

(43) **Pub. Date:** **Aug. 10, 2023**

This invention is in the area of improved compounds and methods for treating selected cancers and hyperproliferative disorders.

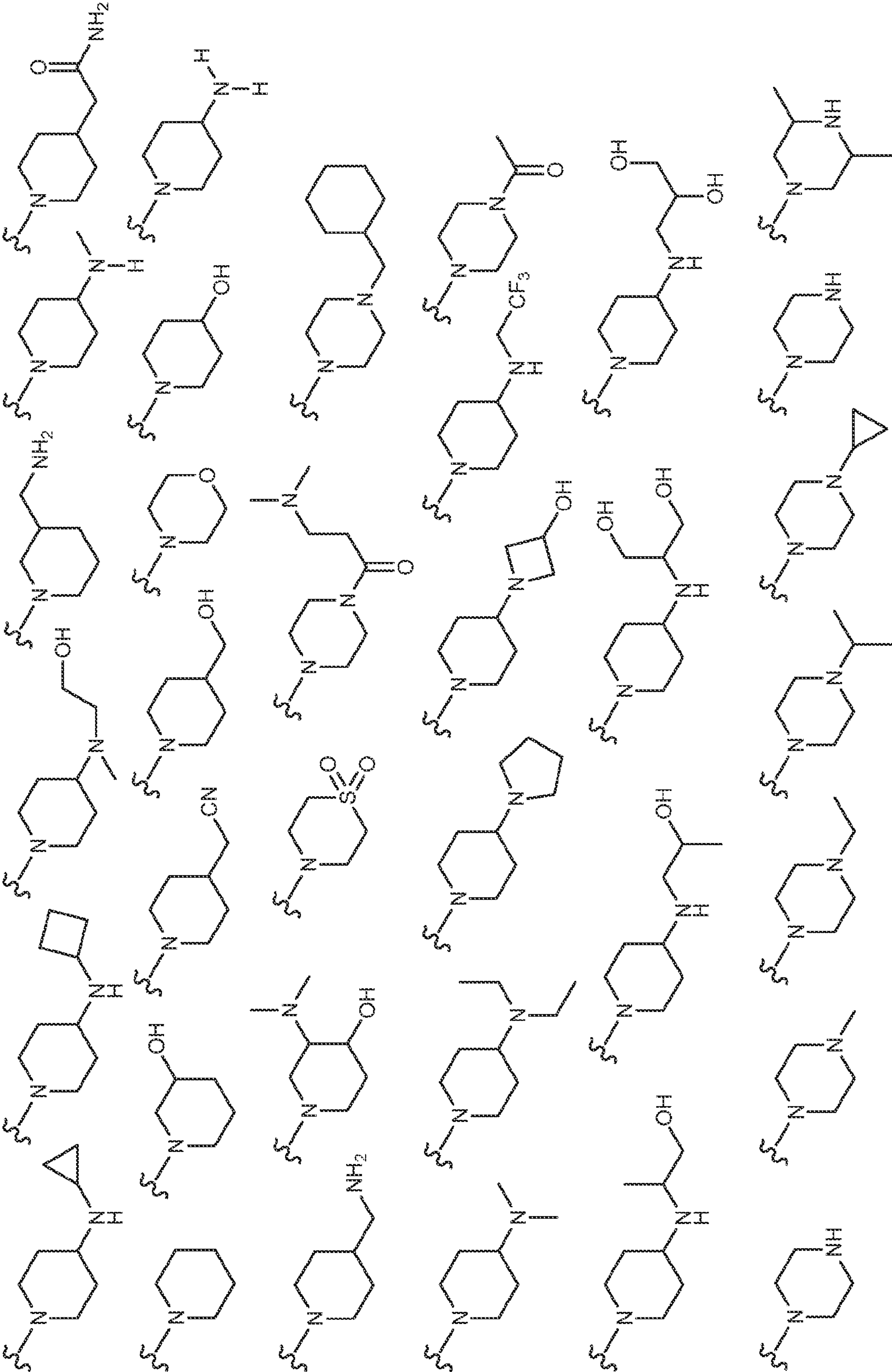


FIG. 1

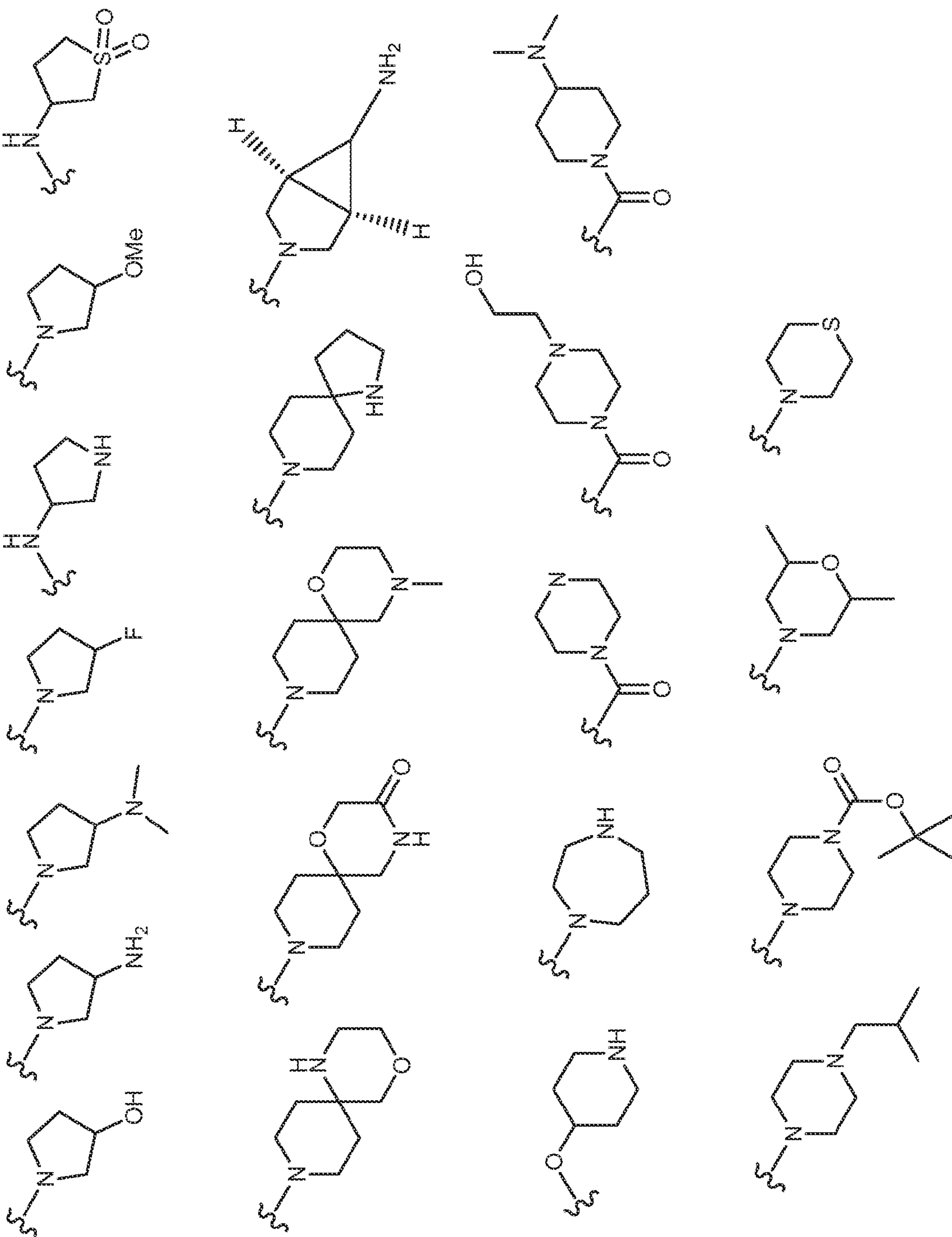


FIG. 3

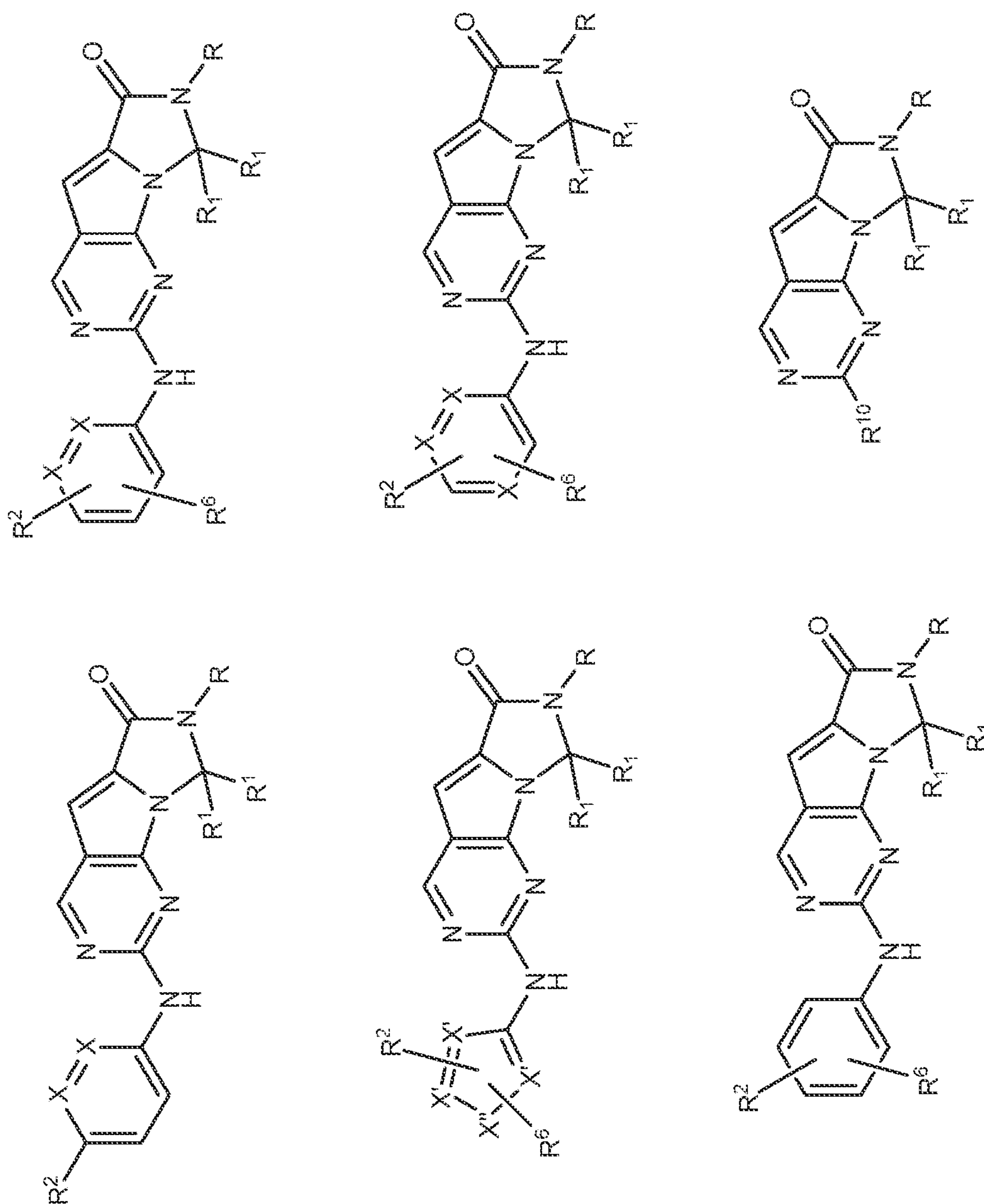


FIG. 4A

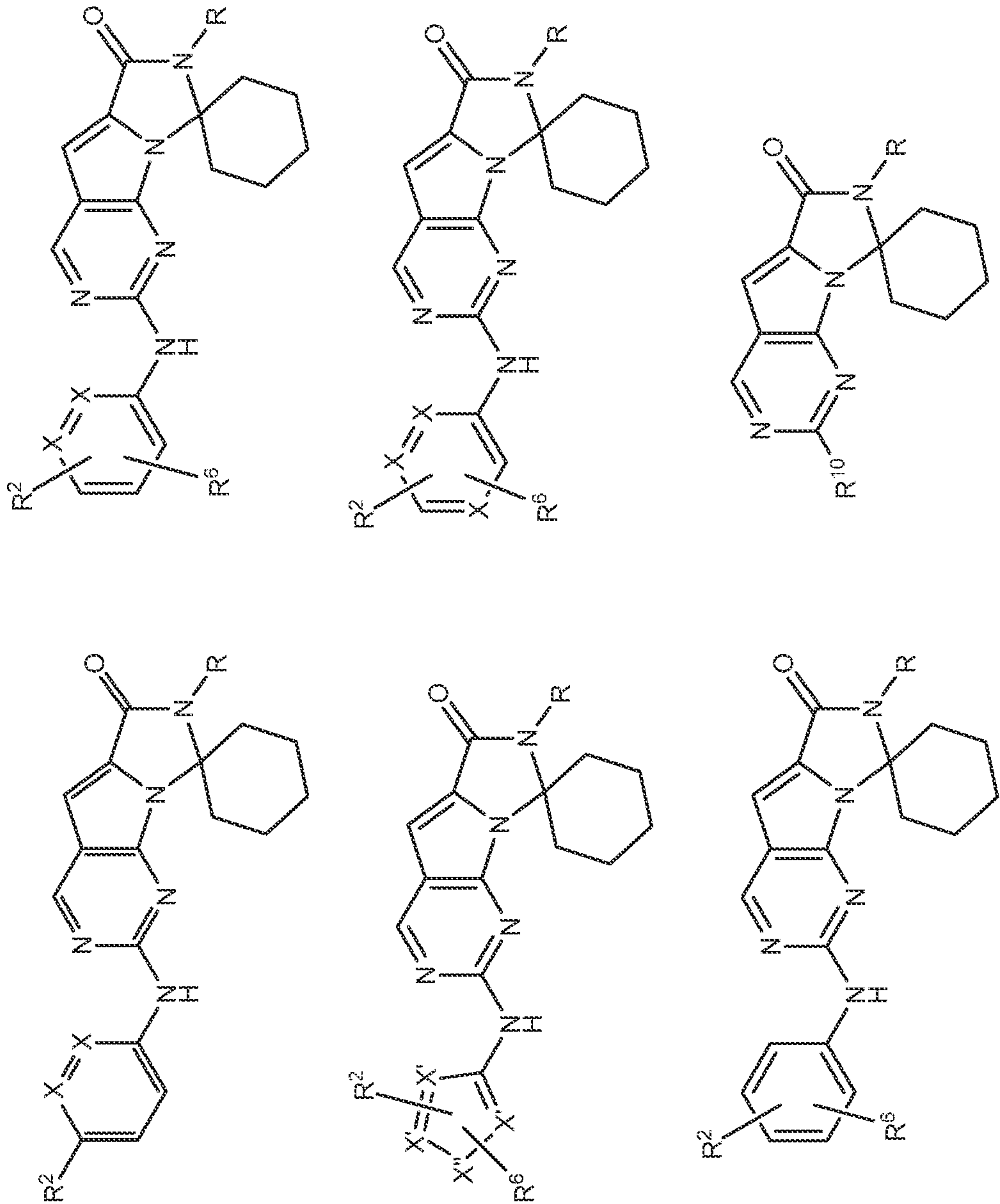


FIG. 4C

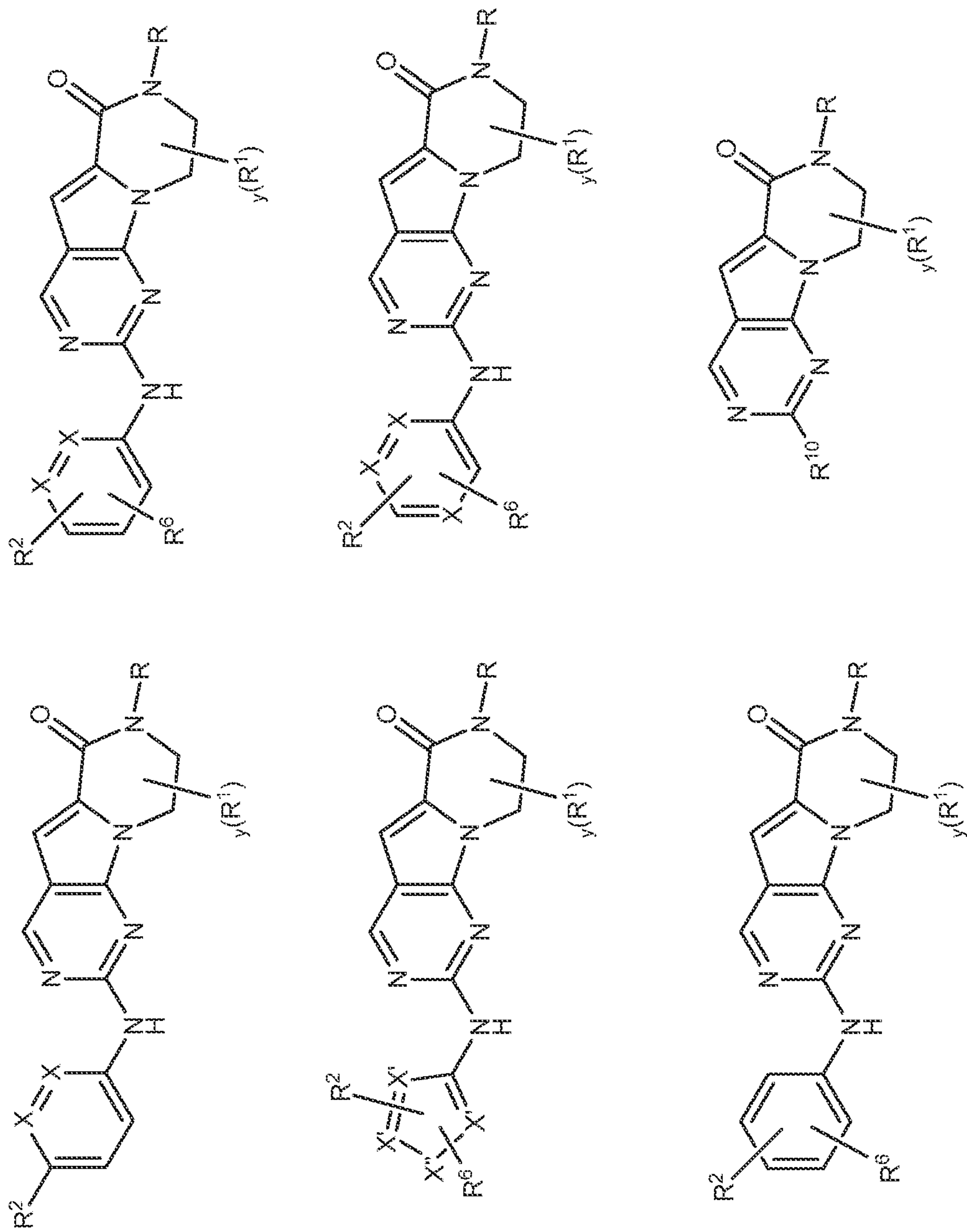


FIG. 5A

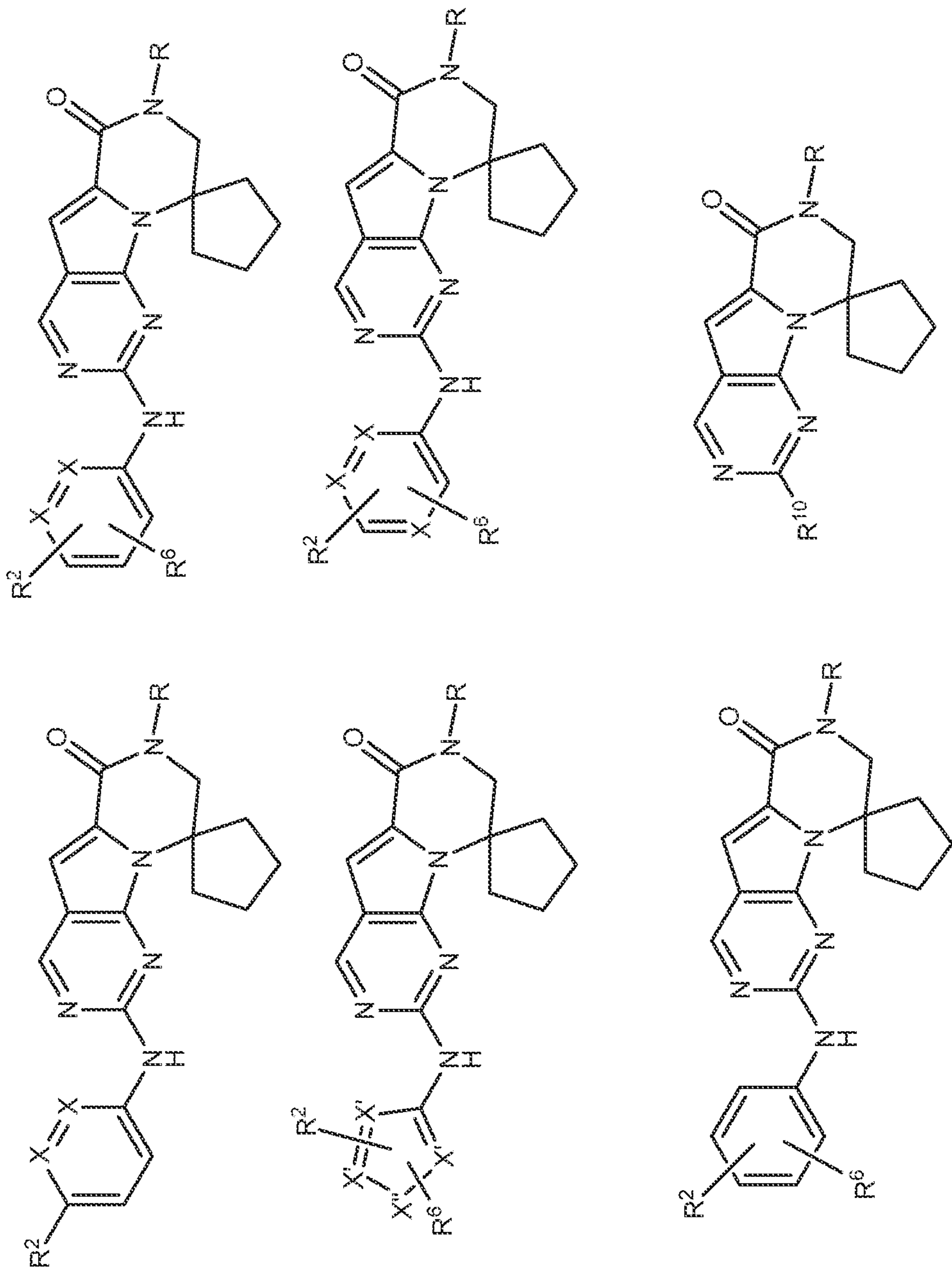


FIG. 5B

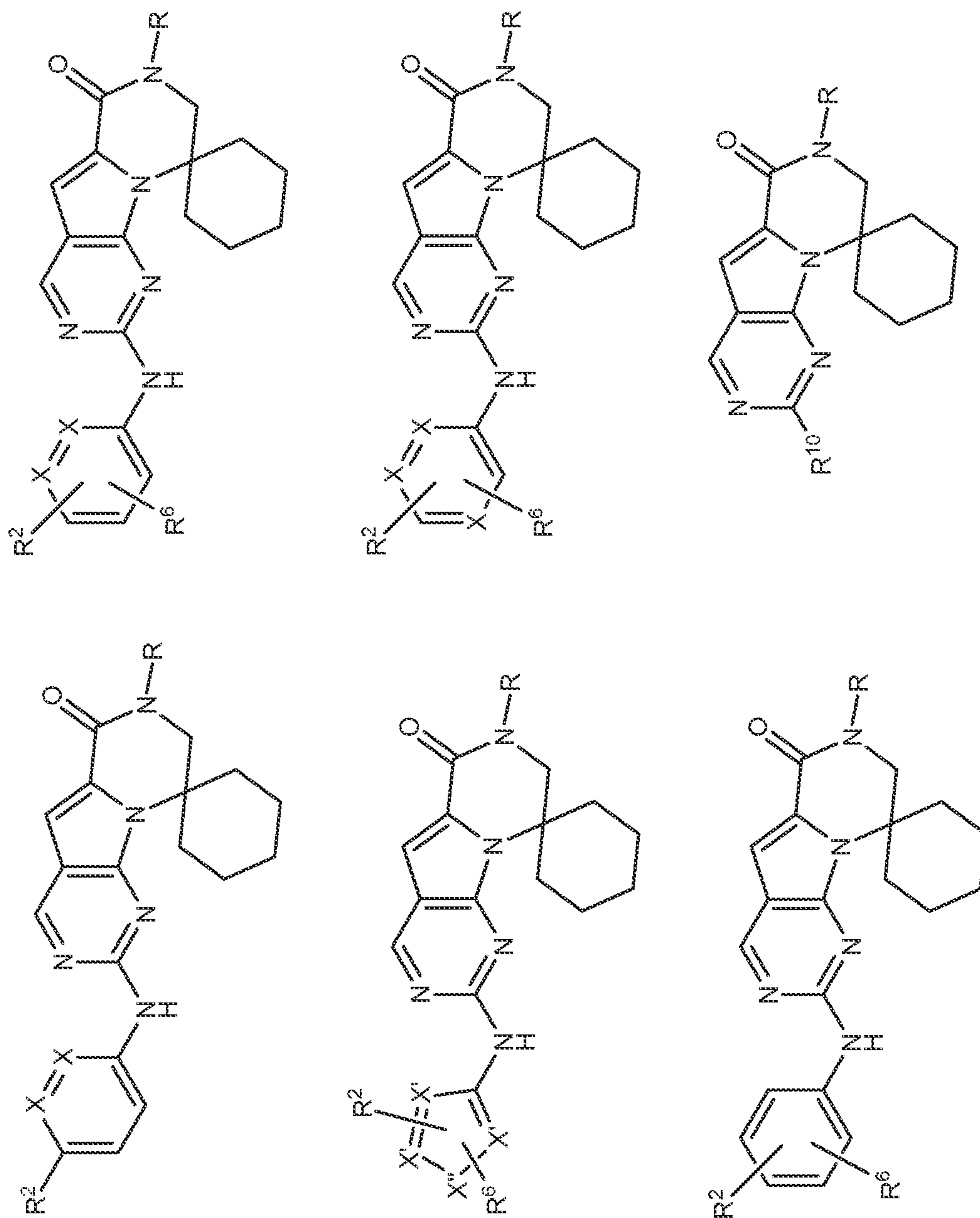


FIG. 5C

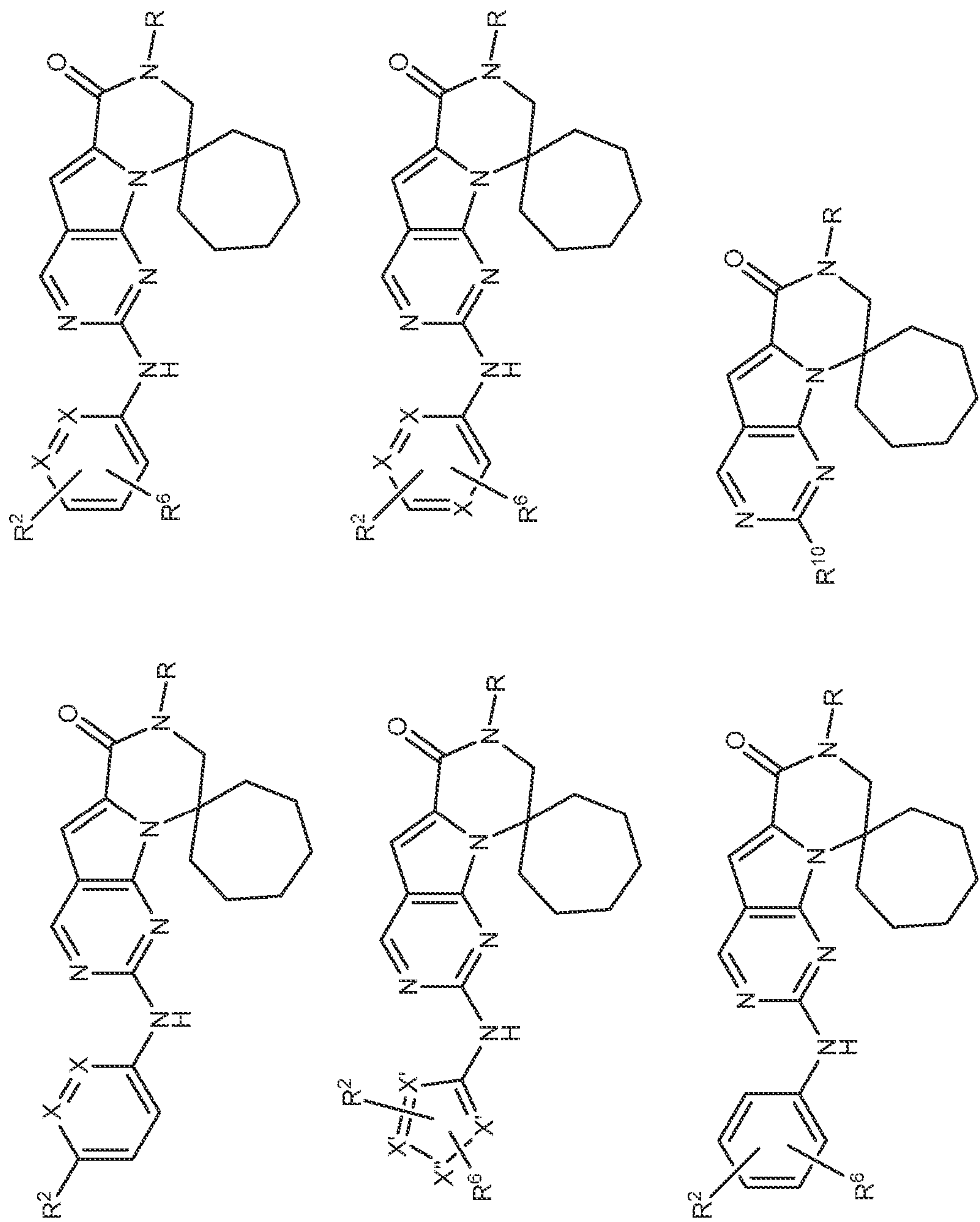


FIG. 5D

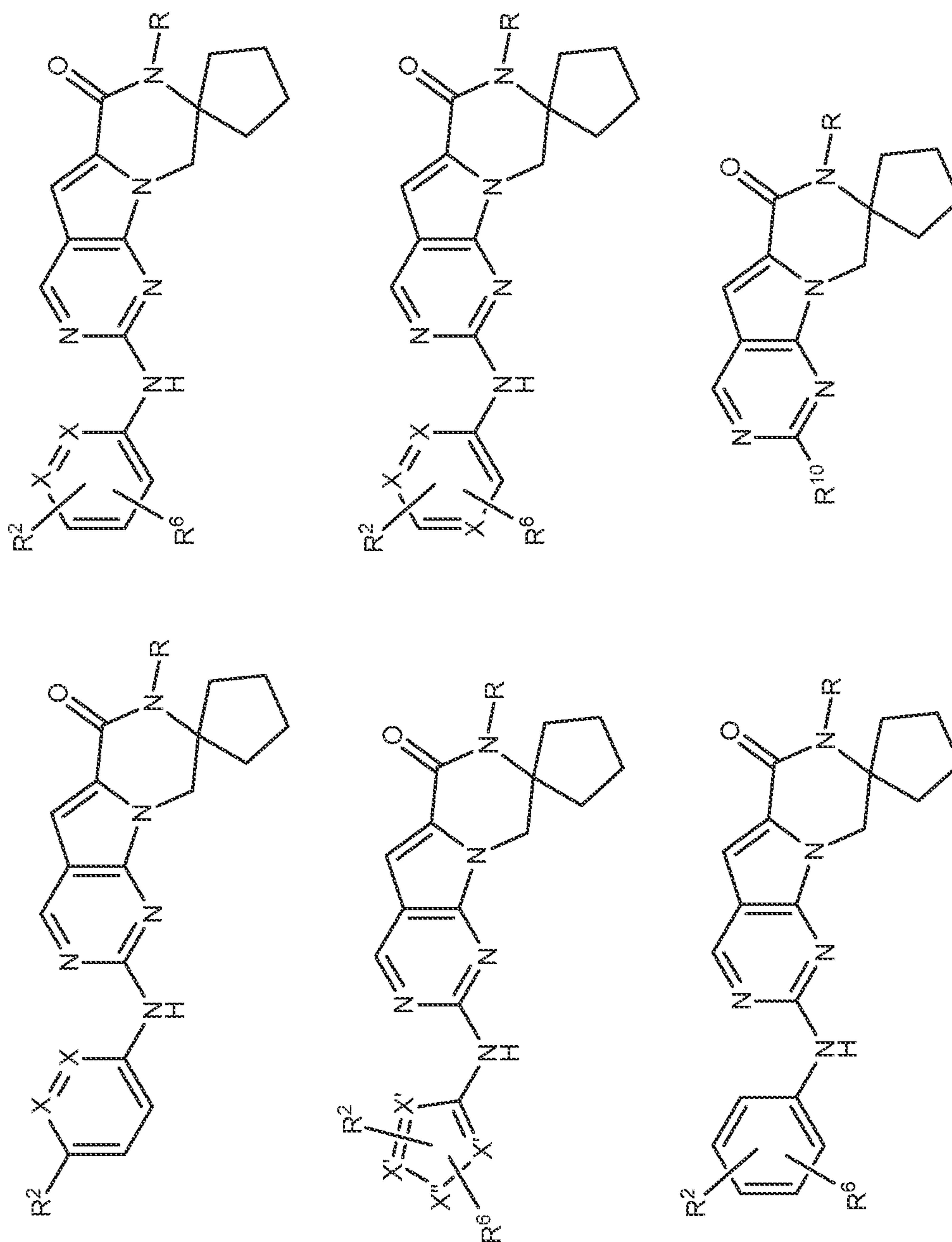


FIG. 6A

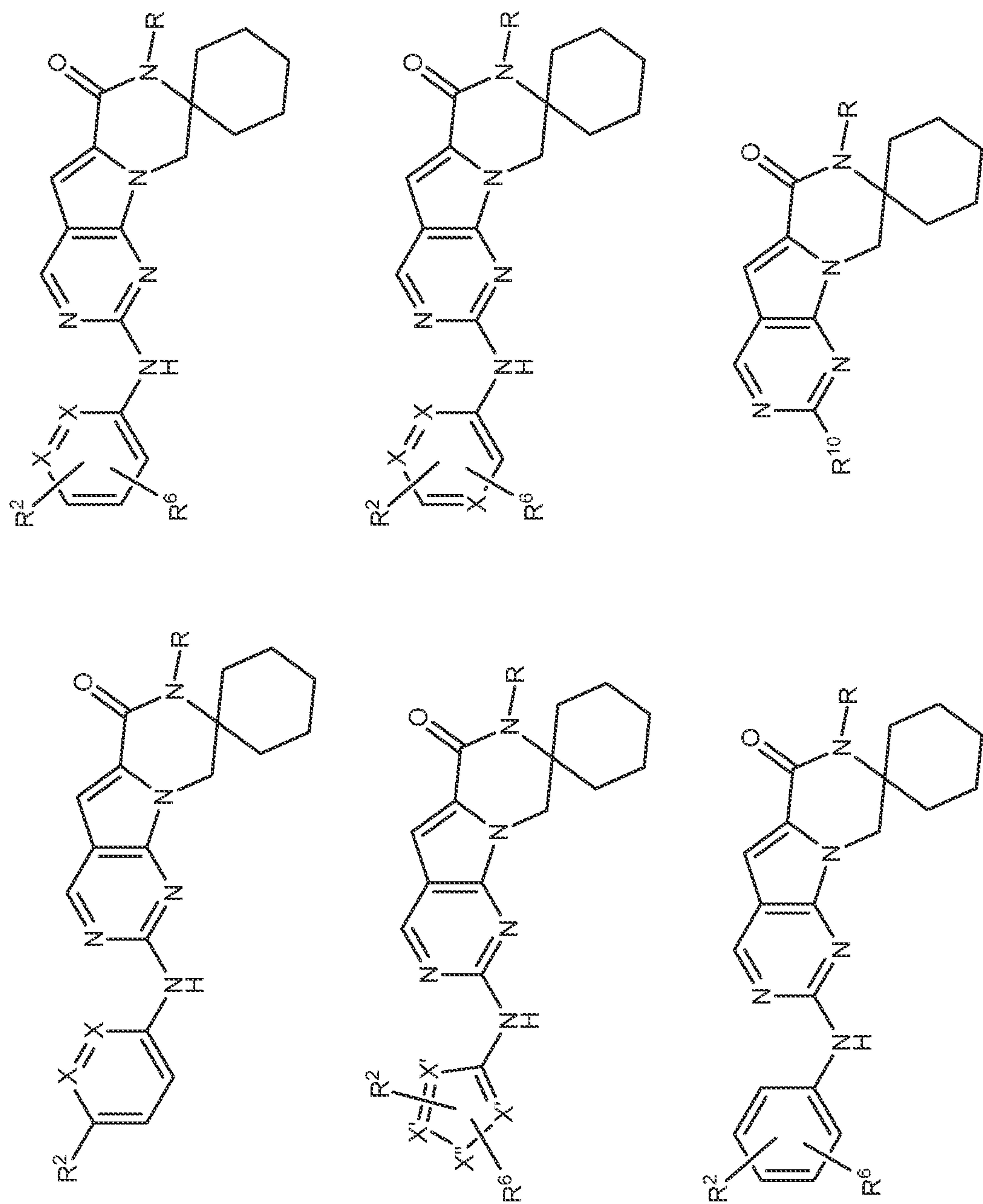


FIG. 6B

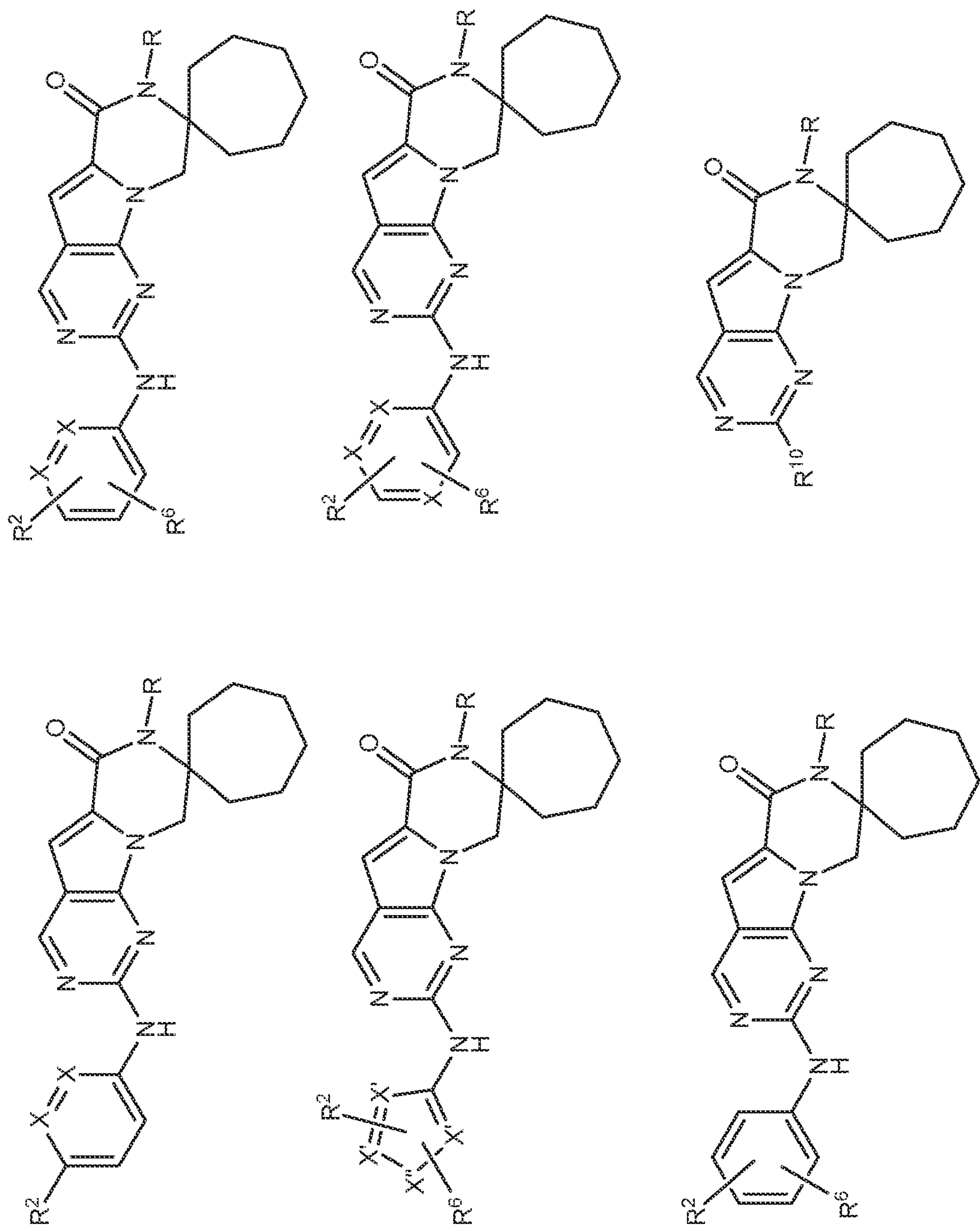


FIG. 6C

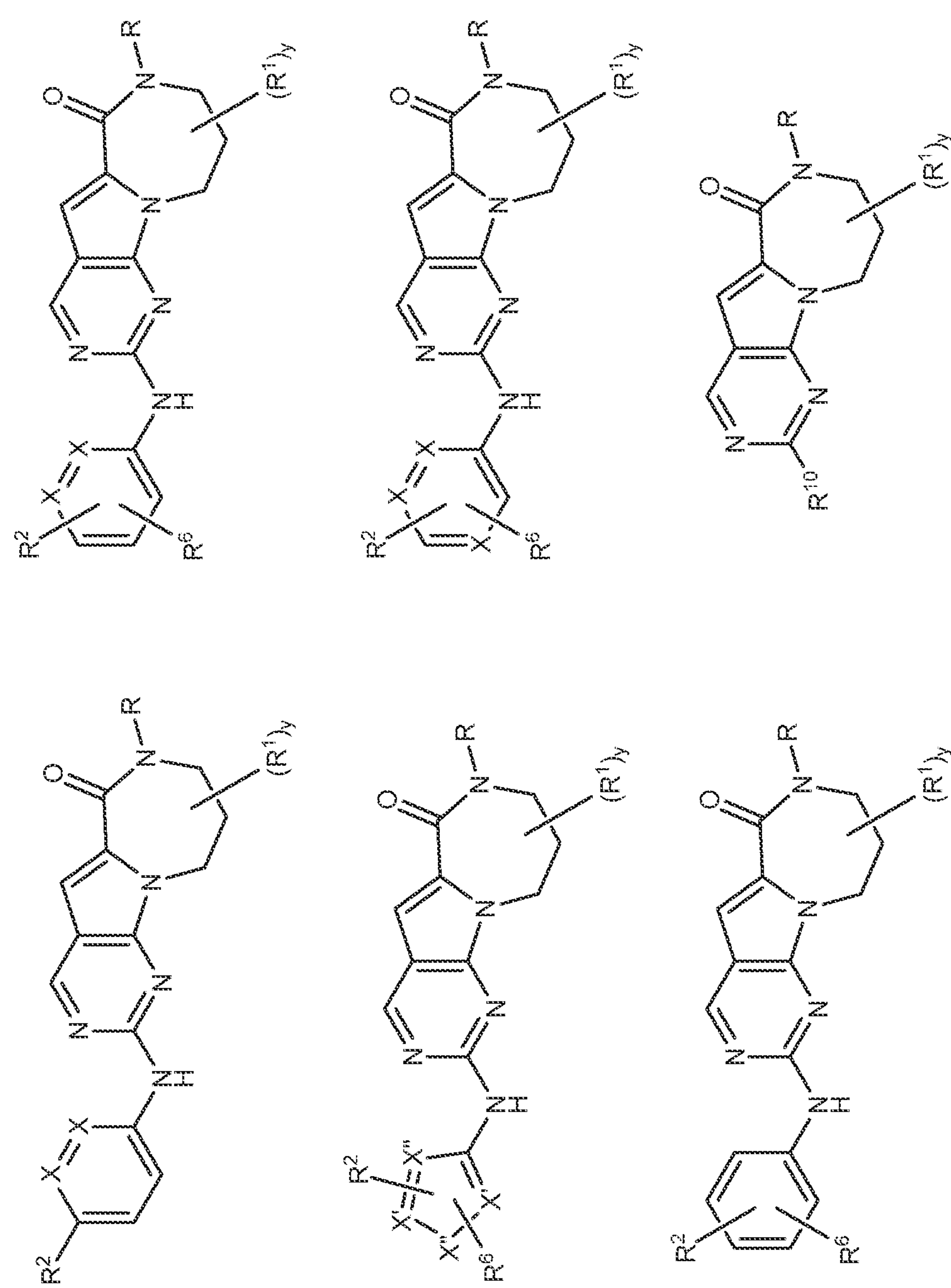


FIG. 7A

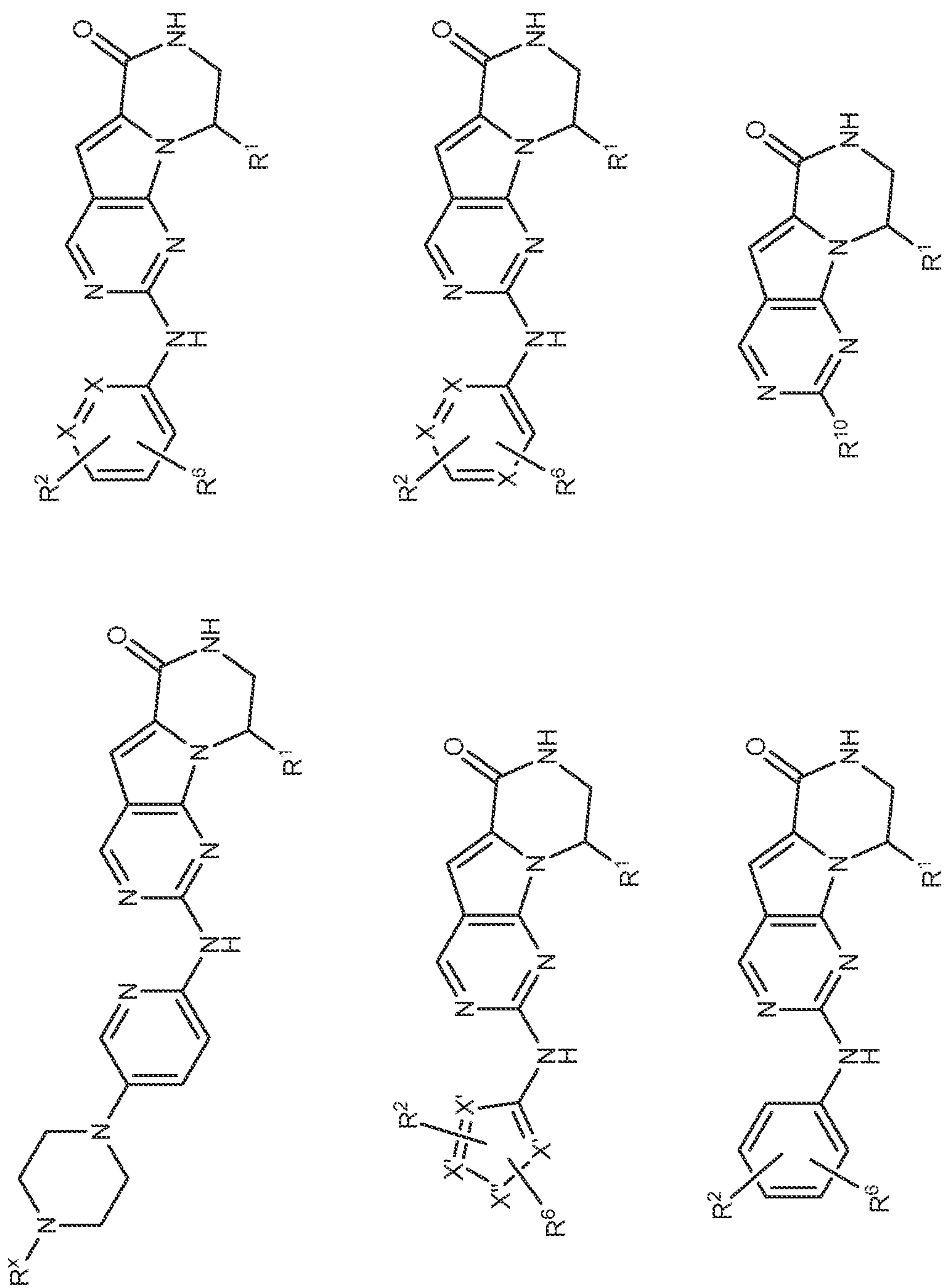


FIG. 8A

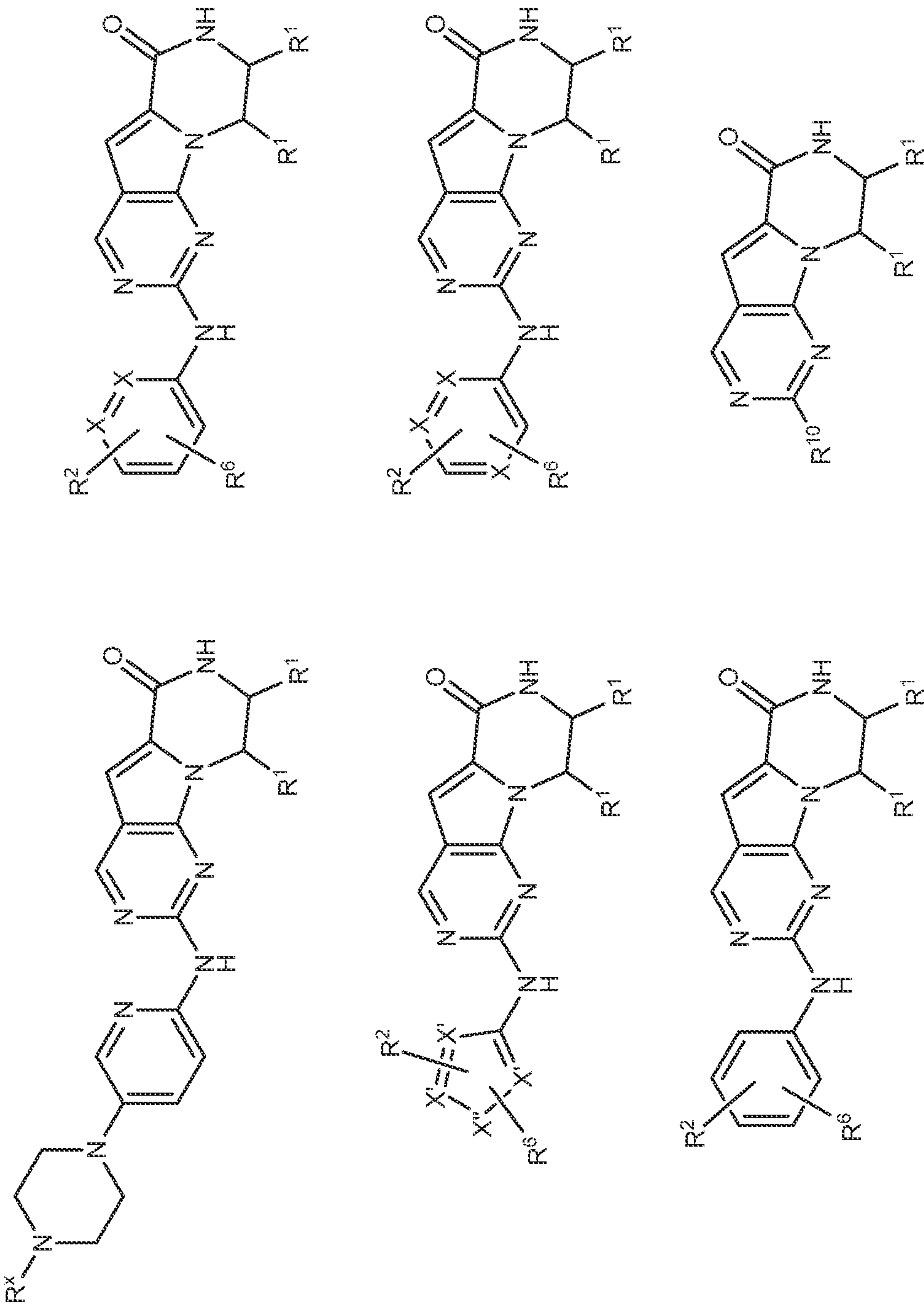


FIG. 8B

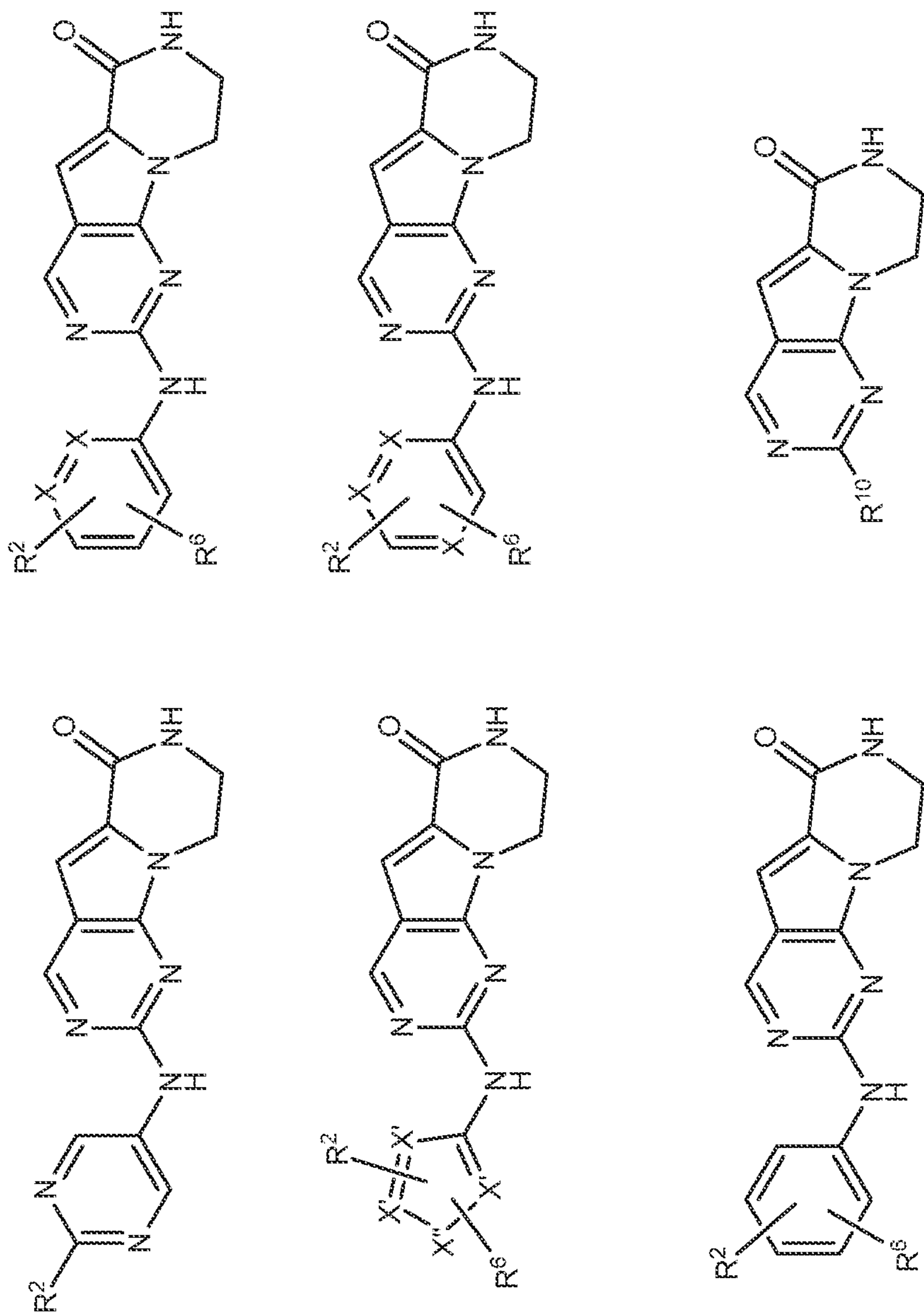


FIG. 8C

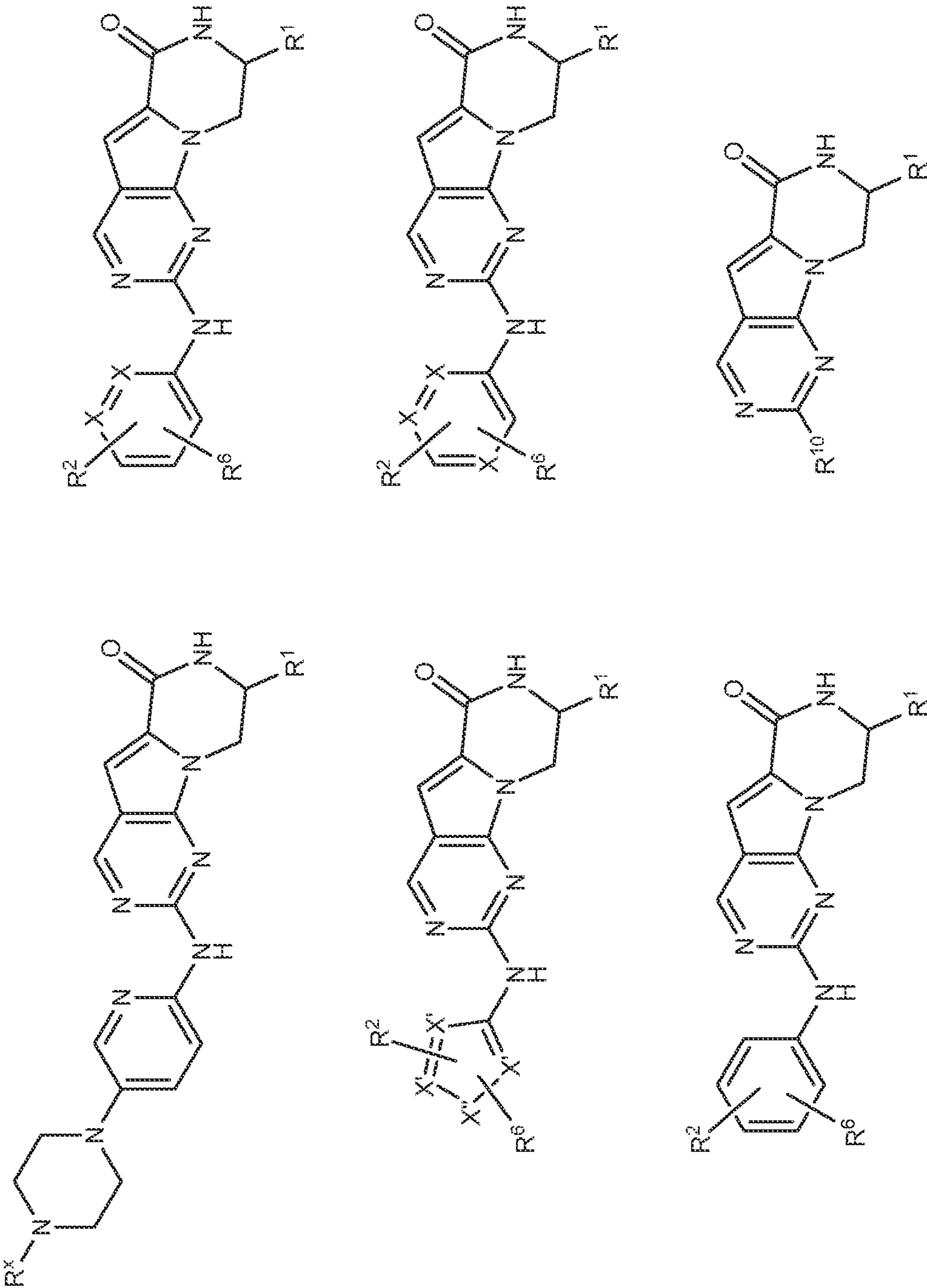


FIG. 8D

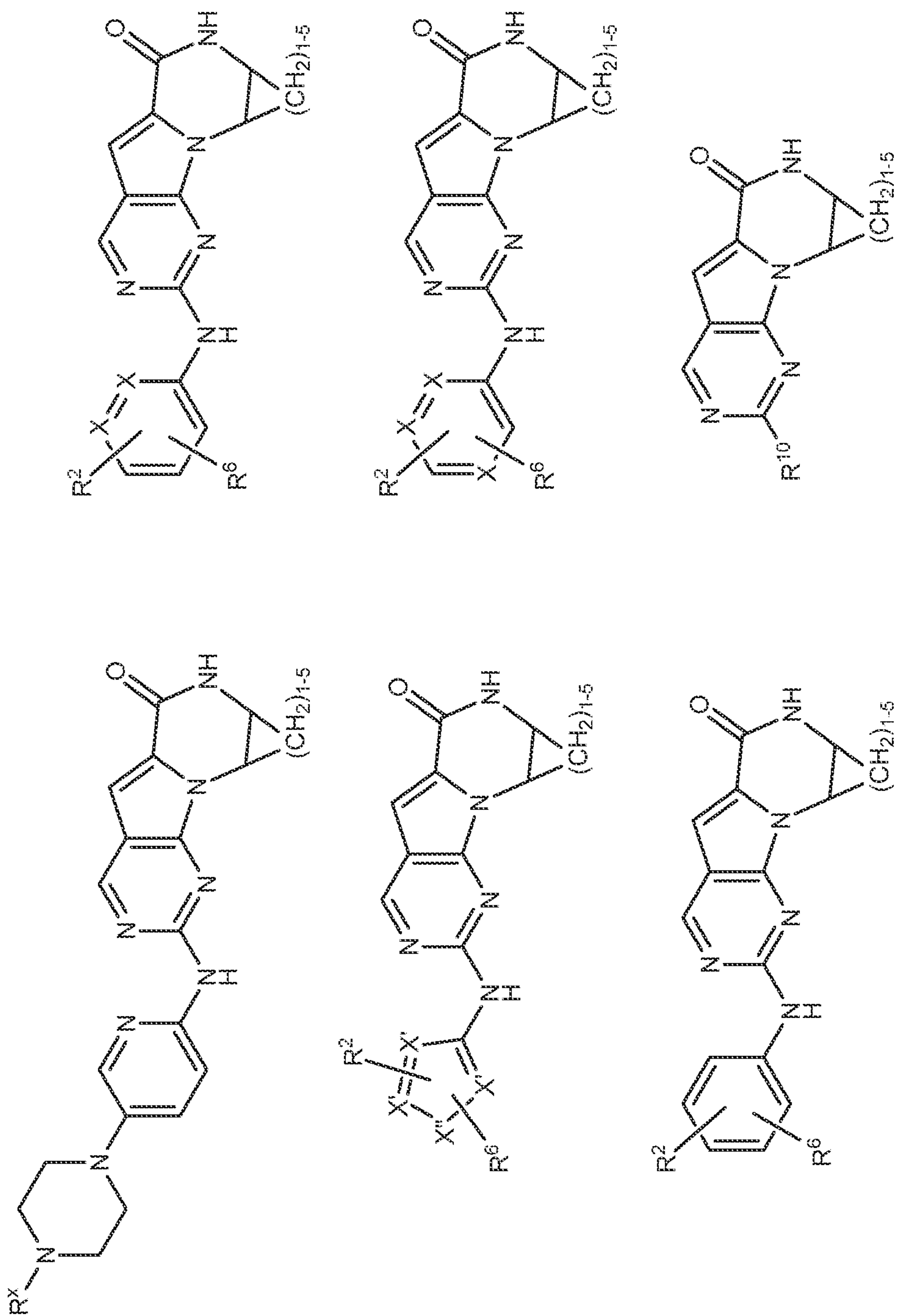


FIG. 8E

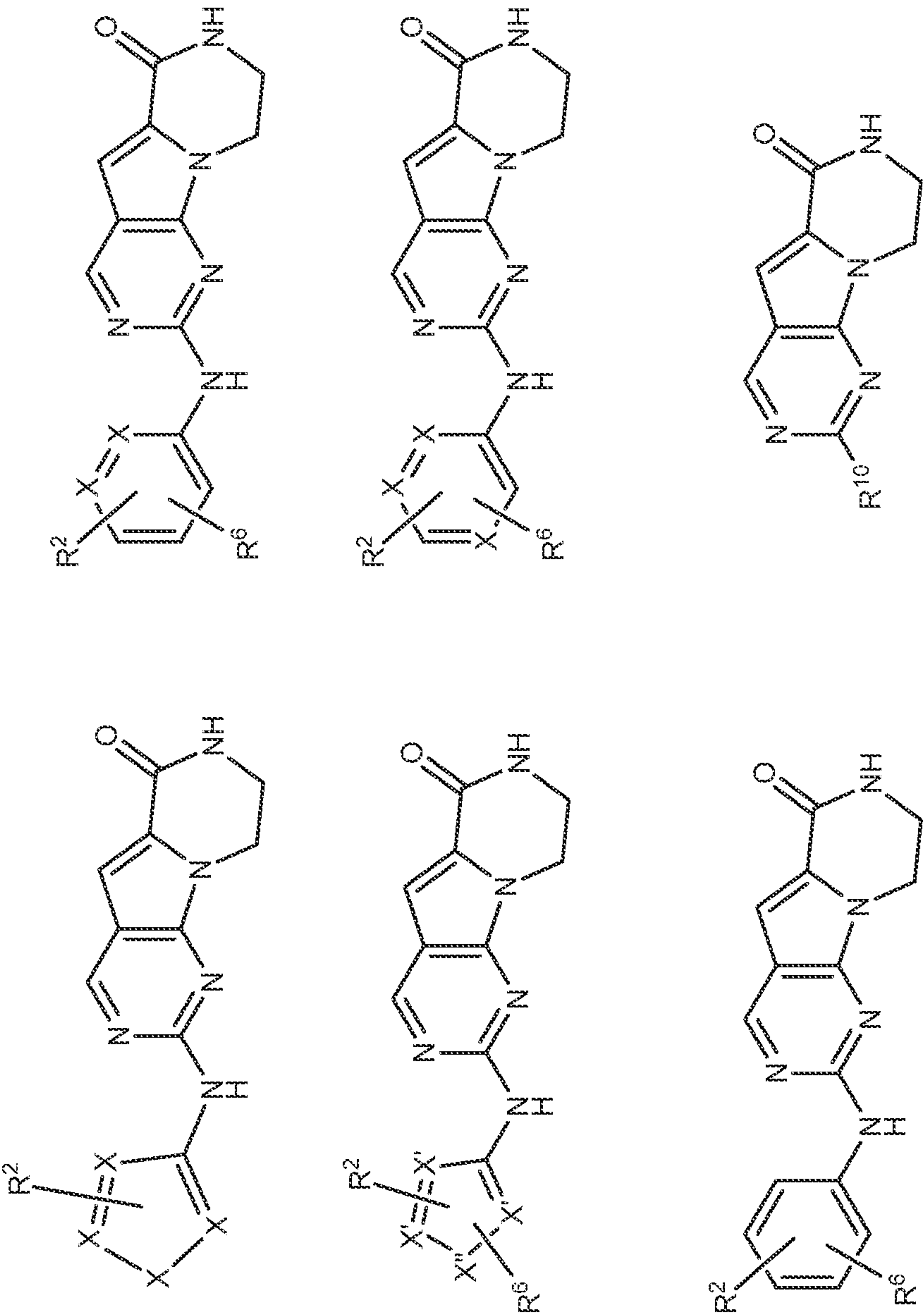


FIG. 8F

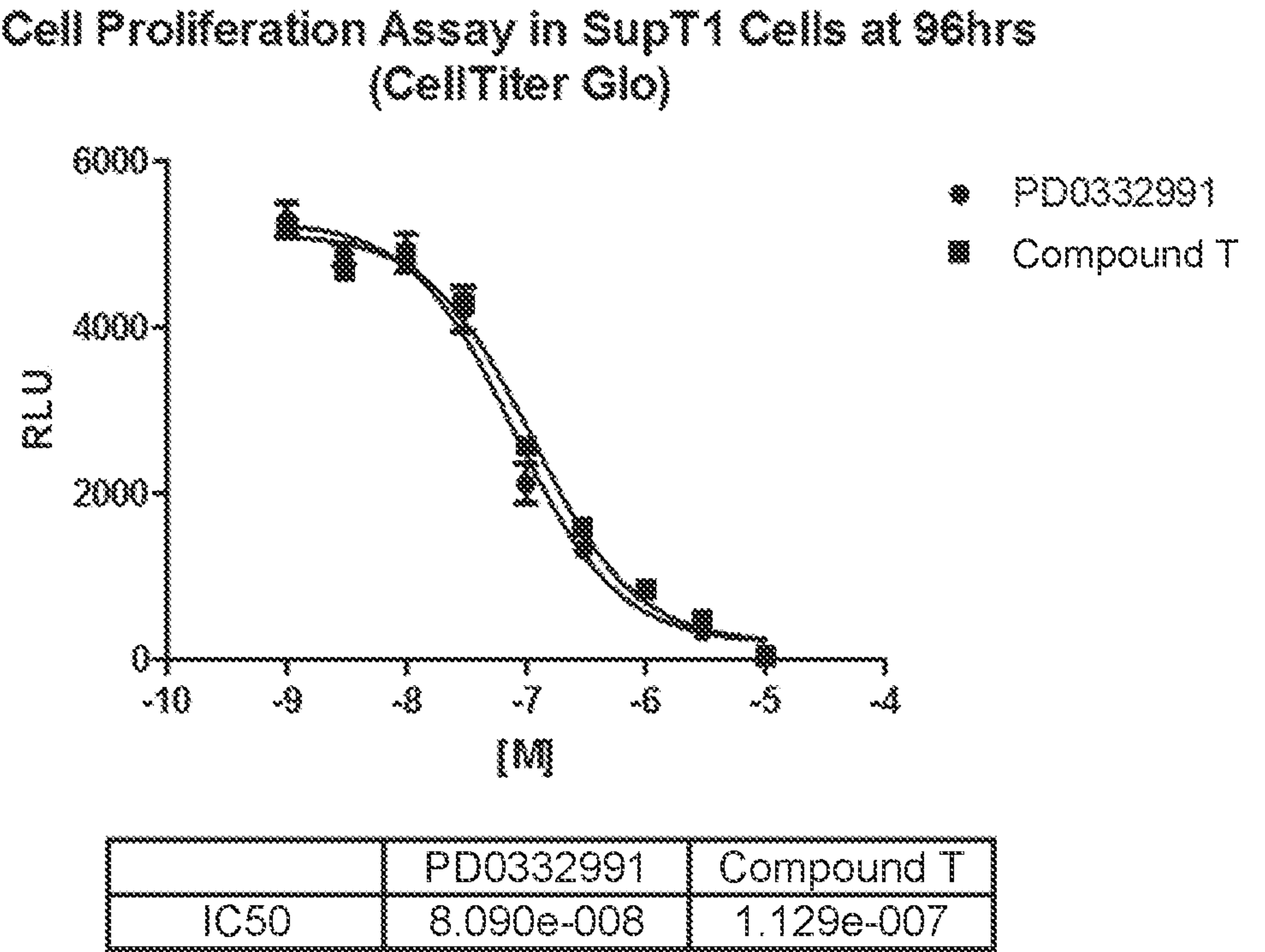
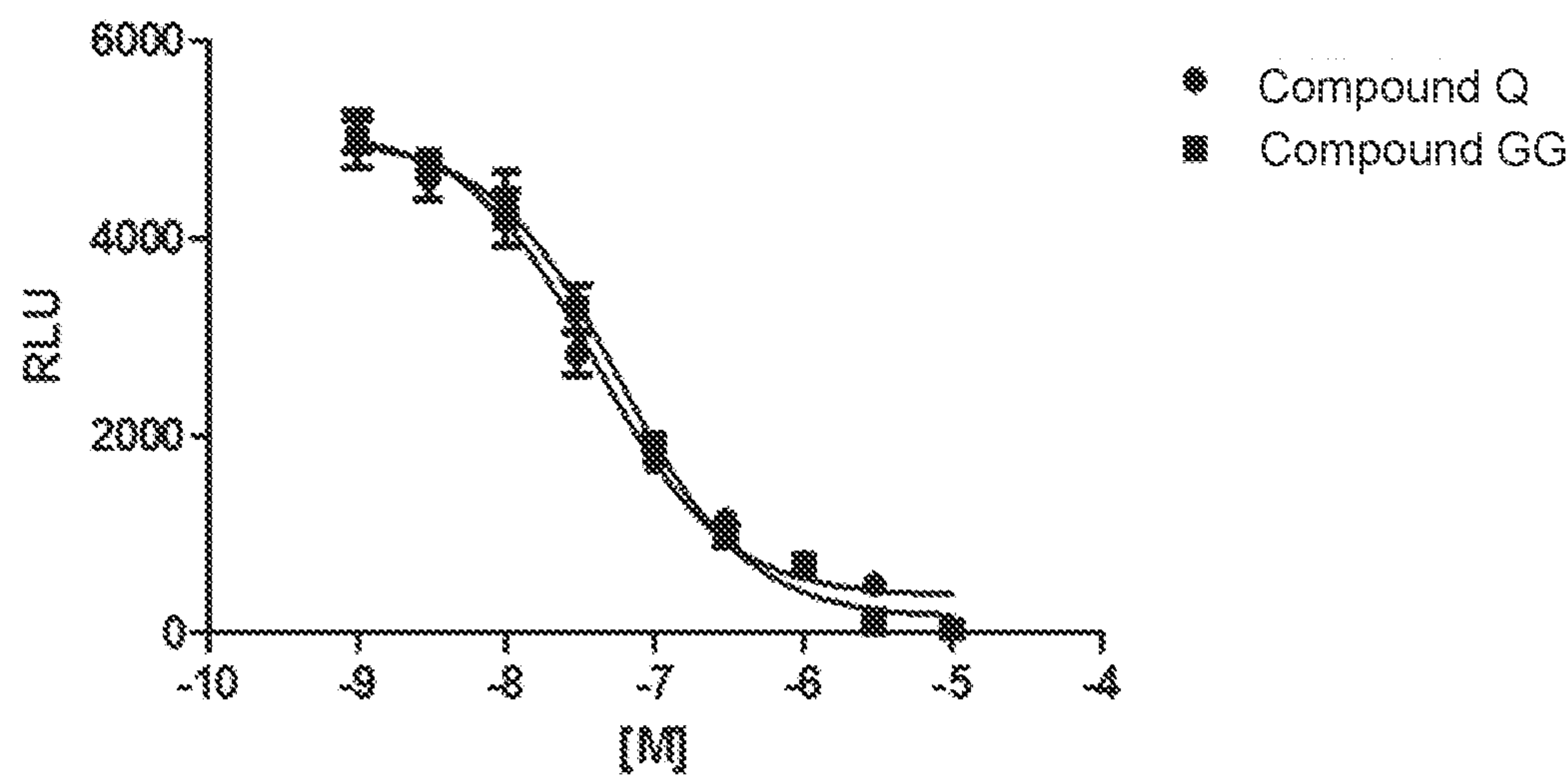


FIG. 9

Cell Proliferation Assay in SupT1 Cells at 96hrs
(CellTiter Glo)



	Compound Q	Compound GG
IC50	4.027e-008	5.745e-008

FIG. 10

HIGHLY ACTIVE ANTI-NEOPLASTIC AND ANTI-PROLIFERATIVE AGENTS

RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Appl. No. 16/926,035, filed Jul. 10, 2020, which is a continuation of U.S. Appl. No. 16/228,308, filed Dec. 20, 2018, which is a continuation of U.S. Appl. No. 15/713,385, filed Sep. 22, 2017; which is a continuation of U.S. Appl. No. 15/201,286, filed Jul. 1, 2016; which is a divisional of U.S. Appl. No. 14/213,784, filed on Mar. 14, 2014; which claims priority to Provisional U.S. Appl. No. 61/798,772, filed Mar. 15, 2013, provisional U.S. Appl. No. 61/861,374, filed on Aug. 1, 2013, provisional U.S. Appl. 61/911,354, filed on Dec. 3, 2013, and provisional U.S. Appl. No. 61/949,795, filed on Mar. 7, 2014. The entirety of each of these applications is hereby incorporated by reference for all purposes.

GOVERNMENT INTEREST

[0002] This invention was made with government support under Grant No. 5R44AI084284 awarded by National Institute of Allergy and Infectious Diseases. The government has certain rights in the invention.

FIELD

[0003] This invention is in the area of improved compounds and methods for treating selected cancers and hyperproliferative disorders.

BACKGROUND

[0004] Cancer is a group of diseases categorized by uncontrolled growth and spread. In the United States in 2013, approximately 1.6 million new cases of cancer were expected to be diagnosed, and over 500,000 people in the U.S. were expected to die from the disease, which is about 1,600 per day. Cancer Facts and Figures 2013, American Cancer Society.

[0005] All cancers involve a malfunction of genes that control cell growth and division. Although all cancers share that characteristic, cancers vary greatly according to tissue or cell type, which specific genes are down or up-regulated, which aspect of the cell cycle is implicated, whether and which cell surface receptors accelerate growth, types of altered metabolism, and which drugs the cancer cells respond to with a therapeutically acceptable effect. Therefore, one of the key goals of cancer research is to identify drugs that show high activity against certain specific target cancers. Non-cancerous cellular hyperproliferation presents a similar problem.

[0006] Lymphoid neoplasms are broadly categorized into precursor lymphoid neoplasms and mature T-cell, B-cell or natural killer cell (NK) neoplasms. Chronic leukemias are those likely to exhibit primary manifestations in blood and bone marrow, whereas lymphomas are typically found in extramedullary sites, with secondary events in the blood or bone. Some mature B-cell disorders exhibit dominant immunosecretory manifestations.

[0007] Over 79,000 new cases of lymphoma were estimated in 2013. Lymphoma is a cancer of lymphocytes, which are a type of white blood cell. Lymphomas are categorized as Hodgkin or non-Hodgkin. Over 48,000 new cases

of leukemias were expected in 2013. They are classified into four main groups according to cell type and rate of growth: acute lymphocytic (ALL), chronic lymphocytic (CLL), acute myeloid (AML), and chronic myeloid (CML).

[0008] WO 2012/061156 filed by Francis Tavares and assigned to G1 Therapeutics describes CDK inhibitors. Also see WO 2013/148748 filed by Francis Tavares and assigned to G1 Therapeutics, directed to Lactam Kinase Inhibitors.

[0009] Accordingly, there is an ongoing need for highly active compounds against specific cancers and cellular hyperproliferation.

SUMMARY OF THE INVENTION

[0010] The present invention includes the use of an effective amount of a compound described herein, or its pharmaceutically acceptable salt, prodrug, or isotopic variant, optionally in a pharmaceutical composition, to treat a host, typically a human, with a selected cancer, tumor, hyperproliferative condition, or an inflammatory or immune disorder as described further herein. Some of the disclosed compounds are highly active against T-cell proliferation and/or B-cell proliferation and/or NK-cell proliferation.

[0011] Disorders include, but are not limited to those involving T-cell proliferation, maintenance of peripheral tolerance, those involving the inappropriate differentiation of Th2 cells, maturation or survival of T and/or B cells, natural killer cell development, or regulation of immunoglobulin class switching in B cells.

[0012] In one embodiment, a compound/method of the present invention is used in combination with another therapy to treat the T, B or NK abnormal cellular proliferation, cancer or disorder. The second therapy can be an immunotherapy. For example, the compound can be conjugated to an antibody, radioactive agent or other targeting agent that directs the compound to the diseased or abnormally proliferating cell. In another embodiment, the compound is used in combination with another pharmaceutical or a biologic agent (for example an antibody) to increase the efficacy of treatment with a combined or a synergistic approach. In an embodiment, the compound can be used with T-cell vaccination, which typically involves immunization with inactivated autoreactive T cells to eliminate a pathogenic autoreactive T cell population. In another embodiment, the compound is used in combination with a bispecific T-cell Engager (BiTE), which is an antibody designed to simultaneously bind to specific antigens on endogenous T cells and malignant cells, linking the two types of cells.

[0013] In summary, the present invention includes the following features:

[0014] A) Selective compounds, methods, and compositions for use as chemotherapeutics for the treatment of T-cell cancers and other T-cell mediated disorders;

[0015] B) Selective compounds, methods, and composition for use as chemotherapeutics for the treatment of B-cell cancers and other B-cell mediated disorders;

[0016] C) Selective compounds, methods, and compositions for use as immunosuppressants and antiinflammatory agents;

[0017] D) Selective compounds, methods and compositions for use against auto-immune disorders;

[0018] E) The compounds of Formulas I, II, III, IV, and V as described herein, and pharmaceutically acceptable

compositions, salts, and prodrugs thereof, for use in medical therapy;

[0019] F) The compounds of Formulas I, II, III, IV, and V as described herein, and pharmaceutically acceptable compositions, salts, and prodrugs thereof, for use against T-cell cancers and other T-cell mediated disorders;

[0020] G) The compounds of Formulas I, II, III, IV, and V as described herein, and pharmaceutically acceptable compositions, salts, and prodrugs thereof, for use against B-cell cancers and B-cell mediated disorders;

[0021] H) The compounds of Formulas I, II, III, IV, and V as described herein, and pharmaceutically acceptable compositions, salts, and prodrugs thereof, for use in the treatment of immune disorders or inflammatory conditions;

[0022] I) The compounds of Formulas I, II, III, IV, and V as described herein, and pharmaceutically acceptable compositions, salts, and prodrugs thereof, for use in the treatment of autoimmune disorders;

[0023] J) Processes for the preparation of therapeutic products that contain an effective amount of the compounds of Formulas I, II, III, IV, and V as described herein;

[0024] K) A method for manufacturing a medicament of Formulas I, II, III, IV, and V intended for therapeutic use;

[0025] L) Selective compounds, methods, and compositions for use of the compounds of Formulas I, II, III, IV, and V in combination with one or more other therapeutic agents; and

[0026] M) The compounds of Formulas I, II, III, IV, and V as described herein, and pharmaceutically acceptable compositions, salts, and prodrugs thereof, for use in combination with another one or more additional therapeutic agents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] FIGS. 1-3 illustrate exemplary embodiments of R² of compounds useful in the described invention.

[0028] FIGS. 4A-4C, 5A-5D, 6A-6C, 7A-B, and 8A-8F illustrate exemplary embodiments of the core structure of the compounds useful in the described invention.

[0029] FIG. 9 is a graph showing the cellular proliferation of SupT1 cells (human T-cell lymphoblastic leukemia) treated with PD0332991 (circles) or Compound T (Table 1; squares). The SupT1 cells were seeded in Costar (Tewksbury, Massachusetts) 3093 96 well tissue culture treated white walled/ clear bottom plates. A nine point dose response dilution series from 10 uM to 1 nM was performed and cell viability was determined after four days as indicated using the CellTiter-Glo® assay (CTG; Promega, Madison, Wisconsin, United States of America) following the manufacturer's recommendations. Plates were read on a BioTek (Winooski, Vermont) Synergy2 multi-mode plate reader. The Relative Light Units (RLU) were plotted as a result of variable molar concentration and data was analyzed using Graphpad (LaJolla, California) Prism 5 statistical software to determine the IC₅₀ for each compound.

[0030] FIG. 10 is a graph showing the cellular proliferation of SupT1 cells (human T-cell lymphoblastic leukemia) treated with Compound Q (Table 1; circles) or Compound GG (Table 1; squares). The SupT1 cells were seeded in Costar (Tewksbury, Massachusetts) 3093 96 well tissue cul-

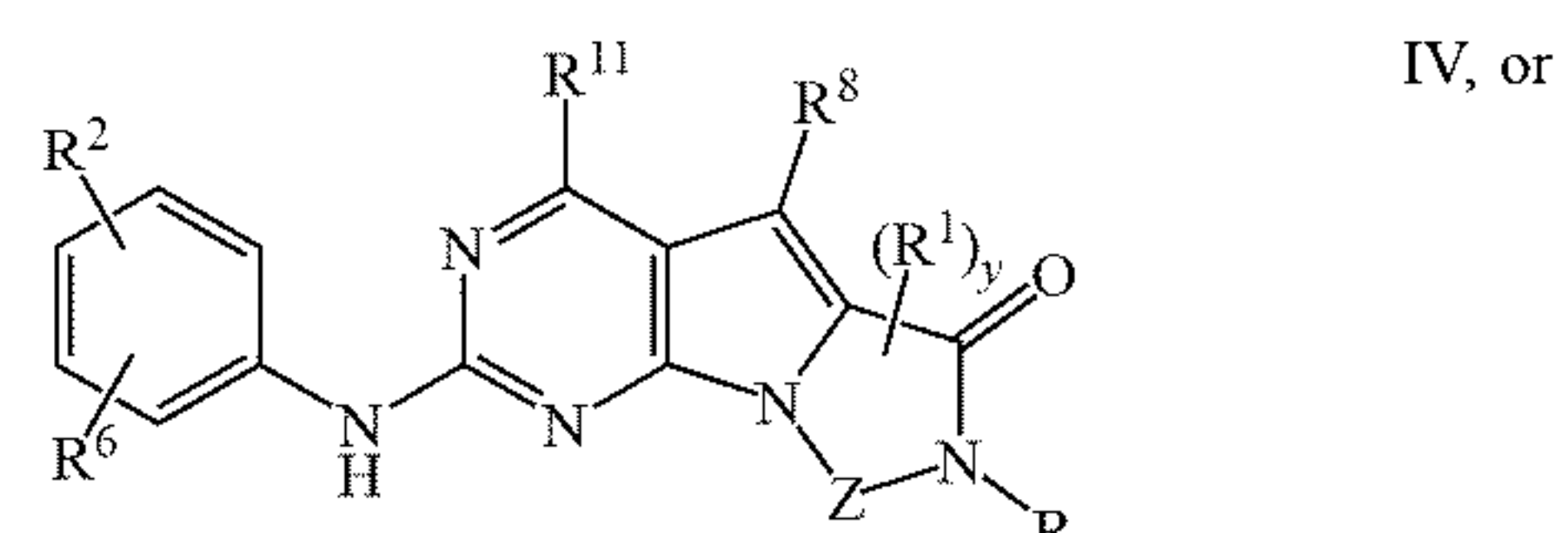
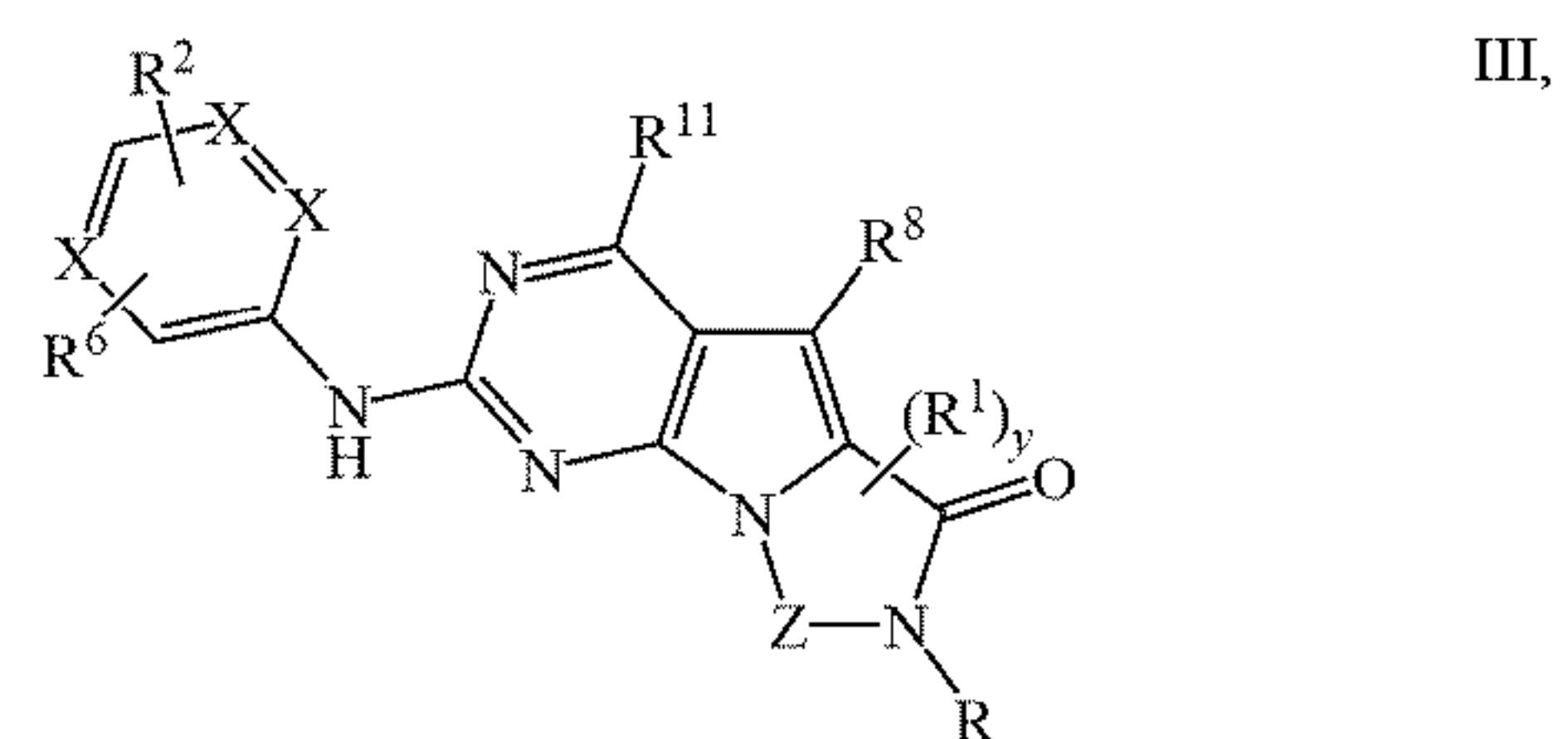
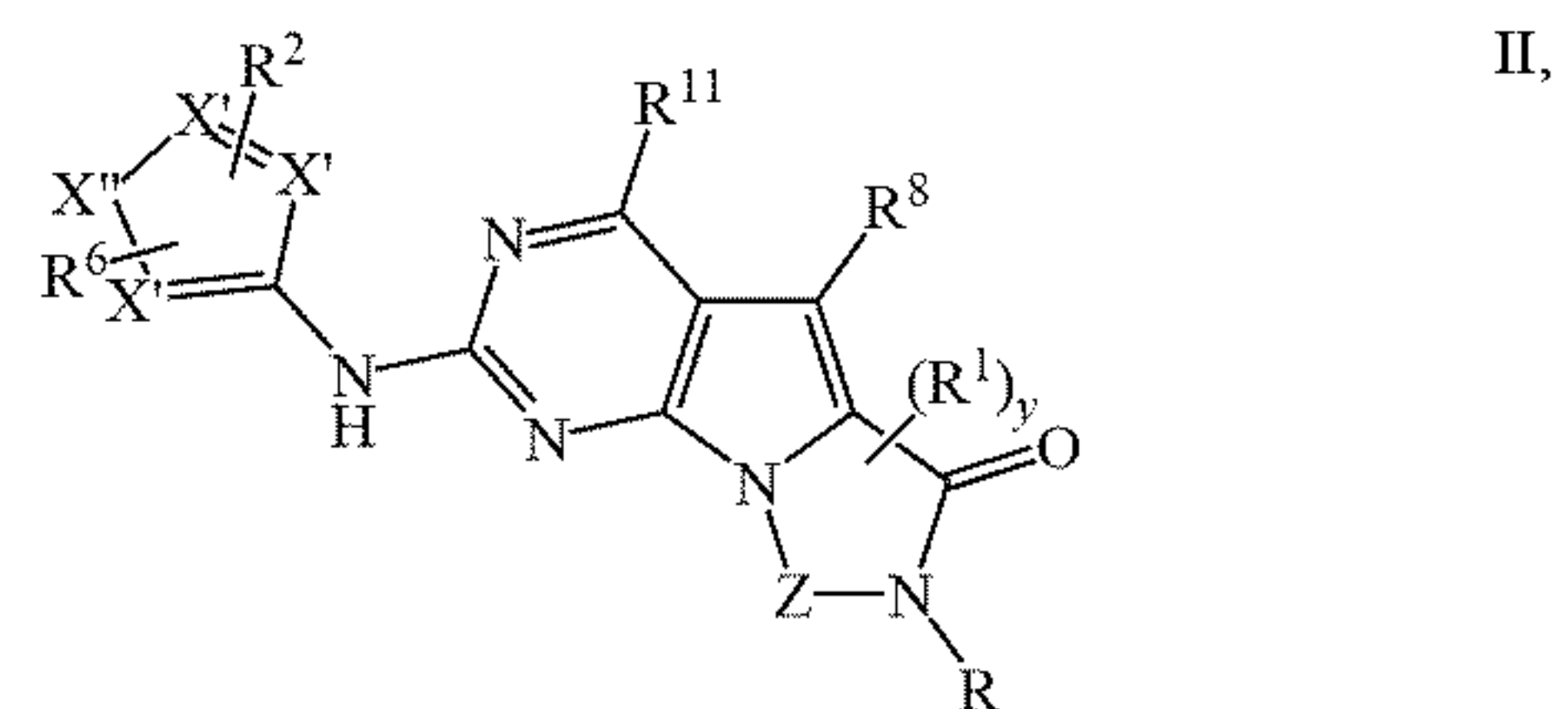
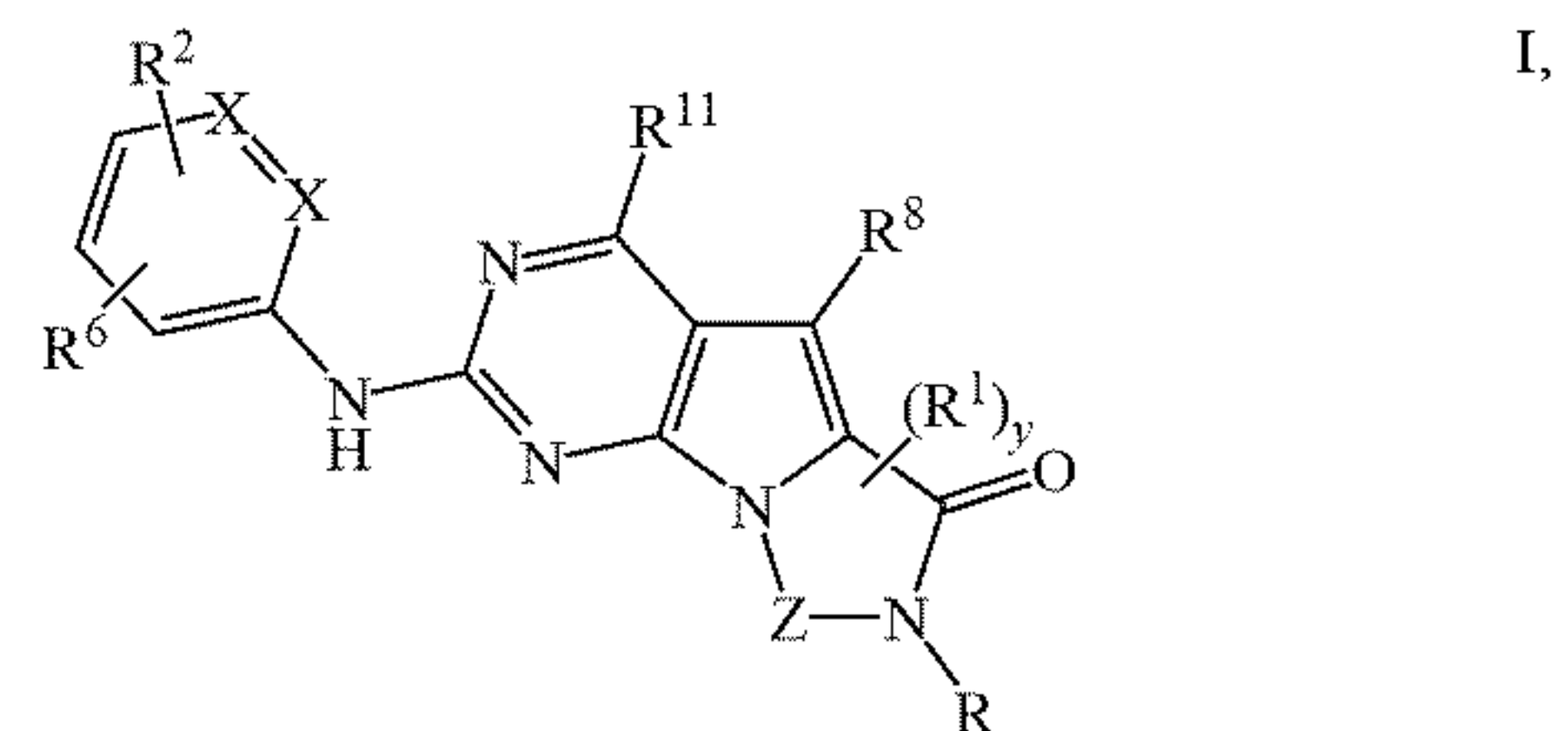
ture treated white walled/ clear bottom plates. A nine point dose response dilution series from 10uM to 1 nM was performed and cell viability was determined after four days as indicated using the CellTiter-Glo® assay (CTG; Promega, Madison, Wisconsin, United States of America) following the manufacturer's recommendations. Plates were read on a BioTek (Winooski, Vermont) Synergy2 multi-mode plate reader. The Relative Light Units (RLU) were plotted as a result of variable molar concentration and data was analyzed using Graphpad (LaJolla, California) Prism 5 statistical software to determine the IC₅₀ for each compound.

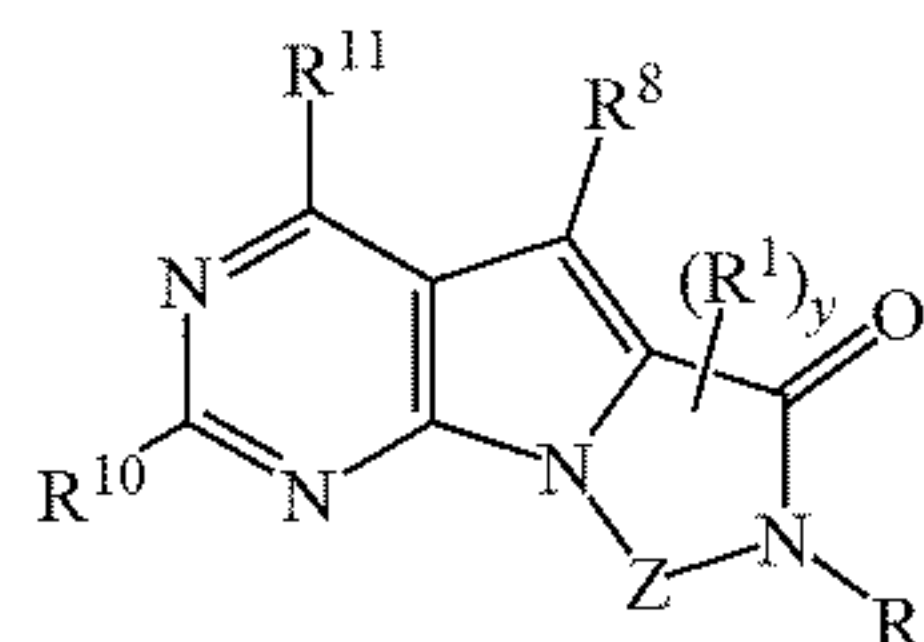
DETAILED DESCRIPTION

[0031] The present invention includes compounds and methods that are highly active against certain cancers and hyperproliferative conditions. In particular, compounds and methods are provided to treat cancers and proliferative disorders of hematopoietic cells, and in particular, T cells, B cells and NK cells. Selected active compounds are also useful to treat inflammatory disorders, auto-immune conditions, and immune disorders.

I. Active Compounds

[0032] In one embodiment, the invention is directed to compounds or the use of such compounds of Formula I, II, III, IV, or V:





V.

or a pharmaceutically acceptable salt thereof; wherein:

[0033] Z is $-(CH_2)_x-$ wherein x is 1, 2, 3 or 4 or $-O-(CH_2)_z-$ wherein z is 2, 3 or 4;

[0034] each X is independently CH or N;

[0035] each X' is independently, CH or N;

[0036] X'' is independently CH_2 , S or NH, arranged such that the moiety is a stable 5-membered ring;

[0037] R, R⁸, and R¹¹ are independently H, C₁-C₃ alkyl or haloalkyl, cycloalkyl or cycloalkyl containing one or more heteroatoms selected from N, O or S; $-(alkylene)_m-$ C₃-C₈ cycloalkyl, $-(alkylene)_m-$ aryl, $-(alkylene)_m-$ heterocyclo, $-(alkylene)_m-$ heteroaryl, $-(alkylene)_m-$ NR³R⁴, $-(alkylene)_m-$ C(O)-NR³R⁴; $-(alkylene)_m-$ O-R⁵, $-(alkylene)_m-$ S(O)_n-R⁵, or $-(alkylene)_m-$ S(O)_n-NR³R⁴ any of which may be optionally independently substituted with one or more R groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atoms may optionally combine to form a ring;

[0038] each R¹ is independently aryl, alkyl, cycloalkyl or haloalkyl, wherein each of said alkyl, cycloalkyl and haloalkyl groups optionally includes O or N heteroatoms in place of a carbon in the chain and two R¹'s on adjacent ring atoms or on the same ring atom together with the ring atom(s) to which they are attached optionally form a 3-8-membered cycle;

[0039] y is 0, 1, 2, 3 or 4;

[0040] R² is $-(alkylene)_m-$ heterocyclo, $-(alkylene)_m-$ heteroaryl, $-(alkylene)_m-$ NR³R⁴, $-(alkylene)_m-$ C(O)-NR³R⁴; $-(alkylene)_m-$ C(O)-O-alkyl; $-(alkylene)_m-$ O-R⁵, $-(alkylene)_m-$ S(O)_n-R⁵, or $-(alkylene)_m-$ S(O)_n-NR³R⁴ any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring and wherein m is 0 or 1 and n is 0, 1 or 2;

[0041] R³ and R⁴ at each occurrence are independently:

[0042] (i) hydrogen or

[0043] (ii) alkyl, cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring; or R³ and R⁴ together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring;

[0044] R⁵ and R^{5*} at each occurrence is:

[0045] (i) hydrogen or

[0046] (ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

[0047] R^x at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-$ OR⁵, $-(alkylene)_m-$ O-alkylene-OR⁵, $-(alkylene)_m-$ S(O)_n-R⁵, $-(alkylene)_m-$ NR³R⁴, $-(alkylene)_m-$ CN, $-(alkylene)_m-$ C(O)-R⁵, $-(alkylene)_m-$ C(S)-R⁵, $-(alkylene)_m-$ C(O)-OR⁵, $-(alkylene)_m-$ O-C(O)-R⁵, $-(alkylene)_m-$ C(S)-OR⁵, $-(alkylene)_m-$ C(O)-NR³R⁴, $-(alkylene)_m-$ C(S)-NR³R⁴, $-(alkylene)_m-$ N(R³)-C(O)-NR³R⁴, $-(alkylene)_m-$ N(R³)-C(S)-NR³R⁴, $-(alkylene)_m-$ N(R³)-C(O)-R⁵, $-(alkylene)_m-$ N(R³)-C(S)-R⁵, $-(alkylene)_m-$ O-C(O)-NR³R⁴, $-(alkylene)_m-$ O-C(S)-NR³R⁴, $-(alkylene)_m-$ SO₂-NR³R⁴, $-(alkylene)_m-$ N(R³)-SO₂-R⁵, $-(alkylene)_m-$ N(R³)-SO₂-NR³R⁴, $-(alkylene)_m-$ N(R³)-C(O)-OR⁵, $-(alkylene)_m-$ N(R³)-C(S)-OR⁵, or $-(alkylene)_m-$ N(R³)-SO₂-R⁵; wherein:

[0048] said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(alkylene)_m-$ CN, $-(alkylene)_m-$ OR^{5*}, $-(alkylene)_m-$ S(O)_n-R^{5*}, $-(alkylene)_m-$ NR^{3*}R^{4*}, $-(alkylene)_m-$ C(O)-R^{5*}, $-(alkylene)_m-$ C(=S)R^{5*}, $-(alkylene)_m-$ C(=O)O R^{5*}, $-(alkylene)_m-$ OC(=O)R^{5*}, $-(alkylene)_m-$ C(S)-OR^{5*}, $-(alkylene)_m-$ C(O)-NR^{3*}R^{4*}, $-(alkylene)_m-$ C(S)-NR^{3*}R^{4*}, $-(alkylene)_m-$ N(R^{3*})-C(O)-NR^{3*}R^{4*}, $-(alkylene)_m-$ N(R^{3*})-C(S)-NR^{3*}R^{4*}, $-(alkylene)_m-$ N(R^{3*})-C(O)-R^{5*}, $-(alkylene)_m-$ N(R^{3*})-C(S)-R^{5*}, $-(alkylene)_m-$ O-C(O)-NR^{3*}R^{4*}, $-(alkylene)_m-$ O-C(S)-NR^{3*}R^{4*}, $-(alkylene)_m-$ SO₂-NR^{3*}R^{4*}, $-(alkylene)_m-$ N(R^{3*})-SO₂-R^{5*}, $-(alkylene)_m-$ N(R^{3*})-SO₂-NR^{3*}R^{4*}, $-(alkylene)_m-$ N(R^{3*})-C(O)-OR^{5*}, $-(alkylene)_m-$ N(R^{3*})-C(S)-OR^{5*}, or $-(alkylene)_m-$ N(R^{3*})-SO₂-R^{5*};

[0049] n is 0, 1 or 2, and

[0050] m is 0 or 1;

[0051] R^{3*} and R^{4*} at each occurrence are independently:

[0052] (i) hydrogen or

[0053] (ii) alkyl, alkenyl, alkynyl cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance; or R^{3*} and R^{4*} together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more R^x groups as allowed by valance; and

[0054] R⁶ is H or lower alkyl, $-(alkylene)_m-$ heterocyclo, $-(alkylene)_m-$ heteroaryl, $-(alkylene)_m-$ NR³R⁴, $-(alkylene)_m-$ C(O)-NR³R⁴; $-(alkylene)_m-$ O-R⁵, $-(alkylene)_m-$ S(O)_n-R⁵, or $-(alkylene)_m-$ S(O)_n-NR³R⁴ any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atoms may optionally combine to form a ring; and

[0055] R¹⁰ is (i) NHR⁴, wherein R⁴ is unsubstituted or substituted C₁-C₈ alkyl, cycloalkylalkyl, or -TT-RR, C₁-C₈ cycloalkyl or cycloalkyl containing one or more heteroatoms selected from N, O, and S; TT is an

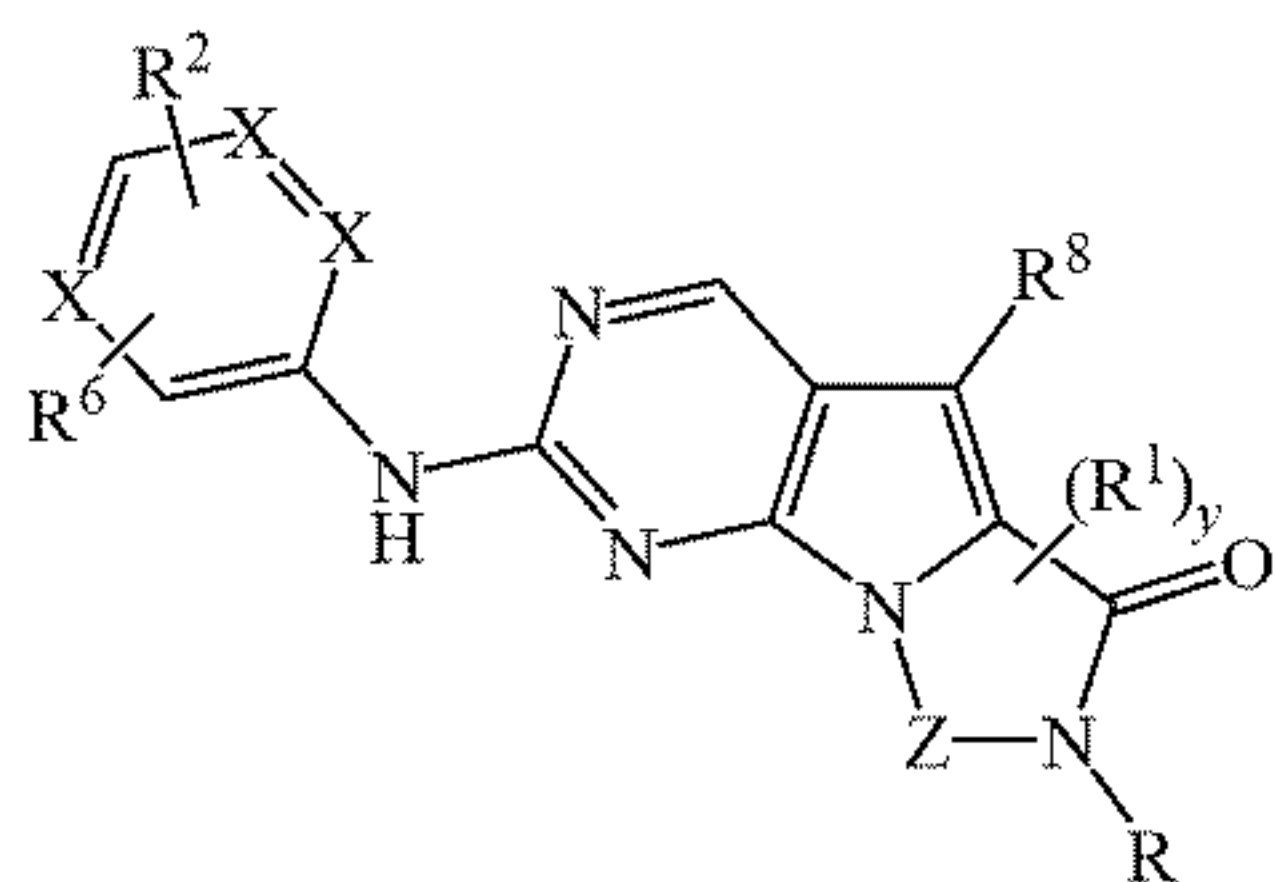
unsubstituted or substituted C₁-C₈ alkyl or C₃-C₈ cycloalkyl linker; and RR is a hydroxyl, unsubstituted or substituted C₁-C₆ alkoxy, amino, unsubstituted or substituted C₁-C₆ alkylamino, unsubstituted or substituted di-C₁-C₆ alkylamino, unsubstituted or substituted C₆-C₁₀ aryl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, unsubstituted or substituted C₃-C₁₀ carbocycle, or unsubstituted or substituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S; or (ii) -C(O)-R¹² or -C(O)O-R¹³, wherein R¹² is NHR⁴ or

[0056] R⁴ and R¹³ is R⁴;

[0057] or a pharmaceutically acceptable salt, prodrug or isotopic variant, for example, partially or fully deuterated form thereof.

[0058] In some aspects, the compound is of Formula I or Formula II and R⁶ is absent.

[0059] In some aspects, the compound is of Formula III:



and the variables are as defined for compounds of Formulae I and II and pharmaceutically acceptable salts thereof.

[0060] In some aspects, R^x is not further substituted.

[0061] In some aspects, R² is -(alkylene)_m-heterocyclo, -(alkylene)_m-heteroaryl, -(alkylene)_m-NR³R⁴, -(alkylene)_m-C(O)-NR³R⁴, -(alkylene)_m-O-R⁵, -(alkylene)_m-S(O)_n-R⁵, or -(alkylene)_m-S(O)_n-NR³R⁴ any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring and wherein m is 0 or 1 and n is 0, 1 or 2.

[0062] In some aspects, R⁸ is hydrogen or C₁-C₃ alkyl.

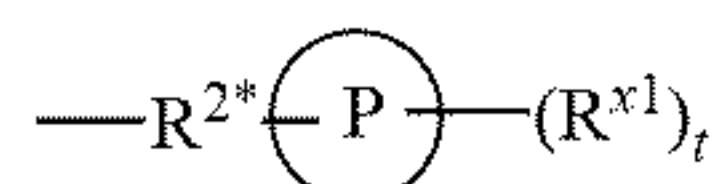
[0063] In some aspects, R is hydrogen or C₁-C₃ alkyl.

[0064] In some aspects, R² is -(alkylene)_m-heterocyclo, -(alkylene)_m-NR³R⁴, -(alkylene)_m-C(O)-NR³R⁴, -(alkylene)_m-C(O)-O-alkyl or -(alkylene)_m-OR⁵ any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring.

[0065] In some aspects, R² is -(alkylene)_m-heterocyclo, -(alkylene)_m-NR³R⁴, -(alkylene)_m-C(O)-NR³R⁴, -(alkylene)_m-C(O)-O-alkyl or -(alkylene)_m-OR⁵ without further substitution.

[0066] In some aspects, m in R² is 1. In a further aspect, the alkylene in R² is methylene.

[0067] In some aspects, R² is



wherein:

[0068] R^{2*} is a bond, alkylene, -(alkylene)_m-O-(alkylene)_m-, -(alkylene)_m-C(O)-(alkylene)_m-, -(alkylene)_m-S(O)₂-(alkylene)_m- and -(alkylene)_m-NH-(alkylene)_m- wherein each m is independently 0 or 1;

[0069] P is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group;

[0070] each R^{x1} is independently -(alkylene)_m-(C(O))_m-(alkylene)_m-(N(R^N))_m-(alkyl)_m wherein each m is independently 0 or 1 provided at least one m is 1, -(C(O))-O-alkyl, -(alkylene)_m-cycloalkyl wherein m is 0 or 1, -N(R^N)-cycloalkyl, -C(O)-cycloalkyl, -(alkylene)_m-heterocyclyl wherein m is 0 or 1, or -N(R^N)-heterocyclyl, -C(O)-heterocyclyl, -S(O)₂-(alkylene)_m wherein m is 1 or 2, wherein:

[0071] R^N is H, C₁ to C₄ alkyl or C₁ to C₆ heteroalkyl, and

[0072] wherein two R^{x1} can, together with the atoms to which they attach on P, which may be the

[0073] same atom, form a ring; and

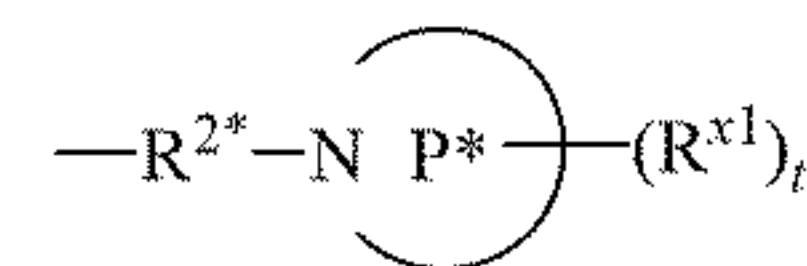
[0074] t is 0, 1 or 2.

[0075] In some aspects, each R^{x1} is only optionally substituted by unsubstituted alkyl, halogen or hydroxy.

[0076] In some aspects, R^{x1} is hydrogen or unsubstituted C₁-C₄ alkyl.

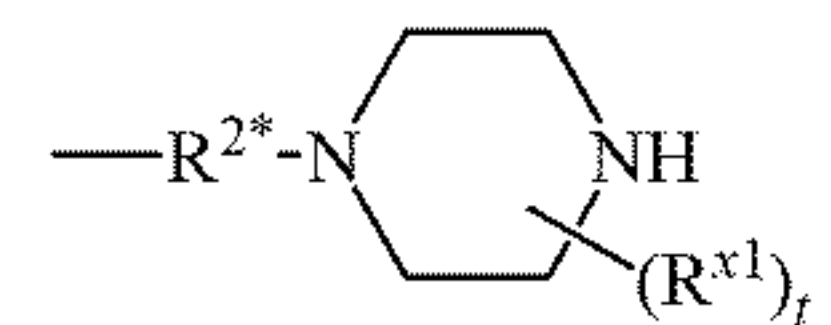
[0077] In some aspects, at least one R^{x1} is -(alkylene)_m-heterocyclyl wherein m is 0 or 1.

[0078] In some aspects, R² is

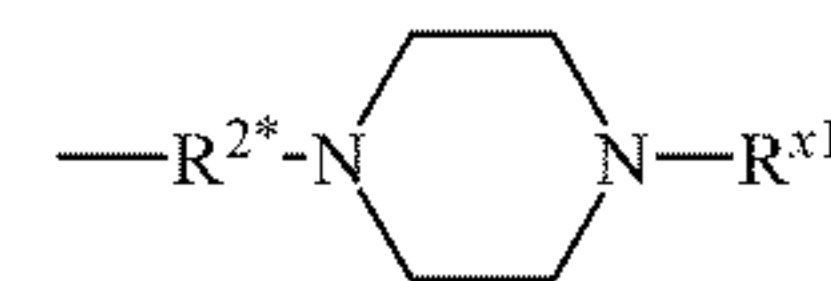


wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group.

[0079] In some aspects, R² is



[0080] In some aspects, R² is



[0081] In some aspects, R² is



wherein:

[0082] R^{2*} is a bond, alkylene, -(alkylene)_m-O-(alkylene)_m-, -(alkylene)_m-C(O)-(alkylene)_m-, -(alkylene)_m-S(O)₂-(alkylene)_m- and -(alkylene)_m-NH-(alkylene)_m- wherein each m is independently 0 or 1;

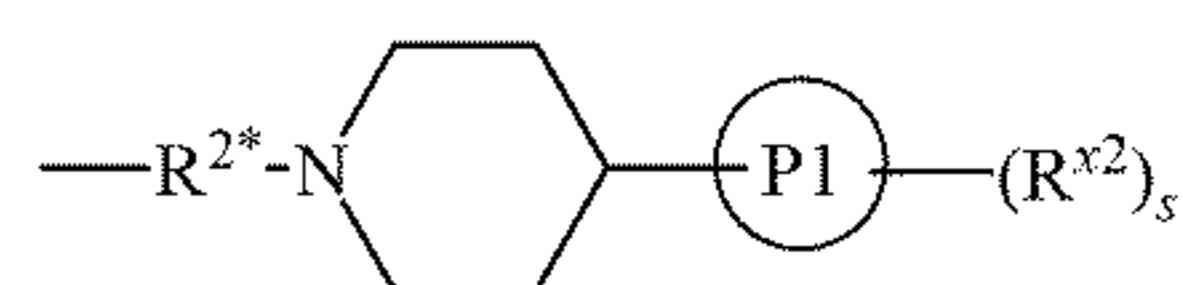
[0083] P is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group;

[0084] P1 is a 4- to 6-membered monocyclic saturated heterocyclyl group;

[0085] each R^{x2} is independently hydrogen or alkyl; and

[0086] s is 0, 1 or 2.

[0087] In some aspects, R² is

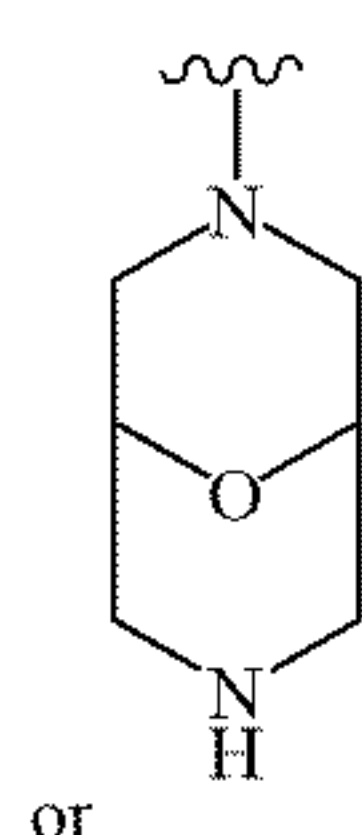
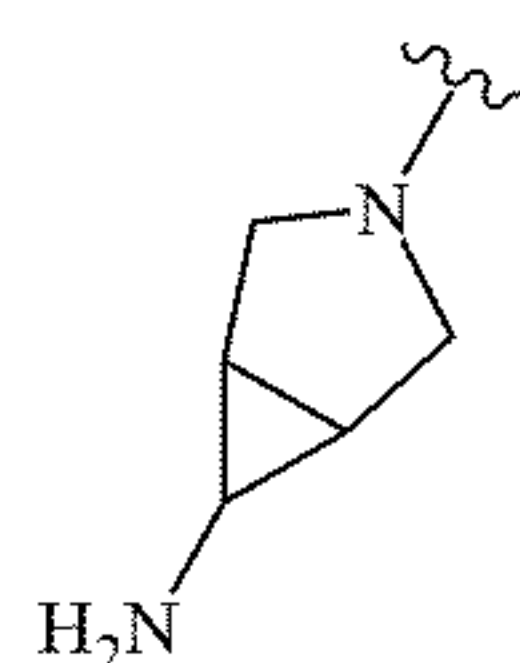
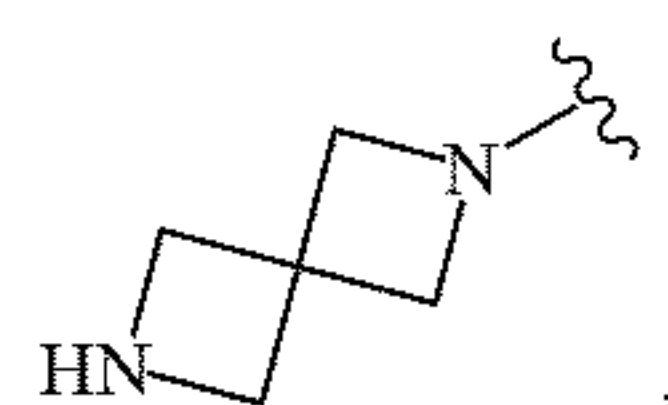
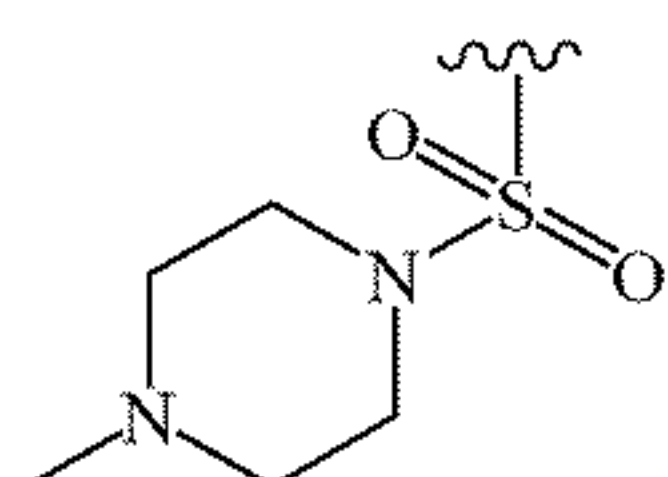
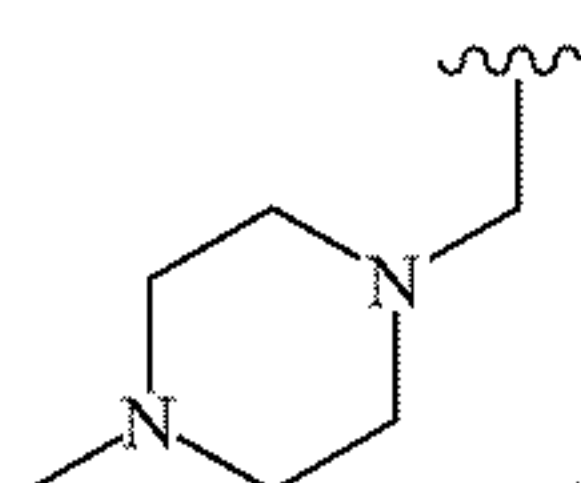
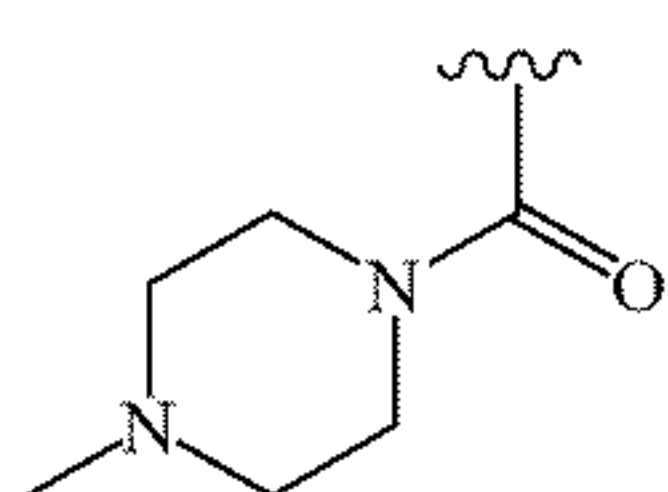


[0088] In some aspects, P1 includes at least one nitrogen.

[0089] In some aspects, any alkylene in R^{2*} in any previous aspect is not further substituted.

[0090] In some aspects, R² is selected from the structures depicted in FIGS. 1-3.

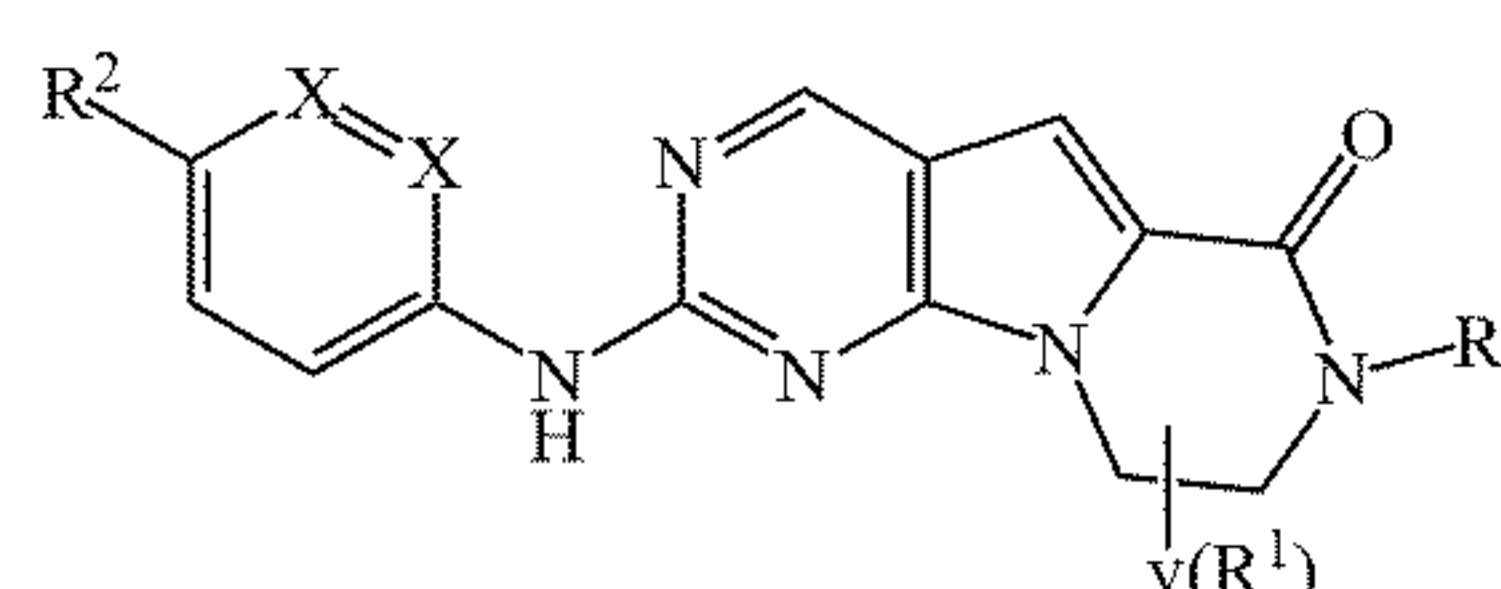
[0091] In some aspects, R² is



or

[0092] In some aspects, the compound has general Formula I and more specifically one of the general structures in FIGS. 4-8 wherein the variables are as previously defined.

[0093] In some aspects, the compound has general Formula Ia:



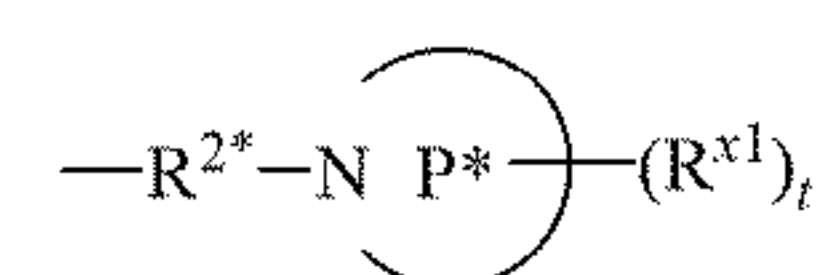
Ia

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

[0094] In some embodiments, the compound has Formula Ia and R is alkyl.

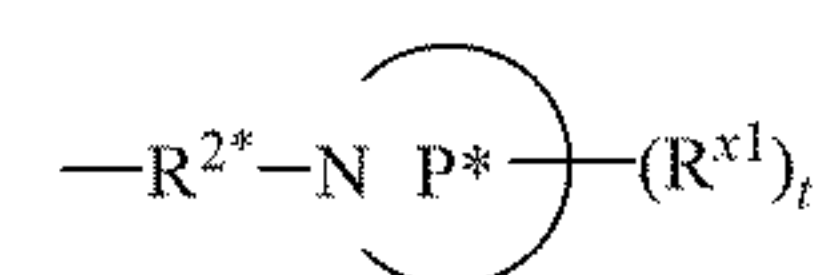
[0095] In some embodiments, the compound has Formula Ia and R is H.

[0096] In some embodiments, the compound has Formula Ia and R² is



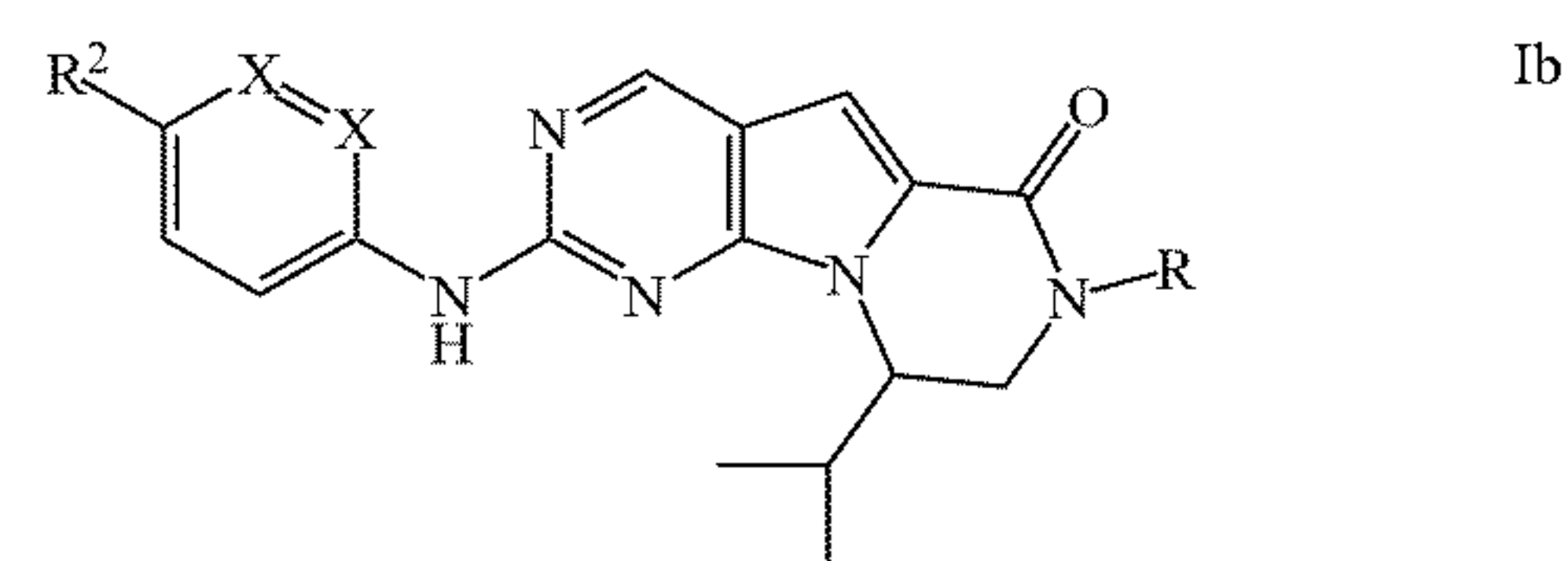
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0097] In some embodiments, the compound has Formula Ia and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or unsubstituted C₁-C₄ alkyl and R^{2*} is as previously defined.

[0098] In some embodiments, the compound has Formula Ib:



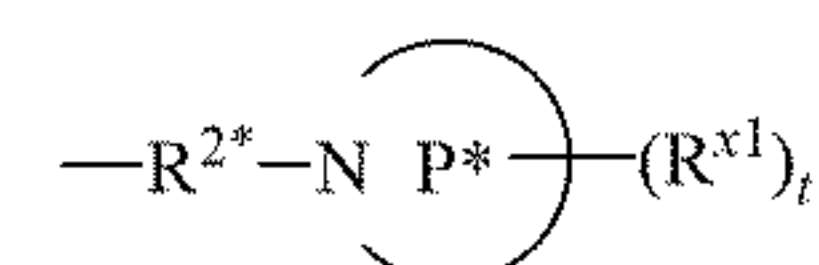
Ib

wherein R² and R are as previously defined.

[0099] In some embodiments, the compound has Formula Ib and R is alkyl.

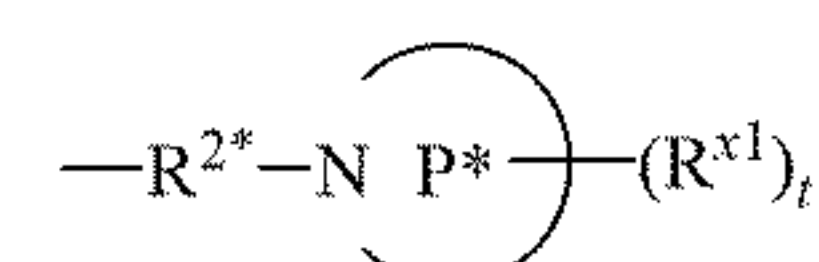
[0100] In some embodiments, the compound has Formula Ib and R is H.

[0101] In some embodiments, the compound has Formula Ib and R² is



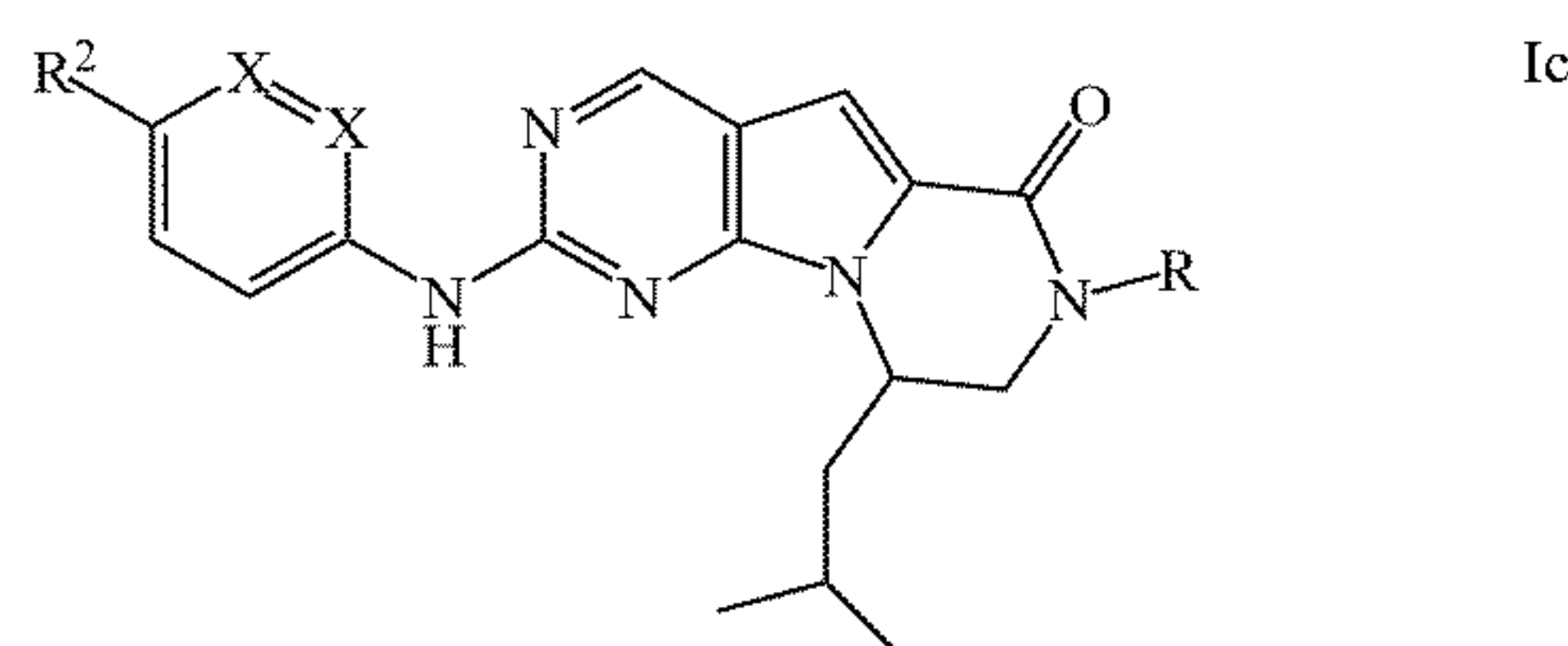
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0102] In some embodiments, the compound has Formula Ib and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl and R^{2*} is as previously defined.

[0103] In some embodiments, the compound has Formula Ic:

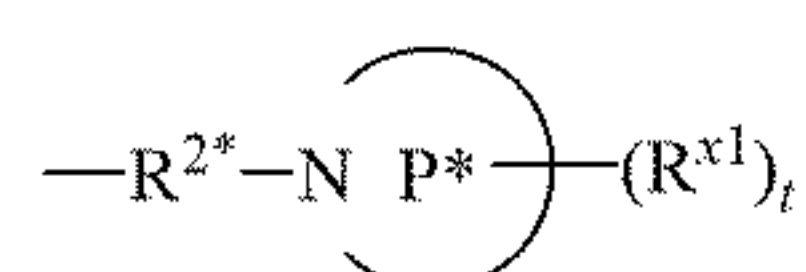


wherein R² and R are as previously defined.

[0104] In some embodiments, the compound has Formula Ic and R is alkyl.

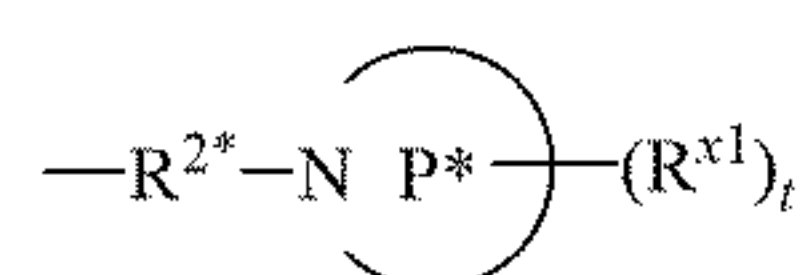
[0105] In some embodiments, the compound has Formula Ic and R is H.

[0106] In some embodiments, the compound has Formula Ic and R² is



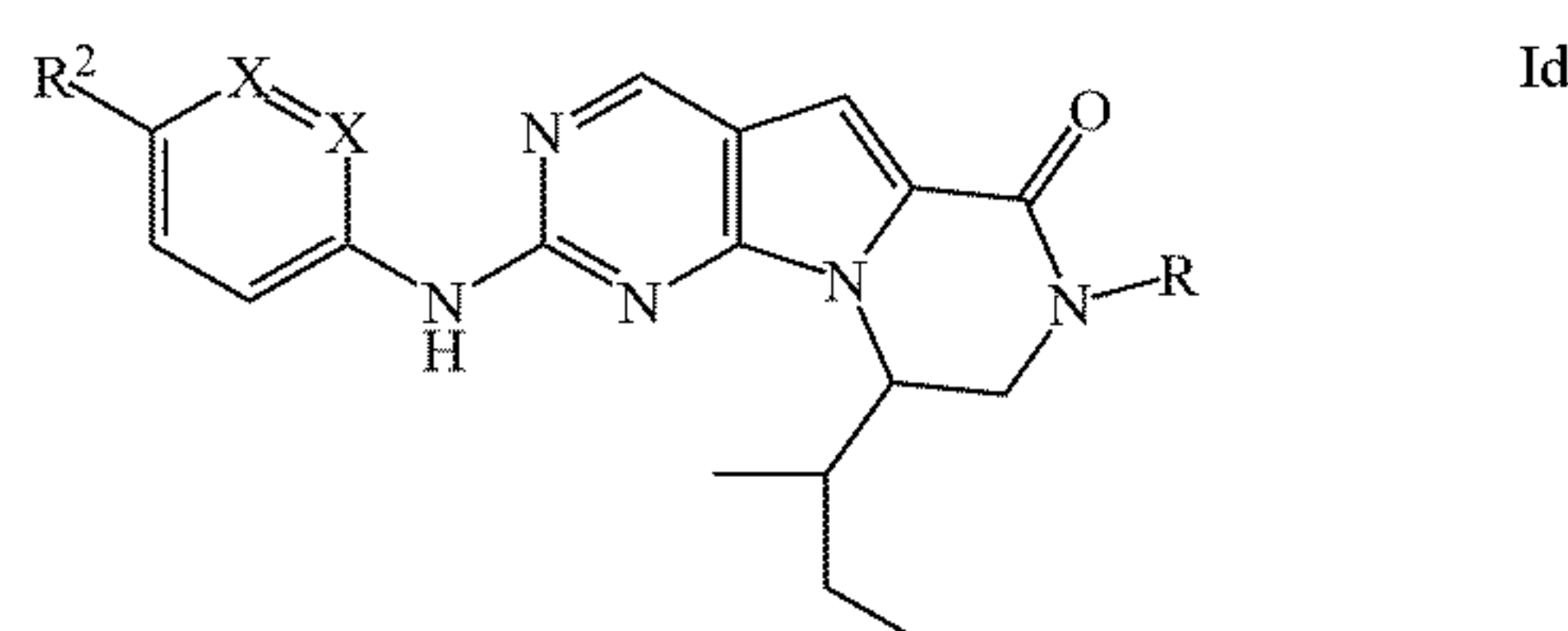
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0107] In some embodiments, the compound has Formula Ic and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl and R^{2*} is as previously defined.

[0108] In some embodiments, the compound has Formula Id:

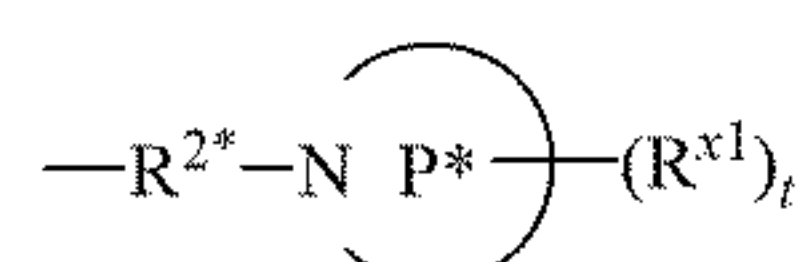


wherein R² and R are as previously defined.

[0109] In some embodiments, the compound has Formula Id and R is alkyl.

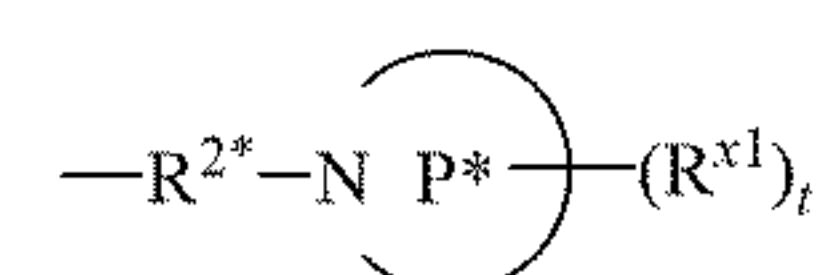
[0110] In some embodiments, the compound has Formula Id and R is H.

[0111] In some embodiments, the compound has Formula Id and R² is



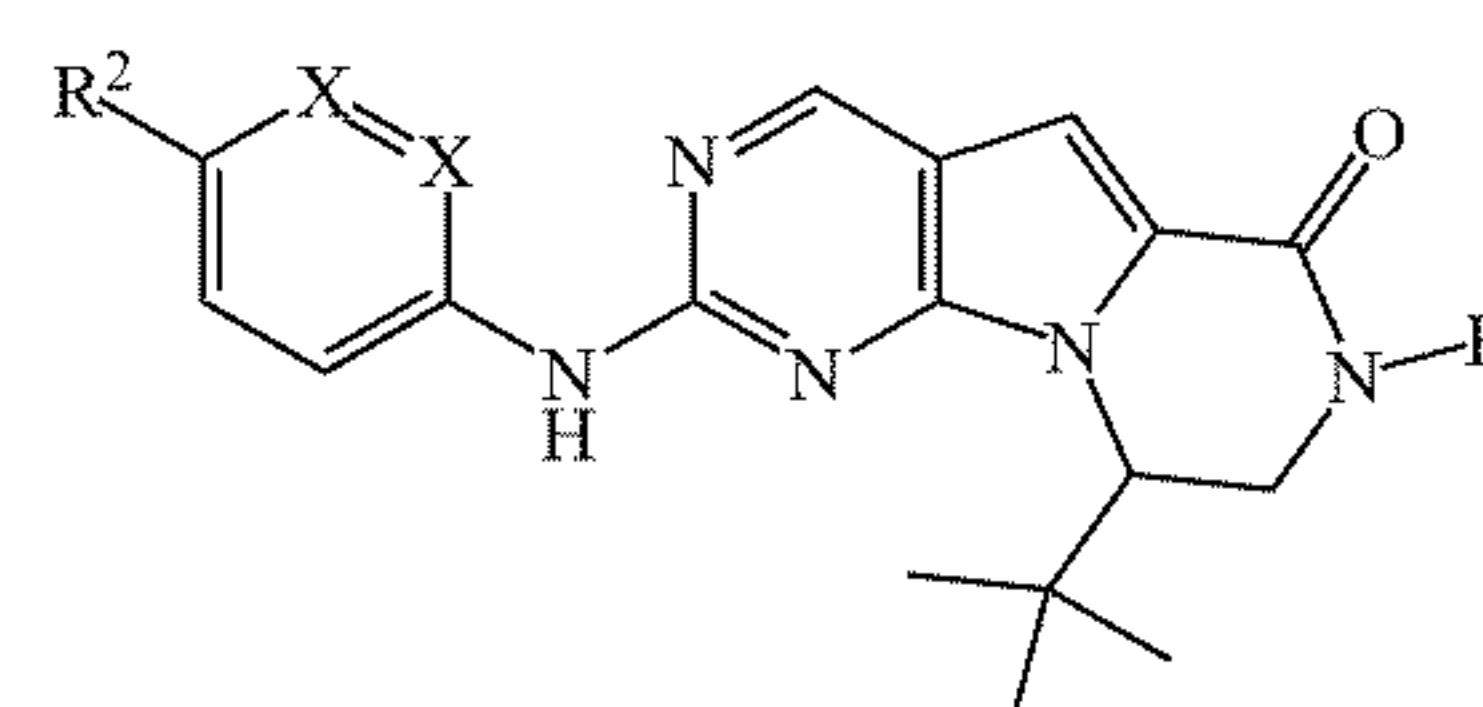
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0112] In some embodiments, the compound has Formula Id and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl and R^{2*} is as previously defined.

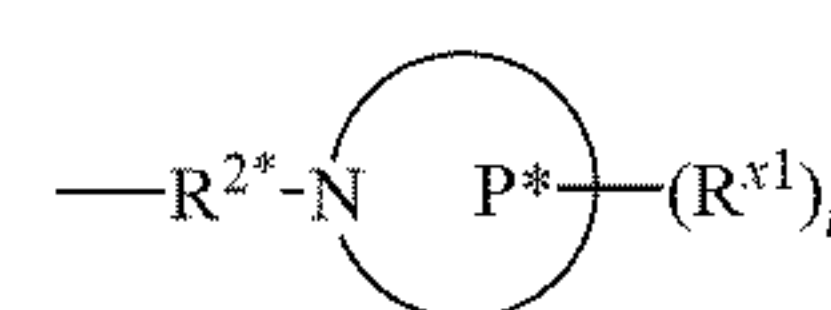
[0113] In some embodiments, the compound has Formula Ie:



[0114] In some embodiments, the compound has Formula Ie and R is alkyl.

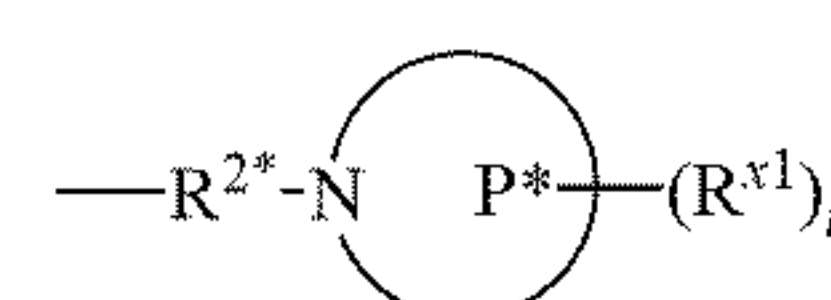
[0115] In some embodiments, the compound has Formula Ie and R is H.

[0116] In some embodiments, the compound has Formula Ie and R² is



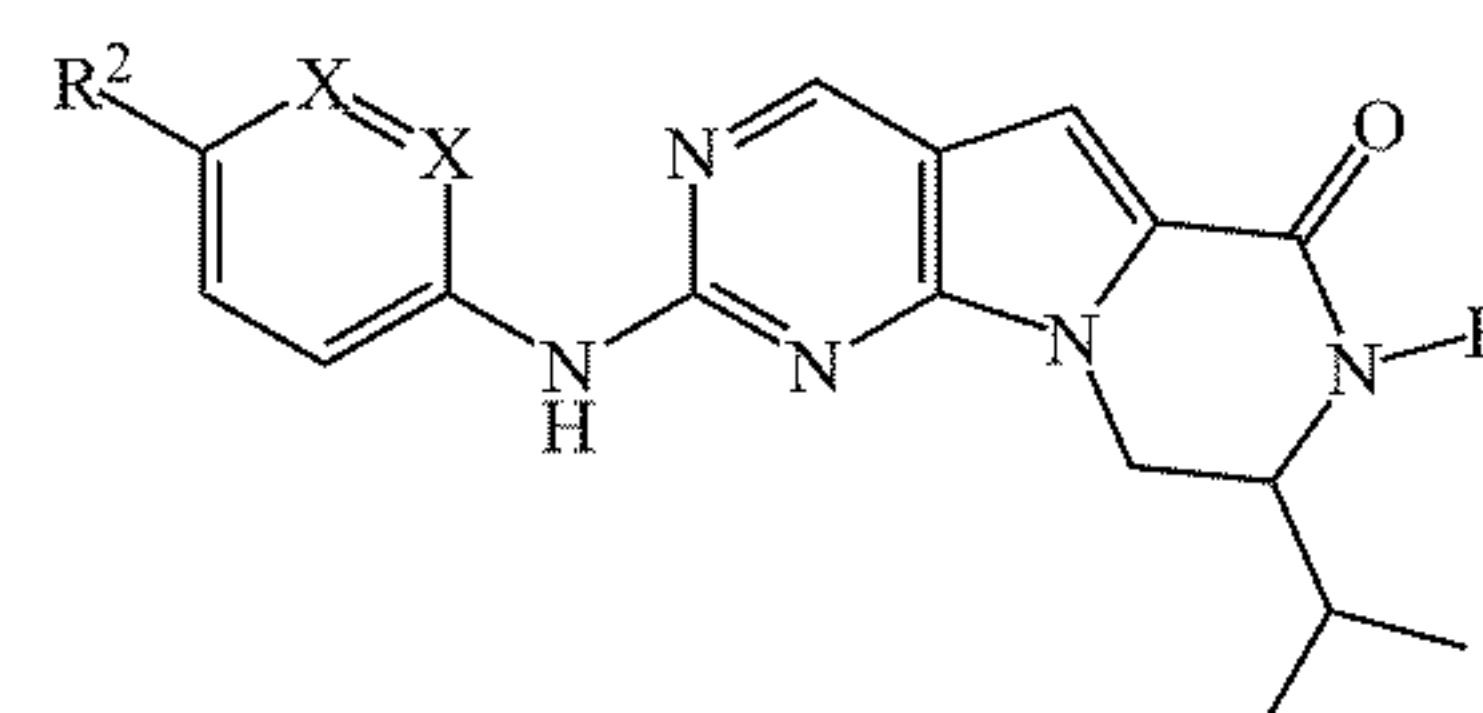
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0117] In some embodiments, the compound has Formula Ie and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl and R^{2*} is as previously defined.

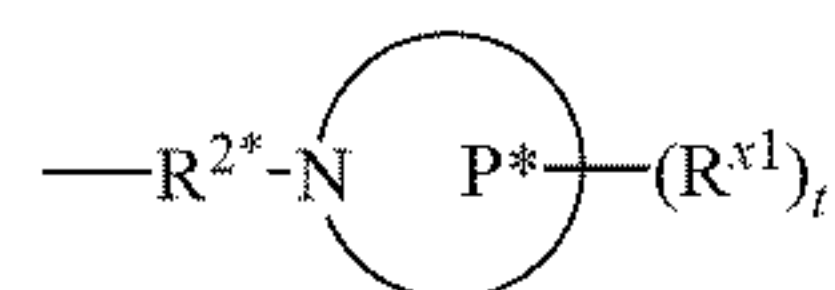
[0118] In some embodiments, the compound has Formula If:



[0119] In some embodiments, the compound has Formula If and R is alkyl.

[0120] In some embodiments, the compound has Formula If and R is H.

[0121] In some embodiments, the compound has Formula If and R² is



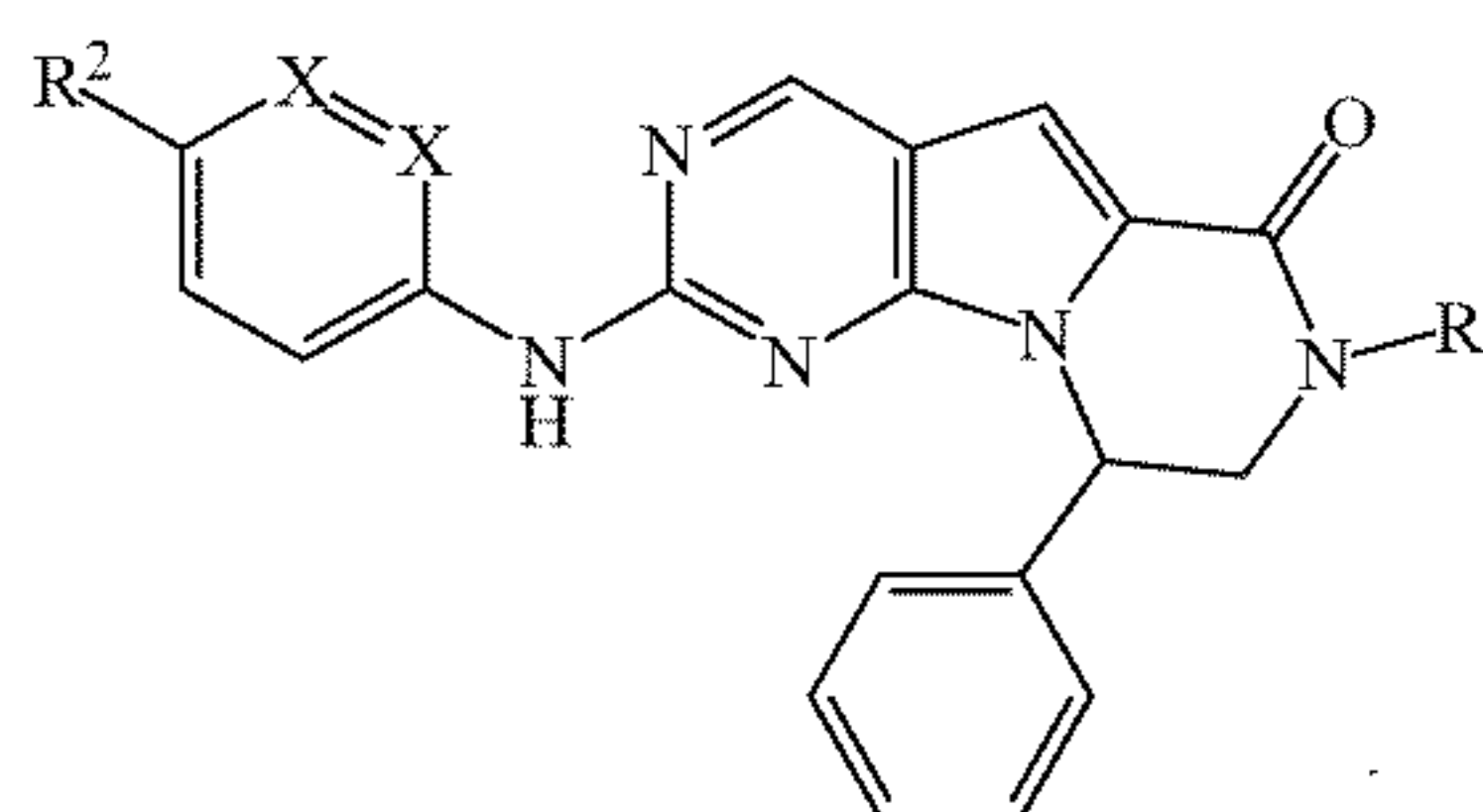
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0122] In some embodiments, the compound has Formula If and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl and R^{2*} is as previously defined.

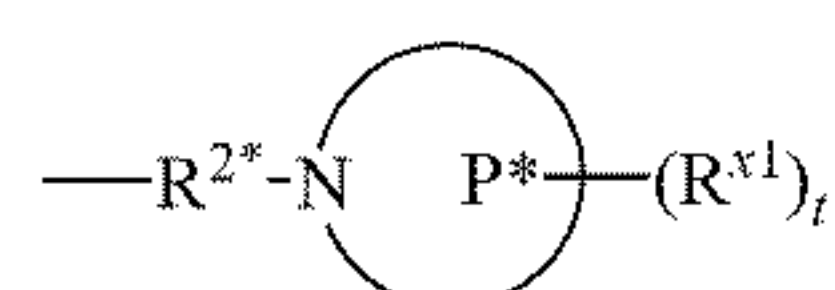
[0123] In some embodiments, the compound has Formula Ig:



[0124] In some embodiments, the compound has Formula Ig and R is alkyl.

[0125] In some embodiments, the compound has Formula Ig and R is H.

[0126] In some embodiments, the compound has Formula Ig and R² is



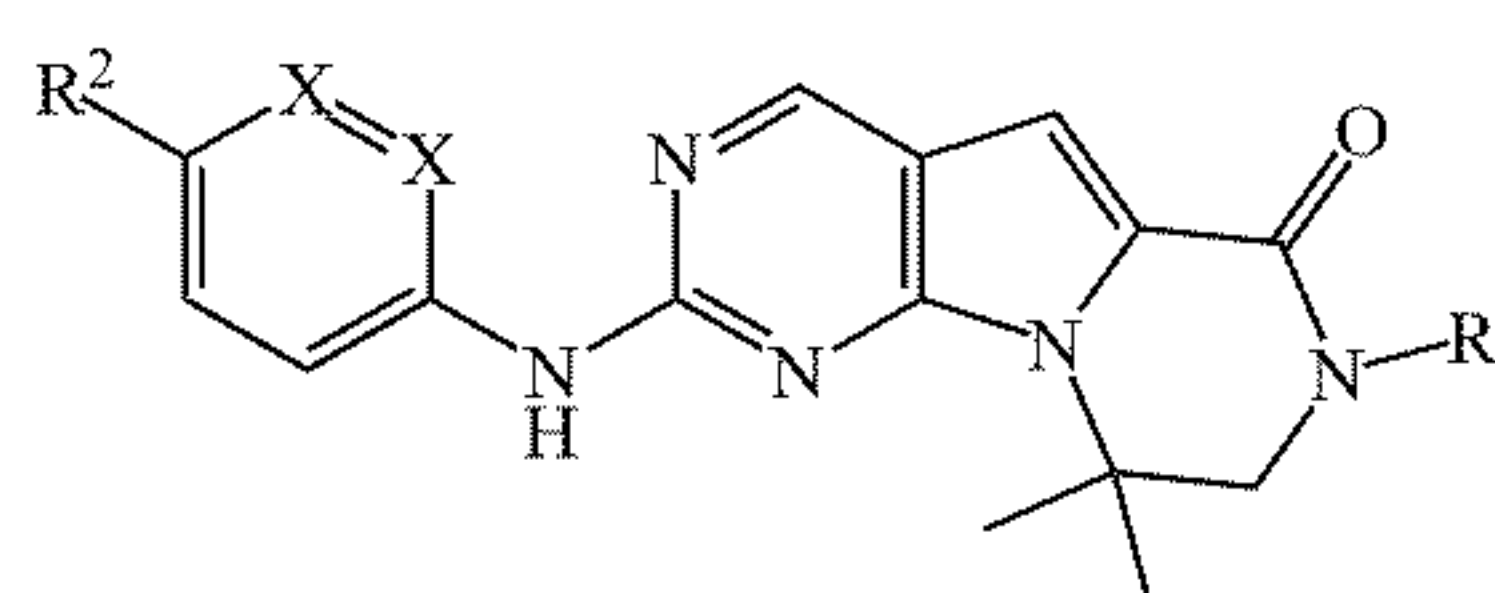
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0127] In some embodiments, the compound has Formula Ig and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl and R^{2*} is as previously defined.

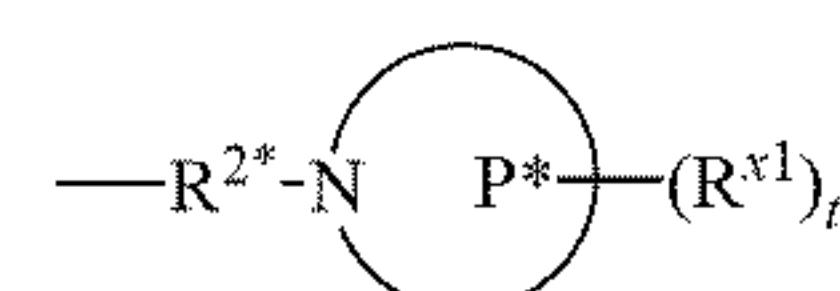
[0128] In some embodiments, the compound has Formula Ih:



[0129] In some embodiments, the compound has Formula Ih and R is alkyl.

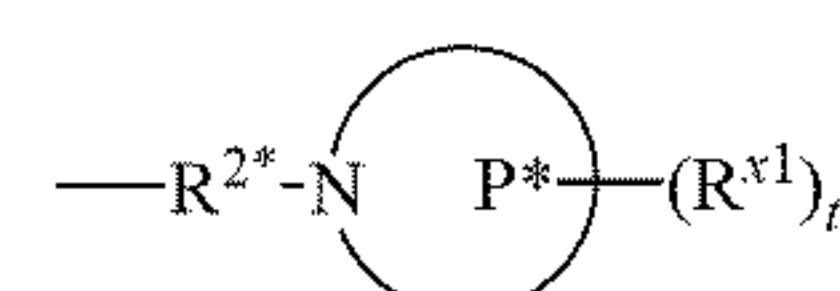
[0130] In some embodiments, the compound has Formula Ih and R is H.

[0131] In some embodiments, the compound has Formula Ih and R² is



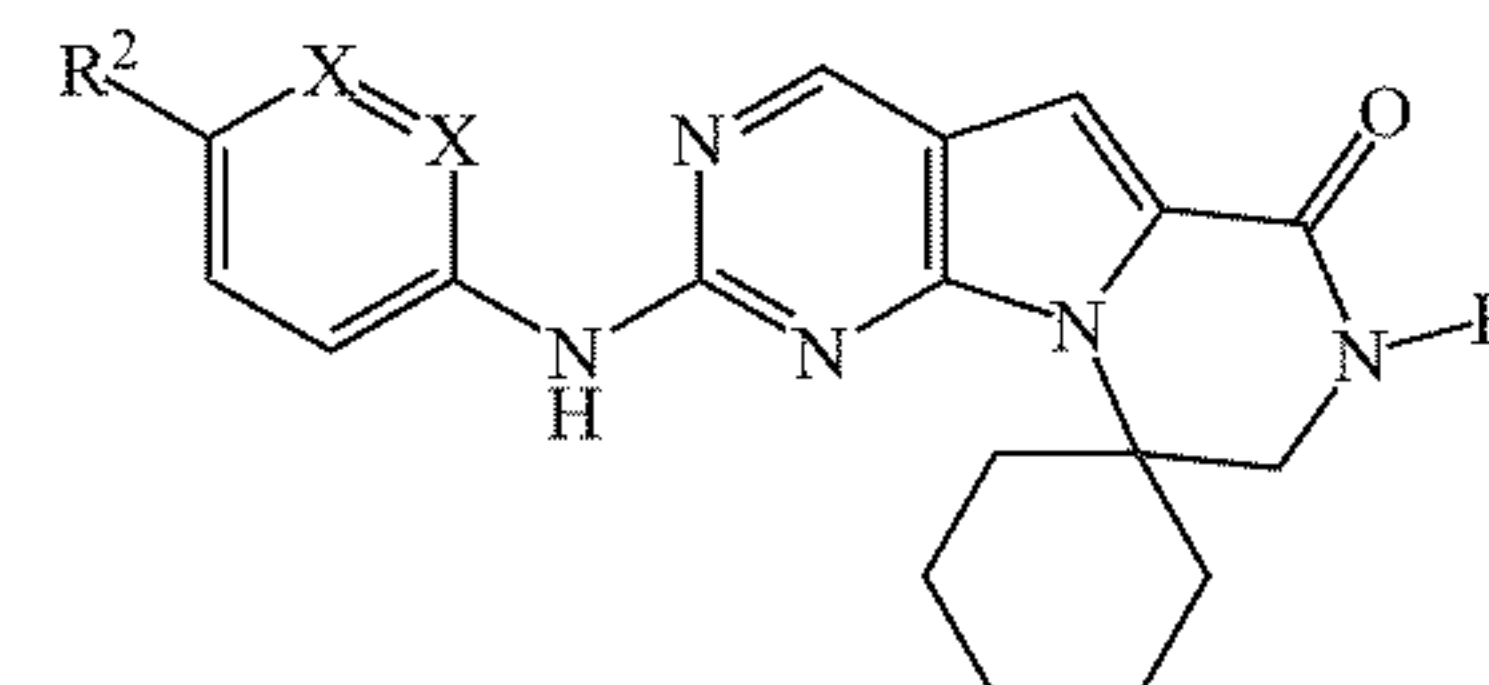
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0132] In some embodiments, the compound has Formula Ih and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl and R^{2*} is as previously defined.

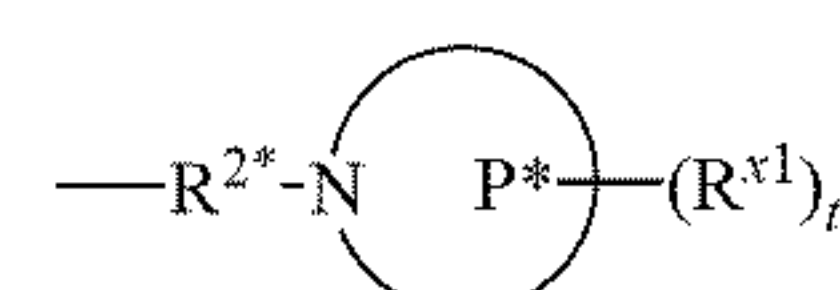
[0133] In some embodiments, the compound has Formula Ii:



[0134] In some embodiments, the compound has Formula Ii and R is alkyl.

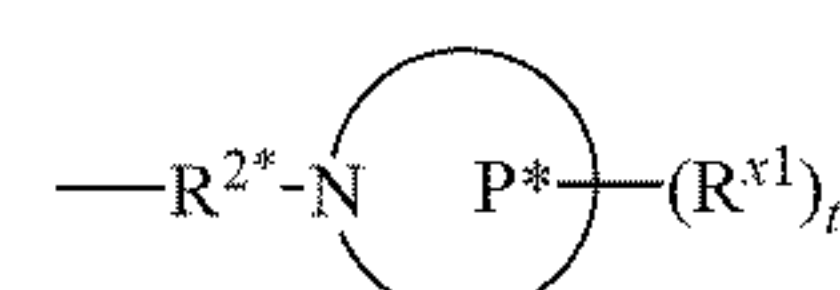
[0135] In some embodiments, the compound has Formula Ii and R is H.

[0136] In some embodiments, the compound has Formula Ii and R² is



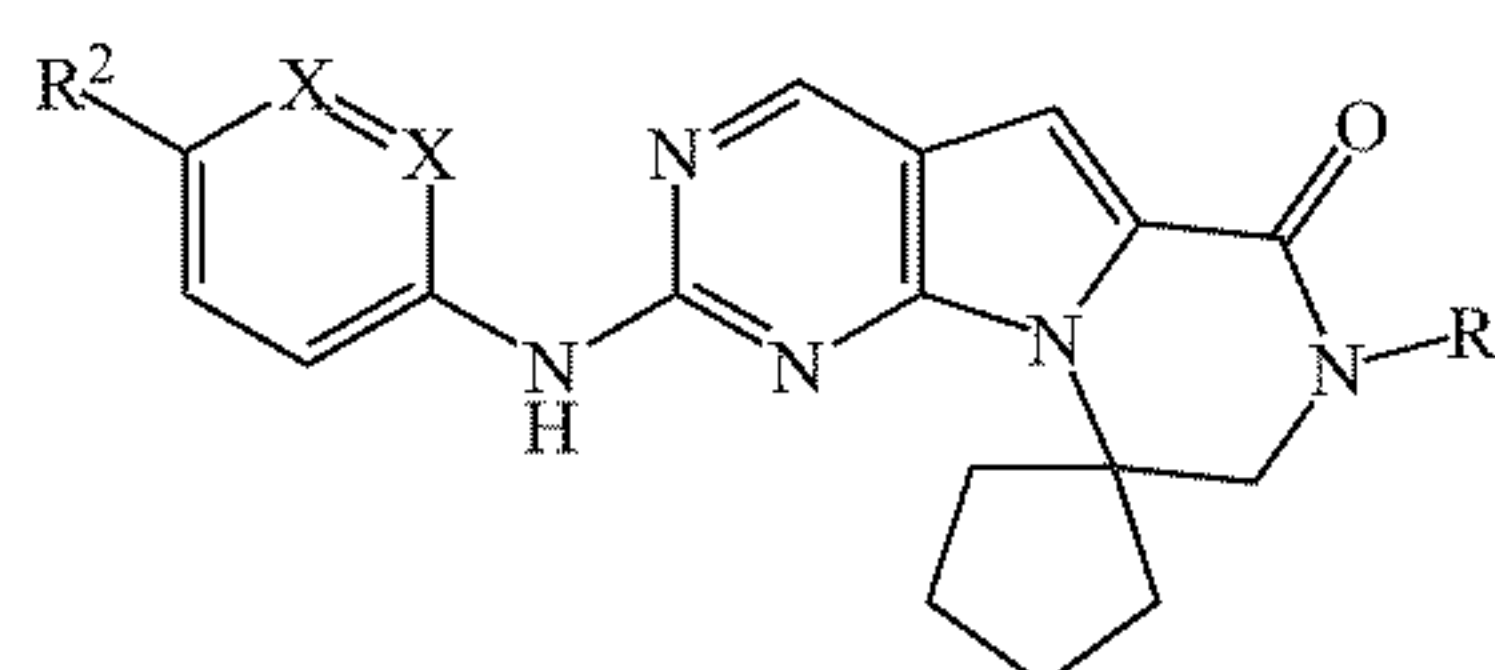
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

[0137] In some embodiments, the compound has Formula Ii and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl and R^{2*} is as previously defined.

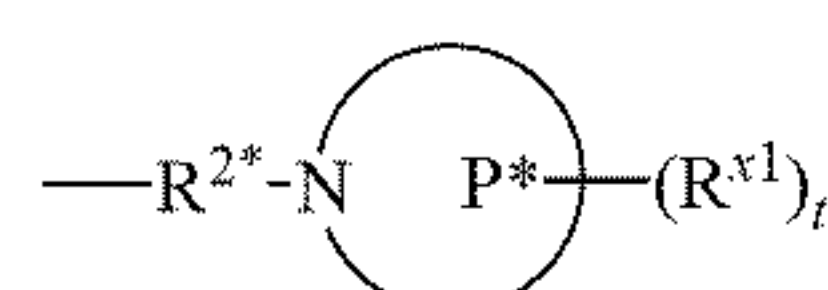
[0138] In some embodiments, the compound has Formula Ij:



[0139] In some embodiments, the compound has Formula Ij and R is alkyl.

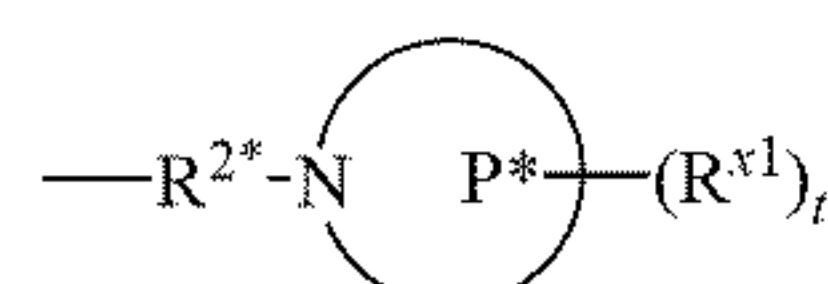
[0140] In some embodiments, the compound has Formula Ij and R is H.

[0141] In some embodiments, the compound has Formula Ij and R² is



wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group.

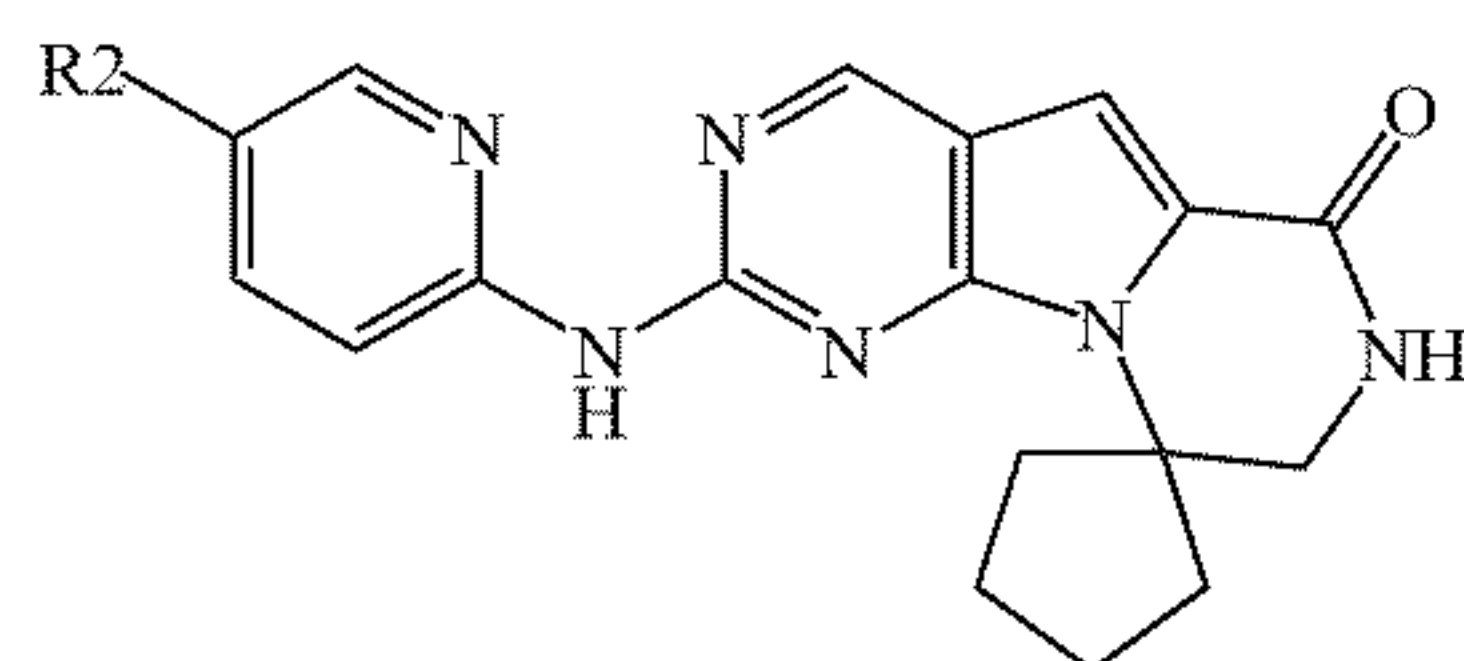
[0142] In some embodiments, the compound has Formula Ij and R² is



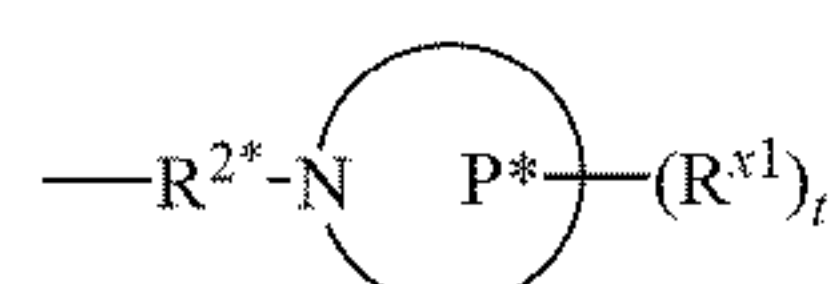
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl.

[0143] In some embodiments, the compound has Formula Ij and R is H, and both X are N.

[0144] In some embodiments, the compound has the structure:

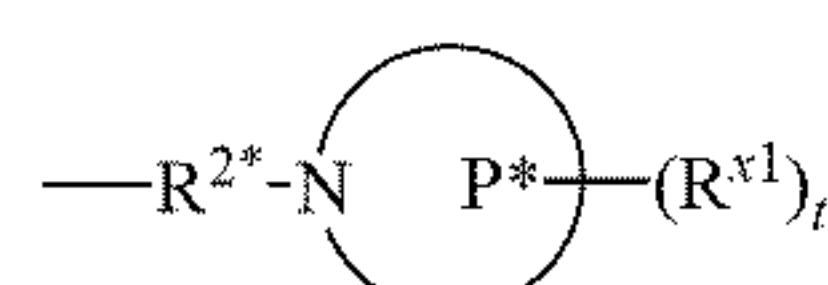


[0145] In some embodiments, the compound has Formula Ik and R² is



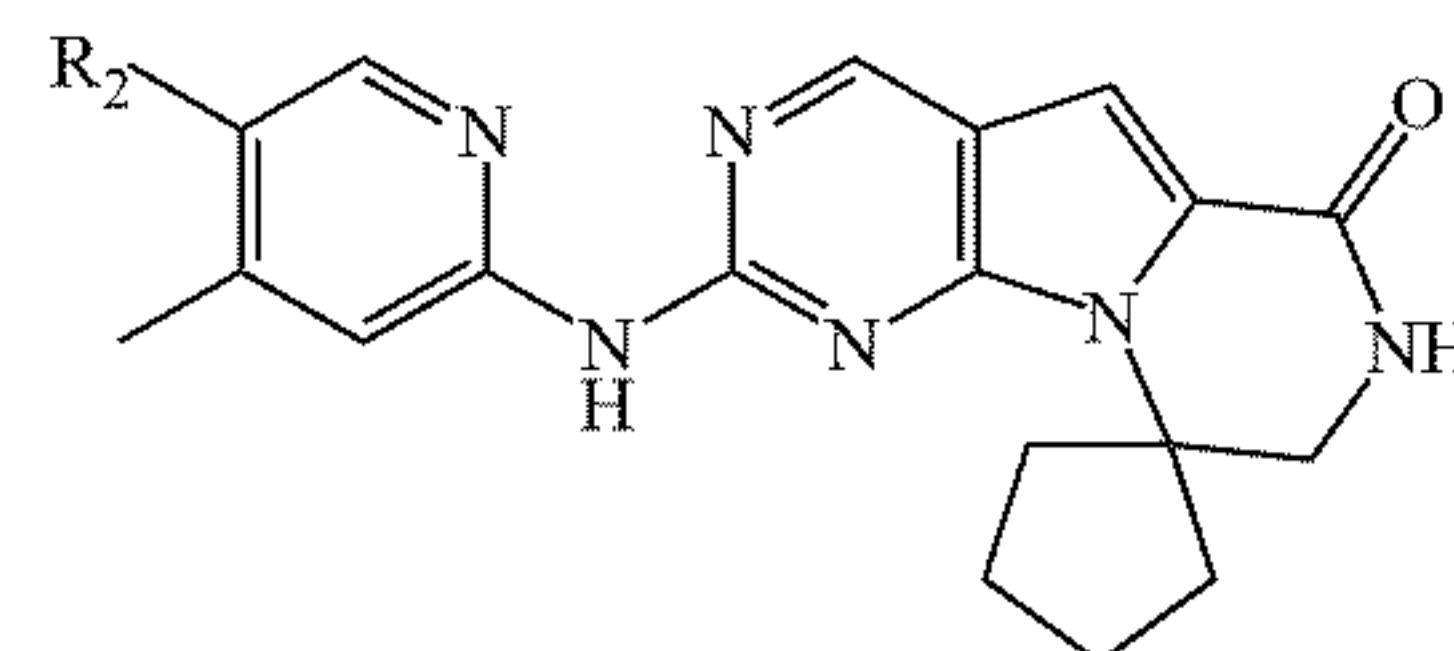
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group.

[0146] In some embodiments, the compound has Formula Ik and R² is

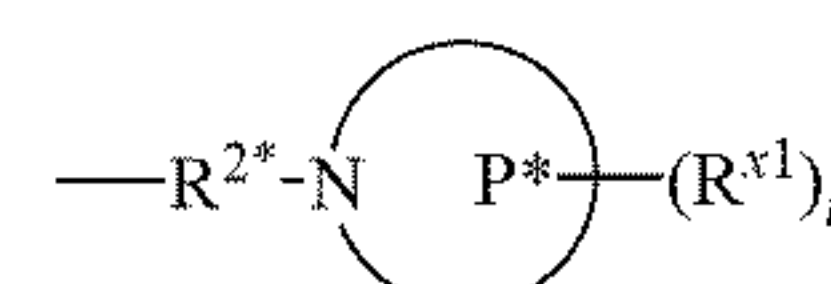


wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl.

[0147] In some embodiments, the compound has Formula II:

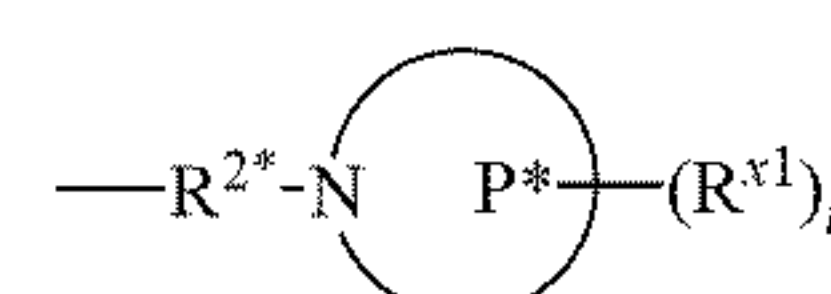


[0148] In some embodiments, the compound has Formula II and R² is



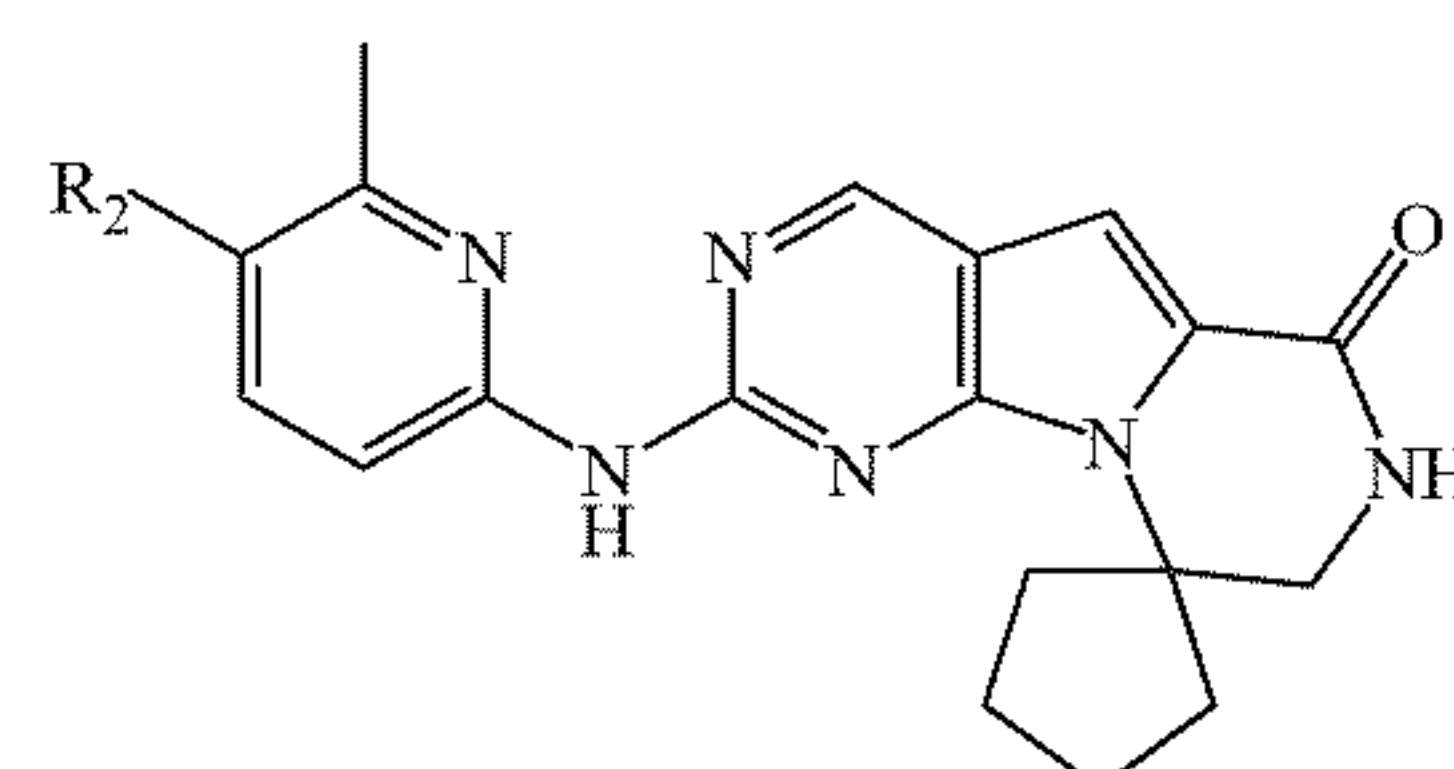
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group.

[0149] In some embodiments, the compound has Formula II and R² is

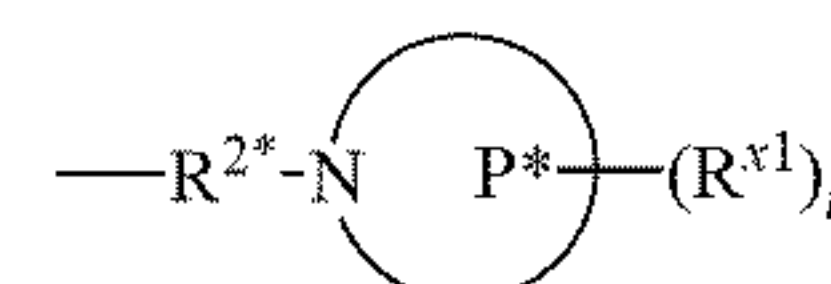


wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl.

[0150] In some embodiments, the compound has Formula Im:

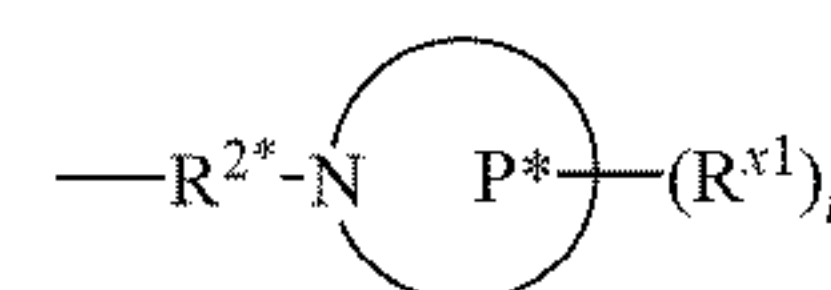


[0151] In some embodiments, the compound has Formula Im and R² is



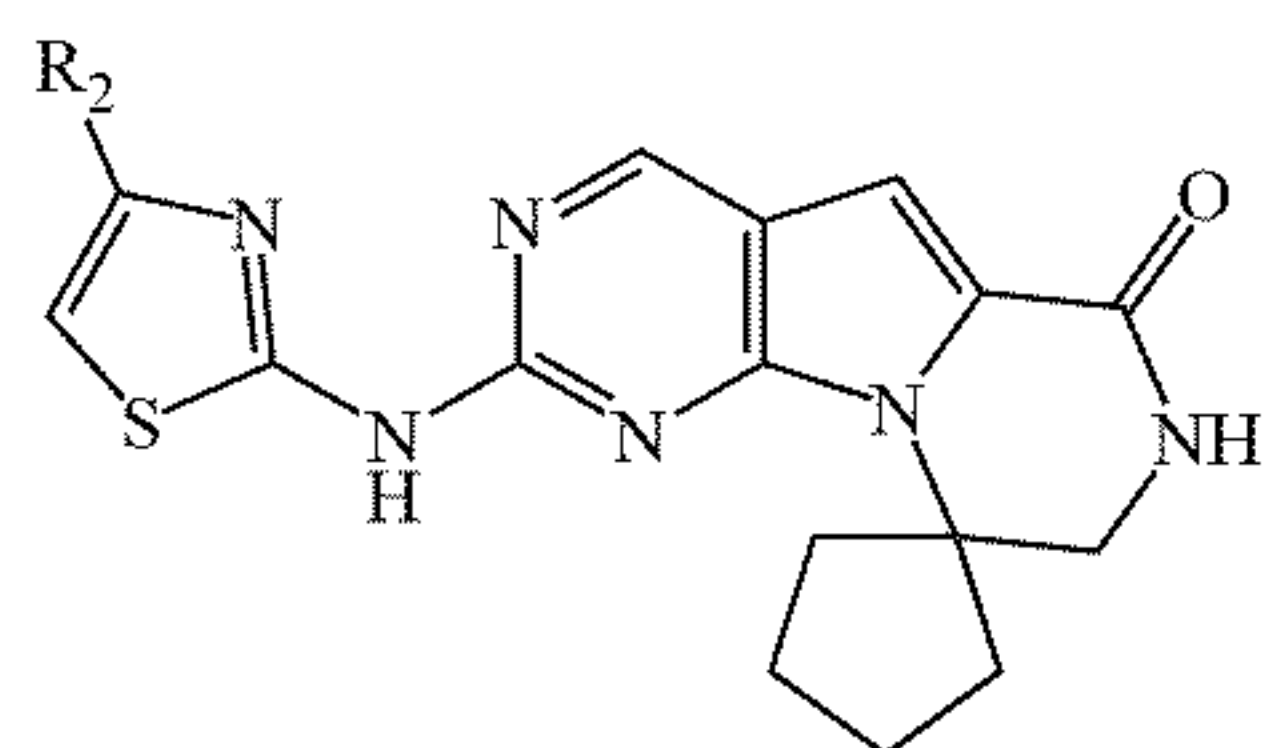
wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group.

[0152] In some embodiments, the compound has Formula Im and R² is

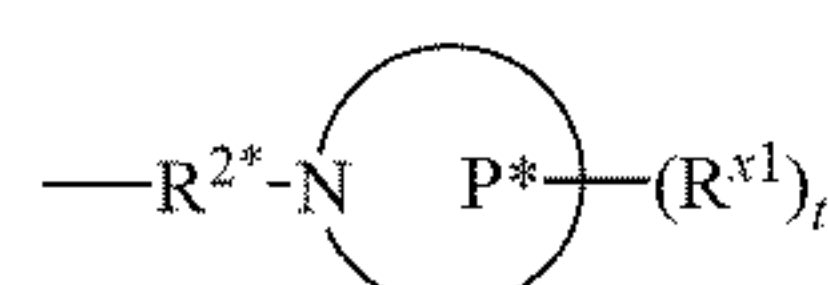


wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C₁-C₄ alkyl.

[0153] In some embodiments, the compound has Formula IIa:

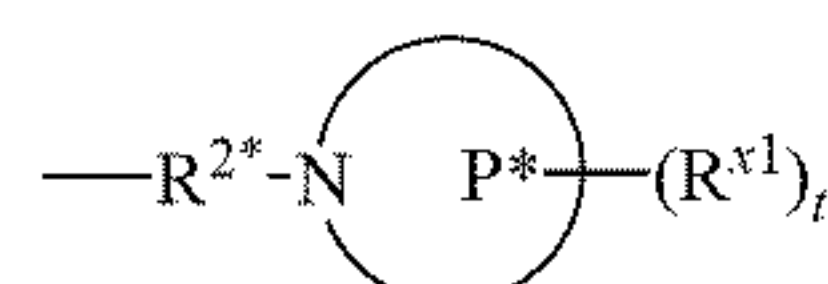


[0154] In some embodiments, the compound has Formula IIa and R^2 is



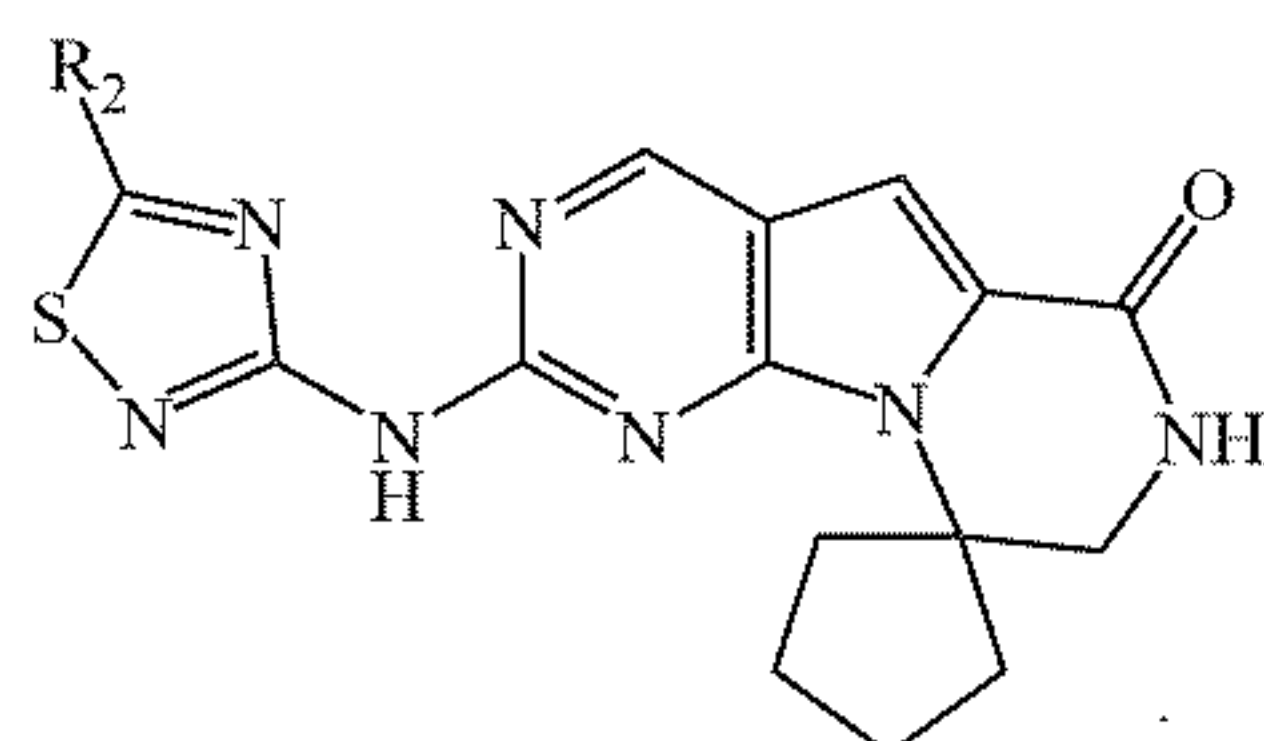
wherein P^* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group.

[0155] In some embodiments, the compound has Formula IIa and R^2 is

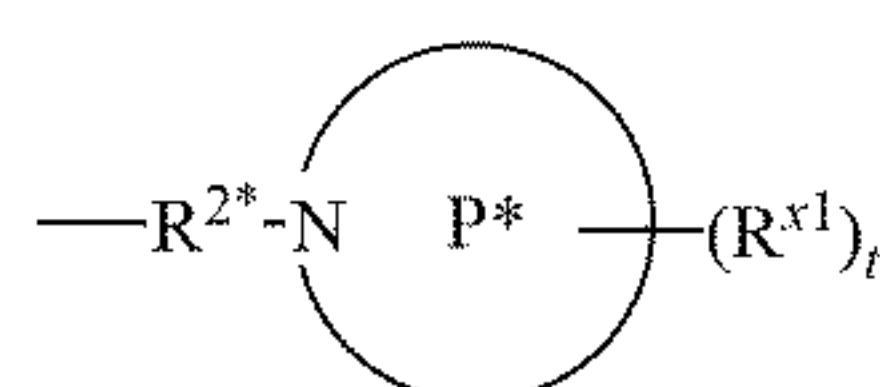


wherein P^* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C_1 - C_4 alkyl.

[0156] In some embodiments, the compound has Formula IIb:

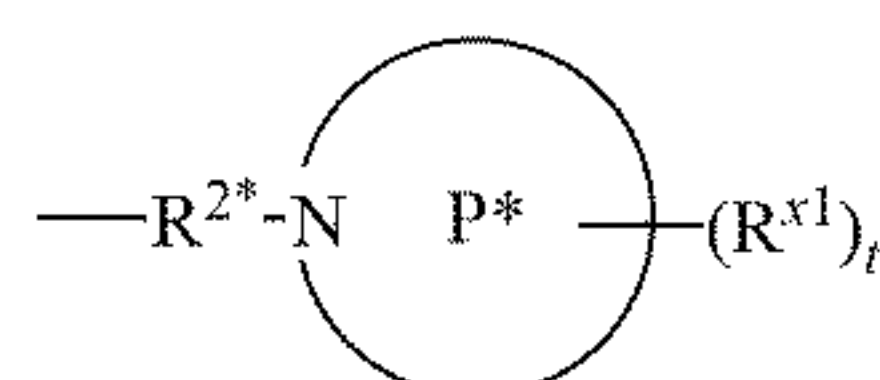


[0157] In some embodiments, the compound has Formula Im and R^2 is



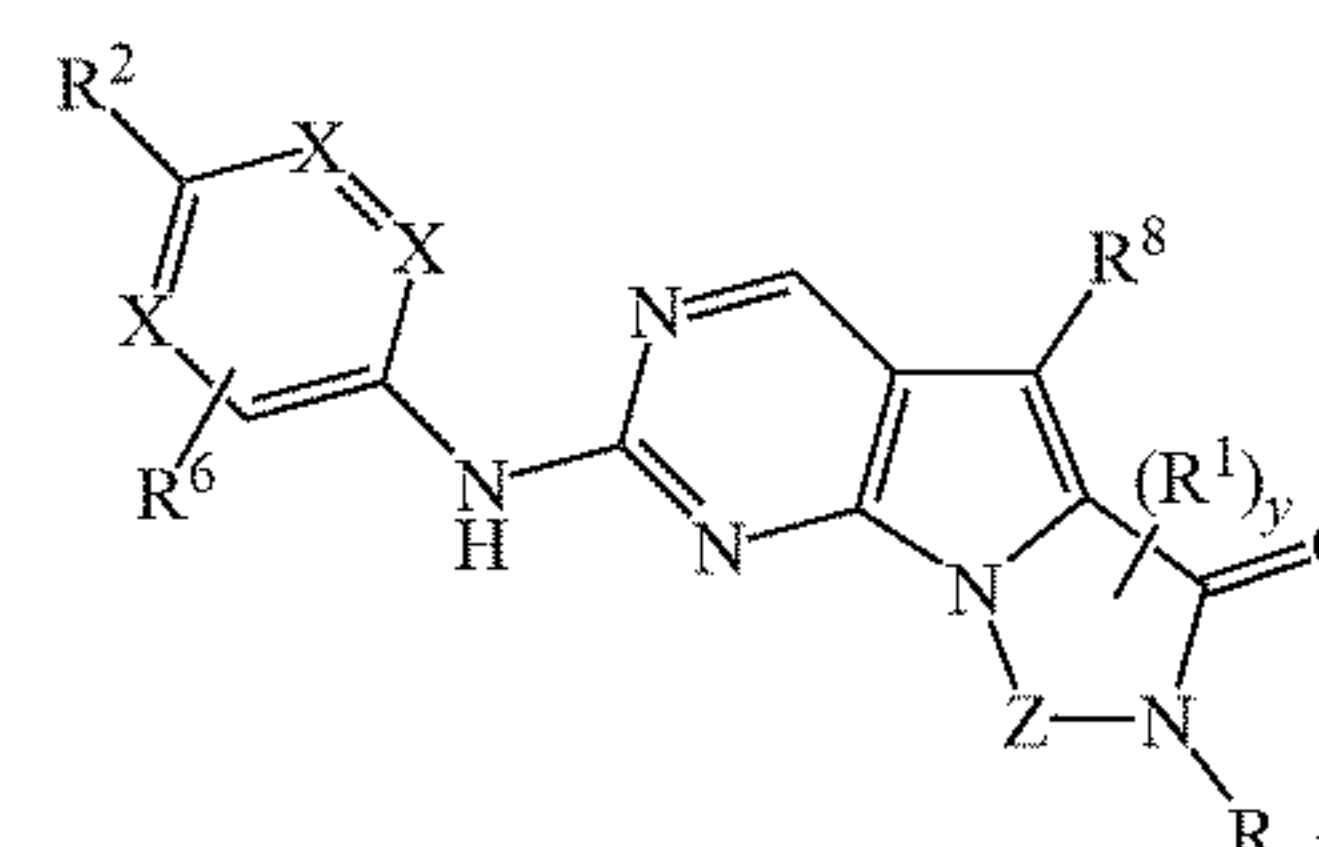
wherein P^* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group.

[0158] In some embodiments, the compound has Formula Im and R^2 is



wherein P^* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group, R^{x1} is hydrogen or C_1 - C_4 alkyl.

[0159] In some aspects, the active compound is:



Isotopic Substitution

[0160] The present invention includes compounds and the use of compounds with desired isotopic substitutions of atoms, at amounts above the natural abundance of the isotope, i.e., enriched. Isotopes are atoms having the same atomic number but different mass numbers, i.e., the same number of protons but a different number of neutrons. By way of general example and without limitation, isotopes of hydrogen, for example, deuterium (^2H) and tritium (^3H) may be used anywhere in described structures. Alternatively or in addition, isotopes of carbon, e.g., ^{13}C and ^{14}C , may be used. A preferred isotopic substitution is deuterium for hydrogen at one or more locations on the molecule to improve the performance of the drug. The deuterium can be bound in a location of bond breakage during metabolism (an α -deuterium kinetic isotope effect) or next to or near the site of bond breakage (a β -deuterium kinetic isotope effect).

[0161] Substitution with isotopes such as deuterium can afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased in vivo half-life or reduced dosage requirements. Substitution of deuterium for hydrogen at a site of metabolic break down can reduce the rate of or eliminate the metabolism at that bond. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including protium (^1H), deuterium (^2H) and tritium (^3H). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0162] The term “isotopically-labeled” analog refers to an analog that is a “deuterated analog”, a “ ^{13}C -labeled analog,” or a “deuterated/ ^{13}C -labeled analog.” The term “deuterated analog” means a compound described herein, whereby a H-isotope, i.e., hydrogen/protium (^1H), is substituted by a H-isotope, i.e., deuterium (^2H). Deuterium substitution can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted by at least one deuterium. In certain embodiments, the isotope is 90, 95 or 99% or more enriched in an isotope at any location of interest. In some embodiments it is deuterium that is 90, 95 or 99% enriched at a desired location.

[0163] Further specific compounds that fall within the present invention and that can be used in the disclosed methods of treatment and compositions include the structures listed in Table 1 below.

TABLE 1

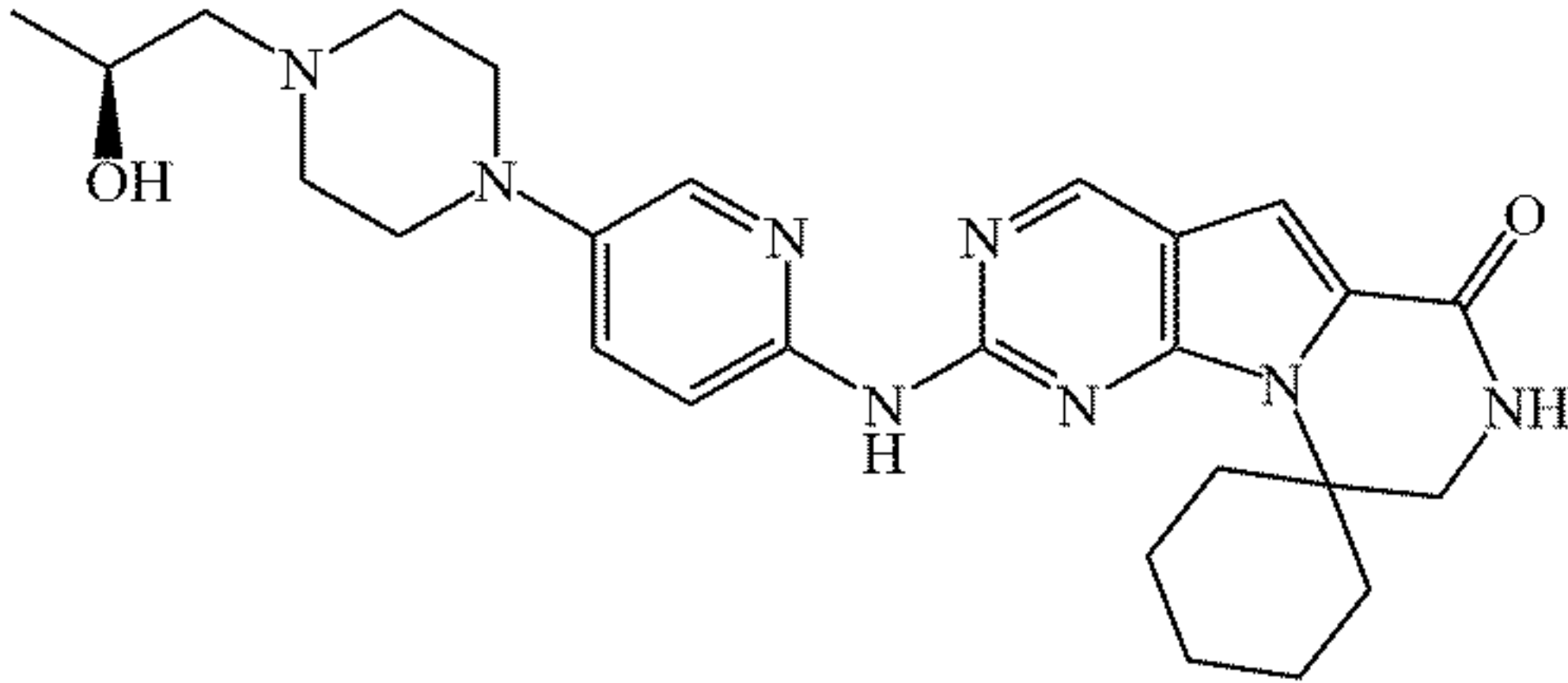
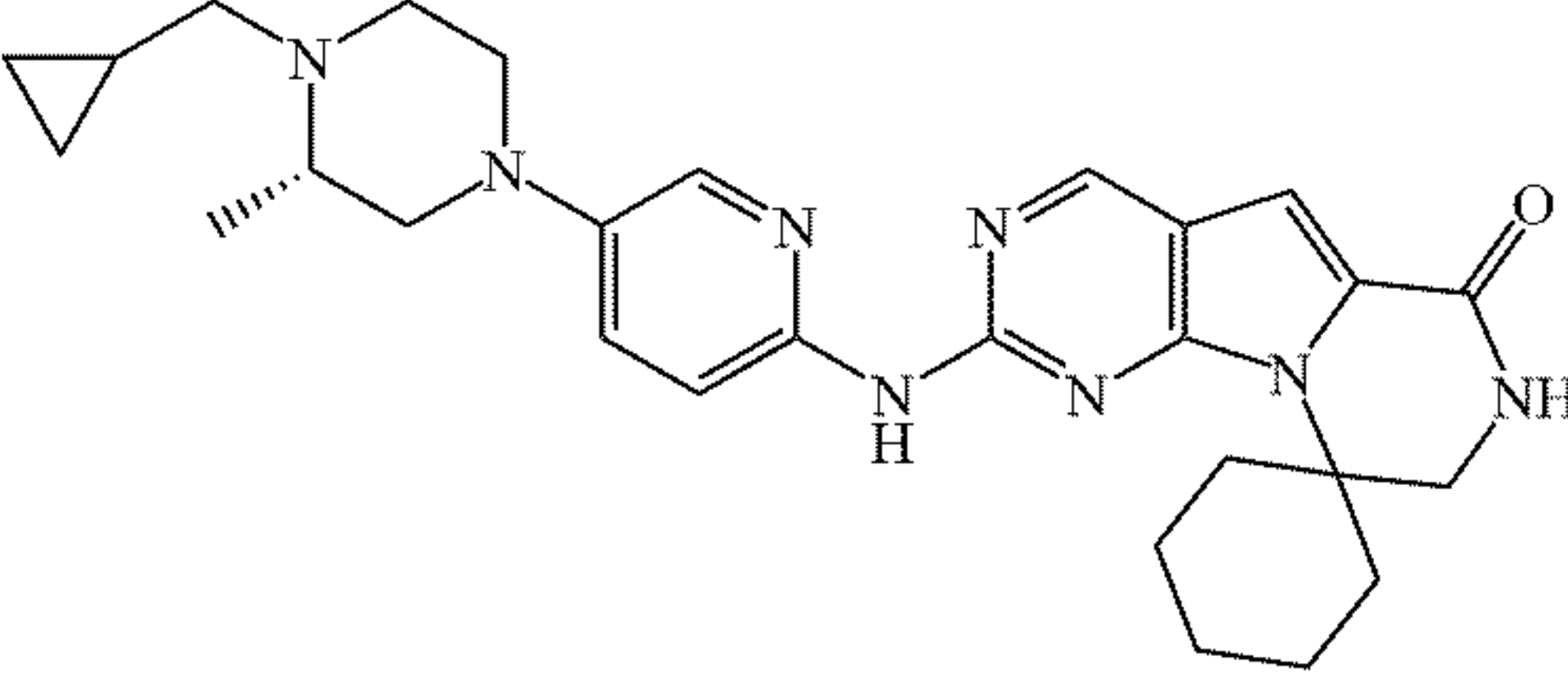
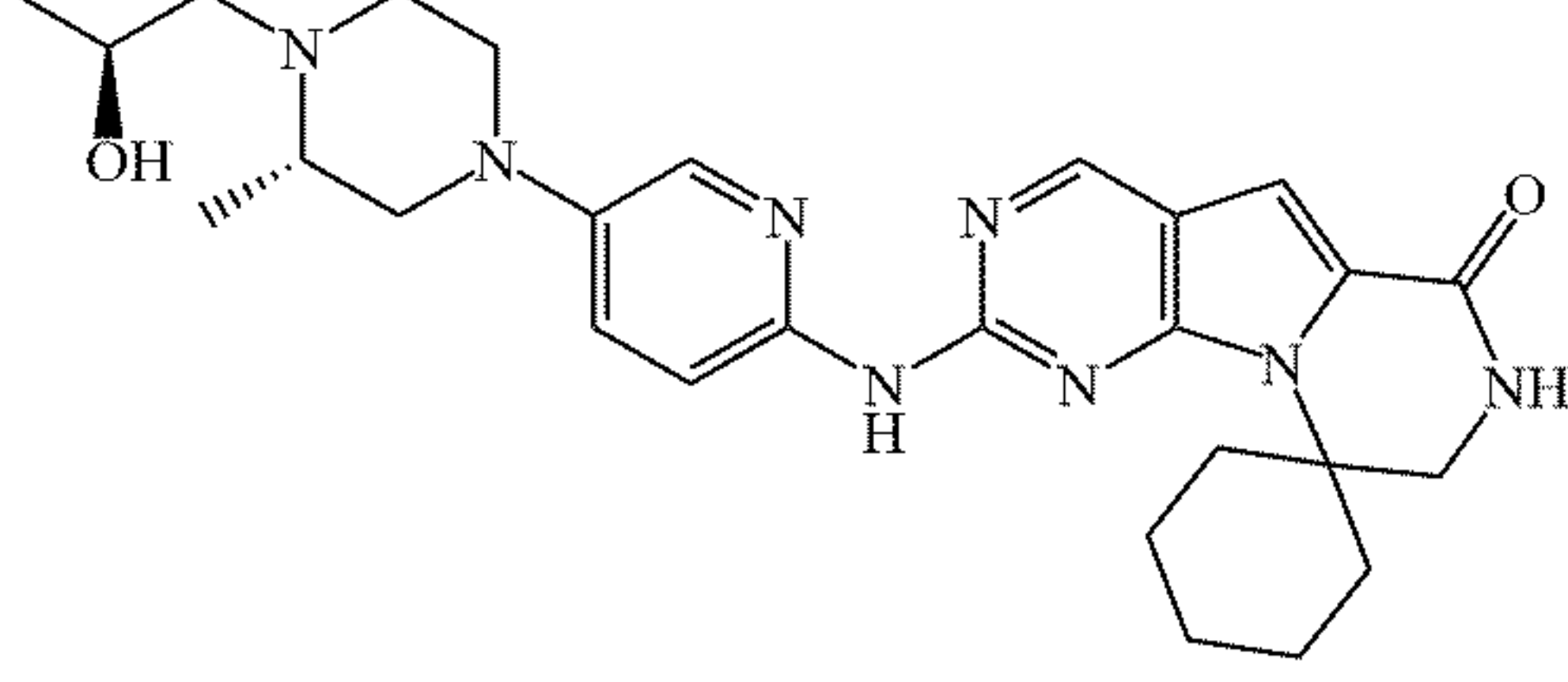
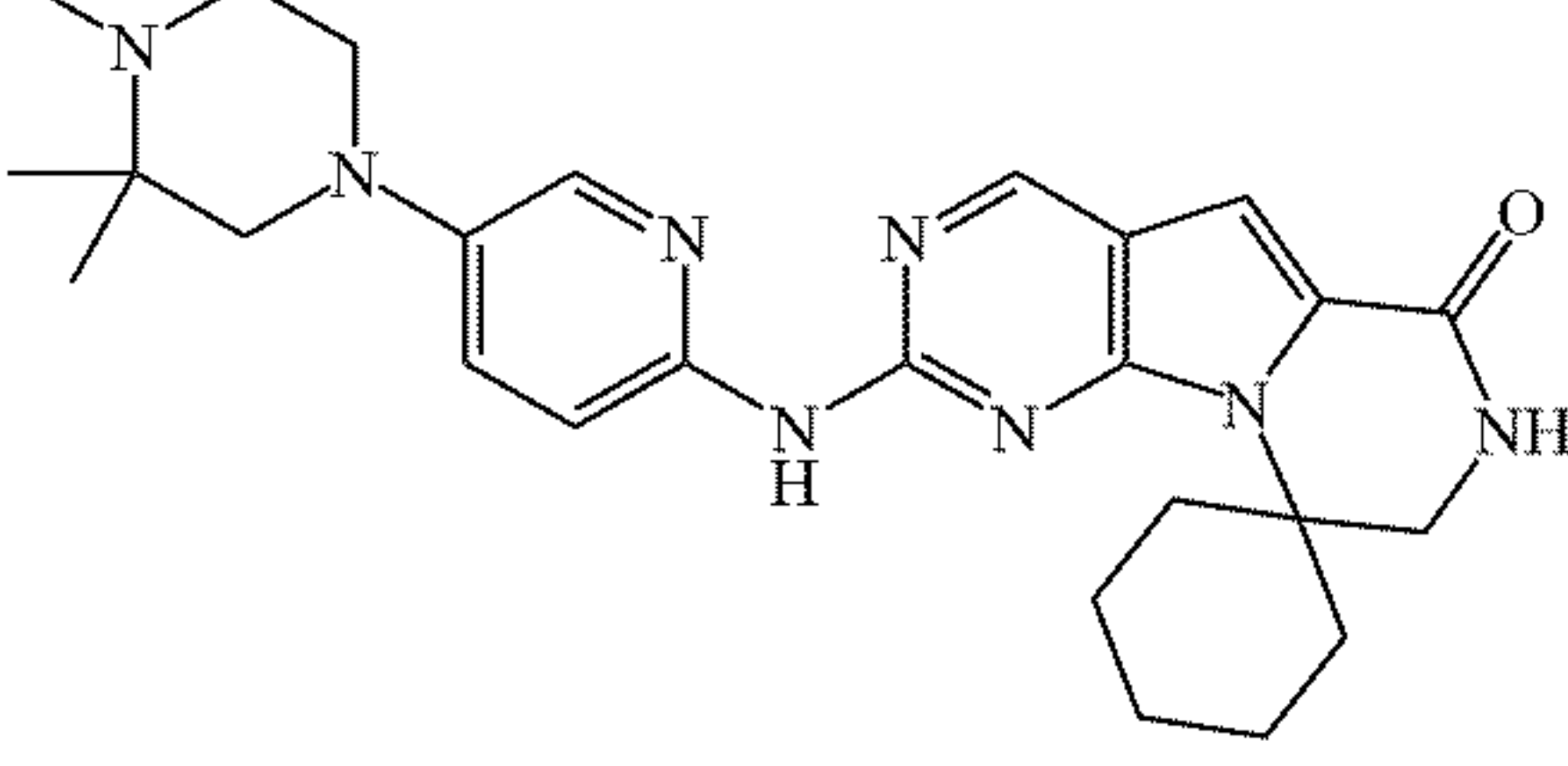
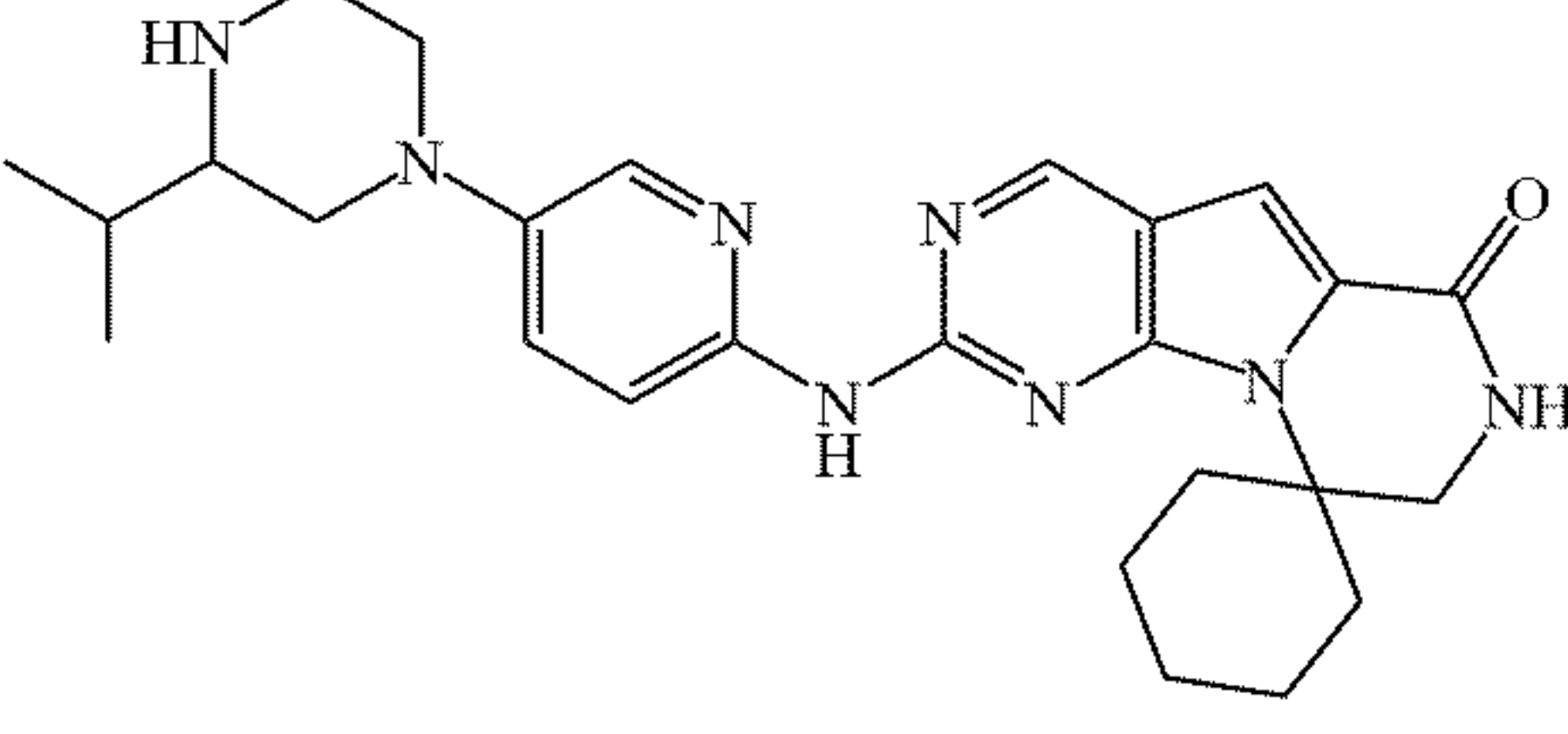
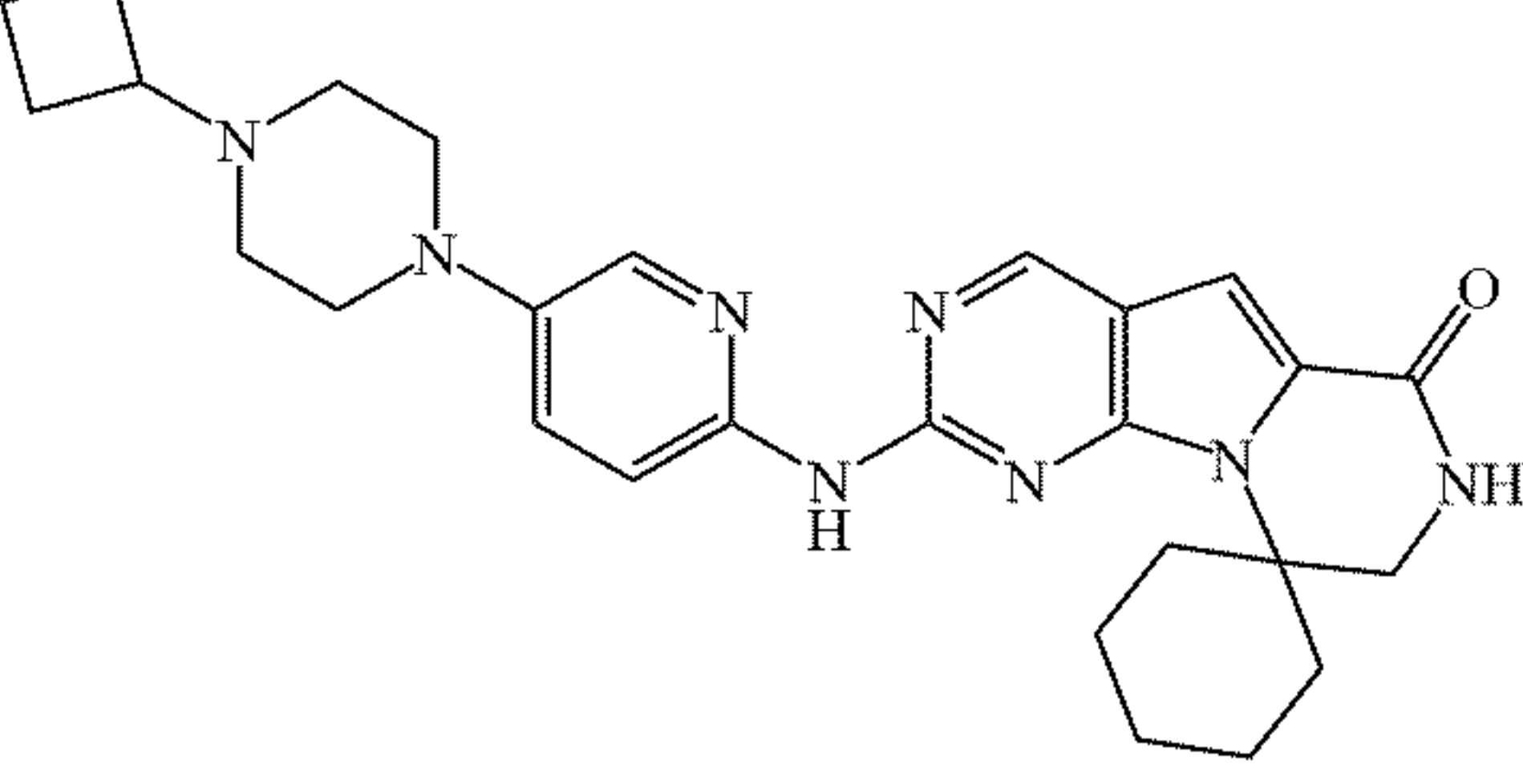
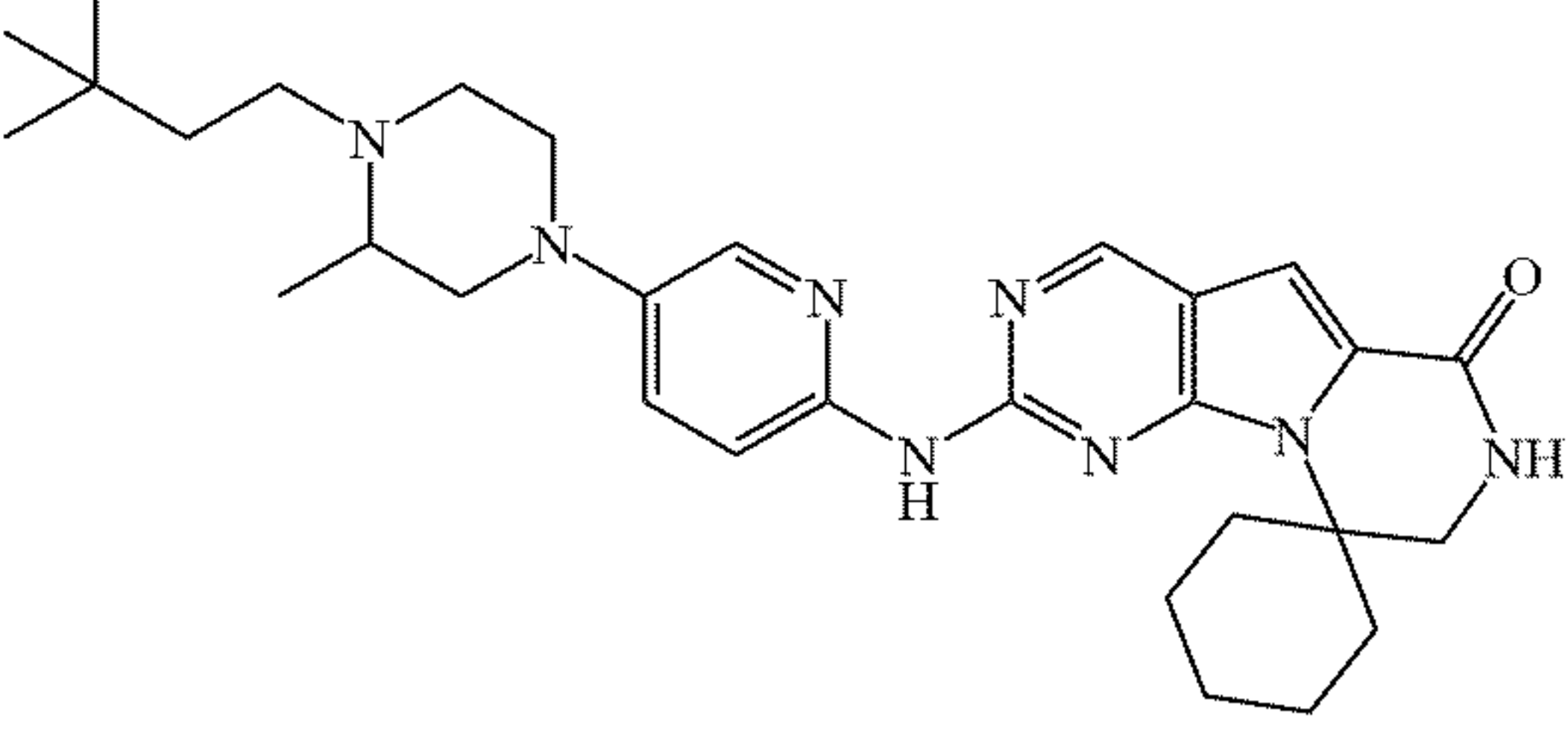
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
A	
B	
C	
D	
E	
F	
G	

TABLE 1-continued

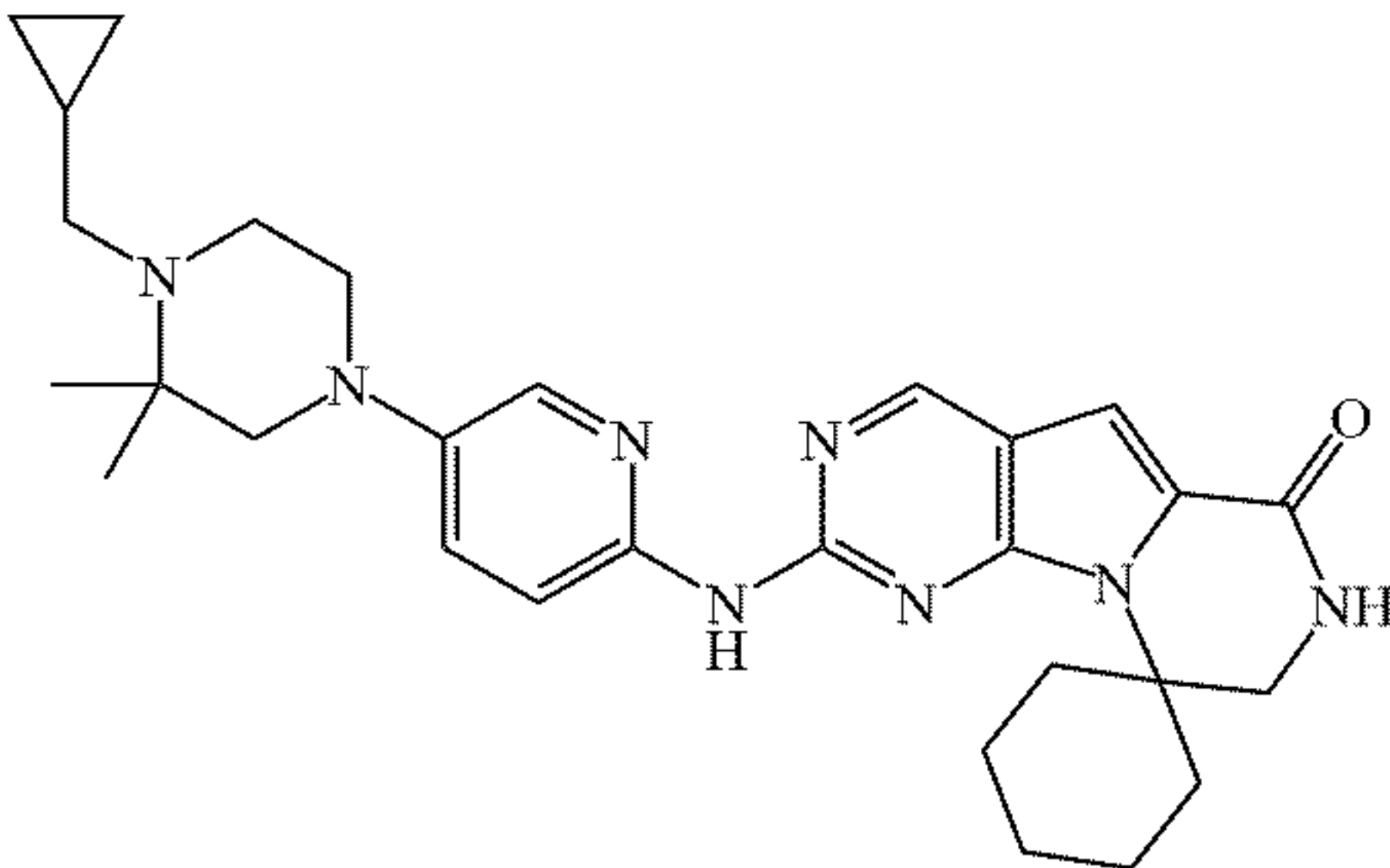
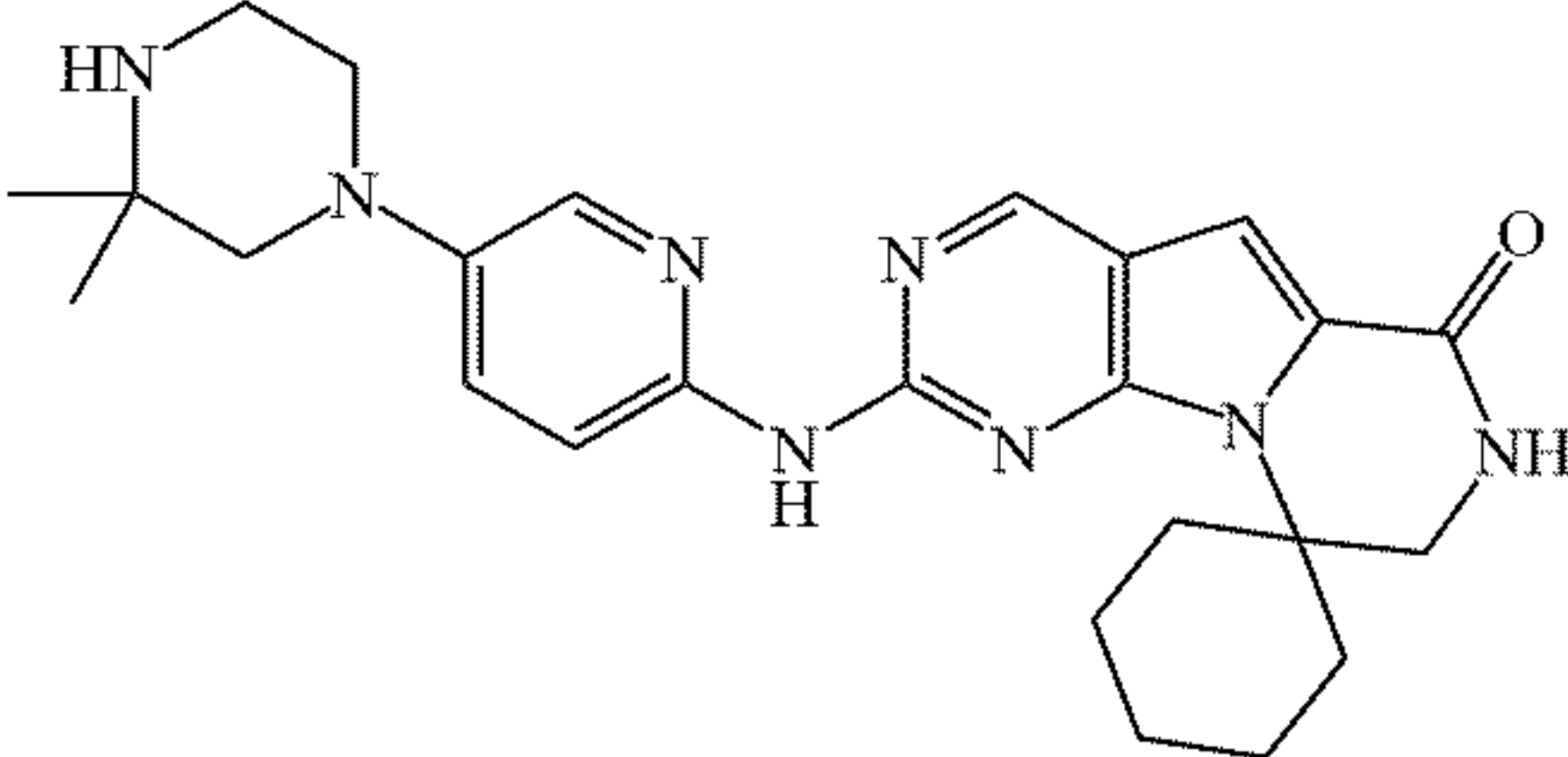
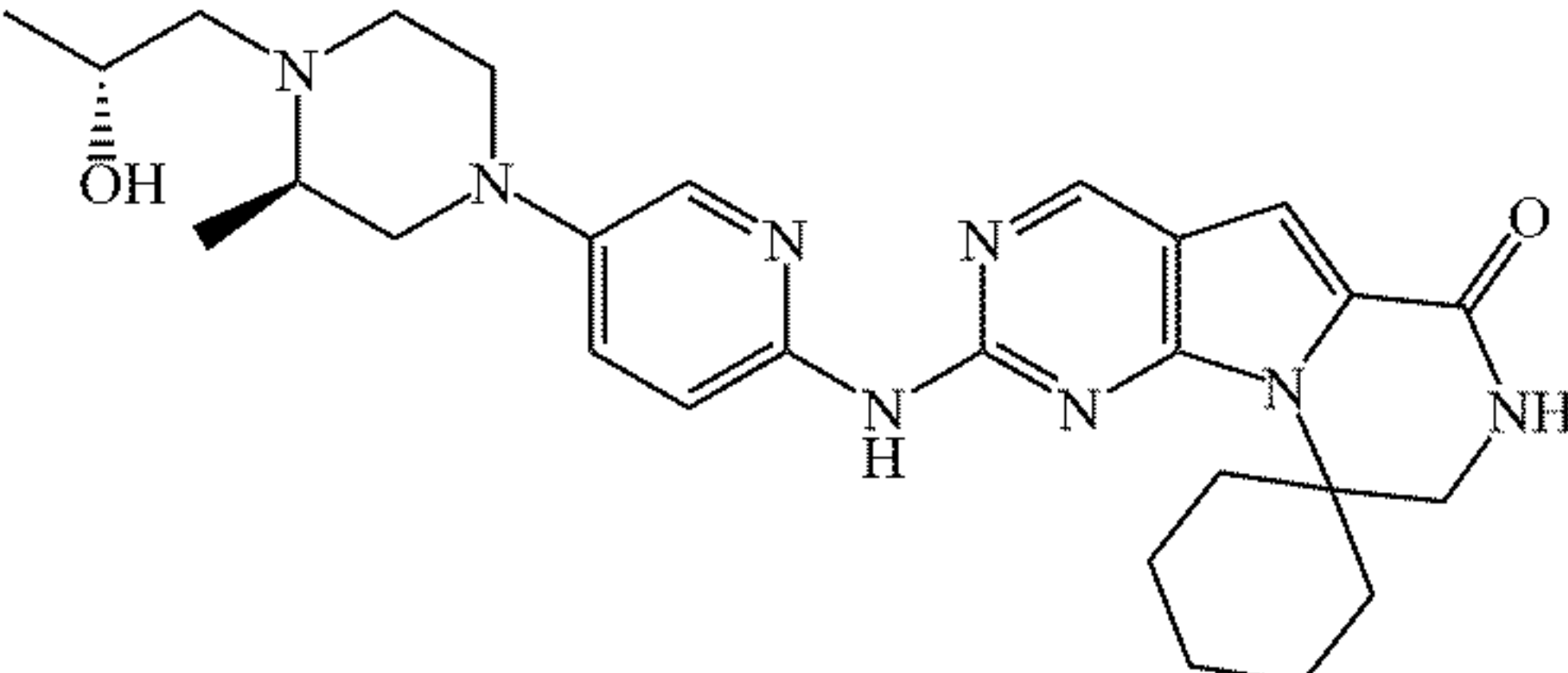
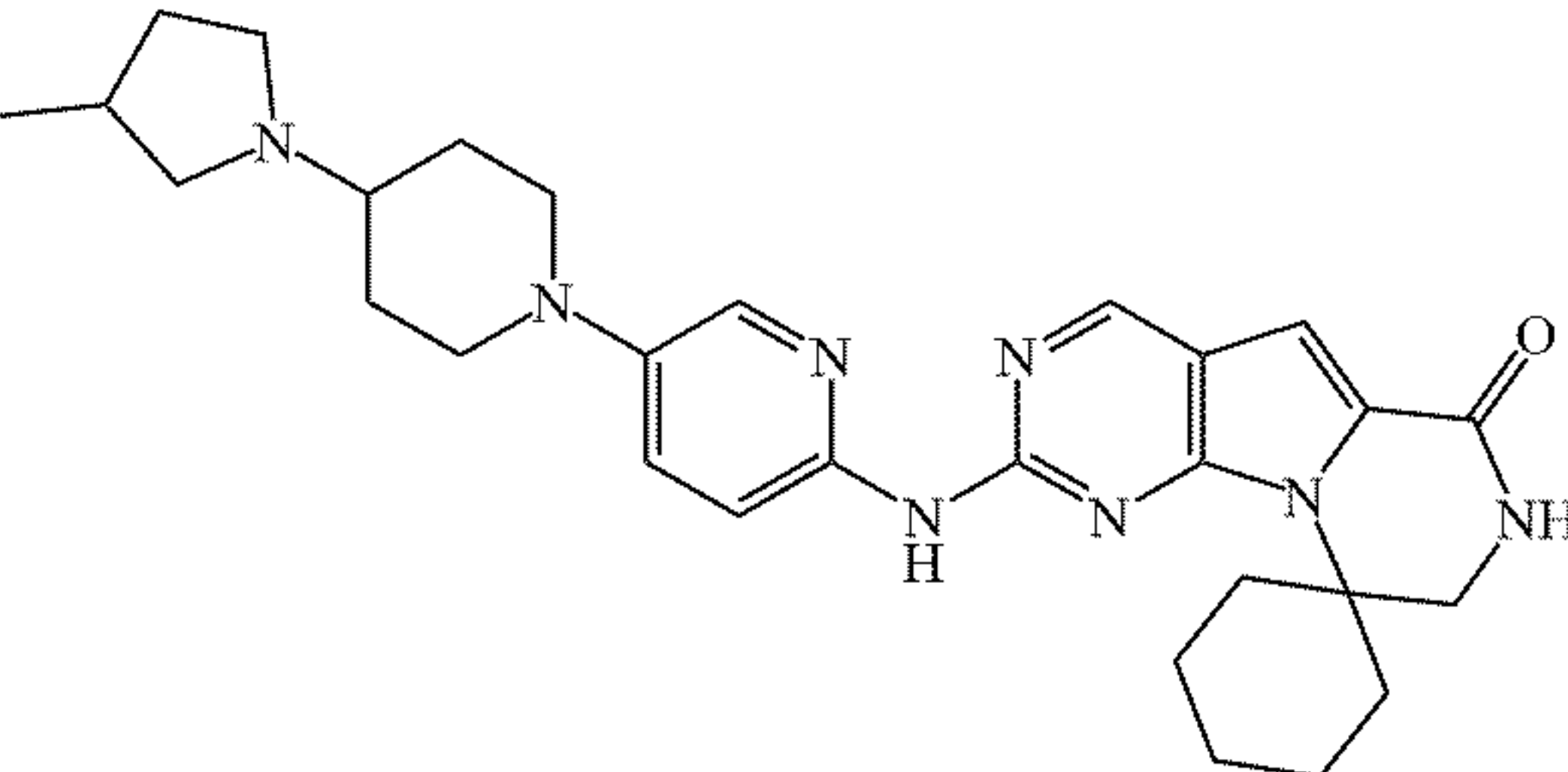
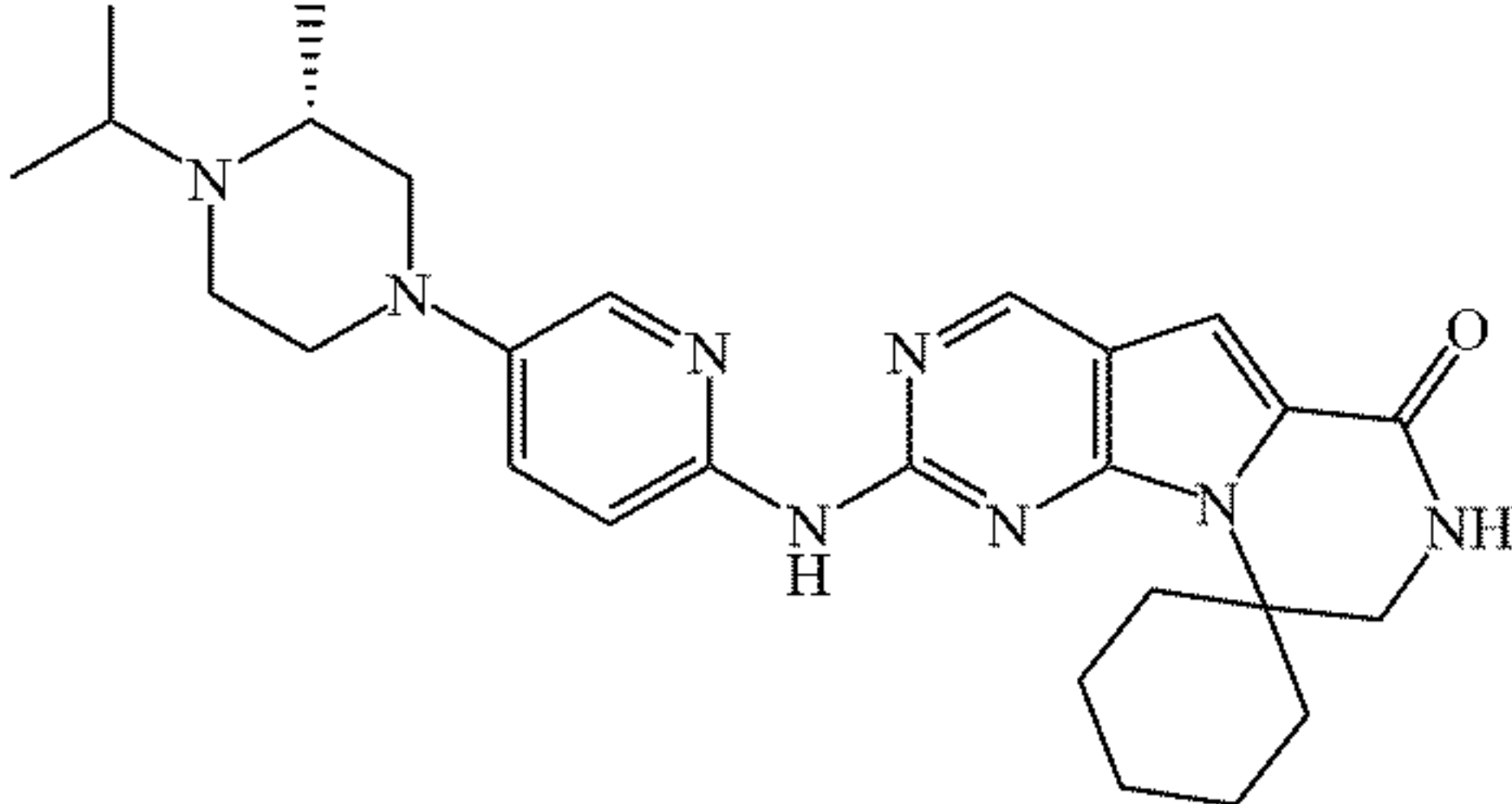
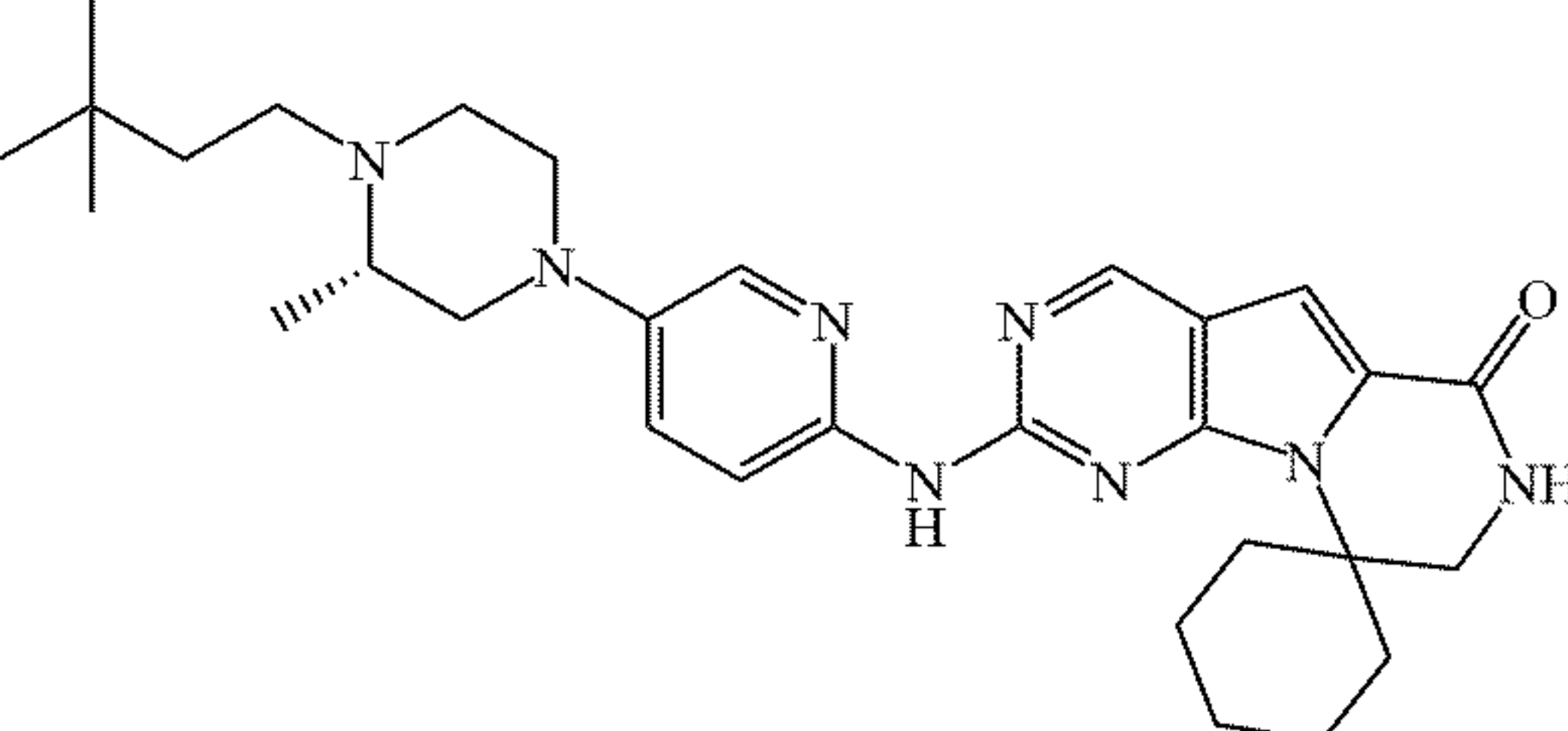
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
H	
I	
J	
K	
L	
M	

TABLE 1-continued

Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
N	
O	
P	
Q	
R	
S	

TABLE 1-continued

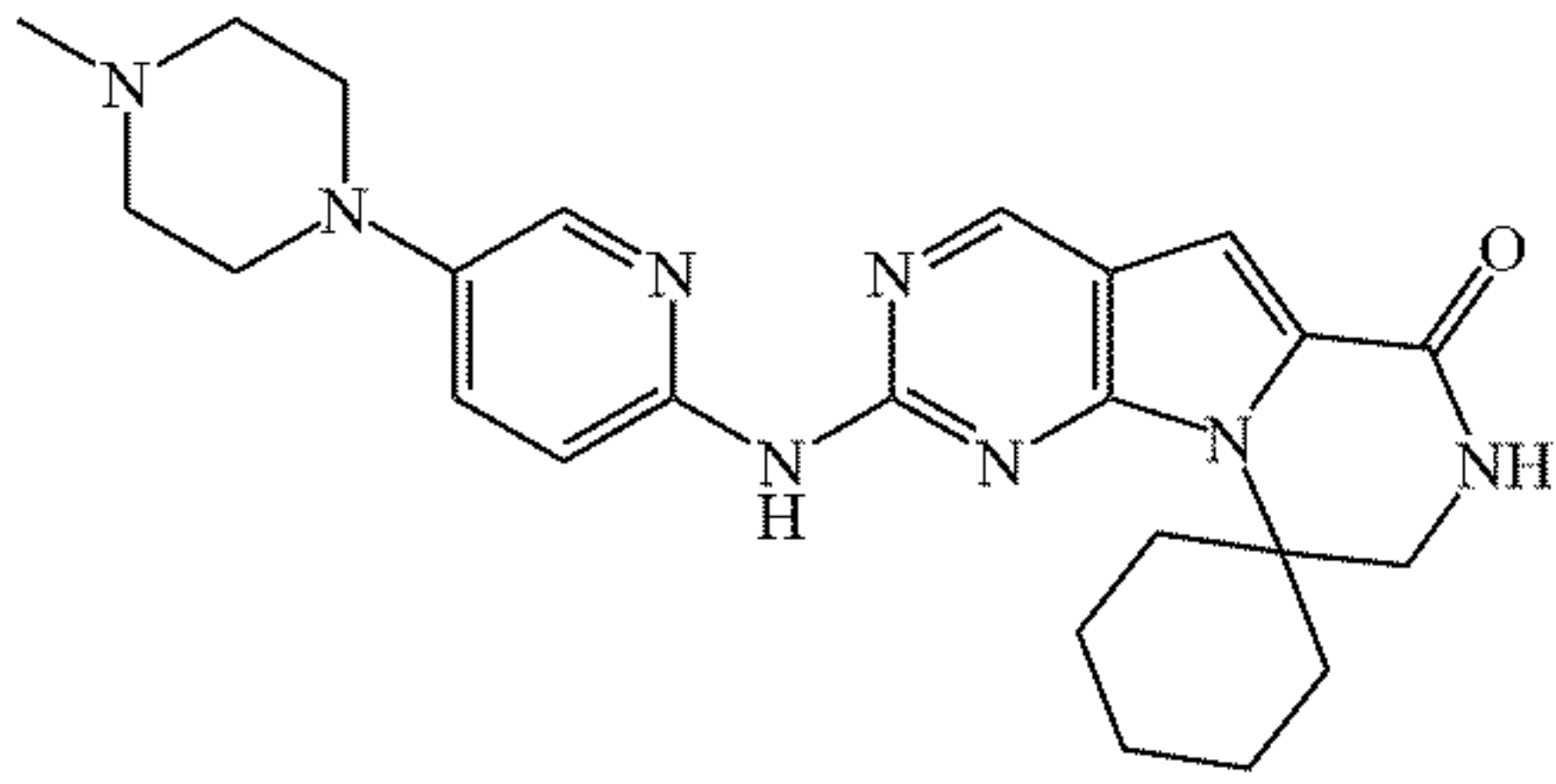
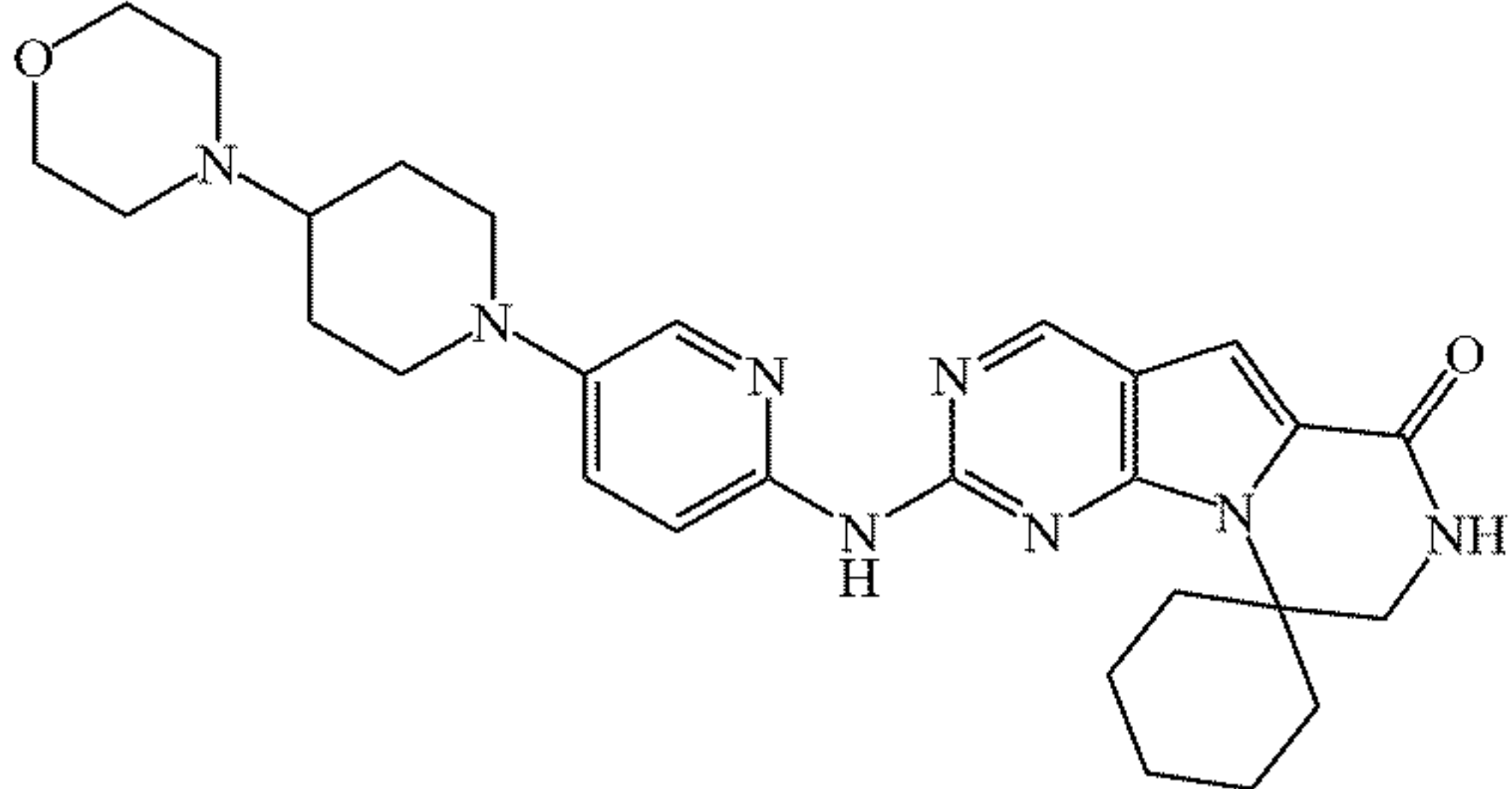
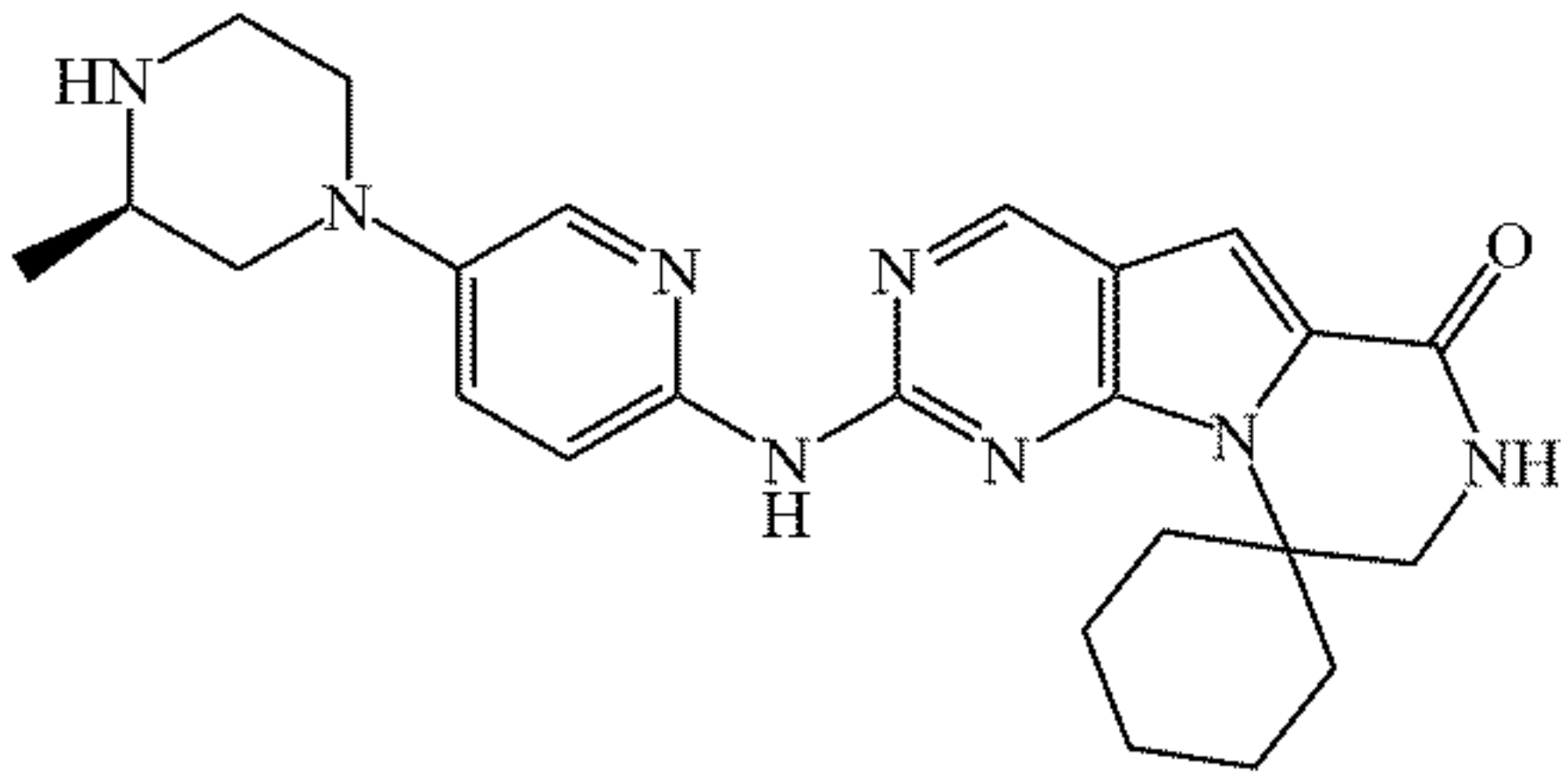
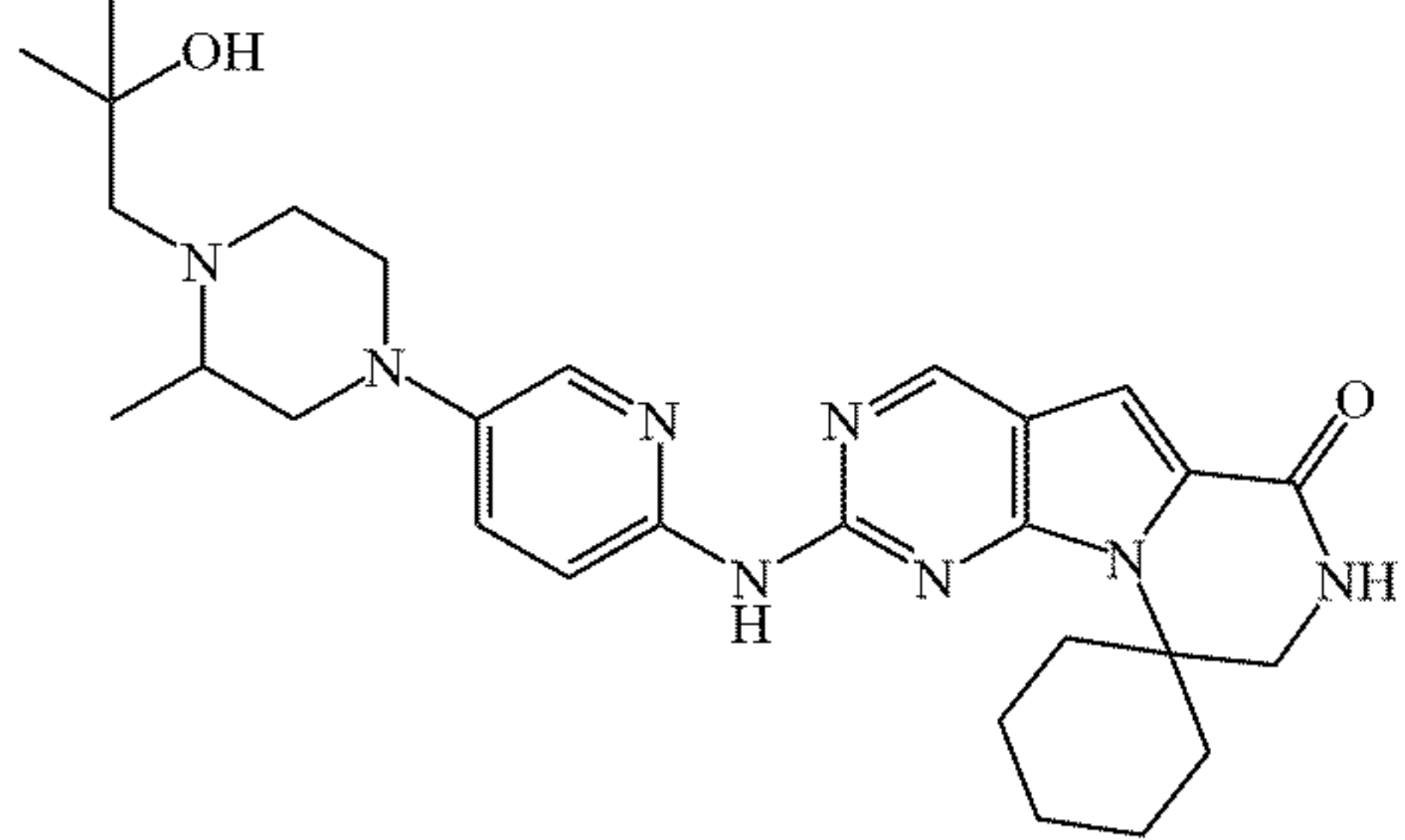
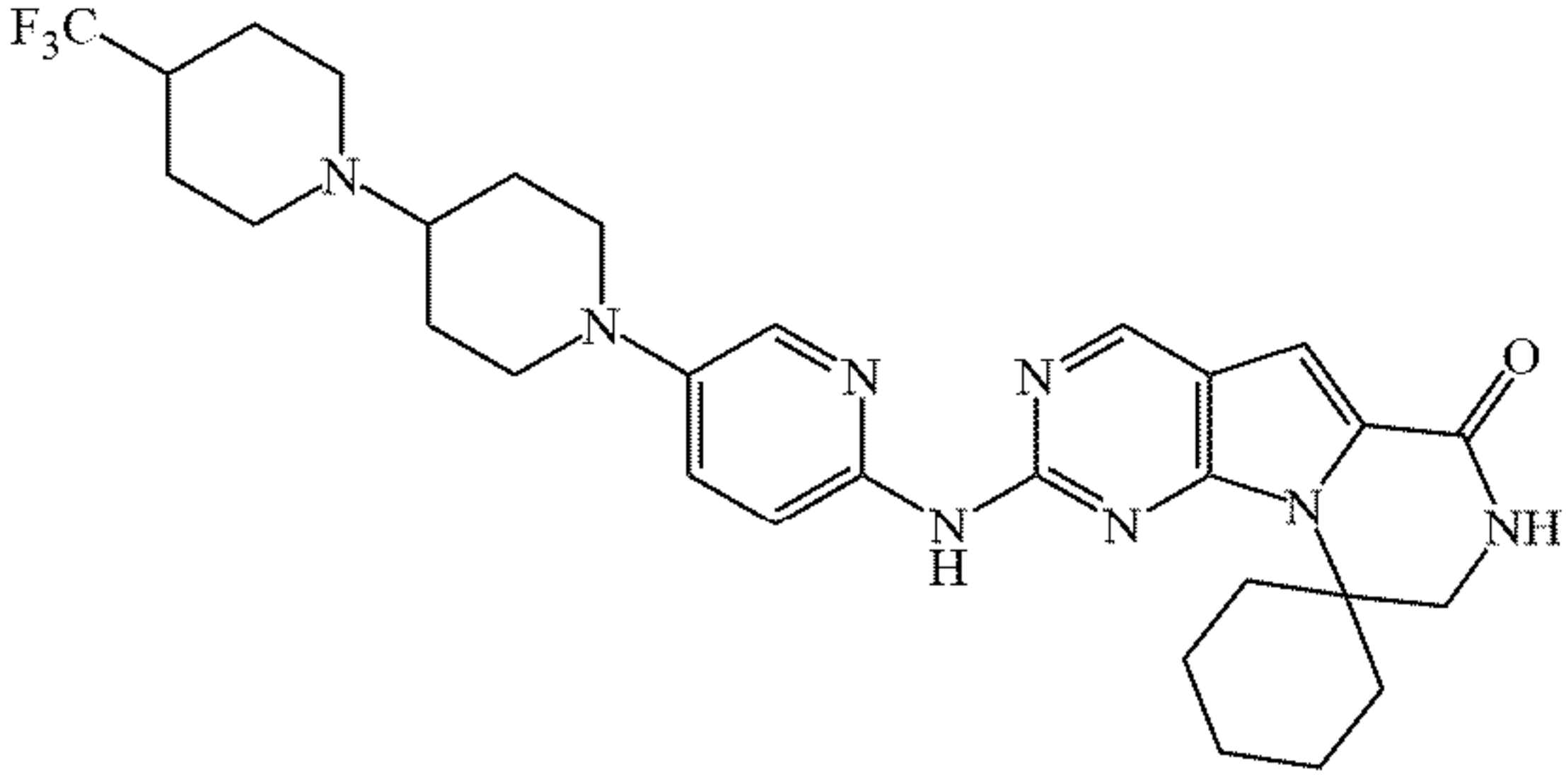
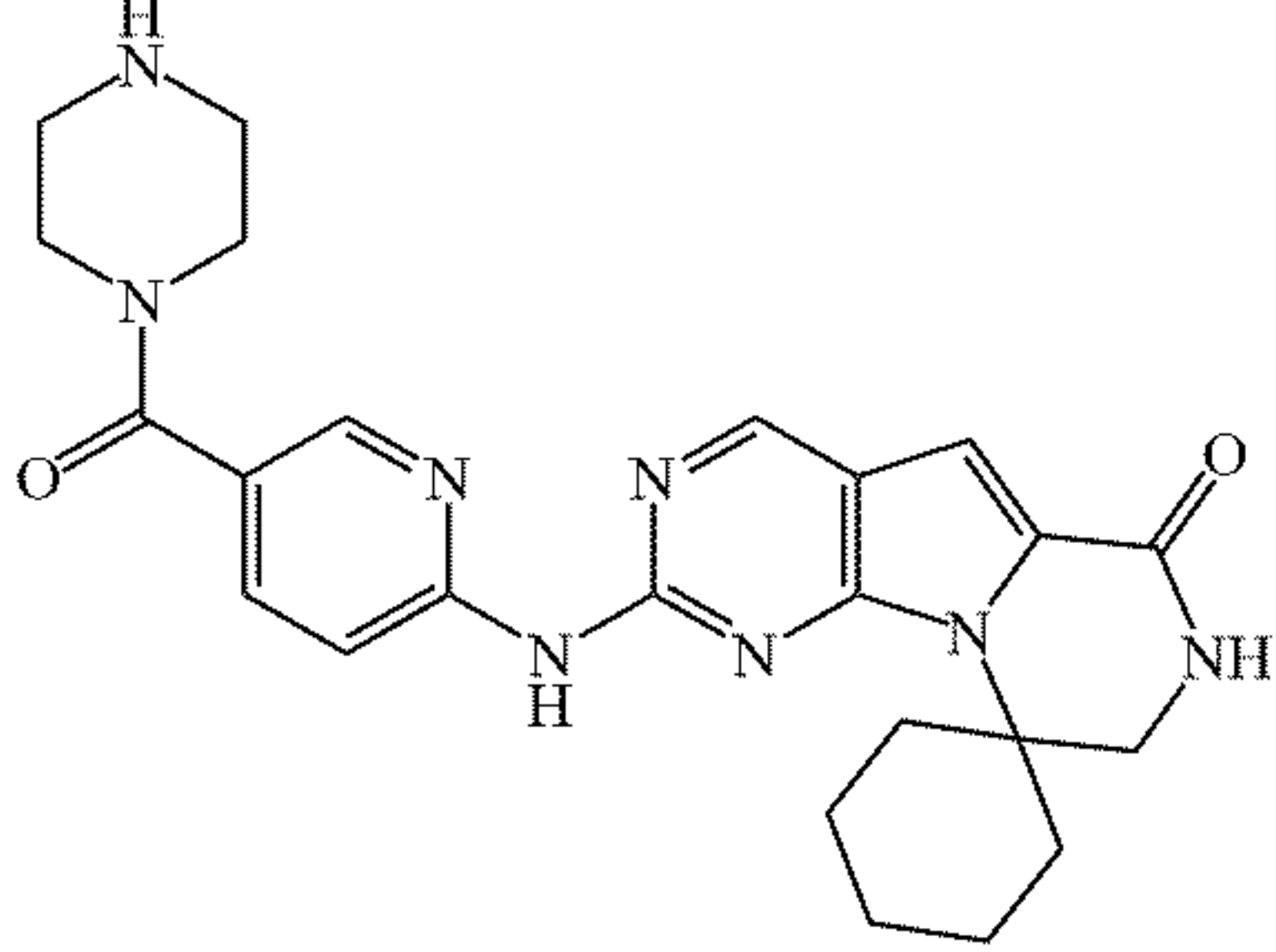
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
T	
U	
V	
W	
X	
Y	

TABLE 1-continued

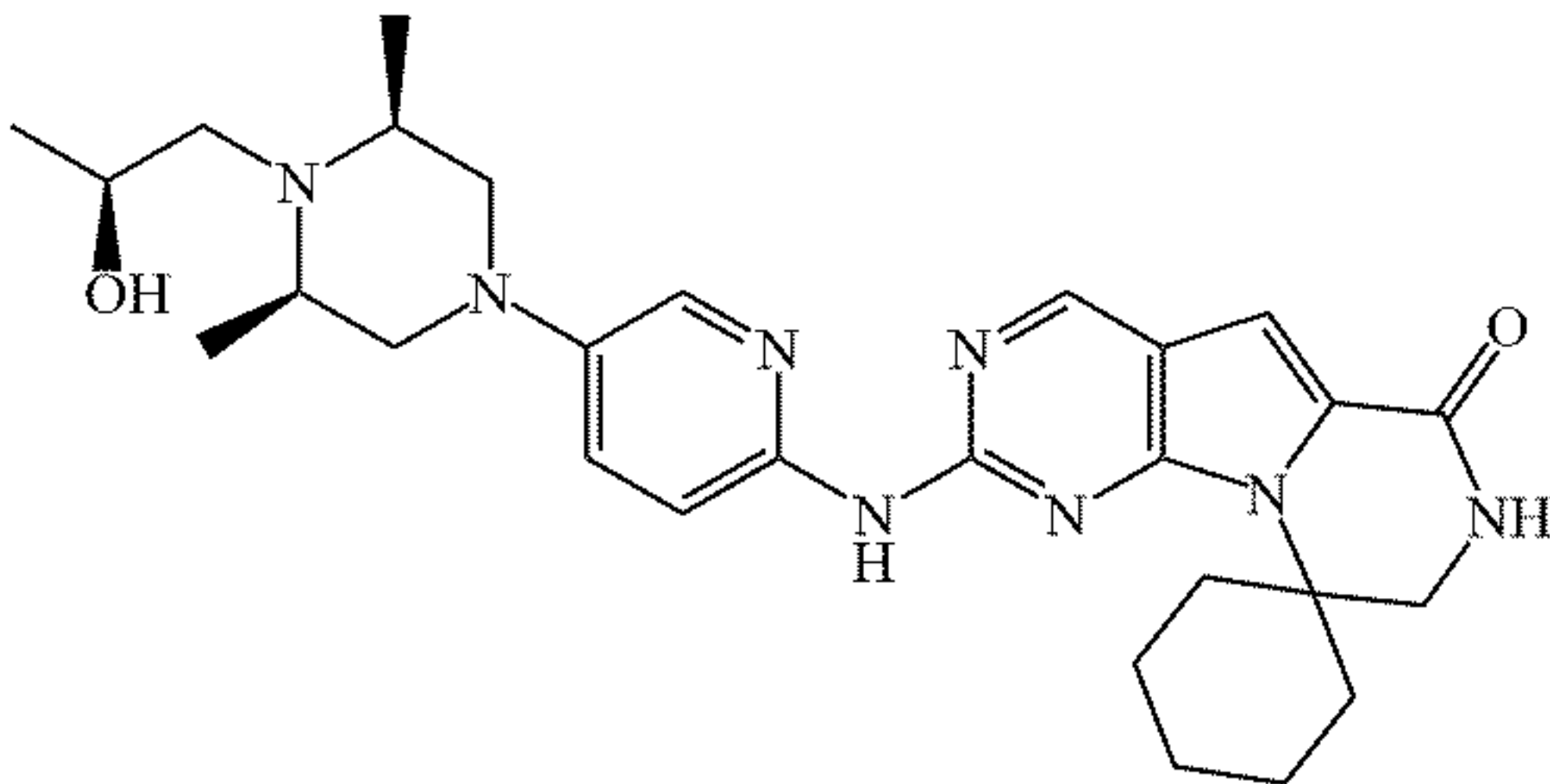
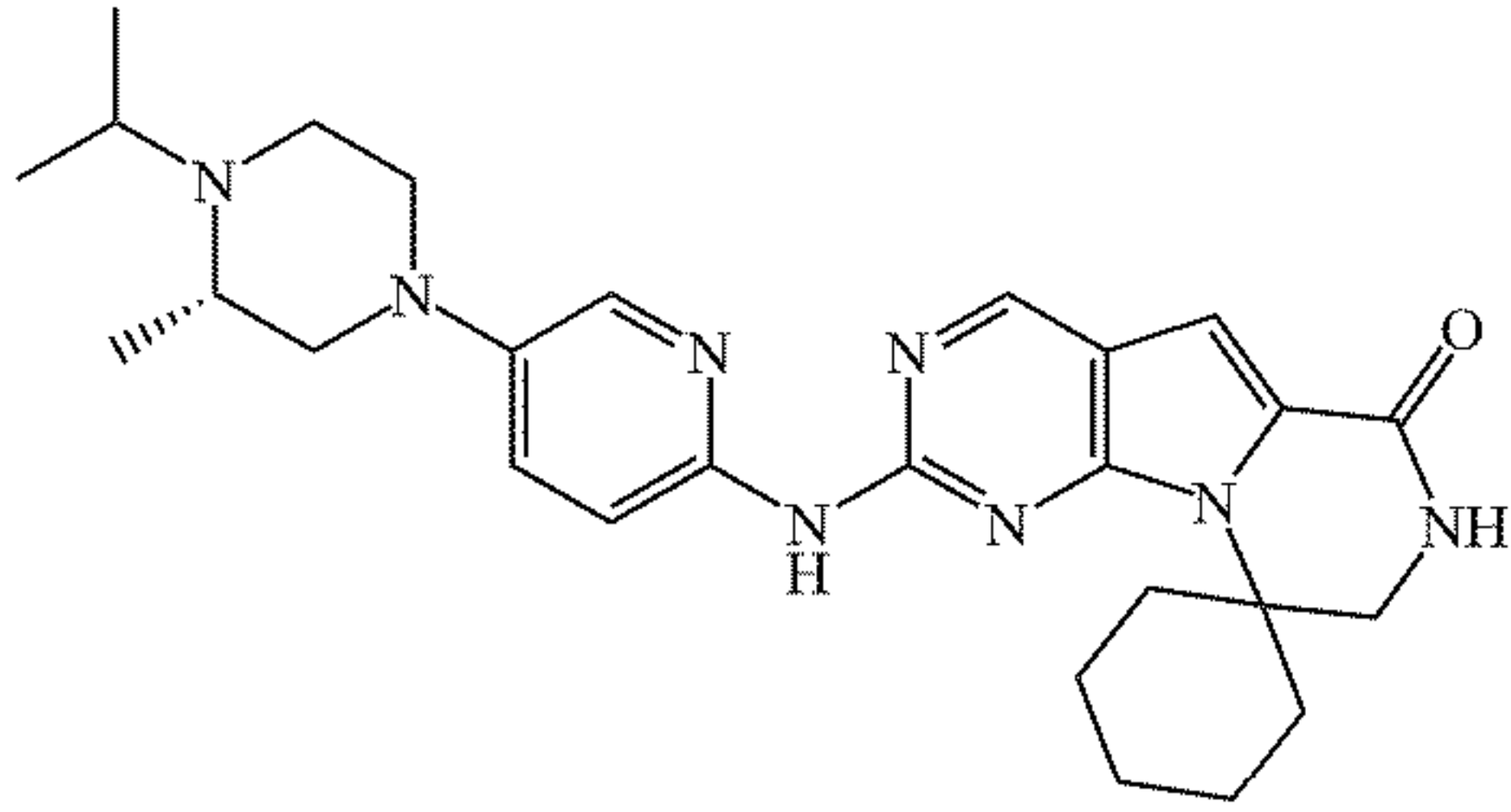
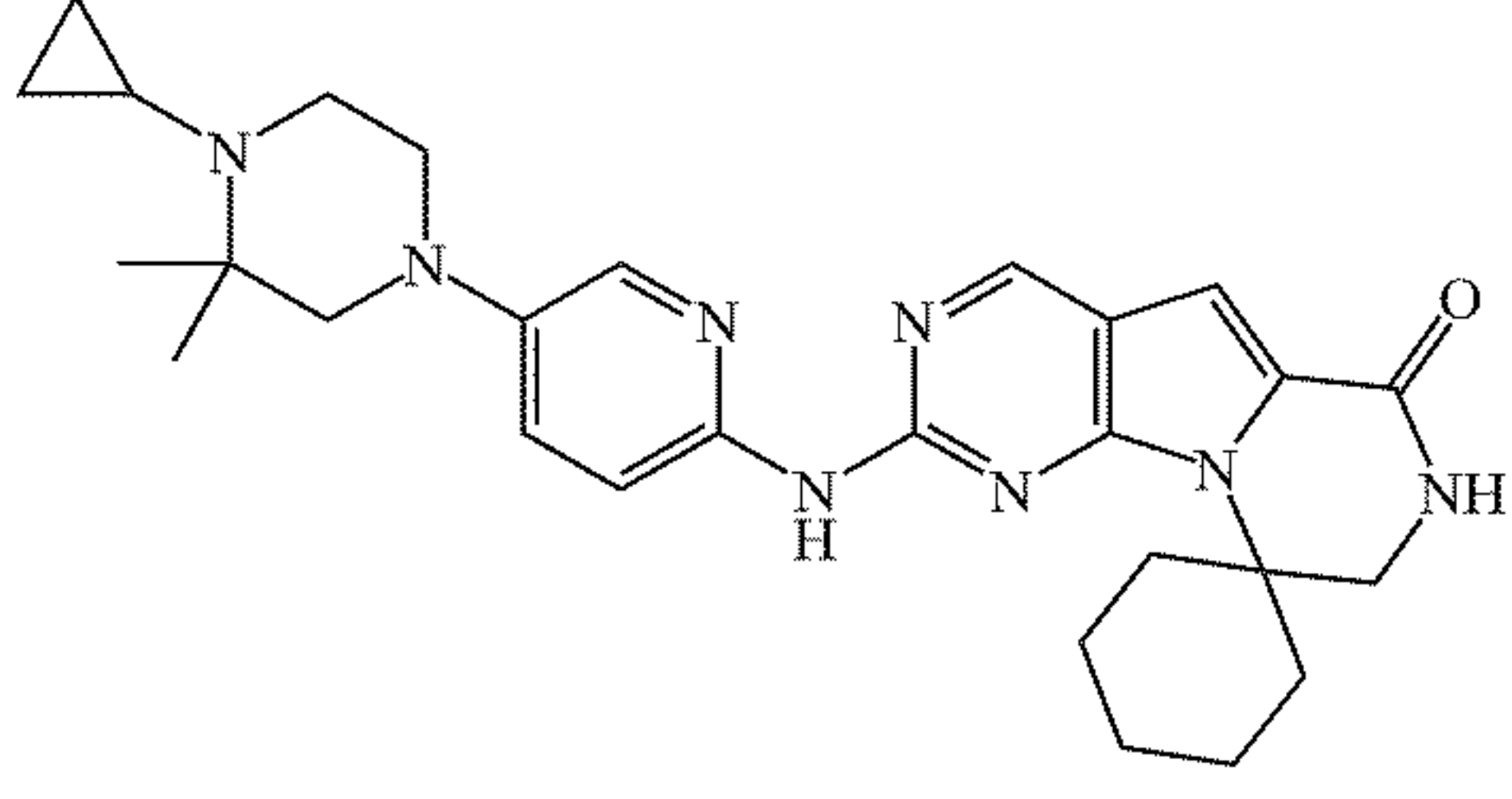
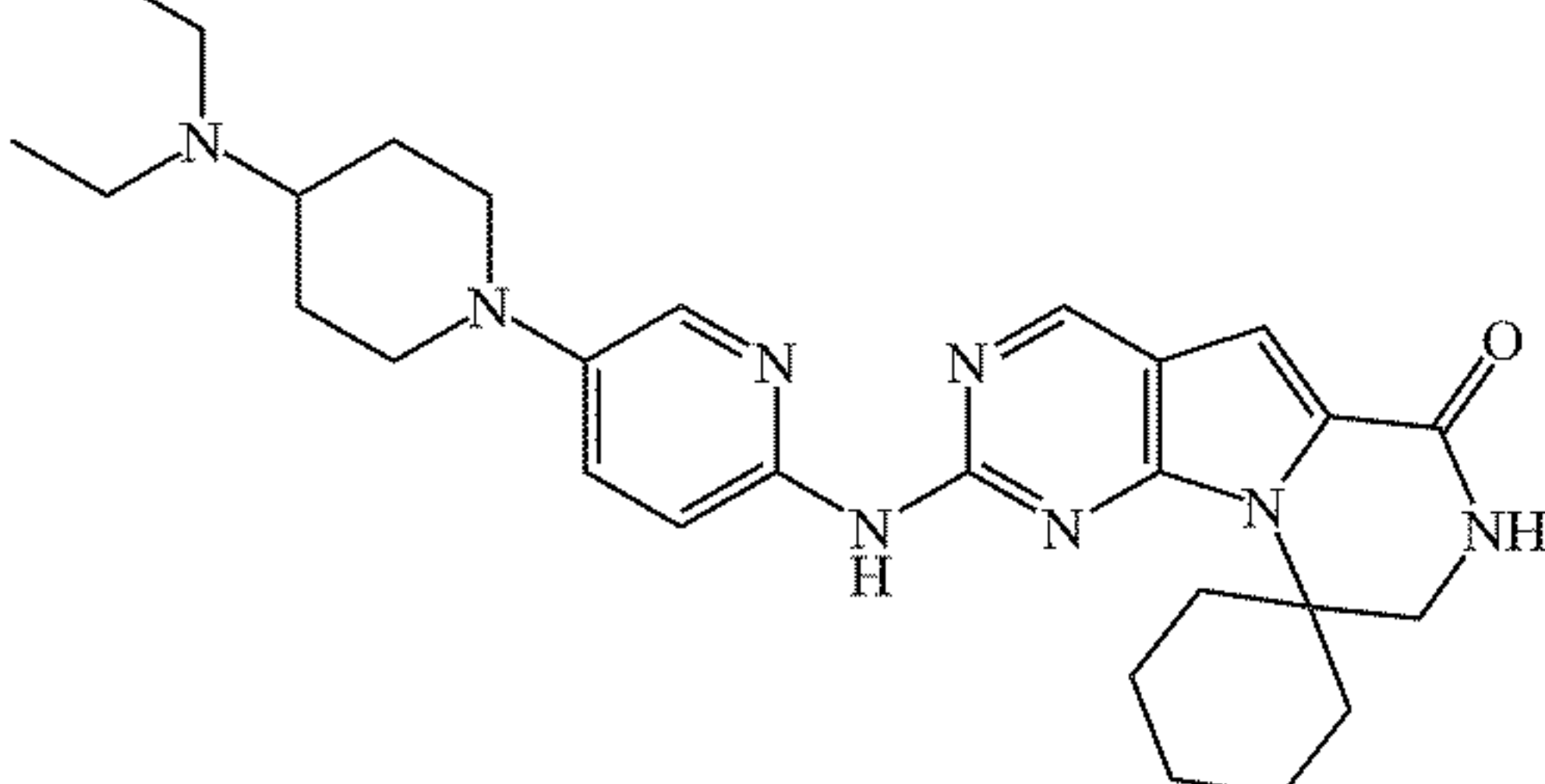
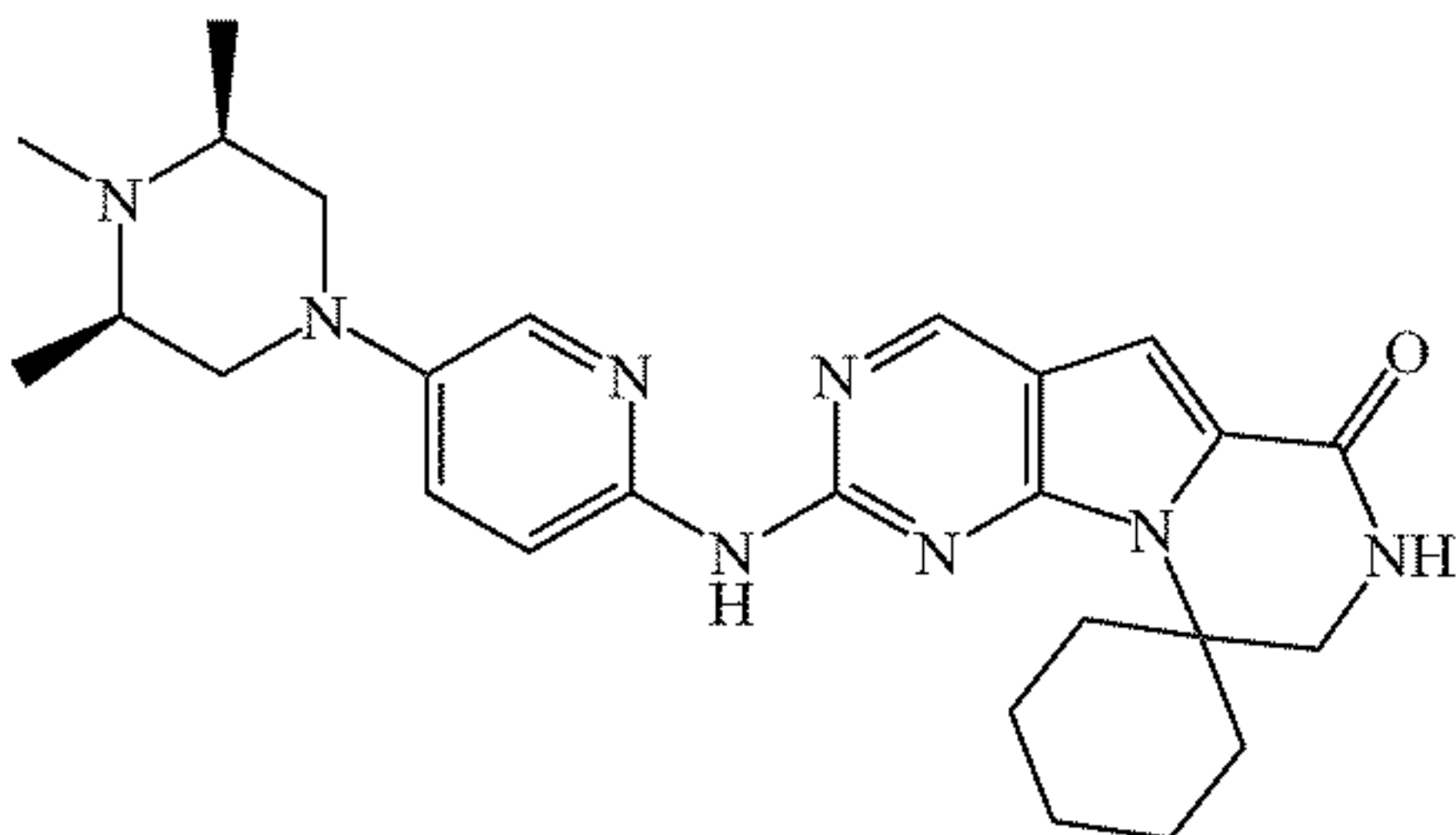
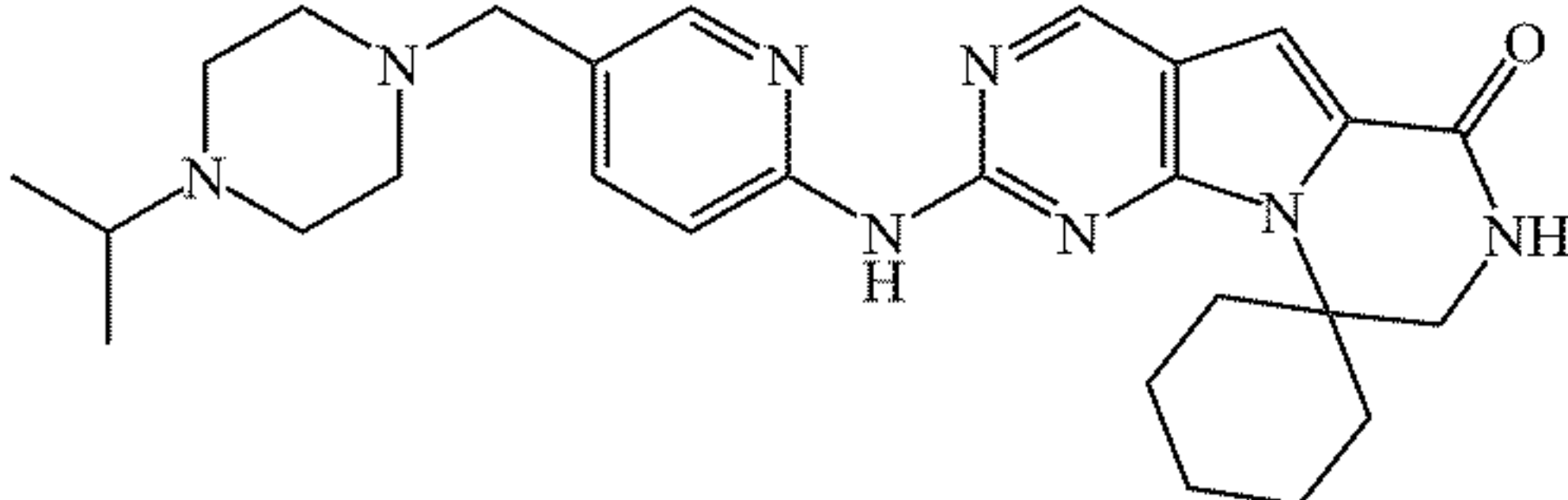
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
Z	
AA	
BB	
CC	
DD	
EE	

TABLE 1-continued

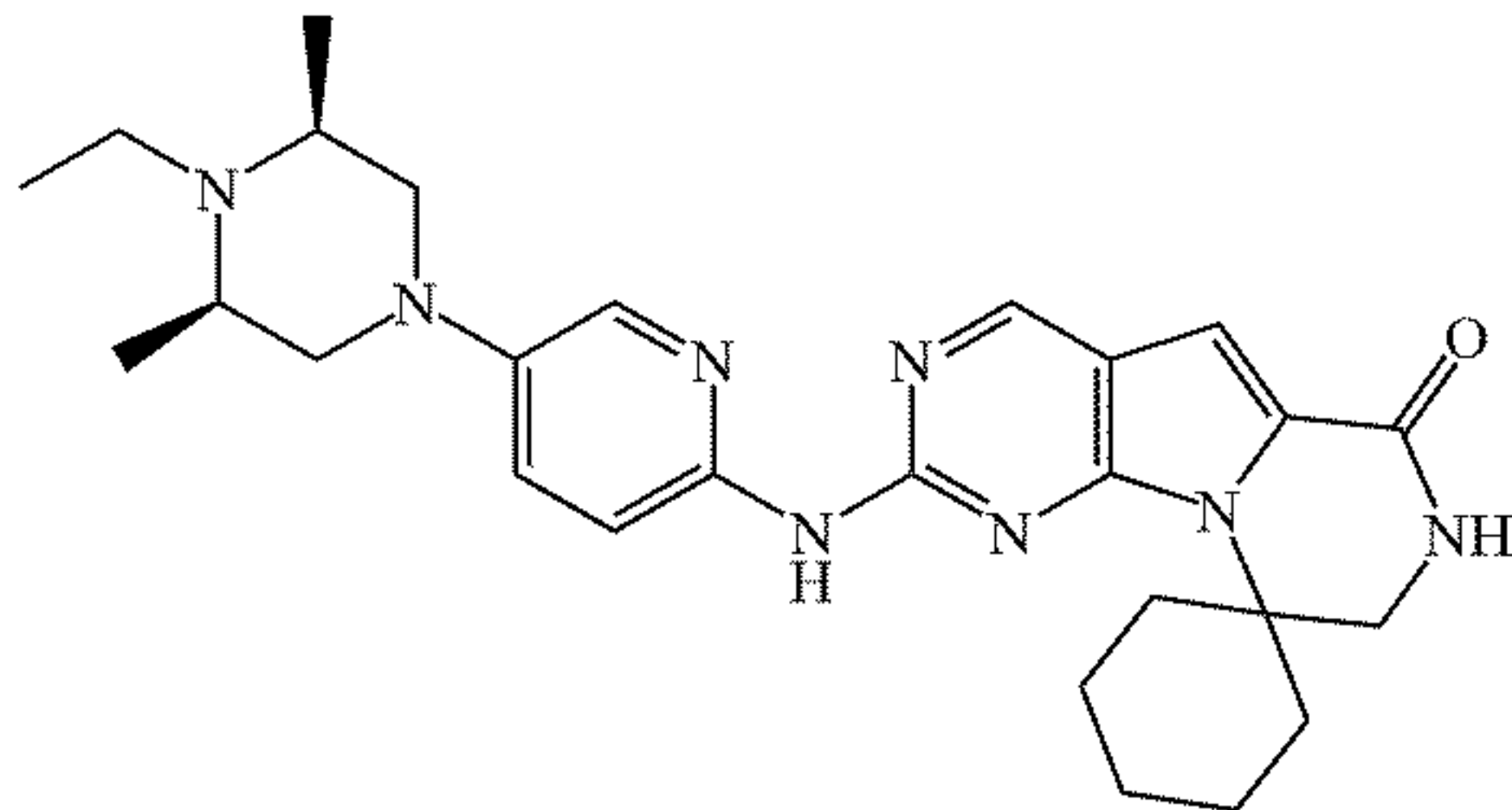
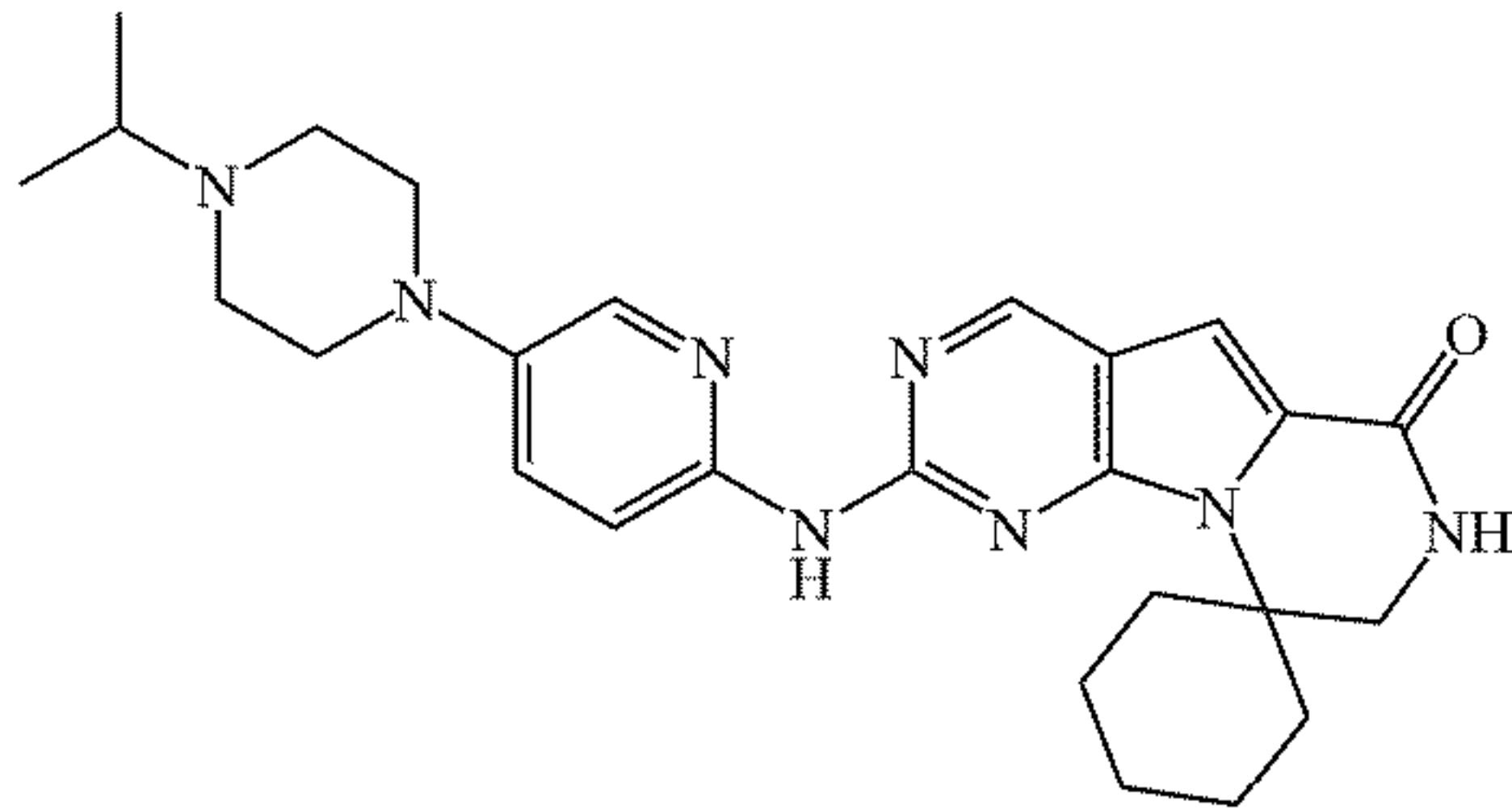
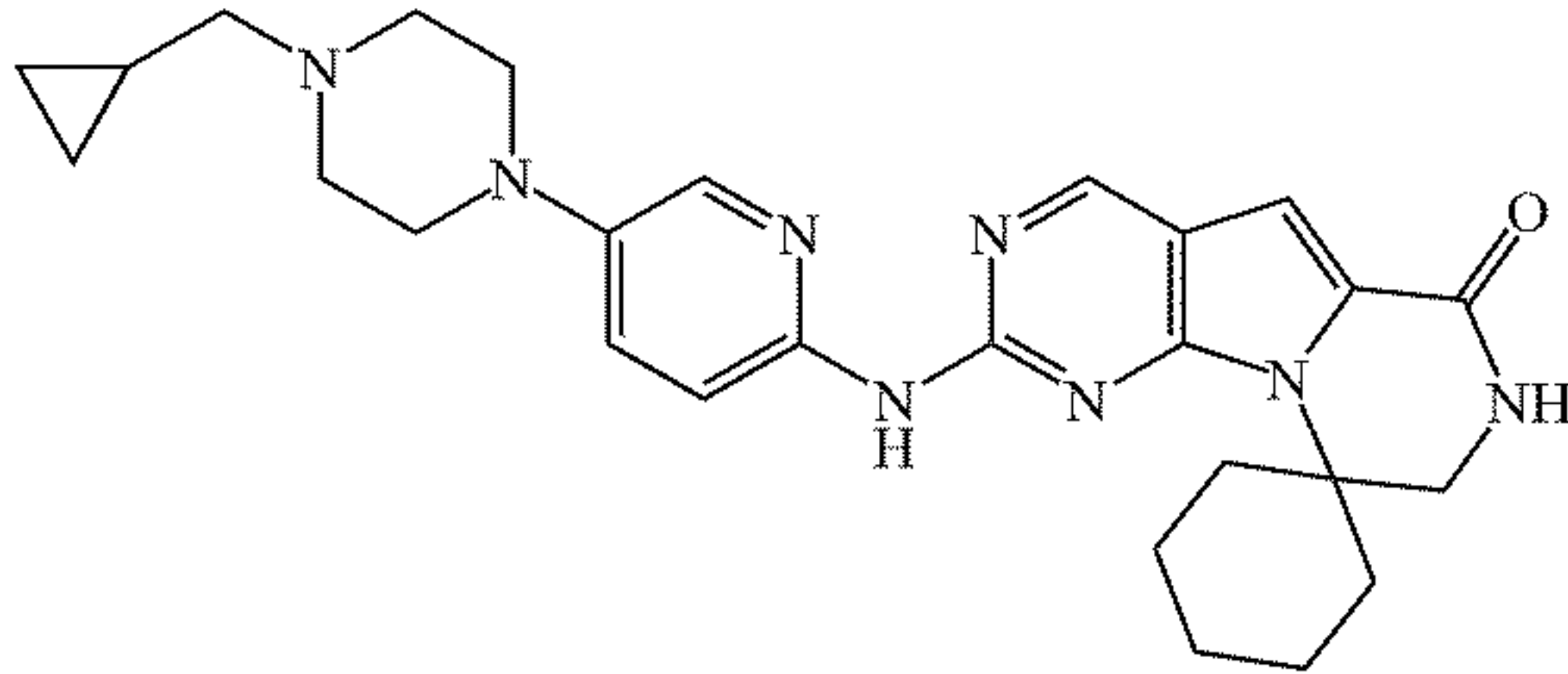
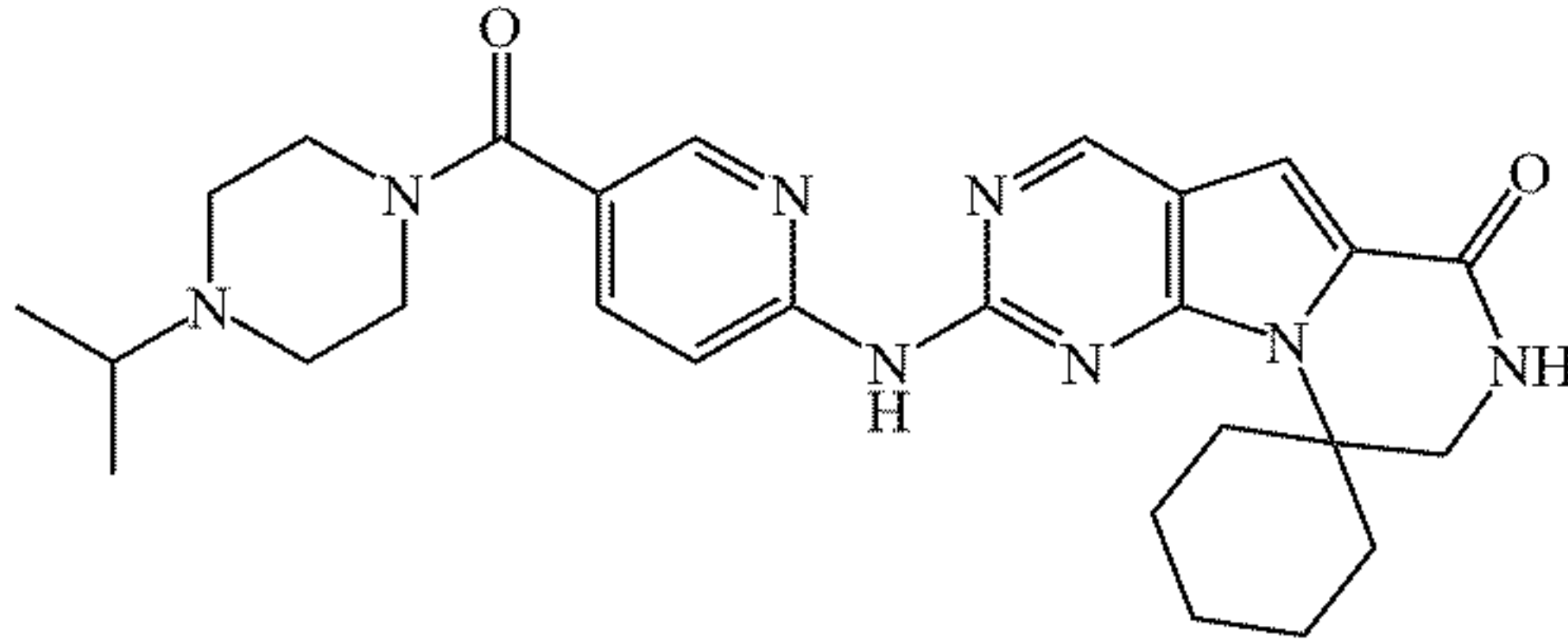
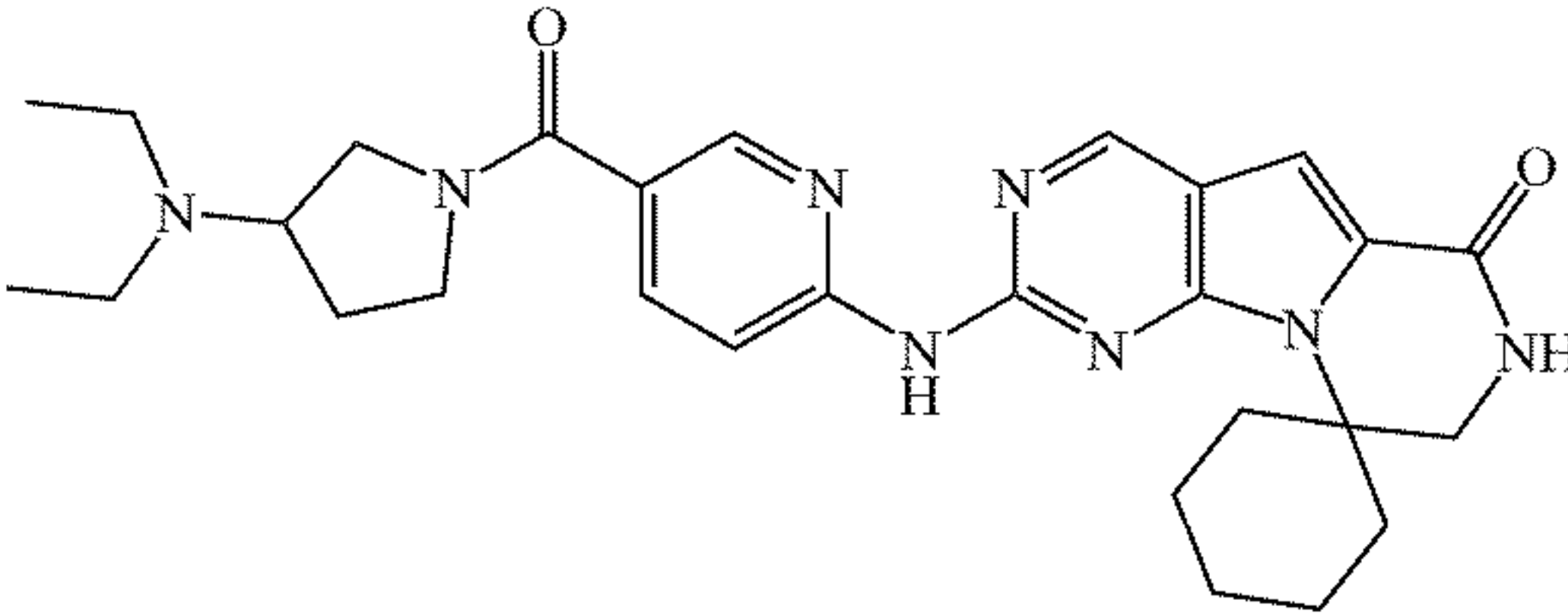
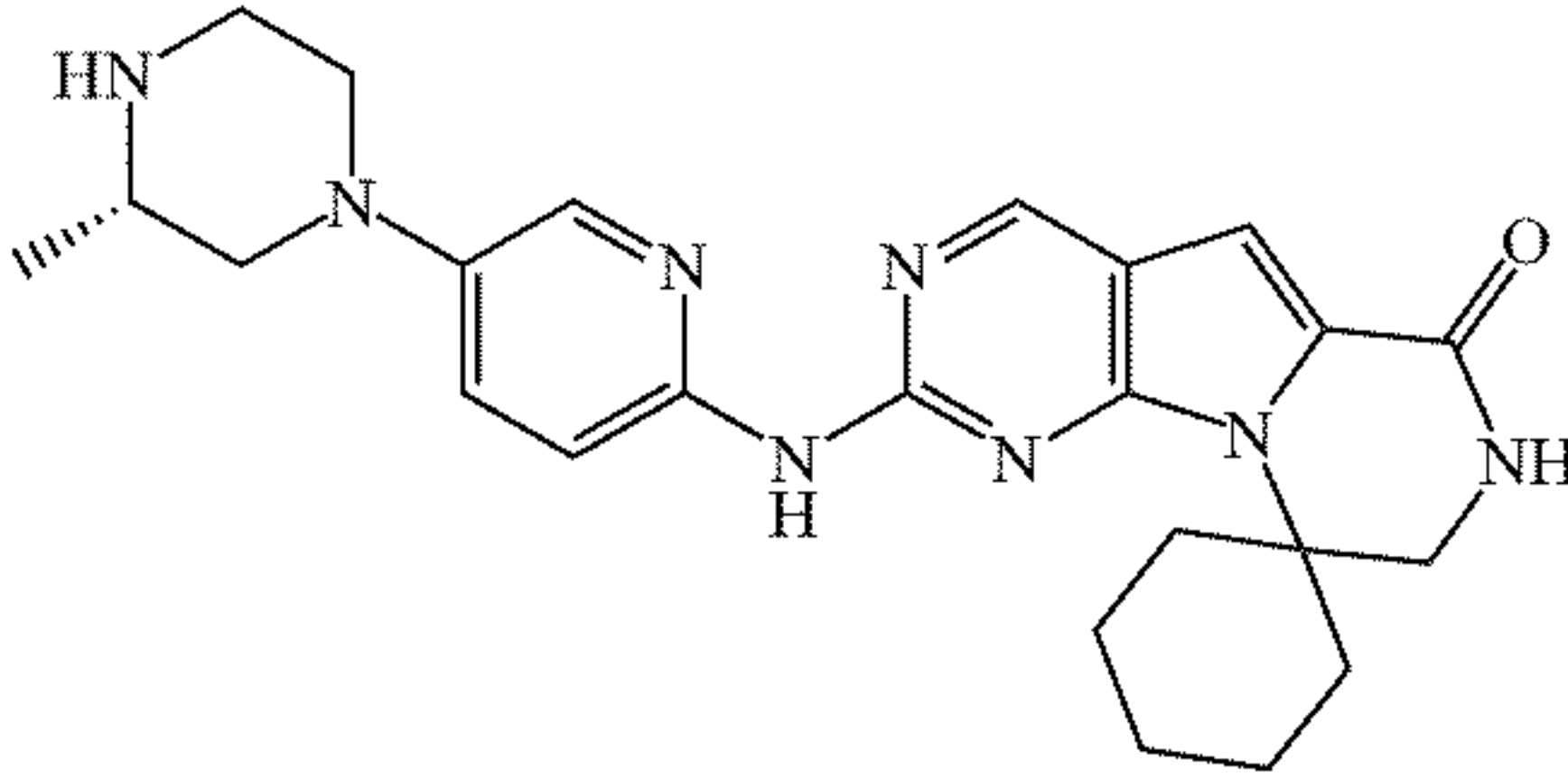
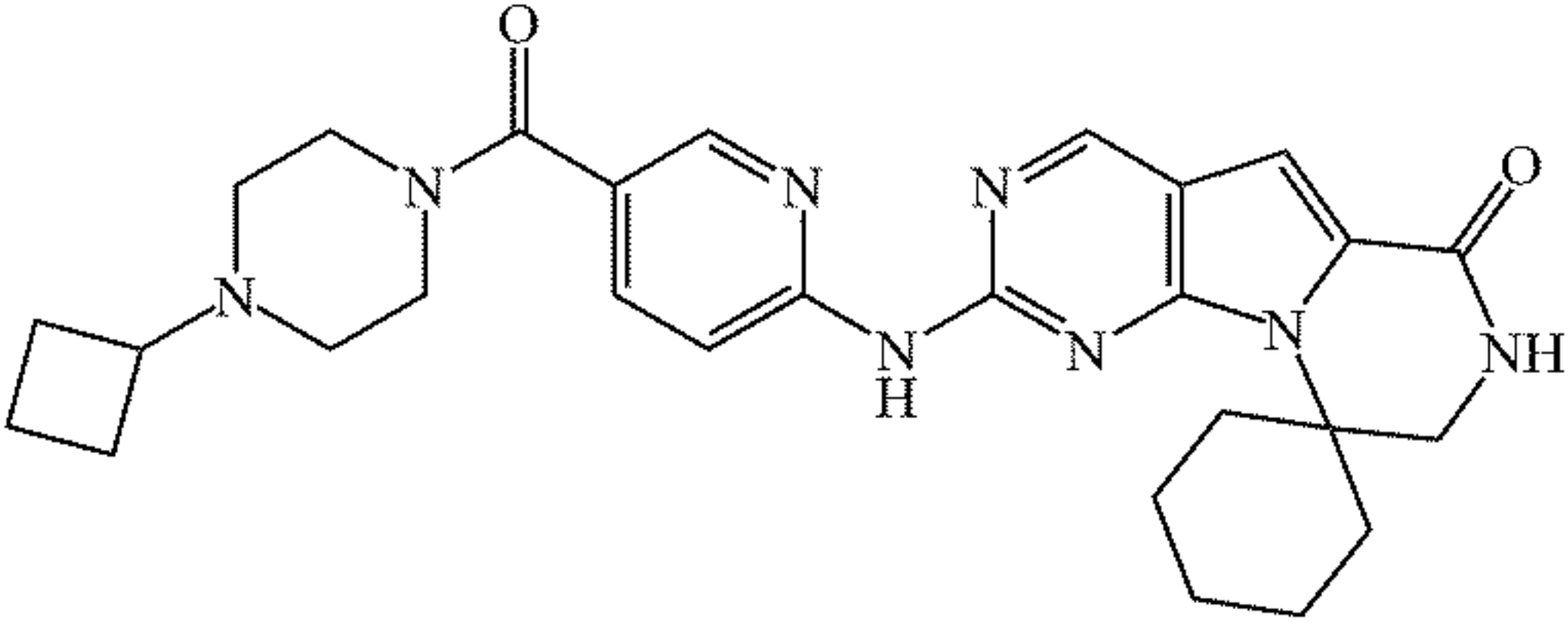
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
FF	
GG	
HH	
II	
JJ	
KK	
LL	

TABLE 1-continued

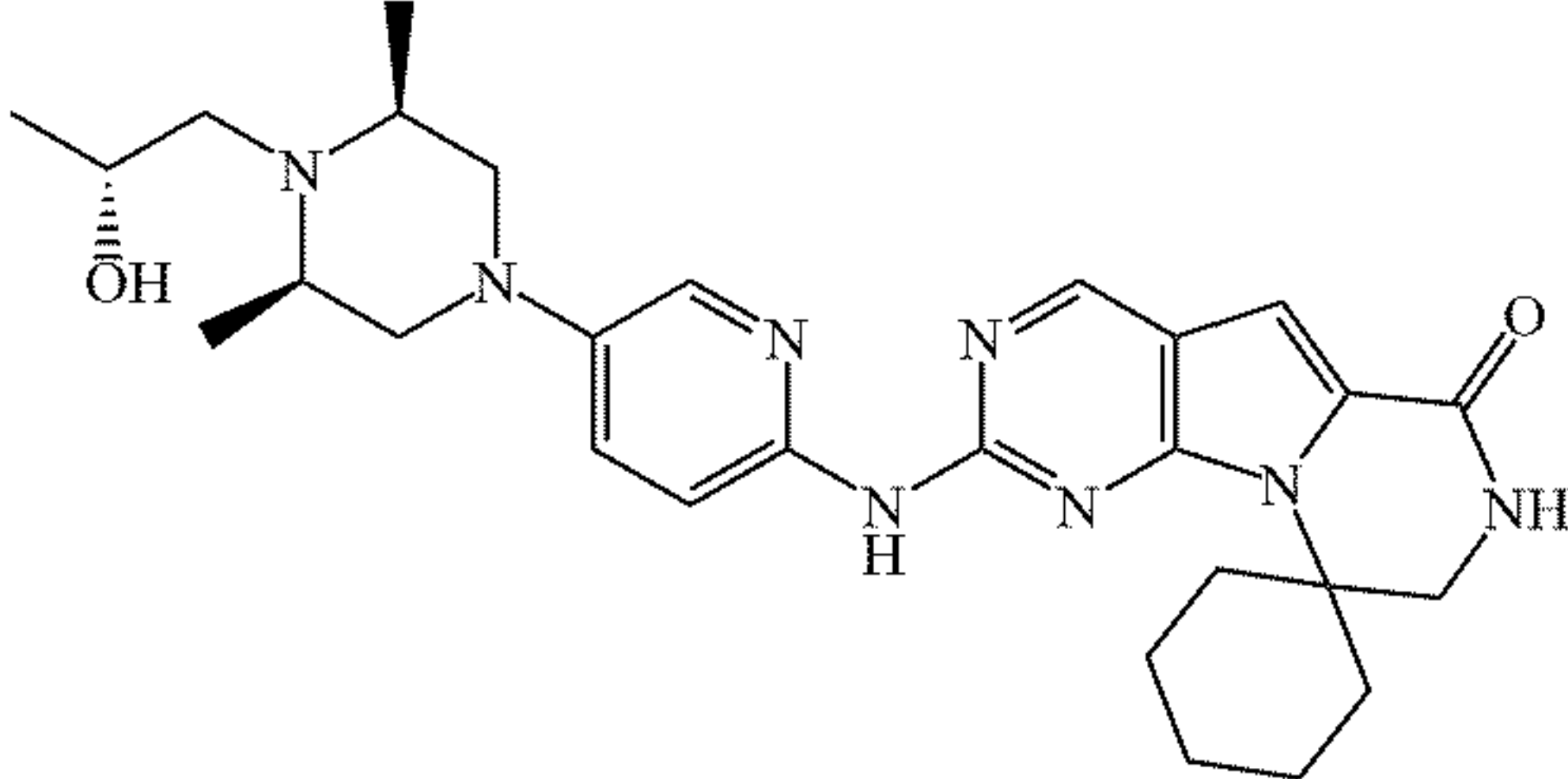
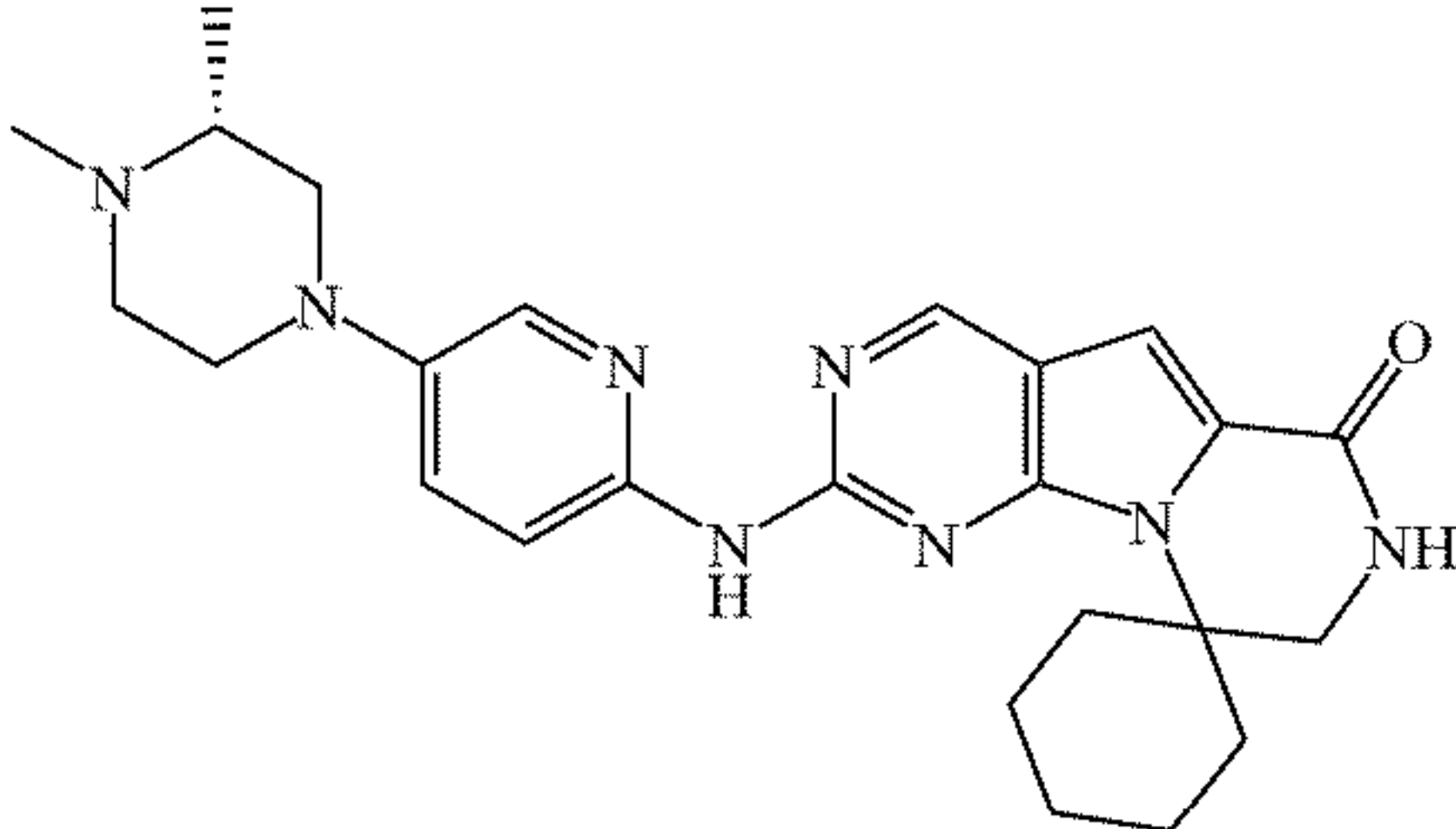
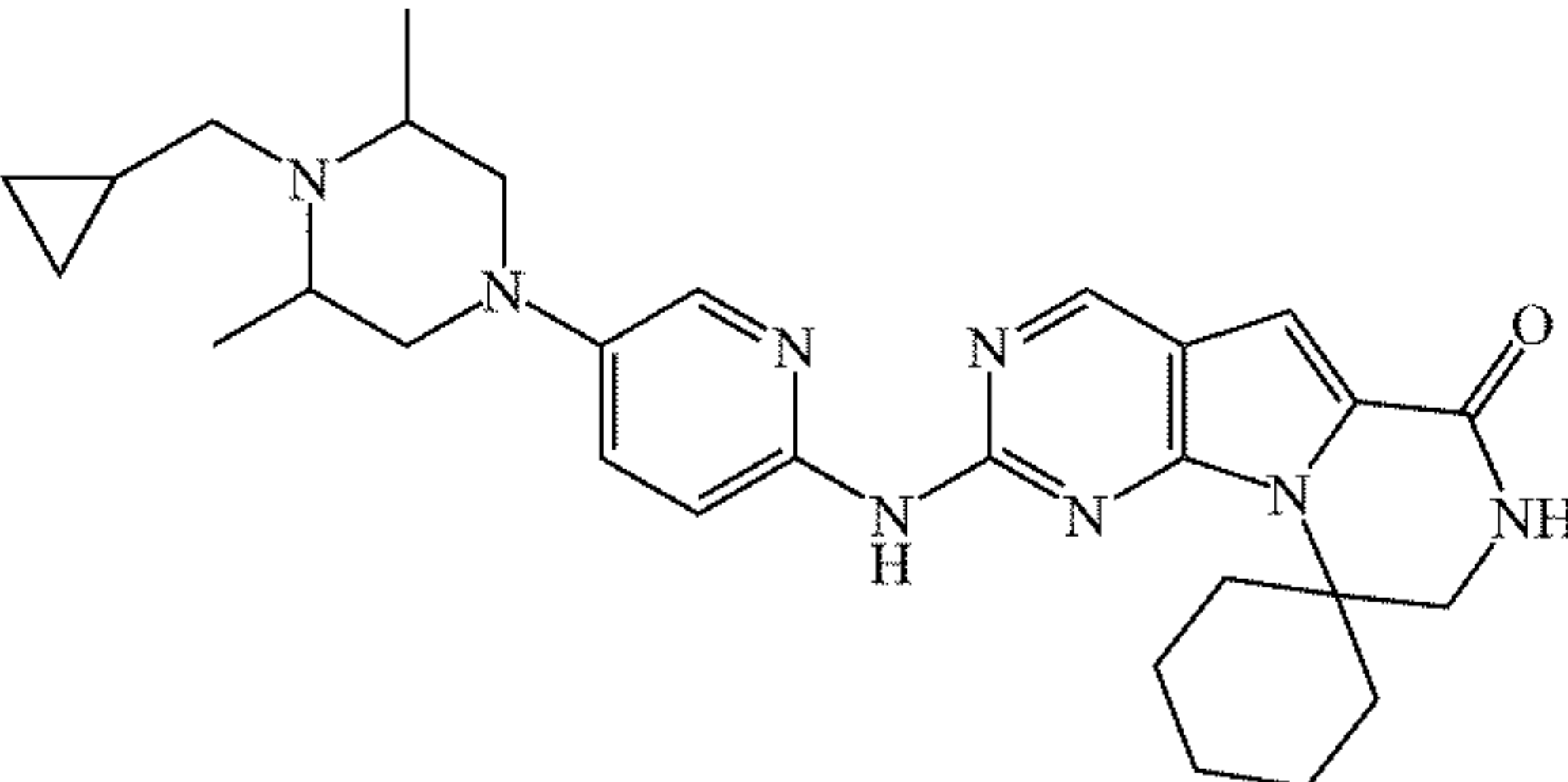
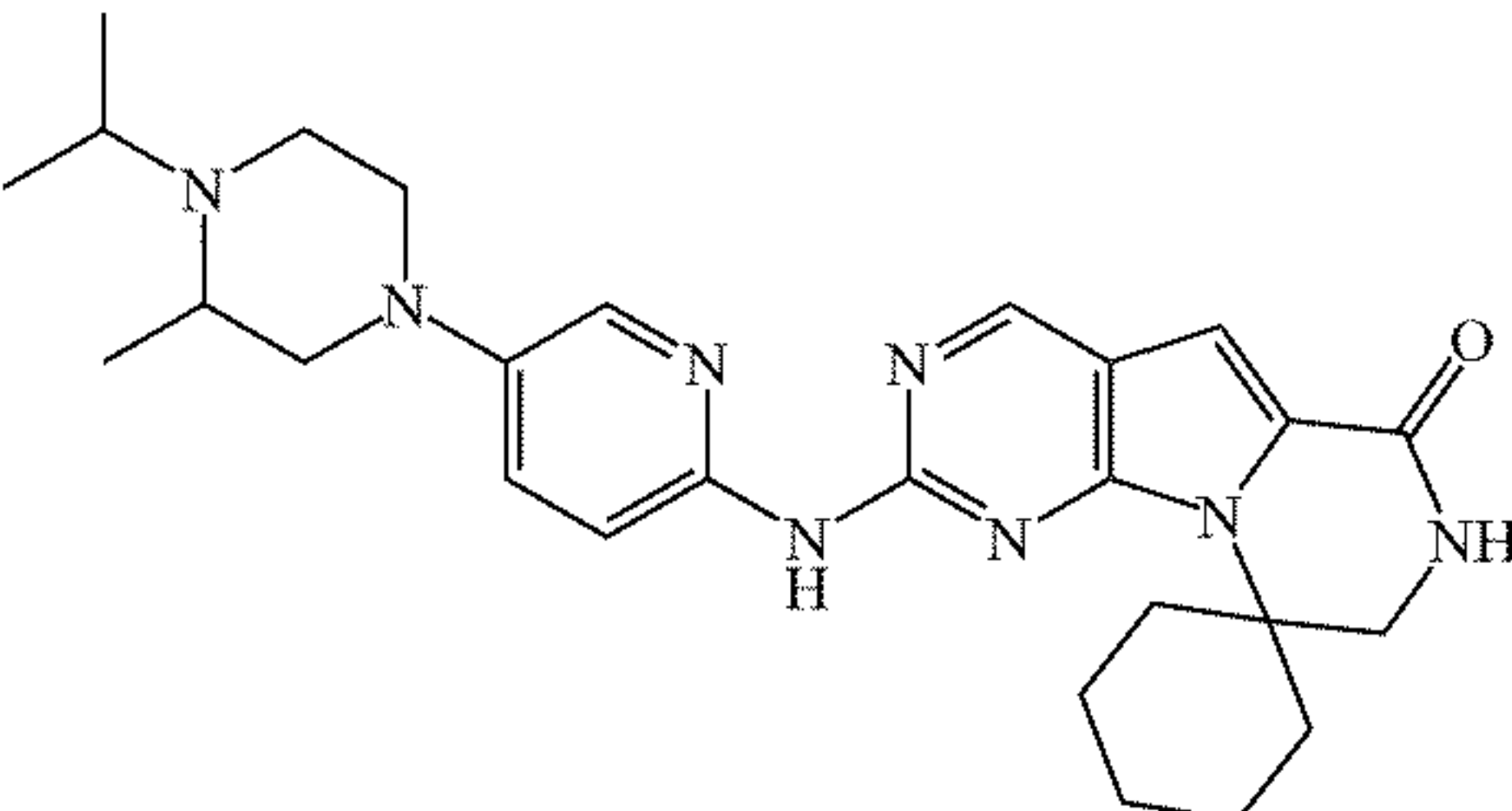
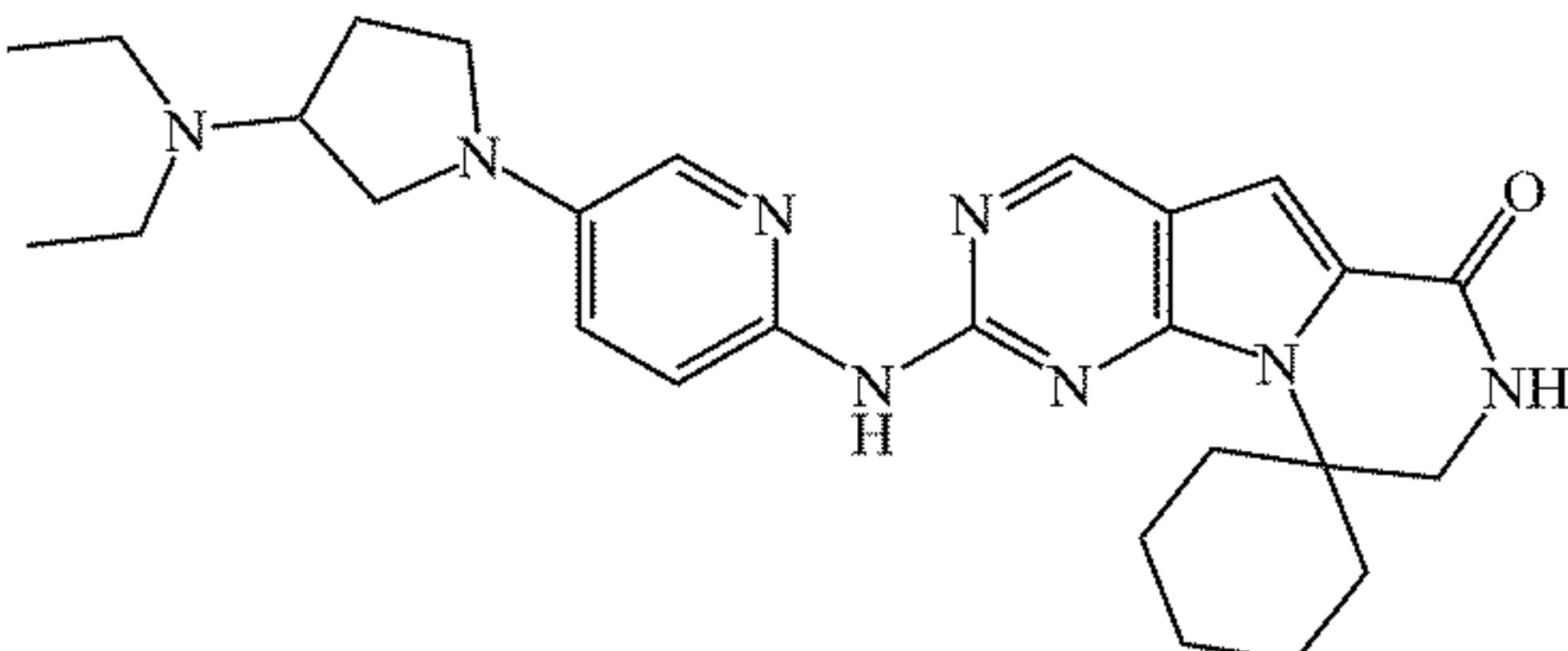
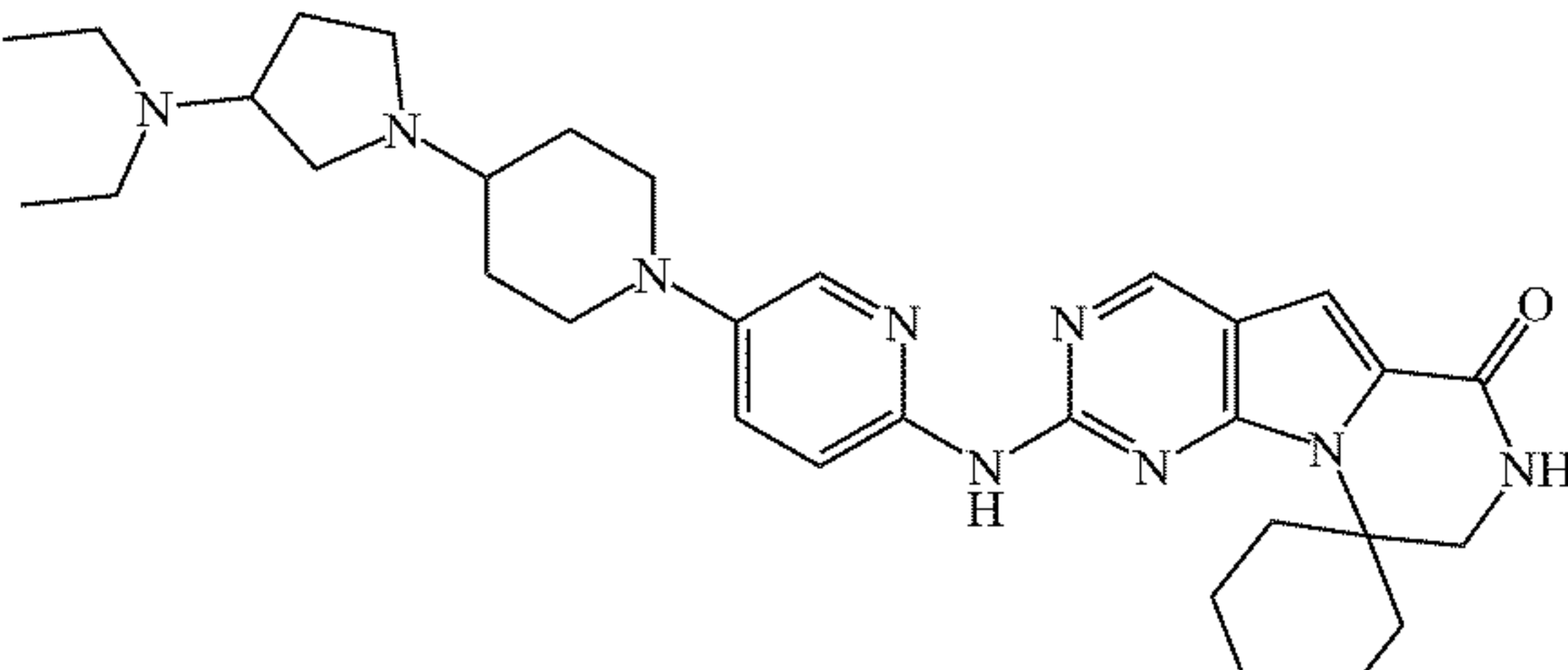
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
MM	
NN	
OO	
PP	
QQ	
RR	

TABLE 1-continued

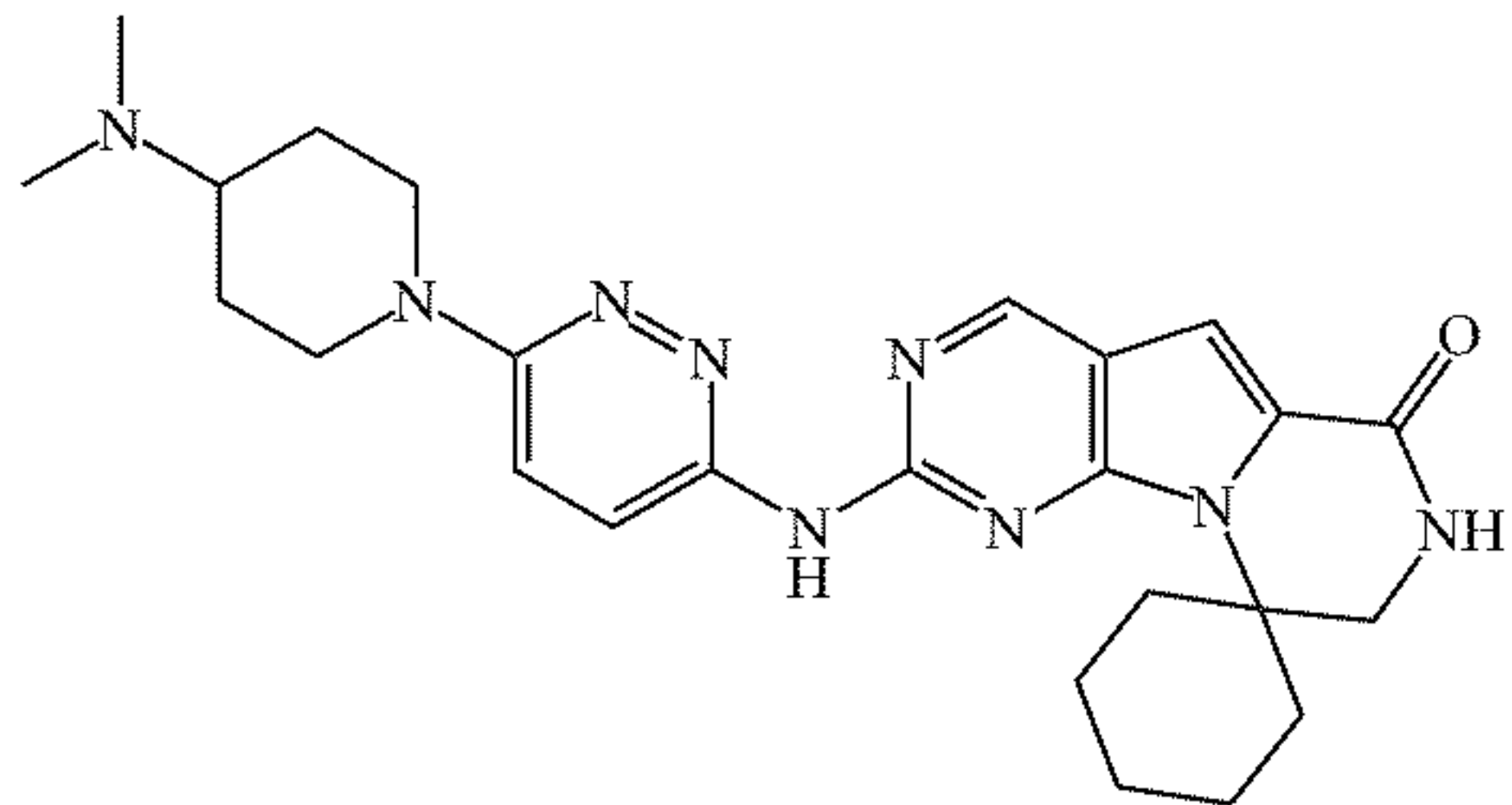
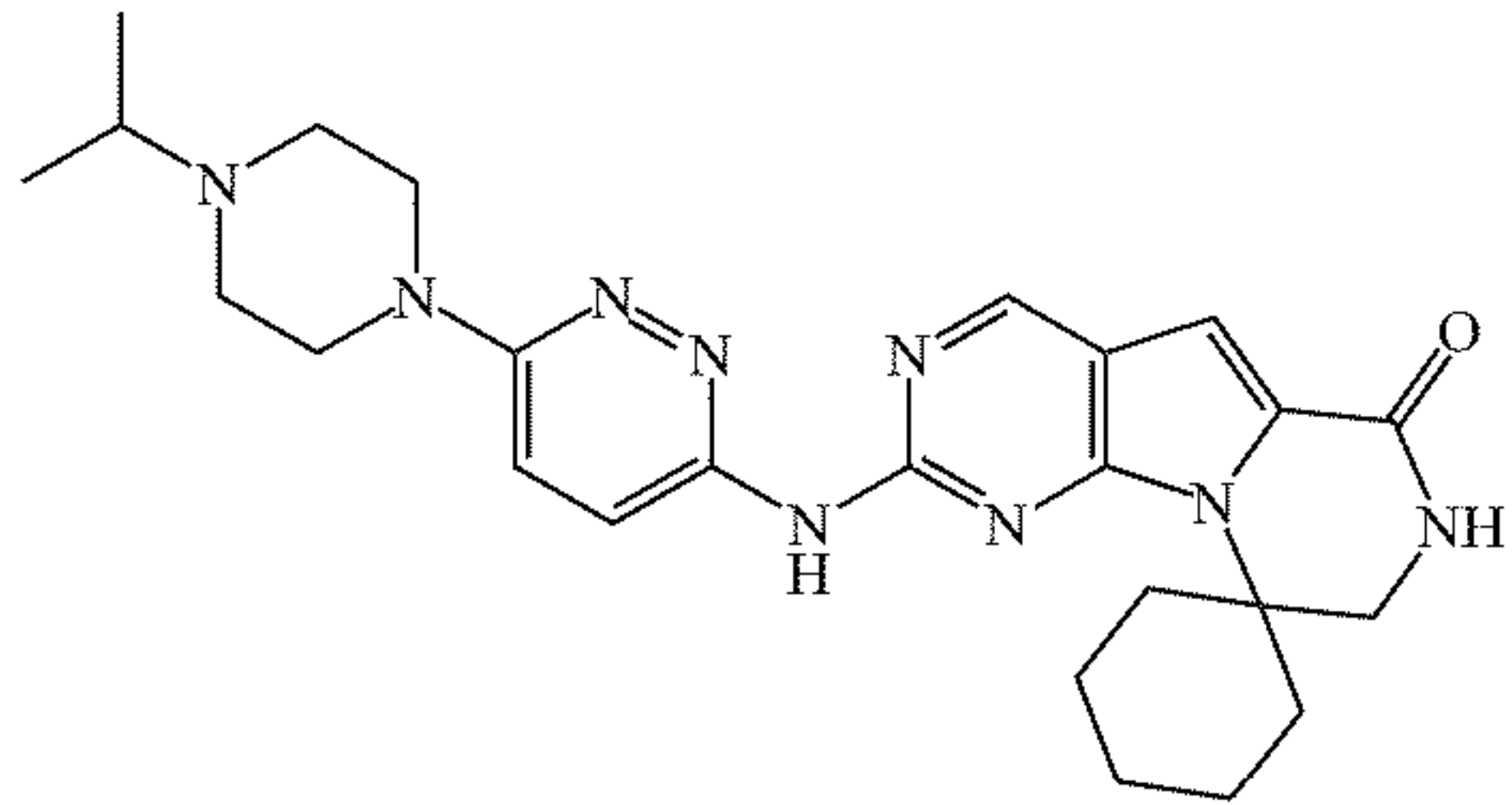
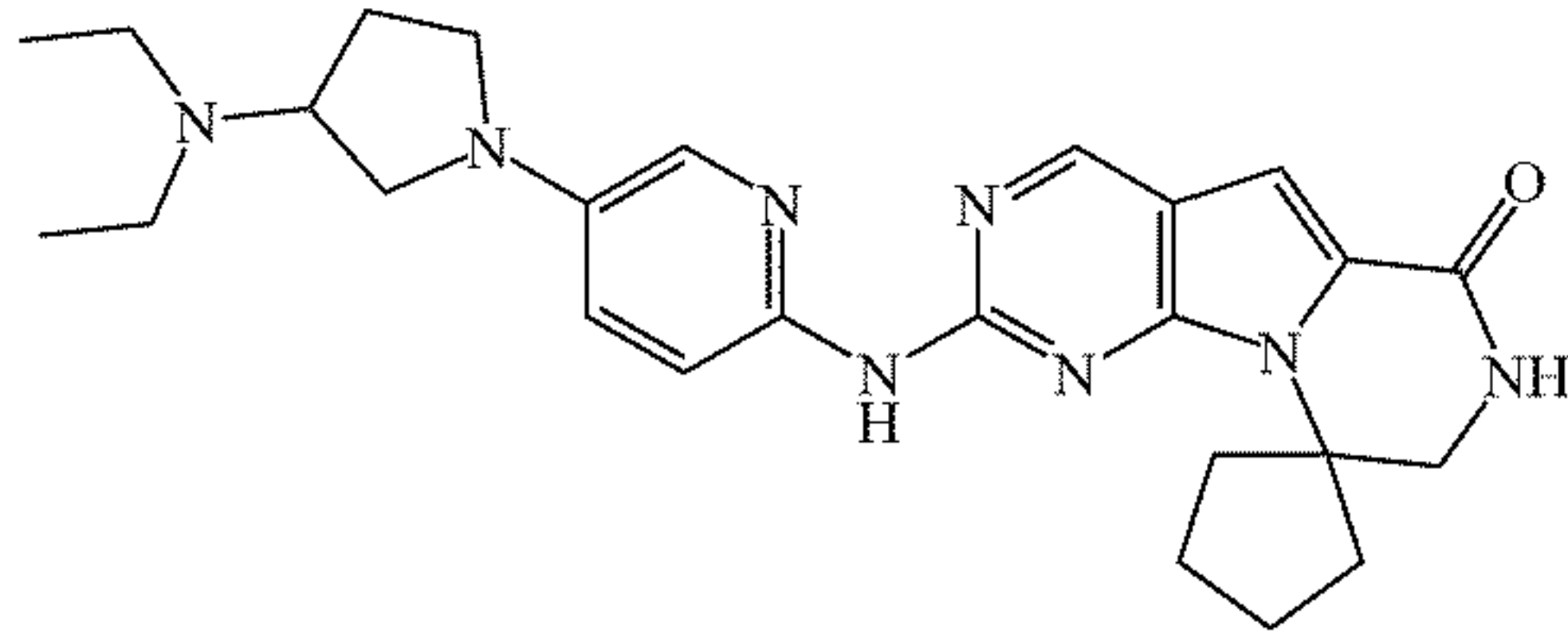
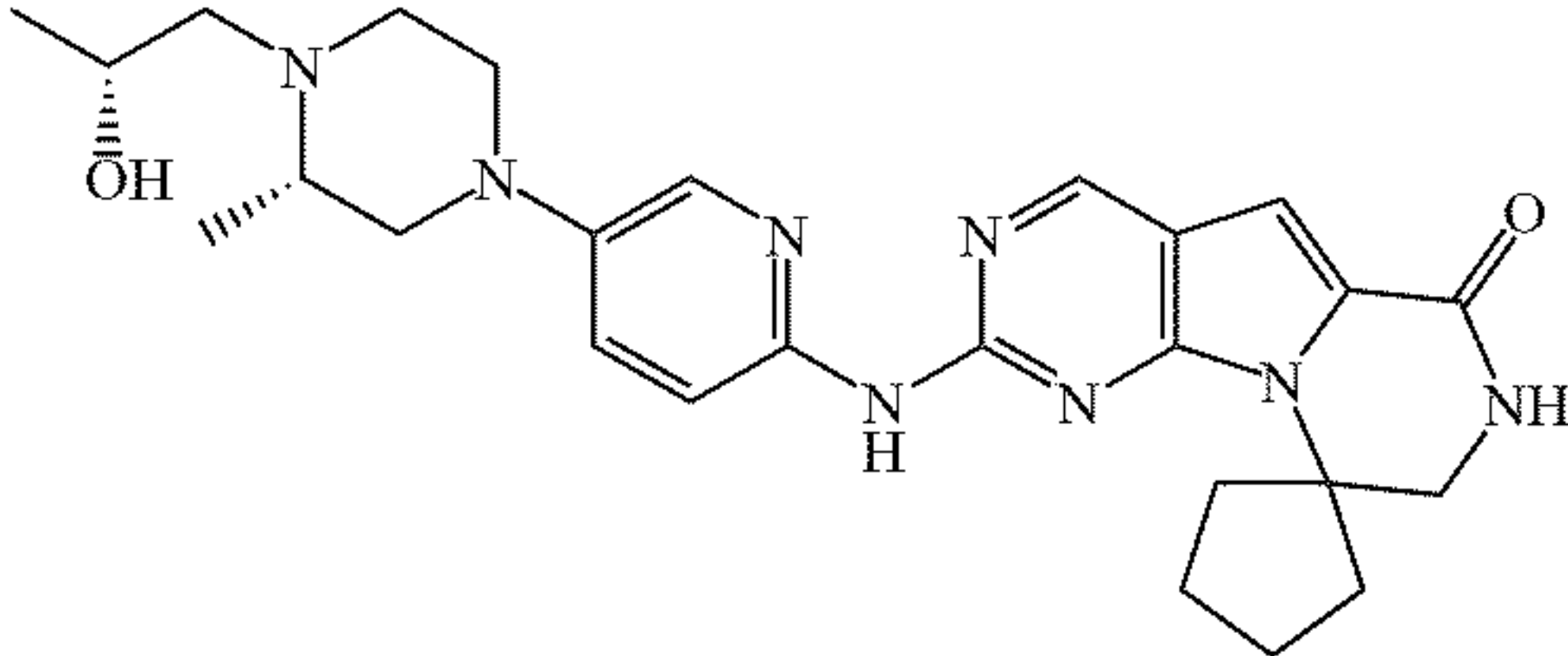
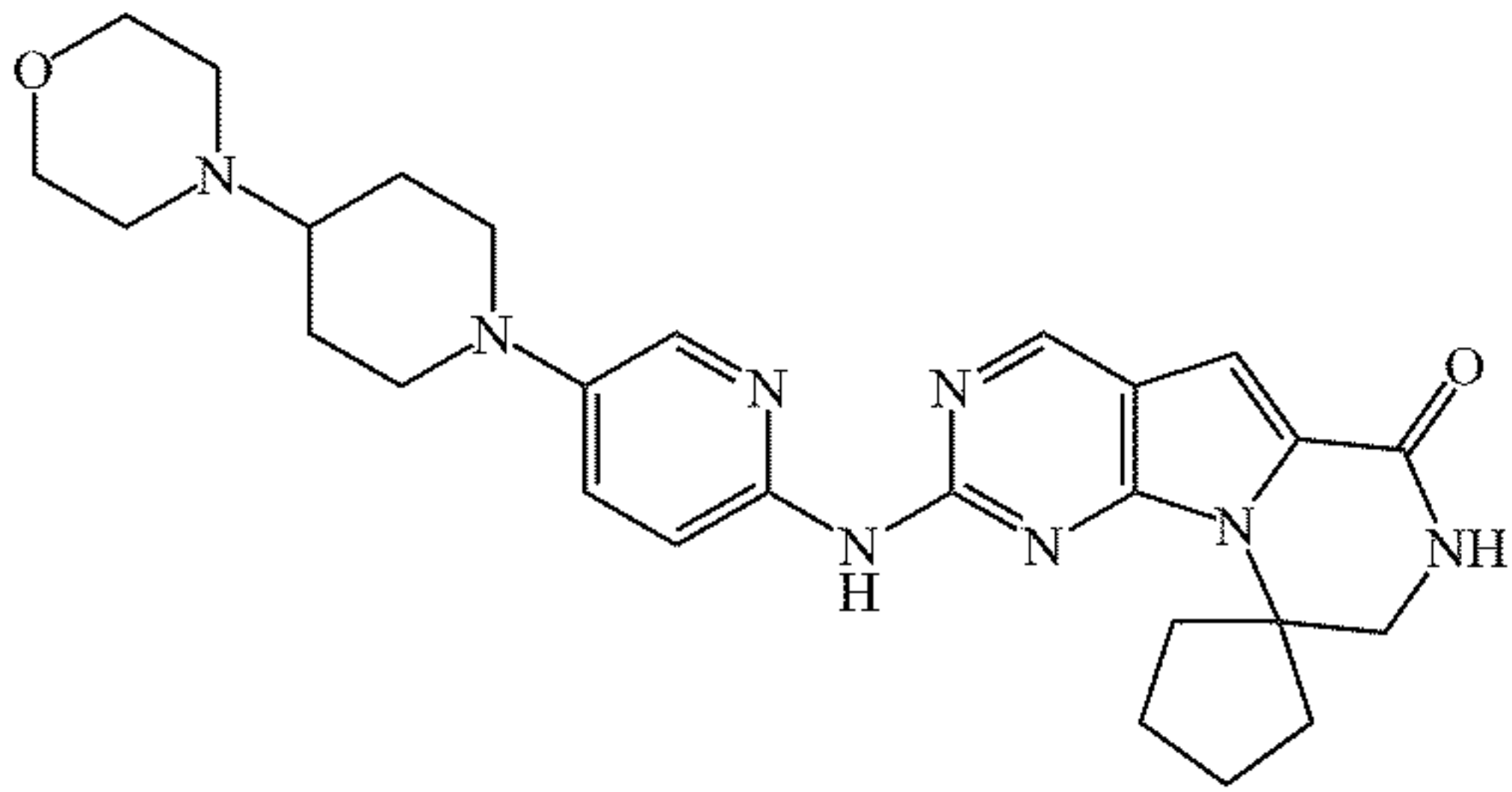
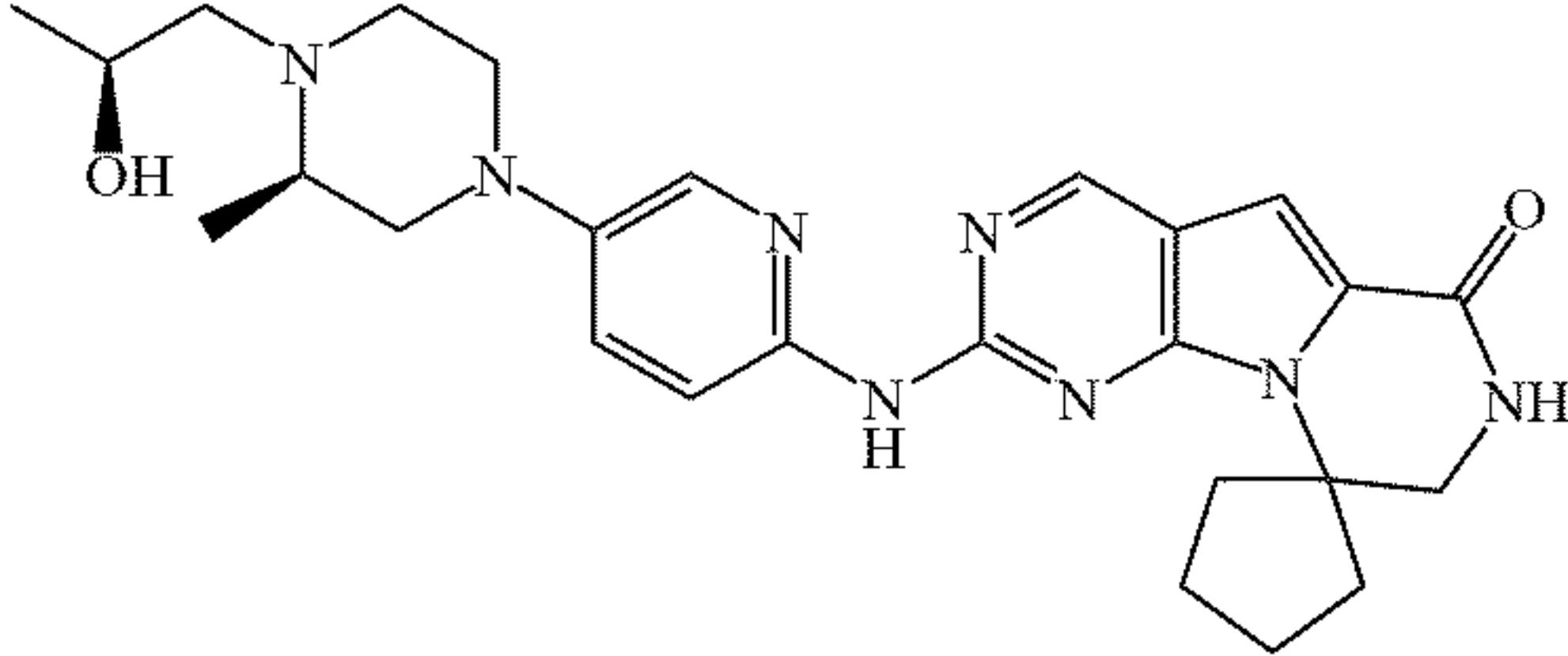
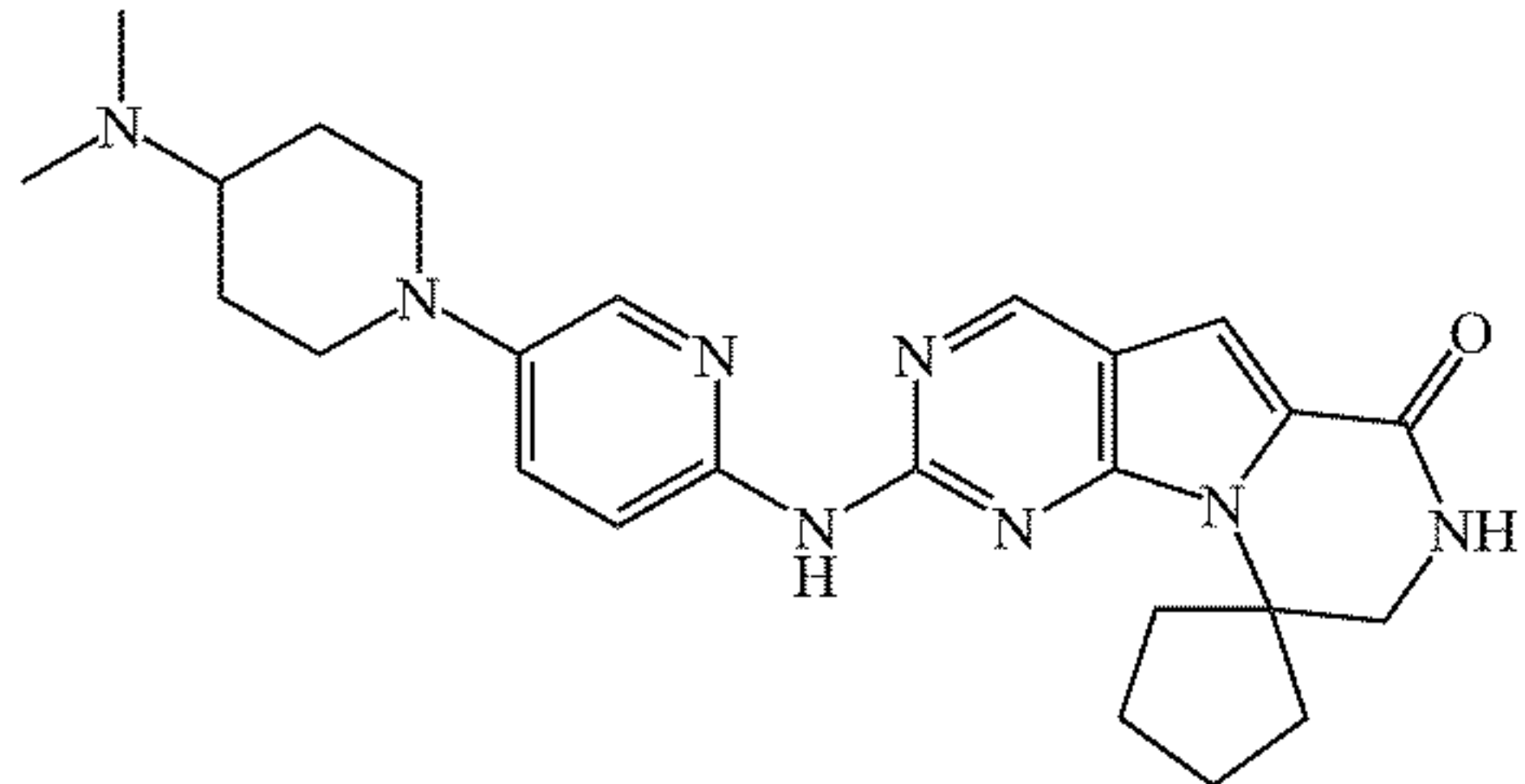
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
SS	
TT	
UU	
VV	
WW	
XX	
YY	

TABLE 1-continued

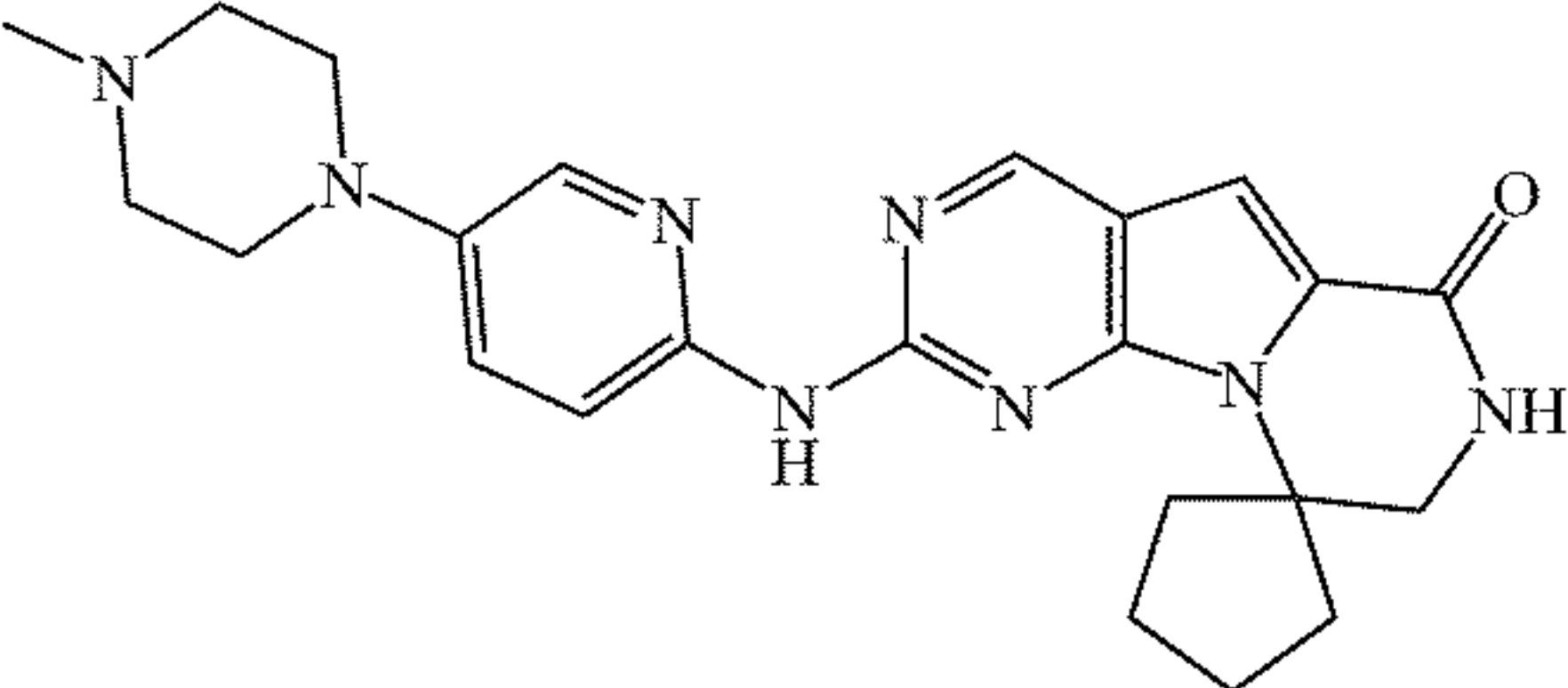
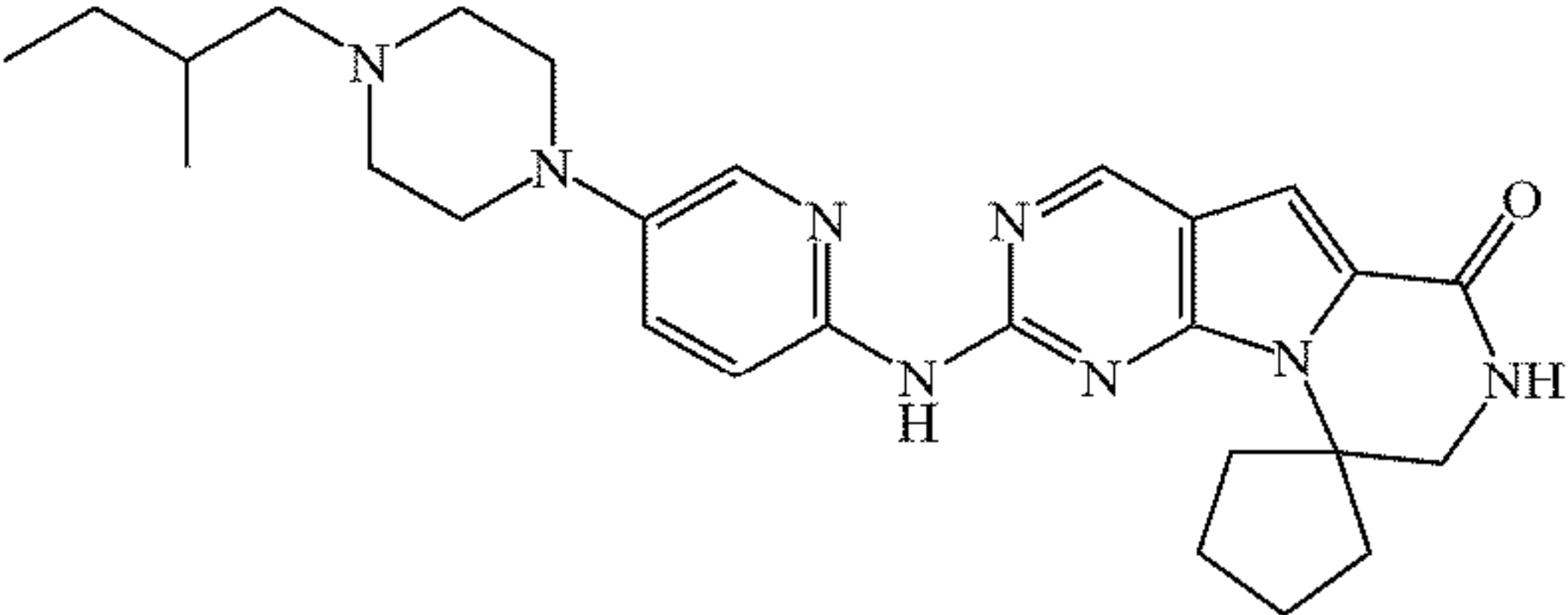
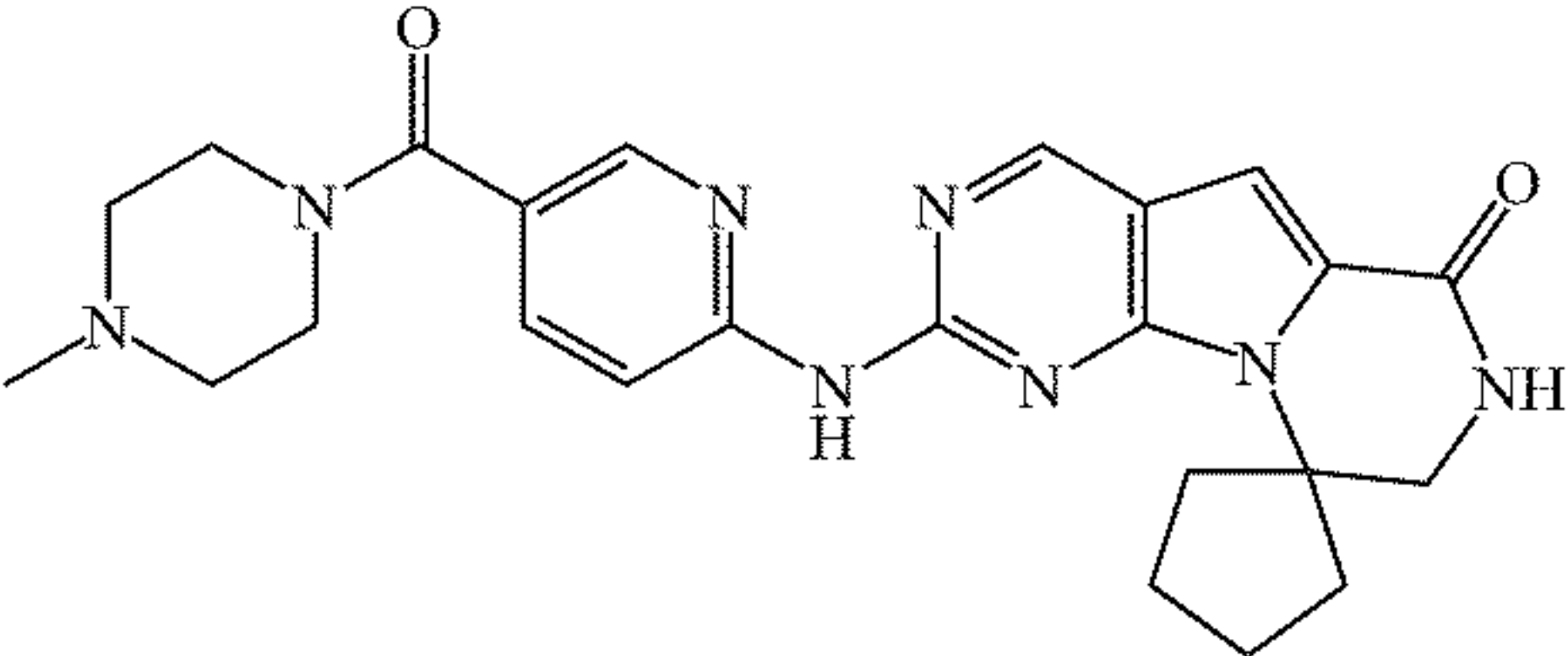
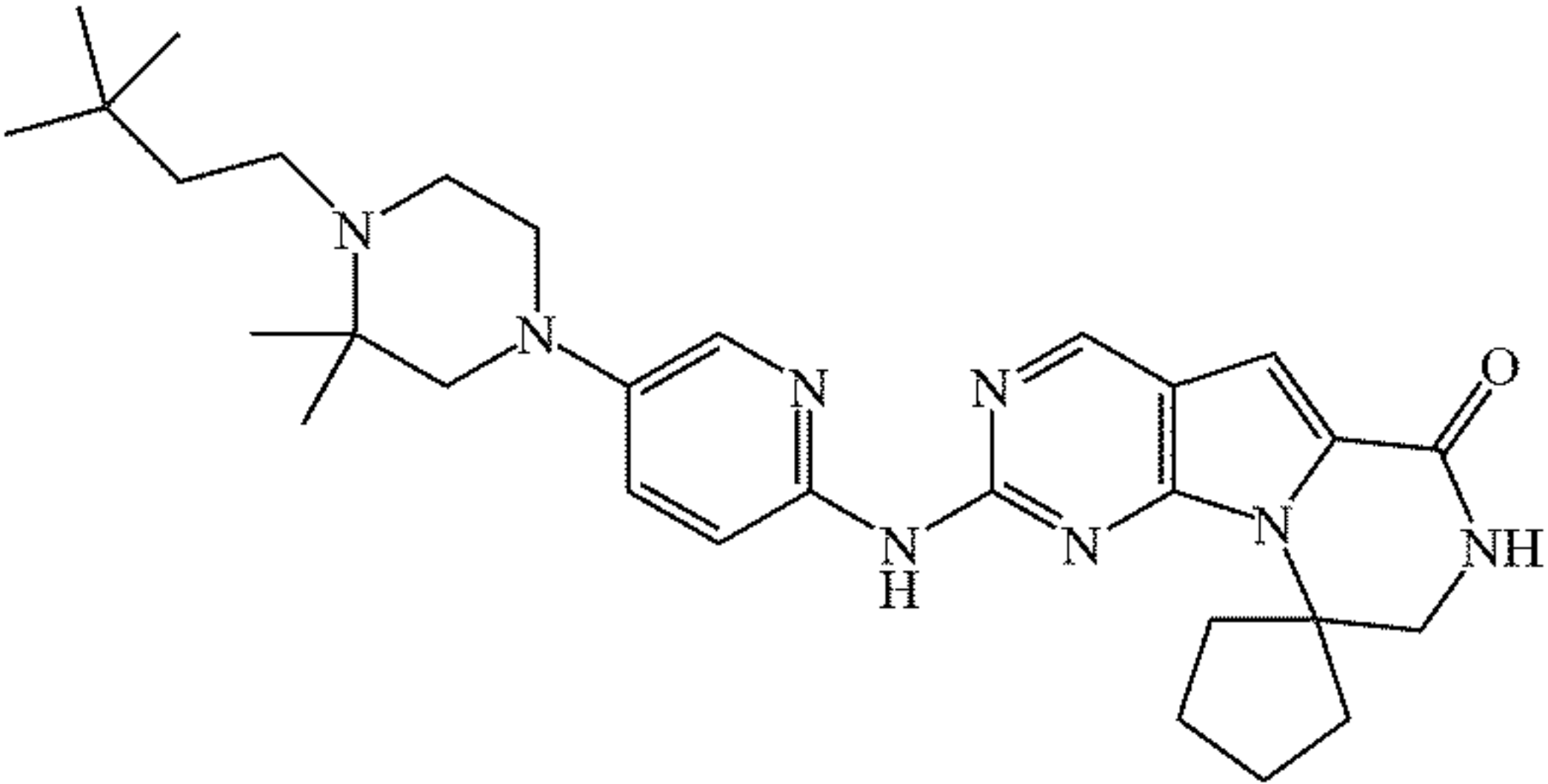
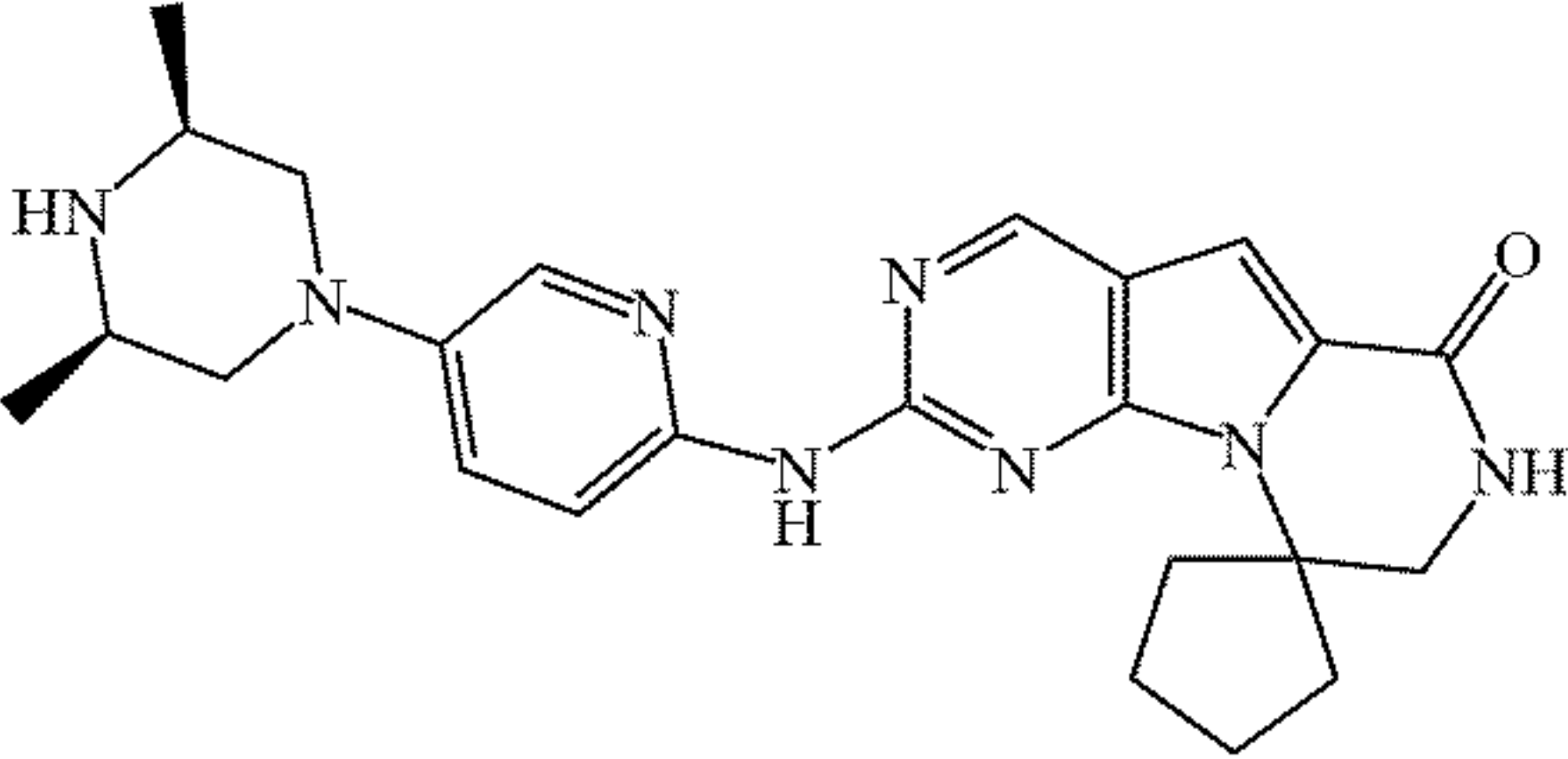
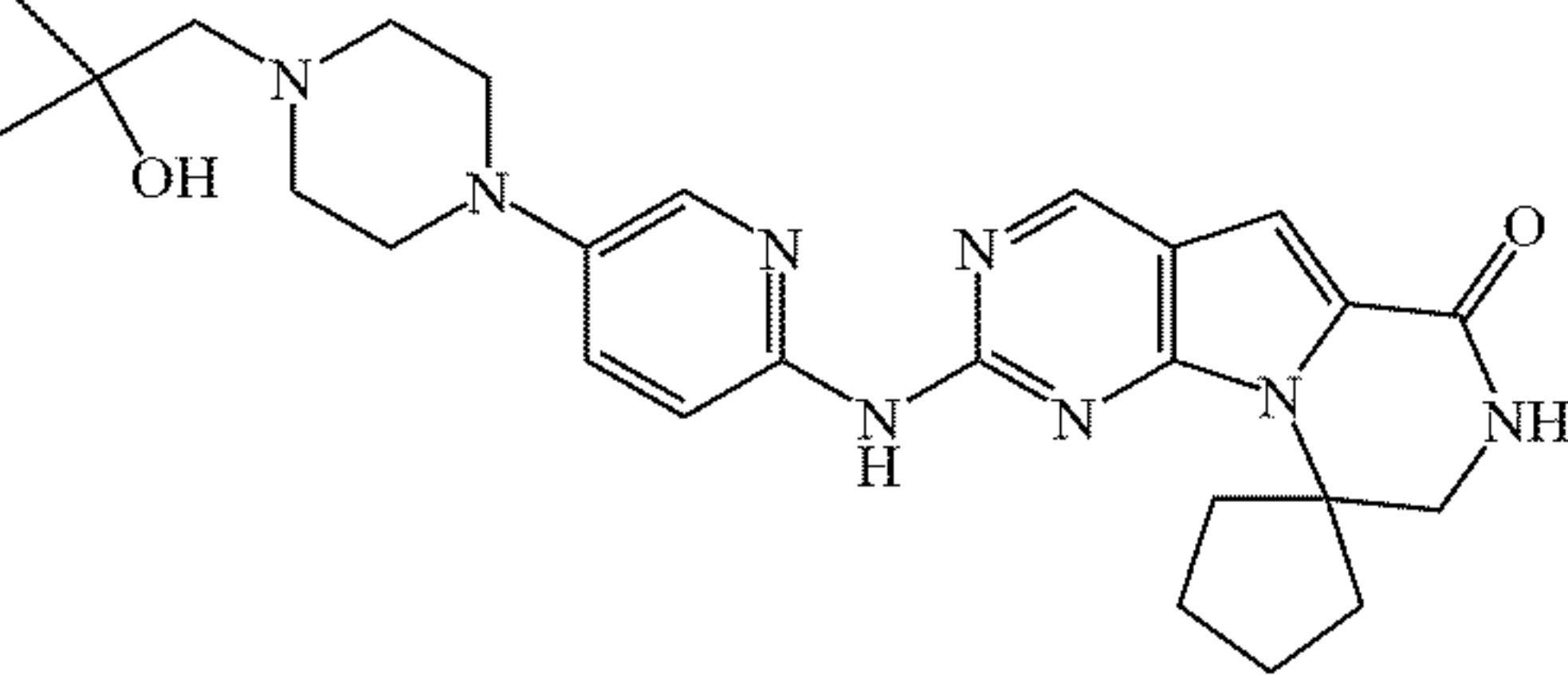
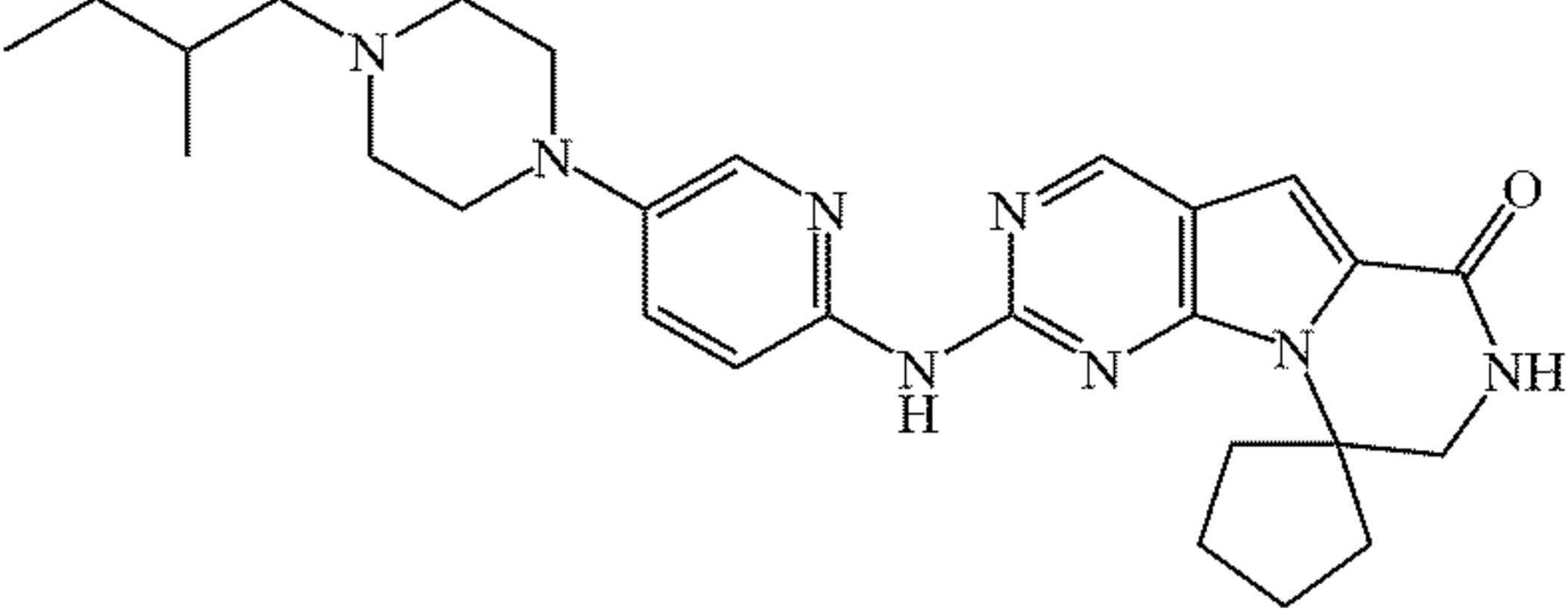
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
ZZ	
AAA	
BBB	
CCC	
DDD	
EEE	
FFF	

TABLE 1-continued

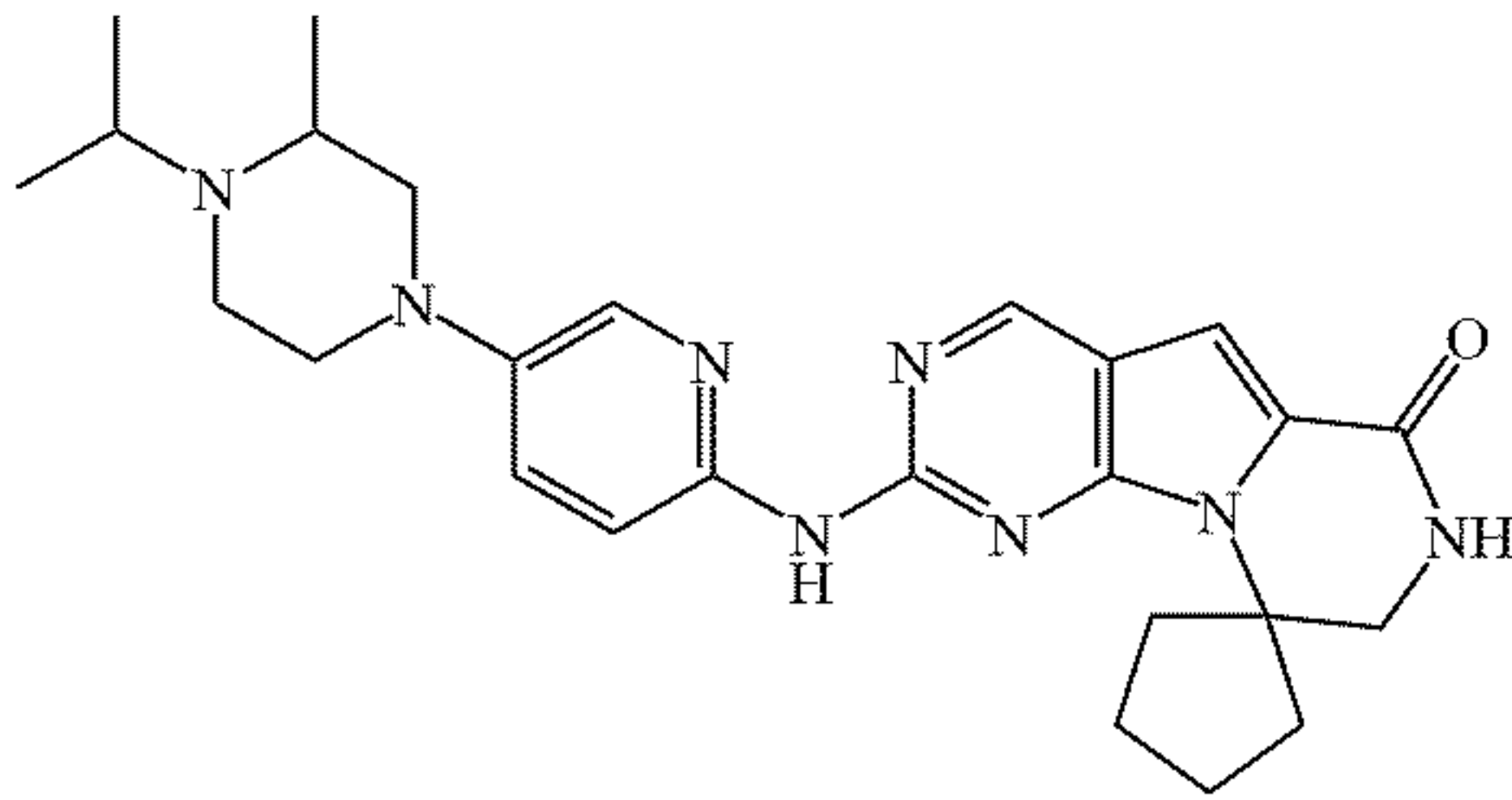
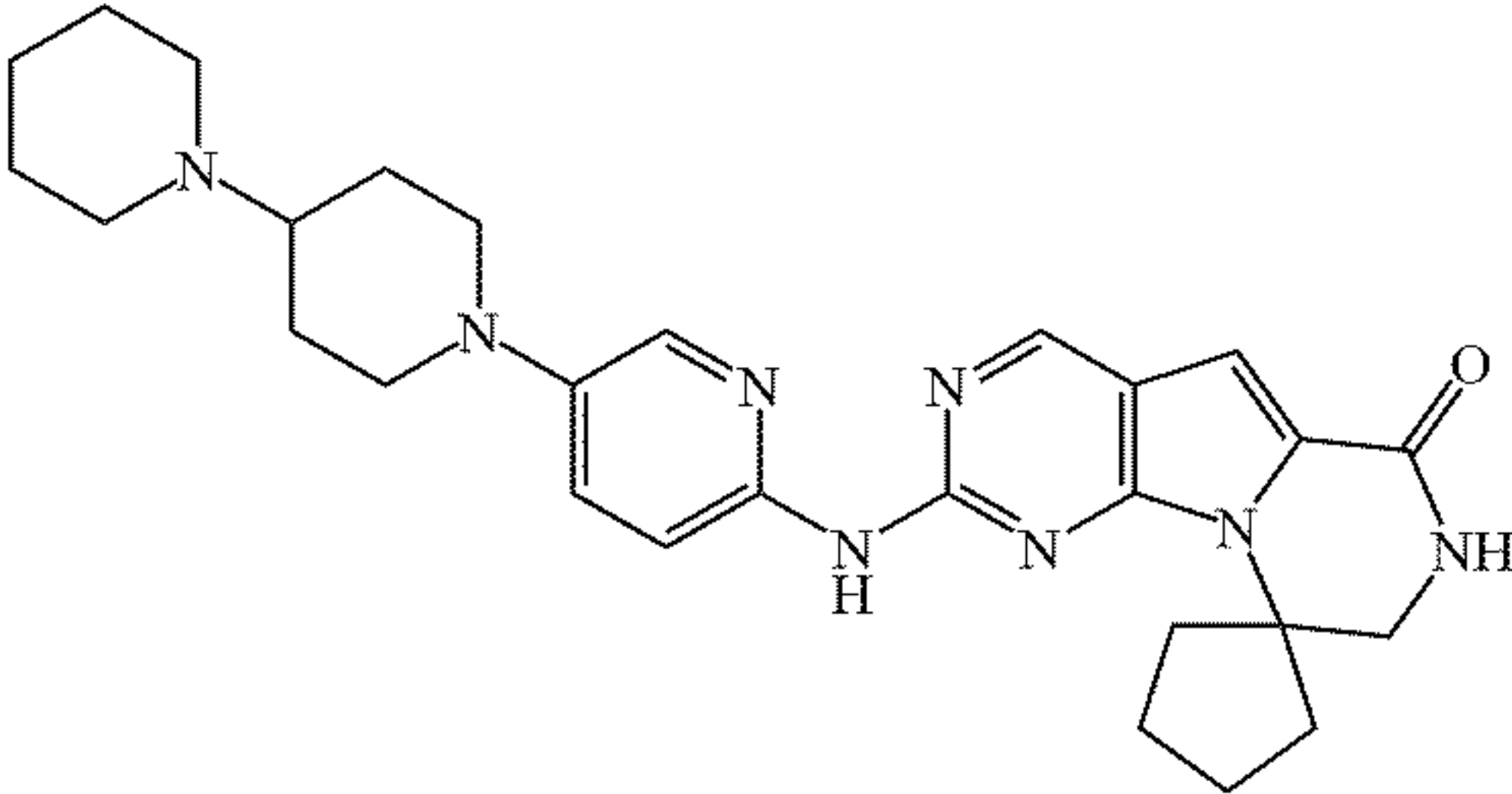
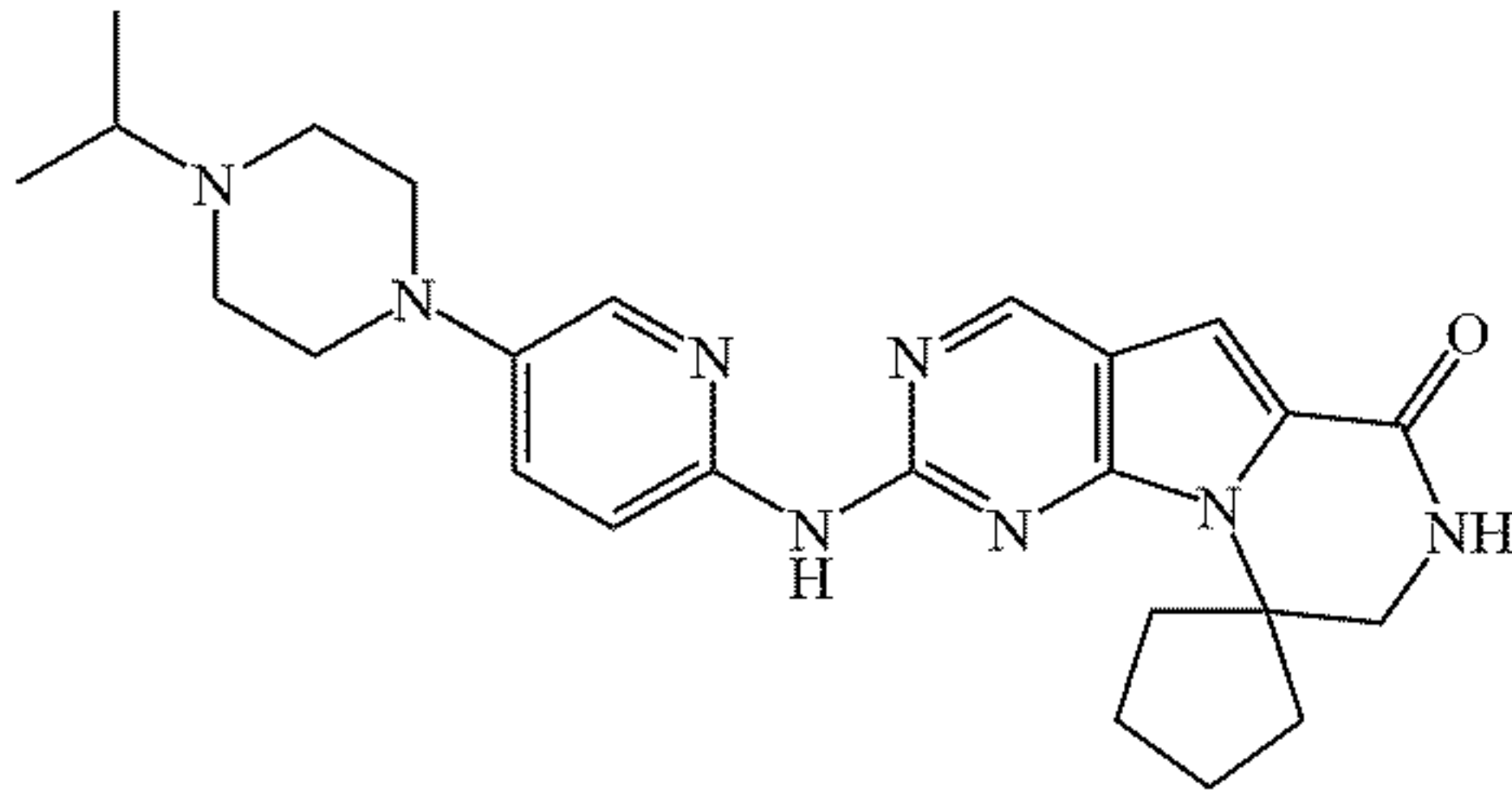
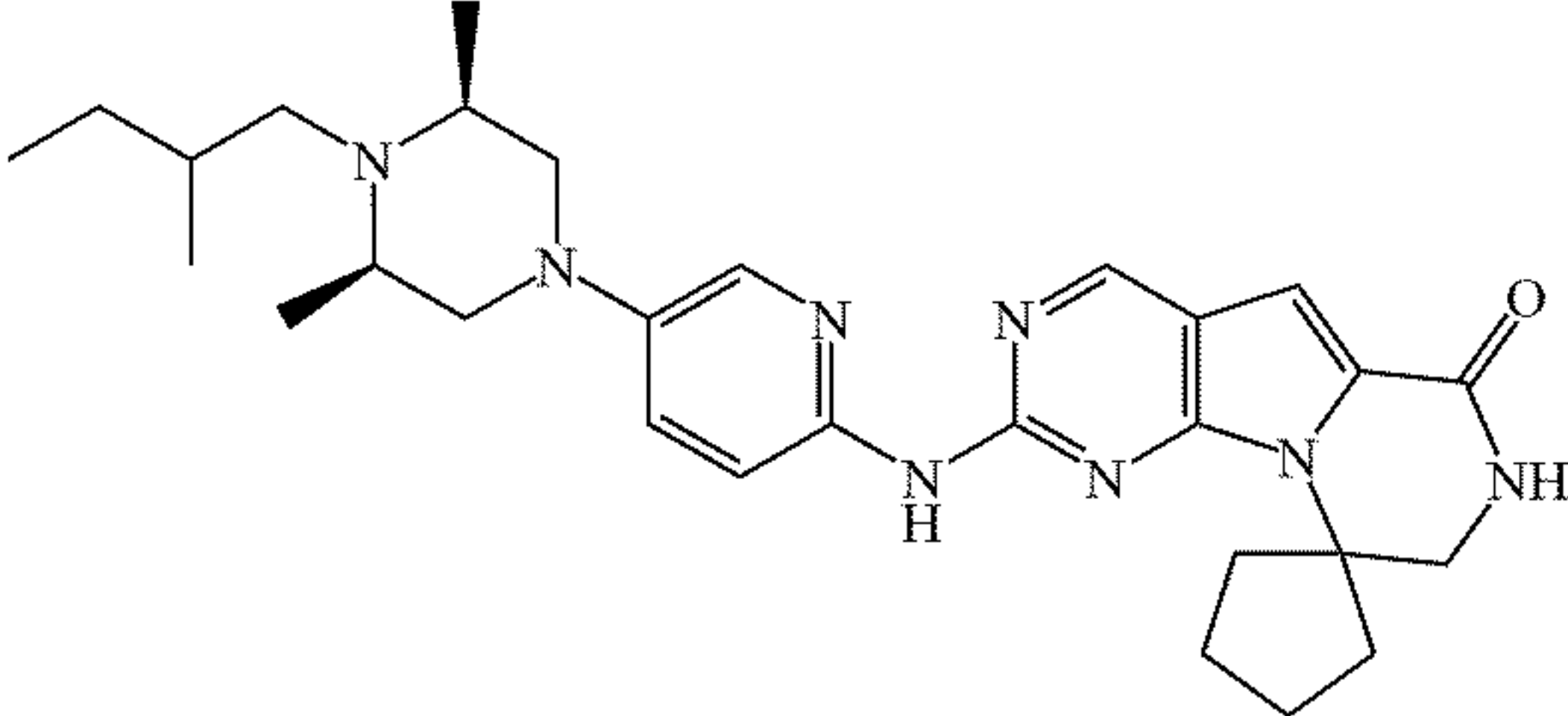
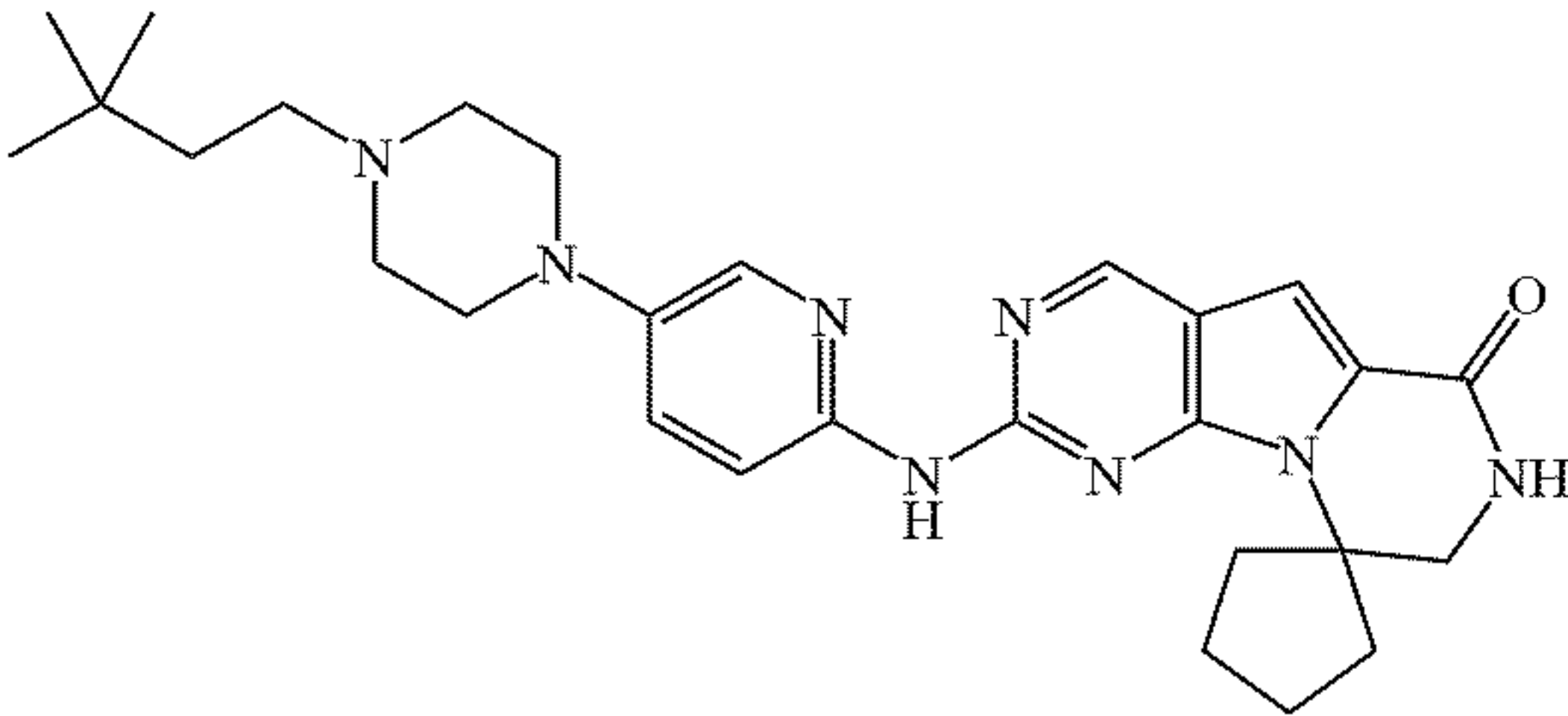
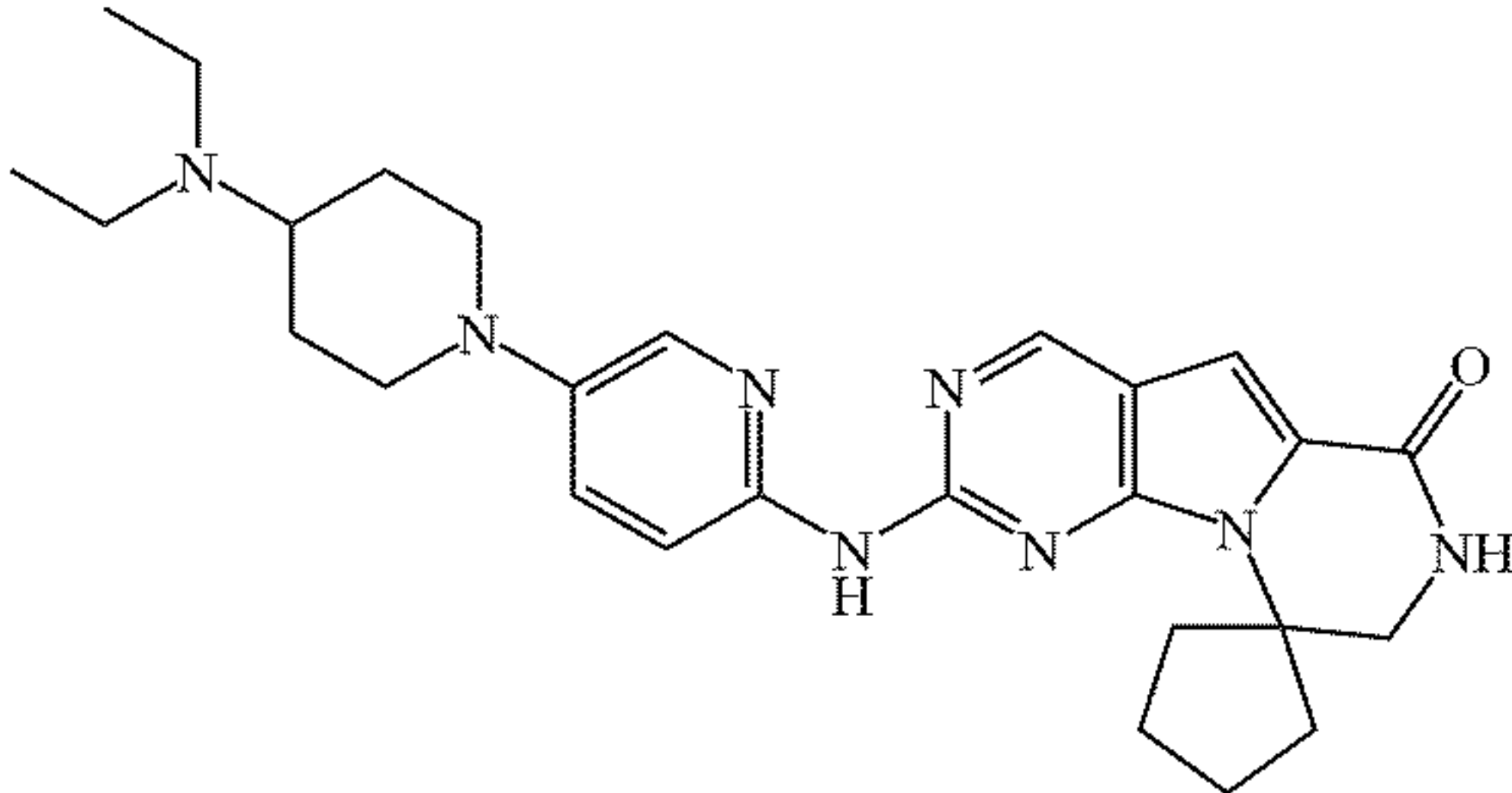
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
GGG	
HHH	
III	
JJJ	
KKK	
LLL	

TABLE 1-continued

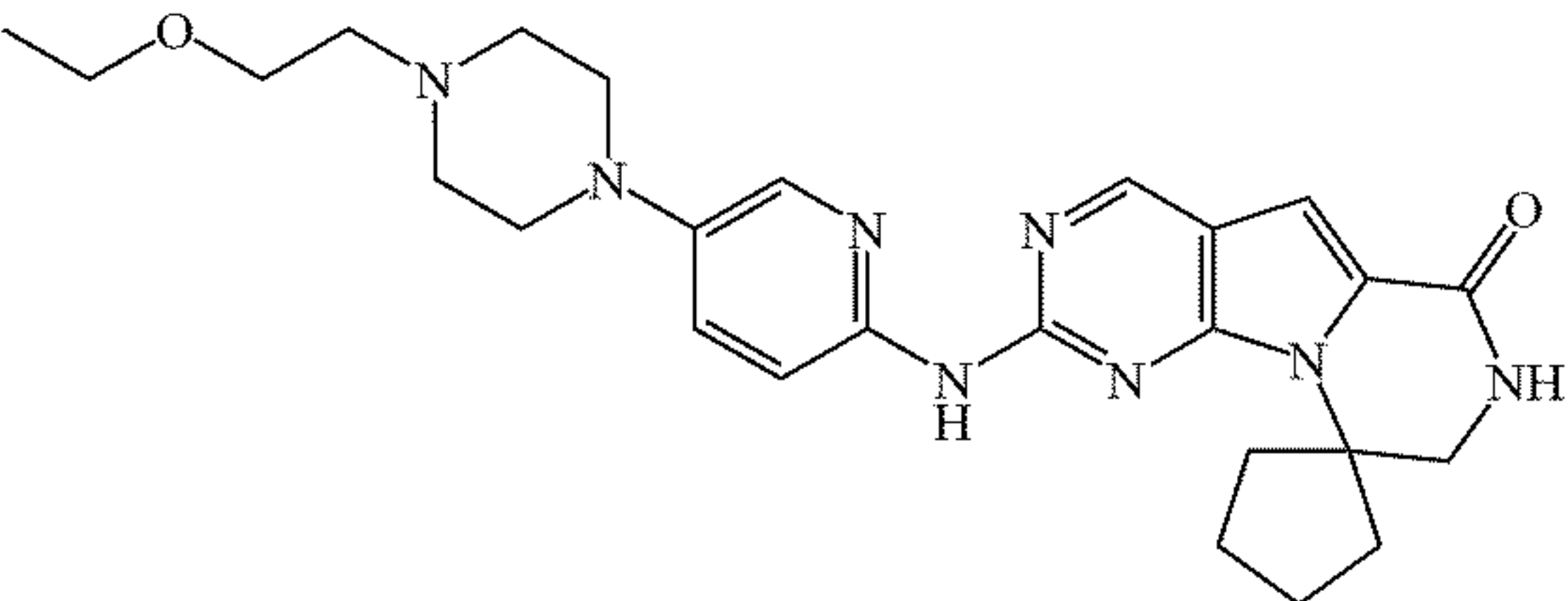
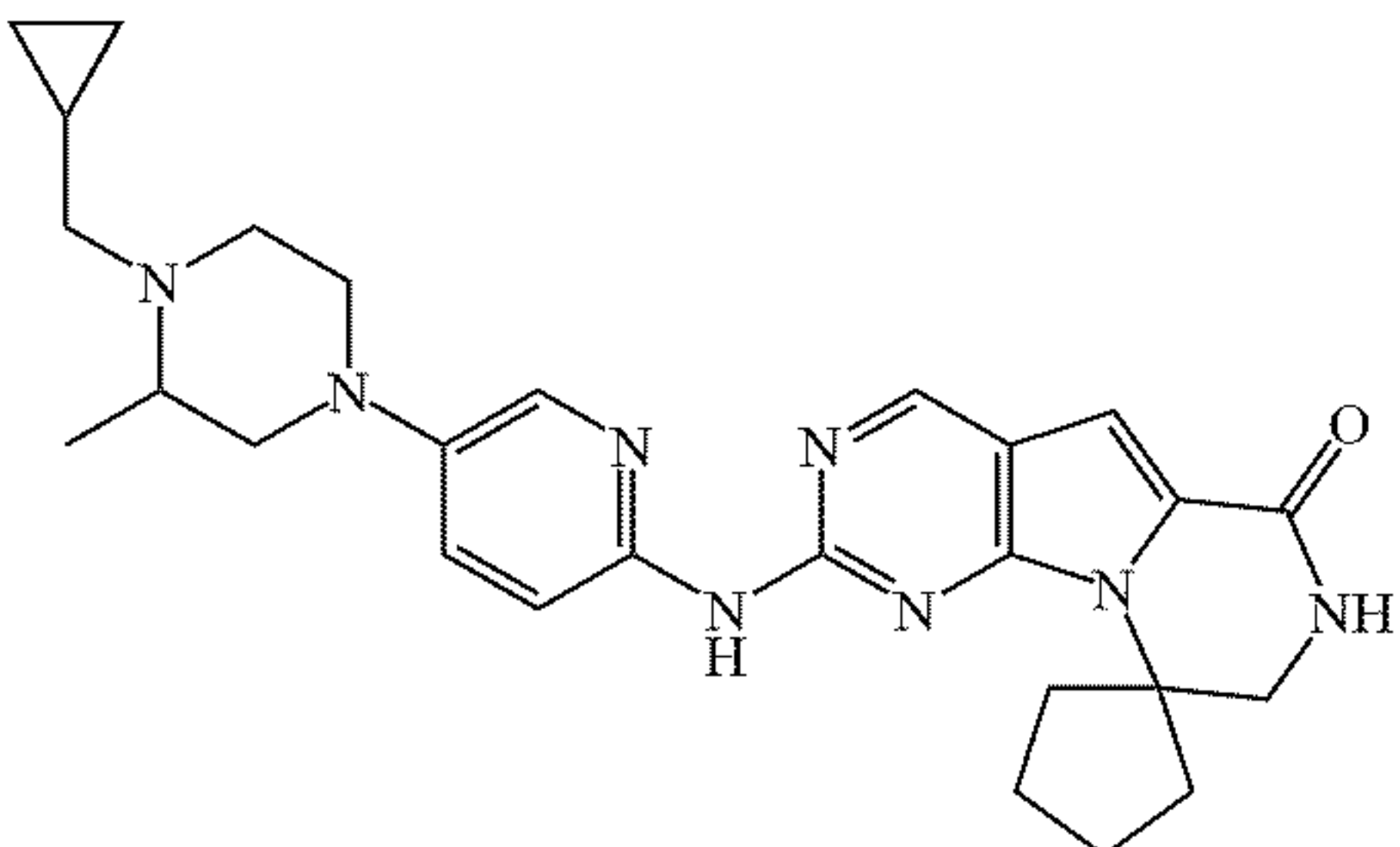
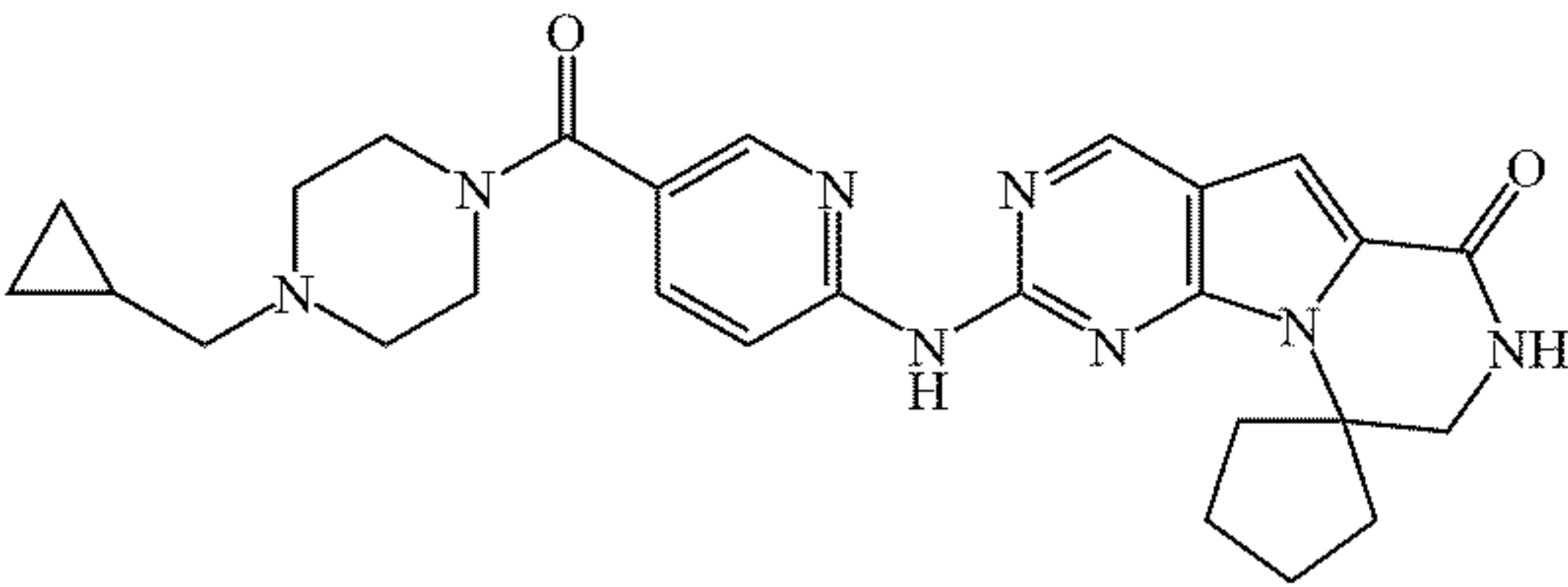
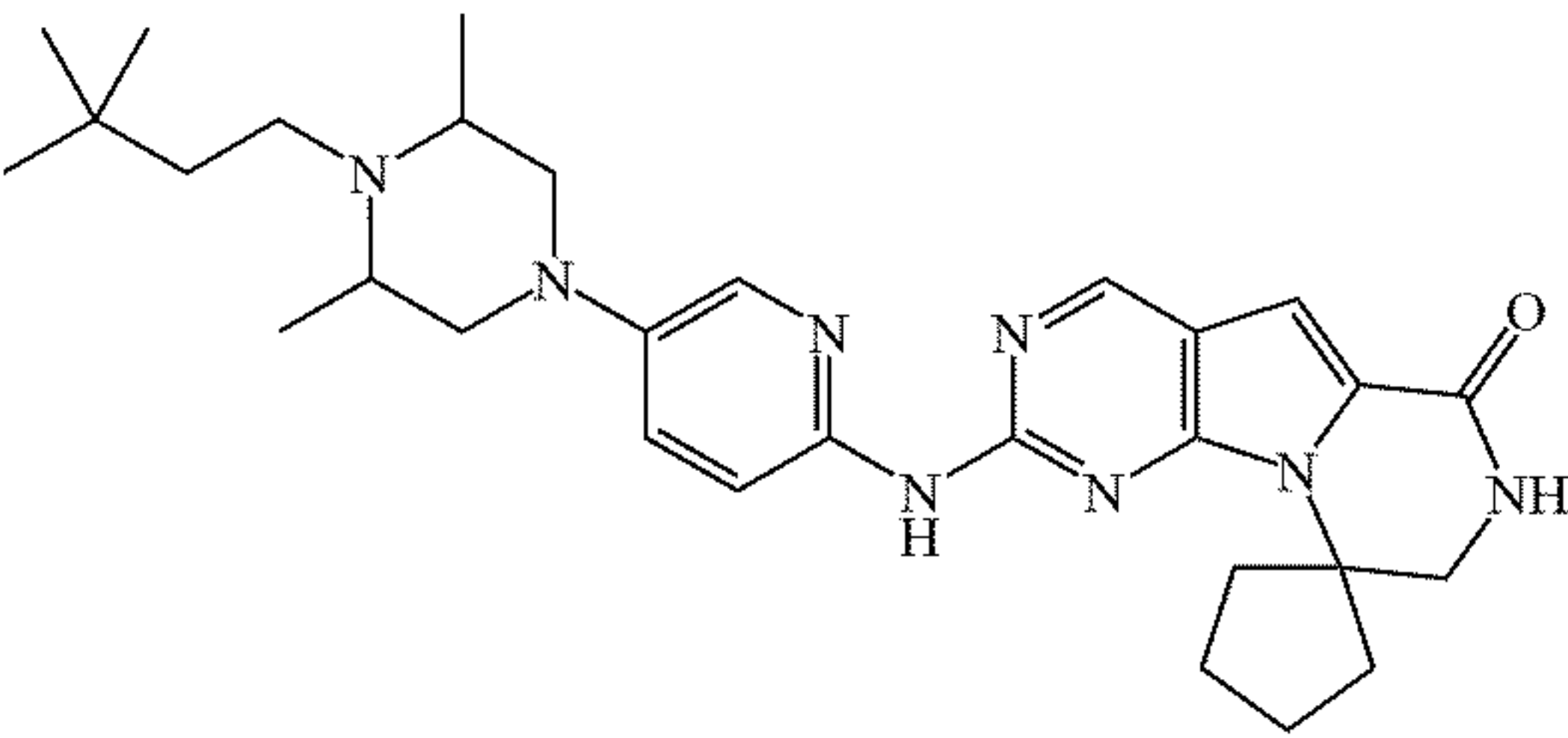
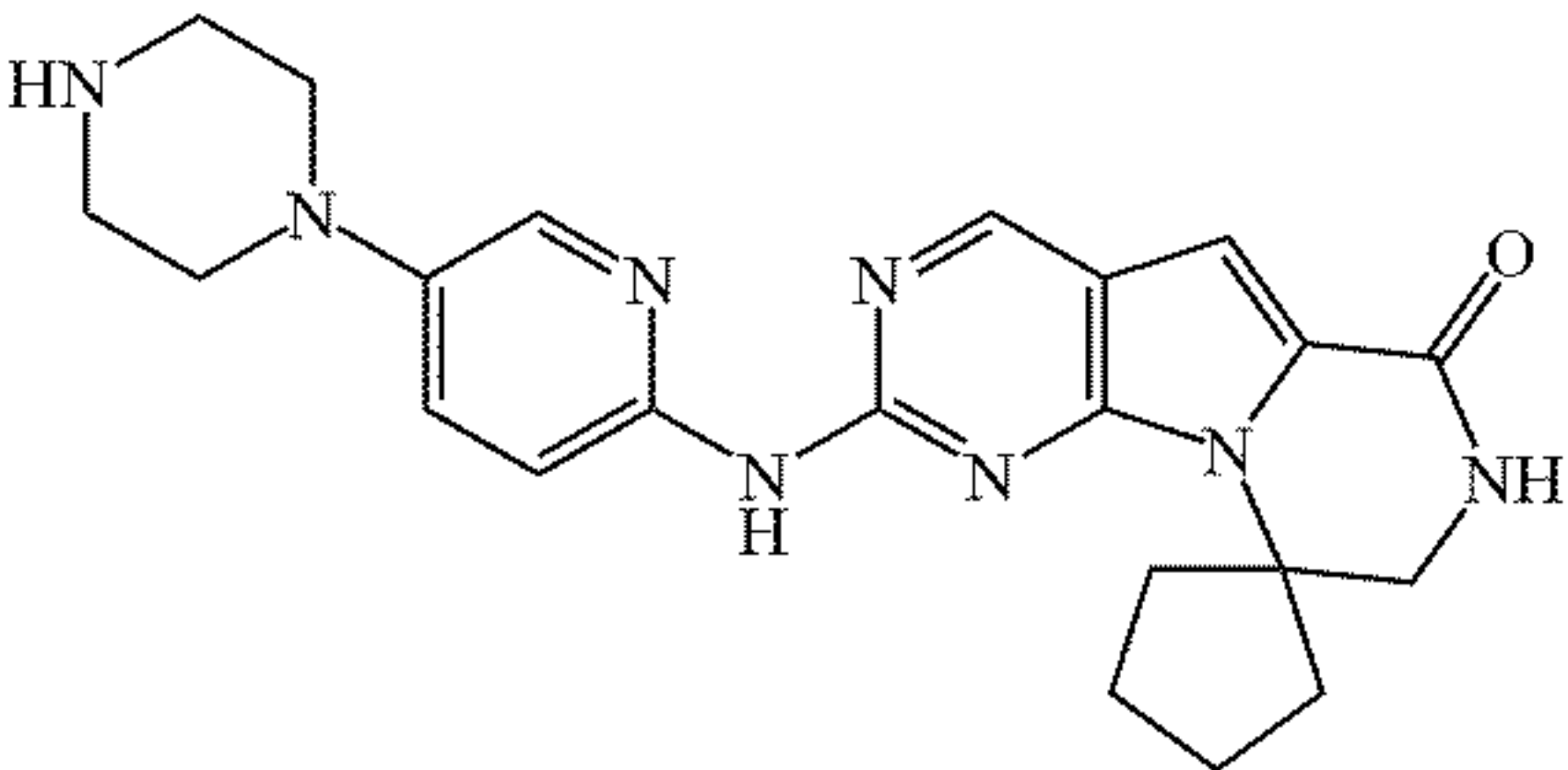
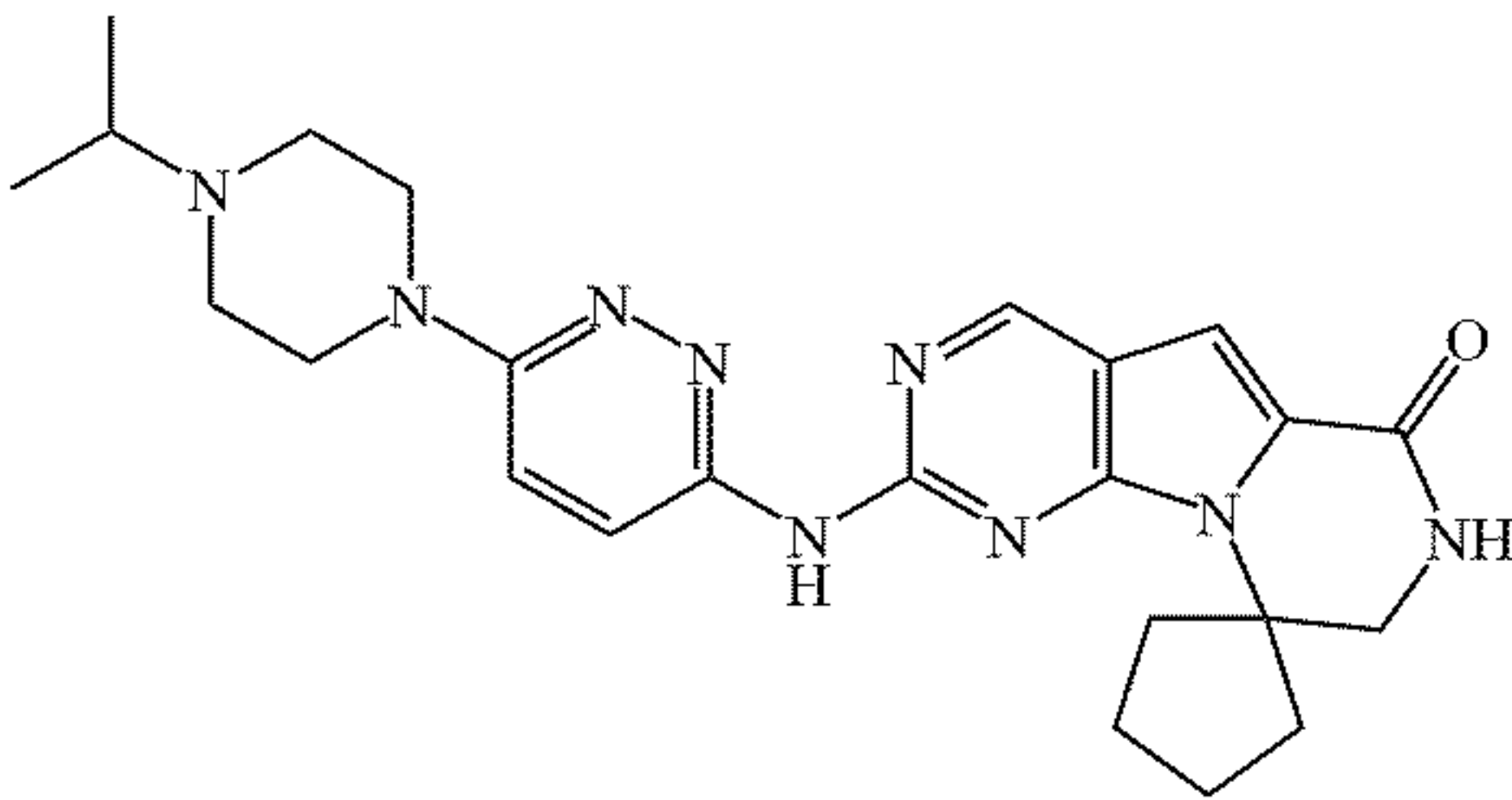
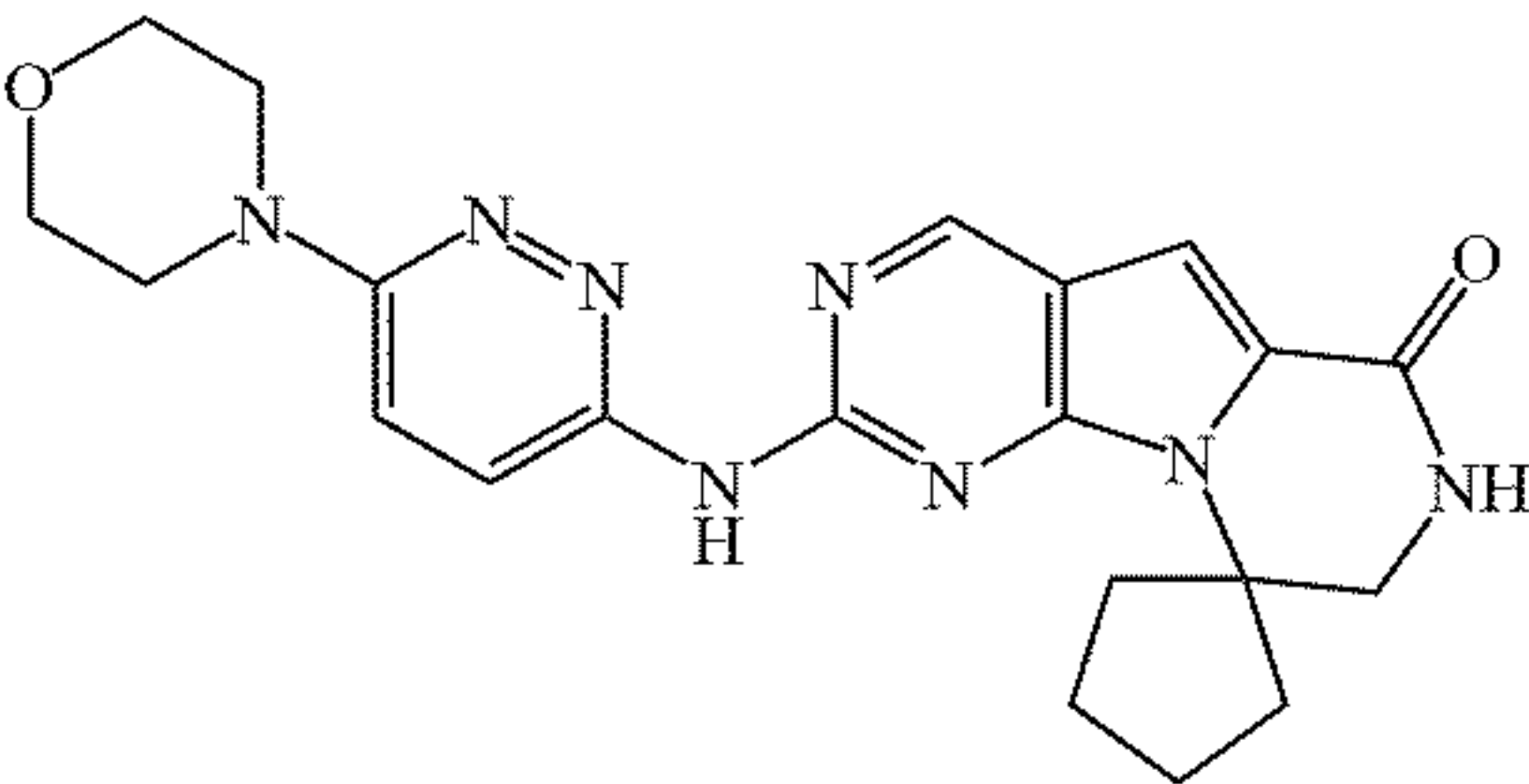
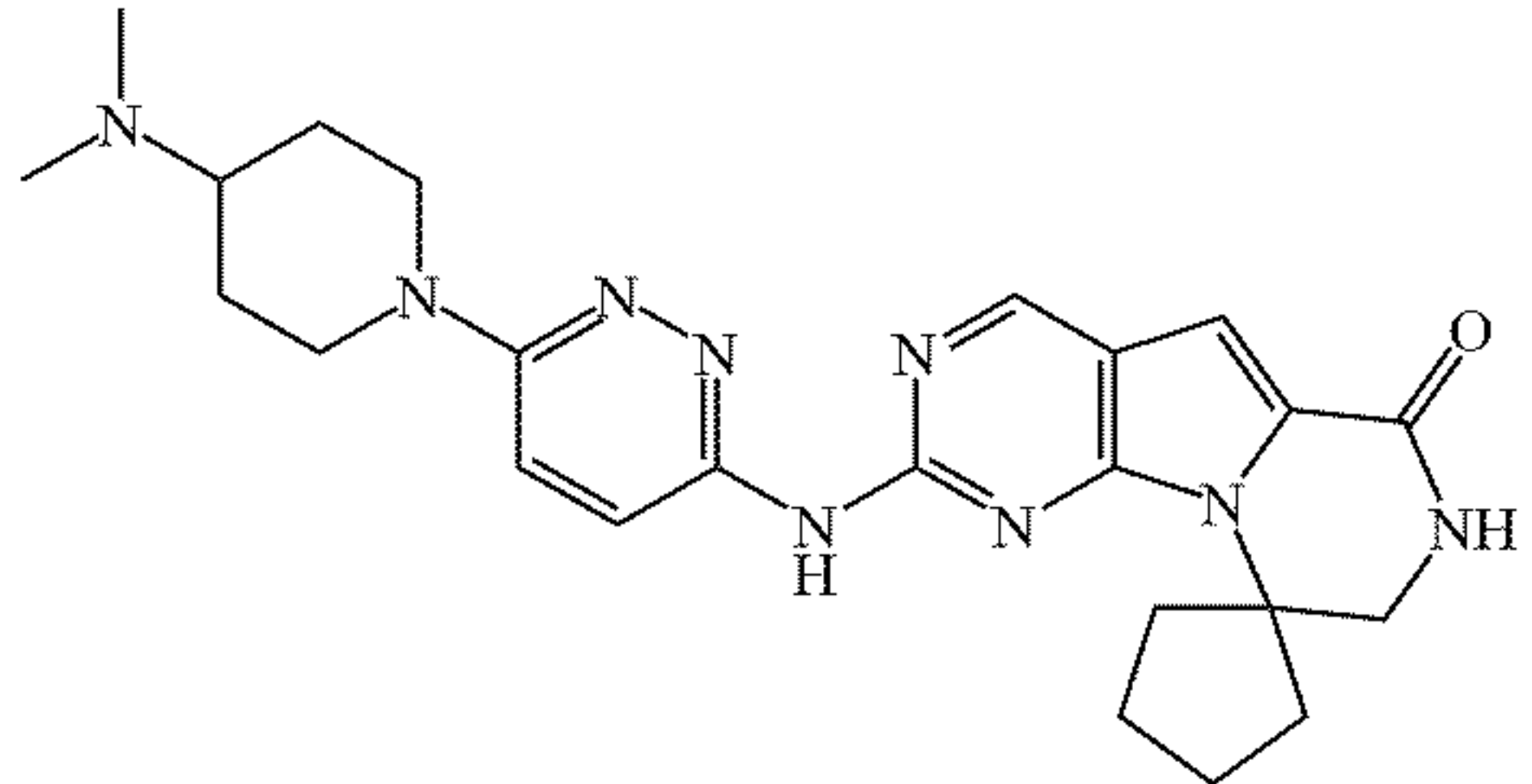
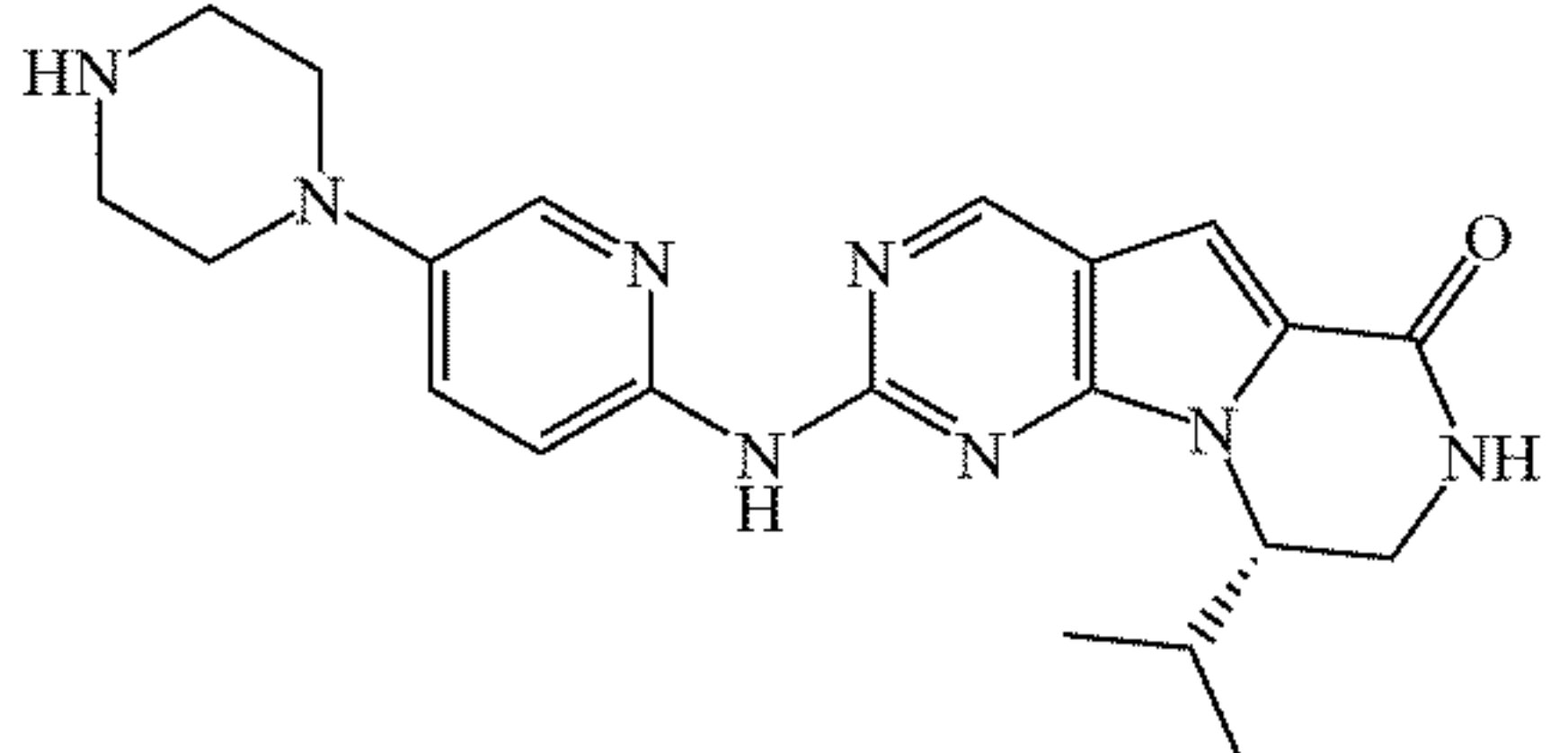
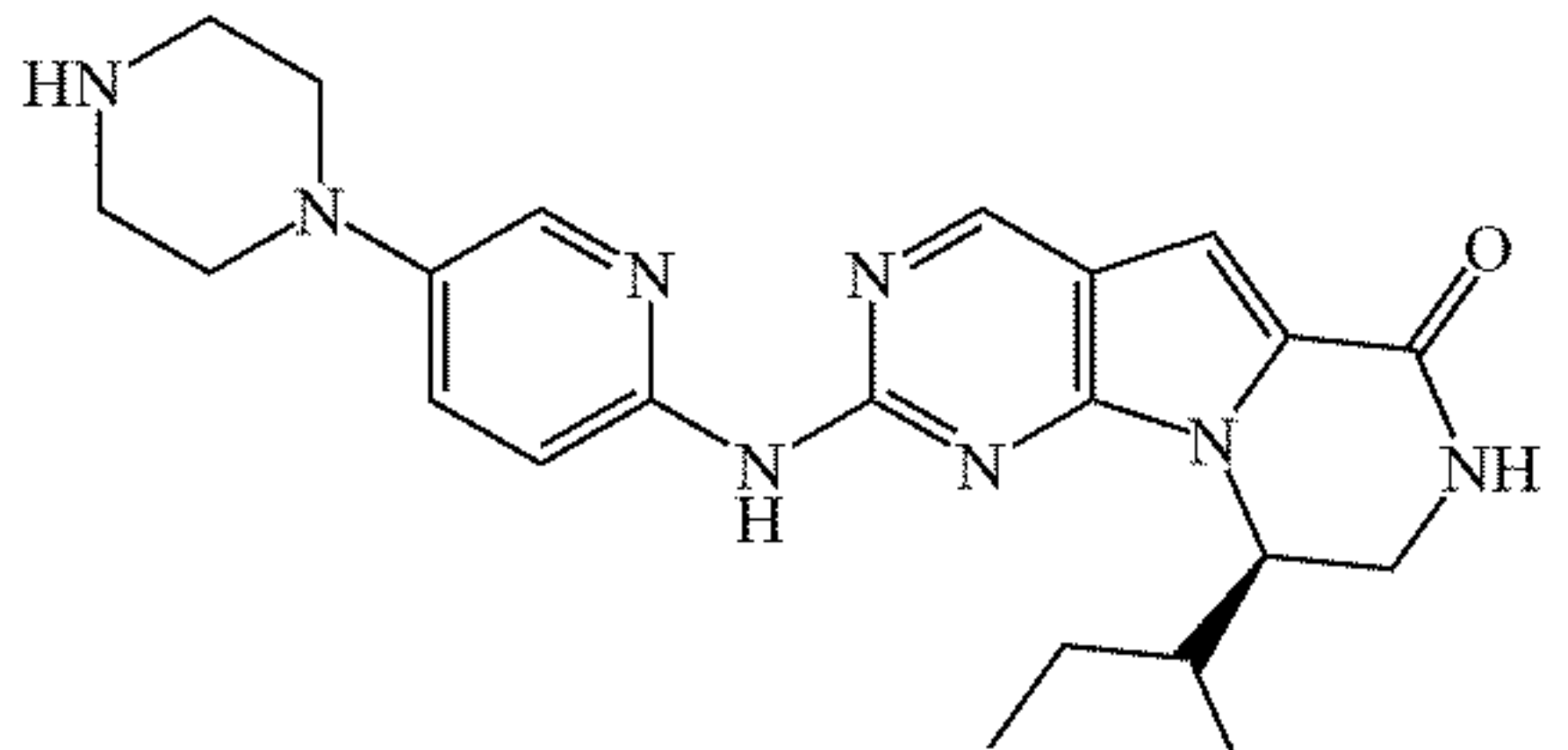
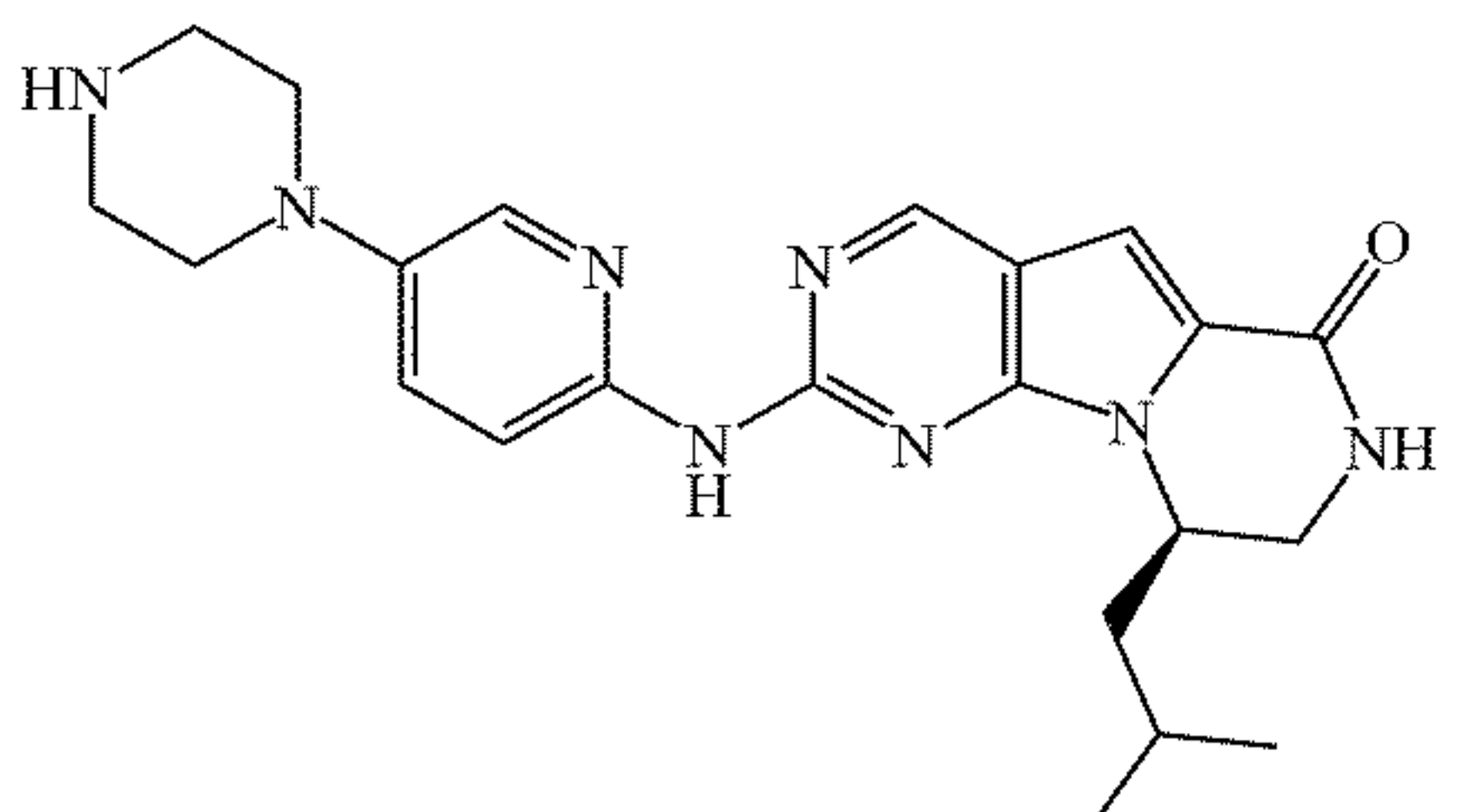
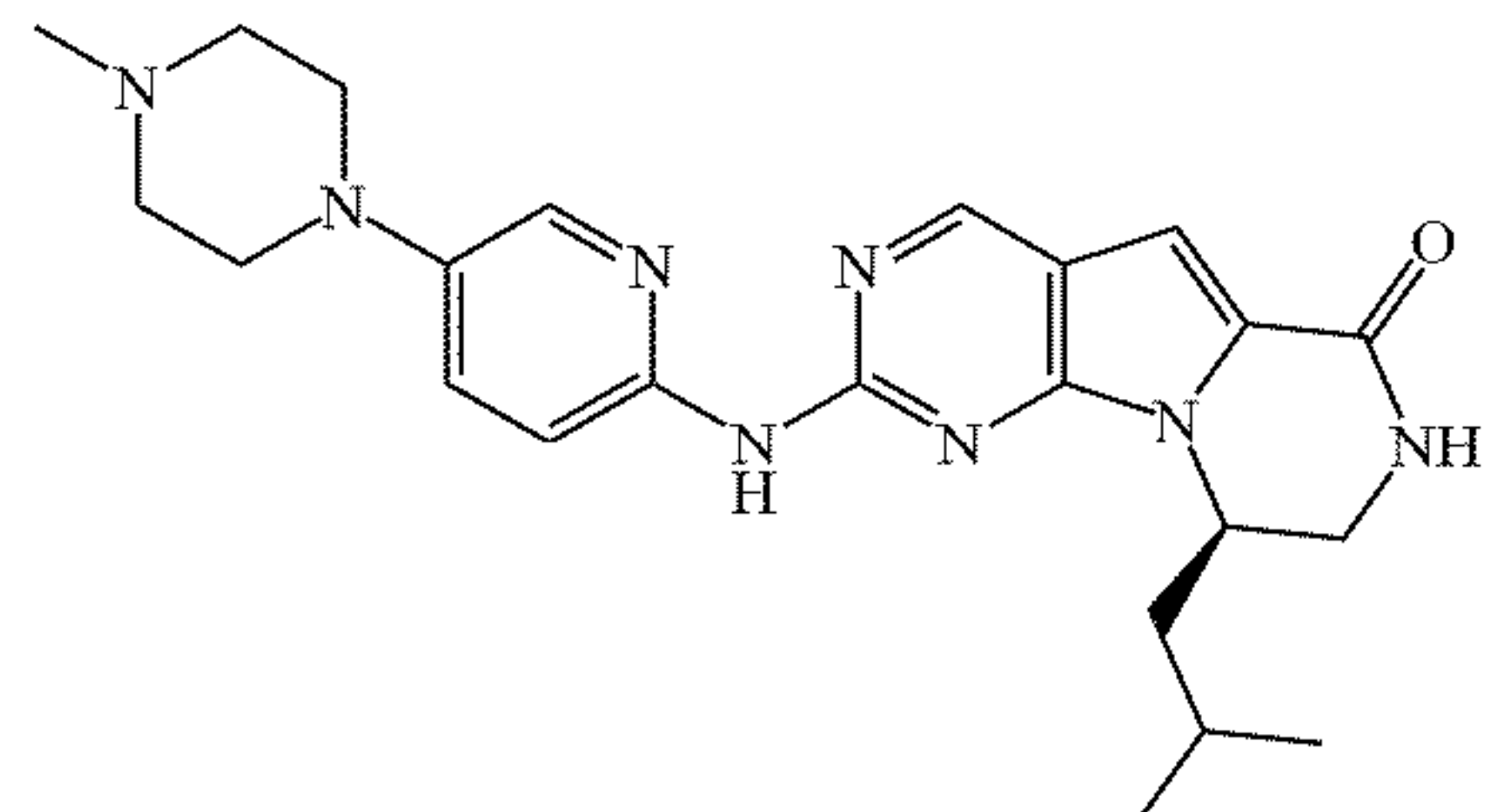
Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
MMM	
NNN	
OOO	
PPP	
QQQ	
RRR	
SSS	

TABLE 1-continued

Exemplary Non-limiting Structures of Anti-Neoplastic and Anti-Proliferative Agents	
Structure Reference	Structure
TTT	
UUU	
VVV	
WWW	
XXX	

Definitions

[0164] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. As used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg (2007) *Advanced Organic Chemistry 5th Ed.* Vols. A and B, Springer Science+Business Media LLC, New York. The practice of the present invention will employ, unless otherwise indicated, conventional methods of synthetic organic chemistry, mass spectroscopy, preparative and analytical methods of chromatography, protein

chemistry, biochemistry, recombinant DNA techniques and pharmacology. Conventional methods of organic chemistry include those included in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th Edition*, M.B. Smith and J. March, John Wiley & Sons, Inc., Hoboken, NJ, 2007.

[0165] The term “alkyl,” either alone or within other terms such as “haloalkyl” and “alkylamino,” embraces linear or branched radicals having one to about twelve carbon atoms. “Lower alkyl” radicals have one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl and the like. The term “alkylene” embraces bridging divalent linear and branched alkyl radicals. Examples include methylene, ethylene, propylene, isopropylene and the like.

[0166] The term “alkenyl” embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. “Lower alkenyl” radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms “alkenyl” and “lower alkenyl,” embrace radicals having “cis” and “trans” orientations, or alternatively, “E” and “Z” orientations.

[0167] The term “alkynyl” denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. “Lower alkynyl” radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[0168] Alkyl, alkenyl, and alkynyl radicals may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

[0169] The term “alkylamino” embraces “N-alkylamino” and “N,N-dialkylamino” where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. “Lower alkylamino” radicals have one or two alkyl radicals of one to six carbon atoms attached to a nitrogen atom. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

[0170] The term “halo” means halogens such as fluorine, chlorine, bromine or iodine atoms.

[0171] The term “haloalkyl” embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo as defined above. Examples include monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. “Lower haloalkyl” embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. “Perfluoroalkyl” means an alkyl radical having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

[0172] The term “aryl”, alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term “aryl” embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said “aryl” group may have 1 or more substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy, lower alkylamino, and the like. An aryl group may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

[0173] The term “heterocyclyl” (or “heterocyclo”) embraces saturated, and partially saturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Heterocyclic rings comprise monocyclic 6-8 membered rings, as well as 5-16 membered bicyclic ring systems (which can include bridged fused and spiro-fused bicyclic ring systems). It does not include rings containing -O-O-, -O-S- or -S-S- portions.

Said “heterocyclyl” group may have 1 to 3 substituents such as hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino, lower alkylamino, and the like.

[0174] Examples of saturated heterocyclo groups include saturated 3- to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl, dihydrothiazolyl, and the like.

[0175] Particular examples of partially saturated and saturated heterocyclo groups include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4- tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7- trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3- dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

[0176] Heterocyclo groups also includes radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl].

[0177] The term “heteroaryl” denotes aryl ring systems that contain one or more heteroatoms selected from the group O, N and S, wherein the ring nitrogen and sulfur atom(s) are optionally oxidized, and nitrogen atom(s) are optionally quarternized. Examples include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5- oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl,

thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

[0178] The term “heteroarylalkyl” denotes alkyl radicals substituted with a heteroaryl group. Examples include pyridylmethyl and thienylethyl.

[0179] The term “sulfonyl”, whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $\text{-SO}_2\text{-}$.

[0180] The terms “carboxy” or “carboxyl”, whether used alone or with other terms, such as “carboxyalkyl”, denotes -C(O)-OH .

[0181] The term “carbonyl”, whether used alone or with other terms, such as “aminocarbonyl”, denotes -C(O)- .

[0182] The term “aminocarbonyl” denotes an amide group of the Formula -C(O)-NH_2 .

[0183] The terms “heterocycloalkyl” embrace heterocyclic-substituted alkyl radicals. Examples include piperidylmethyl and morpholinylethyl.

[0184] The term “arylalkyl” embraces aryl-substituted alkyl radicals. Examples include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

[0185] The term “cycloalkyl” includes saturated carbocyclic groups of 3 to 10 carbons. Lower cycloalkyl groups include $\text{C}_3\text{-C}_6$ rings. Examples include cyclopentyl, cyclopropyl, and cyclohexyl. Cycloalkyl groups may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

[0186] The term “cycloalkylalkyl” embraces cycloalkyl-substituted alkyl radicals. “Lower cycloalkylalkyl” radicals are cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Examples of include cyclohexylmethyl. The cycloalkyl in said radicals may be additionally substituted with halo, alkyl, alkoxy and hydroxy.

[0187] The term “cycloalkenyl” includes carbocyclic groups having one or more carbon-carbon double bonds including “cycloalkyldienyl” compounds. Examples include cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

[0188] The term “comprising” is meant to be open ended, including the indicated component but not excluding other elements.

[0189] The term “oxo” as used herein contemplates an oxygen atom attached with a double bond.

[0190] The term “nitro” as used herein contemplates -NO_2 .

[0191] The term “cyano” as used herein contemplates -CN .

[0192] As used herein, the term “prodrug” means a compound which when administered to a host in vivo is converted into the parent drug. As used herein, the term “parent drug” means any of the presently described chemical compounds that are useful to treat any of the disorders described herein, or to control or improve the underlying cause or symptoms associated with any physiological or pathological disorder described herein in a host, typically a human. Prodrugs can be used to achieve any desired effect, including to enhance properties of the parent drug or to improve the pharmaceutic or pharmacokinetic properties of the parent. Prodrug strategies exist which provide choices in modulating the conditions for in vivo generation of the parent drug, all of which are deemed included herein. Nonlimiting exam-

ples of prodrug strategies include covalent attachment of removable groups, or removable portions of groups, for example, but not limited to acylation, phosphorylation, phosphonylation, phosphoramidate derivatives, amidation, reduction, oxidation, esterification, alkylation, other carboxy derivatives, sulfoxy or sulfone derivatives, carbonylation or anhydride, among others.

[0193] The term “host” refers to an individual, preferably a mammal such as a human. The term “host” can include domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, monkey, rabbit, rat, guinea pig, etc.) and birds.

Method of Treatment of Selected Cancer, Tumors, Hyperproliferative Conditions, and Inflammatory and Immune Disorders

[0194] In certain aspects, the invention includes the use of an effective amount of a compound described herein, or its pharmaceutically acceptable salt, prodrug or isotopic variant optionally in a pharmaceutical composition, to treat a host, typically a human, with a selected cancer, tumor, hyperproliferative condition or an inflammatory or immune disorder. Some of the disclosed compounds are highly active against T-cell proliferation. Given the paucity of drugs for T-cell cancers and abnormal proliferation, the identification of such uses represents a substantial improvement in the medical therapy for these diseases.

[0195] Abnormal proliferation of T-cells, B-cells, and/or NK-cells can result in a wide range of diseases such as cancer, proliferative disorders and inflammatory/immune diseases. A host, for example a human, afflicted with any of these disorders can be treated with an effective amount of a compound as described herein to achieve a decrease in symptoms (a palliative agent) or a decrease in the underlying disease (a disease modifying agent).

[0196] Examples include T-cell or NK-cell lymphoma, for example, but not limited to: peripheral T-cell lymphoma; anaplastic large cell lymphoma, for example anaplastic lymphoma kinase (ALK) positive, ALK negative anaplastic large cell lymphoma, or primary cutaneous anaplastic large cell lymphoma; angioimmunoblastic lymphoma; cutaneous T-cell lymphoma, for example mycosis fungoides, Sezary syndrome, primary cutaneous anaplastic large cell lymphoma, primary cutaneous CD30+ T-cell lymphoproliferative disorder; primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma; primary cutaneous gamma-delta T-cell lymphoma; primary cutaneous small/medium CD4+ T-cell lymphoma, and lymphomatoid papulosis; Adult T-cell Leukemia/Lymphoma (ATLL); Blastic NK-cell Lymphoma; Enteropathy-type T-cell lymphoma; Hematosplenic gamma-delta T-cell Lymphoma; Lymphoblastic Lymphoma; Nasal NK/T-cell Lymphomas; Treatment-related T-cell lymphomas; for example lymphomas that appear after solid organ or bone marrow transplantation; T-cell prolymphocytic leukemia; T-cell large granular lymphocytic leukemia; Chronic lymphoproliferative disorder of NK-cells; Aggressive NK cell leukemia; Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection); Hydroa vacciniforme-like lymphoma; Adult T-cell leukemia/lymphoma; Enteropathy-associated T-cell lymphoma; Hepatos-

plenic T-cell lymphoma; or Subcutaneous panniculitis-like T-cell lymphoma.

[0197] In one embodiment, a compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human, with a lymphoma or lymphocytic or myelocytic proliferation disorder or abnormality. For example, the compounds as described herein can be administered to a host suffering from a Hodgkin Lymphoma or a Non-Hodgkin Lymphoma. For example, the host can be suffering from a Non-Hodgkin Lymphoma such as, but not limited to: an AIDS-Related Lymphoma; Anaplastic Large-Cell Lymphoma; Angioimmunoblastic Lymphoma; Blastic NK-Cell Lymphoma; Burkitt's Lymphoma; Burkitt-like Lymphoma (Small Non-Cleaved Cell Lymphoma); Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Cutaneous T-Cell Lymphoma; Diffuse Large B-Cell Lymphoma; Enteropathy-Type T-Cell Lymphoma; Follicular Lymphoma; Hepatosplenic Gamma-Delta T-Cell Lymphoma; Lymphoblastic Lymphoma; Mantle Cell Lymphoma; Marginal Zone Lymphoma; Nasal T-Cell Lymphoma; Pediatric Lymphoma; Peripheral T-Cell Lymphomas; Primary Central Nervous System Lymphoma; T-Cell Leukemias; Transformed Lymphomas; Treatment-Related T-Cell Lymphomas; or Waldenstrom's Macroglobulinemia.

[0198] Alternatively, a compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human, with a Hodgkin Lymphoma, such as, but not limited to: Nodular Sclerosis Classical Hodgkin's Lymphoma (CHL); Mixed Cellularity CHL; Lymphocyte-depletion CHL; Lymphocyte-rich CHL; Lymphocyte Predominant Hodgkin Lymphoma; or Nodular Lymphocyte Predominant HL.

[0199] Alternatively, a compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human with a specific B-cell lymphoma or proliferative disorder such as, but not limited to: multiple myeloma; Diffuse large B cell lymphoma; Follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT); Small cell lymphocytic lymphoma; Mediastinal large B cell lymphoma; Nodal marginal zone B cell lymphoma (NMZL); Splenic marginal zone lymphoma (SMZL); Intravascular large B-cell lymphoma; Primary effusion lymphoma; or Lymphomatoid granulomatosis;; B-cell prolymphocytic leukemia; Hairy cell leukemia; Splenic lymphoma/leukemia, unclassifiable; Splenic diffuse red pulp small B-cell lymphoma; Hairy cell leukemia-variant; Lymphoplasmacytic lymphoma; Heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease; Plasma cell myeloma; Solitary plasmacytoma of bone; Extraosseous plasmacytoma; Primary cutaneous follicle center lymphoma; T cell/histiocyte rich large B-cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; Primary mediastinal (thymic) large B-cell lymphoma; Primary cutaneous DLBCL, leg type; ALK+ large B-cell lymphoma; Plasmablastic lymphoma; Large B-cell lymphoma arising in HHV8-associated multicentric; Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-

cell lymphoma; or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

[0200] In one embodiment, a compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human with leukemia. For example, the host may be suffering from an acute or chronic leukemia of a lymphocytic or myelogenous origin, such as, but not limited to: Acute lymphoblastic leukemia (ALL); Acute myelogenous leukemia (AML); Chronic lymphocytic leukemia (CLL); Chronic myelogenous leukemia (CML); juvenile myelomonocytic leukemia (JMML); hairy cell leukemia (HCL); acute promyelocytic leukemia (a subtype of AML); large granular lymphocytic leukemia; or Adult T-cell chronic leukemia. In one embodiment, the patient suffers from an acute myelogenous leukemia, for example an undifferentiated AML (M0); myeloblastic leukemia (M1; with/without minimal cell maturation); myeloblastic leukemia (M2; with cell maturation); promyelocytic leukemia (M3 or M3 variant [M3V]); myelomonocytic leukemia (M4 or M4 variant with eosinophilia [M4E]); monocytic leukemia (M5); erythroleukemia (M6); or megakaryoblastic leukemia (M7).

[0201] In another embodiment, a compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human with an autoimmune disorder. Examples include, but are not limited to: Acute disseminated encephalomyelitis (ADEM); Addison's disease; Agammaglobulinemia; Alopecia areata; Amyotrophic lateral sclerosis (Also Lou Gehrig's disease; Motor Neuron Disease); Ankylosing Spondylitis; Antiphospholipid syndrome; Antisynthetase syndrome; Atopic allergy; Atopic dermatitis; Autoimmune aplastic anemia; Autoimmune arthritis; Autoimmune cardiomyopathy; Autoimmune enteropathy; Autoimmune granulocytopenia; Autoimmune hemolytic anemia; Autoimmune hepatitis; Autoimmune hypoparathyroidism; Autoimmune inner ear disease; Autoimmune lymphoproliferative syndrome; Autoimmune myocarditis; Autoimmune pancreatitis; Autoimmune peripheral neuropathy; Autoimmune ovarian failure; Autoimmune polyendocrine syndrome; Autoimmune progesterone dermatitis; Autoimmune thrombocytopenic purpura; Autoimmune thyroid disorders; Autoimmune urticarial; Autoimmune uveitis; Autoimmune vasculitis; Balo disease/Balo concentric sclerosis; Behçet's disease; Berger's disease; Bickerstaffs encephalitis; Blau syndrome; Bullous pemphigoid; Cancer; Castleman's disease; Celiac disease; Chagas disease; Chronic inflammatory demyelinating polyneuropathy; Chronic inflammatory demyelinating polyneuropathy; Chronic obstructive pulmonary disease; Chronic recurrent multifocal osteomyelitis; Churg-Strauss syndrome; Cicatricial pemphigoid; Cogan syndrome; Cold agglutinin disease; Complement component 2 deficiency; Contact dermatitis; Cranial arteritis; CREST syndrome; Crohn's disease; Cushing's Syndrome; Cutaneous leukocytoclastic angiitis; Dego's disease; Dercum's disease; Dermatitis herpetiformis; Dermatomyositis; Diabetes mellitus type 1; Diffuse cutaneous systemic sclerosis; Discoid lupus erythematosus; Dressler's syndrome; Drug-induced lupus; Eczema; Endometriosis; Enthesitis-related arthritis;

Eosinophilic fasciitis; Eosinophilic gastroenteritis; Eosinophilic pneumonia; Epidermolysis bullosa acquisita; Erythema nodosum; Erythroblastosis fetalis; Essential mixed cryoglobulinemia; Evan's syndrome; Extrinsic and intrinsic reactive airways disease (asthma); Fibrodysplasia ossificans progressive; Fibrosing alveolitis (or Idiopathic pulmonary fibrosis); Gastritis; Gastrointestinal pemphigoid; Glomerulonephritis; Goodpasture's syndrome; Graves' disease; Guillain-Barre syndrome (GBS); Hashimoto's encephalopathy; Hashimoto's thyroiditis; Hemolytic anemia; Henoch-Schonlein purpura; Herpes gestationis (Gestational Pemphigoid); Hidradenitis suppurativa; Hughes-Stovin syndrome; Hypogammaglobulinemia; Idiopathic inflammatory demyelinating diseases; Idiopathic pulmonary fibrosis; Idiopathic thrombocytopenic purpura; IgA nephropathy; Immune glomerulonephritis; Immune nephritis; Immune pneumonitis; Inclusion body myositis; inflammatory bowel disease; Interstitial cystitis; Juvenile idiopathic arthritis aka Juvenile rheumatoid arthritis; Kawasaki's disease; Lambert-Eaton myasthenic syndrome; Leukocytoclastic vasculitis; Lichen planus; Lichen sclerosus; Linear IgA disease (LAD); Lupoid hepatitis aka Autoimmune hepatitis; Lupus erythematosus; Majeed syndrome; microscopic polyangiitis; Miller-Fisher syndrome; mixed connective tissue disease; Morphea; Mucha-Habermann disease aka Pityriasis lichenoides et varioliformis acuta; Multiple sclerosis; Myasthenia gravis; Myositis; Ménière's disease; Narcolepsy; Neuromyelitis optica (also Devic's disease); Neuromyotonia; Ocular cicatricial pemphigoid; Opsoclonus myoclonus syndrome; Ord's thyroiditis; Palindromic rheumatism; PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcus); Paraneoplastic cerebellar degeneration; Paroxysmal nocturnal hemoglobinuria (PNH); Parry Romberg syndrome; Pars planitis; Parsonage-Turner syndrome; Pemphigus vulgaris; Perivenous encephalomyelitis; Pernicious anaemia; POEMS syndrome; Polyarteritis nodosa; Polymyalgia rheumatic; Polymyositis; Primary biliary cirrhosis; Primary sclerosing cholangitis; Progressive inflammatory neuropathy; Psoriasis; Psoriatic arthritis; pure red cell aplasia; Pyoderma gangrenosum; Rasmussen's encephalitis; Raynaud phenomenon; Reiter's syndrome; relapsing polychondritis; restless leg syndrome; retroperitoneal fibrosis; rheumatic fever; rheumatoid arthritis; Sarcoidosis; Schizophrenia; Schmidt syndrome; Schnitzler syndrome; Scleritis; Scleroderma; Sclerosing cholangitis; serum sickness; Sjogren's syndrome; Spondyloarthropathy; Stiff person syndrome; Still's disease; Subacute bacterial endocarditis (SBE); Susac's syndrome; Sweet's syndrome; Sydenham chorea; sympathetic ophthalmia; systemic lupus erythematosus; Takayasu's arteritis; temporal arteritis (also known as "giant cell arteritis"); thrombocytopenia; Tolosa-Hunt syndrome; transverse myelitis; ulcerative colitis; undifferentiated connective tissue disease; undifferentiated spondyloarthropathy; urticarial vasculitis; vasculitis; vitiligo; viral diseases such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV) and Human Papilloma Virus (HPV); or Wegener's granulomatosis. In some embodiments, the autoimmune disease is an allergic con-

dition, including those from asthma, food allergies, atopic dermatitis, and rhinitis.

[0202] In yet another embodiment, a compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human with a disease involving the immune system. In one example, a compound disclosed herein can be used to prevent organ transplant rejection (e.g., allograft rejection and graft versus host disease).

[0203] A compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human with a skin disorders such as psoriasis (for example, psoriasis vulgaris), atopic dermatitis, skin rash, skin irritation, skin sensitization (e.g., contact dermatitis or allergic contact dermatitis). For example, certain substances including some pharmaceuticals when topically applied can cause skin sensitization. In some embodiments, the skin disorder is treated by topical administration of compounds known in the art in combination with the compounds disclosed herein.

[0204] A compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human with a proliferative condition such as a myeloproliferative disorder (MPD), polycythemia vera (PV), essential thrombocythemia (ET), myeloid metaplasia with myelofibrosis (MMM), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), and the like.

[0205] A compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human with an inflammatory disorder. Example inflammatory diseases include inflammatory diseases of the eye (e.g., iritis, uveitis, conjunctivitis, or related disease), inflammatory diseases of the respiratory tract (e.g., the upper respiratory tract including the nose and sinuses such as rhinitis or sinusitis or the lower respiratory tract including bronchitis, chronic obstructive pulmonary disease, and the like), inflammatory myopathy such as myocarditis, and other inflammatory diseases.

[0206] A compound disclosed herein, or its salt, prodrug, or isotopic variant can be used in an effective amount to treat a host, for example a human with an inflammatory ischemic event such as stroke or cardiac arrest.

[0207] In another embodiment, the compounds provided herein is useful for the treatment of primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis, and secondary acute myelogenous leukemia. In another embodiment, the compounds provided herein can be used to treat patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. In some embodiments, the host to be treated (e.g., a human) is determined to be non-responsive or resistant to one or more therapies for myeloproliferative disorders. In a particular embodiment, provided herein is a method of treating a myeloproliferative neoplasm in a host in need thereof, comprising administering to the host an effective amount of a composition comprising a compound

described herein, or a pharmaceutically acceptable salt thereof.

Combination Therapy

[0208] In one aspect of the invention, the compounds disclosed herein can be beneficially administered in combination with another therapeutic regimen for beneficial, additive or synergistic effects.

[0209] In one embodiment, a compound/method of the present invention is used in combination with another therapy to treat the T, B or NK abnormal cellular proliferation including cancer or disorder. The second therapy can be an immunotherapy. As discussed in more detail below, the compound can be conjugated to an antibody, radioactive agent or other targeting agent that directs the compound to the diseased or abnormally proliferating cell. In another embodiment, the compound is used in combination with another pharmaceutical or a biologic agent (for example an antibody) to increase the efficacy of treatment with a combined or a synergistic approach. In an embodiment, the compound can be used with T-cell vaccination, which typically involves immunization with inactivated autoreactive T cells to eliminate a pathogenic autoreactive T cell population. In another embodiment, the compound is used in combination with a bispecific T-cell Engager (BiTE), which is an antibody designed to simultaneously bind to specific antigens on endogenous T cells and malignant cells, linking the two types of cells.

[0210] In one embodiment, the additional therapy is a monoclonal antibody (MAb). Some MAbs stimulate an immune response that destroys cancer cells. Similar to the antibodies produced naturally by B cells, these MAbs “coat” the cancer cell surface, triggering its destruction by the immune system. FDA-approved MAbs of this type include rituximab, which targets the CD20 antigen found on non-Hodgkin lymphoma cells, and alemtuzumab, which targets the CD52 antigen found on B-cell chronic lymphocytic leukemia (CLL) cells. Rituximab may also trigger cell death (apoptosis) directly. Another group of MAbs stimulates an anticancer immune response by binding to receptors on the surface of immune cells and inhibiting signals that prevent immune cells from attacking the body’s own tissues, including cancer cells. Other MAbs interfere with the action of proteins that are necessary for tumor growth. For example, bevacizumab targets vascular endothelial growth factor (VEGF), a protein secreted by tumor cells and other cells in the tumor’s microenvironment that promotes the development of tumor blood vessels. When bound to bevacizumab, VEGF cannot interact with its cellular receptor, preventing the signaling that leads to the growth of new blood vessels. Similarly, cetuximab and panitumumab target the epidermal growth factor receptor (EGFR), and trastuzumab targets the human epidermal growth factor receptor 2 (HER-2). MAbs that bind to cell surface growth factor receptors prevent the targeted receptors from sending their normal growth-promoting signals. They may also trigger apoptosis and activate the immune system to destroy tumor cells. Another group of cancer therapeutic MAbs are the immunoconjugates. These MAbs, which are sometimes called immunotoxins or antibody-drug conjugates, consist of an antibody

attached to a cell-killing substance, such as a plant or bacterial toxin, a chemotherapy drug, or a radioactive molecule. The antibody latches onto its specific antigen on the surface of a cancer cell, and the cell-killing substance is taken up by the cell. FDA-approved conjugated MAbs that work this way include ⁹⁰Y- ibritumomab tiuxetan, which targets the CD20 antigen to deliver radioactive yttrium-90 to B-cell non-Hodgkin lymphoma cells; ¹³¹I-tositumomab, which targets the CD20 antigen to deliver radioactive iodine-131 to non-Hodgkin lymphoma cells; and ado-trastuzumab emtansine, which targets the HER-2 molecule to deliver the drug DM1, which inhibits cell proliferation, to HER-2 expressing metastatic breast cancer cells.

[0211] Immunotherapies with T cells engineered to recognize cancer cells via bispecific antibodies (bsAbs) or chimeric antigen receptors (CARs) are particularly promising approaches with potential to ablate both dividing and non/slow-dividing subpopulations of cancer cells.

[0212] Bispecific antibodies, by simultaneously recognizing target antigen and an activating receptor on the surface of an immune effector cell, offer an opportunity to redirect immune effector cells to kill cancer cells. The other approach is the generation of chimeric antigen receptors by fusing extracellular antibodies to intracellular signaling domains. Chimeric antigen receptor-engineered T cells are able to specifically kill tumor cells in a MHC-independent way.

[0213] General anticancer pharmaceutical agents include: Vincristine (Oncovin®) or liposomal vincristine (Marqibo®), Daunorubicin (daunomycin or Cerubidine®) or doxorubicin (Adriamycin®), Cytarabine (cytosine arabinoside, ara-C, or Cytosar®), L-asparaginase (Elspar®) or PEG-L-asparaginase (pegaspargase or Oncaspar®), Etoposide (VP-16), Teniposide (Vumon®), 6-mercaptopurine (6-MP or Purinethol®), Methotrexate, Cyclophosphamide (Cytoxan®), Prednisone, Dexamethasone (Decadron®), imatinib (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), bosutinib (Bosulif®), and ponatinib (Iclusig™), Trastuzumab (Herceptin®), Pertuzumab (Perjeta™), Lapatinib (Tykerb®), Gefitinib (Iressa®), Erlotinib (Tarceva®), Cetuximab (Erbix®), Panitumumab (Vectibix®), Vandetanib (Caprelsa®), Vemurafenib (Zelboraf®), Vorinostat (Zolinza®), Romidepsin (Istodax®), Bexarotene (Tagretin®), Alitretinoin (Panretin®), Tretinoin (Vesanoid®), Carfilizomib (Kyprolis™), Pralatrexate (Foloty®), Bevacizumab (Avastin®), Ziv-aflibercept (Zaltrap®), Sorafenib (Nexavar®), Sunitinib (Sutent®), Pazopanib (Votrient®), Regorafenib (Stivarga®), and Cabozantinib (Cometriq™).

[0214] Current chemotherapeutic drugs used to treat AML are cytarabine (cytosine arabinoside or ara-C) and the anthracycline drugs (such as daunorubicin/daunomycin, idarubicin, and mitoxantrone). Some of the other chemo drugs that may be used to treat AML include: Cladribine (Leustatin®, 2-CdA), Fludarabine (Fludara®), Topotecan, Etoposide (VP-16), 6-thioguanine (6-TG), Hydroxyurea (Hydrea®), Corticosteroid drugs, such as prednisone or dexamethasone (Decadron®), Methotrexate (MTX), 6-mercaptopurine (6-MP), Azacitidine (Vidaza®), Decitabine (Dacogen®)

[0215] Current chemotherapeutic drugs for CLL and other lymphomas include: purine analogs such as fludara-

bine (Fludara®), pentostatin (Nipent®), and cladribine (2-CdA, Leustatin®), and alkylating agents, which include chlorambucil (Leukeran®) and cyclophosphamide (Cytosan®) and bendamustine (Treanda®). Other drugs sometimes used for CLL include doxorubicin (Adriamycin®), methotrexate, oxaliplatin, vincristine (Oncovin®), etoposide (VP-16), and cytarabine (ara-C). Other drugs include Rituximab (Rituxan), Obinutuzumab (Gazyva™), Ofatumumab (Arzerra®), Alemtuzumab (Campath®) and Ibrutinib (Imbruvica™)

[0216] Current chemotherapies for CML include: Interferon, imatinib (Gleevec), the chemo drug hydroxyurea (Hydrea®), cytarabine (Ara-C), busulfan, cyclophosphamide (Cytosan®), and vincristine (Oncovin®). Omacetaxine (Synribo®) is a chemo drug that was approved to treat CML that is resistant to some of the TKIs now in use.

[0217] CMML is now treated with Deferasirox (Exjade®), cytarabine with idarubicin, cytarabine with topotecan, and cytarabine with fludarabine, Hydroxyurea (hydroxycarbamate, Hydrea®), azacytidine (Vidaza®) and decitabine (Dacogen®).

[0218] Erythropoietin (Epo® or Procrit®), a growth factor that promotes red blood cell production, can help avoid transfusions of red blood cells in some patients. Recently it has been found that combining erythropoietin with a growth factor for white blood cells (G-CSF, Neupogen®, or filgrastim) improves the patient's response to the erythropoietin. Darbepoetin (Aranesp®) is a long-acting form of erythropoietin. It works in the same way but can be given less often. Oprelvekin (Neumega®, interleukin-11, or IL-11) can be used to stimulate platelet production after chemotherapy and in some other diseases.

[0219] Therapies for multiple myeloma include Pomalidomide (Pomalyst®), Carfilzomib (Kyprolis™), Everolimus (Afinitor®), dexamethasone (Decadron), prednisone and methylprednisolone (Solu-medrol®) and hydrocortisone.

[0220] Therapies for Hodgkins disease include Brentuximab vedotin (Adcetris™): anti-CD-30, Rituximab, Adriamycin® (doxorubicin), Bleomycin, Vinblastine, Dacarbazine (DTIC).

[0221] Monoclonal antibodies for Non-Hodgkins disease include Rituximab (Rituxan®), Ibritumomab (Zevalin®), tositumomab (Bexxar®), Alemtuzumab (Campath®) (CD52 antigen), Ofatumumab (Arzerra®), Brentuximab vedotin (Adcetris®) and Lenalidomide (Revlimid®).

[0222] B-cell Lymphoma approved therapies include:

[0223] Diffuse large B-cell lymphoma: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), plus the monoclonal antibody rituximab (Rituxan). This regimen, known as R-CHOP, is usually given for about 6 months.

[0224] Primary mediastinal B-cell lymphoma: R-CHOP

[0225] Follicular lymphoma: rituximab (Rituxan) combined with chemo, using either a single chemo drug (such as bendamustine or fludarabine) or a combination of drugs, such as the CHOP or CVP (cyclophosphamide, vincristine, prednisone regimens. The radioactive monoclonal antibodies, ibritumomab (Zevalin) and tositumomab (Bexxar) are also possible treatment options. For patients who may not be able to tolerate more intensive chemo regi-

mens, rituximab alone, milder chemo drugs (such as chlorambucil or cyclophosphamide).

[0226] Chronic lymphocytic leukemia/small lymphocytic lymphoma: R-CHOP

[0227] Mantle cell lymphoma: fludarabine, cladribine, or pentostatin; bortezomib (Velcade) and lenalidomide (Revlimid) and ibrutinib (Imbruvica) Extranodal marginal zone B-cell lymphoma - mucosa-associated lymphoid tissue (MALT) lymphoma: rituximab; chlorambucil or fludarabine or combinations such as CVP, often along with rituximab.

[0228] Nodal marginal zone B-cell lymphoma: rituximab (Rituxan) combined with chemo, using either a single chemo drug (such as bendamustine or fludarabine) or a combination of drugs, such as the CHOP or CVP (cyclophosphamide, vincristine, prednisone regimens. The radioactive monoclonal antibodies, ibritumomab (Zevalin) and tositumomab (Bexxar) are also possible treatment options. For patients who may not be able to tolerate more intensive chemo regimens, rituximab alone, milder chemo drugs (such as chlorambucil or cyclophosphamide).

[0229] Splenic marginal zone B-cell lymphoma: rituximab; patients with Hep C – anti-virals

[0230] Burkitt lymphoma: methotrexate; hyper-CVAD - cyclophosphamide, vincristine, doxorubicin (also known as Adriamycin), and dexamethasone. Course B consists of methotrexate and cytarabine; CODOX-M – cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine; etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) Lymphoplasmacytic lymphoma -rituximab

[0231] Hairy cell leukemia – cladribine (2-CdA) or pentostatin; rituximab; interferon-alfa

[0232] Current therapies for T-cell lymphomas include:

[0233] Precursor T-lymphoblastic lymphoma/leukemia - cyclophosphamide, doxorubicin (Adriamycin), vincristine, L-asparaginase, methotrexate, prednisone, and, sometimes, cytarabine (ara-C). Because of the risk of spread to the brain and spinal cord, a chemo drug such as methotrexate is also given into the spinal fluid. Skin lymphomas: Gemcitabine Liposomal doxorubicin (Doxil); Methotrexate; Chlorambucil; Cyclophosphamide; Pentostatin; Etoposide; Temozolomide; Pralatrexate; R-CHOP

[0234] Angioimmunoblastic T-cell lymphoma: prednisone or dexamethasone

[0235] Extranodal natural killer/T-cell lymphoma, nasal type: CHOP

[0236] Anaplastic large cell lymphoma: CHOP; pralatrexate (Folotylin), targeted drugs such as bortezomib (Velcade) orromidepsin (Istodax), or immunotherapy drugs such as alemtuzumab (Campath) and denileukin diftitox (Ontak)

[0237] Primary central nervous system (CNS) lymphoma - methotrexate; rituximab

[0238] A more general list of suitable chemotherapeutic agents include, but are not limited to, radioactive molecules, toxins, also referred to as cytotoxins or cytotoxic agents, which includes any agent that is detrimental to the viability of cells, agents, and liposomes or other vesicles containing chemotherapeutic compounds. Examples

of suitable chemotherapeutic agents include but are not limited to 1-dehydrotestosterone, 5-fluorouracil decarbazine, 6-mercaptopurine, 6-thioguanine, actinomycin D, adriamycin, aldesleukin, alkylating agents, allopurinol sodium, altretamine, amifostine, anastrozole, anthramycin (AMC)), anti-mitotic agents, cis-dichlorodiamine platinum (II) (DDP) cisplatin), diamino dichloro platinum, anthracyclines, antibiotics, antis, asparaginase, BCG live (intravesical), betamethasone sodium phosphate and betamethasone acetate, bicalutamide, bleomycin sulfate, busulfan, calcium leucovorin, calicheamicin, capecitabine, carboplatin, lomustine (CCNU), carmustine (BSNU), Chlorambucil, Cisplatin, Cladribine, Colchicin, conjugated estrogens, Cyclophosphamide, Cyclophosphamide, Cytarabine, Cytarabine, cytochalasin B, Cytosan, Dacarbazine, Dactinomycin, dactinomycin (formerly actinomycin), daunirubicin HCL, daunorubicin citrate, denileukin diftitox, Dexrazoxane, Dibromomannitol, dihydroxy anthracin dione, Docetaxel, dolasetron mesylate, doxorubicin HCL, dronabinol, E. coli L-asparaginase, emetine, epoetin- α , Erwinia L-asparaginase, esterified estrogens, estradiol, estramustine phosphate sodium, ethidium bromide, ethinyl estradiol, etidronate, etoposide citrororum factor, etoposide phosphate, filgrastim, floxuridine, fluconazole, fludarabine phosphate, fluorouracil, flutamide, folinic acid, gemcitabine HCL, glucocorticoids, goserelin acetate, gramicidin D, granisetron HCL, hydroxyurea, idarubicin HCL, ifosfamide, interferon α -2b, irinotecan HCL, letrozole, leucovorin calcium, leuprolide acetate, levamisole HCL, lidocaine, lomustine, maytansinoid, mechlorethamine HCL, medroxyprogesterone acetate, megestrol acetate, melphalan HCL, mercaptopurine, mesna, methotrexate, methyltestosterone, mithramycin, mitomycin C, mitotane, mitoxantrone, nilutamide, octreotide acetate, ondansetron HCL, paclitaxel, pamidronate disodium, pentostatin, pilocarpine HCL, plimycin, polifeprosan 20 with carmustine implant, porfimer sodium, procaine, procarbazine HCL, propranolol, rituximab, sargramostim, streptozotocin, tamoxifen, taxol, teniposide, teniposide, testolactone, tetracaine, thioepa chlorambucil, thioguanine, thiotepa, topotecan HCL, toremifene citrate, trastuzumab, tretinoin, valrubicin, vinblastine sulfate, vincristine sulfate, and vinorelbine tartrate.

[0239] Additional therapeutic agents that can be administered in combination with the compounds disclosed herein can include bevacizumab, sunitinib, sorafenib, 2-methoxyestradiol, finasunate, vatalanib, vandetanib, aflibercept, volociximab, etaracizumab, cilengitide, erlotinib, cetuximab, panitumumab, gefitinib, trastuzumab, ataciccept, rituximab, alemtuzumab, aldesleukine, atlizumab, tocilizumab, temsirolimus, everolimus, lucatumumab, dacetuzumab, atiprimod, natalizumab, bortezomib, carfilzomib, marizomib, tanespimycin, saquinavir mesylate, ritonavir, nelfinavir mesylate, indinavir sulfate, belinostat, panobinostat, mapatumumab, lexatumumab, oblimersen, plitidepsin, talmapimod, enzastaurin, tipifarnib, perifosine, imatinib, dasatinib, lenalidomide, thalidomide, simvastatin, and celecoxib.

[0240] In one aspect of the present invention, the compounds disclosed herein are combined with at least one immunosuppressive agent. The immunosuppressive agent may be selected from the group consisting of a cal-

cineurin inhibitor, e.g. a cyclosporin or an ascomycin, e.g. Cyclosporin A (NEORAL®), tacrolimus, a mTOR inhibitor, e.g. rapamycin or a derivative thereof, e.g. Sirolimus (RAPAMUNE®), Everolimus (Certican®), temsirolimus, biolimus-7, biolimus-9, a rapalog, e.g. azathioprine, campath 1H, a S1P receptor modulator, e.g. fingolimod or an analogue thereof, an anti IL-8 antibody, mycophenolic acid or a salt thereof, e.g. sodium salt, or a prodrug thereof, e.g. Mycophenolate Mofetil (CELLCEPT®), OKT3 (ORTHOCLONE OKT3®), Prednisone, ATGAM®, THYMOGLOBULIN®, Brequinar Sodium, 15-deoxyspergualin, tresperimus, Leflunomide ARAVA®, anti-CD25, anti-IL2R, Basiliximab (SIMULECT®), Daclizumab (ZENAPAX®), mizorbine, methotrexate, dexamethasone, pimecrolimus (Elidel®), abatacept, belatacept, etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), an anti-LFA-1 antibody, natalizumab (Antegren®), Enlimomab, ABX-CBL, antithymocyte immunoglobulin, siplizumab, and efalizumab.

[0241] Drugs sometimes used to treat autoimmune disorders include: methylprednisolone oral, Kenalog inj, Medrol oral, Medrol (Pak) oral, Depo-Medrol inj, prednisolone oral, Solu-Medrol inj, Solu-Medrol IV, Cortef oral, hydrocortisone oral, cortisone oral, Celestone Soluspan inj, Orapred oral, Orapred ODT oral, methylprednisolone acetate inj, betamethasone acet & sod phos inj, Veripred 20 oral, Solu-Medrol (PF) inj, methylprednisolone sodium succ IV, Solu-Medrol (PF) IV, methylprednisolone sodium succ inj, Solu-Cortef inj, Pediapred oral, Millipred oral, Aristospan Intra-Articular inj, hydrocortisone sod succinate inj, prednisolone sodium phosphate oral, methylprednisolone sod suc(PF) IV, Flo-Pred oral, triamcinolone hexacetonide inj, A-Hydrocort inj, A-Methapred inj, Millipred DP oral, prednisolone acetate oral, Aristospan Intralesional inj, methylprednisolone sod suc(PF) inj, hydrocortisone sod succ (PF) inj, Solu-Cortef (PF) injection and dexamethasone in 0.9 % NaCl IV.

Drug Conjugates

[0242] In one embodiment, the activity of an active compound for a purpose described herein can be augmented through conjugation to an agent that targets the diseased or abnormally proliferating cell or otherwise enhances activity, delivery, pharmacokinetics or other beneficial property.

[0243] For example, the compound can be administered as an antibody-drug conjugates (ADC). In certain embodiments, a selected compound described herein can be administered in conjugation or combination with an antibody or antibody fragment. Fragments of an antibody can be produced through chemical or genetic mechanisms. In one embodiment, the antibody fragment is an antigen binding fragment. For example, the antigen binding fragment can be selected from an Fab, Fab', (Fab')₂, or Fv. In one embodiment, the antibody fragment is a Fab. Monovalent F(ab) fragments have one antigen binding site. In one embodiment, the antibody is a divalent (Fab')₂ fragment, which has two antigen binding regions that are linked by disulfide bonds. In one embodiment, the antigen fragment is a (Fab'). Reduction of F(ab')₂ fragments produces two

monovalent Fab' fragments, which have a free sulfhydryl group that is useful for conjugation to other molecules.

[0244] In one embodiment, a selected compound described herein can be administered in conjugation or combination with a Fv fragment. Fv fragments are the smallest fragment made from enzymatic cleavage of IgG and IgM class antibodies. Fv fragments have the antigen-binding site made of the VH and VC regions, but they lack the CH1 and CL regions. The VH and VL chains are held together in Fv fragments by non-covalent interactions.

[0245] In one embodiment, a selected compound as described herein can be administered in combination with an antibody fragment selected from the group consisting of an ScFv, diabody, triabody, tetrabody, Bis-scFv, minibody, Fab2, or Fab3 antibody fragment. In one embodiment, the antibody fragment is a ScFv. Genetic engineering methods allow the production of single chain variable fragments (ScFv), which are Fv type fragments that include the VH and VL domains linked with a flexible peptide. When the linker is at least 12 residues long, the ScFv fragments are primarily monomeric. Manipulation of the orientation of the V-domains and the linker length creates different forms of Fv molecules. Linkers that are 3-11 residues long yield scFv molecules that are unable to fold into a functional Fv domain. These molecules can associate with a second scFv molecule, to create a bivalent diabody. In one embodiment, the antibody fragment administered in combination with a selected compound described herein is a bivalent diabody. If the linker length is less than three residues, scFv molecules associate into triabodies or tetrabodies. In one embodiment, the antibody fragment is a triabody. In one embodiment, the antibody fragment is a tetrabody. Multivalent scFvs possess greater functional binding affinity to their target antigens than their monovalent counterparts by having binding to two more target antigens, which reduces the off-rate of the antibody fragment. In one embodiment, the antibody fragment is a minibody. Minibodies are scFv-CH3 fusion proteins that assemble into bivalent dimers. In one embodiment, the antibody fragment is a Bis-scFv fragment. Bis-scFv fragments are bispecific. Miniaturized ScFv fragments can be generated that have two different variable domains, allowing these Bis-scFv molecules to concurrently bind to two different epitopes.

[0246] In one embodiment, a selected compound described herein is administered in conjugation or combination with a bispecific dimer (Fab2) or trispecific dimer (Fab3). Genetic methods are also used to create bispecific Fab dimers (Fab2) and trispecific Fab trimers (Fab3). These antibody fragments are able to bind 2 (Fab2) or 3 (Fab3) different antigens at once.

[0247] In one embodiment, a selected compound described herein is administered in conjugation or combination with an rIgG antibody fragment. rIgG antibody fragments refers to reduced IgG (75,000 daltons) or half-IgG. It is the product of selectively reducing just the hinge-region disulfide bonds. Although several disulfide bonds occur in IgG, those in the hinge-region are most accessible and easiest to reduce, especially with mild reducing agents like 2-mercaptoethylamine (2-MEA). Half-IgG are frequently prepared for the purpose of targeting the exposing hinge-region sulfhydryl groups that can be targeted for

conjugation, either antibody immobilization or enzyme labeling.

[0248] In other embodiments, a selected active compound described herein can be linked to a radioisotope to increase efficacy, using methods well known in the art. Any radioisotope that is useful against the T, B or NK abnormal cells can be incorporated into the conjugate, for example, but not limited to ^{131}I , ^{123}I , ^{192}Ir , ^{32}P , ^{90}Sr , ^{198}Au , ^{226}Ra , ^{90}Y , ^{241}Am , ^{252}Cf , ^{60}Co , or ^{137}Cs .

[0249] Of note, the linker chemistry can be important to efficacy and tolerability of the drug conjugates. The thioether linked T-DM1 increases the serum stability relative to a disulfide linker version and appears to undergo endosomal degradation, resulting in intra-cellular release of the cytotoxic agent, thereby improving efficacy and tolerability. See, Barginear, M.F. and Budman, D.R., Trastuzumab-DM1: A review of the novel immune-conjugate for HER2-overexpressing breast cancer, *The Open Breast Cancer Journal*, 1:25-30, 2009.

[0250] Examples of early and recent antibody-drug conjugates, discussing drugs, linker chemistries and classes of targets for product development that may be used in the present invention can be found in the reviews by Casi, G. and Neri, D., Antibody-drug conjugates: basic concepts, examples and future perspectives, *J. Control Release* 161(2):422-428, 2012, Chari, R.V., Targeted cancer therapy: conferring specificity to cytotoxic drugs, *Acc. Chem. Rev.*, 41(1):98-107, 2008, Sapra, P. and Shor, B., Monoclonal antibody-based therapies in cancer: advances and challenges, *Pharmacol. Ther.*, 138(3):452-69, 2013, Schliemann, C. and Neri, D., Antibody-based targeting of the tumor vasculature, *Biochim. Biophys. Acta.*, 1776(2):175-92, 2007, Sun, Y., Yu, F., and Sun, B.W., Antibody-drug conjugates as targeted cancer therapeutics, *Yao Xue Xue Bao*, 44(9):943-52, 2009, Teicher, B.A., and Chari, R.V., Antibody conjugate therapeutics: challenges and potential, *Clin. Cancer Res.*, 17(20):6389-97, 2011, Firer, M.A., and Gellerman, G.J., Targeted drug delivery for cancer therapy: the other side of antibodies, *J. Hematol. Oncol.*, 5:70, 2012, Vlachakis, D. and Kossida, S., Antibody Drug Conjugate bioinformatics: drug delivery through the letterbox, *Comput. Math. Methods Med.*, 2013; 2013:282398, Epub 2013 Jun 19, Lambert, J.M., Drug-conjugated antibodies for the treatment of cancer, *Br. J. Clin. Pharmacol.*, 76(2):248-62, 2013, Concalves, A., Tredan, O., Villanueva, C. and Dumontet, C., Antibody-drug conjugates in oncology: from the concept to trastuzumab emtansine (T-DM1), *Bull. Cancer*, 99(12):1183-1191, 2012, Newland, A.M., Brentuximab vedotin: a CD-30-directed antibody-cytotoxic drug conjugate, *Pharmacotherapy*, 33(1):93-104, 2013, Lopus, M., Antibody-DM1 conjugates as cancer therapeutics, *Cancer Lett.*, 307(2):113-118, 2011, Chu, Y.W. and Poison, A., Antibody-drug conjugates for the treatment of B-cell non-Hodgkin's lymphoma and leukemia, *Future Oncol.*, 9(3):355-368, 2013, Bertholjotti, I., Antibody-drug conjugate - a new age for personalized cancer treatment, *Chimia*, 65(9): 746-748, 2011, Vincent, K.J., and Zurini, M., Current strategies in antibody engineering: Fc engineering and pH - dependent antigen binding, bispecific antibodies and antibody drug conjugates, *Biotechnol. J.*, 7(12): 1444-1450, 2012, Haeuw, J.F., Caussanel, V., and Beck, A.,

Immunoconjugates, drug-armed antibodies to fight against cancer, *Med. Sci.*, 25(12): 1046-1052, 2009 and Govindan, S.V., and Goldenberg, D.M., Designing immunoconjugates for cancer therapy, *Expert Opin. Biol. Ther.*, 12(7):873-890, 2012.

Pharmaceutical Compositions and Dosage Forms

[0251] The active compounds described herein, or their salt or prodrug can be administered to the host using any suitable approach which achieves the desired therapeutic result. The amount and timing of active compound administered will, of course, be dependent on the host being treated, the instructions of the supervising medical specialist, on the time course of the exposure, on the manner of administration, on the pharmacokinetic properties of the particular active compound, and on the judgment of the prescribing physician. Thus, because of host to host variability, the dosages given below are a guideline and the physician can titrate doses of the compound to achieve the treatment that the physician considers appropriate for the host. In considering the degree of treatment desired, the physician can balance a variety of factors such as age and weight of the host, presence of preexisting disease, as well as presence of other diseases. Pharmaceutical formulations can be prepared for any desired route of administration including, but not limited to, systemic, topical, oral, intravenous, subcutaneous, transdermal, buccal, sublingual, intraaortal, intranasal, parenteral, or aerosol administration, as discussed in greater detail below.

[0252] The therapeutically effective dosage of any active compound described herein will be determined by the health care practitioner depending on the condition, size and age of the patient as well as the route of delivery. In one non-limited embodiment, a dosage from about 0.1 to about 200 mg/kg has therapeutic efficacy, with all weights being calculated based upon the weight of the active compound, including the cases where a salt is employed. In some embodiments, the dosage can be the amount of compound needed to provide a serum concentration of the active compound of up to between about 1 and 5, 10, 20, 30, or 40 μM . In some embodiments, a dosage from about 10 mg/kg to about 50 mg/kg can be employed for oral administration. Typically, a dosage from about 0.5 mg/kg to 5 mg/kg can be employed for intramuscular injection. In some embodiments, dosages can be from about 1 $\mu\text{mol/kg}$ to about 50 $\mu\text{mol/kg}$, or, optionally, between about 22 $\mu\text{mol/kg}$ and about 33 $\mu\text{mol/kg}$ of the compound for intravenous or oral administration. An oral dosage form can include any appropriate amount of active material, including for example from 5 mg to, 50, 100, 200, or 500 mg per tablet or other solid dosage form.

[0253] In accordance with certain embodiments of the invention, in the presently disclosed methods, pharmaceutically active compounds as described herein can be administered orally as a solid or as a liquid, or can be administered intramuscularly, intravenously, or by inhalation as a solution, suspension, or emulsion. In some embodiments, the compounds or salts also can be administered by inhalation, intravenously, or intramuscularly as a liposomal suspension. When administered through inhalation the active compound or salt can be in the form of a plurality of solid particles or droplets having any desired particle size, and for example, from about 0.01, 0.1 or 0.5 to about 5, 10, 20 or more microns, and optionally from about 1 to about 2 microns. Compounds as disclosed in the present invention have demonstrated good pharmacokinetic and pharmacodynamics properties, for instance when administered by the oral or intravenous routes.

[0254] The pharmaceutical formulations can comprise an active compound described herein or a pharmaceutically acceptable salt thereof, in any pharmaceutically acceptable carrier. If a solution is desired, water may be the carrier of choice for water-soluble compounds or salts. With respect to the water-soluble compounds or salts, an organic vehicle, such as glycerol, propylene glycol, polyethylene glycol, or mixtures thereof, can be suitable. In the latter instance, the organic vehicle can contain a substantial amount of water. The solution in either instance can then be sterilized in a suitable manner known to those in the art, and for illustration by filtration through a 0.22-micron filter. Subsequent to sterilization, the solution can be dispensed into appropriate receptacles, such as depyrogenated glass vials. The dispensing is optionally done by an aseptic method. Sterilized closures can then be placed on the vials and, if desired, the vial contents can be lyophilized.

[0255] In addition to the active compounds or their salts, the pharmaceutical formulations can contain other additives, such as pH-adjusting additives. In particular, useful pH-adjusting agents include acids, such as hydrochloric acid, bases or buffers, such as sodium lactate, sodium acetate, sodium phosphate, sodium citrate, sodium borate, or sodium gluconate. Further, the formulations can contain antimicrobial preservatives. Useful antimicrobial preservatives include methylparaben, propylparaben, and benzyl alcohol. An antimicrobial preservative is typically employed when the formulations is placed in a vial designed for multi-dose use. The pharmaceutical formulations described herein can be lyophilized using techniques well known in the art.

[0256] For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch (e.g., potato or tapioca starch) and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate, and talc are often very useful for tabletting purposes. Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules. Materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of the presently disclosed host matter can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[0257] In yet another embodiment of the host matter described herein, there are provided injectable, stable, sterile formulations comprising an active compound as described herein, or a salt thereof, in a unit dosage form in a sealed container. The compound or salt is provided in the form of a lyophilizate, which is capable of being reconstituted with a suitable pharmaceutically acceptable carrier to form liquid formulation suitable for injection thereof into a host. When the compound or salt is substantially water-insoluble, a sufficient amount of emulsifying agent, which is physiologically acceptable, can be employed in sufficient quantity to emulsify the compound or salt in an aqueous carrier. Particularly useful emulsifying agents include phosphatidyl cholines and lecithin.

[0258] Additional embodiments provided herein include liposomal formulations of the active compounds disclosed herein. The technology for forming liposomal suspensions is well known in the art. When the compound is an aqueous-soluble salt, using conventional liposome technology, the same can be incorporated into lipid vesicles. In such an instance, due to the water solubility of the active compound, the active compound can be substantially entrained within the hydrophilic center or core of the liposomes. The lipid layer employed can be of any conventional composition and can either contain cholesterol or can be cholesterol-free. When the active compound of interest is water-insoluble, again employing conventional liposome formation technology, the salt can be substantially entrained within the hydrophobic lipid bilayer that forms the structure of the liposome. In either instance, the liposomes that are produced can be reduced in size, as through the use of standard sonication and homogenization techniques. The liposomal formulations comprising the active compounds disclosed herein can be lyophilized to produce a lyophilizate, which can be reconstituted with a pharmaceutically acceptable carrier, such as water, to regenerate a liposomal suspension.

[0259] Pharmaceutical formulations also are provided which are suitable for administration as an aerosol by inhalation. These formulations comprise a solution or suspension of a desired compound described herein or a salt thereof, or a plurality of solid particles of the compound or salt. The desired formulations can be placed in a small chamber and nebulized. Nebulization can be accomplished by compressed air or by ultrasonic energy to form a plurality of liquid droplets or solid particles comprising the compounds or salts. The liquid droplets or solid particles may for example have a particle size in the range of about 0.5 to about 10 microns, and optionally from about 0.5 to about 5 microns. The solid particles can be obtained by processing the solid compound or a salt thereof, in any appropriate manner known in the art, such as by micronization. Optionally, the size of the solid particles or droplets can be from about 1 to about 2 microns. In this respect, commercial nebulizers are available to achieve this purpose. The compounds can be administered via an aerosol suspension of respirable particles in a manner set forth in U.S. Pat. No. 5,628,984, the disclosure of which is incorporated herein by reference in its entirety.

[0260] When the pharmaceutical formulations suitable for administration as an aerosol is in the form of a liquid, the formulations can comprise a water-soluble active compound in a carrier that comprises water. A surfactant can be present, which lowers the surface tension of the formulations sufficiently to result in the formation of droplets within the desired size range when hosted to nebulization.

[0261] The term “pharmaceutically acceptable salts” as used herein refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with hosts (e.g., human hosts) without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the presently disclosed host matter.

[0262] Thus, the term “salts” refers to inorganic and organic acid addition salts of compounds of the presently disclosed compounds. These salts can be prepared by any means known in the art, including, without limitation, in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in

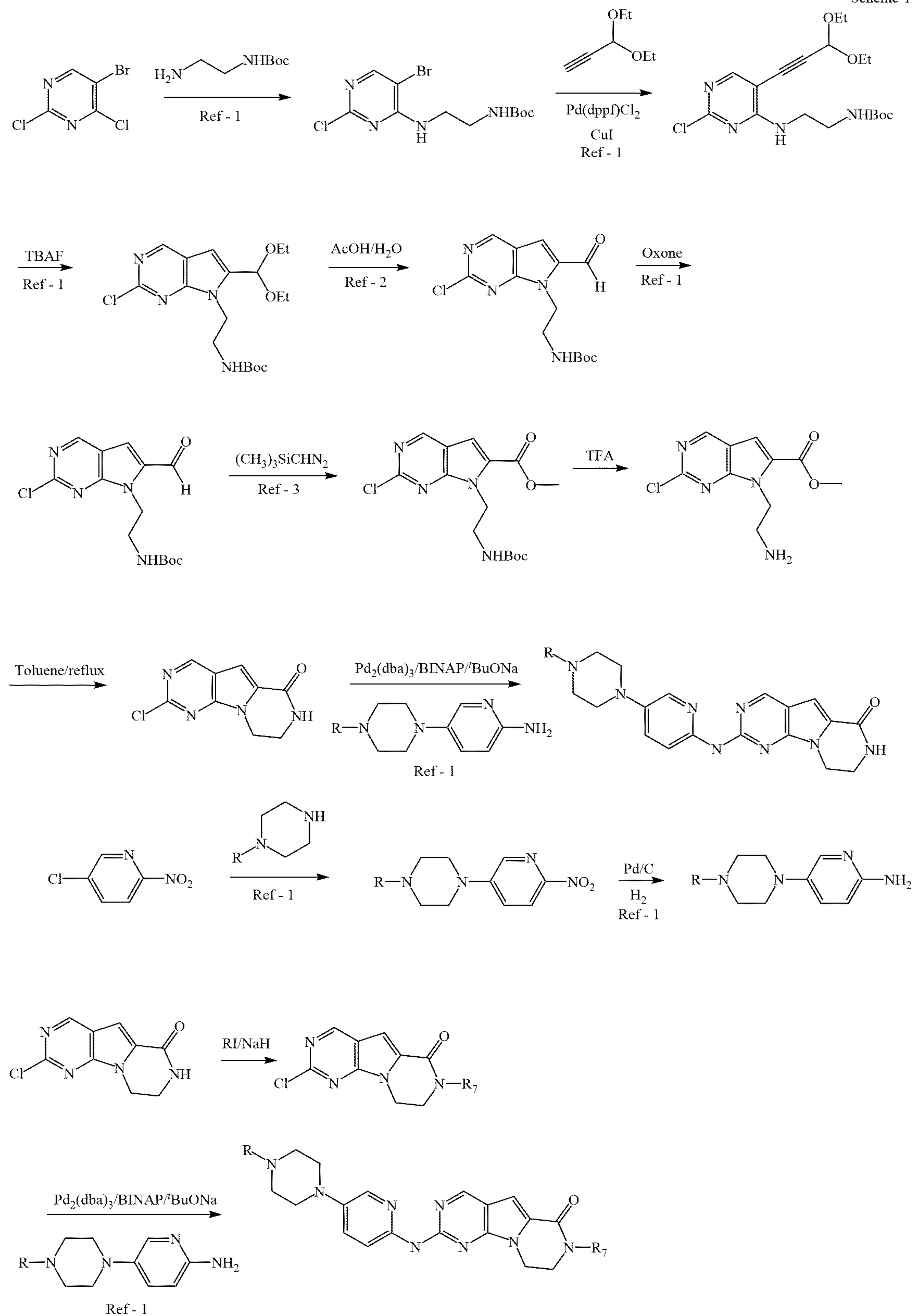
its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. As the compounds of the presently disclosed host matter are basic compounds, they are all capable of forming a wide variety of different salts with various inorganic and organic acids. Acid addition salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form can be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms may differ from their respective salt forms in certain physical properties such as solubility in polar solvents. Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metal hydroxides, or of organic amines. Examples of metals used as cations, include, but are not limited to, sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines include, but are not limited to, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine. The base addition salts of acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form can be regenerated by contacting the salt form with an acid and isolating the free acid in a conventional manner. The free acid forms may differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents.

[0263] Salts can be prepared from inorganic acids sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorus, and the like. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, laurylsulphonate and isethionate salts, and the like. Salts can also be prepared from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and the like. Representative salts include acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Pharmaceutically acceptable salts can include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Also contemplated are the salts of amino acids such as arginate, gluconate, galacturonate, and the like. See, for example, Berge et al., J. Pharm. Sci., 1977, 66, 1-19, which is incorporated herein by reference.

Syntheses

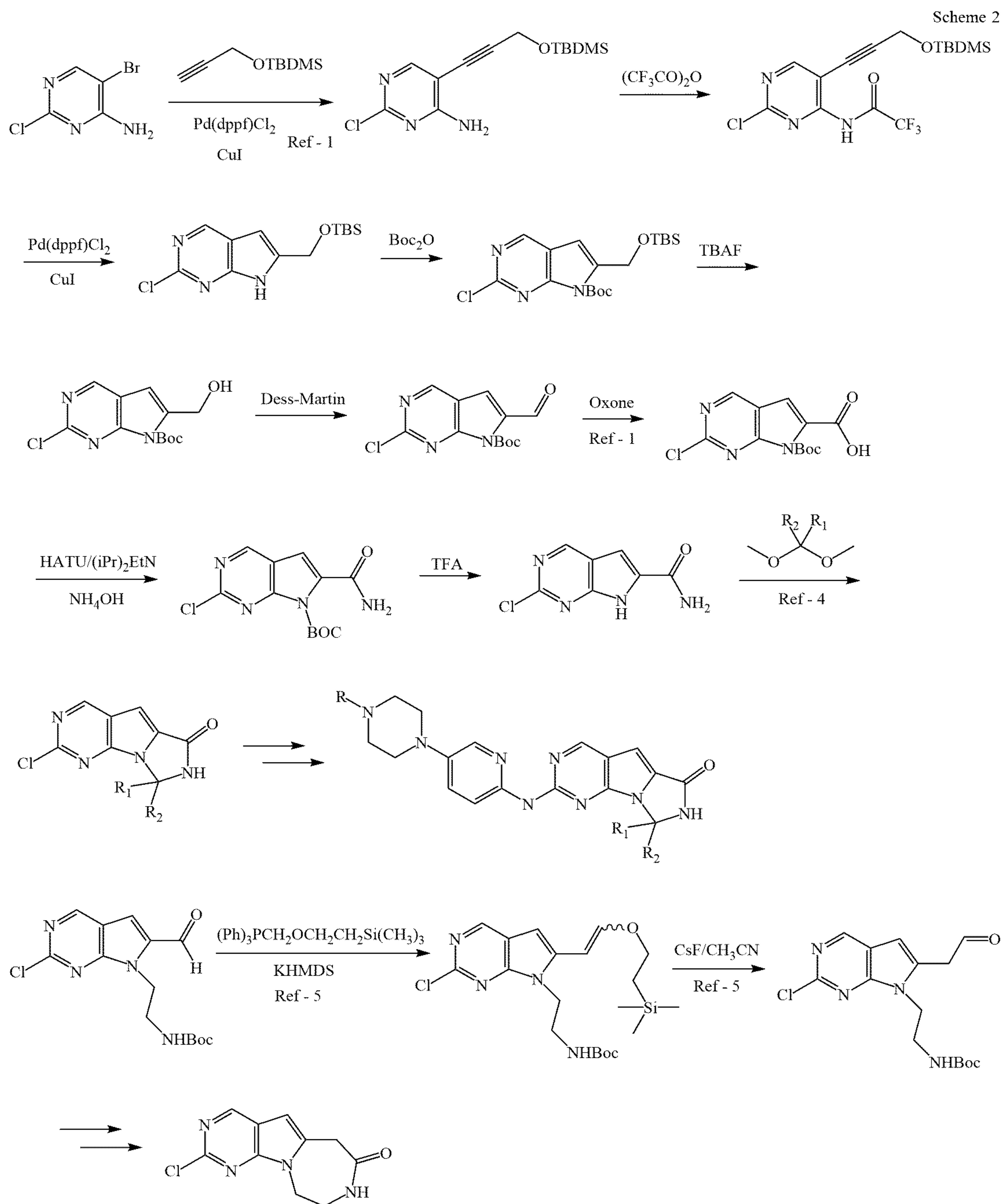
[0264] The disclosed compounds can be made by the following general schemes:

Scheme 1

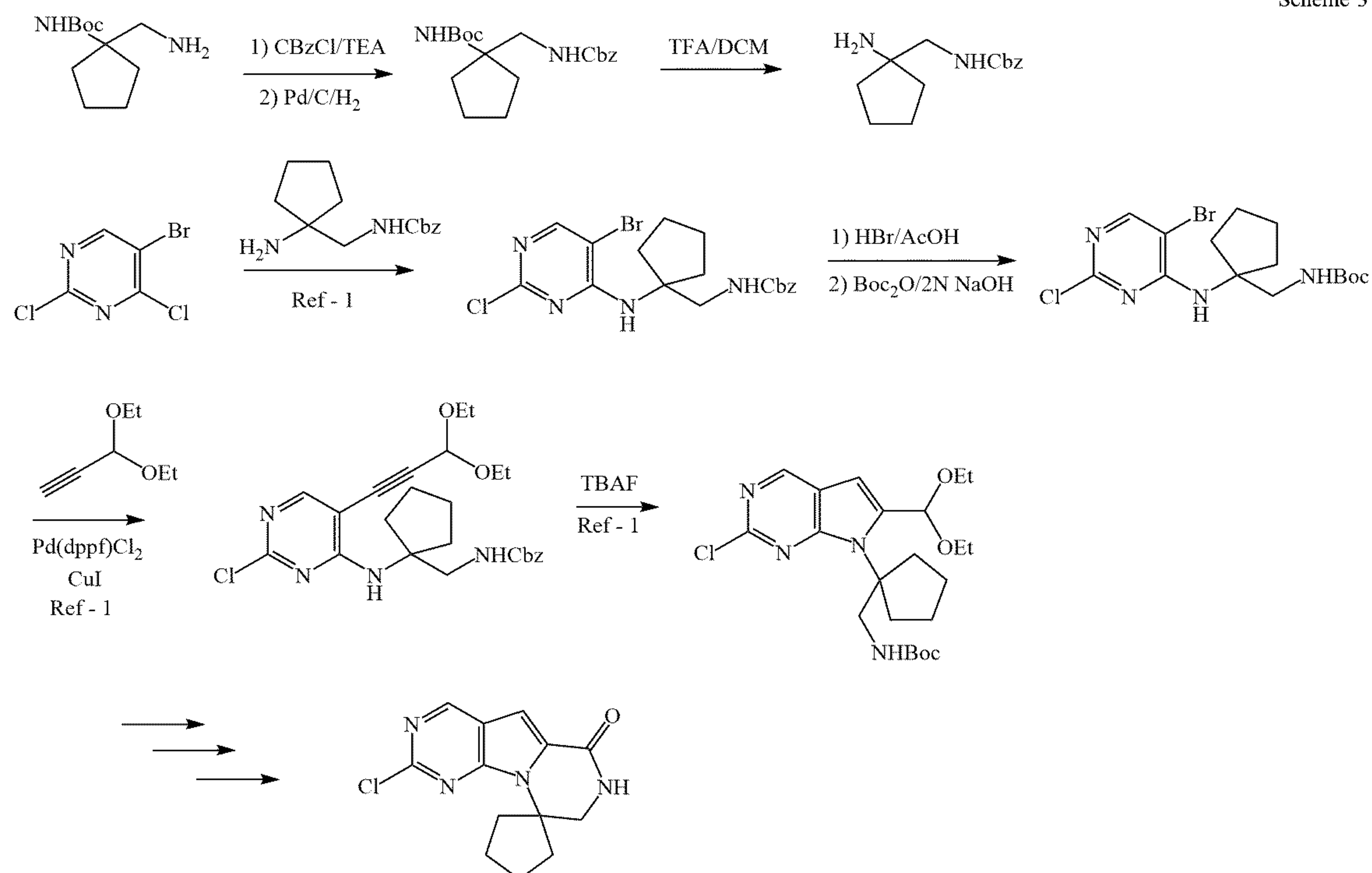


[0265] In Scheme 1, Ref-1 is WO 2010/020675 A1; Ref-2 is White, J. D.; et al. *J. Org. Chem.* 1995, 60, 3600; and Ref-3 Presser, A. and Hufner, A. *Monatshefte für Chemie* 2004, 135, 1015.

[0266] In Scheme 2, Ref-1 is WO 2010/020675 A1; Ref-4 is WO 2005/040166 A1; and Ref-5 is Schoenauer, K and Zbiral, E. *Tetrahedron Letters* 1983, 24, 573.

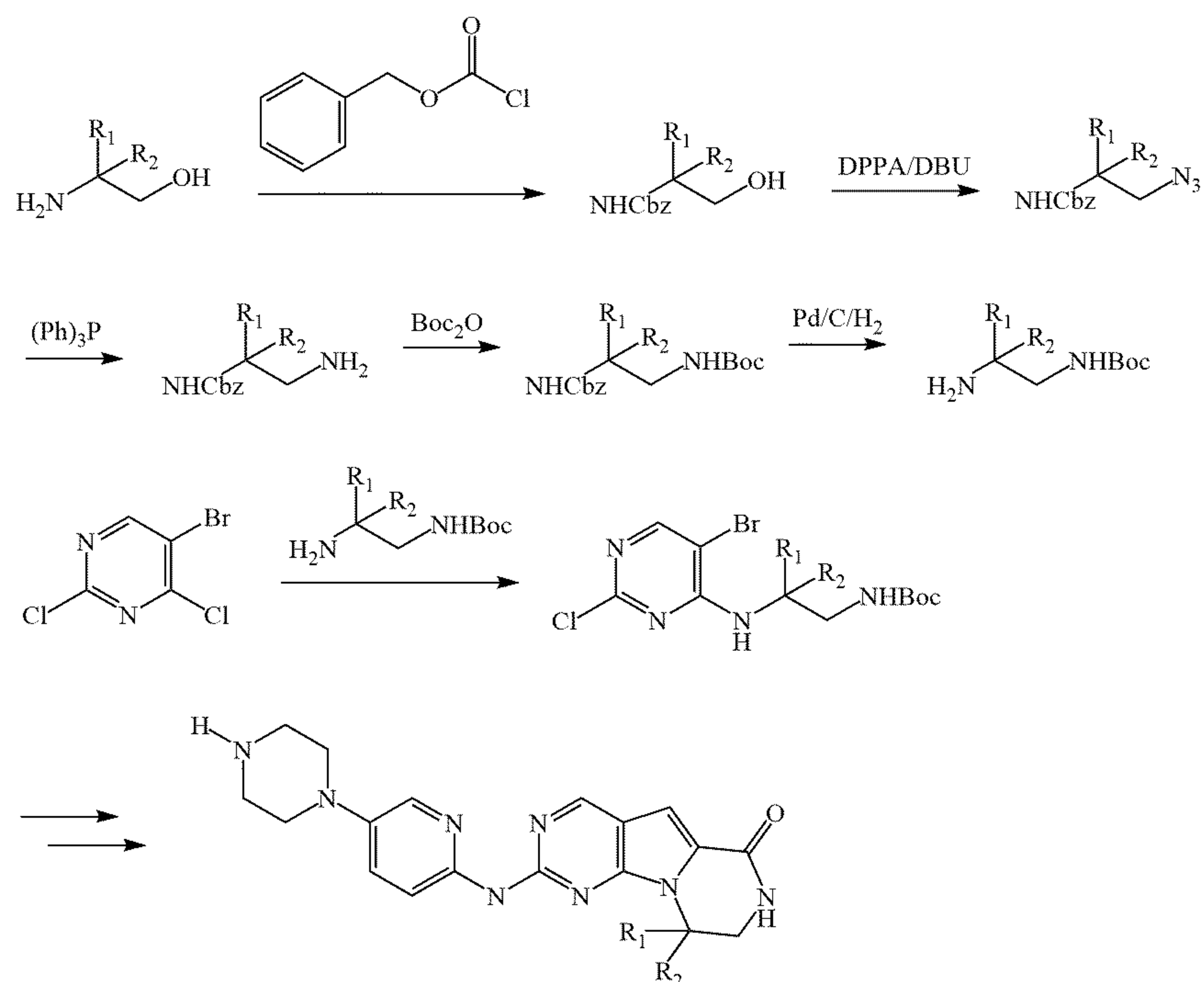


Scheme 3

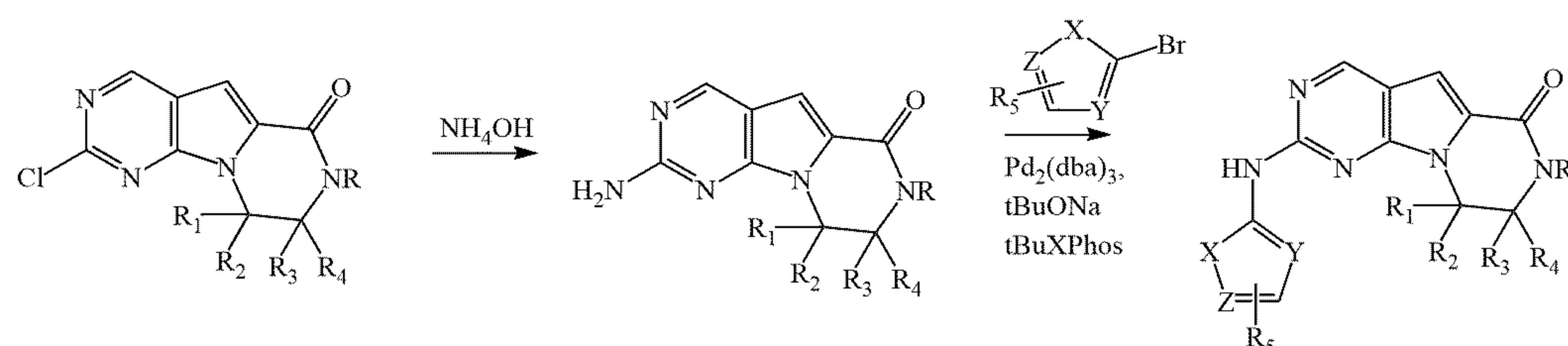


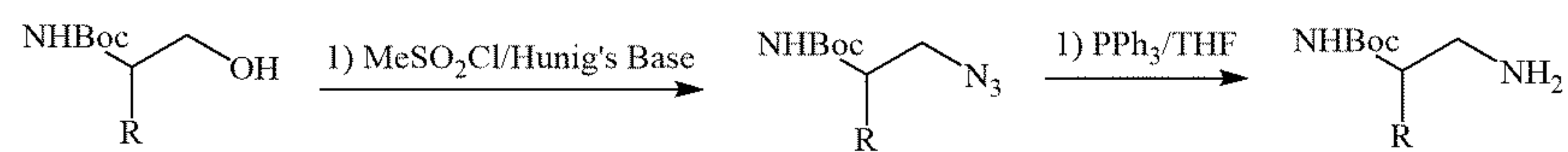
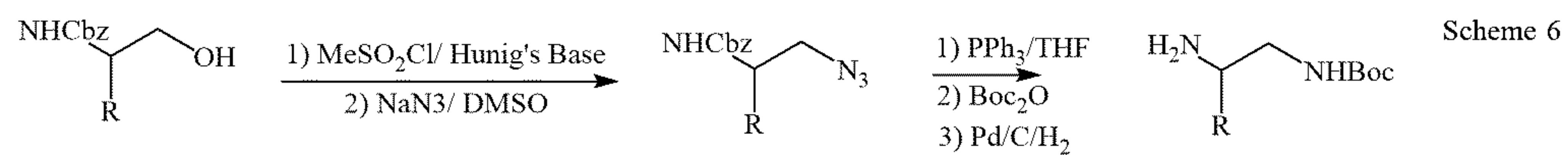
[0267] In Scheme 3, Ref — 1 is WO 2010/020675 A1.

Scheme 4

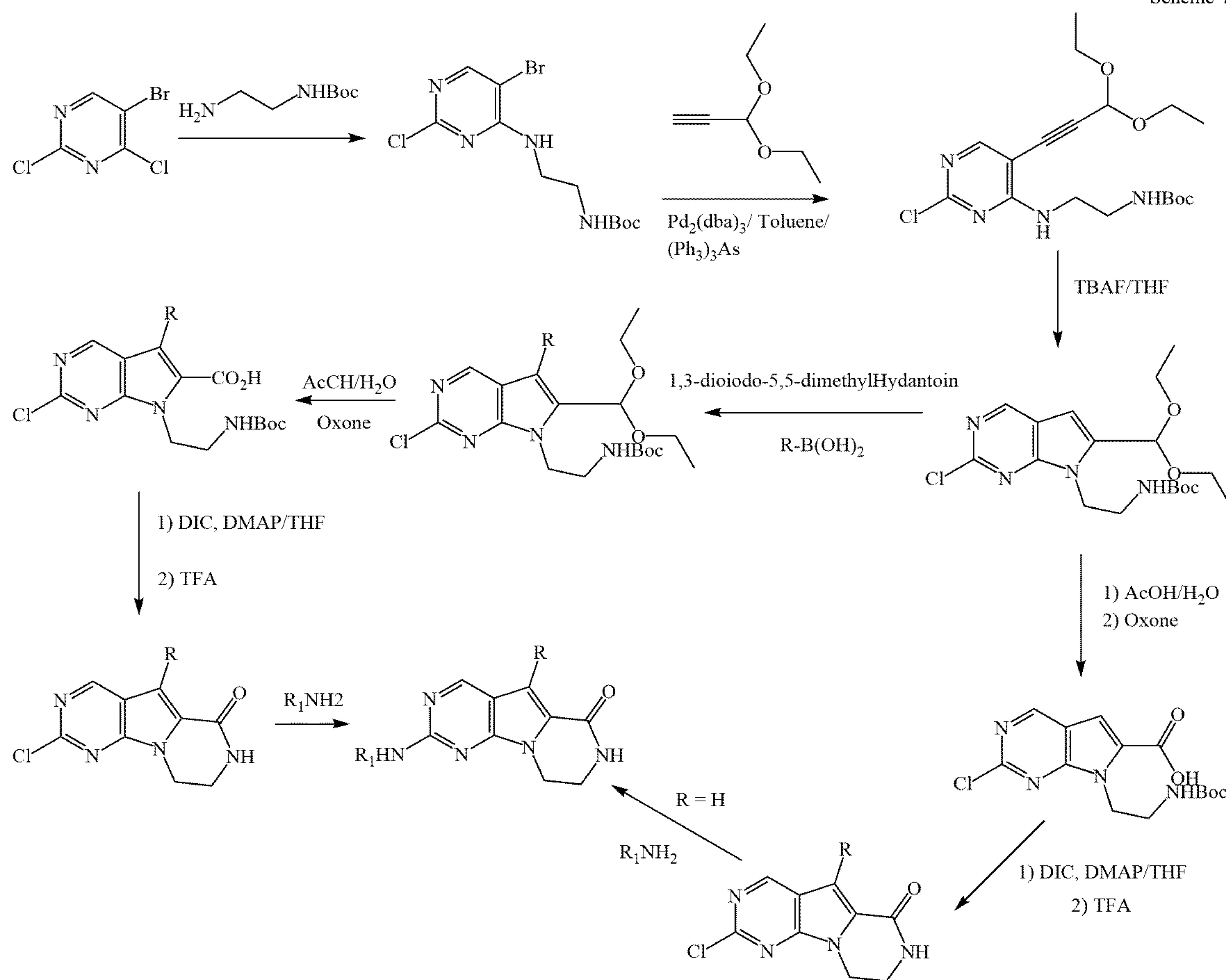


Scheme 5

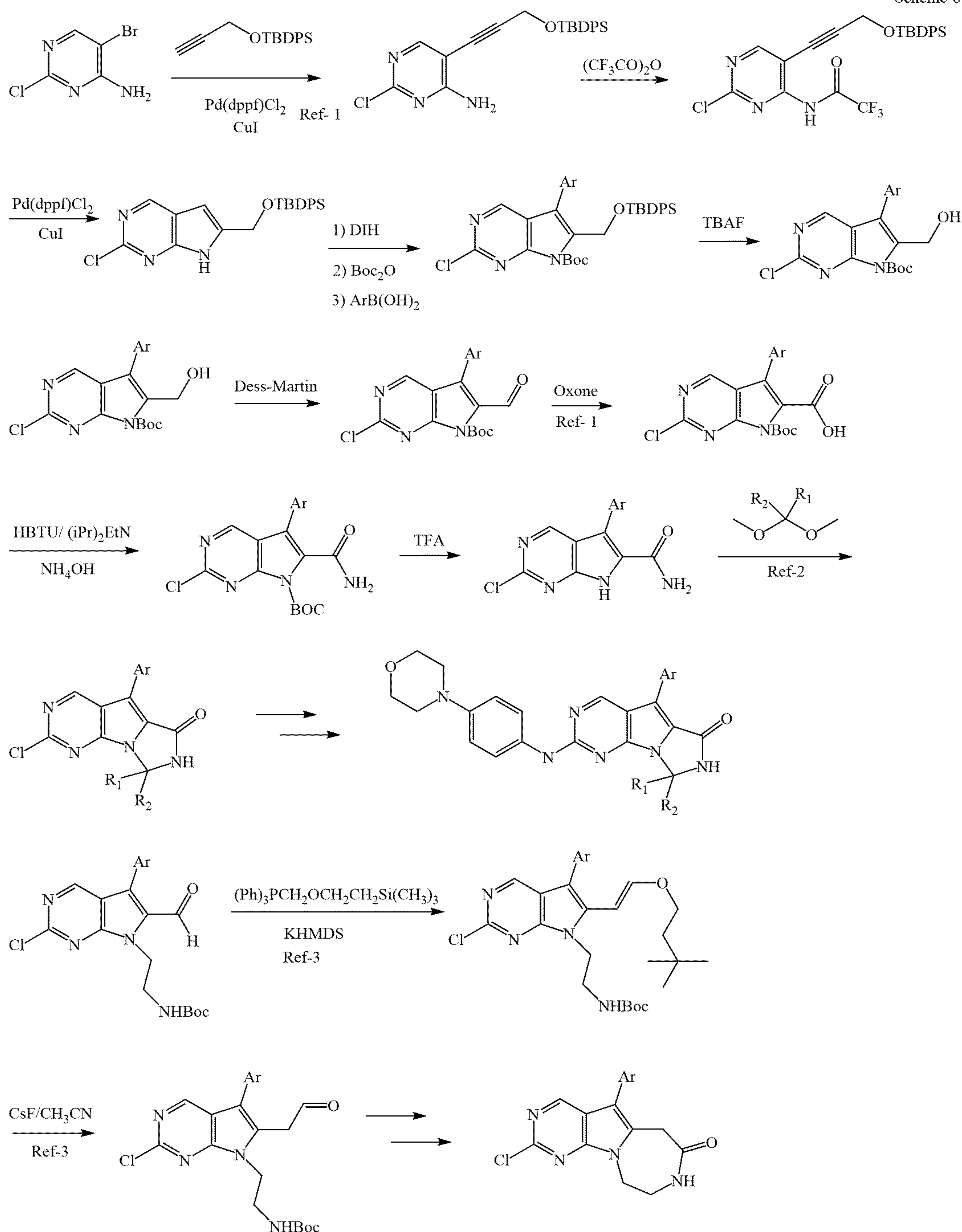




Scheme 7



Scheme 8



DIH = 1,3-Diiodo-3,3-dimethyl-hyantion

[0268] In Scheme 8, Ref-1 is WO 2010/020675 A1; Ref-2 is WO 2005/040166 A1; and Ref-3 is Schoenauer, K and Zbiral, E. *Tetrahedron Letters* 1983, 24, 573.

[0269] Alternatively, the lactam can be generated by reacting the carboxylic acid with a protected amine in the presence of a strong acid and a dehydrating agent, which can be together in one moiety as a strong acid anhydride. Examples

of strong acid anhydrides include, but are not limited to, trifluoroacetic acid anhydride, tribromoacetic acid anhydride, trichloroacetic acid anhydride, or mixed anhydrides. The dehydrating agent can be a carbodiimide based compound such as but not limited to DCC (N,N-dicyclohexylcarbodiimide), EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) or DIC (N,N-diisopropylcarbodiimide). An

additional step may be necessary to take off the N-protecting group and the methodologies are known to those skilled in the art.

[0270] Other amine intermediates and final amine compounds can be synthesized by those skilled in the art. It will be appreciated that the chemistry can employ reagents that comprise reactive functionalities that can be protected and de-protected and will be known to those skilled in the art at the time of the invention. See for example, Greene, T.W. and Wuts, P.G.M., *Greene's Protective Groups in Organic Synthesis*, 4th edition, John Wiley and Sons.

EXAMPLES

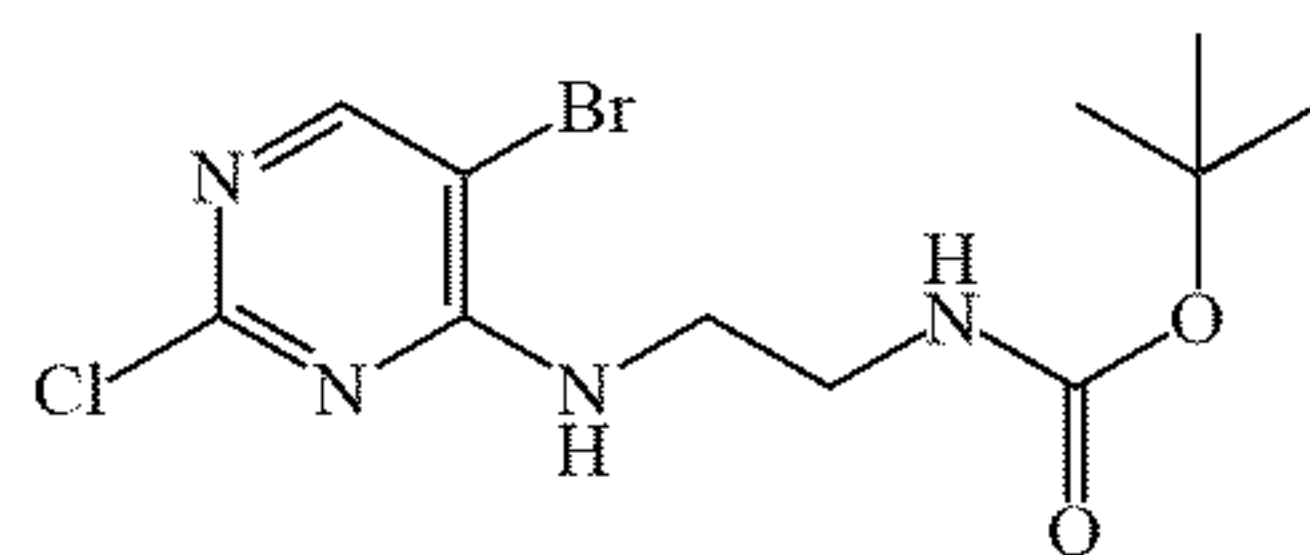
[0271] Intermediates B, E, K, L, 1A, 1E and 1CA were prepared according to the methods of Tavares, F.X. and Strum, J.C., See, US 8598,186 entitled CDK inhibitors.

[0272] Pats. US 8598186 entitled CDK Inhibitors to Tavares, F.X. and Strum, J.C., WO 2013/163239 entitled Synthesis of Lactams to Tavares, F.X., and WO 2013/148748 entitled Lactam Kinase Inhibitors to Tavares, F.X. are herein incorporated by reference in their entirety.

Example 1

Synthesis of Tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate, Compound 1

[0273]

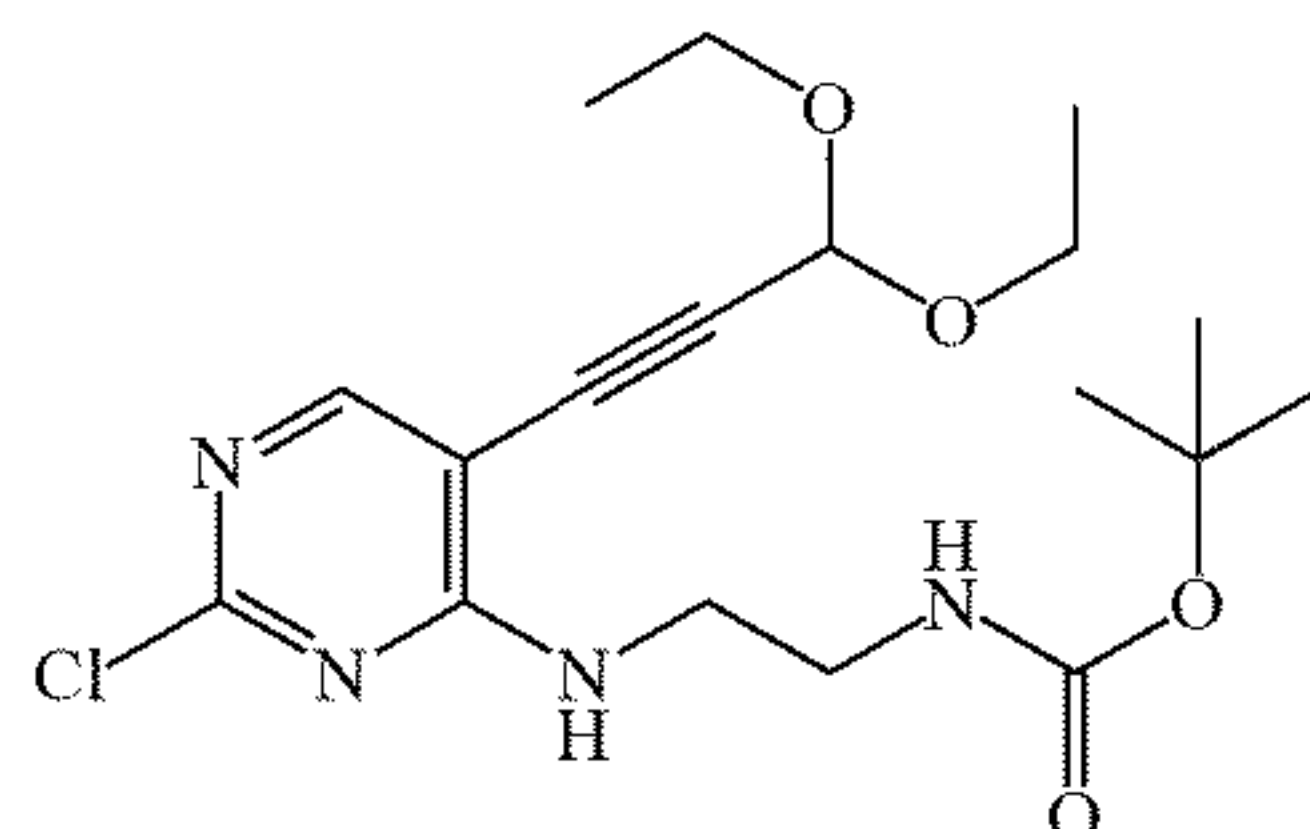


[0274] To a solution of 5-bromo-2,4-dichloropyrimidine (3.2 g, 0.0135 mol) in ethanol (80 mL) was added Hunig's base (3.0 mL) followed by the addition of a solution of N-(tert-butoxycarbonyl)-1,2-diaminoethane (2.5 g, 0.0156 mole) in ethanol (20 mL). The contents were stirred overnight for 20 hrs. The solvent was evaporated under vacuum. Ethyl acetate (200 mL) and water (100 mL) were added and the layers separated. The organic layer was dried with magnesium sulfate and then concentrated under vacuum. Column chromatography on silica gel using hexane/ethyl acetate (0- 60%) afforded tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate. ¹HNMR (d6-DMSO) δ ppm 8.21 (s, 1H), 7.62 (brs, 1H), 7.27 (brs, 1H), 3.39 (m, 2H), 3.12 (m, 2H), 1.34 (s, 9H). LCMS (ESI) 351 (M + H).

Example 2

Synthesis of Tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate, Compound 2

[0275]

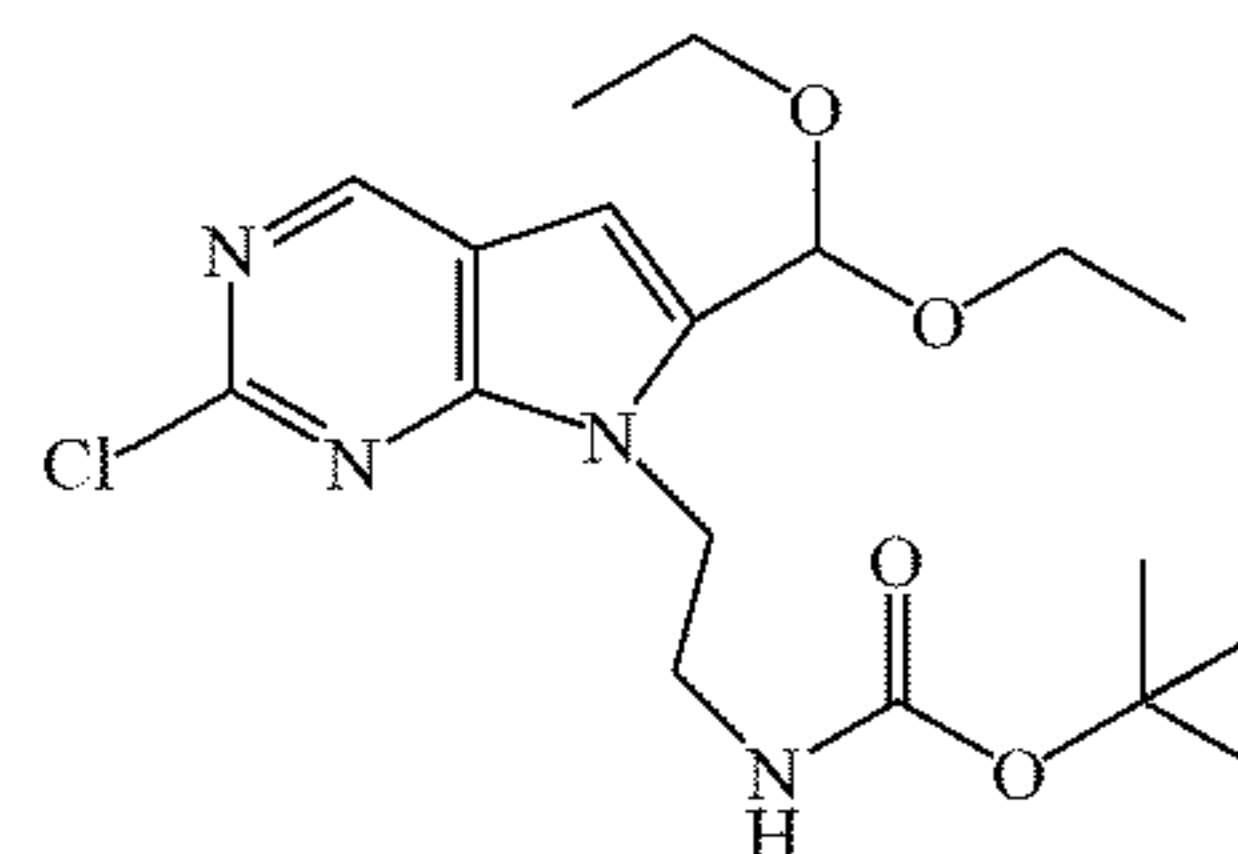


[0276] To tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate (1.265 g, 3.6 mmol) in THF (10 mL) was added the acetal (0.778 mL, 5.43 mmol), Pd(dppf)CH₂Cl₂ (148 mg), and triethylamine (0.757 mL, 5.43 mmol). The contents were degassed and then purged with nitrogen. To this was then added CuI (29 mg). The reaction mixture was heated at reflux for 48 hrs. After cooling, the contents were filtered over CELITE™ and concentrated. Column chromatography of the resulting residue using hexane/ethyl acetate (0- 30%) afforded tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate. ¹HNMR (d6-DMSO) δ ppm 8.18 (s, 1H), 7.63 (brs, 1H), 7.40 (brs, 1H), 5.55 (s, 1H), 3.70 (m, 2H), 3.60 (m, 2H), 3.42 (m, 2H), 3.15 (m, 2H), 1.19 - 1.16 (m, 15H). LCMS (ESI) 399 (M + H).

Example 3

Synthesis of Tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate, Compound 3

[0277]

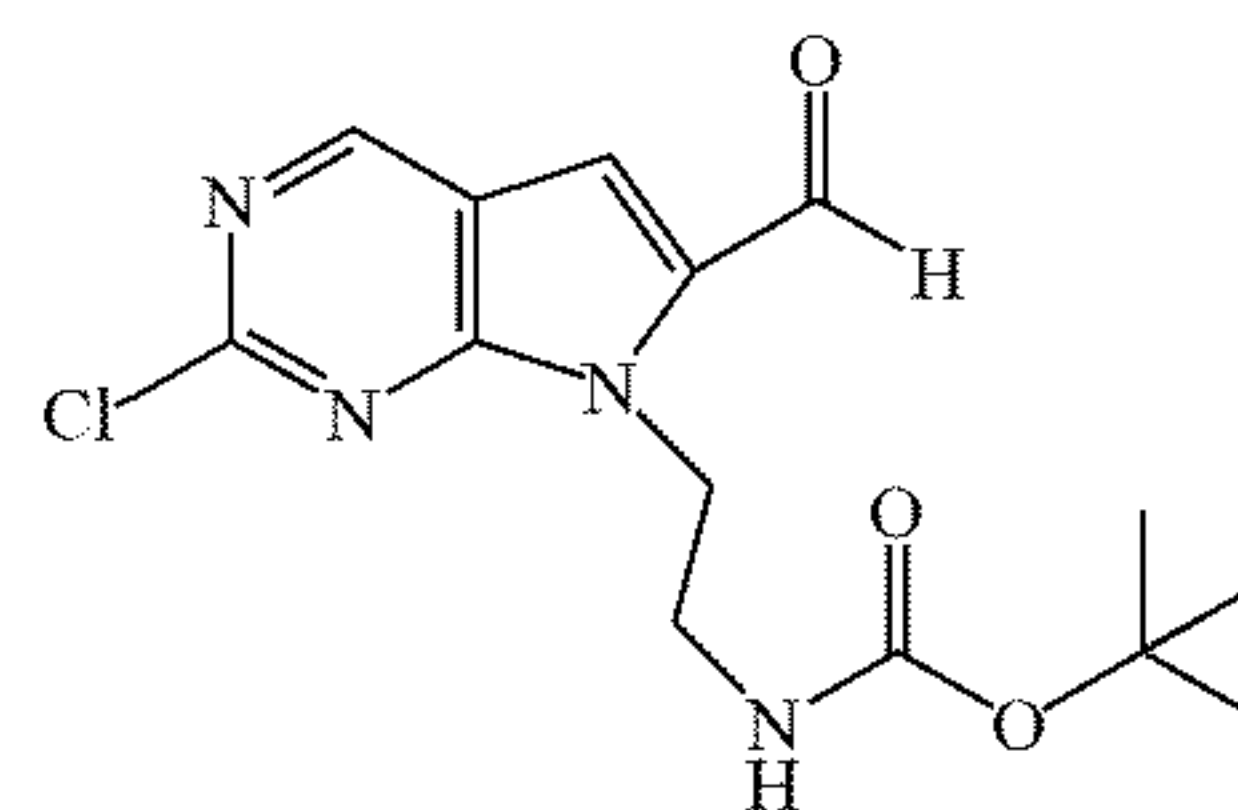


[0278] To a solution of the coupled product (2.1 g, 0.00526 mole) in THF (30 mL) was added TBAF solid (7.0 g). The contents were heated to and maintained at 65 degrees for 2 hrs. Concentration followed by column chromatography using ethyl acetate/hexane (0-50%) afforded tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate as a pale brown liquid (1.1 g). ¹HNMR (d6-DMSO) δ ppm 8.88 (s, 1H), 6.95 (brs, 1H), 6.69 (s, 1H), 5.79 (s, 1H), 4.29 (m, 2H), 3.59 (m, 4H), 3.34 (m, 1H), 3.18 (m, 1H), 1.19 (m, 9H), 1.17 (m, 6H). LCMS (ESI) 399 (M + H).

Example 4

Synthesis of Tert-butyl N-[2-(2-chloro-6-formyl-pyrrolo[2,3-d]pyrimidin-7-yl)ethyl]carbamate, Compound 4

[0279]



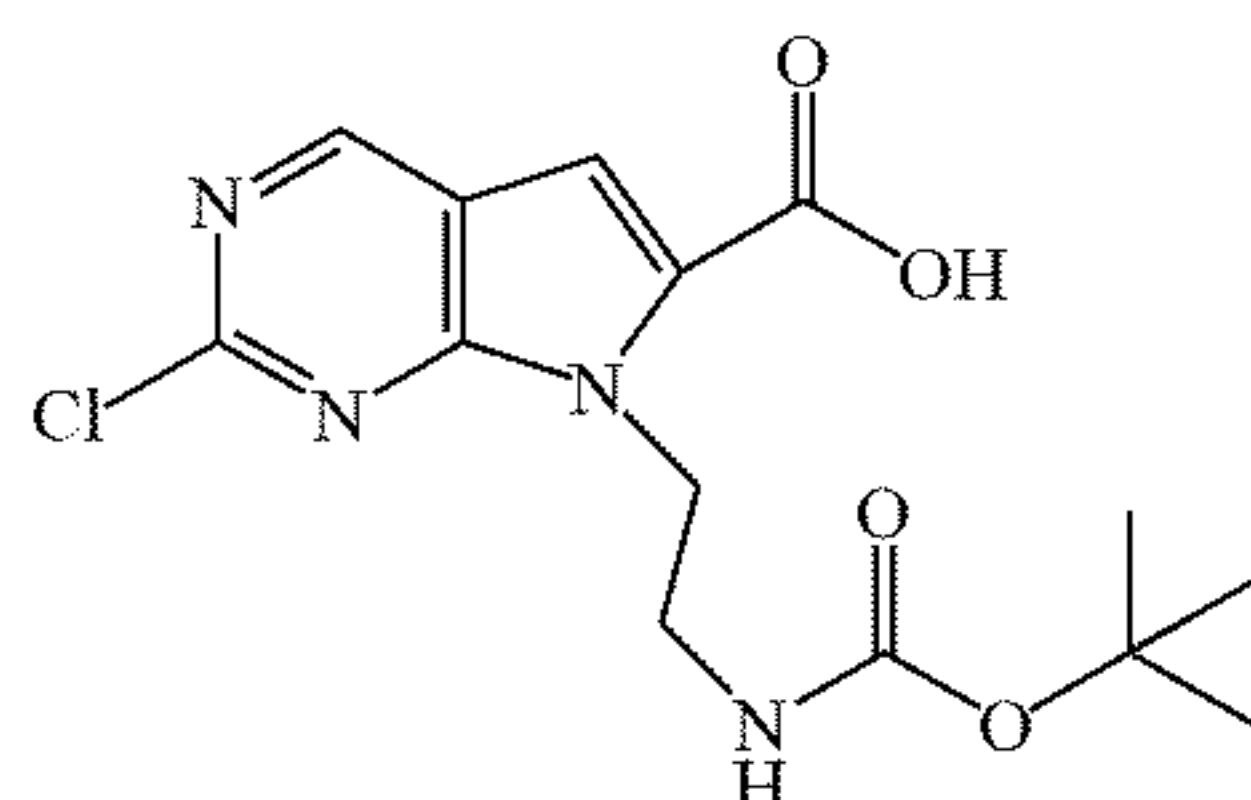
[0280] To the acetal (900 mg) from the preceding step was added AcOH (8.0 mL) and water (1.0 mL). The reaction was stirred at room temperature for 16 hrs. Conc. and column chromatography over silica gel using ethyl acetate/hexanes (0- 60%) afforded tert-butyl N-[2-(2-chloro-6-formyl-pyrrolo[2,3-d]pyrimidin-7-yl)ethyl]carbamate as a foam (0.510 g). ¹HNMR (d6-DMSO) δ ppm 9.98 (s, 1H), 9.18

(s, 1H), 7.66 (s, 1H), 6.80 (brs, 1H), 4.52 (m, 2H), 4.36 (m, 2H), 1.14 (s, 9H). LCMS (ESI) 325 (M + H).

Example 5

Synthesis of 7-[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid, Compound 5

[0281]

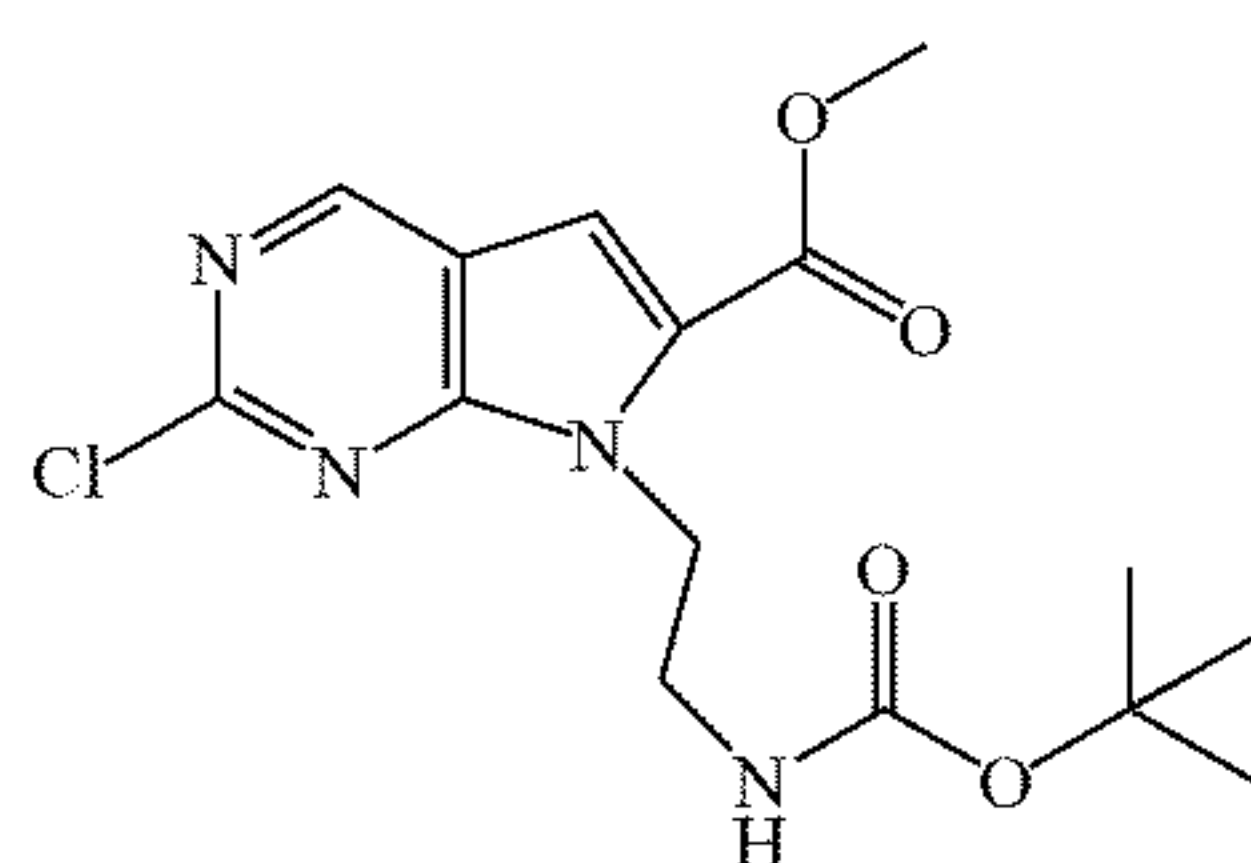


[0282] To the aldehyde (0.940 g) from the preceding step in DMF (4 mL) was added oxone (1.95 g, 1.1 eq). The contents were stirred at room temp for 7 hrs. Silica gel column chromatography using hexane/ethyl acetate (0- 100%) afforded 7-[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid (0.545 g). ¹HNMR (d6-DMSO) δ ppm 9.11 (s, 1H), 7.39 (s, 1H), 4.38 (m, 2H), 4.15 (m, 2H), 1.48 (m, 9H). LCMS (ESI) 341(M + H).

Example 6

Synthesis of Methyl 7-[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylate, Compound 6

[0283]

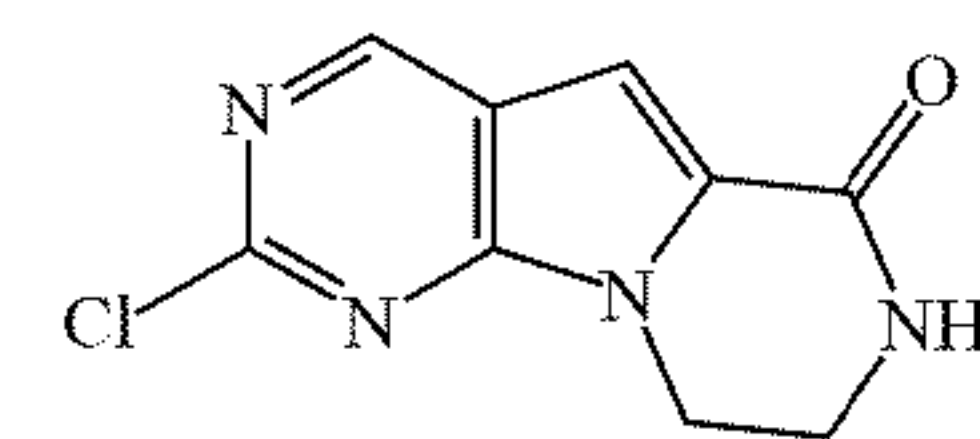


[0284] To a solution of 2-chloro-7-propyl-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid (0.545 g, 0.00156 mole) from the preceding step in toluene (3.5 mL) and MeOH (1 mL) was added TMS-diazomethane (1.2 mL). After stirring overnight at room temperature, the excess of TMS-diazomethane was quenched with acetic acid (3 mL) and the reaction was concentrated under vacuum. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (0- 70%) to afford methyl 7-[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylate as an off white solid (0.52 g). ¹HNMR (d6-DMSO) δ ppm 9.10 (s, 1H), 7.45 (s, 1H), 6.81 (brs, 1H), 4.60 (m, 2H), 3.91 (s, 3H), 3.29 (m, 2H), 1.18 (m, 9H). LCMS (ESI) 355 (M + H).

Example 7

Synthesis of Chloro Tricyclic Amide, Compound 7

[0285]

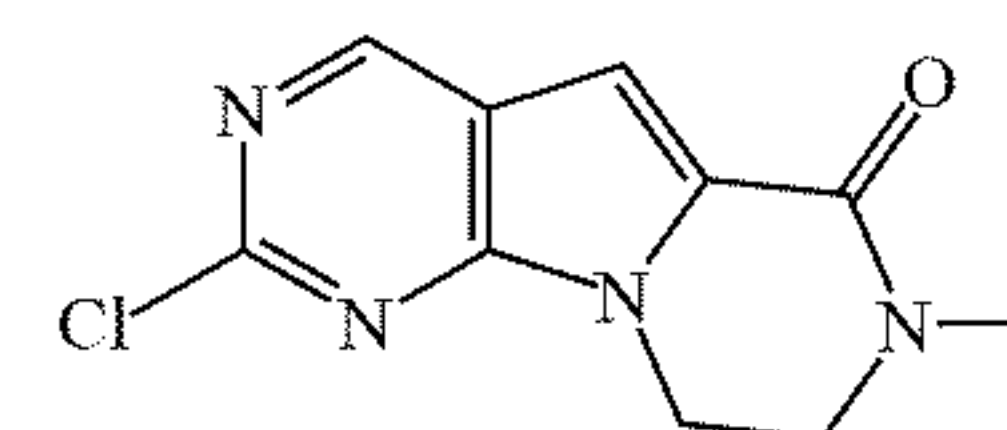


[0286] To methyl 7-[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylate (0.50 g, 0.0014 mole) from the preceding step in dichloromethane (2.0 mL) was added TFA (0.830 mL). The contents were stirred at room temperature for 1 hr. Concentration under vacuum afforded the crude amino ester which was suspended in toluene (5 mL) and Hunig's base (0.5 mL). The contents were heated at reflux for 2 hrs. Concentration followed by silica gel column chromatography using hexane/ethyl acetate (0- 50%) afforded the desired chloro tricyclic amide (0.260 g). ¹HNMR (d6-DMSO) δ ppm 9.08 (s, 1H), 8.48 (brs, 1H), 7.21 (s, 1H), 4.33 (m, 2H), 3.64 (m, 2H). LCMS (ESI) 223 (M + H).

Example 8

Synthesis of Chloro-N-Methyltricyclic Amide, Compound 8

[0287]

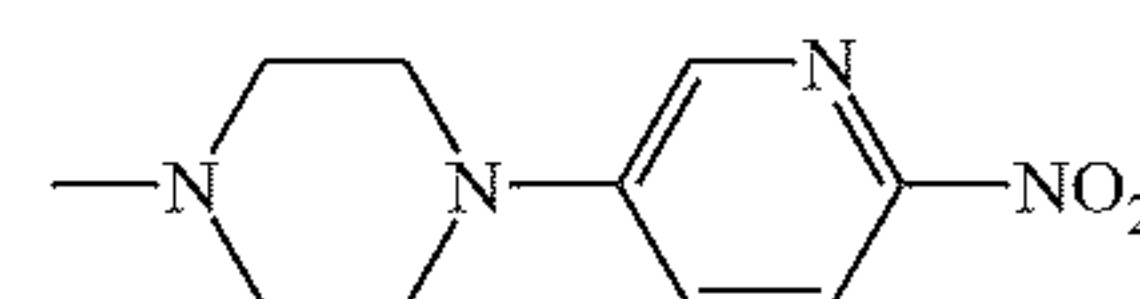


[0288] To a solution of the chloro tricyclic lactam, Compound 7, (185 mg, 0.00083 mole) in DMF (2.0 mL) was added sodium hydride (55% dispersion in oil, 52 mg). After stirring for 15 mins, methyl iodide (62 μL, 1.2 eq). The contents were stirred at room temperature for 30 mins. After the addition of methanol (5 mL), sat NaHCO₃ was added followed by the addition of ethyl acetate. Separation of the organic layer followed by drying with magnesium sulfate and concentration under vacuum afforded the N-methylated amide in quantitative yield. ¹HNMR (d6-DMSO) δ ppm 9.05 (s, 1H), 7.17 (s, 1H), 4.38 (m, 2H), 3.80 (m, 2H), 3.05 (s, 3H). LCMS (ESI) 237 (M + H).

Example 9

Synthesis of 1-methyl-4-(6-nitro-3-pyridyl)piperazine, Compound 9

[0289]

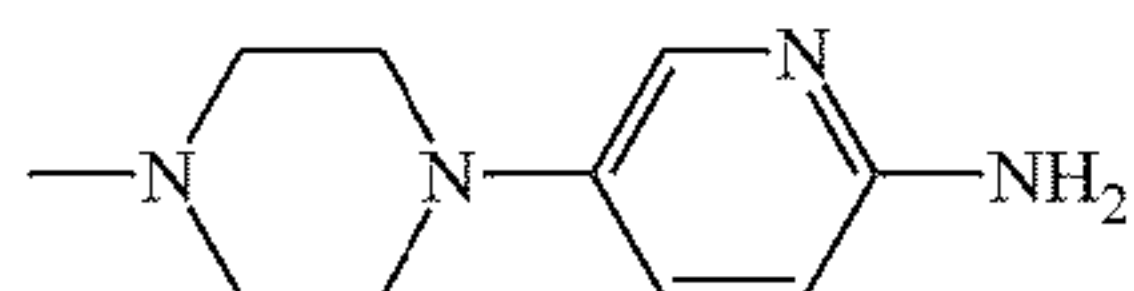


[0290] To 5-bromo-2-nitropyridine (4.93 g, 24.3 mmole) in DMF (20 mL) was added N-methylpiperazine (2.96 g, 1.1 eq) followed by the addition of DIPEA (4.65 mL, 26.7 mmole). The contents were heated at 90 degrees for 24 hrs. After addition of ethyl acetate (200 mL), water (100 mL) was added and the layers separated. Drying followed by concentration afforded the crude product which was purified by silica gel column chromatography using (0-10%) DCM/Methanol. ¹HNMR (d6-DMSO) δ ppm 8.26 (s, 1H), 8.15 (1H, d, J = 9.3 Hz), 7.49 (1H, d, J = 9.4 Hz), 3.50 (m, 4H), 2.49 (m, 4H), 2.22 (s, 3H).

Example 10

Synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine, Compound 10

[0291]

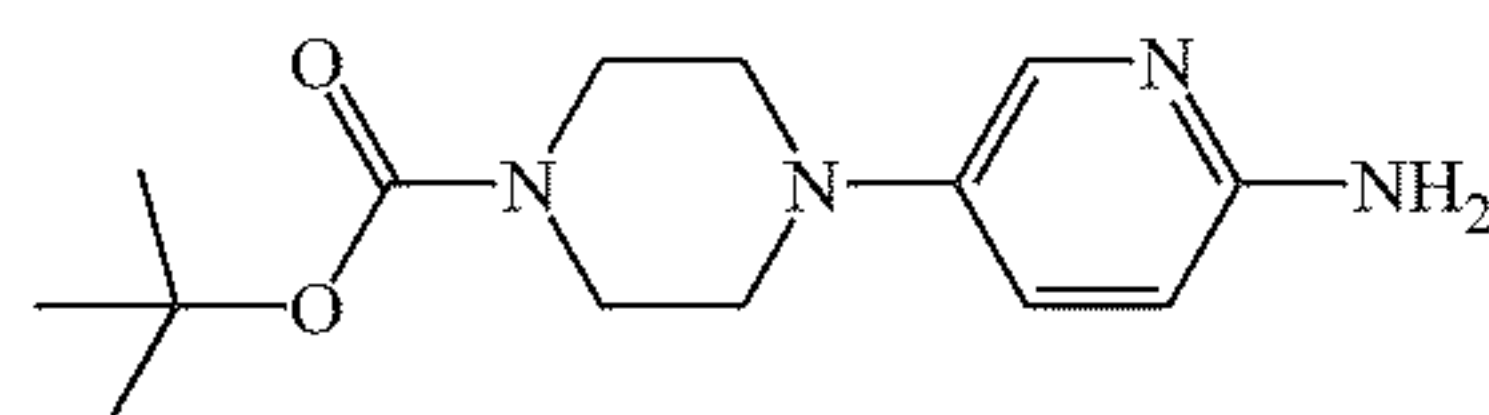


[0292] To 1-methyl-4-(6-nitro-3-pyridyl)piperazine (3.4 g) in ethyl acetate (100 mL) and ethanol (100 mL) was added 10% Pd/C (400 mg) and then the reaction was stirred under hydrogen (10 psi) overnight. After filtration through CELITE™, the solvents were evaporated and the crude product was purified by silica gel column chromatography using DCM/ 7N ammonia in MeOH (0- 5%) to afford 5-(4-methylpiperazin-1-yl)pyridin-2-amine (2.2 g). ¹HNMR (d6-DMSO) δ ppm 7.56 (1H, d, J = 3 Hz), 7.13 (1H, m), 6.36 (1H, d, J = 8.8 Hz), 5.33 (brs, 2H), 2.88 (m, 4H), 2.47 (m, 4H), 2.16 (s, 3H).

Example 11

Synthesis of Tert-butyl 4-(6-amino-3-pyridyl)piperazine-1-carboxylate, Compound 11

[0293]

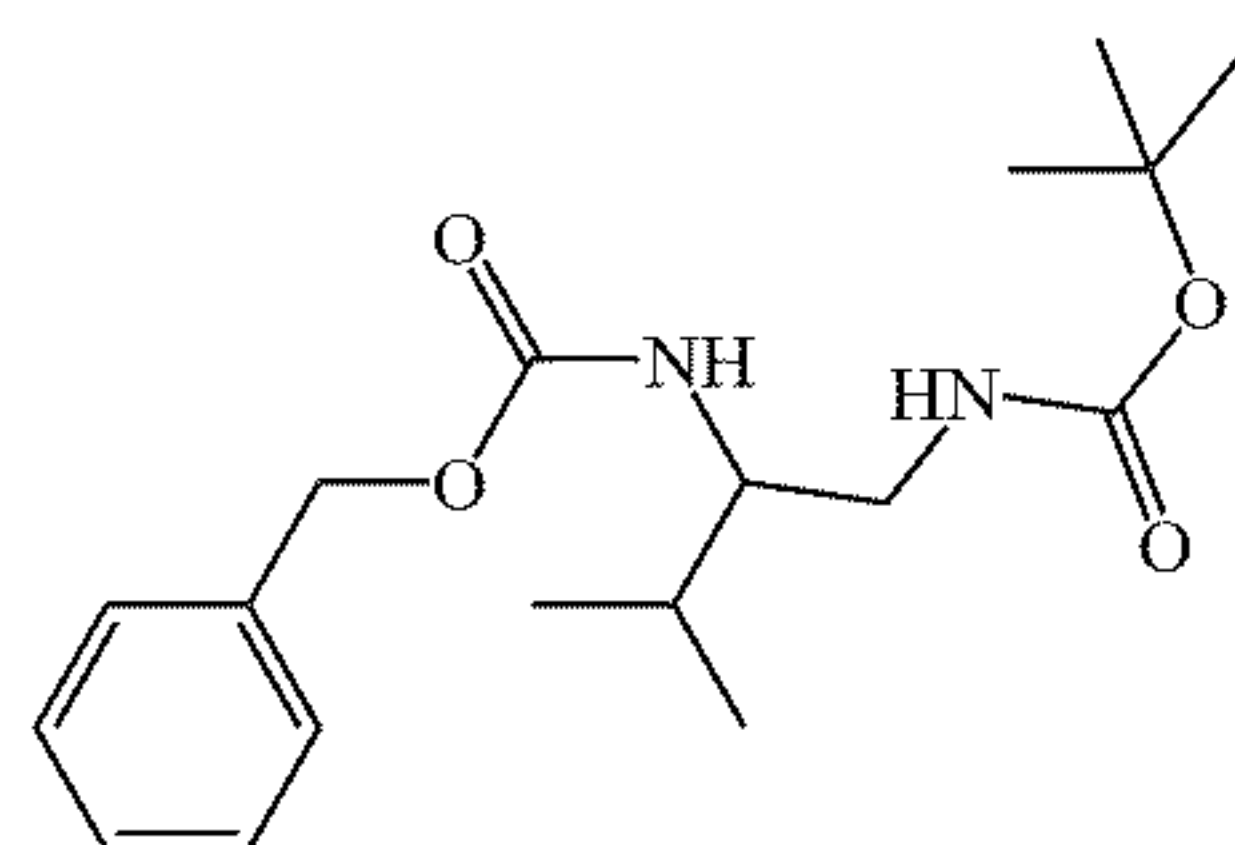


[0294] This compound was prepared as described in WO 2010/020675 A1.

Example 12

Synthesis of Tert-Butyl N-[2-(benzyloxycarbonylamino)-3-methyl-butyl] Carbamate, Compound 12

[0295]



[0296] To benzyl N-[1-(hydroxymethyl)-2-methyl-propyl]carbamate (11.0 g, 0.0464 mole) in dioxane (100 mL) cooled to 0° C. was added diphenylphosphoryl azide (10.99 mL, 1.1 eq) followed by the addition of DBU (8.32 mL, 1.2 eq). The contents were allowed to warm to room temperature and stirred for 16 hrs. After the addition of ethyl acetate (300 mL) and water (100 mL), the organic layer was separated and washed with satd. NaHCO₃ (100 mL). The organic layer was then dried (magnesium sulfate) and concentrated under vacuum. To this intermediate in DMSO (100 mL) was added sodium azide (7.54 g) and the contents then heated to 90 degrees for 2 hrs. After addition of ethyl acetate and water the layers were separated. The organic layer was dried with magnesium sulfate

followed by concentration under vacuum to afford an oil that was purified by silica gel column chromatography using hexane/ethyl acetate (0- 70%) to afford benzyl N-[1-(azidomethyl)-2-methyl-propyl] carbamate 6.9 g as a colorless oil.

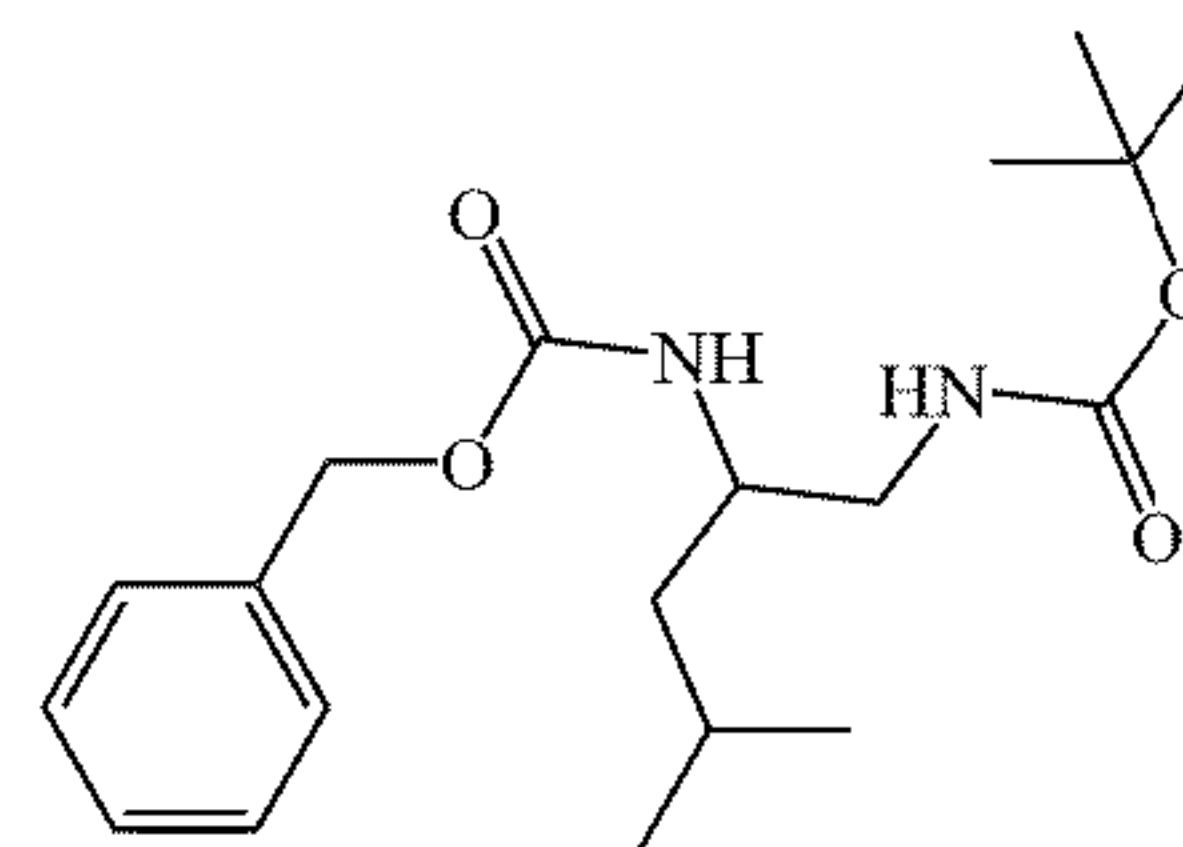
[0297] To benzyl N-[1-(azidomethyl)-2-methyl-propyl] carbamate (6.9 g, 0.0263 mole) in THF (100 mL) was added triphenyl phosphine (7.59 g, 1.1 eq). The contents were stirred for 20 hrs. After addition of water (10 mL), and stirring for an additional 6 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was purified by silica gel column chromatography using DCM/ MeOH (0 - 10%) to afford benzyl N-[1-(aminomethyl)-2-methyl-propyl] carbamate as a yellow oil.

[0298] To benzyl N-[1-(aminomethyl)-2-methyl-propyl] carbamate (4.65 g, 0.019 mole) in THF (70 mL) was added 2 N NaOH (20 mL) followed by the addition of di-tert-butyl dicarbonate (5.15 g, 1.2 eq). After stirring for 16 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was purified using hexane/ethyl acetate (0- 40%) over a silica gel column to afford intermediate A, tert-butyl N-[2-(benzyloxycarbonylamino)-3-methyl-butyl] carbamate, (6.1 g). ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.89 (d, J=6.73 Hz, 3 H) 0.92 (d, J=6.73 Hz, 3 H) 1.38 (s, 9 H) 1.70 -1.81 (m, 1 H) 3.18 (d, J=5.56 Hz, 2 H) 3.47 - 3.60 (m, 1 H) 4.76 (s, 1 H) 4.89 (d, J=7.90 Hz, 1 H) 5.07 (s, 2 H) 7.25 - 7.36 (m, 5 H). LCMS (ESI) 337 (M + H).

Example 13

Synthesis of Tert-butyl N-[2-(benzyloxycarbonylamino)-4-methyl-pentyl] Carbamate, Compound 13

[0299]



[0300] To a solution of benzyl N-[1-(hydroxymethyl)-3-methyl-butyl]carbamate (6.3 g, 0.025 mole) in DCM (100 mL) was added diisopropylethyl amine (5.25 mL, 1.2 eq) followed by the addition of methane sulfonylchloride (2.13 mL, 1.1 eq) at 0 degrees. After stirring for 3 hrs, water (100 mL) was added and the organic layer separated. After drying with magnesium sulfate and concentration under vacuum, the crude [2-(benzyloxycarbonylamino)-4-methyl-pentyl] methanesulfonate which was taken directly to the next step.

[0301] To the crude [2-(benzyloxycarbonylamino)-4-methyl-pentyl] methanesulfonate from the above reaction in DMF (50 mL), was added sodium azide 2.43 g. The reaction mixture was then heated to 85 degrees for 3 hrs. After cooling, ethyl acetate (300 mL) and water was added. The organic layer was separated, dried with magnesium sulfate and then concentrated under vacuum to afford the crude benzyl N-[1-(azidomethyl)-3-methyl-butyl] carbamate. To this crude intermediate was added THF (100 mL) followed by triphenylphosphine 7.21 g and stirred under nitrogen for

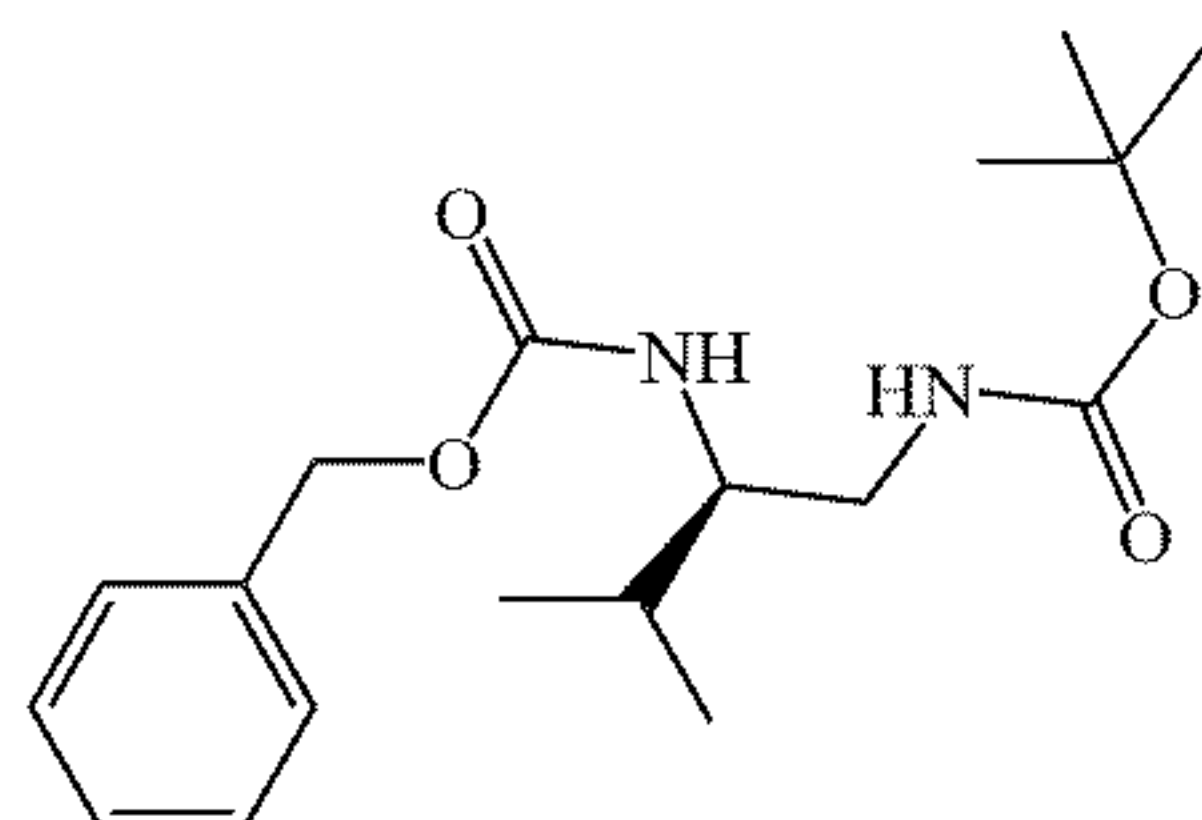
16 hrs. After addition of water (10 mL), and stirring for an additional 6 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was columned using DCM/MeOH (0 - 10%) to afford benzyl N-[1-(aminomethyl)-3-methyl-butyl] carbamate (4.5 g).

[0302] To benzyl N-[1-(aminomethyl)-3-methyl-butyl] carbamate (4.5 g, 0.018 mole) in THF (60 mL) was added 2N NaOH (18 mL) followed by the addition of di-tert-butyl dicarbonate (4.19 g, 1.07 eq). After stirring for 16 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was taken to the next step. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.89 (d, J=6.73 Hz, 6 H) 1.25 - 1.34 (m, 1 H) 1.39 (s, 9 H) 1.57 - 1.71 (m, 2 H) 3.04 - 3.26 (m, 2 H) 3.68 - 3.80 (m, 1 H) 4.72 - 4.89 (m, 2 H) 5.06 (s, 2 H) 7.25 - 7.38 (m, 5 H). LCMS (ESI) 351 (M + H).

Example 14

Synthesis of Tert-butyl N-[(2R)-2-(benzyloxycarbonylamino)-3-methyl-butyl] Carbamate, Compound 14

[0303]

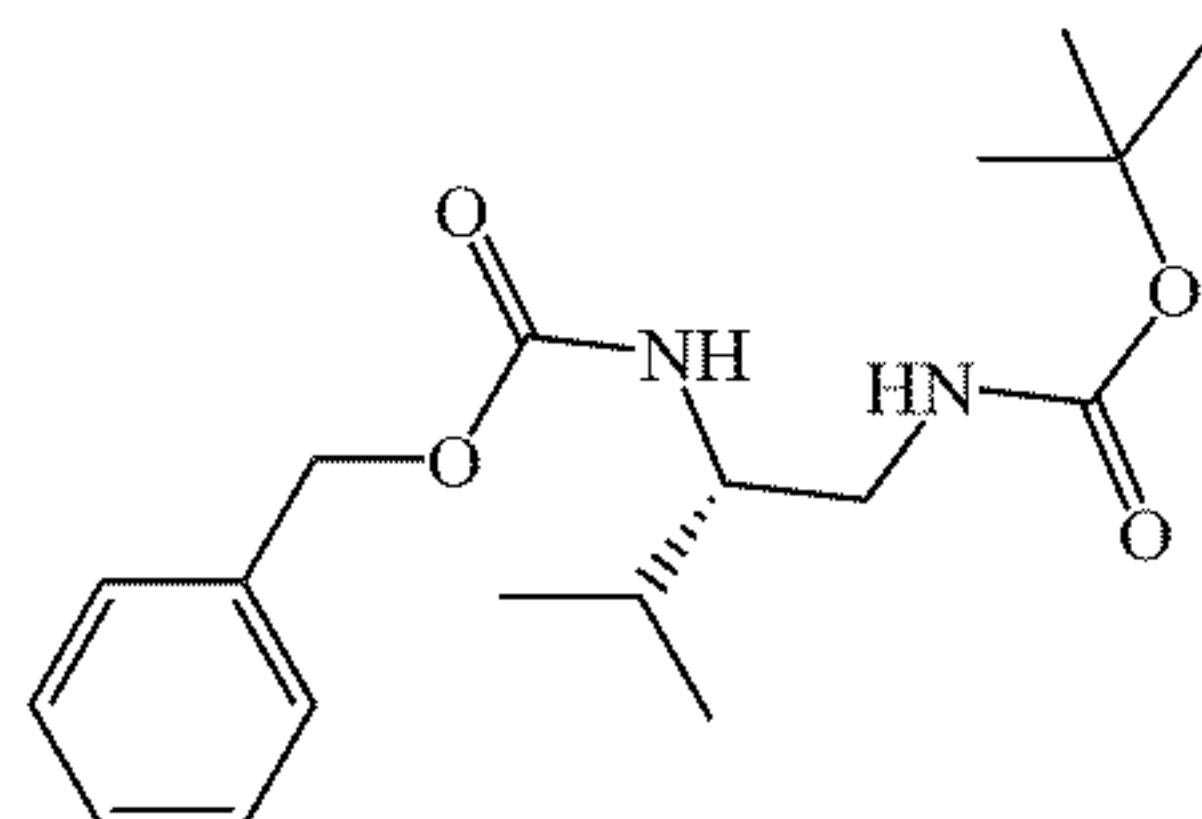


[0304] Compound 14 was synthesized from benzyl N-[(1R)-1-(hydroxymethyl)-2-methyl-propyl] carbamate using similar synthetic steps as that described for Compound 13. The analytical data (NMR and mass spec) was consistent with that for Compound 12.

Example 15

Synthesis of Tert-butyl N-[(2S)-2-(benzyloxycarbonylamino)-3-methyl-butyl]carbamate, Compound 15

[0305]

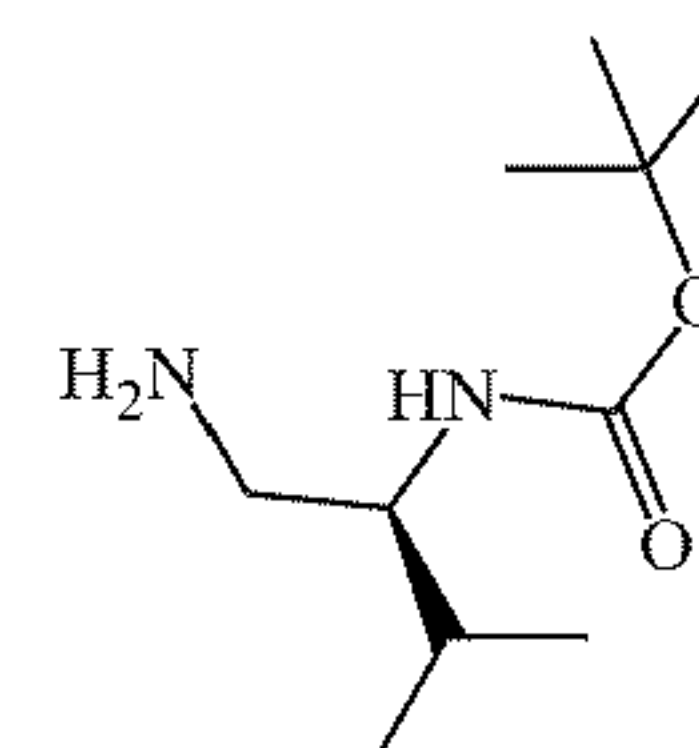


[0306] Compound 15 was synthesized from benzyl N-[(1S)-1-(hydroxymethyl)-2-methyl-propyl] carbamate using similar synthetic steps as that described for Compound 13. The analytical data (NMR and mass spec) was consistent with that for Compound 12.

Example 16

Synthesis of Tert-butyl N-[(1S)-1-(aminomethyl)-2-methyl-propyl]carbamate, Compound 16

[0307]



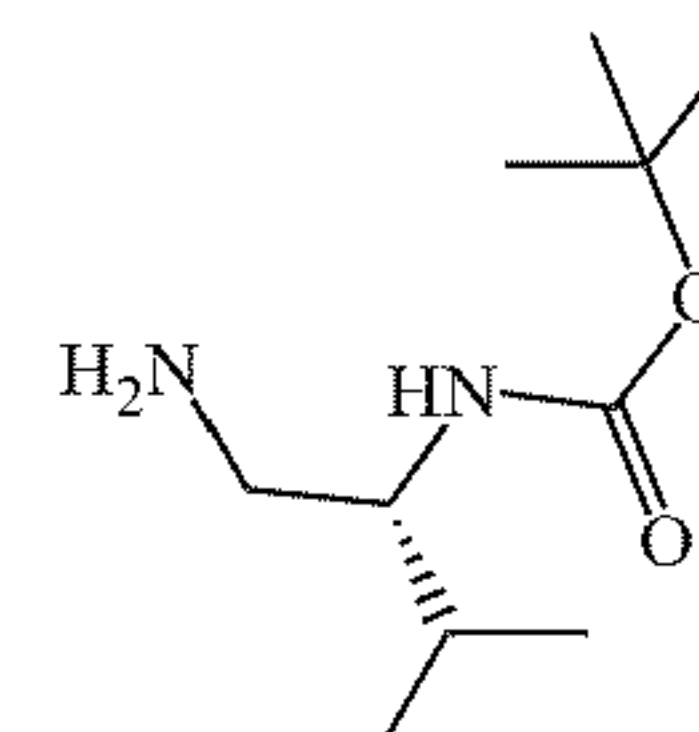
[0308] To a solution of tert-butyl N-[(1S)-1-(hydroxymethyl)-2-methyl-propyl]carbamate carbamate (6.3 g, 0.025 mole) in THF (100 mL) was added diisopropylethyl amine (5.25 mL, 1.2 eq) followed by the addition of methane sulfonylchloride (2.13 mL, 1.1 eq) at 0 degrees. After stirring for 3 hrs, water (100 mL) was added and the organic layer separated. After drying with magnesium sulfate and concentration under vacuum, the crude [(2S)-2-(tert-butoxycarbonylamino)-3-methyl-butyl] methanesulfonate was taken directly to the next step.

[0309] To the crude [(2S)-2-(tert-butoxycarbonylamino)-3-methyl-butyl] methanesulfonate from the above reaction in DMSO (50 mL), was added sodium azide (2.43 g). The reaction mixture was then heated to 85 degrees for 3 hrs. After cooling, ethyl acetate (300 mL) and water were added. The organic layer was separated, dried with magnesium sulfate and then concentrated under vacuum to afford the crude benzyl N-[1-(azidomethyl)-3-methyl-butyl] carbamate. To this crude intermediate was added THF (100 mL) followed by triphenylphosphine (7.21 g) and the reaction was stirred under nitrogen for 16 hrs. After addition of water (10 mL), and stirring for an additional 6 hrs, ethyl acetate was added and the layers separated. After drying with magnesium sulfate and concentration under vacuum, the crude product was purified by silica gel column chromatography using DCM/MeOH (0 - 10%) to afford benzyl N-[1-(aminomethyl)-3-methylbutyl] carbamate (4.5 g). LCMS (ESI) 203 (M + H).

Example 17

Synthesis of Tert-butyl N-[(1R)-1-(aminomethyl)-2-methyl-propyl]carbamate, Compound 17

[0310]

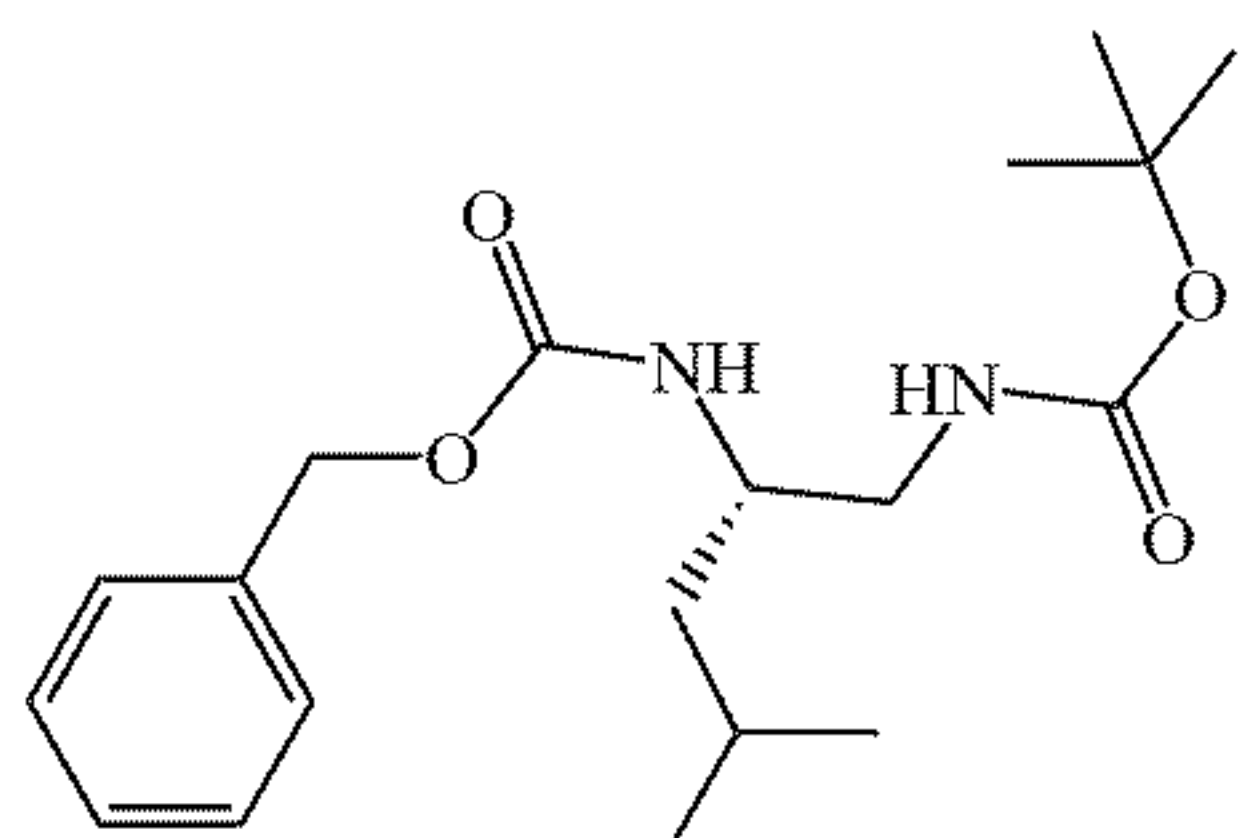


[0311] Compound 17 was synthesized from tert-butyl N-[(1R)-1-(hydroxymethyl)-2-methylpropyl] carbamate using a similar synthetic sequence as described for Compound 16. The analytical data (NMR and mass spec) was consistent with Compound 16.

Example 18

Synthesis of Tert-butyl N-[(2S)-2-(benzyloxycarbonylamino)-4-methyl-pentyl] Carbamate, Compound 18

[0312]

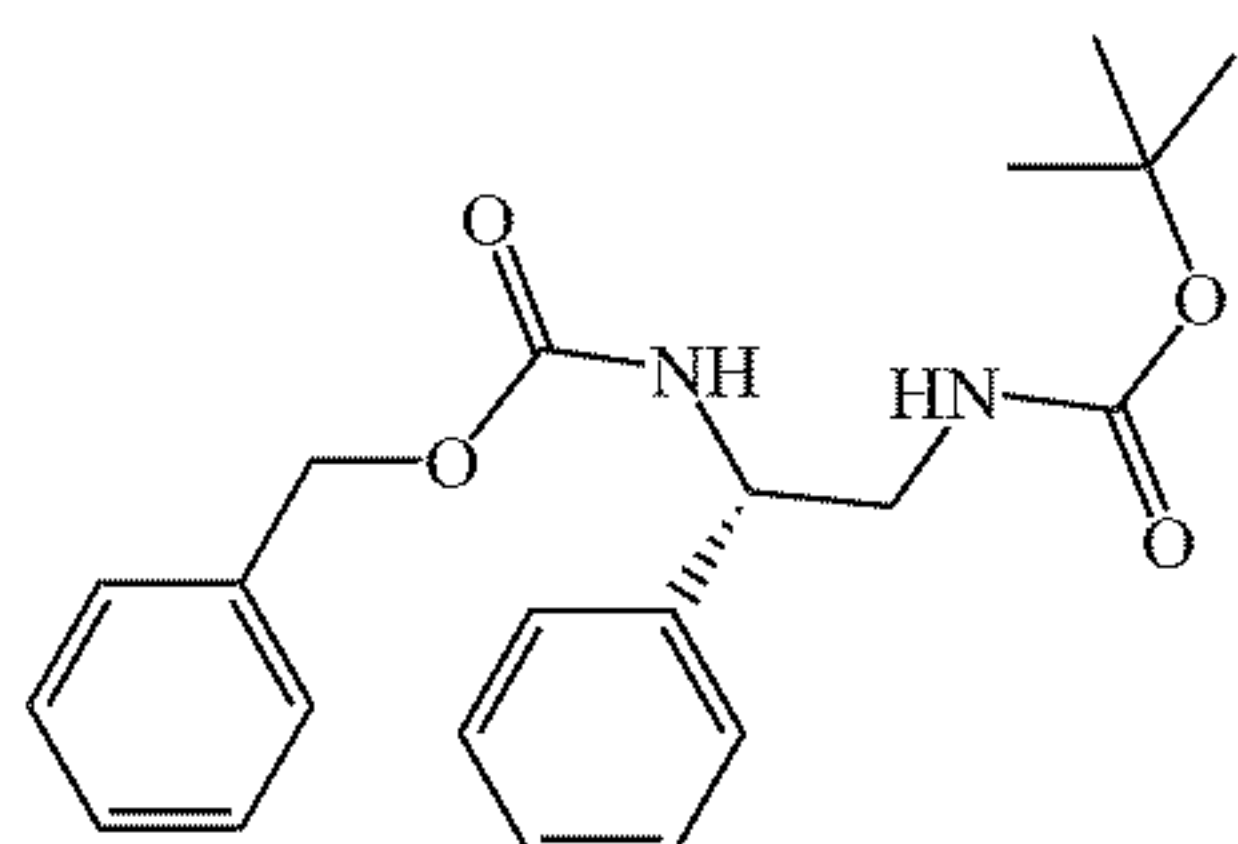


[0313] Compound 18 was synthesized from benzyl N-[(1S)-1-(hydroxymethyl)-3-methylbutyl]carbamate using a similar synthetic sequence as described for Compound 13. The analytical data (NMR and mass spec) was consistent with Compound 13.

Example 19

Synthesis of Tert-butyl N-[(2S)-2-(benzyloxycarbonylamino)-2-phenyl-ethyl] Carbamate, Compound 19

[0314]

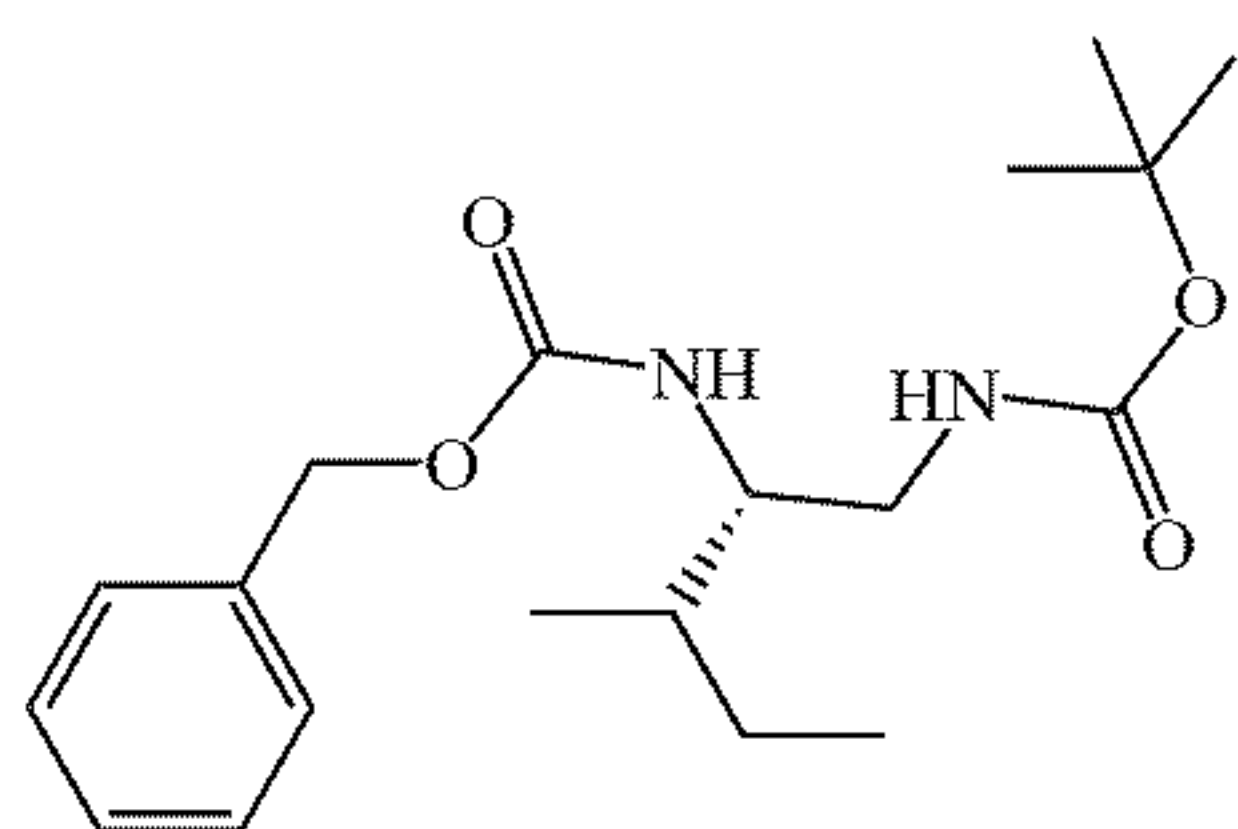


[0315] Compound 19 was synthesized from benzyl N-[(1S)-2-hydroxy-1-phenyl-ethyl] carbamate using a similar synthetic sequence as described for Compound 13. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.20 - 1.33 (m, 9 H) 3.11 (t, J=6.29 Hz, 2 H) 4.59 - 4.68 (m, 1 H) 4.88 - 5.01 (m, 2 H) 6.81 (t, J=5.42 Hz, 1 H) 7.14 - 7.35 (m, 10 H) 7.69 (d, J=8.49 Hz, 1 H). LCMS (ESI) 371 (M + H).

Example 20

Synthesis of Tert-butyl N-[(2S)-2-(benzyloxycarbonylamino)-3-methyl-pentyl] Carbamate, Compound 20

[0316]

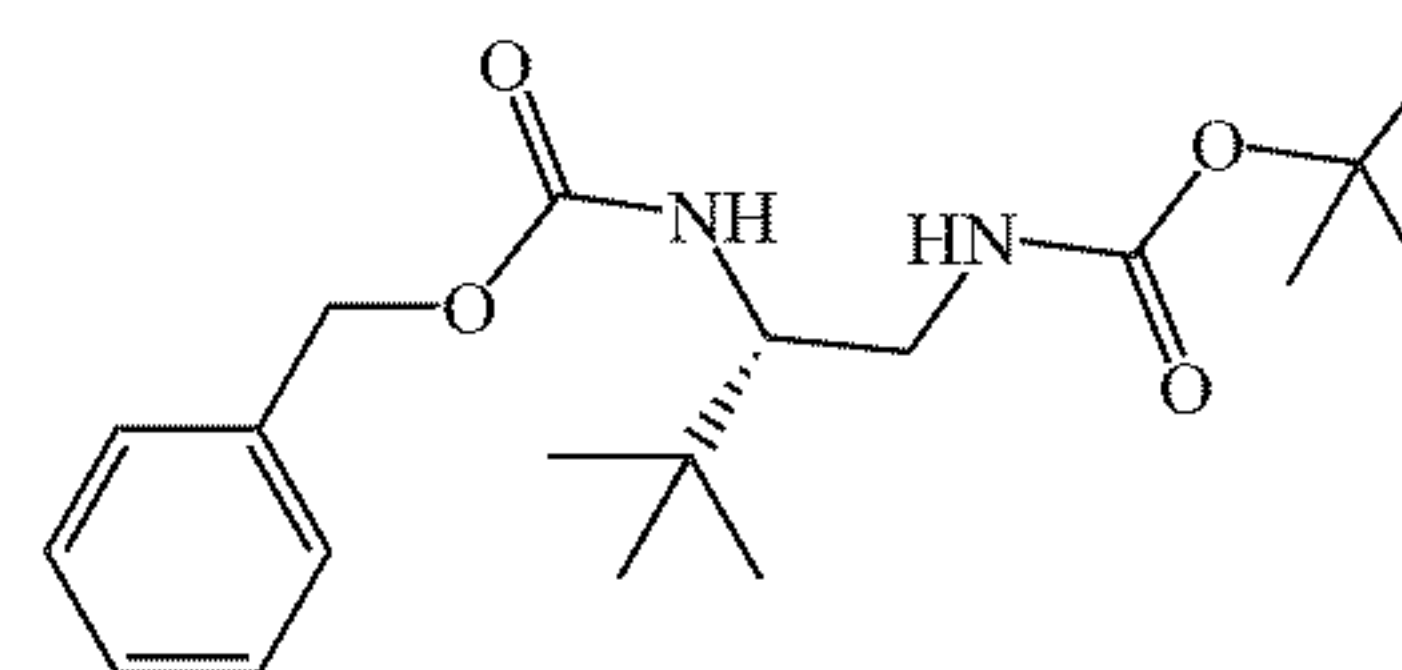


[0317] Compound 20 was synthesized from benzyl N-[(1S)-1-(hydroxymethyl)-2-methyl-butyl] carbamate using a similar synthetic sequence as described for Compound 13. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.85 - 0.92 (m, 6 H) 1.05 - 1.15 (m, 1 H) 1.35 - 1.41 (m, 9 H) 1.45 - 1.56 (m, 2 H) 3.14 - 3.24 (m, 2 H) 3.54 - 3.64 (m, 1 H) 4.78 (s, 1 H) 4.96 (d, J=7.91 Hz, 1 H) 5.06 (s, 2 H) 7.27 - 7.37 (m, 5 H). LCMS (ESI) 351 (M + H).

Example 21

Synthesis of Tert-butyl N-[(2S)-2-(benzyloxycarbonylamino)-3,3-dimethyl-butyl] Carbamate, Compound 21

[0318]

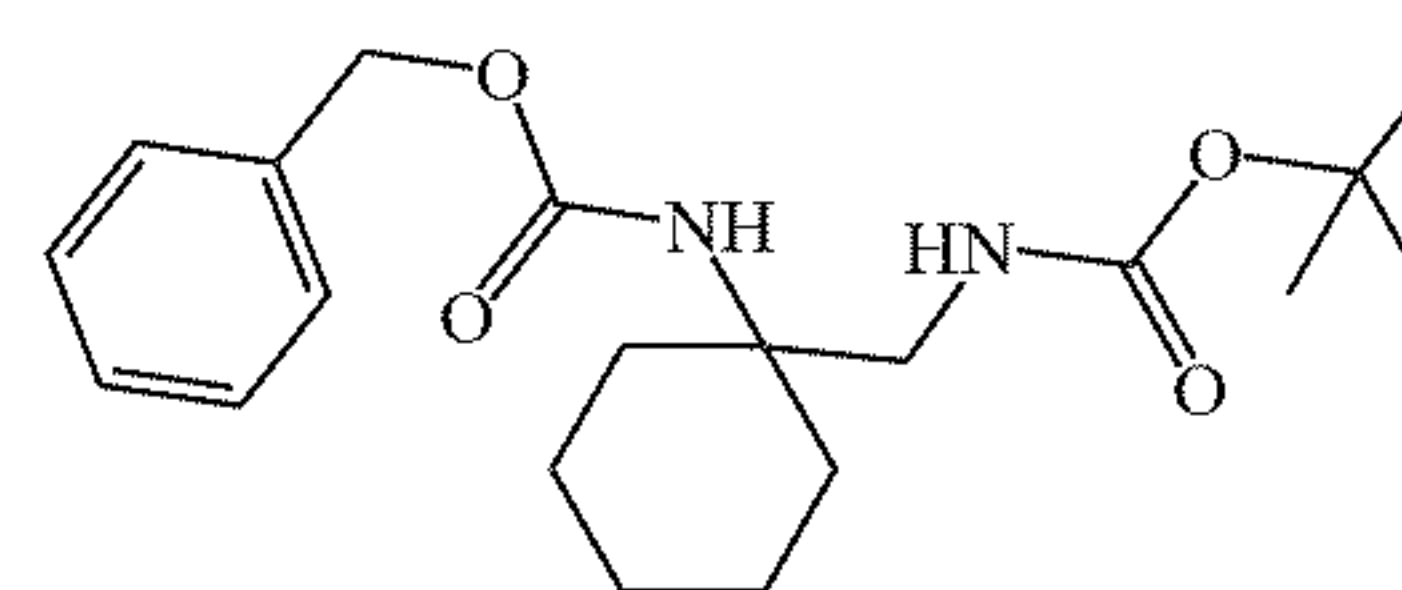


[0319] Compound 21 was synthesized from benzyl N-[(1S)-1-(hydroxymethyl)-2,2-dimethyl-propyl]carbamate using a similar synthetic sequence as described for Compound 13. LCMS (ESI) 351.

Example 22

Synthesis of Tert-butyl N-[[1-(benzyloxycarbonylamino)cyclohexyl]methyl] Carbamate, Compound 22

[0320]

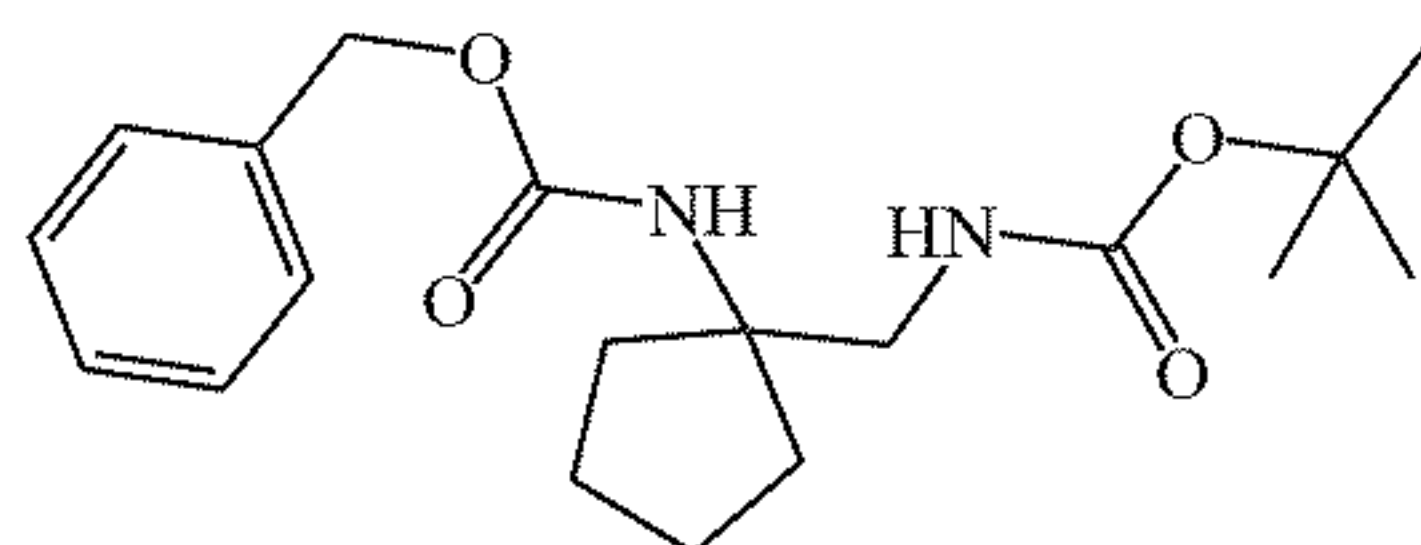


[0321] To a solution of benzyl N-[1-(aminomethyl)cyclohexyl]carbamate (10.0 g, 0.0381 mole) in THF (150 mL) was added di-tert-butyl dicarbonate (9.15 g, 1.1 eq) and the contents were stirred at room temperature for 16 hrs. Ethyl acetate and water were then added. The organic layer was separated, dried over magnesium sulfate and then concentrated under vacuum to afford tert-butyl N-[[1-(benzyloxycarbonylamino)cyclohexyl]methyl] carbamate (13.1 g). ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.92 - 1.54 (m, 17 H) 1.76 - 2.06 (m, 2 H) 3.09 (d, J=6.15 Hz, 2 H) 4.92 (s, 2 H) 6.63 (d, J=17.27 Hz, 1 H) 7.16 - 7.49 (m, 6 H). LCMS (ESI) 363 (M + H).

Example 23

Synthesis of Tert-butyl N-[[1-(benzyloxycarbonylamino)cyclopentyl]methyl] Carbamate, Compound 23

[0322]

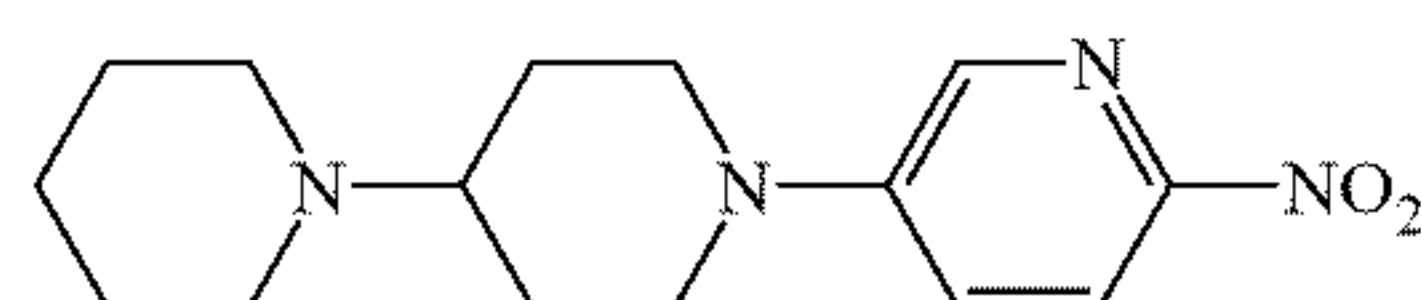


[0323] tert-butyl N-[[1-(benzyloxycarbonylamino)cyclopentyl]methyl]carbamate was synthesized in an analogous manner to tert-butyl N-[[1-(benzyloxycarbonylamino)cyclohexyl]methyl] carbamate. LCMS (ESI) 349 (M + H).

Example 24

Synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine, Compound 24

[0324]

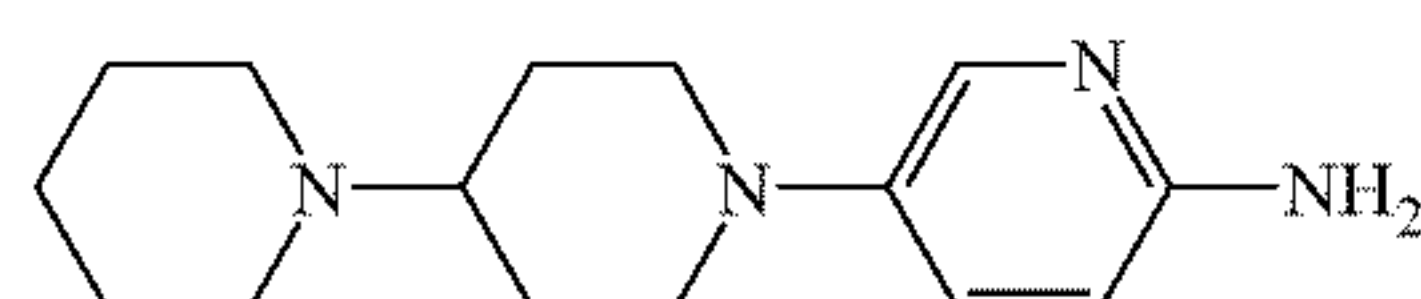


[0325] To 5-bromo-2-nitropyridine (1.2 g, 5.9 mmol) in DMSO (4 mL) was added 1-(4-piperidyl)piperidine (1.0 g, 5.9 mmole) and triethylamine (0.99 mL, 7.1 mmole). The contents were heated to 120° C. in a CEM Discovery microwave system for 3 hours. The crude reaction was then purified by silica gel column chromatography with DCM/methanol (0-20%) to afford 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine as an oil (457 mg). ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.26 - 1.36 (m, 2 H) 1.43 (m, 6 H) 1.76 (m, 2 H) 2.37 (m, 5 H) 2.94 (t, J=12.74 Hz, 2 H) 4.06 (d, J=13.47 Hz, 2 H) 7.41 (dd, J=9.37, 2.64 Hz, 1 H) 8.08 (d, J=9.37 Hz, 1 H) 8.20 (d, J=2.64 Hz, 1 H).

Example 25

Synthesis of 5-[4-(1-piperidyl)-1-piperidyl]pyridin-2-amine, Compound 25

[0326]

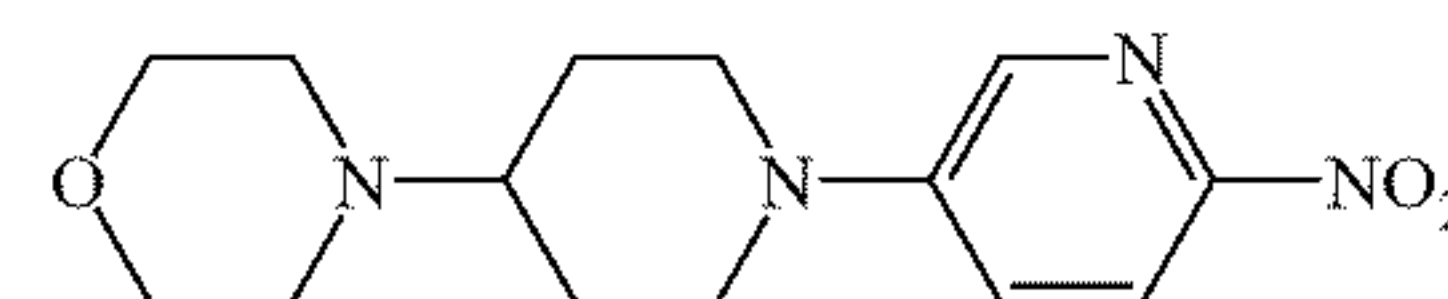


[0327] 5-(1-piperidyl)-1-piperidyl]pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.13 - 1.37 (m, 6 H) 1.40 - 1.63 (m, 6 H) 1.71 (m, 2 H), 2.24 (m, 1H) 2.43 (m, 2 H) 3.33 (d, J=12.30 Hz, 2 H) 5.31 (s, 2 H) 6.33 (d, J=8.78 Hz, 1 H) 7.10 (dd, J=8.78, 2.93 Hz, 1 H) 7.55 (d, J=2.64 Hz, 1 H). LCMS (ESI) 261 (M + H).

Example 26

Synthesis of 4-[1-(6-nitro-3-pyridyl)-4-piperidyl] Morpholine, Compound 26

[0328]

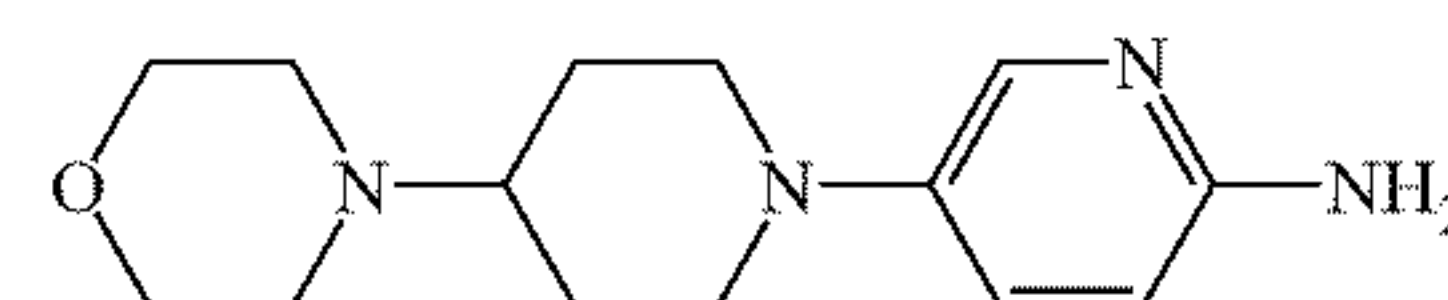


[0329] 4-(6-nitro-3-pyridyl)-4-piperidyl]morpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.41 (m, 2 H) 1.82 (m, 2 H) 2.42 (m, 5 H) 2.98 (t, J=12.44 Hz, 2 H) 3.52 (s, 4 H) 4.04 (d, J=12.88 Hz, 2 H) 7.42 (d, J=9.37 Hz, 1 H) 8.08 (d, J=9.08 Hz, 1 H) 8.21 (s, 1 H).

Example 27

Synthesis of 5-(4-morpholino-1-piperidyl) Pyridin-2-amine, Compound 27

[0330]

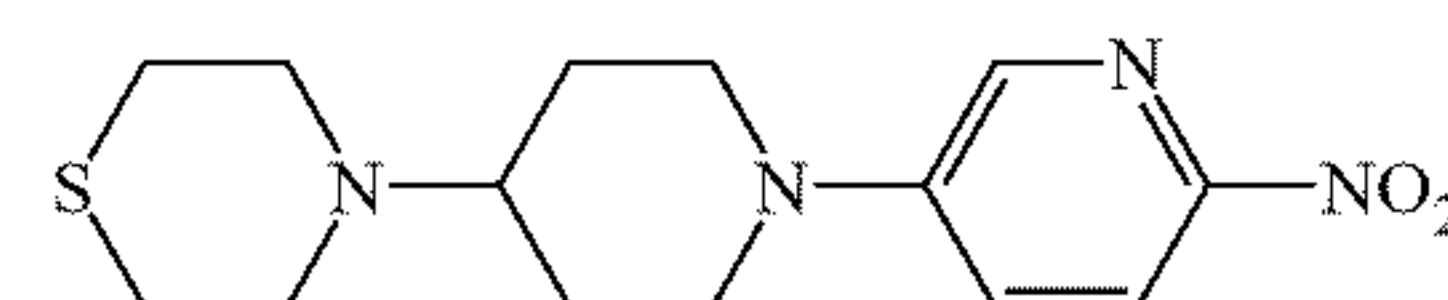


[0331] 5-morpholino-1-piperidyl]pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-methylpiperazin-1-yl]pyridin-2-amine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.34 - 1.52 (m, 2 H) 1.78 (m, 2 H) 2.14 (m, 1 H) 2.43 (m, 4 H) 3.32 (d, J=12.30 Hz, 4 H) 3.47 - 3.59 (m, 4 H) 5.32 (s, 2 H) 6.34 (d, J=8.78 Hz, 1 H) 7.11 (dd, J=8.93, 2.78 Hz, 1 H) 7.47 - 7.62 (m, 1 H). LCMS (ESI) 263 (M + H).

Example 28

Synthesis of 4-[1-(6-nitro-3-pyridyl)-4-piperidyl] Thiomorpholine, Compound 28

[0332]

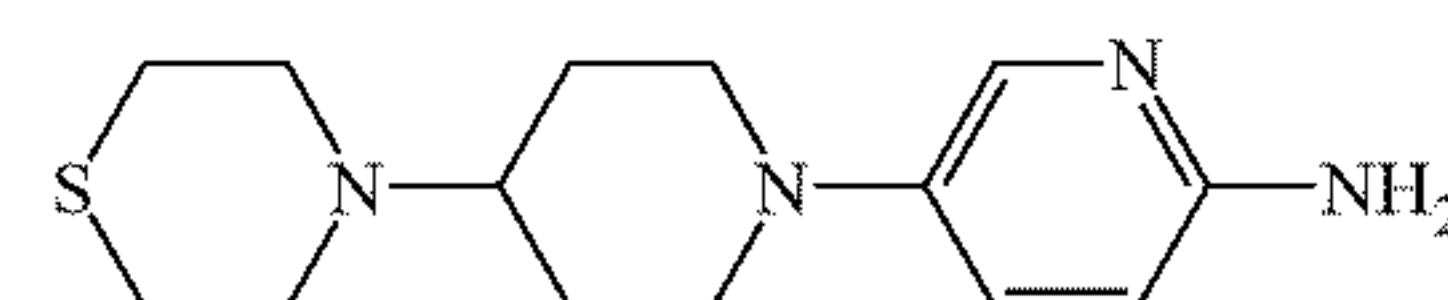


[0333] 4-(6-nitro-3-pyridyl)-4-piperidyl] thiomorpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.40 - 1.52 (m, 2H) 1.71 (m, 2 H) 2.49 - 2.55 (m, 4 H) 2.56 - 2.63 (m, 1 H) 2.68 - 2.75 (m, 4 H) 2.88 - 2.98 (m, 2 H) 4.09 (d, J=13.18 Hz, 2 H) 7.42 (dd, J=9.22, 3.07 Hz, 1 H) 8.08 (d, J=9.37 Hz, 1 H) 8.20 (d, J=3.22 Hz, 1 H).

Example 29

Synthesis of 5-(4-thiomorpholino-1-piperidyl) Pyridin-2-amine, Compound 29

[0334]

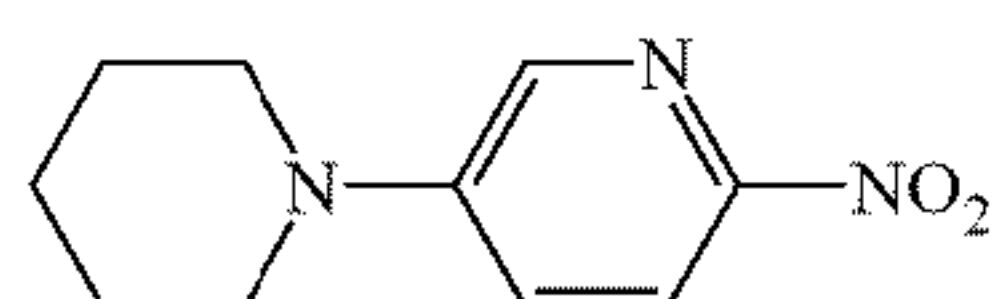


[0335] 5-thiomorpholino-1-piperidyl) pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.47 - 1.59 (m, 2 H) 1.65 (m, 2 H) 2.22 - 2.38 (m, 1 H) 2.50 - 2.59 (m, 6 H) 2.68 - 2.82 (m, 4 H) 3.33 (d, J=12.00 Hz, 2 H) 5.31 (s, 2 H) 6.33 (d, J=9.08 Hz, 1 H) 7.10 (dd, J=8.78, 2.93 Hz, 1 H) 7.55 (d, J=2.64 Hz, 1 H). LCMS (ESI) 279 (M + H).

Example 30

Synthesis of 2-nitro-5-(1-piperidyl)pyridine, Compound 30

[0336]

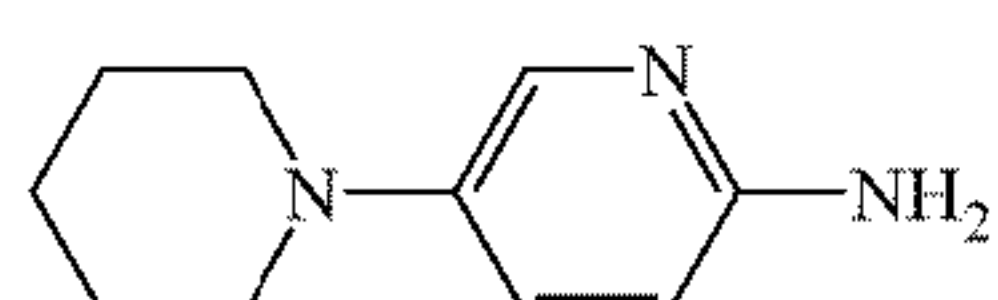


[0337] 2-nitro(1-piperidyl) pyridine was synthesized in a manner similar to that used in the synthesis of 2-nitro[4-(1-piperidyl)-1-piperidyl]pyridine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.56 (m, 6 H) 3.49 (d, J=4.39 Hz, 4 H) 7.30 - 7.47 (m, 1 H) 8.02 - 8.12 (m, 1 H) 8.15 - 8.26 (m, 1 H).

Example 31

Synthesis of 5-(1-piperidyl)pyridin-2-amine, Compound 31

[0338]

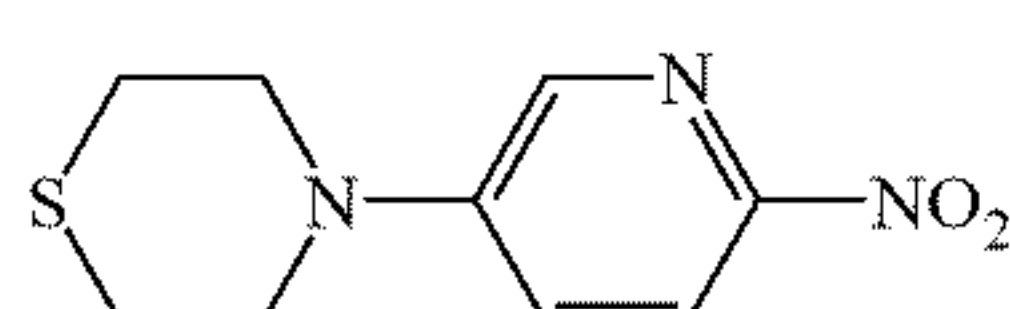


[0339] 5-piperidyl) pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.39 - 1.46 (m, 2 H) 1.51 - 1.62 (m, 4 H) 2.75 - 2.92 (m, 4 H) 5.30 (s, 2 H) 6.34 (d, J=8.78 Hz, 1 H) 7.09 (dd, J=8.78, 2.93 Hz, 1 H) 7.54 (d, J=2.93 Hz, 1 H). LCMS (ESI) 178 (M + H).

Example 32

Synthesis of 4-(6-nitro-3-pyridyl) Thiomorpholine, Compound 32

[0340]

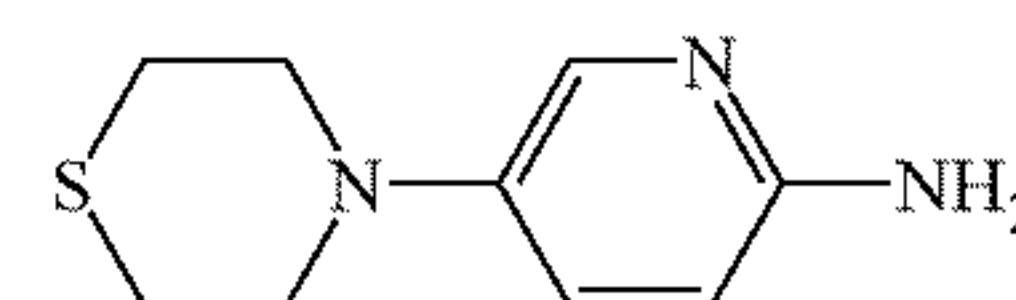


[0341] 4-nitro-3-pyridyl) thiomorpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 2.56 - 2.69 (m, 4 H) 3.79 - 3.92 (m, 4 H) 7.43 (dd, J=9.22, 3.07 Hz, 1 H) 8.10 (d, J=9.37 Hz, 1 H) 8.20 (d, J=2.93 Hz, 1 H).

Example 33

Synthesis of 5-thiomorpholinopyridin-2-amine, Compound 33

[0342]

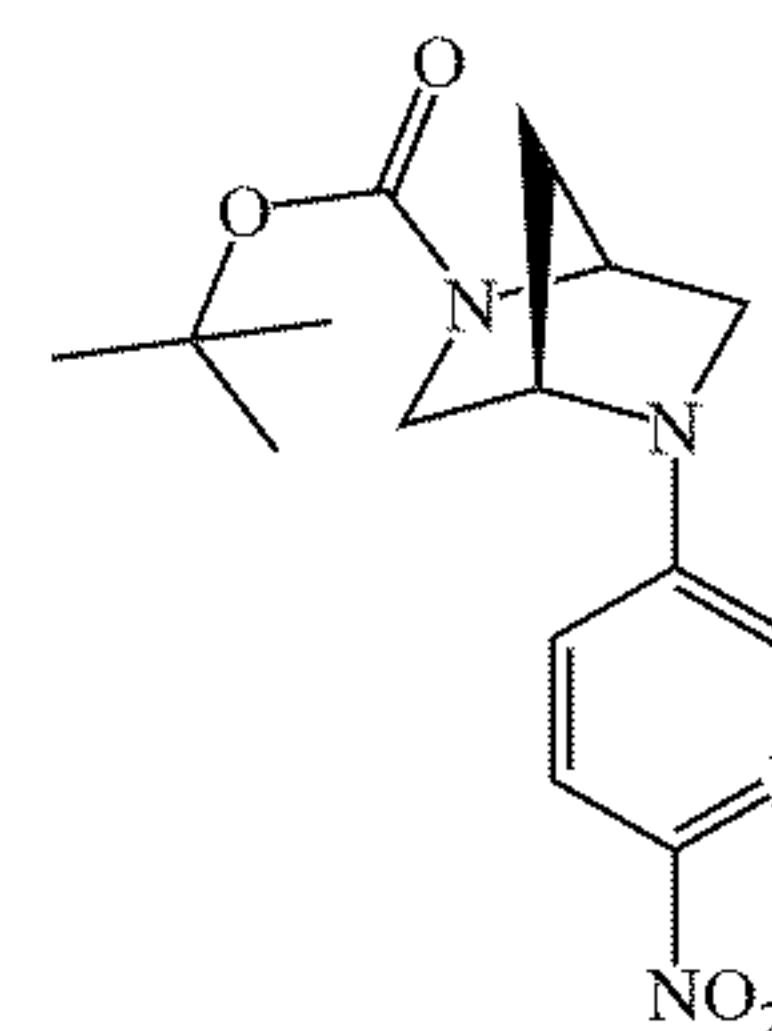


[0343] 5-thiomorpholinopyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl) pyridin-2-amine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 2.59 - 2.73 (m, 4 H) 3.04 - 3.20 (m, 4 H) 5.41 (s, 2 H) 6.35 (d, J=8.78 Hz, 1 H) 7.10 (dd, J=8.78, 2.93 Hz, 1 H) 7.57 (d, J=2.64 Hz, 1 H). LCMS (ESI) 196 (M + H).

Example 34

Synthesis of Tert-butyl (4R)-5-(6-nitro-3-pyridyl)-2,5-diazabicyclo[2.2.1]heptane-2-Carboxylate, Compound 34

[0344]

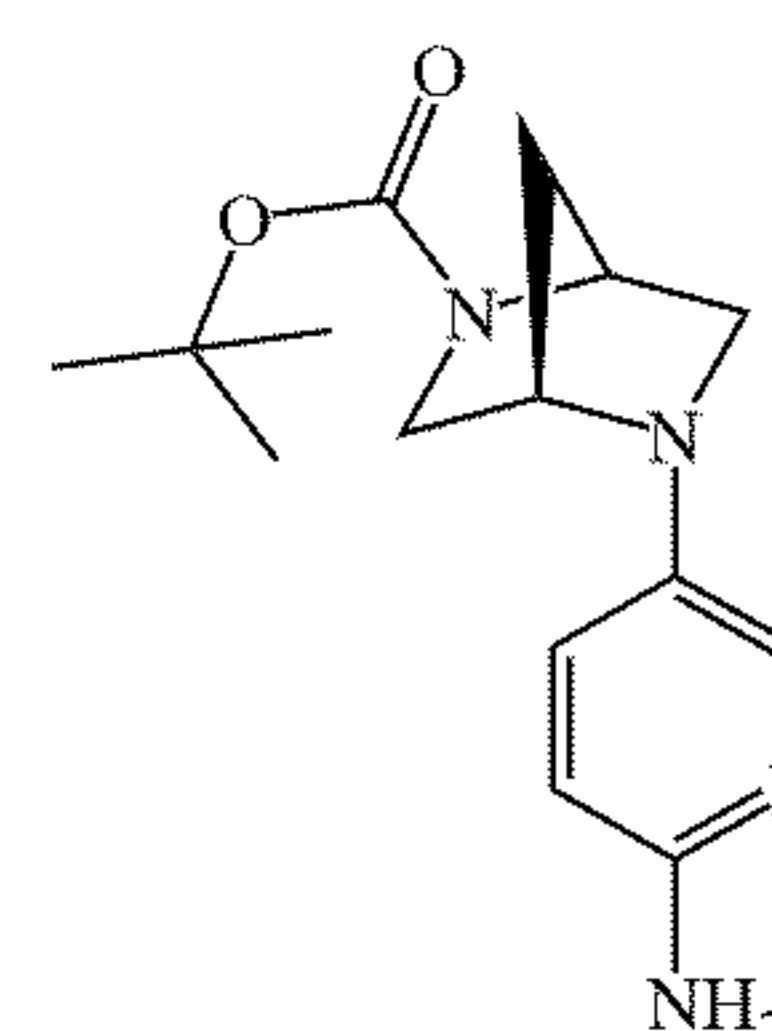


[0345] tert-butyl (4R)-5-(6-nitro-3-pyridyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.33 (d, J=32.21 Hz, 11 H) 1.91 (m, 2 H) 3.15 (d, J=10.25 Hz, 1 H) 3.58 (m, 1 H) 4.46 (m, 1 H) 4.83 (s, 1 H) 7.16 (s, 1 H) 7.94 (s, 1 H) 8.05-8.16 (m, 1 H).

Example 35

Synthesis of Tert-butyl (4R)-5-(6-amino-3-pyridyl)-2,5-diazabicyclo[2.2.1]heptane-2-Carboxylate, Compound 35

[0346]



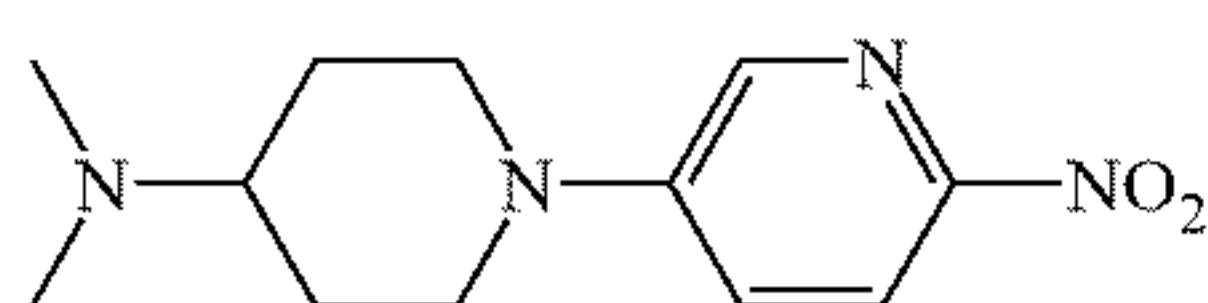
[0347] tert-butyl (4R)-5-(6-amino-3-pyridyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was prepared in a man-

ner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.31 (d, J=31.91 Hz, 11 H) 1.83 (m, 2 H) 2.71 -2.82 (m, 1 H) 3.44 (m, 1 H) 4.30 (d, 2H) 5.08 (s, 2 H) 6.35 (d, J=8.78 Hz, 1 H) 6.77 - 6.91 (m, 1 H) 7.33 (s, 1 H). LCMS (ESI) 291 (M + H).

Example 36

Synthesis of N,N-dimethyl-1-(6-nitro-3-pyridyl) Piperidin-4-amine, Compound 36

[0348]

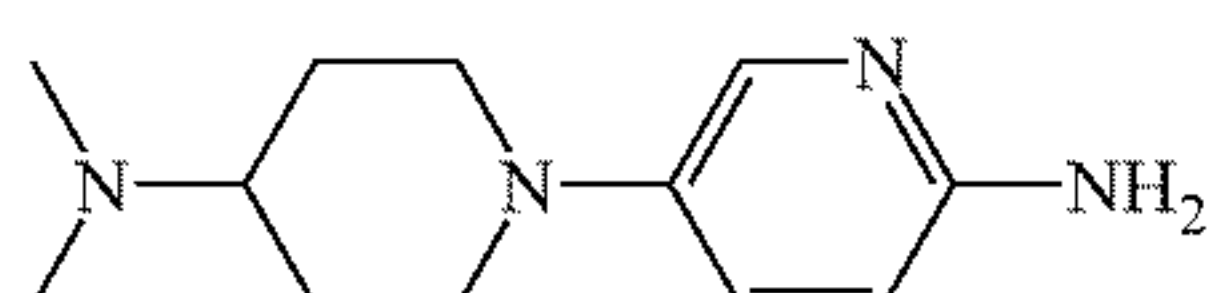


[0349] N,N-dimethyl-1-(6-nitro-3-pyridyl)piperidin-4-amine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.30 - 1.45 (m, 2 H) 1.79 (m, 2 H) 2.14 (s, 6 H) 2.33 (m, 1 H) 2.92 - 3.04 (m, 2 H) 4.03 (d, J=13.76 Hz, 2 H) 7.42 (dd, J=9.22, 3.07 Hz, 1 H) 8.04 - 8.11 (m, 1 H) 8.21 (d, J=2.93 Hz, 1 H).

Example 37

Synthesis of 5-[4-(dimethylamino)-1-piperidyl] Pyridin-2-amine, Compound 37

[0350]

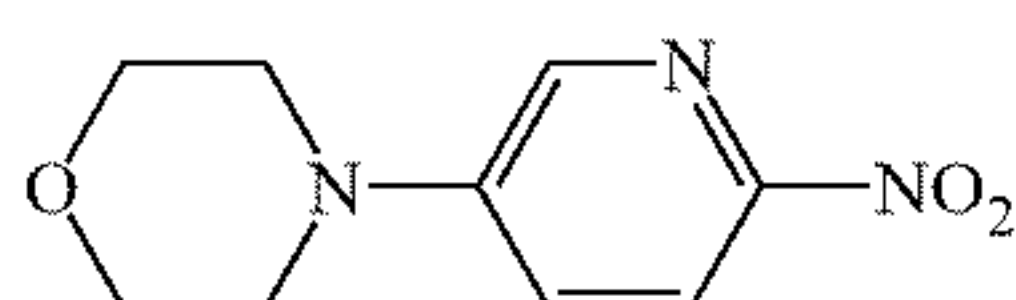


[0351] 5-(dimethylamino)-1-piperidyl]pyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.35 - 1.50 (m, 2 H) 1.69 - 1.81 (m, 2 H) 2.00 - 2.10 (m, 1 H) 2.11 - 2.22 (s, 6 H) 3.17 - 3.36 (m, 4 H) 5.19 - 5.38 (s, 2 H) 6.34 (d, J=8.78 Hz, 1 H) 7.10 (dd, J=8.78, 2.93 Hz, 1 H) 7.55 (d, J=2.63 Hz, 1 H). LCMS (ESI) 221 (M + H).

Example 38

Synthesis of 4-(6-nitro-3-pyridyl) Morpholine, Compound 38

[0352]

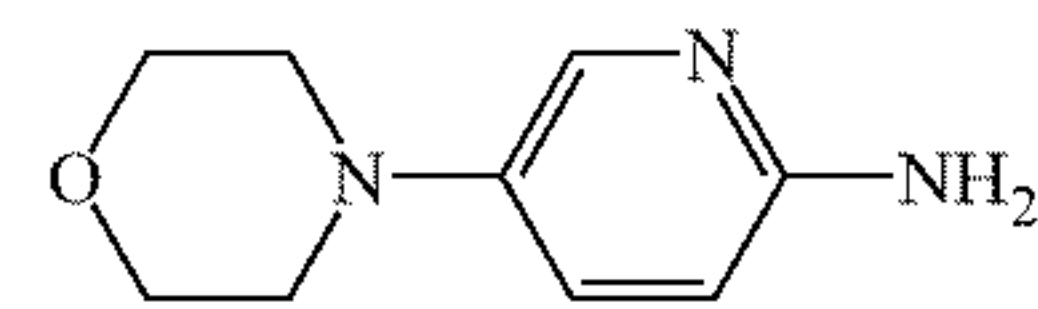


[0353] 4-nitro-3-pyridyl) morpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl] pyridine.

Example 39

Synthesis of 5-morpholinopyridin-2-amine, Compound 39

[0354]

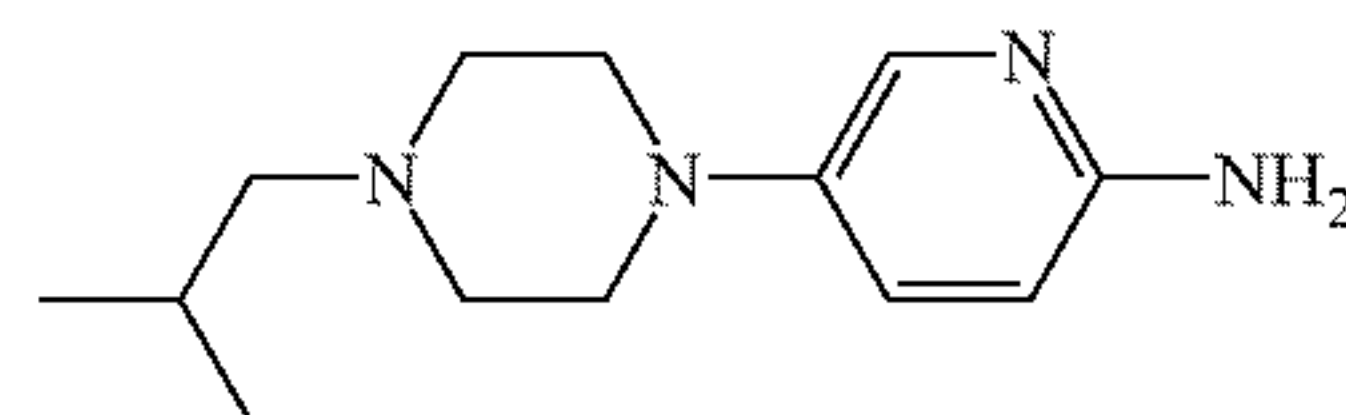


[0355] 5-morpholinopyridin-2-amine was prepared in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl) pyridin-2-amine. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 2.91 - 3.00 (m, 4 H) 3.76 - 3.84 (m, 4 H) 4.19 (br. s., 2 H) 6.45 (d, J=8.78 Hz, 1 H) 7.12 (dd, J=8.78, 2.93 Hz, 1 H) 7.72 (d, J=2.93 Hz, 1 H).

Example 40

Synthesis of 5-(4-isobutylpiperazin-1-yl) Pyridin-2-amine, Compound 40

[0356]

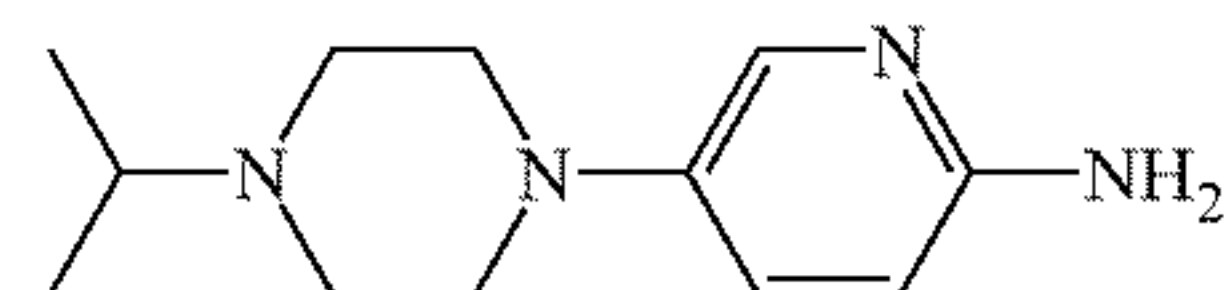


[0357] 1-isobutyl-4-(6-nitro-3-pyridyl)piperazine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine which was then converted 5-(4-isobutylpiperazin-1-yl)pyridin-2-amine in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.88 (d, J=6.73 Hz, 6 H) 1.71 - 1.84 (m, 1 H) 2.10 (d, J=7.32 Hz, 2 H) 2.46 - 2.58 (m, 4 H) 2.97 - 3.07 (m, 4 H) 4.12 (s, 2 H) 6.45 (d, J=8.78 Hz, 1 H) 7.14 (dd, J=8.78, 2.93 Hz, 1 H) 7.75 (d, J=2.93 Hz, 1 H). LCMS (ESI) 235 (M + H).

Example 41

Synthesis of 5-(4-isopropylpiperazin-1-yl) Pyridin-2-amine, Compound 41

[0358]

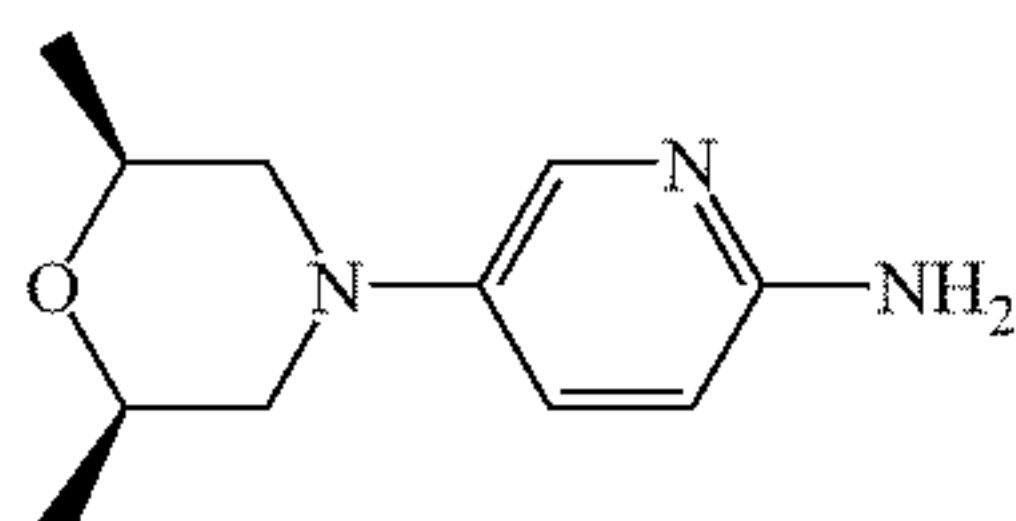


[0359] 1-isopropyl-4-(6-nitro-3-pyridyl)piperazine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine which was then converted to 5-(4-isopropylpiperazin-1-yl)pyridin-2-amine in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 1.06 (d, J=6.44 Hz, 6 H) 2.59 - 2.75 (m, 5 H) 2.97 - 3.10 (m, 4 H) 4.13 (s, 2 H) 6.45 (d, J=8.78 Hz, 1 H) 7.15 (dd, J=9.08, 2.93 Hz, 1 H) 7.76 (d, J=2.93 Hz, 1 H). LCMS (ESI) 221 (M + H).

Example 42

Synthesis of 5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-2-amine, Compound 42

[0360]

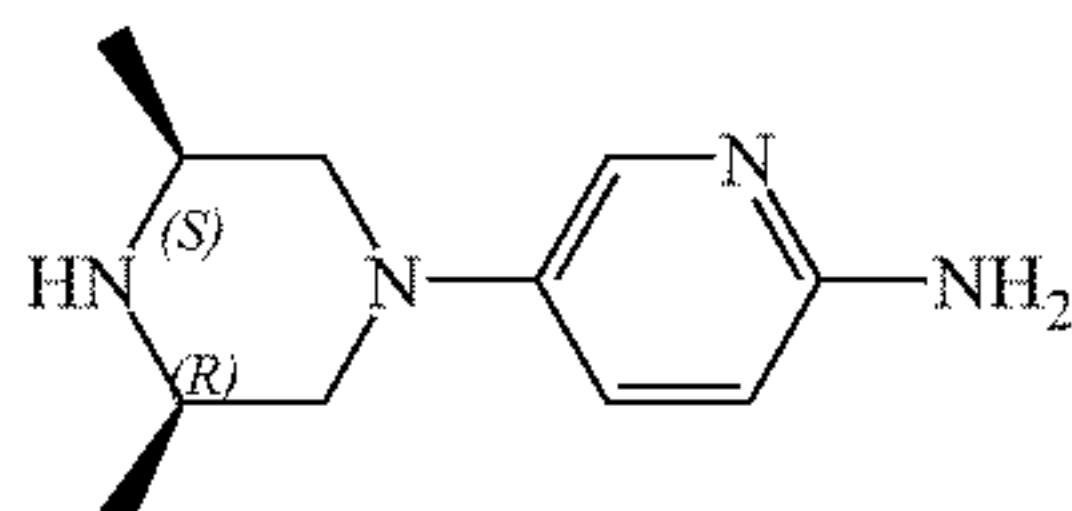


[0361] (2S,6R)-2,6-dimethyl-4-(6-nitro-3-pyridyl)morpholine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine which was then converted to 5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-2-amine in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 1.20 (d, J=6.44 Hz, 6 H) 2.27 - 2.39 (m, 2 H) 3.11 - 3.21 (m, 2 H) 3.70 - 3.84 (m, 2 H) 4.15 (s, 2 H) 6.45 (d, J=8.78 Hz, 1 H) 7.12 (dd, J=8.78, 2.93 Hz, 1 H) 7.72 (d, J=2.63 Hz, 1 H). LCMS (ESI) 208 (M + H).

Example 43

Synthesis of 5-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyridin-2-amine, Compound 43

[0362]

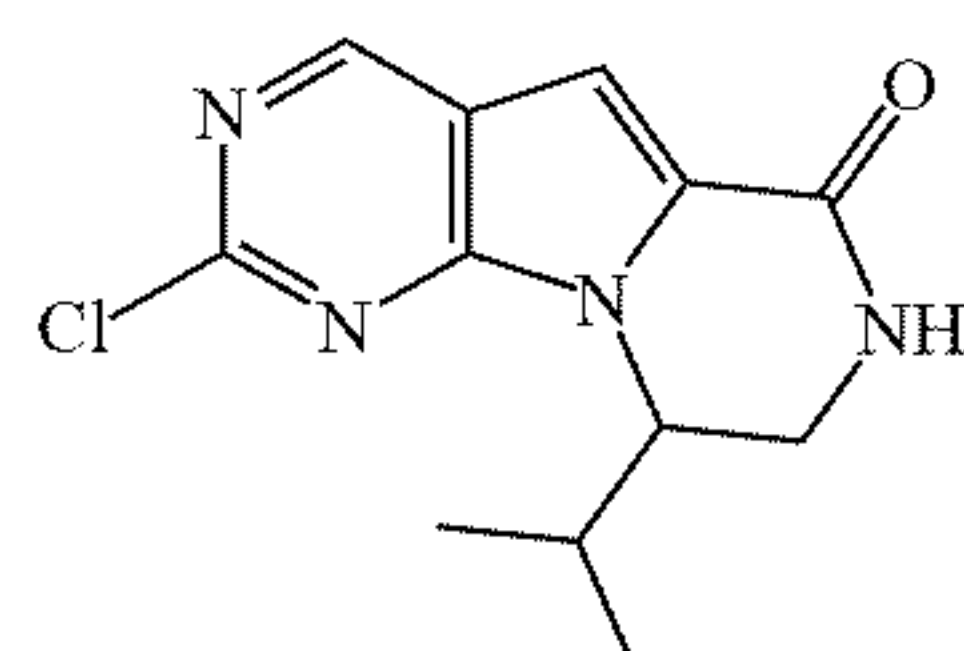


[0363] (3S,5R)-3,5-dimethyl-1-(6-nitro-3-pyridyl)piperazine was synthesized in a manner similar to that used in the synthesis of 2-nitro-5-[4-(1-piperidyl)-1-piperidyl]pyridine which was then converted to 5-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyridin-2-amine in a manner similar to that used in the synthesis of 5-(4-methylpiperazin-1-yl)pyridin-2-amine. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 1.09 (d, J=6.44 Hz, 6 H) 2.20 (t, J=10.83 Hz, 2 H) 2.95 - 3.08 (m, 2 H) 3.23 (dd, J=11.71, 2.05 Hz, 2 H) 4.13 (s, 2 H) 6.45 (d, J=8.78 Hz, 1 H) 7.14 (dd, J=8.78, 2.93 Hz, 1 H) 7.73 (d, J=2.63 Hz, 1 H). LCMS (ESI) 207 (M + H).

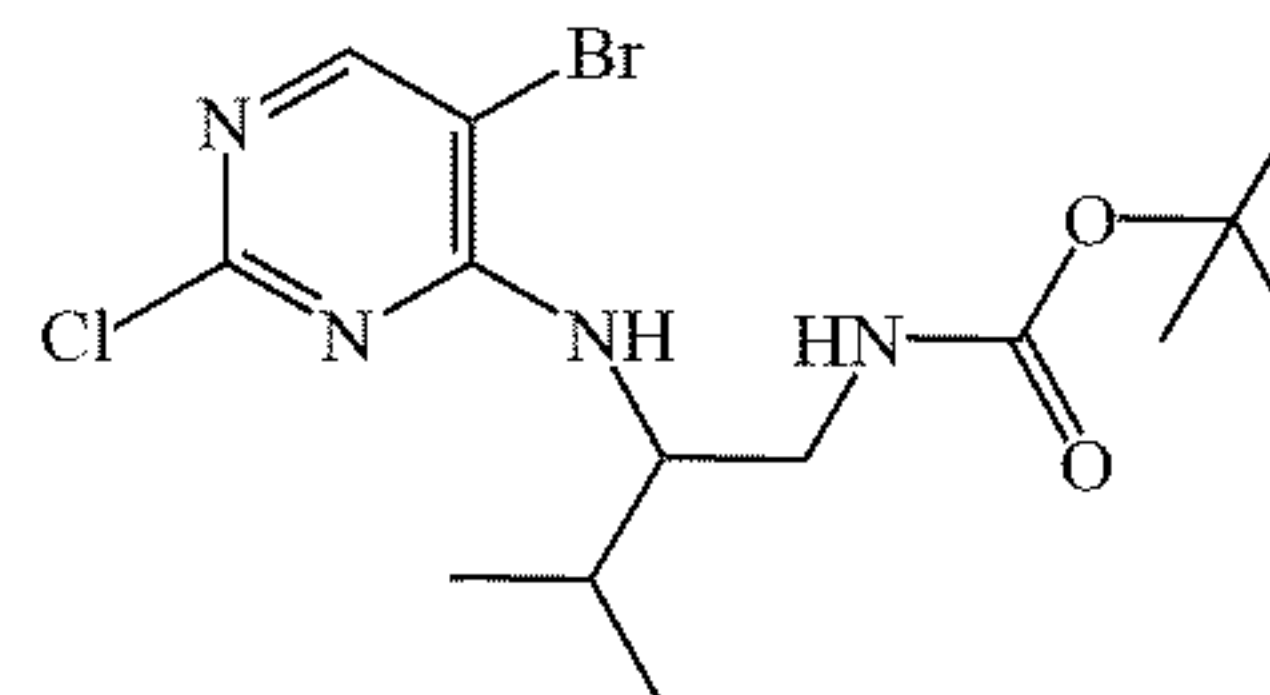
Example 44

Synthesis of Compound 44

[0364]



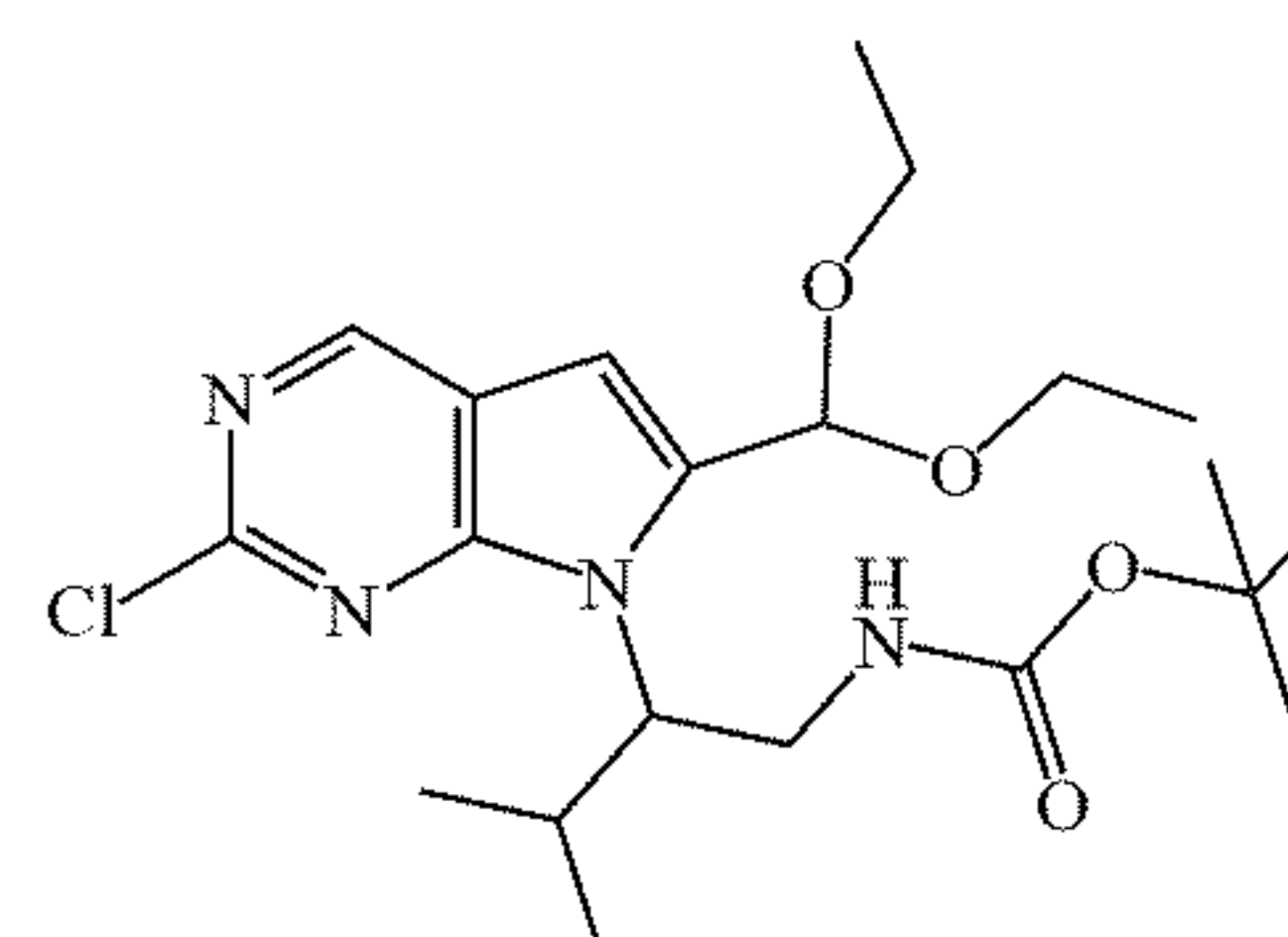
tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl] carbamate



[0365] A solution of intermediate A in ethanol (100 mL) was hydrogenated under 30 psi of hydrogen using 10% Pd/C (0.7 g) in a pressure bomb for 7 hrs. After filtration of the reaction mixture through CELITE™, the organic layer was concentrated under vacuum to afford tert-butyl N-(2-amino-3-methyl-butyl) carbamate (3.8 g).

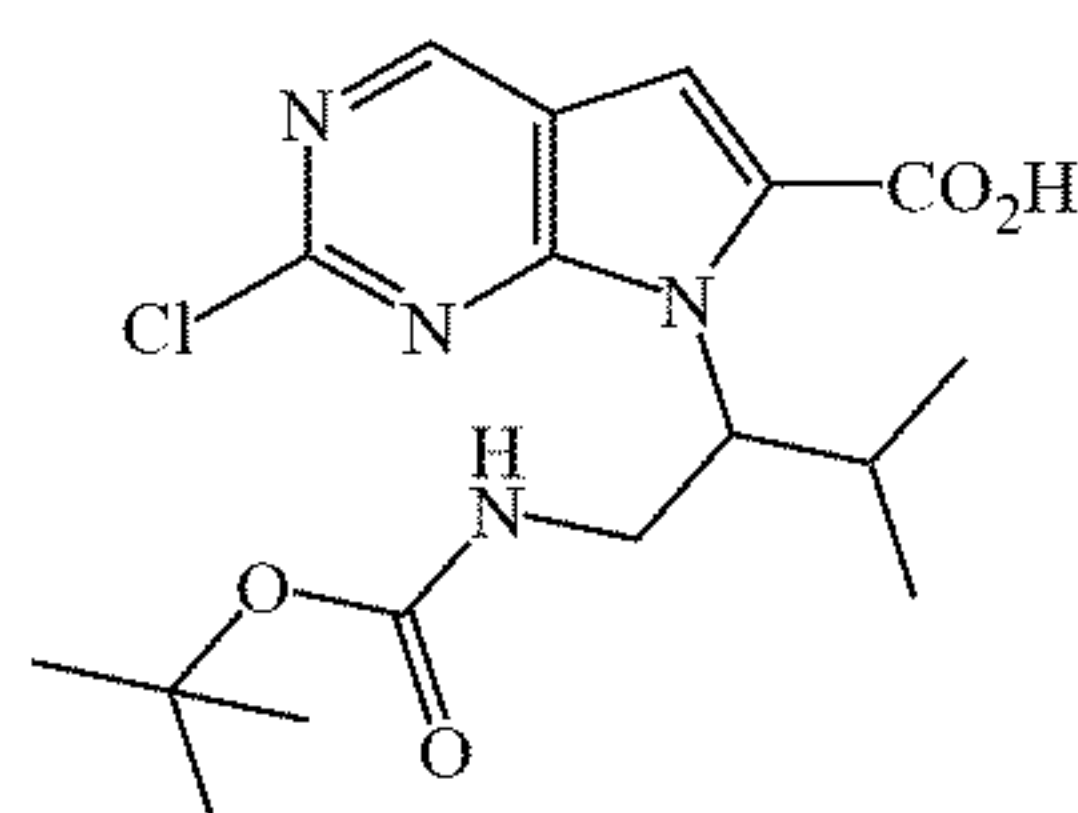
[0366] To a solution of 5-bromo-2,4-dichloro-pyrimidine (7.11 g, 0.0312 mole) in ethanol (100 mL) was added diisopropylethyl amine (5.45 mL, 1.0 eq) and tert-butyl N-(2-amino-3-methylbutyl) carbamate (6.31 g, 0.0312 mole). The reaction mixture was stirred at room temperature for 20 hrs. After concentration under vacuum, ethyl acetate and water were added. The organic layer was separated, dried with magnesium sulfate and then concentrated under vacuum. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (0- 30%) to afford tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl) amino]-3-methyl-butyl] carbamate. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.77 - 0.85 (d, J=6.5 Hz, 3 H) 0.87 (d, J=6.73 Hz, 3 H) 1.31 - 1.39 (m, 9 H) 1.82 - 1.93 (m, 1 H) 2.94 (d, J=5.56 Hz, 1 H) 3.08 - 3.22 (m, 2 H) 3.98 (d, J=8.20 Hz, 1 H) 6.96 (d, J=8.78 Hz, 1 H) 8.21 (s, 1 H). LCMS (ESI) 393 (M + H).

[0367] tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]-3-methylbutyl]carbamate



[0368] tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]-3-methylbutyl]carbamate was synthesized by hosting tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate to Sonogoshira conditions as described for tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate followed by subsequent treatment with TBAF as described in the synthesis of tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.11 (d, J=6.44 Hz, 3 H) 1.18 (t, J=7.03 Hz, 6 H) 1.21 - 1.26 (m, 12 H) 2.88 (br. s., 1 H) 3.43 - 3.78 (m, 6 H) 3.97 - 4.08 (m, 1 H) 5.61 (s, 1 H) 6.65 (s, 1 H) 6.71 - 6.78 (m, 1 H) 8.87 (s, 1 H). LCMS (ESI) 441 (M + H).

[0369] 7-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0370] To a solution tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate in THF was added TBAF and the contents were heated at reflux for 3 hrs. Ethyl acetate and water were then added and the organic layer separated, dried with magnesium sulfate and then concentrated under vacuum. To this crude reaction was added acetic acid/water (9:1) and the contents were stirred for 12 hrs at room temperature. After concentration under vacuum, sat NaHCO₃ and ethyl acetate were added. The organic layer was separated, dried and then concentrated under vacuum. The crude reaction product thus obtained was dissolved in DMF, oxone was then added and the contents stirred for 3 hrs. After addition of ethyl acetate, the reaction mixture was filtered through CELITE™ and concentrated under vacuum. Column chromatography of the crude product over silica gel using hexane/ethyl acetate (0- 100%) afforded 7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.85 (d, J=7.03 Hz, 3 H) 0.97 (d, J=6.73 Hz, 3 H) 1.52 (s, 9 H) 1.99 - 2.23 (m, 1 H) 3.98 (dd, J=14.05, 3.51 Hz, 1 H) 4.47 - 4.71 (m, 2 H) 7.47 (s, 1 H) 9.17 (s, 1 H). LCMS (ESI) 383 (M + H).

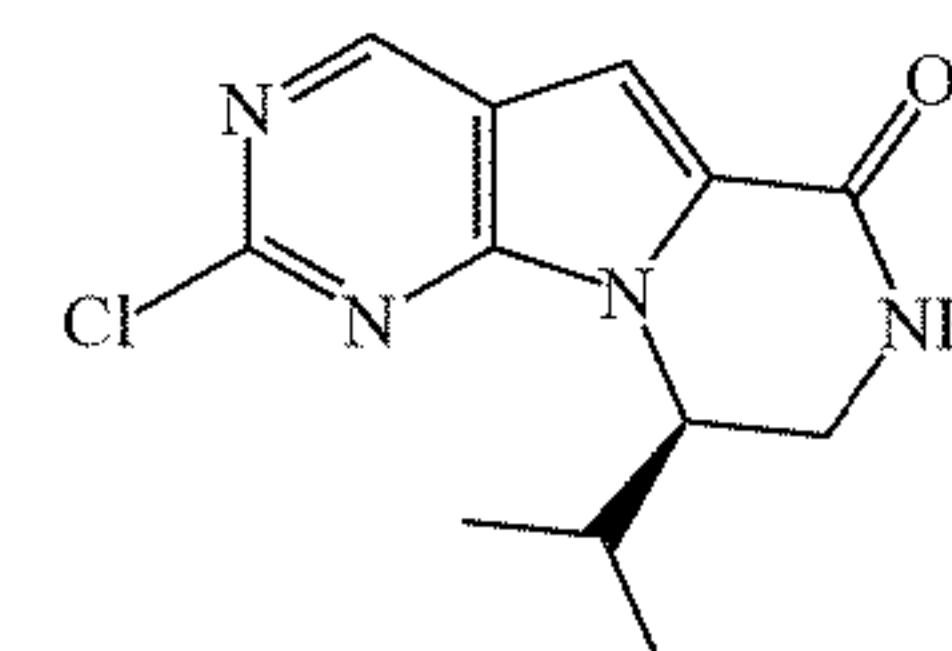
Compound 44

[0371] To 7-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid (0.050 g, 0.00013 mole) in DCM (1.5 mL) was added DIC (32.7 mg) and DMAP (10 mg). The contents were stirred for 2 hrs. Trifluoroacetic acid (0.4 mL) was then added and stirring continued for an additional 30 minutes. After addition of satd NaHCO₃ to neutralize the excess acid, ethyl acetate was added and the organic layer separated, dried using magnesium sulfate and then concentrated under vacuum. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (0-100%) to afford the product. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.72 (d, J=6.73 Hz, 3 H) 0.97 (d, J=6.73 Hz, 3 H) 2.09 - 2.22 (m, 1 H) 3.57 (dd, J=13.18, 4.98 Hz, 1 H) 3.72 (dd, J=13.61, 4.25 Hz, 1 H) 4.53 (dd, J=8.05, 3.95 Hz, 1 H) 7.20 (s, 1 H) 8.34 (d, J=4.98 Hz, 1 H) 9.08 (s, 1 H). LCMS (ESI) 265 (M + H).

Example 45

Synthesis of Compound 45

[0372]

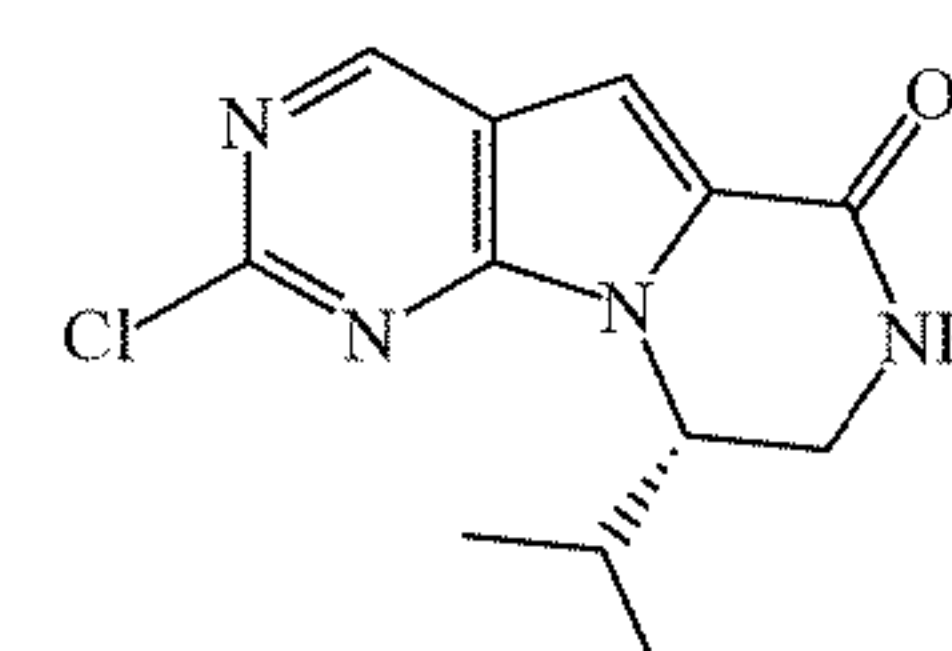


[0373] Compound 14 was hydrogenated with 10% Pd/C to afford the intermediate tert-butyl N-[(2R)-2-amino-3-methyl-butyl] carbamate, which was then treated with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for Compound 44 to afford Compound 45. The analytical data is consistent with that reported for the racemate (Intermediate 1A).

Example 46

Synthesis of Compound 46

[0374]

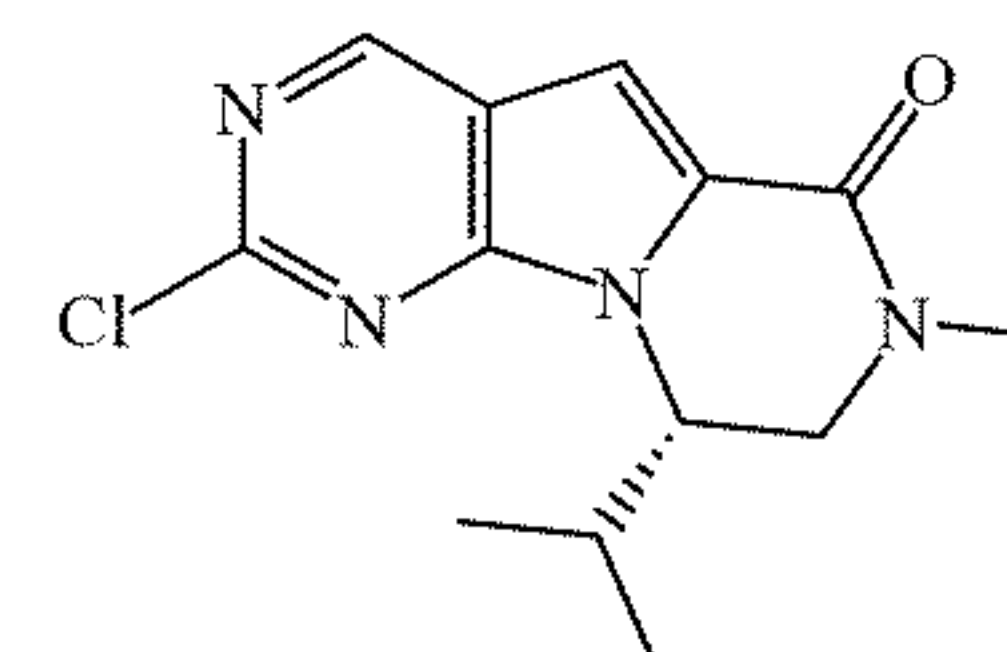


[0375] Compound 15 was hydrogenated with 10% Pd/C to afford the intermediate tert-butyl N-[(2S)-2-amino-3-methyl-butyl]carbamate, which was then treated with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for Compound 44 to afford Compound 46. The analytical data (NMR and LCMS) was consistent with that reported for the racemate Compound 44.

Example 47

Synthesis of Compound 47

[0376]

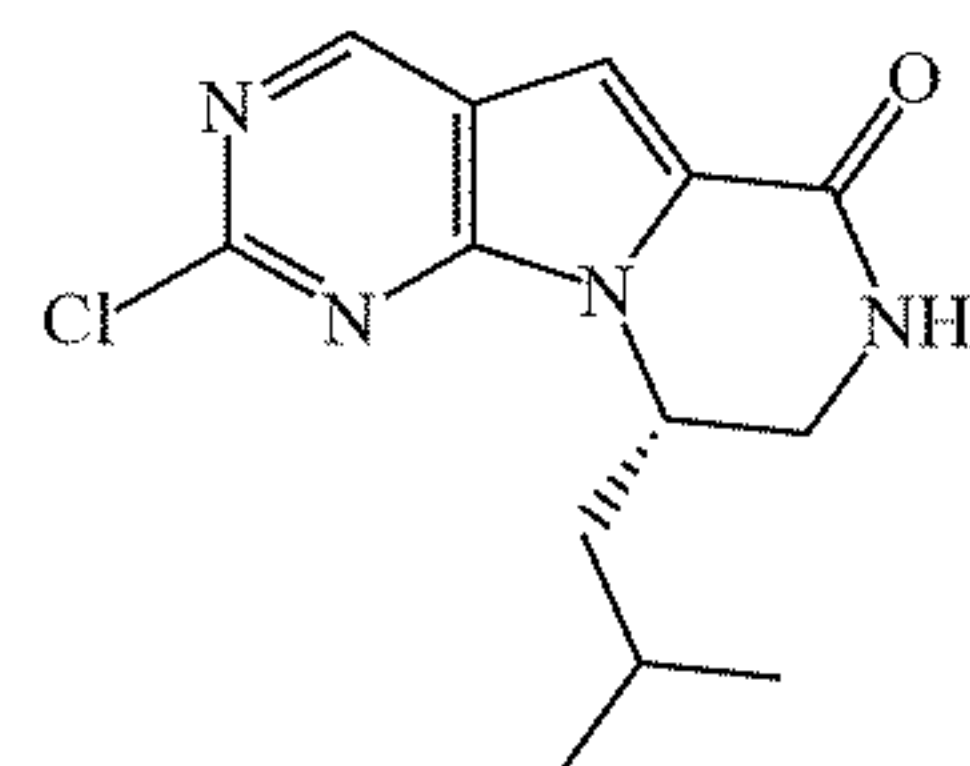


[0377] To a solution of Compound 44 (80 mg, 0.00030 mole) in DMF (3 mL) was added a 60% dispersion of sodium hydride in oil (40 mg). After stirring for 15 minutes, methyl iodide (37 μL, 2eq) was added. The contents were stirred at room temperature for 30 minutes. Saturated NaHCO₃ was then added followed by ethyl acetate. The organic layer was dried with magnesium sulfate and then concentrated under vacuum to afford the product. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.74 (d, J=6.73 Hz, 3 H) 0.91 (d, J=6.73 Hz, 3 H) 2.04 - 2.20 (m, 1 H) 3.04 (s, 3 H) 3.69 (dd, J=13.76, 1.17 Hz, 1 H) 3.96 (dd, J=13.76, 4.68 Hz, 1 H) 4.58 (dd, J=7.32, 3.51 Hz, 1 H) 7.16 (s, 1 H) 9.05 (s, 1 H). LCMS (ESI) 279 (M + H).

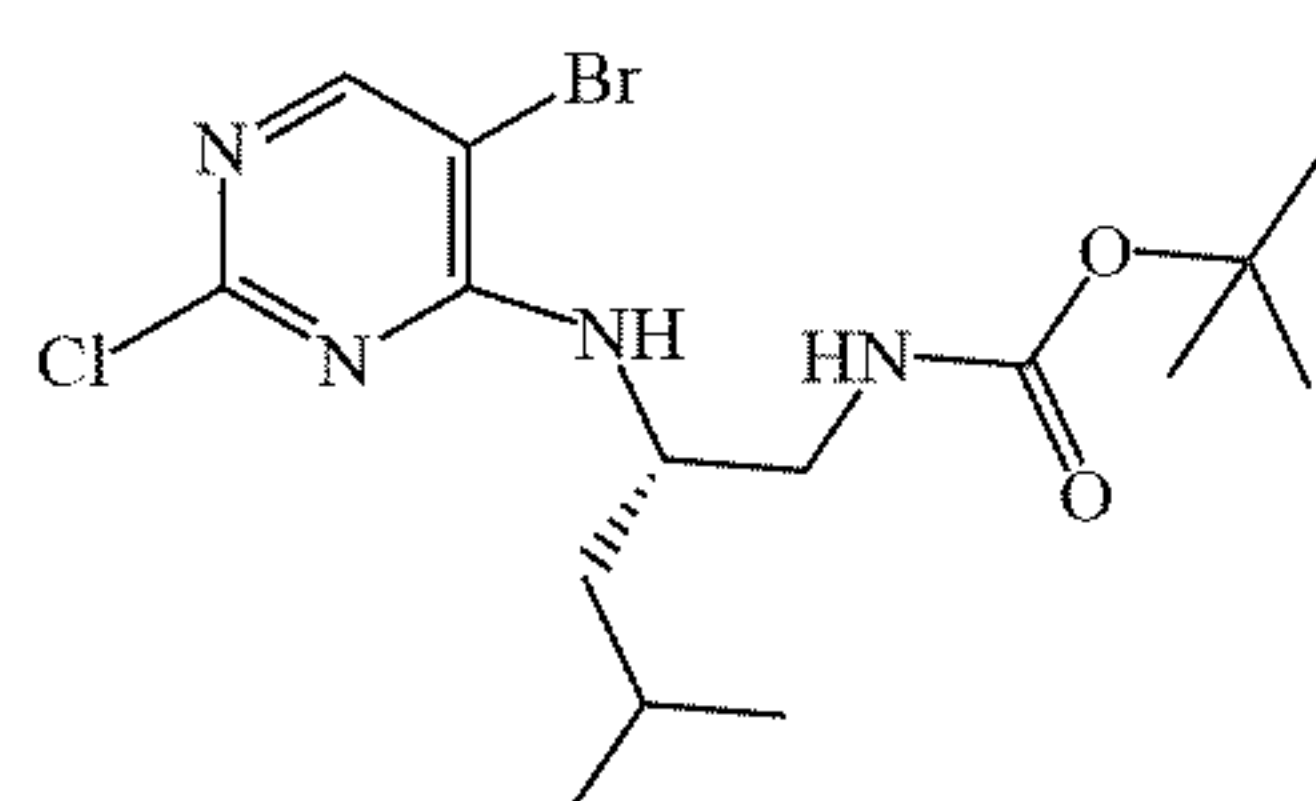
Example 48

Synthesis of Compound 48

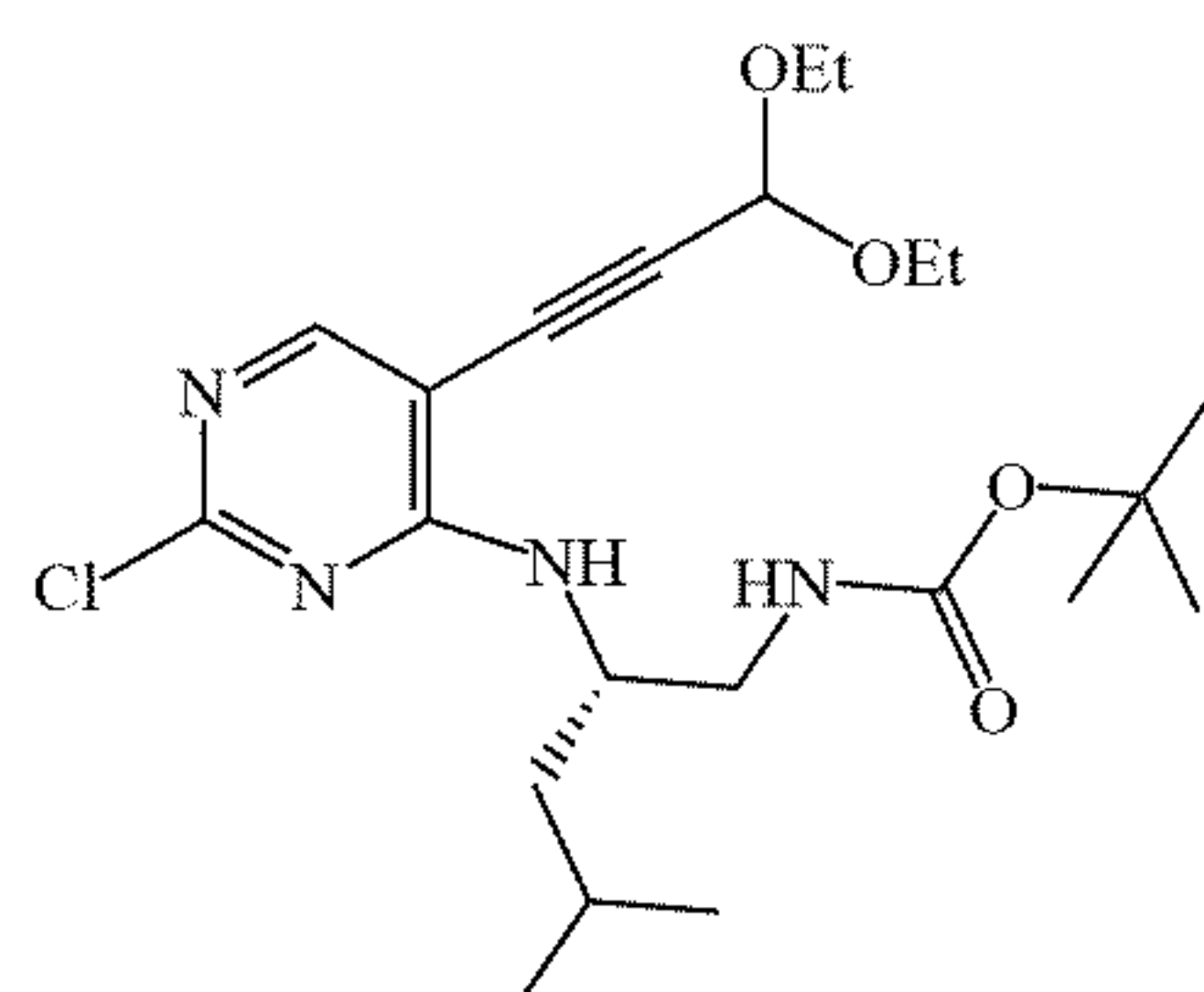
[0378]



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

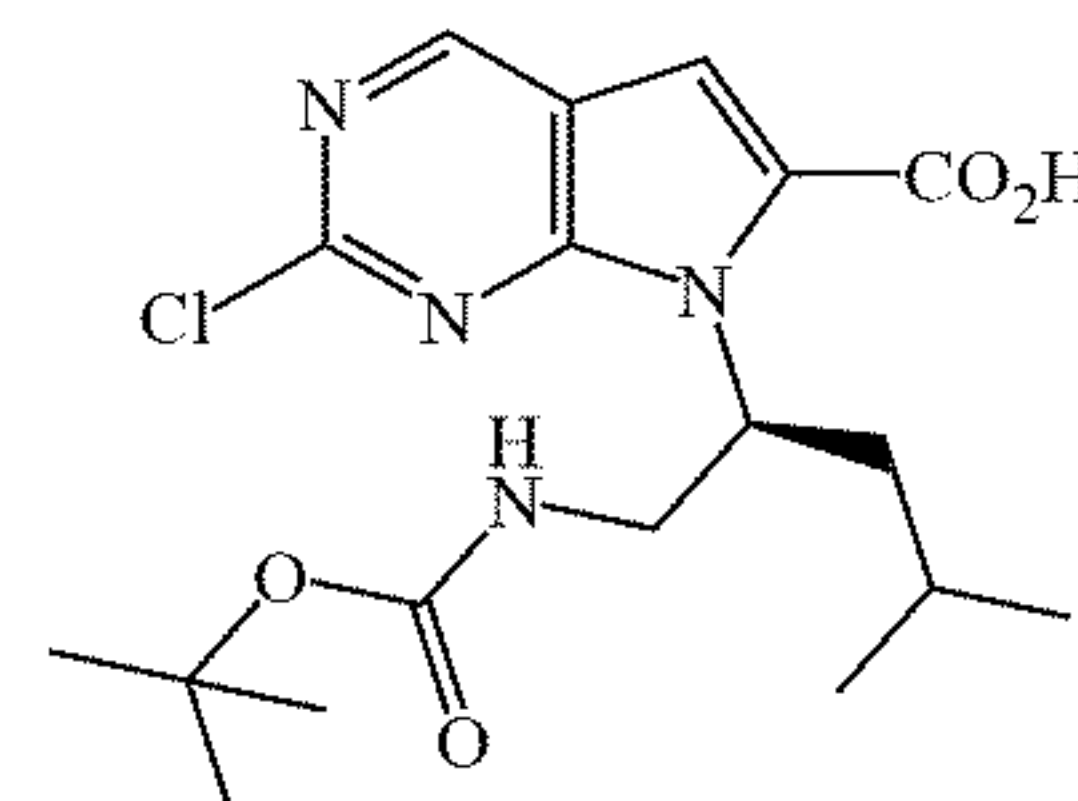


[0379] Compound 18 was hydrogenated with 10% Pd/C in ethanol under a blanket of hydrogen at 50 psi in a pressure bomb to afford tert-butyl N-[(2S)-2-amino-4-methyl-pentyl]carbamate which was then reacted with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methylbutyl]carbamate to afford tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-4-methyl-pentyl]carbamate. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.91 (d, J=6.44 Hz, 3 H) 0.94 (d, J=6.44 Hz, 3 H) 1.32 - 1.51 (m, 11 H) 1.55 - 1.67 (m, 1 H) 3.28 (t, J=5.86 Hz, 2 H) 4.21 - 4.42 (m, 1 H) 4.84 (s, 1 H) 5.84 (d, J=7.32 Hz, 1 H) 8.07 (s, 1 H). LCMS (ESI) 407 (M + H).



[0380] To a solution of tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-4-methyl-pentyl]carbamate (5.0 g, 12.3 mmole) in toluene (36 mL) and triethylamine (7.2 mL) was added under nitrogen, 3,3-diethoxyprop-1-yne (2.8 mL, 19.7 mmole), Pd₂(dba)₃ (1.1 g, 1.23 mmole), and triphenylarsine (3.8 g, 12.3 mmole). The contents were heated to 70 degrees for 24 hrs. After cooling to room temperature, the reaction mixture was filtered through CELITE™ and then concentrated under vacuum. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (0- 30%) to afford (2S)-

N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. LCMS (ESI) 455 (M + H).



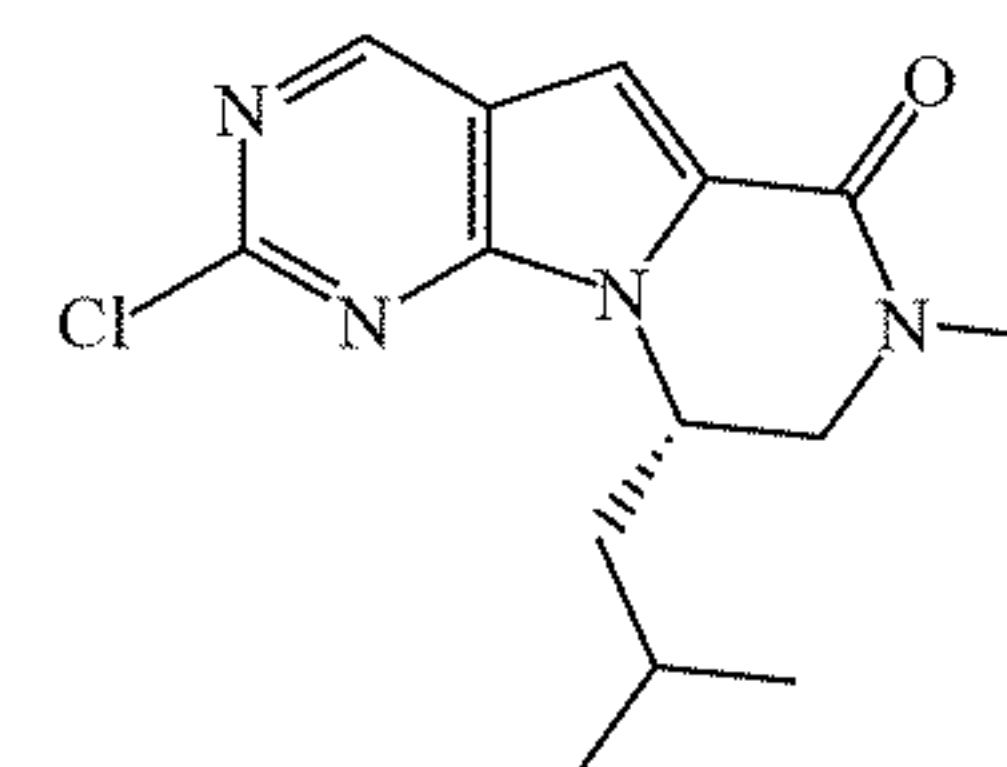
[0381] 7-[(1S)[(tert-butoxycarbonylamino)methyl]-3-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using the analogous synthetic sequence as that described for 7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.88 (d, J=6.44 Hz, 3 H) 0.97 (d, J=6.44 Hz, 3 H) 1.47 (s, 9 H) 1.49 - 1.54 (m, 1 H) 1.56 (t, J=7.17 Hz, 2 H) 3.98 (dd, J 13.91, 3.07 Hz, 1 H) 3.76 (dd, J=13.31, 4.13 Hz, 1 H) 4.38 (d, J=14.05 Hz, 1 H) 4.90 (t, J=7.17 Hz, 1 H) 7.41 (s, 1 H) 9.11 (s, 1 H). LCMS (M + H) 397.

[0382] Compound 48 was synthesized using an analogous synthetic sequence as that described for Compound 44. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.82 (d, J=6.73 Hz, 3 H) 0.97 (d, J=6.44 Hz, 3 H) 1.34 - 1.46 (m, 1 H) 1.48 - 1.65 (m, 2 H) 3.40 (dd, J=13.32, 5.42 Hz, 1 H) 3.76 (dd, J=13.47, 4.10 Hz, 1 H) 4.76 - 4.92 (m, 1 H) 7.17 (s, 1 H) 8.34 (d, J=5.27 Hz, 1 H) 9.04 (s, 1 H). LCMS (ESI) 279 (M + H).

Example 49

Synthesis of Compound 49

[0383]

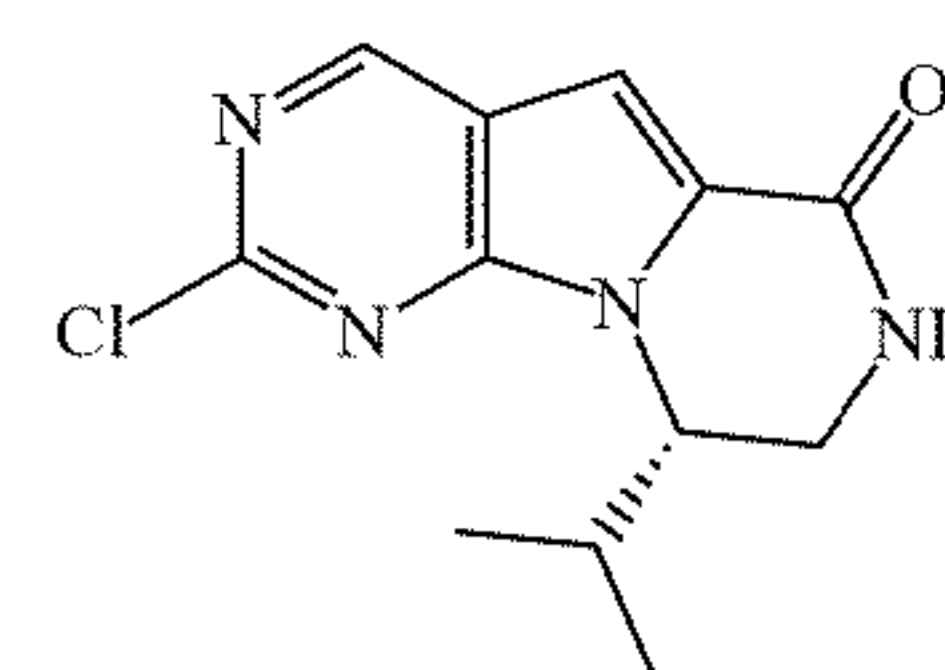


[0384] Compound 49 was synthesized in a manner similar to that described for Compound 47. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.82 (d, J=6.44 Hz, 3 H) 0.97 (d, J=6.44 Hz, 3 H) 1.37 - 1.68 (m, 3 H) 3.04 (s, 3 H) 3.56 (d, J=13.47 Hz, 1 H) 4.00 (dd, J=13.32, 4.25 Hz, 1 H) 4.82 - 4.94 (m, 1 H) 7.16 (s, 1 H) 9.03 (s, 1 H). LCMS (ESI) 293 (M + H).

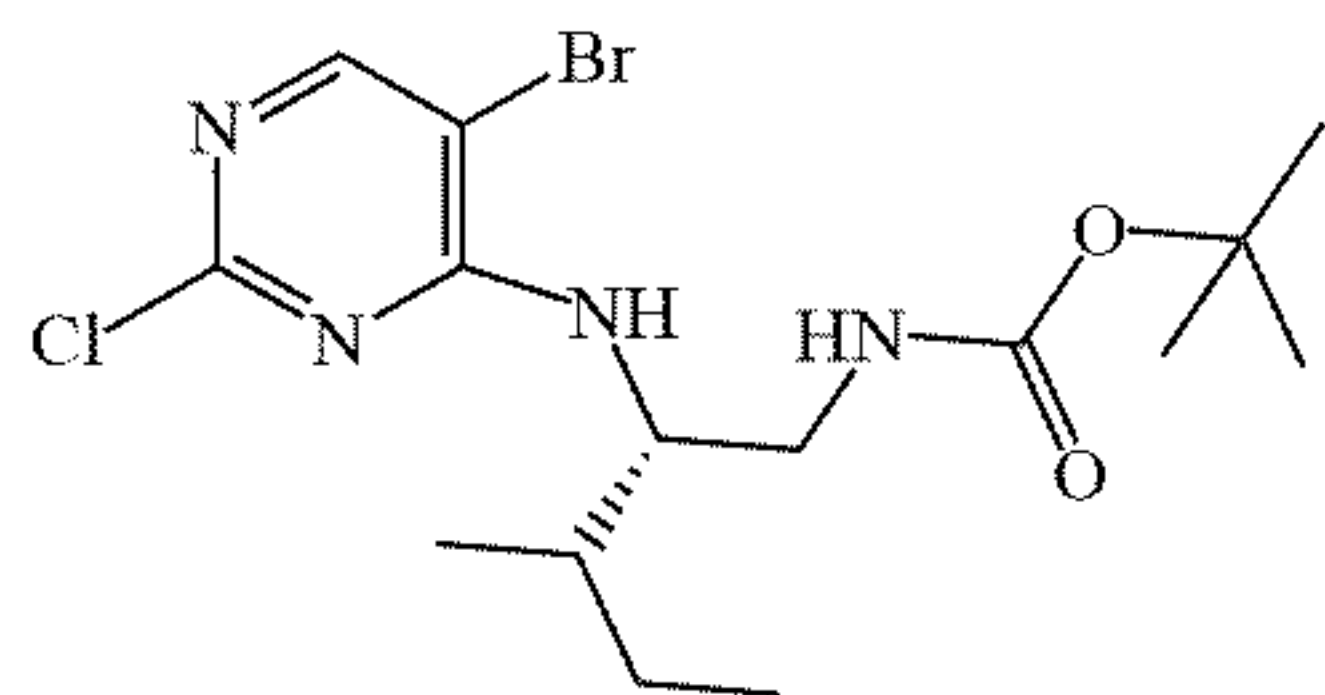
Example 50

Synthesis of Compound 50

[0385]

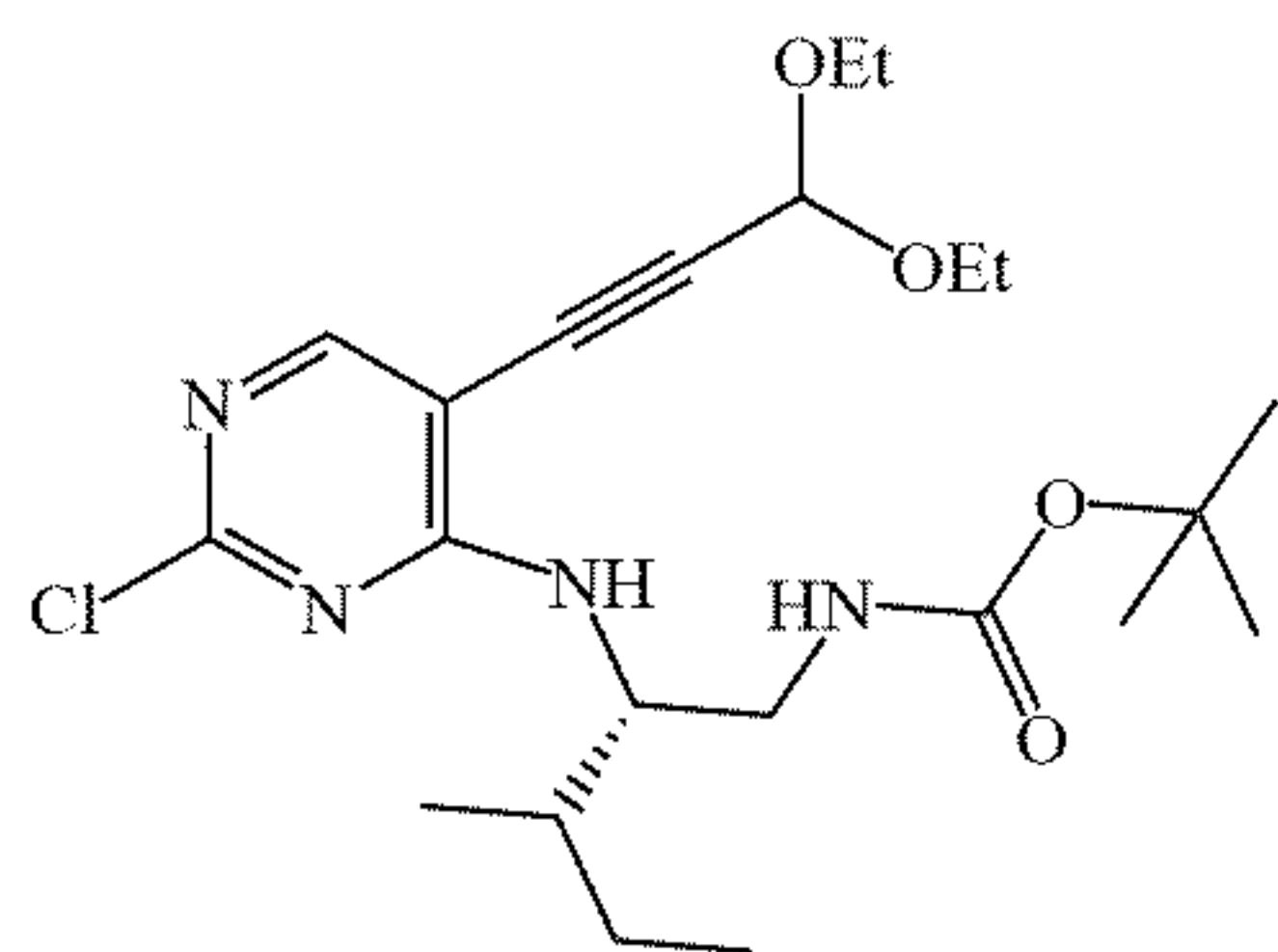


tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-pentyl]carbamate



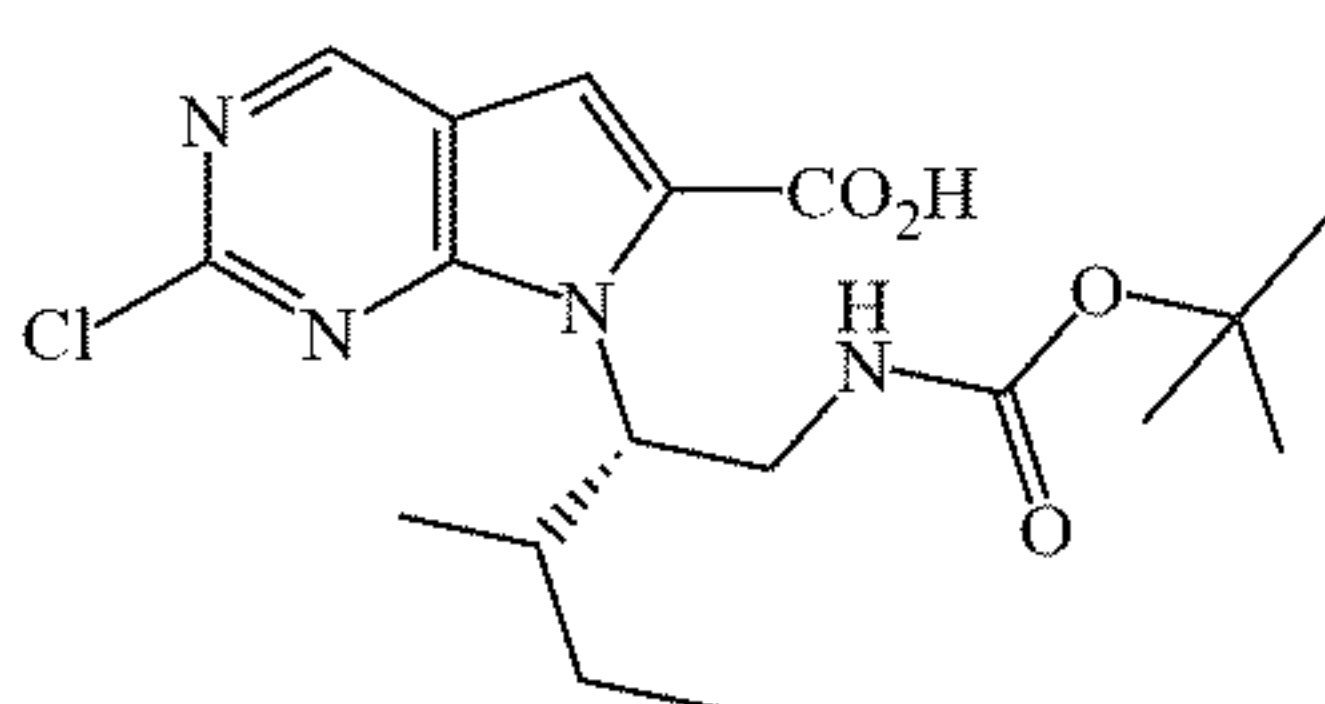
[0386] Compound 20 was hydrogenated using 10% Pd/C under hydrogen at 50 psi in a pressure vessel to afford tert-butyl N-[(2S)-2-amino-3-methyl-pentyl]carbamate which was reacted with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate to afford tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-pentyl]carbamate. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.88 - 0.95 (m, 6 H) 1.11 - 1.20 (m, 1 H) 1.34 (s, 9 H) 1.44 - 1.54 (m, 1 H) 1.64 - 1.72 (m, 1 H) 3.17 - 3.27 (m, 1 H) 3.33 - 3.43 (m, 1 H) 4.11 - 4.21 (m, 1 H) 4.81 (s, 1 H) 5.92 (d, J=8.20 Hz, 1 H) 8.05 (s, 1 H). LCMS (ESI) 407.

[0387] tert-butyl N-[(2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-3-methylpentyl]carbamate



[0388] tert-butyl N-[(2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-3-methyl-pentyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methylpentane-1,2-diamine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.76 - 0.89 (m, 6 H) 1.03 (q, J=7.22 Hz, 3 H) 1.10 - 1.17 (m, 3 H) 1.25 - 1.42 (m, 11 H) 1.59 - 1.73 (m, 1 H) 3.35 - 3.47 (m, 4 H) 3.51 - 3.73 (m, 2 H) 3.99 - 4.11 (m, 1 H) 5.52 - 5.56 (m, 1 H) 6.76 - 7.03 (m, 2 H) 8.12 - 8.23 (m, 1 H). LCMS (ESI) 455 (M + H).

[0389] 7-[(S)[(tert-butoxycarbonylamino)methyl]-2-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0390] 7-[(1S)[(tert-butoxycarbonylamino)methyl]-2-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using the analogous synthetic

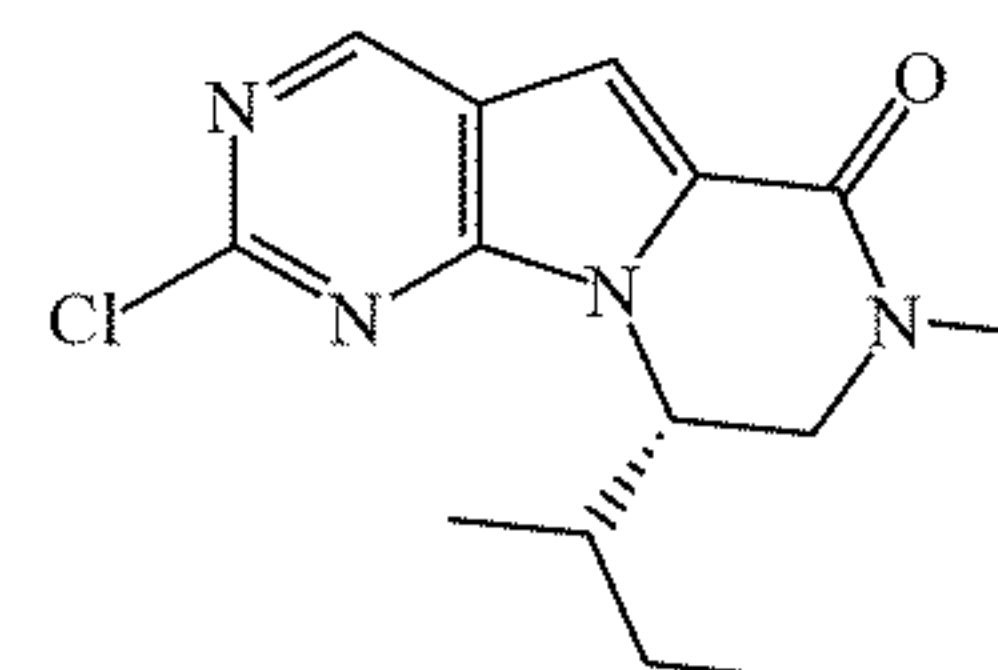
sequence as that described for 7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.80 (t, J=7.47 Hz, 3 H) 0.86 (d, J=7.03 Hz, 3 H) 1.06 - 1.30 (m, 2 H) 1.48 (s, 9 H) 1.79 - 1.96 (m, 1 H) 3.95 (dd, J=14.05, 3.22 Hz, 1 H) 4.52 (d, J=14.35 Hz, 1 H) 4.61 - 4.73 (m, 1 H) 7.43 (s, 1 H) 9.13 (s, 1 H). LCMS (ESI) 397 (M + H).

[0391] Compound 50 was synthesized using an analogous synthetic sequence as that described for Compound 44. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.74 (t, J=7.32 Hz, 3 H) 0.89 (d, J=6.73 Hz, 3 H) 1.00 - 1.12 (m, 2 H) 1.82 - 1.94 (m, 1 H) 3.55 (dd, J=13.91, 4.83 Hz, 1 H) 3.70 (dd, J=13.61, 4.25 Hz, 1 H) 4.57 (dd, J=7.91, 4.10 Hz, 1 H) 7.17 (s, 1 H) 8.31 (d, J=5.27 Hz, 1 H) 9.05 (s, 1 H). LCMS (ESI) 279 (M + H).

Example 51

Synthesis of Compound 51

[0392]

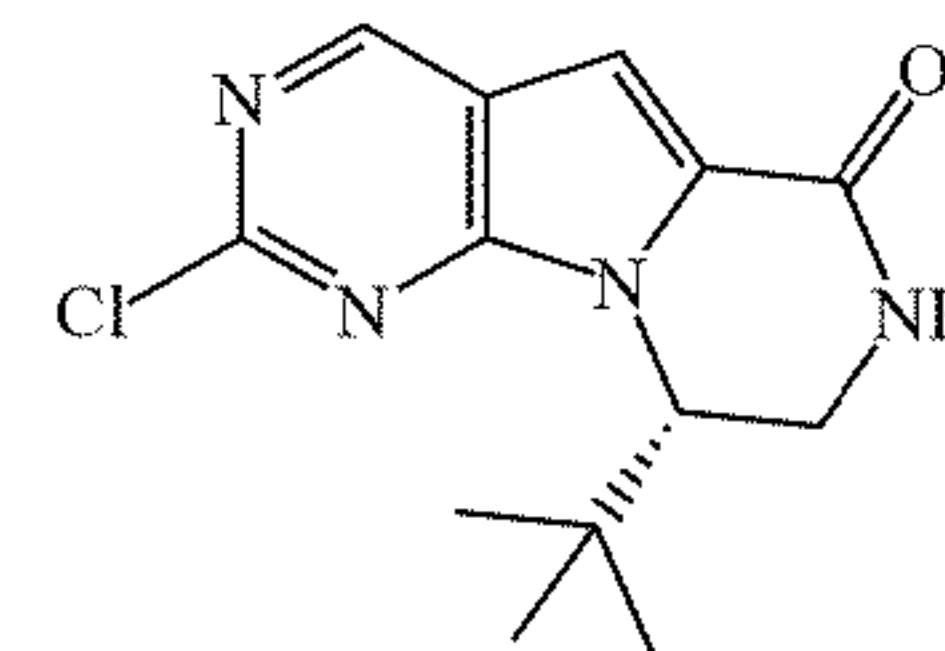


[0393] Compound 51 was synthesized in a manner similar to Compound 47. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.77 (t, J=7.47 Hz, 3 H) 0.84 (d, J=6.73 Hz, 3 H) 1.07 - 1.16 (m, 2 H) 1.82 - 1.95 (m, 1 H) 3.03 (s, 3 H) 3.68 (d, J=13.76 Hz, 1 H) 3.96 (dd, J=13.76, 4.39 Hz, 1 H) 4.59 - 4.70 (m, 1 H) 7.16 (s, 1 H) 9.04 (s, 1 H). LCMS (ESI) 293 (M + H).

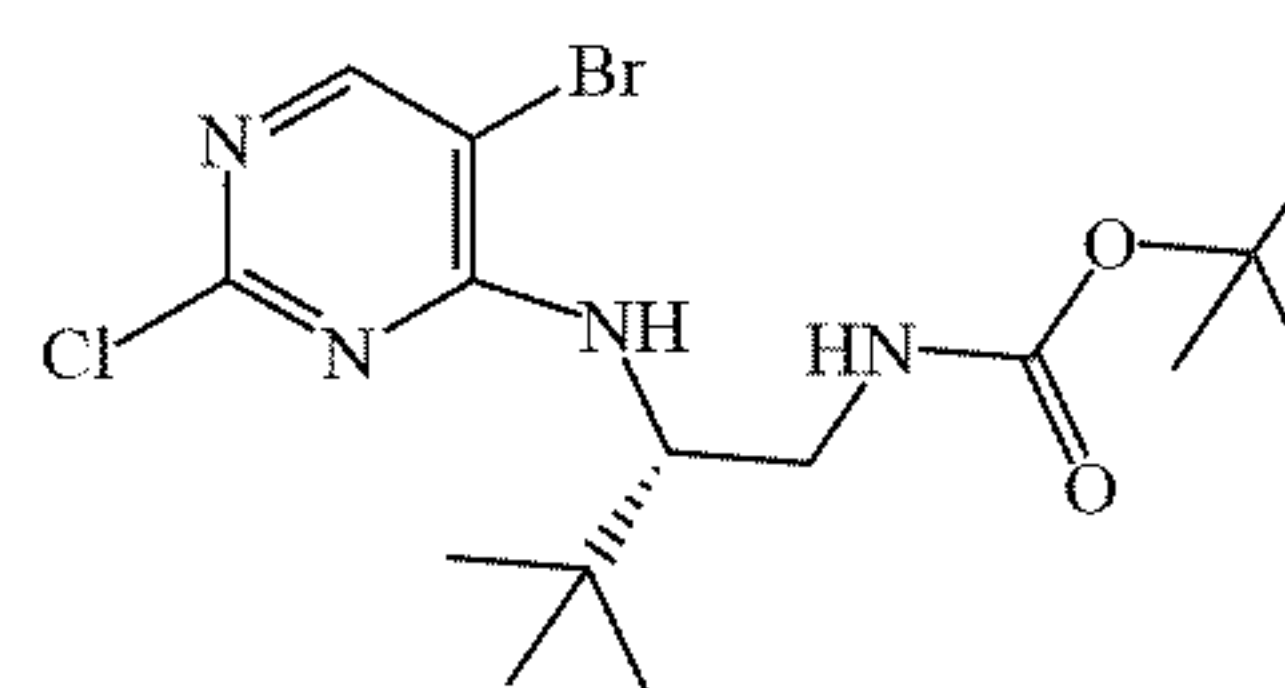
Example 52

Synthesis of Compound 52

[0394]



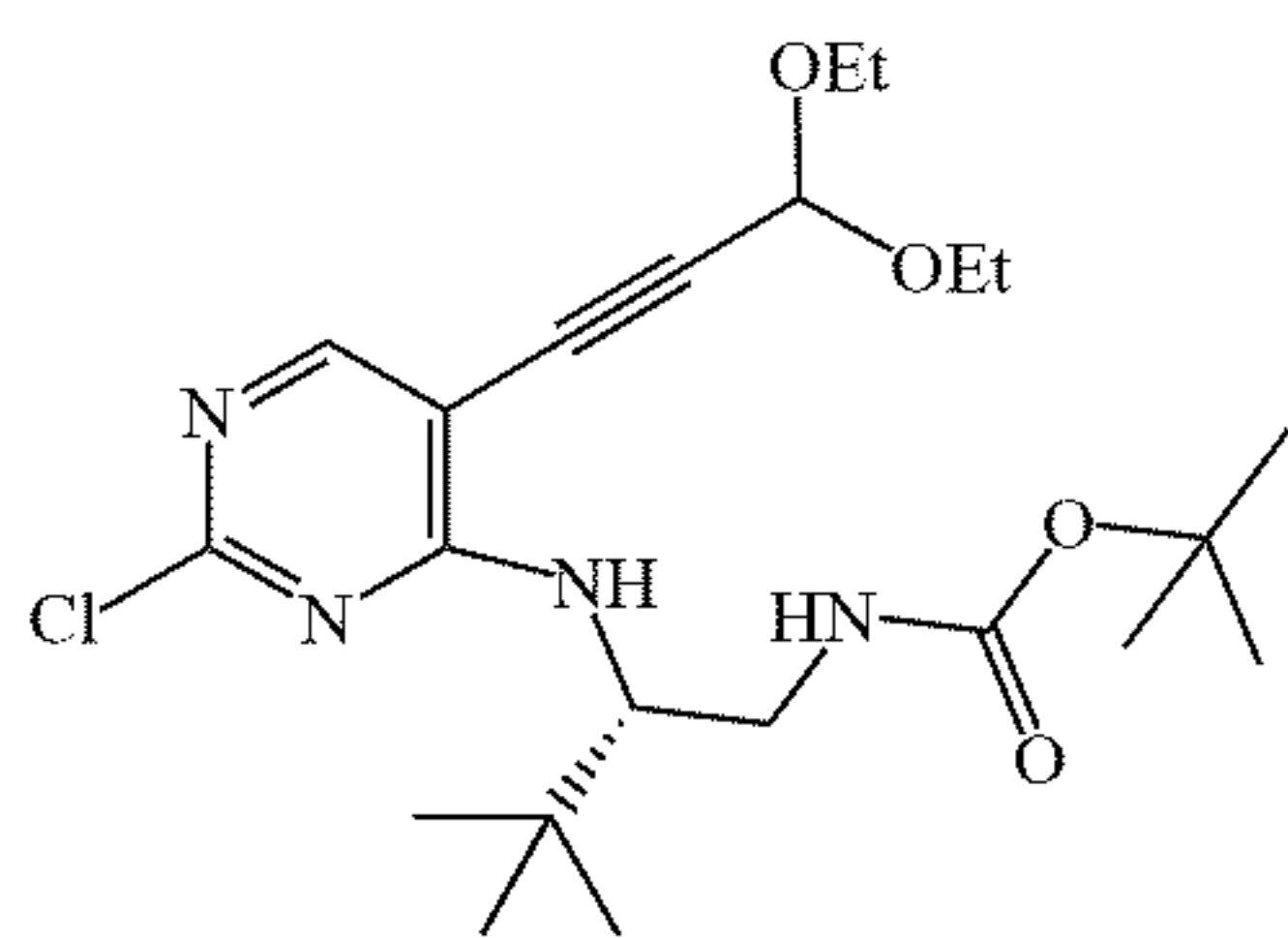
tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3,3-dimethyl-butyl]carbamate



[0395] Compound 21 was hydrogenated using 10% Pd/C under hydrogen at 50 psi in a pressure vessel to afford tert-butyl N-[(2S)-2-amino-3,3-dimethyl-butyl]carbamate

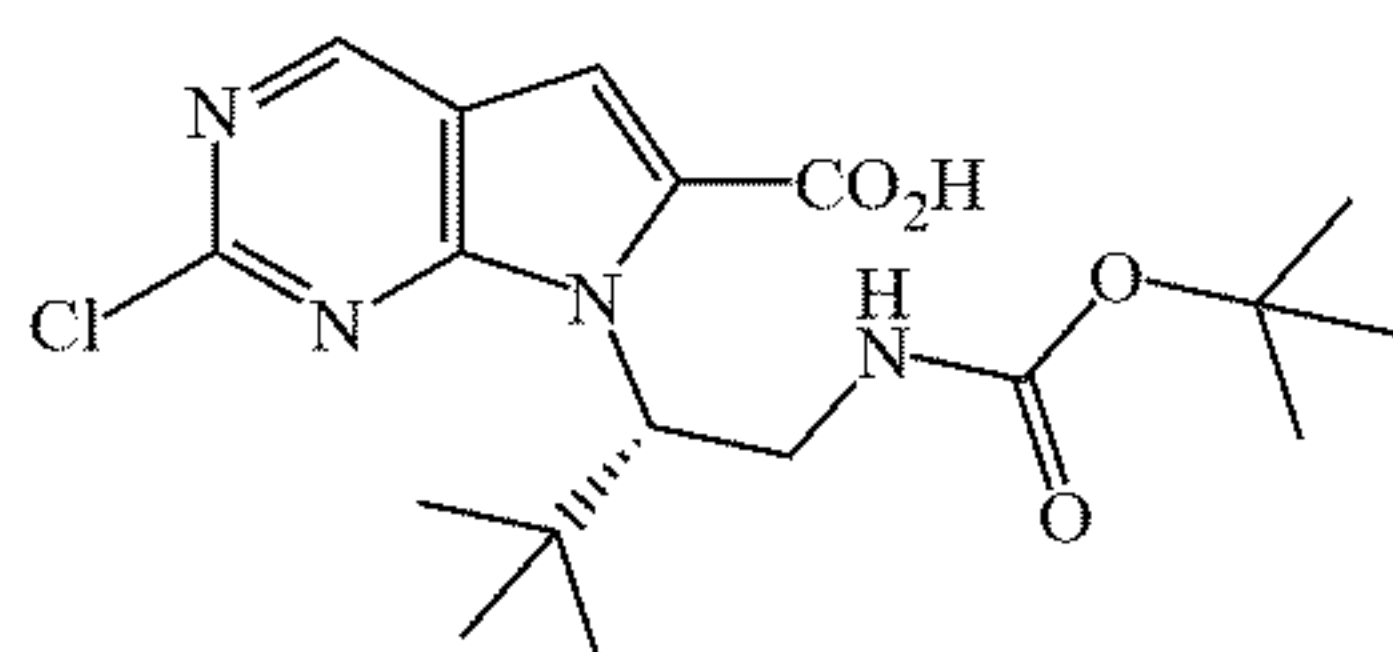
which was then reacted with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described using analogous reaction conditions as described for tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate to afford tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3,3-dimethyl-butyl]carbamate. LCMS (ESI) 407 (M + H).

[0396] tert-butyl N-[(2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-3,3-dimethylbutyl]carbamate



[0397] tert-butyl N-[(2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-3,3-dimethyl-butyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methylpentane-1,2-diamine. LCMS (ESI) 455 (M + H).

[0398] 7-[(1S)[(tert-butoxycarbonylamino)methyl]-2,2-dimethyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



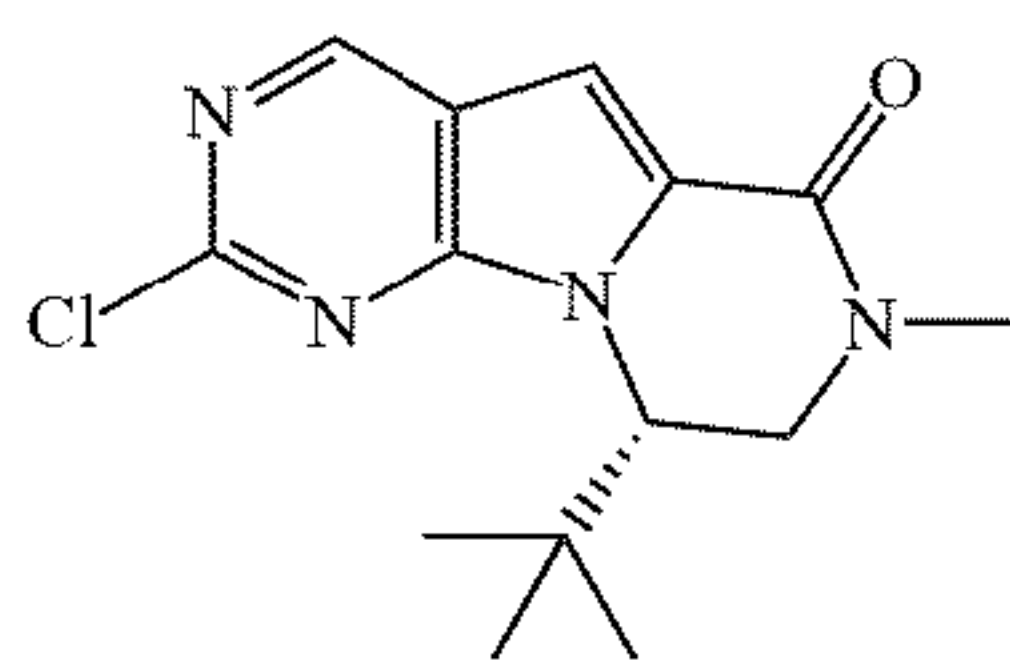
[0399] 7-[(1S)[(tert-butoxycarbonylamino)methyl]-2,2-dimethyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using the analogous synthetic sequence as that described for 7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 397 (M + H).

[0400] Intermediate 1F was synthesized using an analogous synthetic sequence as that described for intermediate 1A. LCMS (ESI) 279 (M + H).

Example 53

Synthesis of Compound 53

[0401]

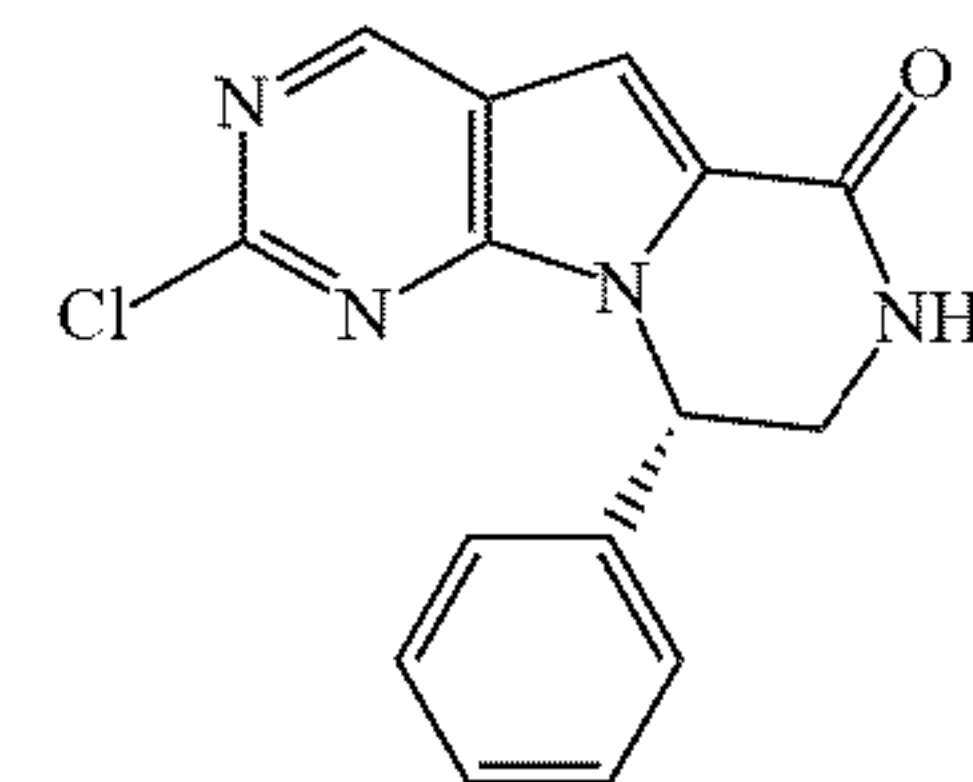


[0402] Compound 53 was synthesized in a manner similar to that described for Intermediate 1CA. LCMS (ESI) 293 (M + H).

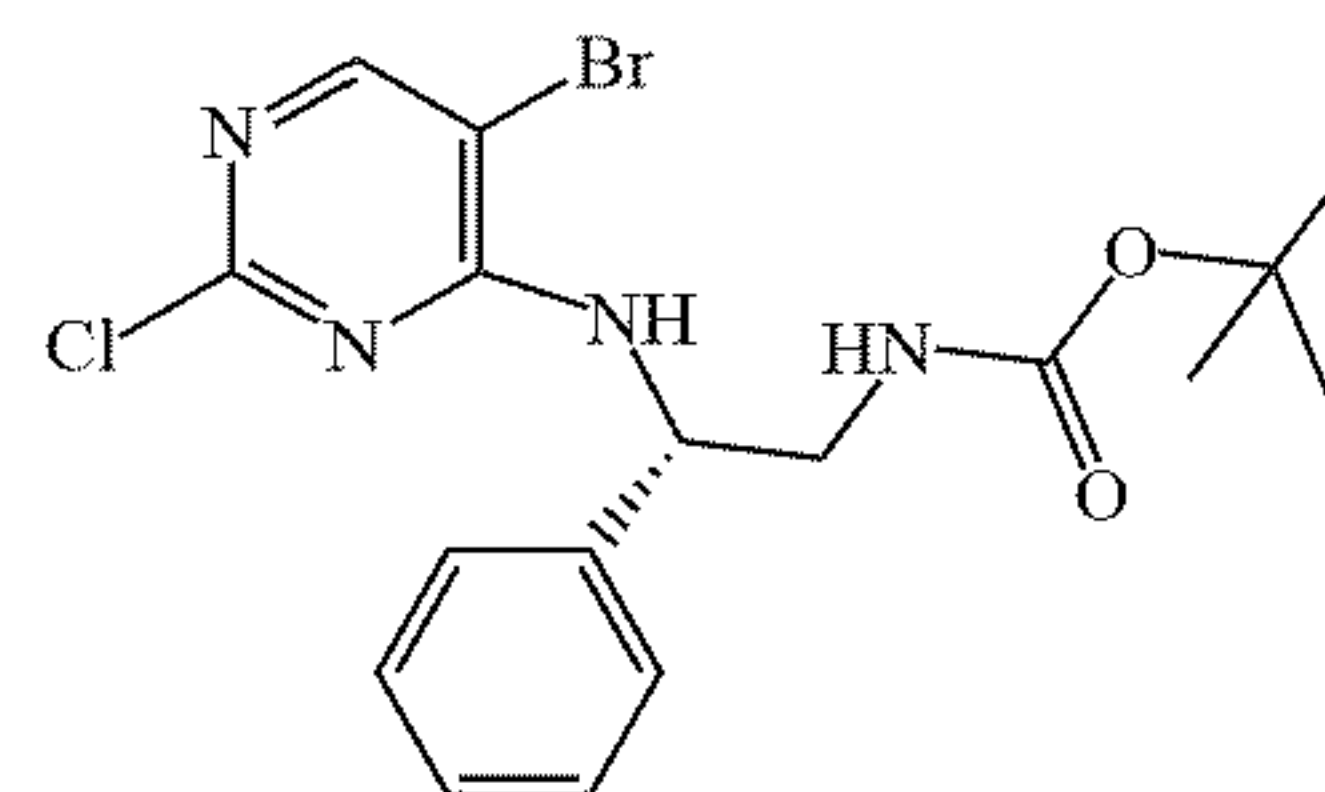
Example 54

Synthesis of Compound 54

[0403]

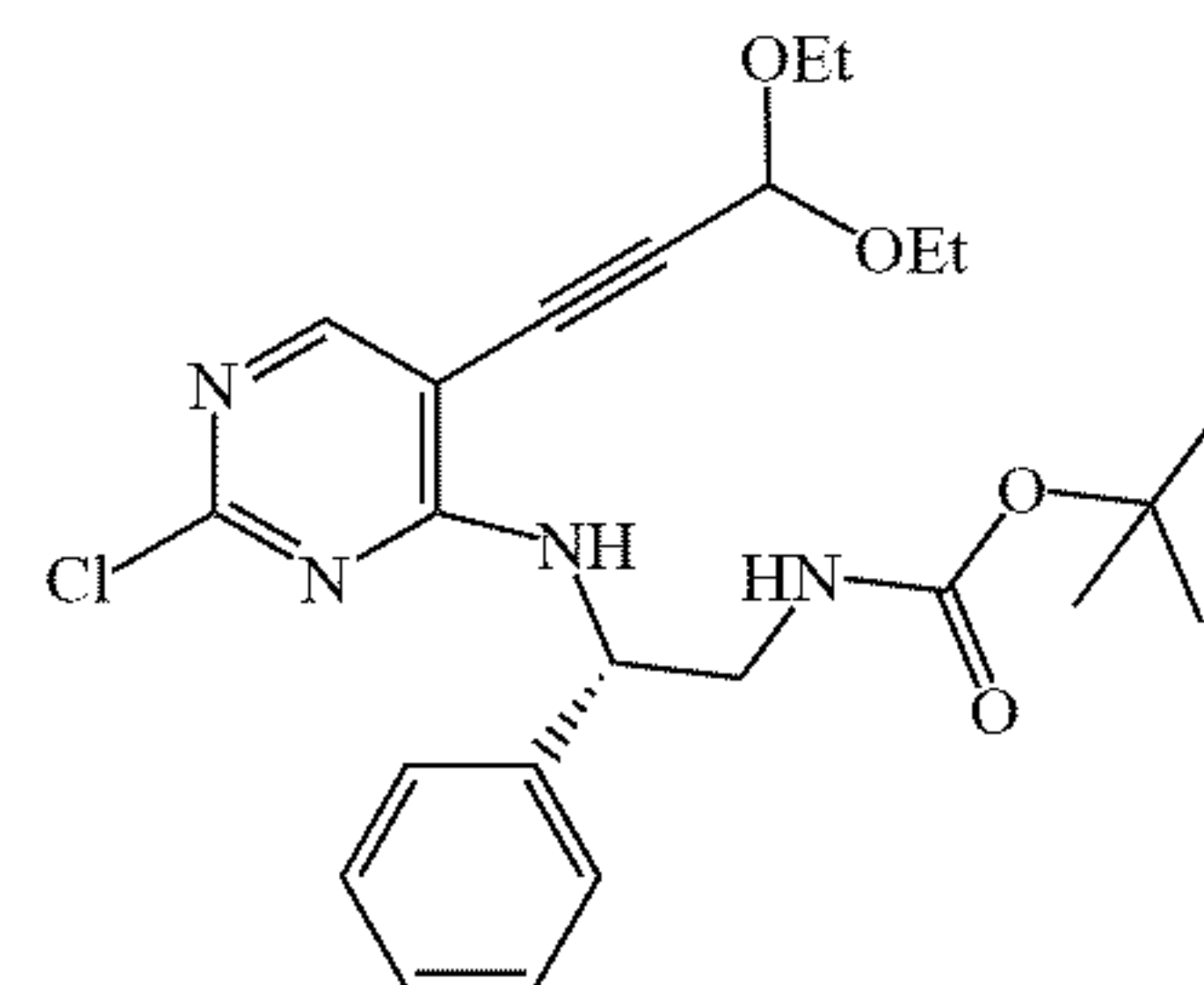


tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-phenyl-ethyl]carbamate



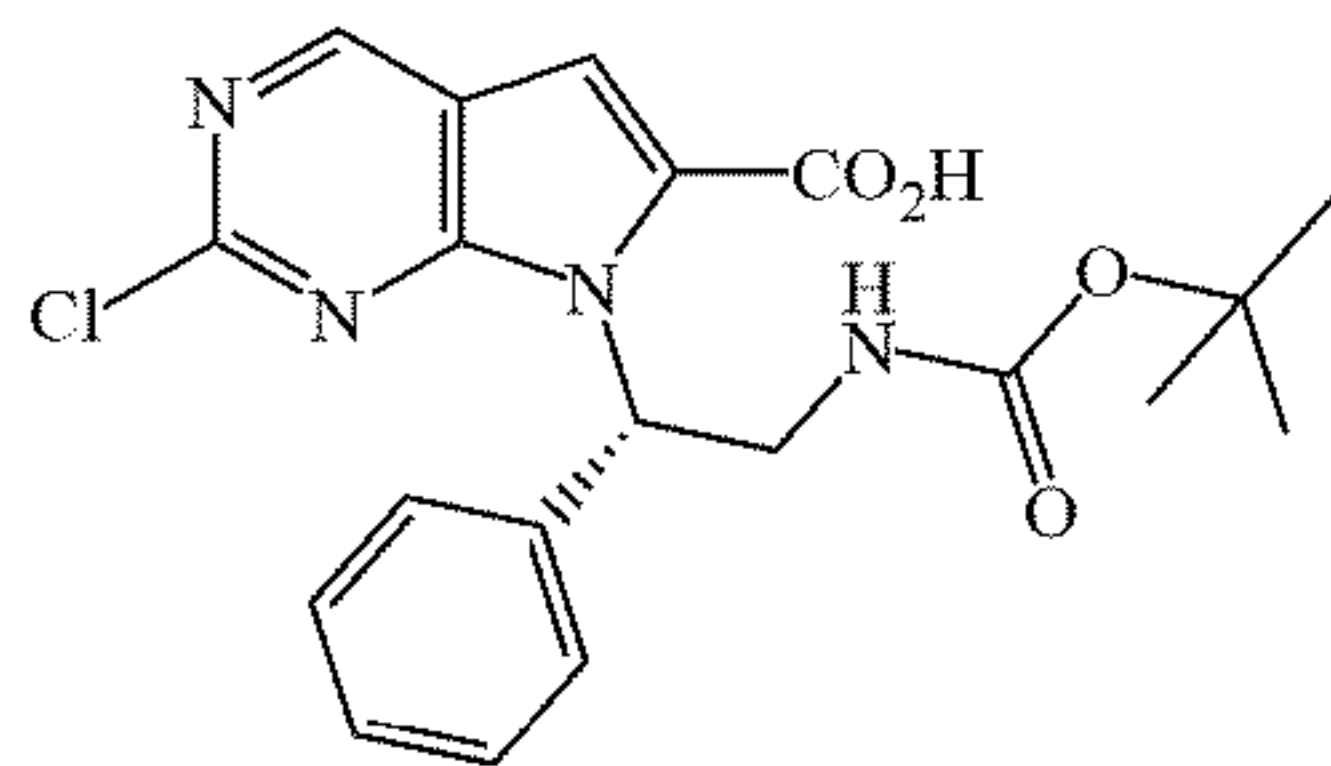
[0404] Compound 21 was hydrogenated using 10% Pd/C under hydrogen at 50 psi in a pressure vessel to afford tert-butyl N-[(2S)-2-amino-2-phenyl-ethyl]carbamate which was then reacted with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate to afford tert-butyl N-[(2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-phenyl-ethyl]carbamate. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.32 (s, 9 H) 3.29 - 3.50 (m, 2 H) 5.12 - 5.24 (m, 1 H) 7.10 (t, J=5.27 Hz, 1 H) 7.21 (t, J=6.88 Hz, 1 H) 7.26 - 7.34 (m, 4 H) 7.89 (d, J=7.32 Hz, 1 H) 8.24 (s, 1 H). LCMS (ESI) 427 (M + H).

[0405] tert-butyl N-[(2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-phenylethyl]carbamate



[0406] tert-butyl N-[(2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-phenyl-ethyl]carbamate was synthesized using similar experimental conditions to those used in the synthesis of (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methylpentane-1,2-diamine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.14 (t, J=7.03 Hz, 6 H) 1.32 (s, 9 H) 3.39 (s, 2 H) 3.52 - 3.61 (m, 2 H) 3.64 - 3.73 (m, 2 H) 5.17 - 5.26 (m, 1 H) 5.57 (s, 1 H) 7.07 - 7.14 (m, 1 H) 7.20 - 7.25 (m, 1 H) 7.26 - 7.33 (m, 4 H) 7.90 (d, J=7.61 Hz, 1 H) 8.19 (s, 1 H). LCMS (ESI) 475 (M + H).

[0407] 7-[(1S)(tert-butoxycarbonylamino)-1-phenylethyl]chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0408] 7-[(1S)(tert-butoxycarbonylamino)-1-phenylethyl]chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using the analogous synthetic sequence as that described for 7-[1-[(tert-butoxycarbonylamino)methyl]methyl-propyl]chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 417 (M + H).

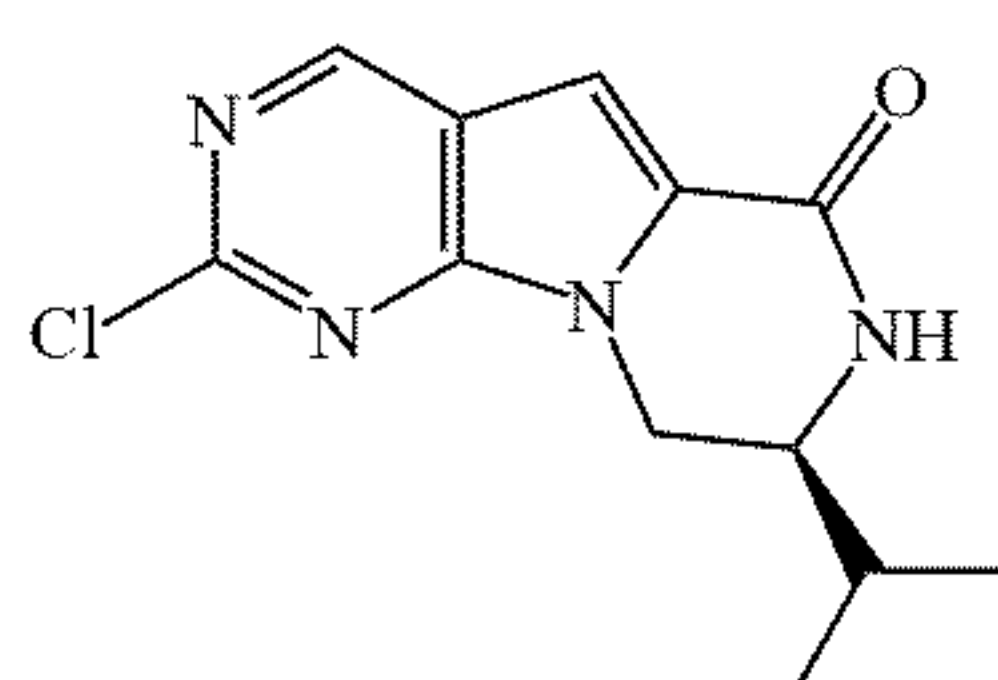
Compound 54

[0409] Compound 54 was synthesized using an analogous synthetic sequence as that described for Compound 44. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 3.58 - 3.69 (m, 1 H) 4.13 (dd, J=13.47, 4.39 Hz, 1 H) 6.07 (d, J=3.81 Hz, 1 H) 6.85 (d, J=7.32 Hz, 2 H) 7.19 - 7.31 (m, 3 H) 7.34 (s, 1 H) 8.27 (d, J=5.27 Hz, 1 H) 9.13 (s, 1 H). LCMS (ESI) 299 (M + H).

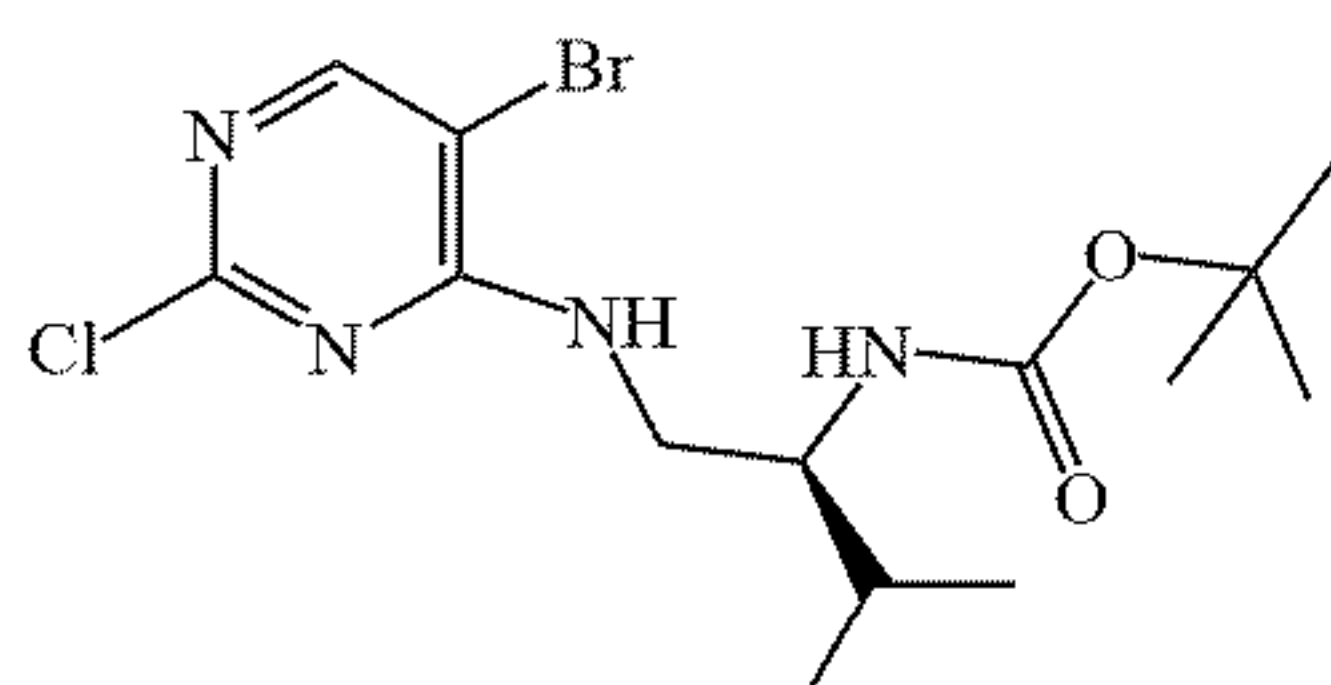
Example 55

Synthesis of Compound 55

[0410]

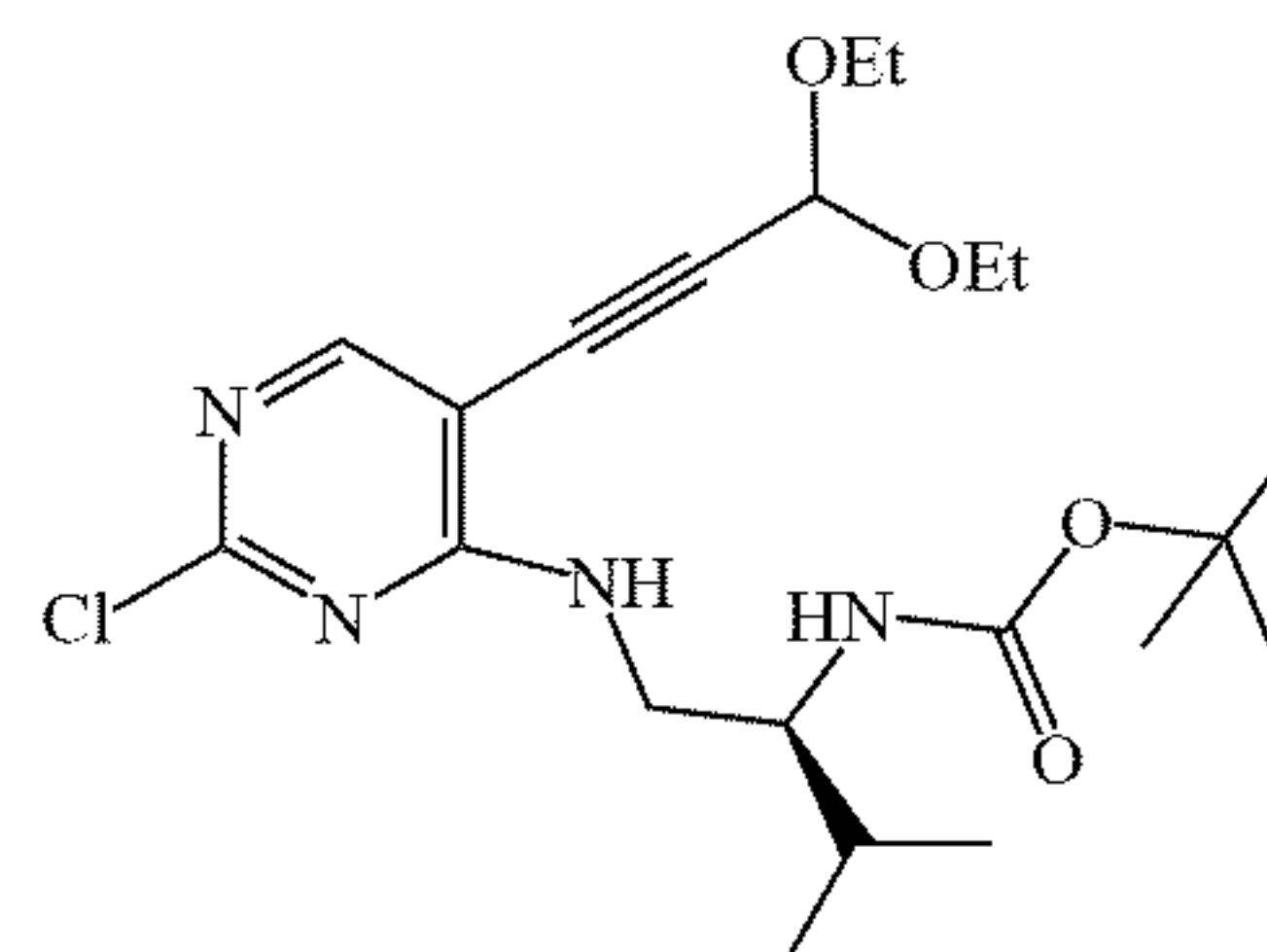


tert-butyl N-[(1S)-1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]methyl]-2-methyl-propyl] carbamate



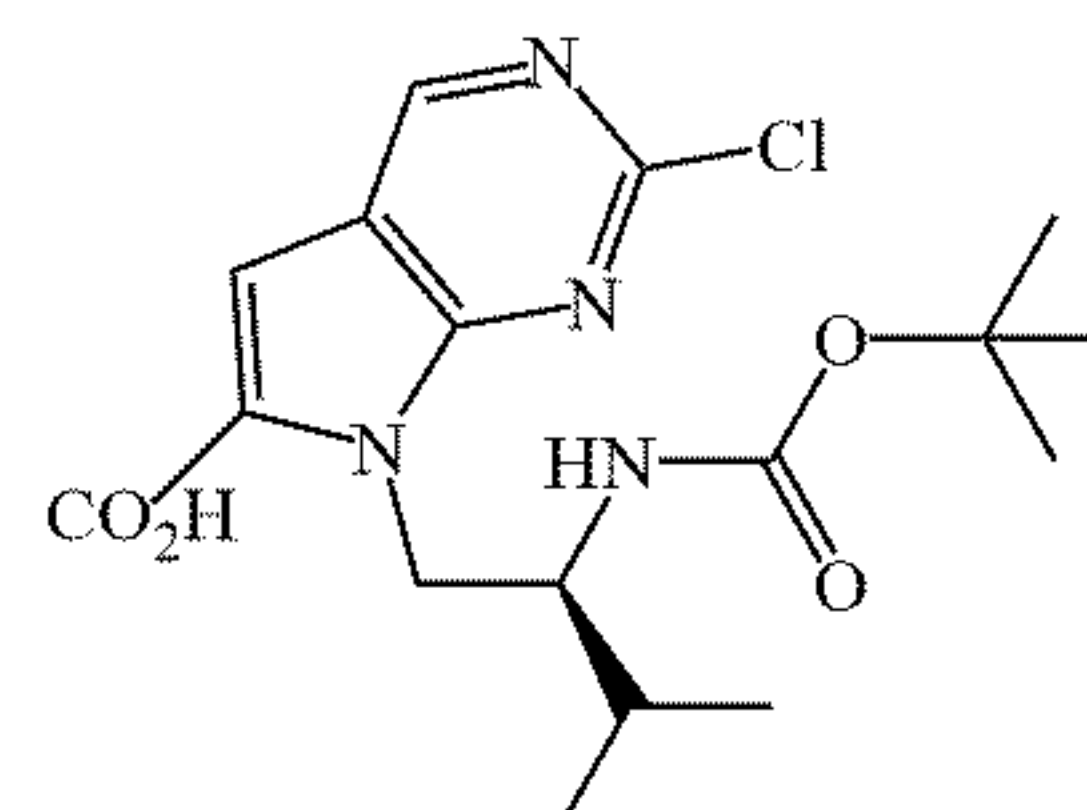
[0411] tert-butyl N-[(1S)-1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]methyl]-2-methylpropyl]carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate E using analogous reaction conditions as described for tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.95 - 1.02 (m, 6 H) 1.35 - 1.45 (m, 9 H) 1.75 - 1.90 (m, 1 H) 3.35 - 3.48 (m, 1 H) 3.52 - 3.61 (m, 1 H) 3.64 - 3.76 (m, 1 H) 4.56 (d, J=8.49 Hz, 1 H) 6.47 (s, 1 H) 8.07 (s, 1 H). LCMS (ESI) 393 (M + H).

[0412] tert-butyl N-[(1S)-1-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]-2-methyl-propyl] carbamate



[0413] tert-butyl N-[(1S)-1-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]-2-methyl-propyl]carbamate was synthesized using similar experimental conditions to those used in the synthesis (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.90 - 1.00 (m, 6 H) 1.18 - 1.25 (m, 6 H) 1.34 - 1.36 (m, 9 H) 1.69 - 1.90 (m, 1 H) 3.34 - 3.82 (m, 6 H) 4.53 - 4.77 (m, 1 H) 5.45 - 5.55 (m, 1 H) 6.37 (dd, J=15.37, 6.59 Hz, 1 H) 6.56 (s, 1 H) 8.05 (s, 1 H). LCMS (ESI) 441 (M + H).

[0414] 7-[(2S)(tert-butoxycarbonylamino)-3-methyl-butyl]chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0415] 7-[(2S)(tert-butoxycarbonylamino)-3-methyl-butyl]chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using the analogous synthetic sequence as that described for 7-[1-[(tert-butoxycarbonylamino)methyl]methyl-propyl]chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 0.90 (d, J=6.73 Hz, 3 H) 0.96 (d, J=7.03 Hz, 3 H) 1.55 - 1.66 (m, 10 H) 4.14 (dd, J=13.61, 3.95 Hz, 1 H) 4.52 - 4.63 (m, 1 H) 4.84 (dd, J=13.61, 1.32 Hz, 1 H) 7.37 (s, 1 H) 8.95 (s, 1 H). LCMS (ESI) 383 (M + H).

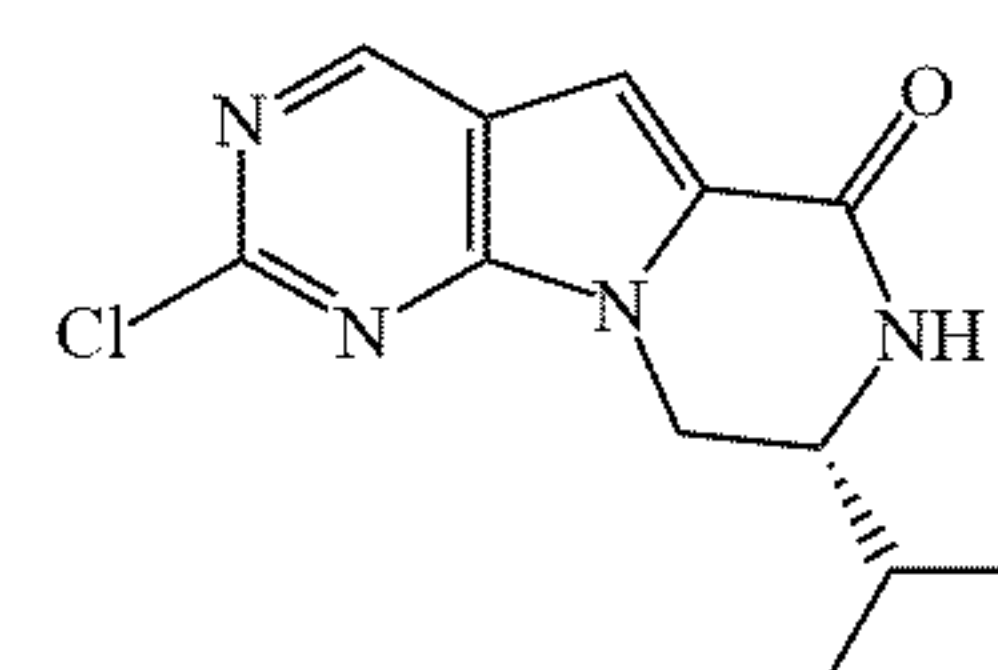
Compound 55

[0416] Compound 55 was synthesized using an analogous synthetic sequence as that described for Compound 44. LCMS (ESI) 265 (M + H).

Example 56

Synthesis of Compound 56

[0417]

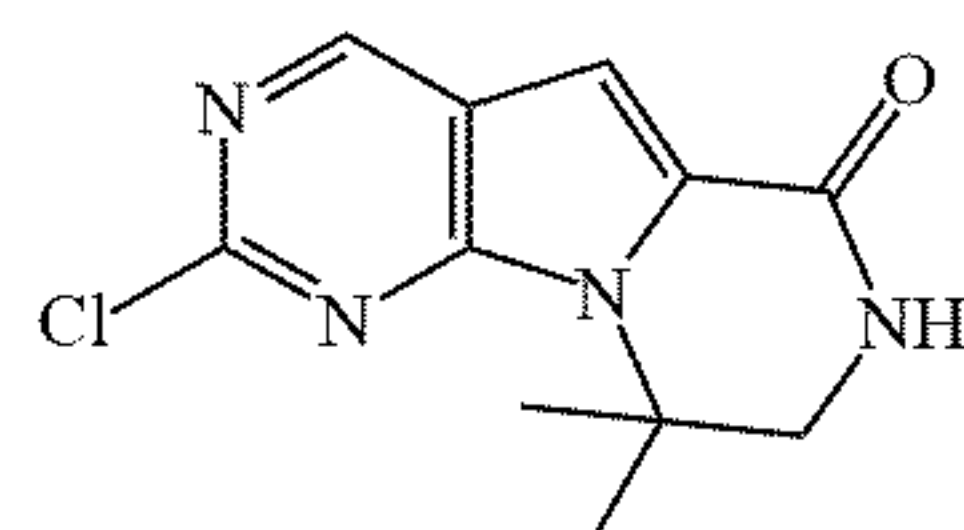


[0418] Compound 56 was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Compound 17 as starting materials, and following a similar sequence of synthetic steps as for Compound 55. The analytical data was consistent with that described for its antipode (Compound 55). ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.88 (d, J=6.44 Hz, 6 H) 1.73 - 1.86 (m, 1 H) 3.67 - 3.76 (m, 2 H) 4.11 - 4.21 (m, 1 H) 7.13 - 7.19 (m, 1 H) 8.56 (s, 1 H) 9.05 (s, 1 H). LCMS (ESI) 265 (M + H).

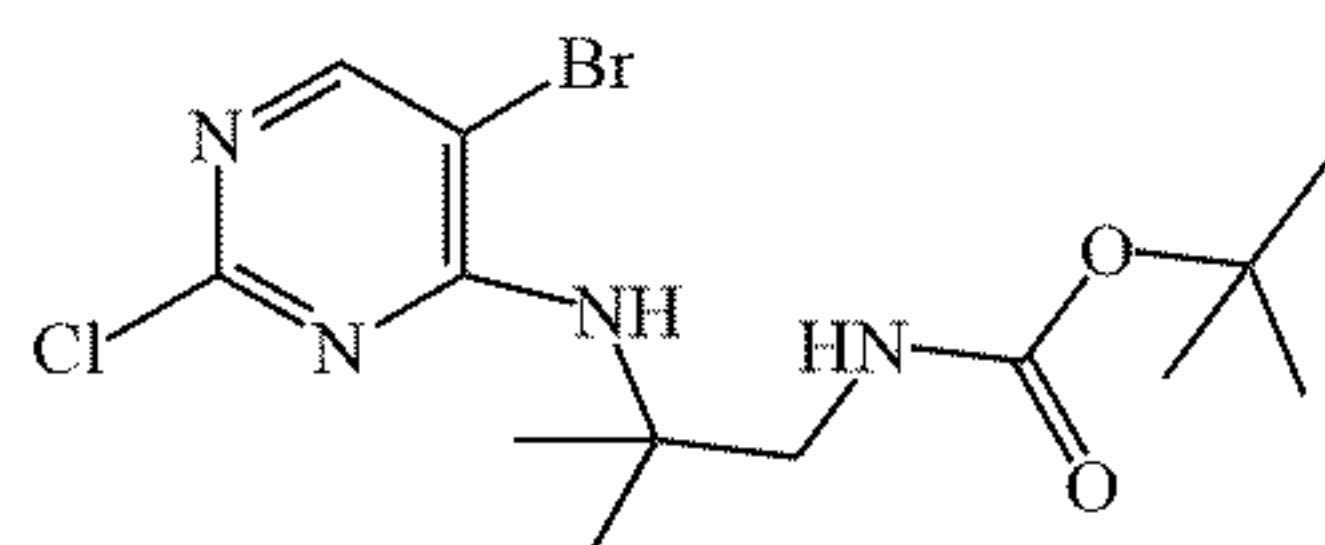
Example 57

Synthesis of Compound 57

[0419]

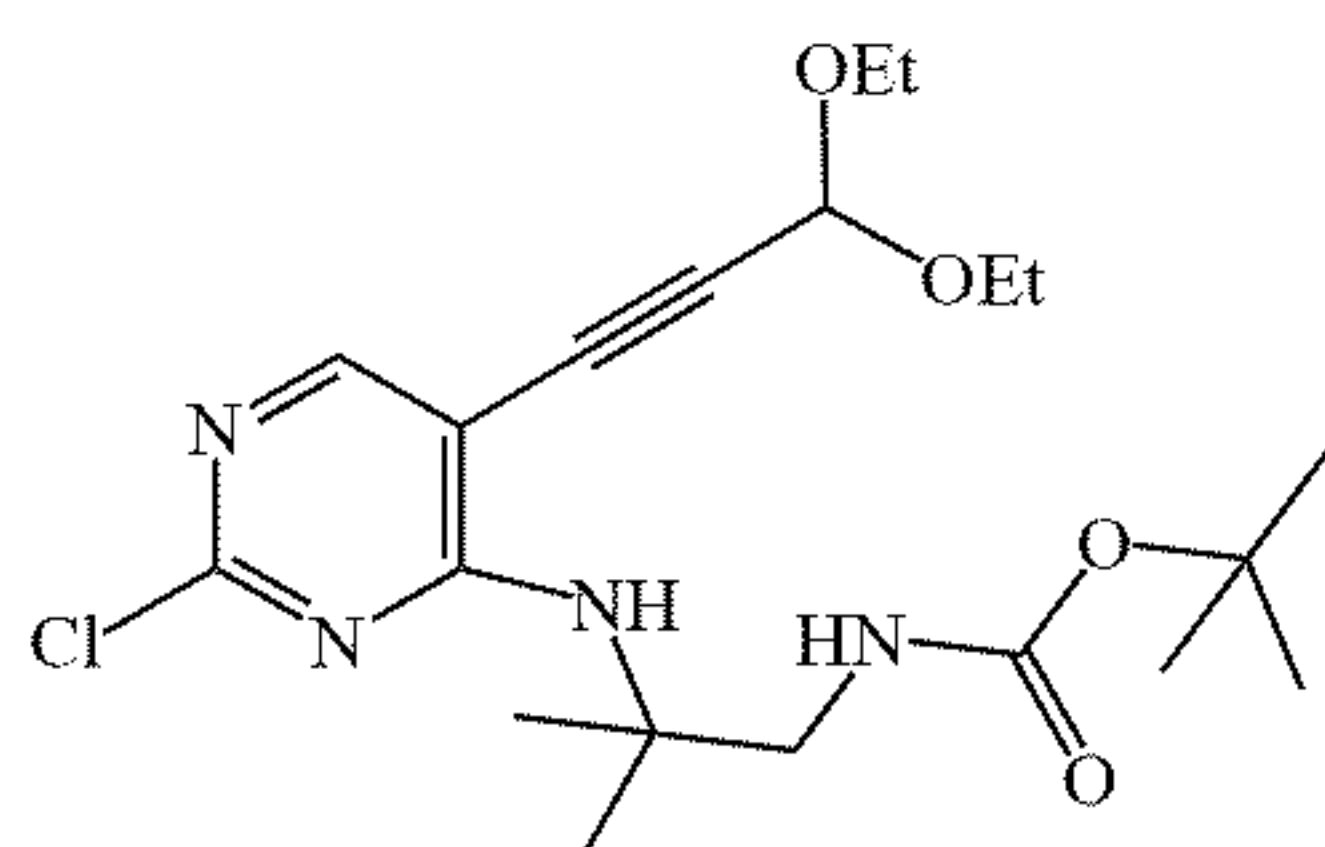


tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-methyl-propyl]carbamate



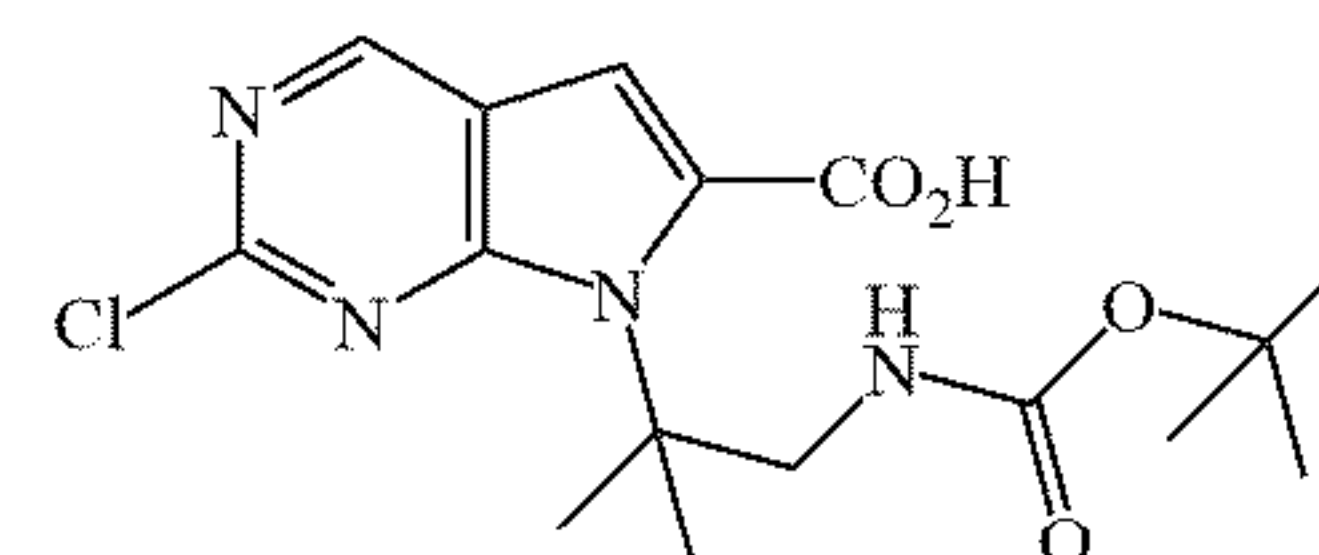
[0420] tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-methyl-propyl]carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and tert-butyl N-(2-amino-2-methylpropyl)carbamate using analogous reaction conditions as described for tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate. LCMS (ESI) 379 (M + H).

[0421] tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methylpropyl]carbamate



[0422] tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methylpropyl]carbamate was synthesized using similar experimental conditions to those used in the synthesis of (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.11 - 1.22 (m, 6 H) 1.31 - 1.45 (m, 15 H) 3.10 - 3.24 (m, 2 H) 3.51 - 3.76 (m, 4 H) 5.60 (s, 1 H) 6.94 (s, 1 H) 7.33 (t, J=6.44 Hz, 1 H) 8.18 (s, 1 H). LCMS (ESI) 427 (M + H).

[0423] 7-(tert-butoxycarbonylamino)-1,1-dimethyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0424] 7-(tert-butoxycarbonylamino)-1,1-dimethyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using the analogous synthetic sequence as that described for 7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.43 (s, 9H) 1.73 (s, 6 H) 4.06 (s, 2 H) 7.46 (s, 1 H) 9.23 (s, 1H). LCMS (ESI) 369 (M + H).

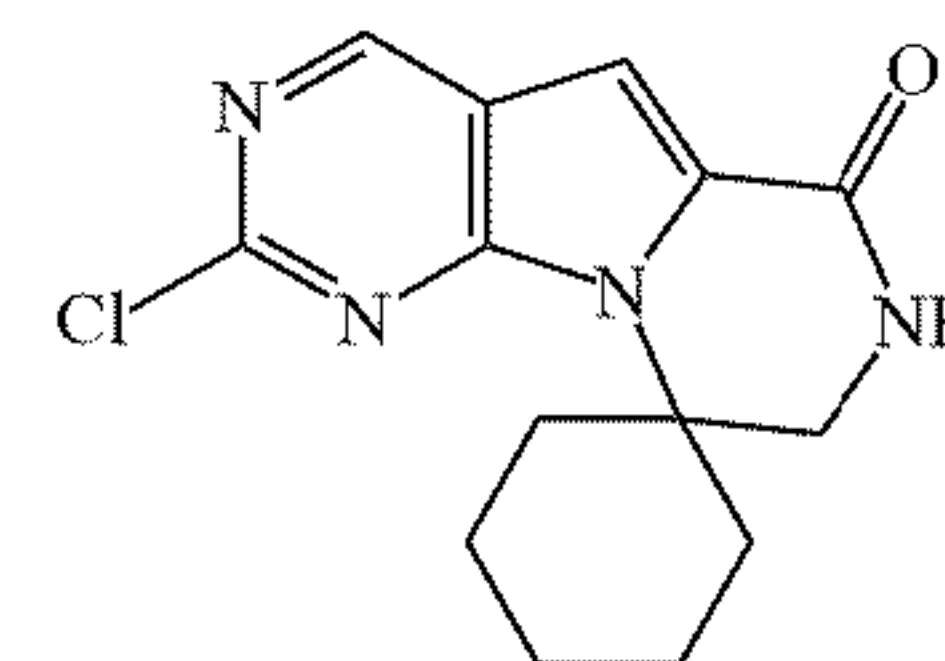
Compound 57

[0425] Compound 57 was synthesized using an analogous synthetic sequence as that described for Compound 44. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.73 (s, 6 H) 3.50 (d, J=2.93 Hz, 2 H) 7.25 (s, 1 H) 8.46 - 8.55 (m, 1 H) 9.07 (s, 1 H). LCMS (ESI) 251 (M + H).

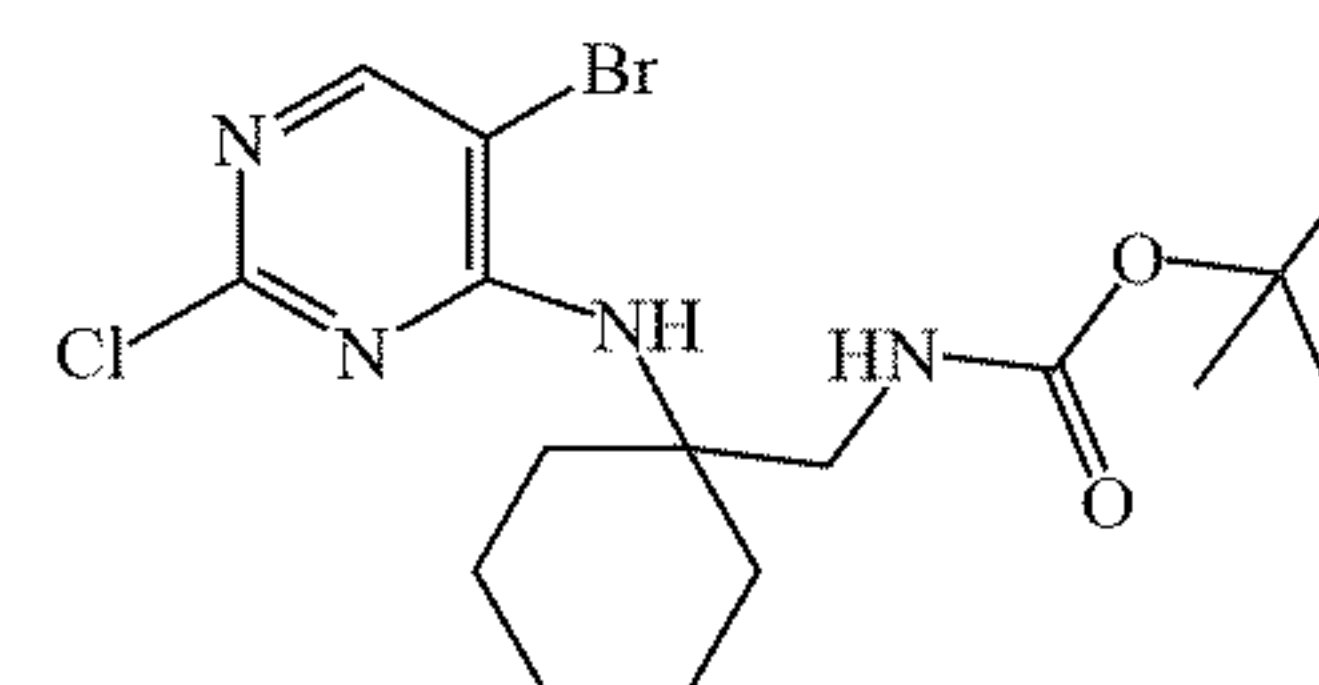
Example 58

Synthesis of Compound 58

[0426]

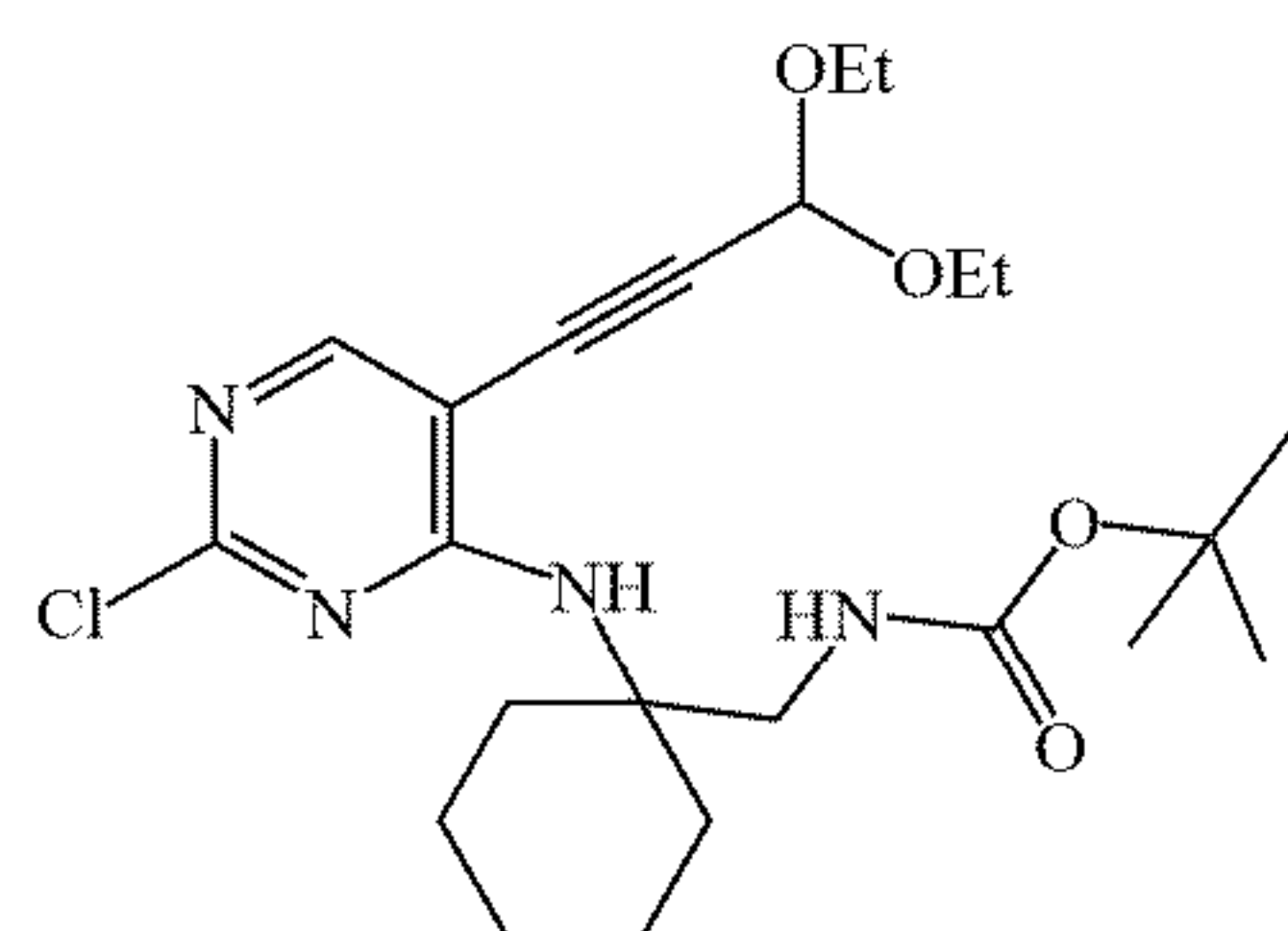


[0427] tert-butyl N-[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclohexyl]methyl]carbamate



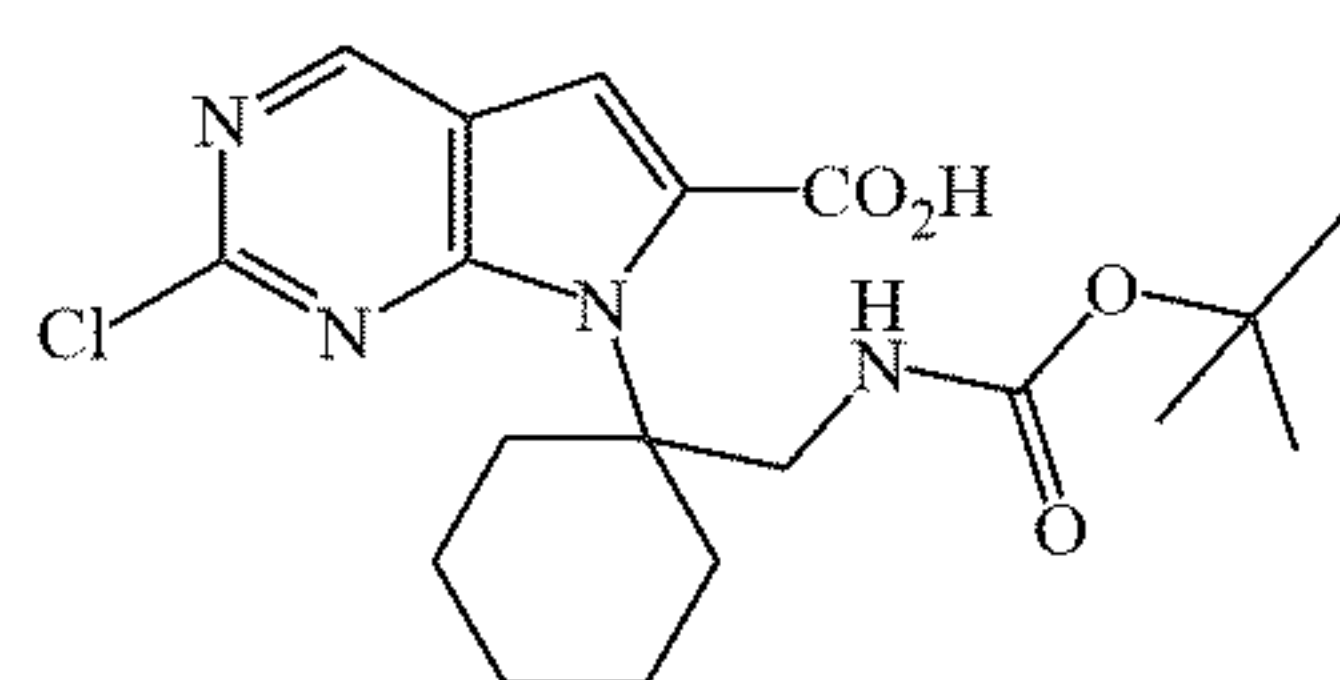
[0428] tert-butyl N-[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclohexyl]methyl] carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate K using the analogous reaction conditions as described for tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl] carbamate. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.18 - 1.54 (m, 17 H) 2.23 (d, J=14.35 Hz, 2 H) 3.36 (d, J=6.44 Hz, 2 H) 5.82 (s, 1 H) 6.93 (s, 1 H) 8.22 (s, 1 H). LCMS (ESI) 419 (M + H).

[0429] tert-butyl N-[1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclohexyl] methyl] carbamate



[0430] tert-butyl N-[[1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclohexyl]methyl] carbamate was synthesized using similar experimental conditions to those used in the synthesis of (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.08 - 1.16 (m, 6 H) 1.17 - 1.54 (m, 17 H) 2.13 (br. s., 2 H) 3.36 (d, J=6.73 Hz, 2 H) 3.50 - 3.69 (m, 4 H) 5.72 (s, 1 H) 6.94 (s, 1 H) 5.72 (br. s., 1 H) 8.17 (s, 1 H). LCMS (ESI) 467 (M + H).

[0431] 7-[(tert-butoxycarbonylamino)methyl]cyclohexyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0432] 7-[(tert-butoxycarbonylamino)methyl]cyclohexyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.37 - 1.54 (m, 13 H) 1.75 (br. s., 4 H) 2.74 (br. s., 2 H) 3.78 - 3.84 (m, 2 H) 7.44 - 7.51 (m, 1 H) 8.23 (s, 1 H) 9.11 (s, 1 H). LCMS (ESI) 409 (M + H).

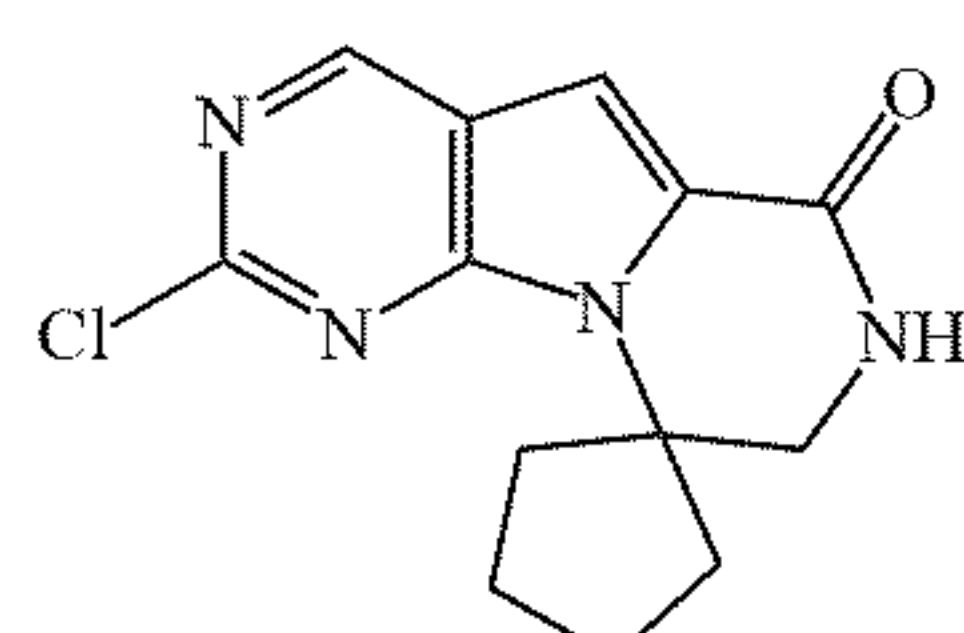
Compound 58

[0433] Compound 58 was synthesized using an analogous synthetic sequence as that described for Compound 44. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.28 (br. s., 2 H) 1.42 (br. s., 2 H) 1.70 (br. s., 4 H) 1.85 - 1.95 (m, 2 H) 2.69 (m, 2 H) 7.16 - 7.25 (m, 1 H) 8.41 (br. s., 1 H) 9.04 (s, 1 H). LCMS 291 (M + H).

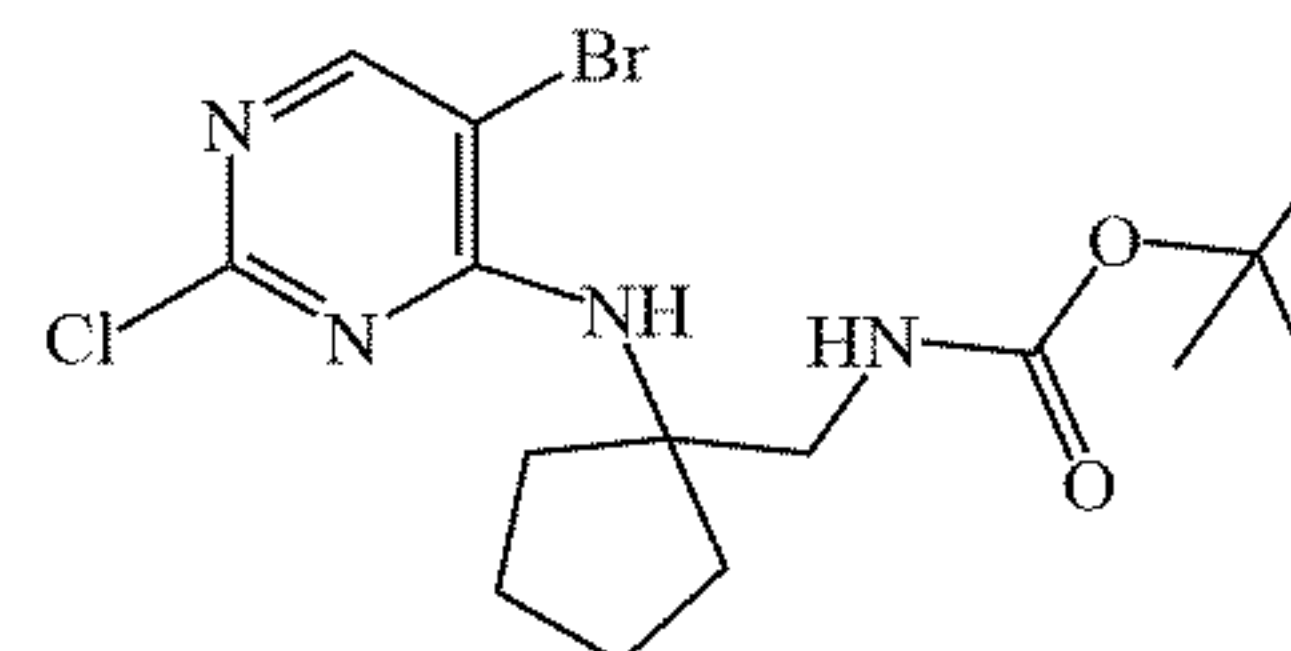
Example 59

Synthesis of Compound 59

[0434]

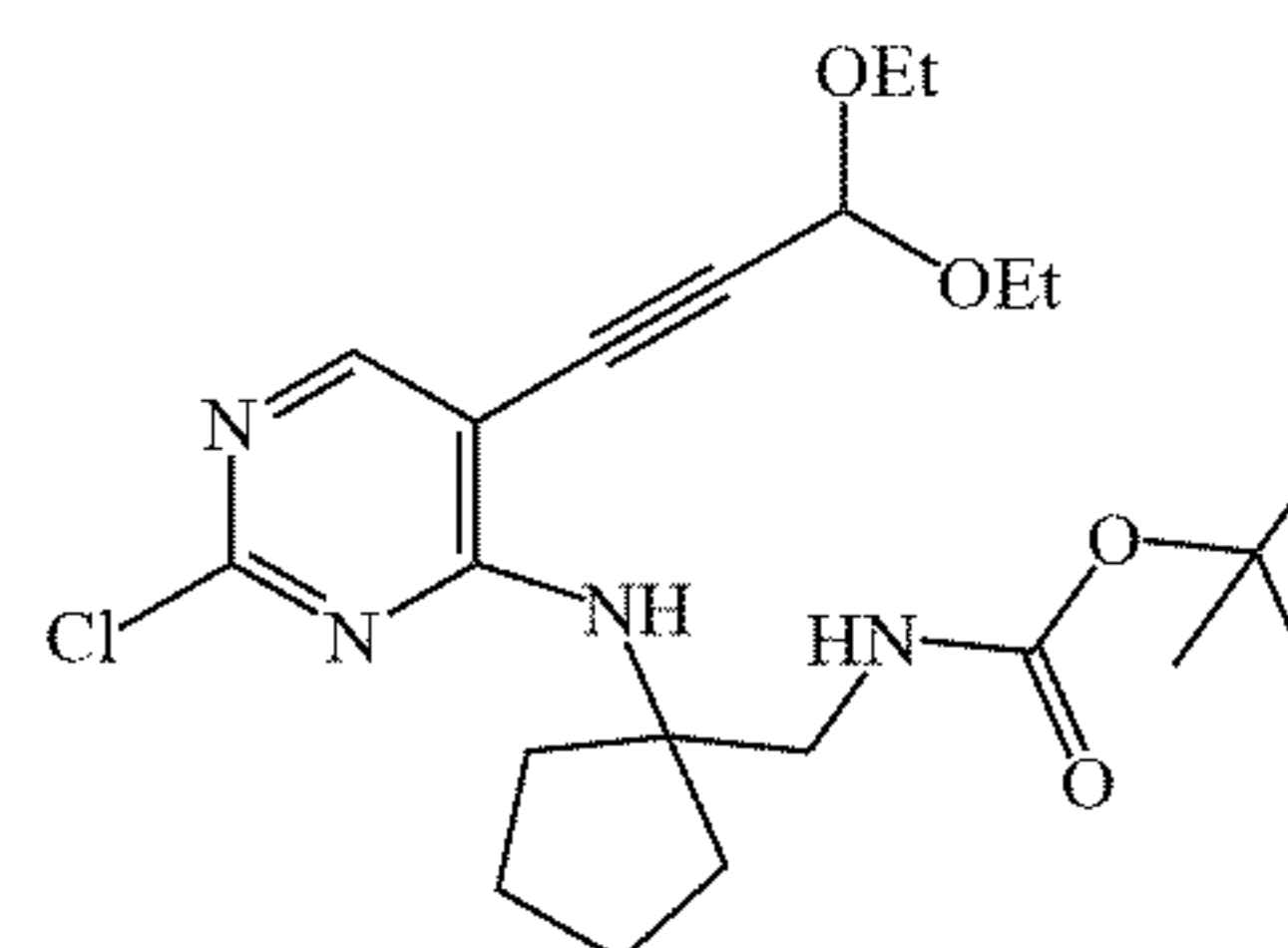


[0435] tert-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]methyl] carbamate



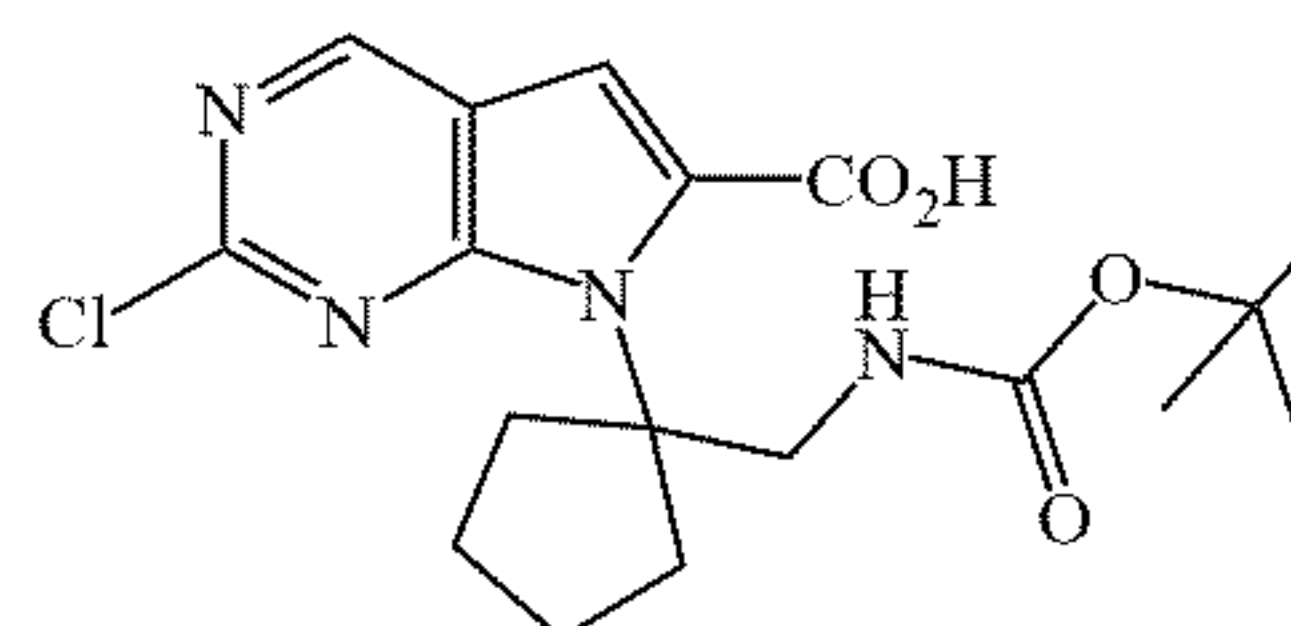
[0436] tert-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl] methyl] carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate L using analogous reaction conditions as described for tert-butyl N-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.34 (s, 9 H) 1.50 - 1.58 (m, 2 H) 1.63 - 1.78 (m, 4 H) 1.96 - 2.06 (m, 2 H) 3.25 (d, J=6.15 Hz, 2 H) 6.71 (s, 1 H) 7.18 (t, J=6.29 Hz, 1 H) 8.20 (s, 1 H). LCMS (ESI) 405 (M + H).

[0437] tert-butyl N-[[1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclopentyl] methyl] carbamate



[0438] tert-butyl N-[[1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclopentyl]methyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. LCMS (ESI) 453 (M + H).

[0439] 7-[(tert-butoxycarbonylamino)methyl]cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0440] 7-[(tert-butoxycarbonylamino)methyl]cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using the analogous synthetic sequence as that described for 7-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.47 (s, 9 H) 1.74 (br. s., 2 H) 1.88 (br. s., 2 H) 2.04 (br. s., 2 H) 2.41 - 2.45 (m, 2 H) 4.06 (s, 2 H) 7.45 (s, 1 H) 9.11 (s, 1 H). LCMS (ESI) 395 (M + H).

Compound 59

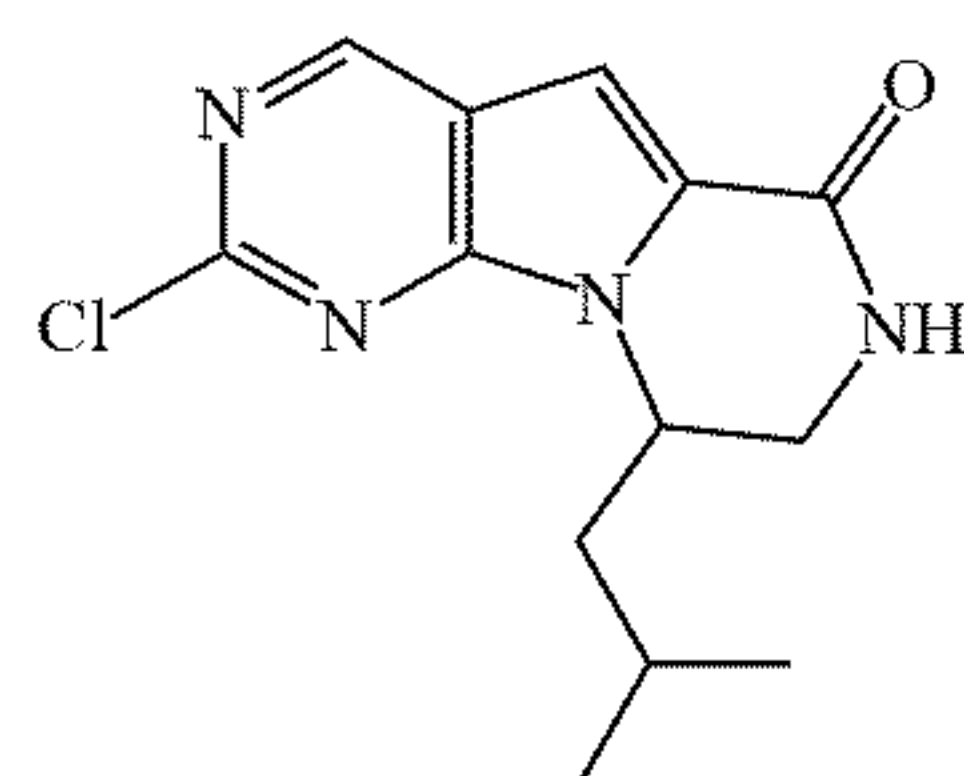
[0441] Compound 59 was synthesized using an analogous synthetic sequence as that described for Compound 44.

¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.72 (br. s., 2 H) 1.86 - 1.93 (m, 2 H) 1.99 (d, J=3.81 Hz, 2 H) 2.40 (br. s., 2 H) 3.48 (d, J=2.34 Hz, 2 H) 7.22 (s, 1 H) 8.53 (br. s., 1 H) 9.05 (s, 1 H). LCMS (ESI) 277 (M + H).

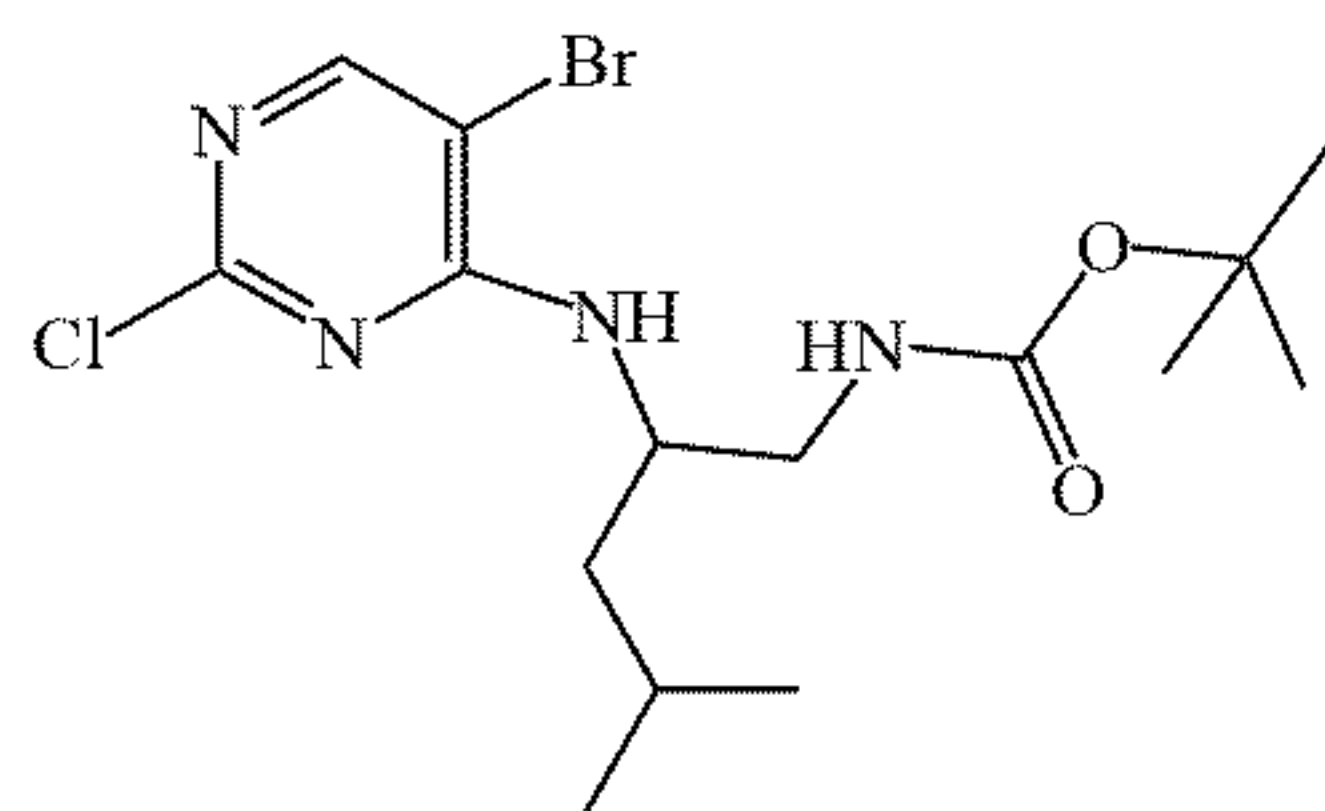
Example 60

Synthesis of Compound 60

[0442]

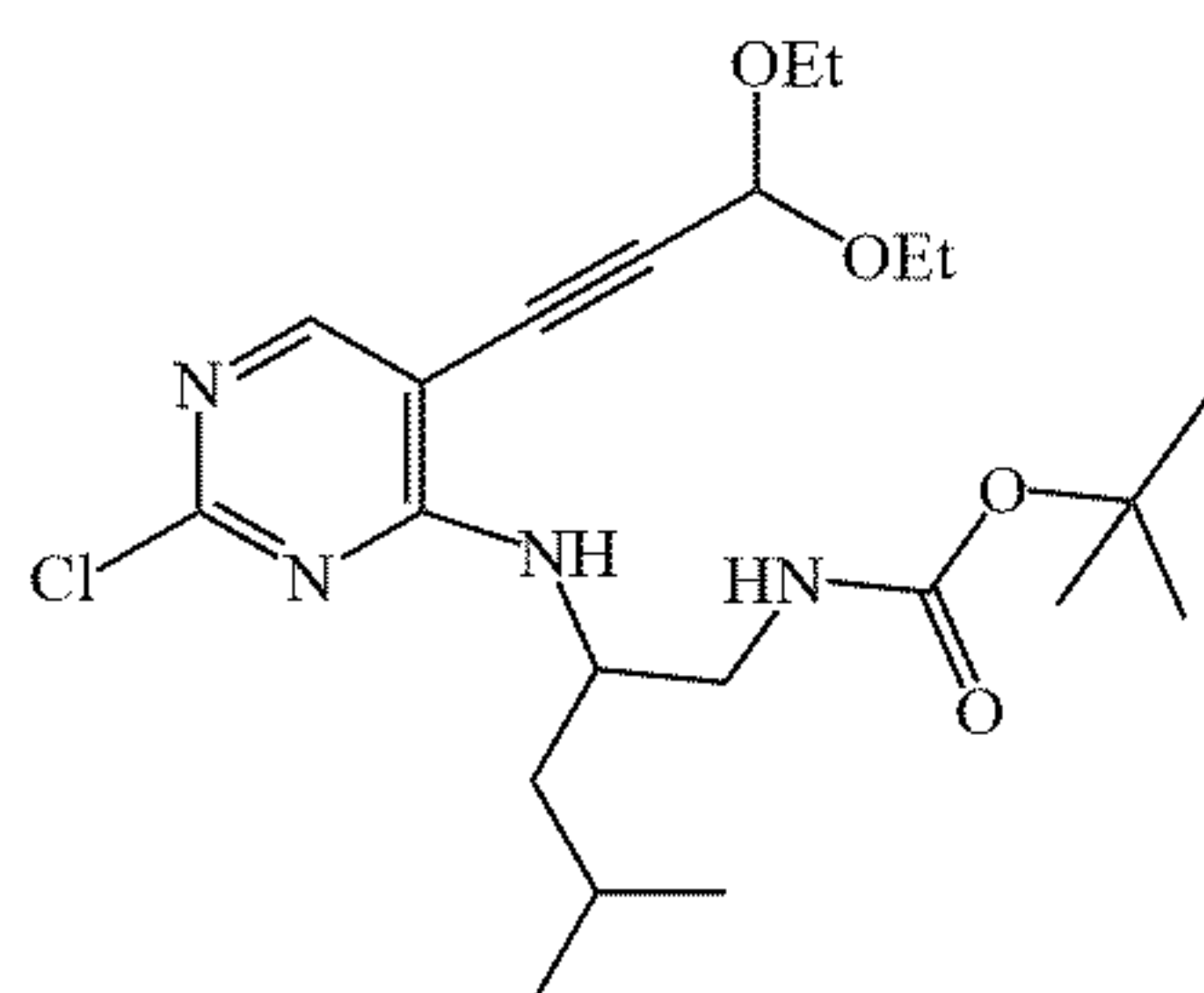


[0443] tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-4-methyl-pentyl] carbamate

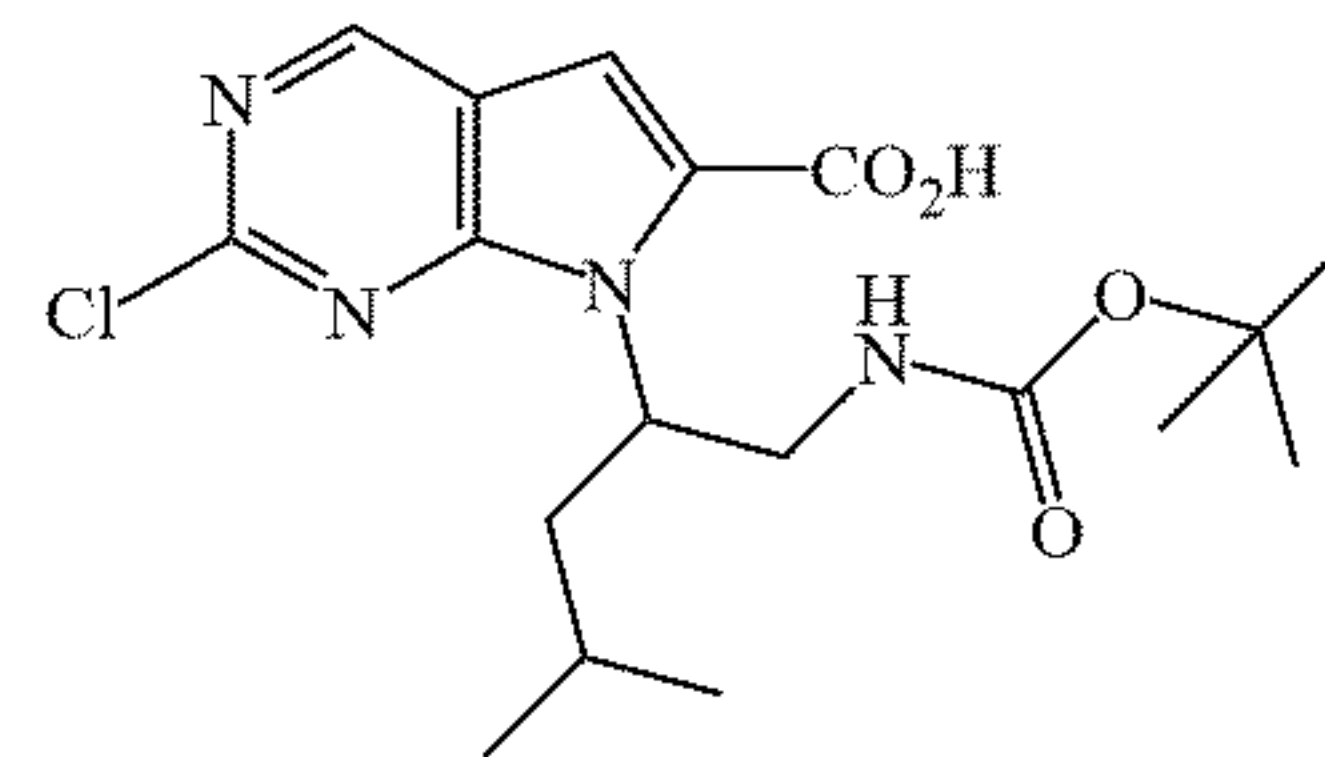


[0444] tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-4-methyl-pentyl]carbamate was synthesized using 5-bromo-2,4-dichloro-pyrimidine and Intermediate B using analogous reaction conditions as described for tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate. The analytical data is consistent with that described for the L-enantiomer.

[0445] tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-4-methyl-pentyl] carbamate



[0446] tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-4-methylpentyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate. ¹HNMR (600 MHz, CHLOROFORM-d) δ ppm 1.21 - 1.31 (m, 12 H) 1.38 - 1.46 (m, 11 H) 1.70 (m, 1H) 3.24 (m, 2 H) 3.65 - 3.82 (m, 4 H) 4.86 (br s., 1H), 5.65 (s, 1 H) 5.85 (br s., 1H) 6.94 (s, 1 H) 8.21 (s, 1 H). LCMS (ESI) 455 (M + H). [0447] 7-[(tert-butoxycarbonylamino)methyl]-3-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0448] 7-[(tert-butoxycarbonylamino)methyl]-3-methyl-butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using analogous synthetic sequence as that described for 7-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. The analytical data was consistent with that described for the L-isomer.

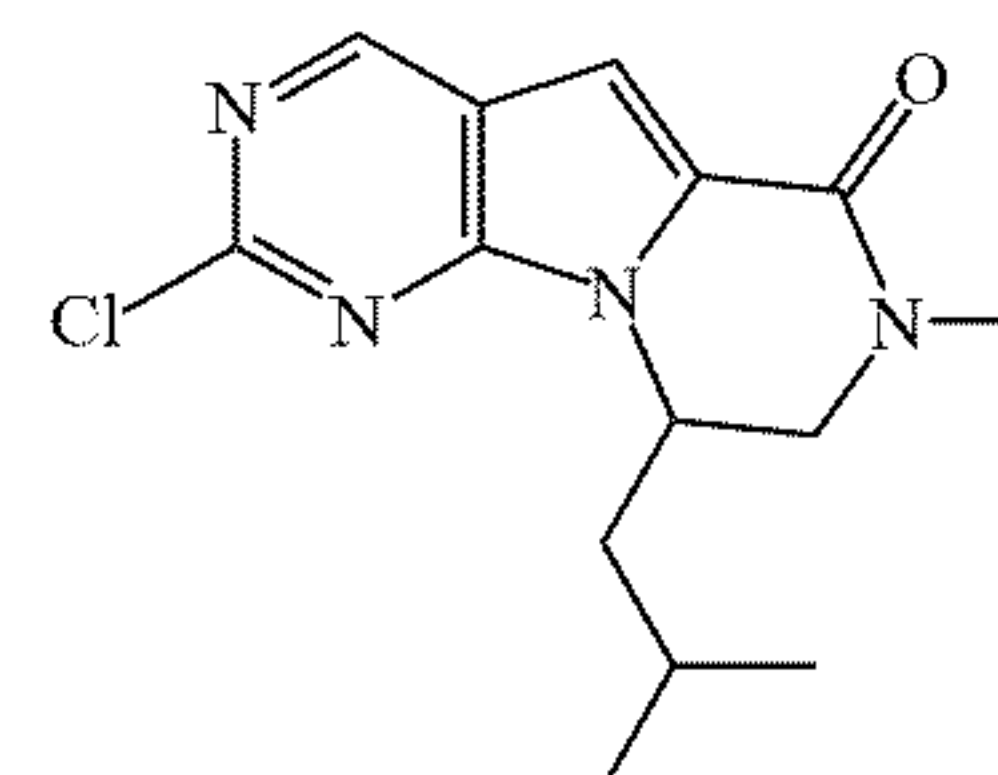
Compound 60

[0449] Compound 60 was synthesized using an analogous synthetic sequence as that described for Compound 44. The analytical data was consistent with that described for the L-isomer.

Example 61

Synthesis of Compound 61

[0450]

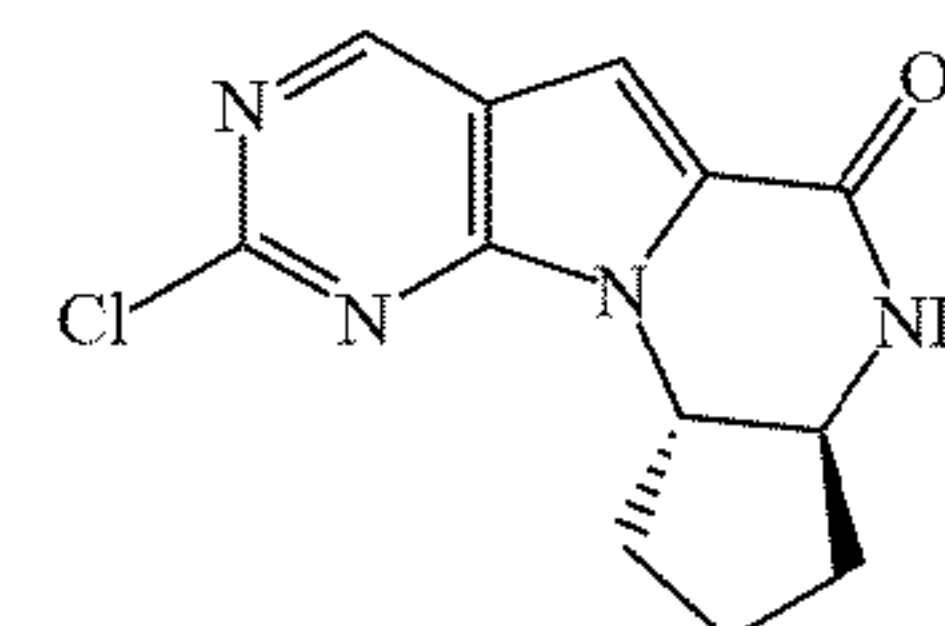


[0451] To a solution of Compound 60 (100 mg, 0.00024 mole) in DMF (3.0 mL) was added sodium hydride (60 % dispersion in oil), (27.6 mg, 3 eq). After stirring for 15 mins, methyl iodide (30, 2 eq) was added. The contents were stirred at room temperature for 30 mins. After the addition of sat NaHCO₃, ethyl acetate was added. Separation of the organic layer followed by drying with magnesium sulfate and concentration under vacuum afforded the product. Analytical data was similar to the Compound 49.

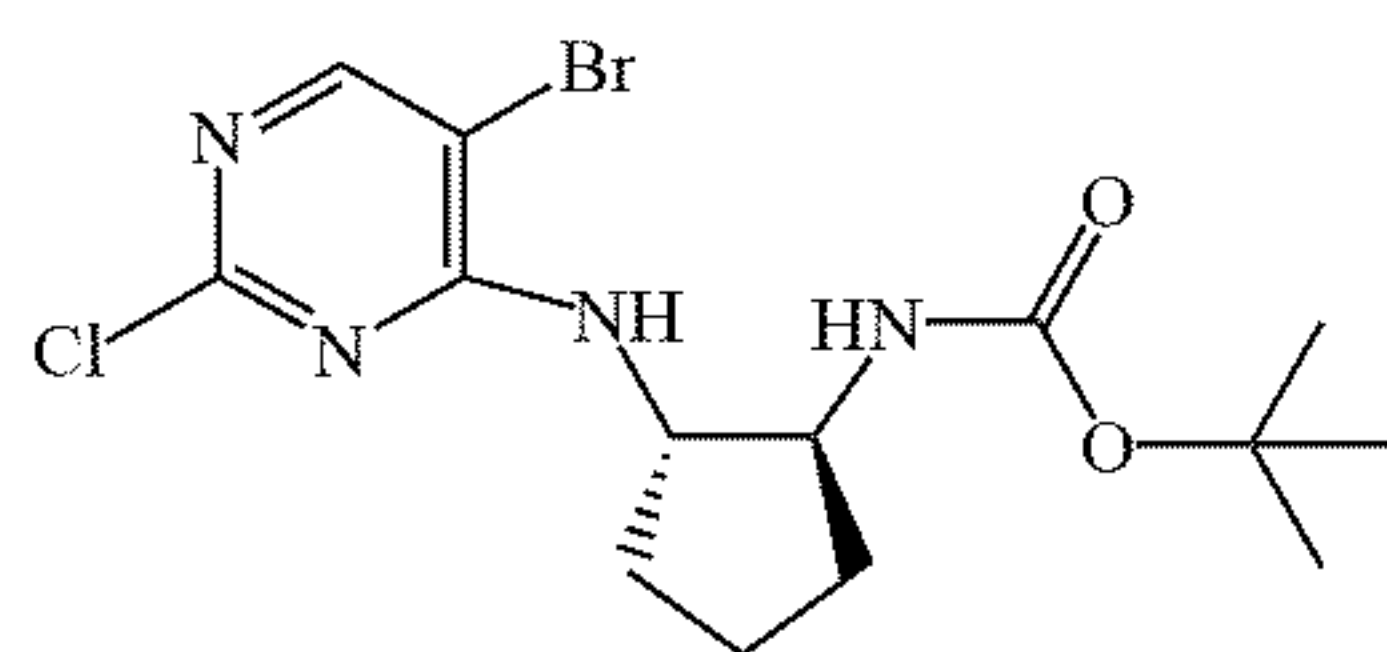
Example 62

Synthesis of Compound 62

[0452]

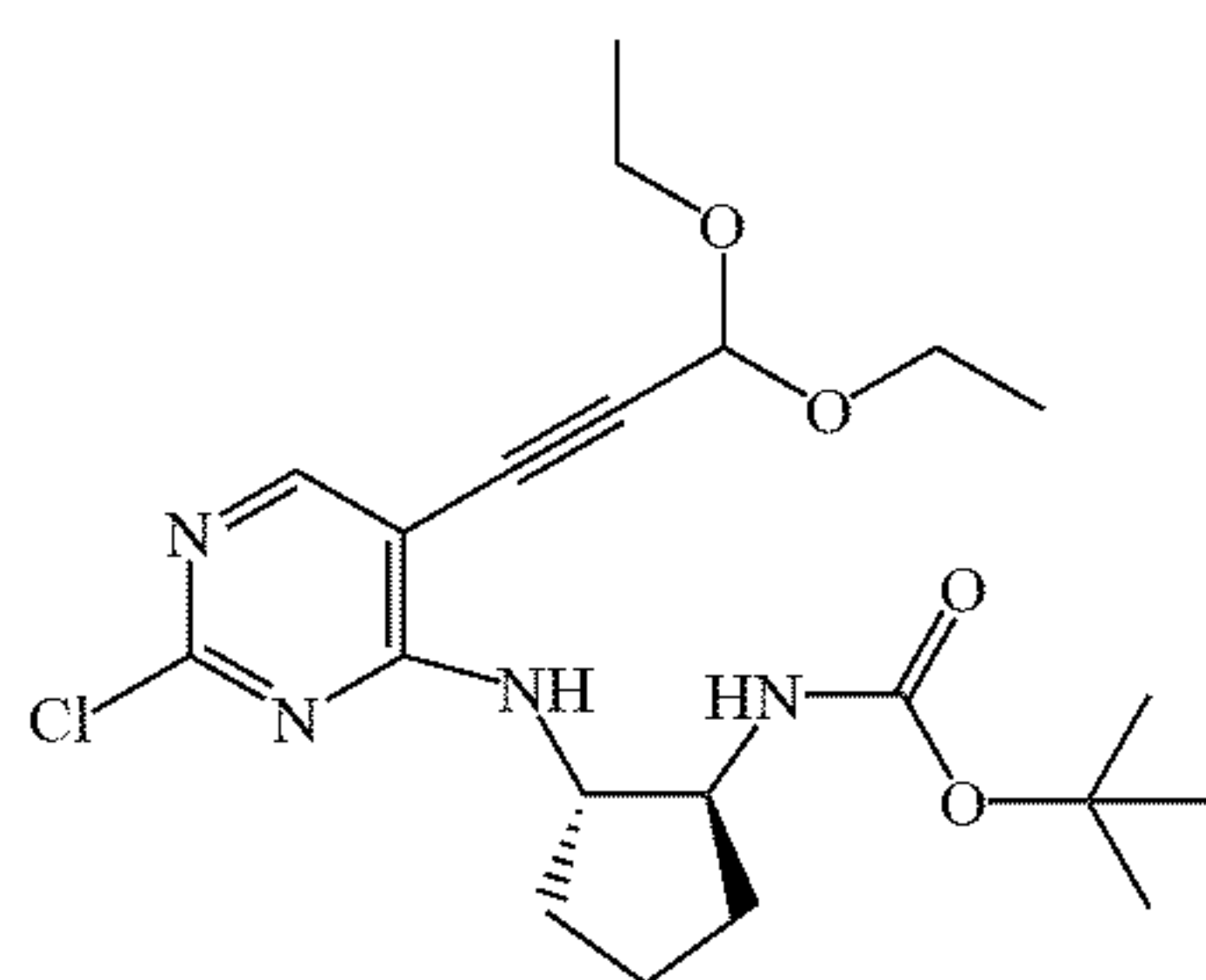


tert-butyl N-[(1S,2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]carbamate



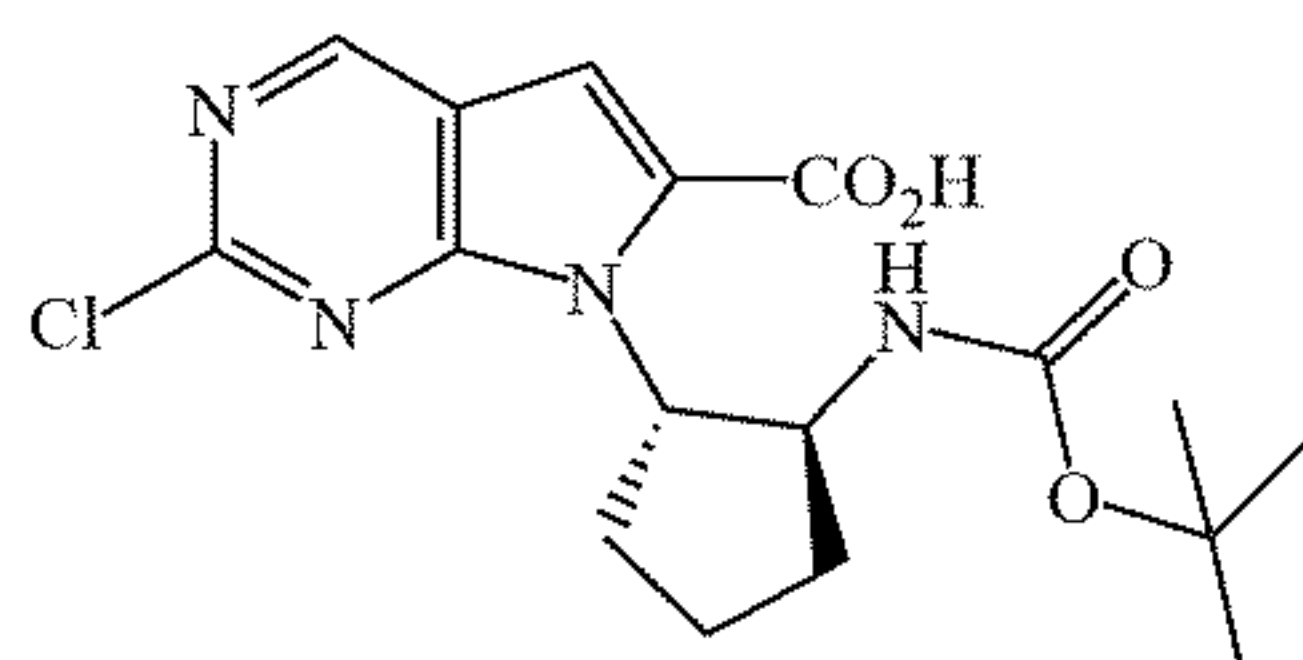
[0453] tert-butyl N-[(1S,2S)-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]carbamate was synthesized by treating tert-butyl N-[(1S,2S)-2-aminocyclopentyl]carbamate with 5-bromo-2,4-dichloro-pyrimidine using analogous reaction conditions as described for tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-3-methyl-butyl]carbamate. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.27 (s, 9 H) 1.42 - 1.54 (m, 2 H) 1.56 - 1.65 (m, 2 H) 1.80 - 1.88 (m, 1 H) 1.96 - 2.01 (m, 1 H) 3.88 - 3.96 (m, 1 H) 4.03 - 4.09 (m, 1 H) 6.91 (d, J=8.20 Hz, 1 H) 7.41 (d, J=7.32 Hz, 1 H) 8.18 (s, 1 H). LCMS (ESI) 391 (M + H).

[0454] tert-butyl N-[(1S,2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclopentyl]carbamate



[0455] tert-butyl N-[(1S,2S)-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclopentyl]carbamate was synthesized using similar experimental conditions to that used in the synthesis of (2S)-N2-[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]-4-methyl-pentane-1,2-diamine. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.13 (t, 6 H) 1.28 (s, 9 H) 1.42 - 1.52 (m, 2 H) 1.58 - 1.65 (m, 2 H) 1.81 - 1.90 (m, 1 H) 1.99 - 2.08 (m, 1 H) 3.49 - 3.60 (m, 2 H) 3.63 - 3.71 (m, 2 H) 3.84 - 3.93 (m, 1 H) 3.96 - 4.04 (m, 1 H) 5.53 (s, 1 H) 6.96 (d, J=7.90 Hz, 1 H) 7.34 (d, J=7.03 Hz, 1 H) 8.14 (s, 1 H). LCMS (ESI) 439 (M + H).

[0456] 7-[(1S,2S)-2-(tert-butoxycarbonylamino)cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid



[0457] 7-[(1S,2S)-2-(tert-butoxycarbonylamino)cyclopentyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using the analogous synthetic sequence as that described for 7-[1-[(tert-butoxycarbonylamino)methyl]-2-methyl-propyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.41 - 1.52 (m, 9 H) 1.55 - 1.68 (m, 1 H) 1.88 - 2.00 (m, 2 H) 2.05 - 2.15 (m, 1 H) 2.26 - 2.35 (m, 1 H) 2.71 -

2.89 (m, 1 H) 4.01 - 4.16 (m, 1 H) 4.28 - 4.45 (m, 1 H) 7.41 (s, 1 H) 9.11 (s, 1 H). LCMS (ESI) 381 (M + H).

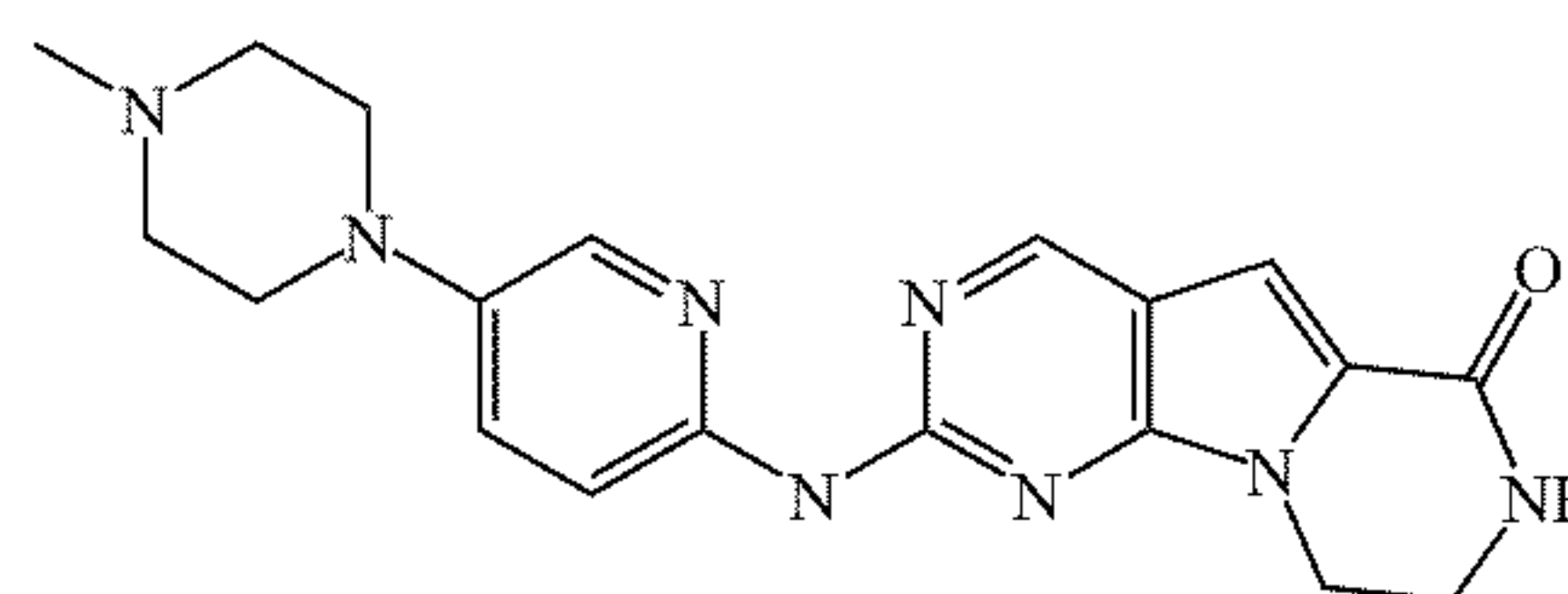
Compound 62

[0458] Compound 62 was synthesized using an analogous synthetic sequence as that described for Compound 44. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.48 - 1.60 (m, 1 H) 1.88 - 1.98 (m, 3 H) 1.99 - 2.08 (m, 1 H) 2.66 - 2.75 (m, 1 H) 3.63 - 3.74 (m, 1 H) 3.99 - 4.12 (m, 1 H) 7.21 (s, 1 H) 8.89 (s, 1 H) 9.04 (s, 1 H). LCMS (ESI) 263 (M + H).

Example 63

Synthesis of Compound 63

[0459]

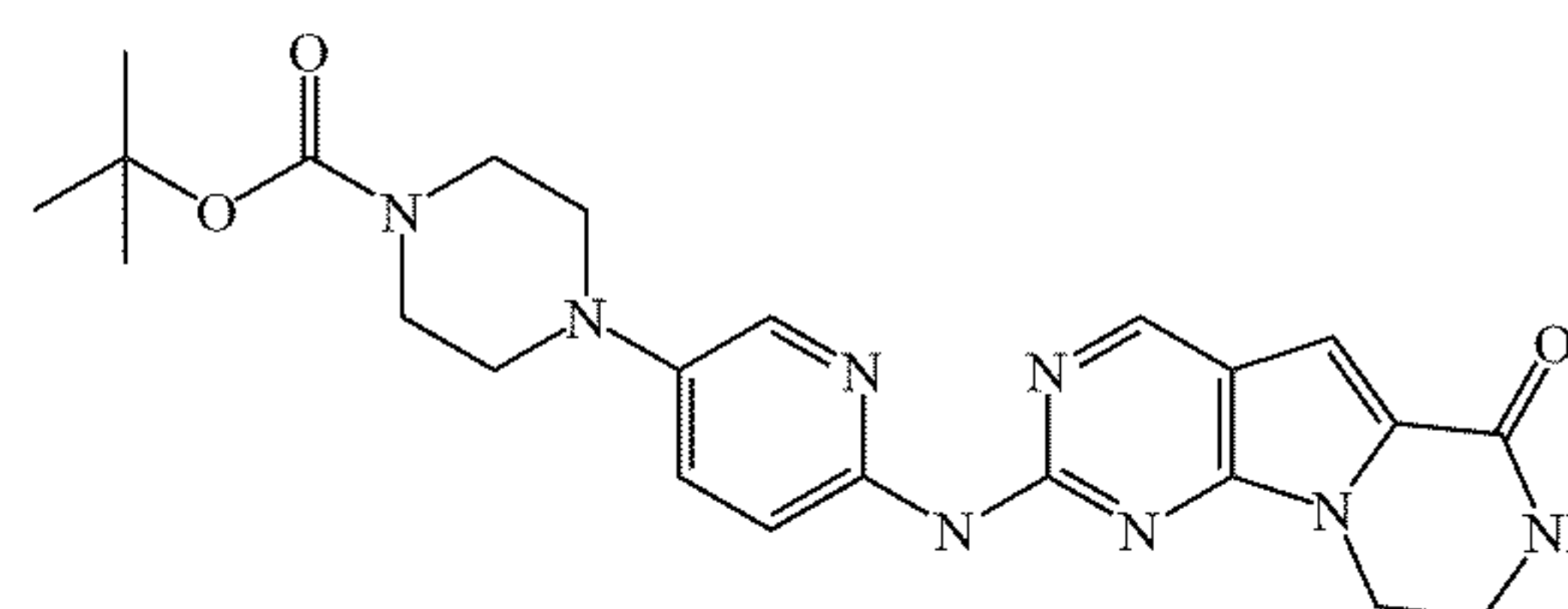


[0460] To chloro tricyclic lactam (0.050 g, 0.225 mmole) in dioxane (2.0 mL) under nitrogen was added 5-(4-methyl-piperazin-1-yl)pyridin-2-amine (0.052 g, 1.2 eq, 0.270 mmole) followed by the addition of Pd₂(dba)₃ (18.5 mg), BINAP (25 mg) and sodium-tert-butoxide (31 mg, 0.324 mmole). The contents of the flask are degassed for 10 minutes and then heated to 100 degrees for 12 hours. The crude reaction was loaded on a silica gel column and eluted with DCM/MeOH (0-15%) to afford the desired product (26 mg). To this compound dissolved in DCM/MeOH (10%) was added 3 N HCl in iso-propanol (2 eq) and the reaction was stirred overnight. Concentration under vacuum afforded the hydrochloride salt. ¹HNMR (d₆-DMSO) δ ppm 11.13 (brs, 1H), 9.07 (s, 1H), 8.42 (s, 1H), 8.03 (br m 1H), 7.99 (s, 1H), 7.67 (brm, 1H), 7.18 (s, 1H), 4.33 (m, 2H), 3.79 (m, 2H), 3.64 (m, 2H), 3.50 (m, 2H), 3.16 (m, 4H), 2.79 (s, 3H). LCMS (ESI) 379 (M + H).

Example 64

Synthesis of Compound 64

[0461]



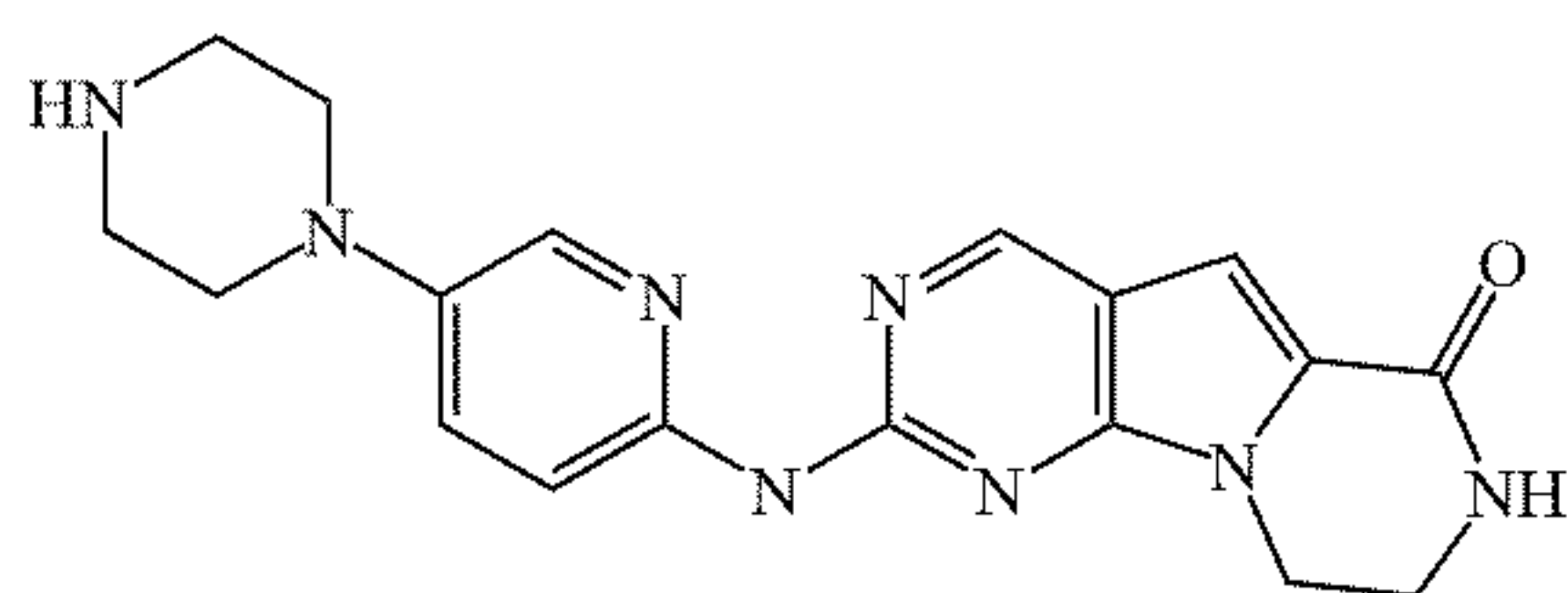
[0462] To chloro tricyclic lactam (0.075 g, 0.338 mmole) in dioxane (3.5 mL) under nitrogen was added tert-butyl 4-(6-amino-3-pyridyl)piperazine-1-carboxylate (0.098 g, 1.05 eq) followed by the addition of Pd₂(dba)₃ (27 mg), BINAP (36 mg) and sodium-tert-butoxide (45 mg). The contents were heated at reflux for 11 hrs. The crude reaction was loaded onto a silica gel column and eluted with DCM/

MeOH (0- 10%) to afford the desired product (32 mg). ¹HNMR (d6-DMSO) δ ppm 9.48 (s, 1H), 8.84 (s, 1H), 8.29 (s, 1H), 8.18 (s, 1H), 7.99 (s, 1H), 7.42 (m, 1H), 6.98 (s, 1H), 4.23 (m, 2H), 3.59 (m, 2H), 3.45 (m, 4H), 3.50 (m, 2H), 3.05 (m, 4H). LCMS (ESI) 465 (M + H).

Example 65

Synthesis of Compound 65

[0463]

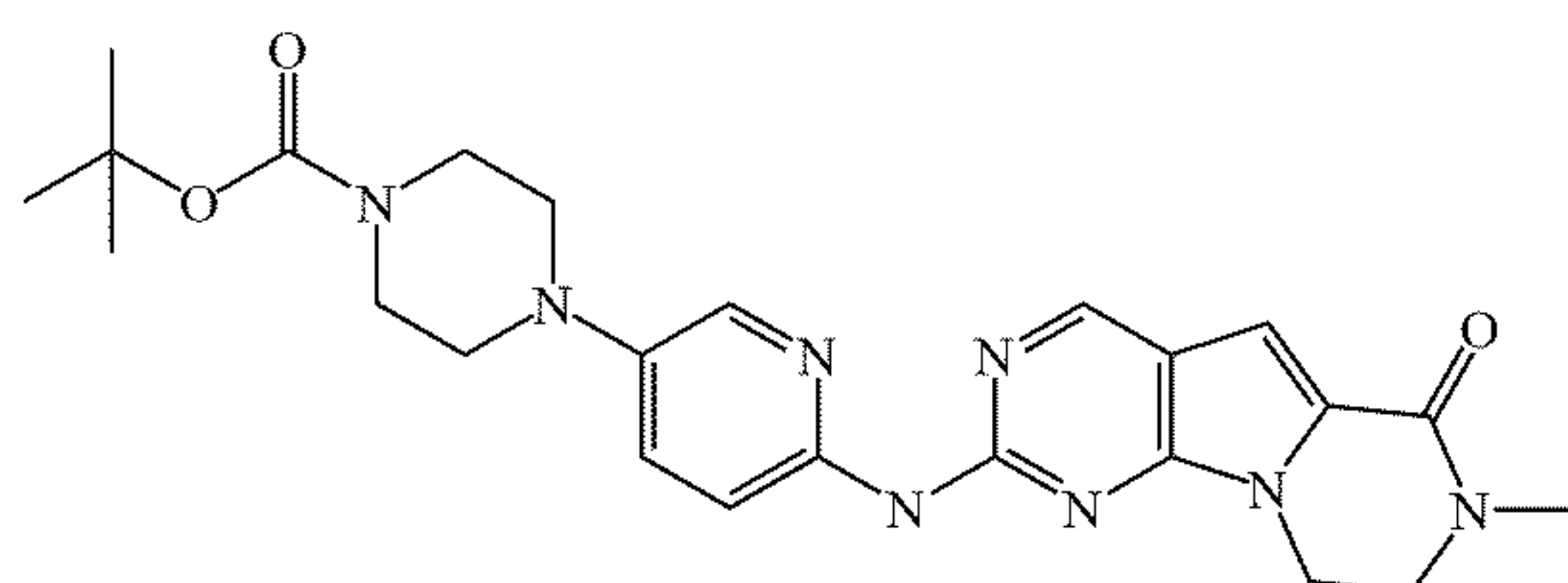


[0464] To a solution of Compound 64 (23 mg) in 10% DCM/MeOH was added 10 mL of a 3 M solution of HCl in iso-propanol. The contents were stirred for 16 hrs. Concentration of the reaction mixture afforded the hydrochloride salt. ¹HNMR (d6-DMSO) δ ppm 9.01 (s, 1H), 7.94 (m, 1H), 7.86 (m, 1H), 7.23 (s, 1H), 4.30 (m, 2H), 3.64 (m, 2H), 3.36 (m, 4H), 3.25 (m, 4H). LCMS (ESI) 465 (M + H).

Example 66

Synthesis of Compound 66

[0465]

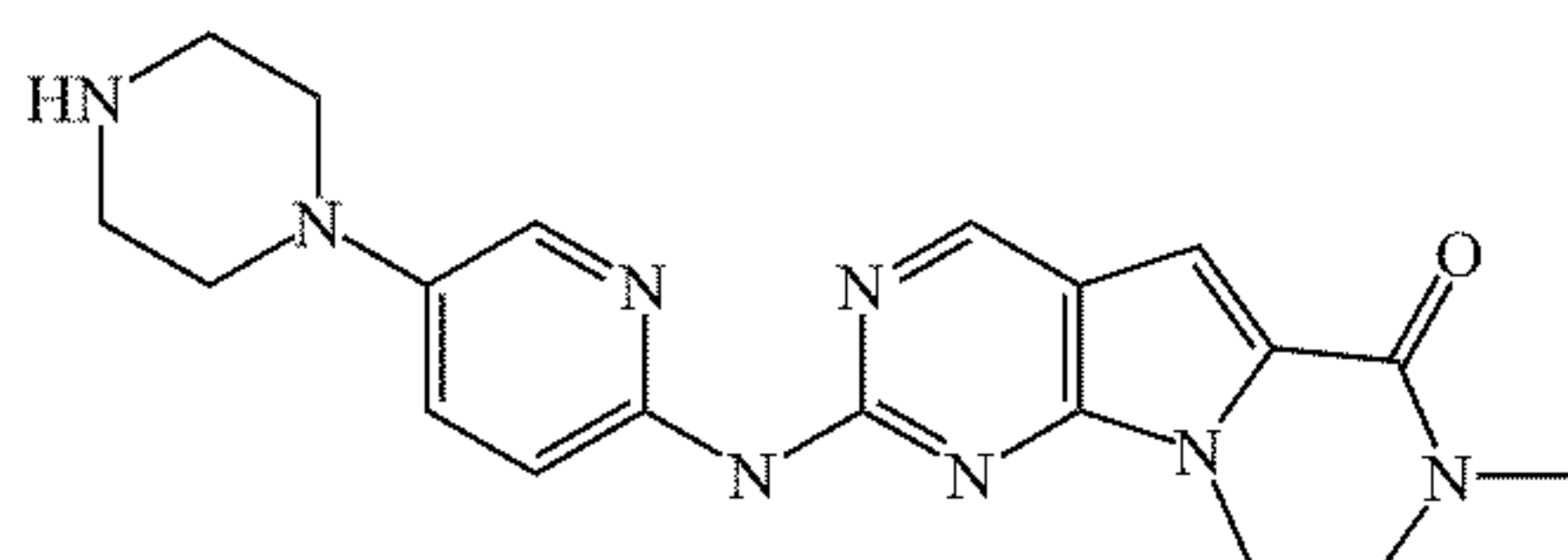


[0466] To chloro-N-methyltricyclic amide (0.080 g, 0.338 mmole) in dioxane (3.5 mL) under nitrogen was added tert-butyl 4-(6-amino-3-pyridyl)piperazine-1-carboxylate 0.102 g (1.1 eq) followed by the addition of Pd₂(dba)₃ (27 mg), BINAP (36 mg) and sodium-tert-butoxide (45 mg). The contents were heated at reflux for 11 hrs. The crude product was purified using silica gel column chromatography with an eluent of dichloromethane/methanol (0-5%) to afford the desired product (44 mg). ¹HNMR (d6-DMSO) δ ppm 9.49 (s, 1H), 8.85 (s, 1H), 8.32 (m, 1H), 8.02 (s, 1H), 7.44 (m, 1H), 7.00 (s, 1H), 4.33 (m, 2H), 3.80 (m, 2H), 3.48 (m, 4H), 3.07 (m, 4H), 3.05 (s, 3H), 1.42 (s, 9H). LCMS (ESI) 479 (M + H).

Example 67

Synthesis of Compound 67

[0467]

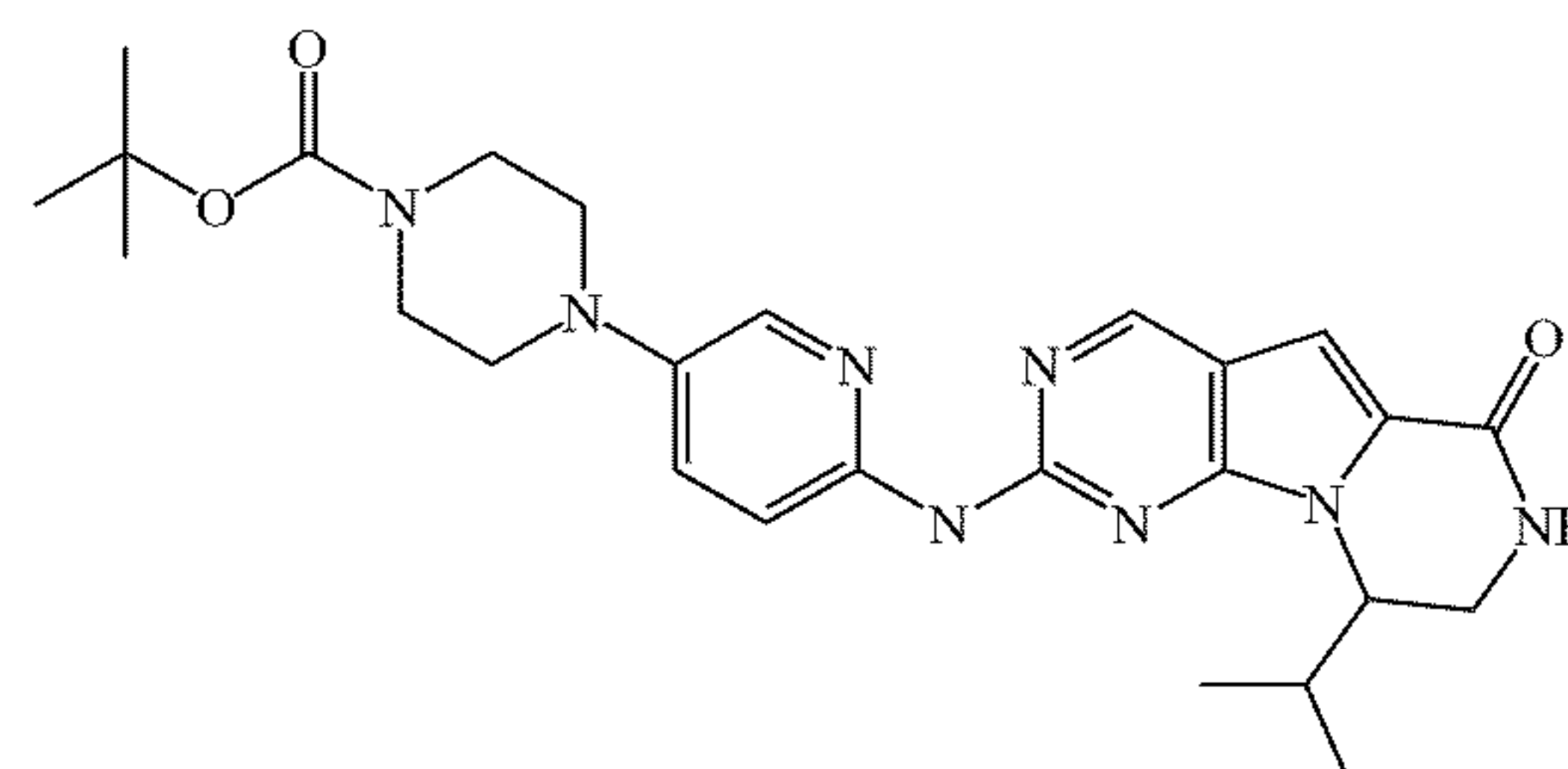


[0468] To Compound 66 (32 mg) was added 3 N HCL (10 mL) in isopropanol and the contents were stirred at room temperature overnight for 16 hrs. Concentration afforded the hydrochloride salt. ¹HNMR (d6-DMSO) δ ppm 9.13 (m, 2H), 8.11 (m, 1H), 8.10 (s, 1H), 7.62 (m, 1H), 7.21 (s, 1H), 4.43 (m, 2H), 3.85 (m, 2H), 3.41 (m, 4H), 3.28 (m, 4H), 3.08 (s, 3H). LCMS (ESI) 379 (M + H).

Example 68

Synthesis of Compound 68

[0469]

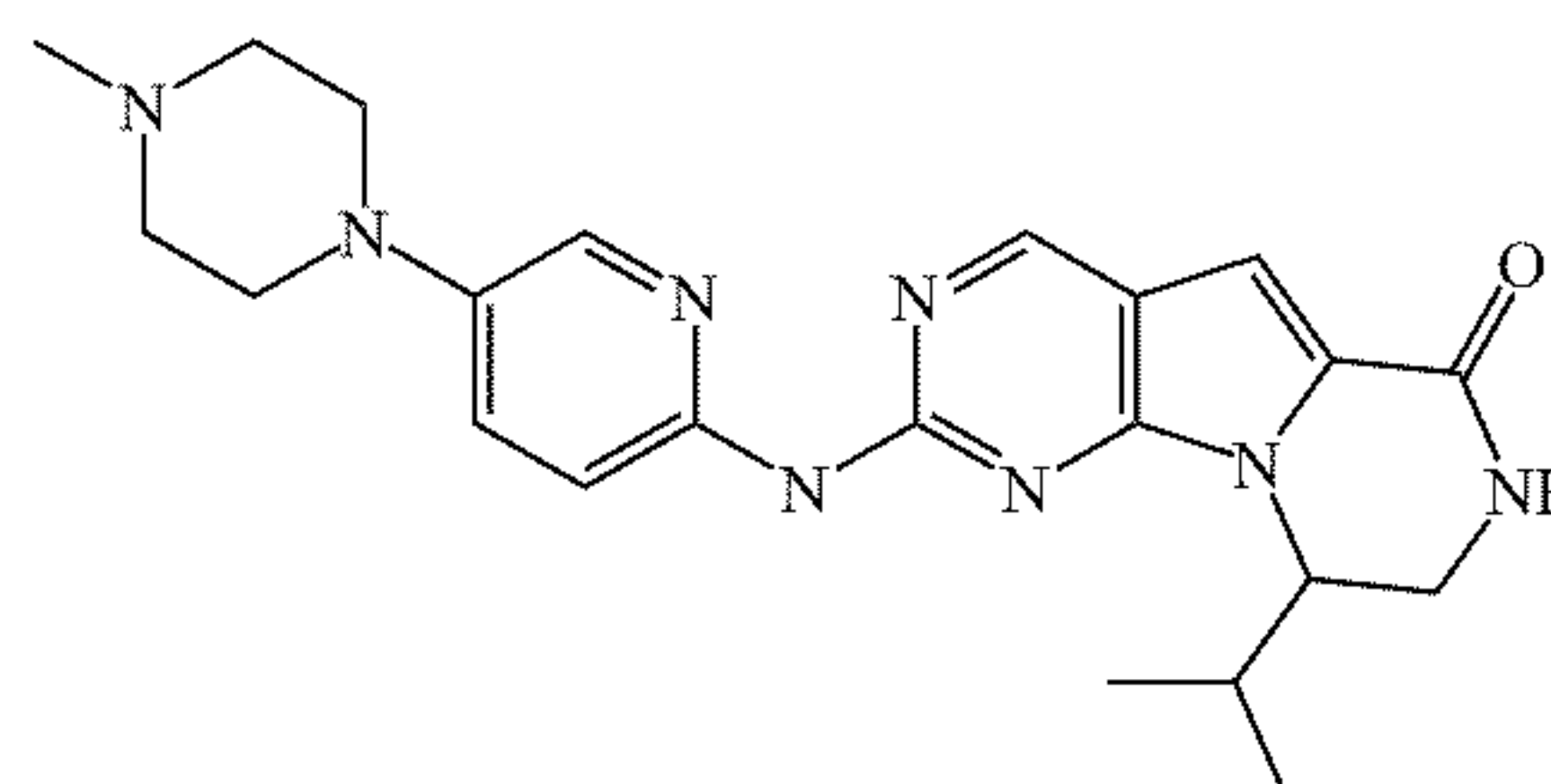


[0470] Compound 68 was synthesized using similar experimental conditions to that described for compound 64. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.79 (d, J=7.03 Hz, 3 H) 1.01 (d, J=6.73 Hz, 3 H) 1.35 - 1.48 (m, 9 H) 2.16 (dd, J=14.64, 6.73 Hz, 1 H) 3.00 - 3.14 (m, 4 H) 3.40 - 3.51 (m, 4 H) 3.51 - 3.60 (m, 1 H) 3.63 - 3.74 (m, 1 H) 4.44 (dd, J=7.90, 3.81 Hz, 1 H) 6.99 (s, 1 H) 7.46 (dd, J=8.93, 2.78 Hz, 1 H) 7.94 - 8.09 (m, 2 H) 8.31 (dd, J=9.08, 1.46 Hz, 1 H) 8.85 (s, 1 H) 9.46 (s, 1 H). LCMS (ESI) 507 (M + H).

Example 69

Synthesis of Compound 69

[0471]

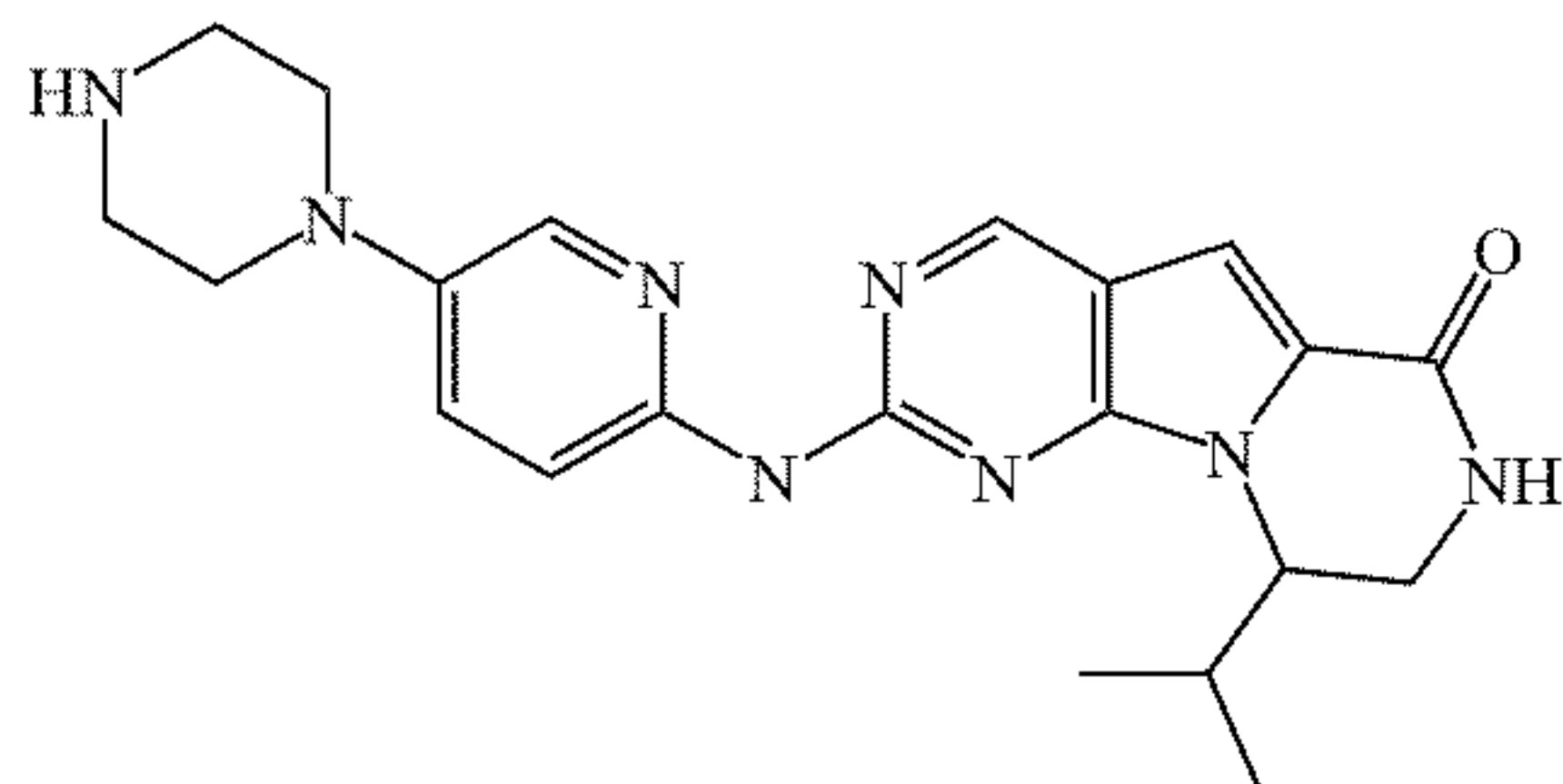


[0472] Compound 69 was synthesized using similar experimental conditions to those described for compound 63 and was recovered as an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.77 - 0.86 (m, 3 H) 0.96 (d, J=7.03 Hz, 3 H) 2.10 - 2.24 (m, 1 H) 3.07 (s, 3 H) 3.37 - 3.79 (m, 8 H) 4.00 (dd, J=13.61, 4.54 Hz, 2 H) 4.63 - 4.73 (m, 1 H) 7.20 (s, 1 H) 7.58 - 7.71 (m, 1 H) 7.99 (d, J=2.34 Hz, 1 H) 8.12 (d, J=9.37 Hz, 1 H) 9.11 (s, 1 H) 9.41 (br. s., 2 H) 11.76 (br. s., 1 H). LCMS (ESI) 421 (M + H).

Example 70

Synthesis of Compound 70

[0473]

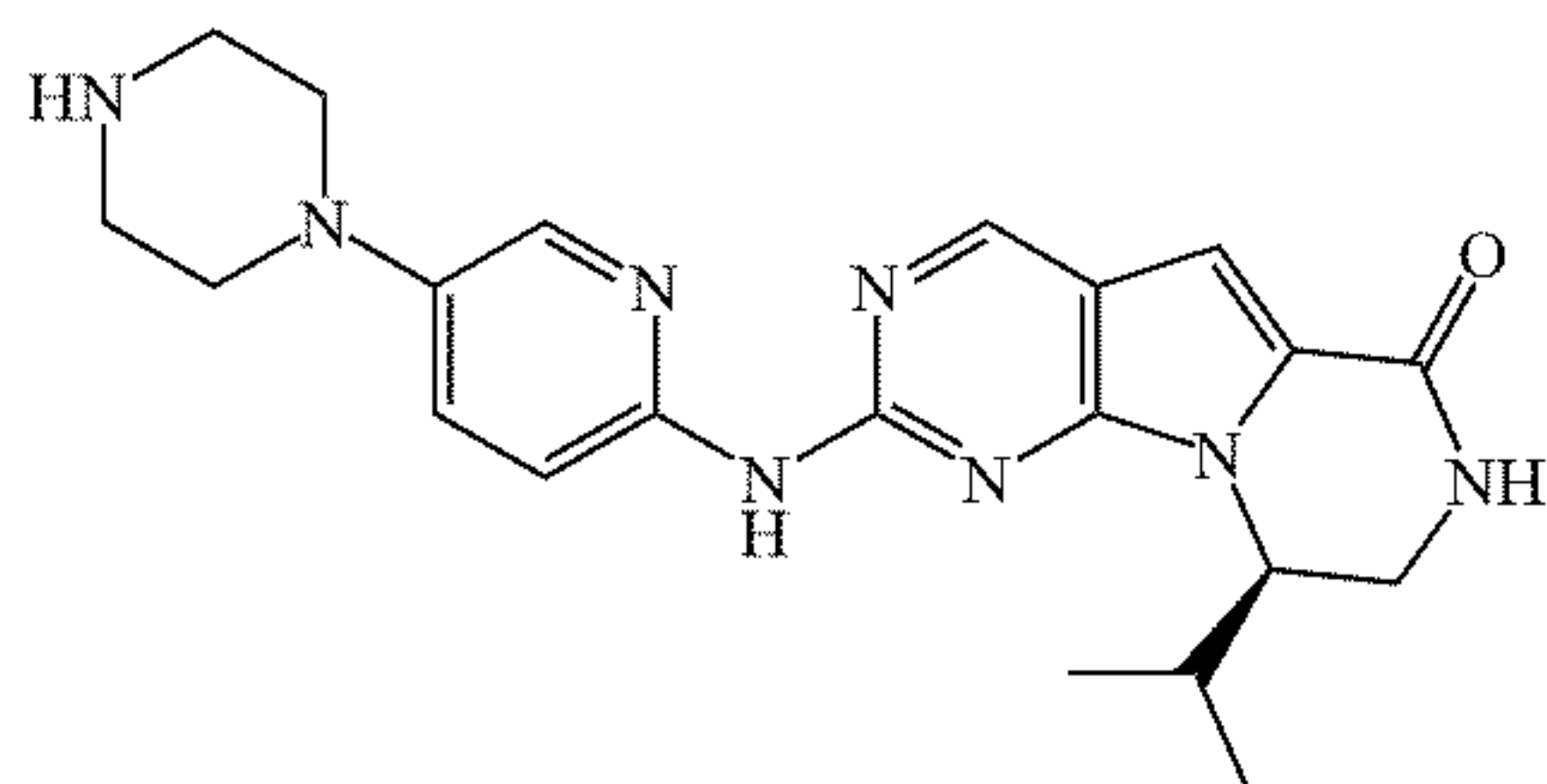


[0474] Compound 70 was synthesized using similar experimental conditions to those described for compounds 64 and 65 and was recovered as an HCl salt. The characterization data (NMR and LCMS) was consistent with that reported for compound 71 .

Example 71

Synthesis of Compound 71

[0475]

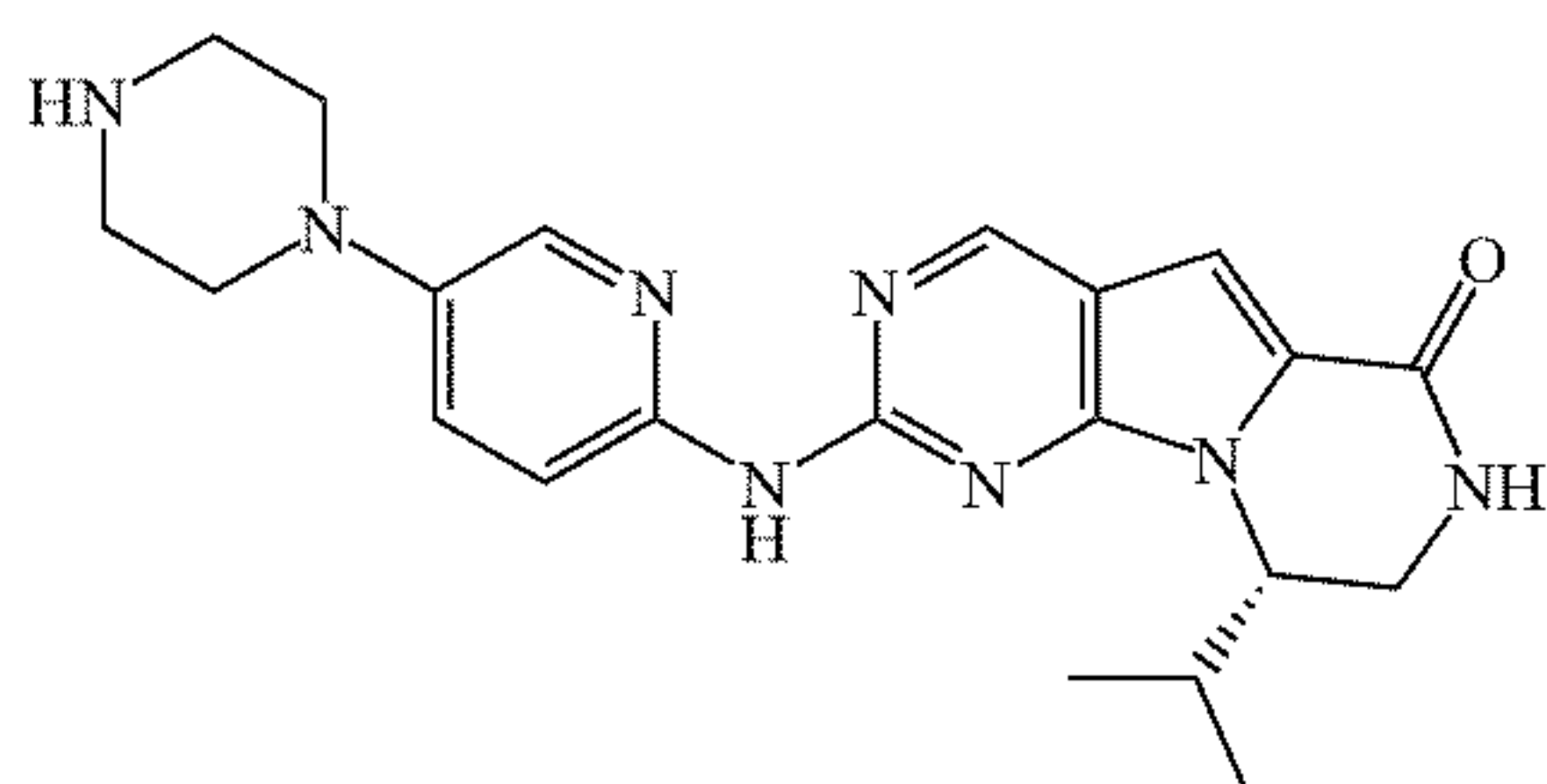


[0476] Compound 71 was synthesized using similar experimental conditions to those described for compounds 64 and 65 and was recovered as an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.79 (d, J=6.73 Hz, 3 H) 1.01 (d, J=6.73 Hz, 3 H) 2.18 (dd, J=14.49, 7.17 Hz, 1 H) 3.18 -3.84 (m, 10 H) 4.53 - 4.71 (m, 1 H) 7.24 (s, 1 H) 7.65 (d, J=9.37 Hz, 1 H) 8.01 (d, J=2.64 Hz, 1 H) 8.14 (d, J=1.46 Hz, 1 H) 8.35 (d, J=5.27 Hz, 1 H) 9.14 (s, 1 H) 9.46 (s, 2 H) 11.80 (s, 1 H) LCMS (ESI) 407 (M+H).

Example 72

Synthesis of Compound 72 (Compound UUU)

[0477]



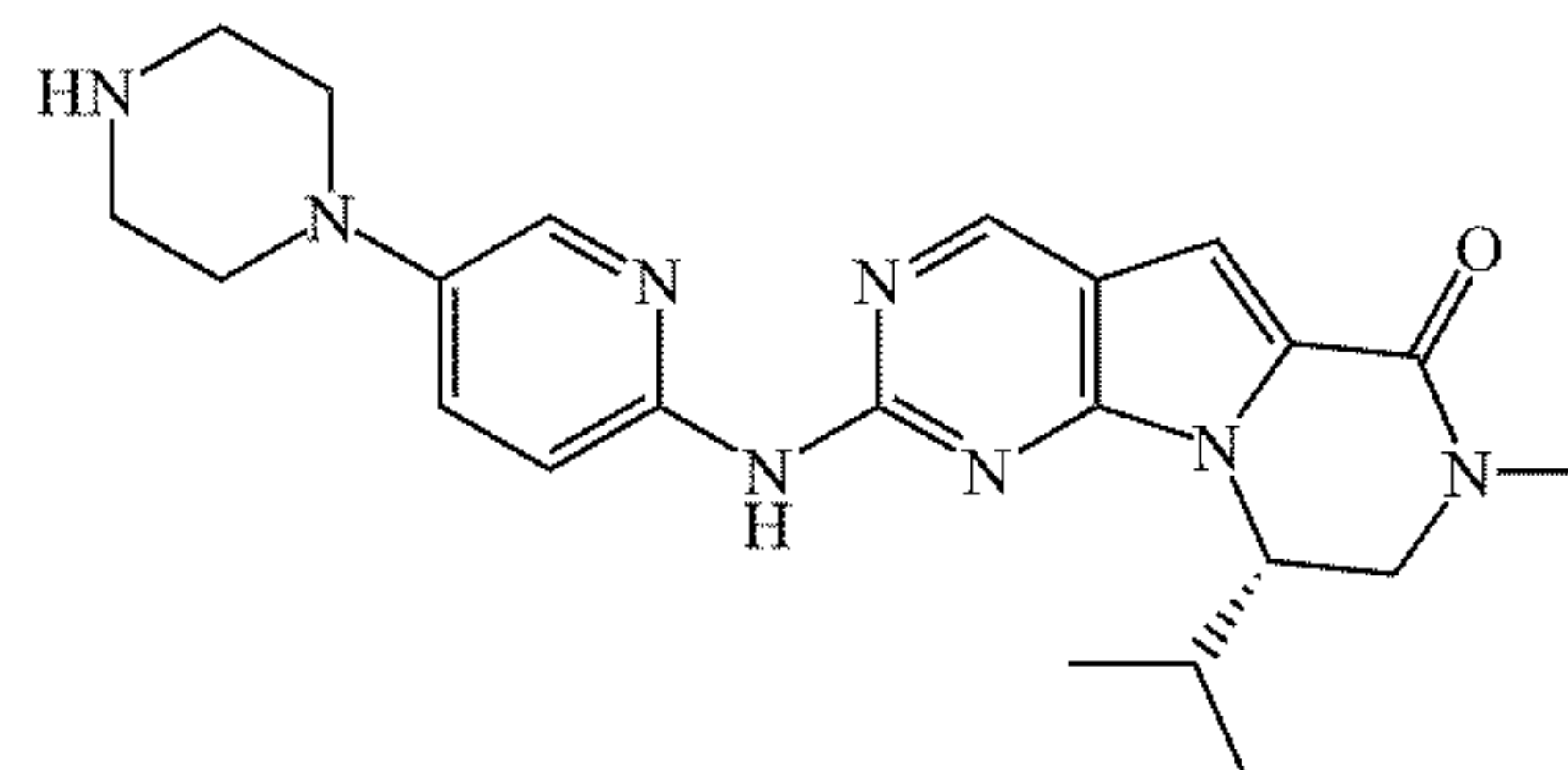
[0478] Compound 72 was synthesized using similar experimental conditions to that described for compounds 64 and 65 and was recovered as an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.77 (d, J=7.03 Hz, 3 H) 0.99 (d, J=6.73 Hz, 3 H) 2.10 - 2.24 (m, 1 H) 3.18 - 3.81 (m, 10 H) 4.54 - 4.69 (m, 1 H) 7.22 (s, 1 H) 7.63 (d, J=9.08 Hz, 1 H) 7.99 (d, J=2.63 Hz, 1 H) 8.11 (s, 1 H)

8.33 (d, J=5.27 Hz, 1 H) 9.12 (s, 1 H) 9.43 (s, 2 H) 11.77 (s, 1 H). LCMS (ESI) 407 (M+H).

Example 73

Synthesis of Compound 73

[0479]

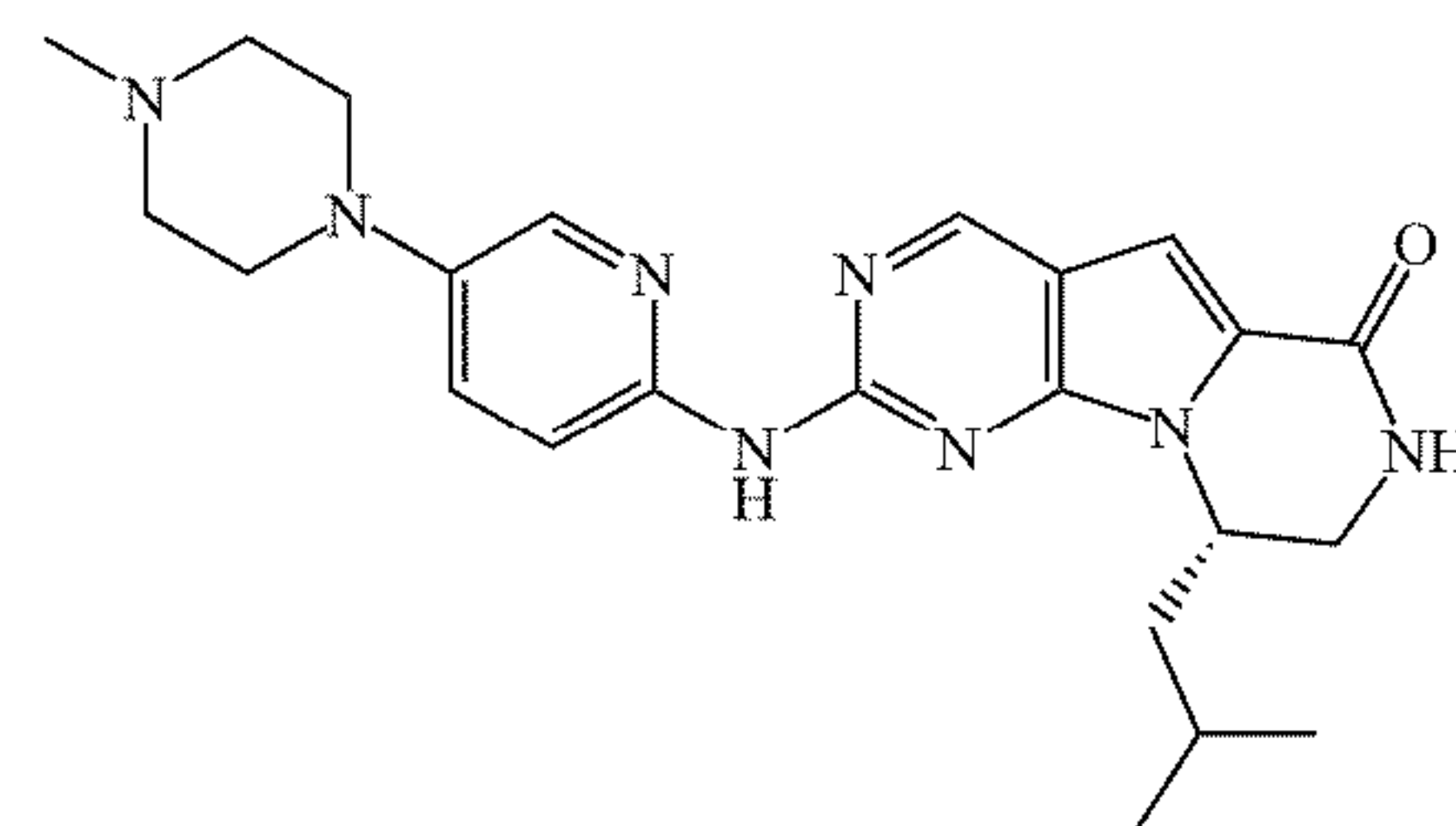


[0480] Compound 73 was synthesized using similar experimental conditions to those described for compounds 64 and 65 and was recovered as an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.84 (d, J=6.73 Hz, 3 H) 0.98 (d, J=6.73 Hz, 3 H) 2.12 - 2.26 (m, 1 H) 3.09 (s, 3 H) 3.22 -3.81 (m, 8 H) 4.01 (dd, J=13.61, 4.25 Hz, 2 H) 4.59 - 4.72 (m, 1 H) 7.19 (s, 1 H) 7.74 (s, 1 H) 7.96 - 8.10 (m, 2 H) 9.08 (s, 1 H) 9.22 (s, 2 H). LCMS (ESI) 421 (M+H).

Example 74

Synthesis of Compound 74

[0481]

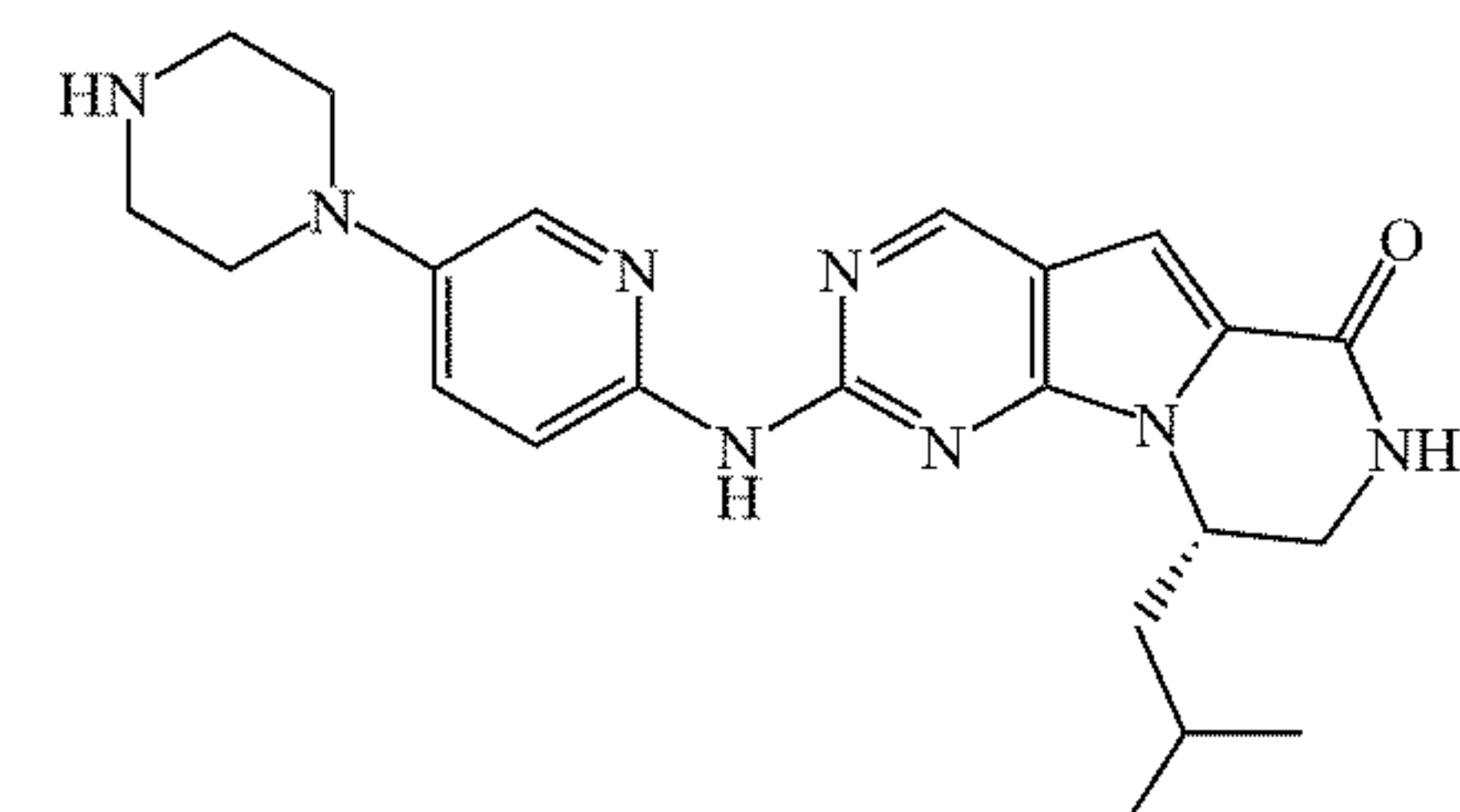


[0482] Compound 74 was synthesized using similar experimental conditions to those described for compound 63 and was recovered as an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.85 (d, J=4.98 Hz, 3 H) 0.95 (d, J=4.98 Hz, 3 H) 1.42 - 1.70 (m, 3 H) 2.77 (d, J=2.93 Hz, 3 H) 3.07 -4.14 (m, 10 H) 4.95 (s, 1 H) 7.20 (s, 1 H) 7.66 (d, J=9.66 Hz, 1 H) 7.94 (s, 1 H) 8.08 - 8.16 (m, 1 H) 8.33 (d, J=4.68 Hz, 1 H) 9.09 (s, 1 H) 11.38 (s, 1 H) 11.71 (s, 1 H). LCMS (ESI) 435 (M+H).

Example 75

Synthesis of Compound 75

[0483]

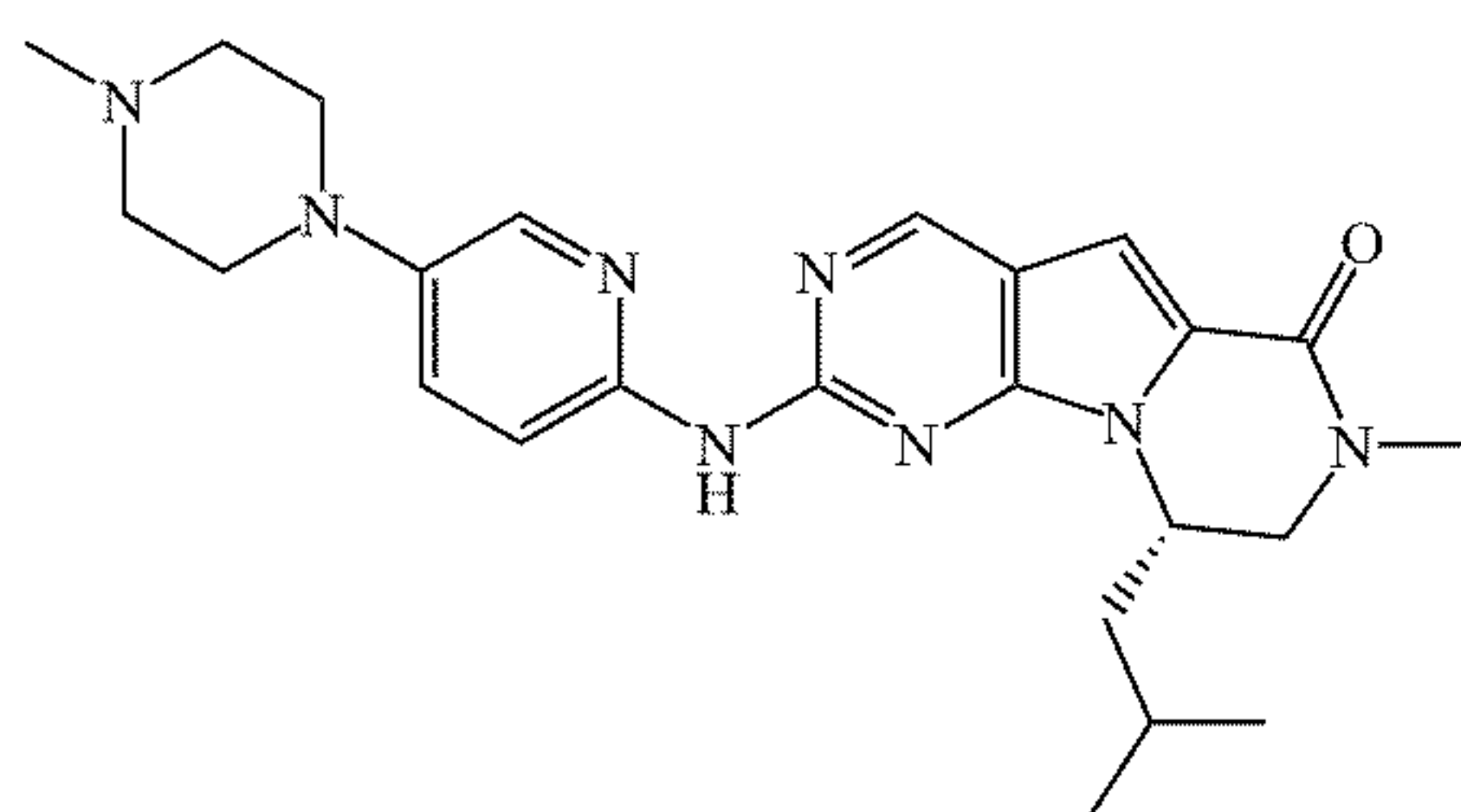


[0484] Compound 75 was synthesized using similar experimental conditions to those described for compounds 64 and 65 and was recovered as an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.87 (d, J=6.15 Hz, 3 H) 0.94 (d, J=6.15 Hz, 3 H) 1.57 (d, J=84.61 Hz, 3 H) 3.05 (s, 3 H) 3.13 - 3.55 (m, 8 H) 3.69 (d, J=78.17 Hz, 2 H) 4.90 (s, 1 H) 7.15 (s, 1 H) 7.63 - 7.85 (m, 1 H) 7.93 (s, 1 H) 8.26 (s, 1 H) 9.03 (s, 1 H) 9.20 (s, 2 H). LCMS (ESI) 421 (M+H).

Example 76

Synthesis of Compound 76

[0485]

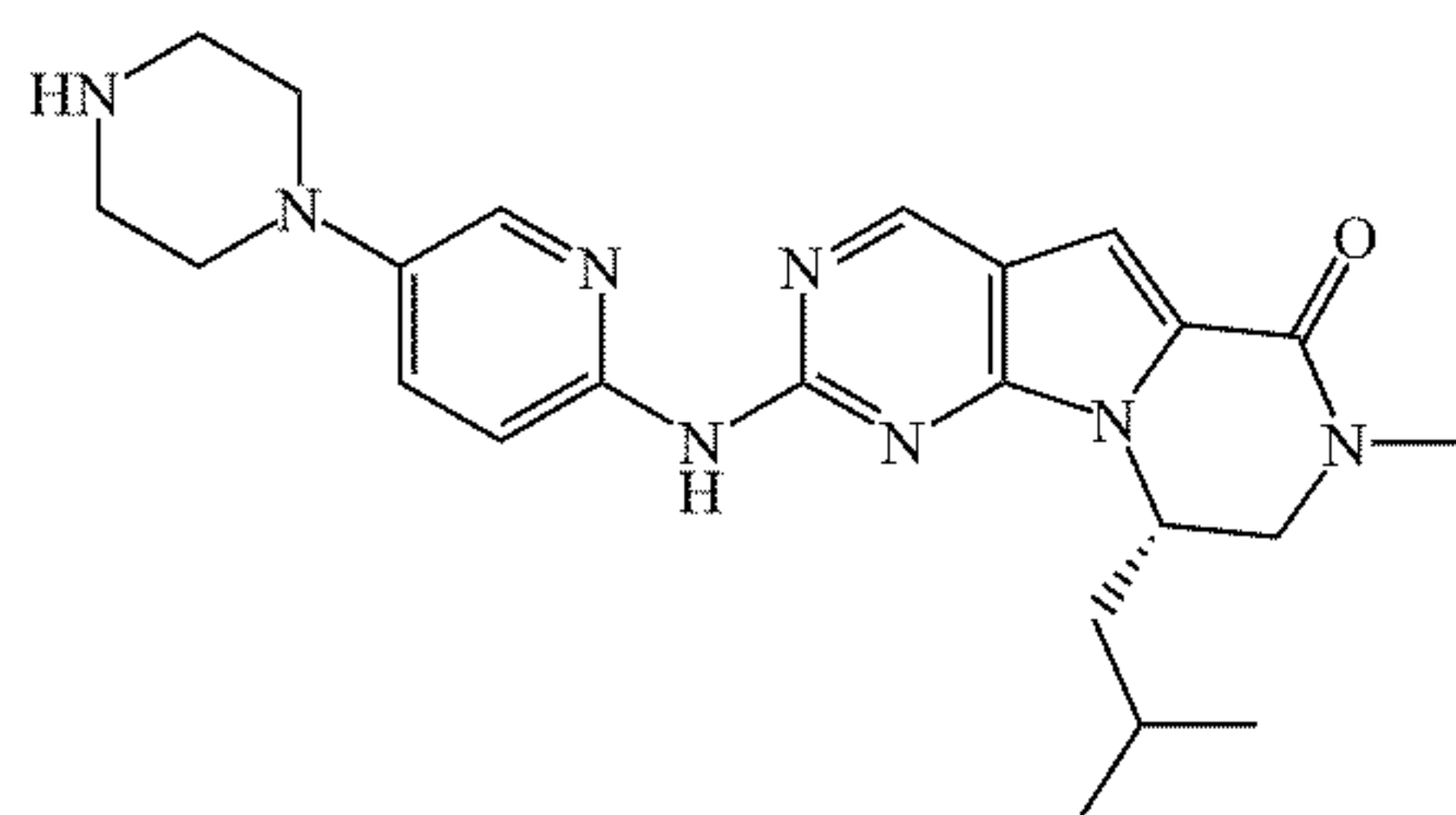


[0486] Compound 76 was synthesized using similar experimental conditions to those described for compound 63 and was recovered as an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.85 (d, J=6.44 Hz, 3 H) 0.95 (d, J=6.44 Hz, 3 H) 1.43 - 1.70 (m, 3 H) 2.78 (d, J=2.93 Hz, 3 H) 3.05 (s, 3 H) 3.24 - 3.84 (m, 8 H) 4.01 (d, J=9.66 Hz, 2 H) 4.89 - 5.01 (m, 1 H) 7.15 (s, 1 H) 7.77 (s, 1 H) 7.91 - 8.05 (m, 2 H) 9.03 (s, 1 H) 10.96 - 11.55 (m, 2 H). LCMS (ESI) 449 (M+H).

Example 77

Synthesis of Compound 77

[0487]

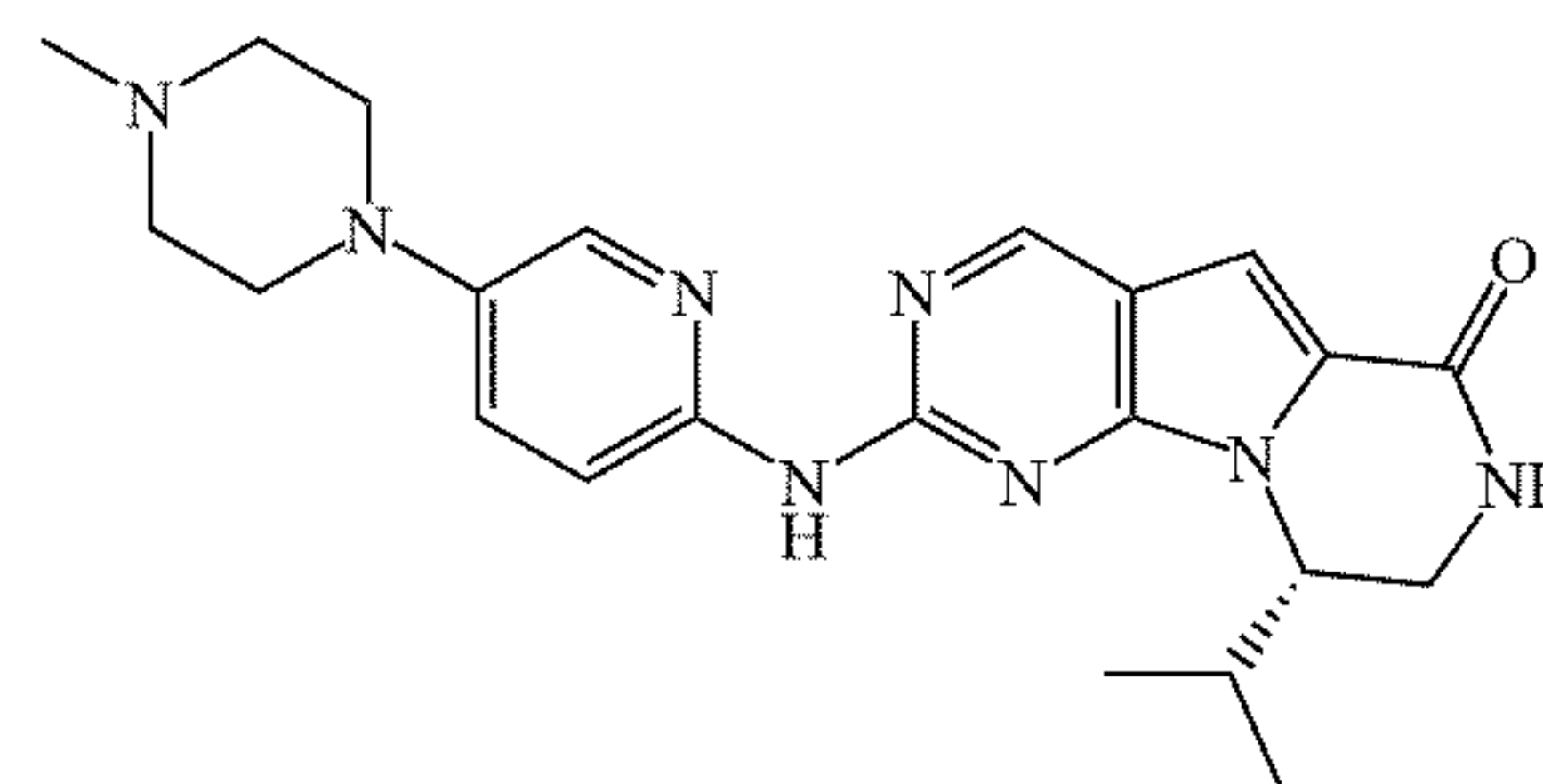


[0488] Compound 77 was synthesized using similar experimental conditions to those described for compounds 64 and 65 and was recovered as an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.83 - 0.88 (d, J=6.15 Hz, 3 H) 0.95 (d, J=6.15 Hz, 3 H) 1.40 - 1.71 (m, 3 H) 3.28 - 3.83 (m, 8 H) 4.00 (d, J=3.22 Hz, 2 H) 4.91 - 5.08 (m, 1 H) 7.17 (s, 1 H) 7.68 (d, J=9.66 Hz, 1 H) 7.93 (s, 1 H) 8.07 (s, 1 H) 9.06 (s, 1 H) 9.40 (s, 2 H) 11.59 (s, 1 H). LCMS (ESI) 435 (M+H).

Example 78

Synthesis of Compound 78

[0489]

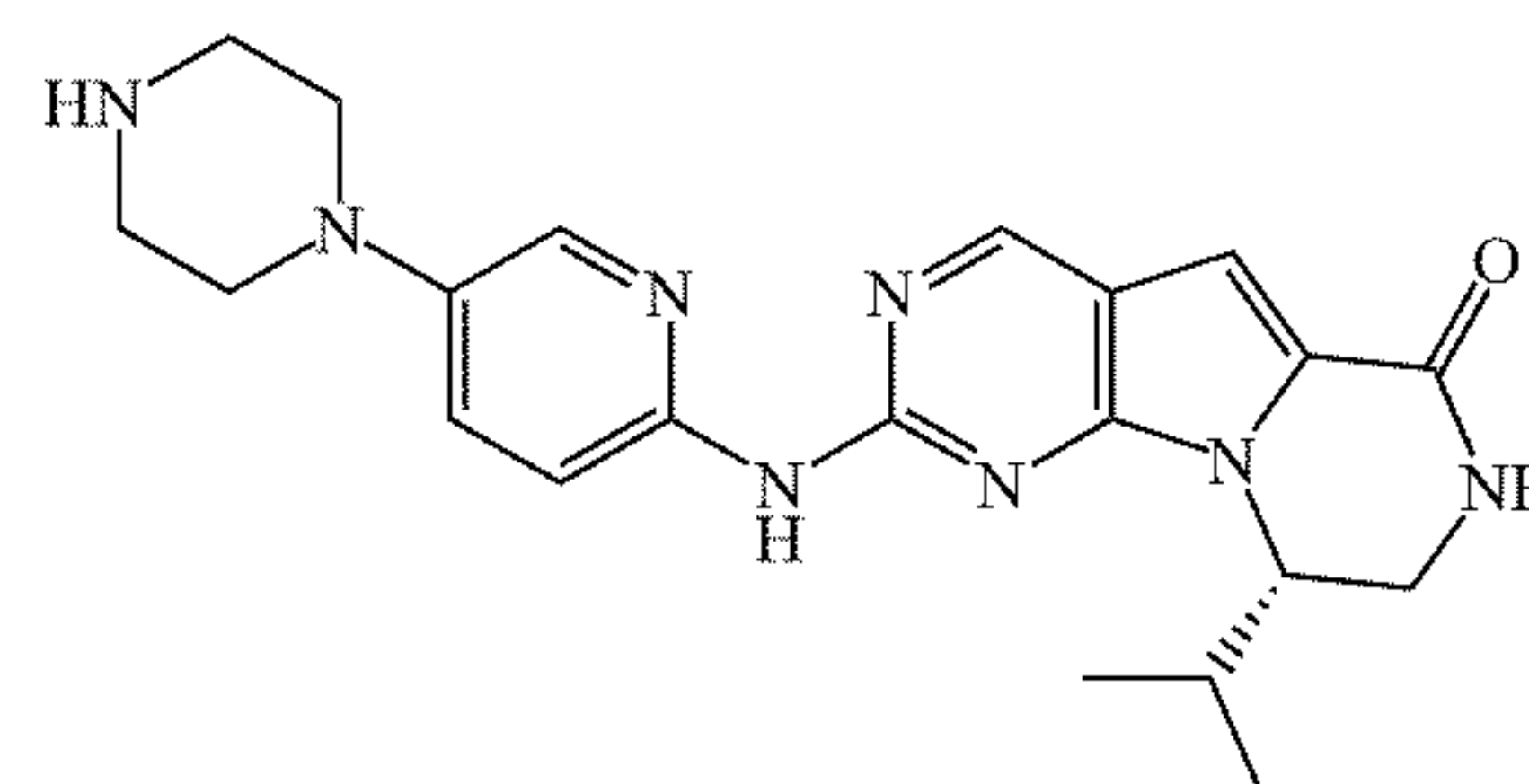


[0490] To Compound 50 0.060 g (0.205 mmole) was added 5-(4-methylpiperazin-1-yl)pyridin-2-amine (35.42 mg, 0.9 eq) followed by the addition of 1,4-dioxane (3 mL). After degassing with nitrogen, Pd₂dba₃ (12 mg), BINAP (16 mg) and sodium tert-butoxide (24 mg) were added. The contents were then heated at 90 degrees in a CEM Discovery microwave for 3 hrs. The reaction was then loaded onto a silica gel column and purified by eluting with DCM/MeOH (0- 15%). ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.75 (t, J=7.47 Hz, 3 H) 0.91 (d, J=6.73 Hz, 3 H) 1.04 - 1.20 (m, 2 H) 1.80 - 1.98 (m, 1 H) 2.77 (d, J=3.81 Hz, 3 H) 2.94 - 3.90 (m, 10 H) 4.54 - 4.68 (m, 1 H) 7.06 - 7.23 (m, 2 H) 7.56 - 7.75 (m, 1 H) 7.90 - 8.12 (m, 2 H) 8.29 (s, 1 H) 9.07 (s, 1 H) 10.98 - 11.74 (m, 2 H). LCMS (ESI) 435 (M + H).

Example 79

Synthesis of Compound 79

[0491]

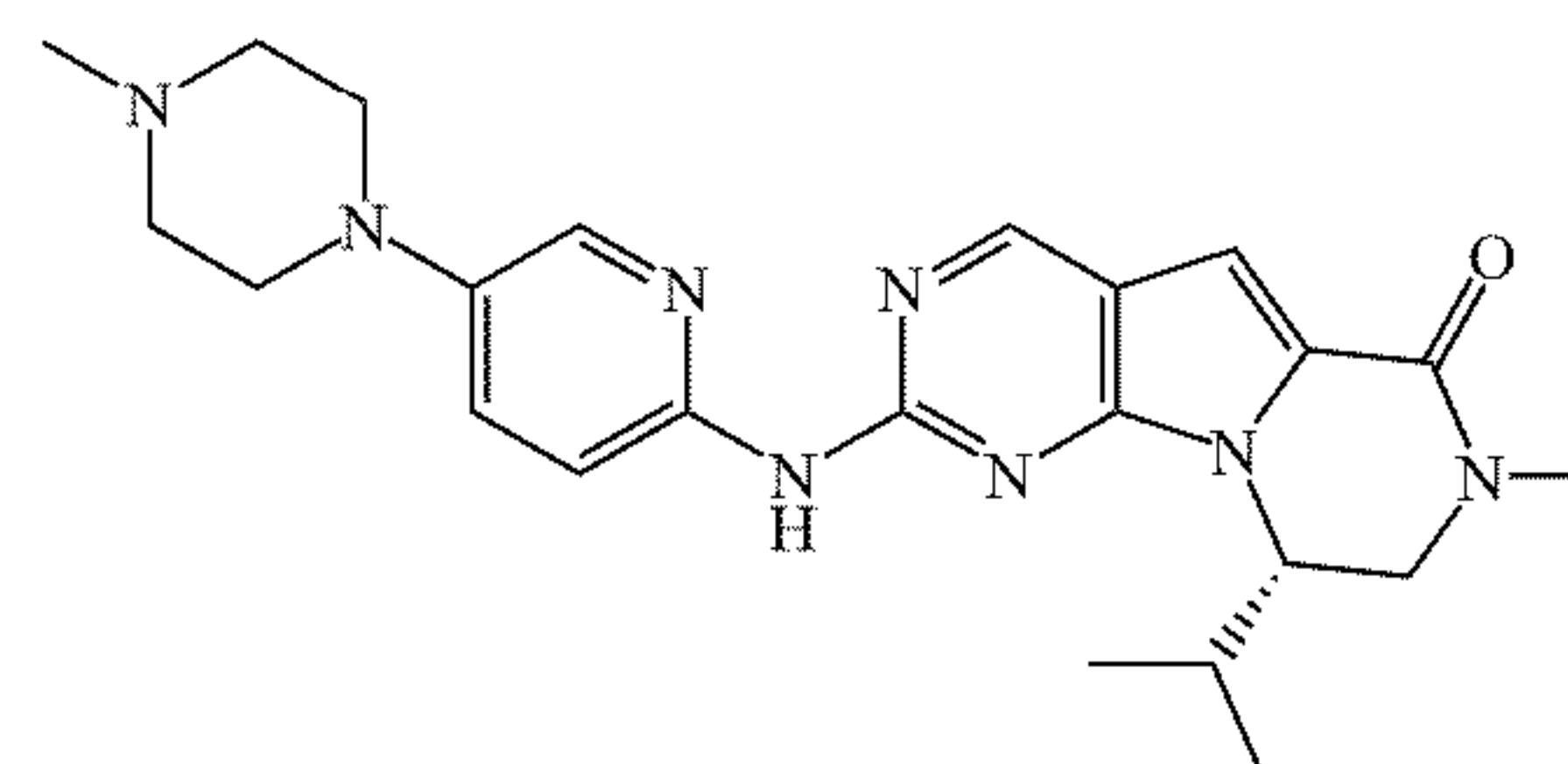


[0492] Compound 79 was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.75 (t, J=7.32 Hz, 3 H) 0.90 (d, J=6.73 Hz, 3 H) 1.07 - 1.15 (m, 2H) 1.85 - 1.94 (m, 1 H) 3.17 - 3.75 (m, 10 H) 4.58 - 4.67 (m, 1 H) 7.17 (s, 1 H) 7.71 (s, 1 H) 7.96 (s, 1 H) 7.98 - 8.05 (m, 1 H) 8.28 (d, J=4.10 Hz, 1 H) 9.06 (s, 1 H) 9.39 (s, 2 H). LCMS (ESI) 421 (M+H).

Example 80

Synthesis of Compound 80

[0493]



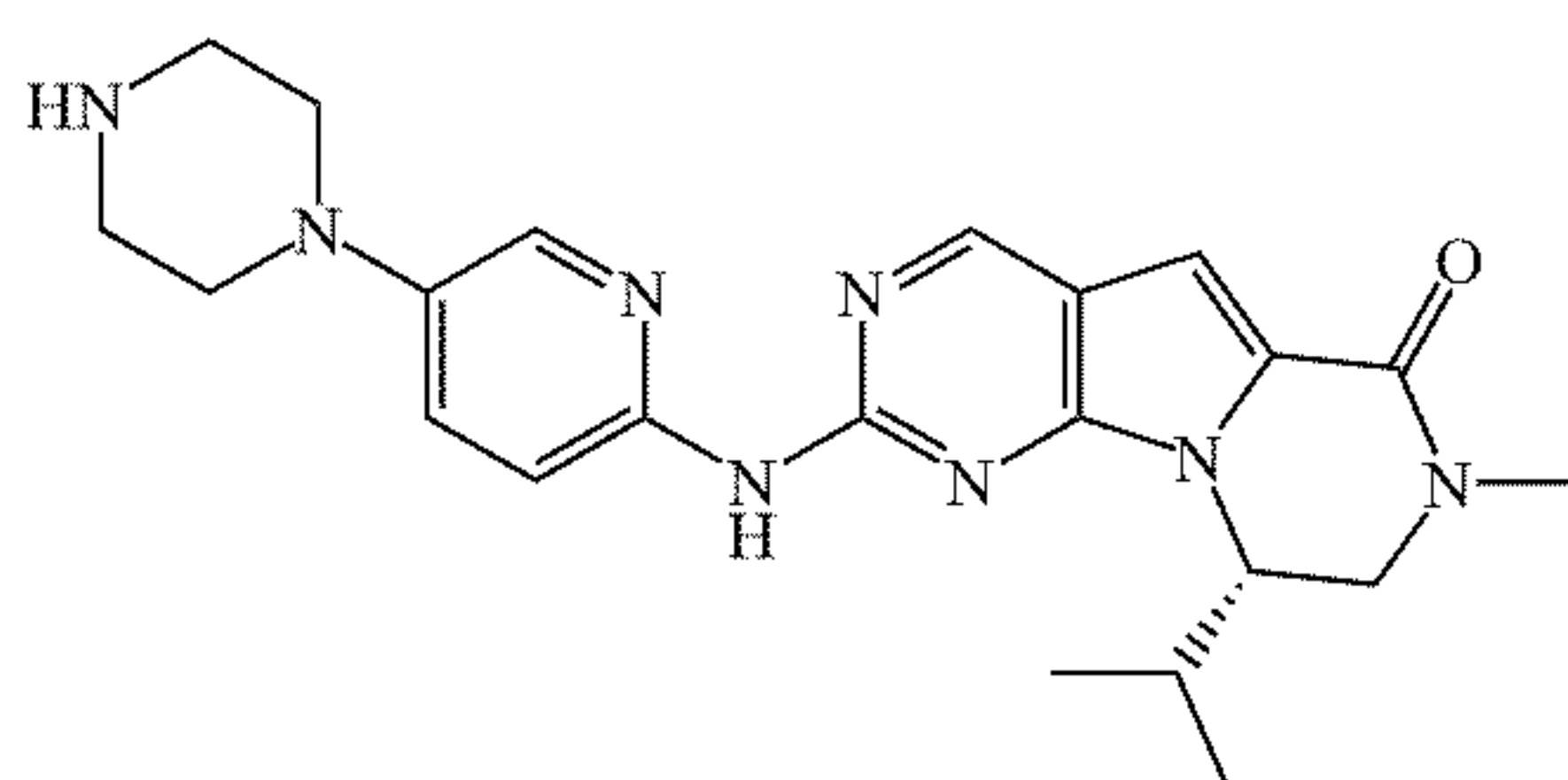
[0494] Compound 80 was synthesized in a similar manner to that described for compound 78. ¹HNMR (600 MHz,

DMSO- d_6) δ ppm 0.78 (t, $J=7.32$ Hz, 3 H) 0.86 (d, $J=6.73$ Hz, 3 H) 1.13 - 1.21 (m, 2 H) 1.84 - 1.96 (m, 1 H) 2.77 (d, $J=4.39$ Hz, 3 H) 3.04 (s, 3 H) 3.11 - 3.84 (m, 8 H) 3.98 (dd, $J=13.61, 4.25$ Hz, 2 H) 4.66 - 4.74 (m, 1 H) 7.17 (s, 1 H) 7.64 (s, 1 H) 7.96 (d, $J=2.34$ Hz, 1 H) 8.03 - 8.13 (m, 1 H) 9.08 (s, 1 H) 11.26 (s, 1 H) 11.66 (s, 1 H). LCMS (ESI) 449 (M+H).

Example 81

Synthesis of Compound 81

[0495]

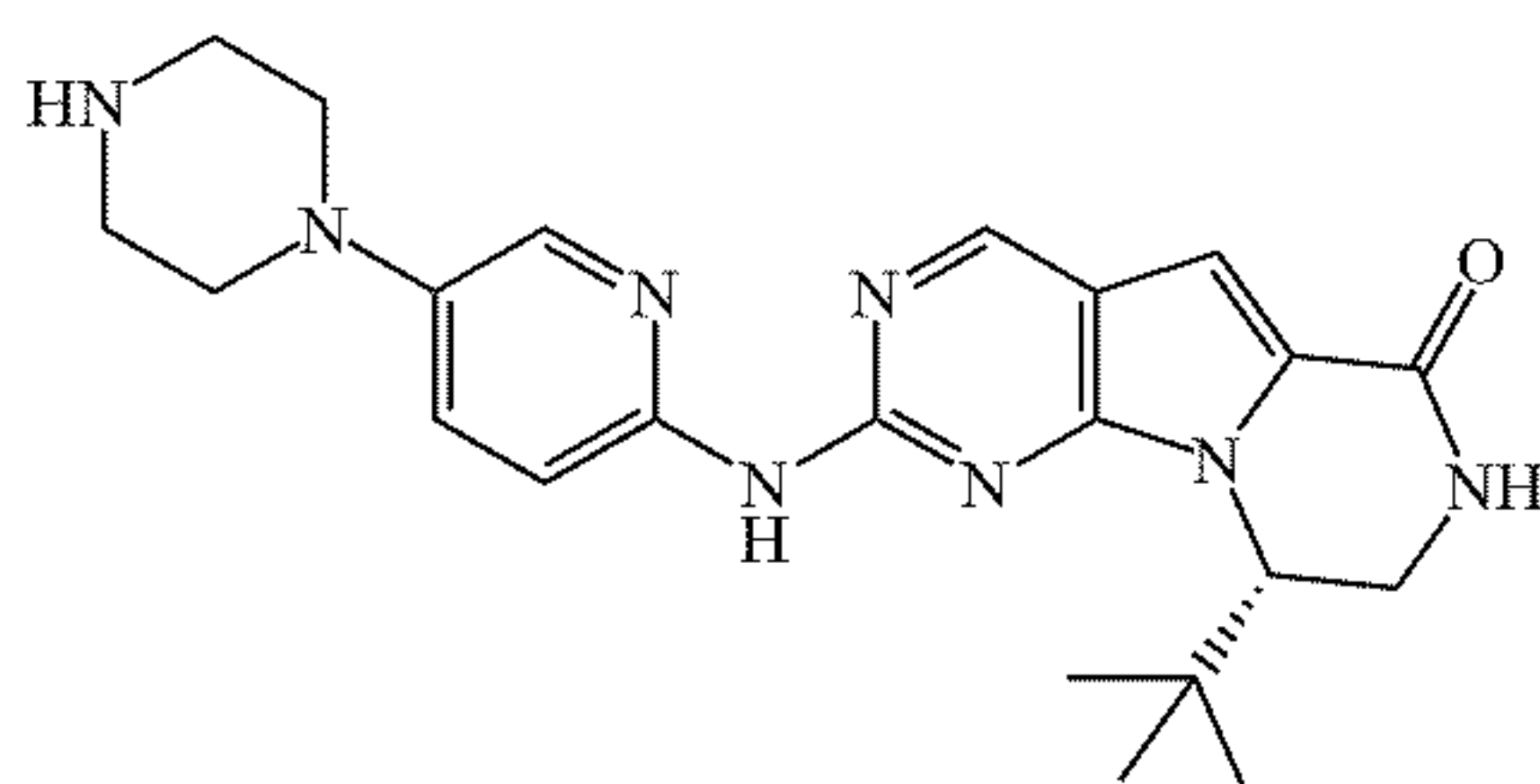


[0496] The compound was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HCl salt. ^1H NMR (600 MHz, DMSO- d_6) δ ppm 0.78 (t, $J=7.32$ Hz, 3 H) 0.85 (d, $J=6.73$ Hz, 3 H) 1.10 - 1.27 (m, 2 H) 1.82 - 1.99 (m, 1 H) 3.04 (s, 3 H) 3.28 - 3.77 (m, 8 H) 3.97 (dd, $J=13.91, 4.54$ Hz, 2 H) 4.62 - 4.75 (m, 1 H) 7.07 - 7.24 (m, 1 H) 7.62 - 7.75 (m, 1 H) 7.94 (d, $J=2.34$ Hz, 1 H) 7.97 - 8.08 (m, 1 H) 9.05 (s, 1 H) 9.29 (s, 2 H). LCMS (ESI) 435 (M+H).

Example 82

Synthesis of Compound 82

[0497]

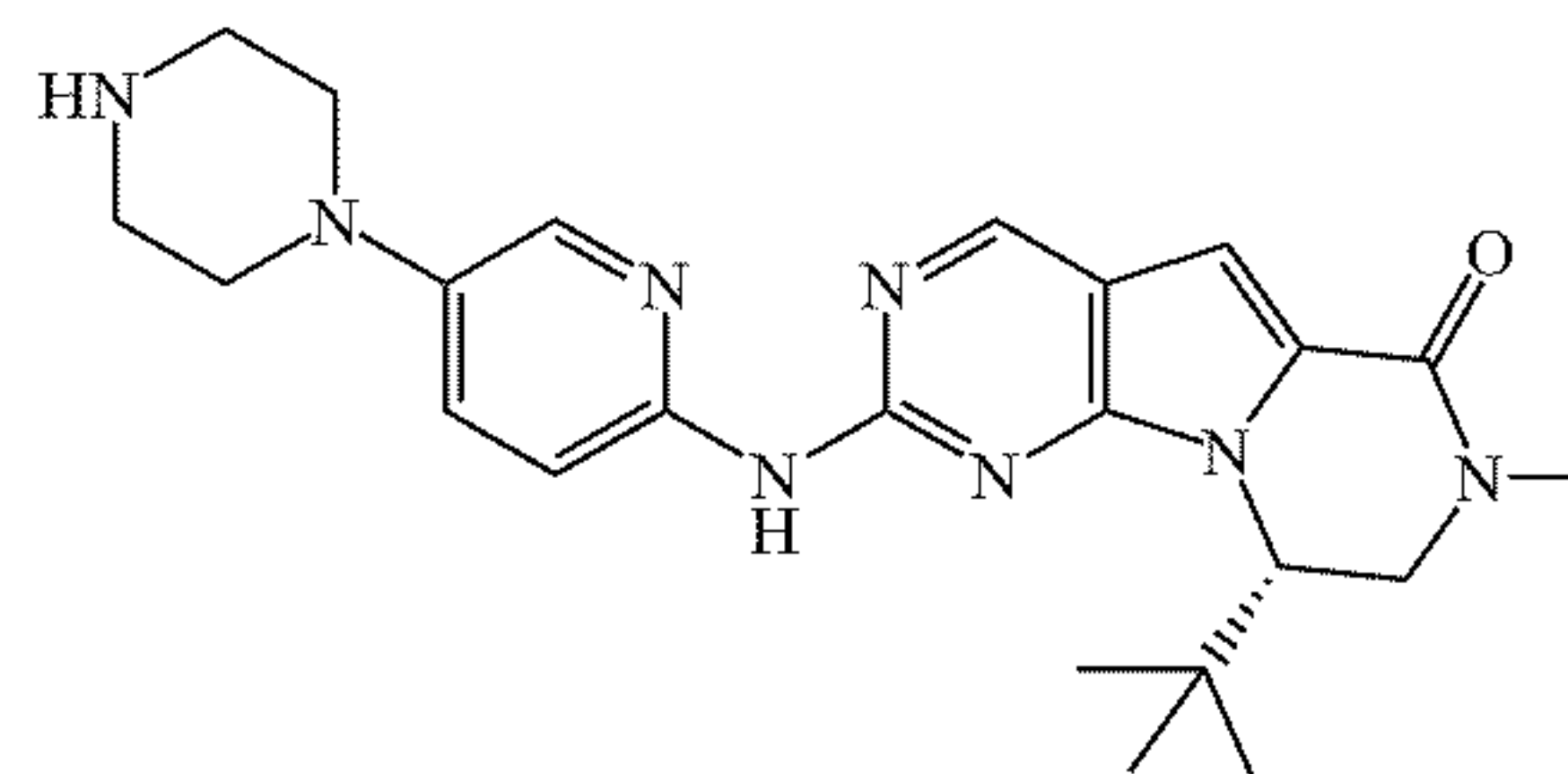


[0498] The compound was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HCl salt. ^1H NMR (600 MHz, DMSO- d_6) δ ppm 0.96 (s, 9 H) 3.15 - 3.87 (m, 10 H) 4.42 - 4.53 (m, 1 H) 6.99 (s, 1 H) 7.24 (s, 1 H) 8.06 (s, 1 H) 8.11 - 8.21 (m, 1 H) 8.79 - 8.98 (m, 2 H) 9.25 (s, 2 H) 9.88 (s, 1 H). LCMS (ESI) 421 (M+H).

Example 83

Synthesis of Compound 83

[0499]

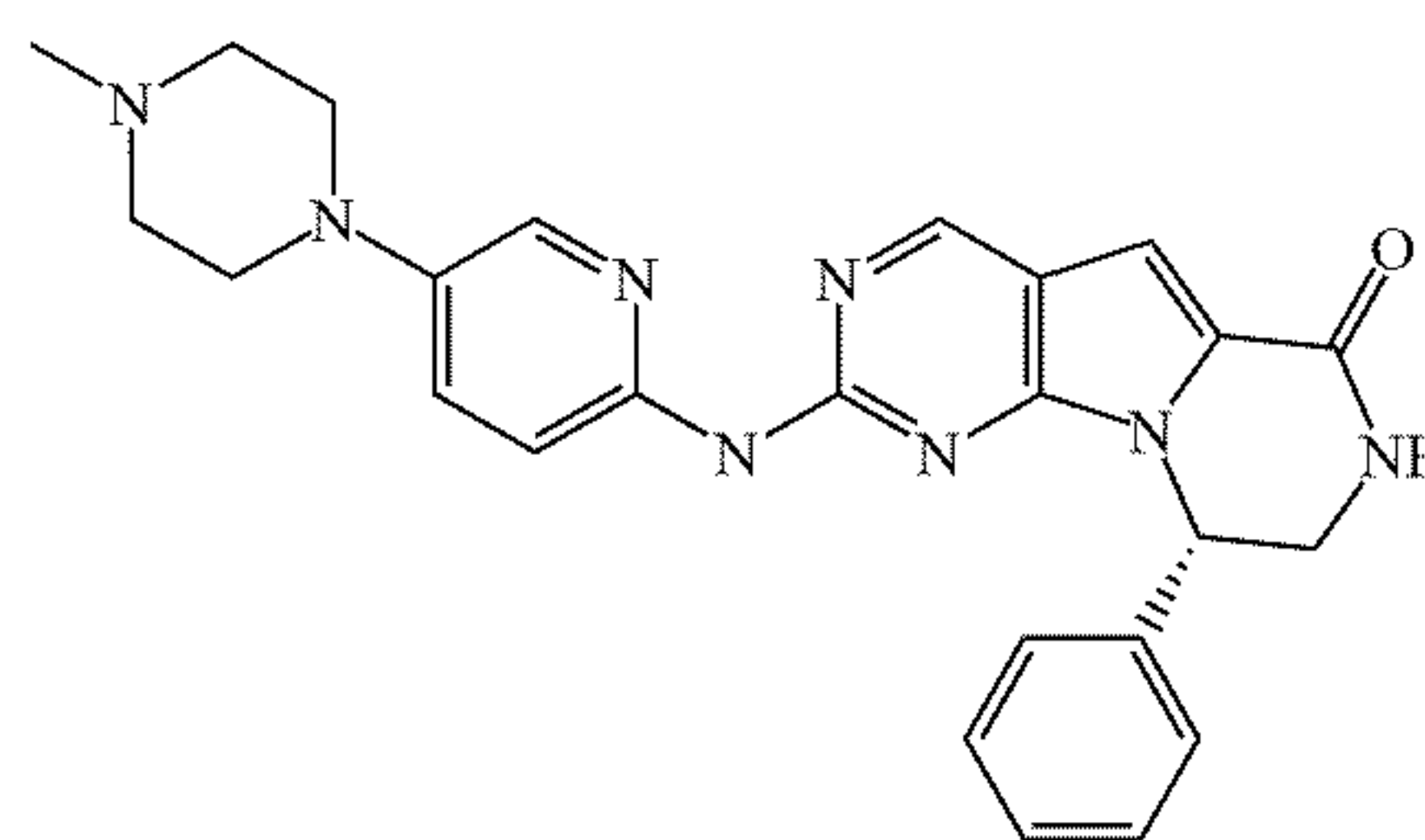


[0500] Compound 83 was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HCl salt. ^1H NMR (600 MHz, DMSO- d_6) δ ppm 0.95 (s, 9 H) 2.79 (d, $J=4.10$ Hz, 3 H) 3.06 - 3.86 (m, 10 H) 4.56 - 4.67 (m, 1 H) 7.17 (s, 1 H) 7.70 (s, 1 H) 7.96 (d, $J=2.63$ Hz, 1 H) 7.99 - 8.08 (m, 1 H) 8.26 (s, 1 H) 9.06 (s, 1 H) 10.80 (s, 1 H). LCMS (ESI) 435 (M+H).

Example 84

Synthesis of Compound 84

[0501]

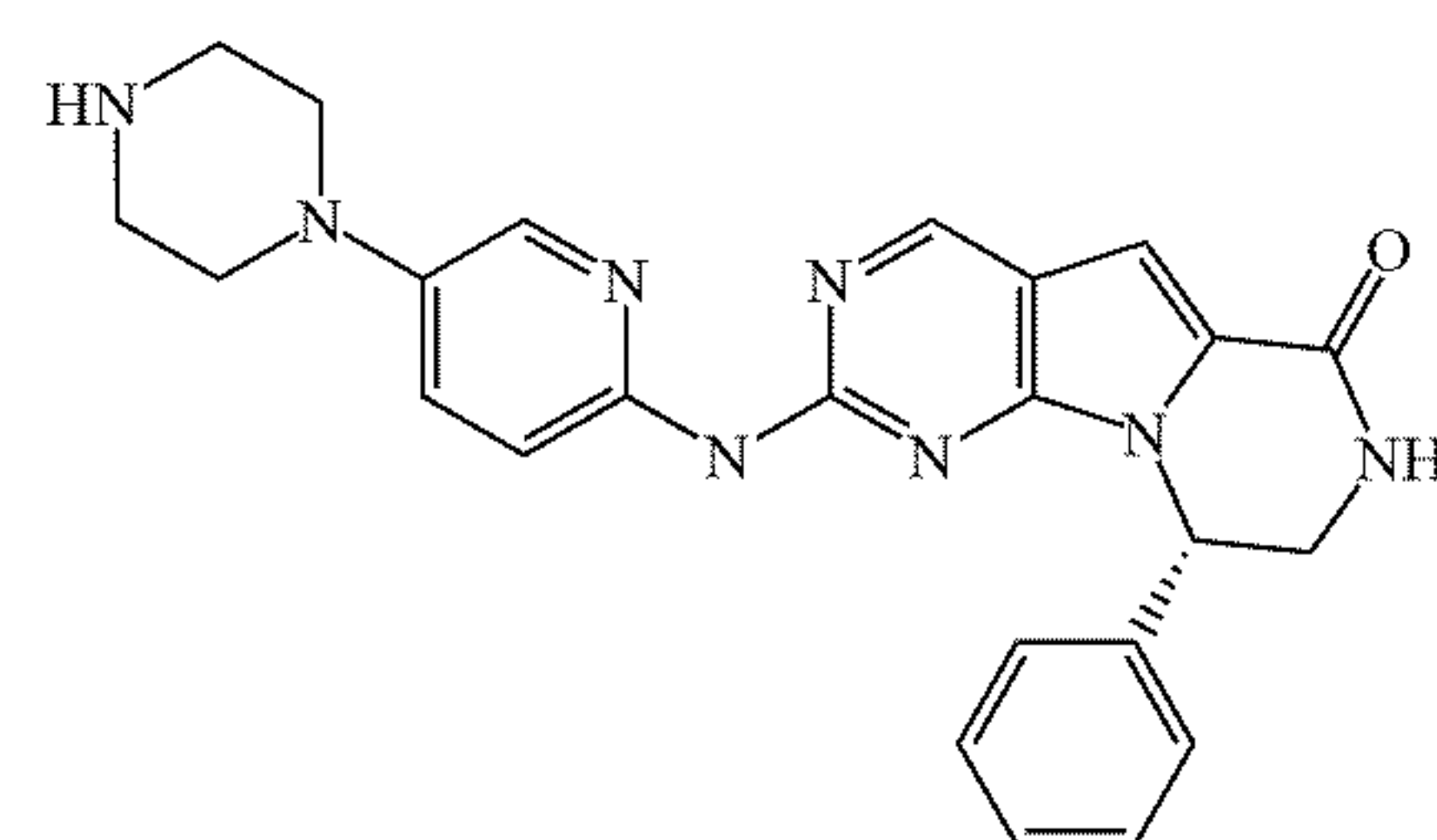


[0502] Compound 84 was synthesized in a similar manner to that described for compound 78 and was converted to an HCl salt. ^1H NMR (600 MHz, DMSO- d_6) δ ppm 2.75 - 2.81 (m, 3 H) 3.12 - 3.16 (m, 2 H) 3.46 - 3.54 (m, 4 H) 3.60 - 3.69 (m, 2 H) 3.72 - 3.79 (m, 1 H) 4.07 - 4.18 (m, 2 H) 6.06 - 6.09 (m, 1 H) 6.90 (d, $J=7.61$ Hz, 2 H) 7.20 - 7.31 (m, 3 H) 7.33 (s, 1 H) 7.49 - 7.55 (m, 1 H) 7.62 - 7.70 (m, 1 H) 7.92 (d, $J=2.93$ Hz, 1 H) 8.22 (s, 1 H) 9.14 (s, 1 H). LCMS (ESI) 455 (M + H).

Example 85

Synthesis of Compound 85

[0503]



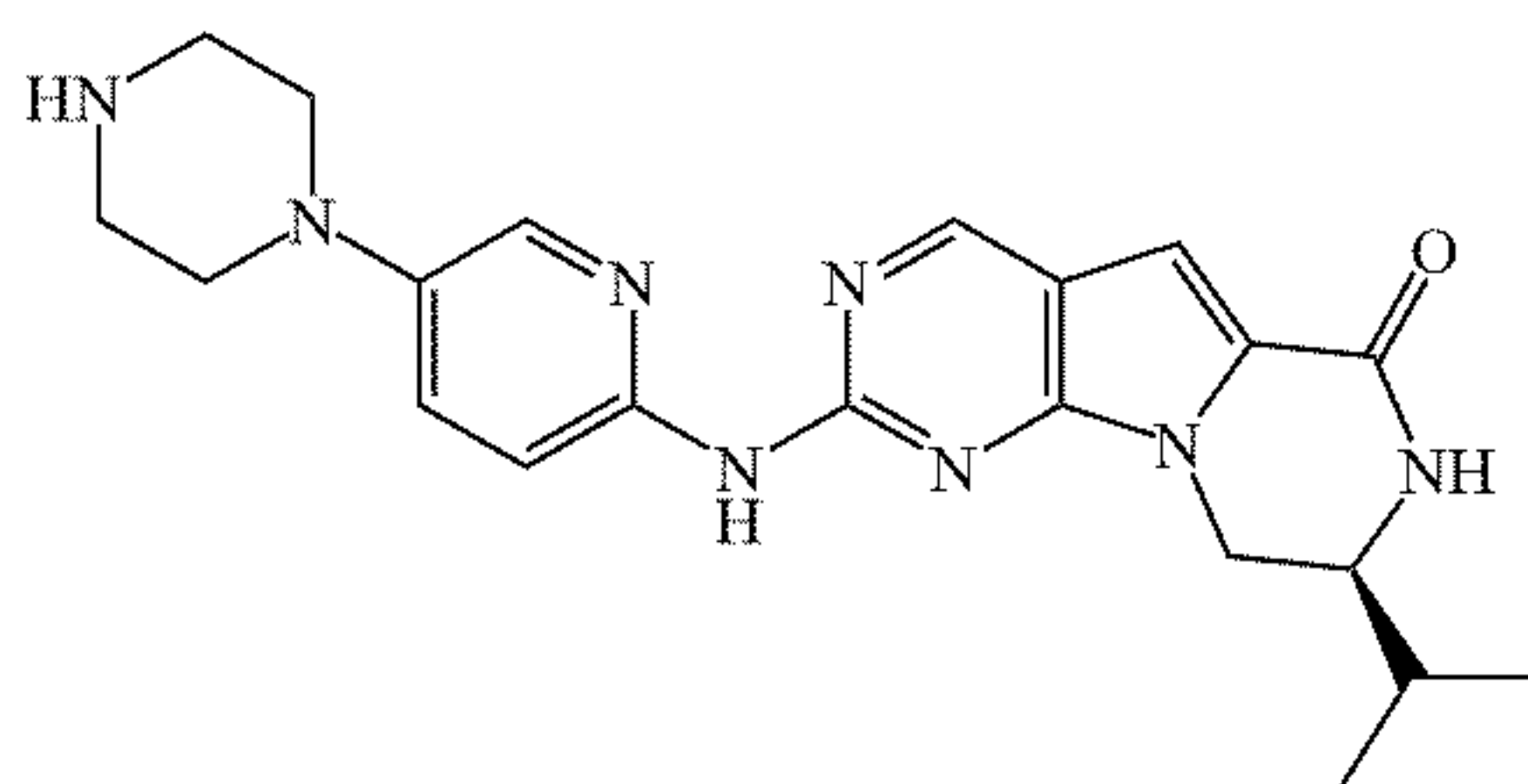
[0504] Compound 85 was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an

HC1 salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 3.21 (s, 4 H) 3.35 - 3.67 (m, 5 H) 4.07 - 4.20 (m, 2 H) 6.13 (s, 1 H) 6.90 (d, J=7.32 Hz, 2 H) 7.22 - 7.31 (m, 3 H) 7.36 (s, 1 H) 7.48 (d, J=9.37 Hz, 1 H) 7.93 (d, J=2.34 Hz, 1 H) 8.04 - 8.11 (m, 1 H) 8.25 (d, J=4.98 Hz, 1 H) 9.17 (s, 1 H) 11.77 (br. s., 1H). LCMS (ESI) 441 (M + H).

Example 86

Synthesis of Compound 86

[0505]

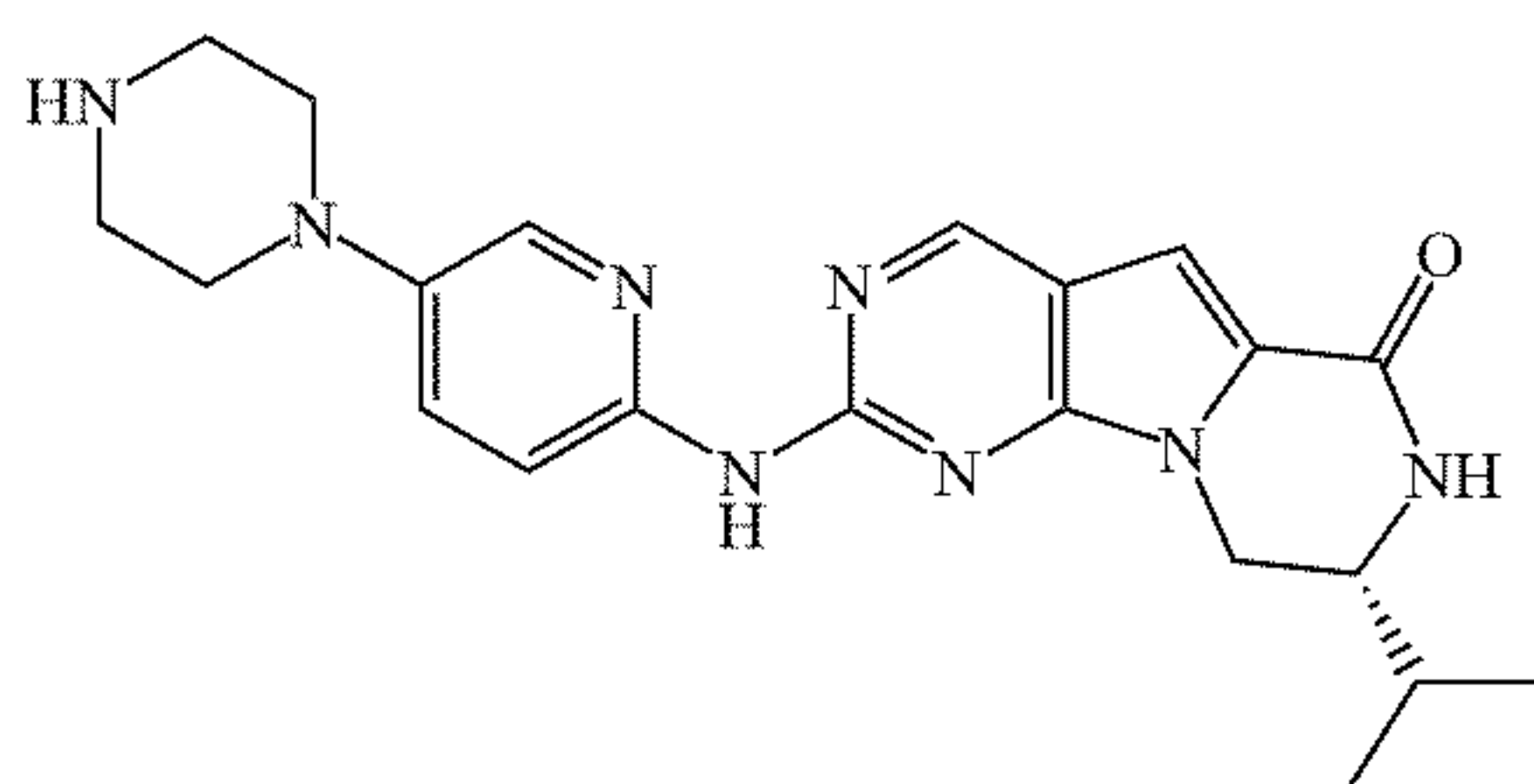


[0506] Compound 86 was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HC1 salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.90 (d, J=6.15 Hz, 6 H) 1.72 - 1.89 (m, 1 H) 3.15 - 3.92 (m, 9 H) 4.10 - 4.46 (m, 2 H) 7.18 (s, 1 H) 7.59 (d, J=8.78 Hz, 1 H) 8.00 (s, 1 H) 8.13 (d, J=9.37 Hz, 1 H) 8.55 (s, 1 H) 9.09 (s, 1 H) 9.67 (s, 2 H) 11.91 (s, 1 H). LCMS (ESI) 407 (ESI).

Example 87

Synthesis of Compound 87

[0507]

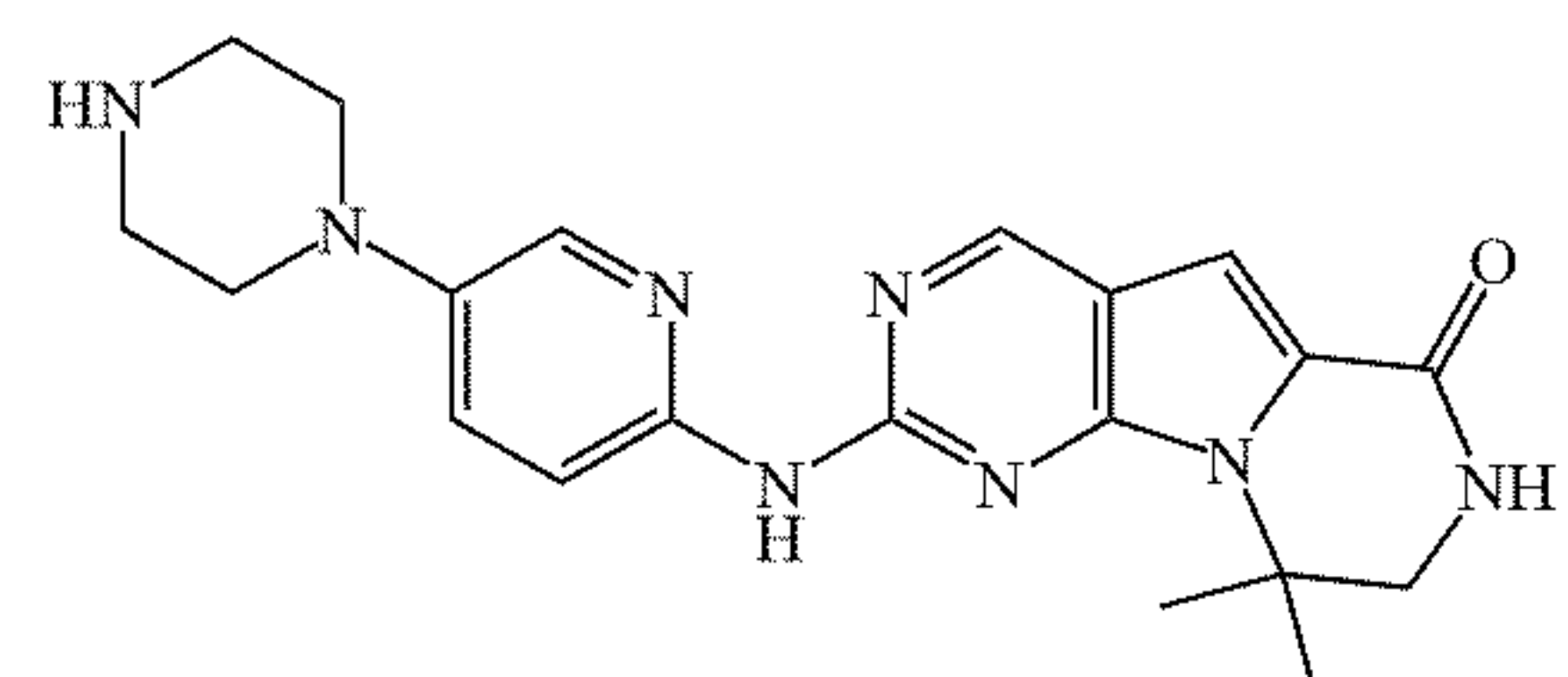


[0508] Compound 87 was synthesized in a manner similar to compound 86 and was converted to an HC1 salt. The characterization data (NMR and LCMS) was similar to that obtained for the antipode compound 86.

Example 88

Synthesis of Compound 88

[0509]

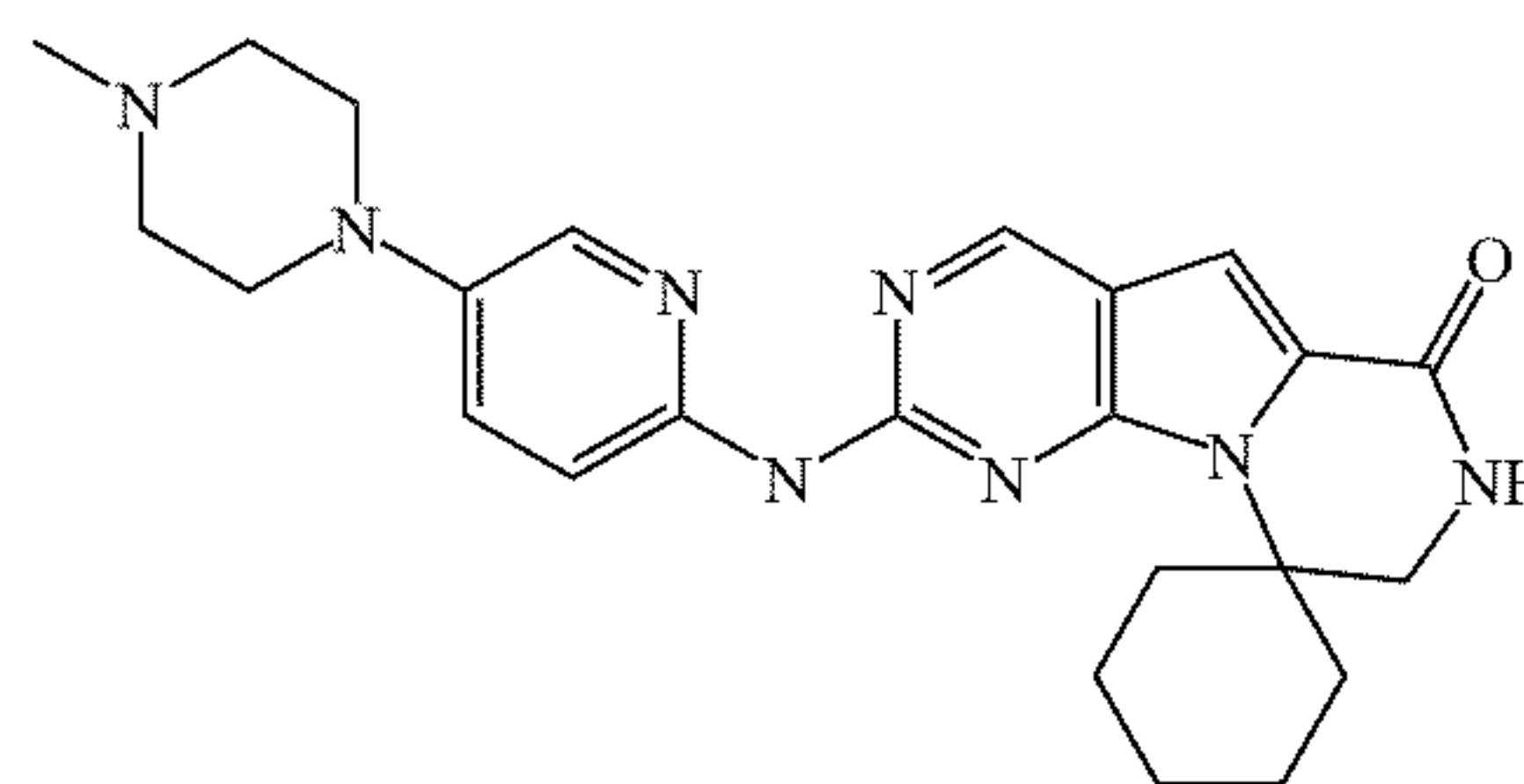


[0510] Compound 88 was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HC1 salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.78 (s, 6 H) 3.40 - 3.53 (m, 6 H) 3.64 - 3.73 (m, 4 H) 7.27 (s, 1 H) 7.66 (d, J=9.37 Hz, 1 H) 7.98 (d, J=2.34 Hz, 1 H) 8.12 (br. s., 1 H) 8.47 (br. s., 1 H) 9.11 (s, 1 H) 9.45 (br. s., 2 H) 11.62 (br. s., 1 H). LCMS (ESI) 393 (M + H).

Example 89

Synthesis of Compound 89 (Also Referred to as Compound T)

[0511]

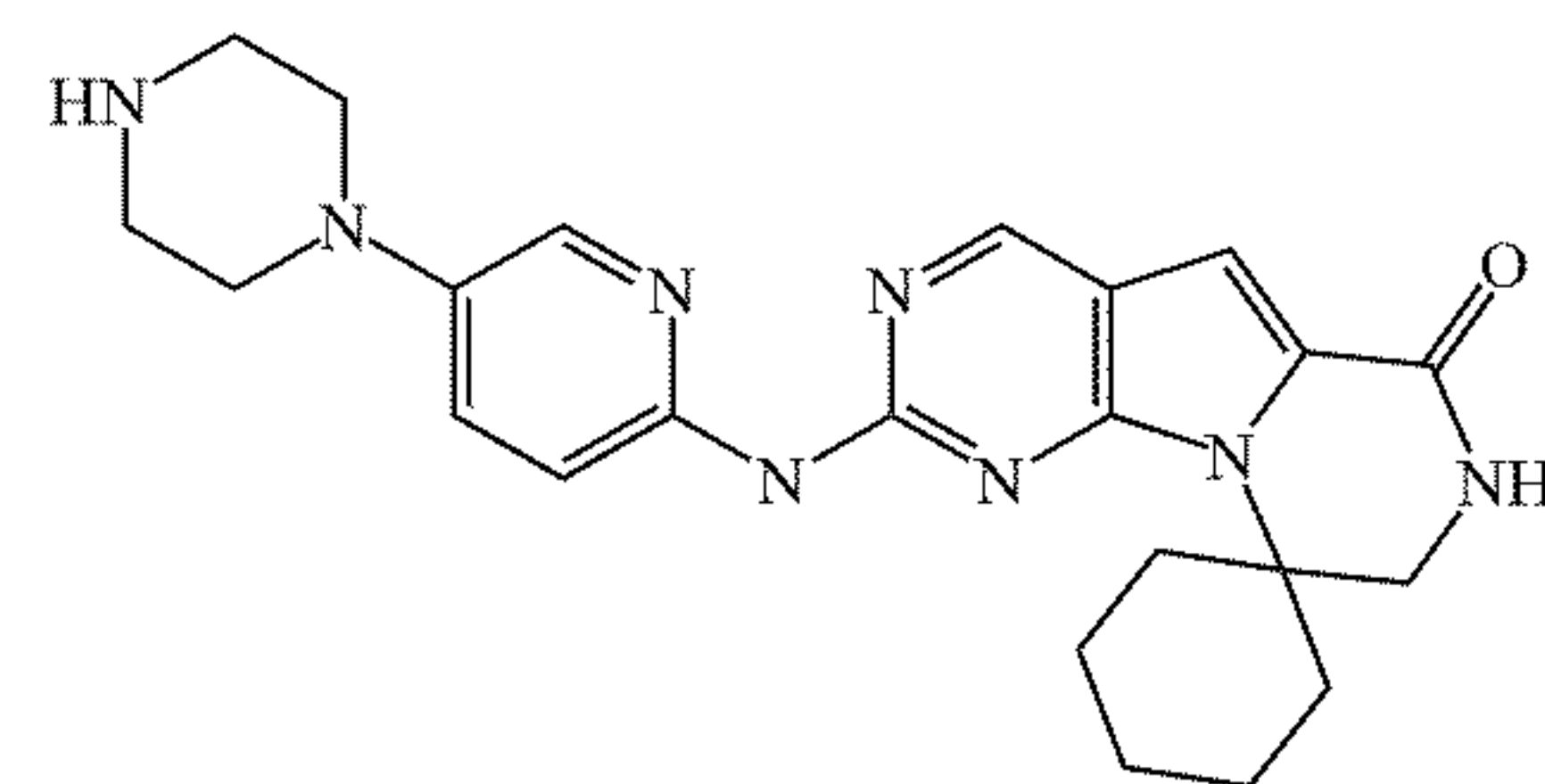


[0512] Compound 89 was synthesized in a similar manner to that described for compound 78 and was converted to an HC1 salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.47 (br. s., 6 H) 1.72 (br. s., 2 H) 1.92 (br. s., 2 H) 2.77 (br. s., 3 H) 3.18 (br. s., 2 H) 3.46 (br. s., 2 H) 3.63 (br. s., 2 H) 3.66 (d, J=6.15 Hz, 2 H) 3.80 (br. s., 2 H) 7.25 (s, 1 H) 7.63 (br. s., 2 H) 7.94 (br. s., 1 H) 8.10 (br. s., 1 H) 8.39 (br. s., 1 H) 9.08 (br. s., 1 H) 11.59 (br. s., 1 H). LCMS (ESI) 447 (M + H).

Example 90

Synthesis of Compound 90 (Also Referred to as Compound Q)

[0513]

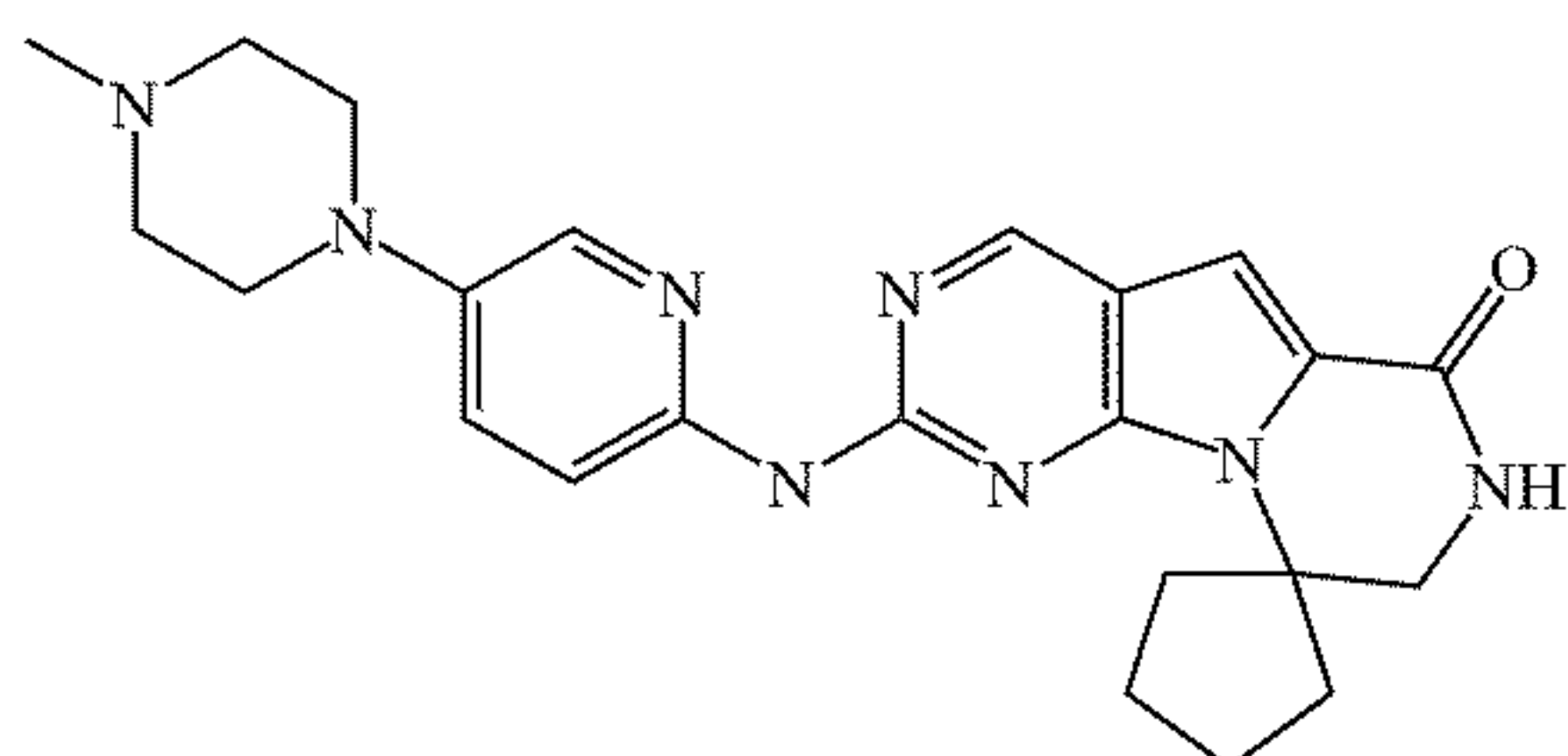


[0514] Compound 90 was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HC1 salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.27 - 1.64 (m, 6 H) 1.71 (br. s., 2 H) 1.91 (br. s., 2 H) 2.80 (br. s., 1 H) 3.17 - 3.24 (m, 2 H) 3.41 (br. s., 4 H) 3.65 (br. s., 4 H) 7.26 (br. s., 1 H) 7.63 (br. s., 1 H) 7.94 (br. s., 1 H) 8.13 (br. s., 1 H) 8.40 (br. s., 1 H) 9.09 (br. s., 1 H) 9.62 (br. s., 1 H) 11.71 (br. s., 1 H). LCMS (ESI) 433 (M + H).

Example 91

Synthesis of Compound 91 (Also Referred to as Compound ZZ)

[0515]

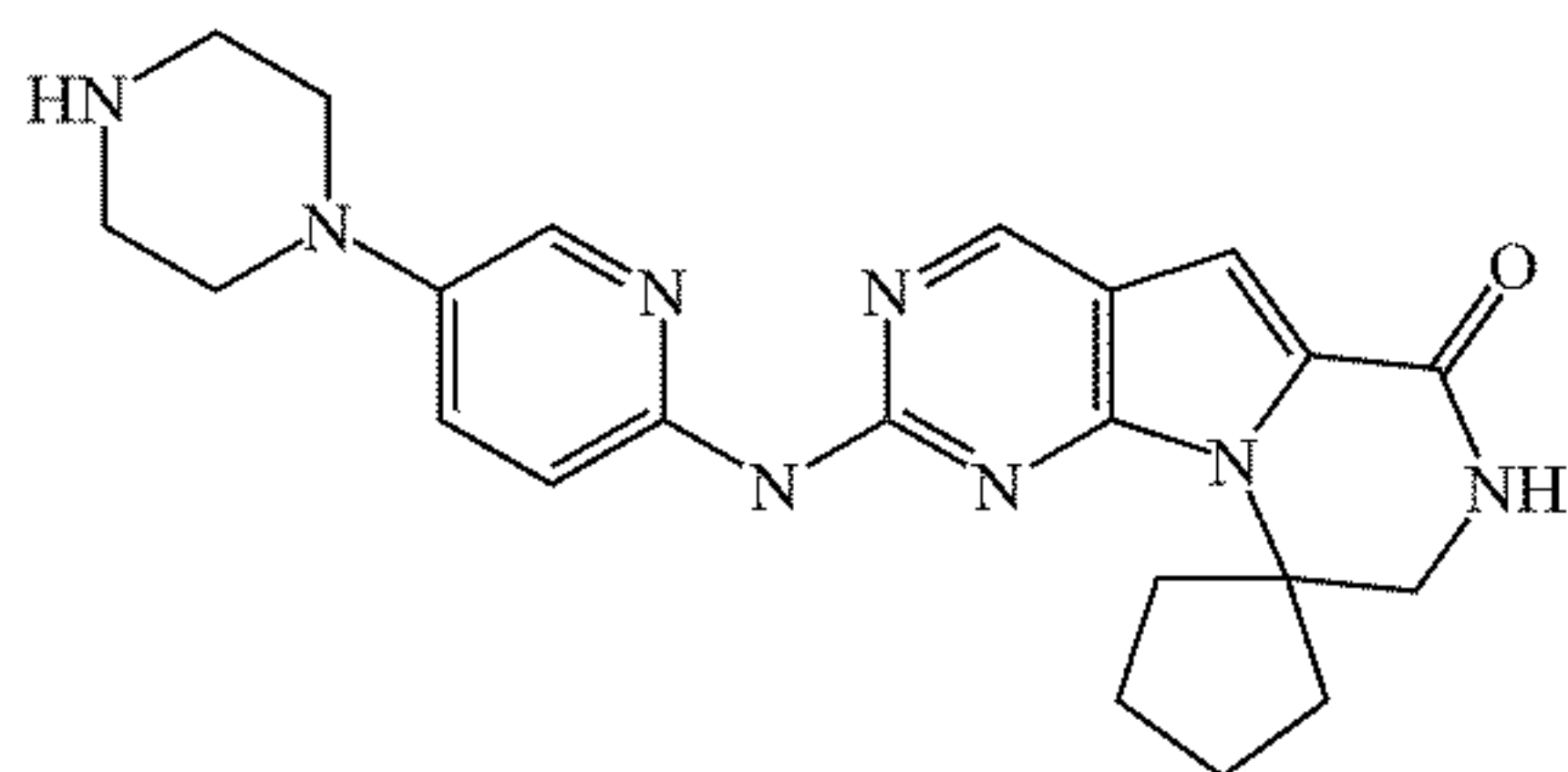


[0516] Compound 91 was synthesized using similar conditions to those described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.64 - 1.75 (m, 2 H) 1.83 - 1.92 (m, 2 H) 1.96 - 2.06 (m, 2 H) 2.49 - 2.58 (m, 2 H) 2.79 (d, 7=3.81 Hz, 3 H) 3.06 - 3.18 (m, 4 H) 3.59 - 3.69 (m, 2 H) 3.73 - 3.83 (m, 2 H) 4.04 - 4.12 (m, 2 H) 7.17 (br. s., 1 H) 7.60 - 7.70 (m, 2 H) 7.70 - 7.92 (m, 2 H) 7.96 (br. s., 1 H) 8.41 (br. s., 1 H) 8.98 (br. s., 1 H) 10.77 (br. s., 1 H). LCMS (ESI) 433 (M + H).

Example 92

Synthesis of Compound 92

[0517]

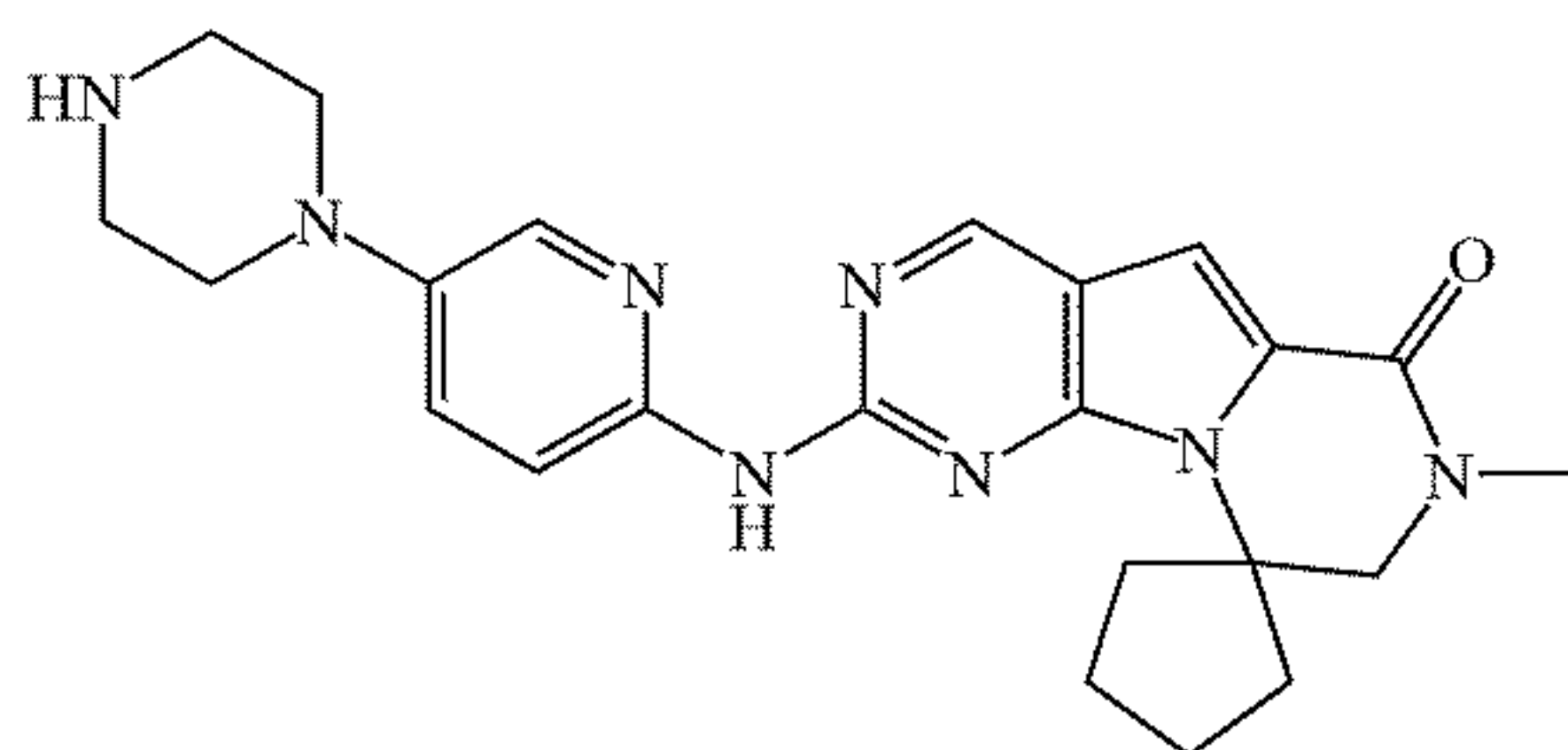


[0518] Compound 92 was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.64 - 1.75 (m, 2 H) 1.84 - 1.92 (m, 2 H) 1.96 - 2.05 (m, 2 H) 2.48 - 2.56 (m, 2 H) 3.22 (br. s., 4 H) 3.42 - 3.48 (m, 4 H) 3.60 - 3.69 (m, 2 H) 4.05 - 4.13 (m, 1 H) 7.18 (s, 1 H) 7.65 (d, J=13.47 Hz, 1 H) 7.70 - 7.77 (m, 1 H) 7.94 (d, J=1.76 Hz, 1 H) 8.42 (br. s., 1 H) 9.00 (s, 1 H) 9.15 (br. s., 2 H). LCMS (ESI) 419 (M + H).

Example 93

Synthesis of Compound 93

[0519]



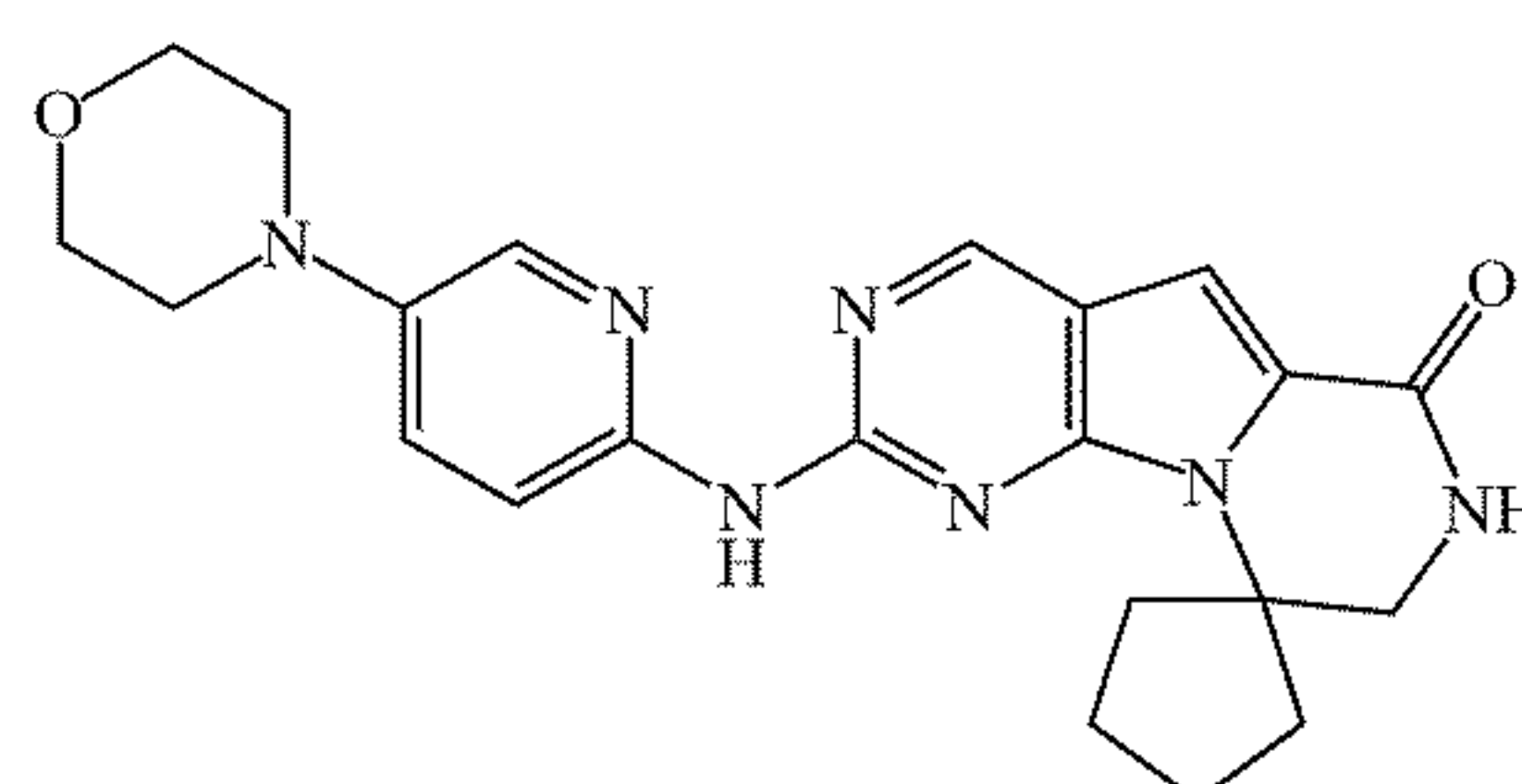
[0520] Compound 93 was synthesized in a similar manner to that described for compound 78 followed by the deblocking step described for compound 65 and was converted to an

HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.76 (br. s., 2 H) 1.89 (br. s., 2 H) 2.03 (br. s., 2 H) 2.47 - 2.58 (m, 2 H) 3.04 (s, 3 H) 3.22 (br. s., 4 H) 3.39 (br. s., 4 H) 3.66 (s, 2 H) 7.21 (s, 1 H) 7.67 (d, J=9.37 Hz, 1 H) 7.93 (br. s., 1 H) 7.98 - 8.09 (m, 1 H) 9.04 (s, 1 H) 9.34 (br. s., 2 H) 11.31 (br. s., 1 H). LCMS (ESI) 433 (M + H).

Example 94

Synthesis of Compound 94

[0521]

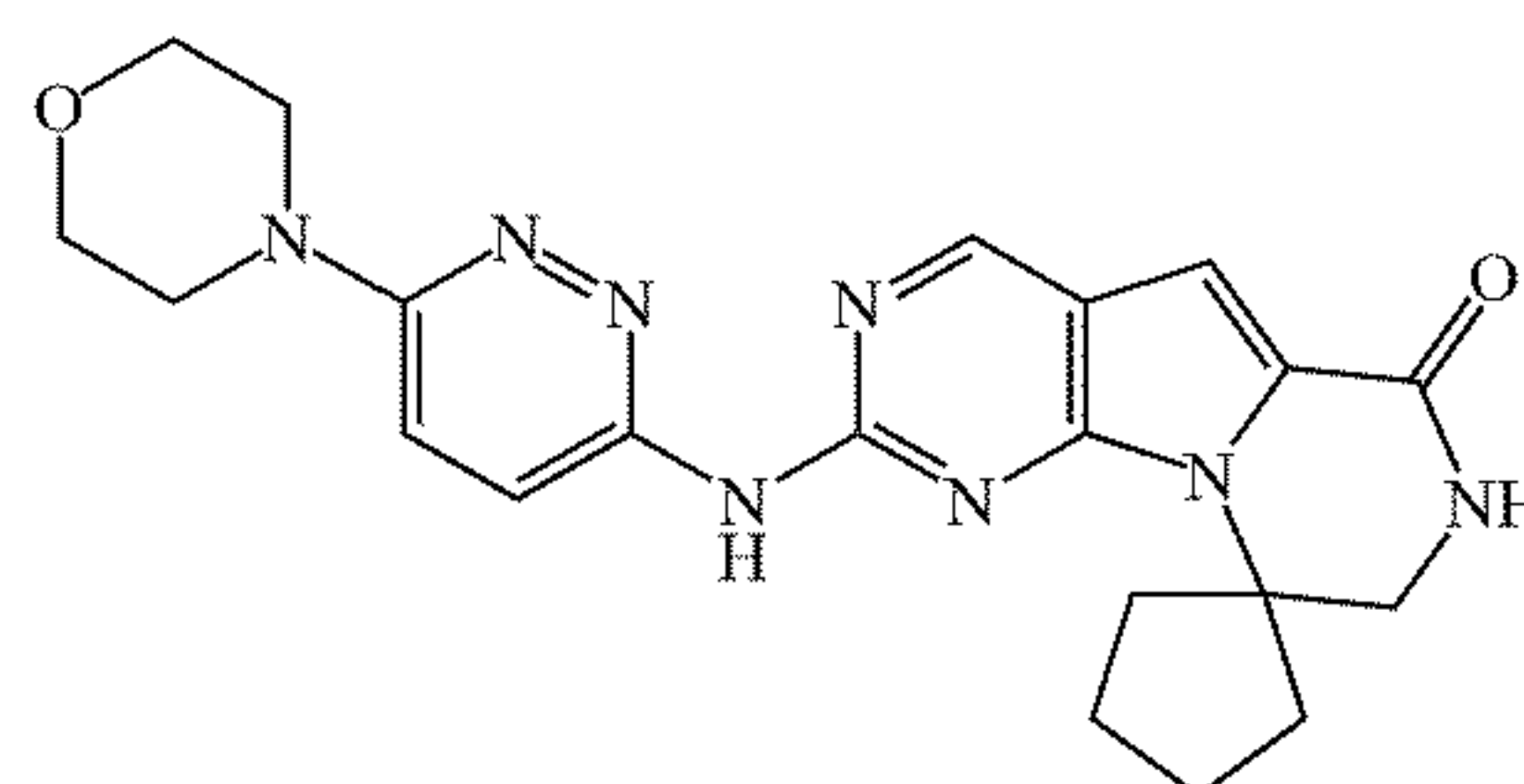


[0522] Compound 94 was synthesized using similar conditions to that described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.66 - 1.77 (m, 2 H) 1.84 - 1.94 (m, 2 H) 1.96 - 2.08 (m, 2 H) 2.48 - 2.57 (m, 2 H) 3.36 - 3.52 (m, 4 H) 3.60 - 3.80 (m, 6 H) 7.21 (s, 1 H) 7.53 - 7.74 (m, 2 H) 7.86 (s, 1 H) 8.02 (s, 1 H) 8.45 (s, 1 H) 9.03 (s, 1 H) 11.19 (br. s., 1 H). LCMS (ESI) 420 (M+H).

Example 95

Synthesis of Compound 95

[0523]

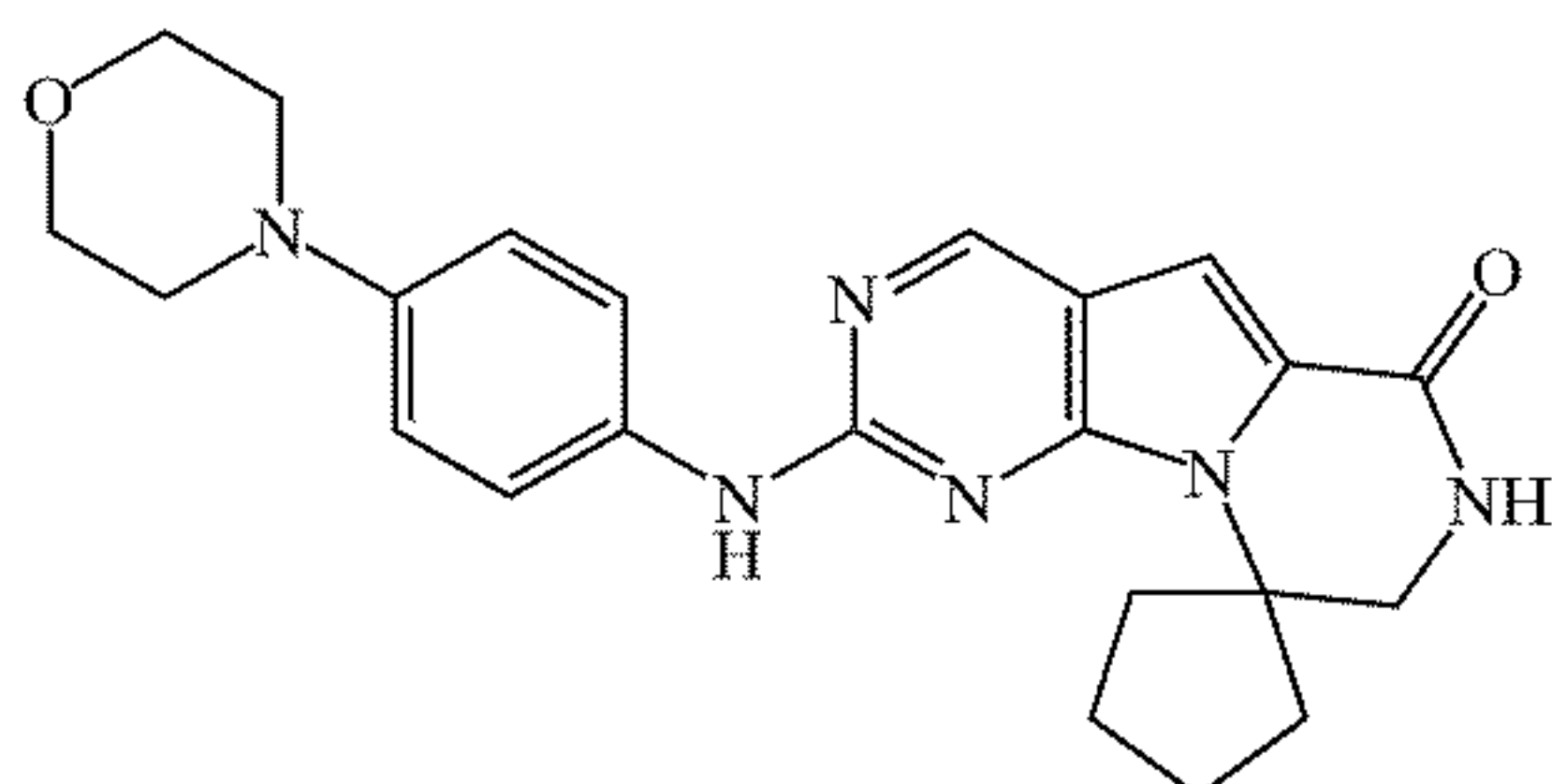


[0524] Compound 95 was synthesized using similar conditions to that described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.65 - 1.79 (m, 2 H) 1.85 - 1.95 (m, 2 H) 1.97 - 2.08 (m, 2 H) 2.47 - 2.54 (m, 2 H) 3.40 - 3.58 (m, 5 H) 3.65 (dd, J=21.67, 5.56 Hz, 1 H) 3.69 - 3.78 (m, 4 H) 7.24 (s, 1 H) 7.97 - 8.17 (m, 2 H) 8.48 (s, 1 H) 9.08 (s, 1 H) 11.81 (s, 1 H). LCMS (ESI) 421 (M+H).

Example 96

Synthesis of Compound 96

[0525]

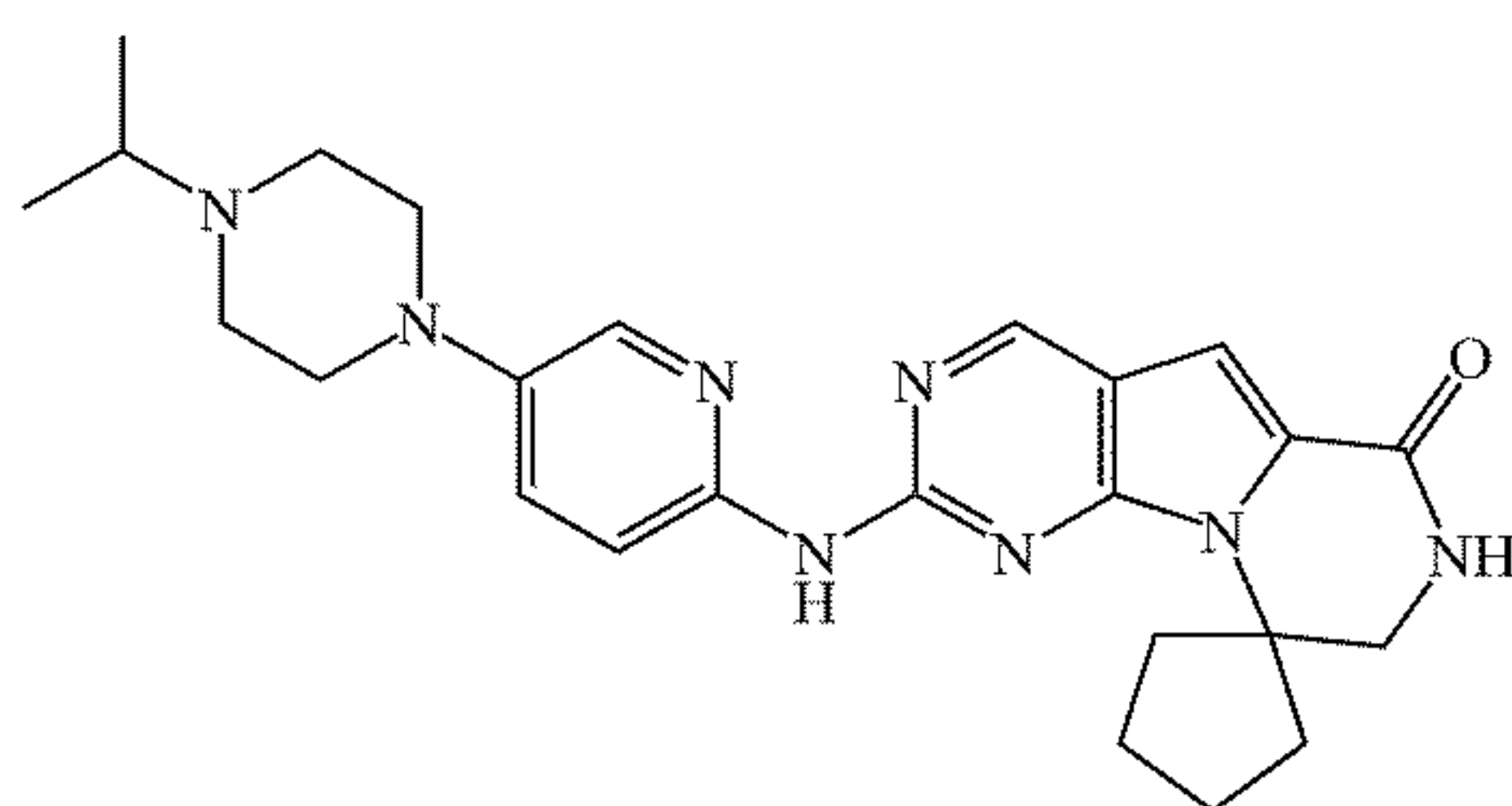


[0526] Compound 96 was synthesized using similar conditions to that described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.55 - 1.74 (m, 2 H) 1.80 - 1.98 (m, 4 H) 2.48 - 2.60 (m, 2 H) 3.40 - 3.50 (m, 4 H) 3.57 - 3.72 (m, 2 H) 3.90 - 4.20 (m, 4 H) 7.08 (s, 1 H) 7.37 - 7.57 (m, 2 H) 7.70 (m, 2 H) 8.32 (s, 1 H) 8.88 (s, 1 H) 9.98 (s, 1 H). LCMS (ESI) 419 (M+H).

Example 97

Synthesis of Compound 97 (Also Referred to as Compound III)

[0527]

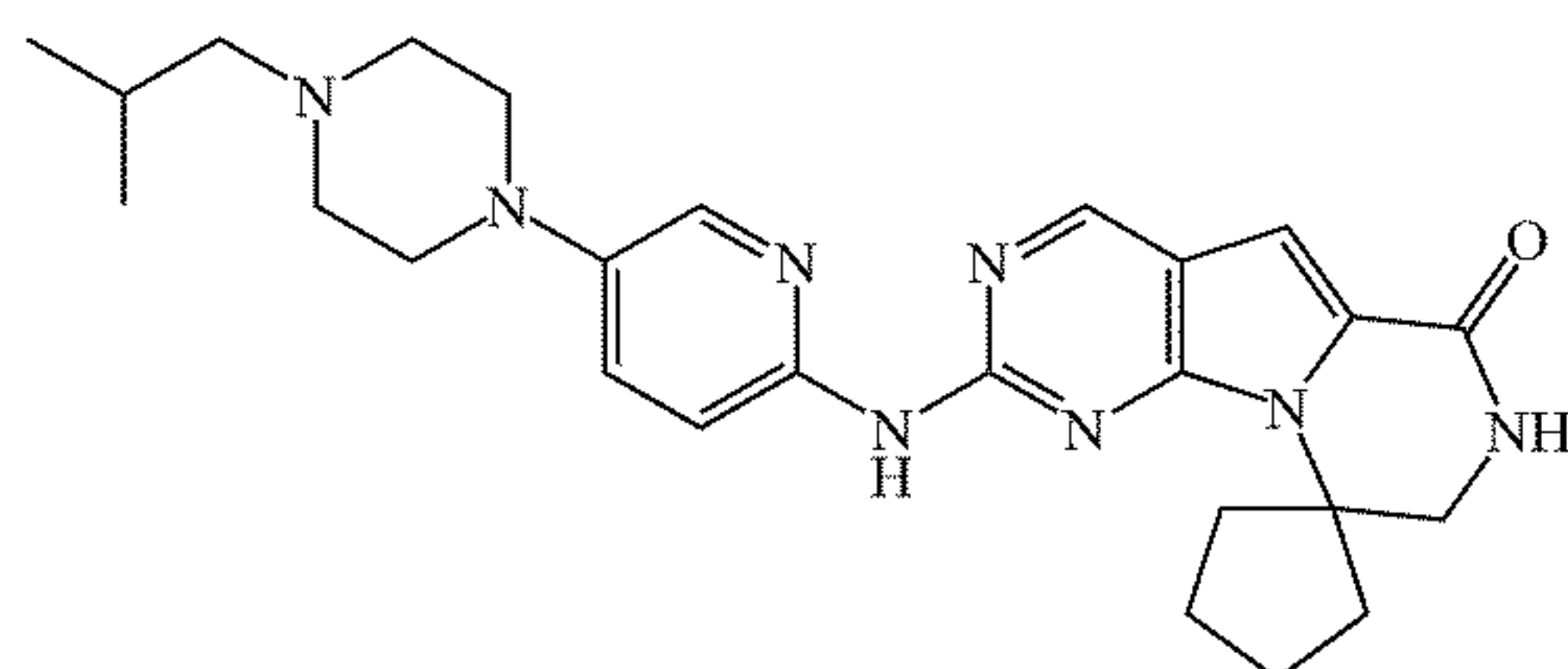


[0528] Compound 97 was synthesized using similar conditions to that described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.30 (d, J=5.27 Hz, 6 H) 1.65 - 1.78 (m, 2 H) 1.83 - 1.95 (m, 2 H) 1.97 - 2.10 (m, 2 H) 2.45 - 2.55 (m, 2H) 3.25 - 3.36 (m, 1 H) 3.39 - 3.48 (m, 4 H) 3.60 - 3.70 (m, 4 H) 3.75 - 4.15 (m, 2 H) 7.24 (s, 1 H) 7.54 - 7.75 (m, 2 H) 7.95 (s, 1 H) 8.10 (s, 1 H) 8.49 (s, 1 H) 9.07 (s, 1 H) 11.25 (s, 1 H) 11.48 (s, 1 H). LCMS (ESI) 461 (M+H).

Example 98

Synthesis of Compound 98

[0529]



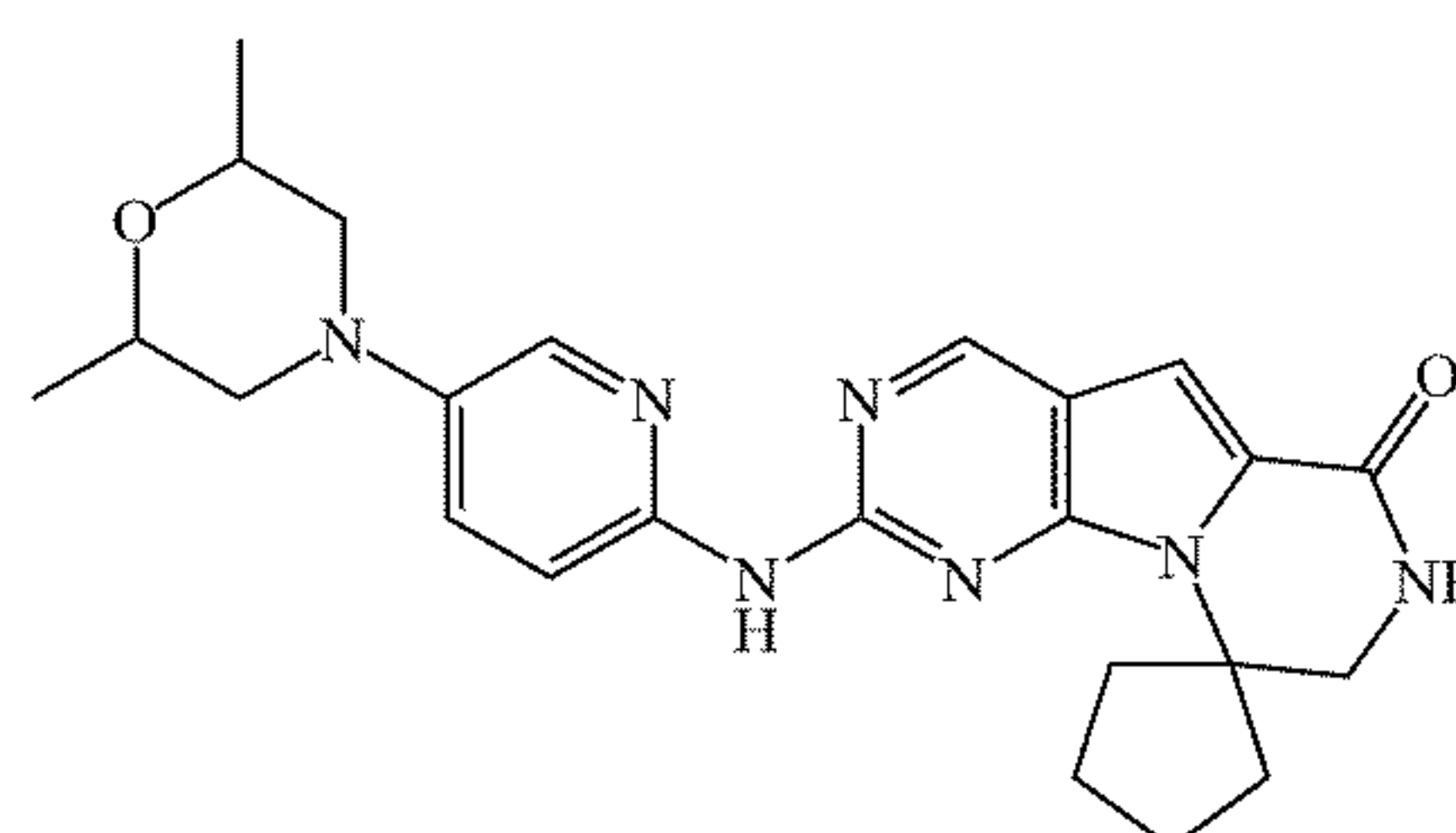
[0530] Compound 98 was synthesized using similar conditions to that described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ

ppm 0.99 (d, J=6.15 Hz, 6 H) 1.65 - 1.78 (m, 2 H) 1.90 (m, 2 H) 1.97 - 2.08 (m, 2 H) 2.08 - 2.17 (m, 1 H) 2.45 - 2.55 (m, 2H) 2.88 - 3.02 (m, 2 H) 3.33 - 3.48 (m, 4 H) 3.50 - 3.90 (m, 6 H) 7.24 (s, 1 H) 7.67 (s, 2 H) 7.94 (s, 1 H) 8.12 (s, 1 H) 8.49 (s, 1 H) 9.07 (s, 1 H) 10.77 (s, 1 H) 11.51 (s, 1 H). LCMS (ESI) 475 (M+H).

Example 99

Synthesis of Compound 99

[0531]

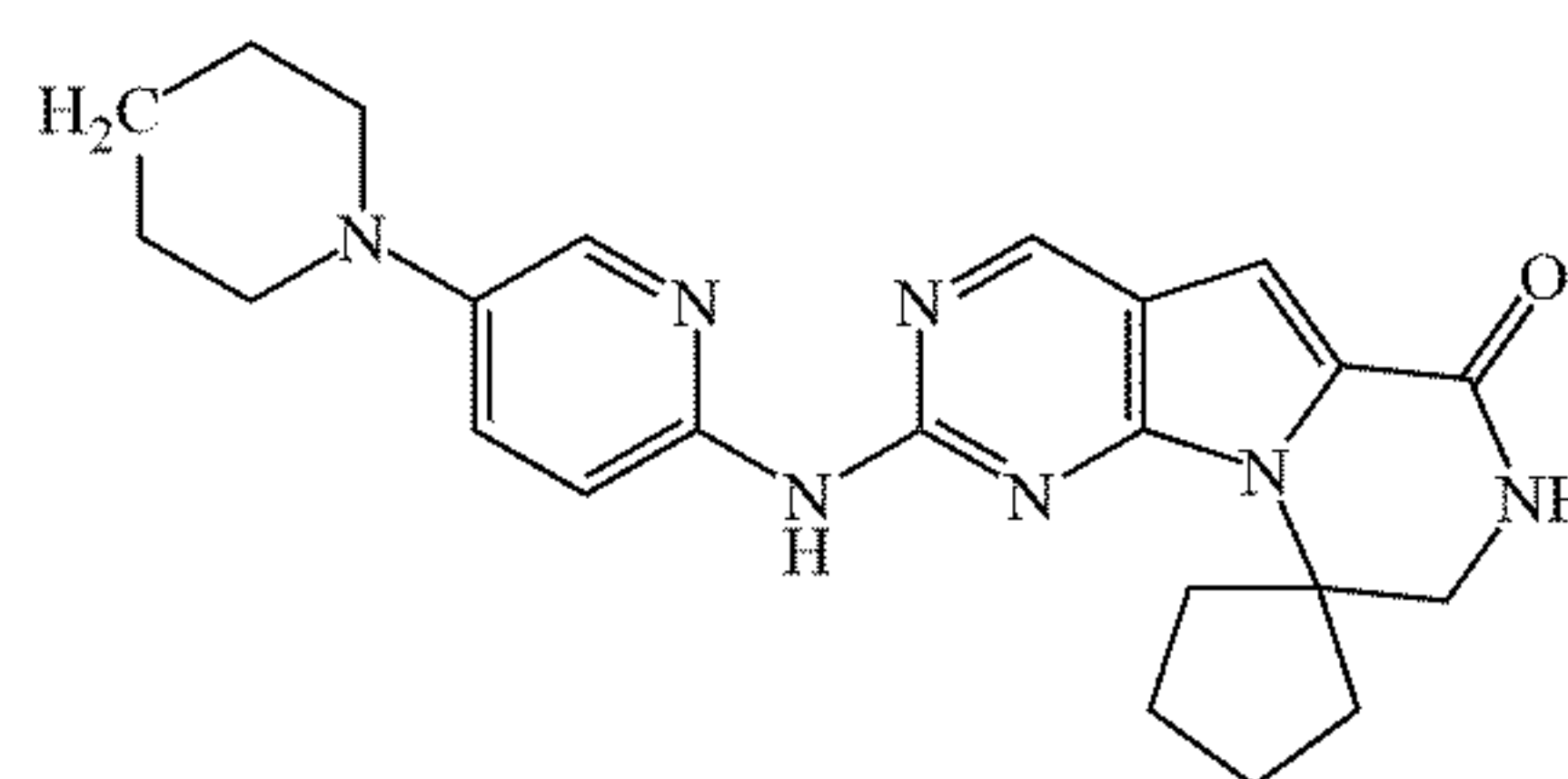


[0532] Compound 99 was synthesized using similar conditions to those described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.13 (d, J=5.86 Hz, 6 H) 1.66 - 1.77 (m, 2 H) 1.84 - 1.94 (m, 2 H) 1.97 - 2.09 (m, 2 H) 2.40 - 2.53 (m, 2 H) 3.37 - 3.49 (m, 2 H) 3.50 - 3.59 (m, 2 H) 3.59 - 3.73 (m, 4 H) 7.23 (s, 1 H) 7.64 (m, 3 H) 7.85 (s, 1 H) 8.11 (s, 1 H) 8.47 (s, 1 H) 9.05 (s, 1 H) 11.35 (br s., 1H). LCMS (ESI) 448 (M+H).

Example 100

Synthesis of Compound 100

[0533]

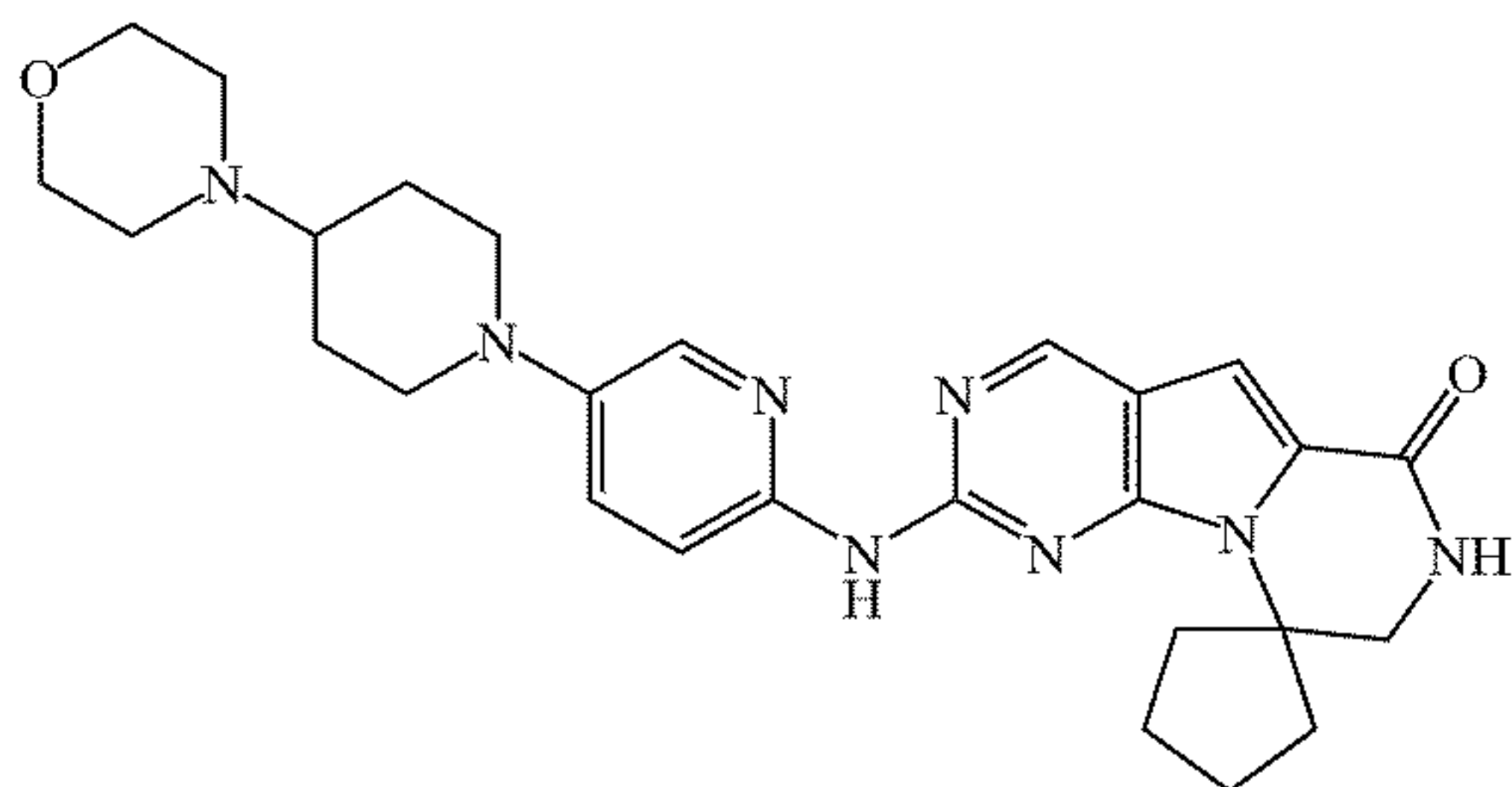


[0534] Compound 100 was synthesized using similar conditions to that described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.50 - 1.57 (m, 2 H) 1.62 - 1.68 (m, 3 H) 1.68 - 1.75 (m, 2 H) 1.84 - 1.92 (m, 2 H) 1.97 - 2.08 (m, 2 H) 2.48 - 2.53 (m, 2 H) 3.14 - 3.23 (m, 4 H) 3.43 - 3.47 (m, 2 H) 3.58 - 3.70 (m, 2 H) 7.22 (s, 1 H) 7.58 - 7.70 (m, 2 H) 7.85 - 8.00 (m, 1 H) 8.16 (d, 1 H) 8.46 (s, 1 H) 9.04 (s, 1 H) 11.37 (br s., 1H). LCMS (ESI) 418 (M + H).

Example 101

Synthesis of Compound 101 (Also Referred to as Compound WW)

[0535]

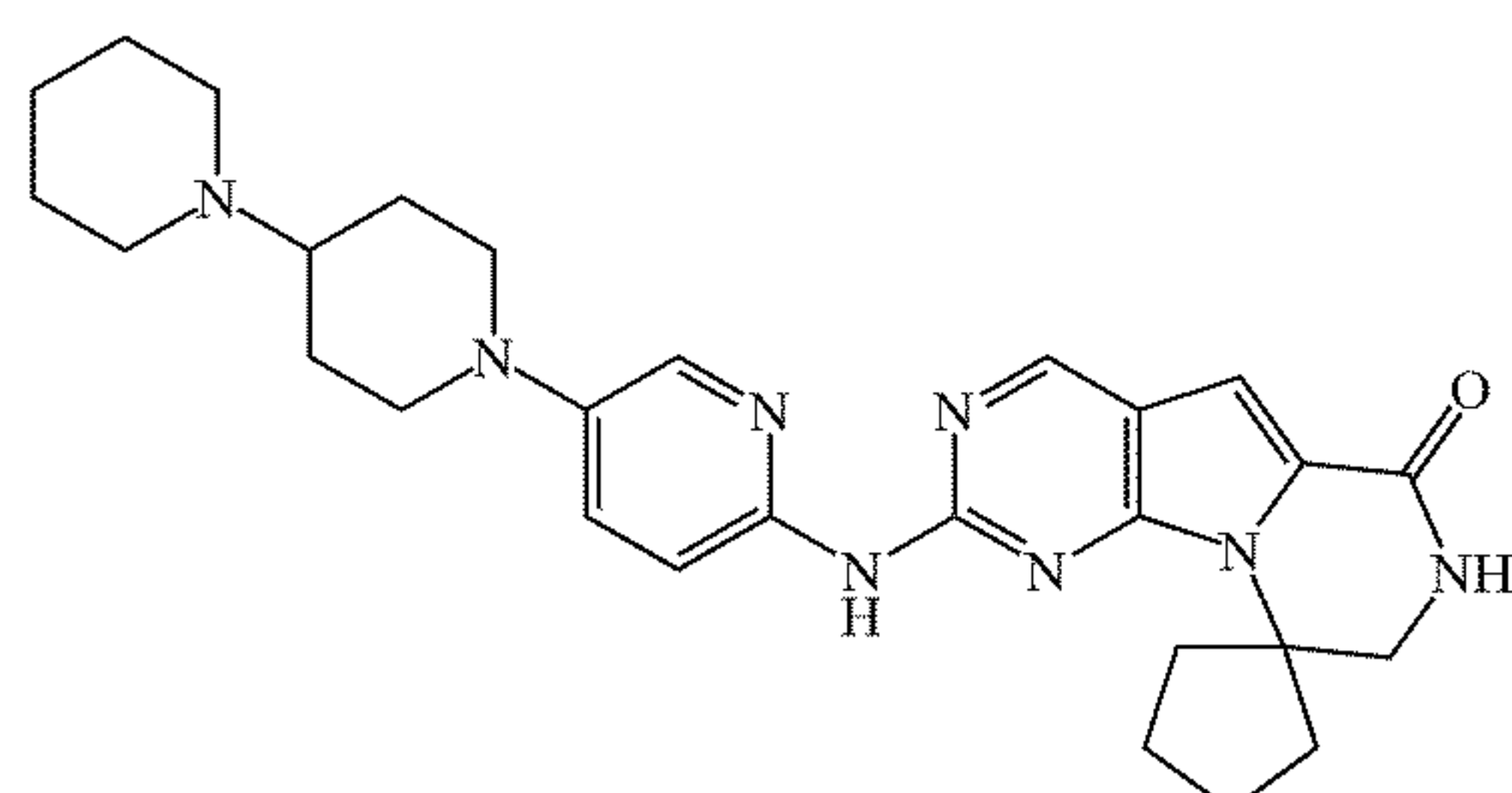


[0536] Compound 101 was synthesized using similar conditions to those described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.72 (s, 2 H) 1.90 (s, 4 H) 2.03 (s, 2 H) 2.21 (s, 2 H) 2.48 - 2.54 (m, 2 H) 2.73 (s, 2 H) 3.03 (s, 2 H) 3.25 - 3.35 (m, 1 H) 3.38 - 3.48 (m, 4 H) 3.65 - 3.99 (m, 5 H) 7.23 (s, 1 H) 7.63 (d, J=9.66 Hz, 1 H) 7.90 (s, 1 H) 8.13 (s, 1 H) 8.47 (s, 1 H) 9.06 (s, 1 H) 10.50 (br s., 1H). LCMS (ESI) 503 (M + H).

Example 102

Synthesis of Compound 102 (Also Referred to as Compound HHH)

[0537]

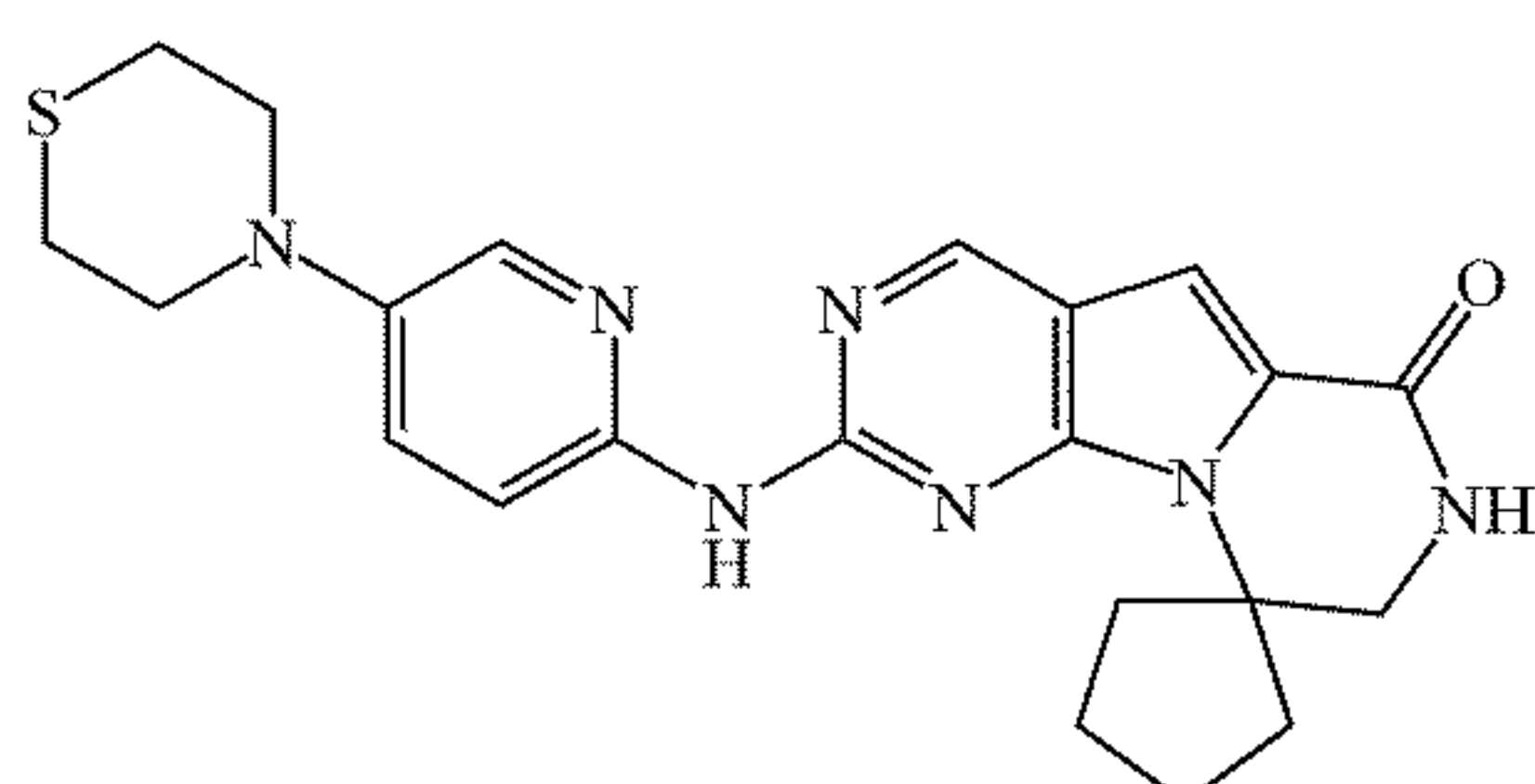


[0538] Compound 102 was synthesized using similar conditions to those described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.63 - 1.85 (m, 6 H) 1.87 - 1.92 (m, 2 H) 1.99 - 2.06 (m, 2 H) 2.15 - 2.23 (m, 2 H) 2.47 - 2.53 (m, 1 H) 2.69 - 2.79 (m, 2 H) 2.81 - 2.91 (m, 2 H) 2.98 - 3.08 (m, 2 H) 3.32 - 3.48 (m, 4 H) 3.57 - 3.72 (m, 4 H) 3.77 - 3.85 (m, 2 H) 7.22 (s, 1 H) 7.60 - 7.68 (m, 2 H) 7.90 (s, 1 H) 8.07 (s, 1 H) 8.46 (s, 1 H) 9.04 (s, 1 H). 11.41 (br s., 1H). LCMS (ESI) 501 (M + H).

Example 103

Synthesis of Compound 103

[0539]

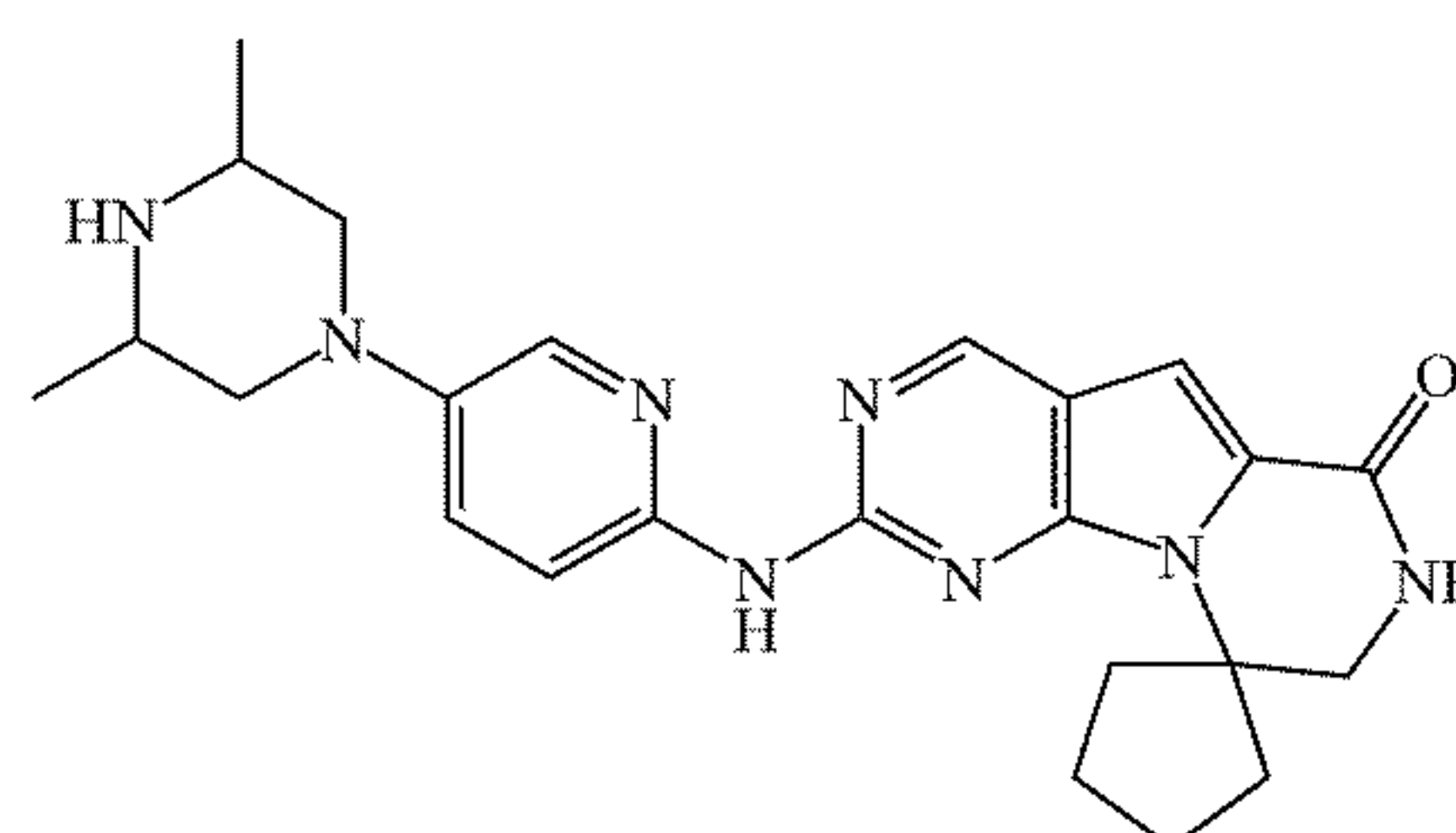


[0540] Compound 103 was synthesized using similar conditions to those described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.64 - 1.76 (m, 2 H) 1.87 - 1.93 (m, 2 H) 2.00 - 2.07 (m, 2 H) 2.48 - 2.53 (m, 2 H) 2.67 - 2.72 (m, 4 H) 3.44 - 3.47 (m, 2 H) 3.50 - 3.55 (m, 4 H) 7.24 (s, 1 H) 7.61 (d, J=9.37 Hz, 2 H) 7.86 (d, J=2.63 Hz, 1 H) 8.09 (d, J=12.88 Hz, 1 H) 8.48 (s, 1 H) 9.06 (s, 1 H) 11.41 (br s., 1H). LCMS (ESI) 436 (M + H).

Example 104

Synthesis of Compound 104

[0541]

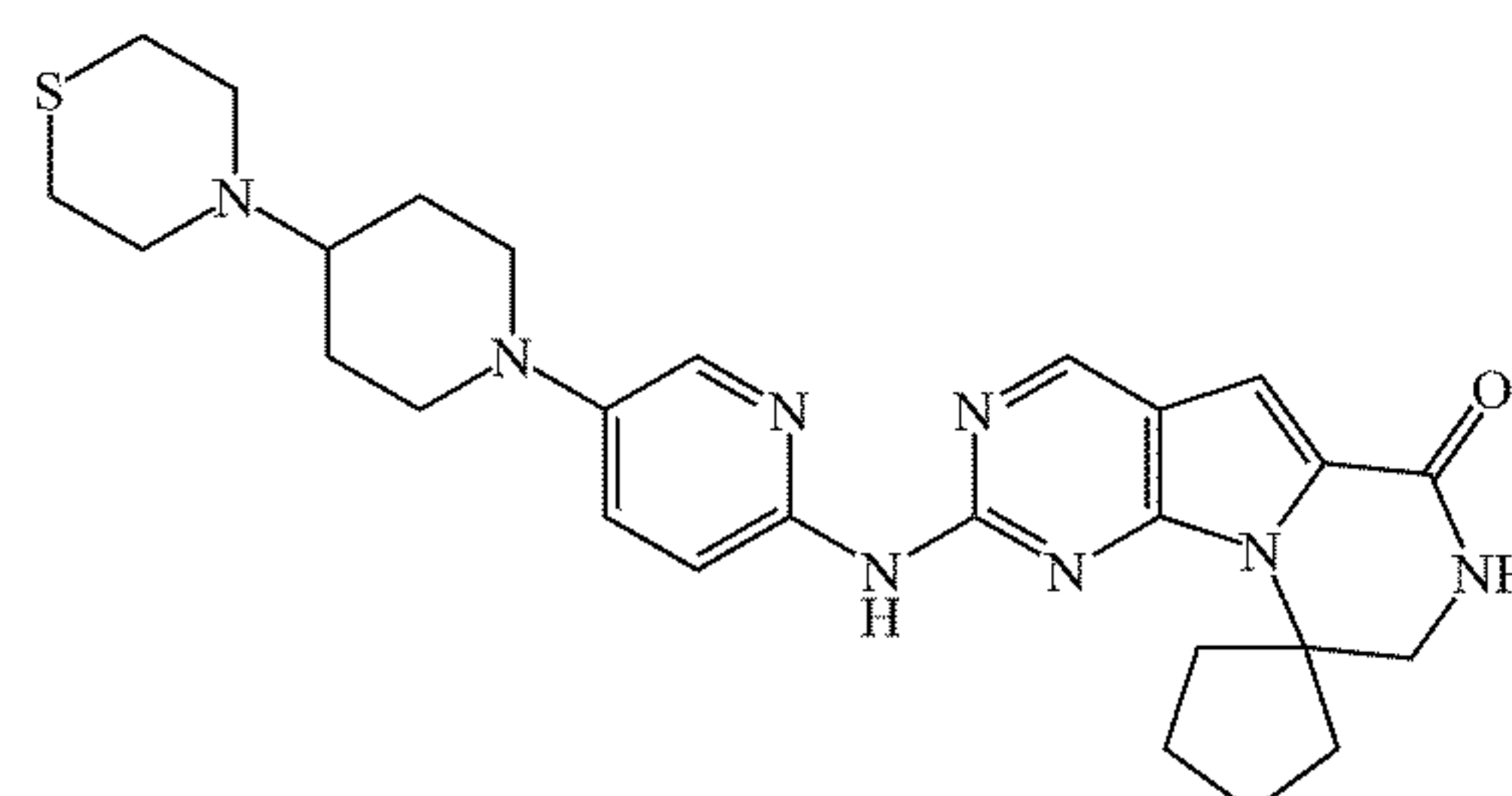


[0542] Compound 104 was synthesized using similar conditions to those described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.29 (d, J=6.73 Hz, 6 H) 1.66 - 1.79 (m, 2 H) 1.84 - 1.95 (m, 2 H) 1.98 - 2.09 (m, 2 H) 2.46 - 2.55 (m, 2 H) 3.29 - 3.39 (m, 2H) 3.58 - 3.70 (m, 4H) 3.77 - 3.86 (m, 4H) 7.24 (s, 1 H) 7.66 (d, J=9.37 Hz, 1 H) 7.96 (d, J=2.93 Hz, 1 H) 8.08 (s, 1 H) 8.48 (s, 1 H) 9.06 (s, 1 H) 9.28 (s, 1 H) 9.67 (s, 1 H) 11.36 (s, 1H). LCMS (ESI) 447 (M + H).

Example 105

Synthesis of Compound 105

[0543]

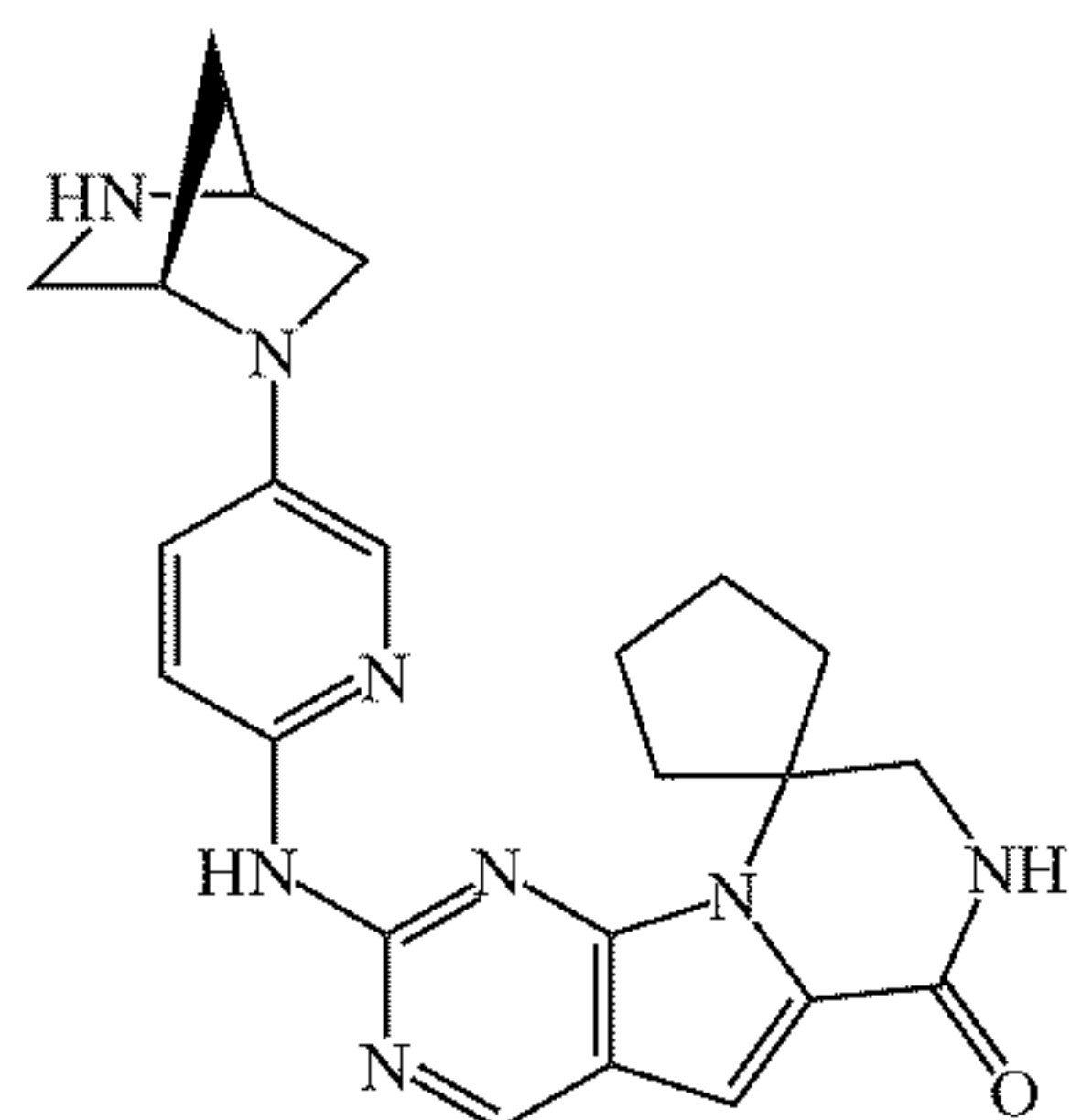


[0544] Compound 105 was synthesized using similar conditions to those described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.73 (s, 2 H) 1.76 - 1.85 (m, 2 H) 1.85 - 1.94 (m, 2 H) 1.98 - 2.07 (m, 2 H) 2.19 - 2.26 (m, 2 H) 2.48 - 2.52 (m, 1 H) 2.70 - 2.81 (m, 4 H) 3.13 - 3.20 (m, 1 H) 3.30 - 3.48 (m, 3 H) 3.58 - 3.71 (m, 4 H) 3.78 - 3.84 (m, 4 H) 7.24 (s, 1 H) 7.62 (d, J=9.37 Hz, 2 H) 7.89 (d, J=1.17 Hz, 1 H) 8.09 - 8.18 (m, 1 H) 8.48 (s, 1 H) 9.06 (s, 1 H) 11.46 (br s., 1H). LCMS (ESI) 519 (M + H).

Example 106

Synthesis of Compound 106

[0545]

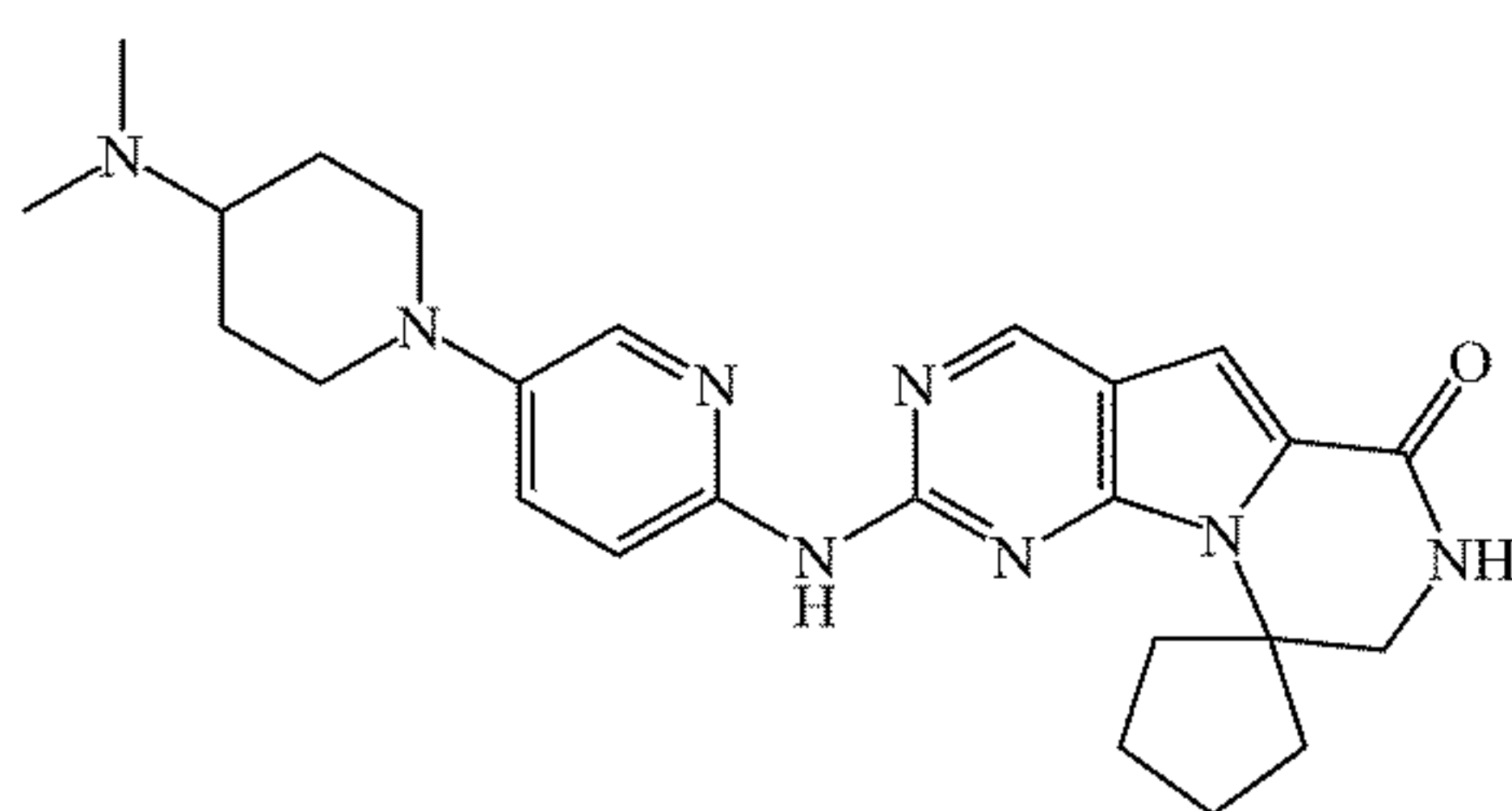


[0546] Compound 106 was synthesized using similar conditions to those described for compound 78 followed by the deblocking step described for compound 65 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.65 - 1.75 (m, 2 H) 1.85 - 1.93 (m, 2 H) 1.93 - 1.99 (m, 1 H) 2.00 - 2.06 (m, 2 H) 2.08 - 2.14 (m, 1 H) 2.47 - 2.55 (m, 2 H) 3.07 - 3.25 (m, 2 H) 3.25 - 3.69 (m, 5 H) 4.46 (s, 1 H) 4.67 (s, 1 H) 7.22 (s, 1 H) 7.58 - 7.69 (m, 2 H) 8.46 (s, 1 H) 9.02 (s, 1 H) 9.34 (s, 1 H) 9.65 (s, 1 H). LCMS (ESI) 431 (M + H).

Example 107

Synthesis of Compound 107 (Also Referred to as Compound YY)

[0547]

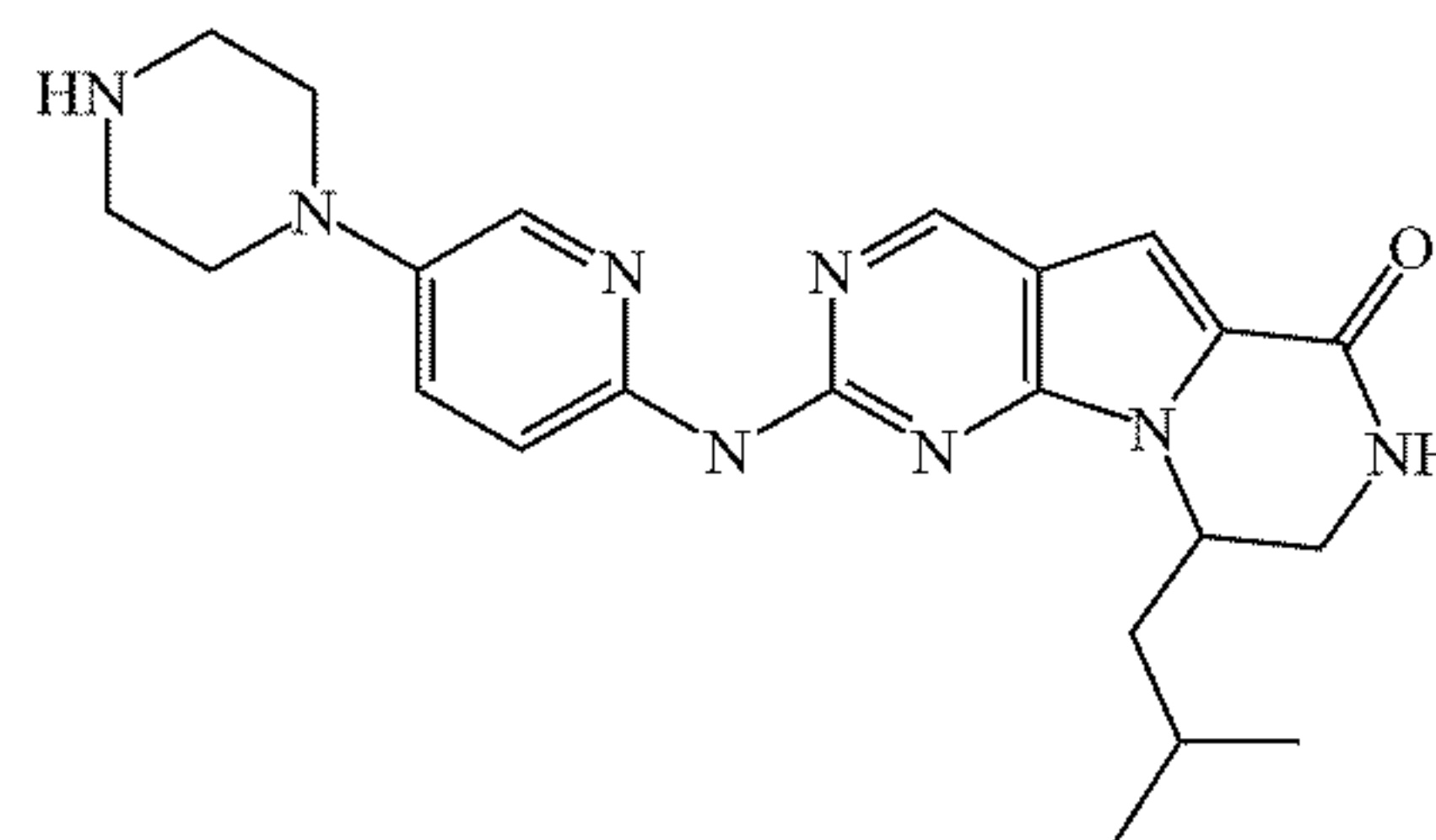


[0548] Compound 107 was synthesized using similar conditions to those described for compound 78 and was converted to an HCl salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.65 - 1.82 (m, 3 H) 1.89 (br. s., 2 H) 1.98 - 2.08 (m, 2 H) 2.13 (br. s., 2 H) 2.47 - 2.55 (m, 2 H) 2.68 (d, J=4.98 Hz, 6 H) 2.71 - 2.80 (m, 2 H) 3.29 - 3.71 (m, 10 H) 7.16 - 7.26 (m, 1 H) 7.67 (d, J=9.66 Hz, 2 H) 7.91 (d, J=2.05 Hz, 1 H) 8.14 (br. s., 1 H) 8.48 (br. s., 1 H) 9.05 (s, 1 H) 11.14 (br. s., 1 H) 11.43 (br. s., 1 H). LCMS (ESI) 461 (M + H).

Example 108

Synthesis of Compound 108

[0549]

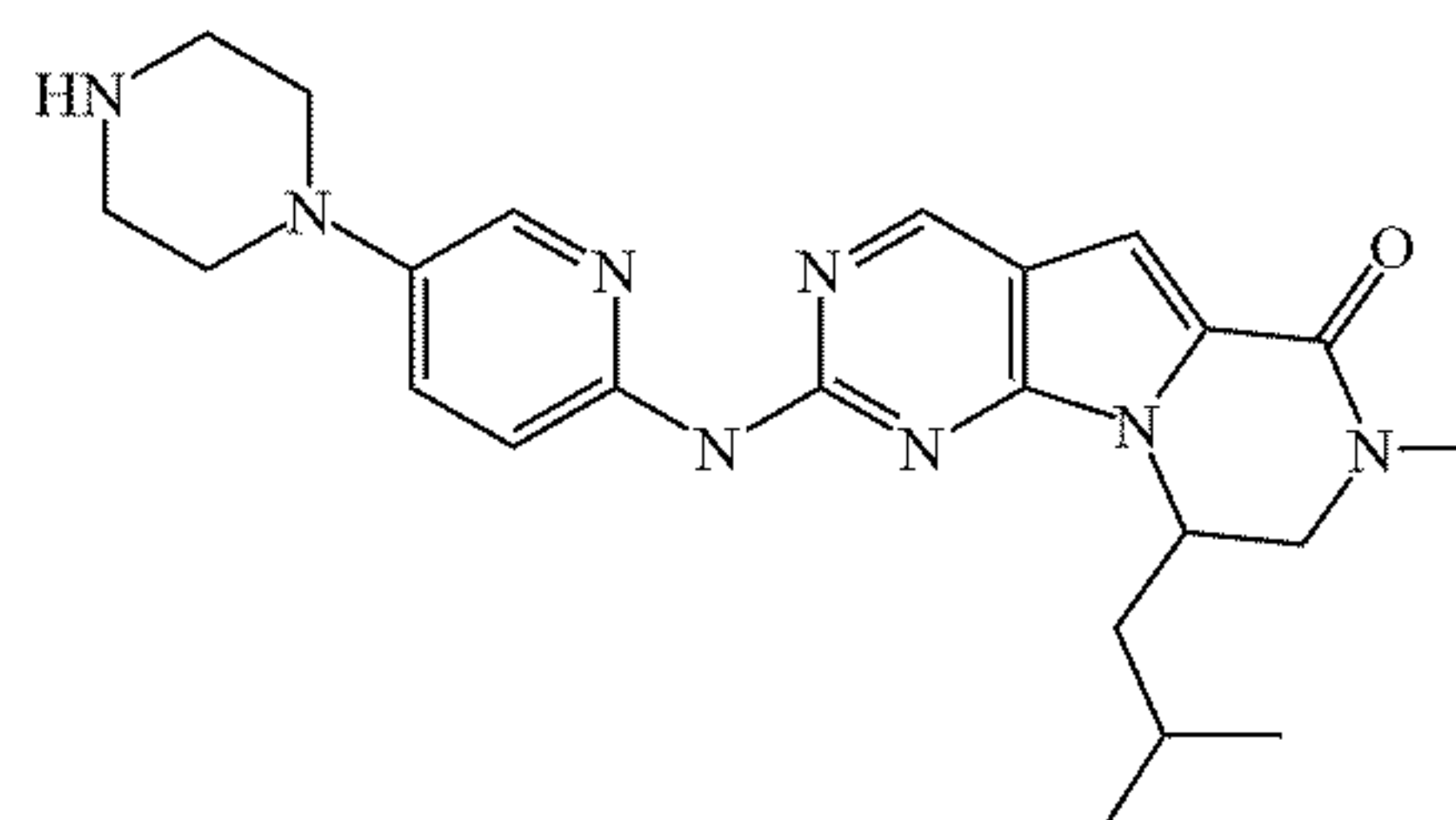


[0550] Compound 108 was synthesized in a manner similar to that described for compounds 64 and 65 and was recovered as an HCl salt. The analytical data was consistent with that described for the antipode compound 75.

Example 109

Synthesis of Compound 109

[0551]

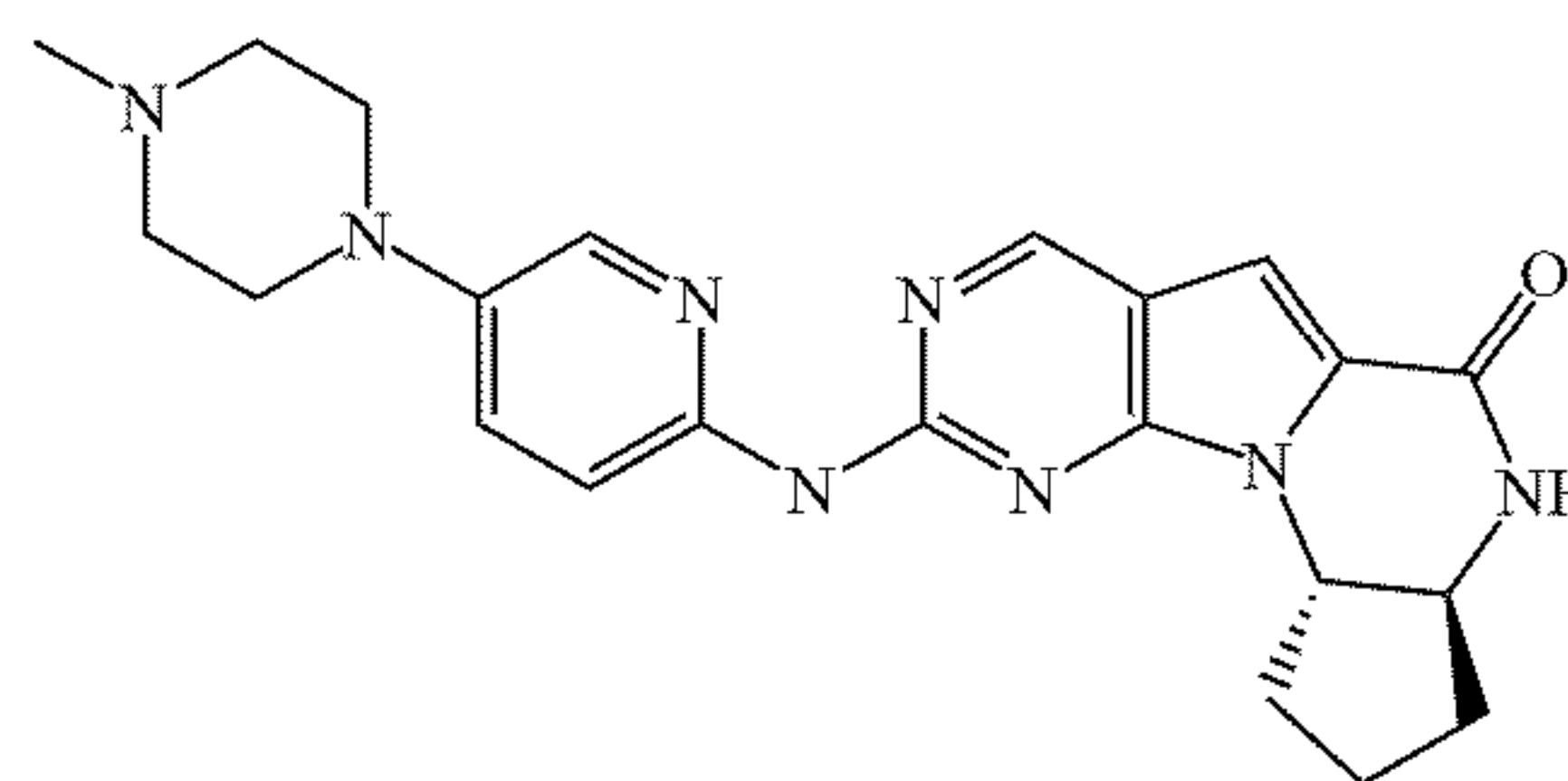


[0552] Compound 109 was synthesized in a manner similar to that described for compounds 64 and 65 and was recovered as an HCl salt. The analytical data was consistent with that described for the antipode compound 75.

Example 110

Synthesis of Compound 110

[0553]

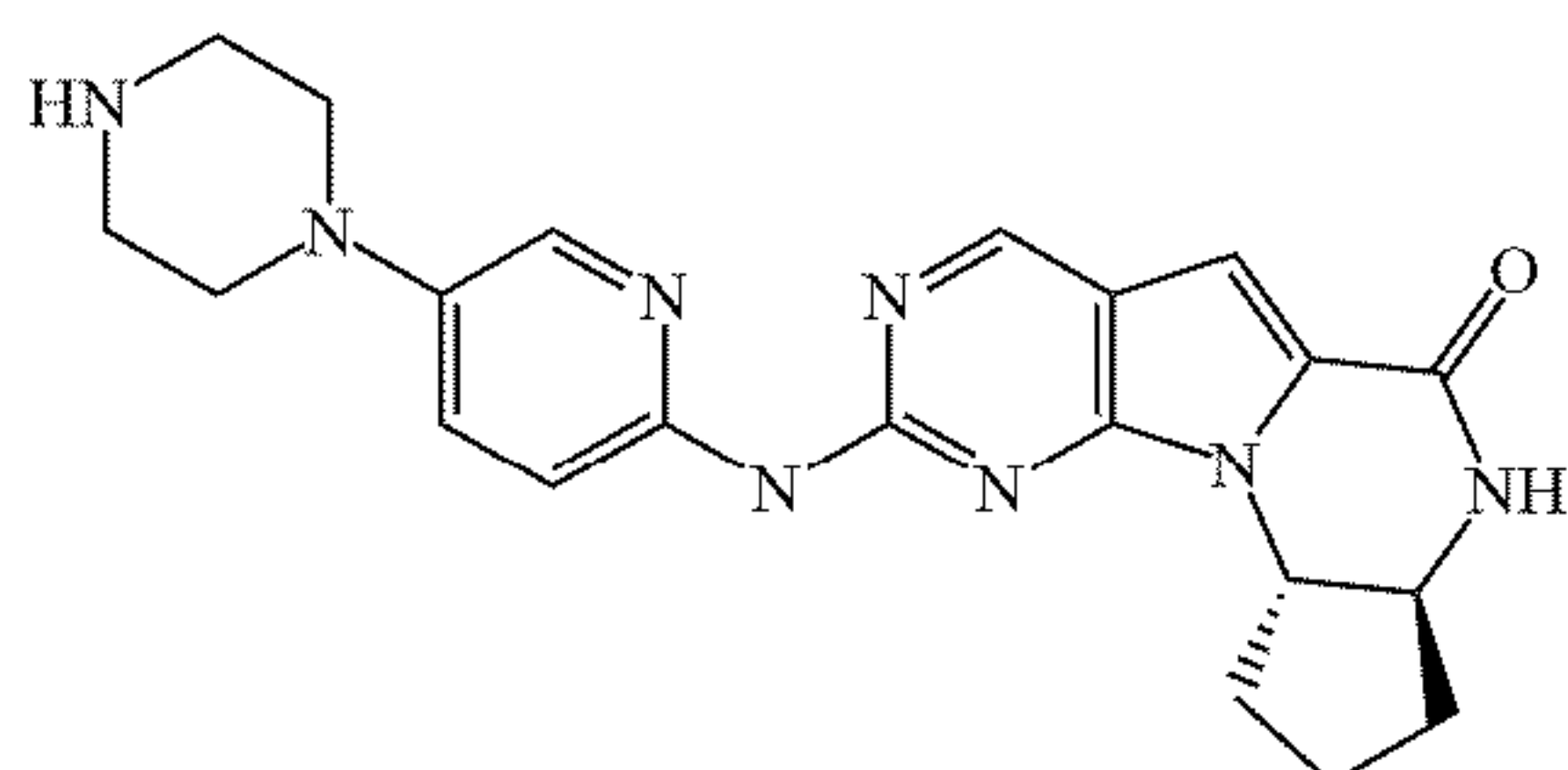


[0554] Compound 110 was synthesized in a similar manner to that described for compound 78 and then converted to its hydrochloride salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.50 - 1.65 (m, 1 H) 1.92 - 2.02 (m, 3 H) 2.06 - 2.15 (m, 1 H) 2.78 (d, J=3.81 Hz, 4 H) 3.10 - 3.20 (m, 4 H) 3.47 - 3.51 (m, 2 H) 3.64 - 3.71 (m, 1 H) 3.76 - 3.83 (m, 2 H) 3.98 - 4.14 (m, 1 H) 7.20 (s, 2 H) 7.77 (s, 1 H) 7.97 (s, 2 H) 8.81 (s, 1 H) 9.03 (s, 1 H) 10.97 (br s., 1H). LCMS (ESI) 419 (M + H).

Example 111

Synthesis of Compound 111

[0555]

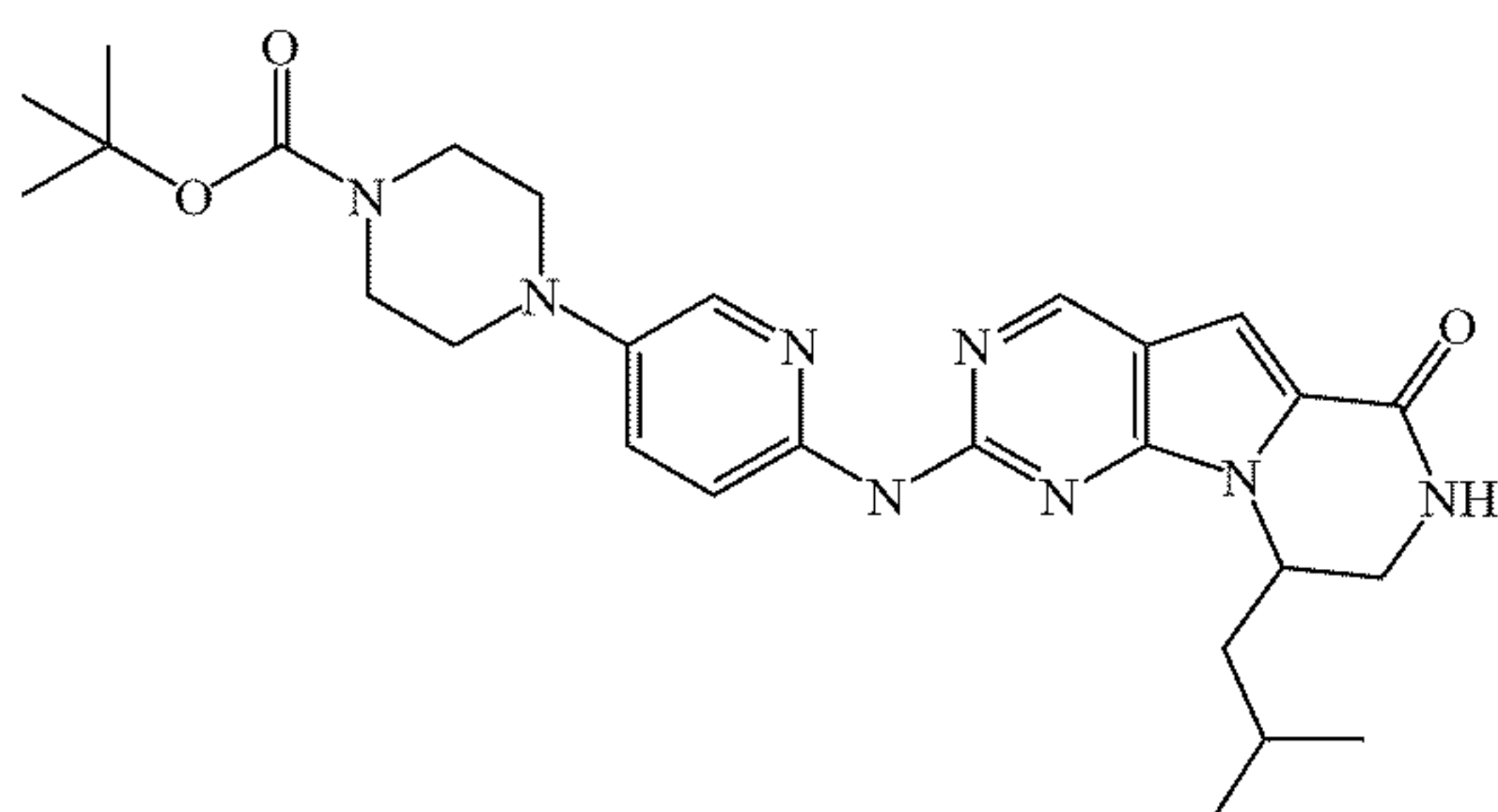


[0556] Compound 111 was synthesized in a similar manner to that described for compound 78 and then converted to its hydrochloride salt. ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.54 - 1.59 (m, 1 H) 1.92 - 2.01 (m, 3 H) 2.06 - 2.15 (m, 1 H) 2.76 - 2.84 (m, 1 H) 3.17 - 3.24 (m, 6 H) 3.64 - 3.71 (m, 2 H) 4.02 - 4.11 (m, 2 H) 7.22 (s, 2 H) 7.64 (s, 1 H) 7.97 (s, 2 H) 8.75 (s, 1 H) 8.97 (s, 1 H) 9.21 (s, 1 H). LCMS (ESI) 405 (M + H).

Example 112

Synthesis of Compound 112

[0557]

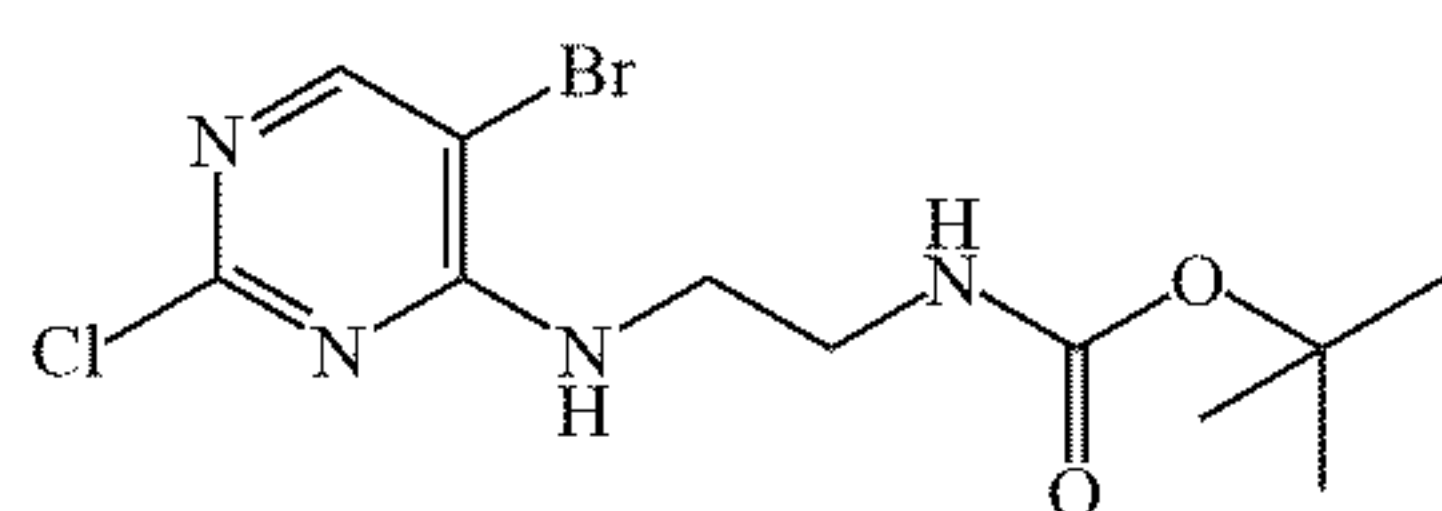


[0558] Compound 112 was synthesized using similar experimental conditions to that described for compound 64.

Example 113

Synthesis of Tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate, Compound 113

[0559]



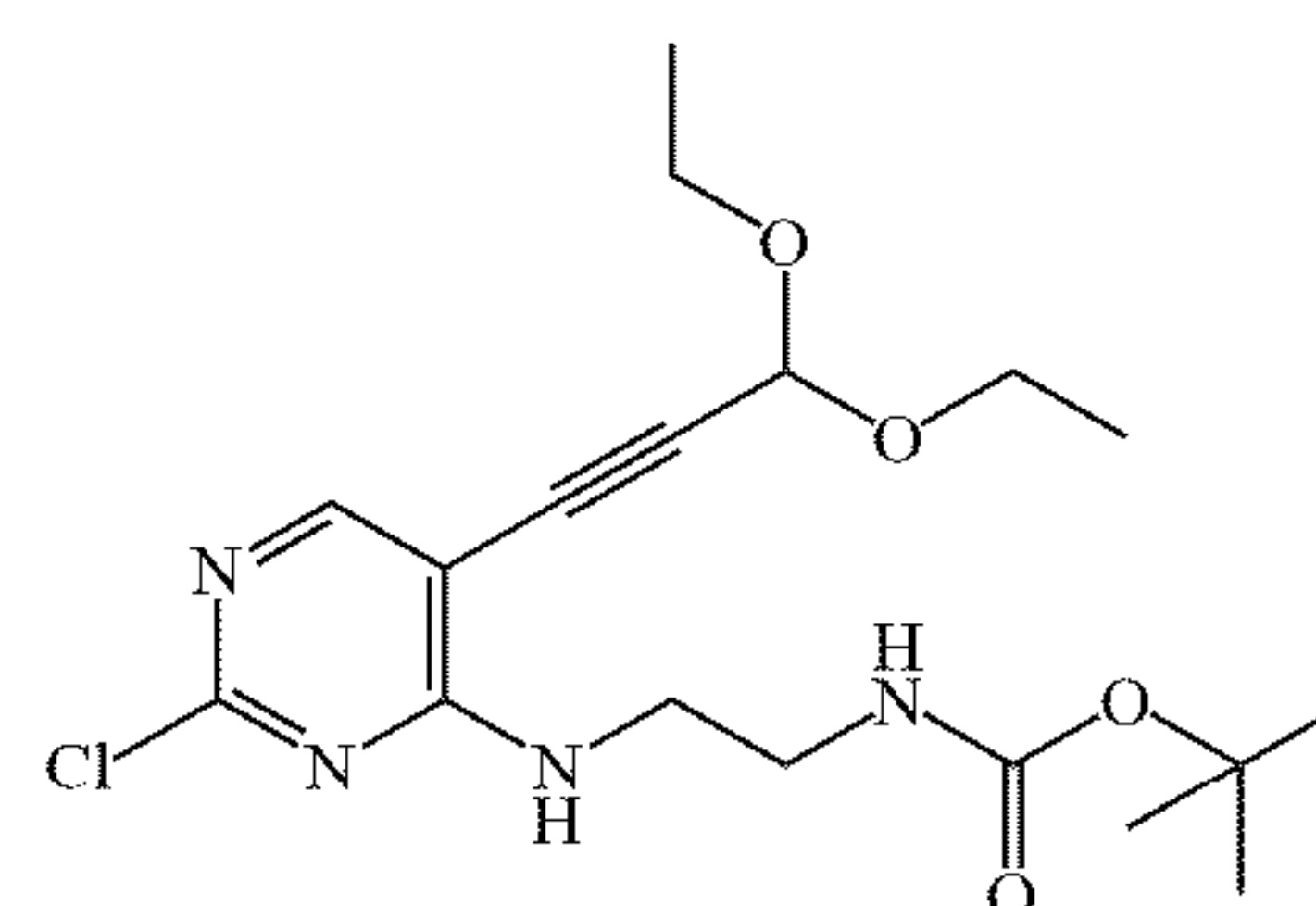
[0560] To a solution of 5-bromo-2,4-dichloropyrimidine (12.80 g, 0.054 mole) in ethanol (250 mL) was added Hunig's base (12.0 mL) followed by the addition of a solution of N-(tert-butoxycarbonyl)-1,2-diaminoethane (10 g,

0.0624 mole) in ethanol (80 mL). The contents were stirred overnight for 20 hrs. The solvent was evaporated under vacuum. Ethyl acetate (800 mL) and water (300 mL) were added and the layers separated. The organic layer was dried with magnesium sulfate and then concentrated under vacuum. Column chromatography on silica gel using hexane/ethyl acetate (0- 60%) afforded tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate. LCMS (ESI) 351 (M + H).

Example 114

Synthesis of Tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate, Compound 114

[0561]

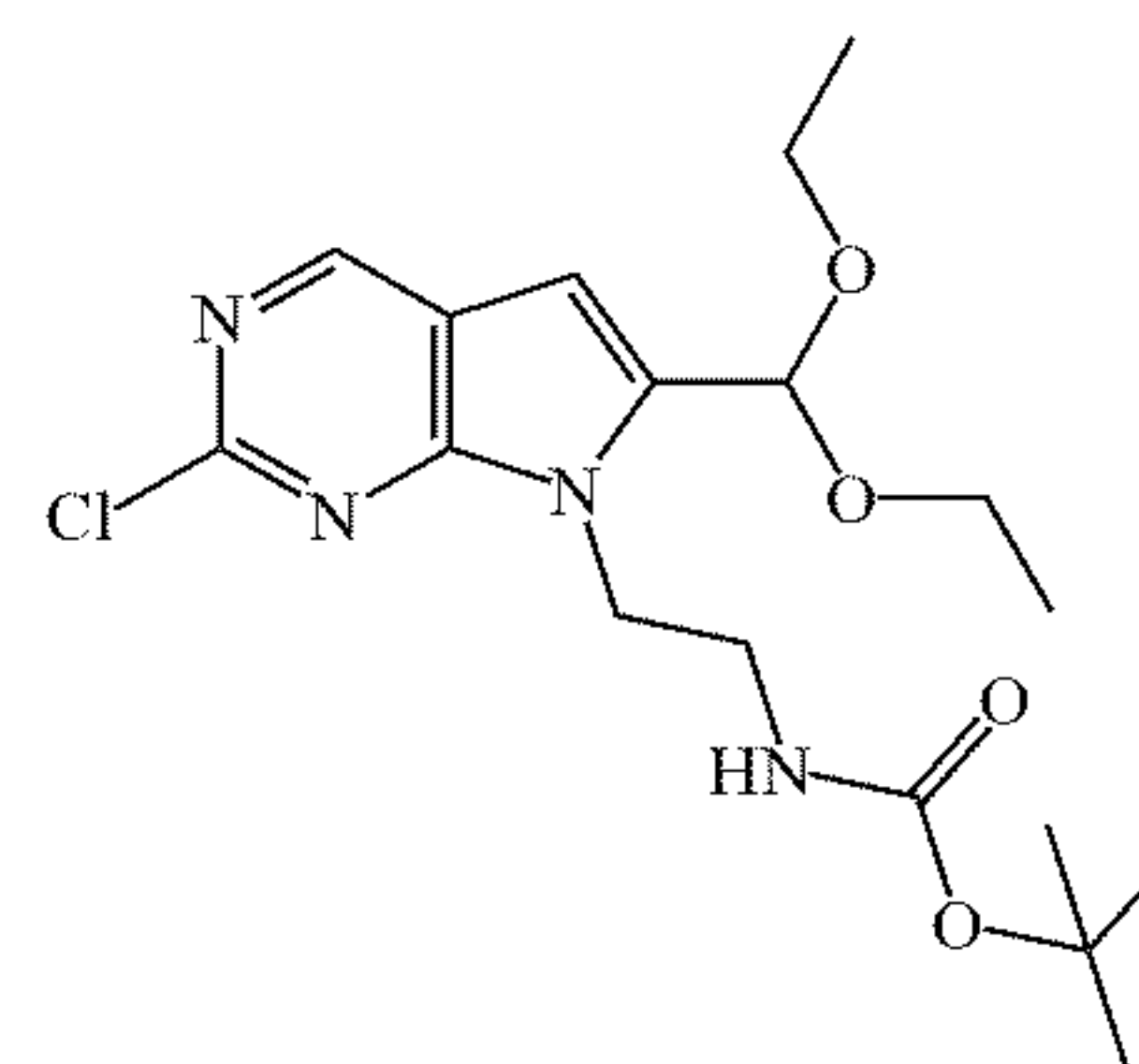


[0562] To tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate (5 g, 14.23 mmole) in toluene (42 mL) and triethylamine (8.33 mL) under nitrogen was added triphenyl arsine (4.39 g), 3,3-diethoxyprop-1-yne (3.24 mL) and Pddba (1.27 g). The contents were heated at 70 degrees for 24 hrs. After filtration through CELITE®, the crude reaction was columned using hexane/ethyl acetate (0- 20%) to afford the desired product 3.9 g). Column chromatography of the resulting residue using hexane/ethyl acetate (0- 30%) afforded tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate. LCMS (ESI) 399 (M + H).

Example 115

Synthesis of Tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate, Compound 115

[0563]



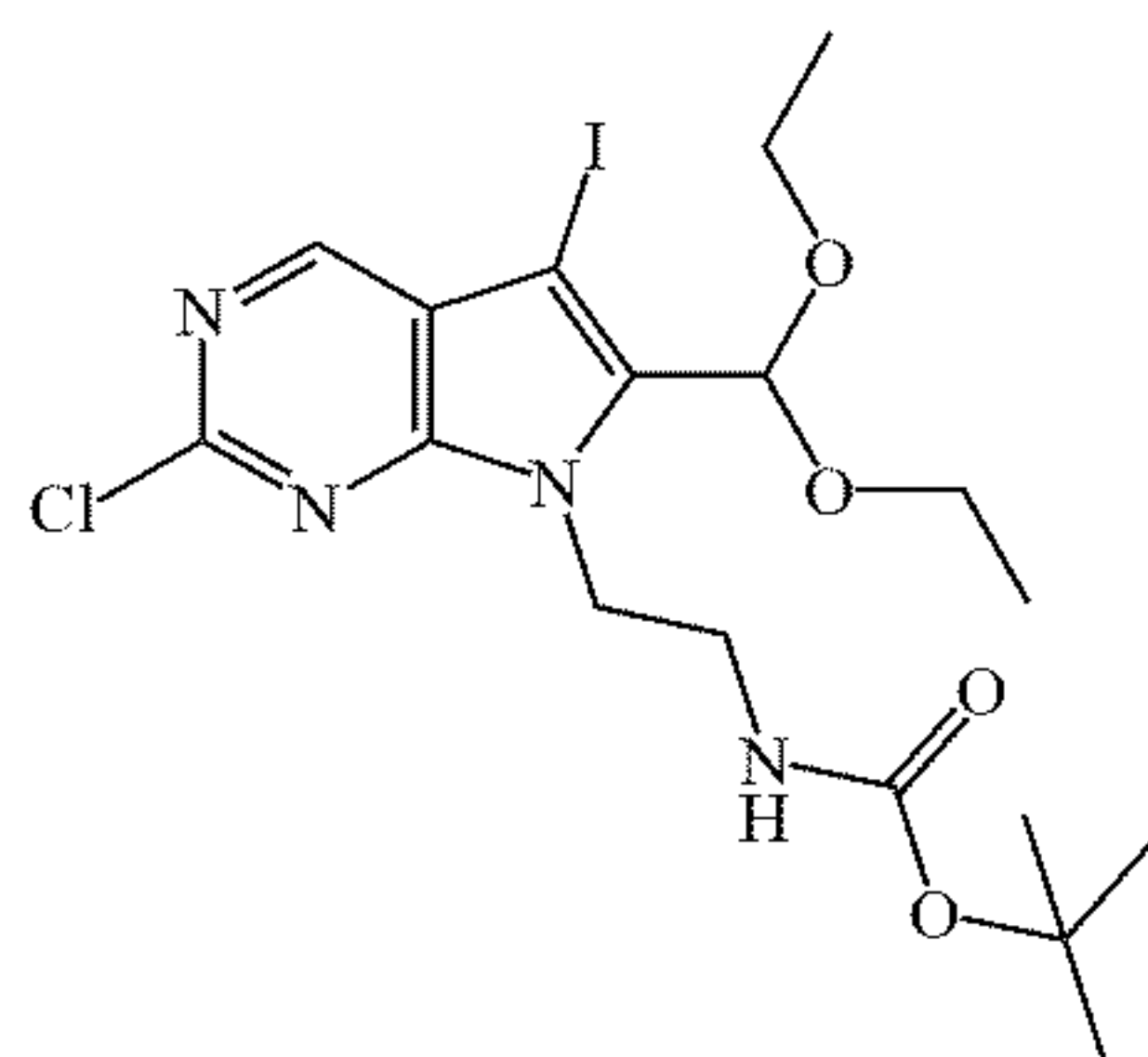
[0564] To a solution of Compound 114 (3.9 g, 0.00976 mole) in THF (60 mL) was added TBAF

(68.3 mL, 7eq). The contents were heated to 45 degrees for 2 hrs. Concentration followed by column chromatography using ethyl acetate/hexane (0-50%) afforded tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate as a pale brown liquid (1.1 g). ¹HNMR (d₆-DMSO) 6 ppm 8.88 (s, 1H), 6.95 (brs, 1H), 6.69 (s, 1H), 5.79 (s, 1H), 4.29 (m, 2H), 3.59 (m, 4H), 3.34 (m, 1H), 3.18 (m, 1H), 1.19 (m, 9H), 1.17 (m, 6H). LCMS (ESI) 399 (M+H).

Example 116

Synthesis of Tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)-5-iodo-pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate, Compound 116

[0565]

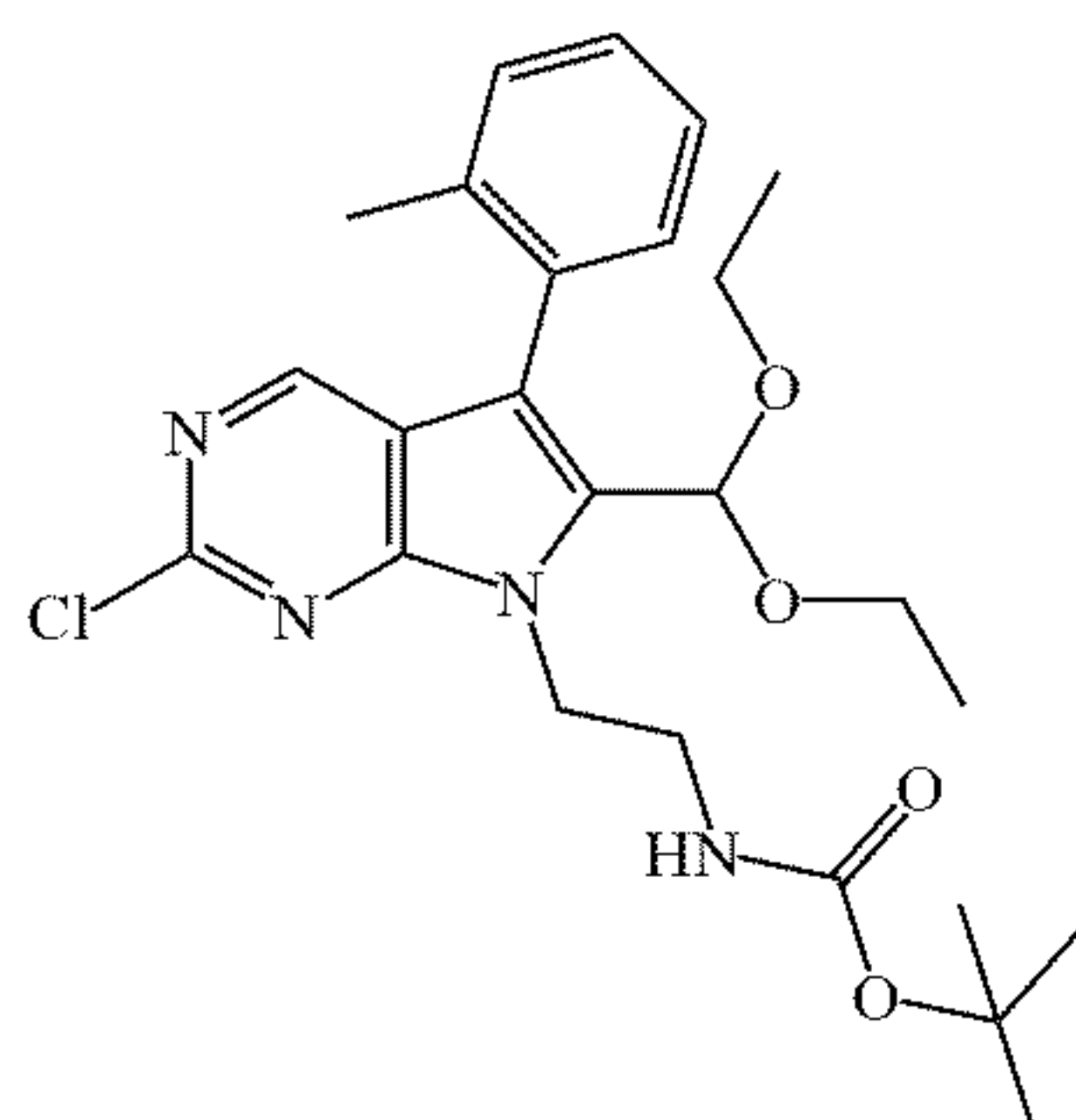


[0566] To tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate (0.1 g, 0.00025 mol) in acetonitrile (2 mL) was added 1,3-diiodo-5,5-dimethylhydantoin (95 mg, 1 eq), and solid NaHCO₃ (63 mg, 3 eq). The reaction was stirred at room temperature for 16 hrs. The reaction was filtered and concentrated in vacuo. The product was purified by silica gel column chromatography using hexane/ethyl acetate (0 - 50%) to afford tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)-5-iodo-pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate as a pale yellow solid (0.03 g). LCMS (ESI) 525 (M + H).

Example 117

Synthesis of tert-Butyl N-[2-[2-chloro-6-(diethoxymethyl)-5-(o-tolyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate, Compound 117

[0567]

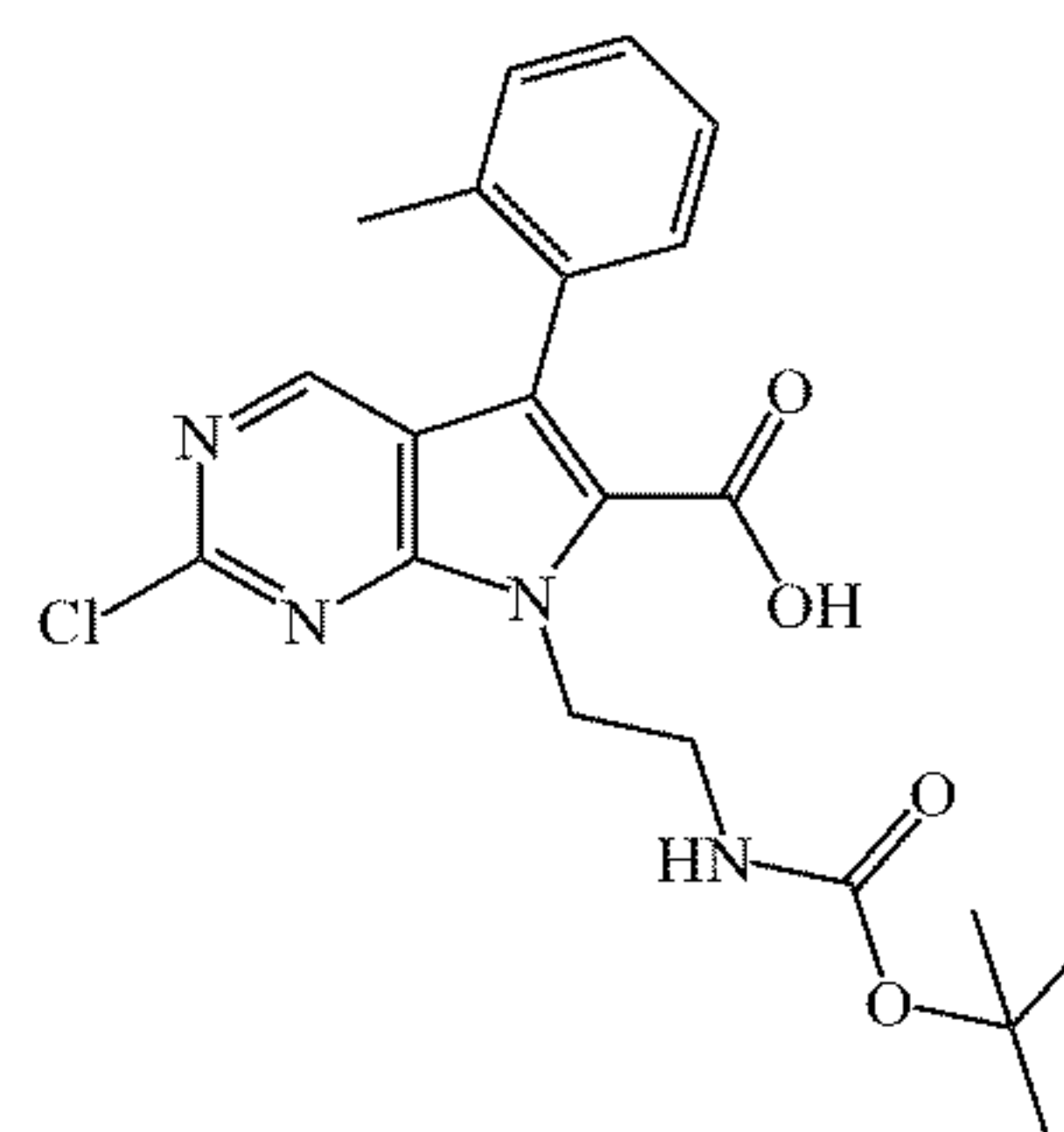


[0568] To tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)-5-iodo-pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate (0.1 g, 0.19 mmole) in dioxane (3 mL) was added 2-methyl-phenylboronic acid (28 mg), tetrakis(triphenylphosphine) palladium (25 mg) and potassium phosphate (250 mg) in water (0.3 mL). The reaction was heated in a CEM Discovery microwave at 90° C. for 3 hrs. The crude reaction was loaded onto silica gel and columned using hexane/ethyl acetate (0 -30%) to afford tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)-5-(o-tolyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate (0.06 g). LCMS (ESI) 489 (M + H).

Example 118

Synthesis of 7-[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-5-(o-tolyl)pyrrolo[2,3-d]pyrimidine-6-carboxylic Acid, Compound 118

[0569]

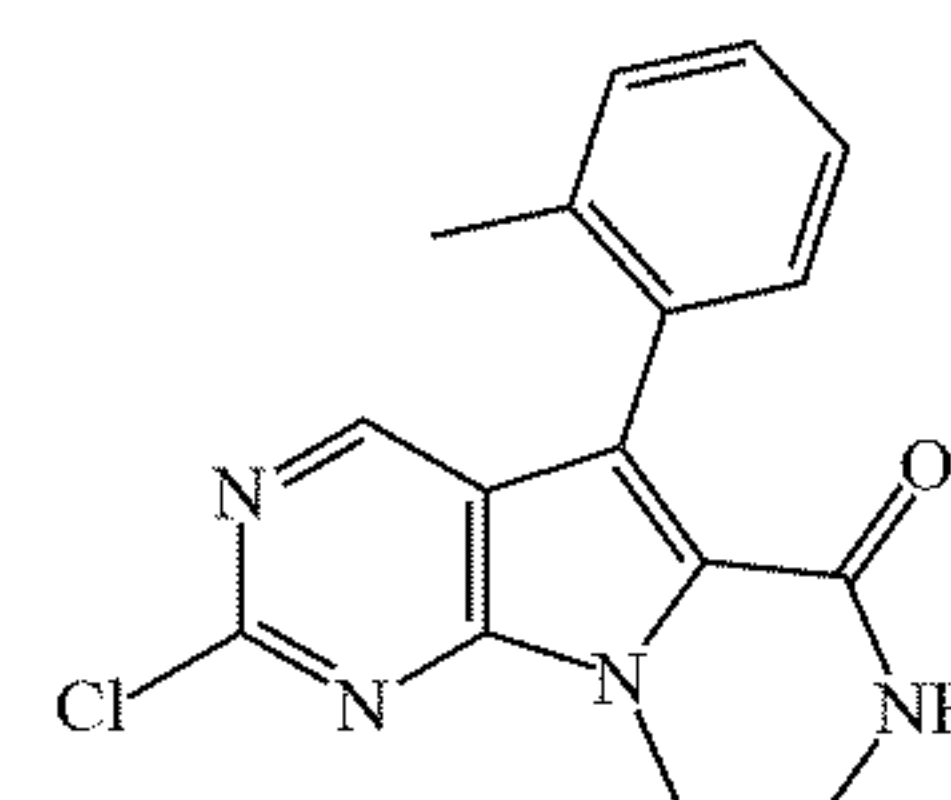


[0570] To tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)-5-(o-tolyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate (0.85 g, 1.74 mmole) in AcOH (10 mL) was added water (1.5 mL). The reaction was stirred at room temperature for 16 hrs. The crude reaction was then concentrated under vacuum. After the addition of ethyl acetate (50 mL), the organic layer was washed with satd. NaHCO₃. The organic layer was dried with magnesium sulfate and then concentrated under vacuum to afford the crude intermediate, tert-butyl N-[2-[2-chloro-6-formyl-5-(o-tolyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate. To this crude intermediate in DMF (5 mL) was added oxone (1.3 g). After stirring for 2.5 hrs, water (20 mL) and ethyl acetate (100 mL) were added. The organic layer was separated, dried and then concentrated under vacuum to afford the crude product which was columned over silica gel using hexane/ethyl acetate (0 - 50%) to afford 7-[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-5-(o-tolyl)pyrrolo[2,3-d]pyrimidine-6-carboxylic acid (0.112 g). LCMS (ESI) 431 (M + H).

Example 119

Synthesis of Compound 119

[0571]

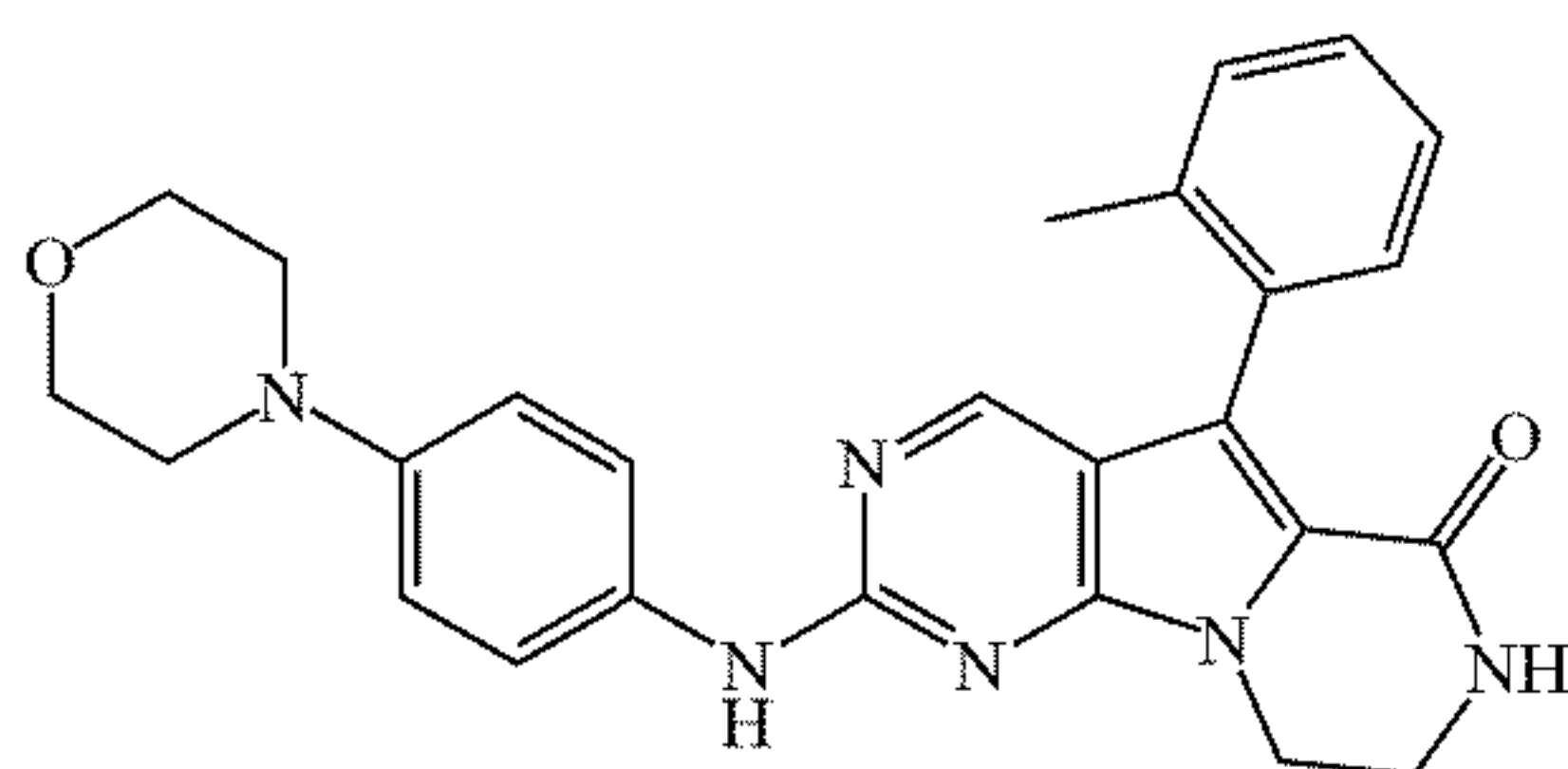


[0572] To 7-(tert-butoxycarbonylamino)ethyl]-2-chloro-5-(o-tolyl)pyrrolo[2,3-d]pyrimidine-6-carboxylic acid (0.1 g, 0.261 mmol) in DCM (4.1 mL) was added DMAP (20 mg) followed by the addition of N,N'-diisopropylcarbodiimide (0.081 mL, 2eq). After stirring for 3 hrs, TFA (0.723 mL) was added. Stirring was then continued for another 30 minutes. The reaction mixture was neutralized with satd. NaHCO₃. DCM (20 mL) was then added and the organic layer separated, dried with magnesium sulfate and then concentrated under vacuum to afford the crude product which was columned using hexane/ethyl acetate (0-100%) to afford chloro tricyclic amide Compound 119 (0.65 g). LCMS (ESI) 313 (M + H).

Example 120

Synthesis of Compound 120

[0573]

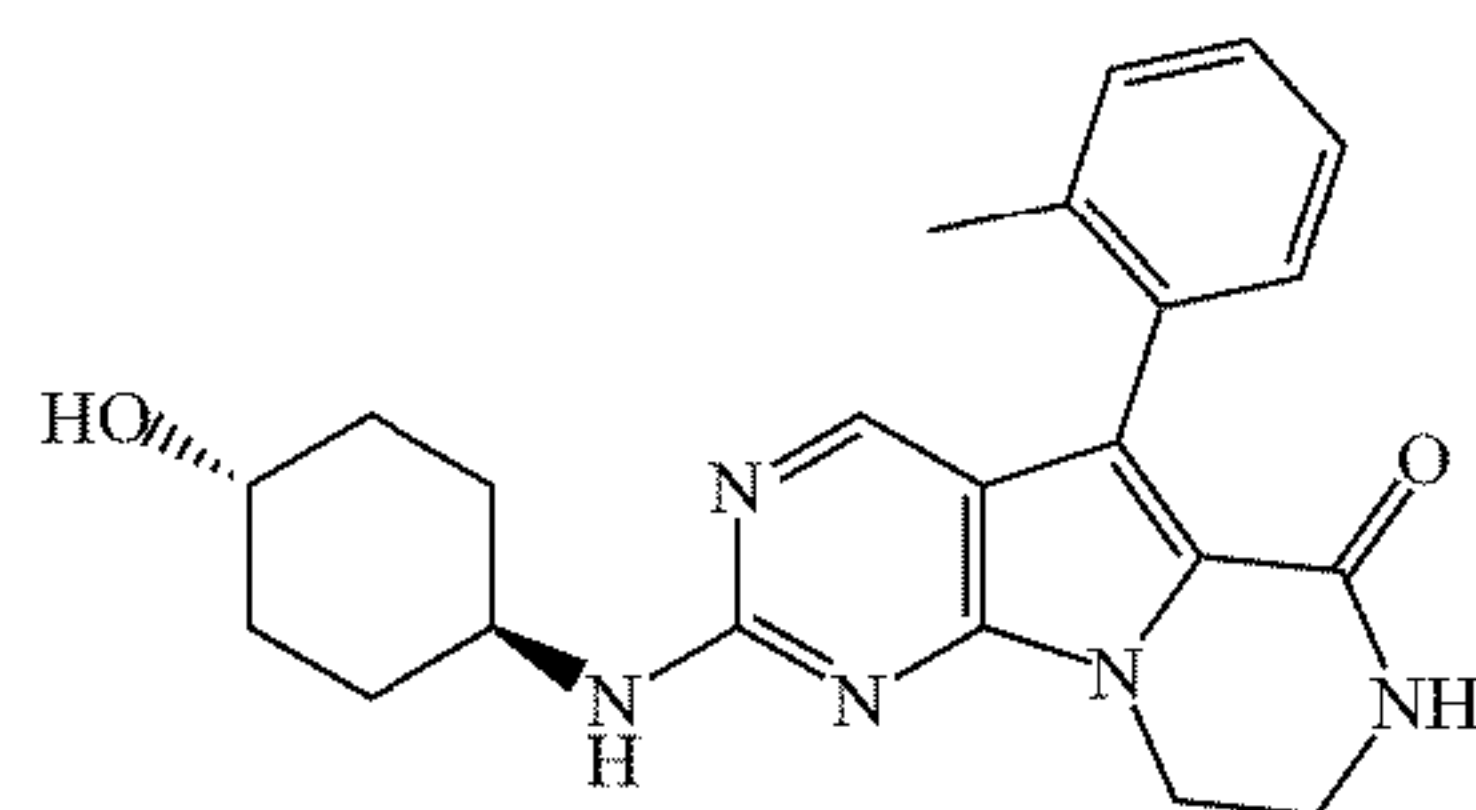


[0574] To the chloro tricyclic amide (0.040 g, 0.128 mmole) (Compound 119) in dioxane (2.5 mL) under nitrogen was added Pd₂(dba)₃ (12 mg), sodium tert-butoxide (16 mg), BINAP (16 mg) and 4-morpholinoaniline (22.7 mg, 1eq). The reaction mixture was heated at 90° C. in a CEM Discovery microwave for 3.0 hrs. The crude reaction was loaded onto a silica gel column and the contents eluted with DCM/MeOH (0-6%) to afford the product (10 mg). LCMS (ESI) 455 (M + H). ¹HNMR (600 MHz, DMSO-d₆) δ ppm 2.14 (s, 3 H) 3.23 - 3.50 (m, 2 H) 3.57 - 3.73 (m, 2 H), 3.81 - 3.92 (m, 8H), 7.11 - 7.31 (m, 4 H) 7.31 - 7.48 (m, 1 H) 7.58 - 7.73 (m, 1 H) 7.77 - 7.95 (m, 2 H) 8.05 - 8.21 (m, 1 H) 8.44 (s, 1 H) 9.85 - 10.01 (m, 1 H).

Example 121

Synthesis of Compound 121

[0575]



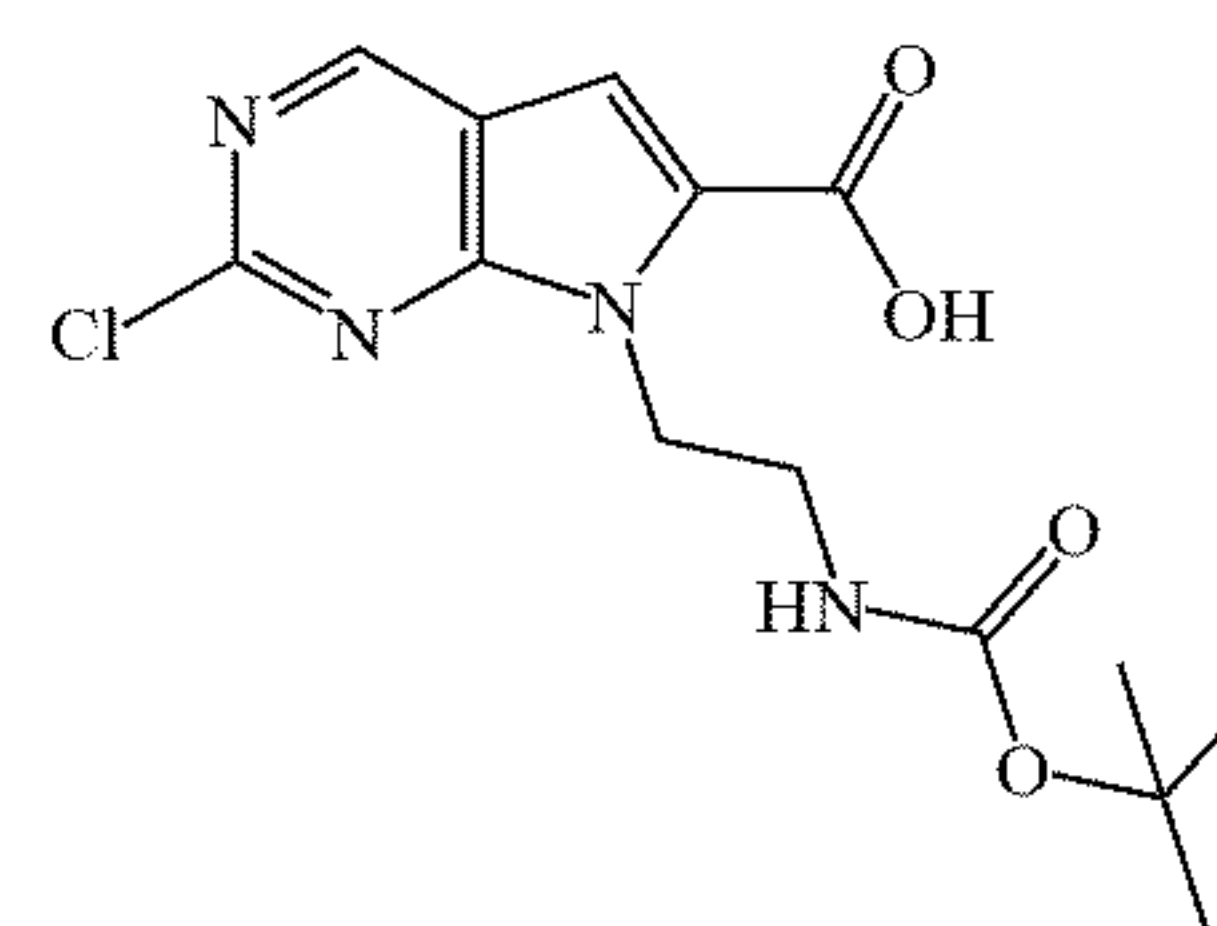
[0576] To the chloro tricyclic amide (0.024 g) (Compound 119) in N-methyl-2-pyrrolidone (NMP) (1.5 mL) was added trans-4-aminocyclohexanol (0.0768 mmol, 26.54 mg, 3 eq) and Hunig's base (0.4 mL). The reaction was heated in a CEM Discovery microwave vessel at 150° C. for 1.2 hrs. The crude reaction was loaded onto a silica gel column and the contents eluted with DCM/MeOH (0 - 10%) to afford the product (21 mg). LCMS (ESI) 392 (M + H). ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.23 (d, J=8.78 Hz, 4 H) 1.84 (br. s., 4 H) 2.11 (s, 3 H) 3.34 - 3.43 (m, 1 H) 3.55

(br. s., 2 H) 3.72 (br. s., 1 H) 4.13 (br. s., 2 H) 4.50 (br. s., 1 H) 7.03 (br. s., 1 H) 7.12 - 7.28 (m, 4 H) 7.96 (br. s., 1 H) 8.18 (br. s., 1 H).

Example 122

Synthesis of 7-[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic Acid, Compound 122

[0577]

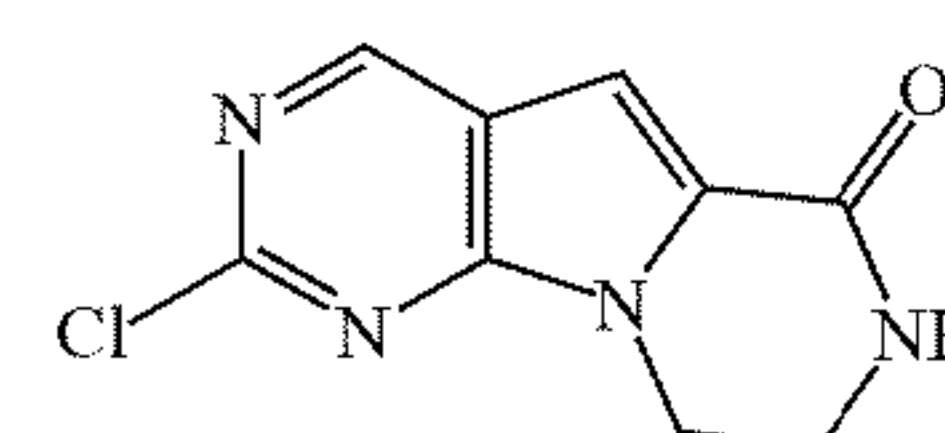


[0578] 7-(tert-butoxycarbonylamino)ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using a similar experimental procedure as that described for the synthesis of 7-(tert-butoxycarbonylamino)ethyl]-2-chloro-5-(o-tolyl)pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 341 (M + H).

Example 123

Synthesis of Compound 123

[0579]

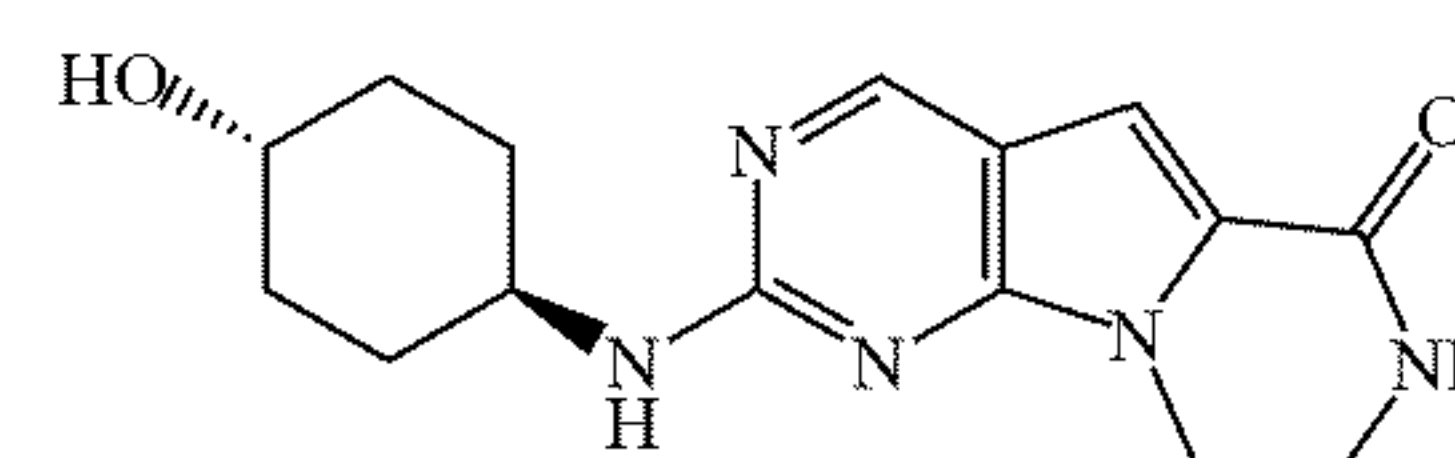


[0580] Chloro tricyclic amide, Compound 123, was synthesized using a similar experimental procedure as that described for the synthesis of chloro tricyclic amide (Compound 119). LCMS (ESI) 223 (M + H).

Example 124

Synthesis of Compound 124

[0581]

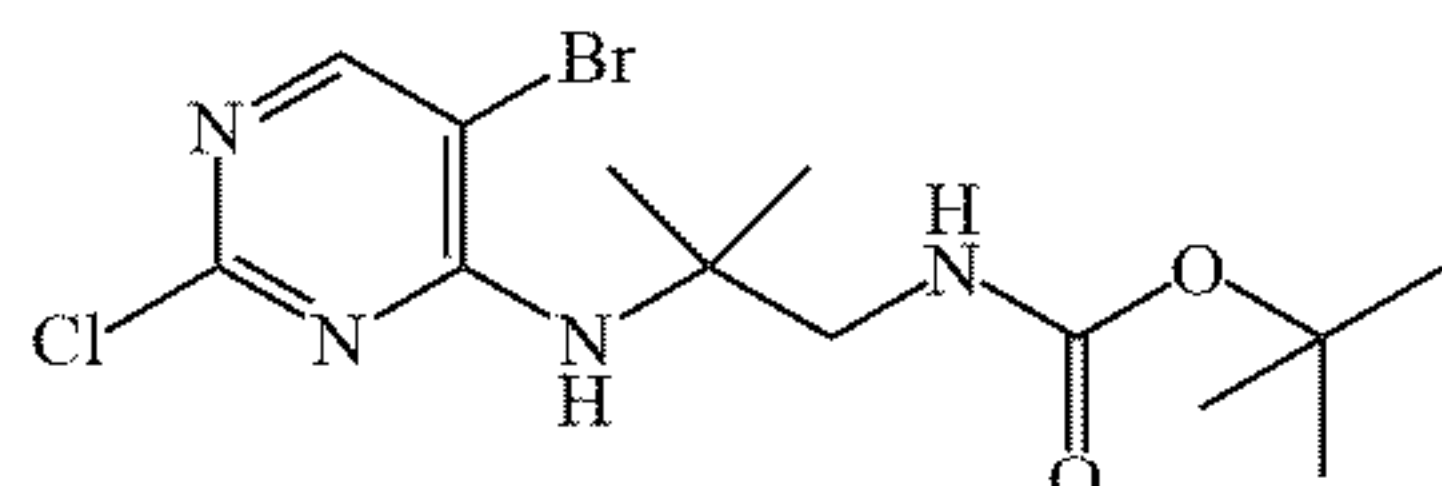


[0582] To the chloro tricyclic amide, Compound 123 (0.035 g, 0.00157 mole) in NMP (1.5 mL) was added Hunig's base (0.3 mL) followed by the addition of the trans-4-aminocyclohexanol (54.2 mg). The reaction mixture was heated at 150° C. for 1.5 hrs. The crude reaction was loaded onto a silica gel column and the column was eluted with DCM/MeOH (0 - 10%) to afford the product (5 mg). LCMS (ESI) 302 (M + H).

Example 125

Synthesis of Tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-methylpropyl]carbamate, Compound 125

[0583]

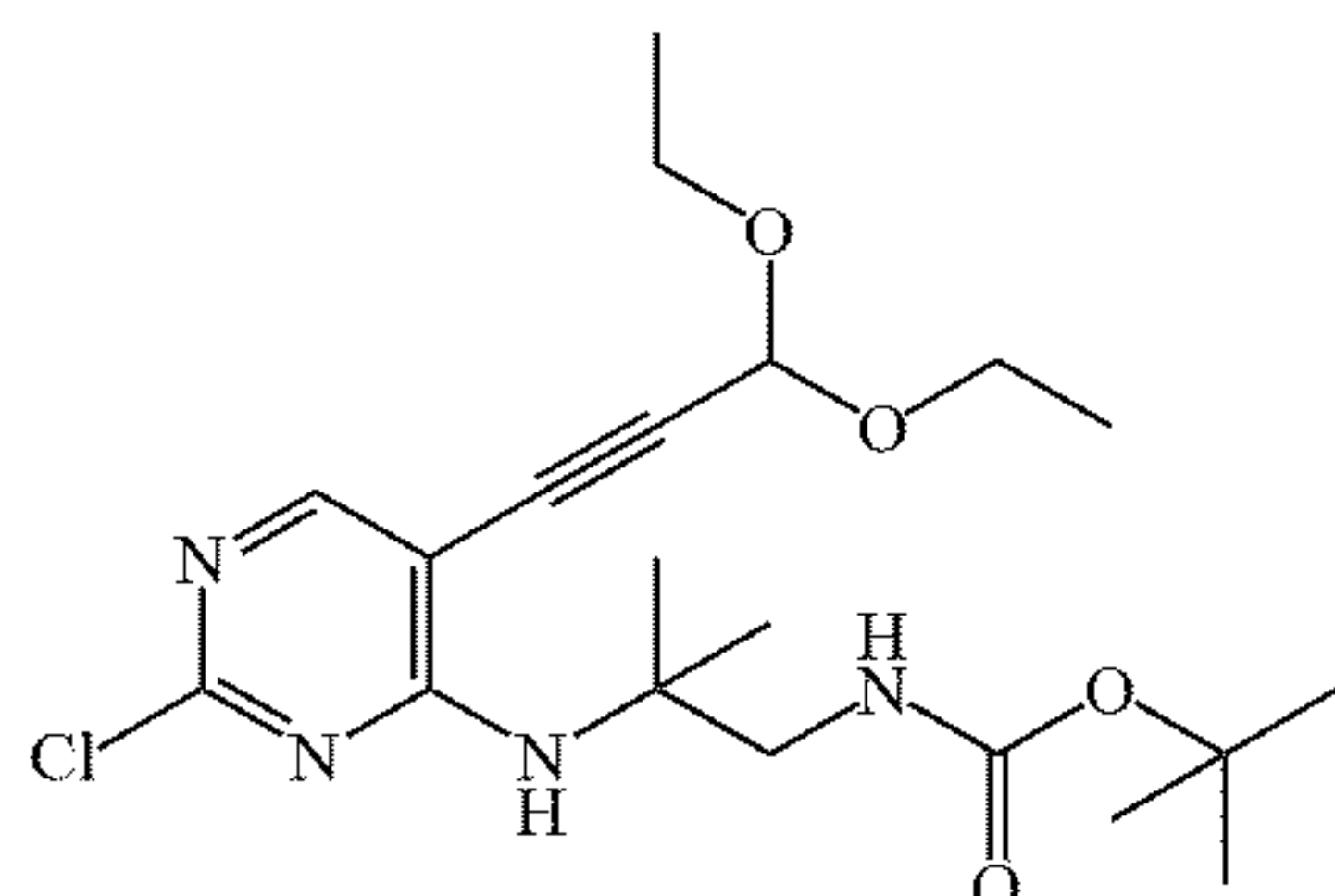


[0584] tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-methyl-propyl]carbamate was synthesized by treating 5-bromo-2,4-dichloropyrimidine with tert-butyl N-(2-amino-2-methyl-propyl)carbamate using similar experimental conditions as described for the synthesis of tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate. LCMS (ESI) (M+H) 379.

Example 126

Synthesis of Tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methyl-propyl]carbamate, Compound 126

[0585]



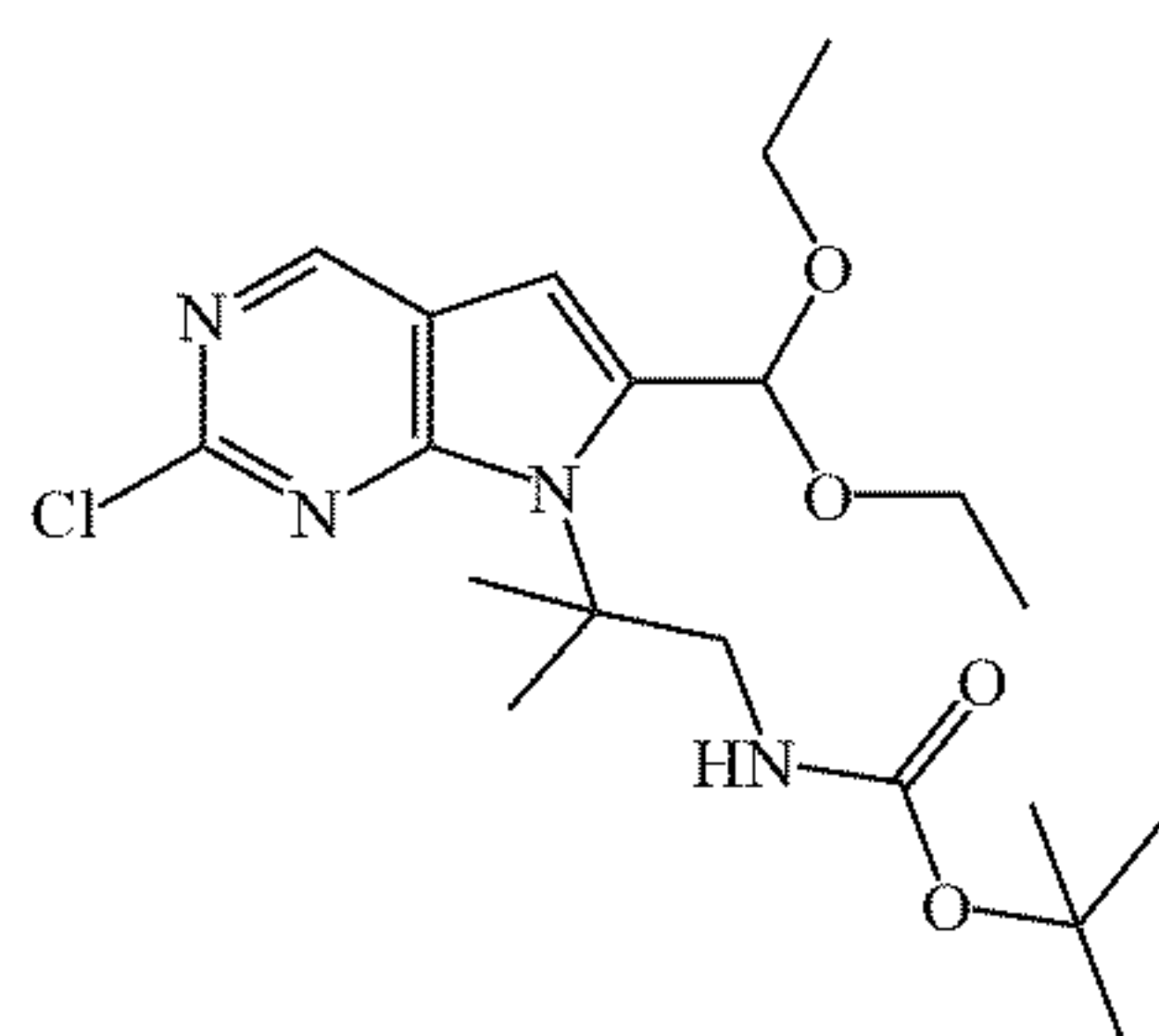
[0586] tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methylpropyl]carbamate was synthesized by treating tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-methyl-propyl]carbamate with 3,3-diethoxyprop-1-yne in the presence of a catalyst such as Pd(PPh₃)₄ using similar experimental conditions as described for the synthesis of tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate.

[0587] LCMS (ESI) (M+H) 427.

Example 127

Synthesis of Tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-propyl]carbamate, Compound 127

[0588]

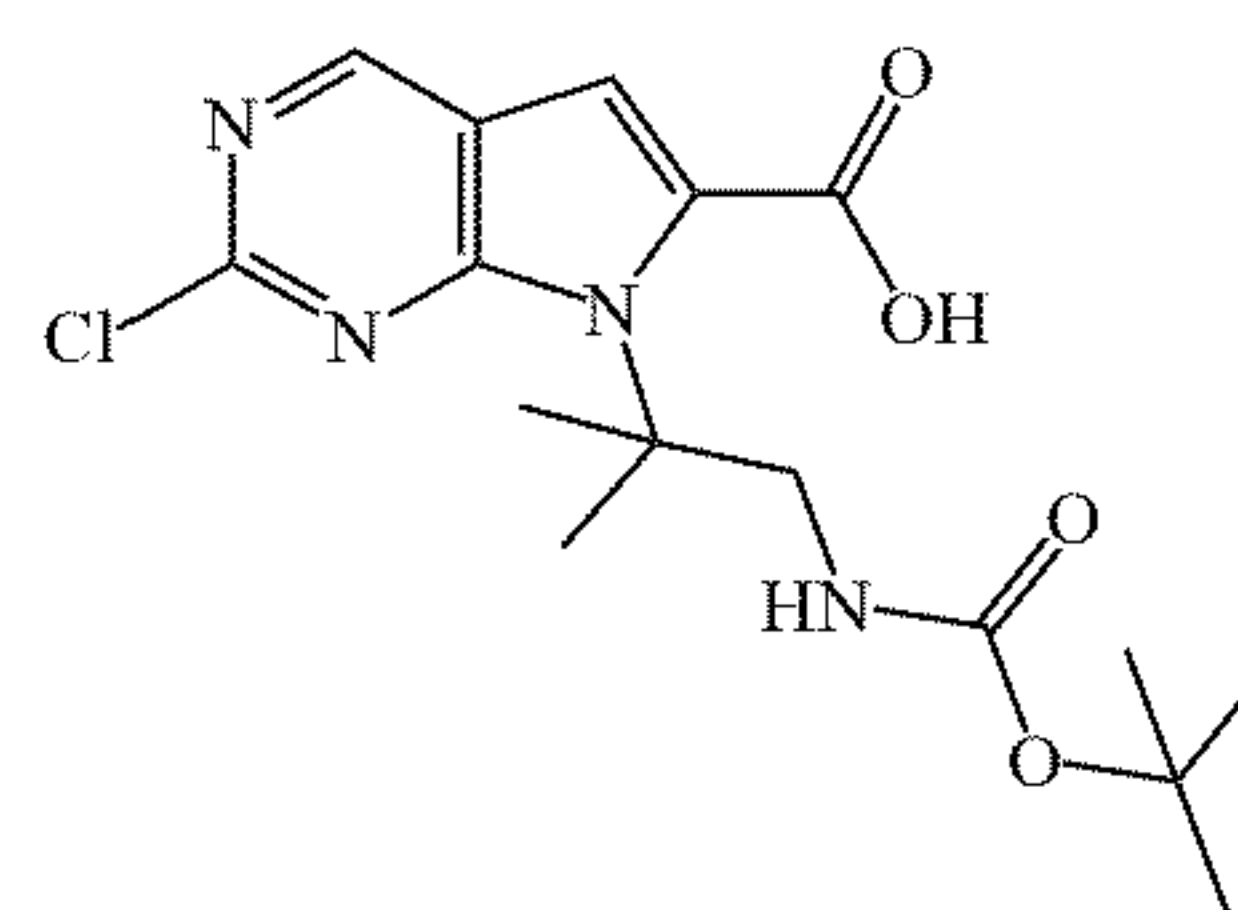


[0589] tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]-2-methylpropyl]carbamate was synthesized by treating tert-butyl N-[2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methyl-propyl]carbamate with TBAF using similar experimental conditions as described for the synthesis tert-butyl N-[2-[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate. LCMS (ESI) (M+H) 427.

Example 128

Synthesis of 7-[2-(tert-butoxycarbonylamino)-1,1-dimethyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic Acid, Compound 128

[0590]

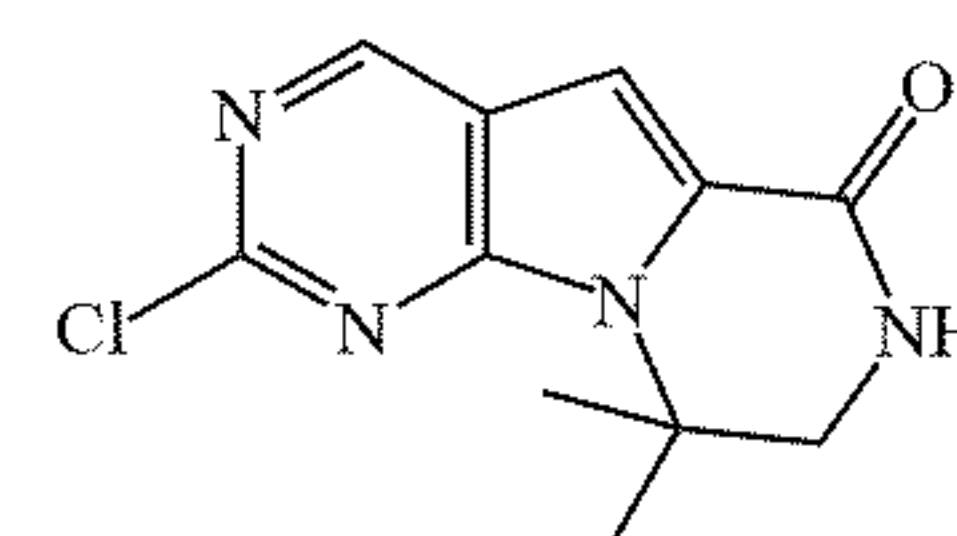


[0591] 7-(tert-butoxycarbonylamino)-1,1-dimethyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using a similar experimental procedure as that described for the synthesis of 7-(tert-butoxycarbonylamino)ethyl]-2-chloro-5-(o-tolyl)pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 369 (M + H).

Example 129

Synthesis of Compound 129

[0592]

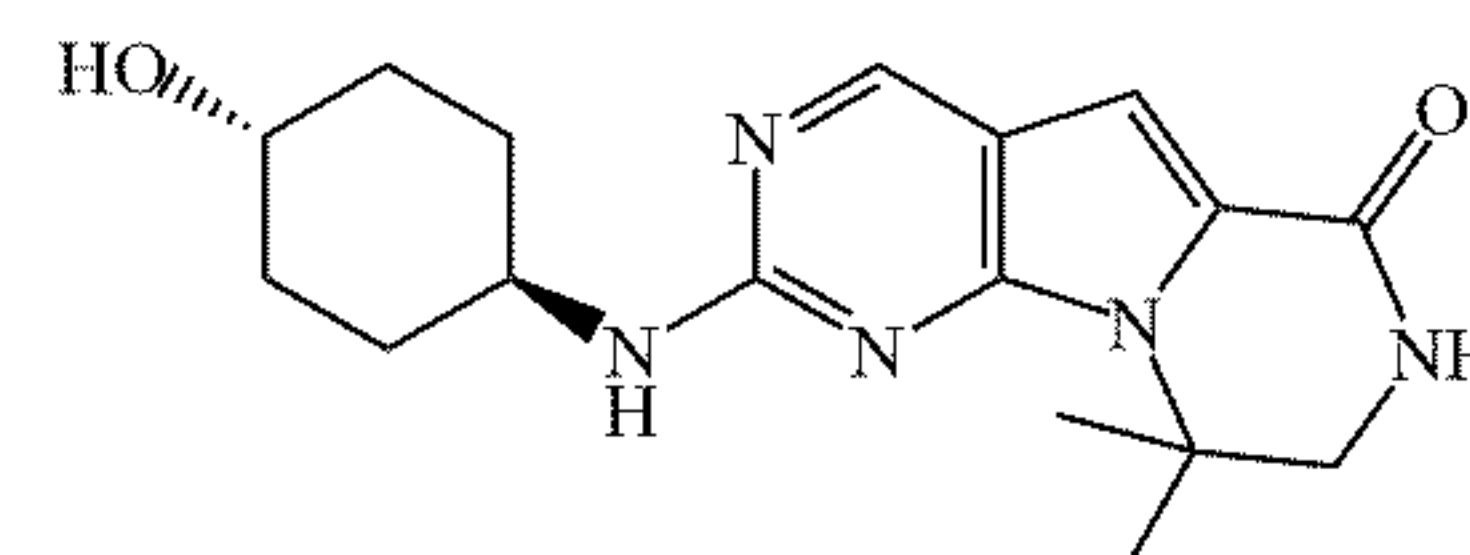


[0593] Chloro tricyclic amide, Compound 129, was synthesized using a similar procedure as that described for the synthesis of chloro tricyclic amide, Compound 119. LCMS (ESI) 251 (M + H).

Example 130

Synthesis of Compound 130

[0594]



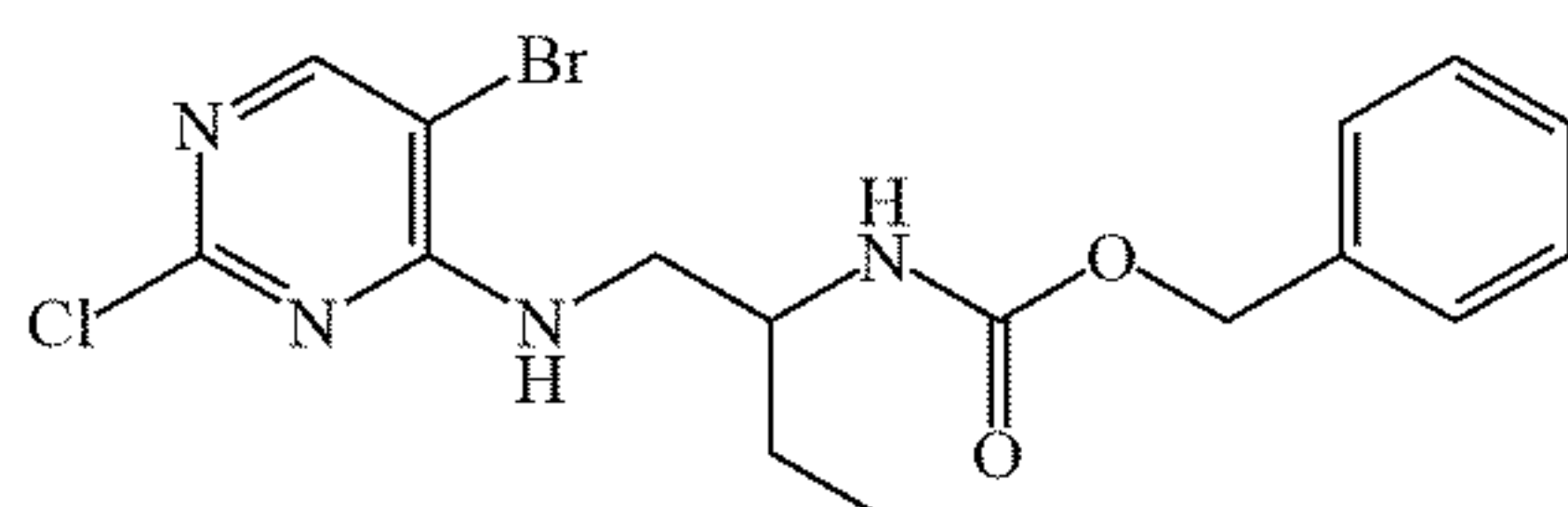
[0595] Compound 130 was synthesized by treating chloro-tricyclic amine Compound 129 with trans-4-aminocyclohexanol using similar experimental conditions as for compound 124. LCMS (ESI) 330 (M + H). ¹HNMR (600 MHz, DMSO-d₆) 6 ppm 1.07 - 1.34 (m, 4 H) 1.47 - 2.05 (m, 10 H) 3.09 (m, 1H) 3.51 (d, J = 2.91 Hz, 2 H) 3.57 (m, 1H) 4.50

(br. s., 1 H) 6.89 (s, 1 H) 6.94 - 7.05 (m, 1 H) 8.04 (br. s., 1 H) 8.60 (s, 1 H) 9.00 (br. s., 1 H).

Example 131

Synthesis of Benzyl N-[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]methyl]propyl]carbamate, Compound 131

[0596]

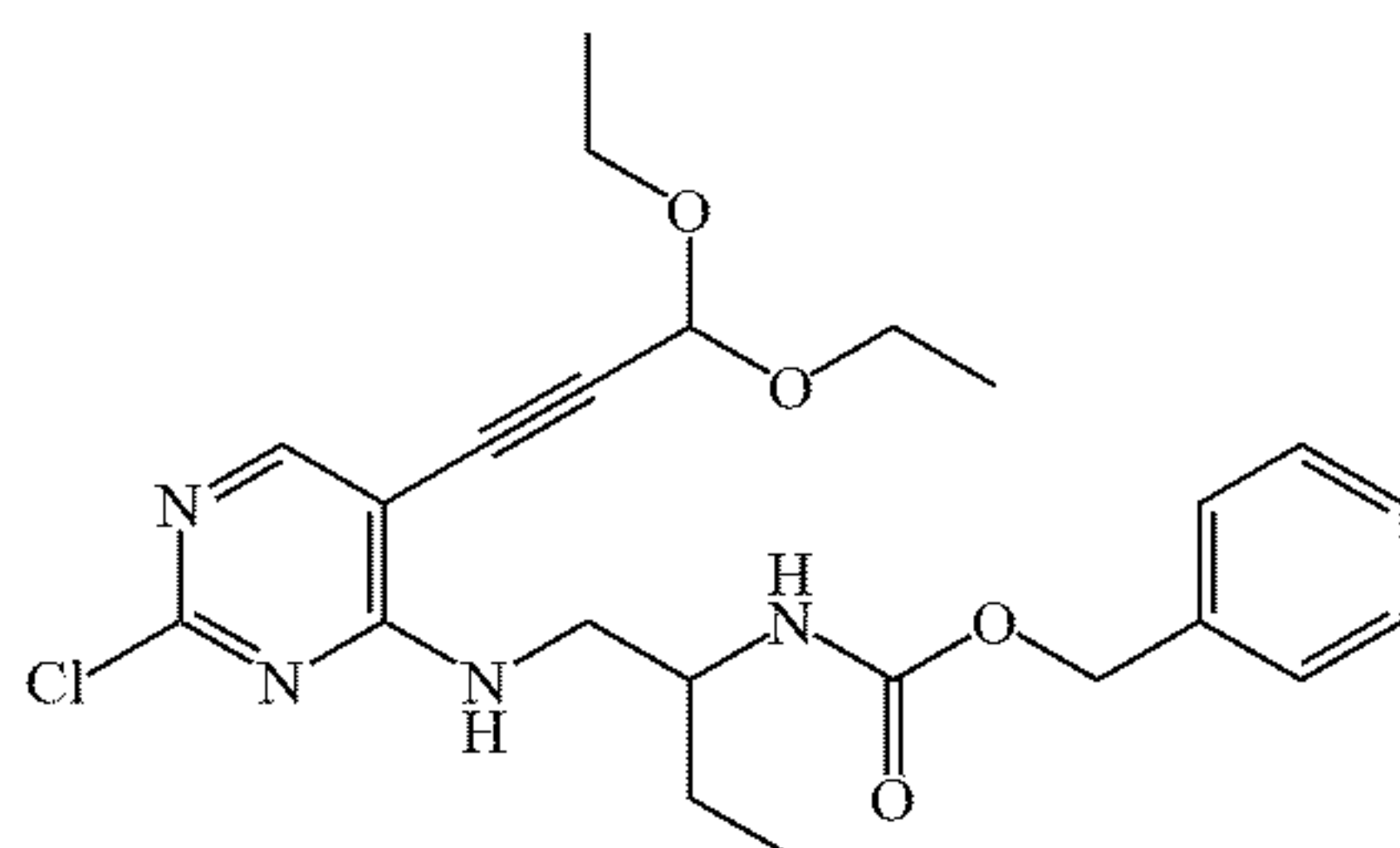


[0597] Benzyl N-[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]methyl]propyl]carbamate was synthesized by treating 5-bromo-2,4-dichloropyrimidine with benzyl N-[1-(aminomethyl)propyl]carbamate using similar experimental conditions as described for the synthesis of tert-butyl N-[2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate. LCMS (ESI) (M+H) 413.

Example 132

Synthesis of Benzyl N-[1-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]propyl]carbamate, Compound 132

[0598]

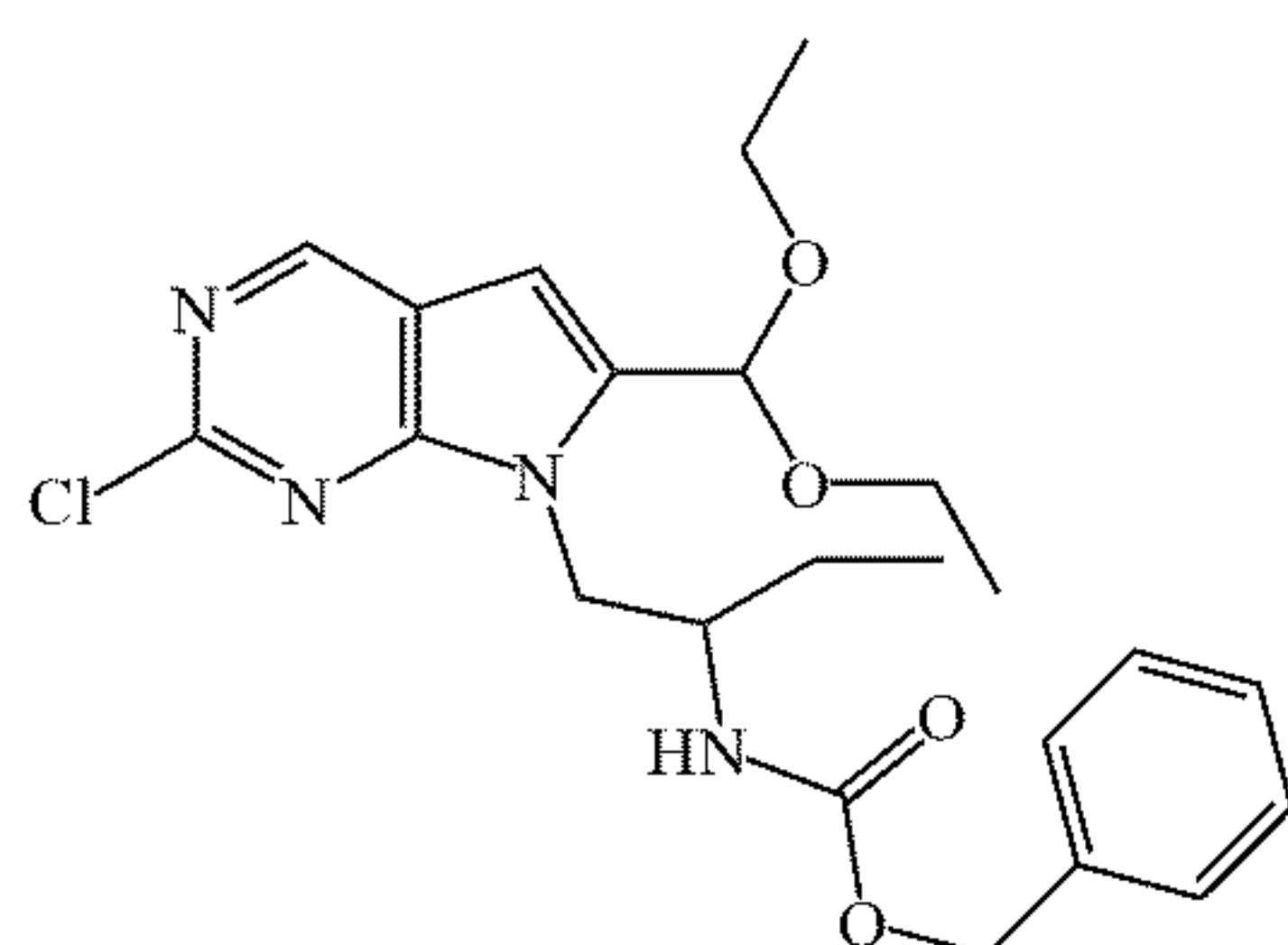


[0599] Benzyl N-[1-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]propyl]carbamate was prepared by treating benzyl N-[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]methyl]propyl]carbamate with 3,3-diethoxyprop-1-yne in the presence of a catalyst such as Pd(PPh₃)₄ using similar experimental conditions as described for the synthesis of tert-butyl N-[2-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate. LCMS (ESI) (M+H) 461.

Example 133

Synthesis of Benzyl N-[1-[[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]methyl]propyl]carbamate, Compound 133

[0600]

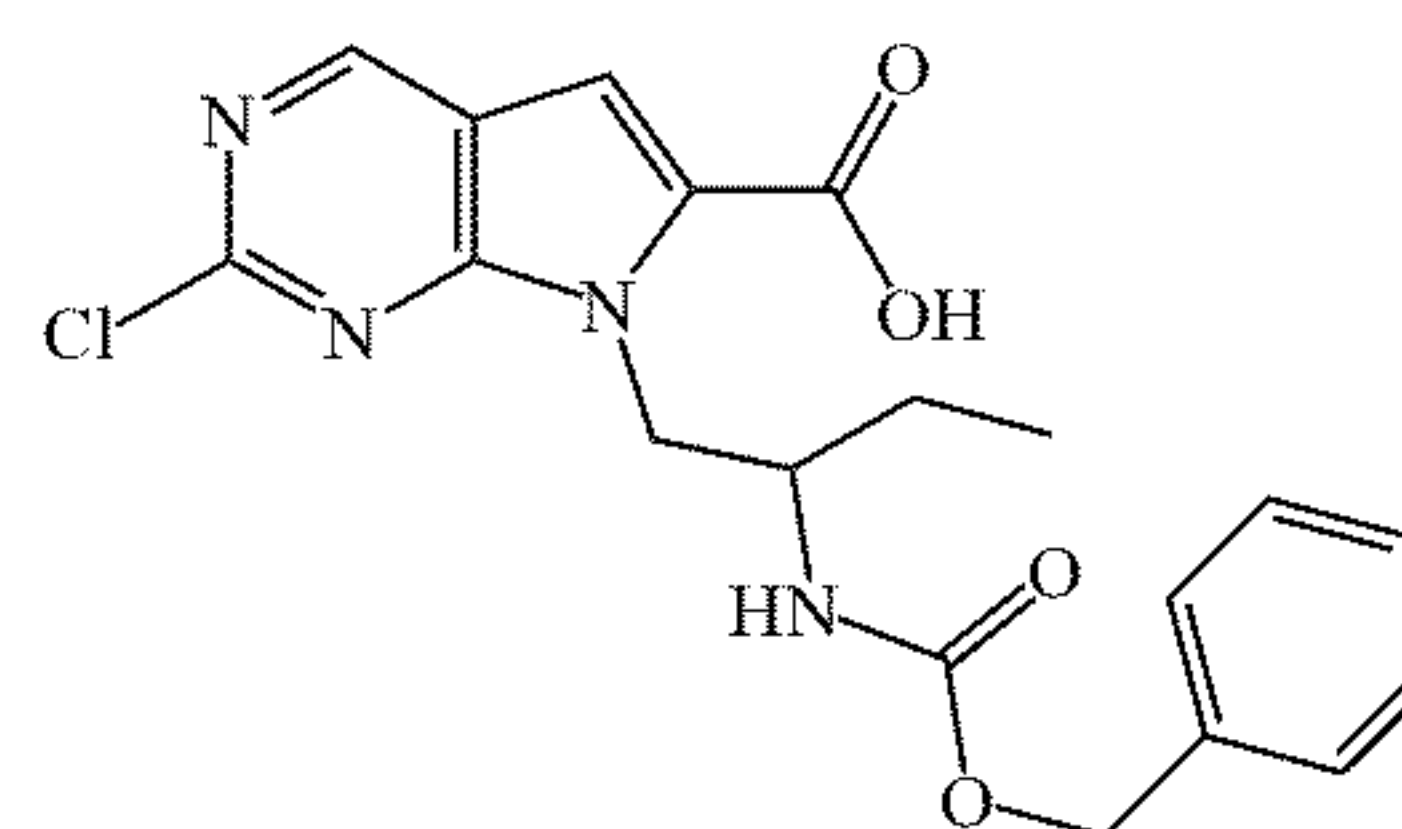


[0601] Benzyl N-[1-[[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]methyl]propyl]carbamate was synthesized by treating benzyl N-[1-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]propyl]carbamate with TBAF using similar experimental conditions as described for the synthesis tert-butyl N-[2-[[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate. LCMS (ESI) (M+H) 461.

Example 134

Synthesis of 7-[2-(benzyloxycarbonylamino)butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-Carboxylic Acid, Compound 134

[0602]

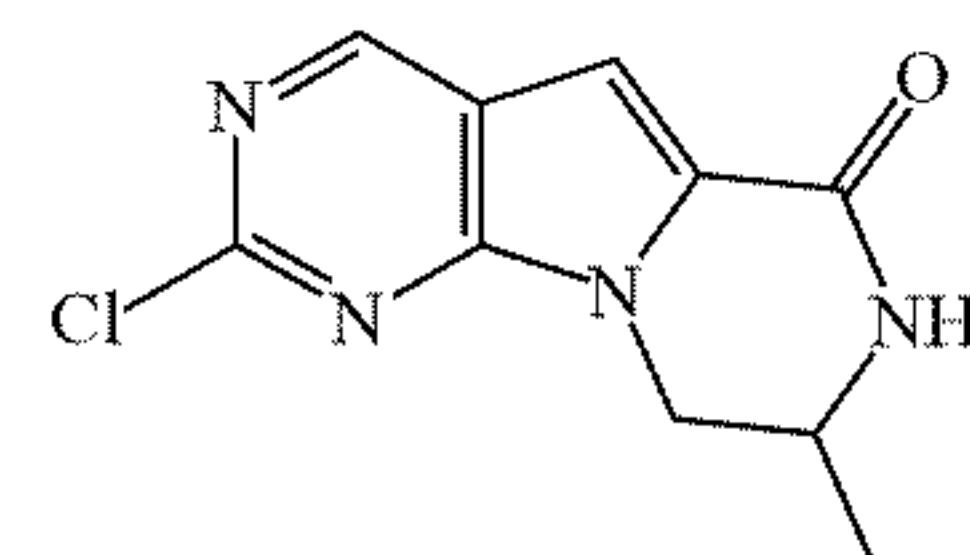


[0603] 7-[2-(benzyloxycarbonylamino)butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using a similar experimental procedure as that described for the synthesis of 7-(tert-butoxycarbonylamino)ethyl]-2-chloro-5-(o-tolyl)pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 403 (M + H).

Example 135

Synthesis of Compound 135

[0604]

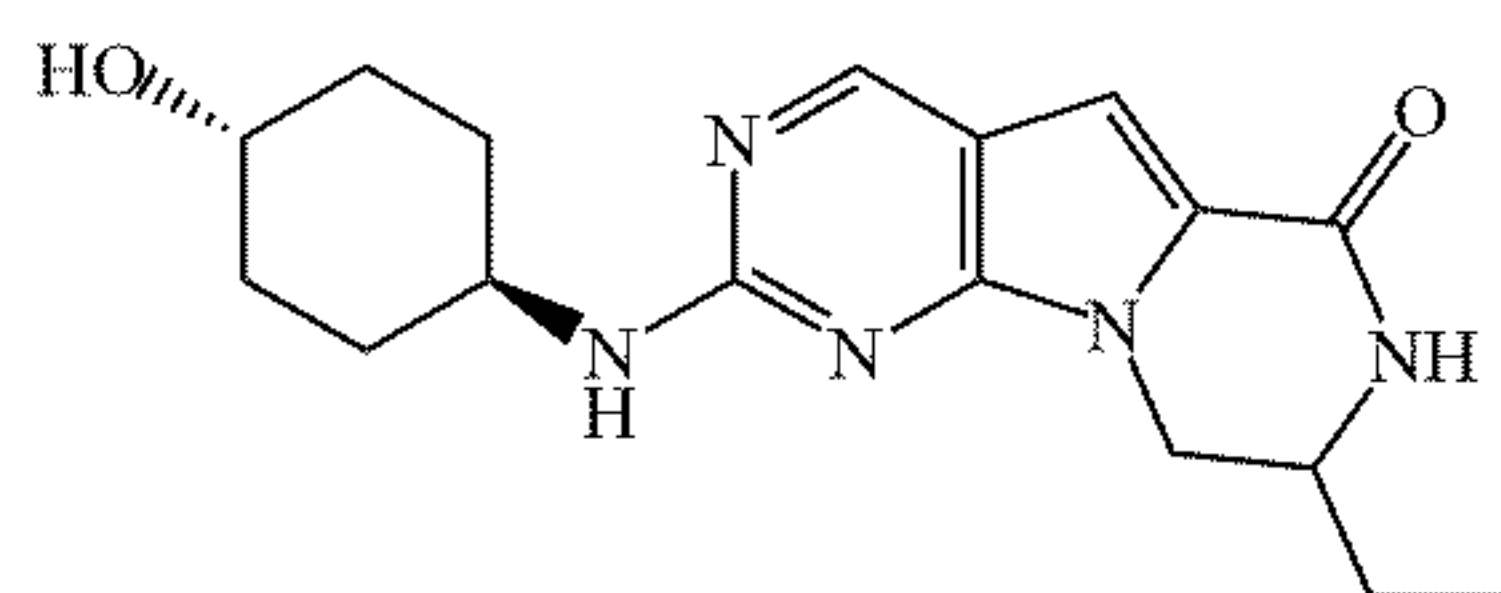


[0605] To a solution of 7-[2-(benzyloxycarbonylamino)butyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid in dichloromethane was added HBr, the reaction was stirred at 45 degrees for 3 hrs. After concentration, 2N NaOH was added to basify (pH = 8.0) the reaction followed by the addition of THF (20 mL). Boc₂O was then added (1.2 eq) and the reaction was stirred for 16 hrs. To the crude reaction mixture was then added ethyl acetate (100 mL) and water (50 mL) and the organic phase was separated, dried (magnesium sulfate) and then concentrated under vacuum. To the crude product was added dichloromethane (30 mL) followed by DIC and DMAP. After stirring for 2 hrs, TFA was added and the contents stirred for an hour. The solvents were evaporated under vacuum and the residue basified with satd. NaHCO₃. Ethyl acetate was then added and the organic layer separated, dried (magnesium sulfate) and then concentrated under vacuum. Column chromatography with hexane/ethyl acetate (0 -100%) afforded the desired chlorotricyclic core, Compound 135. LCMS (ESI) 251 (M + H).

Example 136

Synthesis of Compound 136

[0606]

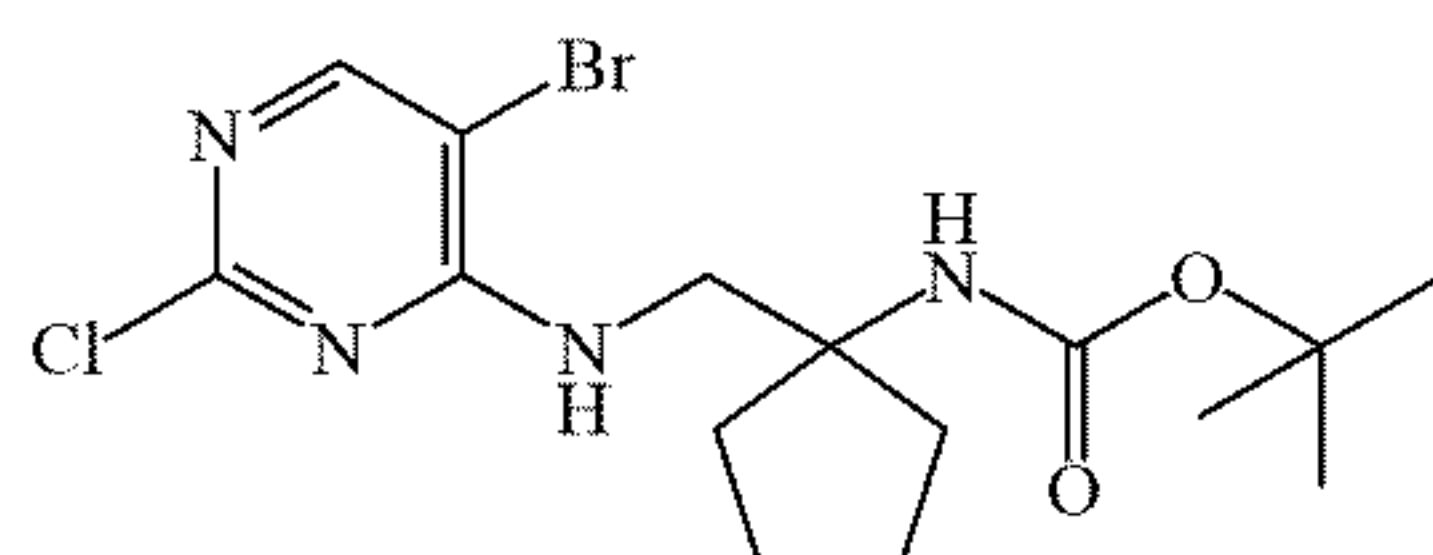


[0607] Compound 136 was synthesized by treating chlorotricyclic amine, Compound 135, with trans-4-aminocyclohexanol using similar experimental conditions as for compound 124. LCMS (ESI) 330 (M + H). ¹HNMR (600 MHz, DMSO-d₆) δ ppm 0.80 - 0.95 (m, 3 H) 1.35 - 1.92 (m, 10 H) 3.66 (br. m., 3 H) 4.17 (br. s., 2 H) 4.47 (br. s., 1 H) 6.85 (s, 1 H) 6.96 (br. s., 1 H) 8.15 (br. s., 1 H) 8.62 (br. s., 1 H).

Example 137

Synthesis of Tert-butyl N-[1-[[[5-bromo-2-chloro-pyrimidin-4-yl]amino]methyl]cyclopentyl]carbamate, Compound 137

[0608]

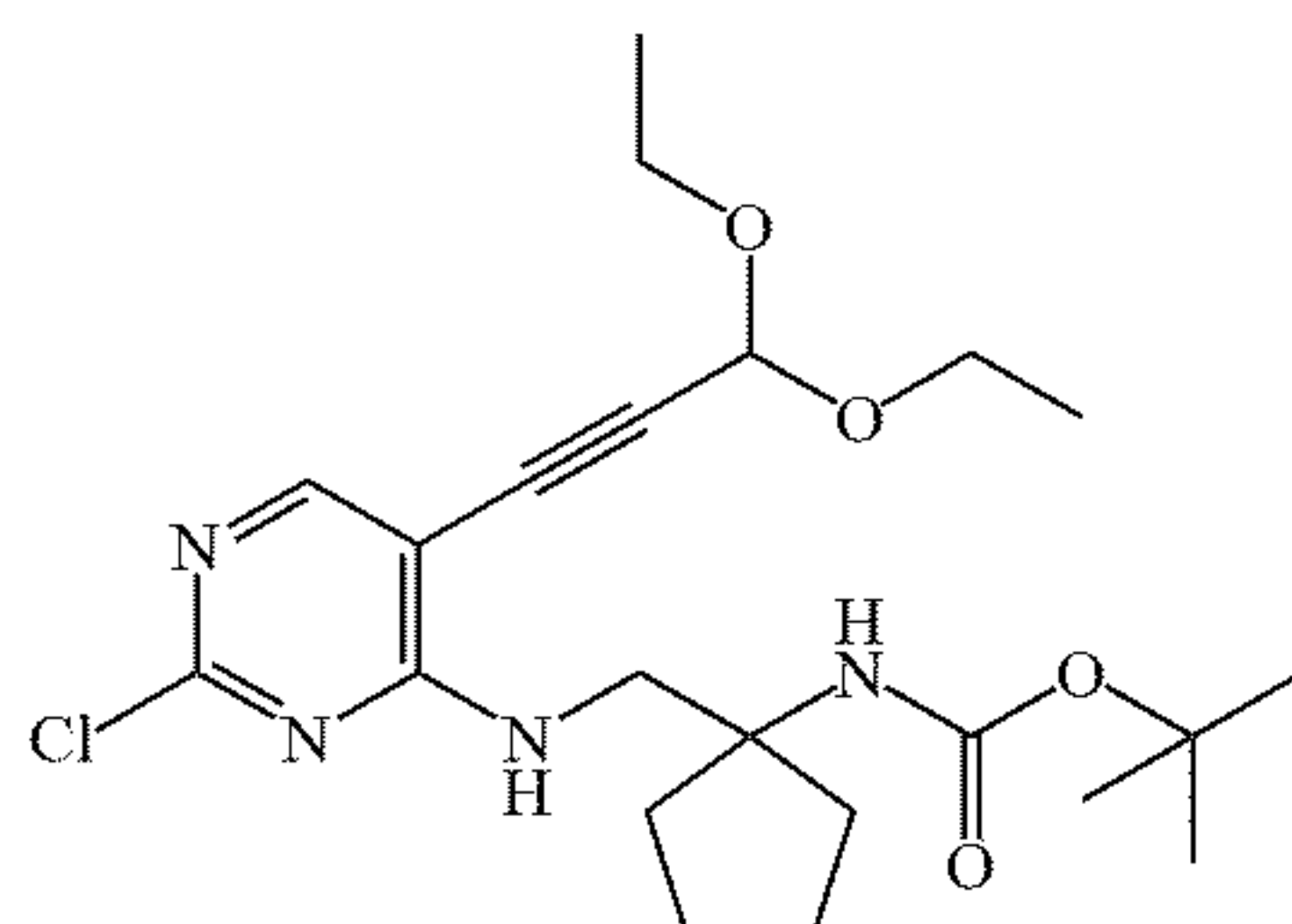


[0609] tert-butyl N-[1-[[[5-bromo-2-chloro-pyrimidin-4-yl]amino]methyl]cyclopentyl]carbamate was synthesized by treating 5-bromo-2,4-dichloropyrimidine with tert-butyl N-[1-(aminomethyl)cyclopentyl]carbamate using similar experimental conditions as described for the synthesis of tert-butyl N-[2-[[[5-bromo-2-chloro-pyrimidin-4-yl]amino]ethyl]carbamate. LCMS (ESI) 405 (M+H).

Example 138

Synthesis of Tert-butyl N-[1-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]cyclopentyl]carbamate, Compound 138

[0610]



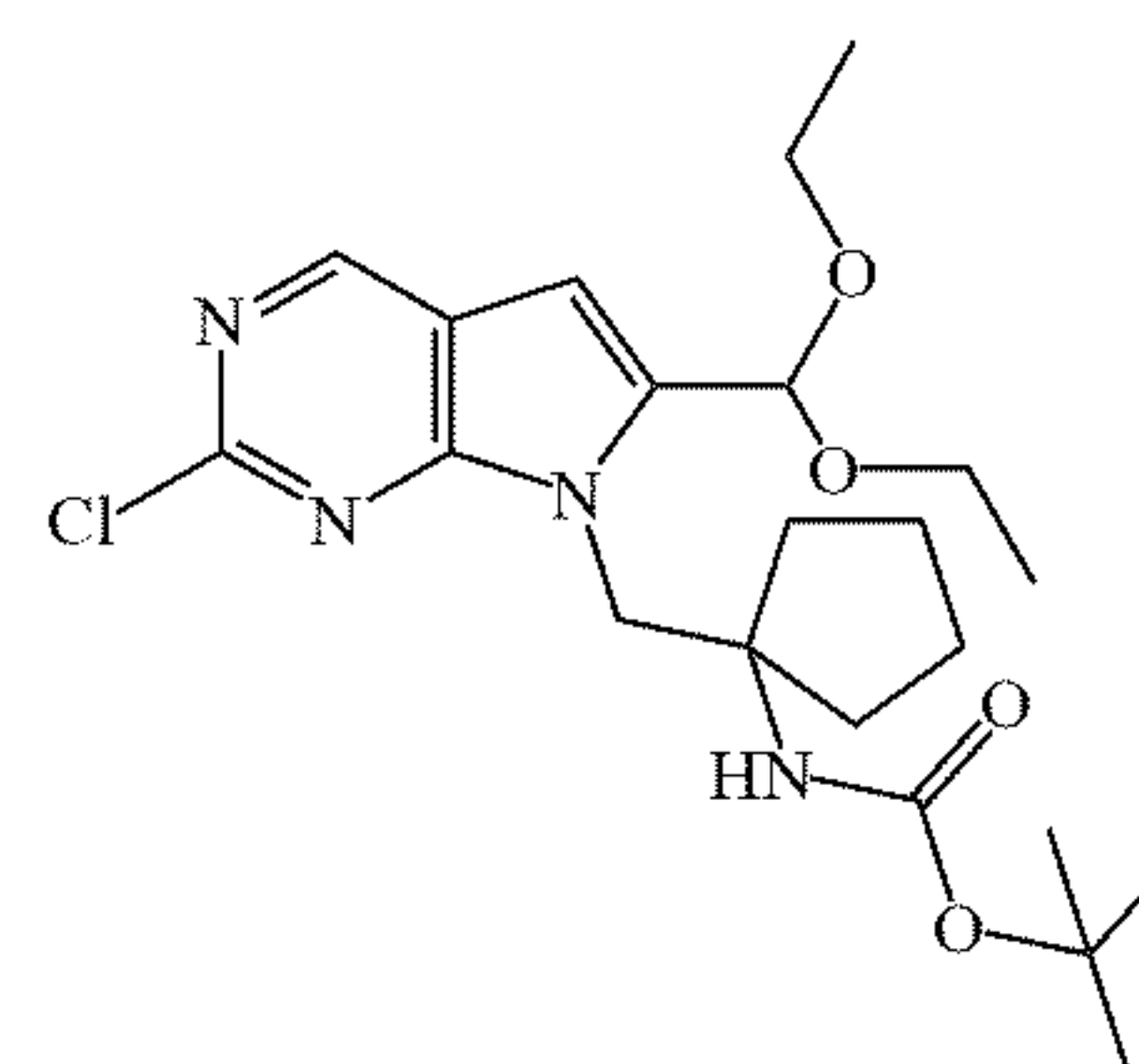
[0611] tert-butyl N-[1-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]methyl]cyclopentyl]carbamate was synthesized by treating tert-butyl N-[1-[[[5-bromo-2-chloro-pyrimidin-4-yl]amino]methyl]cyclopentyl]carbamate with 3,3-diethoxyprop-1-yne in the presence of a catalyst such as Pd(dba)₃ using similar experimental conditions as described for the synthesis of tert-butyl N-[2-[[[2-

chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate LCMS (ESI) 453 (M+H).

Example 139

Synthesis of Tert-butyl N-[1-[[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]methyl]cyclopentyl]carbamate, Compound 139

[0612]

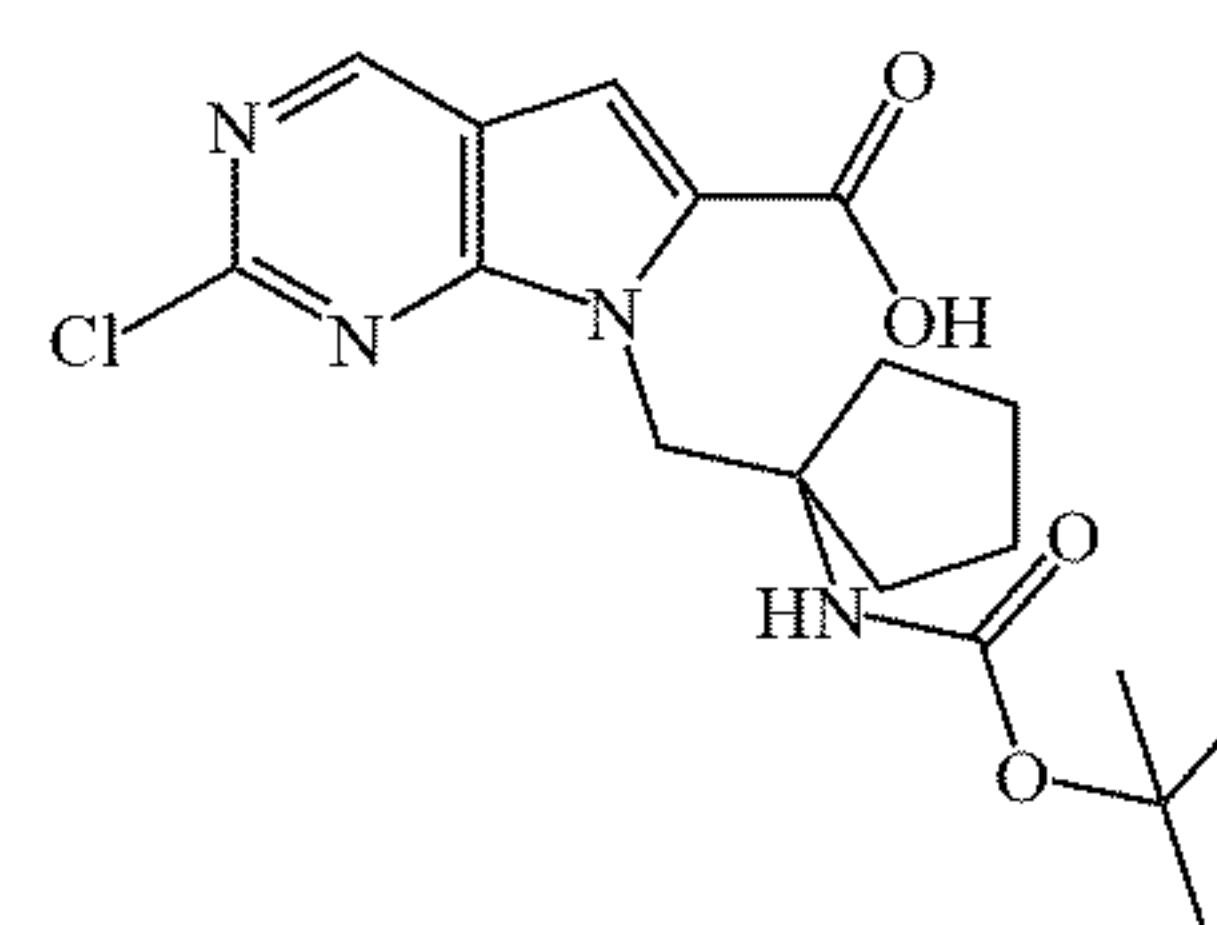


[0613] tert-butyl N-[1-[[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]methyl]cyclopentyl]carbamate was synthesized by treating tert-butyl N-[2-[[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methylpropyl]carbamate with TBAF using similar experimental conditions as described for the synthesis of tert-butyl N-[2-[[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate. LCMS (ESI) 453 (M+H).

Example 140

Synthesis of 7-[[[1-(tert-butoxycarbonylamino)cyclopentyl]methyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic Acid, Compound 140

[0614]

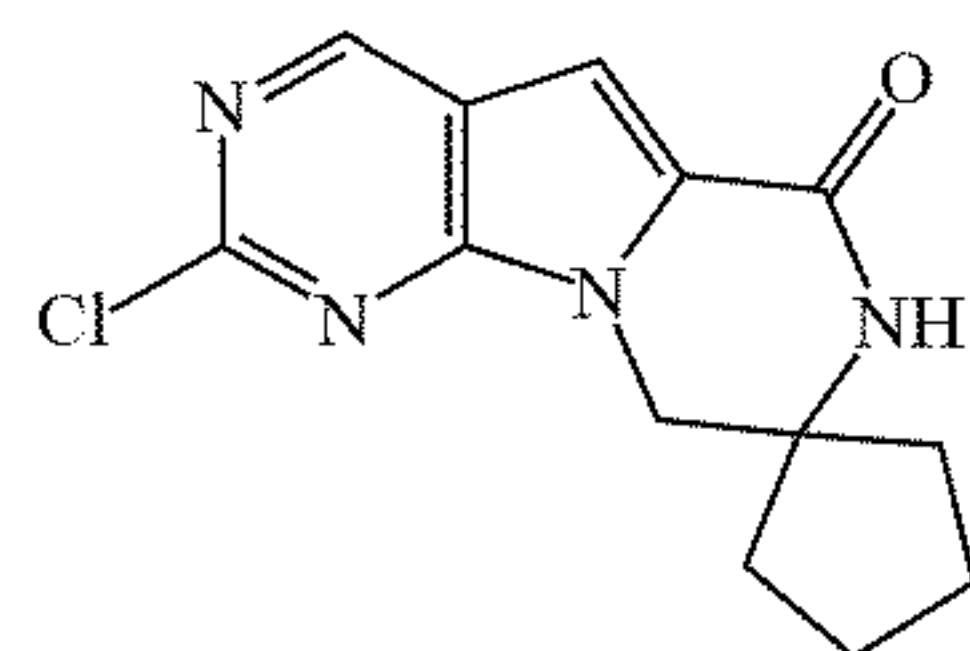


[0615] 7-[[[1-(tert-butoxycarbonylamino)cyclopentyl]methyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using a similar experimental procedure as that described for the synthesis of 7-[[[2-(tert-butoxycarbonylamino)ethyl]-2-chloro-5-(o-tolyl)pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 395 (M + H).

Example 141

Synthesis of Compound 141

[0616]

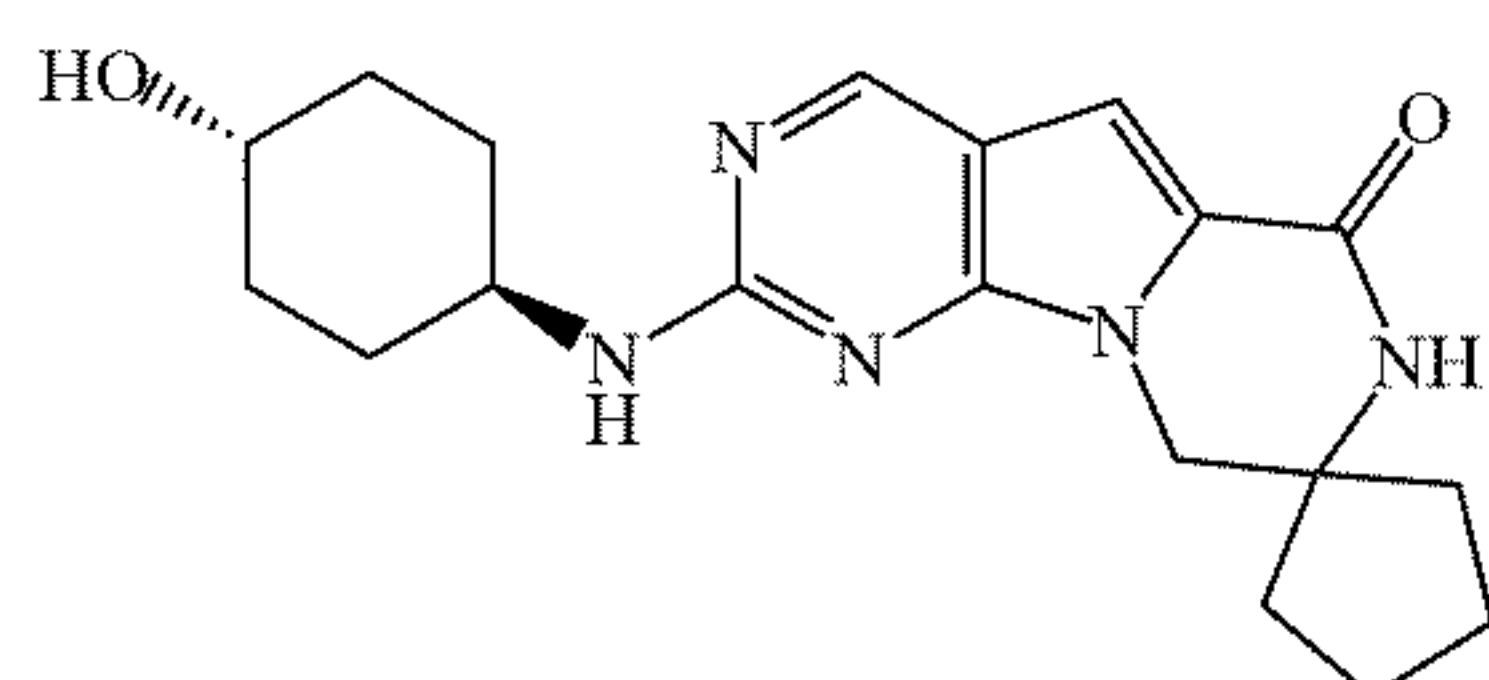


[0617] Chlorotricyclic core Compound 141 was synthesized using a similar experimental procedure as that described for the synthesis of chloro tricyclic amide Compound 119. LCMS (ESI) 277 (M + H).

Example 142

Synthesis of Compound 142

[0618]

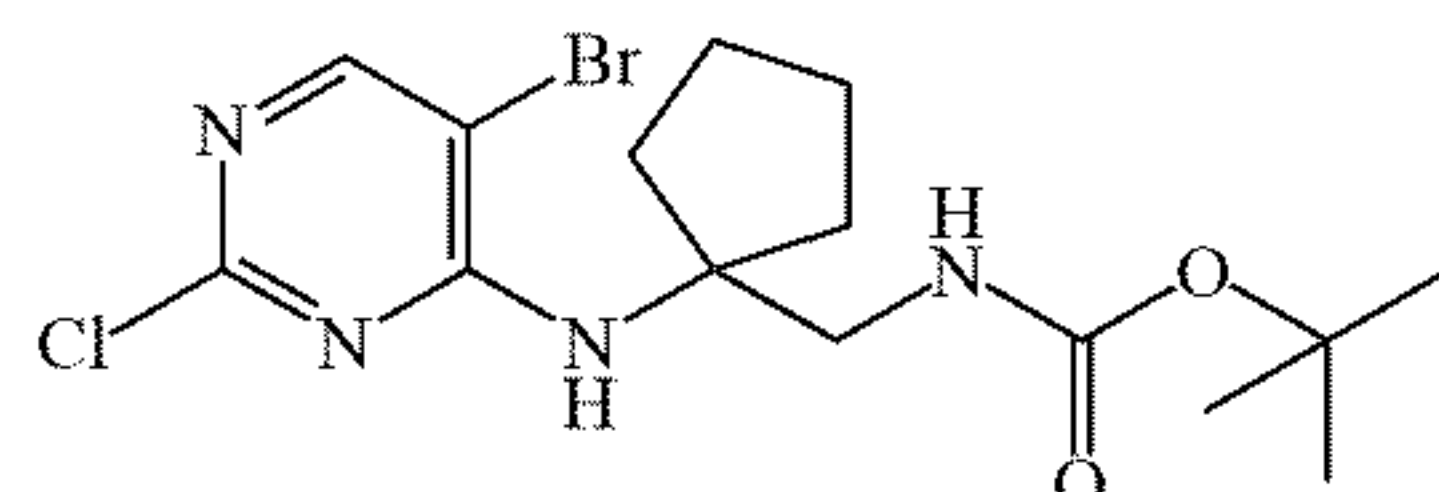


[0619] Compound 142 was synthesized by treating chlorotricyclic amine, Compound 141, with trans-4-aminocyclohexanol using similar experimental conditions as for Compound 124. LCMS (ESI) 356 (M + H). ¹HNMR (600 MHz, DMSO-d₆) δ ppm 1.08 - 1.32 (m, 8 H) 1.60 - 2.09 (m, 8 H) 3.03 - 3.17 (m, 1 H) 3.35 (s, 2 H) 3.54 - 3.62 (m, 1 H) 4.51 (d, J=4.39 Hz, 1 H) 6.88 (s, 1 H) 6.96 (br. s., 1 H) 8.07 (br. s., 1 H) 8.58 (s, 1 H).

Example 143

Synthesis of Tert-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]methyl]carbamate, Compound 143

[0620]

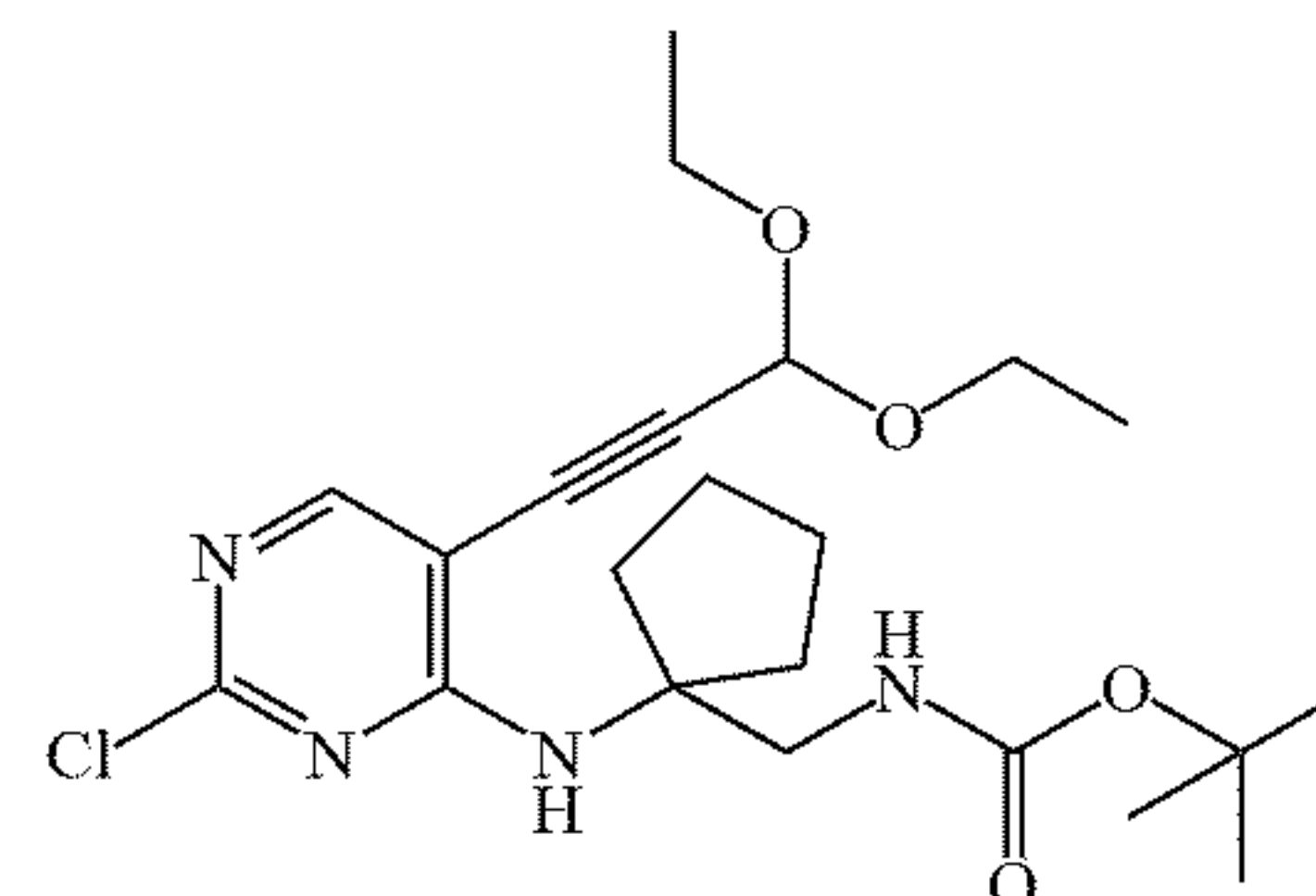


[0621] tert-butyl N-[[1-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]cyclopentyl]methyl]carbamate was synthesized by treating 5-bromo-2,4-dichloropyrimidine with tert-butyl N-[(1-aminocyclopentyl)methyl]carbamate using similar experimental conditions as described for the synthesis of tert-butyl N-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]ethyl]carbamate. LCMS (ESI) 405 (M+H).

Example 144

Synthesis of Tert-butyl N-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methyl-propyl]carbamate, Compound 144

[0622]



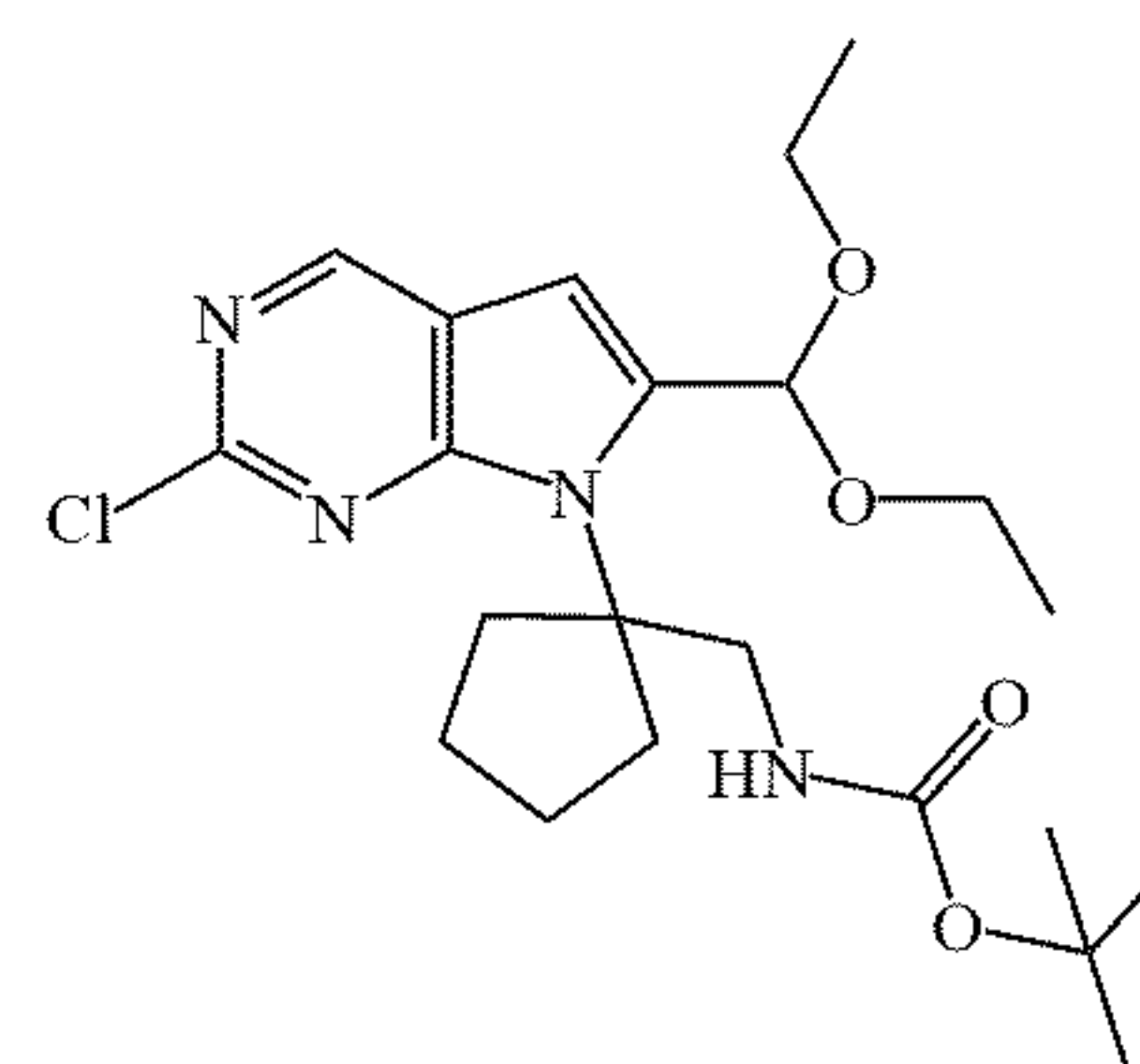
[0623] tert-butyl N-[[1-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]cyclopentyl]methyl]carbamate was synthesized by treating tert-butyl N-2-[(5-bromo-2-chloro-pyrimidin-4-yl)amino]-2-methyl-propyl]carbamate with 3,3-diethoxyprop-1-yne in the presence of a catalyst such as Pddba using similar experimental conditions as described for the synthesis of tert-butyl N-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]ethyl]carbamate.

[0624] LCMS (ESI) 453 (M+H).

Example 145

Synthesis of Tert-butyl N-[[1-[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl]methyl]carbamate, Compound 145

[0625]

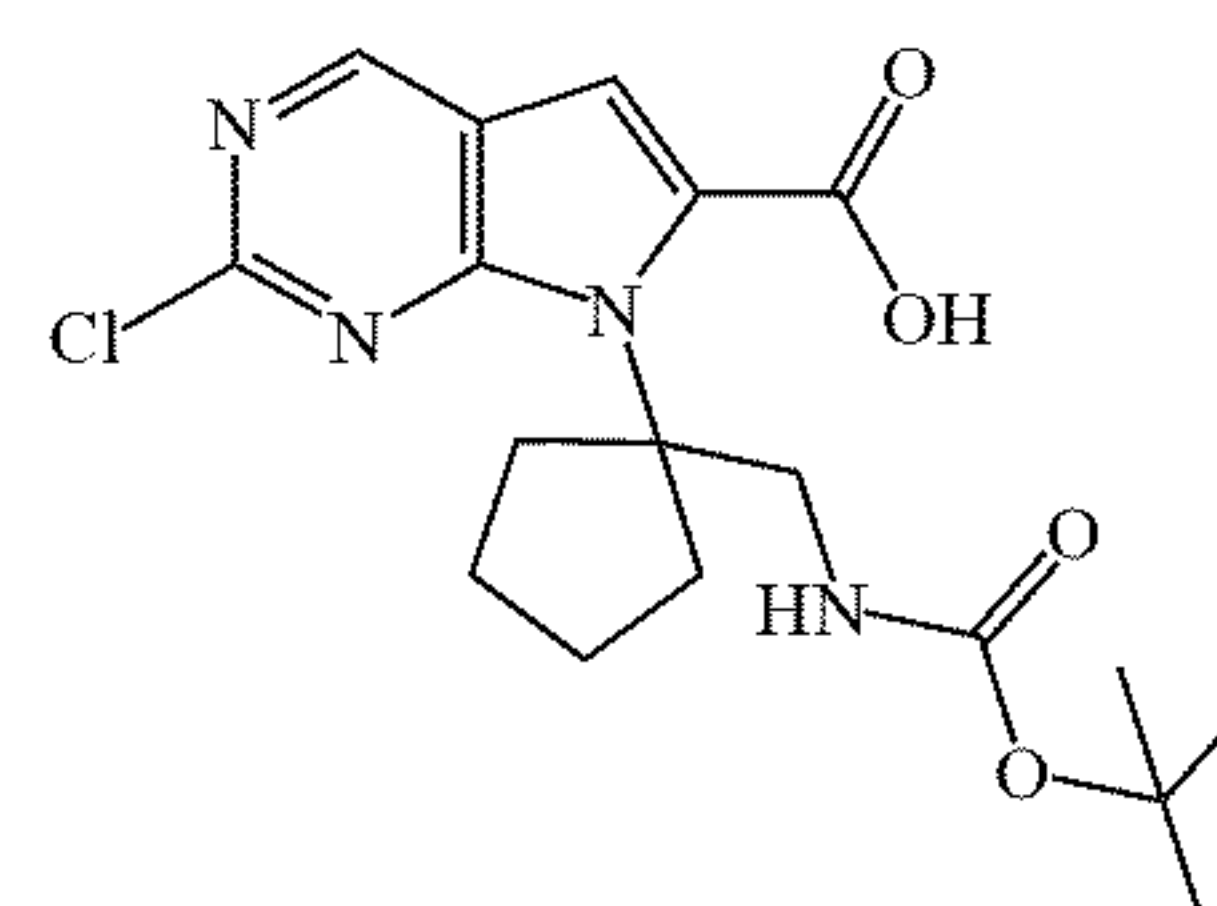


[0626] tert-Butyl N-[[1-[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]cyclopentyl]methyl]carbamate was synthesized by treating tert-butyl N-2-[[2-chloro-5-(3,3-diethoxyprop-1-ynyl)pyrimidin-4-yl]amino]-2-methyl-propyl]carbamate with TBAF using similar experimental conditions as described for the synthesis tert-butyl N-2-[[2-chloro-6-(diethoxymethyl)pyrrolo[2,3-d]pyrimidin-7-yl]ethyl]carbamate. LCMS (ESI) 4534 (M+H).

Example 146

Synthesis of 7-[2-(tert-butoxycarbonylamino)-1,1-dimethyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6carboxylic Acid, Compound 146

[0627]

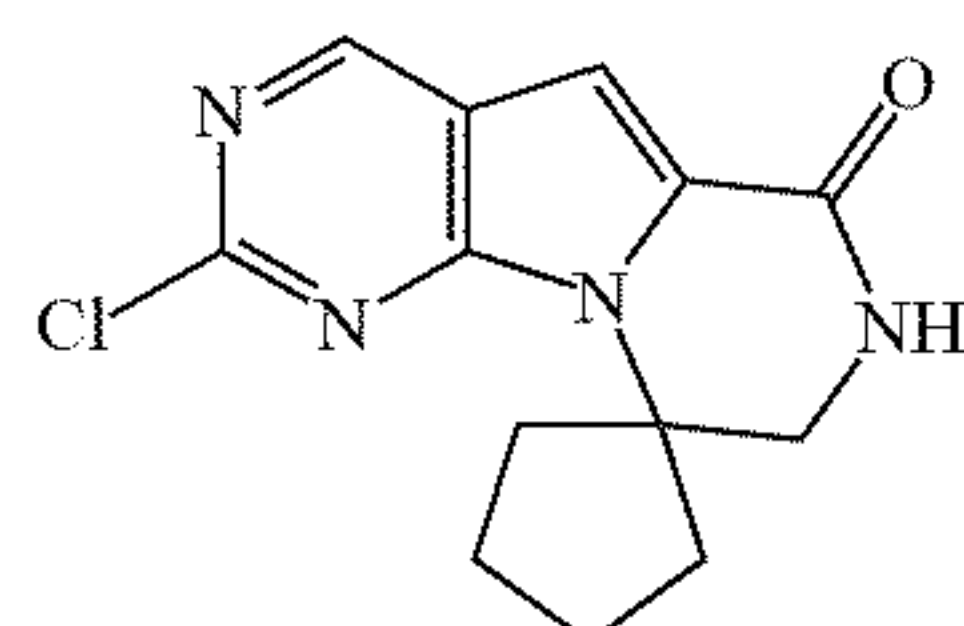


[0628] 7-(tert-Butoxycarbonylamino)-1,1-dimethyl-ethyl]-2-chloro-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid was synthesized using a similar experimental procedure as that described for the synthesis of 7-(tert-butoxycarbonylamino)ethyl]-2-chloro-5-(o-tolyl)pyrrolo[2,3-d]pyrimidine-6-carboxylic acid. LCMS (ESI) 395 (M + H).

Example 147

Synthesis of Compound 147

[0629]

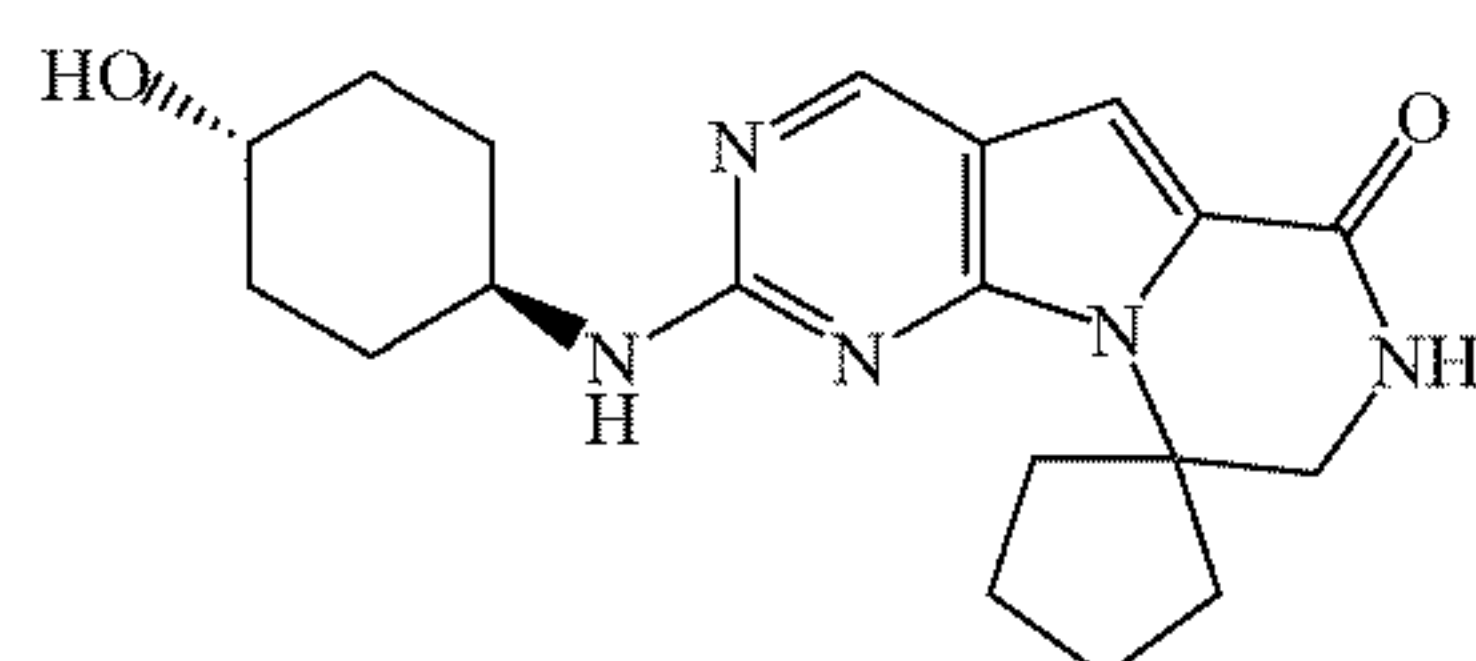


[0630] Chloro tricyclic amide, Compound 147 was synthesized using a similar experimental procedure as that described for the chloro tricyclic amide, Compound 119. LCMS (ESI) 277 (M + H).

Example 148

Synthesis of Compound 148

[0631]

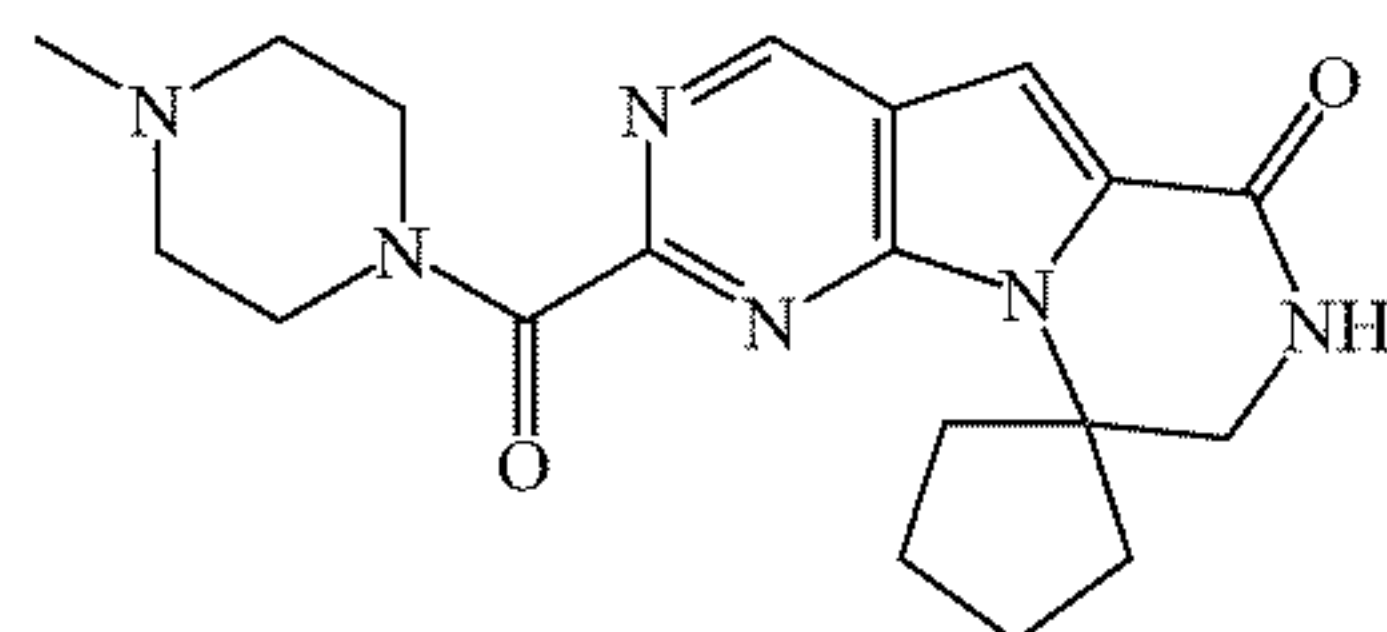


[0632] Compound 148 was synthesized by treating chlorotricyclic amine, Compound 147, with trans-4-aminocyclohexanol using similar experimental conditions as for Compound 124. LCMS (ESI) 356 (M + H). ¹HNMR (600 MHz, DMSO-d₆) 6 ppm 1.06 - 1.35 (m, 8 H) 1.45 - 1.95 (m, 8 H) 3.10 (m, 1 H) 3.58 (br. s., 2 H) 3.95 (br. s., 1 H) 4.49 (br. s., 1 H) 6.84 (s, 1 H) 6.85 - 6.93 (m, 1 H) 8.29 (s, 1 H) 8.61 (br. s., 1 H).

Example 149

Synthesis of Compound 149

[0633]



[0634] Step 1: Compound 59 is Boc protected according to the method of A. Sarkar et al. (JOC, 2011, 76, 7132-7140).

[0635] Step 2: Boc-protected Compound 59 is treated with 5 mol% NiCl₂(Ph₃)₂, 0.1 eq triphenylphosphine, 3 eq Mn, 0.1 eq tetraethylammonium iodide, in DMI under CO₂ (1 atm) at 25° C. for 20 hours to convert the aryl halide derivative into the carboxylic acid.

[0636] Step 3: The carboxylic acid from Step 2 is converted to the corresponding acid chloride using standard conditions.

[0637] Step 4: The acid chloride from Step 3 is reacted with N-methyl piperazine to generate the corresponding amide.

[0638] Step 5: The amide from Step 4 is deprotected using trifluoroacetic acid in methylene chloride to generate the target compound. Compound 149 was purified by silica gel column chromatography eluting with a dichloromethane - methanol gradient to provide Compound 149.

[0639] Each of Compounds 119 through 147 and corresponding compounds with various R⁸, R¹ and Z definitions may be reacted with sodium hydride and an alkyl halide or other halide to insert the desired R substitution prior to reaction with an amine, such as described above for the synthesis of Compound 120, to produce the desired product of Formulae I, II, III, IV, or V.

Example 150

Inhibition of Cellular Proliferation

[0640] FIG. 9 is a graph showing the cellular proliferation of SupT1 cells (human T-cell lymphoblastic leukemia) treated with PD0332991 (circles) or Compound T (Table 1; squares). FIG. 10 is a graph showing the cellular proliferation of SupT1 cells (human T-cell lymphoblastic leukemia) treated with Compound Q (Table 1; circles) or Compound GG (Table 1; squares). The SupT1 cells were seeded in Costar (Tewksbury, Massachusetts) 3093 96 well tissue culture treated white walled/ clear bottom plates. A nine point dose response dilution series from 10 uM to 1 nM was performed and cell viability was determined after four days as indicated using the CellTiter-Glo® assay (CTG; Promega, Madison, Wisconsin, United States of America) following the manufacturer's recommendations. Plates were read on a BioTek (Winooski, Vermont) Synergy2 multi-mode plate reader. The Relative Light Units (RLU) were plotted as a result of variable molar concentration and data was analyzed using Graphpad (LaJolla, California) Prism 5 statistical software to determine the IC₅₀ for each compound.

Example 151

Inhibition of Cellular Proliferation in T-Cell and B-Cell Specific Cancer Cells

[0641] The compounds listed in Table 1 were tested for the inhibition of cellular proliferation using Sup T1 (human T-cell lymphoblastic leukemia) and Daudi (human B- lymphoblastoid cell from Burkitt's Lymphoma patient). FIGS. 9 and 10 and Example 150 illustrate how the EC₅₀s were measured.

[0642] Most of the compounds tested showed significant inhibition of the SupT1 T-cell lymphoblastic leukemia cell line. The range for the EC₅₀ of the compounds tested that were necessary for inhibition of SupT1 T-cell lymphoblastic leukemia cell proliferation was 9.3 nM to 3037 nM. Many of the compounds also had significant effects on the inhibition of the B-cell lymphoblastoid cell line (Daudi). The range for the EC₅₀ of the compounds tested that were necessary for inhibition of Daudi B-cell lymphoblastoid cell proliferation was 111 nM to 3345 nM.

TABLE 2

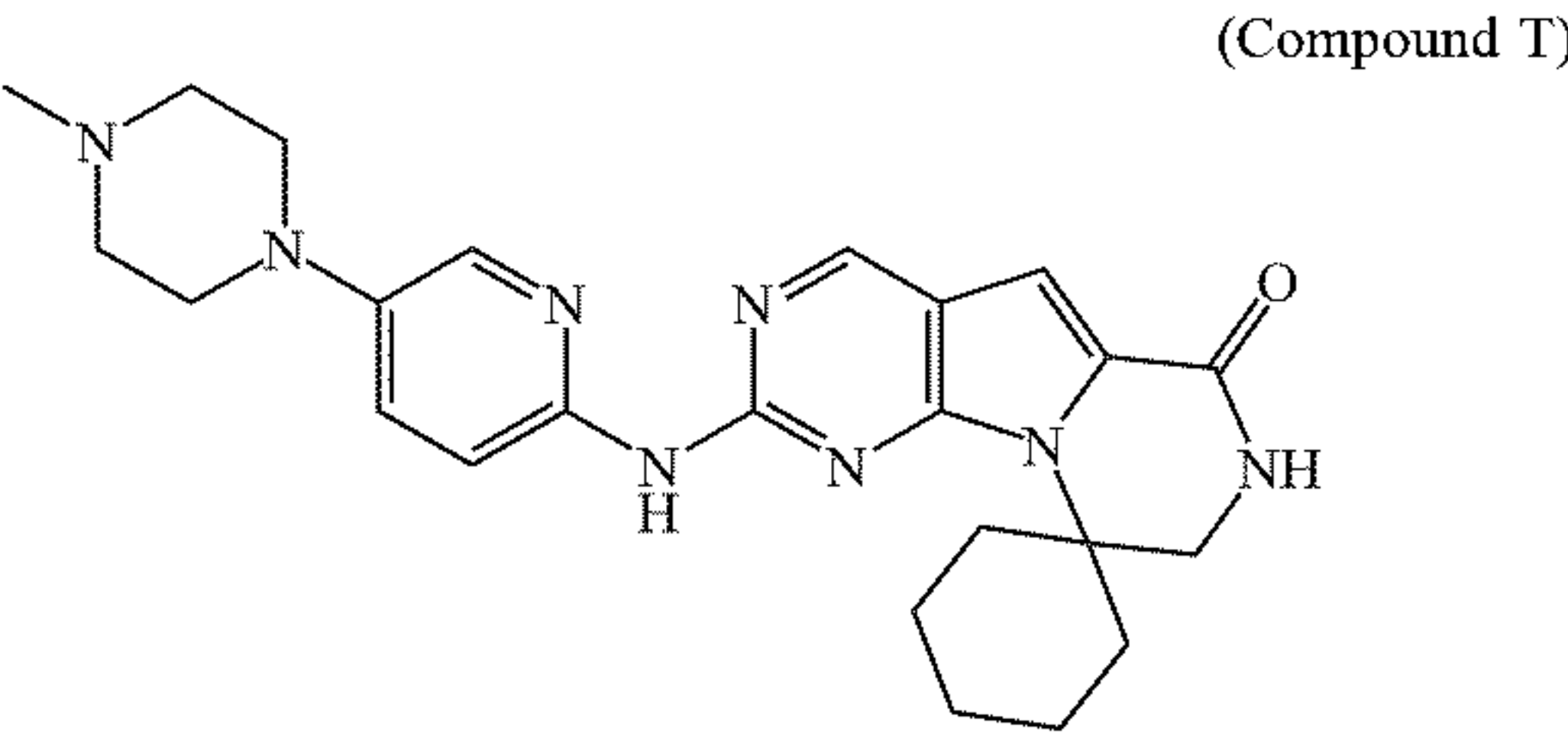
Inhibition of Cellular Proliferation in Cancer Cells			
Structure	SupT1 Cellular EC ₅₀ [nM]	Daudi Cellular EC ₅₀ [nM]	
A	57	281	
B	96	385	
C	74	373	
D	55	297	
E	9.3	140	
F	107	692	
G	156	1530	
H	118	719	
I	39	249	
J	47	362	
K	134	167	
L	153	1262	
M	184	1455	
N	34	122	
O	44	123	
P	33	140	
Q	40	561	
R	43	299	
S	110	634	
T	113	392	
U	48	363	
V	35	194	
W	57	731	
X	36	318	
Y	85	548	
Z	87	359	
AA	58	233	
BB	70	472	
CC	17	111	
DD	105	546	
EE	89	259	
FF	90	380	
GG	57	784	
HH	79	681	
II	42	347	
JJ	49	389	
KK	112	147	
LL	84	501	
MM	84	681	
NN	84	1042	
OO	114	880	
PP	81	260	
QQ	68	851	
RR	102	158	
SS	11	967	
TT	92	589	
UU	228	3163	
VV	115	683	
WW	77	1692	
XX	94	499	
YY	97	356	
ZZ	272	584	
AAA	15	3345	
BBB	41	758	
CCC	133	1865	
DDD	161	839	
EEE	65	475	
FFF	ND	ND	
GGG	161	586	
HHH	85	984	
III	230	775	
JJJ	143	448	
KKK	ND	ND	
LLL	241	1548	
MMM	37	294	
NNN	160	519	

TABLE 2-continued

Inhibition of Cellular Proliferation in Cancer Cells			
Structure	SupT1 Cellular EC ₅₀ [nM]	Daudi Cellular EC ₅₀ [nM]	
OOO	104	668	
PPP	3037	ND	
QQQ	258	485	
RRR	278	2011	
SSS	305	>3000	
TTT	587	3299	
UUU	311	1425	
VVV	224	1072	
WWW	264	1266	
XXX	270	1170	

We claim:

1. A method of treating acute myelogenous leukemia (AML) in a human in need thereof comprising administering to the host an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the compound, or its pharmaceutically acceptable salt thereof, is administered in combination with a second active agent.

3. The method of claim 1, wherein the AML is selected from undifferentiated AML, myeloblastic leukemia with minimal cell maturation, myeloblastic leukemia with cell maturation, promyelocytic leukemia, myelomonocytic leukemia, myelomonocytic leukemia with eosinophilia, monocytic leukemia, erythroleukemia, or megakaryoblastic leukemia.

4. The method of claim 3, wherein the AML is undifferentiated AML.

5. The method of claim 3, wherein the AML is myeloblastic leukemia with minimal cell maturation.

6. The method of claim 3, wherein the AML is myeloblastic leukemia with cell maturation.

7. The method of claim 3, wherein the AML is promyelocytic leukemia.

8. The method of claim 3, wherein the AML is myelomonocytic leukemia.

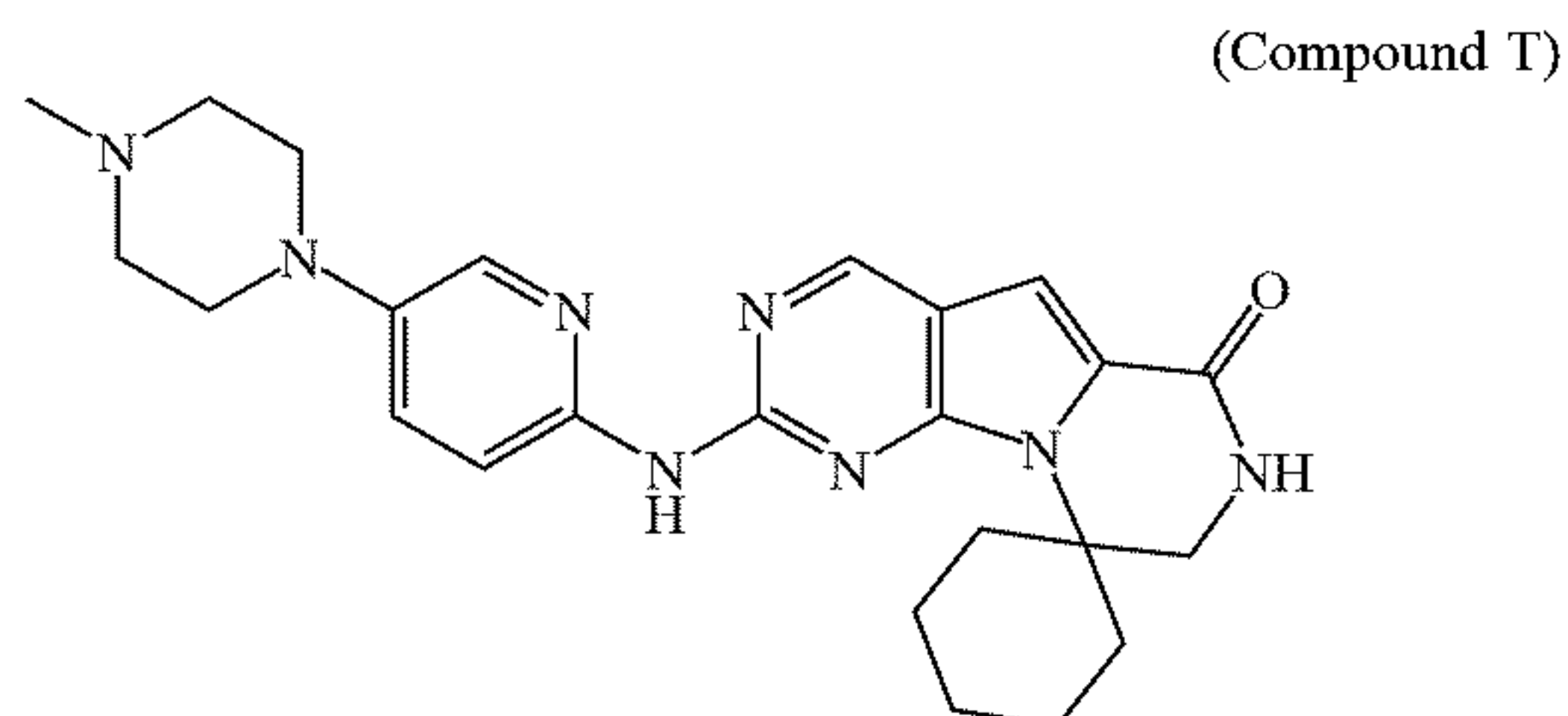
9. The method of claim 3, wherein the AML is myelomonocytic leukemia with eosinophilia.

10. The method of claim 3, wherein the AML is monocytic leukemia.

11. The method of claim 3, wherein the AML is erythroleukemia.

12. The method of claim 3, wherein the AML is megakaryoblastic leukemia.

13. A method of treating a B-cell lymphoma in a human in need thereof comprising administering to the host an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof.

14. The method of claim **13**, wherein the compound, or its pharmaceutically acceptable salt thereof, is administered in combination with a second active agent.

15. The method of claim **13**, wherein the B-cell lymphoma is selected from diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, nodal marginal zone B-cell lymphoma (NMZL), splenic marginal zone B-cell lymphoma (SMZL), extranodal marginal zone mucosa-associated lymphoid tissue (MALT) B-cell lymphoma, intravascular large B-cell lymphoma, splenic diffuse red pulp small B-cell lymphoma, T cell/histocyte-rich large B-cell lymphoma, primary mediastinal (thymic) large B-cell lymphoma, ALK+ large B-cell lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, unclassifiable B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma, unclassifiable B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

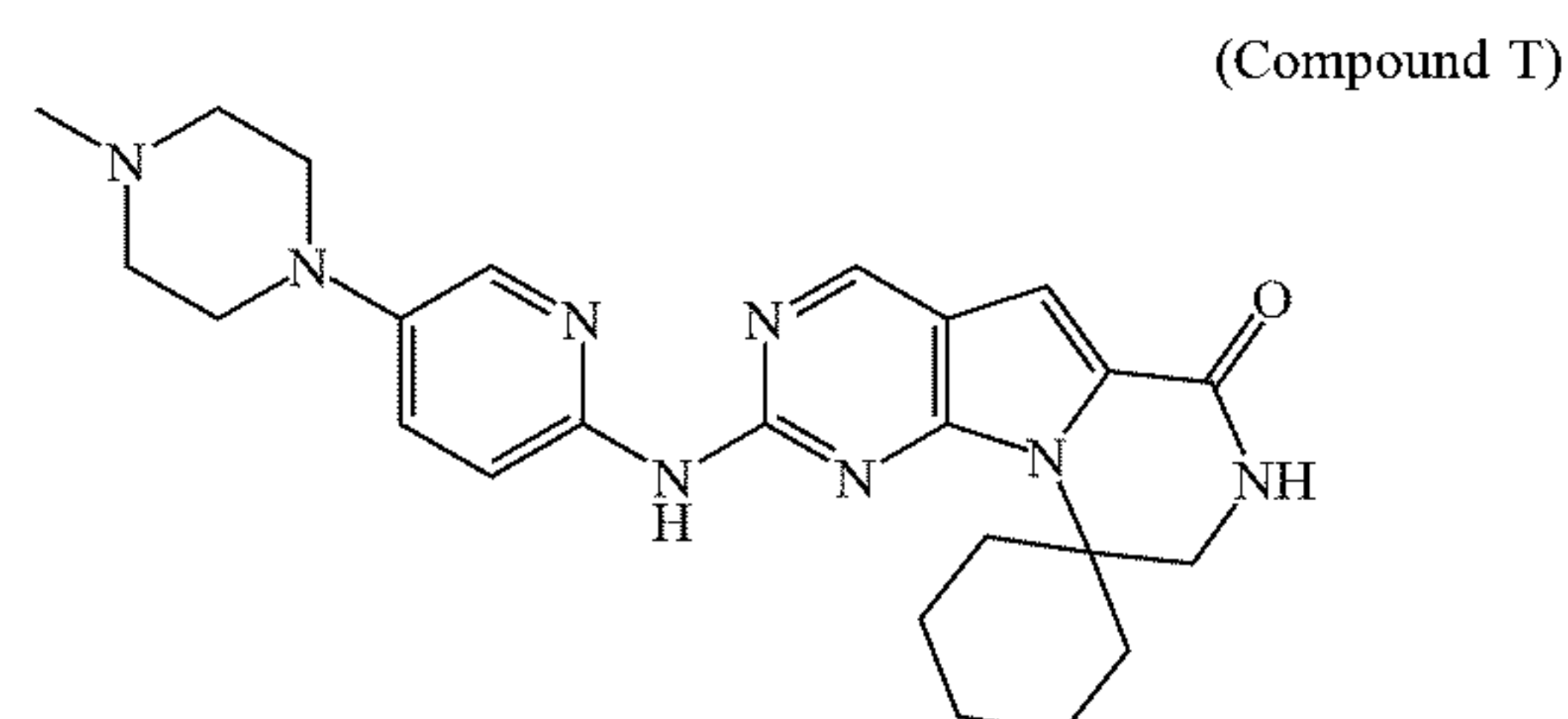
16. The method of claim **15**, wherein the B-cell lymphoma is primary mediastinal B-cell lymphoma.

17. The method of claim **15**, wherein the B-cell lymphoma is extranodal marginal zone mucosa-associated lymphoid tissue (MALT) B-cell lymphoma.

18. The method of claim **15**, wherein the B-cell lymphoma is nodal marginal zone B-cell lymphoma (NMZL).

19. The method of claim **15**, wherein the B-cell lymphoma is splenic marginal zone B-cell lymphoma (SMZL).

20. A method of treating a multiple myeloma in a human in need thereof comprising administering to the host an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof.

21. The method of claim **20**, wherein the compound, or its pharmaceutically acceptable salt thereof, is administered in combination with a second active agent.

* * * * *