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(71) Demandeurs/Applicants:
GENOSCO, US;
OSCOTEC INC., KR

(72) Inventeurs/Inventors:
KIM, HONG WOO, US;
LEE, JAEKYOO, US;
SONG, HO-JUHN, US;
KIM, YOUNGSAM, KR;
LEE, HEE KYU, KR;
...

(74) Agent: BERESKIN & PARR LLP/S.E.N.C.R.L.,S.R.L.

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(54) Title: KINASE INHIBITORS

(57) **Abrégé/Abstract:**

The present invention provides a new group of protein kinase inhibitors, pyrido[4,3,-d]pyrimidin-5-one derivatives, and pharmaceutically acceptable salts thereof that are useful for treating cell proliferative disease and disorder such as cancer, autoimmune diseases, infection, cardiovascular disease and neurodegenerative disease and disorder. The present invention provides methods for synthesizing and administering the protein kinase inhibitor compounds. The present invention also provides pharmaceutical formulations comprising at least one of the protein kinase inhibitor compounds together with a pharmaceutically acceptable carrier, diluent or excipient therefor. The invention also provides useful intermediates generated during the syntheses of the pyrido[4,3,-d]pyrimidin-5-one derivatives.

(72) **Inventeurs(suite)/Inventors(continued)**: CHOI, JANG-SIK, KR; LIM, SUN-HEE, KR; CHANG, SUNHWA, KR;
KOH, JONG SUNG, KR

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(71) Applicants (for all designated States except US):
GENOSCO [US/US]; 6190 Valley View Street, Buena Park, CA 90620 (US). **OSCOTEC INC.** [KR/KR]; 2-17 Omok-ri, Seonggeo-eup, Seobuk-gu, Cheonan, Chungnam 330-831 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KIM, Hong Woo** [KR/US]; 112 5th Street, Cambridge, MA 02141 (US). **KOH, Jong Sung** [KR/KR]; A-204, Hanyang Apt., Yoi-do-dong, Youngdeungpo-gu, Seoul 150-889 (KR). **LEE, Jaekyoo** [KR/US]; 19 Elm Street, North Andover, MA 01845 (US). **SONG, Ho-Juhn** [KR/US]; 141 Argilla Road, Andover, MA 01810 (US). **KIM, Youngsam** [KR/KR]; 99 Samseon-dong, 5-ga, Seongbuk-gu, Seoul 136-045 (KR). **LEE, Hee Kyu** [KR/KR]; 379-1401 Samik Sowol Apt., Ogeum-dong, Gunpo Si, Gyeonggi-Do 435-756 (KR). **CHOI, Jang-Sik** [KR/KR]; 105-1304, Gyeongnam Anusville Apt., Dujeong-dong, Seobuk-gu, Cheonan-si, Chungcheongnam-do 331-829 (KR). **LIM, Sun-Hee** [KR/KR]; 106-1103 Buyeong Apt., Jiksan-eup, Suheol-ri, Seobuk-gu, Cheonan-si Chungcheongnam-do 331-748 (KR). **CHANG, Sunhwa** [KR/KR]; 105-504

Dongil Highvill Apt., Yonggok-dong, Dongnam-gu, Cheonan-si, Chungcheongnam-do 330-809 (KR).

(74) Agents: **BROOK, David, E.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Rd, P.O. Box 9133, Concord, MA 01742-9133 (US).

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(57) Abstract: The present invention provides a new group of protein kinase inhibitors, pyrido[4,3,-d]pyrimidin-5-one derivatives, and pharmaceutically acceptable salts thereof that are useful for treating cell proliferative disease and disorder such as cancer, autoimmune diseases, infection, cardiovascular disease and neurodegenerative disease and disorder. The present invention provides methods for synthesizing and administering the protein kinase inhibitor compounds. The present invention also provides pharmaceutical formulations comprising at least one of the protein kinase inhibitor compounds together with a pharmaceutically acceptable carrier, diluent or excipient therefor. The invention also provides useful intermediates generated during the syntheses of the pyrido[4,3,-d]pyrimidin-5-one derivatives.

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KINASE INHIBITORS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/256,222, filed on October 29, 2009. The entire teachings of the above application are incorporated herein by
5 reference.

BACKGROUND OF THE INVENTION

Protein kinases include a large set of structurally related phosphoryl transferases which catalyze the transfer of the terminal phosphate from ATP to the hydroxyl group of tyrosine, serine and/or threonine residues of proteins. Protein kinases are categorized into families by the
10 substrates they phosphorylate, for example, protein tyrosine kinases (PTK) and protein serine/threonine kinases.

Phosphorylation via protein kinase(s) results in a functional change of the target protein (substrate) by changing enzyme activity, cellular location or association with other proteins. Protein kinases play vital role, not only in controlling cell growth and differentiation, but also in
15 regulating a wide variety of cellular signal transduction pathways in which protein kinases effectively regulate production of growth factors and various cytokines such as tumor necrosis factor (TNF)- α . Examples of protein-tyrosine kinases include SYK, PYK2, FAK, ALK, AXL, CSF1R, FLT3, JAK2 (JH1 domain-catalytic), JAK3 (JH1 domain-catalytic), KIT, KIT (D816V), KIT (V559D, T670I), PDGFRB, RET, TYK2 and ZAP70. Examples of protein-serine/threonine
20 kinases include PIM1, AURKA, AURKB, BMPR2, JNK1, JNK2, JNK3, LKB1, LRRK2, LRRK2(G2019S), MLK1, PAK4, PLK4, RSK2 (Kin.Dom.1-N-terminal), SNARK, SRPK3 and TAK1.

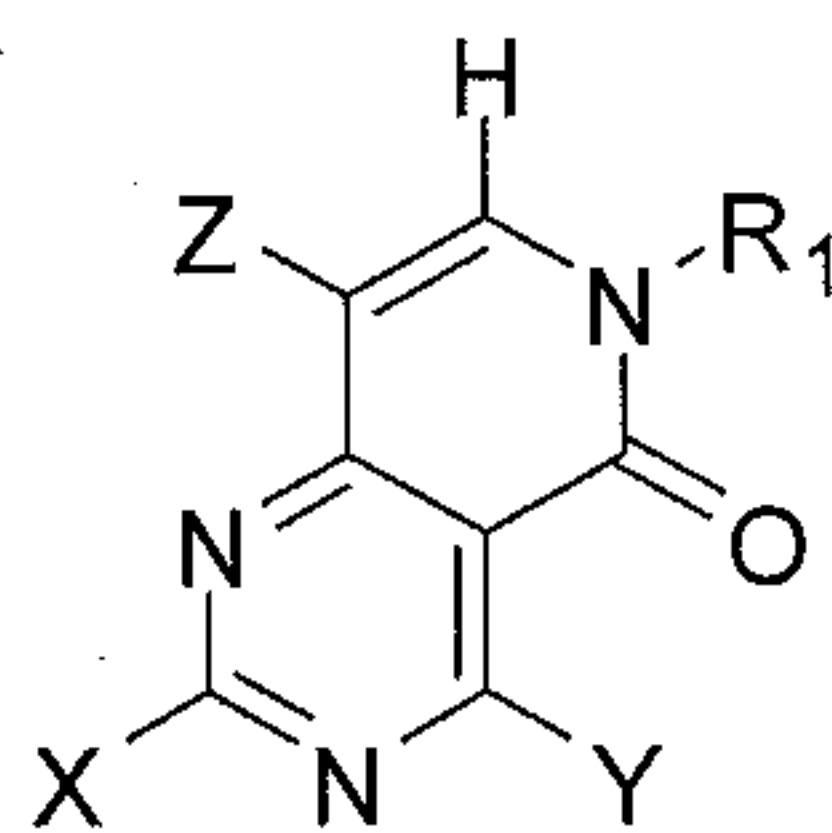
Misregulation of these protein kinases has been implicated in numerous diseases and disorders such as central nervous system disorders (e.g., Alzheimer's disease), inflammatory and
25 autoimmune disorders (e.g., asthma, rheumatoid arthritis, Crohn's disease, and inflammatory bowel syndrome, and psoriasis), bone diseases (e.g., osteoporosis), metabolic disorders (e.g., diabetes), blood vessel proliferative disorders, ocular diseases, cardiovascular disease, cancer, restenosis, pain sensation, transplant rejection and infectious diseases. Although biological and clinical importance of protein kinases has been recognized in the field, a continuing need exists
30 for compounds which inhibit protein kinases to provide an effective and safe clinical therapy for

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the diseases associated with or mediated by protein kinases. A need also exists for methods of administering such compounds, pharmaceutical formulations and medicaments to patients or subjects in need thereof.

5 SUMMARY OF THE INVENTION

The present invention provides compounds having Formula (I), and pharmaceutical acceptable salts, N-oxide derivatives, produg derivatives, protected derivatives, individual isomers and mixture of isomers thereof.



Formula (I)

R¹, X, Y, and Z are described in detail below.

The compounds of Formula (I) are useful for inhibiting one or more protein kinases and
15 for treating diseases and disorders that are mediated by the protein kinases, such as cancer, autoimmune diseases, infection, cardiovascular disease, and neurodegenerative diseases.

In one aspect, the present invention provides pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier. In certain embodiments, such pharmaceutical compositions are formulated for intravenous administration, subcutaneous
20 administration, inhalation, oral administration, rectal administration, parenteral, intravitreal administration, intramuscular administration, intranasal administration, dermal administration, topical administration, otic administration, ophthalmic administration, buccal administration, tracheal administration, bronchial administration, or sublingual administration. In other embodiments, such pharmaceutical composition are formulated as tablets, a pills, capsules, a
25 liquid, an inhalant, a nasal spray solution, a suppository, a solution, a gel, an emulsion, an ointment, eye drops or ear drops.

In one aspect, the present invention provides methods of inhibiting SYK, PYK2, FAK, ZAP70, PIM1, FLT3, RET, JAK2, JAK3, LRRK2, LRRK2(G2019S), ALK, AURKA, AXL, BMPR2, CSF1R, JNK1, JNK2, JNK3, KIT, KIT(D816V), LKB1, MLK1, PAK4, PDGFRB,

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PLK4, RSK2, SNARK, SRPK3, TAK1, or TYK2 signaling *in vivo* or *in vitro*, comprising administering to said subject an effective amount of the compound of Claim 1.

In one aspect, the present invention provides methods for treating a cell-proliferative disease or condition, such as cancer, comprising administering to a subject in need of such
5 treatment a therapeutically effective amount of the compound of Formula (I) or pharmaceutically acceptable salts, pharmaceutical compositions or medicaments thereof, wherein the cell proliferative disease or condition include, for example, lymphoma, osteosarcoma, melanoma, breast cancer, renal cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, lung cancer, uterine cancer or gastrointestinal cancer. In one
10 aspect, the present invention provides methods of inhibiting growth of cancer cells with the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a medicament for treating a SYK, PYK2, FAK, ZAP70, PIM1, FLT3, RET, JAK2, JAK3, LRRK2, LRRK2(G2019S), ALK, AURKA, AXL, BMPR2, CSF1R, JNK1, JNK2, JNK3, KIT, KIT(D816V), LKB1, MLK1,
15 PAK4, PDGFRB, PLK4, RSK2, SNARK, SRPK3, TAK1, or TYK2-mediated disease, disorder or condition in a patient comprising a therapeutically effective amount of the compound of Formula (I).

In another aspect, the present invention provides the use of the compound of Formula (I) in the manufacture of a medicament for treating a SYK, PYK2, FAK, ZAP70, PIM1, FLT3,
20 RET, JAK2, JAK3, LRRK2, LRRK2(G2019S), ALK, AURKA, AXL, BMPR2, CSF1R, JNK1, JNK2, JNK3, KIT, KIT(D816V), LKB1, MLK1, PAK4, PDGFRB, PLK4, RSK2, SNARK, SRPK3, TAK1, or TYK2-mediated disease, disorder or condition.

In another aspect, the present invention provides methods for inhibiting a protein kinase, comprising administering to a subject in need thereof, a therapeutically effective amount of the
25 compound of Formula (I) or a pharmaceutically acceptable salt or pharmaceutical composition thereof. The protein kinase includes, but is not limited to, SYK, PYK2, FAK, ZAP70, PIM1, FLT3, RET, JAK2, JAK3, LRRK2, LRRK2(G2019S), ALK, AURKA, AXL, BMPR2, CSF1R, JNK1, JNK2, JNK3, KIT, KIT(D816V), LKB1, MLK1, PAK4, PDGFRB, PLK4, RSK2, SNARK, SRPK3, TAK1, or TYK2 kinase.

30 In another aspect, the present invention provides methods for inhibiting a protein kinase, comprising contacting to a cell with the compound of Formula (I). In certain embodiment, the compound of Formula (I) effectively inhibits activity of one or more kinases selected from SYK, PYK2, FAK, ZAP70, PIM1, FLT3, RET, JAK2, JAK3, LRRK2, LRRK2(G2019S), ALK,

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AURKA, AXL, BMPR2, CSF1R, JNK1, JNK2, JNK3, KIT, KIT(D816V), LKB1, MLK1, PAK4, PDGFRB, PLK4, RSK2, SNARK, SRPK3, TAK1, and TYK2.

In another aspect, the present invention provides methods for treating a protein kinase-mediated disease or condition comprising administering to a subject in need of such treatment a
5 therapeutically effective amount of the compound of Formula (I) or a pharmaceutically acceptable salt, a pharmaceutical composition or a medicament thereof. The protein kinase includes, but is not limited to, SYK, PYK2, FAK, ZAP70, PIM1, FLT3, RET, JAK2, JAK3, LRRK2, LRRK2(G2019S), ALK, AURKA, AXL, BMPR2, CSF1R, JNK1, JNK2, JNK3, KIT, KIT(D816V), LKB1, MLK1, PAK4, PDGFRB, PLK4, RSK2, SNARK, SRPK3, TAK1, and
10 TYK2.

In certain embodiments, protein kinase-mediated diseases or conditions are inflammatory diseases or conditions, respiratory diseases or autoimmune diseases or conditions, such as asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohn's disease, bronchitis, dermatitis, allergic rhinitis, psoriasis,
15 scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, breast cancer, HIV associated diseases or lupus.

In another aspect, the present invention provides methods for treating a neurological/neurodegenerative disease or condition by administering to a subject a therapeutically effective amount of the compound of Formula (I) or a pharmaceutically
20 acceptable salt. In certain embodiment, such neurological/neurodegenerative disease or condition includes, for example, Alzheimer's disease, cerebral edema, cerebral ischemia, multiple sclerosis, neuropathies, Parkinson's disease, blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury), as well as the neurological aspects of disorders such as degenerative disc disease and sciatica.

In another aspect, the present invention provides methods for treating a cardiovascular
25 disease by administering to a subject a therapeutically effective amount of the compound of Formula (I) or a pharmaceutically acceptable salt. Such a cardiovascular disease affects the heart or blood vessels and includes, for example, atherosclerosis, arrhythmia, angina, myocardial ischemia, myocardial infarction, cardiac or vascular aneurysm, vasculitis, stroke, peripheral
30 obstructive arteriopathy of a limb, an organ, or a tissue, reperfusion injury following ischemia of an organ or a tissue, endotoxic, surgical, or traumatic shock, hypertension, valvular heart disease, heart failure, abnormal blood pressure, vasoconstriction, vascular abnormality, or inflammation.

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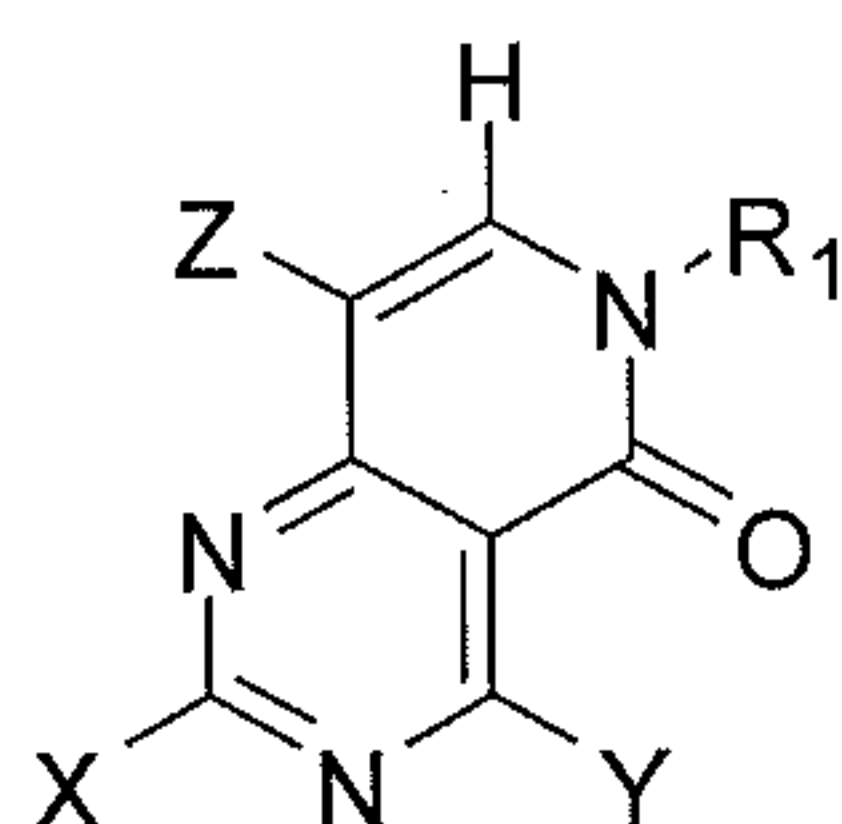
In another aspect, the present invention provides methods of treating a kinase-mediated disease or condition by administering to a subject a therapeutically effective amount of the compound of Formula (I) or a pharmaceutically acceptable salt in combination with a second therapeutic agent.

5 In the above methods for using the compound of the invention, the compound of Formula (I) or a pharmaceutically acceptable salt is administered to a system comprising cells or tissues. In certain embodiments, the compound of Formula (I), a pharmaceutically acceptable salt, a pharmaceutical composition or a medicament thereof is administered to a human or animal subject.

10 DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a group of pyrido[4,3,-*d*]pyrimidin-5-one derivatives and pharmaceutically acceptable salts thereof that are useful for inhibiting one or more protein kinases and for treating diseases and disorders that are mediated by the protein kinases, for
15 example, cell proliferative disease, autoimmune diseases, infection, cardiovascular disease, and neurodegenerative diseases. The present invention also provides methods of synthesizing and administering the pyrido[4,3,-*d*]pyrimidin-5-one derivatives. The present invention provides pharmaceutical formulations comprising at least one of the compounds together with a pharmaceutically acceptable carrier, diluent or excipient therefor. The invention also provides
20 useful intermediates generated during syntheses of the pyrido[4,3,-*d*]pyrimidin-5-one derivative compounds.

Disclosed herein is a novel class of compounds having Formula (I), and pharmaceutical acceptable salts, N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof for inhibiting protein kinases.



Formula (I)

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When R^1 is H and X is NR^2R^3 or NR^4R^5 , then

Y is NHR^6 and

5 Z is selected from H, halogen, C_1 - C_3 alkyl, C_2 - C_4 alkynyl, aryl, heteroaryl, or C_3 - C_8 cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl or heteroaryl is optionally substituted with halo, alkyl, or cyano; wherein:

R^2 and R^3 , taken together with the nitrogen atom to which they are bonded form:

10

i) a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R^2 and R^3 are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is independently substituted at one or more carbon atoms with 1-2 R^7 and optionally substituted at one or more carbon atoms with 0-4 R^8 , wherein R^7 is hydroxy, heterocycloalkyl, or NR^9R^9 and R^8 is hydroxy(C_1 - C_6)alkyl, aryl, $COOR^9$, $(CH_2)_nNR^9R^9$, or $(CH_2)_nNR^9R^{10}$, wherein each n is independently 1, 2, or 3 and the aryl is optionally substituted with halo;

15

20

or

ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone;

25

each R^9 is independently selected from H, C_1 - C_6 alkyl, C_3 - C_6 alkynyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_3 - C_6 cycloalkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, aryl(C_1 - C_6) alkyl, or heteroaryl, wherein the alkyl, alkynyl, alkylcyano, alkylsulfone, sulfonamide, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, or heteroaryl is optionally substituted with R^{25} ;

30

R^{10} is $C(O)R^9$, $COOR^9$, $C(O)NR^9R^9$, or $S(O)_nR^9$, in which n is 1 or 2;

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R^4 is selected from H, C_1 - C_6 alkyl, or hydroxy(C_1 - C_6)alkyl;

R^5 is aryl(C_1 - C_3)alkyl, wherein the aryl group is independently substituted at one or more carbon atoms with 1-3 R^{11} , wherein R^{11} is independently selected from OR^9 , NR^9R^9 , NR^9COR^9 , or $NR^9S(O)_nR^9$, wherein n is 1 or 2;

R^6 is selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, or heteroaryl, in which the heterocycloalkyl, aryl, or heteroaryl of R^6 is optionally substituted with an aryl selected from the group consisting of:

- i) a 5-6 membered monocyclic aryl group;
- ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone;
- iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone; and
- iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carbonyl, carboxamide, or sulfoxamide; or

the heterocycloalkyl, aryl, or heteroaryl of R^6 can be also optionally substituted at one or more carbon atoms with R^{12} , wherein each R^{12} is independently selected from C_1 - C_6 alkyl, CF_3 , OCF_3 , $S(O)_n(C_1$ - $C_4)$ alkyl, halo(C_1 - C_4)alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl (C_1 - C_6)alkyl, heteroaryl, halo, haloalkyl, SR^{13} , OR^{13} , $OC(O)R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $COOR^{13}$, NO_2 , CN , $C(O)R^{13}$, $C(O)C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $CONR^{15}R^{16}$, $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$, or $NR^{15}R^{16}$, wherein each n is independently 1 or 2 and the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} , wherein the aryl and heteroaryl of R^{12} is independently selected from:

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- 5
- i) a 5-6 membered monocyclic aryl group;
 - ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide or sulfone;
 - iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently nitrogen, oxygen, sulfur, sulfoxide or sulfone; or
 - 10 iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carbonyl, carboxamide, or sulfoxamide;

15 each R^{13} is independently selected from H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, haloalkyl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkyl cyano, alkyl sulfone, alkyl sulfonamide, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} ;

20 R^{14} is $C(O)R^{13}$, $COOR^{13}$, $C(O)NR^{13}R^{13}$, $SO_2NR^{13}R^{13}$, or $S(O)_nR^{13}$, wherein n is 1 or 2;

25 R^{15} and R^{16} , taken together with the nitrogen atom to which they are bonded, form:

- i) a 3-8 membered saturated or partially saturated monocyclic group, wherein the 3-8 membered saturated or partially saturated monocyclic group is optionally substituted with R^{25} ;
- 30 ii) an 8-12 membered saturated or partially saturated bicyclic group, wherein the 8-12 membered saturated or partially saturated bicyclic group is optionally substituted with R^{25} ;

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- iii) a 3-8 membered saturated or partially saturated monocyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein the 3-8 membered saturated or partially saturated monocyclic group having 1-2 heteroatoms is optionally substituted with R^{13} or R^{14} ; or
- iv) a 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone, sulfoxide, wherein the 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms is optionally substituted with R^{13} or R^{14} ; and

each R^{25} is independently selected from hydroxy, hydroxy(C_1 - C_6)alkyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl(C_1 - C_6)alkyl, aryl, halo, haloalkyl, oxo, oxime, CF_3 , SR^{13} , OCF_3 , OR^{13} , $OC(O)CH_2R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $NHC(O)R^{13}$, $(CH_2)_nNR^{13}R^{13}$, $COOR^{13}$, CN , $C(O)R^{13}$, $C(O)CF_3$, $CONR^{15}R^{16}$, $CONH_2$, $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$, or $NR^{15}R^{16}$, wherein each n is independently 1 or 2 and the heterocycloalkyl is optionally substituted with C_1 - C_3 alkyl.

When R^1 is H and Y is NHR^{17} or R^{17} , then

X is OR^{18} , $NR^{15}R^{16}$, NHR^{18} , $NR^{18}R^{19}$, or $NR^{19}R^{20}$ and

Z is H, halogen, C_1 - C_3 alkyl, C_2 - C_4 alkynyl, aryl, heteroaryl, or C_3 - C_8 cycloalkyl, wherein the alkyl, alkynyl, cycloalkyl, aryl, or heteroaryl is optionally substituted with halo, alkyl, or cyano, wherein:

R^{17} is selected from aryl(C_1 - C_6)alkyl, aryl, or heteroaryl, wherein the aryl, or the heteroaryl is substituted at one or more carbon atoms with at least one R^{21} and 0-2 R^{22} and the aryl group of said aryl(C_1 - C_6)alkyl is optionally substituted with halo;

R^{21} is independently selected from amino, hydroxy, CF_3 , OCF_3 , O-aryl, $S(O)_nR^{13}$, or $NR^{15}R^{16}$ ($R^{15}R^{16}$ are as described above);

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5 R^{22} is independently H, C_1 - C_6 alkyl, CF_3 , OCF_3 , $S(O)_n(C_1-C_4)alkyl$, halo(C_1 - C_4)alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, heteroaryl, halo, SR^{13} , OR^{13} , $OC(O)R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $COOR^{13}$, NO_2 , CN , $C(O)R^{13}$, $C(O)C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $CONR^{15}R^{16}$, $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$, $NR^{13}C(O)NR^{13}R^{13}$, $NR^{13}C(O)R^{13}$, $NR^{13}(COOR^{13})$, $NR^{13}S(O)_nR^{13}$, or $NR^{15}R^{16}$, wherein each n is independently 1 or 2 and wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} ;

10 R^{18} is selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, hydroxy(C_2 - C_6)alkyl, amino(C_2 - C_6)alkyl, haloalkyl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} ;

15 each R^{19} is independently selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, hydroxy(C_2 - C_6)alkyl, amino(C_2 - C_6)alkyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, haloalkyl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkyl cyano, alkylsulfone, sulfonamide, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} ;

20 R^{20} is $C(O)R^{19}$, $COOR^{19}$, $C(O)NR^{19}R^{19}$ or $S(O)_nR^{19}$, in which n is 1 or 2;

25 each R^{25} is independently selected from hydroxy, hydroxy(C_1 - C_6)alkyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl(C_1 - C_6)alkyl, aryl, halo, haloalkyl, oxo, oxime, CF_3 , SR^{13} , OCF_3 , OR^{13} , $OC(O)CH_2R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $NHC(O)R^{13}$, $(CH_2)_nNR^{13}R^{13}$, $COOR^{13}$, CN , $C(O)R^{13}$, $C(O)CF_3$, $CONR^{15}R^{16}$, $CONH_2$, $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$,

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or $\text{NR}^{15}\text{R}^{16}$, wherein each n is independently 1 or 2 and the heterocycloalkyl is optionally substituted with $\text{C}_1\text{-C}_3$ alkyl.

When R^1 is CH_3 , then

X is NH_2 or NHR^6 as described above,

Y is NHR^6 or R^6 as described above, and

Z is H, halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl, heteroaryl, or $\text{C}_3\text{-C}_8$ cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl, or heteroaryl is optionally substituted with halo, alkyl, or cyano.

In certain aspect, R^1 is H, X is NR^2R^3 , and Y is NHR^6 . Z can be H, halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl, heteroaryl, or $\text{C}_3\text{-C}_8$ cycloalkyl, in which the alkyl, cycloalkyl, aryl, alkynyl, or heteroaryl is optionally substituted with halo, alkyl, or cyano. NHR^6 is described below.

NR^2R^3 is a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R^2 and R^3 are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is independently substituted at one or more carbon atoms with 1-2 R^7 and optionally substituted at one or more carbon atoms with 0-4 R^8 . R^7 is hydroxy, heterocycloalkyl, or NR^9R^9 and R^8 is hydroxy($\text{C}_1\text{-C}_6$)alkyl, aryl, COOR^9 , $(\text{CH}_2)_n\text{NR}^9\text{R}^9$, or $(\text{CH}_2)_n\text{NR}^9\text{R}^{10}$, in which each n is independently 1, 2, or 3. The aryl is optionally substituted with halo. The 3-8 membered saturated or partially saturated monocyclic group can be optionally substituted with hydroxy or amine. In one embodiment, the 3-8 membered saturated or partially saturated monocyclic group is azetidine, piperidine or pyrrolidine, in which the azetidine, piperidine or pyrrolidine is independently substituted with 1-3 hydroxy or amino group and optionally and independently substituted with hydroxymethyl at the one or more carbon atoms. In another embodiment, NR^2R^3 is selected from an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone.

In certain aspects, R^1 is H, X is NR^4R^5 , and Y is NHR^6 . Z can be H, halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl, heteroaryl, or $\text{C}_3\text{-C}_8$ cycloalkyl, wherein the alkyl, cycloalkyl, aryl,

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alkynyl, or heteroaryl is optionally substituted with halo, alkyl, or cyano. NHR^6 is described below.

R^4 is selected from H, $\text{C}_1\text{-C}_6$ alkyl, or hydroxy($\text{C}_1\text{-C}_6$) alkyl and R^5 is aryl($\text{C}_1\text{-C}_3$)alkyl. The aryl group of aryl($\text{C}_1\text{-C}_3$)alkyl of R^5 is independently substituted at the one or more carbon atoms with 1-3 R^{11} . R^{11} is independently selected from OR^9 , NR^9R^9 , NR^9COR^9 , or $\text{NR}^9\text{S(O)}_n\text{R}^9$, in which n is 1 or 2. R^9 is independently selected from H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ alkynyl, $\text{C}_2\text{-C}_6$ alkyl cyano, $\text{C}_2\text{-C}_6$ alkyl sulfone, $\text{C}_3\text{-C}_6$ alkyl sulfone, $\text{C}_3\text{-C}_6$ cycloalkyl sulfone, $\text{C}_2\text{-C}_6$ sulfonamide, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_8$ heterocycloalkyl, $\text{C}_4\text{-C}_6$ cycloalkenyl, aryl, aryl($\text{C}_1\text{-C}_6$)alkyl, haloalkyl, or heteroaryl, in which the alkyl, alkenyl, alkynyl, alkyl cyano, alkyl sulfone, sulfonamide, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} .

In certain aspects, Y is NHR^6 . R^6 is selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_8$ heterocycloalkyl, $\text{C}_4\text{-C}_6$ cycloalkenyl, aryl, aryl($\text{C}_1\text{-C}_6$)alkyl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} .

In one embodiment, the aryl of R^6 is an optionally substituted aryl selected from the group consisting of: i) a 5-6 membered monocyclic aryl group; ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone; iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide or sulfone; and iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carbonyl, carboxamide, or sulfoxamide. The aryl of R^6 is optionally substituted at one or more carbon atoms with R^{12} . The aryl of R^6 is phenyl optionally substituted at one or more carbon atoms with R^{12} .

In one embodiment, R^{12} is independently selected from $\text{C}_1\text{-C}_6$ alkyl, OCF_3 , CF_3 , $\text{S(O)}_n(\text{C}_1\text{-C}_4)\text{alkyl}$, halo($\text{C}_1\text{-C}_4$)alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_8$ heterocycloalkyl, $\text{C}_4\text{-C}_6$ cycloalkenyl, aryl, aryl($\text{C}_1\text{-C}_6$)alkyl, heteroaryl, halo, haloalkyl, SR^{13} , OR^{13} , OC(O)R^{13} , $\text{NR}^{13}\text{R}^{13}$, $\text{NR}^{13}\text{R}^{14}$, COOR^{13} , NO_2 , CN , C(O)R^{13} , C(O)C(O)R^{13} , $\text{C(O)NR}^{13}\text{R}^{13}$, $\text{CONR}^{15}\text{R}^{16}$, $\text{S(O)}_n\text{R}^{13}$, $\text{S(O)}_n\text{NR}^{13}\text{R}^{13}$, or $\text{NR}^{15}\text{R}^{16}$, wherein each n is independently 1 or 2; and wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} . In one embodiment, R^{12} is independently selected from $\text{C}_1\text{-C}_6$ alkyl, CF_3 , OCF_3 , $\text{S(O)}_n(\text{C}_1\text{-C}_4)\text{alkyl}$, halo($\text{C}_1\text{-C}_4$)alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_8$ heterocycloalkyl, $\text{C}_4\text{-C}_6$ cycloalkenyl, aryl,

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aryl(C₁-C₆)alkyl, heteroaryl, halo, SR¹³, OR¹³, OC(O)R¹³, NR¹³R¹³, NR¹³R¹⁴, COOR¹³, NO₂,
CN, C(O)R¹³, C(O)NR¹³R¹³, CONR¹⁵R¹⁶, S(O)_nR¹³, S(O)_nNR¹³R¹³, or NR¹⁵R¹⁶, wherein each n
is independently 1 or 2. In one embodiment, R¹² is independently selected from CF₃, OCF₃,
COOCH₃, methoxy, methyl, fluoro, chloro, bromo, iodo, S(O)₂CH₃, morpholino, piperazinyl, or
5 acetylpiperazinyl. In one embodiment, the aryl of R¹² is independently selected from: i) a 5-6
membered monocyclic aryl group; ii) an 8-10 membered bicyclic aryl group having 0-5
heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone; iii) an
8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms
independently nitrogen, oxygen, sulfur, sulfoxide, or sulfone; or iv) an 8-10 membered
10 unsaturated or partially unsaturated bicyclic aryl group having a carboxamide, or sulfoxamide.

In one embodiment, R¹² can be SR¹³, OR¹³, OC(O)R¹³, NR¹³R¹³, NR¹³R¹⁴, COOR¹³, CN,
C(O)R¹³, C(O)NR¹³R¹³, S(O)_nR¹³, S(O)_nNR¹³R¹³, or NR¹⁵R¹⁶, in which each R¹³ is
independently selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₂-C₆ alkylcyano, C₂-
C₆ alkyl sulfone, C₂-C₆ sulfonamide, C₃-C₆ cycloalkyl, C₃-C₈ heterocycloalkyl, C₄-C₆
15 cycloalkenyl, aryl, alkoxy, aryl(C₁-C₆)alkyl, haloalkyl, or heteroaryl and R¹⁴ is C(O)R¹³,
COOR¹³, C(O)NR¹³R¹³, SO₂NR¹³R¹³, or S(O)_nR¹³, wherein n is 1 or 2 and the alkyl, alkenyl,
alkynyl, alkyl cyano, alkyl sulfone, alkyl sulfonamide, cycloalkyl, heterocycloalkyl,
cycloalkenyl, aryl, alkoxy, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R²⁵.

In one embodiment, R¹² is NR¹⁵R¹⁶, in which R¹⁵ and R¹⁶, taken together with the
20 nitrogen atom to which they are bonded, form: i) a 3-8 membered saturated or partially saturated
monocyclic group, wherein the 3-8 membered saturated or partially saturated monocyclic group
is optionally substituted with R²⁵; ii) an 8-12 membered saturated or partially saturated bicyclic
group, wherein the 8-12 membered saturated or partially saturated bicyclic group is optionally
substituted with R²⁵; iii) a 3-8 membered saturated or partially saturated monocyclic group
25 having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein the
3-8 membered saturated or partially saturated monocyclic group having 1-2 heteroatoms is
optionally substituted with R¹³ or R¹⁴; or iv) an 8-12 membered saturated or partially saturated
bicyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone, sulfoxide,
wherein the 8-12 membered saturated or partially saturated bicyclic group having 1-3
30 heteroatoms is optionally substituted with R¹³ or R¹⁴.

In one embodiment, R⁶ is the optionally substituted 5-6 membered monocyclic aryl group
or 9-10 membered bicyclic aryl group. In one embodiment, the optionally substituted 5-6
membered monocyclic aryl group is phenyl. In another embodiment, 9-10 membered bicyclic

aryl group is naphthyl, quinoliny, indazolyl, indolyl, or dihydrobenzodioxynyl. In one embodiment, the phenyl of R^6 is optionally substituted with 1-4 groups of methyl ($-CH_3$), methoxy ($-OCH_3$), methylsulfone ($-S(O)_2CH_3$), amino (NH_2), hydroxyl ($-OH$), CF_3 , OCF_3 , halo (F, Br, I, or Cl), phenyl, phenoxy, piperazinyl, acetylpiperrazinyl, or morpholino.

5 In one embodiment, R^1 is H; Y is NHR^{17} or R^{17} ; and X is NHR^{18} . Z is selected from H, halogen, C_1 - C_3 alkyl, C_2 - C_4 alkynyl, aryl, heteroaryl, or C_3 - C_8 cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl or heteroaryl is optionally substituted with halo, alkyl, or cyano.

In one embodiment, R^{17} is aryl(C_1 - C_6)alkyl, aryl or heteroaryl, wherein the aryl or the heteroaryl of R^{17} is substituted at two or more carbon atoms with at least one R^{21} and 0-2 R^{22} .

10 In one embodiment, R^{21} is amino, hydroxy, CF_3 , OCF_3 , O-aryl, $S(O)_nR^{13}$, or $NR^{15}R^{16}$.

In embodiment, R^{22} can be independently selected from H, C_1 - C_6 alkyl, CF_3 , OCF_3 , $S(O)_n(C_1$ - $C_4)$ alkyl, halo(C_1 - C_4)alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl C_1 - C_6 alkyl, heteroaryl, halo, haloalkyl, SR^{13} , OR^{13} , $OC(O)R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $COOR^{13}$, NO_2 , CN, $C(O)R^{13}$, $C(O)C(O)R^{13}$, $C(O)NR^{13}R^{13}$,
15 $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$, or $NR^{15}R^{16}$, in which each n is independently 1 or 2; and the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heteroarylalkyl, or heteroaryl is optionally substituted with R^{25} ; and the aryl group of said aryl(C_1 - C_6)alkyl is optionally substituted with halo.

In one embodiment, the aryl of O-aryl of R^{21} is independently selected from: i) a 5-6
20 membered monocyclic aryl group; ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide or sulfone; iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently nitrogen, oxygen, sulfur, sulfoxide or sulfone; or iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carboxamide or sulfoxamide.

25 In one embodiment, the aryl or heteroaryl of R^{17} is a 5-6 membered monocyclic aryl group substituted with at least one group selected from CF_3 , OCF_3 , O-aryl, or $NR^{15}R^{16}$ at the one or more carbon atoms. In one embodiment, the monocyclic aryl group is phenyl substituted with at least one group selected from CF_3 , OCF_3 , O-aryl, or $NR^{15}R^{16}$ at the one or more carbon atoms, in which $NR^{15}R^{16}$ is optionally substituted morpholino, piperazinyl, homopiperazinyl,
30 thiomorpholino, piperidinyl, or pyrrolidinyl. The piperazinyl, homopiperazinyl, piperidinyl, or pyrrolidinyl is optionally substituted at one or more carbon atoms with 1, 2 or 3 R^{25} or at one nitrogen atom with R^{13} or R^{14} .

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R^{18} is selected from C_1 - C_6 alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, haloalkyl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} .

5 In one embodiment, R^{18} is C_1 - C_6 alkyl optionally substituted with one or more aryl, alkyl, halo, R^{23} or R^{24} . Each R^{23} is independently CF_3 , OCF_3 , SR^{13} , OR^{13} , $NR^{13}R^{13}$, $S(O)_nNR^{13}R^{13}$, $S(O)_nR^{13}$, or $NR^{15}R^{16}$, each of n being independently 1 or 2. Each R^{24} is selected from a 5-8 membered monocyclic group having 1-3 heteroatoms, an 8-12 membered bicyclic group having 1-5 heteroatoms, or an 11-14 membered tricyclic group having 1-8 heteroatoms. The
10 heteroatoms of R^{24} are independently oxygen, nitrogen, or sulfur and R^{24} is optionally substituted with R^{13} or R^{14} . Zero, one, two, three or four atoms of R^{24} are optionally and independently substituted with R^{13} . In one embodiment, the aryl group attached to C_1 - C_6 alkyl of R^{18} is optionally and independently substituted at one or more carbon atoms with 1-3 R^{11} which is independently selected from OR^9 , NR^9R^9 , NR^9COR^9 , or $NR^9S(O)_nR^9$, wherein n is 1 or 2. In one
15 embodiment, the C_1 - C_6 alkyl of R^{18} is C_2 - C_4 alkyl optionally substituted with 1-3 groups selected from amino, hydroxy, phenyl, benzyl, or morpholino.

In another embodiment, R^{18} is C_3 - C_6 alkenyl optionally substituted with one or more, aryl, alkyl, halo, R^{23} , or R^{24} . Each R^{23} is independently selected from CF_3 , OCF_3 , SR^{13} , OR^{13} , $NR^{13}R^{13}$, $S(O)_nNR^{13}R^{13}$, $S(O)_nR^{13}$, or $NR^{15}R^{16}$, in which each n is independently 1 or 2. Each
20 R^{24} is independently selected from: a 5-8 membered monocyclic group having 1-3 heteroatoms; an 8-12 membered bicyclic having 1-5 heteroatoms; or an 11-14 membered tricyclic group having 1-8 heteroatoms and the heteroatoms of R^{24} is independently selected from oxygen, nitrogen or sulfur. R^{24} is optionally substituted with R^{13} or R^{14} . In some embodiment, zero, one, two, three or four atoms of R^{24} are optionally and independently substituted with R^{13} .

25 In yet another embodiment, R^{18} is C_3 - C_6 cycloalkyl optionally substituted with one or more, aryl, alkyl, halo, R^{23} or R^{24} . Each R^{23} is independently selected from CF_3 , OCF_3 , SR^{13} , OR^{13} , $NR^{13}R^{13}$, $(CH_2)_nNR^{13}R^{13}$, $S(O)_nNR^{13}R^{13}$, $S(O)_nR^{13}$, or $NR^{15}R^{16}$, in which each n is independently 1 or 2. Each R^{24} is independently selected from a 5-8 membered monocyclic group having 1-3 heteroatoms, an 8-12 membered bicyclic group having 1-5 heteroatoms, or an
30 11-14 membered tricyclic group having 1-8 heteroatoms, and the heteroatoms of R^{24} is independently selected from oxygen, nitrogen or sulfur. R^{24} is optionally substituted with R^{13} or R^{14} . In one embodiment, zero, one, two, three or four atoms of R^{24} are optionally and independently substituted with R^{13} .

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In yet another embodiment, R^{18} is C_3 - C_8 heterocycloalkyl. In one embodiment, the C_3 - C_8 heterocycloalkyl is a 5-7 membered monocycle having a heteroatom. The heteroatom is independently selected from oxygen, nitrogen, sulfur, or sulfone and the nitrogen atom is optionally substituted with R^{19} . R^{19} is independently selected from hydroxy(C_2 - C_6)alkyl, amino(C_2 - C_6)alkyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, or C_4 - C_8 heterocycloalkyl. In one embodiment, the 5-7 monocycle is optionally substituted morpholine, tetrahydrofuran, thiomorpholine, piperazine, or homopiperazine.

In certain aspects, R^1 is H, Y is NHR^{17} or R^{17} , and X is OR^{18} . Z is H, halogen, C_1 - C_3 alkyl, C_2 - C_4 alkynyl, aryl, heteroaryl, or C_3 - C_8 cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl, or heteroaryl is optionally substituted with halo, alkyl, or cyano. R^{17} and R^{18} are described above.

In certain aspects, R^1 is H; Y is NHR^{17} or R^{17} ; and X is $NR^{18}R^{19}$. Z is selected from H, halogen, C_1 - C_3 alkyl, C_2 - C_4 alkynyl, aryl, heteroaryl, or C_3 - C_8 cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl or heteroaryl is optionally substituted with halo, alkyl, or cyano. R^{17} and R^{18} are as described above. R^{19} is independently selected from hydroxy(C_2 - C_6)alkyl, amino(C_2 - C_6)alkyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, or C_4 - C_8 heterocycloalkyl.

In certain aspects, R^1 is H; Y is NHR^{17} or R^{17} ; and X is $NR^{19}R^{20}$. Z is selected from H, halogen, C_1 - C_3 alkyl, C_2 - C_4 alkynyl, aryl, heteroaryl, or C_3 - C_8 cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl or heteroaryl is optionally substituted with halo, alkyl, or cyano. R^{17} is described above. R^{19} is independently selected from hydroxy(C_2 - C_6)alkyl, amino(C_2 - C_6)alkyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, or C_4 - C_8 heterocycloalkyl. R^{20} is selected from $C(O)R^{19}$, $COOR^{19}$, $C(O)NR^{19}R^{19}$, or $S(O)_nR^{19}$, in which n is 1 or 2.

In one embodiment, R^1 is H; Y is NHR^{17} or R^{17} ; and X is $NR^{15}R^{16}$. Z is selected from H, halogen, C_1 - C_3 alkyl, C_2 - C_4 alkynyl, aryl, heteroaryl, or C_3 - C_8 cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl or heteroaryl is optionally substituted with halo, alkyl, or cyano. R^{17} is described above. R^{15} and R^{16} of $NR^{15}R^{16}$, taken together with the nitrogen atom to which they are bonded, form: i) a 3-8 membered saturated or partially saturated monocyclic group, wherein the 3-8 membered saturated or partially saturated monocyclic group is optionally substituted with R^{25} ; ii) an 8-12 membered saturated or partially saturated bicyclic group, wherein the 8-12 membered saturated or partially saturated bicyclic group is optionally substituted with R^{25} ; iii) a 3-8 membered saturated or partially saturated monocyclic group having 1-3 heteroatoms selected

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from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein the 3-8 membered saturated or partially saturated monocyclic group having 1-2 heteroatoms is optionally substituted with R^{13} or R^{14} ; or iv) an 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone, sulfoxide, wherein the 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms is optionally substituted with R^{13} or R^{14} .

In one embodiment, $NR^{15}R^{16}$ is the 4-6 membered saturated monocyclic group optionally and independently substituted at one or more carbon atoms with 1-4 R^{25} . In one embodiment, the 4-6 membered saturated monocyclic group is selected from piperidine or pyrrolidine optionally substituted with 1-4 groups selected from hydroxy, amino, C_1 - C_6 alkyl, hydroxy(C_1 - C_6)alkyl, amino(C_1 - C_6)alkyl, or phenyl.

In another embodiment, $NR^{15}R^{16}$ is a 5-8 membered saturated heterocyclic group having 1-2 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone, or sulfoxide, wherein said 5-8 membered saturated heterocyclic group is optionally substituted with hydroxy, amino, C_1 - C_6 alkyl, or phenyl at one or more carbon atoms or nitrogen atoms. The 5-8 membered saturated heterocyclic group is selected from morpholine, thiomorpholine, piperazine or homopiperazine optionally substituted with 1-4 groups selected from hydroxy, amino, C_1 - C_6 alkyl and phenyl, wherein each C_1 - C_6 alkyl is optionally substituted with one or more amino, or hydroxy. The 1-2 heteroatoms are nitrogen and nitrogen atoms are independently substituted with C_1 - C_6 alkyl, $C(O)C_1$ - C_3 alkyl, or $S(O)_2C_1$ - C_3 alkyl, wherein the alkyl is optionally and independently substituted with amino or hydroxy.

In one embodiment, the aryl group of R^{25} is selected from: i) a 5-6 membered monocyclic aryl group; ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide or sulfone; iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone; or iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carbonyl, carboxamide, or sulfoxamide.

In one embodiment, R^1 is methyl, X is selected from NH_2 or NHR^6 , and Y is selected from R^6 or NHR^6 .

In one embodiment, Z is H, halo, C_1 - C_3 alkyl, alkynyl or phenyl.

Examples of the present invention includes:

4-(3,5-dimethoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3,-*d*]pyrimidin-6(6*H*)-one;

4-(3,5-dimethoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)
pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3,5-dimethoxyphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one
hydrochloride;

5 4-(3,5-dimethoxyphenylamino)-2-(4-morpholinopiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

methyl 1-(4-(3,5-dimethoxyphenyl amino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)-4-
hydroxy piperidine-4-carboxylate;

10 2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidine-5(6*H*)-
one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-
5(6*H*)-one hydrochloride;

(*S*)-2-(pyrrolidin-3-ylamino)-4-(4-trifluoromethylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

15 2-((1*R*,4*R*)-4-aminocyclohexyl amino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

2-(2-morpholinoethoxy)-4-(3-(trifluoro methyl)phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one hydrochloride;

20 2-(4-methylpiperazin-1-yl)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-
5(6*H*)-one;

(*R*)-2-(3-hydroxypyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-
5(6*H*)-one;

25 2-(piperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one hydrochloride;

2-(4-hydroxypiperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

30 2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

N-(2-((5-oxo-4-(3-(trifluoromethyl) phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-
ylamino)methyl)phenyl)methanesulfonamide;

- (*S*)-2-(3-hydroxypyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(4-aminopiperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;
- 5 *N*-(1-(5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)piperidin-4-yl)cyclopropanesulfonamide;
- 2-(piperidin-4-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;
- (*S*)-2-(3-aminopyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-10 5(6*H*)-one hydrochloride;
- 2-morpholino-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-((1*R*,4*R*)-4-hydroxycyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(4-oxopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 15 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(3-(3-(trifluoromethyl)phenyl)-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(cyclopropylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 20 2-(cyclopentylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- (*R*)-2-(pyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;
- 2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 25 2-(benzylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(benzyl(methyl)amino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- (*S*)-2-(1-(4-fluorophenyl)ethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-((tetrahydro-2*H*-pyran-4-yl)methylamino)-4-(4-(trifluoromethyl)phenyl amino)pyrido[4,3-30 *d*]pyrimidin-5(6*H*)-one;
- 2-(4-fluorobenzylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(piperidin-4-ylmethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

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2-(tetrahydro-2*H*-pyran-4-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(1,4-diazepan-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

5 2-(thiazolidin-3-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
N-(2-((5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide;

(*S*)-2-(1-cyclohexylethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

10 2-(cyclohexylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
(*R*)-2-(1-methylpyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(1-isopropylpyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

15 2-((1-methylpiperidin-4-yl)methylamino)-4-(4-(trifluoromethyl)phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1-isopropylpiperidin-4-yl)methylamino)-4-(4-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

20 2-(4-((dimethylamino)methyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-methylthiazol-2-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*S*)-2-(1-(methylsulfonyl)pyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

25 2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

30 ethyl 1-(5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)piperidine-4-carboxylate;

2-(4-(4-(2-hydroxyethyl)piperazine-1-carbonyl)piperidin-1-yl)-4-(4-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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2-(4-(4-(hydroxymethyl)piperidine-1-carbonyl)piperidin-1-yl)-4-(4-(trifluoro
methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*S*,2*R*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

5 2-((1*S*,2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

10 2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

2-((1*R*,4*R*)-4-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

2-(4-ethylpiperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

15 2-(2-morpholinoethylamino)-4-(3(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

2-(3-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

2-(4-(methylsulfonyl)piperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

20 2-(morpholinoamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
2-(4-acetylpiperazin-1-yl)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

(*R*)-2-(2-hydroxy-1-phenylethylamino)-4-(3-(trifluoromethyl)phenylaminopyrido[4,3-
d]pyrimidin-5(6*H*)-one;

25 (*S*)-2-(2-hydroxy-1-phenylethylamino)-4-(3-(trifluoromethyl)phenylaminopyrido[4,3-
d]pyrimidin-5(6*H*)-one;

(*R*)-2-(1-hydroxy-3-phenylpropan-2-ylamino)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

30 (*S*)-2-(1-hydroxy-3-phenylpropan-2-yl amino)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

1-(5-oxo-4-(3-(trifluoromethyl)phenyl amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-
yl)piperidine-4-carboxamide;

- (*R*)-2,2,2-trifluoro-*N*-(1-(5-oxo-4-(3-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)pyrrolidin-3-yl)acetamide;
- 2-(4-(4-chlorophenyl)-4-hydroxy piperidin-1-yl)-4-(3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 5 2-((1*S*,2*S*)-2-(phenylsulfonyl)cyclohexyl amino)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-((1*S*,2*R*)-2-aminocyclohexylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-thiomorpholino-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 10 2-(4-sulfonylpyrido)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(4-morpholinopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- N*-((1*R*,2*S*)-2-(5-oxo-4-(3-(trifluoro methyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)cyclohexyl) acetamide;
- 15 *N*-((1*R*,4*R*)-4-(5-oxo-4-(3-(trifluoro methyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)cyclohexyl) acetamide;
- 2-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl amino)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(4-aminopiperidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one
- 20 hydrochloride;
- 4-(3-bromophenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(4-aminopiperidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;
- 4-(3-bromophenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
- 25 one;
- (*S*)-4-(3-bromophenylamino)-2-(4-(1-hydroxypropan-2-ylamino)piperidin-1-yl) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- (*R*)-2-(4-(3-aminopyrrolidin-1-yl) piperidin-1-yl)-4-(3-bromophenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;
- 30 (*R*)-2-(3-aminopyrrolidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;
- 4-(3-bromophenylamino)-2-(3-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*S*)-2-(3-aminopyrrolidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

5 4-(4-bromophenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
2-(4-aminopiperidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*S*)-4-(3-bromophenylamino)-2-(4-(1-hydroxypropan-2-ylamino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

10 4-(3-bromophenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(*m*-tolylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(4-hydroxypiperidin-1-yl)-4-(*m*-tolyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(3,5-bis(trifluoromethyl)phenylamino) pyrido[4,3-

15 *d*]pyrimidin-5(6*H*)-one;

(2-((1*R*, 2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one with (2-((1*S*, 2*R*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3- *d*]pyrimidin-

20 5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-morpholinopyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5 bis(trifluoromethyl)phenyl amino)-2-((1*r*,4*r*)-4-hydroxycyclohexyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(2-aminobenzylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

25

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-methylpiperazin-1-yl)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

30 (*S*)-4-(3,5-bis(trifluoromethyl)phenylamino)-2-(pyrrolidin-3-ylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(piperidin-4-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(1-methylpiperidin-4-ylamino)pyrido [4,3-
d]pyrimidin-5(6*H*)-one;

(*S*)-4-(3,5-bis(trifluoromethyl) phenyl amino)-2-(1-methylpyrrolidin-3-ylamino) pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

5 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl) pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

10 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(2-hydroxyethyl)piperazin-1-yl) pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

(*R*)-4-(3,5-bis(trifluoromethyl)phenyl amino)-2-(3-hydroxypyrrolidin-1-yl)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(3-hydroxyazetidin-1-yl)pyrido[4,3-*d*]pyrimidin-
5(6*H*)-one;

15 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(2-hydroxyethyl)piperidin-1-yl) pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

N-((1*r*,4*r*)-4-(4-(3,5-bis(trifluoromethyl) phenylamino)-5-oxo-5,6-dihydropyrido [4,3-
d]pyrimidin-2-ylamino)cyclohexyl) acetamide;

20 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(3-oxopiperazin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(piperazin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one
hydrochloride;

methyl 1-(4-(3,5-bis(trifluoromethyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-
yl)-4-hydroxy piperidine-4-carboxylate;

25 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-
yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*, 4*R*)-4-aminocyclohexylamino)-4-(3,5-bis(trifluoromethyl)phenylamino) pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

30 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(hydroxyimino)piperidin-1-yl)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

(*S*)-4-(phenoxyphenylamino)-2-(pyrrolidin-3-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one
hydrochloride;

2-(4-hydroxypiperidin-1-yl)-4(4-(methylsulfonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

- N*-(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide;
- 2-(4-hydroxypiperidin-1-yl)-4-(4-(methyl sulfonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 5 4-(4-(methylsulfonyl)phenylamino)-2-(4-morpholinopiperidin-1-yl)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;
- 2-(4-hydroxypiperidin-1-yl)-4-(3-(methyl sulfonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- N*-(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl
- 10 amino)methyl)phenyl)cyclopropane sulfonamide;
- N*-methyl-*N*-(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)cyclopropanesulfonamide;
- (*S*)-2-(3-aminopyrrolidin-1-yl)-4-(4-(methylsulfonyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;
- 15 2-(4-hydroxypiperidin-1-yl)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 4-(4-(4-acetylpiperazin-1-yl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- (*S*)-4-(4-morpholinophenylamino)-2-(pyrrolidin-3-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;
- 20 2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-sulfonylphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 4-(4-(4-acetylpiperazin-1-yl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
- 2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-
- 25 5(6*H*)-one;
- 4-(4-(5-oxo-2-(piperidin-4-ylmethyl amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-4-ylamino)phenyl) morpholine 4-oxide hydrochloride;
- 4-(4-morpholinophenylamino)-2-(piperidin-4-ylmethylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;
- 30 *N*-methyl-*N*-(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)cyclopropanesulfonamide;
- N*-(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)cyclopropanesulfonamide;

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N-(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino) methyl)phenyl)methanesulfonamide;

2-(2-aminobenzylamino)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-
5 5(6*H*)-one;

2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-
5(6*H*)-one;

2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(benzo[*d*][1,3]dioxol-5-ylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

10 2-(4-hydroxypiperidin-1-yl)-4-(3,4,5-trimethoxyphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino) pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

15 2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)
phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino) pyrido[4,3-*d*]
20 pyrimidin-5(6*H*)-one;

2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenyl
amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3,4,5-trimethoxyphenylamino)pyrido
[4,3-*d*]pyrimidin-5(6*H*)-one;

25 4-(3,5-dimethylphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

4-(4-chloro-3-methoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]

30 pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino) pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

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2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenyl
amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

5 4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido [4,3-*d*]
pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-
yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

4-(3-chloro-5-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-
10 yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3-bromo-5-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-
yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethoxy)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-
yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

15 2-(4-hydroxypiperidine-1-yl)-6-methyl-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

6-methyl-4-(phenylamino)-2-(3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one;

methyl 4-(6-methyl-2-morpholino-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-4-ylamino)

20 benzoate;

6-methyl-2-(methylamino)-4-(4-(piperazine-1-carbonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-
5(6*H*)-one hydrochloride;

methyl 4-(6-methyl-2-(methylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-4-ylamino)
benzoate;

25 2-amino-6-methyl-4-(phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

4-(4-fluorobenzylamino)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

6-methyl-2-(methylamino)-4-(phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-methoxybenzylamino)-6-methyl-4-(phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxycyclohexylamino)-6-methyl-4-(phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

30 4-(4-methoxyphenyl)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxyphenyl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-methoxyphenyl)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-aminophenyl)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

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1-(4-fluorophenyl)-3-(4-(6-methyl-2-(methylamino)-5-oxo-5,6-dihydropyrido [4,3-*d*]pyrimidin-4-yl)phenyl)urea;

8-bromo-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one;

5 8-bromo-2-(4-hydroxy-4-(hydroxymethyl) piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

8-chloro-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

10 8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;
(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-bromo-3-methylphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

15 8-bromo-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl) phenylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

20 8-chloro-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

25 (*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-bromo-3-methylphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

8-bromo-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one;

30 8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

8-chloro-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino) pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

5 4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

10 4-(4-chloro-3-methoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)
pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenyl
amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)
pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

15 8-bromo-2-(4-hydroxy-4-(hydroxymethyl) piperidin-1-yl)-4-(3-(trifluoromethyl)phenyl
amino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

4-(3,4-dimethoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3-bromo-4-methoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*] pyrimidin-
5(6*H*)-one;

20 (*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-phenoxyphenylamino)pyrido[4,3-*d*] pyrimidin-
5(6*H*)-one hydrochloride;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-phenoxyphenyl
amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

25 4-(3,4-dimethoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

4-(3-bromo-4-methoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-8-bromo-4-(4-phenoxyphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-
one hydrochloride;

30 (*R*)-2-(3-aminopyrrolidin-1-yl)-8-iodo-4-(4-phenoxyphenylamino)pyrido[4,3-*d*] pyrimidin-
5(6*H*)-one hydrochloride;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-8-
iodopyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)-8-iodopyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-chloro-3-(trifluoromethyl)
phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride;

5 2-(4-hydroxypiperidin-1-yl)-8-iodo-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-
5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(4-morpholino-3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-methoxy-3-(trifluoromethyl)phenylamino)
10 pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-chloro-3-(trifluoromethoxy)phenylamino)
pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride;

4-(4-chloro-3-(trifluoromethoxy)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

15 4-(3-bromo-5-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

(*R*)-6-(3-aminopyrrolidin-1-yl)-4-iodo-8-(4-(trifluoromethyl)phenylamino)isoquinolin-1(2*H*)-
one hydrochloride;

(*R*)-6-(3-aminopyrrolidin-1-yl)-4-bromo-8-(4-(trifluoromethyl)phenylamino)isoquinolin-1(2*H*)-
20 one hydrochloride;

(*S*)-6-(3-aminopyrrolidin-1-yl)-4-bromo-8-(4-(trifluoromethyl)phenylamino)isoquinolin-1(2*H*)-
one hydrochloride;

4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-ylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-
d]pyrimidin-5(6*H*)-one;

25 2-(4-hydroxypiperidin-1-yl)-4-(naphthalen-2-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(quinolin-5-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3*H*-indol-2-ylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one; and

2-(4-hydroxypiperidin-1-yl)-4-(4-phenoxyphenylamino)-8-phenylpyrido[4,3-*d*] pyrimidin-
5(6*H*)-one.

30 The term “alkyl,” used alone or as part of a larger moiety such as “arylalkyl” or
“cycloalkyl” refers to a straight or branched hydrocarbon radical having from 1 to 15 carbon
atoms (unless stated otherwise) and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-

butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl and the like. An alkyl can be unsubstituted or substituted with one or more suitable substituents.

The term "cycloalkyl" refers to a monocyclic or polycyclic hydrocarbon ring group and includes, for example, cyclopropyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclobutyl, adamantyl,
5 norpinanyl, decalanyl, norbornyl, cyclohexyl, cyclopentyl, and the like. A cycloalkyl group can be unsubstituted or substituted with one or more suitable substituents.

The term "hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom such as N, S, and O.

The term "heterocycloalkyl" means a non-aromatic monocyclic or polycyclic ring
10 comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 4 heteroatoms selected from N, O, S, sulfone, or sulfoxide. A heterocycloalkyl group can have one or more carbon-carbon double bonds or carbon-heteroatom double bonds in the ring group as long as the ring group is not rendered aromatic by their presence. Examples of
heterocycloalkyl groups include azetidine, aziridinyl, pyrrolidinyl, pyrrolidino, piperidinyl,
15 piperidino, piperazinyl, homopiperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, pyranal, and the like. A heterocycloalkyl group can be unsubstituted or substituted with one or more suitable substituents.

As used herein, the term "halo" includes fluoro, chloro, bromo, and iodo.

20 As used herein, the term "alkenyl" refers to straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one double bond and includes ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like. An alkenyl can be unsubstituted or substituted with one or more suitable substituents.

As used herein, the term "alkynyl" refers to straight and branched hydrocarbon radicals
25 having from 2 to 6 carbon atoms and one triple bond and includes ethynyl, 3-butyn-1-yl, propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, and the like. An alkynyl can be unsubstituted or substituted with one or more suitable substituents.

As used herein, the term "alkoxy" refers to the alkyl groups above bound through oxygen, examples of which include methoxy, ethoxy, isopropoxy, tert-butoxy, and the like. In
30 addition, alkoxy also refers to polyethers such as $-O-(CH_2)_2-O-CH_3$, and the like. An alkoxy can be unsubstituted or substituted with one or more suitable substituents.

As used herein, the term "aryl" refers to unsubstituted or substituted aromatic monocyclic or polycyclic groups and includes, for example, phenyl and naphthyl. The term "aryl" also

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includes phenyl rings fused to non-aromatic carbocyclic ring or to a heterocyclyl group. The term “aryl” may be interchangeably used with “aryl ring,” “aromatic group,” and “aromatic aromatic ring.” Heteroaryl groups have 4 to 14 atoms, 1 to 9 of which are independently selected from the group consisting of O, S and N. Heteroaryl groups have 1-3 heteroatoms in a 5-8
5 membered aromatic group. An aryl or heteroaryl can be a mono- or bicyclic aromatic group. Typical aryl and heteroaryl groups include, for example, phenyl, quinolinyl, indazolyl, indolyl, dihydrobenzodioxynyl, 3-chlorophenyl, 2,6-dibromophenyl, pyridyl, 3-methylpyridyl, benzothienyl, 2,4,6-tribromophenyl, 4-ethylbenzothienyl, furanyl, 3,4-diethylfuranyl, naphthyl, 4,7-dichloronaphthyl, pyrrole, pyrazole, imidazole, thiazole, and the like. An aryl or heteroaryl
10 can be unsubstituted or substituted with one or more suitable substituents.

As used herein, the term “monocyclic aryl group” refers to an unsubstituted or substituted aryl and includes, for example, phenyl.

As used herein, the term “haloalkyl” refers to any alkyl radical having one or more hydrogen atoms replaced by a halogen atom. Examples of haloalkyl include -CF₃, -CFH₂, -
15 CF₂H, and the like.

As used herein, the term “arylalkyl” refers to any alkyl radical having one or more hydrogen atoms replaced by an aryl group. Examples of arylalkyl include benzyl (C₆H₅CH₂-) and the like.

As used herein, the term “hydroxyalkyl” refers to any hydroxy derivative of alkyl radical.
20 The term “hydroxyalkyl” includes any alkyl radical having one or more hydrogen atoms replaced by a -OH group.

As used herein, the term “kinase panel” refers to a list of kinases, including but not limited to, ABL1(E255K)-phosphorylated, ABL1(T315I)-phosphorylated, ABL1-phosphorylated, ACVR1B, ADCK3, AKT1, AKT2, ALK, AURKA, AURKB, AXL, BMPR2,
25 BRAF, BRAF(V600E), BTK, CDK11, CDK2, CDK3, CDK7, CDK9, CHEK1, CSF1R, CSNK1D, CSNK1G2, DCAMKL1, DYRK1B, EGFR, EGFR(L858R), EPHA2, ERBB2, ERBB4, ERK1, FAK, FGFR2, FGFR3, FLT1, FLT3, FLT4, GSK3B, IGF1R, IKK- α , IKK- β , INSR, JAK2(JH1 domain-catalytic), JAK3(JH1 domain-catalytic), JNK1, JNK2, JNK3, KIT, KIT(D816V), KIT(V559D,T670I), LKB1, LRRK2, LRRK2(G2019S), MAP3K4, MAPKAPK2,
30 MARK3, MEK1, MEK2, MET, MKNK1, MKNK2, MLK1, MTOR, p38-alpha, p38-beta, PAK1, PAK2, PAK4, PCTK1, PDGFRA, PDGFRB, PDPK1, PIK3C2B, PIK3CA, PIK3CG, PIM1, PIM2, PIM3, PKAC-alpha, PLK1, PLK3, PLK4, PRKCE, PYK2, RAF1, RET, RIOK2, ROCK2, RSK2, SNARK, SRC, SRPK3, SYK, TAK1, TGFBR1, TIE2, TRKA, TSSK1B,

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TYK2(JH1domain-catalytic), ULK2, VEGFR2, YANK3 and ZAP70. Kinase assay panels containing the kinases described herein are commercially available for biochemically profiling kinase inhibitors for their selectivity.

As used herein, the term “dermatological disorder” refers to a skin disorder. Such dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsson Syndrome, and urticaria.

As used herein, the term “neurogenerative disease” or “nervous system disorder” refers to conditions that alter the structure or function of the brain, spinal cord or peripheral nervous system, including but not limited to Alzheimer’s disease, cerebral edema, cerebral ischemia, multiple sclerosis, neuropathies, Parkinson’s disease, those found after blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury), as well as the neurological aspects of disorders such as degenerative disk disease and sciatica. The acronym “CNS” refers to the central nervous system (brain and spinal cord).

As used herein, the term “respiratory disease” refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, trachea, bronchi, and lungs. Respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

As used herein, the term “cancer” refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize. The types of cancer include, but are not limited to, solid tumors, such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma) or hematological tumors (such as the leukemias).

As used herein, the term “fibrosis” or “fibrosing disorder” refers to conditions that follow acute or chronic inflammation and are associated with the abnormal accumulation of cells and/or

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collagen and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, joints, lung, or skin, and includes such disorders as idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis.

As used herein, the term “inflammatory disorders” refers to those diseases or conditions
5 that are characterized by one or more of the signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and loss of function, which may be partial or complete, temporary or permanent. Inflammation takes
10 many forms and includes, but is not limited to, inflammation that is one or more of the following, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute,
15 suppurative, toxic, traumatic, and/or ulcerative. Inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis, temporal arteritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter’s); gastrointestinal tract; skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

As used herein, the term “cardiovascular disease” refers to diseases affecting the heart or
20 blood vessels or both, including but not limited to atherosclerosis, arrhythmia, angina, myocardial ischemia, myocardial infarction, cardiac or vascular aneurysm, vasculitis, stroke, peripheral obstructive arteriopathy of a limb, an organ, or a tissue, reperfusion injury following ischemia of an organ or a tissue, endotoxic, surgical, or traumatic shock, hypertension, valvular heart disease, heart failure, abnormal blood pressure, vasoconstriction, vascular abnormality, or
25 inflammation.

As used herein, the term “bone disease” means a disease or condition of the bone, including, but not limited to, inappropriate bone remodeling, loss or gain, osteopenia, osteomalacia, osteofibrosis, osteoporosis and Paget’s disease.

As used herein, the term “inhibitor” refers to a compound which inhibits one or more
30 kinases described herein. For example, the term “SYK inhibitor” refers to a compound which inhibits the SYK receptor or reduces the signaling effect.

As used herein, the term “pharmaceutically acceptable” refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds

described herein. Such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compounds described herein.

As used herein, the term “pharmaceutical combination” means a product that results from the mixing or combining of more than one active ingredient.

As used herein, the term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

As used herein, the term “prodrug” refers to an agent that is converted into the parent drug *in vivo*.

As used herein, the term “protein kinase-mediated disease” or a “disorder or disease or condition mediated by inappropriate protein kinase activity” refers to any disease state mediated or modulated by protein kinases described herein. Such disease states include, but are not limited to, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohn’s disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsson Syndrome, rheumatoid arthritis, multiple sclerosis, inflammatory bowel syndrome, HIV, lupus, lymphoma, osteosarcoma, melanoma, breast cancer, renal cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, lung cancer, uterine cancer, gastrointestinal cancer, Alzheimer’s disease, Parkinson’s disease, osteoporosis, osteopenia, osteomalacia, osteofibrosis, Paget’s disease, diabetes, blood vessel proliferative disorders, ocular diseases, cardiovascular disease, restenosis, fibrosis, atherosclerosis, arrhythmia, angina, myocardial ischemia, myocardial infarction, cardiac or vascular aneurysm, vasculitis, stroke, peripheral obstructive arteriopathy, reperfusion injury following ischemia of an organ or a tissue, endotoxic, surgical or traumatic shock, hypertension, valvular heart disease, heart failure, abnormal blood pressure, vasoconstriction, vascular abnormality, transplant rejection and infectious diseases including viral and fungal infections.

As used herein, the term “kinase-mediated disease” or “kinase-mediated disease” or a “disorder or disease or condition mediated by inappropriate kinase activity” refers to any disease

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state mediated or modulated by a kinase mechanism. For example “SYK-mediated disease” refers to any disease state mediated or modulated by SYK mechanisms. Such SYK-mediated disease states include, but are not limited to, inflammatory, respiratory diseases and autoimmune diseases, such as, by way of example only, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohn’s disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, cancer, HIV-associated disease and lupus.

As used herein, the term “PYK2-mediated disease” or a “disorder or disease or condition mediated by inappropriate PYK2 activity” refers to any disease state mediated or modulated by PYK2 kinase mechanisms. Such disease states include, but are not limited to, osteoporosis, arthritis, myeloid leukemia, hypo-osmolality, sarcoma, blast crisis, glioma, erythroleukemia and cancer.

As used herein, the term “ZAP70-mediated disease” or a “disorder or disease or condition mediated by inappropriate ZAP70 activity” refers to any disease state mediated or modulated by ZAP70 kinase mechanisms. Such disease states include, but are not limited to, immunodeficiency diseases characterized by a selective absence of CD8-positive T-cells.

As used herein, the term “FAK-mediated disease” or a “disorder or disease or condition mediated by inappropriate FAK activity” refers to any disease state mediated or modulated by FAK kinase mechanisms. Such disease states include, but are not limited to, cancer, macular degeneration or a condition associated with aberrantly increased levels of angiogenesis.

As used herein, the term “PIM1-mediated disease” or a “disorder or disease or condition mediated by inappropriate PIM1 activity” refers to any disease state mediated or modulated by PIM1 kinase mechanisms. Such disease states include, but are not limited to, cancer, myeloproliferative diseases, autoimmune diseases, allergic reactions and in organ transplantation rejection syndromes.

As used herein, the term “FLT3-mediated disease” or a “disorder or disease or condition mediated by inappropriate FLT3 activity” refers to any disease state mediated or modulated by FLT3 kinase mechanisms. Such disease states include, but are not limited to, leukemia including acute myelogenous leukemia or a condition associated with aberrantly increased levels of FLT3 kinase.

As used herein, the term “RET-mediated disease” or a “disorder or disease or condition mediated by inappropriate RET activity” refers to any disease state mediated or modulated by

RET kinase mechanisms. Such disease states include, but are not limited to, thyroid cancer, a condition associated with aberrantly increased levels of RET kinase.

As used herein, the term “JAK2-mediated disease” or a “disorder or disease or condition mediated by inappropriate JAK2 activity” refers to any disease state mediated or modulated by JAK2 kinase mechanisms. Such disease states include, but are not limited to, polycythemia vera, essential thrombocythemia, other myeloproliferative disorders cancer, or a condition associated with aberrantly increased levels of JAK2 kinase.

As used herein, the term “LRRK2-mediated disease” or a “disorder or disease or condition mediated by inappropriate LRRK2 activity” refers to any disease state mediated or modulated by LRRK2 kinase mechanisms. Such disease states include, but are not limited to, Parkinson’s disease, other neurodegenerative disease or a condition associated with aberrantly increased levels of angiogenesis.

As used herein, the term “therapeutically effective amount” refers to any amount of a compound which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term “treat,” “treating” or “treatment” refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

As used herein, the term “solvate” refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I) or a pharmaceutically acceptable salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Non-limiting examples of suitable solvents include water, acetone, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid.

As used herein, the term “subject” or “patient” encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, humans, chimpanzees, apes

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monkeys, cattle, horses, sheep, goats, swine; rabbits, dogs, cats, rats, mice, guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like.

As used herein, the term “administration” or “administering” of the subject compound refers to providing a compound of the invention and/or prodrugs thereof to a subject in need of
5 treatment.

As used herein, the term “carrier” refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues.

As used herein, the term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of
10 the subject being treated.

As used herein, the term “diluent” refers to chemical compounds that are used to dilute a compound described herein prior to delivery. Diluents can also be used to stabilize compounds described herein.

As used herein, the term “effective amount” or “therapeutically effective amount” refer to
15 a sufficient amount of a compound described herein being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological
system. For example, an “effective amount” for therapeutic uses is the amount of the
20 composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case may be determined using techniques, such as a dose escalation study.

I. Human Protein Kinases

25 Protein kinases play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. Protein kinases catalyze and regulate the process of phosphorylation, whereby the kinases covalently attach phosphate groups to proteins or lipid targets in response to a variety of extracellular signals. Examples of such stimuli include
hormones, neurotransmitters, growth and differentiation factors, cell cycle events, environmental
30 stresses and nutritional stresses. An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

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The compounds of the present invention were screened against the kinase panel and inhibited the activity of at least one kinase on the panel. Examples of kinases include, but are not limited to, SYK, ZAP70, PYK2, FAK, ALK, AXL, CSF1R, FLT3, JAK2(JH1domain-catalytic), JAK3(JH1domain-catalytic), PDGFRB, RET, PIM1, AURKA, AURKB, BMPR2, 5 JNK1, JNK2, JNK3, KIT, KIT(D816V), KIT(V559D, T670I), LKB1, LRRK2, LRRK2(G2019S), MLK1, PAK4, PLK4, RSK2, SNARK, SRPK3, TAK1 and TYK2 kinases and mutant forms thereof. As such, the compounds and compositions of the invention are useful for treating diseases or disorders in which such kinases contribute to the pathology and/or symptomology of a disease or disorder associated with such kinases. Such diseases or disorders 10 include, but are not limited to, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, psoriasis, metastasis, cancer-related pain and neuroblastoma, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative 15 diseases, cancer, cardiovascular diseases, respiratory diseases, allergies and asthma, Alzheimer's disease, and hormone related diseases, benign and malignant proliferative disorders, diseases resulting from inappropriate activation of the immune system and diseases resulting from inappropriate activation of the nervous systems, allograft rejection, graft vs. host disease, diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, 20 psoriasis, arthritis, osteoarthritis, rheumatoid arthritis, synovial pannus invasion in arthritis, multiple sclerosis, myasthenia gravis, diabetes mellitus, diabetic angiopathy, retinopathy of prematurity, infantile hemangiomas, non-small cell lung, bladder and head and neck cancers, prostate cancer, breast cancer, ovarian cancer, gastric and pancreatic cancer, psoriasis, fibrosis, atherosclerosis, restenosis, autoimmune disease, allergy, respiratory diseases, asthma, 25 transplantation rejection, inflammation, thrombosis, retinal vessel proliferation, inflammatory bowel disease, Crohn's disease, ulcerative colitis, bone diseases, transplant or bone marrow transplant rejection, lupus, chronic pancreatitis, cachexia, septic shock, fibroproliferative and differentiative skin diseases or disorders, central nervous system diseases, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, disorders or conditions related to nerve 30 damage and axon degeneration subsequent to a brain or spinal cord injury, acute or chronic cancer, ocular diseases, viral infections, heart disease, lung or pulmonary diseases or kidney or renal diseases and bronchitis.

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The compounds described herein are inhibitors of kinase activity and have therapeutic benefit in the treatment of disorders associated with inappropriate kinase activity, in particular in the treatment and prevention of disease states mediated by kinase. Therefore, the present invention provides methods of regulating, and in particular inhibiting, signal transduction cascades in which a kinase plays a role. The method generally involves administering to a subject or contacting a cell expressing the kinase with an effective amount of a compound described herein, prodrug, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, to regulate or inhibit the signal transduction cascade. The methods are also used to regulate, and in particular inhibit, downstream processes or cellular responses elicited by activation of the particular kinase signal transduction cascade. The methods are also practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with activation of the kinase-dependent signal transduction cascade.

2. Pharmaceutical Composition

For the therapeutic uses of compounds provided herein, including compounds of Formula (I), or pharmaceutically acceptable salts, solvates, N-oxides, prodrugs and isomers thereof, such compounds are administered in therapeutically effective amounts either alone or as part of a pharmaceutical composition. Accordingly, provided herein are pharmaceutical compositions, which comprise at least one compound provided herein, including at least one compound of Formula (I), pharmaceutically acceptable salts and/or solvates thereof, and one or more pharmaceutically acceptable carriers, diluents, adjuvant or excipients. In addition, such compounds and compositions are administered singly or in combination with one or more additional therapeutic agents. The methods of administration of such compounds and compositions include, but are not limited to, intravenous administration, inhalation, oral administration, rectal administration, parenteral, intravitreal administration, subcutaneous administration, intramuscular administration, intranasal administration, dermal administration, topical administration, ophthalmic administration, buccal administration, tracheal administration, bronchial administration, sublingual administration or otic administration. Compounds provided herein are administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, lotions, gels, ointments or creams for topical administration, and the like.

The therapeutically effective amount will vary depending on, among others, the disease indicated, the severity of the disease, the age and relative health of the subject, the potency of the compound administered, the mode of administration and the treatment desired. The required dosage will also vary depending on the mode of administration, the particular condition to be
5 treated and the effect desired.

Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Pharmaceutically acceptable acidic/anionic salts include, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate,
10 glyceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, malonate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, hydrogensulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts. Pharmaceutically
15 acceptable basic/cationic salts include, the sodium, potassium, calcium, magnesium, diethanolamine, N-methyl-D-glucamine, L-lysine, L-arginine, ammonium, ethanolamine, piperazine and triethanolamine salts.

A pharmaceutically acceptable acid addition salt is formed by reaction of the free base form a compound of Formula (I) with a suitable inorganic or organic acid including, but not
20 limited to, hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be, for example, a hydrobromide, hydrochloride,
25 sulfate, nitrate, phosphate, succinate, maleate, formate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate) or hexanoate salt.

The free acid or free base forms of the compounds of the invention may be prepared from
30 the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form may be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the

invention in a base addition salt form may be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

Compounds of the invention in unoxidized form may be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of the invention may be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*, (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985; the entire teachings of which are incorporated herein by reference).

Protected derivatives of the compounds of the invention may be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry," 3rd edition, John Wiley and Sons, Inc., 1999, the entire teachings of which are incorporated herein by reference.

Compounds of the invention may be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. Resolution of enantiomers may be carried out using covalent diastereomeric derivatives of the compounds of the invention, or by using dissociable complexes (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubility, reactivity, etc.) and may be readily separated by taking advantage of these dissimilarities. The diastereomers may be separated by chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981, the entire teachings of which are incorporated herein by reference.

Compounds of Formula (I) are made by processes described herein and in the Examples. In certain embodiments, compounds of Formula (I) are made by:

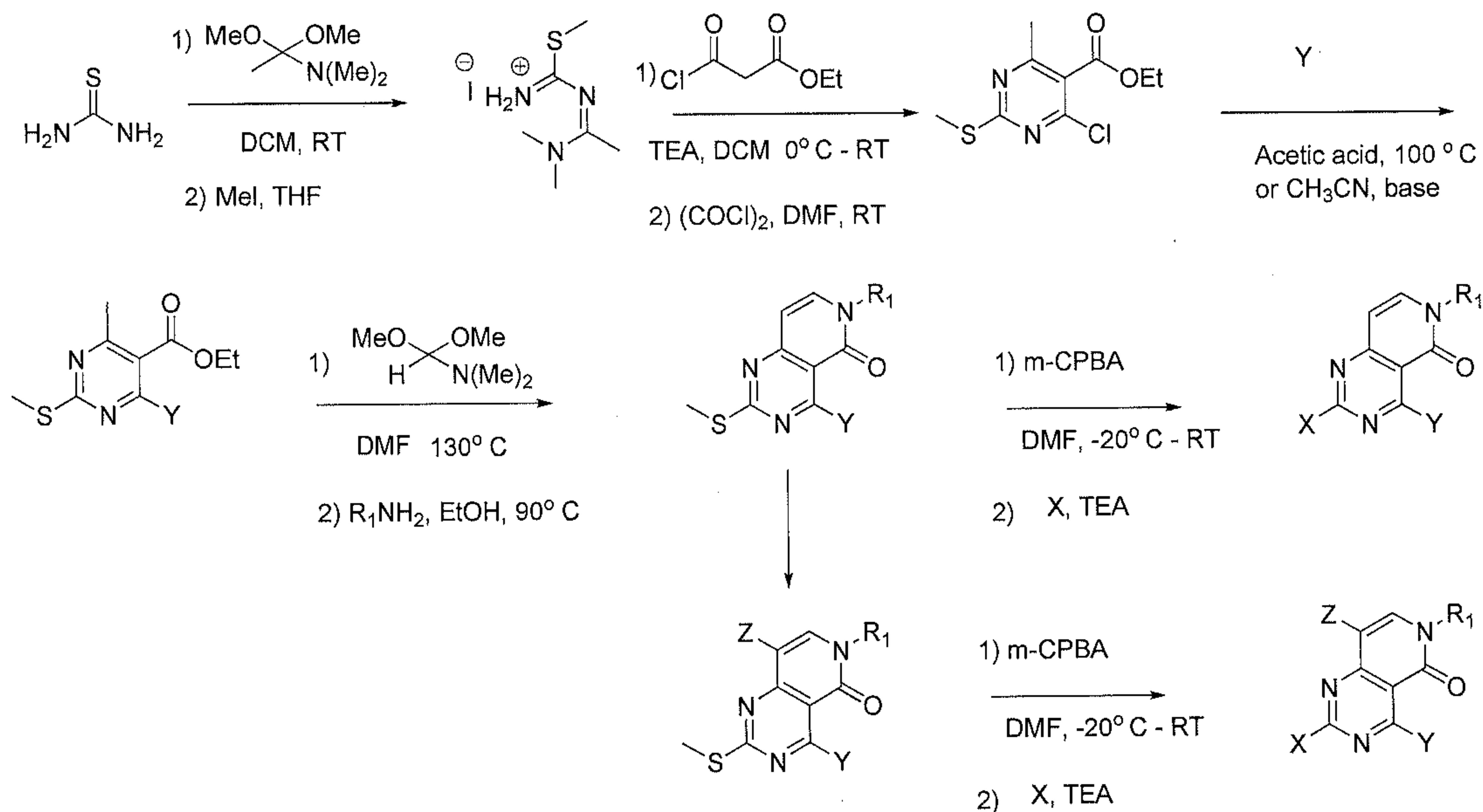
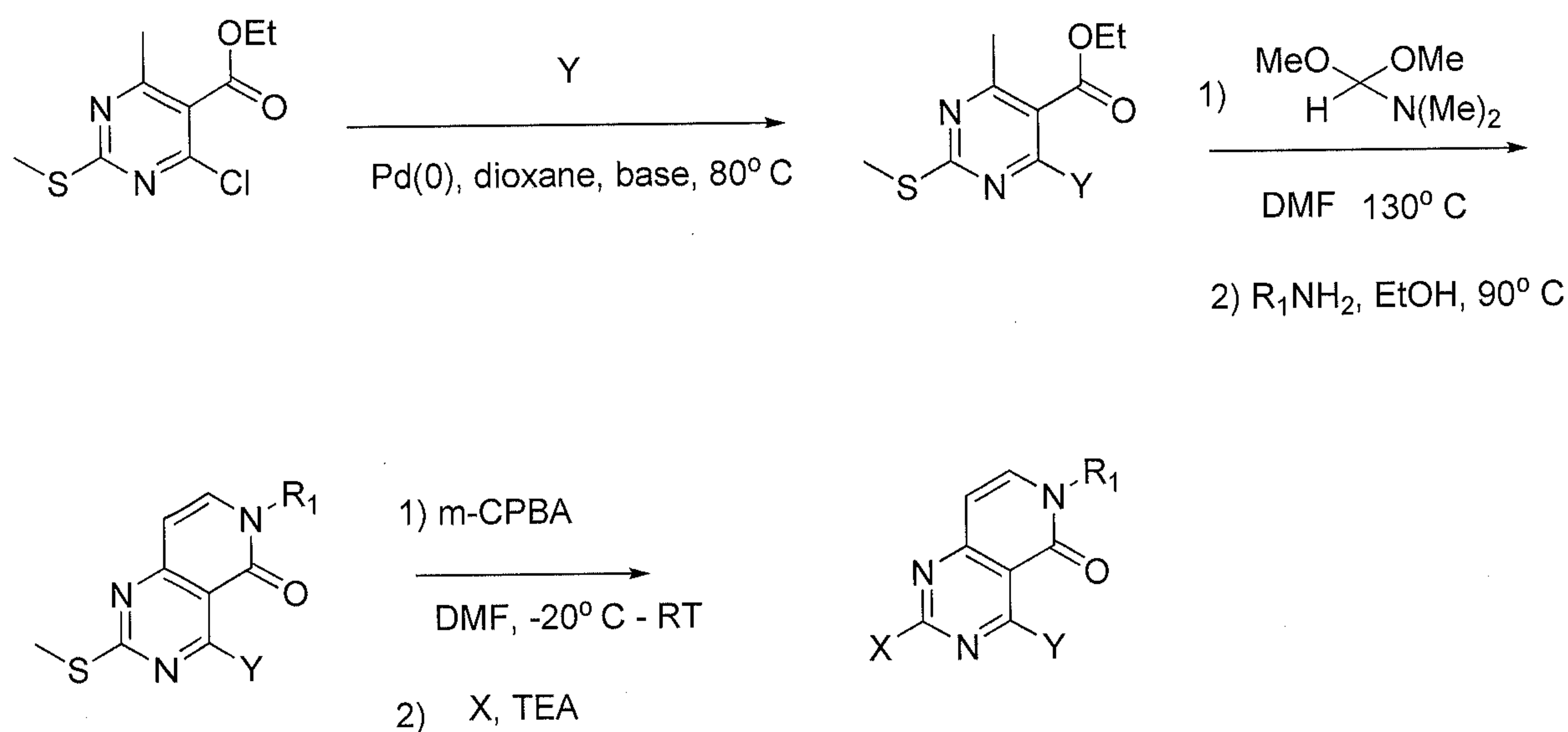
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(a) optionally converting a compound of the invention into a pharmaceutically acceptable salt;
(c) optionally converting a salt form of a compound of the invention to a non-salt form; (d)
optionally converting an unoxidized form of a compound of the invention into a
pharmaceutically acceptable N-oxide; (e) optionally converting an N-oxide form of a compound
5 of the invention to its unoxidized form; (f) optionally resolving an individual isomer of a
compound of the invention from a mixture of isomers; (g) optionally converting a non-
derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative;
and (h) optionally converting a prodrug derivative of a compound of the invention to its non-
derivatized form.

10 The teachings of all patents, published applications and references cited herein are
incorporated by reference in their entirety.

EXAMPLES

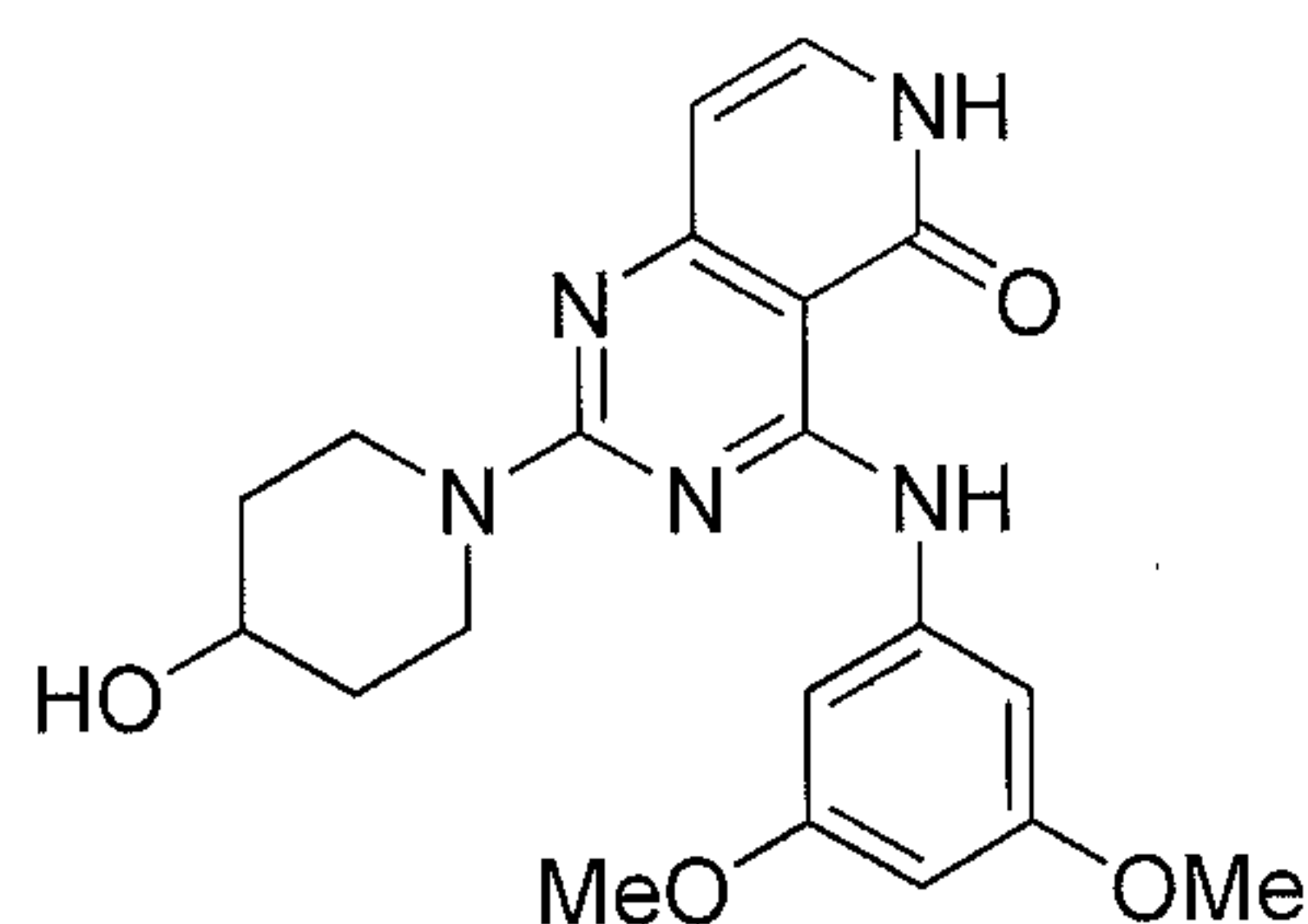
The present invention is further exemplified by the following examples that illustrate the preparation of compounds of Formula (I) according to the invention. The examples are for illustrative purpose only and are not intended, nor should they be construed as limiting the invention in any manner.

Scheme1**Scheme2**

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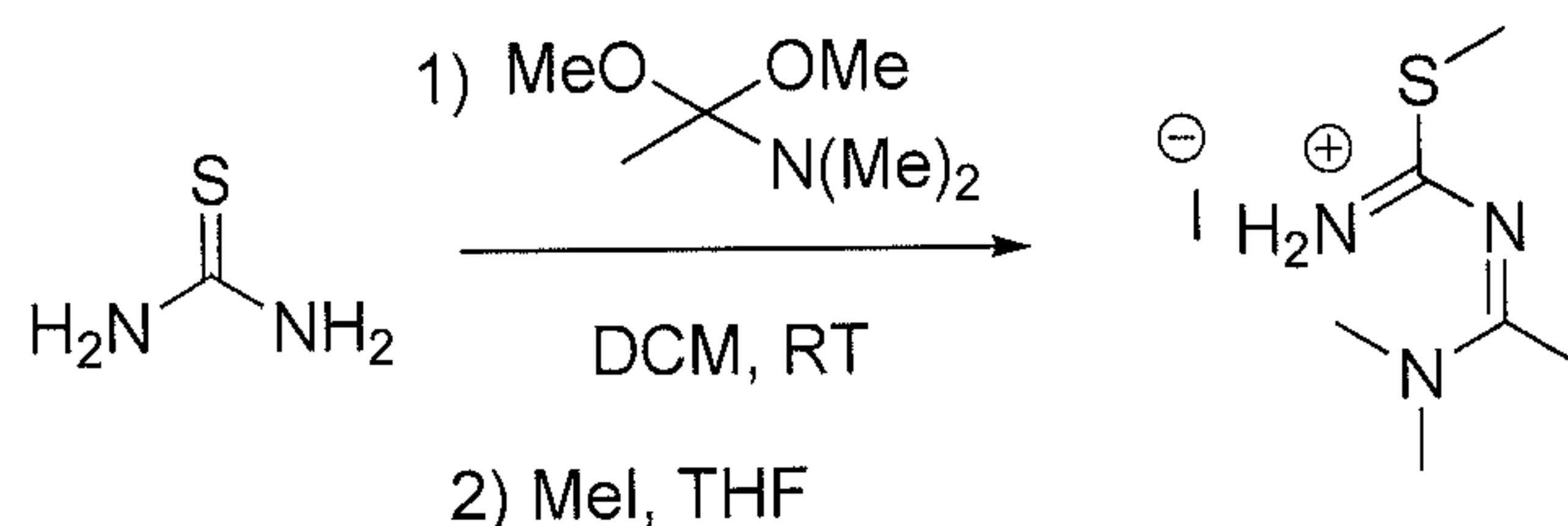
Example 1

Synthesis of 4-(3,5-dimethoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3,-
d]pyrimidin-6(6H)-one



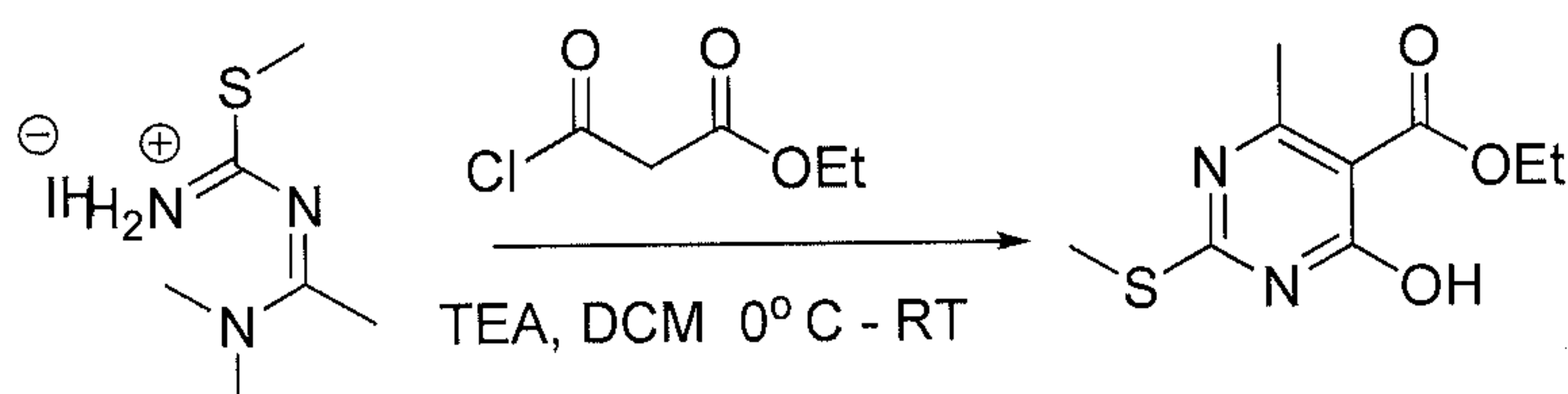
Compound No. 1

Example 1a: (1-Dimethylamino-ethylidene)-2-methyl-isothiurea



To the slurry of thiourea (13.6g, 178.6 mmol) in 130 mL DCM was added *N,N*-
dimethylacetamide dimethylacetal (25 g, 187.6 mmol). The reaction mixture was stirred at room
temperature for 5 hours. The mixture was condensed under reduced pressure providing an
orange residue. To the residue was added 100 mL THF resulting orange suspension. To the
suspension was added iodomethane (14.5 mL) under ice bath, and it was warmed to room
temperature. The mixture was further stirred at room temperature for 2 hours resulting
precipitates. The reaction was monitored by TLC. The precipitates obtained from the solution
were filtered and washed with cold THF yielding pale brown solids (44.89 g, 87.5 %).

Example 1b: Ethyl-4-hydroxy-6-methyl-2-(methylthio)pyrimidine-5-carboxylate

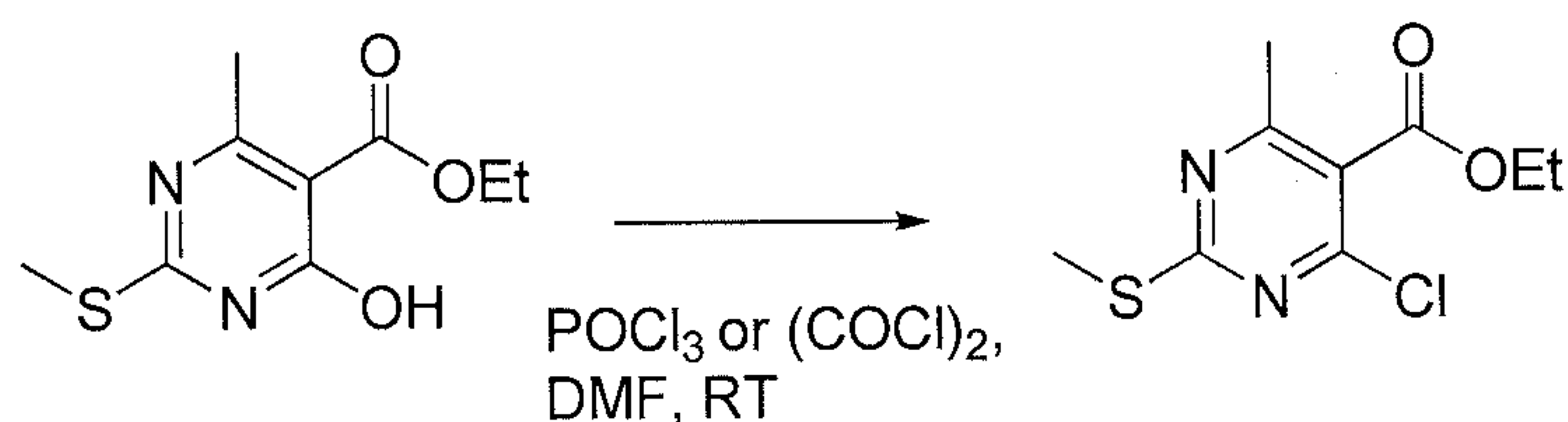


To the slurry of (1-dimethylamino-ethylidene)-2-methyl-isothiurea (25 g, 7.1 mmol) in
200 mL DCM was added ethyl-3-chloro-oxo-propionate (15.7 g, 104.5 mmol). The reaction
mixture was cooled under ice bath. To the solution was slowly added triethylamine (30.3 mL,
220 mmol) dropwise, and the mixture was further stirred at room temperature for 2-3 hours. The

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reaction mixture was washed with water, 2N HCl solution. The separated organic layer was dried over MgSO_4 , condensed under reduced pressure yielding yellow residue. The residue was recrystallized from EtOAc yielding light yellow solids (6.49 g, 33 %). MS m/z : 229.1 ($\text{M}+\text{H}$)⁺.

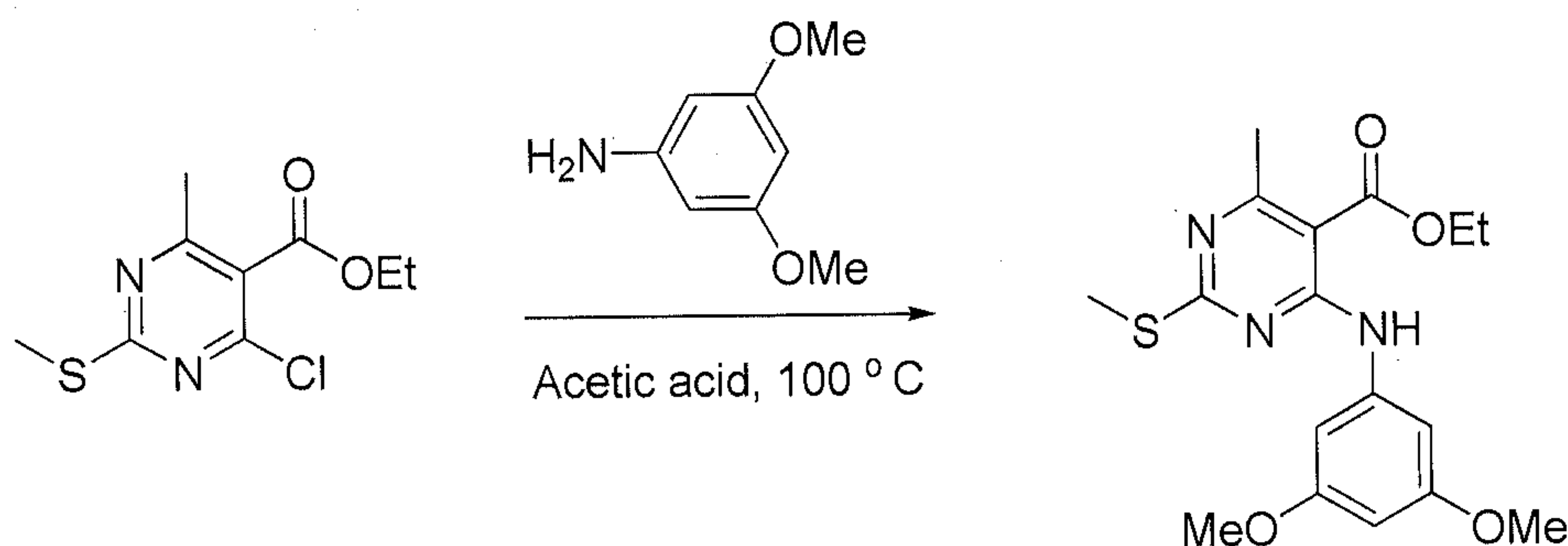
5 *Example 1c*: Ethyl 4-chloro-6-methyl-2-(methylthio)pyrimidine-5-carboxylate



A 100 mL round-bottomed flask was charged with ethyl-4-hydroxy-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (6.49 g, 28.4 mmol) in 14 mL POCl_3 . To the solution was added N, N-diisopropylethylamine (1.2 mL), the reaction mixture was stirred at 80~90°C for 2
10 hours. The mixture was condensed under reduced pressure yielding the dark brown residue. To the residue was added iced water, then diluted with DCM, and saturated aqueous NaHCO_3 solution. The separated organic layer was dried over MgSO_4 . The solvent was removed by a rotavapor providing dark brown oily product (6.76 g, 96 %). MS m/z : 246.9 ($\text{M}+\text{H}$)⁺, 248.9 (isotope).

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Example 1d: Ethyl 4-(3,5-dimethoxyphenylamino)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate

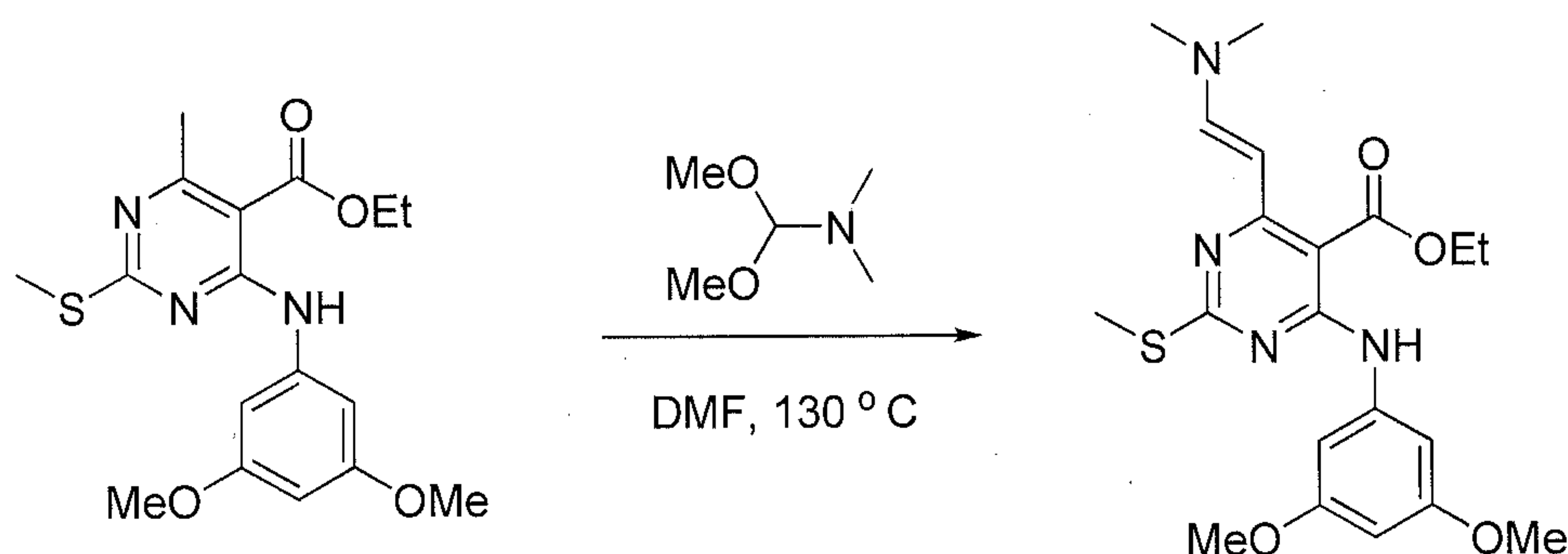


A 200 mL RB flask was charged with ethyl 4-chloro-6-methyl-2-(methylthio)
20 pyrimidine-5-carboxylate (2.76 g, 11.1 mmol) in 40 mL acetonitrile. To the solution was added 3,5-dimethoxy aniline (1.784 g, 11.4 mmol), and conc. HCl solution (494 μL , 5.6 mmol), the reaction mixture was stirred at 60~70°C for 2 hours. The mixture was diluted with ethyl acetate and saturated aqueous NaHCO_3 solution. It was stirred for an additional 5 minutes. The separated organic layer was dried over MgSO_4 , and condensed under reduced

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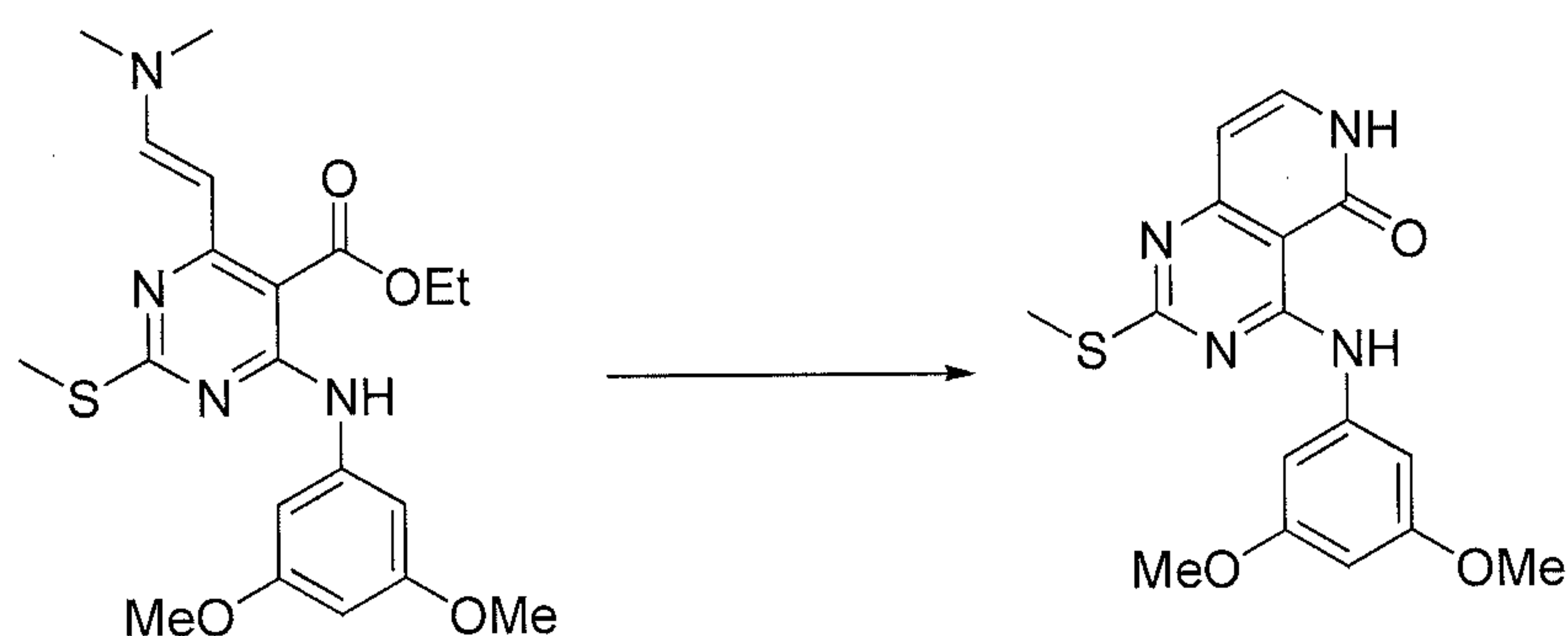
pressure yielding the residue. The residue was recrystallized from acetonitrile, dried under reduced pressure providing pale yellow solids (2.92 g, 72 %). MS m/z: 364.1(M+H)⁺.

Example 1e: (E)-Ethyl 4-(3,5-dimethoxyphenylamino)-6-(2-(dimethylamino)vinyl)-2-(methylthio)pyrimidine-5-carboxylate



To the solution of ethyl 4-(3,5-dimethoxyphenylamino)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (2.7 g, 7.4 mmol) in 30 mL DMF was added *N,N*-dimethylformamide dimethylacetal (1.58 mL, 11.1 mmol). The reaction mixture was stirred at 130°C for 2 hour. After monitoring the reaction by TLC was cooled to room temperature, then the mixture was diluted with DCM and water. After extracted three times by DCM from the aqueous layer, the combined organic layer was dried over MgSO₄. The solution was condensed under reduced pressure yielding crude mixture (3.16 g). The mixture was used for the next step without further purification.

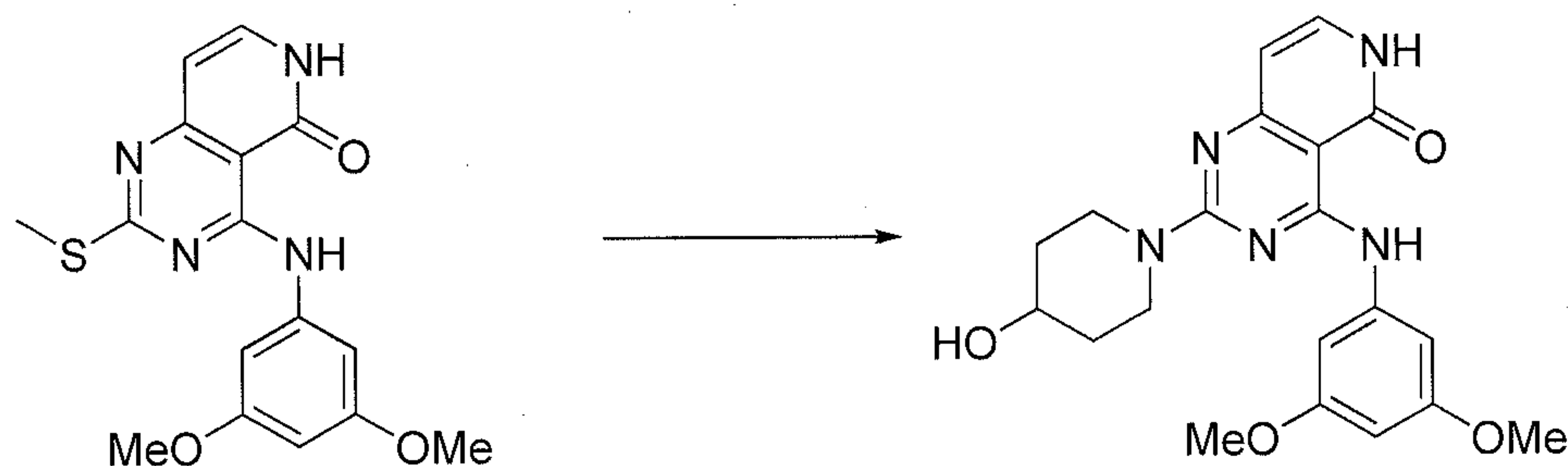
Example 1f: 4-(3,5-Dimethoxyphenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one



The crude of (E)-ethyl 4-(3,5-dimethoxyphenylamino)-6-(2-(dimethylamino)vinyl)-2-(methylthio)pyrimidine-5-carboxylate (3.16 g) was dissolved in 45 mL EtOH. To the solution was added 30% NH₄OH solution (5.2 mL), the reaction mixture was stirred at 75~85°C for 10 hours. The mixture was cooled to room temperature. The solids formed from the solution were filtered. The filtrate was condensed under reduced pressure resulting in the solid residue. The

residue was recrystallized from ethyl acetate. The combined solids were dried under reduced pressure yielding light yellow solids (1.47 g). MS m/z: 344.9 (M+H)⁺.

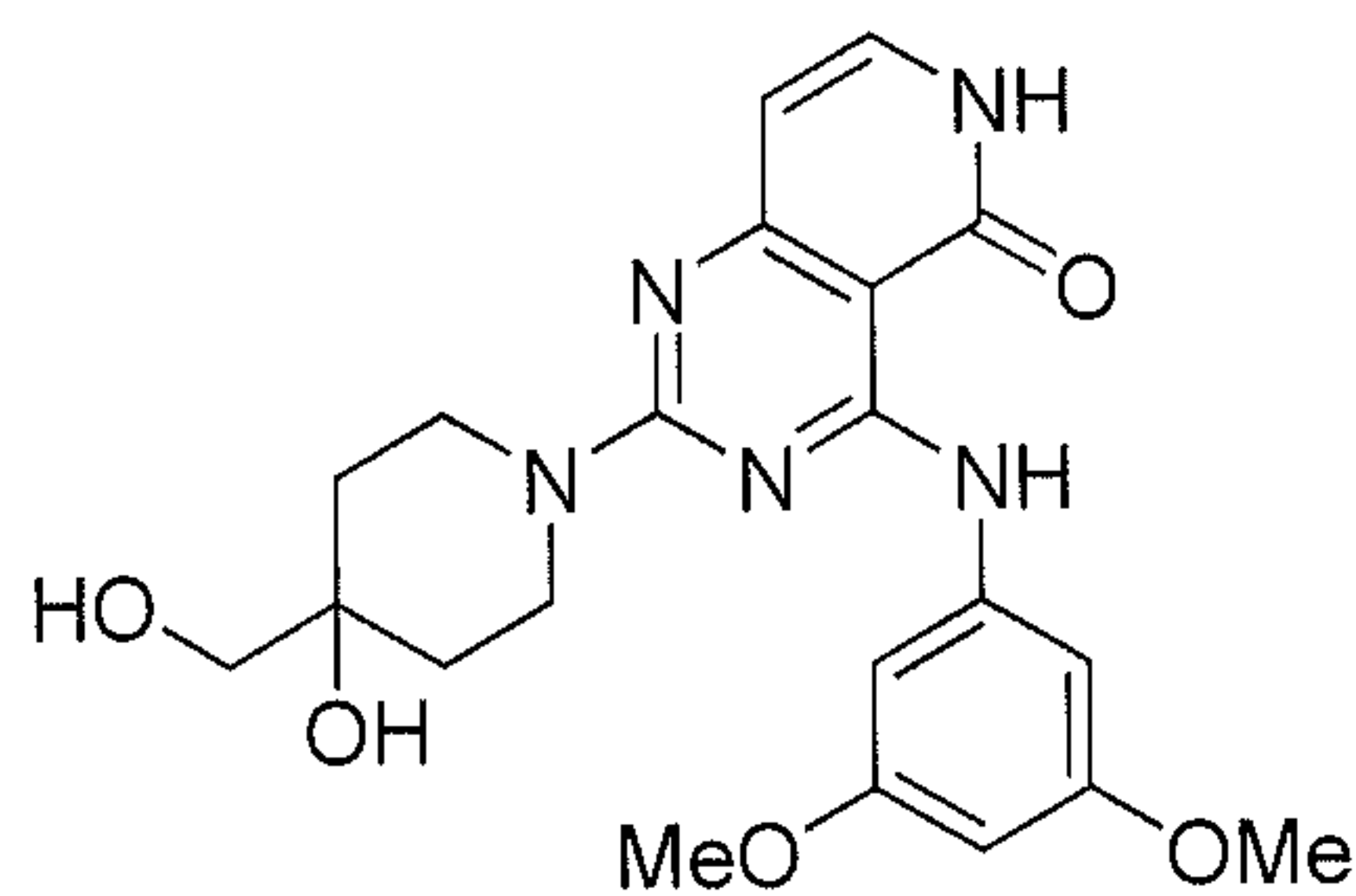
Example 1g: 4-(3,5-dimethoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-6(6*H*)-one



A 20 mL reaction vessel was charged with 4-(3, 5-dimethoxyphenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (151 mg, 0.44 mmol) in 7 mL DMF at -20° C. The solution was kept at the temperature for 30 min. To the solution was added *m*-CPBA (146.4 mg, 1.32 mmol) at the temperature, and further stirred for 30 min with being warmed to room temperature. The reaction was monitored by LC-MS, confirming the corresponding oxide. To the reaction mixture was added triethylamine (354 µL, 1.32 mmol), and 4-hydroxypiperidine (134 mg, 1.32 mmol), and stirred at the temperature for 2 h. The reaction was monitored by LC-MS. The solvent was removed by a rotavapor yielding light brown residue. To the residue was added acetonitrile (10 mL) providing the title compound 4-(3, 5-dimethoxyphenylamino)-2-(4-hydroxypiperidin-1-yl) pyrido[4,3-*d*]pyrimidin-6(6*H*)-one (131 mg, 75%). MS m/z: 398 (M+H)⁺.

Example 2

Synthesis of 4-(3,5-dimethoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one



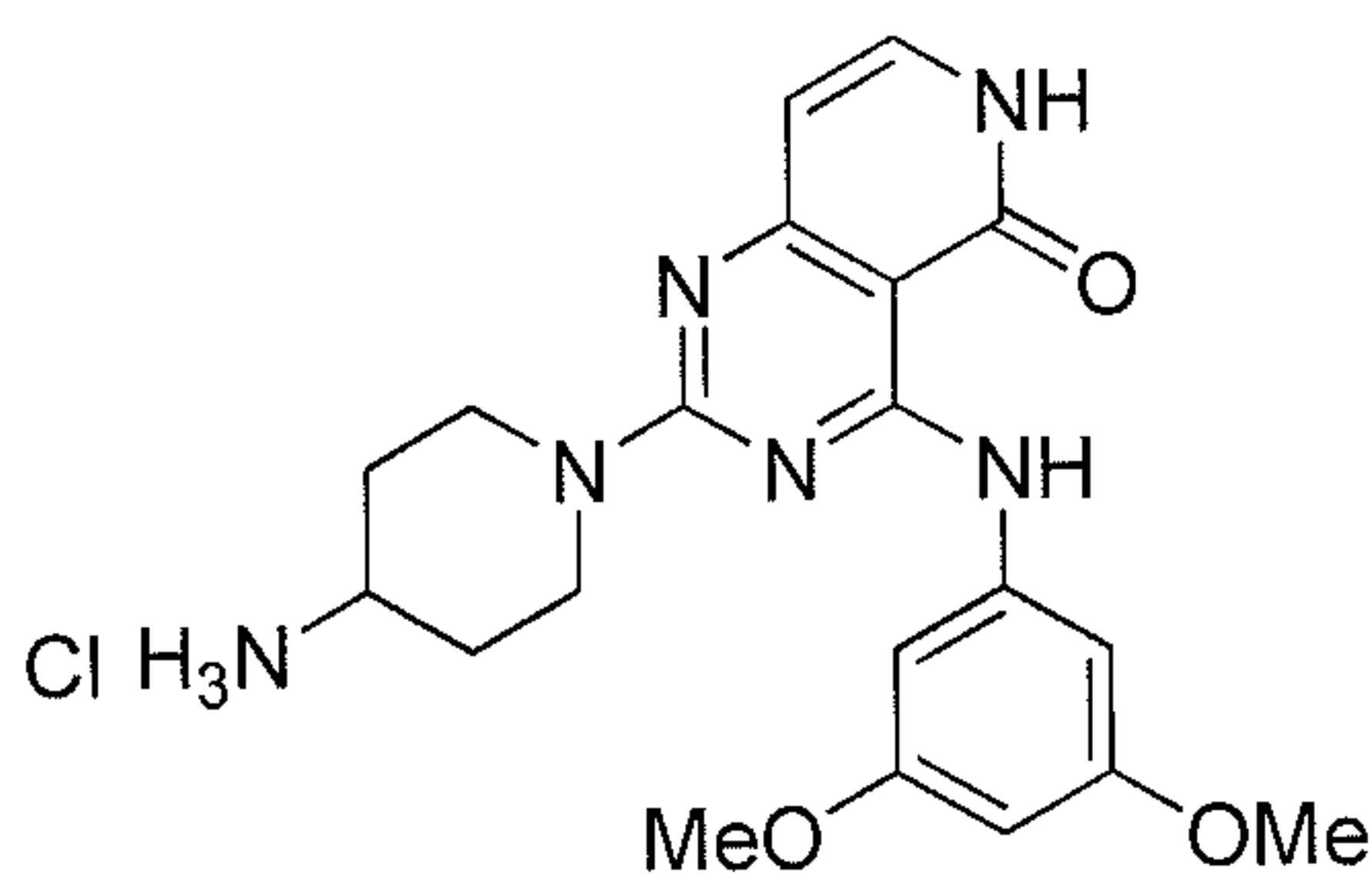
Compound No. 2

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A 20 mL reaction vessel was charged with 4-(3,5-dimethoxyphenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (70 mg, 0.32 mmol) in 7 mL DMF at -20° C. The solution was kept at the temperature for 30 min. To the cold solution was added *m*-CPBA (148 mg, 0.60 mmol) at the temperature, and further stirred for 30 min with being warmed to room temperature. The reaction was monitored by LC-MS, confirming the corresponding oxide. To the reaction mixture was added triethylamine (83 μ L, 0.6 mmol), and methyl 4-hydroxypiperidine-4 carboxylate (96 mg, 0.60 mmol), and stirred at the temperature for 2 h. The reaction was monitored by LC-MS. The solvent was removed by a rotavapor yielding light yellow solid, methyl 1-(4-hydroxy-(3,5-dimethoxyphenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)-4-hydroxypiperidine-4-carboxylate (57 mg, 63%). It was dissolved in 8 mL dry THF in a 20 mL reaction vessel. To the mixture was added 1.0 M DIBAL in toluene (1.95 mL, 1.95 mmol) at 0°C. It was stirred at the temperature for 2 hours. The reaction mixture was quenched with 20 mL MeOH. The solvents were removed by a rotavapor yielding a light yellow residue. The residue was redissolved in the mixture of MeOH and DCM yielding the white precipitates. They were filtered and the filtrate was condensed under reduced pressure providing the white powder, the title compound, (26 mg, 24 %). MS *m/z*: 458 (*M*+1)⁺.

Example 3

Synthesis of 2-(4-aminopiperidin-1-yl)-4-(3,5-dimethoxyphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride



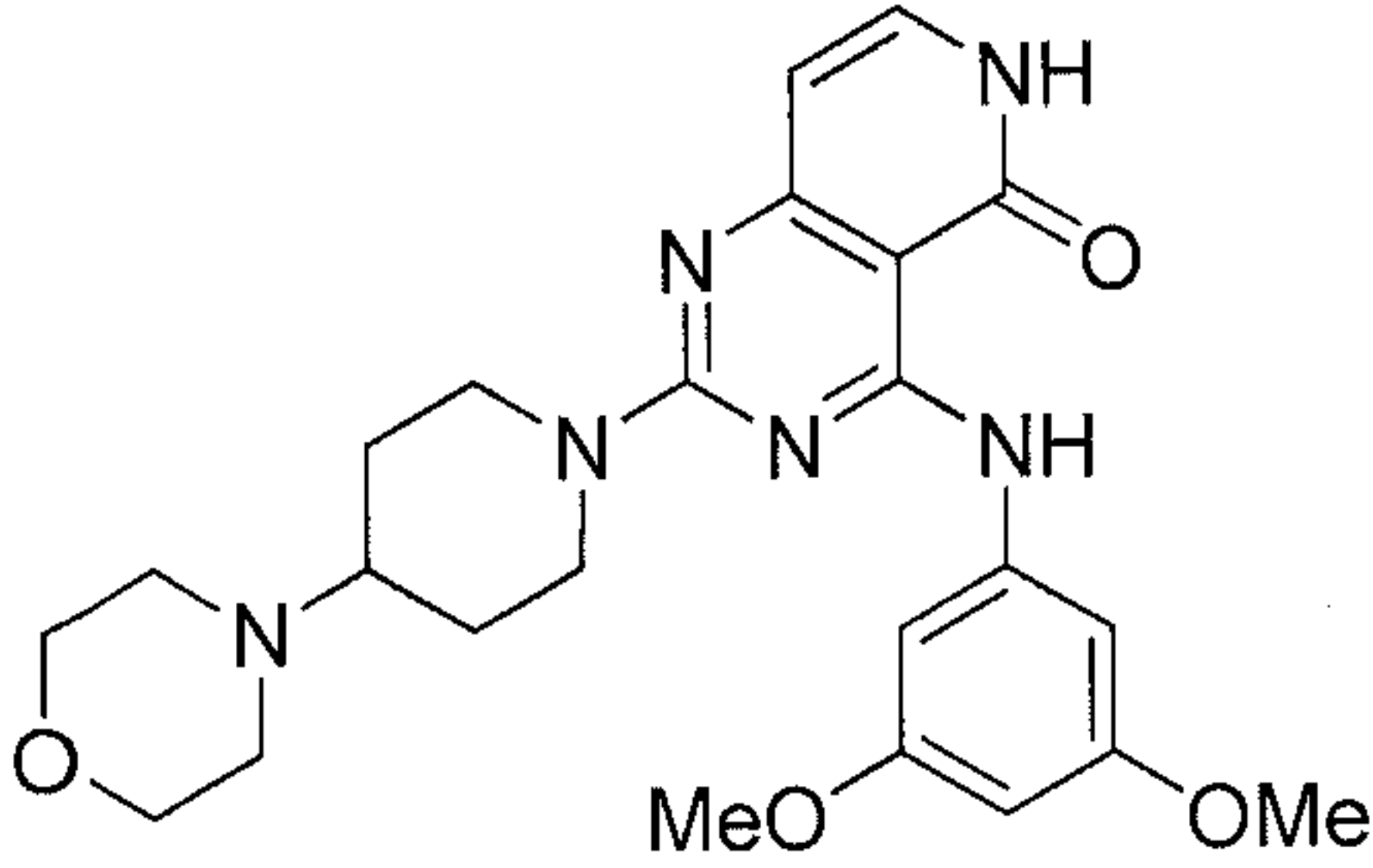
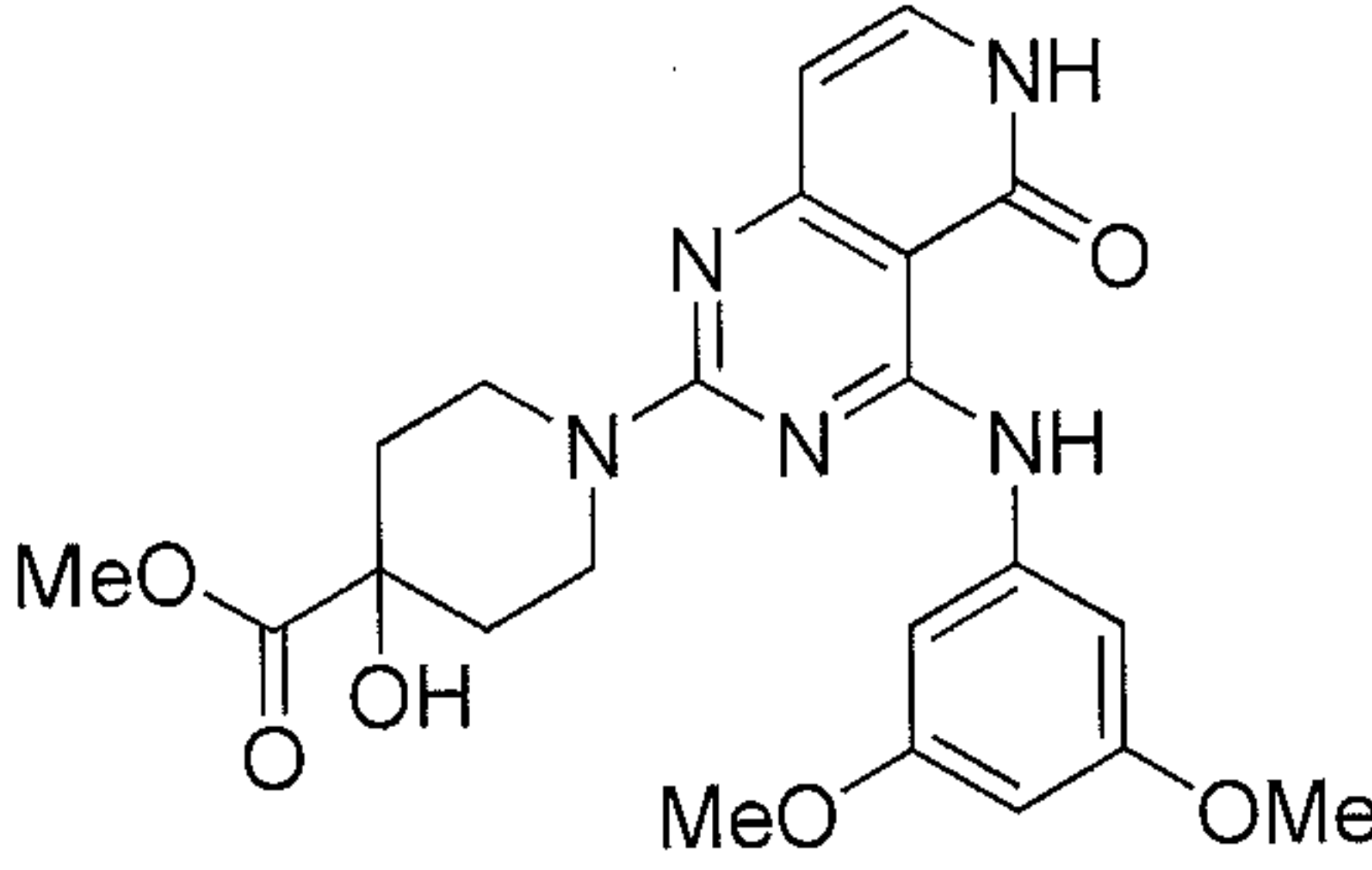
Compound No. 3

The title compound (Compound 3; MS *m/z*: 398 (*M*+H)⁺) was prepared as described in *Example 1g* starting from 4-(3,5-dimethoxyphenyl amino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (40 mg, 0.29 mmol) and 4-(*boc*-amino) piperidine and treating with 4 N HCl in dioxane (17 mg).

The following 4-(3,5-dimethoxyphenylamino)-2-(amino substituted)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one compounds were prepared from 4-(3,5 Dimethoxyphenylamino)-2-

- 50 -

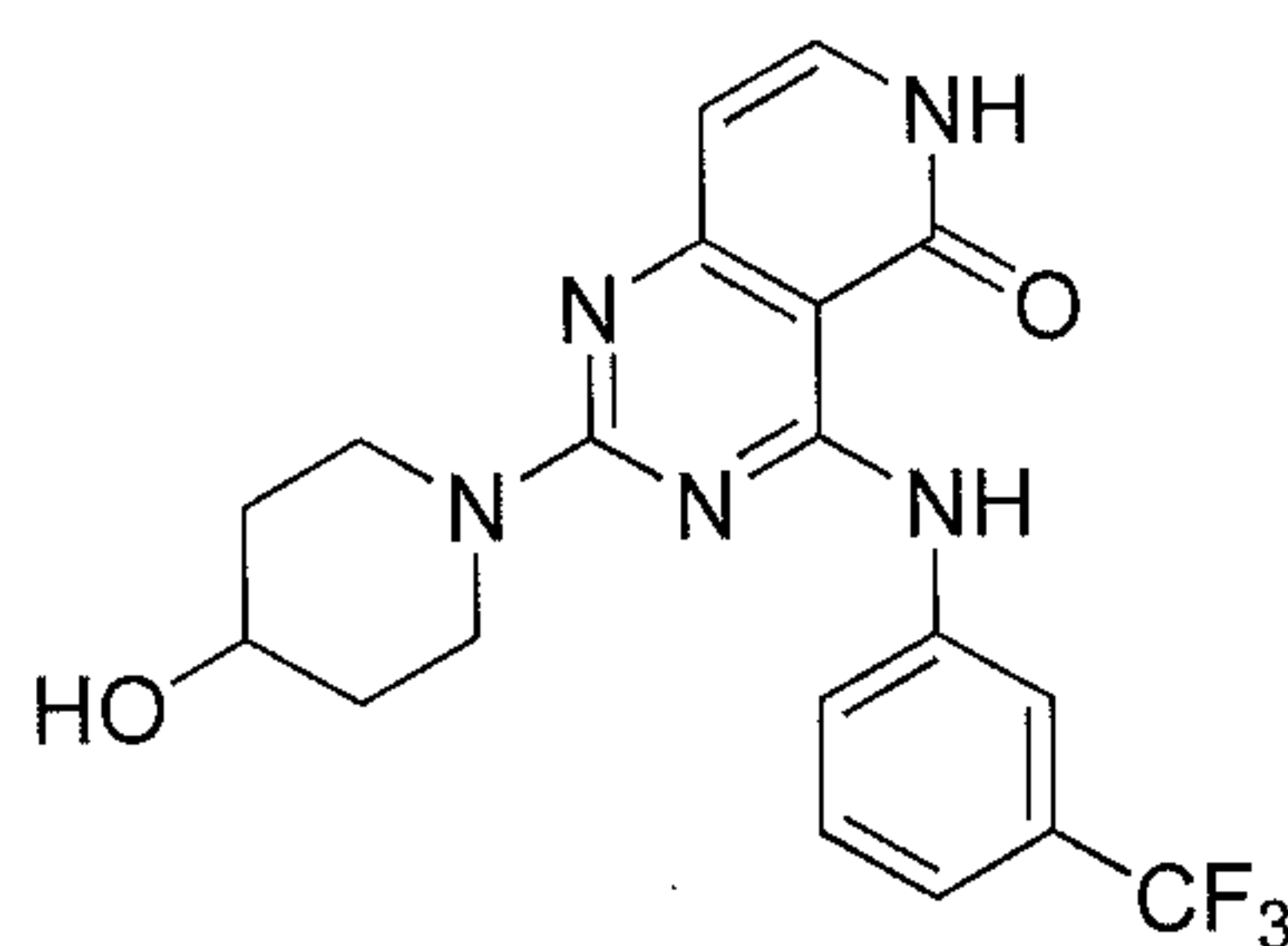
(methylthio) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one and the corresponding amine following the procedure similar to that described in *Example 1g*.

NO.	Structure	Name	Mass (M+1)
4		4-(3,5-dimethoxyphenylamino)-2-(4-morpholinopiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	467
5		methyl 1-(4-(3,5-dimethoxyphenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-yl)-4-hydroxypiperidine-4-carboxylate	456

5

Example 6

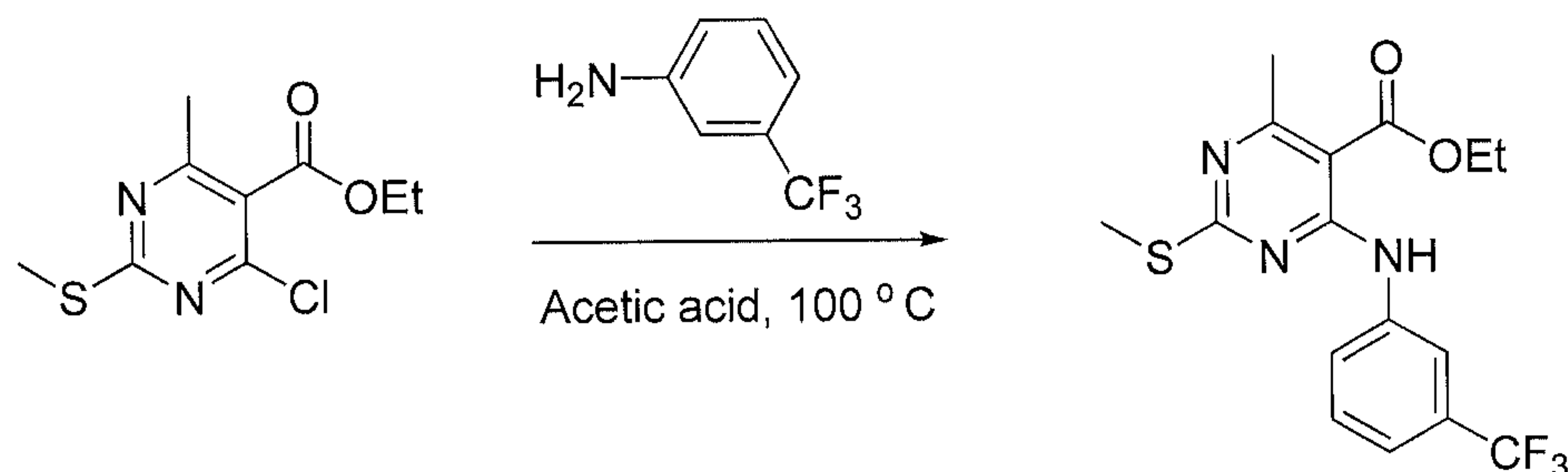
Synthesis of 2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidine-5(6*H*)-one



Compound No. 6

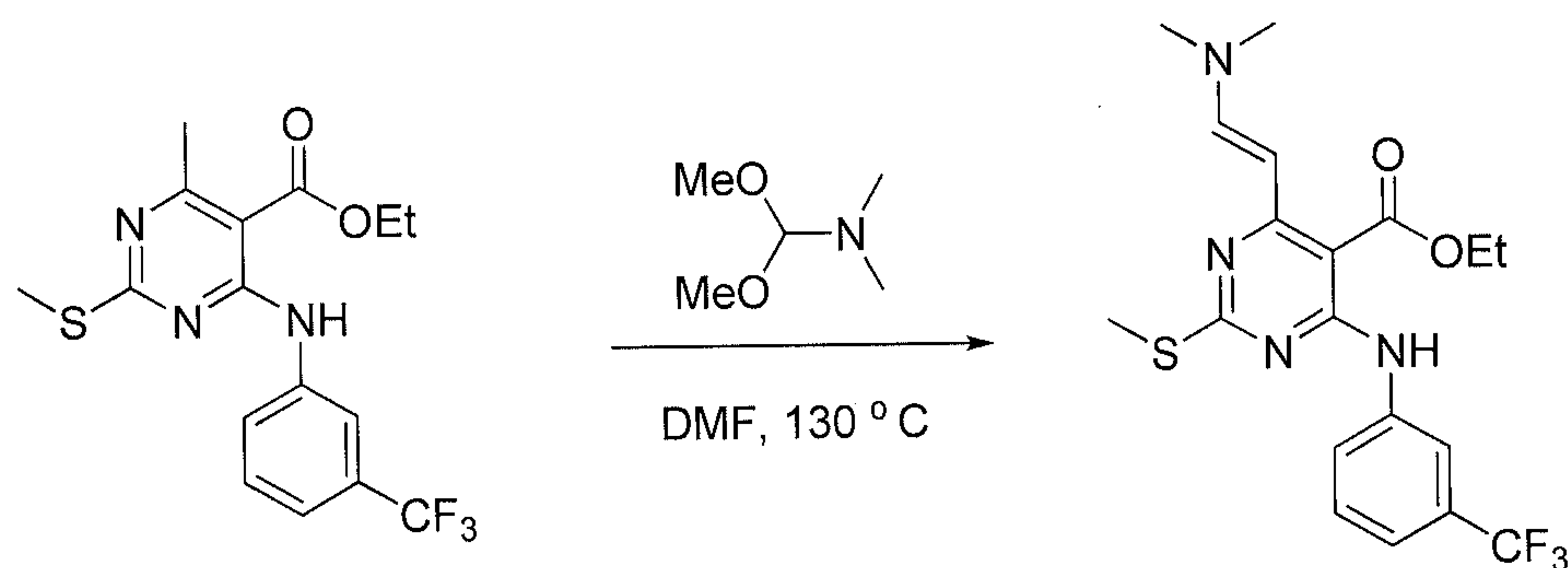
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Example 6a: Ethyl 4-methyl-2-(methylthio)-6-(3-(trifluoromethyl)phenylamino) pyrimidine-5-carboxylate



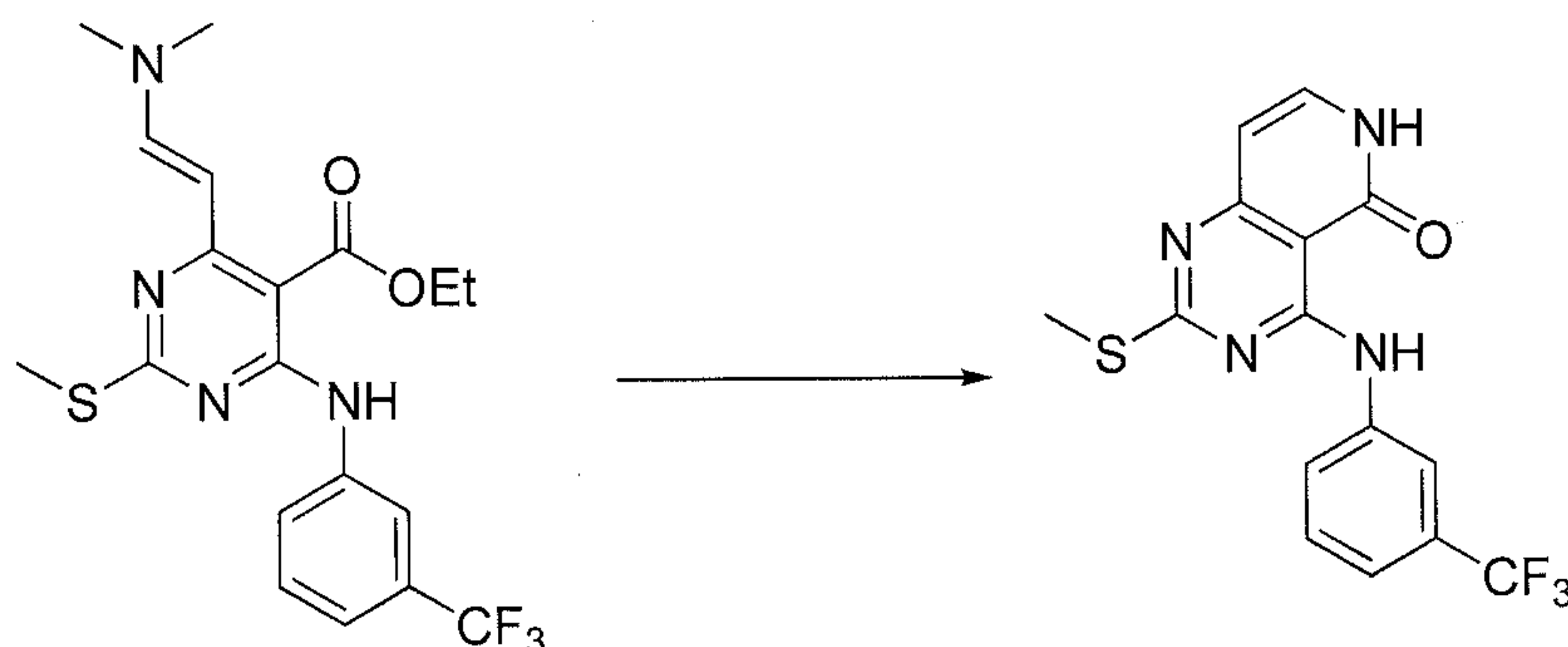
The title compound (; MS m/z: 372.2 (M+H)⁺) was prepared as described in *example 1d* by starting from ethyl 4-chloro-6-methyl-2-(methyl thio)pyrimidine-5-carboxylate (1.2 g, 4.86 mmol) and 3-(trifluoromethyl) aniline (611 uL, 4.86 mmol) and continuing until the reaction yielded dark brown solids (ethyl 4-methyl-2-(methylthio)-6-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxylate (1.76 g, 97.4 %)).

Example 6b: (E)-Ethyl 4-(2-(dimethylamino)vinyl)-2-(methylthio)-6-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxylate



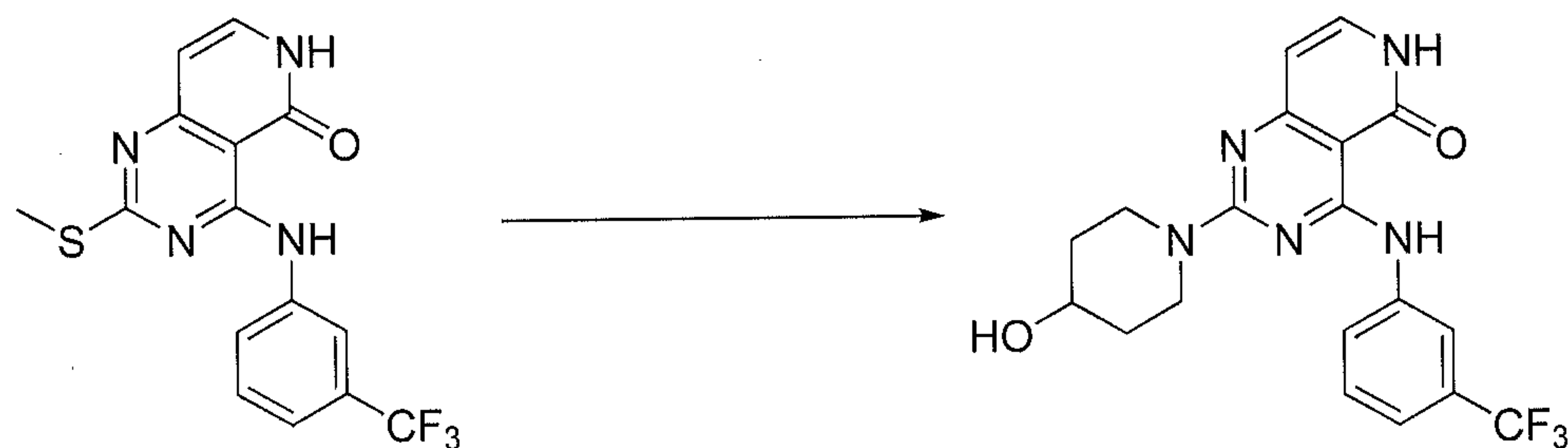
The title compound was prepared as described in *Example 1e* by starting from ethyl 4-methyl-2-(methylthio)-6-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxylate 1.76 g(4.74 mmol) and *N,N*-dimethyl formamide dimethylacetal (947 uL, 7.1 mmol) and continuing until the reaction yeilded the crude title compound. This was used for the next step without further purification.

Example 6c: 2-(Methylthio)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one



The title compound was prepared as described in *Example 1f* by starting from (E)-ethyl 4-(2-(dimethylamino) vinyl)-2-(methylthio)-6-(3-(trifluoromethyl)phenylamino)pyrimidine-5-carboxylate and 30% NH₄OH solution and continuing until the reaction yield brown solids, 2-(methylthio)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (912 mg). MS *m/z*: 353.1 (M+H)⁺.

Example 6d: 2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino) pyrido[4,3-*d*]pyrimidine-5(6*H*)-one

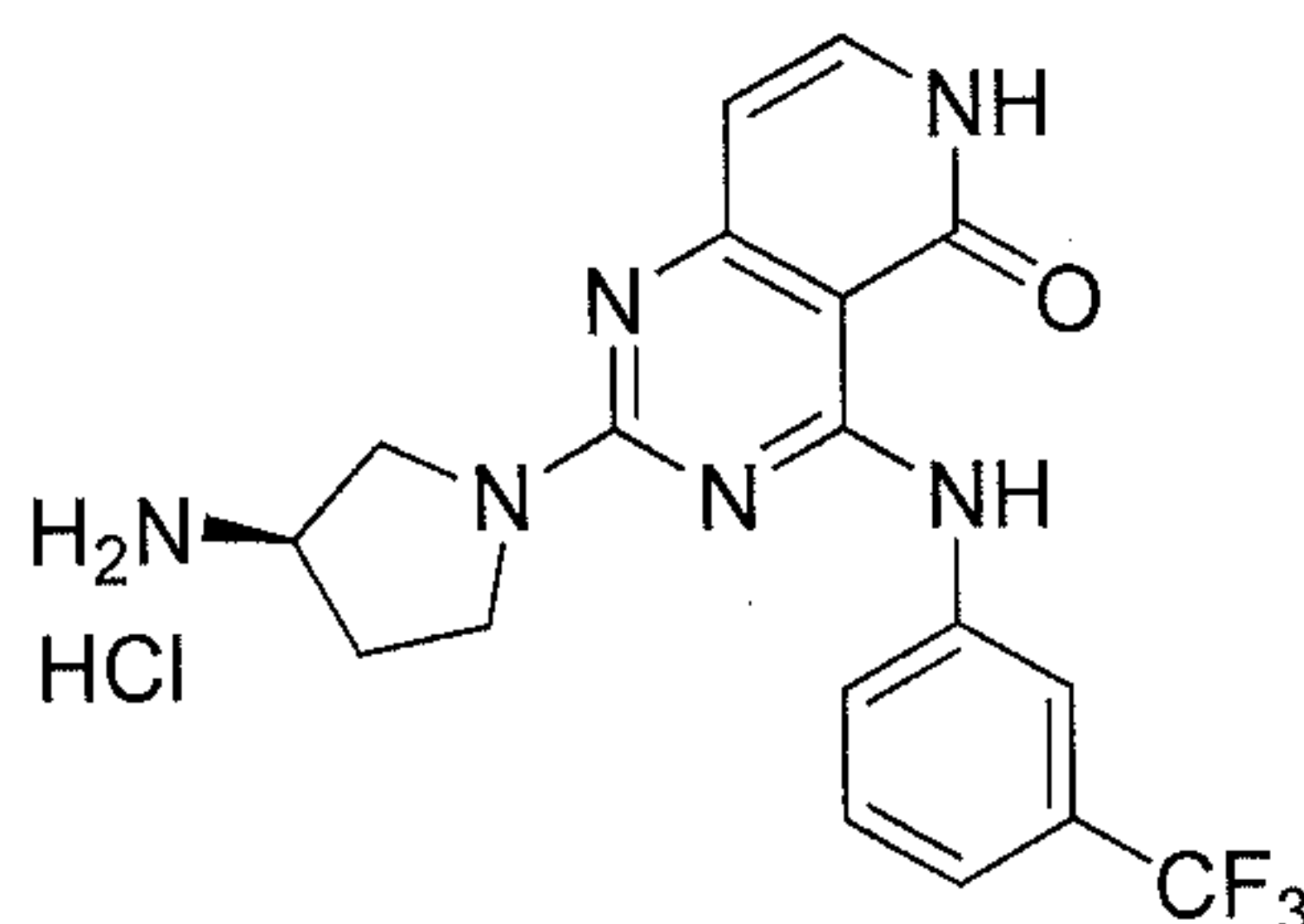


The title compound was prepared as described in *Example 1g* by starting from 2-(methylthio)-4-(3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (100 mg, 0.26 mmol) and 4-hydroxypiperidine to yield the title compound (73 mg) as white solids. MS *m/z*: 406 (M+H)⁺, ¹H NMR (300 MHz,), δ ppm 1.21-1.35 (m, 4H), 3.76-3.78 (m, 1H), 4.26-4.28 (m, 4H), 6.17 (d, *J* = 7.2 Hz, 1H), 7.38 – 7.68 (m, 4H), 7.90 (s, 1H), 8.61 (s, 1H), 11.42 (s, 1H), 12.10 (s, 1H).

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Example 7

Synthesis of (R)-2-(3-aminopyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride

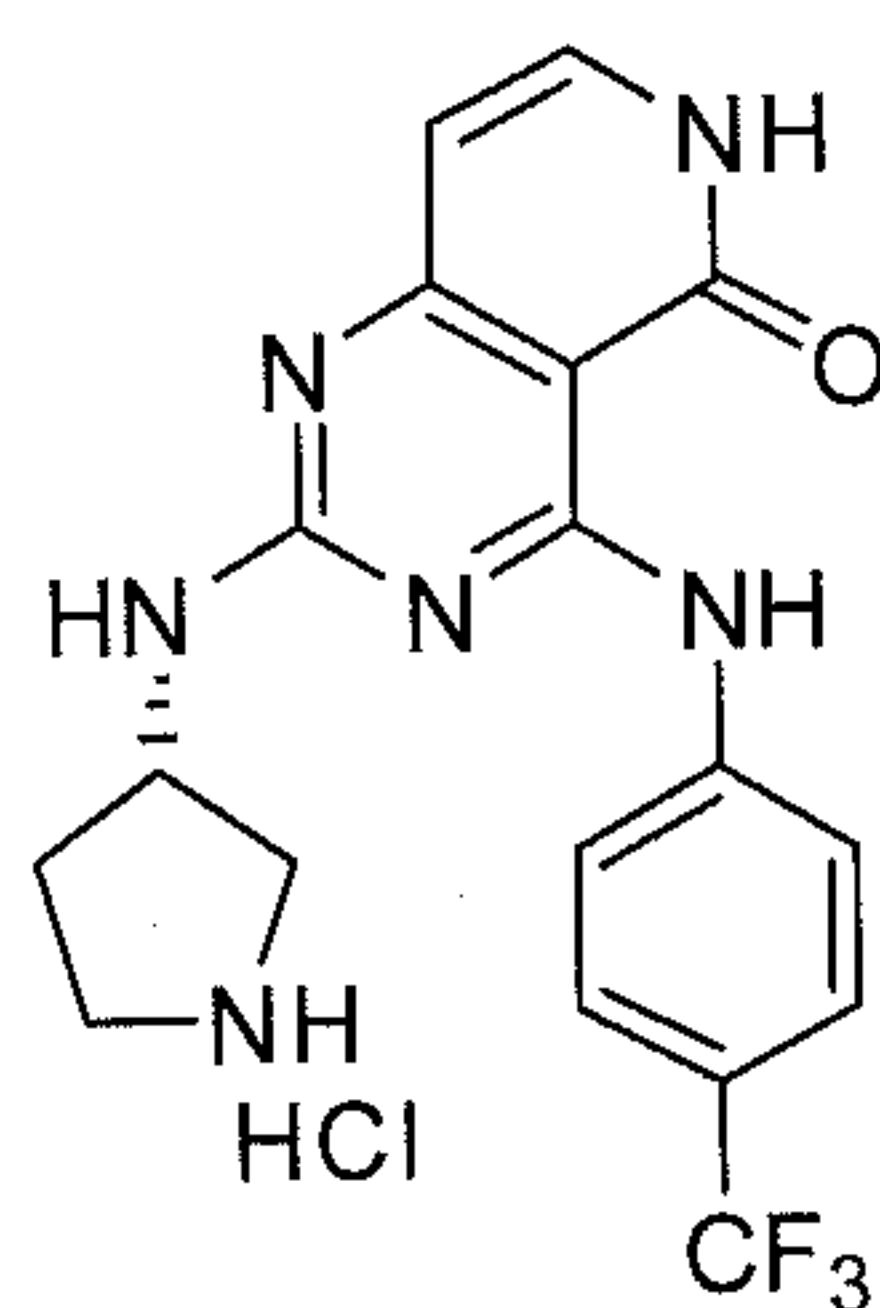


Compound No. 7

The title compound (Compound No. 7) was prepared as described in *Example 1g* by starting from 2-(methylthio)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one (100mg, 0.28 mmol) and (R)-(+)-(Boc-amino)pyrrolidine (107 mg, 0.57 mmol) (93 mg, 93%) and treating with 4 N HCl in dioxane. MS m/z: 405. 2 (M+1)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 12.46 (d, 9Hz, 1H), 8.37 (s, 3H), 7.94~7.52 (m, 3H), 6.75 (d, 36.6Hz, 1H), 4.00~3.86 (m, 5H), 2.40~2.09 (m, 2H).

Example 8

Synthesis of (S)-2-(pyrrolidin-3-ylamino)-4-(4-trifluoromethylphenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one

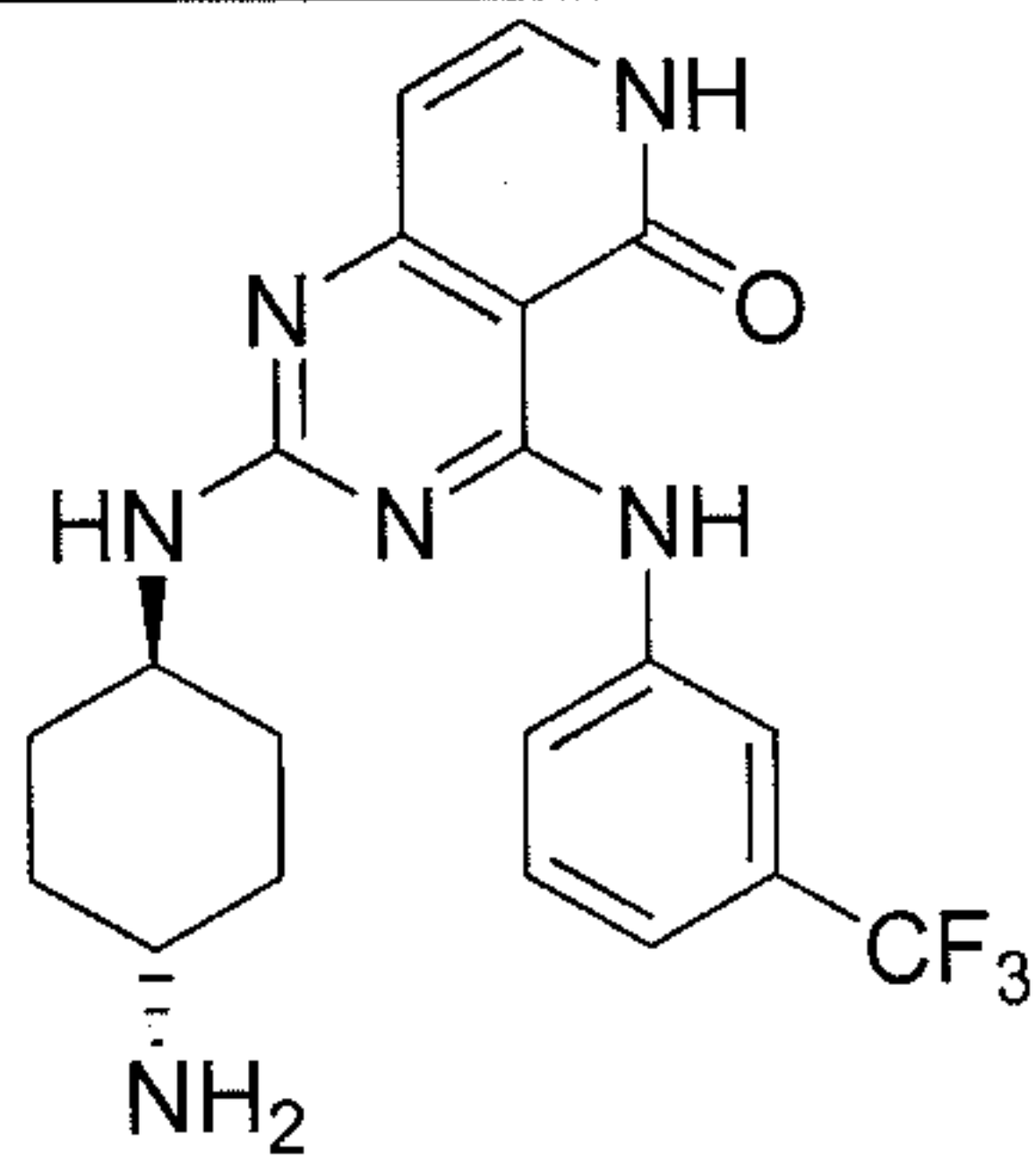
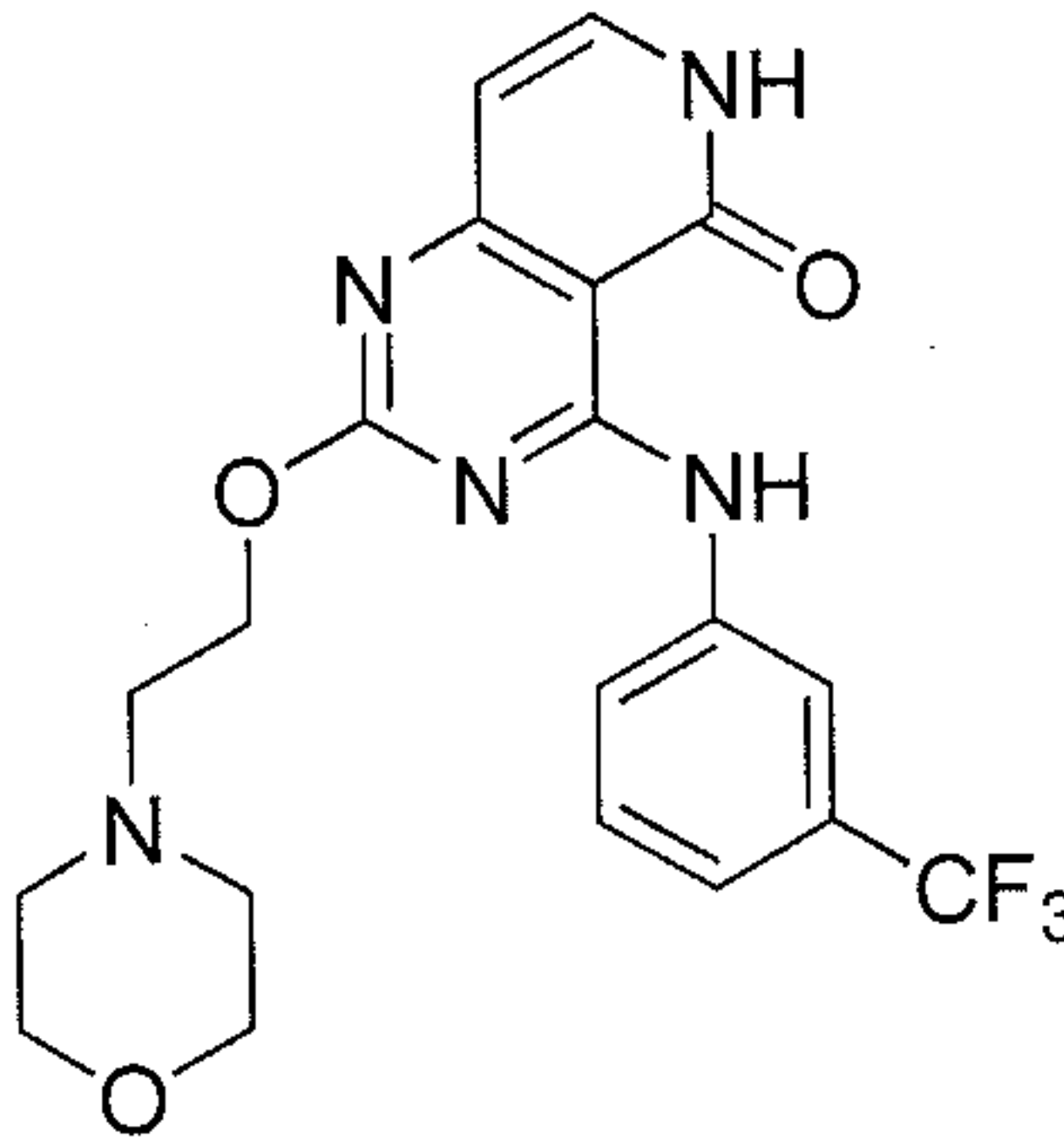
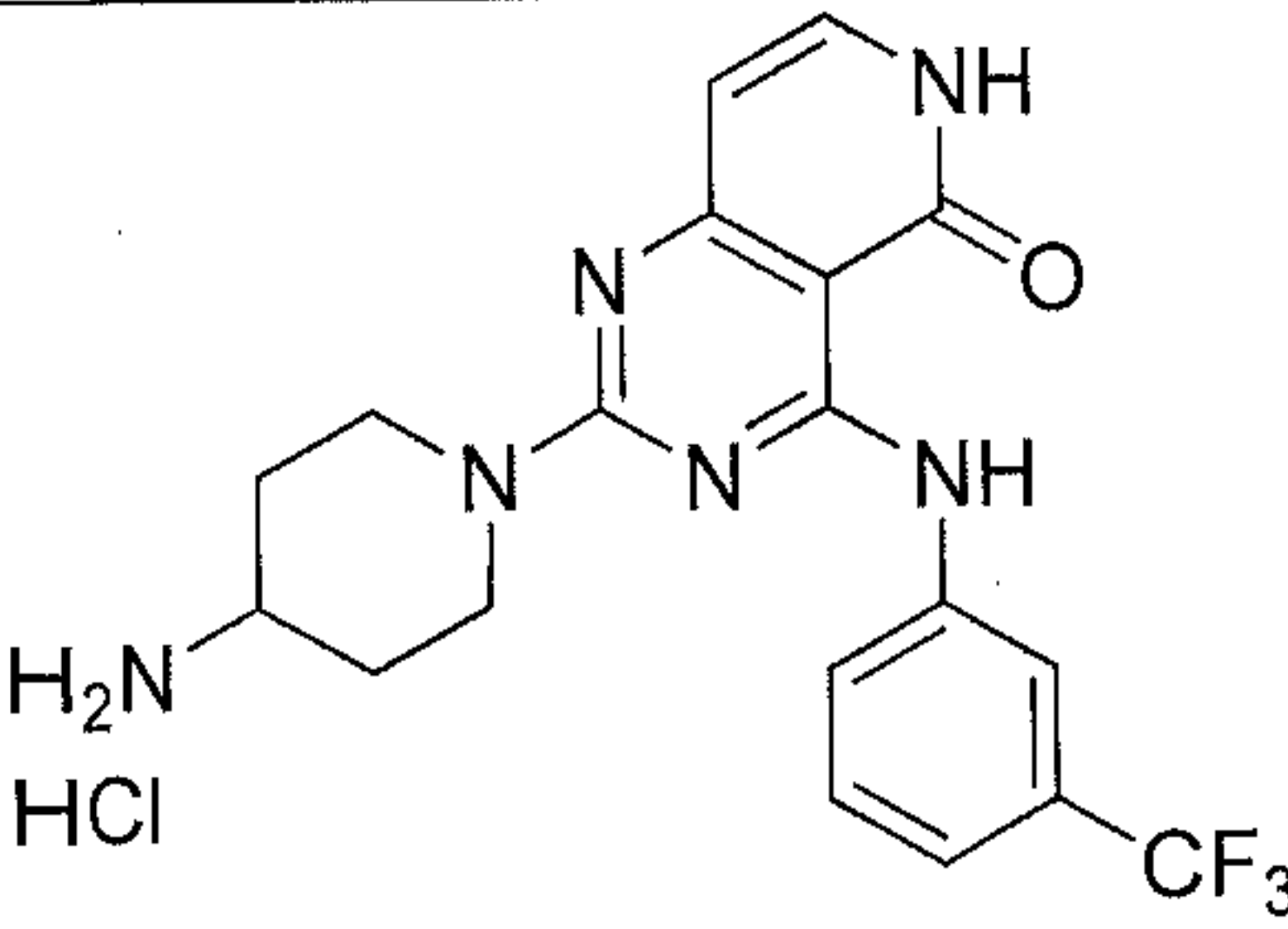
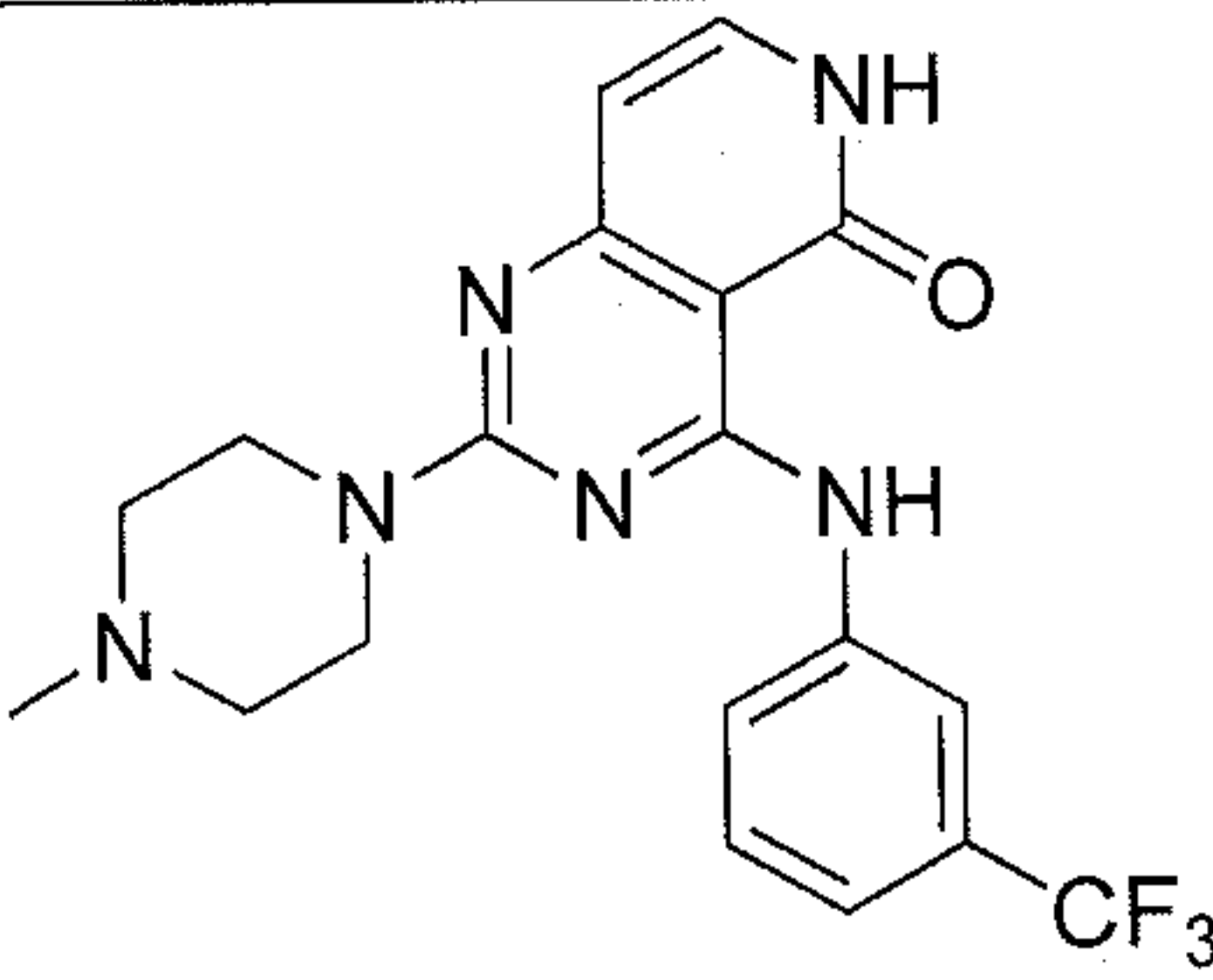


Compound No. 8

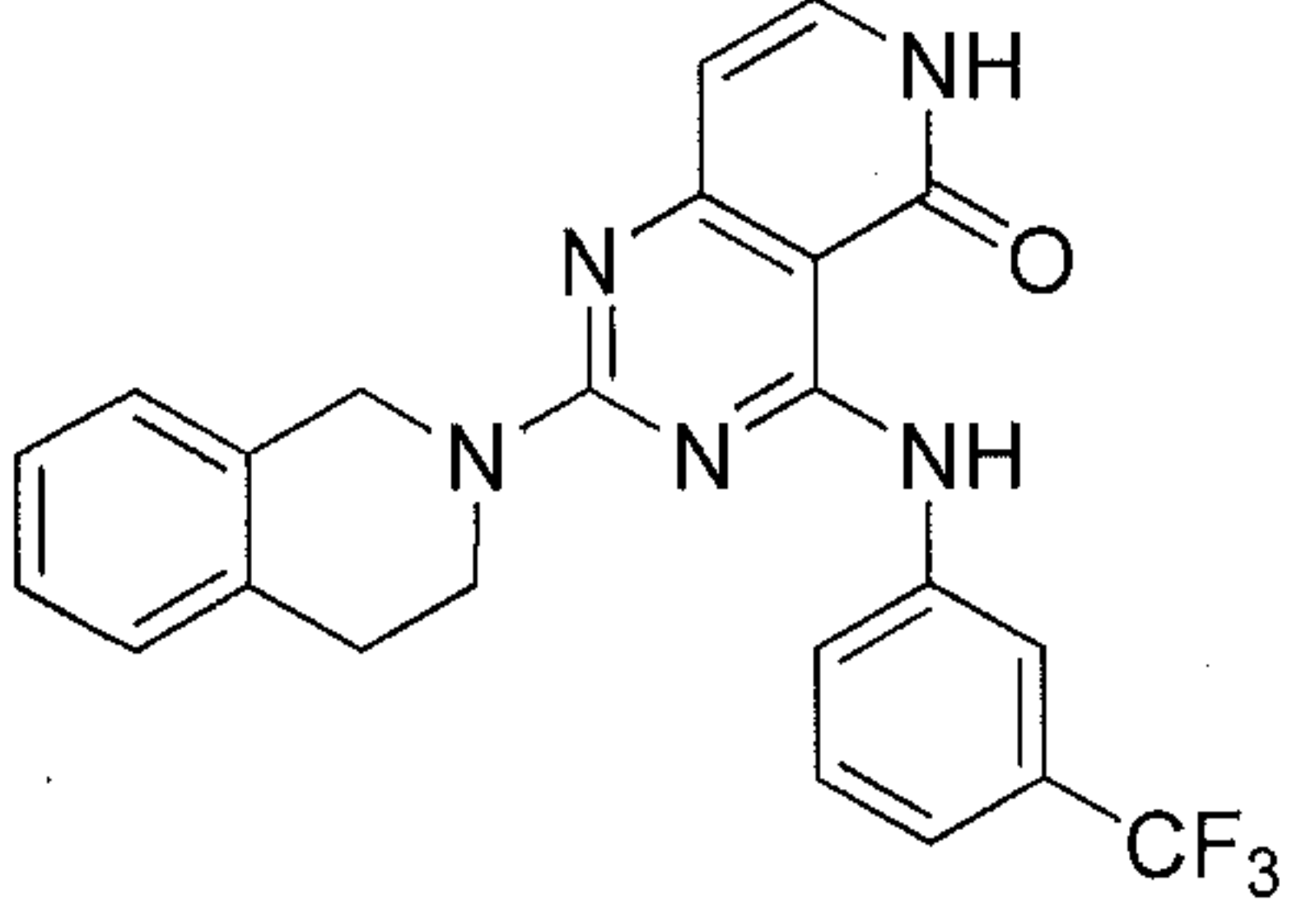
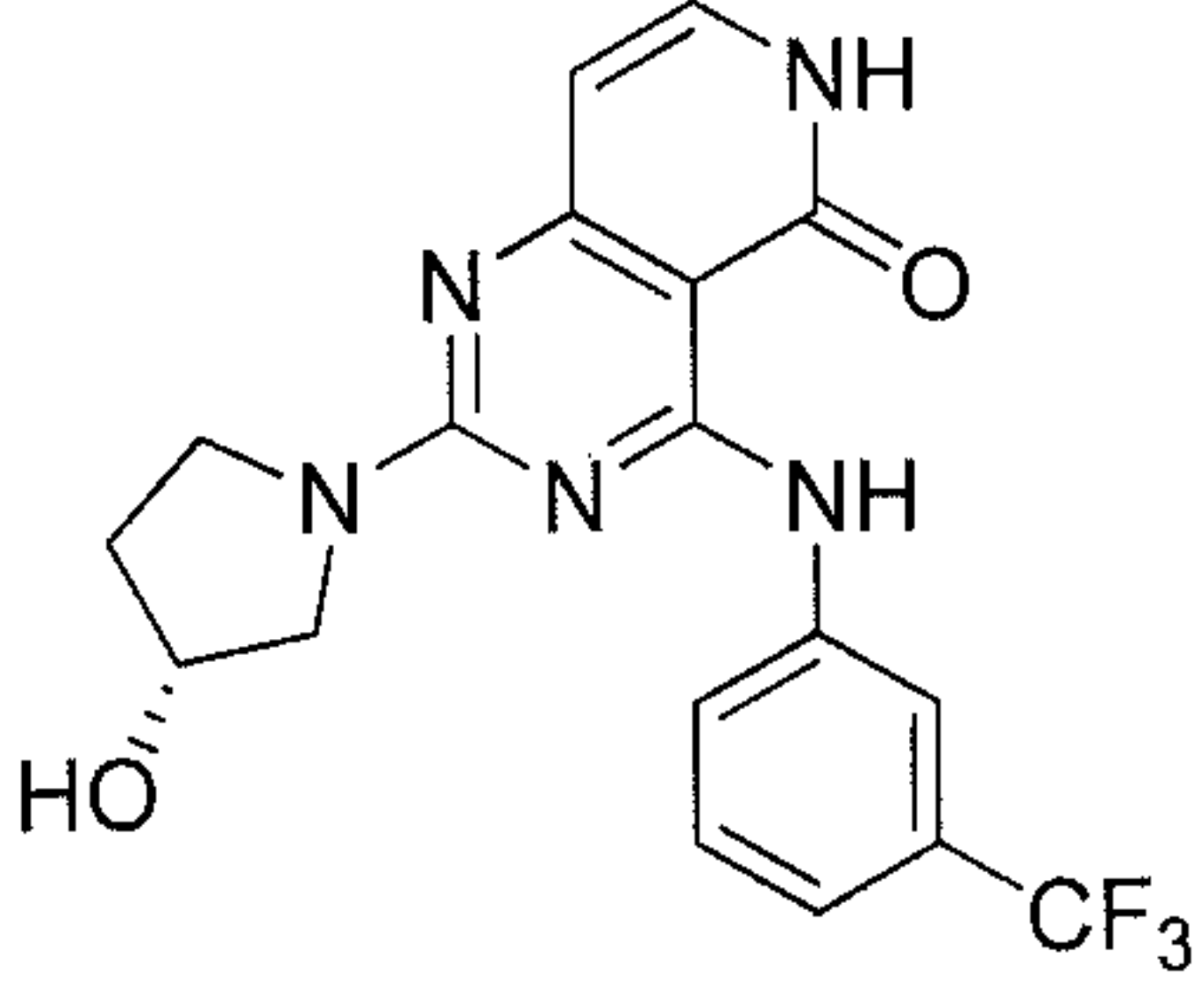
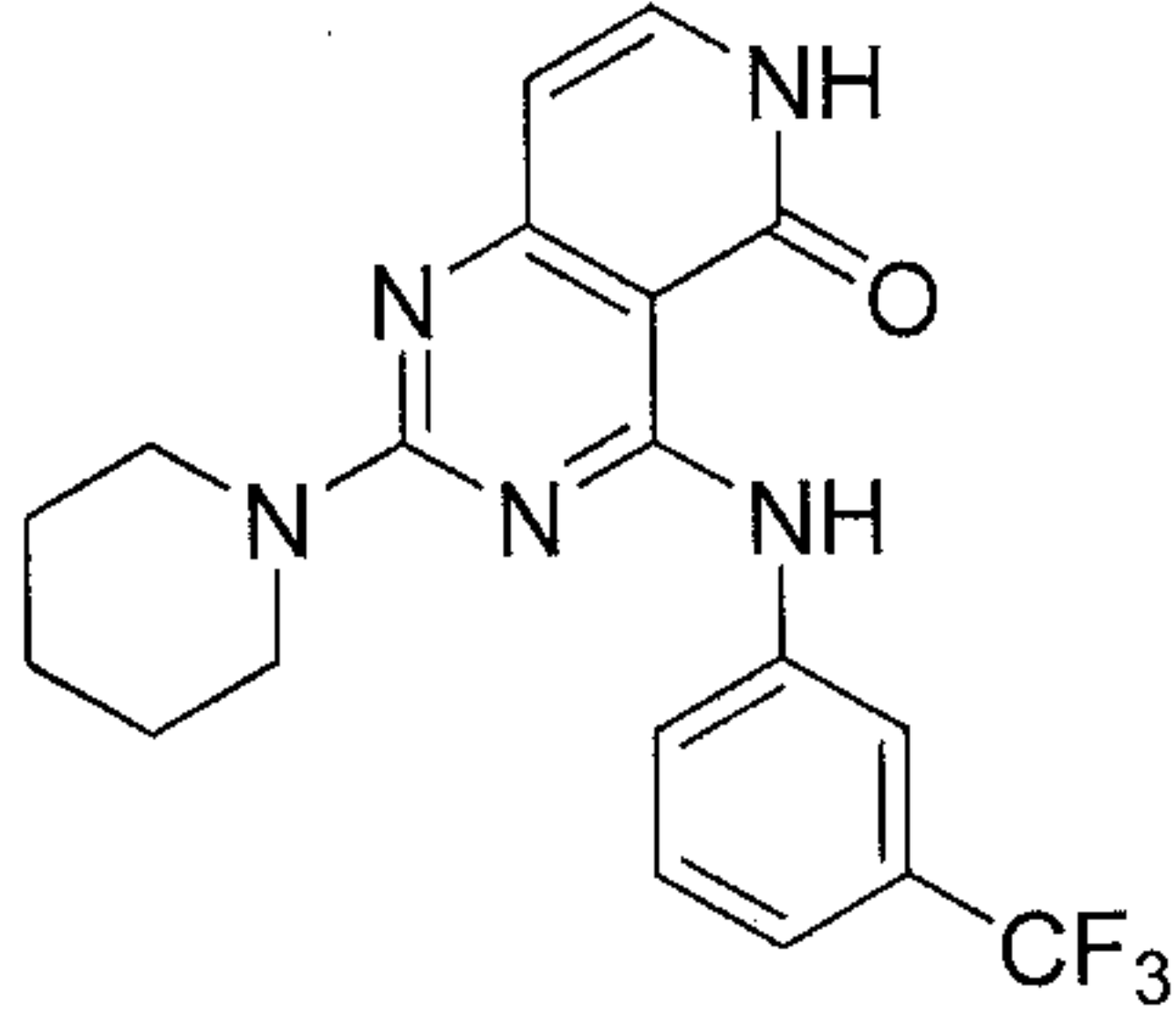
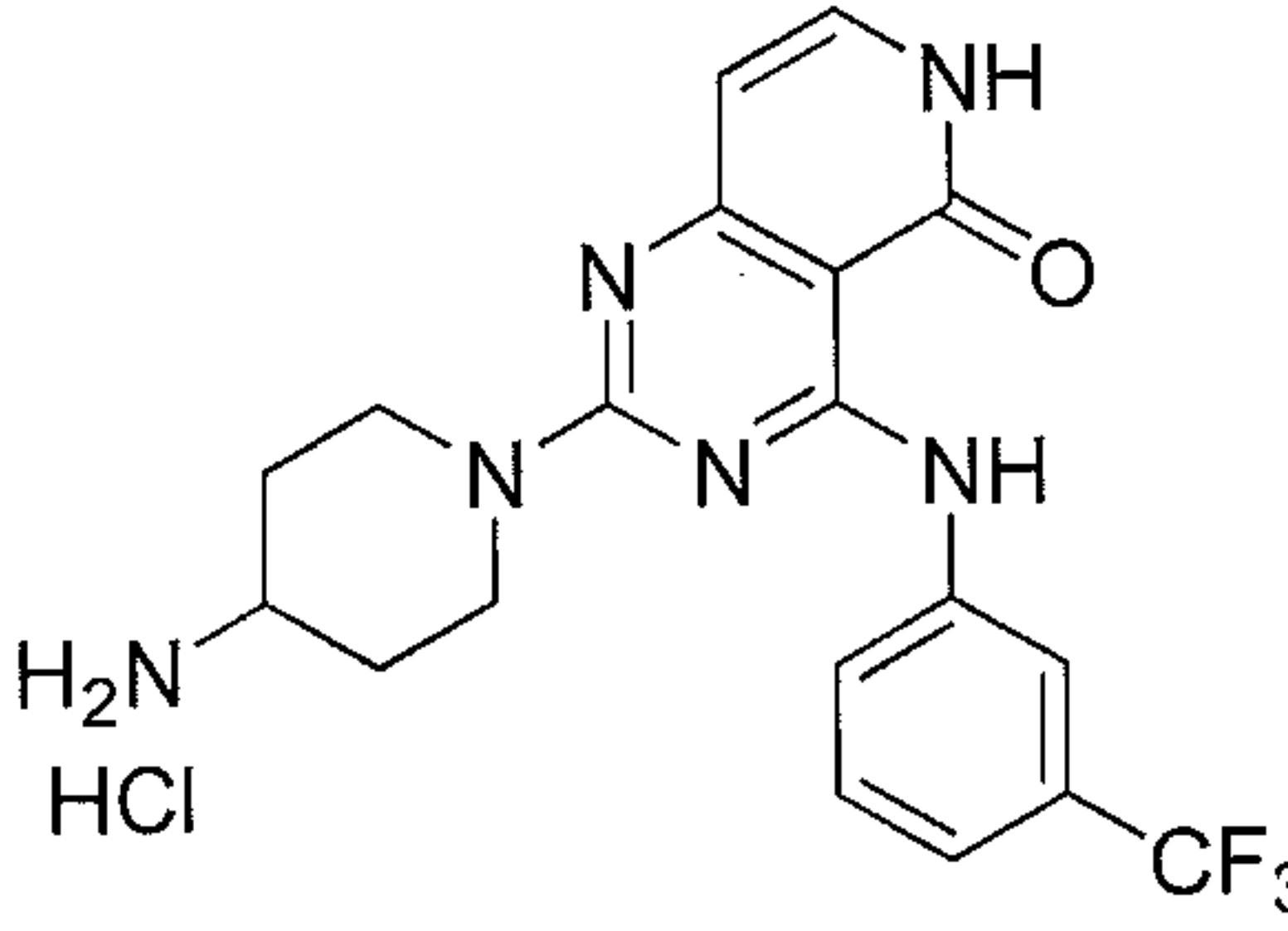
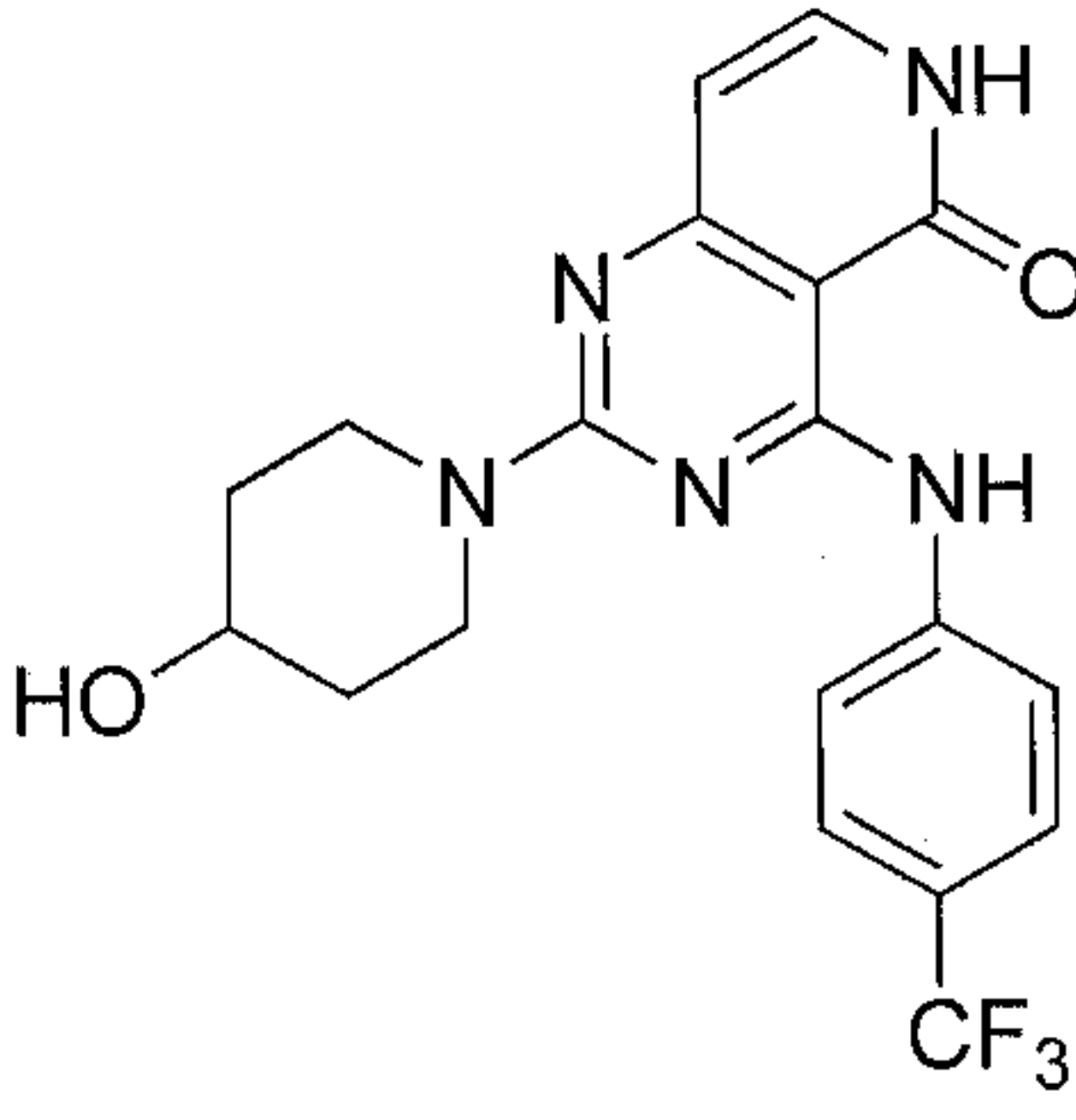
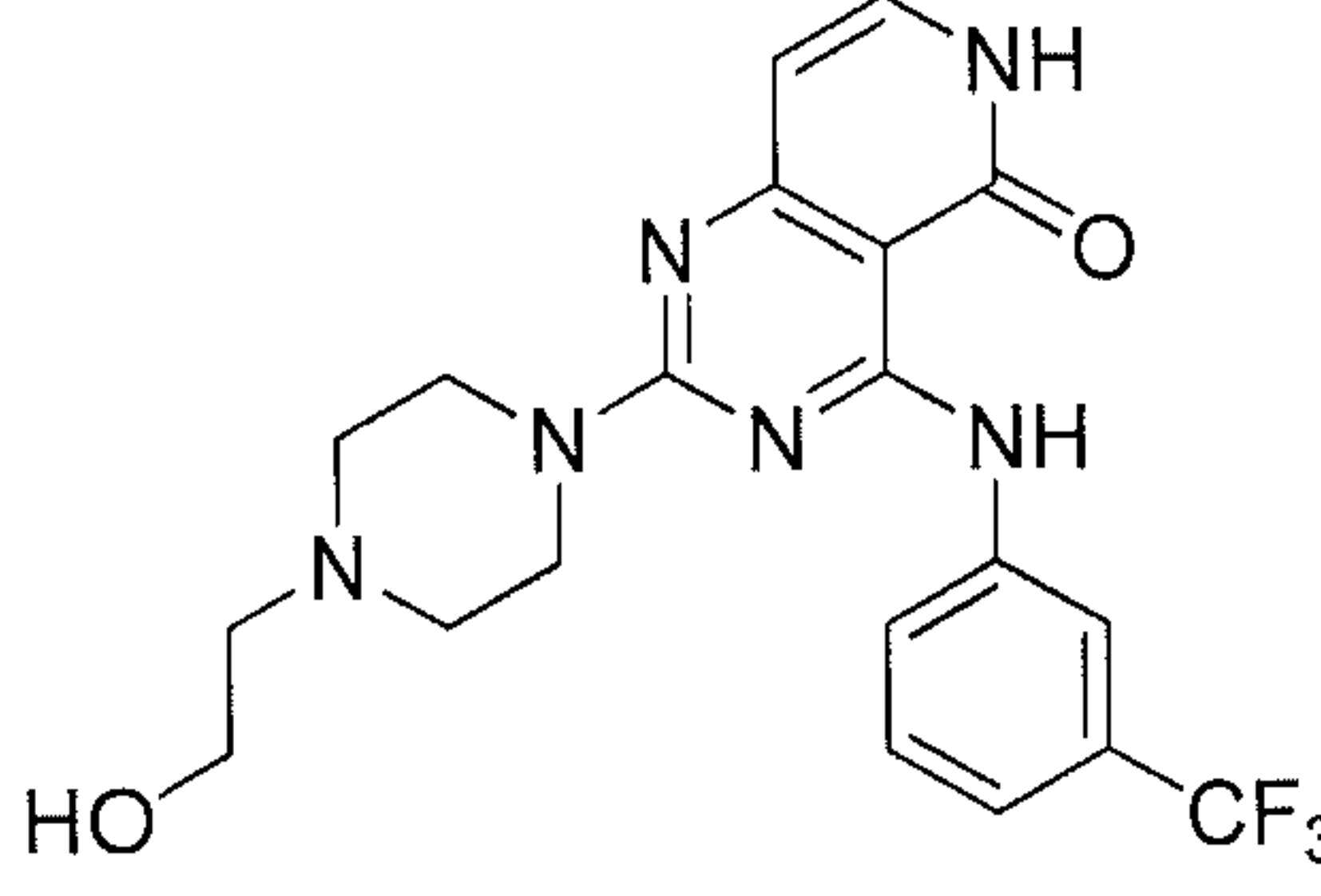
Compound No. 8 was prepared as described in *Example 1g* starting from 2-(methylthio)-4-(4-(trifluoro methyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one (160 mg, 0.45 mmol) and (S)-(-)-1-boc-3-aminopyrrolidine (167 mg, 0.90 mmol) and treated with 4 N HCl in dioxane to yield the title compound (110 mg, 57 %). MS m/z: 391 (M+1)⁺.

The following 4-(3-(trifluoromethyl)phenylamino)-2-(amino substituted)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one compounds were prepared from 4-(3-(trifluoromethyl)phenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one and the corresponding amine following the procedure similar to that described in *Example 6d*.

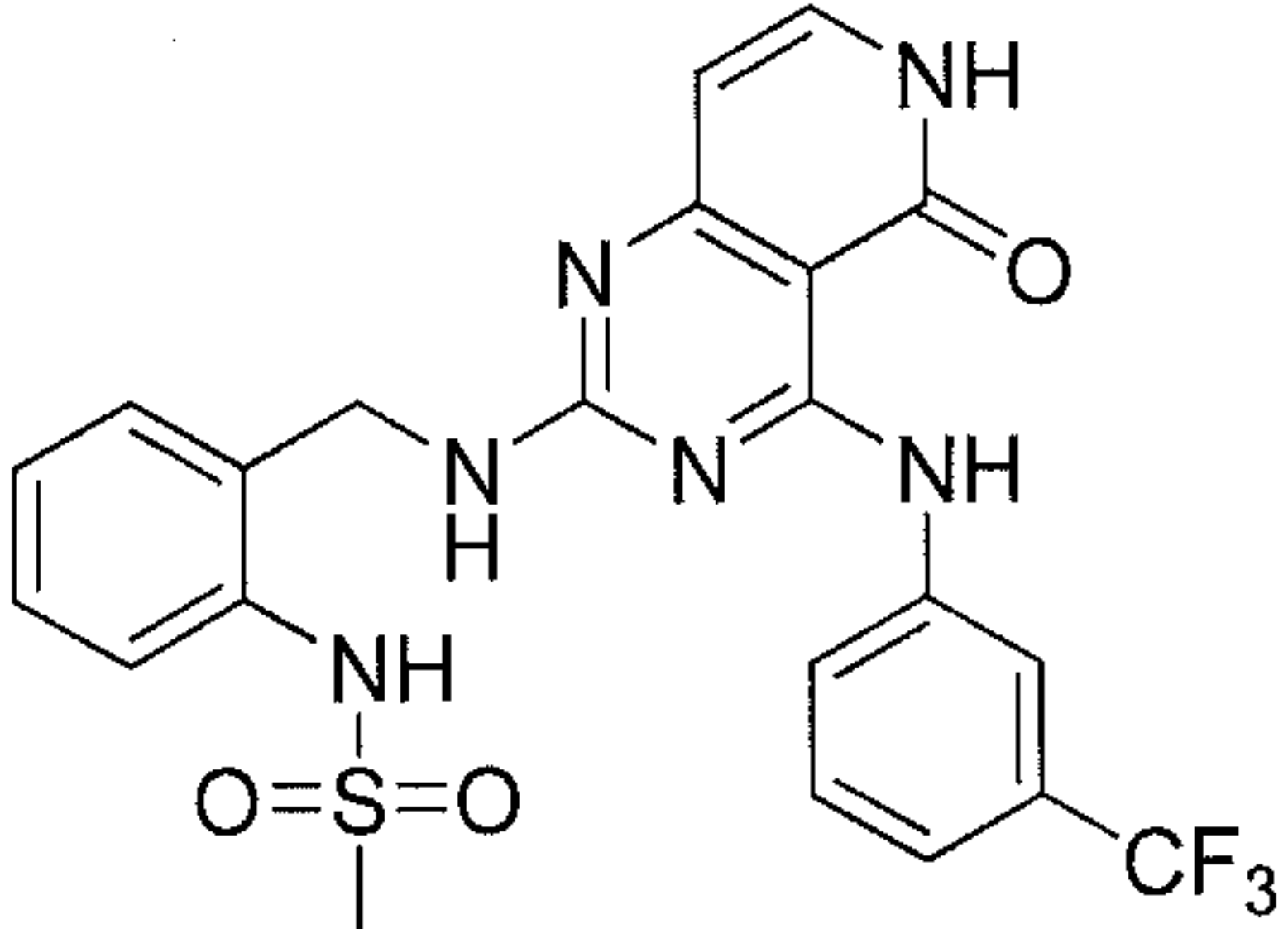
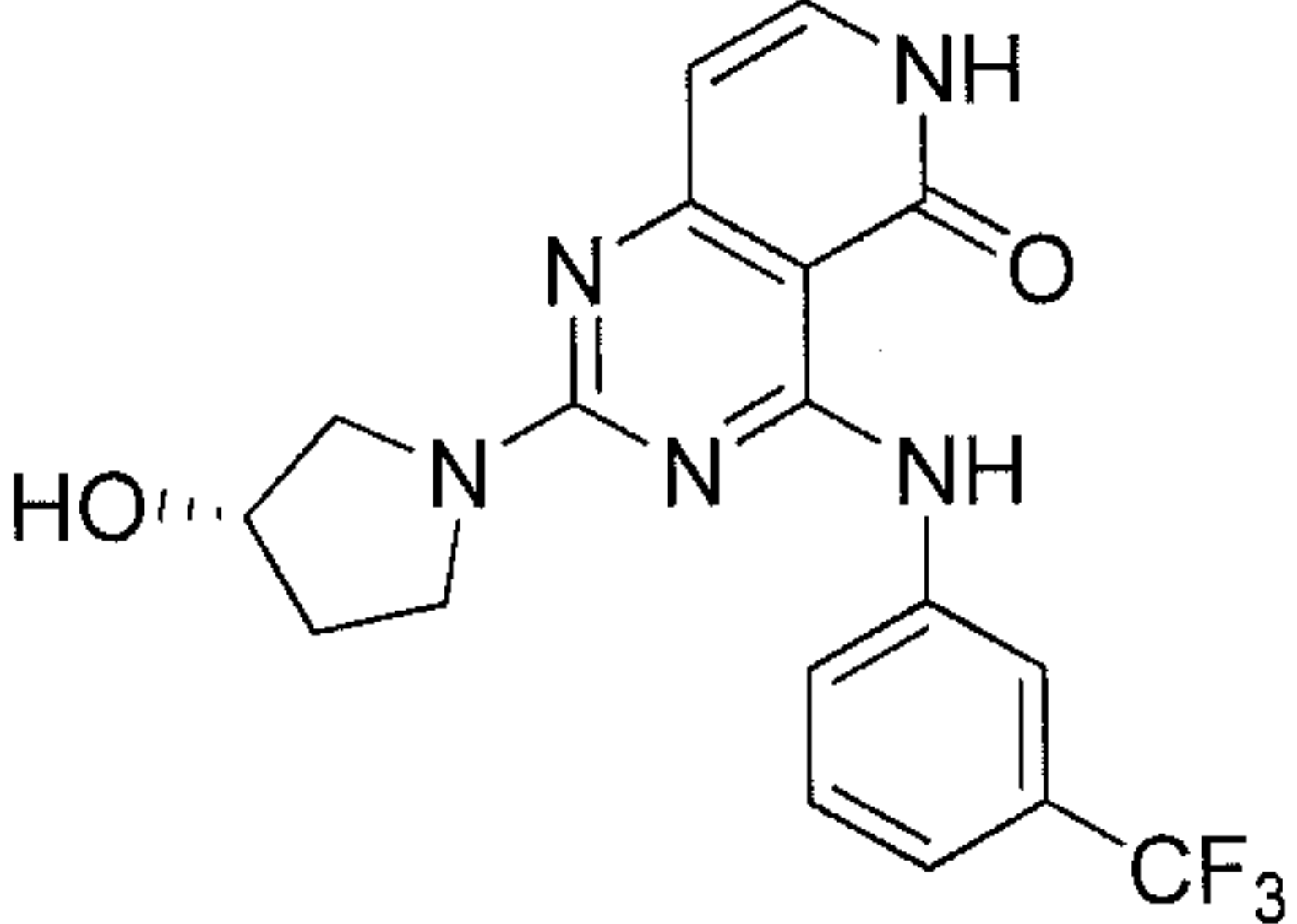
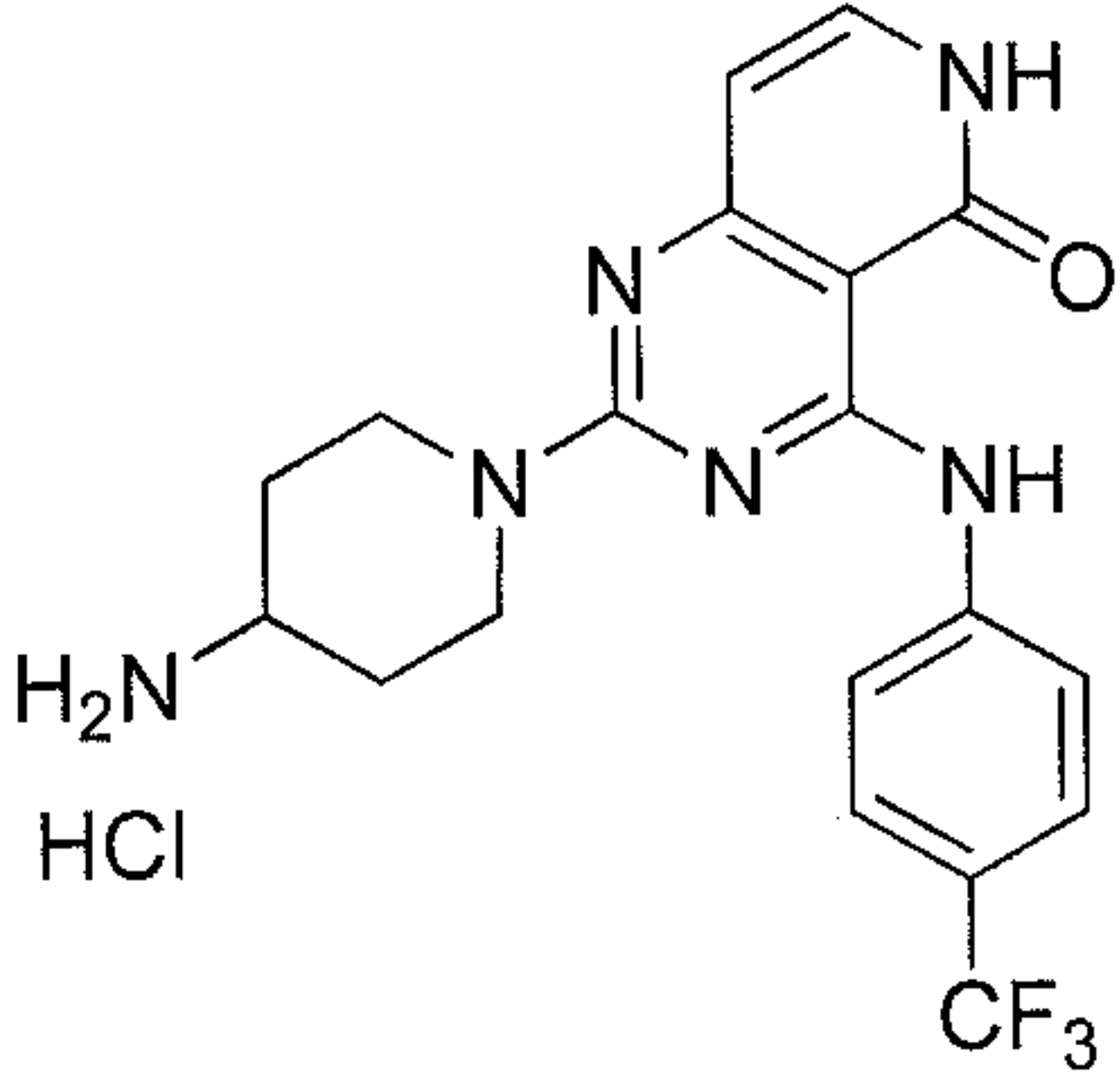
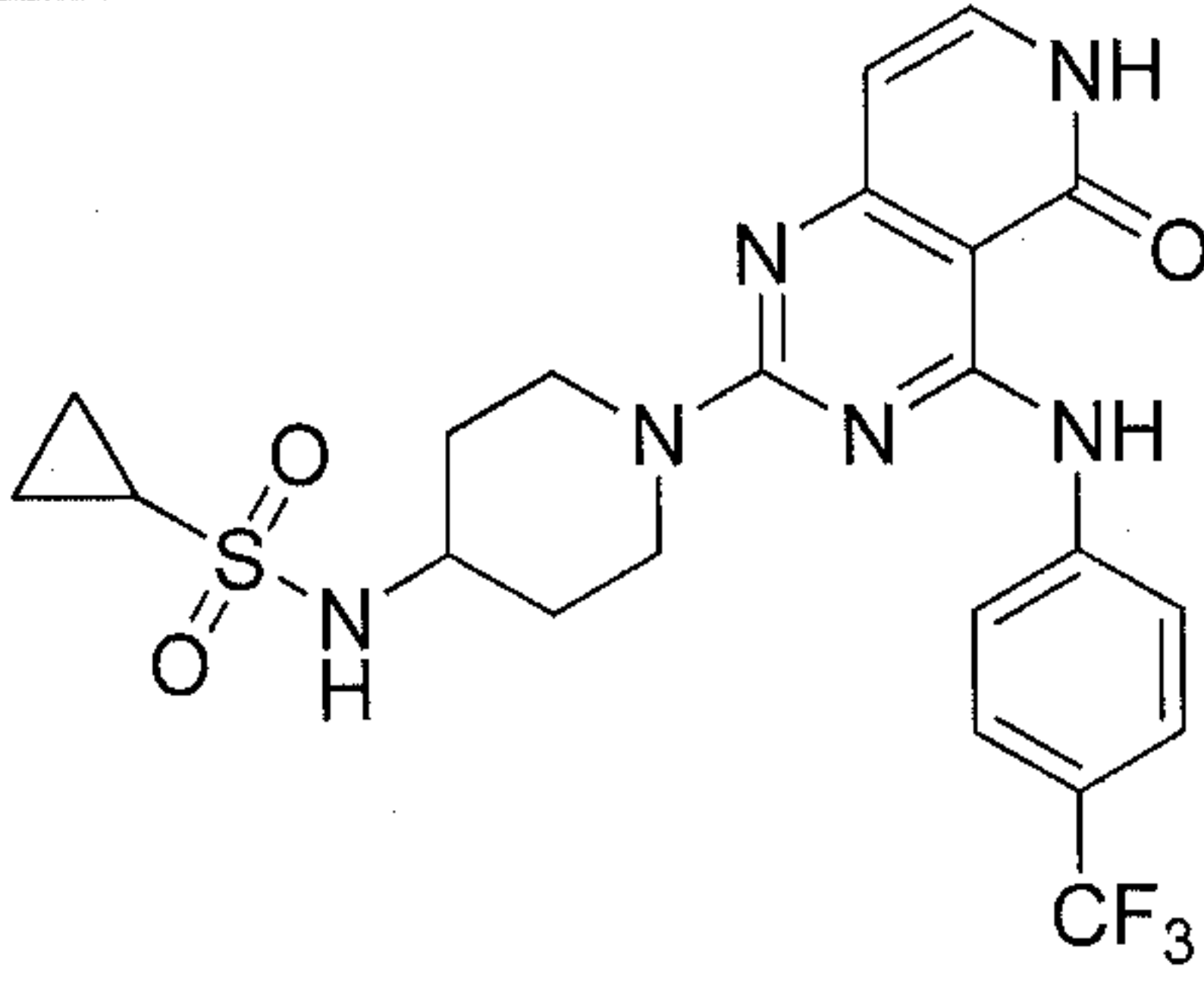
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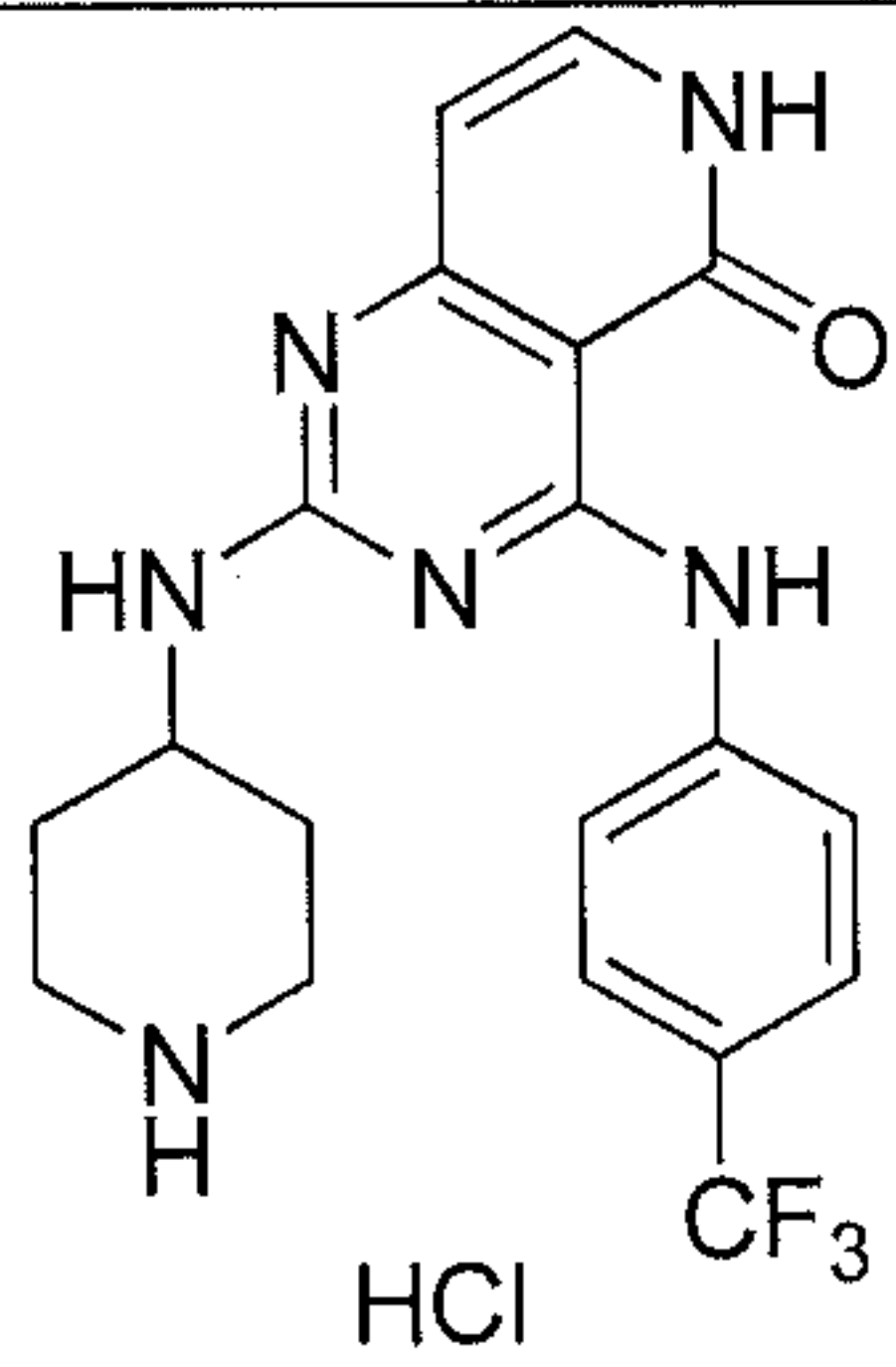
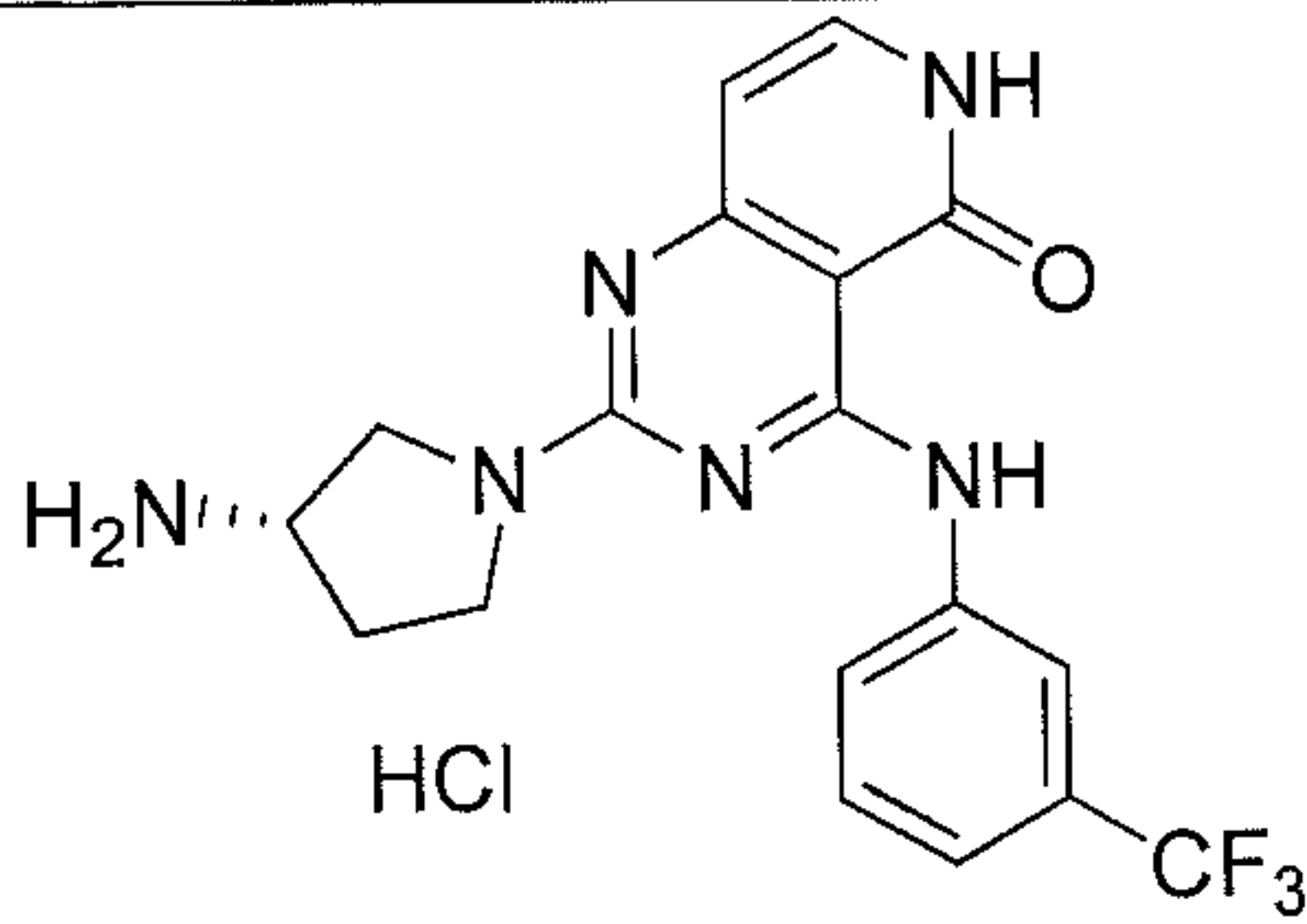
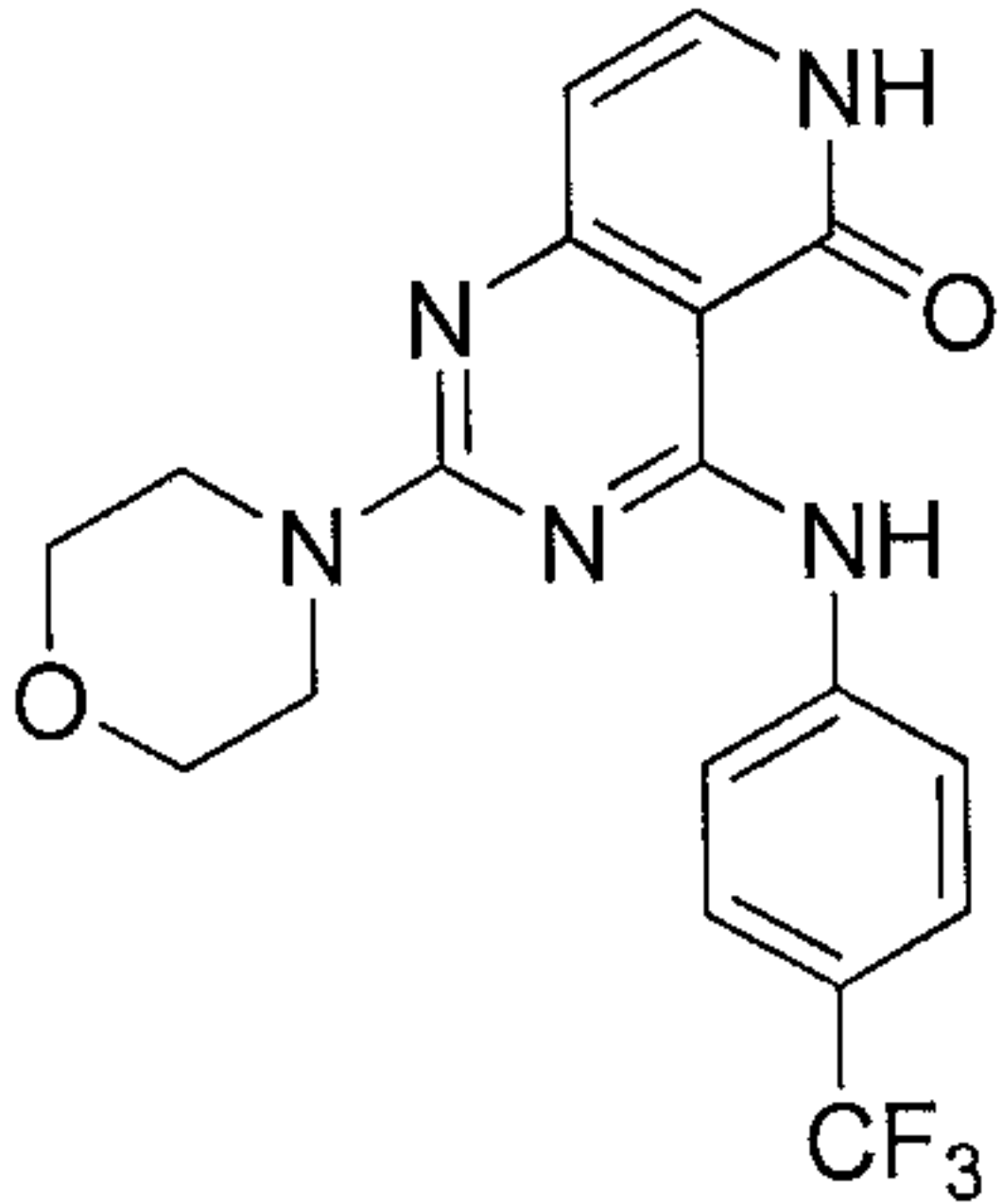
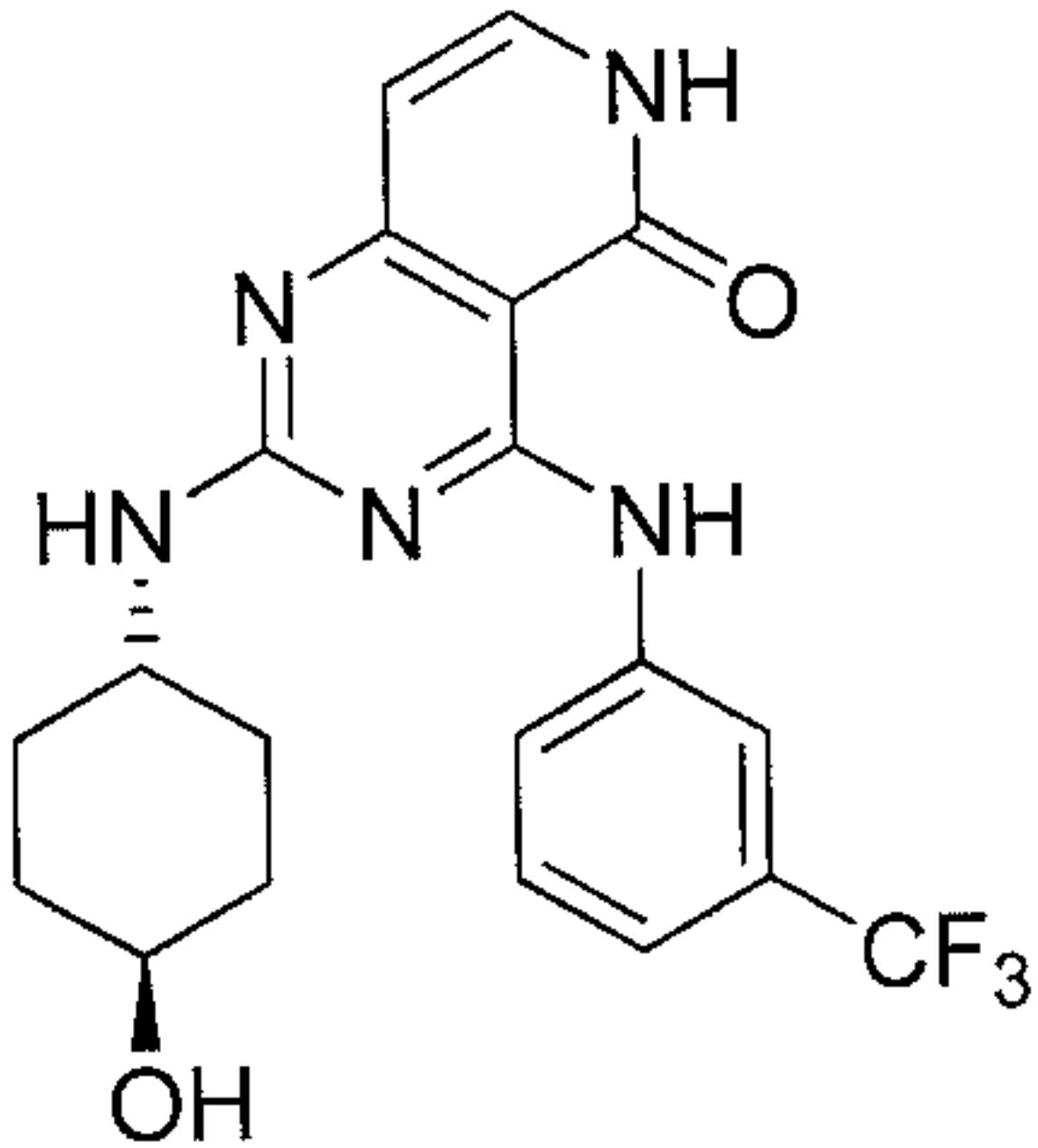
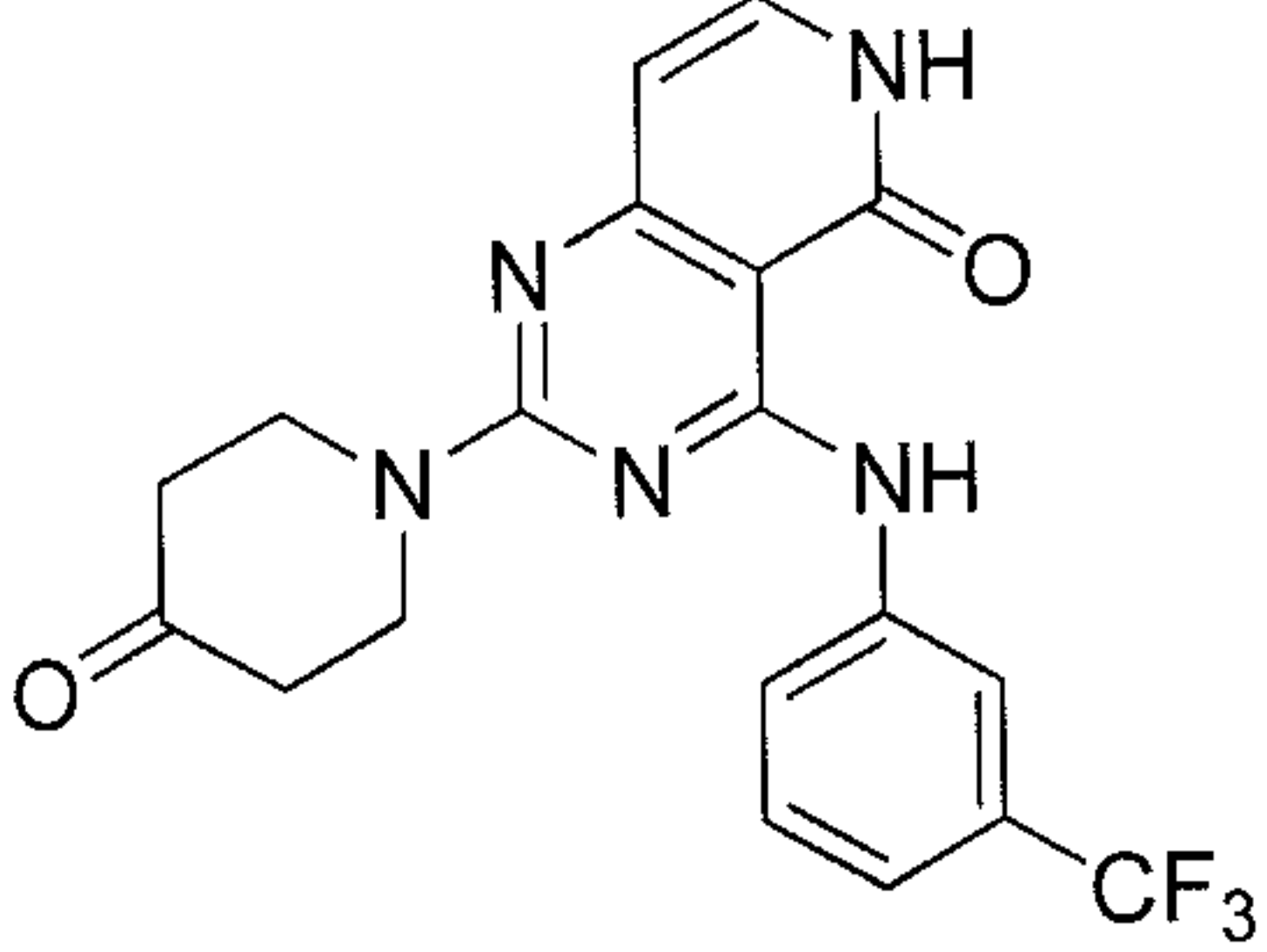
NO.	Structure	Name, NMR (300 MHz, DMSO- <i>d</i> ₆)	Mass (M+1)
9		2-((1 <i>R</i> ,4 <i>R</i>)-4-aminocyclohexyl amino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	419
10		2-(2-morpholinoethoxy)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.11 (s, 1H), 11.45 (br s, 1H), 8.54 (s, 1H), 7.68 (d, <i>J</i> = 6.30 Hz, 1H), 7.61~7.57 (m, 1H), 7.43~7.40 (m, 2H), 6.17 (d, <i>J</i> = 5.40 Hz, 1H), 4.44 (s 1H), 3.81 (s, 4H), 3.55~3.47 (m, 4H), 2.45~2.39 (m, 4H)	436
11	 HCl	2-(4-aminopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	405
12		2-(4-methylpiperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	405

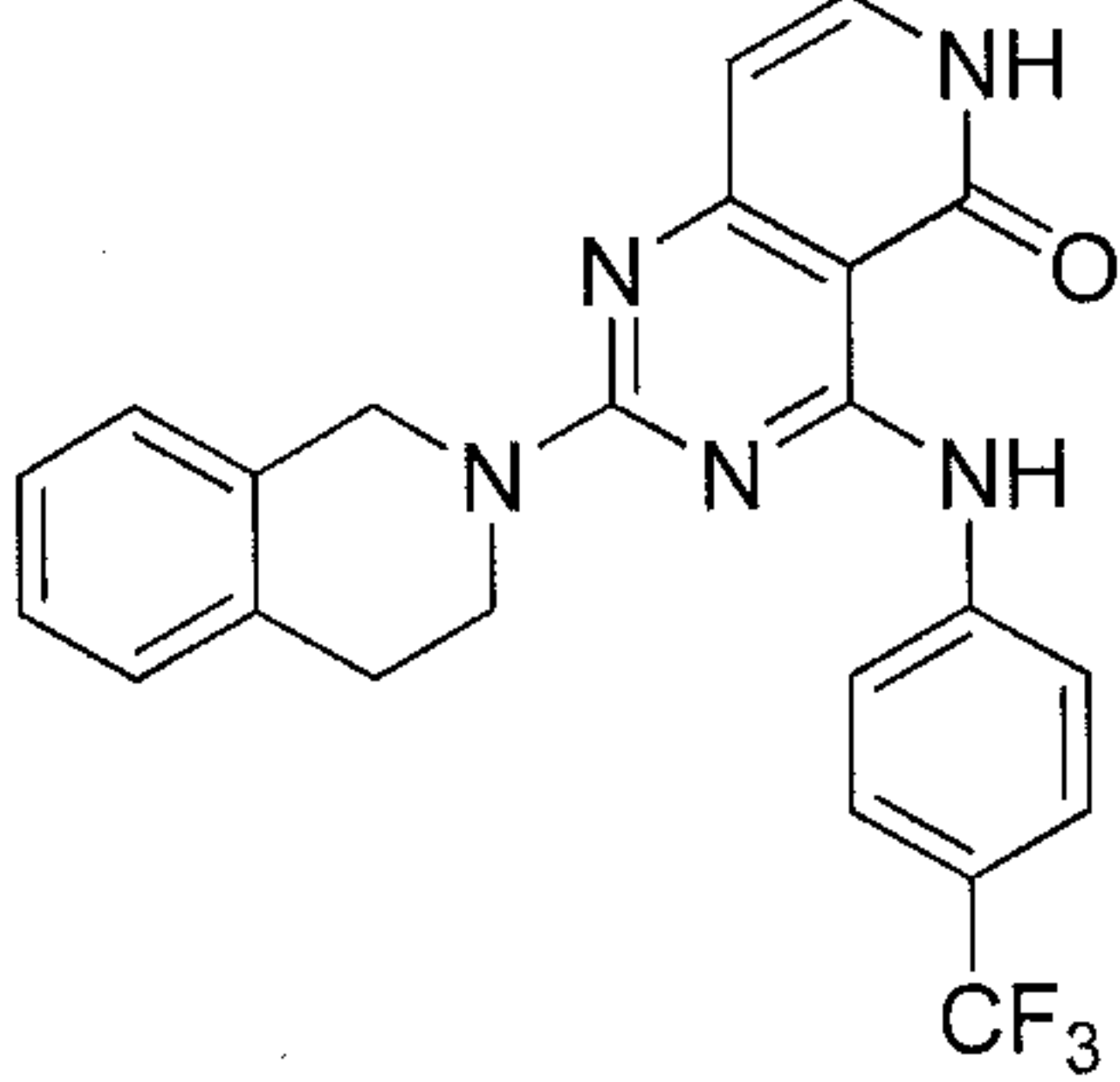
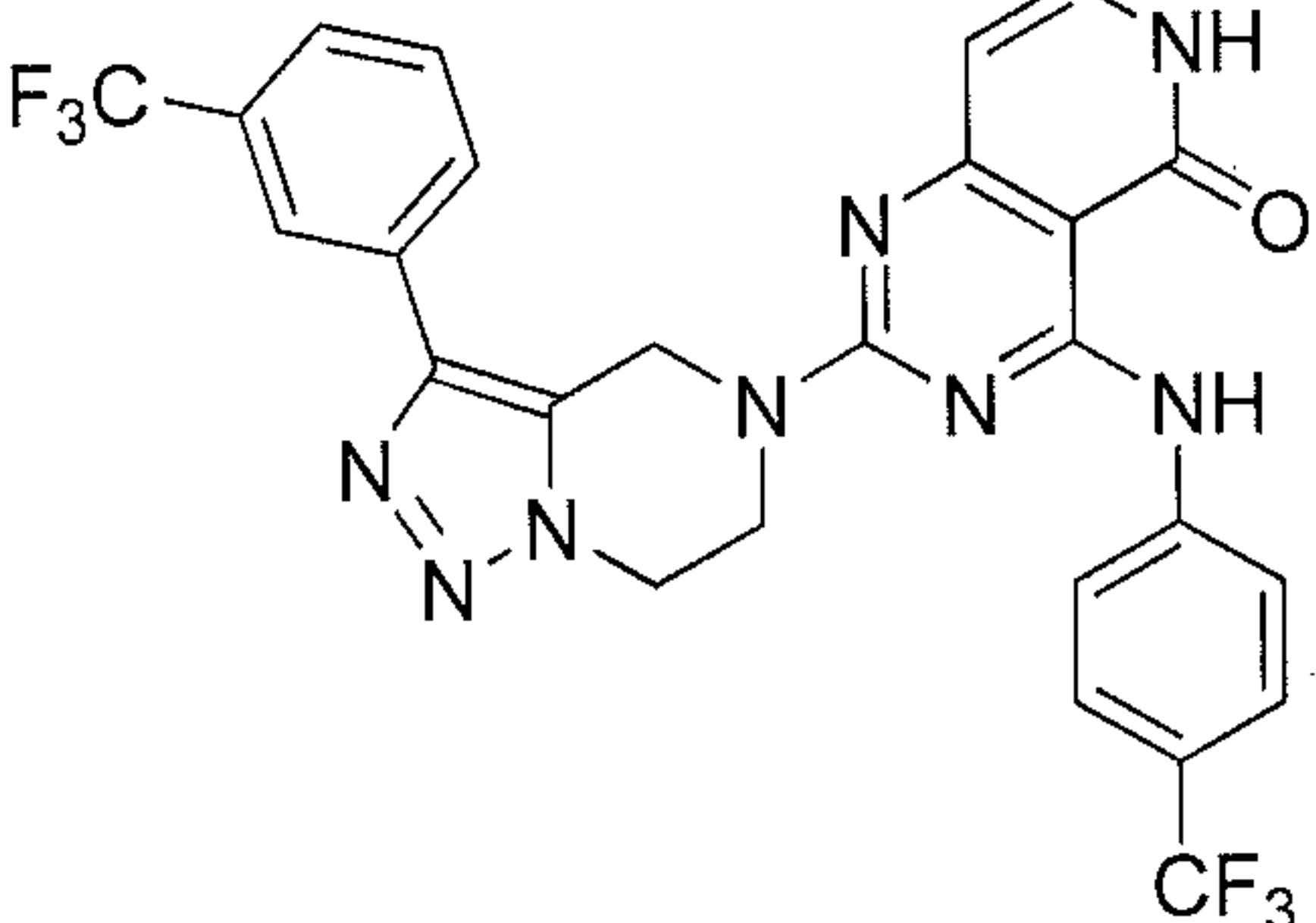
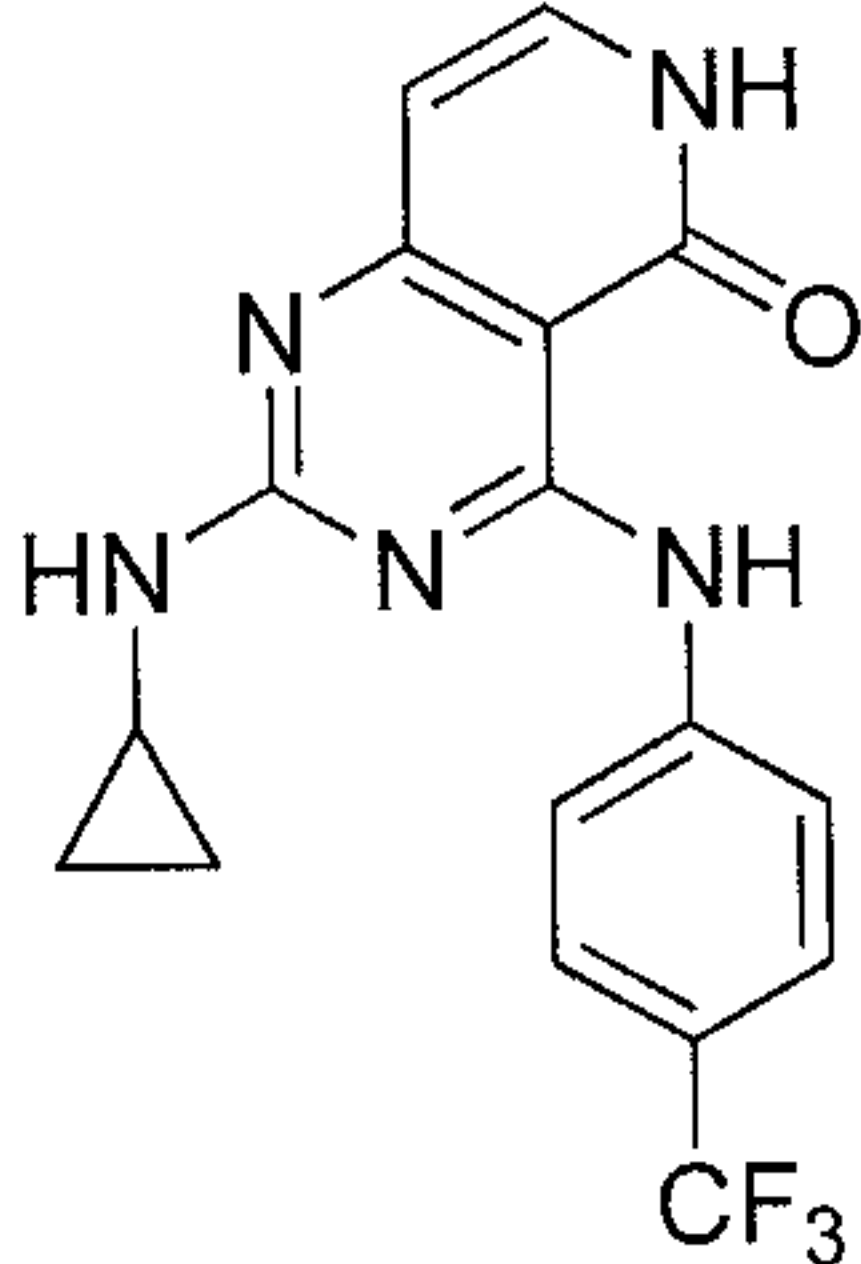
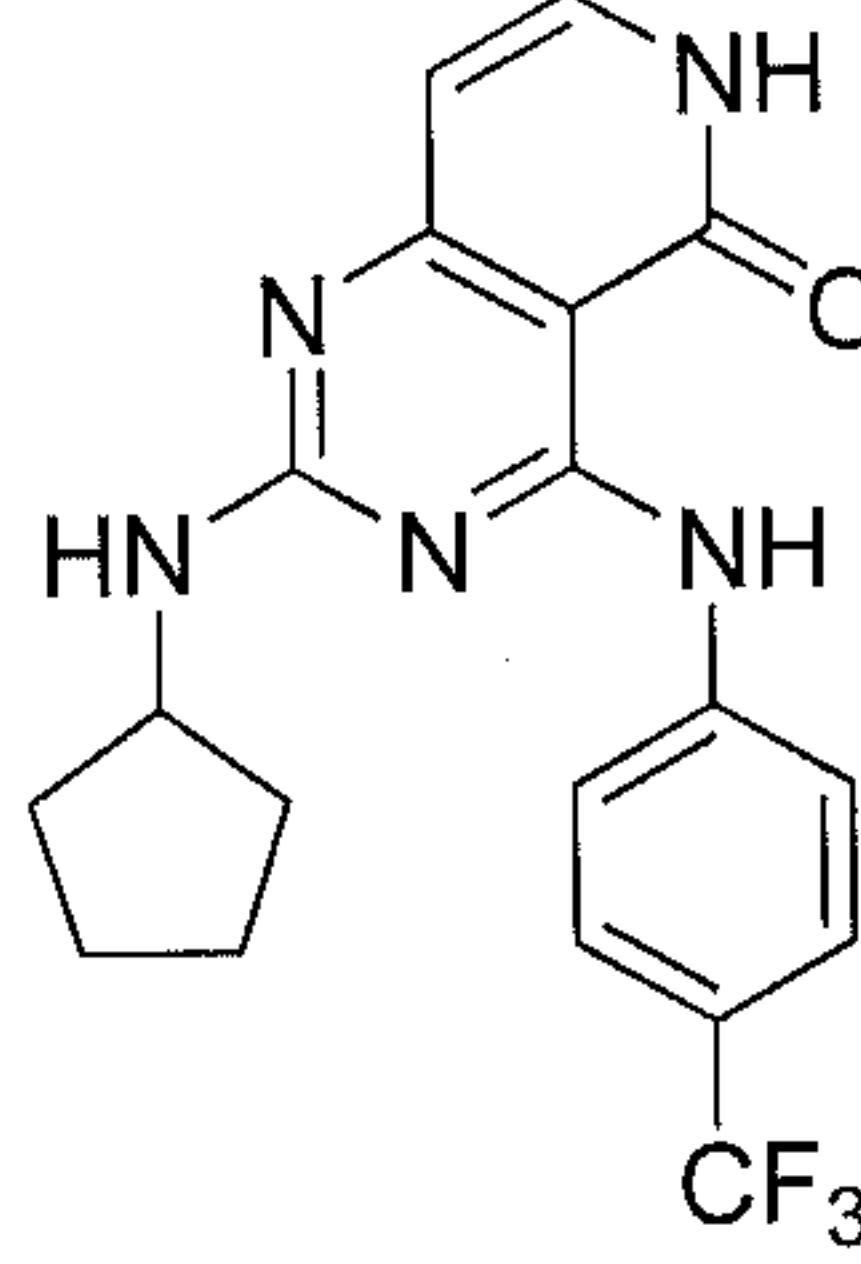
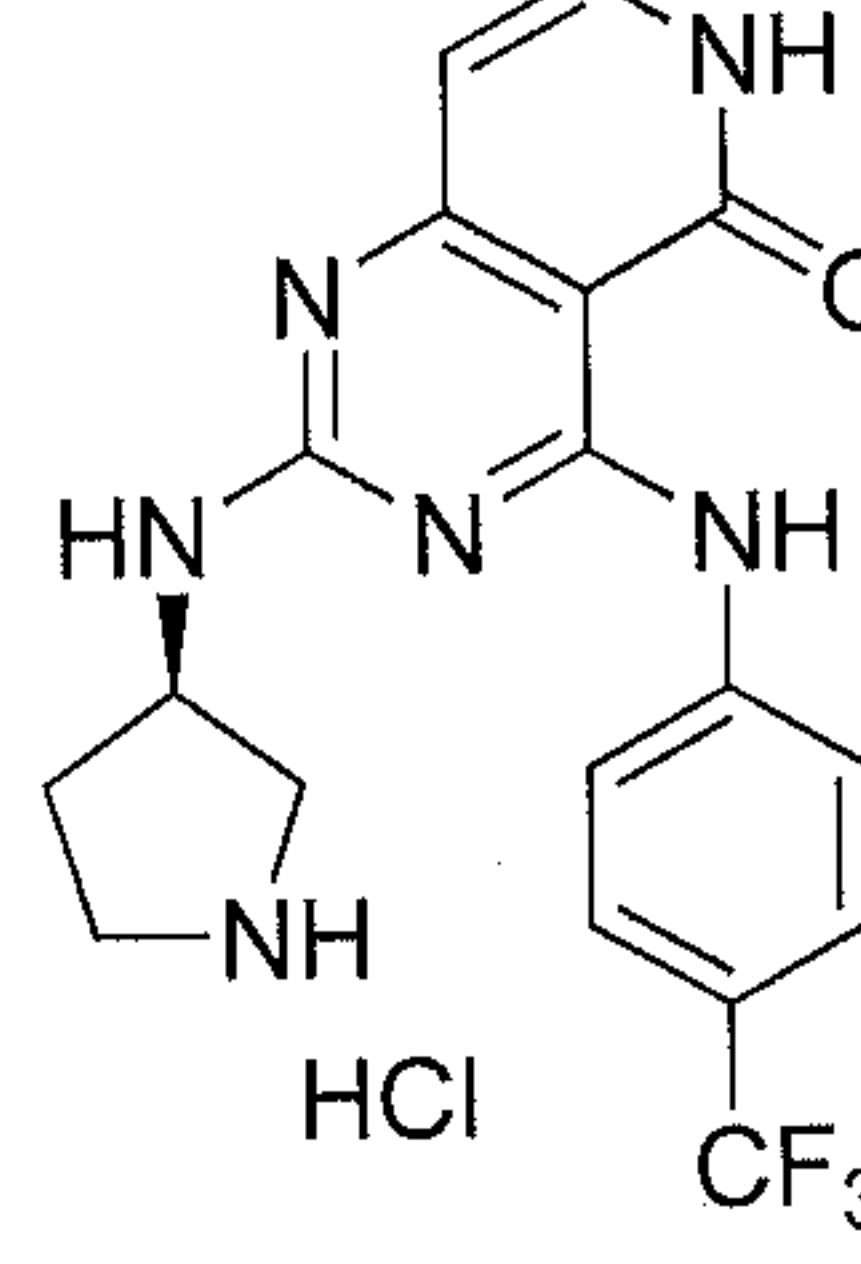
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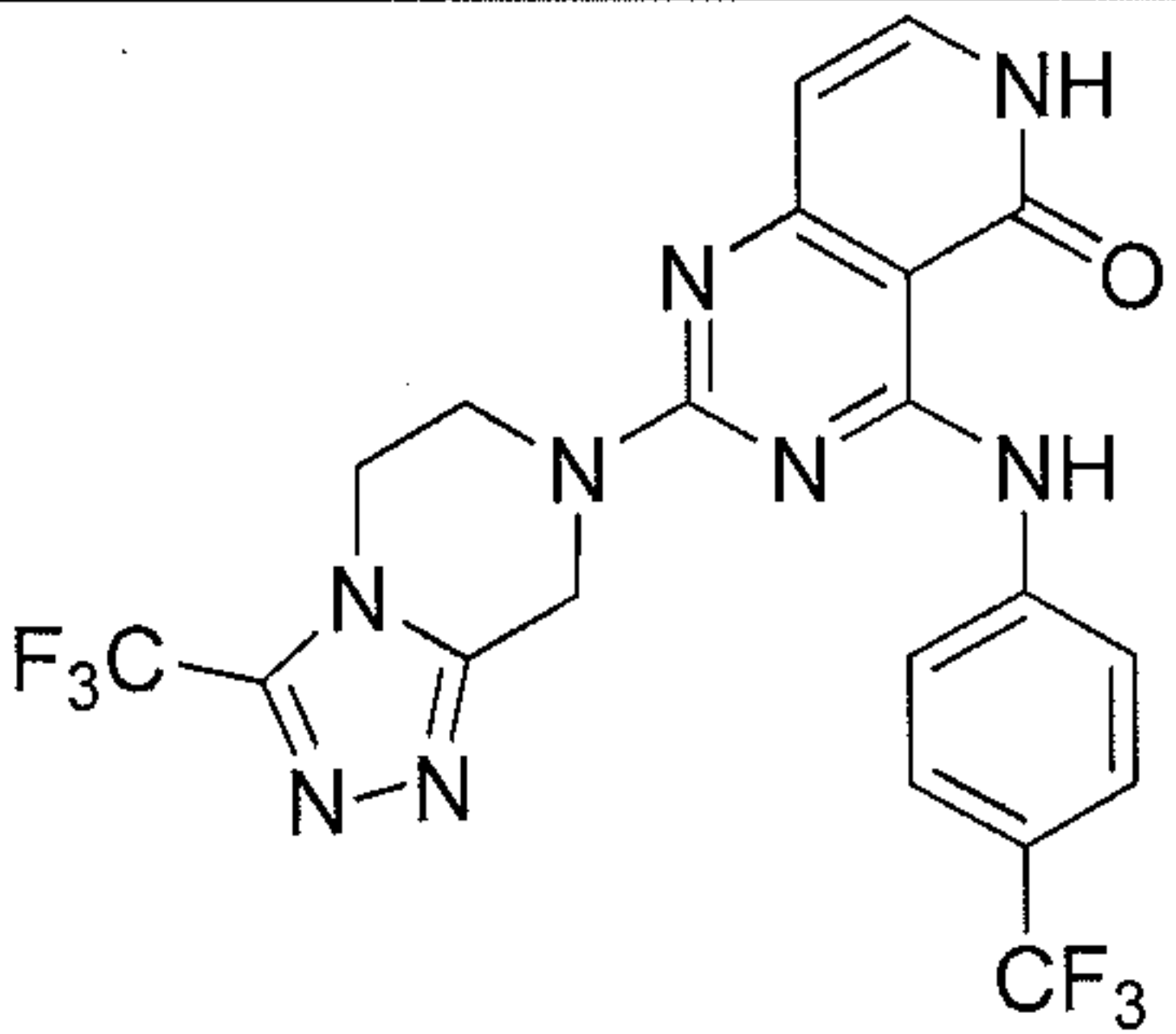
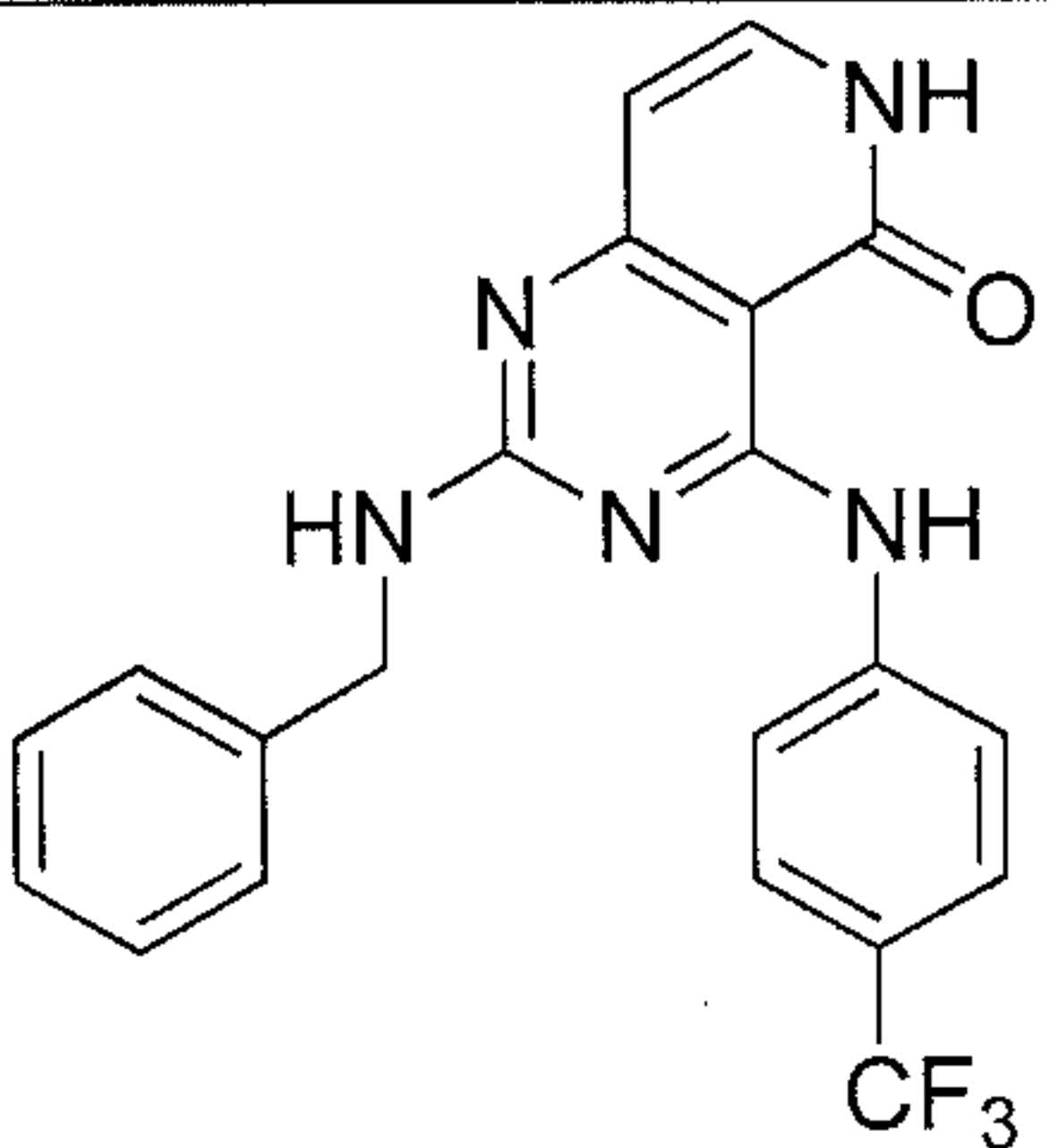
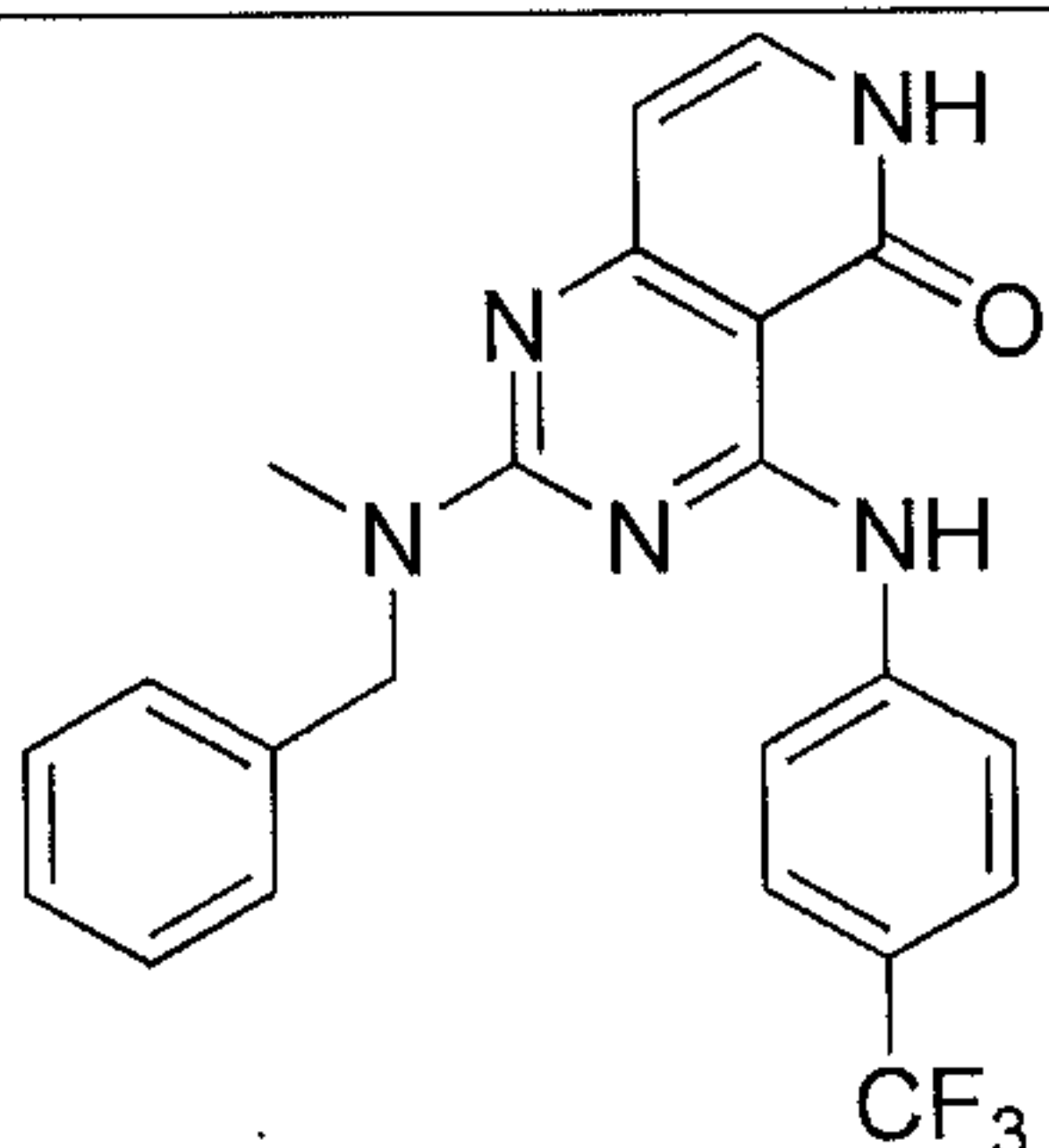
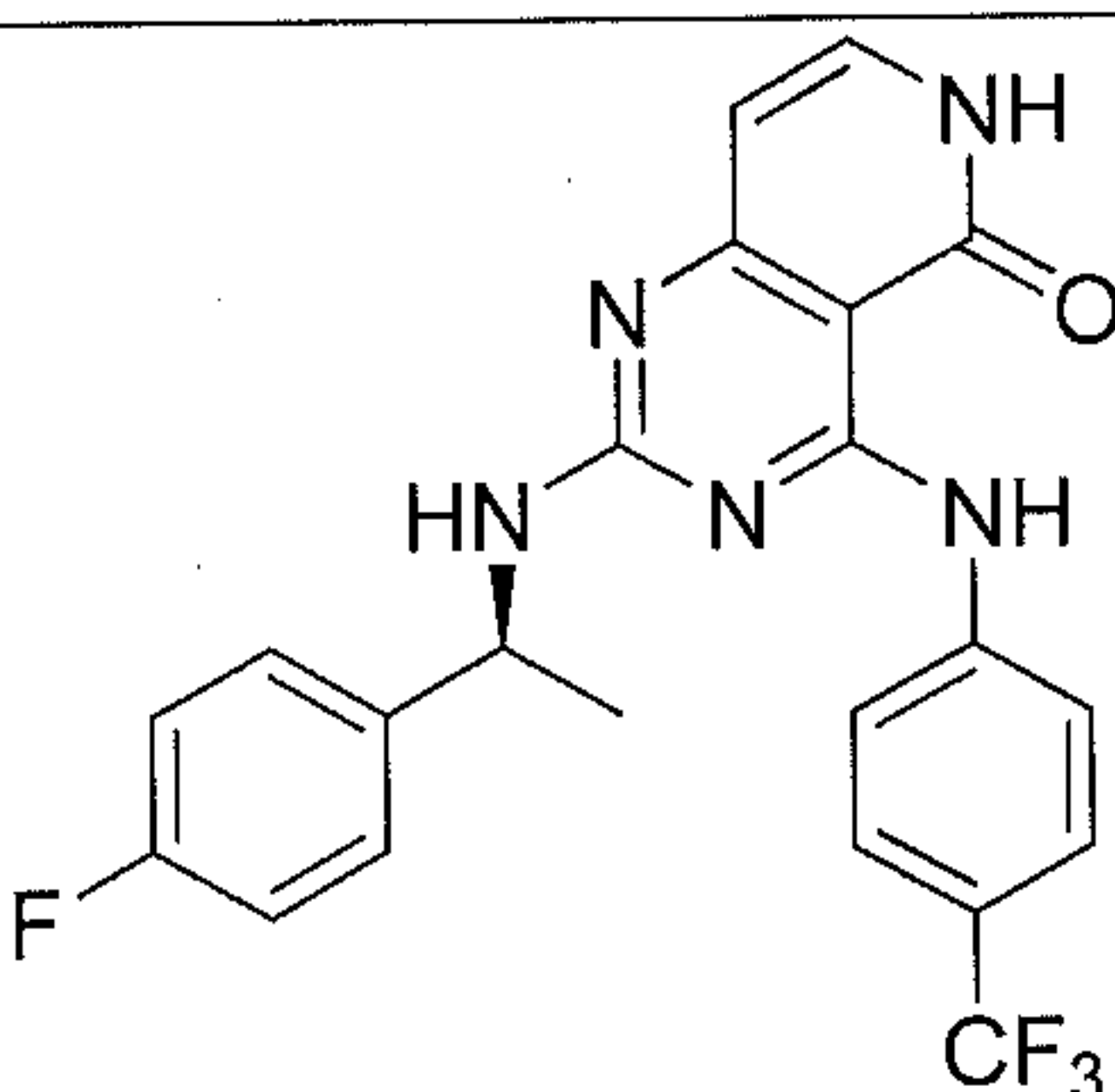
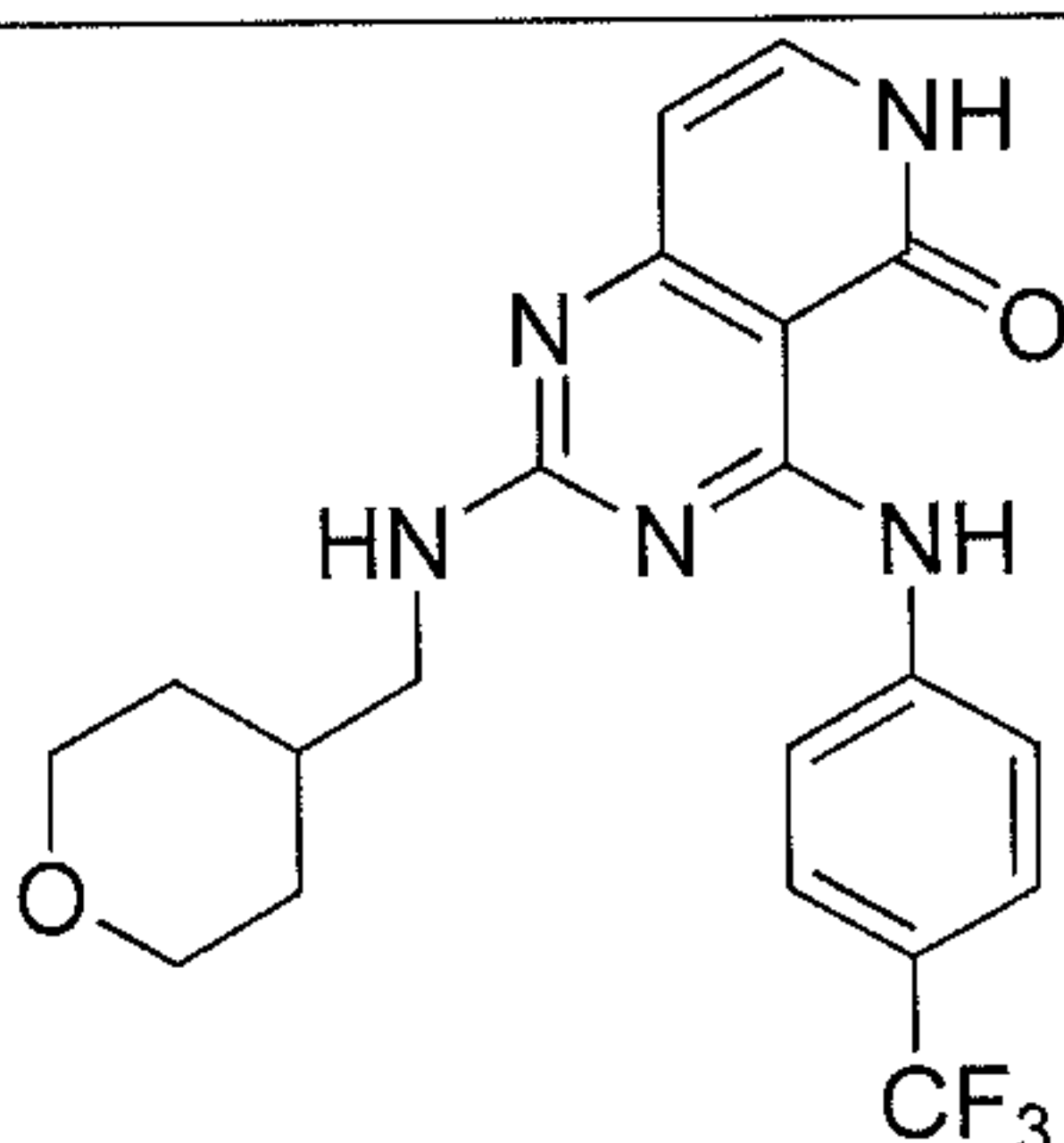
13		2-(3,4-dihydroisoquinolin-2(1H)-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	438
14		(<i>R</i>)-2-(3-hydroxypyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	392
15		2-(piperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	390
16		2-(4-aminopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	405
17		2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	405
18		2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.11 (s, 1H), 11.45 (br s, 1H), 8.54 (s, 1H), 7.68 (d, <i>J</i> = 6.30 Hz, 1H), 7.61~7.57	435

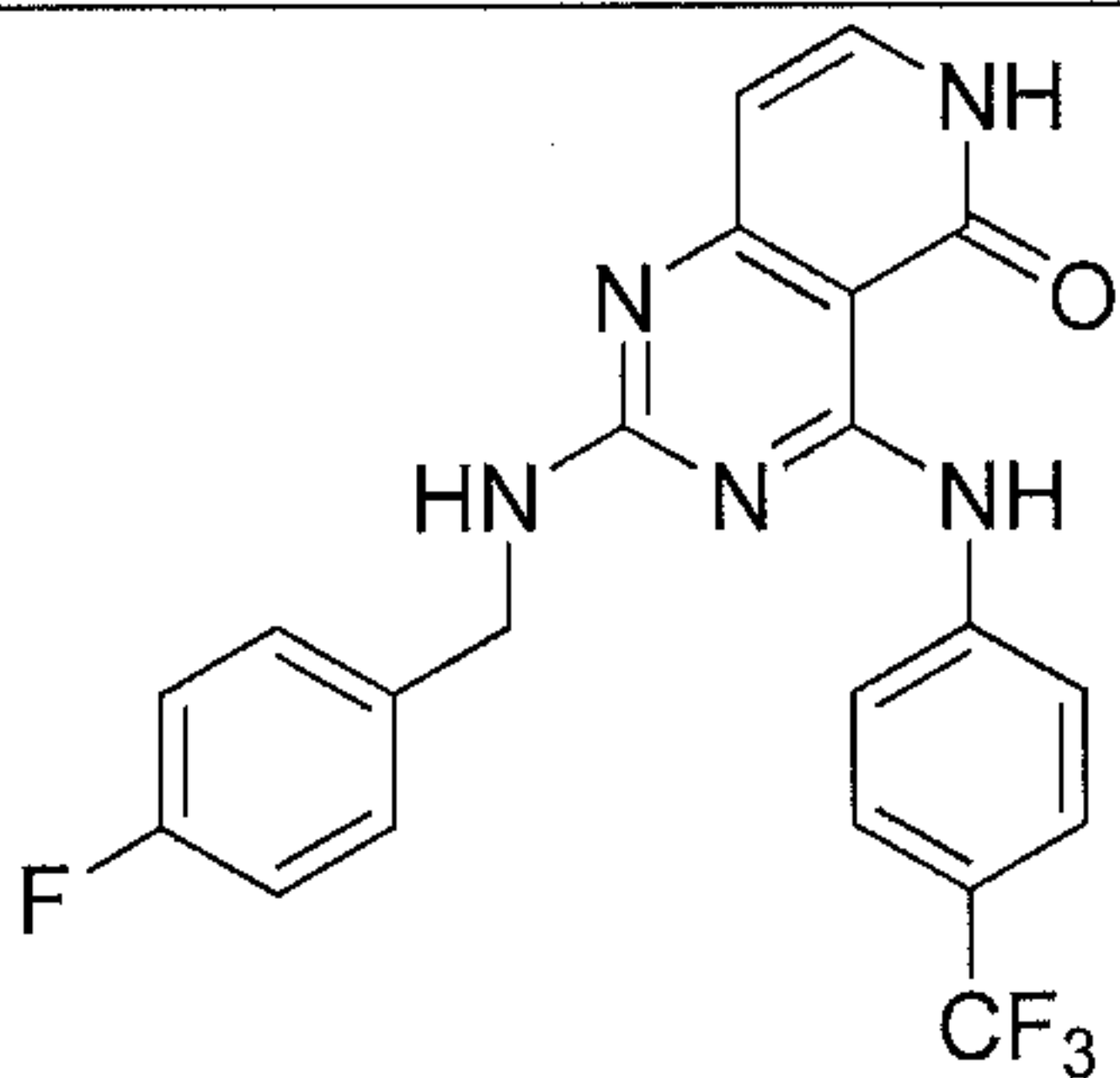
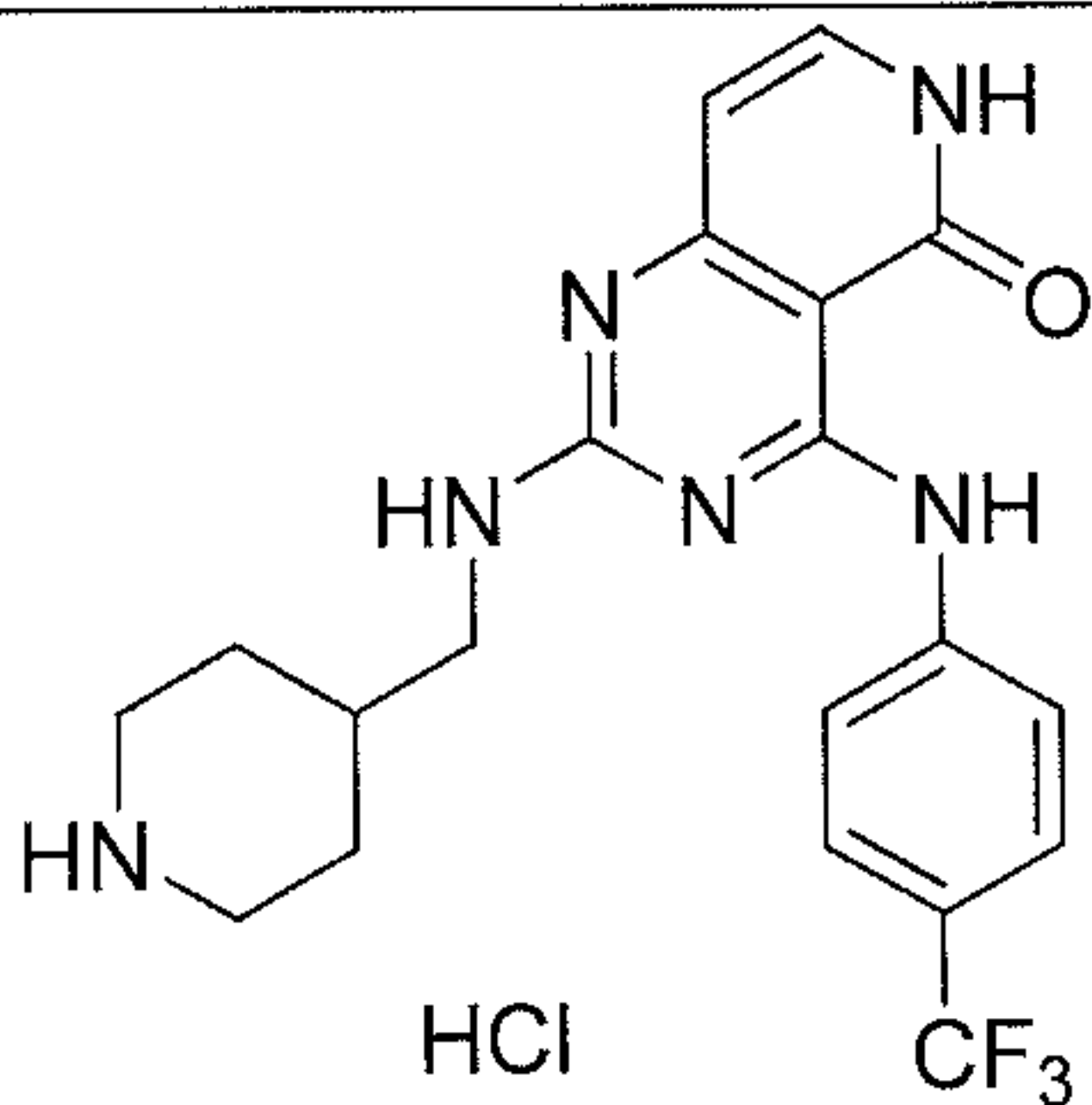
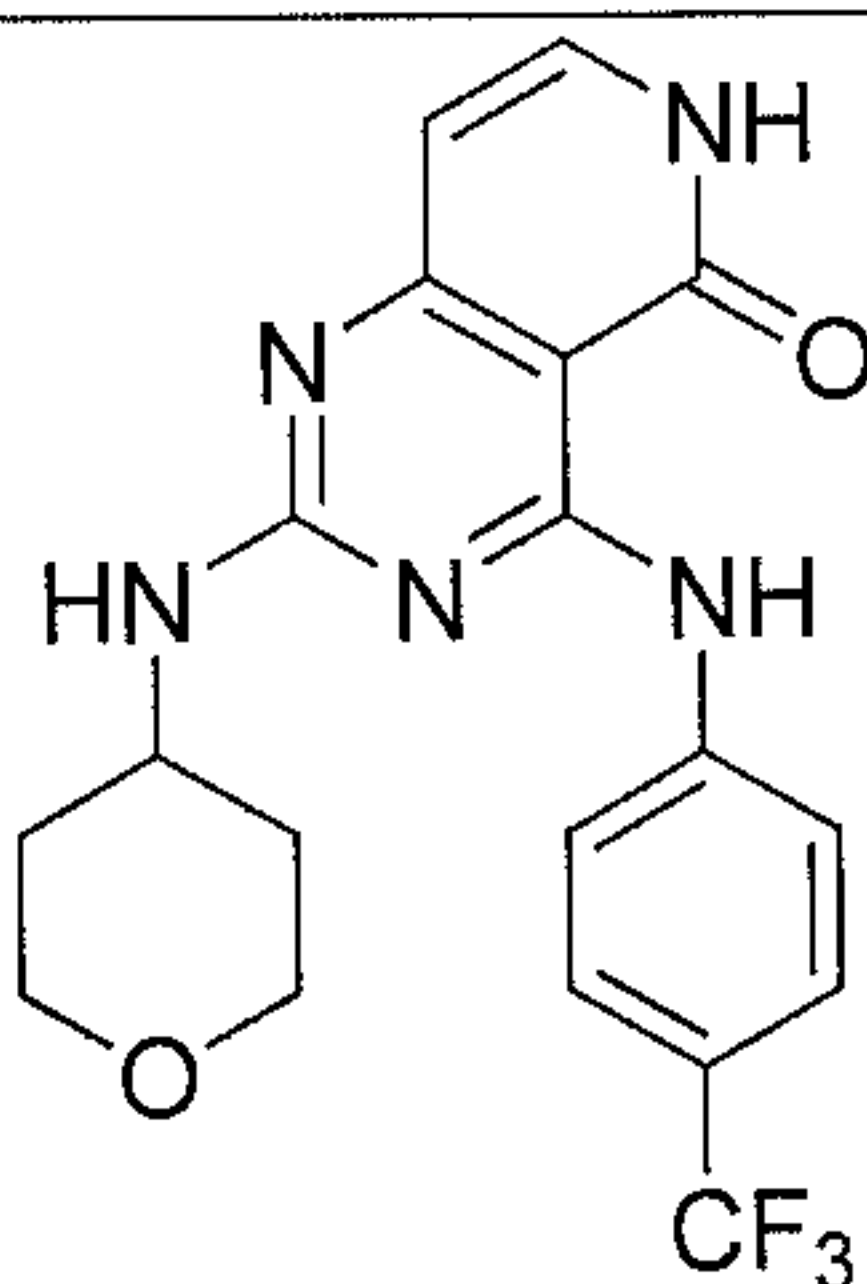
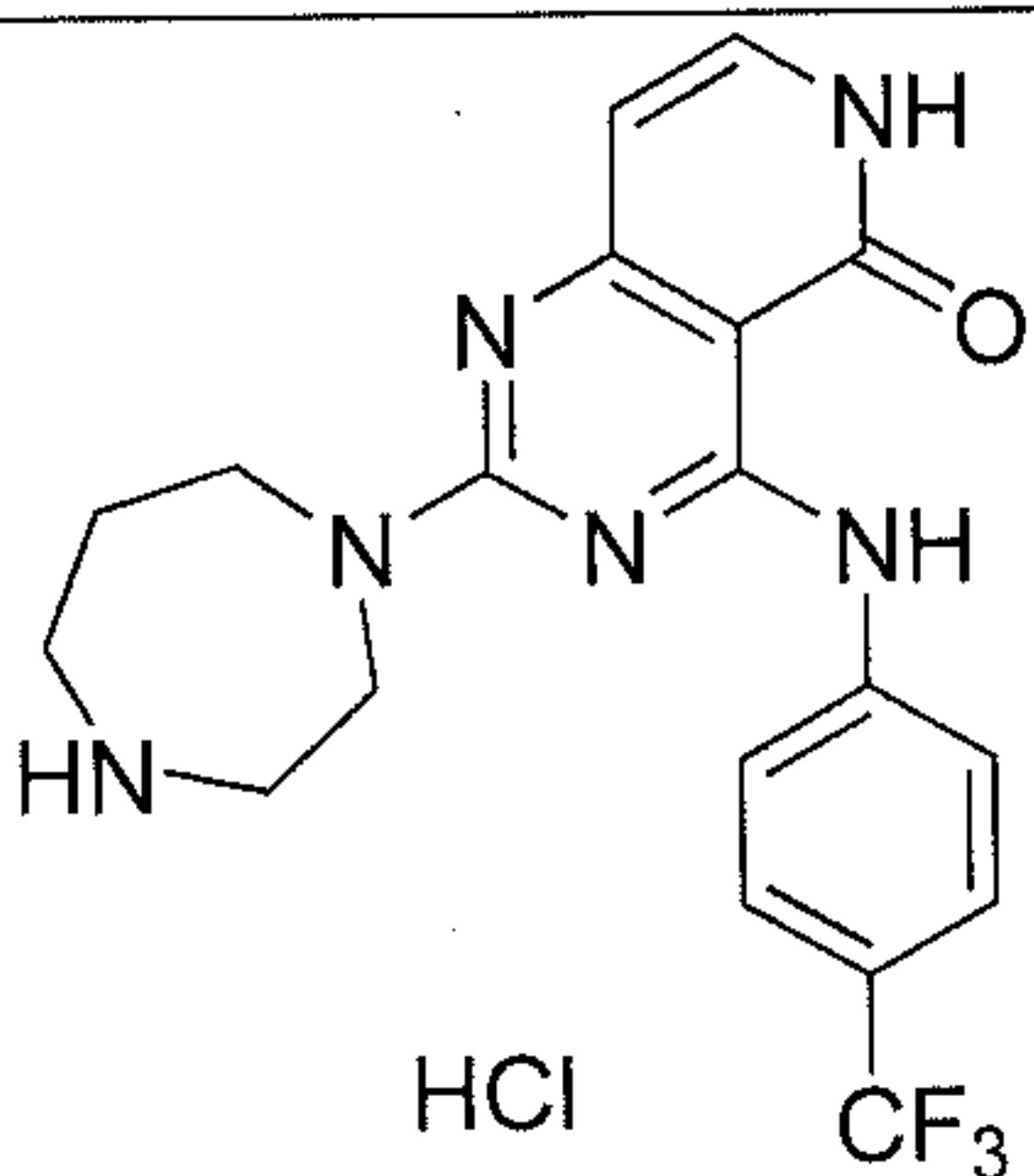
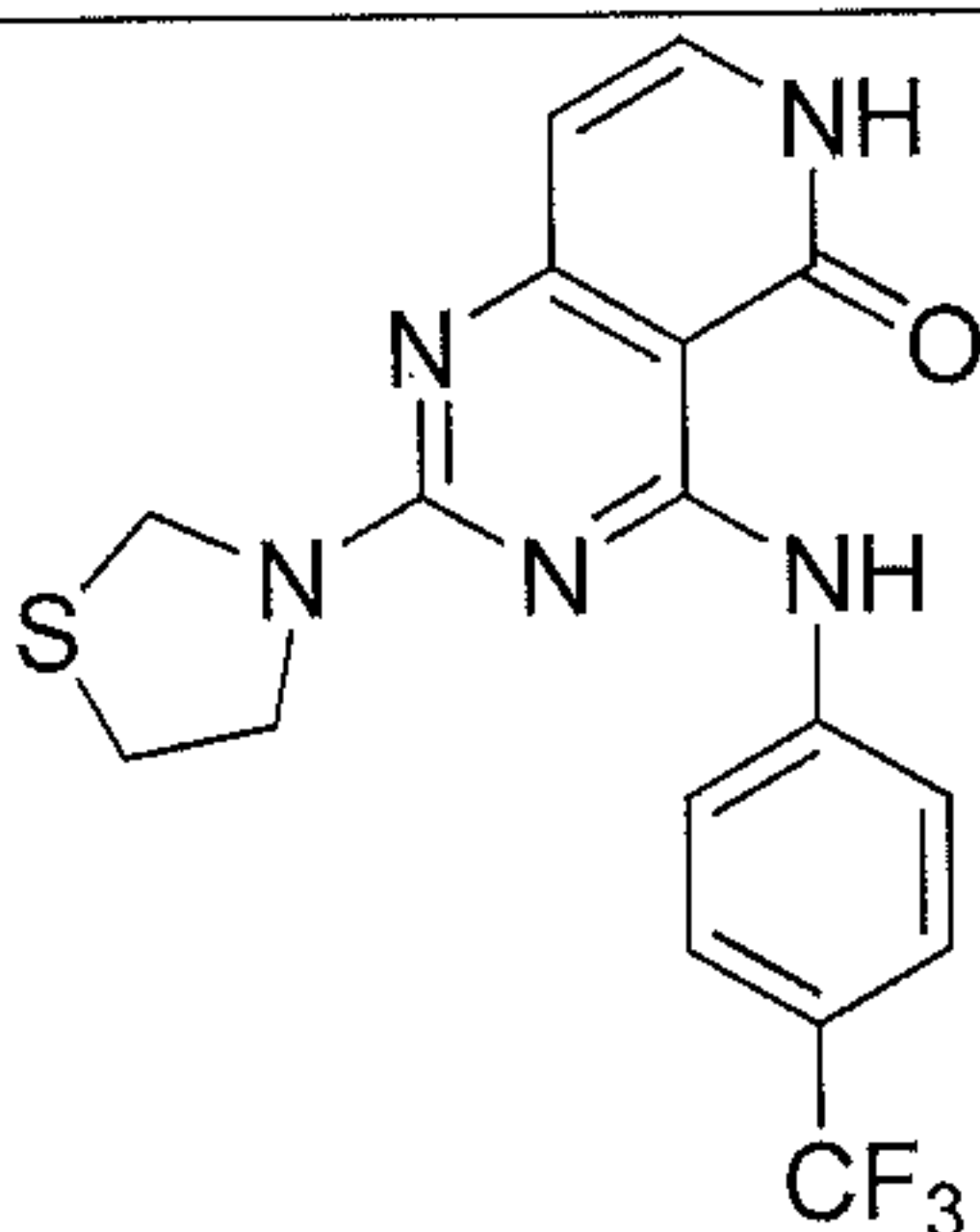
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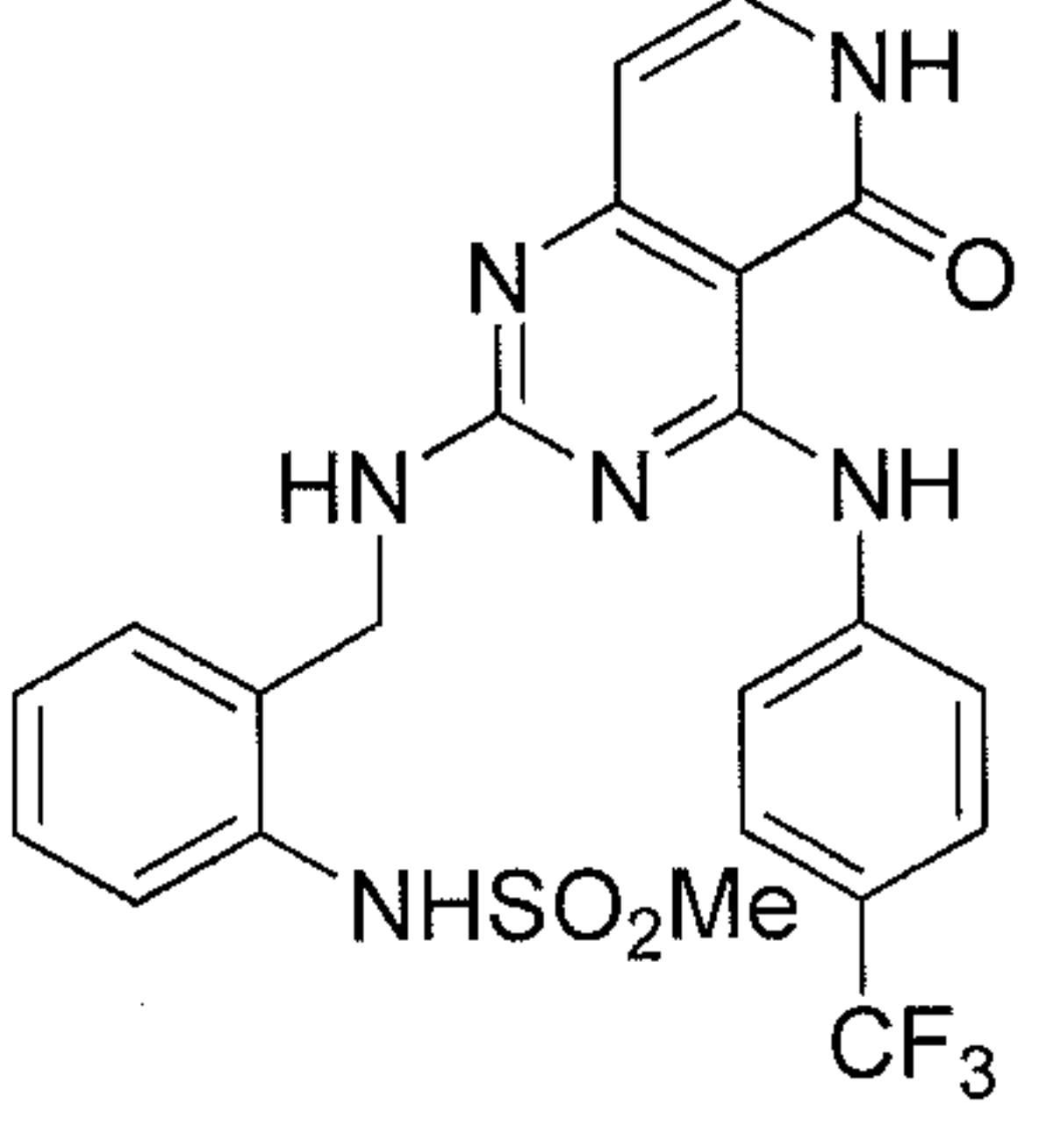
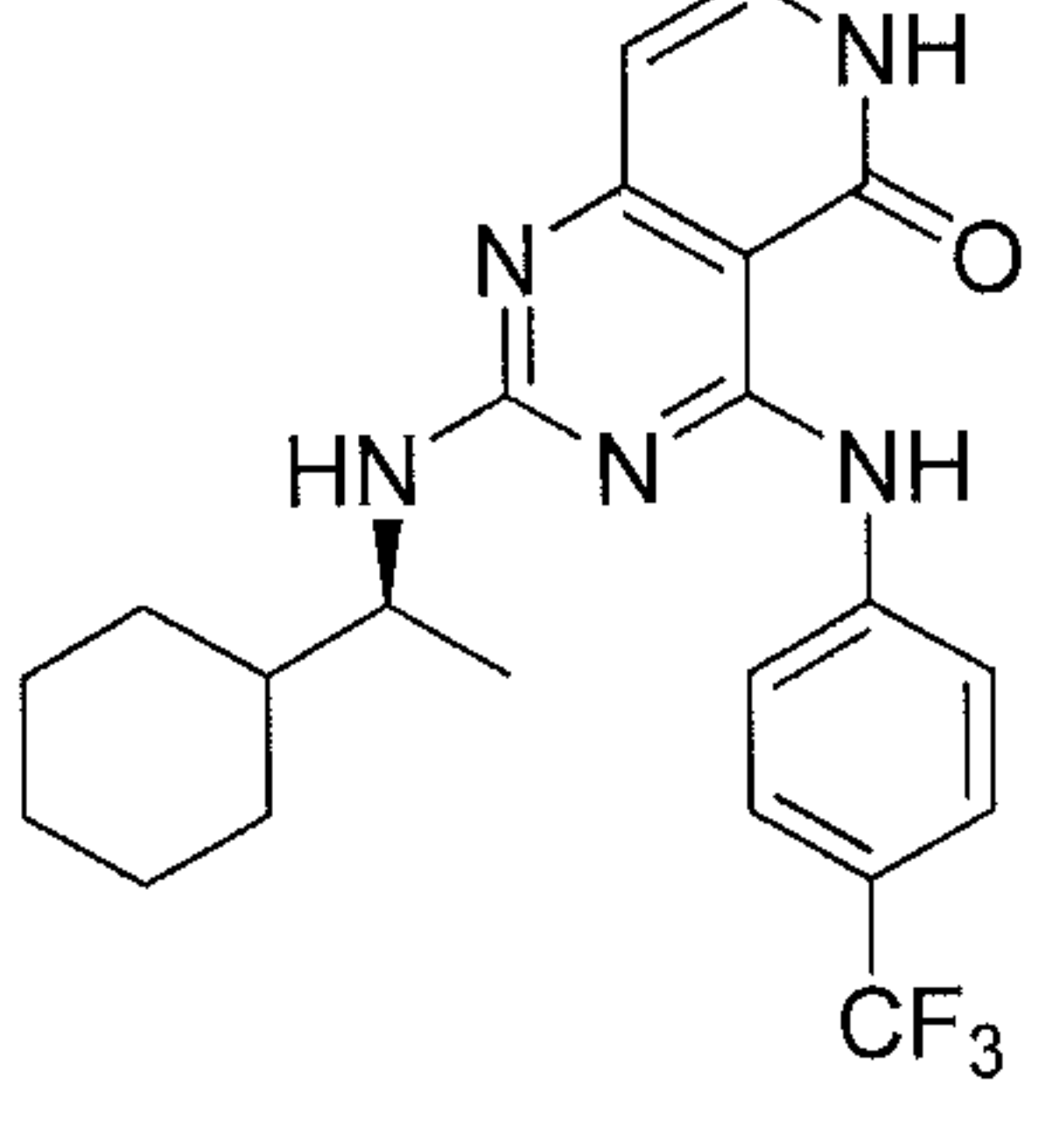
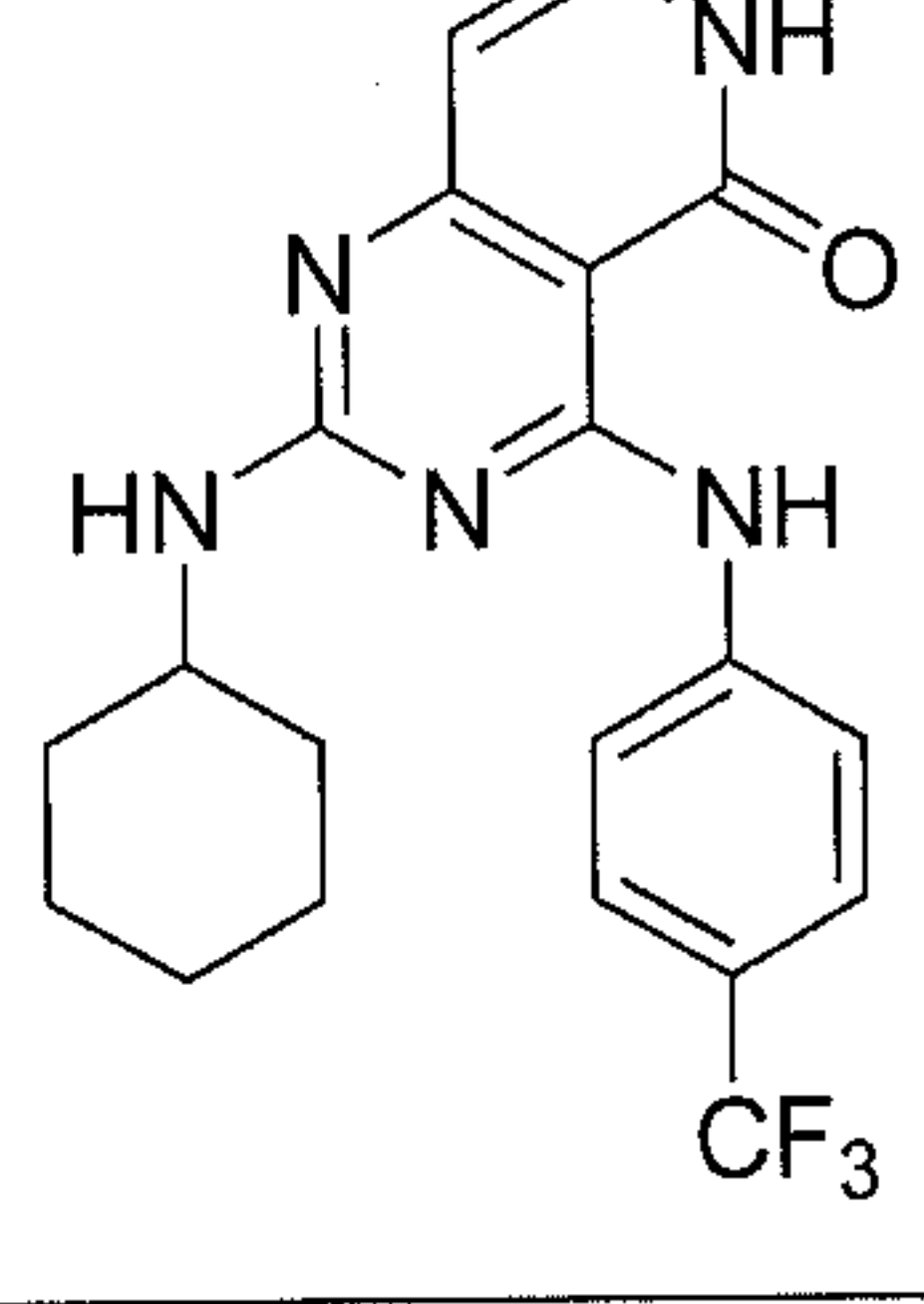
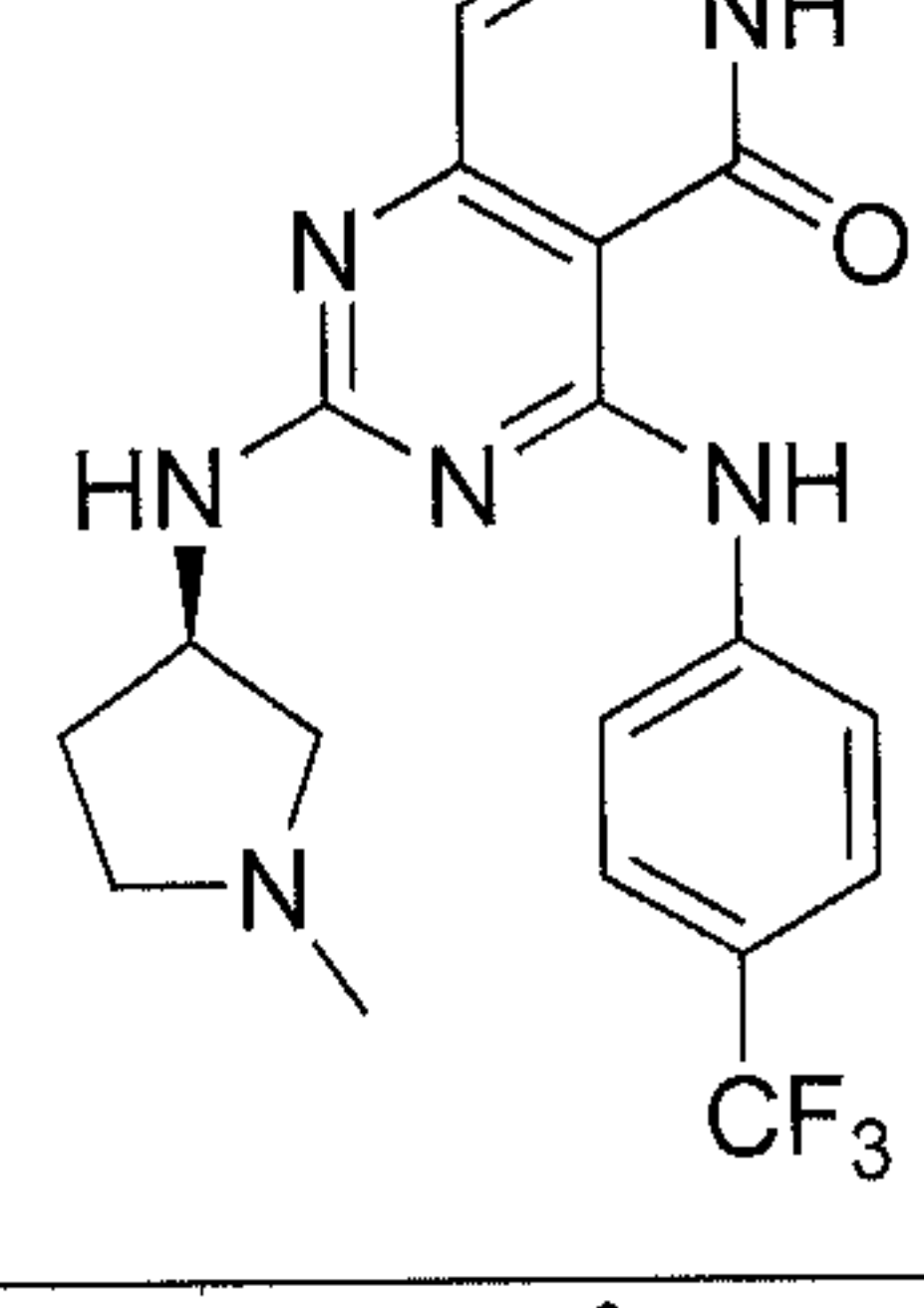
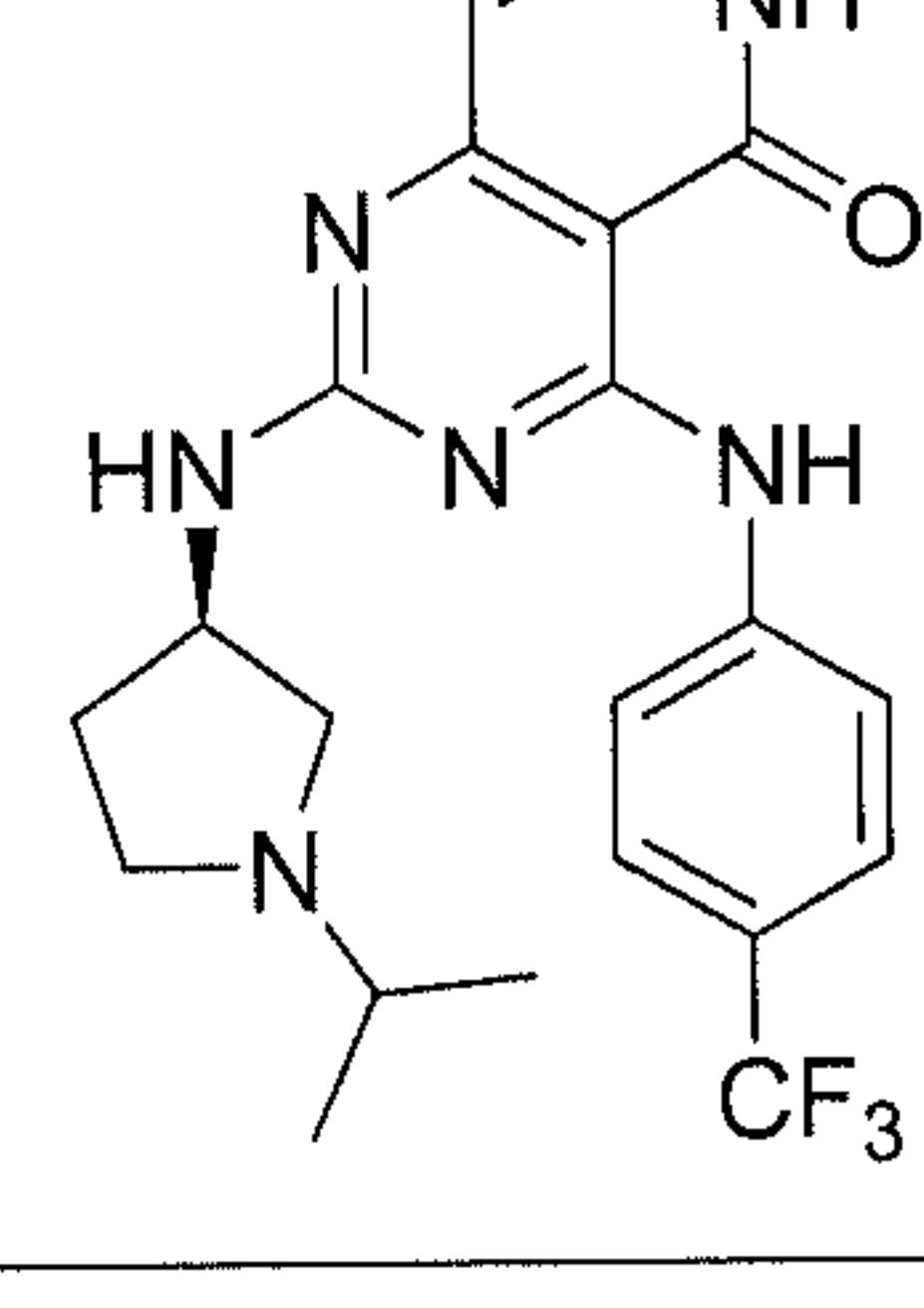
		(m, 1H), 7.43~7.40 (m, 2H), 6.17 (d, J = 5.40 Hz, 1H), 4.44 (s 1H), 3.81 (s, 4H), 3.55~3.47 (m, 4H), 2.45~2.39 (m, 4H)	
19		<i>N</i> -(2-((5-oxo-4-(3-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide 12.21 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.65~7.20 (m, 8H), 6.54 (d, J = 7.20 Hz, 1H), 3.06 (s, 2H), 2.89 (s, 3H)	505
20		(<i>S</i>)-2-(3-hydroxypyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	392
21		2-(4-aminopiperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	405
22		<i>N</i> -(1-(5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-yl)piperidin-4-yl)cyclopropanesulfonamide	509

23		2-(piperidin-4-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	405
24		(<i>S</i>)-2-(3-aminopyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	391
25		2-morpholino-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	392
26		2-((1 <i>R</i> ,4 <i>R</i>)-4-hydroxycyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	420
27		2-(4-oxopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	404

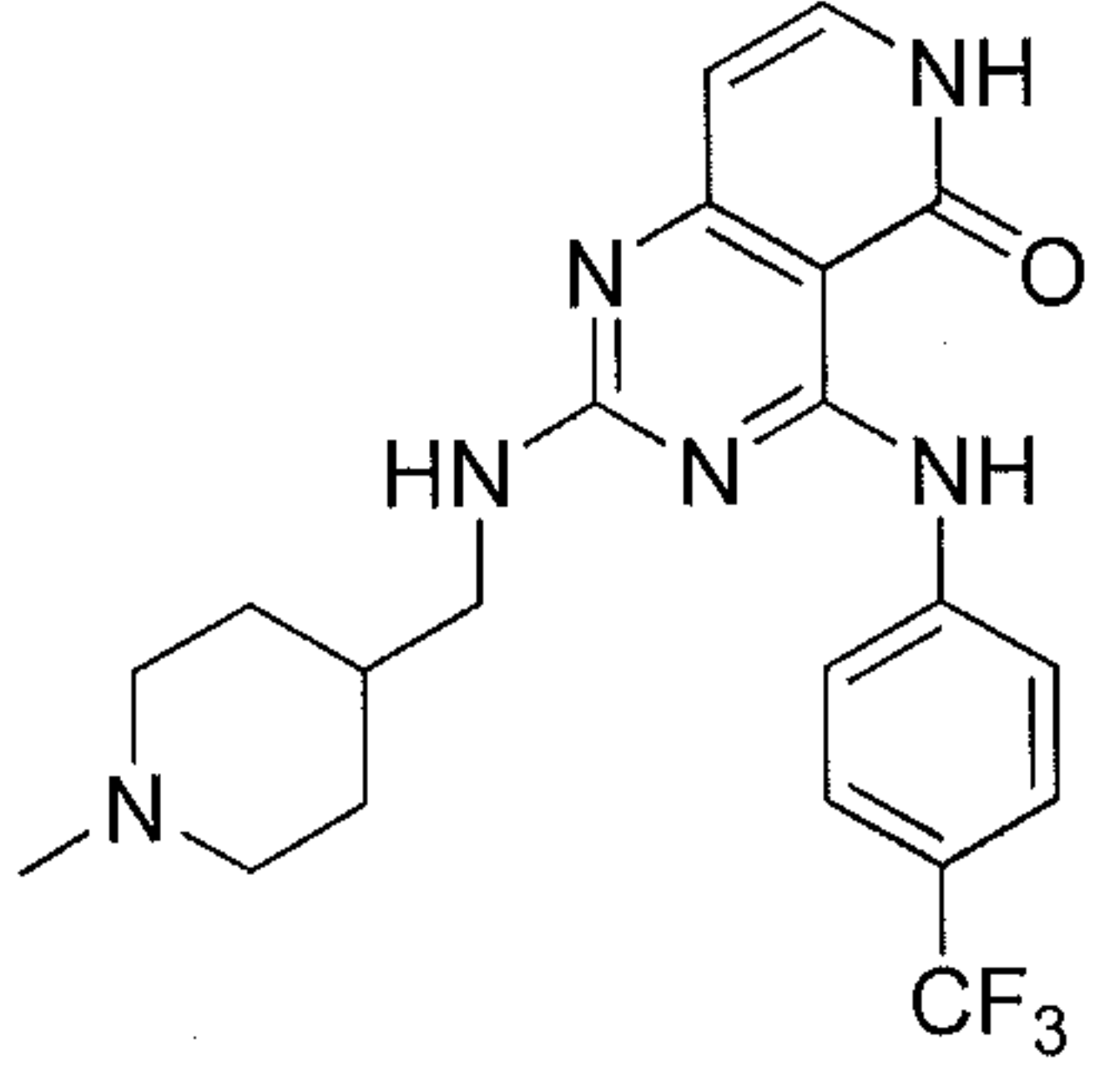
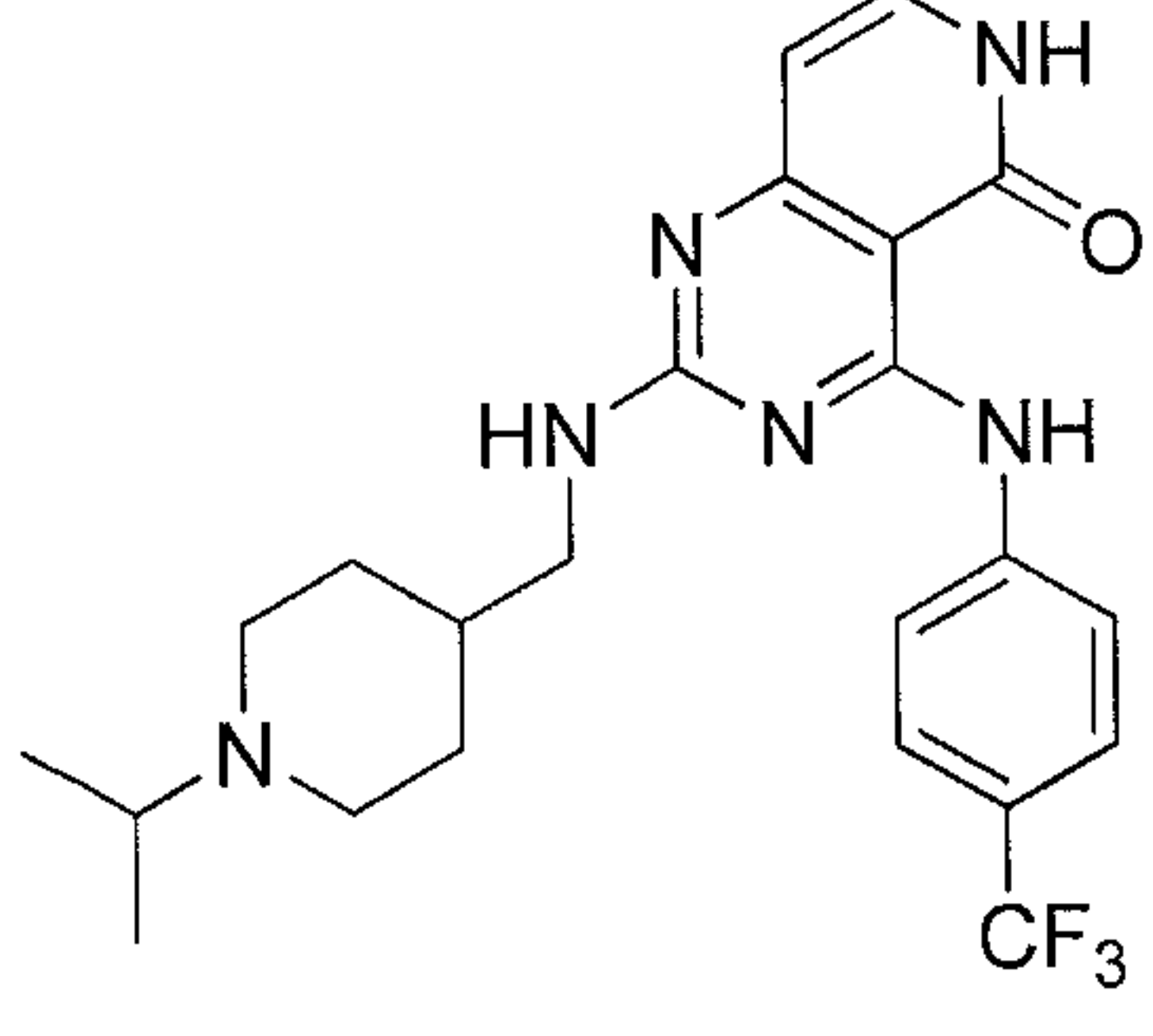
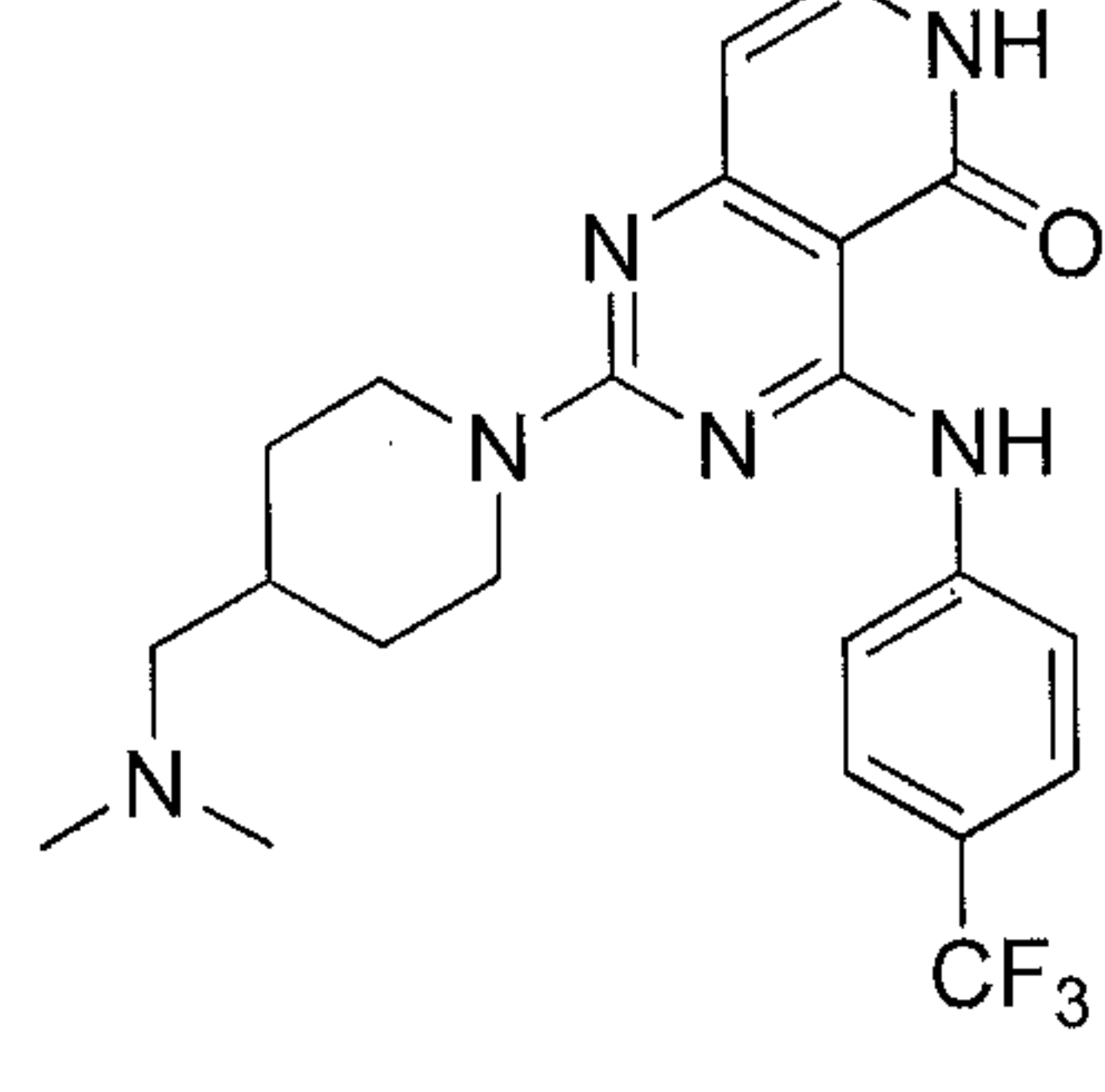
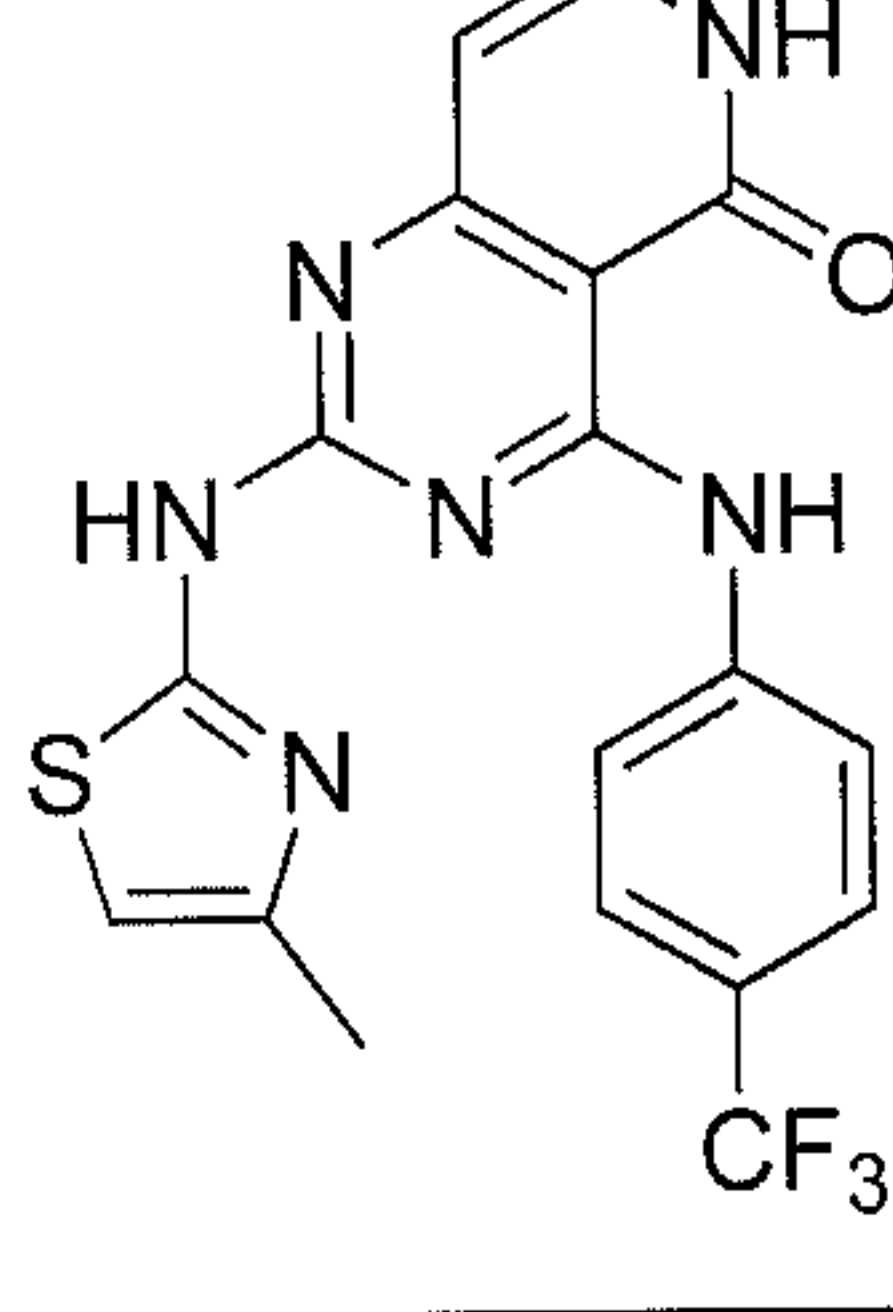
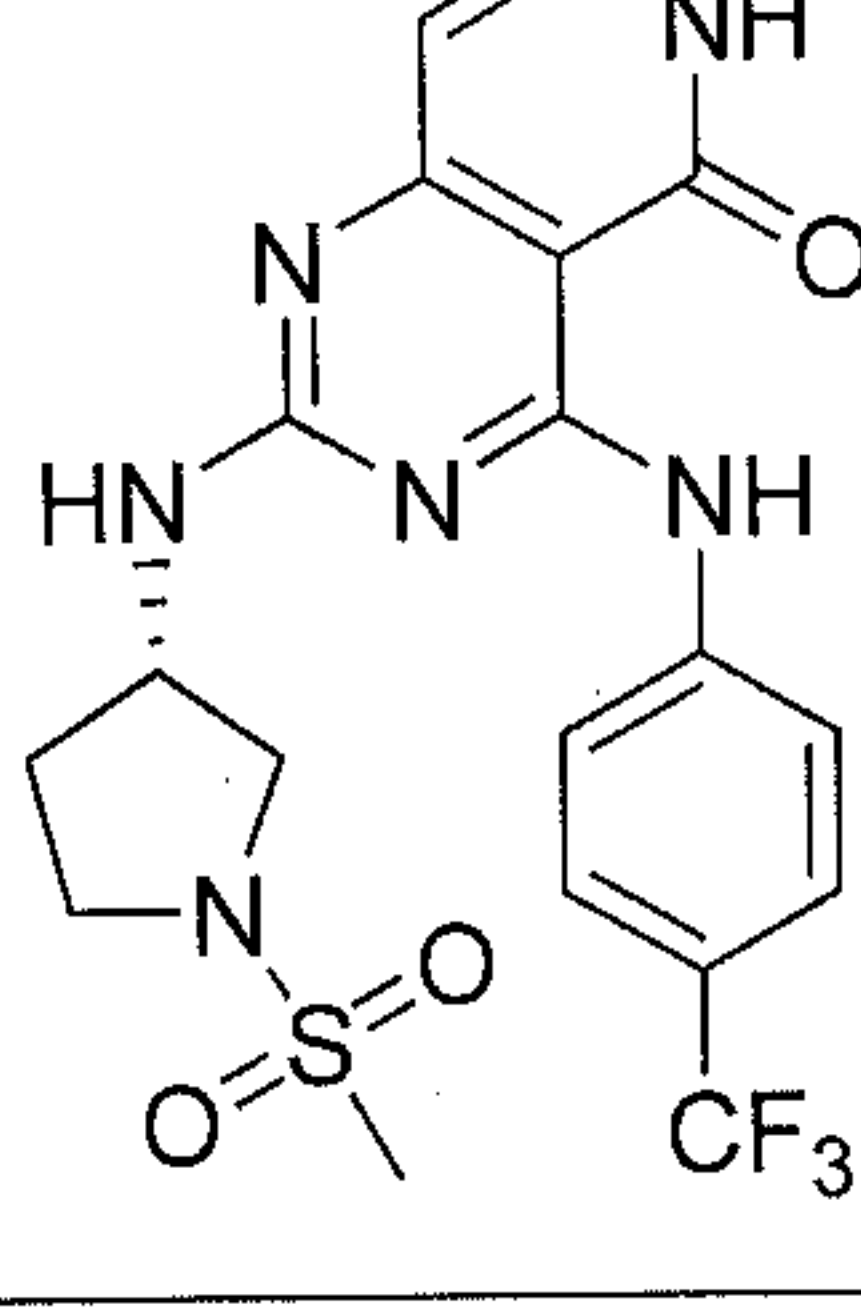
28		2-(3,4-dihydroisoquinolin-2(<i>1H</i>)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	438
29		2-(3-(3-(trifluoromethyl)phenyl)-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	573
30		2-(cyclopropylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	362
31		2-(cyclopentylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	390
32		(<i>R</i>)-2-(pyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	391

33		2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrazin-7(8 <i>H</i>)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	497
34		2-(benzylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	412
35		2-(benzyl(methyl)amino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	426
36		(<i>S</i>)-2-(1-(4-fluorophenyl)ethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	444
37		2-(((tetrahydro-2 <i>H</i> -pyran-4-yl)methyl)amino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	420

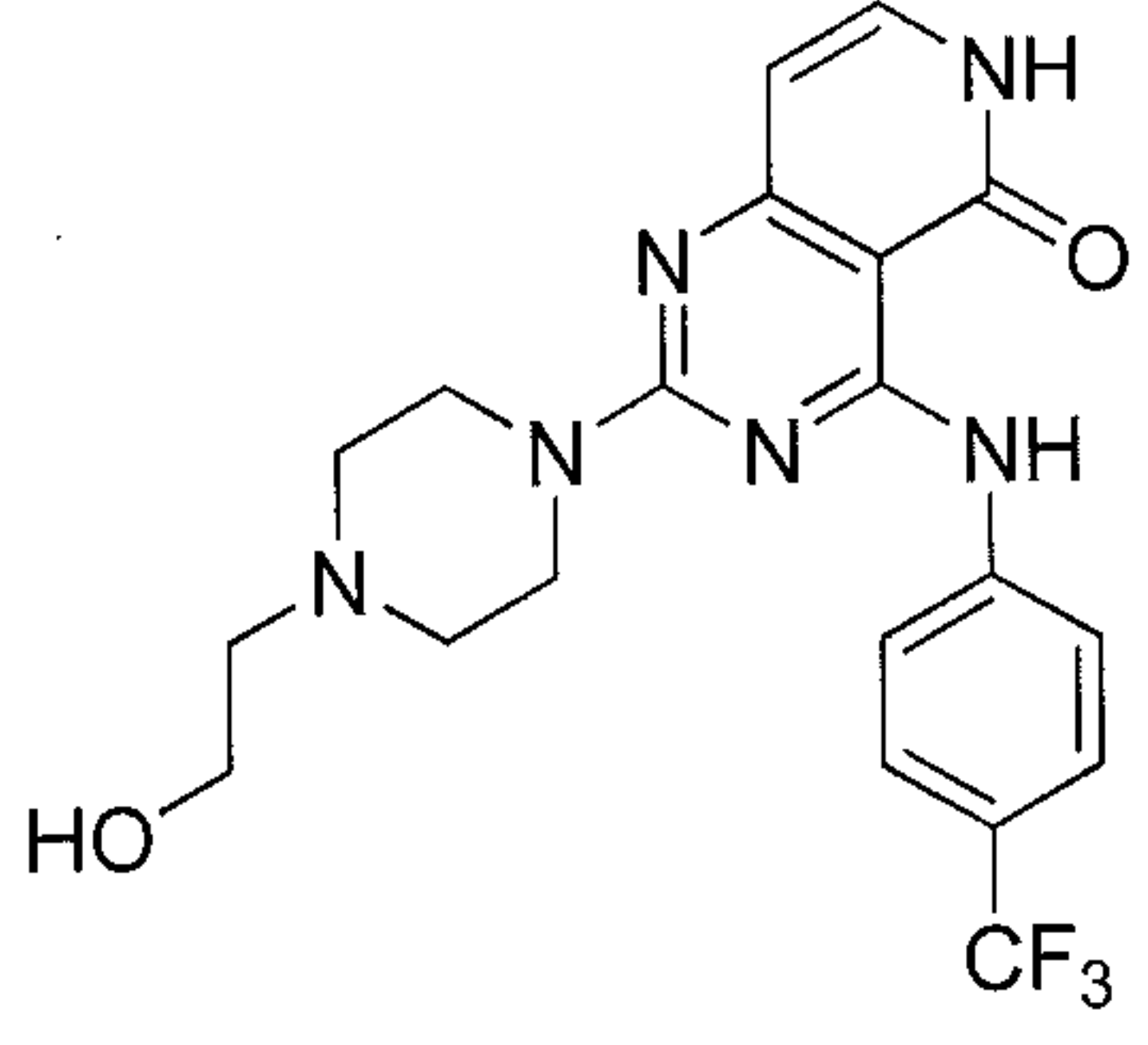
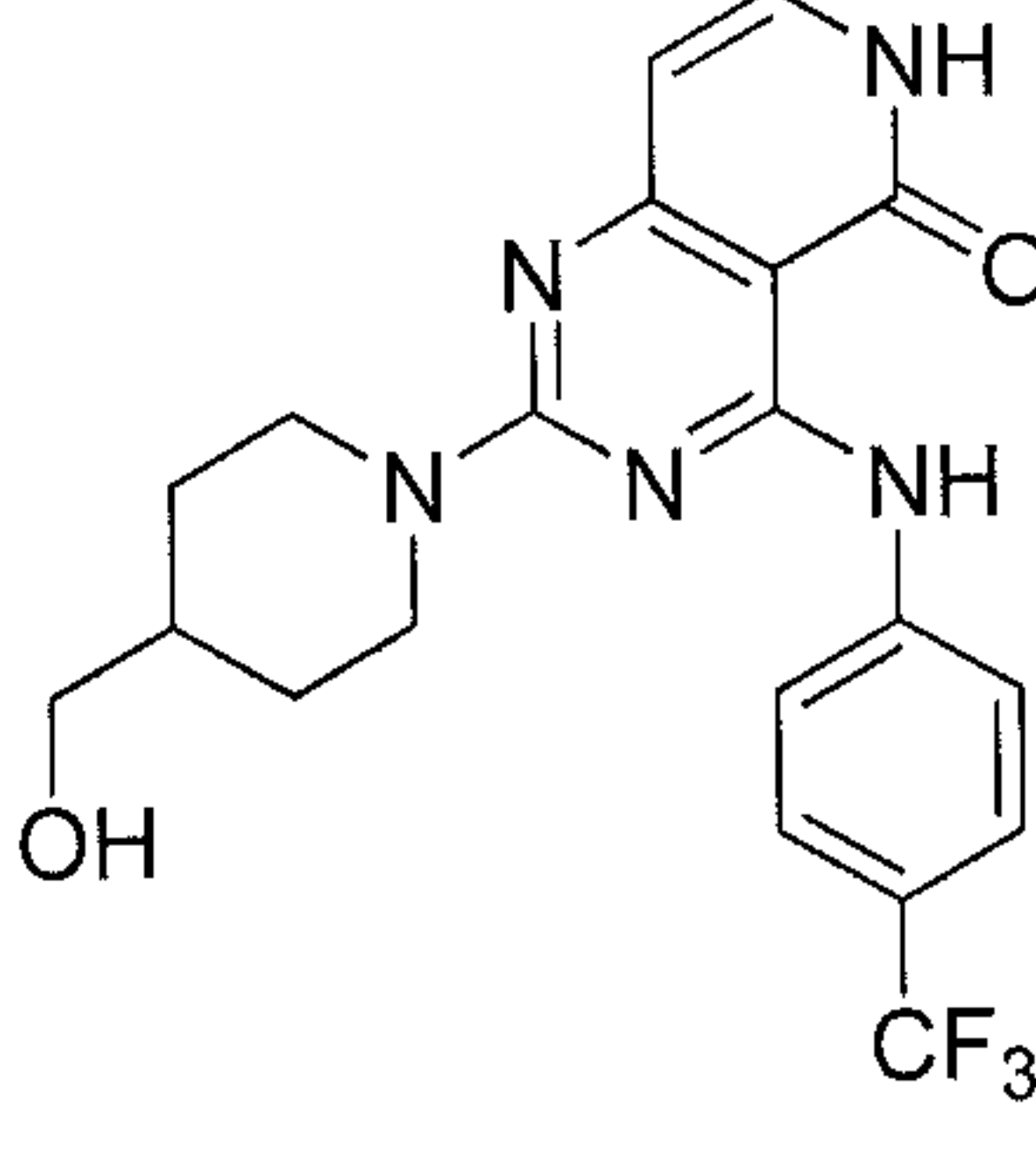
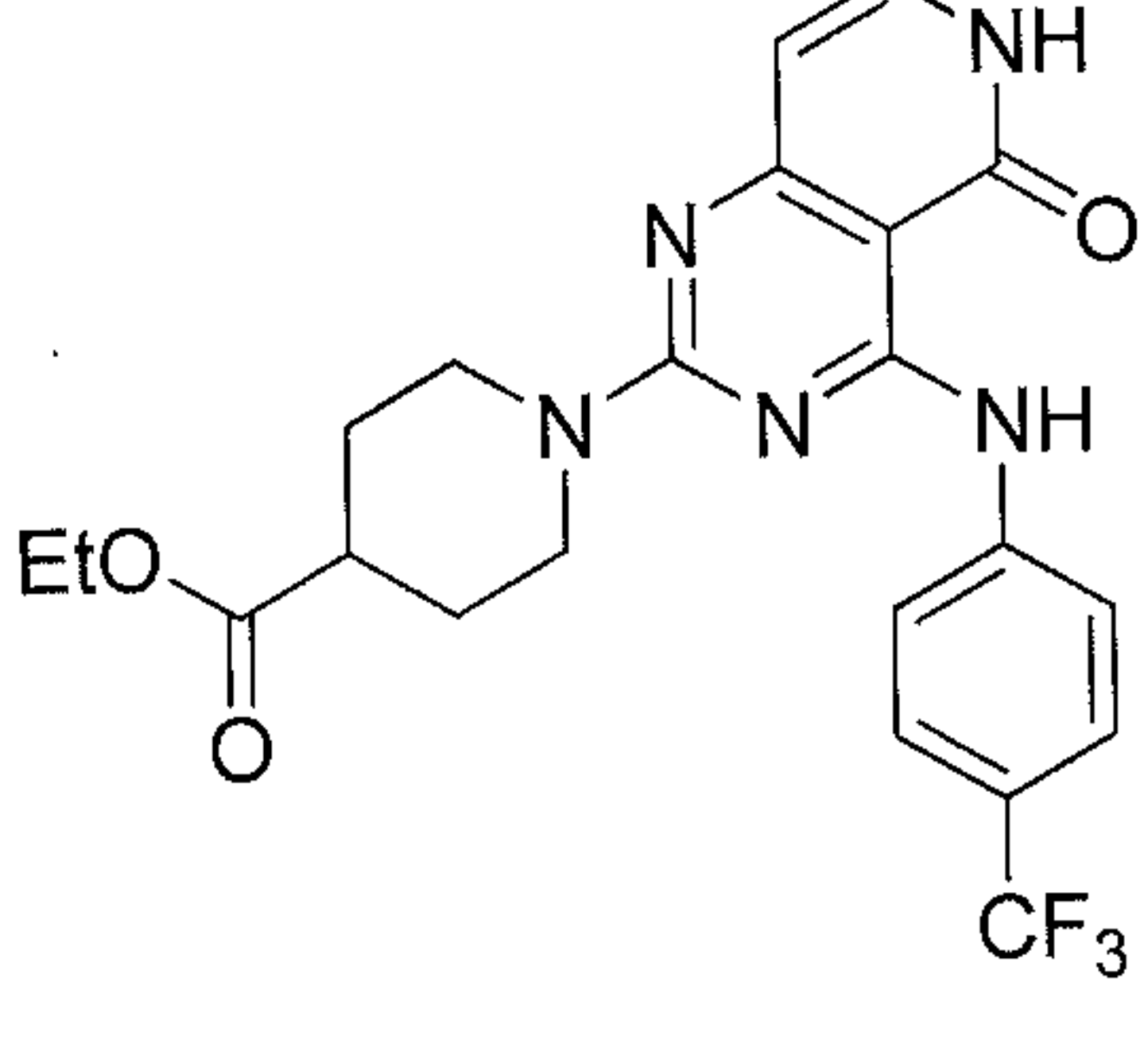
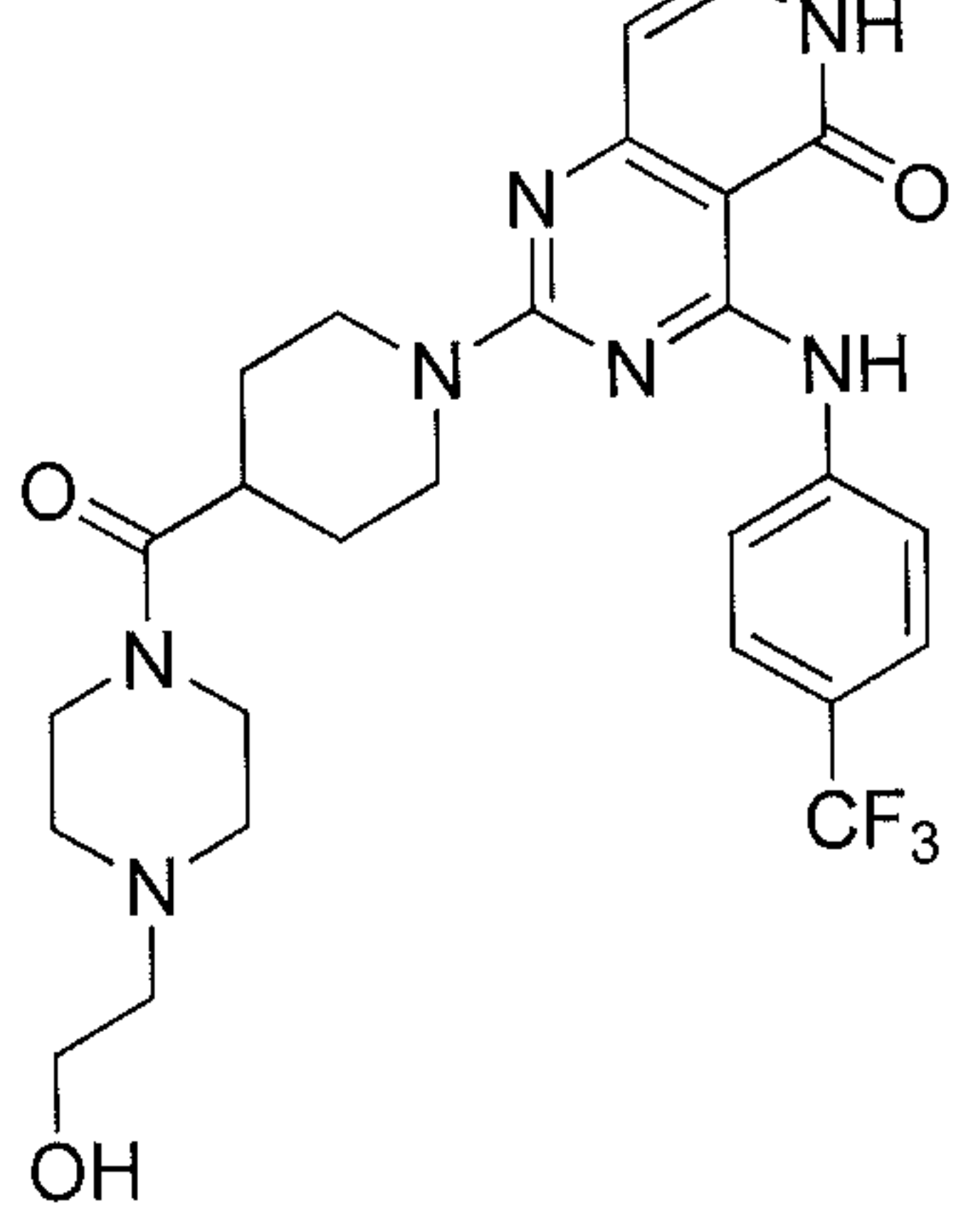
38		2-(4-fluorobenzylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	430
39		2-(piperidin-4-ylmethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	419
40		2-(tetrahydro-2 <i>H</i> -pyran-4-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	406
41		2-(1,4-diazepan-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	405
42		2-(thiazolidin-3-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	394

43		<i>N</i> -(2-((5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide	505
44		(<i>S</i>)-2-(1-cyclohexylethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	432
45		2-(cyclohexylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	404
46		(<i>R</i>)-2-(1-methylpyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	405
47		(<i>R</i>)-2-(1-isopropylpyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	433

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48		2-((1-methylpiperidin-4-yl)methylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	433
49		2-((1-isopropylpiperidin-4-yl)methylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	461
50		2-(4-((dimethylamino)methyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	447
51		2-(4-methylthiazol-2-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	419
52		(<i>S</i>)-2-(1-(methylsulfonyl)pyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	469

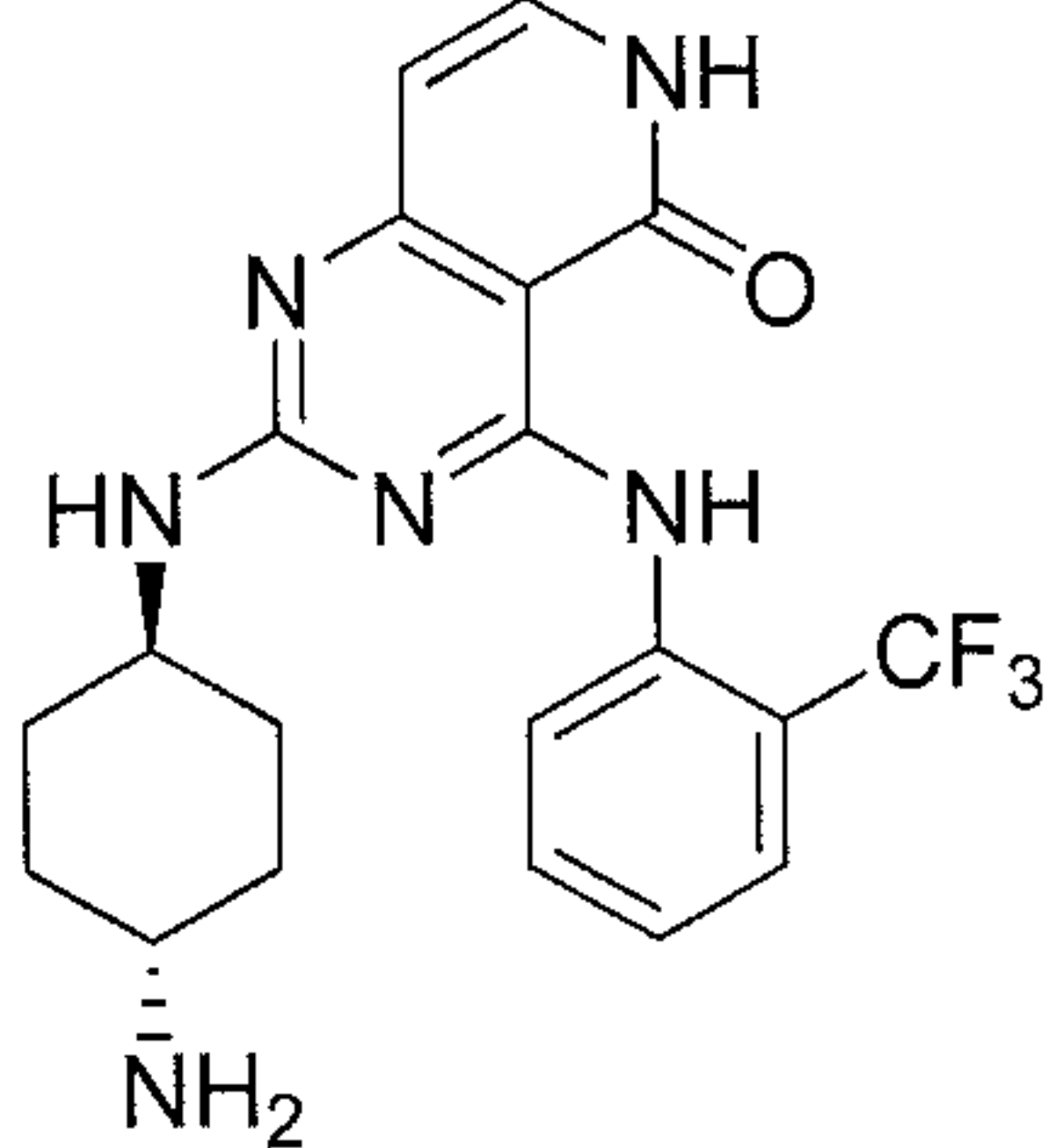
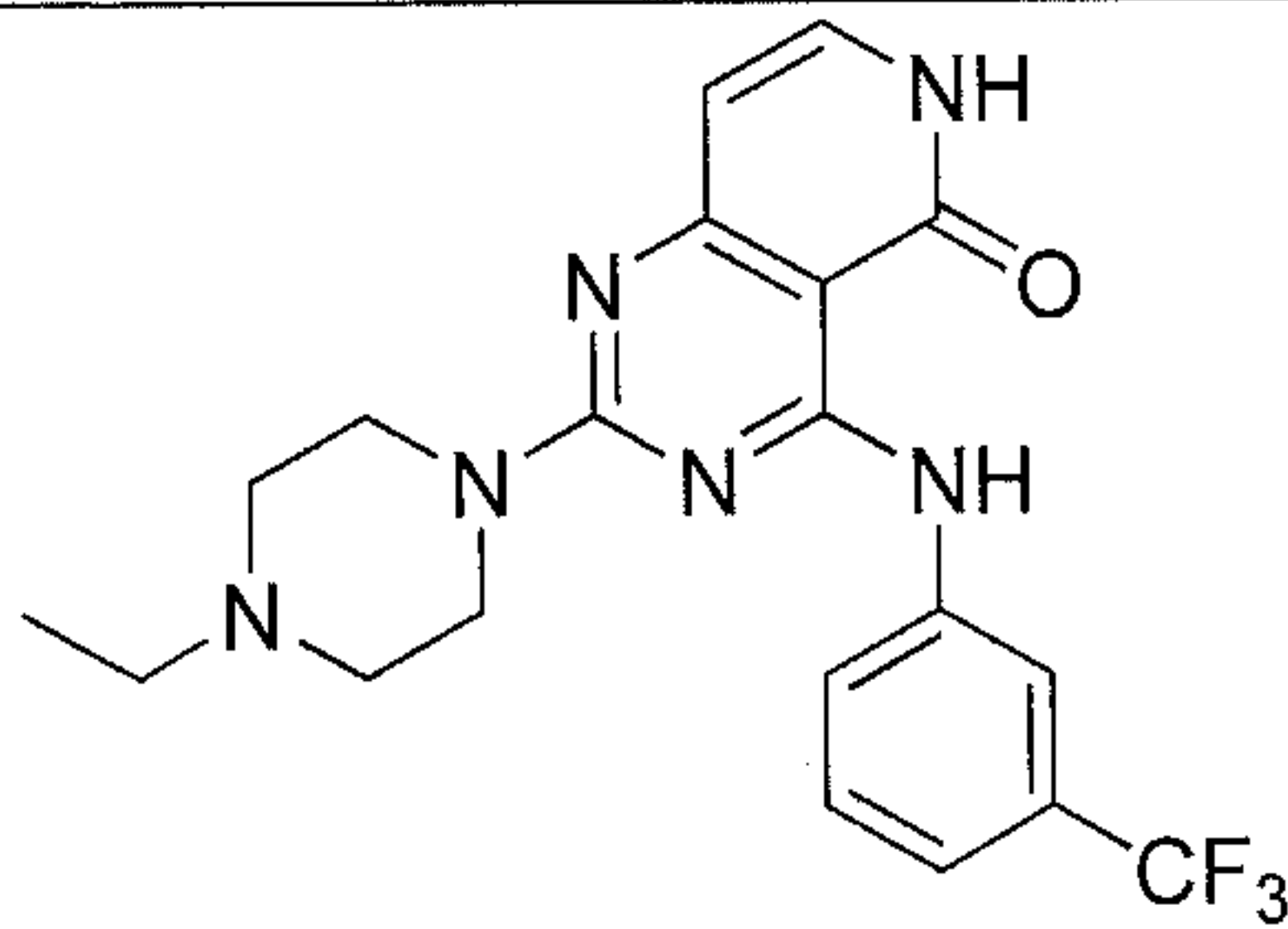
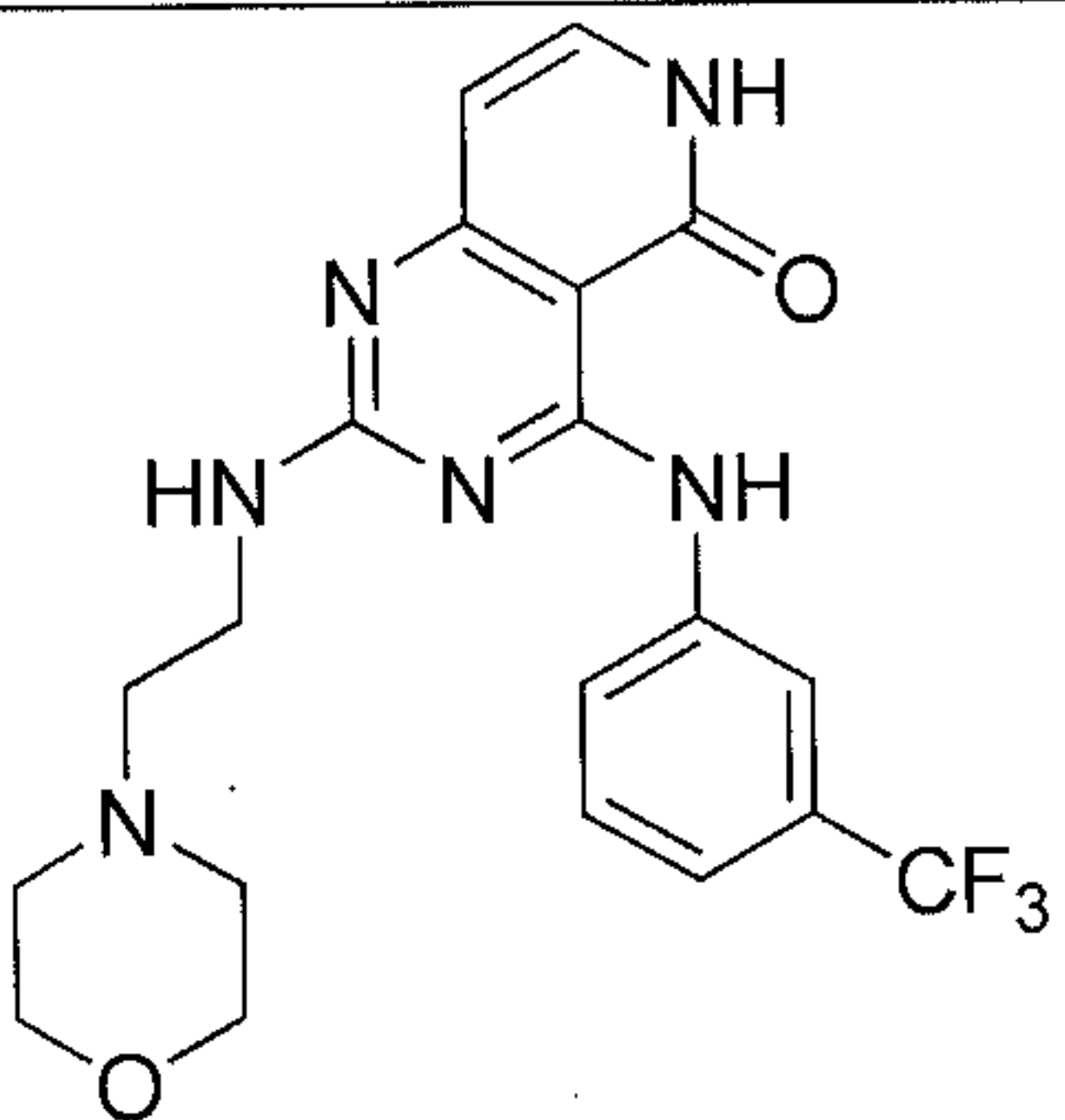
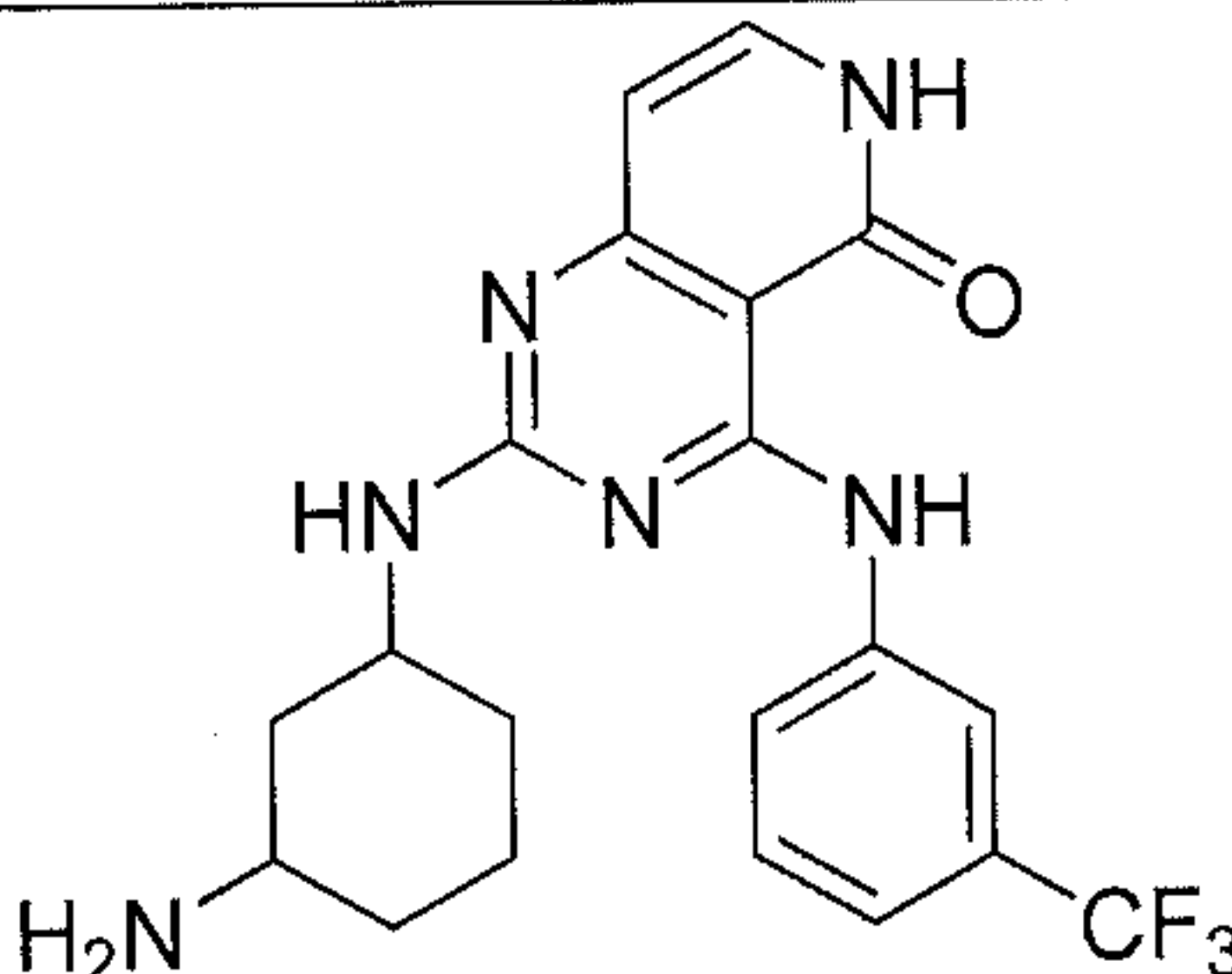
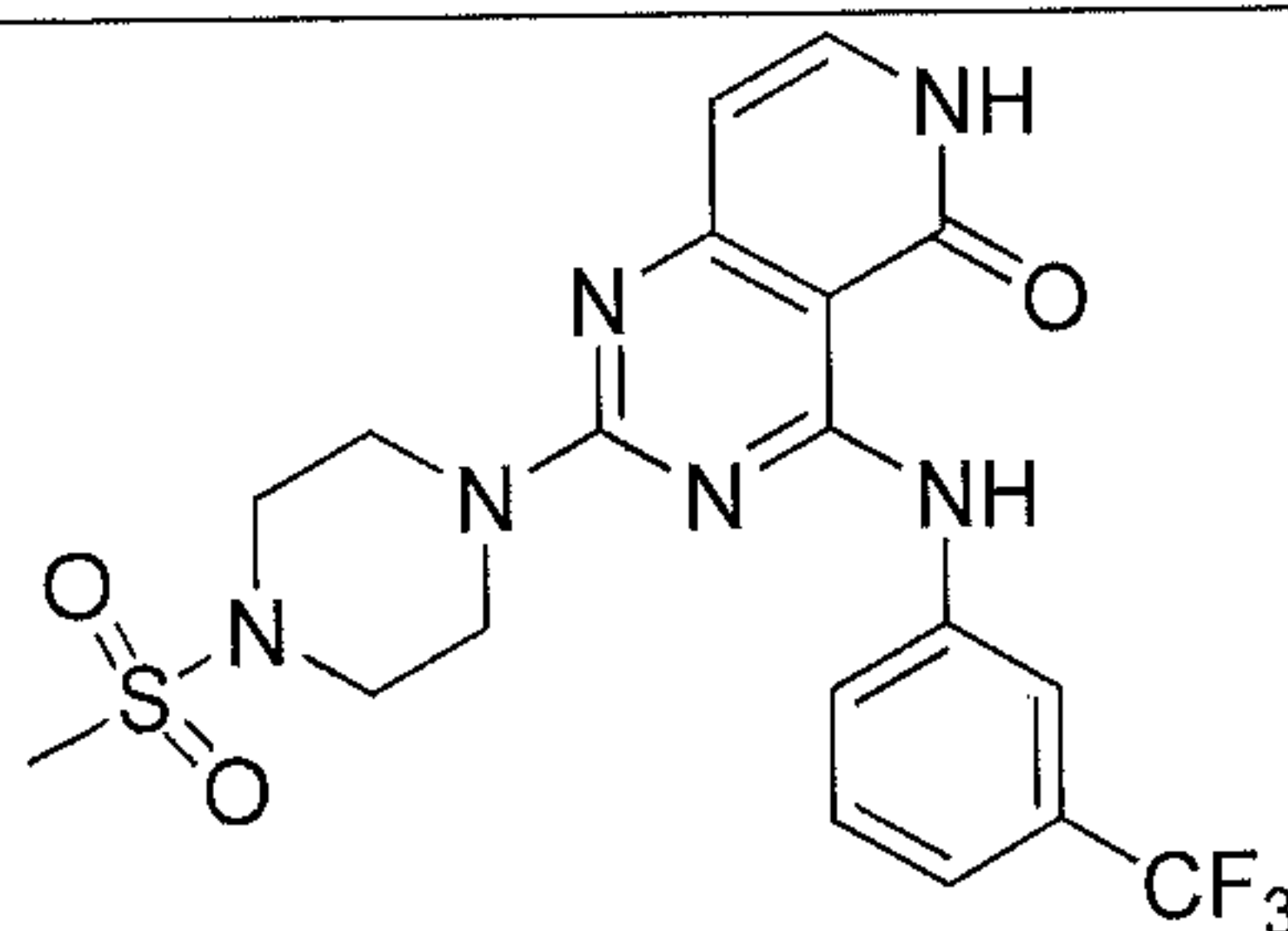
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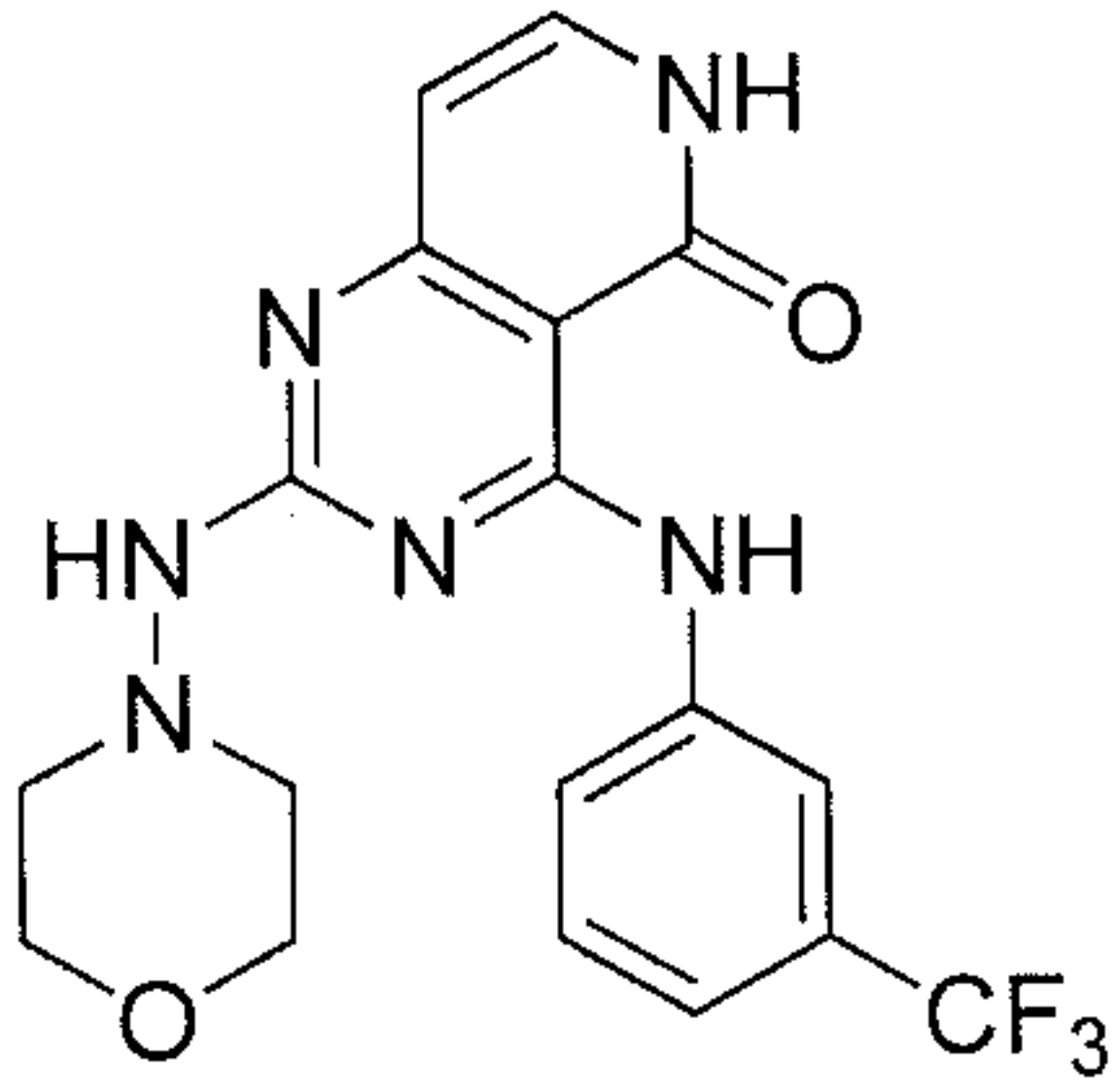
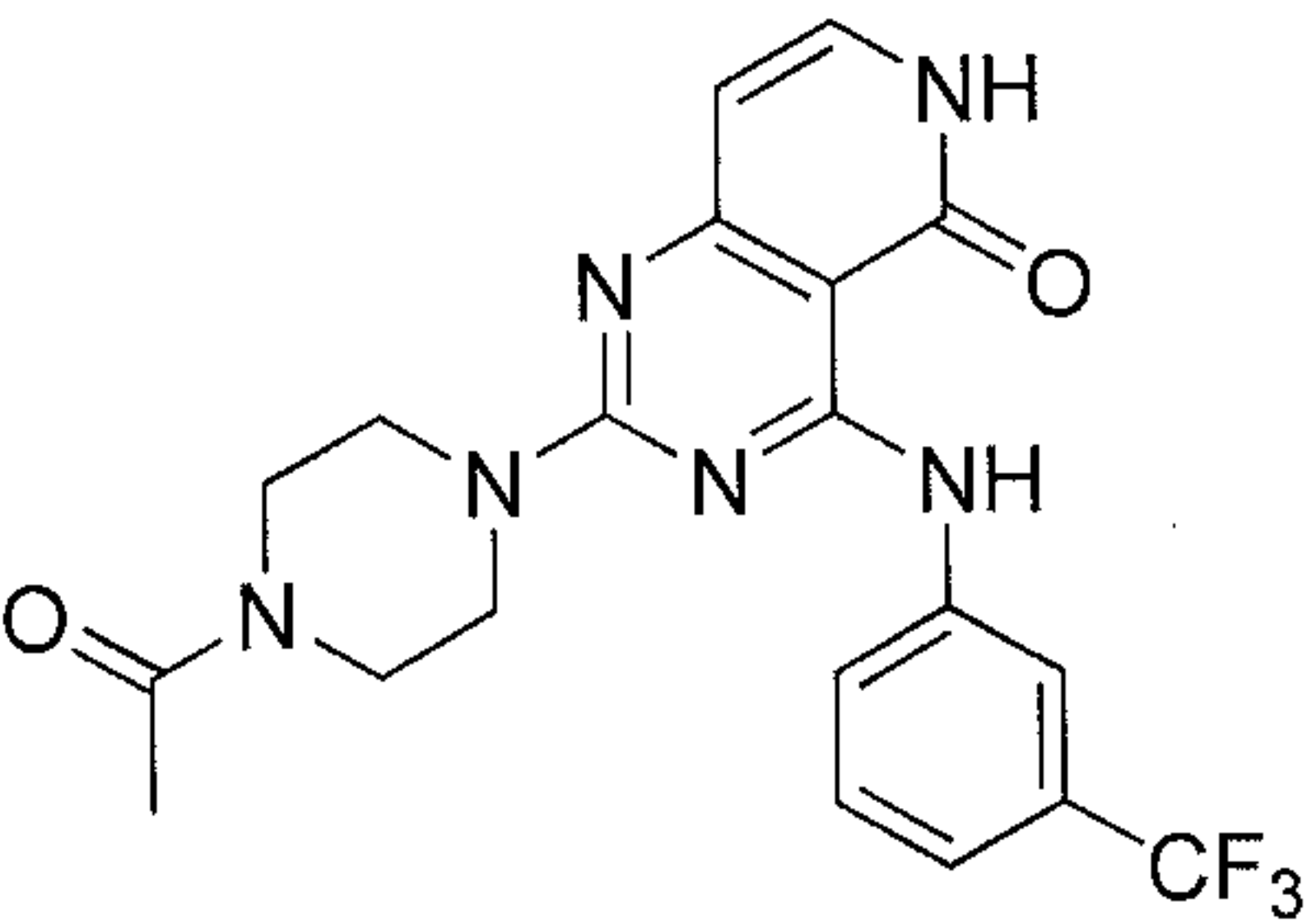
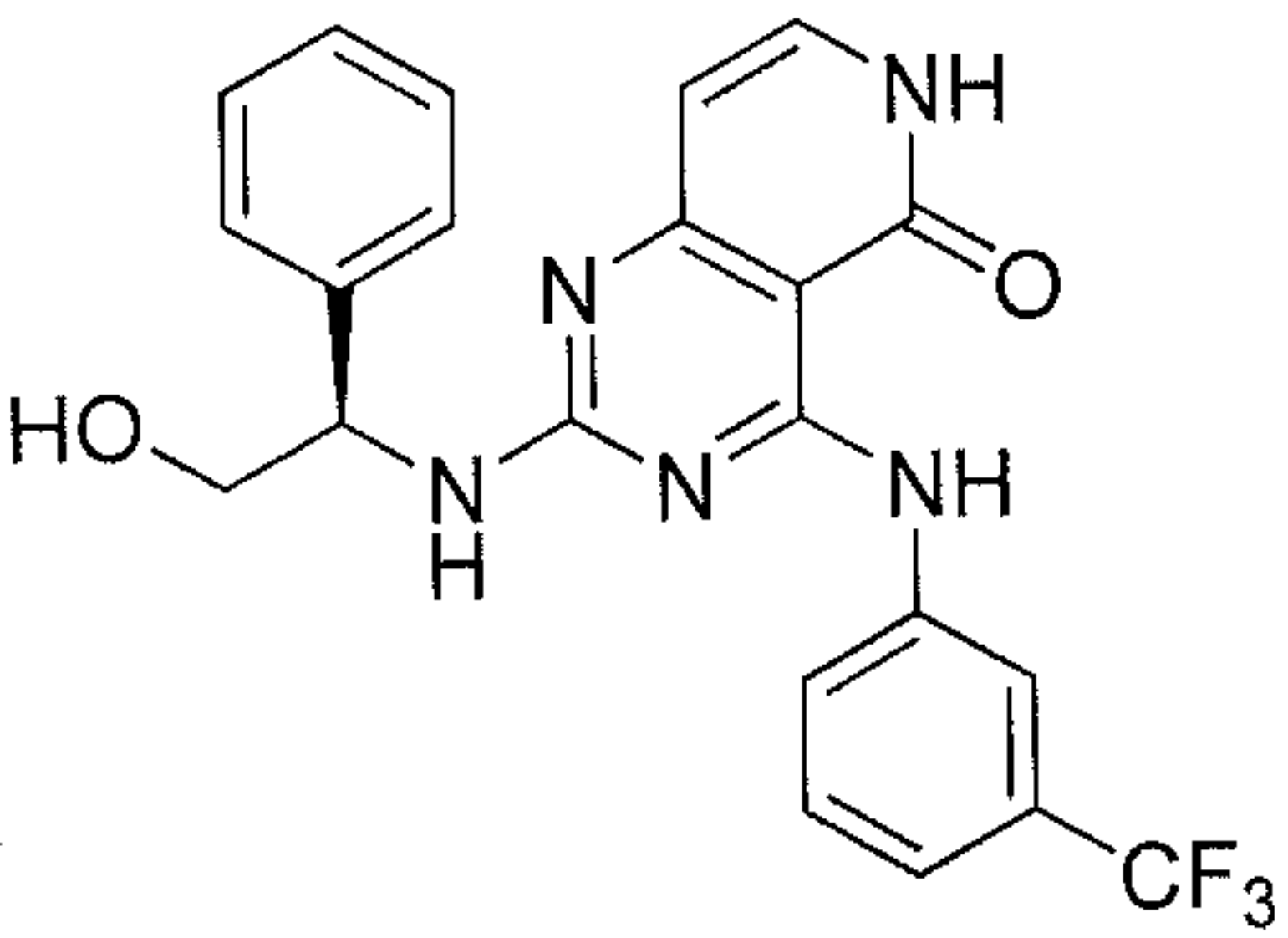
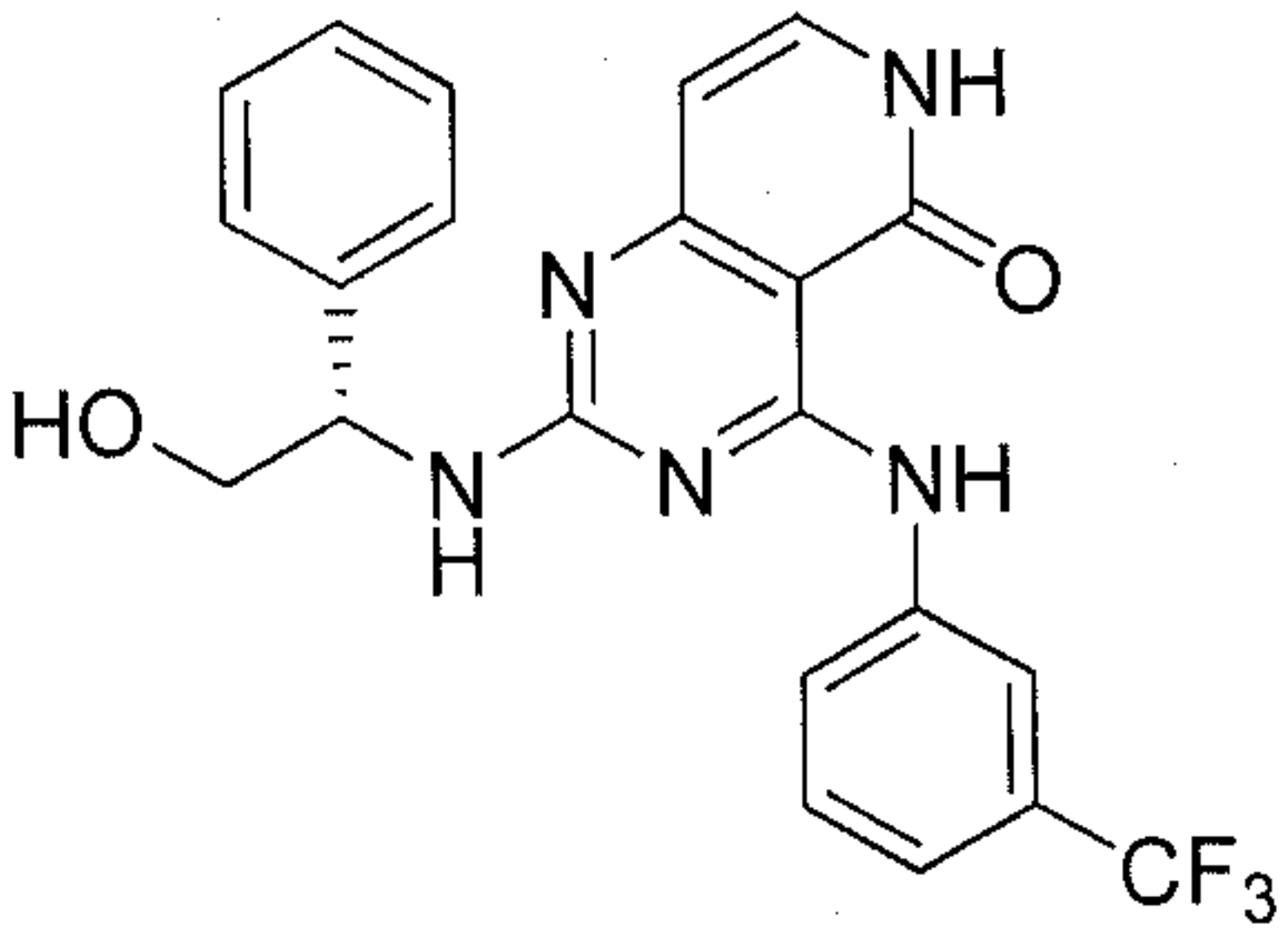
53		2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	435
54		2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	420
55		ethyl 1-(5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-yl)piperidine-4-carboxylate	462
56		2-(4-(4-(2-hydroxyethyl)piperazine-1-carbonyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	546

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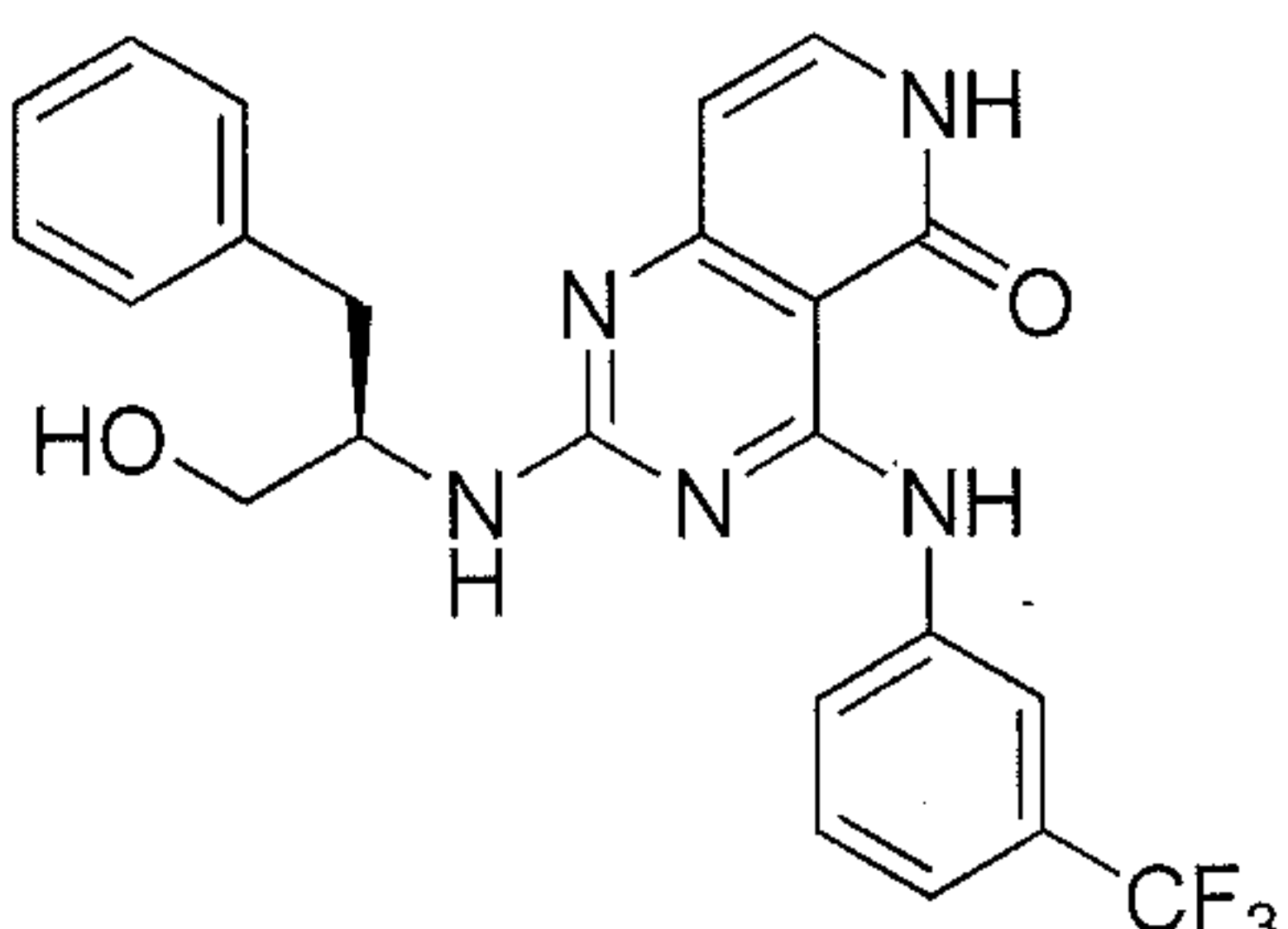
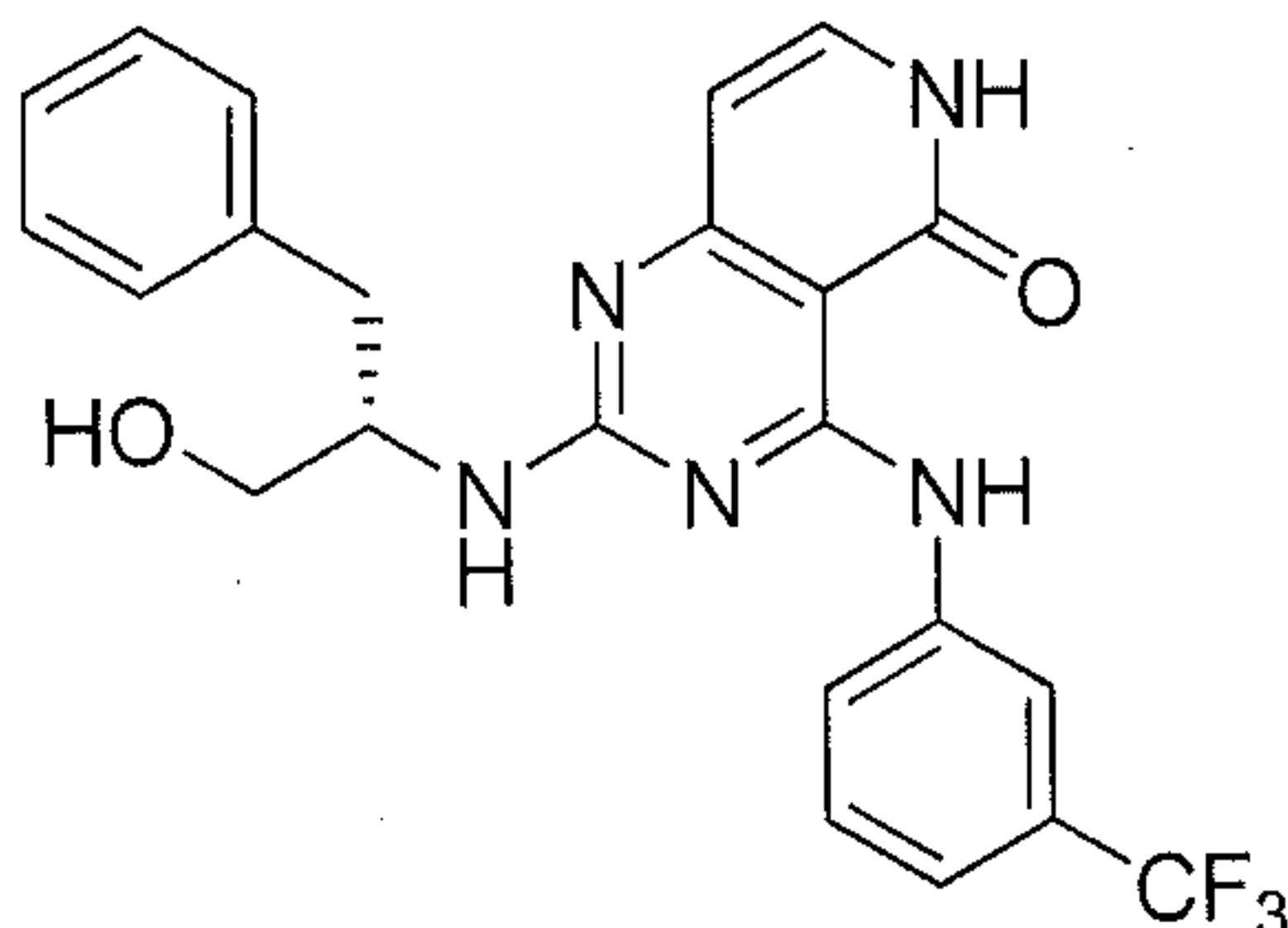
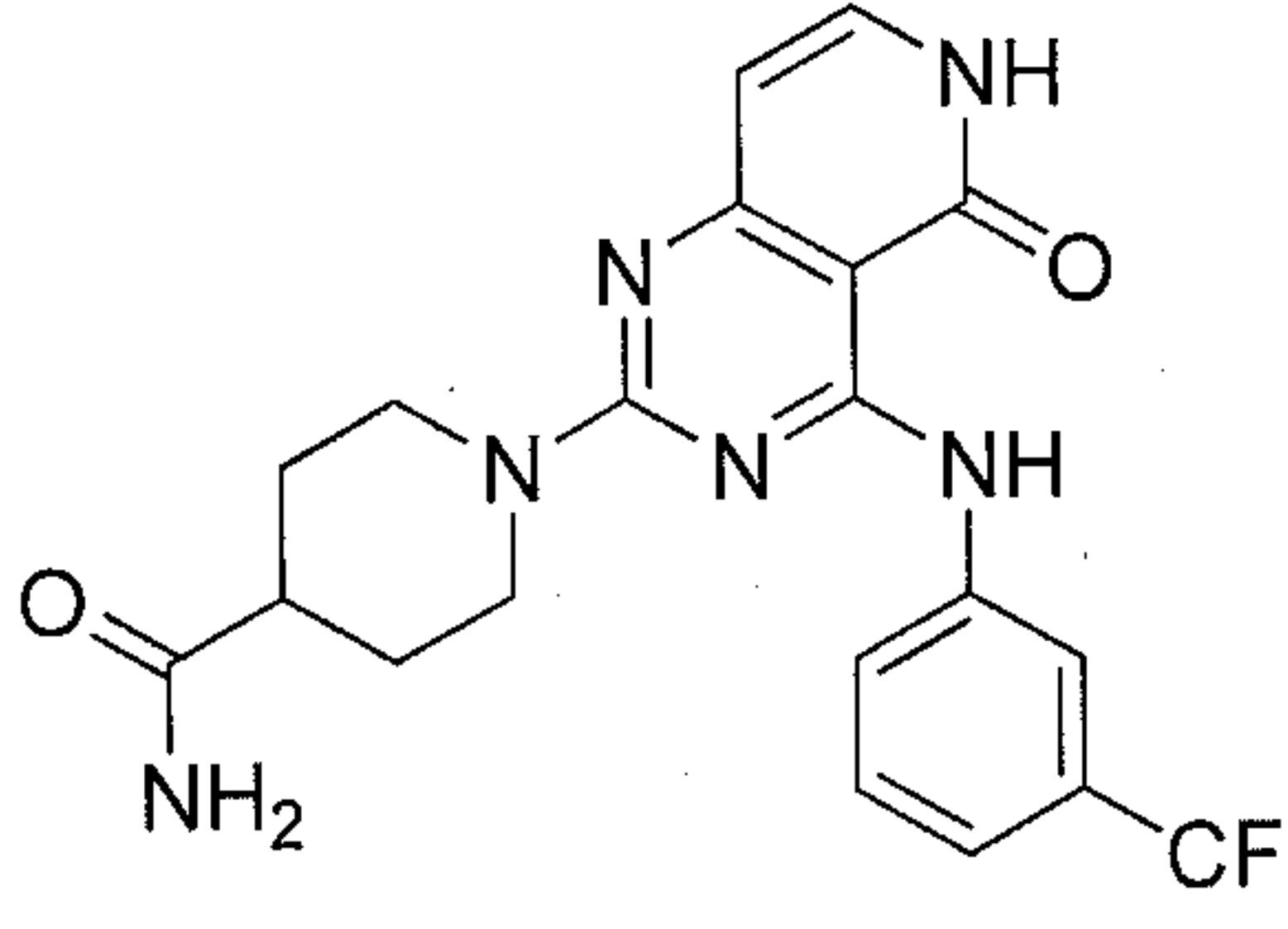
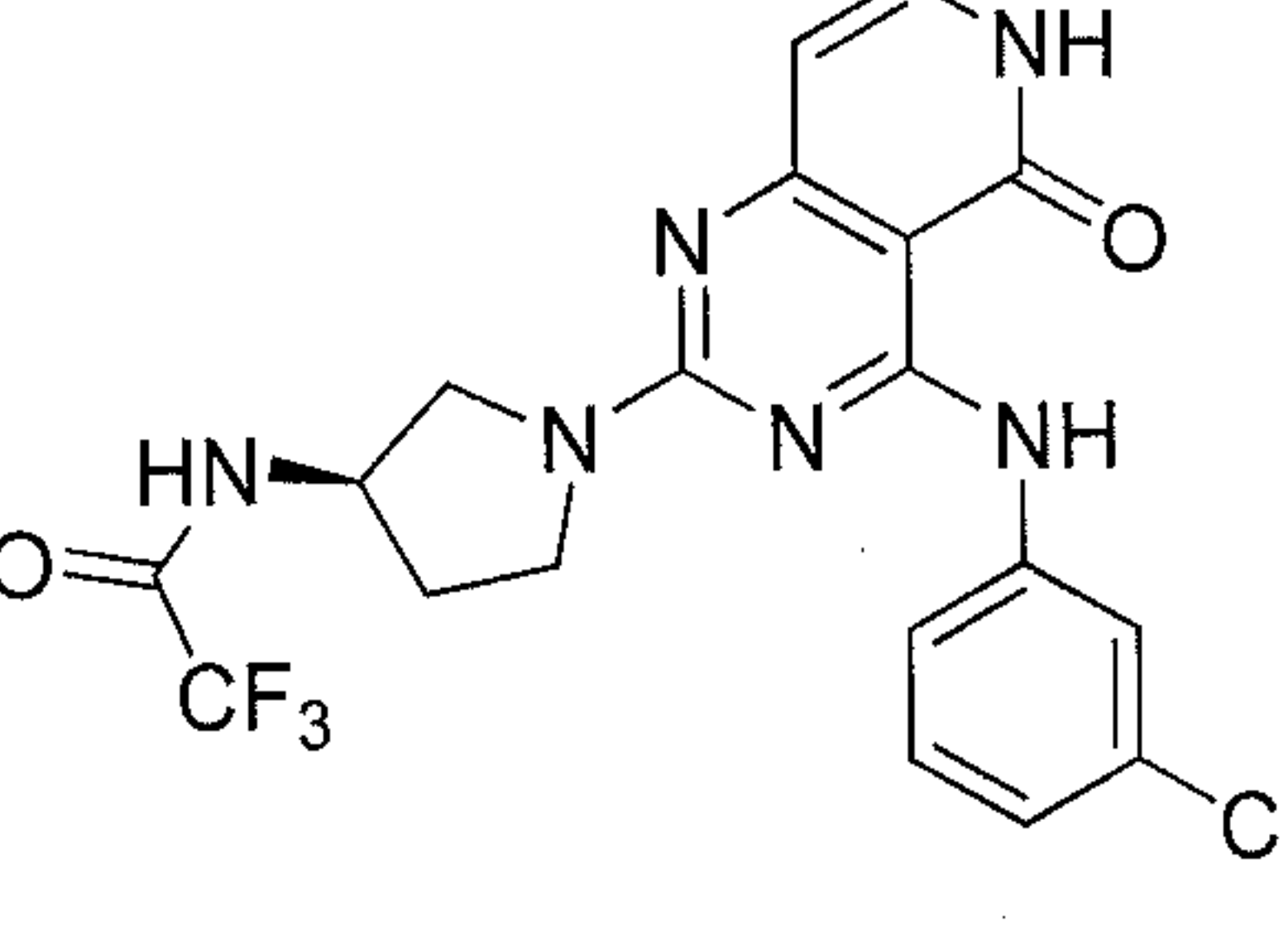
57		2-(4-(4-(hydroxymethyl)piperidin-1-yl)-4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	531
58		2-((1 <i>S</i> ,2 <i>R</i>)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	419
59		2-((1 <i>S</i> ,2 <i>S</i>)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	419
60		2-((1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.0 (s, 1H), 8.50 (s, 1H), 7.85-7.80 (m, 2H), 7.73 (m, 1H), 7.52 (m, 1H), 6.06 (d, 1H), 3.1 (m, 1H), 1.77 (br s, 2H), 1.55 (br s, 5H), 1.32 (br s, 2H)	419
61		2-((1 <i>R</i> ,2 <i>R</i>)-2-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.02 (s, 1H), 8.43 (s, 1H), 7.83-7.78 (m, 2H), 7.62 (m, 1H), 7.50 (m, 1H), 6.04 (d, 1H), 3.0 (m, 1H), 2.0 (br d, 2H), 1.69 (br d, 2H), 1.27-1.17 (br, 5H)	419

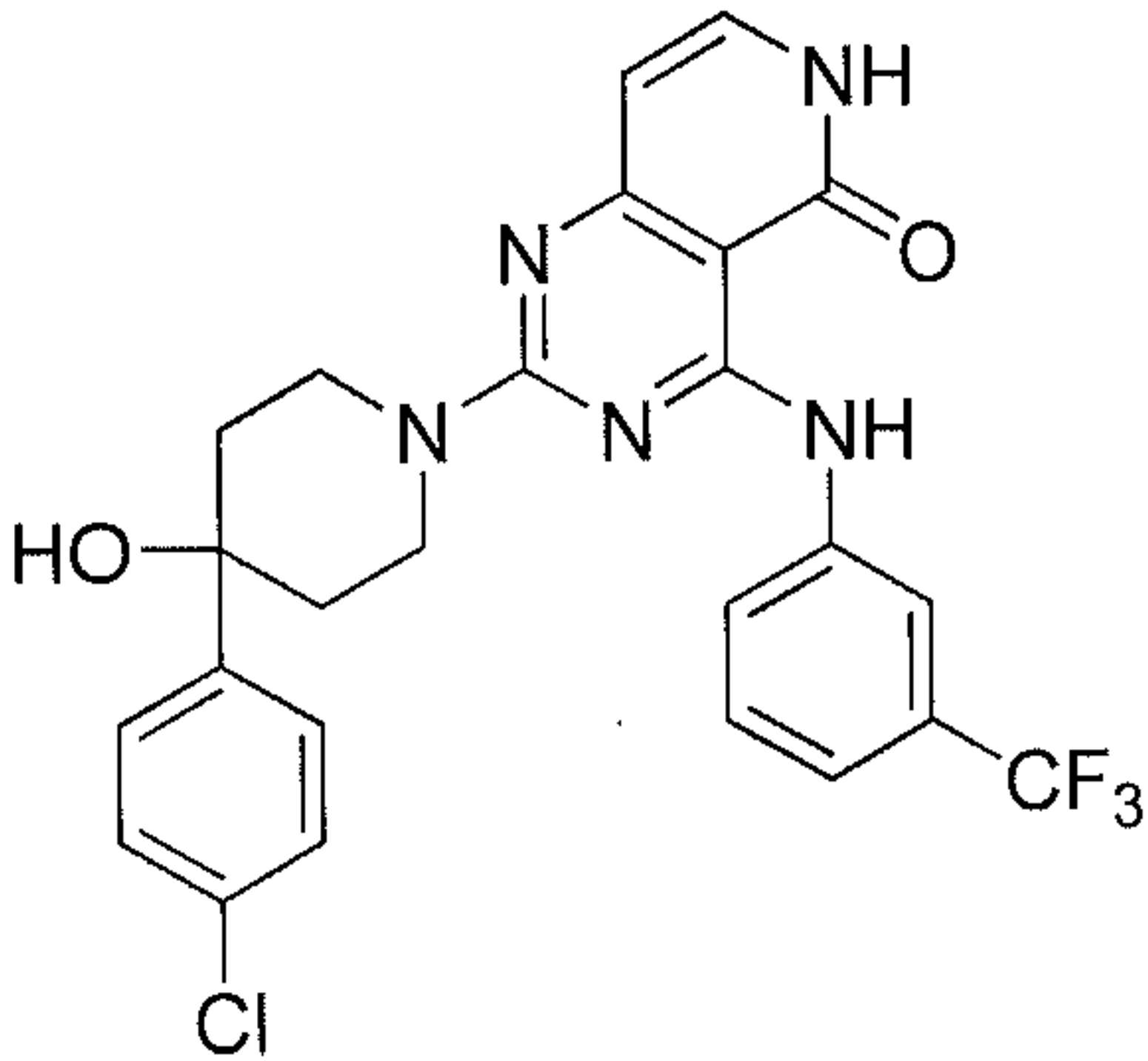
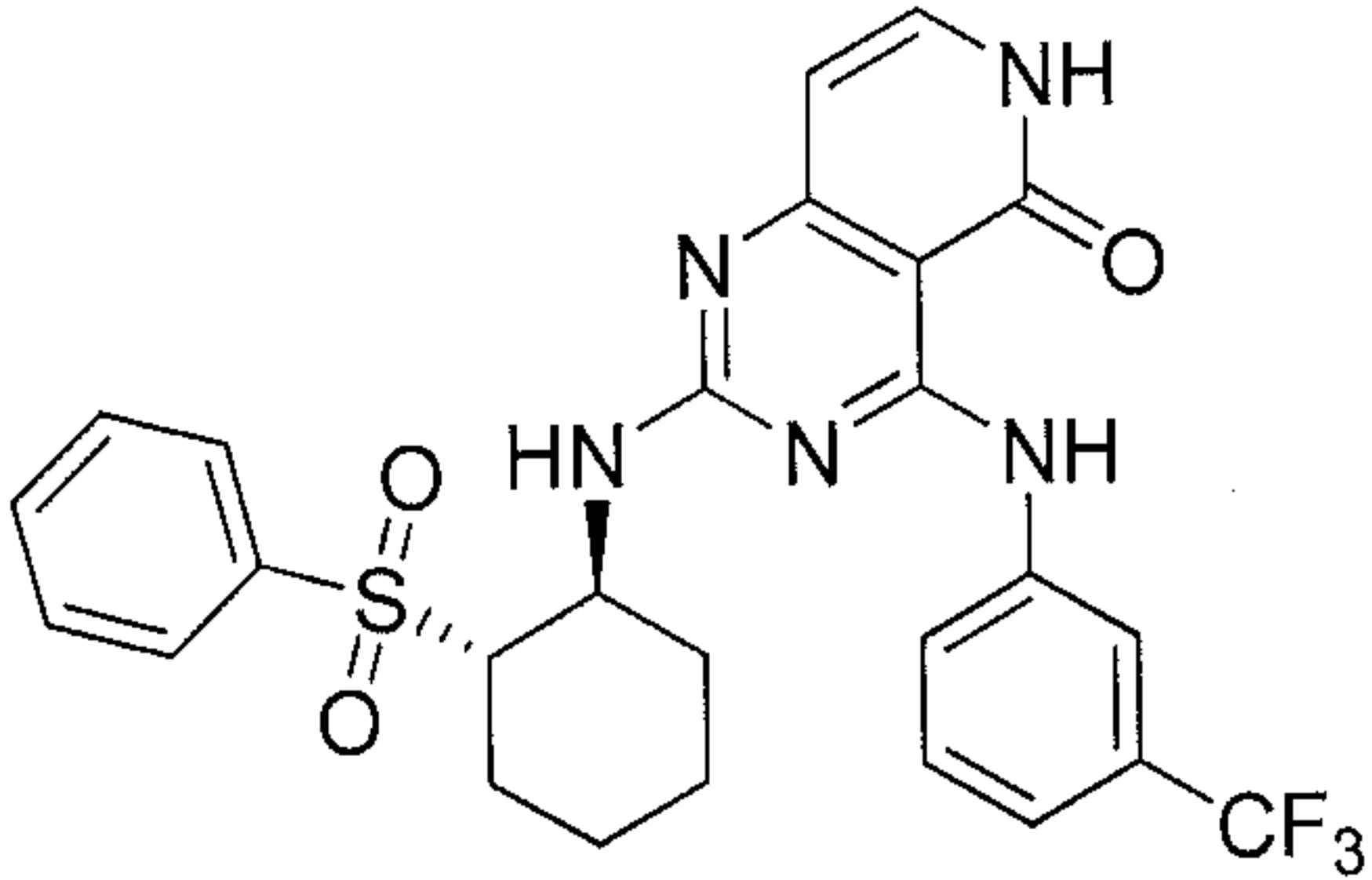
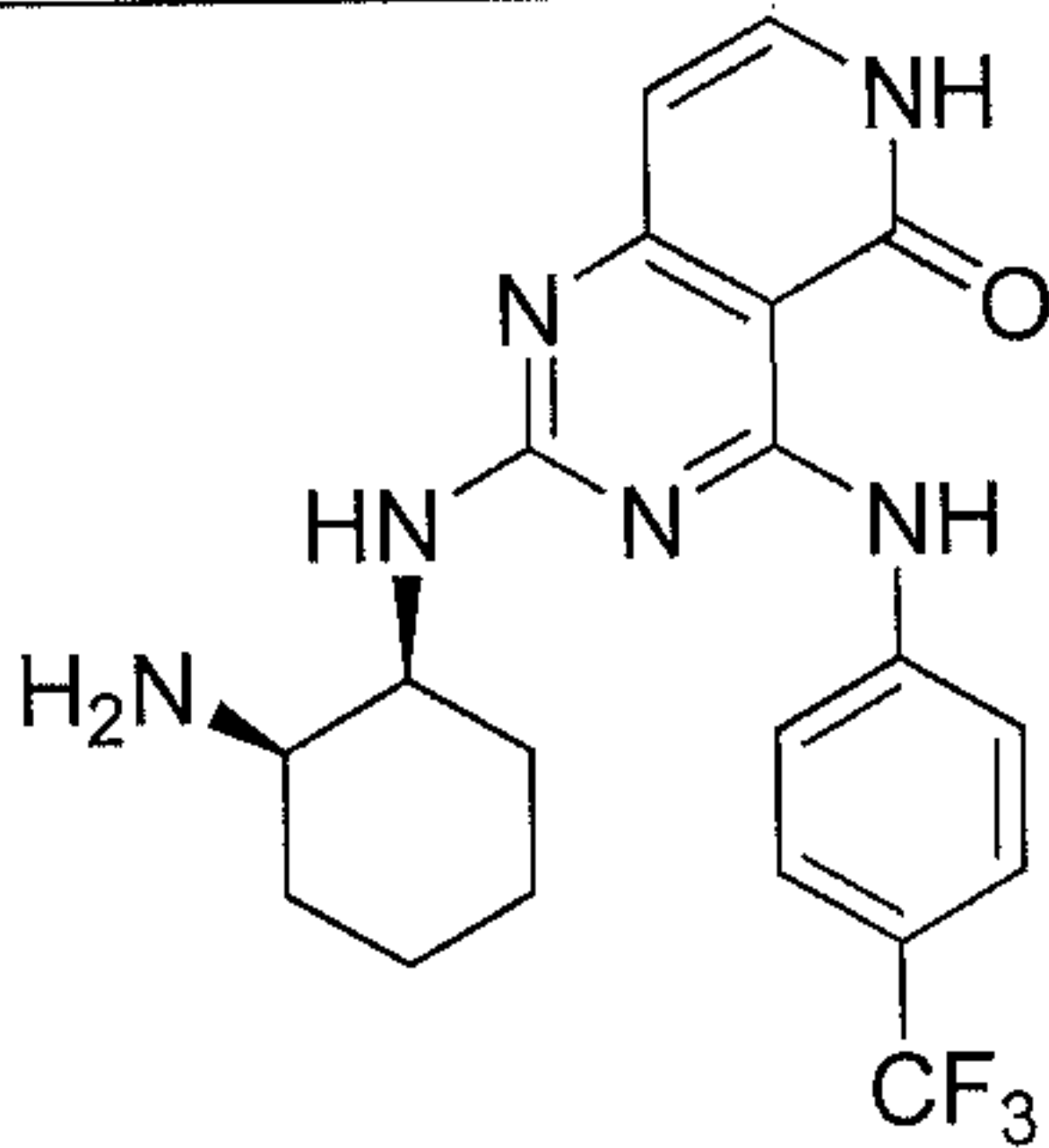
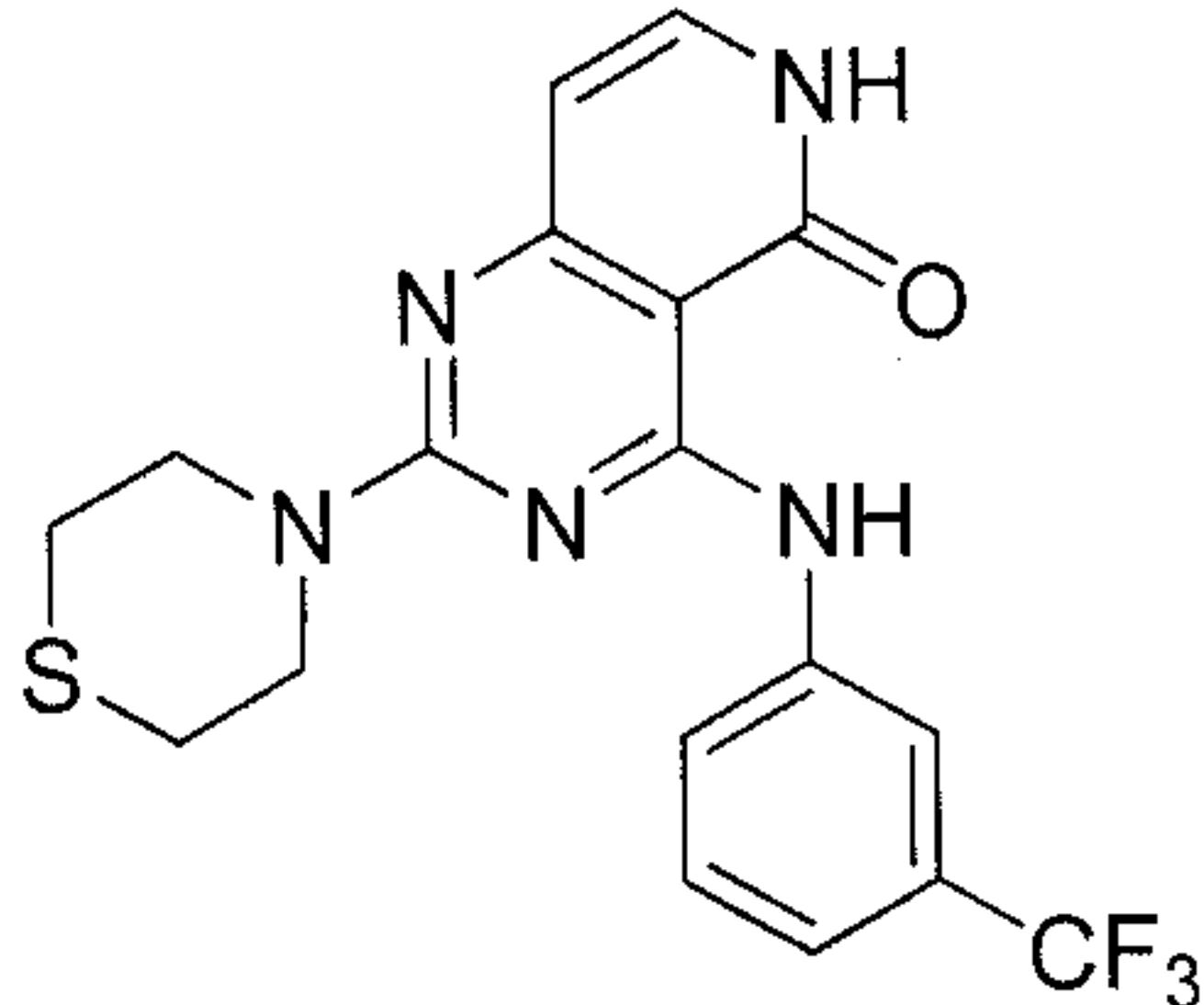
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62		2-((1 <i>R</i> ,4 <i>R</i>)-4-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.0 (s, 1H), 8.44 (d, 1H), 7.88-7.82 (m, 2H), 7.72(t, 1H), 7.49 (d, 1H), 6.04 (d, 1H), 1.95-1.85 (m, 5H), 1.32-1.19 (m, 5H)	419
63		2-(4-ethylpiperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	419
64		2-(2-morpholinoethylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	435
65		2-(3-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	419
66		2-(4-(methylsulfonyl)piperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	469

67		2-(morpholinoamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.12 (s, 1H), 11.50 (s, 1H), 8.50 (s, 1H), 7.68-7.56 (m, 2H), 7.44-7.7.41 (m, 2H), 6.20-6.17 (d, 1H), 4.12 (s, 4H), 2.73 (m, 4H)	407
68		2-(4-acetylpiperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.14 (s, 1H), 11.55 (s, 1H), 8.48 (s, 1H), 7.73 (d, <i>J</i> = 7.50 Hz, 1H), 7.63~7.56 (m, 2H), 7.45 (t, <i>J</i> = 7.50, 1H), 6.20 (d, <i>J</i> = 7.20 Hz, 1H), 3.84 (d, <i>J</i> = 2.13 Hz, 4H), 3.54 (s, 4H), 2.06 (s, 3H)	433
69		(<i>R</i>)-2-(2-hydroxy-1-phenylethylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.18 (s, 1H), 8.14 (s, 1H), 7.84~7.76 (m, 2H), 7.66~7.48 (m, 2H), 7.43~7.17 (m, 6H), 6.11 (d, <i>J</i> = 7.20 Hz, 1H), 5.05 (s, 1H), 4.93 (s, 1H), 4.09~4.04 (m, 1H), 3.73~3.46 (m, 1H)	442
70		(<i>S</i>)-2-(2-hydroxy-1-phenylethylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.19 (s, 1H), 8.14 (s, 1H), 8.01 (d, <i>J</i> = 7.80, 1H), 7.91~7.82 (m, 4H), 7.66~7.19 (m, 4H), 6.11 (d, <i>J</i> = 7.50, 1H), 5.25~5.23 (m, 1H), 5.07~4.90 (m, 1H), 4.16~4.12 (m, 2H), 3.65~3.51 (m, 1H)	442

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71		(<i>R</i>)-2-(1-hydroxy-3-phenylpropan-2-ylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.14 (s, 1H), 8.41 (s, 1H), 7.87 (s, 2H), 7.83 (d, <i>J</i> = 10.00 Hz, 2H), 7.57 (t, <i>J</i> = 10.40 Hz, 1H), 7.46~7.12 (m, 6H), 6.05 (d, <i>J</i> = 7.50, 1H), 4.80 (s, 1H), 4.20 (s, 1H), 3.49~3.29 (m, 2H), 2.97~2.85 (m, 1H), 2.78 (d, <i>J</i> = 6.90 Hz, 1H)	456
72		(<i>S</i>)-2-(1-hydroxy-3-phenylpropan-2-ylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.14 (s, 1H), 11.42 (s, 1H), 8.41 (s, 1H), 7.95 (s, 2H), 7.83~7.73 (m, 2H), 7.57 (t, <i>J</i> = 15.90 Hz, 1H), 7.47~7.09 (m, 4H), 6.05 (d, <i>J</i> = 7.20 Hz, 1H), 4.22~4.20 (m, 1H), 2.97~2.85 (m, 3H), 2.76~2.73 (m, 2H)	456
73		1-(5-oxo-4-(3-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-yl)piperidine-4-carboxamide 12.12 (s, 1H), 8.61 (s, 1H), 7.65~7.56 (m, 1H), 7.51~7.38 (m, 3H), 7.32 (s, 1H), 6.17 (d, <i>J</i> = 7.50 Hz, 1H), 4.68 (s, 2H), 3.02 (t, <i>J</i> = 12.90 Hz, 1H), 2.45~2.40 (m, 4H), 1.80~1.56 (m, 4H)	432
74		(<i>R</i>)-2,2,2-trifluoro-N-(1-(5-oxo-4-(3-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-yl)pyrrolidin-3-yl)acetamide 12.24 (s, 1H), 11.48 (s, 1H), 9.75 (d, <i>J</i> = 6.6 Hz, 1H), 7.74~7.67 (m, 2H), 7.42~7.30 (m, 2H), 6.21~6.17 (m, 1H), 3.87~3.79 (m, 1H), 3.74~3.55 (m, 4H), 2.07-	487

		2.04 (m, 2H)	
75		2-(4-(4-chlorophenyl)-4-hydroxy piperidin-1-yl)-4-(3-(trifluoromethyl) phenylamino)pyrido[4,3-<i>d</i>]pyrimidin- 5(6<i>H</i>)-one 12.13 (s, 1H), 8.66 (s, 1H), 7.88-7.83 (m, 4H), 7.62-7.38 (m, 5H), 6.19-6.17 (d, <i>J</i>= 7.2Hz, 1H), 5.40-5.34 (m, 1H), 3.14-3.11 (m, 6H), 2.15-2.05 (m, 2H)	516
76		2-((1<i>S</i>,2<i>S</i>)-2-(phenylsulfonyl)cyclohexyl amino)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-<i>d</i>]pyrimidin-5(6<i>H</i>)-one	544
77		2-((1<i>S</i>,2<i>R</i>)-2-aminocyclohexylamino)-4- (4-(trifluoromethyl)phenylamino)pyrido [4,3-<i>d</i>]pyrimidin-5(6<i>H</i>)-one	419
78		2-thiomorpholino-4-(3-(trifluoromethyl) phenylamino)pyrido[4,3-<i>d</i>]pyrimidin- 5(6<i>H</i>)-one 12.12 (s, 1H), 11.50 (s, 1H), 8.50 (s, 1H) 7.68-7.56 (m, 2H), 7.44-7.41 (m, 2H), 6.20-6.17 (m, 1H), 4.12 (s, 4H), 2.73 (m, 4H)	408

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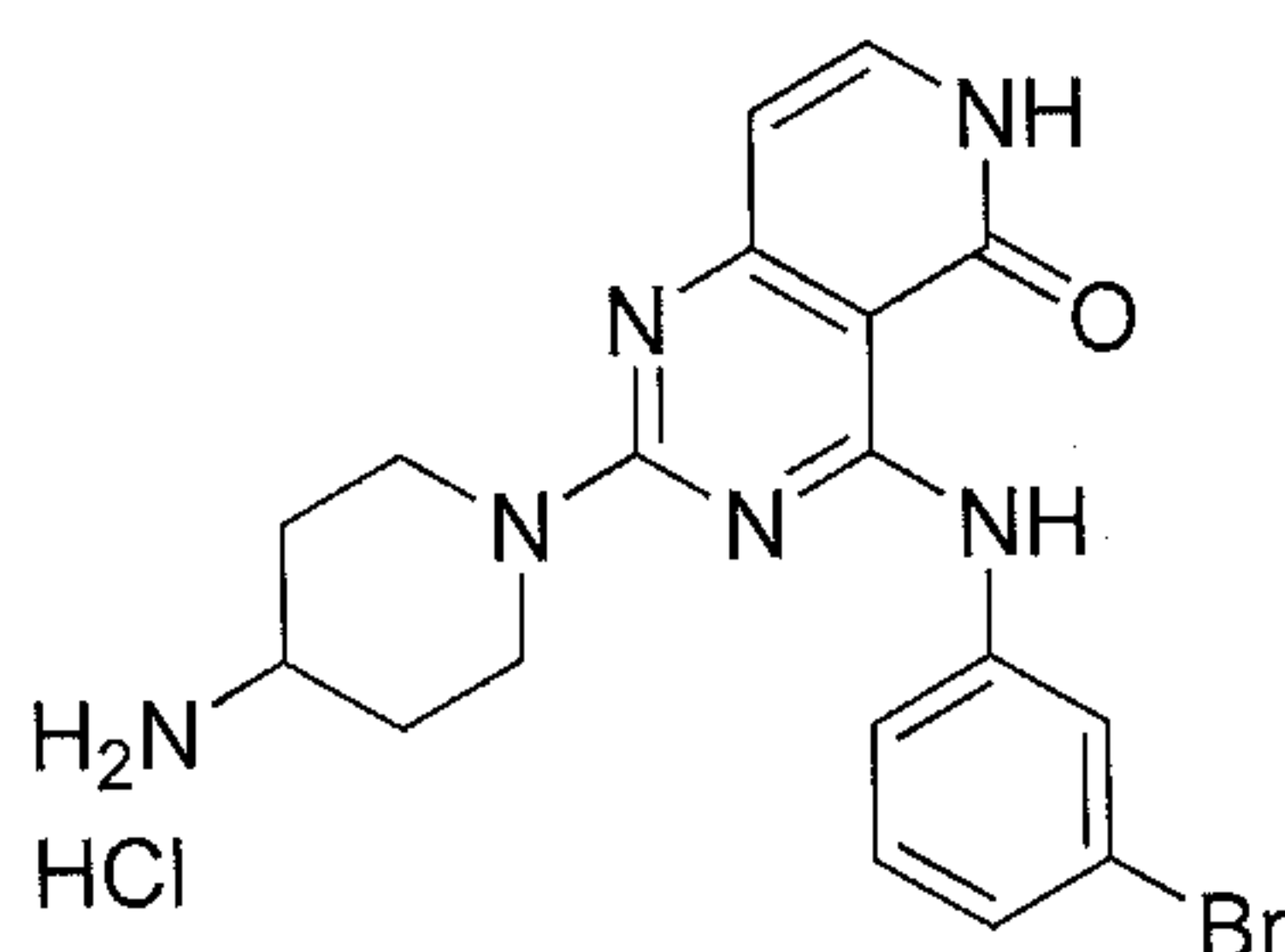
79		2-(4-sulfonylpiperido)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	440
80		2-(4-morpholinopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	475
81		<i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-2-(5-oxo-4-(3-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)cyclohexyl)acetamide 12.51 (s, 1H), 8.30 (s, 1H), 7.89-7.80 (m, 3H), 7.70-7.60 (m, 2H), 6.38-6.35 (d, <i>J</i> = 6.9, 1H), 4.13 (s, 1H), 1.64 (s, 3H), 1.54-1.37 (m, 8H), 1.96 (s, 2H)	461
82		<i>N</i> -((1 <i>R</i> ,4 <i>R</i>)-4-(5-oxo-4-(3-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)cyclohexyl)acetamide 12.43 (s, 1H), 8.43 (s, 1H), 7.90-7.55 (m, 6H), 6.35 (s, 1H), 3.49 (s, 1H), 3.46 (s, 1H), 2.48 (s, 1H), 1.85-1.79 (m, 4H), 1.78-1.74 (m, 4H)	461
83		2-((1 <i>R</i> ,2 <i>R</i>)-2-(dimethylamino)cyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 12.33 (s, 1H), 8.81 (s, 1H), 7.58 (m, 2H), 7.41 (s, 1H), 7.37-7.35 (m, 1H), 7.29-7.27 (d, <i>J</i> = 8.4Hz, 1H), 6.06-6.03 (d,	447

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		$J=6.9\text{Hz}$, 1H), 3.91 (m, 1H), 2.15 (m, 7H), 1.98 (m, 1H), 1.80-1.77(m, 2H), 1.64(m, 1H), 1.78(m, 5H)	
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Example 84

Synthesis of 2-(4-aminopiperidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride

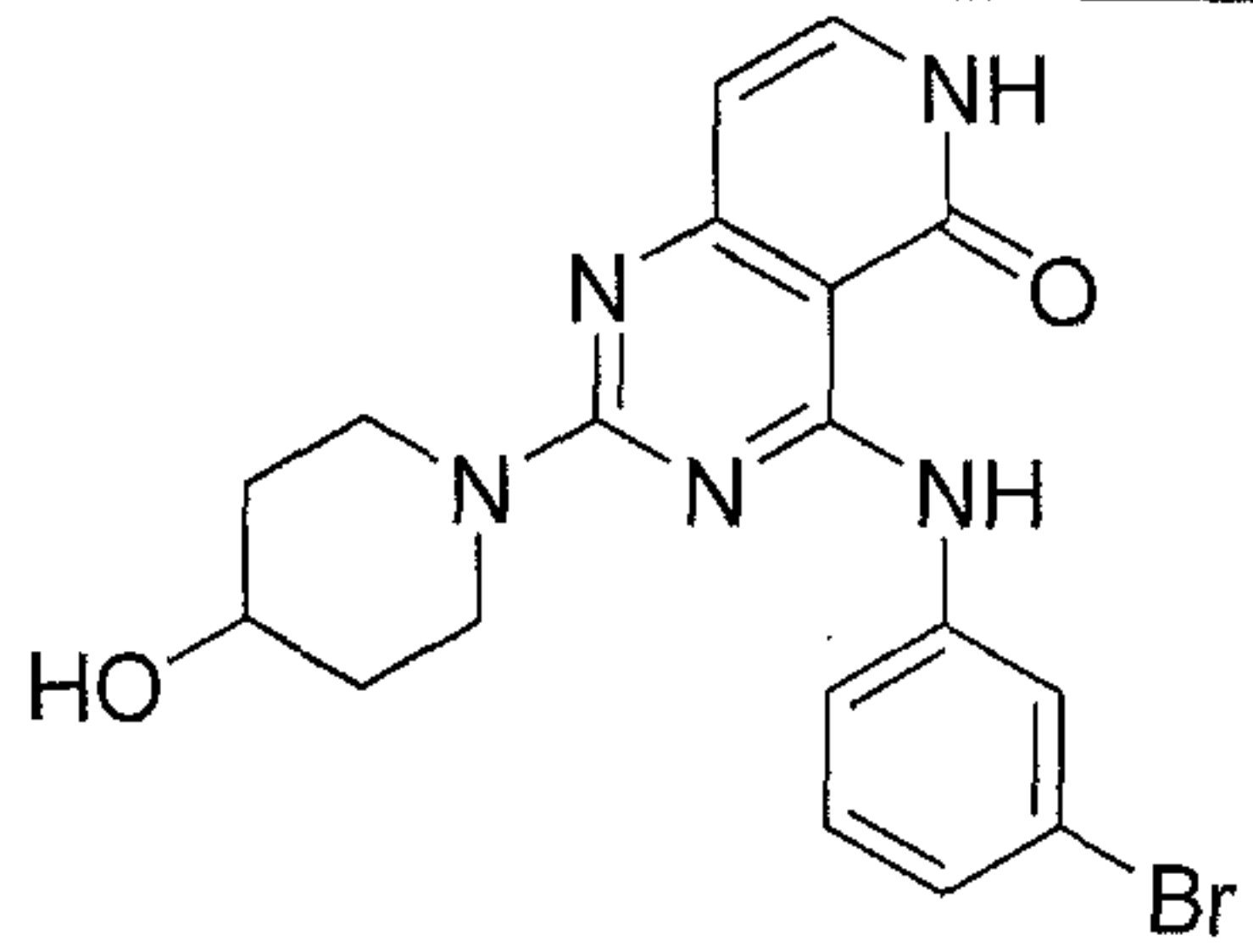
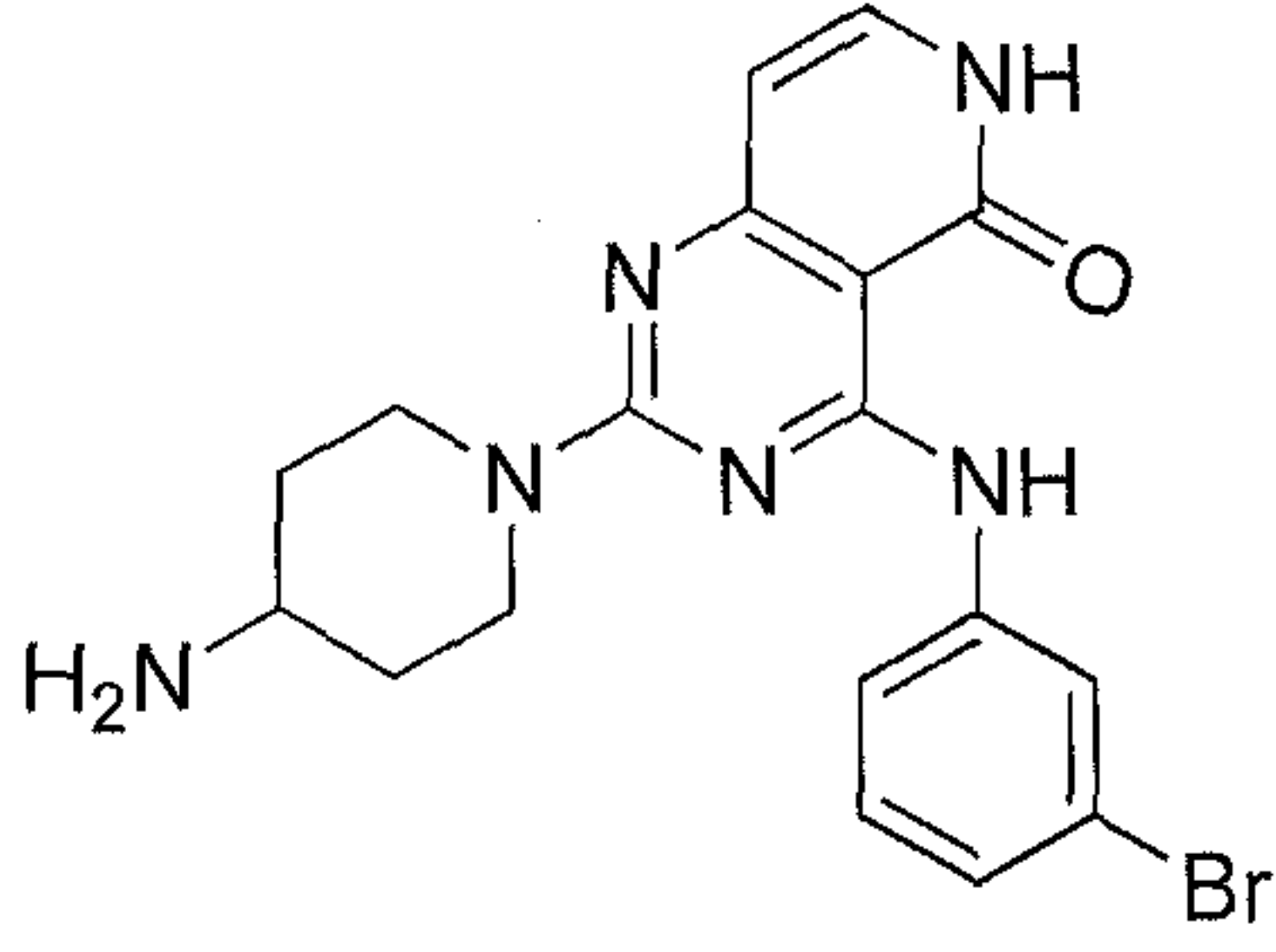
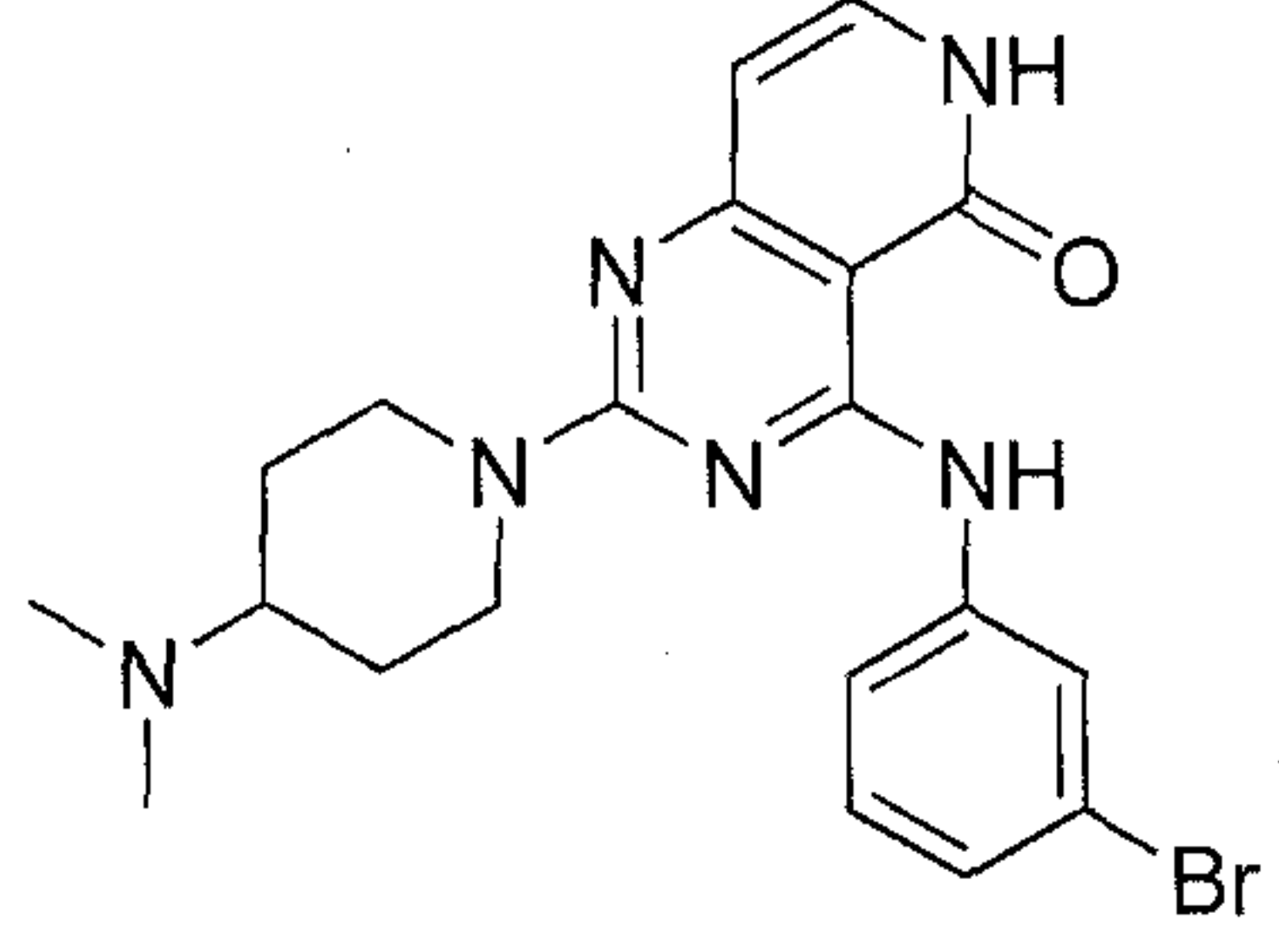
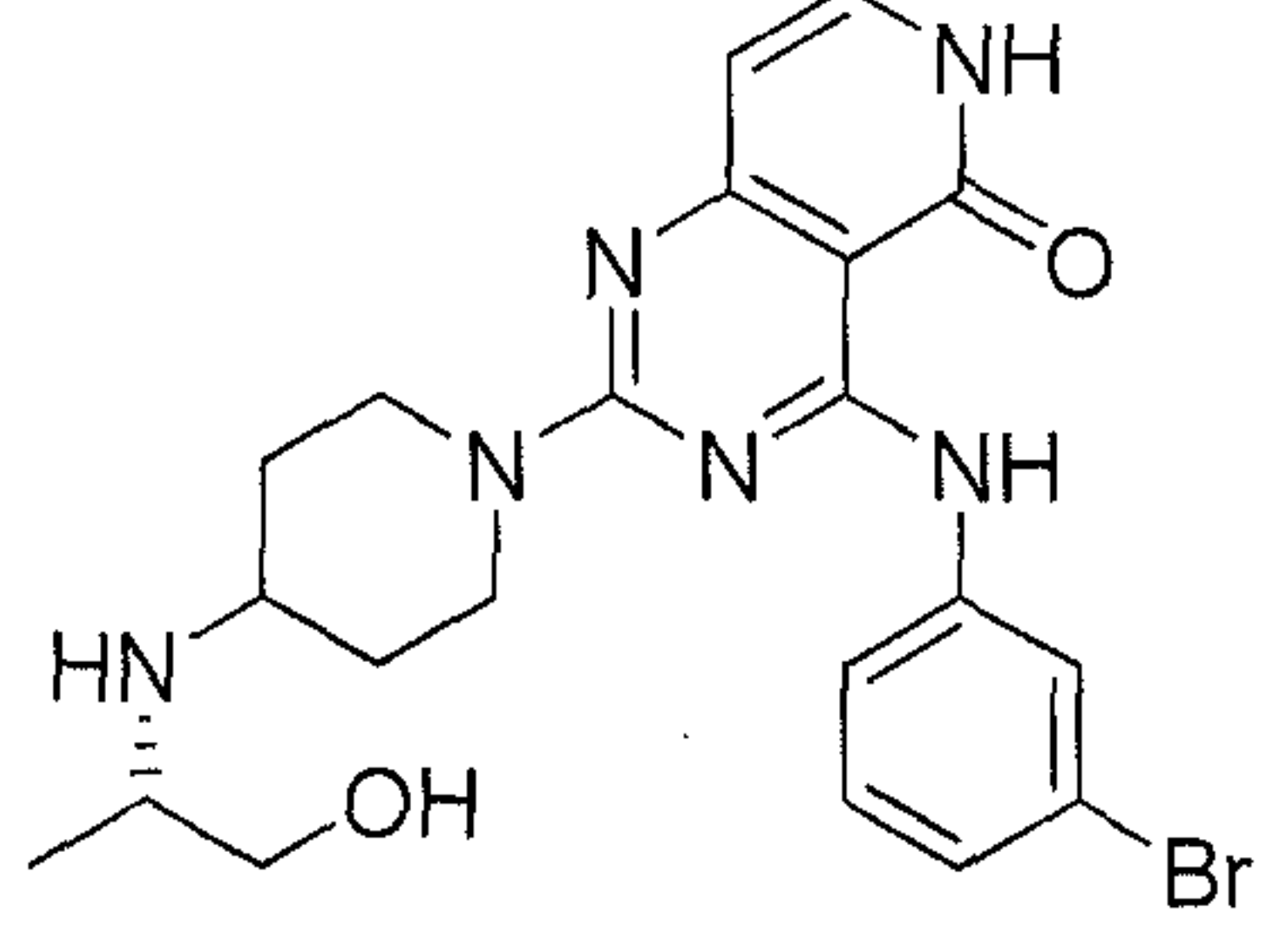
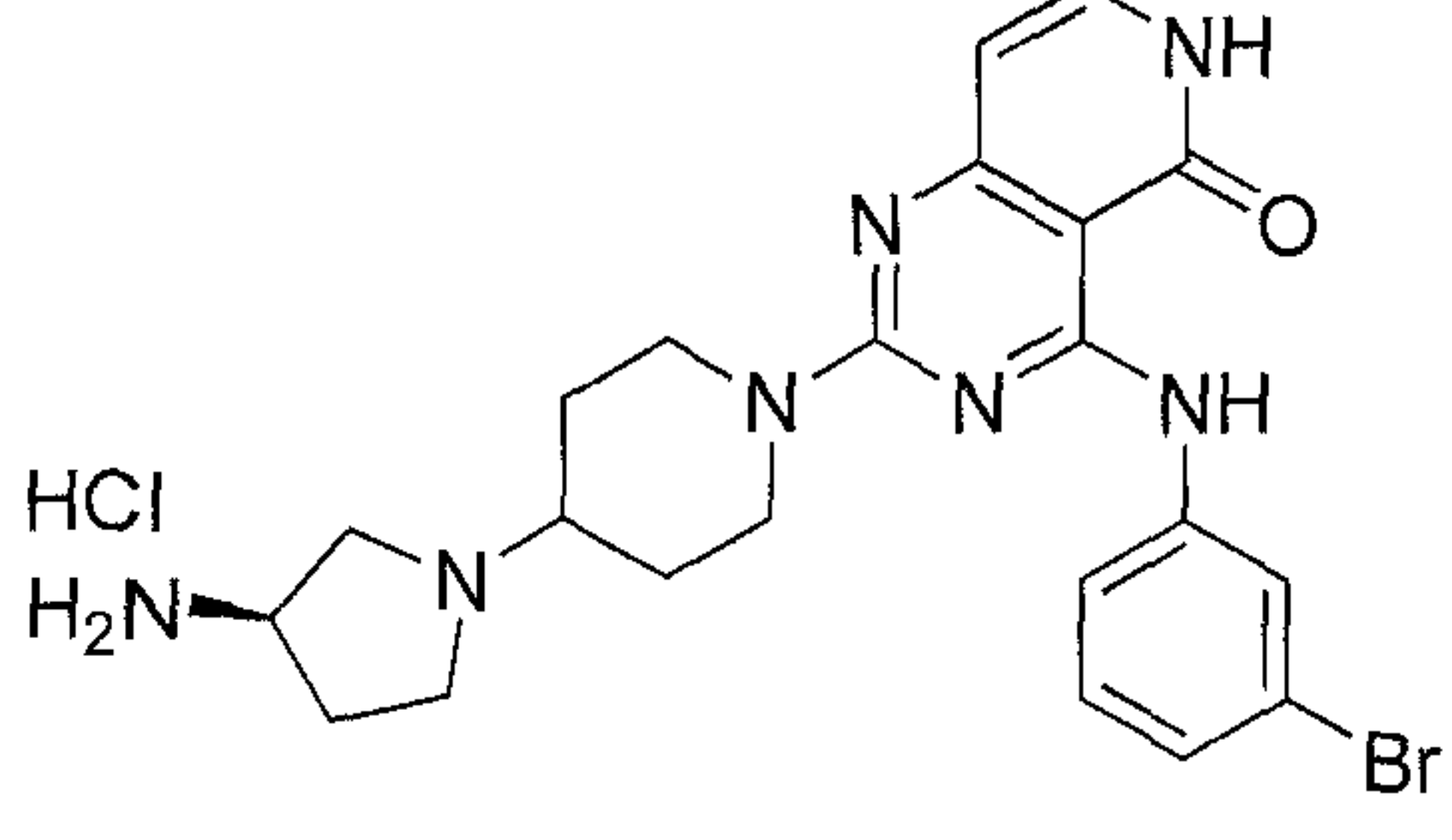
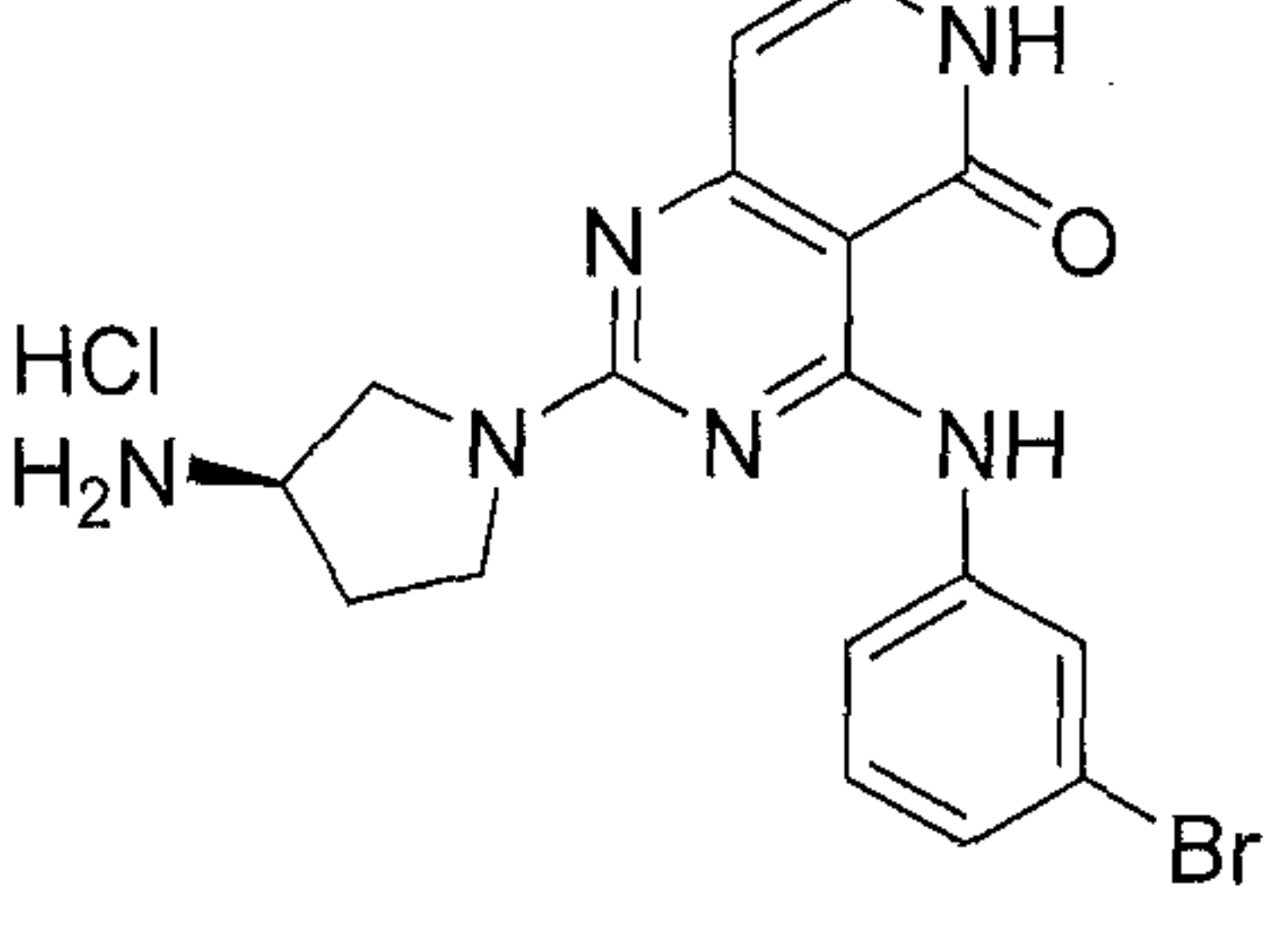


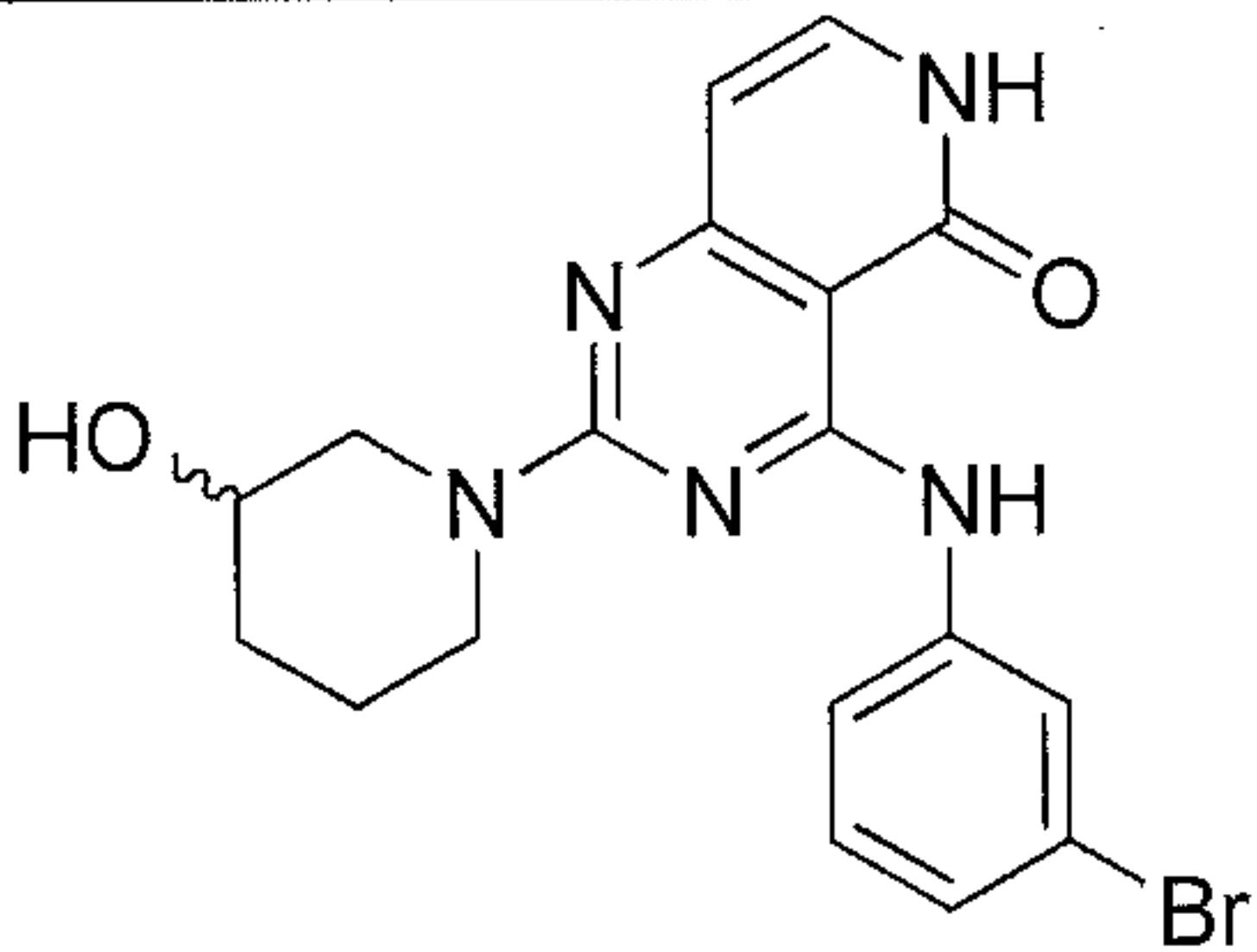
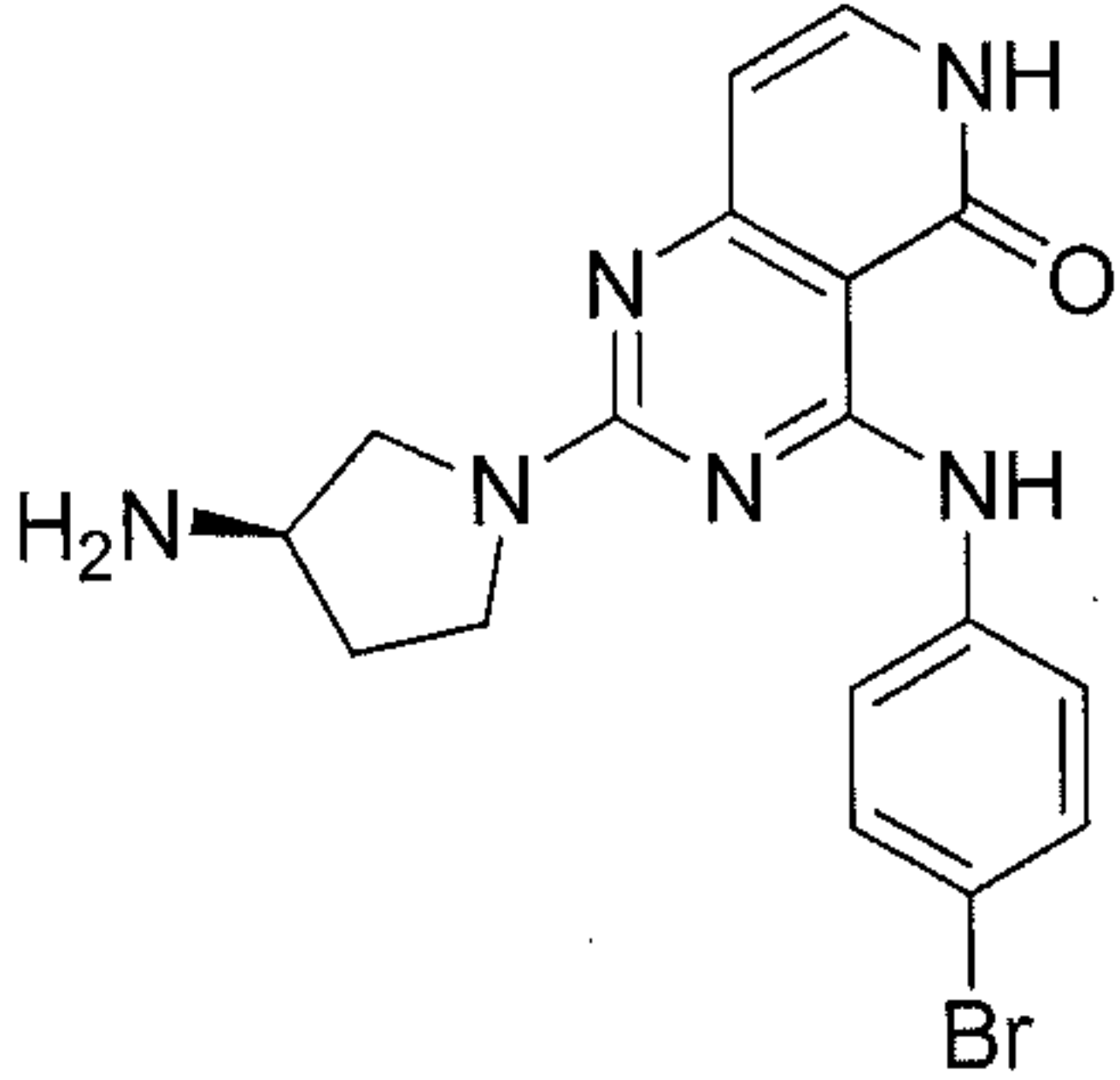
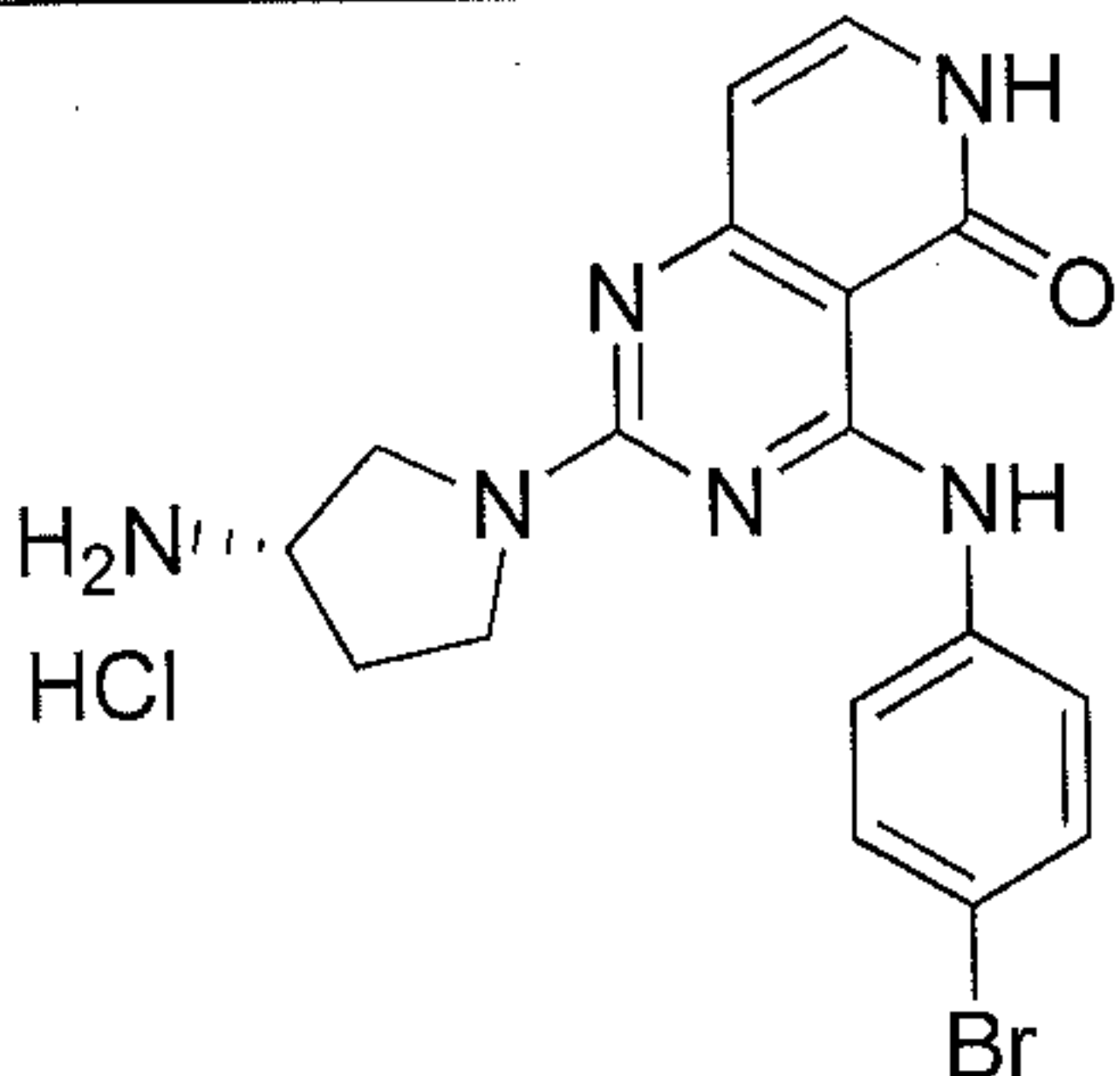
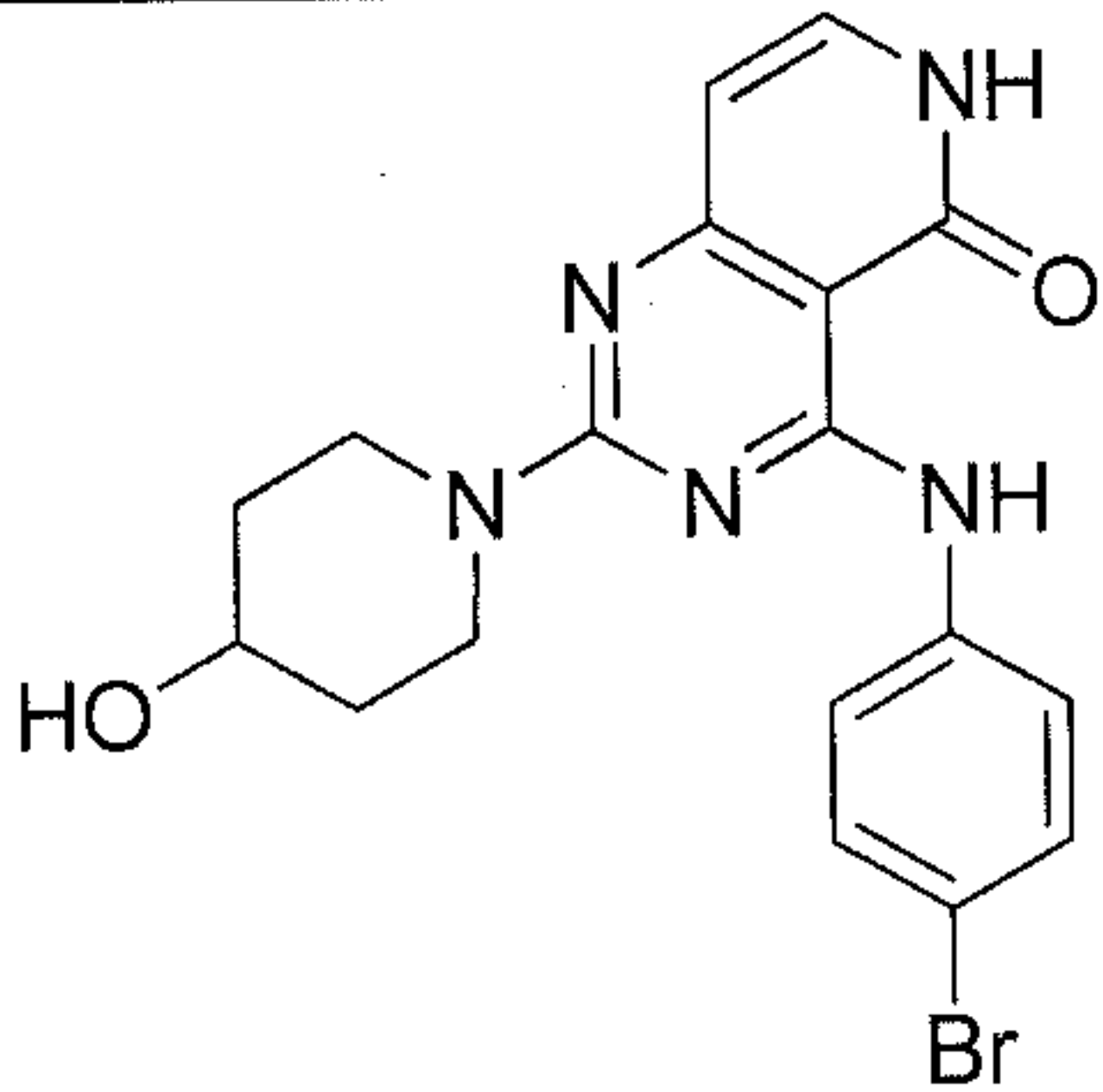
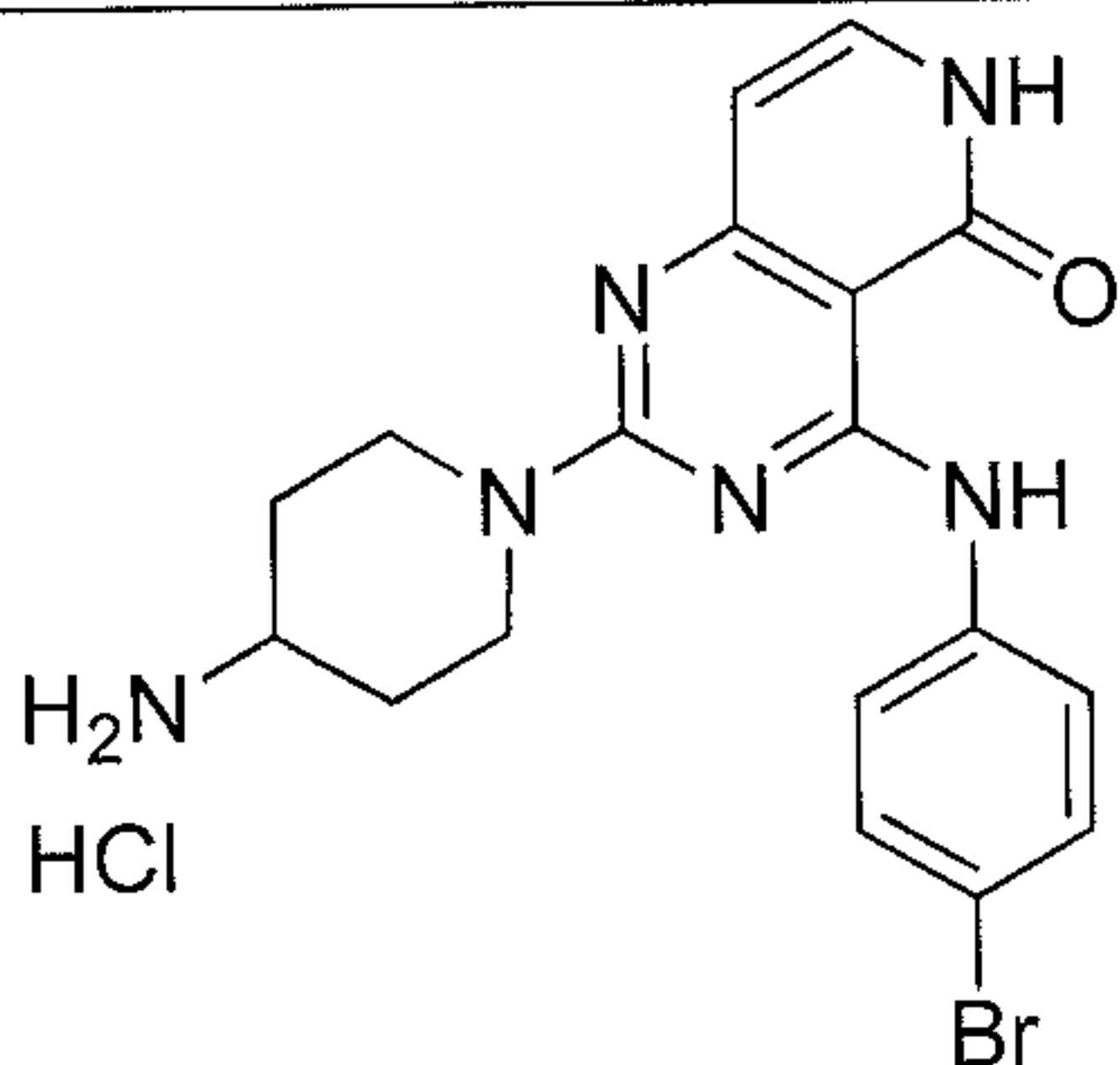
Compound No. 84

Compound 84 was prepared as described in *Example 1g* starting from 2-(methylthio)-4-(3-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (80mg, 0.23 mmol) and 4-(boc-amino) piperidine (70 mg, 0.35 mmol) and treating with 4 N HCl in dioxane to yield the title compound (15mg, 15%). MS m/z : 405. 2 ($M+1$)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.12 (s, 1H), 11.92 (s, 1H), 8.24 (s, 1H), 8.09 (s, 3H), 7.59~7.50 (m, 2H), 7.40~7.36 (m, 2H), 6.48 (s, 1H), 4.70 (s, 2H), 2.08~0.87 (m, 7H).

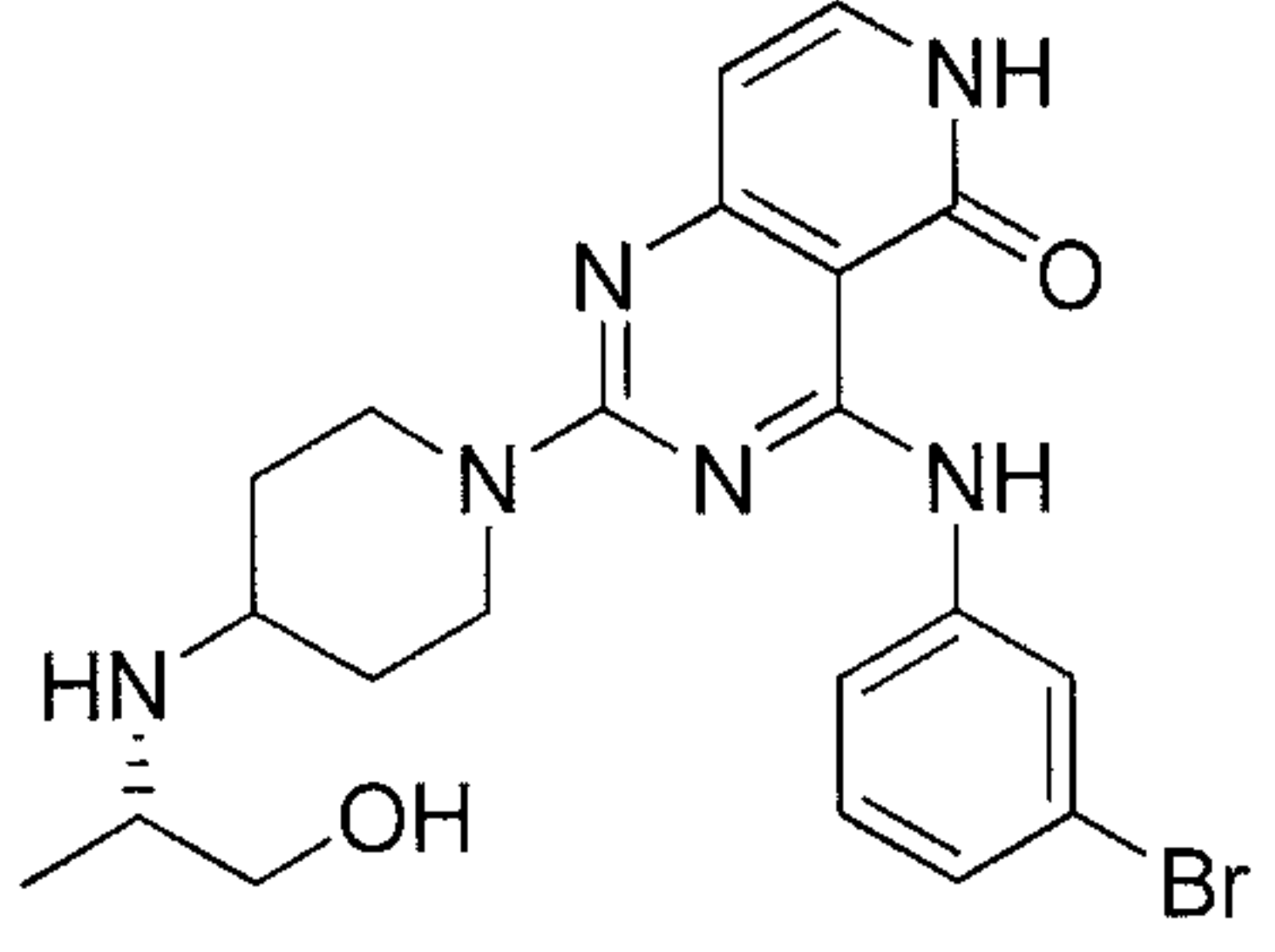
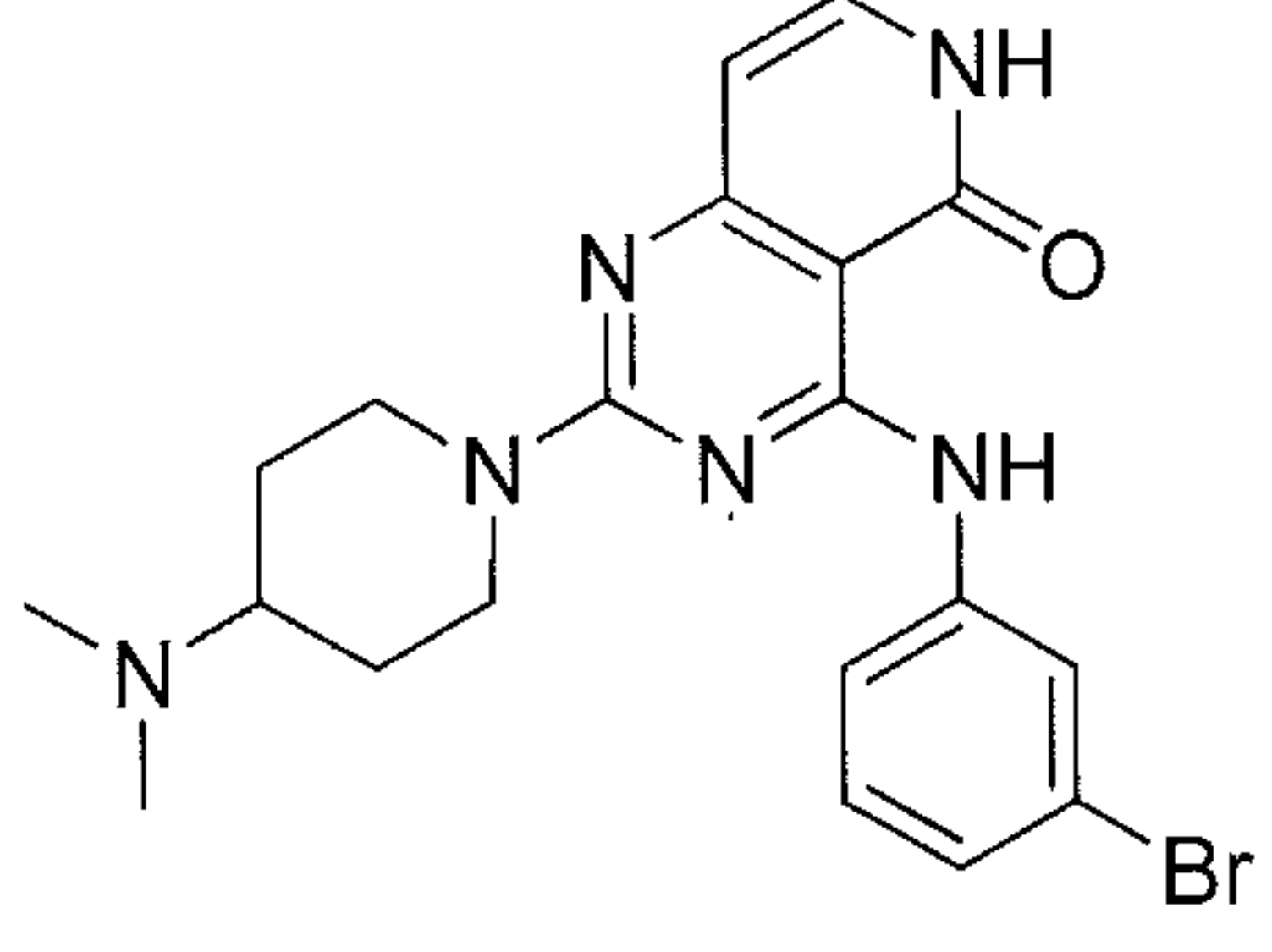
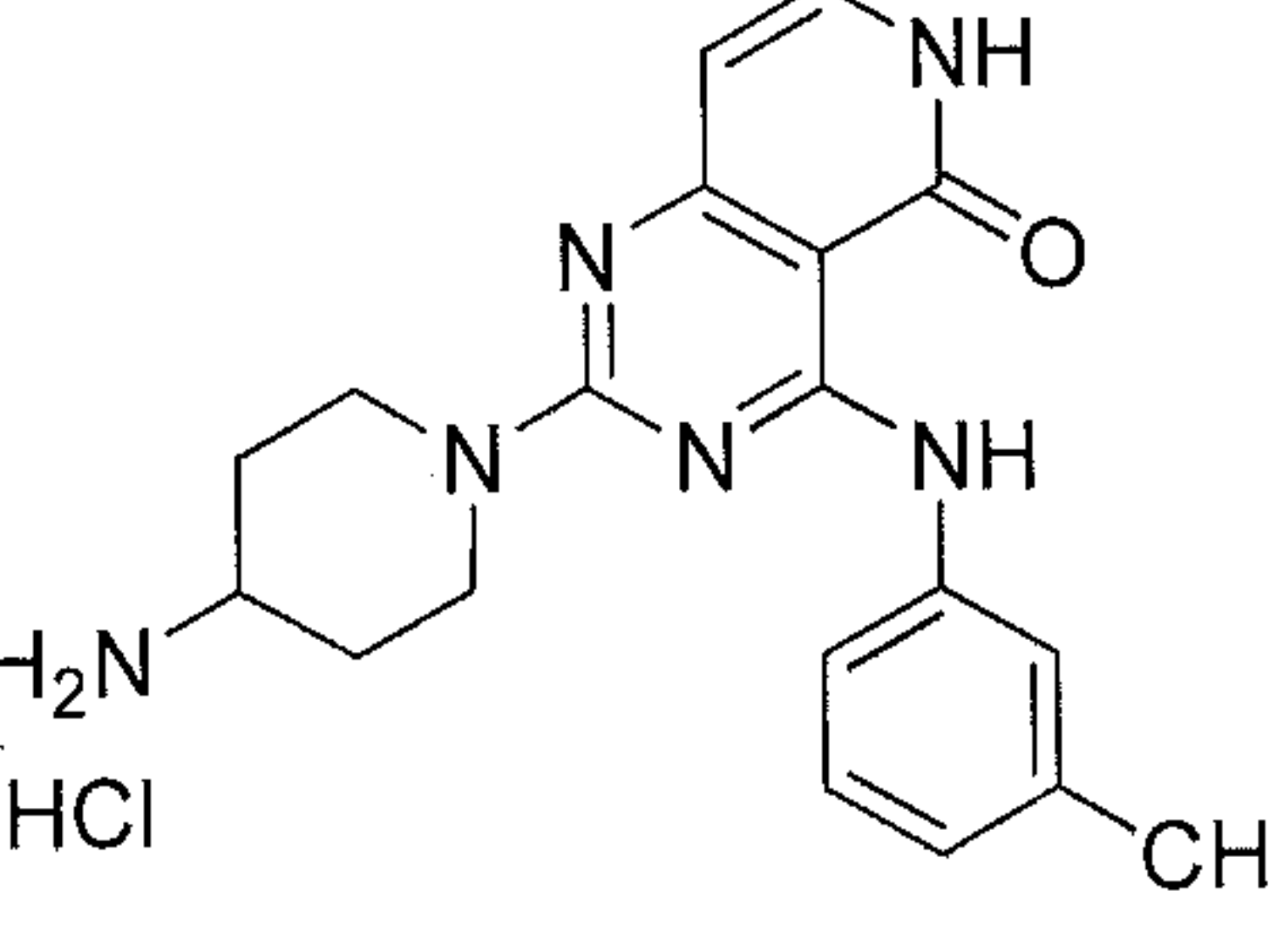
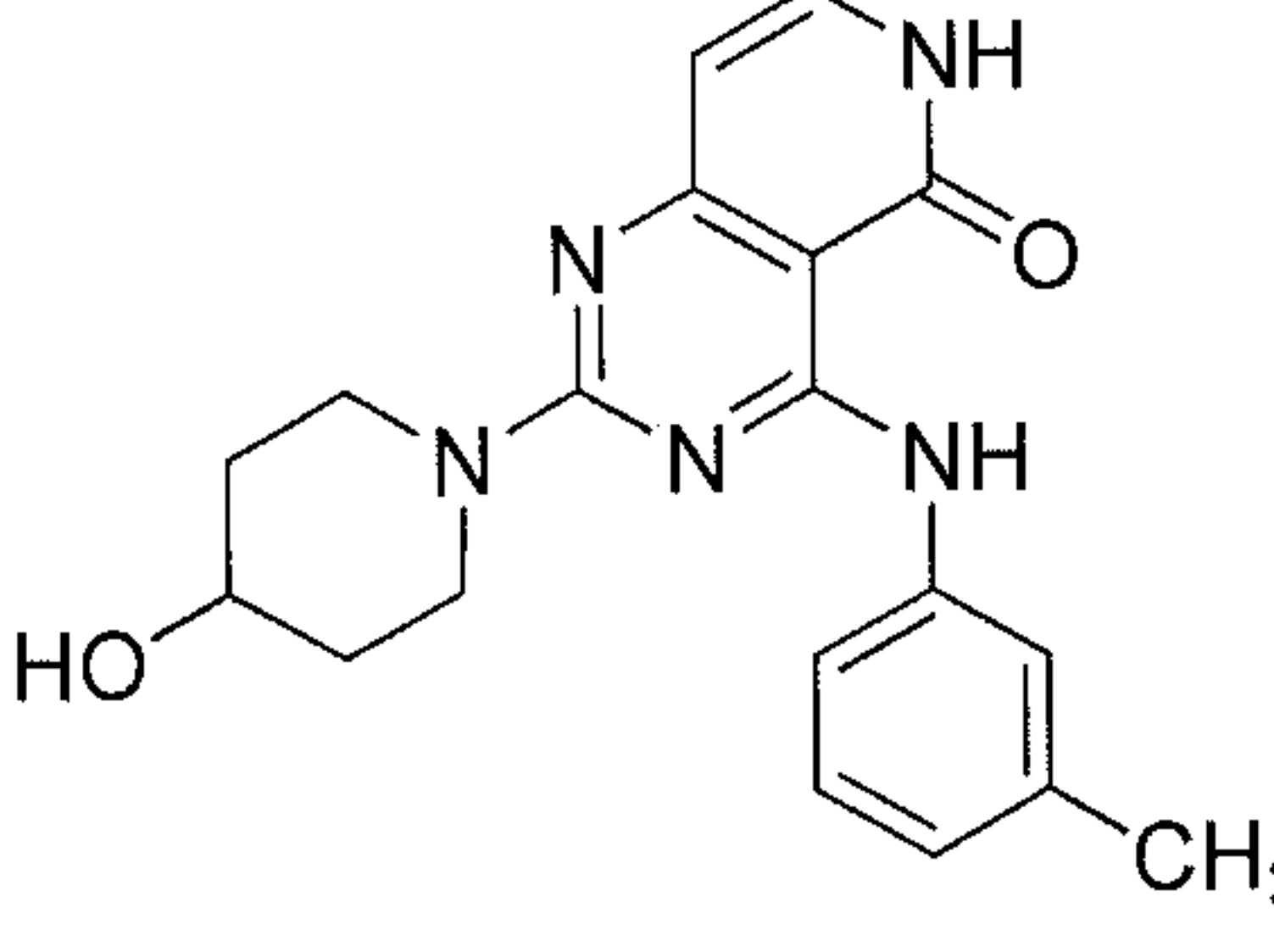
The following 4-(3-bromophenylamino)-2-(amino substituted)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one compounds were prepared from 4-(3-bromophenylamino)-2-(methylthio) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one and the corresponding amine following the procedure similar to that described in *Example 84*.

NO.	Structure	Name	Mass ($M+1$)
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85		4-(3-bromophenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	417
86		2-(4-aminopiperidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	416
87		4-(3-bromophenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	444
88		(<i>S</i>)-4-(3-bromophenylamino)-2-(4-(1-hydroxypropan-2-ylamino)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	474
89		(<i>R</i>)-2-(4-(3-aminopyrrolidin-1-yl)piperidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	485
90		(<i>R</i>)-2-(3-aminopyrrolidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	422

91		4-(3-bromophenylamino)-2-(3-hydroxy piperidin-1-yl)pyrido[4,3-d]pyrimidin-5(6H)-one	417
92		(R)-2-(3-aminopyrrolidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride	402
93		(S)-2-(3-aminopyrrolidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride	402
94		4-(4-bromophenylamino)-2-(4-hydroxy piperidin-1-yl)pyrido[4,3-d]pyrimidin-5(6H)-one	417
95		2-(4-aminopiperidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride	416

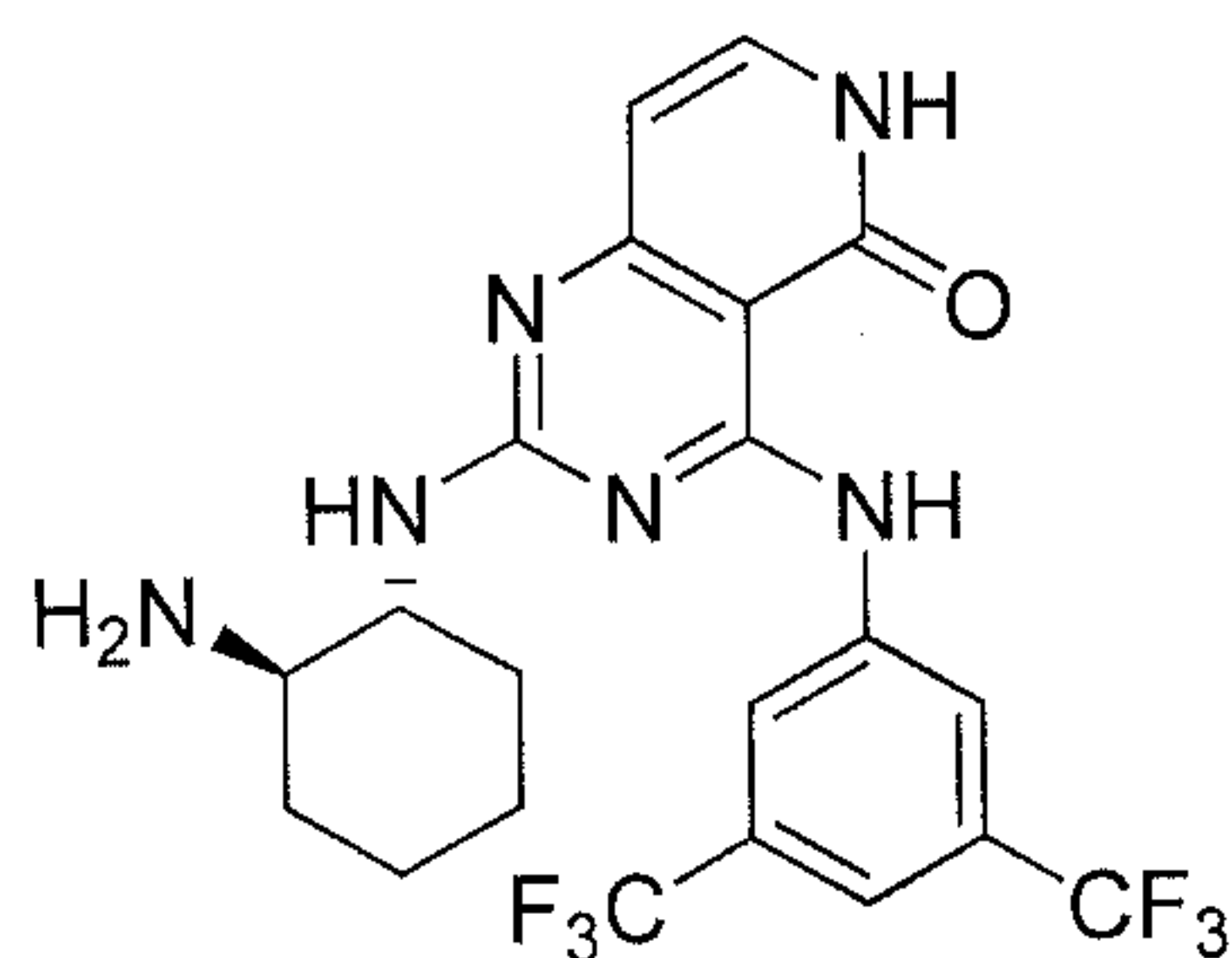
- 73 -

96		(S)-4-(3-bromophenylamino)-2-(4-(1-hydroxypropan-2-ylamino)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	473
97		4-(3-bromophenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	443
98		2-(4-aminopiperidin-1-yl)-4-(m-tolylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	351
99		2-(4-hydroxypiperidin-1-yl)-4-(m-tolylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	352

Example 100

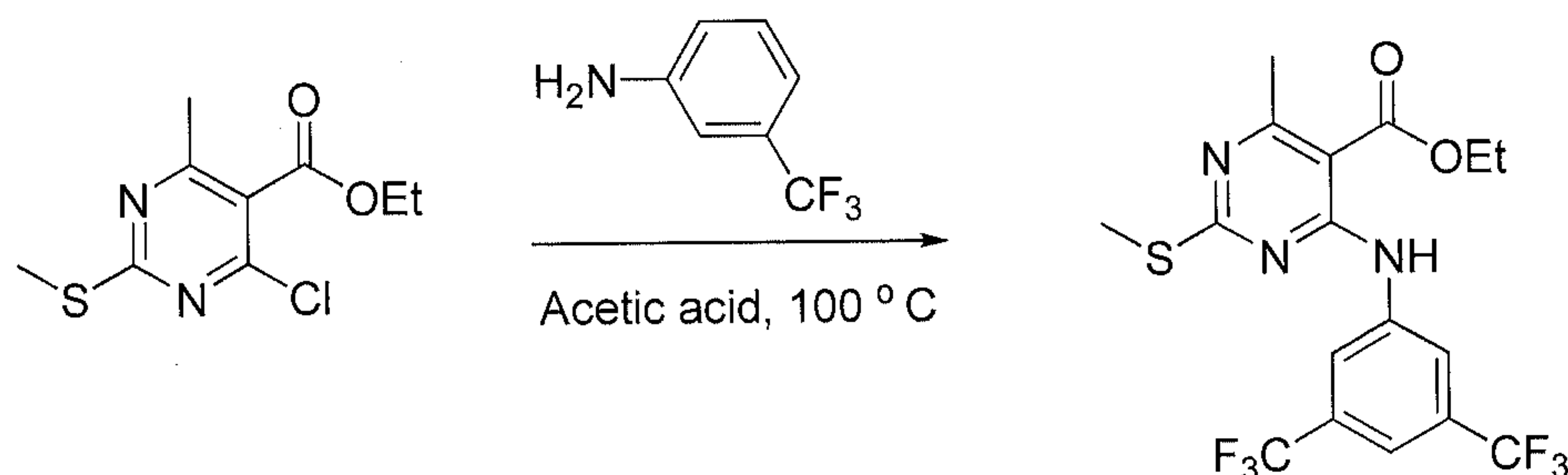
Synthesis of 2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

5



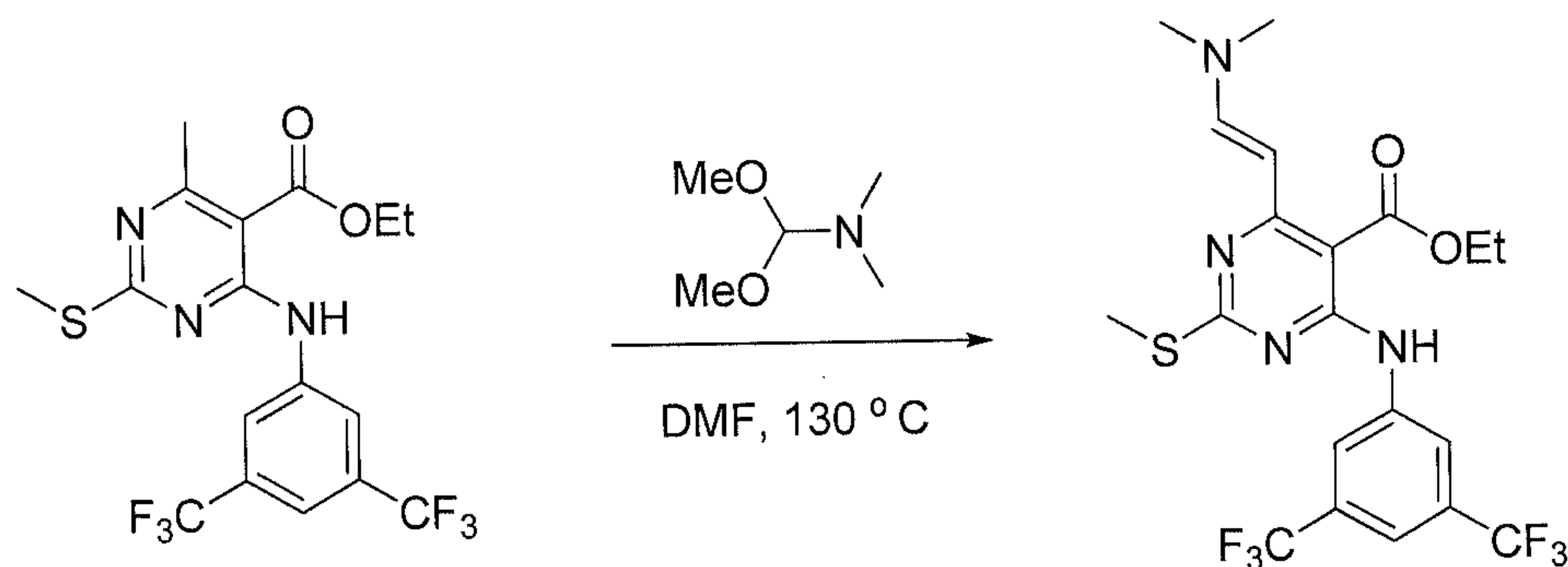
Compound No. 100

Example 100a: Ethyl 4-(3,5-bis(trifluoromethyl)phenylamino)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate



The title compound was prepared as described in *Example 1d* by starting from ethyl 4-chloro-6-methyl-2-(methyl thio)pyrimidine-5-carboxylate (1.2 g, 4.86 mmol) and 3,5-bis(trifluoromethyl) aniline (777 uL, 4.86 mmol) and continuing until the reaction yielded the brown solids, title compound ethyl 4-(3, 5-bis(trifluoromethyl)phenyl amino)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (1.53 g, 70.2 %). MS m/z: 440.1 (M+1)⁺.

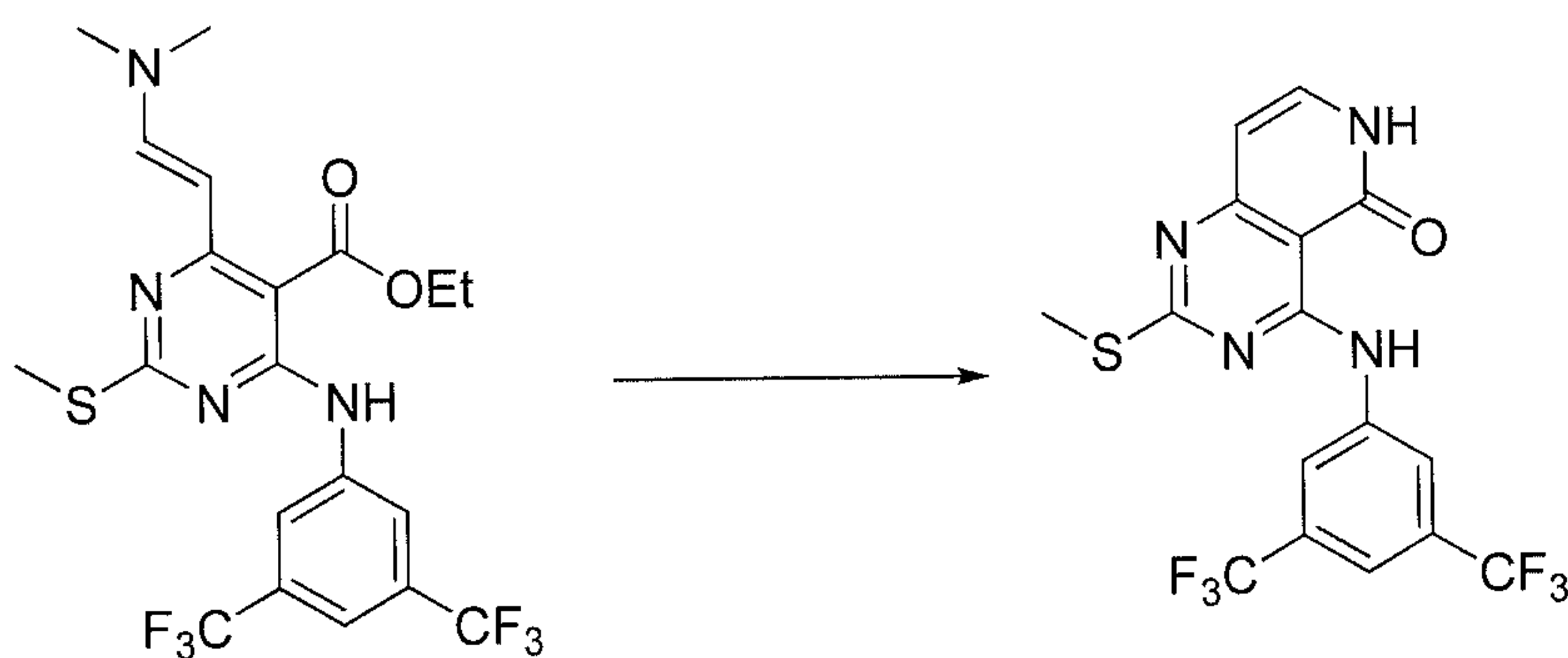
Example 100b: (E)-Ethyl 4-(3,5-bis(trifluoromethyl)phenylamino)-6-(2-(dimethylamino)vinyl)-2-(methylthio)pyrimidine-5-carboxylate



The title compound was prepared as described in *Example 1e* by starting from ethyl 4-(3,5-bis (trifluoro methyl)phenylamino)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (1.52 g, 3.6 mmol) and N,N-dimethylformamide dimethylacetal (743 uL, 5.2 mmol) and continuing until the reaction yielded the crude title compound (E)-ethyl 4-(3,5-bis(trifluoromethyl)phenylamino)-6-(2-(dimethyl amino)vinyl)-2-(methyl thio)pyrimidine-5-carboxylate. The resultant compound was used for the next step without further purification.

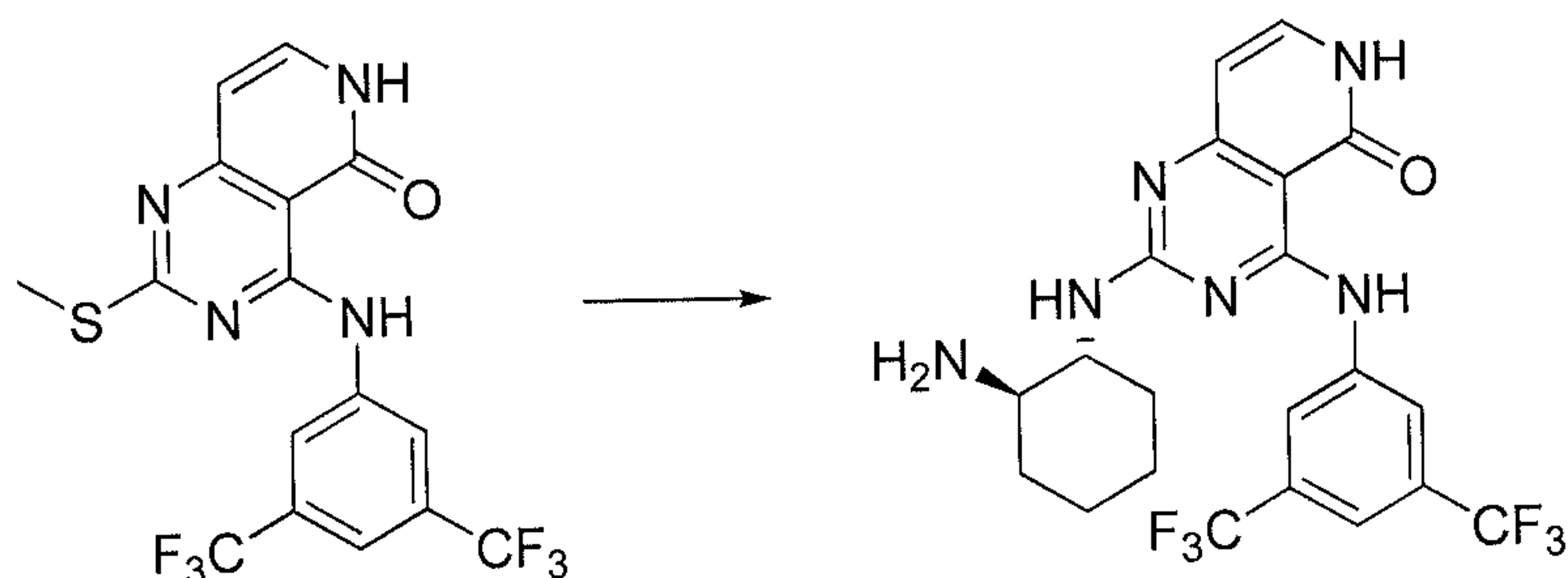
Example 100c: 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

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The title compound was prepared as described in *Example 1f* by starting from (E)-ethyl 4-(3,5-bis(trifluoromethyl) phenylamino)-6-(2-(dimethylamino)vinyl)-2-(methylthio)pyrimidine-5-carboxylate and aq. NH_4OH solution and continuing until the reaction yielded pale yellow solids, title compound (537 mg). MS m/z : 421.1 ($M+1$)⁺.

Example 100d: 2-((1*R*, 2*R*)-2-amino cyclohexylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

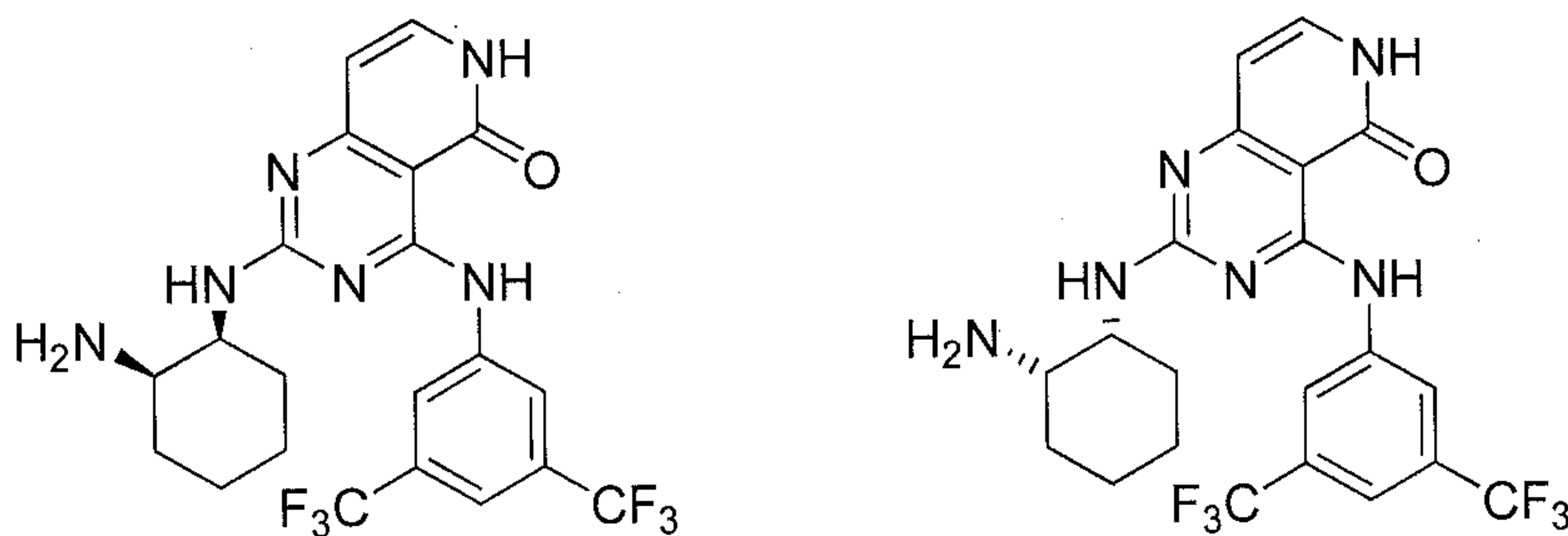


The title compound was prepared as described in *Example 1g* by starting from 4-(3,5-bis(trifluoromethyl)phenyl amino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (100 mg, 0.24 mmol) and (±)-trans-1,2-diamino cyclohexane and continuing until the reaction yielded the title compound, 2-((1*R*, 2*R*)-2-aminocyclohexylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one. MS m/z : 487 ($M+1$)⁺ ¹H NMR (300MHz, DMSO-*d*₆) δ ppm 1.25- 1.97 (m, 10H), 6.10 (d, J = 7.2 Hz, 1H), 7.41 – 7.44 (m, 3H), 7.41 – 7.76 (m, 4H), 8.47 (s, 2H), 12.49 (s, 1H).

Example 101

Synthesis of 2-((1*R*, 2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one with (2-((1*S*, 2*R*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl) phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

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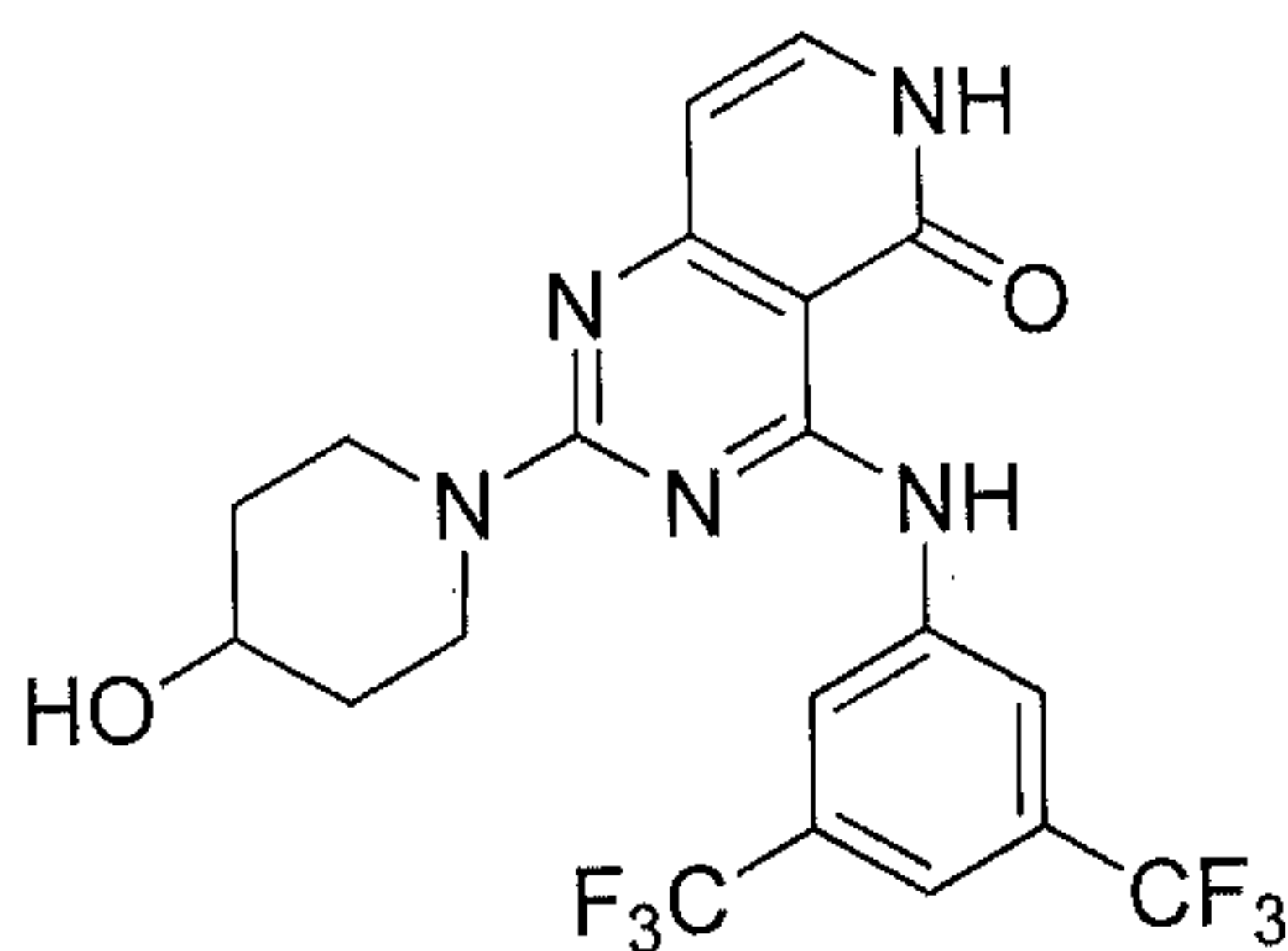


Compound No. 101

5 The title compound was prepared as described in *Example 2d* by starting from 2-(methylthio)-4-(3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one 100 mg(0.26 mmol), (1*R*, 2*S*)-2-aminocyclo hexylamine and continuing until the reaction yielded white solids, the title compound, (2-((1*R*, 2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (92 mg, 77.4 %). MS *m/z*:
10 419.3 (M+H)⁺.

Example 102

Synthesis of 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

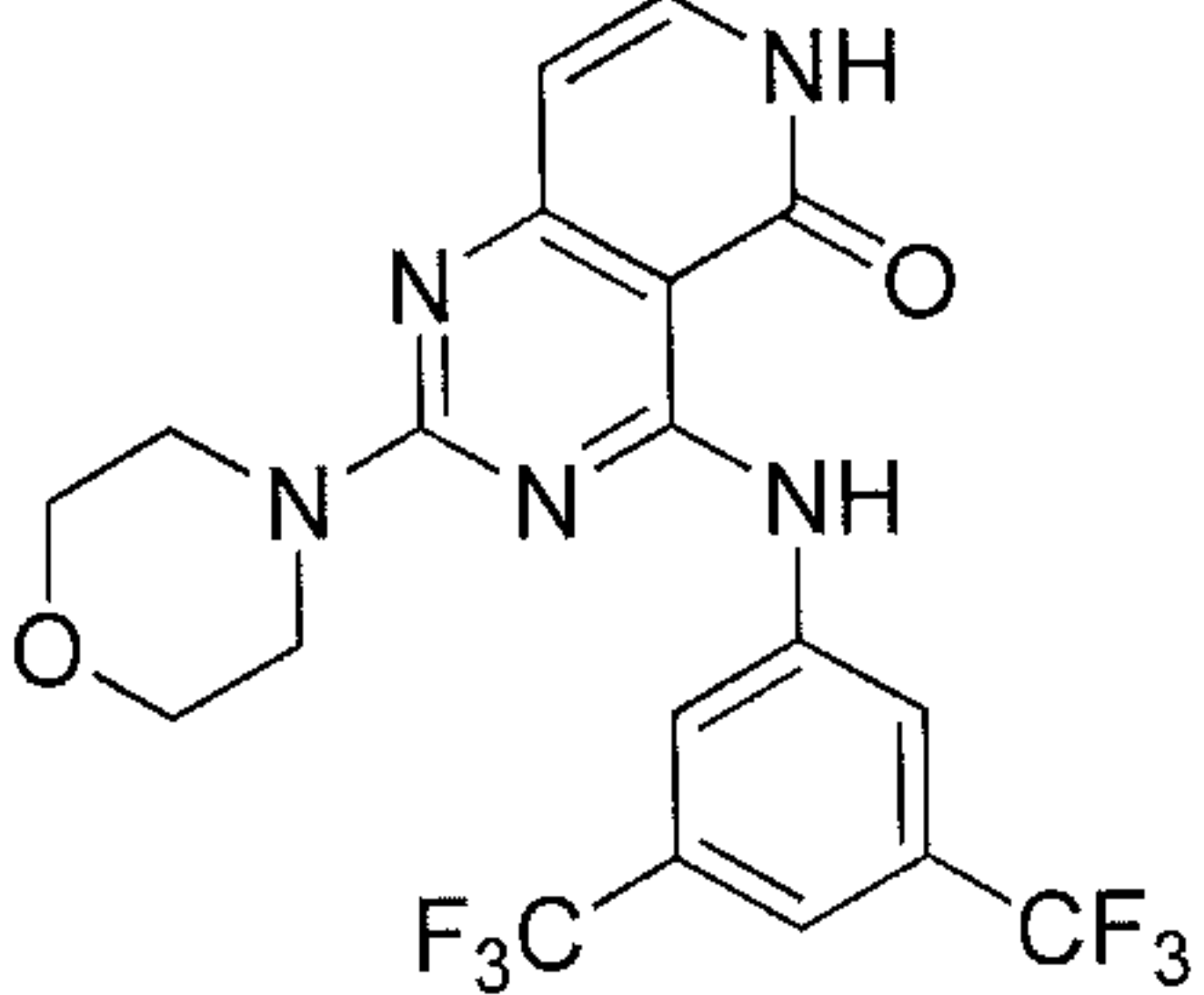
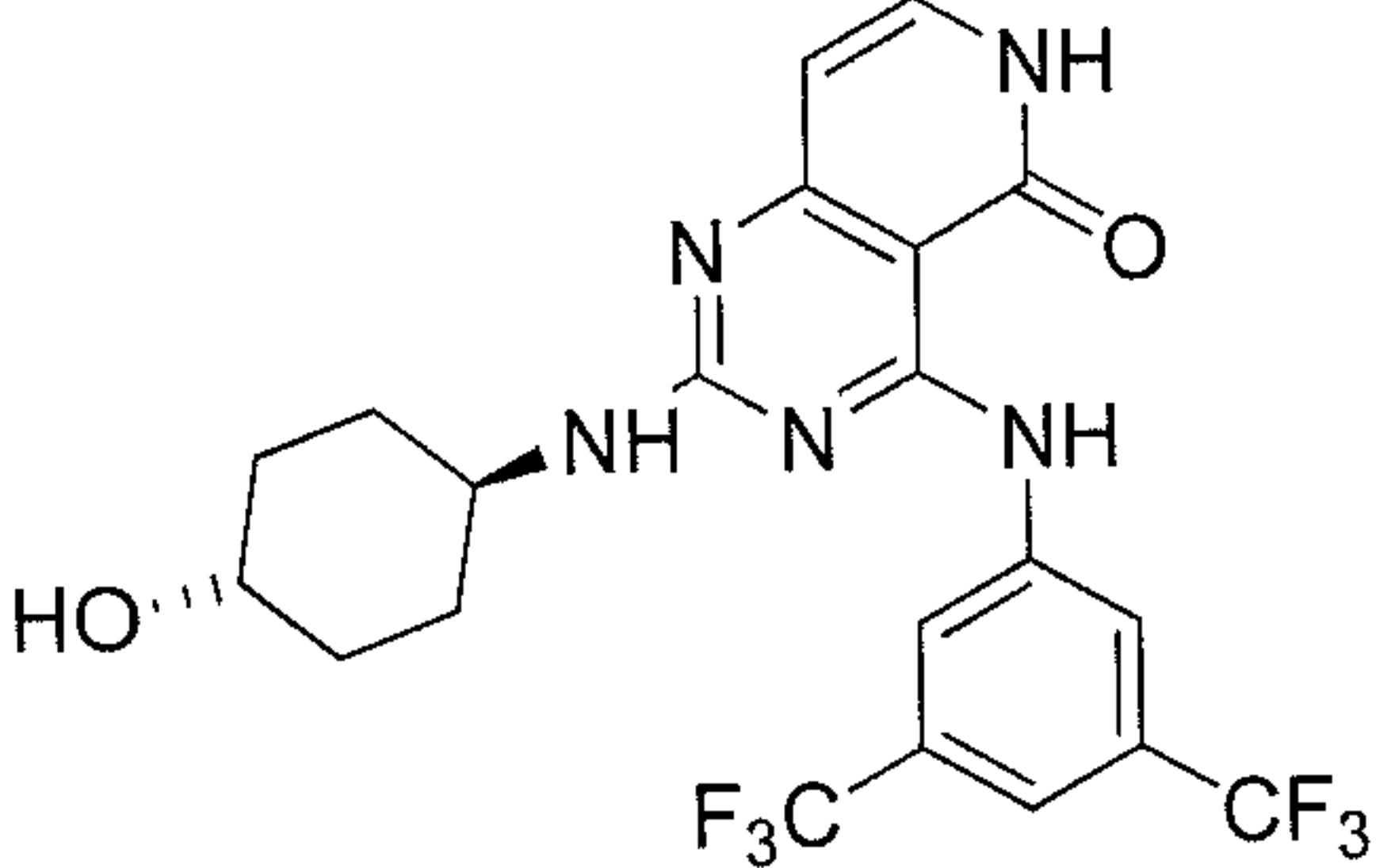
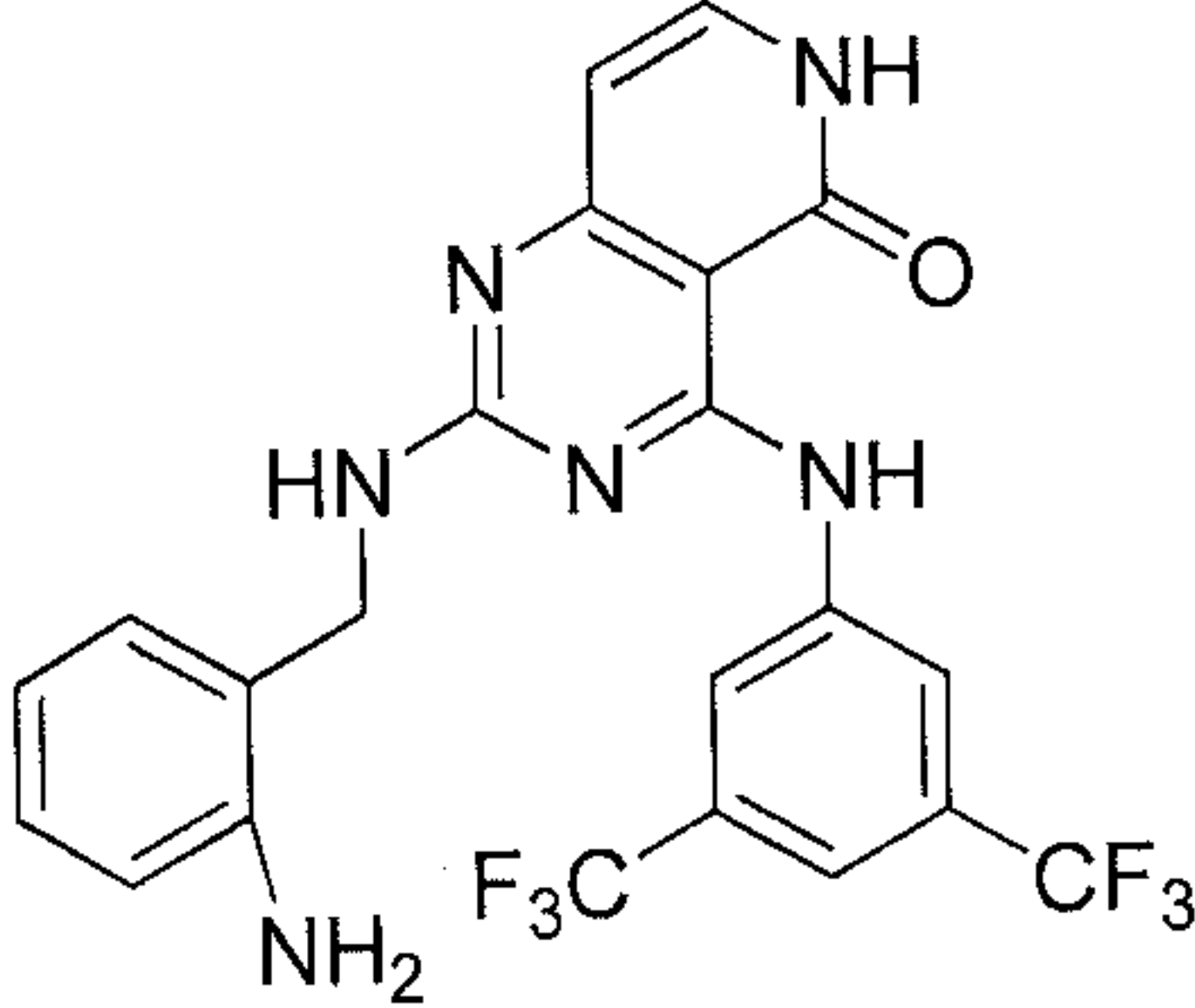
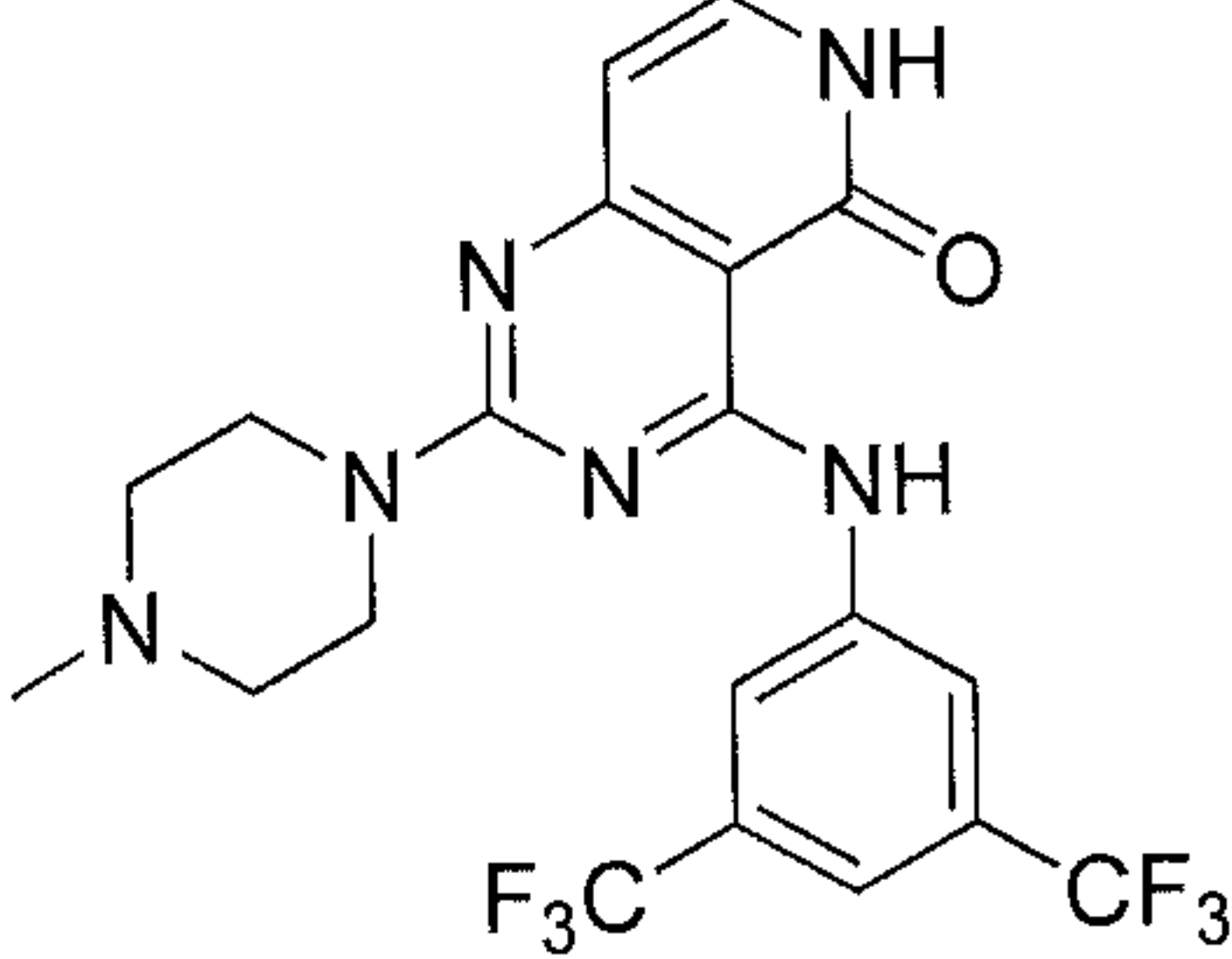


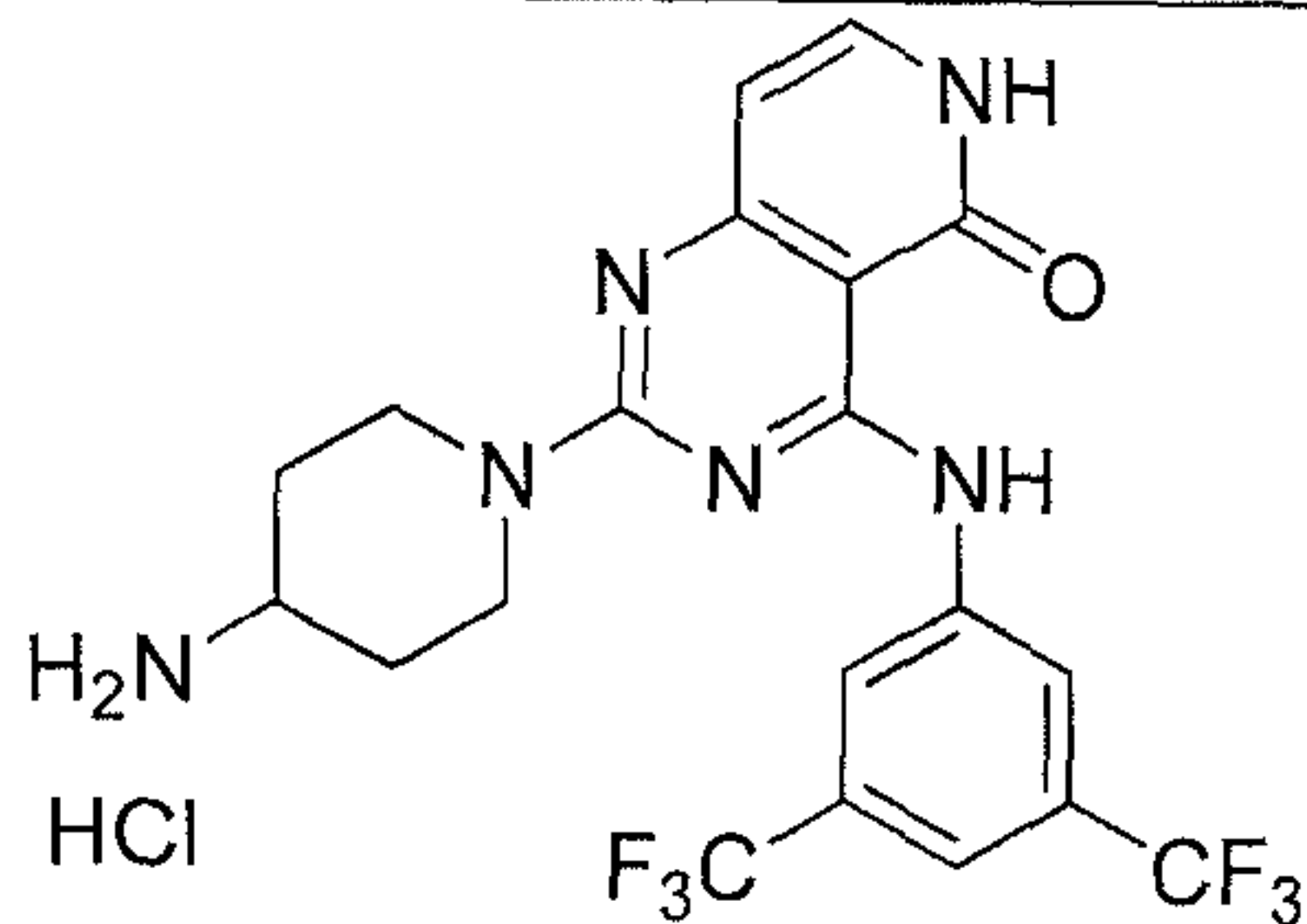
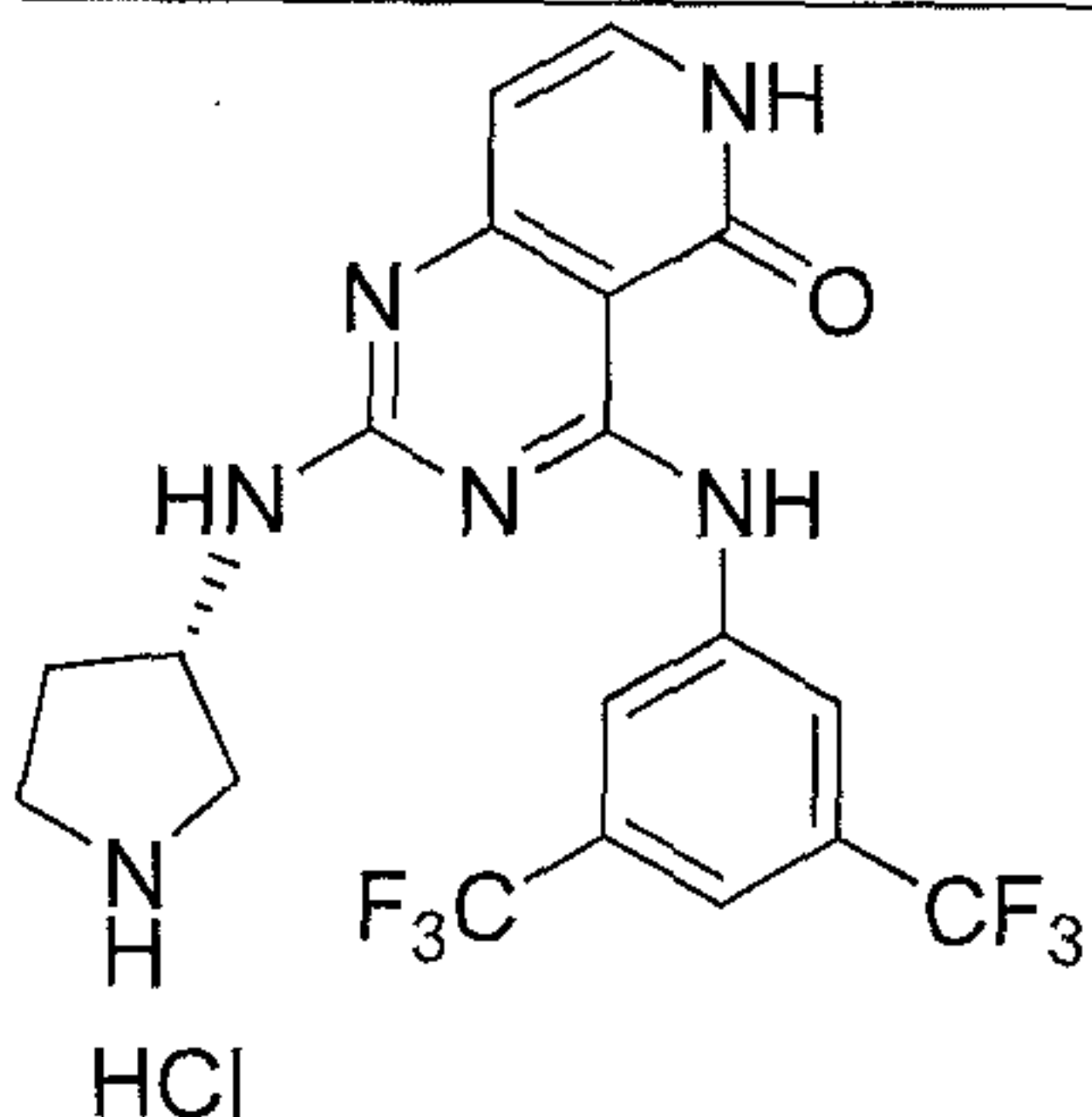
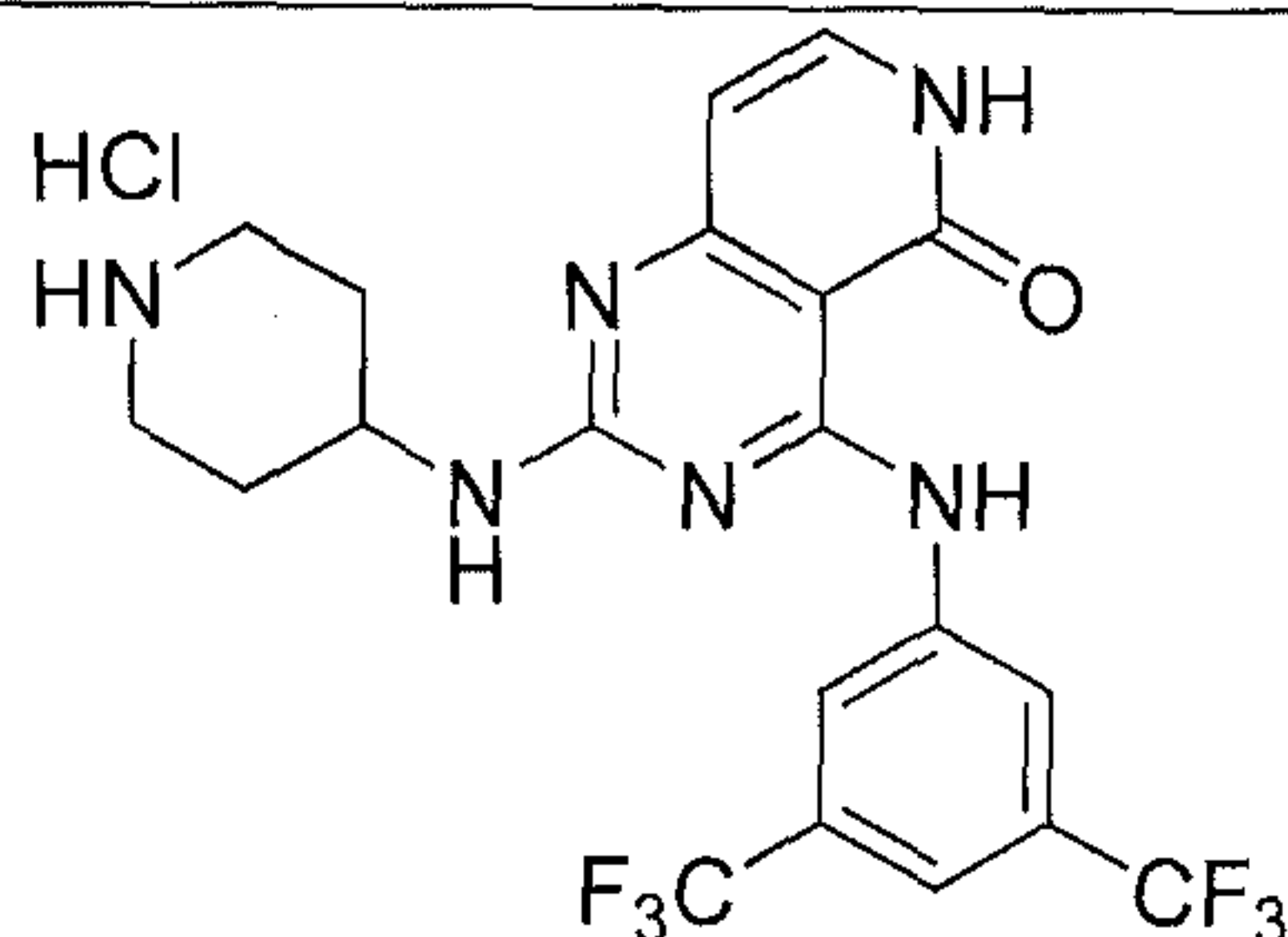
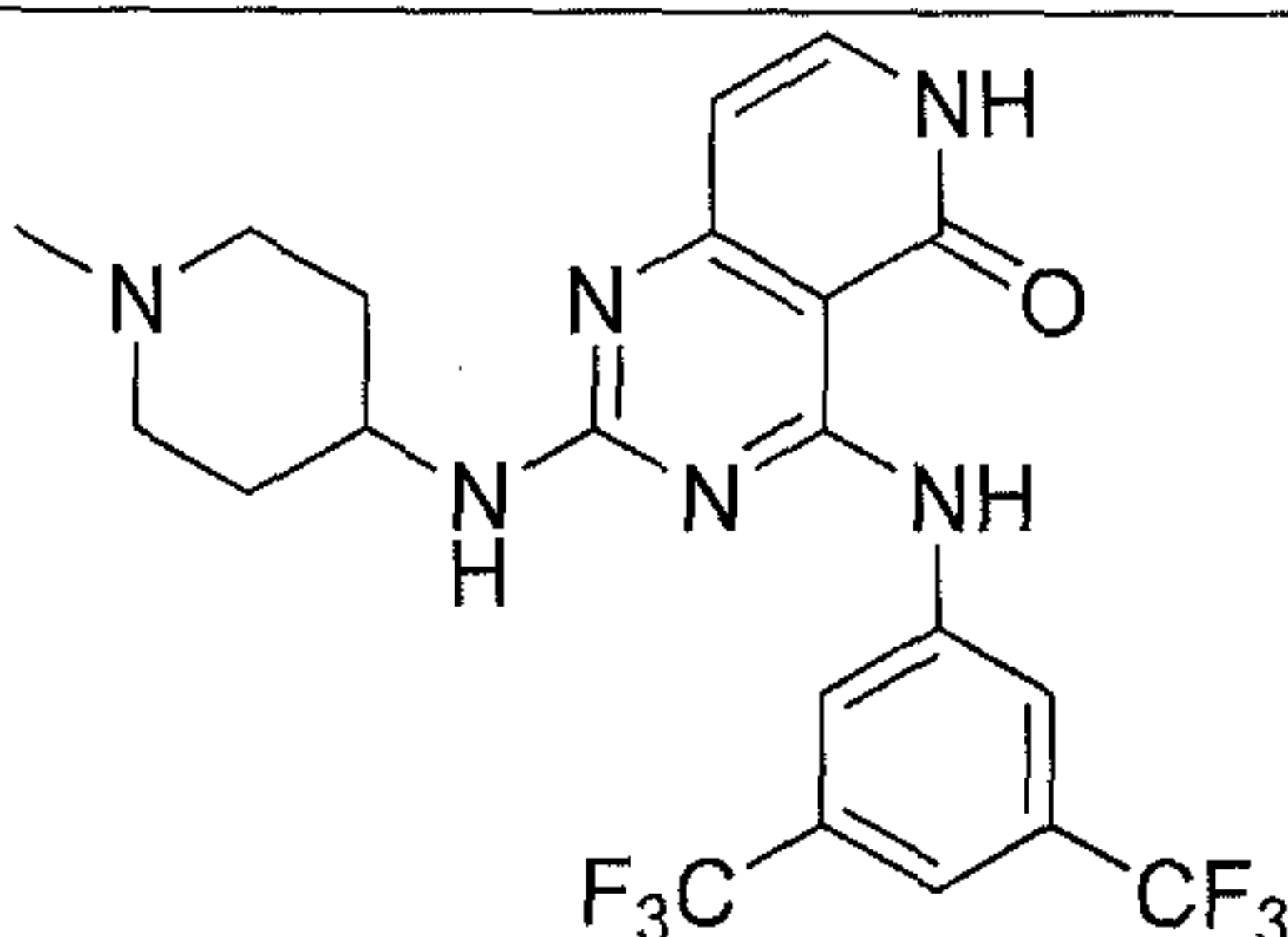
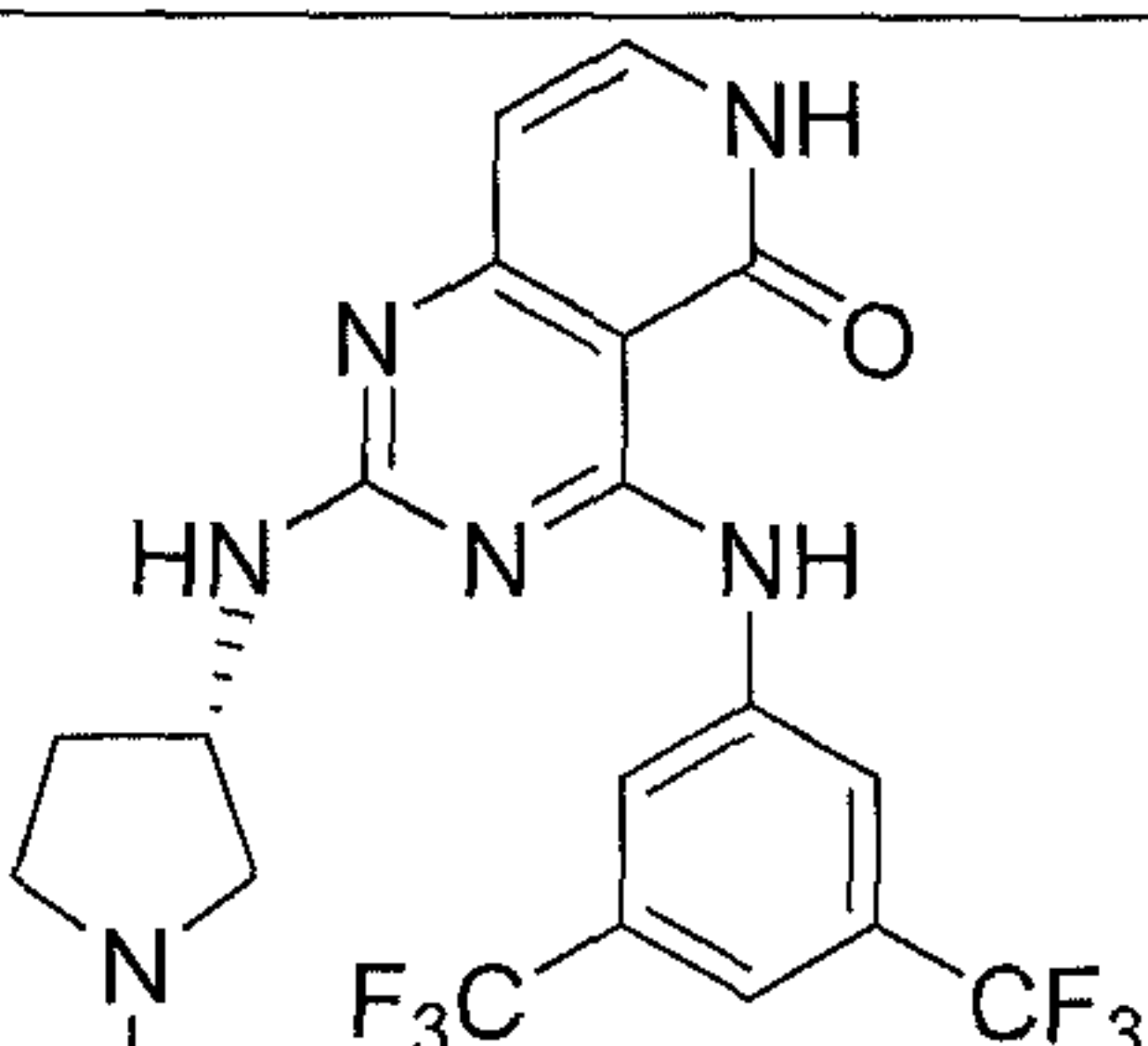
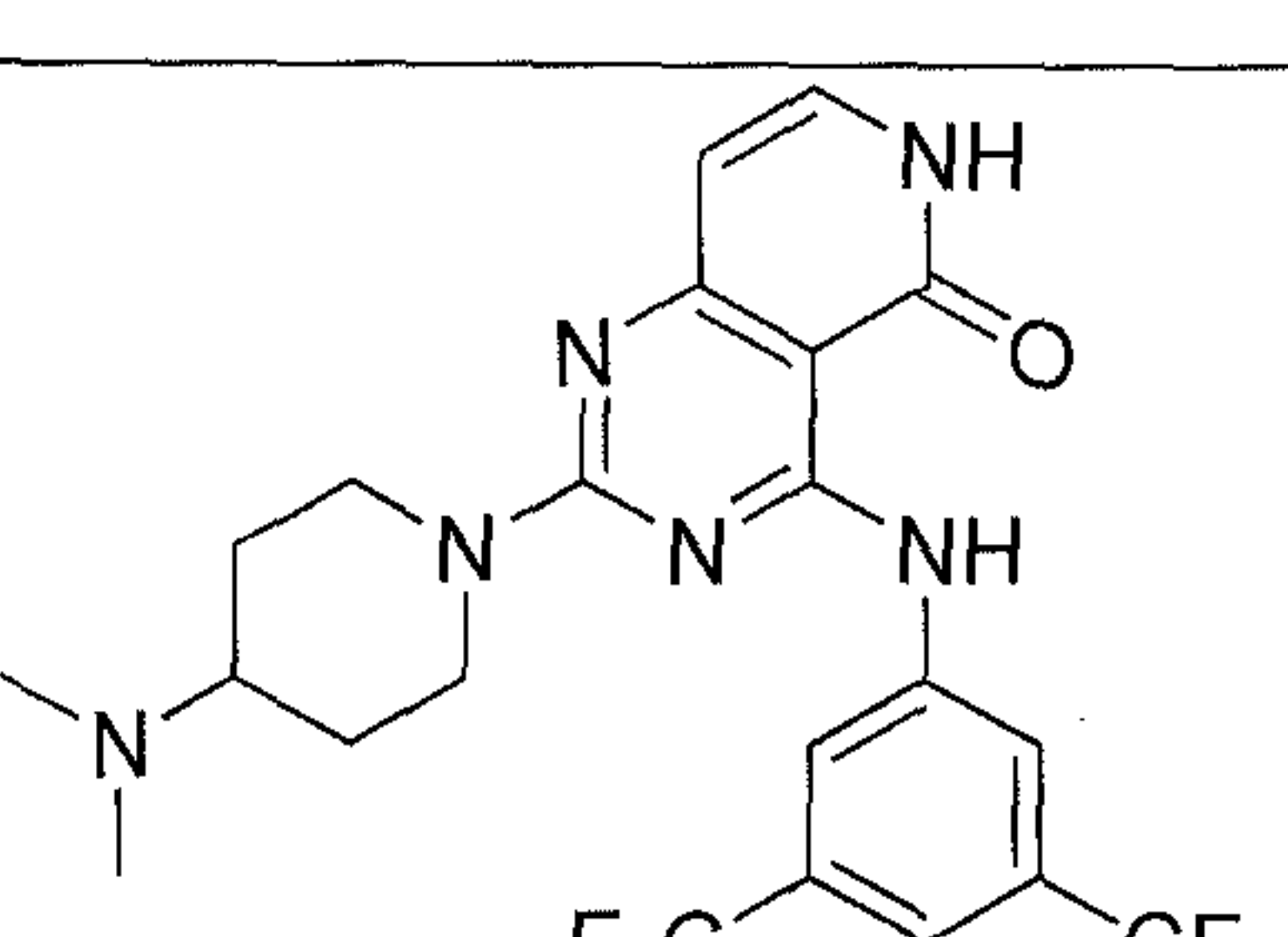
Compound No. 102

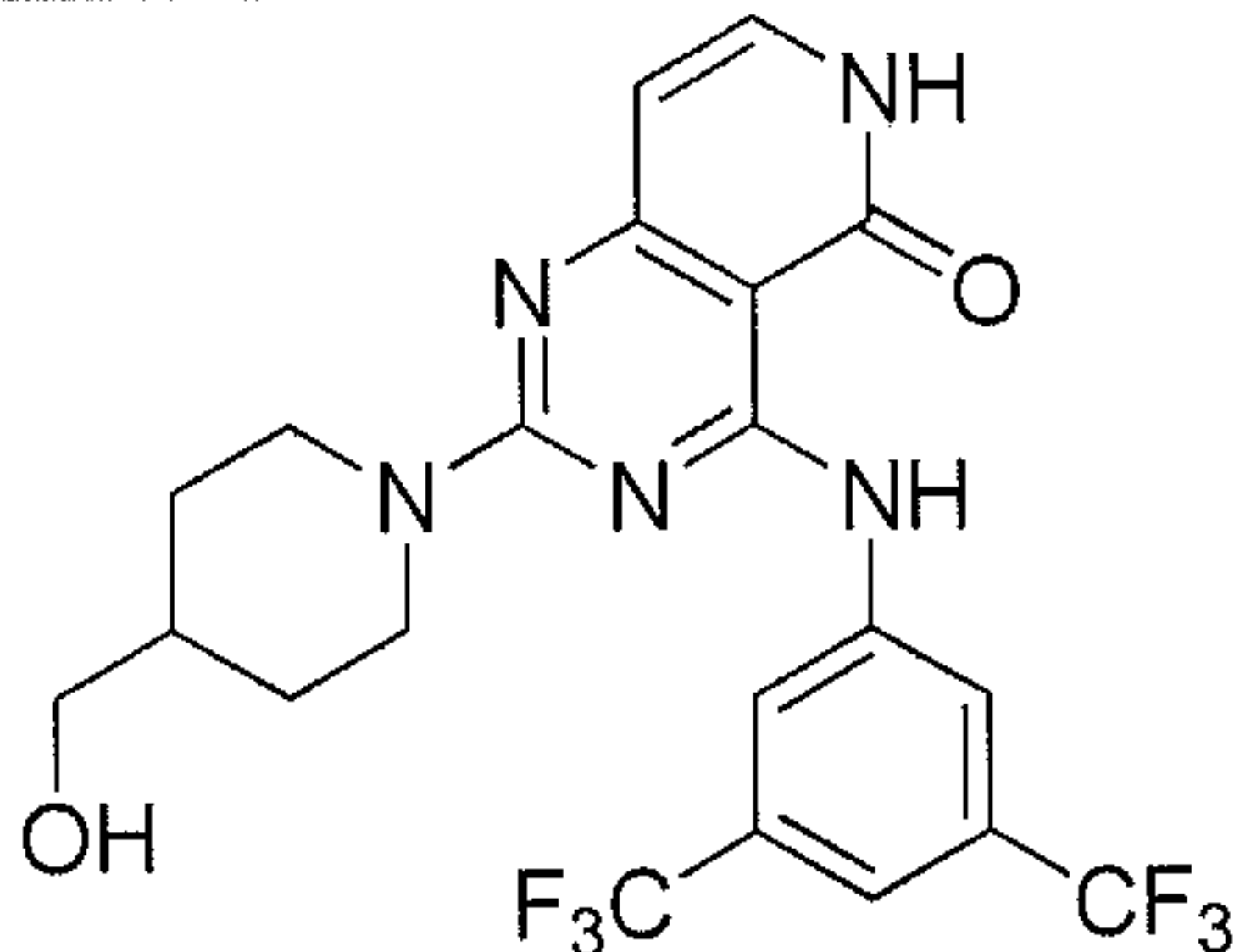
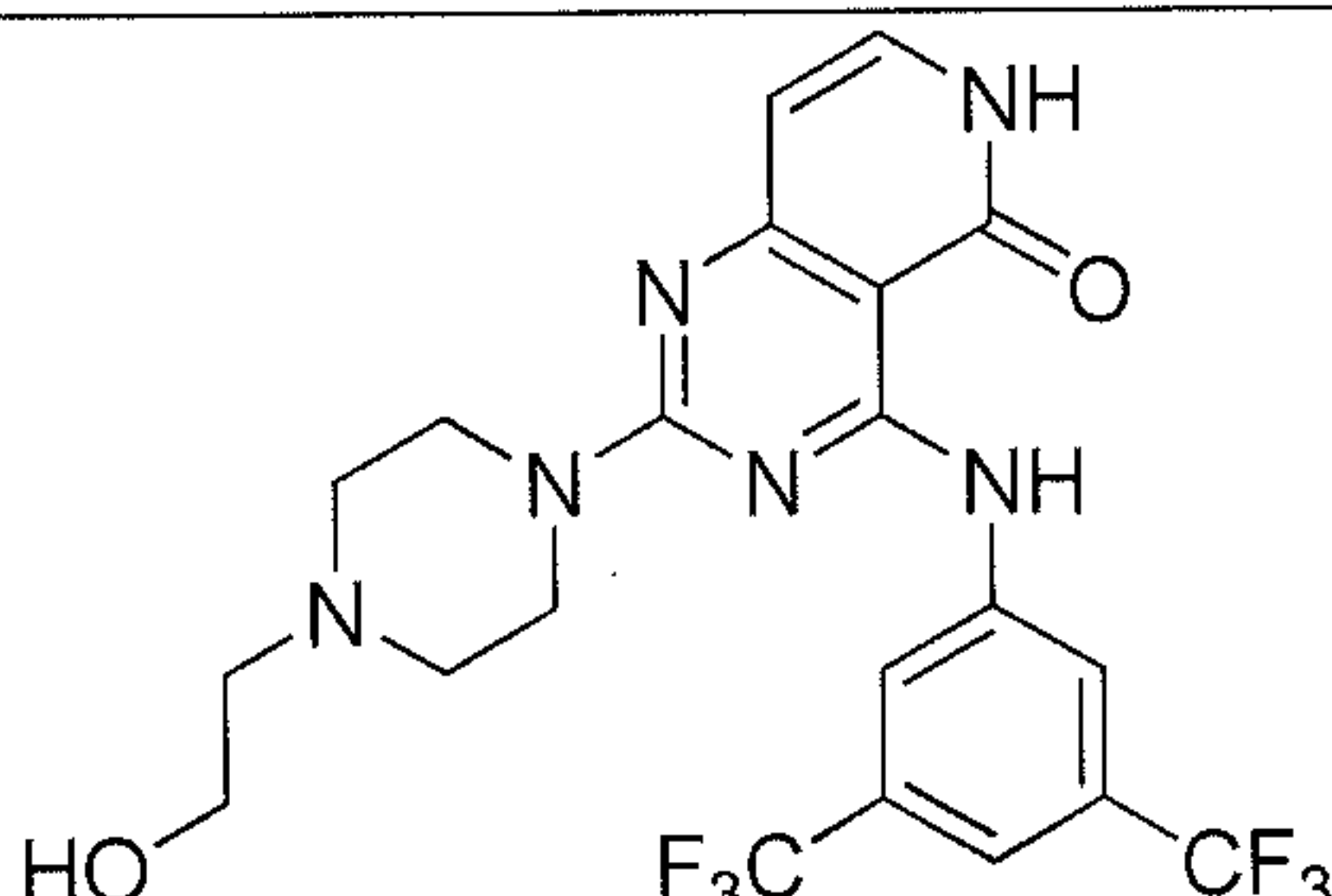
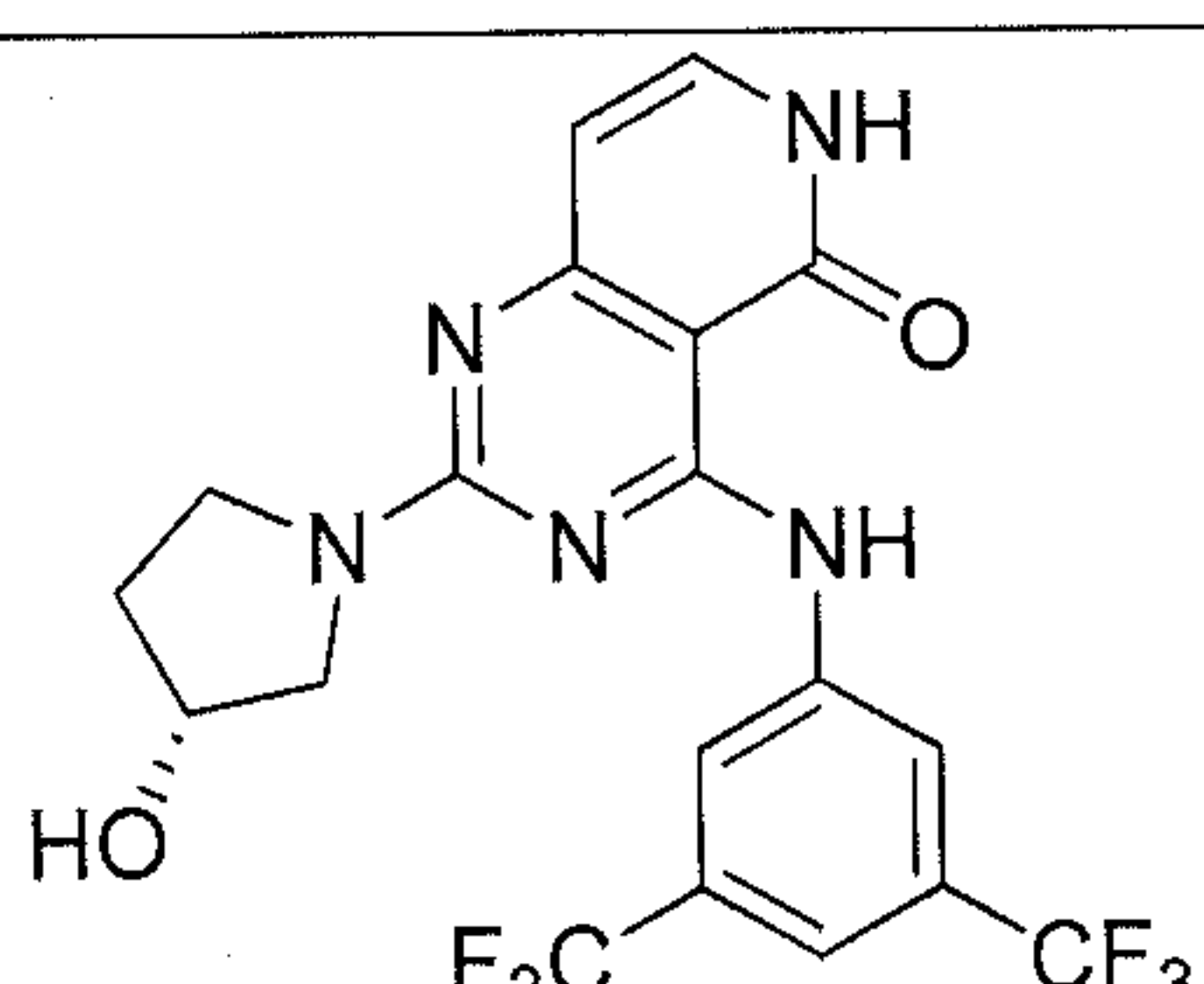
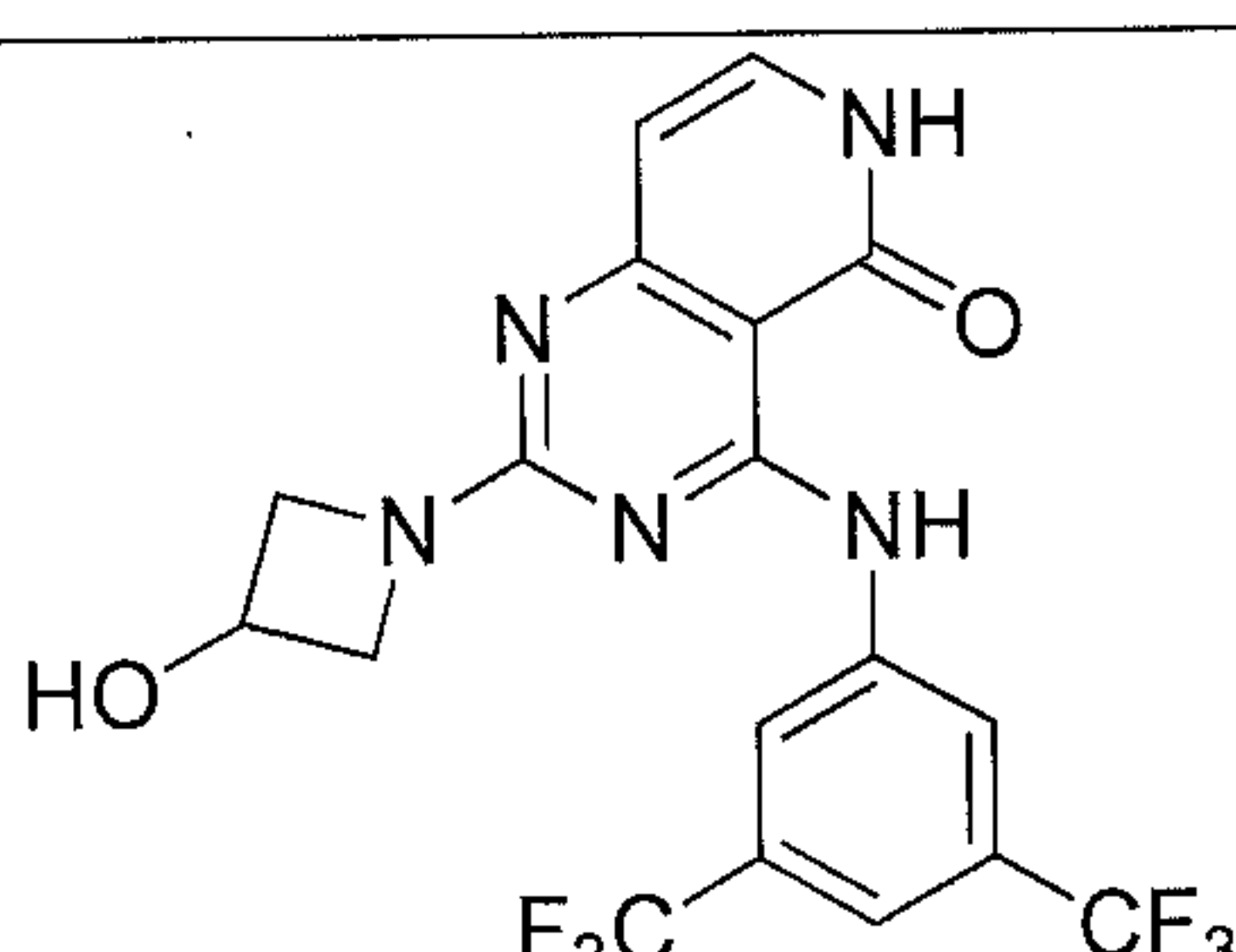
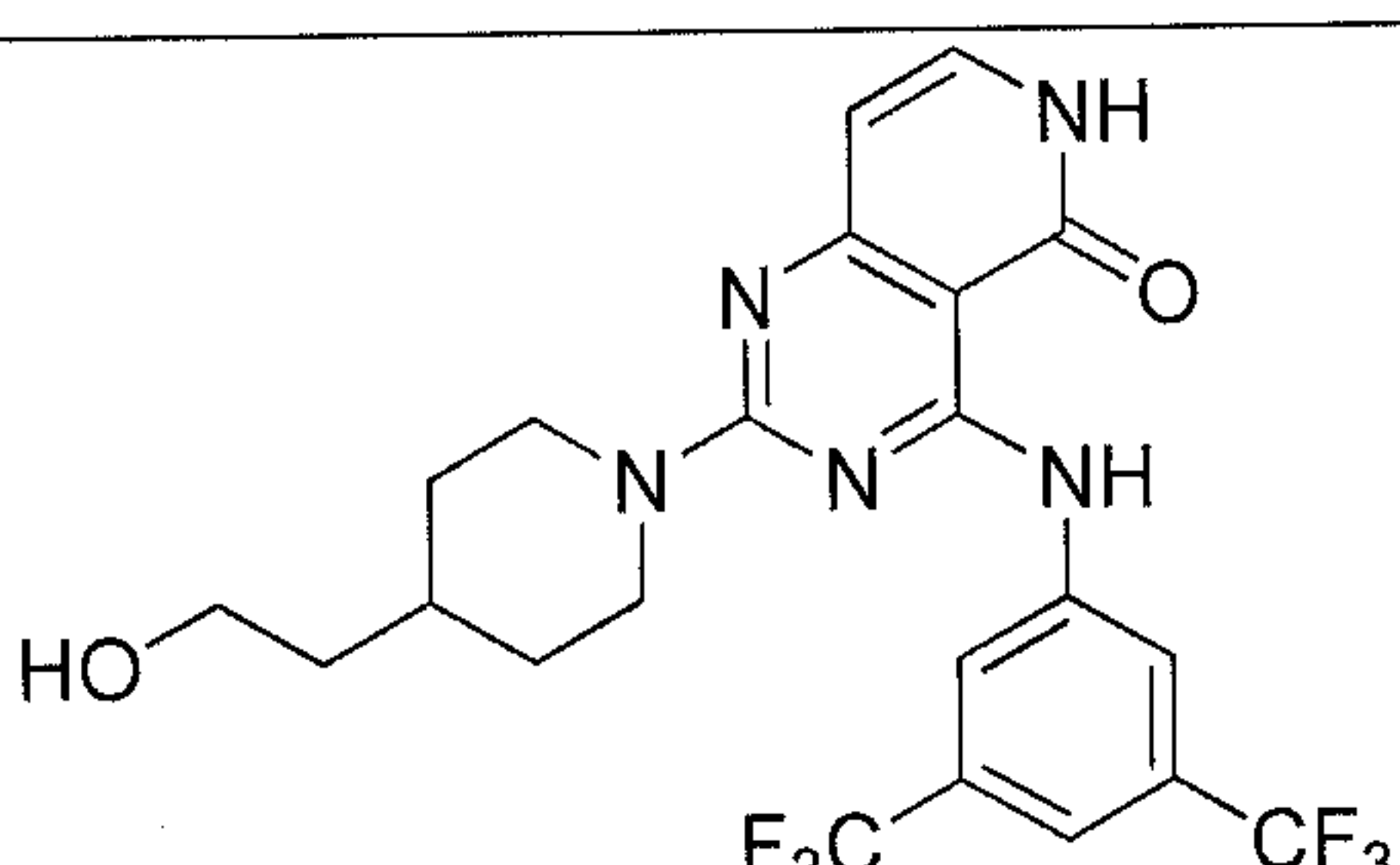
15 Compound No. 102 was prepared as described in *Example 1g* by starting from 4-(3,5-bis(trifluoromethyl)phenyl amino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (70 mg, 0.17 mmol) and 4-hydroxy piperidine (20.6mg, 0.2 mmol) and continuing until the reaction yielded light brown solids of Compound No. 102 (60 mg, 76 %). MS *m/z*;¹H NMR (300MHz, DMSO-*d*₆) δ ppm 474.1(M+1)⁺, 12.27 (s, 1H), 8.47 (s, 2H), 7.74 (s, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 6.17 (d, *J* = 7.2 Hz, 1H), 4.24 (b, 2H), 3.78 (m, 1H), 3.45-3.39 (m, 2H), 1.81-1.77 (m, 2H),
20 1.38 (m, 2H).

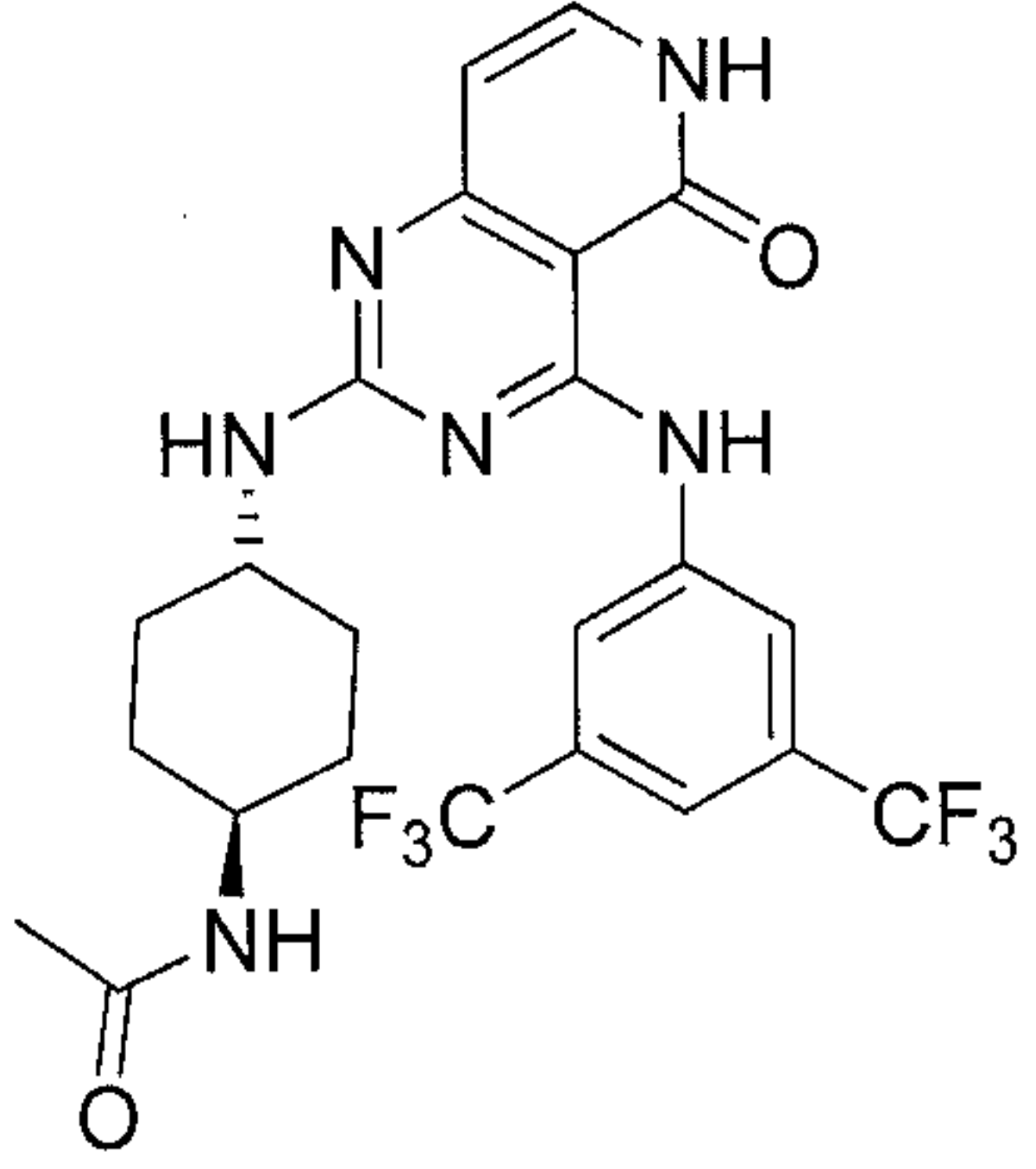
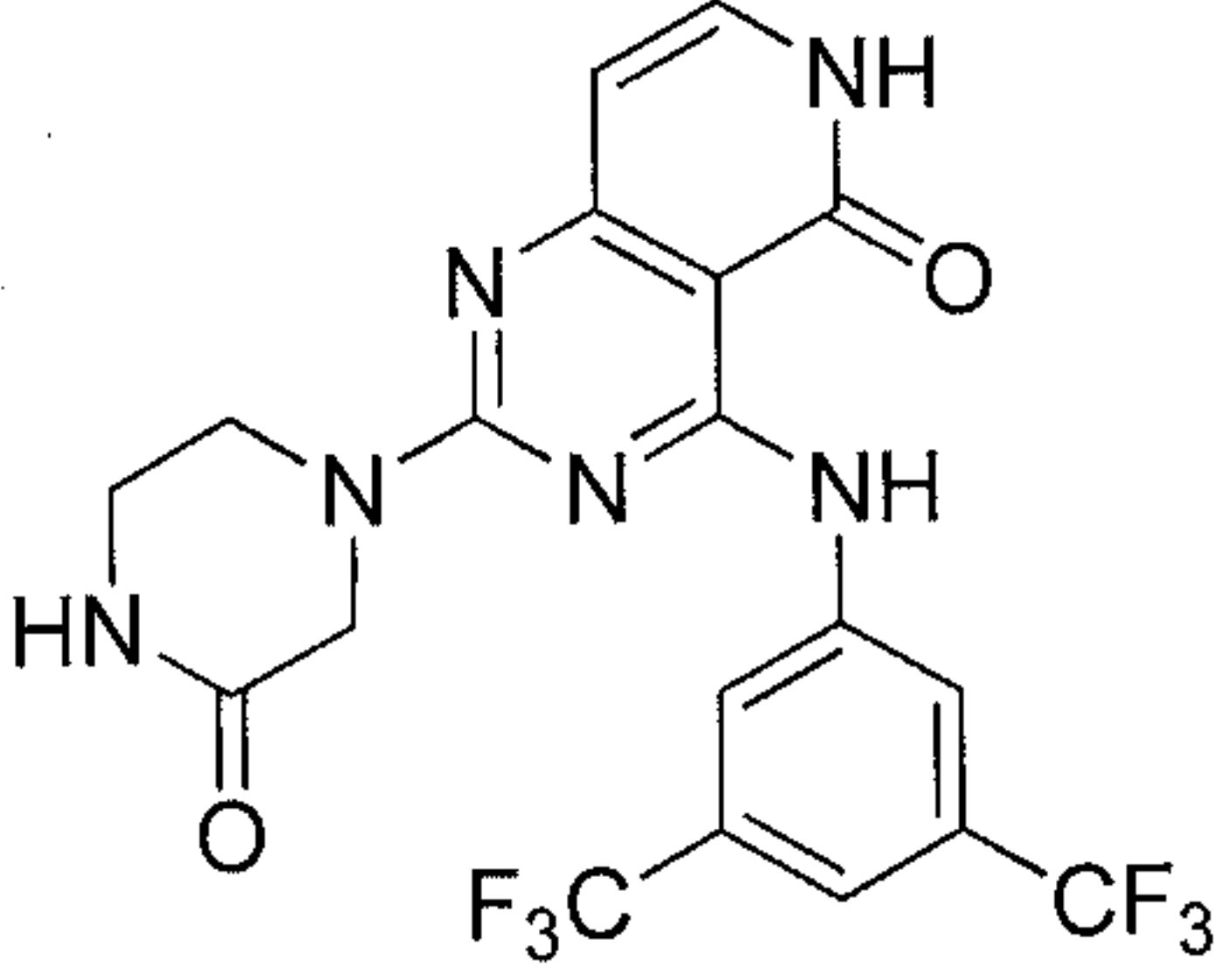
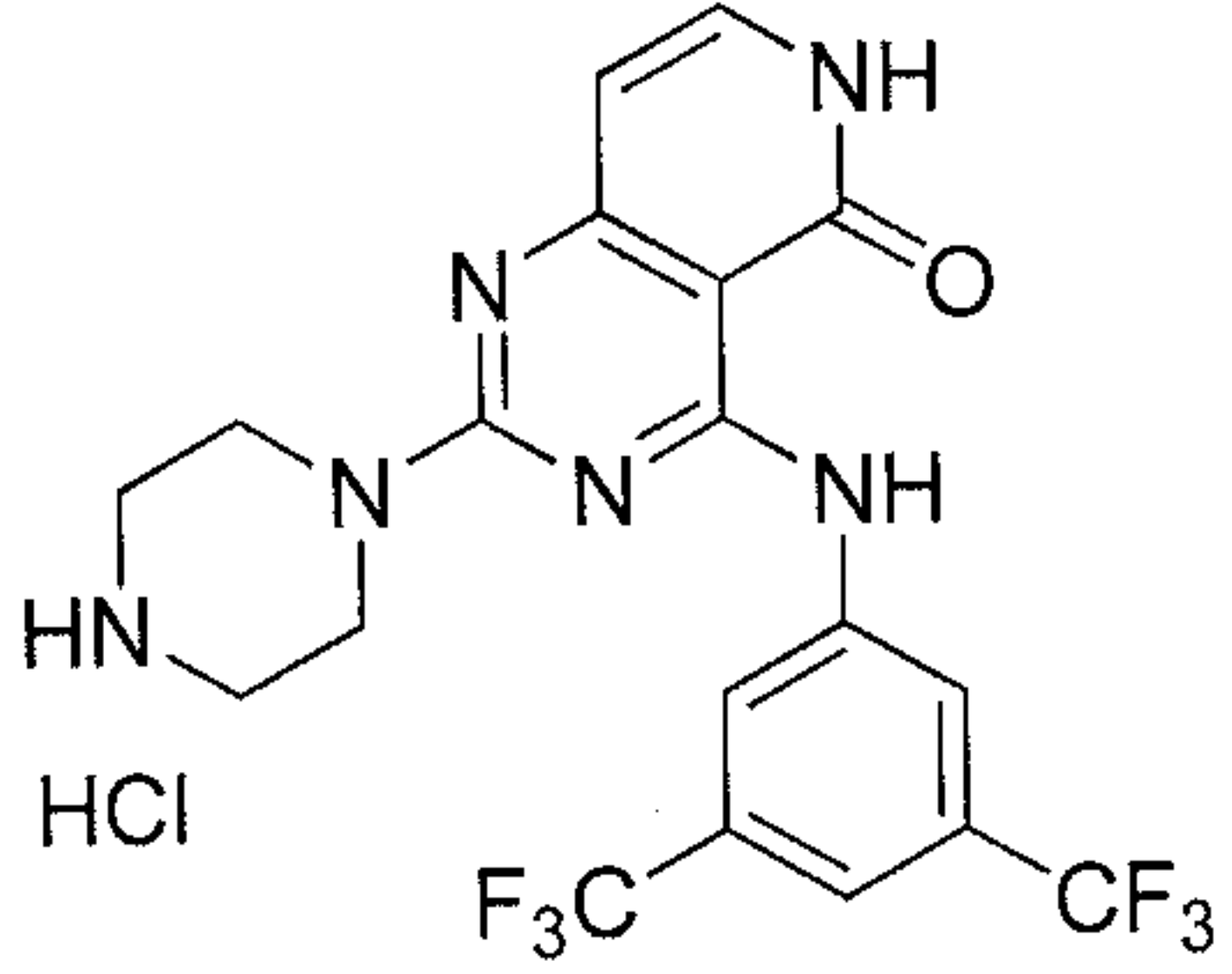
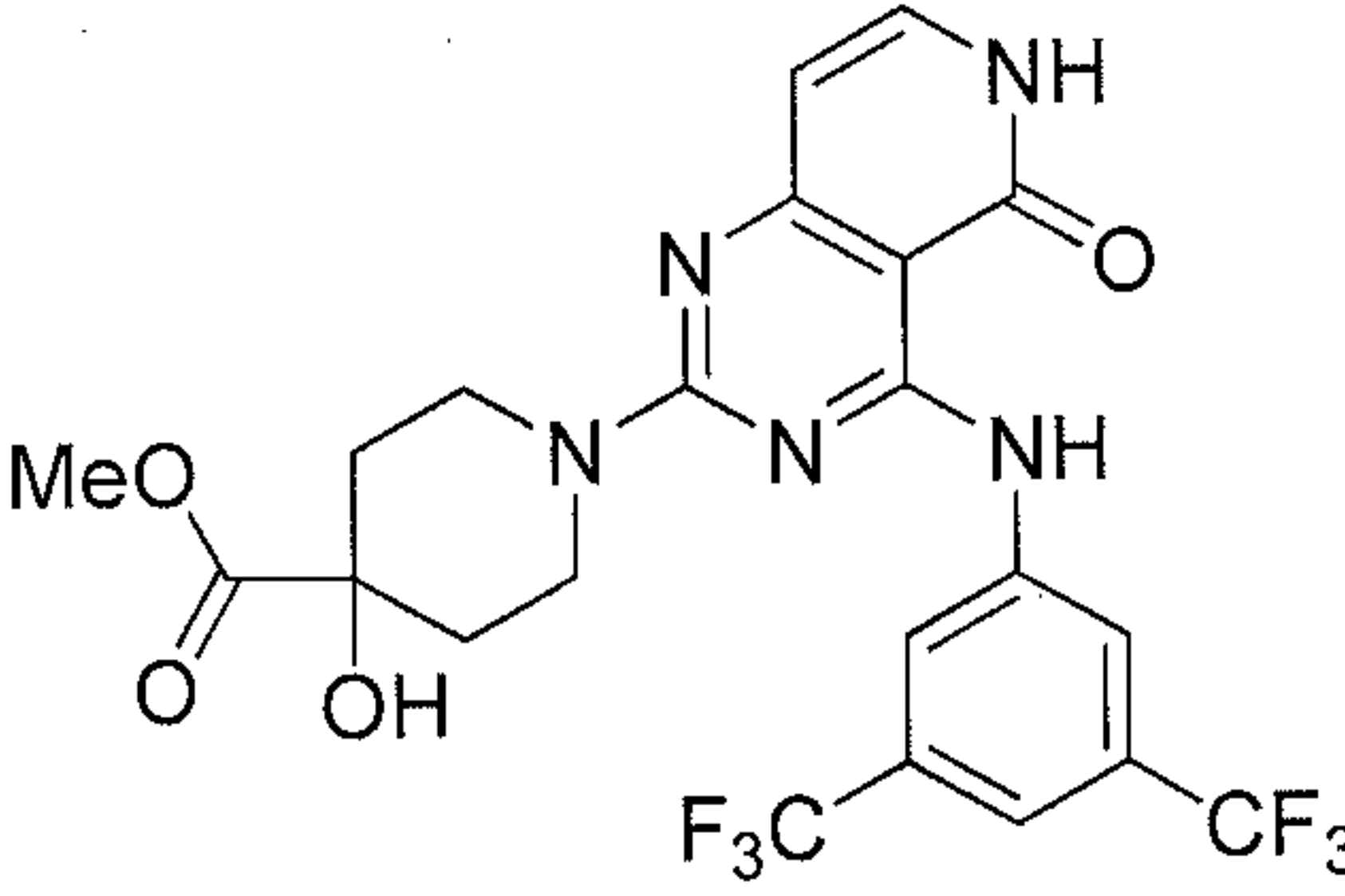
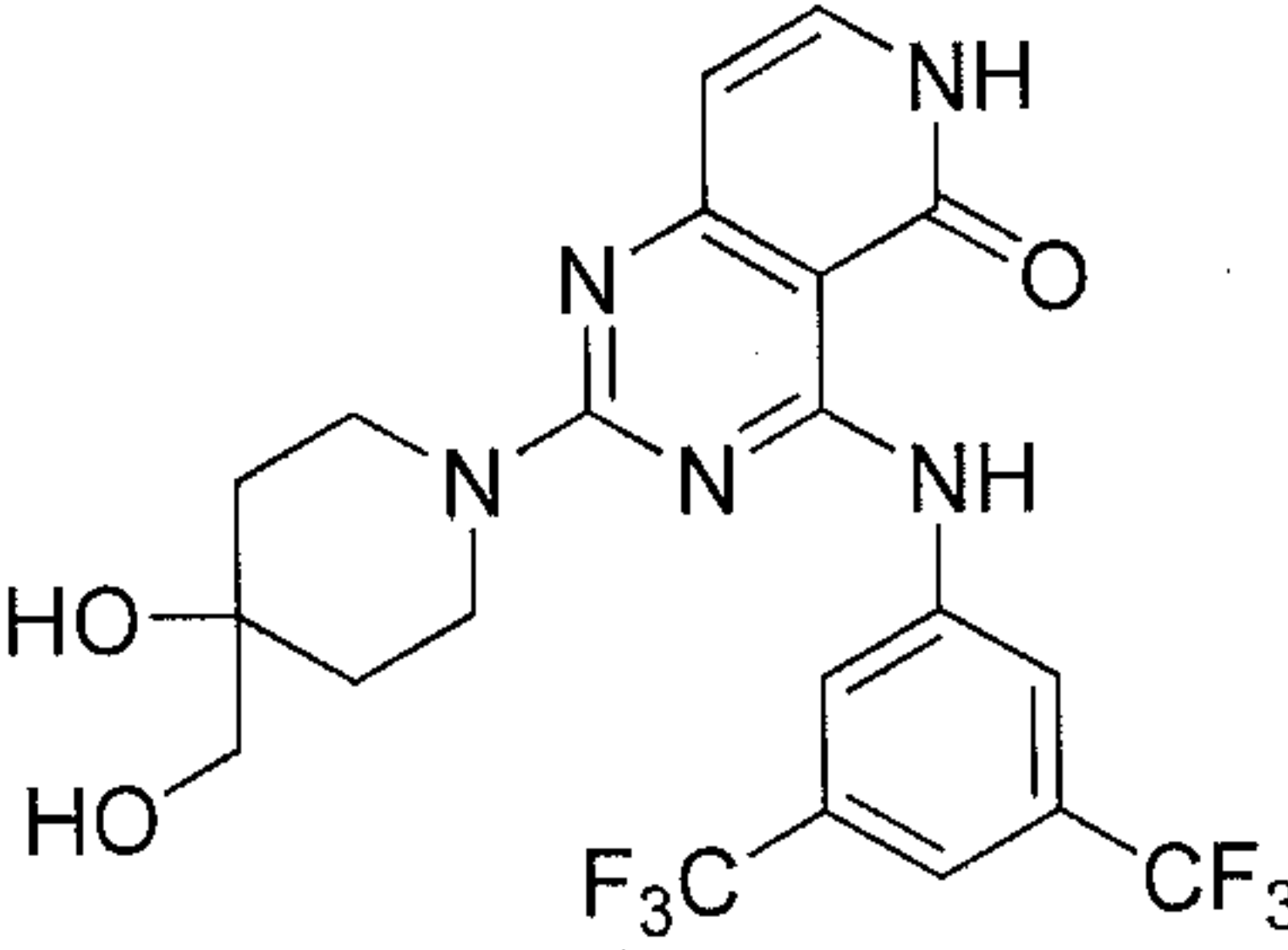
The following 4-(3,5-bis-(trifluoromethyl)phenylamino)-2-(amino substituted)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one compounds were prepared from 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one and the corresponding amine following the procedure similar to that described in *Example 100d*.

5

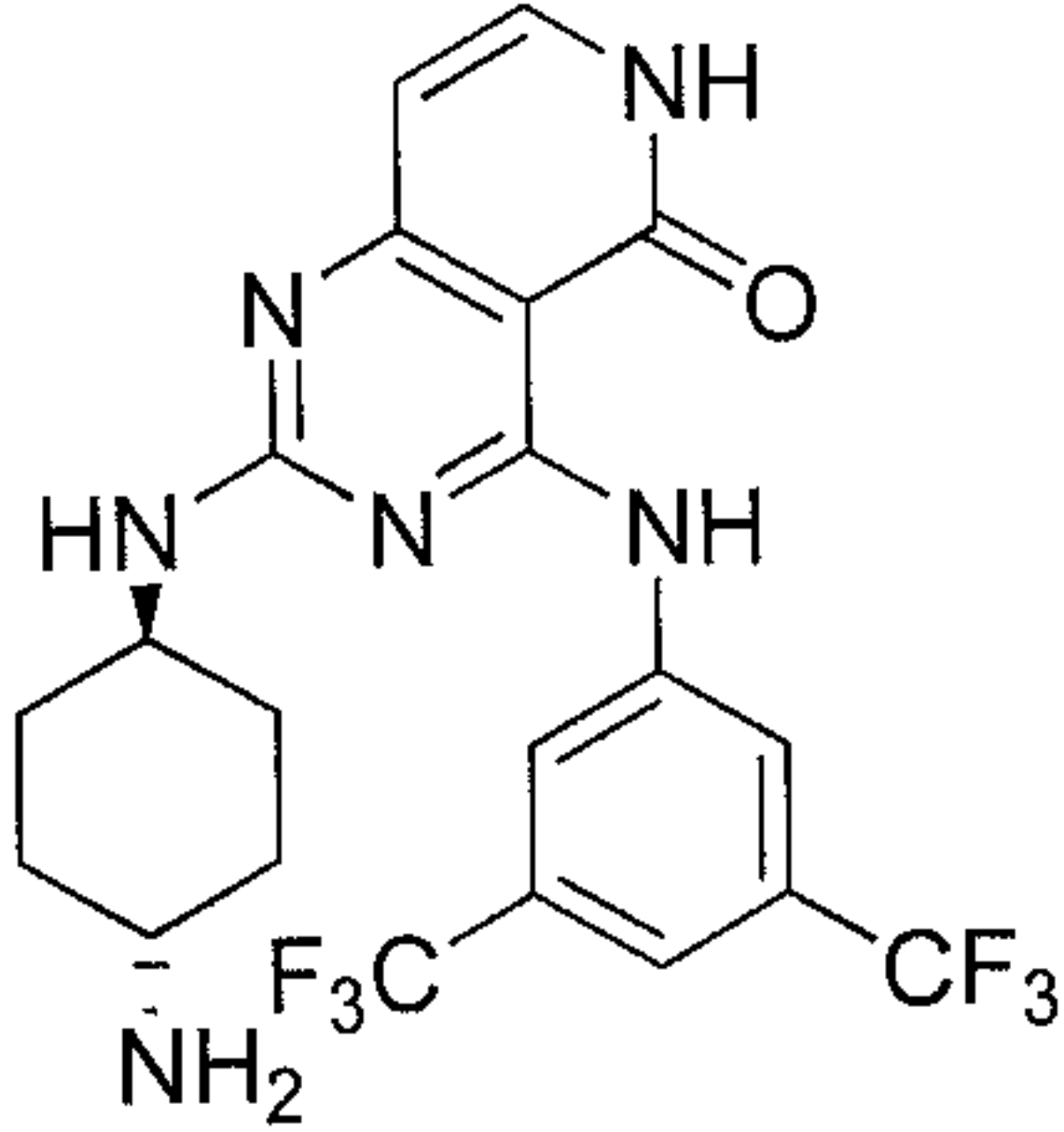
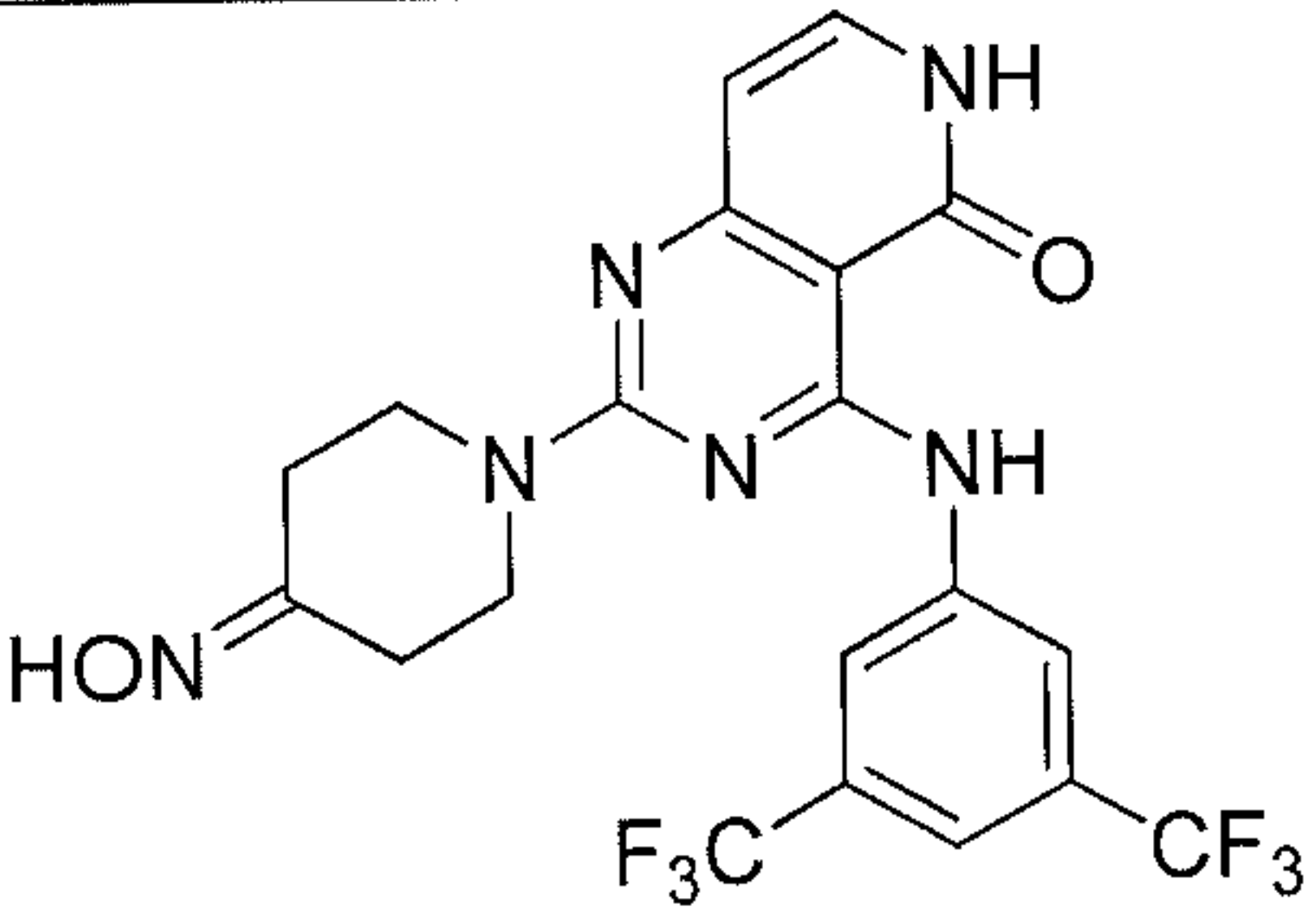
NO.	Structure	Name	Mass (M+1)
103		4-(3,5-bis(trifluoromethyl)phenylamino)-2-morpholinopyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	460
104		4-(3,5 bis(trifluoromethyl)phenyl amino)-2-((1r,4r)-4-hydroxycyclohexyl amino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	488
105		2-(2-aminobenzylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	495
106		4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-methylpiperazin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	473

107		2-(4-aminopiperidin-1-yl)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	473
108		(<i>S</i>)-4-(3,5-bis(trifluoromethyl)phenylamino)-2-(pyrrolidin-3-ylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	459
109		4-(3,5-bis(trifluoromethyl)phenylamino)-2-(piperidin-4-ylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	473
110		4-(3,5-bis(trifluoromethyl)phenylamino)-2-(1-methylpiperidin-4-ylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	487
111		(<i>S</i>)-4-(3,5-bis(trifluoromethyl)phenylamino)-2-(1-methylpyrrolidin-3-ylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	473
112		4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	501

113		4-(3,5-bis(trifluoromethyl)phenylamino)- 2-(4-(hydroxymethyl)piperidin-1-yl) pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	488
114		4-(3,5-bis(trifluoromethyl)phenylamino)- 2-(4-(2-hydroxyethyl)piperazin-1-yl) pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	503
115		(<i>R</i>)-4-(3,5-bis(trifluoromethyl)phenyl amino)-2-(3-hydroxypyrrolidin-1-yl) pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	460
116		4-(3,5-bis(trifluoromethyl)phenylamino)- 2-(3-hydroxyazetidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	446
117		4-(3,5-bis(trifluoromethyl)phenylamino)- 2-(4-(2-hydroxyethyl)piperidin-1-yl) pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	502

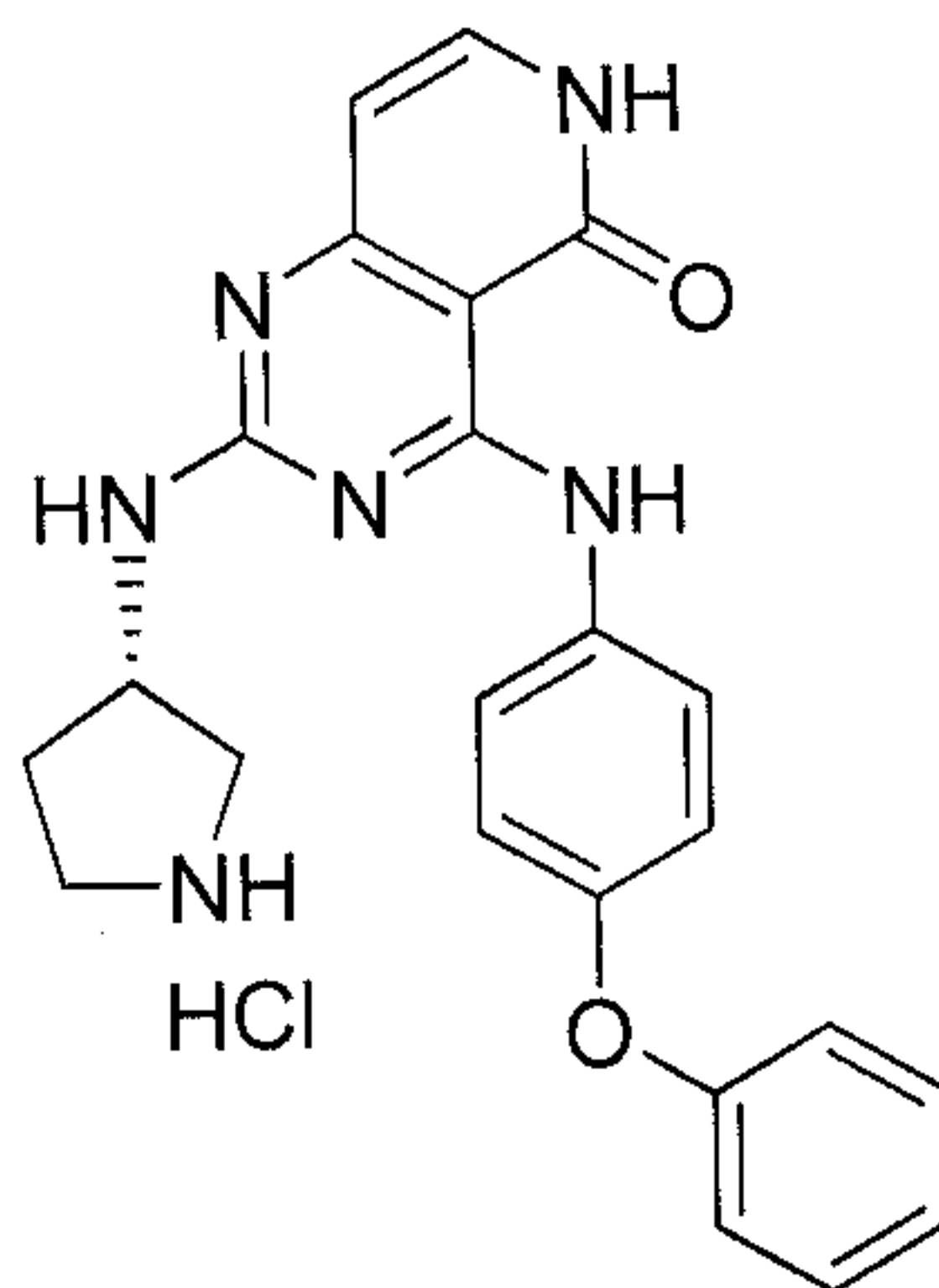
118		<i>N</i> -((1 <i>r</i> ,4 <i>r</i>)-4-(4-(3,5-bis(trifluoro methyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)cyclohexyl)acetamide	529
119		4-(3,5-bis(trifluoromethyl)phenylamino)-2-(3-oxopiperazin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	473
120		4-(3,5-bis(trifluoromethyl)phenylamino)-2-(piperazin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	495
121		methyl 1-(4-(3,5-bis(trifluoromethyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-yl)-4-hydroxypiperidine-4-carboxylate	532
122		4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	504

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123		2-(((1R, 4R)-4-aminocyclohexylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	487
124		4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(hydroxyimino)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	487

Example 125

Synthesis of (*S*)-4-(phenoxyphenylamino)-2-(pyrrolidin-3-ylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride



5

Compound No. 125

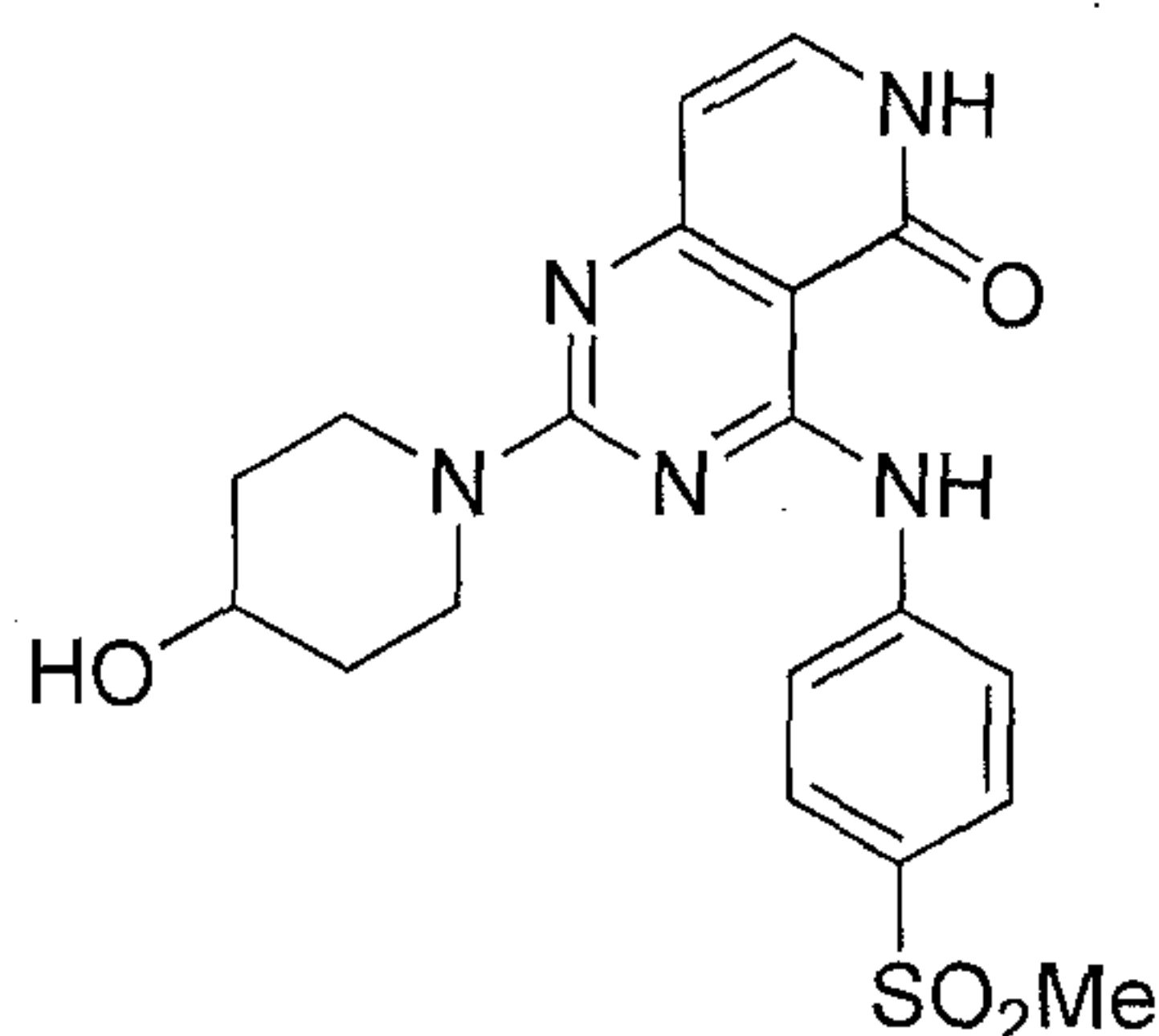
Compound No. 125 was prepared as described in *Example 1g* by starting from 2-(methylthio)-4-(4-phenoxy phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (87 mg, 0.23 mmol) and (*S*)-(-)-1-boc-3-amino pyrrolidine (129 mg, 0.69 mmol) and treating with 4 N HCl in dioxane continuing until the reaction yielded the title compound (54 mg, 52 %). MS *m/z*: 415 (*M*+1)⁺.

10

- 82 -

Example 126

Synthesis of 2-(4-hydroxypiperidin-1-yl)-4(4-(methylsulfonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

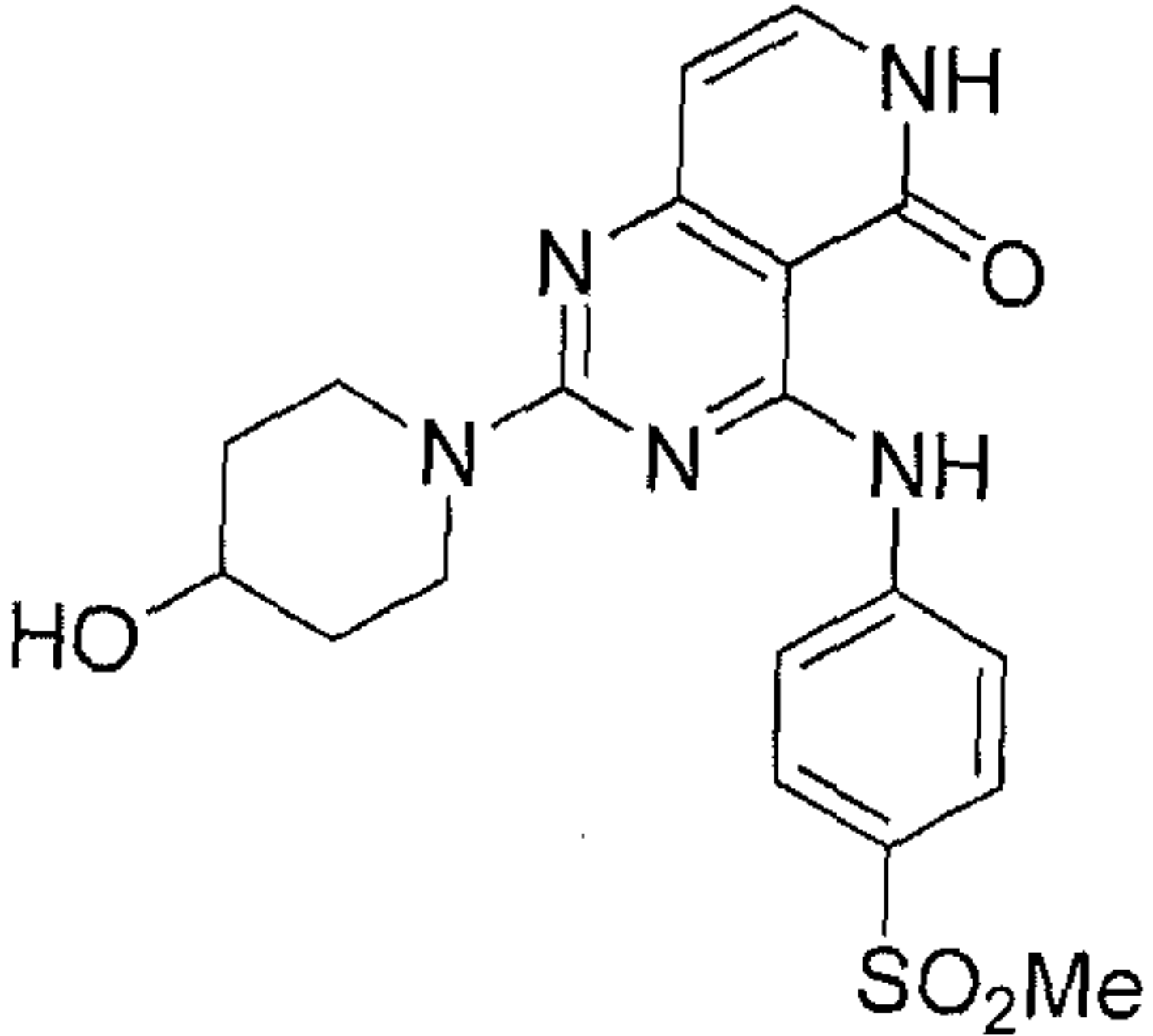
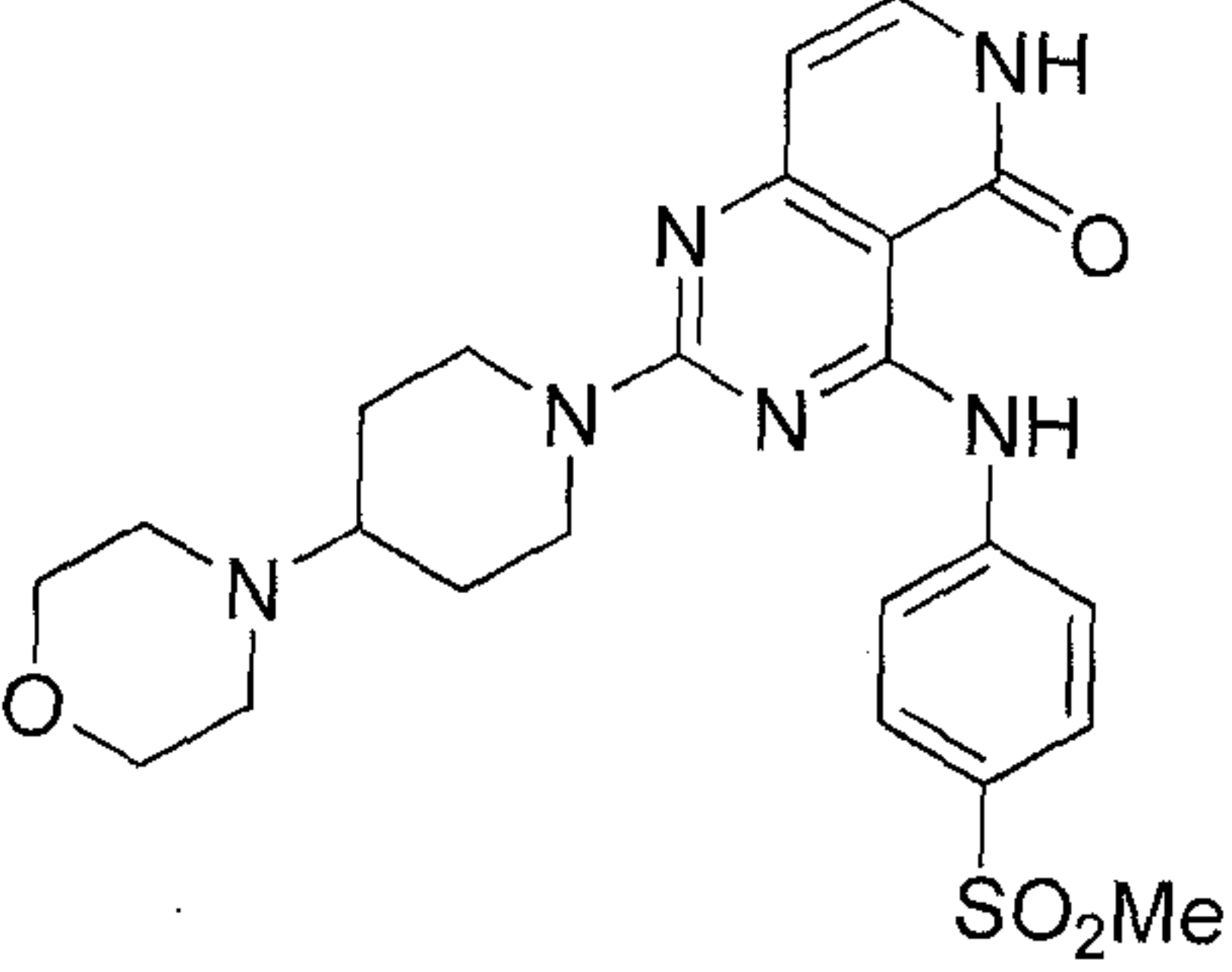
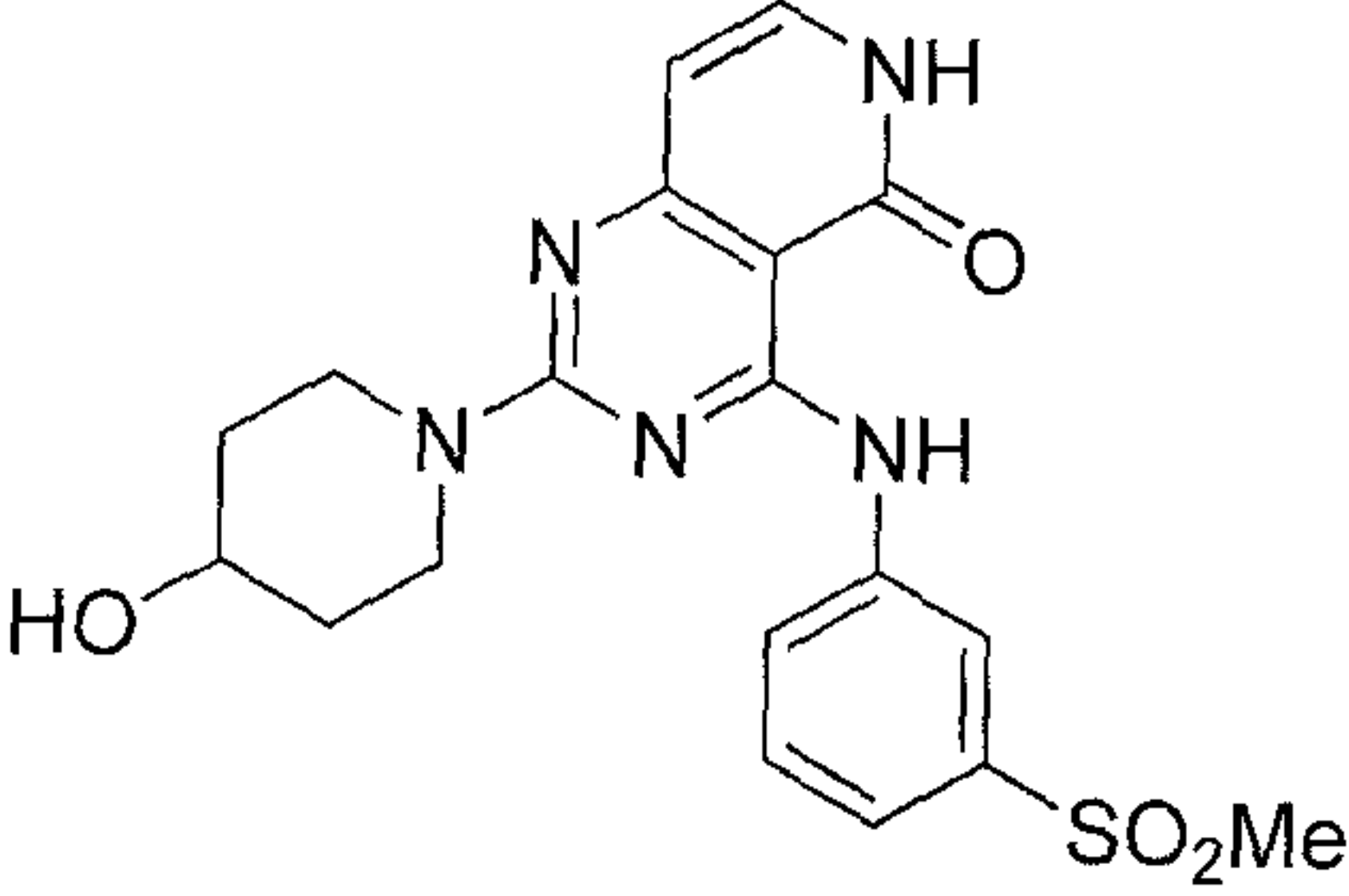
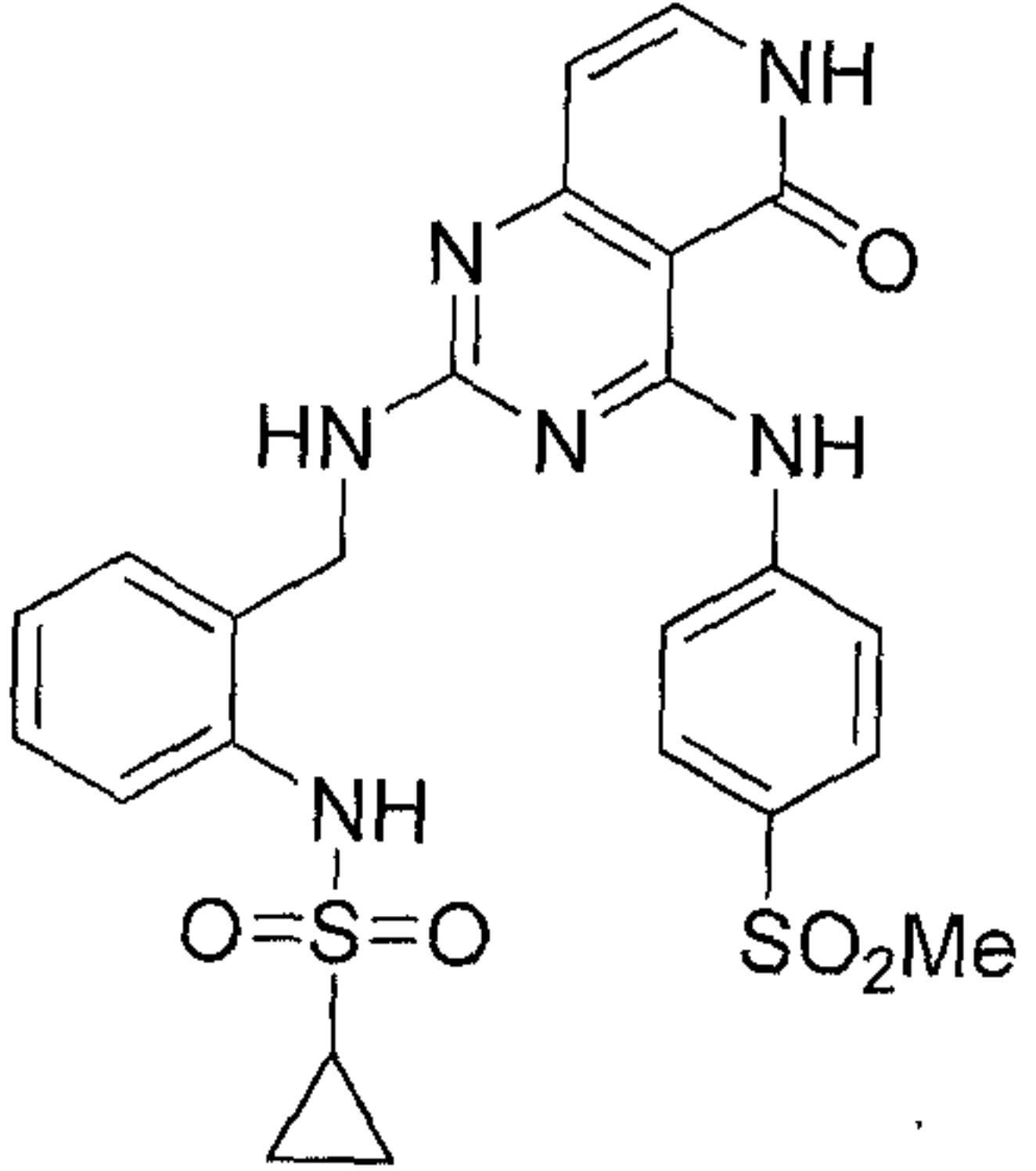
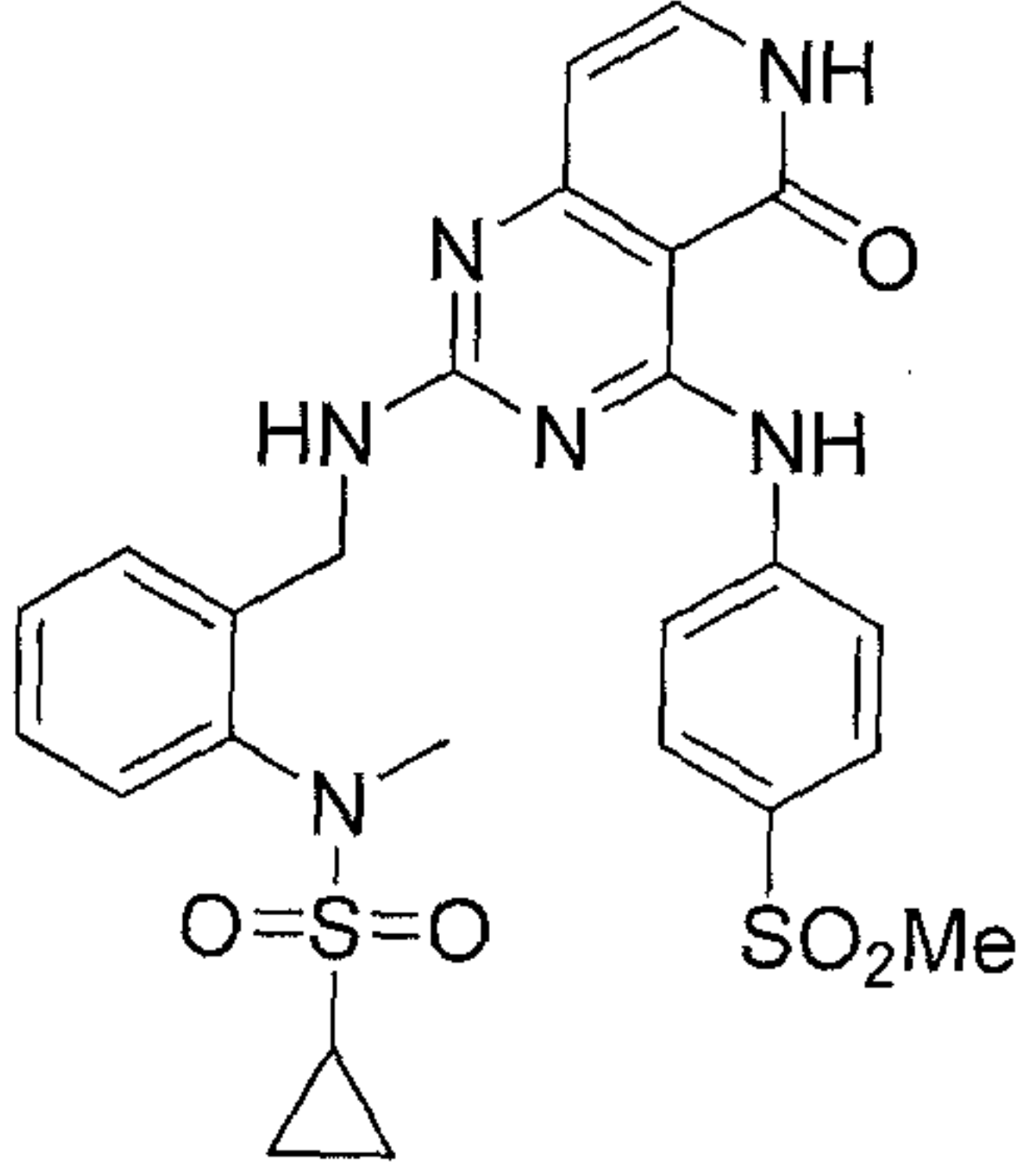


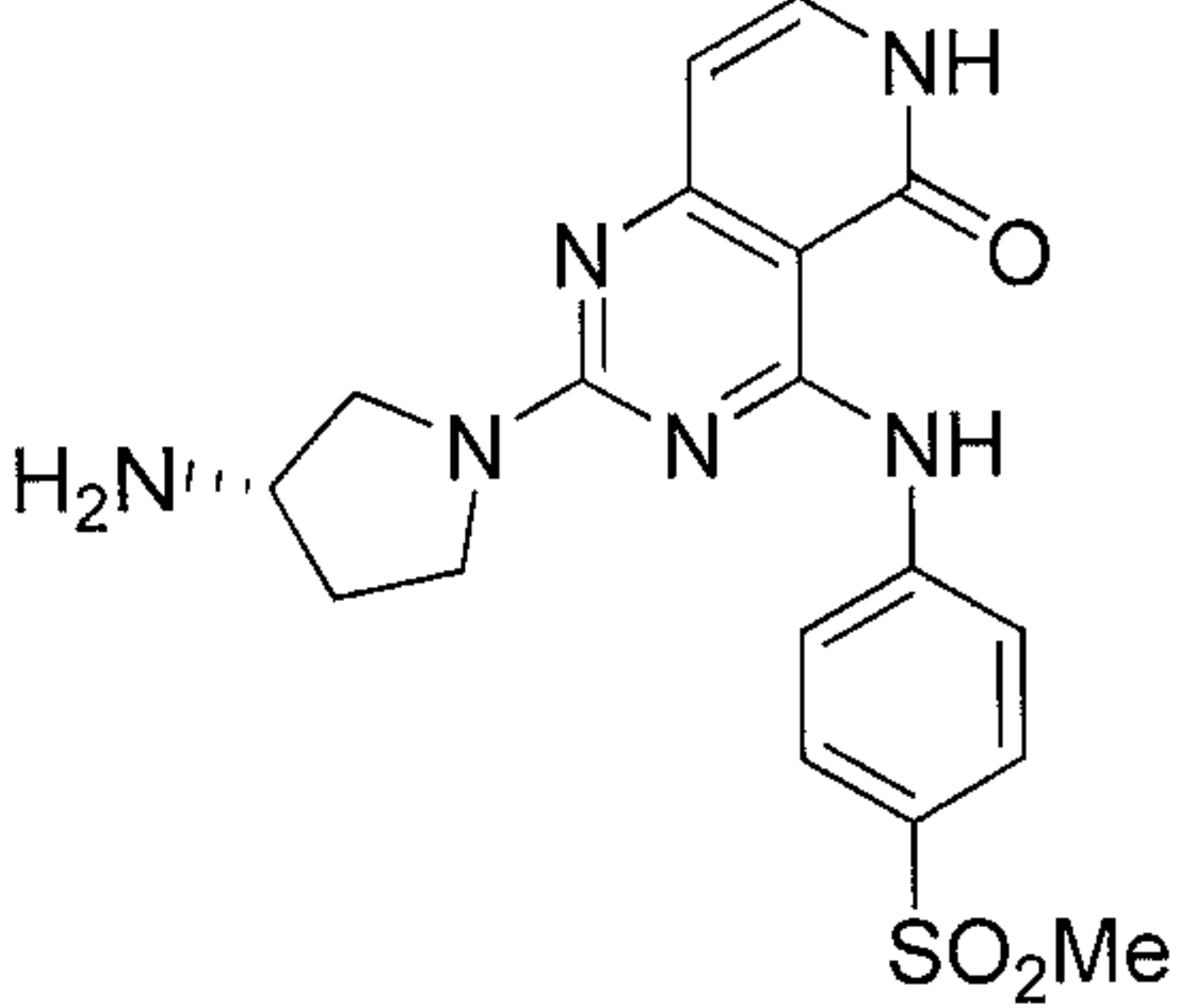
Compound No. 126

Compound No. 126 was prepared as described in *Example 1g* by starting from 4-(4-(methylsulfonyl)phenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (60 mg, 0.17 mmol) and 4-hydroxypiperidine (34.1 mg, 0.33 mmol) and continuing until the reaction yielded yellow solids (39 mg, 57 %). MS *m/z*: 416.4 (*M*+1)⁺.

The following 4-(4-(methylsulfonyl)phenylamino)-2-(amino substituted)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one compounds were prepared from 4-(4-(methylsulfonyl)phenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one and the corresponding amine following the procedure similar to that described in *Example 126*.

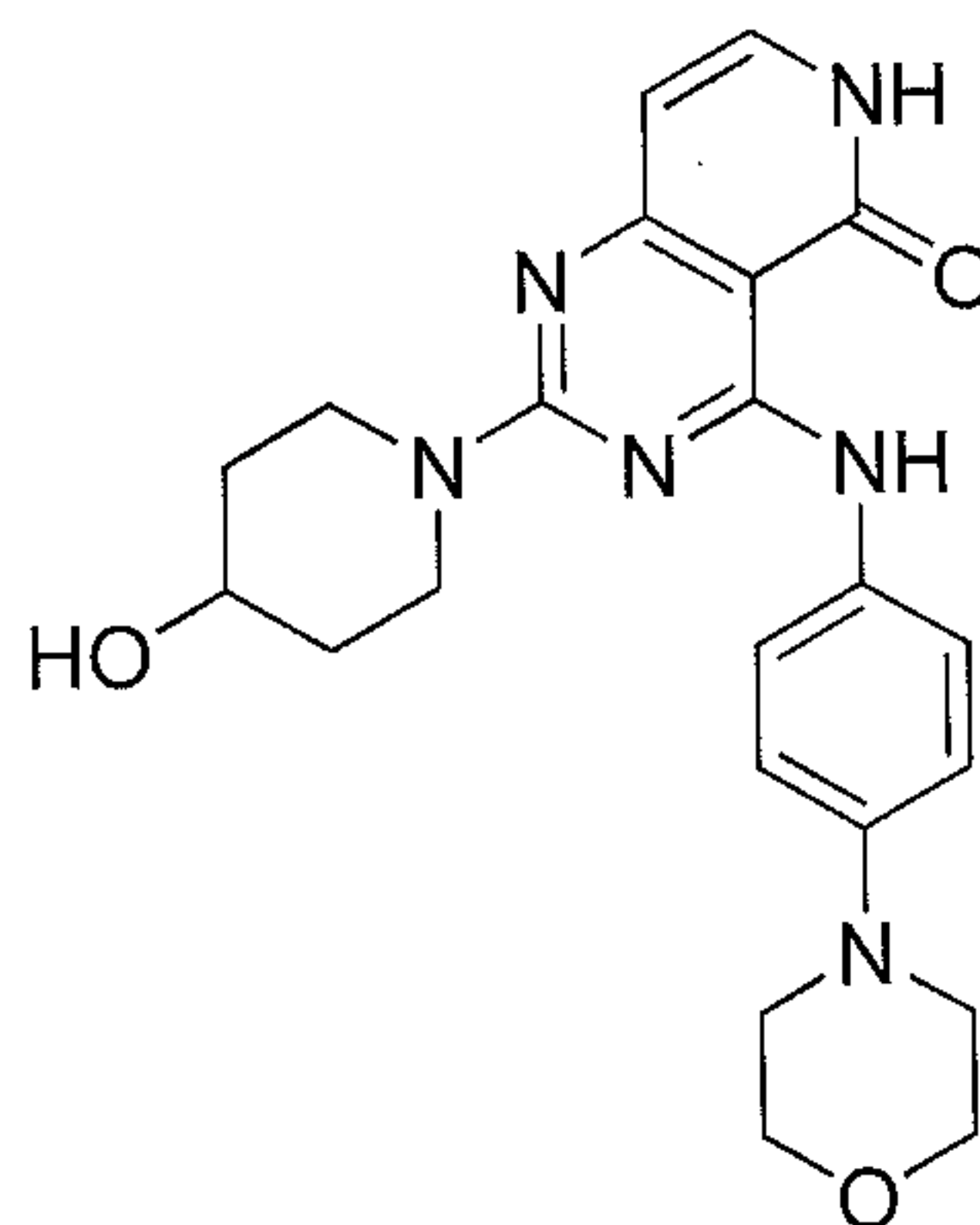
NO.	Structure	Name	Mass (<i>M</i> +1)
127		<i>N</i> -(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide	515

128		2-(4-hydroxypiperidin-1-yl)-4-(4-(methylsulfonyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	416
129		4-(4-(methylsulfonyl)phenylamino)-2-(4-morpholinopiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	485
130		2-(4-hydroxypiperidin-1-yl)-4-(3-(methylsulfonyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	415
131		N-(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-yl amino)methyl)phenyl)cyclopropane sulfonamide	541
132		N-methyl-N-(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-yl amino)methyl)phenyl)cyclopropanesulfonamide	555

133		(S)-2-(3-aminopyrrolidin-1-yl)-4-(4-(methylsulfonyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one	401
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Example 134

Synthesis of 2-(4-hydroxypiperidin-1-yl)-4-(4-morpholinophenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one



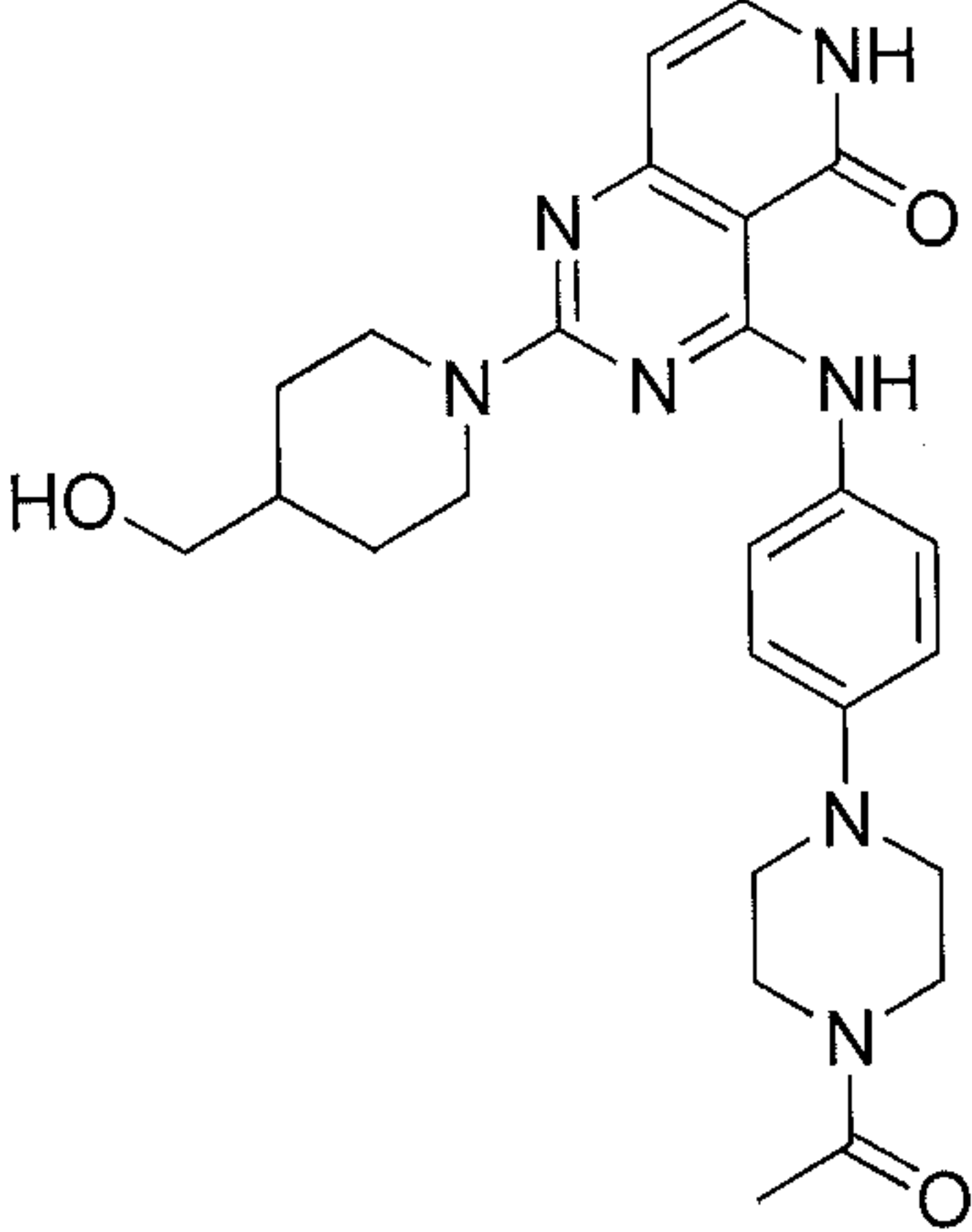
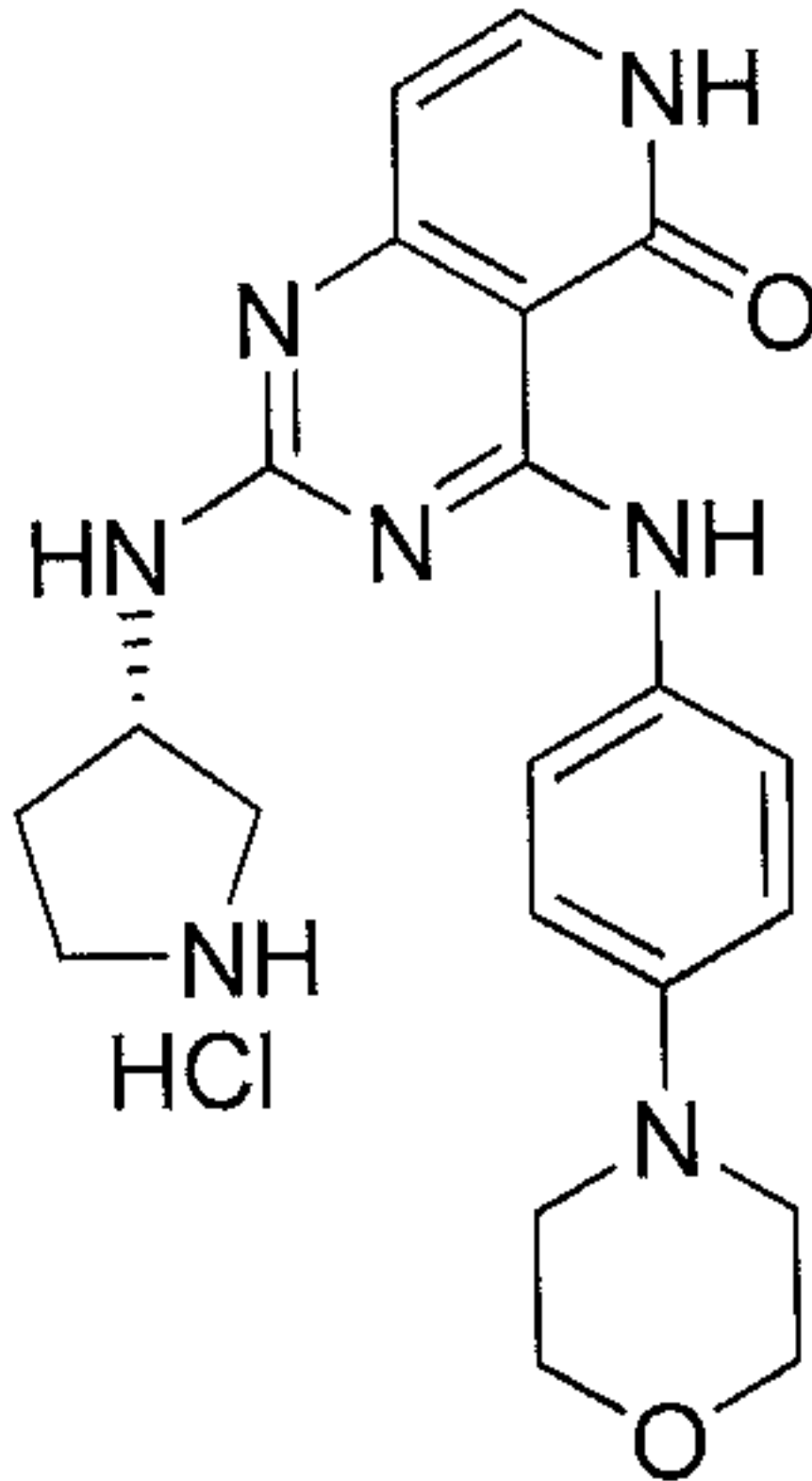
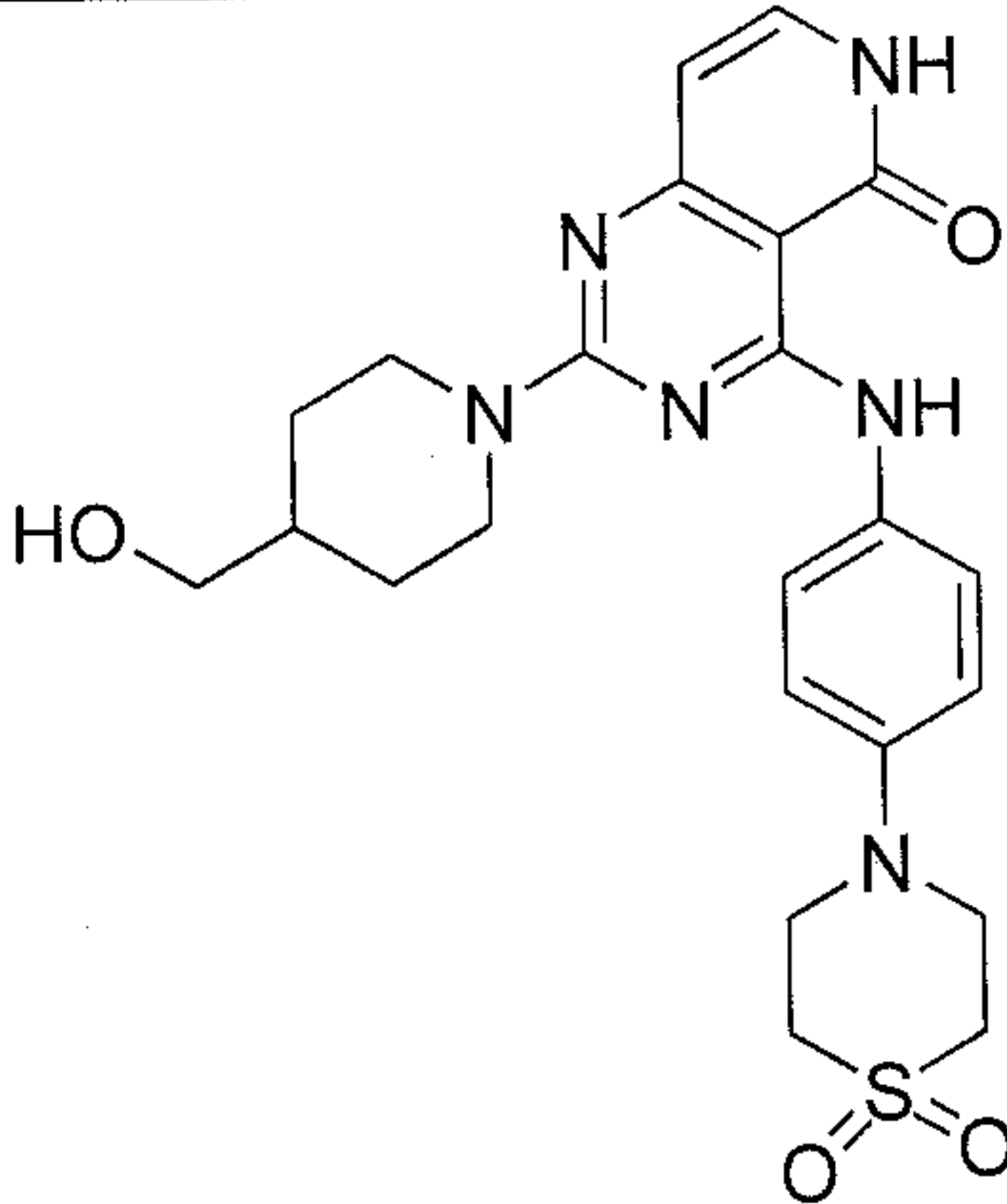
Compound No. 134

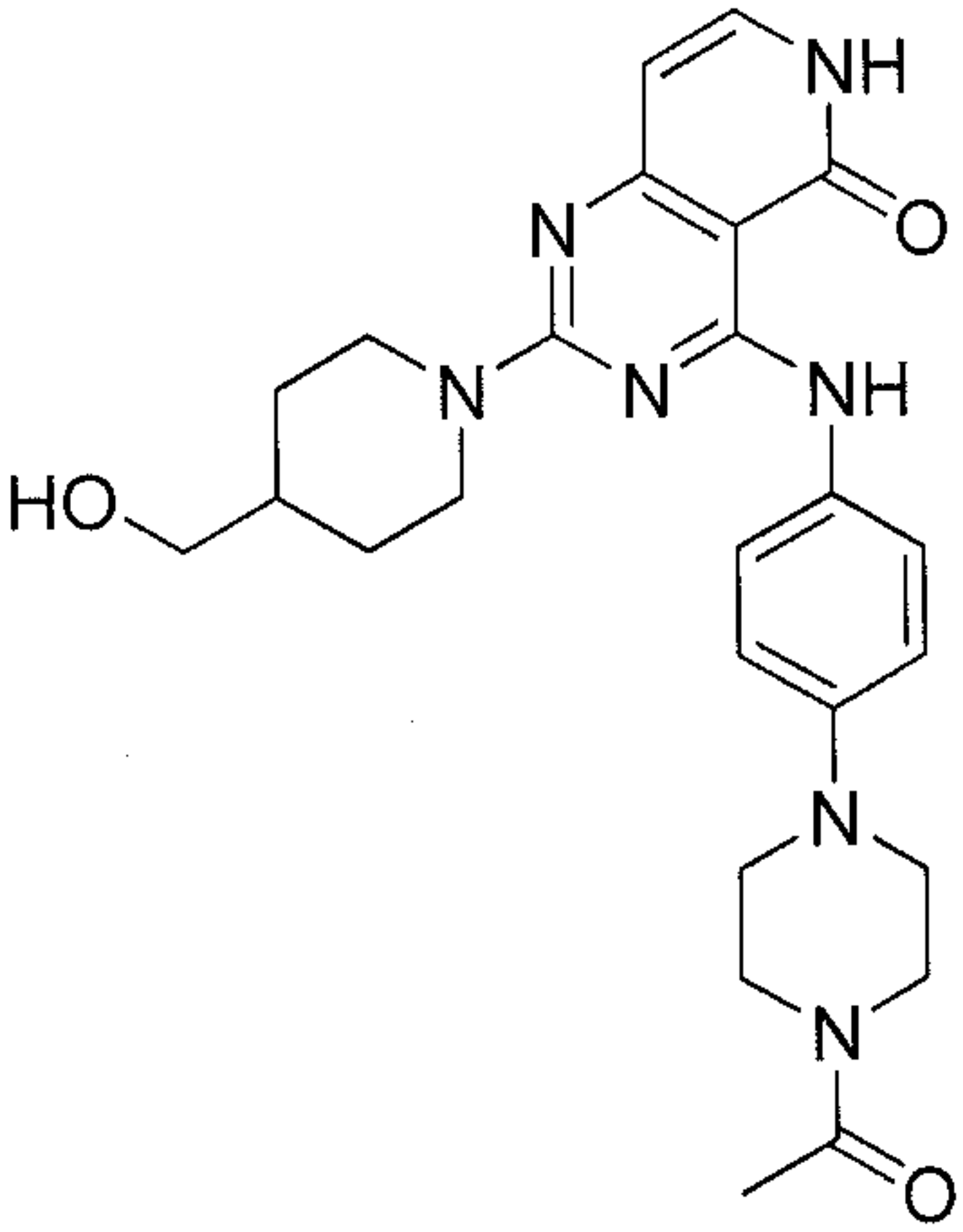
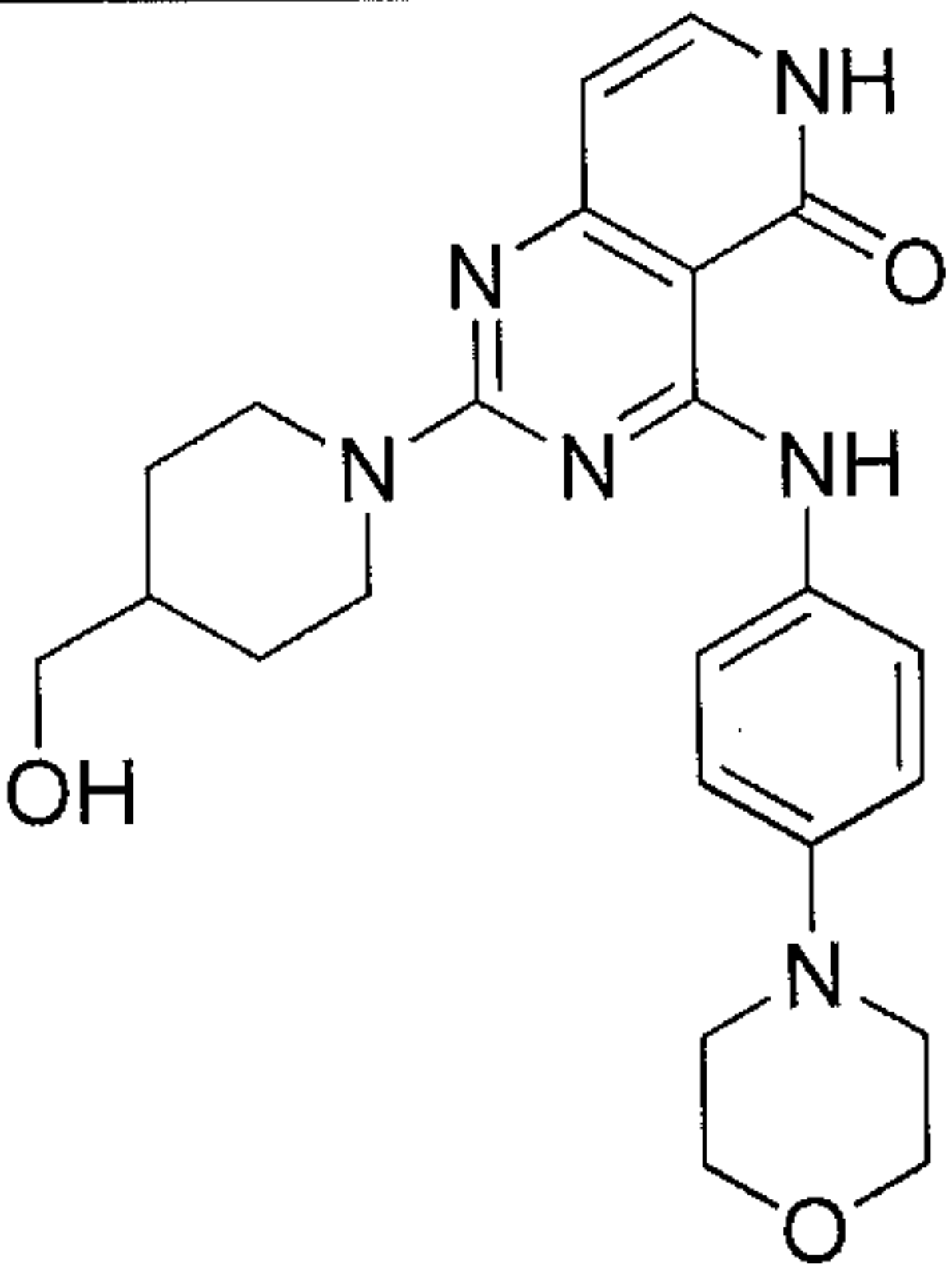
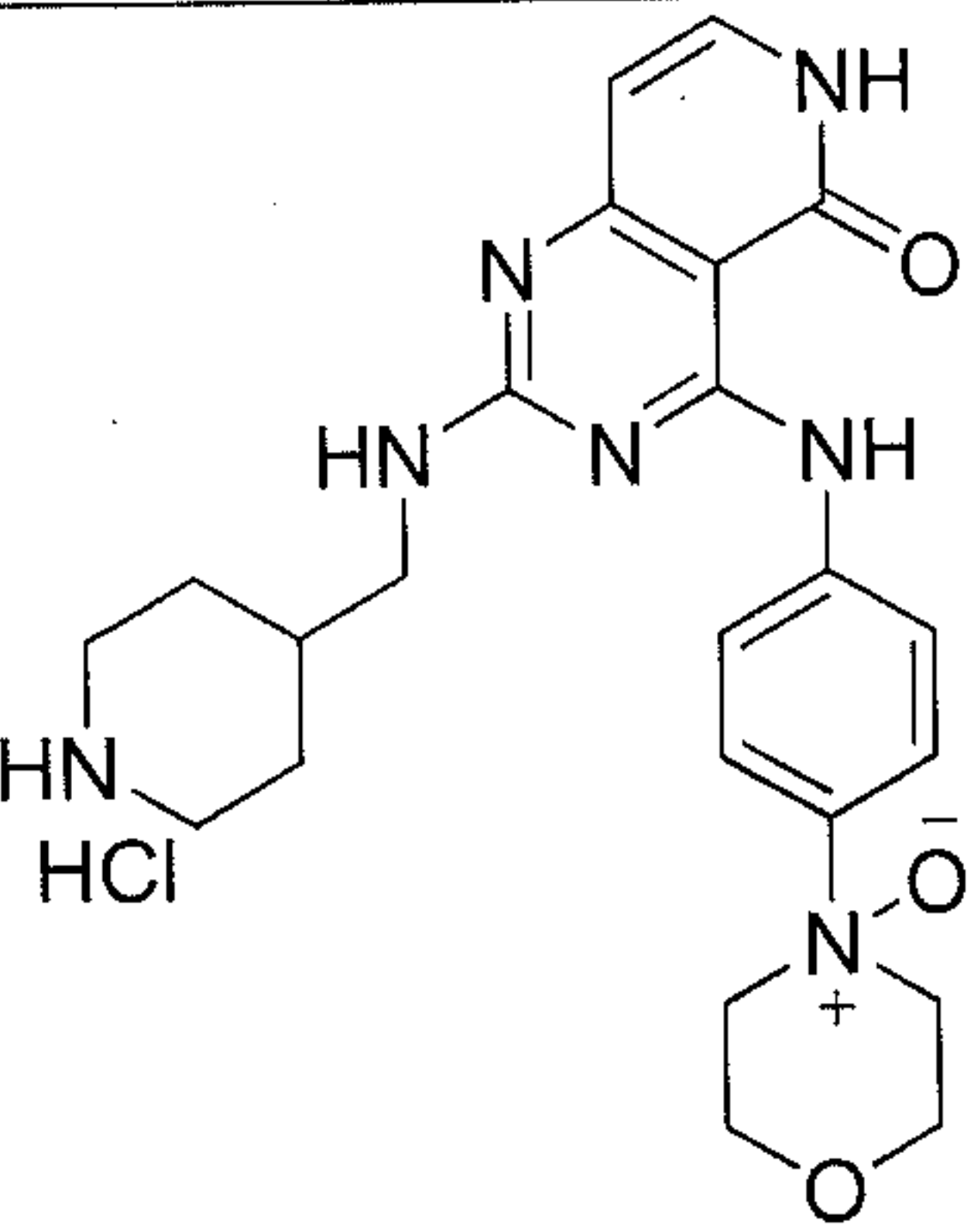
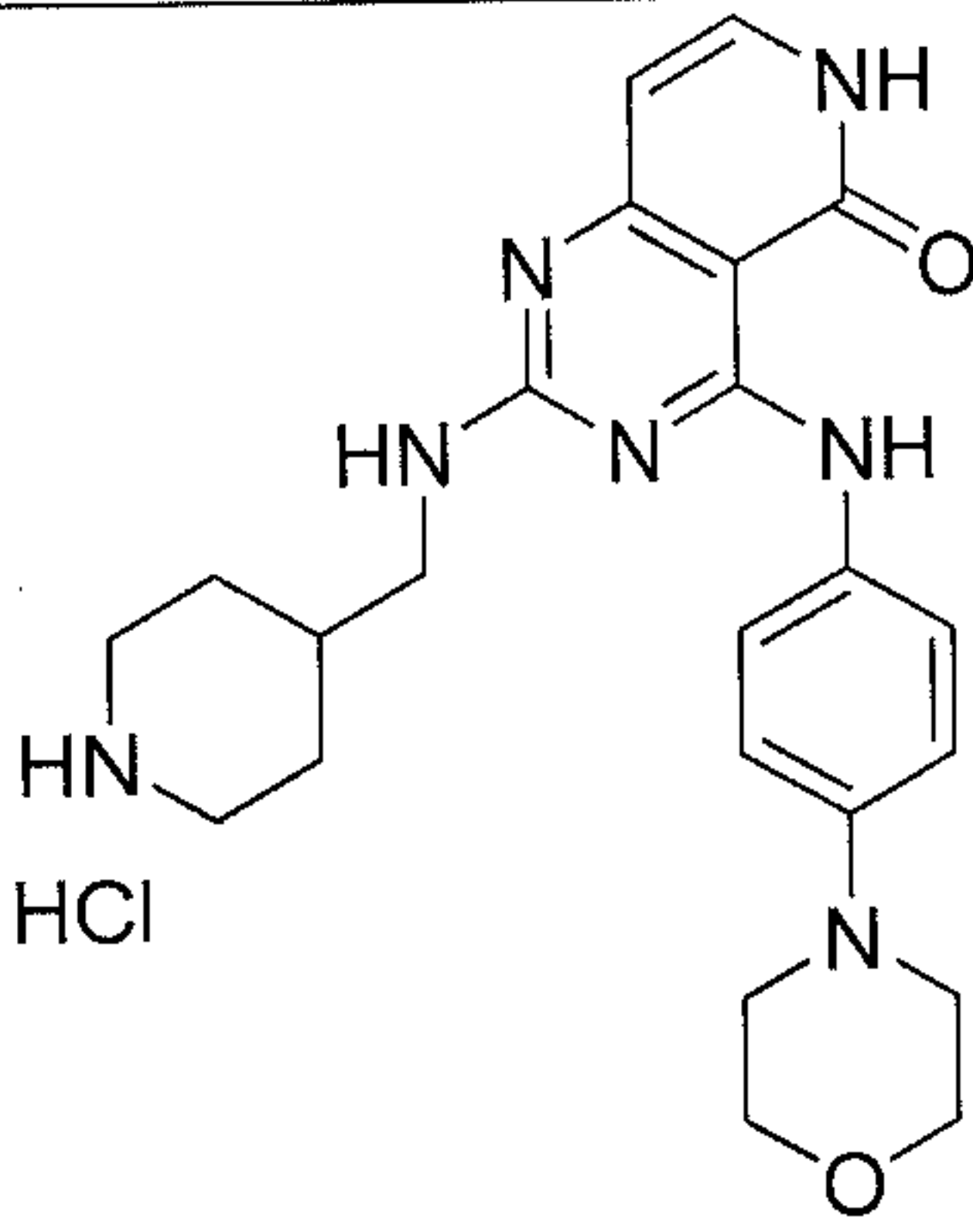
5
10
15
A 20 mL reaction vessel was charged with 2-(methylthio)-4-(4-morpholinophenyl amino)pyrido[4,3-d]pyrimidin-5(6H)-one (74 mg, 0.20 mmol) and 4-hydroxypiperidine (60.6 mg, 0.60 mmol) in 7 mL DMF at -20° C. The solution was kept at the temperature for 30 minutes. To the solution was added *m*-CPBA (148 mg, 0.6 mmol) at the temperature, and further stirred for 30 minutes with being warmed to room temperature. The reaction was monitored by LC-MS, confirming the corresponding oxide. To the reaction mixture was added triethylamine (354 µL, 1.32 mmol), and 4-hydroxypiperidine (134 mg, 1.32 mmol), and stirred at the temperature for 2 hours. The reaction was monitored by LC-MS. The solvent was removed by a rotavapor yielding light brown residue. The residue was dissolved in 10 mL THF. To the solution was added CuI (0.4 mmol, 76.2 mg), and diisopropylethylamine (69 µL, 0.4 mmol). The mixture was stirred at room temperature for 30 minutes. The mixture was diluted with EtOAc, and washed with 30% ammonium hydroxide solution. The separated organic layer was dried over sodium sulfate. The solvent was removed by a rotavapor yielding the brown residue. To

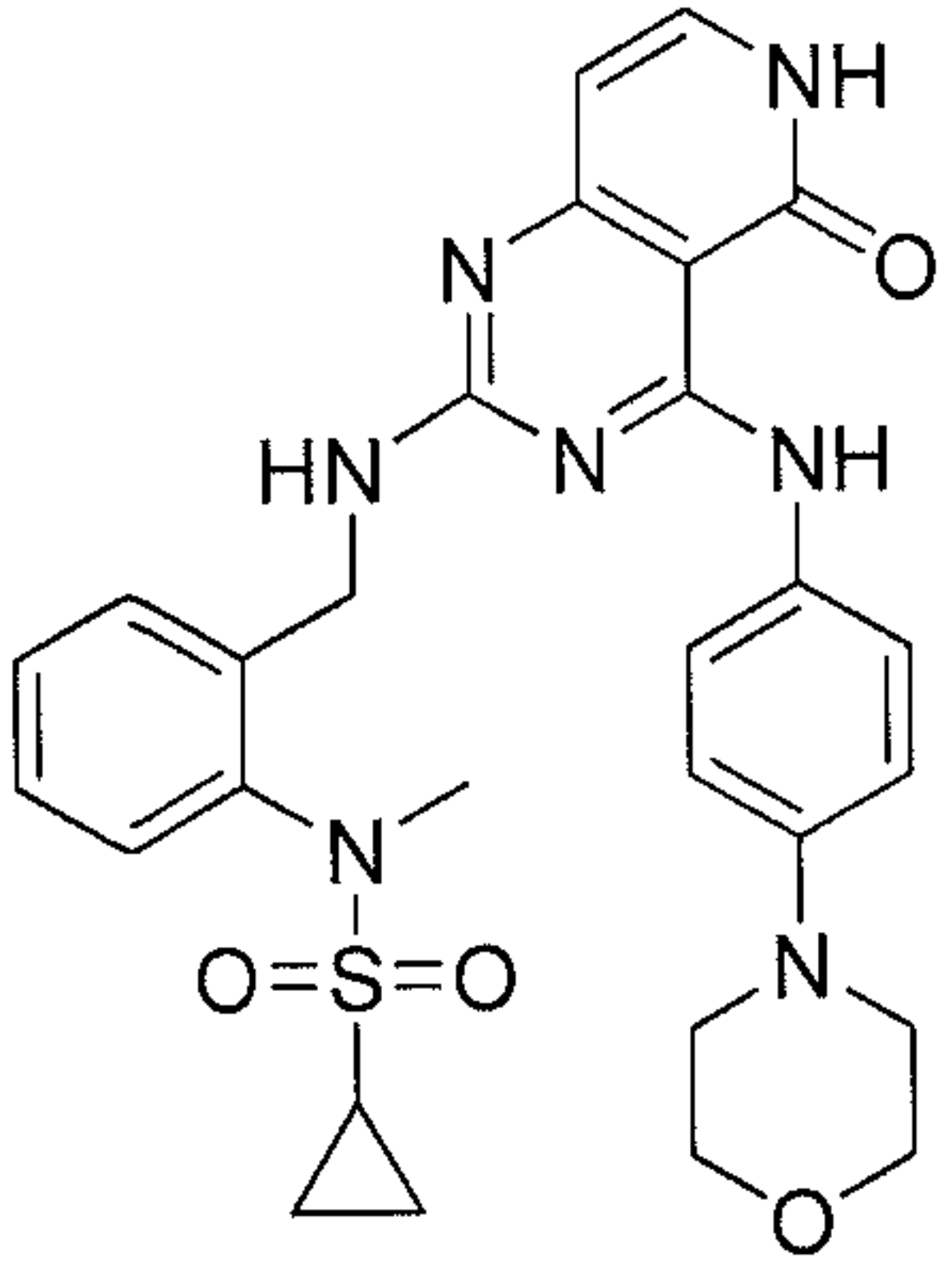
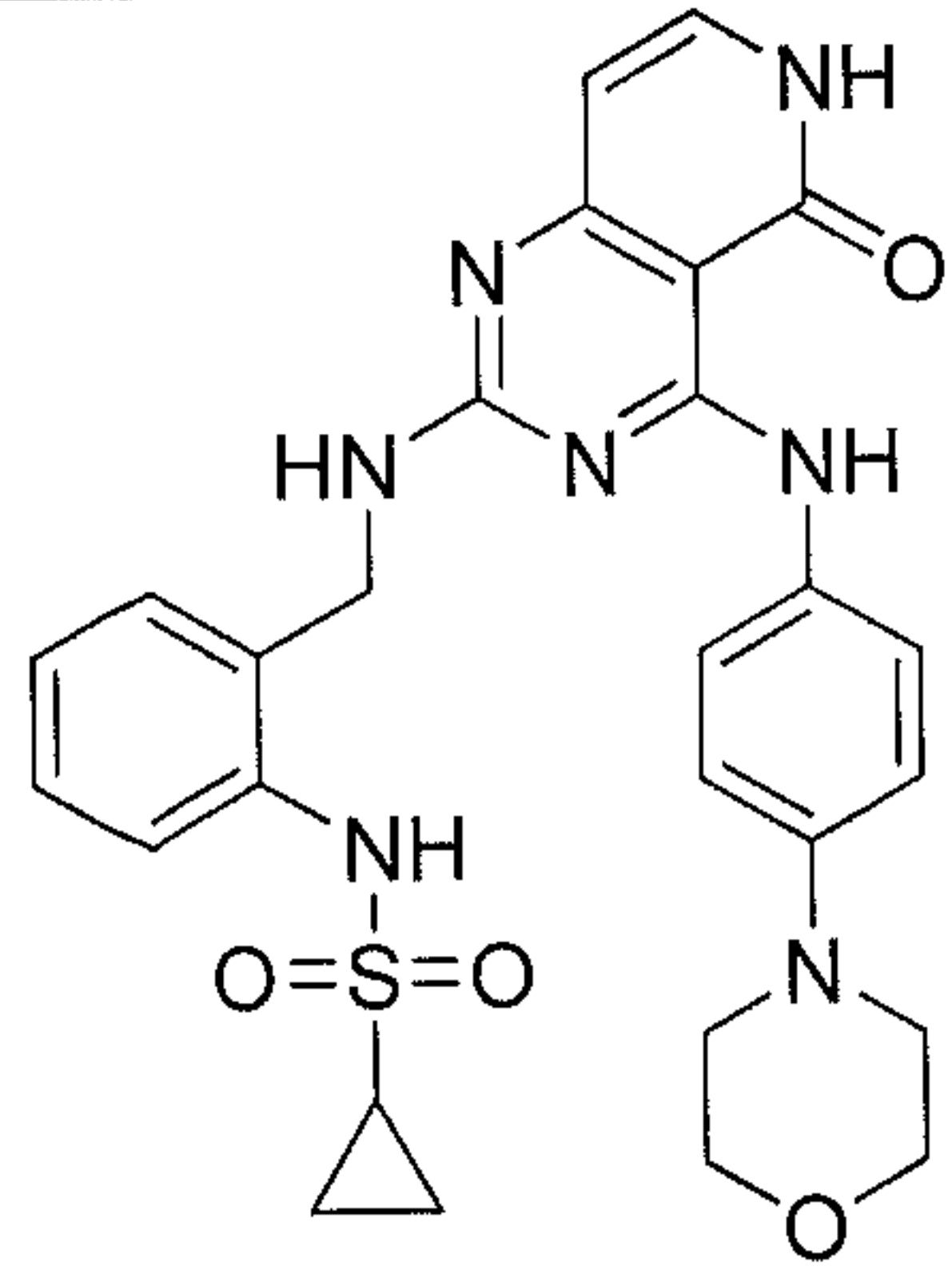
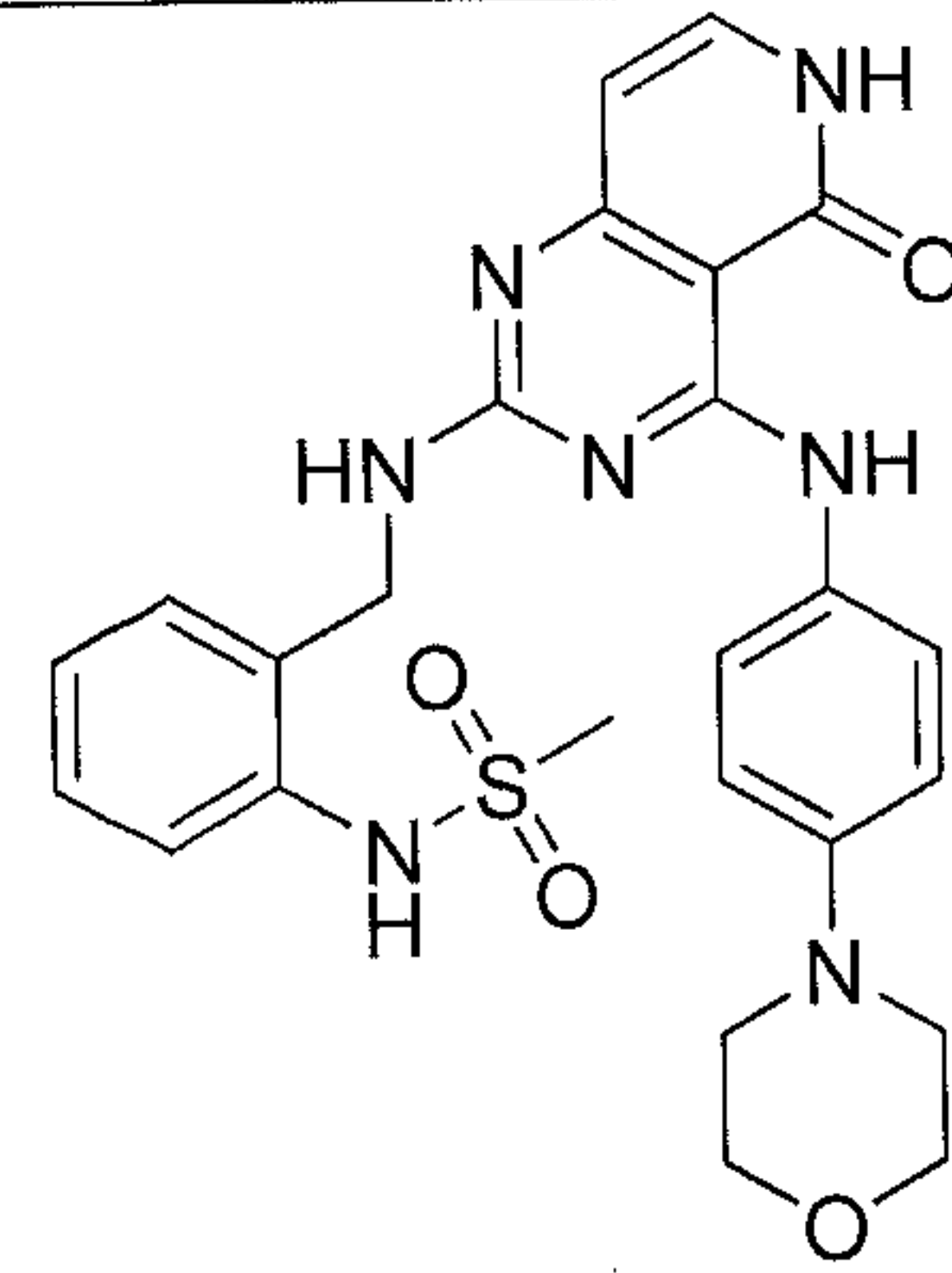
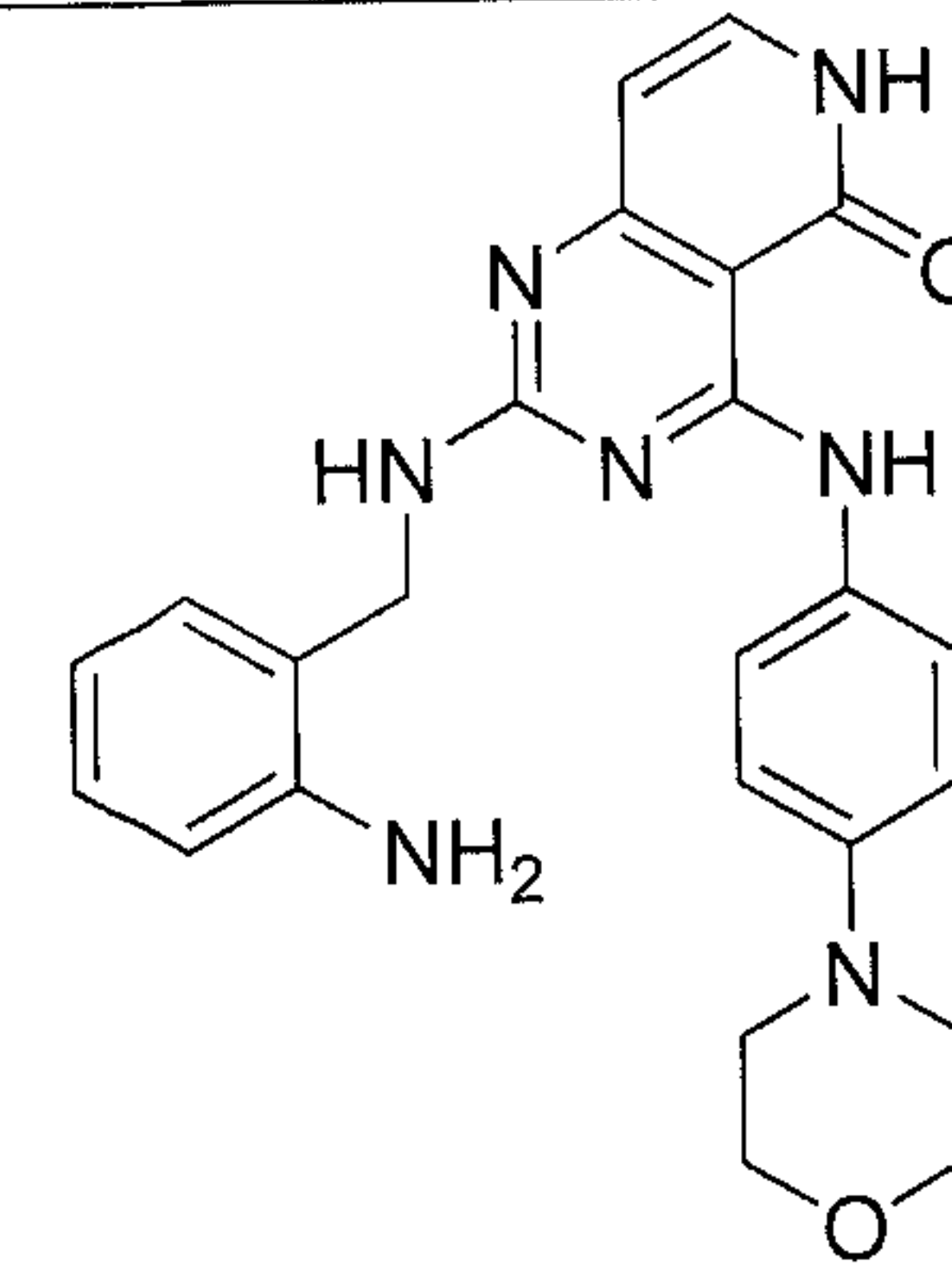
- 85 -

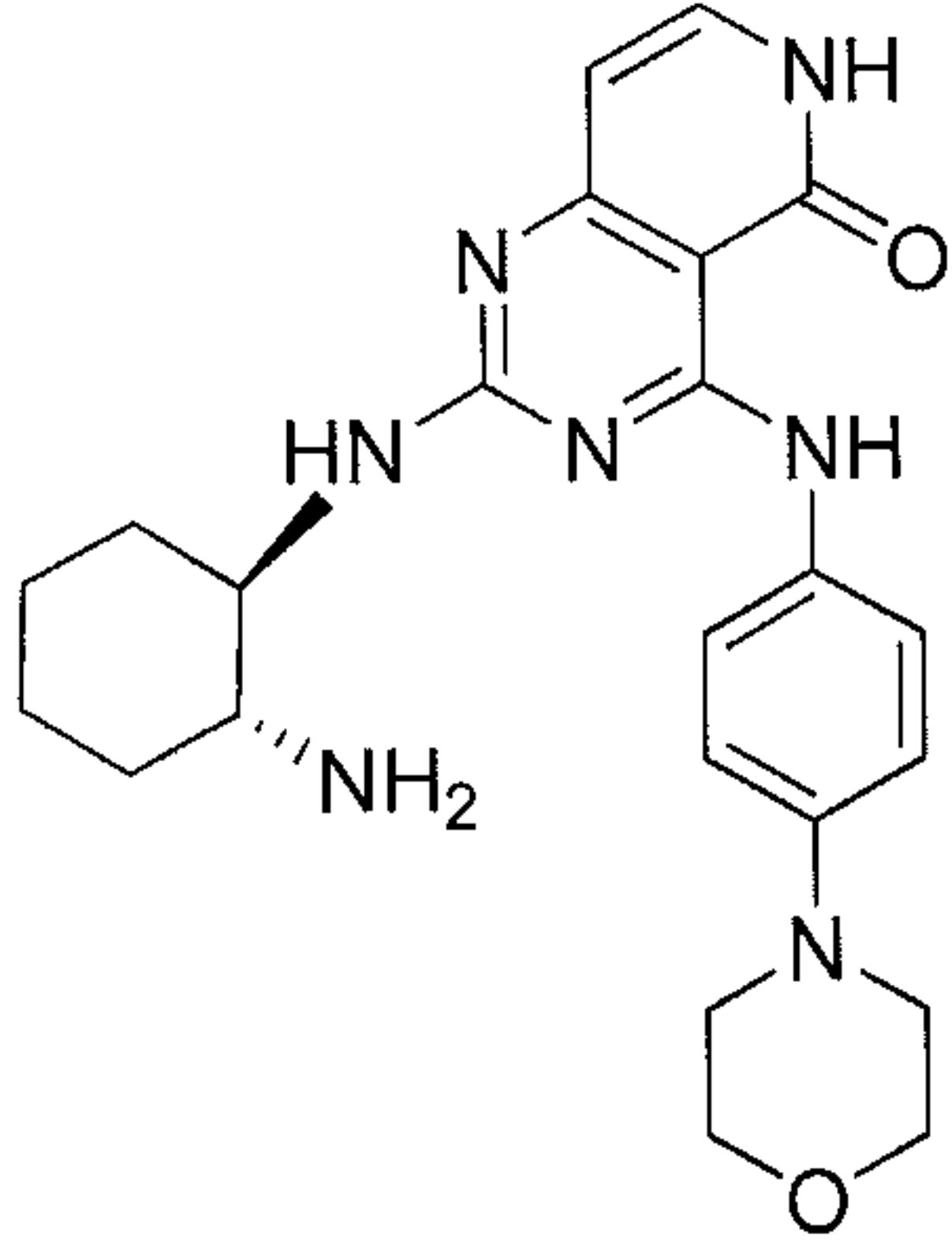
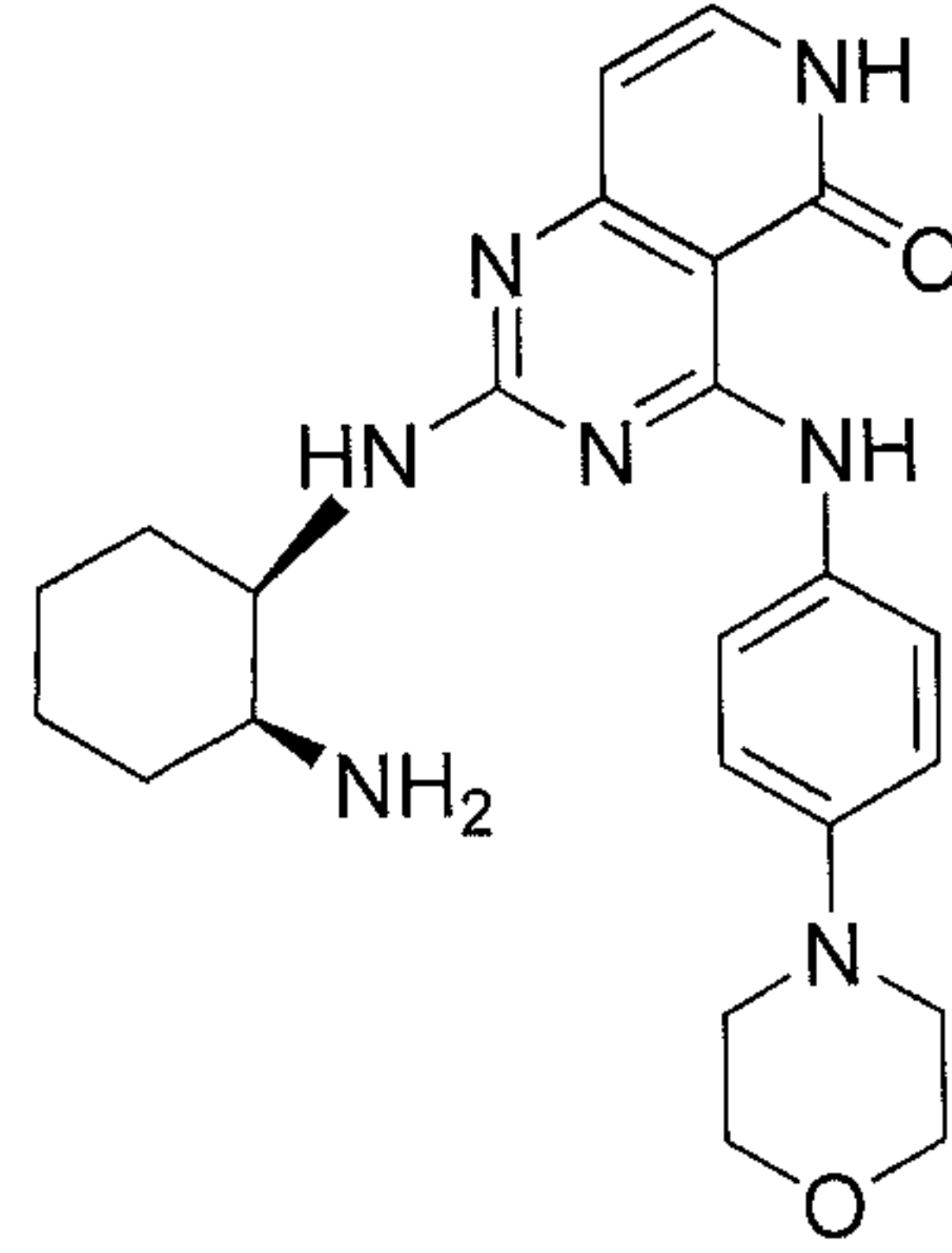
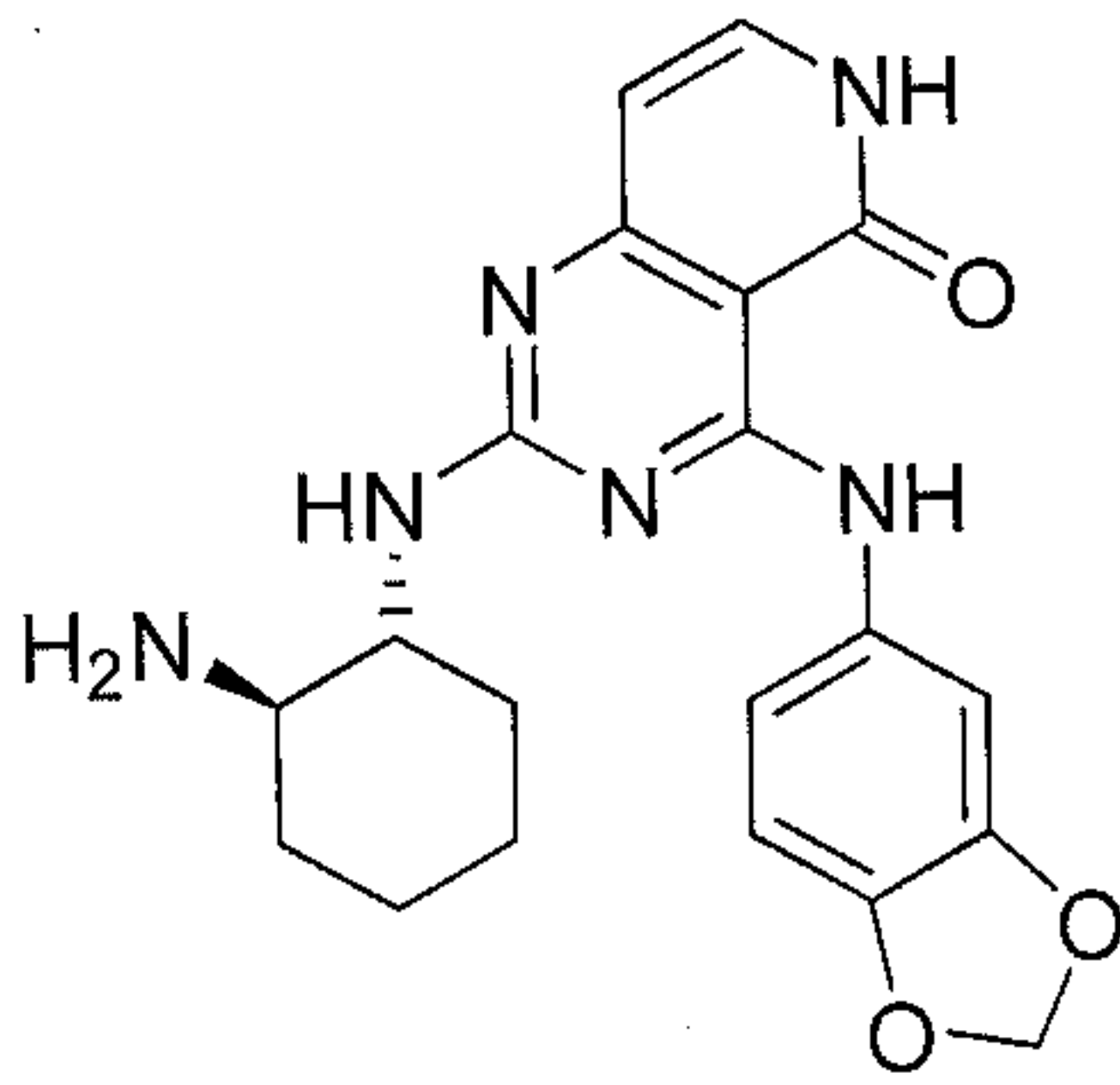
the residue was added acetonitrile (10 mL) resulting in precipitates. Filtered and dried under reduced pressure to give the yellow solids (9 mg, 11%). MS m/z: 423. 2 (M+1)⁺.

The following 4-(4-morpholinophenylamino)-2-(amino substituted)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one compounds were prepared from 4-(4-morpholinophenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one and the corresponding amine following the procedure similar to that described in *Example 134*.

NO.	Structure	Name, NMR (300 MHz, DMSO-d6)	Mass (M+1)
135		4-(4-(4-(hydroxymethyl)piperidin-1-yl)phenyl amino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	478
136		(<i>S</i>)-4-(4-morpholinophenylamino)-2-(pyrrolidin-3-ylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	408
137		2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-(4-sulfonylpiperidin-1-yl)phenyl amino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	485

138		4-(4-(4-acetylpiperazin-1-yl)phenyl amino)-2-(4-(hydroxymethyl)piperidin -1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	478
139		2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-morpholinophenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	437
140		4-(4-(5-oxo-2-(piperidin-4-ylmethyl amino) -5,6-dihydropyrido[4,3- <i>d</i>] pyrimidin-4-ylamino)phenyl) morpholine 4-oxide hydrochloride	452
141		4-(4-morpholinophenylamino)-2-(piperidin-4-ylmethylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	436

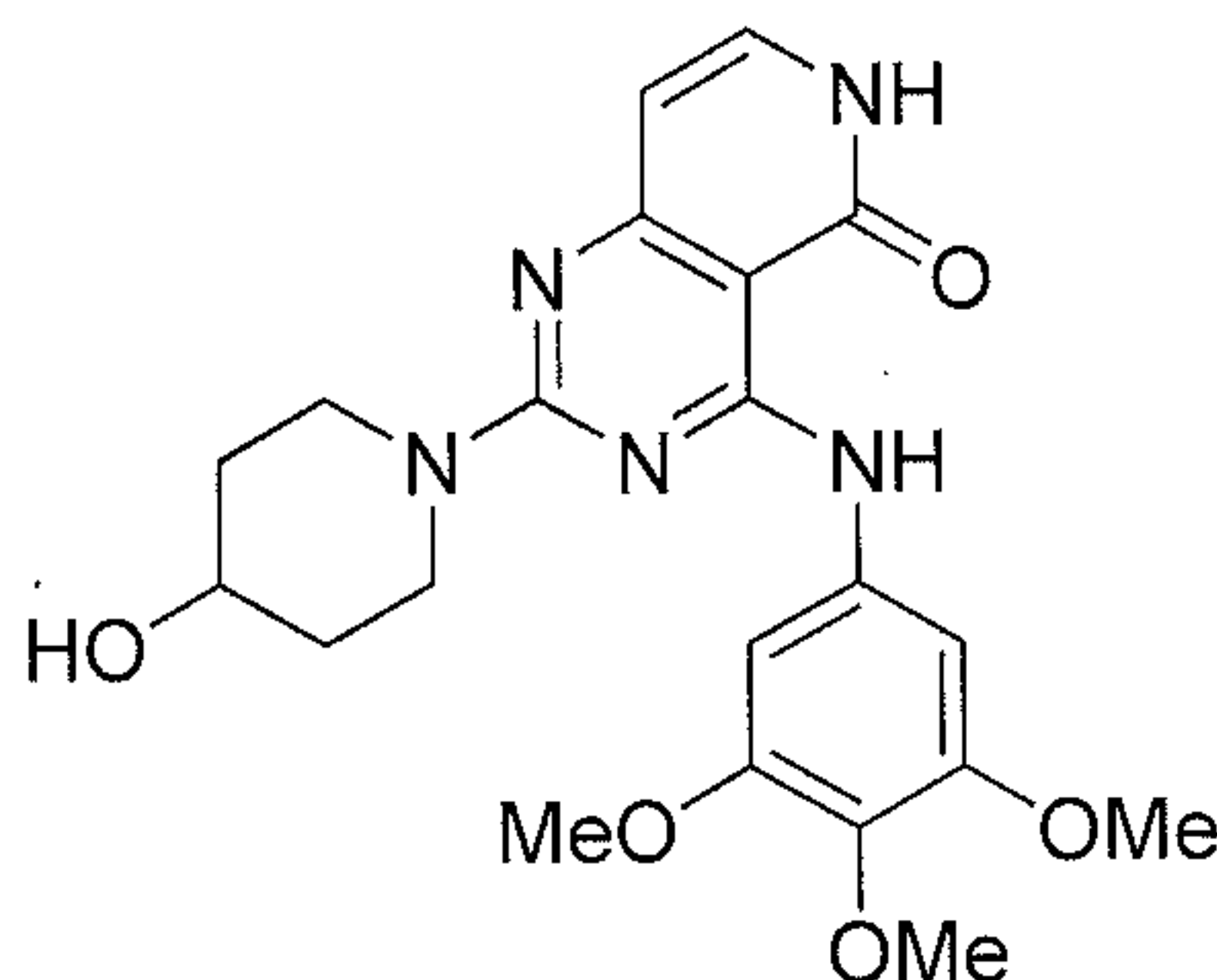
142		<i>N</i> -methyl- <i>N</i> -(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)methyl)phenyl)cyclopropanesulfonamide	562
143		<i>N</i> -(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)methyl)phenyl)cyclopropanesulfonamide	548
144		<i>N</i> -(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide	522
145		2-(2-aminobenzylamino)-4-(4-morpholinophenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	444

146		2-((1 <i>R</i> ,2 <i>R</i>)-2-aminocyclohexylamino)-4-(4-morpholinophenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	436
147		2-((1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexylamino)-4-(4-morpholinophenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	436
148		2-((1 <i>R</i> ,2 <i>R</i>)-2-aminocyclohexylamino)-4-(benzo[<i>d</i>][1,3]dioxol-5-ylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one 11.83 (d, <i>J</i> = 10.50 Hz, 1H), 7.83 (d, <i>J</i> = 1.50 Hz, 1H), 7.56 (d, <i>J</i> = 7.50 Hz, 1H), 7.50 (d, <i>J</i> = 8.10 Hz, 1H), 7.33 (s, 1H), 6.16 (d, <i>J</i> = 7.20 Hz, 1H), 6.01 (s, 1H), 3.89 (s, 1H), 3.71 (d, <i>J</i> = 10.80 Hz, 1H), 2.00 (s, 2H), 1.70 (s, 2H), 1.22 (s, 4H)	395

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Example 149

Synthesis of 2-(4-hydroxypiperidin-1-yl)-4-(3,4,5-trimethoxyphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

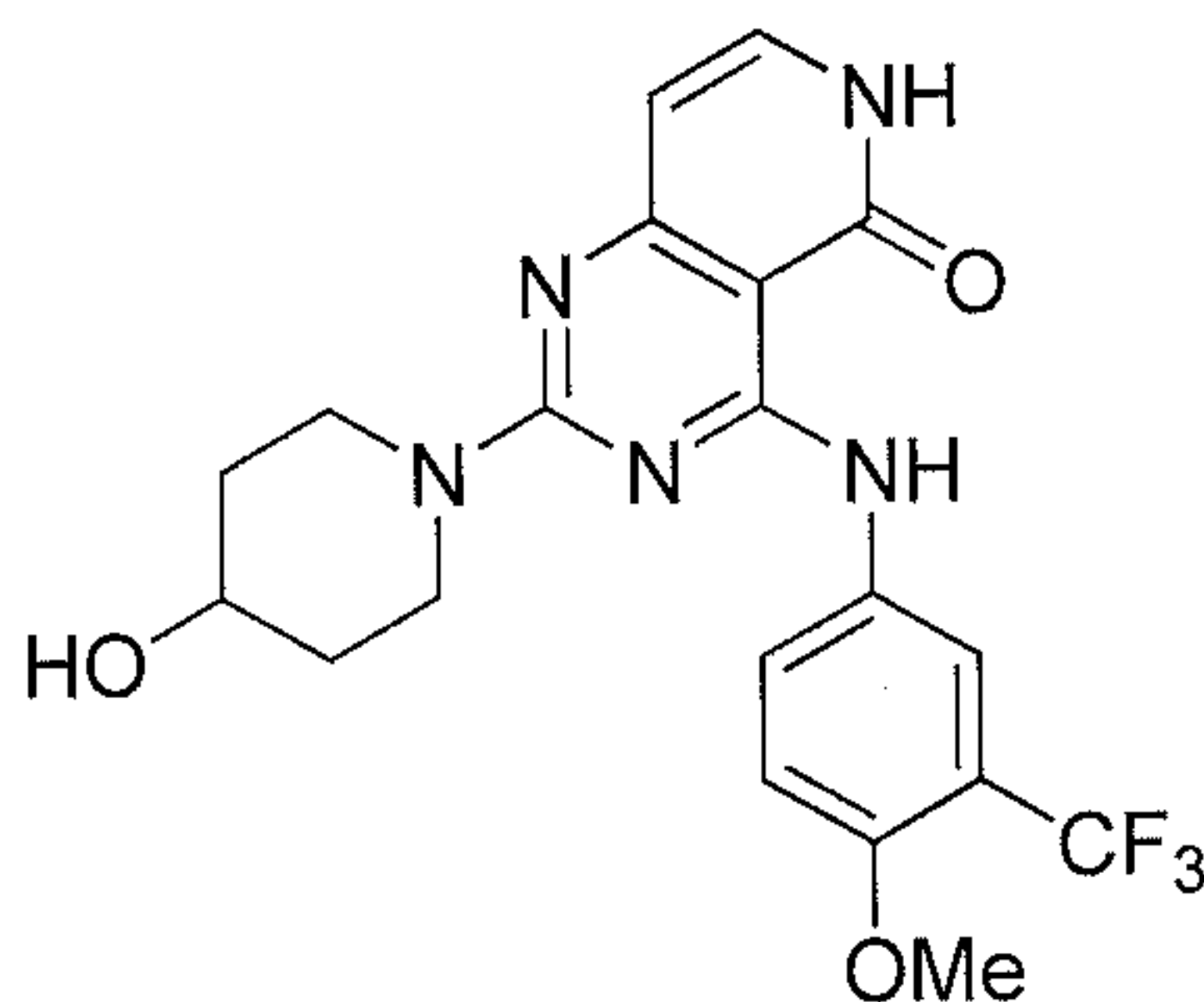


Compound No. 149

Prepared as described in *Example 1g* starting from 4-(3,4,5-trimethoxyphenylamino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (112 mg, 0.30 mmol), and 4-hydroxypiperidine (91 mg, 0.90 mmol) to give the pale brown solids (112 mg, 87 %). MS *m/z*: 428 (*M*+1)⁺ ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.16- 1.81 (m, 6H), 3.64 (s, 3H), 3.80 (s, 6H), 4.35 (d, *J* = 13.2 Hz, 2H), 4.80 (d, *J* = 4.2 Hz, 1H), 6.14 (d, *J* = 7.2 Hz, 1H), 7.08 (s, 2H), 7.36 (d, *J* = 6.9 Hz, 1H), 11.35 (s, 1H), 11.87 (s, 1H).

Example 150

Synthesis of 2-(4-hydroxypiperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino) pyrido [4,3-*d*] pyrimidin-5(6*H*)-one



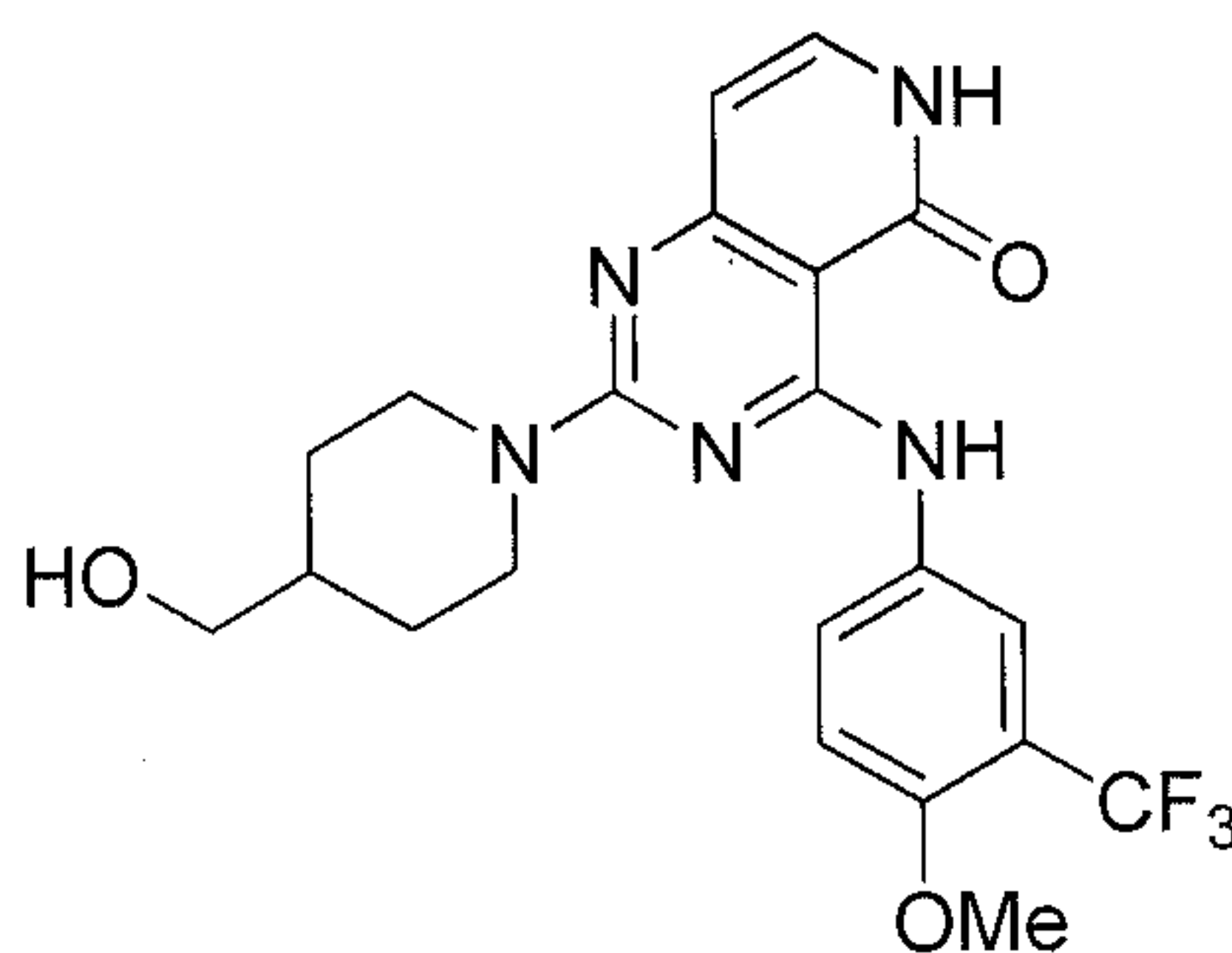
Compound No. 150

Compound No. 150 was prepared as described in *Example 1g* by starting from 4-(4-methoxy-3-(trifluoromethyl)phenyl amino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (70

mg, 0.18 mmol) and 4-hydroxy piperidine (55 mg, 0.54 mmol) and continuing until the reaction yielded light yellow solids (57 mg, 73 %). MS m/z: 436 (M+1)⁺.

Example 151

- 5 Synthesis of 2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl) phenylamino) pyrido[4,3*d*] pyrimidin-5(6*H*)-one

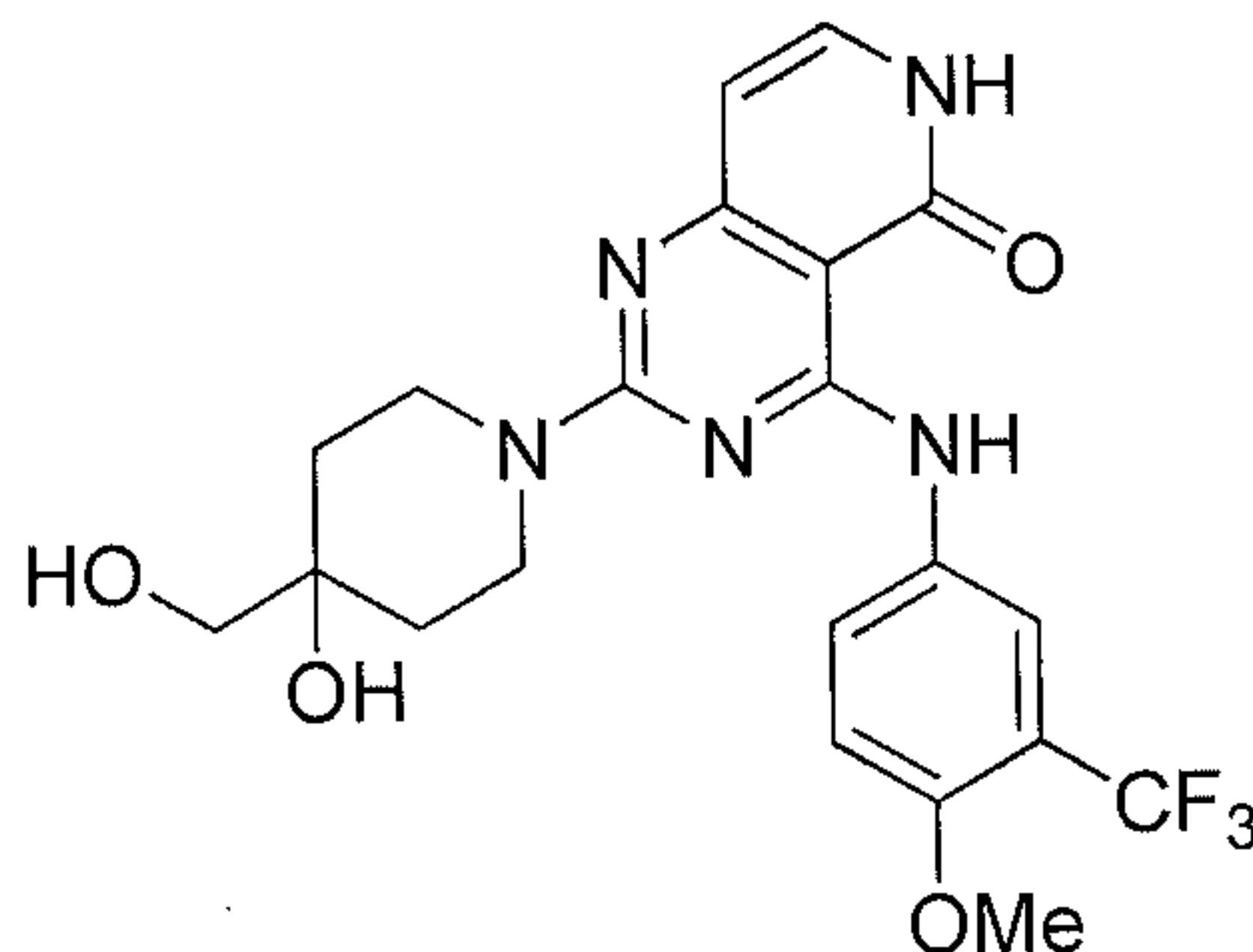


Compound No. 151

- 10 Compound No. 151 was prepared as described in *Example 1g* by starting from 4-(4-methoxy-3-(trifluoromethyl)phenyl amino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (70 mg, 0.18 mmol) and 4-piperidine methanol (67 mg, 0.54 mmol) and continuing until the reaction yielded light yellow solids (67 mg, 83 %). MS m/z: 450.4 (M+1)⁺.

Example 152

- 15 Synthesis of 2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3*d*]pyrimidin-5(6*H*)-one



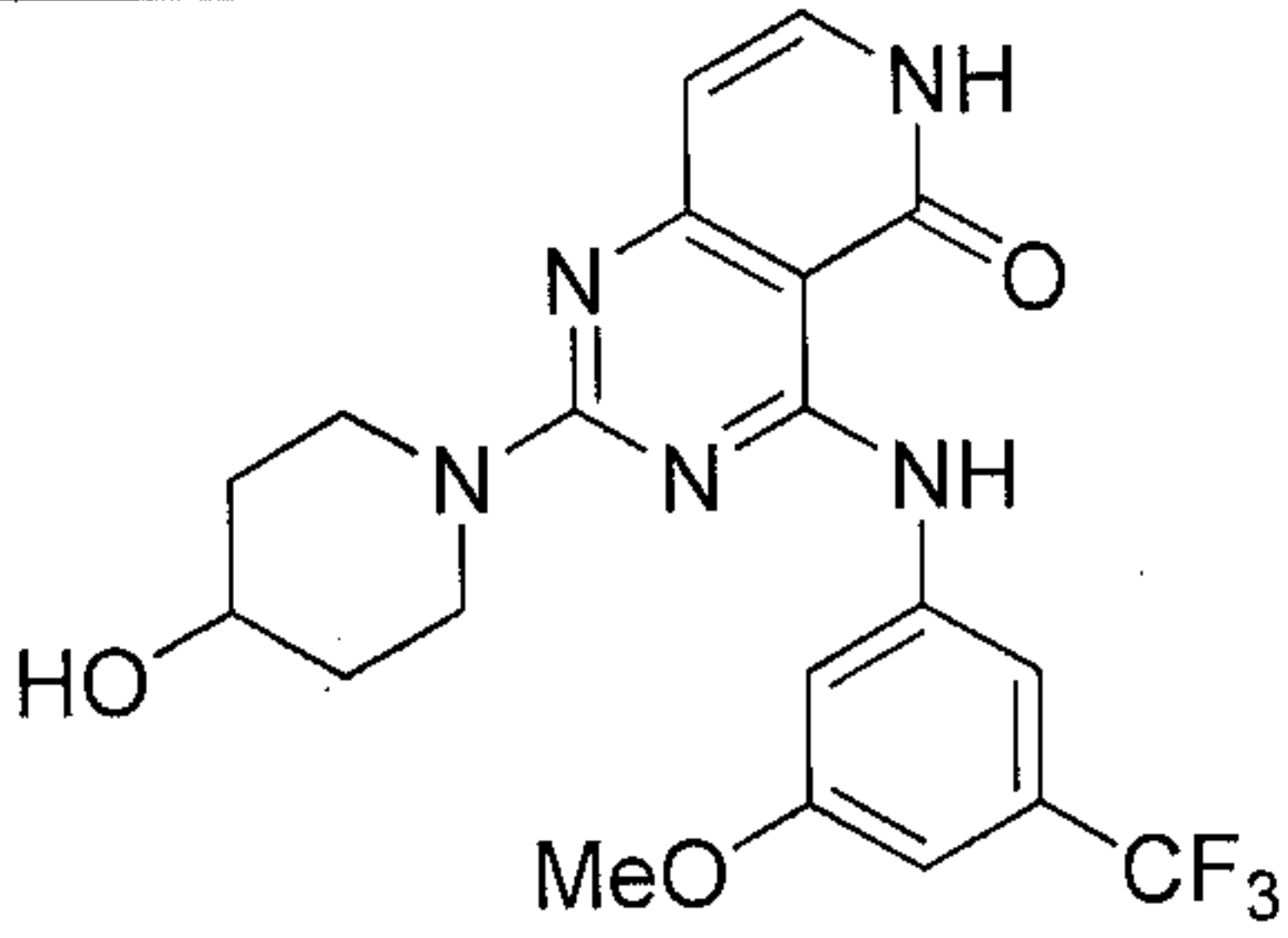
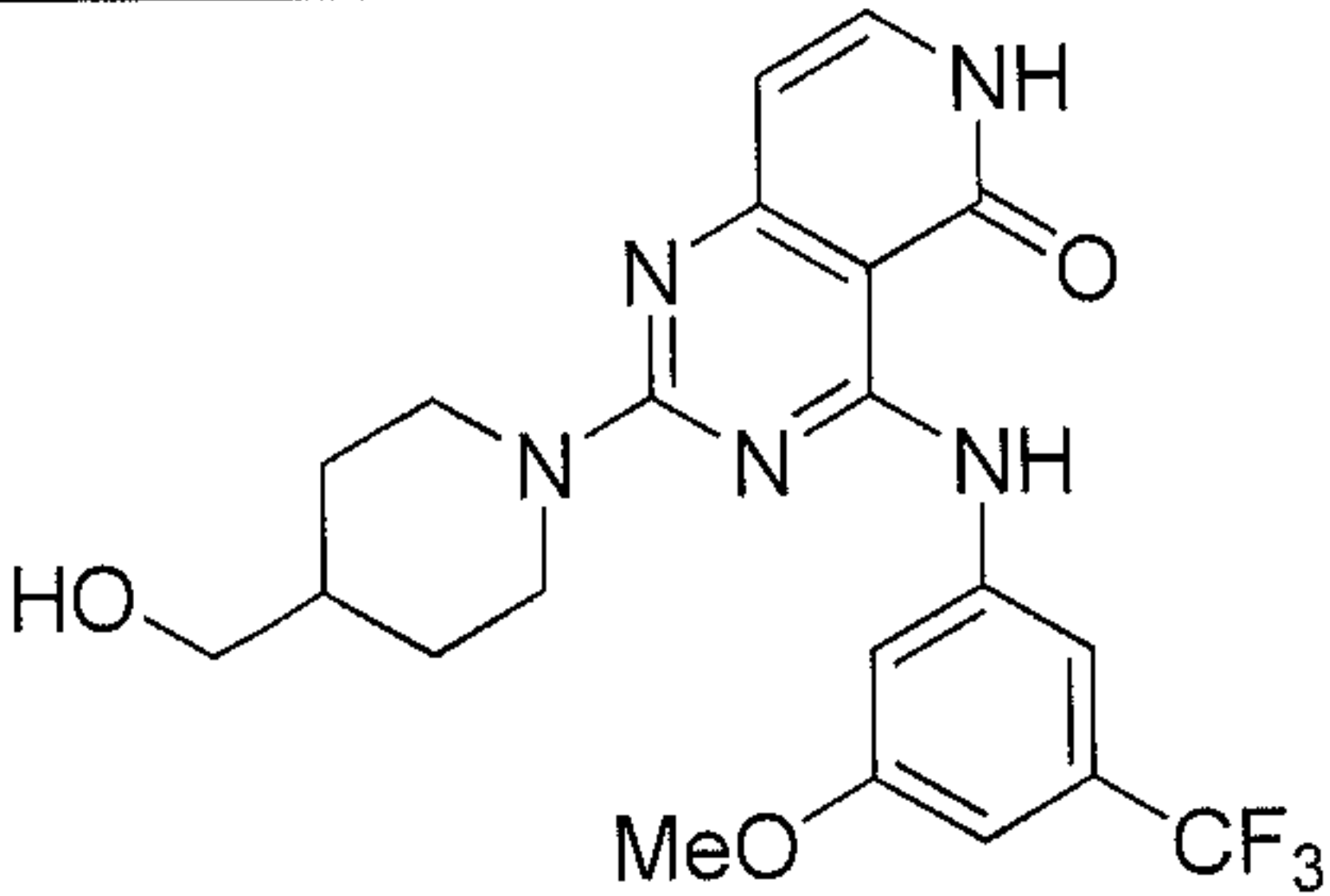
Compound No. 152

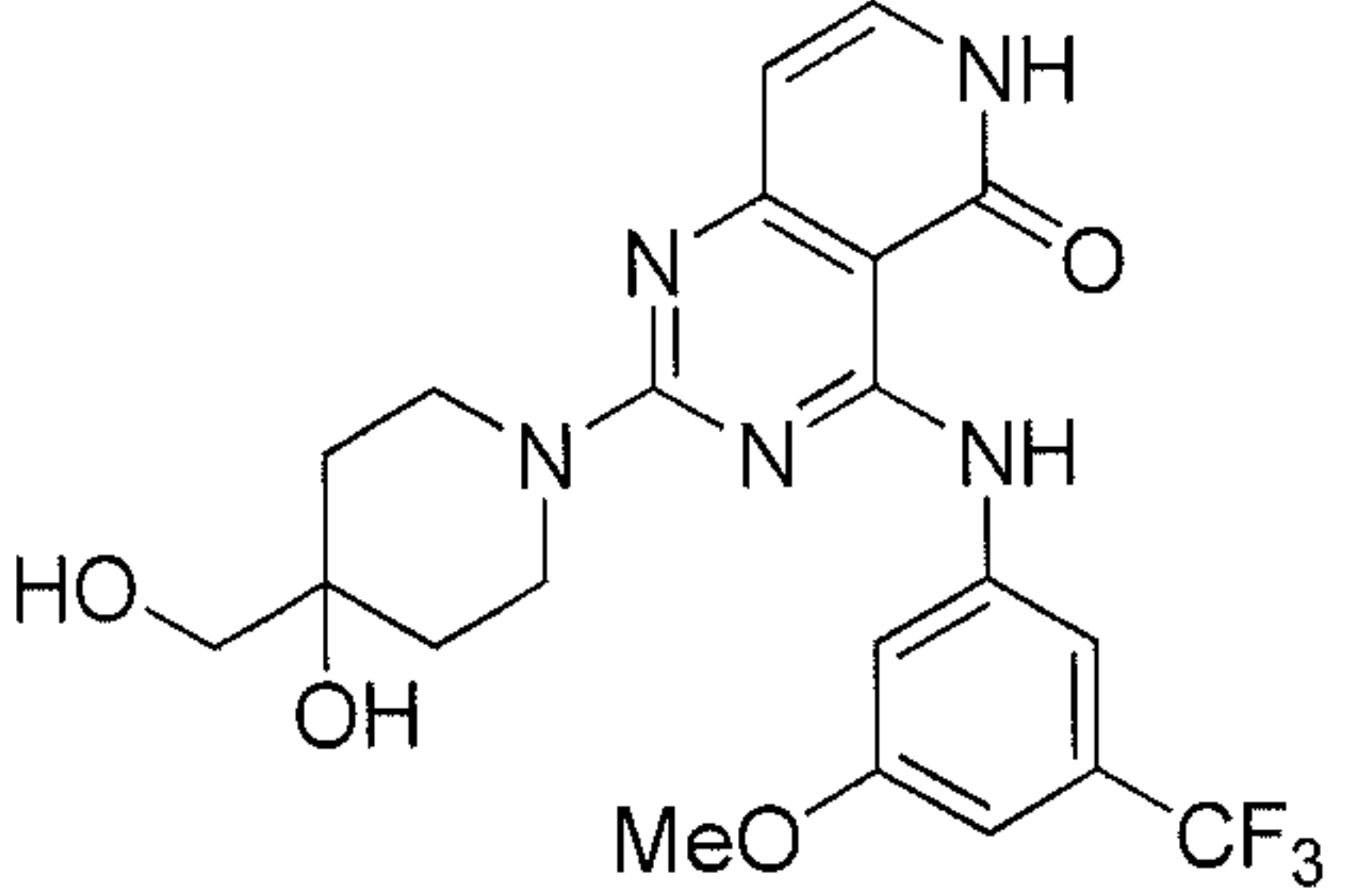
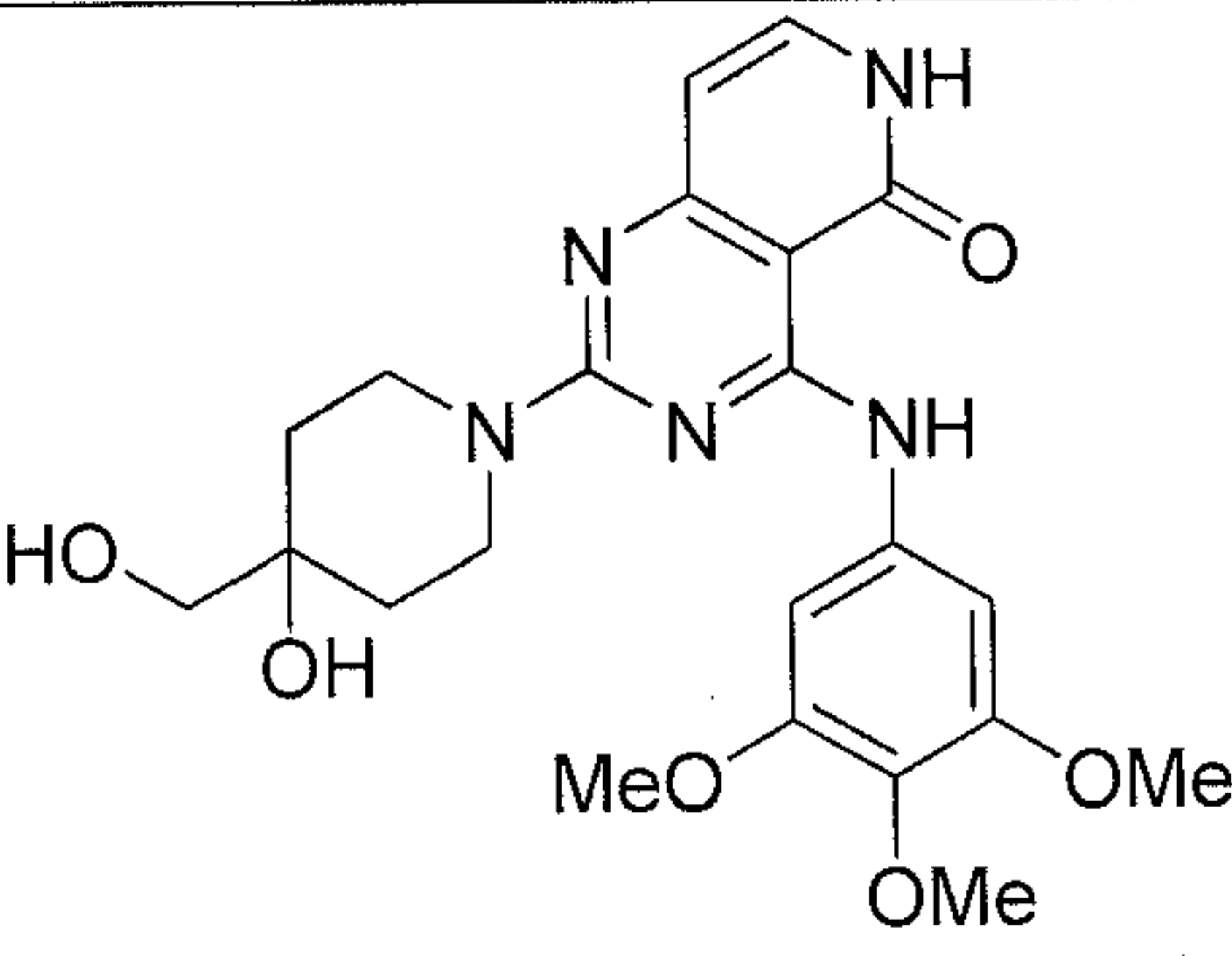
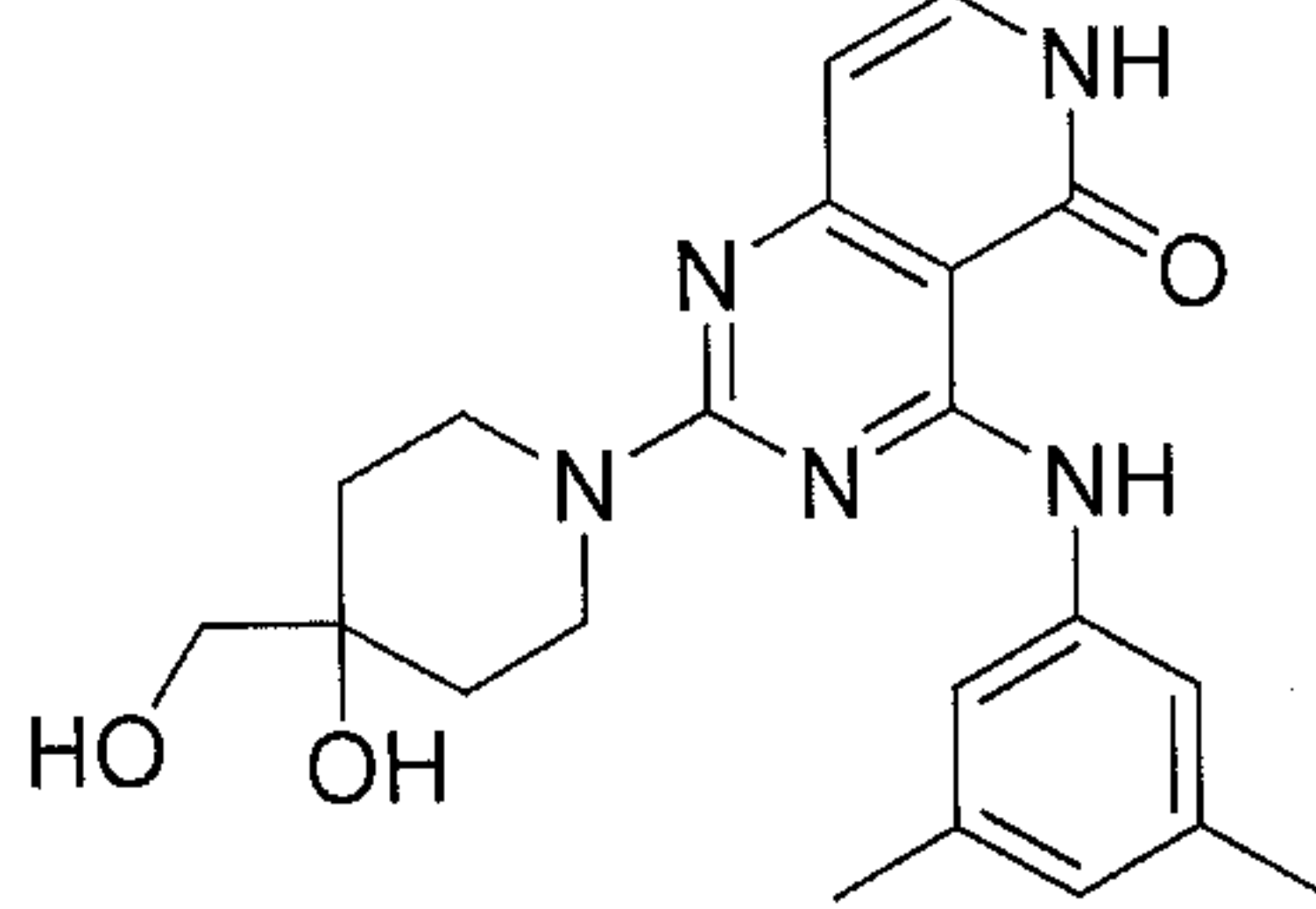
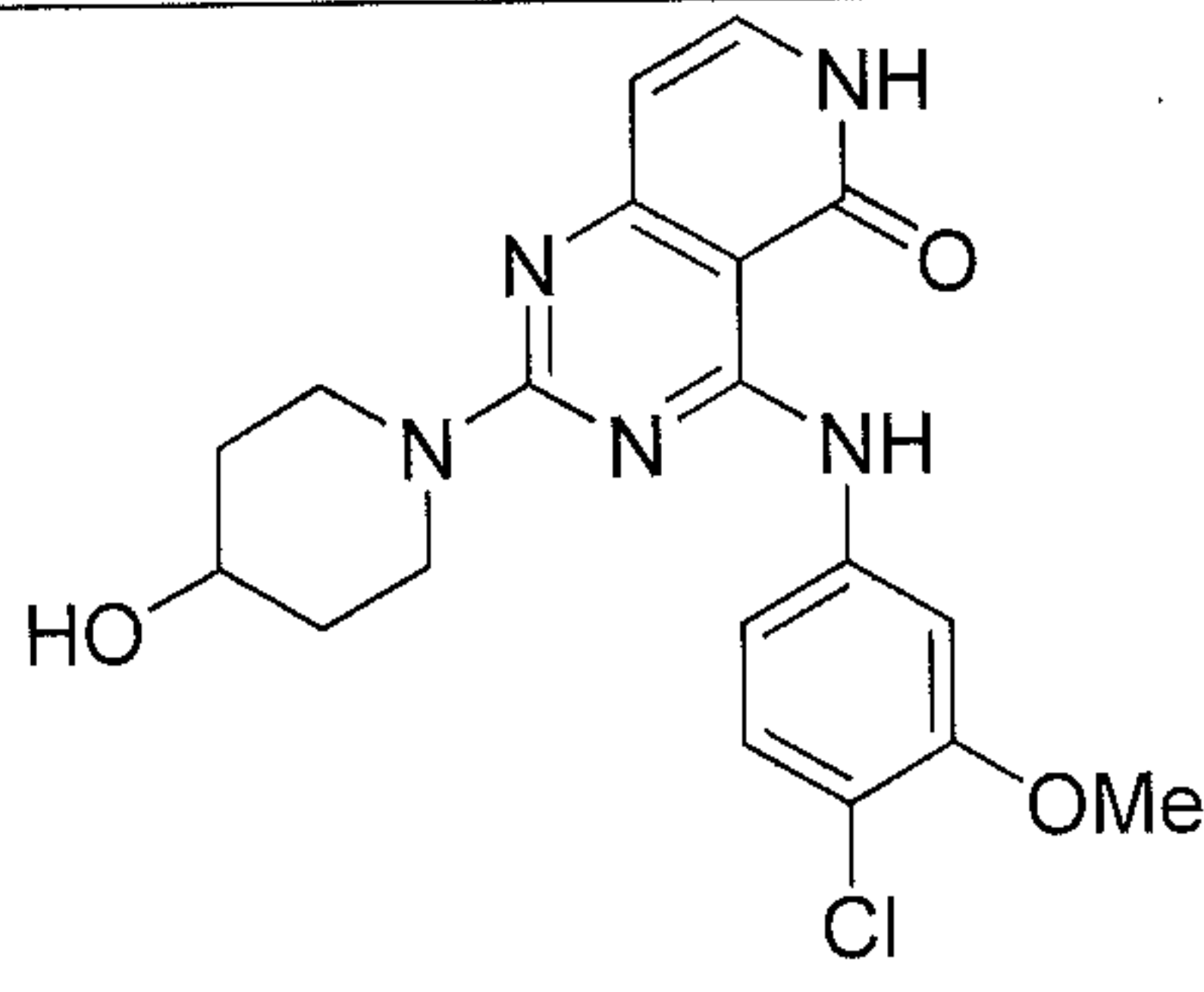
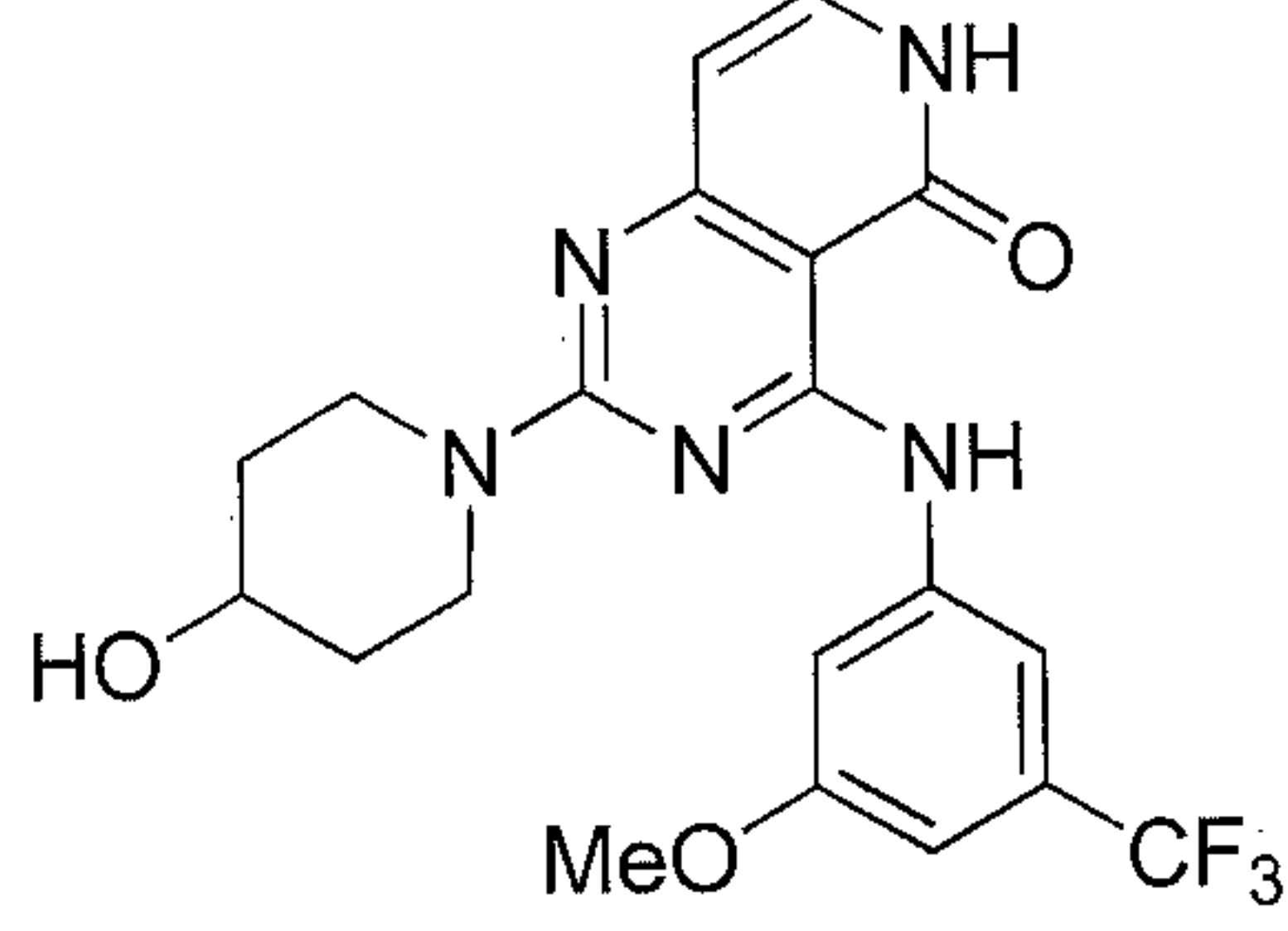
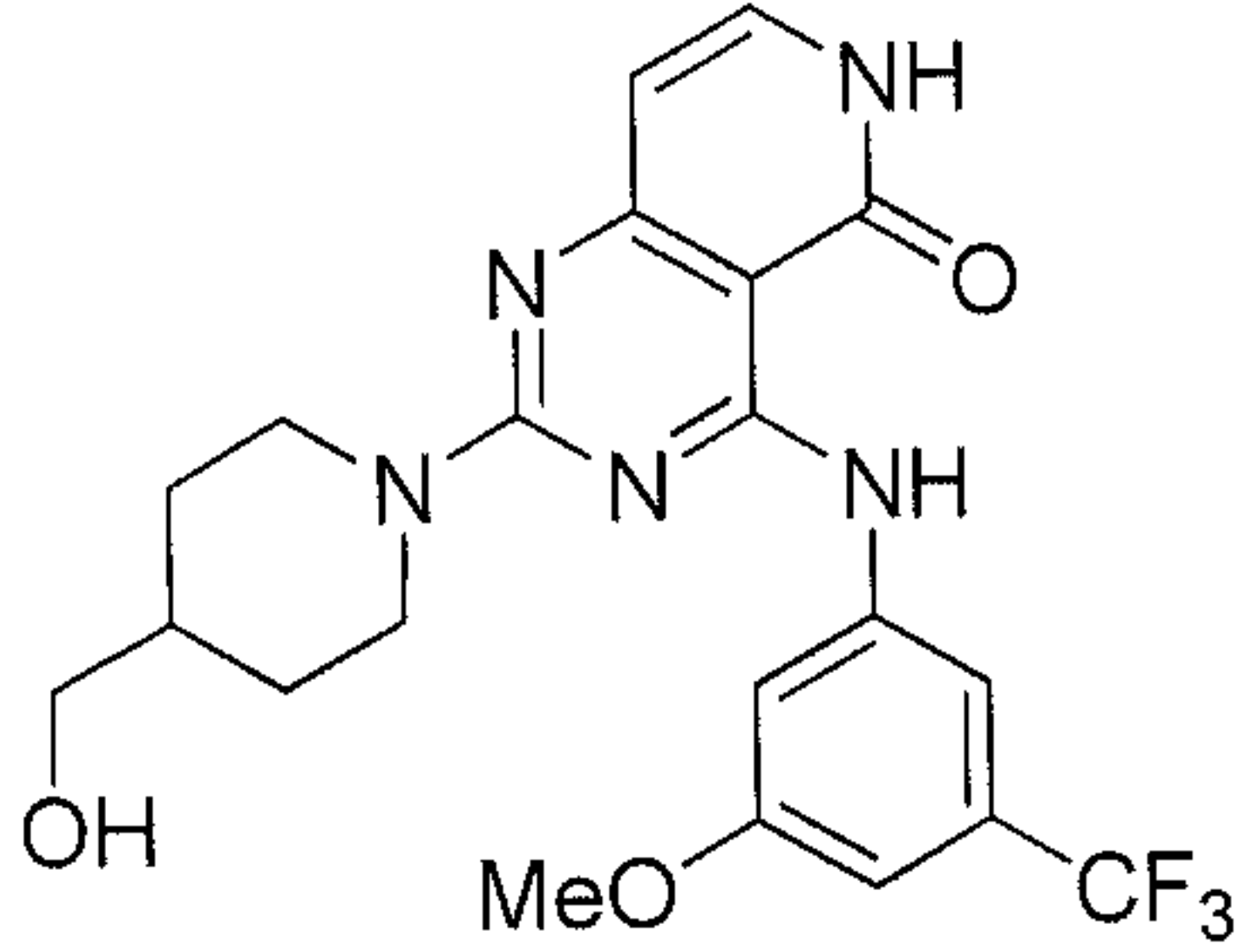
20

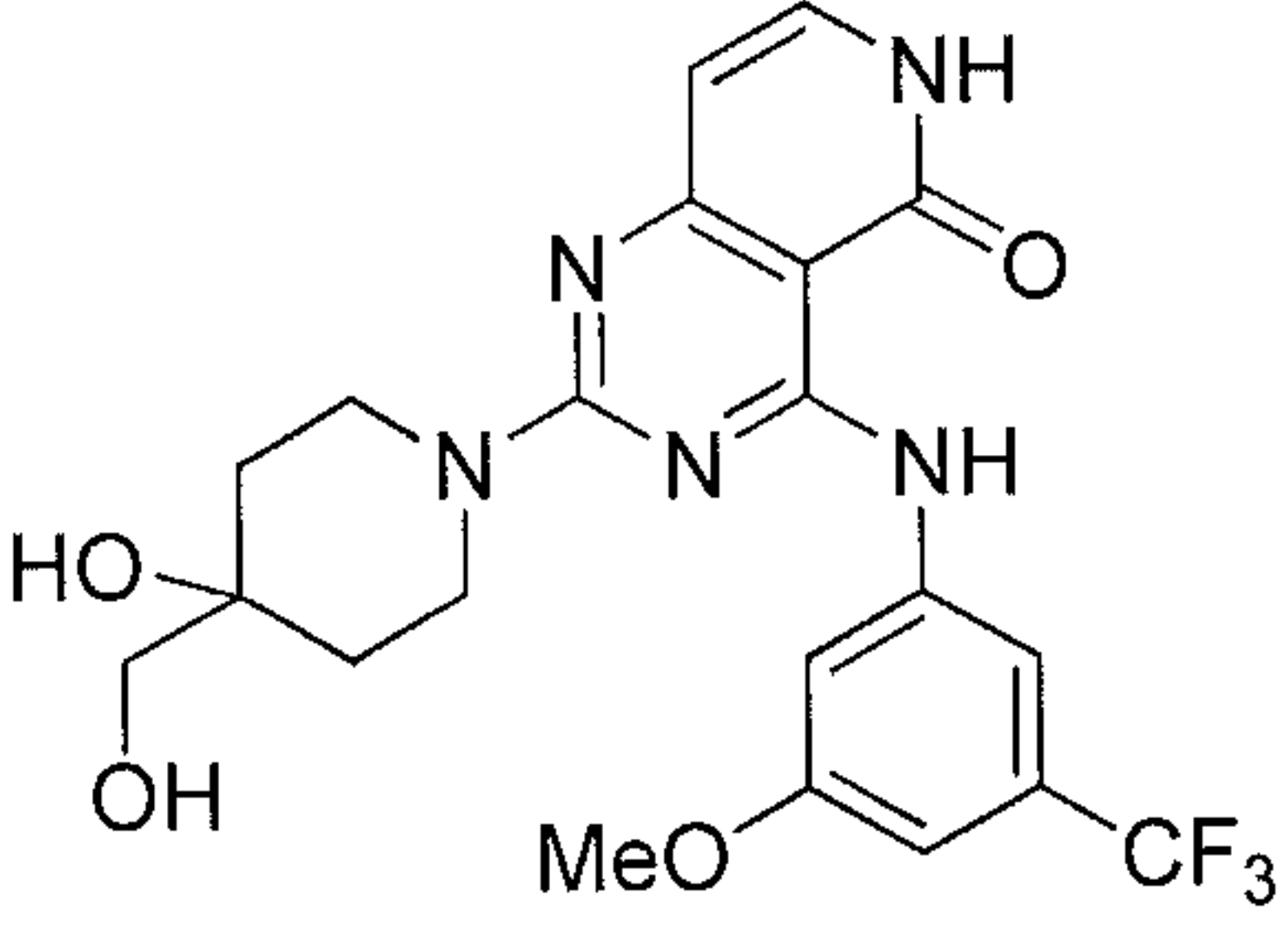
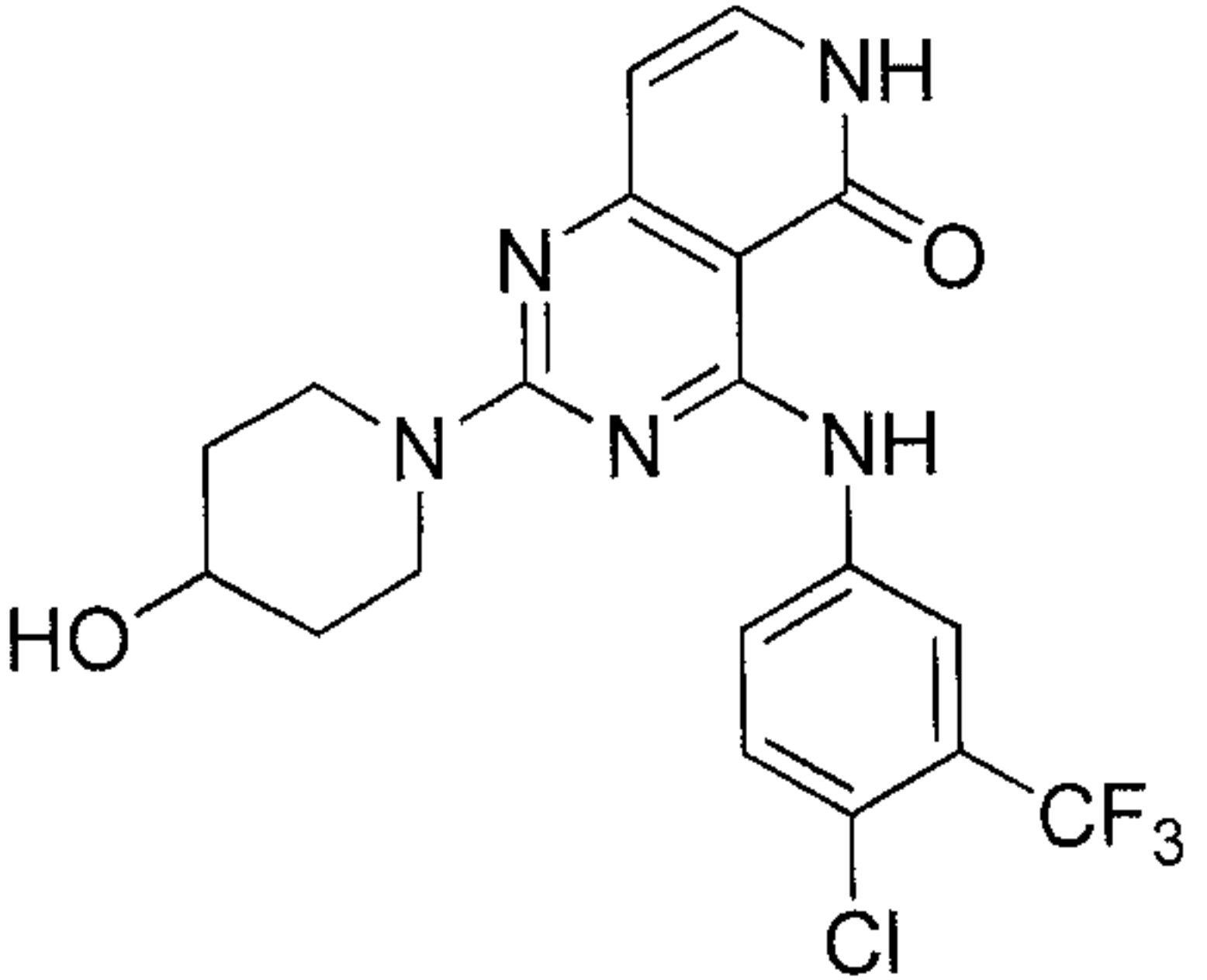
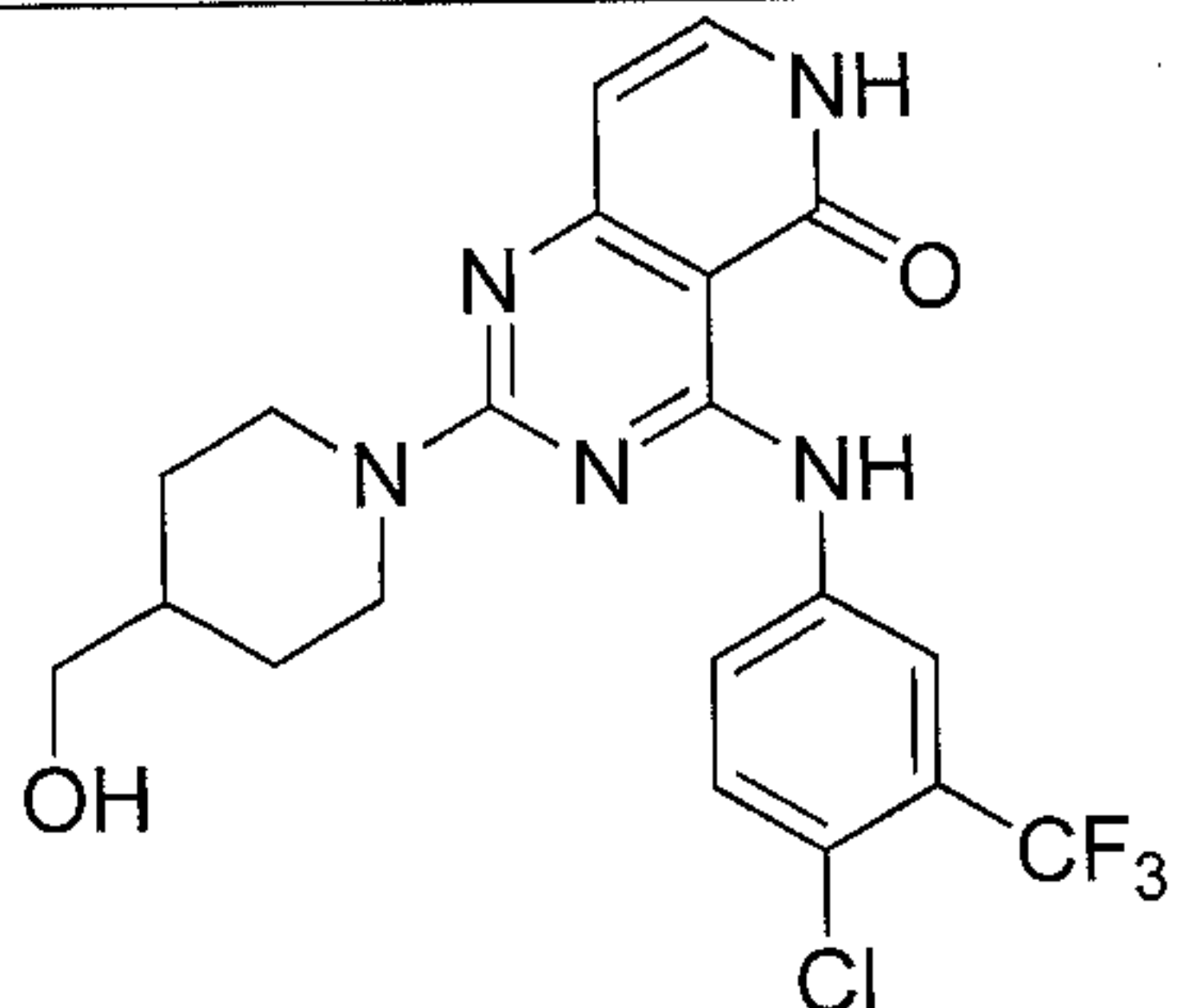
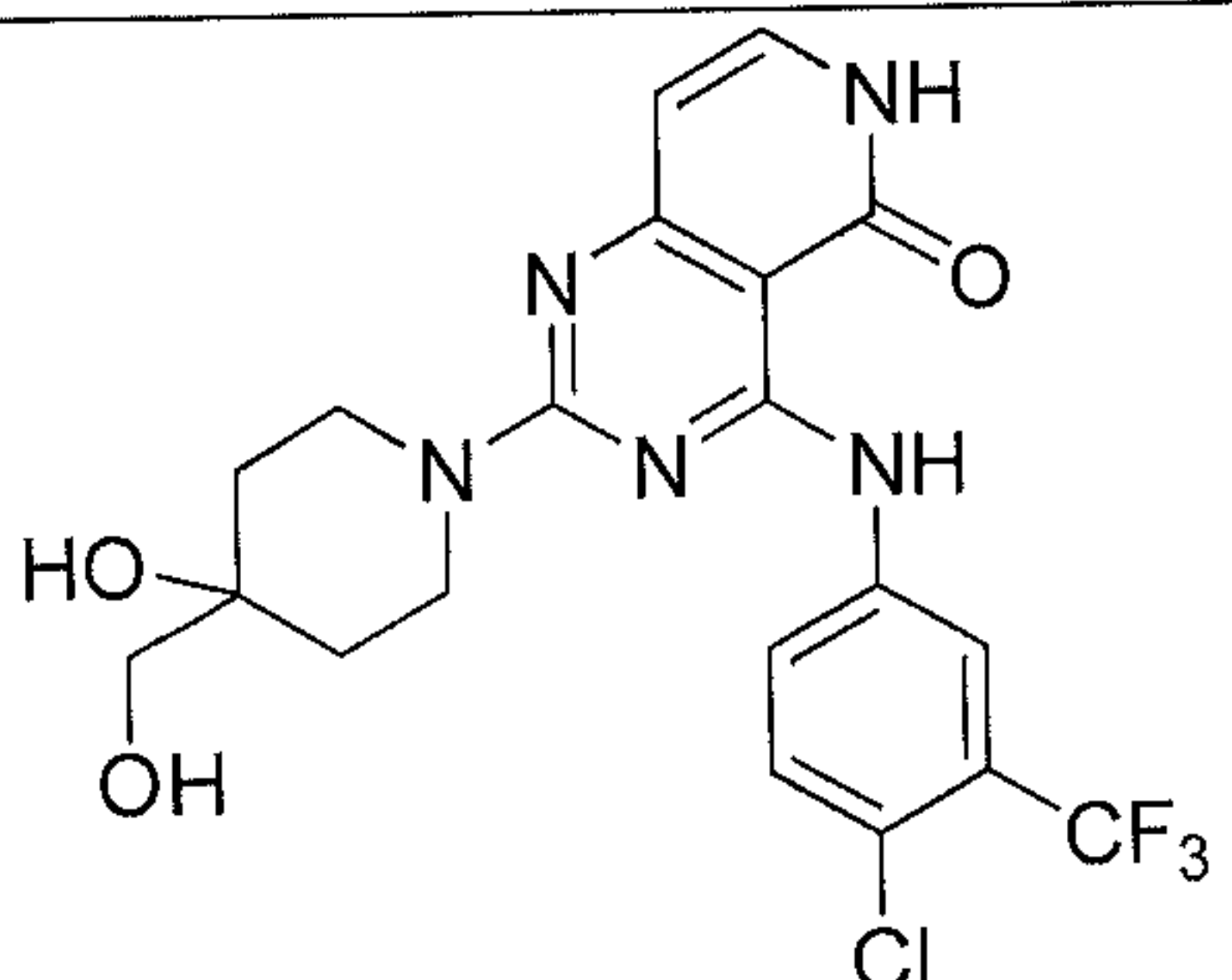
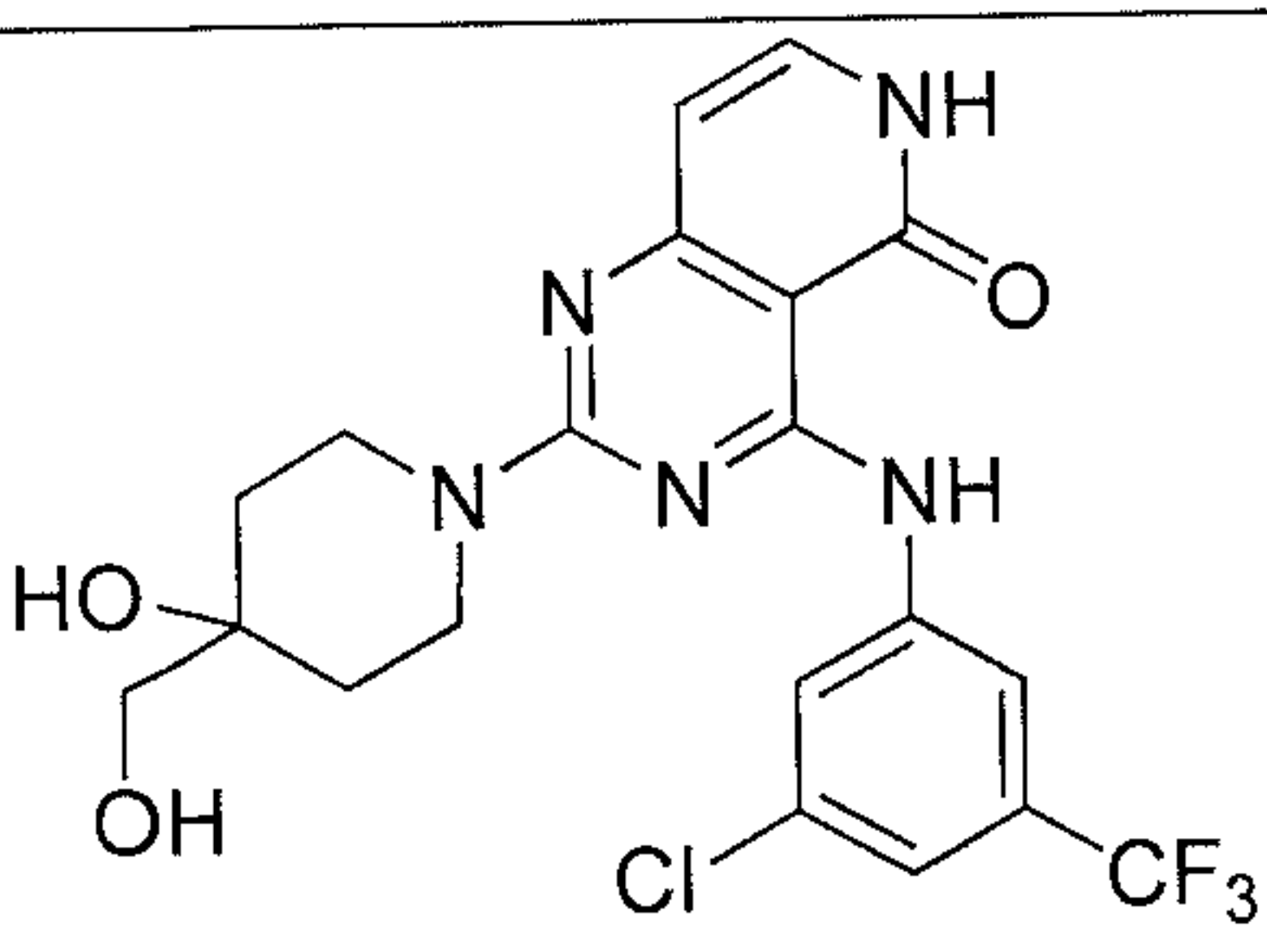
A 20 mL reaction vessel was charged with 4-(4-methoxy-3-(trifluoromethyl)phenyl amino)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (70 mg, 0.18 mmol) in 7 mL DMF at -

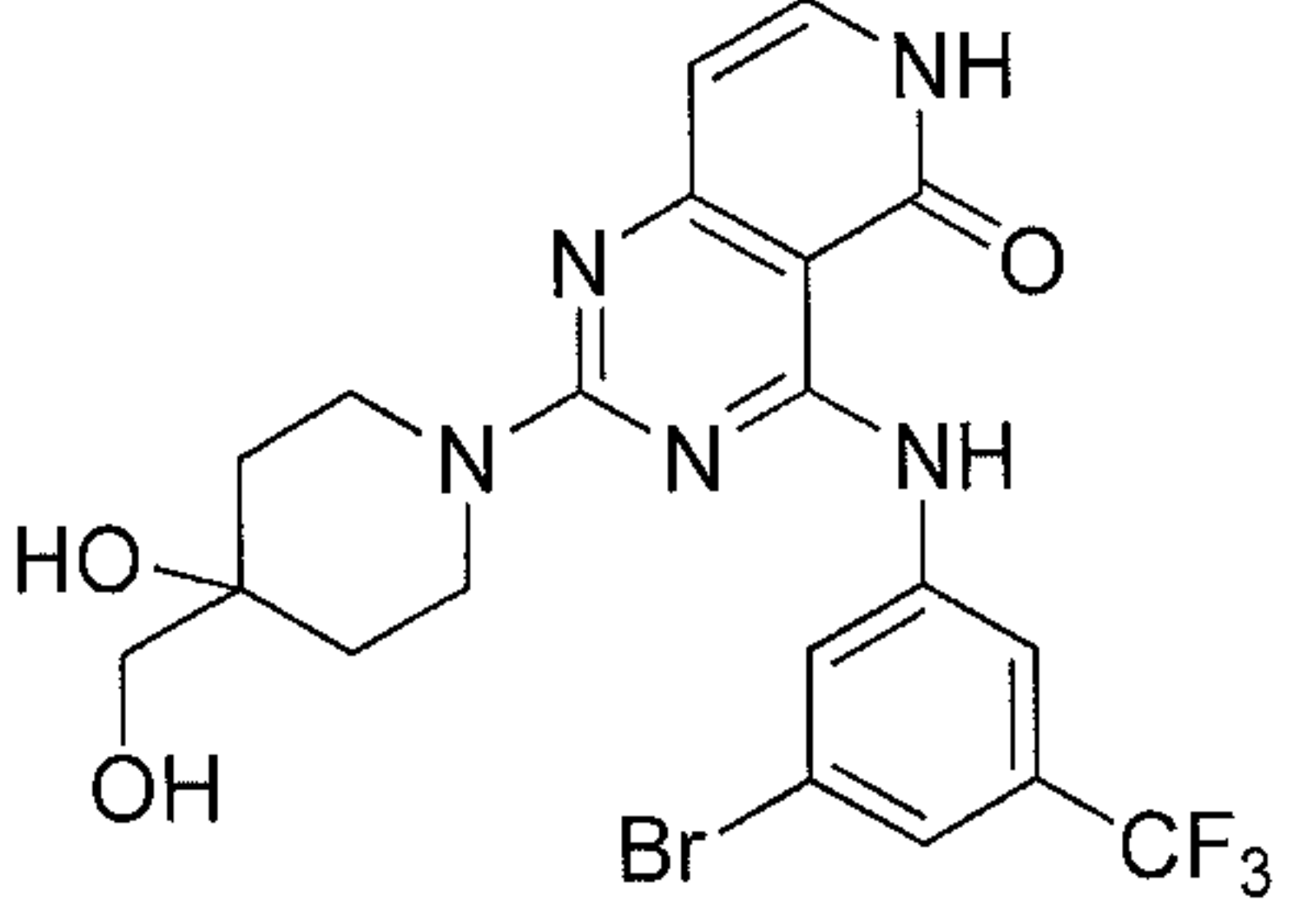
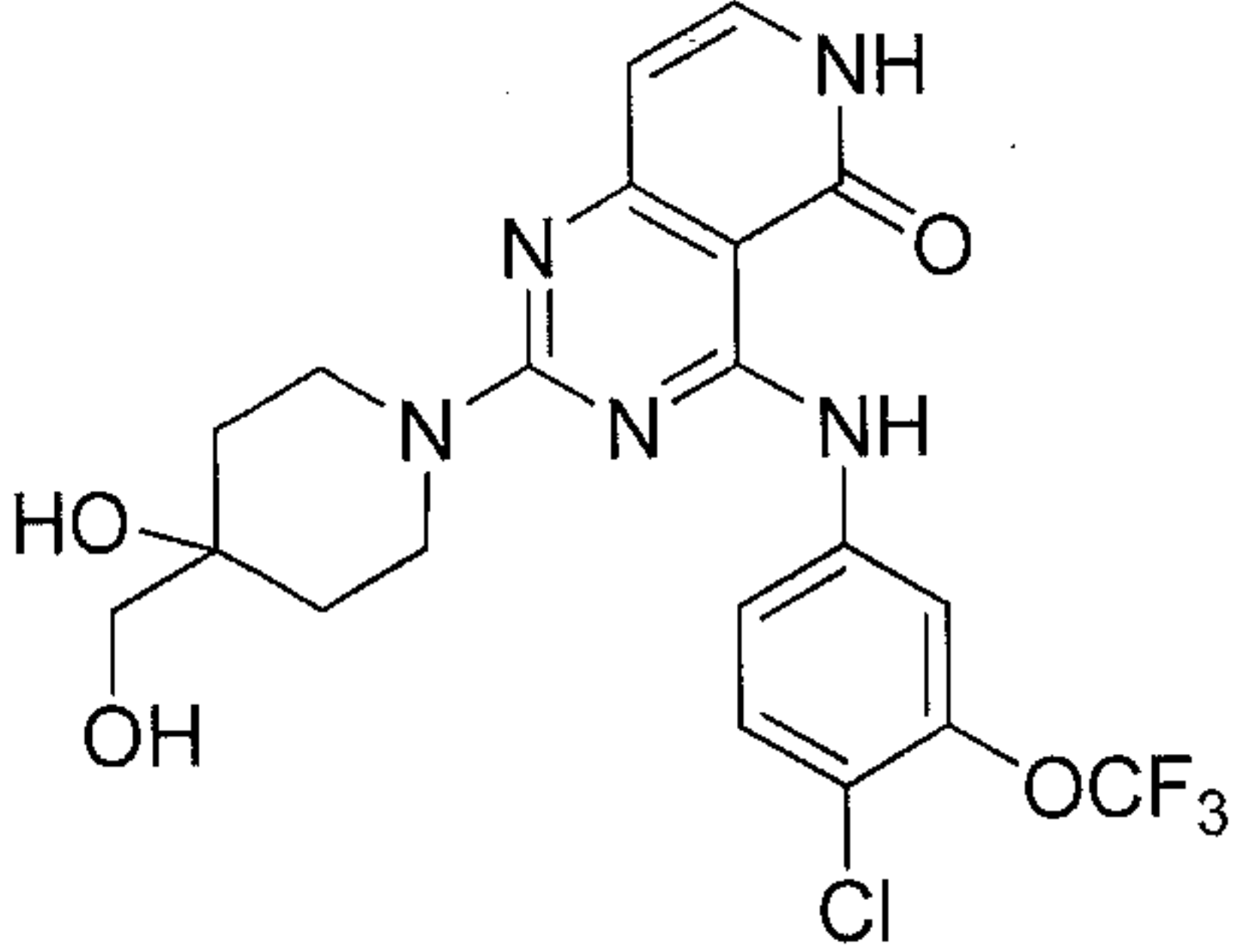
20° C. The solution was kept at the temperature for 30 min. To the cold solution was added *m*-CPBA (133 mg, 0.54 mmol) at the temperature, and further stirred for 30 min with being warmed to room temperature. The reaction was monitored by LC-MS, confirming the corresponding oxide. To the reaction mixture was added triethylamine (75 µL, 1.32 mmol) and methyl 4-hydroxy piperidine-4 carboxylate (57 mg, 0.36 mmol), and stirred at the temperature for 2 hours. The reaction was monitored by LC-MS. The solvent was removed by a rotavapor yielding light yellow solid, methyl 4-hydroxy-1-(4-(4-methoxy-3-(trifluoromethyl)phenylamino)-5-oxo-5,6-dihydro pyrido[4,3-*d*]pyrimidin-2-yl) piperidine-4-carboxylate (65 mg, 73%). It was dissolved in 8 mL dry THF in a 20 mL reaction vessel. To the mixture was added 1.0 M DIBAL in toluene (1.95 mL, 1.95 mmol) at 0° C. It was stirred at the temperature for 2 hours. The reaction mixture was quenched with 20 mL MeOH. The solvents were removed by a rotavapor yielding a light yellow residue. The residue was dissolved in the mixture of MeOH and DCM yielding the white precipitates. They were filtered and the filtrate was condensed under reduced pressure providing a white powder, the title compound, (25 mg, 41 %). MS *m/z*: 466 (*M*+1)⁺.

The following compounds were prepared from the procedure similar to that described for *Example 151 and 152*.

NO.	Structure	Name	Mass (<i>M</i> +1)
153		2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino) pyrido[4,3 <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	435
154		2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino) pyrido[4,3 <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	450

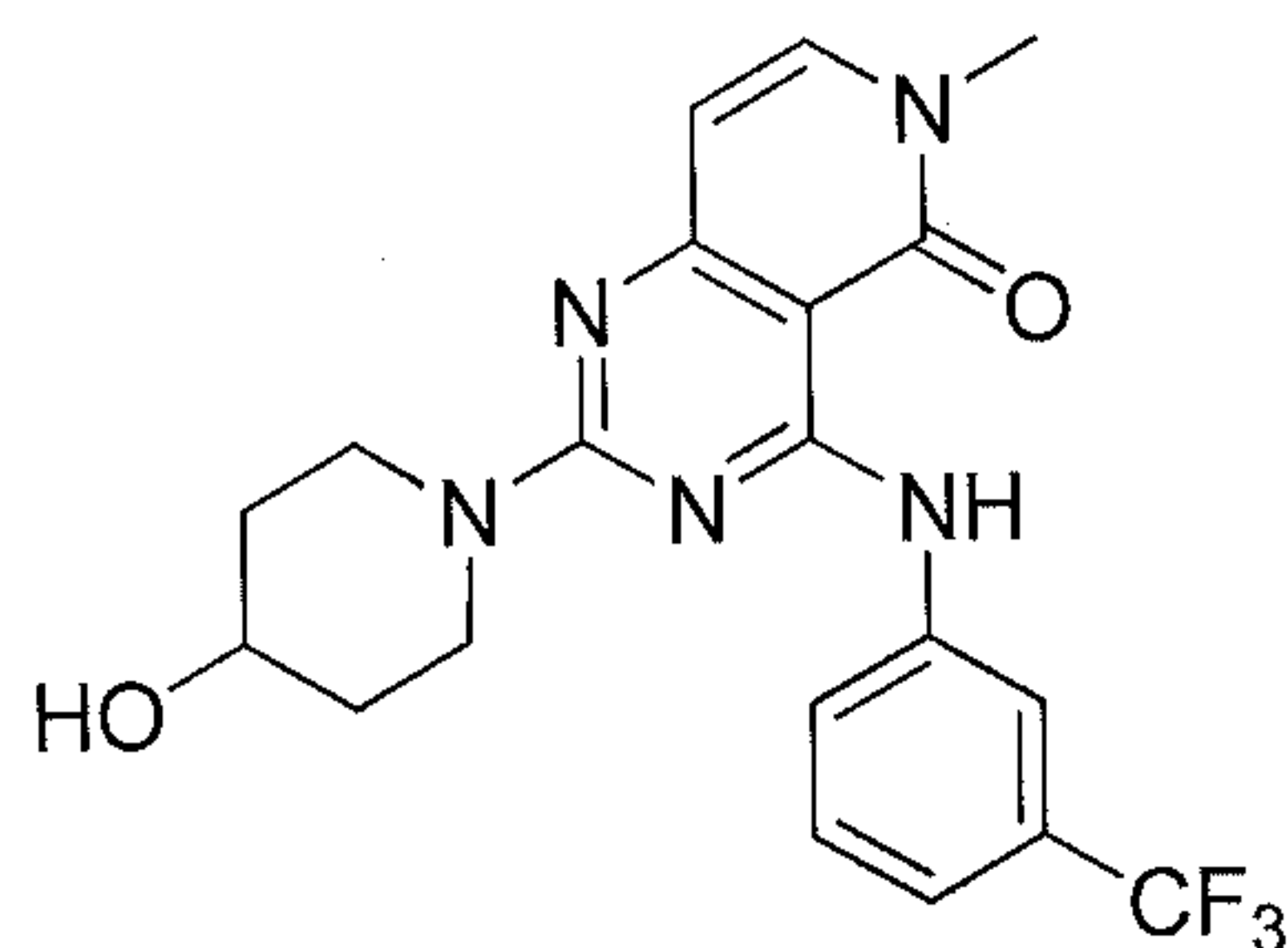
155		2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one	466
156		2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3,4,5-trimethoxyphenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one	458
157		4-(3,5-dimethylphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-5(6H)-one	396
158		4-(4-chloro-3-methoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-d]pyrimidin-5(6H)-one	402
159		2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one	436
160		2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one	450

161		2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	466
162		4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	440
163		4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	454
164		4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	470
165		4-(3-chloro-5-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	470

166		4-(3-bromo-5-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	514
167		4-(4-chloro-3-(trifluoromethoxy)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	486

Example 168

Synthesis of 2-(4-hydroxypiperidine-1-yl)-6-methyl-4-(3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one



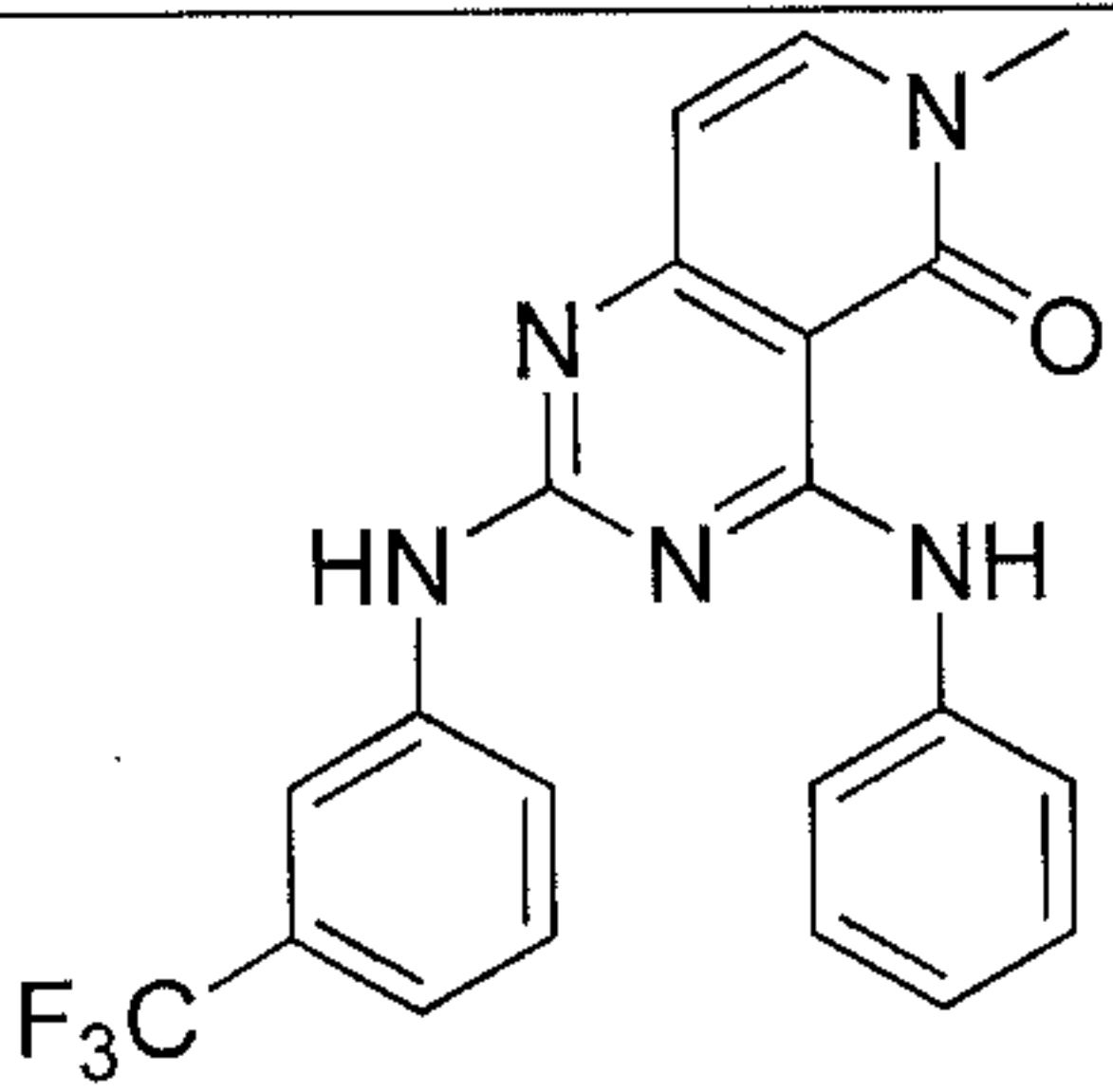
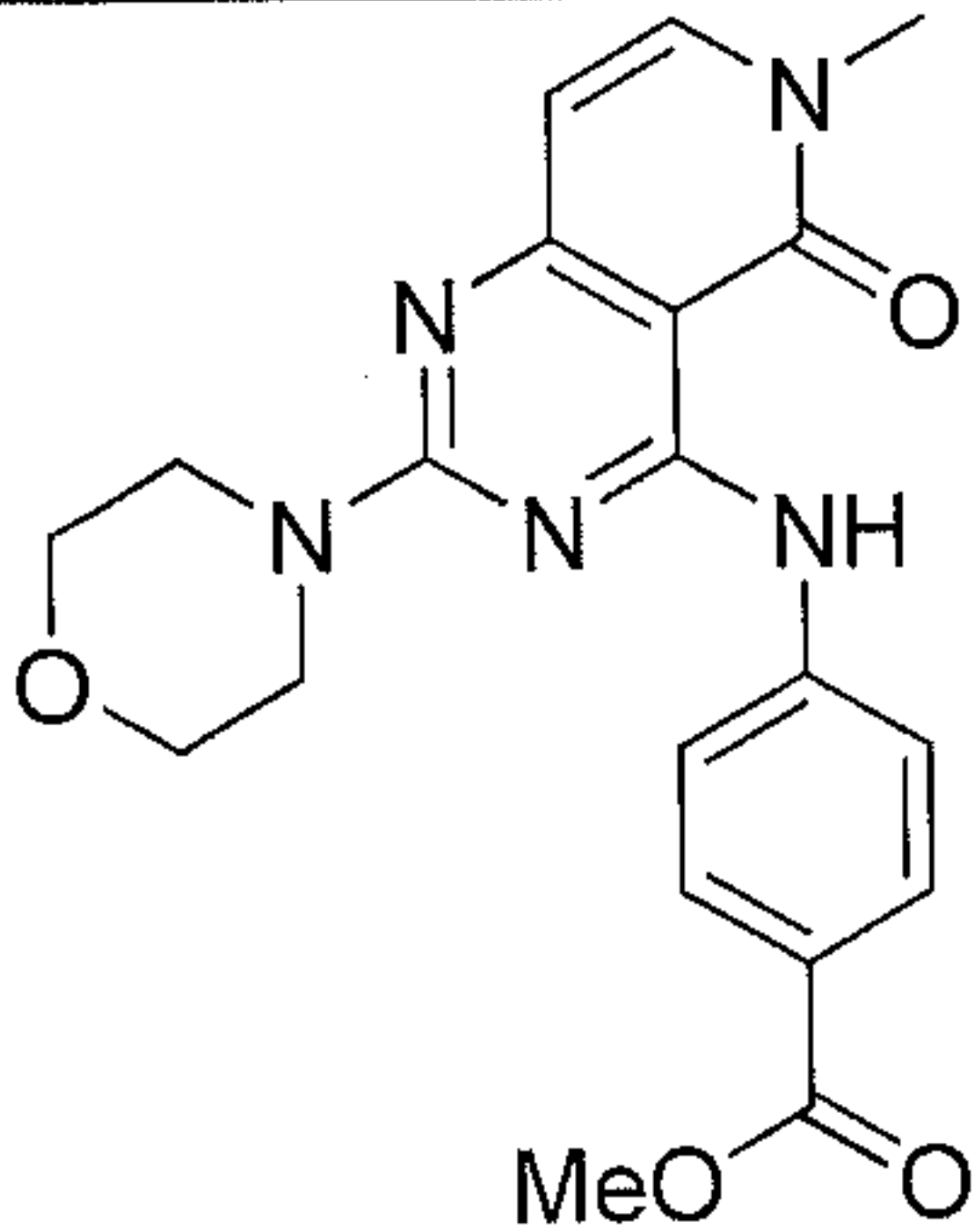
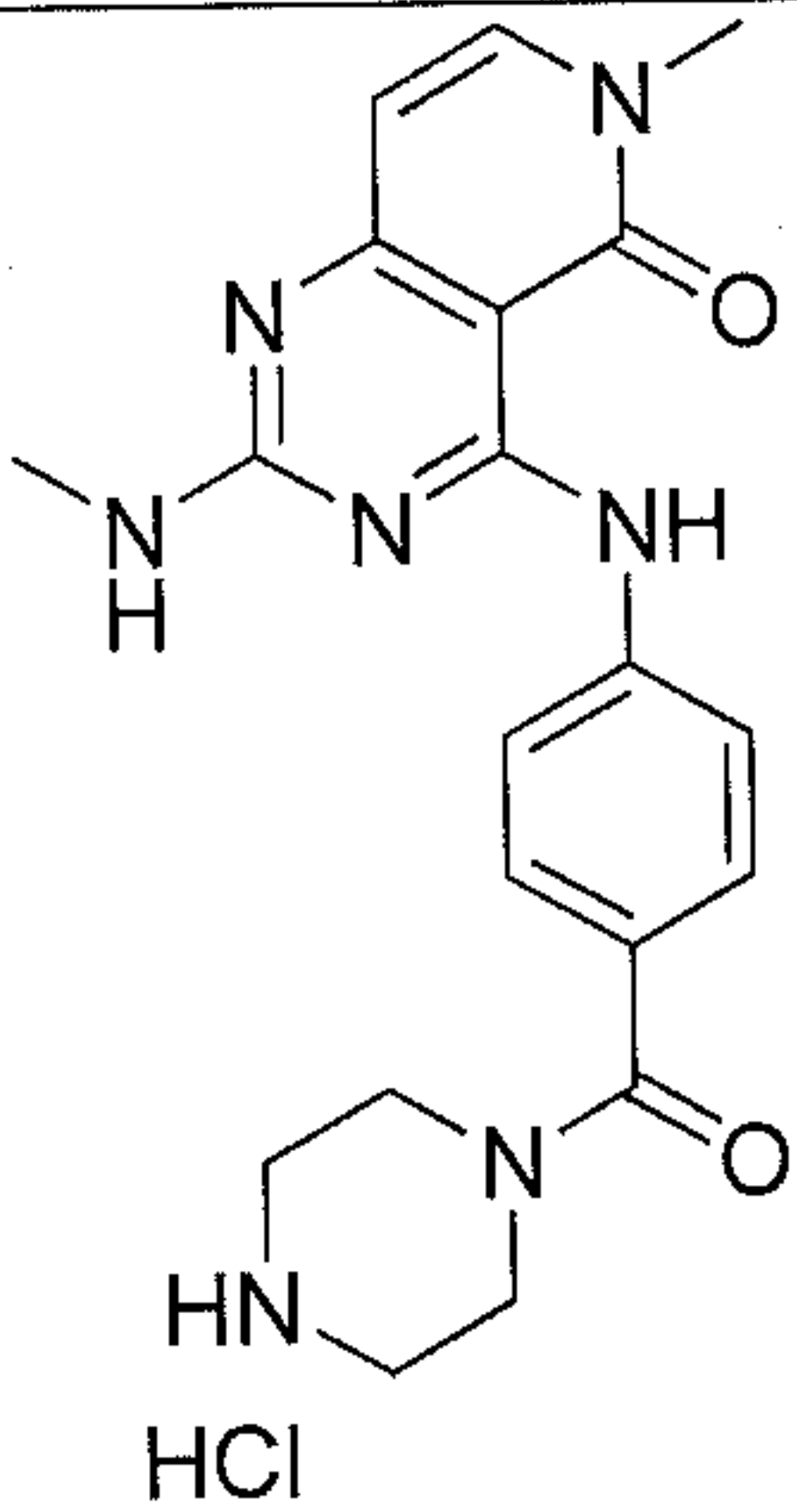
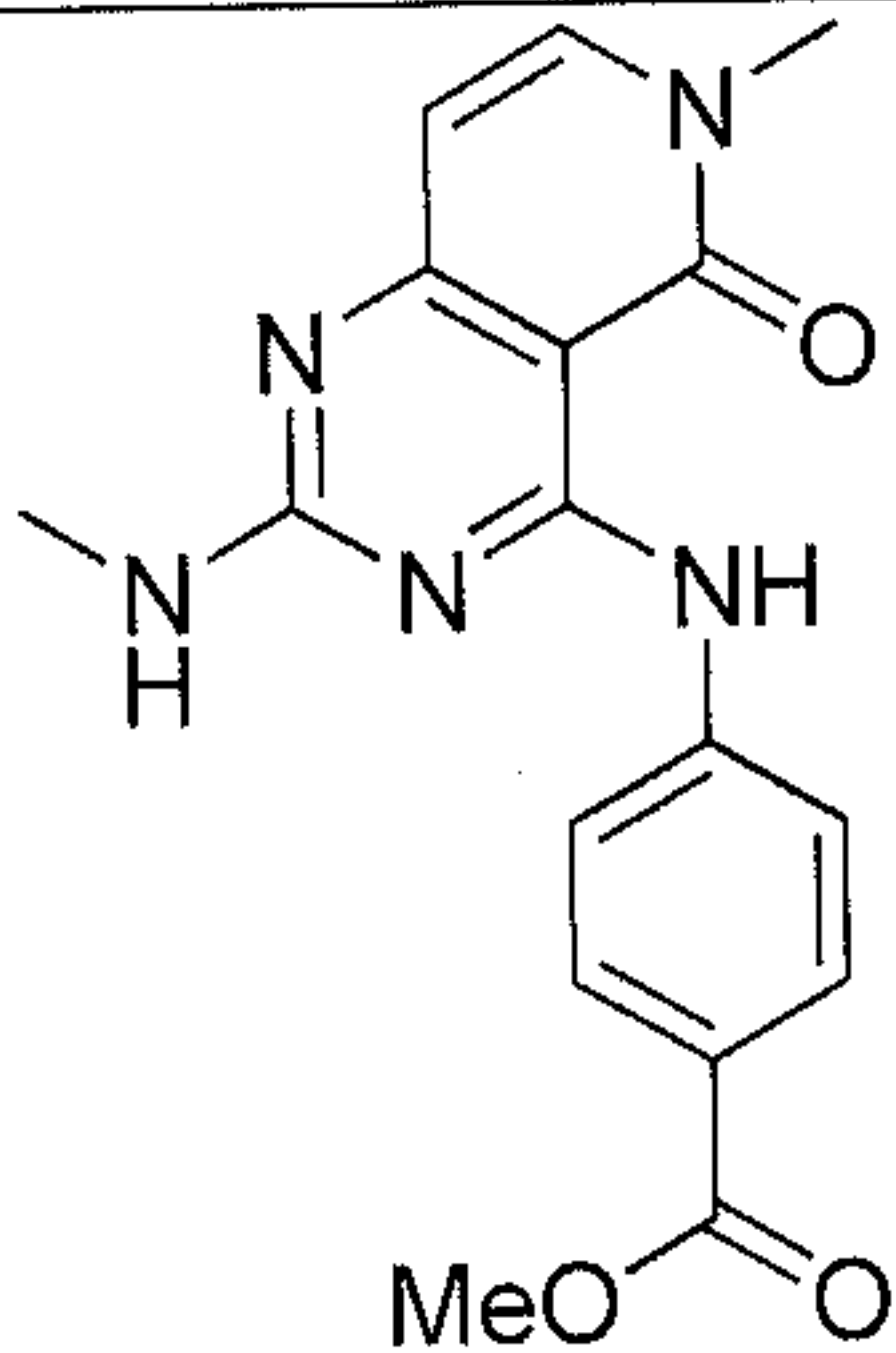
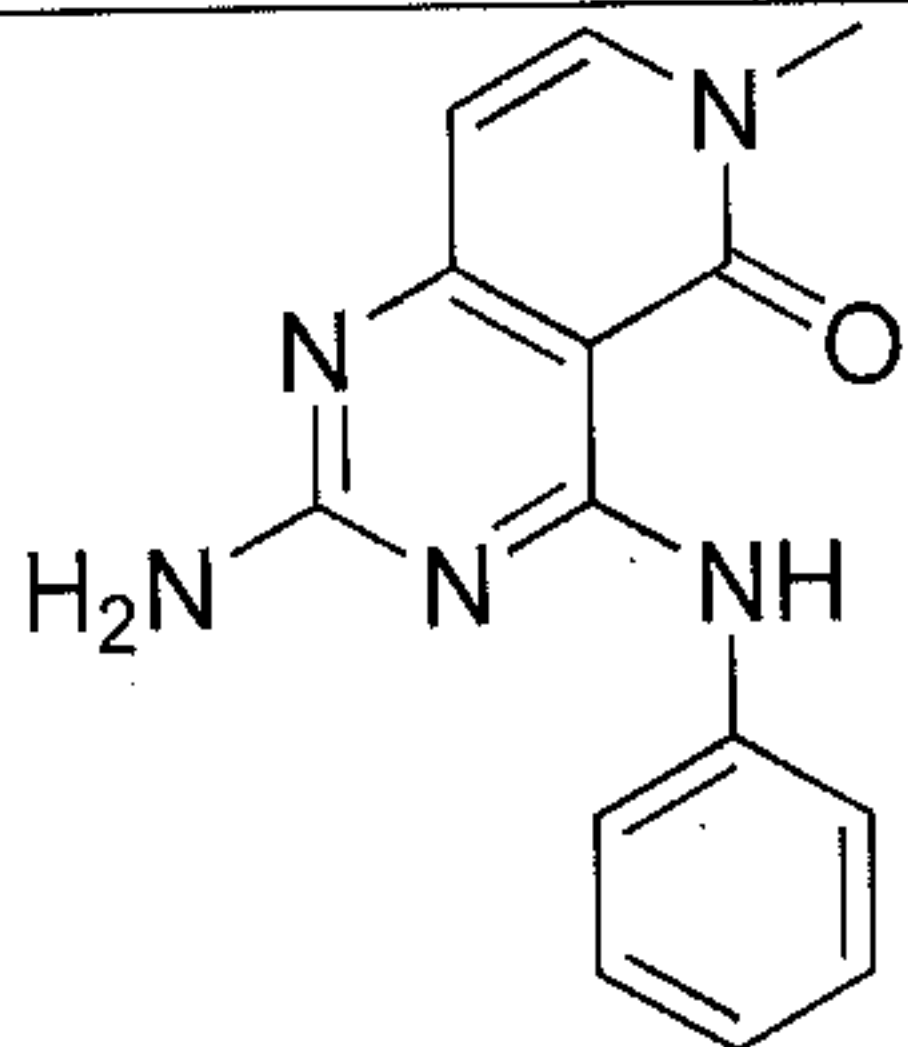
Compound No. 168

5

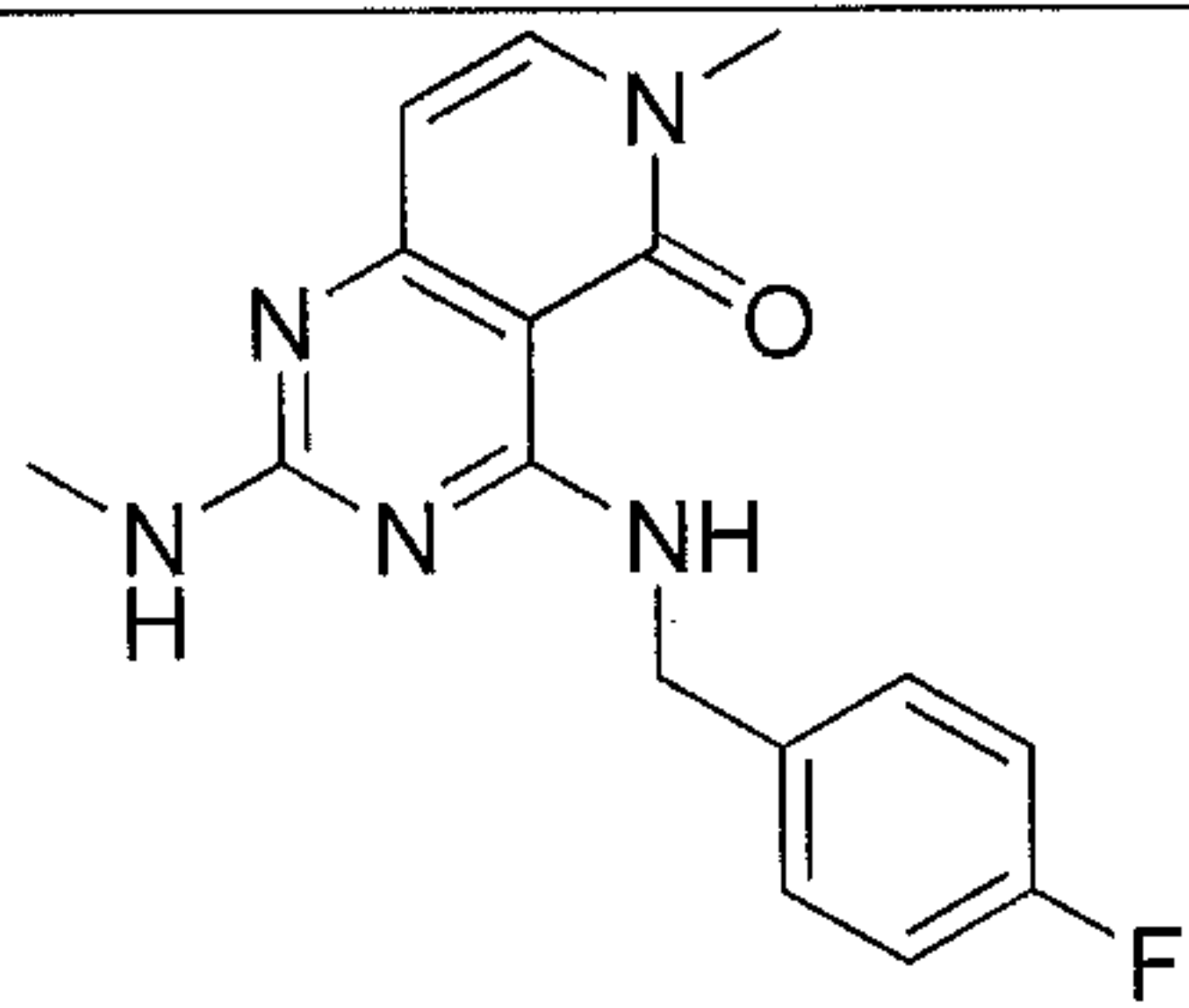
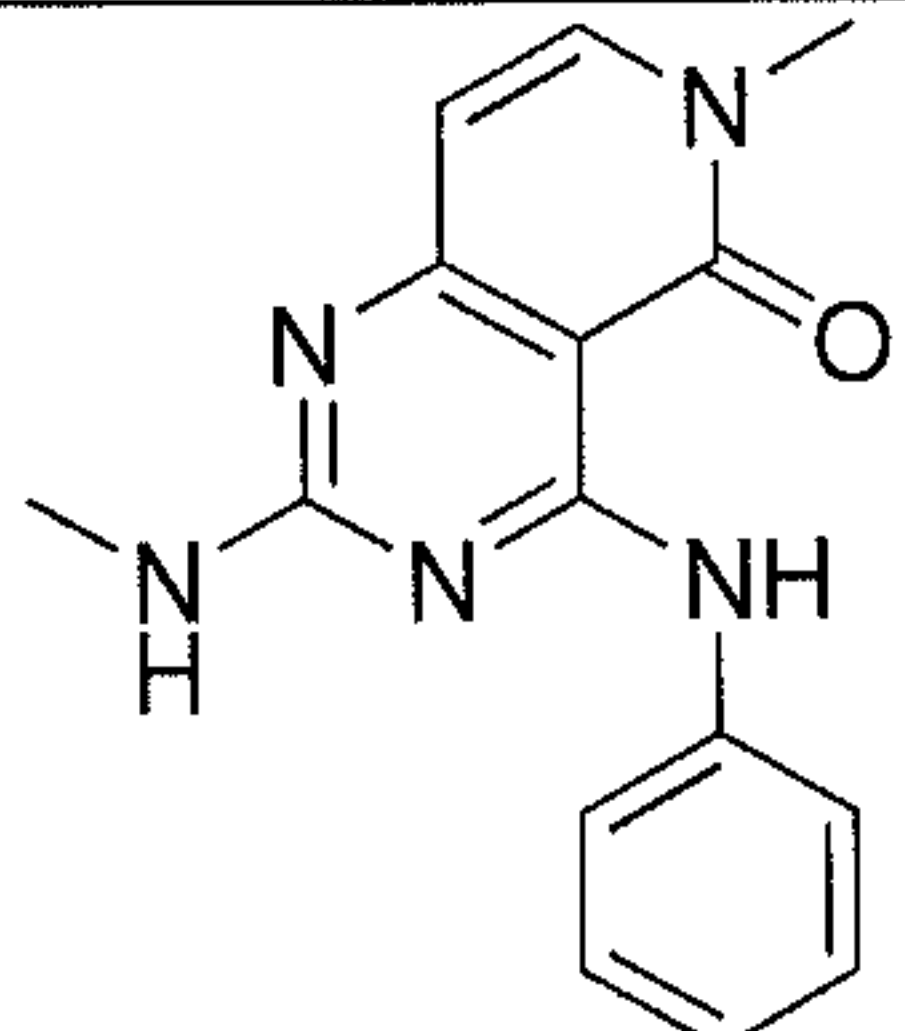
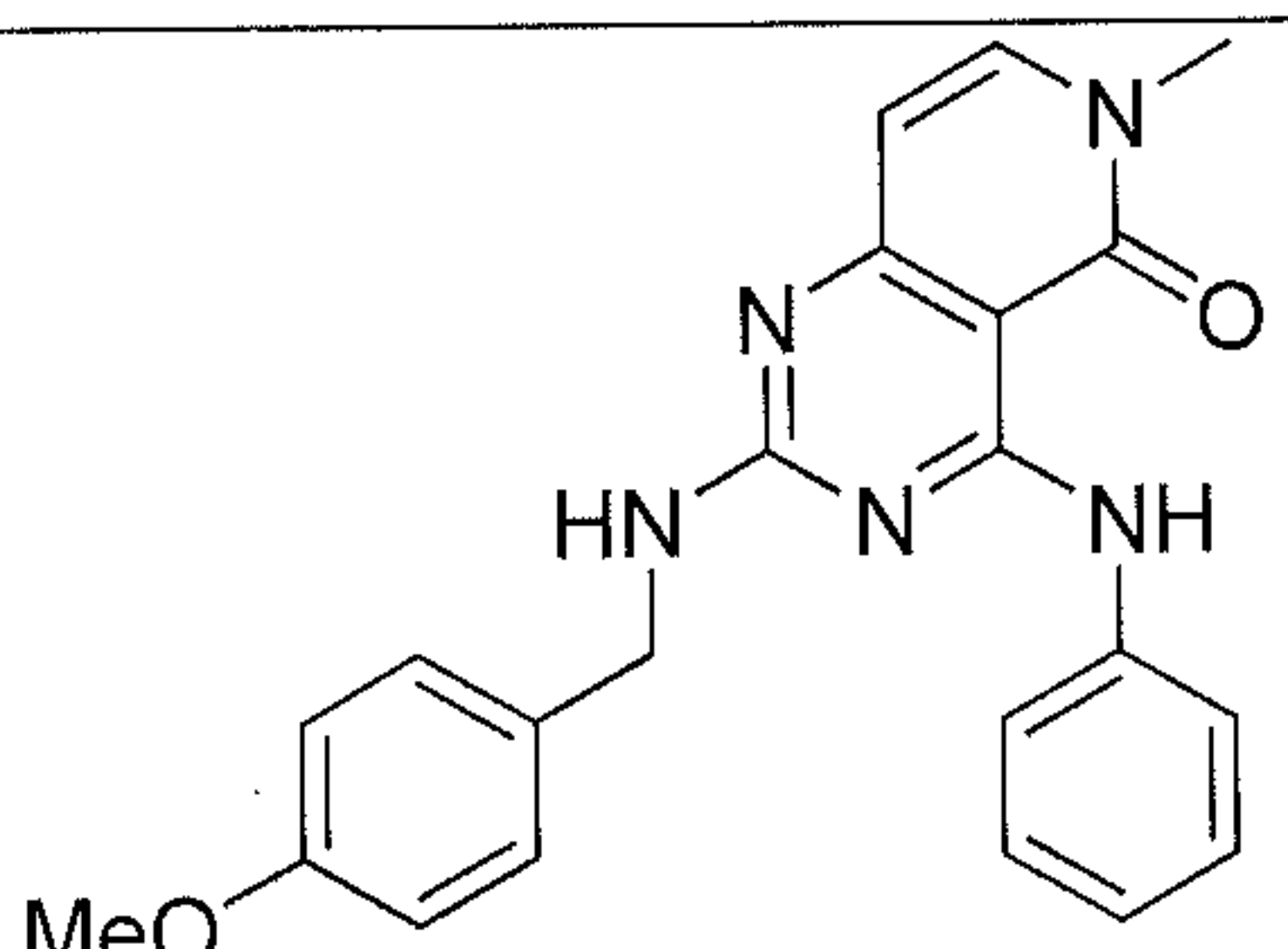
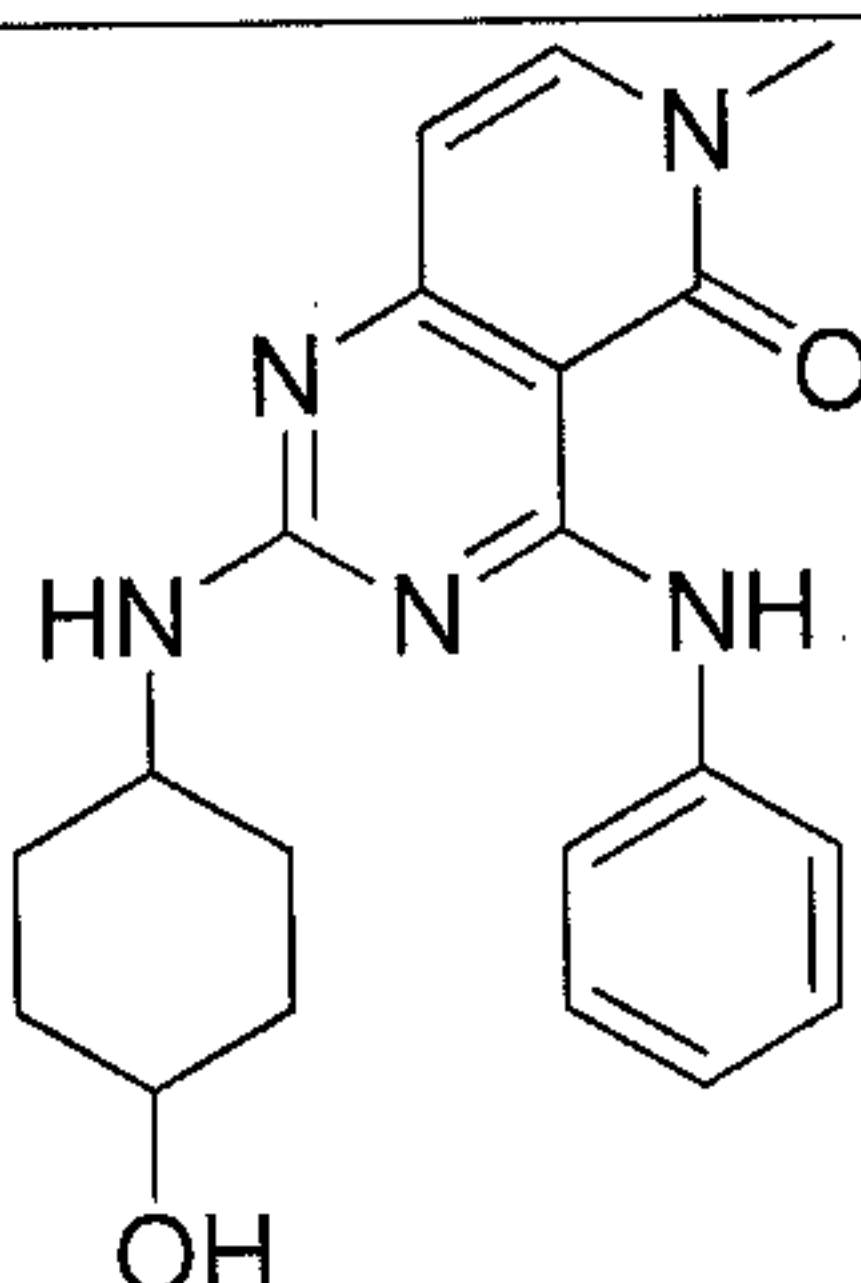
Compound No. 168 was prepared as described in *Example 2d* by starting from 6-methyl-2-(methylthio)-4-(3-trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (90 mg, 0.24 mmol) and 4-hydroxy piperidine (35 mg, 0.35 mmol) and continuing until the reaction

10 yielded the title compound (35 mg, 33 %) . MS m/z: 420 (M+1)⁺.

The following compounds were prepared from the procedure similar to that described in *Example 159*.

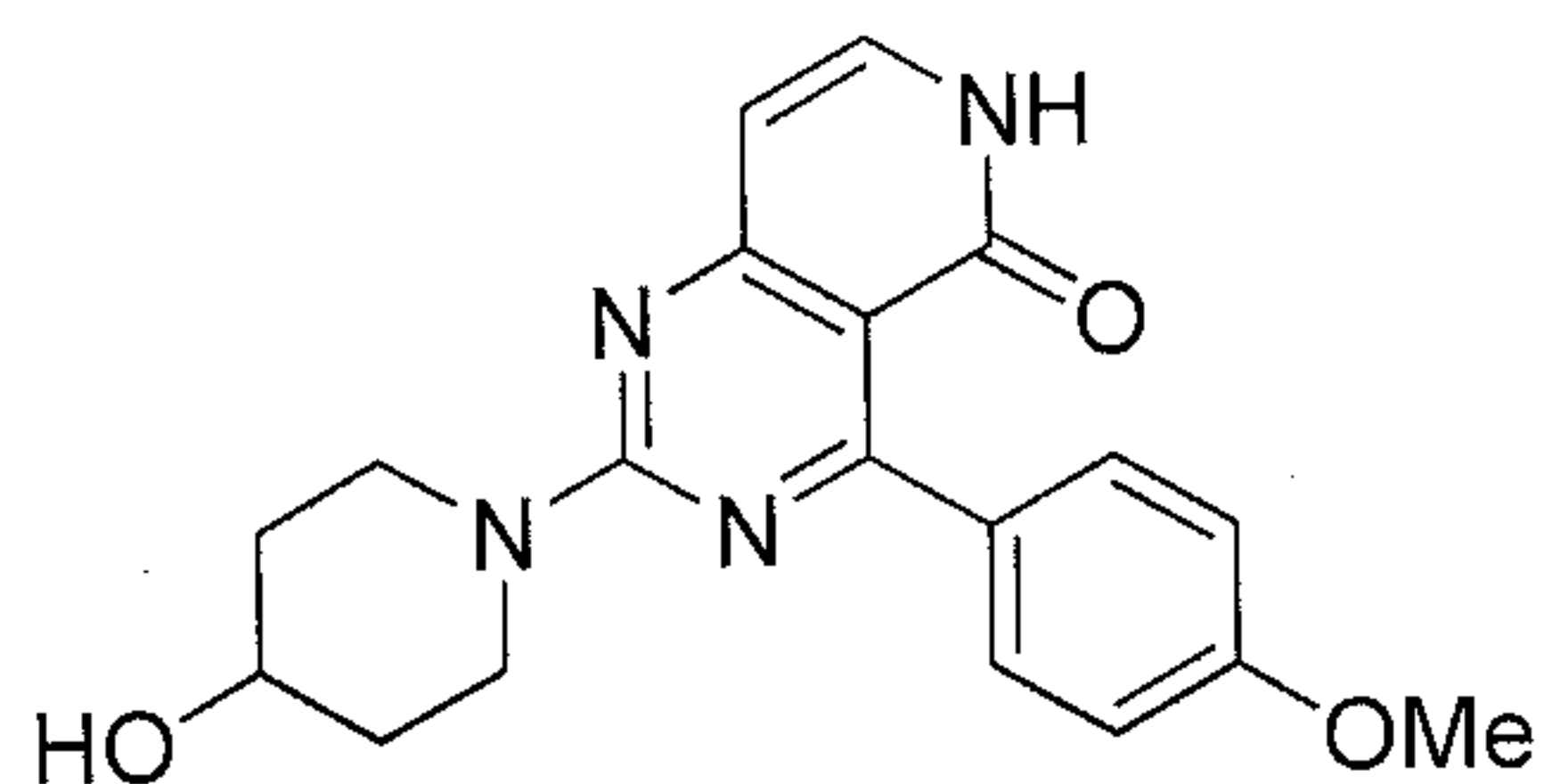
NO.	Structure	Name	Mass (M+1)
169		6-methyl-4-(phenylamino)-2-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	412
170		methyl 4-(6-methyl-2-morpholino-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-4-ylamino)benzoate	396
171		6-methyl-2-(methylamino)-4-(4-(piperazine-1-carbonyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	394
172		methyl 4-(6-methyl-2-(methylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-4-ylamino)benzoate	340
173		2-amino-6-methyl-4-(phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	268

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174		4-(4-fluorobenzylamino)-6-methyl-2-(methylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	314
175		6-methyl-2-(methylamino)-4-(phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	282
176		2-(4-methoxybenzylamino)-6-methyl-4-(phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	388
177		2-(4-hydroxycyclohexylamino)-6-methyl-4-(phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	366

Example 178Synthesis of 4-(4-methoxyphenyl)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

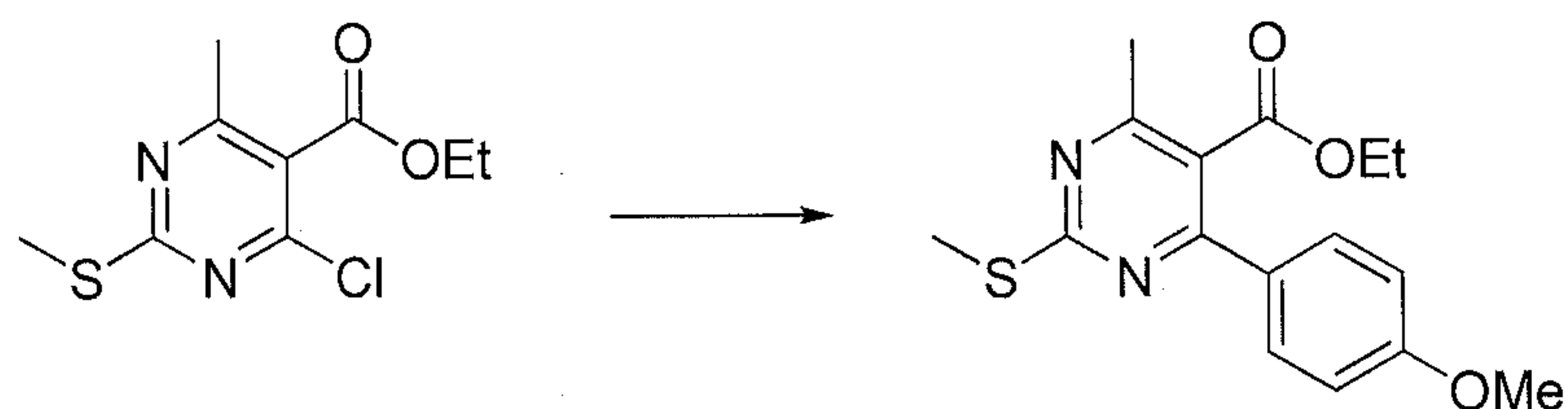
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Compound No. 178

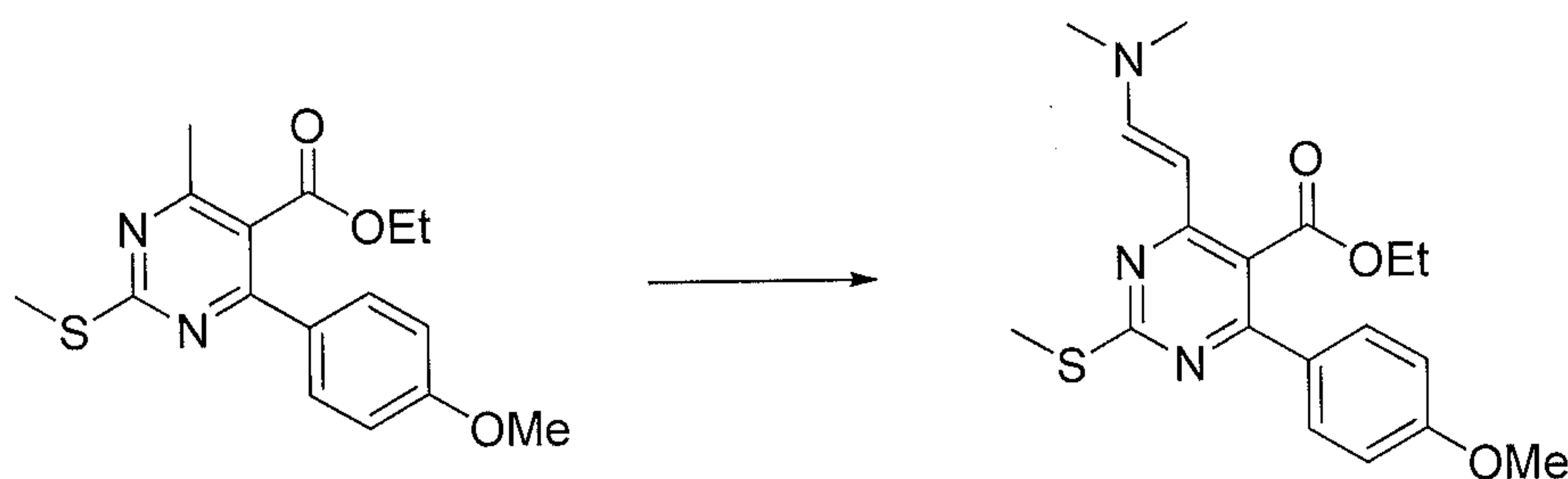
- 97 -

Example 178a: Ethyl 4-(4-methoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate



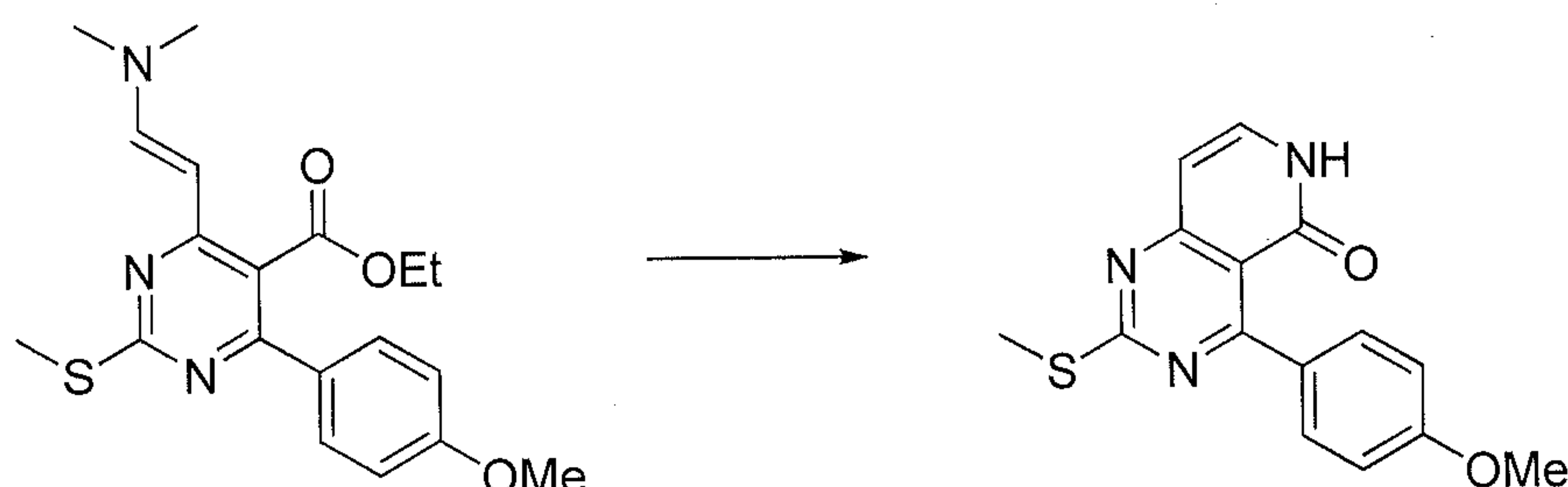
A 20 mL reaction vessel was charged with ethyl 4-chloro-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (1.00 g, 4.06 mmol), 4-(tert-butoxycarbonylamino)phenylboronic acid (1.00 g, 4.22 mmol), and tetrakis(triphenyl)phosphine)palladium(0) (0.17 g, 0.15 mmol) in 10 mL dioxane. The reaction mixture was purged with N₂ for 25 minutes with stirring. To the mixture was added potassium carbonate (1.17 g, 8.44 mmol) in 4 mL H₂O. The biphasic mixture was purged with N₂ for 10 minutes. The mixture was stirred at 90°C for 14 hours. The mixture was diluted with EtOAc, and washed with H₂O. The separated organic layer was dried over Na₂SO₄. The solvents were removed by a rotavapor yielding brown oily residue. The residue was purified by silica gel chromatography using a gradient 0-5 % MeOH in dichloromethane providing white solid (1.12 g, 68 %). MS m/z: 319 (M+1)⁺.

Example 178b: (E)-Ethyl 4-(2-(dimethylamino)vinyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate



To the solution of ethyl 4-(4-methoxyphenyl)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (0.67 g, 1.75 mmol) in 5 mL DMF was added *N,N*-dimethylformamide dimethyl acetal (0.32 mL, 2.50 mmol). The reaction mixture was stirred at 130°C for 2 hours. After monitoring the reaction by TLC was cooled to room temperature, then the mixture was diluted with DCM and water. After extracted three times by DCM from the aqueous layer, the combined organic layer was dried over MgSO₄. The solution was condensed under reduced pressure yielding crude mixture (467 mg). The mixture was used for the next step without further purification.

Example 178c: 4-(4-Methoxyphenylamino)-6-methyl-(methylthio)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

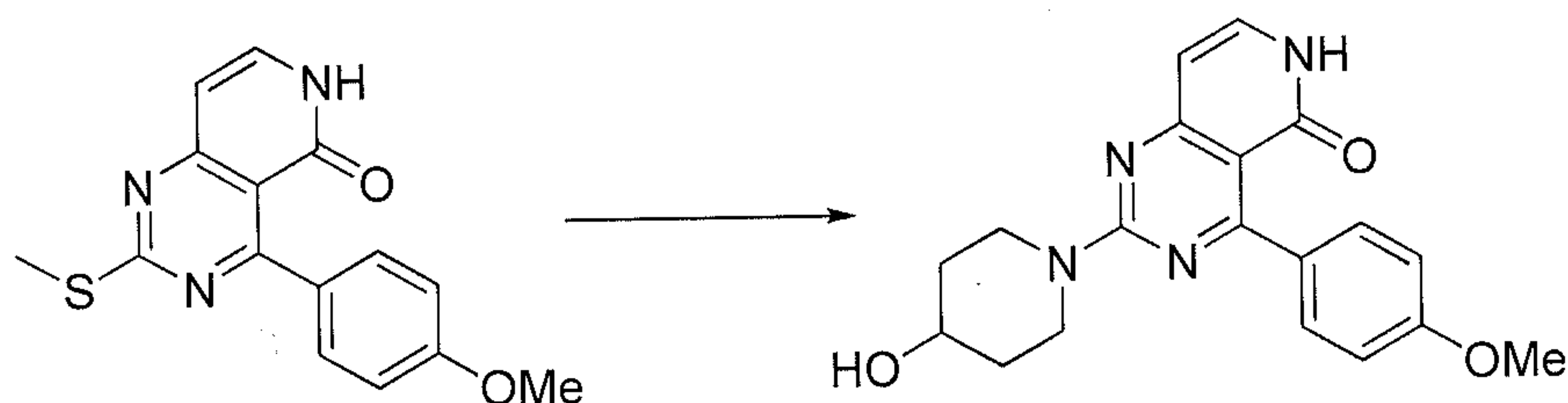


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The crude of (E)-ethyl 4-(2-(dimethylamino)vinyl)-6-(4-methoxyphenyl)-2-(methylthio)pyrimidine-5-carboxylate (467 mg) was dissolved in 45 mL EtOH. To the solution was added 30% NH₄OH solution (3.0 mL), the reaction mixture was stirred at 90°C for 10 hour. The mixture was cooled to room temperature. The solid formed from the solution were filtered. It was purified by silica gel chromatography using a gradient of 0-5 % MeOH in dichloromethane providing light yellow solid (246 mg, 46 % for the two steps). MS *m/z*: 344.9 (M+H)⁺.

10

Example 178d: 4-(4-Methoxyphenyl)-6-methyl-2-(methylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one



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A 20 mL reaction vessel was charged with (4-methoxyphenylamino)-6-methyl(methylthio) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (69 mg, 0.23 mmol) in 4 mL DMF at -20°C. The solution was kept at the temperature for 30 minutes. To the solution was added *m*-CPBA (170 mg, 0.69 mmol) at the temperature, and further stirred for 30 minutes with being warmed to room temperature. The reaction was monitored by LC-MS, confirming the corresponding oxide. To the reaction mixture was added triethylamine (96 µL, 0.69 mmol) and 4-hydroxypiperidine (70 mg, 0.69 mmol), and stirred at the temperature for 2 hours. The reaction was monitored by LC-MS. The solvent was removed by a rotavapor yielding a light brown residue. To the residue was added acetonitrile (10 mL) resulting precipitates. They were

20

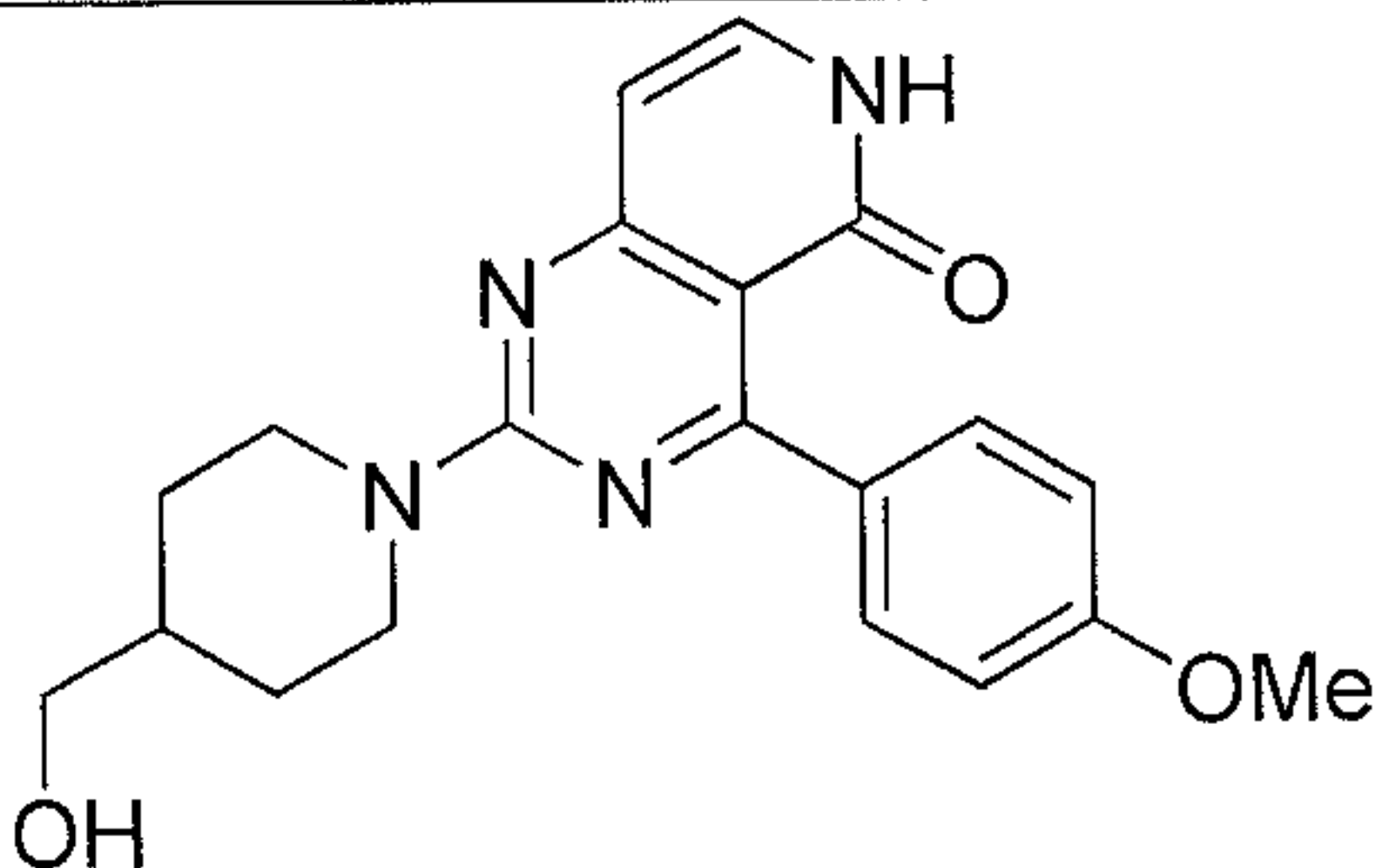
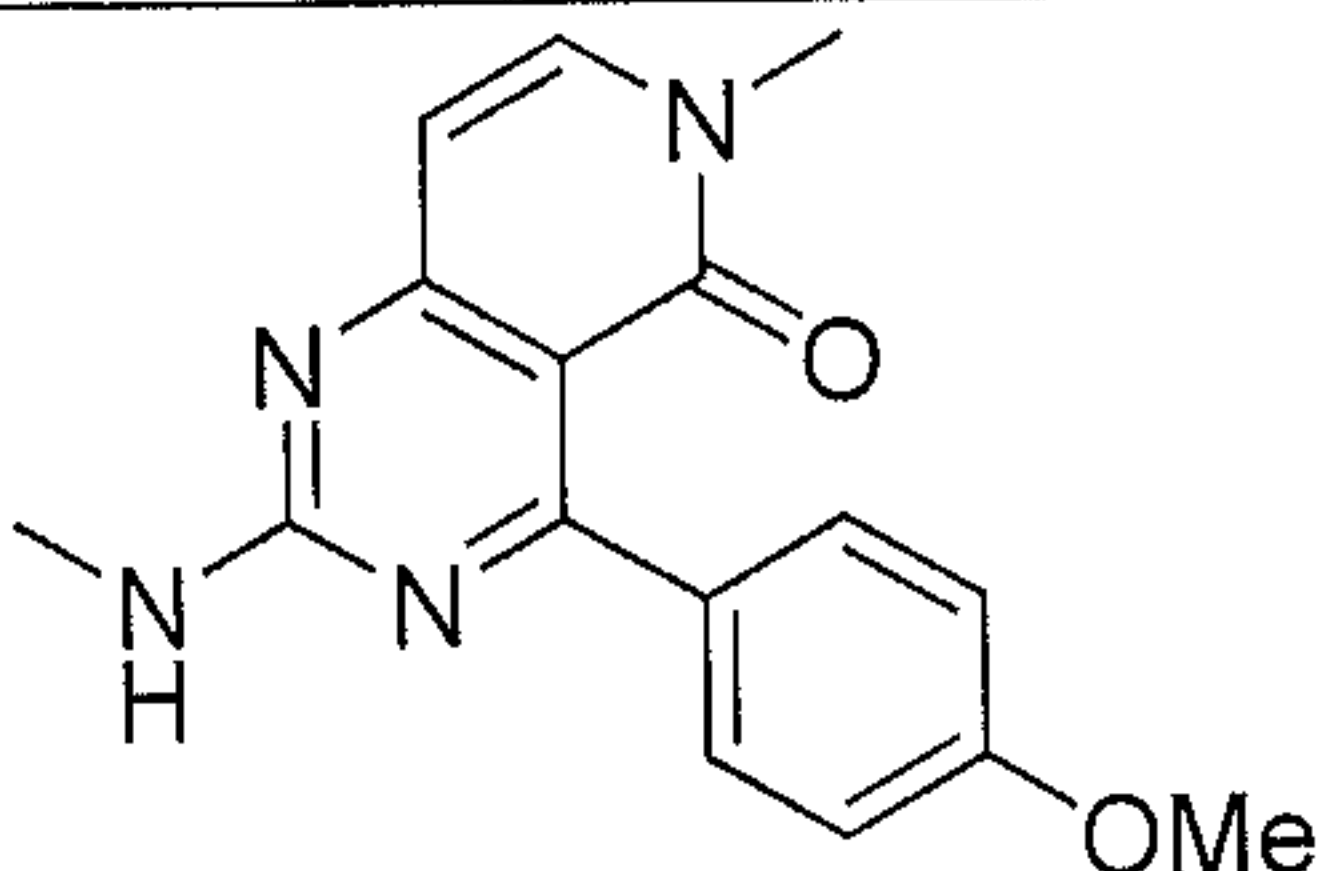
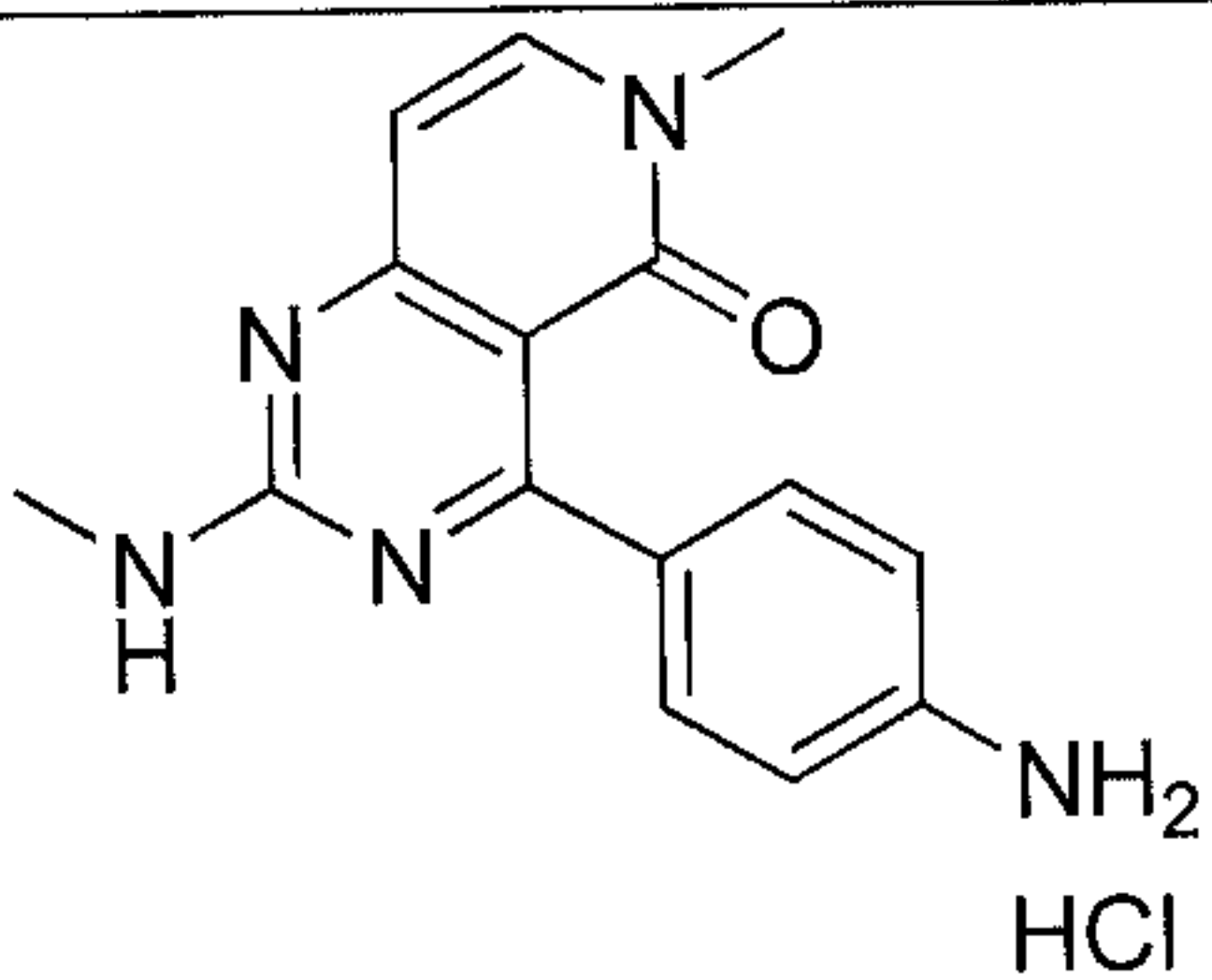
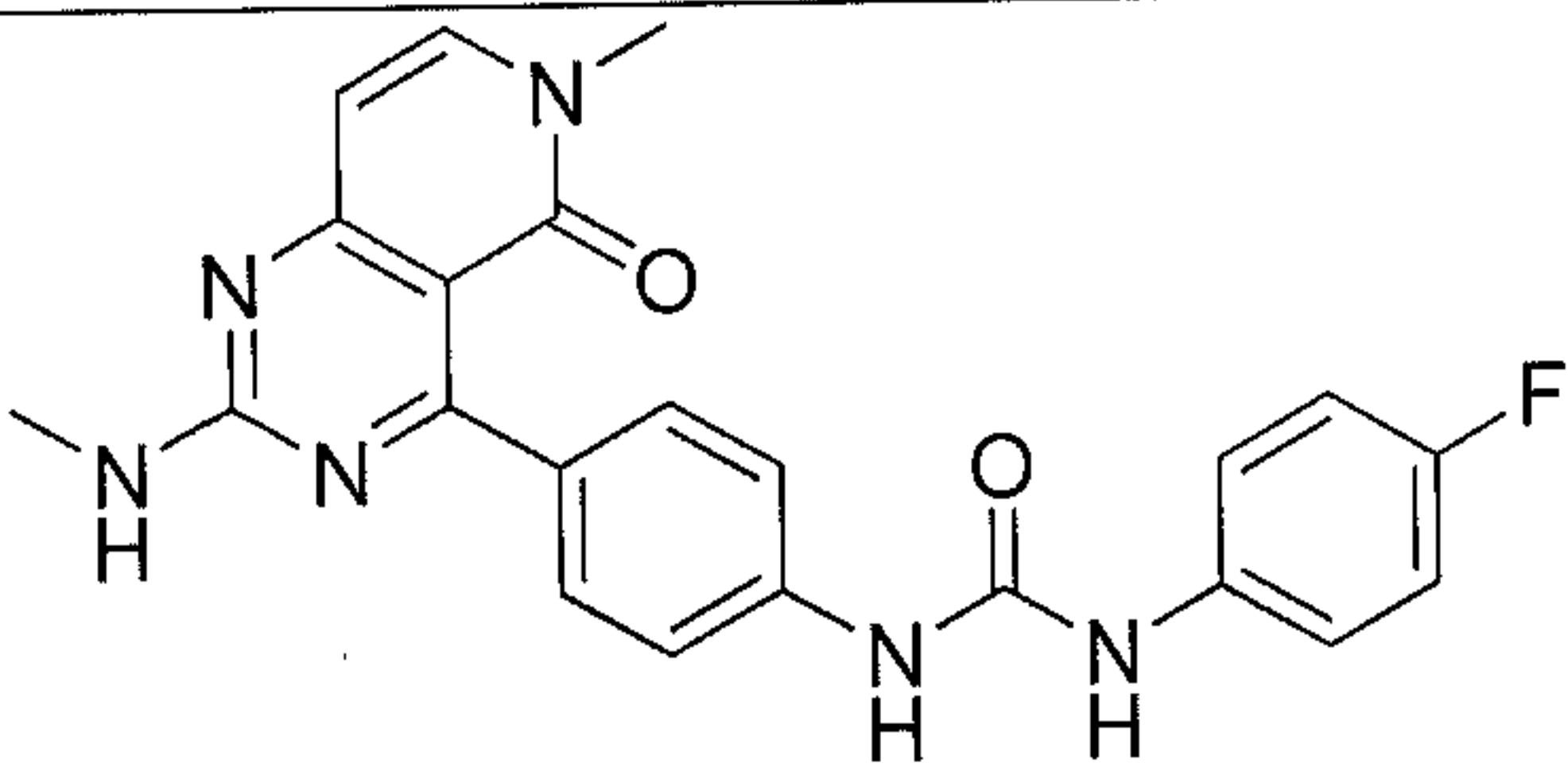
25

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filtered and dried under reduced pressure providing the title compound as light yellow solid (56 mg, 69 %). MS m/z: 353 (M+H)⁺.

The following compounds were prepared from the procedure similar to that described in *Example 178*.

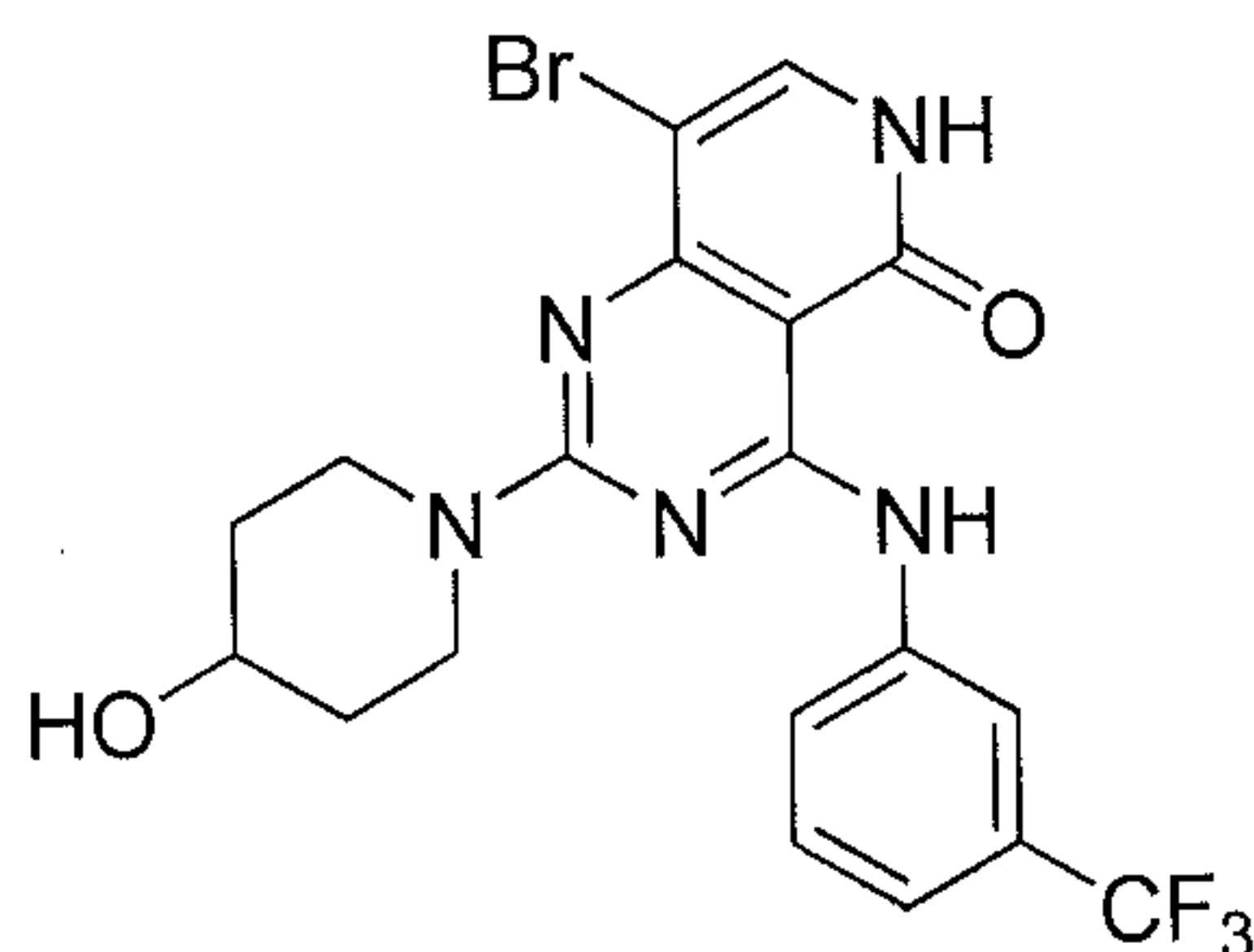
5

NO.	Structure	Name	Mass (M+1)
179		2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxyphenyl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	367
180		4-(4-methoxyphenyl)-6-methyl-2-(methylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	297
181		4-(4-aminophenyl)-6-methyl-2-(methylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	282
182		1-(4-fluorophenyl)-3-(4-(6-methyl-2-(methylamino)-5-oxo-5,6-dihydropyrido[4,3- <i>d</i>]pyrimidin-4-yl)phenyl)urea	419

- 100 -

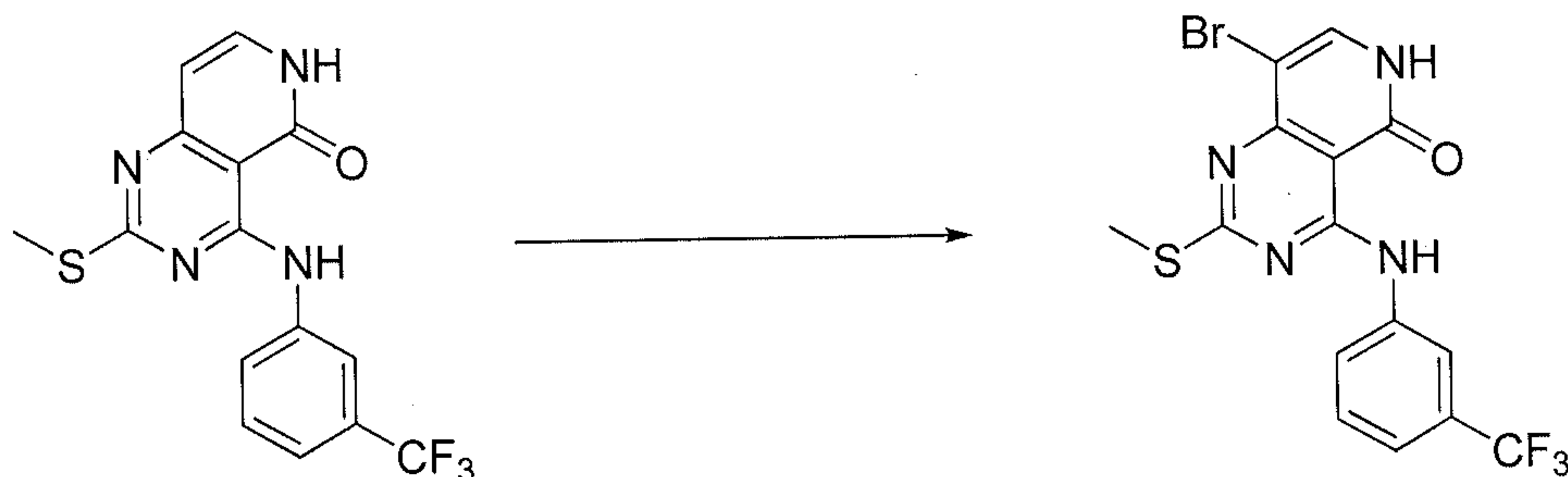
Example 183

Synthesis of 8-bromo-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one



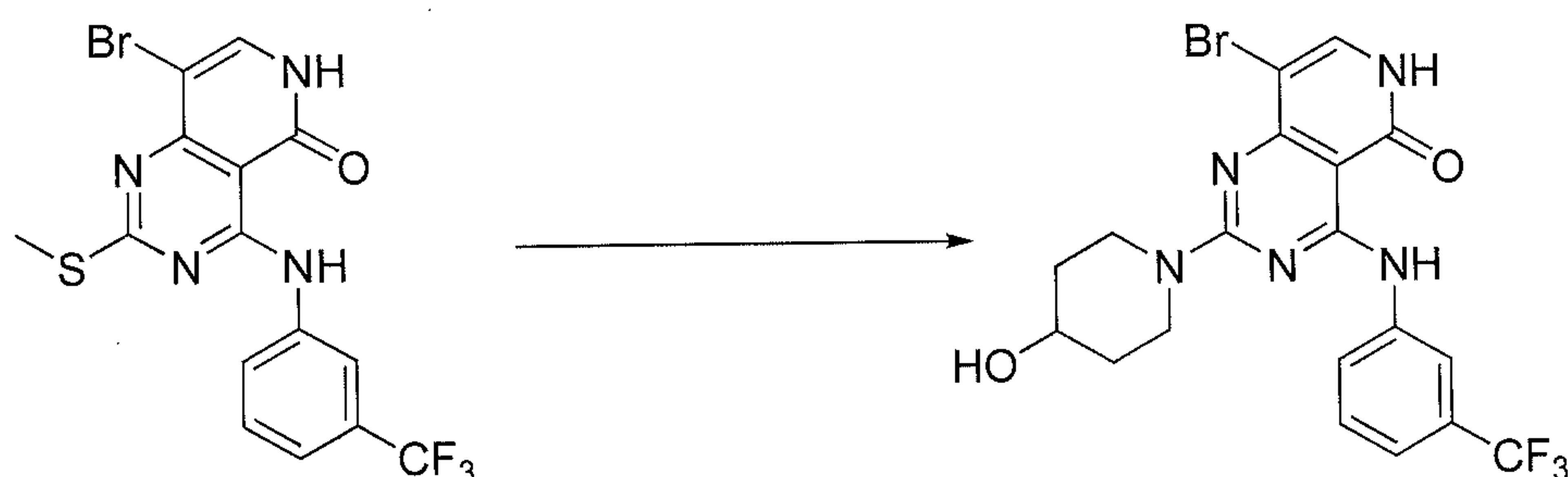
Compound No. 183

Example 183a: 8-bromo-2-(methylthio)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one



A 20 mL reaction vessel was charged with 2-(methylthio)-4-(3-(trifluoromethyl) phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (135 mg, 0.38 mmol), and *N*-bromosuccinimide (68 mg, 0.38 mmol) in 7 mL dry DMF. The reaction mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressuring yielding yellow residue. The residue was recrystallized from acetonitrile providing yellow solid (100 mg, 74 %). MS *m/z*: 431, 433 (*M*+*H*)⁺.

Example 183b: 2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidine-5(6*H*)-one



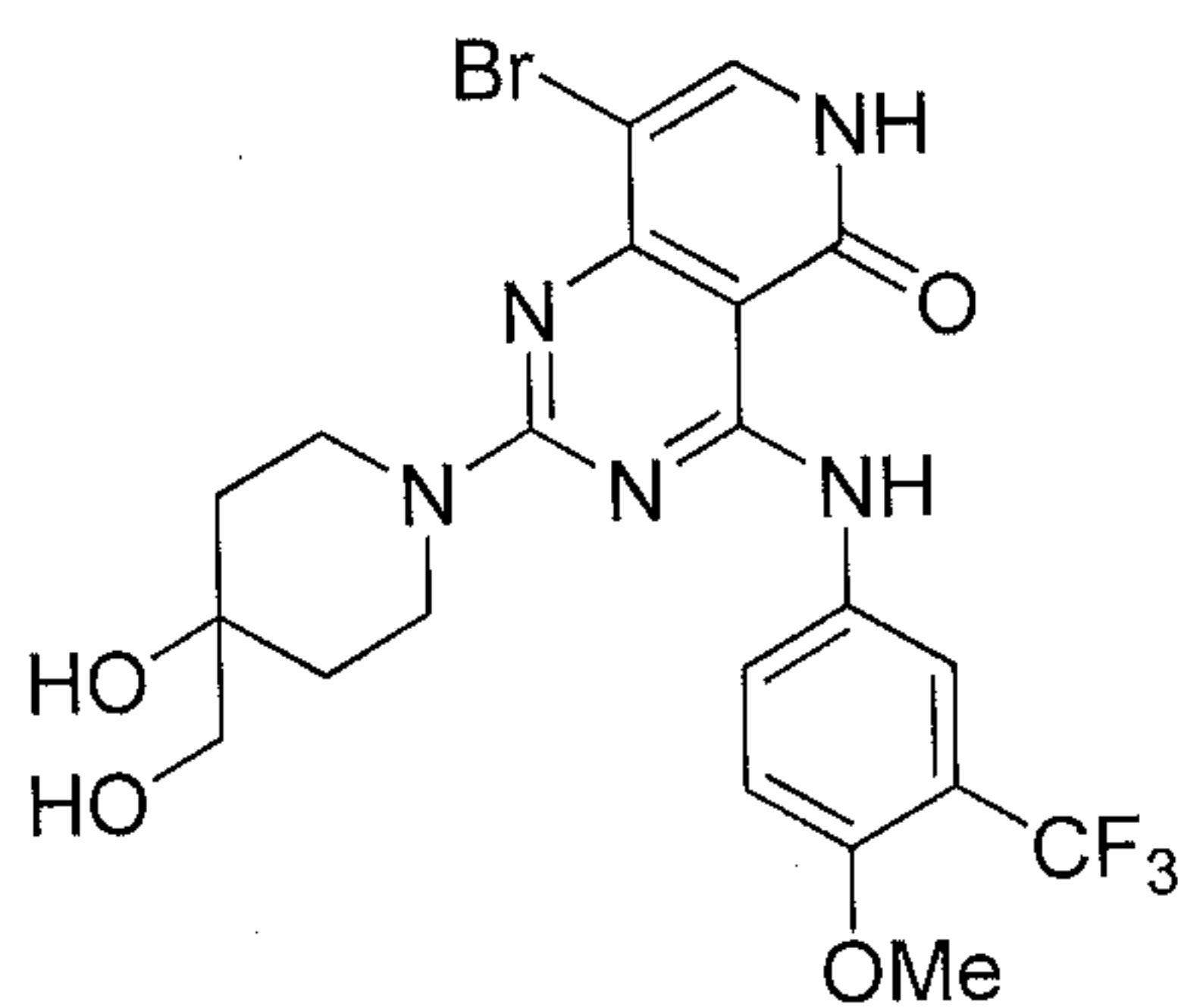
5

The title compound was prepared as described in *Example 1g* by starting from 8-bromo-2-(methylthio)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one (60 mg, 0.26 mmol) and 4-hydroxypiperidine and continuing until the reaction yielded the title compound (40 mg, 60 %) as grey solid. MS *m/z*: 484 and 486 (*M*+*H*)⁺.

10

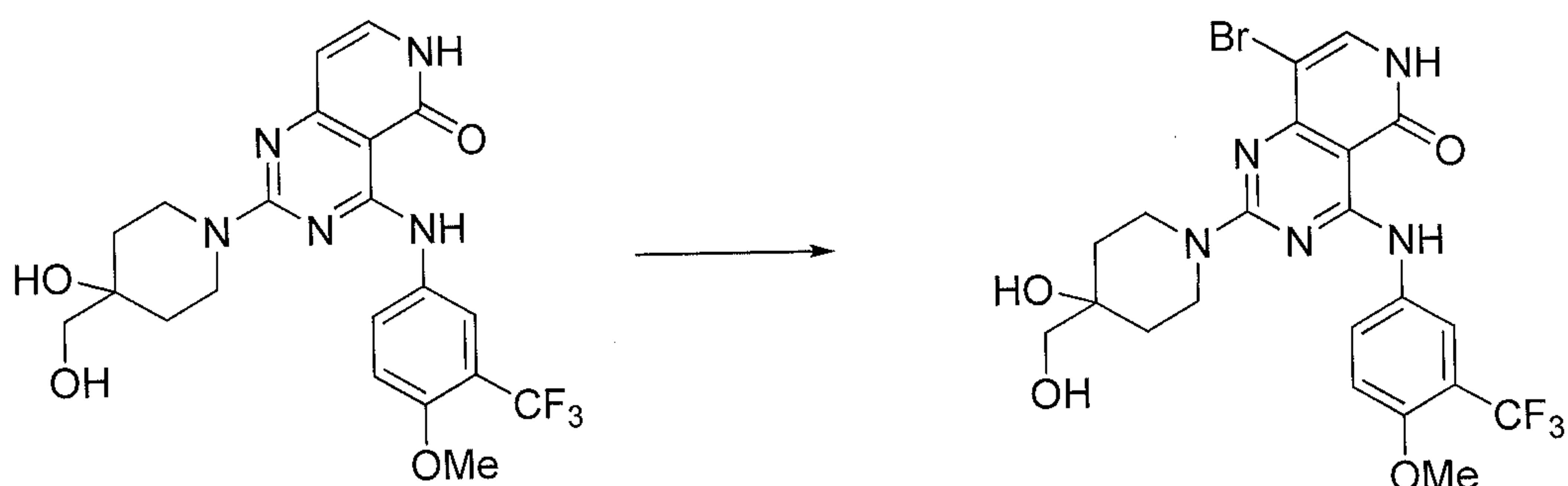
Example 184

Synthesis of 8-bromo-2-(4-hydroxy-4-(hydroxymethyl) piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one



Compound No. 184

15

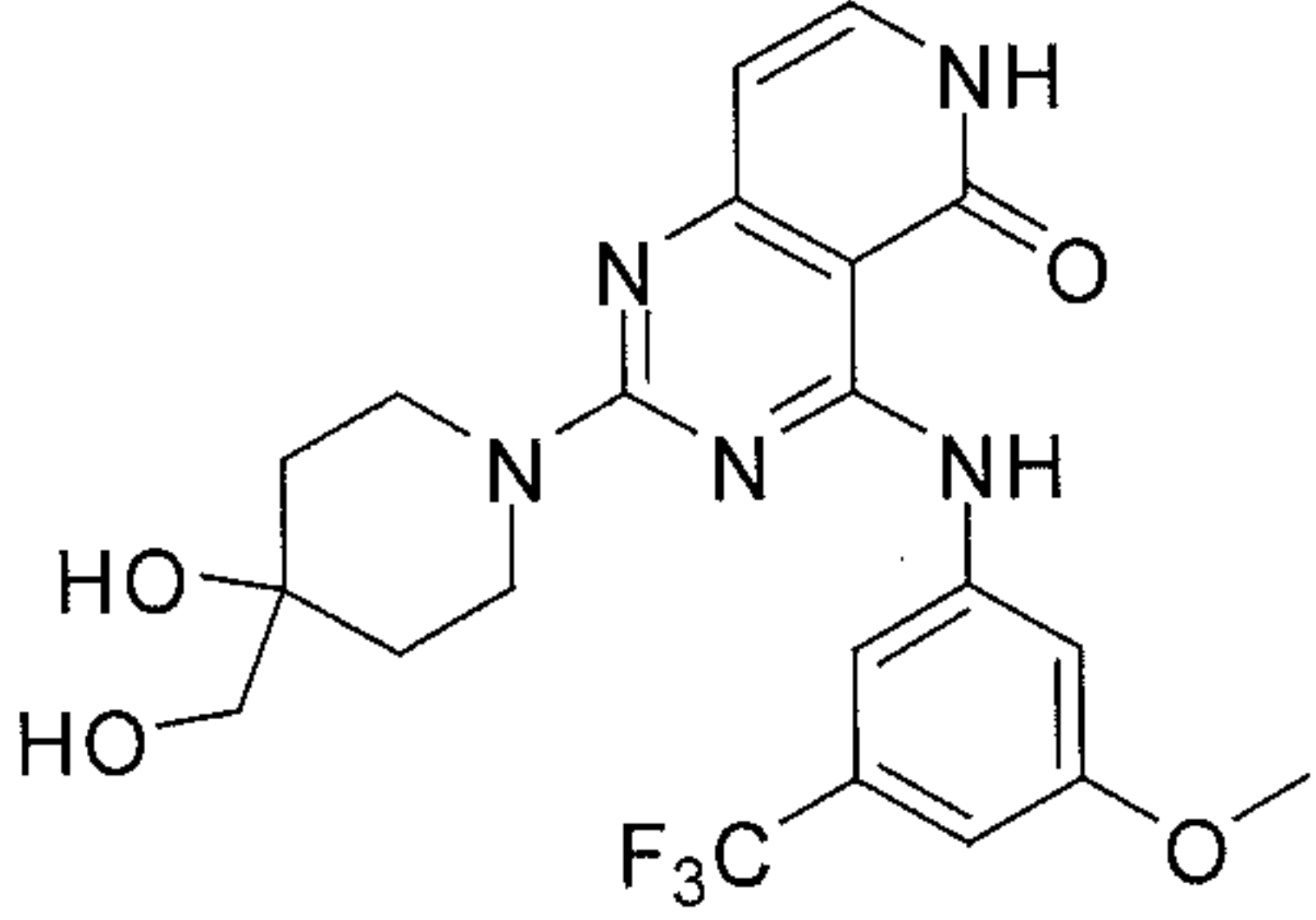
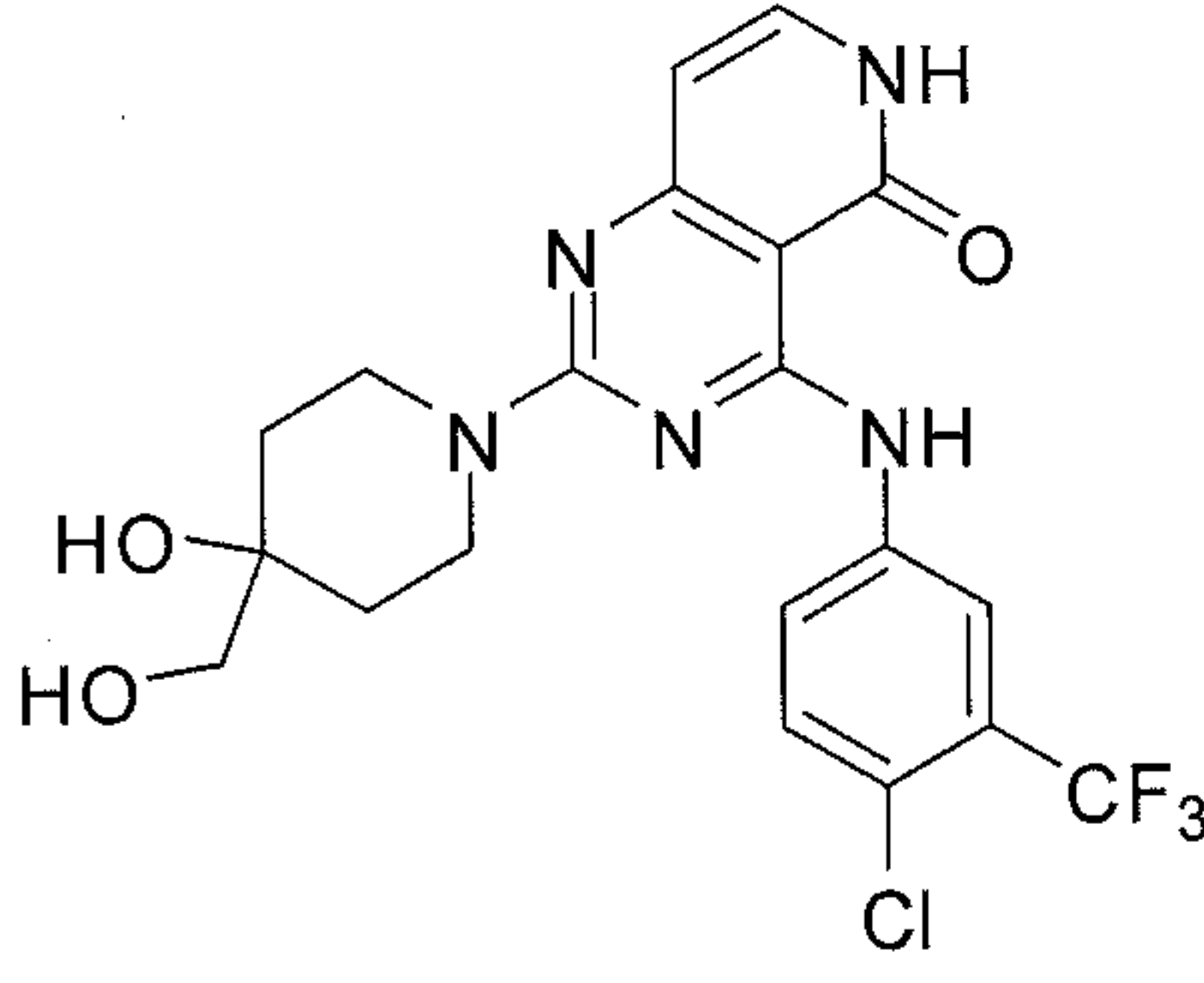
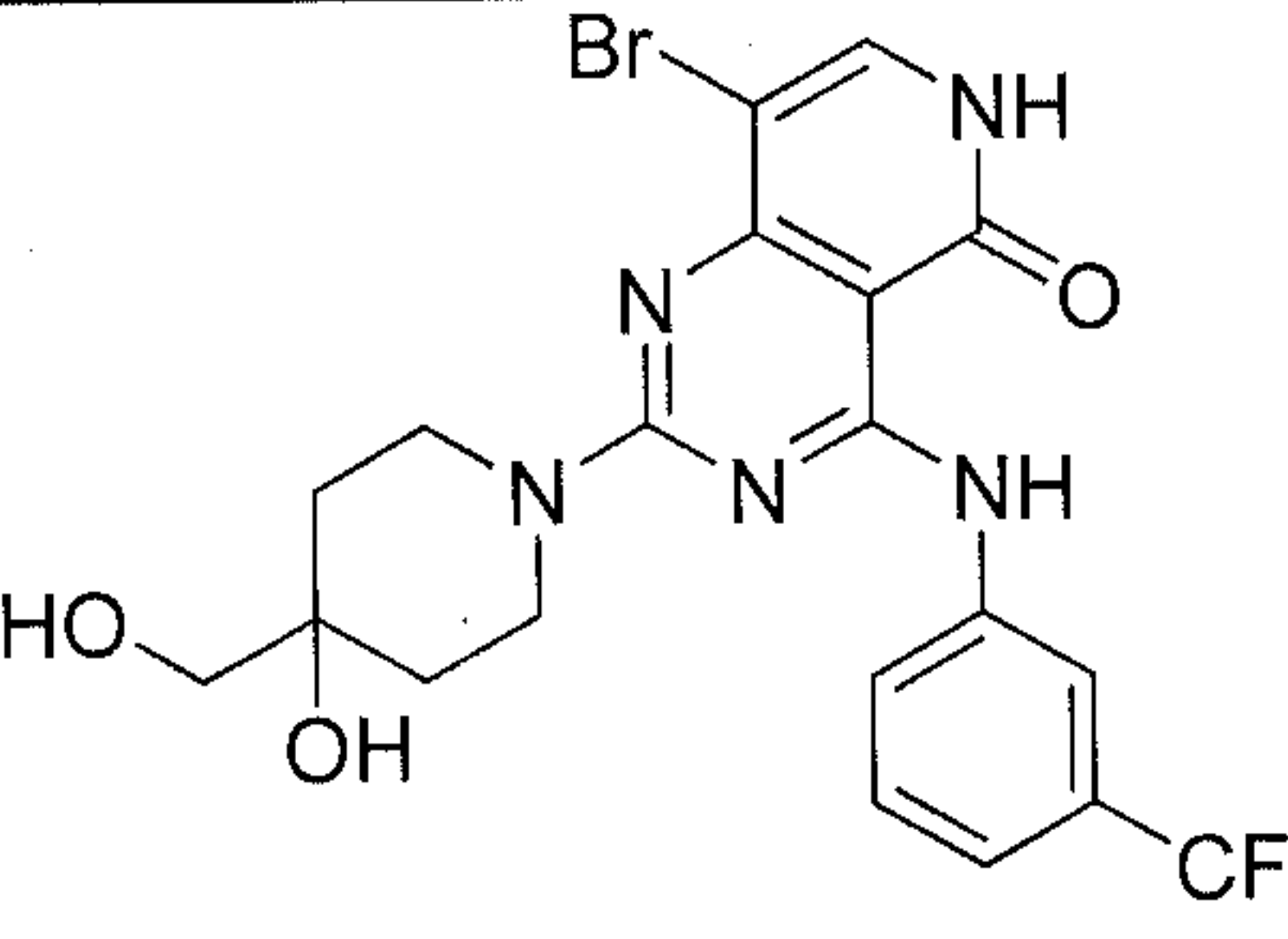
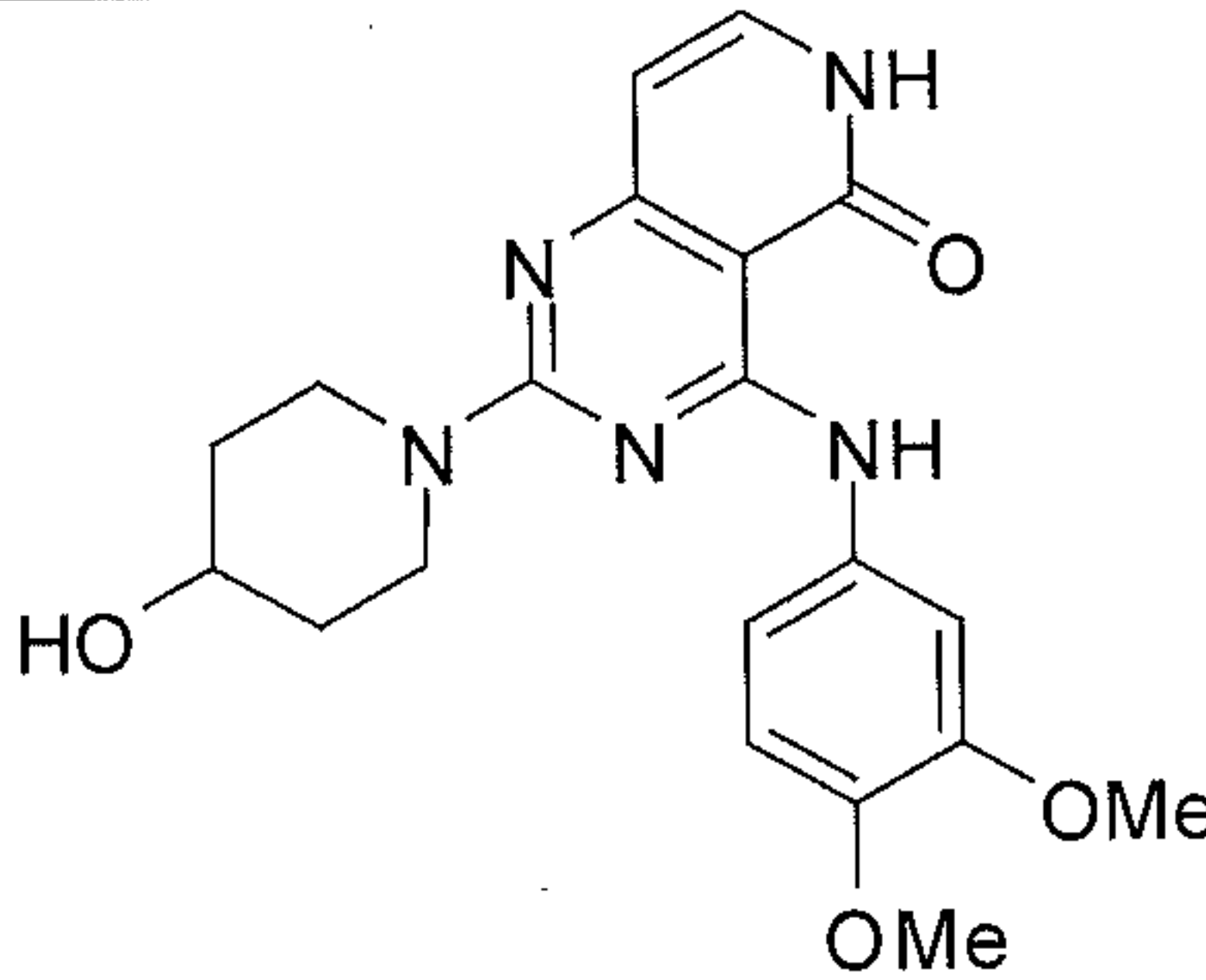
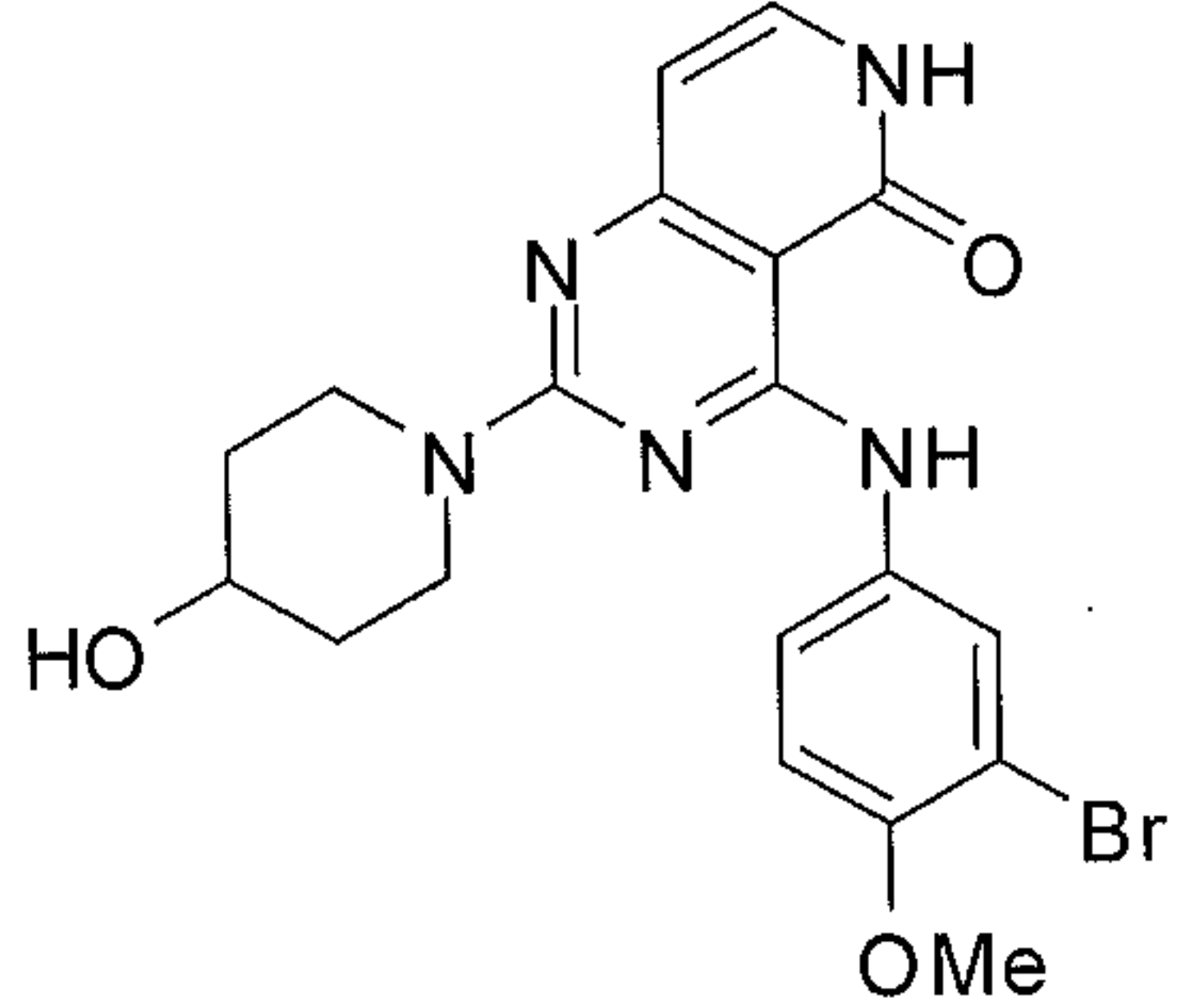


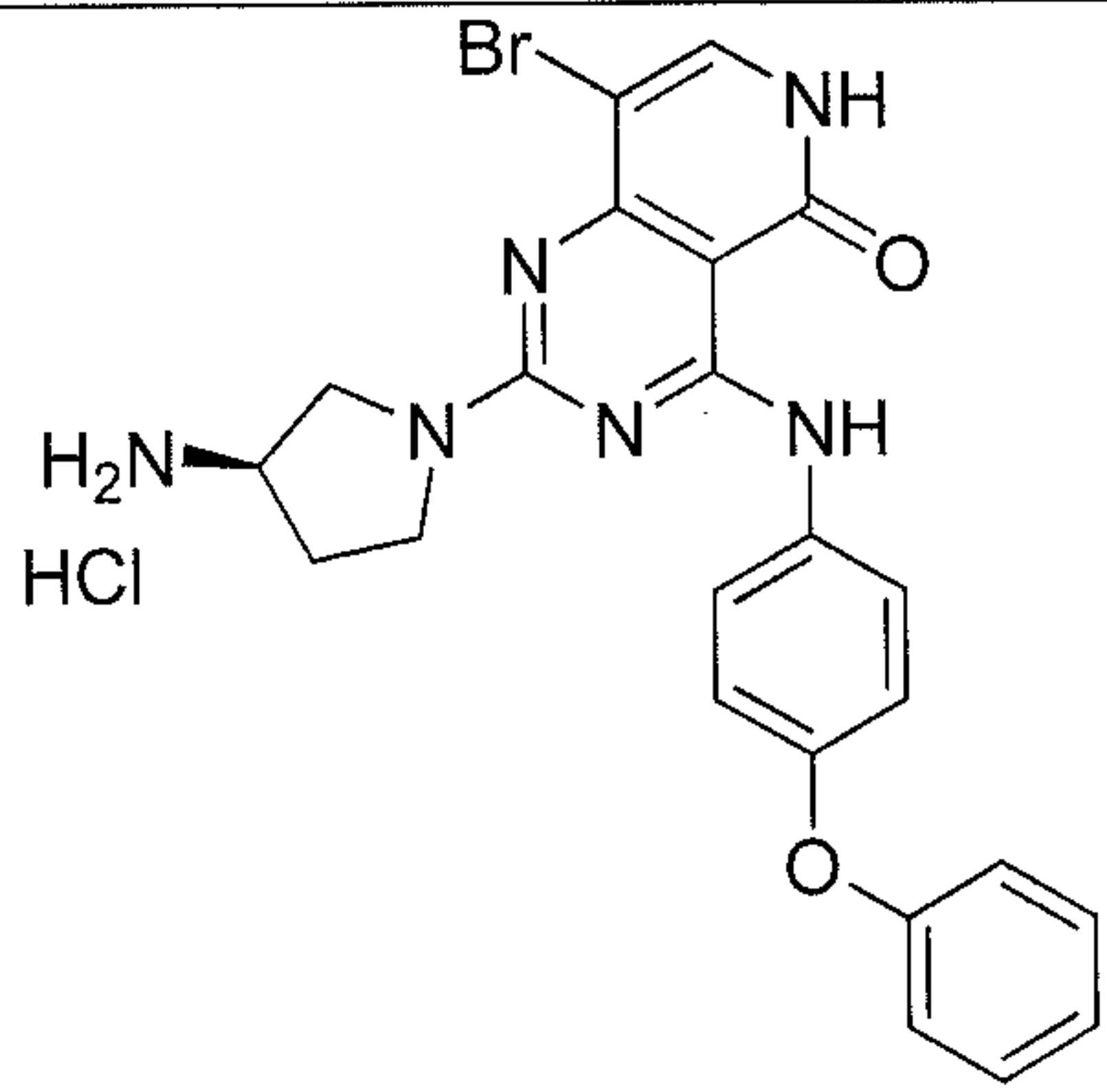
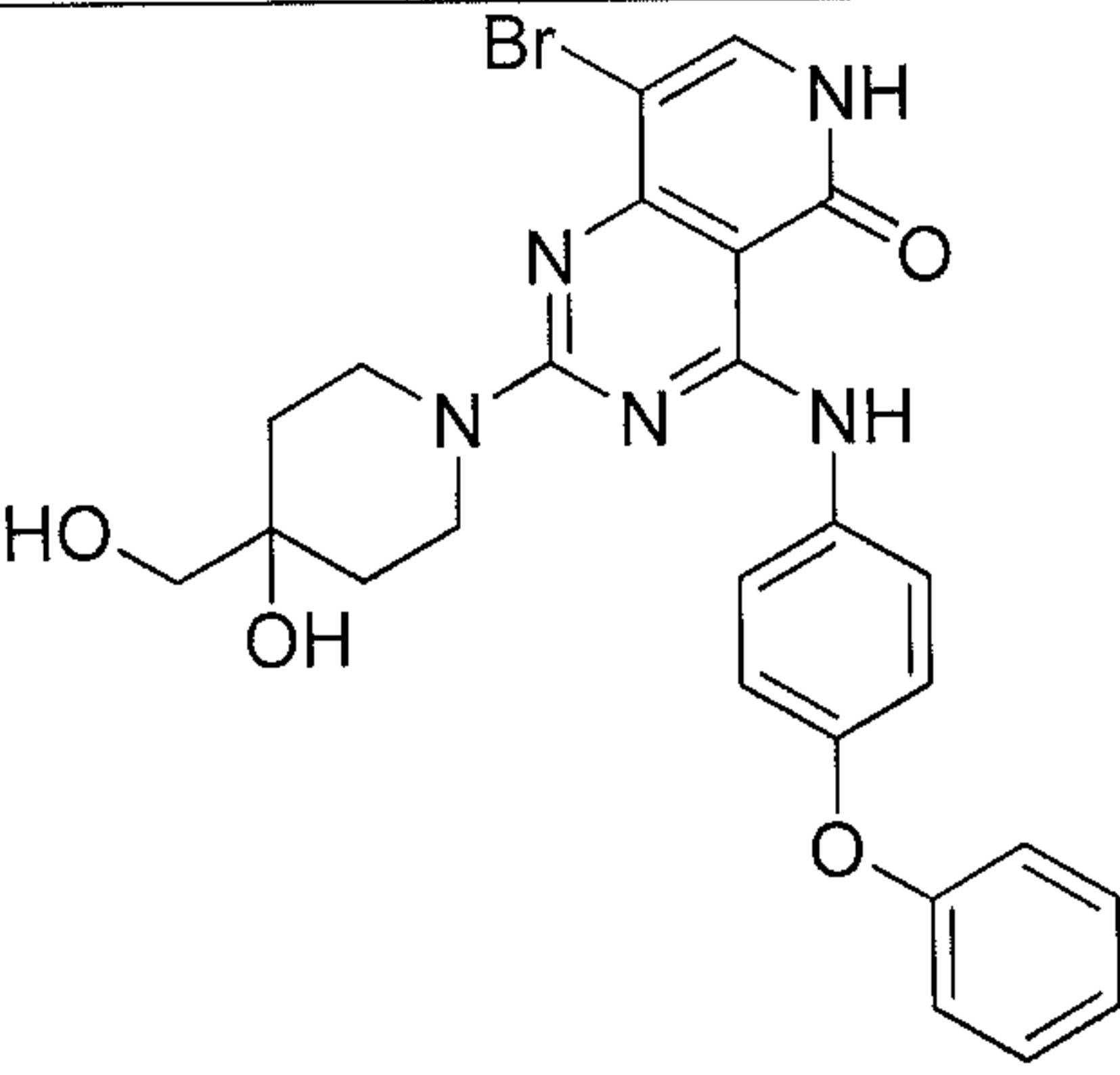
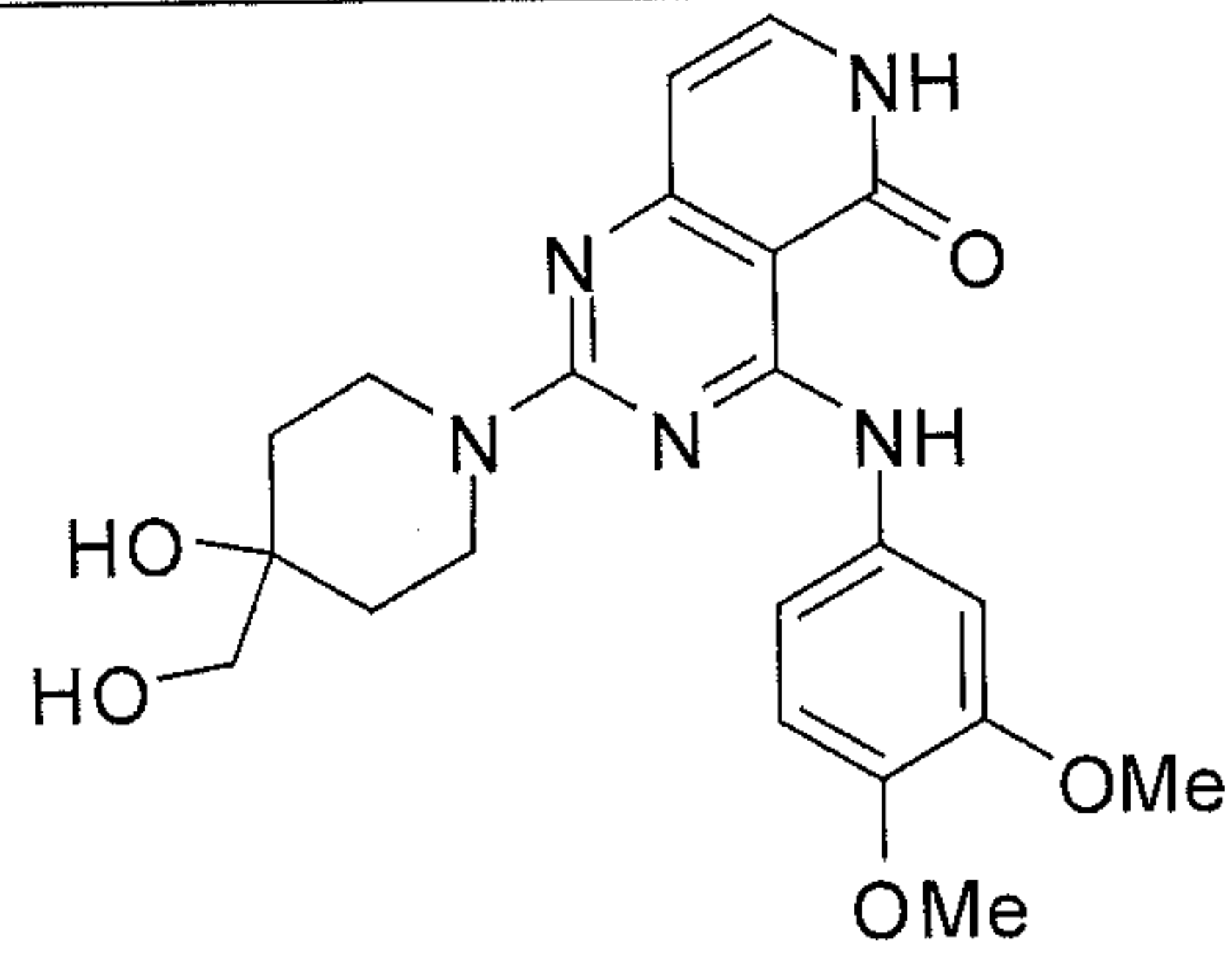
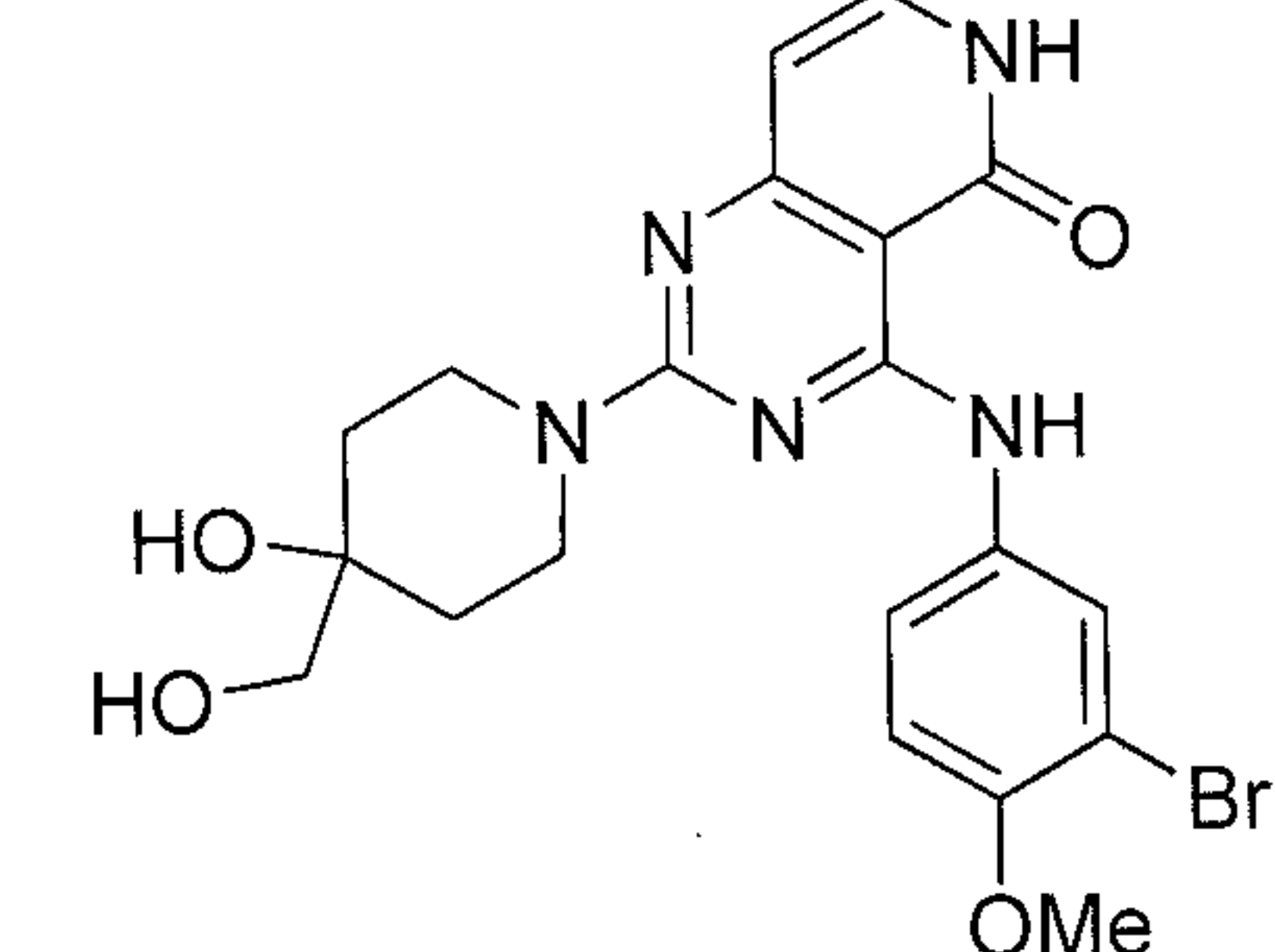
The title compound was prepared as described in *Example 183a* by starting from 2-(4-hydroxy-4-(hydroxymethyl) piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one and *N*-bromosuccinimide and continuing until the reaction yielded the title compound as pale brown solid. MS *m/z*: 544 and 546 (*M*+*H*)⁺.

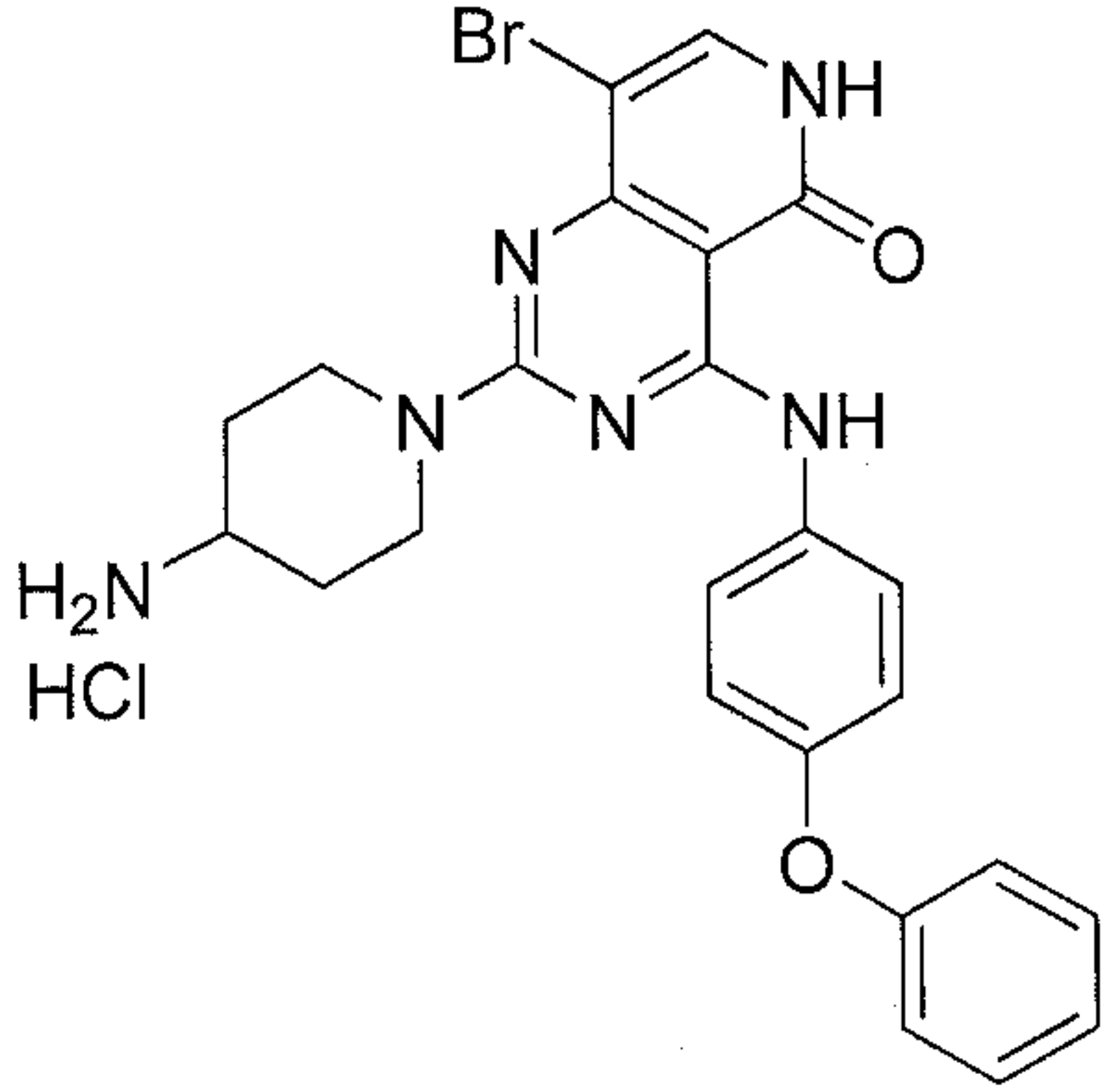
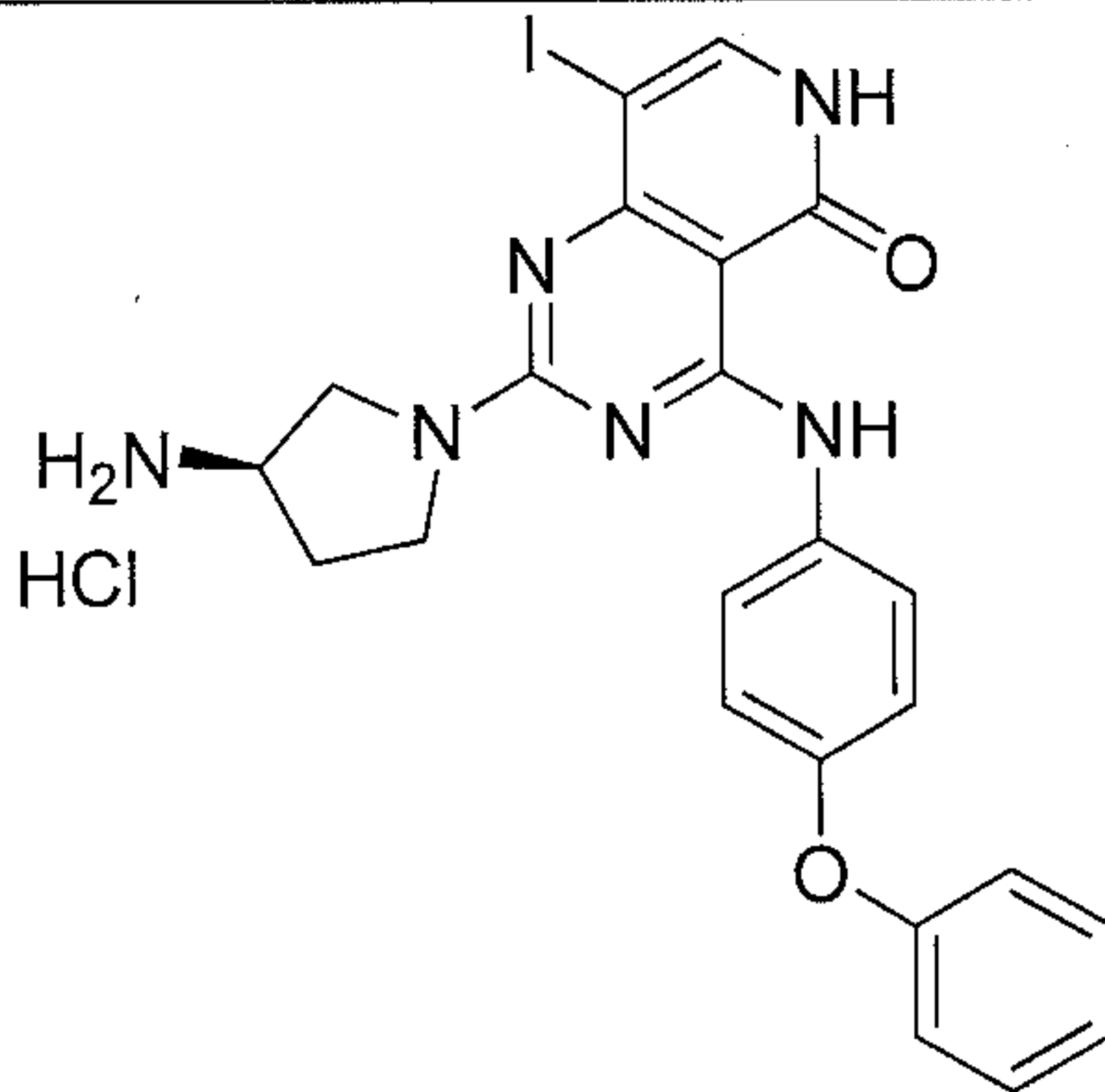
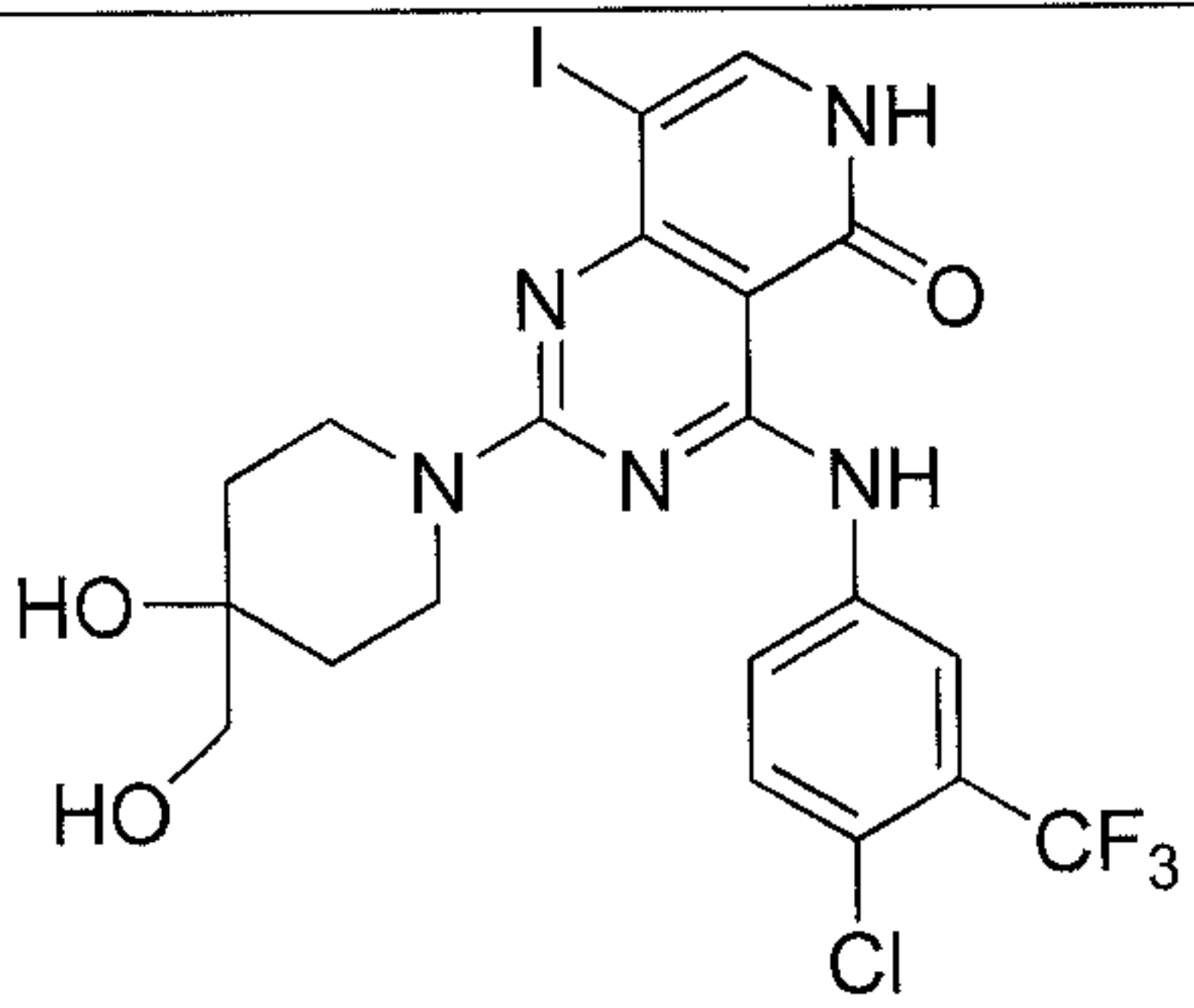
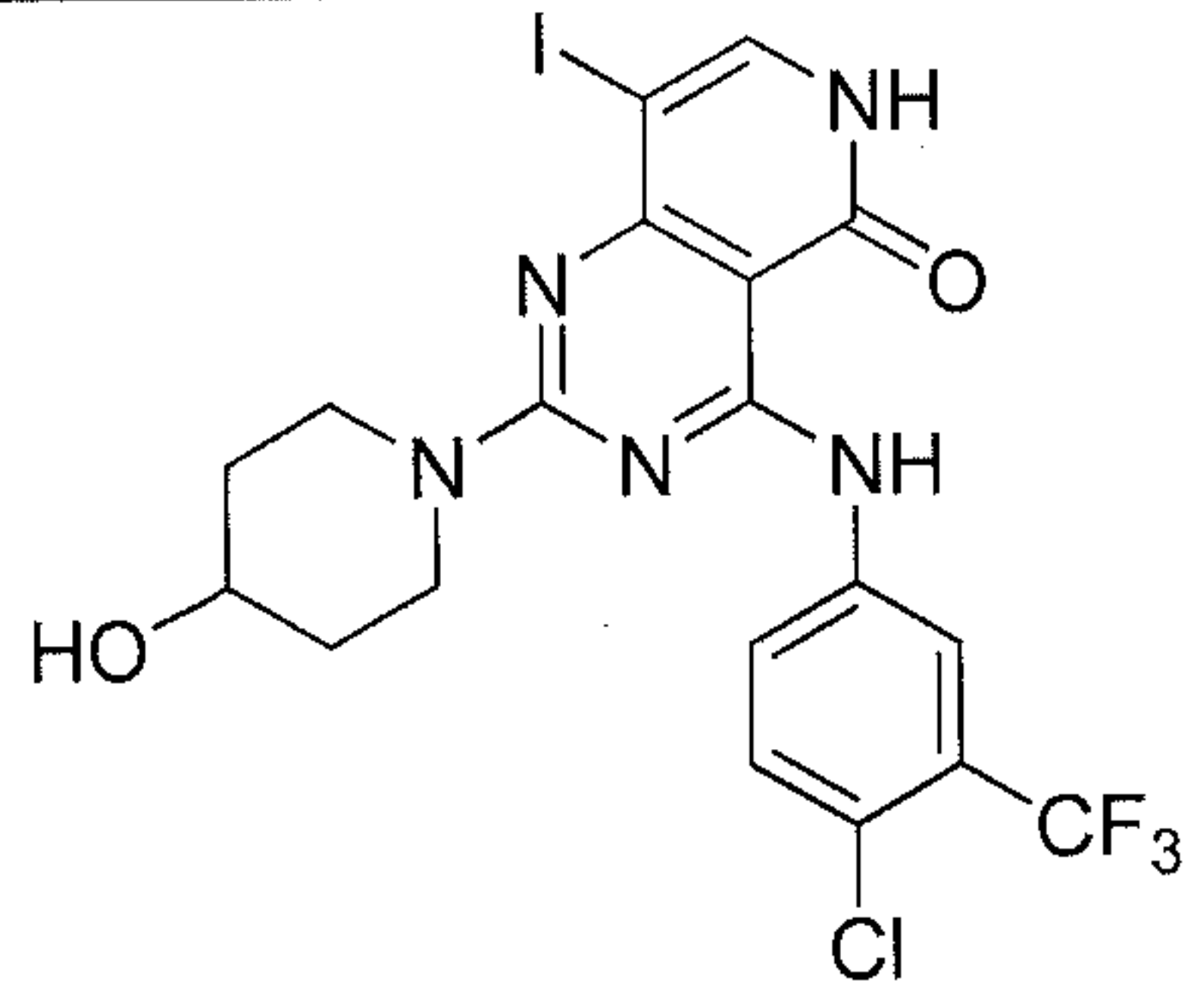
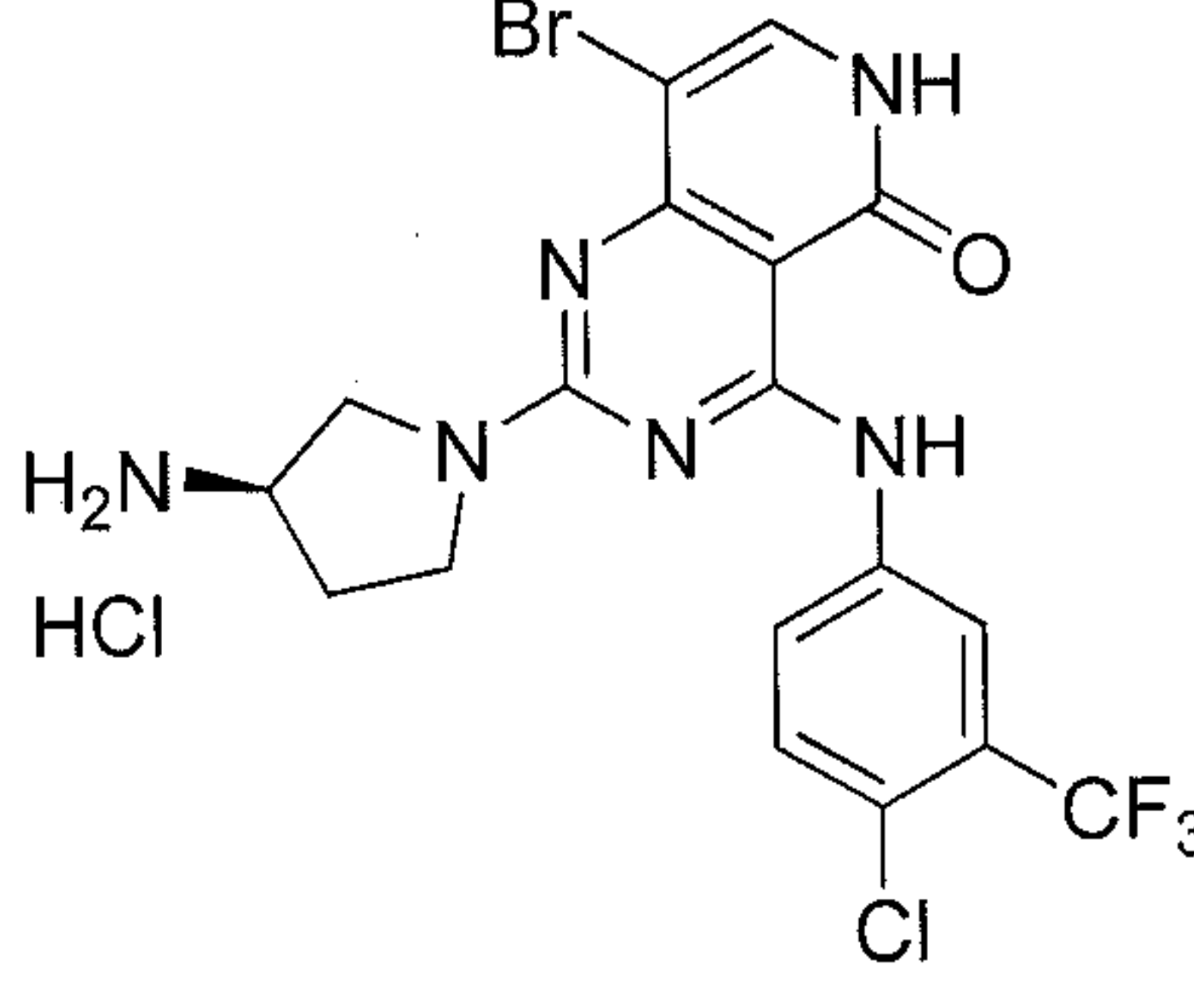
5 The following compounds were prepared from the procedure similar to that described in *Examples 183 and 184*.

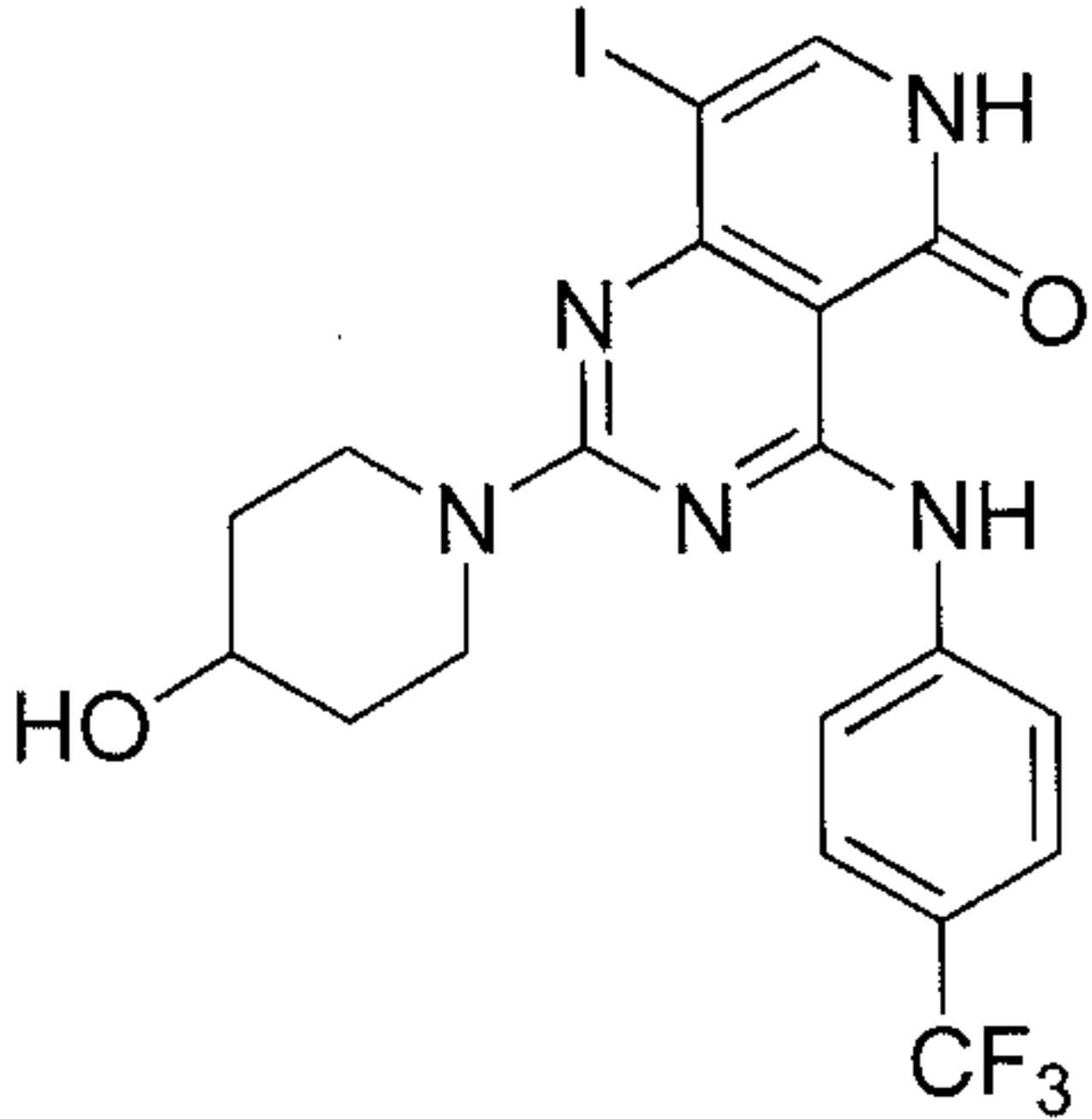
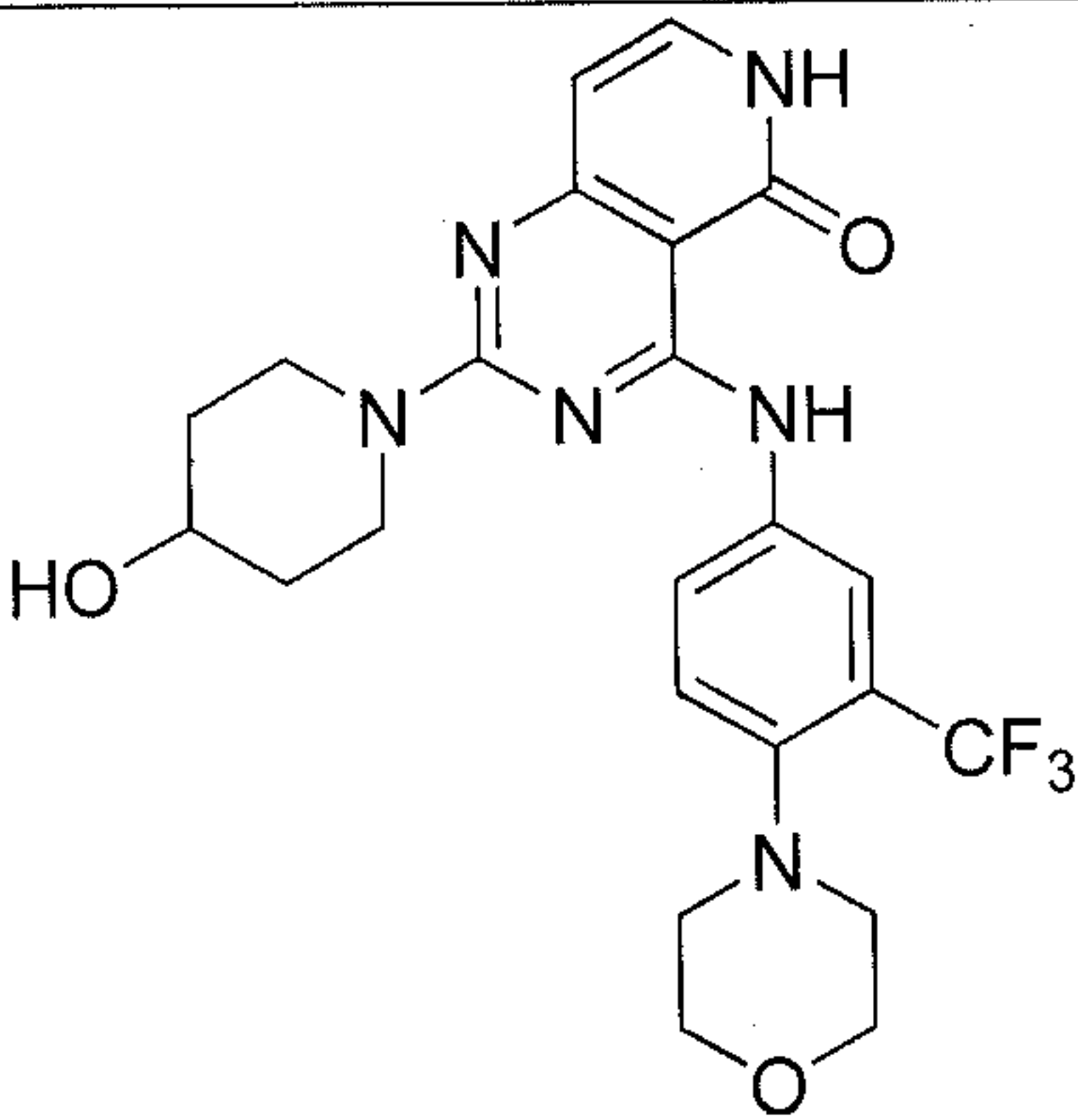
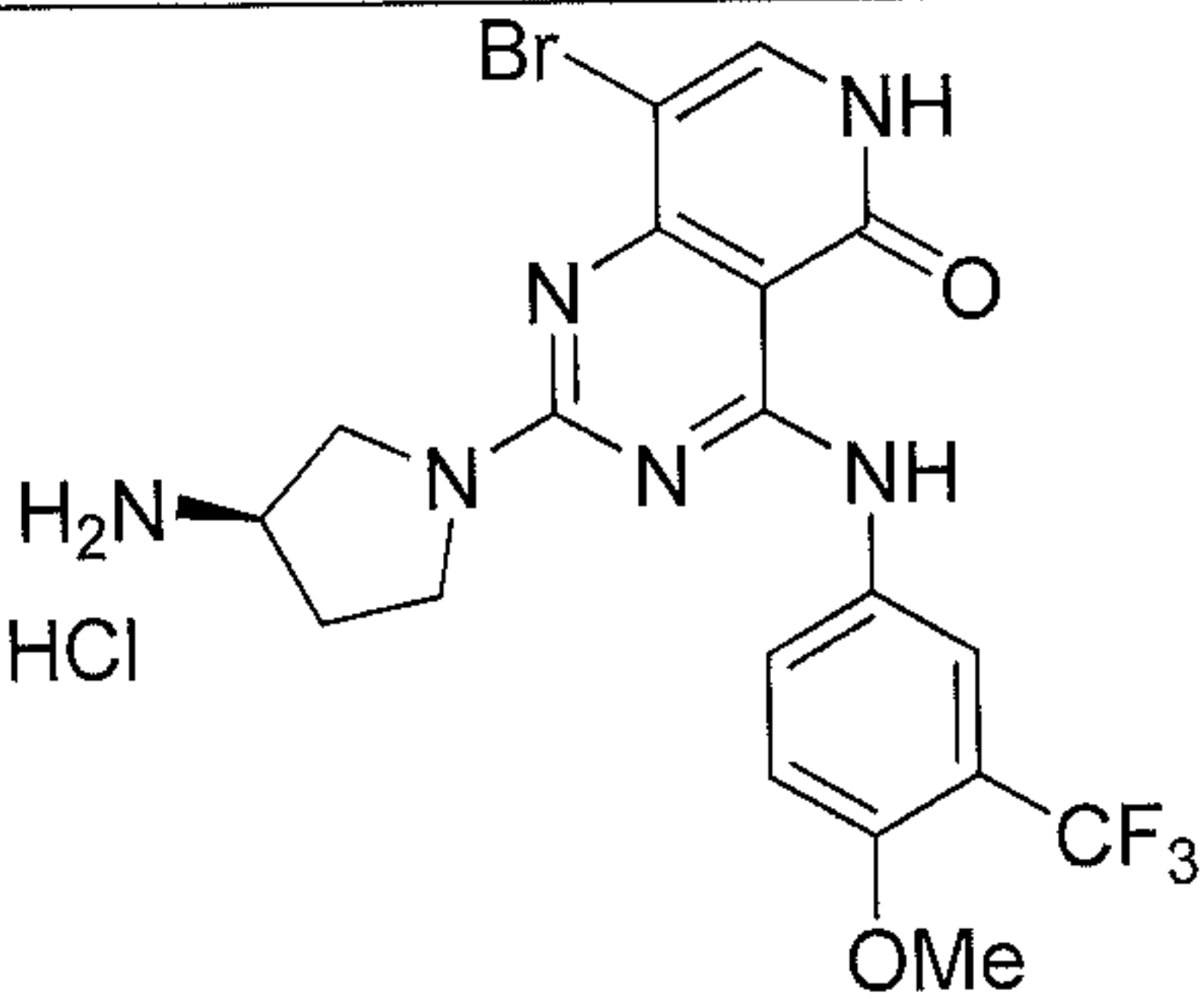
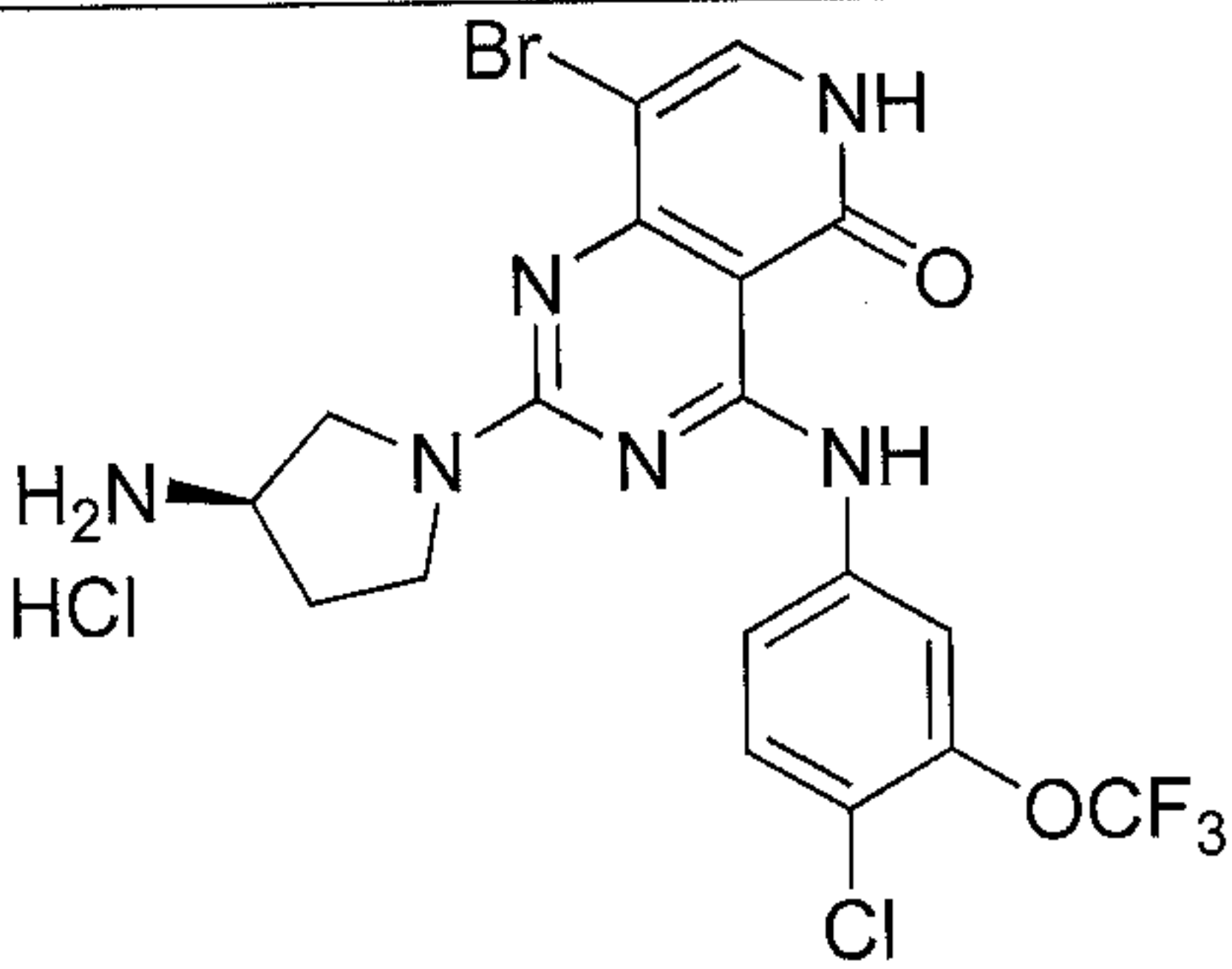
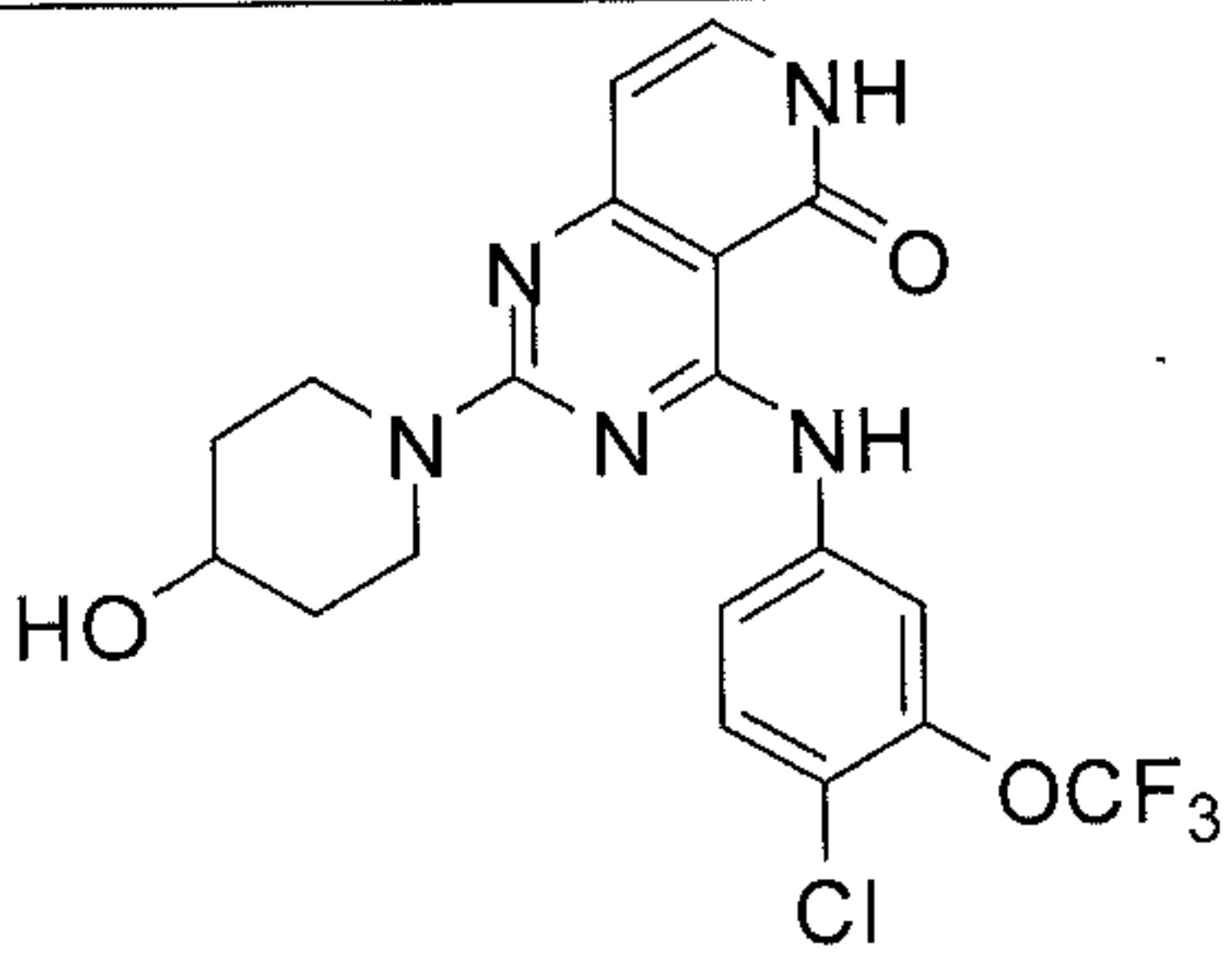
NO.	Structure	Name	Mass (<i>M</i> +1)
185		8-chloro-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	440
186		8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	514
187		(<i>R</i>)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	469
188		(<i>R</i>)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-bromo-3-methylphenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	529

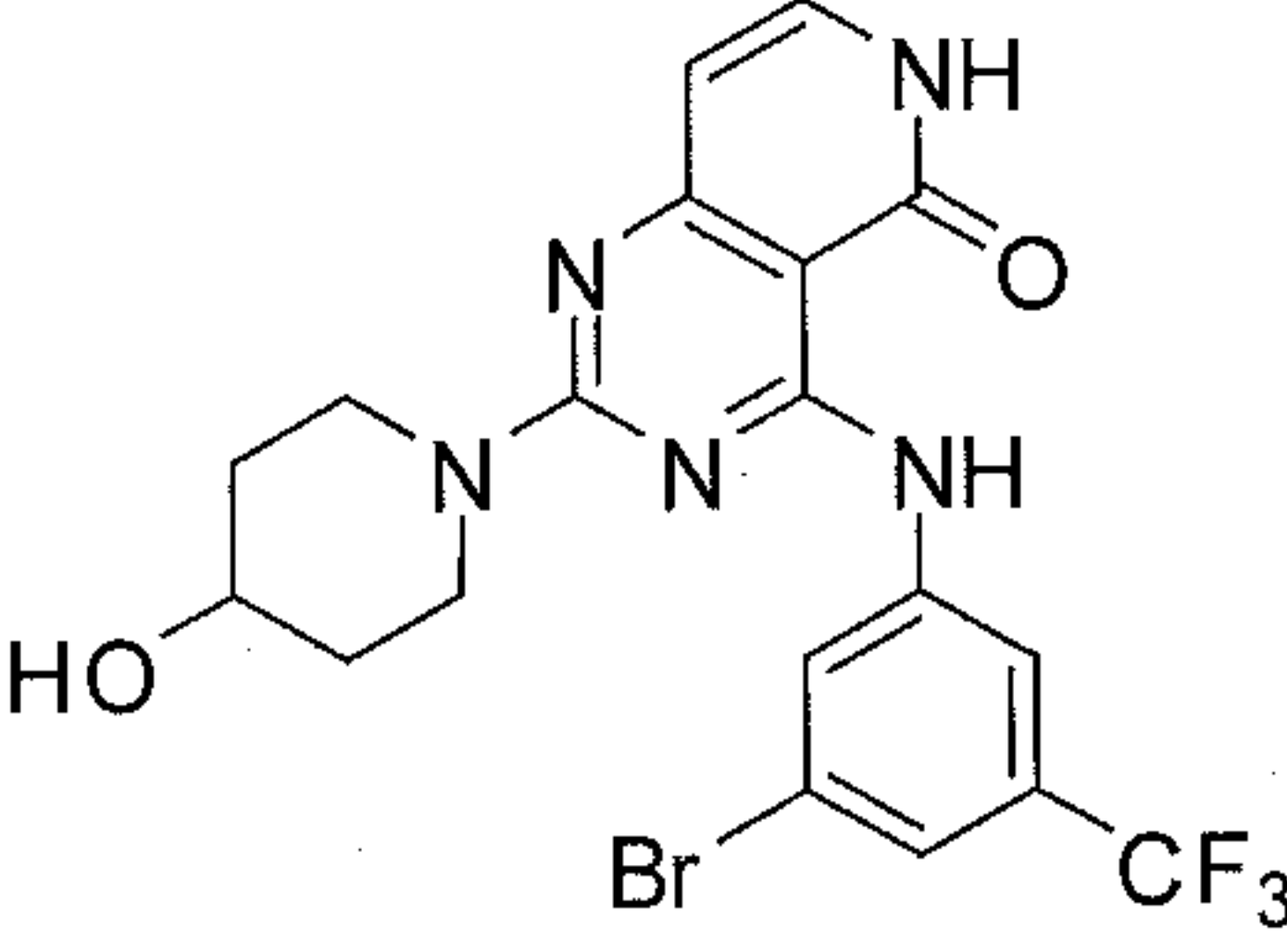
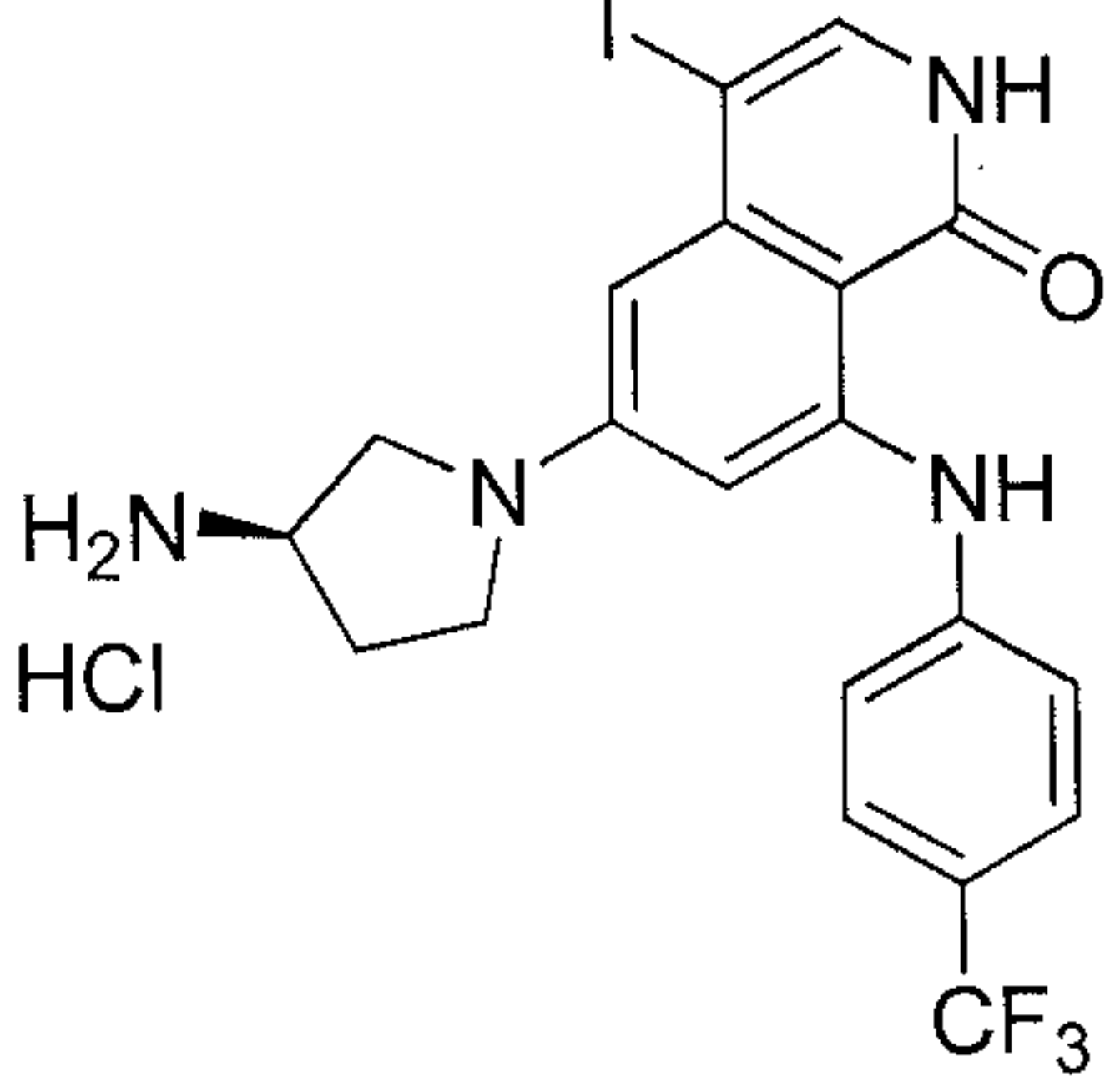
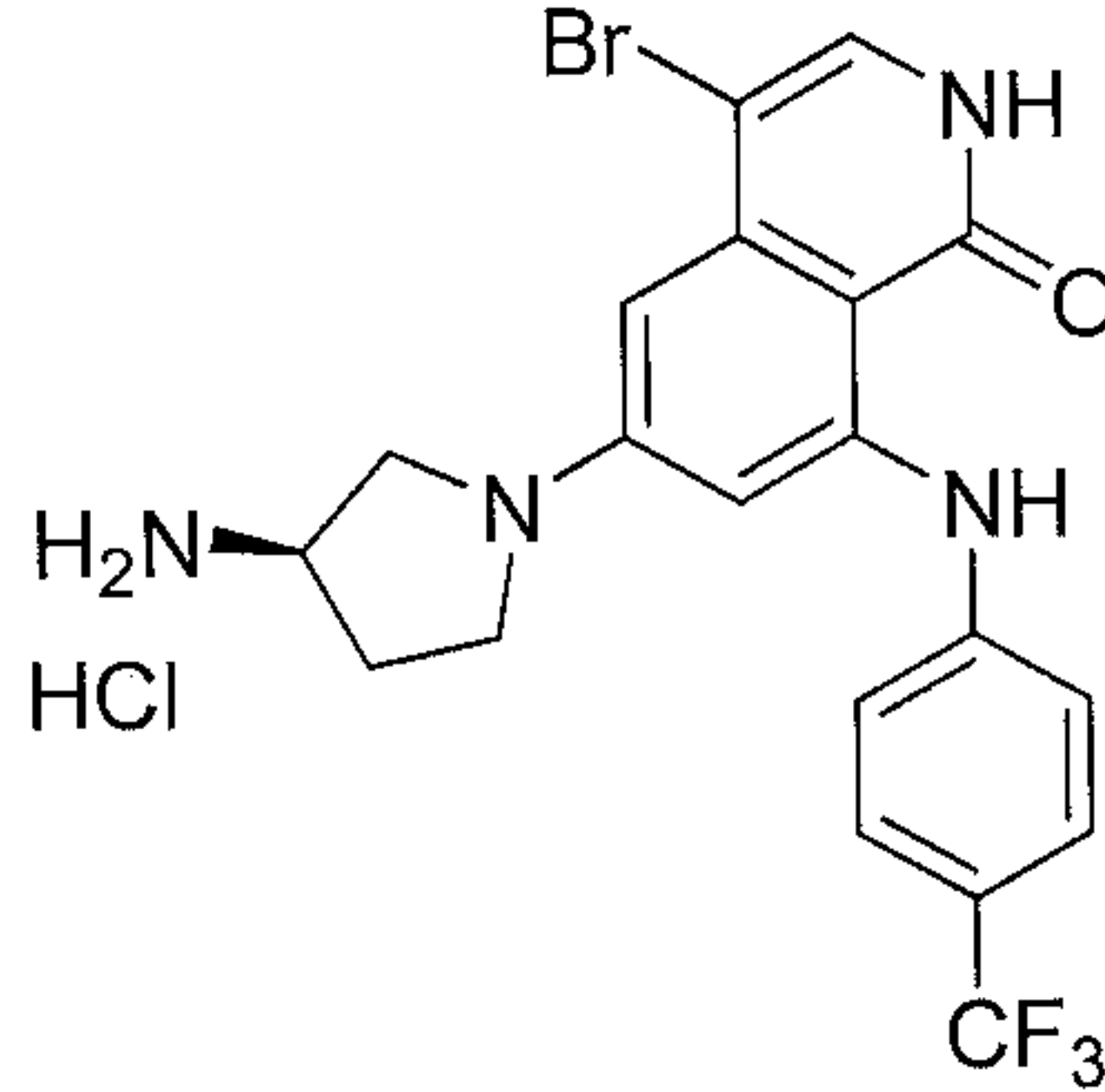
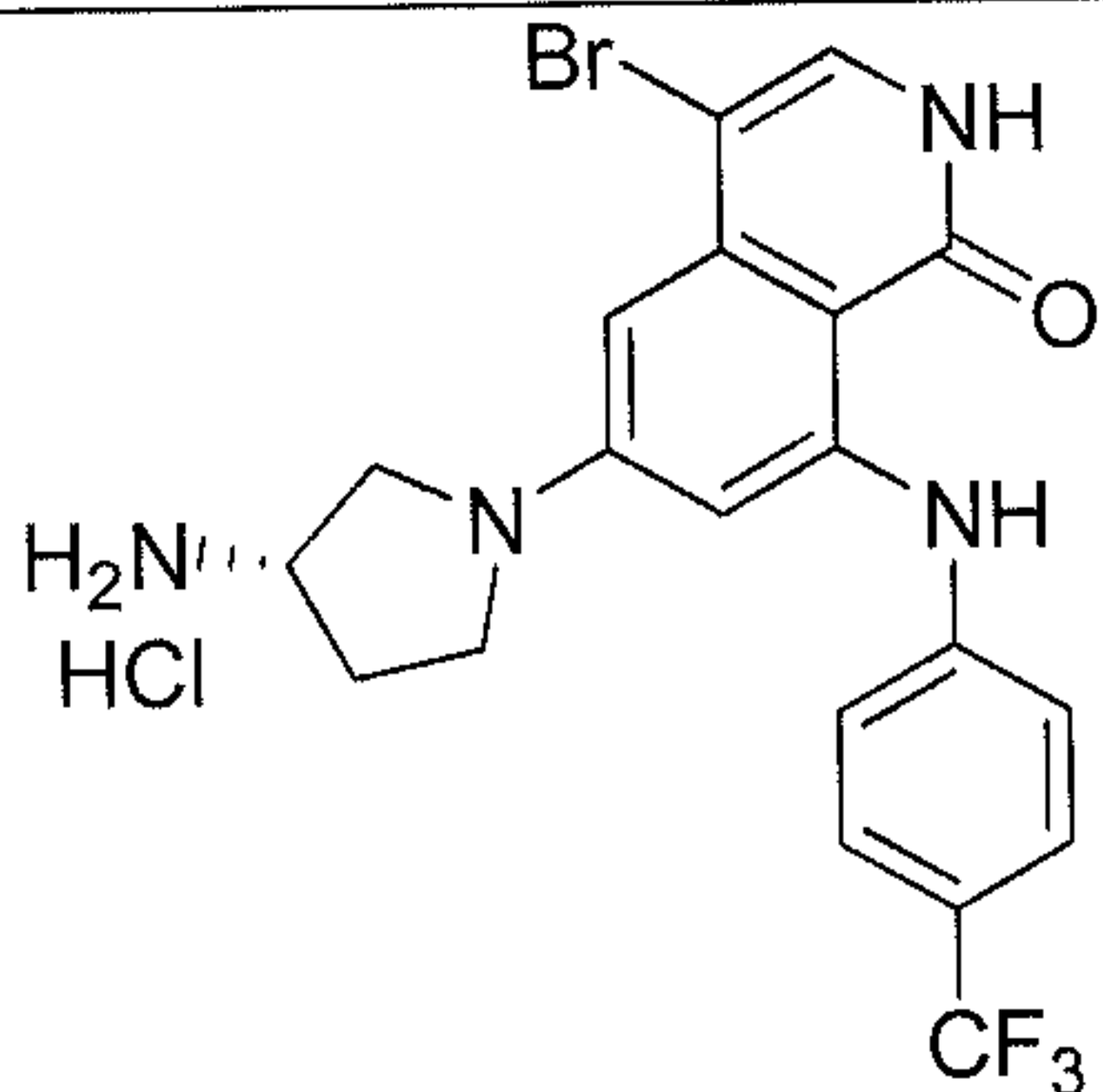
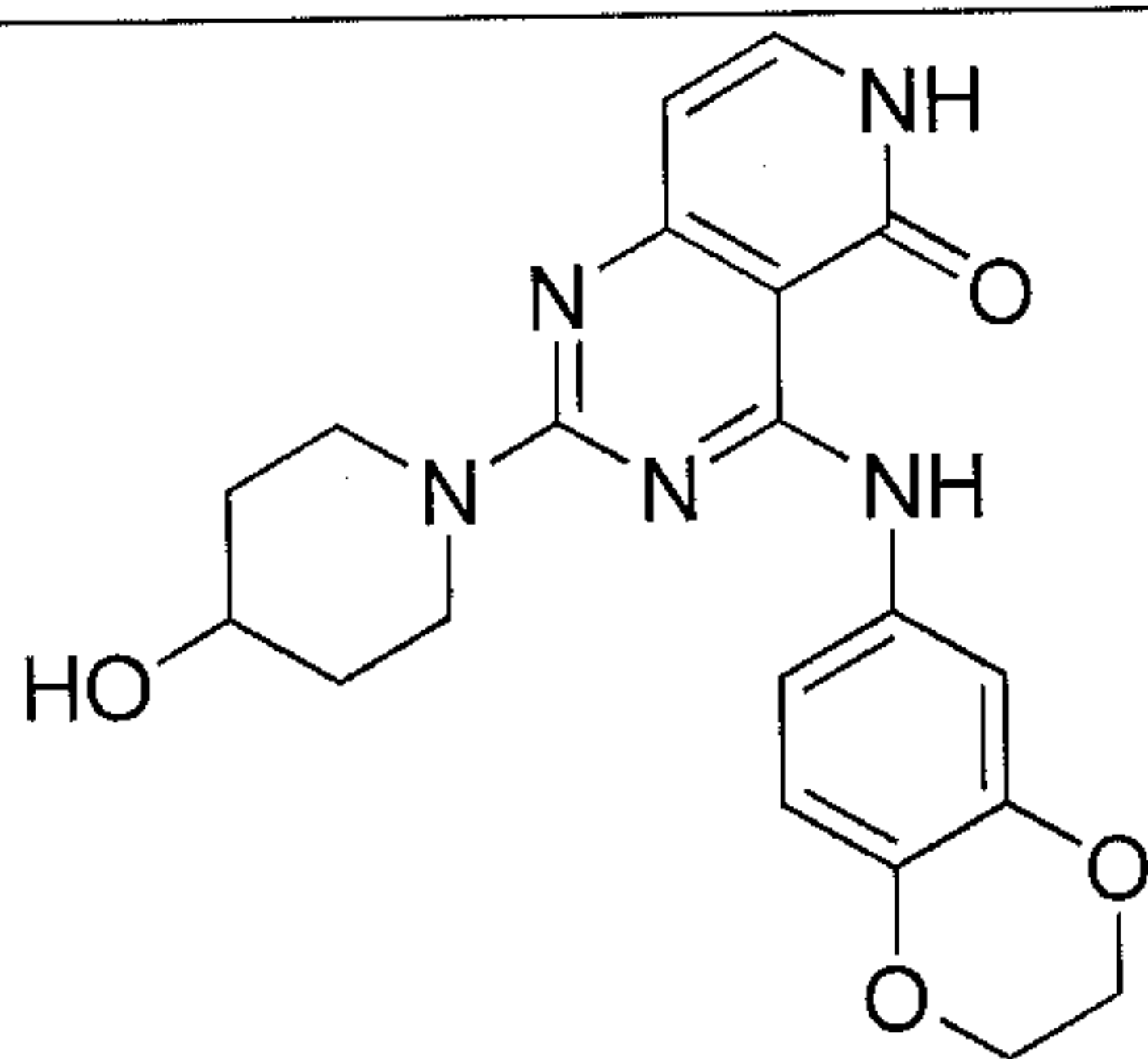
NO.	Structure	Name	Mass (M+1)
189		2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	436
190		2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	450
191		4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	440
192		4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	454
193		4-(4-chloro-3-methoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	432

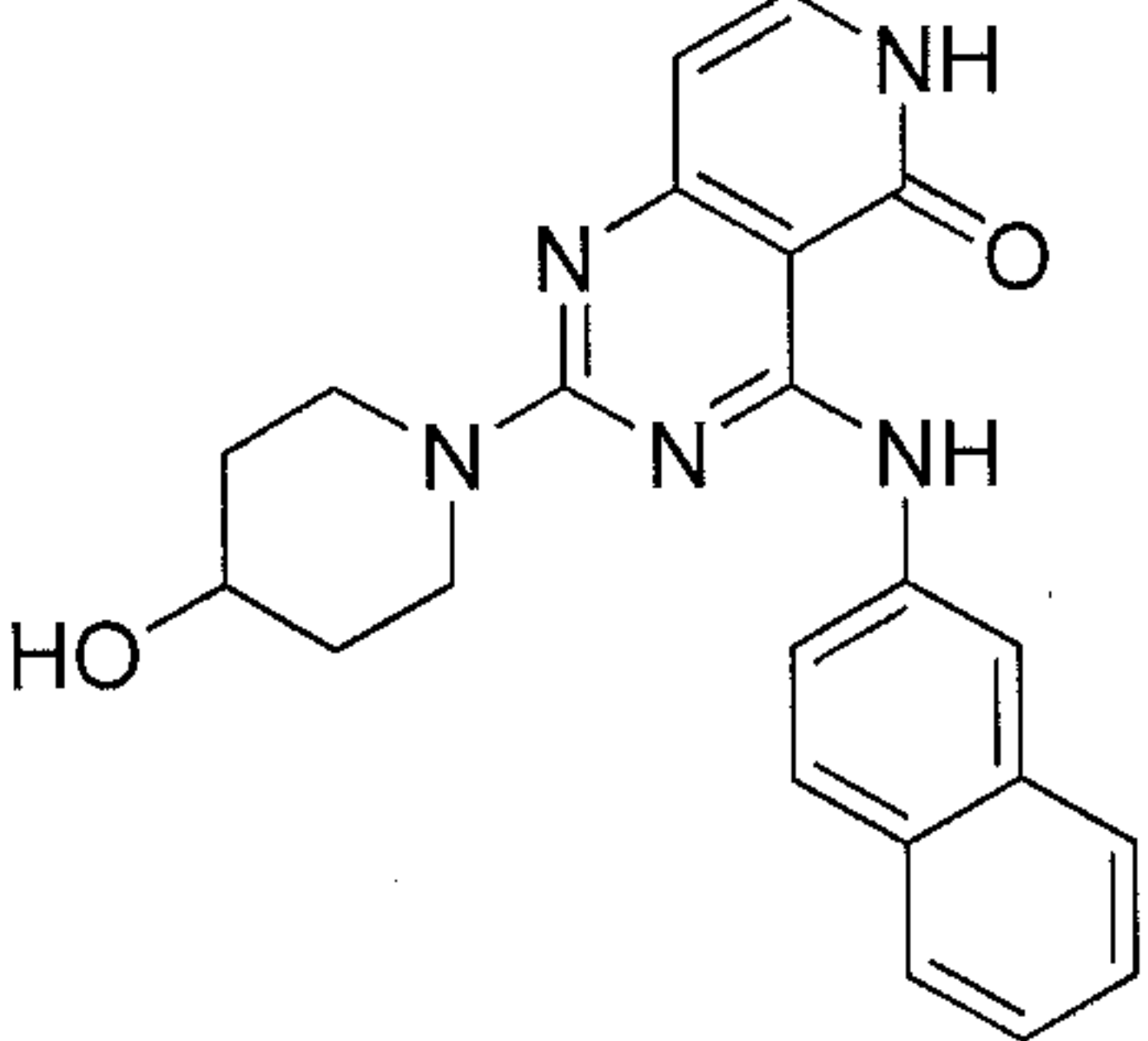
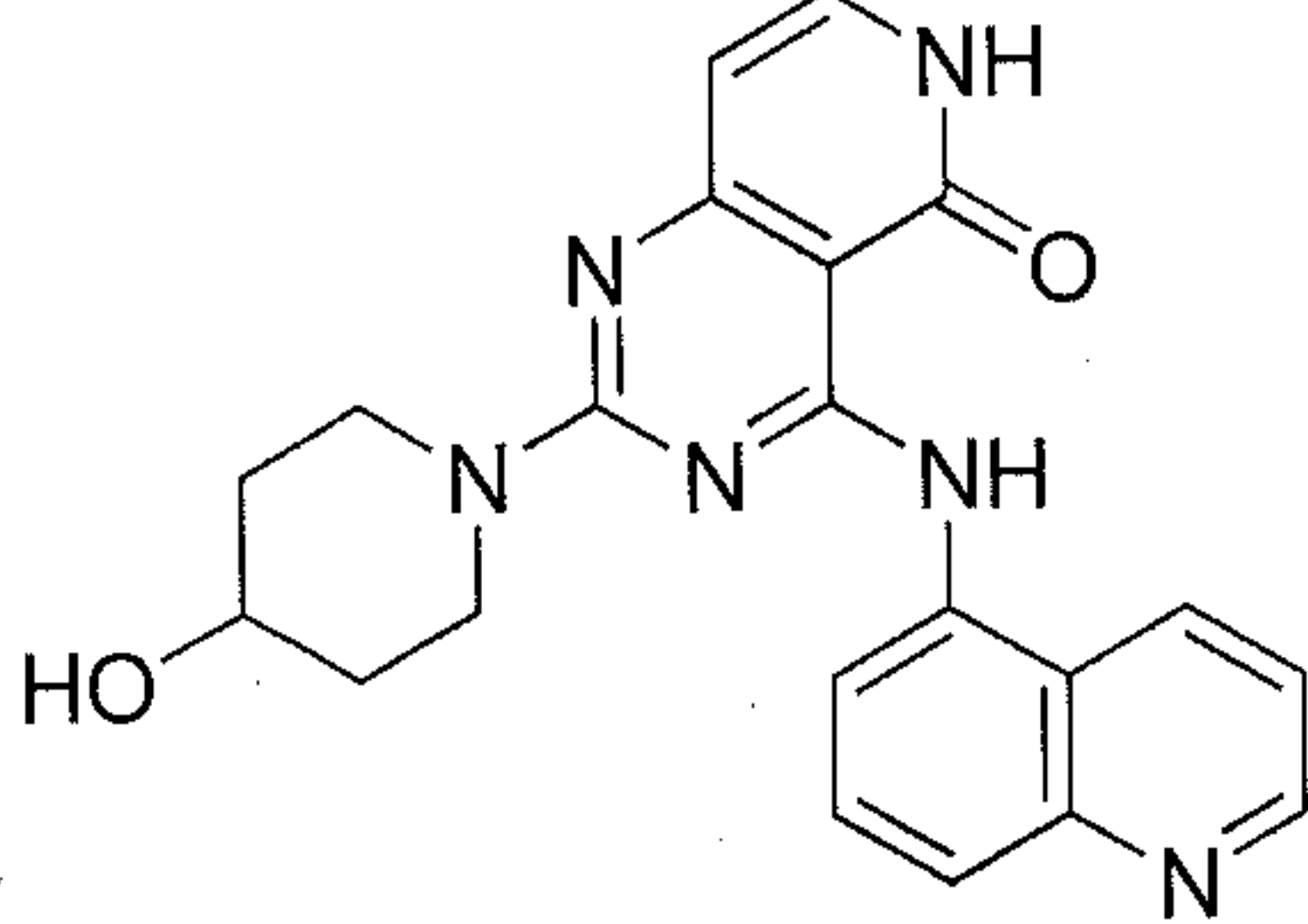
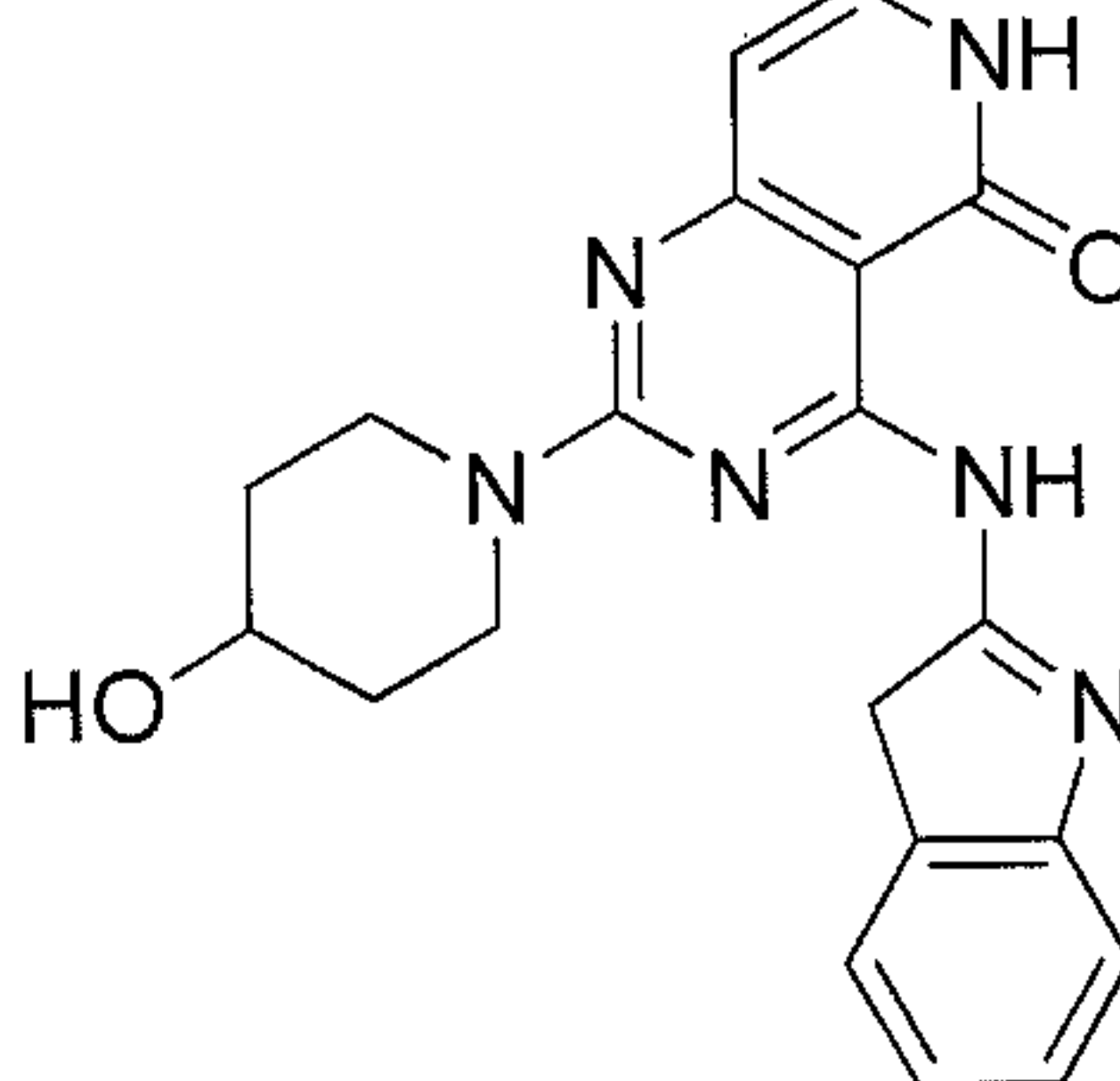
194		2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenyl amino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	466
195		4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	470
196		8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	514
197		4-(3,4-dimethoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	398
198		4-(3-bromo-4-methoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	447

199		(R)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-phenoxyphenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	493
200		8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-phenoxyphenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	538
201		4-(3,4-dimethoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	428
202		4-(3-bromo-4-methoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	477

203		2-(4-aminopiperidin-1-yl)-8-bromo-4-(4-phenoxyphenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	507
204		(<i>R</i>)-2-(3-aminopyrrolidin-1-yl)-8-iodo-4-(4-phenoxyphenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	541
205		4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-8-iodopyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	596
206		4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)-8-iodopyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	566
207		(<i>R</i>)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-chloro-3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	509

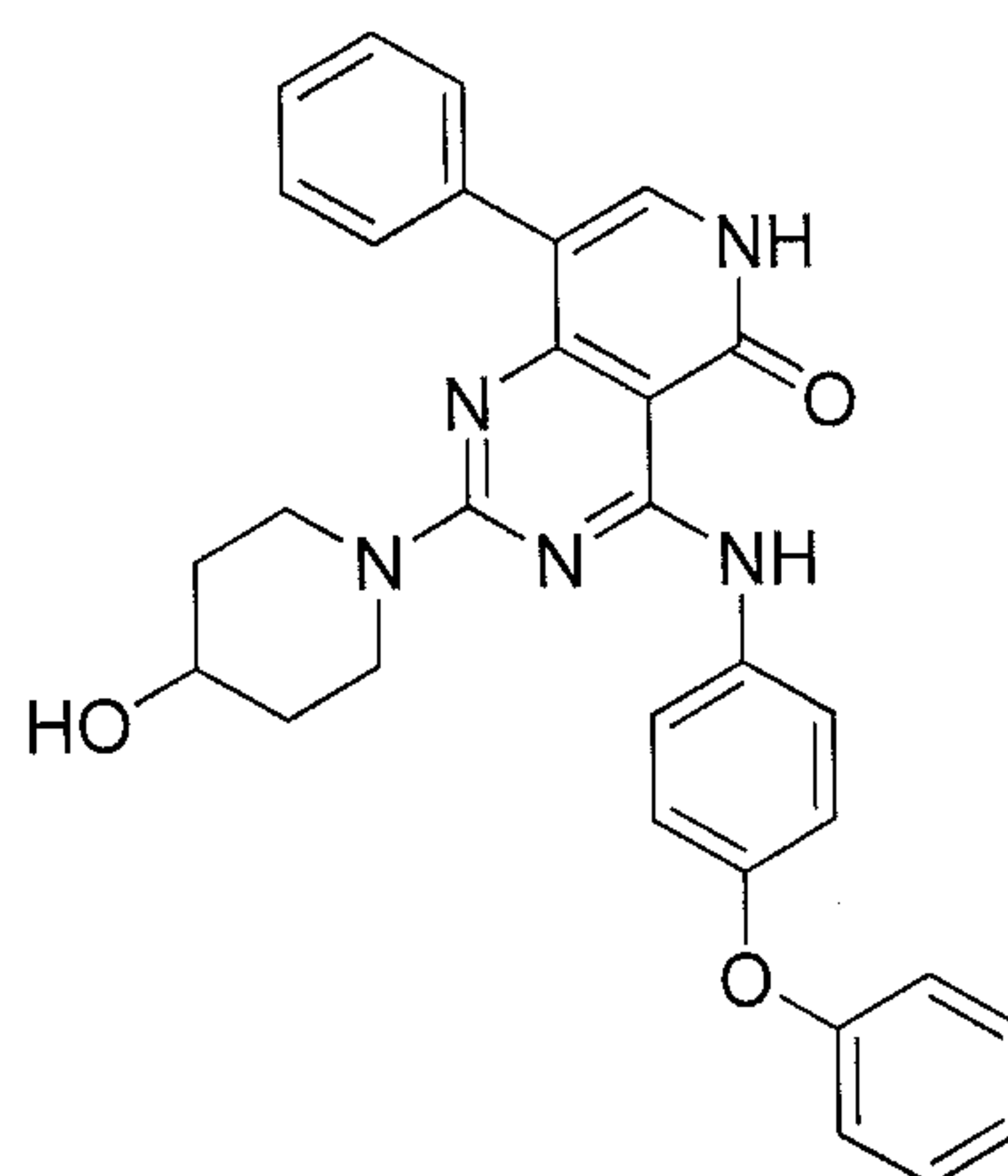
208		2-(4-hydroxypiperidin-1-yl)-8-iodo-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	503
209		2-(4-hydroxypiperidin-1-yl)-4-(4-morpholino-3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	491
210		(<i>R</i>)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	499
211		(<i>R</i>)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-chloro-3-(trifluoromethoxy)phenylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one hydrochloride	519
212		4-(4-chloro-3-(trifluoromethoxy)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	456

213		4-(3-bromo-5-(trifluoromethyl)phenylamino)- 2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>] pyrimidin-5(6 <i>H</i>)-one	485
214		(<i>R</i>)-6-(3-aminopyrrolidin-1-yl)-4-iodo-8-(4- (trifluoromethyl)phenylamino)isoquinolin- 1(2 <i>H</i>)-one hydrochloride	517
215		(<i>R</i>)-6-(3-aminopyrrolidin-1-yl)-4-bromo-8-(4- (trifluoromethyl)phenylamino)isoquinolin- 1(2 <i>H</i>)-one hydrochloride	471
216		(<i>S</i>)-6-(3-aminopyrrolidin-1-yl)-4-bromo-8-(4- (trifluoromethyl)phenylamino)isoquinolin- 1(2 <i>H</i>)-one hydrochloride	471
217		4-(2,3-dihydrobenzo[<i>b</i>][1,4]dioxin-6-ylamino)- 2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	396

218		2-(4-hydroxypiperidin-1-yl)-4-(naphthalen-2-ylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	388
219		2-(4-hydroxypiperidin-1-yl)-4-(quinolin-5-ylamino)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	389
220		4-(3 <i>H</i> -indol-2-ylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3- <i>d</i>]pyrimidin-5(6 <i>H</i>)-one	377

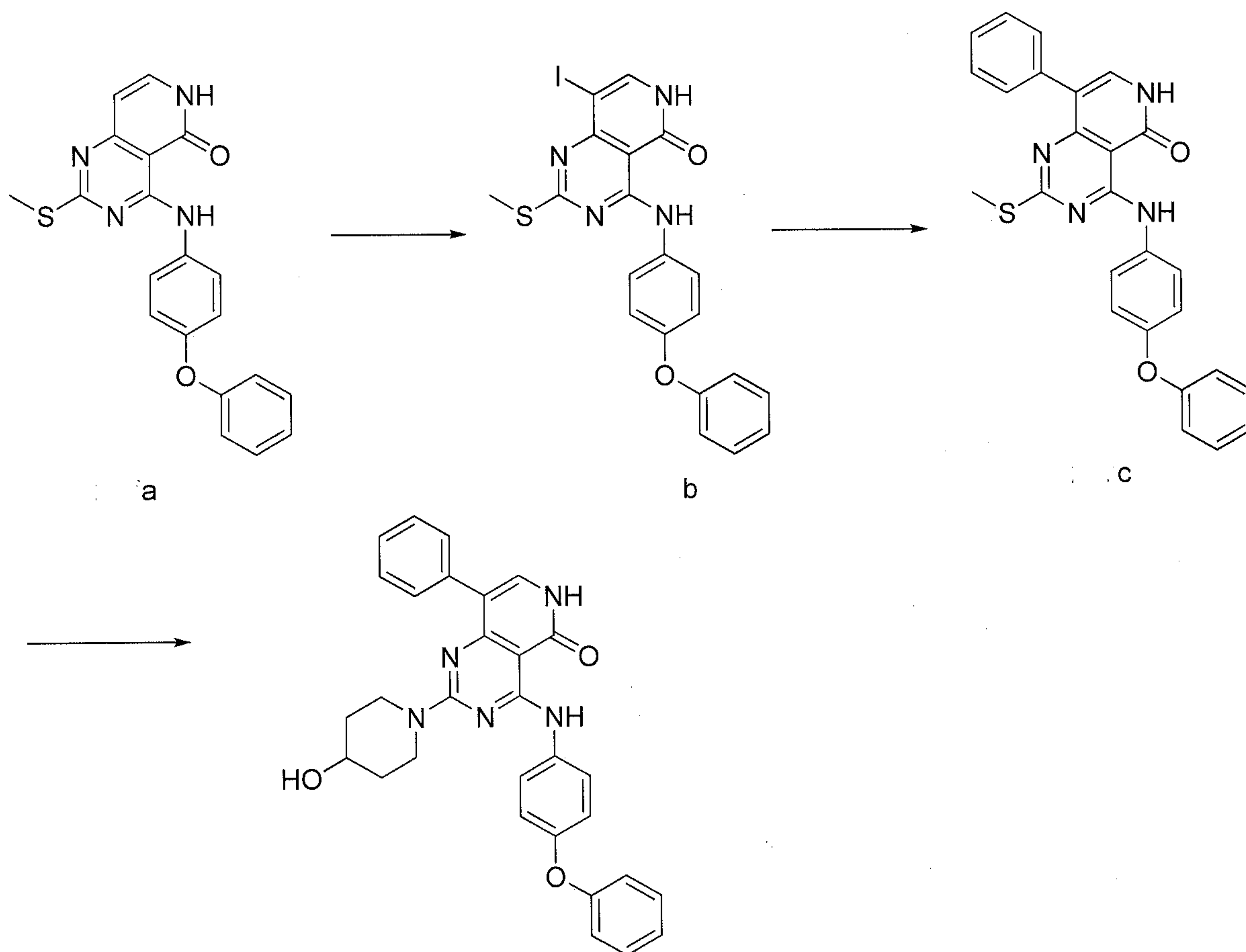
Example 221

Synthesis of 2-(4-hydroxypiperidin-1-yl)-4-(4-phenoxyphenylamino)-8-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one



Compound No. 221

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A 20 mL reaction vessel was charged with 2-(methylthio)-4-(4-phenoxyphenyl amino)pyrido[4,3-*d*]pyrimidin-5(6H)-one (221a, 182 mg, 0.48 mmol) and *N*-iodosuccinimide (158 mg, 0.70 mmol) in 8 mL dry DMF. The reaction mixture was stirred at 60 °C for 2 hours. The solvent was removed under reduced pressure yielding the pale brown solid (221b) after being recrystallized from acetonitrile (210 mg, 87%). A 20 mL reaction vessel was charged with 8-iodo-2-(methylthio)-4-(4-phenoxyphenylamino)pyrido[4,3-*d*]pyrimidin-5(6H)-one (221b, 52 mg, 0.10 mmol), benzenboronic acid (18 mg, 0.15 mmol), tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol), and 2.0 M aq. sodium carbonate solution in 6 ml dioxane. The mixture was purged with nitrogen for 30 min. Then the reaction mixture was heated at 80 °C for 3h. The solvent was removed under reduced pressure yielding the brown residue. The residue was purified by silica gel chromatography using a gradient of 0-5 % MeOH in dichloromethane yielding 221. Then 221 was prepared as described in *Example 1g* starting from 2-(methylthio)-4-(4-phenoxyphenylamino)-8-phenylpyrido[4,3-*d*]pyrimidin-5(6H)-one, and 4-hydroxypiperidine to give title compound. MS *m/z*: 506 (M+H)⁺.

BIOLOGICAL ASSAYS

1. Kinase Inhibition Assay

Compounds of the present invention were assayed to measure their capacity to inhibit a
5 kinase panel which includes, but are not limited to, spleen tyrosine kinase (SYK), zeta-chain-
associated protein kinase 70 (ZAP70), PTK2B protein tyrosine kinase 2 (PYK2), focal adhesion
kinase (FAK), provirus integration of maloney kinase 1 (PIM1), rearranged during transfection
kinase (RET), Fms-like tyrosine kinase 3 (FLT3), Janus kinase 2 (JAK2), and leucine-rich repeat
kinase 2 (LRRK2).

10 FLT3 is a member of the type III receptor tyrosine kinase (RTK) family. The ligand for
FLT3 is expressed by the marrow stromal cells and other cells and synergizes with other growth
factors to stimulate proliferation of stem cells, progenitor cells, dendritic cells, and natural killer
cells. FLT3 has been implicated in hematopoietic disorders which are pre-malignant disorders
including myeloproliferative disorders, such as thrombocythemia, essential thrombocytosis (ET),
15 angiogenic myeloid metaplasia, myelofibrosis (MF), myelofibrosis with myeloid metaplasia
(MMM), chronic idiopathic myelofibrosis (IMF), and polycythemia vera (PV), the cytopenias,
and pre-malignant myelodysplastic syndromes. Hematological malignancies include leukemias,
lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma),
and myeloma-for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML),
20 acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid
leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL),
anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile
myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia
(AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes
25 (MDSs), myeloproliferative disorders (MPD), multiple myeloma, (MM) and myeloid sarcoma.
Aberrant expression FLT3 has been documented in both adult and childhood leukemias
including acute myeloid leukemia (AML), AML with trilineage myelodysplasia (AML/TMDS),
acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS).

RET is the receptor for members of the glial cell line derived neurotrophic factor
30 (GDNF) family of extracellular signalling molecules (GFL's). RET signal transduction is
central to the development of normal kidneys and the enteric nervous system. RET loss of
function mutations are associated with the development of Hirschsprung's disease, while gain of

function mutations are associated with development of various types of cancer, including medullar thyroid carcinoma and multiple endocrine neoplasias type II and III.

Spleen tyrosine kinase (SYK) is a member of the SYK family of tyrosine kinases which are non-receptor cytoplasmic tyrosine kinases sharing a characteristic dual SH2 domain separated by a linker domain. SYK plays a role in transmitting signals from a variety of cell surface receptors including CD74, Fc Receptor, and integrins. Abnormal function of SYK has been implicated in instances of hematopoietic malignancies. Several transforming viruses, such as Epstein Barr virus, bovine leukemia virus, and mouse mammary tumor virus, are known to contain "Immunoreceptor Tyrosine Activation Motifs" (ITAMs) that lead to activation of SYK.

ZAP70 is an enzyme belonging to the protein tyrosine kinase family, and it plays a role in thymocyte development, T-cell development, and lymphocyte activation. ZAP70 is phosphorylated on tyrosine residues upon T-cell antigen receptor (TCR) stimulation and functions in the initial step of TCR-mediated signal transduction in combination with the Src family kinases, Lck and Fyn. Mutations in this gene cause selective T-cell defect, a severe combined immunodeficiency disease characterized by a selective absence of CD8-positive T-cells.

PYK2 is a cytoplasmic protein tyrosine kinase involved in calcium-induced regulation of ion channels and activation of the map kinase signaling pathway. The encoded protein may represent an important signaling intermediate between neuropeptide-activated receptors or neurotransmitters that increase calcium flux and the downstream signals that regulate neuronal activity. The encoded protein undergoes rapid tyrosine phosphorylation and activation in response to increases in the intracellular calcium concentration, nicotinic acetylcholine receptor activation, membrane depolarization, or protein kinase C activation. Its activation is highly correlated with the stimulation of c-Jun N-terminal kinase activity. PYK2 is implicated in diseases such as osteoporosis, arthritis, myeloid leukemia, hypo-osmolality, sarcoma, blast crisis, glioma, erythroleukemia, and cancer.

FAK (encoded by the gene PTK2) is a non-receptor tyrosine kinase that integrates signals from integrins and growth factor receptor. FAK plays a role in the regulation of cell survival, growth, spreading, migration and invasion and is regulated and activated by phosphorylation on multiple tyrosine residues. Overexpression of FAK mRNA and/or protein has been implicated in cancers of the breast, colon, thyroid, and prostate. Phosphorylation of FAK is increased in malignant tissues as compared to normal tissues.

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JAK1 is a member of the protein-tyrosine kinase (PTK) family and characterized by the presence of a second phosphotransferase-related domain immediately N-terminal to the PTK domain. JAK1 is involved in the interferon-alpha/beta and -gamma signal transduction pathways. The reciprocal interdependence between JAK1 and TYK2 activities in the interferon-alpha pathway, and between JAK1 and JAK2 in the interferon-gamma pathway may reflect a requirement for these kinases in the correct assembly of interferon receptor complexes.

JAK2 has been implicated in signaling by members of the type II cytokine receptor family (e.g. interferon receptors), the GM-CSF receptor family (IL-3R, IL-5R and GM-CSF-R), the gp130 receptor family (e.g. IL-6R), and the single chain receptors (e.g. Epo-R, Tpo-R, GH-R, PRL-R). JAK2 gene fusions with the TEL(ETV6) (TEL-JAK2) and PCM1 genes have been found in leukemia patients. Further, mutations in JAK2 have been implicated in polycythemia vera, essential thrombocythemia, and other myeloproliferative disorders. This mutation, a change of valine to phenylalanine at the 617 position, rendered hematopoietic cells more sensitive to growth factors such as erythropoietin and thrombopoietin.

JAK3 is a tyrosine kinase of the Janus family. JAK3 is predominantly expressed in immune cells and transduces a signal in response to its activation via tyrosine phosphorylation by interleukin receptors. Mutations that abrogate Janus kinase 3 function cause an autosomal severe combined immunodeficiency disease (SCID). Mice that do not express JAK3 have T-cells and B-cells that fail to respond to many cytokines. Since JAK3 expression is restricted mostly to hematopoietic cells, its role in cytokine signaling is thought to be more restricted than other JAKs. JAK3 is involved in signal transduction by receptors that employ the common gamma chain (γ C) of the type I cytokine receptor family (e.g. IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, and IL-21R).

Provirus Integration of Maloney Kinase (PIM-Kinase) was identified as one of the frequent proto-oncogenes capable of being transcriptionally activated by Maloney retrovirus integration event in mice, causing lymphomas in affected mice. PIM 1, 2 and 3 are serine/threonine kinases normally function in survival and proliferation of hematopoietic cells in response to growth factors and cytokines. Transgenic mice overexpressing PIM1 or PIM2 show increased incidence of T-cell lymphomas, while overexpression in conjunction with c-myc is associated with incidence of B-cell. Aberrant PIM expression has been reported in many human malignancies including prostate cancer, hepatocellular carcinoma, and pancreatic cancer. PIM kinases are involved in the early differentiation process of Helper T-cells, which coordinate the immunological response in autoimmune diseases, allergic reaction and tissue transplant

rejection. In addition to a potential role in cancer treatment and myeloproliferative diseases, an inhibitor of PIM can be useful to control expansion of immune cells in other pathologic condition such as autoimmune diseases, allergic reactions and in organ transplantation rejection syndroms.

5

METHODS

Inhibition of enzymatic SYK, ZAP70, PYK2, FAK, PIM1, RET, FLT3, JAK2 and LRRK2 kinase activity

Compounds of the invention were initially diluted to 10mM in 100% DMSO (CALBIOCHEM™) for storage and made into kinase buffer solution to create a compound concentration ranging from 1uM and 10uM. Serial dilutions of compounds of the invention were dispensed into a 96-well plate (GREINER BIOSCIENCES™) at 6μL each. Purified full-length human SYK, ZAP70, PIM1, PYK2 and truncated human FAK, RET, FLT3, JAK2, and LRRK2 (CARNA BIOSCIENCES™) were diluted in kinase buffer and added to the compound solutions and pre-incubated for 30 minutes at room temperature (1 hour for PYK2). Next, ATP (TEKNOVA™) and substrate solution (suggested manufacture substrates of PerkinElmer™, for example, Ulight™-TK peptide for SYK, Ulight™-PolyGT for ZAP70, FAK, and PYK2, and Ulight™-CREBtide for PIM1 (PERKINELMER™)) was added (12uL each) to the wells containing the compound solution and enzyme. The reaction mixture was incubated for 1 hour (2 hours for PYK2). Following the incubation, the stop solution made with EDTA, water, and Lance detection buffer (PERKINELMER™) was added (12μL each) to stop phosphorylation. Following the addition of the stop solution and 5 minutes of shaking, the detection solution containing the Europium-labeled antibody (suggested manufacture substrates of PerkinElmer™, for example, PT66 for SYK, ZAP70, PYK2, and FAK, and Anti-Creb for PIM1), water, and Lance detection buffer was added (12μL each) to the reaction mixture and incubated again for 50 minutes. Substrate phosphorylation was a function of the 665nm emission measured following the addition of the detection solution and 50 minutes of incubation.

RESULTS

Compounds of Formula (I) exhibited useful pharmacological properties. As used herein, zero % inhibition indicates no inhibition on the kinase activity (e.g., as seen in control treated with no inhibitor), whereas 100% inhibition indicates complete inhibition of the kinase activity.

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Compounds of Formula (I) exhibited various levels of inhibition of the protein kinases on the panel. Certain compounds exhibited percentage inhibition of greater than 80% against one or more of the kinase at 1 μ M concentration as shown in Table 2.

For example, Compound 6 of Formula (I), namely, 2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidine-5(6*H*)-one, was shown to inhibit the kinase activity of SYK (88%), Zap70 (49%), PYK2 (83%), FAK (78%) and PIM1 (32%) at a concentration of 1 μ M and that of RET (IC₅₀, 94.2 nM) and LRRK2 (IC₅₀, 54nM; *see* Table 2). Table 2 illustrates the percentage / molar inhibition of SYK, ZAP70, PYK2, FAK, PIM1, RET, FLT3, JAK2 and LRRK2 by the representative compounds of Formula (I).

10

Table 2 Inhibition Activity of Various Kinases

Compound no.	SYK	ZAP70	PYK2	FAK	PIM1
6	88 %	49 %	83 %	78 %	32 %
7	92.6 %	42.0 %	84.9 %	83.5 %	51.4 %
9	84 %	32 %	89 %	83 %	64 %
84	95.7 %	54.6 %	92.8 %	92.9 %	71.2 %
100	37.7 %	9 %	88.4 %	21.9 %	n.d.
101	90 %	45 %	85 %	77 %	61 %
126	95.1 %	49.3 %	39.5 %	80.8 %	12.7%
151	8.2 nM	n.d.	90.2 nM	216.9 nM	n.d.
152	2.7 nM	n.d.	84.3 nM	337.1 nM	n.d.
168	3 %	6.2 %	1 %	4.9 %	7.3 %
R406	96.8 %	58.5 %	74.3 %	46.5 %	n.d.

	RET	FLT3	JAK2	LRRK2
1	200.2 nM	242.1 nM	59.4 nM	n.d.
2	363.2 nM	367.6 nM	73.8 nM	n.d.
6	94.2 nM	n.d.	n.d.	54 nM
8	2.6 nM	0.2 nM	12.7 nM	n.d.
102	n.d.	n.d.	n.d.	325 nM
125	3.4 nM	0.6 nM	24.9 nM	n.d.
134	7.3 nM	n.d.	3.7 nM	n.d.

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136	1.3 nM	0.1 nM	3.9 nM	n.d.
137	5.8 nM	12.4 nM	1.6 nM	n.d.
139	4.1 nM	9.1 nM	1.6 nM	n.d.
149	32.7 nM	151.1 nM	151 nM	n.d.
150	115.3 nM	106 nM	65.3 nM	n.d.
178	7.5 uM	4.8 uM	n.d.	n.d.
Staurosporine	2.2 nM	0.2 nM	0.3 nM	7.8 nM

* n.d., not determined

2. Tumor Necrosis Factor (TNF)- α Release Assay

Compounds of the invention are tested for their effects on TNF- α release in human acute monocytic leukemia cell line (THP-1) to illustrate efficacy of the invention at the cellular level. TNF- α is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. The primary role of TNF- α is in the regulation of immune cells. TNF- α is known to induce apoptotic cell death and inflammation and to inhibit early tumorigenesis and viral replication. Dysregulation and, in particular, overproduction of TNF- α have been implicated in a variety of human diseases, autoimmune disease, inflammation, arthritis, cancer and many other diseases associated TNF- α dysregulation.

Production or release of TNF- α is controlled by type of stimulus to which the cell responds. SYK activity is involved in mediating TNF- α production. When stimulated by IgG, cells increase TNF- α production in a SYK dependent manner (*i.e.*, the SYK dependent pathway). However, when stimulated by lipopolysaccharide (LPS), they produce TNF- α in a SYK independent manner.

METHODS

Compounds of the invention were tested for their TNF- α release effect on THP-1 cells. For SYK dependent TNF- α release assay (*i.e.*, via IgG stimulation), THP-1 cells derived from human monocytic cells were obtained from the American Type Culture Collection (ATCC, Manassas, VA). This cell line was maintained with an Roswell Park Memorial Institute (RPMI) medium (GIBCO™) containing 10 fetal bovine serum (FBS; GIBCO™) and 0.05 mM 2-mercaptoethanol. The THP-1 cells were seeded at 1×10^5 cells/100 μ L/well into human IgG (10 μ g/well, INVITROGEN™)-coated 96 well culture plate, and serially diluted compound was then added. After an 18-hour incubation period at 37°C, supernatants were collected for the

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determination of the TNF- α level by enzyme-linked immunosorbent assay (ELISA), and the remaining cells were subjected to an MTT (yellow tetrazolium salt) assay to determine the cytotoxic effects of compound.

For SYK independent TNF- α release assay (i.e., via lipopolysaccharide (LPS)-stimulation), THP-1 cells derived from human monocytic cells were obtained from the American Type Culture Collection (ATCC, Manassas, VA). This cell line was maintained with an RPMI medium (GIBCO™) containing 10 fetal bovine serum (FBS, GIBCO™) and 0.05 mM 2-mercaptoethanol. The THP-1 cells were seeded at 1×10^5 cells/100 μ L /well into 96-well culture plates, and treated with lipopolysaccharide (1 μ g/ml), and serially diluted compound was then added. After an 18-hour incubation period at 37°C, supernatants were collected for the determination of the TNF- α level by ELISA, and the remaining cells were subjected to an MTT assay to determine the cytotoxic effects of compound.

RESULTS

Compounds of Formula (I) exhibited useful pharmacological properties. As used herein, control used without the presence of an inhibitor indicates zero % inhibition of TNF- α release.

In certain embodiments, compounds of Formula (I) exhibited a percentage inhibition of greater than 50 at 0.3 μ M concentration in a SYK dependent manner (e.g., IgG stimulation). Specifically, at 0.3 μ M concentration, Compounds 6 and 151 of the present invention exhibited a percentage inhibition greater than those exhibited by R406, a widely known kinase inhibitor, in SYK dependent TNF- α release assay (i.e., IgG stimulated release). Furthermore, Compound 6 of the present invention exhibited a percentage inhibition greater than or equal to those exhibited by dexamethasone, a well known inhibitor of TNF- α , in SYK independent TNF- α release assay (i.e., LPS stimulated release).

For example, Compound 152 of Formula (I), 2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one (see table 3, Compound 151) exhibited a higher percentage inhibition of TNF- α release in a SYK dependent manner at a concentration of 0.3 μ M. The percentage inhibition data of the representative compounds of Formula (I) is shown in Table 3.

Table 3 Inhibition of TNF- α Release

Compound no.	IgG stimulation		LPS stimulation	
	At 0.3 μ M	At 1 μ M	At 0.3 μ M	At 1 μ M
6	51.9	83.0	58.0	68.9
152	80.5	82.9	n.d.	n.d.
R406	49.9	87.4	n.d.	n.d.
Dexamethasone	n.d.	n.d.	n.d.	68.4

* n.d.; not determined

3. Cell Viability Assay: RET Inhibition

5 Compounds of the invention are tested for their effects on cell viability in various human cancer cell lines such as MTC-TT to illustrate efficacy of the invention.

The RET proto-oncogene encodes a receptor tyrosine kinase for members of the glial cell line-derived neurotrophic factor family of extracellular signaling molecules. RET loss of function mutations are associated with the development of Hirschsprung's disease, while gain of
10 function mutations are involved in the development of various types of human cancer, including medullary thyroid carcinoma, multiple endocrine neoplasias type 2A (MEN2A) and 2B (MEN2B), pheochromocytoma and parathyroid hyperplasia.

METHODS

15 In order to address RET dependent cell viability, the medullary thyroid carcinoma cell line, MTC-TT representing MEN2A was utilized to test compounds of the invention. MTC-TT were cultured at RPMI containing 15 bovine calf serum (HyclonTM of ThermoTM) and supplemented with 2mM L-Glutamine. The cells were grown at a density of 5×10^4 cells/100 μ L/well in duplicate in 96-well plates for one day and treated with different
20 concentrations of test compound. Cell viability for MTC-TT two days after drug treatment was measured by Cell Titer 96 Aqueous One Solution Reagent (PromegaTM) according to the manufacture instructions. The IC₅₀ value of test compound was calculated at Gradpad Prism 5 unless specified otherwise.

25 RESULTS

As used herein, control used without the presence of an inhibitor indicates 50 inhibition concentration (IC₅₀) of cell viability.

Compounds of Formula (I) exhibited an inhibition range greater than 100 nM at IC₅₀ concentration. Specially, Compounds 8 and 136 of the present invention exhibited an inhibition level greater than those exhibited by Vandetanib and Sunitinib, a widely known kinase inhibitor, in RET induced cancer cell line.

5 For example, Compound 8 of Formula (I), (S)-2-(pyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride, (see table 4) exhibited 6 time higher inhibition in IC₅₀ measurement than those appeared by Vandetanib (AstraZenecaTM) and Sunitinib (PfizerTM), which are an antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR). The IC₅₀
10 inhibition data of the representative compounds of Formula (I) of the present invention is shown in Table 4.

Table 4. Cell Viability by Inhibiting RET kinase

Compound no.	MTC-TT (IC ₅₀ nM)	Compound no.	MTC-TT (IC ₅₀ nM)
8	14	Vandetanib	81.6
136	33	Sunitinib	116.7

4. Cell Viability Assay: Inhibition of FLT3-ITD-Positive Cells

15 Compounds of the invention are tested for their effects on inhibition of FLT3-ITD in human acute leukemia cell line (MV4-11). FLT3 is primarily expressed in immature hematopoietic progenitor as well as in mature myeloid cells. It belongs to type III receptor tyrosine kinase (RTK) family including KIT, FMS, and PDGFR. It is activated by binding to FL, which leads to increased kinase activity and activation of downstream signaling pathway
20 including STAT5, Ras, and PI3Kinase.

The FLT3-ITD (Internal Tandem Duplication) mutations in the juxtamembrane domain are the most frequently observed molecular defect in acute myelogenous leukemia (AML). The FLT3-ITD induces ligand-independent dimerization, autophosphorylation and constitutive activation, and is able to transform hematopoietic cells. Clinically, FLT3-ITD is known to
25 increased leukocytosis, increased blast count, increased relapse rate, decreased disease-free survival, and poor overall survival. Therefore, FLT3-ITD is an attractive molecular target for AML therapy.

METHODS

Compounds of the invention were tested for cell viability effect on MV4-11 cells. For cell viability assay, MV4-11 cells expressing human FLT3-ITD were obtained from the American Type Culture Collection (ATCC, Manassas, VA). This cell line was maintained with an Roswell Park Memorial Institute (RPMI) medium (HyClone™) containing 10 bovine calf serum (BCS; Hyclone™) supplemented iron. The MV4-11 cells were seeded at 2×10^4 cells in 96-well culture plates, and serially diluted compound was then added. After a 72-hour incubation period at 37°C, cell viability was measured using the ATPLite 1step assay (Perkin-Elmer™) that is based on the quantification of ATP from viable cells. CellTiter Aqueous assay (Promega™) was also performed in parallel as an orthogonal assay. IC₅₀ values were calculated using nonlinear regression and defined as the concentration needed for a 50 reduction in luminescence or absorbance treated versus untreated control cells (Prism™ Software).

RESULTS

Compounds of Formula (I) exhibited an inhibition of greater than 10 nM at IC₅₀ concentration. Specially, Compounds 8 and 136 of the present invention exhibited an inhibition level greater than those exhibited by Vandetinib and Sunitinib in FLT3 ITD induced cancer cell line.

For example, Compound 8 of Formula (I), (S)-2-(pyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-d]pyrimidin-5(6H)-one hydrochloride, exhibited 10-30 time higher inhibition in IC₅₀ than those appeared by Sunitinib (Pfizer) and PKC-412(Novartis), widely known antagonists of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR). The IC₅₀ inhibition data of the representative compounds of Formula (I) (e.g., Compound 6 and 136) are shown in Table 5.

Table 5. Cell Viability by FLT3-ITD Induced Cancer Cell Line

Compound no.	MV-4-11 (IC ₅₀ nM)	Compound no.	MV-4-11 (IC ₅₀ nM)
8	0.1	Sunitinib	3.8
136	0.1	PKC-412	11.7

5. Cell Viability Assay: JAK2 Inhibition

Compounds of the invention are tested for their effects on JAK2 inhibition in human erythroleukemic cell line (HEL) to illustrate efficacy at the cellular level. The Janus-associated kinase (JAK) family, comprised of four different protein tyrosine kinases JAK1, JAK2, JAK3, and TYK2, plays an important role in cellular survival, proliferation, and differentiation. A unique mutation in the JAK2 gene encoding a valine-to-phenylalanine substitution, V617F, results in constitutive kinase activity and promotes deregulated hematopoiesis. JAK2 V617F is frequently detected in myeloproliferative disorders (MPDs), a group of clonal hematopoietic stem cell disorders that include polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (IMF), all of which have the potential to transform to acute myeloid leukemia. JAK2 V617F is constitutively phosphorylated and able to activate downstream signaling in the absence of cytokine stimulation.

JAK2 is also a key mediator of signaling, downstream of a variety of cytokine and growth factor receptors. In particular, JAK2 phosphorylate the signal transducers and activators of transcription (STAT) family of proteins. Once phosphorylated, STATs dimerize and translocate to the nucleus where they bind DNA and regulate expression of target genes. JAK2/STAT signaling has been implicated in driving both cell cycle regulation and anti-apoptotic pathways.

METHODS

Compounds of the invention were tested for cell viability effect on HEL cells. For cell viability assay, HEL cells expressing human JAK2 V617F were obtained from the American Type Culture Collection (ATCC, Manassas, VA). This cell line was maintained with an Roswell Park Memorial Institute (RPMI) medium (HyClone™) containing 10 bovine calf serum (BCS; Hyclone™) supplemented iron. The HEL cells were seeded at 2×10^4 cells in 96 well culture plates, and serially diluted compound was then added. After a 72-hour incubation period at 37°C, Cell viability was measured using the ATPLite 1step assay (Perkin-Elmer™) that is based on the quantification of ATP from viable cells. CellTiter Aqueous assay (Promega™) was also performed in parallel as an orthogonal assay. IC₅₀ values were calculated using nonlinear regression and defined as the concentration needed for a 50 reduction in luminescence or absorbance treated versus untreated control cells (Prism™ Software).

RESULTS

Compounds of Formula (I) exhibited an inhibition of greater than 10 nM at IC50 concentration. Specially, compounds 137 and 139 of the present invention exhibited an inhibition level greater than those exhibited by Sorafenib (Bayer), a known kinase inhibitor of Raf, VEGFR and PDGFR in cancer cell line.

For example, Compound 139, 2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one, (see table 6, compound 139) exhibited about 10 time higher inhibition in terms of IC50 measurement than those appeared by Sorafenib (Bayer). The IC50 inhibition data of the representative compounds of Formula (I) of the present invention is shown in Table 6.

Table 6. Cell Viability by Inhibiting JAK2 kinase

Compound no.	HEL (IC50 nM)	Compound no.	HEL (IC50nM)
139	152	Sorafenib	>1000
137	89		

6. Neuroprotection from LRRK2-mediated Dopaminergic Cell Death by Inhibition of LRRK2

Parkinson's disease (PD) is a progressive neurodegenerative disease occurring in about 1 of the population over 65 years old. The degeneration of dopaminergic neurons in the substantia nigra is a major PD pathologic phenotype, resulting in decreased dopamine secretion. During the last decade, more than ten PARK loci were mapped and several genes such as LRRK2, α -synuclein, PINK1, Parkin and DJ-1, have been identified as genes corresponding to these PARK loci.

LRRK2 has been recently identified as a PD causative gene corresponding to the PARK8 locus. LRRK2 is particularly important because symptoms of PD caused by LRRK2 mutations are the most similar to that of idiopathic PD cases. The protein is present largely in the cytoplasm, but also associates with the mitochondrial outer membrane. Expression of mutant LRRK2 induced apoptotic cell death in neuroblastoma cells and in mouse cortical neurons. Some mutations in LRRK2, such as G2019S, have been shown to be associated with PD.

METHODS

SN4741, a murine dopaminergic cell line were cultured in DMEM containing 10 FBS at 37°C, respectively. SN4741 cells (1.5×10^4 /well) were seeded in 48 well plates 1 day before transient transfection with 1 µg of the pcDNA3.1 plasmids of either vector, LRRK wildtype cDNA, LRRK G2019S cDNA, by standard CaCl_2 precipitation. Two days after transfection, cells were treated with 100 µM hydrogen peroxide for 1 day and cell viability was measured by crystal violet assay. For compound treatment, the test compounds were added at 0.05 µM, 0.5 µM and 5µM and the cells were incubated for 1 hour prior to the addition of hydrogen peroxide.

RESULTS

SN4741 cells were transfected with plasmids containing the LRRK2 wild-type or G2019S and incubated them for 2 days followed by addition of 100 µM of hydrogen peroxide for 24 h to sensitize them to oxidative stress. Cell survival was assessed using the crystal violet. As shown in Table 7, after hydrogen peroxide treatment, about 49-51 of cell death in cells transfected with empty vector compared to cells not subjected to oxidative stress. Cells over-expressing LRRK2 wild-type and G2019S showed increased cell death by 35.7-40.4 and 29.1-30.8, respectively, consistent with the previous data that combination of either LRRK2 wild-type or G2019S expression with oxidative stress synergistically increased cell death, with the strongest effect being observed with G2019S.

As shown in Table 7, Compound 6 of Formula (I), which is 2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidine-5(6*H*)-one, and Compound 102, which is 4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one, exhibited increased protective effects against LRRK2-associated cell death in SN4741 cells overexpressing either LRRK2 wild-type or LRRK2 G2019S at 0.05uM and higher as compared with those observed with vector control, DMSO, or H_2O_2 controls.

Table 7. Percent Cell Death

		Compounds	
	Concentration	102	6
Vector	DMSO	49.0	51.7
	0.05uM	50.0	54.2
	0.5uM	54.4	57.5
	5uM	50.5	42.5
LRRK2 WT	DMSO	40.4	35.7

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	0.05uM	49.9	62.2
	0.5uM	55.3	62.2
	5uM	46.5	49.7
LRRK2 G2019S	DMSO	29.4	29.1
	0.05uM	54.9	53.5
	0.5uM	56.0	56.9
	5uM	44.0	45.8
H ₂ O ₂ Control	N.T	51.3	
	DMSO	50.6	

N.T; H₂O₂ treatment only without compound treatment

7. *In Vitro* Kinase Inhibition

5 Up to 518 different kinases have been identified in humans. They act on small molecules such as lipids, carbohydrates, amino acids, and nucleotides. To determine the scope of inhibitory effects of a representative compound of Formula (I) on known kinases, Compound 6 was tested against 104 commercially available kinases (Ambit Biosciences™) *in vitro*. 104 kinases included

10 ABL1(E255K)-phosphorylated, ABL1(T315I)-phosphorylated, ABL1-phosphorylated, ACVR1B, ADCK3, AKT1, AKT2, ALK, AURKA, AURKB, AXL, BMPR2, BRAF, BRAF(V600E), BTK, CDK11, CDK2, CDK3, CDK7, CDK9, CHEK1, CSF1R, CSNK1D, CSNK1G2, DCAMKL1, DYRK1B, EGFR, EGFR(L858R), EPHA2, ERBB2, ERBB4, ERK1, FAK, FGFR2, FGFR3, FLT1, FLT3, FLT4, GSK3B, IGF1R, IKK- α , IKK- β , INSR, JAK2(JH1domain-catalytic), JAK3(JH1domain-catalytic), JNK1, JNK2, JNK3, KIT,

15 KIT(D816V), KIT(V559D,T670I), LKB1, LRRK2, LRRK2(G2019S), MAP3K4, MAPKAPK2, MARK3, MEK1, MEK2, MET, MKNK1, MKNK2, MLK1, MTOR, p38-alpha, p38-beta, PAK1, PAK2, PAK4, PCTK1, PDGFRA, PDGFRB, PDPK1, PIK3C2B, PIK3CA, PIK3CG, PIM1, PIM2, PIM3, PKAC-alpha, PLK1, PLK3, PLK4, PRKCE, PYK2, RAF1, RET, RIOK2, ROCK2, RSK2, SNARK, SRC, SRPK3, SYK, TAK1, TGFBR1, TIE2, TRKA, TSSK1B,

20 TYK2(JH1domain-catalytic), ULK2, VEGFR2, YANK3 and ZAP70.

RESULTS

Inhibition activity of Compound 6 was reported as percent control where lower numbers indicate stronger activities. Table 8 summarizes 29 different kinases whose activity was

25 significantly inhibited by the presence of Compound 6. Conventionally, the percent control of less than 35 is deemed to be significant inhibition of kinase activity as the numeric value 35 is frequently used as a threshold.

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Table 8.**Kinase Inhibition Profile of the Percent Control Less than 35**

Kinase	% inhibition	Kinase	% inhibition
ALK	29	LRRK2	2.2
AURKA	31	LRRK2(G2019S)	2.2
AXL	11	MLK1	2.8
BMPR2	0	PAK4	21
CSF1R	5.2	PDGFRB	19
FAK	34	PLK4	13
FLT3	28	PYK2	32
JAK2	3	RET	16
JAK3	4.4	RSK2	18
JNK1	4.8	SNARK	3.6
JNK2	25	SRPK3	2.6
JNK3	7	SYK	8.4
KIT	11	TAK1	1
KIT(D816V)	9.3	TYK2	16
LKB1	18		

8. Growth Inhibition of Cancer Cell Lines

5 The compounds of the invention exhibited potent inhibition of various cancer cell lines. The National Institute of Health (NIH) 60 cell lines (U.S. Department of Health & Human Services) were used to test the compounds. The tested cancer cell lines include, for example, CCRF-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226, SR, A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522, COLO 205, HCC-2998, 10 HCT-116, HCT-15, HT29, KM12, SW-620, SF-268, SF-295, SF-539, SNB-19, SNB-75, U251, LOX IMVI, MALME-3M, M14, MDA-MB-435, SK-MEL-28, SK-MEL-5, UACC-257, UACC-62, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, NCI/ADR-RES, SK-OV-3, 786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, UO-31, PC-3, DU-145, MCF7, MDA-MB-231/ATCC, HS 578T, BT-549, T-47D, and MDA-MB-468.

15

RESULTS

Compound 6 was tested for its potency in growth inhibition (IC₅₀) and cytotoxicity (LC₅₀) toward listed NIH 60 cell lines. Compound 6 exhibited potency of nM to μ M concentration range. As shown in Table 9, Compound 6 repressed proliferation of cell lines

associated with leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer.

Table 9. Cell Viability and Inhibition by Compound 6 (Molar Concentration)

Cancer type	Cell line	GI50	IC50	LC50	TGI
Leukemia	CCRF-CEM	2.09E-06	4.07E-06	0.0001	0.0001
Leukemia	HL-60(TB)	8.71E-07	1.86E-06	0.0001	5.01E-06
Leukemia	K-562	3.16E-06	3.98E-06	0.0001	0.0001
Leukemia	MOLT-4	2.24E-06	3.63E-06	0.0001	7.76E-06
Leukemia	RPMI-8226	2.95E-06	5.5E-06	0.0001	9.12E-05
Leukemia	SR	7.08E-07	2.51E-06	0.0001	2.69E-05
NSCLC	A549/ATCC	3.80E-06	6.31E-06	0.0001	0.0001
NSCLC	EKVX	2.88E-06	7.59E-06	0.0001	1.2E-05
NSCLC	HOP-62	4.37E-06	8.91E-06	7.94E-05	1.86E-05
NSCLC	HOP-92	1.00E-04	0.0001	0.0001	0.0001
NSCLC	NCI-H226	3.24E-06	8.32E-06	0.0001	1.78E-05
NSCLC	NCI-H23	3.24E-06	6.92E-06	5.01E-05	1.38E-05
NSCLC	NCI-H322M	2.29E-06	2.14E-05	0.0001	2.88E-05
NSCLC	NCI-H460	1.62E-06	2.4E-06	6.46E-05	1.51E-05
NSCLC	NCI-H522	2.34E-06	7.59E-06	3.47E-05	0.00001
Colon Cancer	COLO 205	3.09E-06	5.25E-06	4.57E-05	1.45E-05
Colon Cancer	HCC-2998	1.12E-05	2.51E-05	0.0001	3.8E-05
Colon Cancer	HCT-116	8.71E-07	1.32E-06	7.59E-05	1.23E-05
Colon Cancer	HCT-15	5.37E-07	7.59E-07	0.0001	3.16E-05
Colon Cancer	HT29	3.89E-06	7.08E-06	0.0001	9.55E-05
Colon Cancer	KM12	1.45E-06	2.69E-06	2.4E-05	5.37E-06
Colon Cancer	SW-620	1.91E-06	2.82E-06	7.41E-05	1.29E-05
CNS Cancer	SF-268	3.09E-06	1.29E-05	0.0001	3.55E-05
CNS Cancer	SF-295	2.95E-06	6.76E-06	5.62E-05	7.76E-06
CNS Cancer	SF-539	5.25E-06	1.35E-05	0.0001	3.89E-05
CNS Cancer	SNB-19	1.82E-05	6.46E-05	0.0001	0.0001
CNS Cancer	SNB-75	5.75E-06	7.76E-05	0.0001	8.13E-05
CNS Cancer	U251	6.17E-06	1.17E-05	0.0001	0.0001
Melanoma	LOX IMVI	1.41E-06	2.63E-06	9.12E-05	1.66E-05
Melanoma	MALME-3M	2.63E-06	9.77E-06	3.24E-05	7.94E-06
Melanoma	M14	1.55E-06	3.31E-06	3.24E-05	8.32E-06
Melanoma	MDA-MB-435	1.29E-06	2.57E-06	9.77E-06	3.55E-06
Melanoma	SK-MEL-28	4.68E-06	1.1E-05	5.01E-05	1.74E-05
Melanoma	SK-MEL-5	1.23E-06	2.14E-06	5.13E-06	2.51E-06

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Melanoma	UACC-257	4.27E-06	8.71E-06	4.57E-05	1.29E-05
Melanoma	UACC-62	1.82E-06	3.98E-06	2.75E-05	6.92E-06
Ovarian Cancer	OVCAR-3	1.35E-06	3.63E-06	4.68E-05	3.98E-06
Ovarian Cancer	OVCAR-4	1.74E-06	9.12E-06	0.0001	3.63E-05
Ovarian Cancer	OVCAR-5	2.82E-05	7.41E-05	0.0001	9.33E-05
Ovarian Cancer	OVCAR-8	3.31E-06	5.01E-06	0.0001	4.07E-05
Ovarian Cancer	NCI/ADR-RES	2.34E-06	4.37E-06	0.0001	7.41E-06
Ovarian Cancer	SK-OV-3	4.90E-07	2E-05	0.0001	0.0001
Renal Cancer	786-0	2.04E-06	8.13E-06	0.0001	0.0001
Renal Cancer	A498	2.51E-06	0.0001	0.0001	0.0001
Renal Cancer	ACHN	7.08E-07	2.24E-06	0.0001	8.51E-05
Renal Cancer	CAKI-1	2.82E-07	1.29E-06	0.0001	6.31E-06
Renal Cancer	RXF 393	1.45E-06	2.14E-05	0.0001	2.34E-05
Renal Cancer	SN12C	4.07E-06	1.29E-05	0.0001	0.0001
Renal Cancer	TK-10	6.03E-06	3.63E-05	0.0001	4.47E-05
Renal Cancer	UO-31	7.76E-07	1.62E-05	0.0001	2.29E-05
Prostate Cancer	PC-3	2.29E-06	4.68E-06	9.33E-05	1.29E-05
Prostate Cancer	DU-145	1.55E-06	6.03E-06	0.0001	1.95E-05
Breast Cancer	MCF7	2.82E-06	4.07E-06	0.0001	1.26E-05
Breast Cancer	MDA-MB-231/ATCC	1.23E-05	0.0001	0.0001	0.0001
Breast Cancer	HS 578T	1.95E-06	4.37E-05	0.0001	1.41E-05
Breast Cancer	BT-549	1.58E-06	4.57E-06	1.41E-05	4.37E-06
Breast Cancer	T-47D	3.09E-06	8.51E-06	0.0001	2.63E-05
Breast Cancer	MDA-MB-468	1.78E-06	4.68E-06	0.0001	7.08E-06

*NSCLC: Non-Small Cell Lung Cancer; GI, growth inhibition; LC, lethal concentration; TGI, total growth inhibition.

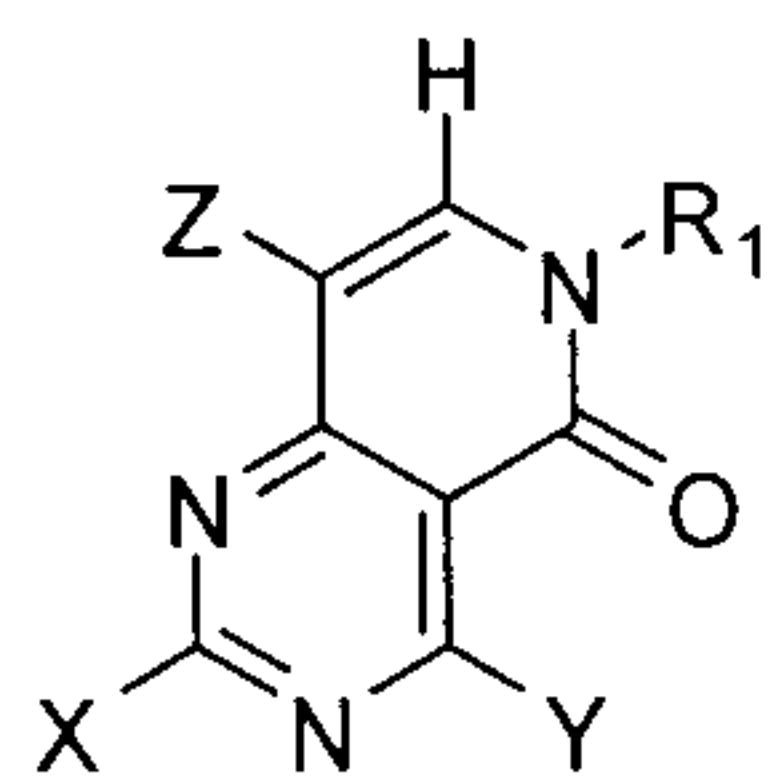
5 While this invention has been particularly shown and described to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

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CLAIMS

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein: (a) when R¹ is H and X is NR²R³ or NR⁴R⁵, then

Y is NHR⁶ and

Z is selected from H, halogen, C₁-C₃ alkyl, C₂-C₄ alkynyl, aryl, heteroaryl, or C₃-C₈ cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl or heteroaryl is optionally substituted with halo, alkyl, or cyano; wherein:

R² and R³, taken together with the nitrogen atom to which they are bonded form:

- i) a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R² and R³ are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is independently substituted at one or more carbon atoms with 1-2 R⁷ and optionally substituted at one or more carbon atoms with 0-4 R⁸, wherein R⁷ is hydroxy, heterocycloalkyl, or NR⁹R⁹ and R⁸ is hydroxy(C₁-C₆)alkyl, aryl, COOR⁹, (CH₂)_nNR⁹R⁹, or (CH₂)_nNR⁹R¹⁰, wherein each n is independently 1, 2, or 3 and the aryl is optionally substituted with halo; or
- ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone;

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each R^9 is independently selected from H, C_1 - C_6 alkyl, C_3 - C_6 alkynyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_3 - C_6 cycloalkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, aryl, aryl(C_1 - C_6) alkyl, or heteroaryl, wherein the alkyl, alkynyl, alkylcyano, alkylsulfone, sulfonamide, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, or heteroaryl is optionally substituted with R^{25} ;

R^{10} is $C(O)R^9$, $COOR^9$, $C(O)NR^9R^9$, or $S(O)_nR^9$, wherein n is 1 or 2;

R^4 is selected from H, C_1 - C_6 alkyl, or hydroxy(C_1 - C_6)alkyl;

R^5 is aryl(C_1 - C_3)alkyl, wherein the aryl group is independently substituted at one or more carbon atoms with 1-3 R^{11} , wherein R^{11} is independently selected from OR^9 , NR^9R^9 , NR^9COR^9 , or $NR^9S(O)_nR^9$, wherein n is 1 or 2;

R^6 is selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, or heteroaryl, wherein the heterocycloalkyl, aryl, or heteroaryl is optionally substituted, wherein the heterocycloalkyl, aryl, or heteroaryl of R^6 is optionally substituted with an aryl selected from the group consisting of:

- i) a 5-6 membered monocyclic aryl group;
- ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone;
- iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone;
- and
- iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carbonyl, carboxamide, or sulfoxamide; or

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the heterocycloalkyl, aryl, or heteroaryl of R^6 is optionally substituted at one or more carbon atoms with R^{12} , wherein each R^{12} is independently selected from C_1 - C_6 alkyl, CF_3 , OCF_3 , $S(O)_n(C_1$ - $C_4)$ alkyl, halo(C_1 - C_4)alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl (C_1 - C_6)alkyl, heteroaryl, halo, haloalkyl, SR^{13} , OR^{13} , $OC(O)R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $COOR^{13}$, NO_2 , CN , $C(O)R^{13}$, $C(O)C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$, or $NR^{15}R^{16}$, wherein each n is independently 1 or 2 and the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} ,

wherein the aryl and heteroaryl of R^{12} is independently selected from:

- i) a 5-6 membered monocyclic aryl group;
- ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide or sulfone;
- iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently nitrogen, oxygen, sulfur, sulfoxide or sulfone; or
- iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carbonyl, carboxamide, or sulfoxamide;

each R^{13} is independently selected from H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, haloalkyl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkyl cyano, alkyl sulfone, alkyl sulfonamide, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} ;

R^{14} is $C(O)R^{13}$, $COOR^{13}$, $C(O)NR^{13}R^{13}$, $SO_2NR^{13}R^{13}$, or $S(O)_nR^{13}$, wherein n is 1 or 2;

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R^{15} and R^{16} , taken together with the nitrogen atom to which they are bonded, form:

- i) a 3-8 membered saturated or partially saturated monocyclic group, wherein the 3-8 membered saturated or partially saturated monocyclic group is optionally substituted with R^{25} ;
- ii) an 8-12 membered saturated or partially saturated bicyclic group, wherein the 8-12 membered saturated or partially saturated bicyclic group is optionally substituted with R^{25} ;
- iii) a 3-8 membered saturated or partially saturated monocyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein the 3-8 membered saturated or partially saturated monocyclic group having 1-2 heteroatoms is optionally substituted with R^{13} or R^{14} ; or
- iv) a 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone, sulfoxide, wherein the 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms is optionally substituted with R^{13} or R^{14} ;

(b) when R^1 is H and Y is NHR^{17} or R^{17} , then

X is OR^{18} , NHR^{18} , $NR^{15}R^{16}$, $NR^{18}R^{19}$, or $NR^{19}R^{20}$; and

Z is H, halogen, C_1 - C_3 alkyl, C_2 - C_4 alkynyl, aryl, heteroaryl, or C_3 - C_8 cycloalkyl, wherein the alkyl, alkynyl, cycloalkyl, aryl, or heteroaryl is optionally substituted with halo, alkyl, or cyano, wherein:

R^{17} is selected from aryl(C_1 - C_6)alkyl, aryl, or heteroaryl, wherein the aryl, or the heteroaryl is substituted at one or more carbon atoms with at least one R^{21} and 0-2 R^{22} and the aryl group of said aryl(C_1 - C_6)alkyl is optionally substituted with halo;

R^{21} is independently selected from OH, CF_3 , OCF_3 , O-aryl, or $NR^{15}R^{16}$;

R^{22} is independently H, C_1 - C_6 alkyl, CF_3 , OCF_3 , $S(O)_n(C_1$ - $C_4)$ alkyl, halo(C_1 - C_4)alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8

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heterocycloalkyl, C₄-C₆ cycloalkenyl, aryl, aryl(C₁-C₆)alkyl, heteroaryl, halo, SR¹³, OR¹³, OC(O)R¹³, NR¹³R¹³, NR¹³R¹⁴, COOR¹³, NO₂, CN, C(O)R¹³, C(O)C(O)R¹³, C(O)NR¹³R¹³, S(O)_nR¹³, S(O)_nNR¹³R¹³, NR¹³C(O)NR¹³R¹³, NR¹³C(O)R¹³, NR¹³(COOR¹³), NR¹³S(O)_nR¹³, or NR¹⁵R¹⁶, wherein each n is independently 1 or 2 and wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R²⁵;

R¹⁸ is selected from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₈ heterocycloalkyl, C₄-C₆ cycloalkenyl, aryl, aryl(C₁-C₆)alkyl, hydroxy(C₂-C₆)alkyl, amino(C₂-C₆)alkyl, haloalkyl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R²⁵;

each R¹⁹ is independently selected from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ alkynyl, hydroxy(C₂-C₆)alkyl, amino(C₂-C₆)alkyl, C₂-C₆ alkyl cyano, C₂-C₆ alkyl sulfone, C₂-C₆ sulfonamide, C₃-C₆ cycloalkyl, C₃-C₈ heterocycloalkyl, C₄-C₆ cycloalkenyl, aryl, aryl(C₁-C₆)alkyl, haloalkyl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkyl cyano, alkylsulfone, sulfonamide, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R²⁵;

R²⁰ is C(O)R¹⁹ COOR¹⁹, C(O)NR¹⁹R¹⁹ or S(O)_nR¹⁹, wherein n is 1 or 2;

each R²⁵ is independently selected from hydroxy, hydroxy(C₁-C₆)alkyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₈ heterocycloalkyl, C₄-C₆ cycloalkenyl, aryl(C₁-C₆)alkyl, aryl, halo, haloalkyl, oxo, oxime, CF₃, SR¹³, OCF₃, OR¹³, OC(O)CH₂R¹³, NR¹³R¹³, NR¹³R¹⁴, NHC(O)R¹³, (CH₂)_nNR¹³R¹³, COOR¹³, CN, C(O)R¹³, C(O)CF₃, CONR¹⁵R¹⁶, CONH₂, S(O)_nR¹³, S(O)_nNR¹³R¹³, or NR¹⁵R¹⁶, wherein each n is independently 1 or 2 and the heterocycloalkyl is optionally substituted with C₁-C₃ alkyl; and

(c) when R¹ is CH₃, then

X is NH₂ or NHR⁶,

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Y is NHR^6 or R^6 , and

Z is H, halogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_2\text{-C}_4$ alkynyl, aryl, heteroaryl, or $\text{C}_3\text{-C}_8$ cycloalkyl, wherein the alkyl, cycloalkyl, aryl, alkynyl, or heteroaryl is optionally substituted with halo, alkyl, or cyano, or

a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein R^1 is H and X is NR^2R^3 or wherein R^1 is H and X is NR^4R^5 , or wherein Z is H, halo, $\text{C}_1\text{-C}_3$ alkyl, alkynyl or phenyl.
3. The compound of Claim 2, wherein NR^2R^3 is a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R^2 and R^3 are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is independently substituted at one or more carbon atoms with 1-2 R^7 and optionally substituted at one or more carbon atoms with 0-4 R^8 , wherein R^7 is hydroxy, heterocycloalkyl, or NR^9R^9 and R^8 is hydroxy($\text{C}_1\text{-C}_6$)alkyl, aryl, COOR^9 , $(\text{CH}_2)_n\text{NR}^9\text{R}^9$, or $(\text{CH}_2)_n\text{NR}^9\text{R}^{10}$, wherein each n is independently 1, 2, or 3 and the aryl is optionally substituted with halo or wherein NR^2R^3 is selected from an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone, or wherein Y is NHR^6 .
4. The compound of Claim 3, wherein the 3-8 membered saturated or partially saturated monocyclic group is substituted with hydroxy or amine.
5. The compound of Claim 4, wherein the 3-8 membered saturated or partially saturated monocyclic group is azetidine, piperidine or pyrrolidine, wherein the azetidine, piperidine or pyrrolidine is independently substituted with 1-3 hydroxy or amino group and optionally and independently substituted with hydroxymethyl at the one or more carbon atoms.
6. The compound of Claim 2, wherein R^4 is selected from H, $\text{C}_1\text{-C}_6$ alkyl, or hydroxy($\text{C}_1\text{-C}_6$) alkyl and R^5 is aryl($\text{C}_1\text{-C}_3$)alkyl, wherein the aryl group of aryl($\text{C}_1\text{-C}_3$)alkyl of R^5

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is independently substituted at the one or more carbon atoms with 1-3 R^{11} , wherein R^{11} is independently selected from OR^9 , NR^9R^9 , NR^9COR^9 , or $NR^9S(O)_nR^9$, wherein n is 1 or 2.

7. The compound of Claim 3, wherein R^9 is independently selected from H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_3 - C_6 alkyl sulfone, C_3 - C_6 cycloalkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, haloalkyl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkyl cyano, alkyl sulfone, sulfonamide, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} .
8. The compound of Claim 3, wherein R^6 is selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} .
9. The compound of Claim 8, wherein the aryl of R^6 is an optionally substituted aryl selected from the group consisting of:
 - i) a 5-6 membered monocyclic aryl group;
 - ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone;
 - iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide or sulfone; and
 - iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carbonyl, carboxamide, or sulfoxamide,
 or wherein R^6 is the optionally substituted 5-6 membered monocyclic aryl group or 9-10 membered bicyclic aryl group.

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10. The compound of Claim 9, wherein the aryl of R^6 is optionally substituted at one or more carbon atoms with R^{12} , wherein each R^{12} is independently selected from C_1 - C_6 alkyl, OCF_3 , CF_3 , $S(O)_n(C_1-C_4)alkyl$, $halo(C_1-C_4)alkyl$, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl C_1 - C_6 alkyl, heteroaryl, halo, haloalkyl, SR^{13} , OR^{13} , $OC(O)R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $COOR^{13}$, NO_2 , CN , $C(O)R^{13}$, $C(O)C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$, or $NR^{15}R^{16}$, wherein each n is independently 1 or 2; and wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} .
11. The compound of Claim 10, wherein R^{12} is independently selected from C_1 - C_6 alkyl, CF_3 , OCF_3 , $S(O)_n(C_1-C_4)alkyl$, $halo(C_1-C_4)alkyl$, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, heteroaryl, halo, SR^{13} , OR^{13} , $OC(O)R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $COOR^{13}$, NO_2 , CN , $C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$, or $NR^{15}R^{16}$, wherein each n is independently 1 or 2.
12. The compound of Claim 11, wherein R^{12} is an aryl and the aryl is independently selected from:
 - i) a 5-6 membered monocyclic aryl group;
 - ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone;
 - iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently nitrogen, oxygen, sulfur, sulfoxide, or sulfone; or
 - iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carboxamide, or sulfoxamide.
13. The compound of Claim 11, wherein R^{12} is SR^{13} , OR^{13} , $OC(O)R^{13}$, $NR^{13}R^{13}$, $NR^{13}R^{14}$, $COOR^{13}$, CN , $C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $S(O)_nR^{13}$, $S(O)_nNR^{13}R^{13}$, or $NR^{15}R^{16}$, wherein each R^{13} is independently selected from H , C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_2 - C_6 alkylcyano, C_2 - C_6 alkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, alkoxy, aryl(C_1 - C_6)alkyl, haloalkyl, or

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heteroaryl and R^{14} is $C(O)R^{13}$, $COOR^{13}$, $C(O)NR^{13}R^{13}$, $SO_2NR^{13}R^{13}$, or $S(O)_nR^{13}$, wherein n is 1 or 2 and the alkyl, alkenyl, alkynyl, alkyl cyano, alkyl sulfone, alkyl sulfonamide, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, alkoxy, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} .

14. The compound Claim 13, wherein R^{12} is $NR^{15}R^{16}$.
15. The compound Claim 14, wherein R^{15} and R^{16} , taken together with the nitrogen atom to which they are bonded, form:
 - i) a 3-8 membered saturated or partially saturated monocyclic group, wherein the 3-8 membered saturated or partially saturated monocyclic group is optionally substituted with R^{25} ;
 - ii) an 8-12 membered saturated or partially saturated bicyclic group, wherein the 8-12 membered saturated or partially saturated bicyclic group is optionally substituted with R^{25} ;
 - iii) a 3-8 membered saturated or partially saturated monocyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein the 3-8 membered saturated or partially saturated monocyclic group having 1-2 heteroatoms is optionally substituted with R^{13} or R^{14} ; or
 - iv) an 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone, sulfoxide, wherein the 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms is optionally substituted with R^{13} or R^{14} .
16. The compound of Claim 9, wherein the optionally substituted 5-6 membered monocyclic aryl group is phenyl and 9-10 membered bicyclic aryl group is naphthyl, quinolinyl, indazolyl, indolyl, or dihydrobenzodioxynyl.
17. The compound of Claim 16, wherein the phenyl group is optionally substituted with 1-4 groups selected from the group consisting of methyl, methoxy, methylsulfone, amino, hydroxy, CF_3 , OCF_3 , halo, phenyl, phenoxy, piperazinyl, and morpholino.
18. The compound of Claim 1, wherein R^1 is H and Y is NHR^{17} or R^{17} .
19. The compound of Claim 18, wherein X is NHR^{18} or OR^{18} or wherein

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X is $\text{NR}^{18}\text{R}^{19}$, or wherein

X is $\text{NR}^{19}\text{R}^{20}$, or wherein

X is $\text{NR}^{15}\text{R}^{16}$.

20. The compound of Claim 18, wherein R^{17} is aryl($\text{C}_1\text{-C}_6$)alkyl, aryl or heteroaryl, wherein the aryl or the heteroaryl of R^{17} is substituted at two or more carbon atoms with at least one R^{21} and 0-2 R^{22} , wherein R^{21} is independently selected from OH, CF_3 , OCF_3 , O-aryl, or $\text{NR}^{15}\text{R}^{16}$ and R^{22} is independently selected from H, $\text{C}_1\text{-C}_6$ alkyl, CF_3 , OCF_3 , $\text{S}(\text{O})_n(\text{C}_1\text{-C}_4)\text{alkyl}$, halo($\text{C}_1\text{-C}_4$)alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_8$ heterocycloalkyl, $\text{C}_4\text{-C}_6$ cycloalkenyl, aryl, aryl $\text{C}_1\text{-C}_6$ alkyl, heteroaryl, halo, haloalkyl, SR^{13} , OR^{13} , $\text{OC}(\text{O})\text{R}^{13}$, $\text{NR}^{13}\text{R}^{13}$, $\text{NR}^{13}\text{R}^{14}$, COOR^{13} , NO_2 , CN, $\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{13}$, $\text{S}(\text{O})_n\text{R}^{13}$, $\text{S}(\text{O})_n\text{NR}^{13}\text{R}^{13}$, or $\text{NR}^{15}\text{R}^{16}$, wherein each n is independently 1 or 2; and wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, heteroarylalkyl, or heteroaryl is optionally substituted with R^{25} ; and wherein the aryl group of said aryl($\text{C}_1\text{-C}_6$)alkyl is optionally substituted with halo.
21. The compound of Claim 20, wherein the aryl of O-aryl is independently selected from:
- i) a 5-6 membered monocyclic aryl group;
 - ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide or sulfone;
 - iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently nitrogen, oxygen, sulfur, sulfoxide or sulfone; or
 - iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carboxamide or sulfoxamide,

or wherein

the aryl of R^{17} is a 5-6 membered monocyclic aryl group substituted with at least one group selected from CF_3 , OCF_3 , O-aryl, or $\text{NR}^{15}\text{R}^{16}$ at the one or more carbon atoms.

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22. The compound of Claim 21, wherein when the aryl of R^{17} is a 5-6 membered monocyclic aryl group substituted with at least one group selected from CF_3 , OCF_3 , O-aryl, or $NR^{15}R^{16}$ at the one or more carbon atoms, the monocyclic aryl group is phenyl substituted with at least one group selected from CF_3 , OCF_3 , O-aryl, or $NR^{15}R^{16}$ at the one or more carbon atoms.
23. The compound of Claim 19, wherein $NR^{15}R^{16}$ is morpholino, piperazinyl, homopiperazinyl, thiomorpholino, piperidinyl, or pyrrolidinyl, wherein the piperazinyl, homopiperazinyl, piperidinyl, or pyrrolidinyl is optionally substituted at one or more carbon atoms with 1, 2 or 3 R^{25} or at one nitrogen atom with R^{13} or R^{14} .
24. The compound of Claim 19, wherein, when X is NHR^{18} or OR^{18} , R^{18} is selected from C_1 - C_6 alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_8 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, haloalkyl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, arylalkyl, haloalkyl, or heteroaryl is optionally substituted with R^{25} .
25. The compound of Claim 24, wherein R^{18} is C_1 - C_6 alkyl optionally substituted with one or more aryl, alkyl, halo, R^{23} or R^{24} , wherein each R^{23} is independently CF_3 , OCF_3 , SR^{13} , OR^{13} , $NR^{13}R^{13}$, $S(O)_nNR^{13}R^{13}$, $S(O)_nR^{13}$, or $NR^{15}R^{16}$, each of n being independently 1 or 2 and wherein each R^{24} is selected from a 5-8 membered monocyclic group having 1-3 heteroatoms, an 8-12 membered bicyclic group having 1-5 heteroatoms, or an 11-14 membered tricyclic group having 1-8 heteroatoms, wherein said heteroatoms of R^{24} are independently oxygen, nitrogen, or sulfur, wherein R^{24} is optionally substituted with R^{13} or R^{14} .
26. The compound of Claim 25, wherein zero, one, two, three or four atoms of R^{24} are optionally and independently substituted with R^{13} , or wherein

the aryl is optionally and independently substituted at one or more carbon atoms with 1-3 R^{11} , wherein R^{11} is independently selected from OR^9 , NR^9R^9 , NR^9COR^9 , or $NR^9S(O)_nR^9$, wherein n is 1 or 2, or wherein

the C_1 - C_6 alkyl is C_2 - C_4 alkyl optionally substituted with 1-3 groups selected from the group consisting of amino, hydroxy, phenyl, benzyl, and morpholino.

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27. The compound of Claim 24, wherein R^{18} is C_3 - C_6 alkenyl optionally substituted with one or more, aryl, alkyl, halo, R^{23} , or R^{24} , wherein each R^{23} is independently selected from CF_3 , OCF_3 , SR^{13} , OR^{13} , $NR^{13}R^{13}$, $S(O)_nNR^{13}R^{13}$, $S(O)_nR^{13}$, or $NR^{15}R^{16}$, wherein each n is independently 1 or 2, and wherein each R^{24} is independently selected from: a 5-8 membered monocyclic group having 1-3 heteroatoms; an 8-12 membered bicyclic having 1-5 heteroatoms; or an 11-14 membered tricyclic group having 1-8 heteroatoms, wherein said heteroatoms of R^{24} is independently selected from oxygen, nitrogen or sulfur, and wherein R^{24} is optionally substituted with R^{13} or R^{14} .
28. The compound of Claim 27, wherein zero, one, two, three or four atoms of R^{24} are optionally and independently substituted with R^{13} .
29. The compound of Claim 24, wherein R^{18} is C_3 - C_6 cycloalkyl optionally substituted with one or more, aryl, alkyl, halo, R^{23} or R^{24} ; wherein each R^{23} is independently selected from CF_3 , OCF_3 , SR^{13} , OR^{13} , $NR^{13}R^{13}$, $(CH_2)_nNR^{13}R^{13}$, $S(O)_nNR^{13}R^{13}$, $S(O)_nR^{13}$, or $NR^{15}R^{16}$, wherein each n is independently 1 or 2; and wherein each R^{24} is independently selected from a 5-8 membered monocyclic group having 1-3 heteroatoms, an 8-12 membered bicyclic group having 1-5 heteroatoms, or an 11-14 membered tricyclic group having 1-8 heteroatoms, wherein said heteroatoms of R^{24} is independently selected from oxygen, nitrogen or sulfur, and wherein R^{24} is optionally substituted with R^{13} or R^{14} .
30. The compound of Claim 29, wherein zero, one, two, three or four atoms of R^{24} are optionally and independently substituted with R^{13} .
31. The compound of Claim 18, wherein when X is $NR^{18}R^{19}$, R^{18} is C_3 - C_6 cycloalkyl optionally substituted with one or more aryl, alkyl, halo, R^{23} , or R^{24} , or wherein when X is $NR^{18}R^{19}$, R^{19} is independently selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 alkynyl, hydroxy(C_2 - C_6)alkyl, amino(C_2 - C_6)alkyl, C_2 - C_6 alkyl cyano, C_2 - C_6 alkyl sulfone, C_2 - C_6 sulfonamide, C_3 - C_6 cycloalkyl, C_4 - C_6 heterocycloalkyl, C_4 - C_6 cycloalkenyl, aryl, aryl(C_1 - C_6)alkyl, haloalkyl, or heteroaryl.
32. The compound of Claim 24, wherein R^{18} is C_3 - C_8 heterocycloalkyl, wherein the C_3 - C_8 heterocycloalkyl is a 5-7 membered monocycle having a heteroatom, wherein said

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heteroatom is independently selected from oxygen, nitrogen, sulfur, or sulfone;
wherein the nitrogen atom is optionally substituted with R¹⁹.

33. The compound of Claim 32, wherein the monocycle is optionally substituted morpholine, tetrahydrofuran, thiomorpholine, piperazine or homopiperazine.
34. The compound of Claim 19, wherein, when X is NR¹⁹R²⁰, R¹⁹ is independently selected from hydroxy(C₂-C₆)alkyl, amino(C₂-C₆)alkyl, C₂-C₆ alkyl cyano, C₂-C₆ alkyl sulfone, C₂-C₆ sulfonamide, C₃-C₆ cycloalkyl, or C₄-C₈ heterocycloalkyl, or wherein when X is NR¹⁹R²⁰, R²⁰ is selected from C(O)R¹⁹, COOR¹⁹, C(O)NR¹⁹R¹⁹, or S(O)_nR¹⁹, wherein n is 1 or 2.
35. The compound of Claim 19, wherein, when X is NR¹⁵R¹⁶, R¹⁵ and R¹⁶ of NR¹⁵R¹⁶, taken together with the nitrogen atom to which they are bonded, form:
 - i) a 3-8 membered saturated or partially saturated monocyclic group, wherein the 3-8 membered saturated or partially saturated monocyclic group is optionally substituted with R²⁵;
 - ii) an 8-12 membered saturated or partially saturated bicyclic group, wherein the 8-12 membered saturated or partially saturated bicyclic group is optionally substituted with R²⁵;
 - iii) a 3-8 membered saturated or partially saturated monocyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein the 3-8 membered saturated or partially saturated monocyclic group having 1-2 heteroatoms is optionally substituted with R¹³ or R¹⁴; or
 - iv) an 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone, sulfoxide, wherein the 8-12 membered saturated or partially saturated bicyclic group having 1-3 heteroatoms is optionally substituted with R¹³ or R¹⁴.
36. The compound of Claim 35, wherein NR¹⁵R¹⁶ is the 4-6 membered saturated monocyclic group optionally and independently substituted at one or more carbon atoms with 1-4 R²⁵, or wherein

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NR¹⁵R¹⁶ is a 5-8 membered saturated heterocyclic group having 1-2 heteroatoms selected from nitrogen, oxygen, sulfur, sulfone, or sulfoxide, wherein said 5-8 membered saturated heterocyclic group is optionally substituted with hydroxy, amino, C₁-C₆ alkyl, or phenyl at one or more carbon atoms or nitrogen atoms.

37. The compound of Claim 36, wherein the aryl group of R²⁵ is selected from:

- i) a 5-6 membered monocyclic aryl group;
- ii) an 8-10 membered bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide or sulfone;
- iii) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, sulfoxide, or sulfone; or
- iv) an 8-10 membered unsaturated or partially unsaturated bicyclic aryl group having a carbonyl, carboxamide, or sulfoxamide,

or wherein

the 4-6 membered saturated monocyclic group is selected from piperidine or pyrrolidine optionally substituted with 1-4 groups selected from hydroxy, amino, C₁-C₆ alkyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, or phenyl.

38. The compound of Claim 36, wherein the 5-8 membered saturated heterocyclic group is selected from morpholine, thiomorpholine, piperazine or homopiperazine optionally substituted with 1-4 groups selected from hydroxy, amino, C₁-C₆ alkyl and phenyl, wherein each C₁-C₆ alkyl is optionally substituted with one or more amino, or hydroxyl, or wherein

the 1-2 heteroatoms are nitrogen and nitrogen atoms are independently substituted with C₁-C₆ alkyl, C(O) C₁-C₃ alkyl, or S(O)₂C₁-C₃ alkyl, wherein the alkyl is optionally and independently substituted with amino or hydroxy.

39. The compound of Claim 1, wherein R¹ is methyl, X is selected from NH₂ or NHR⁶, and Y is selected from R⁶ or NHR⁶.

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40. A compound selected from:

4-(3,5-dimethoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-6(6*H*)-one;

4-(3,5-dimethoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3,5-dimethoxyphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

4-(3,5-dimethoxyphenylamino)-2-(4-morpholinopiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

methyl 1-(4-(3,5-dimethoxyphenyl amino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)-4-hydroxy piperidine-4-carboxylate;

2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidine-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*S*)-2-(pyrrolidin-3-ylamino)-4-(4-trifluoromethylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,4*R*)-4-aminocyclohexyl amino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

2-(2-morpholinoethoxy)-4-(3-(trifluoro methyl)phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(4-methylpiperazin-1-yl)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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2-(3,4-dihydroisoquinolin-2(1H)-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(3-hydroxypyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(piperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(4-hydroxypiperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

N-(2-((5-oxo-4-(3-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide;

(*S*)-2-(3-hydroxypyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

N-(1-(5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)piperidin-4-yl)cyclopropanesulfonamide;

2-(piperidin-4-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*S*)-2-(3-aminopyrrolidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-morpholino-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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2-((1*R*,4*R*)-4-hydroxycyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-oxopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(3-(3-(trifluoromethyl)phenyl)-6,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrazin-5(4*H*)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(cyclopropylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(cyclopentylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(pyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(benzylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(benzyl(methyl)amino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*S*)-2-(1-(4-fluorophenyl)ethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((tetrahydro-2*H*-pyran-4-yl)methylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-fluorobenzylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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2-(piperidin-4-ylmethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(tetrahydro-2*H*-pyran-4-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(1,4-diazepan-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(thiazolidin-3-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

N-(2-((5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide;

(*S*)-2-(1-cyclohexylethylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(cyclohexylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(1-methylpyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(1-isopropylpyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1-methylpiperidin-4-yl)methylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1-isopropylpiperidin-4-yl)methylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-((dimethylamino)methyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-methylthiazol-2-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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(*S*)-2-(1-(methylsulfonyl)pyrrolidin-3-ylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(2-hydroxyethyl)piperazin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

ethyl 1-(5-oxo-4-(4-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)piperidine-4-carboxylate;

2-(4-(4-(2-hydroxyethyl)piperazine-1-carbonyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(4-(hydroxymethyl)piperidine-1-carbonyl)piperidin-1-yl)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*S*,2*R*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*S*,2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,4*R*)-4-aminocyclohexylamino)-4-(2-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-ethylpiperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(2-morpholinoethylamino)-4-(3(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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2-(3-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(methylsulfonyl)piperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(morpholinoamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-acetylpiperazin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(2-hydroxy-1-phenylethylamino)-4-(3-(trifluoromethyl)phenylaminopyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*S*)-2-(2-hydroxy-1-phenylethylamino)-4-(3-(trifluoromethyl)phenylaminopyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(1-hydroxy-3-phenylpropan-2-ylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*S*)-2-(1-hydroxy-3-phenylpropan-2-yl amino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

1-(5-oxo-4-(3-(trifluoromethyl)phenyl amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)piperidine-4-carboxamide;

(*R*)-2,2,2-trifluoro-N-(1-(5-oxo-4-(3-(trifluoromethyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)pyrrolidin-3-yl)acetamide;

2-(4-(4-chlorophenyl)-4-hydroxy piperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*S*,2*S*)-2-(phenylsulfonyl)cyclohexyl amino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*S*,2*R*)-2-aminocyclohexylamino)-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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2-thiomorpholino-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-sulfonylpyrido)-4-(3-(trifluoro methyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-morpholinopiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

N-((1*R*,2*S*)-2-(5-oxo-4-(3-(trifluoro methyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)cyclohexyl) acetamide;

N-((1*R*,4*R*)-4-(5-oxo-4-(3-(trifluoro methyl)phenylamino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)cyclohexyl) acetamide;

2-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl amino)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

4-(3-bromophenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

4-(3-bromophenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*S*)-4-(3-bromophenylamino)-2-(4-(1-hydroxypropan-2-ylamino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(4-(3-aminopyrrolidin-1-yl) piperidin-1-yl)-4-(3-bromophenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*R*)-2-(3-aminopyrrolidin-1-yl)-4-(3-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

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4-(3-bromophenylamino)-2-(3-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*S*)-2-(3-aminopyrrolidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

4-(4-bromophenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(4-bromophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*S*)-4-(3-bromophenylamino)-2-(4-(1-hydroxypropan-2-ylamino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3-bromophenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(*m*-tolylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(4-hydroxypiperidin-1-yl)-4-(*m*-tolyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(2-((1*R*, 2*S*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one with (2-((1*S*, 2*R*)-2-aminocyclohexylamino)-4-(3-(trifluoromethyl) phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-morpholinopyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-((1*r*,4*r*)-4-hydroxycyclohexylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(2-aminobenzylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-methylpiperazin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

(*S*)-4-(3,5-bis(trifluoromethyl)phenylamino)-2-(pyrrolidin-3-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(piperidin-4-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(1-methylpiperidin-4-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*S*)-4-(3,5-bis(trifluoromethyl)phenylamino)-2-(1-methylpyrrolidin-3-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(dimethylamino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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(*R*)-4-(3,5-bis(trifluoromethyl)phenyl amino)-2-(3-hydroxypyrrolidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(3-hydroxyazetidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(2-hydroxyethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

N-((1*r*,4*r*)-4-(4-(3,5-bis(trifluoromethyl) phenylamino)-5-oxo-5,6-dihydropyrido [4,3-*d*]pyrimidin-2-ylamino)cyclohexyl) acetamide;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(3-oxopiperazin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(piperazin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

methyl 1-(4-(3,5-bis(trifluoromethyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl)-4-hydroxy piperidine-4-carboxylate;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*, 4*R*)-4-aminocyclohexylamino)-4-(3,5-bis(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-bis(trifluoromethyl)phenylamino)-2-(4-(hydroxyimino)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*S*)-4-(phenoxyphenylamino)-2-(pyrrolidin-3-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(4-hydroxypiperidin-1-yl)-4(4-(methylsulfonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

N-(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide;

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2-(4-hydroxypiperidin-1-yl)-4-(4-(methyl sulfonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-(methylsulfonyl)phenylamino)-2-(4-morpholinopiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(3-(methyl sulfonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

N-(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-yl amino)methyl)phenyl)cyclopropane sulfonamide;

N-methyl-N-(2-((4-(4-(methylsulfonyl)phenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)cyclopropanesulfonamide;

(*S*)-2-(3-aminopyrrolidin-1-yl)-4-(4-(methylsulfonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-(4-acetylpiperazin-1-yl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*S*)-4-(4-morpholinophenylamino)-2-(pyrrolidin-3-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-sulfonylphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-(4-acetylpiperazin-1-yl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-(5-oxo-2-(piperidin-4-ylmethyl amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-4-ylamino)phenyl)morpholine 4-oxide hydrochloride;

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4-(4-morpholinophenylamino)-2-(piperidin-4-ylmethylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

N-methyl-*N*-(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)cyclopropanesulfonamide;

N-(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)cyclopropanesulfonamide;

N-(2-((4-(4-morpholinophenylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-2-ylamino)methyl)phenyl)methanesulfonamide;

2-(2-aminobenzylamino)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,2*S*)-2-aminocyclohexylamino)-4-(4-morpholinophenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-((1*R*,2*R*)-2-aminocyclohexylamino)-4-(benzo[*d*][1,3]dioxol-5-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(3,4,5-trimethoxyphenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3,4,5-trimethoxyphenylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,5-dimethylphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

4-(4-chloro-3-methoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one

4-(3-chloro-5-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3-bromo-5-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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4-(4-chloro-3-(trifluoromethoxy)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidine-1-yl)-6-methyl-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

6-methyl-4-(phenylamino)-2-(3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

methyl 4-(6-methyl-2-morpholino-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-4-ylamino) benzoate;

6-methyl-2-(methylamino)-4-(4-(piperazine-1-carbonyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

methyl 4-(6-methyl-2-(methylamino)-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidin-4-ylamino) benzoate;

2-amino-6-methyl-4-(phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

4-(4-fluorobenzylamino)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

6-methyl-2-(methylamino)-4-(phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-methoxybenzylamino)-6-methyl-4-(phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxycyclohexylamino)-6-methyl-4-(phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-methoxyphenyl)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxyphenyl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-methoxyphenyl)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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4-(4-aminophenyl)-6-methyl-2-(methylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

1-(4-fluorophenyl)-3-(4-(6-methyl-2-(methylamino)-5-oxo-5,6-dihydropyrido [4,3-*d*]pyrimidin-4-yl)phenyl)urea;

8-bromo-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl) piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

8-chloro-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-bromo-3-methylphenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride;

8-bromo-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl) phenylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

8-chloro-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride;

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(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-bromo-3-methylphenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride;

8-bromo-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido [4,3-*d*]pyrimidin-5(6*H*)-one;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-methoxy-3-(trifluoromethyl) phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

8-chloro-2-(4-hydroxypiperidin-1-yl)-4-(3-(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-methoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(3-methoxy-5-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl) piperidin-1-yl)-4-(3-(trifluoromethyl)phenyl amino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

4-(3,4-dimethoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

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4-(3-bromo-4-methoxyphenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-phenoxyphenylamino)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one hydrochloride;

8-bromo-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)-4-(4-phenoxyphenyl
amino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3,4-dimethoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-
yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3-bromo-4-methoxyphenylamino)-2-(4-hydroxy-4-(hydroxymethyl)piperidin-1-
yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-aminopiperidin-1-yl)-8-bromo-4-(4-phenoxyphenylamino)pyrido[4,3-
d]pyrimidin-5(6*H*)-one hydrochloride;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-iodo-4-(4-phenoxyphenylamino)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one hydrochloride;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxy-4-
(hydroxymethyl)piperidin-1-yl)-8-iodopyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(4-chloro-3-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)-8-
iodopyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-chloro-3-(trifluoromethyl)
phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride;

2-(4-hydroxypiperidin-1-yl)-8-iodo-4-(4-(trifluoromethyl)phenylamino)pyrido[4,3-*d*]
pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(4-morpholino-3-
(trifluoromethyl)phenylamino)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-methoxy-3-
(trifluoromethyl)phenylamino) pyrido[4,3-*d*]pyrimidin-5(6*H*)-one hydrochloride;

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(*R*)-2-(3-aminopyrrolidin-1-yl)-8-bromo-4-(4-chloro-3-(trifluoromethoxy)phenylamino) pyrido[4,3-*d*] pyrimidin-5(6*H*)-one hydrochloride;

4-(4-chloro-3-(trifluoromethoxy)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3-bromo-5-(trifluoromethyl)phenylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*] pyrimidin-5(6*H*)-one;

(*R*)-6-(3-aminopyrrolidin-1-yl)-4-iodo-8-(4-(trifluoromethyl)phenylamino)isoquinolin-1(2*H*)-one hydrochloride;

(*R*)-6-(3-aminopyrrolidin-1-yl)-4-bromo-8-(4-(trifluoromethyl)phenylamino)isoquinolin-1(2*H*)-one hydrochloride;

(*S*)-6-(3-aminopyrrolidin-1-yl)-4-bromo-8-(4-(trifluoromethyl)phenylamino)isoquinolin-1(2*H*)-one hydrochloride;

4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-ylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(naphthalen-2-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-(4-hydroxypiperidin-1-yl)-4-(quinolin-5-ylamino)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

4-(3*H*-indol-2-ylamino)-2-(4-hydroxypiperidin-1-yl)pyrido[4,3-*d*]pyrimidin-5(6*H*)-one; and

2-(4-hydroxypiperidin-1-yl)-4-(4-phenoxyphenylamino)-8-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one.

41. A isomeric compound of Claim 1, or

a pharmaceutical formulation comprising a compound of any one of Claims 1 to 40 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

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42. A therapeutically effective amount of a compound of any one of Claim 1 to 40, or a pharmaceutically acceptable salt thereof, for use in the treatment of a protein kinase-mediated disease in a subject in need thereof, wherein said protein kinase-mediated disease is selected from the group of consisting of asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohn's disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsson Syndrome, rheumatoid arthritis, multiple sclerosis, inflammatory bowel syndrome, HIV associated diseases, lupus, lymphoma, osteosarcoma, melanoma, breast cancer, renal cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, lung cancer, uterine cancer, gastrointestinal cancer, Alzheimer's disease, Parkinson's disease, osteoporosis, osteopenia, osteomalacia, osteofibrosis, Paget's disease, diabetes, blood vessel proliferative disorders, ocular diseases, cardiovascular disease, restenosis, fibrosis, atherosclerosis, arrhythmia, angina, myocardial ischemia, myocardial infarction, cardiac or vascular aneurysm, vasculitis, stroke, peripheral obstructive arteriopathy, reperfusion injury following ischemia of an organ or a tissue, endotoxic, surgical or traumatic shock, hypertension, valvular heart disease, heart failure, abnormal blood pressure, vasoconstriction, vascular abnormality, transplant rejection and infectious diseases including viral and fungal infections.
43. The compound of Claim 42 for the use according to Claim 42, wherein said compound is formulated for administration singly or in combination with one or more additional therapeutic agents.
44. The compound of Claim 43 for the use according to Claim 42, wherein said compound is formulated for administration via intravenous administration, subcutaneous administration, inhalation, oral administration, rectal administration, parenteral, intravitreal administration, intramuscular administration, intranasal administration, dermal administration, topical administration, otic administration, ophthalmic administration, buccal administration, tracheal administration, bronchial administration, or sublingual administration.
45. An effective amount of a compound of any one of Claims 1 to 40 for use in inhibiting SYK, PYK2, FAK, ZAP70, PIM1, FLT3, RET, JAK2, JAK3, LRRK2,

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LRRK2(G2019S), ALK, AURKA, AXL, BMPR2, CSF1R, JNK1, JNK2, JNK3, KIT, KIT(D816V), LKB1, MLK1, PAK4, PDGFRB, PLK4, RSK2, SNARK, SRPK3, TAK1, or TYK2 signaling in a subject in need thereof, or

a compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, for use in inhibiting growth of cancer cells, comprising contacting the cancer cells with said compound, or

an effective amount of a compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a subject in need thereof, or

an effective amount of a compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, for use in the treatment of neurodegenerative disease in a subject in need thereof, or

an effective amount of a compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, for use in the treatment of inflammatory disease in a subject in need thereof.

46. The compound of Claim 45 for the use according to Claim 45, wherein said cancer is leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, or breast cancer.
47. The compound of Claim 45 for the use according to Claim 45, wherein said neurodegenerative disease is Parkinson's disease or Alzheimer's disease, or wherein said inflammatory disease is asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohn's disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, or cancer.
48. A use a compound of any one of Claim 1 to 40, or a pharmaceutically acceptable salt thereof, for treatment of a protein kinase-mediated disease in a subject in need thereof, wherein said protein kinase-mediated disease is selected from the group of consisting of asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress

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syndrome (ARDS), ulcerative colitis, Crohn's disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsson Syndrome, rheumatoid arthritis, multiple sclerosis, inflammatory bowel syndrome, HIV associated diseases, lupus, lymphoma, osteosarcoma, melanoma, breast cancer, renal cancer, prostate cancer, colorectal cancer, thyroid cancer, ovarian cancer, pancreatic cancer, neuronal cancer, lung cancer, uterine cancer, gastrointestinal cancer, Alzheimer's disease, Parkinson's disease, osteoporosis, osteopenia, osteomalacia, osteofibrosis, Paget's disease, diabetes, blood vessel proliferative disorders, ocular diseases, cardiovascular disease, restenosis, fibrosis, atherosclerosis, arrhythmia, angina, myocardial ischemia, myocardial infarction, cardiac or vascular aneurysm, vasculitis, stroke, peripheral obstructive arteriopathy, reperfusion injury following ischemia of an organ or a tissue, endotoxic, surgical or traumatic shock, hypertension, valvular heart disease, heart failure, abnormal blood pressure, vasoconstriction, vascular abnormality, transplant rejection and infectious diseases including viral and fungal infections.

49. The use of Claim 48, wherein said compound is formulated for administration singly or in combination with one or more additional therapeutic agents.
50. The use of Claim 49, wherein said compound is formulated for administration via intravenous administration, subcutaneous administration, inhalation, oral administration, rectal administration, parenteral, intravitreal administration, intramuscular administration, intranasal administration, dermal administration, topical administration, otic administration, ophthalmic administration, buccal administration, tracheal administration, bronchial administration, or sublingual administration.
51. A use of a compound of any one of Claims 1 to 40 for inhibiting SYK, PYK2, FAK, ZAP70, PIM1, FLT3, RET, JAK2, JAK3, LRRK2, LRRK2(G2019S), ALK, AURKA, AXL, BMPR2, CSF1R, JNK1, JNK2, JNK3, KIT, KIT(D816V), LKB1, MLK1, PAK4, PDGFRB, PLK4, RSK2, SNARK, SRPK3, TAK1, or TYK2 signaling in a subject in need thereof, or

a use compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, for inhibiting growth of cancer cells, or

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a use of a compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, for treatment of cancer, or

a use of a compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, for treatment of neurodegenerative disease, or

a use of a compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, for treatment of inflammatory disease in a subject in need thereof.

52. The use of Claim 51, wherein said cancer is leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, or breast cancer.

53. The use of Claim 51, wherein said neurodegenerative disease is Parkinson's disease or Alzheimer's disease, or

wherein said inflammatory disease is asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohn's disease, bronchitis, dermatitis, allergic rhinitis, psoriasis, scleroderma, urticaria, rheumatoid arthritis, multiple sclerosis, or cancer.