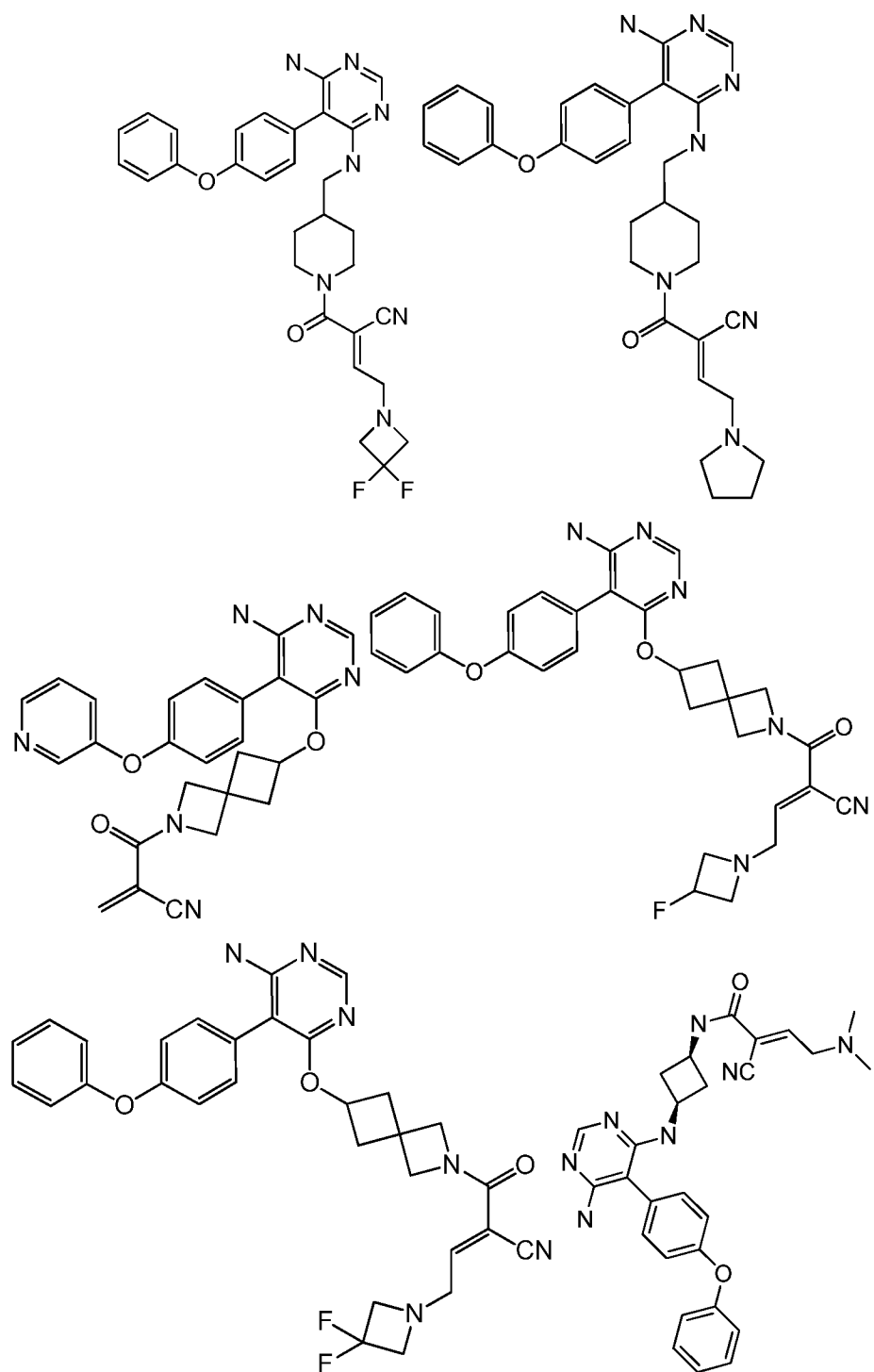


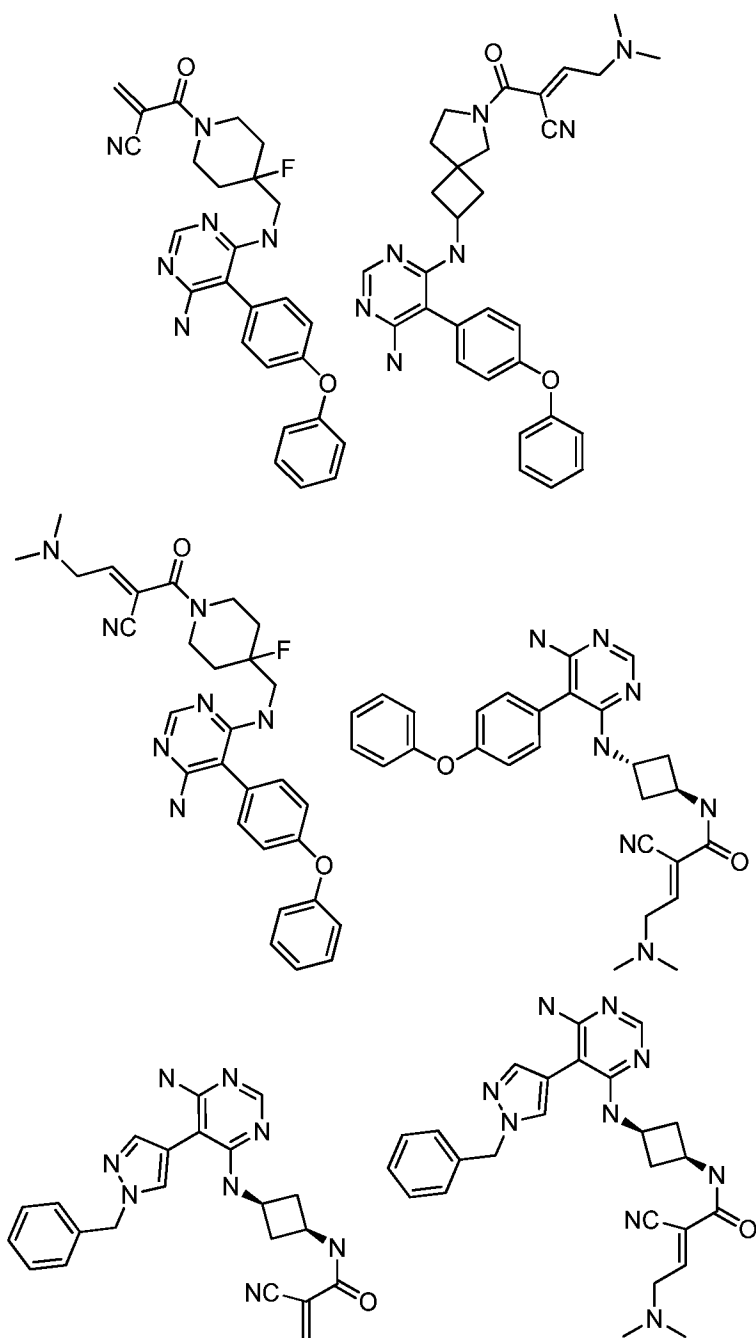
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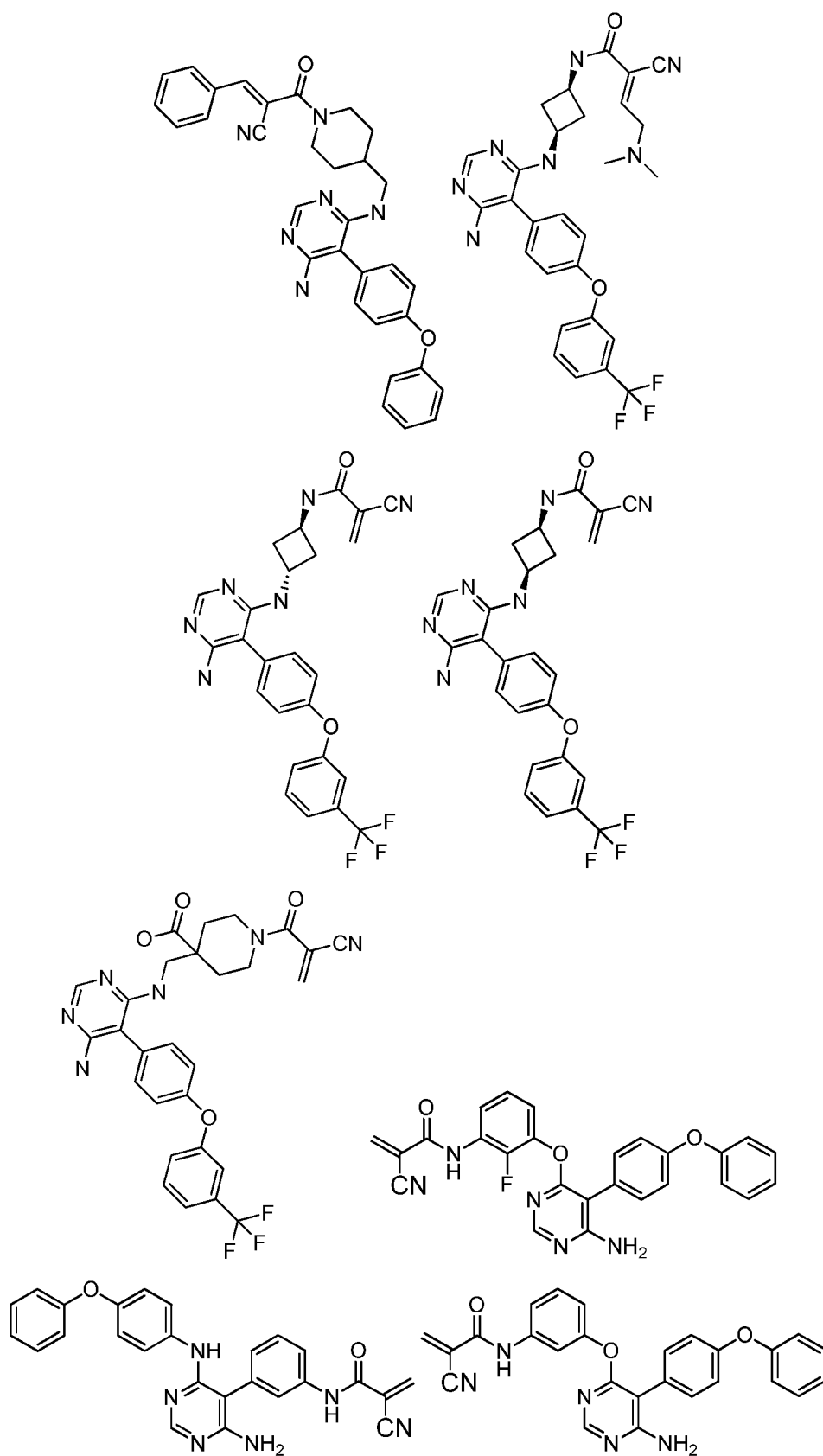


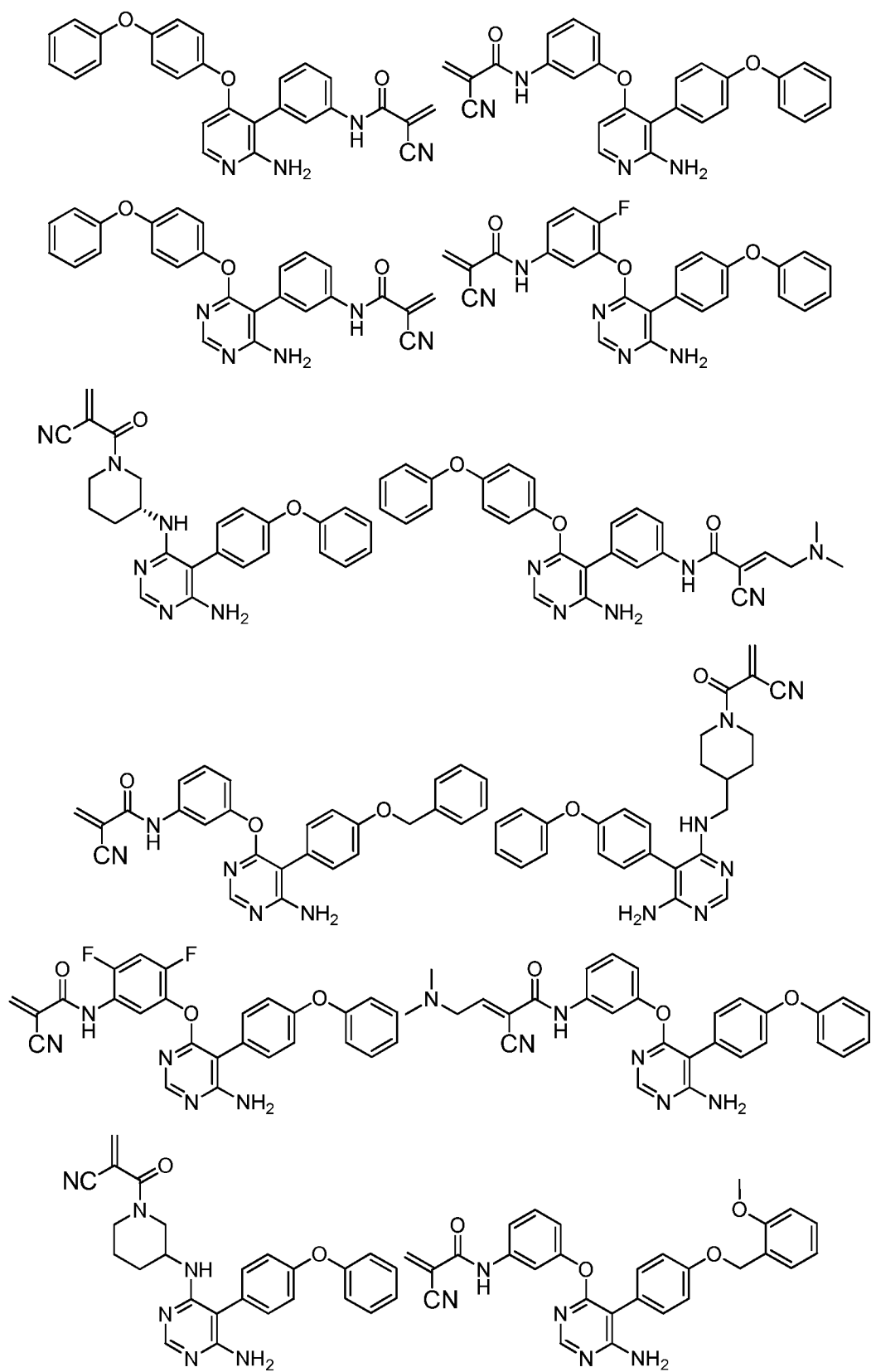


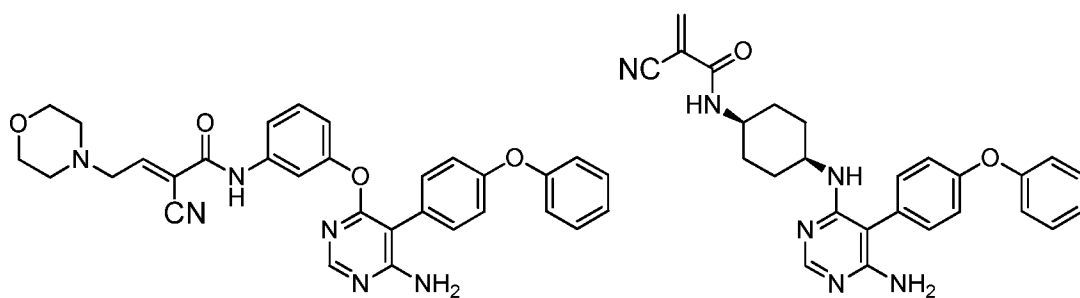
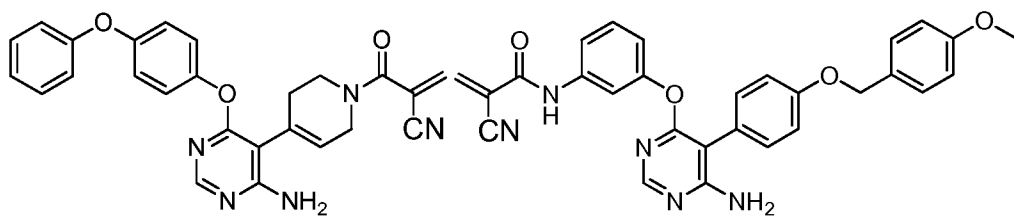
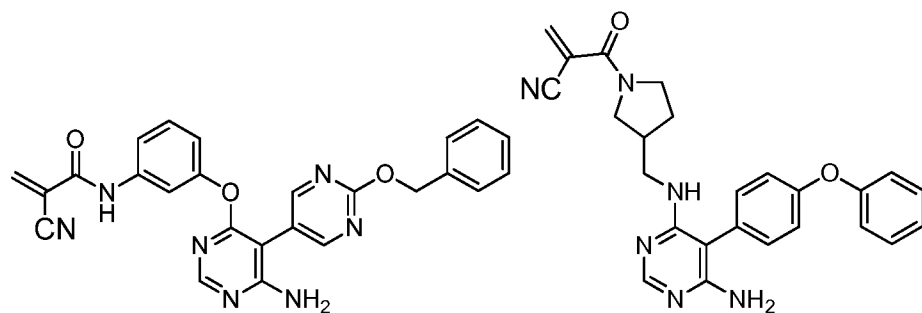
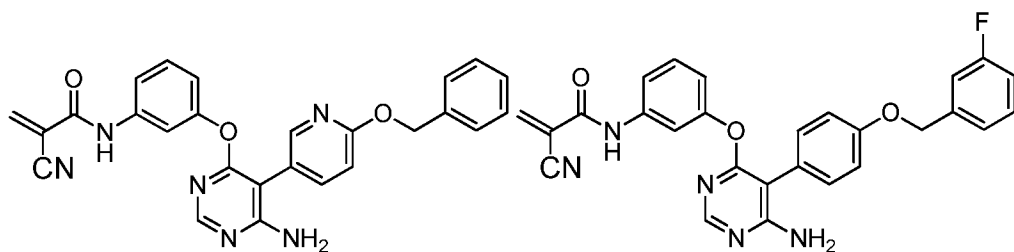
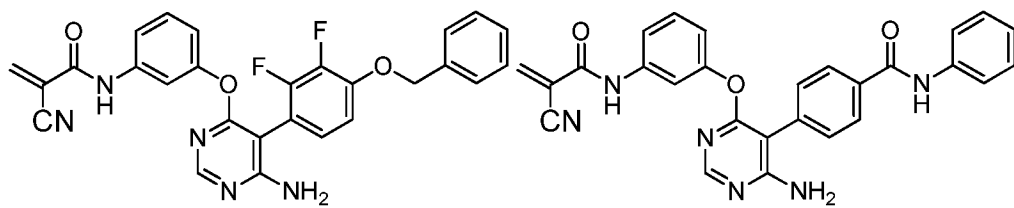
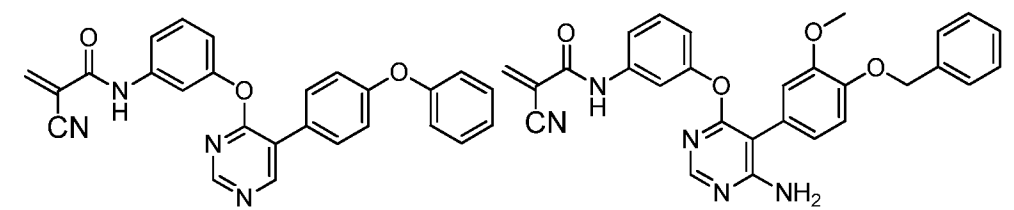




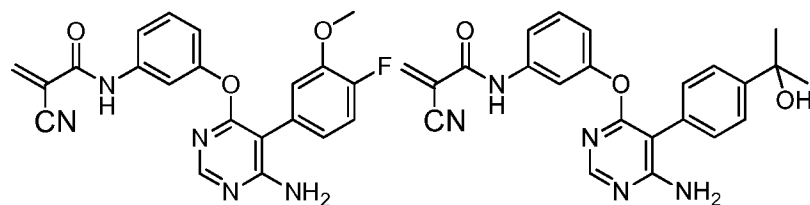
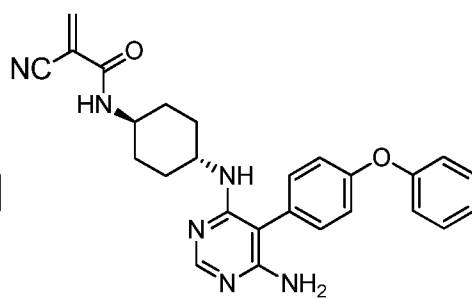
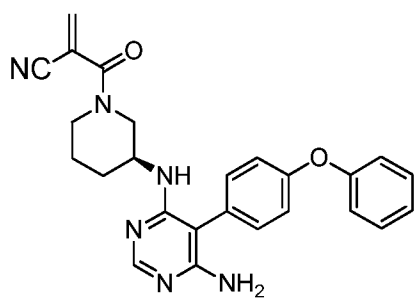
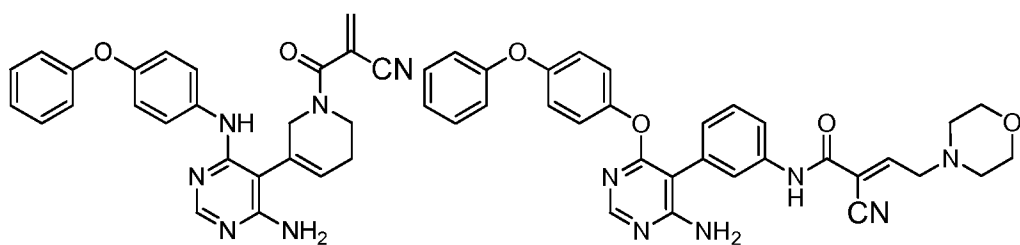
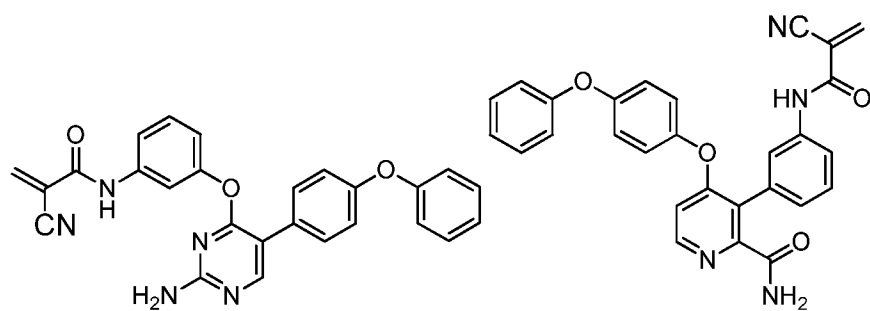
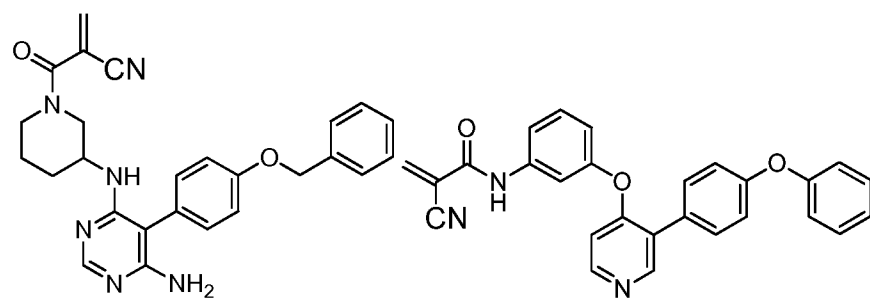
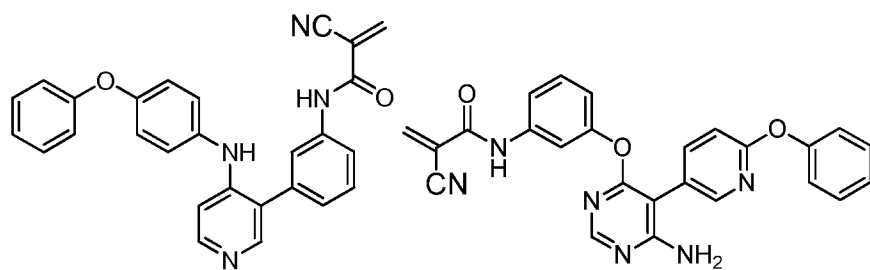


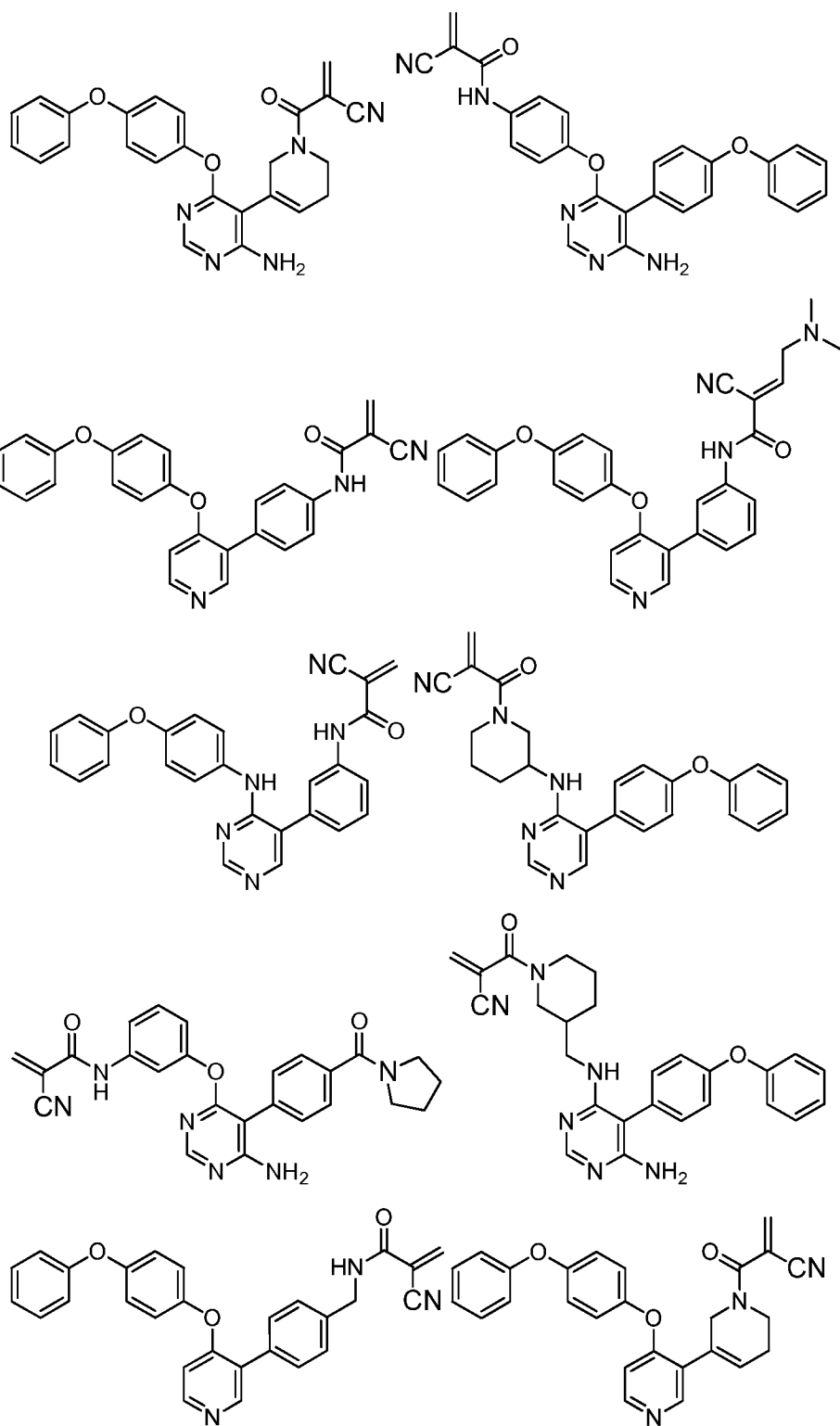


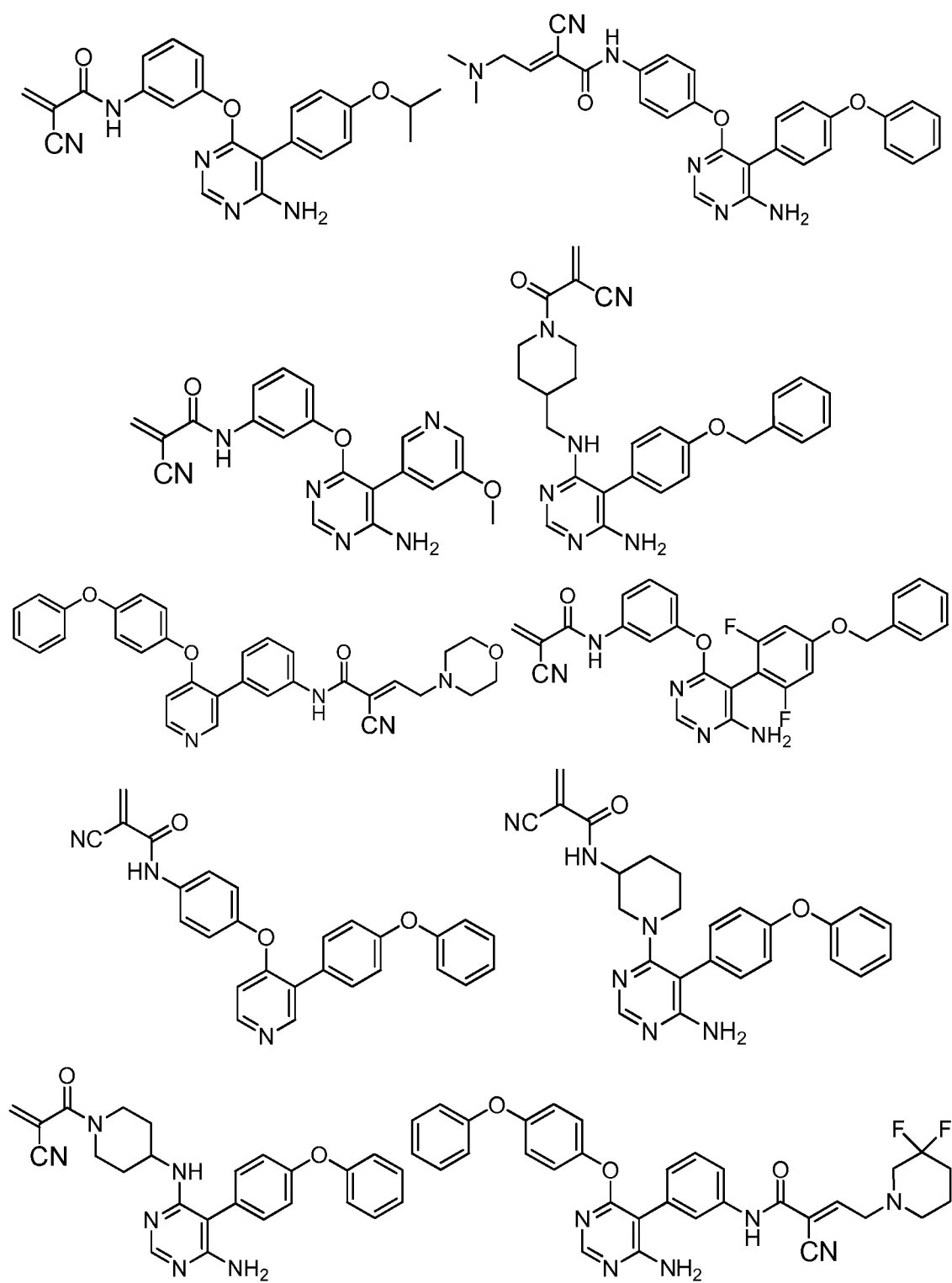


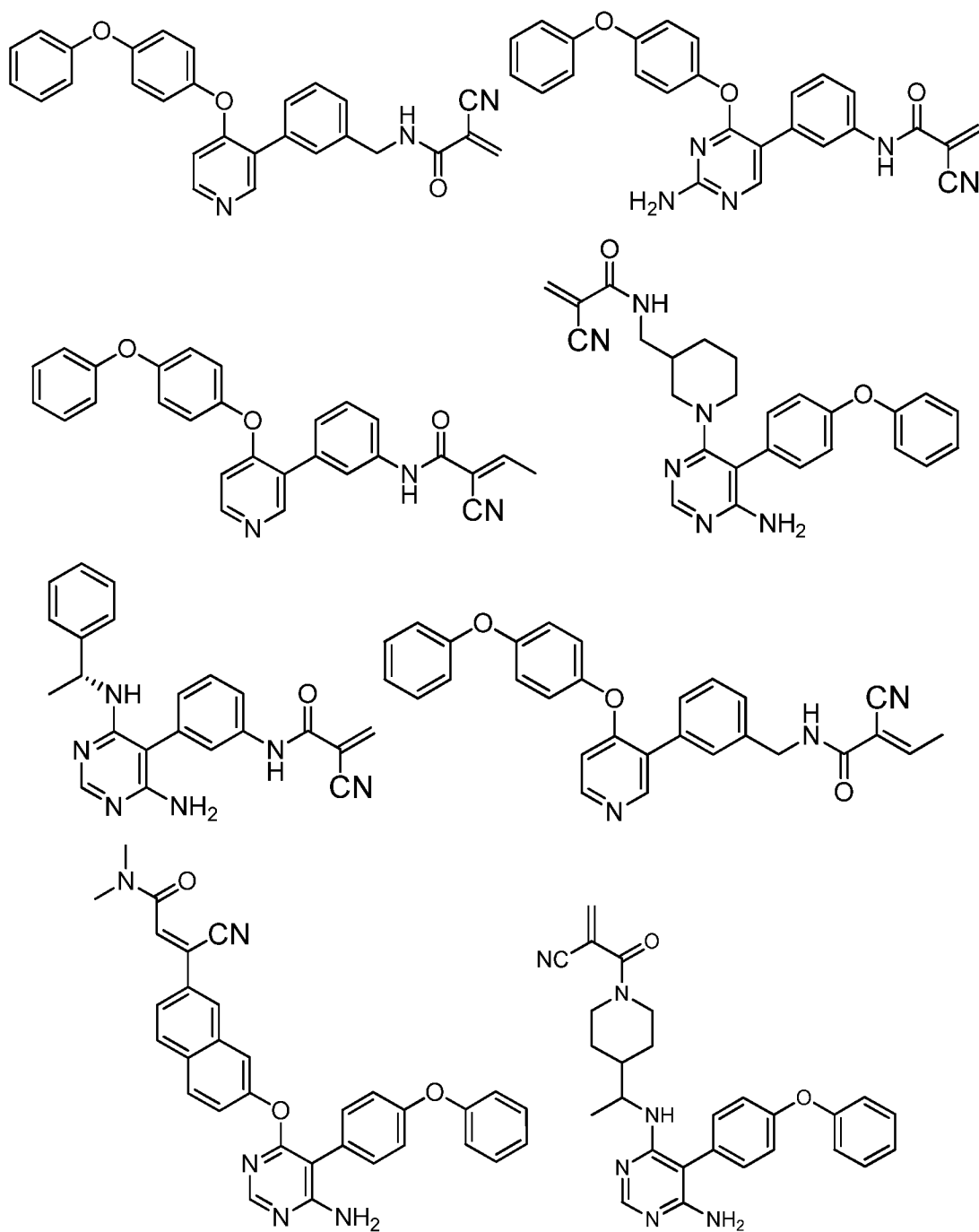


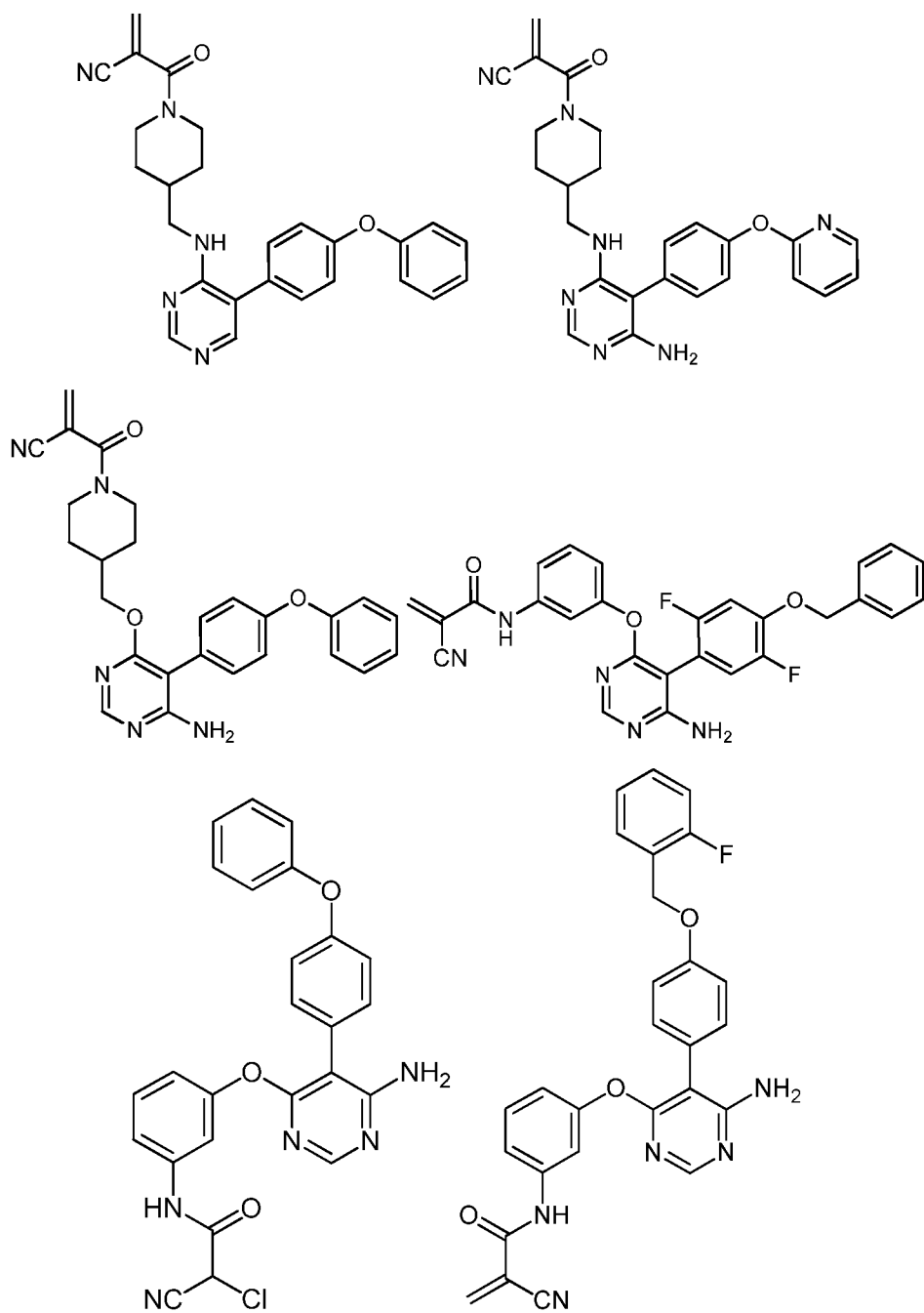
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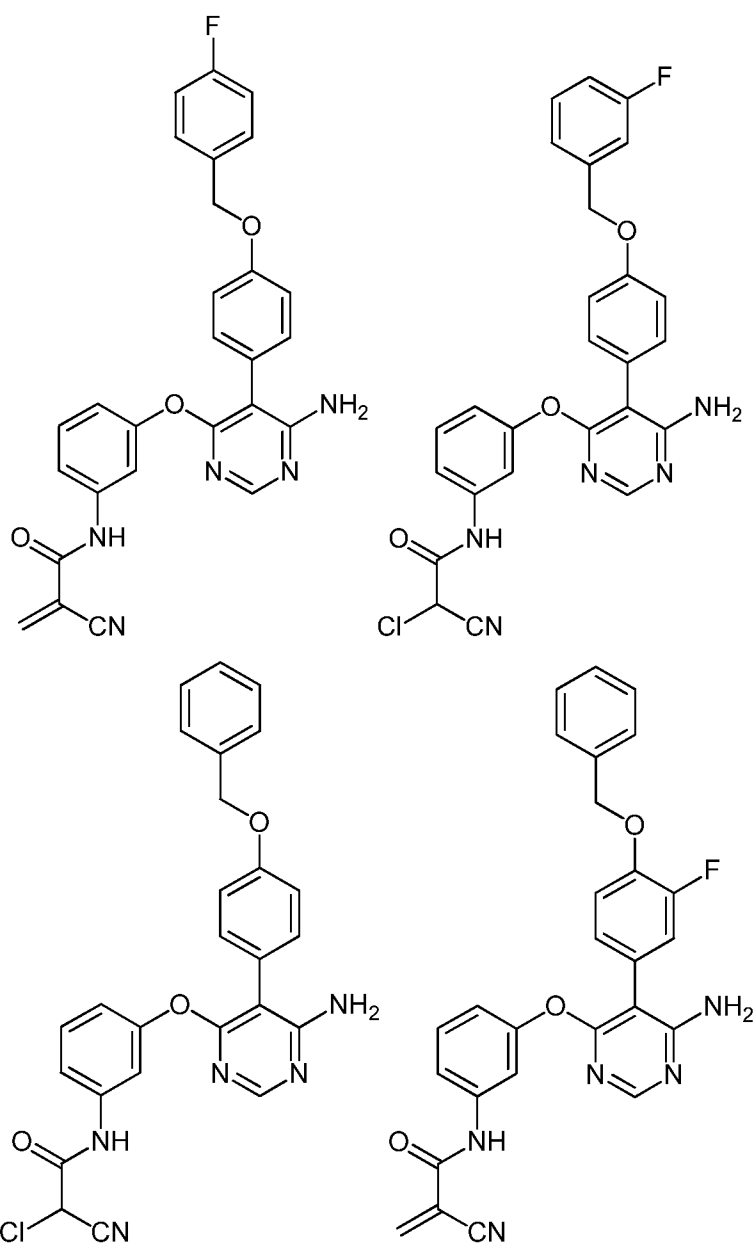


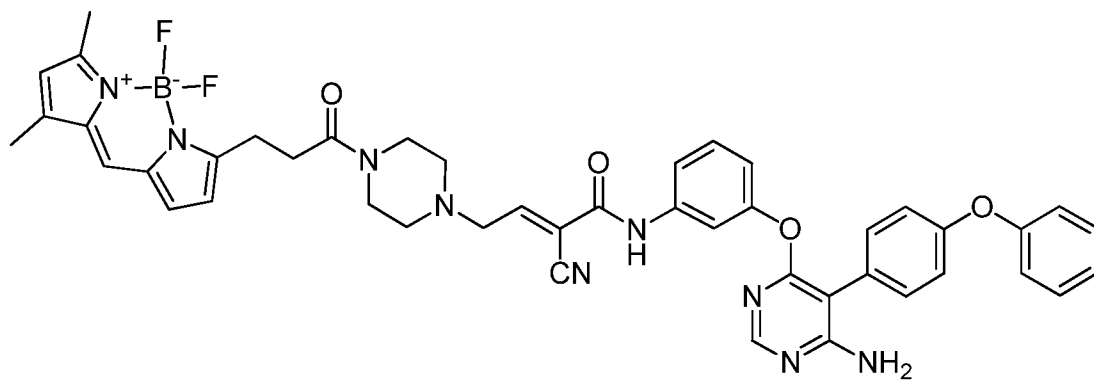
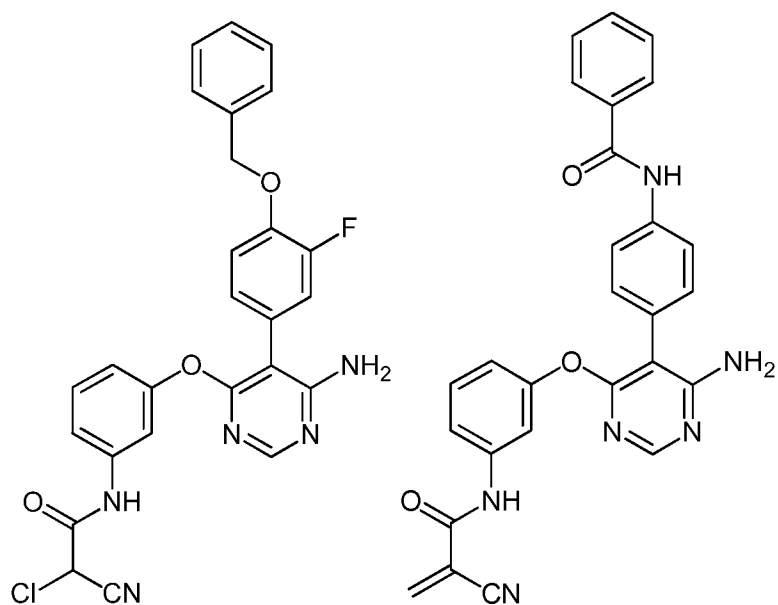
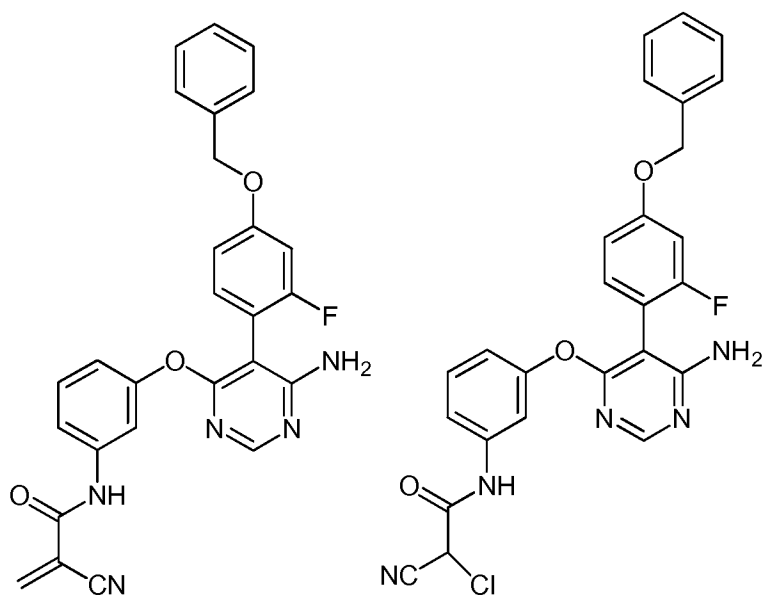


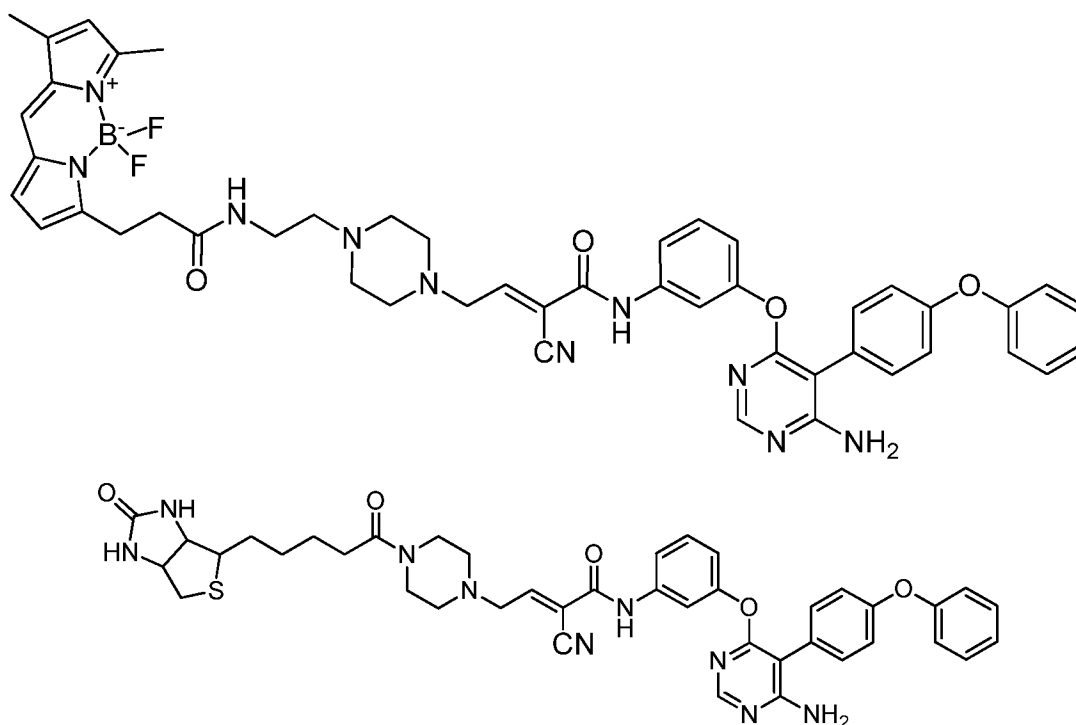












Biological Activity

5

Description of In Vitro Assays

BTK IC₅₀ Enzyme Assay

The following describes a microfluidic, off-chip mobility shift kinase assay used to measure inherent potency of compounds against BTK enzyme. Compounds described by

embodiments of the present invention were assayed using this protocol and the data from the same is recorded in Table 3 within the column labeled: "Time Dependent BTK Enzyme Assay IC₅₀". These IC₅₀ values are reported in ranges wherein: A < 100nM, B < 1uM, and C > 1uM.

- 2.5X stocks of full-length human BTK (08-080) from CarnaBio USA, Inc., Natick, MA, 1.6X ATP and appropriate kinKDR peptide substrate (FITC-AHA-EEPLYWSFPAKKK-NH₂) were prepared in kinase reaction buffer consisting of 25 mM MgCl₂, 0.015% Brij-35 (30%), 100 mM Hepes, pH 7.5, and 10 mM DTT.
- 5 uL of enzyme buffer and 7.5 uL of ATP/kinKDR peptide substrate mix were added to Matrix (#115304) 384-well, sterile, polypropylene plates (Thermo Fisher Scientific, Hudson, NH) with 125 nL of serially diluted compounds prepared in 100% DMSO, and incubated for 90 min. at 27°C. Following the incubation period, reactions were stopped by adding 60 uL

stop buffer consisting of 100 mM Hepes, pH 7.5, 0.015% Brij-35 (30%), 0.277% Coating Reagent #3 (Caliper Life Sciences, Mountain View, CA), 5% DMSO. Stopped reactions were monitored at -2 PSI, -3000 V/-700 V in a LabChip 3000 plate reader from Caliper Life Sciences, a PerkinElmer Company (Hopkinton, MA), and the activity was measured by off-chip mobility shift assay measuring the charge/mass difference between substrate and product resulting from peptide phosphorylation. IC₅₀ and efficacy were determined by plotting log [Inhibitor] vs. % Activity in GeneData Screener (Basel, Switzerland). Compounds described by embodiments of the present invention were assayed using this protocol and the data from the same is recorded in Table 3 within the column labeled: "Time Dependent PBMC BTK Enzyme Assay IC₅₀." These IC₅₀ values are reported in ranges wherein: A < 100nM, B < 1uM, and C > 1uM.

Time Dependent Human Whole Blood IC₅₀ Assay

Compounds described by embodiments of the present invention are assayed using a human whole blood assay.

Time Dependent PMBC IC₅₀ Assay

Compounds described by embodiments of the present invention are assayed using a time dependent PMBC assay.

Table 3 presents IC₅₀ values, derived from the in vitro assays detailed above, for selected compounds described by embodiments of the present invention.

Table 3

Compound No.	Time Dependent BTK Enzyme Assay IC ₅₀
(1)	C
(2)	B
(3)	B
(4)	A

Description of In Vivo Data

Systemic Lupus Erythematosus Mouse Model (SLE)

The compounds of the invention are evaluated in an interferon-alpha accelerated SLE mouse model. NZB/W F1 mice receive i.v. injection at day 0 and day 1 of 10^8 infectious units of adenovirus (ADV-IFN- α) to deliver a transient overexpression on interferon alpha. Oral dosing of the different group treatments is initiated on day 14 and continued daily at 24 hour intervals until the end of the study. Treatment groups consist of 20% Kleptose HPB in Na-citrate buffer (vehicle) or 0.1, 0.3, 1, or 3 mg/kg of the compound of the invention. The disease activity of each individual animal is calculated by the following Formula: Disease activity = $(0.5 * (\text{days with proteinuria of individual animal} / \text{mean of days with proteinuria of vehicle group}) + 0.5 * (\text{AUC of individual animal} / \text{mean AUC of vehicle group})) * 100$. NZB/W F1 mice receive i.v. injections at day 0 and day 1 of 10^8 infectious units of adenovirus (ADV-IFN- α) to deliver a transient overexpression on interferon alpha. Oral dosing of the different group treatments (n=10) is initiated on day 14 and continues daily at 24 hour intervals until the end of the study. Treatment groups consist of 20% Kleptose HPB in Na-citrate buffer (vehicle), 0.1, 0.3, 1, or 3 mg/kg of the compound of the invention or Cell Cept®. Statistical analysis is performed using Two way ANOVA with Bonferroni post test with all groups compared to vehicle treated group (*=p<0.05, **=p<0.01, ***=p<0.001).

Rat Collagen-Induced Arthritis Model

The compound of the invention is evaluated in a collagen-induced arthritis model in rats. Anesthetized female Lewis rats receive subcutaneous/intradermal injections of 300 μ l of Freund's Incomplete Adjuvant containing 4 mg/ml bovine type II collagen, at the base of the tail and 2 sites on the back on days 0 and 6. The data from the oral dosing of the different group treatments is initiated on day 6 and continues daily at 24 hour intervals, for 11 days up to day 16. Treatment groups consist of 20% Hydroxy-Propyl-Beta Cyclodextrin in H₂O (vehicle) or 0.3, 1, 3, or 10 mg/kg of the compound, or methotrexate (MTX) at 0.1 mg/kg. Caliper measurements of ankles are taken every day beginning on day 9 (or day 0 of arthritis). Animals are sacrificed on day 17.

Mouse Collagen-Induced Arthritis Model

The compound of the invention is evaluated in a collagen-induced arthritis model in mice. Male DBA/10IaHsd mice are injected intradermally at the base of the tail with 150 μ l of Freund's Complete Adjuvant containing bovine type II collagen on day 0 and on day 21. On day 18, mice are randomized by body weight into treatment groups. Oral treatment is initiated after enrollment on day 18 and continues daily at 24 h intervals up to day 33. Mice are treated with 20% Hydroxy-Propyl-Beta Cyclodextrin in H₂O (vehicle) or the compound at either 1, 3, 10, or 30 mg/kg or with methotrexate (MTX) at 0.5 mg/kg. On study days 22–34

onset of arthritis occurs. Mice are sacrificed on day 34. Clinical scores are given for each of the paws (right front, left front, right rear, left rear) on arthritis days 18–34.

Mouse Passive cutaneous anaphylaxis (PCA)

5 The compound of the invention is evaluated in a PCA model in mice. In vivo anaphylaxis mediated through the FcεRI receptor is a mast-cell-dependent allergic response to local or systemic exposure to allergens, which cross-link and activate antigen-specific IgE bound to the FcεRI on the mast cell surface leading to mast cell activation and degranulation. The murine PCA model mimicks these events *in vivo* and can be used for testing the efficacy of
10 newly developed compounds targeting tyrosine kinases that are downstream of FcεRI like BTK. The data from experiments where 10-week old female BALB/c mice are injected intradermally with immunoglobulin E (IgE) directed against the hapten 2,4-dinitrophenyl (DNP). 24h after sensitization, mice are challenged by systemic administration of DNP coupled to human serum albumin (HSA), together with Evan's blue dye. Mice are dosed
15 orally with three doses of Cpd B. 1h before challenge. Evan's blue extravasation is measured in the back 30 minutes after the challenge.

Anti-IgD-induced CD69 Upregulation in Mouse Whole Blood

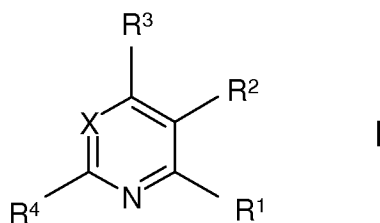
The compound of the invention is evaluated for anti-IgD-induced CD69 upregulation in
20 mouse whole blood. BCR activation induces the expression of the surface cluster of differentiation 69 (CD69) which is the earliest inducible cell surface glycoprotein acquired during lymphoid activation and is currently used as a marker for B cell activation both *in vitro* and *ex vivo*. Female C57Bl/6 mice are administered orally with Cyclodextrin or 1.19, 3.96 or 11.9 mg/kg of the compound 1h before blood collection. Half an hour after intraperitoneal
25 injection of heparin, blood is collected in heparinized tubes and B cells are stimulated with 10 µl of PBS or polyclonal goat anti-mouse IgD antiserum for 4h. CD69 upregulation in individual cells is determined by flow cytometric analysis using rat anti-mouse B220-PerCP-Cy5.5 and hamster anti-mouse CD69-PE monoclonal antibodies for immunostaining.

30 While a number of embodiments of this invention are described herein, it is apparent that the basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

35

CLAIMS

1. A kinase inhibitor, comprising (i) a compound of Formula (I)



5 in which

X is CH or N;

R¹ is NR⁵[C(R⁵)₂]_nHet², NH₂, CONH₂ or H;

R² is Hal, Ar¹ or Het¹;

10 R³ is NH₂, NR⁵[C(R⁵)₂]_nHet², O[C(R⁵)₂]_nHet², NR⁵[C(R⁵)₂]_nCyc, O[C(R⁵)₂]_nCyc, NR⁵[C(R⁵)₂]_nAr², O[C(R⁵)₂]_nAr², NR⁵[C(R⁵)₂]_nHet¹, O[C(R⁵)₂]_nHet¹, NR⁵[C(R⁵)₂]_nA, O[C(R⁵)₂]_nA, NR⁵(CH₂)_pNR⁵R⁶, O(CH₂)_pNR⁵R⁶, NR⁵(CH₂)_pCR⁷R⁸NR⁵R⁶ or Het²;

R⁴ is H, CH₃ or NH₂;

R⁵ is H or alkyl having 1, 2, 3 or 4 C atoms;

15 R⁶ is N(R⁵)₂CH₂CH=CHCONH-, Het³CH₂CH=CHCONH-, CH₂=CHCONH(CH₂)_n-, Het⁴(CH₂)_nCOHet³-diyl-CH₂CH=CHCONH-, HC≡CCO-, CH₃C≡CCO-, CH₂=CH-CO-, CH₂=C(CH₃)CONH-, CH₃CH=CHCONH(CH₂)_n-, N≡CCR⁷R⁸CONH(CH₂)_n-, Het⁴NH(CH₂)_pCOHet³-diyl-CH₂CH=CHCONH-,

20 Het⁴(CH₂)_pCONH(CH₂CH₂O)_p(CH₂)_pCOHet³-diyl-CH₂CH=CHCONH-, CH₂=CHSO₂-, ACH=CHCO-, CH₃CH=CHCO-, Het⁴(CH₂)_pCONH(CH₂)_pHet³-diyl-CH₂CH=CHCONH-, Ar³CH=CHSO₂-, CH₂=CHSO₂NH- or N(R⁵)CH₂CH=CHCO-;

R⁷, R⁸ are together alkylene having 2, 3, 4, or 5 C atoms;

25 Ar¹ is phenyl or naphthyl, each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, Hal, (CH₂)_nNH₂, CONHAr³, (CH₂)_nNHCOA, O(CH₂)_nAr³, OCyc, A, COHet³, OA and/or OHet³ (CH₂);

Ar² is phenyl, naphthyl or pyridyl each of which is unsubstituted or mono-, di- or trisubstituted by R⁶, Hal, OH, OAr³, (CH₂)_nNH₂, (CH₂)_nNHCOA and/or Het³;

30

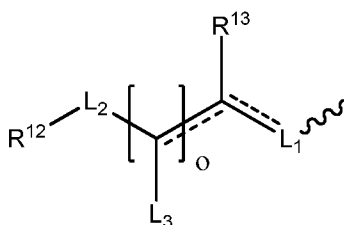
Ar³ is phenyl, which is unsubstituted or mono-, di- or trisubstituted by OH, OA, Hal, CN and/or A;

- Het¹ is a mono-or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by R⁶, Hal, OH, O(CH₂)_nAr³ and/or (CH₂)_nAr³;
- Het² is a mono- or bicyclic saturated heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by R⁶, Het³, CycSO₂, OH, Hal, COOH, OA, COA, COHet³, CycCO, SO₂ and/or =O;
- Het³ is a monocyclic unsaturated, saturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by Hal, A and/or =O;
- Het⁴ is a bi- or tricyclic unsaturated, saturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di-, tri- or tetrasubstituted by A, NO₂, Hal and/or =O;
- Cyc is cyclic alkyl having 3, 4, 5 or 6 C atoms, which is unsubstituted, monosubstituted or disubstituted by R⁶, Hal and/or OH and which may comprise a double bond;
- A is unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl and/or in which one or two non-adjacent CH₂ and/or CH-groups may be replaced by O, NH and/or by N;
- Hal is F, Cl, Br or I;
- n is 0, 1, 2, 3 or 4; and
- p is 1, 2, 3, 4, 5 or 6;

and (ii) an electrophilic warhead comprising a Michael acceptor, wherein the warhead is coupled to the compound of Formula (I) at R¹, R² or R³;

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

2. The inhibitor according to Claim 1, wherein the warhead is a compound of Formula (VI)



(VI)

in which

R^{11} , R^{12} are, independently from one another, H, A, Cyc, Ar^1 , Ar^2 , Ar^3 , Het^1 , Het^2 , Het^3 or Het^4 , which have the meanings indicated in Claim 1;

5 R^{13} is an electron withdrawing group selected from nitrile and ester;

L_1 is $-CO-$, $-CONH-$, $=CH-(CH_2)_m-$, $=CH-(CH_2)_mNH-$ or $-(CH_2)_m-$;

L_2 is $CONR^{11}$ or absent;

L_3 is absent or together with R^{12} forms a 4-8 membered carbocyclic, aryl, heterocyclic, or heteroaryl ring;

10 m is 1, 2, 3 or 4; and

o is 0 or 1.

3. The inhibitor according to Claim 1 or 2, wherein the warhead comprises a cyanoacrylamide group.

15

4. The inhibitor according to Claim 2 or 3, in which

R^{11} , R^{12} are, independently from one another, H, A or Ar^3 ;

R^{13} is CN;

L_1 is $-CO-$, $=CH-(CH_2)_m-$ or $-(CH_2)_m-$;

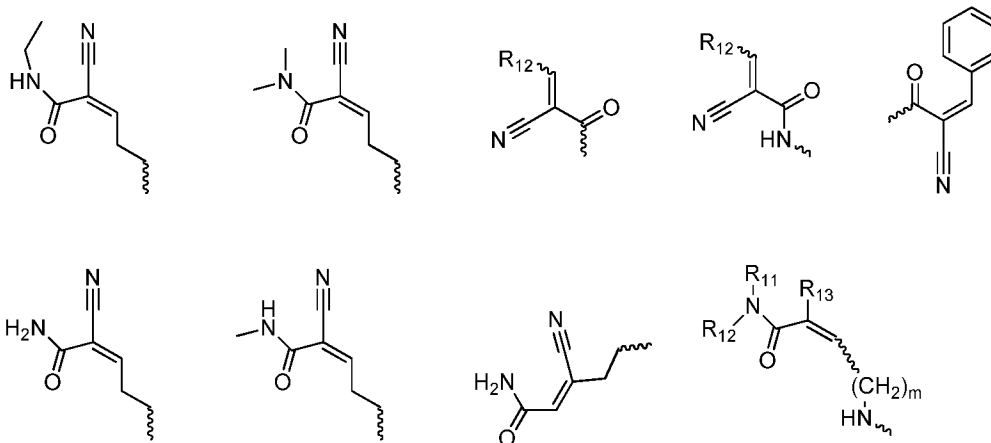
20 L_2 is $CONR^{11}$ or absent;

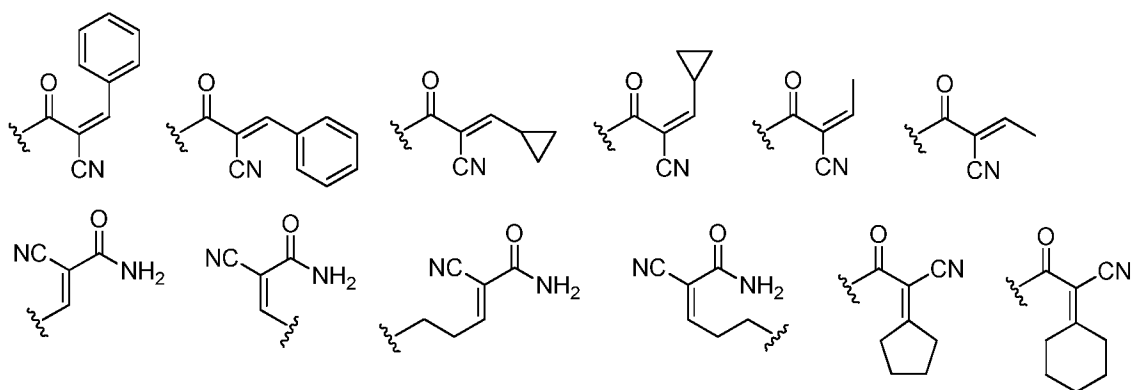
m is 1 or 2; and/or

o is 0 or 1.

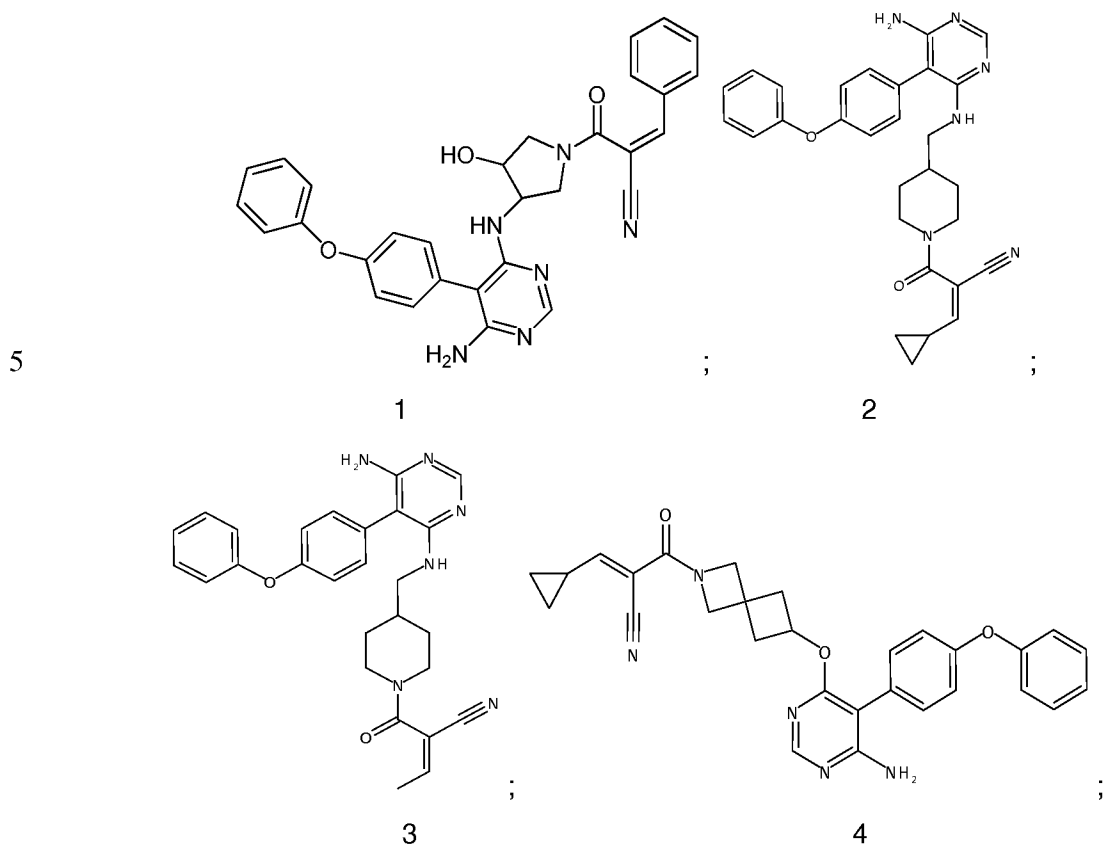
5. The inhibitor according to any of Claims 2-4, wherein the warhead is selected from the group of:

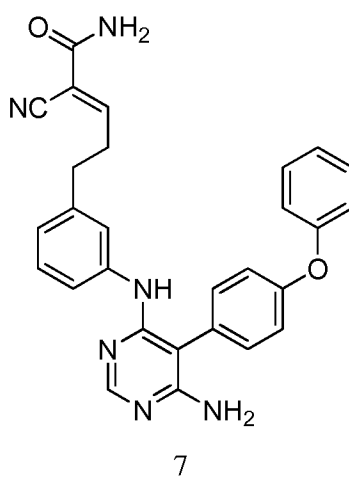
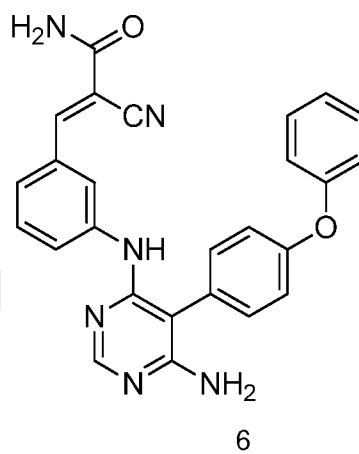
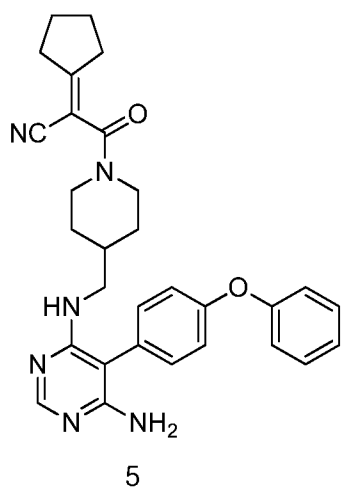
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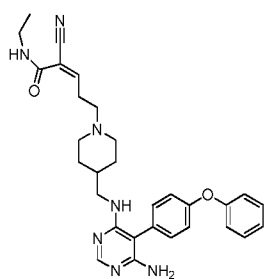


6. The inhibitor according to any of Claims 1-5, which is selected from the group of:

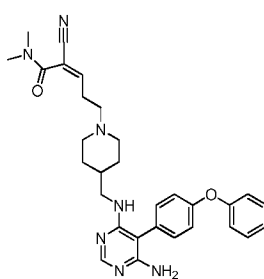




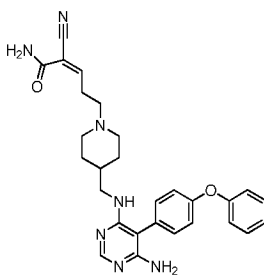
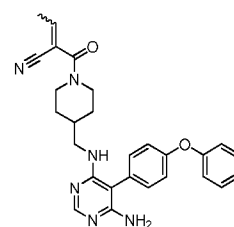
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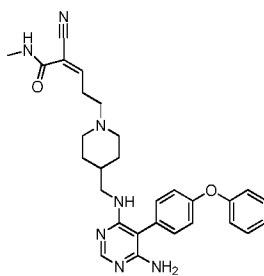
and the E isomer



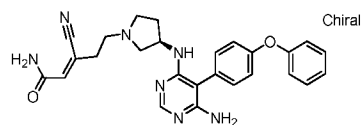
and the E isomer



and the E isomer



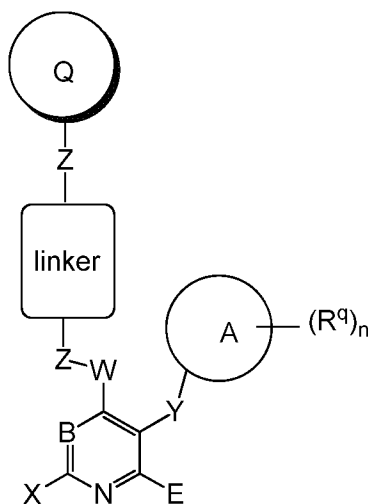
and the E isomer



and the E isomer

Chiral

7. A kinase inhibitor of Formula (II)



(II)

in which

- 5 X is H or CH₃ or NH₂;
 Y is absent;
 B is N or CH;
 E is NH₂ or H;
 W is NR, O or cyclic amine;
 10 Z is, independently, CH₂, CH₂-CH₂, =CH-CH₂, CH=CH, NH or absent;
 Linker is -(CH₂)_n; an optionally substituted group selected from phenyl, aryl,
 heteroaryl, branched or unbranched alkyl, 5-6 membered monocyclic
 heteroaryl having 1-4 heteroatoms independently selected from
 15 nitrogen or oxygen, a 4-7 membered saturated or partially unsaturated
 heterocycle having 1-3 heteroatoms independently selected from
 nitrogen or oxygen, a 7-10 membered bicyclic saturated or partially
 unsaturated heterocycle having 1-5 heteroatoms independently
 selected from nitrogen or oxygen, and a 7-10 membered bicyclic
 20 saturated or partially unsaturated heterocyclic ring having 1-5
 heteroatoms attached to a hetero saturated ring; a cycloalkane
 optionally substituted by heteroatoms independently selected from
 nitrogen or oxygen; a cycloalkane optionally substituted with -NH or
 OH; fused or bridged rings; or an optionally substituted spirocycle that
 optionally contains one or more heteroatoms;
 25 A is a mono- or bicyclic aromatic homo- or heterocycle having 0, 1, 2, 3
 or 4 N and/or O atoms and 5, 6, 7, 8, 9 or 10 skeleton C atoms, which

may be unsubstituted or, independently of one another, mono-, di- or trisubstituted by Hal, OH or OR;

Hal is F, Cl, Br or I;

R is, independently, hydrogen; oxygen; an optionally substituted group selected from C₁₋₆ linear or cyclic aliphatic, benzyl, phenyl, a 4-7 membered heterocycle having 1-2 heteroatoms independently selected from nitrogen or oxygen, and 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen or oxygen; a mono- or bicyclic aromatic homo- or heterocycle having 0, 1, 2, 3 or 4 N and/or O atoms and 5, 6, 7, or 8 C skeleton atoms, which may be unsubstituted or, independently of one another, mono-, di- or trisubstituted by Hal, A, OH, NH₂, nitrile and/or CH(Hal)₃; or unbranched or branched linear alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 C atoms in which one or two CH₂ groups may be replaced by O, -NH-, -CO-, -NHCOO-, -NHCONH-, -CONH-, -NHCO- or -CH=CH- and/or in which 1-3 H atoms may be replaced by Hal;

R^q is R, A, Hal, OR, O(CH₂)_rOR, NO₂, C(O)R, CO₂R, C(O)N(R)₂, NRC(O)R, NRC(O)NR₂, NRSO₂R or N(R)₂;

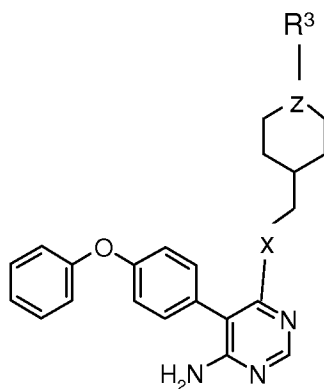
r is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4; and

Q is an electrophilic group, which is a warhead according to any of Claims 1-5;

and pharmaceutically usable salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios.

8. A kinase inhibitor of Formula (IV)



Formula (IV)

and pharmaceutically acceptable salts, solvates, solvates of salts, or prodrugs thereof,

wherein:

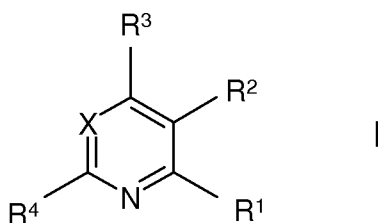
Z is N or CH,

X is O or NH, and

R³ is selected from Table 1.

9. A process for preparing a kinase inhibitor comprising the steps of:

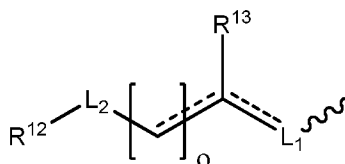
a) reacting a compound of Formula (I)



(I)

in which R¹-R⁴ and X have the meanings indicated in Claim 1,

with a warhead of Formula (VI)



(VI)

in which L₁, L₂, R¹², R¹³ and o have the meanings indicated in Claim 2,

to yield the kinase inhibitor according to Claim 1 and 2;

and optionally

(b) converting a base or an acid of the kinase inhibitor into one of its salts.

10. A medicament comprising at least one inhibitor according to any of Claims 1-8 and/or a pharmaceutically usable salt, tautomer or stereoisomers thereof, including mixtures thereof in all ratios.

11. A pharmaceutical composition comprising as active ingredient at least one inhibitor according to any of Claims 1-8 and/or a pharmaceutically usable salt, tautomer or

stereoisomer thereof, including mixtures thereof in all ratios, together with pharmaceutically tolerable excipients and/or adjuvants, optionally in combination with one or more further active ingredients.

- 5 12. An inhibitor according to any of Claims 1-8 and/or a pharmaceutically usable salt, tautomer or stereoisomer thereof, including mixtures thereof in all ratios, for use in the prophylactic or therapeutic treatment and/or monitoring of a disease that is caused, mediated and/or propagated by BTK activity.
- 10 13. A method for treating a disease that is caused, mediated and/or propagated by BTK activity, wherein at least one inhibitor according to any of Claims 1-8 and/or a pharmaceutically usable salt, tautomer or stereoisomer thereof, including mixtures thereof in all ratios, is administered to a mammal in need of such treatment.
- 15 14. The method according to Claim 13, wherein the disease is a solid tumour, which is selected from the group of tumours of the squamous epithelium, bladder, stomach, kidneys, head, neck, oesophagus, cervix, thyroid, intestine, liver, brain, prostate, urogenital tract, lymphatic system, larynx, lung, blood and immune system.
- 20 15. The method according to Claim 14, wherein the disease is a tumour, which is selected from the group of lung adenocarcinoma, small-cell lung carcinoma, pancreatic cancer, glioblastoma, colon carcinoma, breast carcinoma, monocytic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphatic leukaemia and chronic lymphatic leukaemia.
- 25 16. The method of claim 13, wherein the disease is rheumatoid arthritis or systemic lupus erythematosus.
- 30 17. A method for inhibiting BTK, wherein a system expressing BTK is contacted with at least one inhibitor according to any of Claims 1-8 and/or a pharmaceutically usable salt, tautomer or stereoisomer thereof, including mixtures thereof in all ratios, under conditions such that BTK is inhibited.