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(54) Titre : COMPOSES CONDENSES DE PYRIDINE, DE PYRIMIDINE ET DE TRIAZINE EN TANT QU'INHIBITEURS  
DU CYCLE CELLULAIRE

(54) Title: FUSED PYRIDINE, PYRIMIDINE AND TRIAZINE COMPOUNDS AS CELL CYCLE INHIBITORS

(57) **Abrégé/Abstract:**

Compounds, pharmaceutical compositions and methods are provided that are useful in the treatment of CDK4-mediated disorders, such as cancer. The subject compounds are fused pyridine, pyrimide and triazine derivatives.





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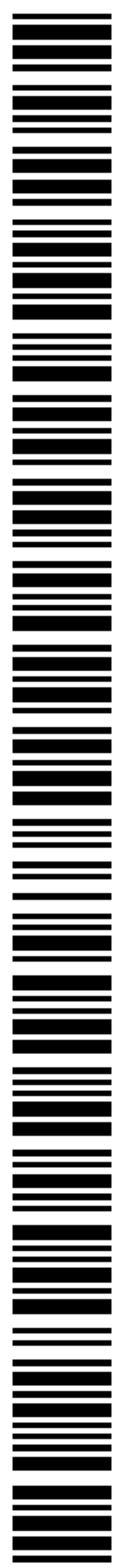
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# **DEMANDES OU BREVETS VOLUMINEUX**

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NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

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# **JUMBO APPLICATIONS / PATENTS**

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE  
THAN ONE VOLUME.**

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## FUSED PYRIDINE, PYRIMIDINE AND TRIAZINE COMPOUNDS AS CELL CYCLE INHIBITORS

### FIELD OF THE INVENTION

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cancer.

### BACKGROUND OF THE INVENTION

Cyclin-dependent kinases (Cdks) are a family of serine/ threonine protein kinases playing important cellular functions. The cyclins are the regulatory subunits that activate the catalytic Cdks. Cdk1/Cyclin B1, Cdk2/Cyclin A, Cdk2/Cyclin E, Cdk4/Cyclin D, Cdk6/Cyclin D are critical regulators of cell cycle progression. Cdks also regulate transcription, DNA repair, differentiation, senescence and apoptosis (Morgan D.O., *Annu. Rev. Cell. Dev. Biol.* 1997; 13:261-291).

Small molecule inhibitors of Cdks have been developed to treat cancer (de Carcer G et al., *Curr Med Chem.* 2007; 14:969-85). Large amount of genetic evidence support that Cdks play critical roles in the development of most human cancers (Malumbres M. et al, *Nature Rev Cancer*, 2001; 1:222-231). Genetic alterations in Cdks, their substrates or regulators have been shown to be associated with human cancer. Endogenous protein inhibitors of Cdks including p16, p21 and p27 inhibit Cdk activity and their overexpression result in cell cycle arrest and inhibition of tumor growth in preclinical models (Kamb A., *Curr. Top. Microbiolo. Immunol.*, 1998; 227:139-148).

Small molecule inhibitors of Cdks may also be used to treat variety of other diseases that result from aberrant cell proliferation, including cardiovascular disorders, renal diseases, certain infectious diseases and autoimmune diseases. Cell proliferation regulatory pathways including genes involved in the cell cycle G1 and S phase checkpoint (p53, pRb, p15, p16, and Cyclins A, D, E, Cdk 2 and Cdk4) have been associated with plaque progression, stenosis and restenosis after angioplasty. Over-expression of the Cdk inhibitor protein p21 has been shown to inhibit vascular smooth muscle proliferation and intimal hyperplasia following angioplasty (Chang M.W. et al., *J. Clin. Invest.*, 1995; 96:2260; Yang Z-Y. et al., *Proc. Natl. Acad. Sci. (USA)* 1996; 93:9905). A small molecule Cdk2 inhibitor CVT-313 (Ki = 95 nM) was shown to cause in significant inhibition of neointima formation in animal models (Brooks E.E. et al., *J. Biol. Chem.* 1997; 272:29207-29211). Disregulation of cell cycle has been associated with polycystic kidney diseases, which are characterized by the growth of fluid-filled cysts in renal tubules. Treatment with small molecule inhibitors of Cdks yielded effective arrest of cystic disease in mouse models (Bukanov N. O., et al., *Nature*, 2006; 444:949-952). Infection by a variety of infectious agents, including fungi, protozoan parasites such as *Plasmodium falciparum*, and DNA and RNA viruses may be treated with Cdk inhibitors. Cdks have been shown to be required for replication of herpes simplex virus (HSV) (Schang L.M. et al., *J. Virol.* 1998; 72:5626). Cdks are essential proteins in yeast. Synovial tissue hyperplasia plays important roles in the development of



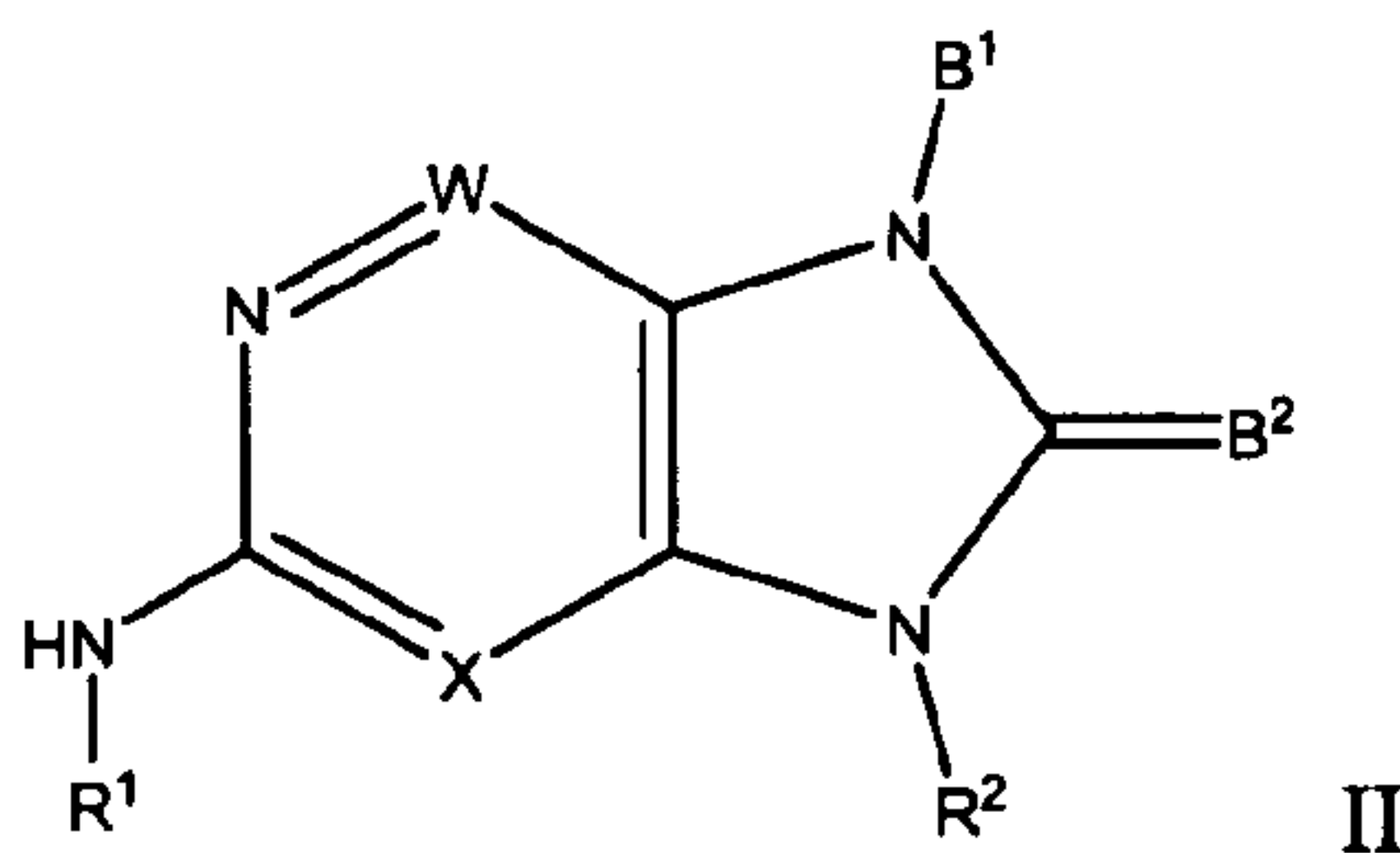
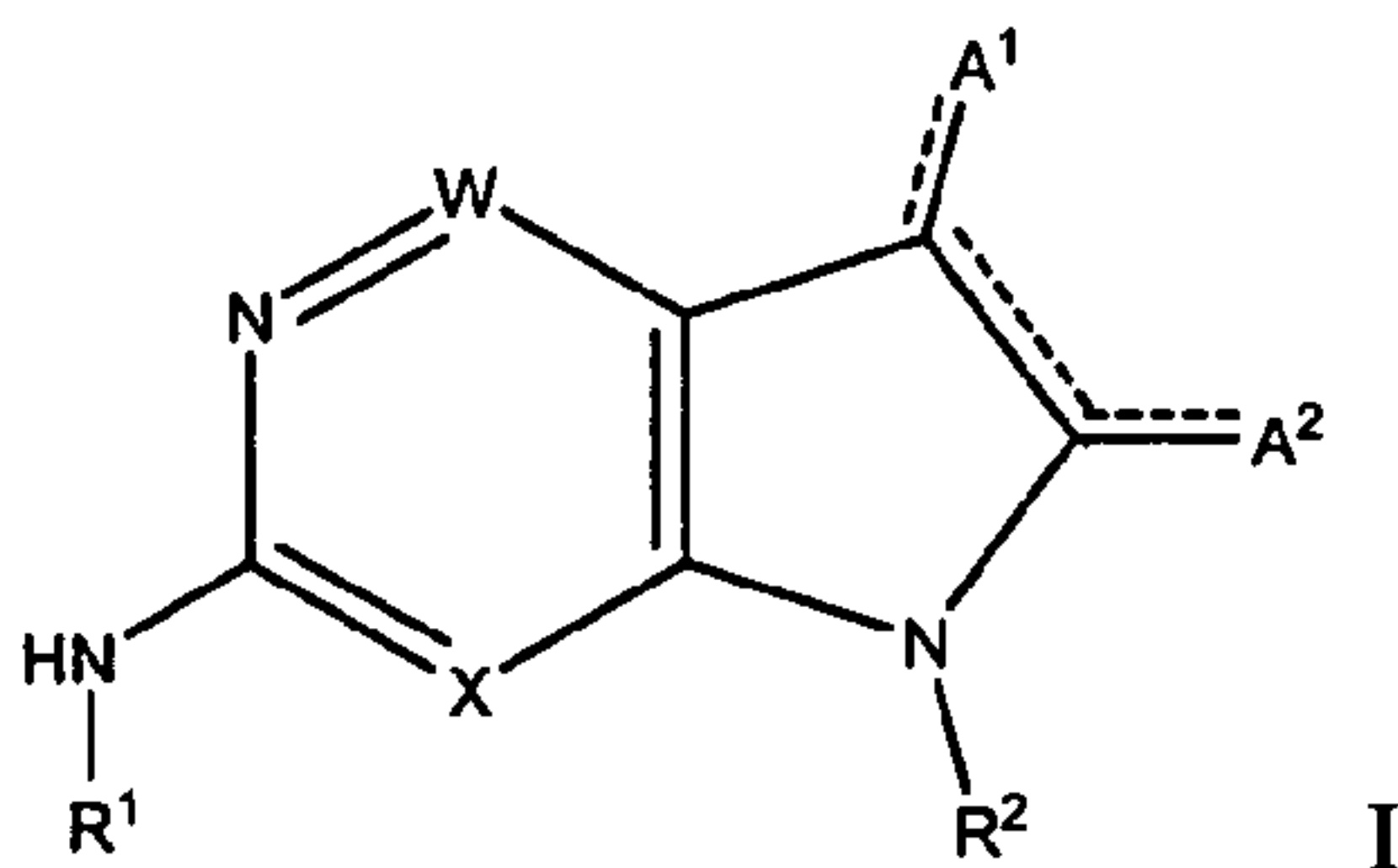
rheumatoid arthritis; inhibition of synovial tissue proliferation may suppress inflammation and prevent joint destruction. It has been shown that over-expression of Cdk inhibitor protein p16 inhibited synovial fibroblast growth (Taniguchi K. et al., *Nat. Med.* 1999; 5:760-767) and joint swelling was substantially inhibited in animal arthritis models.

Selective inhibitors of some Cdks may also be used to protect normal untransformed cells by inhibiting specific phases of cell cycle progression (Chen et al. *J. Natl. Cancer Institute*, 2000; 92:1999-2008). Pre-treatment with a selective Cdk inhibitor prior to the use of a cytotoxic agent that inhibits a different phase of the cell cycle may reduce the side effects associated with the cytotoxic chemotherapy and possibly increase the therapeutic window. It has been shown that induction of cellular protein inhibitors of Cdks (p16, p27 and p21) conferred strong resistance to paclitaxel- or cisplatin-mediated cytotoxicity on the inhibitor-responsive cells but not on the inhibitor-unresponsive cells (Schmidt, M, *Oncogene*, 2001 20:6164-71).

### DESCRIPTION OF THE INVENTION

A class of compounds useful in treating cancer is defined by the following Formula I or II

A compound of Formula I or II



enantiomers, diastereomers, salts and solvates thereof wherein

W and X are independently CH or N;

A<sup>1</sup> and A<sup>2</sup> together with ring carbon atoms to which they are attached combine to form benzene, cyclopentadiene, pyridine, pyridone, pyrimidine, pyrazine, pyridazine, 2H-pyran, pyrrole, imidazole, pyrazole, triazole, furan, oxazole, isoxazole, oxadiazole, thiophene, thiazole, isothiazole or thiadiazole



any of which may be optionally partially saturated, and any of which may be optionally independently substituted with one or more  $R^x$  groups as allowed by valance;

$B^1$  and  $B^2$  together with the ring atoms to which they are attached combine to form dihydropyridine, dihydropyridone, dihydropyrimidine, dihydropyrimidone, dihydropyrazine, dihyrdopyridazine, pyrrole, imidazole, pyrazole, triazole, or tetrazole any of which may be optionally partially saturated, and any of which may be optionally independently substituted with one or more  $R^x$  groups as allowed by valance;

$R^1$  is  $-Y-(alkylene)_m-R^a$ ;

$Y$  is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl or heteroaryl any of which may be optionally independently substituted with one or more  $R^x$  groups as allowed by valance;

$R^a$  is heterocyclo, heteroaryl,  $-NR^3R^4$ ,  $-C(=O)NR^3R^4$ ,  $-O-R^5$ ,  $-S(O)_n-R^5$ , or  $-S(O)_n-NR^3R^4$  any of which may be optionally independently substituted with one or more  $R^x$  groups as allowed by valance, and wherein two  $R^x$  groups bound to the same or adjacent atom may optionally combine to form a ring;

$R^2$  is alkyl, cycloalkyl, heterocyclo, aryl,  $-S(O)_nR^5$ ,  $-C(=O)R^5$ ,  $-C(=S)R^5$ ,  $-C(=O)OR^5$ ,  $-C(=S)OR^5$ ,  $-C(=O)NR^3R^4$ ,  $-C(=S)NR^3R^4$ ,  $-SO_2NR^3R^4$ , any of which may be optionally independently substituted with one or more  $R^x$  groups as allowed by valance;

$R^3$  and  $R^4$  at each occurrence are independently

(i) hydrogen or

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

or  $R^3$  and  $R^4$  together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more  $R^x$  groups as allowed by valance, and wherein two  $R^x$  groups bound to the same or adjacent atom may optionally combine to form a ring;

$R^{3*}$  and  $R^{4*}$  at each occurrence are independently

(i) hydrogen or

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

or  $R^{3*}$  and  $R^{4*}$  together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more  $R^x$  groups as allowed by valance;

$R^5$  and  $R^{5*}$  at each occurrence is

(i) hydrogen or



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

$R^x$  at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl,  $-(alkylene)_m-OR^5$ ,  $-(alkylene)_m-S(O)_nR^5$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^5$ ,  $-(alkylene)_m-C(=S)R^5$ ,  $-(alkylene)_m-C(=O)OR^5$ ,  $-(alkylene)_m-OC(=O)R^5$ ,  $-(alkylene)_m-C(=S)OR^5$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^5$ ,  $-(alkylene)_m-N(R^3)C(=S)R^5$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^5$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^5$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^5$ , or  $-(alkylene)_m-N(R^3)SO_2R^5$ ;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more  $-(alkylene)_m-CN$ ,  $-(alkylene)_m-OR^{5*}$ ,  $-(alkylene)_m-S(O)_nR^{5*}$ ,  $-(alkylene)_m-NR^3R^{4*}$ ,  $-(alkylene)_m-C(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)R^{5*}$ ,  $-(alkylene)_m-C(=O)OR^{5*}$ ,  $-(alkylene)_m-OC(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)OR^{5*}$ ,  $-(alkylene)_m-C(=O)NR^3R^{4*}$ ,  $-(alkylene)_m-C(=S)NR^3R^{4*}$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^{4*}$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^{4*}$ ,  $-(alkylene)_m-N(R^3)C(=O)R^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)R^{5*}$ ,  $-(alkylene)_m-OC(=O)NR^3R^{4*}$ ,  $-(alkylene)_m-OC(=S)NR^3R^{4*}$ ,  $-(alkylene)_m-SO_2NR^3R^{4*}$ ,  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^{4*}$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^{5*}$ , or  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ;

$n$  is independently 0, 1 or 2; and

$m$  is independently 0 or 1.

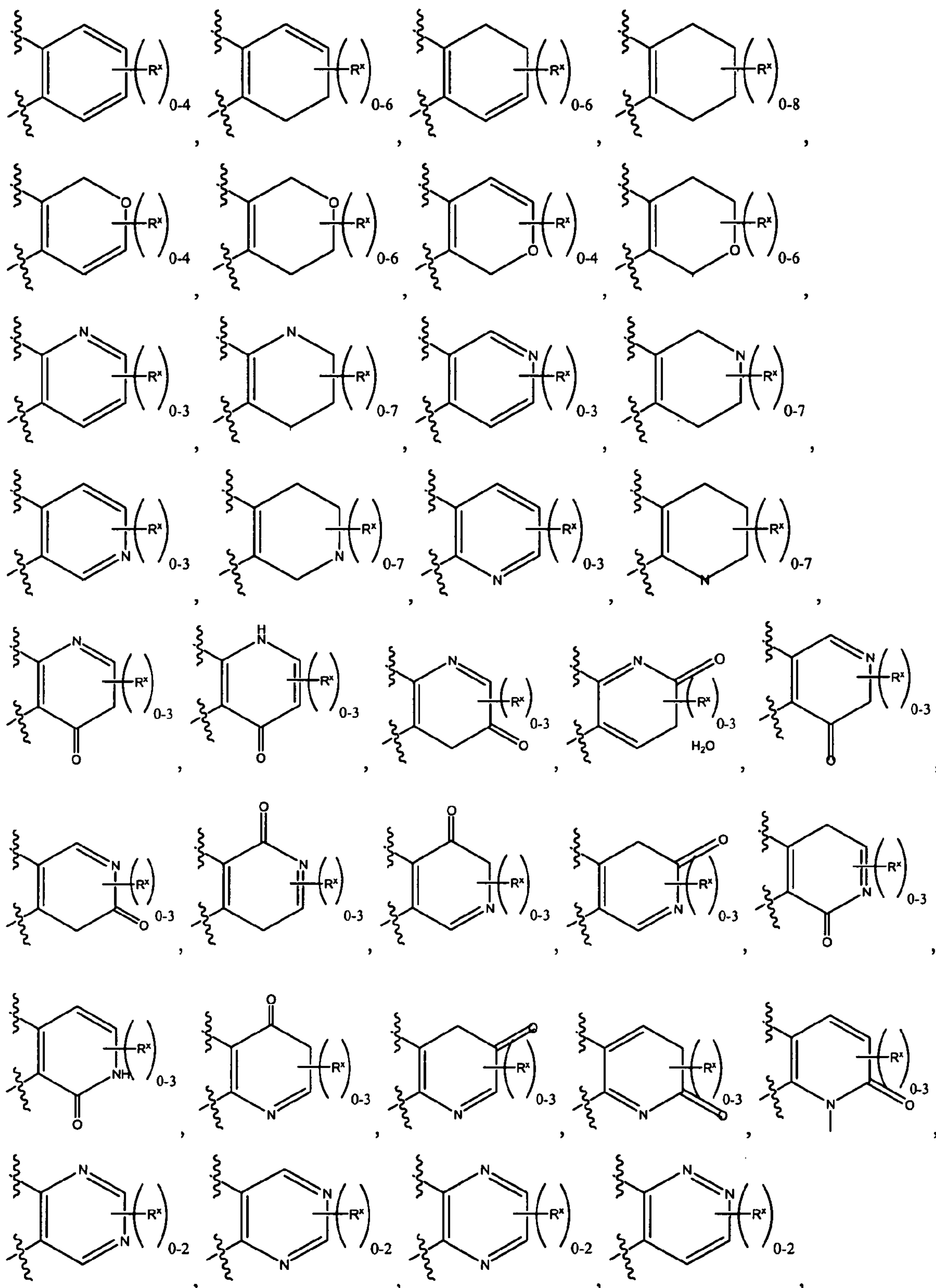
Compounds of this invention are selective inhibitors of cyclin dependent kinase Cdk4, which is to say that they inhibit Cdk4 with higher potency than they inhibit tyrosine kinases and other serine-threonine kinases including other cyclin-dependent kinases such as Cdk1. Cdk6 is structurally and functionally similar to Cdk4.

Compounds of the present invention also inhibit Cdk6 at similar concentrations to those to inhibit Cdk4. Preferred embodiments of the present invention are compounds of the formula 1 inhibit Cdk4 at least about 100-fold more potently than they inhibit Cdk1.

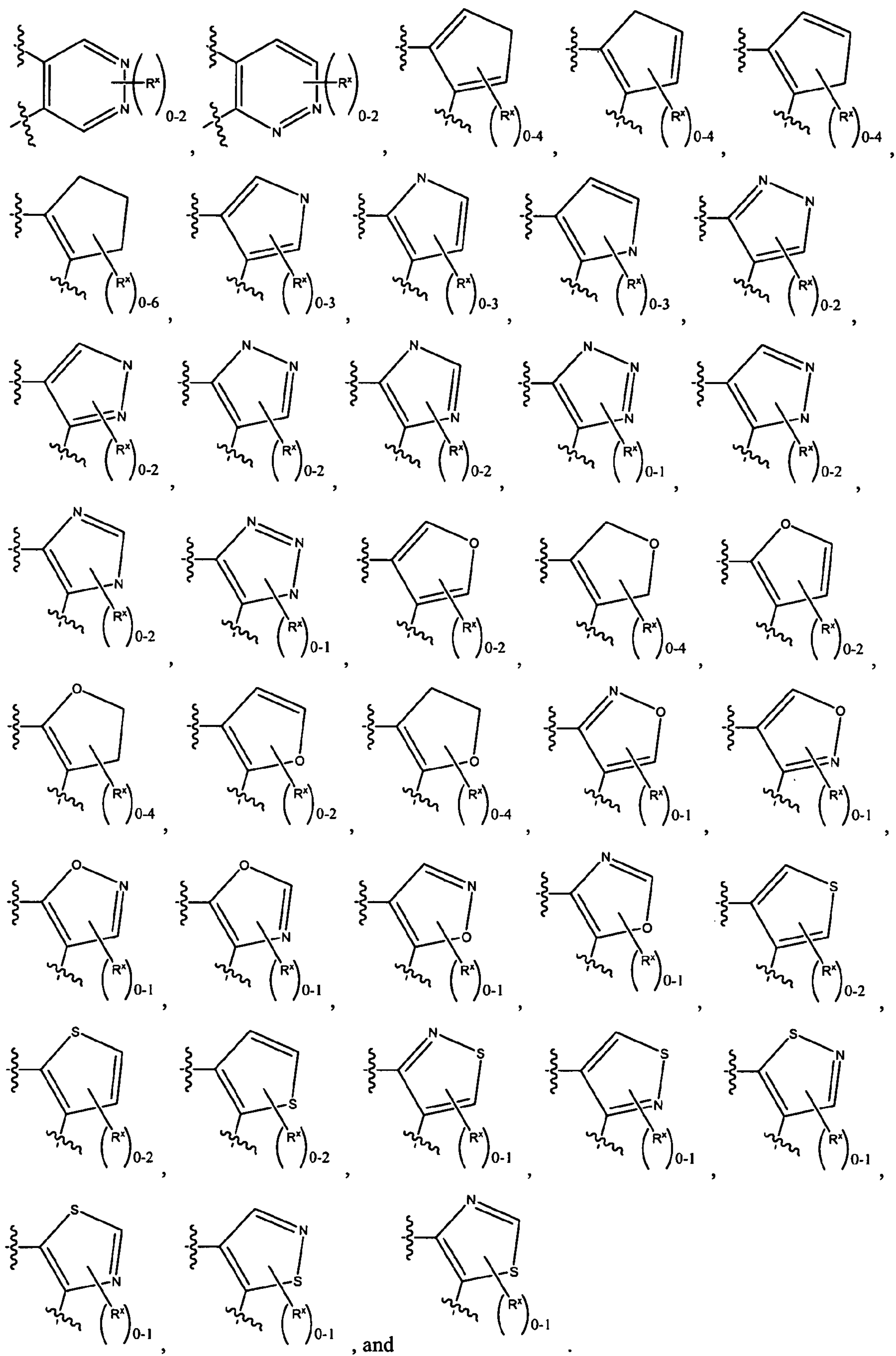
The compounds of the present invention are useful for treating cancer including leukemia and solid cancer of the lung, breast, prostate, and skin such as melanoma, and other diseases with abnormal cell proliferation including but not limited to psoriasis, HSV, HIV, restenosis, and atherosclerosis.



Preferred compounds within the scope of Formula I include compounds wherein A<sup>1</sup> and A<sup>2</sup> together with the ring atoms to which they are attached combine to form

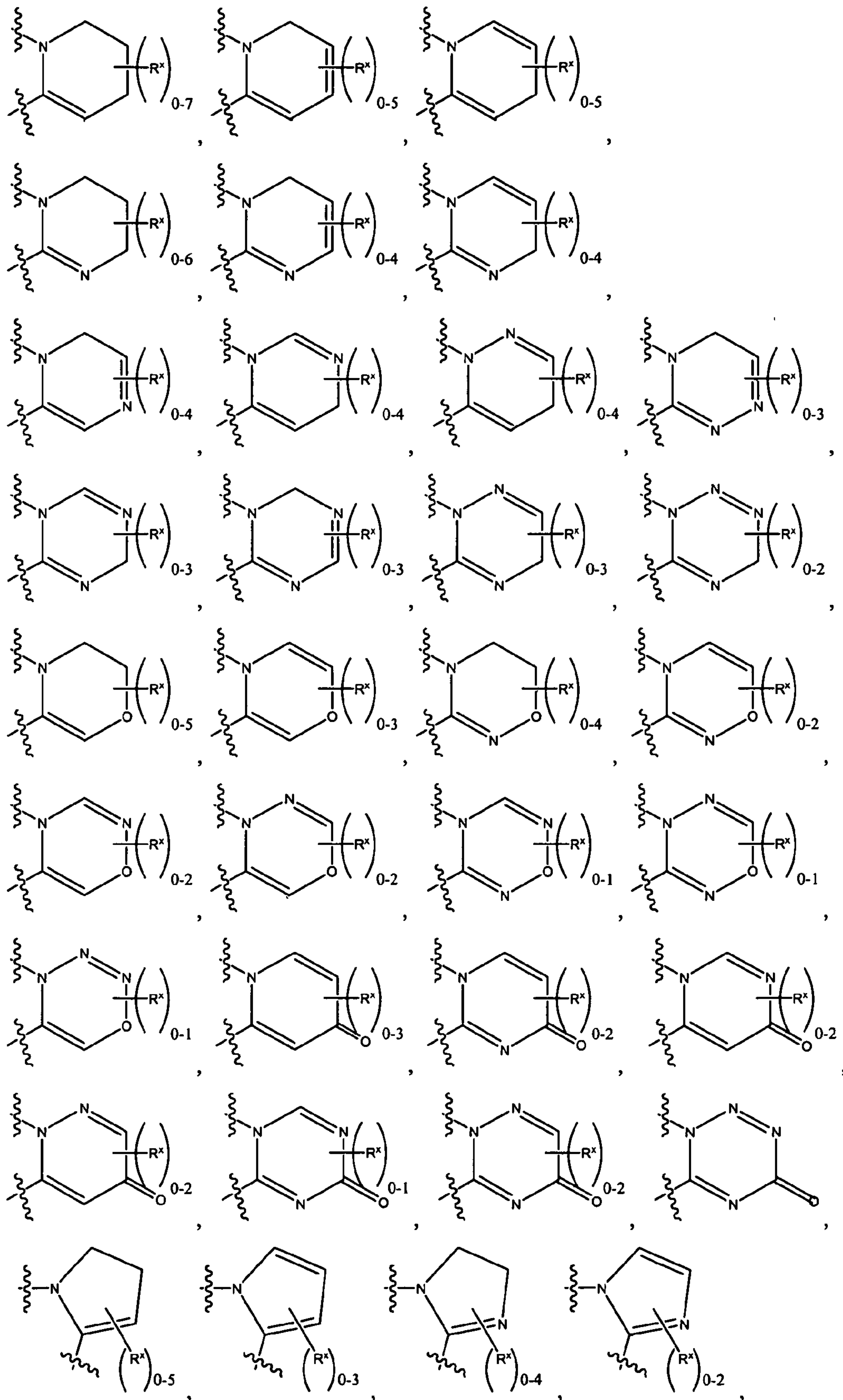




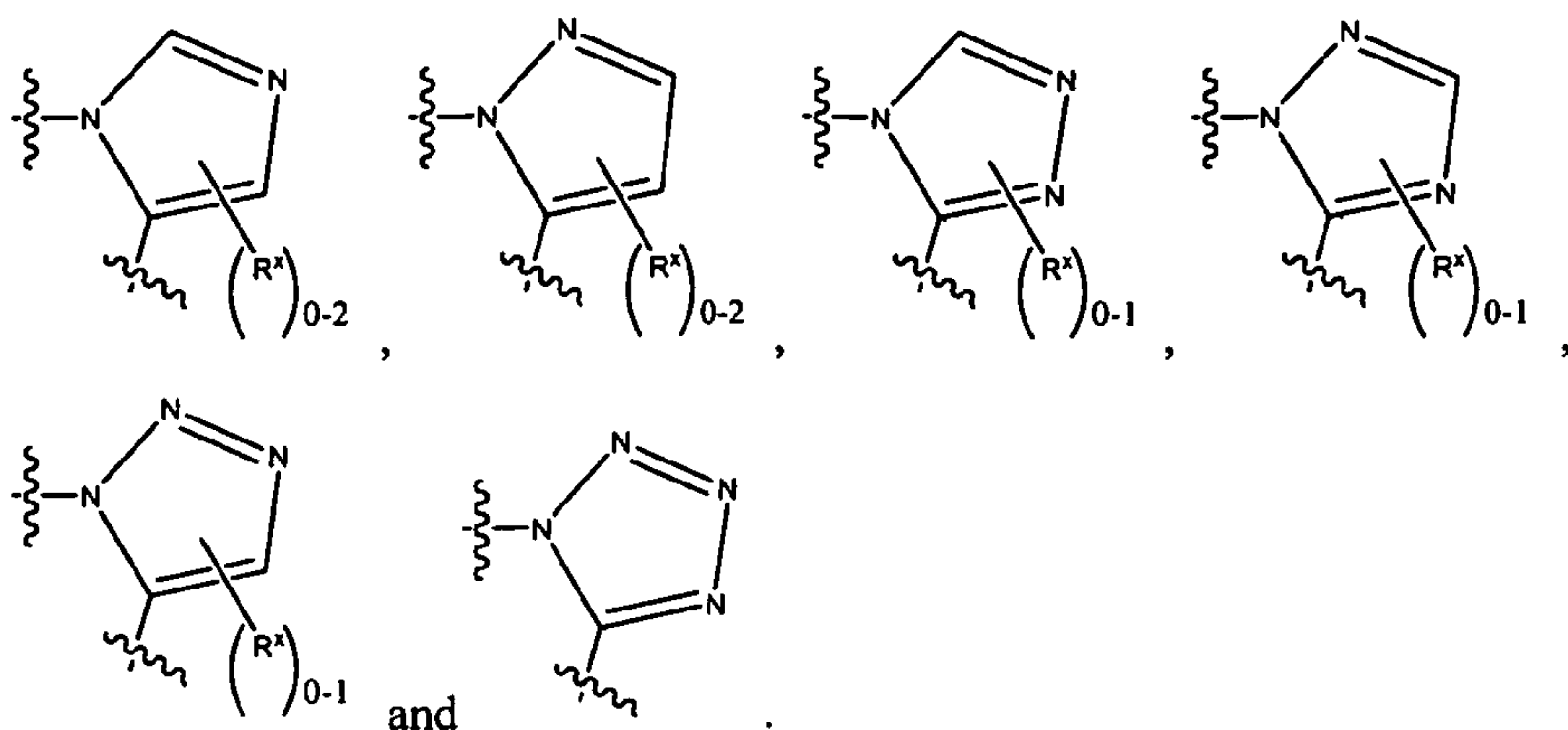




Preferred compounds within the scope of Formula II include compounds wherein B<sup>1</sup> and B<sup>2</sup> together with the ring atoms to which they are attached combine to form

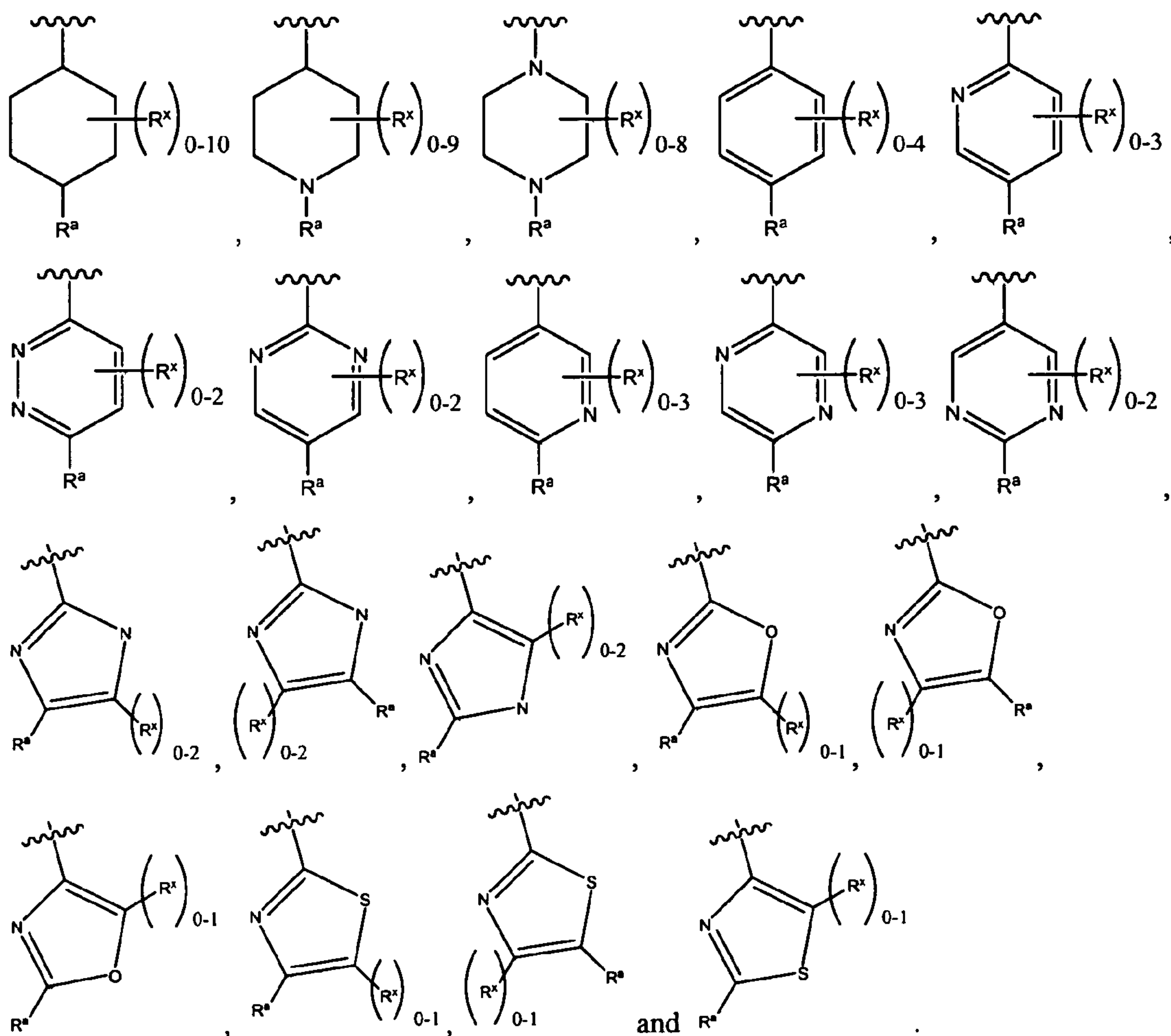






Preferred compounds within the scope of Formula I and II include compounds where Y is cyclopentyl, cyclohexyl, piperidiny, piperaziny, phenyl, pyridiny, pyrimidinyl, cyclopentadienyl, pyrrolyl, imidazolyl, oxazolyl or thiazolyl.

Preferred compounds within the scope of Formula I and II further include compounds where  $R^1$  is selected from



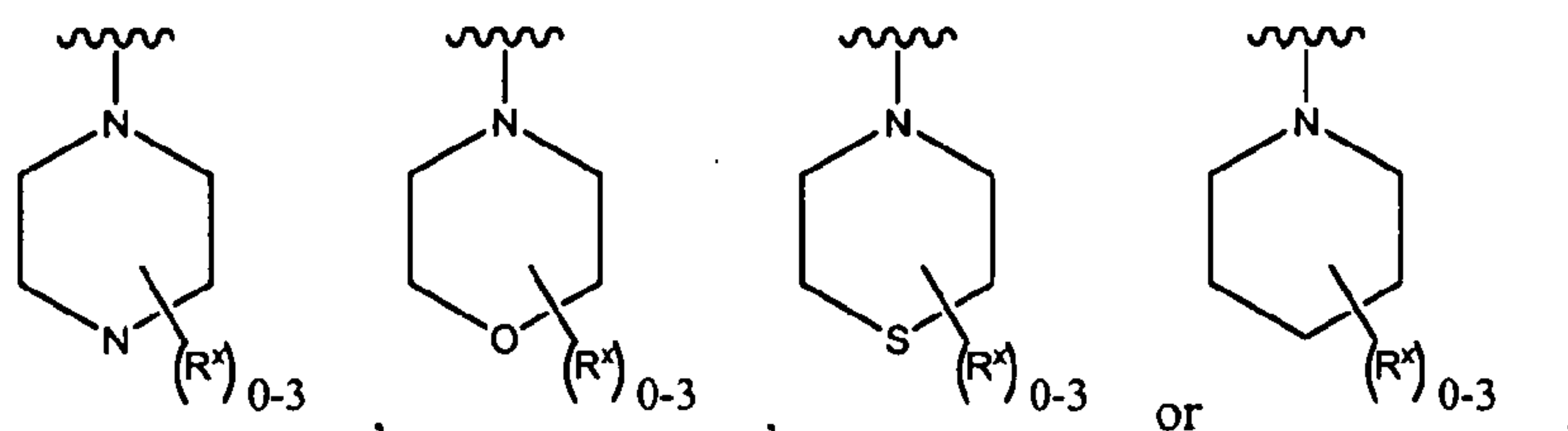


Preferred compounds within the scope of Formula I and II further include compounds where  $R^a$  is selected from

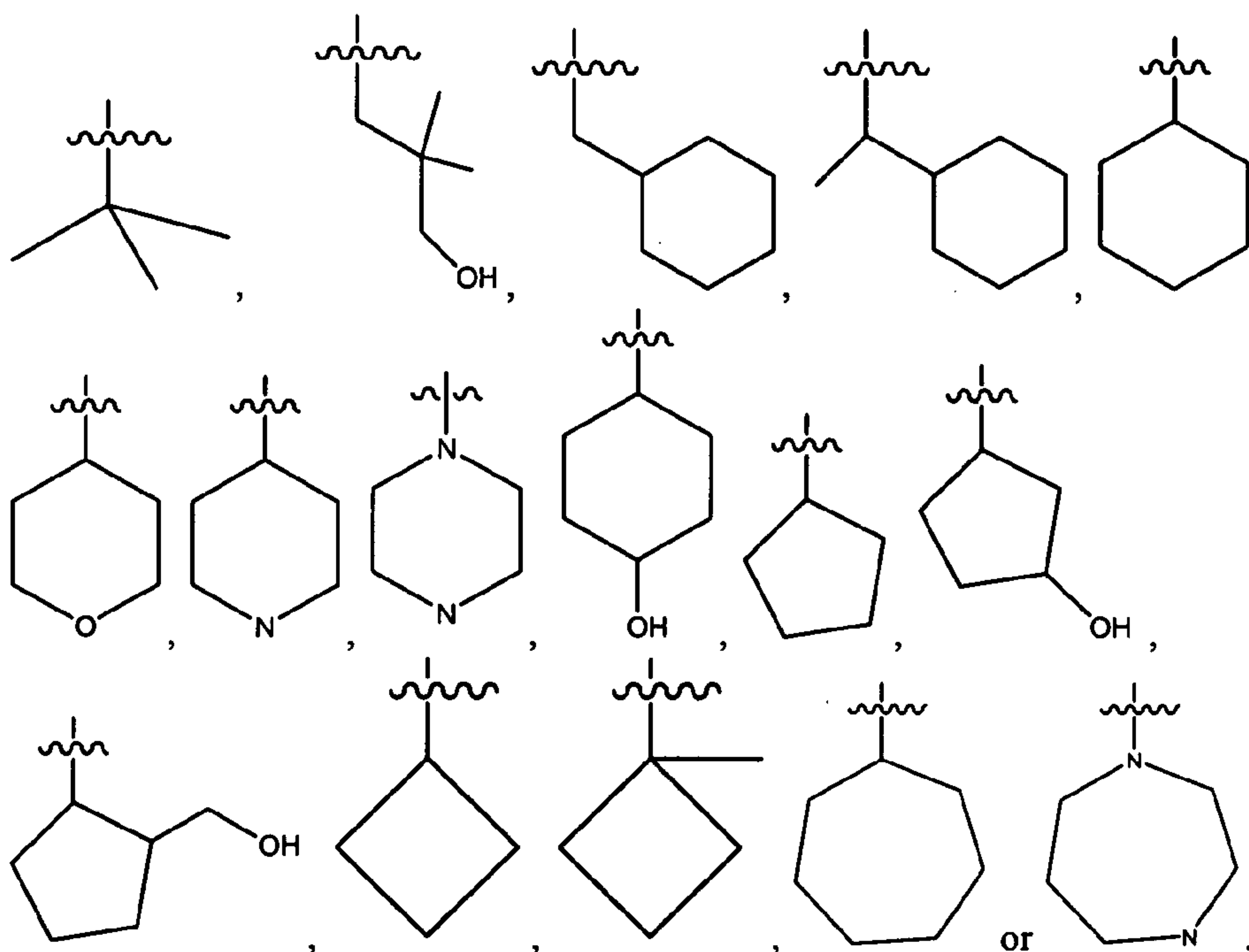
(a)  $-OR^5$  or  $-S(O)_nR^5$  where  $R^5$  is alkyl optionally independently substituted with one or more  $-OR^{5*}$ , or  $-NR^3R^{4*}$ ;

(b)  $-C(=O)NR^3R^4$  or  $-NR^3R^4$  where  $R^3$  and  $R^4$  are independently alkyl optionally independently substituted with one or more  $-OR^{5*}$ , or  $-NR^3R^{4*}$ ;

or  $R^3$  and  $R^4$  together with the nitrogen atom to which they are attached combine to form

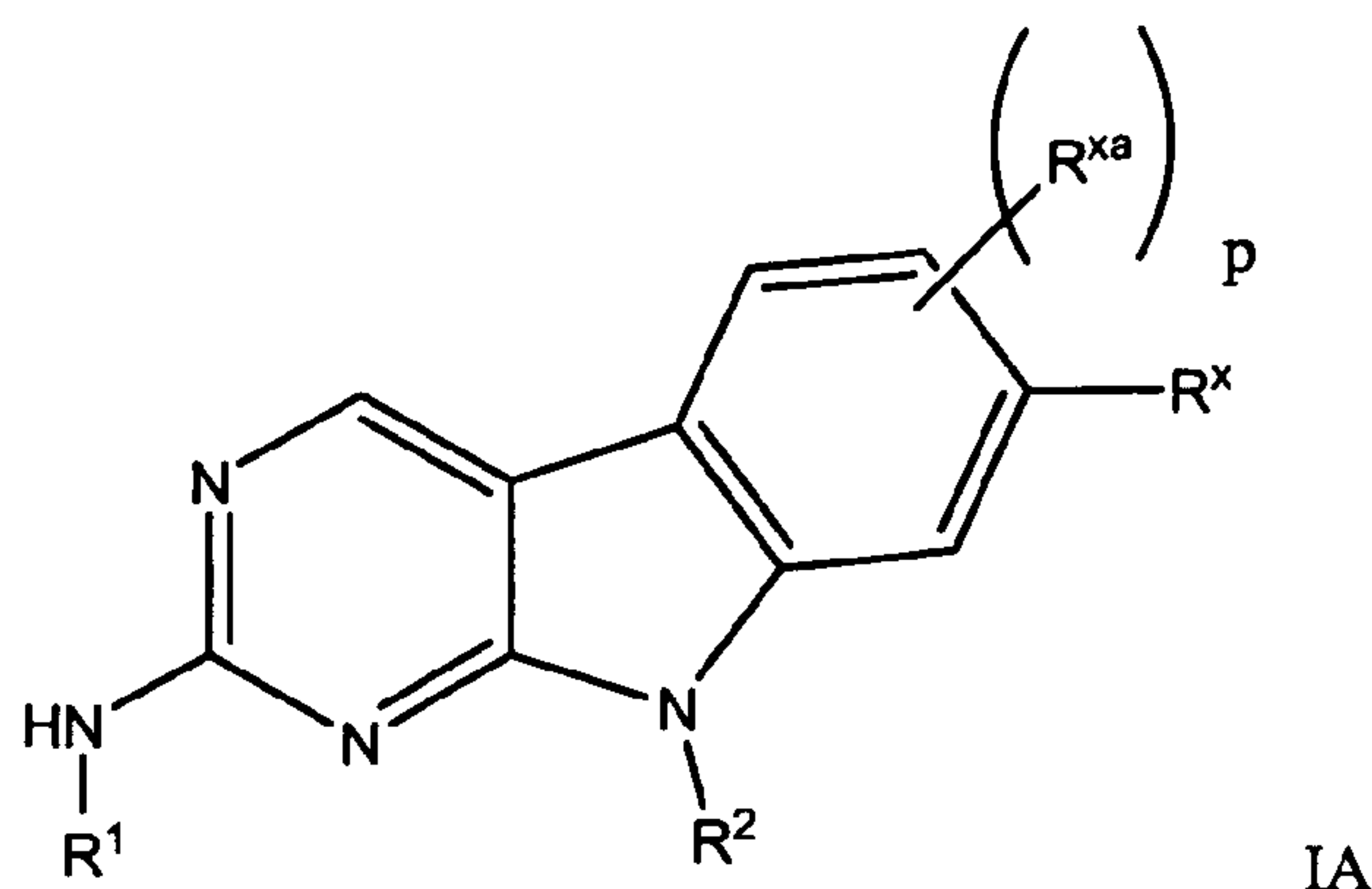


Preferred compounds within the scope of Formula I and II further include compounds where  $R^2$  is



Preferred compounds within the scope of Formula I include compounds of the following formula IA





wherein  $R^{xa}$  is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl,  $-(alkylene)_m-OR^5$ ,  $-(alkylene)_m-S(O)_nR^5$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^5$ ,  $-(alkylene)_m-C(=S)R^5$ ,  $-(alkylene)_m-C(=O)OR^5$ ,  $-(alkylene)_m-OC(=O)R^5$ ,  $-(alkylene)_m-C(=S)OR^5$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^5$ ,  $-(alkylene)_m-N(R^3)C(=S)R^5$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^5$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^5$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^5$ , or  $-(alkylene)_m-N(R^3)SO_2R^5$ ;

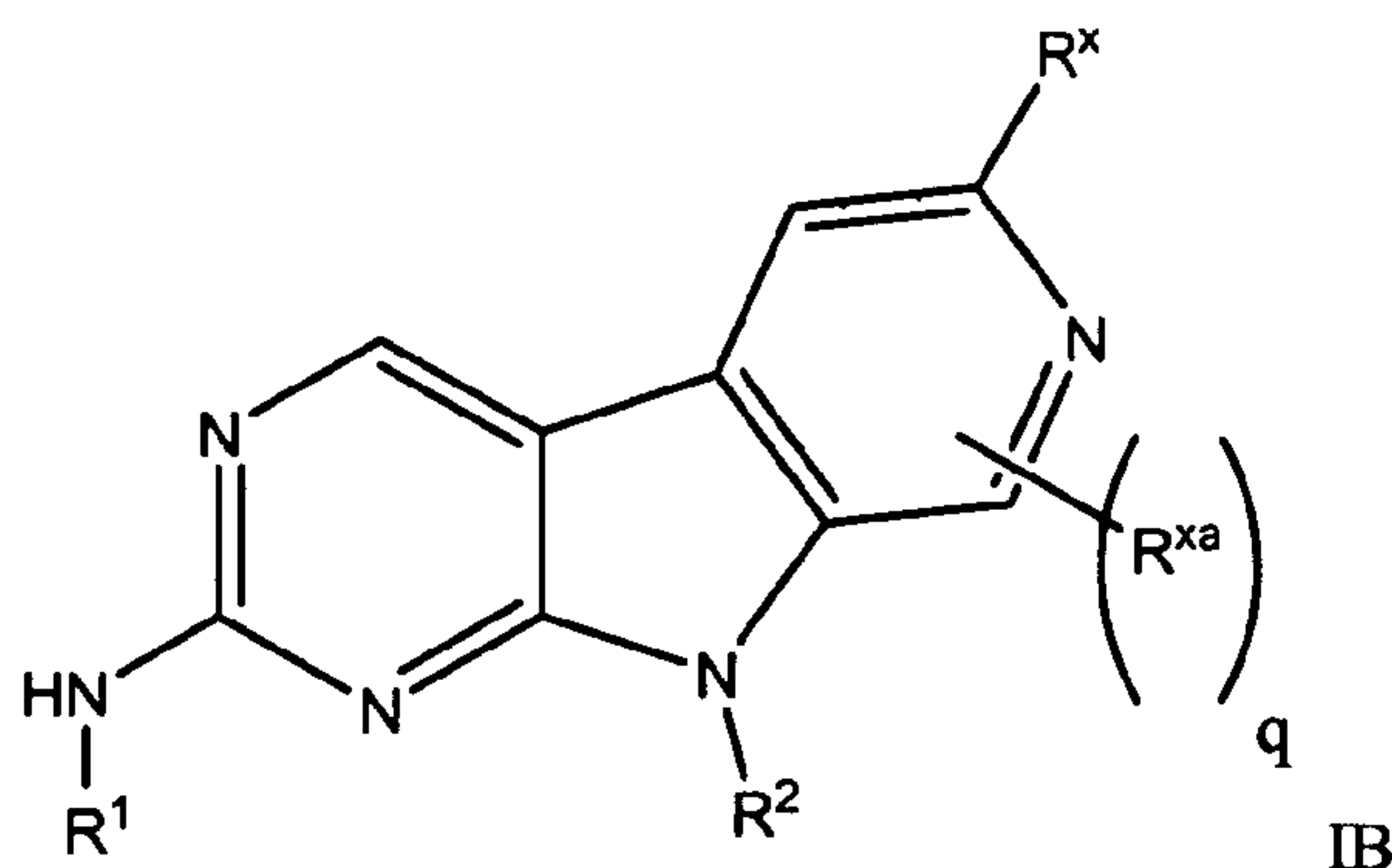
wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more  $-(alkylene)_m-OR^{5*}$ ,  $-(alkylene)_m-S(O)_nR^{5*}$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)R^{5*}$ ,  $-(alkylene)_m-C(=O)OR^{5*}$ ,  $-(alkylene)_m-OC(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)OR^{5*}$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)R^{5*}$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^{5*}$ , or  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ;

$m$  is 0 or 1 ; and  
 $p$  is zero to three.

Preferred compounds within the scope of Formula IA include compounds having any of the preferred  $Y$ ,  $R^1$ ,  $R^a$  and/or  $R^2$  substituents previously listed above.

Preferred compounds within the scope of Formula I include compounds having the following  
 Formula IB





wherein  $R^{xa}$  is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl,  $-(alkylene)_m-OR^5$ ,  $-(alkylene)_m-S(O)_nR^5$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^5$ ,  $-(alkylene)_m-C(=S)R^5$ ,  $-(alkylene)_m-C(=O)OR^5$ ,  $-(alkylene)_m-OC(=O)R^5$ ,  $-(alkylene)_m-C(=S)OR^5$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^5$ ,  $-(alkylene)_m-N(R^3)C(=S)R^5$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^5$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^5$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^5$ , or  $-(alkylene)_m-N(R^3)SO_2R^5$ ;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more  $-(alkylene)_m-OR^{5*}$ ,  $-(alkylene)_m-S(O)_nR^{5*}$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)R^{5*}$ ,  $-(alkylene)_m-C(=O)OR^{5*}$ ,  $-(alkylene)_m-OC(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)OR^{5*}$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)R^{5*}$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^{5*}$ , or  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ;

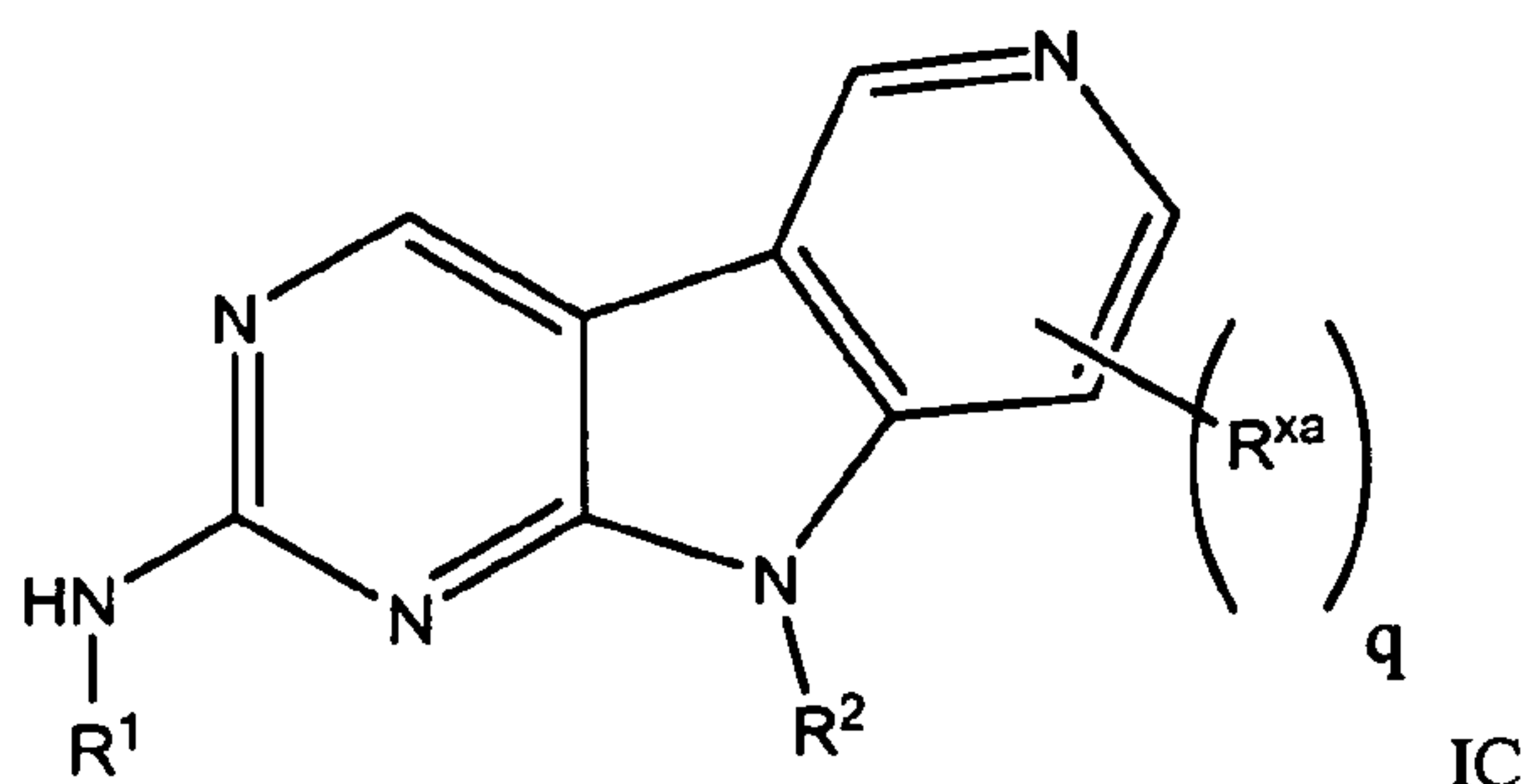
$m$  is 0 or 1 ; and

$q$  is zero to two.

Preferred compounds within the scope of Formula IB include compounds having any of the preferred  $Y$ ,  $R^1$ ,  $R^a$  and/or  $R^2$  substituents previously listed above.

Preferred compounds within the scope of Formula I include compounds having the following Formula IC





wherein  $R^{xa}$  is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl,  $-(alkylene)_m-OR^5$ ,  $-(alkylene)_m-S(O)_nR^5$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^5$ ,  $-(alkylene)_m-C(=S)R^5$ ,  $-(alkylene)_m-C(=O)OR^5$ ,  $-(alkylene)_m-OC(=O)R^5$ ,  $-(alkylene)_m-C(=S)OR^5$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^5$ ,  $-(alkylene)_m-N(R^3)C(=S)R^5$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^5$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^5$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^5$ , or  $-(alkylene)_m-N(R^3)SO_2R^5$ ;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more  $-(alkylene)_m-OR^{5*}$ ,  $-(alkylene)_m-S(O)_nR^{5*}$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)R^{5*}$ ,  $-(alkylene)_m-C(=O)OR^{5*}$ ,  $-(alkylene)_m-OC(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)OR^{5*}$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)R^{5*}$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^{5*}$ , or  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ;

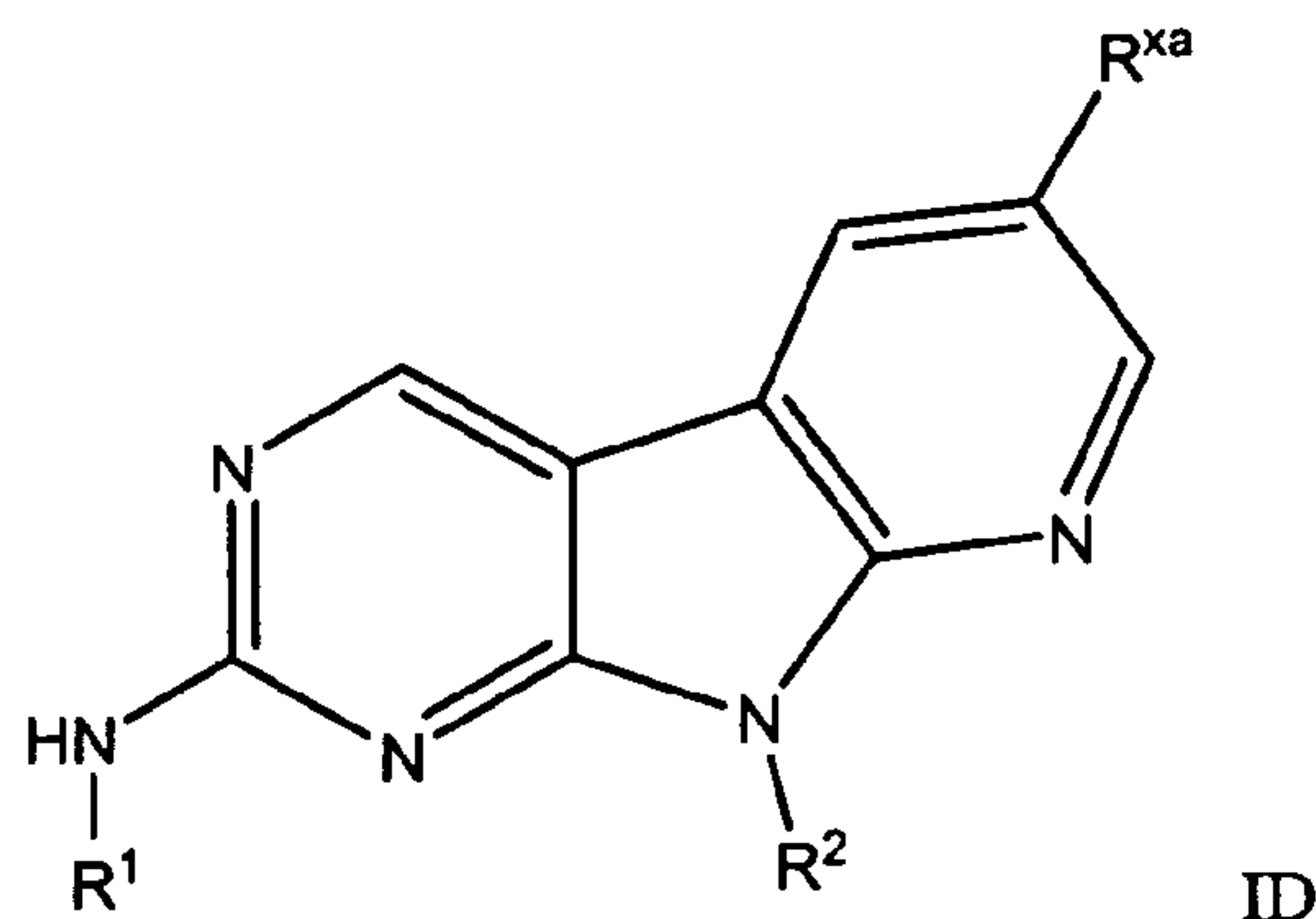
$m$  is 0 or 1 ; and

$q$  is zero to two.

Preferred compounds within the scope of Formula IC include compounds having any of the preferred  $Y$ ,  $R^1$ ,  $R^2$  and/or  $R^3$  substituents previously listed above.

Preferred compounds within the scope of Formula I include compounds having the following Formula ID





wherein  $R^{xa}$  is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl,  $-(alkylene)_m-OR^5$ ,  $-(alkylene)_m-S(O)_nR^5$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^5$ ,  $-(alkylene)_m-C(=S)R^5$ ,  $-(alkylene)_m-C(=O)OR^5$ ,  $-(alkylene)_m-OC(=O)R^5$ ,  $-(alkylene)_m-C(=S)OR^5$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^5$ ,  $-(alkylene)_m-N(R^3)C(=S)R^5$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^5$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^5$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^5$ , or  $-(alkylene)_m-N(R^3)SO_2R^5$ ;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more  $-(alkylene)_m-OR^{5*}$ ,  $-(alkylene)_m-S(O)_nR^{5*}$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)R^{5*}$ ,  $-(alkylene)_m-C(=O)OR^{5*}$ ,  $-(alkylene)_m-OC(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)OR^{5*}$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)R^{5*}$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^{5*}$ , or  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ;

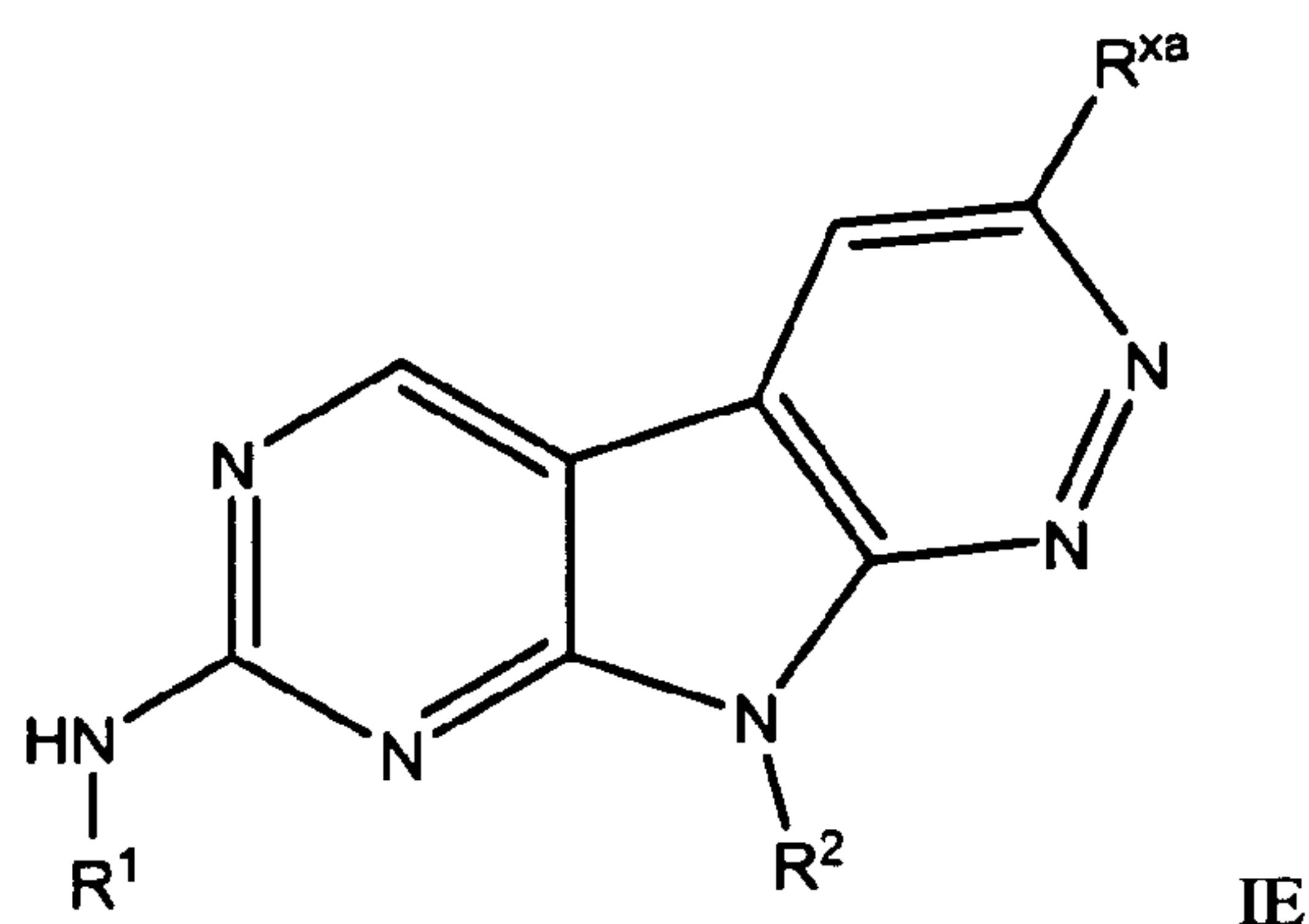
$m$  is 0 or 1 ; and

$q$  is zero to two.

Preferred compounds within the scope of Formula ID include compounds having any of the preferred  $Y$ ,  $R^1$ ,  $R^a$  and/or  $R^2$  substituents previously listed above.

Preferred compounds within the scope of Formula I include compounds having the following Formula IE





wherein  $R^{xa}$  is at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl,  $-(alkylene)_m-OR^5$ ,  $-(alkylene)_m-S(O)_nR^5$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^5$ ,  $-(alkylene)_m-C(=S)R^5$ ,  $-(alkylene)_m-C(=O)OR^5$ ,  $-(alkylene)_m-OC(=O)R^5$ ,  $-(alkylene)_m-C(=S)OR^5$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^5$ ,  $-(alkylene)_m-N(R^3)C(=S)R^5$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^5$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^5$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^5$ , or  $-(alkylene)_m-N(R^3)SO_2R^5$ ;

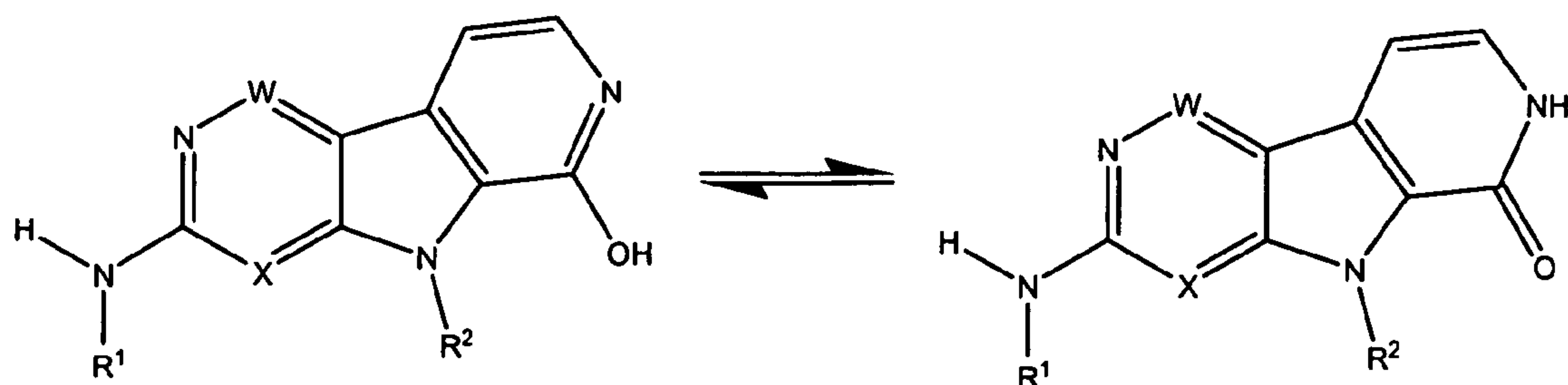
wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more  $-(alkylene)_m-OR^{5*}$ ,  $-(alkylene)_m-S(O)_nR^{5*}$ ,  $-(alkylene)_m-NR^3R^4$ ,  $-(alkylene)_m-C(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)R^{5*}$ ,  $-(alkylene)_m-C(=O)OR^{5*}$ ,  $-(alkylene)_m-OC(=O)R^{5*}$ ,  $-(alkylene)_m-C(=S)OR^{5*}$ ,  $-(alkylene)_m-C(=O)NR^3R^4$ ,  $-(alkylene)_m-C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=S)NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)R^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)R^{5*}$ ,  $-(alkylene)_m-OC(=O)NR^3R^4$ ,  $-(alkylene)_m-OC(=S)NR^3R^4$ ,  $-(alkylene)_m-SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ,  $-(alkylene)_m-N(R^3)SO_2NR^3R^4$ ,  $-(alkylene)_m-N(R^3)C(=O)OR^{5*}$ ,  $-(alkylene)_m-N(R^3)C(=S)OR^{5*}$ , or  $-(alkylene)_m-N(R^3)SO_2R^{5*}$ ;

$m$  is 0 or 1 ; and  
 $q$  is zero to two.

Preferred compounds within the scope of Formula IE include compounds having any of the preferred  $Y$ ,  $R^1$ ,  $R^a$  and/or  $R^2$  substituents previously listed above.

Certain compounds within the scope of the present invention exist as keto-enol tautomers. For example compounds such as the following:





The current invention further provides a method of treating disorders or conditions consisting of abnormal cell proliferation, such as cancer, atherosclerosis, postsurgical vascular stenosis, restenosis, and endometriosis; infections, including viral infections such as DNA viruses like herpes and RNA viruses like HIV, and fungal infections; autoimmune diseases such as psoriasis, inflammation like rheumatoid arthritis, lupus, type 1 diabetes, diabetic nephropathy, multiple sclerosis, and glomerulonephritis, organ transplant rejection, including host versus graft disease, in a mammal, including human, comprising administering to said mammal an amount of a compound of formula I or II, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

This invention further provides compounds of Formula I and II that are useful for treating abnormal cell proliferation such as cancer. The invention provides a method of treating a abnormal cell proliferation disorder such as myeloid disorders, lymphoid disorders, Hodgkin's hairy cells, leukemia, cancers of the breast, lung, colon, ovary, cervix, prostate, testis, esophagus, stomach, skin, bone, pancreas, thyroid, biliary passages, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, glioblastoma, neuroblastoma, keratocanthoma, epidermoid carcinoma, large cell carcinoma, adenocarcinoma, adenocarcinoma, adenoma, adenocarcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma, and kidney carcinoma, comprising administering a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, to a subject with one or more above disorders.

Embodiment of this invention is also a method of treating subjects with diseases caused by vascular smooth muscle cell proliferation. The method comprises administering to a subject with such a disorder an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

This invention further provides a method of treating a subject suffering from gout comprising administering to said subject in need of treatment an amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, sufficient to treat the condition.

The present invention further provides a method of treating a subject with kidney disease, such as polycystic kidney disease, comprising administering to said subject in need of treatment an amount of a compound of formula I and II, or a pharmaceutically acceptable salt thereof, sufficient to treat the condition.



### **DEFINITIONS**

The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer, pancreatic cancer, cervical cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer. The terms "treating," "treatment," and "therapy" as used herein refer to curative therapy, prophylactic therapy, and preventative therapy.

The term "mammal" as used herein refers to any mammal classified as a mammal, including humans, cows, horses, dogs and cats. In a preferred embodiment of the invention, the mammal is a human.

The term "treatment" includes therapeutic treatment as well as prophylactic treatment (either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals).

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. For example, effective neoplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkylene" embraces bridging divalent alkyl radicals such as methylene, ethylene, propylene, isopropylene and the like. The term "lower alkyl substituted with R<sup>2</sup>" does not include an acetal moiety.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Most preferred lower alkenyl radicals are radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.



The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

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

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

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

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

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



haloalkyl, nitro, cyano, alkoxy, lower alkylamino, and the like. Phenyl substituted with -O-CH<sub>2</sub>-O- forms the aryl benzodioxolyl substituent.

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

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

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

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

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



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

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

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ( $\text{-SO}_2\text{NH}_2$ ).

The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" where sulfamyl radicals are independently substituted with one or two alkyl radical(s). More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, and N-ethylaminosulfonyl.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $\text{-CO}_2\text{H}$ .

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes  $\text{-(C=O)-}$ .

The term "aminocarbonyl" denotes an amide group of the formula  $\text{-C(=O)NH}_2$ .

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals independently substituted with one or two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The terms "heterocyclylalkylenyl" and "heterocyclylalkyl" embrace heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkyl radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.



The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH<sub>3</sub>S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups, which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups, which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C<sub>1</sub>-C<sub>3</sub>-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups, which have been independently substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl



substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with alkylaminoalkoxy radicals. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminomethoxyethoxy, N-methylaminoethoxyethoxy, N,N-dimethylaminoethoxyethoxy, N,N-diethylaminomethoxymethoxy and the like.

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH<sub>2</sub> groups.

The term "halosulfonyl" embraces sulfonyl radicals substituted with a halogen radical. Examples of such halosulfonyl radicals include chlorosulfonyl and fluorosulfonyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C<sub>1</sub>-C<sub>3</sub>-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

The term "heteroaryloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heteroarylalkoxy" embraces oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having optionally substituted heteroaryl radicals attached to lower alkoxy radical as described above.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C<sub>3</sub>-C<sub>6</sub> rings. More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "5-6-membered cycloalkylalkyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals



include cyclohexylmethyl. The cycloalkyl in said radicals may be additionally substituted with halo, alkyl, alkoxy and hydroxy.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Preferred cycloalkenyl groups include C<sub>3</sub>-C<sub>6</sub> rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

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

The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of an angiogenesis mediated disease state, including those described previously. The compounds of the present invention are useful in the manufacture of an anti-cancer medicament.

The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of the current invention in association with a least one pharmaceutically acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating angiogenesis related disorders in a subject having or susceptible to such disorder, the method comprising treating the subject with a therapeutically effective amount of a compound of the current invention.

## COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of the current invention may also be



administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anticancer or cytotoxic agent.

Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiaazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myrr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline



SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, caliche mycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thiazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of  $\alpha$ -carotene,  $\alpha$ -difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphetinile, amsacrine, Angiostat, ankinomycin, antineoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium,



Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, aneastim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1 a,



interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminogluthethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Alternatively, the present compounds may also be used in co-therapies with VEGFR inhibitors including

N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-1-phthalazinamine;

4-[4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide;



N-[2-(diethylamino)ethyl]-5-[(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide;  
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide;  
 N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyloxy)methoxy]-4-quinazolinamine;  
 3-[5,6,7,13-tetrahydro-9-[(1-methylethoxy)methyl]-5-oxo-12H-indeno[2,1-a]pyrrolo[3,4-c]carbazol-12-yl]propyl ester N,N-dimethyl-glycine;  
 N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide;  
 N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine  
 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide  
 N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-4-quinazolinamine  
 N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine  
 N-(3-((((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((3-(1,3-oxazol-5-yl)phenyl)amino)-3-pyridinecarboxamide;  
 2-(((4-fluorophenyl)methyl)amino)-N-(3-((((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;  
 N-[3-(Azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide.  
 6-fluoro-N-(4-(1-methylethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;  
 2-((4-pyridinylmethyl)amino)-N-(3-(((2S)-2-pyrrolidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;  
 N-(3-(1,1-dimethylethyl)-1H-pyrazol-5-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;  
 N-(3,3-dimethyl-2,3-dihydro-1-benzofuran-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;  
 N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;  
 2-((4-pyridinylmethyl)amino)-N-(3-((2-(1-pyrrolidinyl)ethyl)oxy)-4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;  
 N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;  
 N-(4-(pentafluoroethyl)-3-(((2S)-2-pyrrolidinylmethyl)oxy)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;  
 N-(3-((3-azetidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;  
 N-(3-(4-piperidinyl)oxy)-5-(trifluoromethyl)phenyl)-2-((2-(3-pyridinyl)ethyl)amino)-3-pyridinecarboxamide;



N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;  
 2-(1H-indazol-6-ylamino)-N-[3-(1-methylpyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-  
 nicotinamide;  
 N-[1-(2-dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(1H-indazol-6-ylamino)-  
 nicotinamide;  
 2-(1H-indazol-6-ylamino)-N-[3-(pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;  
 N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;  
 N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;  
 N-[4-(tert-butyl)-3-(3-piperidylpropyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide;  
 N-[5-(tert-butyl)isoxazol-3-yl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide; and  
 N-[4-(tert-butyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide.

Other compounds described in the following patents and patent applications can be used in combination therapy: US 6,258,812, US 2003/0105091, WO 01/37820, US 6,235,764, WO 01/32651, US 6,630,500, US 6,515,004, US 6,713,485, US 5,521,184, US 5,770,599, US 5,747,498, WO 02/68406, WO 02/66470, WO 02/55501, WO 04/05279, WO 04/07481, WO 04/07458, WO 04/09784, WO 02/59110, WO 99/45009, WO 00/59509, WO 99/61422, US 5,990,141, WO 00/12089 and WO 00/02871.

In some embodiments, the combination comprises a composition of the present invention in combination with at least one anti-angiogenic agent. Agents are inclusive of, but not limited to, *in vitro* synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

Exemplary anti-tumor agents include HERCEPTIN™ (trastuzumab), which may be used to treat breast cancer and other forms of cancer, and RITUXAN™ (rituximab), ZEVALIN™ (ibritumomab tiuxetan), and LYMPHOCIDE™ (epratuzumab), which may be used to treat non-Hodgkin's lymphoma and other forms of cancer, GLEEVAC™ which may be used to treat chronic myeloid leukemia and gastrointestinal stromal tumors, and BEXXAR™ (iodine 131 tositumomab) which may be used for treatment of non-Hodgkins's lymphoma.

Exemplary anti-angiogenic agents include KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™ or VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as ERBITUX™ (IMC-C225), and VECTIBIX™ (panitumumab) IRESSA™ (gefitinib), TARCEVA™ (erlotinib), anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically



binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents. The pharmaceutical compositions of the present invention can also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor "c-Met" as well as small molecules inhibitors of the c-Met kinase activity.

Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., US Publication No. 2003/0162712; US Patent No. 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, Wiley, US Patent No. 6,727,225), ADAM disintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., US Publication No. 2002/0042368), specifically binding anti-ephrin receptor and/or anti-ephrin antibodies or antigen binding regions (US Patent Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

Additional anti-angiogenic/anti-tumor agents include: SD-7784 (Pfizer, USA); cilengitide (Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, USA); TLC ELL-12, (Elan, Ireland); anecortave acetate, (Alcon, USA); alpha-D148 Mab, (Amgen, USA); CEP-7055, (Cephalon, USA); anti-Vn Mab, (Crucell, Netherlands); DAC: antiangiogenic, (ConjuChem, Canada); Angiocidin, (InKine Pharmaceutical, USA); KM-2550, (Kyowa Hakko, Japan); SU-0879, (Pfizer, USA); CGP-79787, (Novartis, Switzerland, EP 970070); ARGENT technology, (Ariad, USA); YIGSR-Stealth, (Johnson & Johnson, USA); fibrinogen-E fragment, (BioActa, UK); angiogenesis inhibitor, (Trigen, UK); TBC-1635, (Encysive Pharmaceuticals, USA); SC-236, (Pfizer, USA); ABT-567, (Abbott, USA); Metastatin, (EntreMed, USA); angiogenesis inhibitor, (Tripep, Sweden); maspin, (Sosei, Japan); 2-methoxyestradiol, (Oncology Sciences Corporation, USA); ER-68203-00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz-93, (Tsumura, Japan); TAN-1120, (Takeda, Japan); FR-111142, (Fujisawa, Japan, JP 02233610); platelet factor 4, (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist, (Boreon, Denmark); cancer therapy, (University of South Carolina, USA); bevacizumab (pINN), (Genentech, USA); angiogenesis inhibitors, (SUGEN, USA); XL 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb, alpha5beta3 integrin, second generation, (Applied Molecular Evolution, USA and MedImmune, USA); gene therapy, retinopathy, (Oxford BioMedica, UK); enzastaurin hydrochloride (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA and Sanofi-Synthelabo, France); BC 1, (Genoa Institute of Cancer Research, Italy); angiogenesis inhibitor, (Alchemia, Australia); VEGF antagonist, (Regeneron, USA); rBPI 21 and BPI-derived antiangiogenic, (XOMA, USA); PI 88, (Progen, Australia); cilengitide



(pINN), (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); cetuximab (INN), (Aventis, France); AVE 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin, (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA); ANGIOSTATIN, (Boston Childrens Hospital, USA); 2-methoxyestradiol, (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o-guanidines, ( Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenesis, (EntreMed, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol, (EntreMed, USA); angonex, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); tumor necrosis factor-alpha inhibitors, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S-3APG , (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alpha5 betal, (Protein Design, USA); KDR kinase inhibitor, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sankyo, Japan); combretastatin A4 prodrug, (Arizona State University, USA); chondroitinase AC, (IBEX, Canada); BAY RES 2690, (Bayer, Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetrathiomolybdate, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, vascular endothelium growth factor, (Xenova, UK); irsogladine (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); squalamine (pINN), (Genaera, USA); RPI 4610, (Sirna, USA); cancer therapy, (Marinova, Australia); heparanase inhibitors, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VGA 1102, (Taisho, Japan);



VEGF receptor modulators, (Pharmacopeia, USA); VE-cadherin-2 antagonists, (ImClone Systems, USA); Vasostatin, (National Institutes of Health, USA); vaccine, Flk-1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan); TumStatin, (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1), (Merck & Co, USA); Tie-2 ligands, (Regeneron, USA); and, thrombospondin 1 inhibitor, (Allegheny Health, Education and Research Foundation, USA).

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as VEGF antagonists, other kinase inhibitors including p38 inhibitors, KDR inhibitors, EGF inhibitors (such as panitumumab), CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, NSAID's,  $\alpha_v\beta_3$  inhibitors, phosphatidylinositol 3-kinase inhibitors, AKT/PCK inhibitors, proteasome inhibitors (such as Velcade<sup>TM</sup>), Trail receptor agonists (such as AMG 655), Trail (such as AMG 951), XIAP inhibitors, BCL2 inhibitors, Aurora kinase inhibitors, Raf kinases inhibitors, ubiquitin ligase inhibitors, HGF inhibitors (such as AMG 102), and c-Met inhibitors (such as compounds described WO 06/116713 and U.S. Serial No. 11/879,034).

Also included in the family of compounds of the current are the pharmaceutically acceptable salts and solvates thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the current invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic,  $\beta$ -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of the current invention include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding

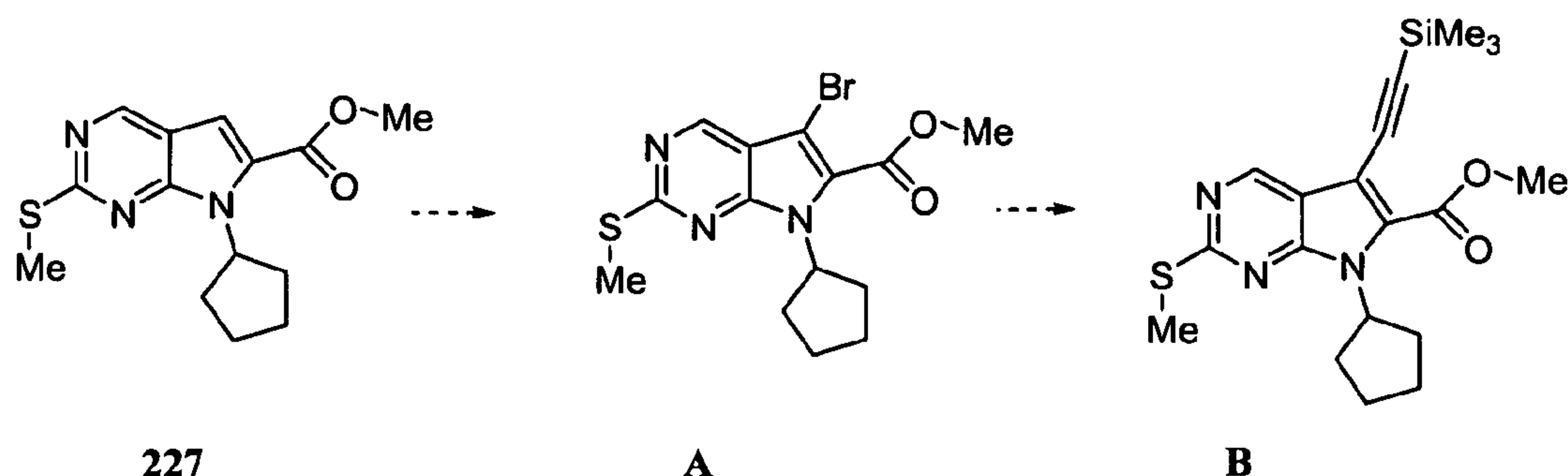


compound of the invention by reacting, for example, the appropriate acid or base with the compound of the current invention. When a basic group and an acid group are present in the same molecule, a compound of the current invention may also form internal salts.

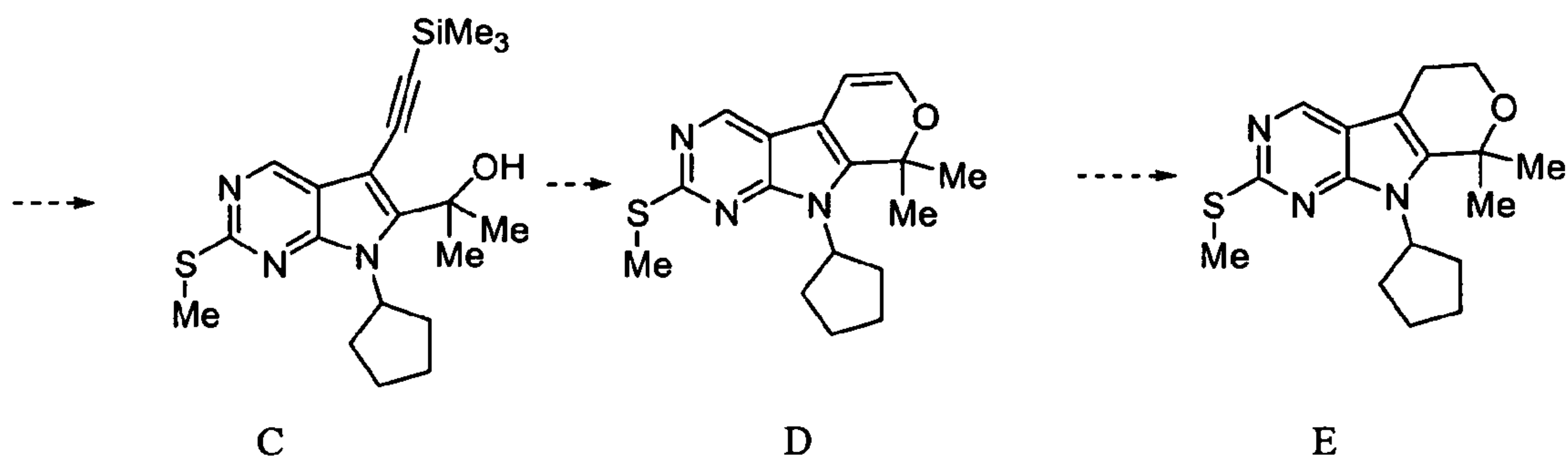
### **GENERAL SYNTHETIC PROCEDURES**

The compounds of the invention can be synthesized according to the procedures illustrated in the following working examples, as well as by alternative methods known to those of ordinary skill in the art..

Additional analogs can be prepared by the following general schemes.

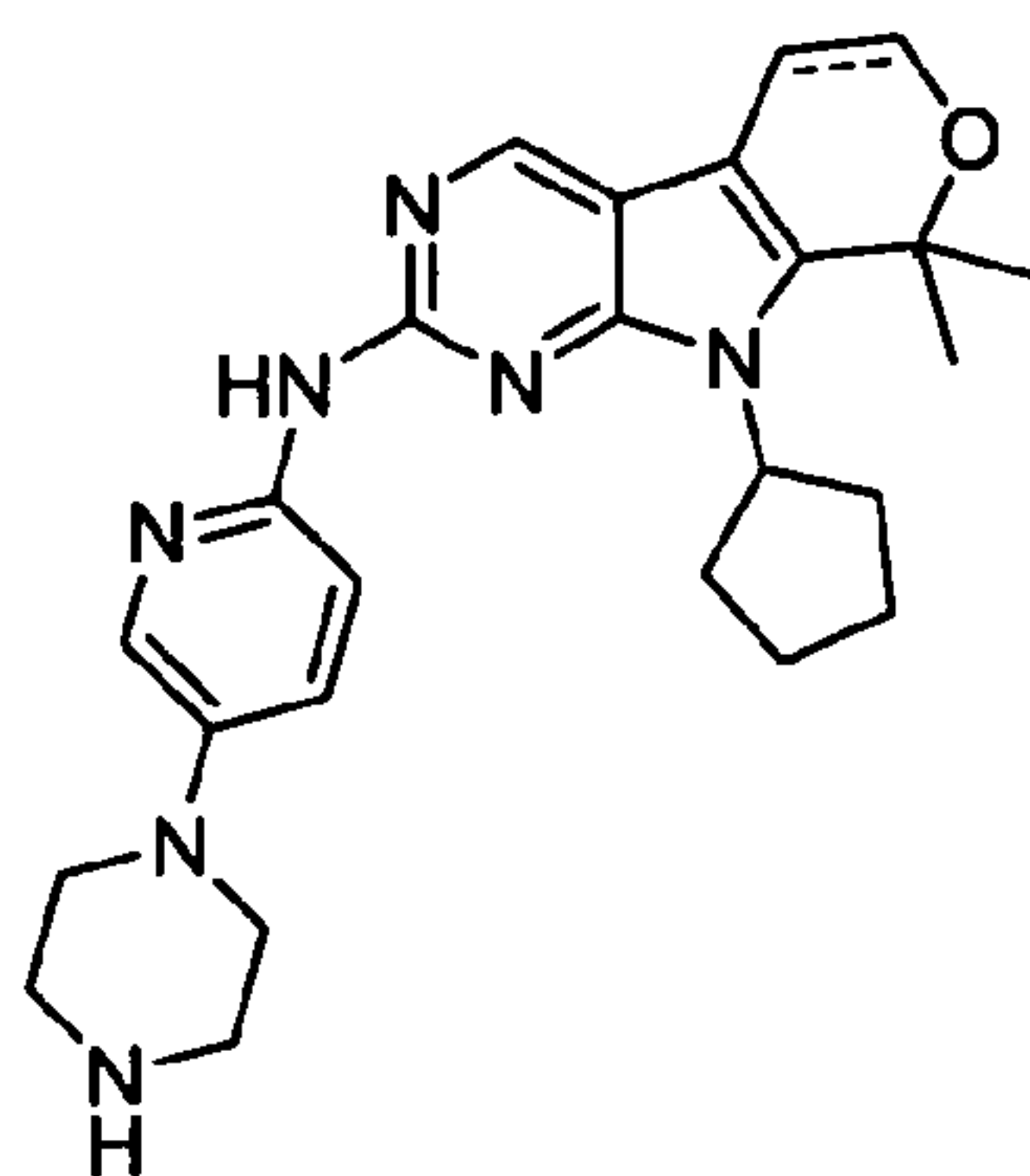


Bromination of compound **227** with NBS in analogy to the preparation of compound **230** of example 168 provides bromo ester **A**. Sonagshira coupling provides the alkyne **B**. Grignard addition provides the tertiary alcohol **C**. Mild acidic workup provides the fused pyran **D**.

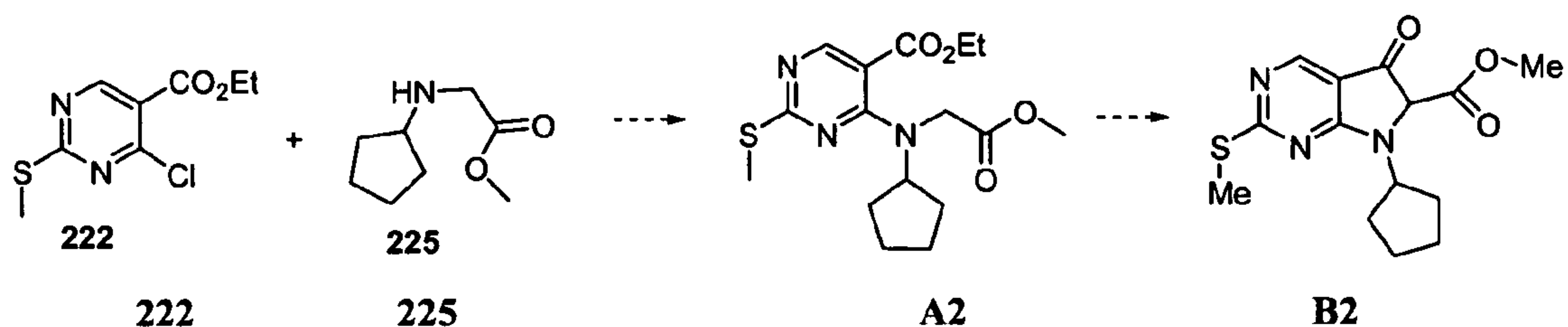


The thiomethyl group of compounds **D** and **E** can be converted to typical substituted heteroaryl and aryl amines in analogy to example 168 providing inhibitors such as **F** and **G**.

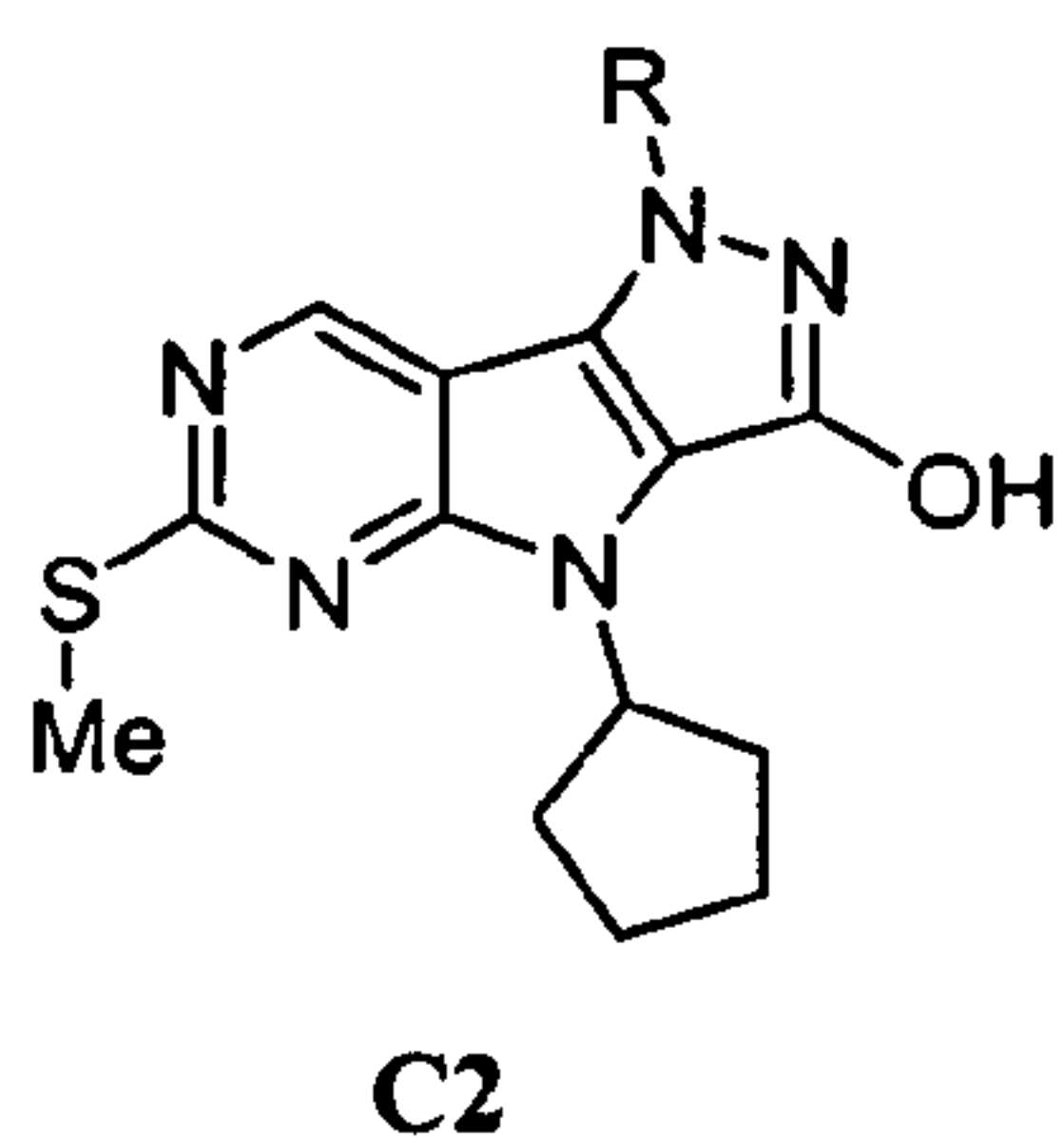




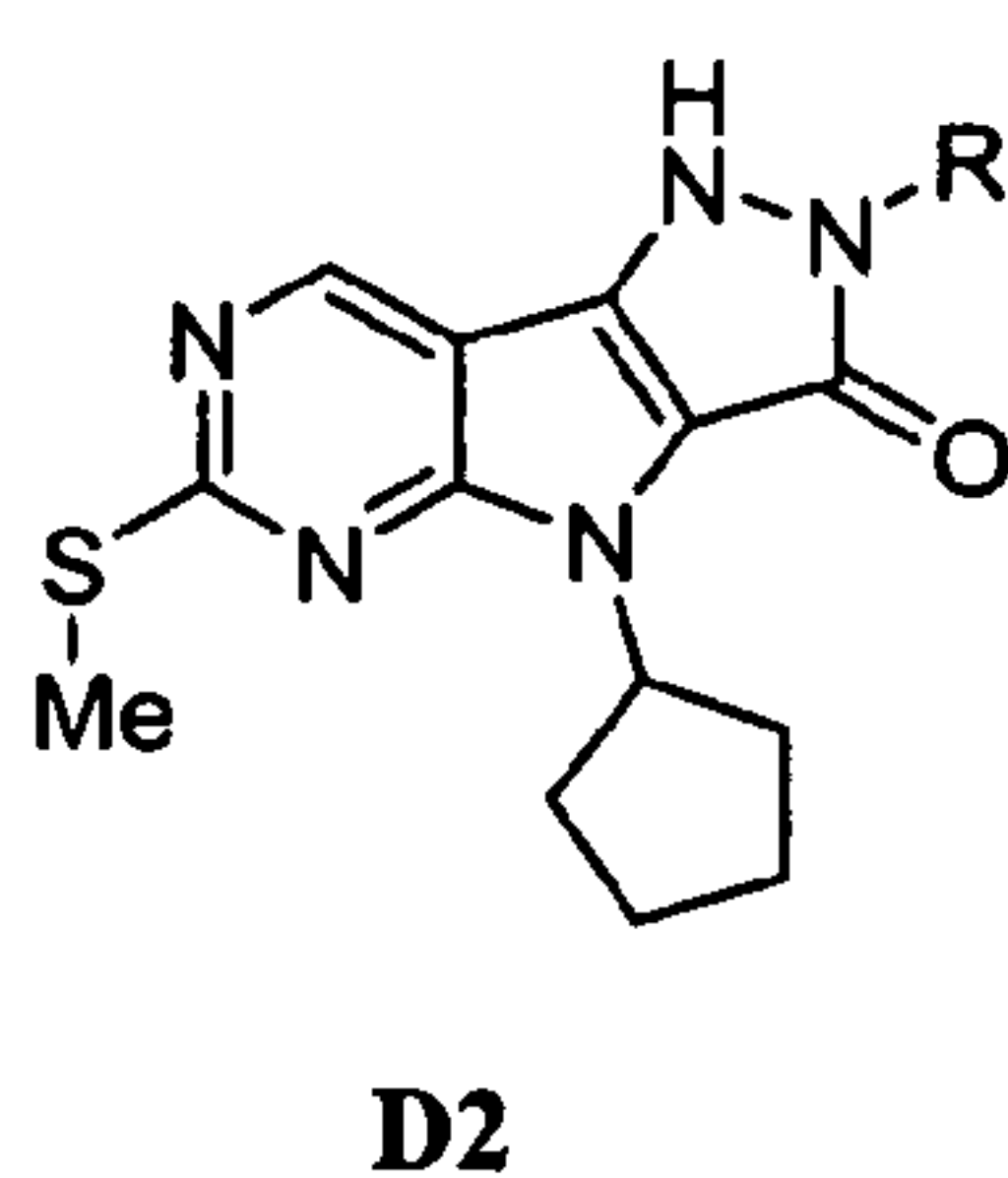
F/G



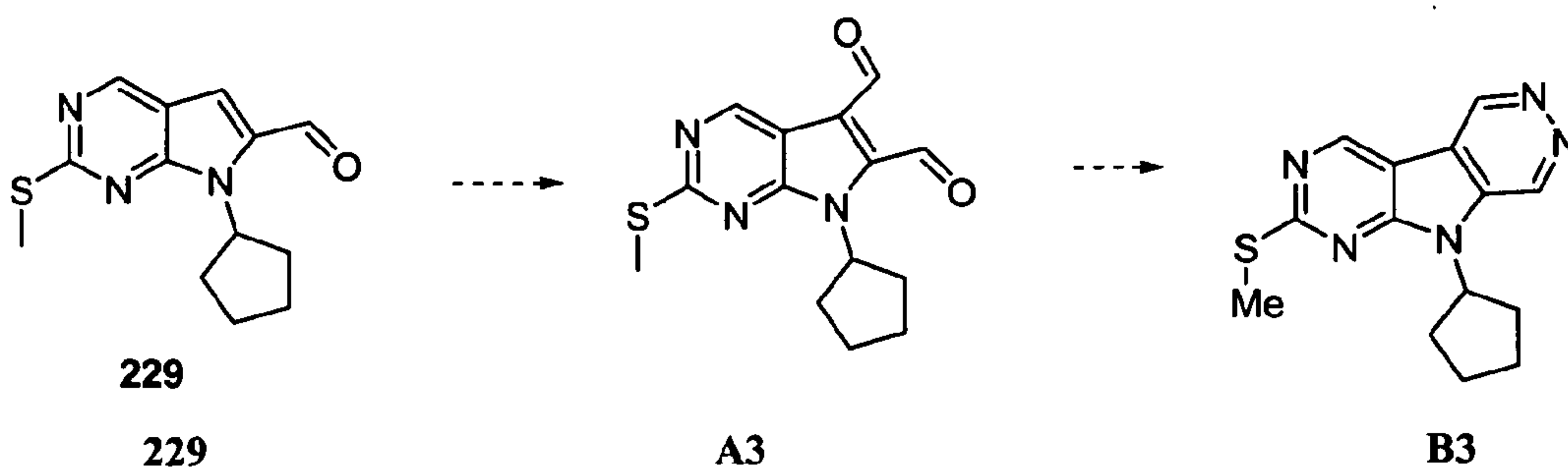
Condensation of amine **225** with pyrimidine **222** provides diester **A2** which can undergo claisen condensation to the keto ester **B2**, which is a versatile intermediate for a number of transformations. Condensation with hydrazines can lead to fused pyrazoles such a **C2** and **D2**, which can be further modified to examples of this invention.



C2

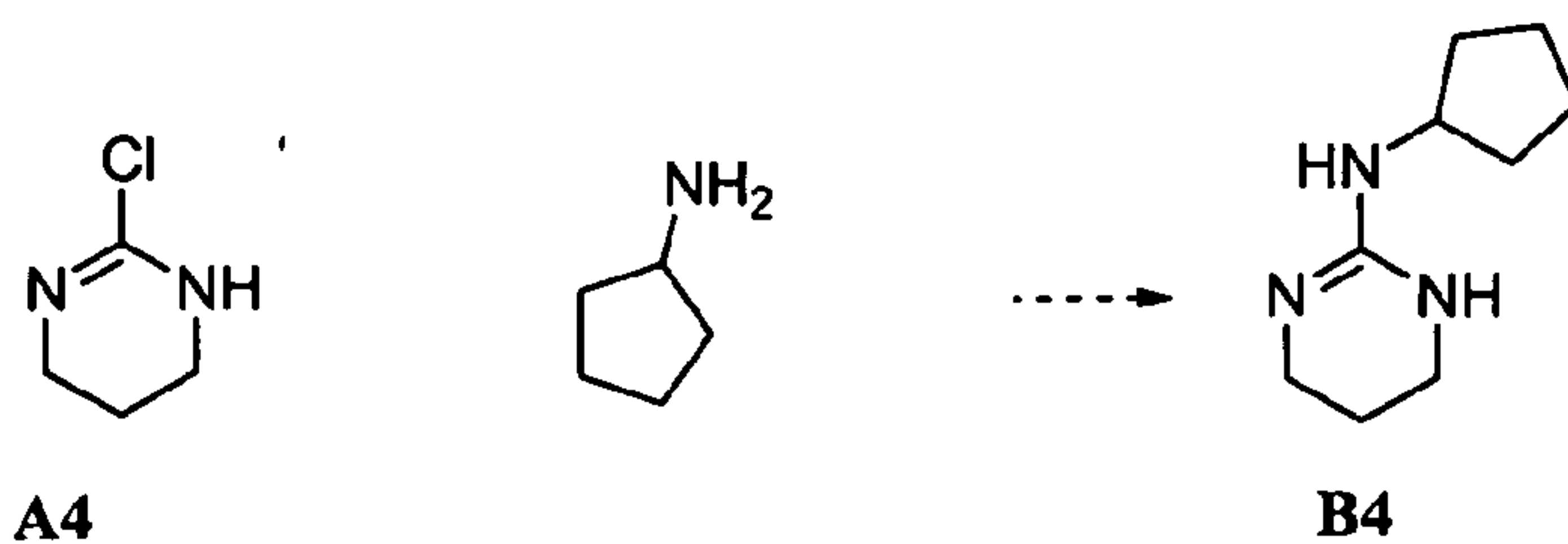


D2

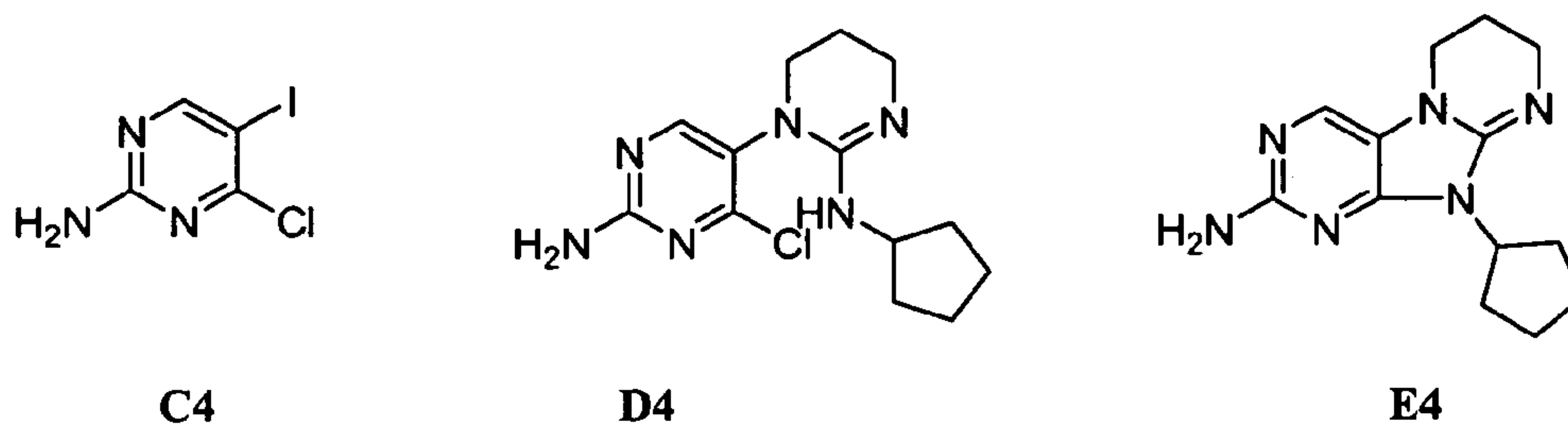




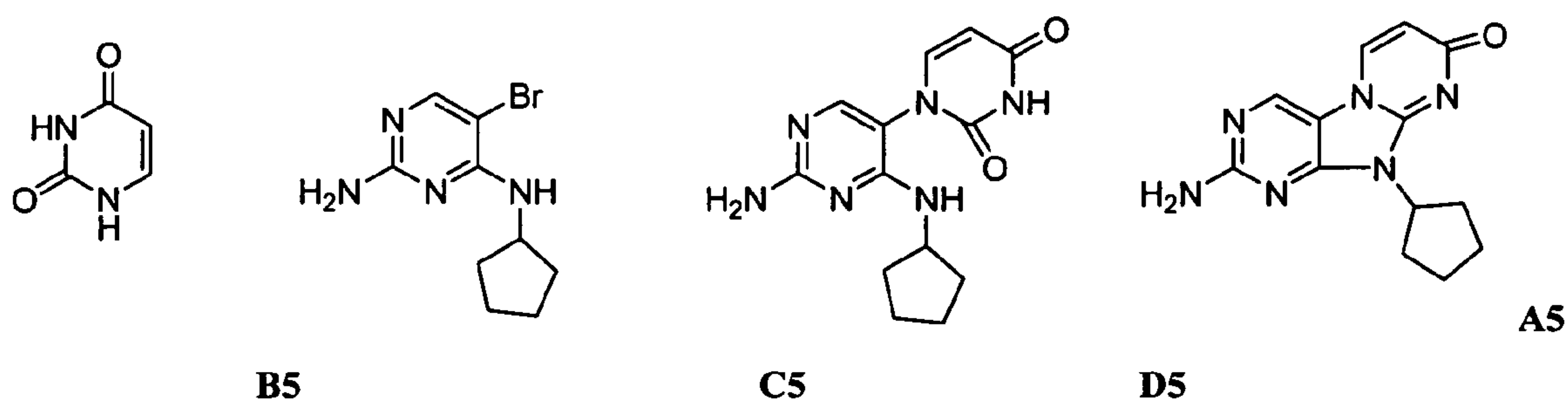
Aldehyde **229** can be formylated to an equivalent of the dialdehyde **A3** which can be used to form the fused pyridazine **B3**, which can be further modified to examples of this invention.



According to Kan, Wai Ming; Lin, Shih-Hsun; Chern, Ching-Yuh SynComm V35 p2633 y2005, amines such as cyclopentyl amine can be added to chloroformamidines such as **A4** to form guanidines such as **B4**. Buchwald coupling with halopyrimidines such as **C4** followed by intramolecular cyclization can provide substrates for elaboration to examples of this invention. The 5 and 7-member ring analogs of **A4** are also useable.

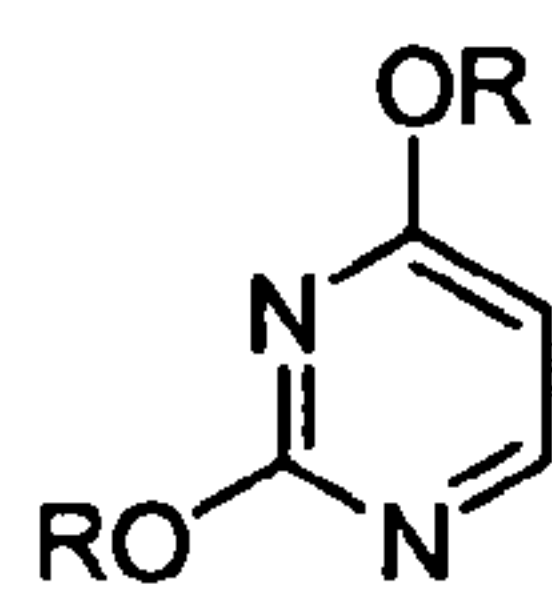


The use of uracil **A5** or dialkoxypyrimidine heterocycles can lead to more elaborate analogs.

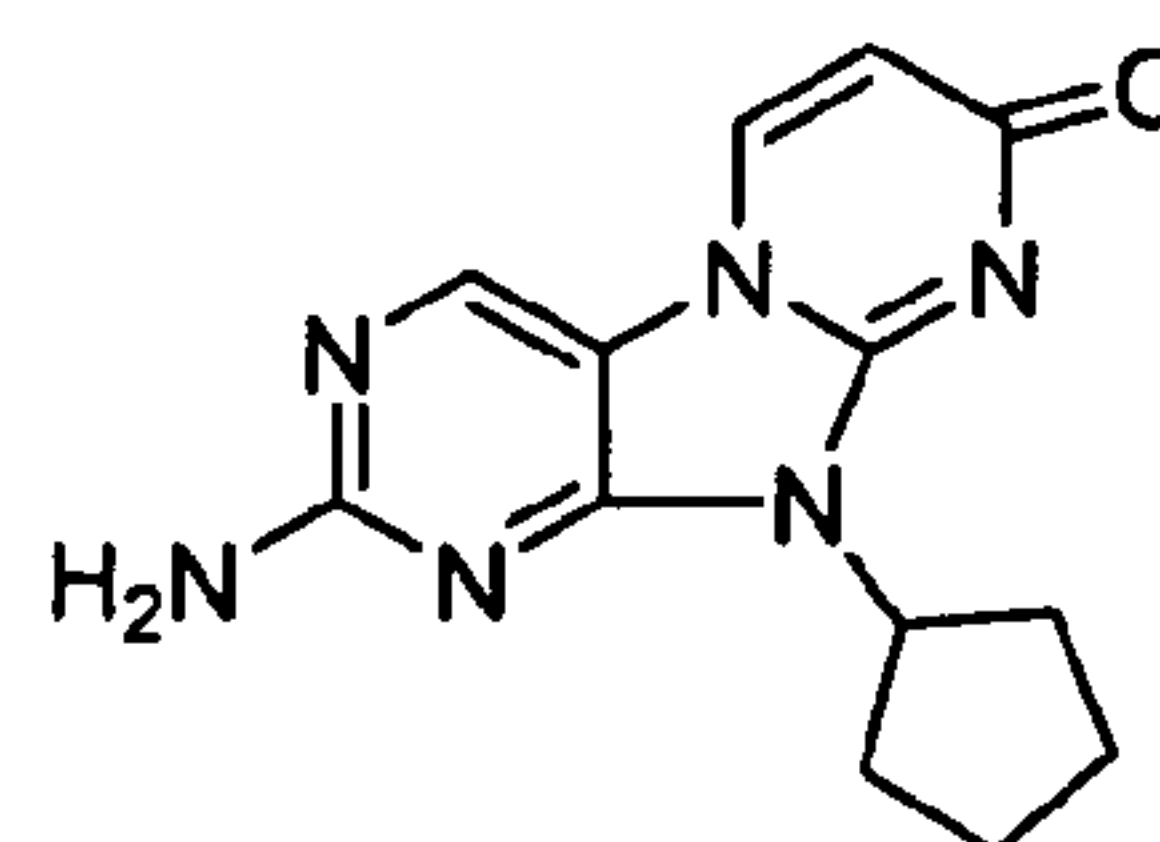
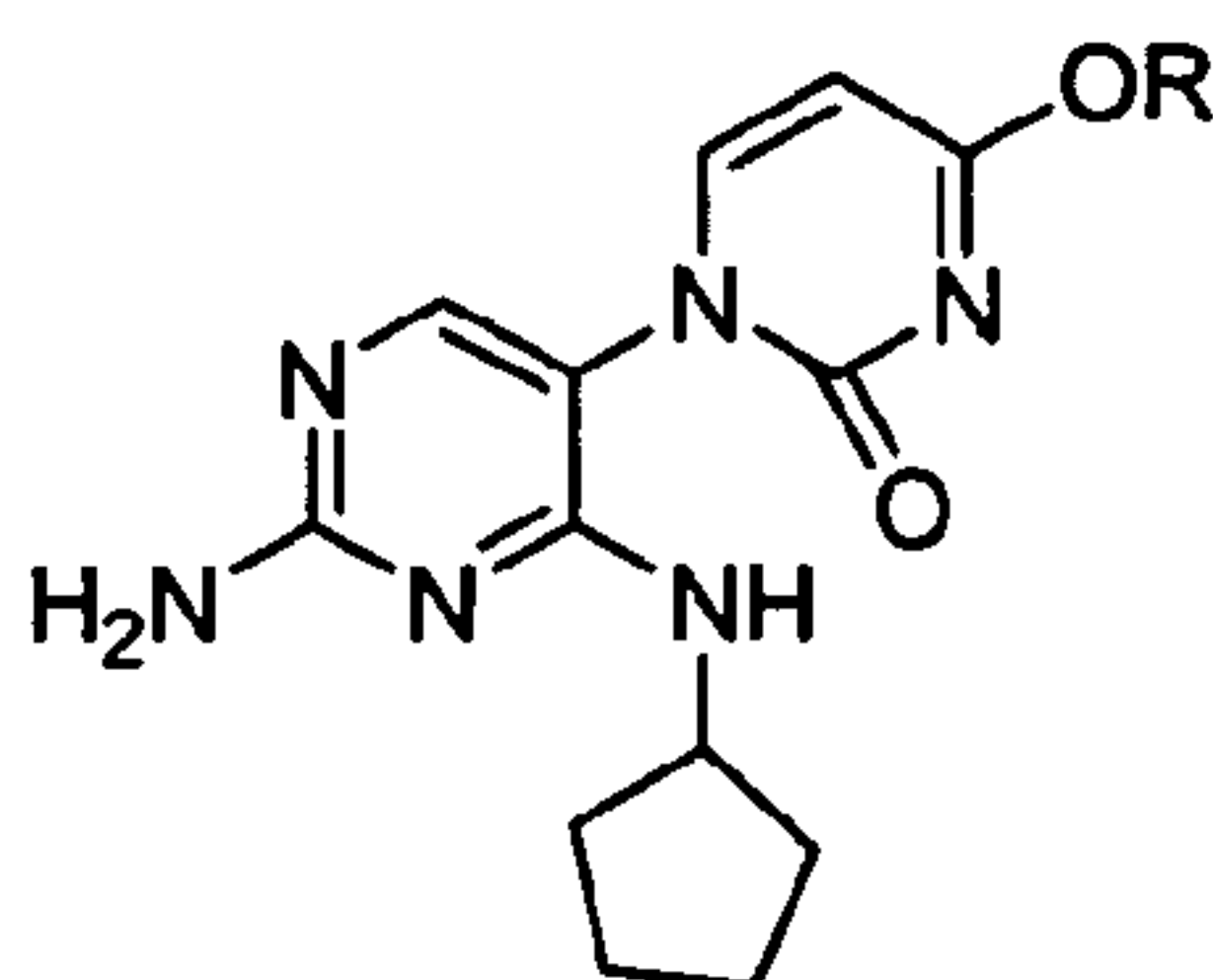


or





C6



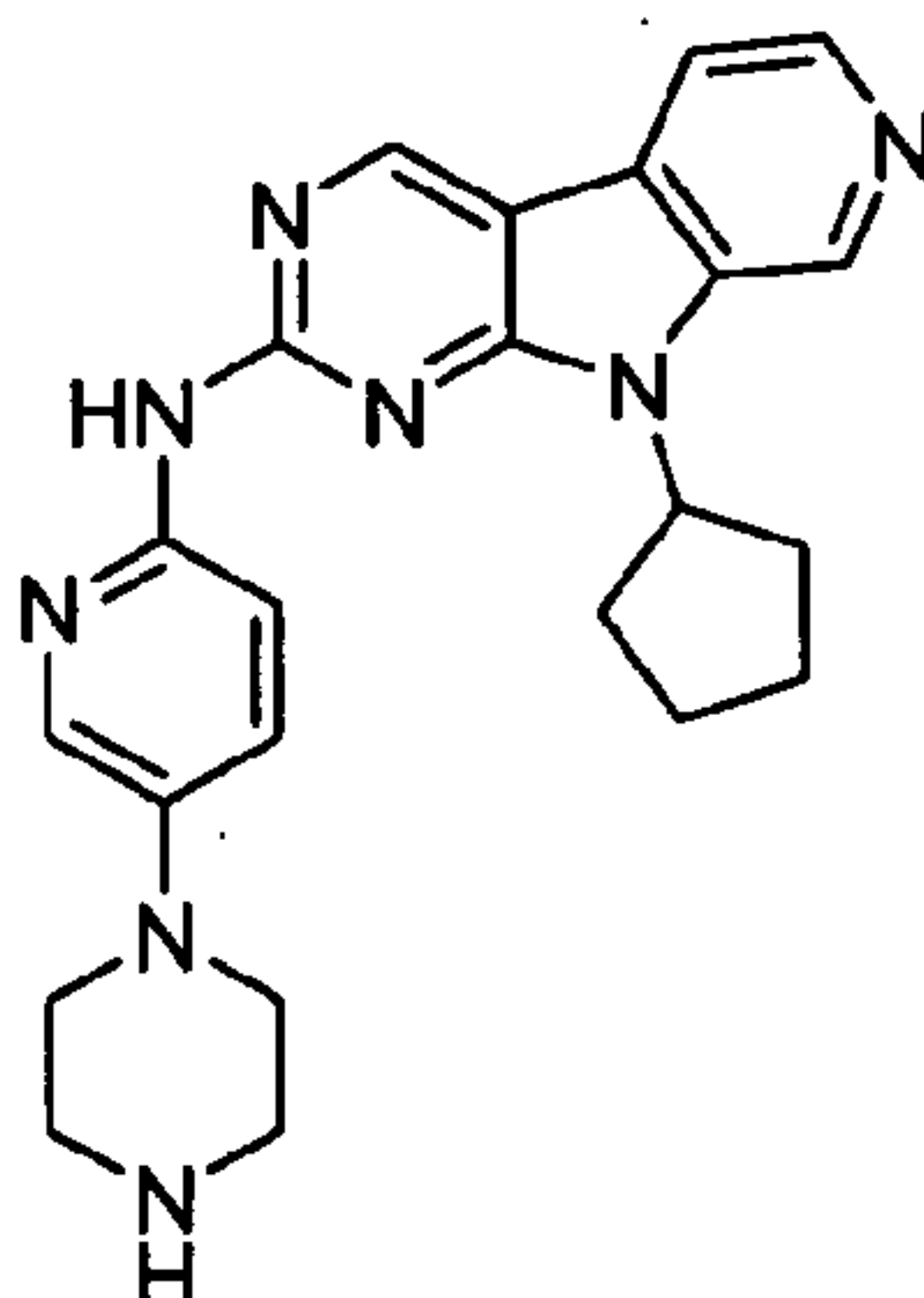
D5

A6

### EXAMPLES

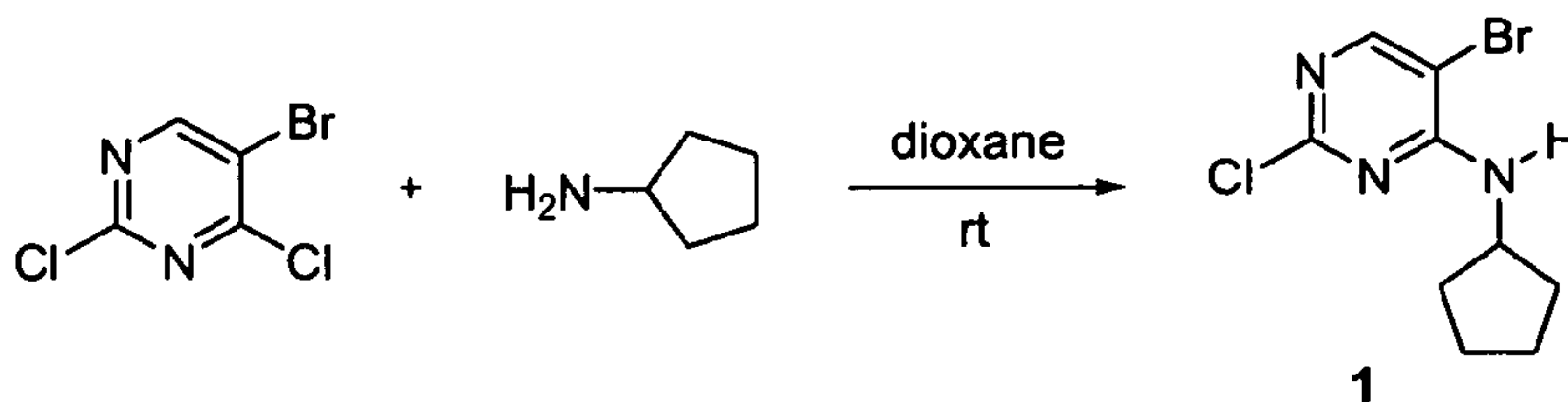
The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results.

#### EXAMPLE 1



7

**9-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

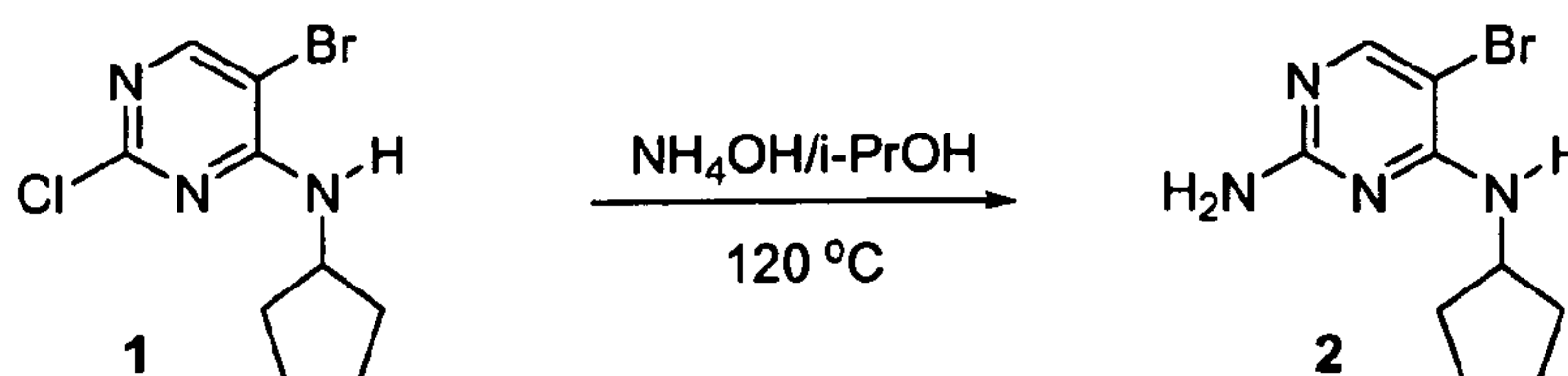


1

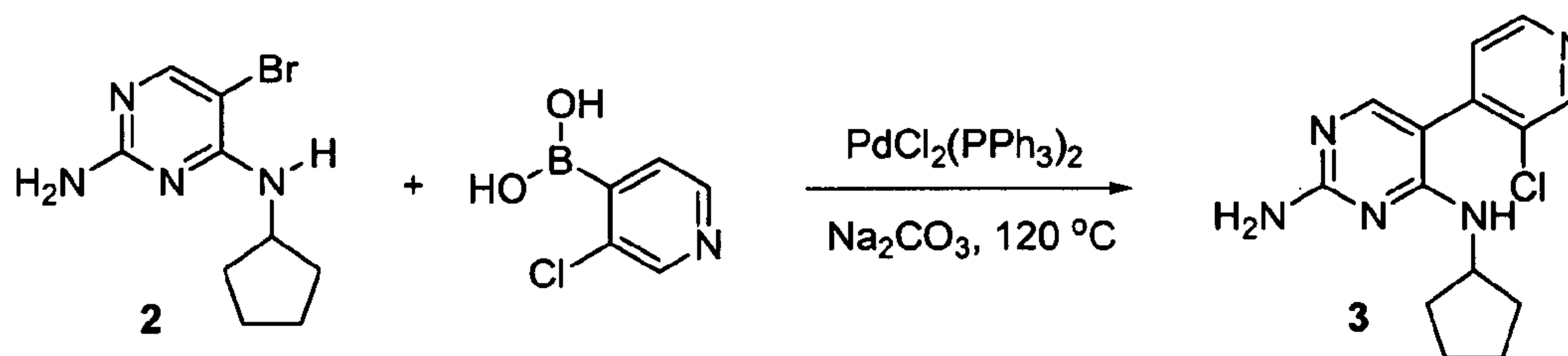
**5-Bromo-2-chloro-N-cyclopentylpyrimidin-4-amine (1):** To a solution of 5-bromo-2,4-dichloropyrimidine (45.6 g, 200 mmol) in dioxane (400 mL) was added *N*-cyclopentylamine (20.4 g, 240 mmol) at room temperature. The mixture thus obtained was stirred at room temperature for 6 h. The reaction mixture was then diluted with ethyl acetate and washed with brine and dried over  $\text{MgSO}_4$ . The solvent was evaporated to give the title compound as a light yellow solid (56 g, 100%) which was used in next step without further purification.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.23 (1H, s), 7.37 (1H,



d, J=7.3 Hz), 4.31 (1H, m), 1.92 (2H, m), 1.71 (2H, m), 1.53-1.59 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 276.0, Calculated 275.9.

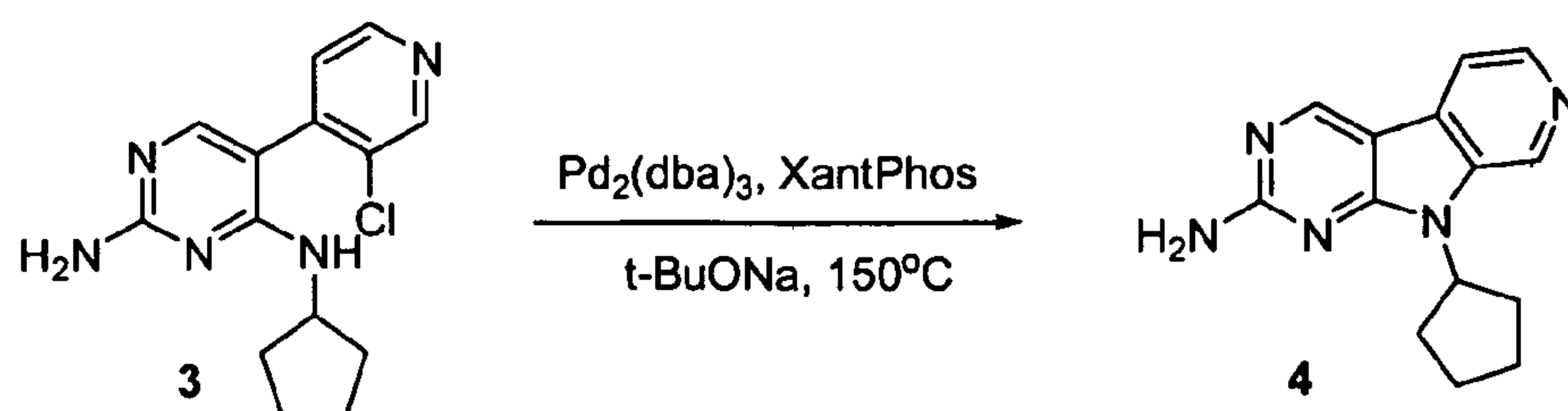


**5-Bromo-N<sup>4</sup>-cyclopentylpyrimidine-2,4-diamine (2):** A solution of **1** (45 g, 200 mmol) in 28% NH<sub>4</sub>OH/iso-propanol (1/1, 400 mL) was heated at 120 °C in a sealed tube for 22 h. The product was extracted with dichloromethane and the organic layers were washed with brine and dried. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with 25% ethyl acetate in hexanes to give the titled compound (**2**) as a white solid (34 g, 66%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 7.77 (1H, s), 6.19 (2H, br. s), 6.12 (1H, d, 1H, J = 7.3 Hz), 4.33(1H, m) 1.90 (2H, m), 1.69 (2H, m), 1.49-1.55 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 257.0, Calculated 257.0.

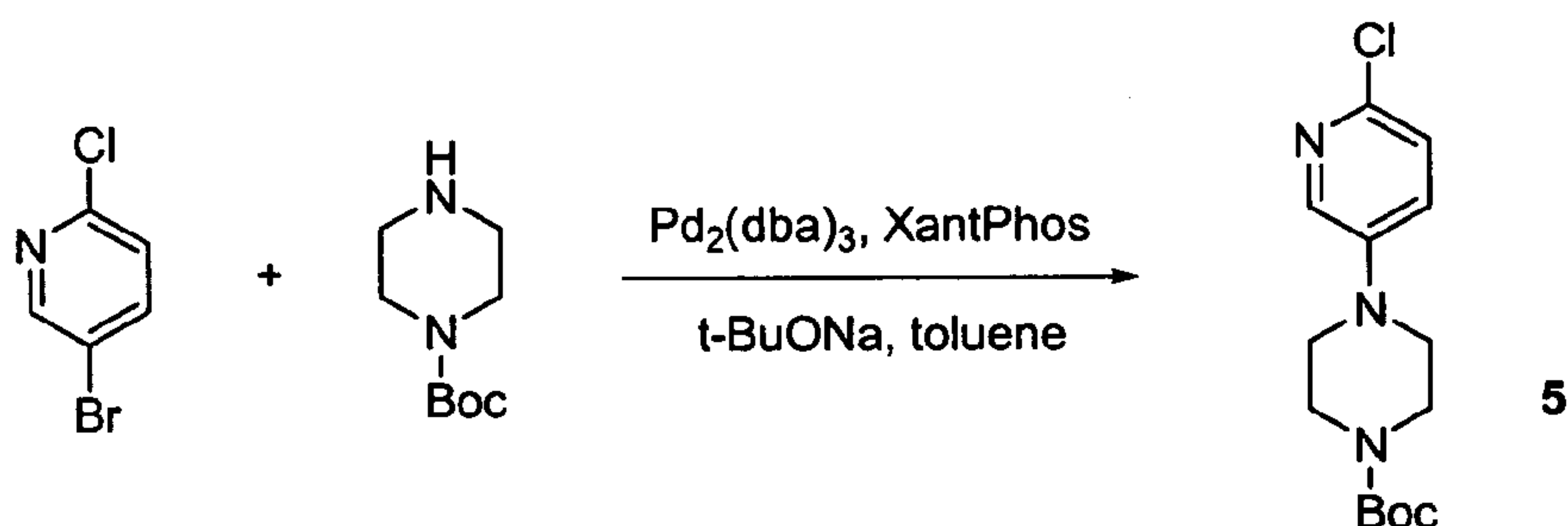


**5-(3-Chloropyridin-4-yl)-N<sup>4</sup>-cyclopentylpyrimidine-2,4-diamine (3):** To a solution of **2** (2.57 g, 10.0 mmol) in dioxane (75 mL) were added 3-chloropyridine-4-boronic acid (4.72 g, 10.0 mmol), trans-dichlorobis(triphenylphosphine)-palladium(II) (702 mg, 1.0 mmol), and sodium carbonate (3.82 g, 36 mmol, in 36 mL of water). The mixture thus obtained was purged with N<sub>2</sub> for 10 min and heated at 120°C in a sealed tube for 22 h. The reaction mixture was diluted with water and the product was extracted with chloroform. The organic layers were dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 2.5% methanol in dichloromethane to give the title compound (**3**) as a white solid (2.31 g, 80%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.64 (1H, s), 8.50 (1H, d, J = 4.9 Hz), 7.51 (1H, s), 7.34 (1H, d, 1H, J = 4.9 Hz), 6.21 (2H, d, 1H, br s), 5.97 (1H, d, J = 7.6 Hz), 4.43 (1 H, p, J = 7.4Hz), 1.84 (2H, m), 1.62 (2H, m), 1.40-1.49 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 290.0, Calculated 290.1.



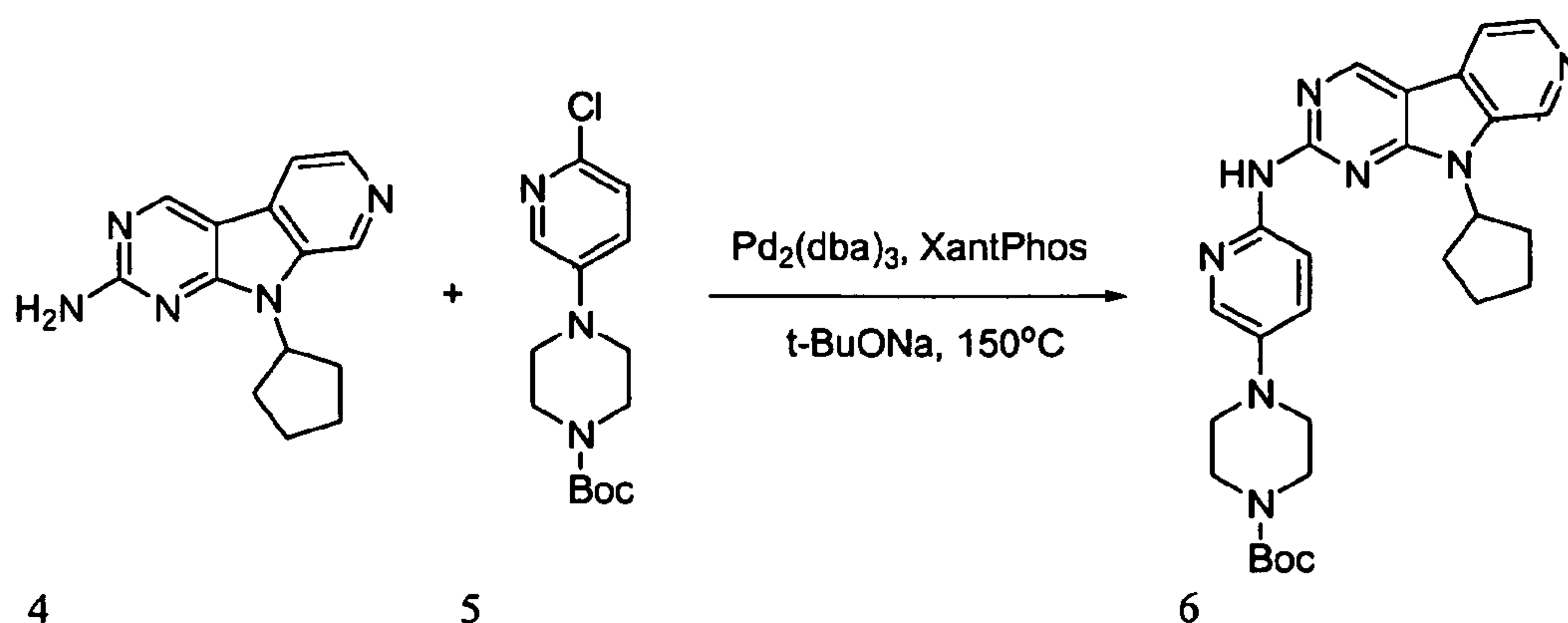


**9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (4):** To a solution of **3** (2.3 g, 7.9 mmol) in dioxane (60 mL) were added tris(dibenzylideneacetone)dipalladium (0) (368 mg, 0.4 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (696 mg, 1.2 mmol), and sodium *t*-butoxide (1.15 g, 12 mmol). The mixture thus obtained was heated at 150 °C under microwave irradiation for 3 h. The reaction mixture was passed through a short pack silica gel column and concentrated. The residue was purified by flash chromatography on silica gel eluting with 2% methanol in dichloromethane to give the title compound (**4**) as a white solid (1.71 g, 85%). <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.05 (1H, s), 8.87 (1H, br. s), 8.37 (1H, d, *J* = 4.9 Hz), 7.93 (1H, d, *J* = 5.1 Hz), 6.97 (2H, br. s), 5.33 (1H, p, *J* = 8.6 Hz), 2.27 (2H, m), 2.04 (4H, m), 1.76 (2H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 254.1, Calculated 254.1.

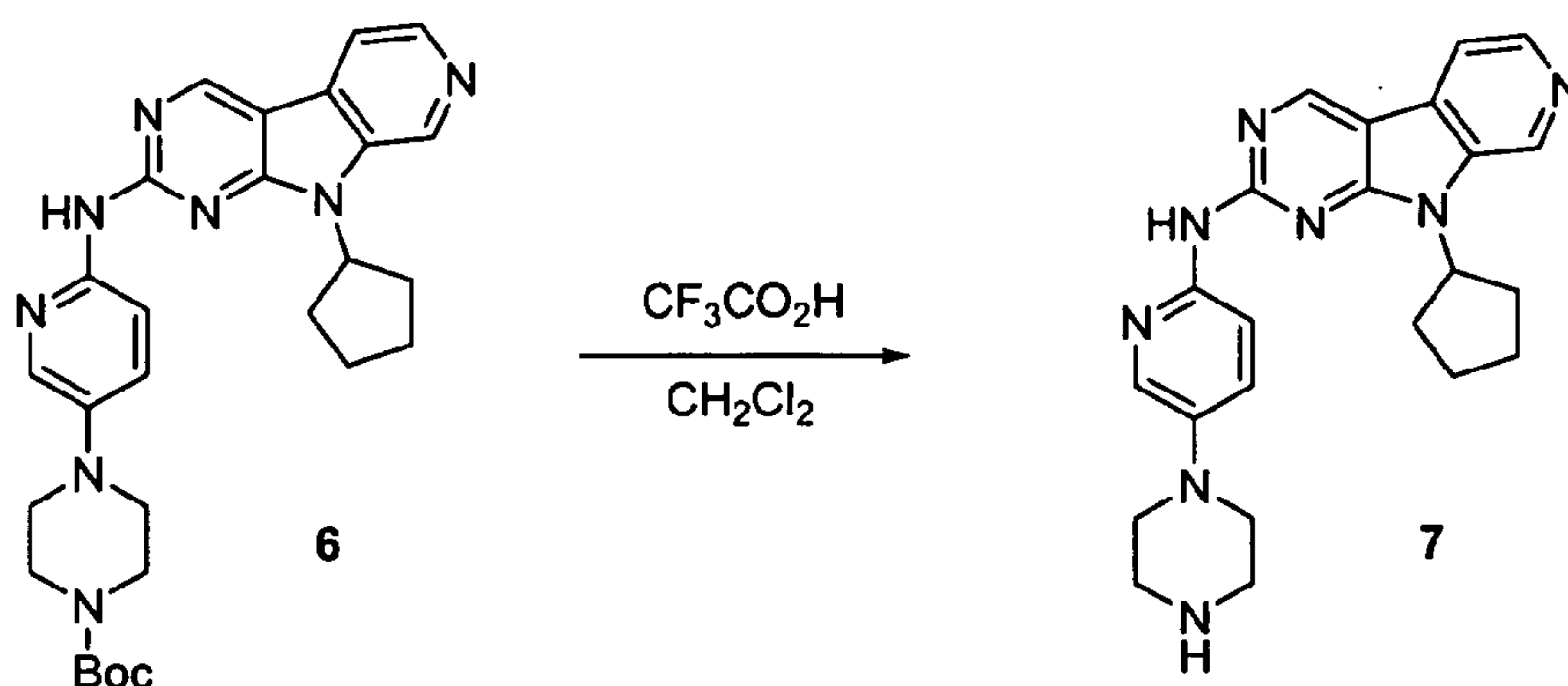


**4-(4-Chloro-pyrid-2-yl)-piperidine-1-carboxylic acid t-butyl ester (5):** As reported in Ji, J.; Li, T.; Bunnelle, W. H., *Org. Lett.* **2003**, 5, (24), 4611-4614, *t*-butyl 1-piperazinecarboxylate (11.18 g, 60 mmol), sodium *t*-butoxide (8.64 g, 90 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (1.10 g, 1.20 mmol), and XantPhos (2.08 g, 3.6 mmol) were added to a solution of 5-bromo-2-chloropyridine (11.54 g, 60 mmol) in toluene (300 mL). The mixture was evacuated and purged with argon (3 cycles), then heated at 100 °C for 5 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (1200 mL) and washed with water (300 mL). The organic solution was concentrated under pressure, and the residue was purified by flash chromatography on silica gel eluting with 17% ethyl acetate in hexane to give compound **5** as a light yellow solid (14.56 g, 82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.02 (1H, s), 7.19 – 7.18 (2H, m), 3.59 (4H, dd, *J* = 12 Hz, *J* = 4 Hz), 3.14 (4H, dd, *J* = 12 Hz, *J* = 4 Hz), 1.49 (9H, s) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 298.1, Calculated 298.1.





**t-Butyl 4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (6):** To a solution of compound 4 (1.6 g, 6.3 mmol) in dioxane (60 mL) were added compound 5 (2.3 g, 7.6 mmol), tris(dibenzylideneacetone) dipalladium (0) (293 mg, 0.32 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (370 mg, 0.64 mmol), and sodium *t*-butoxide (908 mg, 9.45 mmol). The mixture thus obtained was heated at 150 °C under microwave irradiation for 1 h. The reaction mixture was passed through a short pack silica gel column and concentrated to give the title compound 6 as a yellow solid (3.28 g) which was used in next step without further purification. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.11 (1H, s), 8.93 (1H, br. s), 8.53 (1H, d, *J* = 5.1 Hz), 8.44 (1H, d, *J* = 9.3 Hz), 8.28 (1H, br. s), 8.09 (1 H, d, *J* = 2.9Hz), 7.87 (1H, dd, *J* = 5.1Hz, 0.9Hz), 7.41 (1H, dd, *J* = 9.3Hz, 2.9Hz), 5.40 (1H, p, *J* = 8.8Hz), 3.65 (4H, t, *J* = 5.2Hz), 3.15 (4H, t, *J* = 4.9Hz), 2.46 (2H, m), 2.15-2.4 (4H, m), 1.91 (2H, m), 1.52 (9H, s) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 515.2, Calculated 515.3.

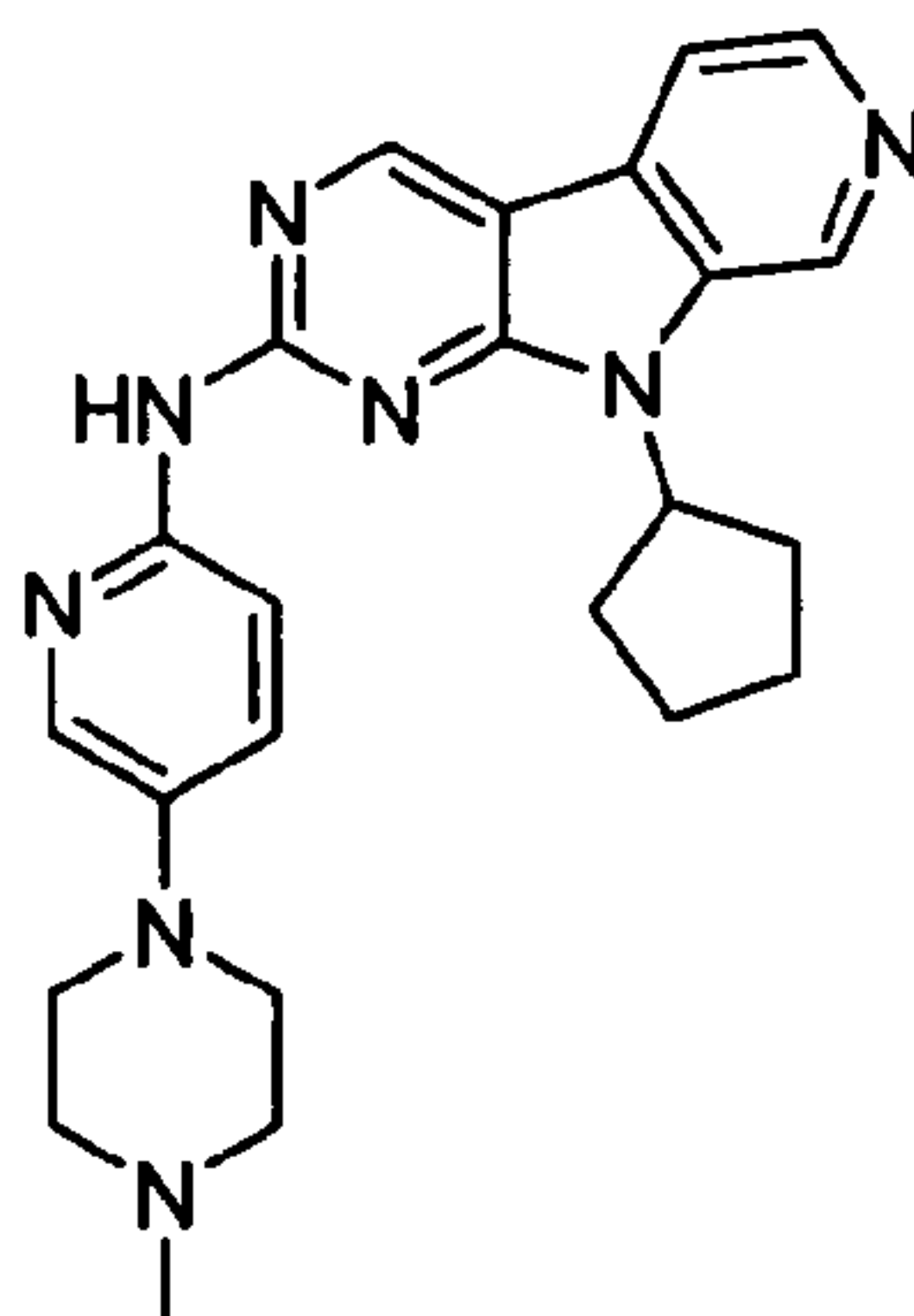


**9-Cyclopentyl-*N*-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (7):** A solution of compound 6 (3.28 g, 6.37 mmol) in TFA/DCM (60, 1:1) was stirred at room temperature for 30 min. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/methanol/NH<sub>4</sub>OH (200:10:1) to give the title compound (7) as an off-white solid (2.60 g, 98%). <sup>1</sup>H NMR (400 MHz, *DMSO-d*<sub>6</sub>) δ 9.86 (1H, s), 9.28 (1H, s), 9.01 (1H, s), 8.68 (1H, br s), 8.45 (1H, d, *J* = 4 Hz), 8.23 (1 H, d, *J* = 8 Hz), 8.10 (1H, d, *J* = 4



Hz), 8.04 (1H, d,  $J = 8$  Hz), 7.54 (1H, dd,  $J = 8$  Hz,  $J = 4$  Hz), 5.43 (1H, p,  $J = 8$  Hz), 3.35 (4H, m), 3.26 (4H, m), 2.40 (2H, m), 2.03-2.10 (4H, m), 1.78 (2H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 415.1, Calculated 415.2.

### EXAMPLE 2

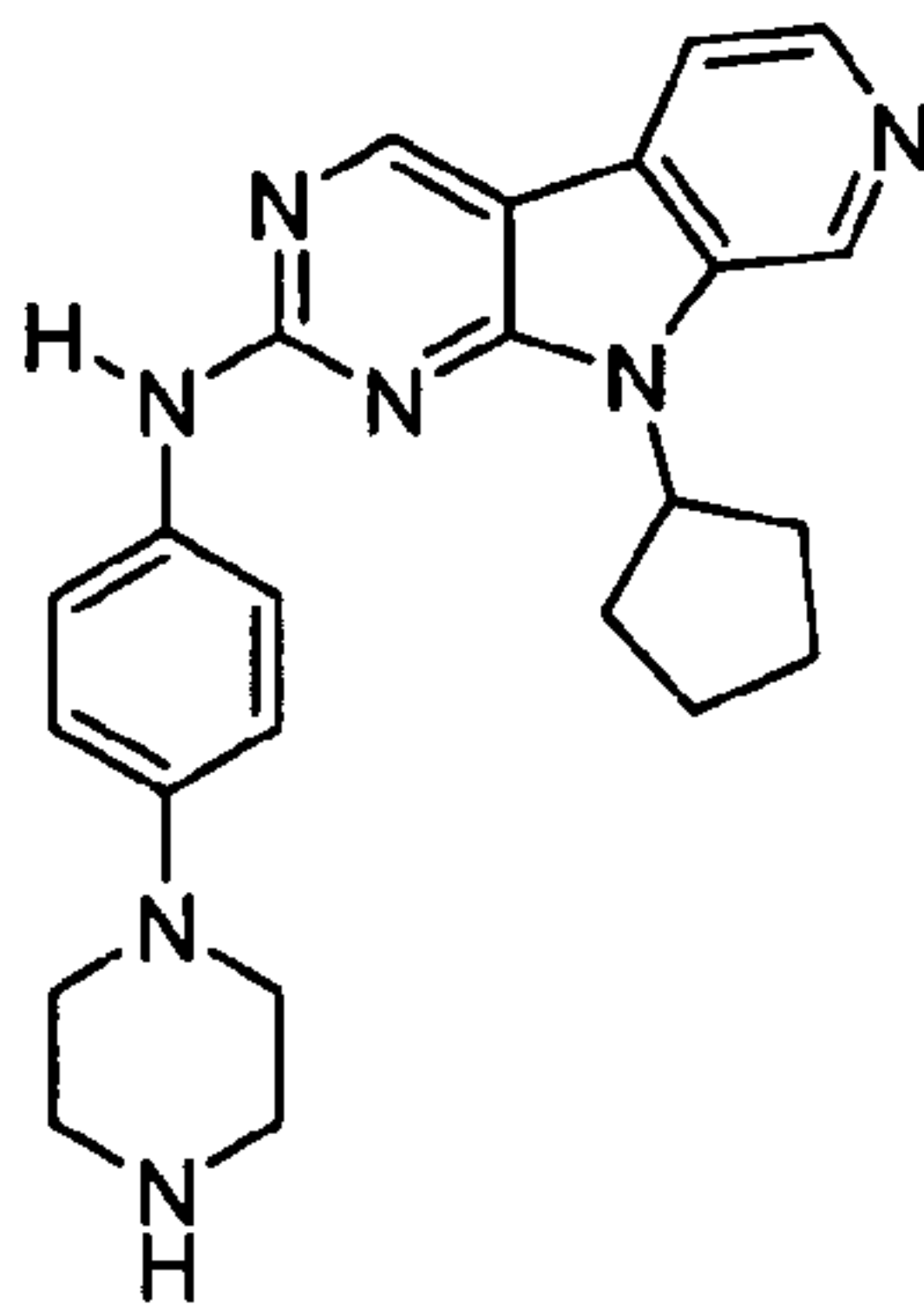


8

#### 9-Cyclopentyl-*N*-(5-(1-(*N*<sup>4</sup>-methylpiperazinyl))-2-pyridinyl)-9H-pyrido- [4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine

Compound 8 was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.07 (1H, s), 8.90 (1H, s), 8.51 (1H, d,  $J = 5$  Hz), 8.39 (1H, d,  $J = 8$  Hz), 8.06 (1H, s), 8.05 (1H, s), 7.84 (1H, d,  $J = 5$  Hz), 7.39 (1H, dd,  $J = 8$  Hz,  $J = 2$  Hz), 5.39 (1H, p,  $J = 8$  Hz), 3.22 (4H, t,  $J = 5$  Hz), 2.63 (4H, t,  $J = 5$  Hz), 2.44 (2H, m), 2.39 (3H, s), 2.14-2.21 (4H, m), 1.88 (2H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 429.2, Calculated 429.2.

### EXAMPLE 3

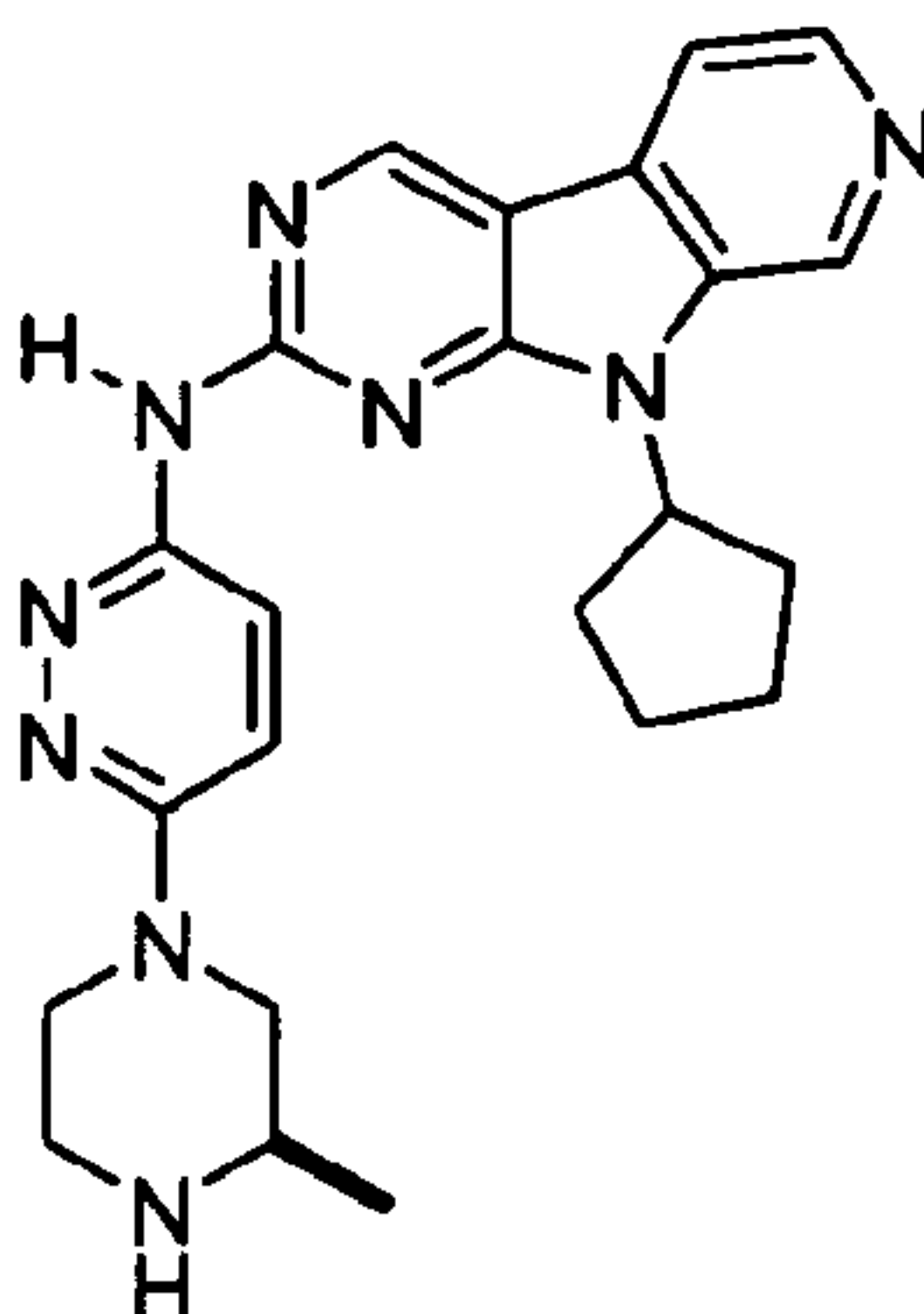


9

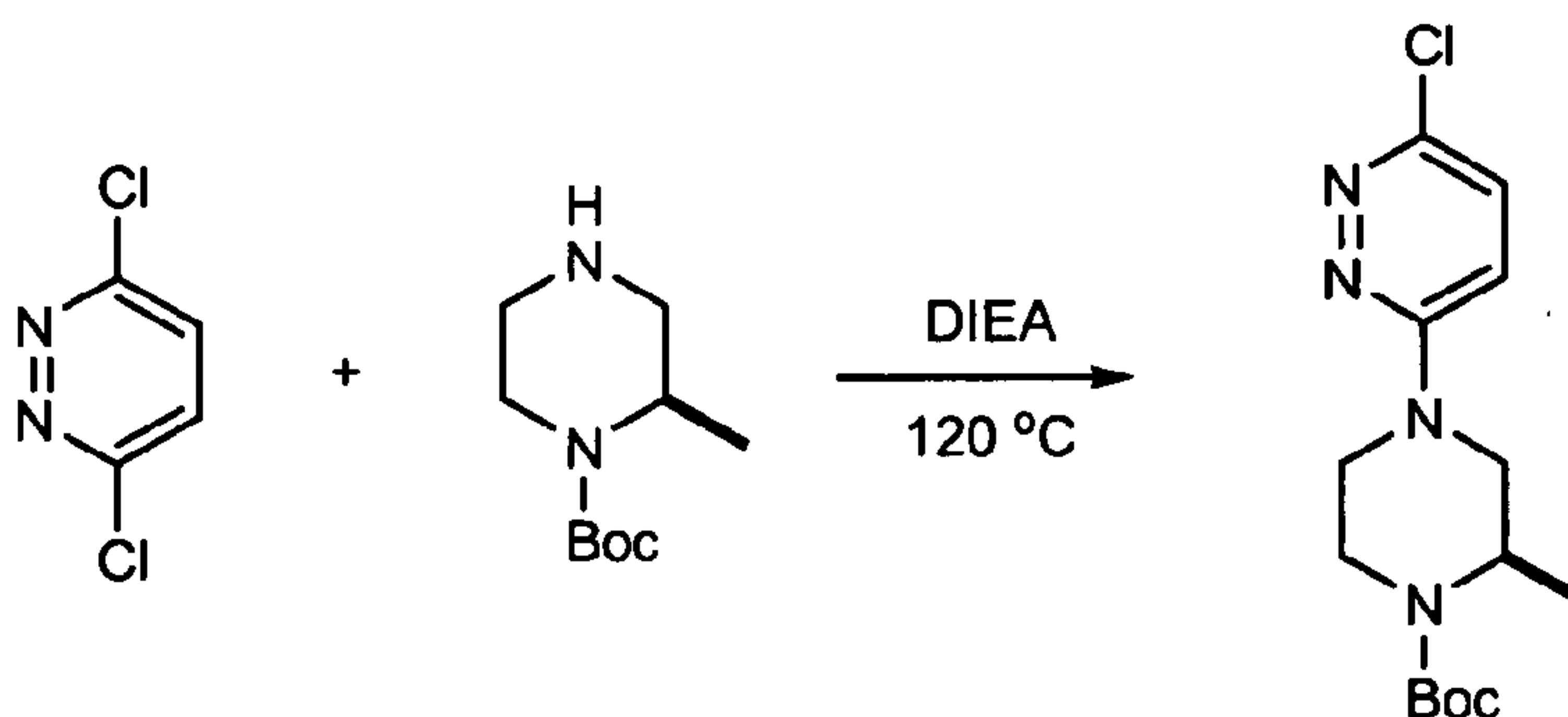
#### (9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(4-piperazin-1-yl-phenyl)-amine

Compound 9 was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  9.39 (1 H, s), 9.15 (1 H, s), 8.49 (2 H, s), 7.72 (2 H, d,  $J=5.0$  Hz), 7.11 (2 H, d,  $J=5.0$  Hz), 5.33 (1 H, m), 3.43 (8 H, m), 2.54 (2 H, m), 2.22 (2 H, m), 2.21 (2 H, m), 1.86 (2 H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 414.2, Calculated 414.2.



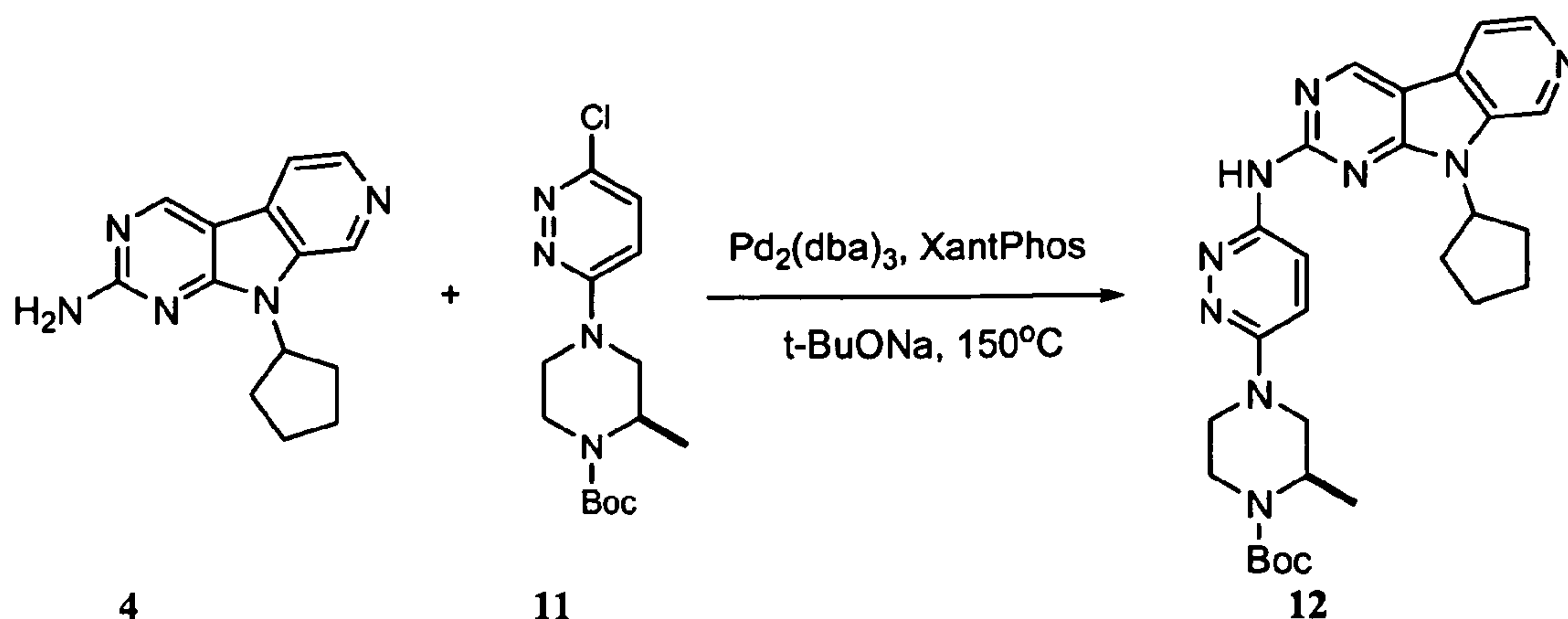
**EXAMPLE 4****10**

**(R)-9-cyclopentyl-N-(6-(1-(3-methylpiperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

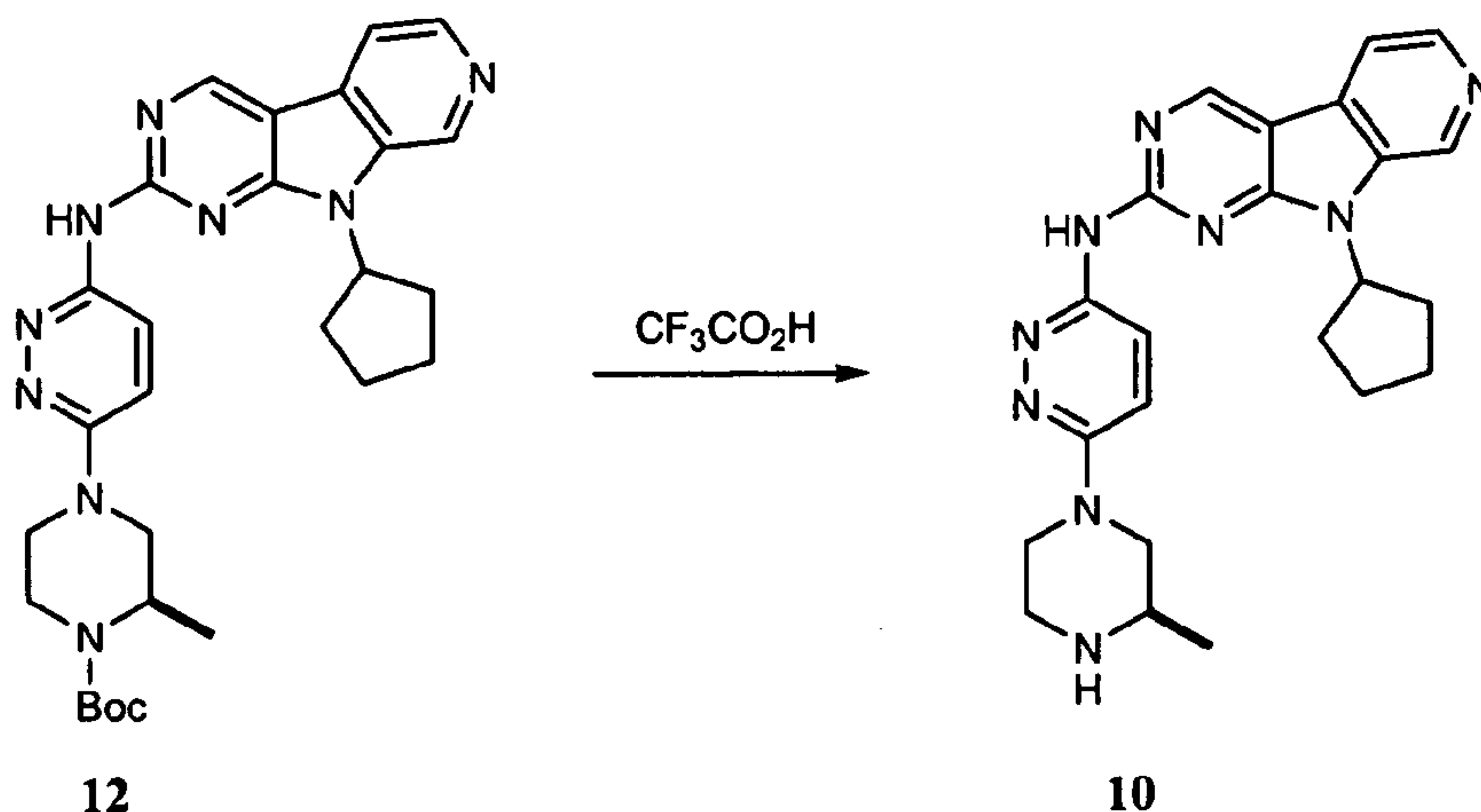
**11**

**(R)-tert-butyl 4-(6-chloropyridazin-3-yl)-2-methylpiperazine-1-carboxylate (11):** A mixture of 3,6-dichloropyridazine (298 mg, 2 mmol) and (R)-1-N-Boc-2-methyl piperazine (401 mg, 2.0 mmol) in N,N-diisopropylethylamine (0.7 mL, 4 mmol) was stirred at 120 °C for 5 h. The reaction mixture was diluted with ethyl acetate and washed with brine (2x), then dried over MgSO<sub>4</sub>. The salts were removed by filtration and the filtrate was concentrated and the residue was purified by chromatography on silica gel eluting with 20% to 80% ethyl acetate in hexane to give compound **11** as a light yellow solid (511 mg, 82%). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.24 (1H, d, J = 10 Hz), 6.88 (1H, d, J = 10 Hz), 4.38 (1H, br s), 4.17 (1H, d, J = 10 Hz), 4.05 – 3.97 (2H, m), 3.39 (1H, dd, J = 15 Hz, J = 5 Hz), 3.29 (1H, ddd, J = 15 Hz, J = 10 Hz, J = 5 Hz), 1.51 (9H, s), 1.21 (3H, d, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 313.1, Calculated 313.1.



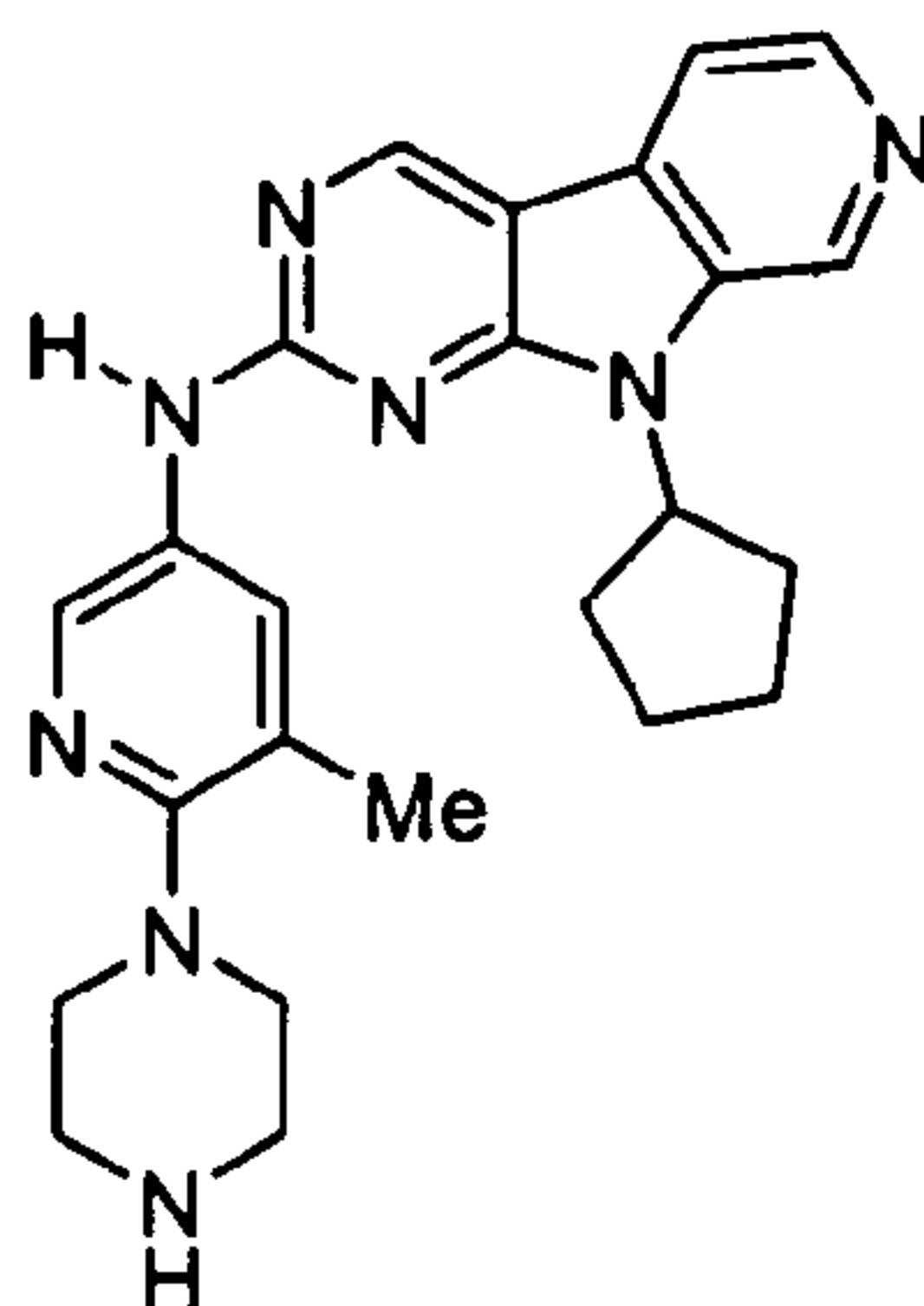


**t-Butyl 4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinecarboxylate (12):** To a solution of compound **4** (112 mg, 0.40 mmol) in dioxane (4 mL) were added compound **11** (150 mg, 0.48 mmol), tris(dibenzylideneacetone)dipalladium (0) (18.4 mg, 0.02 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (35 mg, 0.06 mmol), and sodium *t*-butoxide (58 mg, 0.60 mmol). The mixture thus obtained was heated at 150 °C under microwave irradiation for 1 h. The reaction mixture was passed through short pack silica gel column and concentrated to give a crude **12** (purity = 85%) as a yellow solid (240 mg) which was used in next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 530.3, Calculated 530.3.



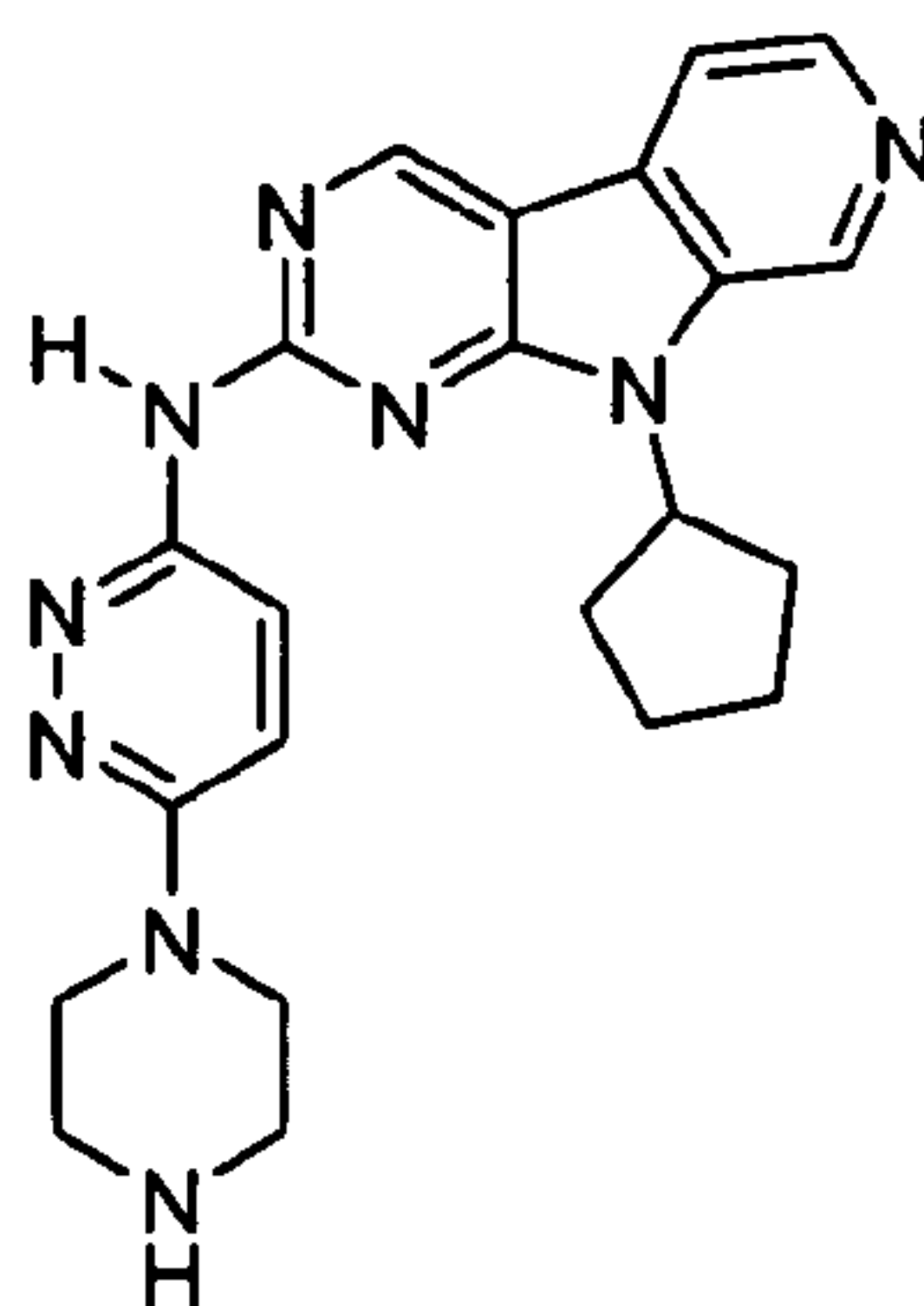
**(R)-9-cyclopentyl-N-(6-(1-(3-methylpiperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine (10):** A solution of compound **12** (240 mg, purity = 85%, 0.385 mmol) in TFA/DCM (4 mL, 1:1) was stirred at room temperature for 30 min. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting with  $\text{CH}_2\text{Cl}_2/\text{methanol}/\text{NH}_4\text{OH}$  (200:10:1) to give compound **10** as an off-white solid (120 mg, 73%).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.19 (1H, s), 9.27 (1H, s), 9.01 (1H, s), 8.46 (1H, d,  $J = 5$  Hz), 8.18 (1H, d,  $J = 10$  Hz), 8.05 (1H, d,  $J = 5$  Hz), 7.40 (1H, d,  $J = 10$  Hz), 5.34 (1H, p,  $J = 10$  Hz), 4.11 (2H, m), 2.97 (1H, m), 2.79 – 2.72 (3H, m), 2.44 – 2.34 (3H, m), 2.09 – 2.04 (4H, m), 1.74 (2H, m), 1.04 (3H, d,  $J = 5$  Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 430.2, Calculated 430.2.



**EXAMPLE 5****13**

**9-cyclopentyl-N-(5-methyl-6-(1-piperazinyl)-3-pyridinyl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

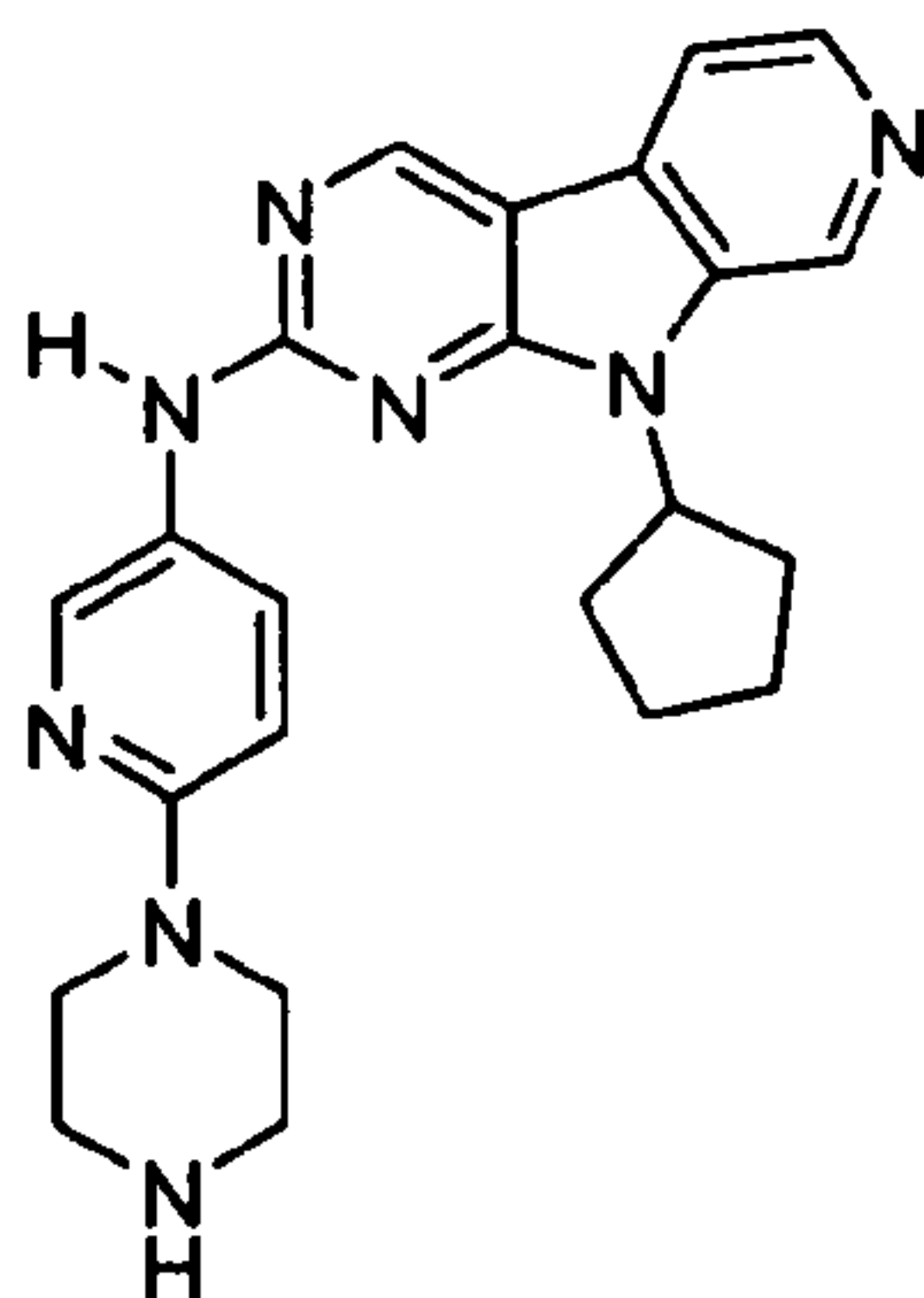
Compound **13** was prepared using chemistry similar to that described in example 4.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.42 (1H, br s), 9.57 (1H, s), 9.38 (1H, s), 8.86 (2H, br s), 8.67 (1H, d, ), 8.57 (1H, d,  $J = 6.1\text{Hz}$ ), 8.52 (1H, d,  $J = 2.7\text{Hz}$ ), 8.03 (1H, s), 5.33 (1H, p,  $J = 8.8\text{ Hz}$ ), 3.26 (8H, m), 2.43 (2H, m), 2.32 (3H, s), 2.13 (2H, m), 2.00 (2H, m), 1.74 (2H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 429.2, Calculated 429.2.

**EXAMPLE 6****14**

**9-cyclopentyl-N-(6-(1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

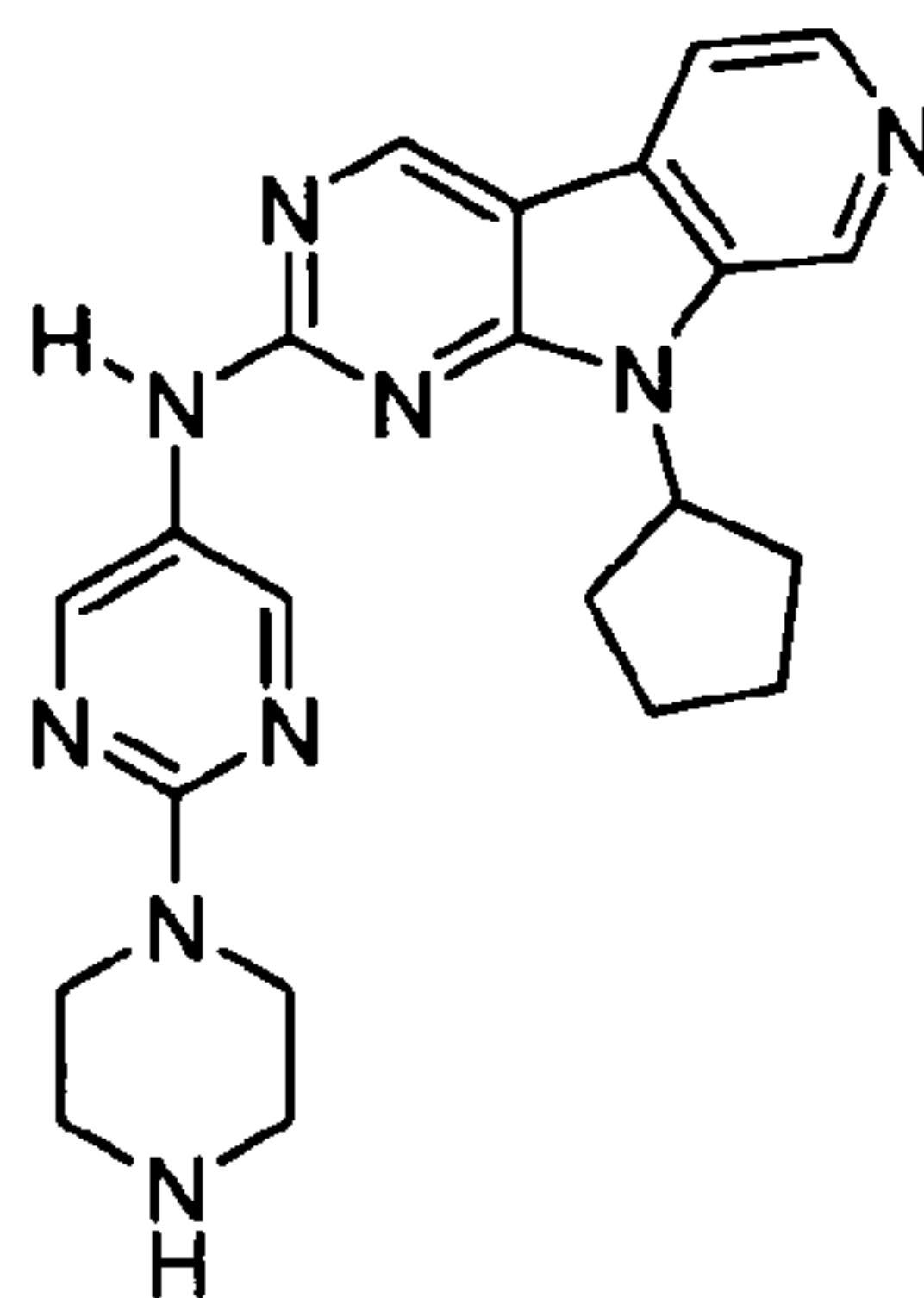
Compound **14** was prepared using chemistry similar to that described in example 4.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.16 (1H, br s), 9.63 (1H, s), 9.41 (1H, s), 9.01 (2H, br s), 8.71 (1H, d,  $J = 6.1\text{Hz}$ ), 8.64 (1H, d,  $J = 6.1\text{Hz}$ ), 8.23 (1H, d,  $J = 9.8\text{Hz}$ ), 7.69 (1H, d,  $J = 9.8\text{Hz}$ ), 5.37 (1H, p,  $J = 8.8\text{ Hz}$ ), 3.82 (4H, t,  $J = 5.4\text{ Hz}$ ), 3.29 (4H, m), 2.39 (2H, m), 2.13 (2H, m), 2.04 (2H, m), 1.74 (2H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 416.2, Calculated 416.2.



**EXAMPLE 7****15**

**9-cyclopentyl-N-(6-(1-piperazinyl)-3-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

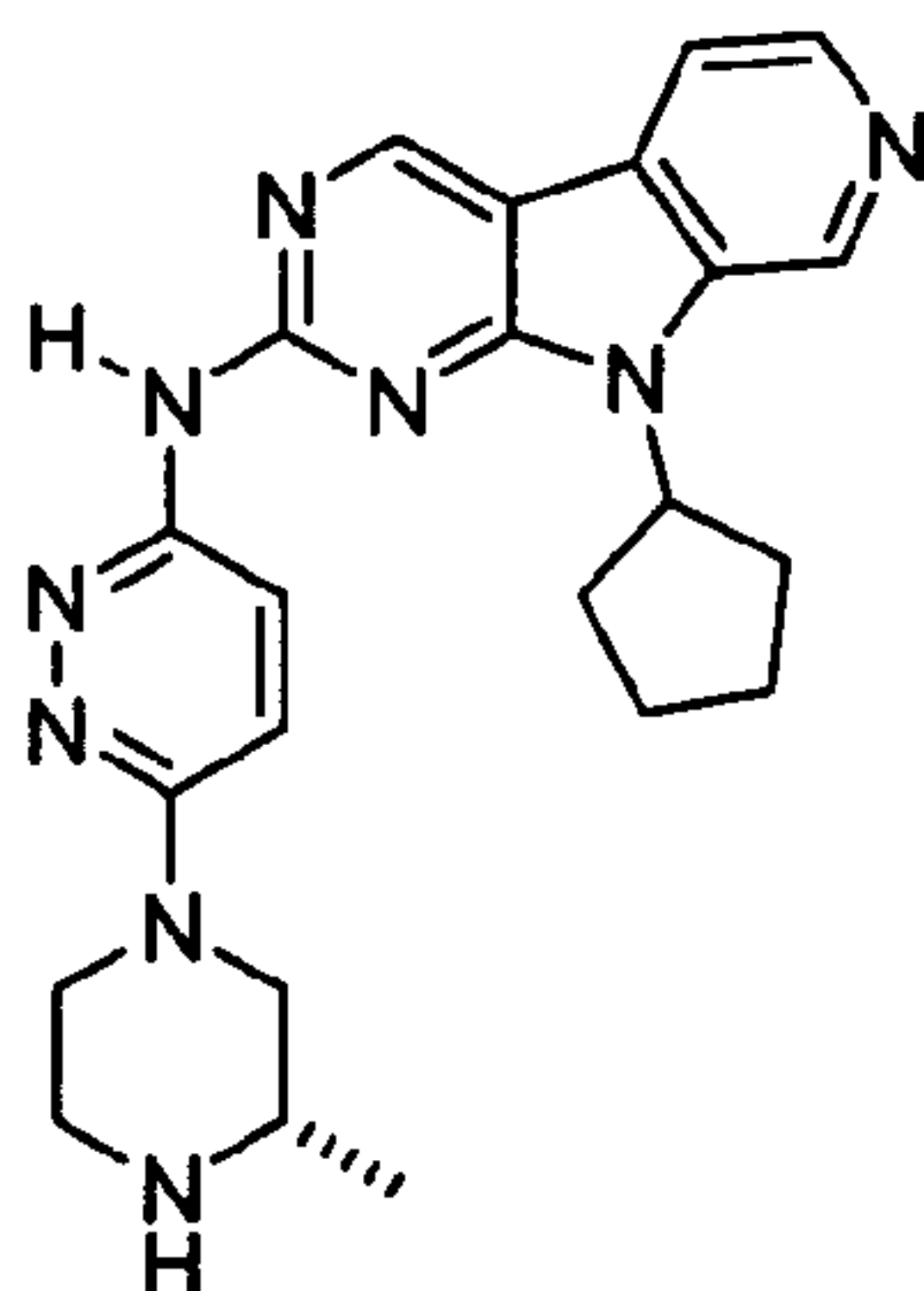
Compound **15** was prepared using chemistry similar to that described in example 4. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.43 (1H, s), 9.18 (1H, s), 8.65 (1H, d, J = 2.6 Hz), 8.53 (2H, s), 8.10 (1H, dd, J = 9.0 Hz, 2.4 Hz), 7.11 (1H, d, J = 9.3 Hz), 5.37 (1H, p, J = 8.6 Hz), 3.85 (4H, t, J = 5.3 Hz), 3.40 (4H, t, J = 5.1 Hz), 2.49 (2H, m), 2.23 (2H, m), 2.21 (2H, m), 1.86 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 415.1, Calculated 415.2.

**EXAMPLE 8****16**

**9-cyclopentyl-N-(2-(1-piperazinyl)-5-pyrimidinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

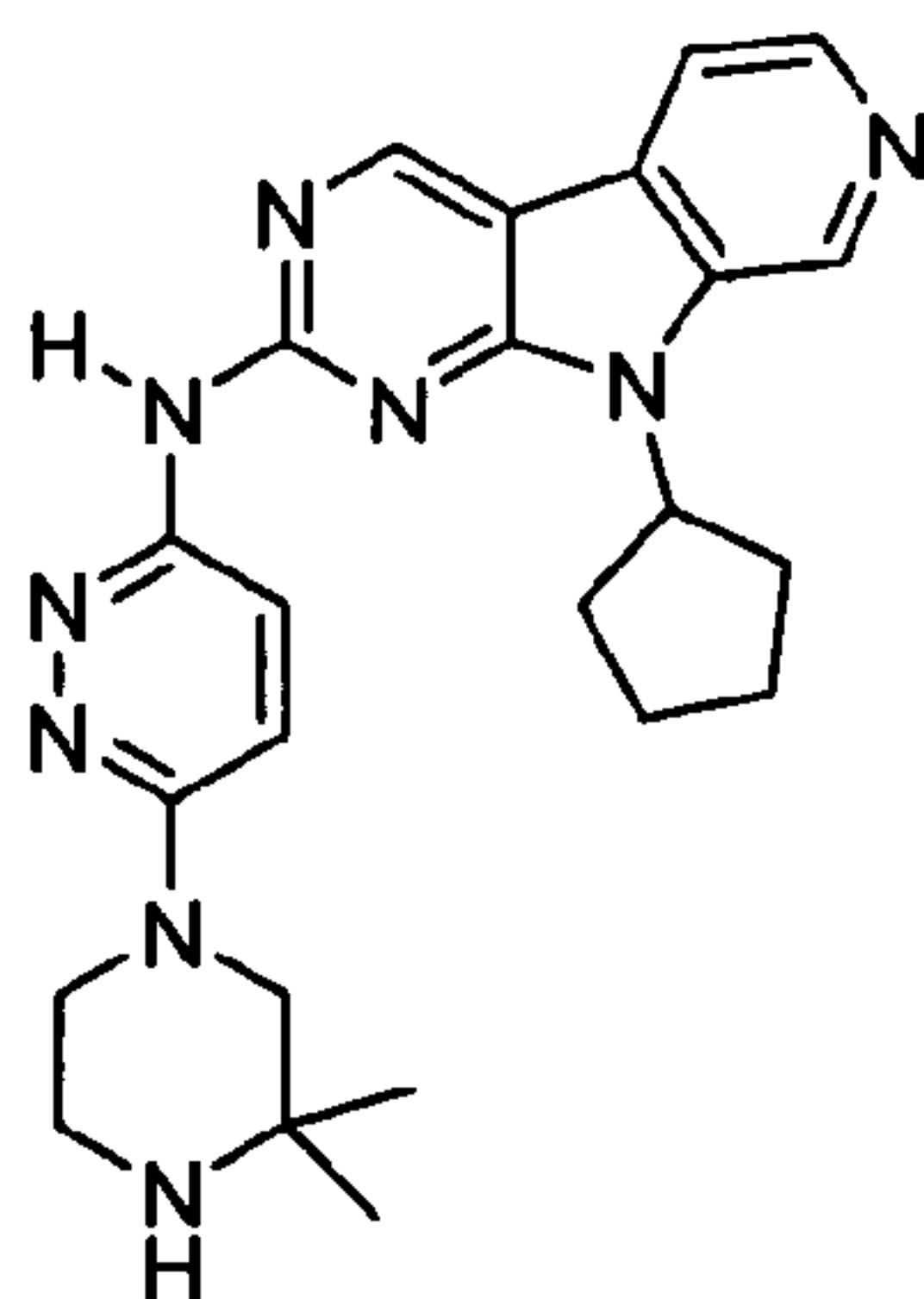
Compound **16** was prepared using chemistry similar to that described in example 4. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.40 (1H, s), 9.16 (1H, s), 8.82 (2H, s), 8.51 (1H, d, J = 6.1 Hz), 8.49 (1H, d, J = 6.1 Hz), 5.35 (1H, p, J = 8.5 Hz), 4.12 (4H, t, J = 5.4 Hz), 3.35 (4H, t, J = 5.4 Hz), 2.47 (2H, m), 2.23 (2H, m), 2.10 (2H, m), 1.85 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 416.2, Calculated 416.2.



**EXAMPLE 9****17**

**(S)-9-cyclopentyl-N-(6-(1-(3-methylpiperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

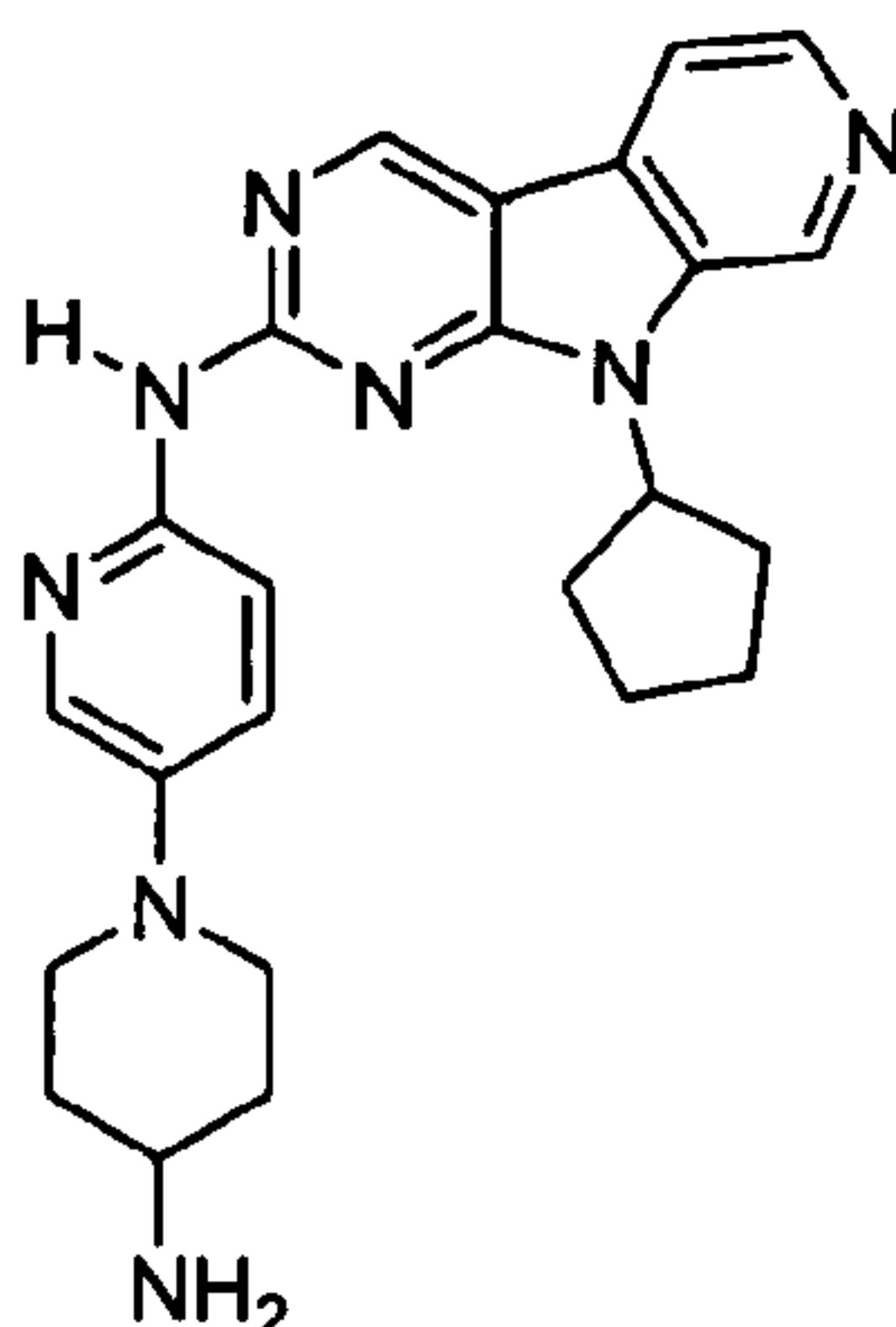
Compound **17** was prepared using chemistry similar to that described in example 4. <sup>1</sup>H NMR (500 MHz, *DMSO-d<sub>6</sub>*) δ 10.19 (1H, s), 9.27 (1H, s), 9.01 (1H, s), 8.46 (1H, d, J = 5 Hz), 8.18 (1H, d, J = 10 Hz), 8.05 (1H, d, J = 5 Hz), 7.40 (1H, d, J = 10 Hz), 5.34 (1H, p, J = 10 Hz), 4.11 (2H, m), 2.97 (1H, m), 2.79 – 2.72 (3H, m), 2.44 – 2.34 (3H, m), 2.09 – 2.04 (4H, m), 1.74 (2H, m), 1.04 (3H, d, J = 5 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 430.2, Calculated 430.2.

**EXAMPLE 10****18**

**9-cyclopentyl-N-(6-(1-(3,3-dimethylpiperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

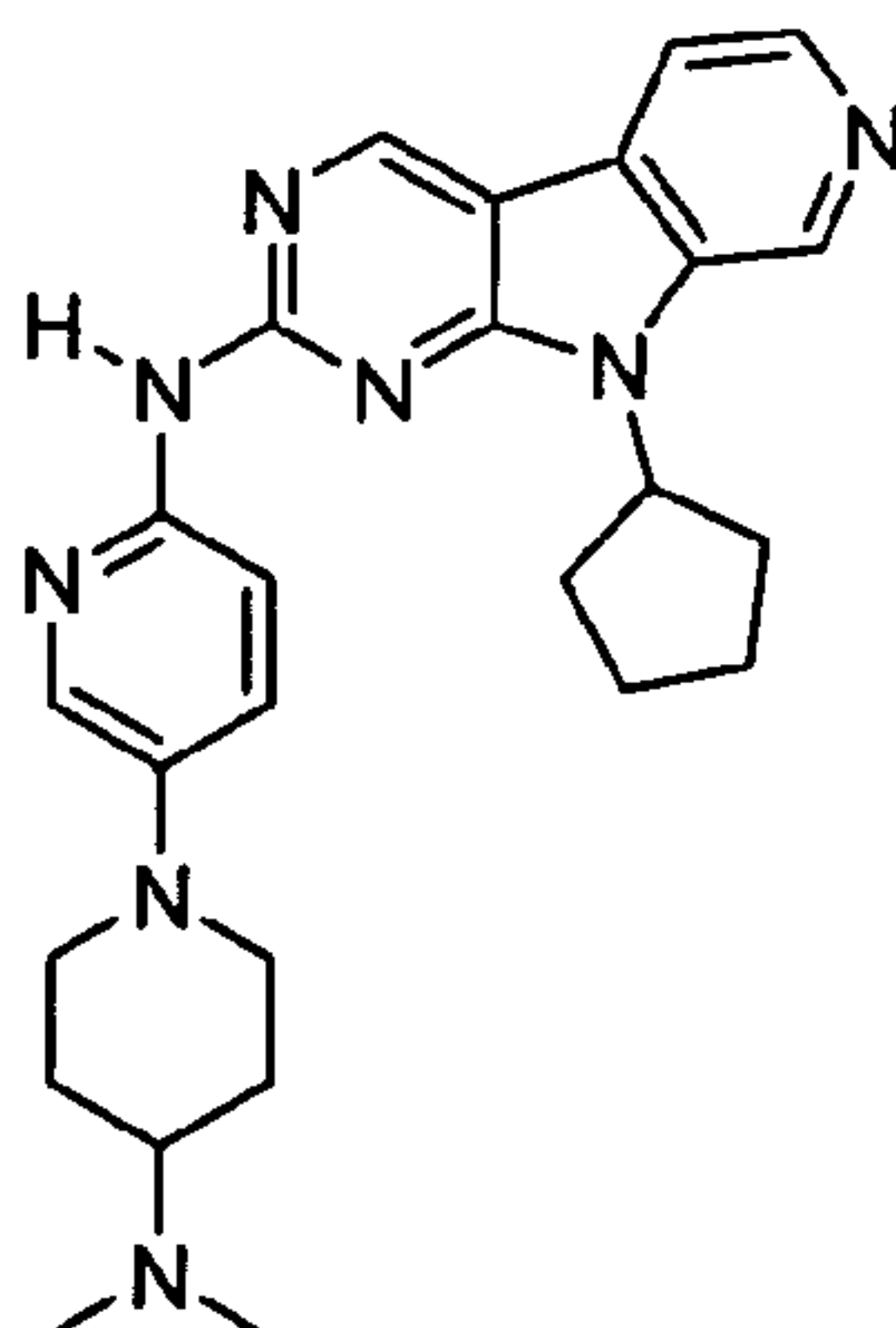
Compound **18** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *CDCl<sub>3</sub>*) δ 9.37 (1H, br s), 9.19 (1H, s), 8.87 (1H, s), 8.50 – 8.46 (2H, m), 7.84 (1H, d, J = 5 Hz), 7.04 (1H, d, J = 5 Hz), 5.34 (1H, p, J = 10 Hz), 3.54 (2H, t, J = 5 Hz), 3.36 (2H, br s), 3.07 (2H, t, J = 5 Hz), 2.36 (2H, m), 2.17 (2H, m), 2.09 (2H, m), 1.84 (2H, m), 1.21 (6H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 444.2, Calculated 444.3.



**EXAMPLE 11****19**

**9-cyclopentyl-N-(5-(1-(4-aminopiperidin-2-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

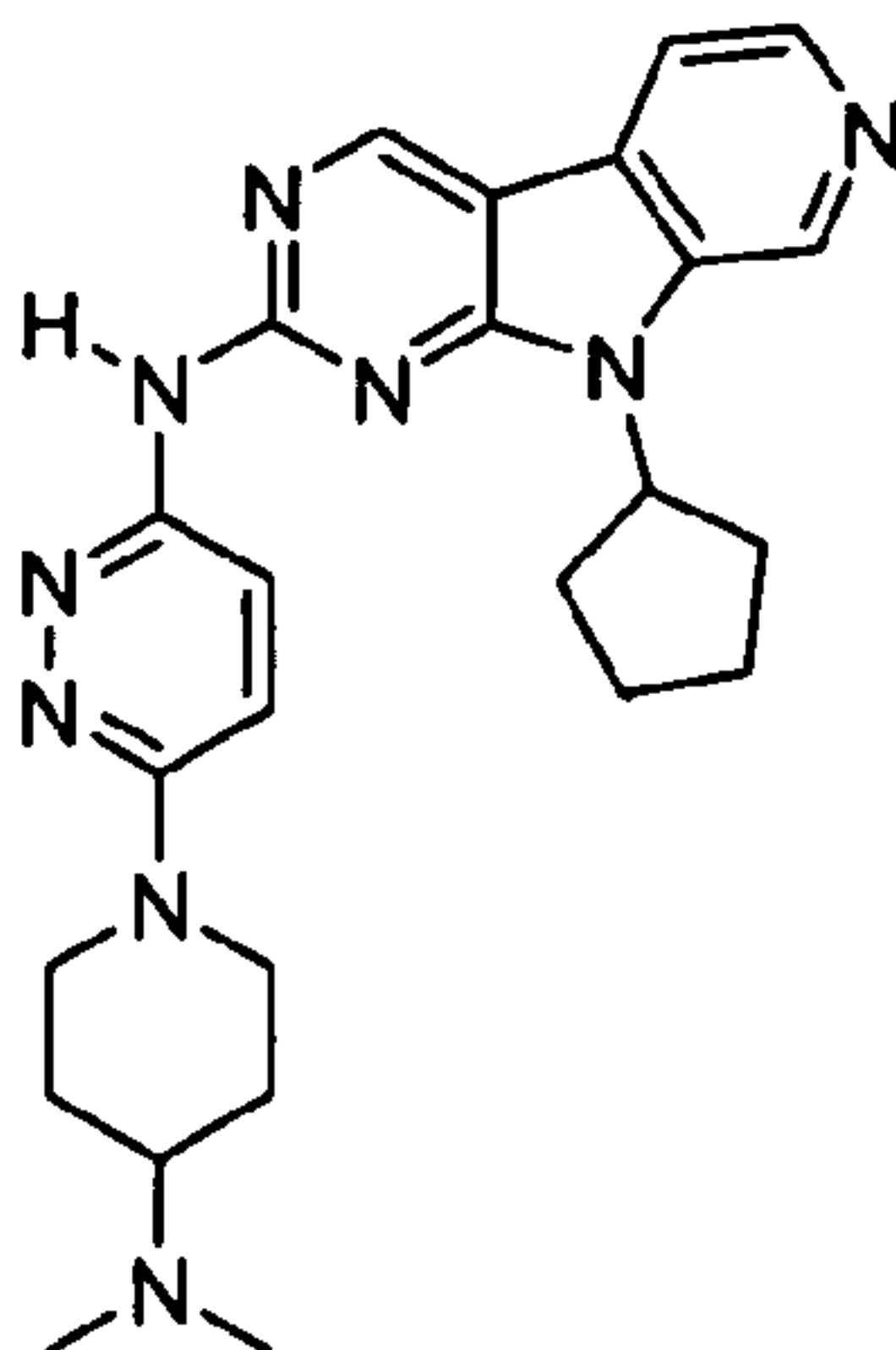
Compound **19** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.72 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.15 (1H, d, J = 10 Hz), 8.03 (1H, d, J = 5 Hz), 8.02 (1H, d, J = 2 Hz), 7.46 (1H, dd, J = 10 Hz, J = 2 Hz), 5.36 (1H, p, J = 5 Hz), 3.61 (2H, m), 2.77 – 2.71 (3H, m), 2.41 – 2.36 (3H, m), 2.09 – 2.05 (4H, m), 1.83 – 1.76 (4H, m), 1.39 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2, Calculated 429.2.

**EXAMPLE 12****20**

**9-cyclopentyl-N-(5-(1-(*N,N*-dimethylaminopiperidin-2-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

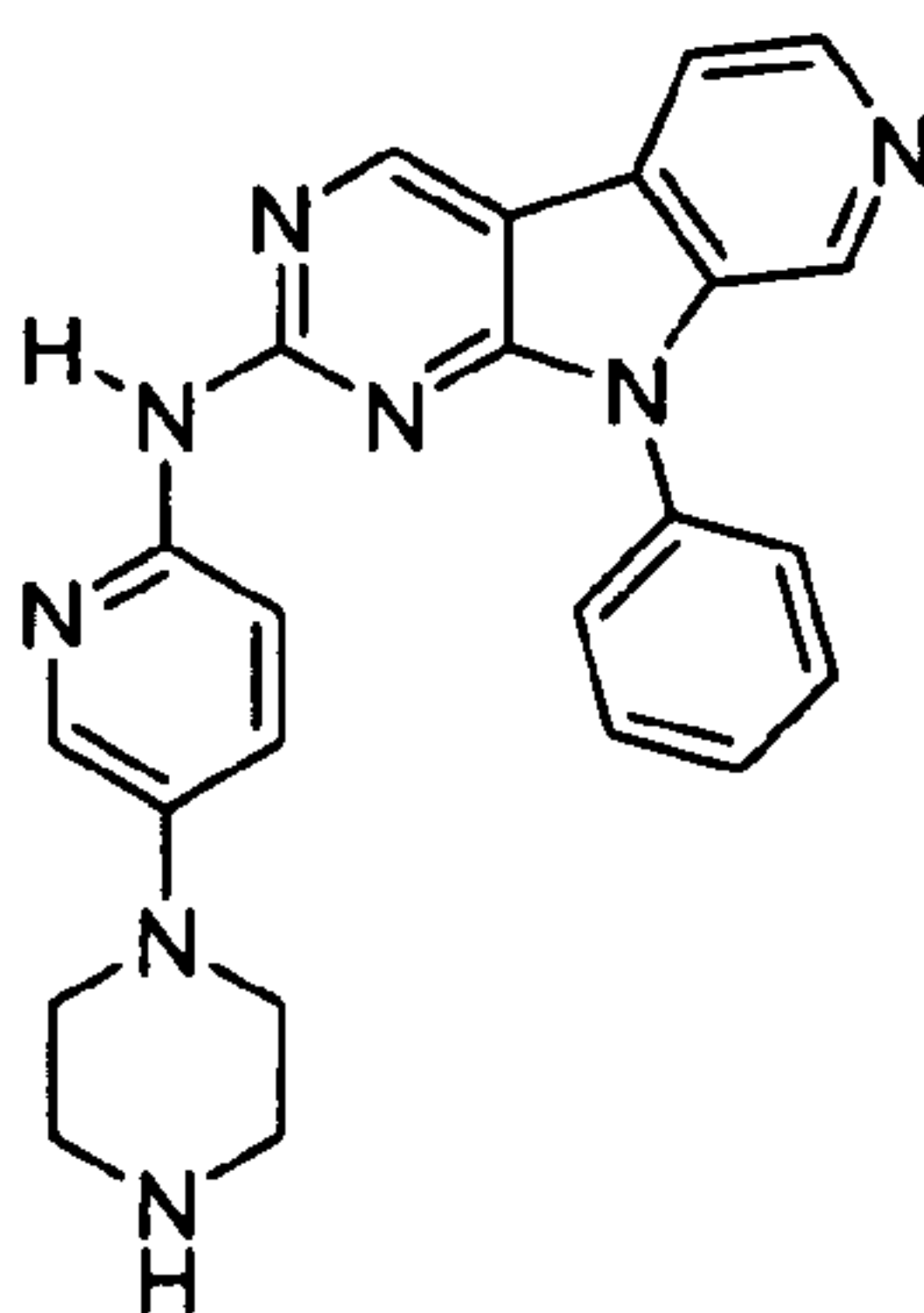
Compound **20** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.07 (1H, s), 8.90 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.38 (1H, d, J = 10 Hz), 8.12 (1H, s), 8.07 (1H, d, J = 2 Hz), 7.84 (1H, d, J = 5 Hz), 7.41 (1H, dd, J = 10 Hz, J = 2 Hz), 5.38 (1H, p, J = 10 Hz), 3.68 (2H, m), 2.77 (2H, td, J = 15 Hz, J = 5 Hz), 2.44 (2H, m), 2.34 (6H, s), 2.29 (1H, m), 2.22 – 2.14 (4H, m), 1.97 (2H, m), 1.88 (2H, m), 1.72 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 457.2, Calculated 457.3.



**EXAMPLE 13****21**

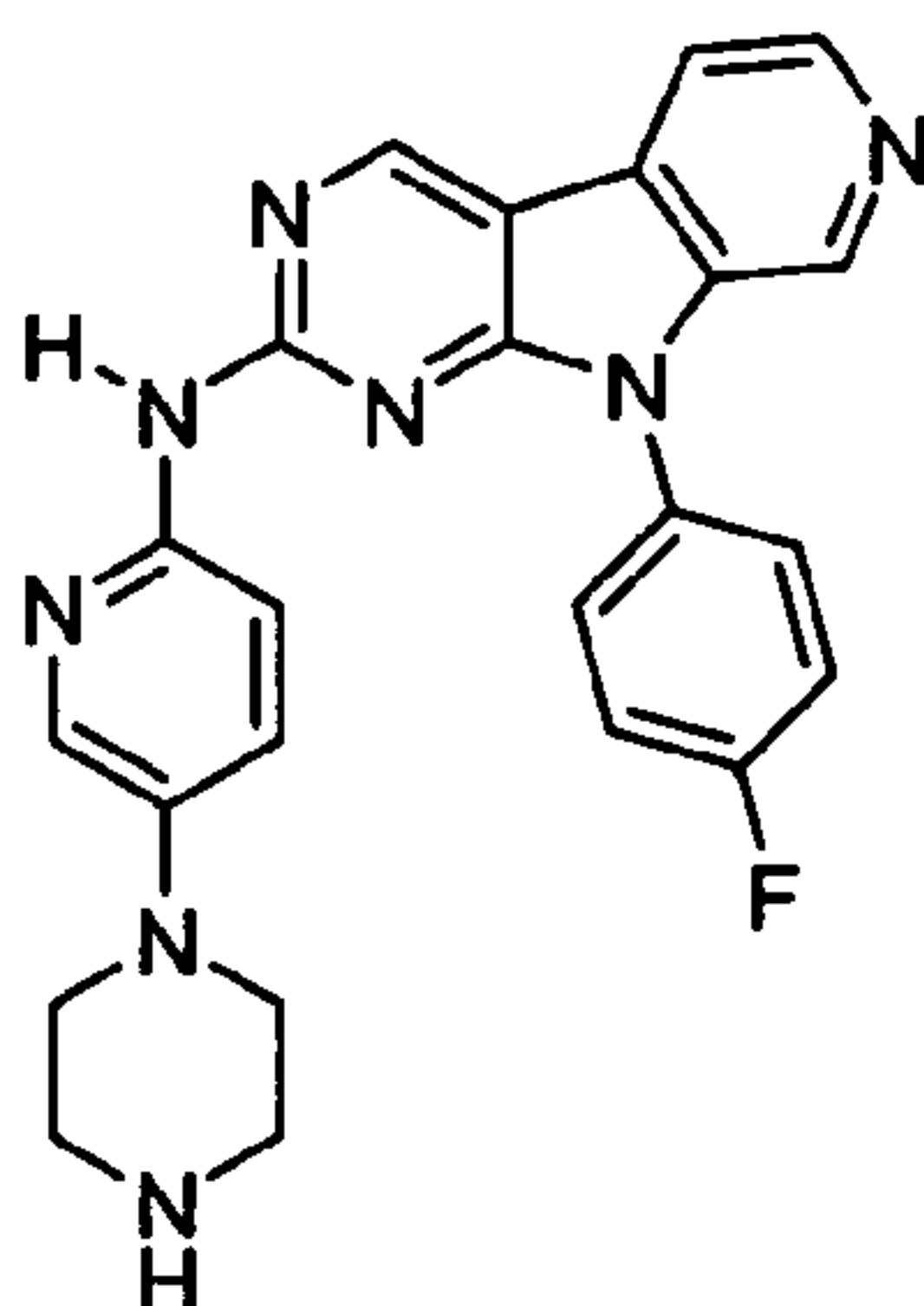
**9-cyclopentyl-N-(6-(1-(*N,N'*-dimethylaminopiperadiny)-3-pyridaziny)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

Compound **21** was prepared using chemistry similar to that described in example 4. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 10.17 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.16 (1H, d, J = 10 Hz), 8.04 (1H, d, J = 5 Hz), 7.42 (1H, d, J = 10 Hz), 5.33 (1H, p, J = 10 Hz), 4.30 (2H, m), 2.88 (2H, td, J = 15 Hz, J = 5 Hz), 2.36 – 2.32 (3H, m), 2.19 (6H, s), 2.10 – 2.02 (4H, m), 1.84 (2H, m), 1.74 (2H, m), 1.42 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 458.2, Calculated 458.3.

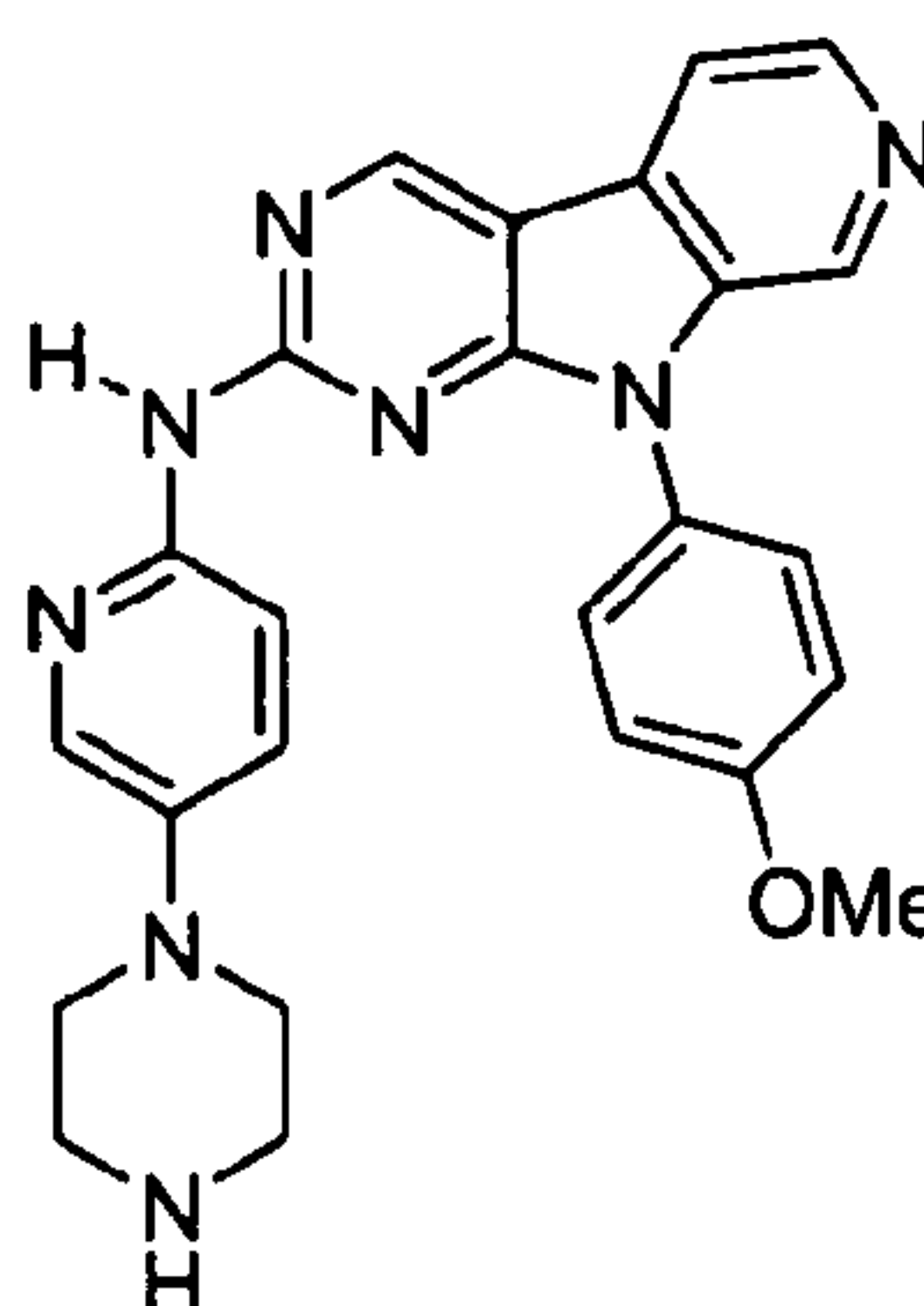
**EXAMPLE 14****22**

**9-Phenyl-N-(5-(1-piperaziny)-2-pyridiny)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**  
Compound **22** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 8.76 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.13 (1H, d, J = 5 Hz), 8.08 (1H, d, J = 10 Hz), 7.97 (1H, br s), 7.82 – 7.80 (2H, m), 7.32 – 7.30 (2H, m), 7.57 (1H, dd, J = 10 Hz, J = 5 Hz), 7.31 (1H, dd, J = 10 Hz, J = 5 Hz), 3.03 (4H, m), 2.85 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 423.2, Calculated 423.2.



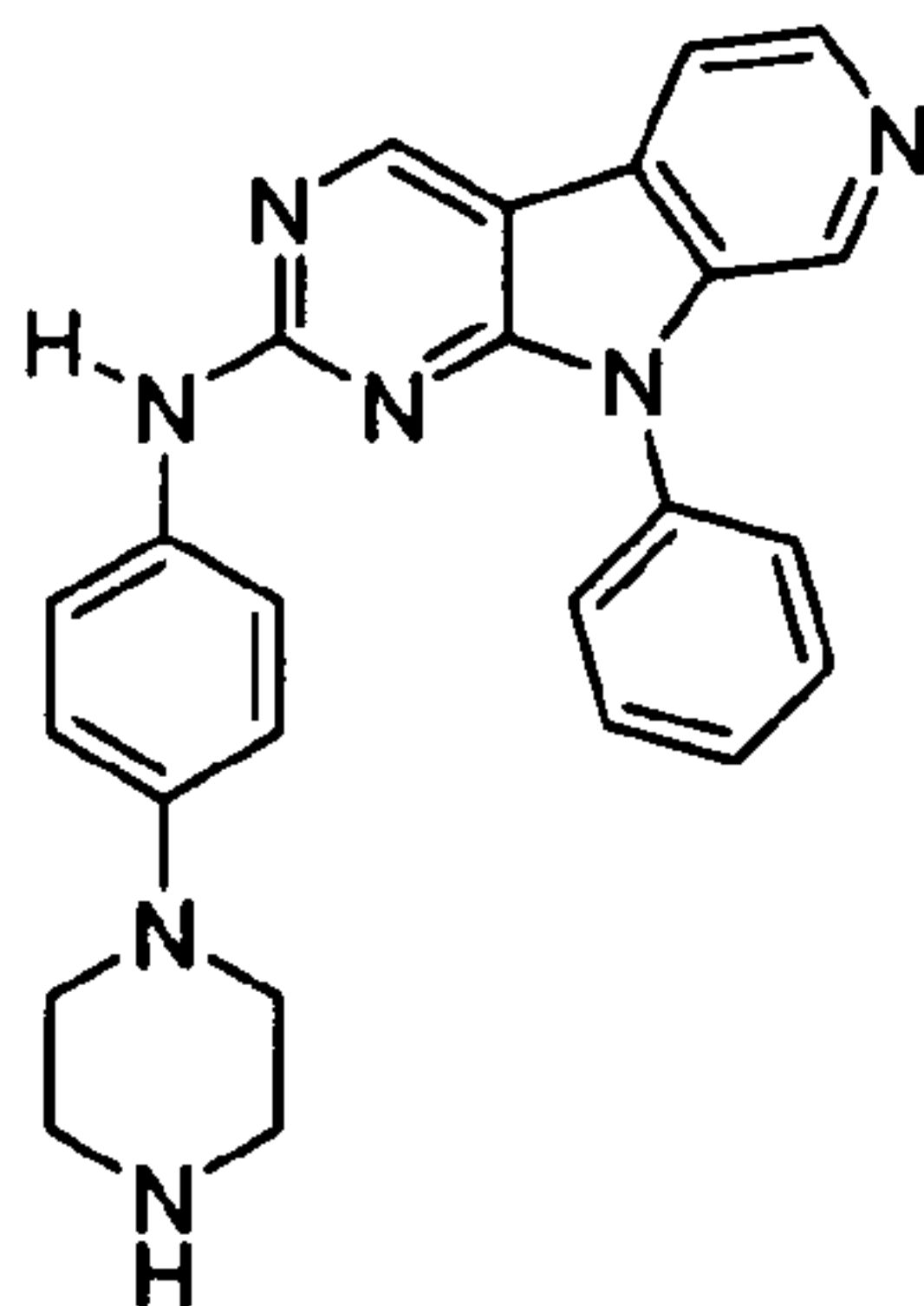
**EXAMPLE 15****23****9-(4-fluorophenyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **23** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.86 (1H, s), 9.37 (1H, s), 8.73 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.13 (1H, d, J = 5 Hz), 8.06 (1H, d, J = 10 Hz), 7.97 (1H, s), 7.87 (2H, d, J = 5 Hz), 7.55 (2H, dd, J = 10 Hz, J = 5 Hz), 7.34 (1H, dd, J = 10 Hz, J = 5 Hz), 3.03 (4H, m), 2.85 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 441.1, Calculated 441.2.

**EXAMPLE 16****24****9-(4-methoxyphenyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

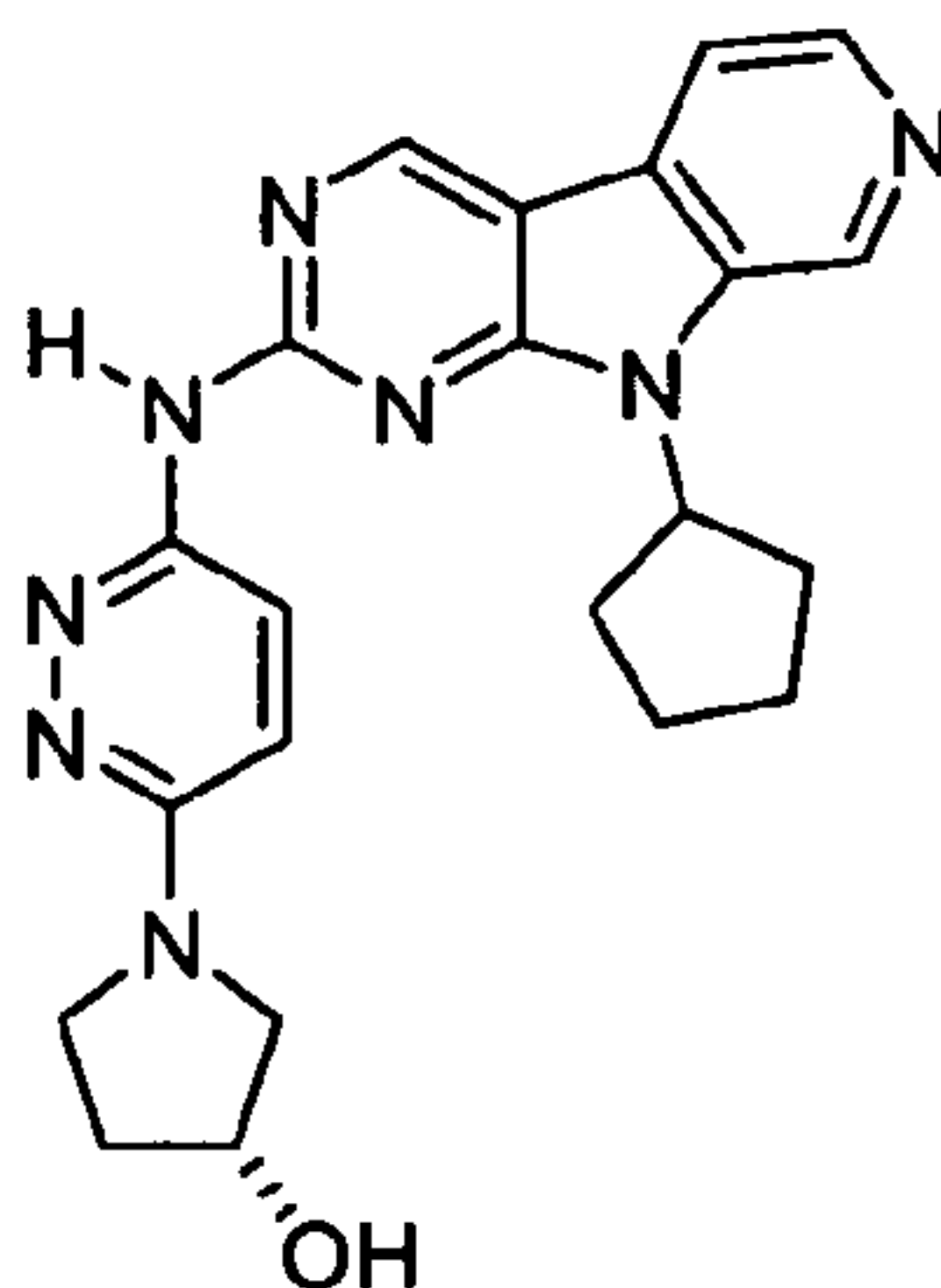
Compound **24** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.82 (1H, s), 9.36 (1H, s), 8.68 (1H, s), 8.50 (1H, d, J = 5 Hz), 8.11 (1H, d, J = 5 Hz), 8.08 (1H, s), 7.98 (1H, d, J = 5 Hz), 7.70 (2H, d, J = 10 Hz), 7.34 (1H, d, J = 10 Hz), 7.25 (1H, d, J = 10 Hz), 3.89 (3H, s), 3.05 (4H, m), 2.88 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 453.2, Calculated 453.2.



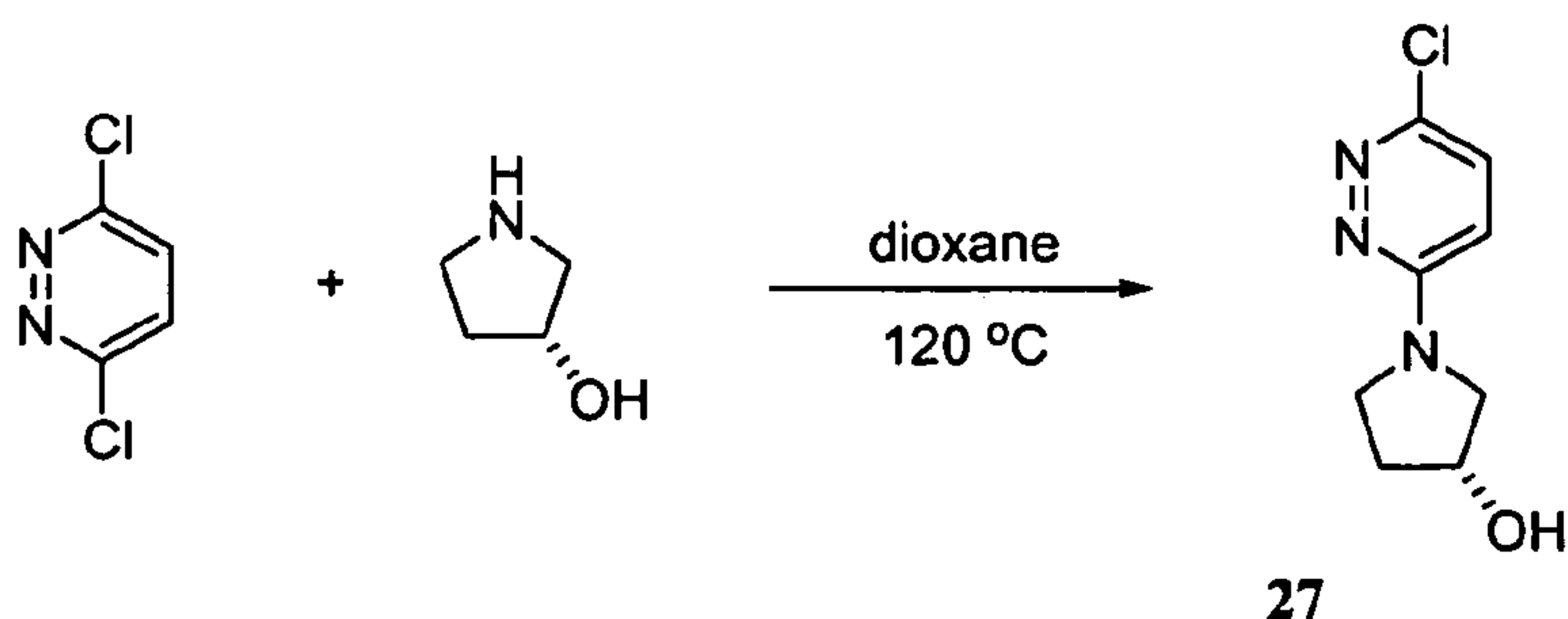
**EXAMPLE 17****25**

**(9-Phenyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(4-piperazin-1-yl-phenyl)-amine**

Compound **25** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.10 (1H, s), 8.87 (1H, s), 8.58 (1H, d, J = 5 Hz), 7.87 (1H, s), 7.74 (2H, d, J = 5 Hz), 7.67 (2H, dd, J = 10 Hz, J = 5 Hz), 7.58 – 7.53 (3H, m), 6.92 (2H, d, J = 5 Hz), 3.13 (4H, m), 3.07 (4H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 422.2, Calculated 422.2.

**EXAMPLE 18****26**

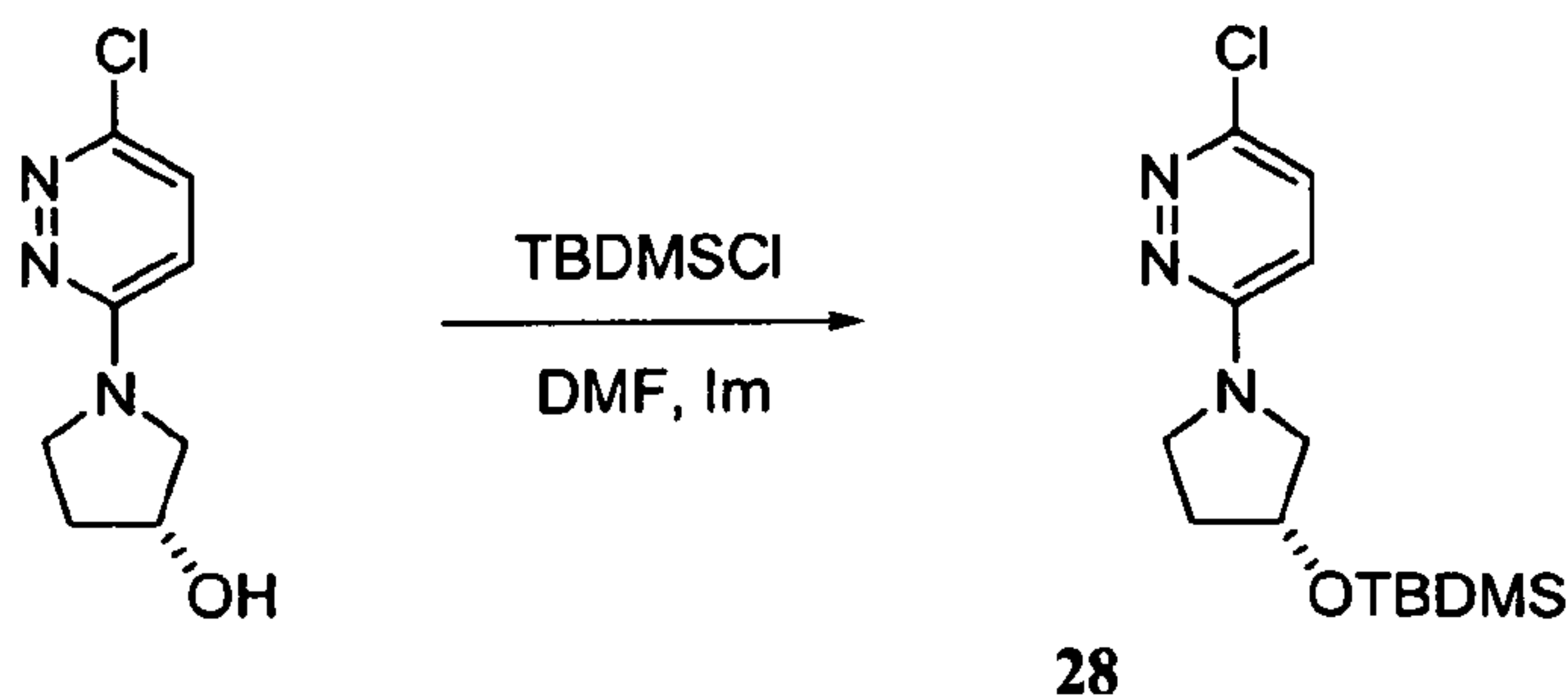
**(R)-9-cyclopentyl-N-(6-(3-hydroxypyrrolidin-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

**27**

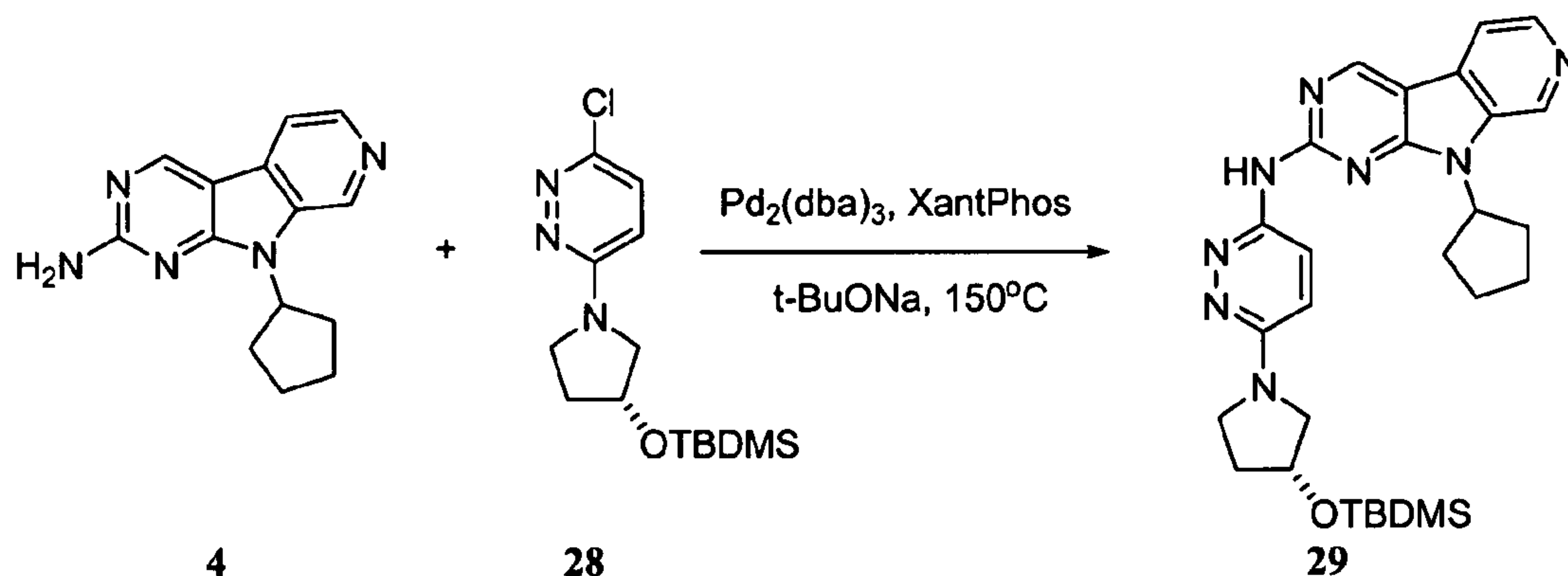
**(R)-1-(6-Chloropyridazin-3-yl)pyrrolidin-3-ol (27):** A solution of 3,6-dichloropyridazine (1.49 g, 10 mmol) and (R)-3-hydroxypyrrolidine (871 mg, 10 mmol) in dioxane (20 mL) was heated at 120 °C for 10 h. The reaction mixture was diluted with ethyl acetate and washed with 5% NaHCO<sub>3</sub> and brine, dried. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting



with 2.5% methanol in dichloromethane to give the compound **27** as a yellow solid (815 mg, 41%). LCMS-ESI (POS), M/Z, M+1: Found 200.0, Calculated 200.0.

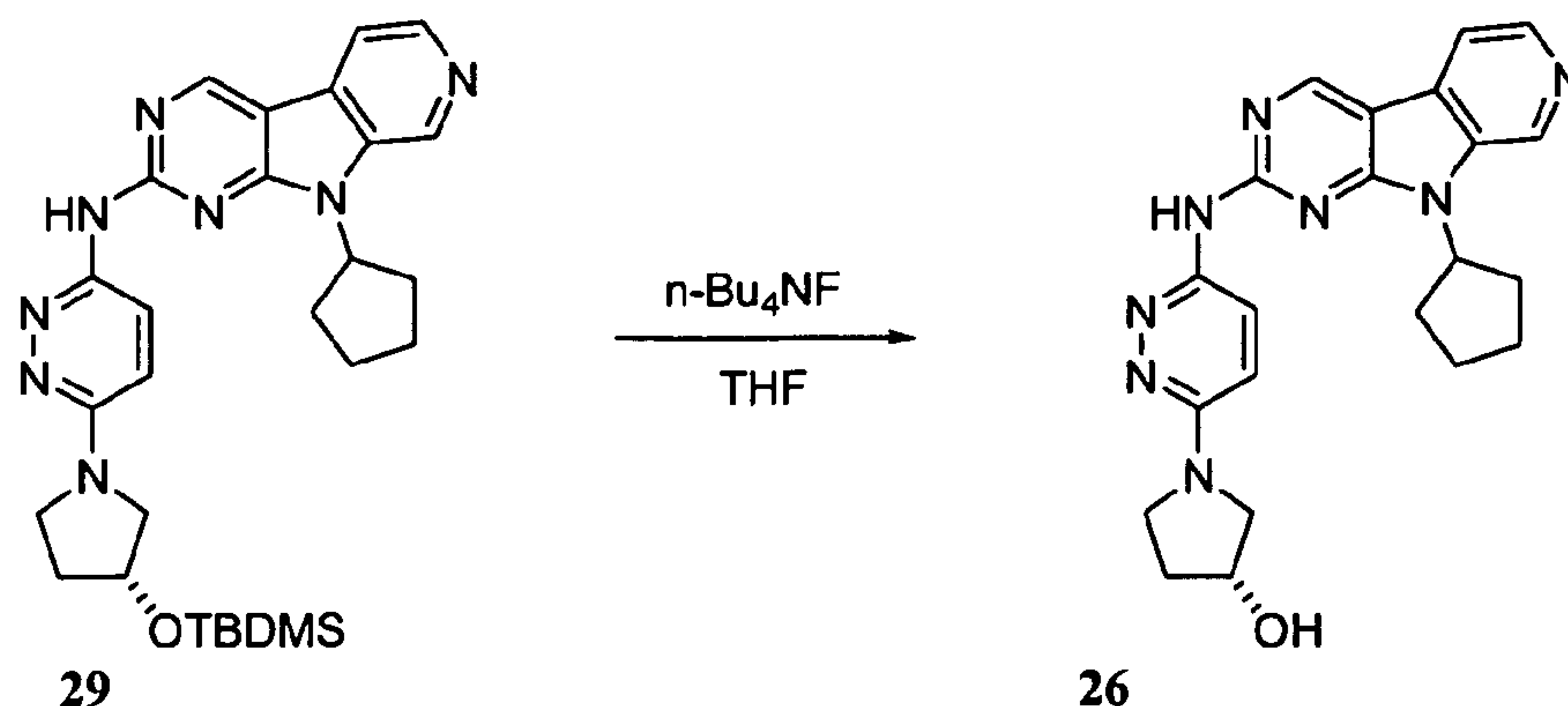


**(R)-3-(3-(tert-butyldimethylsilyloxy)pyrrolidin-1-yl)-6-chloropyridazine (28):** To a solution of compound **27** (815 mg, 4.08 mmol) in DMF (15 mL) were added *t*-butyldimethylsilyl chloride (738 mg, 4.9 mmol) and imidazole (556 mg, 8.16 mmol). The thus obtained solution was stirred at room temperature for 6 h. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting with 15% to 50% to give the compound **28** as a white solid (1.087 g, 85%). LCMS-ESI (POS), M/Z, M+1: Found 314.1, Calculated 314.1.



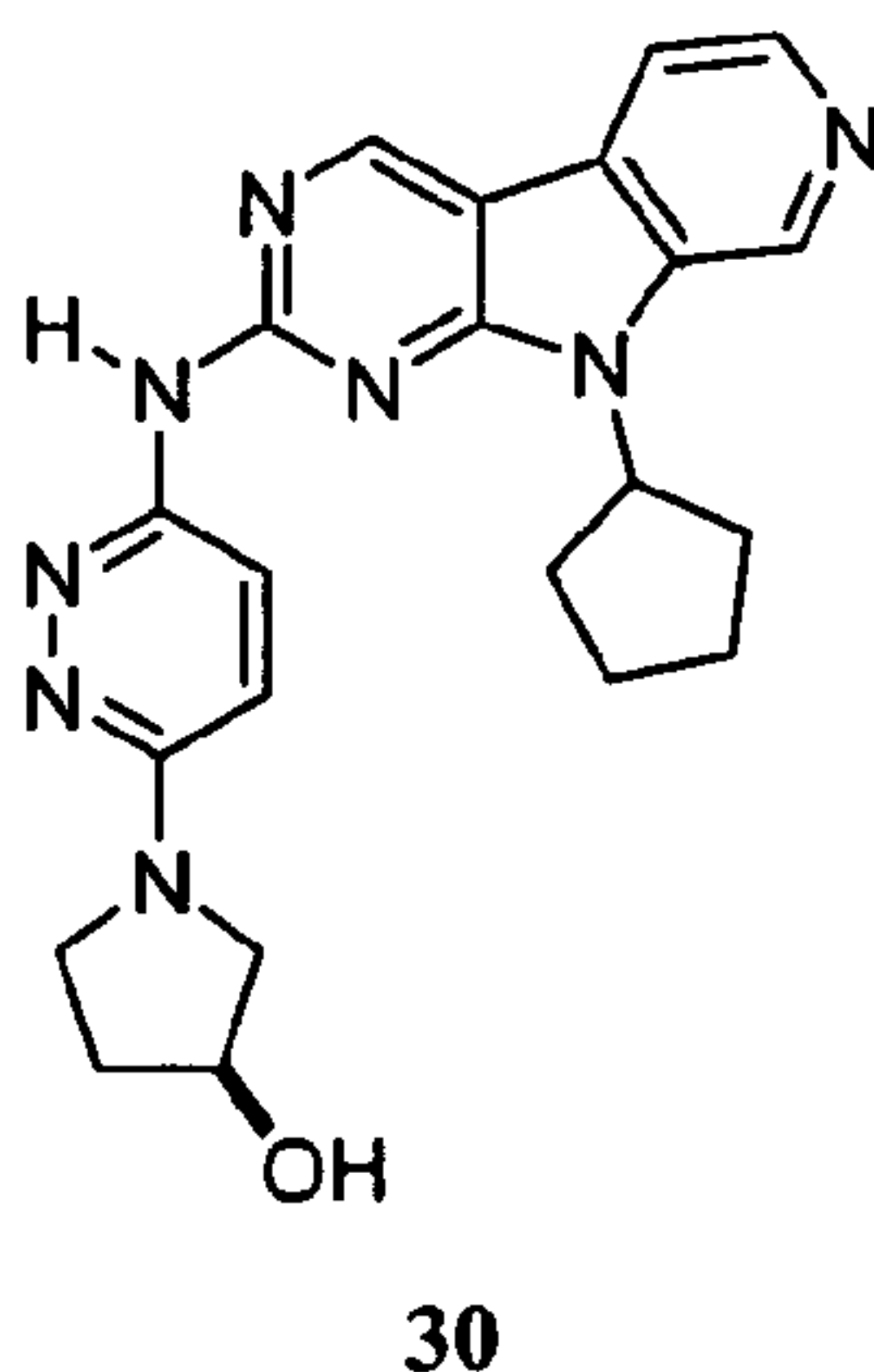
**(R)-9-Cyclopentyl-N-(6-(3-(tert-butyldimethylsilyloxy)pyrrolidin-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine (29):** To a solution of compound **4** (202 mg, 0.80 mmol) in dioxane (8 mL) were added compound **28** (313 mg, 1.0 mmol), tris(dibenzylideneacetone)dipalladium (0) (36.8 mg, 0.04 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (69.4 mg, 0.12 mmol), and sodium *t*-butoxide (115 mg, 1.2 mmol). The mixture thus obtained was heated at 150 °C under microwave irradiation for 1 h. The reaction mixture was passed through a short pack silica gel column and concentrated to give compound **29** as a yellow solid (316 mg, 82% purity) which was used in next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 531.1, Calculated 531.2.





**(R)-9-cyclopentyl-N-(6-(3-hydroxypyrrolidin-1-yl)-3-pyridazinyl)-9H-pyrido-[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine (26):** A solution of compound **29** (316 mg, purity 82%, 0.49 mmol) in THF (4 mL) was treated with 1M tetrabutylammonium fluoride in THF (1 mL) at room temperature for 0.5 h. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting with 2.5% methanol in dichloromethane to give a yellow solid. The yellow solid was washed with dichloromethane to give compound **26** as a light yellow solid (182 mg, 90%). <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 10.05 (1H, s), 9.24 (1H, s), 8.99 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.10 (1H, d, J = 10 Hz), 8.03 (1H, d, J = 5 Hz), 6.99 (1H, d, J = 10 Hz), 5.32 (1H, p, J = 10 Hz), 5.00 (1H, d, J = 5 Hz), 4.43 (1H, br s), 3.58 – 3.51 (3H, m), 3.40 (1H, m), 2.37 – 2.30 (2H, m), 2.09 – 2.02 (5H, m), 1.95 (1H, m), 1.74 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 417.3, Calculated 417.2.

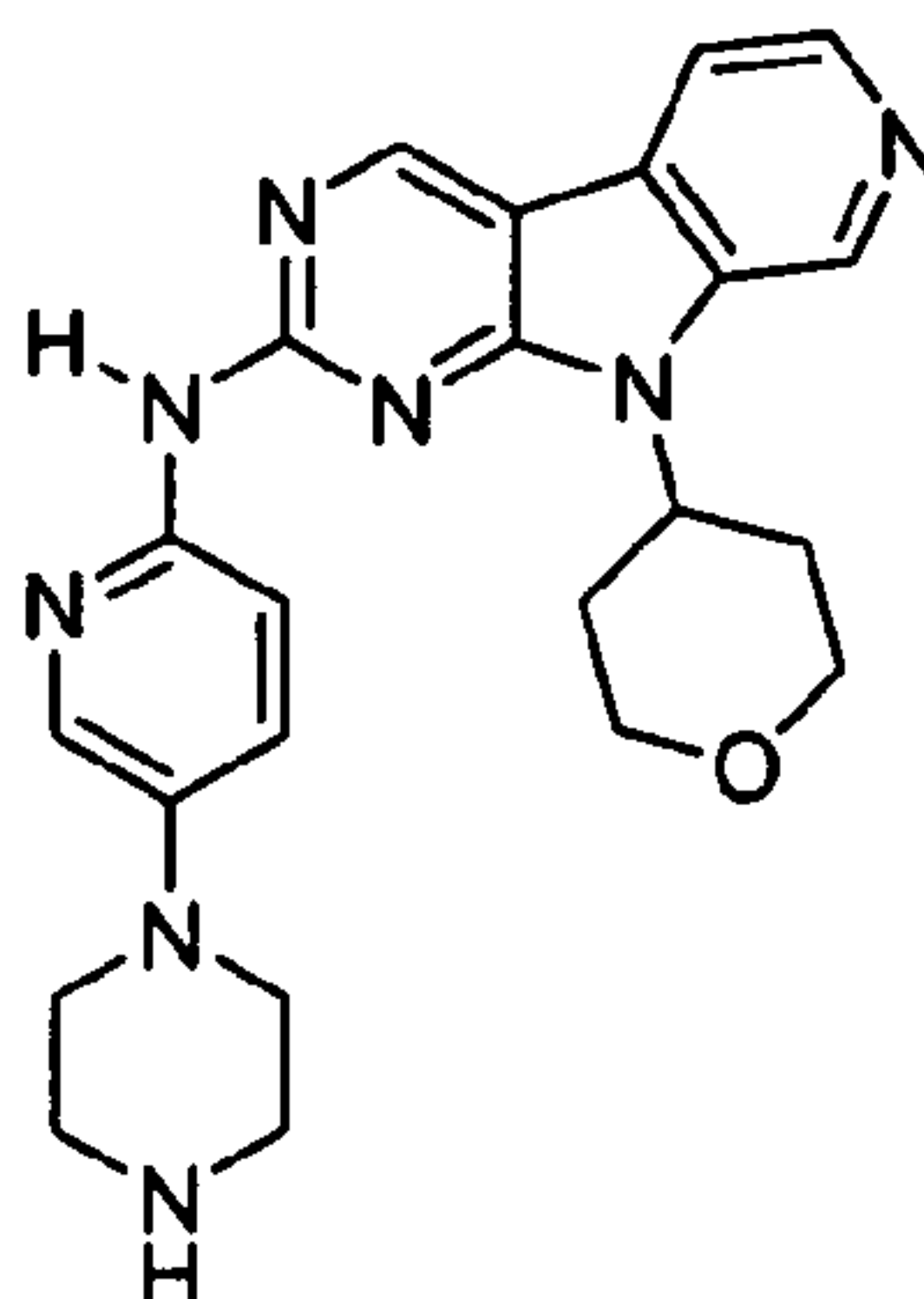
#### EXAMPLE 19



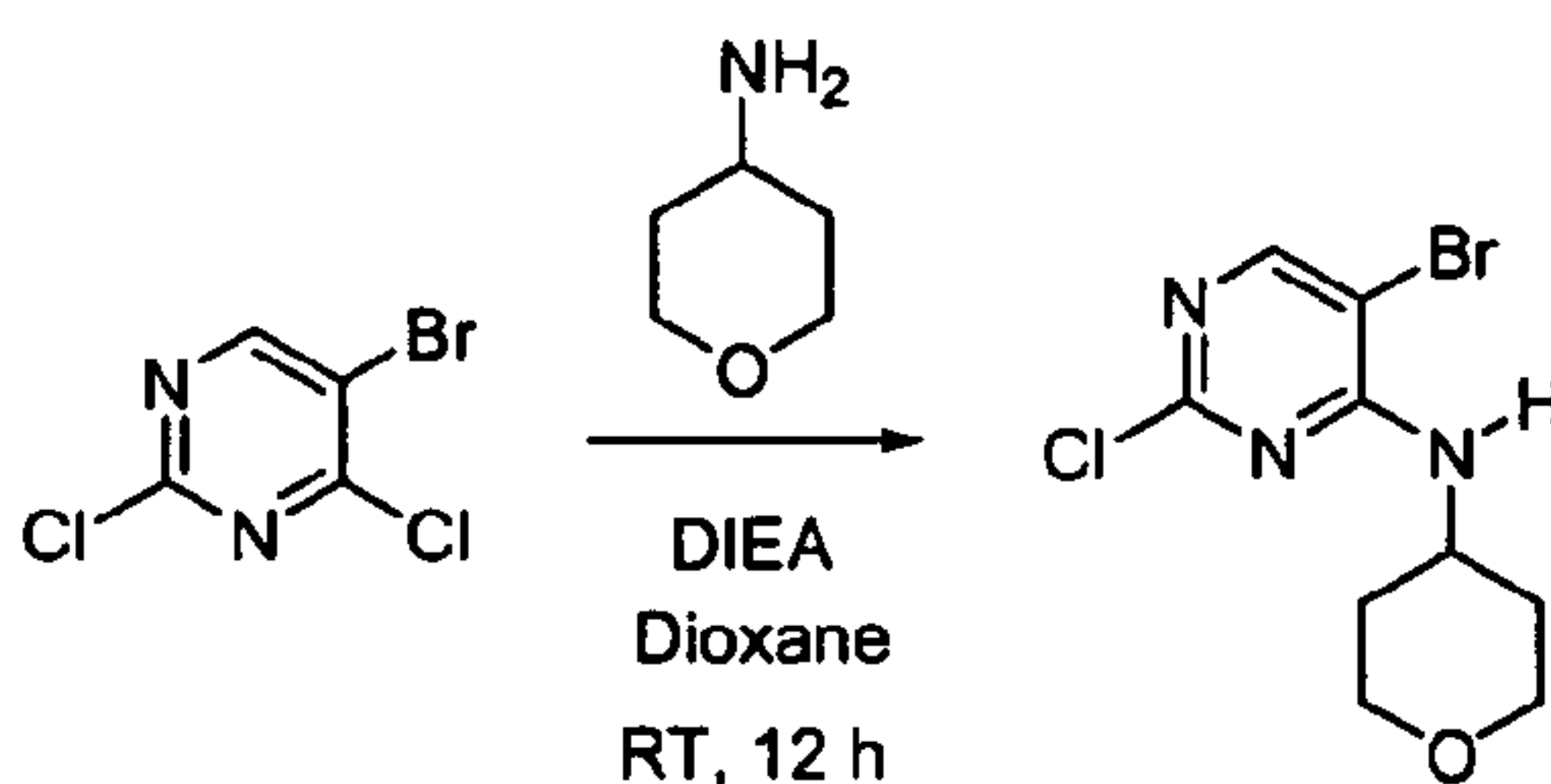
**(S)-9-cyclopentyl-N-(6-(3-hydroxypyrrolidin-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

Compound **30** was prepared using chemistry similar to that described in example 18. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 10.05 (1H, s), 9.24 (1H, s), 8.99 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.10 (1H, d, J = 10 Hz), 8.03 (1H, d, J = 5 Hz), 6.99 (1H, d, J = 10 Hz), 5.32 (1H, p, J = 10 Hz), 5.00 (1H, d, J = 5 Hz), 4.43 (1H, br s), 3.58 – 3.51 (3H, m), 3.40 (1H, m), 2.37 – 2.30 (2H, m), 2.09 – 2.02 (5H, m), 1.95 (1H, m), 1.74 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 417.3, Calculated 417.2.

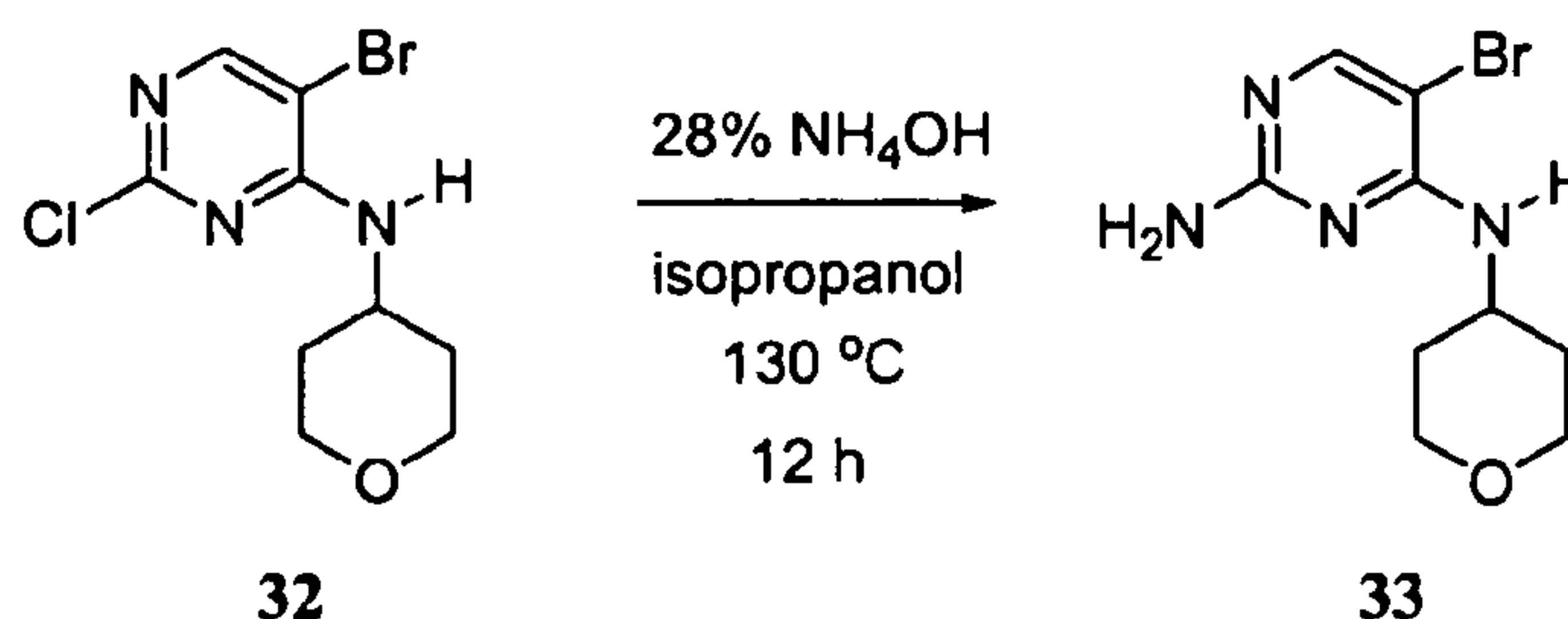


**EXAMPLE 20****31**

**(5-Piperazin-1-yl-pyridine-2-yl)-[9-(tetrahydro-pyran-4-yl)-9H-pyrido-  
[4',3',4,5]pyrrolo[2,3-d]pyrimidin-2-yl]-amine**

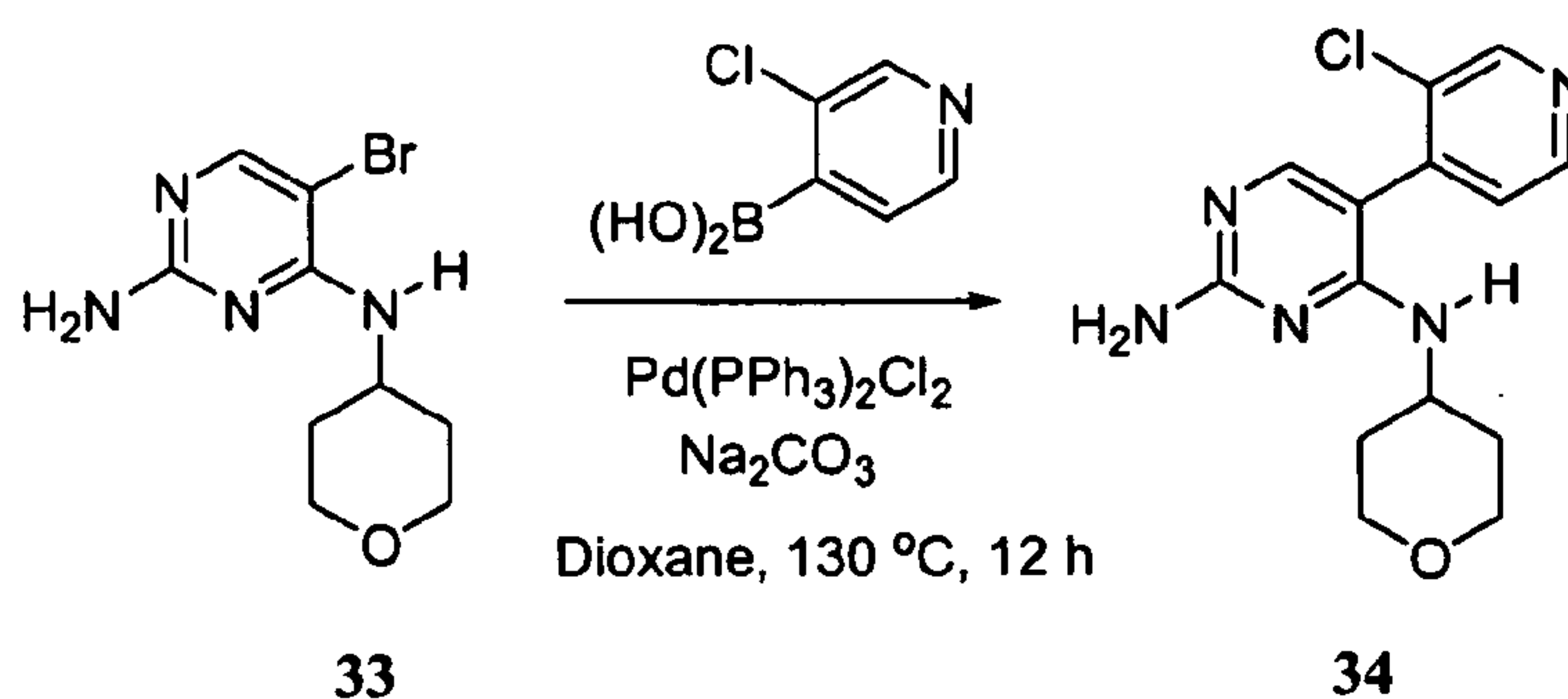
**32**

**(5-bromo-2-chloro-pyrimidin-4-yl)-(tetrahydro-pyran-4-yl)-amine (32).** 5-Bromo-2, 4-dichloropyrimidine (5.0 g, 21.9 mmol), tetrahydro-2H-pyran-4-amine (2.22 g, 21.9 mmol), and N-ethyl-N-isopropylpropan-2-amine (4.25 g, 32.9 mmol) were dissolved in dioxane (50 ml) and the reaction was stirred at room temperature for 12 hours. Ethyl acetate was added to the reaction mixture and the organic layer was washed with water and brine. The organic layer was dried with sodium sulfate. Removal of solvent gave (5-bromo-2-chloro-pyrimidin-4-yl)-(tetrahydro-pyran-4-yl)-amine (**32**) as a light yellow solid (6.75g, 99%). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 8.04 (1 H, s), 4.14-4.21 (1 H, m), 3.89 (2 H, dd, J = 11.4, 4.3 Hz) 3.43 (2 H, td, J = 11.9, 2.0 Hz), 1.80 (2 H, ddd, J = 12.6, 4.2, 1.8 Hz), 1.63 (2 H, qd, J = 12.2, 4.5, Hz); LCMS-ESI (POS), M/Z, M+1: Found 292.0, Calculated 292.

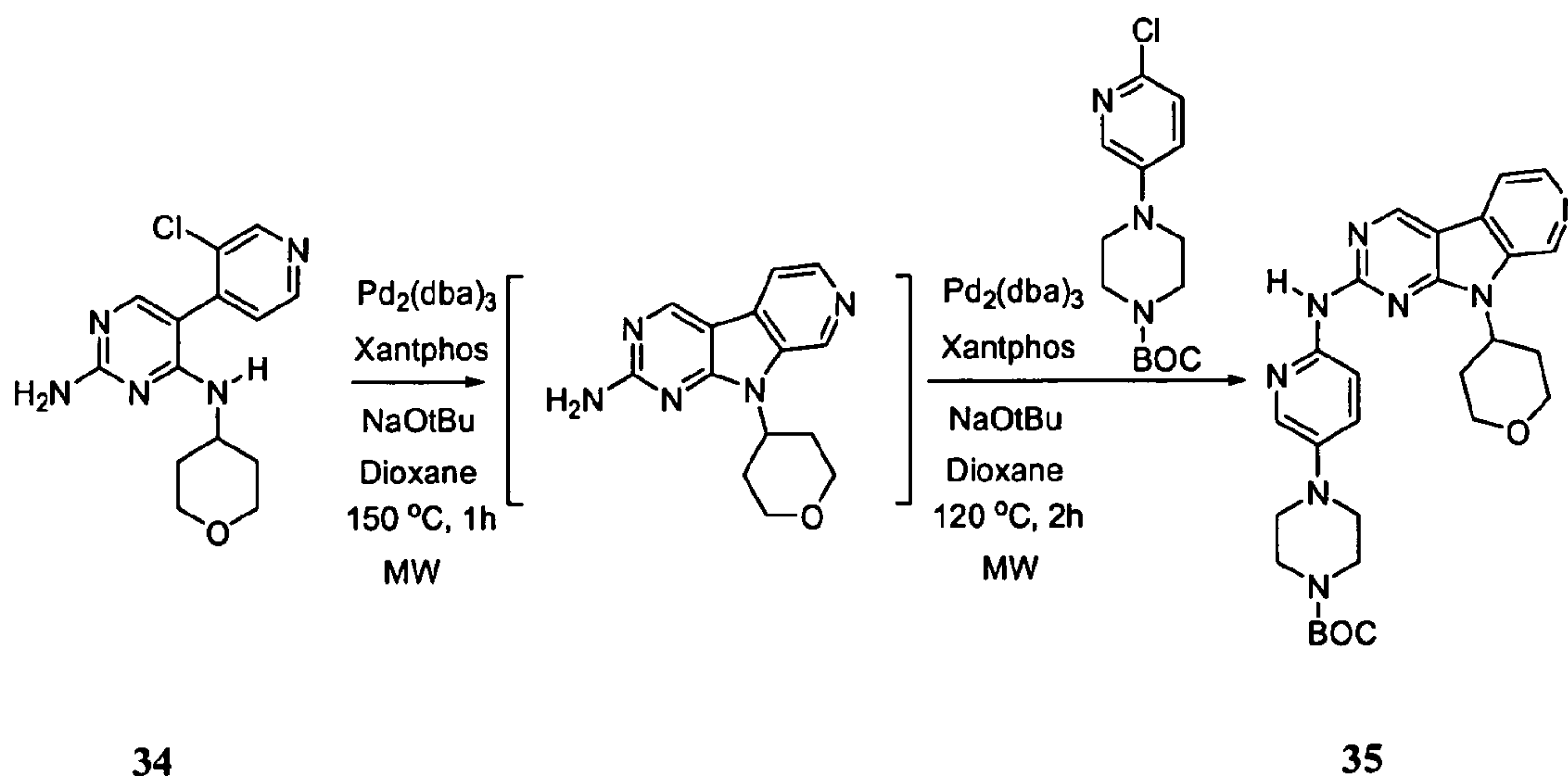
**32****33**



**5-Bromo-N<sup>4</sup>-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine (33):** To a suspension of compound 32 (6.60 g, 23 mmol) in isopropyl alcohol (40 ml) was added ammonia (aq. 28%, 80 ml). This reaction mixture was heated to 130°C for 14 hours in a pressure vessel. The reaction mixture was cooled down to room temperature and to this mixture was added ethyl acetate. The reaction mixture was washed with water and brine. The ethyl acetate layer was dried with sodium sulfate and concentrated to give compound 33 (4.75 g, 77%). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 7.79 (1 H, s), 4.24 (1 H, m), 3.99-4.02 (2 H, dd, *J*=11.0, 2.2 Hz), 3.52 (2 H, td, *J*=11.9, 2.0 Hz), 1.92-1.96 (2 H, m), 1.69 (2 H, m); LCMS-ESI (POS), *M/Z*, *M*+1: Found 273, Calculated 273.0

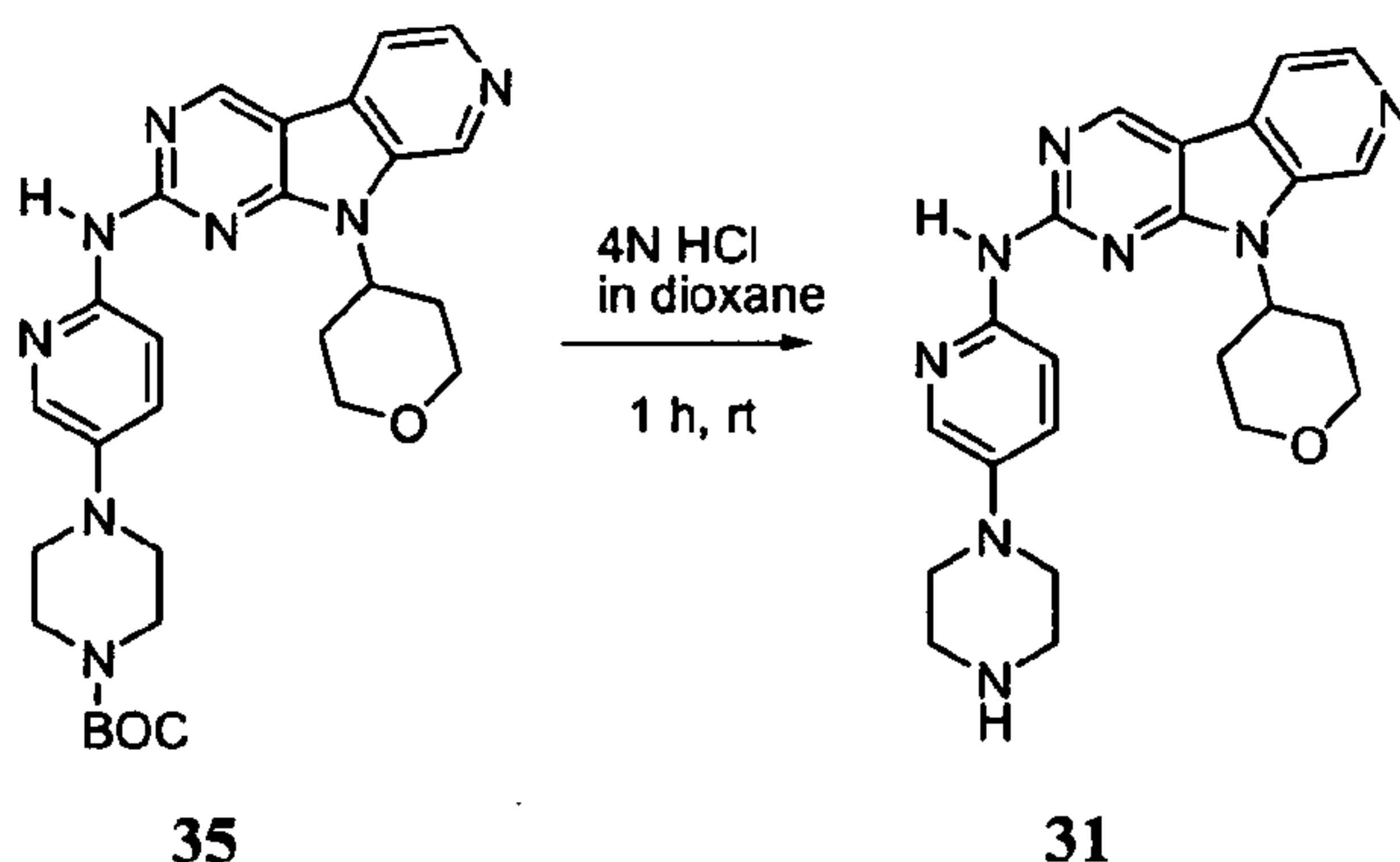


**5-(3-Chloro-pyridin-4-yl)-N<sup>4</sup>-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine (34):** A mixture of compound 33 (2.03g, 7.43 mmol), 3-chloropyridin-4-ylboronic acid (3.51 g, 22.3 mmol), and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.522 g, 0.743 mmol) in dioxane (44 ml) in a pressure vessel was purged with N<sub>2</sub> for 20 minutes and to this mixture was added aq. Na<sub>2</sub>CO<sub>3</sub> (1 M, 22 mL) by syringe. The reaction was further purged with N<sub>2</sub> for another 20 minutes and then heated to 130 °C for 12 hours. DCM was added to the reaction and the mixture was washed with water and brine. The organic layer was dried with sodium sulfate and concentrated to provide compound 34 (2.07 g, crude, 98%) which was used in the next reaction without further purification. LCMS-ESI (POS), *M/Z*, *M*+1: Found 306.1, Calculated 306.1.



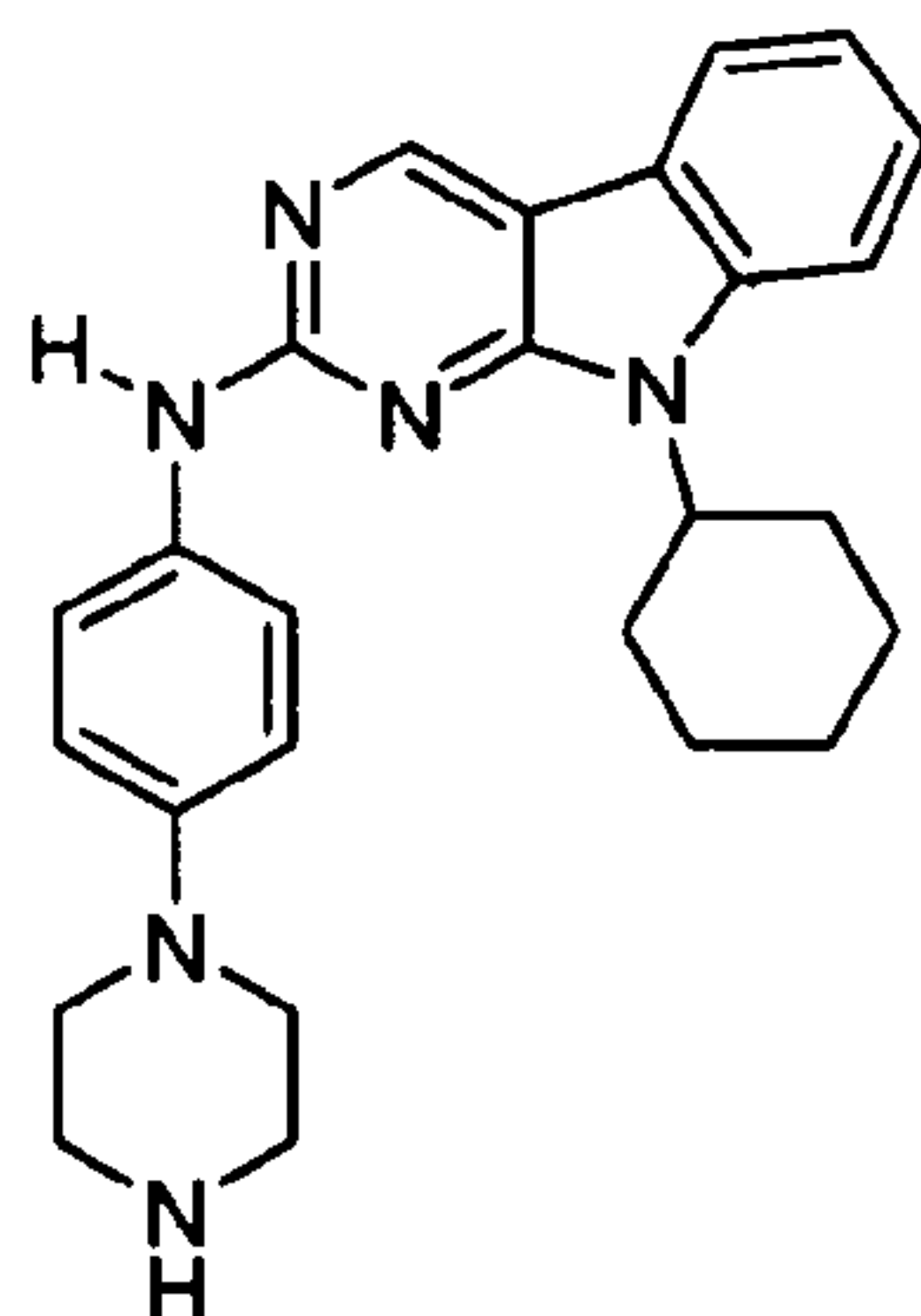


**4-{6-[9-(Tetrahydro-pyran-4-yl)-9H-pyrido[4',3',4,5]pyrrolo[2,3-*d*]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic acid *tert*-butyl ester (35):** Compound 34 (150 mg, 491  $\mu$ mol), Pd<sub>2</sub>(dba)<sub>3</sub> (22.5 mg, 24.5  $\mu$ mol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (28.4 mg, 49.1  $\mu$ mol), sodium 2-methylpropan-2-olate (118 mg, 1226  $\mu$ mol) in dioxane (4 ml) was purged with N<sub>2</sub> for 20 minutes. The reaction was heated up to 150 °C in microwave for 1 hour. Then a solution of compound 5 (146 mg, 491  $\mu$ mol) in dioxane (1 ml) was added to the reaction mixture and the reaction was purged with N<sub>2</sub> for another 20 minutes. This reaction was heated to 120°C under microwave irradiation for 2 hours. DCM was added to the reaction and the mixture was washed with water and brine. The organic layer was dried with sodium sulfate and concentrated. Purification by flash chromatography (DCM/methanol) gave compound 35 (102 mg). LCMS-ESI (POS), M/Z, M+1: Found 531.2, Calculated 531.3



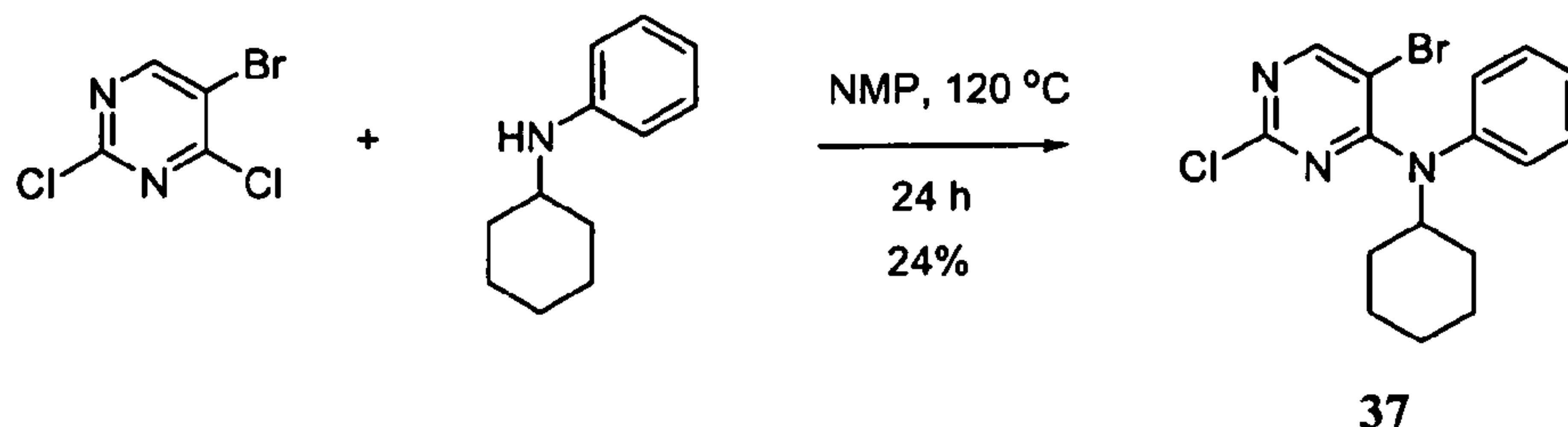
**(5-Piperazin-1-yl-pyridine-2-yl)-[9-(tetrahydro-pyran-4-yl)-9H-pyrido[4',3',4,5]pyrrolo-[2,3-*d*]pyrimidin-2-yl]-amine (31):** Compound 35 (100 mg) was treated with 5 mL of 4 N HCl in dioxane for 1 hour. The product, which was not soluble in dioxane, was collected and then washed with ethyl acetate and a small amount of methanol to obtain compound 31 as its HCl salt (20 mg, 25%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 9.65 (1 H, s), 9.59 (1 H, s), 9.37 (1 H, s), 8.27 (2 H, s), 8.14 (1 H, s), 8.05 (1 H, s), 7.80 (1 H, s), 5.20 (2 H, m), 4.10 (2 H, d, *J*=3.2 Hz), 3.71 (br s), 3.6 (2 H, m), 3.46 (4 H, s), 3.27 (4 H, s), 2.83 (2 H, dd, *J*=11.9, 3.8 Hz), 1.90 (2 H, d, *J*=10.5 Hz); LCMS-ESI (POS), M/Z, M+1: Found 431.2, Calculated 431.2

### EXAMPLE 21

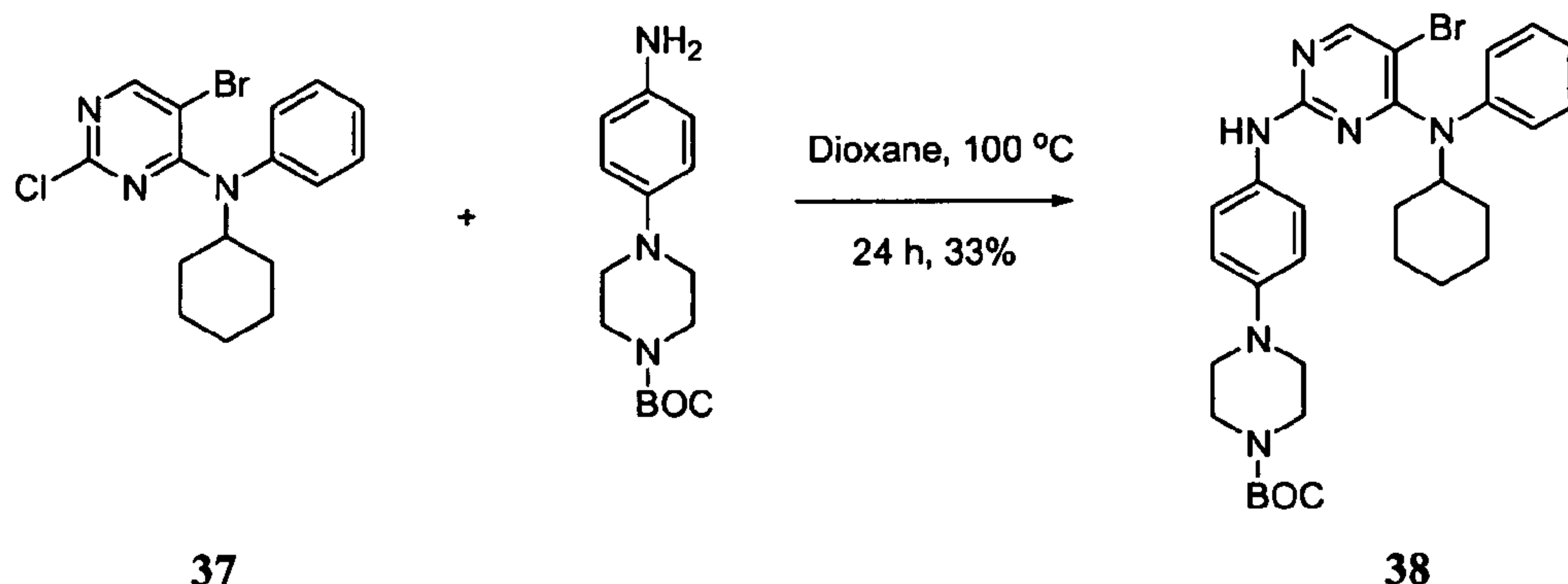




36

**(9-Cyclohexyl-9H-pyrimido[4,5-b]indol-2-yl)-(4-piperazin-1-yl-phenyl)-amine**

**(5-Bromo-2-chloro-pyrimidin-4-yl)-cyclohexyl-phenyl-amine (37):** 5-Bromo-2,4-dichloro-pyrimidine (2.17 ml, 17.14 mmol) and cyclohexyl-phenyl-amine (2.0 g, 11.43 mmol) were dissolved in N-methylpyrrolidone (NMP) (25 ml), and this reaction was heated to 120 °C for 24 hours. The reaction was cooled to room temperature and diluted with ethyl acetate, washed with water and brine. The organic phase was dried using sodium sulfate and concentrated. Purification by flash chromatography (ethyl acetate/hexane) gave compound **37** as a yellow solid (855 mg, 24%). <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ ppm 8.27 (1 H, s), 7.41 (3 H, m), 7.21 (2 H, m), 4.62 (1 H, m), 1.93 (2 H, d, *J*=10 Hz), 1.75 (2 H, d, *J*=10 Hz), 1.58 (1 H, d, *J*=10 Hz), 1.34 (2 H, m), 1.15 (2 H, m), 0.91 (1 H, m).

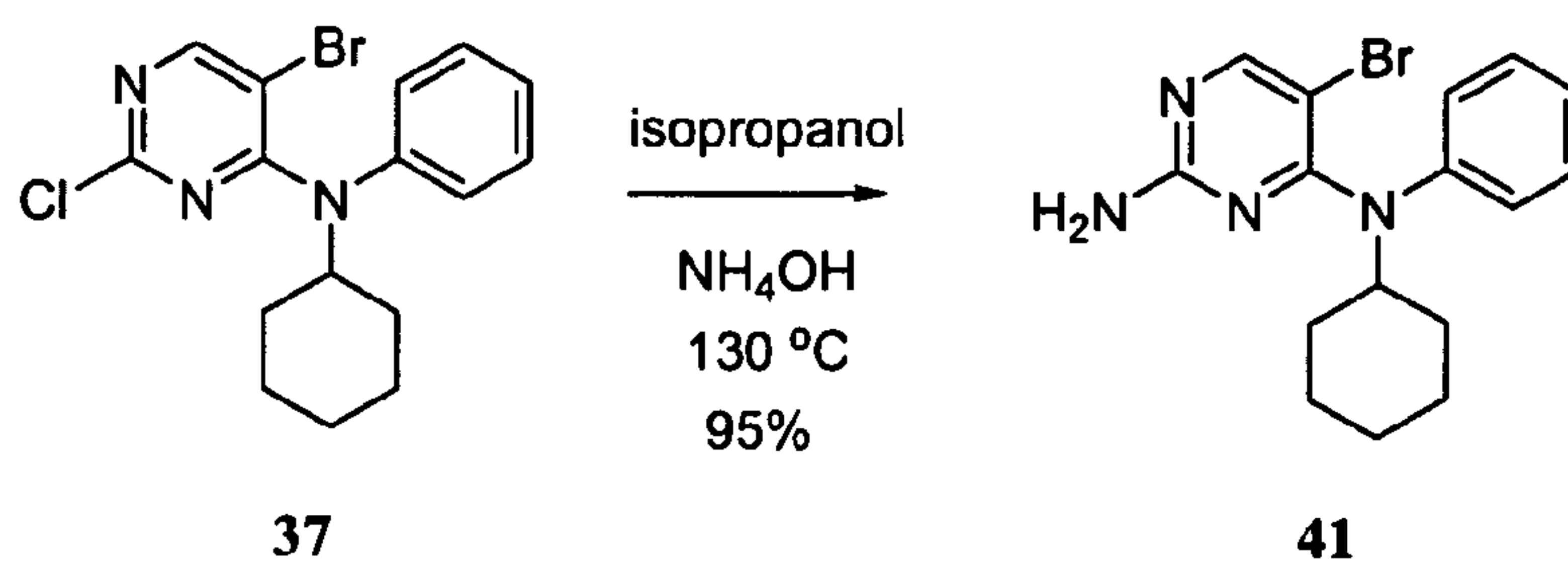


**4-{4-[5-Bromo-4-(cyclohexyl-phenyl-amino)-pyrimidin-2-ylamino]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (38):** Compound **37** (0.42 g, 1.15 mmol) and 4-(4-amino-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.64 g, 2.30 mmol) were dissolved in dioxane (2 mL), and this mixture was heated at 100 °C for 24 hours. The reaction was cooled to room temperature and diluted with ethyl acetate. This mixture was washed with water and brine. The organic layer was dried with sodium sulfate and purified by flash chromatography (ethyl acetate/hexane) to give compound **38** as a yellow solid (0.23 g, 33%). <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ ppm 9.18 (1 H, s), 7.97 (1 H, s), 7.55 (2 H, d, *J*=10 Hz), 7.37 (2 H, m), 7.31 (1 H, m), 7.12 (2 H, m), 6.89 (2 H, d, *J*=10 Hz), 4.68 (1 H, m), 3.44 (4 H, m), 3.00 (4 H, m), 1.91 (2 H, d, *J*=10 Hz), 1.72 (2 H, d, *J*=10 Hz), 1.57 (1 H, d, *J*=10 Hz), 1.41 (9 H, s), 1.35 (2 H, m), 1.14 (2 H, m), 0.92 (1 H, m); LCMS-ESI (POS), *M/Z*, *M*+1: Found 609.2, Calculated 607.2/609.2.

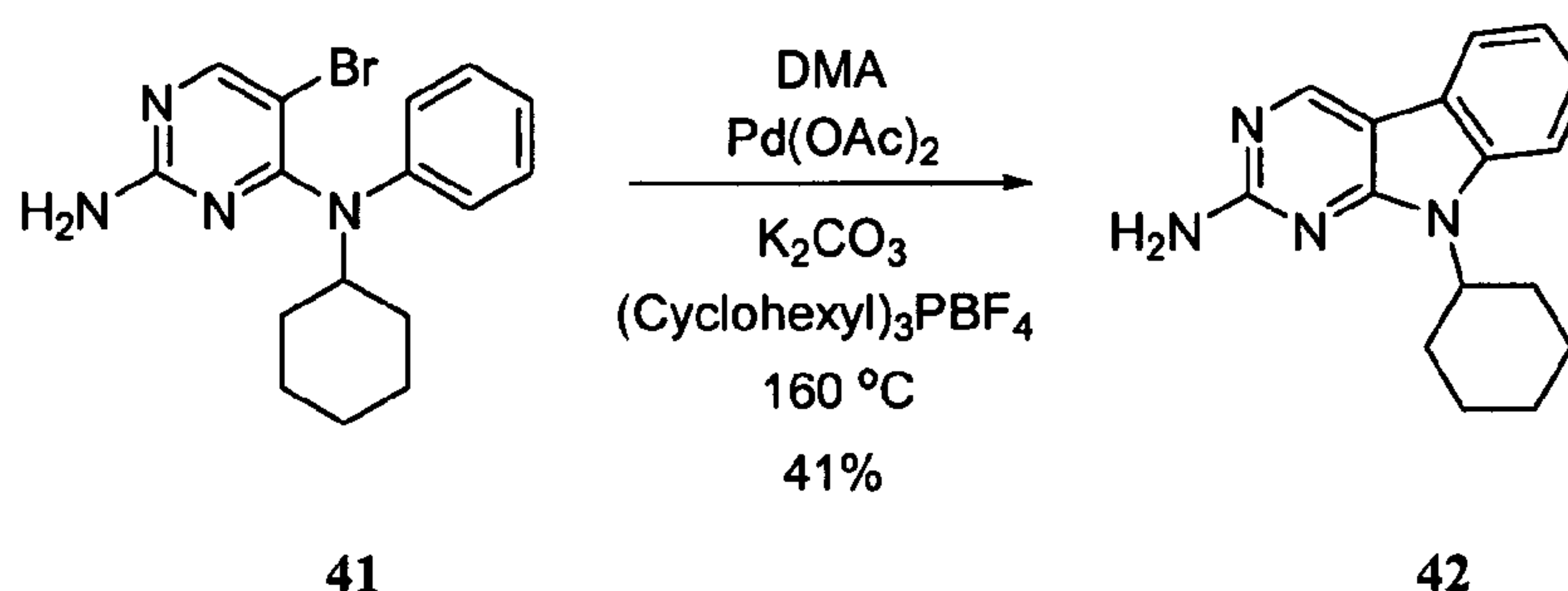




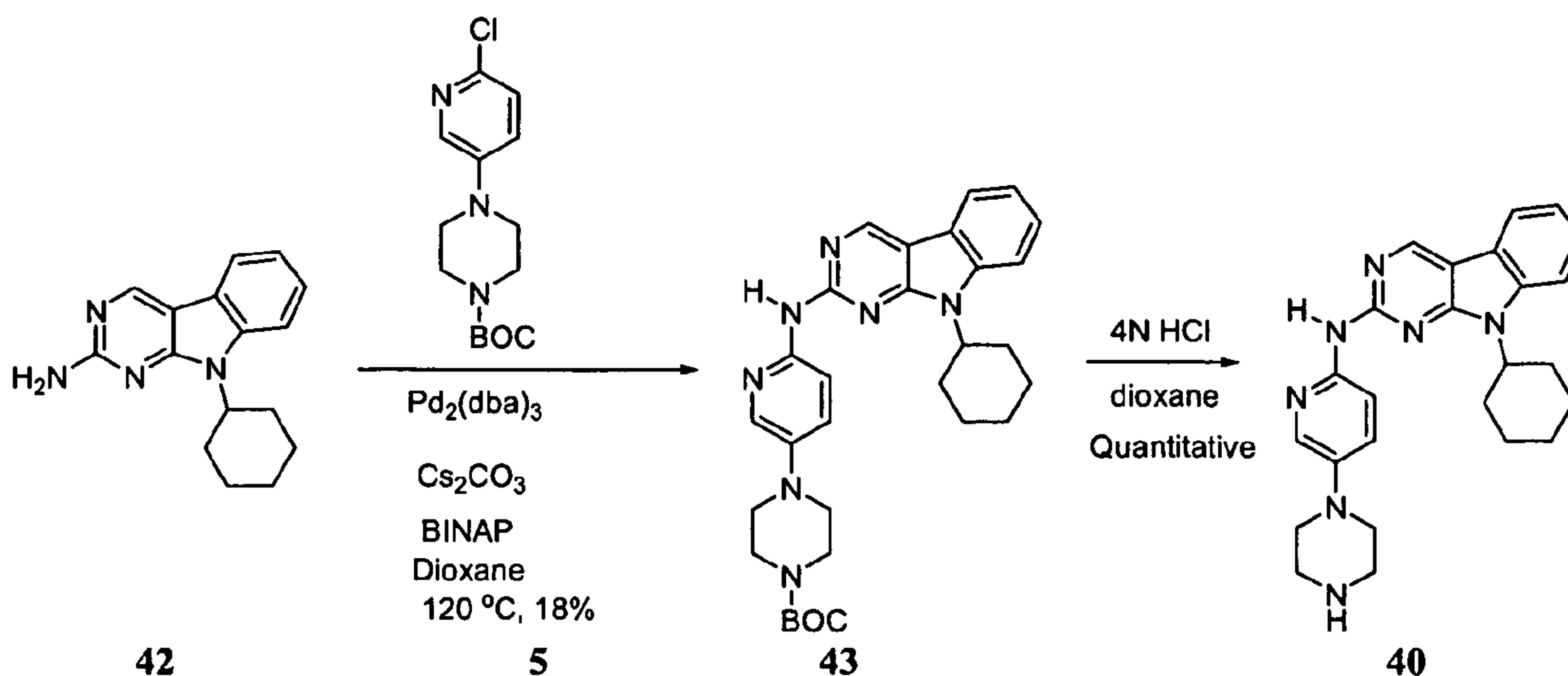




**5-Bromo-N4-cyclohexyl-N4-phenyl-pyrimidine-2,4-diamine (41):** Compound 41 was prepared using chemistry similar to that described in example 1. LCMS-ESI (POS), M/Z, M+1: Found 348.3, Calculated 348.3.



**9-Cyclohexyl-9H-pyrimido[4,5-*b*]indol-2-ylamine (42).** A mixture of compound 41 (0.35 g, 0.99 mmol), Pd(OAc)<sub>2</sub> (33 mg, 0.15 mmol), (cyclohexyl)<sub>3</sub>PBF<sub>4</sub> (110 mg, 0.30 mmol), and K<sub>2</sub>CO<sub>3</sub> (138 mg, 0.10 mmol) in DMA (3 mL) was purged with N<sub>2</sub> for 20 minutes and then heated at 160 °C for 3 hours. The reaction was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. Purification by flash chromatography (ethyl acetate/hexane) gave compound 42 as a yellow solid (110 mg, 41%). LCMS-ESI (POS), M/Z, M+1: Found 267.1, Calculated 267.2.



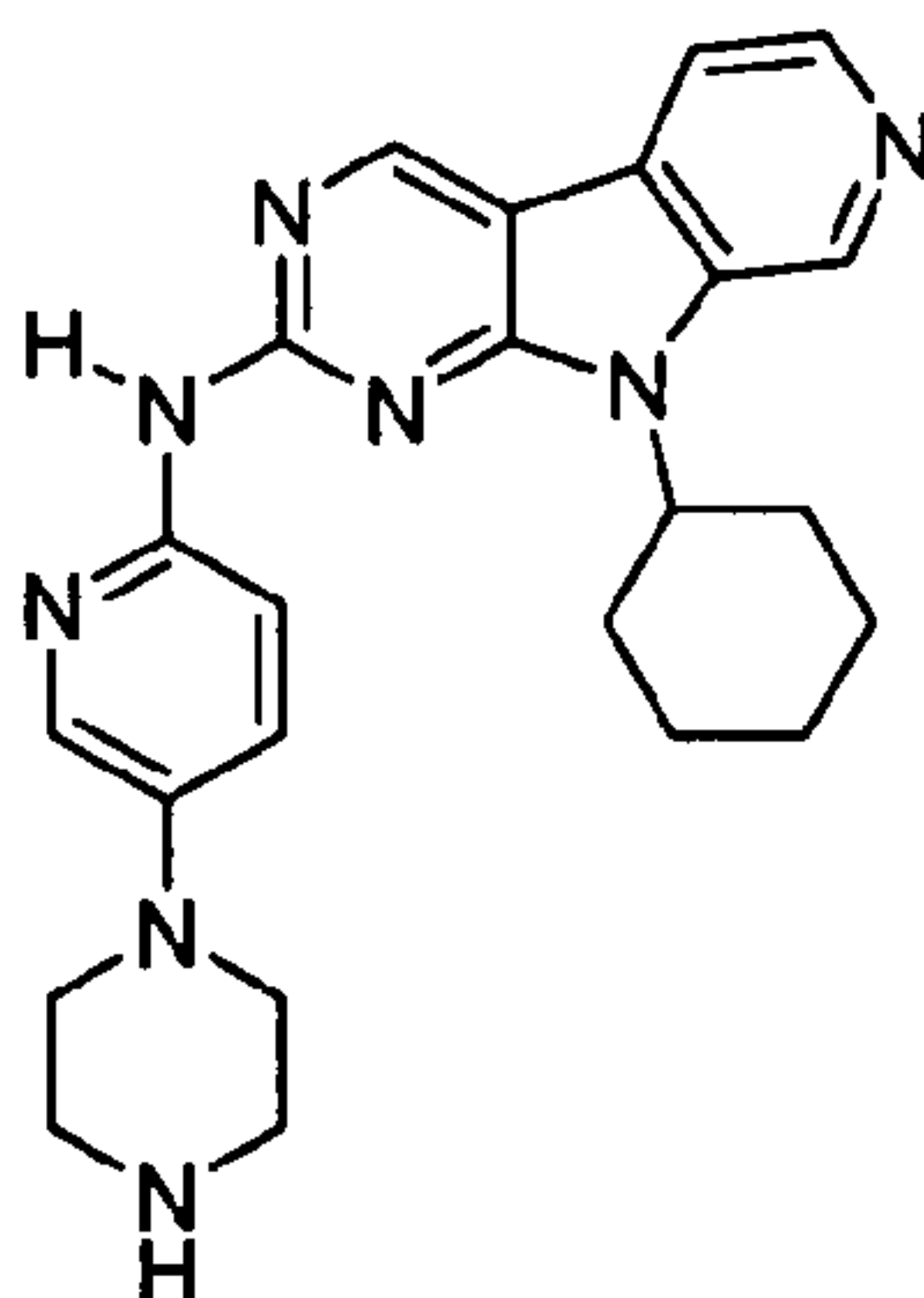
**(9-Cyclohexyl-9H-pyrimido[4,5-*b*]indol-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine (40).**



A mixture of compound **42** (98 mg, 0.37 mmol), compound **5** (121 mg, 0.41 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (17 mg, 0.018 mmol), BINAP (23 mg, 0.037 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (168 mg, 0.52 mmol) in dioxane (3 mL) was purged with N<sub>2</sub> for 20 minutes. The reaction was heated at 120 °C for 14 hours. The reaction was then cooled down to room temperature and diluted with ethyl acetate. The reaction mixture was washed with water and brine. The organic layer was dried with sodium sulfate and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexane) to give compound **43** (34 mg, 18%). LCMS-ESI (POS), M/Z, M+1: Found 528.3, Calculated 528.3.

Compound **43** was then treated with 4N HCl in dioxane (5 mL) for 3 hours. The reaction mixture was concentrated and the residue was purified by Prep-HPLC to give compound **40** as a yellow solid TFA salt (32 mg). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.19 (1 H, s), 8.12 - 8.22 (2 H, m), 7.90 (1 H, d, *J*=7.3 Hz), 7.82 (1 H, d, *J*=7.9 Hz), 7.63 (1 H, t, *J*=7.6 Hz), 7.43 (1 H, t, *J*=7.0 Hz), 7.34 (1 H, d, *J*=7.9 Hz), 4.87 (1 H, s), 3.54 (4 H, s), 3.46 (4 H, s), 2.57 - 2.67 (2 H, m), 2.04 (2 H, d, *J*=14.0 Hz), 1.96 (2 H, d, *J*=11.0 Hz), 1.86 (1 H, d, *J*=12.2 Hz), 1.54 - 1.66 (2 H, m), 1.50 (1 H, d, *J*=12.2 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 428.2, Calculated 428.3.

### Example 23

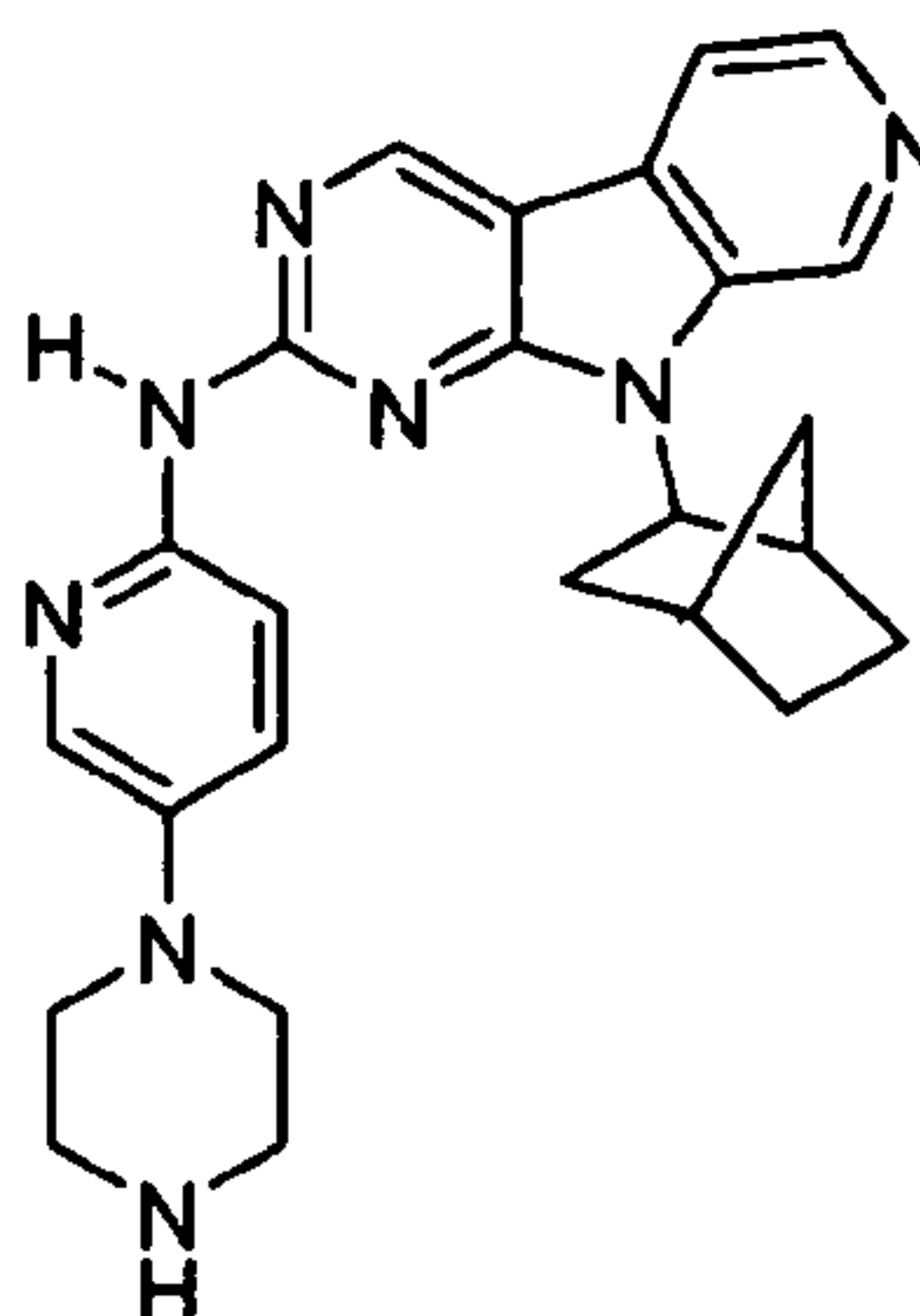


**44**

**(9-Cyclohexyl-9H-pyrido[4',3',4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

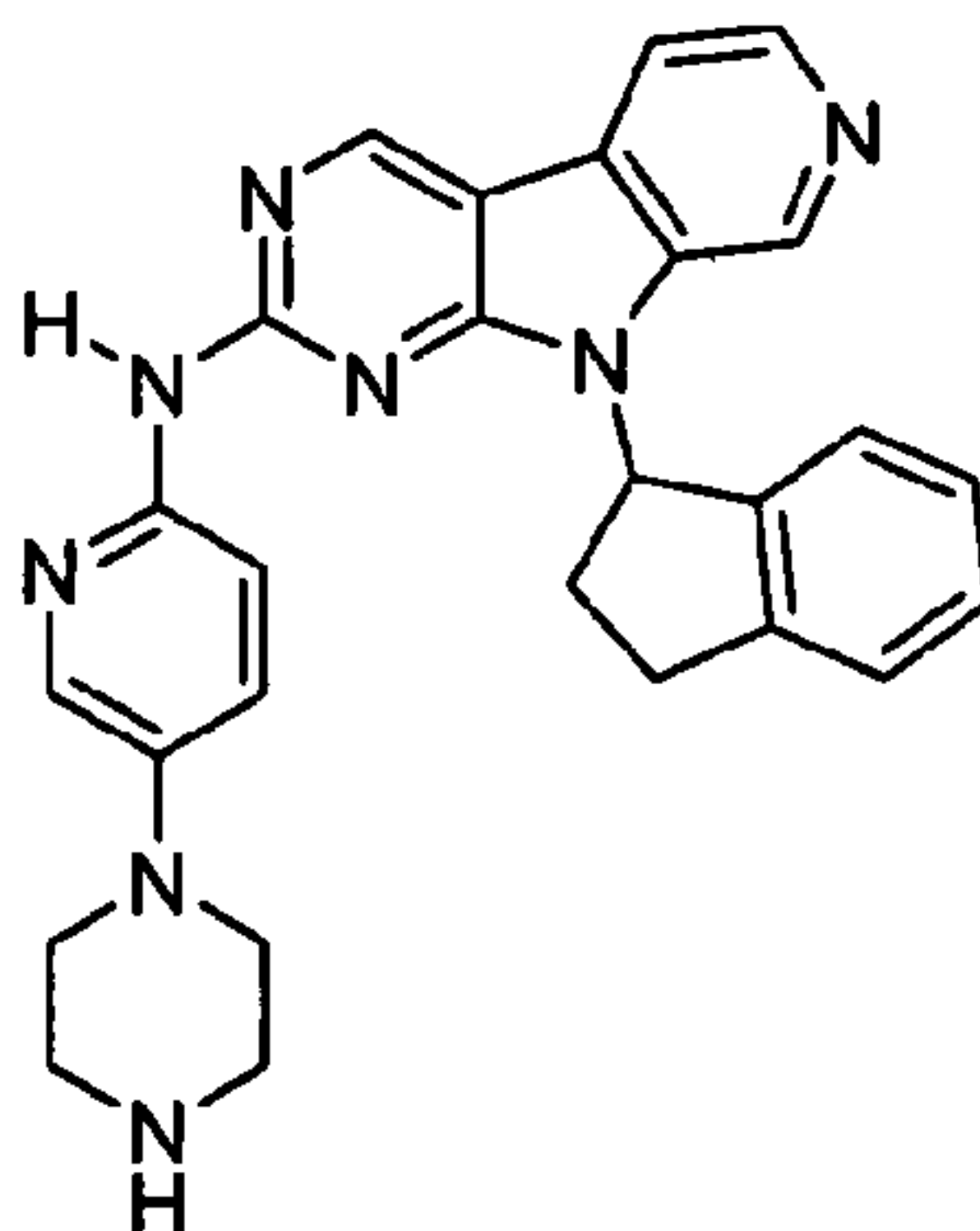
Compound **44** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.84 (1 H, s), 9.59 (1 H, s), 8.88 (1 H, d, *J*=6.1 Hz), 8.74 (1 H, d, *J*=6.1 Hz), 8.32 (1 H, d, *J*=10.0 Hz), 8.12 (1 H, d, *J*=2.9 Hz), 7.67 (1 H, d, *J*=9.5 Hz), 5.03 (1 H, m), 3.76-3.78 (2 H, m), 3.64 (4 H, m), 3.48 (4 H, m), 2.63-2.70 (2 H, m), 2.06-2.09 (4 H, d, *J*=10.8 Hz), 2.03 (2 H, m), 1.64 (1 H, m); LCMS-ESI (POS), M/Z, M+1: Found 429.2, Calculated 429.2



**EXAMPLE 24****45**

**(9-Bicyclo[2.2.1]hept-2-yl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

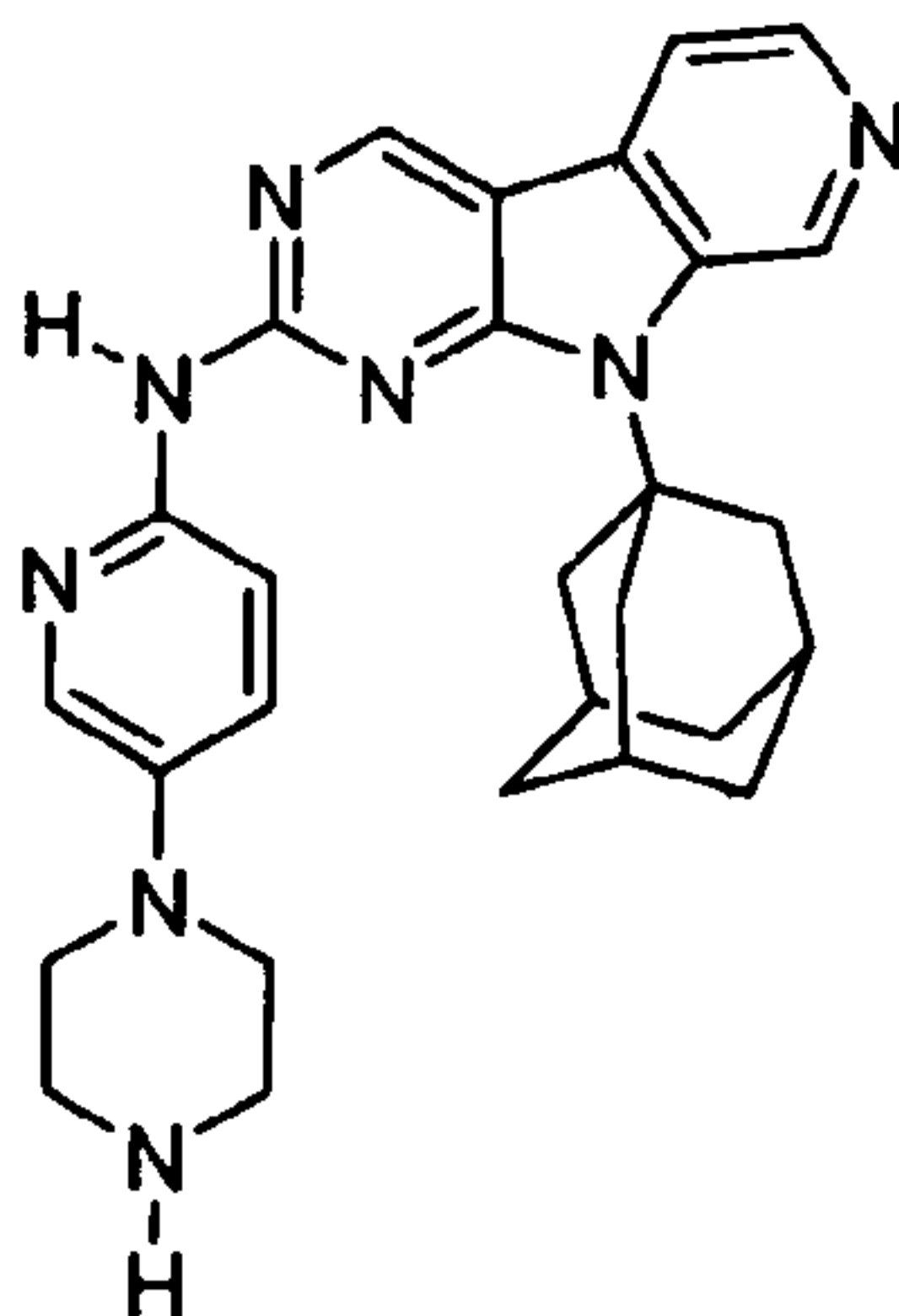
Compound **45** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 10.41 (1 H, s), 9.53 (1 H, s), 9.28 (1 H, s), 8.96 (2 H, s), 8.63 (1 H, d, *J*=10 Hz), 8.14 (2 H, d, *J*=2.4 Hz), 7.65 (1 H, d, *J*=10 Hz), 4.78 (1 H, m), 3.42 (4 H, m), 3.28 (4 H, m), 2.90 (1 H, m), 2.83 (1 H, s), 2.58 (1 H, s), 2.25 (1 H, d, *J*=10 Hz), 2.02 (1 H, t, *J*=10 Hz), 1.60-1.65 (3 H, m), 1.35 (2 H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 441.2, Calculated 441.2.

**EXAMPLE 25****46**

**(9-Indan-1-yl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

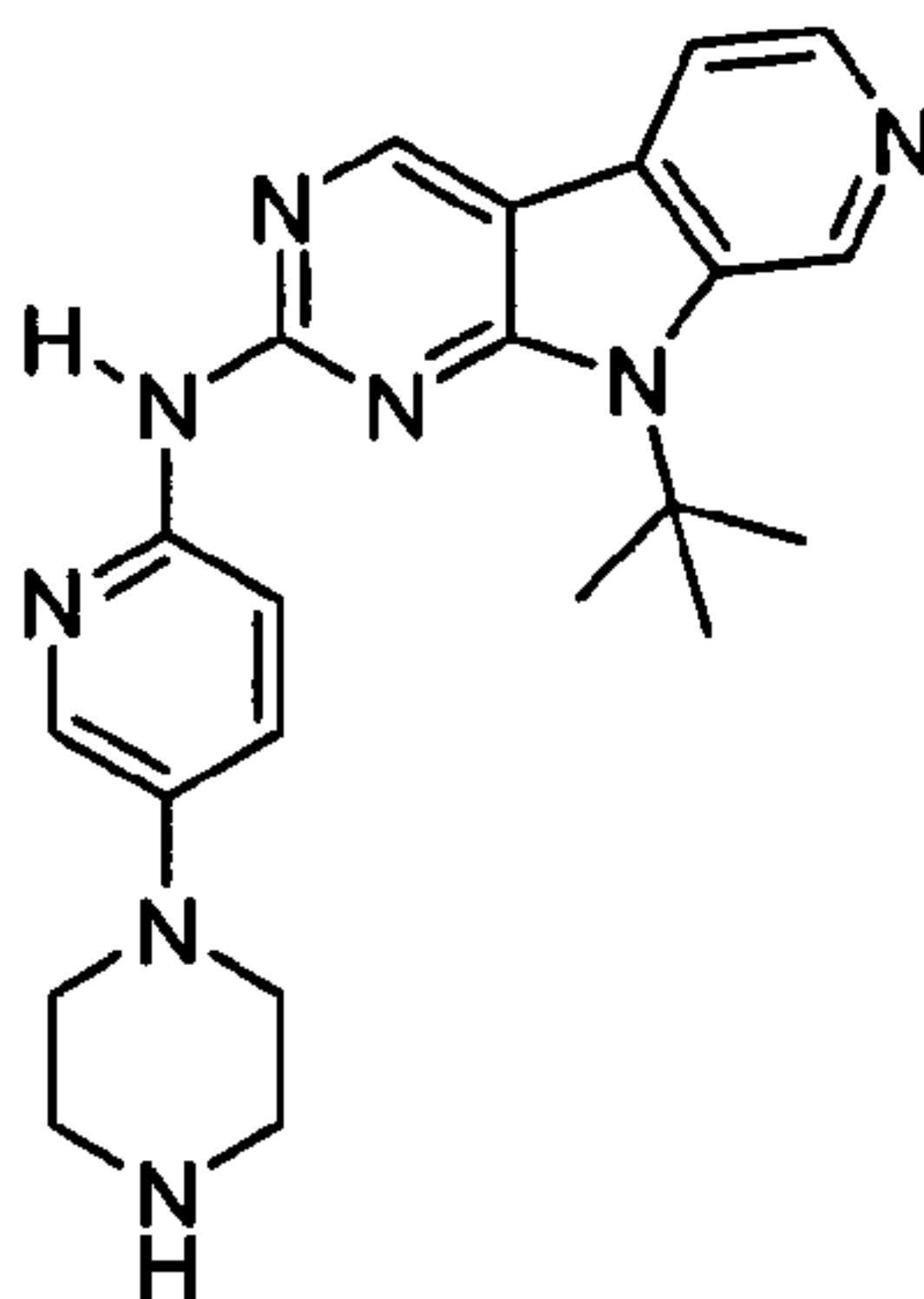
Compound **46** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.63 (1 H, s), 8.58-8.63 (2 H, dd, *J*=5.8, 21.1 Hz), 8.07 (1 H, d, *J*=2.7 Hz), 7.91 (1 H, s), 7.72 (1 H, s), 7.57 (1 H, d, *J*=5.0 Hz), 7.43 (1 H, t, *J*=5.0 Hz), 7.22 (1 H, t, *J*=5.0 Hz), 7.02 (1 H, d, *J*=5.0 Hz), 6.90 (1 H, t, *J*=5.0 Hz), 4.85 (1 H, m), 3.52 (4 H, m), 3.47 (4 H, m), 3.40 (1 H, m), 3.26 (1 H, m), 2.89 (1 H, m), 2.64 (1 H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 463.1, Calculated 463.2.



**EXAMPLE 26****47**

**(9-Adamantan-1-yl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

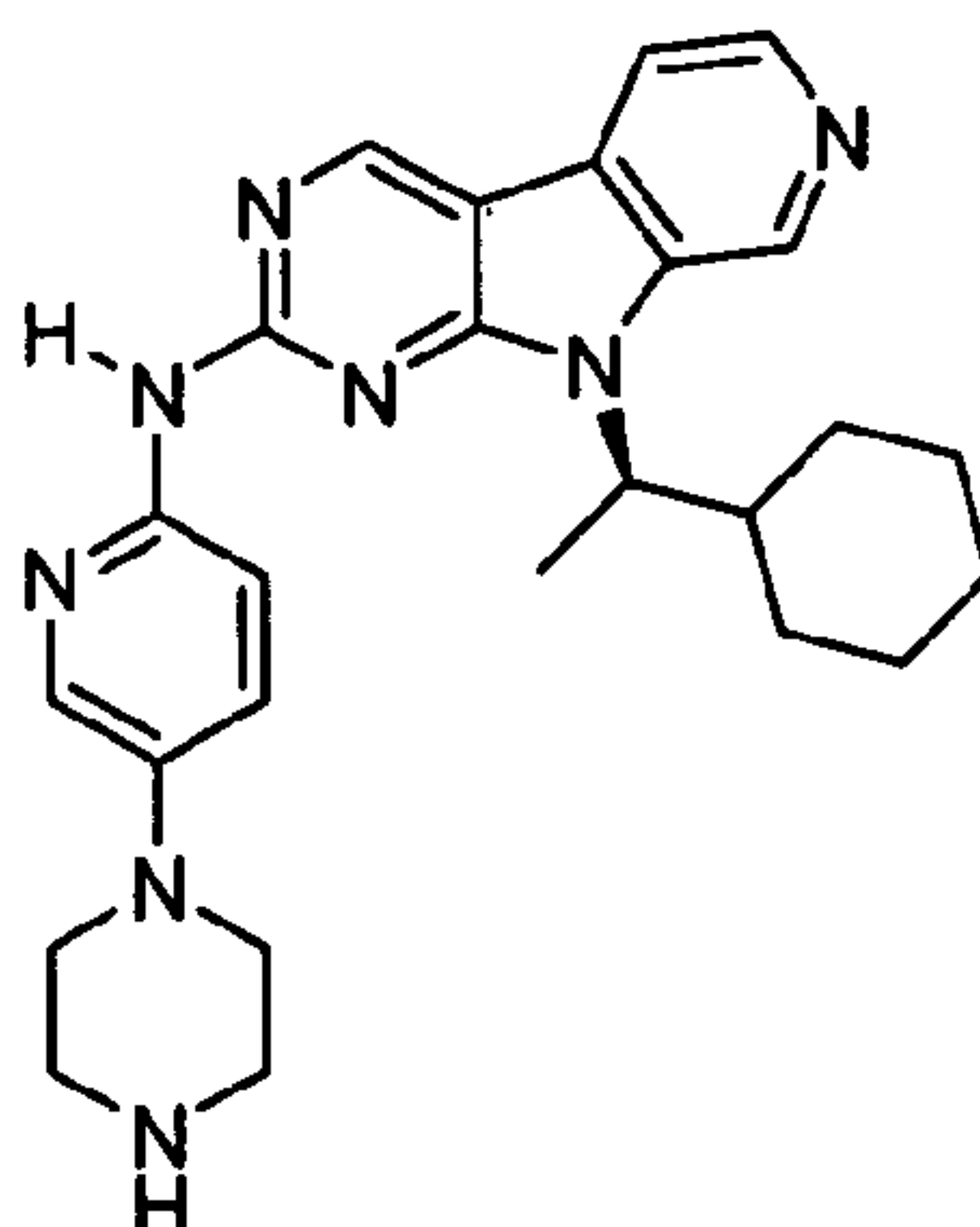
Compound **47** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.60 (1 H, s), 9.53 (1 H, s), 8.62 (1 H, d, *J*=5.0 Hz), 8.56 (1 H, d, *J*=5.0 Hz), 8.12 (1 H, t, *J*=2.5 Hz), 7.95 (1 H, m), 3.52 (4 H, m), 3.47 (4 H, m), 2.95 (6 H, d, *J*=2.5 Hz), 2.38 (3 H, s), 2.04 (1 H, s), 2.01 (2 H, s), 1.94 (2 H, s), 1.91 (1 H, s) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 481.3, Calculated 481.3.

**EXAMPLE 27****48**

**(9-tert-Butyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

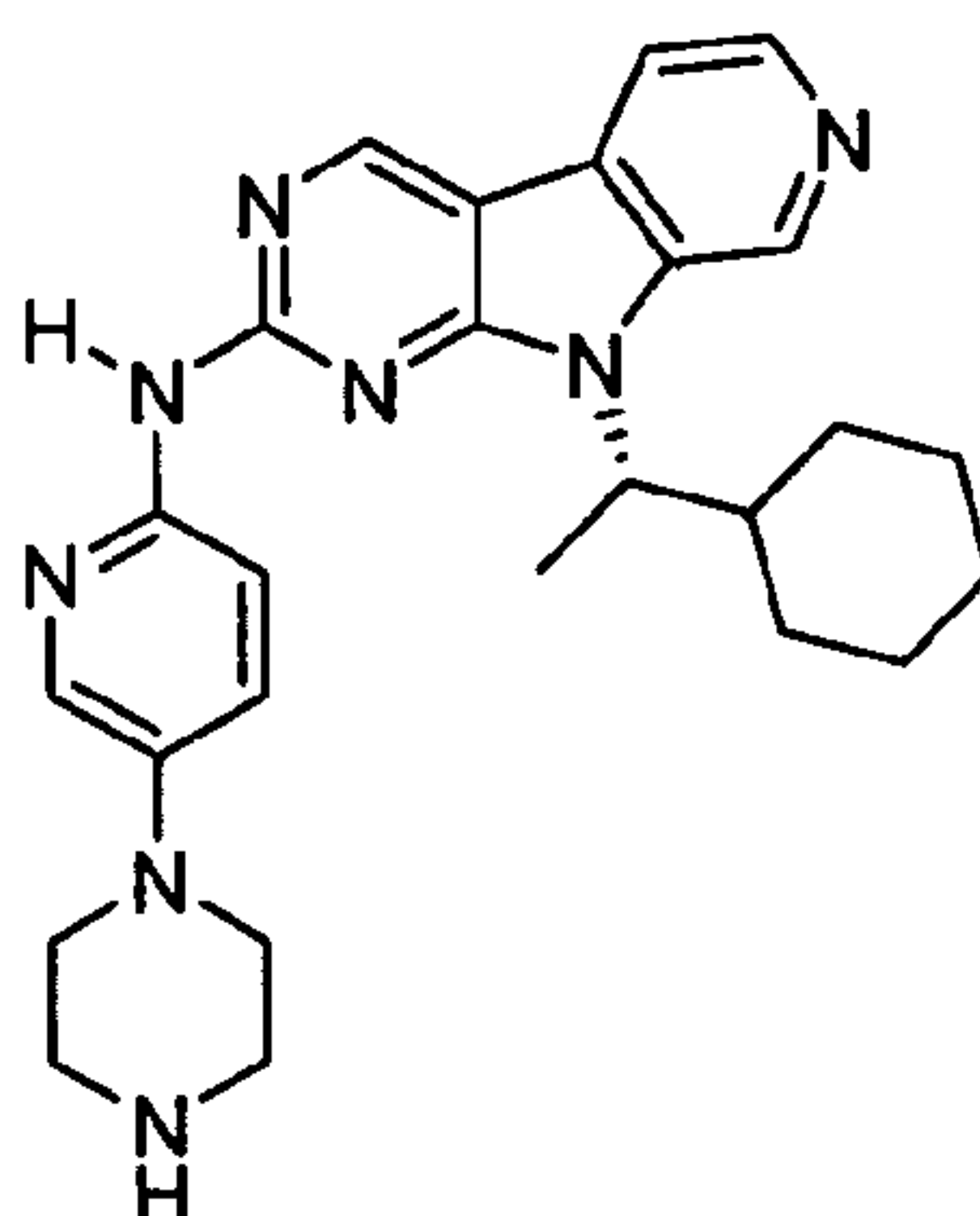
Compound **48** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.85 (1 H, s), 9.60 (1 H, s), 8.88 (1 H, d, *J*=6.1 Hz), 8.71 (1 H, d, *J*=6.1 Hz), 8.33 (1 H, m), 8.11 (1 H, d, *J*=2.9 Hz), 7.69 (1 H, d, *J*=9.5 Hz), 3.61 (4 H, m), 3.48 (4 H, m), 2.17 (9 H, s) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 403.3, Calculated 403.2.



**EXAMPLE 28****49**

**(R)-[9-(1-Cyclohexyl-ethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine**

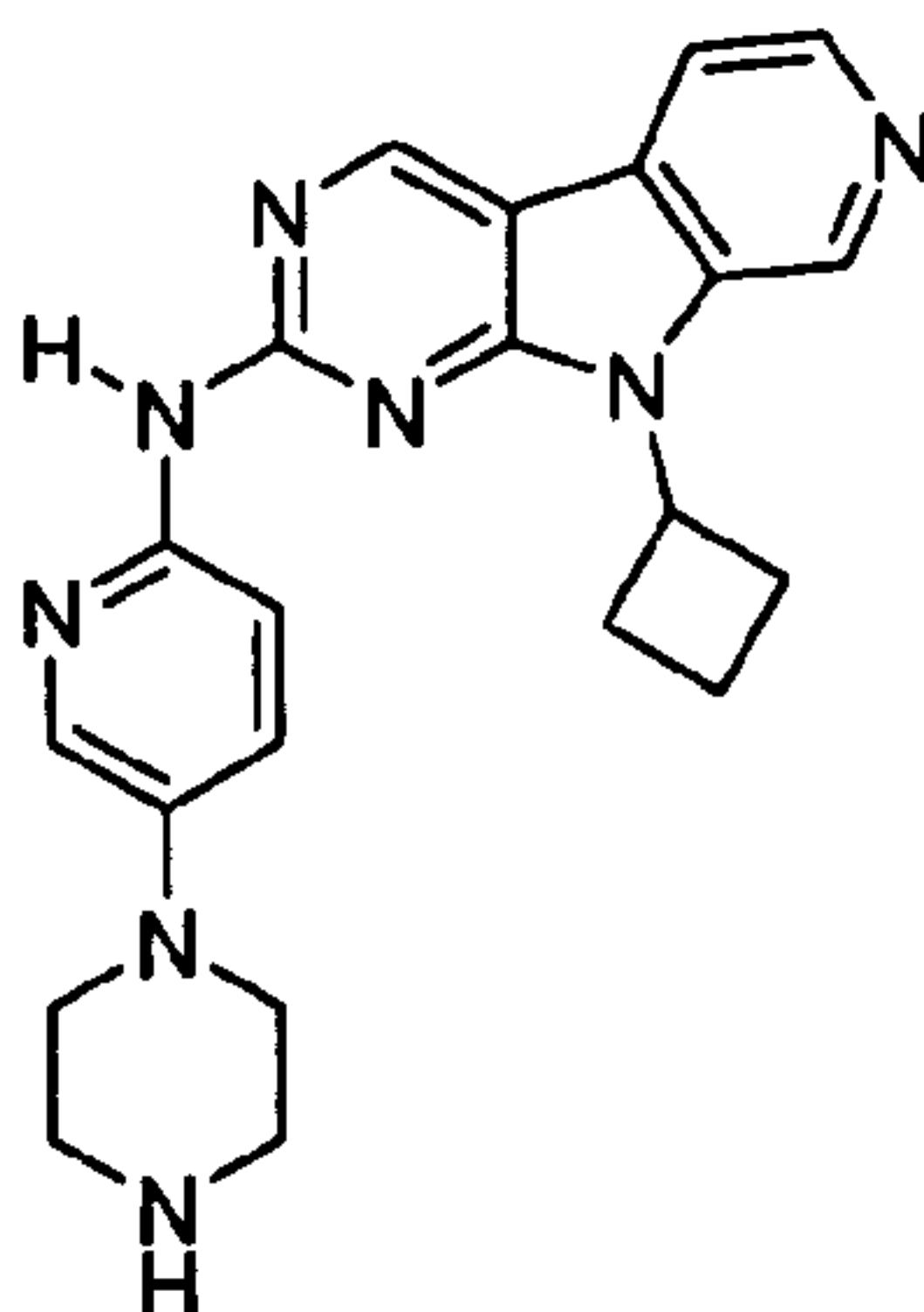
Compound **49** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.68 (1 H, s), 9.43 (1 H, s), 8.69 (2 H, dd, J = 7.3, 10.5 Hz), 8.12 (1 H, s), 8.10 (1 H, s), 7.80 (1 H, d, J = 8.5 Hz), 4.93 (1 H, m), 3.57 (4 H, m), 3.47 (4 H, m), 2.18 (1 H, d, J = 10.1 Hz), 1.92 (1 H, d, J = 10.1 Hz), 1.82 (3 H, d, J = 7.1 Hz), 1.69 (1 H, d, J = 10.0 Hz), 1.59 (1 H, d, J = 10.0 Hz), 1.40 (1 H, m), 1.23 (2 H, m), 1.10 (2 H, m), 0.96 (1 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 457.3, Calculated 457.3.

**EXAMPLE 29****50**

**(S)-[9-(1-Cyclohexyl-ethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine**

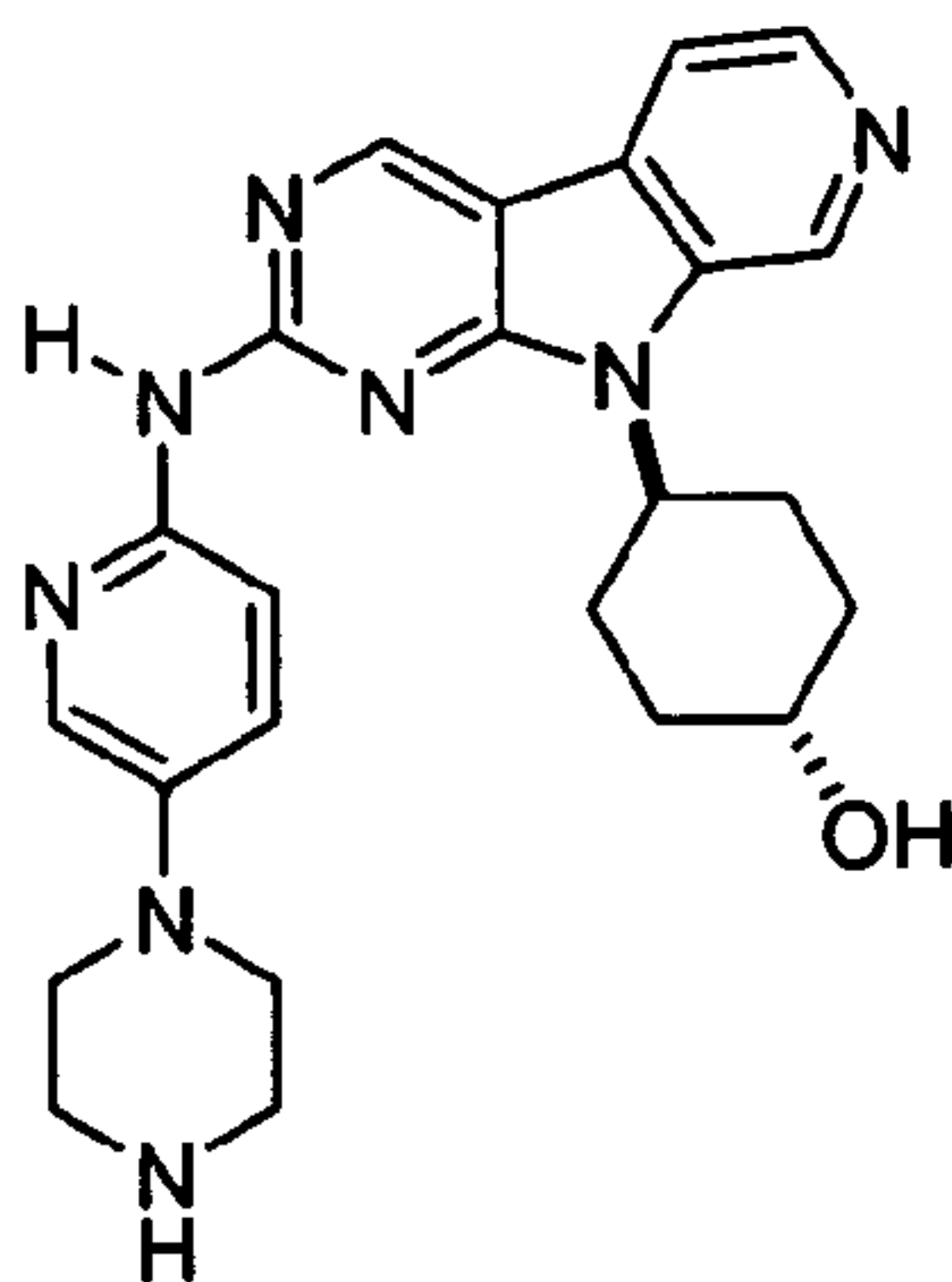
Compound **50** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.68 (1 H, s), 9.43 (1 H, s), 8.69 (2 H, dd, J=7.3, 10.5 Hz), 8.12 (1 H, s), 8.10 (1 H, s), 7.80 (1 H, d, J=8.5 Hz), 4.93 (1 H, m), 3.57 (4 H, m), 3.47 (4 H, m), 2.18 (1 H, d, J=10.1 Hz), 1.92 (1 H, d, J=10.1 Hz), 1.82 (3 H, d, J=7.1 Hz), 1.69 (1 H, d, J=10.0 Hz), 1.59 (1 H, d, J=10.0 Hz), 1.40 (1 H, m), 1.23 (2 H, m), 1.10 (2 H, m), 0.96 (1 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 457.3, Calculated 457.3.



**EXAMPLE 30****51**

**(9-Cyclobutyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

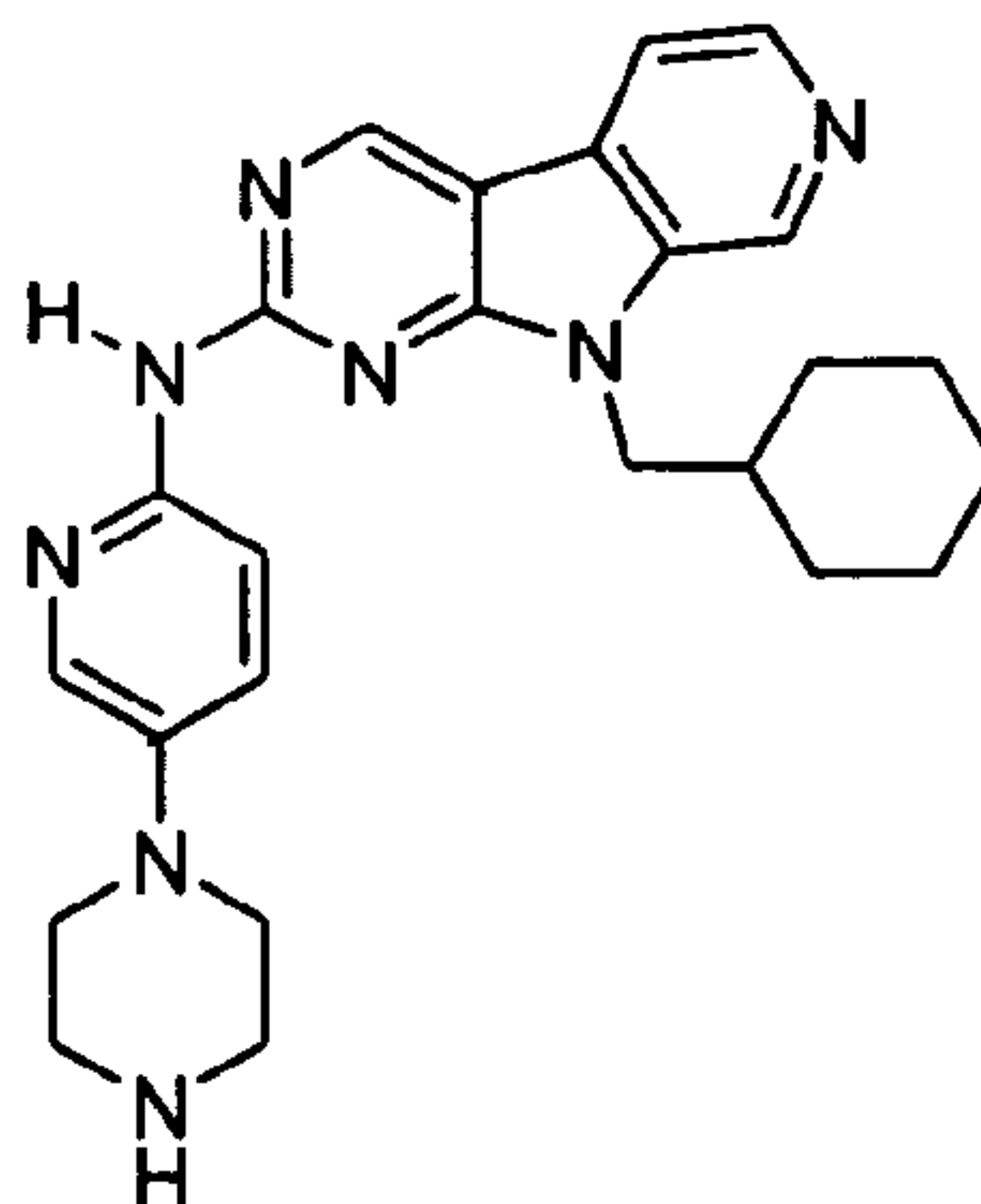
Compound **51** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.68 (1 H, s), 9.40 (1 H, s), 8.67 - 8.72 (2 H, dd, J = 5.0, 15 Hz), 8.13 (1 H, dd, J = 2.3, 10 Hz), 8.10 (1 H, d, J = 2.7 Hz), 7.83 (1 H, d, J = 10.0 Hz), 5.52 (1 H, m), 3.58 (4 H, m), 3.48 (4 H, m), 3.29 (2 H, m), 2.69 (2 H, m), 2.13 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 401.2, Calculated 401.2.

**EXAMPLE 31****52**

**4-[2-(5-Piperazin-1-yl-pyridin-2-ylamino)-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl]-trans-cyclohexanol**

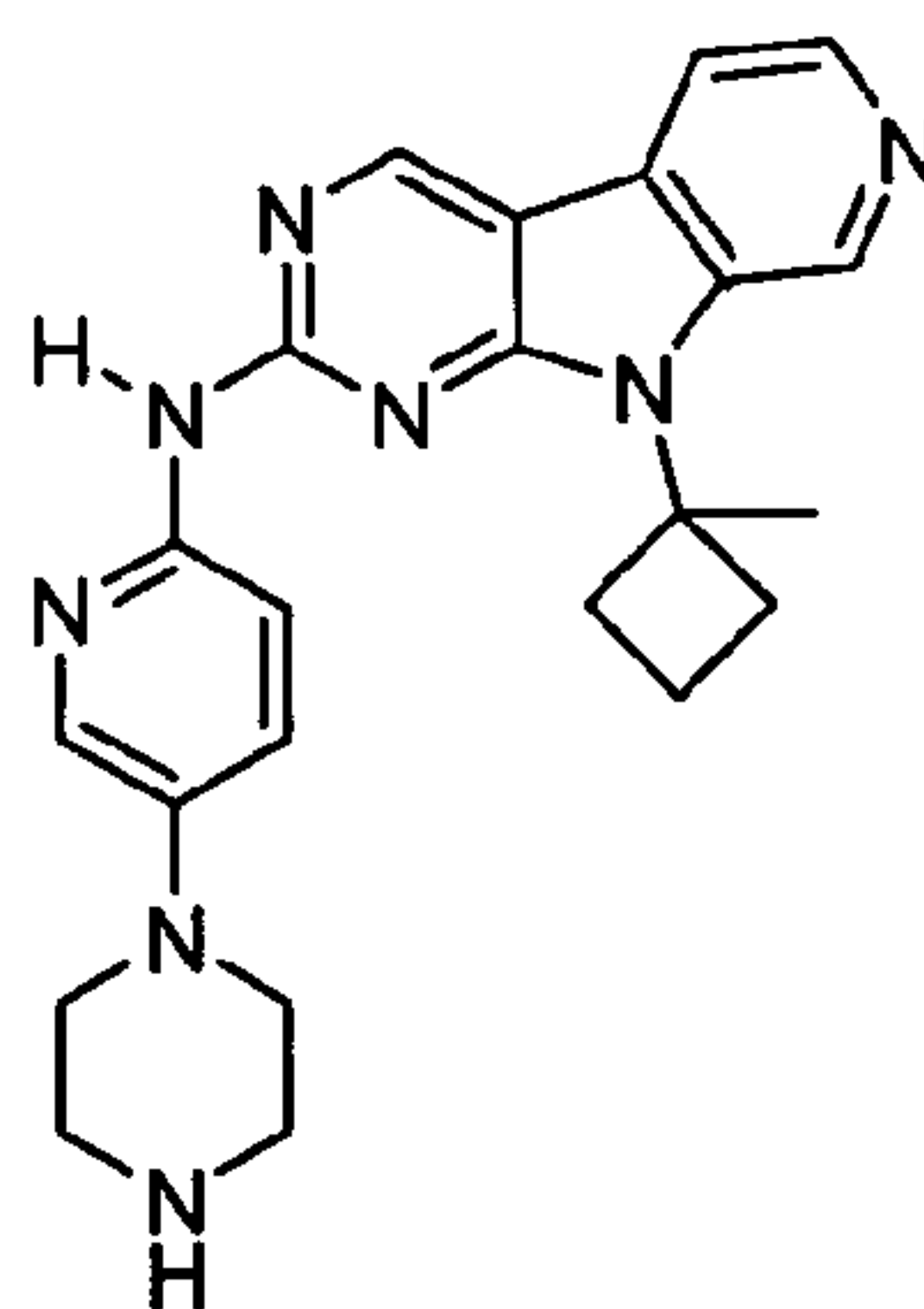
Compound **52** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.62 (1 H, s), 9.42 (1 H, s), 8.64 (2 H, s), 8.11 (1 H, d, J = 2.5 Hz), 8.02 (1 H, d, J = 10.0 Hz), 7.87 (1 H, d, J = 10.0 Hz), 4.98 (1 H, m), 3.89 (1 H, m), 3.55 (4 H, m), 3.47 (4 H, m), 2.77 (2 H, m), 2.21 (1 H, d, J = 15 Hz), 2.05 (2 H, m), 1.86 (1 H, m), 1.65 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 445.1, Calculated 445.2.



**EXAMPLE 32****53**

**(9-Cyclohexylmethyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

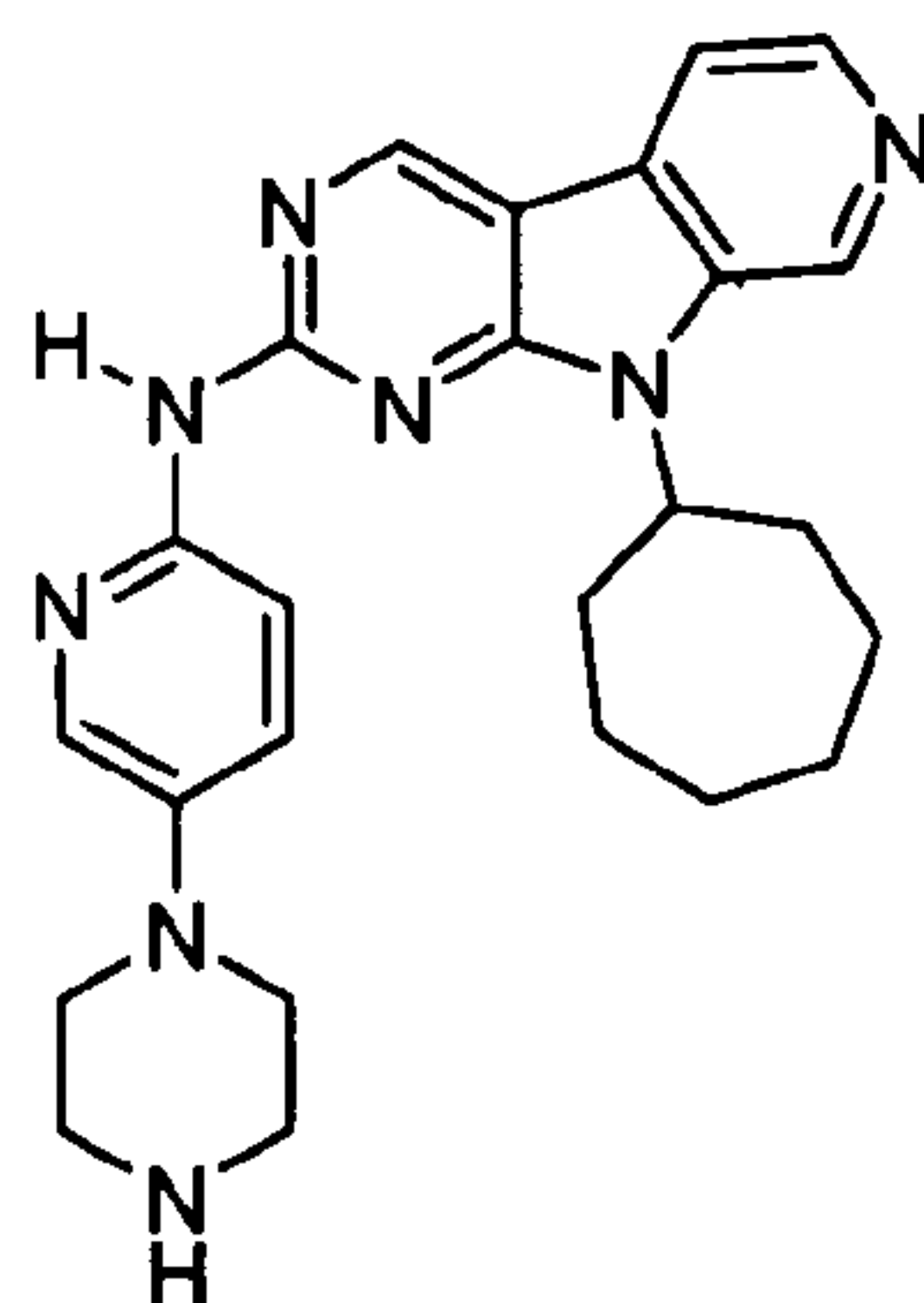
Compound **53** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.73 (1 H, s), 9.60 (1 H, s), 9.56 (2 H, s), 8.75 (2 H, s), 8.14 (1 H, s), 8.08 (1 H, s), 7.96 (1 H, s), 4.41 (2 H, d, *J* = 5.0 Hz), 3.48 (4 H, s), 3.26 (4 H, s), 2.08 (1 H, s), 1.57-1.67 (5 H, m), 1.13 (5 H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 443.2, Calculated 443.3.

**EXAMPLE 33****54**

**[9-(1-Methyl-cyclobutyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl]-(5-piperazin-1-yl-pyridin-2-yl)-amine**

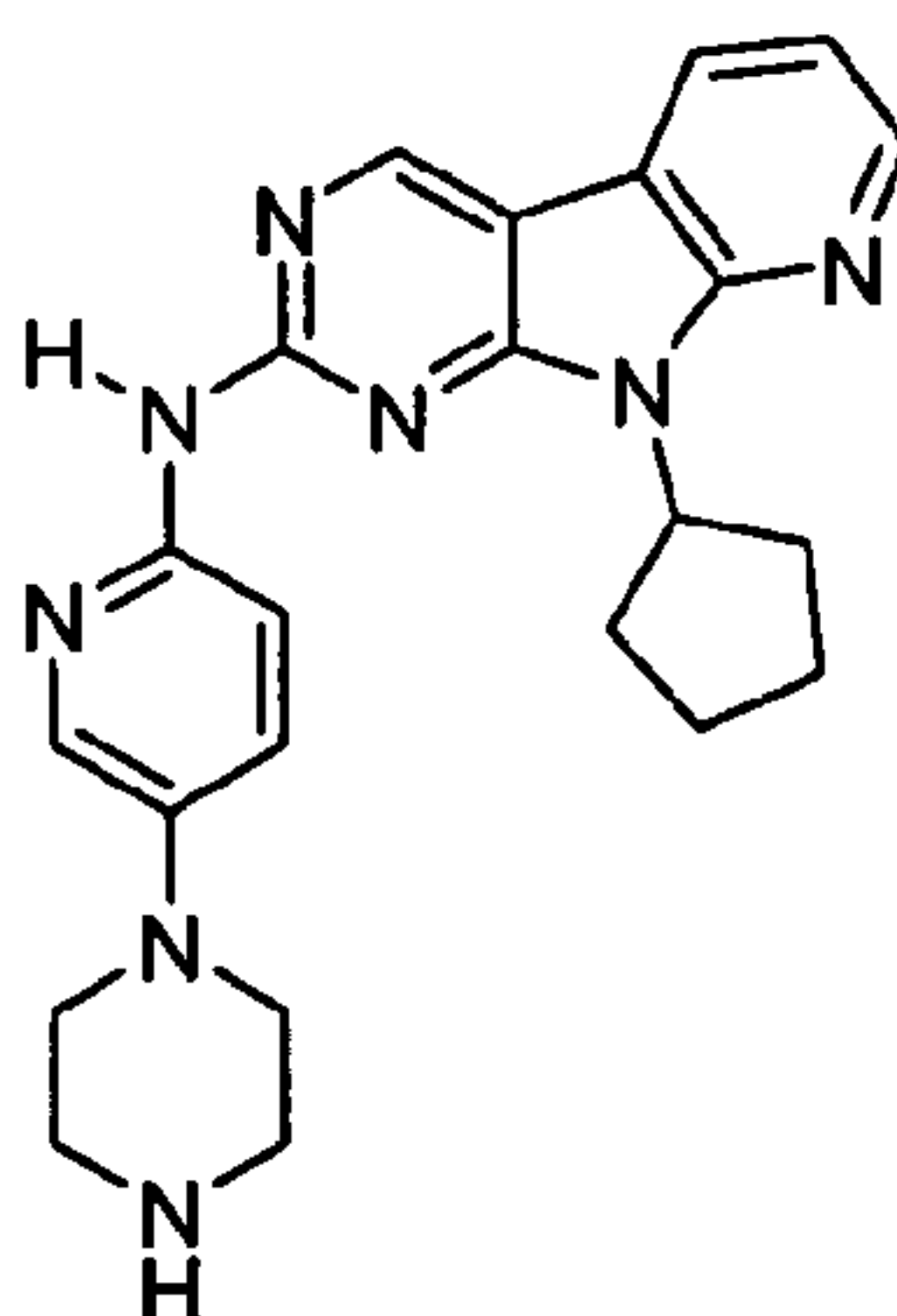
Compound **54** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.66 (1 H, s), 9.07 (1 H, s), 8.71 (1 H, d, *J*=5.0 Hz), 8.67 (1 H, d, *J*=5.0 Hz), 8.14 (1 H, dd, *J*=2.5, 10 Hz), 8.10 (1 H, d, *J*=2.5 Hz), 7.80 (1 H, d, *J*=10 Hz), 3.56 (4 H, m), 3.47 (4 H, m), 3.09 (2 H, q, *J*=5.0 Hz), 2.86 (2 H, t, *J*=2.5 Hz), 2.25 (1 H, m), 2.11 (1 H, m), 1.91 (3 H, s) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 415.1, Calculated 415.2.



**EXAMPLE 34****55**

**(9-Cycloheptyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

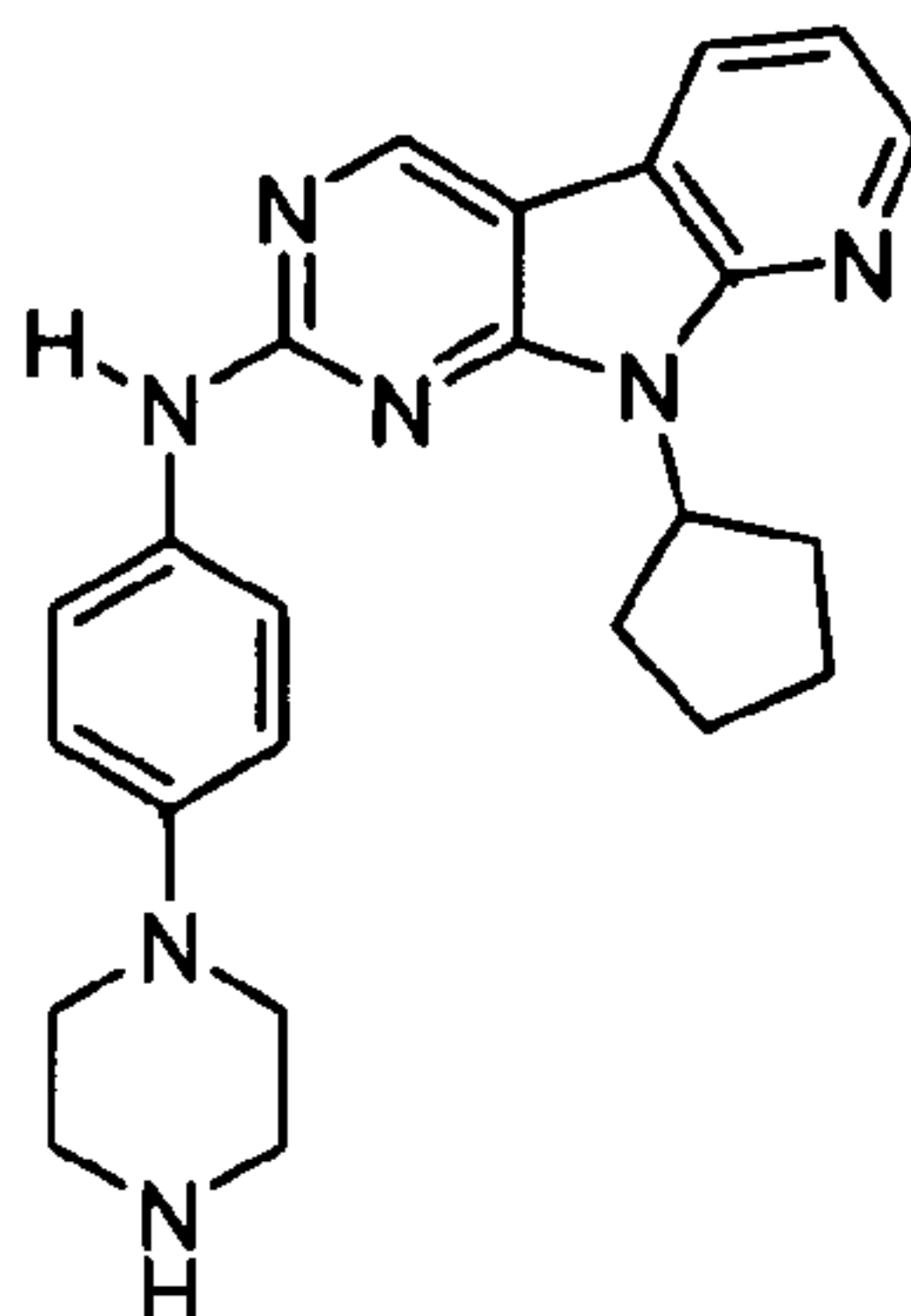
Compound **55** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.80 (1 H, s), 9.59 (1 H, s), 9.42 (2 H, s), 8.72 (2 H, s), 8.14 (1 H, s), 8.08 (1 H, s), 7.85 (1 H, s), 5.05 (1 H, m), 3.47 (4 H, s), 3.27 (4 H, s), 2.58 (1 H, m), 1.88 (1 H, m), 1.67-1.77 (10 H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 443.2, Calculated 443.3.

**EXAMPLE 35****56**

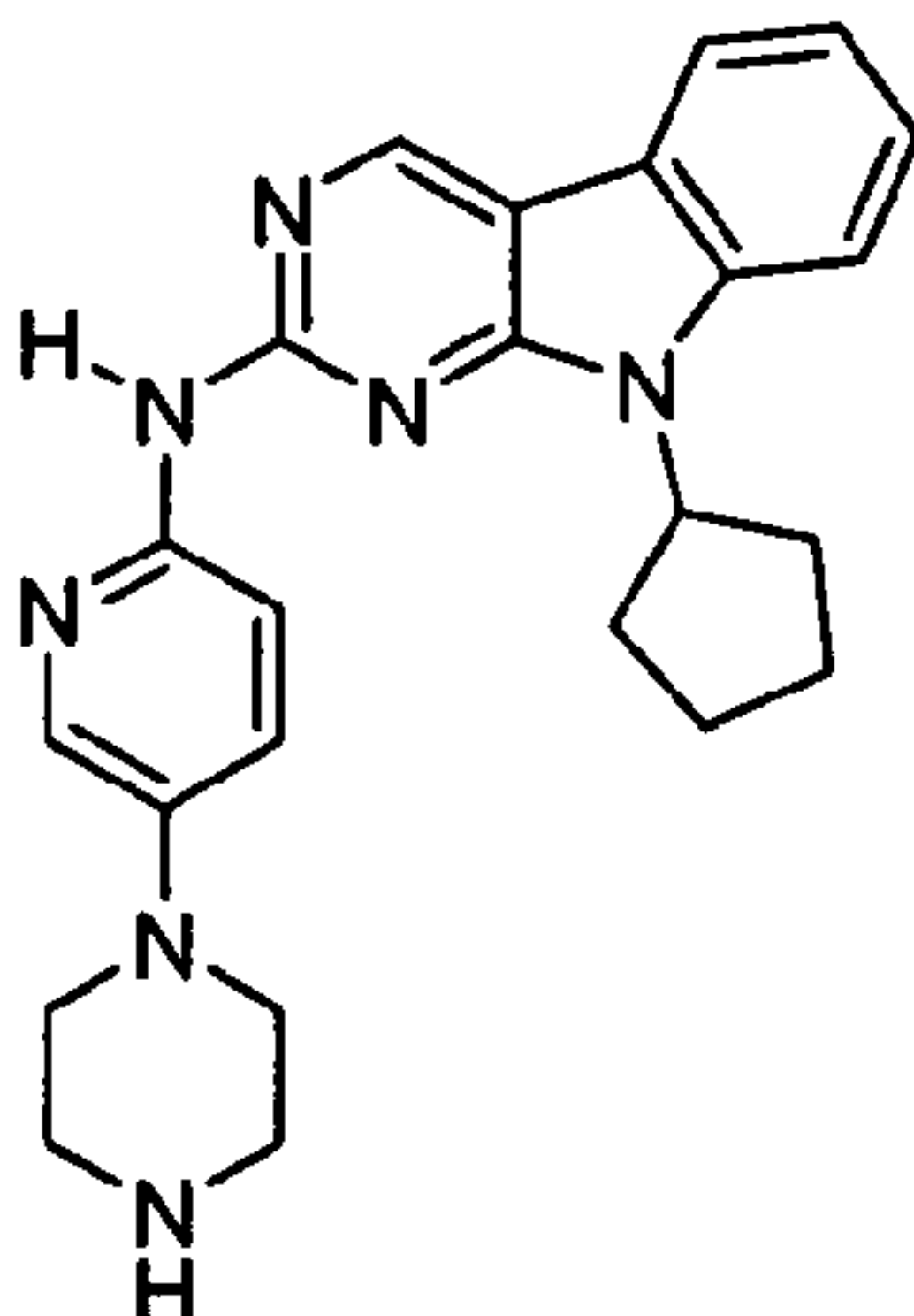
**(9-Cyclopentyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

Compound **56** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.27 (1 H, s), 8.60 (1 H, dd, *J* = 2.5 5.0 Hz), 8.55 (1 H, dd, *J* = 2.5, 5.0 Hz), 8.10 (1 H, d, *J* = 5.0 Hz), 8.00 (1 H, dd, *J* = 5.0, 10.0 Hz), 7.45 (2 H, m), 5.63 (1 H, q, *J* = 10 Hz), 3.53 (4 H, m), 3.47 (4 H, m), 2.62 (2 H, m), 2.23 (2 H, m), 2.15 (2 H, m), 1.87 (2 H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 415.1, Calculated 415.2.



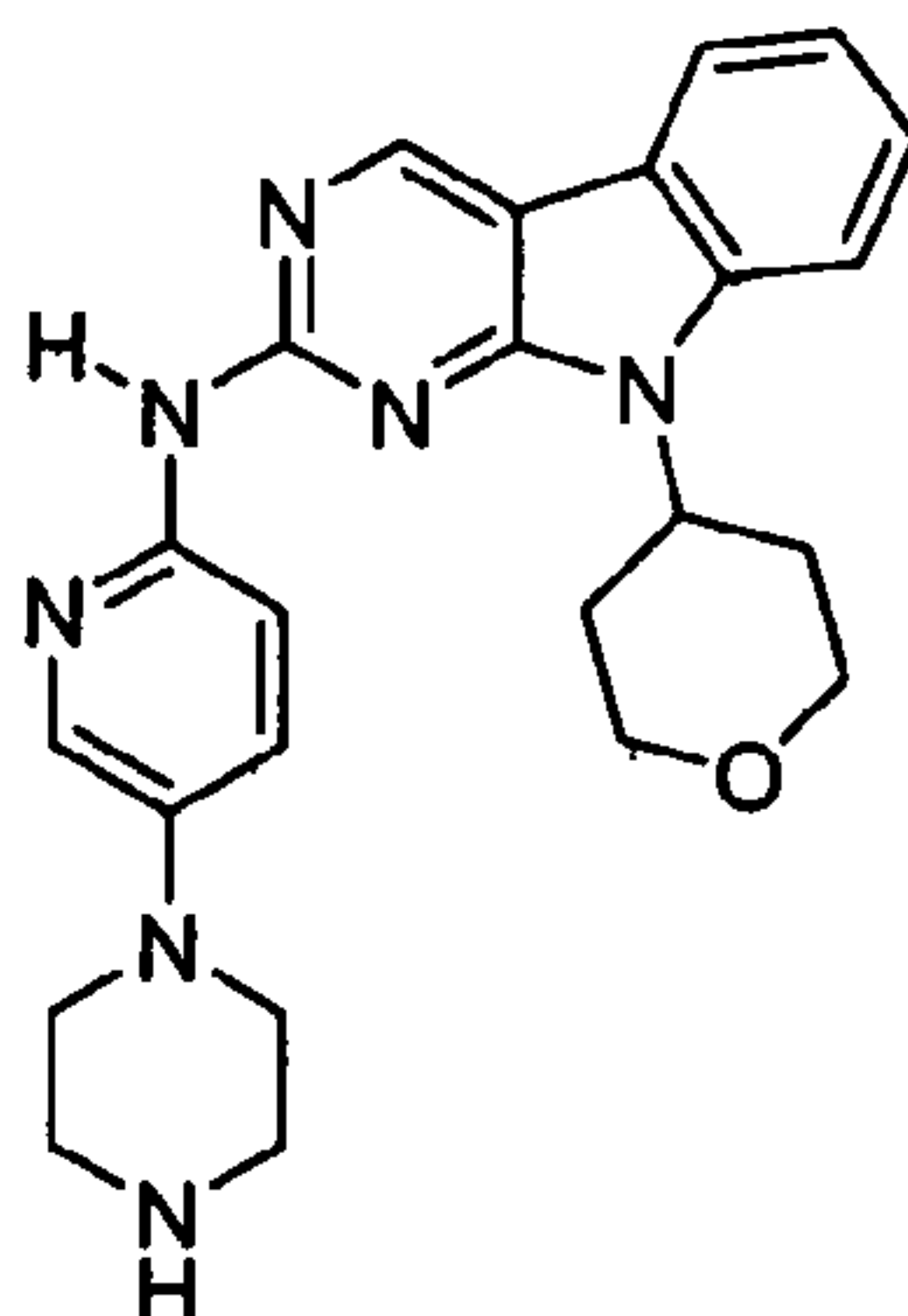
**EXAMPLE 36****57****(9-Cyclopentyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(4-piperazin-1-yl-phenyl)-amine**

Compound **57** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 8.99 (1 H, s), 8.49 (1 H, dd, J = 2.5, 5.0 Hz), 8.40 (1 H, dd, J = 2.5, 5.0 Hz), 7.59 (2 H, d, J = 10 Hz), 7.38 (1 H, dd, J = 5.0, 7.5 Hz), 7.14 (2 H, d, J = 10.0 Hz), 5.53 (1 H, m), 3.44 (8 H, m), 2.52 (2 H, m), 2.06 (4 H, m), 1.77 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 414.2, Calculated 414.2

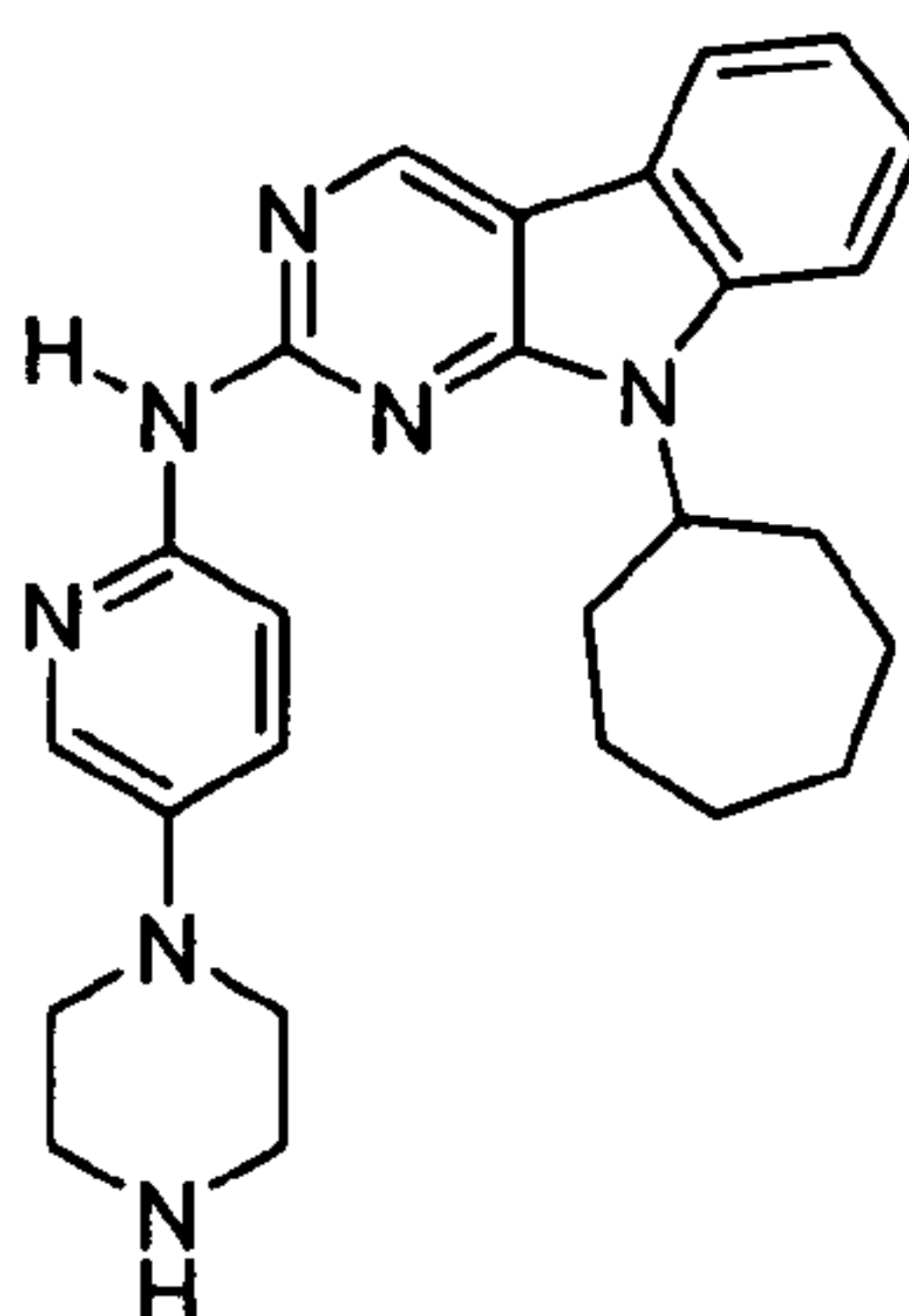
**EXAMPLE 37****58****(9-Cyclopentyl-9H-pyrimido[4,5-b]indol-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

Compound **58** was prepared using chemistry similar to that described in example 22. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.82 (1 H, s), 6.80 (2 H, d, J=6.1 Hz), 6.56 (1H, d, J=8.5 Hz), 6.34 (1 H, d, J=8.5 Hz), 6.24 (1 H, t, J=7.3 Hz), 5.99 - 6.08 (2 H, m), 4.02 - 4.11 (1 H, m), 2.21 (4 H, m), 2.12 (4 H, m), 1.10 (2 H, s), 0.83 (4 H, s), 0.55 (2 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 414.2, Calculated 414.2



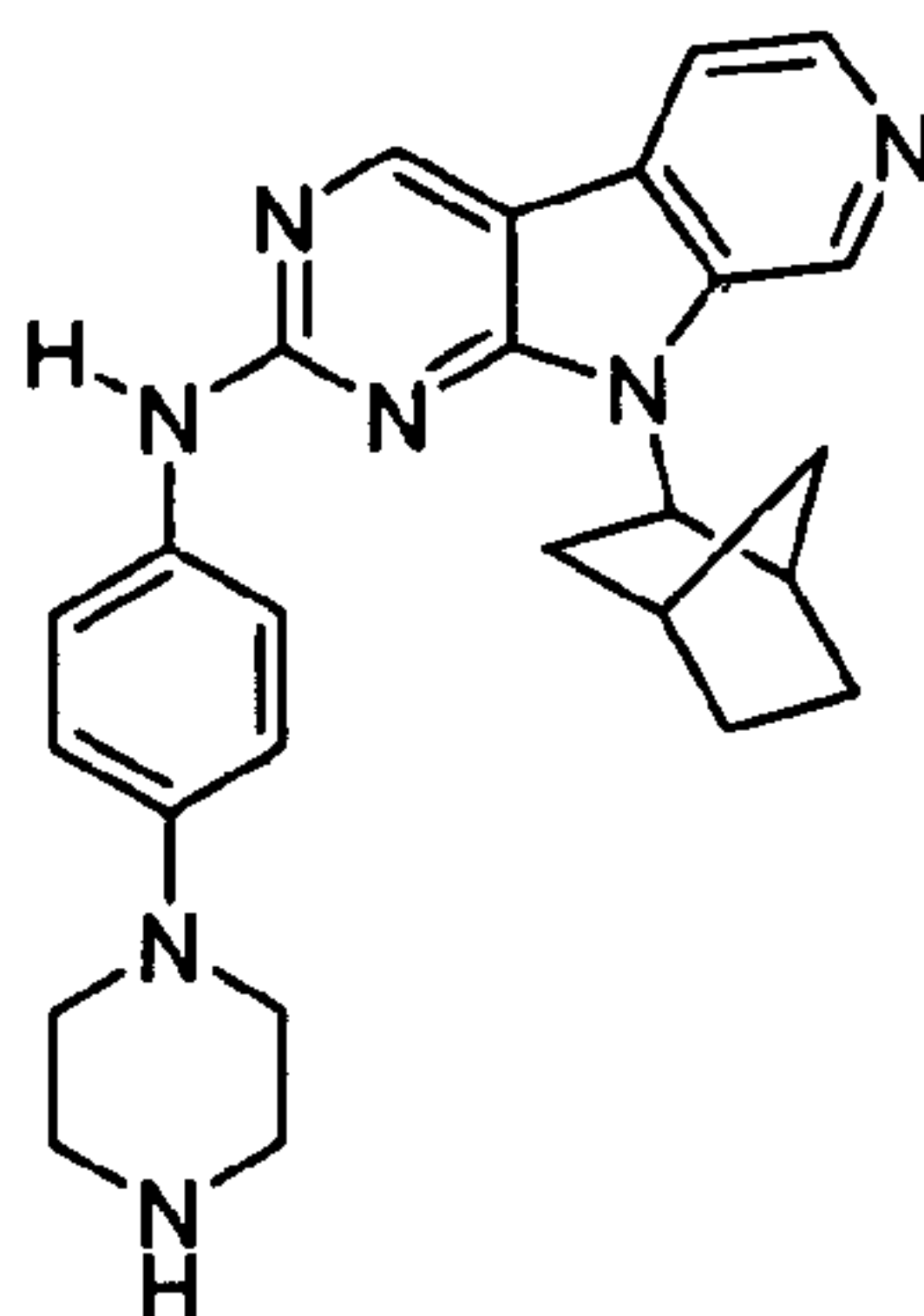
**EXAMPLE 38****59****(5-Piperazin-1-yl-pyridin-2-yl)-[9-(tetrahydro-pyran-4-yl)-9H-pyrimido[4,5-b]indol-2-yl]-amine**

Compound **59** was prepared using chemistry similar to that described in example 22. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.93 (1 H, s), 6.91 (1 H, d, J = 7.9 Hz), 6.86 (1 H, s), 6.65 (1 H, d, J = 8.5 Hz), 6.56 (1 H, d, J = 8.5 Hz), 6.36 (1 H, t, J = 7.9 Hz), 6.16 (1 H, t, J = 7.6 Hz), 6.07 (1 H, d, J = 9.2 Hz), 3.79 (1H, m), 2.91 (2 H, dd, J = 4.3, 11.6 Hz), 2.45 (2 H, m), 2.25 (4 H, m), 2.17 (4 H, s), 1.71 (2 H, dd, J = 12.5, 4.6 Hz), 0.60 (2 H, d, J = 9.8 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 430.1, Calculated 430.2.

**EXAMPLE 39****60****(9-Cycloheptyl-9H-pyrimido[4,5-b]indol-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

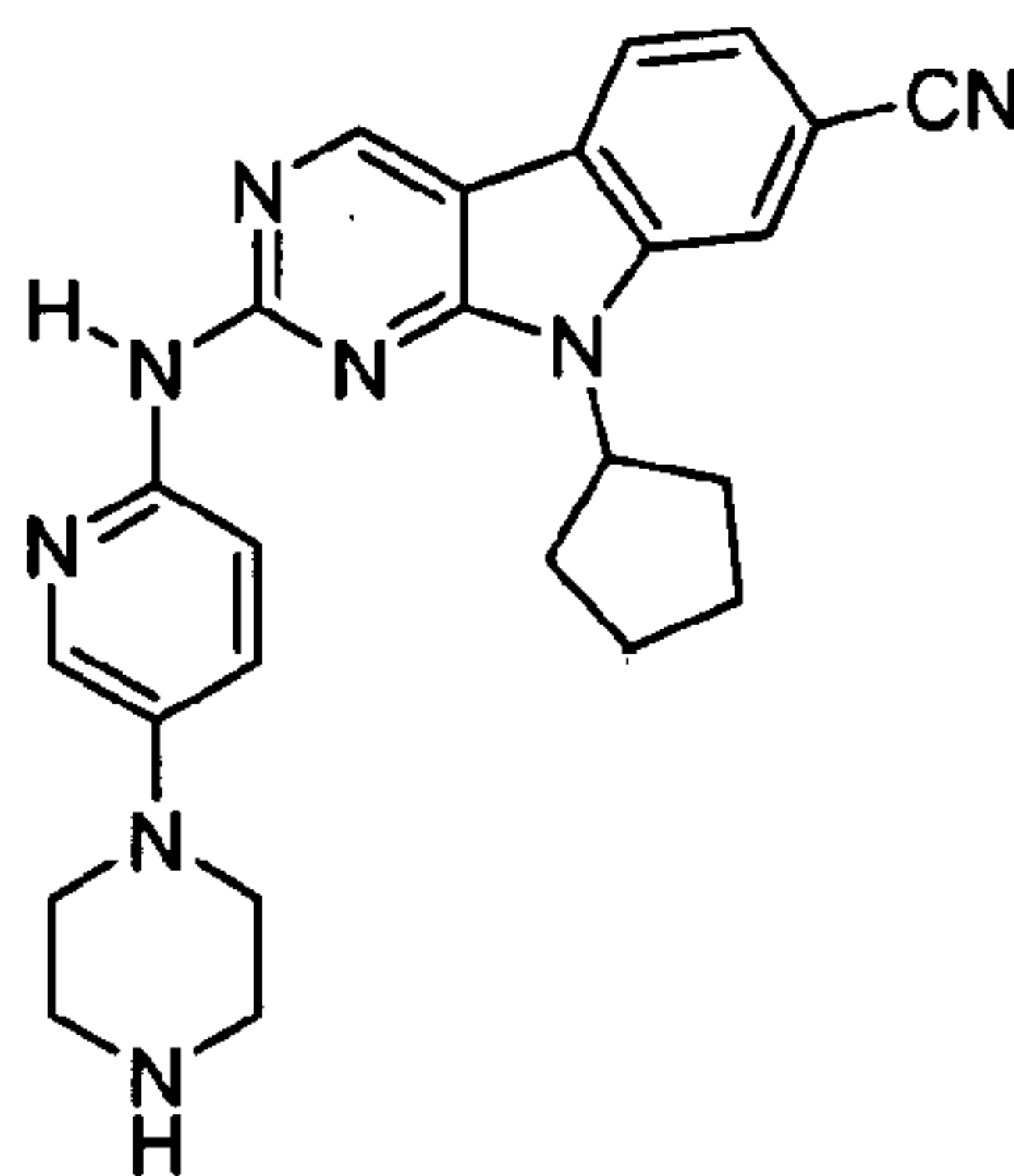
Compound **60** was prepared using chemistry similar to that described in example 22. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.40 (1 H, s), 6.43 (1 H, d, J = 7.3 Hz), 6.38 (1 H, d, J = 3.1 Hz), 6.12 (1 H, dd, J = 9.5, 2.7 Hz), 6.04 (1 H, d, J = 7.9 Hz), 5.89 (1 H, t, J = 10 Hz), 5.69 (1 H, t, J = 10 Hz), 5.50 (1 H, d, J = 10 Hz), 3.36 (1 H, m), 1.76 (4 H, m), 1.70 (4 H, m), 0.86 (2 H, m), 0.23-0.31 (4 H, m), 0.02-0.10 (6 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 442.3, Calculated 442.3.



**EXAMPLE 40****61**

**(9-Bicyclo[2.2.1]hept-2-yl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-(4-piperazin-1-yl-phenyl)-amine**

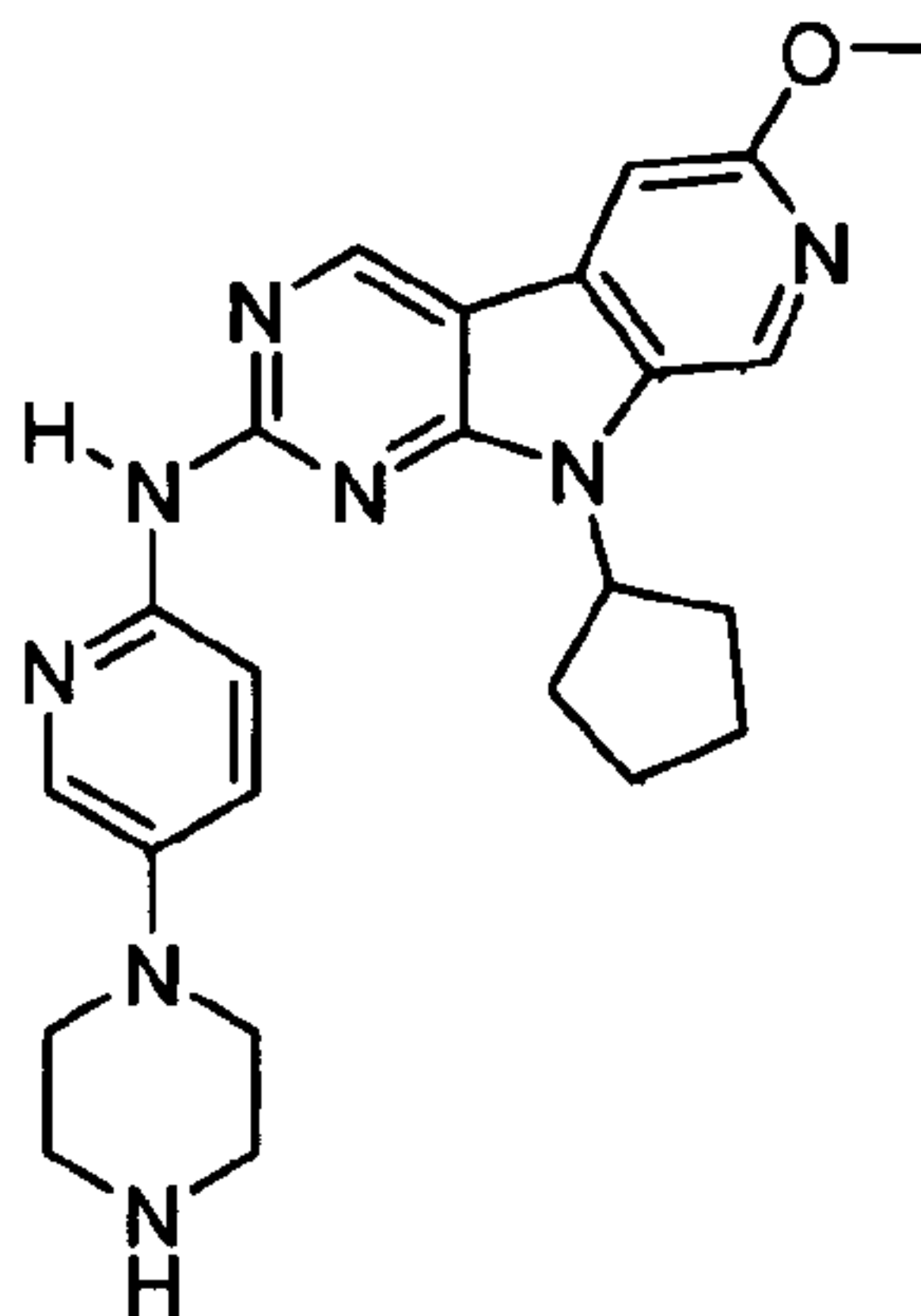
Compound **61** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.37 (1 H, s), 9.10 (1 H, s), 8.50 (2 H, dd, J = 5, 15 Hz), 7.72 (2 H, d, J = 10 Hz), 7.11 (2 H, d, J = 10 Hz), 4.72 (1 H, m), 3.44 (8 H, m), 2.96 (1 H, d, J = 10 Hz), 2.92 (1 H, d, J = 2.5 Hz), 2.58 (1 H, s), 2.33 (1 H, d, J = 10 Hz), 2.08 (1 H, dd, J = 5, 15 Hz), 1.75 (2 H, m), 1.59 (1 H, t, J = 10 Hz), 1.44 (12 H, t, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 440.2, Calculated 440.3.

**EXAMPLE 41****62**

**9-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-9H-pyrimido[4,5-b]indole-7-carbonitrile**

Compound **62** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.33 (1 H, s), 8.34 (1 H, d, J = 8.1 Hz), 8.13 (1 H, s), 8.07 (1 H, d, J = 2.9 Hz), 8.01 (1 H, dd, J = 9.4, 2.8 Hz), 7.71 - 7.73 (1 H, d, J = 10 Hz), 7.63 (1 H, d, J = 9.3 Hz), 5.39 (1 H, m), 3.54 (4 H, m), 3.47 (4 H, m), 2.52 (2 H, m), 2.20 (4 H, m), 1.91 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 439.1, Calculated 439.2.

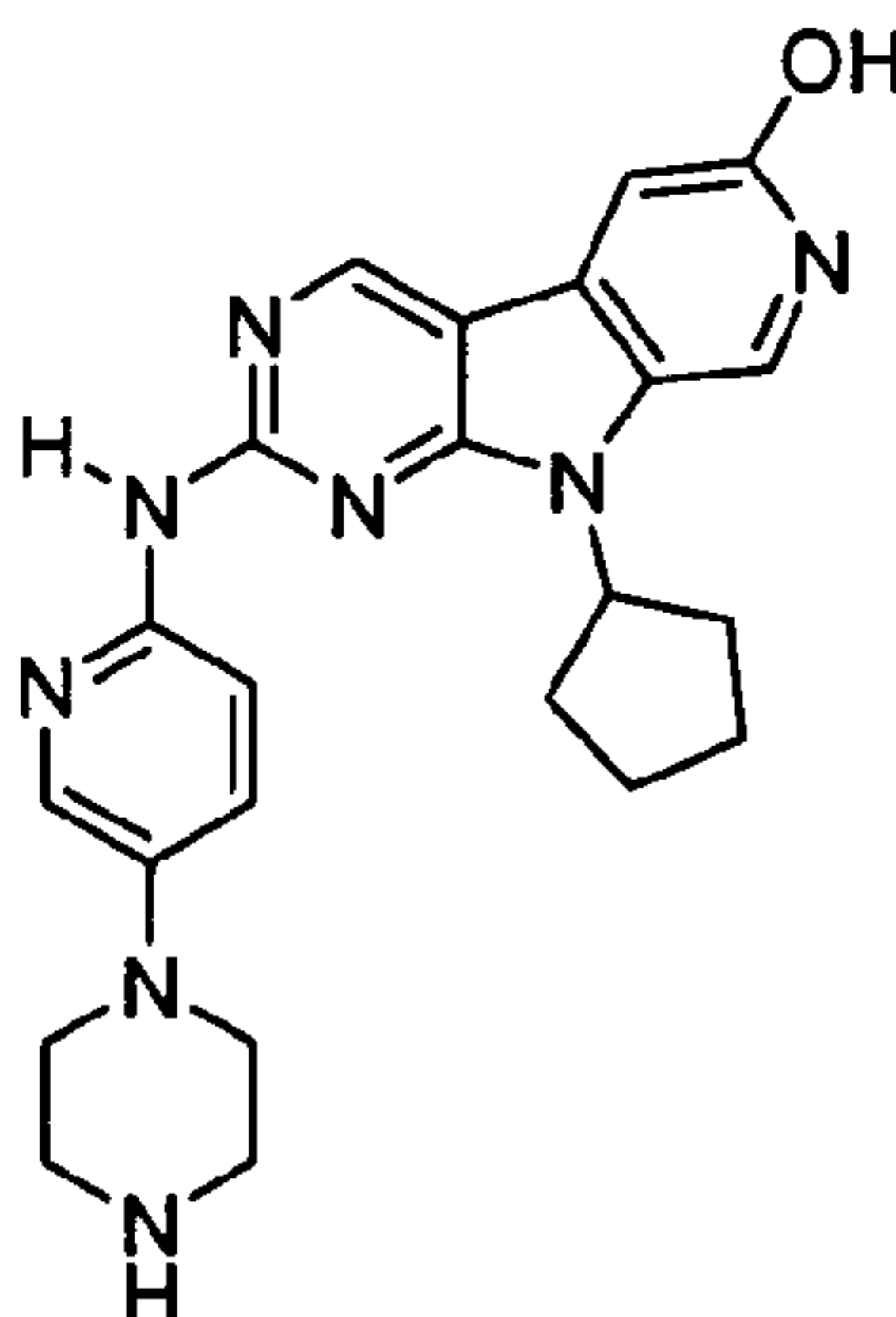


**EXAMPLE 42****63**

**(9-Cyclopentyl-6-methoxy-9H-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)-(5-piperazin-1-yl-pyridin-2-yl)-amine**

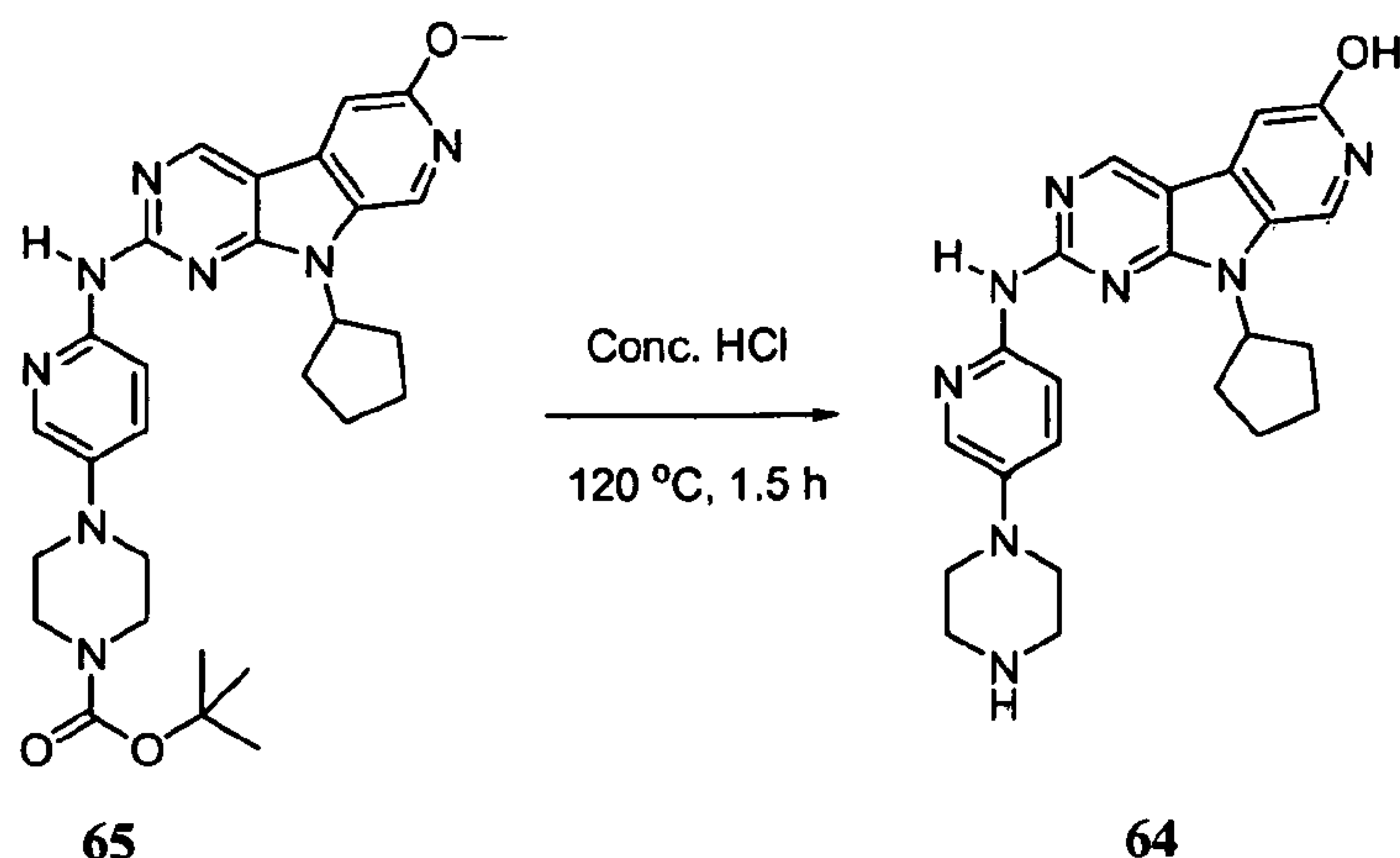
Compound **63** was prepared via compound **65** using chemistry similar to that described in example 1.

<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.36 (1 H, s), 8.66 (1 H, s), 8.18 (1 H, d, J = 2.7 Hz), 8.07 (1 H, dd, J = 9.3, 2.7 Hz), 7.67 (1 H, s), 7.54 (1 H, d, J = 9.3 Hz), 5.50 (1 H, m), 4.11 (3 H, s), 3.62 (4 H, m), 3.54 (4 H, m), 2.49-2.53 (2 H, m), 2.22 - 2.32 (4 H, m), 1.93 - 2.02 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 445.2, Calculated 445.2.

**EXAMPLE 43****64**

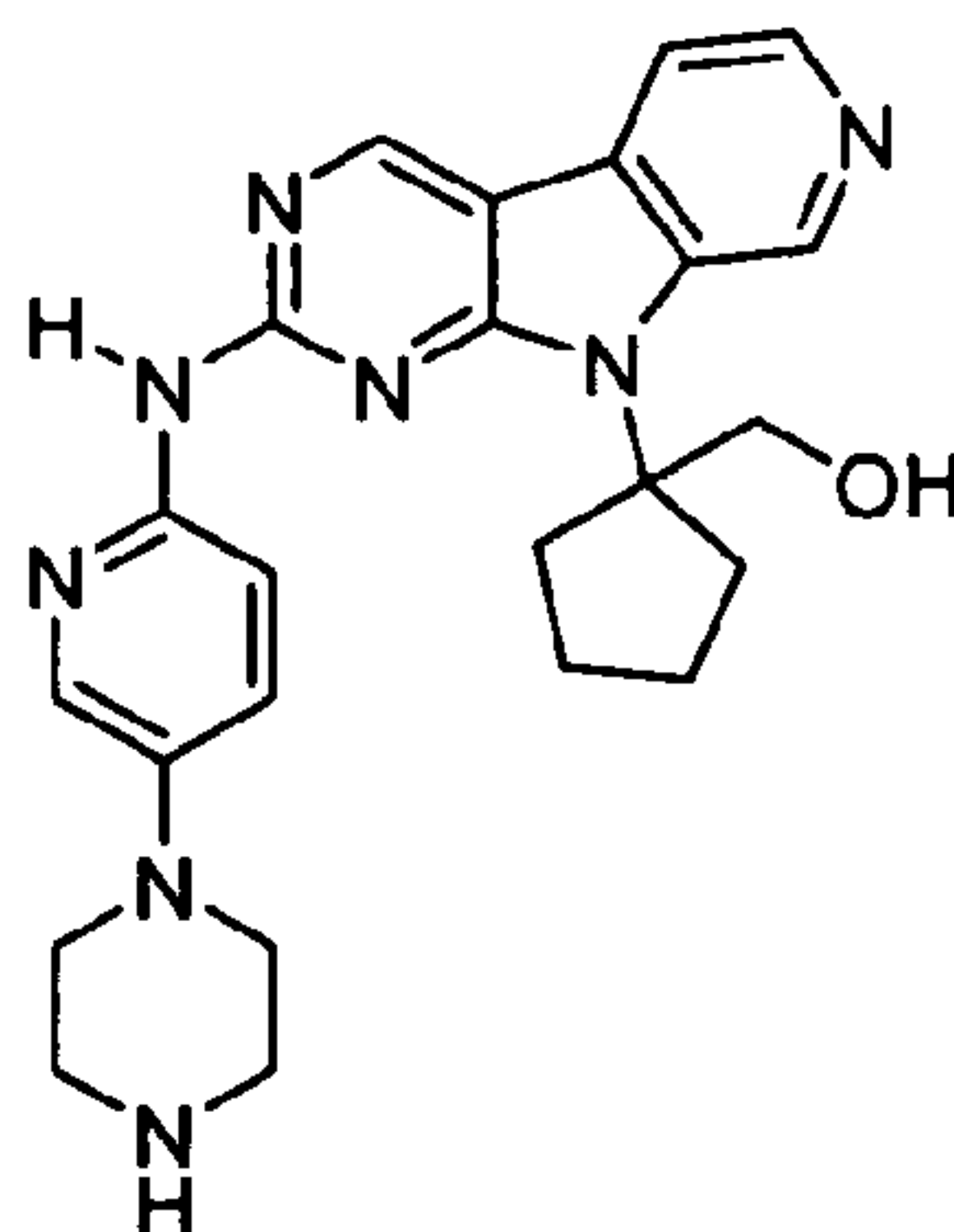
**9-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-6-ol**





**9-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-6-ol (64)** A mixture of compound **65** (366 mg) and conc. HCl (8 mL) was heated at 120 °C in a microwave reactor for 1.5 h. The reaction mixture was concentrated and purified by prep-HPLC to give compound **64** as a yellow solid (21%). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.15 (1 H, s), 8.10 (1 H, d, *J*=2.7 Hz), 7.99 (1 H, dd, *J*=9.3, 2.9 Hz), 7.91 (1 H, s), 7.48 (1 H, d, *J*=9.3 Hz), 7.26 (1 H, s), 5.18 (1 H, s), 3.54 (4 H, m), 3.47 (4 H, m), 2.35-2.37 (2 H, m), 2.11-2.16 (4 H, m), 1.86 (2 H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 431.2, Calculated 431.2.

#### EXAMPLE 44

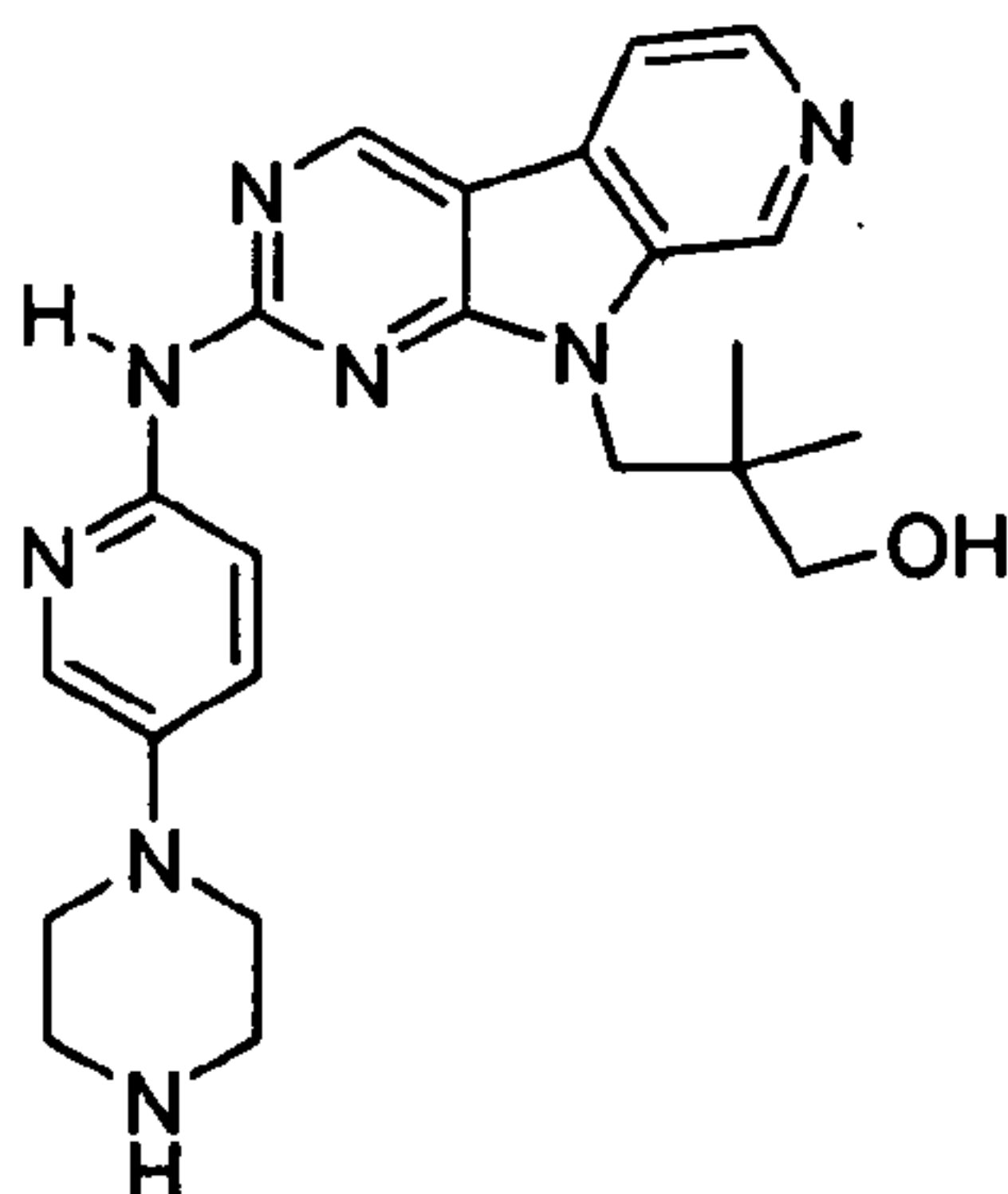


**66**

**{1-[2-(5-Piperazin-1-yl-pyridin-2-ylamino)-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl]-cyclopentyl}-methanol**

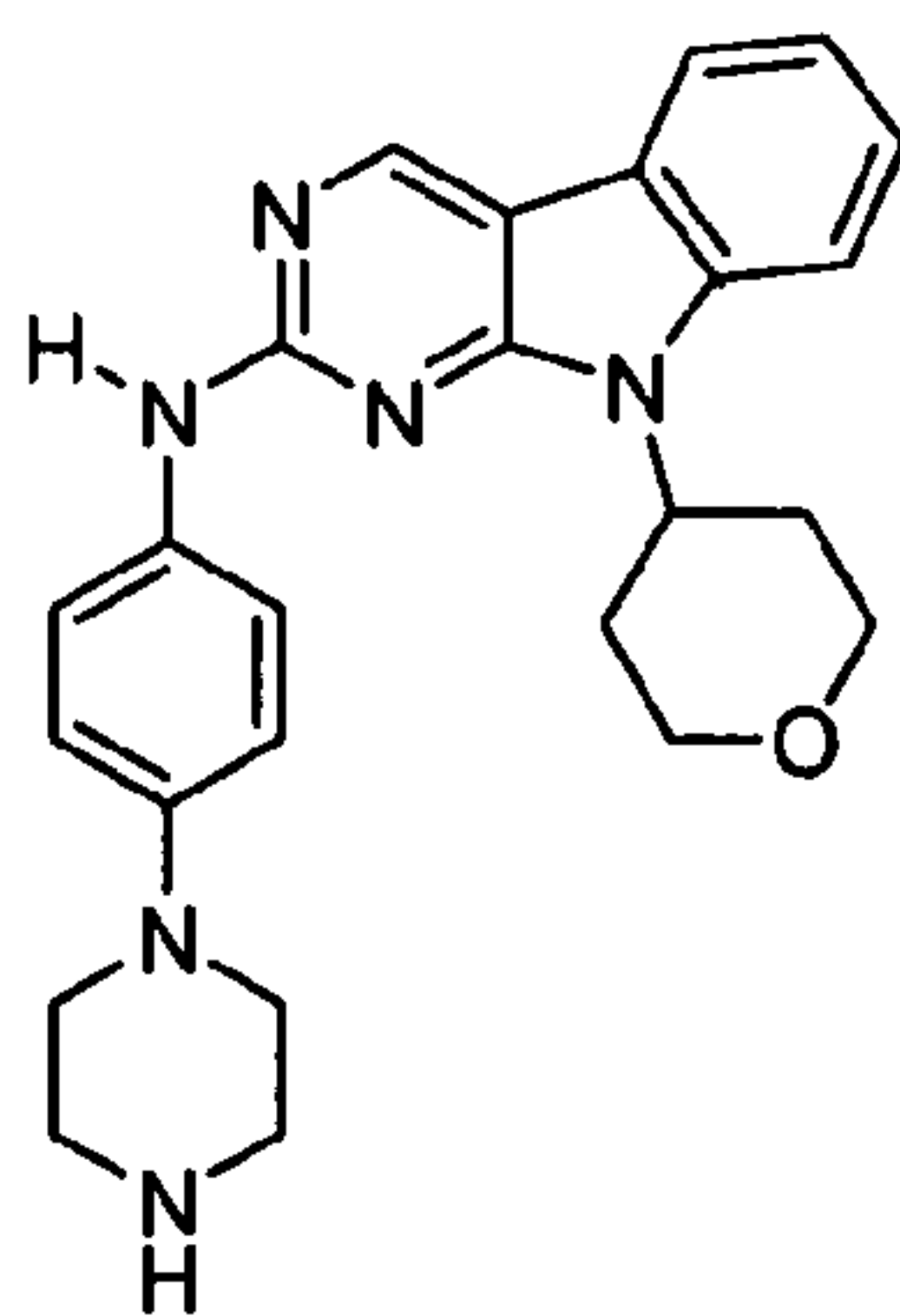
Compound **66** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.67 (1 H, s), 9.36 (1 H, s), 8.70 (1 H, d, *J* = 6.1 Hz), 8.62 (1 H, d, *J* = 6.1 Hz), 8.10 (1 H, d, *J* = 10 Hz), 8.08 (1 H, d, *J* = 2.7 Hz), 7.80 (1 H, d, *J* = 10 Hz), 3.99 (2 H, s), 3.55-3.57 (4 H, m), 3.46-3.48 (4 H, m), 3.07-3.11 (2 H, m), 2.60-2.66 (2 H, m), 1.97-2.01 (2 H, m), 1.89-1.92 (2 H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 445.1, Calculated 445.2.



**EXAMPLE 45****67**

**2,2-Dimethyl-3-[2-(5-piperazin-1-yl-pyridin-2-ylamino)-pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidin-9-yl]-propan-1-ol**

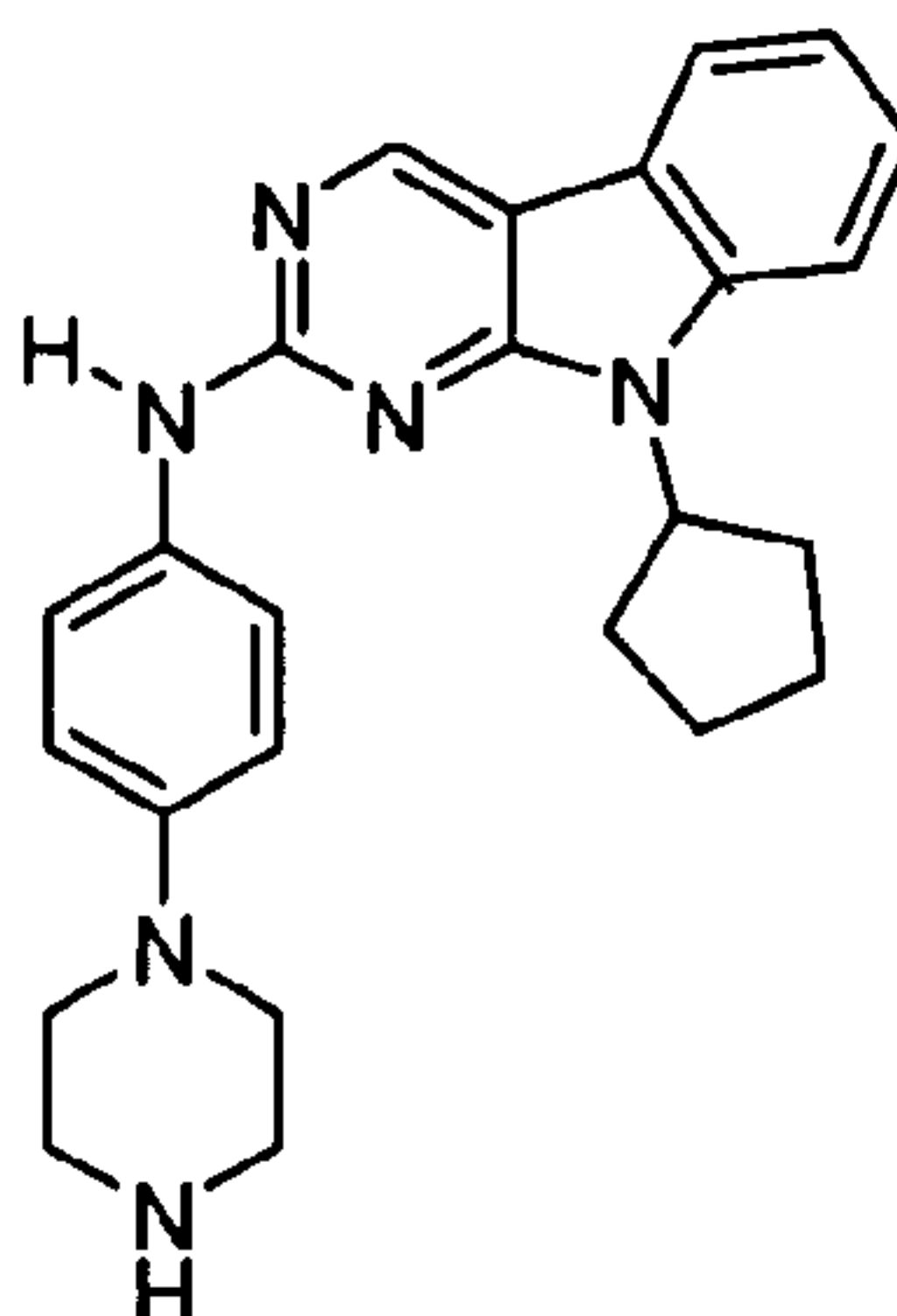
Compound **67** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.66 (1 H, s), 9.52 (1 H, s), 8.68 (2 H, s), 8.14-8.17 (1 H, dd, J = 9.5, 2.9 Hz), 8.04 (1 H, d, J = 2.9 Hz), 7.76 (1 H, d, J = 9.5 Hz), 4.58 (2 H, s), 3.58 (4 H, m), 3.48 (4 H, m), 3.36 (2 H, s), 1.11 (6 H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 433.1, Calculated 433.2.

**EXAMPLE 46****68**

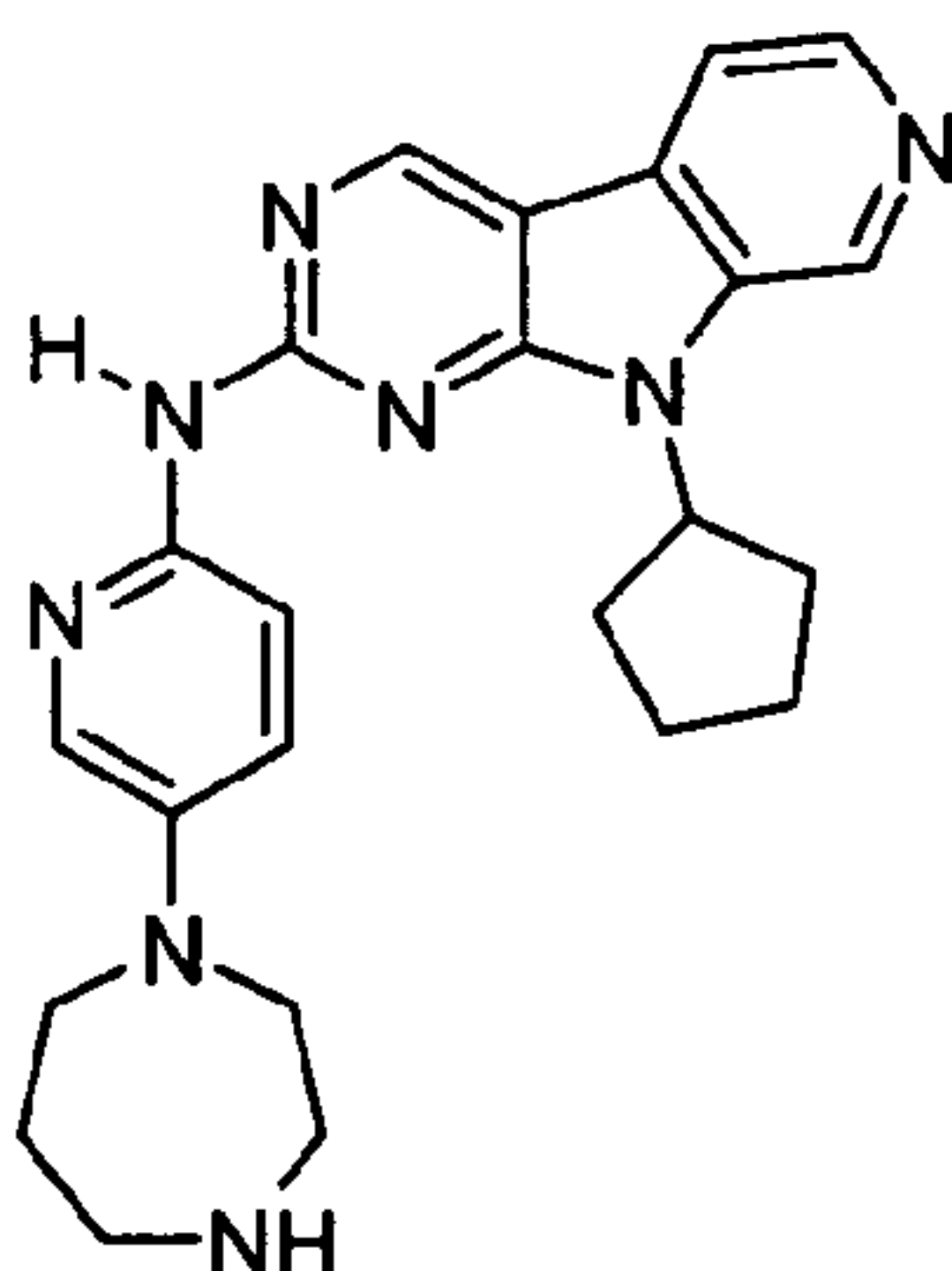
**(4-Piperazin-1-yl-phenyl)-[9-(tetrahydro-pyran-4-yl)-9*H*-pyrimido[4,5-*b*]indol-2-yl]-amine**

Compound **68** was prepared using chemistry similar to that described in example 22. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.40 (1 H, s), 6.55 (1 H, d, J = 9.2 Hz), 6.25 (1 H, d, J = 9.2 Hz), 6.09 (3 H, m), 5.89 (1 H, t, J = 9.2 Hz), 5.64 (2 H, d, J = 9.2 Hz), 3.44 (1 H, m), 2.63 (2 H, dd, J = 5, 10 Hz), 2.16 (2 H, t, J = 10 Hz), 1.94 (4 H, m), 1.89 (4 H, m), 1.42 (2 H, td, J = 5, 15 Hz), 0.35 (2 H, dd, J = 10, 2.5 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2, Calculated 429.2.



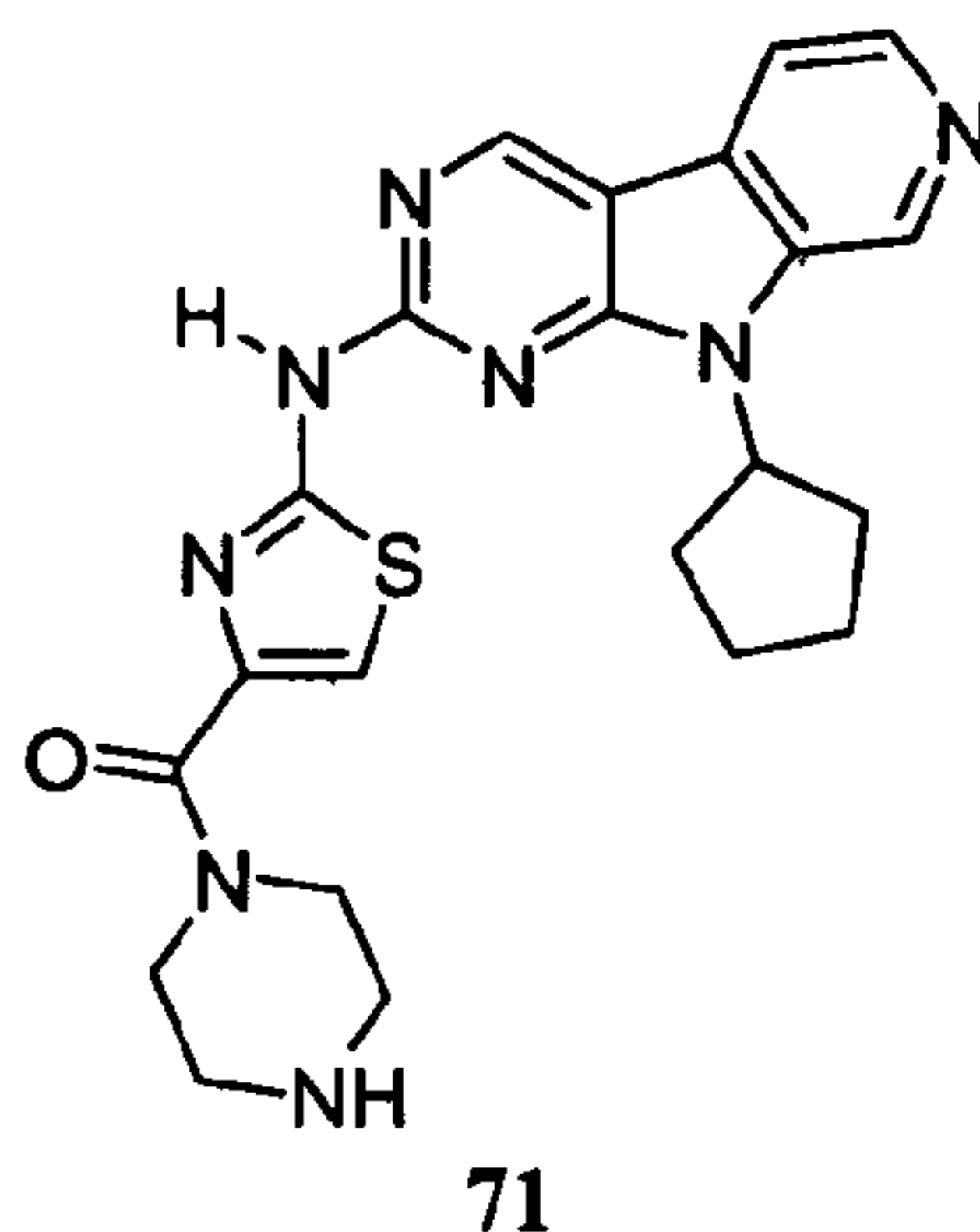
**EXAMPLE 47****69****(9-Cyclopentyl-9H-pyrimido[4,5-b]indol-2-yl)-(4-piperazin-1-yl-phenyl)-amine**

Compound **69** was prepared using chemistry similar to that described in example 22. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 10.05 (1 H, s), 9.30 (1 H, s), 9.22 (1 H, s), 8.16 (1 H, d, J = 7.8 Hz), 7.76 (1 H, d, J = 8.3 Hz), 7.54 - 7.57 (3 H, m), 7.39 (1 H, t, J = 7.5 Hz), 7.09 (2 H, d, J = 9.0 Hz), 5.24 (1 H, m), 3.72 (4 H, m), 3.50 (4 H, m), 2.32 (2 H, m), 2.05 (2 H, m), 1.95 (2 H, m), 1.71 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 413.2, Calculated 413.2.

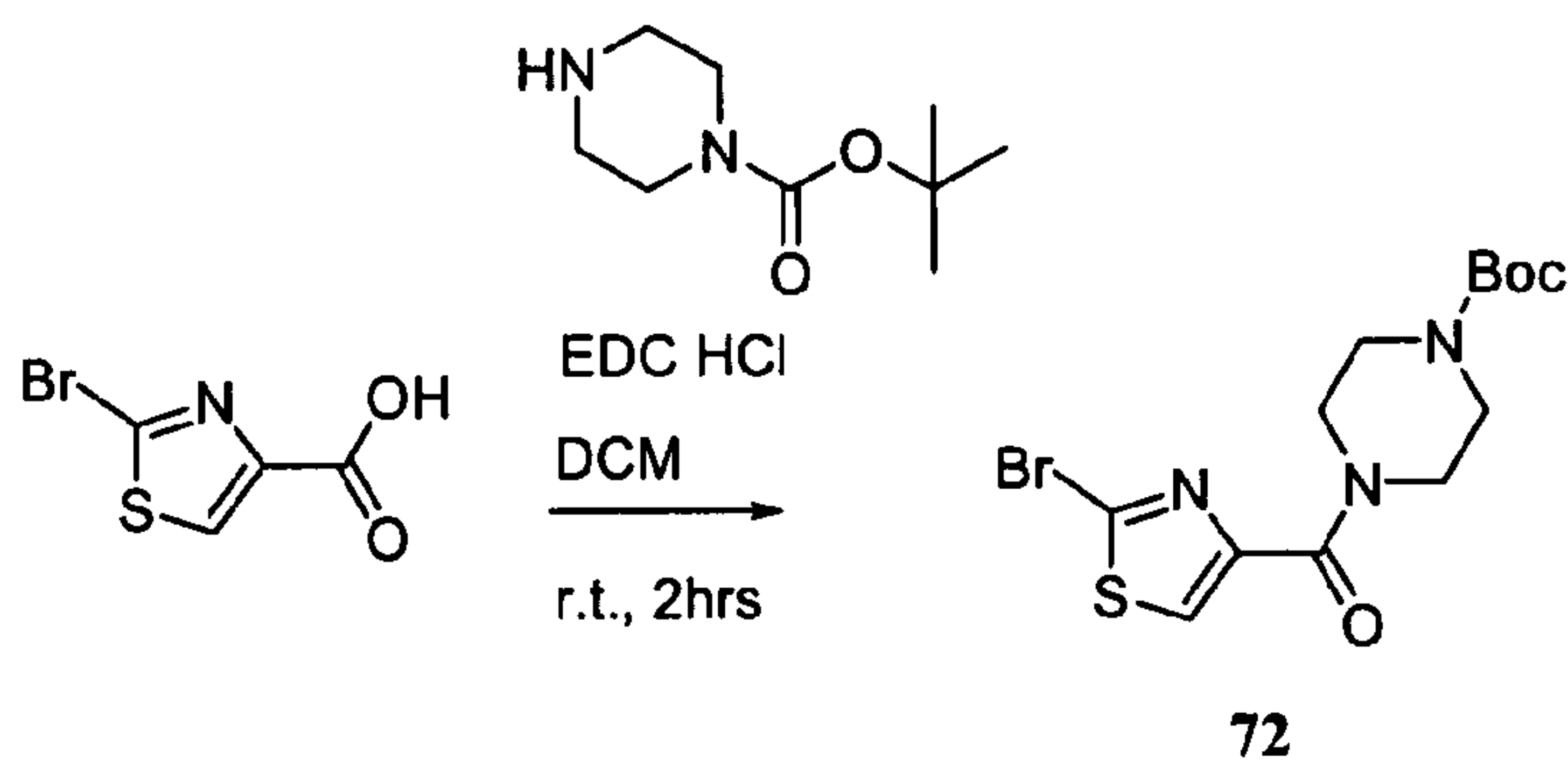
**EXAMPLE 48****70****9-cyclopentyl-N-(5-(1,4-diazepan-1-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **70** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 10.75 (1H, br s), 9.56 (1H, s), 9.34 (1H, s), 8.83 (2H, br s), 8.67 (1H, d, J = 6.3Hz), 8.57 (1H, d, J = 5.9Hz), 7.96 (1H, d, J = 2.7Hz), 7.92 (1H, d, J = 9.4Hz), 7.55 (1H, br s), 5.36 (1H, p, J = 8.7Hz), 3.76 (2H, t, J = 5.0 Hz), 3.56 (2H, t, J = 6.3 Hz), 3.30 (2H, br s), 3.19 (2H, br s), 2.41 (2H, m), 2.09 (6H, m), 1.75 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2

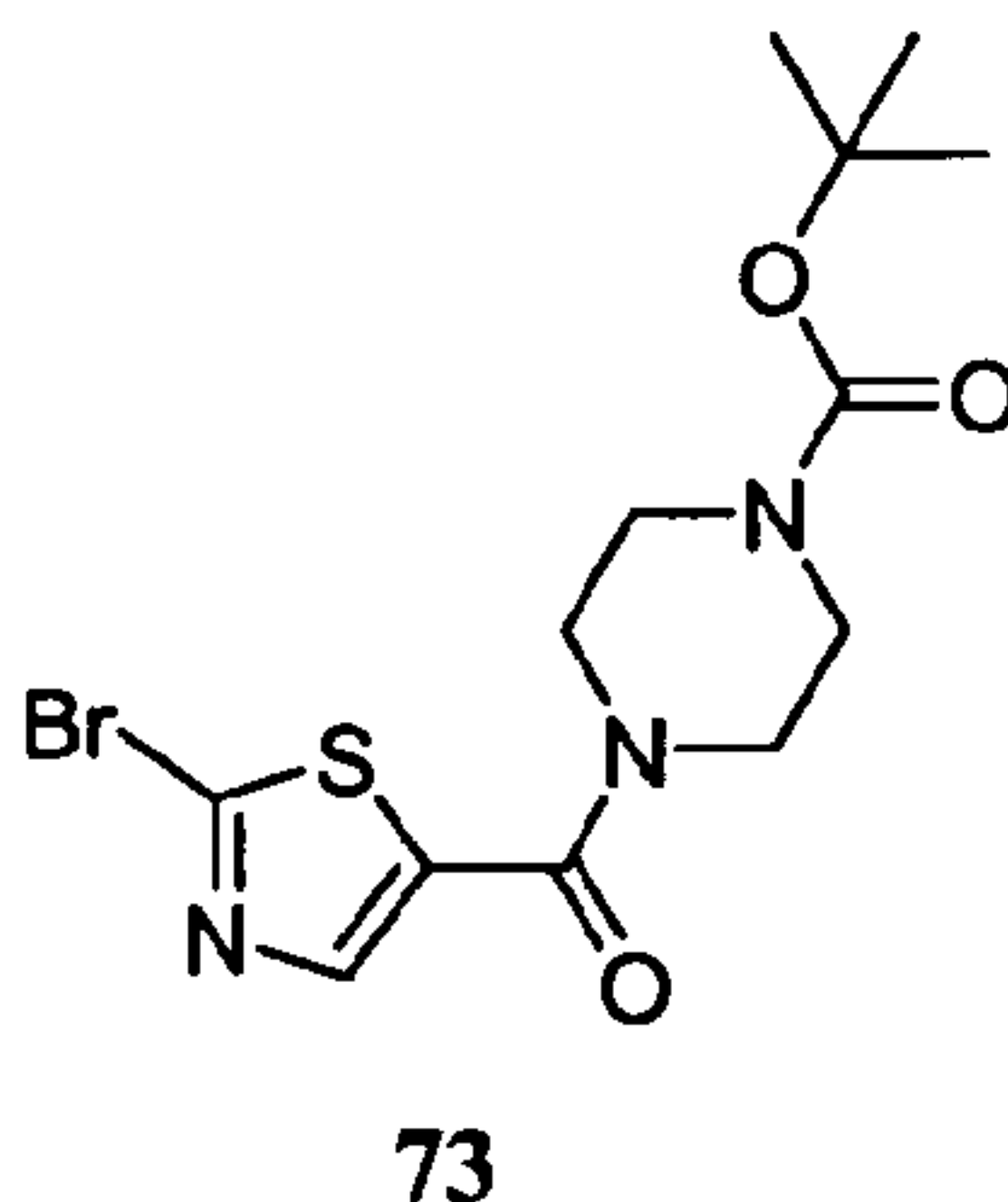


**EXAMPLE 49**

**9-cyclopentyl-N-(4-(1-piperazinylcarbonyl)-1,3-thiazol-2-yl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



**1,1-dimethylethyl 4-((2-bromo-1,3-thiazol-4-yl)carbonyl)-1-piperazinecarboxylate (72):** 2-bromothiazole-4-carboxylic acid (1.31 g, 6.3 mmol) was combined with *tert*-butyl piperazine-1-carboxylate (1.2 g, 6.3 mmol) in DCM (15 mL), and then stirred at 20°C. until it formed a clear solution. N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (1.2 g, 6.3 mmol) was then added, and the reaction was stirred at 20°C. for 2 hours. The reaction was concentrated in vacuum, before transferring it to a separation funnel with ethyl acetate. The organic layer was washed with saturated NaHCO<sub>3</sub>, water, NH<sub>4</sub>Cl, and then with brine. After drying the organic layer with MgSO<sub>4</sub>, it was concentrated in vacuum to yield compound **72** (2.2g, 91%) as a light yellow solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.16 (1H, s), 3.61 (4H, m), 3.38 (4H, m), 1.42 (9H, s) ppm; LCMS-ESI (POS), M/Z, M+1-C<sub>3</sub>H<sub>9</sub>: Found 320.0.

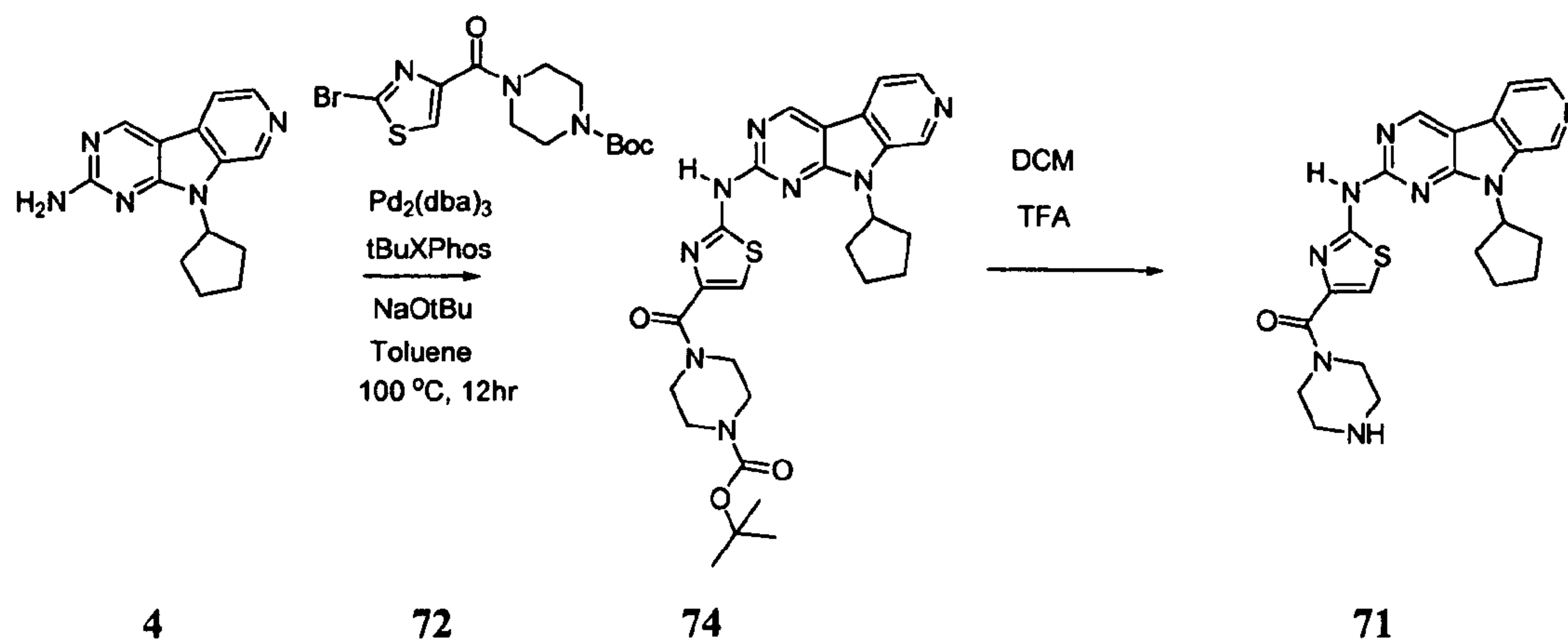


**1,1-dimethylethyl 4-((2-bromo-1,3-thiazol-5-yl)carbonyl)-1-piperazinecarboxylate**



Compound **73** was prepared according to the methods described for compound **72** in example 49.

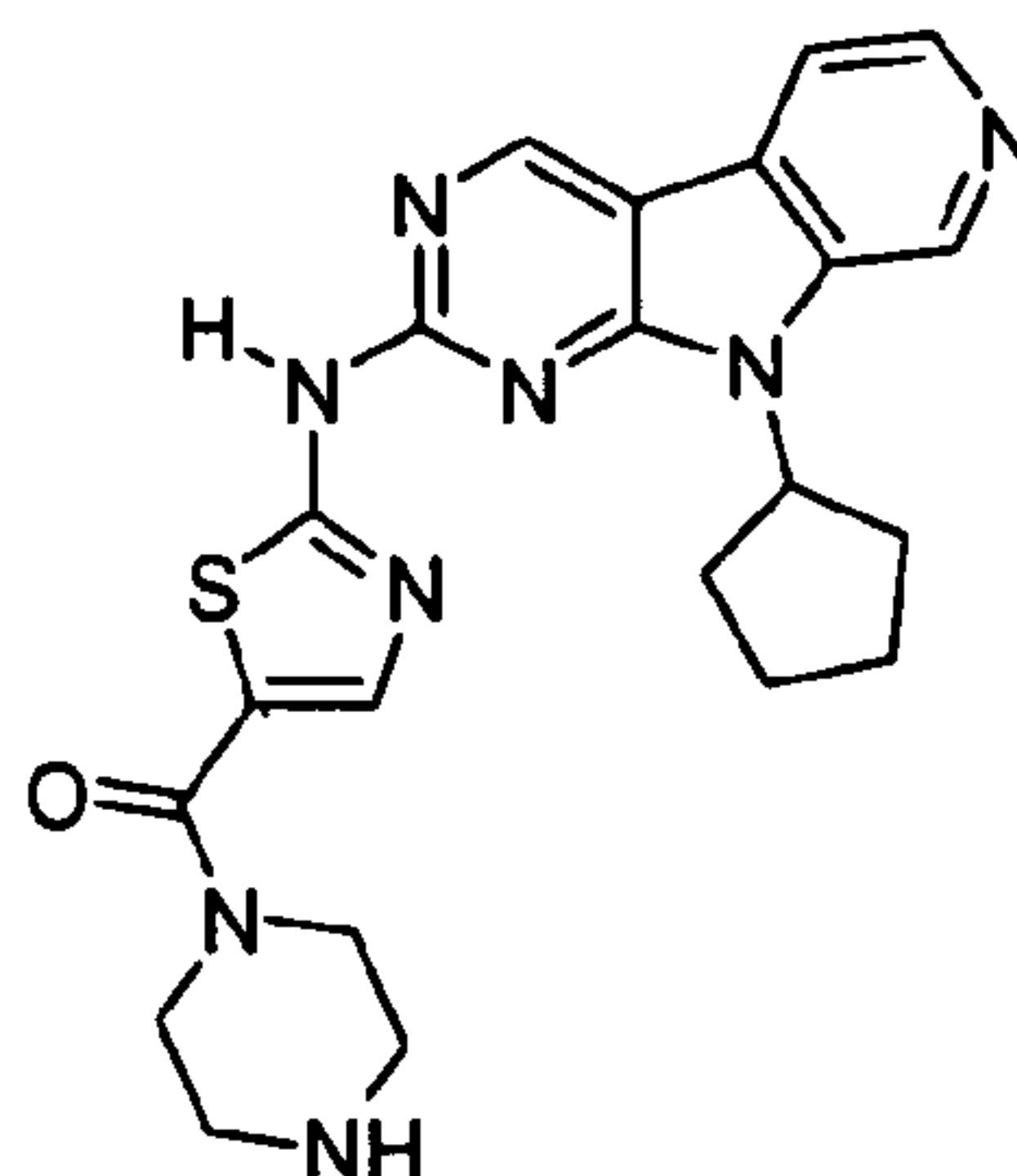
$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.02 (1H, s), 3.62 (4H, m), 3.42 (4H, m), 1.43 (9H, s) ppm.



**1,1-dimethylethyl 4-((2-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1,3-thiazol-4-yl)carbonyl)-1-piperazinecarboxylate (74):** Compound **4** (0.075 g, 0.30 mmol) was combined with sodium 2-methylpropan-2-olate (0.085 g, 0.89 mmol) and compound **72** (0.14 g, 0.38 mmol) in toluene (2mL). This mixture was degassed by bubbling nitrogen through this solution for ~2 min followed by the addition of  $\text{Pd}_2(\text{dba})_3$  (0.014 g, 0.015 mmol) and *t*-Butyl-XPhos (0.025 g, 0.059 mmol). The reaction was heated overnight at 60°C. Additional compound **72**, 0.28 g, 0.76 mmol,  $\text{Pd}_2(\text{dba})_3$  (25 mg), *t*-Butyl-XPhos (54 mg), and the sodium 2-methylpropan-2-olate (0.085 g, 0.89 mmol) were added to the reaction which was heated overnight at 100°C. The reaction was cooled to 20°C and poured into a separation funnel, with ethyl acetate and water. The layers were partitioned and the aqueous layer was washed with ethyl acetate. The combined organic fractions were dried over  $\text{MgSO}_4$  and concentrated. The product was purified by flash column chromatography, eluting with a gradient of DCM-6%methanol/0.3% $\text{NH}_4\text{OH}$ /DCM to yield compound **74** (95mg) as a brown film. LCMS-ESI (POS),  $\text{M}/\text{Z}$ ,  $\text{M}+1$ : Found 549.3.

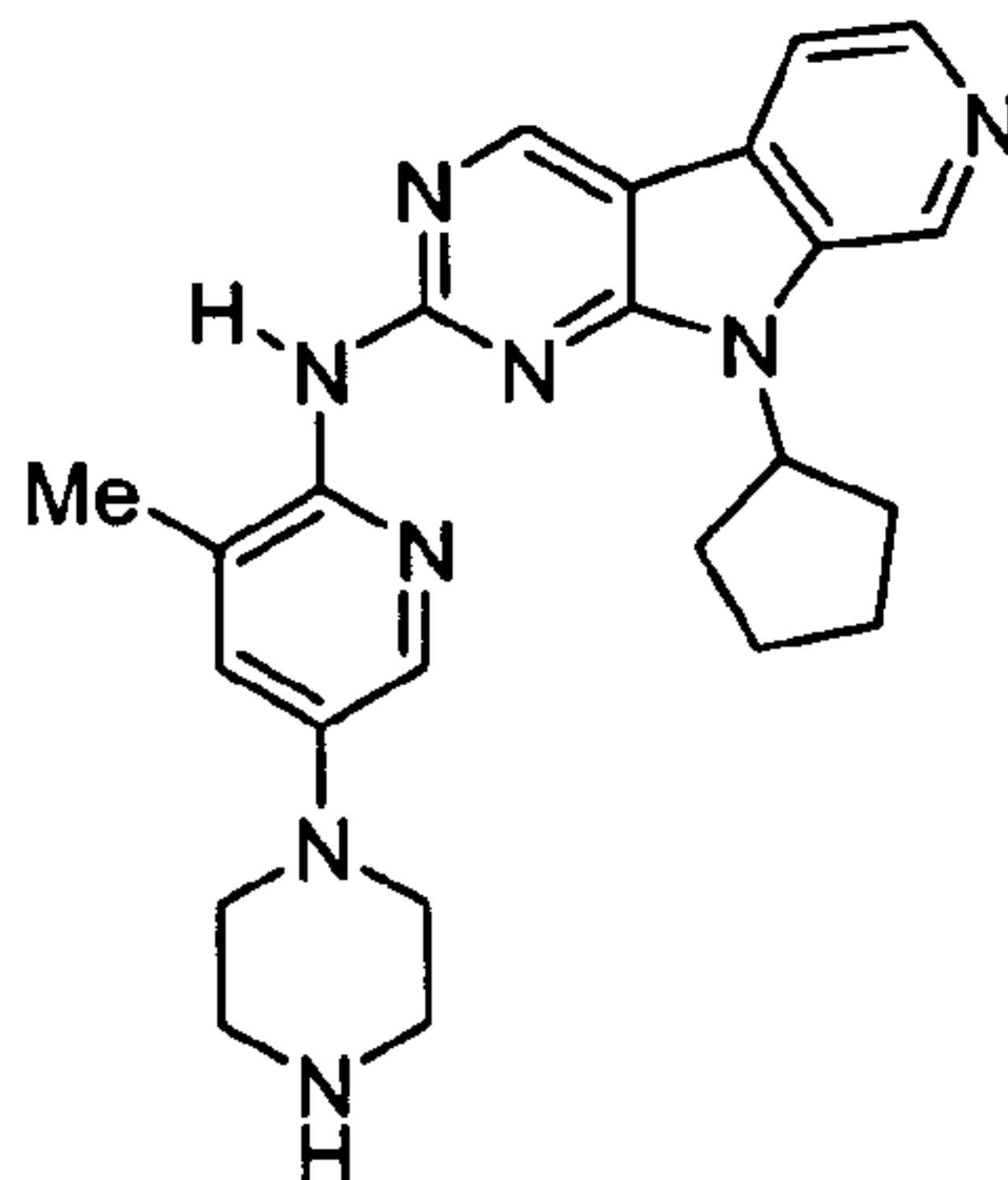
**9-cyclopentyl-N-(4-(1-piperazinylcarbonyl)-1,3-thiazol-2-yl)-9H-pyrido[4',3':4,5]pyrrolo-[2,3-d]pyrimidin-2-amine (71):** Compound **74** was dissolved in DCM (5 mL) and TFA (1.5 mL) and stirred at 20°C for 2.5 hrs. The reaction was concentrated in vacuum and purified by preparative HPLC eluting with a gradient 10%MeCN/water/0.1%TFA -50%MeCN/water/0.1%TFA to provide compound **71** (23 mg) as a yellow solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.63 (1H, s), 9.32 (1H, s), 8.68 (1H, d,  $J = 6.1\text{Hz}$ ), 8.63 (1H, d,  $J = 6.4\text{Hz}$ ), 7.84 (1H, s), 5.56 (1H, p,  $J = 8.1$ ), 4.00-4.29 (4H, br s), 3.39 (4H, t,  $J = 5.3\text{Hz}$ ), 2.63 (2H, m), 2.25 (4H, m), 1.98 (2H, m) ppm; LCMS-ESI (POS),  $\text{M}/\text{Z}$ ,  $\text{M}+1$ : Found 449.2.



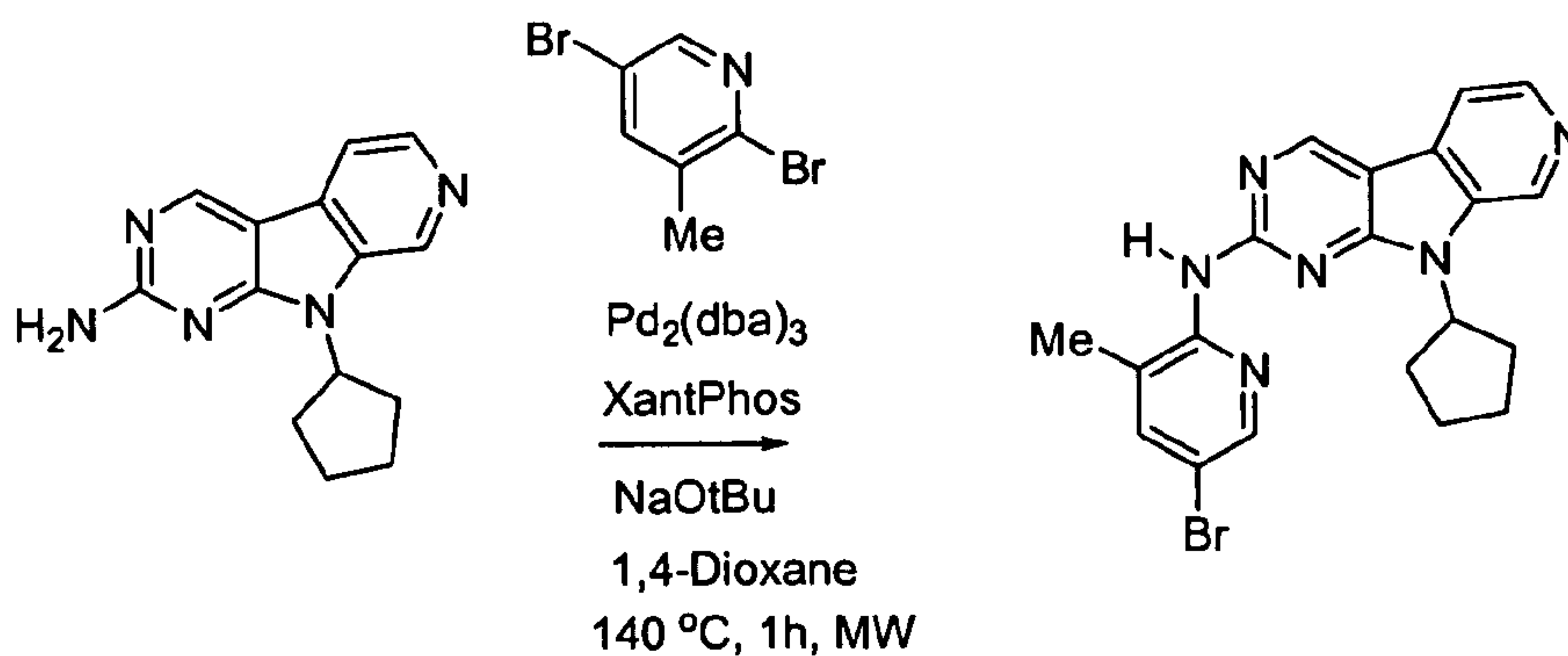
**EXAMPLE 50****75**

**9-cyclopentyl-N-(5-(1-piperazinylcarbonyl)-1,3-thiazol-2-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **75** was prepared according to the methods described in example 49. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.63 (1H, s), 9.34 (1H, s), 8.65 (1H, d, J = 6.1Hz), 8.62 (1H, d, J = 6.1Hz), 7.93 (1H, s), 5.52 (1H, p, J = 9.3Hz), 4.10 (4H, t, J = 5.1Hz), 3.39 (4H, t, J = 5.1Hz), 2.70 (2H, m), 2.28 (4H, m), 1.95 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 449.2.

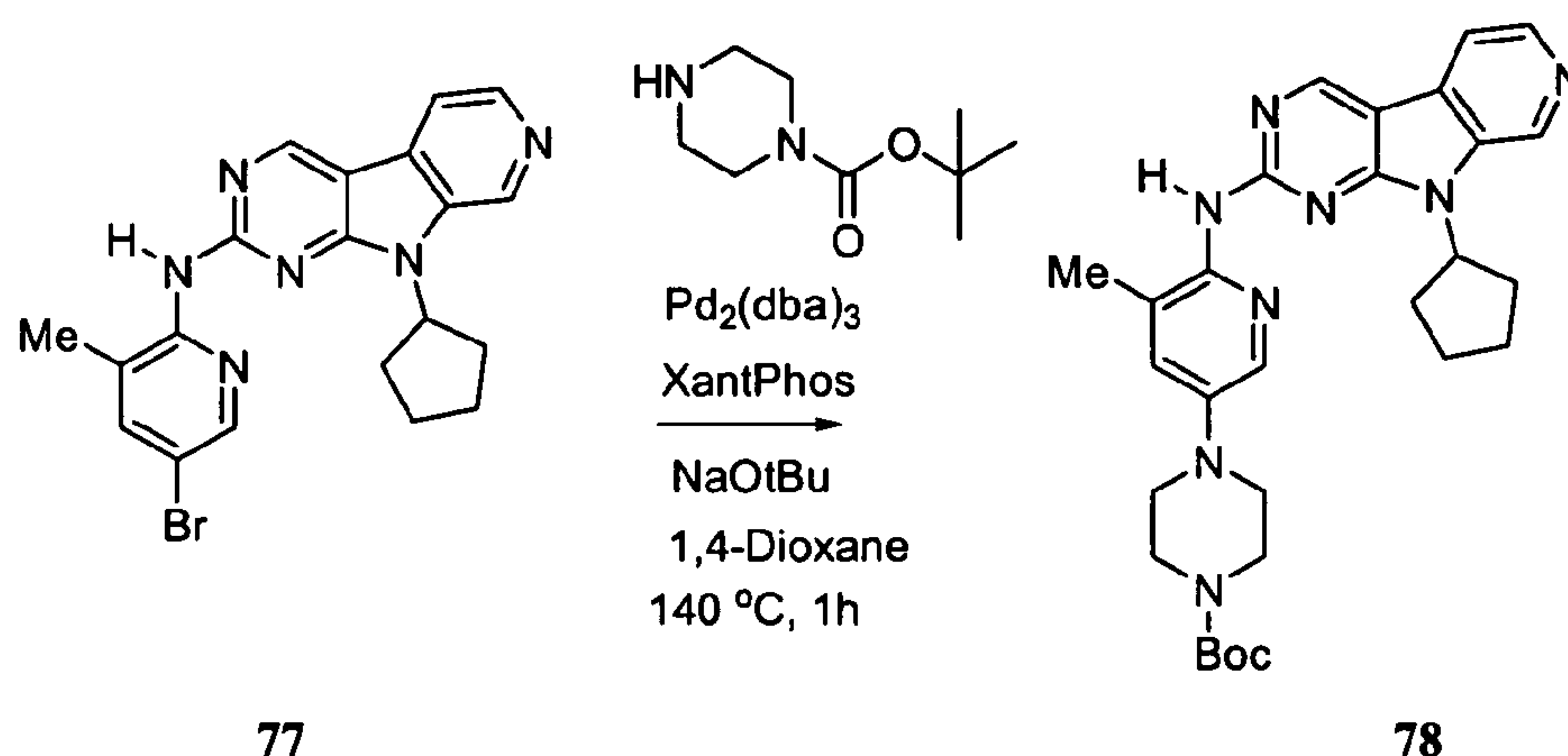
**EXAMPLE 51****76**

**9-cyclopentyl-N-(3-methyl-5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**4****77**

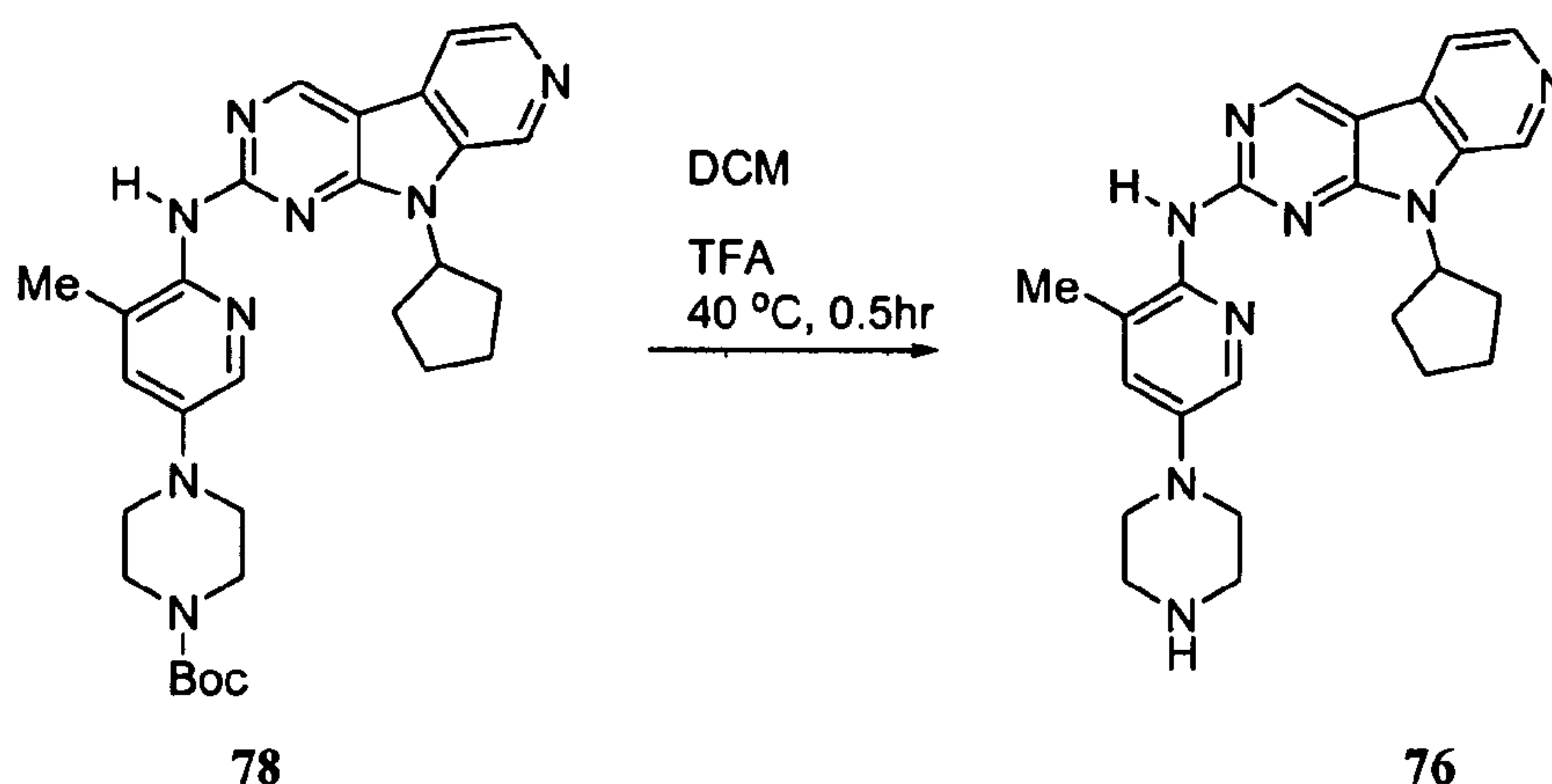


**N-(5-bromo-3-methyl-2-pyridinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (77):** Sodium 2-methylpropan-2-olate (0.142 g, 1.48 mmol) was combined with compound 4 (0.125 g, 0.493 mmol) and 2,5-dibromo-3-methylpyridine (0.149 g, 0.592 mmol) in 1,4-dioxane (3 ml). The reaction mixture was degassed by bubbling nitrogen through the solution for ~ 1min, followed by the addition of XANTPHOS (0.0428 g, 0.0740 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub> (0.0339 g, 0.0370 mmol). The reaction was heated to 140 °C using microwave irradiation for 1 hour. The reaction mixture was poured into sat. NH<sub>4</sub>Cl and extracted with 10% isopropanol/DCM. The organic layer was dried with MgSO<sub>4</sub> and concentrated in vacuum. Purification by flash column chromatography, eluting with a gradient of DCM-5%methanol/DCM provided compound 77 as a yellow solid (150 mg, 71%). LCMS-ESI (POS), M/Z, M+1: Found 423.1



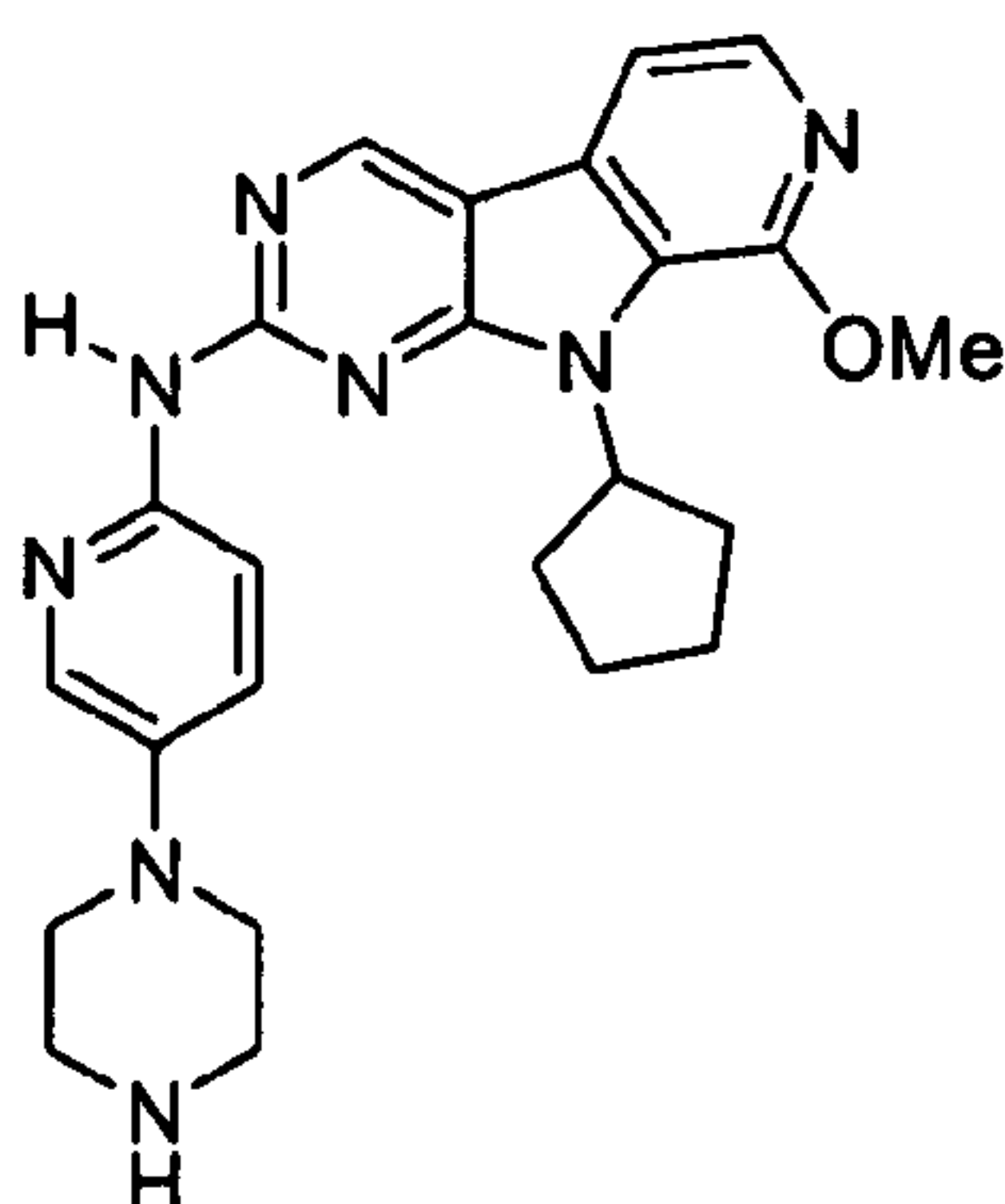
**1,1-dimethylethyl 4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-5-methyl-3-pyridinyl)-1-piperazinecarboxylate (78):** Sodium 2-methylpropan-2-olate (0.100 g, 1.06 mmol) was combined with compound 77 (0.150 g, 0.354 mmol) and *tert*-butyl 1-piperazinecarboxylate (0.099 g, 0.532 mmol) in 1,4-dioxane (3 ml). Nitrogen was bubbled through the solution for 1min before adding XANTPHOS (0.031 g, 0.053 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub> (0.024 g, 0.026 mmol). The reaction mixture was heated to 140°C using microwave irradiation for 1 hour. The reaction mixture was poured into sat. NH<sub>4</sub>Cl, and extracted with 10% isopropanol/DCM. The organic layer was dried over MgSO<sub>4</sub> and concentrated in vacuum. The crude product was purified by flash column chromatography, eluting with a gradient of DCM-7%methanol/DCM to provide compound 78 as a brown oil (100 mg). LCMS-ESI (POS), M/Z, M+1: Found 529.3.





**9-cyclopentyl-N-(3-methyl-5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (76):** Compound 78 (0.100 g, 0.189 mmol) was dissolved in DCM (3 mL) followed by TFA (1 mL) and stirred at 40°C in a water bath for 30 min. Concentration under vacuum provided a yellowish oil which was partially dissolved in water and then filtered. The filtrate was purified by preparative RP-HPLC eluting with a gradient of 5%MeCN/water/0.1%TFA-30%MeCN/water/0.1%TFA to yield compound 76 as a yellow solid (33 mg). <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 10.18 (1H, s), 9.51 (1H, s), 9.31 (1H, s), 8.95 (2H, br s), 8.65 (1H, d, J = 6.2Hz), 8.55 (1H, d, J = 6.1Hz), 8.12 (1H, d, J = 3.0), 7.58 (1H, d, J = 2.4Hz), 5.25 (1H, p, J = 8.3Hz), 3.46 (4H, t, J = 5.4Hz), 3.30 (4H, m), 2.24 (3H, s), 2.18 (2H, m), 2.01 (2H, m), 1.70 (2H, m), 1.55 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2.

#### EXAMPLE 52

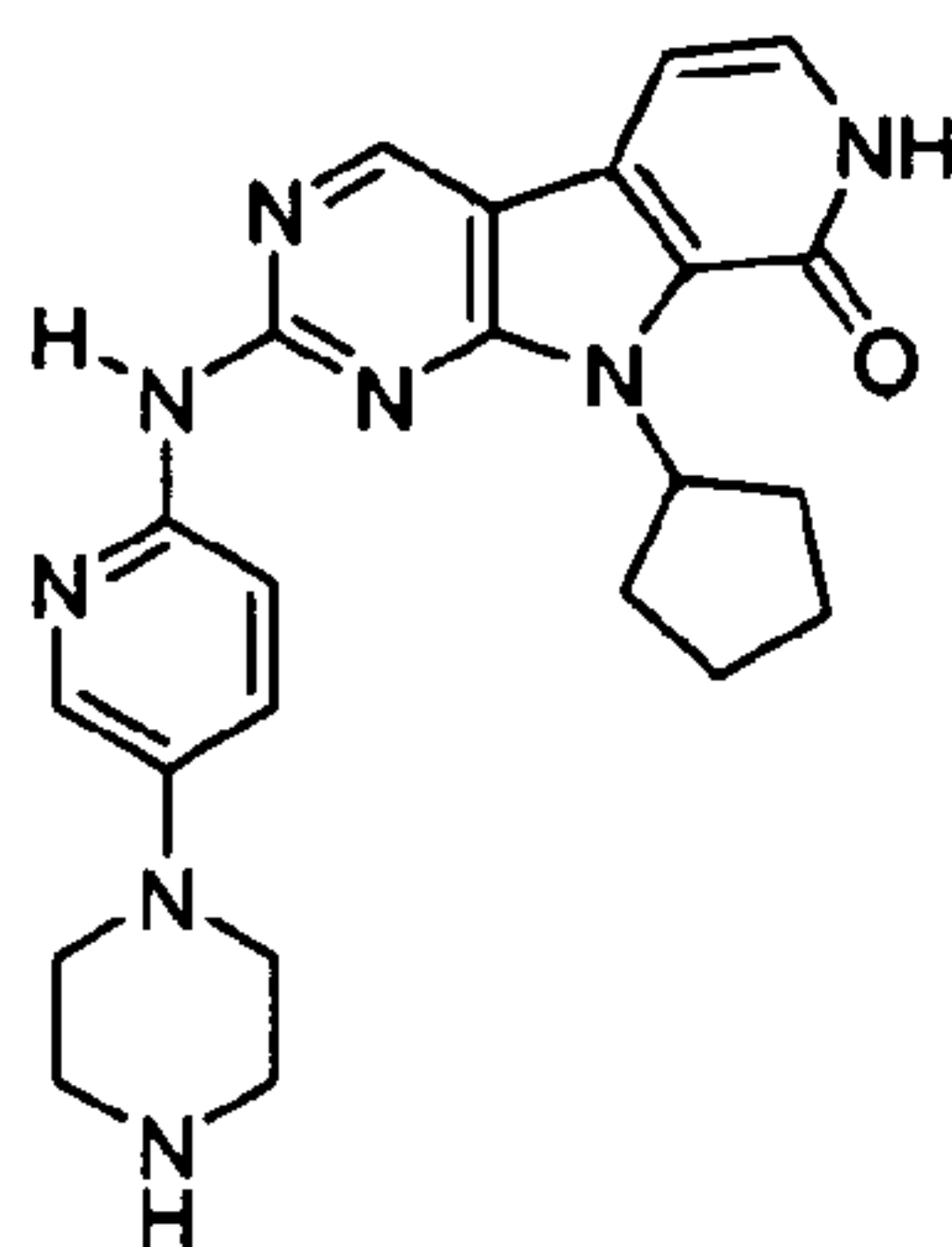


79

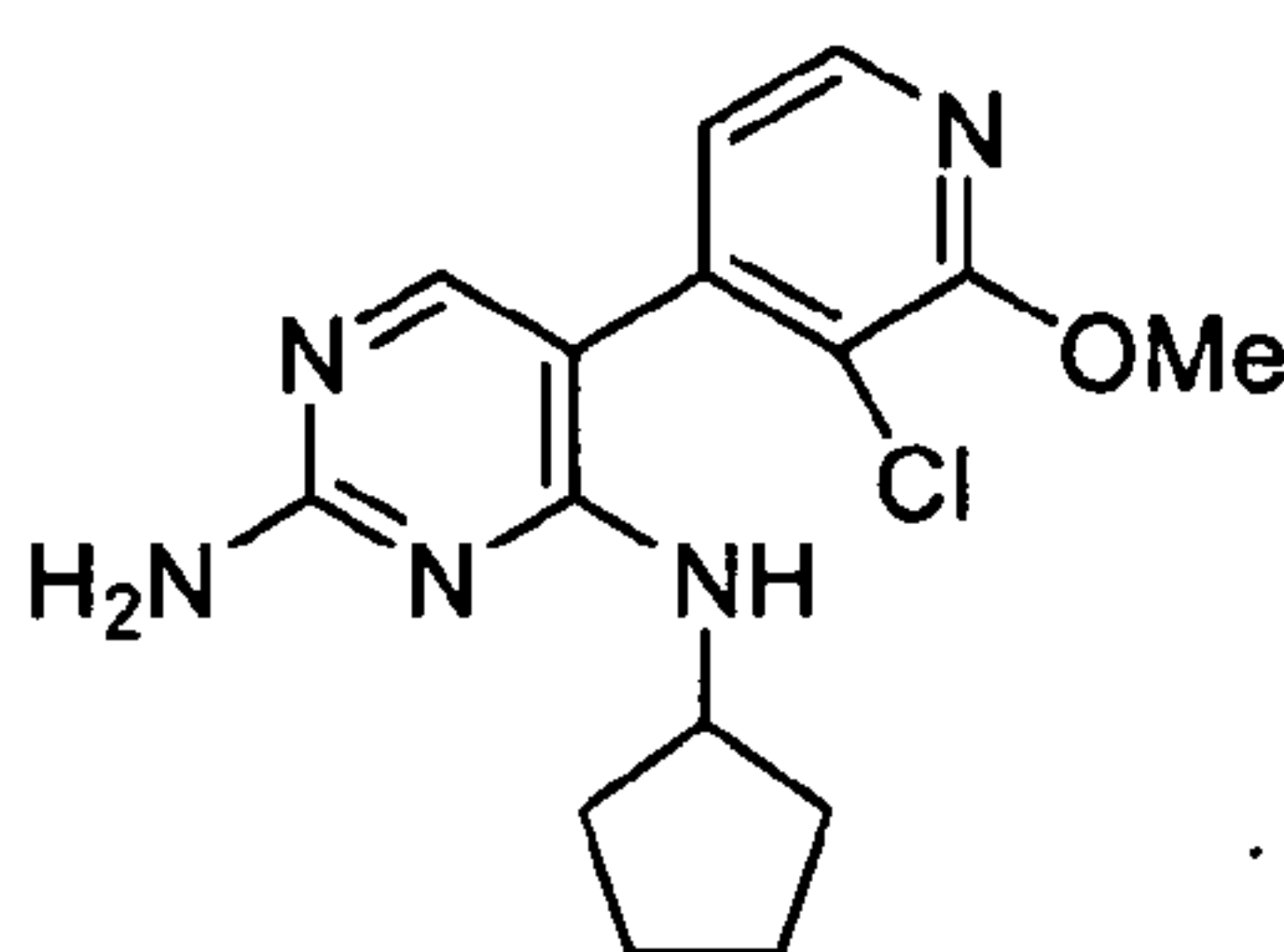
**9-cyclopentyl-8-(methoxy)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound 79 was prepared using compound 82 and chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.12 (1 H, s), 8.24 (1 H, d), 8.02 (1 H, d), 7.98 (1 H, d), 7.63 (1 H, d), 7.56 (1 H, m), 5.90 (1 H, b), 4.15 (3 H, s), 3.20 (4 H, m), 3.06 (4 H, m), 2.50-2.60 (2 H, b), 2.09-2.11 (4 H, b), 1.80 (2 H, b) ppm; LCMS-ESI (POS), M/Z, M+1: Found 445.1, calculated 445.2.



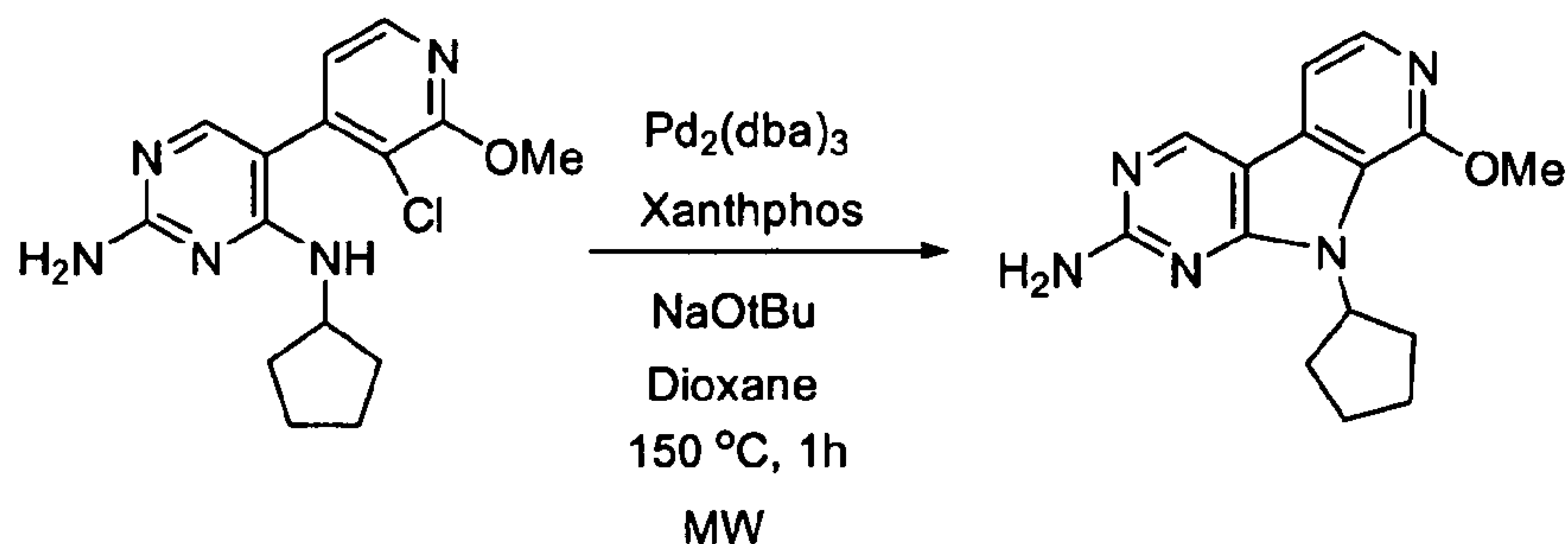
**EXAMPLE 53****80**

**9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-7,9-dihydro-8H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-one**

**81**

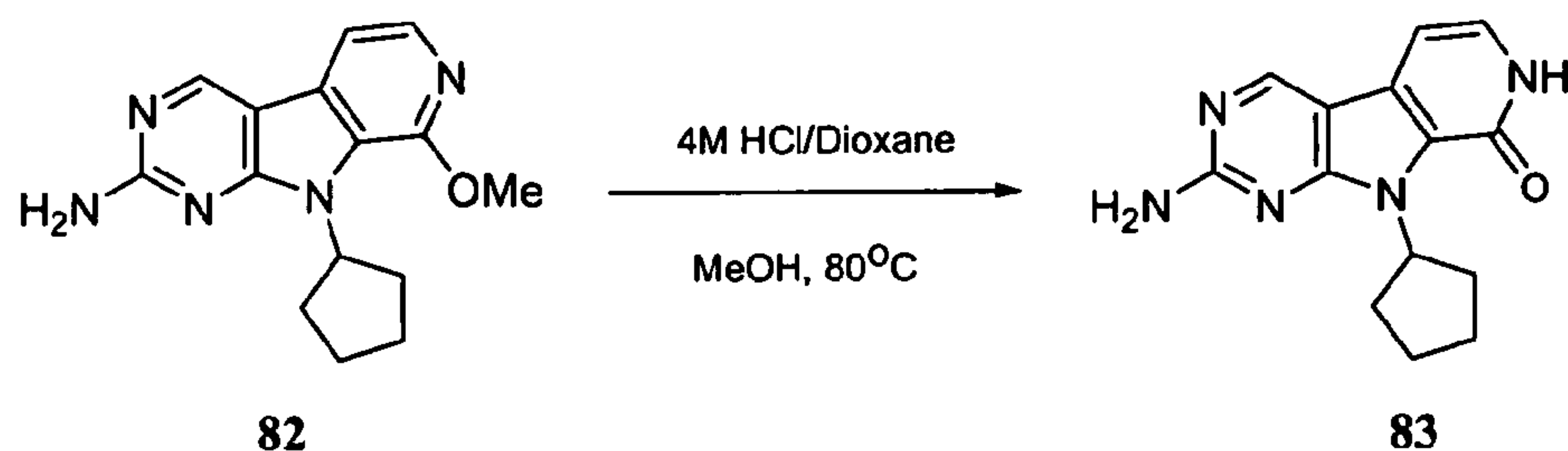
**5-(3-chloro-2-(methoxy)-4-pyridinyl)-N<sup>4</sup>-cyclopentyl-2,4-pyrimidinediamine**

Compound **81** was prepared using chemistry similar to that described in example 1. LCMS-ESI (POS), M/Z, M+1: Found 320.0, calculated 320.1.

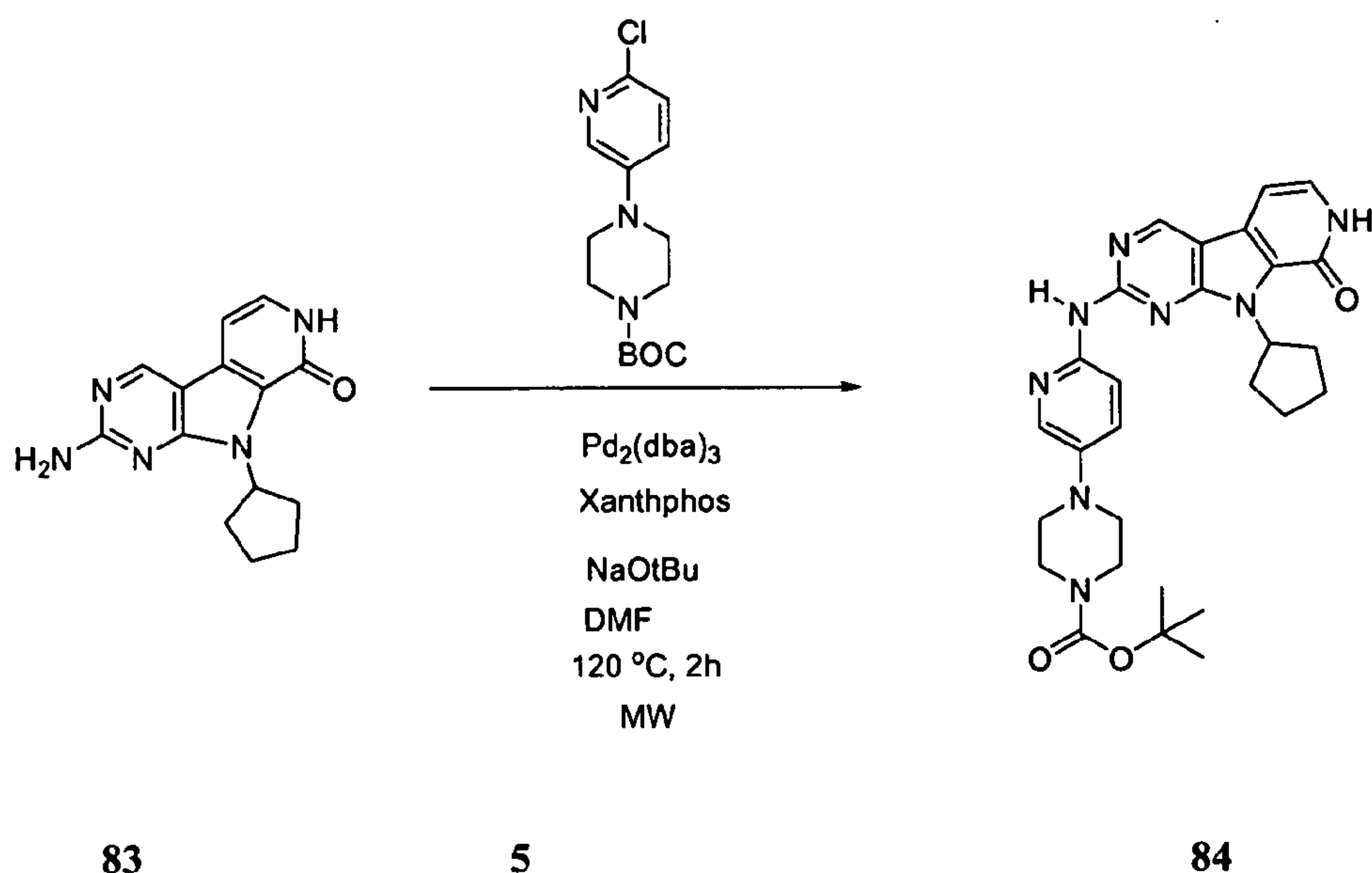
**81****82**

**9-cyclopentyl-8-(methoxy)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine(82):** A solution of Pd<sub>2</sub>(dba)<sub>3</sub> (0.60 g, 0.65 mmol), sodium 2-methylpropan-2-olate (1.9g, 20 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.75 g, 1.3 mmol) and compound **81** (2.08 g, 6.5 mmol) in dioxane (20 mL) was purged with N<sub>2</sub> for 20 min. The reaction mixture was heated at 150°C for one hour under microwave irradiation. The reaction mixture was concentrated and residue was diluted with DCM. Resulting solution was washed with brine, dried and concentrated. Purification by flash chromatography (10% methanol/DCM/1% NH<sub>4</sub>OH) gave compound **82** as a yellow solid (1.8 g, 98%). LCMS-ESI (POS), M/Z, M+1: Found 284.1, calculated 284.1.



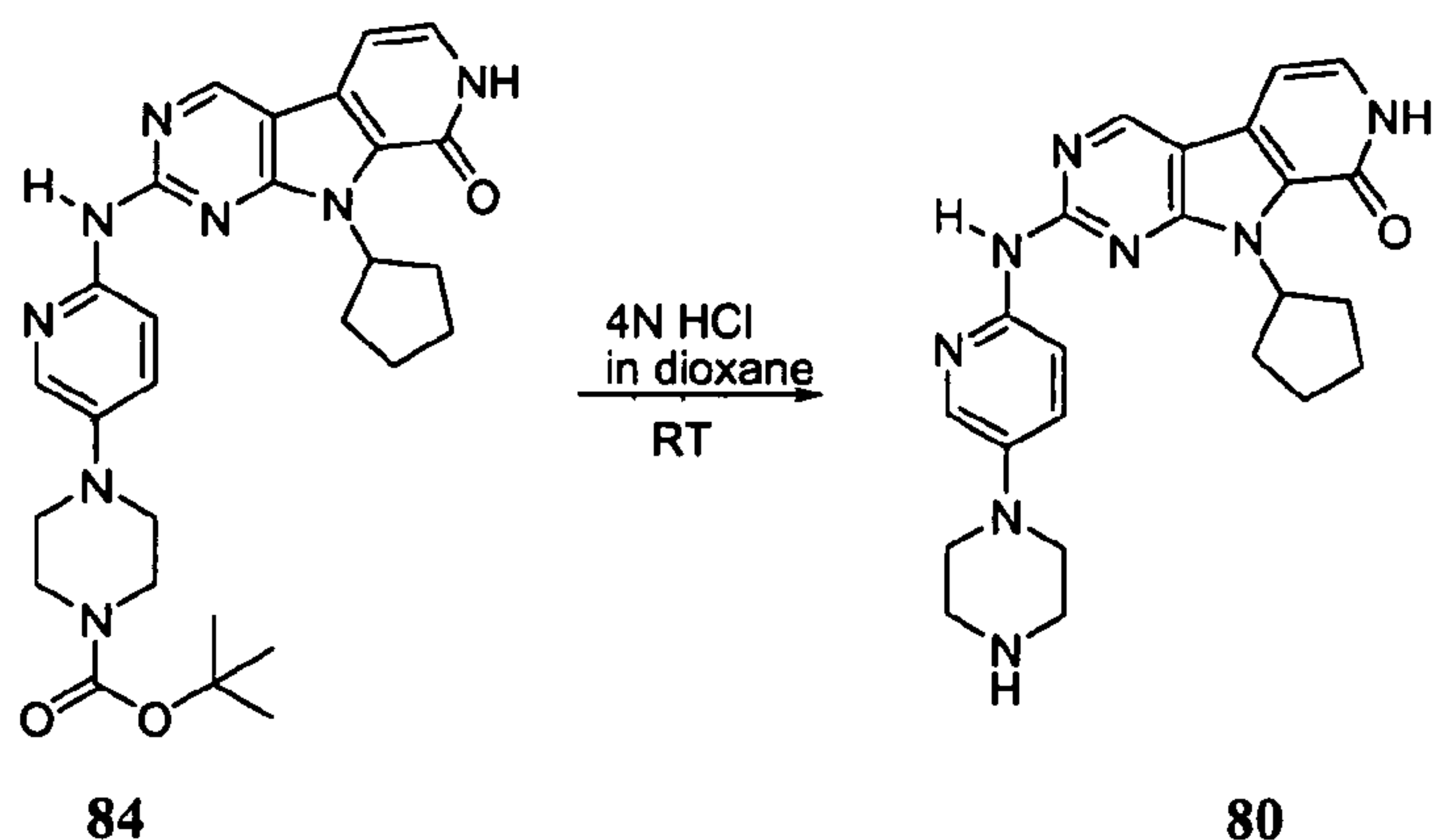


**2-amino-9-cyclopentyl-7,9-dihydro-8H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-one (83):** A solution of compound **82** (1.80g, 6.35 mmol) in 4M HCl in dioxane(60 mL) and methanol(6 mL) was heated at 80°C for one hour. Solid was collected by filtration to give a pale yellow solid as HCl salt which was then dissolved in water and basified by addition of solid sodium bicarbonate to pH 5~6. The precipitate was collected by filtration to provide compound **83** as a white solid.(0.715g, 42%). LCMS-ESI (POS), M/Z, M+1: Found 270.1, calculated 270.1.



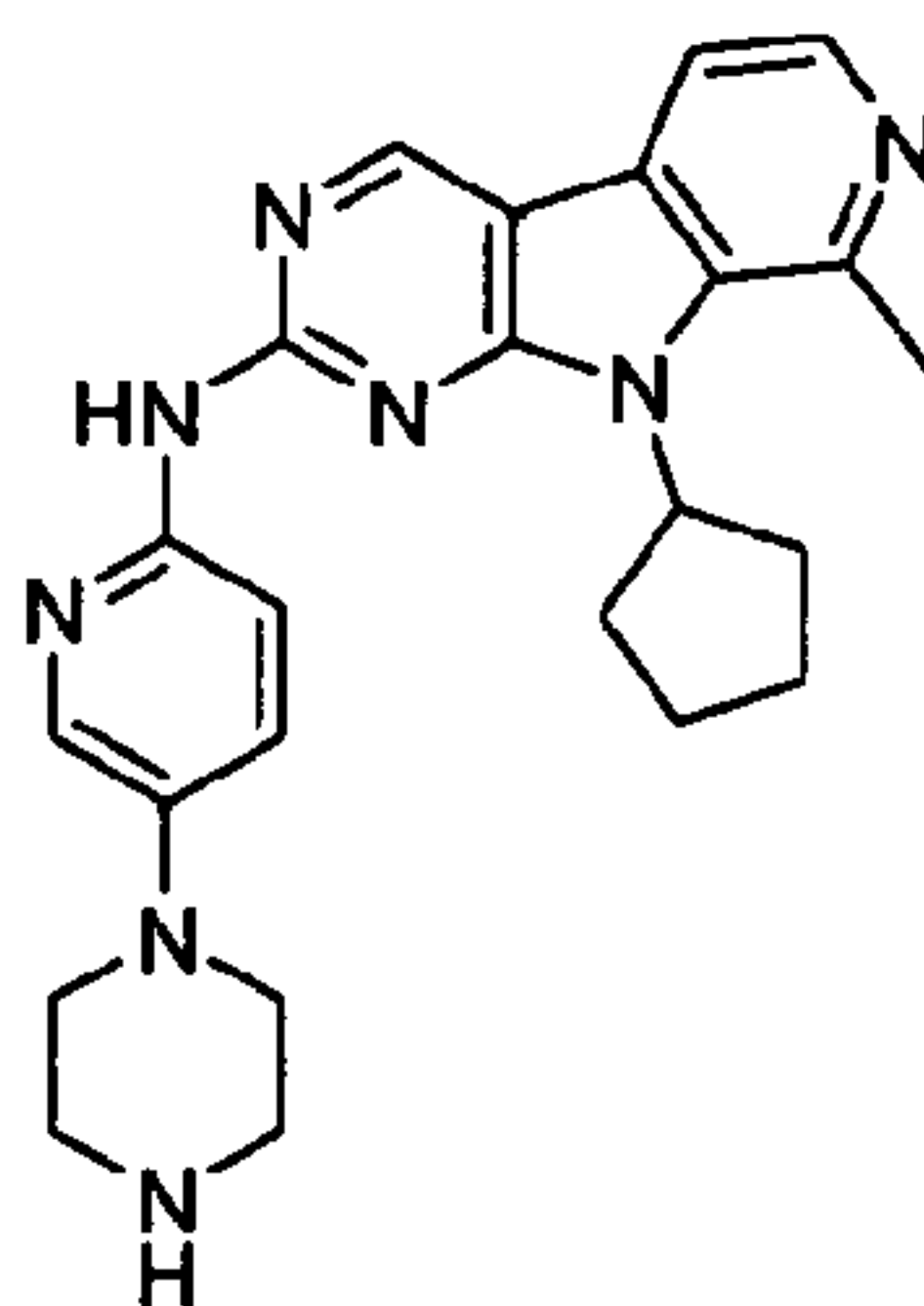
**1,1-dimethylethyl 4-(6-((9-cyclopentyl-8-oxo-8,9-dihydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (84):** Compound **84** was prepared by analogy to example 1. LCMS-ESI (POS), M/Z, M+1: Found 531.2, calculated 531.3.



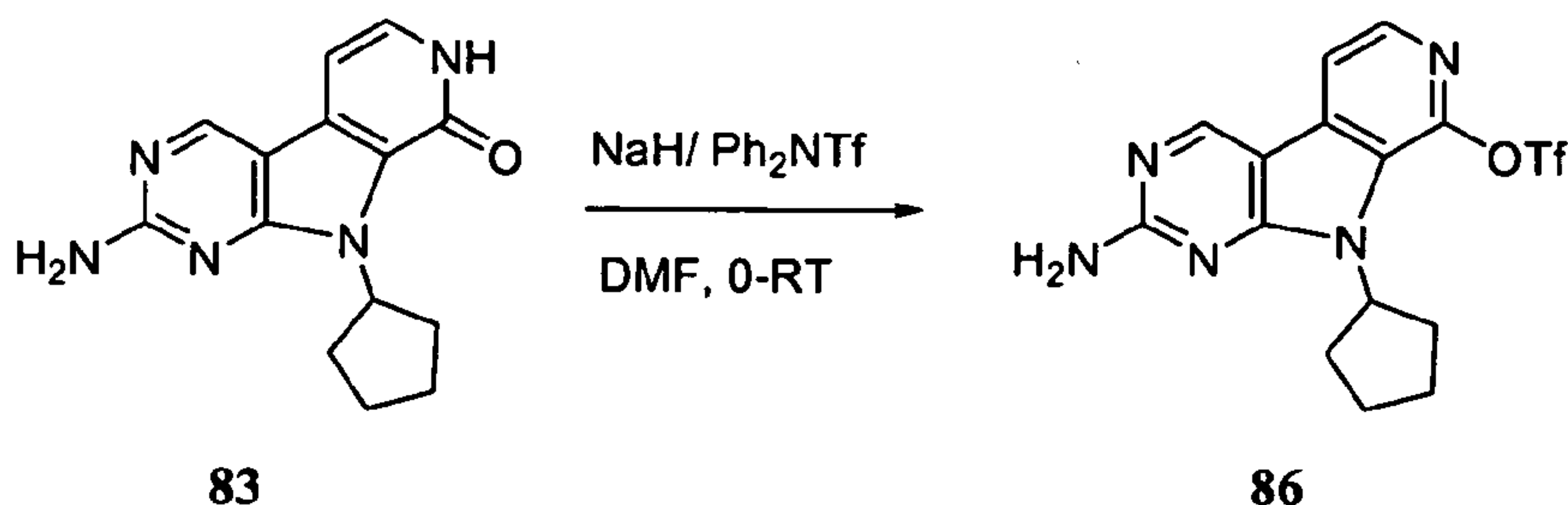


**9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-7,9-dihydro-8H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-8-one (80):** Compound 80 was prepared according to the methods described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.31 (1 H, s), 8.03(1 H, d), 8.01 (1 H, d), 7.75 (1 H, d), 7.35 (1 H, d), 7.16 (1 H, m), 6.25 (1 H, b), 3.52 (4 H, m), 3.47 (4 H, m), 2.50-2.60 (2 H, b), 2.09-2.25 (4 H, b), 1.75 (2 H, b) ppm; LCMS-ESI (POS), M/Z, M+1: Found 431.2, calculated 431.2

#### EXAMPLE 54



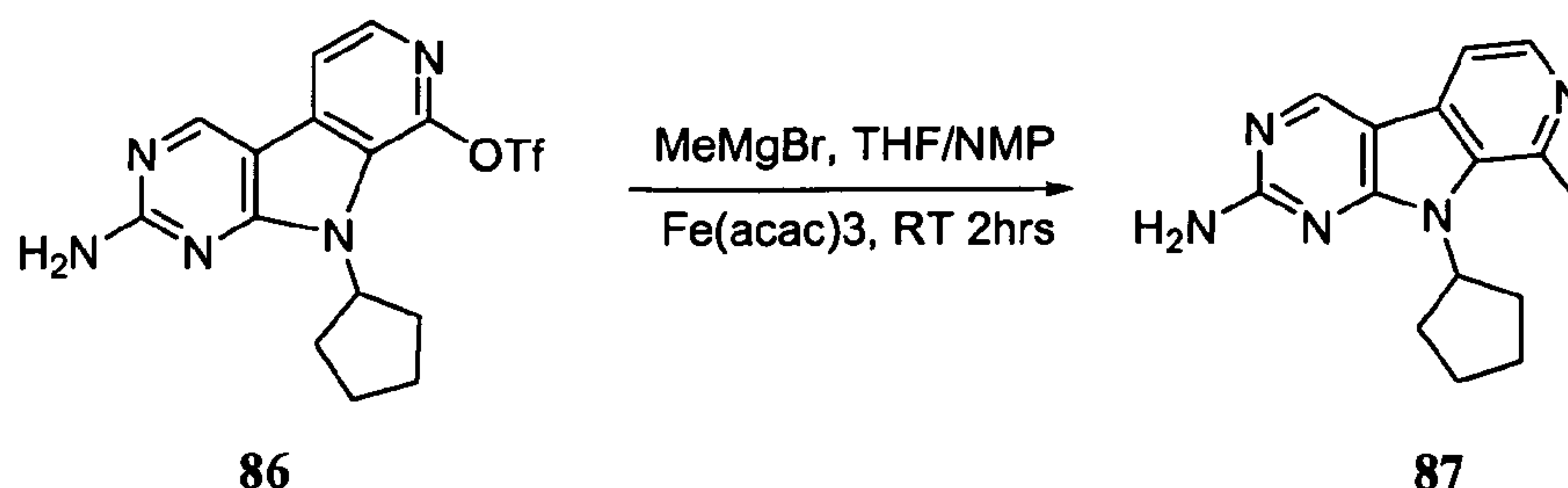
**9-cyclopentyl-8-methyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



**2-Amino-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-yl trifluoromethanesulfonate (86):** Sodium hydride (60% in oil, 16 mg) was added to a solution of compound 83(0.100g, 0.371 mmol) in DMF( 2 mL) and stirred at 0°C for 30 min., then N-phenyl-bis(trifluoromethanesulfonimide)(0.146g, 0.408 mmol) in DMF (1 mL) was added dropwise at 0° C and

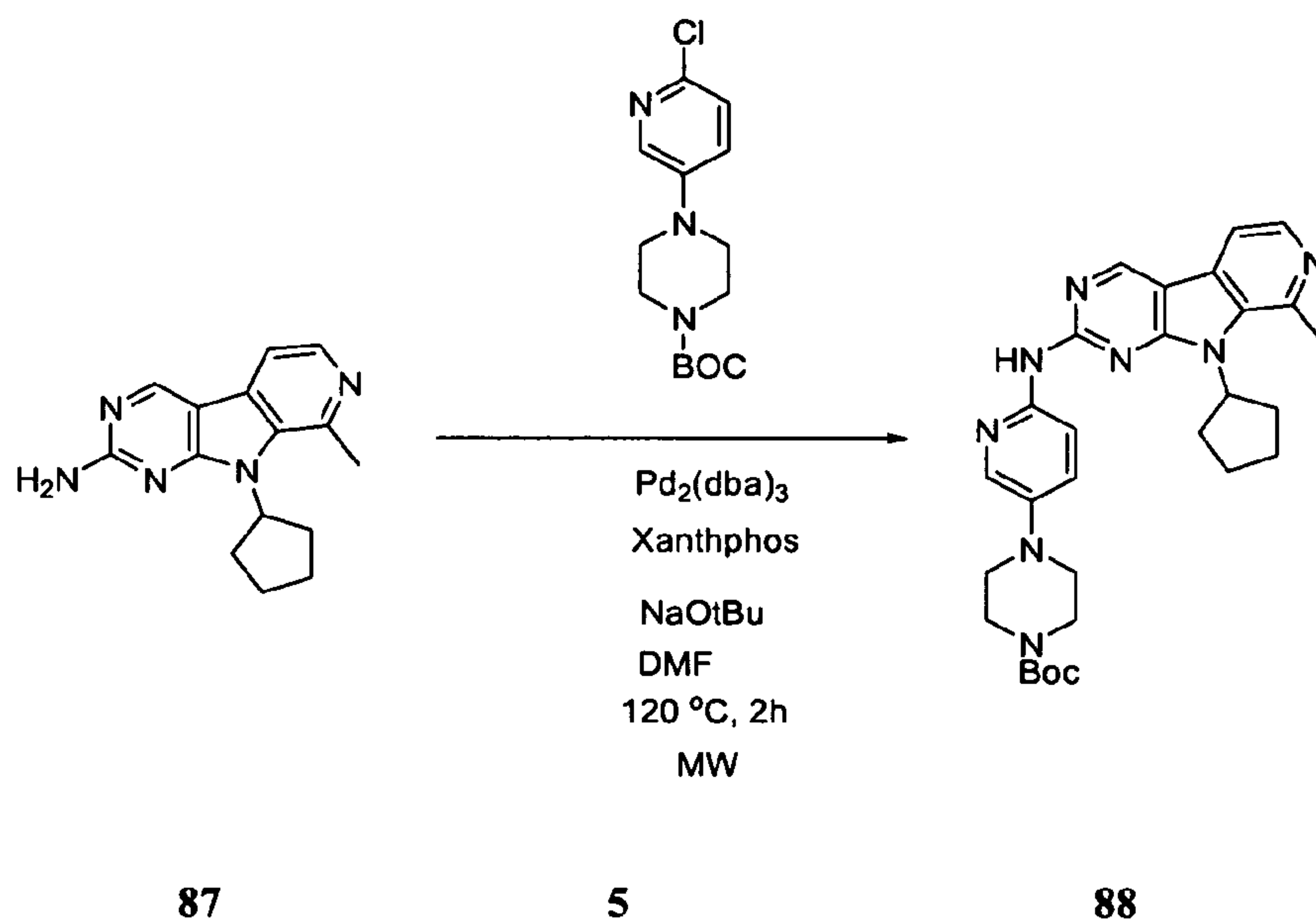


the resulting mixture was stirred at 0 °C for two hours. The reaction mixture was concentrated and dissolved in DCM. The resulting organic solution was washed with brine, dried and concentrated. Purification by flash chromatography(10%methanol/DCM/1%NH<sub>4</sub>OH) gave compound **86** (0.102g, 67%) as a yellow solid. LCMS-ESI (POS), M/Z, M+1: Found 402.1, calculated 402.1.



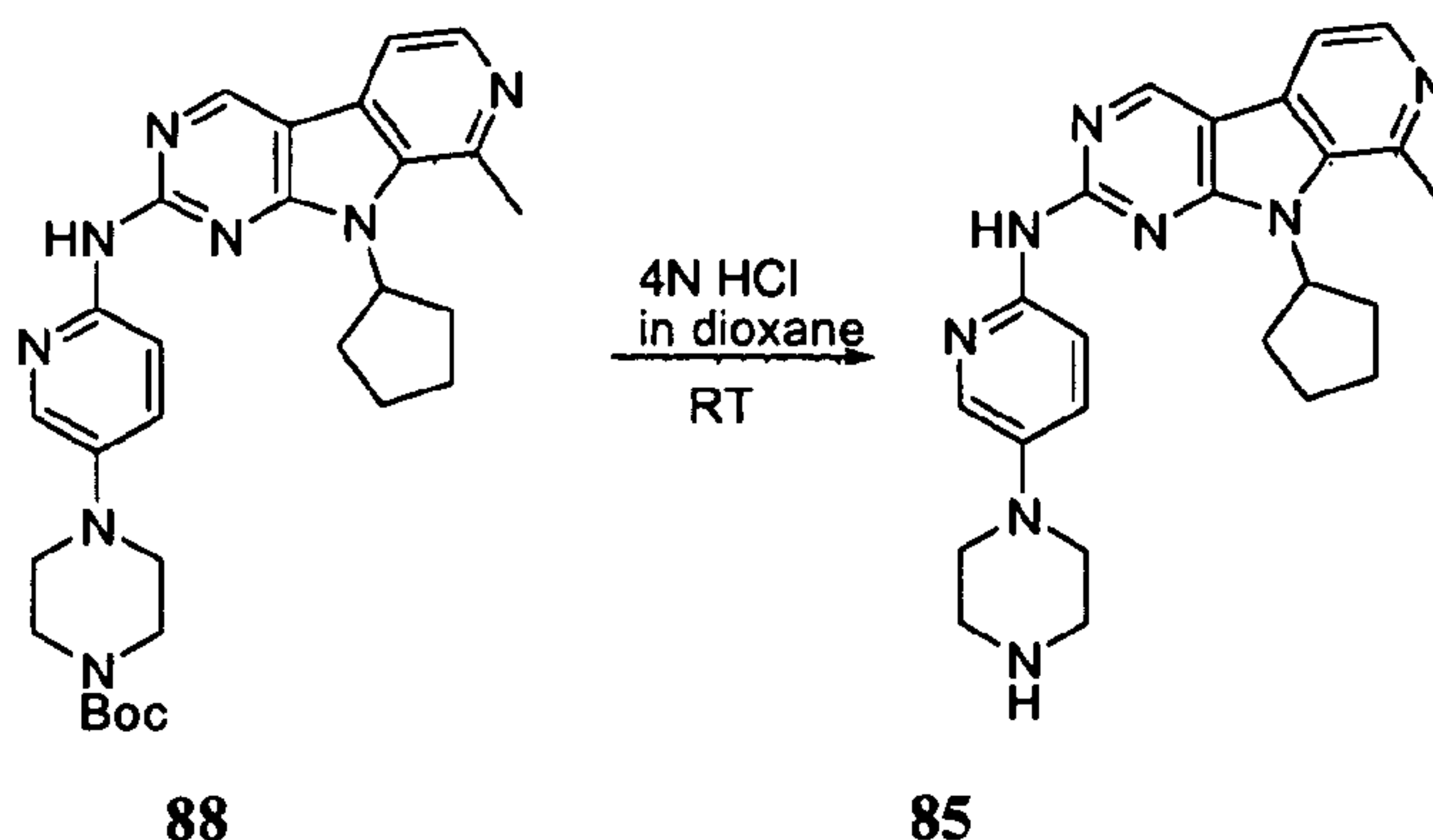
**9-cyclopentyl-8-methyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (87):**

A flame-dried two-necked flask was charged under argon with compound **86** (0.100g, 0.25 mmol), ferric acetylacetonate(0.0044, 0.012 mmol), THF( 2 ml) and N-methylpyrrolidone (0.1 ml). Methylmagnesium bromide (0.27 g, 2.2 mmol, 3M in ether) was added via syringe to the resulting red solution. A yellow precipitate formed immediately. The reaction was stirred at room temperature for 30 min and quenched with 5% NaHCO<sub>3</sub>, then extracted into DCM The resulting organic solution was washed with brine, dried and concentrated. Purification by flash chromatography (10%methanol/DCM/1%NH<sub>4</sub>OH) gave compound **87** as a light yellow solid( 0.036g, 54%). LCMS-ESI (POS), M/Z, M+1: Found 268.1, calculated 268.2.



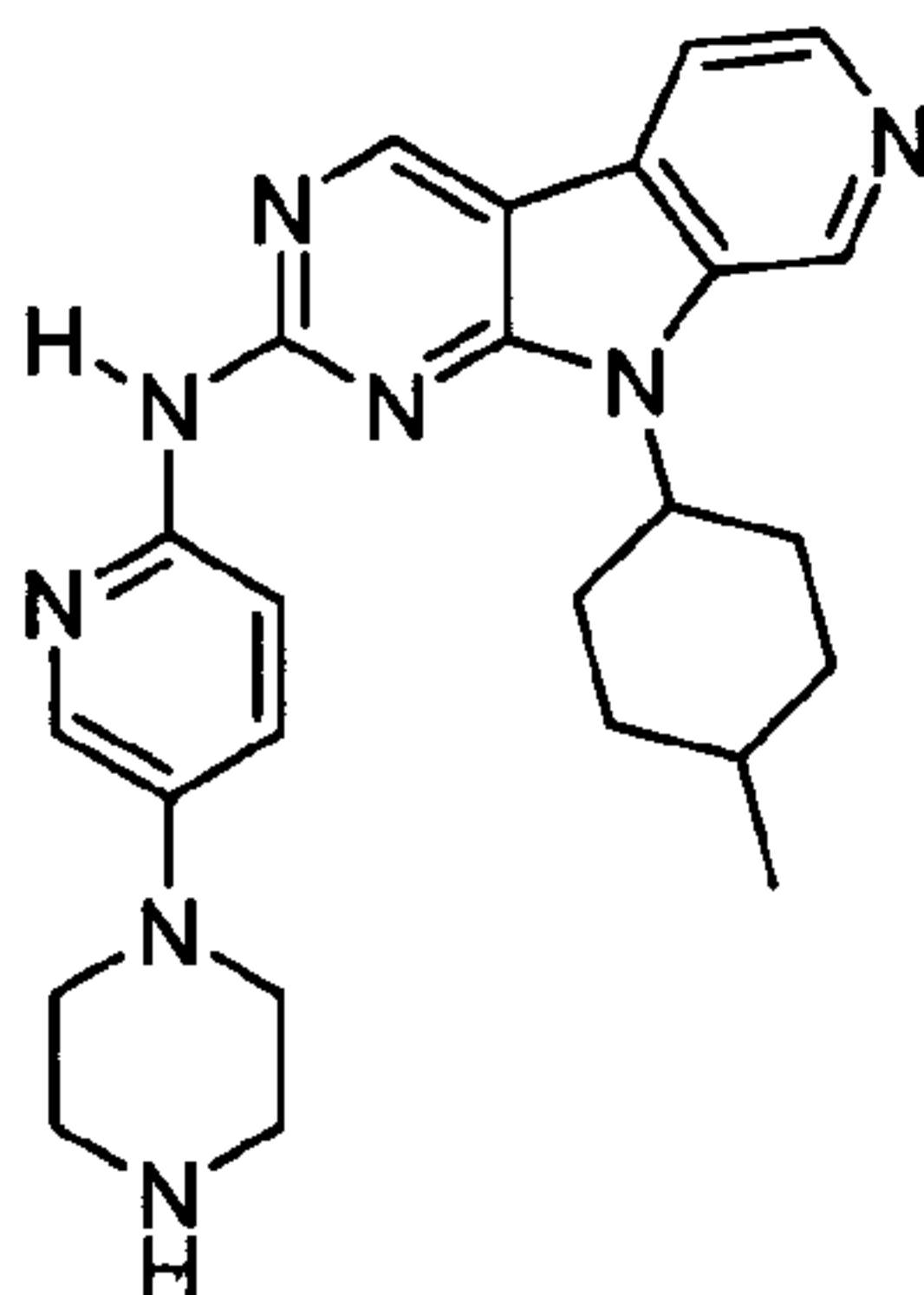
**1,1-dimethylethyl 4-(6-((9-cyclopentyl-8-methyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (88):** Compound **88** was prepared according to the methods described in example 1. LCMS-ESI (POS), M/Z, M+1: Found 529.3, calculated 529.3.





**9-cyclopentyl-8-methyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (85):** Compound 85 was prepared according to the methods described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.01 (1 H, s), 8.36(1H,s), 8.29(2 H, d), 8.01 (1 H, s), 7.62 (1 H, d), 7.28 (1 H, d), 5.36 (1 H, m), 3.09 (4 H, m), 3.02 (4 H, m), 2.95 (3 H, s), 2.73-2.70 (2 H, m), 2.09-1.98 (4 H, m), 1.80 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.2, calculated 429.2.

#### EXAMPLE 55

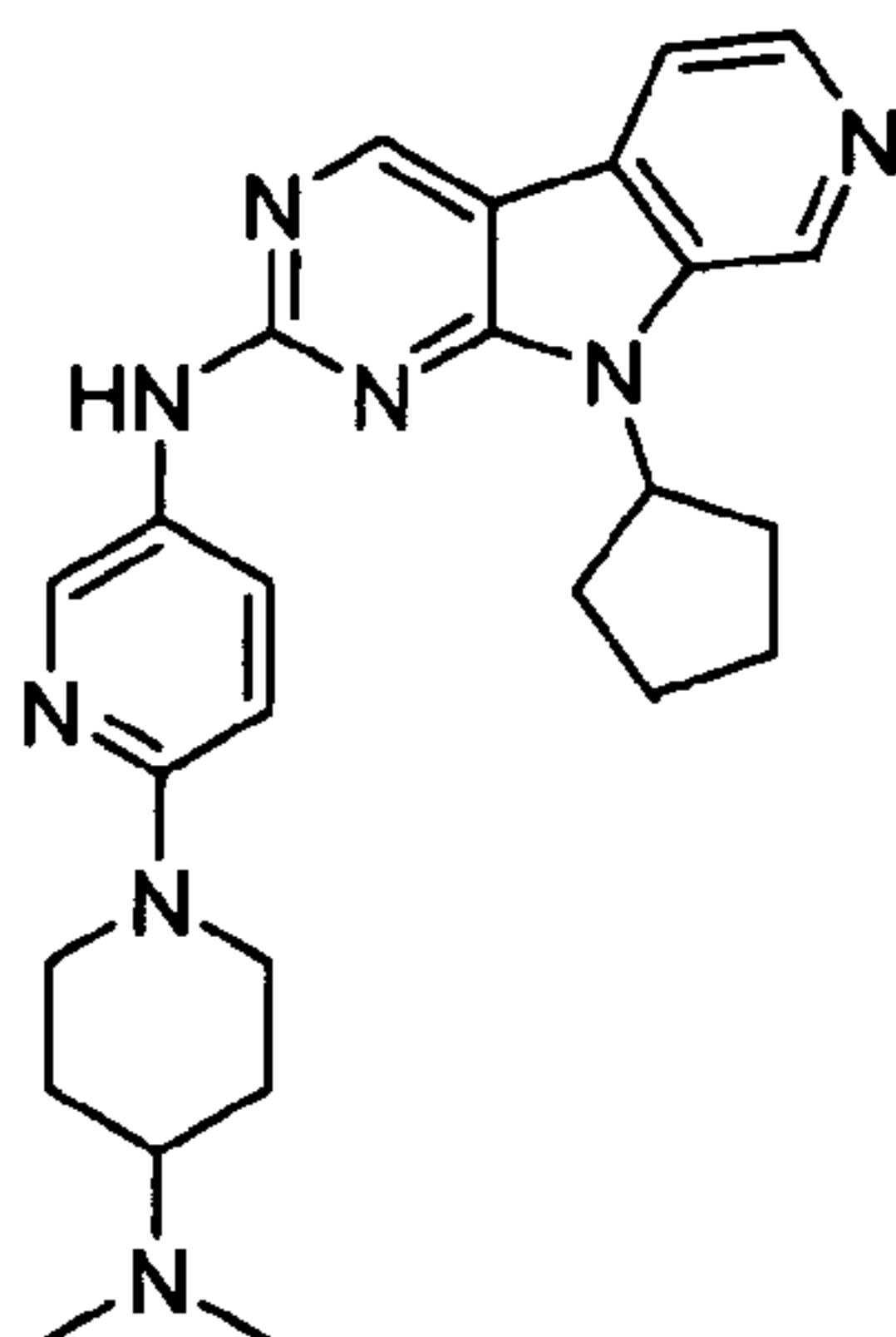


89

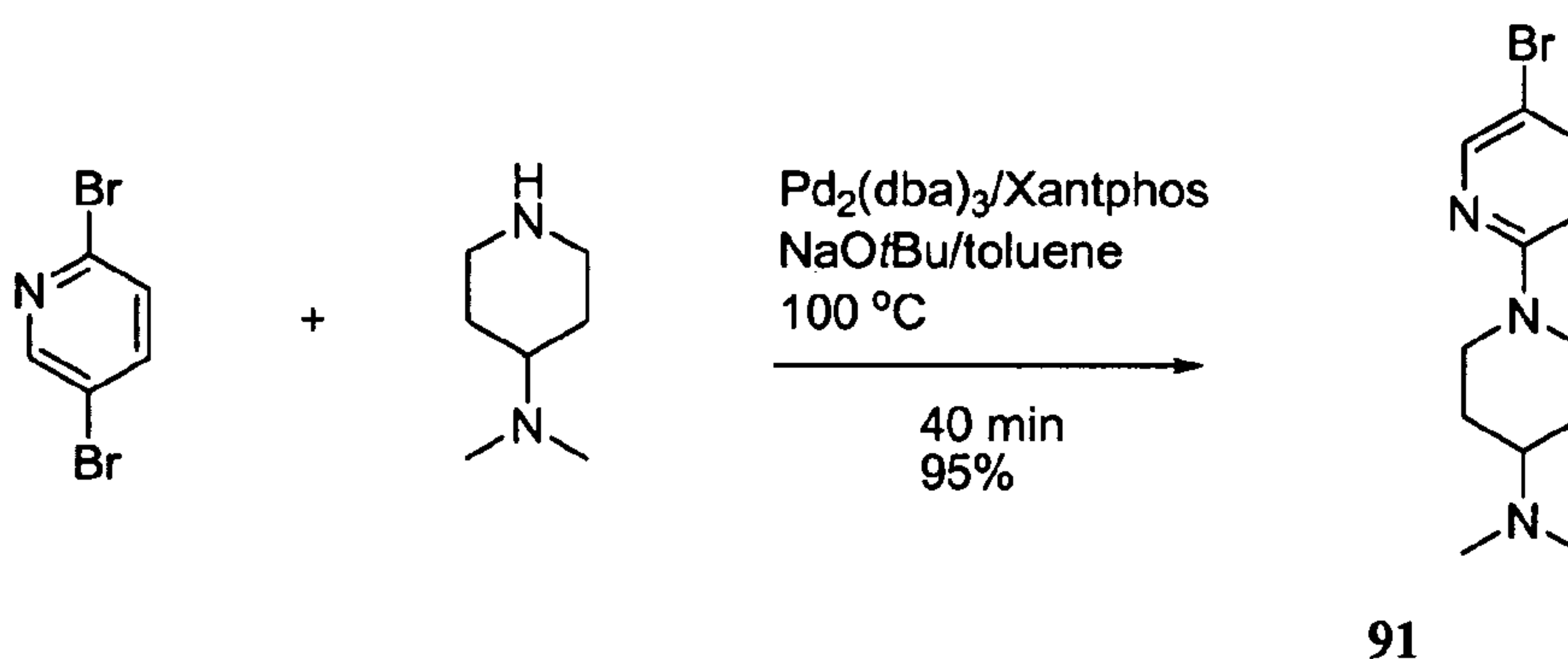
**9-(4-methylcyclohexyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound 89 was prepared according to the methods described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.19 (1 H, s), 8.97(1H,s), 8.39(1 H, d), 8.29(0.5H,d), 8.24 (0.5H, d), 8.05 (1 H, m), 7.53 (1 H, m), 3.20 (4 H, m), 3.07 (4 H, m), 2.80 (1 H, m), 2.60(1H, m), 2.10(1H, b), 1.97 (3 H, b), 1.75 (3 H, m), 1.40 (1 H, m), 1.25(1.5H, d), 1.08 (1.5H, d) ppm; LCMS-ESI (POS), M/Z, M+1: Found 443.2, calculated 443.2.



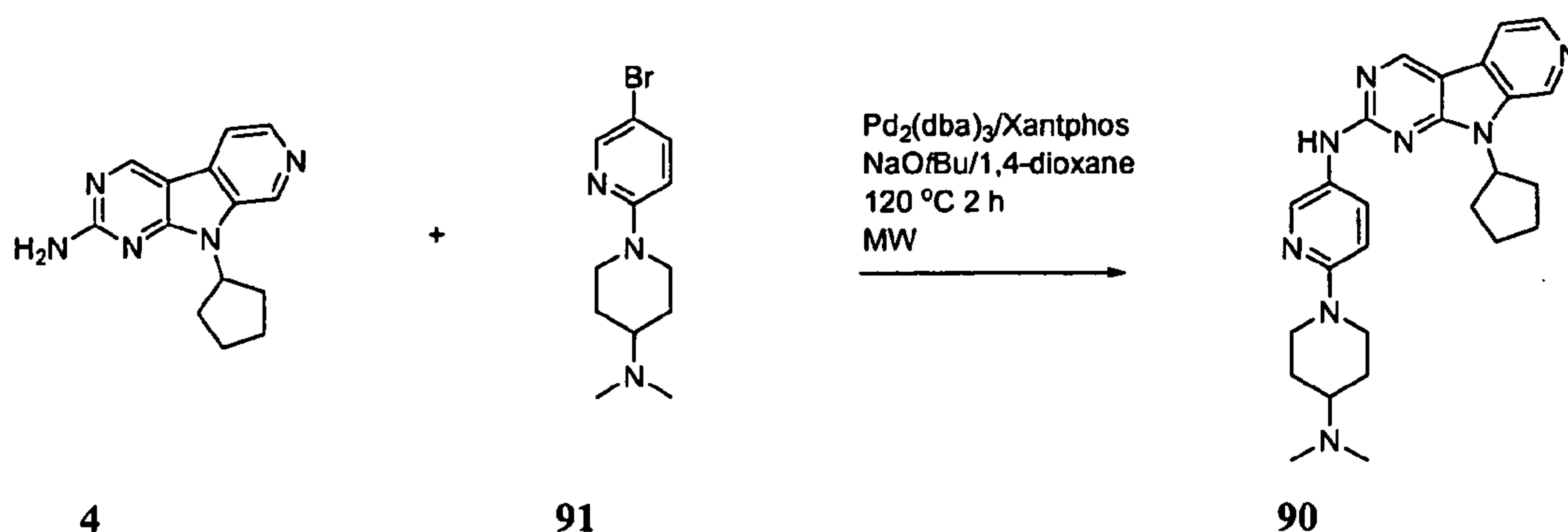
**EXAMPLE 56****90**

**9-cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



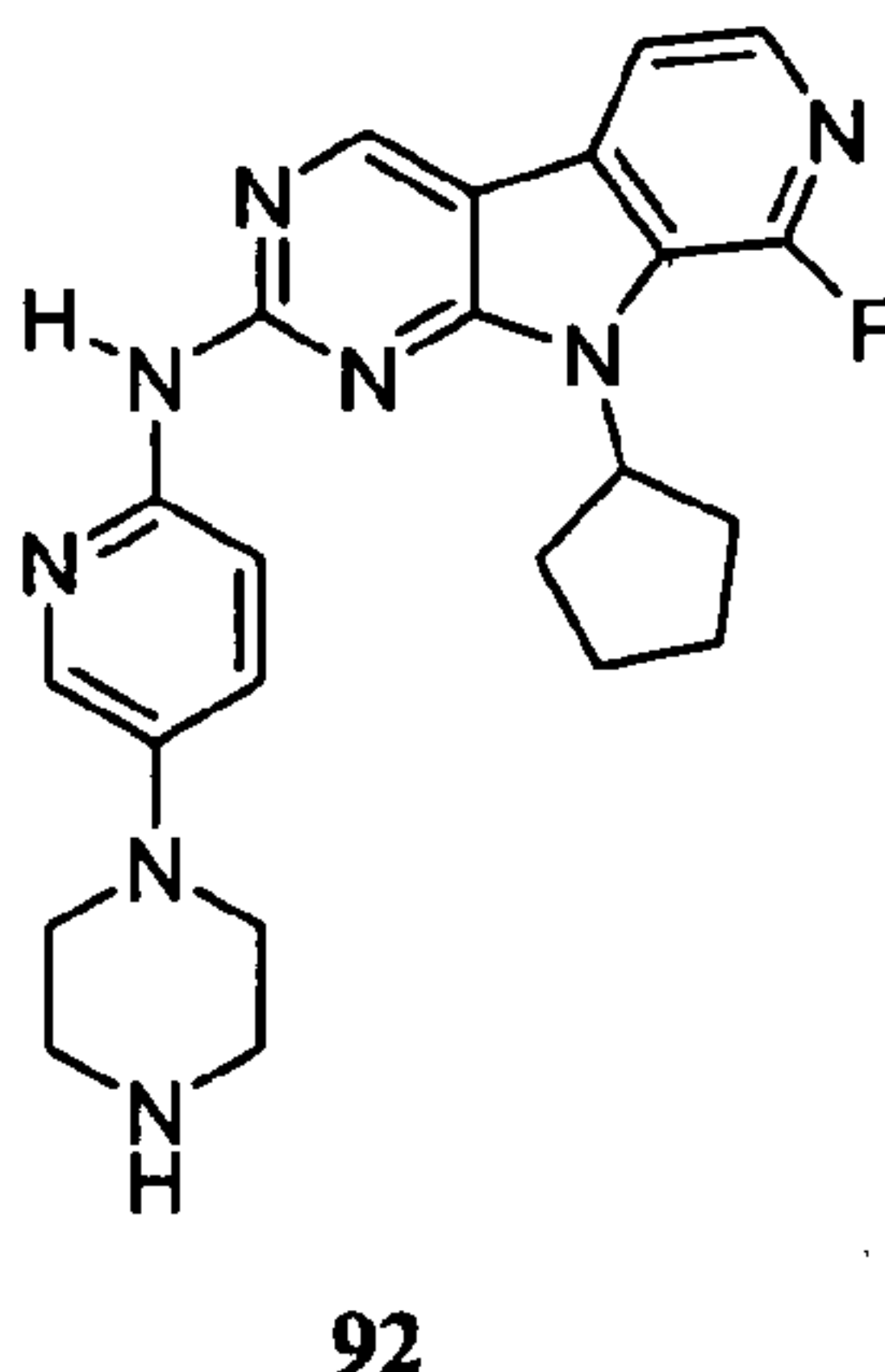
**1-(5-bromopyridin-2-yl)-N,N-dimethylpiperidin-4-amine (91):** To a 100 mL single-necked round-bottom flask were placed 2,5-dibromopyridine (2 g, 8 mmol), 4-(dimethylamino)piperidine (1 ml, 8 mmol), tris(dibenzylideneacetone)dipalladium (o) (0.07 g, 0.08 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.1 g, 0.2 mmol), and sodium *t*-butoxide (1 g, 12 mmol). The flask was subjected to 3 cycles of evacuation and back-filling with  $\text{N}_2$  before toluene (40 mL) was introduced under  $\text{N}_2$ . The resulting mixture was stirred at a preheated oil bath at  $100\text{ }^\circ\text{C}$  for 40 min. The crude mixture was poured into ice and 4 N NaOH aqueous solution and extracted with ethyl acetate (2 X). The combine organics were dried over sodium sulfate and concentrated in vacuo to give 2.7 g crude product. Trituration with ethyl acetate/hexanes gave highly pure 1-(5-bromopyridin-2-yl)-N,N-dimethylpiperidin-4-amine (**91**) (1.9 g, 95%)  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.18 (1 H, d,  $J = 2.3$  Hz), 7.52 (1 H, dd,  $J = 9.0, 2.7$  Hz), 6.58 (1 H, d,  $J = 9.0$  Hz), 4.30 (2 H, d,  $J = 12.9$  Hz), 2.79 - 2.91 (2 H, m), 2.49 (1 H, br. s.), 2.37 (6 H, s), 1.97 (2 H, d,  $J = 12.5$  Hz), 1.45 - 1.60 (2 H, m) ppm.





**9-cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (90):** To a microwave reaction vessel were placed compound **4** (30 mg, 118  $\mu$ mol), compound **91** (50 mg, 178  $\mu$ mol), tris(dibenzylideneacetone)dipalladium (0) (5.4 mg, 5.9  $\mu$ mol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (8.6 mg, 15  $\mu$ mol), and sodium *tert*-butoxide (34 mg, 355  $\mu$ mol). 1,4-dioxane (4 mL) was added and the vessel was purged with N<sub>2</sub> for 3 min, then capped and subjected to microwave irradiation for 2 h at 120°C. After removal of the volatiles, the residue was dissolved in methanol and filtered. The filtrate was subjected to reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 5 to 40%) to give ~ 15 mg of compound **90** as a TFA salt. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  9.43 (1 H, s), 9.16 (1 H, s), 8.65 (1 H, d, *J*=2.3 Hz), 8.48 - 8.57 (2 H, m), 8.12 (1 H, dd, *J*=9.4, 2.3 Hz), 7.21 (1 H, d, *J*=9.4 Hz), 5.29 - 5.47 (1 H, m), 4.45 (2 H, d, *J*=13.7 Hz), 3.49 - 3.58 (1 H, m), 3.03 - 3.18 (2 H, m), 2.92 (6 H, s), 2.37 - 2.54 (2 H, m), 2.04 - 2.29 (6 H, m), 1.76 - 1.93 (4 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 457.3, Calculated 457.2.

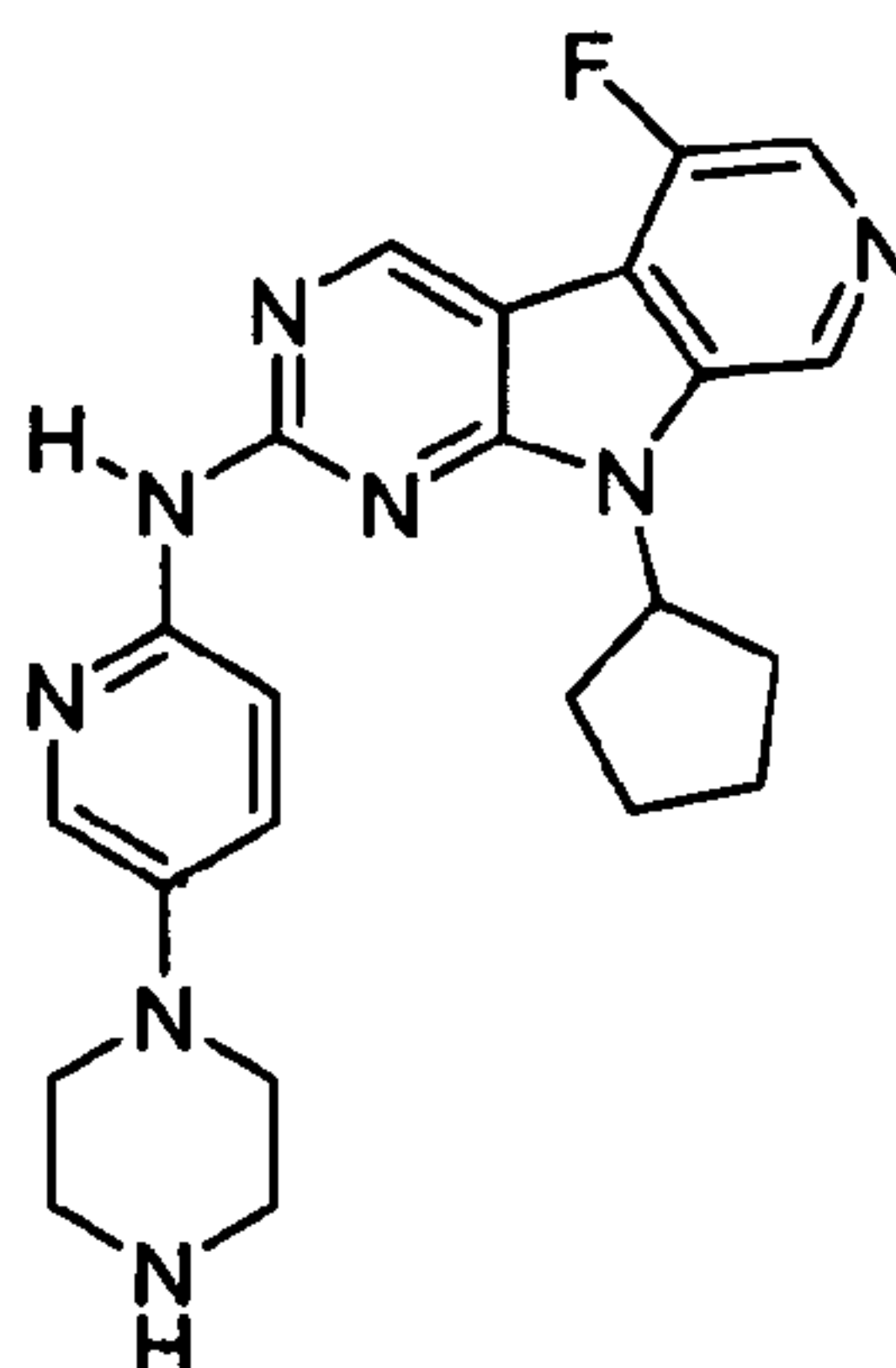
#### EXAMPLE 57



#### **9-Cyclopentyl-8-fluoro-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

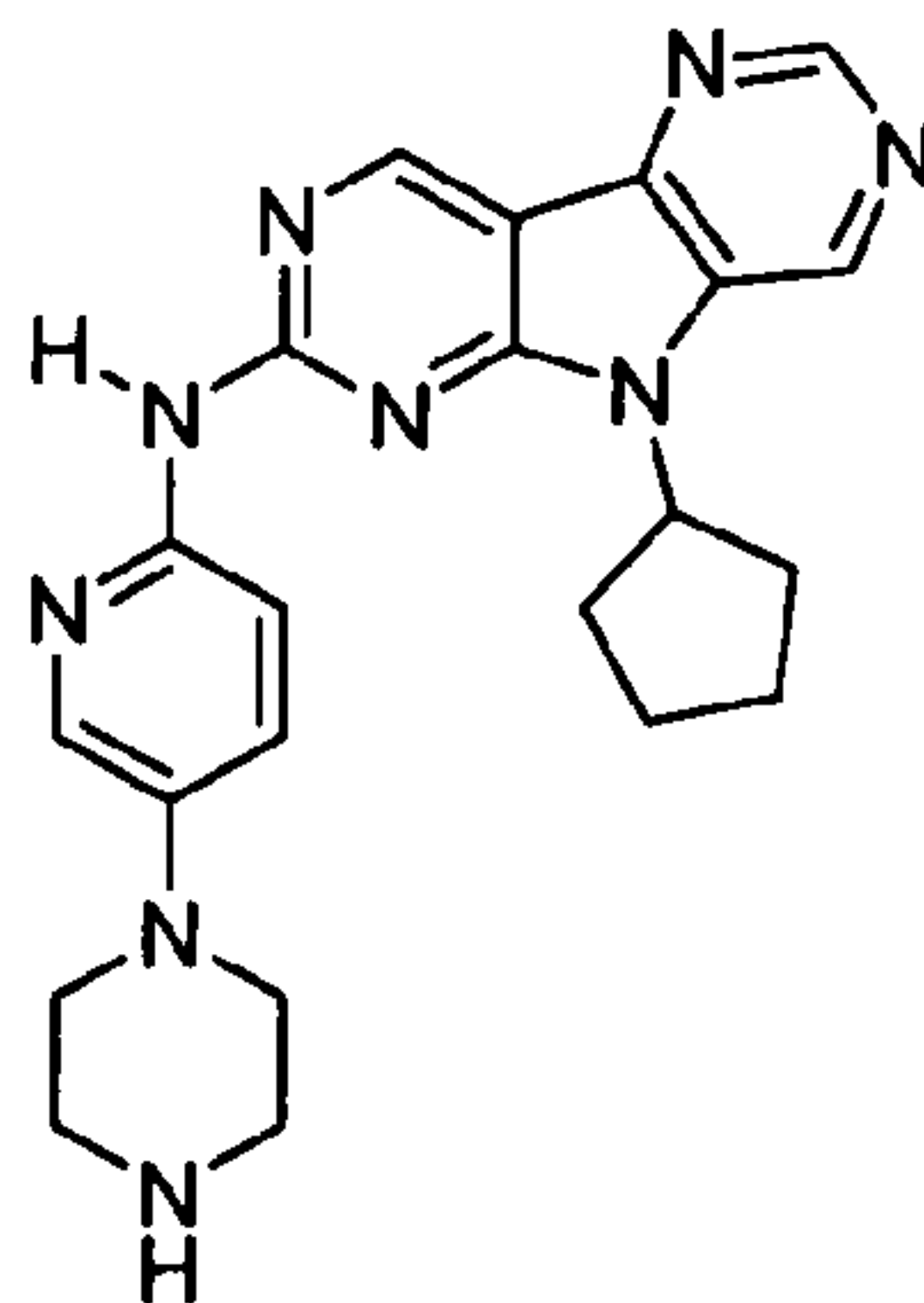
Compound **92** was prepared using chemistry similar to that described in example 22. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  9.46 (1 H, s), 8.10 - 8.15 (3 H, m), 8.05 (1 H, d, *J* = 2.9 Hz), 7.64 (1 H, d, *J* = 9.5 Hz), 5.20 (1 H, m), 3.51 - 3.57 (4 H, m), 3.42 - 3.51 (4 H, m), 2.40-2.50 (2 H, m), 2.10-2.25 (4 H, m), 1.80-1.90 (2H, m) ppm, LCMS-ESI (POS), M/Z, M+1: Found 433.1, Calculated 433.2.



**EXAMPLE 58****93**

**9-Cyclopentyl-5-fluoro-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

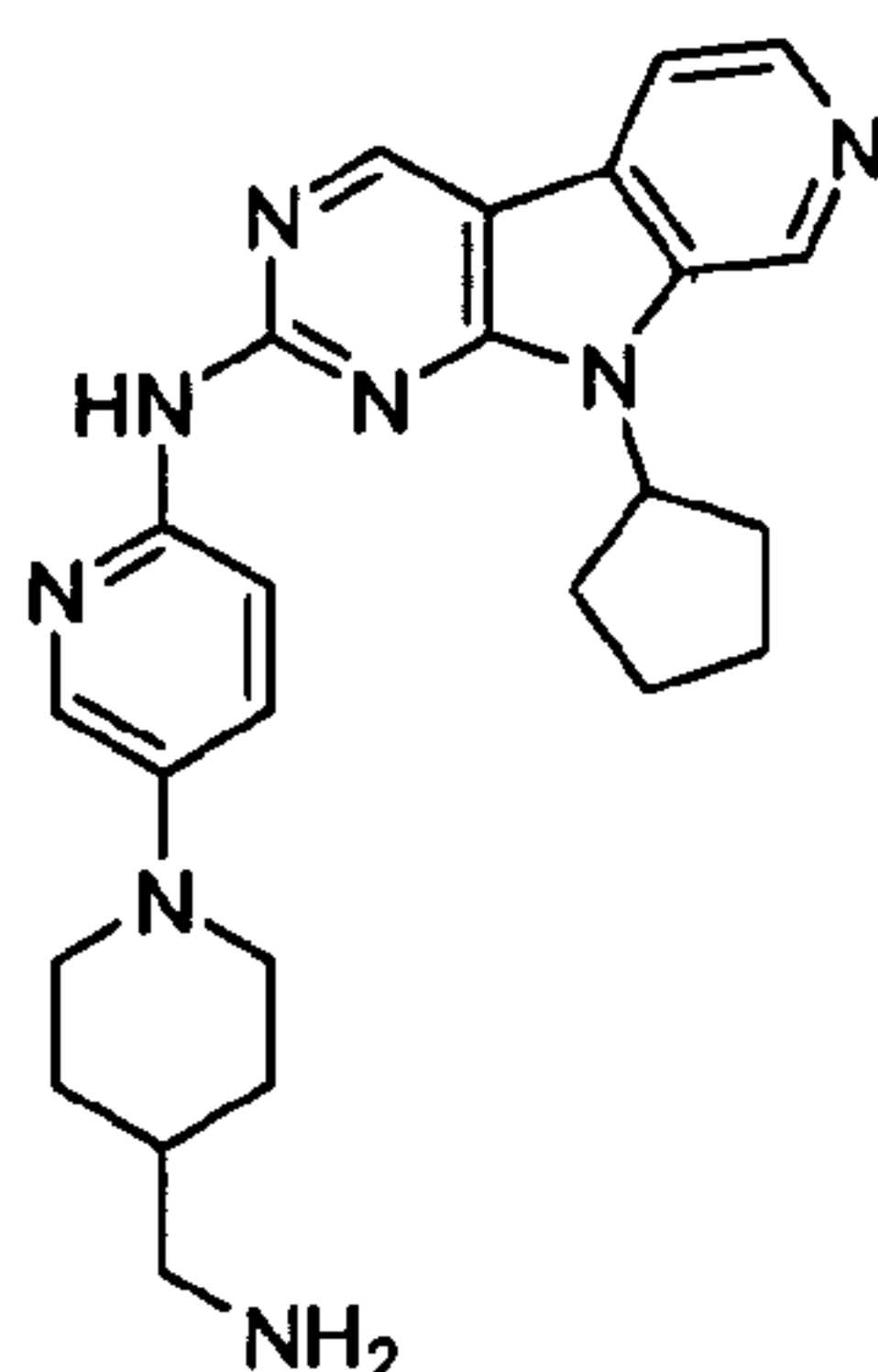
Compound **93** was prepared using chemistry similar to that described in example 22. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.10 (1 H, s), 8.75 (1 H, s), 8.28 (1 H, s), 8.23 (1 H, d, J = 9.0 Hz), 8.02 (1 H, d, J = 2.9 Hz), 7.46-7.49 (1 H, dd, J = 9.0, 2.6 Hz), 5.41 (1 H, m), 3.33 (4 H, m), 3.19 (1 H, m), 2.44-2.49 (2 H, m), 2.11-2.24 (4 H, m), 1.87-1.90 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 433.1, Calculated 433.2.

**EXAMPLE 59****94**

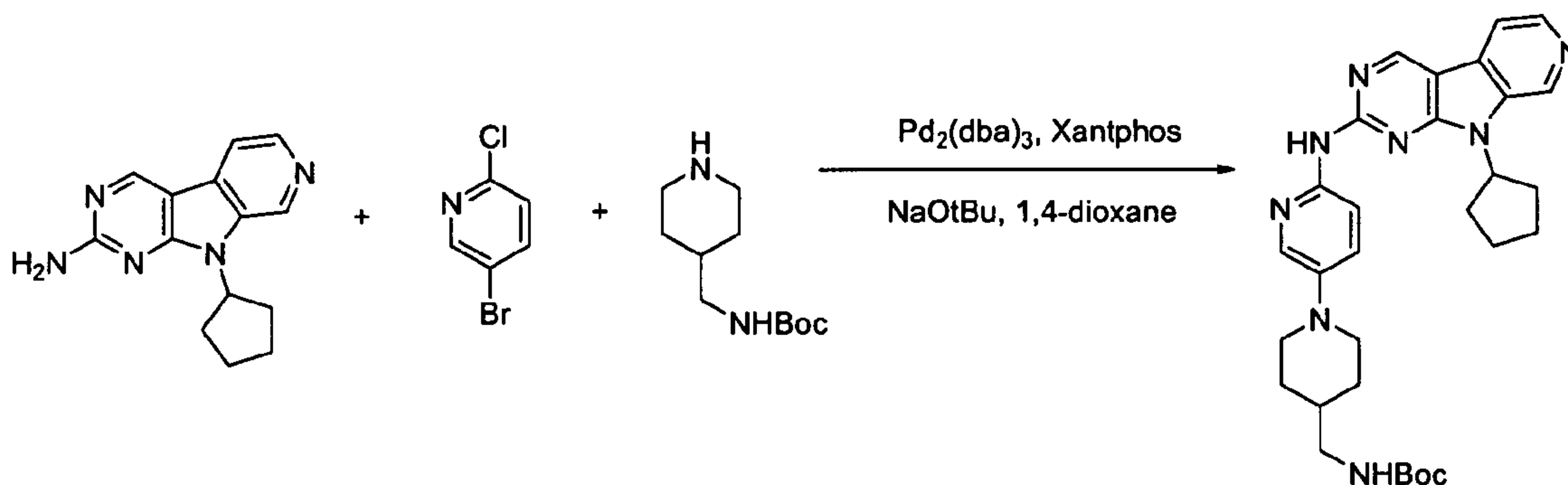
**5-Cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrimido[4',5':4,5]pyrrolo[2,3-d]pyrimidin-7-amine**

Compound **94** was prepared using chemistry similar to that described in example 22. <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 9.21 (1 H, s), 8.96 (1 H, s), 8.83 (1 H, s), 8.32 (3 H, d, J=9.0 Hz), 7.98 (2 H, d, J=2.2 Hz), 7.31 (2 H, dd, J=9.0, 2.7 Hz), 5.23 - 5.31 (1 H, m), 3.05 (4 H, m), 2.95 (4 H, m), 2.47 (1 H, s), 2.28 (2 H, m), 2.10 - 2.20 (2 H, m), 1.98 - 2.08 (2 H, m), 1.70 - 1.84 (2 H, m) ppm, LCMS-ESI (POS), M/Z, M+1: Found 416.2, Calculated 416.2.



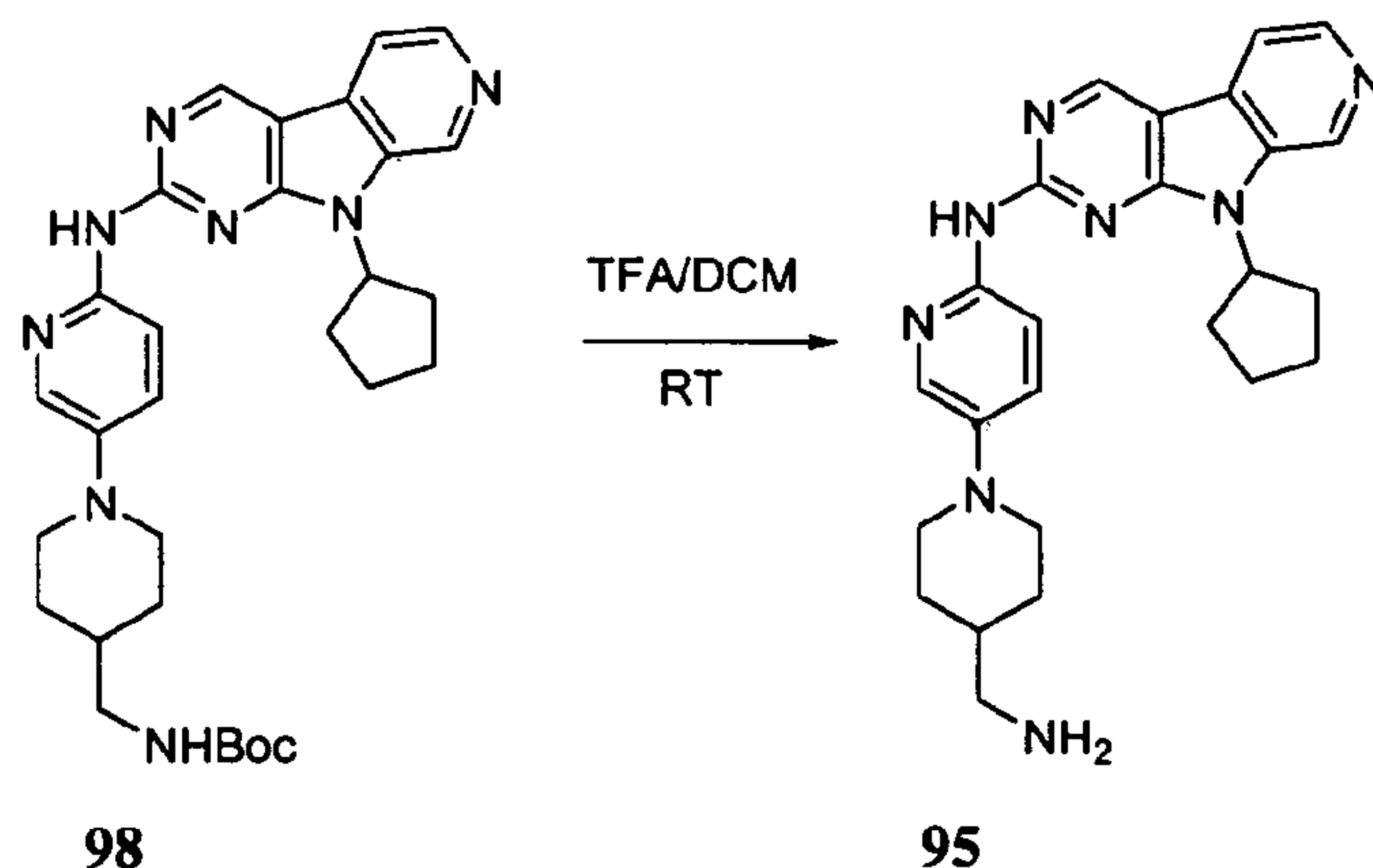
**EXAMPLE 60****95**

**4-Aminomethyl-1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-piperidine**

**4****97****98**

**1,1-Dimethylethyl 1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinemethyl carboxylate (98):** A mixture of 5-bromo-2-chloropyridine (0.019 g, 0.099 mmol), *tert*-butyl piperidin-4-ylmethylcarbamate (97) (0.024 g, 0.099 mmol), Xantphos (0.0086 g, 0.015 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.0068 g, 0.0074 mmol), and sodium *tert*-butoxide (0.014 g, 0.15 mmol) in dioxane was purged with nitrogen gas for 1 min. The reaction was heated at 80°C for 2 hours and then cooled to room temperature. Compound (4) (0.0250 g, 0.099 mmol), Xantphos (0.0086 g, 0.015 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.0068 g, 0.0074 mmol) and sodium *tert*-butoxide (0.014 g, 0.15 mmol) were added. The mixture was purged again with nitrogen again for 1 min. And heated at 100°C for 1.5~2 hours and then cooled to room temperature. The solvent was removed using Gene Vac. The residue was sonicated with 2mL methanol. The solid was removed by filtration, washed with 2x1mL methanol. The combined solution was purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide compound **98** as a TFA salt. LCMS-ESI (POS), M/Z, M+1: 543.2





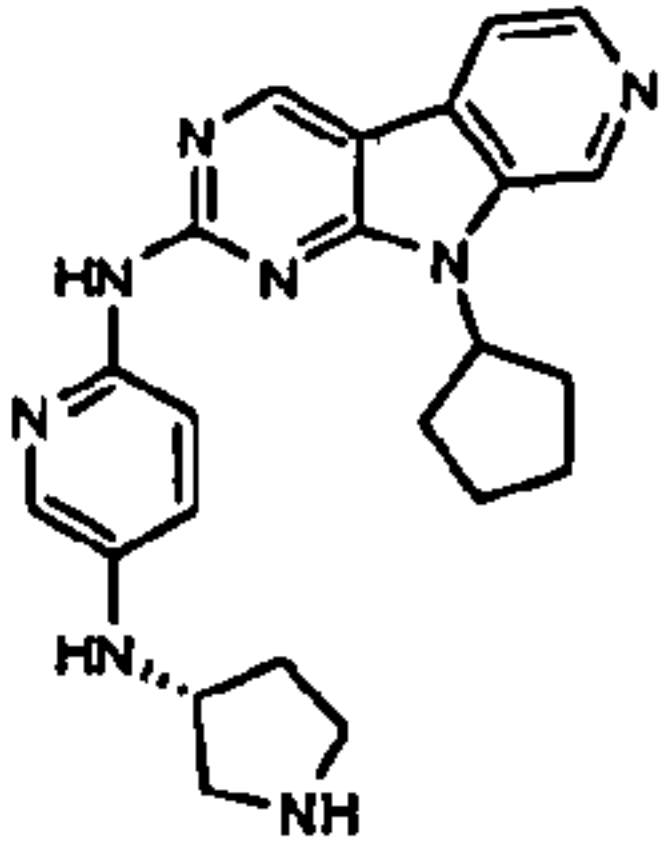
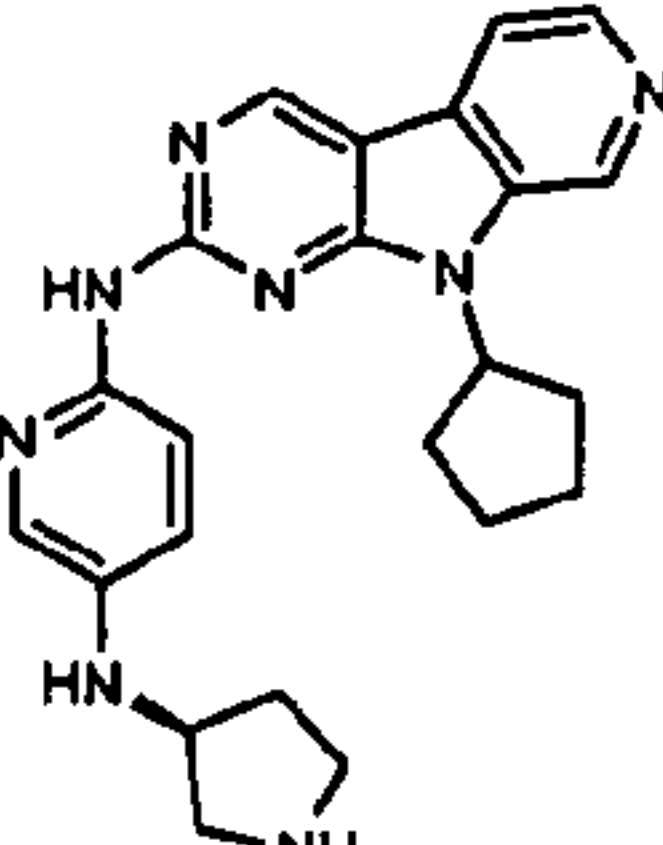
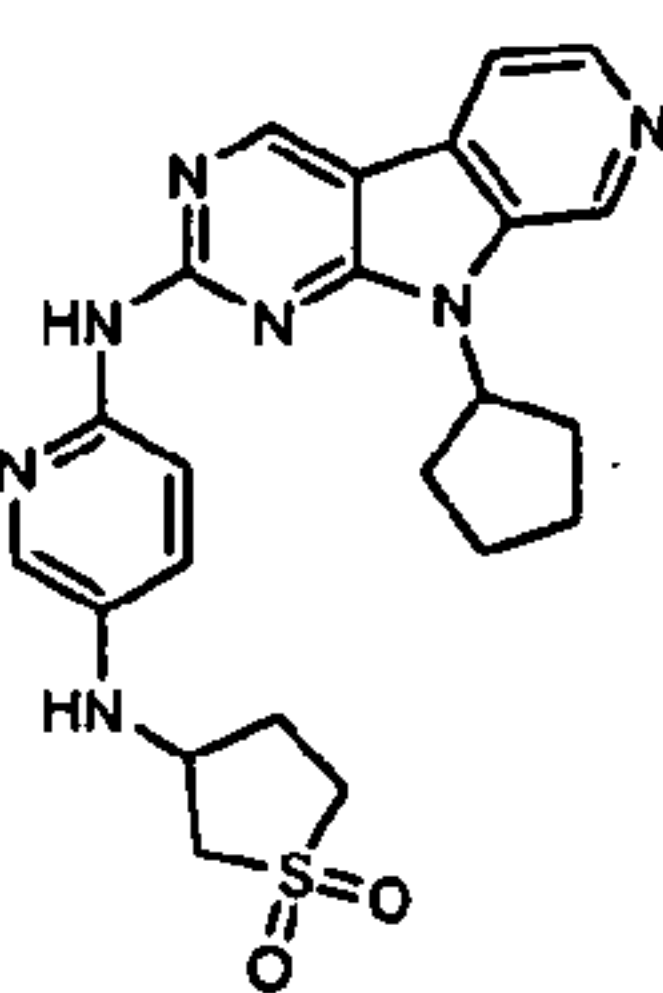
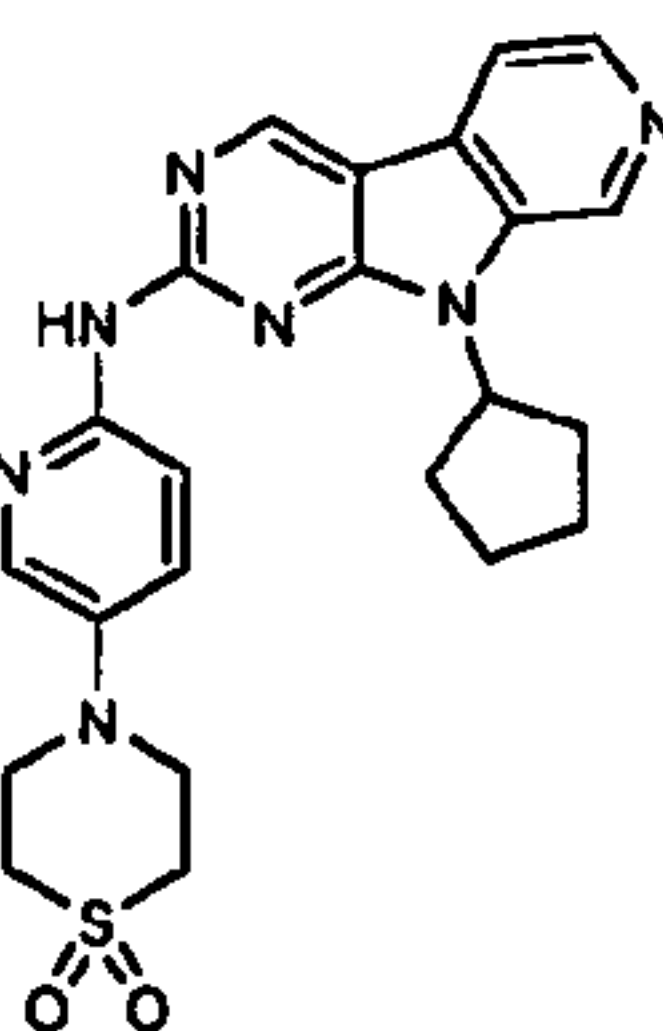
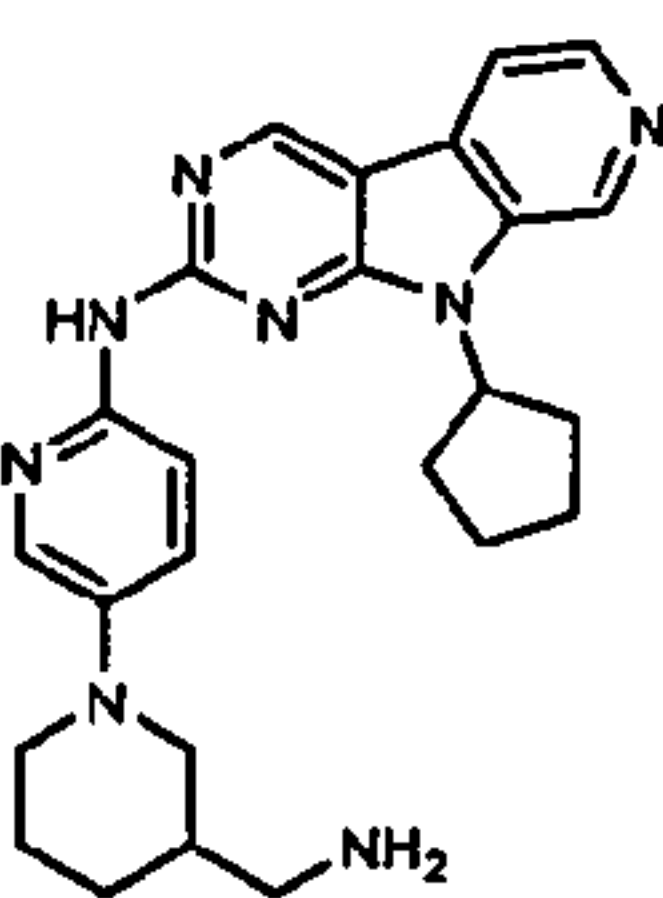
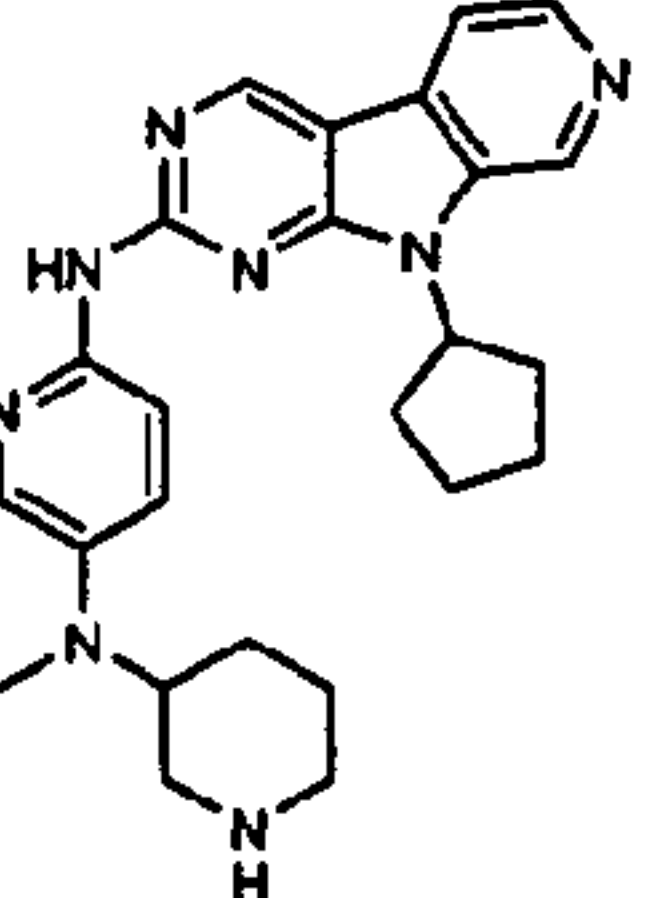
**4-Aminomethyl-1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-piperidine (95):** Compound **98** was treated with 1:1 TFA/DCM (2mL) at room temperature for an hour. The solvent was evaporated. The residue was re-dissolved in 4ml methanol and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide compound **95** as a TFA salt. LCMS retention time (minutes): 0.708. LCMS-ESI (POS), M/Z, M+1: 443.2

Examples 61-100 (listed in Table 1) were prepared using conditions as described for example 60 with deprotection when necessary, replacing 5-bromo-2-chloropyridine and **97** with proper chemical reagents. The reaction conditions such as temperature and reaction time were the same unless indicated in Table 1. All LCMS data was obtained using Agilent 1100 series LC/MSD, column: CAPCELL UG120 (3um, 4.6 mm I.D. x 50 mm), solvent system: water-acetonitrile 95:5 with 0.1% formic acid.

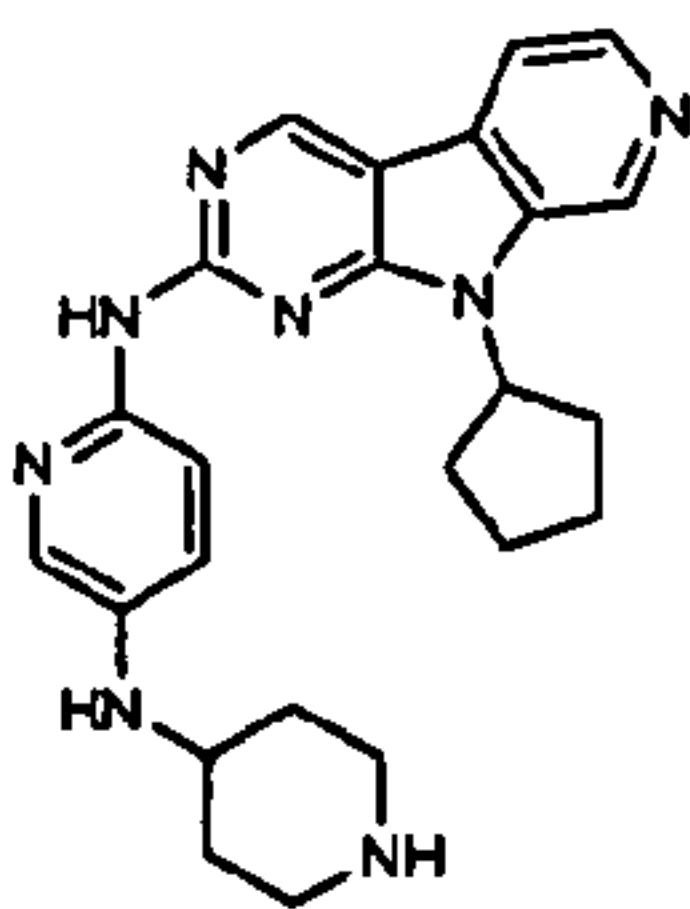
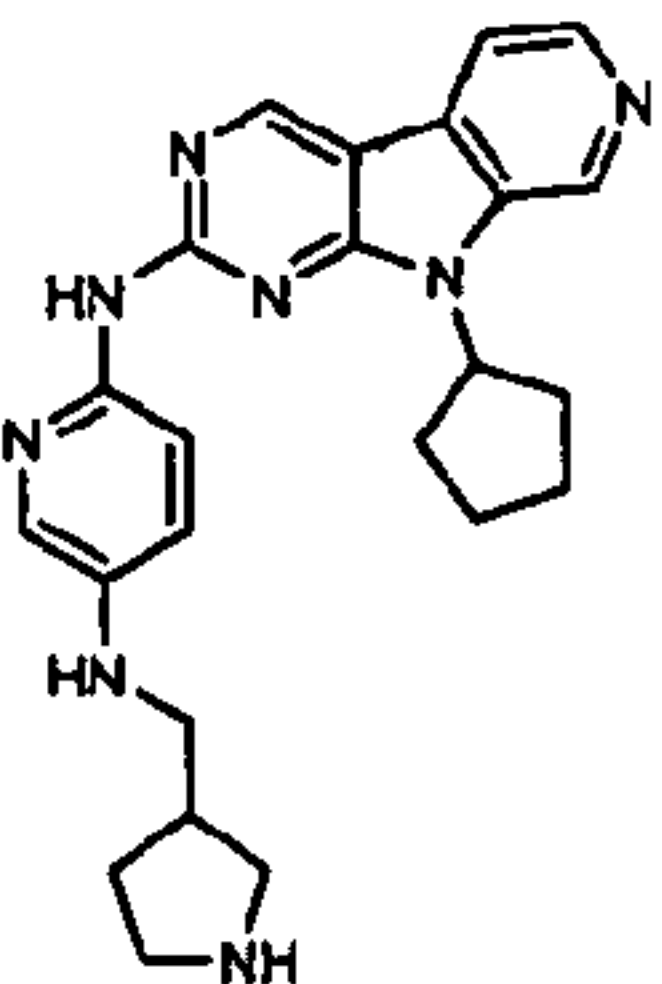
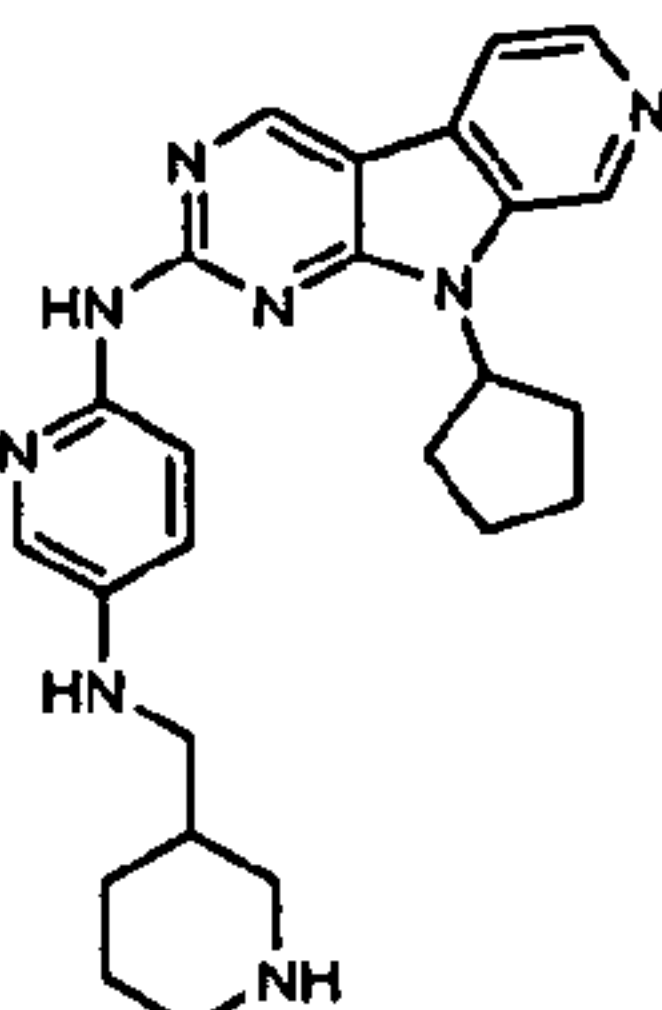
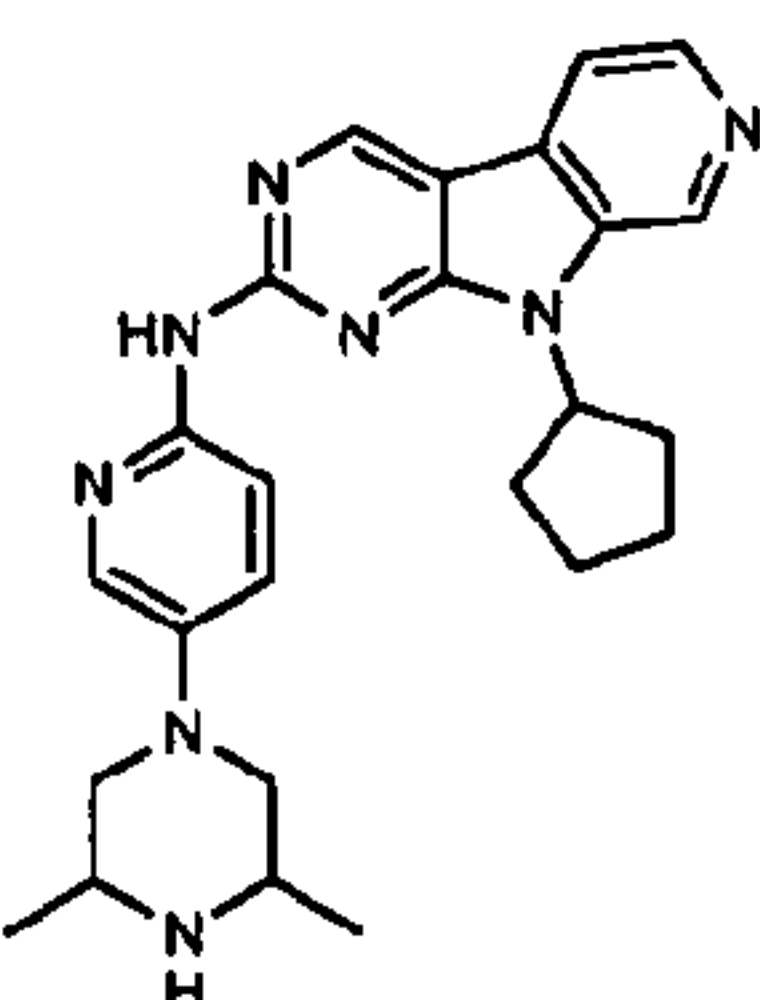
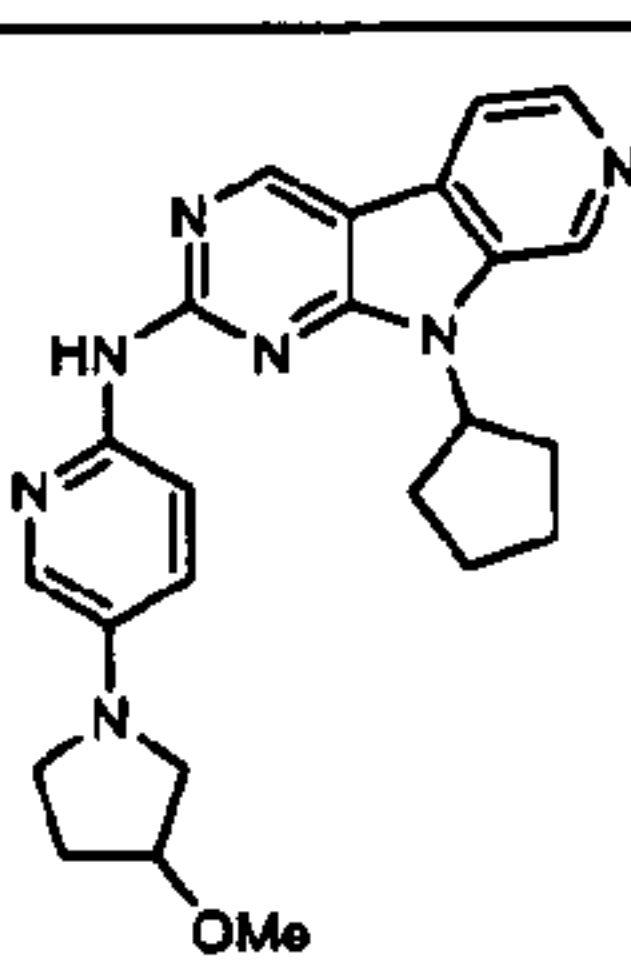
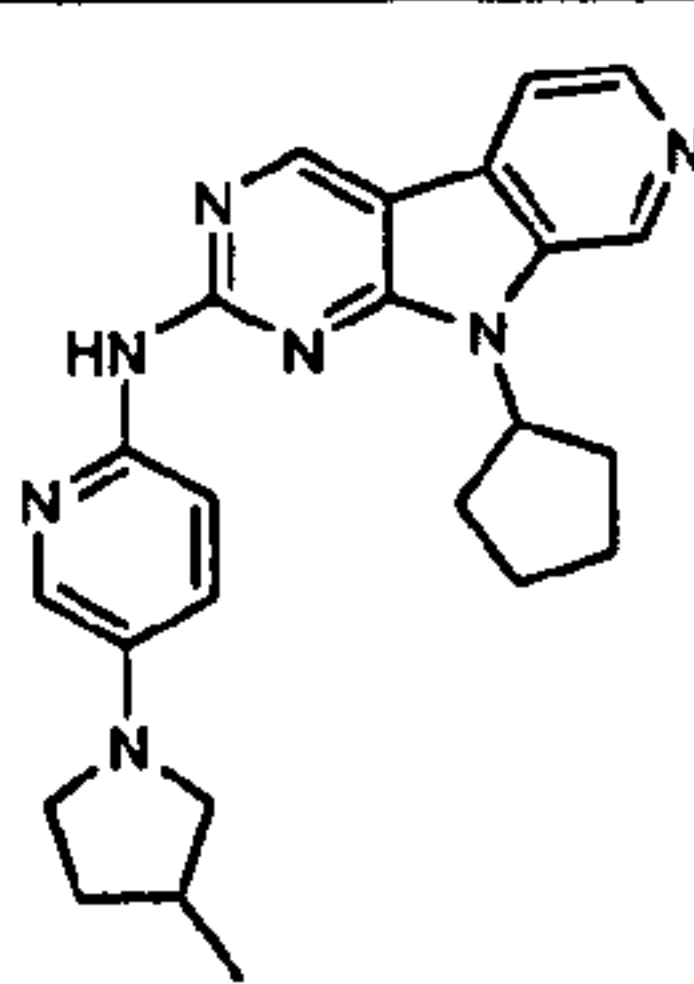
Table 1

| Example # | Structure | Reaction conditions | LSMS retention time (minutes) | LCMS -ESI (M+1) |
|-----------|-----------|---------------------|-------------------------------|-----------------|
| 61        |           |                     | 0.701                         | 429.2           |
| 62        |           |                     | 0.704                         | 429.2           |

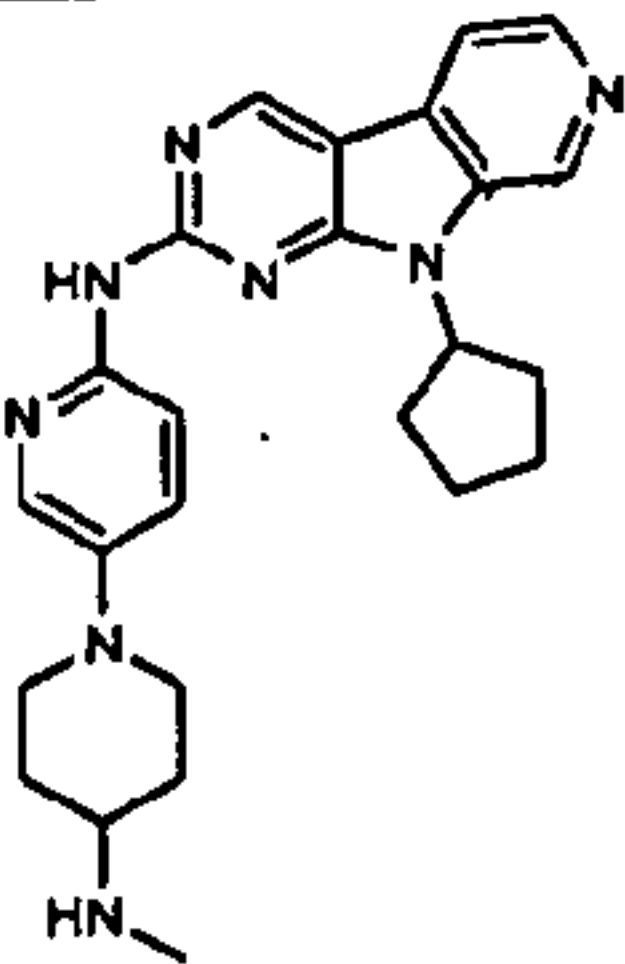
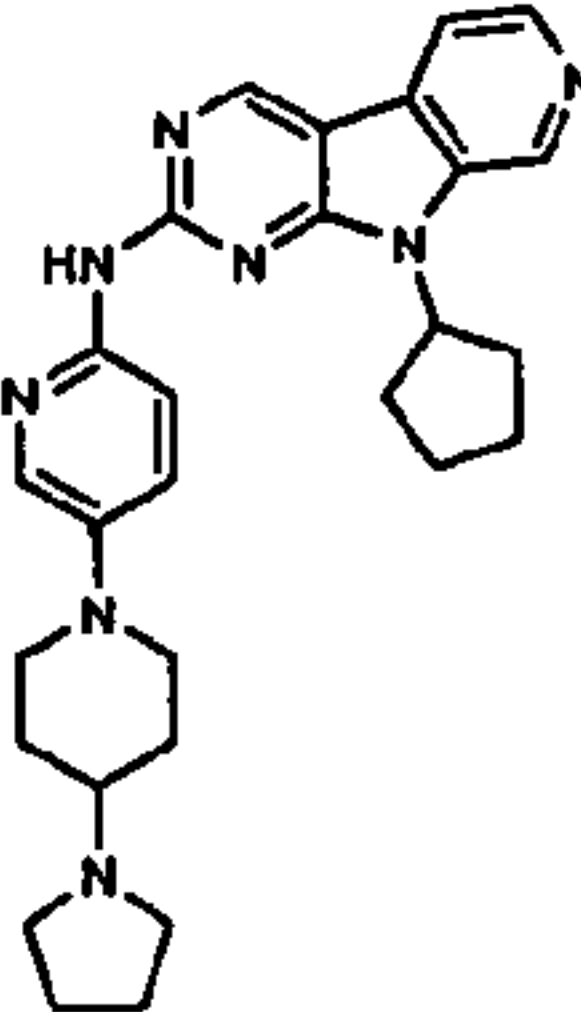
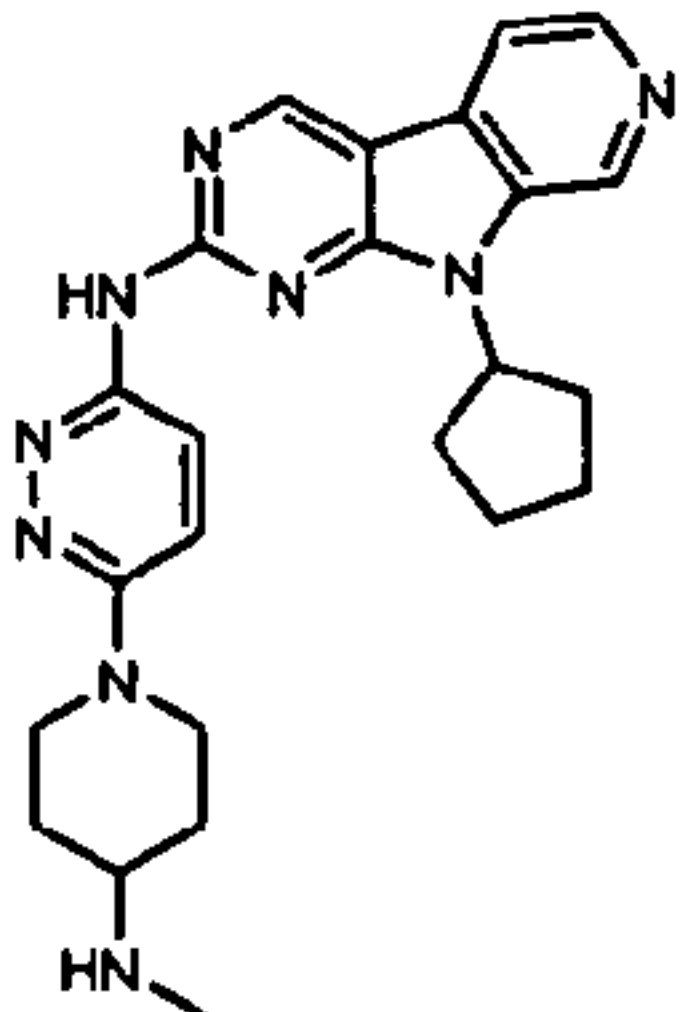
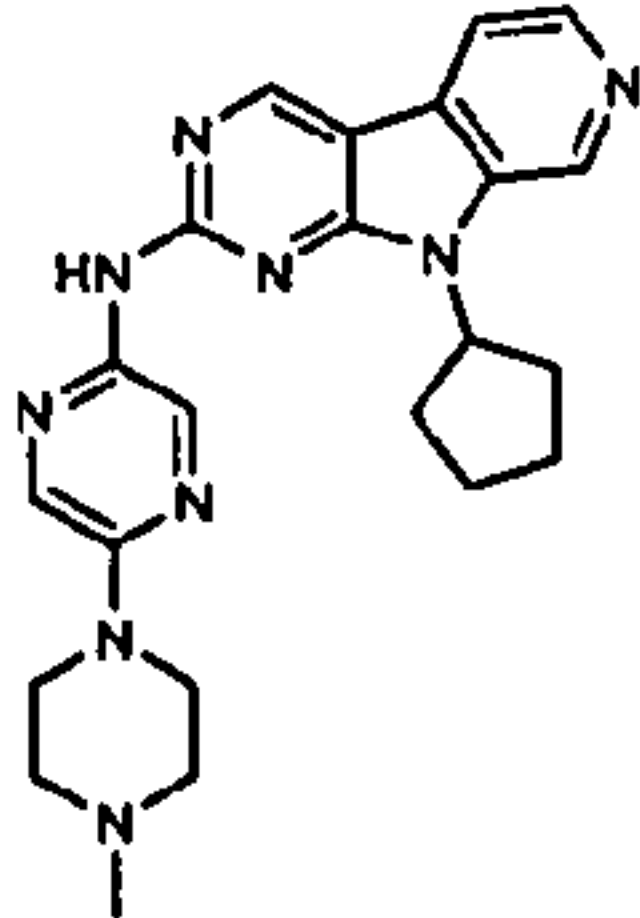
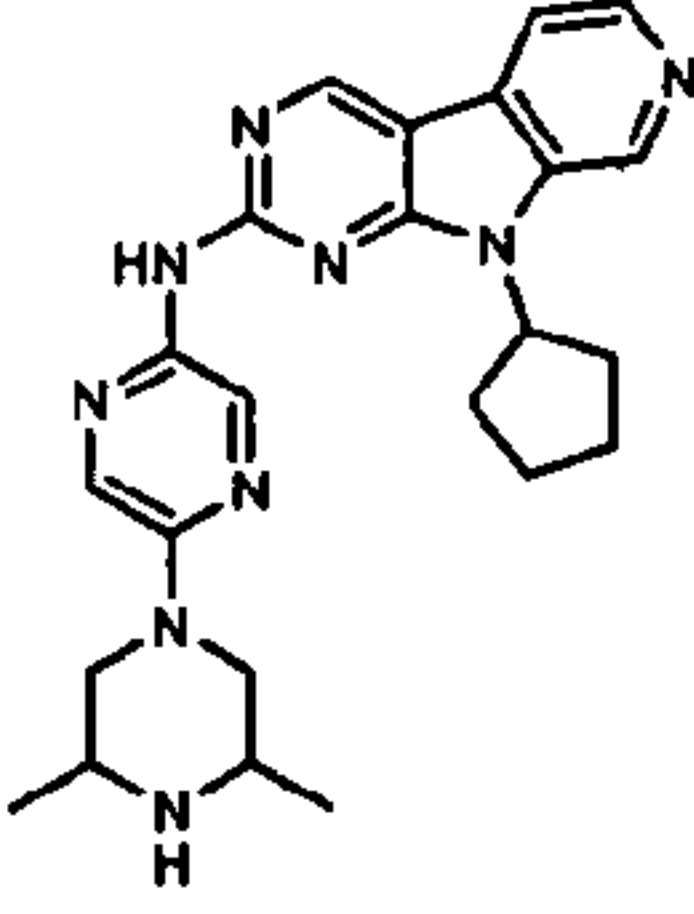
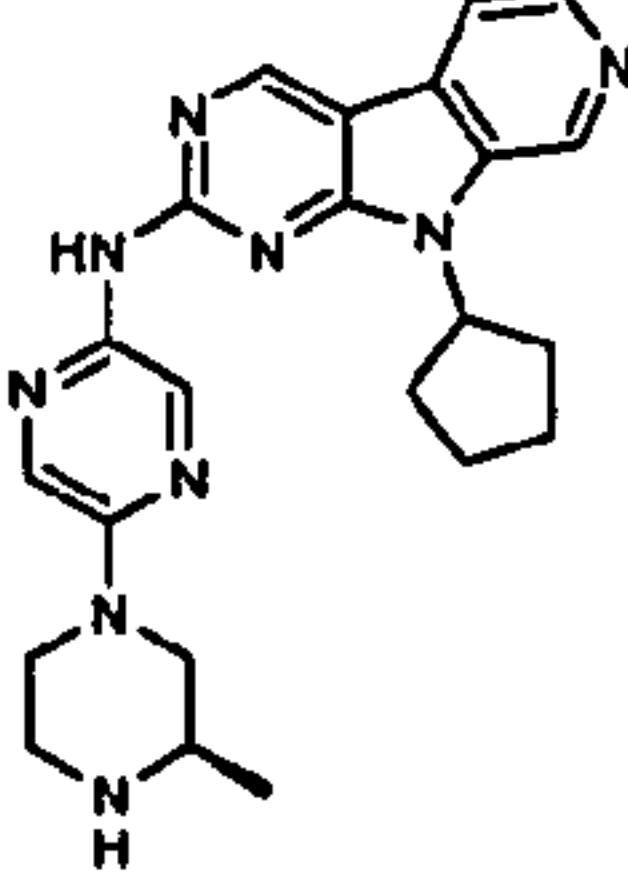


| Example # | Structure                                                                           | Reaction conditions | LSMS retention time (minutes) | LCMS -ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|---------------------|-------------------------------|-----------------|
| 63        |    |                     | 0.660                         | 415.1           |
| 64        |   |                     | 0.660                         | 415.1           |
| 65        |  |                     | 0.842                         | 464.2           |
| 66        |  |                     | 0.878                         | 464.2           |
| 67        |  |                     | 0.753                         | 443.2           |
| 68        |  |                     | 0.742                         | 443.2           |

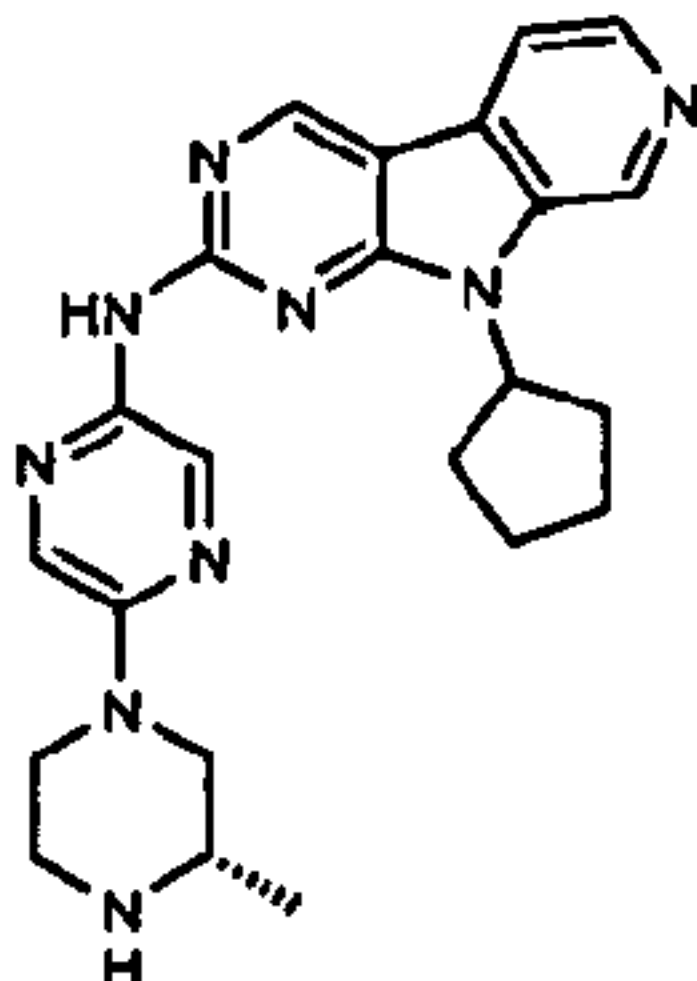
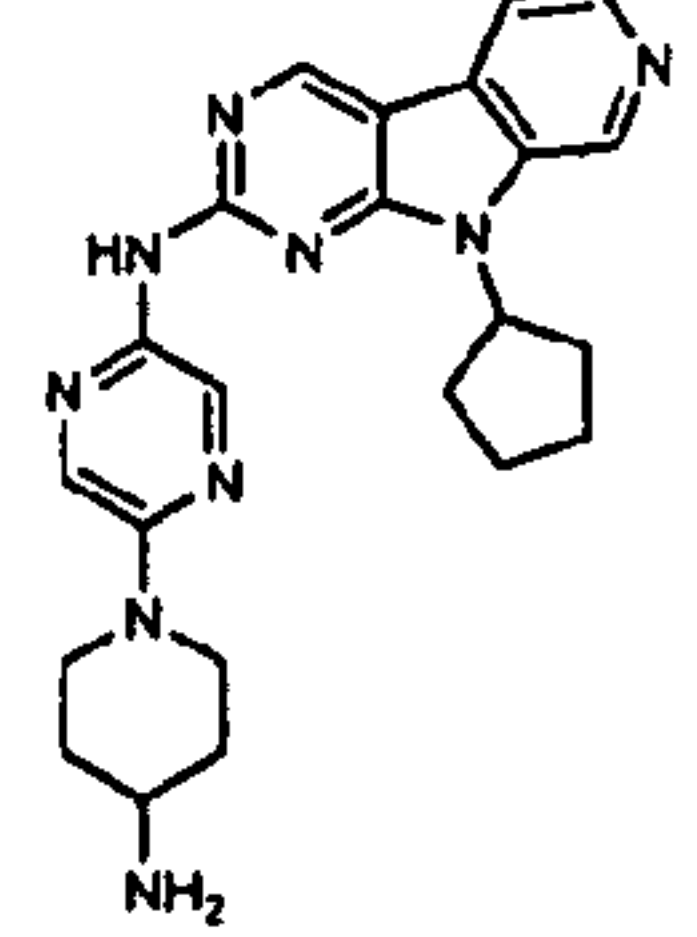
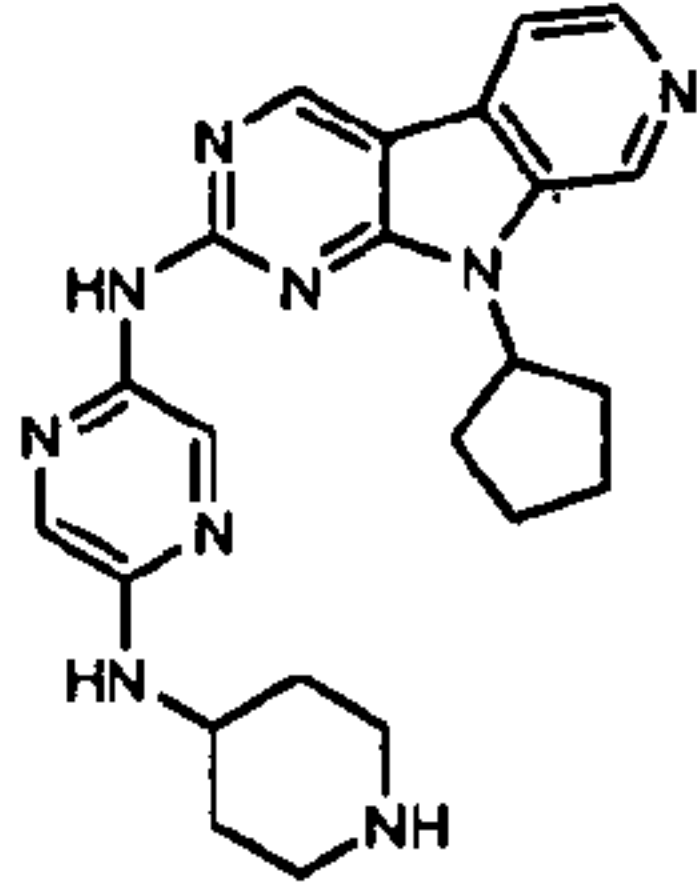
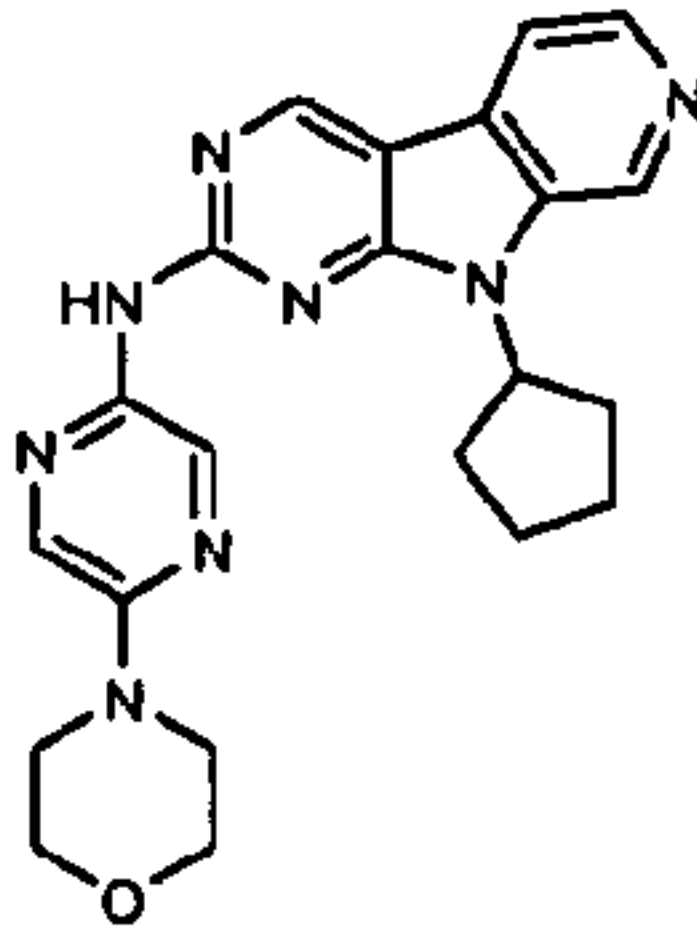
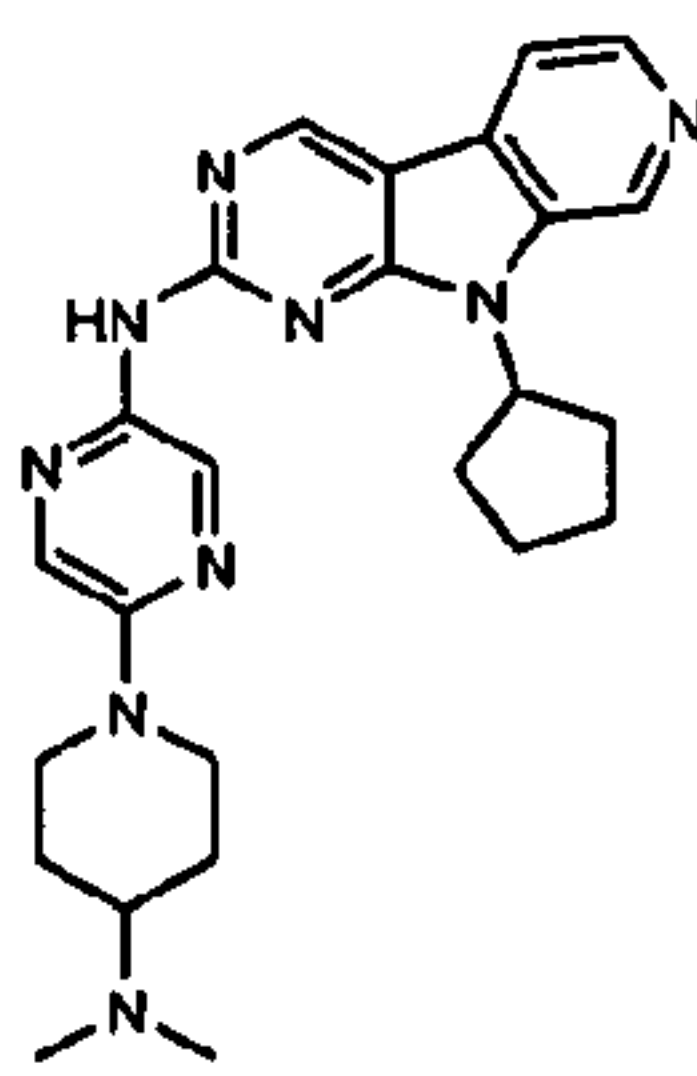
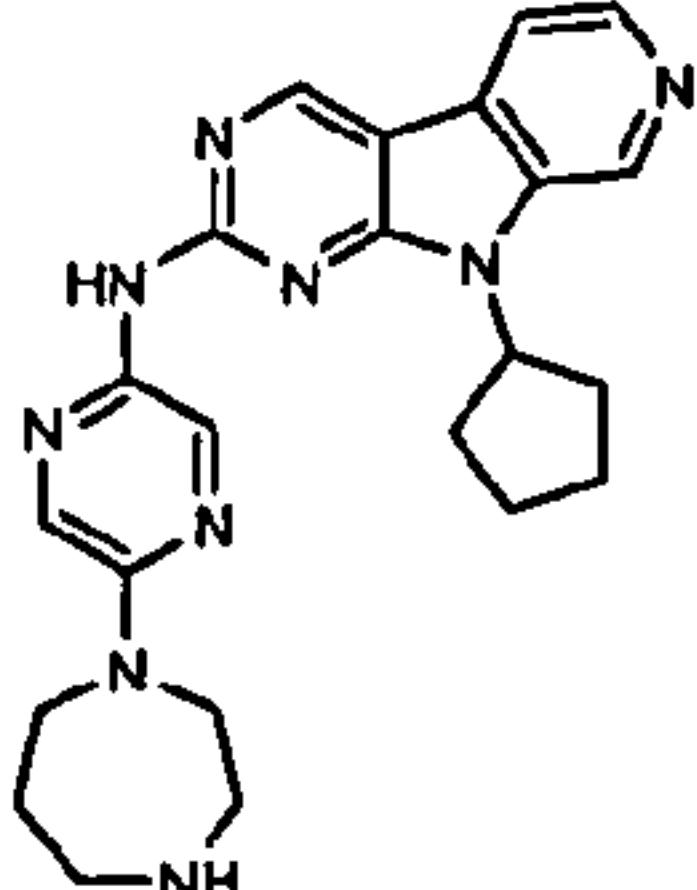


| Example # | Structure                                                                           | Reaction conditions                              | LSMS retention time (minutes) | LCMS -ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------|-----------------|
| 69        |    |                                                  | 0.672                         | 429.2           |
| 70        |   |                                                  | 0.718                         | 429.2           |
| 71        |  |                                                  | 0.735                         | 443.2           |
| 72        |  | Step1. 70°C,<br>2hour;<br>Step2. 90°C,<br>2hour. | 0.696                         | 443.2           |
| 73        |  |                                                  | 0.942                         | 430.1           |
| 74        |  |                                                  | 1.20                          | 414.2           |

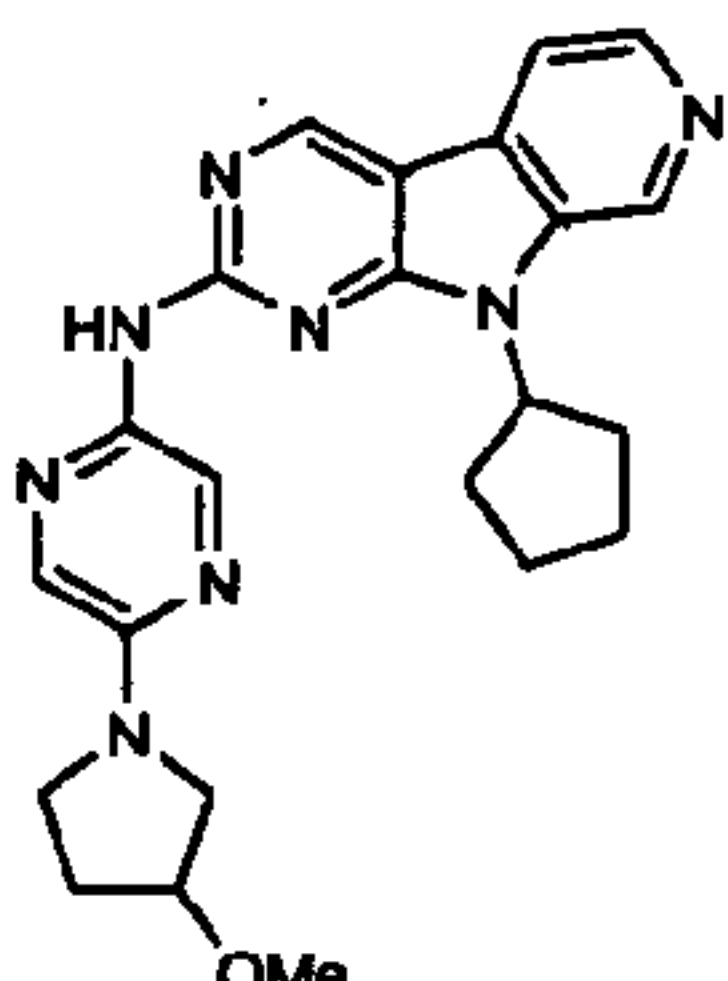
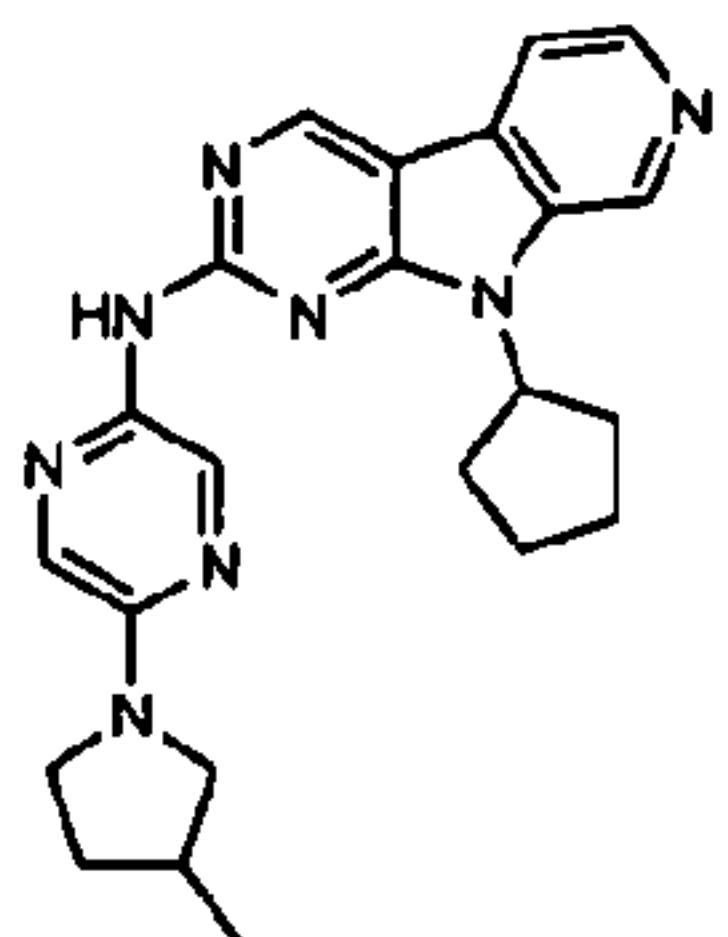
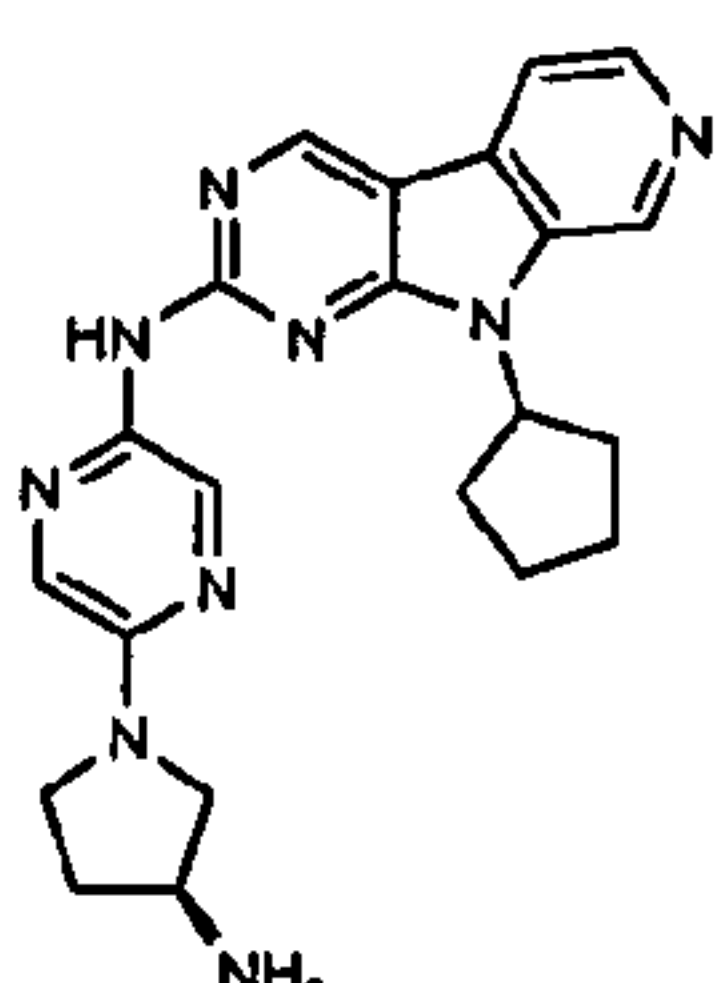
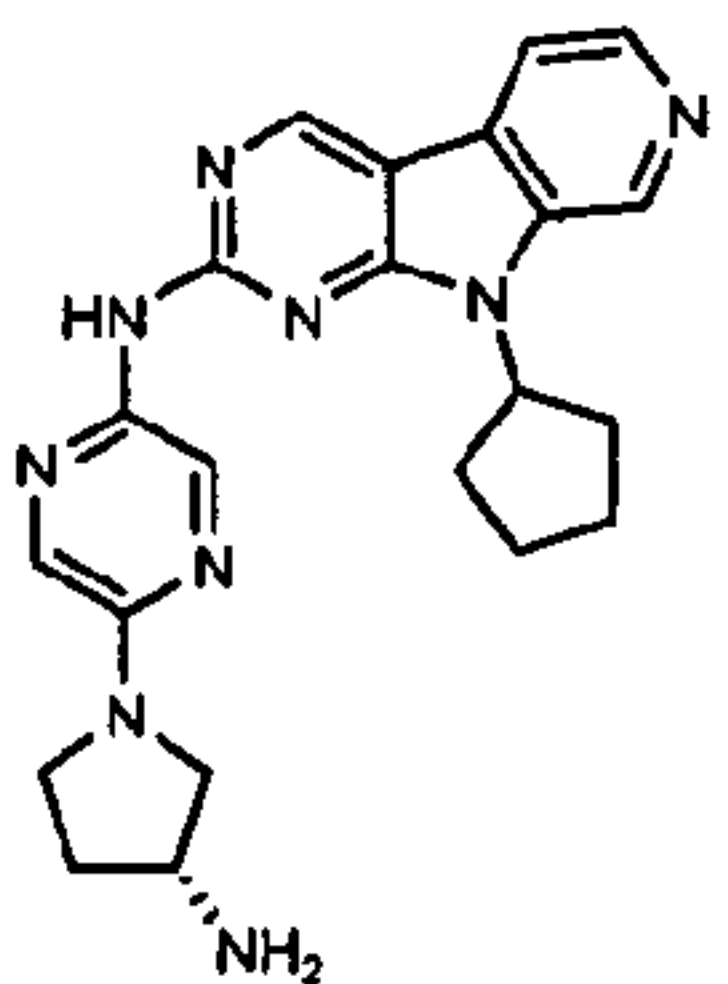
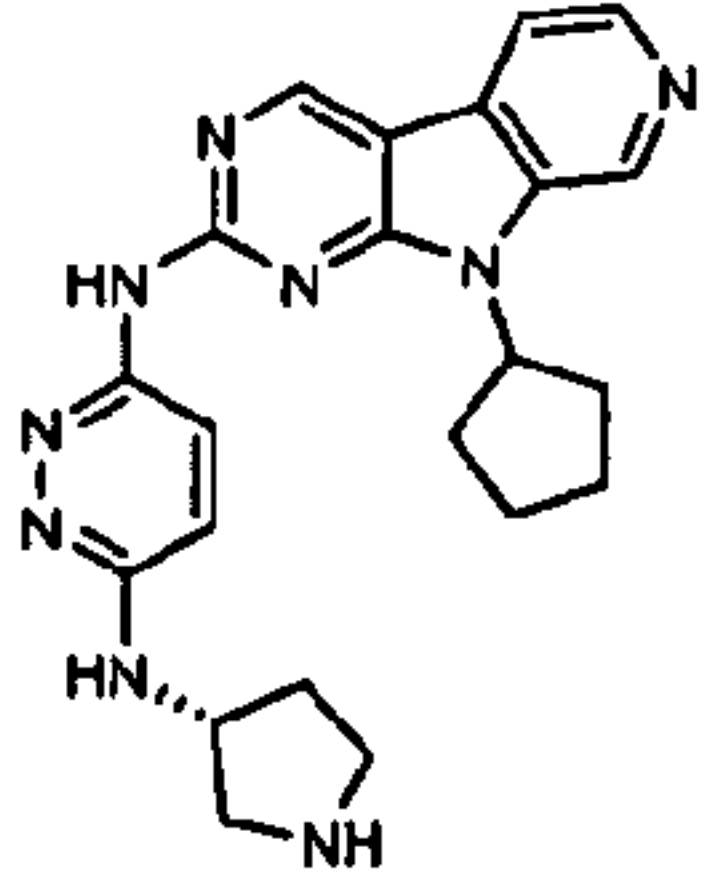
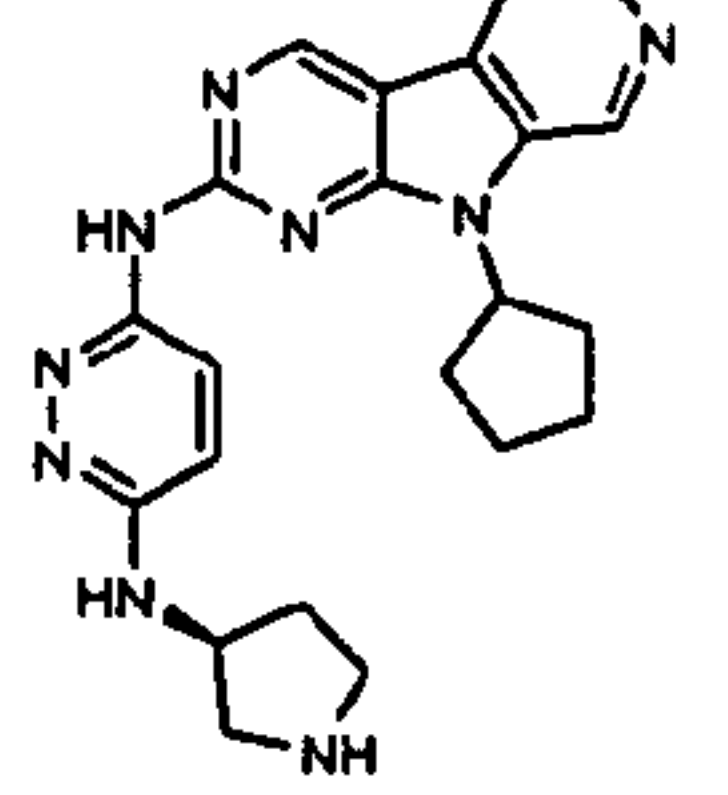


| Example # | Structure                                                                           | Reaction conditions               | LSMS retention time (minutes) | LCMS -ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|-----------------------------------|-------------------------------|-----------------|
| 75        |    |                                   | 0.742                         | 443.2           |
| 76        |   |                                   | 0.765                         | 483.3           |
| 77        |  | Step1. 80°C, 2hour; 120°C, 2hour. | 0.700                         | 444.2           |
| 78        |  | Step1. 60°C, 2hour; 80°C, 2hour.  | 0.736                         | 430.2           |
| 79        |  | Step1. 60°C, 2hour; 80°C, 2hour.  | 0.771                         | 444.2           |
| 80        |  | Step1. 60°C, 2hour; 80°C, 2hour.  | 0.755                         | 430.1           |

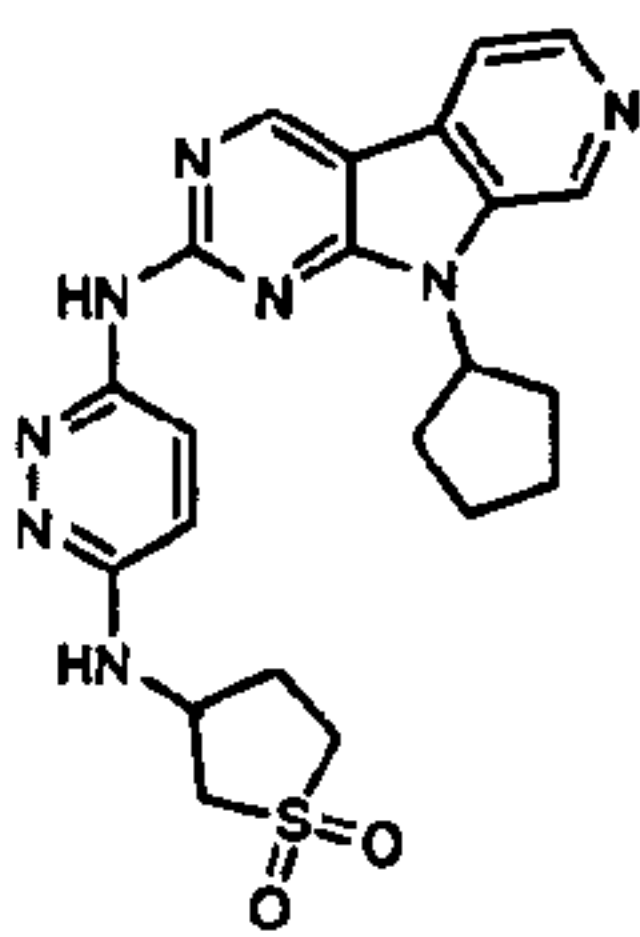
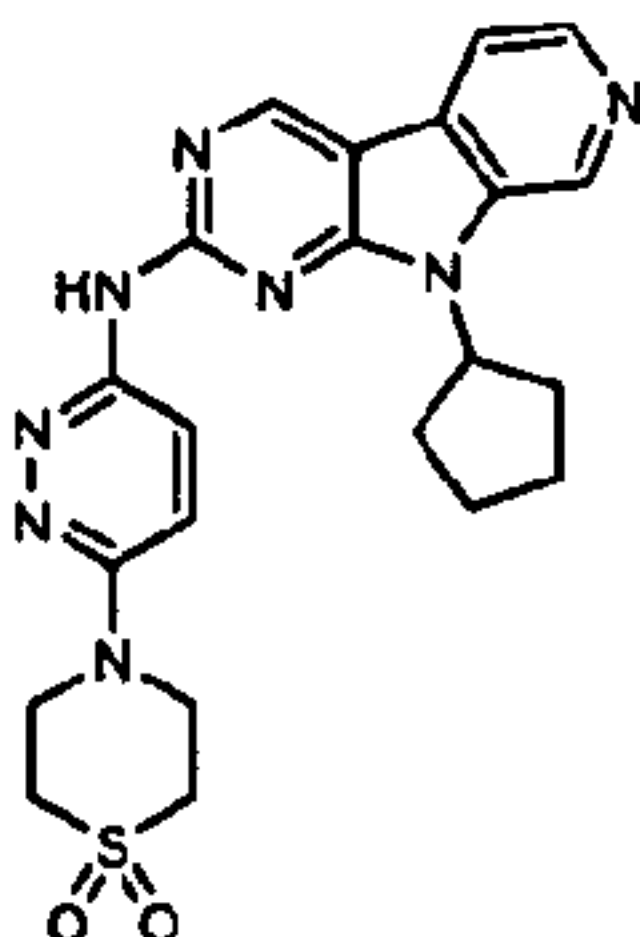
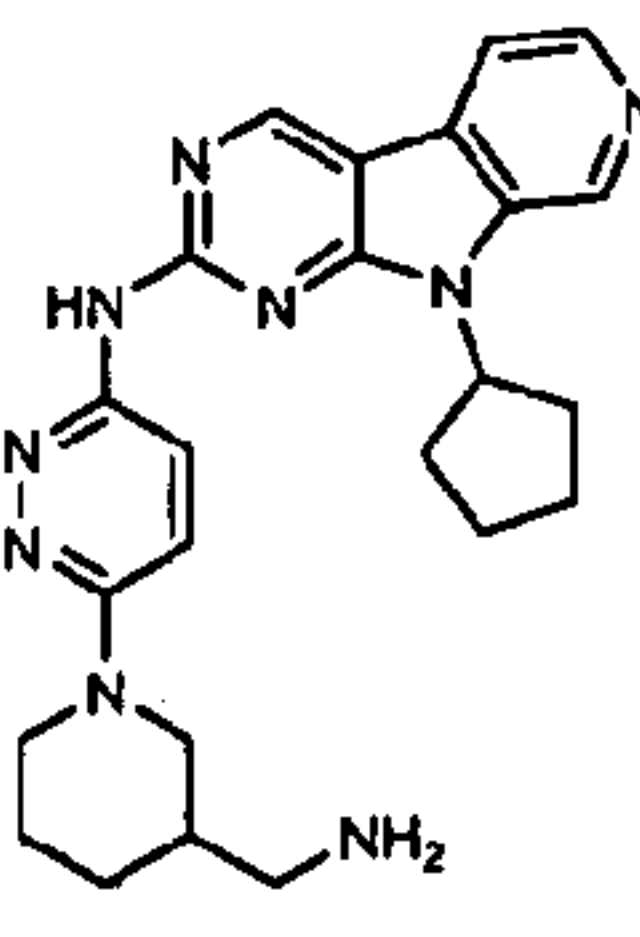
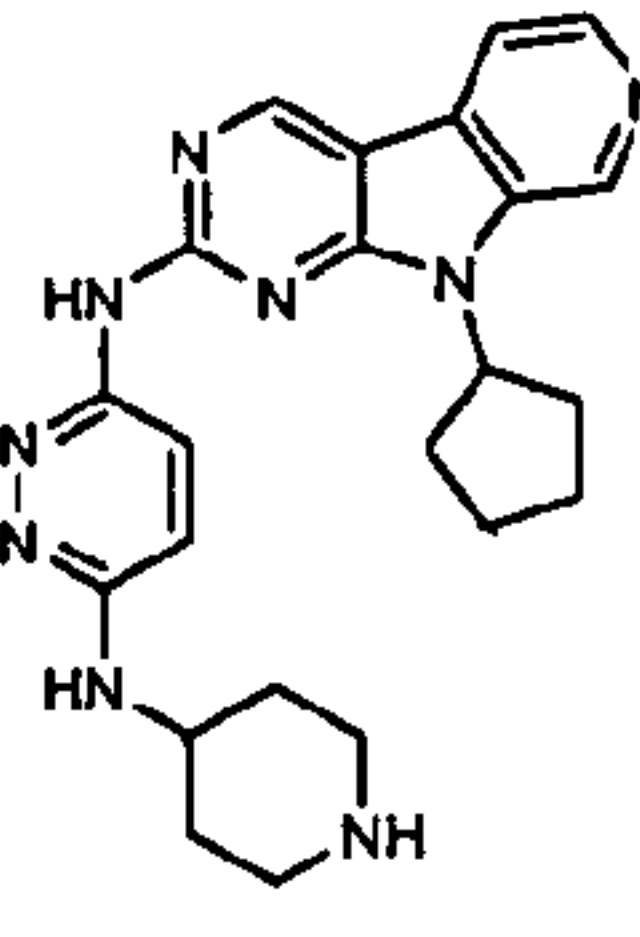
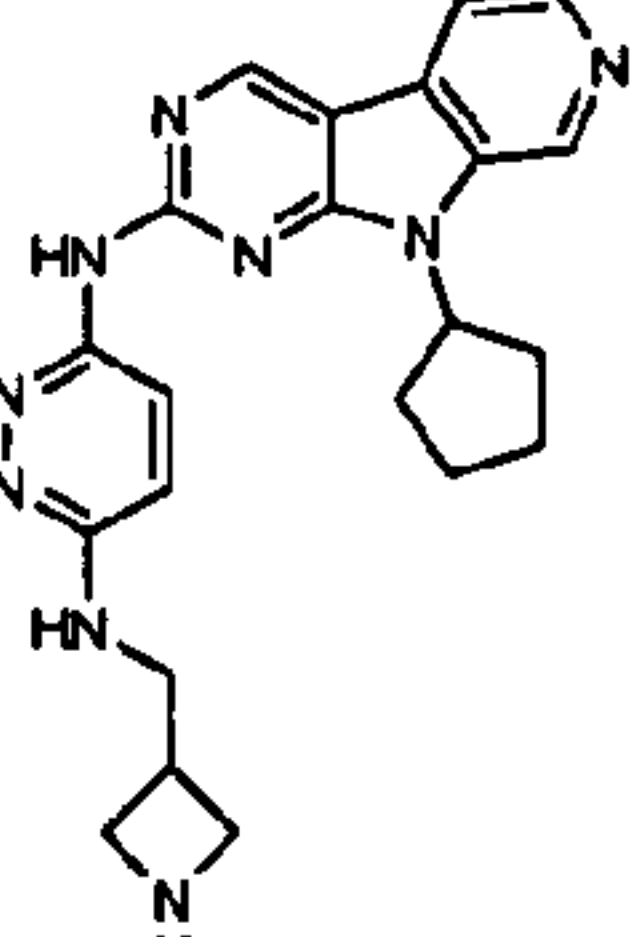
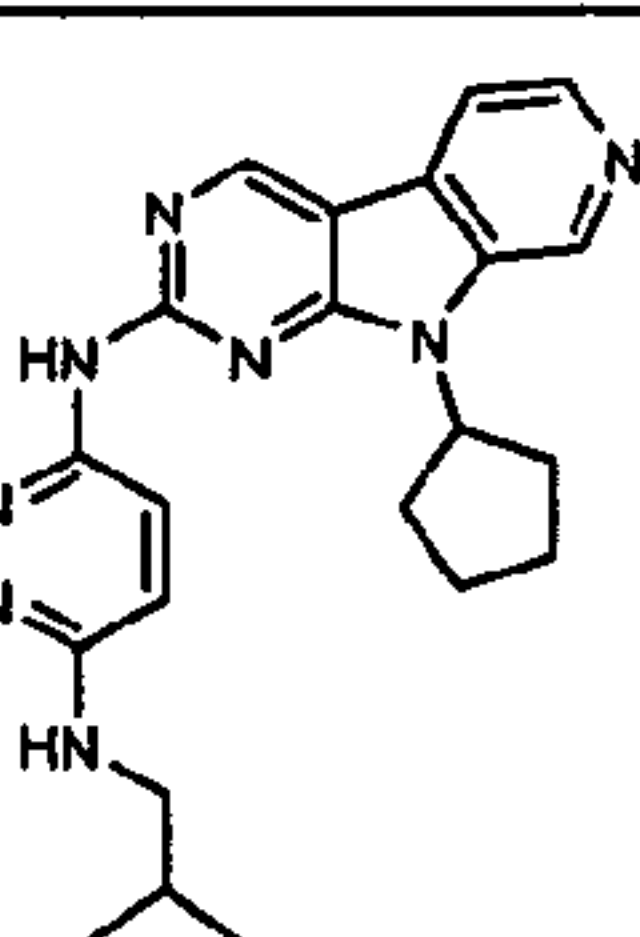


| Example # | Structure                                                                           | Reaction conditions              | LSMS retention time (minutes) | LCMS -ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|----------------------------------|-------------------------------|-----------------|
| 81        |    | Step1. 60°C, 2hour; 80°C, 2hour. | 0.757                         | 430.2           |
| 82        |   | Step1. 60°C, 2hour; 80°C, 2hour. | 0.771                         | 430.2           |
| 83        |  | Step1. 60°C, 2hour; 80°C, 2hour. | 0.738                         | 430.2           |
| 84        |  | Step1. 60°C, 2hour; 80°C, 2hour. | 1.07                          | 417.3           |
| 85        |  | Step1. 60°C, 2hour; 80°C, 2hour. | 0.817                         | 458.2           |
| 86        |  | Step1. 60°C, 2hour; 80°C, 2hour. | 0.823                         | 430.1           |

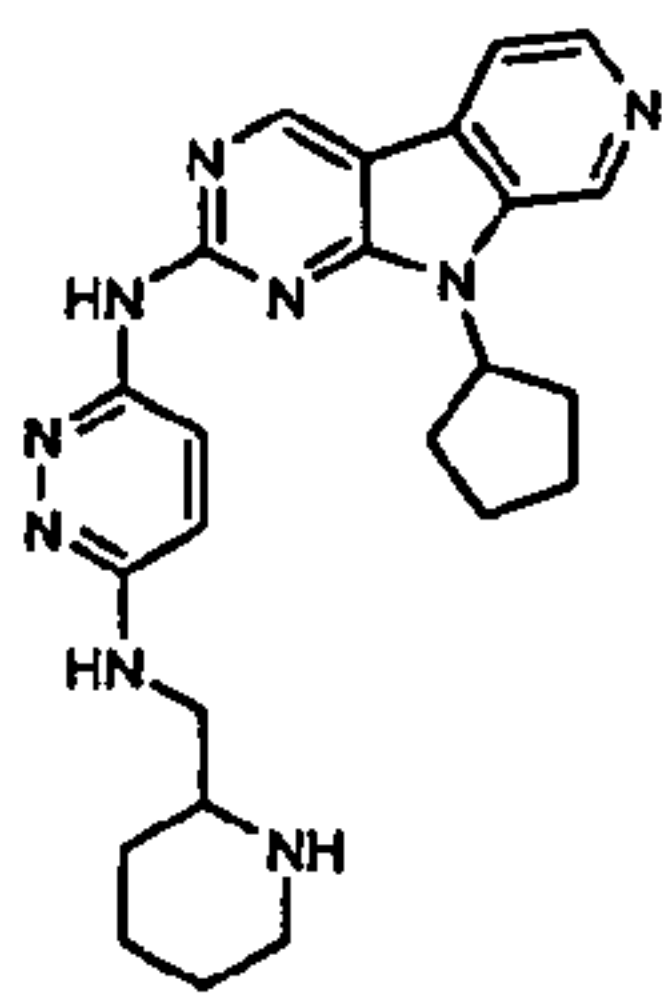
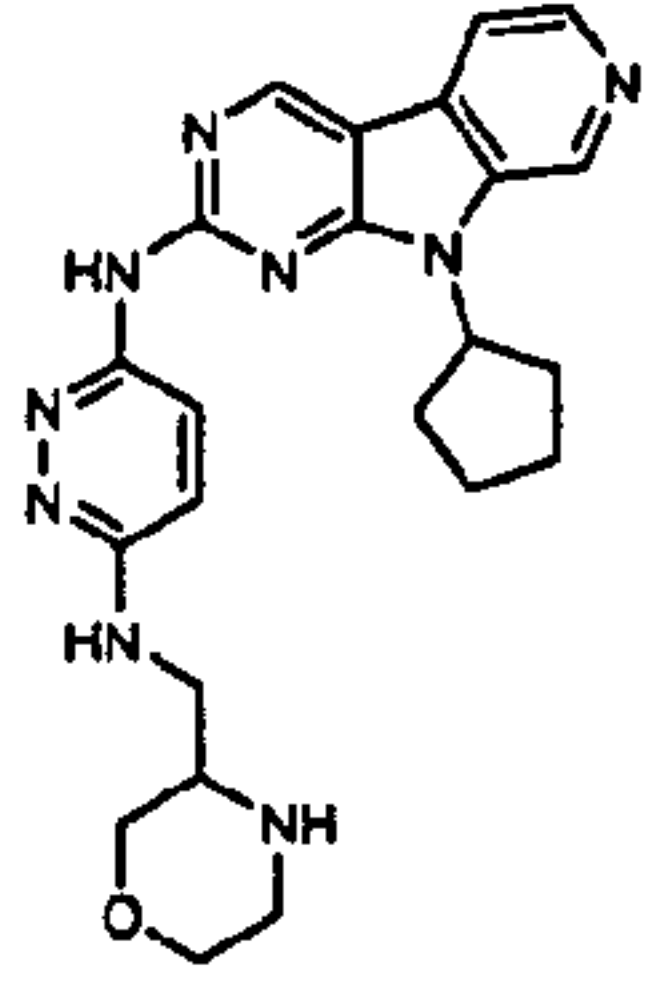


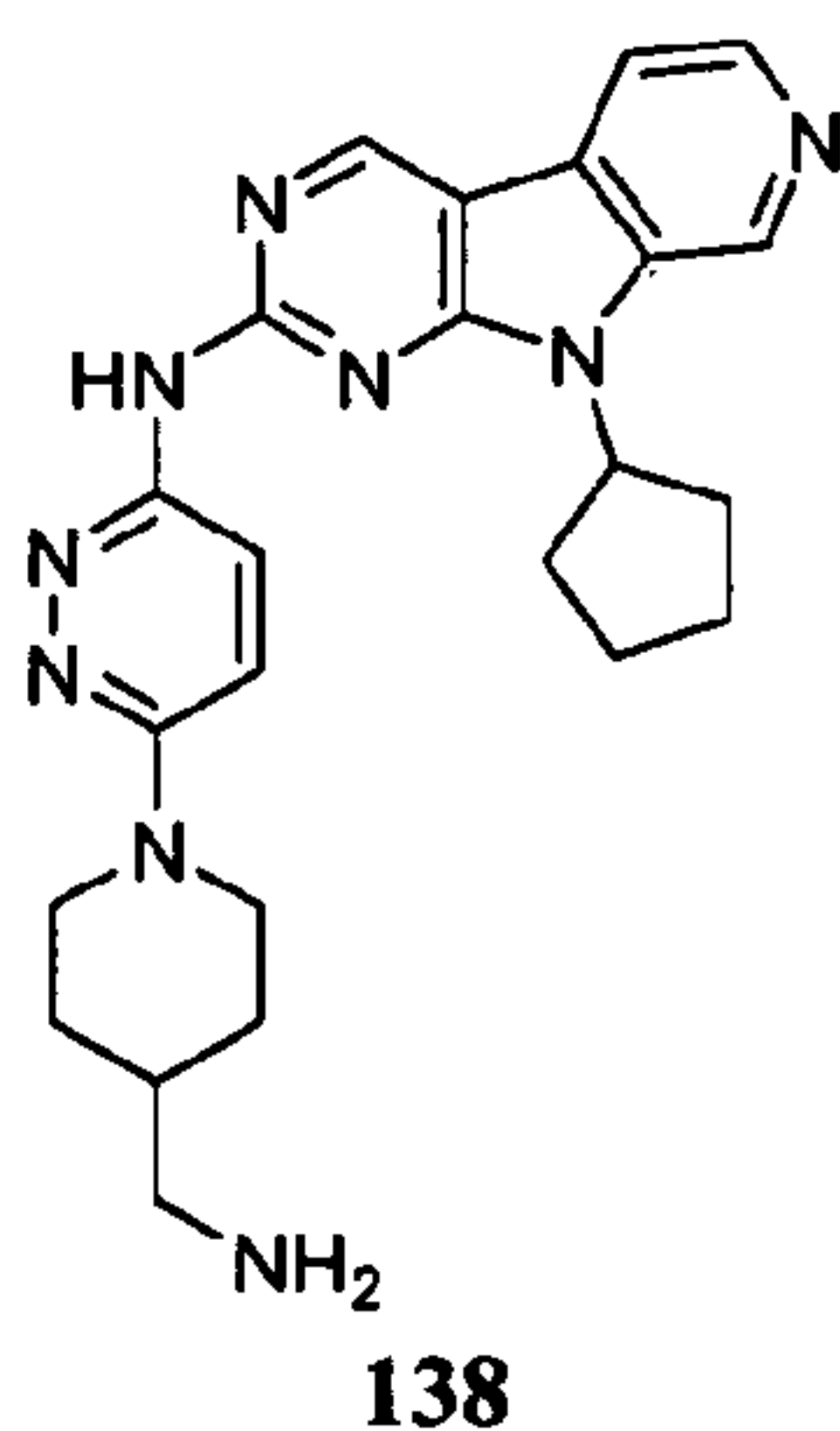
| Example # | Structure                                                                           | Reaction conditions                   | LSMS retention time (minutes) | LCMS -ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|---------------------------------------|-------------------------------|-----------------|
| 87        |    | Step1. 60°C, 2hour; 80°C, 2hour.      | 1.09                          | 431.2           |
| 88        |   | Step1. 60°C, 2hour; 80°C, 2hour.      | 1.27                          | 415.2           |
| 89        |  | Step1. 60°C, 2hour; 80°C, 2hour.      | 0.761                         | 416.2           |
| 90        |  | Step1. 60°C, 2hour; 80°C, 2hour.      | 0.740                         | 416.2           |
| 91        |  | Step1. 70°C, 0.5hour; 100°C, 0.5hour. | 0.642                         | 416.2           |
| 92        |  | Step1. 70°C, 0.5hour; 100°C, 0.5hour. | 0.649                         | 416.2           |



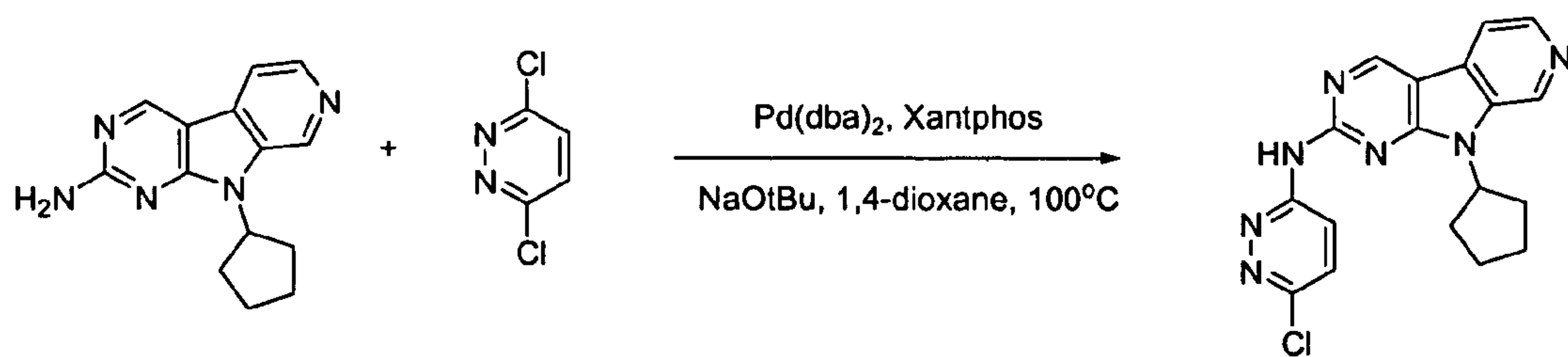
| Example # | Structure                                                                           | Reaction conditions                   | LSMS retention time (minutes) | LCMS -ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|---------------------------------------|-------------------------------|-----------------|
| 93        |    | Step1. 70°C, 0.5hour; 100°C, 0.5hour. | 0.792                         | 465.1           |
| 94        |   | Step1. 70°C, 0.5hour; 100°C, 0.5hour. | 0.848                         | 465.1           |
| 95        |  | Step1. 70°C, 0.5hour; 100°C, 0.5hour. | 0.658                         | 444.2           |
| 96        |  | Step1. 60°C, 0.5hour; 100°C, 0.5hour. | 0.641                         | 430.1           |
| 97        |  | Step1. 70°C, 0.5hour; 100°C, 0.5hour. | 0.624                         | 416.2           |
| 98        |  | Step1. 80°C, 0.5hour; 120°C, 0.5hour. | 0.635                         | 430.2           |



| Example # | Structure                                                                          | Reaction conditions                      | LSMS retention time (minutes) | LCMS -ESI (M+1) |
|-----------|------------------------------------------------------------------------------------|------------------------------------------|-------------------------------|-----------------|
| 99        |   | Step1. 60°C, 0.5hour;<br>100°C, 0.5hour. | 0.675                         | 444.2           |
| 100       |  | Step1. 70°C, 0.5hour;<br>100°C, 0.7hour. | 0.663                         | 446.2           |

**EXAMPLE 101**

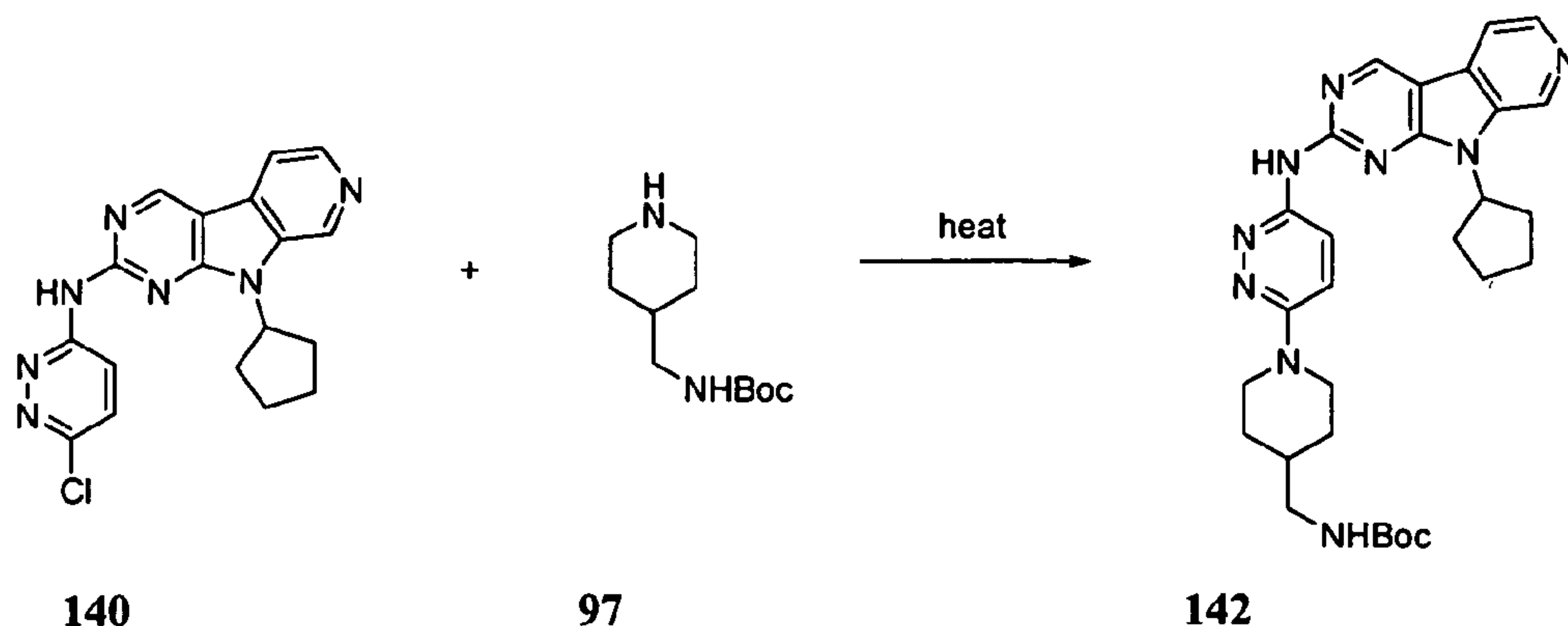
**4-Aminomethyl-1-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-piperidine**

**140**

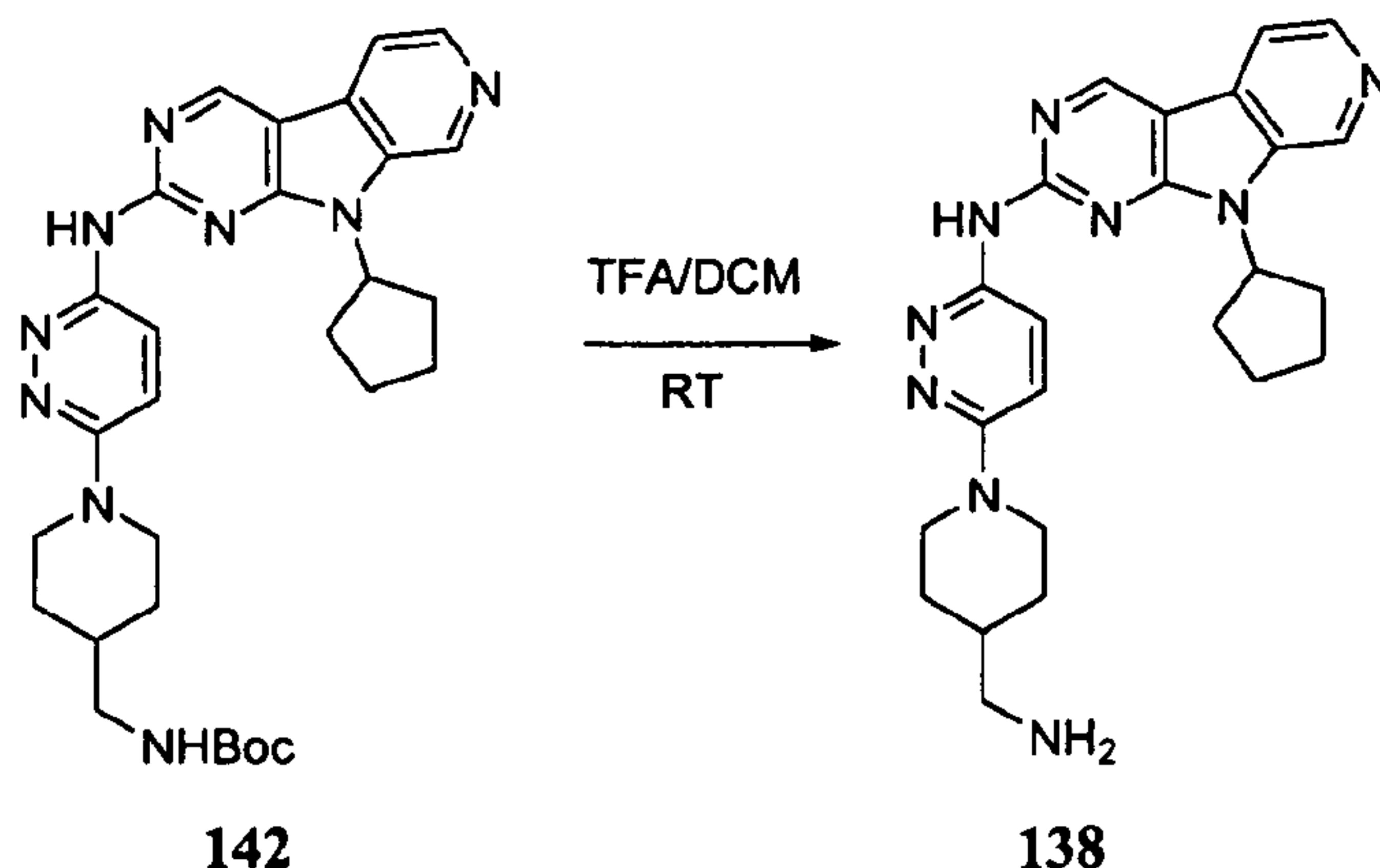
**6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-chloro-pyridazine (140):** A mixture of compound 4 (1.50g, 5.92 mmol), 3,6-dichloropyridazine (0.882g, 5.92 mmol), bis(dibenzylideneacetone)palladium(0.170g, 0.296 mmol), Xantphos(0.514g, 0.888 mmol) and sodium tert-butoxide(0.854, 8.88mmol) in toluene (80mL) was purged with nitrogen. The reaction was then



heated at 100°C for one hour in a sealed vessel. After cooling to room temperature, the mixture was loaded onto a silica gel column and eluted with 2-10% methanol/DCM. Evaporation of combined fractions provided compound **140** (2.1 g) as a yellowish solid. LCMS-ESI, M+1: 366.1



**1,1-Dimethylethyl 1-(6-((9-cyclopentyl-9H-pyrrolo[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-4-piperidinemethyl carboxylate (142):** The neat mixture of compound **140** (0.0300g, 0.0820 mmol) and compound **97** (0.176 g, 0.820 mmol) was heated at 150 °C for 1.5 hours using microwave. The crude material was dissolved in 4mL methanol, filtered and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide the title compound **142** as a TFA salt. LCMS-ESI (POS), M/Z, M+1: 544.3

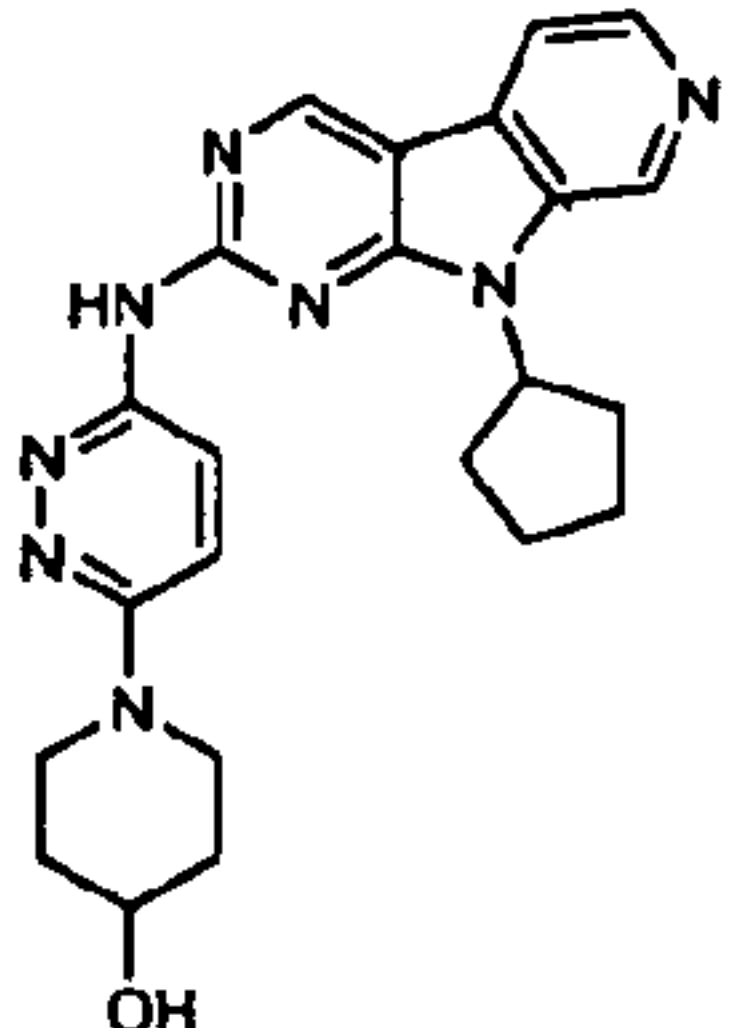
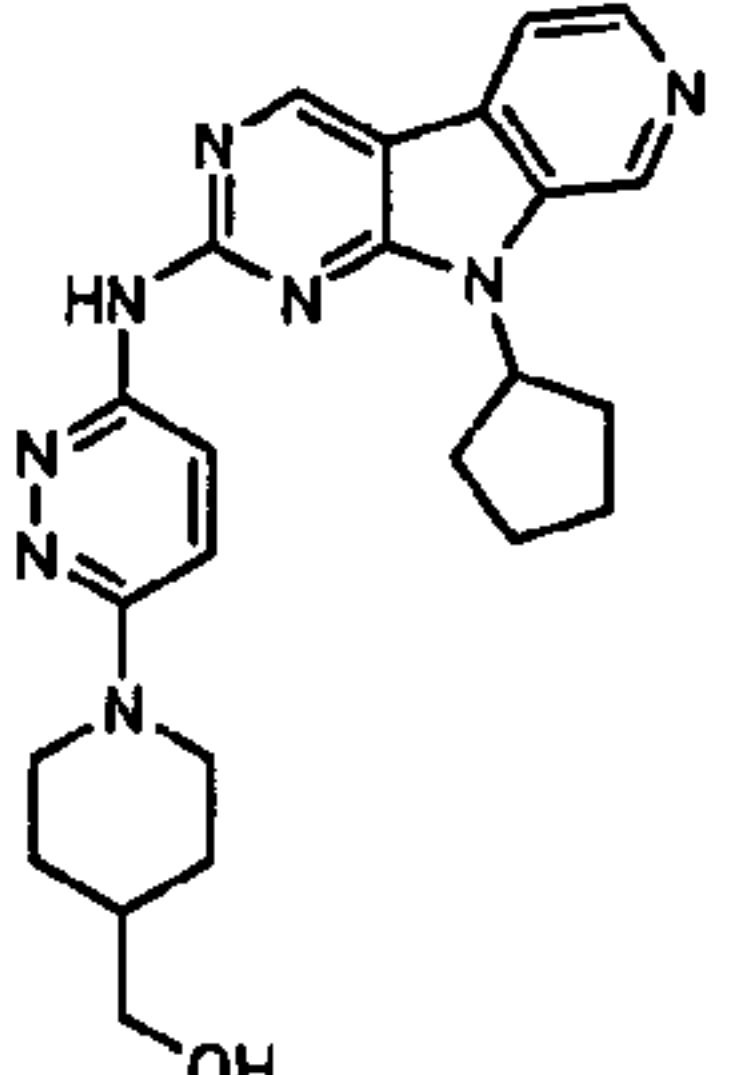
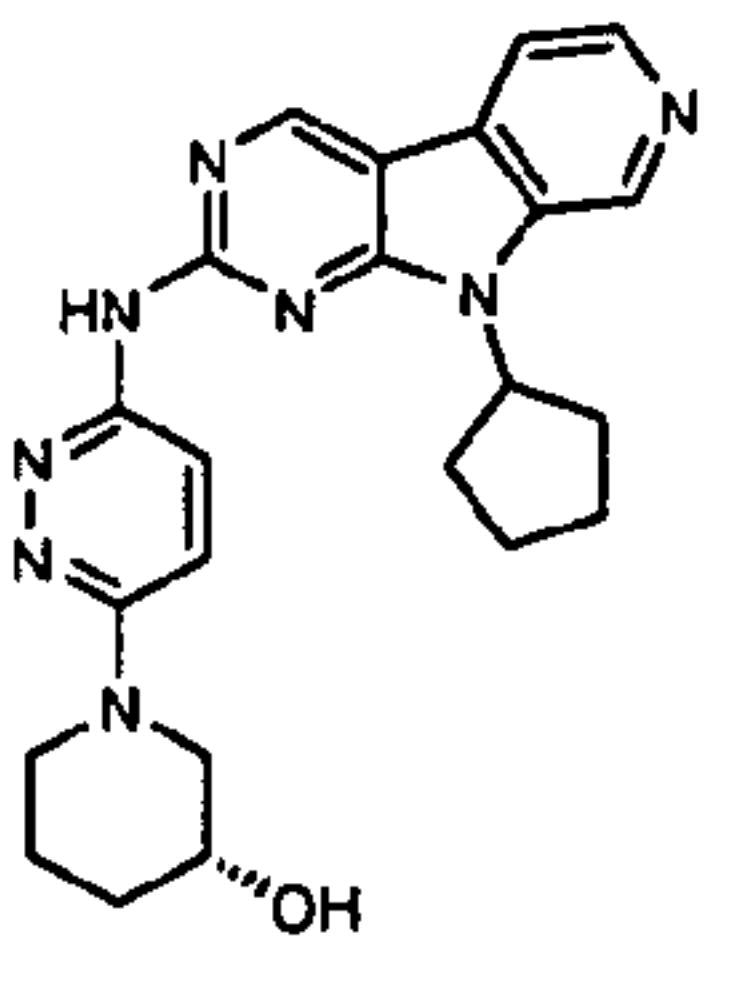
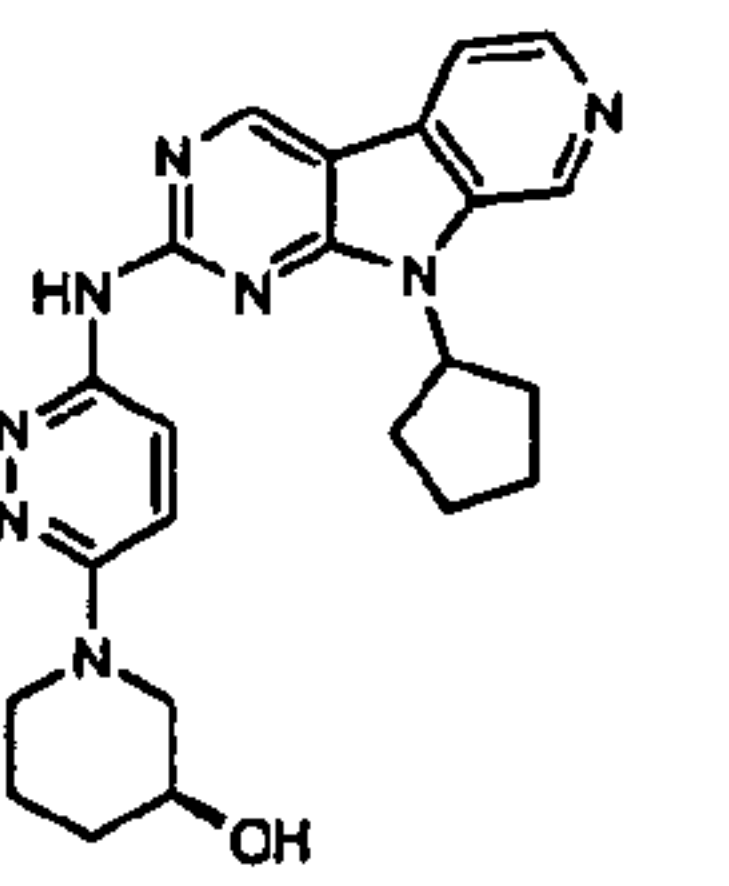
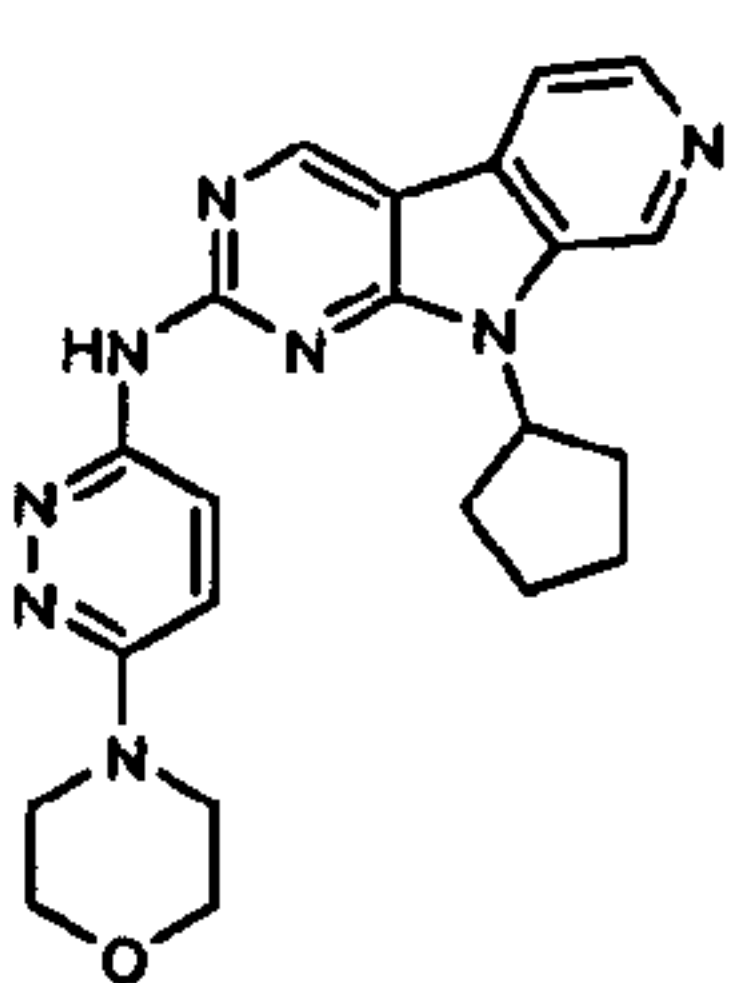


**4-Aminomethyl-1-(6-((9-cyclopentyl-9H-pyrrolo[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-piperidine (138):** Compound **142** was treated with 15% TFA/DCM (2mL) at room temperature for one hour. The solvent was evaporated. The residue was re-dissolved in 4mL methanol and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to provide the desired product as TFA salt. LCMS retention time (minutes): 0.666. LCMS-ESI (POS), M/Z, M+1: 444.3

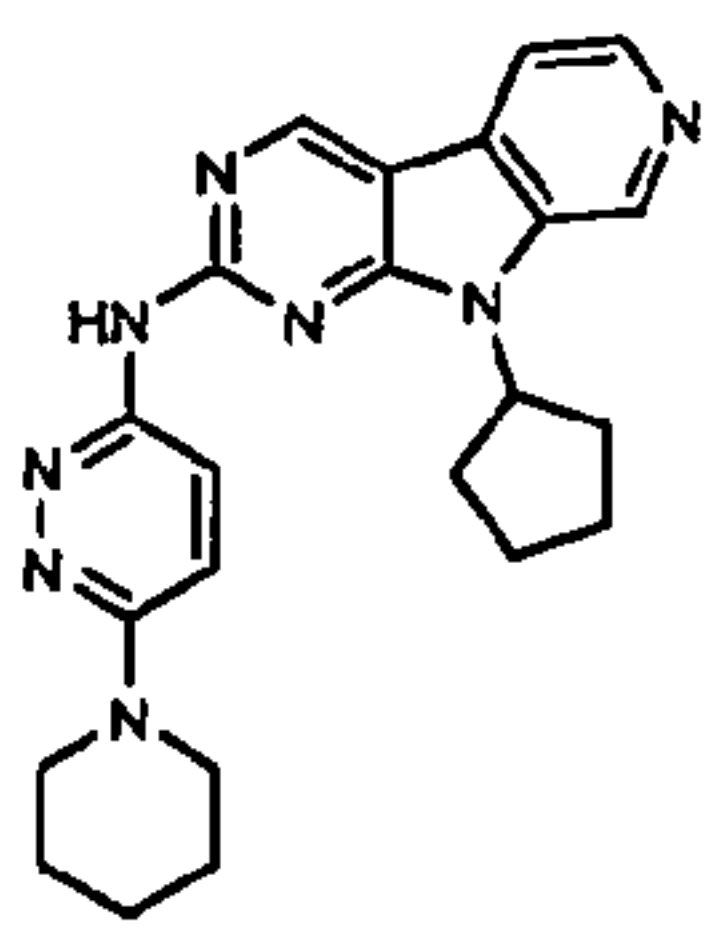
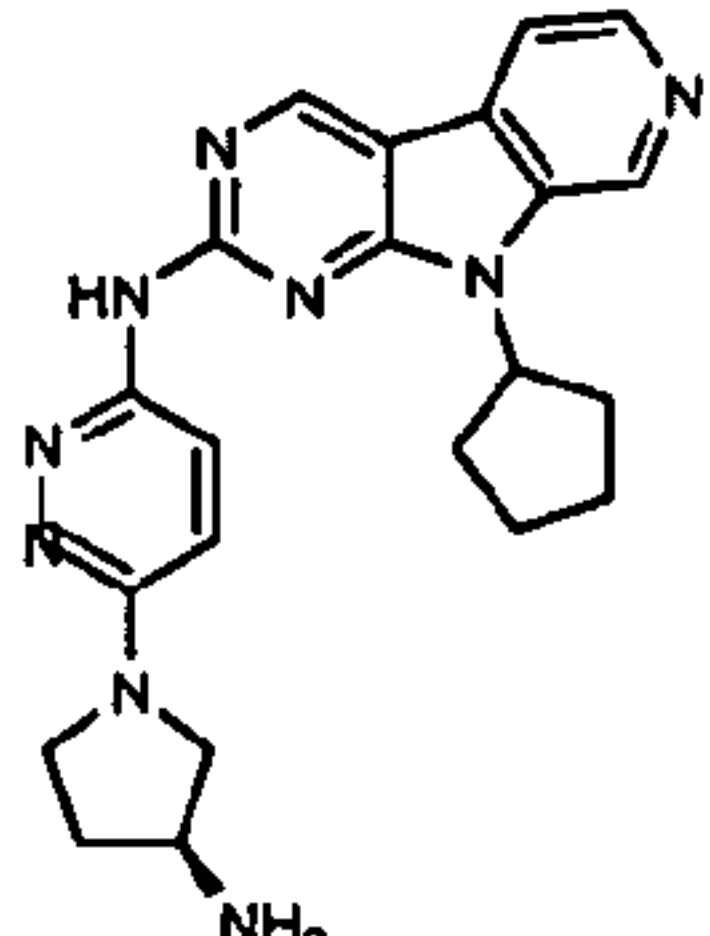
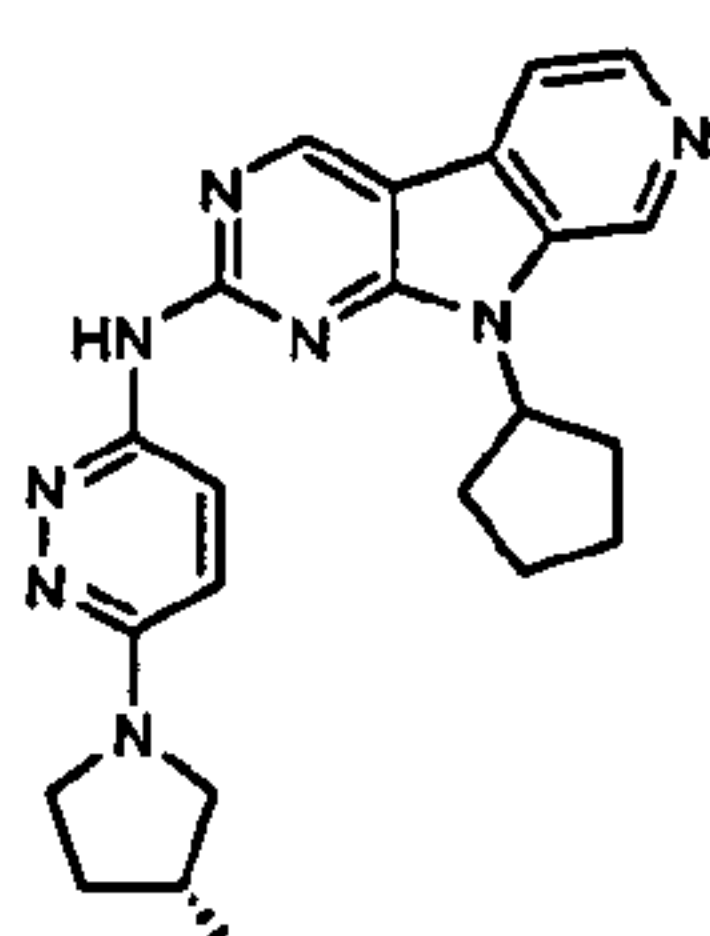
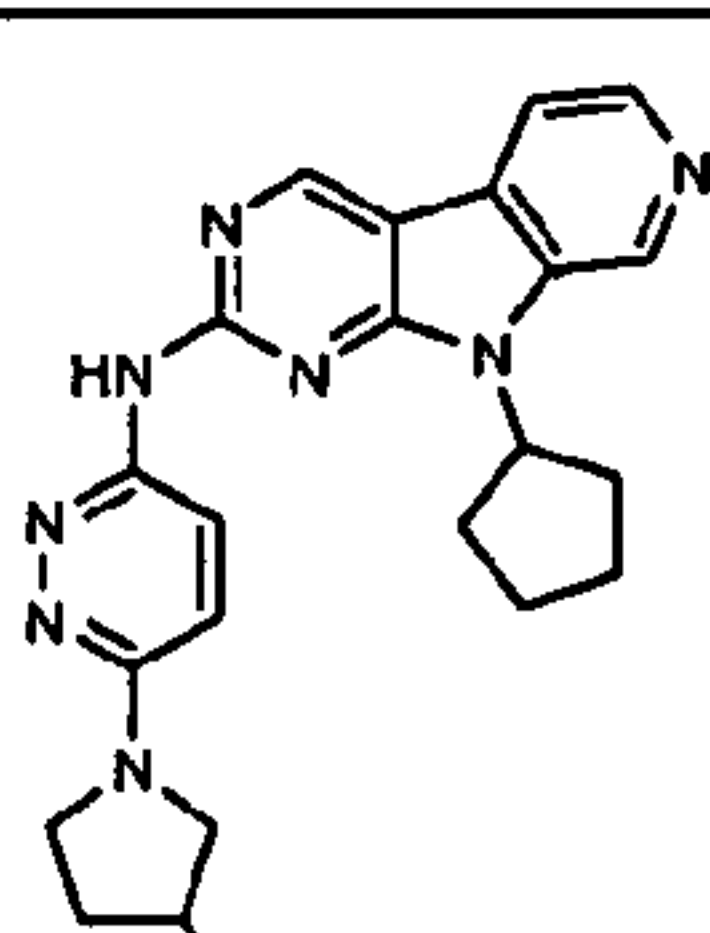
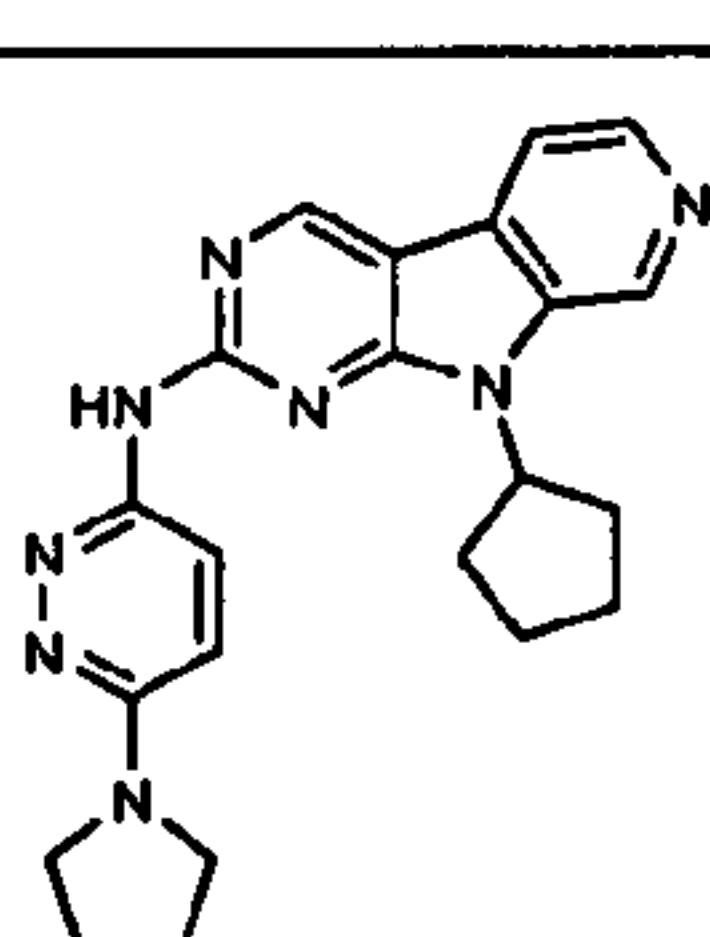
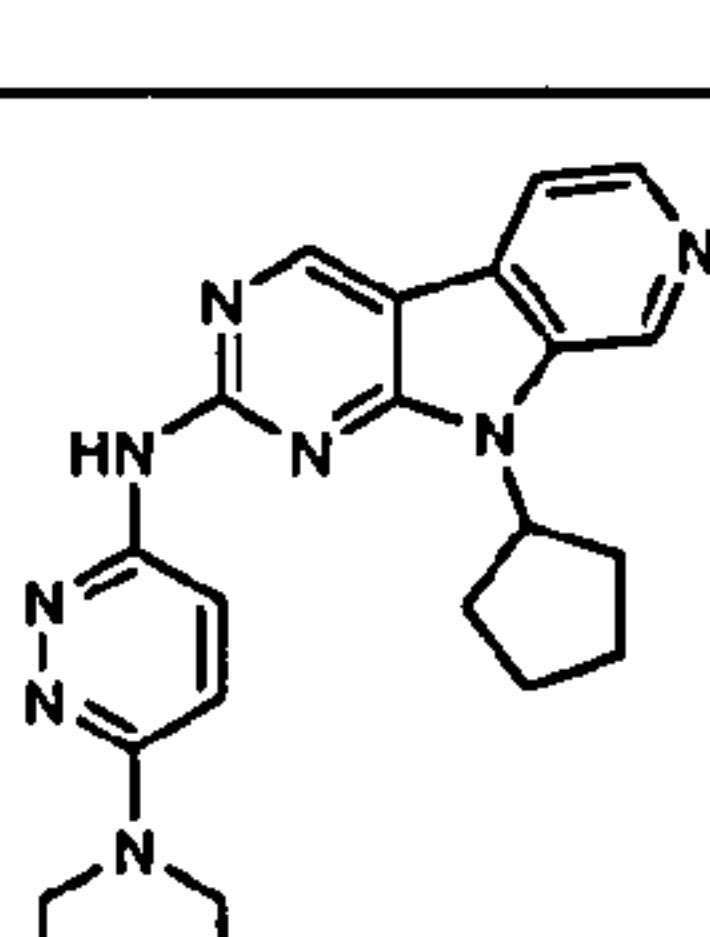


Examples 102-121 (table 2) were prepared using conditions as described for example 101 with deprotection when necessary, replacing compound 97 with proper amine. The reaction conditions such as solvent, temperature, and reaction time for Step 2 were the same unless indicated in Table 2.

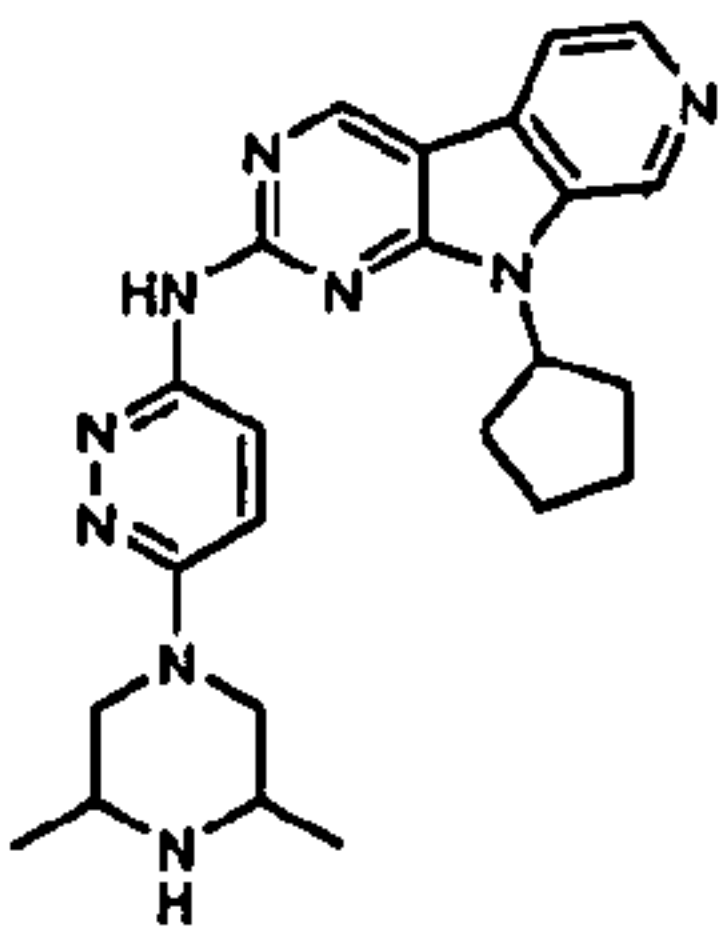
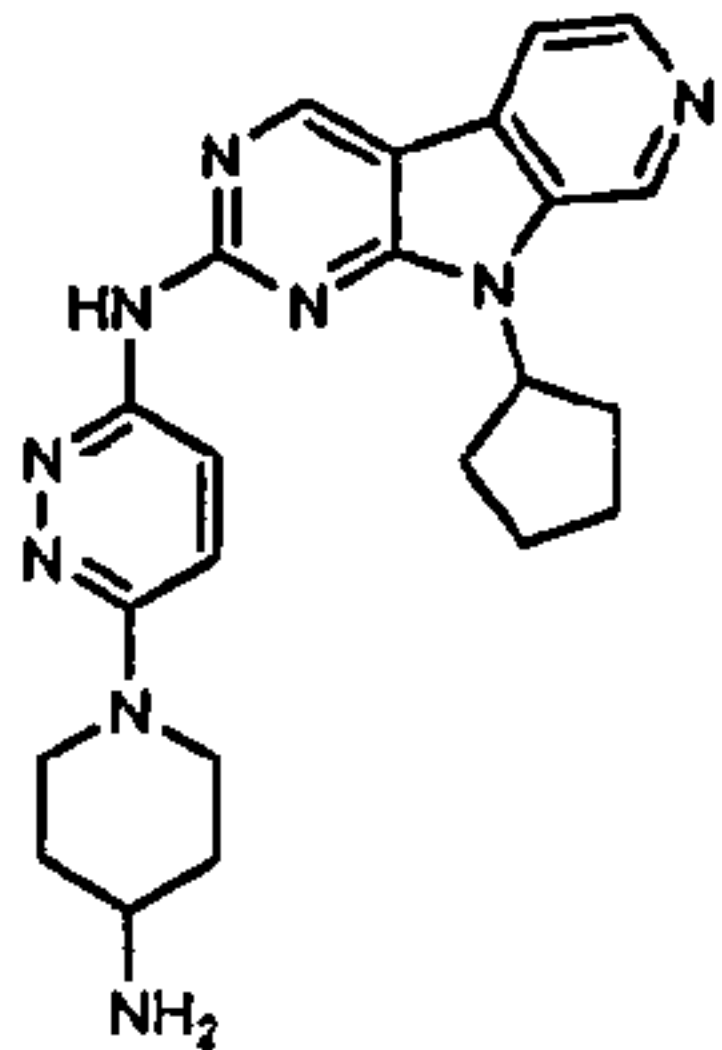
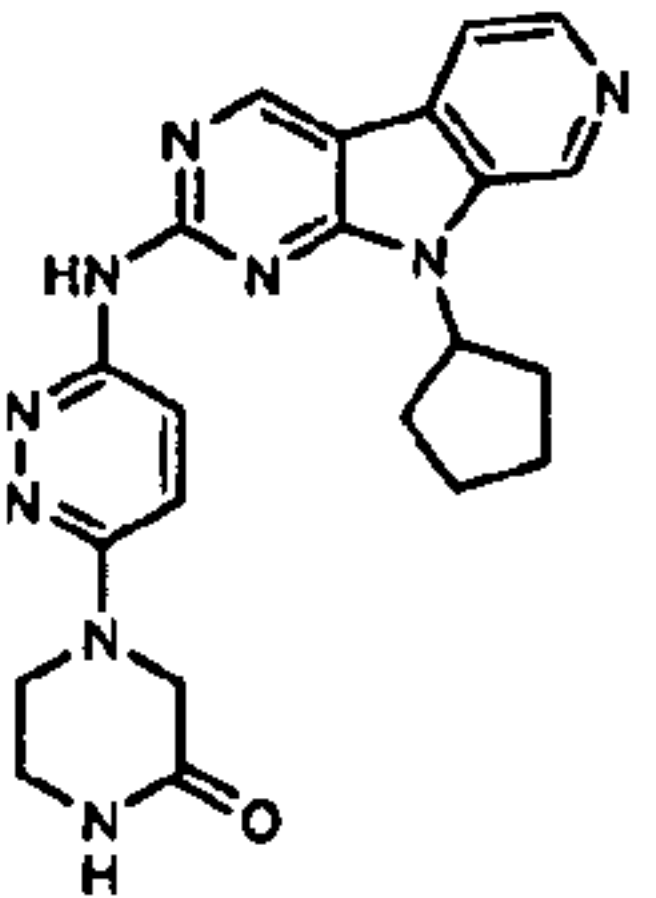
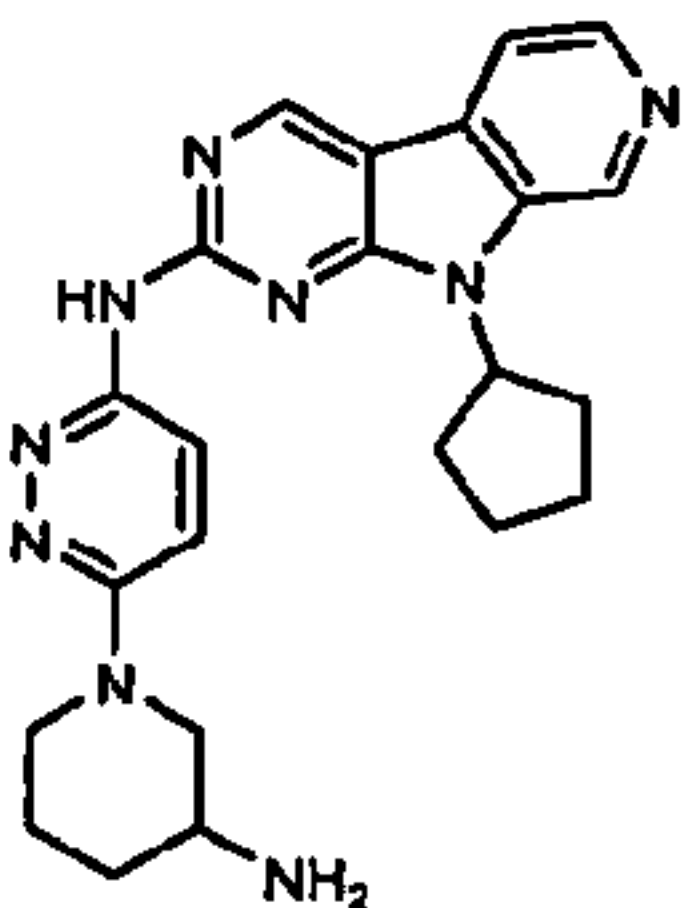
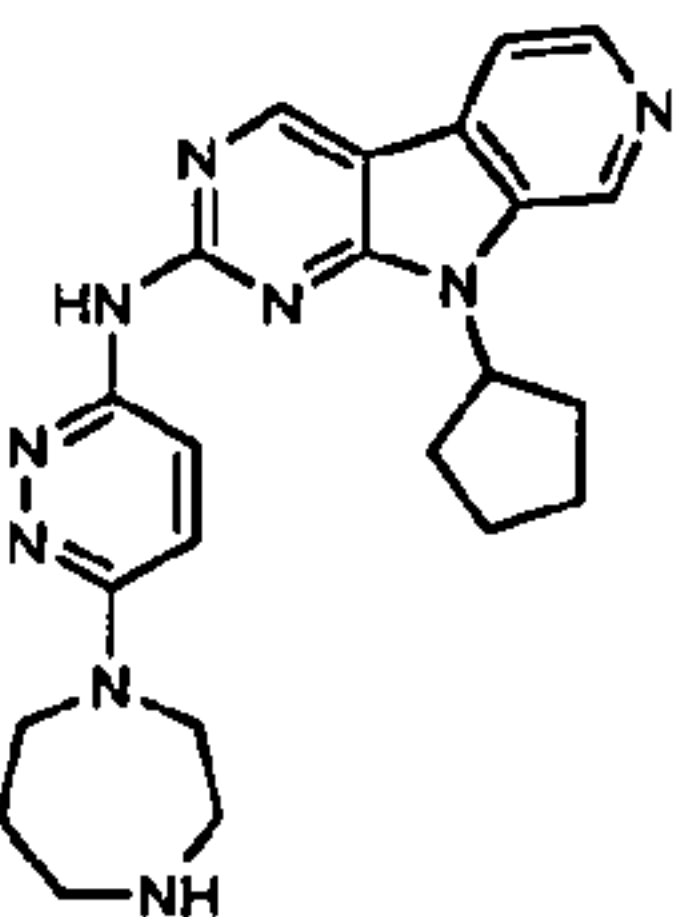
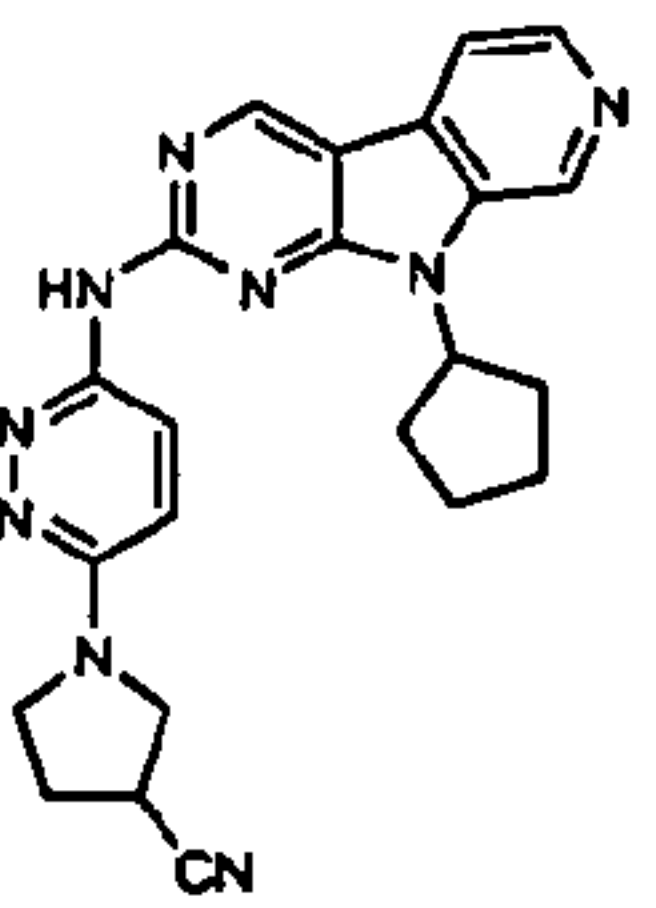
Table 2

| Example # | Structure                                                                           | Reaction Conditions  | LSMS retention time (min) | LCMS-ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|----------------------|---------------------------|----------------|
| 102       |   | DMSO/155°C/1.5 hours | 0.835                     | 431.2          |
| 103       |  | DMSO/155°C/1.5 hours | 0.854                     | 445.1          |
| 104       |  | NMP/180°C/2 hours    | 0.790                     | 431.2          |
| 105       |  | NMP/180°C/2 hours    | 0.800                     | 431.2          |
| 106       |  | DMSO/155°C/1.5 hours | 0.909                     | 417.3          |

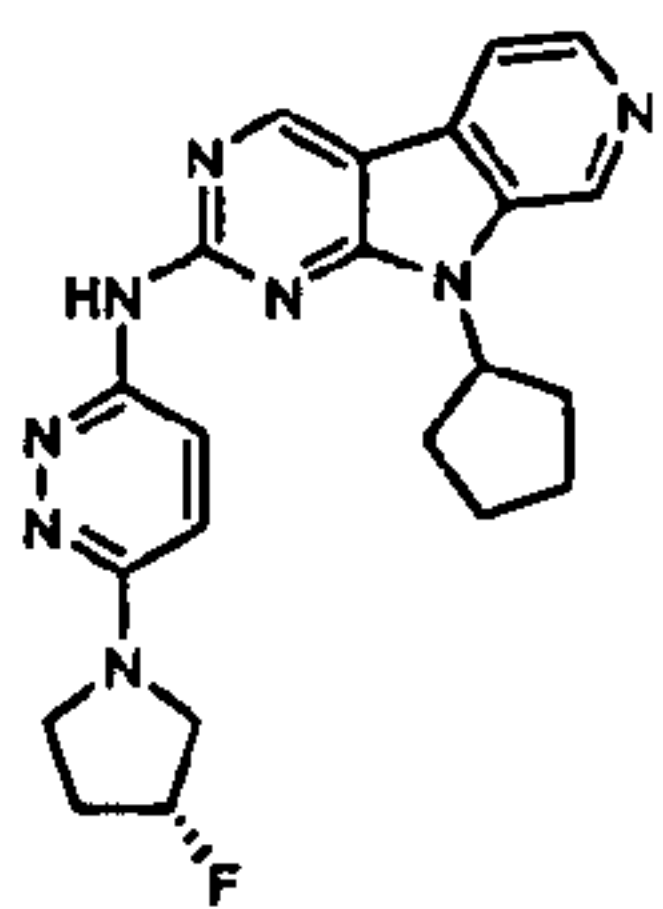
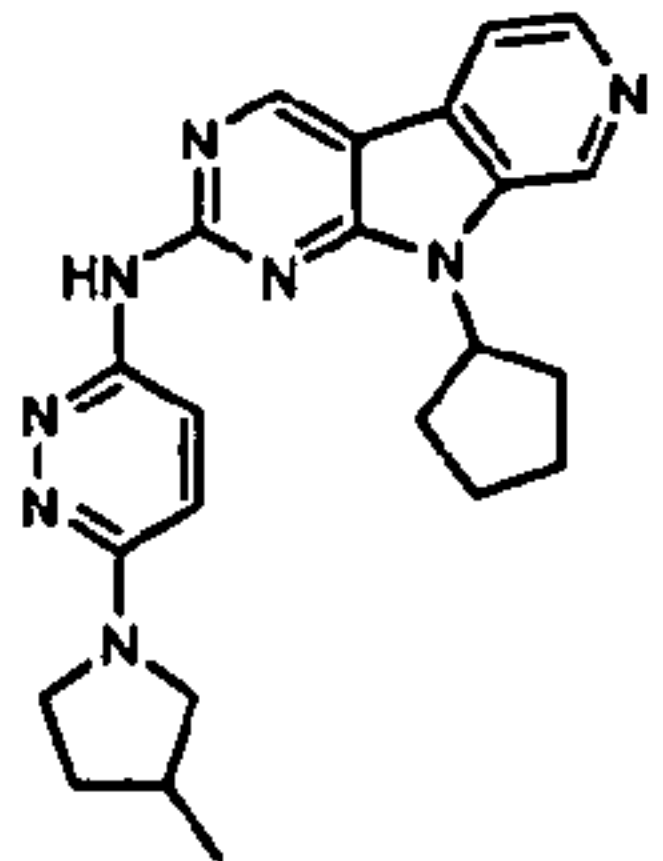
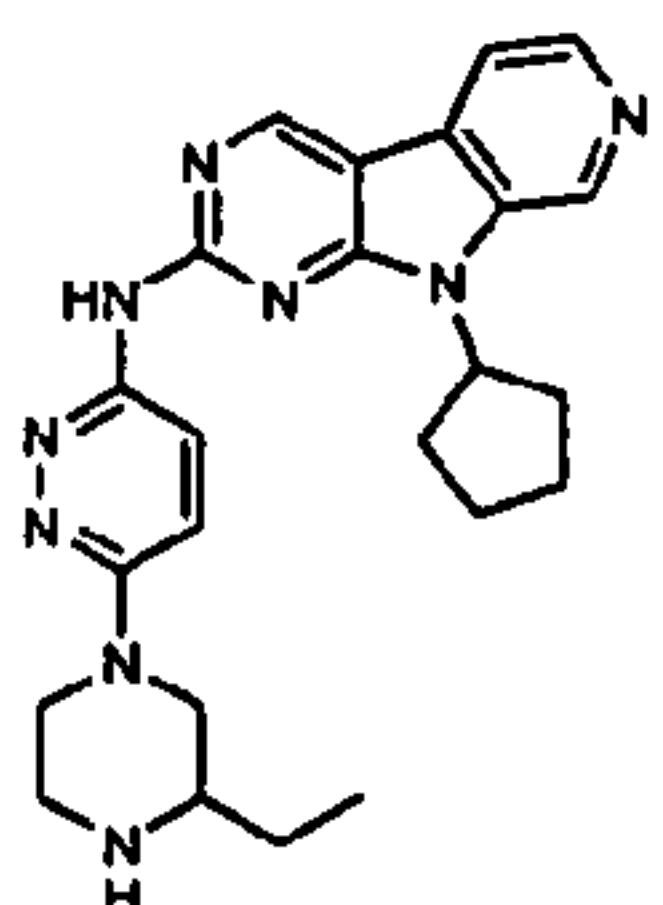


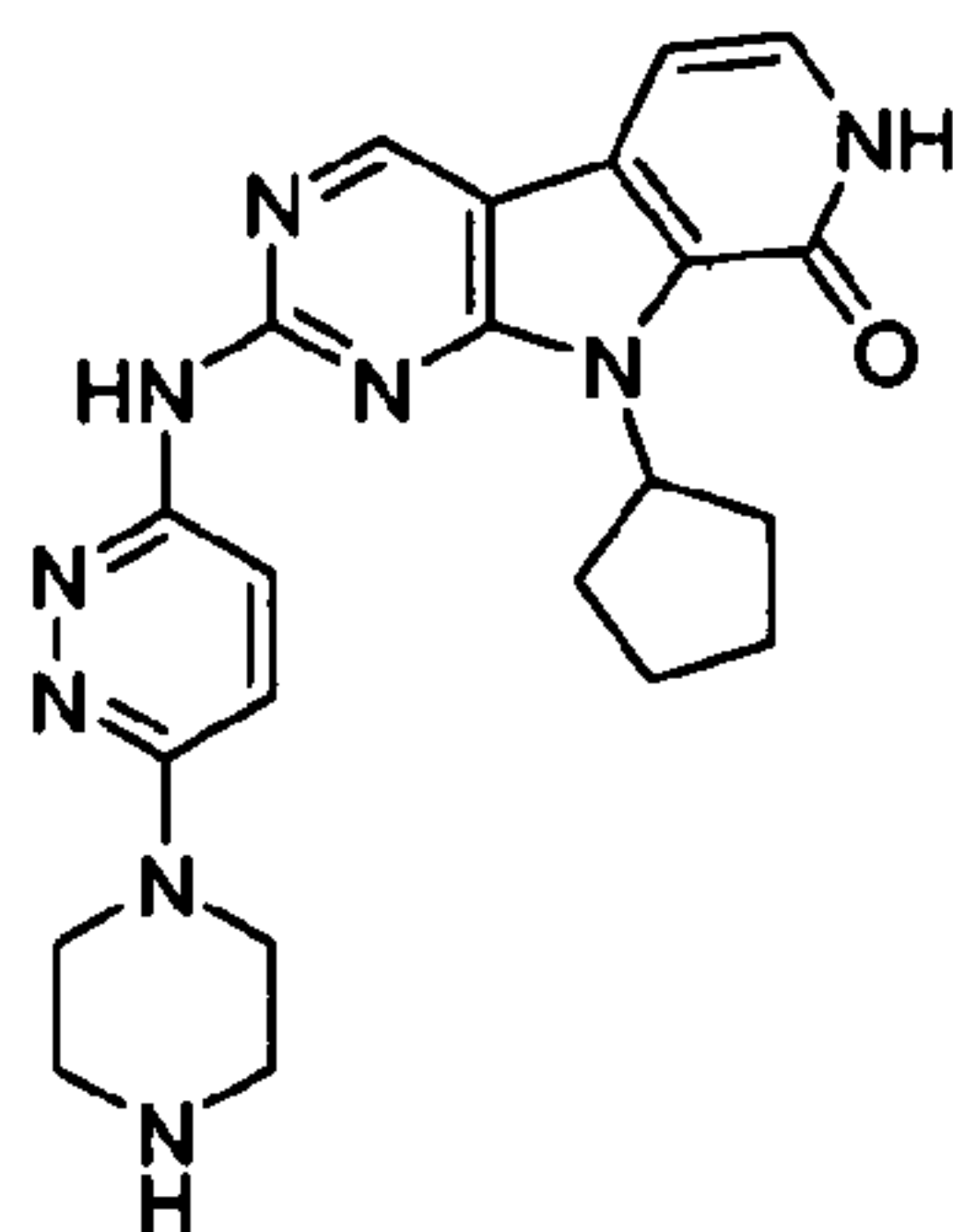
| Example # | Structure                                                                           | Reaction Conditions  | LSMS retention time (min) | LCMS-ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|----------------------|---------------------------|----------------|
| 107       |    | DMSO/150°C/1.5 hours | 0.997                     | 415.1          |
| 108       |   | DMSO/155°C/1.5 hours | 0.659                     | 416.2          |
| 109       |  | DMSO/145°C/0.5 hour  | 0.620                     | 416.1          |
| 110       |  | NMP/165°C/0.7 hour   | 0.808                     | 431.2          |
| 111       |  | DMSO/140°C/1 hour    | 0.850                     | 401.2          |
| 112       |  | NMP/180°C/2 hours    | 0.652                     | 430.1          |



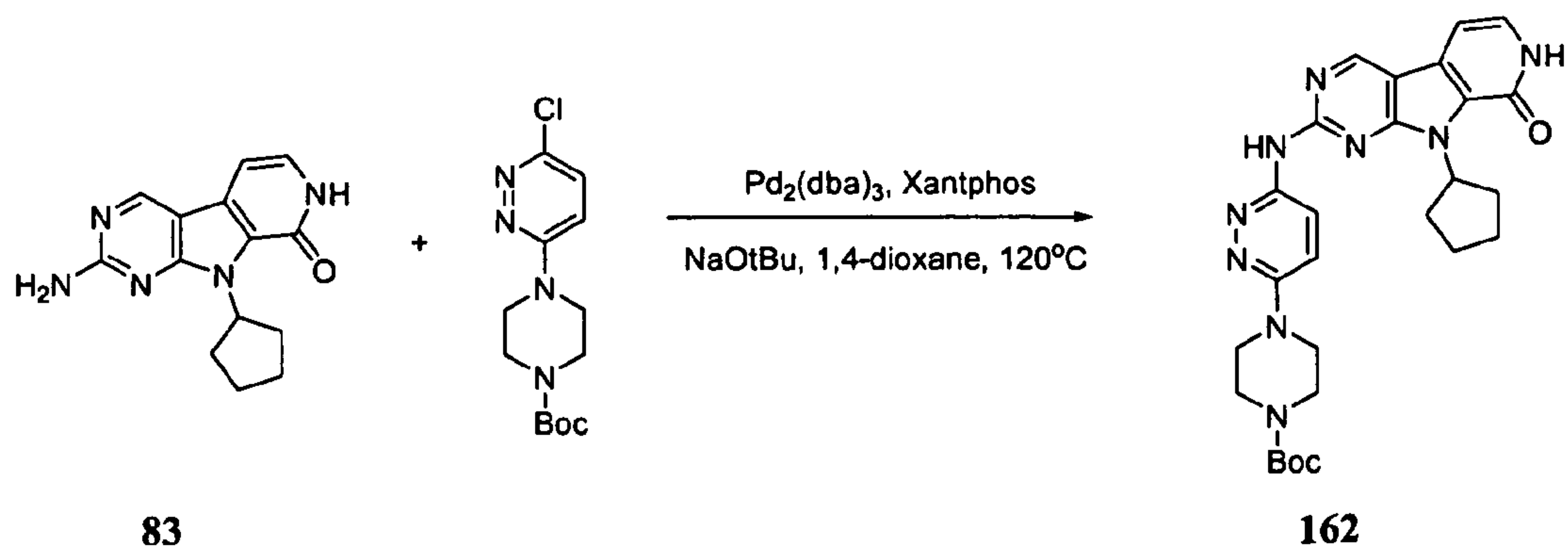
| Example # | Structure                                                                           | Reaction Conditions  | LSMS retention time (min) | LCMS-ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|----------------------|---------------------------|----------------|
| 113       |    | NMP/180°C/1 hour     | 0.747                     | 444.2          |
| 114       |   | NMP/150°C/2 hours    | 0.661                     | 430.1          |
| 115       |  | NMP/185°C/2 hours    | 0.769                     | 430.1          |
| 116       |  | NMP/180°C/1 hour     | 0.680                     | 430.1          |
| 117       |  | DMSO/155°C/1.5 hours | 0.730                     | 430.1          |
| 118       |  | NMP/175°C/1 hour     | 0.836                     | 426.2          |



| Example # | Structure                                                                           | Reaction Conditions | LSMS retention time (min) | LCMS-ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|---------------------|---------------------------|----------------|
| 119       |    | NMP/175°C/1 hour    | 0.828                     | 419.2          |
| 120       |   | NMP/175°C/1 hour    | 0.885                     | 415.1          |
| 121       |  | NMP/175°C/1 hour    | 0.743                     | 444.2          |

**EXAMPLE 122****161**

**9-Cyclopentyl-2-((6-(1-piperazinyl)-3-pyridazinyl)amino)-7,9-dihydro-8H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-one**

**83****162**



**1,1-Dimethylethyl 4-(6-((9-cyclopentyl-8-oxo-8,9-dihydro-7H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinecarboxylate (162):** A mixture of *tert*-butyl 4-(6-chloropyridazin-3-yl)piperazine-1-carboxylate (0.060 g, 0.20 mmol), compound **83** (0.054 g, 0.20 mmol), Xantphos (0.017 g, 0.030 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.014 g, 0.015 mmol), and sodium *tert*-butoxide (0.029 g, 0.30 mmol) in dioxane was purged with nitrogen gas for 1 minute. The reaction was heated at 120°C for 6 hours and then cooled to room temperature. The solvent was removed by filtration. The residue was washed with 2 x 1ml dioxane. The product was then dissolved in 10mL methanol/DCM (1:1) and concentrated. The crude material was re-dissolved in 4mL methanol and purified on a C-18 reversephase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of acetonitrile in water containing 0.1%TFA to give the title compound **162**. LCMS-ESI (POS), M/Z, M+1: 532.3

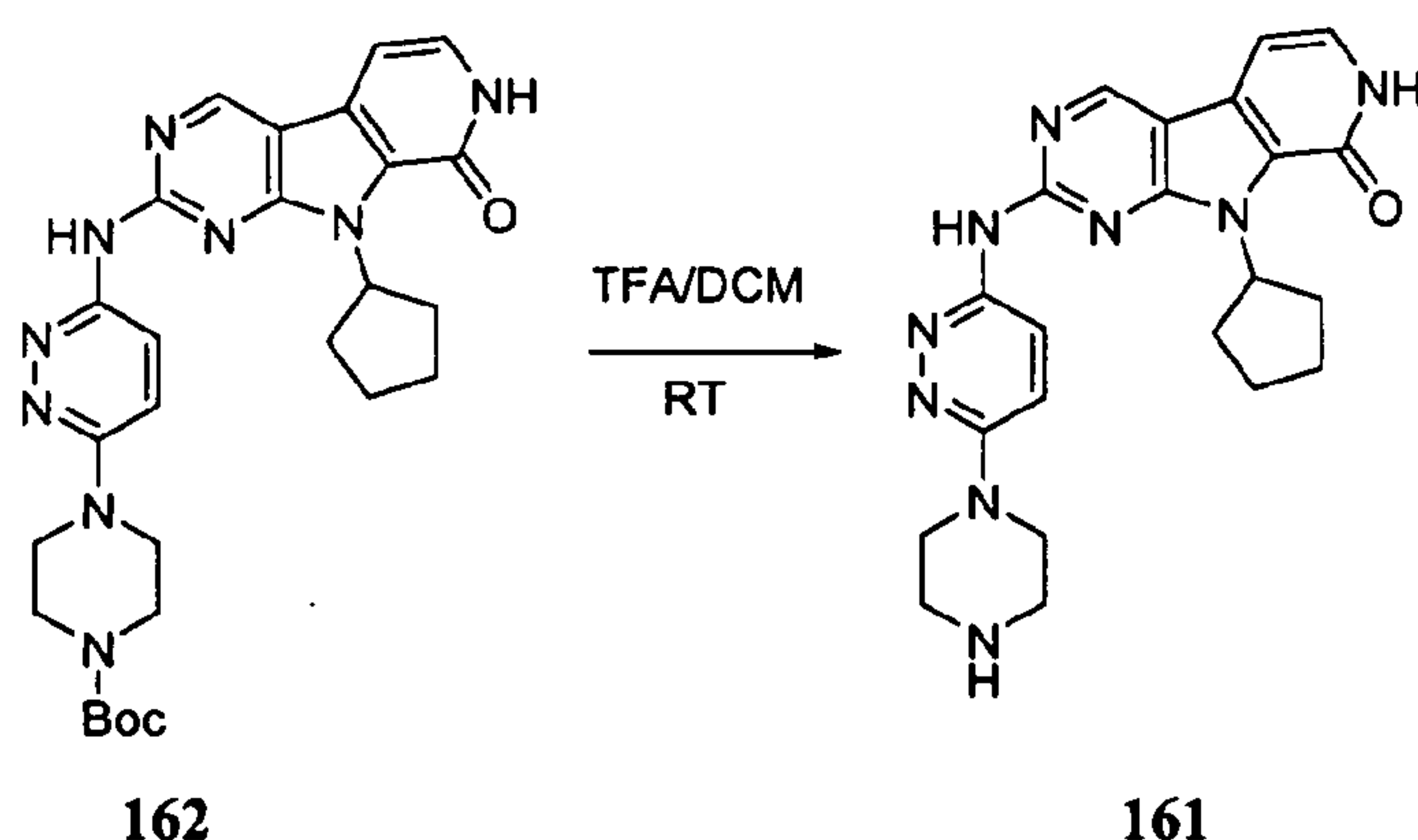
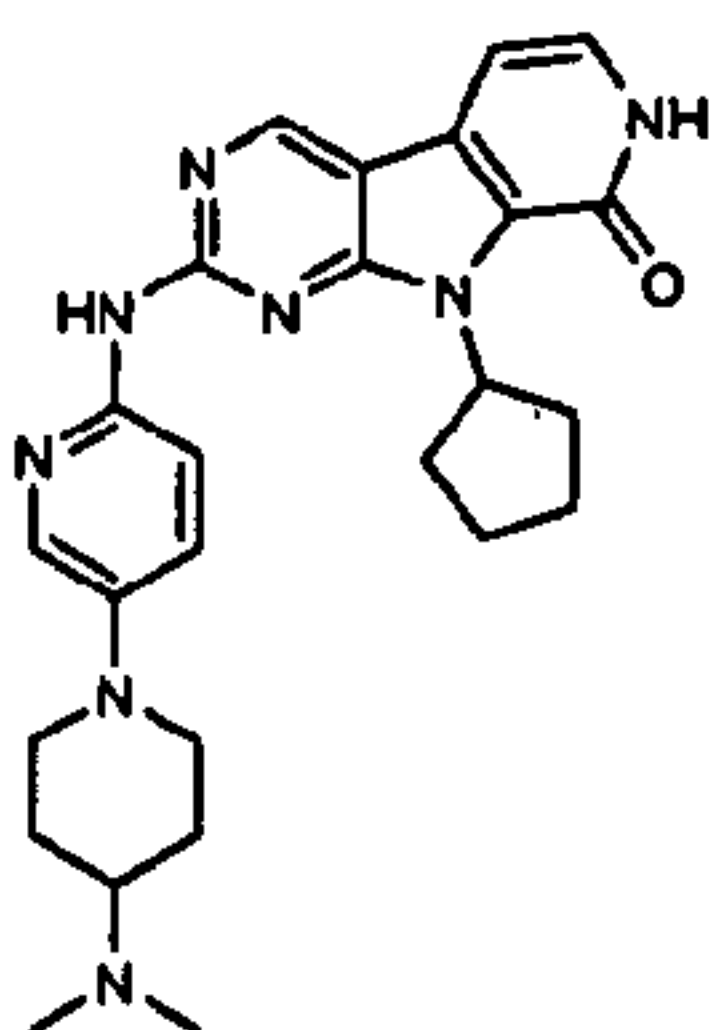
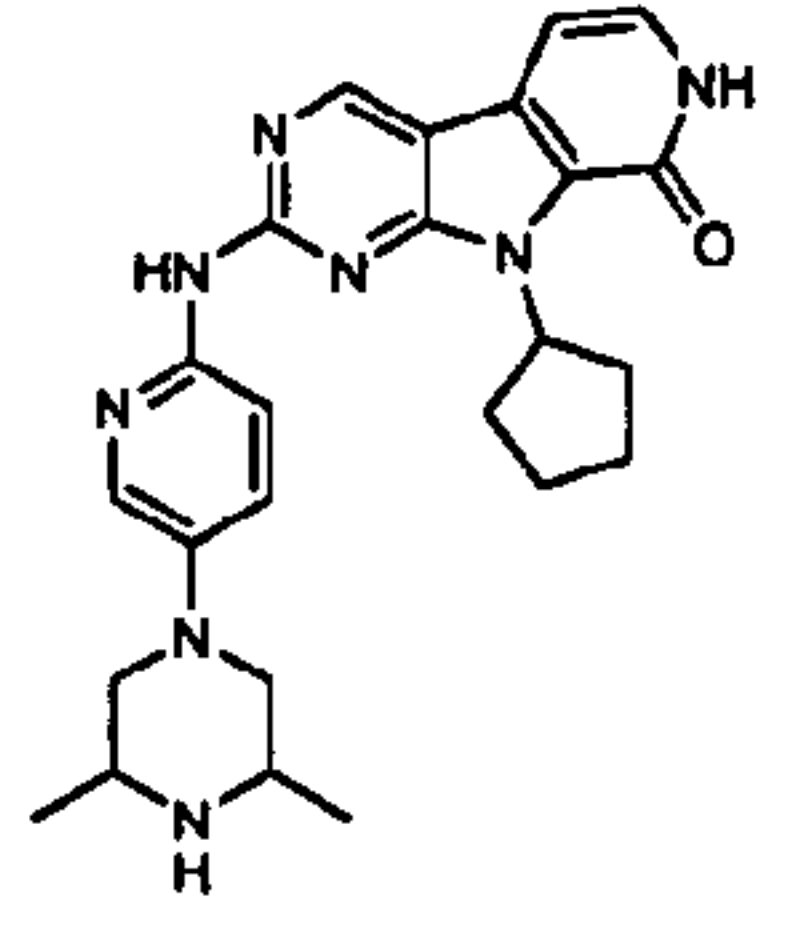
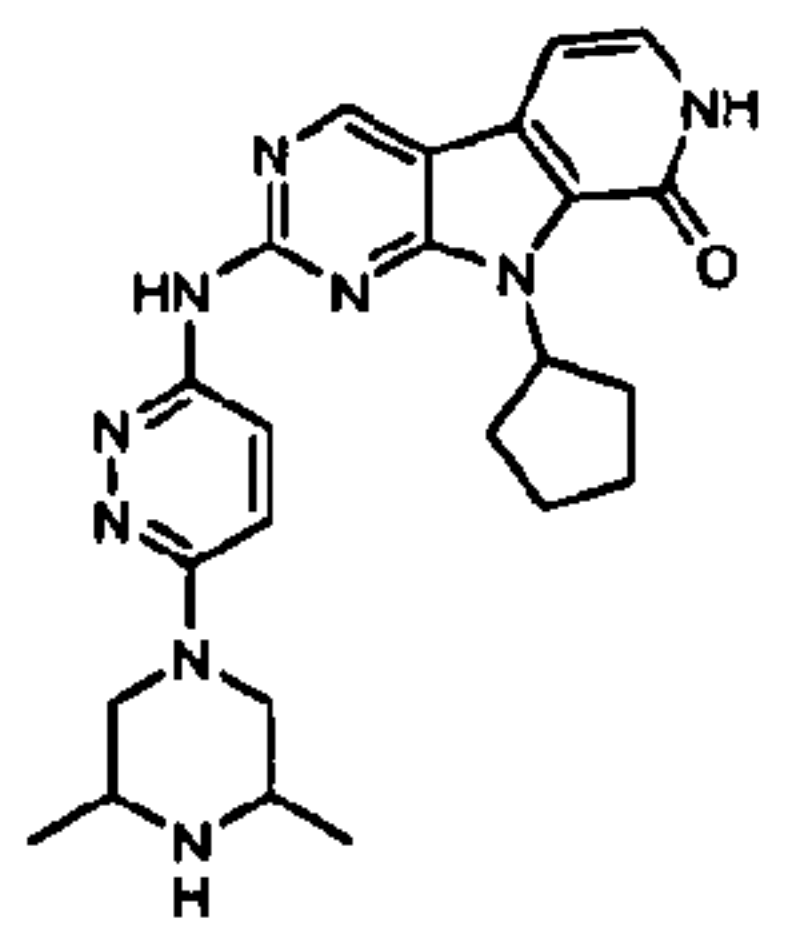
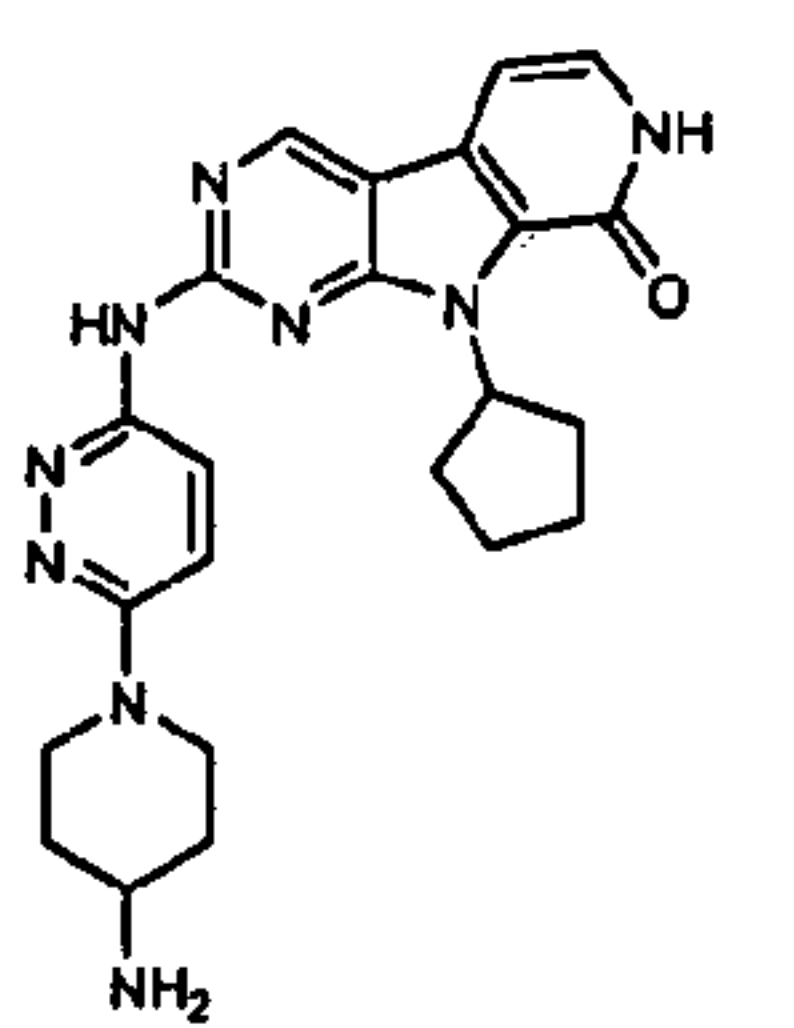
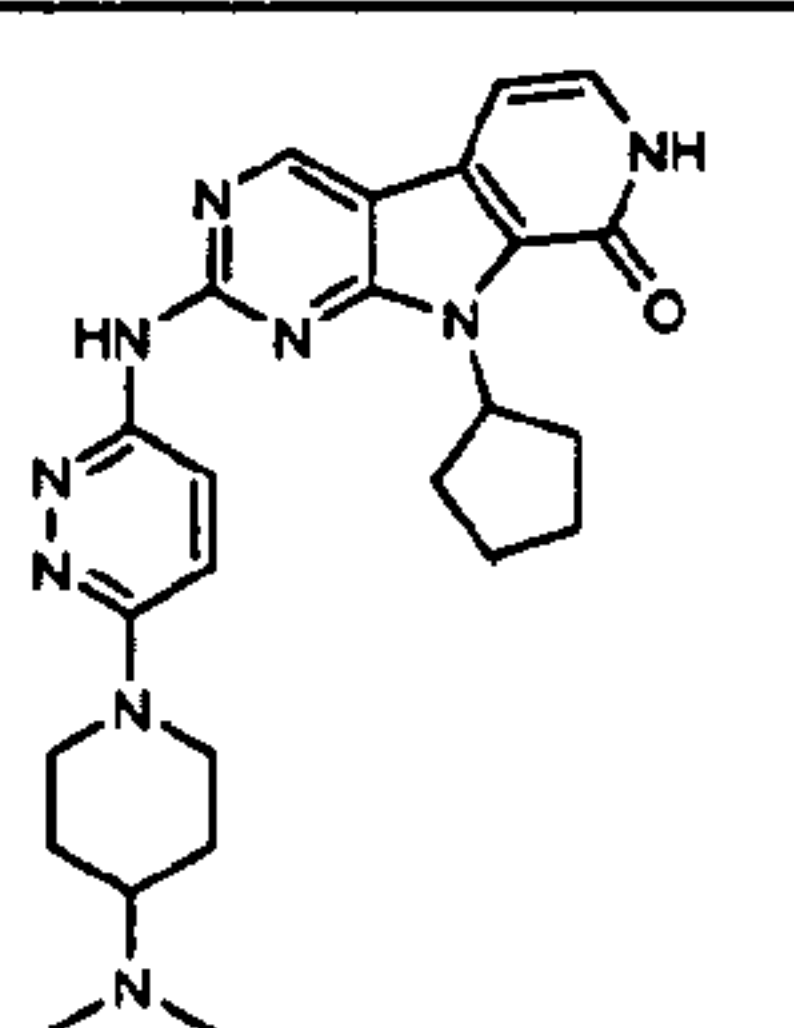
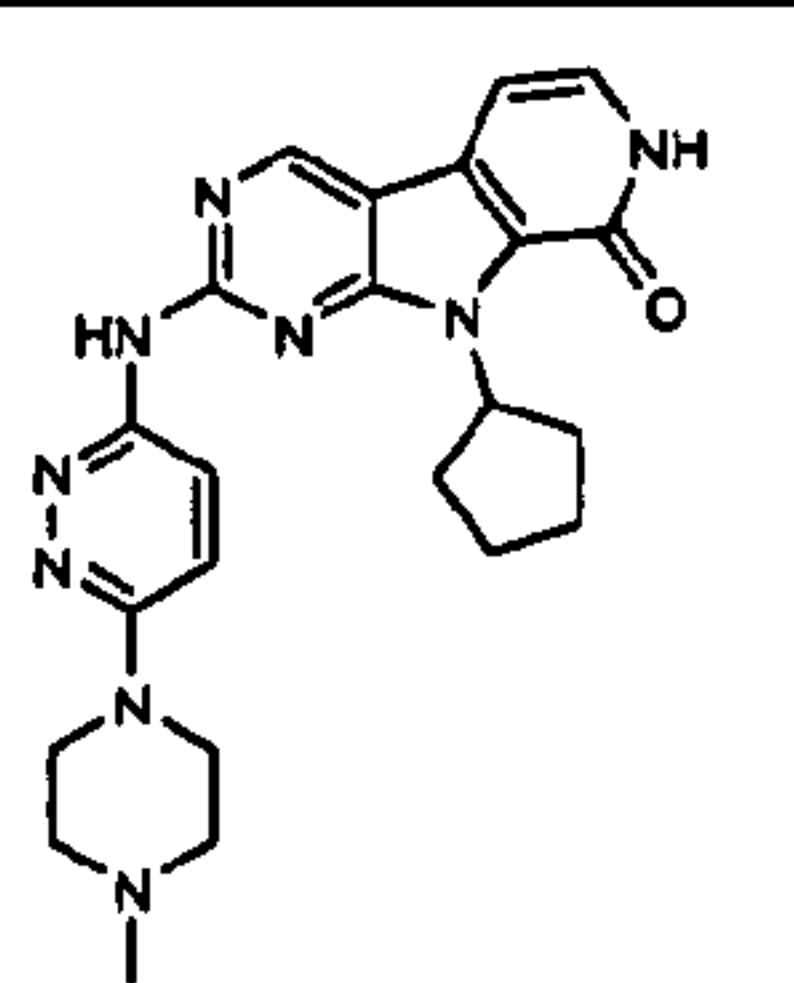


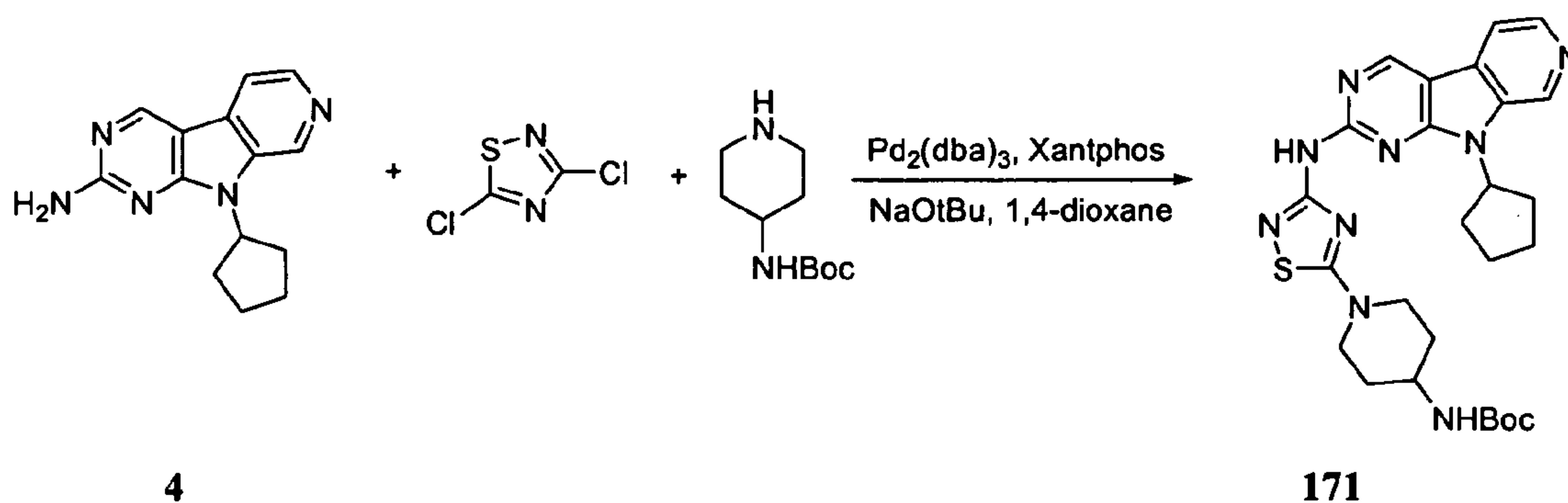
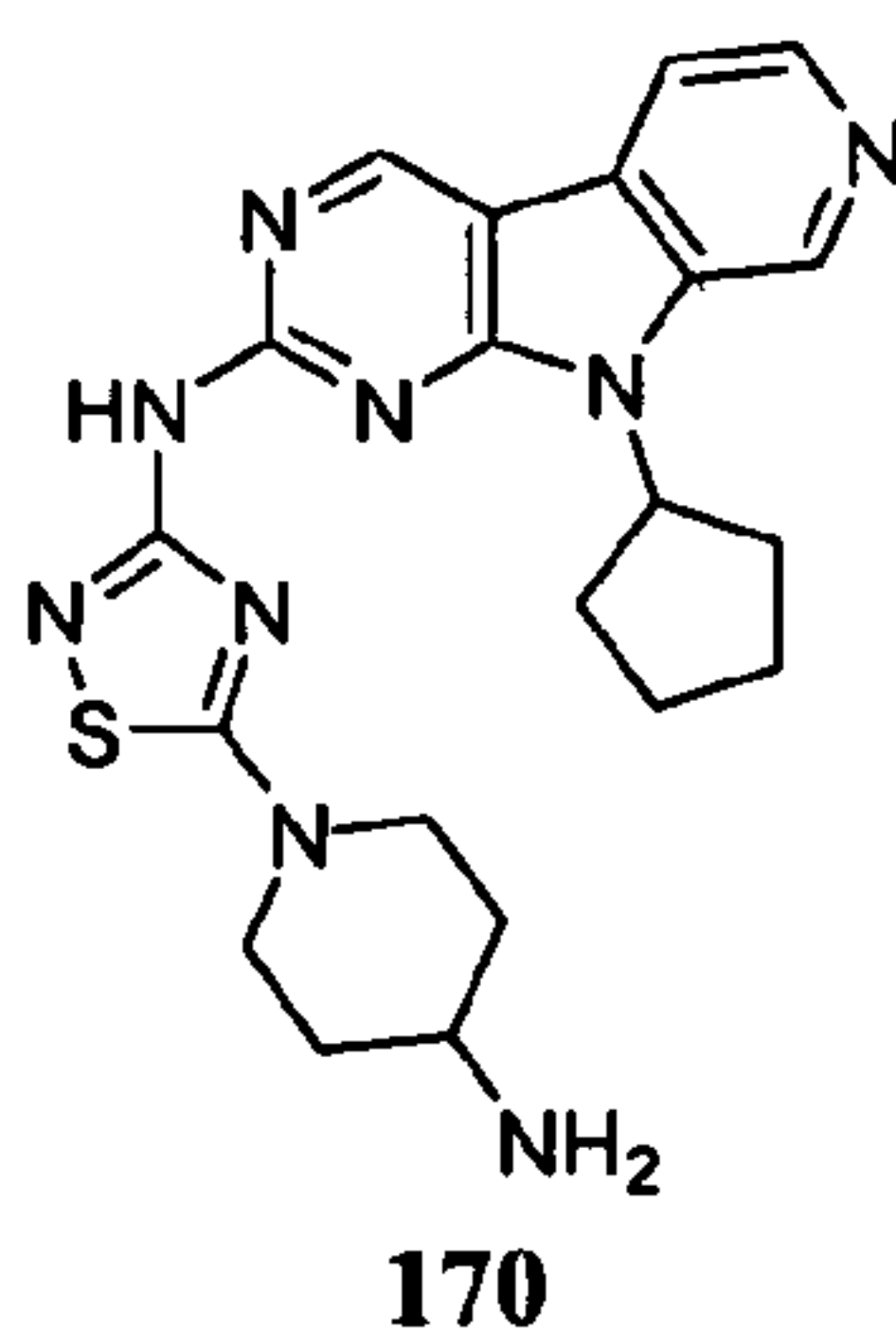


Table 3

| Example # | Structure                                                                            | LCMS retention time (min) | LCMS -ESI (M+1) |
|-----------|--------------------------------------------------------------------------------------|---------------------------|-----------------|
| 123       |    | 0.884                     | 473.4           |
| 124       |   | 0.873                     | 459.2           |
| 125       |  | 0.830                     | 460.2           |
| 126       |  | 0.821                     | 446.2           |
| 127       |  | 0.832                     | 474.2           |
| 128       |  | 0.809                     | 446.2           |



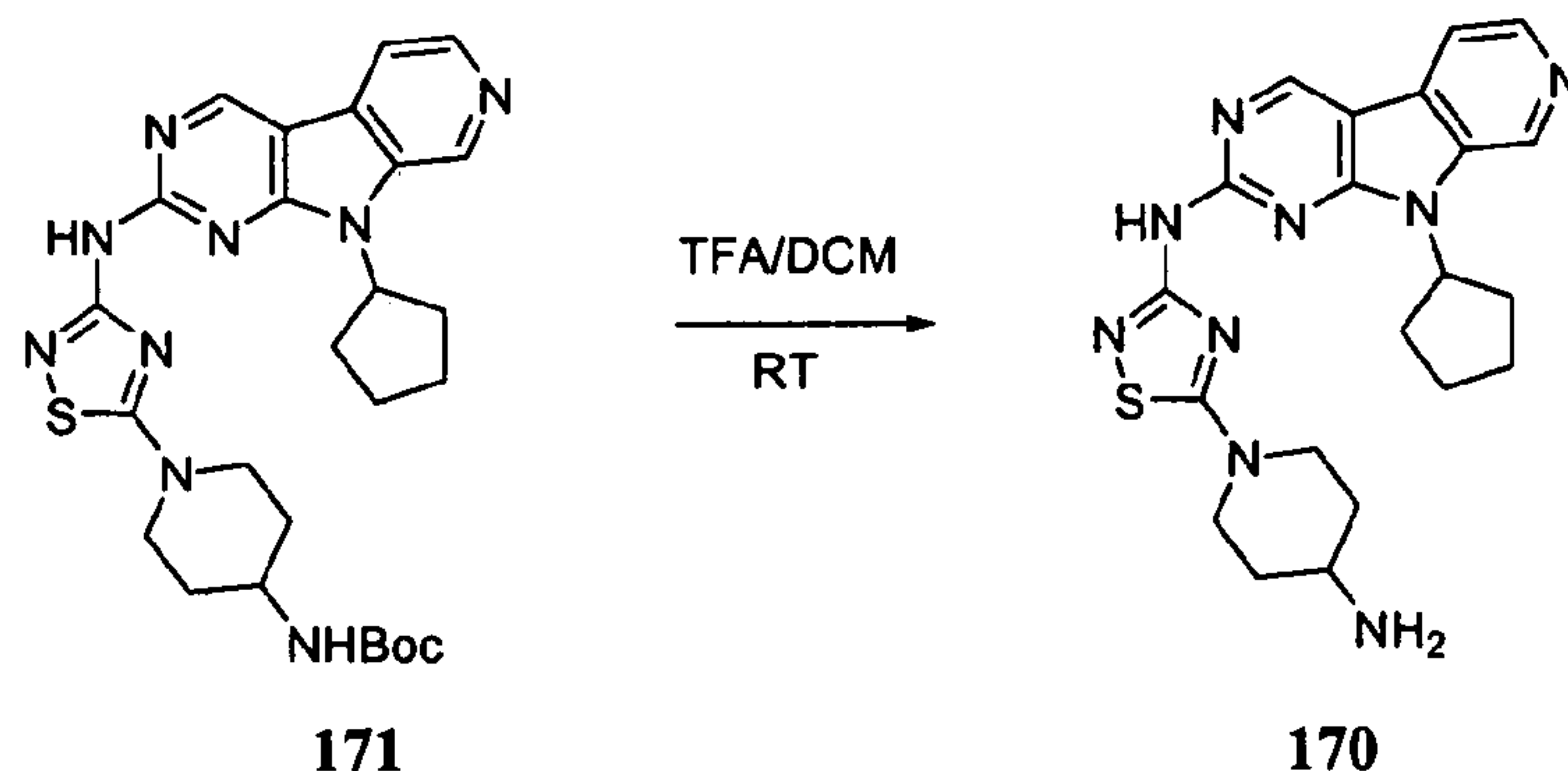
| Example # | Structure | LCMS retention time (min) | LCMS -ESI (M+1) |
|-----------|-----------|---------------------------|-----------------|
| 129       |           | 0.819                     | 446.2           |
| 130       |           | 0.838                     | 460.3           |

**EXAMPLE 131**

**1,1-Dimethylethyl 1-(3-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-5-1,2,4-thiadiazolyl)-4-piperidine carboxylate (171):** A mixture of 3,5-dichloro-1,2,4-thiadiazole (0.015g, 0.099mmol) and *tert*-butyl piperidin-4-ylcarbamate (0.020g, 0.099mol) in 1mL dioxane was purged with nitrogen gas for 1 minute. The reaction was stirred at room temperature for 30 minutes. To it was added compound 4 (0.0250 g, 0.099 mmol), Xantphos (0.0086 g, 0.015 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.0068 g, 0.0074 mmol) and sodium *tert*-butoxide (0.024 g, 0.25 mmol). The mixture was purged



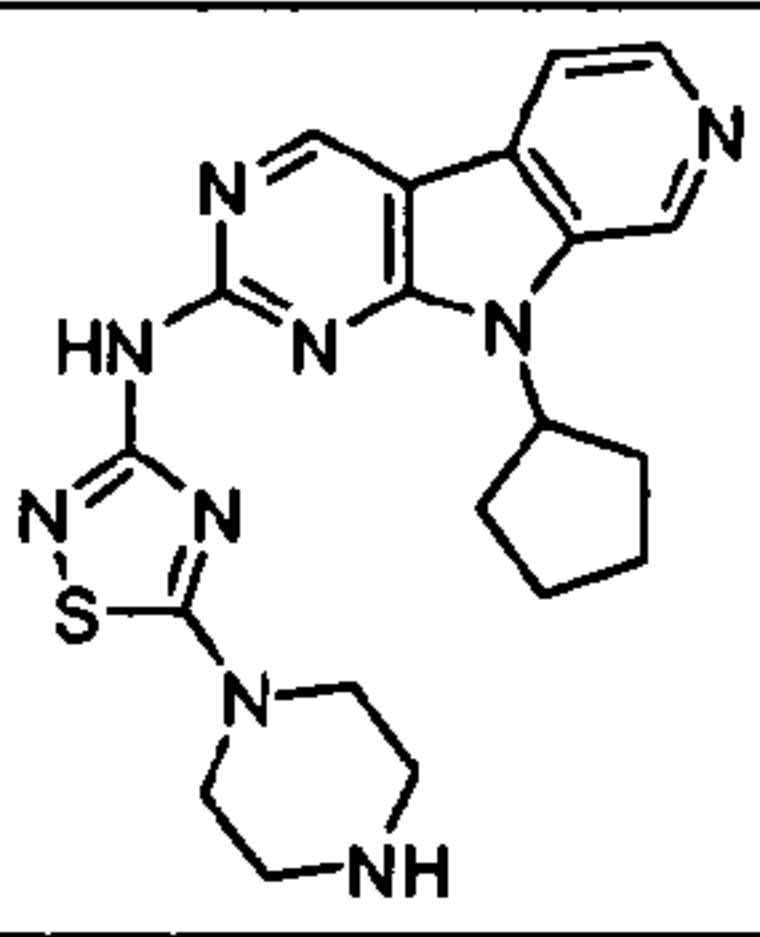
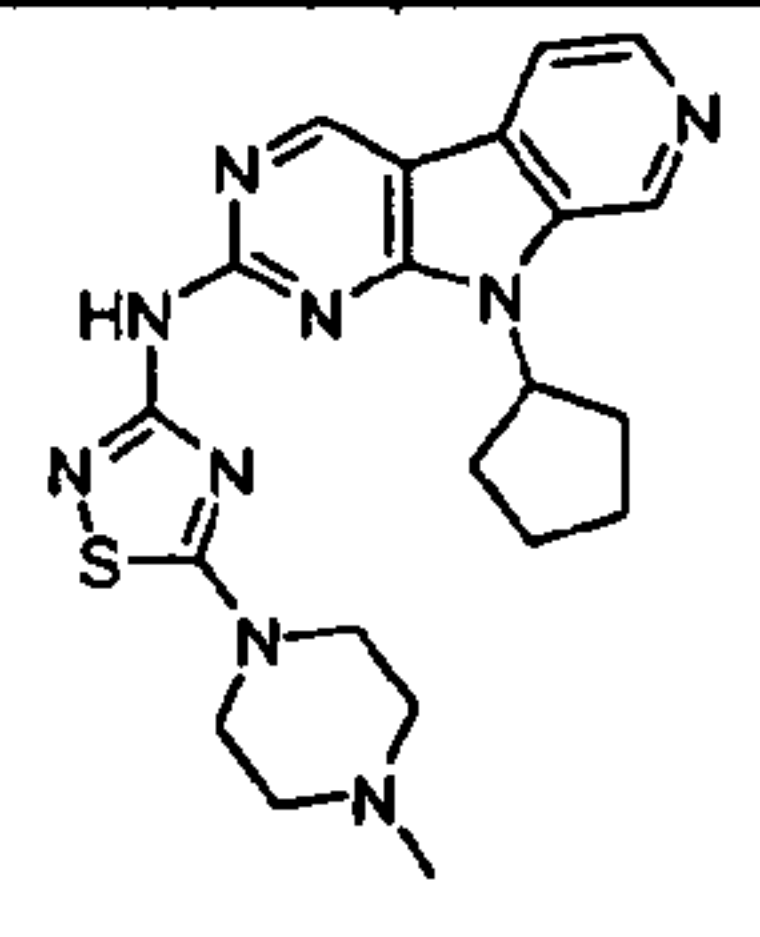
again with nitrogen for 1 min and heated at 115°C for 3 h. After cooling to room temperature, the solvent was removed using Gene Vac. The residue was sonicated with 2mL methanol. The solid was removed by filtration, washed with 2x1mL methanol. The combined solution was purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of CH<sub>3</sub>CN in water containing 0.1%TFA to provide compound **171** as a TFA salt. LCMS-ESI (POS), M/Z, M+1: 536.2



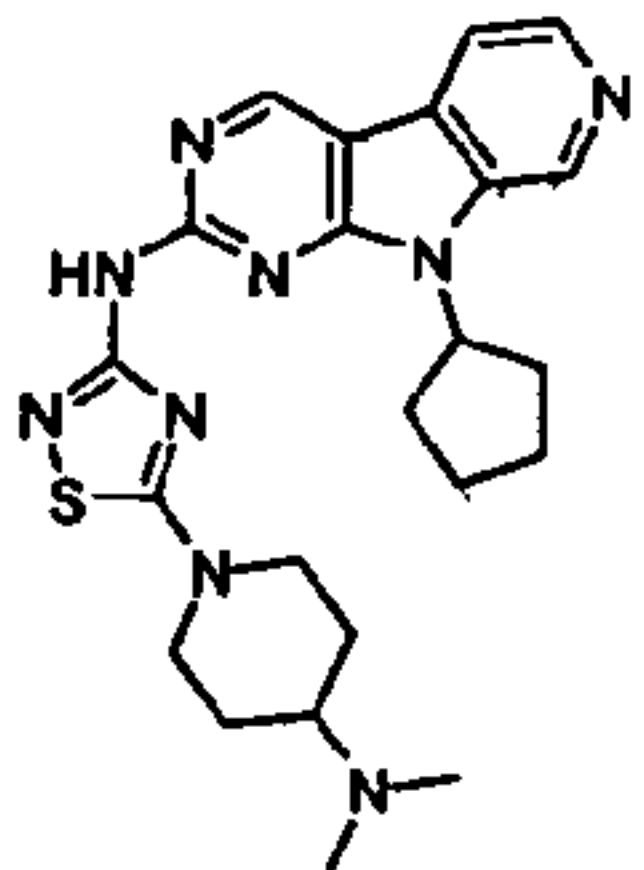
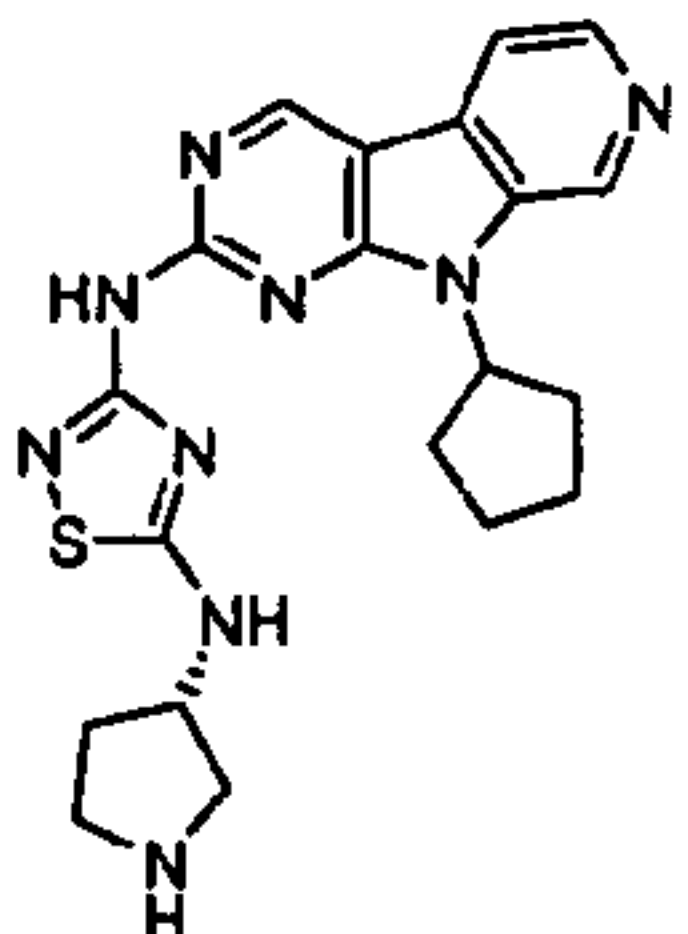
**4-Amino-1-(3-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-5-1,2,4-thiadiazolyl)-piperidine (170):** Compound **171** was treated with 15% TFA/DCM (2mL) at room temperature for an hour. The solvent was evaporated. The residue was re-dissolved in 4mL methanol and purified on a C-18 reverse phase column (150 x 30 mm, 4 micro) using Mass directed preparative HPLC and gradient elution of CH<sub>3</sub>CN in water containing 0.1%TFA to provide compound **170** as a TFA salt. LCMS retention time (time): 0.752. LCMS-ESI (POS), M/Z, M+1: 436.1

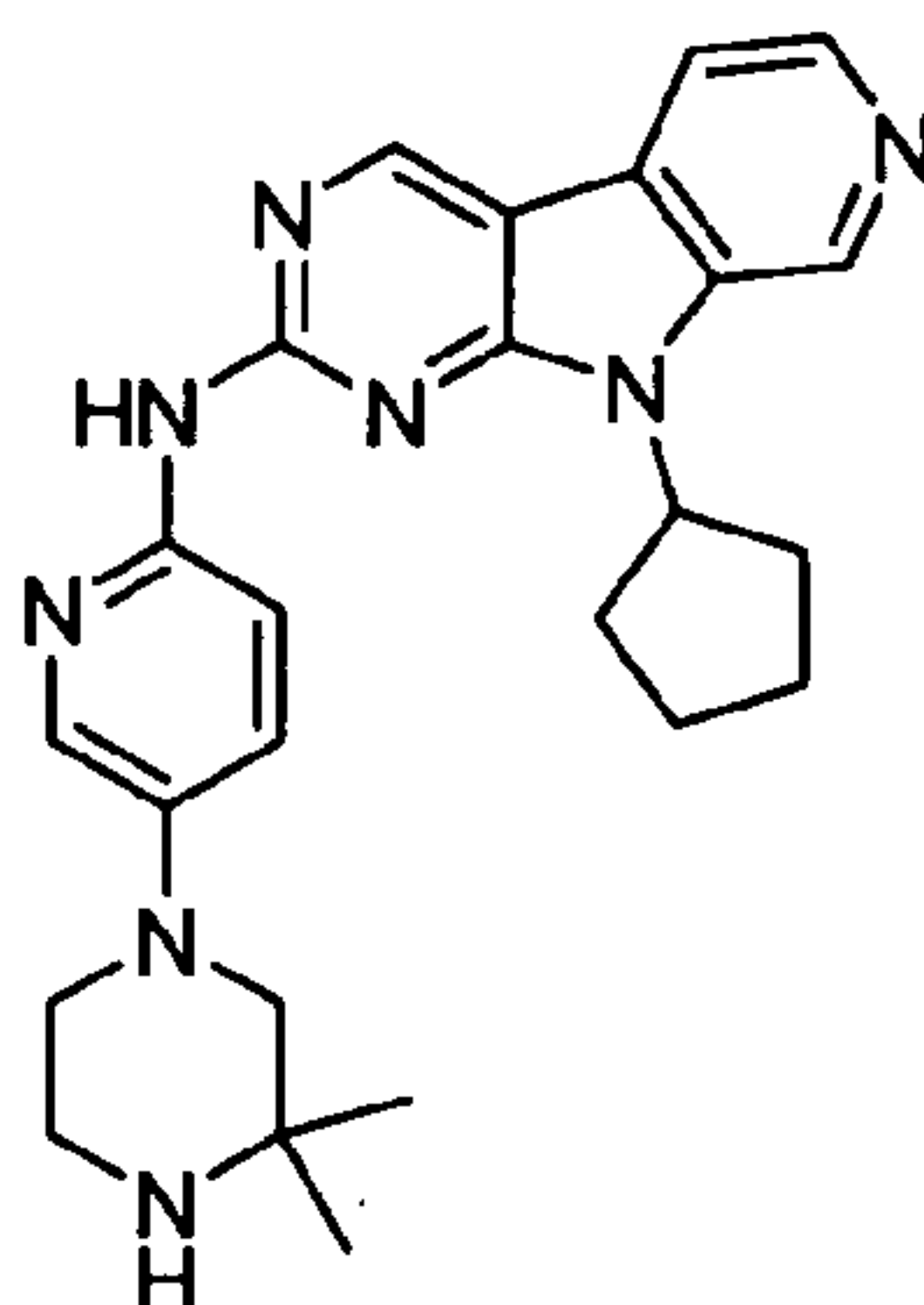
Examples 132-135 (table 4) were prepared using conditions as described for example 131 with deprotection when necessary, replacing *tert*-butyl piperidin-4-ylcarbamate with proper amine.

Table 4

| Example # | Structure                                                                            | LCMS retention time (min) | LCMS-ESI (M+1) |
|-----------|--------------------------------------------------------------------------------------|---------------------------|----------------|
| 132       |  | 0.729                     | 422.2          |
| 133       |  | 0.746                     | 436.1          |



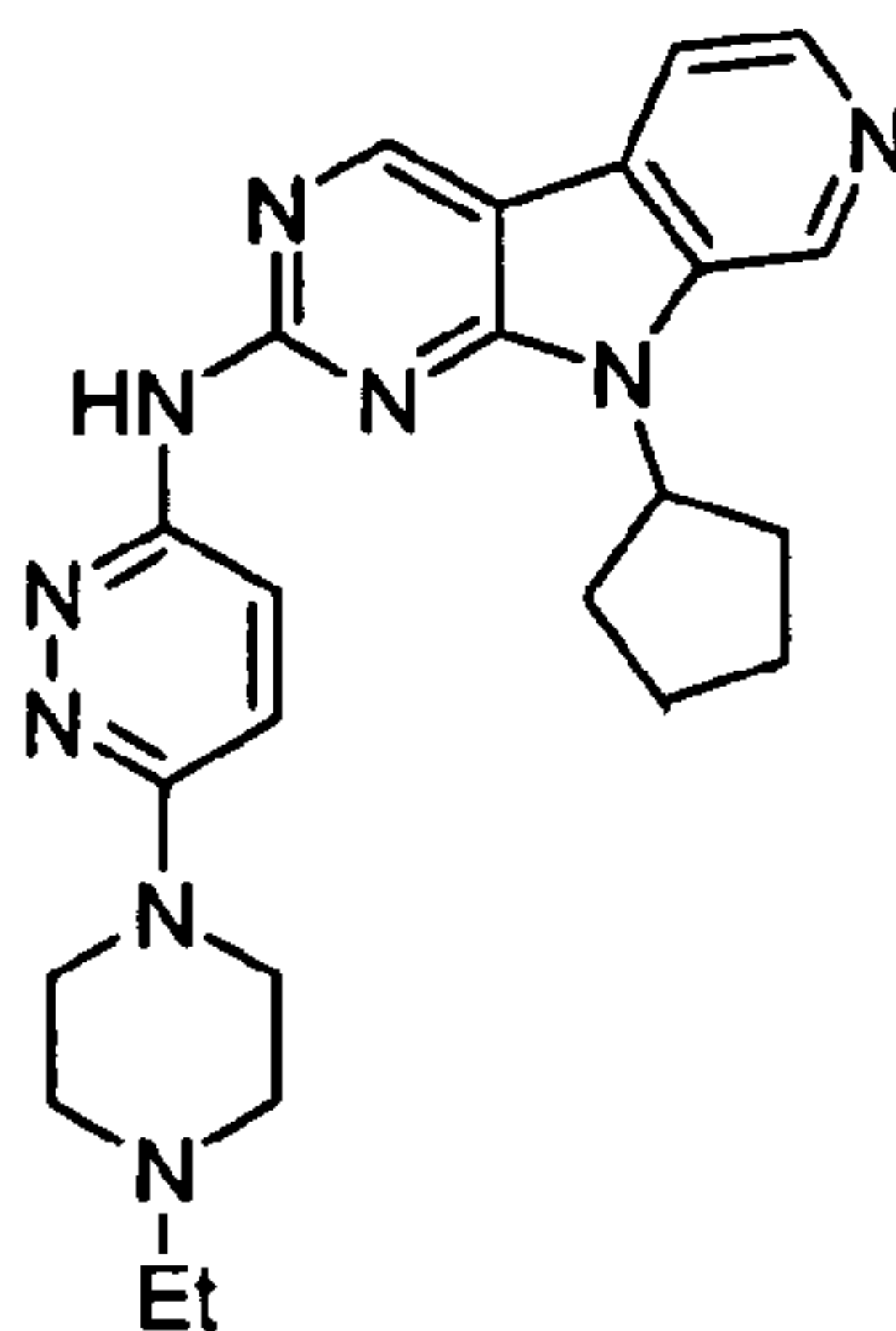
| Example # | Structure                                                                           | LCMS retention time (min) | LCMS-ESI (M+1) |
|-----------|-------------------------------------------------------------------------------------|---------------------------|----------------|
| 134       |   | 0.738                     | 464.2          |
| 135       |  | 0.747                     | 422.2          |

**EXAMPLE 136****172**

**9-Cyclopentyl-N-(5-(3,3-dimethyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

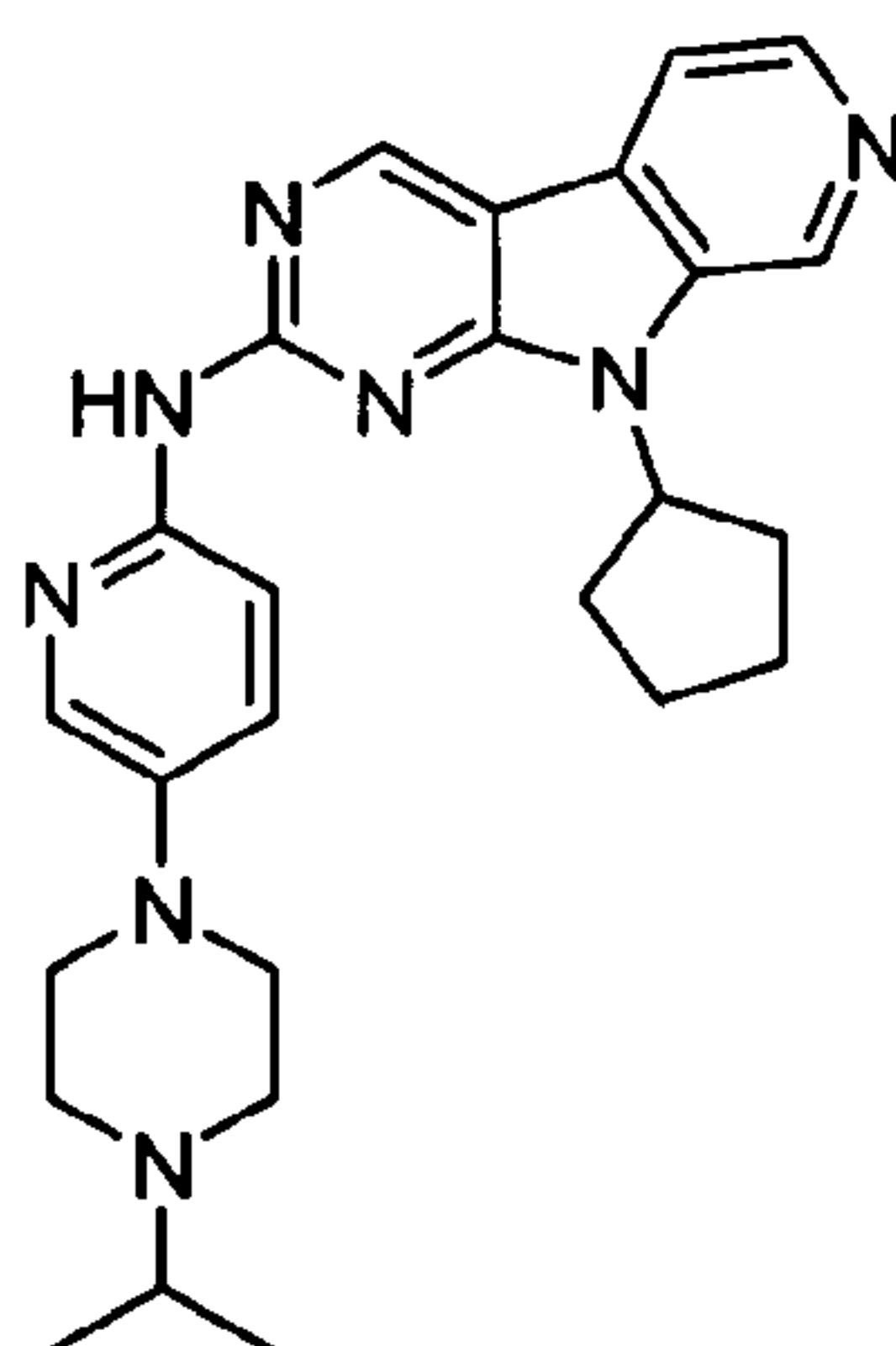
Compound **172** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.76 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.16 (1H, d, J = 10 Hz), 8.02 (1H, d, J = 5 Hz), 8.00 (1H, d, J = 2 Hz), 7.43 (1H, dd, J = 10 Hz, J = 2 Hz), 5.36 (1H, p, J = 10 Hz), 2.99 (2H, t, m), 2.89 (2H, m), 2.83 (2H, s), 2.39 (2H, m), 2.20-2.05 (4H, m), 1.77 (2H, m), 1.13 (6H, s) ppm; LCMS-ESI (POS), M/Z, M+1: Found 442.2, Calculated 442.3.



**EXAMPLE 137****173**

**9-Cyclopentyl-N-(6-(4-ethyl-1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound 173 was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.08 (1H, s), 8.91 (1H, s), 8.55 (1H, d, J = 10 Hz), 8.52 (1H, d, J = 5 Hz), 8.33 (1 H, s), 7.86 (1H, d, J = 5 Hz), 7.09 (1H, d, J = 10 Hz), 5.36 (1H, p, J = 10 Hz), 3.66 (4H, t, J = 5 Hz), 2.63 (4H, t, J = 5 Hz), 2.51 (2H, q, J = 5 Hz), 2.39 (2H, m), 2.20 (2H, m), 2.13 (2H, m), 1.89 (2H, m), 1.16 (3H, t, J = 5 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 443.2, Calculated 443.3.

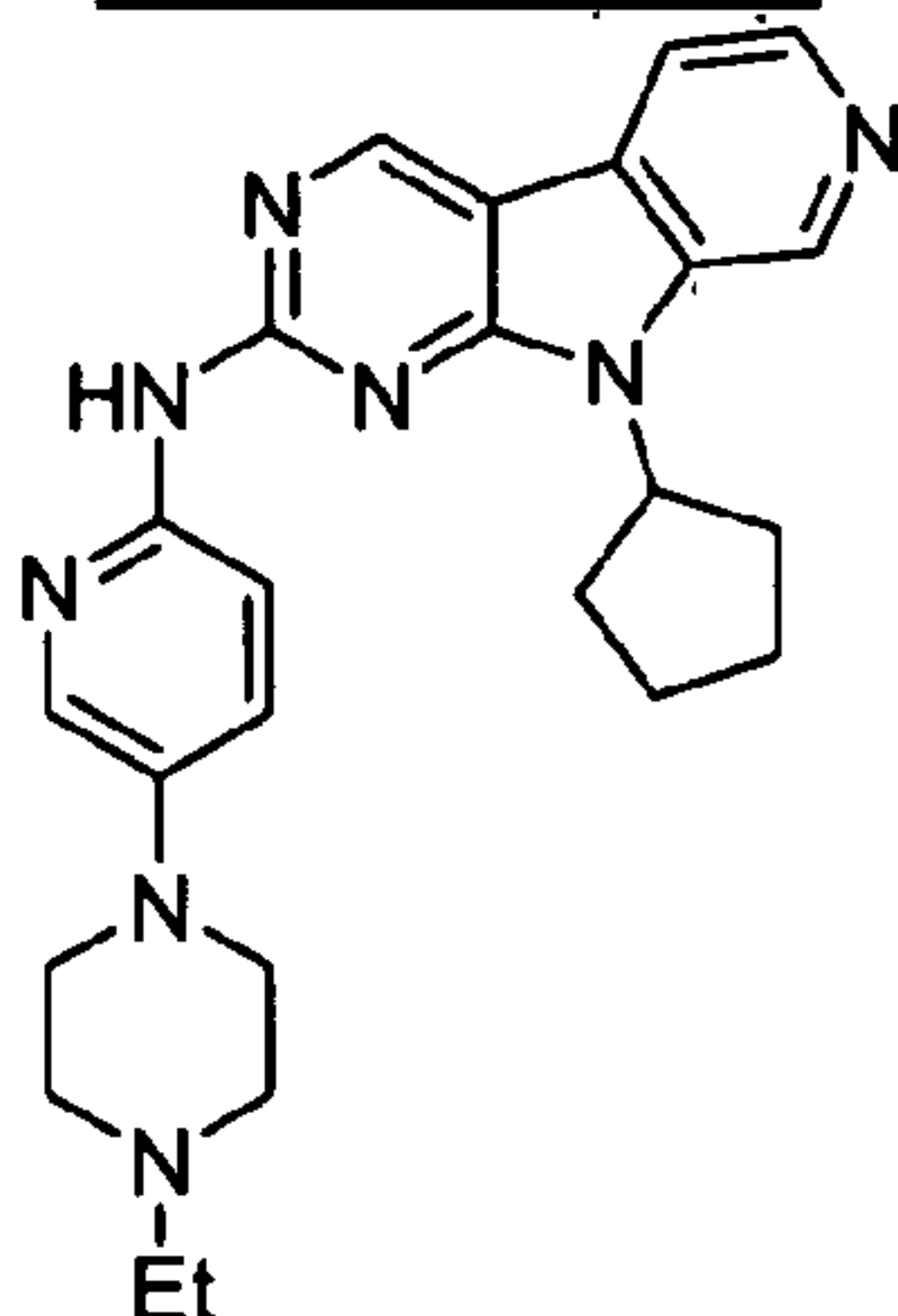
**EXAMPLE 138****174**

**9-Cyclopentyl-N-(5-(4-(1-methylethyl)-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound 174 was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.09 (1H, s), 8.90 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.39 (1H, d, J = 10 Hz), 8.33 (1 H, bs), 8.09 (1H, d, J = 5 Hz), 7.83 (1H, dd, J = 5 Hz, J = 2 Hz), 7.39 (1H, dd, J = 5 Hz,

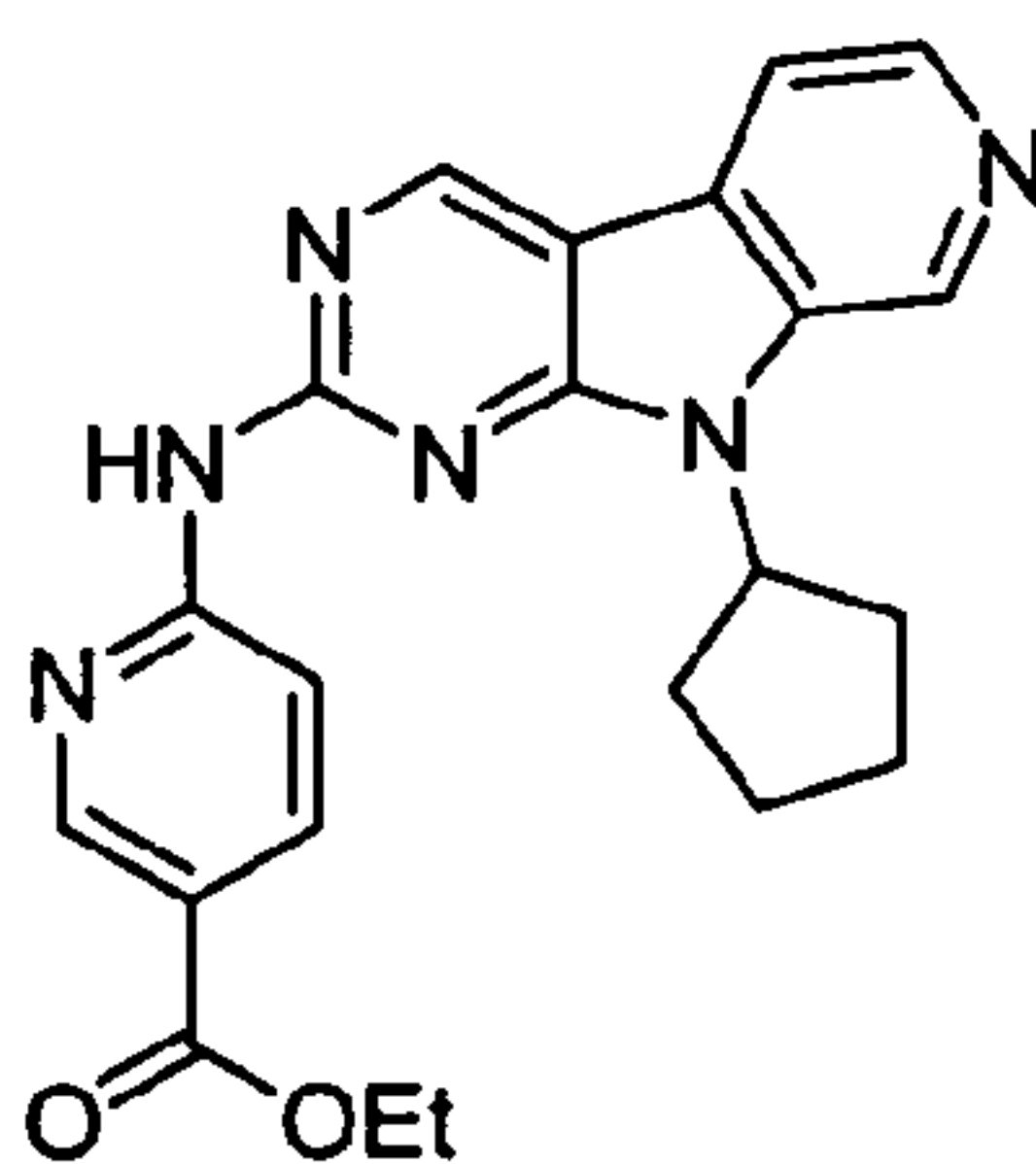


$J = 2$  Hz), 5.36 (1H, p,  $J = 10$  Hz), 3.22 (4H, t,  $J = 5$  Hz), 2.76 (1H, m,  $J = 10$  Hz), 2.74 (4H, t,  $J = 5$  Hz), 2.44 (2H, m), 2.20 (2H, m), 2.14 (2H, m), 1.88 (2H, m), 1.12 (6H, d,  $J = 10$  Hz) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 456.1, Calculated 456.3.

**EXAMPLE 139****175**

**9-Cyclopentyl-N-(5-(4-ethyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **175** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.08 (1H, s), 8.91 (1H, s), 8.52 (1H, d,  $J = 5$  Hz), 8.41 (1H, d,  $J = 10$  Hz), 8.22 (1 H, bs), 8.08 (1H, d,  $J = 2$  Hz), 7.83 (1H, d,  $J = 5$  Hz), 7.40 (1H, dd,  $J = 10$  Hz,  $J = 2$  Hz), 5.36 (1H, p,  $J = 10$  Hz), 3.27 (4H, m), 2.71 (2H, m), 2.56 (2H, m), 2.44 (2H, m), 2.20 (2H, m), 2.14 (2H, m), 1.89 (2H, m), 1.19 (3H, t,  $J = 10$  Hz) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 442.2, Calculated 442.3.

**EXAMPLE 140****176**

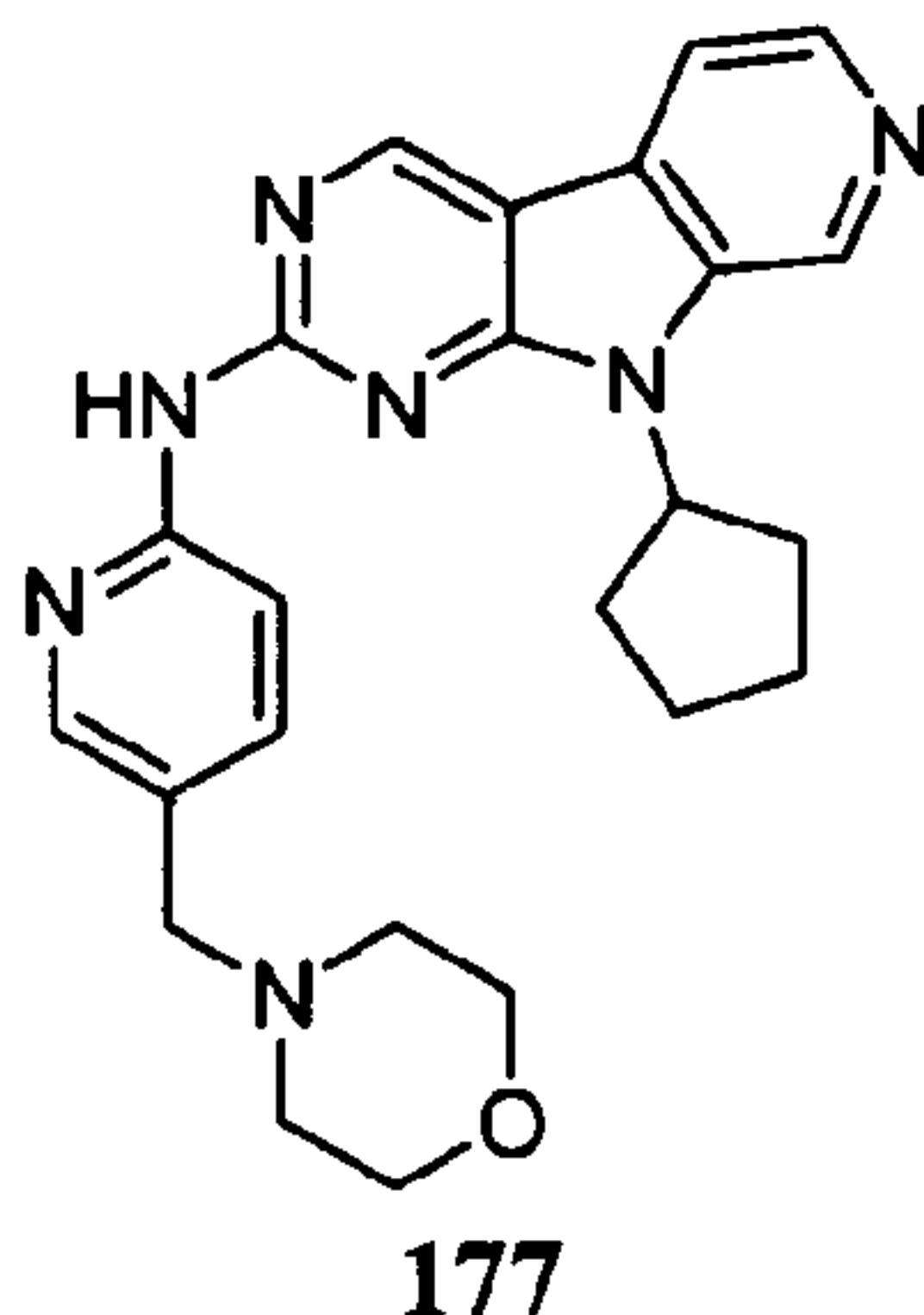
**Ethyl 6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinecarboxylate**

Compound **176** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.80 (1H, s), 9.48 (1H, s), 9.17 (1H, s), 8.87 (1H, d,  $J = 2$  Hz), 8.56 (1H, d,  $J = 5$  Hz), 8.53 (1H, d,  $J = 10$  Hz), 8.31 (1 H, dd,  $J = 10$  Hz,  $J = 2$  Hz), 8.25 (1H, d,  $J =$



5 Hz), 5.36 (1H, p, J = 10 Hz), 4.34 (2H, q, J = 10 Hz), 2.42 (2H, m), 2.16 – 2.08 (4H, m), 1.81 (2H, m), 1.35 (3H, t, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 402.1, Calculated 402.2.

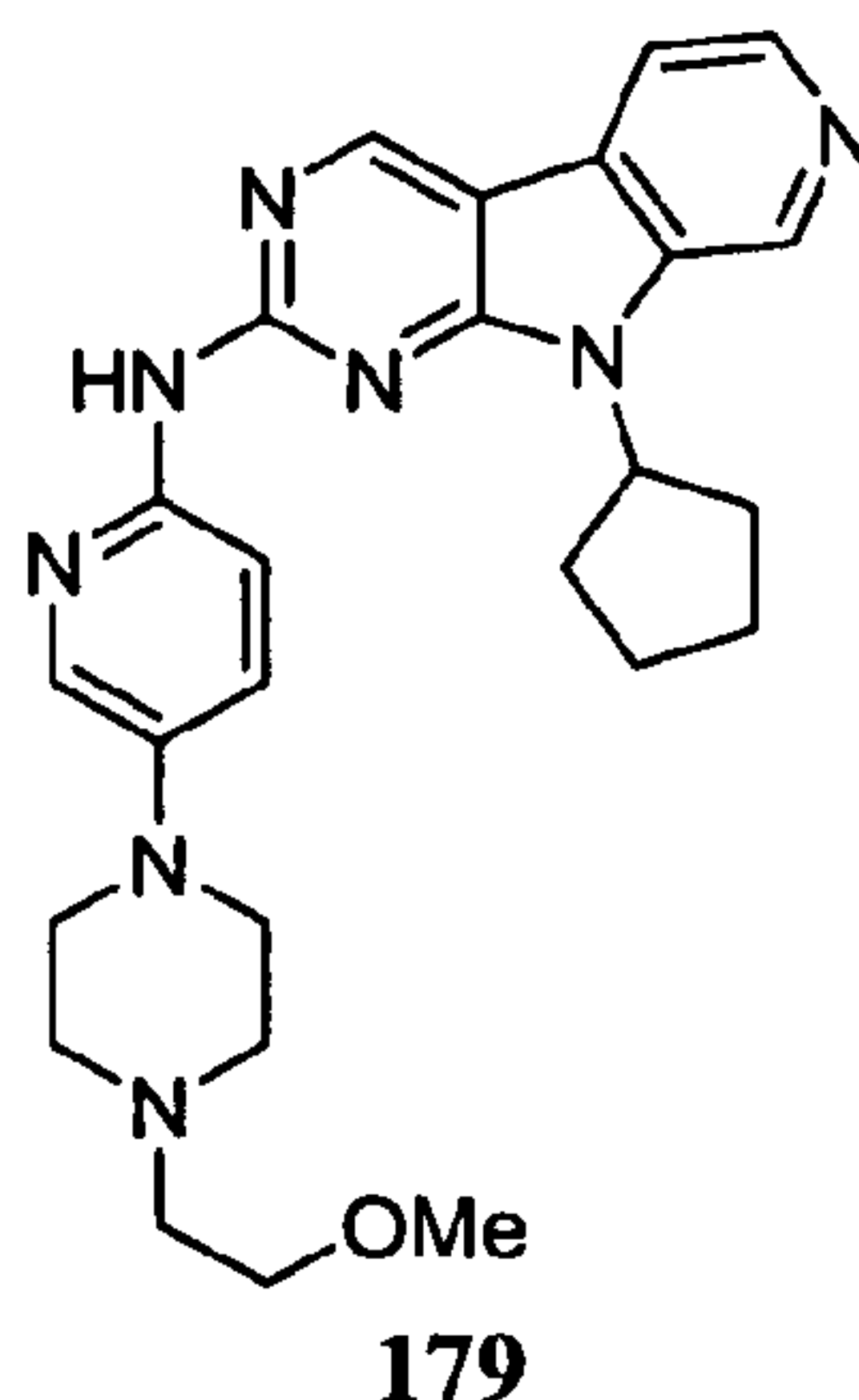
### EXAMPLE 141



**9-Cyclopentyl-N-(5-(4-morpholinylmethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **177** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 10.04 (1H, s), 9.33 (1H, s), 9.04 (1H, s), 8.45 (1H, d, J = 5 Hz), 8.35 (1H, d, J = 10 Hz), 8.23 (1H, d, J = 2 Hz), 8.07 (1H, d, J = 10 Hz), 7.75 (1H, dd, J = 10 Hz, J = 2 Hz), 5.39 (1H, p, J = 10 Hz), 3.58 (4H, t, J = 5 Hz), 2.05 (2H, s), 2.45 – 2.40 (6H, m), 2.20 – 2.06 (4H, m), 1.79 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 429.1, Calculated 429.2.

### EXAMPLE 142

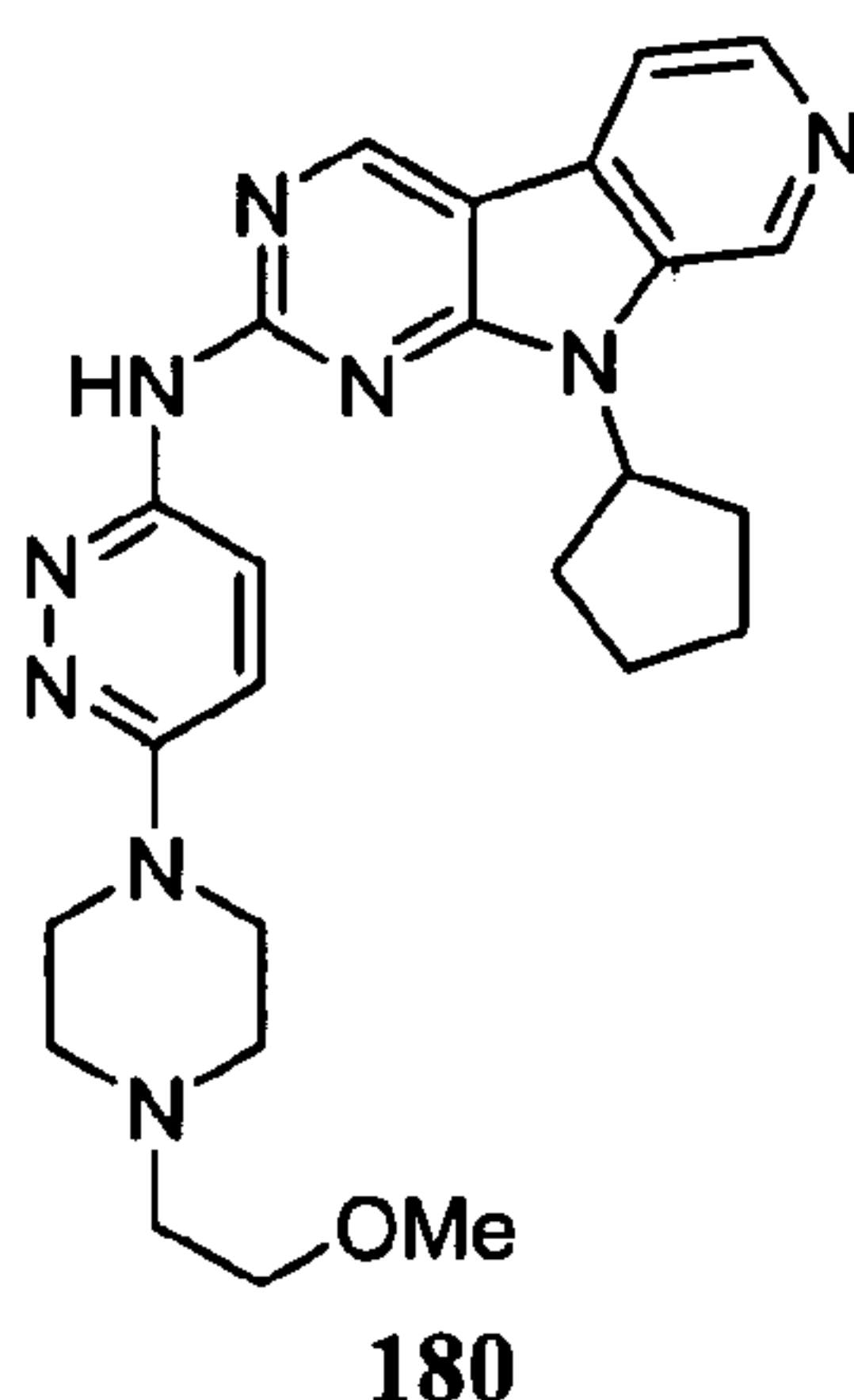


**9-Cyclopentyl-N-(5-(4-(2-(methoxy)ethyl)-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



Compound **179** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz, *DMSO-d6*)  $\delta$  9.74 (1H, s), 9.25 (1H, s), 8.99 (1H, s), 8.43 (1H, d,  $J = 5$  Hz), 8.16 (1H, d,  $J = 10$  Hz), 8.03-8.02 (2 H, m), 7.46 (1H, dd,  $J = 10$  Hz,  $J = 2$  Hz), 5.35 (1H, p,  $J = 10$  Hz), 3.47 (2H, t,  $J = 5$  Hz), 3.25 (3H, s), 3.13 (4H, t,  $J = 5$  Hz), 2.58 (4H, t,  $J = 5$  Hz), 2.53 (2H, t,  $J = 5$  Hz), 2.38 (2H, m), 2.15 – 2.05 (4H, m), 1.76 (2H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 472.2, Calculated 472.2.

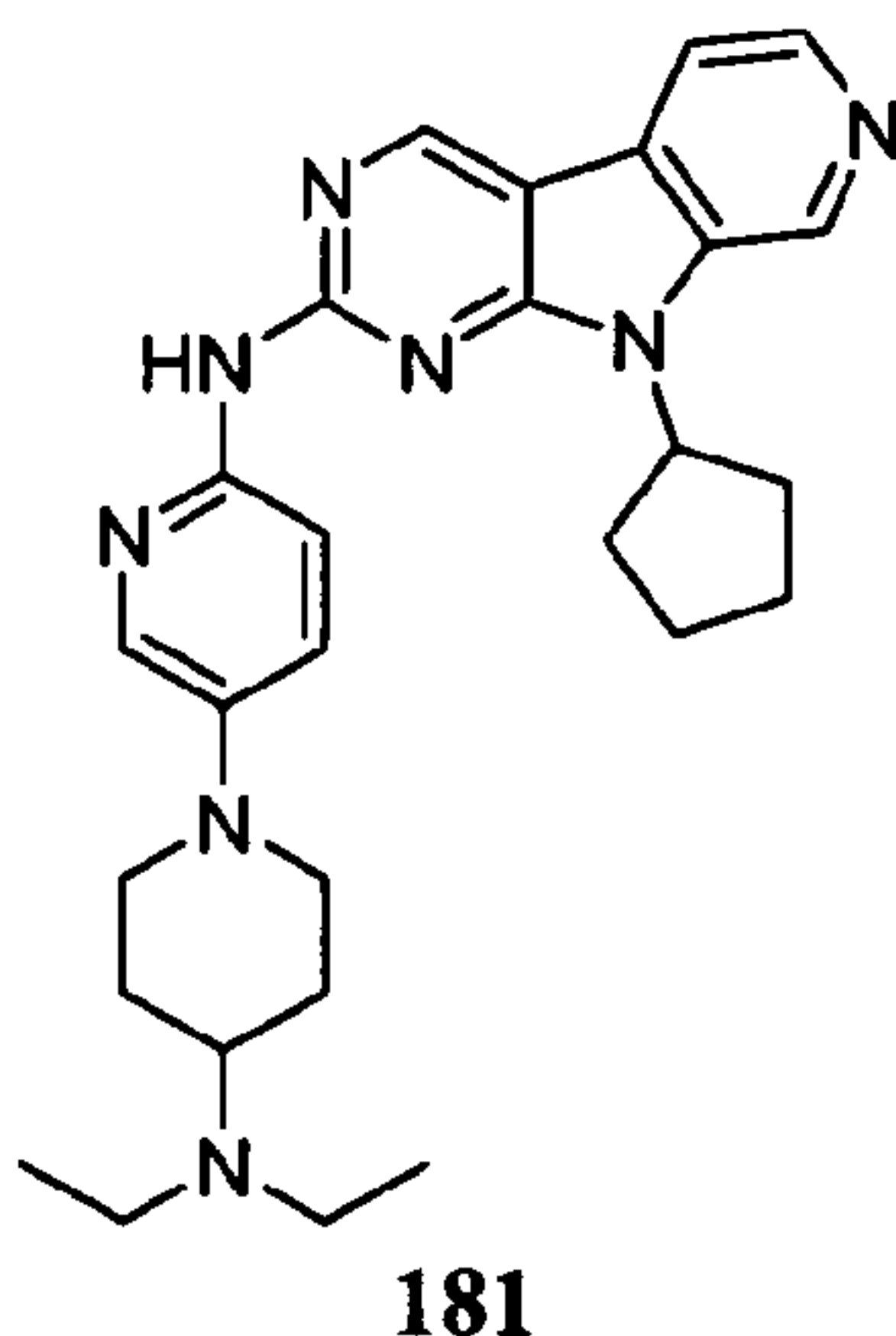
### EXAMPLE 143



**9-Cyclopentyl-N-(6-(4-(2-(methyloxy)ethyl)-1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **180** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz, *CDCl3*)  $\delta$  9.09 (1H, s), 8.92 (1H, s), 8.55 (1H, d,  $J = 10$  Hz), 8.53 (1H, d,  $J = 5$  Hz), 8.40 (1H, bs), 7.86 (1 H, d,  $J = 5$  Hz), 7.09 (1H, d,  $J = 10$  Hz), 5.39 (1H, p,  $J = 10$  Hz), 3.69 (4H, m), 3.60 (2H, t,  $J = 5$  Hz), 2.80 – 2.69 (6H, m), 2.37 (2H, m), 2.20 (2H, m), 2.13 (2H, m), 1.90 (2H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 473.2, Calculated 473.3.

### EXAMPLE 144

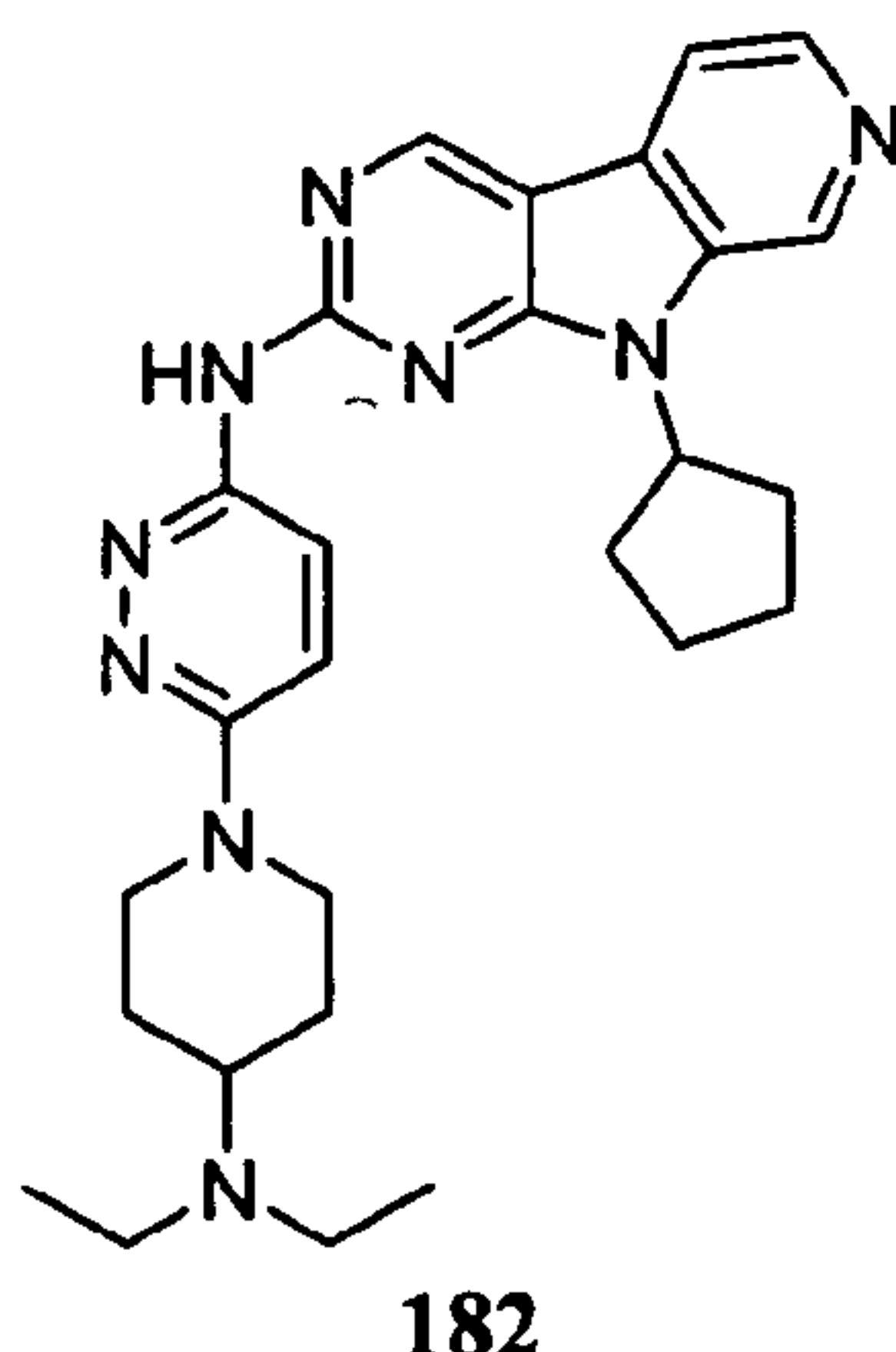


**9-Cyclopentyl-N-(5-(4-(diethylamino)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



Compound **181** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz, *DMSO-d*<sub>6</sub>)  $\delta$  9.74 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, *J* = 5 Hz), 8.15 (1H, d, *J* = 10 Hz), 8.03 (1H, s), 8.02 (1H, d, *J* = 2 Hz), 7.46 (1H, dd, *J* = 10 Hz, *J* = 5 Hz), 5.36 (1H, p, *J* = 10 Hz), 3.72 (2H, d, *J* = 15 Hz), 2.68 (2H, t, *J* = 10 Hz), 2.52 (4H, m), 2.39 (2H, m), 2.07 (4H, m), 1.77 (4H, m), 1.57 (2H, m), 0.98 (6H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 484.2, Calculated 484.3.

#### EXAMPLE 145

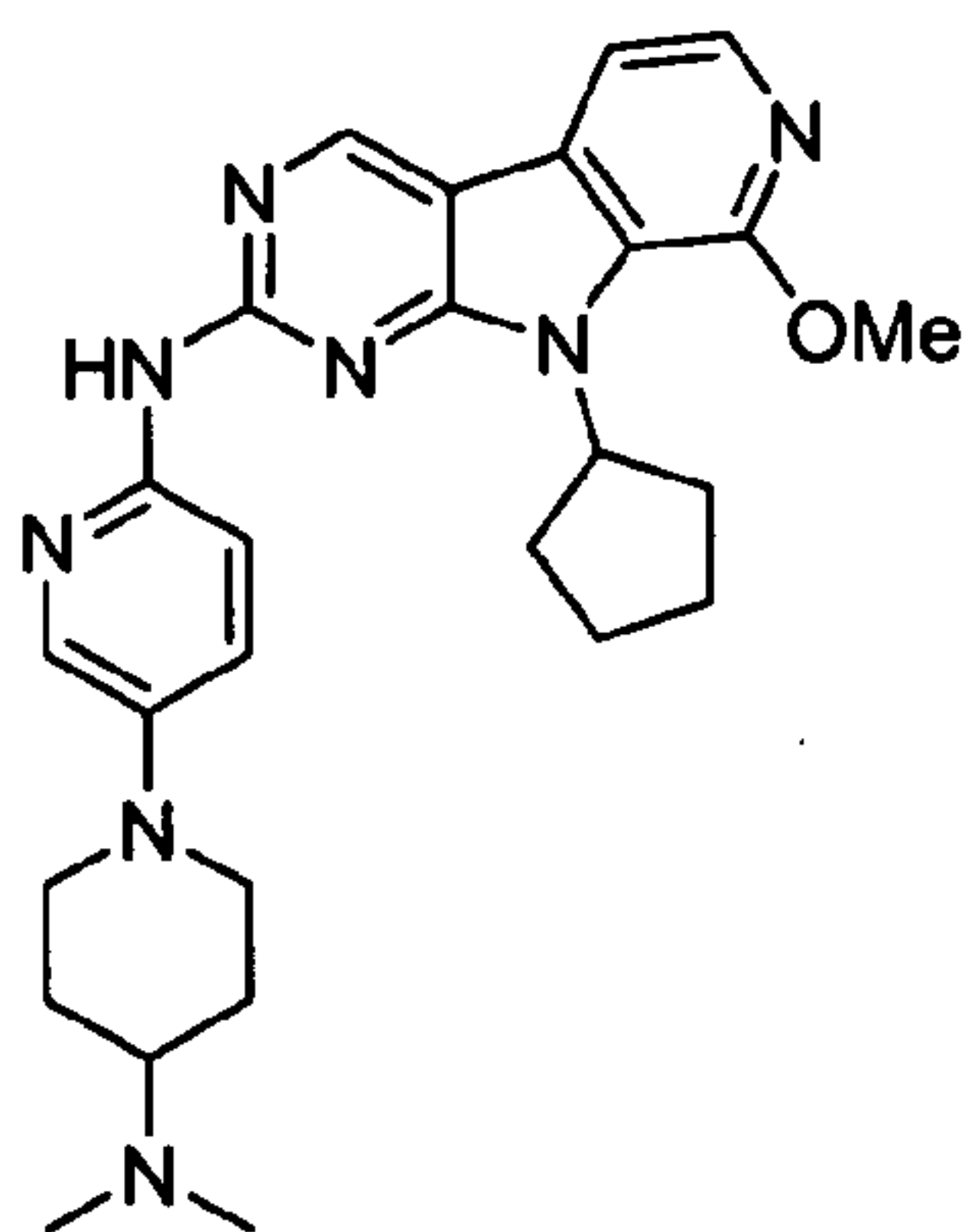


182

**9-Cyclopentyl-N-(6-(4-(diethylamino)-1-piperidiny)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **182** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz, *DMSO-d*<sub>6</sub>)  $\delta$  10.16 (1H, s), 9.26 (1H, s), 9.00 (1H, s), 8.44 (1H, d, *J* = 5 Hz), 8.15 (1H, d, *J* = 10 Hz), 8.03 (1H, s), 7.41 (1H, dd, *J* = 10 Hz), 5.32 (1H, p, *J* = 10 Hz), 4.32 (2H, d, *J* = 15 Hz), 2.68 (2H, t, *J* = 10 Hz), 2.52 (4H, m), 2.39 (2H, m), 2.07 (4H, m), 1.77 (4H, m), 1.57 (2H, m), 0.98 (6H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 485.2, Calculated 485.3.

#### EXAMPLE 146

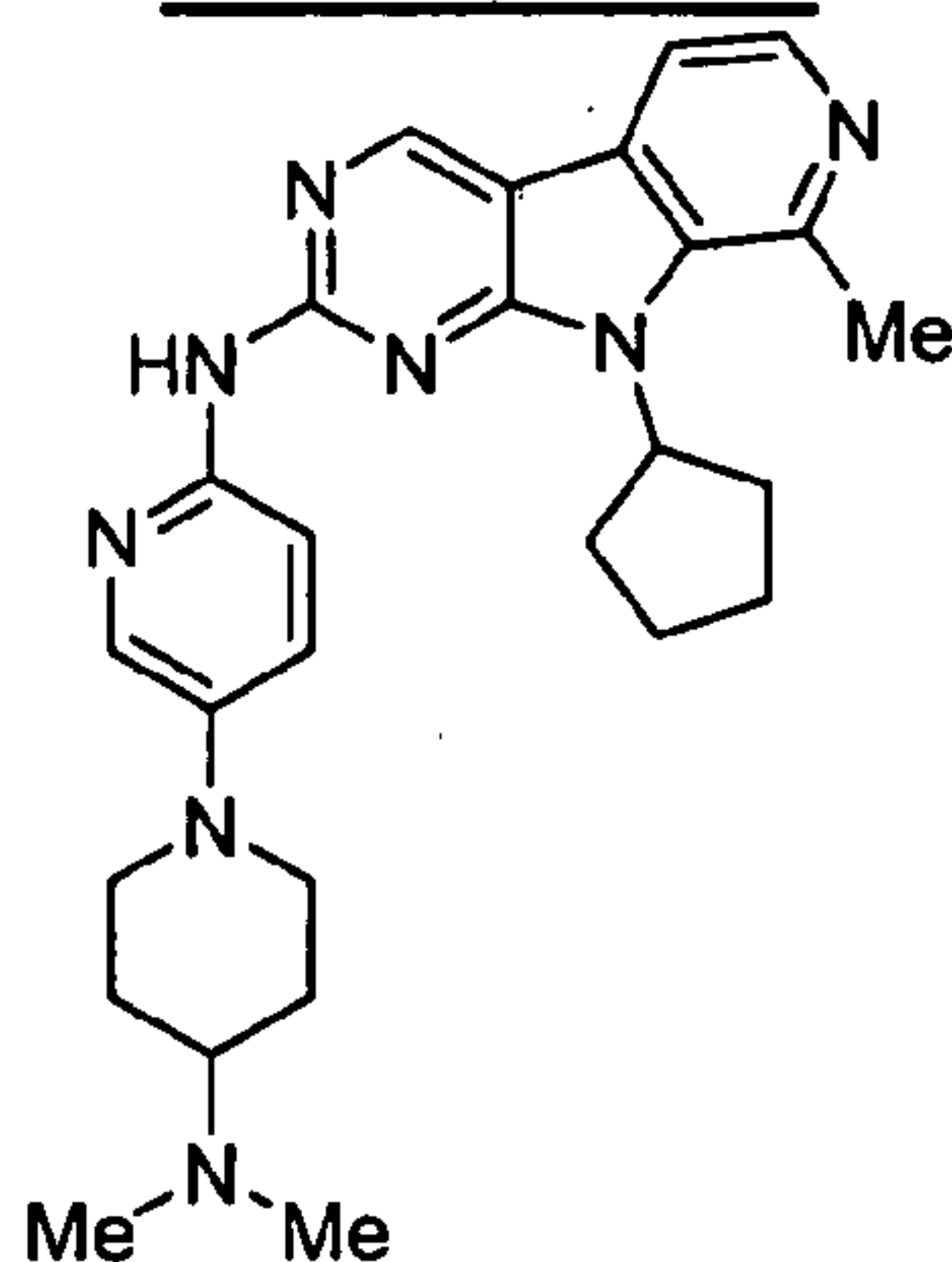


183

**9-Cyclopentyl-N-(5-(4-(dimethylamino)-1-piperidiny)-2-pyridiny)-8-(methoxy)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

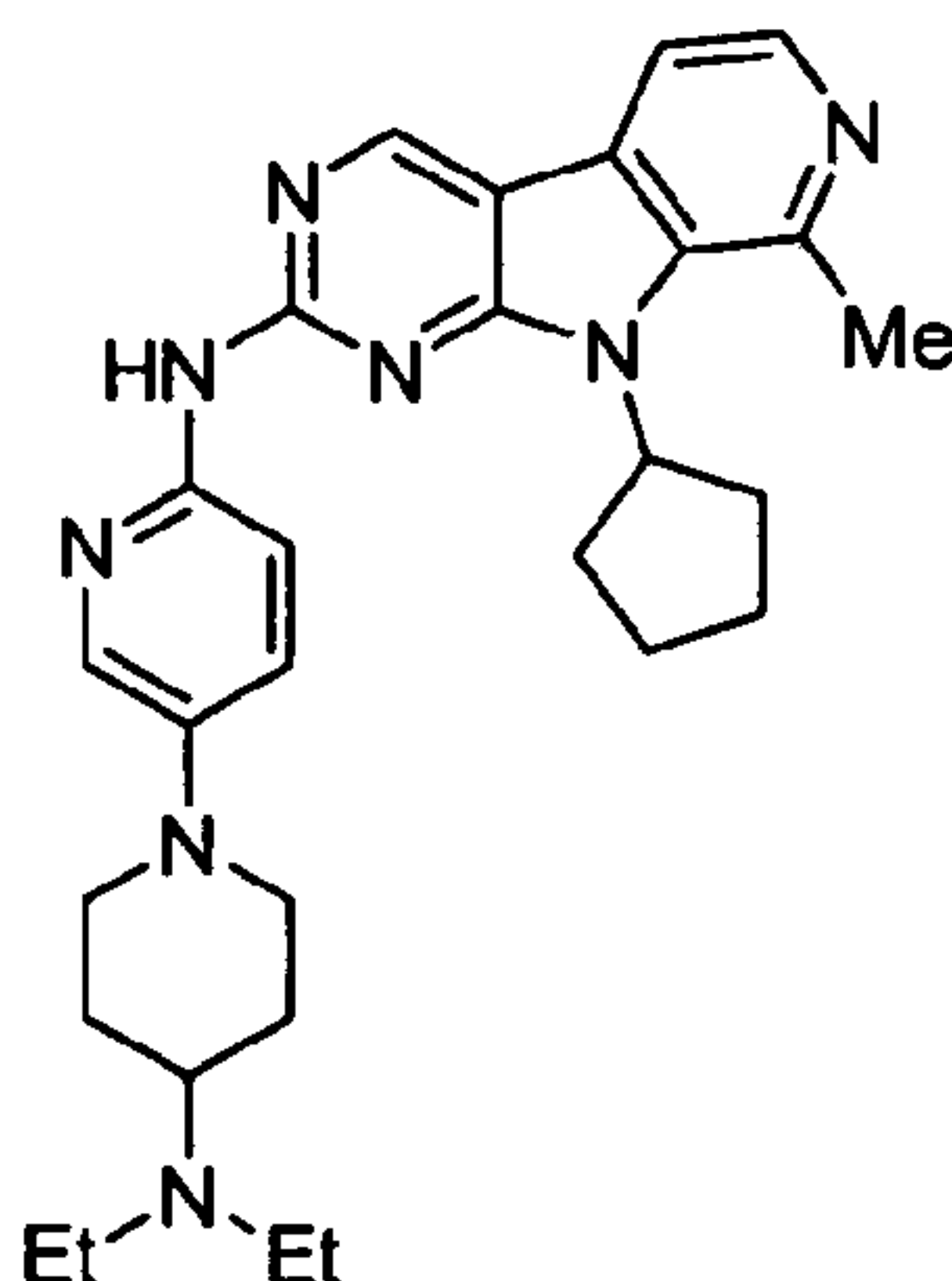


Compound **183** was prepared using chemistry similar to that described in example 53.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.09 (1H, s), 8.38 (1H, d,  $J = 10$  Hz), 8.12 (1H, bs), 7.99 (1H, d,  $J = 5$  Hz), 7.44 (1H, d,  $J = 5$  Hz), 7.37 (1H, dd,  $J = 10$  Hz,  $J = 5$  Hz), 5.81 (1H, p,  $J = 10$  Hz), 4.14 (3H, s), 3.66 (2H, d,  $J = 15$  Hz), 2.75 (2H, t,  $J = 10$  Hz), 2.33 (6H, s), 2.31 (2H, m), 2.08 (4H, m), 1.80 (2H, m), 1.74 (2H, m), 1.69 (2H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 486.2, Calculated 486.3.

**EXAMPLE 147****184**

**9-cyclopentyl-N-(5-(4-(dimethylamino)-1-piperidiny)-2-pyridinyl)-8-methyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **184** was prepared using chemistry similar to that described in example 54.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.12 (1H, s), 8.82 (1H, s), 8.35 (1H, d,  $J = 5$  Hz), 8.33 (1H, d,  $J = 10$  Hz), 8.12 (1H, d,  $J = 2$  Hz), 7.68 (1H, d,  $J = 5$  Hz), 7.35 (1H, dd,  $J = 10$  Hz,  $J = 2$  Hz), 5.42 (1H, p,  $J = 10$  Hz), 3.67 (2H, d,  $J = 15$  Hz), 3.02 (3H, s), 2.82 – 2.73 (4H, m), 2.33 (6H, s), 2.31 (1H, m), 2.14 (2H, m), 2.08 (2H, m), 1.99 (2H, m), 1.80 (2H, m), 1.69 (2H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 470.3, Calculated 470.3.

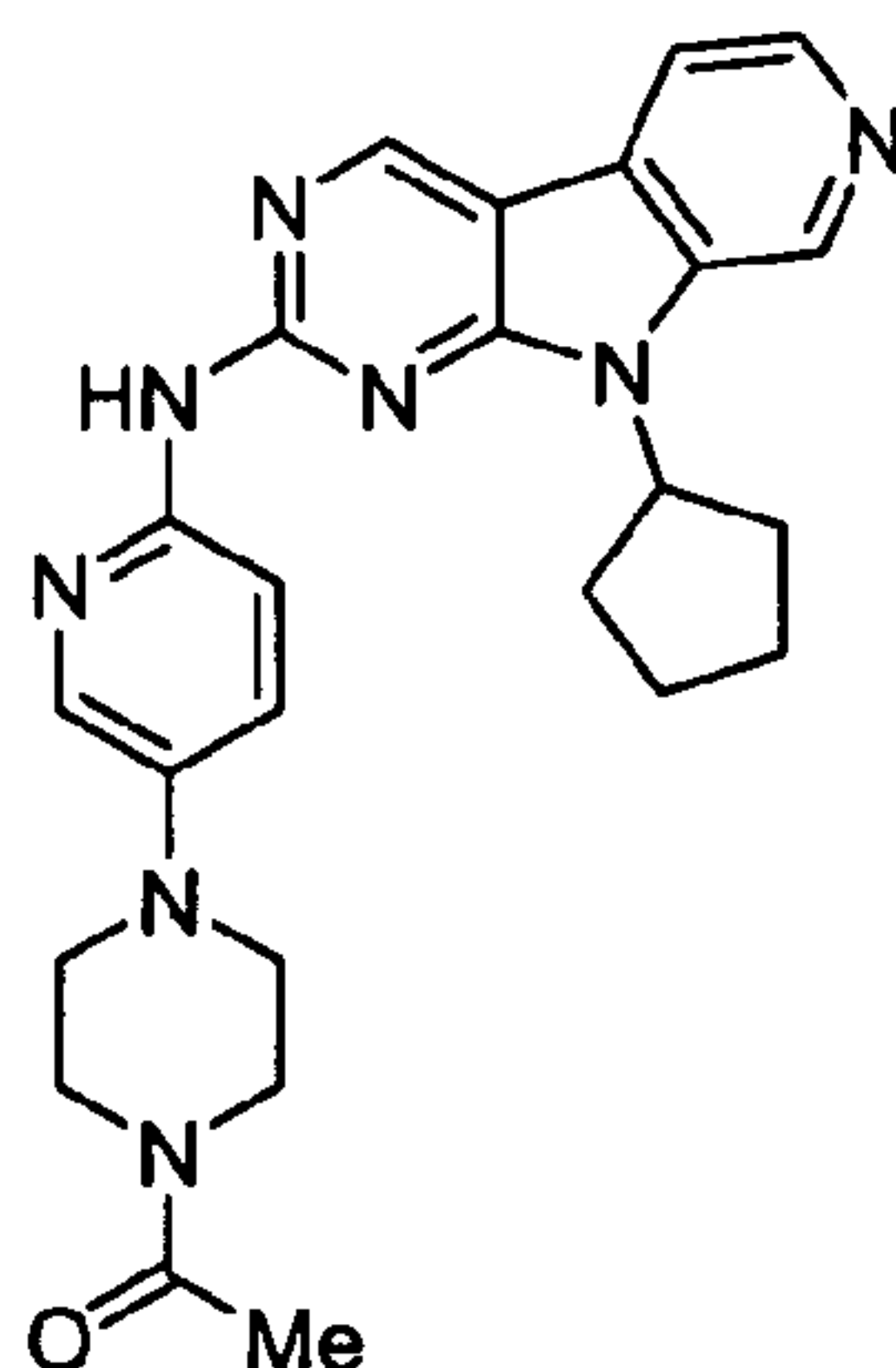
**EXAMPLE 148****185**

**9-Cyclopentyl-N-(5-(4-(diethylamino)-1-piperidiny)-2-pyridinyl)-8-methyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



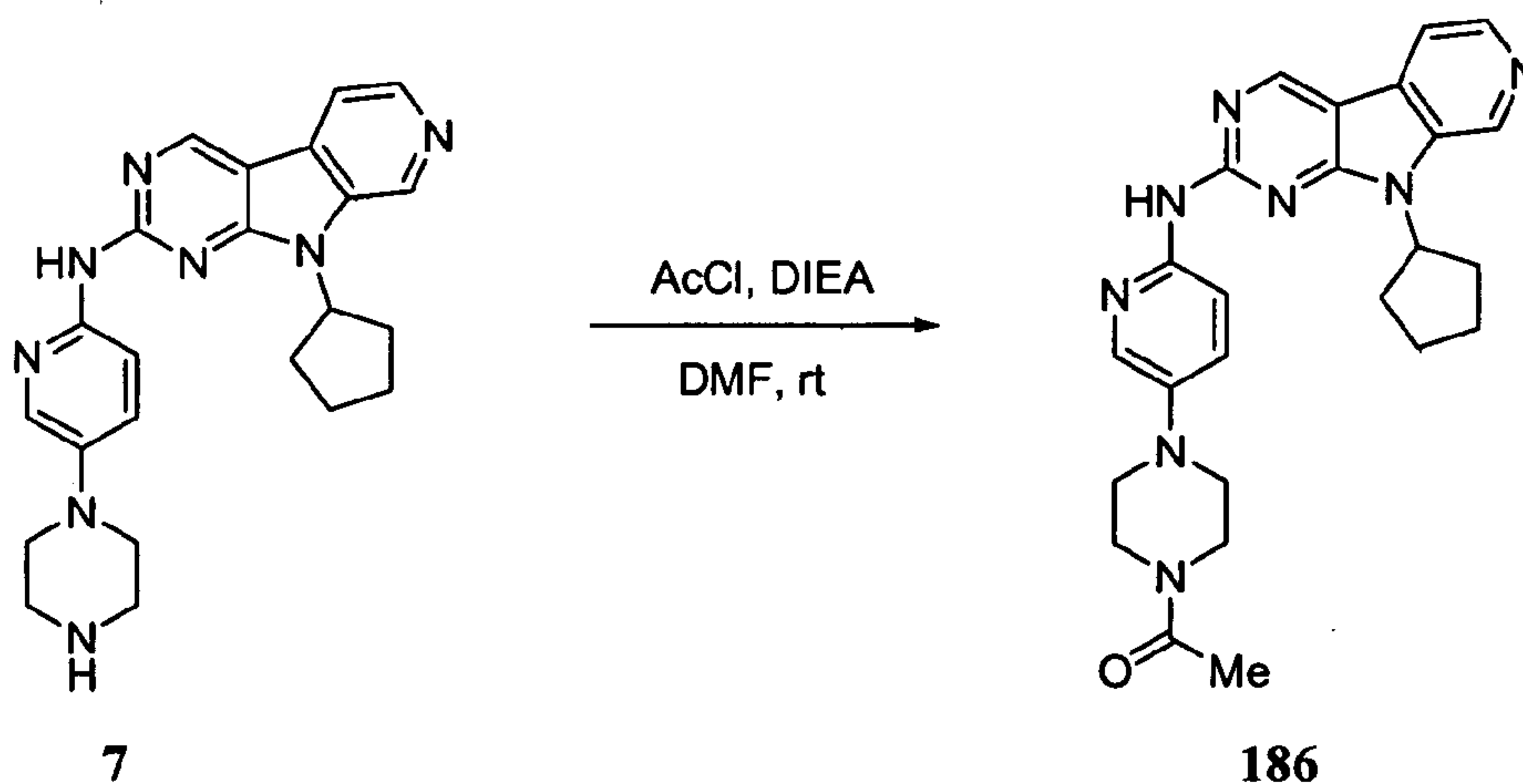
Compound **185** was prepared using chemistry similar to that described in example 54. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.05 (1H, s), 8.37 (1H, d, J = 5 Hz), 8.32 (1H, d, J = 10 Hz), 8.05 (1H, d, J = 2 Hz), 7.99 (1H, s), 7.68 (1H, d, J = 5 Hz), 7.35 (1H, dd, J = 10 Hz, J = 2 Hz), 5.44 (1H, p, J = 10 Hz), 3.68 (2H, d, J = 15 Hz), 3.03 (3H, s), 2.80 – 2.73 (4H, m), 2.63-2.61 (5H, s), 2.16 (1H, m), 2.08 (2H, m), 1.93 (2H, m), 1.80 (2H, m), 1.75 (2H, m), 1.08 (6H, t, J = 10 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 498.3, Calculated 498.3.

### EXAMPLE 149



**186**

***N*-(5-(4-Acetyl-1-piperazinyl)-2-pyridinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



**7**

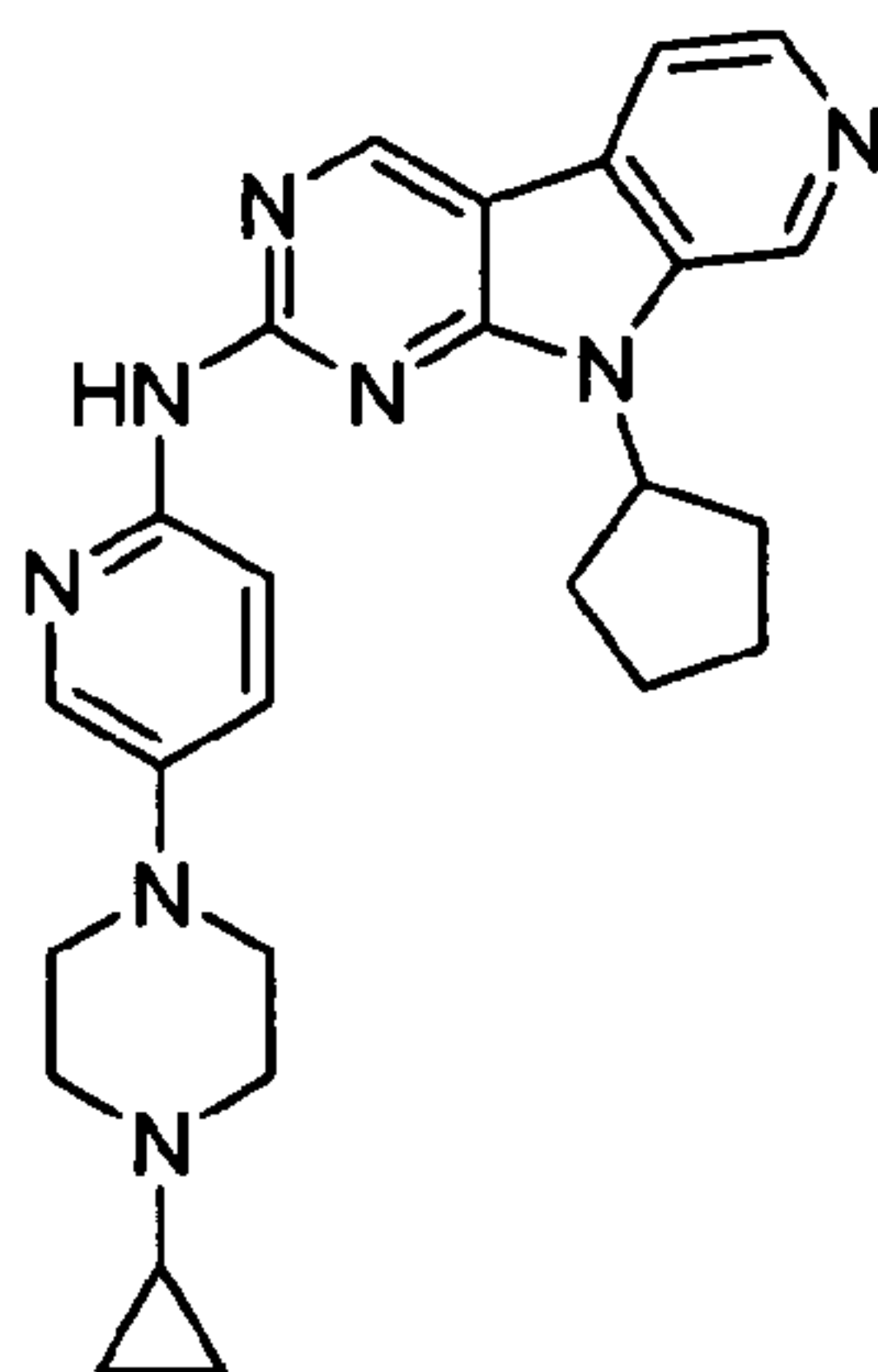
**186**

***N*-(5-(4-Acetyl-1-piperazinyl)-2-pyridinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (186)**: To a solution of compound **7** (207 mg, 0.50 mmol) in DMF (5 mL) were added *N,N*-diisopropylethylamine (174  $\mu$ L, 1.0 mmol) and acetyl chloride (43  $\mu$ L, 0.60 mmol) in DMF (2 mL) at 0 °C and the resulted mixture was stirred at 0 °C for 1 hr. The reaction mixture was concentrated and the residue was washed with water (sonicated) and the



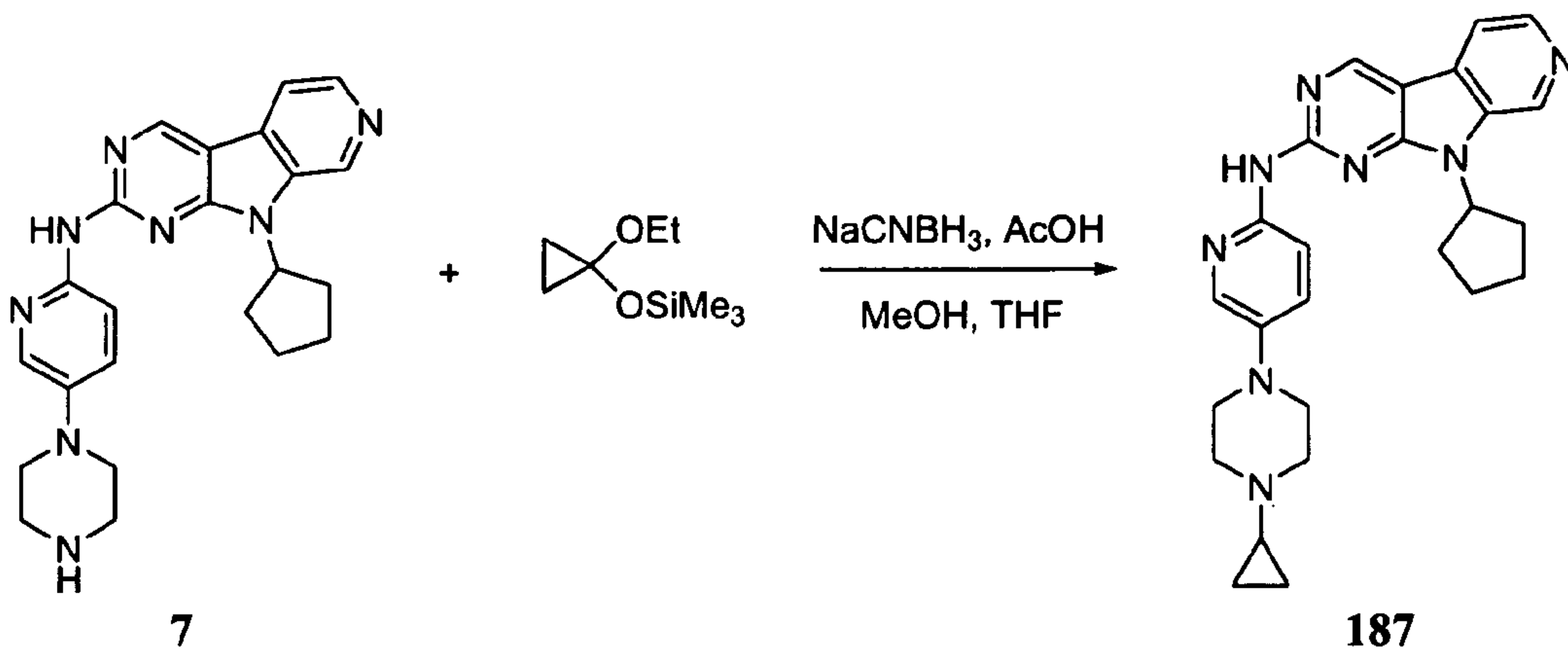
solid was collected by filtration, dried under high vacuum to give compound **186** (170 mg, 74% yield) as a light yellow solid.  $^1\text{H}$  NMR (500 MHz, *DMSO-d*<sub>6</sub>)  $\delta$  9.82 (1H, s), 9.27 (1H, s), 9.01 (1H, s), 8.44 (1 H, d, *J* = 5 Hz), 8.21 (1H, d, *J* = 10 Hz), 8.07 (1H, d, *J* = 2 Hz), 8.04 (1H, d, *J* = 5 Hz), 7.52 (1H, dd, *J* = 10 Hz, *J* = 2 Hz), 5.37 (1H, p, *J* = 10 Hz), 3.61 (4H, q, *J* = 5 Hz), 3.17 (2H, t, *J* = 5 Hz), 3.10 (2H, t, *J* = 5 Hz), (3H, s), 2.40 (2H, m), 2.08 (4H, m), 2.06 (3H, s), 1.78 (2H, m) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 456.1, Calculated 456.2.

### EXAMPLE 150



**187**

**9-Cyclopentyl-*N*-(5-(4-cyclopropyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

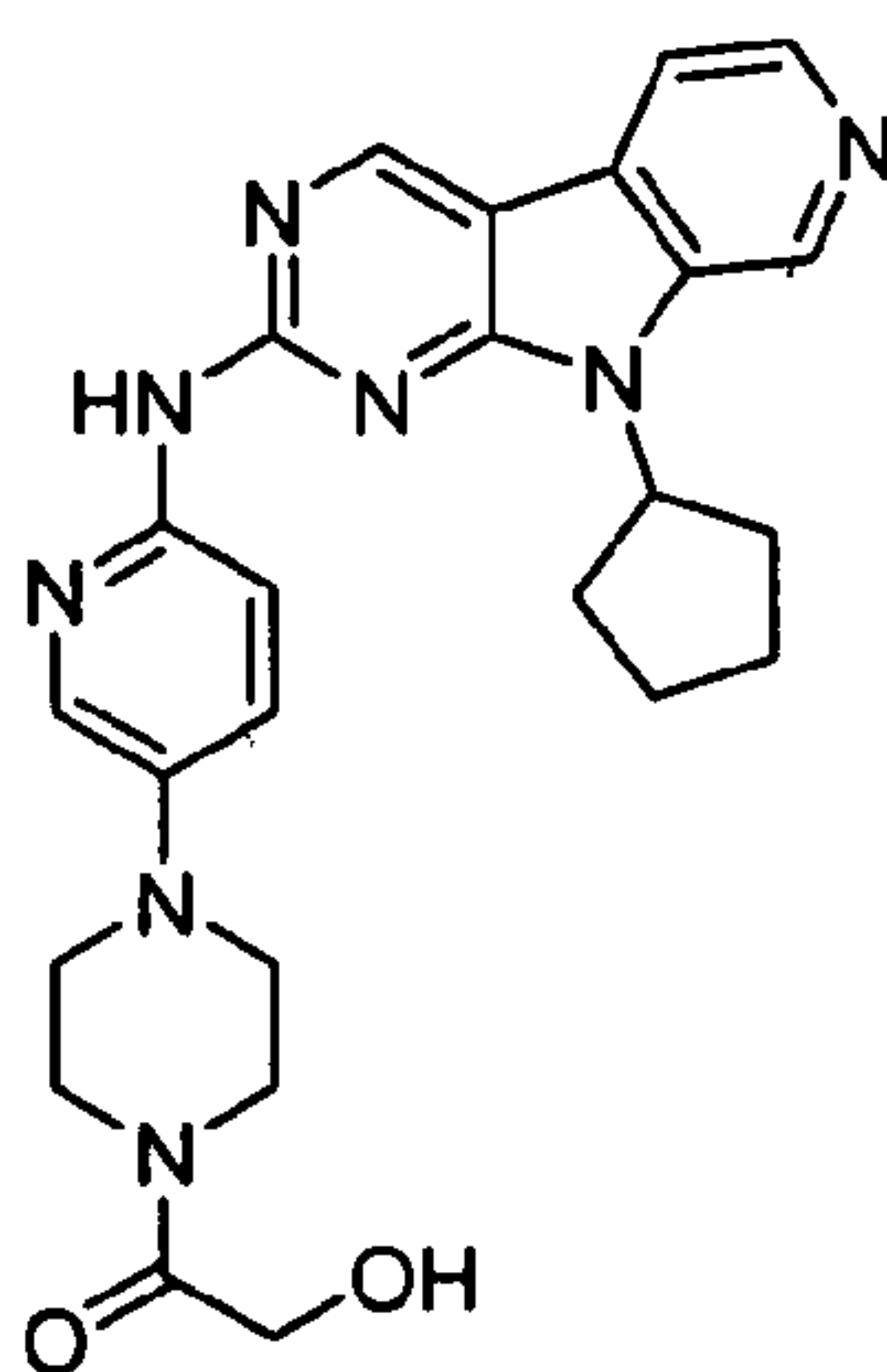


**9-Cyclopentyl-*N*-(5-(4-cyclopropyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (187):** To a solution of compound **7** (207 mg, 0.50 mmol) in THF (5 mL) were added water (0.05 mL), (1-ethoxy-1-cyclopropyloxy)-trimethylsilane (1174 mg, 1.0 mmol), acetic acid (0.55 mL) and sodium cyanoborohydride (1 mL, 1 M in THF, 1.0 mmol). The mixture was stirred at 60 °C overnight. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and washed with saturated  $\text{NaHCO}_3$



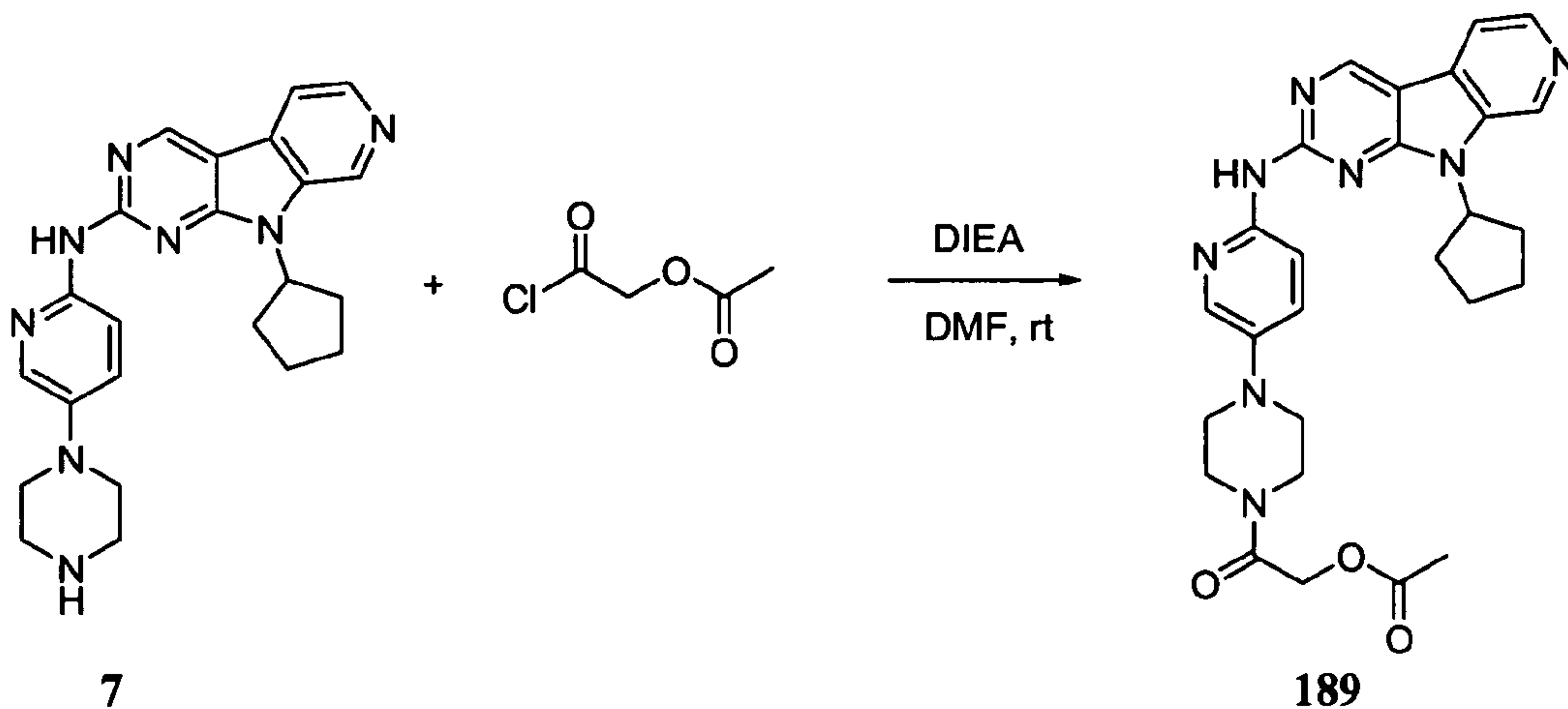
and brine then dried. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting with  $\text{CH}_2\text{Cl}_2$ :methanol: $\text{NH}_4\text{OH}$  (400:10:1) to give compound **187** as a yellow solid (60 mg, 26% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.08 (1H, s), 8.90 (1H, s), 8.51 (1 H, d,  $J = 5$  Hz), 8.39 (1H, d,  $J = 10$  Hz), 8.18 (1H, bs), 8.07 (1H, d,  $J = 2$  Hz), 7.84 (1H, d,  $J = 5$  Hz), 7.39 (1H, dd,  $J = 10$  Hz,  $J = 2$  Hz), 5.38 (1H, p,  $J = 10$  Hz), 3.17 (4H, q,  $J = 5$  Hz), 2.83 (2H, t,  $J = 5$  Hz), 2.42 (2H, m), 2.21- 2.14 (4H, m), 1.88 (2H, m), 1.71 (1H, m), 0.53- 0.46 (4H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 454.2, Calculated 454.3.

### EXAMPLE 151



188

**2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethanol**



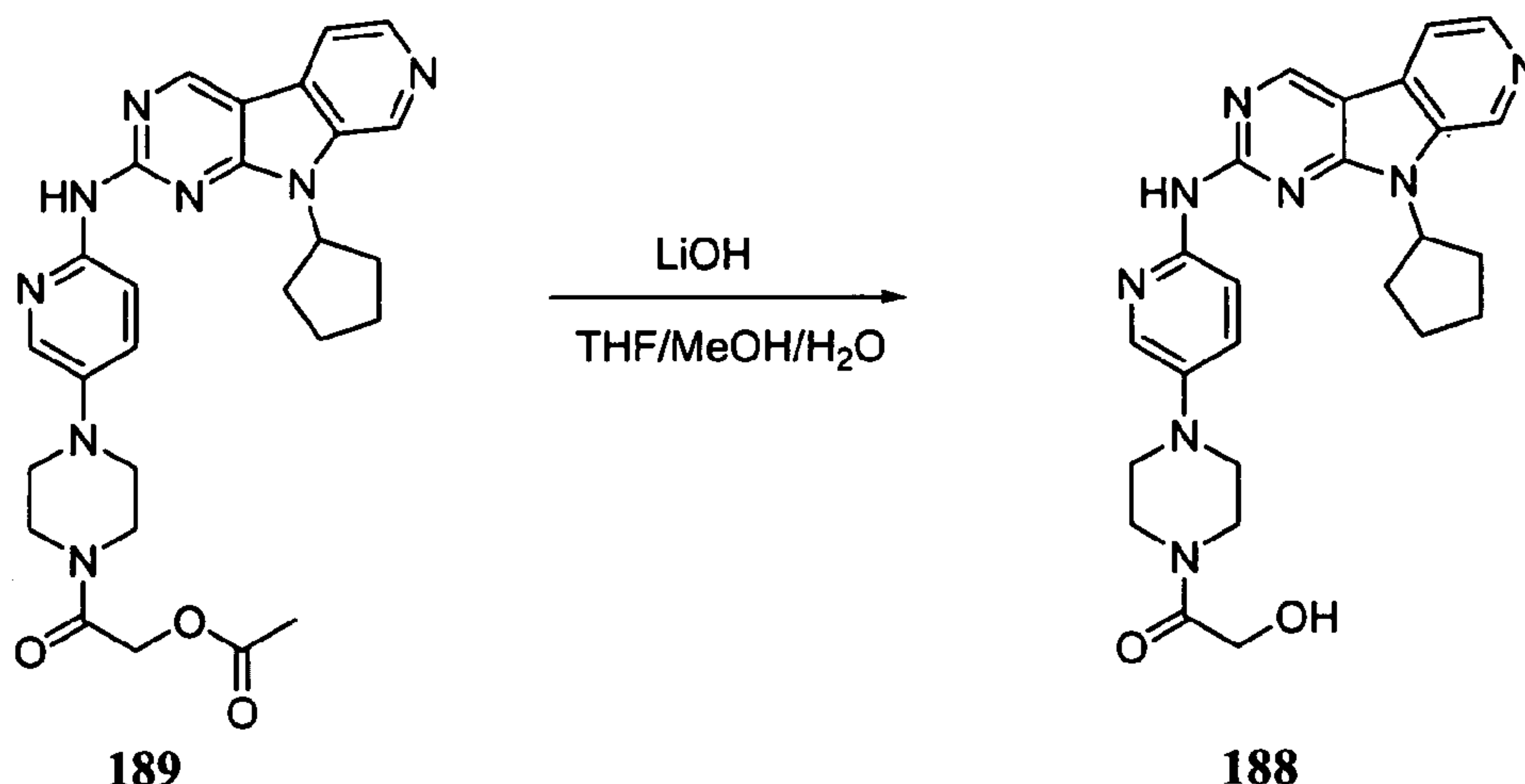
7

189

**2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethyl acetate (189):** To a solution of compound **7** (207 mg, 0.50 mmol) in DMF (5 mL) were added  $N,N$ -diisopropylethylamine (174  $\mu\text{L}$ , 1.0 mmol) and acetoxyacetyl chloride (65  $\mu\text{L}$ , 0.60 mmol) and the resulted mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated to give compound **189** as a yellow

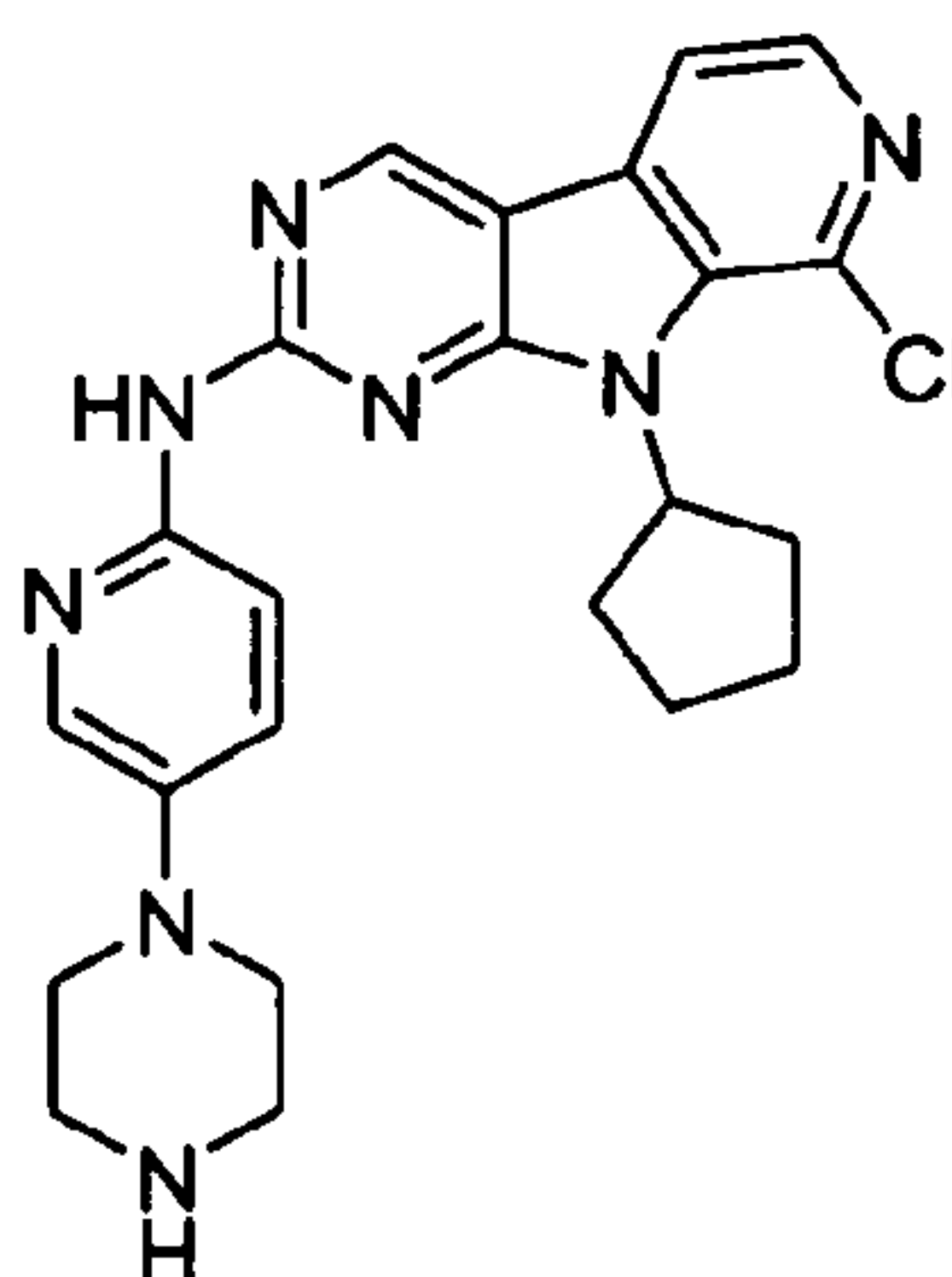


solid which was used in next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 514.2, Calculated 514.2.



**2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethanol (188):** To a solution of compound **189** (~ 0.5 mmol) in THF/methanol/H<sub>2</sub>O (3:1:1, 10 mL) was added 12 mg of LiOH and the mixture was stirred at 60 °C overnight. The reaction mixture was concentrated and the residue was dissolved in dichloromethane then washed with water and brine then dried. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>:methanol:NH<sub>4</sub>OH (400:10:1) to give compound **188** as a yellow solid (150 mg, 63% in two steps). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.82 (1H, s), 9.27 (1H, s), 9.01 (1H, s), 8.44 (1H, d, J = 5 Hz), 8.21 (1H, d, J = 10 Hz), 8.07 (1H, d, J = 2 Hz), 8.04 (1H, d, J = 5 Hz), 7.52 (1H, dd, J = 10 Hz, J = 2 Hz), 5.37 (1H, p, J = 10 Hz), 4.65 (1H, t, J = 5 Hz), 4.15 (2H, d, J = 5 Hz), 3.65 (2H, m), 3.53 (2H, m), 3.15 (4H, m), 2.40 (2H, m), 2.08 (4H, m), 1.78 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 472.2, Calculated 472.3.

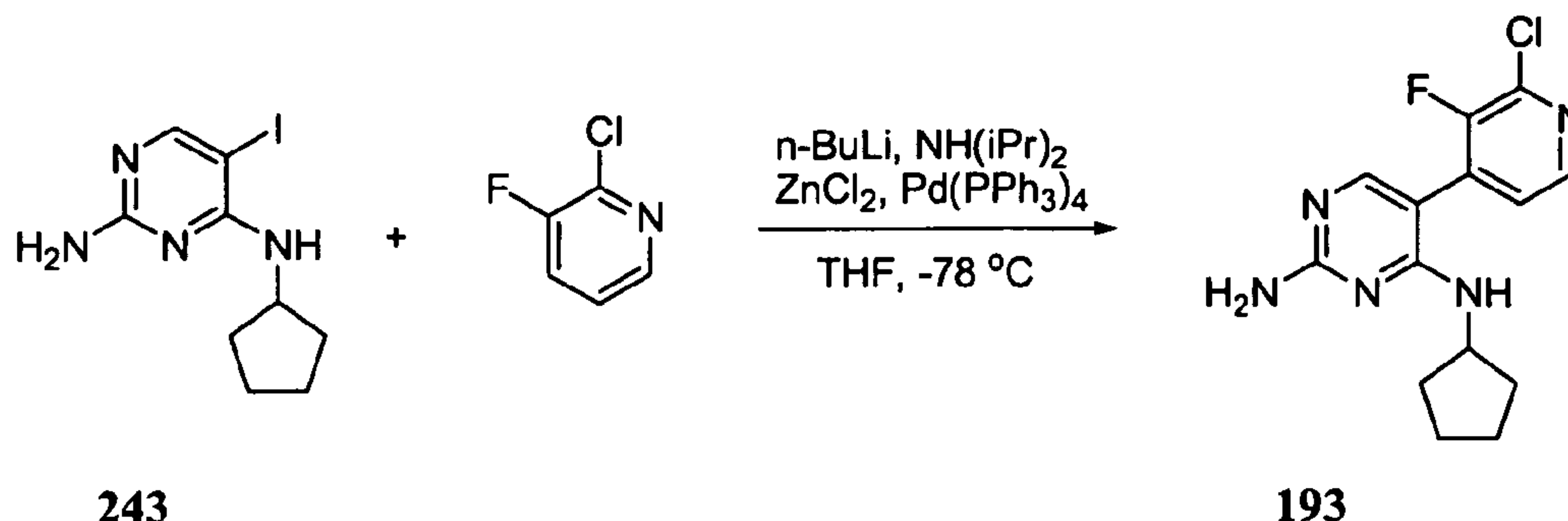
### EXAMPLE 152



**190**

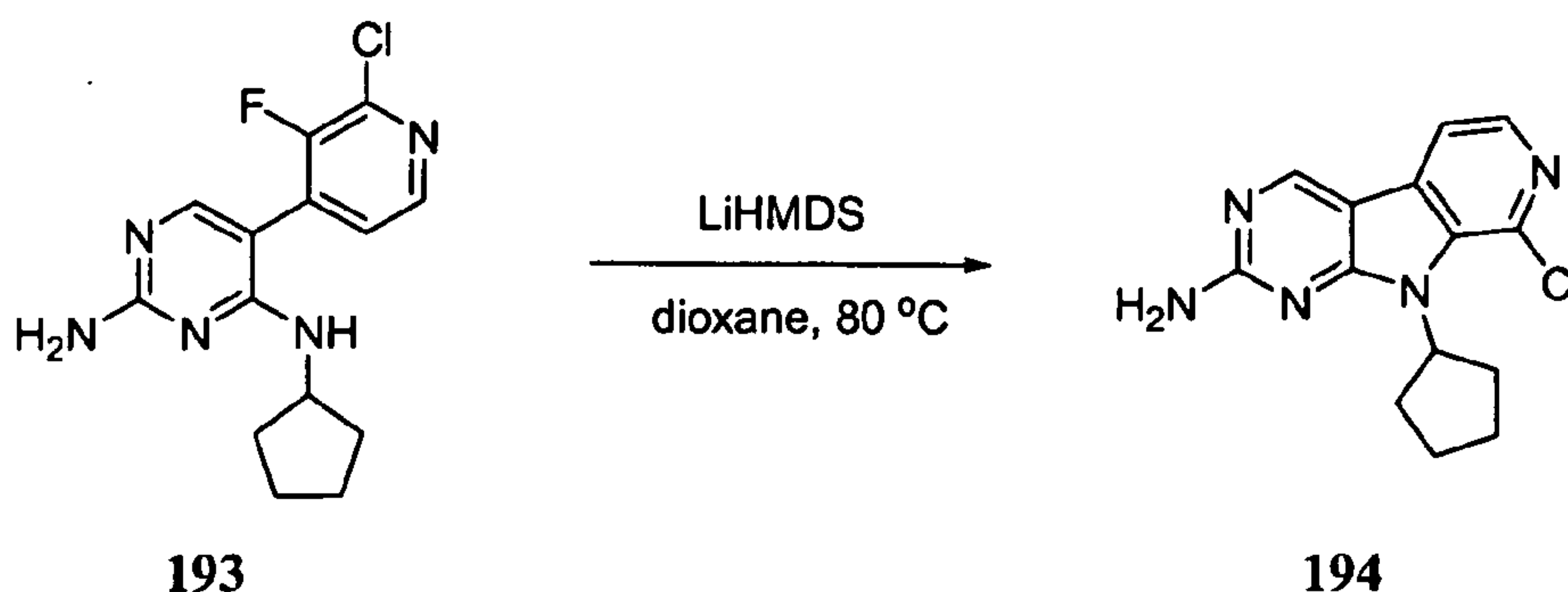


**8-Chloro-9-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



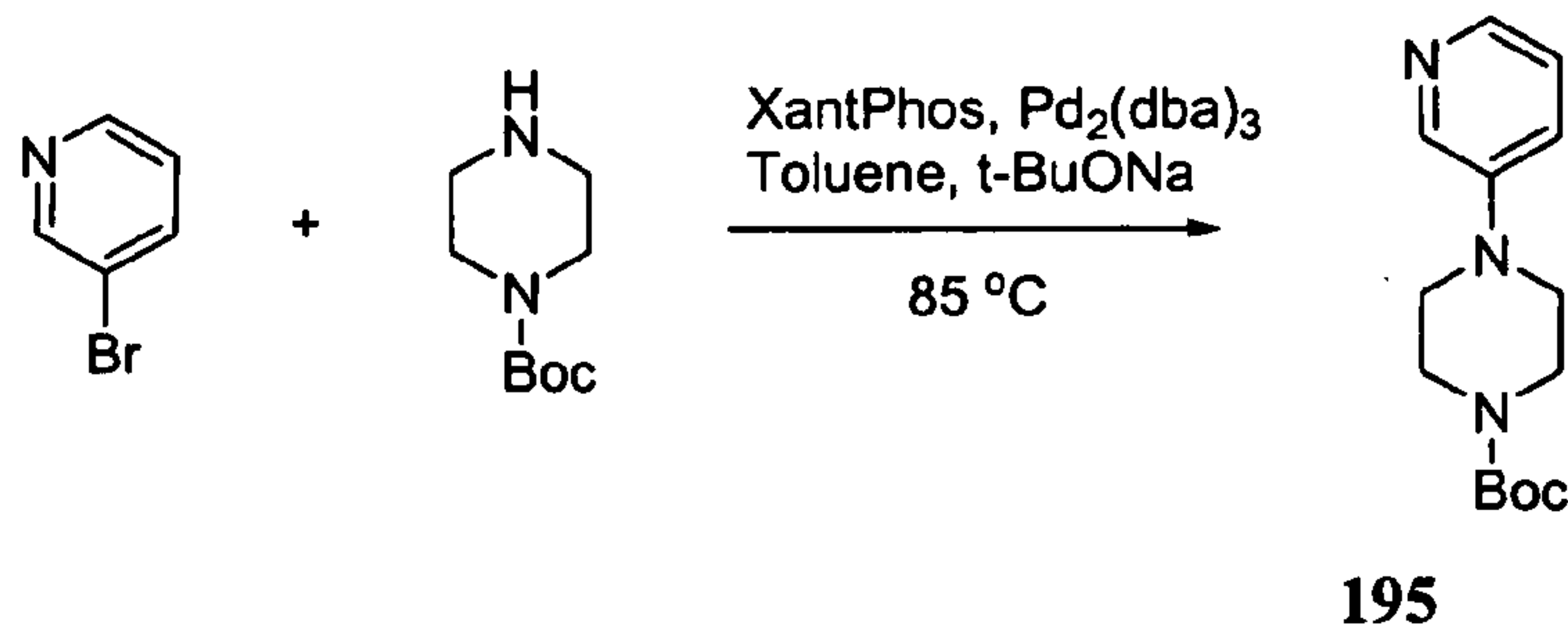
**5-(2-Chloro-3-fluoropyridin-4-yl)-N4-cyclopentylpyrimidine-2,4-diamine (193):** To a 500 mL three-necked round-bottomed flask equipped with a thermometer and a stir bar was added diisopropylamine (14.7 mL, 104 mmol). The flask was cooled in a Et<sub>2</sub>O-dry ice bath and butyllithium 2.5M in hexane (43.0 mL, 107 mmol) was added cautiously. The solution was allowed to warm to room temperature. After stirring at room temperature for 5 minutes, a white solid formed and it was cooled in an Et<sub>2</sub>O-dry ice bath then diluted with 170 mL of anhydrous THF. The solution was then cooled to -75 °C. 2-chloro-3-fluoropyridine (10.3 mL, 104 mmol) was dissolved in 100 mL of anhydrous THF. This solution was then slowly cannulated into the LDA solution over a period of 20 minutes while the temperature was held below -69 °C. The solution was stirred for 30 minutes before a solution of zinc (II) chloride 0.5M in THF (111 mL, 55.4 mmol) was slowly added with the temperature maintained below -68 °C. The yellow solution was then allowed to warm to room temperature. After 30 minutes of stirring at room temperature, compound **243** (see example 200) (10.538 g, 34.6 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (2.00 g, 1.73 mmol) were added and the solution was heated at 60 °C overnight. The solution was concentrated under vacuum, and then cooled in an ice bath. Saturated NH<sub>4</sub>Cl aqueous solution was added with ice and the solution was stirred for 10 minutes and then extracted with DCM. The aqueous layer was washed with 10 % i-PrOH/DCM. The combined organics were dried over MgSO<sub>4</sub> and concentrated under vacuum. The residue obtained was purified by flash chromatography (methanol/DCM/Aq NH<sub>4</sub>OH) to give compound **193** (4.13g, 38.7%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.22 (1 H, d, J= 4.9 Hz), 7.63 (1 H, s), 7.40 (1 H, t, J= 5.1 Hz), 6.28 - 6.41 (3 H, m), 4.37 - 4.49 (1 H, m), 1.78 - 1.93 (2 H, m), 1.57 - 1.69 (2 H, m), 1.36 - 1.54 (4 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 308.0.





**8-Chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (194):**

Compound **193** (3.10 g, 10.1 mmol) was combined with 30 mL of anhydrous 1,4-dioxane. To this was added LiHMDS 1M in THF (30.2 mL, 30.2 mmol) and the solution was heated to 85 °C for 5 hours. The solution was cooled to room temperature and then diluted with ice/sat. NaHCO<sub>3</sub>. The product was extracted with 15% 2-propanol/DCM and the organics were dried over MgSO<sub>4</sub> before being concentrated under vacuum. The residue obtained was purified on CombiFlash column (dry loaded), eluting with a gradient of 2% methanol/DCM to 6% methanol/DCM. Trituration with acetone and ethyl acetate left a light brown solid. Repurification of the supernatants provided additional material. The solids were combined to give compound **194** (1.60 g, 55.2%) as a light brown solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.11 (1 H, s), 8.14 (1 H, d, J = 4.9 Hz), 7.98 (1 H, d, J = 4.9 Hz), 7.07 (2 H, br. s.), 5.90 (1 H, quin, J = 8.7 Hz), 2.44 - 2.49 (2 H, m), 2.04 - 2.13 (2 H, m), 1.95 - 2.03 (2 H, m), 1.63 - 1.73 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 288.1.

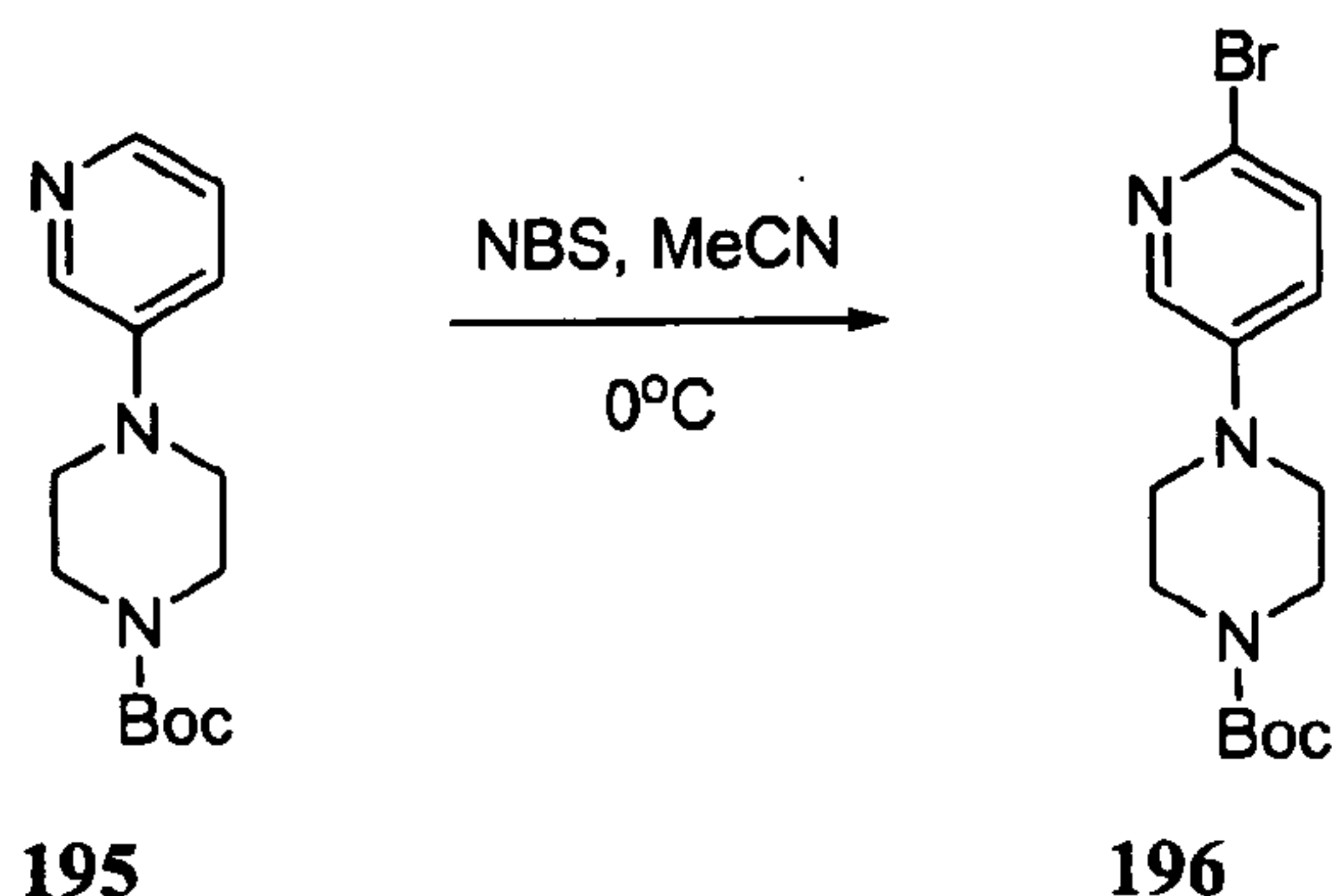


**tert-Butyl 4-(pyridin-3-yl)piperazine-1-carboxylate (195):** Sodium 2-methylpropan-2-olate (1.83 g, 19.1 mmol), 3-bromopyridine (2.010 g, 12.7 mmol), and *tert*-butyl piperazine-1-carboxylate (3.55 g, 19.1 mmol) were combined in 10 mL of anhydrous toluene. N<sub>2</sub> was bubbled through the solution briefly before adding 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.368 g, 0.636 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub> (0.183 g, 0.318 mmol). The solution was then heated to 85 °C overnight.

The solution was cooled to room temperature and diluted with sat's NH<sub>4</sub>Cl and then extracted with DCM. The organics were dried over MgSO<sub>4</sub> and then concentrated under vacuum. The residue obtained was purified on CombiFlash column eluting with a gradient of DCM to 4%

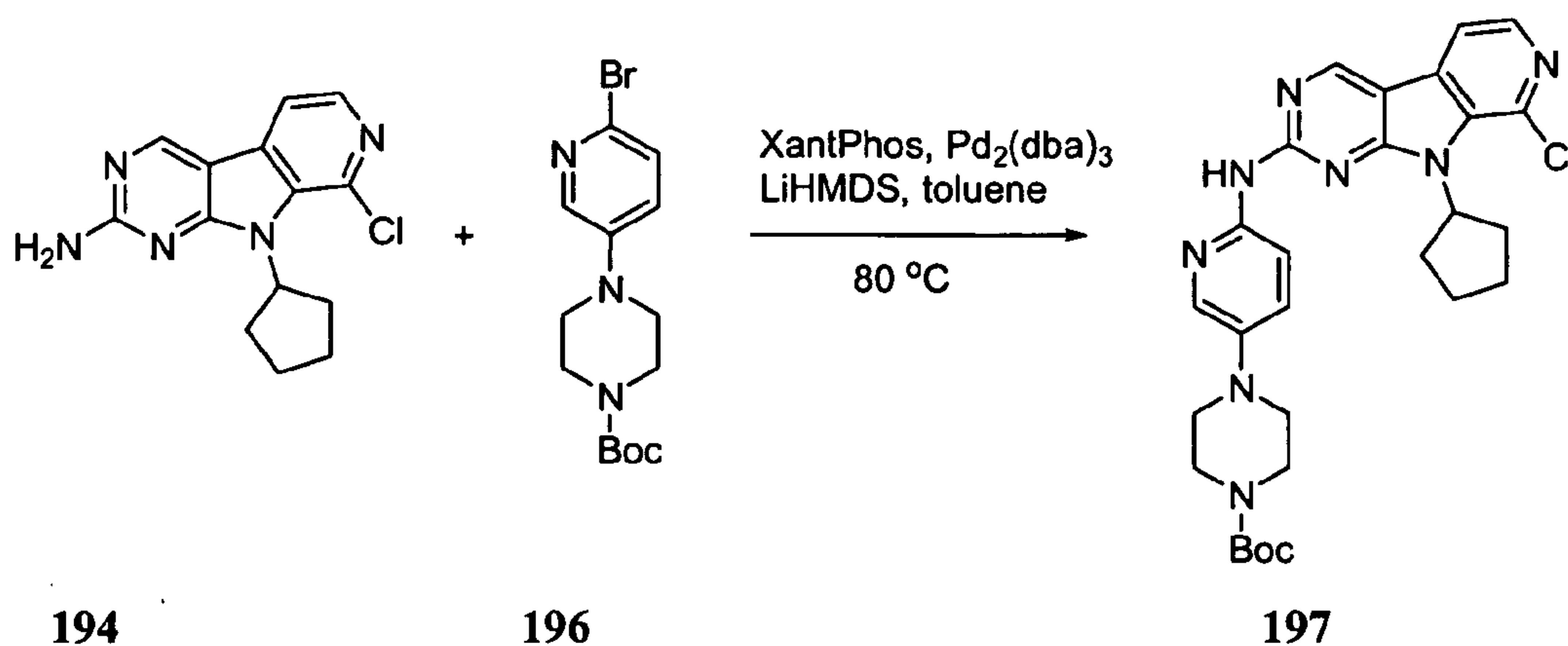


methanol/DCM. The fractions containing the product were combined and concentrated under vacuum to give compound **195** (2.06g, 61.5% yield) as a reddish yellow solid.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.31 (1 H, d,  $J=2.9$  Hz), 8.02 (1 H, dd,  $J=4.5, 1.3$  Hz), 7.33 (1 H, ddd,  $J=8.5, 3.0, 1.5$  Hz), 7.20 - 7.24 (1 H, m), 3.43 - 3.49 (4 H, m), 3.11 - 3.20 (4 H, m), 1.42 (9 H, s) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 264.1.



**tert-Butyl 4-(6-bromopyridin-3-yl)piperazine-1-carboxylate (196):** By the method of Audouze et al. J. Med.Chem. **49** (2006) 3159 – 3171, compound **195** (2.06 g, 7.82 mmol) was dissolved in 40 mL of acetonitrile under an atmosphere of  $\text{N}_2$ .

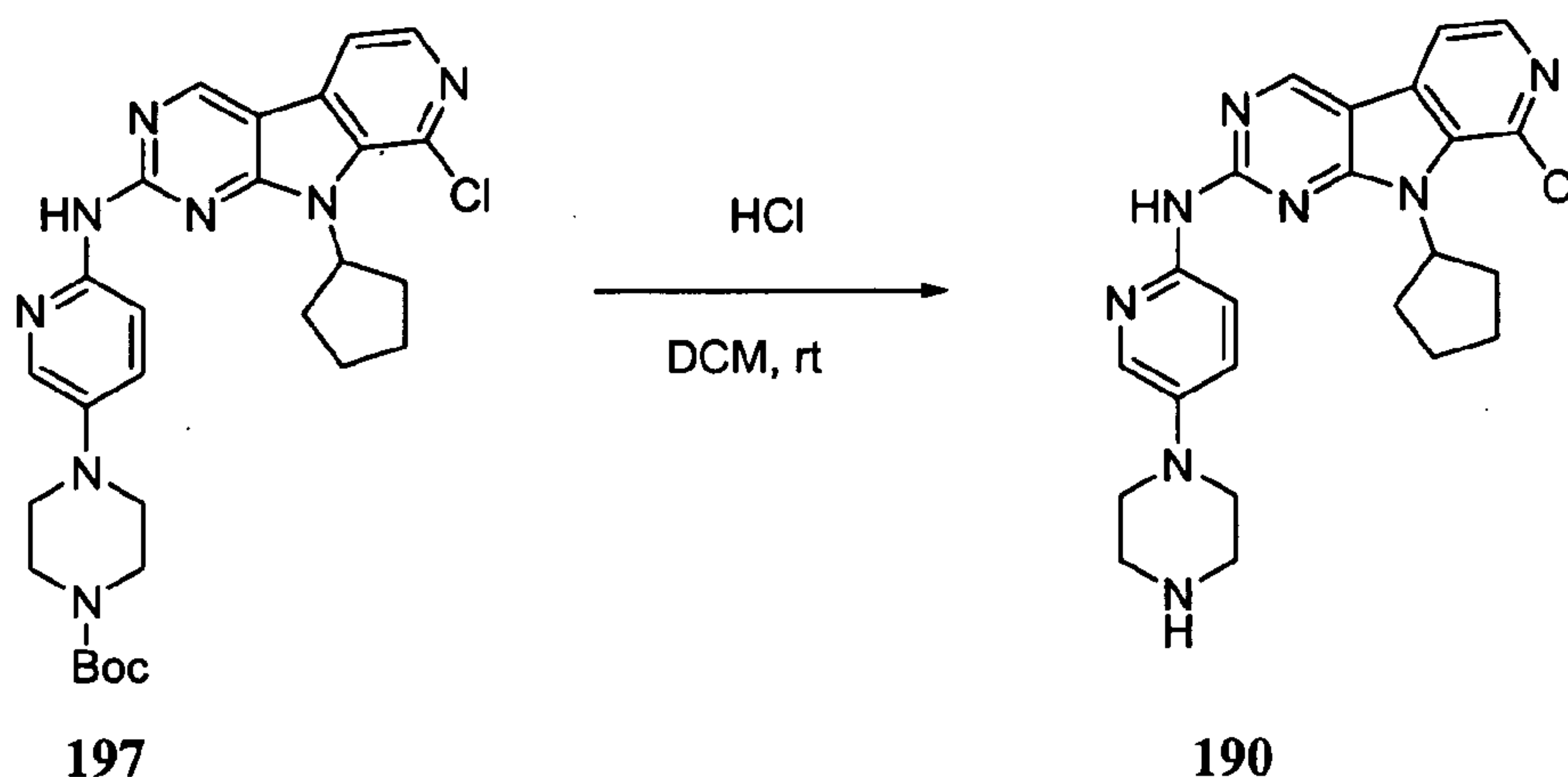
The solution was cooled in a ice bath before a solution of N-bromosuccinimide (1.46 g, 8.21 mmol) in 15 mL of acetonitrile was added over a period of 10 minutes. The solution was then stirred in the ice bath for 2 hours. Added silica gel and DCM, and the slurry was then concentrated under vacuum. Purified on CombiFlash column (dry loaded), eluting with a gradient of 5% ethyl acetate/hexane to 40% ethyl acetate/hexane. The fractions containing the product were combined and concentrated under vacuum to give compound **196** (1.9847 g, 74 % yield) as an off white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.07 (1 H, d,  $J=3.2$  Hz), 7.42 (1 H, d,  $J=8.8$  Hz), 7.34 (1 H, dd,  $J=8.9, 3.3$  Hz), 3.42 - 3.48 (4 H, m), 3.12 - 3.21 (4 H, m), 1.42 (9 H, s) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 342.1.



**tert-Butyl 4-(6-((8-chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (197):** Compound **196** (0.178 g, 0.521



mmol), compound **194** (0.125 g, 0.434 mmol), and LiHMDS 1M in THF (1.30 mL, 1.30 mmol) were combined in 5mL of anhydrous toluene. N<sub>2</sub> was bubbled through the solution briefly before adding Pd<sub>2</sub>(dba)<sub>3</sub> (0.0298 g, 0.0326 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0377 g, 0.0652 mmol). The solution was then heated to 80 °C for 2 hours with microwave irradiation. The solution was diluted with DCM before it was poured into sat's NH<sub>4</sub>Cl. Partitioned the layers and washed the aqueous layer with 10% i-PrOH/DCM. The combined organics were dried over MgSO<sub>4</sub> and then concentrated under vacuum. The residue obtained was purified on CombiFlash column (dry loaded), eluting with a gradient of 60% ethyl acetate/hexane to 100% ethyl acetate. The fractions containing the product were combined and concentrated under vacuum. The residue obtained was repurified on CombiFlash column (dry loaded), eluting with a gradient of 2% methanol/0.1% NH<sub>4</sub>OH (~28% in water)/DCM to 4% methanol/0.2% NH<sub>4</sub>OH(~28% in water)/DCM. The fractions containing the product were combined and concentrated under vacuum. The residue obtained was sonicated in methanol. Filtration provided an off-white solid as compound **197** (0.173 g, 72 %). LCMS-ESI (POS), M/Z, M+1: Found 549.1.

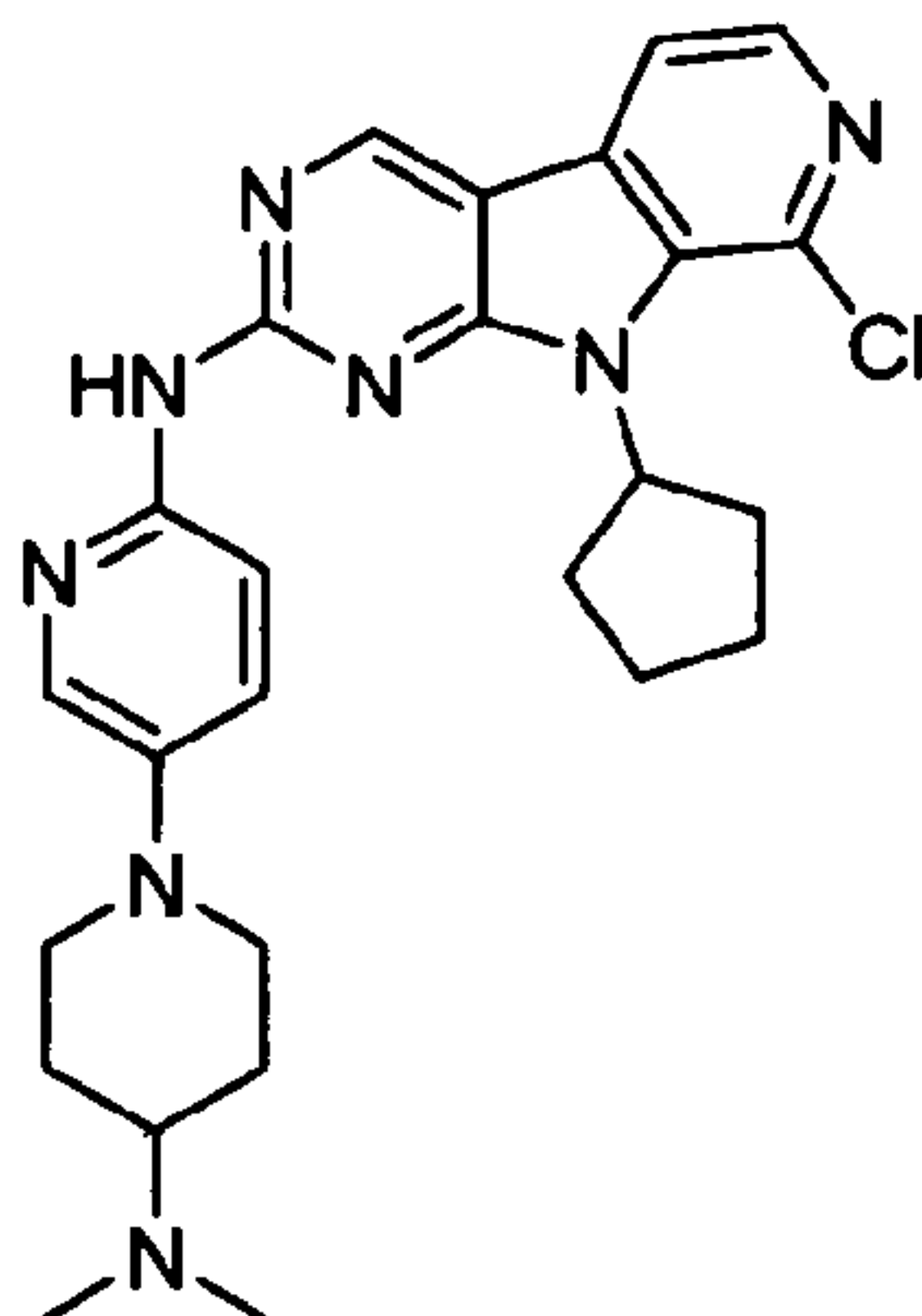


**8-Chloro-9-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (190):** Compound **197** (0.173 g, 0.315 mmol) was dissolved in 10 mL of DCM and to this was added 4N HCl in dioxane (1.97 mL, 7.88 mmol). The solution was stirred at room temperature overnight and then concentrated under vacuum to give a yellow solid. The solid obtained was sonicated in Et<sub>2</sub>O and a yellowish solid was collected on filter paper to give compound **190** as an HCl salt (0.164 g, 100%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 10.56 (1 H, br. s.), 9.42 (1 H, s), 8.87 (2 H, br. s.), 8.28 (1 H, d, J= 4.9 Hz), 8.19 (1 H, d, J= 5.1 Hz), 8.09 (1 H, d, J= 2.9 Hz), 7.97 (1 H, d, J= 9.0 Hz), 7.75 (1 H, dd, J= 9.3, 2.0 Hz), 5.96 - 6.07 (2 H, m, J= 9.2, 8.9, 8.8, 8.8 Hz), 3.37 - 3.43 (4 H, m), 3.26 - 3.33 (4



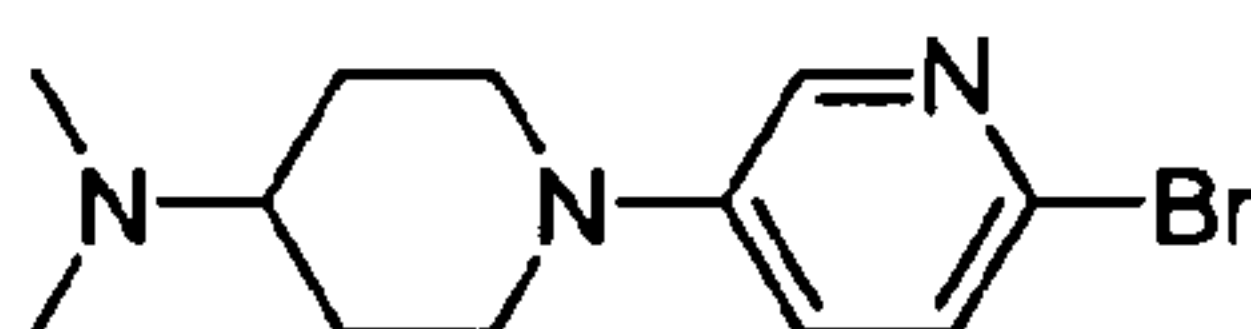
H, m), 2.54 - 2.65 (2 H, m), 2.01 - 2.12 (4 H, m), 1.66 - 1.77 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 449.2.

### EXAMPLE 153



198

**8-Chloro-9-cyclopentyl-N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

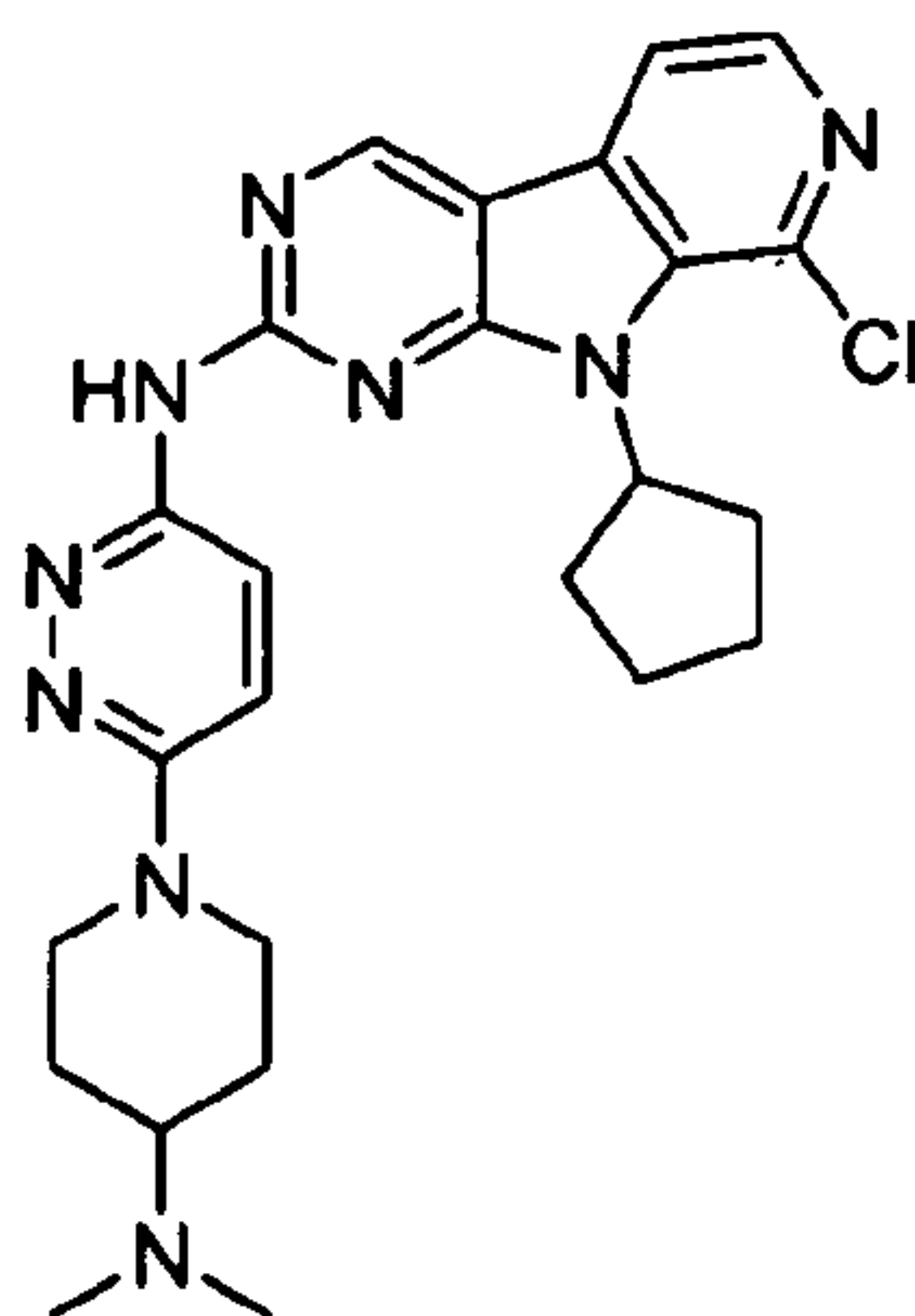


199

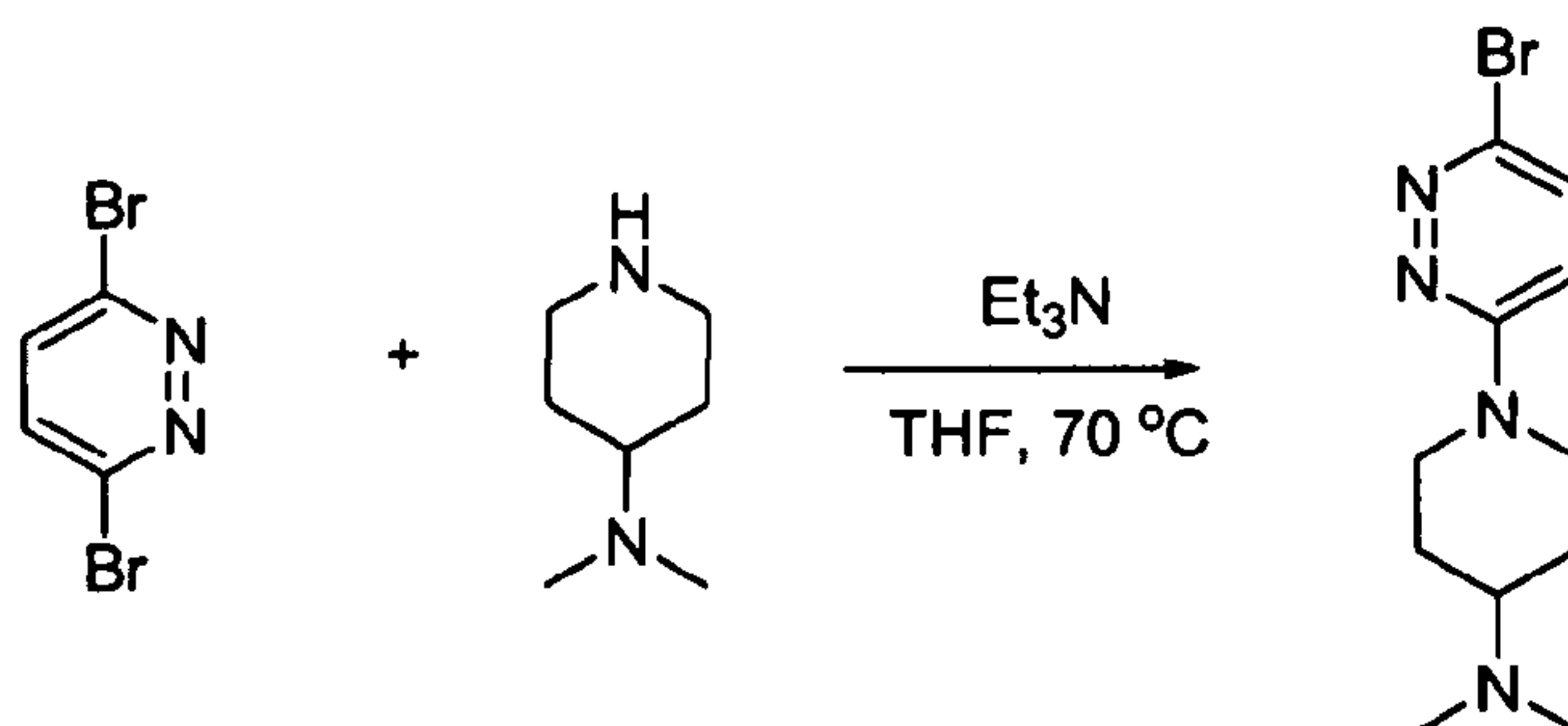
**1-(6-Bromopyridin-3-yl)-N,N-dimethylpiperidin-4-amine (199):** Compound 199 was prepared by analogy to compound 196.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.05(1H, d,  $J = 2.7\text{Hz}$ ), 7.35-7.38 (1H, m), 7.30-7.33 (1H, m), 3.69-3.79 (2H, m), 2.73 (2H, td,  $J = 12.2, 2.7\text{Hz}$ ), 2.19-2.27 (1H, m), 2.17 (6H, s), 1.75-1.86 (2H, m), 1.36-1.50 (2H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 284.0.

**8-Chloro-9-cyclopentyl-N-(5-(4-(dimethylamino)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (198)** Compound 198 was prepared from compound 199 using methods described in example 152.  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  8.79 (1 H, s), 7.97 (1 H, d,  $J = 4.9\text{ Hz}$ ), 7.78 (1 H, br. s.), 7.53 (1 H, br. s.), 7.20 (1 H, br. s.), 6.94 (1 H, d,  $J = 9.0\text{ Hz}$ ), 5.71 (1 H, br. s.), 3.65 (2 H, br. s.), 3.42 (1 H, br. s.), 2.92 (6 H, s), 2.68 - 2.82 (2 H, m), 2.16 - 2.33 (4 H, m), 2.04 (4 H, br. s.), 1.74 (4 H, br. s.) ppm; LCMS-ESI (POS), M/Z, M+1: Found 491.2.



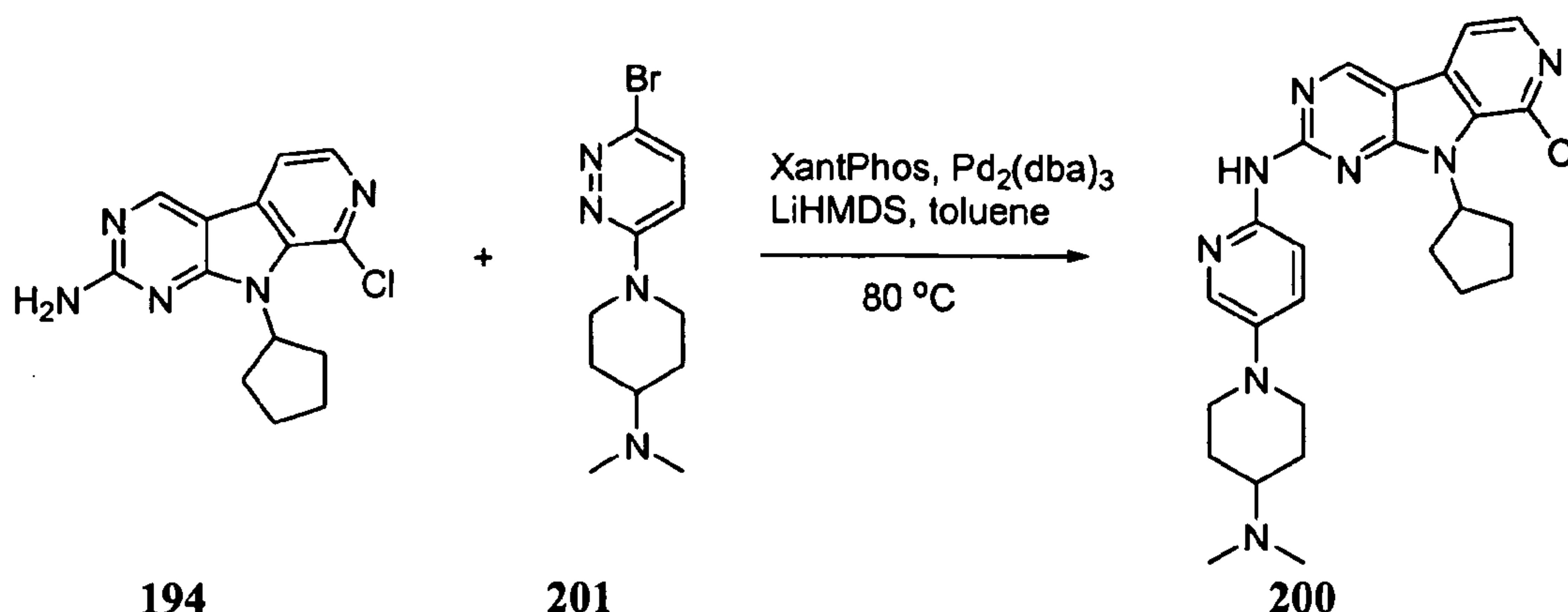
**EXAMPLE 154****200**

**8-Chloro-9-cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**201**

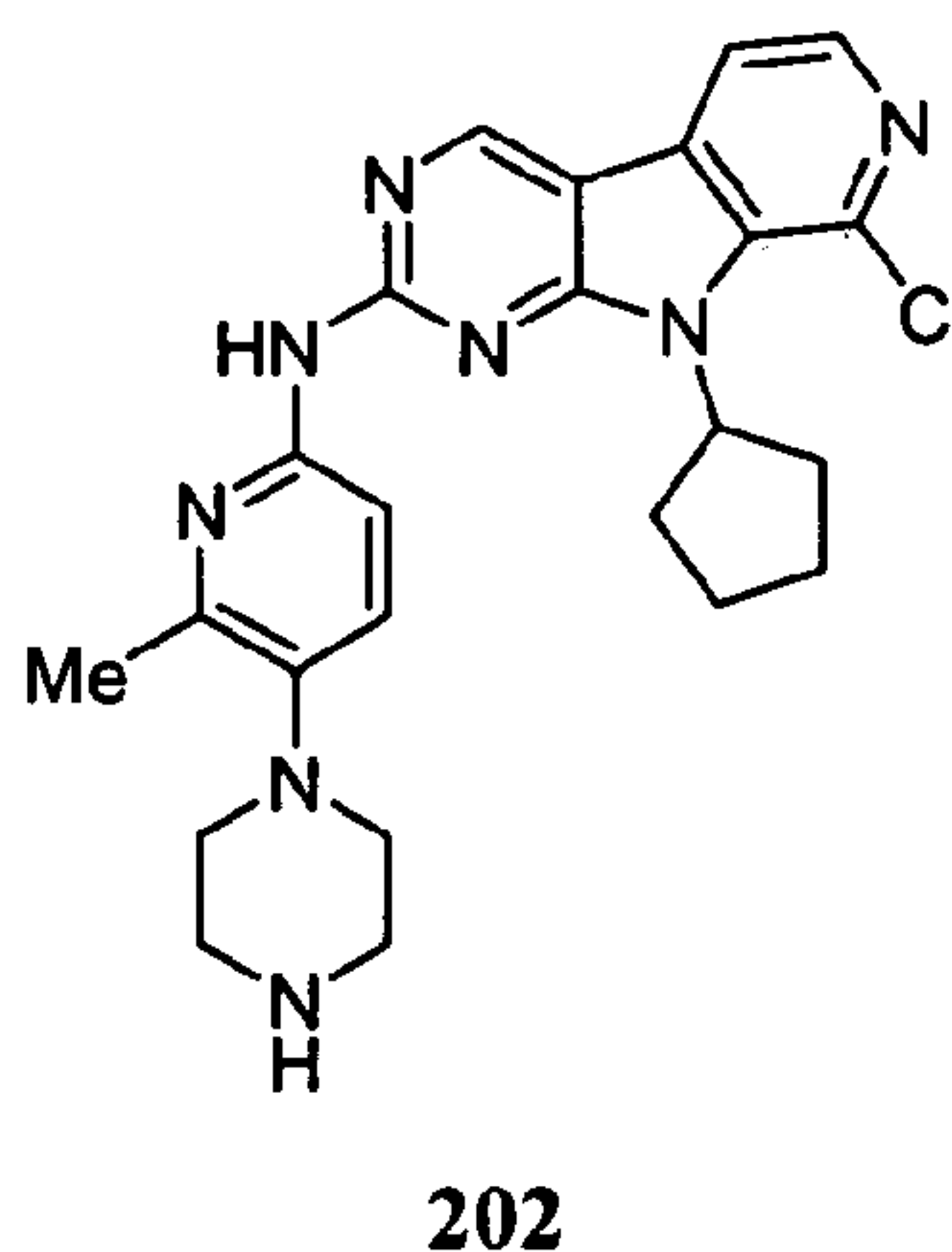
**1-(6-Bromo-3-pyridazinyl)-N,N-dimethyl-4-piperidinamine (201):** N,N-dimethylpiperidin-4-amine (0.505 g, 3.94 mmol), 3,6-dibromopyridazine (0.511 g, 2.15 mmol), and triethylamine (0.599 mL, 4.30 mmol) were combined in 5 mL of THF. The solution was heated at 70 °C for 17 hours. The solution was cooled to room temperature and then purified on CombiFlash column (dry loaded), eluting with 10% methanol/0.5%NH<sub>4</sub>OH(~28% in water)/DCM isocratic. The fractions containing the product were combined and concentrated under vacuum to give compound **201** (0.550 g, 89.8% yield) as an off white solid. <sup>1</sup>H NMR (500 MHz, MeOD-*d*<sub>3</sub>) δ 7.51 (1 H, d, J= 9.8 Hz), 7.24 (1 H, d, J= 9.8 Hz), 4.45 (2 H, d, J= 13.7 Hz), 2.98 (2 H, td, J= 13.0, 2.2 Hz), 2.61 (1 H, tt, J= 11.5, 3.8 Hz), 2.38 (6 H, s), 1.99 - 2.07 (2 H, m), 1.45 - 1.58 (2 H, m, J= 12.5, 12.2, 12.2, 4.2 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 285.0.





**8-chloro-9-cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (200):** Compound **200** was prepared using methods described in Example 152 using **201**. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.48 (1 H, s), 8.31 (1 H, d, J= 5.1 Hz), 8.18 (1 H, d, J= 5.1 Hz), 8.08 (1 H, d, J= 10.3 Hz), 7.89 (1 H, d, J= 10.0 Hz), 6.19 (1 H, quin, J= 8.7 Hz), 4.54 (2 H, d, J= 13.9 Hz), 3.53 - 3.62 (1 H, m), 3.11 - 3.19 (2 H, m), 2.92 (6 H, s), 2.63 - 2.73 (2 H, m), 2.13 - 2.29 (6 H, m), 1.79 - 1.91 (4 H, m) ) ppm; LCMS-ESI (POS), M/Z, M+1: Found 492.2.

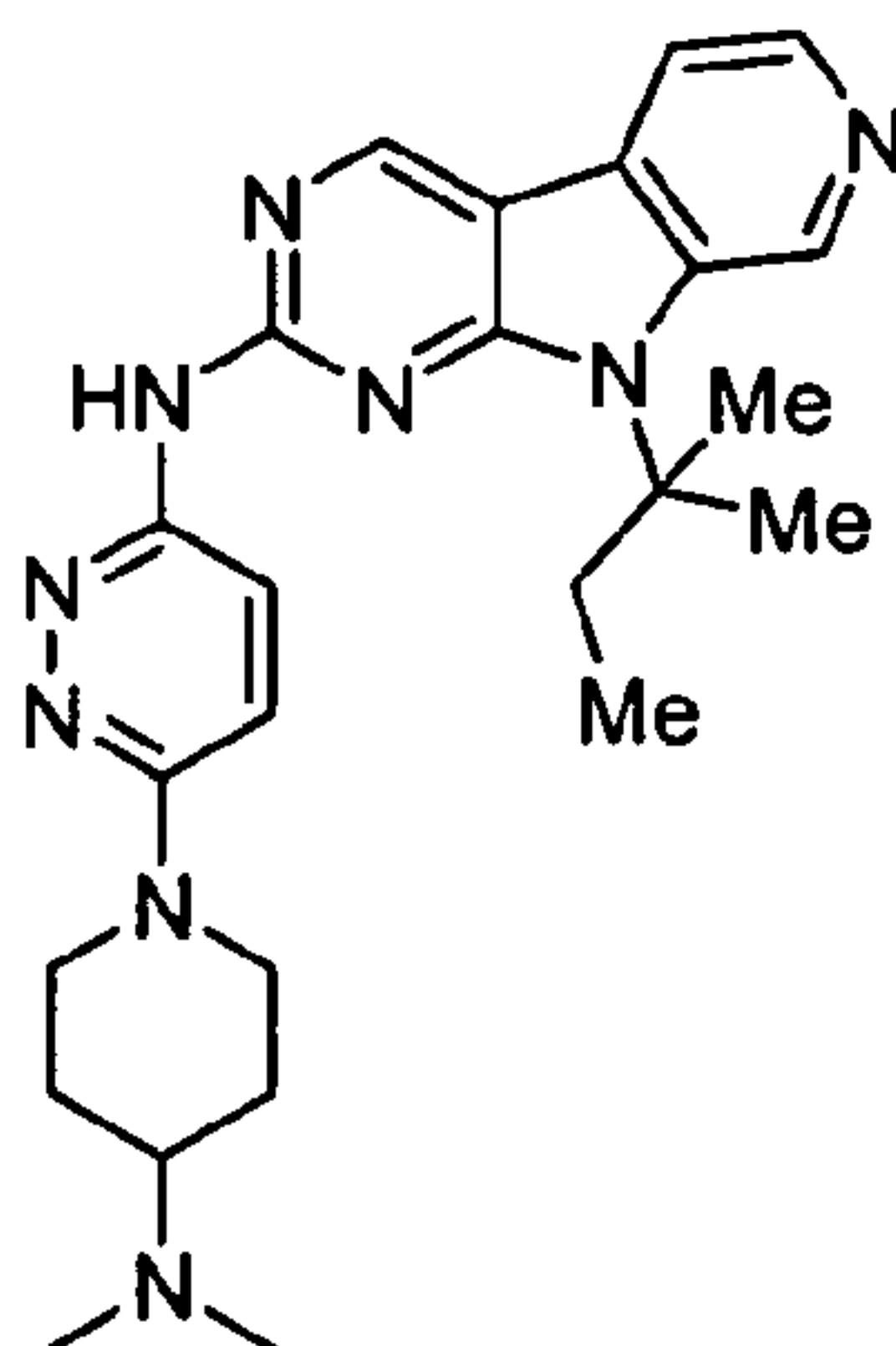
#### **EXAMPLE 155**



**8-Chloro-9-cyclopentyl-N-(6-methyl-5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

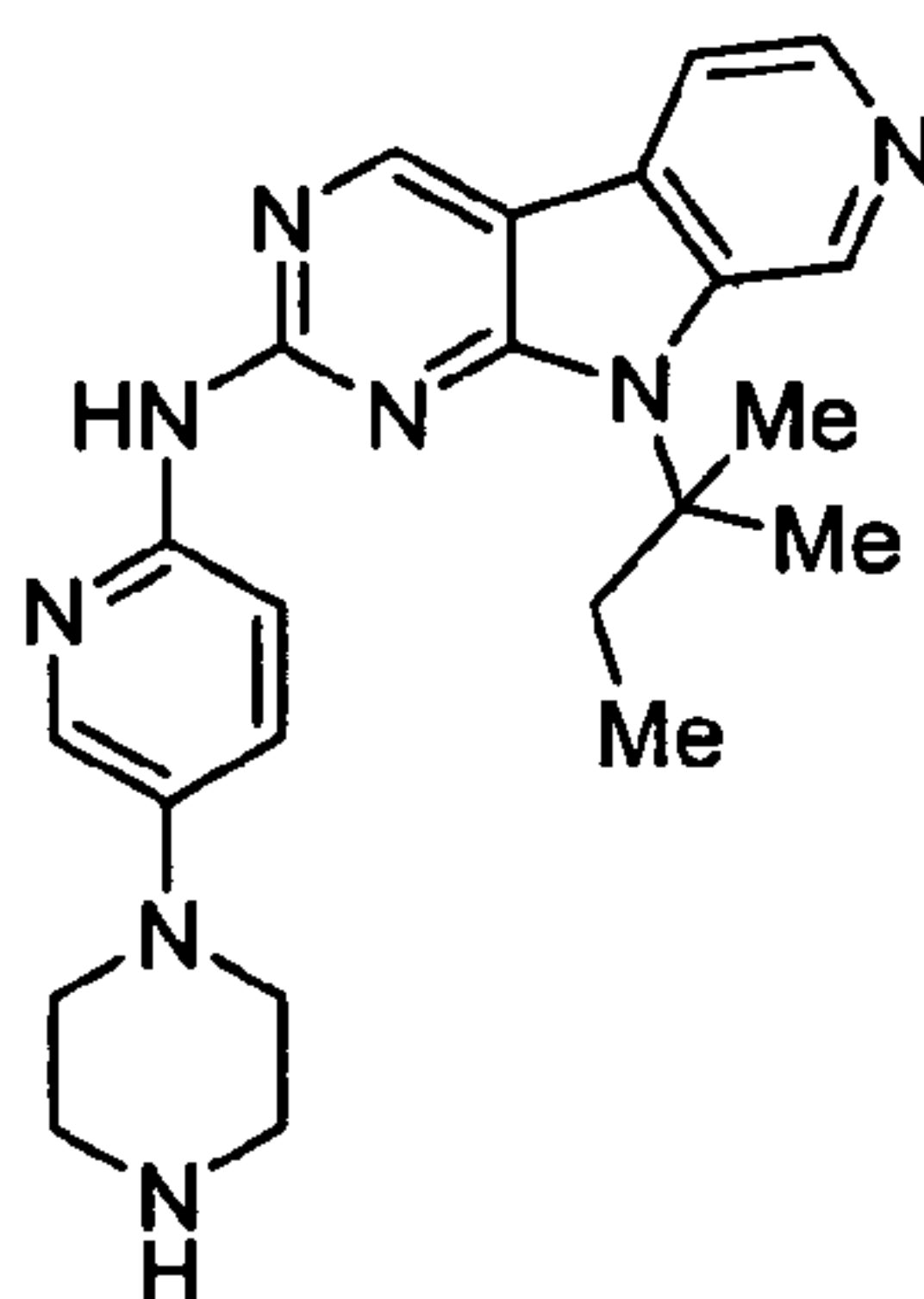
Compound **202** was prepared using methods described in Example 152. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 8.86 (1 H, s), 7.97 (1 H, d, J= 4.9 Hz), 7.80 - 7.93 (2 H, m), 7.10 (1 H, d, J= 9.0 Hz), 5.69 - 5.81 (1 H, m), 3.46 - 3.51 (4 H, m), 3.22 (4 H, br. s.), 2.52 (3 H, br. s.), 2.23 - 2.36 (2 H, m), 1.98 - 2.16 (4 H, m), 1.70 - 1.81 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 463.1.



**EXAMPLE 156****203**

**N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(1,1-dimethylpropyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **203** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.69 (1 H, br. s.), 11.30 - 11.46 (1 H, m), 9.77 (1 H, s), 9.47 (1 H, s), 8.82 (1 H, d,  $J = 6.3$  Hz), 8.72 (1 H, d,  $J = 6.3$  Hz), 8.32 (1 H, d,  $J = 10.2$  Hz), 8.15 (1 H, d,  $J = 10.2$  Hz), 4.51 (2 H, d,  $J = 13.3$  Hz), 3.44 - 3.55 (1 H, m), 3.16 (2 H, t,  $J = 12.3$  Hz), 2.71 (6 H, d,  $J = 5.1$  Hz), 2.36 (2 H, q,  $J = 7.4$  Hz), 2.23 (2 H, d,  $J = 11.7$  Hz), 2.03 (6 H, s), 1.71 - 1.88 (2 H, m), 0.65 (3 H, t,  $J = 7.2$  Hz) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 460.3.

**EXAMPLE 157****204**

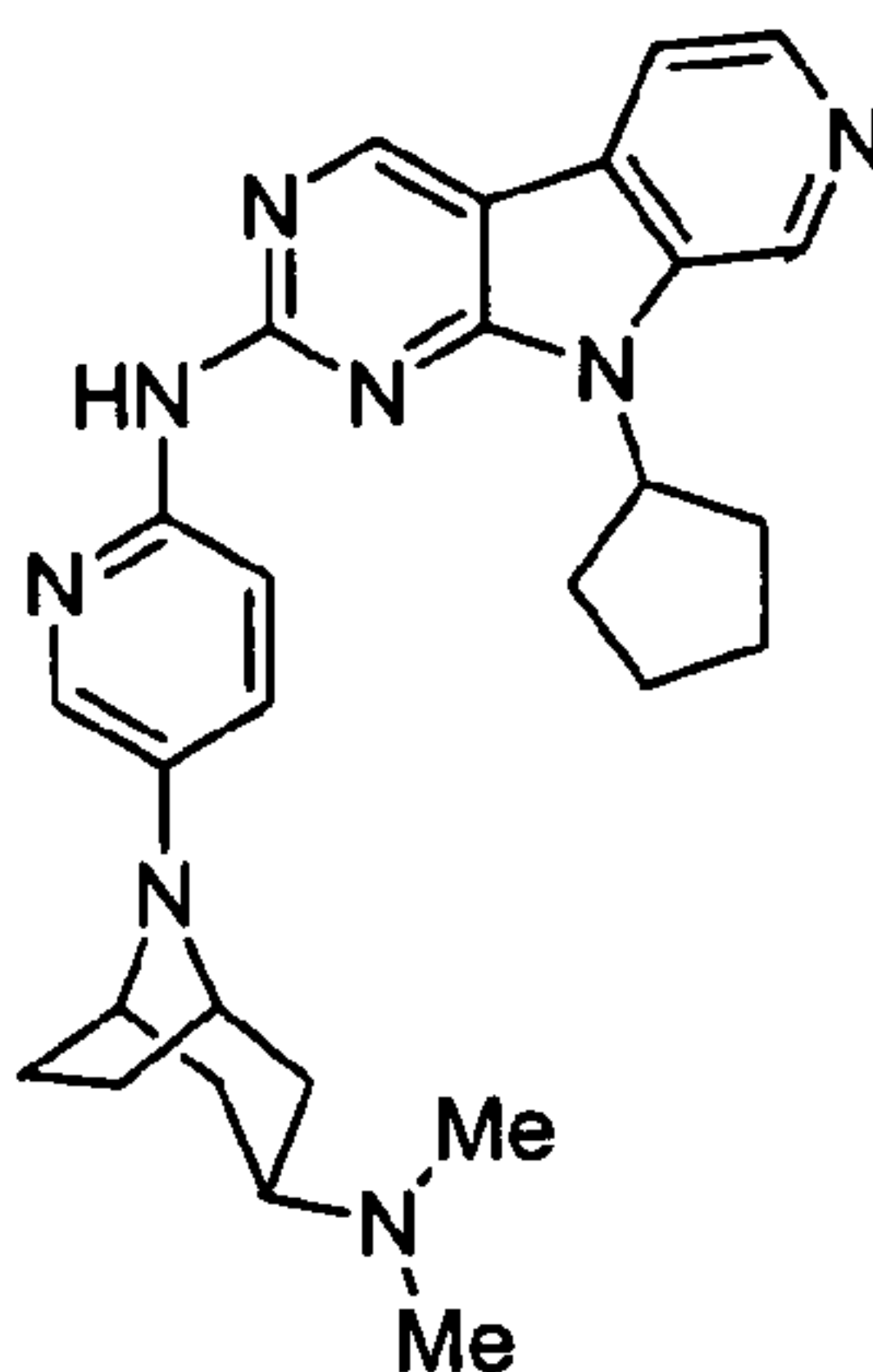
**9-(1,1-dimethylpropyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **204** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.27 (1 H, br. s.), 9.74 (1 H, s), 9.56 (2 H, br. s.), 9.43 (1 H, s), 8.79 (1 H, d,  $J = 5.9$  Hz), 8.70 (1 H, d,  $J = 5.9$  Hz), 8.13 (1 H, d,  $J = 2.3$  Hz), 7.94 - 7.98 (1 H, m),



7.88 - 7.93 (1 H, m), 3.43 - 3.53 (4 H, m), 3.20 - 3.30 (4 H, m), 2.39 (2 H, q, J= 7.2 Hz), 2.04 (6 H, s), 0.66 (3 H, t, J= 7.4 Hz) ppm; LCMS-ESI (POS), M/Z, M+1: Found 417.3.

### EXAMPLE 158

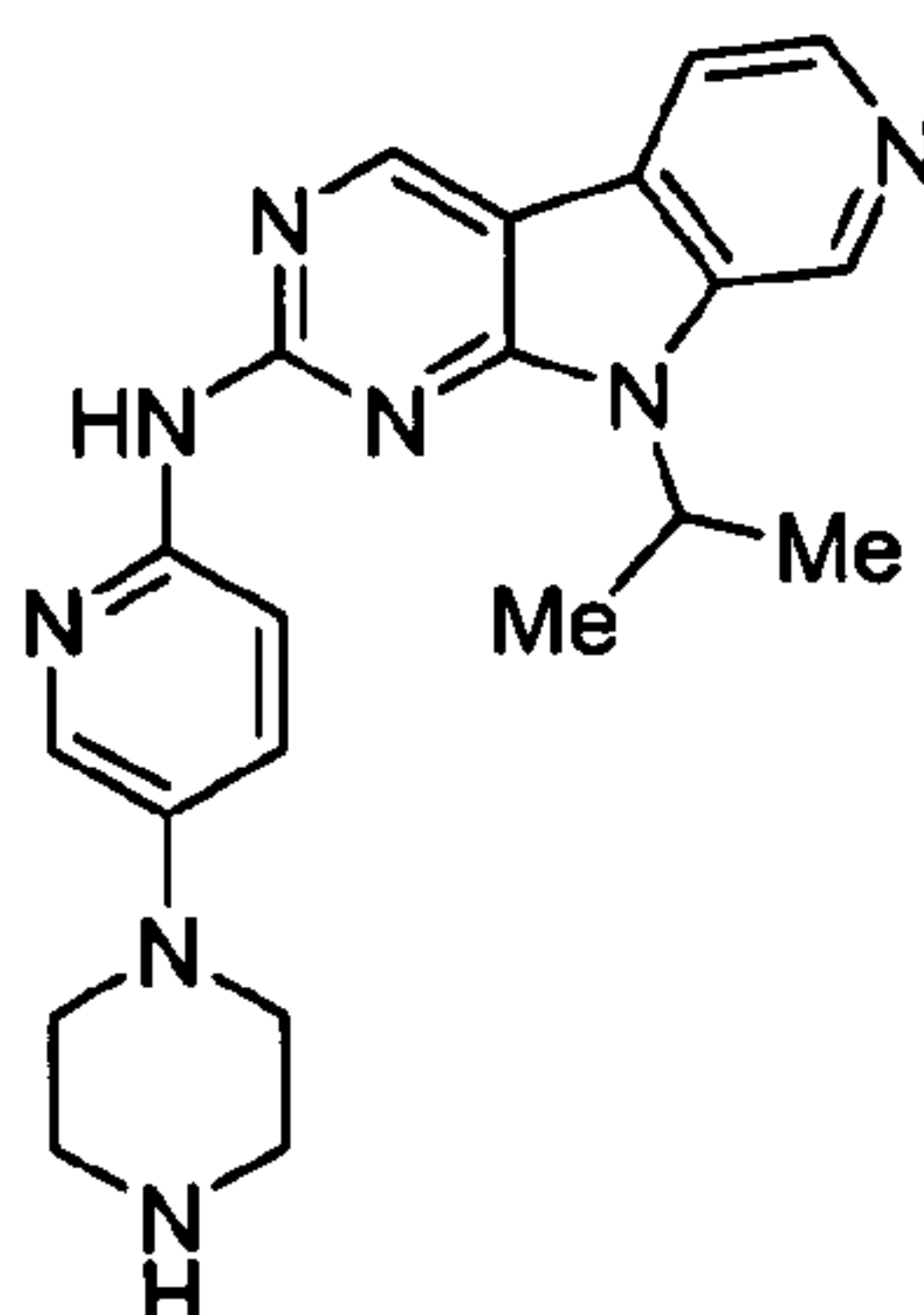


205

**9-cyclopentyl-N-(5-(3-(dimethylamino)-8-azabicyclo[3.2.1]oct-8-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **205** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 11.41 (1 H, br. s.), 10.65 (1 H, br. s.), 9.71 (1 H, s), 9.47 (1 H, s), 8.75 - 8.79 (1 H, m), 8.71 - 8.74 (1 H, m), 8.04 (1 H, d, J= 2.4 Hz), 7.92 - 7.98 (1 H, m), 7.88 (1 H, d, J= 10.3 Hz), 5.43 (1 H, quin, J= 8.7 Hz), 4.46 - 4.51 (2 H, m), 3.62 - 3.72 (1 H, m), 2.62 (6 H, d, J= 4.9 Hz), 2.37 - 2.47 (2 H, m), 2.06 - 2.18 (4 H, m), 1.99 - 2.05 (2 H, m), 1.90 - 1.97 (2 H, m), 1.80 - 1.90 (4 H, m), 1.71 - 1.80 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 483.3.

### EXAMPLE 159



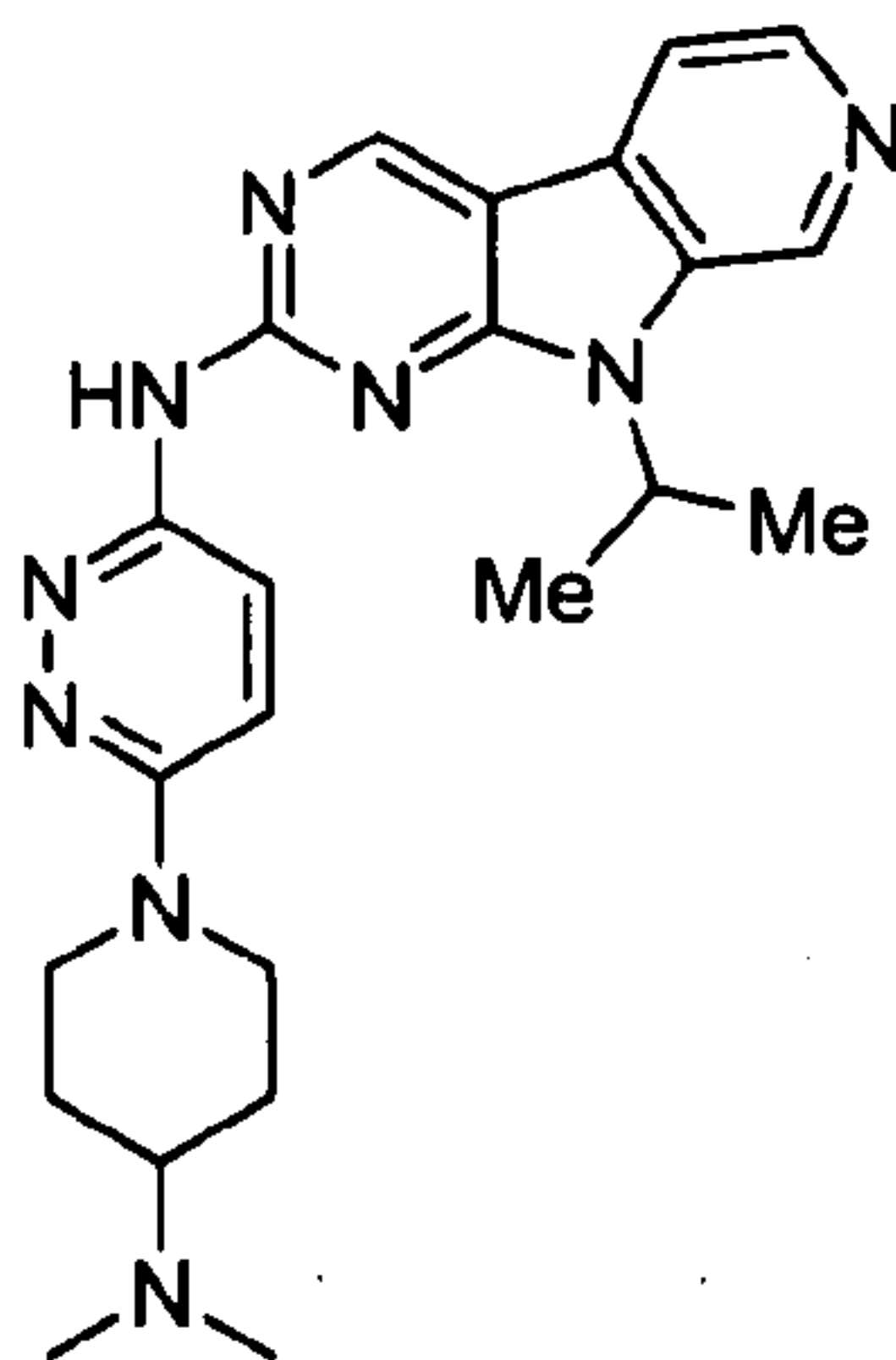
206

**9-(1-methylethyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



Compound **206** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.71 (1 H, s), 9.54 (3 H, br. s.), 8.76 (1 H, d,  $J = 6.1$  Hz), 8.72 (1 H, d,  $J = 6.1$  Hz), 8.14 (1 H, d,  $J = 2.7$  Hz), 8.03 (1 H, d,  $J = 9.3$  Hz), 7.93 (1 H, d,  $J = 9.3$  Hz), 5.35 (1 H, dt,  $J = 13.9, 6.9$  Hz), 3.45 - 3.51 (4 H, m), 3.22 - 3.28 (4 H, m), 1.72 (6 H, d,  $J = 7.1$  Hz) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 389.2.

#### EXAMPLE 160

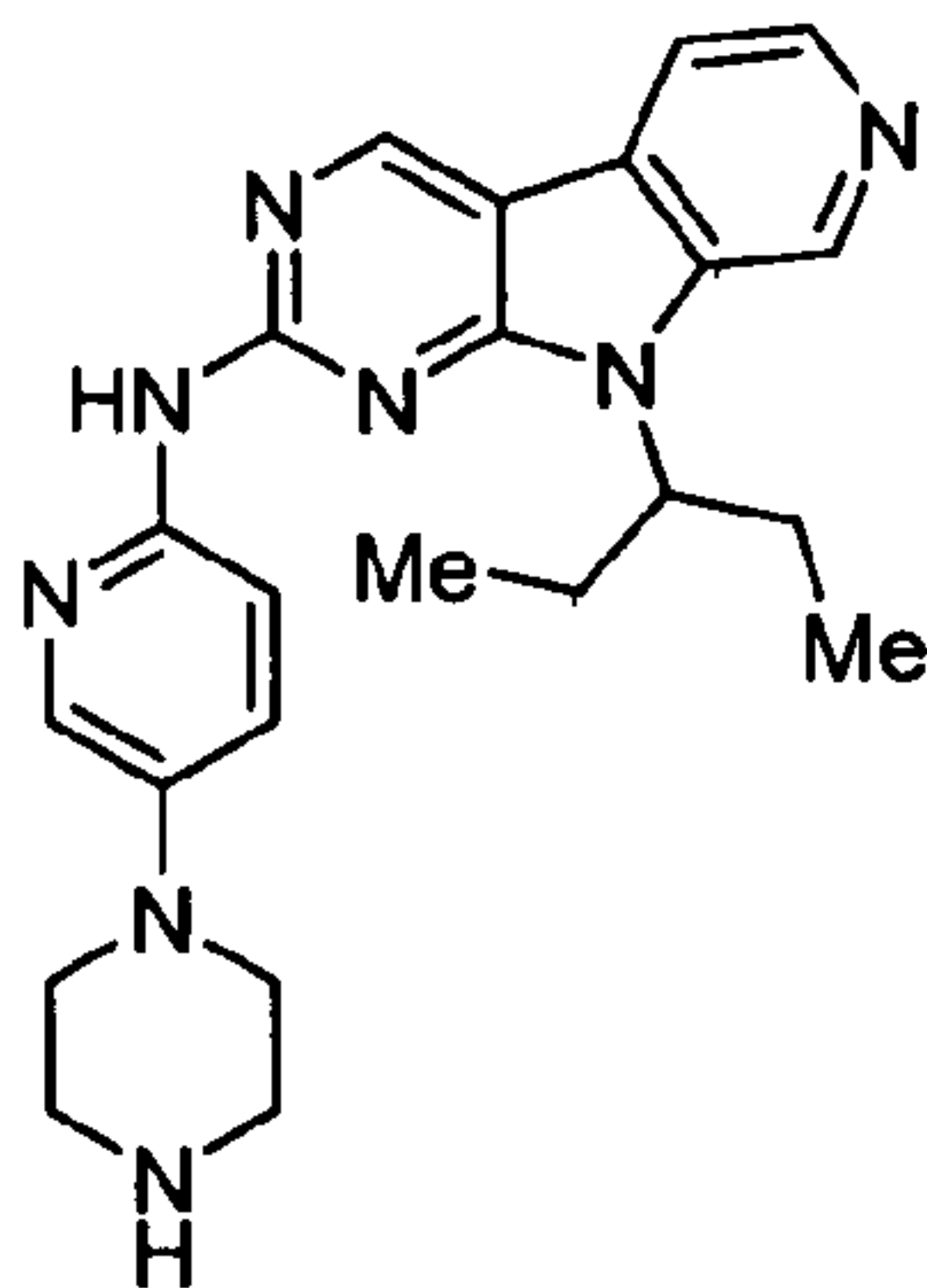


**207**

***N*-(6-(4-(Dimethylamino)-1-piperidiny)-3-pyridazinyl)-9-(1-methylethyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **207** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.18 (1 H, s), 9.26 (1 H, s), 9.09 (1 H, s), 8.44 (1 H, d,  $J = 5.1$  Hz), 8.22 (1 H, d,  $J = 9.5$  Hz), 8.04 (1 H, d,  $J = 5.1$  Hz), 7.44 (1 H, d,  $J = 9.8$  Hz), 5.24 (1 H, dt,  $J = 13.7, 6.8$  Hz), 4.30 (2 H, d,  $J = 12.5$  Hz), 2.88 (2 H, t,  $J = 11.9$  Hz), 2.33 - 2.44 (1 H, m), 1.86 (2 H, d,  $J = 10.0$  Hz), 1.66 (6 H, d,  $J = 6.8$  Hz), 1.36 - 1.49 (2 H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 432.2.

#### EXAMPLE 161



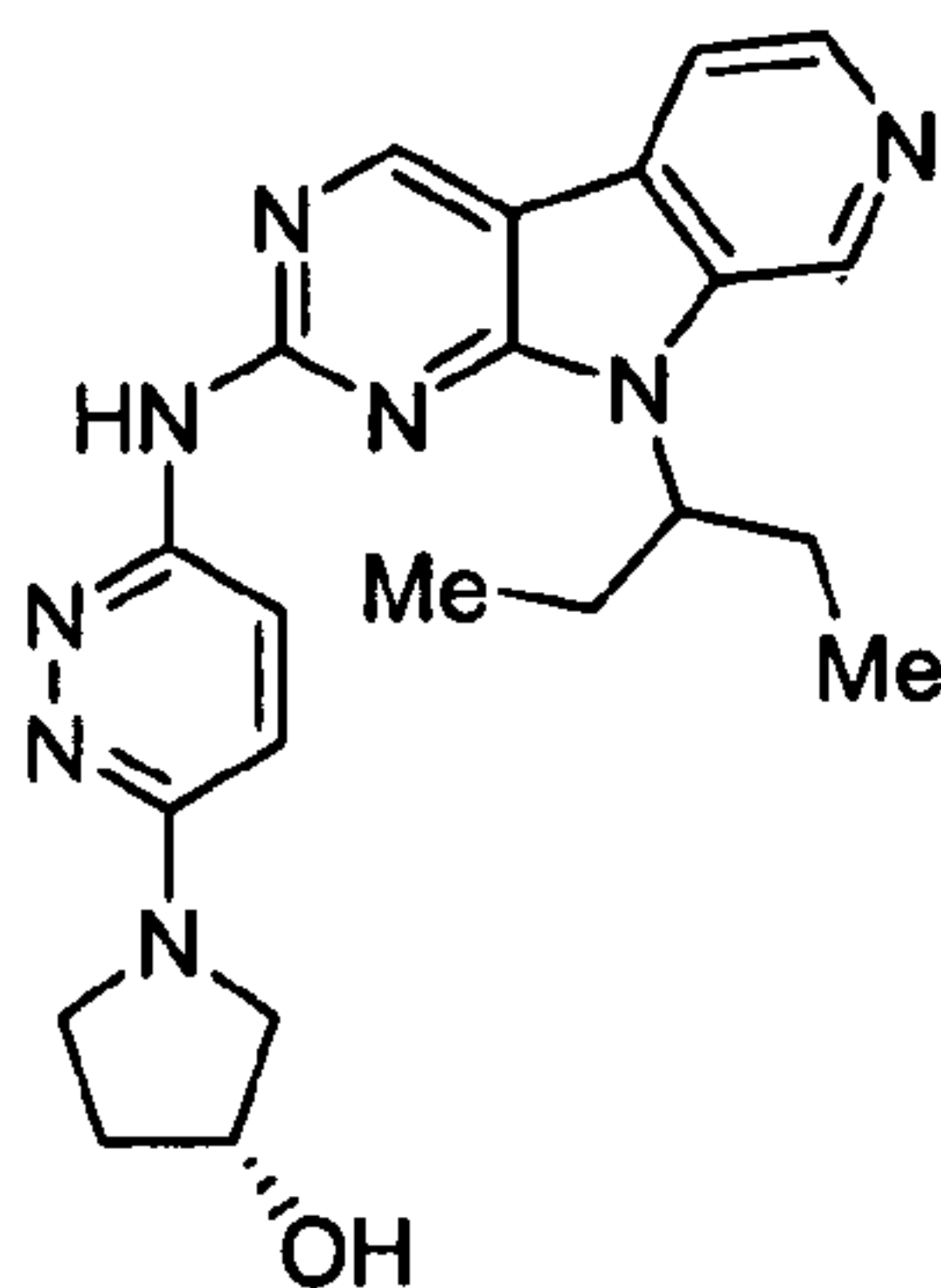
**208**

**9-(1-Ethylpropyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



Compound **208** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.28 (1 H, br. s.), 9.73 (1 H, s), 9.58 (1 H, s), 9.52 (2 H, br. s.), 8.78 (1 H, d,  $J=5.9$  Hz), 8.73 (1 H, d,  $J=6.1$  Hz), 8.14 (1 H, d,  $J=2.7$  Hz), 8.02 (1 H, br. s.), 7.92 (1 H, br. s.), 4.83 - 4.95 (1 H, m), 3.45 - 3.52 (4 H, m), 3.18 - 3.30 (4 H, m), 2.28 - 2.42 (2 H, m), 2.00 - 2.13 (2 H, m), 0.72 (6 H, t,  $J=7.3$  Hz) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 417.3.

### EXAMPLE 162

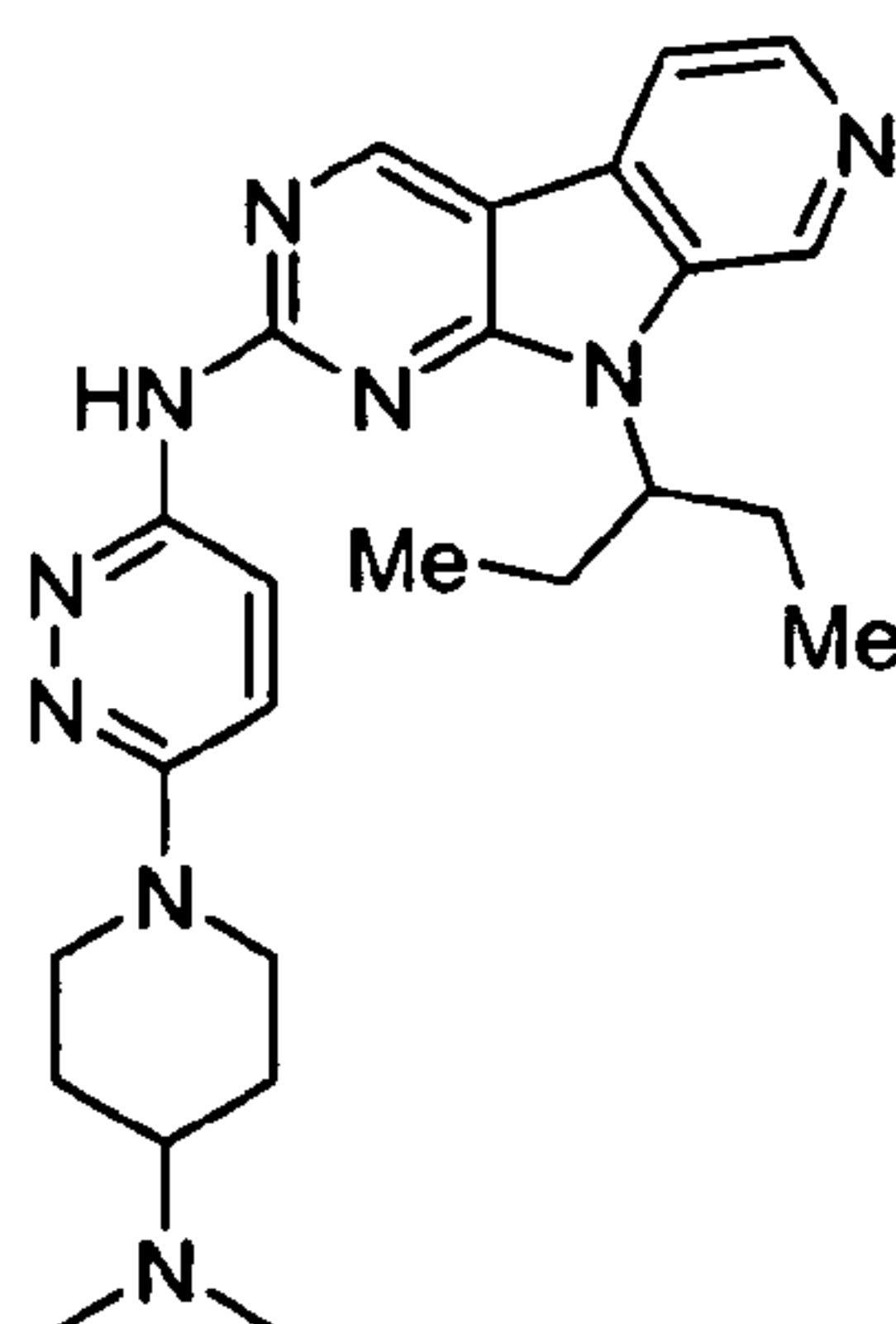


**209**

**(3*R*)-1-(6-((9-(1-Ethylpropyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-amino)-3-pyridazinyl)-3-pyrrolidinol**

Compound **209** was prepared using chemistry similar to that described in example 18.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.44 (1 H, br. s.), 9.75 (1 H, s), 9.62 (1 H, s), 8.78 (1 H, d,  $J=6.2$  Hz), 8.73 (1 H, d,  $J=6.1$  Hz), 8.48 (1 H, d,  $J=10.0$  Hz), 7.92 (1 H, d,  $J=10.0$  Hz), 4.82 - 4.91 (1 H, m), 4.47 - 4.56 (1 H, m), 3.65 - 3.84 (3 H, m), 3.57 - 3.64 (1 H, m), 2.25 - 2.41 (2 H, m), 1.92 - 2.17 (4 H, m), 0.70 (6 H, t,  $J=14.6$  Hz) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 419.2.

### EXAMPLE 163



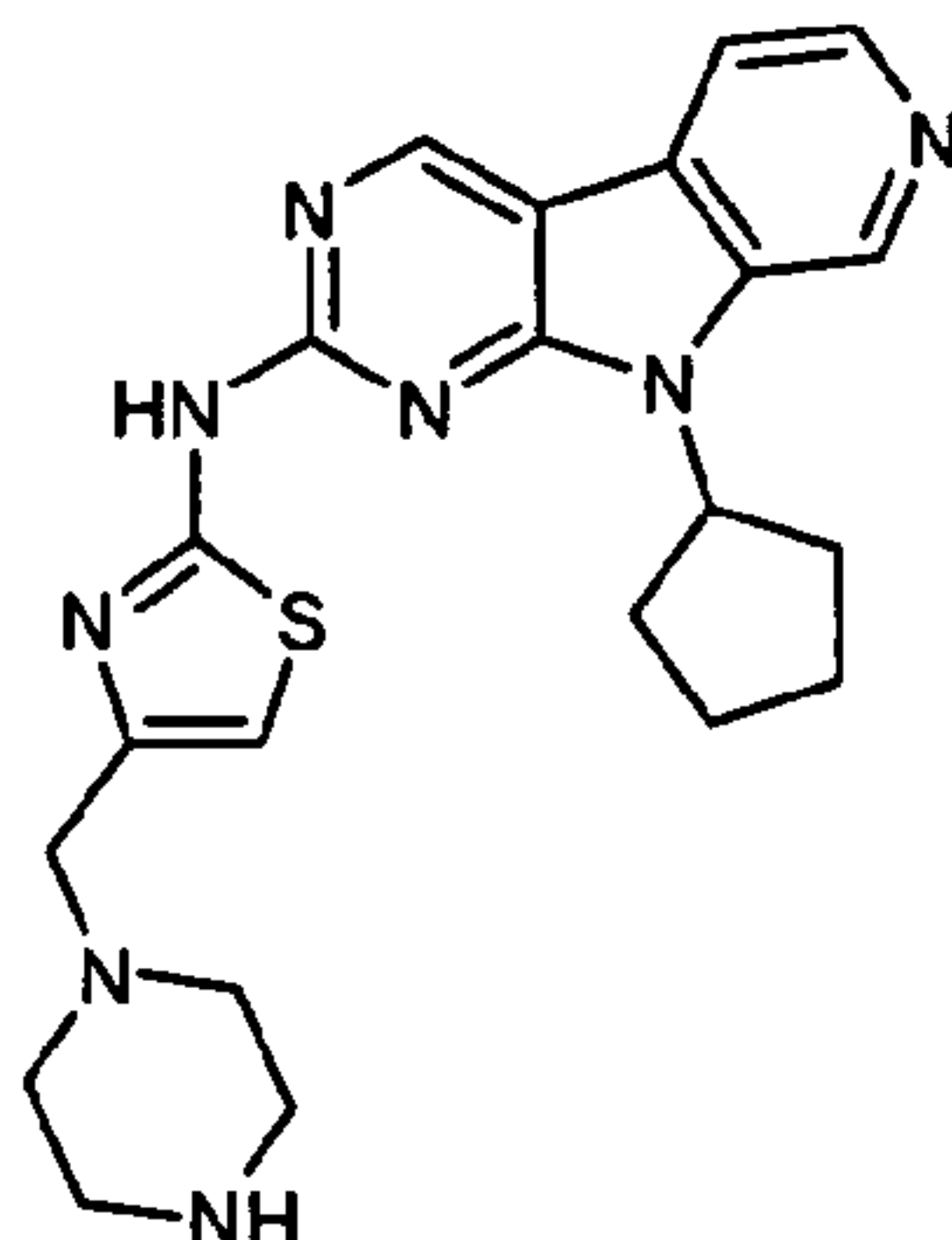
**210**

***N*-(6-(4-(Dimethylamino)-1-piperidinyl)-3-pyridazinyl)-9-(1-ethylpropyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



Compound **210** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.18 (1 H, br. s.), 9.28 (1 H, s), 9.06 (1 H, s), 8.44 (1 H, d,  $J=5.1$  Hz), 8.20 (1 H, d,  $J=9.8$  Hz), 8.05 (1 H, d,  $J=5.1$  Hz), 7.45 (1 H, d,  $J=9.8$  Hz), 4.75 (1 H, br. s.), 4.29 (2 H, d,  $J=13.0$  Hz), 2.88 (2 H, t,  $J=11.6$  Hz), 2.25 - 2.37 (3 H, m), 2.19 (6 H, s), 1.93 - 2.03 (2 H, m), 1.81 - 1.88 (2 H, m), 1.36 - 1.47 (2 H, m), 0.67 (6 H, t,  $J=7.3$  Hz) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 460.3.

#### EXAMPLE 164

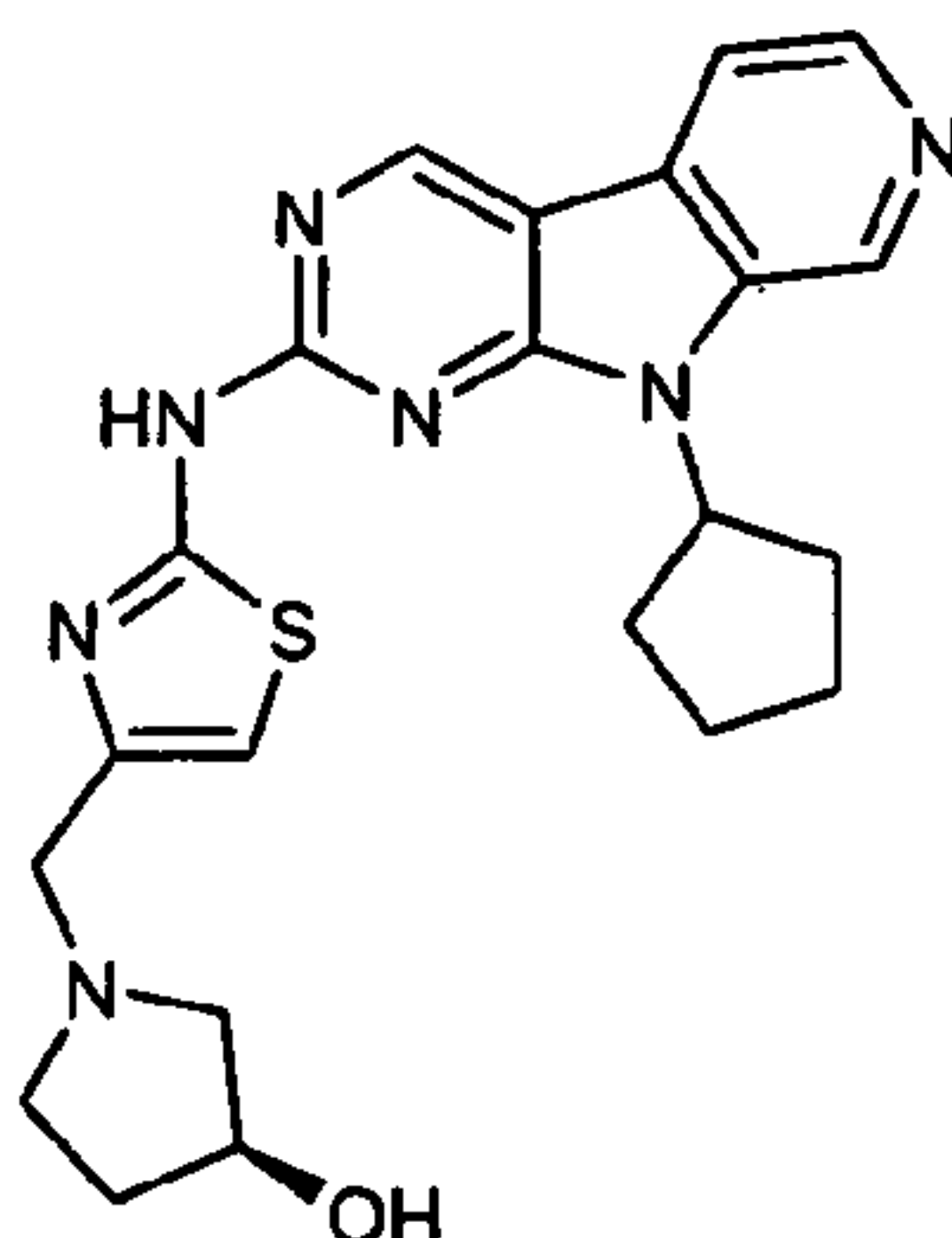


**211**

**9-Cyclopentyl-N-(4-(1-piperazinylmethyl)-1,3-thiazol-2-yl)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **211** was prepared using chemistry similar to that described in example 1.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  12.47 (1 H, br. s.), 9.71 (1 H, s), 9.44 (1 H, s), 9.02 (2 H, br. s.), 8.73 (1 H, d,  $J=6.1$  Hz), 8.65 (1 H, d,  $J=6.1$  Hz), 7.41 (1 H, s), 5.39 - 5.53 (1 H, m), 4.15 (2 H, s), 3.30 (4 H, br. s.), 3.17 (4 H, br. s.,  $J=7.6$  Hz), 2.53 - 2.62 (2 H, m), 2.08 - 2.20 (4 H, m), 1.77 - 1.89 (2 H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 435.2.

#### EXAMPLE 165

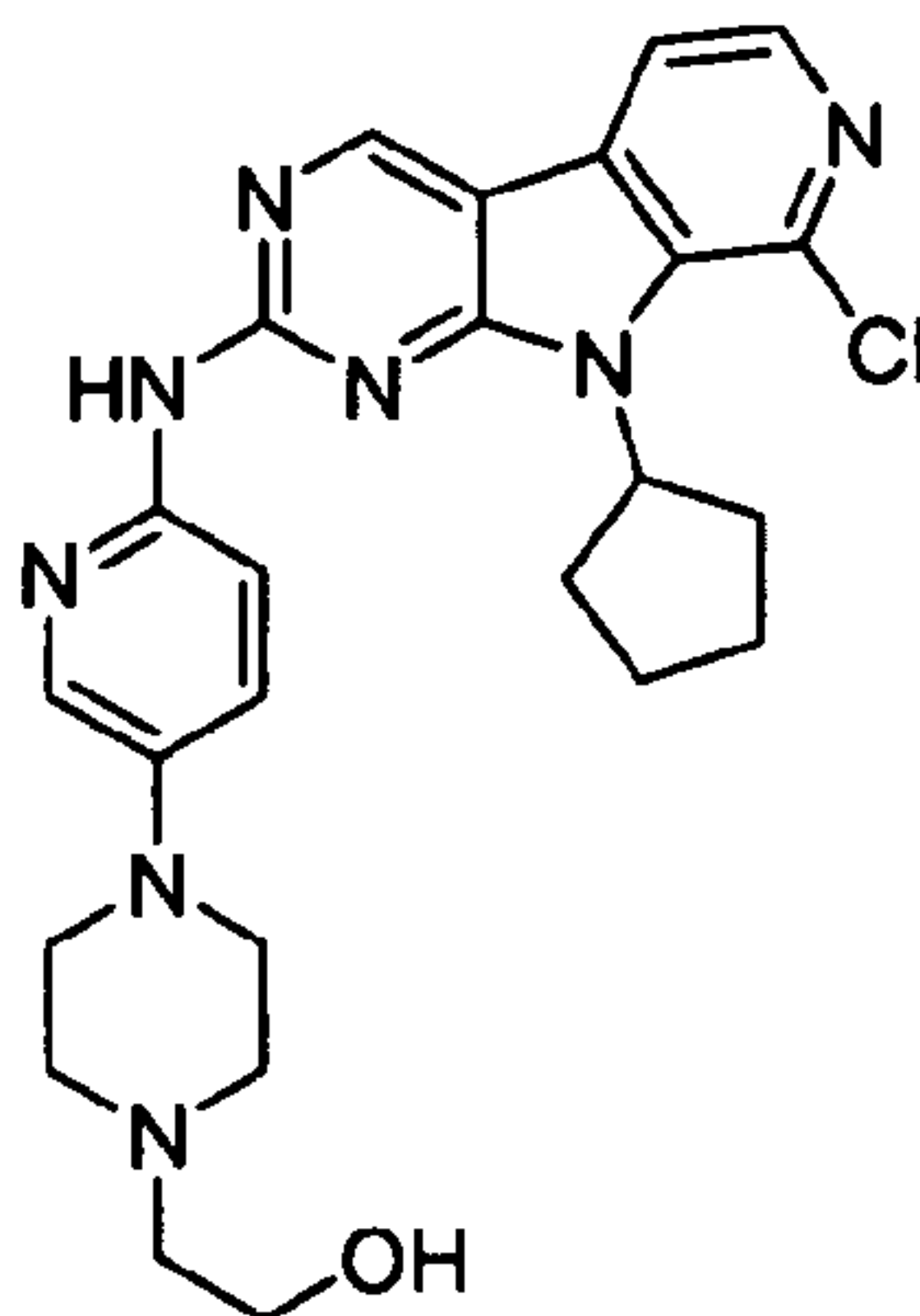


**212**

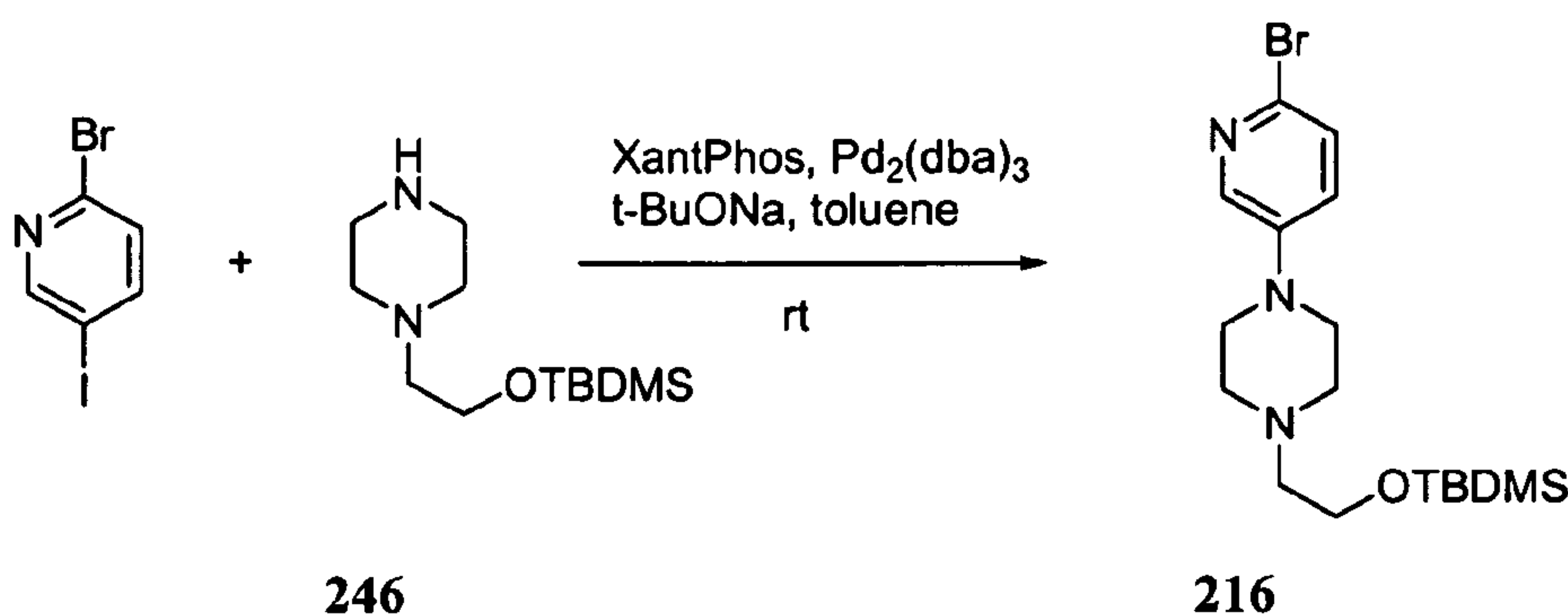
**(3S)-1-((2-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1,3-thiazol-4-yl)methyl)-3-pyrrolidinol**



Compound **212** was prepared using chemistry similar to that described in example 18. <sup>1</sup>H NMR (500 MHz, *MeOD-d*<sub>3</sub>) δ 9.28 (1 H, br. s.), 8.94 (1 H, br. s.), 8.43 (1 H, br. s.), 8.09 (1 H, br. s.), 6.94 (1 H, br. s.), 5.49 - 5.62 (1 H, m), 4.34 - 4.44 (1 H, m), 3.67 - 3.83 (2 H, m), 2.93 - 3.01 (1 H, m), 2.83 - 2.91 (1 H, m), 2.68 - 2.77 (1 H, m), 2.60 - 2.66 (1 H, m), 2.48 - 2.57 (2 H, m), 2.08 - 2.27 (5 H, m), 1.88 - 2.00 (2 H, m), 1.76 (1 H, br. s.) ppm; LCMS-ESI (POS), *M/Z*, *M*+1: Found 436.1.

**EXAMPLE 166****213**

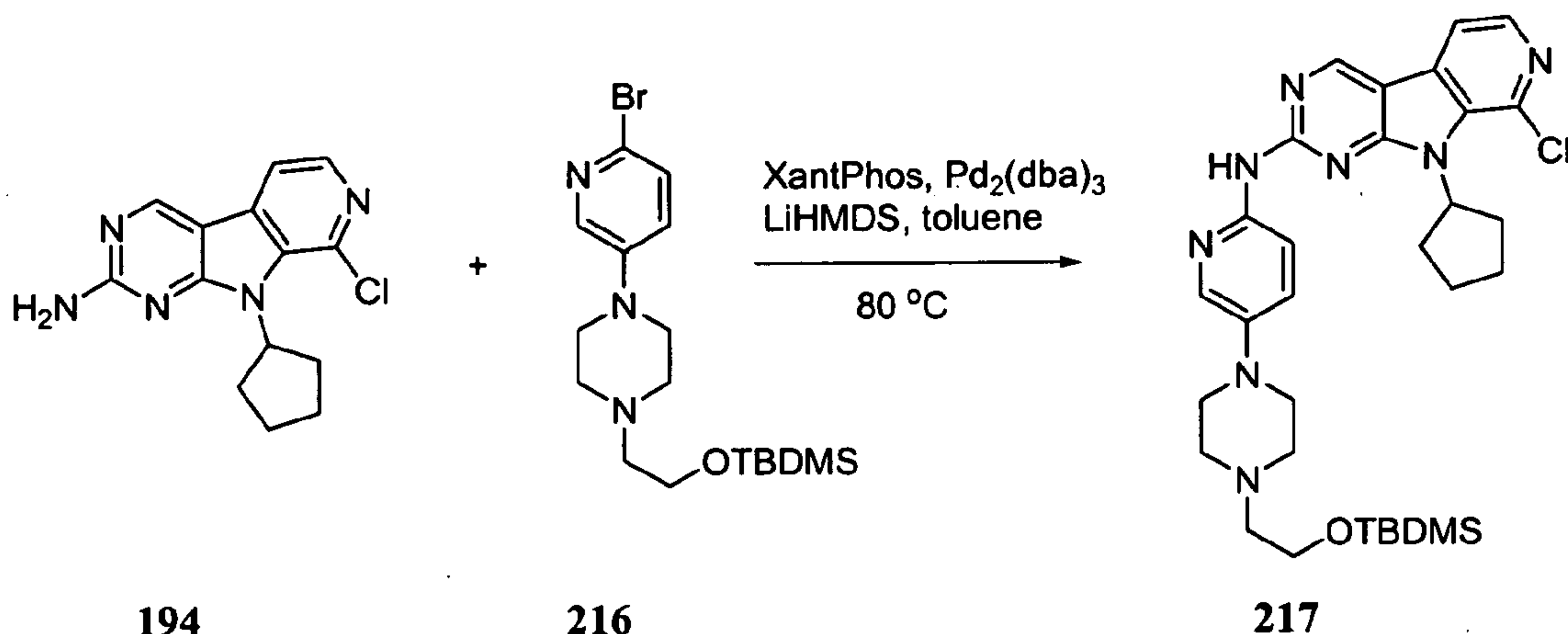
**2-(4-(6-((8-Chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol**



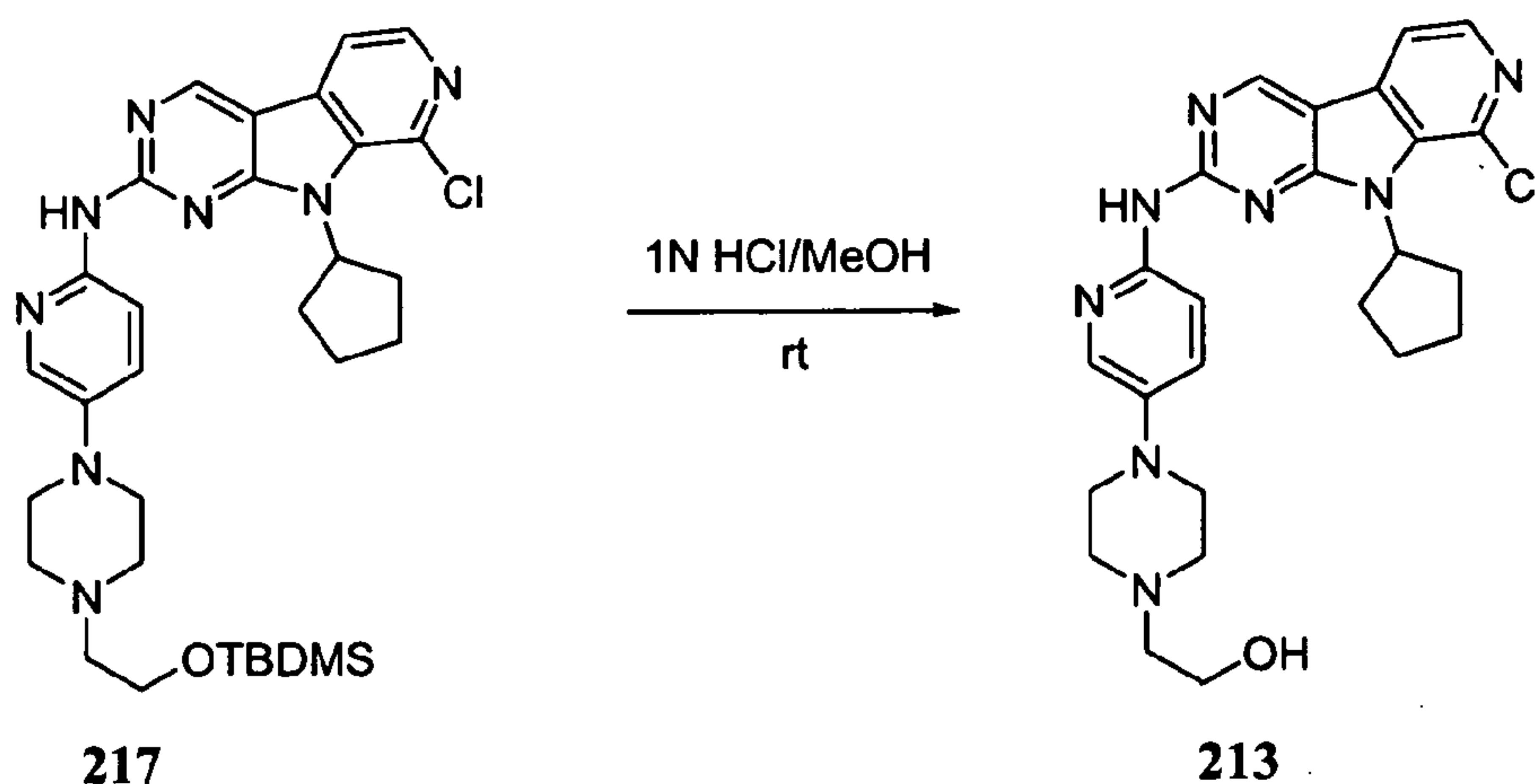
**1-(6-Bromo-3-pyridinyl)-4-(2-((tert-butyl(dimethyl)silyl)oxy)ethyl)piperazine (216)**; 2-Bromo-5-iodopyridine (0.383 g, 1.35 mmol), compound **246** (see example 170) (0.330 g, 1.35 mmol), and sodium 2-methylpropan-2-olate (0.195 g, 2.02 mmol) were combined in 10 mL of anhydrous toluene. N<sub>2</sub> was bubbled briefly through the solution before adding Pd<sub>2</sub>(dba)<sub>3</sub> (0.0309 g, 0.0337 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0391 g, 0.0675 mmol). The solution was then stirred at room temperature overnight. After 17 hours, more 2-bromo-5-iodopyridine (0.383 g, 1.35 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.0309 g, 0.0337 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0391 g, 0.0675 mmol) and sodium 2-methylpropan-2-olate (0.195 g, 2.02 mmol) were added. The solution was stirred at



room temperature for 48 hours.  $\text{NH}_4\text{Cl}$  (300 mg) was added and the solution was stirred at room temperature for 10 min. The product was purified on CombiFlash column (dry loaded), eluting with a gradient of 20% ethyl acetate/hexane to ethyl acetate. The fractions containing the product were combined and concentrated under vacuum to give compound **216** (100mg, 19%) as a tan colored solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 8.01 (1 H, d,  $J=3.2$  Hz), 7.29 (1 H, d,  $J=8.8$  Hz), 7.07 (1 H, dd,  $J=8.8, 3.2$  Hz), 3.79 (2 H, t,  $J=6.1$  Hz), 3.15 - 3.24 (4 H, m), 2.67 - 2.75 (4 H, m), 2.60 (2 H, t,  $J=6.1$  Hz), 0.90 (9 H, s), 0.07 (6 H, s) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 400.1.



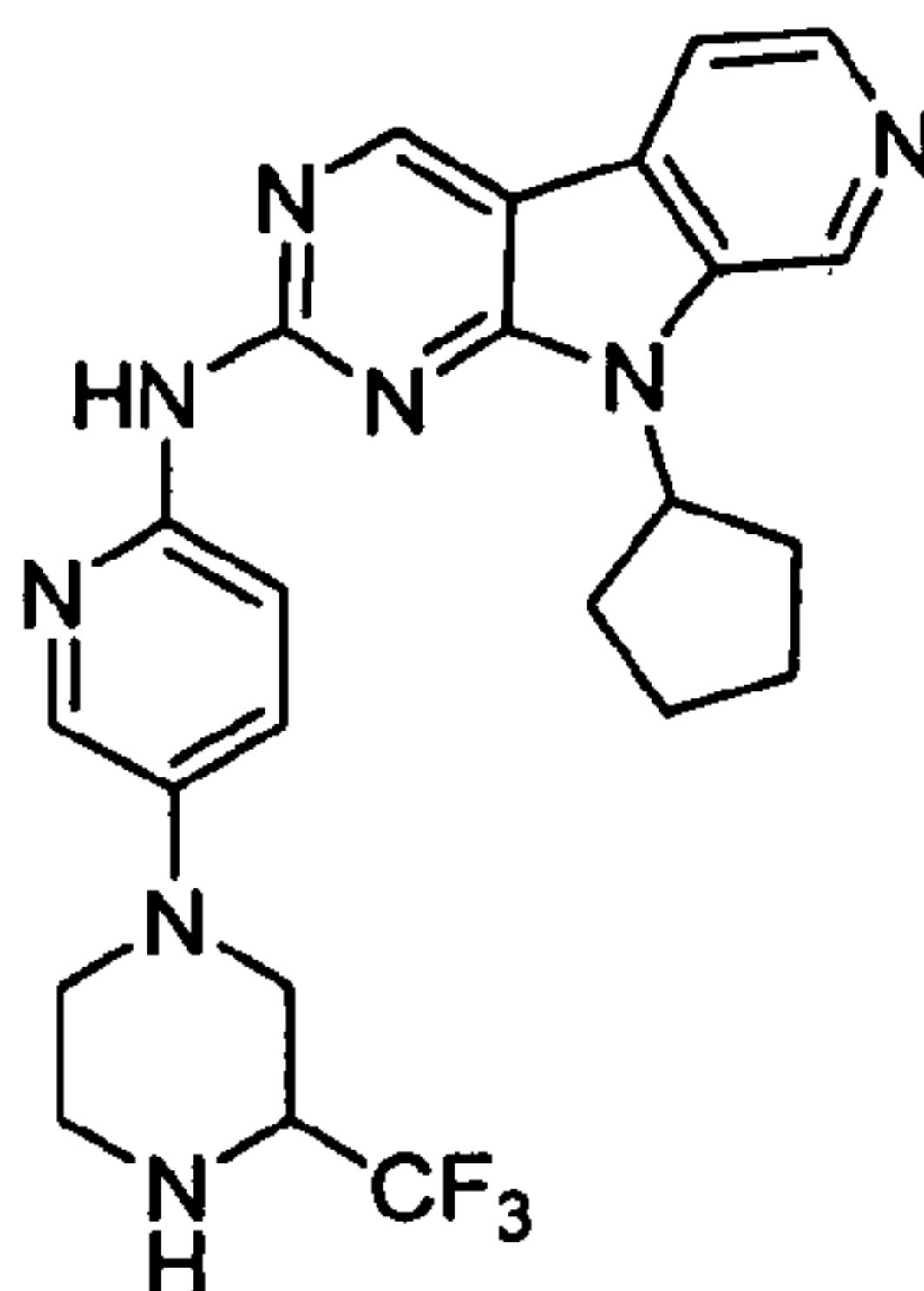
**N-(5-(4-(2-((tert-Butyl(dimethyl)silyl)oxy)ethyl)-1-piperazinyl)-2-pyridinyl)-8-chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (217):** Compound **217** was prepared from compounds **194** and **216** using methods described in example 152. LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 607.4.



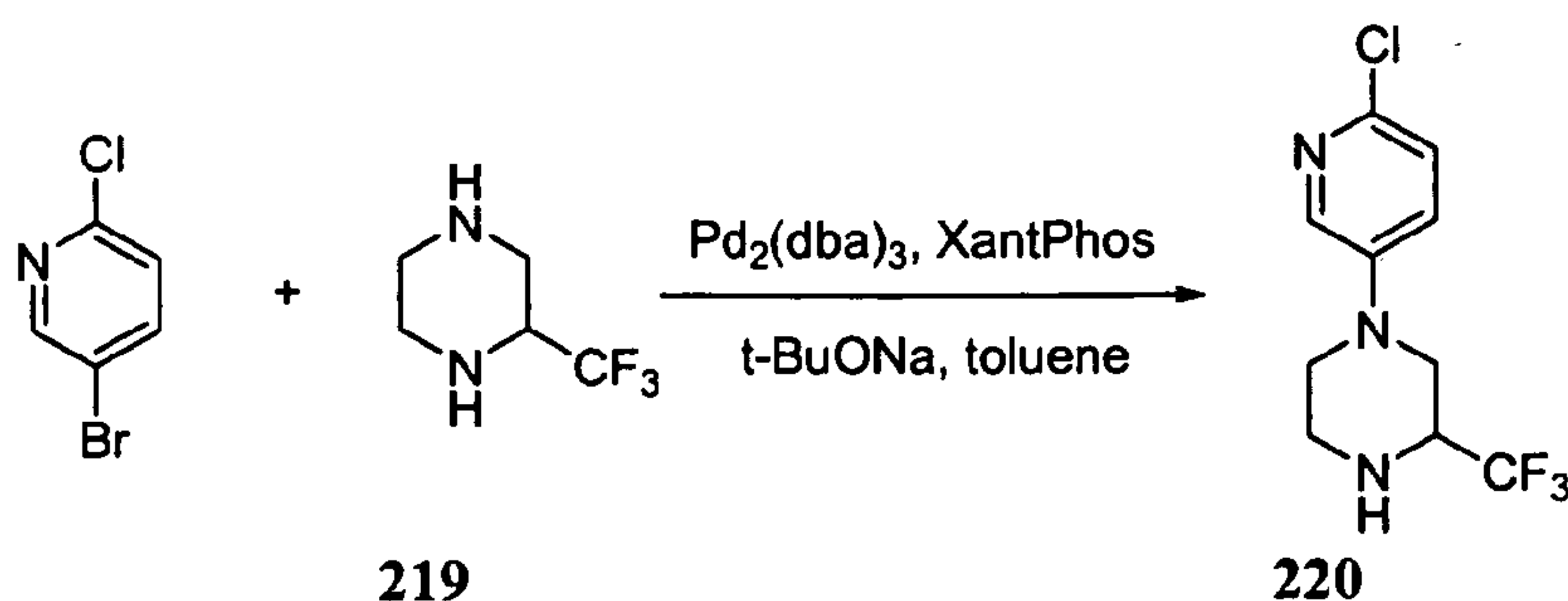
**2-(4-(6-((8-Chloro-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol (213):** Compound **217** (0.094 g, 0.15 mmol) was combined with 10 mL of methanol and 4 mL of 1N HCl. The solution was stirred at room



temperature overnight. The solution was concentrated under vacuum and the residue obtained was purified on CombiFlash column (dry loaded), eluting with a gradient of 2% methanol/0.1%  $\text{NH}_4\text{OH}$  (~28% in water)/DCM to 10% methanol/0.5%  $\text{NH}_4\text{OH}$  (~28% in water)/DCM. The fractions containing the product were combined and concentrated under vacuum to give a yellow solid. The solid was partially dissolved in methanol and then collected on filter paper. Washed the solid off of the filter paper with DCM/methanol through a fritted funnel and then concentrated under vacuum to give compound **213** (0.065 g, 85% yield) as a yellow solid.  $^1\text{H}$ -NMR(500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.92 (1 H, s), 9.33 (1 H, s), 8.22 (1 H, d,  $J$ = 5.1 Hz), 8.10 (1 H, d,  $J$ = 4.9 Hz), 8.04 (1 H, d,  $J$ = 2.9 Hz), 8.02 (1 H, d,  $J$ = 9.0 Hz), 7.46 (1 H, dd,  $J$ = 9.0, 2.9 Hz), 5.95 - 6.05 (1 H, m), 4.43 (1 H, t,  $J$ = 5.4 Hz), 3.54 (2 H, q,  $J$ = 6.1 Hz), 3.12 - 3.19 (4 H, m), 2.55 - 2.65 (6 H, m), 2.45 (2 H, t,  $J$ = 6.4 Hz), 1.98 - 2.08 (4 H, m), 1.65 - 1.75 (2 H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 493.1.

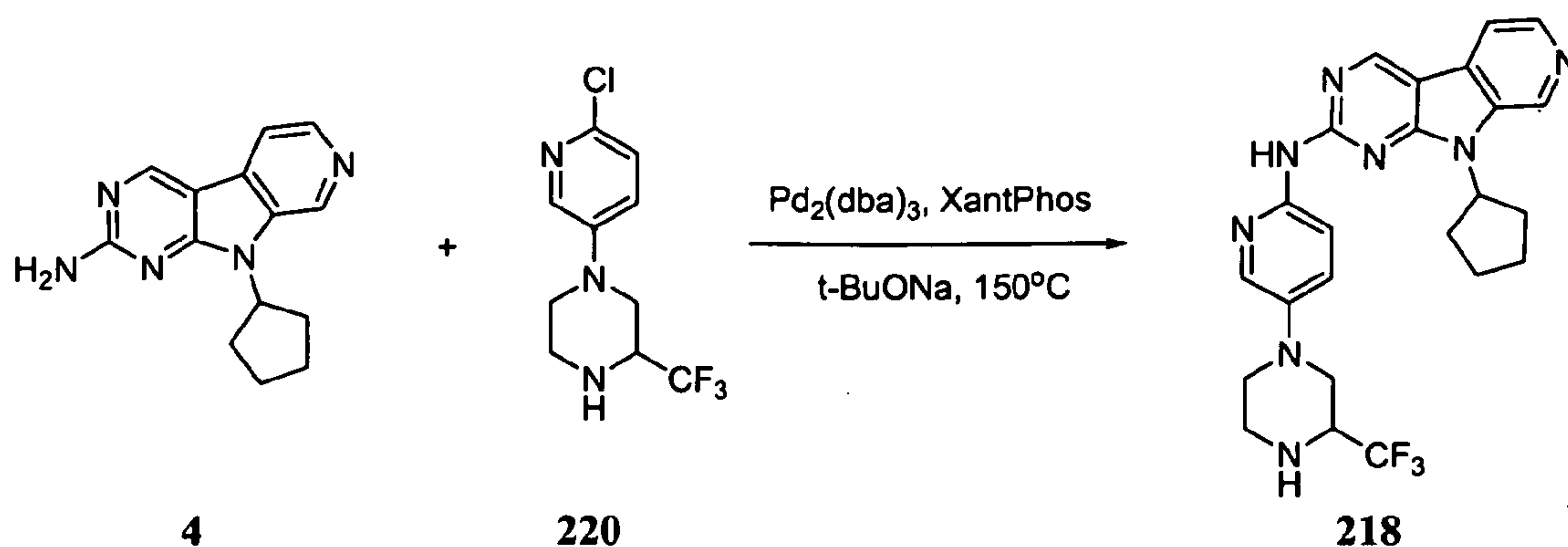
**EXAMPLE 167****218**

**4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-(trifluoromethyl)piperazine**

**219****220**

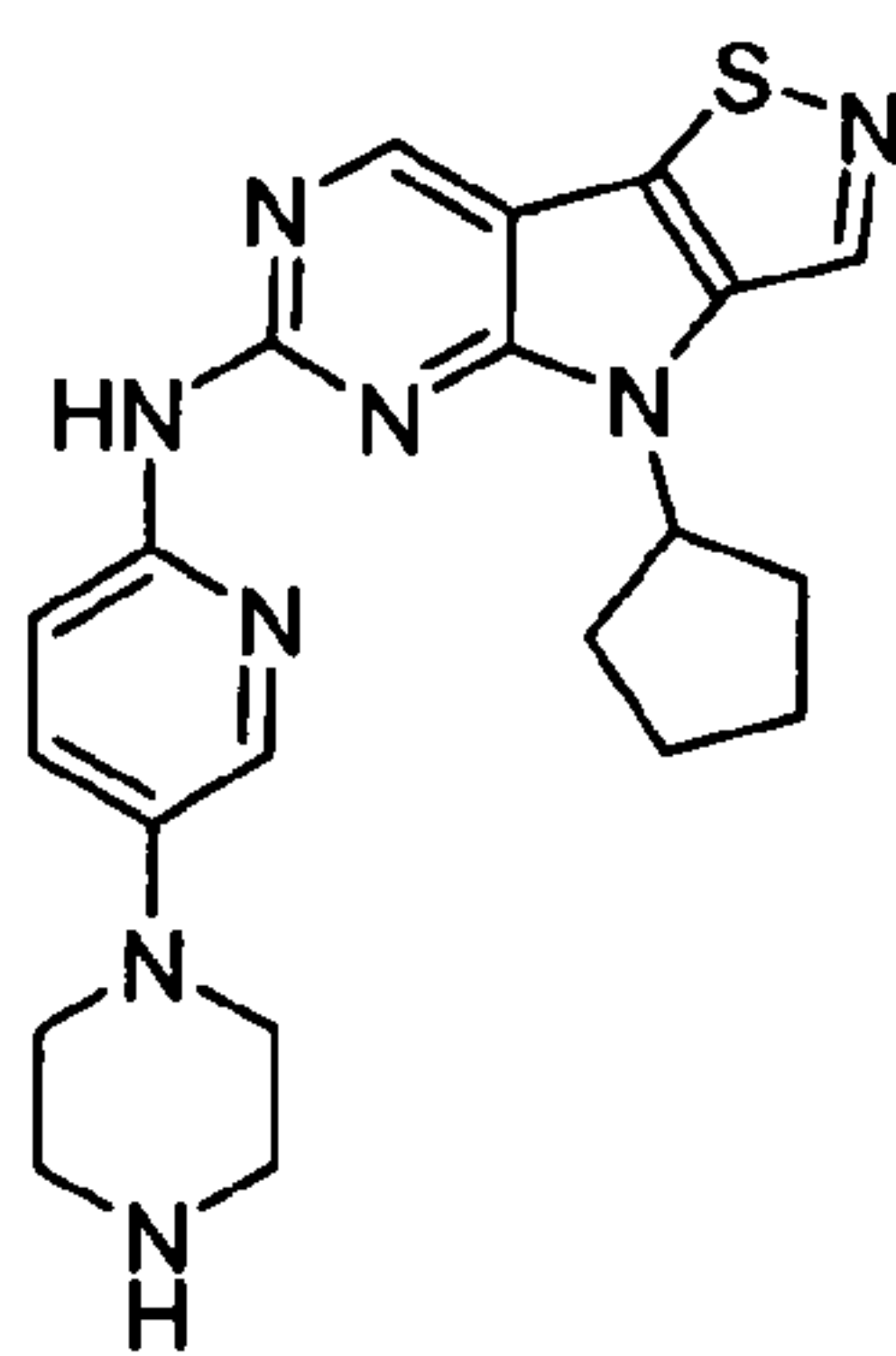
**1-(6-Chloropyridin-3-yl)-3-(trifluoromethyl)piperazine (220):** Compound **220** was prepared using methods described in example 1 using compound **219**.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (s, 1 H) 7.09 - 7.18 (m, 2 H) 3.52 - 3.60 (m, 1 H) 3.34 - 3.48 (m, 2 H) 3.09 - 3.22 (m,  $J$ = 11.98 Hz, 1 H) 2.91 - 3.01 (m, 1 H) 2.75 - 2.88 (m, 2 H) 1.84 (s, 1 H) ppm.





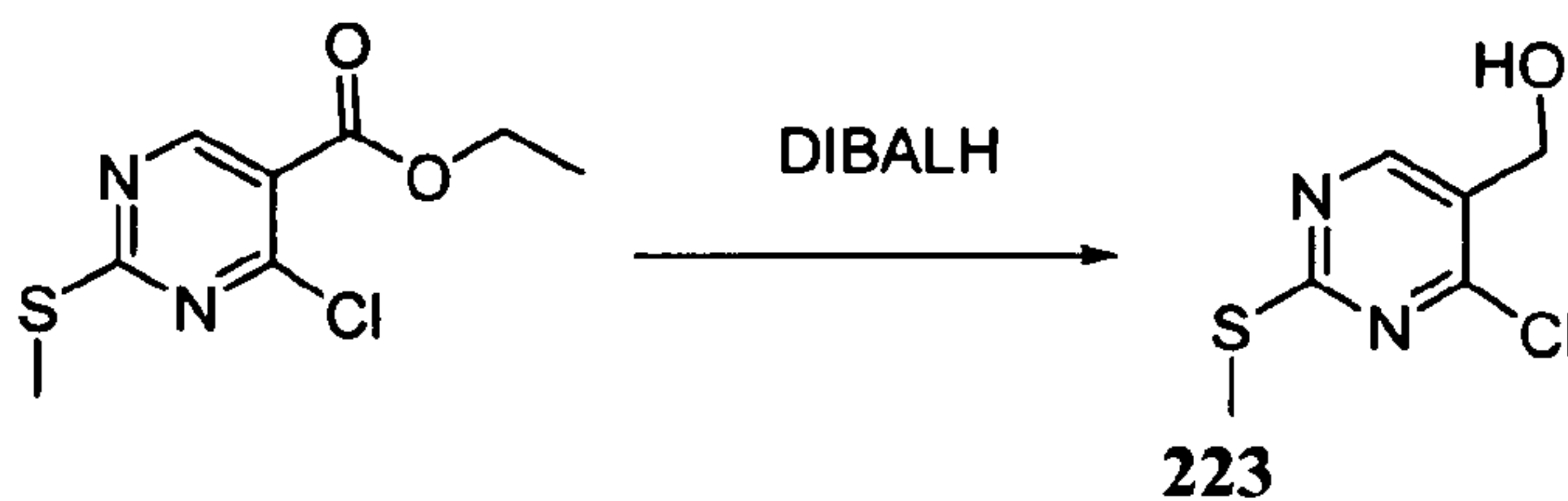
**4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-(trifluoromethyl)piperazine (218):** Compound **218** was prepared from compounds **4** and **220** using methods described in example 1.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.84 (s, 1 H) 9.28 (s, 1 H) 9.00 (s, 1 H) 8.44 (d,  $J = 4.89$  Hz, 1 H) 8.21 (d,  $J = 9.05$  Hz, 1 H) 8.08 (d,  $J = 2.93$  Hz, 1 H) 8.04 (d,  $J = 5.14$  Hz, 1 H) 7.54 (dd,  $J = 9.05, 2.93$  Hz, 1 H) 5.29 - 5.47 (m, 1 H) 3.62 (d,  $J = 11.25$  Hz, 1 H) 3.49 - 3.59 (m, 1 H) 3.46 (d,  $J = 11.49$  Hz, 1 H) 2.98 - 3.10 (m,  $J = 9.78$  Hz, 1 H) 2.79 - 2.95 (m, 2 H) 2.65 - 2.79 (m, 2 H) 2.29 - 2.45 (m, 2 H) 1.95 - 2.18 (m, 4 H) 1.77 (d,  $J = 5.38$  Hz, 2 H) ppm.

#### EXAMPLE 168



**221**

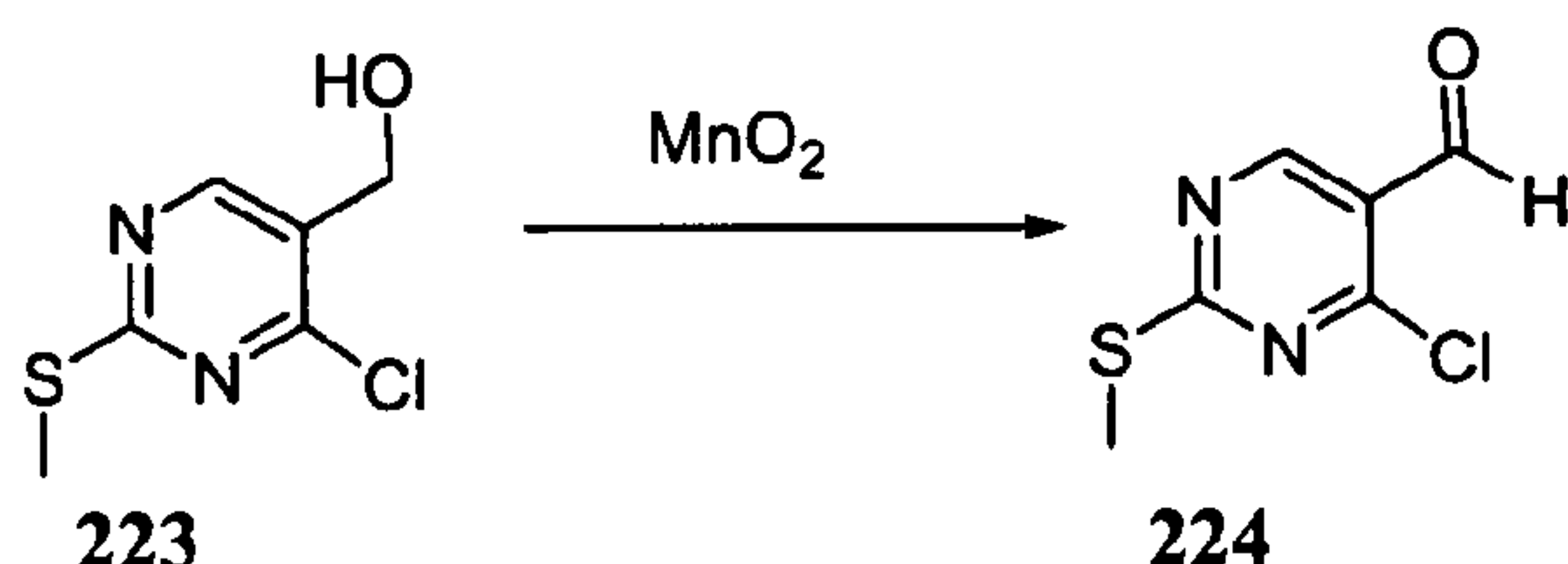
**4-Cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-4H-isothiazolo[5',4':4,5]pyrrolo[2,3-d]pyrimidin-6-amine**



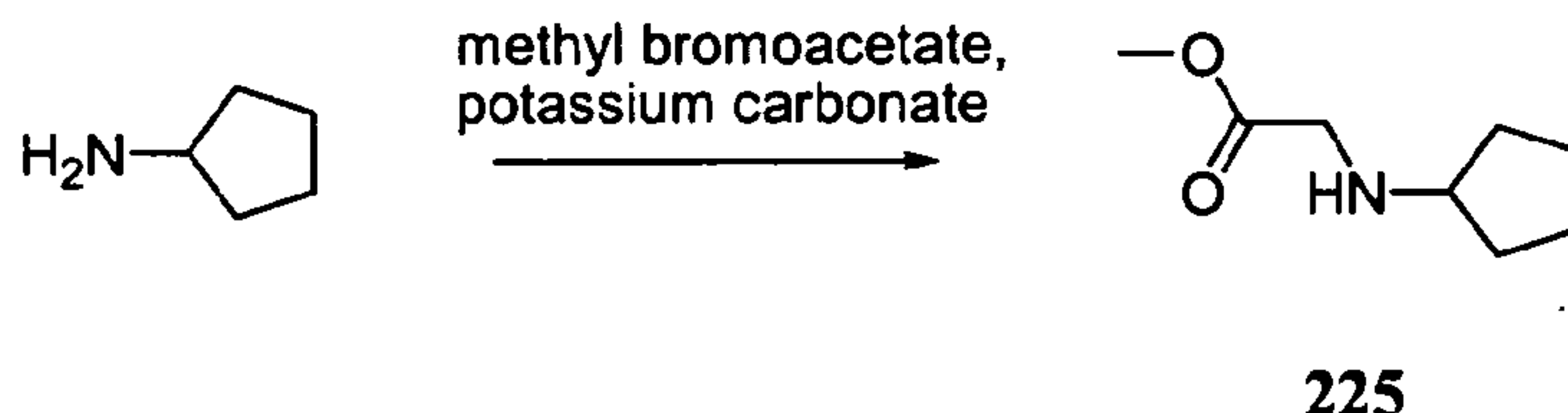
**(4-Chloro-2-(methylthio)pyrimidin-5-yl)methanol (223):** To ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (20.0 g, 86 mmol) in dichloromethane (400 mL) at -78



°C was added diisobutylaluminum hydride, 1.0 M in toluene (172 mL, 172 mmol). The reaction was allowed to warm to 0 °C over 2 h. To the reaction was added a 20% Rochelle's (1600 mL) and diethyl ether (750 mL). The emulsion was stirred for 30 min. The organics were sequestered and the aqueous was extracted further with diethyl ether (2 x 500 mL). The combined organics were washed with water (500 mL), brine (500 mL), dried over MgSO<sub>4</sub>, and concentrated in vacuo and filtered through a plug of silica eluting with 1:1; ethyl acetate:CH<sub>2</sub>Cl<sub>2</sub> to obtain compound **223** (9.6 g, 59% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.55 (s, 1 H) 4.75 (d, J=5.87 Hz, 2 H) 2.58 (s, 3 H) 2.06 - 2.25 (m, J=5.14 Hz, 1 H) ppm.

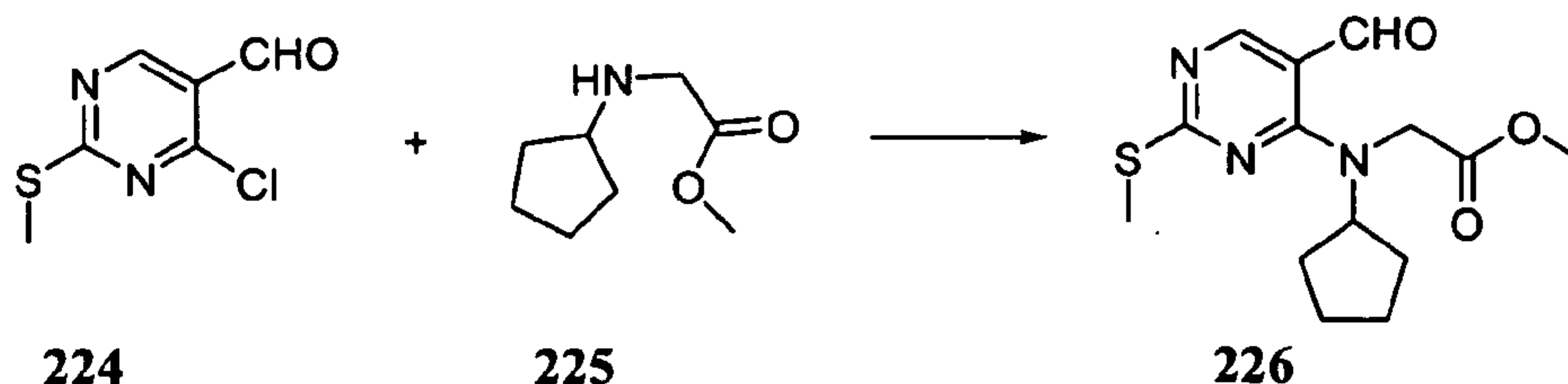


**4-chloro-2-(methylthio)pyrimidine-5-carbaldehyde (224):** Manganese(IV) oxide, <5 micron, activated (38.1 g, 439 mmol) was added to a solution of compound **223** (16.73 g, 87.8 mmol) in chloroform (800 mL). The reaction was stirred overnight, filtered through Celite, and the filtrate was concentrated in vacuo to yield compound **224** (13.7 g, 82.8% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.31 (s, 1 H) 8.88 (s, 1 H) 2.65 (s, 2 H) ppm.



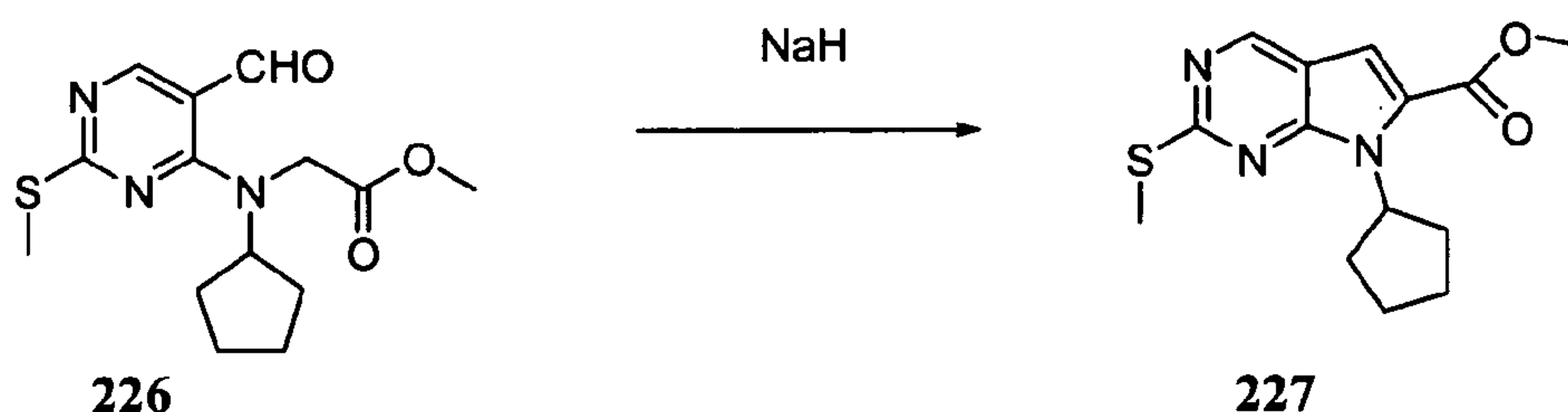
**Methyl 2-(cyclopentylamino)acetate (225):** A solution of methyl bromoacetate (17.4 mL, 188 mmol) in THF (40 mL) was dropwise added to a solution of cyclopentylamine (18.6 mL, 188 mmol) and triethylamine (26.1 mL, 188 mmol) in THF (150 mL) at 0 °C. Following addition, the reaction was allowed to reach room temperature and was stirred overnight. The triethylammonium salts were filtered and rinsed with scant THF. The combined filtrates were concentrated *in vacuo*. The desired product was distilled from the residuals under reduced pressure to yield 20.2 g of compound **225** (68% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ ppm 3.73 (s, 3 H) 3.41 (s, 2 H) 3.00 - 3.13 (m, J=12.90, 6.39, 6.39 Hz, 1 H) 1.77 - 1.87 (m, 2 H) 1.67 - 1.74 (m, 2 H) 1.48 - 1.59 (m, 2 H) 1.29 - 1.41 (m, 2 H) ppm.





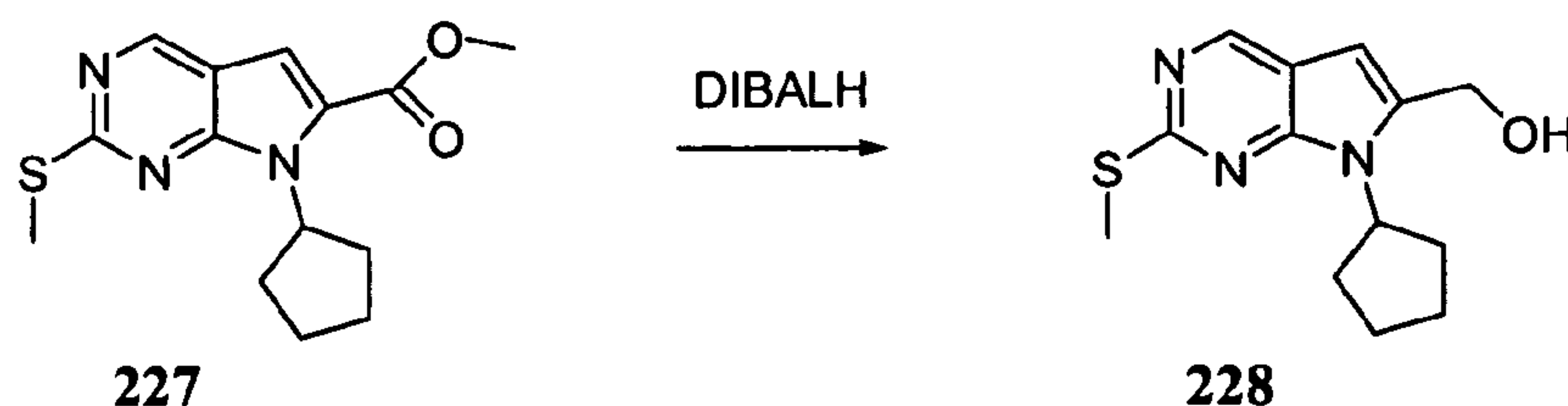
**Methyl 2-(cyclopentyl(5-formyl-2-(methylthio)pyrimidin-4-yl)amino)acetate (226):**

Triethylamine (10.9 mL, 78.2 mmol) was added to a solution of compound **224** (12.3 g, 65.2 mmol) and compound **225** (12.8 g, 81.5 mmol) in THF (200 mL). The reaction was stirred at room temperature. After 6 h, the reaction contents were poured into saturated sodium bicarbonate and extracted with ethyl acetate. The combined organics were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The crude material was crystallized from ethyl acetate and hexanes to afford methyl 2-(cyclopentyl(5-formyl-2-(methylthio)pyrimidin-4-yl)amino)acetate (**226**) (17.55 g, 87.0% yield).



**Methyl 7-cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate (227):**

Sodium hydride (3.85 g, 167 mmol) (freshly washed with hexane) was added to a solution of compound **226** (12.95 g, 41.9 mmol) in benzene (150 mL). The reaction was stirred at 70 °C. After 1 h, the reaction contents were poured into water (300 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organics were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. Silica gel chromatography (gradient elution 0 to 50% ethyl acetate in hexanes) afforded compound **227** (4.24 g, 34.8% yield).

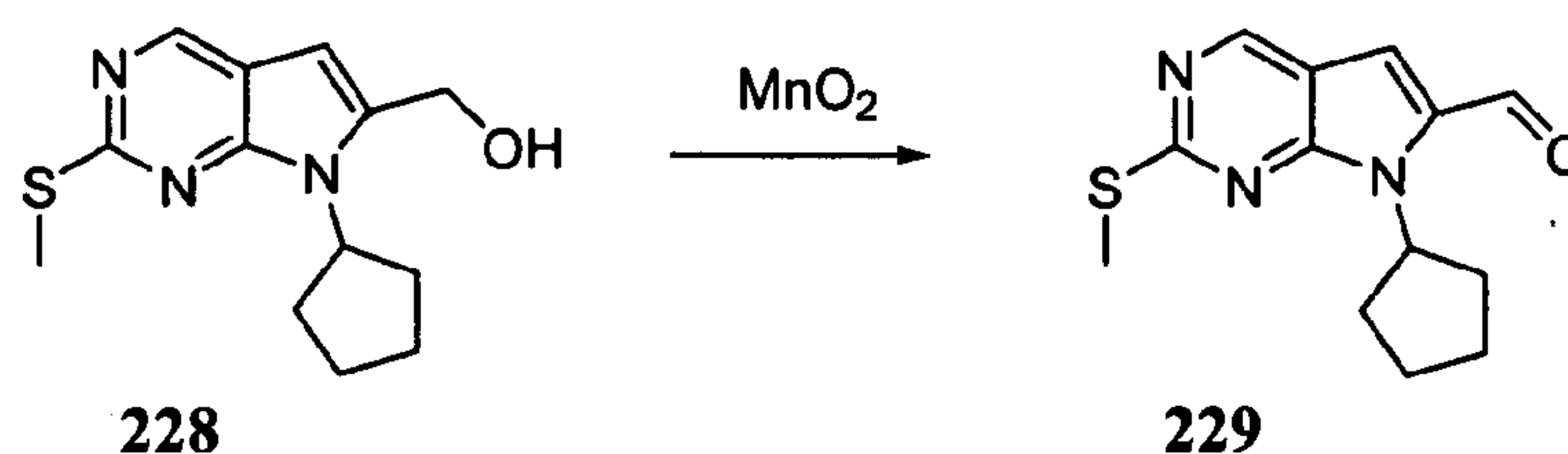


**(7-Cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)methanol (228):**

DIBAL-H (1.0 M in toluene) (33.8 mL, 33.8 mmol) was added dropwise to a solution of compound **227** (4.93 g, 16.9 mmol) in dichloromethane (85 mL) at -78 °C. The reaction was stirred for

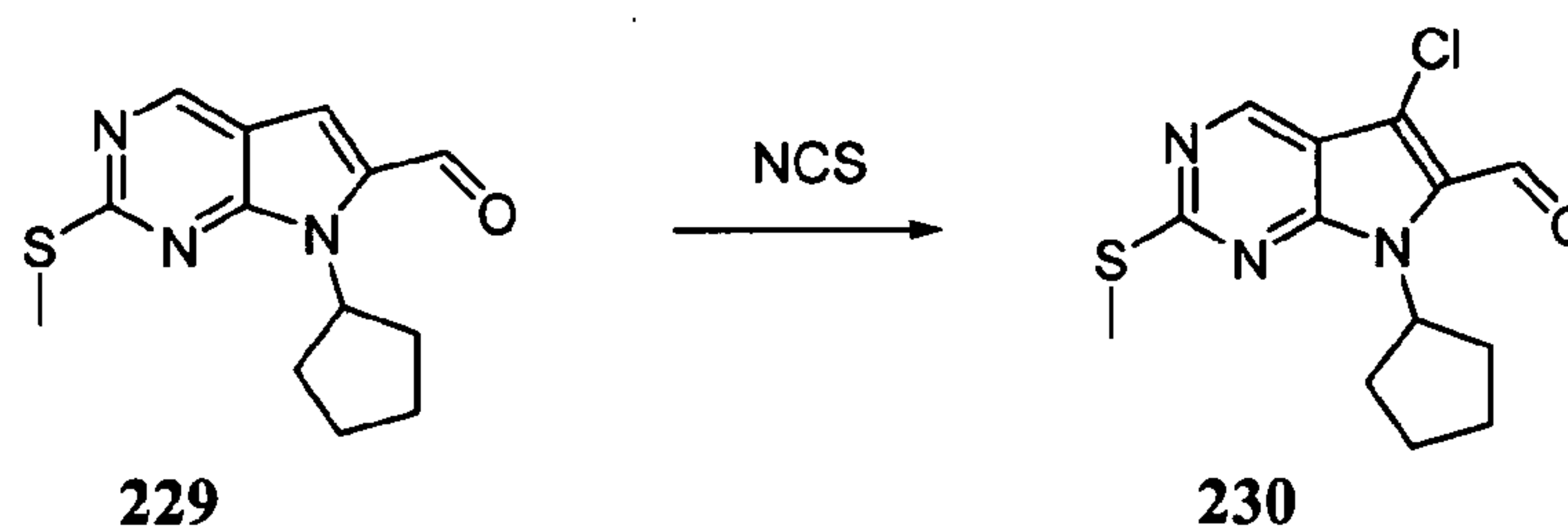


20 minutes, then warmed to 0 °C and quenched with 400 mL of 0.5 M Rochelle's salt saturated with NaCl. The mixture was stirred for 3 h then extracted with ethyl acetate (4 x 250 mL). The combined organics were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to provide 4.36 g of crude. The crude material was taken up in dichloromethane and methanol, plated onto silica gel, and flashed through a plug of silica using 30% ethyl acetate in hexanes, then switching to 10% methanol in DCM to provide compound **228** (3.37 g, 75.6% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.60 (s, 1 H) 6.29 (s, 1 H) 4.83 - 4.95 (m, J= 17.30, 8.59, 8.59 Hz, 1 H) 4.79 (d, J= 5.87 Hz, 2 H) 2.62 (s, 3 H) 2.47 - 2.58 (m, 2 H) 1.97 - 2.15 (m, 5 H) 1.67 - 1.81 (m, 2 H) ppm.



**7-Cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carbaldehyde (229):**

Manganese dioxide (5.56 g, 64.0 mmol) was added to a solution of compound **228** (3.37 g, 12.8 mmol) in dichloromethane (250 mL). After 16 h, the reaction contents were filtered through Celite and organics were removed *in vacuo* to provide compound **229** (3.10 g, 92.7% yield).

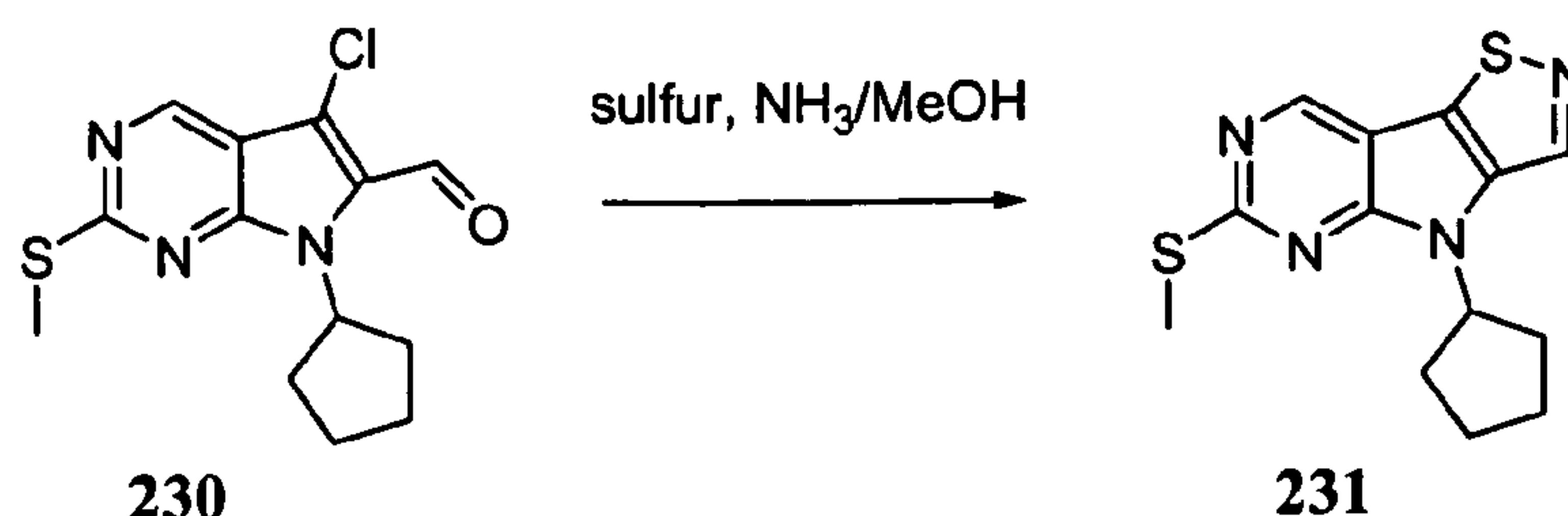


**5-Chloro-7-cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carbaldehyde (230):**

Compound **229** (3.10 g, 11.9 mmol) and *N*-chlorosuccinimide (1.74 g, 13.0 mmol) were dissolved in DMF (30 mL) and stirred at 100 °C. After 1 h, the temperature of the reaction was reduced to 65°C and 0.35 eq of NCS were added. After 30 min, the reaction contents were poured into water (10 x) and saturated bicarbonate was added (300 mL). The aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organics were dried with sodium sulfate and concentrated *in vacuo*. Silica gel chromatography (gradient elution 0 to 7% ethyl acetate in hexanes) afforded 5-chloro-7-cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carbaldehyde (**230**) (1.37 g, 39% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ ppm

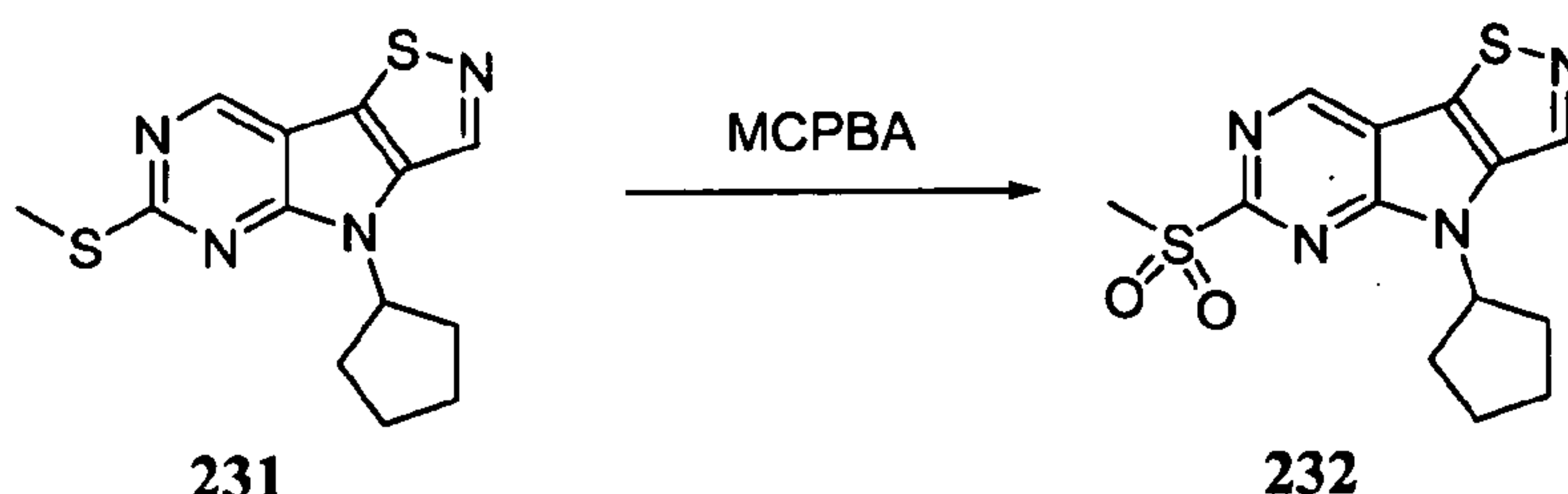


10.17 (s, 1 H) 8.91 (s, 1 H) 5.73 - 5.96 (m, 1 H) 2.63 (s, 3 H) 2.29 - 2.47 (m, 2 H) 1.97 - 2.16 (m, 4 H) 1.63 - 1.83 (m, 2 H) ppm.



**4-Cyclopentyl-6-(methylsulfanyl)-4H-isothiazolo[5',4':4,5]pyrrolo[2,3-d]pyrimidine (231):**

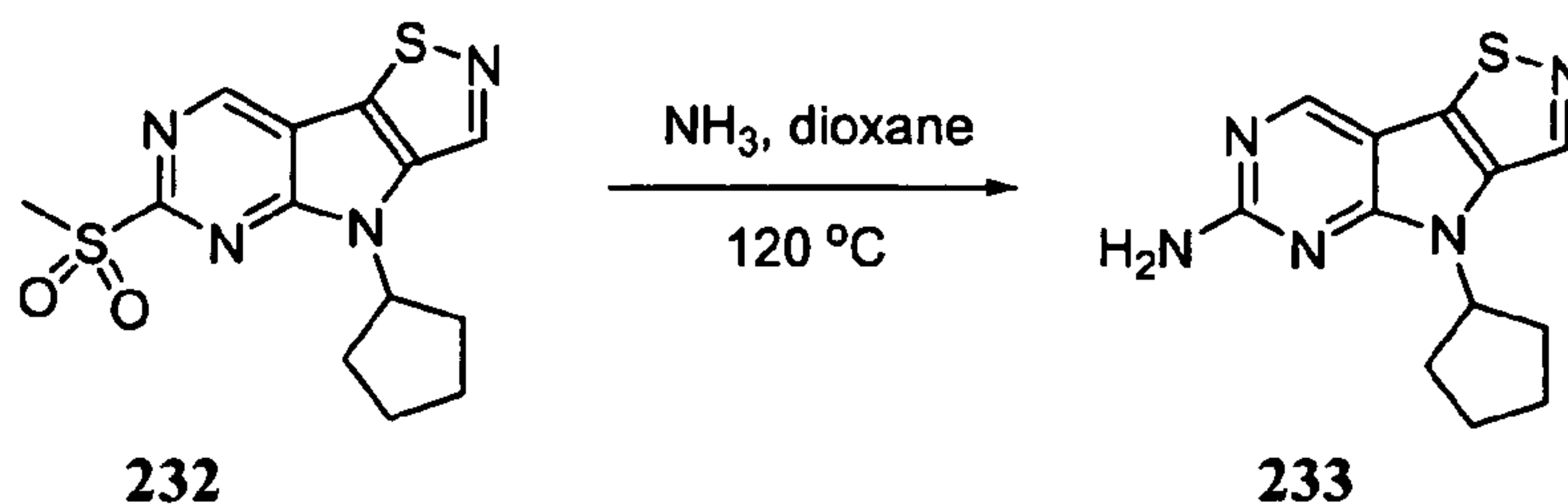
To sulfur (0.238 g, 0.926 mmol) and 5-chloro-7-cyclopentyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-6-carbaldehyde (1.37 g, 4.63 mmol) was added saturated methanolic ammonia (15 mL). The reaction was sealed and stirred at 80 °C overnight. The reaction was cooled to 0 °C and an aliquot was removed and partitioned between dichloromethane and saturated sodium bicarbonate. The organics were removed *in vacuo* and partitioned between dichloromethane (100 mL) and saturated sodium bicarbonate (200 mL). The aqueous was extracted further with dichloromethane (100 mL). The combined organics were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Silica gel chromatography (gradient elution 0 to 25% ethyl acetate in hexanes) afforded compound **231** (1.30 g, 96.6% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.97 (s, 1 H) 8.62 (s, 1 H) 5.36 - 5.52 (m, 1 H) 2.69 (s, 3 H) 2.21 - 2.34 (m, 2 H) 1.97 - 2.18 (m, 4 H) 1.78 - 1.93 (m, 2 H) ppm.



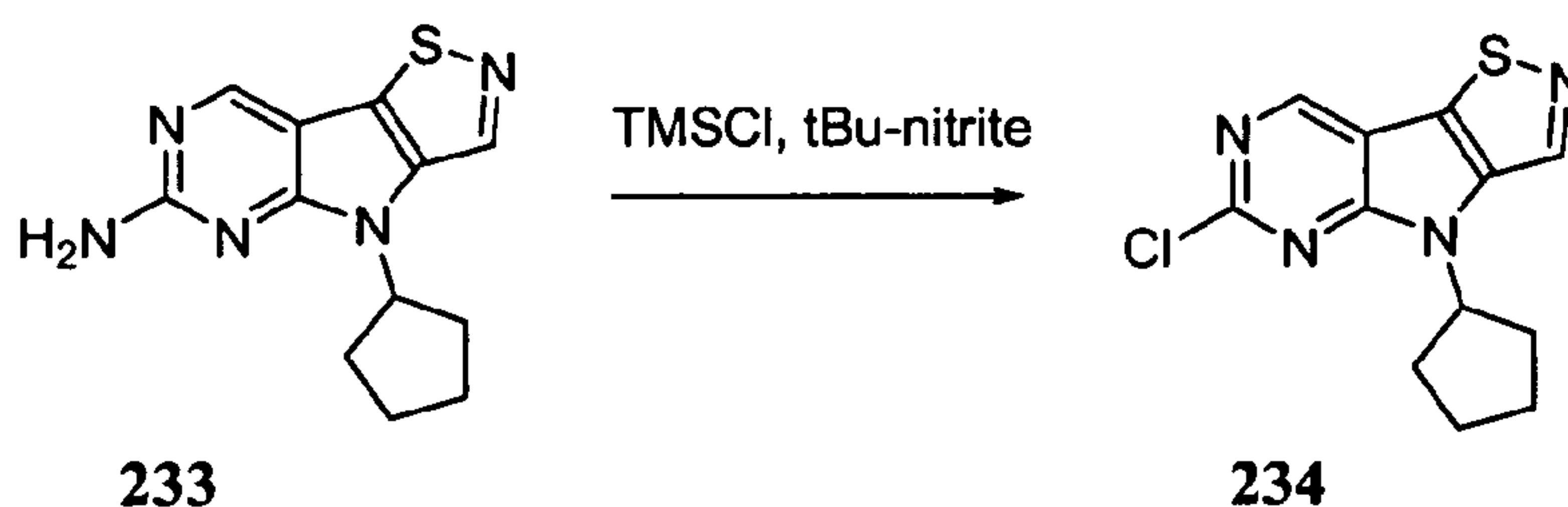
**4-Cyclopentyl-6-(methylsulfonyl)-4H-isothiazolo[5',4':4,5]pyrrolo[2,3-d]pyrimidine (232):**

To reactant **231** (1.30 g, 4.48 mmol) in dichloromethane (25 mL) at 0 °C was added MCPBA (50%) (3.42 g, 9.85 mmol). The reaction was allowed to stir overnight while warming to room temperature. The reaction contents were poured into saturated sodium bicarbonate (150 mL) and extracted with dichloromethane (3 x 75 mL). Silica gel chromatography (gradient elution 20 to 60% ethyl acetate in hexanes) afforded compound **232** (1.30 g, 90.1% yield).

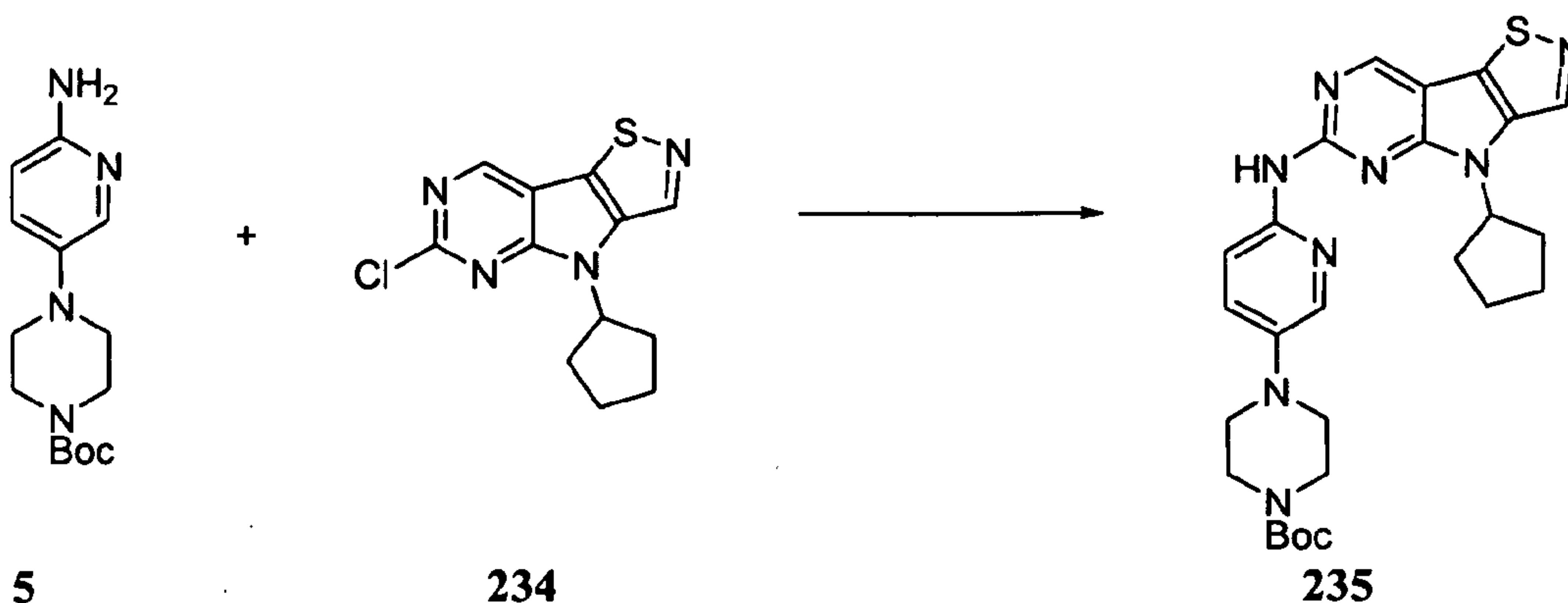




**4-cyclopentyl-pyrimidino[4',5':2,3]4H-pyrrolo[2,3-d]isothiazole-6-amine (233):** In a glass bomb, a solution of compound **232** (1.30 g, 4.06 mmol) in dioxane (35 mL) was saturated with ammonia gas.. The bomb was sealed and the reaction was stirred at 120 °C. After 16 h, LCMS indicated complete consumption of starting material. Solvent was removed *in vacuo*. Silica gel chromatography (gradient elution 20 to 50% THF in hexanes) afforded 430 mg of compound **233** (41% yield).

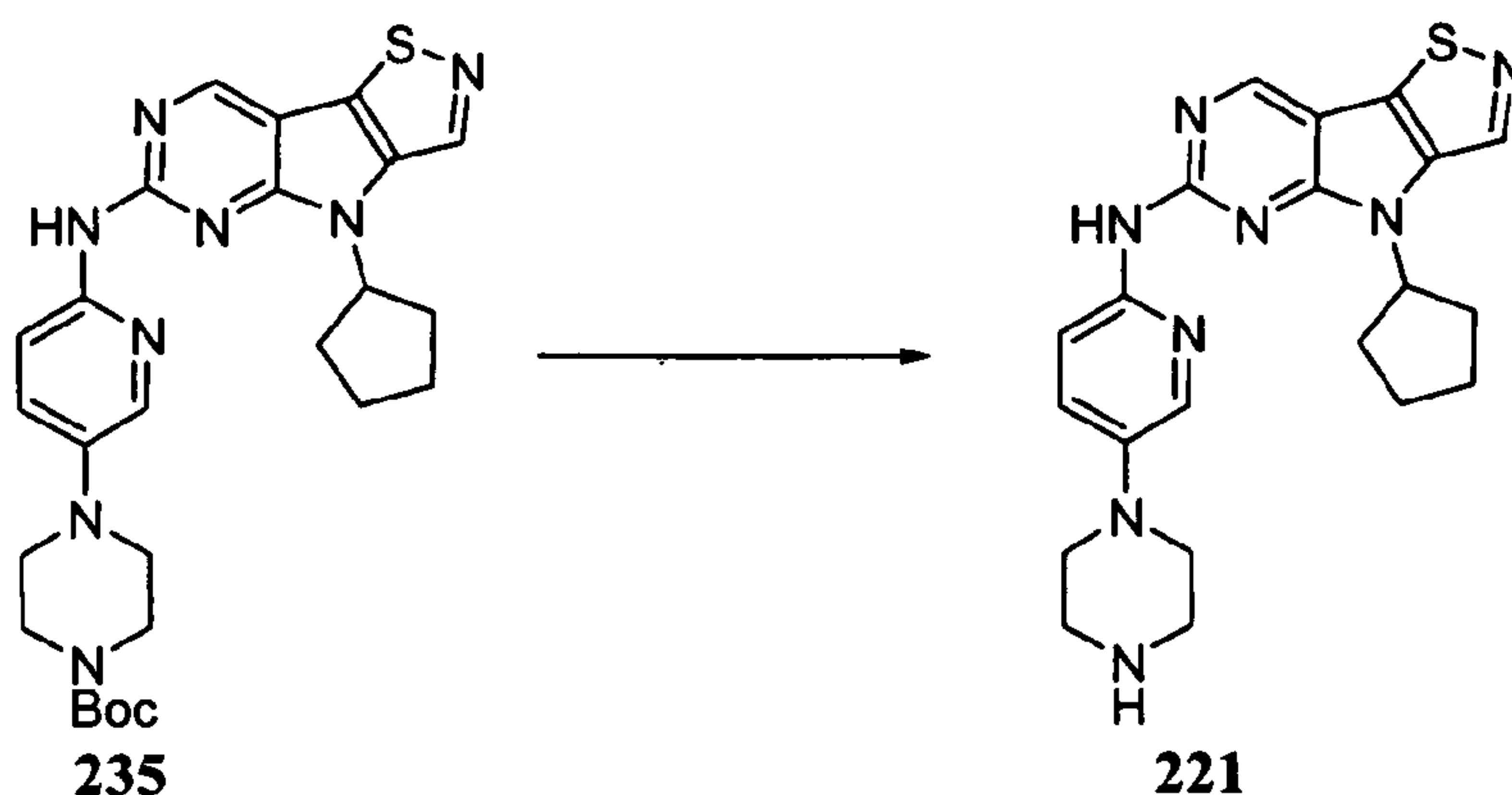


**6-Chloro-4-cyclopentyl-pyrimidino[4',5':2,3]4H-pyrrolo[2,3-d]isothiazole (234):** To a solution of compound **233** (0.100 g, 0.39 mmol) in dichloromethane (10 mL) at 0 °C was added dropwise trimethylsilyl chloride (0.15 mL, 1.2 mmol) followed by addition of *tert*-butyl nitrite (0.2 g, 1.9 mmol). The reaction was stirred at room temperature for 5 days. The reaction contents were poured into saturated sodium bicarbonate (20 mL). The aqueous layer was extracted with dichloromethane (1 x 20 mL). Silica gel chromatography (gradient elution 0 to 30% THF in hexanes) afforded compound **234** (0.025 g, 23% yield) which was carried on without further characterization.



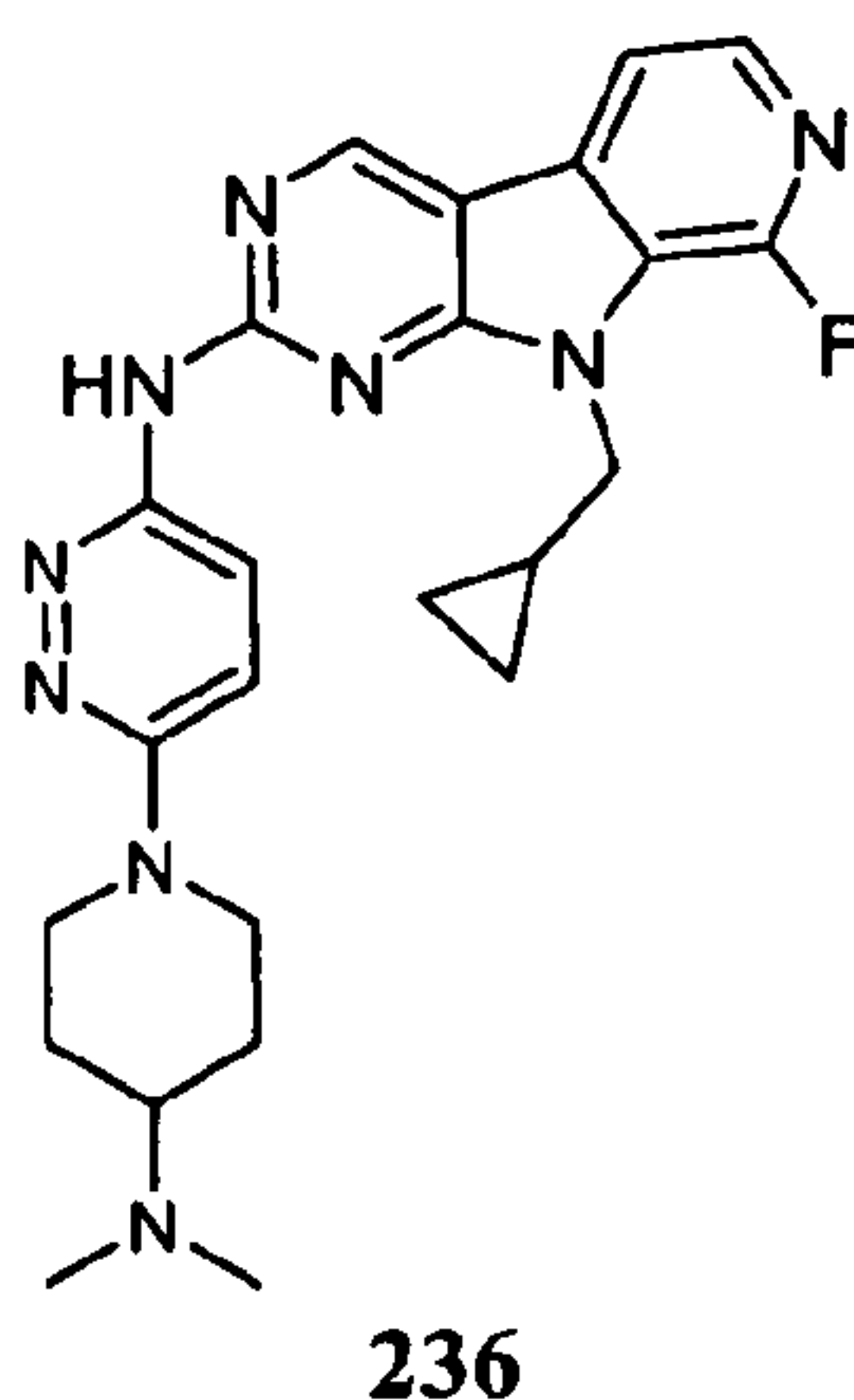


**1,1-Dimethylethyl 4-(6-((4-cyclopentyl-4H-isothiazolo[5',4':4,5]pyrrolo[2,3-d]pyrimidin-6-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (235):** In a screw cap vial were combined compound **5** (0.075 g, 0.27 mmol), compound **234** (0.025 g, 0.090 mmol) and DMSO (0.200 mL). The reaction was sealed and stirred at 100 °C over 4 d. DMSO was removed under high vacuum. Silica gel chromatography (gradient elution 0 to 10% methanol in DCM) afforded 15 mg of compound **235** (32% yield).



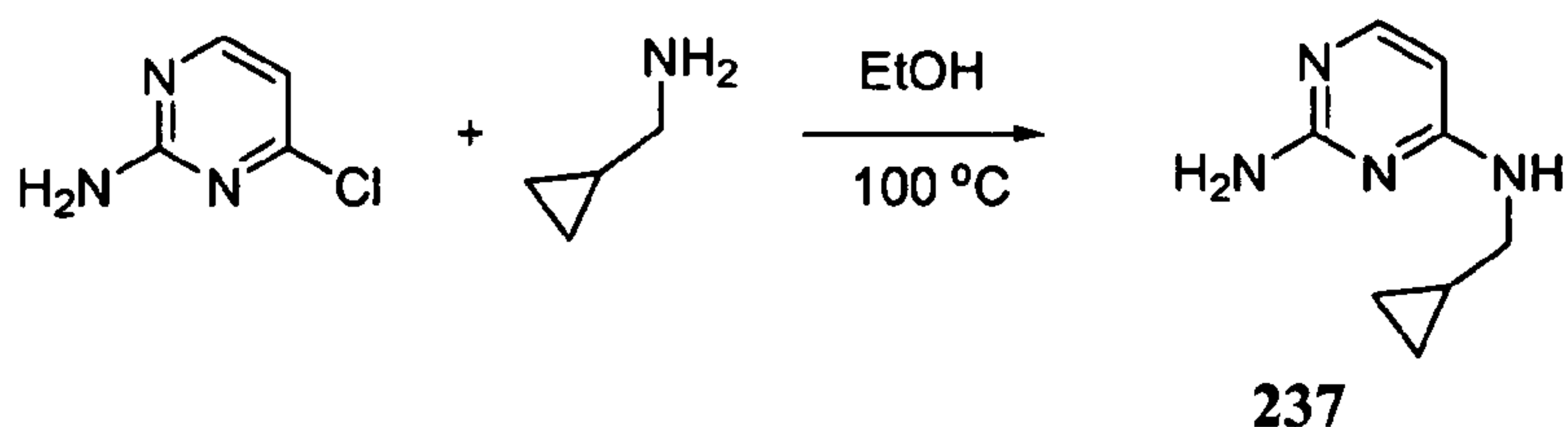
**4-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-pyrimidino[4',5':2,3]4H-pyrrolo[2,3-d]isothiazole-6-amine (221):** Compound **221** was prepared using methods described in Example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 9.57 (s, 1 H) 9.00 (s, 1 H) 8.13 (d, J= 2.45 Hz, 1 H) 8.06 (dd, J= 9.78, 2.69 Hz, 1 H) 7.24 (d, J= 9.54 Hz, 1 H) 5.53 (quin, J= 8.44 Hz, 1 H) 3.38 - 3.48 (m, 8 H) 2.21 - 2.40 (m, 4 H) 2.06 - 2.18 (m, 2 H) 1.83 - 1.95 (m, 2 H) ppm. LCMS-ESI (POS), M/Z, M+1: Found 421.0, Calculated 421.2.

#### EXAMPLE 169

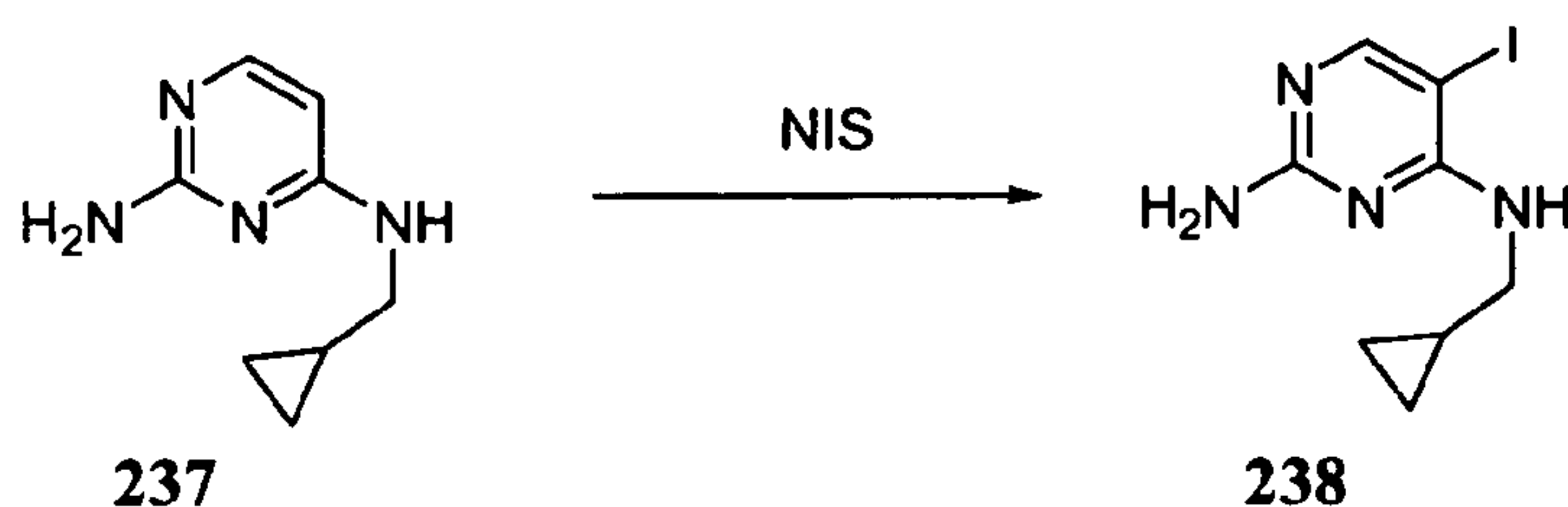


**236**  
**9-Cyclopentyl-8-fluoro-N-(6-(4-dimethylaminopiperidine-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine**

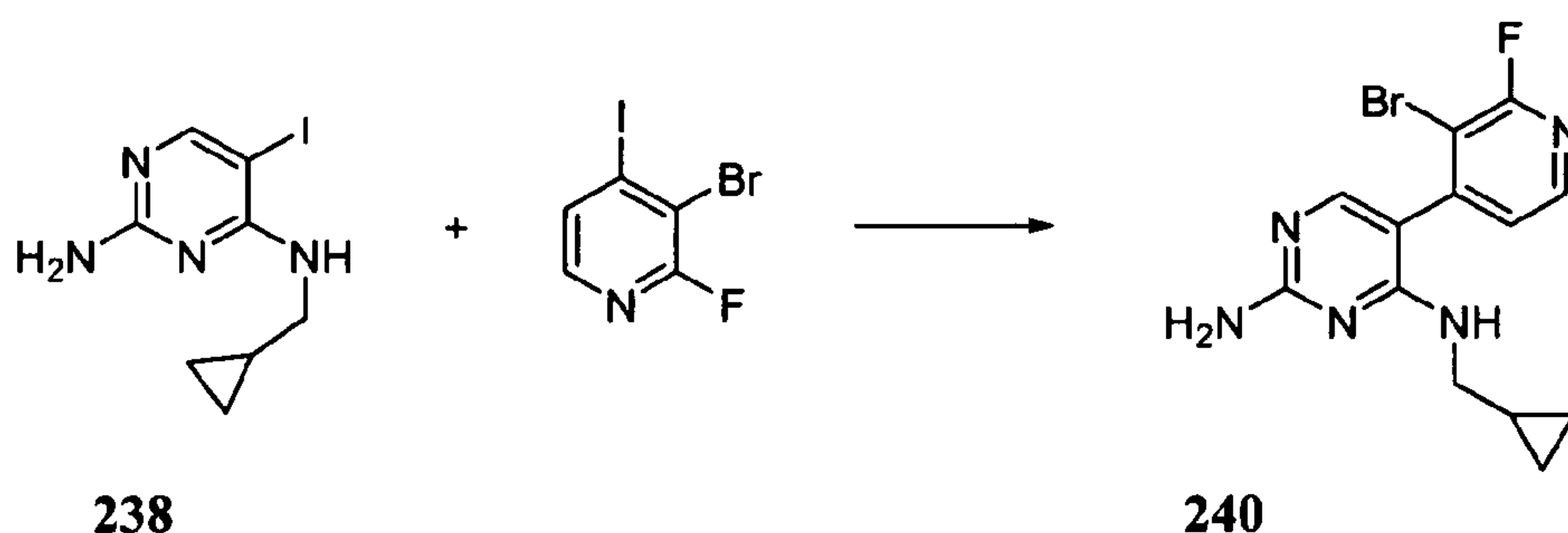




**N4-(cyclopropylmethyl)pyrimidine-2,4-diamine (237):** To cyclopropylmethanamine (3.62 g, 50.9 mmol) in ethanol (90 mL) was added solid 4-chloropyrimidin-2-amine (6.00 g, 46.3 mmol). The reaction was stirred at reflux (100 °C oil bath) for 16 h. The reaction was cooled to room temperature and solvent was removed *in vacuo*. The product **237** obtained in quantitative yield. LCMS-ESI (POS), M/Z, M+1: Found 165.0, Calculated 165.1.



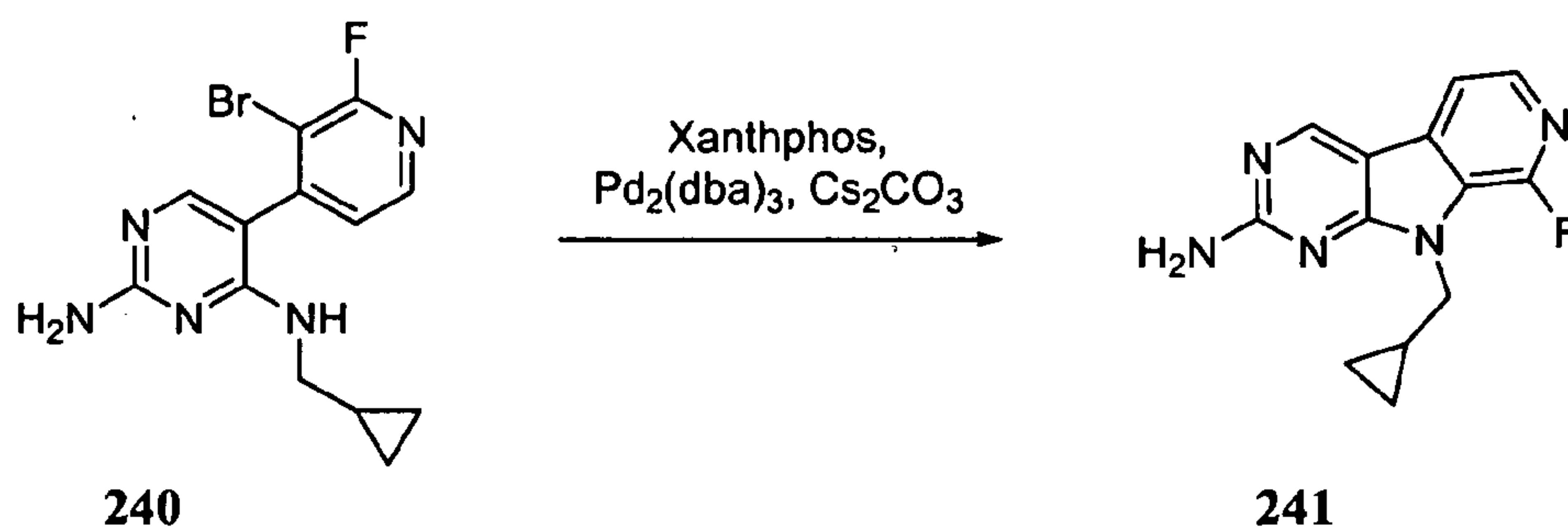
**N4-(Cyclopropylmethyl)-5-iodopyrimidine-2,4-diamine (238):** N-iodosuccinimide (11.5 g, 50.9 mmol) was added to a solution of compound **237** (7.60 g, 46.3 mmol) in AcOH (90 mL). The reaction was warmed to 80 °C and stirred for 1.5 h. Solvent was removed *in vacuo*. The residue was taken up in dichloromethane (200 mL) and water. The aqueous layer was brought to pH 12 with 5 N NaOH and organics were sequestered. The aqueous was extracted further with dichloromethane (2 x 100 mL). The combined organics were treated with solid sodium thiosulfate, dried with MgSO<sub>4</sub> and concentrated *in vacuo*. Silica gel chromatography (gradient elution 10 to 75% ethyl acetate in hexanes) afforded compound **238** (8.0 g, 60% yield).



**5-(3-Bromo-2-fluoropyridin-4-yl)-N4-(cyclopropylmethyl)pyrimidine-2,4-diamine (240):** Isopropylmagnesium chloride, 2 M solution in THF (0.814 mL, 1.63 mmol) was added dropwise over 15 minutes to a degassed solution of 3-bromo-2-fluoro-4-iodopyridine (0.468 g, 1.55 mmol) in Et<sub>2</sub>O (0.150 mL) and THF (0.850) cooled at -78 °C. The solution was stirred for 0.5 h. Zinc chloride, 1.0 M solution in diethyl ether (0.776 mL, 0.776 mmol) was then

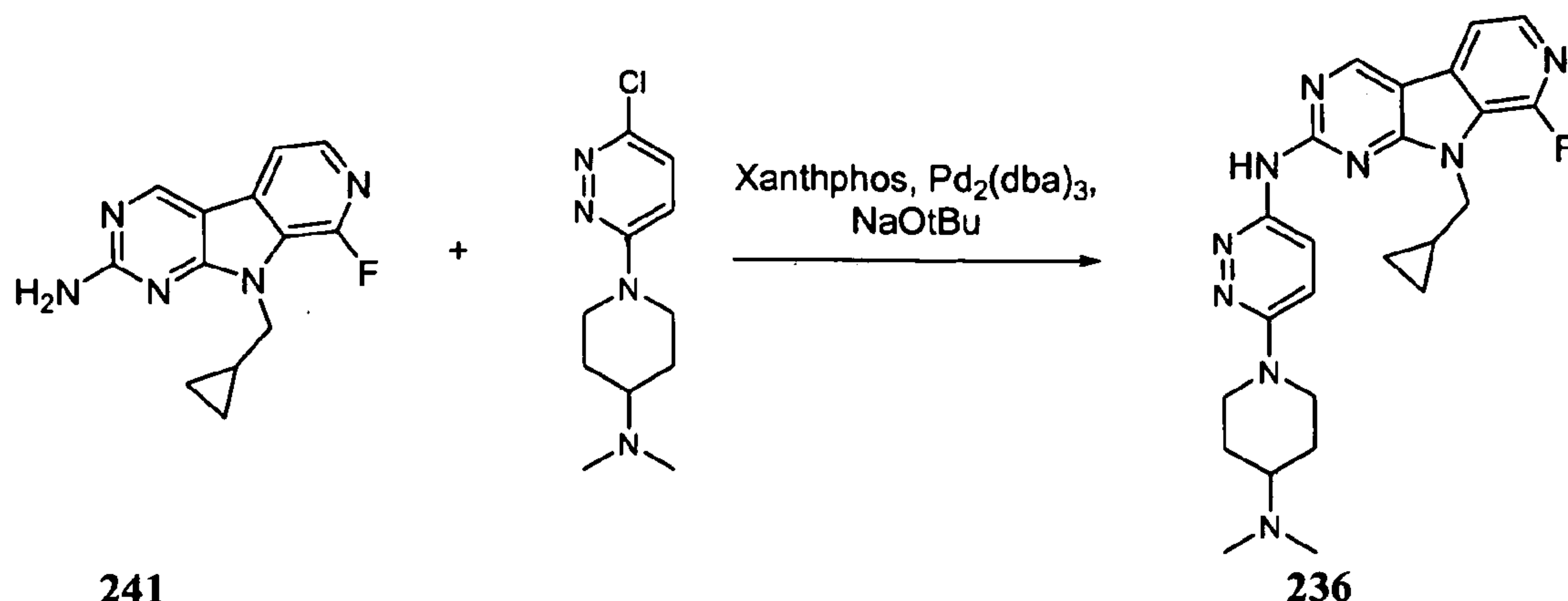


added dropwise to the reaction over 10 minutes. The reaction was allowed to reach room temperature. The reaction warmed to room temperature within 15 min. A solution of compound **238** (0.150 g, 0.517 mmol) and tetrakis(triphenylphosphine)palladium (0.0418 g, 0.0362 mmol) in THF (0.50 mL) was added to the reaction. The reaction was equipped with a reflux condenser and stirred in a 60 °C oil bath. After 2 h the reaction was removed from heat and allowed to stand overnight. Saturated  $\text{NH}_4\text{Cl}$  (0.5 mL) and 12% 2-propanol in  $\text{CH}_2\text{Cl}_2$  (2 mL) were added. The organics were sequestered and the aqueous was extracted with 12% 2-propanol in  $\text{CH}_2\text{Cl}_2$  (4 x 4 mL). The combined organics were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. Silica gel chromatography (elution 3% methanol in DCM with 0.175 %  $\text{NH}_4\text{OH}$  additive) afforded compound **240** (0.140 g, 80.1% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 0.22 (d,  $J=4.40$  Hz, 2 H) 0.46 - 0.59 (m, 2 H) 0.96 - 1.07 (m, 1 H) 3.21 - 3.36 (m, 2 H) 4.51 (br. s., 1 H) 5.11 (br. s., 2 H) 7.16 (d,  $J=4.89$  Hz, 1 H) 7.69 (s, 1 H) 8.22 (d,  $J=4.89$  Hz, 1 H) ppm.



**9-(Cyclopropylmethyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (241):** To a vacuum to argon purged vial containing 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.017 g, 0.030 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.014 g, 0.015 mmol), cesium carbonate (0.19 g, 0.59 mmol) and compound **240** (0.100 g, 0.30 mmol) was added degassed dioxane (2.00 mL). The reaction was stirred at 100 °C. After 4 h, the reaction was cooled and applied directly to silica. Silica gel chromatography (gradient elution 40 to 90% ethyl acetate in hexanes) afforded compound **241** (0.060 g, 79% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 0.45 - 0.57 (m, 4 H) 1.34 - 1.47 (m, 1 H) 4.32 (d,  $J=7.09$  Hz, 2 H) 5.46 (br. s., 2 H) 7.68 (dd,  $J=5.26, 2.81$  Hz, 1 H) 8.02 (dd,  $J=5.13, 1.71$  Hz, 1 H) 8.93 (s, 1 H).

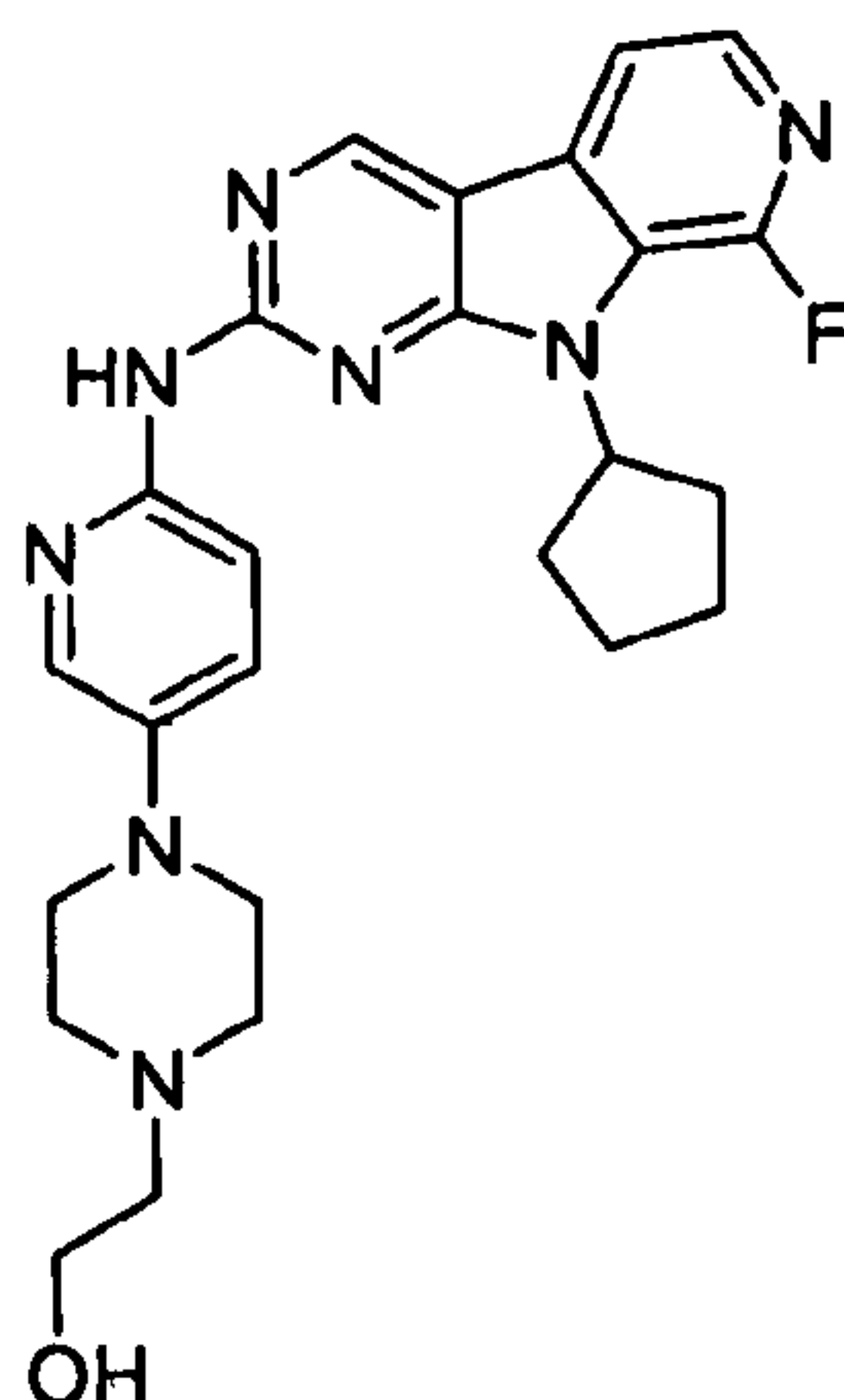




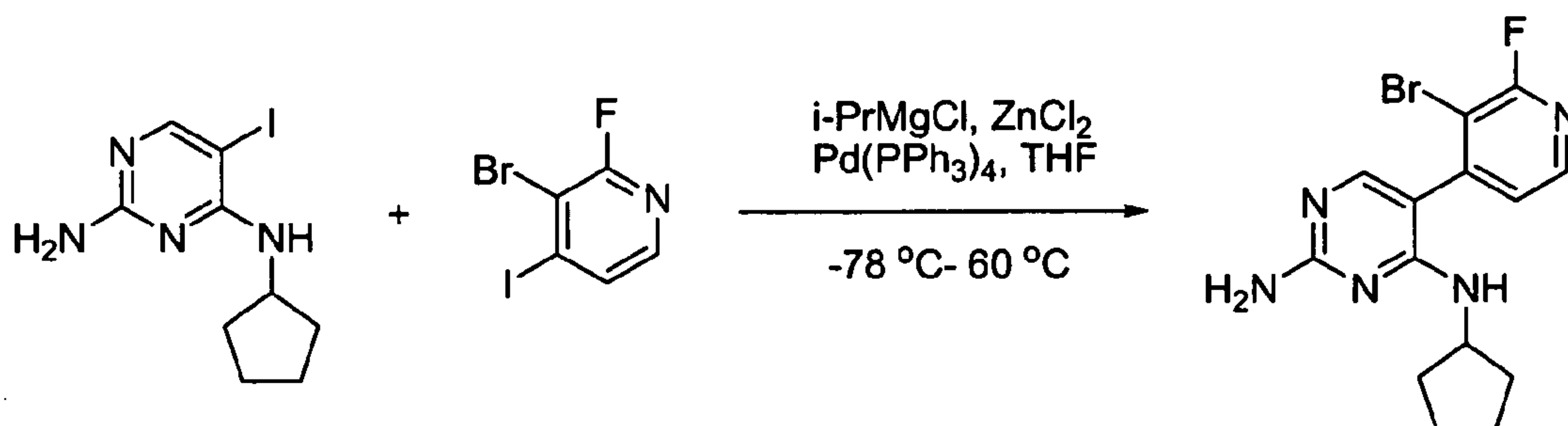
**9-Cyclopentyl-8-fluoro-N-(6-(4-dimethylaminopiperidine-1-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3d]pyrimidin-2-amine (236):** To

tris(dibenzylideneacetone)dipalladium (0) (0.015 g, 0.016 mmol), Xantphos (0.019 g, 0.032 mmol), NaOtBu (0.025 g, 0.26 mmol), 1-(6-chloropyridazin-3-yl)-N,N-dimethylpiperidin-4-amine (0.051 g, 0.21 mmol), and compound **241** (0.0550 g, 0.21 mmol) was added degassed dioxane (1.0 mL). The reaction vessel was sealed and stirred at 105 °C. After 13 h, the reaction contents were poured into saturated sodium bicarbonate (5 mL). The aqueous layer was extracted with 10% methanol in dichloromethane (3 x 10 mL). The combined organics were dried with sodium sulfate and concentrated *in vacuo*. Silica gel chromatography (0.175% NH<sub>4</sub>OH 3% methanol in DCM to 100% 1% NH<sub>4</sub>OH, 7% methanol, CH<sub>2</sub>Cl<sub>2</sub>) yielded compound **236** (0.038 g, 39% yield). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 0.41 - 0.55 (m, 4 H) 1.29 - 1.50 (m, 3 H) 1.85 (d, J=11.98 Hz, 2 H) 2.20 (s, 6 H) 2.34 (tt, J=10.85, 3.58 Hz, 1 H) 2.90 (t, J=11.62 Hz, 2 H) 4.25 - 4.37 (m, 4 H) 7.44 (d, J=10.03 Hz, 1 H) 7.98 - 8.09 (m, 2 H) 8.24 (d, J=9.78 Hz, 1 H) 9.34 (s, 1 H) 10.35 (s, 1 H) ppm. LCMS-ESI (POS), M/Z, M+1: Found 462.0, Calculated 462.2.



**EXAMPLE 170****242**

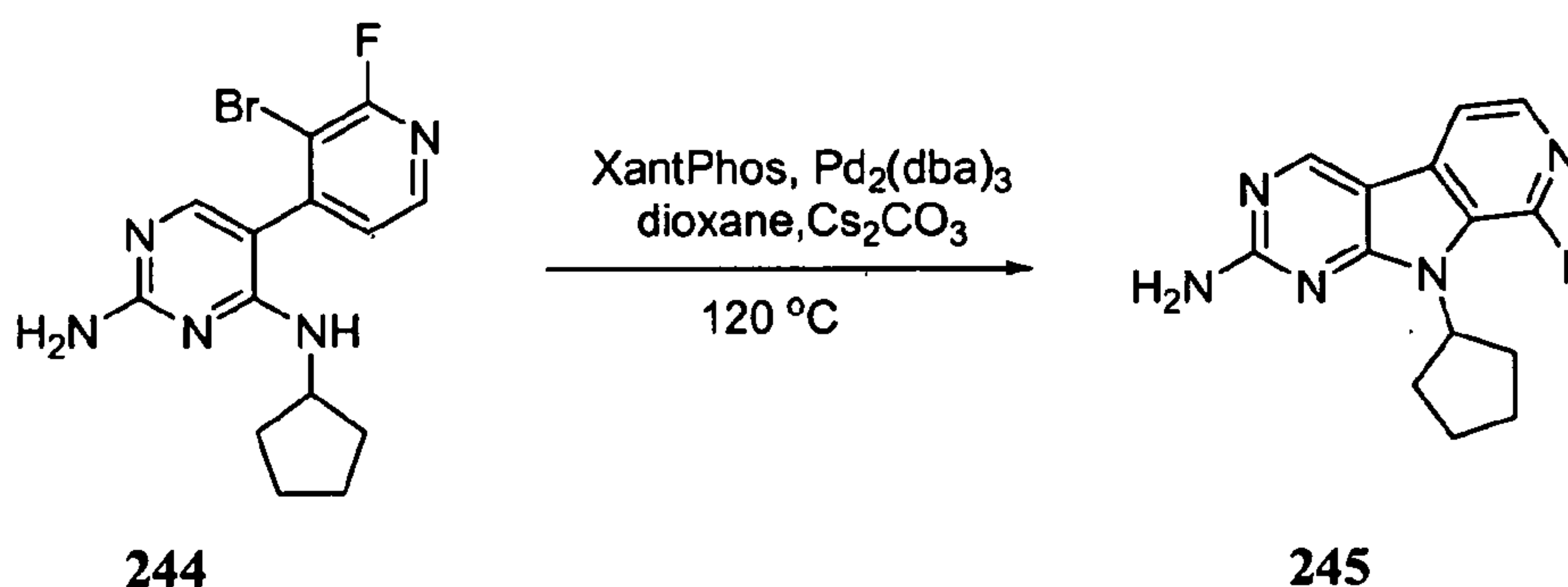
**2-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol**

**243****244**

**5-(3-Bromo-2-fluoro-4-pyridinyl)-N4-cyclopentyl-2,4-pyrimidinediamine (244):** In a dry 3 neck 2 L flask equipped with a dry addition funnel, thermometer and stir bar was added 3-bromo-2-fluoro-4-iodopyridine (83.4 g, 276 mmol) followed by 300 mL of anhydrous THF under an atmosphere of nitrogen. The solution was cooled to -70°C in 2-propanol/dry ice bath. A solution of isopropylmagnesium chloride 2.0 M in diethyl ether (145 mL, 290 mmol) was added drop wise over a period of 30 minutes. The solution was then stirred for 30 minutes before zinc (II) chloride 0.5 M in THF (276 mL, 138 mmol) was cannulated in. The solution was warmed to room temperature and stirred for 1 hour. The addition funnel was replaced with a reflux condenser and N4-cyclopentyl-5-iodopyrimidine-2,4-diamine (**243**, see example 200) (28.00 g, 92.1 mmol) was added, followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (5.32 g, 4.60 mmol). The solution was heated over night at a gentle reflux. After concentrating the solution to 1/10th of the volume under vacuum, it was cooled in an ice bath. To this was added 100 mL of cold saturated NH<sub>4</sub>Cl, followed by 500 mL of water. 500mL of 12% isopropanol/DCM was then added and the solution was stirred at room temperature for 1 hour before being filtered through

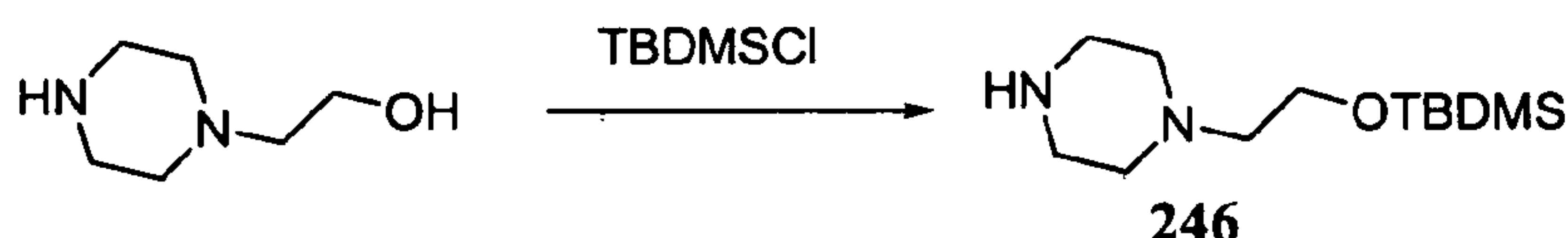


filter paper. The filter cake was washed in succession with water, DCM and 12% 2-propanol /DCM. The filtrate was partitioned in a separation funnel and the aqueous layer was washed with 12% 2-propanol /DCM. The organics were dried over MgSO<sub>4</sub> and then concentrated under vacuum. The residue obtained was partially dissolved in DCM with sonication and filtered off to give compound **244** (26.45g, 81.6%) as a light yellow solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.18 (1 H, d, J= 4.9 Hz), 7.52 (1 H, s), 7.26 (1 H, dd, J= 4.9, 0.7 Hz), 6.34 (2 H, s), 6.12 (1 H, d, J= 7.6 Hz), 4.42 (1 H, sxt, J= 7.4 Hz), 1.76 - 1.96 (2 H, m), 1.55 - 1.68 (2 H, m), 1.31 - 1.53 (4 H, m) ) ppm; LCMS-ESI (POS), M/Z, M+1: Found 352.0.



**9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine(245):**

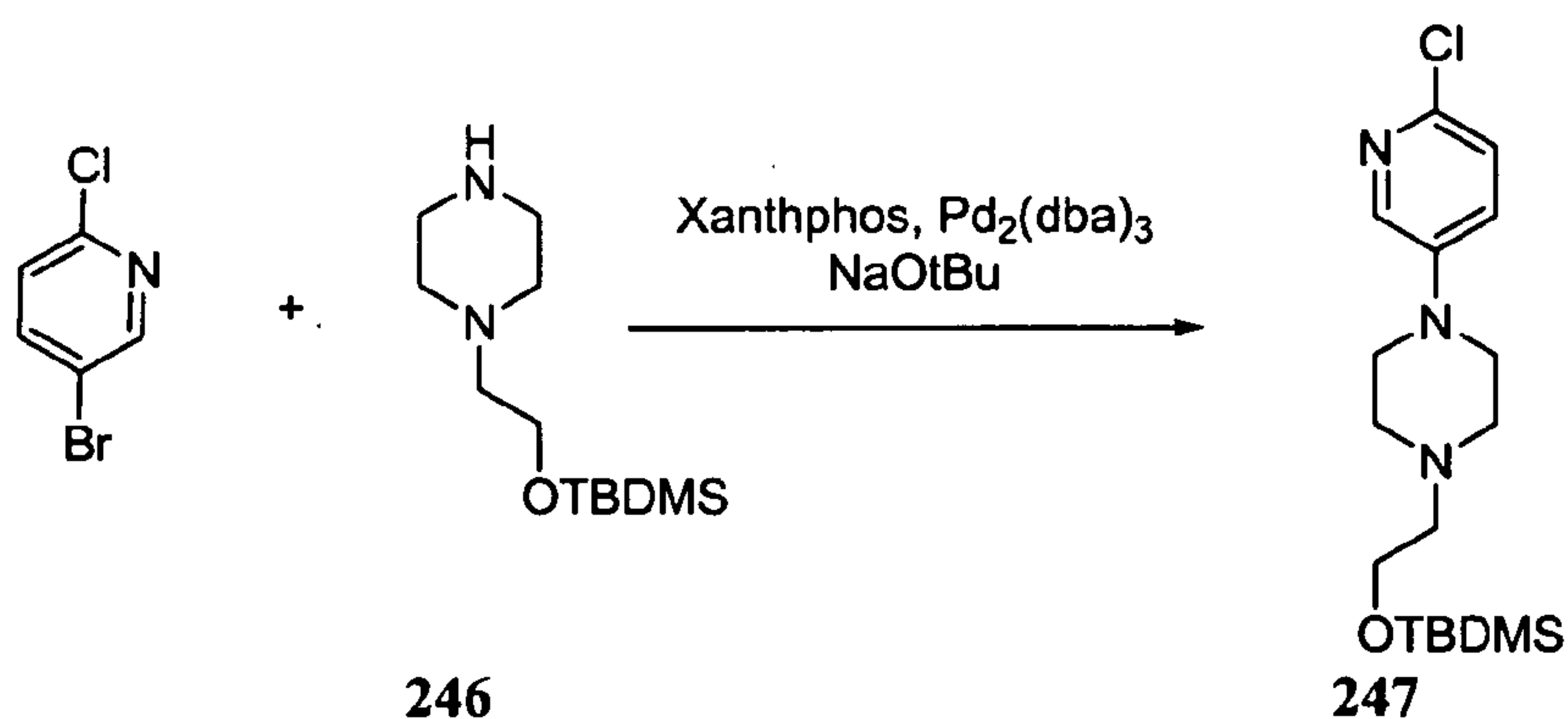
Compound **244** (0.143 g, 0.41 mmol), and cesium carbonate (0.40 g, 1.2 mmol) were combined in 5mL of anhydrous 1,4-dioxane. Nitrogen was bubbled through the solution briefly before adding Pd<sub>2</sub>(dba)<sub>3</sub> (0.037 g, 0.041 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.047 g, 0.081 mmol). The solution was heated at 120 °C with microwave irradiation for 1 hour. The solution was purified on CombiFlash column (dry loaded) eluting with a gradient of 2%methanol/0.1% NH<sub>4</sub>OH(~28% in water)/DCM to 7%methanol/0.35%NH<sub>4</sub>OH(~28% in water)/DCM. The fractions containing the pure product were combined and concentrated under vacuum to give compound **245** (94mg, 85%) as a light brownish solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.10 (1 H, s), 7.94 (1 H, dd, J= 5.2, 1.5 Hz), 7.91 (1 H, dd, J= 5.1, 2.9 Hz), 7.10 (2 H, br. s.), 5.38 - 5.49 (1 H, m), 2.10 - 2.23 (2 H, m), 1.93 - 2.08 (4 H, m), 1.64 - 1.79 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 272.0.



**1-(2-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)ethyl)piperazine (246):** To 1-(2-hydroxyethyl)-piperazine (3.36 g, 25.8 mmol) in dichloromethane (25 mL) was added *tert*-butyldimethylsilylchloride (3.89 g, 25.8 mmol). The reaction mixture was stirred at room

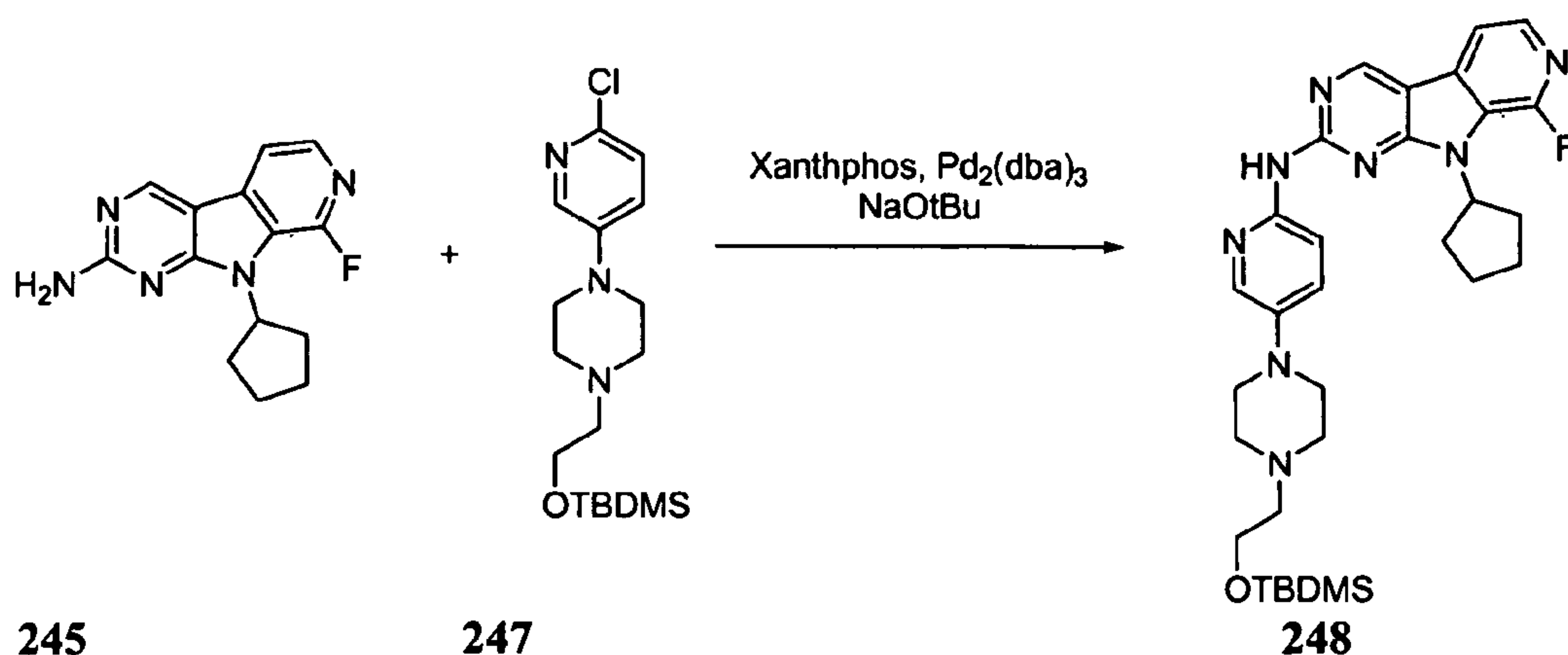


temperature. The reaction mixture was stirred overnight, then diluted 1 x with  $\text{CH}_2\text{Cl}_2$  and extracted against 0.5 N NaOH (100 mL). The aqueous was extracted further with 10 % methanol in  $\text{CH}_2\text{Cl}_2$  (3 x 100 mL). The combined organics were dried with  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. Silica gel chromatography (gradient elution 0 to 100% B (7% methanol in DCM + 1%  $\text{NH}_4\text{OH}$  additive) against A (3% methanol in DCM + 0.175%  $\text{NH}_4\text{OH}$  additive)) afforded compound **246** (4.71 g, 74.7% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.06 (s, 6 H) 0.90 (s, 9 H) 2.36 - 2.59 (m, 6 H) 2.89 (t,  $J$  = 4.77 Hz, 4 H) 3.76 (t,  $J$  = 6.48 Hz, 2 H) ppm.

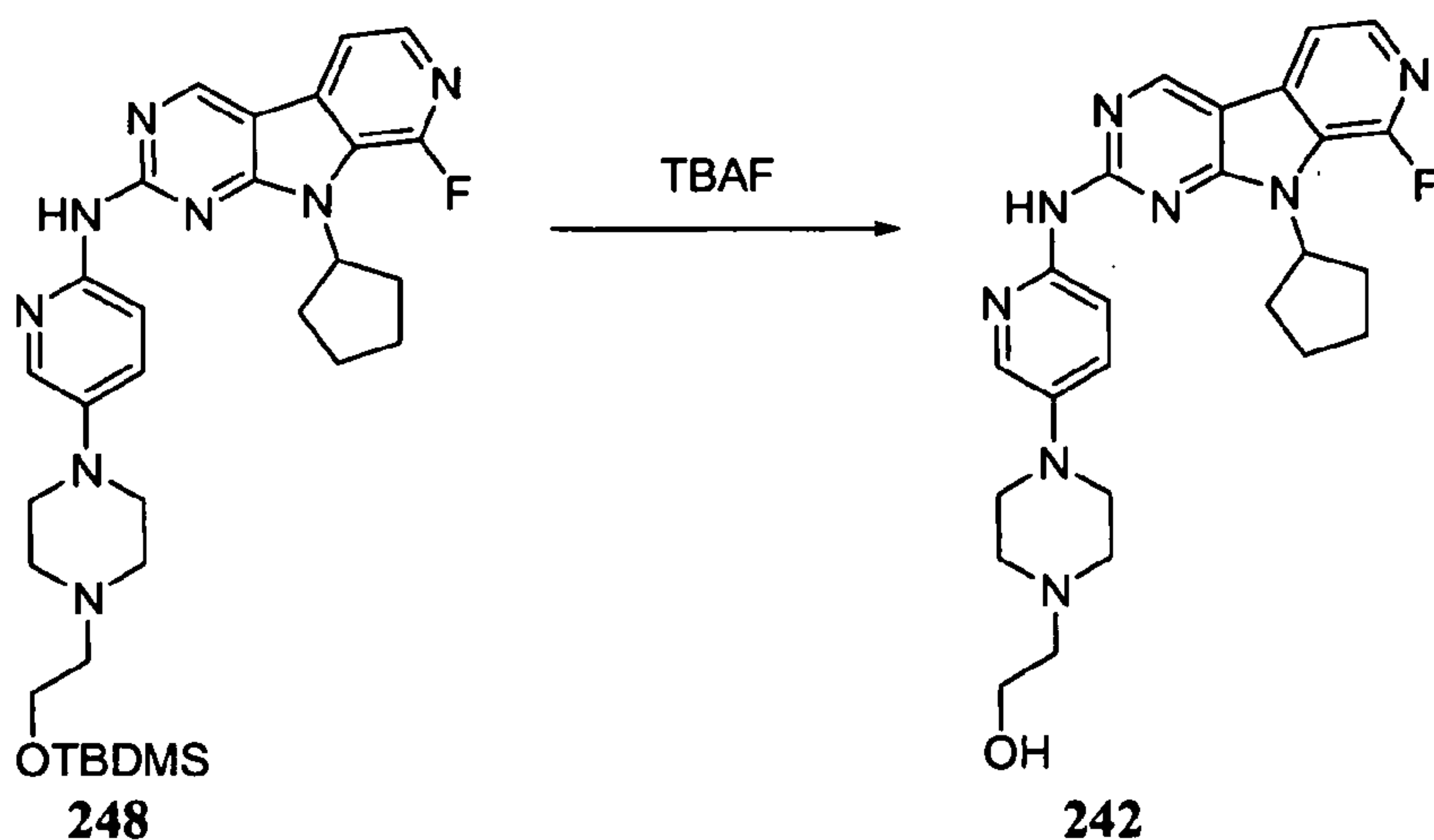


**1-(6-chloro-3-pyridinyl)-4-(2-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)ethyl)-piperazine (247):** 5-Bromo-2-chloropyridine (3.15 g, 16.4 mmol), compound **246** (4.00 g, 16.4 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.749 g, 0.818 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.947 g, 1.64 mmol) and sodium *tert*-butoxide (1.82 g, 19.0 mmol) were combined in a screw cap vial and solvated under argon atmosphere with degassed toluene (44 mL). The reaction was briefly sparged with argon, then sealed and stirred at 100 °C. After 3 h, the reaction contents were poured into saturated sodium bicarbonate (100 mL) and extracted with 10% methanol in dichloromethane (3 x 200 mL). The combined organics were dried with sodium sulfate and concentrated in vacuo. Silica gel chromatography (gradient elution 0 to 100% ethyl acetate in hexanes switching to 3% methanol in DCM) afforded compound **247** (5.40 g, 92.7% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.08 (s, 6 H) 0.91 (s, 9 H) 2.60 (t, J= 5.87 Hz, 2 H) 2.70 (br. s., 4 H) 3.20 (d, J= 4.40 Hz, 4 H) 3.80 (t, J= 6.11 Hz, 2 H) 7.17 (d, J= 1.71 Hz, 2 H) 8.02 (s, 1 H) ppm.





**9-Cyclopentyl-N-(5-(4-(2-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)ethyl)-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (248):** To tris(dibenzylideneacetone)dipalladium (0) (0.0289 g, 0.0316 mmol), xantphos (0.0366 g, 0.0632 mmol), NaOtBu (0.0486 g, 0.506 mmol), compound **247** (0.150 g, 0.421 mmol), and compound **245** (0.114 g, 0.421 mmol) was added degassed dioxane (2.0 mL). The reaction vessel was sealed and stirred at 105 °C overnight. The reaction was loaded directly to silica. Silica gel chromatography (gradient elution 1.5 to 5% 2 M methanolic NH<sub>3</sub> in DCM) afforded compound **248** (0.120 g, 48.2% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.09 (s, 6 H) 0.83 - 1.00 (m, 9 H) 1.75 - 1.90 (m, 2 H) 2.05 - 2.25 (m, 4 H) 2.36 - 2.53 (m, 2 H) 2.63 (br. s., 2 H) 2.75 (br. s., 4 H) 3.22 (br. s., 4 H) 3.82 (br. s., 2 H) 5.54 (quin, J= 9.00 Hz, 1 H) 7.38 (dd, J= 9.00, 2.74 Hz, 1 H) 7.72 (dd, J= 5.09, 3.13 Hz, 1 H) 8.00 - 8.04 (m, 1 H) 8.06 (d, J= 2.74 Hz, 1 H) 8.10 (s, 1 H) 8.36 (d, J= 9.00 Hz, 1 H) 9.08 (s, 1 H) ppm.

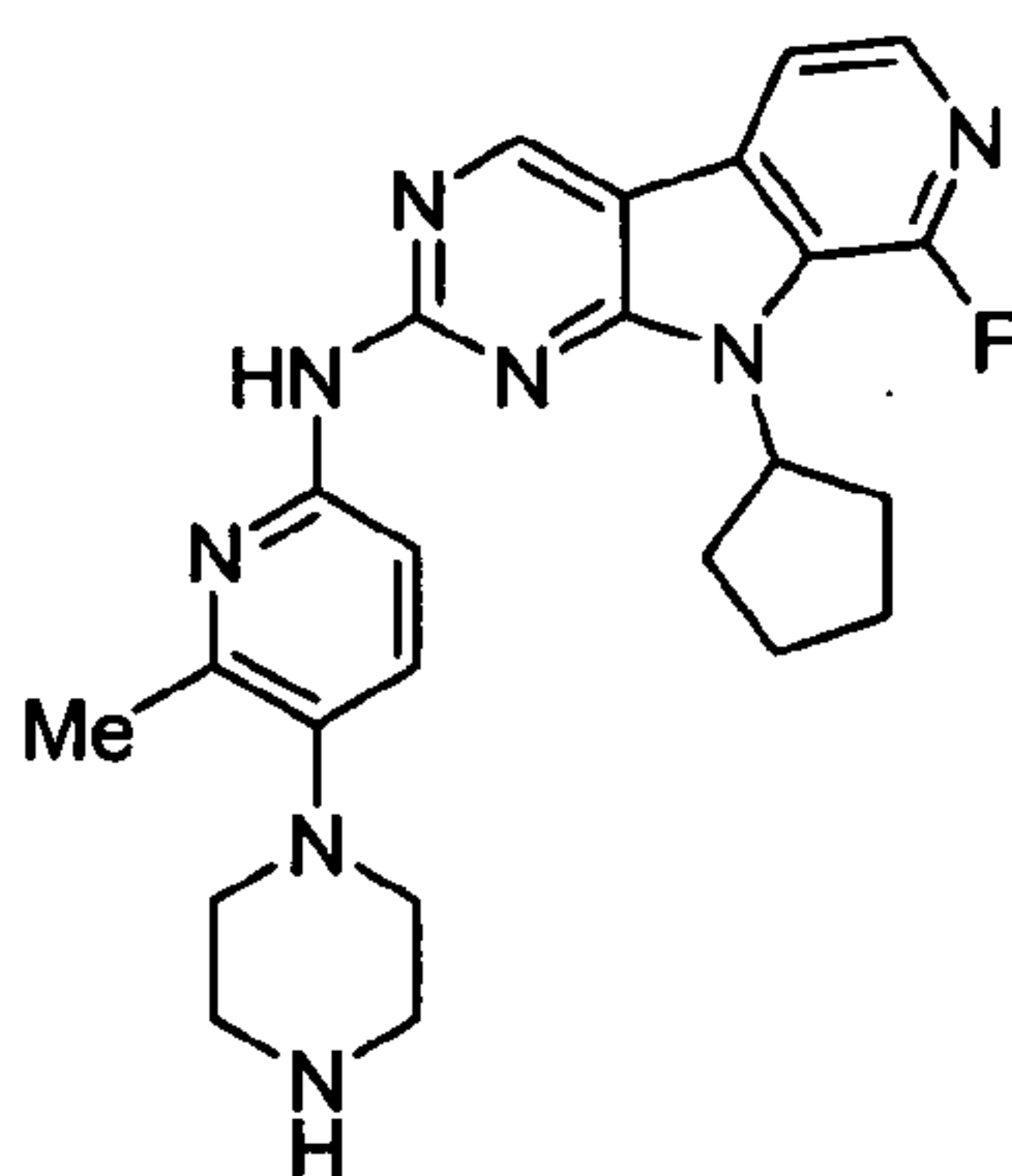


**2-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol (242):** To compound **248** (0.115 g, 0.19 mmol) in THF (1.0 mL) was added tetrabutylammonium fluoride, 1.0 M in THF (0.49 mL,



0.49 mmol). The reaction was stirred at room temperature. After 1 h, the reaction contents were poured into water. The aqueous layer was brought to pH 12 with 5 N NaOH and extracted with 10% methanol in dichloromethane (3 x 25 mL). The combined organics were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Silica gel chromatography (gradient elution 3 to 7.5% 2M methanolic NH<sub>3</sub> in DCM) afforded compound **242** (0.070 g, 75% yield). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 1.68 - 1.80 (m, 2 H) 1.92 - 2.05 (m, 2 H) 2.05 - 2.17 (m, 2 H) 2.25 - 2.40 (m, 2 H) 2.45 (t, J= 6.11 Hz, 2 H) 2.54 - 2.62 (m, 4 H) 3.00 - 3.27 (m, 4 H) 3.54 (q, J= 5.95 Hz, 2 H) 4.43 (t, J= 5.26 Hz, 1 H) 5.45 (quin, J= 9.05 Hz, 1 H) 7.47 (dd, J= 9.17, 2.81 Hz, 1 H) 7.93 - 8.07 (m, 3 H) 8.11 (d, J= 9.05 Hz, 1 H) 9.32 (s, 1 H) 9.89 (s, 1 H) ppm.

### EXAMPLE 171

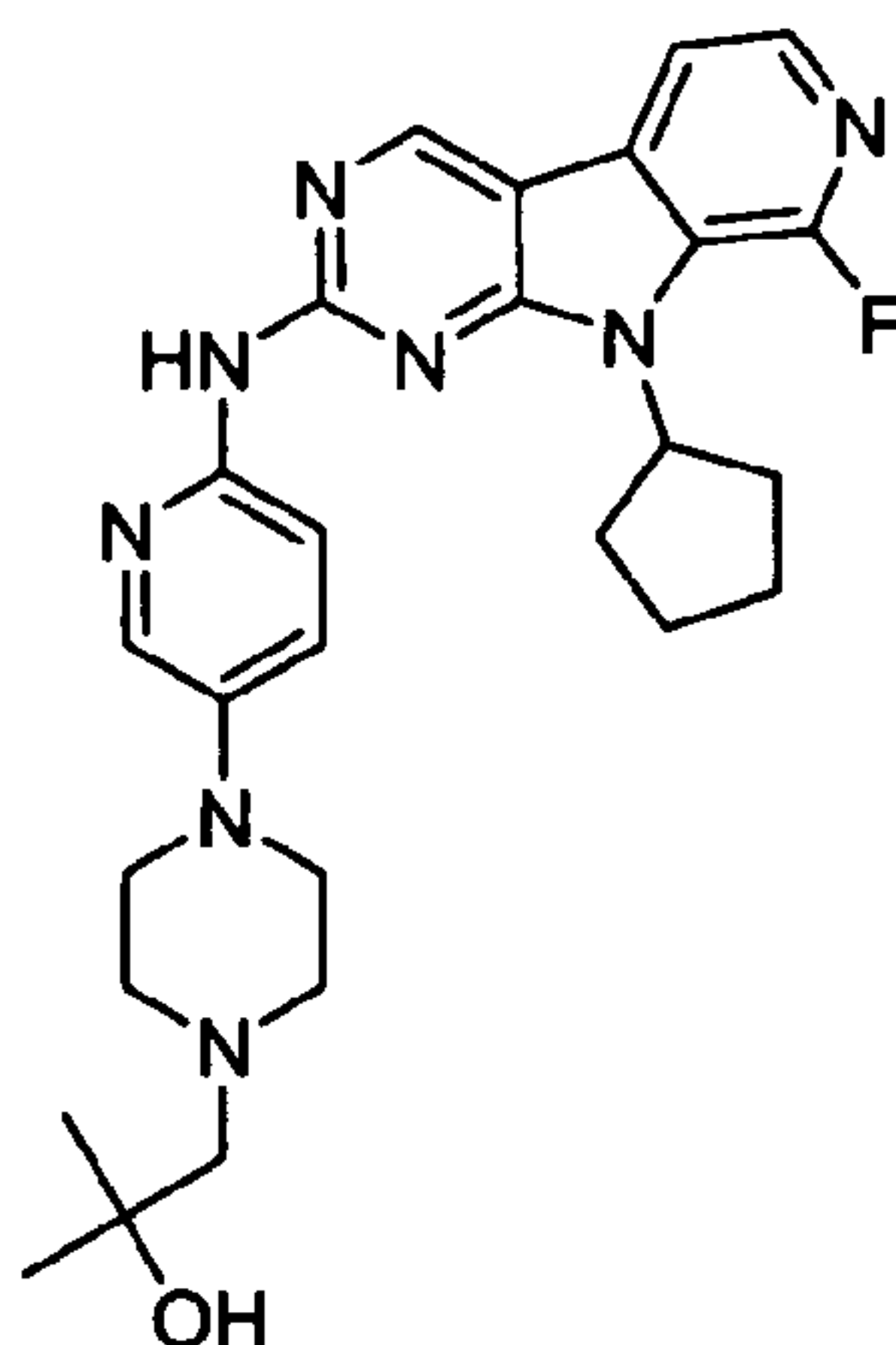


**249**

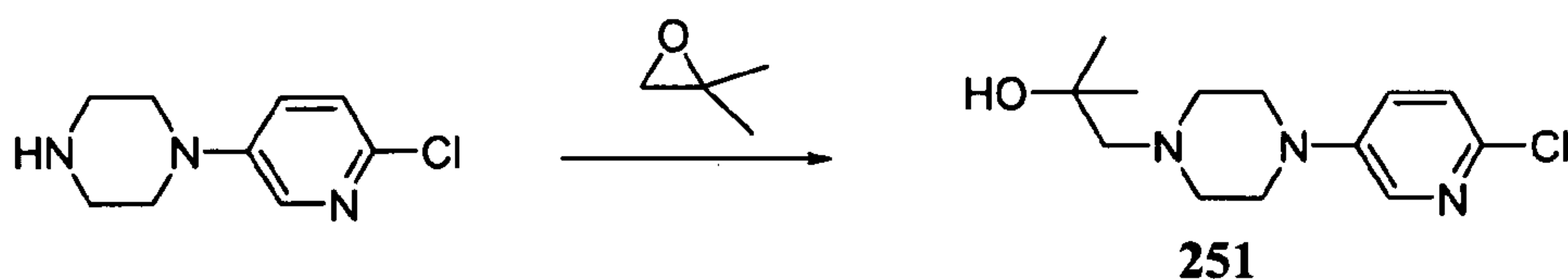
**9-Cyclopentyl-8-fluoro-N-(6-methyl-5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **249** was prepared using methods described in Example 170 and isolated as the HCl salt. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ ppm 8.97 (1 H, s), 8.03 (1 H, d, J=9.0 Hz), 7.87 (1 H, dd, J=5.1, 2.4 Hz), 7.79 (1 H, d, J=4.4 Hz), 7.12 (1 H, d, J=9.0 Hz), 5.35 (1 H, qd, J=8.7, 8.6 Hz), 3.47 - 3.55 (4 H, m), 3.23 - 3.32 (4 H, m), 2.65 (3 H, s), 2.17 - 2.28 (2 H, m), 1.97 - 2.17 (5 H, m), 1.73 - 1.87 (2 H, m) ppm; LCMS-ESI (POS), M/Z, M+1: Found 447.3.

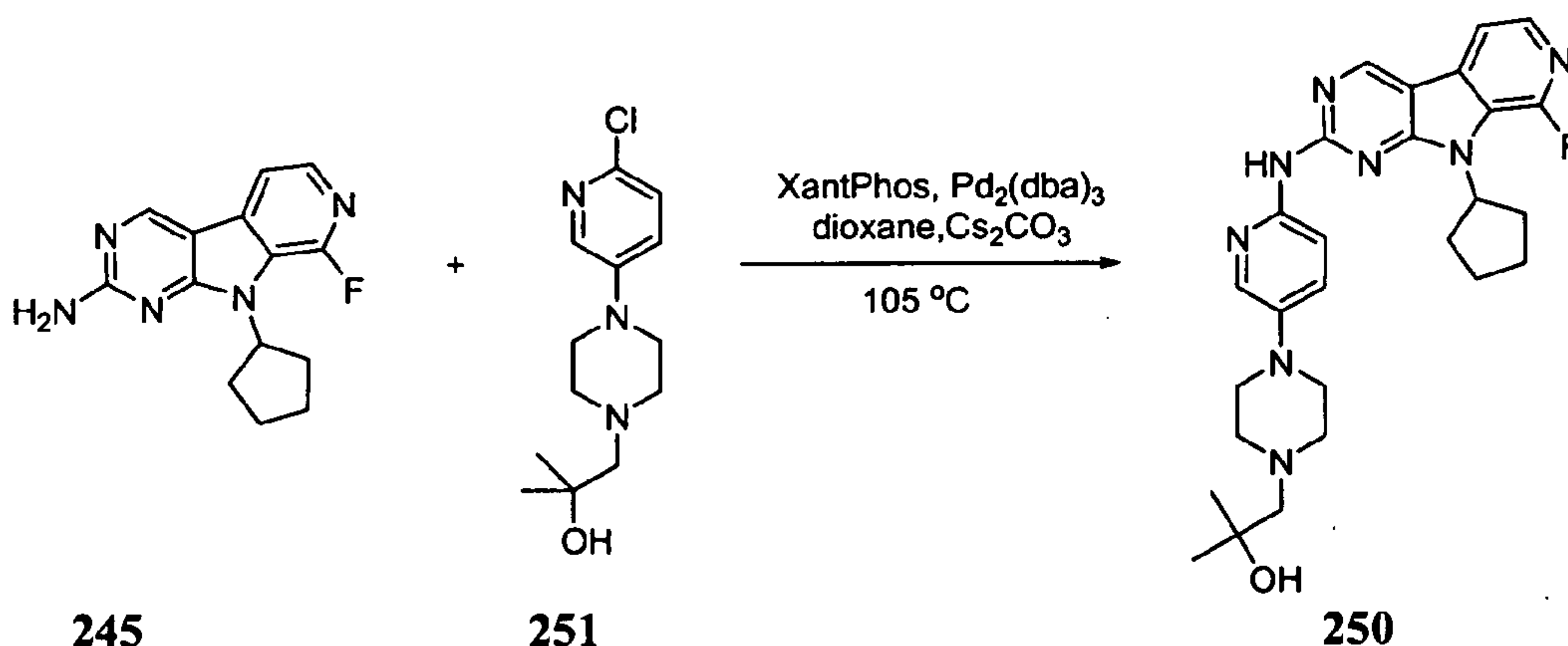


**EXAMPLE 172****250**

**1-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-methyl-2-propanol**

**251**

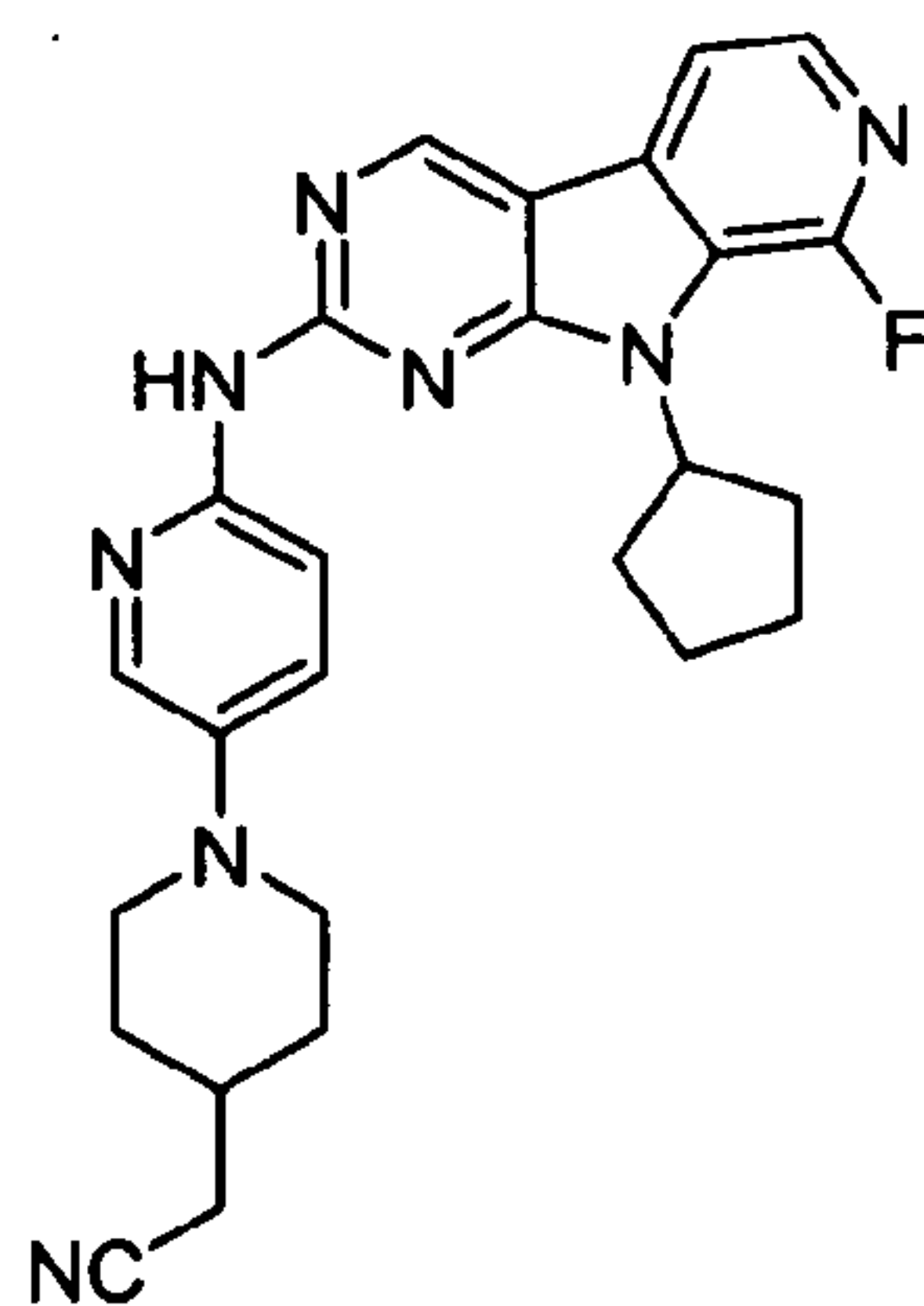
**1-(4-(6-chloro-3-pyridinyl)-1-piperazinyl)-2-methyl-2-propanol (251):** To 1-(6-chloropyridin-3-yl)piperazine (0.600 g, 3.04 mmol) in methanol (1.5 mL) was added dropwise isobutylene oxide (0.274 mL, 3.04 mmol). The reaction was left to stir at room temperature overnight. An additional 0.15 equivalents of isobutylene oxide were added and the reaction was placed in a 55 °C oil bath overnight. Solvent was removed *in vacuo*. Silica gel chromatography (gradient elution 2 to 10% methanol in DCM) afforded compound **251** (0.450 g, 55.0% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.95 - 1.50 (m, 7 H) 2.23 - 3.61 (m, 9 H) 7.12 - 7.24 (m, 2 H) 8.03 (br. s., 1 H) ppm.

**245****251****250**



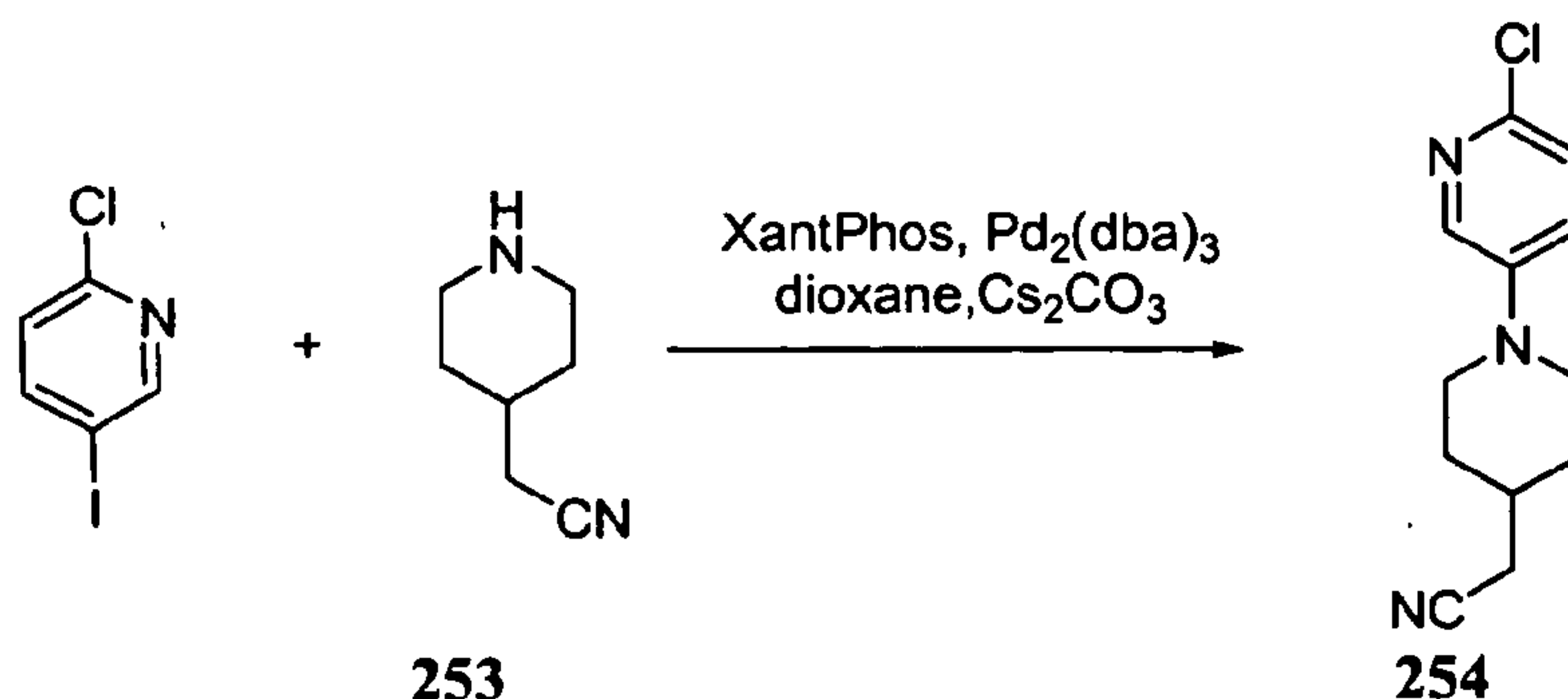
**1-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-methyl-2-propanol (250):** To tris(dibenzylideneacetone)dipalladium (0) (0.0190 g, 0.0207 mmol), Xantphos (0.0240 g, 0.0415 mmol), cesium carbonate (0.126 g, 0.387 mmol), 1-(4-(6-chloropyridin-3-yl)piperazin-1-yl)-2-methylpropan-2-ol (**251**) (0.0746 g, 0.276 mmol), and compound **245** (0.0750 g, 0.276 mmol) was added degassed dioxane (1.1 mL). The reaction was stirred at 105 °C overnight. After 16 h, the reaction was cooled to room temperature and partitioned between dichloromethane (30 mL) and water. The aqueous was brought to pH 12 w/ 5 N NaOH and extracted further with dichloromethane (15 mL) and 10% methanol in dichloromethane (10 mL). The combined organics were dried with sodium sulfate and concentrated *in vacuo*. Silica gel chromatography (1% to 5 % 2M methanolic NH<sub>3</sub> in DCM) afforded compound **250** (0.135 g, 96.8% yield). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 1.13 (s, 6 H) 1.67 - 1.81 (m, 2 H) 1.96 - 2.06 (m, 2 H) 2.07 - 2.16 (m, 2 H) 2.27 (s, 2 H) 2.33 (d, J = 8.56 Hz, 2 H) 2.65 - 2.74 (m, 4 H) 3.10 - 3.17 (m, 4 H) 4.14 (s, 1 H) 5.46 (quin, J = 9.05 Hz, 1 H) 7.47 (dd, J = 9.17, 2.81 Hz, 0 H) 7.97 - 8.07 (m, 3 H) 8.12 (d, J = 9.05 Hz, 0 H) 9.33 (s, 1 H) 9.90 (s, 1 H) ppm.

### EXAMPLE 173



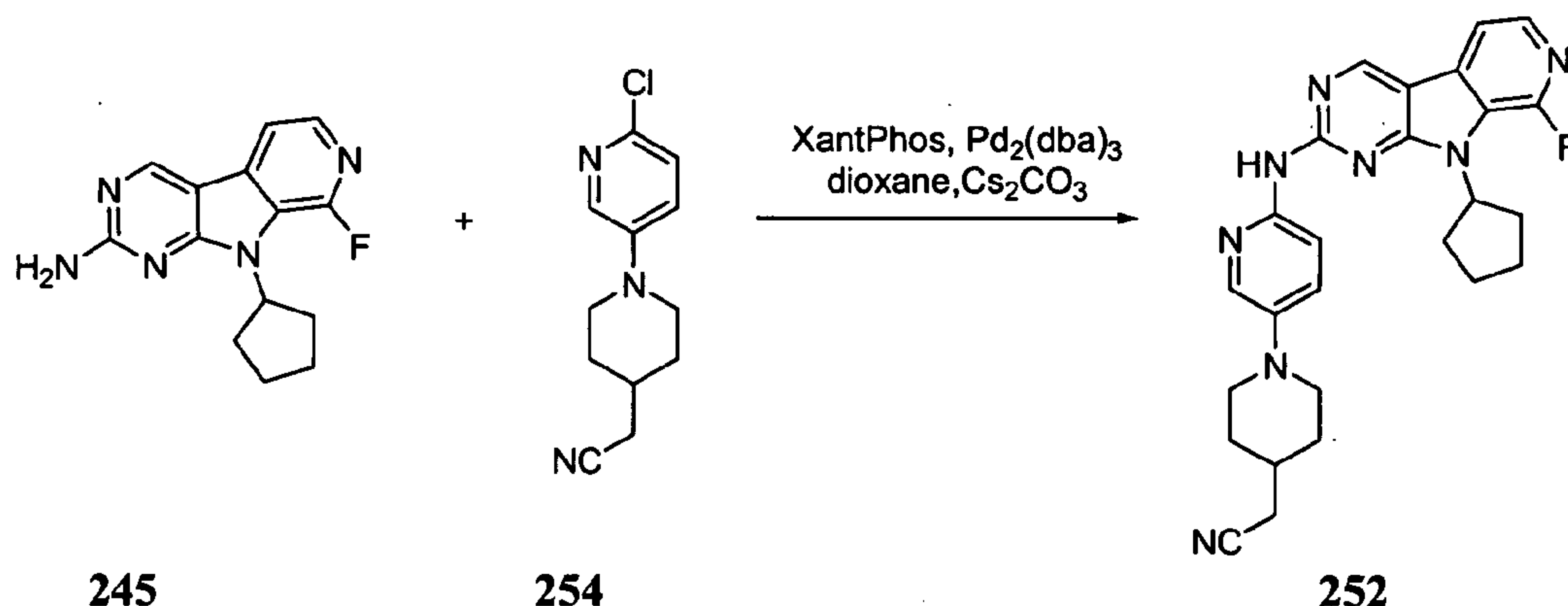
**252**

**(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetonitrile**





**(1-(6-Chloro-3-pyridinyl)-4-piperidinyl)acetonitrile (254):** 2-Chloro-5-iodopyridine (0.278 g, 1.16 mmol), 2-(piperidin-4-yl)acetonitrile hydrochloride (**253**) [Vidaluc, J.-L. et al., *Novel J. Med. Chem.* **1994**, 37, (5), 689-695] (0.186 g, 1.16 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.0531 g, 0.0580 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0671 g, 0.116 mmol) and cesium carbonate (0.945 g, 2.90 mmol) were combined in a screw cap vial and solvated under argon atmosphere with degassed dioxane (4.5 mL). The reaction was briefly sparged with argon, then sealed and stirred at 105 °C. After 3 h, the reaction was poured into water (30 mL) and extracted with 10% methanol in CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organics were dried with sodium sulfate and concentrated *in vacuo*. Silica gel chromatography (gradient elution 10 to 50% ethyl acetate in hexanes) afforded compound **254** (0.110 g, 40.2% yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.23 - 1.44 (m, J=11.98, 11.98, 11.84, 3.72 Hz, 2 H) 1.68 - 1.90 (m, 3 H) 2.54 (d, 2 H) 2.75 (td, J=12.42, 2.15 Hz, 2 H) 3.77 (d, J=12.52 Hz, 2 H) 7.26 (d, J=9.00 Hz, 1 H) 7.42 (dd, J=8.80, 3.33 Hz, 1 H) 8.06 (d, J=3.13 Hz, 1 H) ppm.

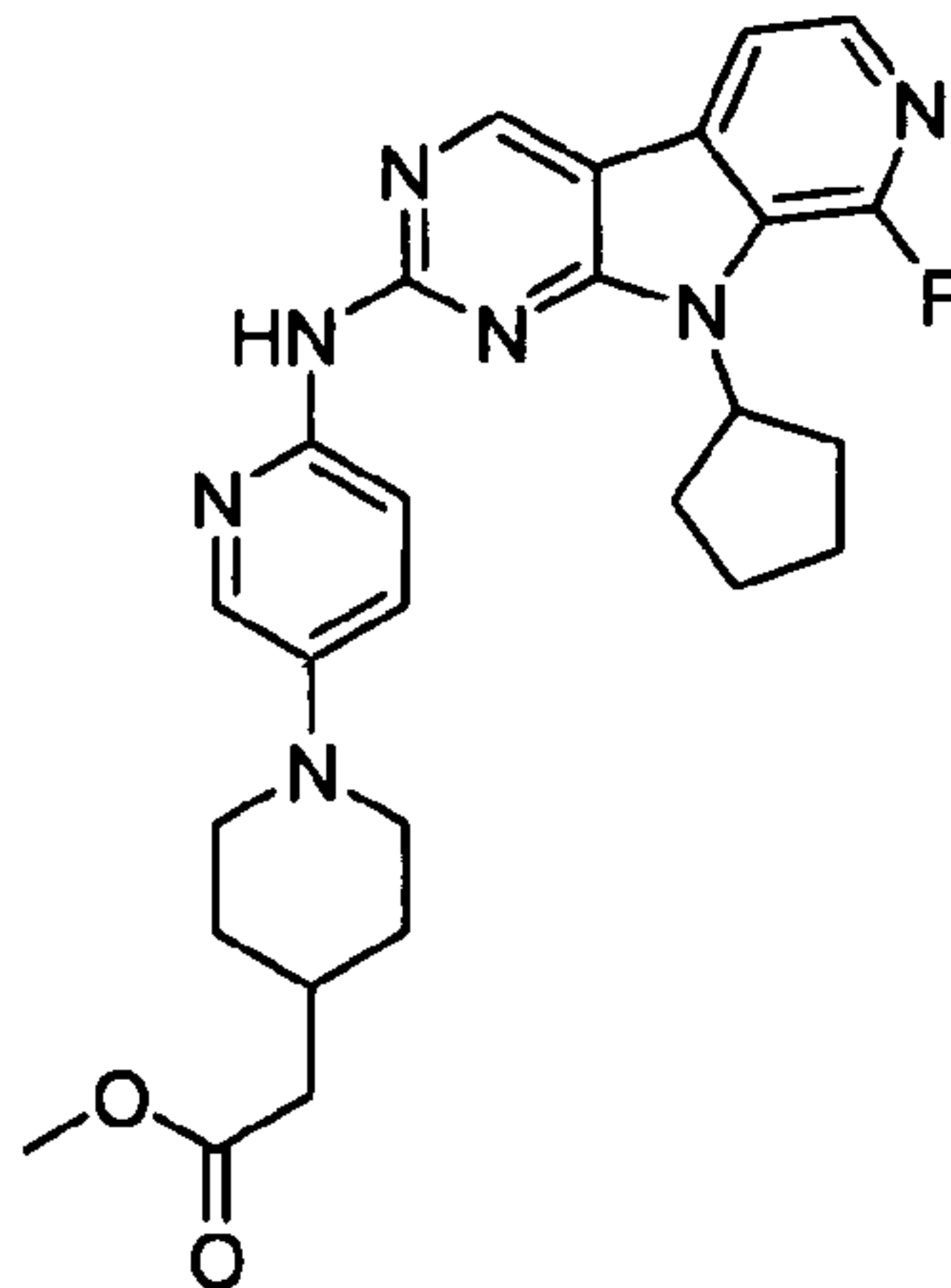


**(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetonitrile (252):** To tris(dibenzylideneacetone)dipalladium (0) (0.0147 g, 0.0160 mmol), xantphos (0.0186 g, 0.0321 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.0975 g, 0.299 mmol), 2-(1-(6-chloropyridin-3-yl)piperidin-4-yl)acetonitrile (0.0504 g, 0.214 mmol), and compound **245** (0.0580 g, 0.214 mmol) was added degassed (Ar) dioxane (1.0 mL). The reaction was stirred at 105 °C overnight. After 16 h, the reaction was cooled to room temperature and loaded directly onto silica gel. Crystallization from THF and HCl salt formation provided compound **252** (55 mg). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.43 (d, J= 10.56 Hz, 2 H) 1.66 - 1.81 (m, 2 H) 1.86 (d, J= 11.35 Hz, 3 H) 2.05 (d, J= 6.26 Hz, 2 H) 2.15 (br. s., 2 H) 2.19 - 2.31 (m, 2 H) 2.59 (d, J= 5.87 Hz, 2 H) 2.85 (t, J= 11.74 Hz, 2 H) 3.75 (d, J= 12.13 Hz, 2 H) 5.53 (quin, J= 9.10 Hz, 1 H) 7.68 (d, J= 9.39 Hz, 1 H) 8.00 (br. s., 1 H) 8.15 (d, J= 5.09 Hz, 1 H)



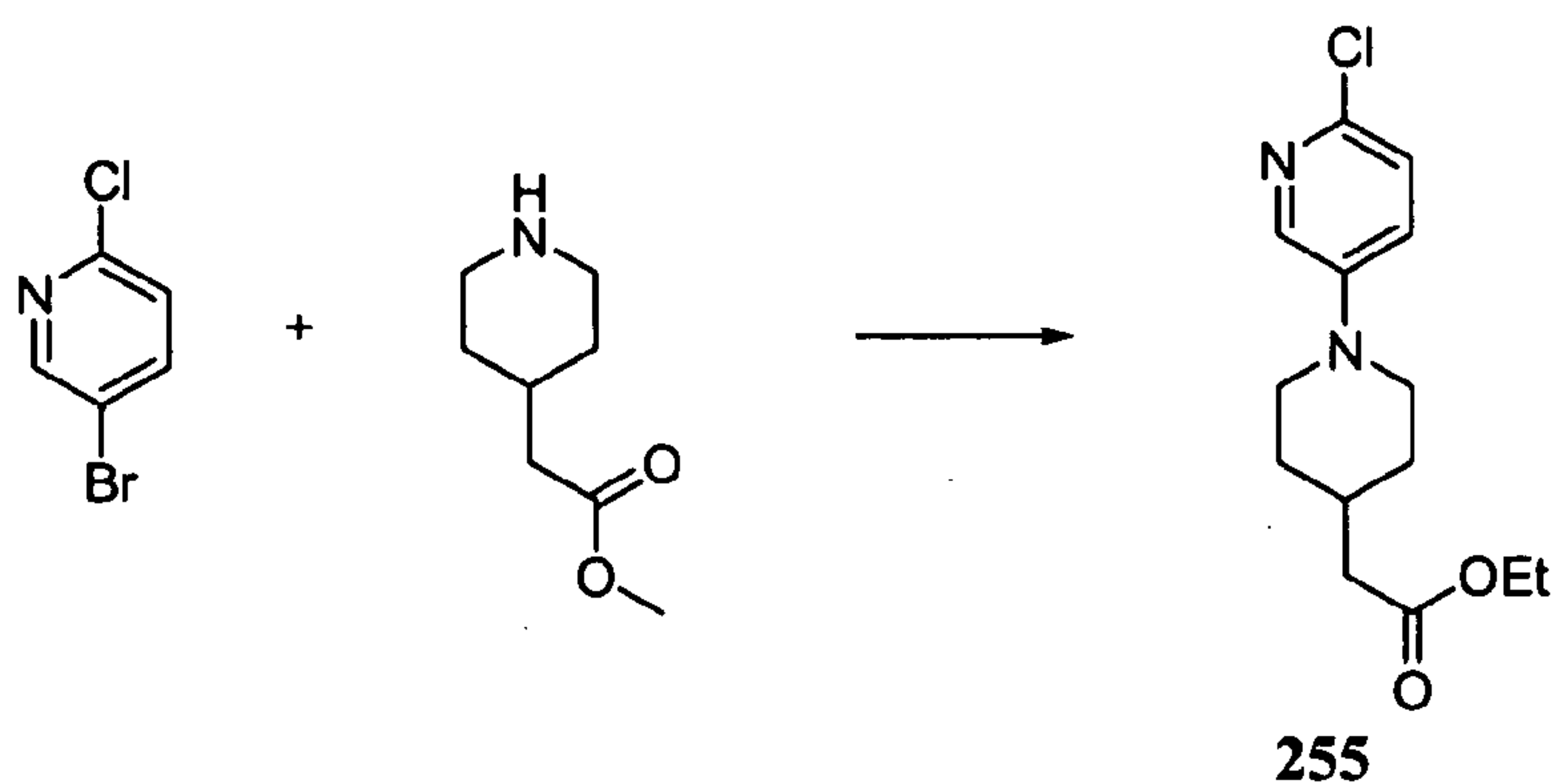
8.20 (dd,  $J = 9.39, 2.74$  Hz, 1 H) 8.30 (dd,  $J = 4.89, 2.93$  Hz, 1 H) 9.55 (s, 1 H) 11.80 (br. s., 1 H) ppm.

### EXAMPLE 174



258

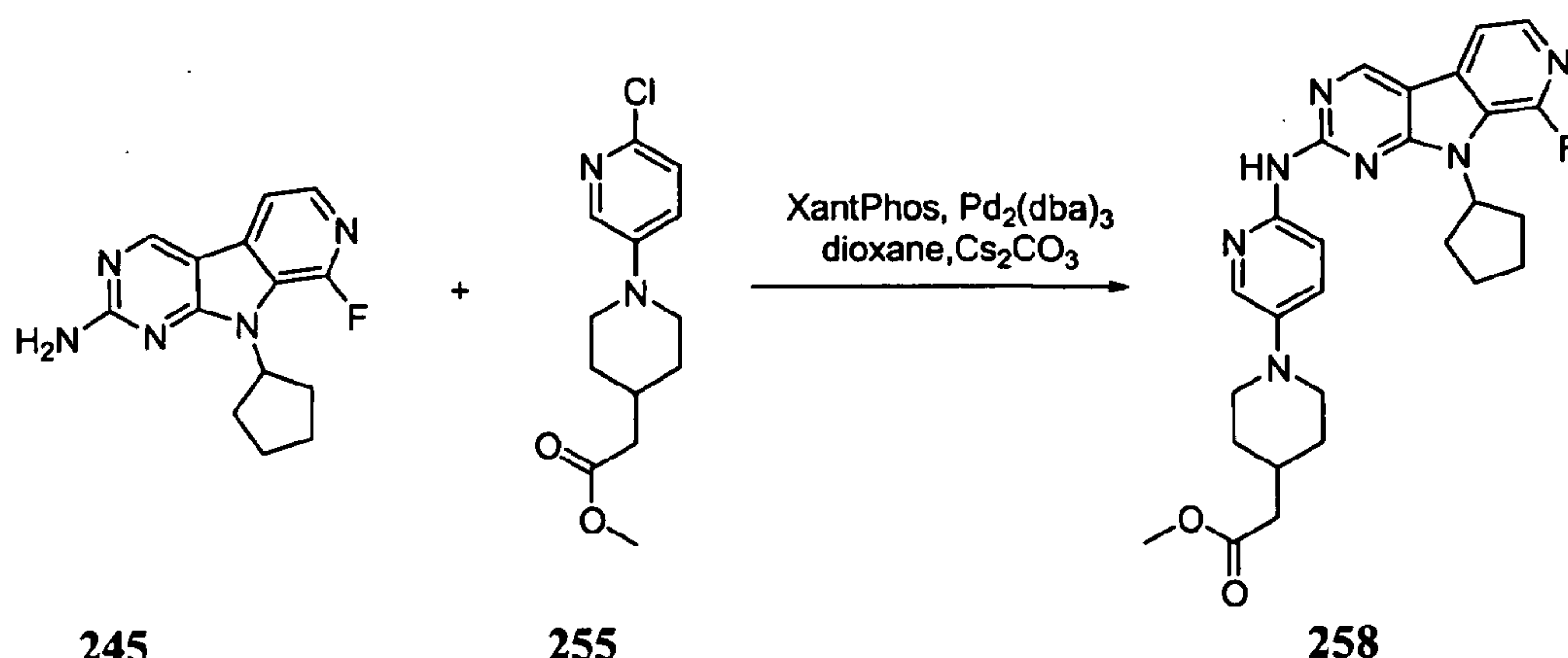
**Methyl (1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetate**



255

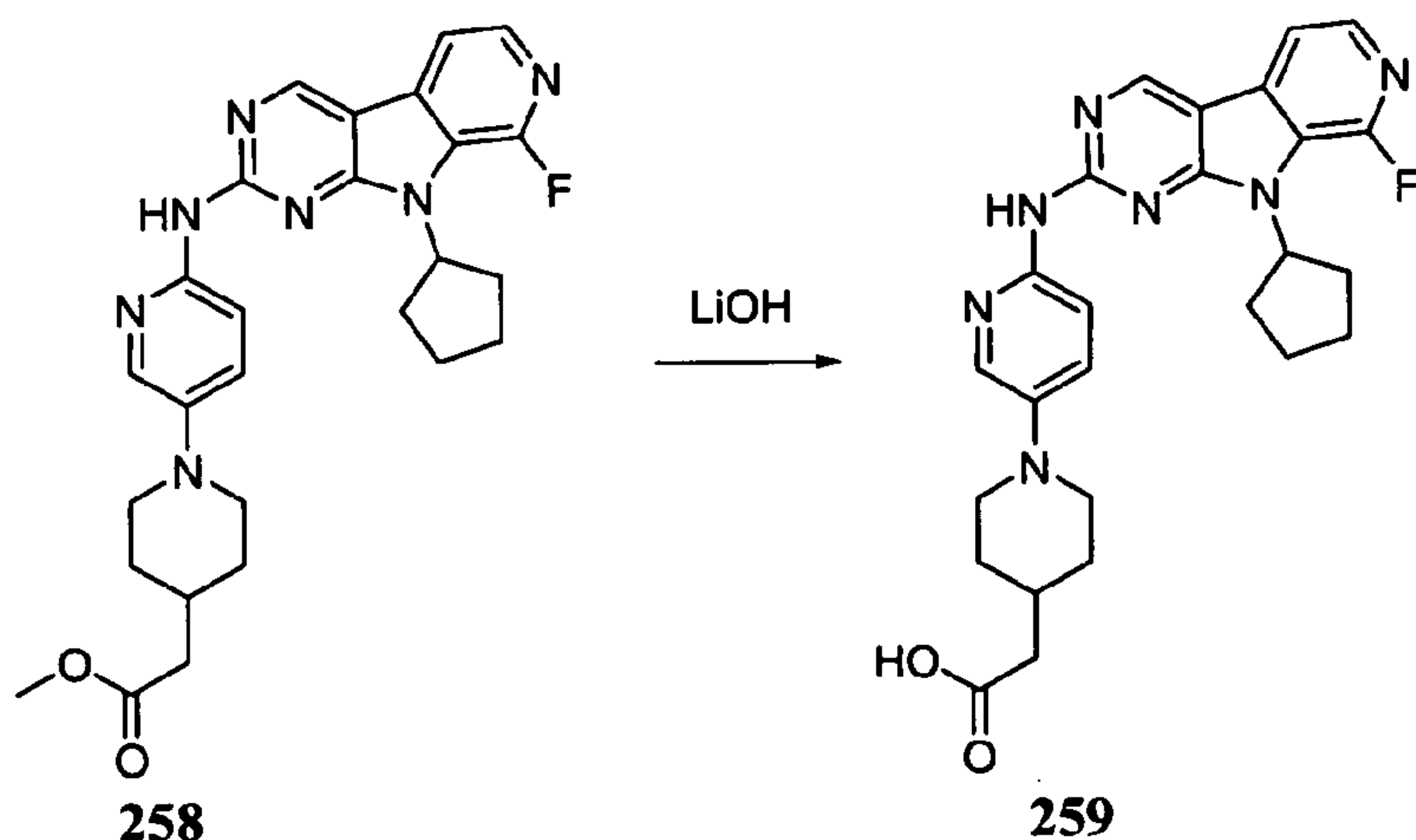
**Ethyl (1-(6-chloro-3-pyridinyl)-4-piperidinyl)acetate (255):** Compound **255** was prepared using methods described in example 173.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.27 (qd,  $J = 12.26, 3.91$  Hz, 2 H) 1.72 (d,  $J = 12.52$  Hz, 2 H) 1.78 - 1.93 (m,  $J = 11.05, 7.38, 7.38, 3.72, 3.72$  Hz, 1 H) 2.29 (d,  $J = 7.04$  Hz, 2 H) 2.72 (td,  $J = 12.32, 2.35$  Hz, 2 H) 3.60 (s, 3 H) 3.72 (d,  $J = 12.52$  Hz, 2 H) 7.25 (d,  $J = 9.00$  Hz, 1 H) 7.40 (dd,  $J = 9.00, 3.13$  Hz, 1 H) 8.04 (d,  $J = 3.13$  Hz, 1 H) ppm.





**Methyl (1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidyl)acetate (258):** Compound 258 was prepared using methods described for Example 173 and isolated as the HCl salt. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 1.39 (br. s., 2 H) 1.71 - 1.86 (m, 4 H) 1.93 (d, J= 8.80 Hz, 1 H) 2.05 (t, J= 6.72 Hz, 2 H) 2.15 (d, J= 7.58 Hz, 2 H) 2.20 - 2.31 (m, 2 H) 2.34 (d, J= 6.85 Hz, 2 H) 2.86 (br. s., 2 H) 3.63 (s, 3 H) 3.71 (d, J= 12.47 Hz, 2 H) 5.54 (quin, J= 9.11 Hz, 1 H) 7.69 (br. s., 1 H), 8.01 (br. s., 1 H) 8.13 - 8.18 (m, 1 H) 8.20 (dd, J= 9.54, 2.20 Hz, 1 H) 8.30 (dd, J= 4.52, 2.81 Hz, 1 H) 9.56 (s, 1 H) ppm. LCMS-ESI (POS), M/Z, M+1: Found 504.2, Calculated 504.2.

### EXAMPLE 175

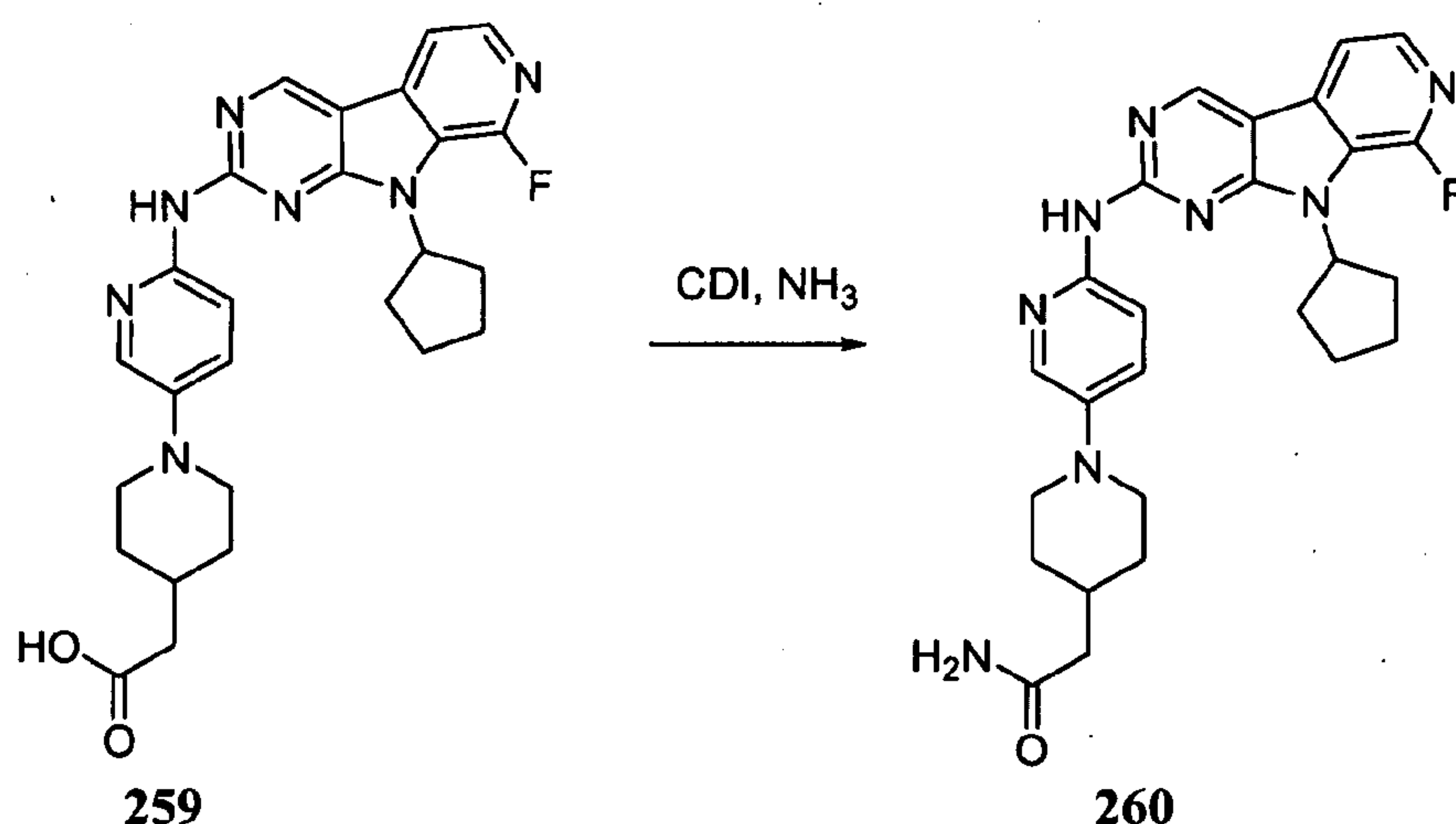


**(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidyl)acetic acid (259):** Compound 258 (0.100 g, 0.20 mmol) was suspended in dioxane (4.8 mL) and methanol (4.8 mL). A solution of lithium hydroxide, monohydrate (0.0092 g, 0.22 mmol) in 2.0 mL of water was added to the suspension. The reaction was warmed to 70 °C. After 1 hour, solvent was removed *in vacuo*. The residue was dissolved in water (3 mL). Dichloromethane was added (1 mL) and the pH was brought to ca.



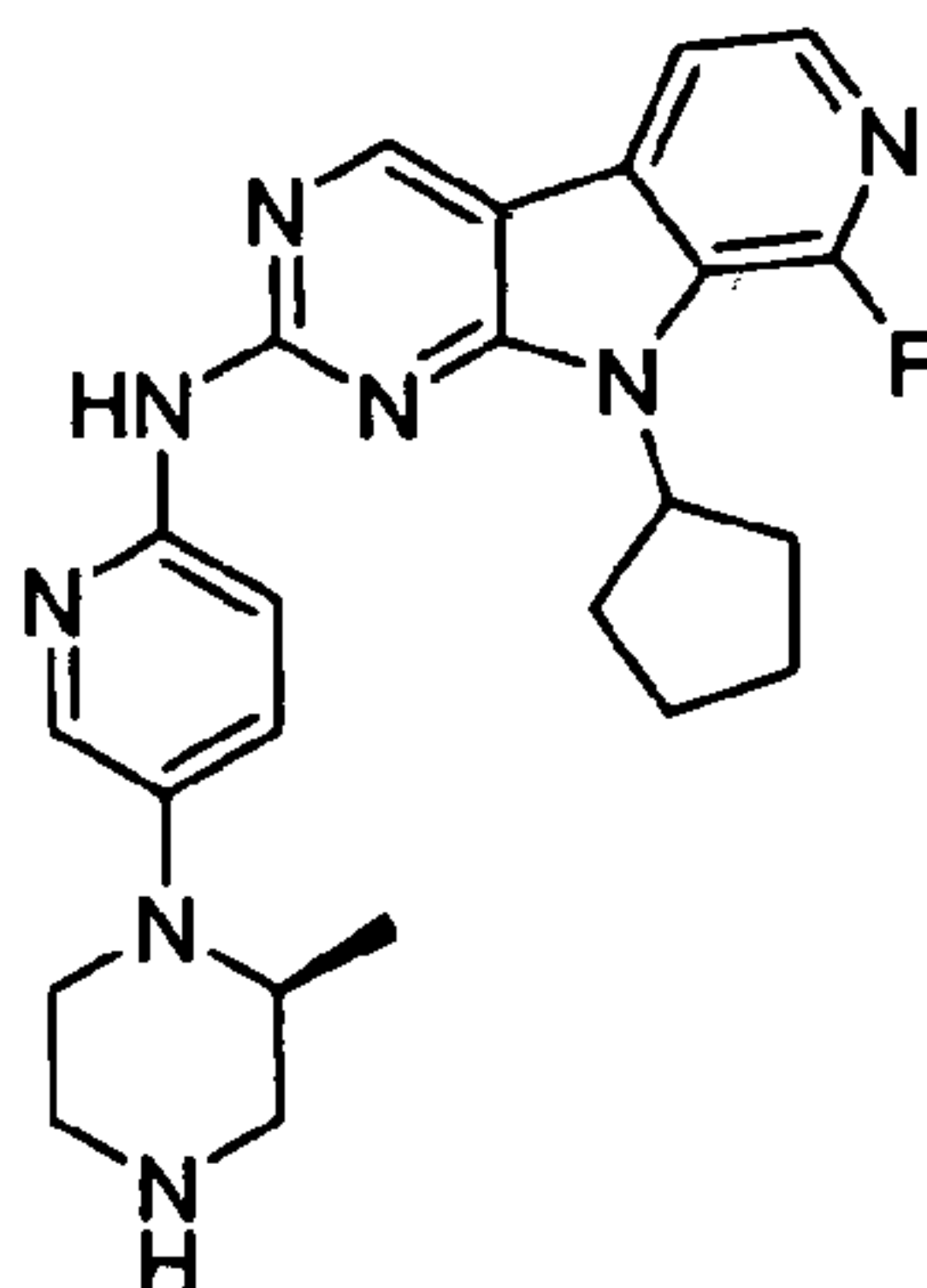
pH 10 with dilute NaOH. The organics were removed and the aqueous was brought to ca. pH 4 with dilute HCl. The resulting precipitate was filtered. Purification by RP-HPLC on C18 column (10-90% CH<sub>3</sub>CN in water with 0.1% TFA) provided compound **259** (5 mg) as a TFA salt. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 1.28 - 1.41 (m, J= 12.17, 12.01, 12.01, 3.18 Hz, 2 H) 1.68 - 1.94 (m, 5 H) 1.99 - 2.09 (m, 2 H) 2.09 - 2.19 (m, 2 H) 2.21 - 2.34 (m, 4 H) 2.81 (t, J= 11.49 Hz, 2 H) 3.71 (d, J= 12.23 Hz, 2 H) 5.53 (quin, J= 9.11 Hz, 1 H) 7.72 (d, J= 9.05 Hz, 1 H) 7.98 (br. s., 1 H) 8.06 (d, J= 8.56 Hz, 1 H) 8.11 - 8.18 (m, 1 H) 8.25 (dd, J= 4.65, 2.93 Hz, 1 H) 9.51 (s, 1 H) 11.43 (br. s., 1 H) ppm. LCMS-ESI (POS), M/Z, M+1: Found 490.1, Calculated 490.2.

### EXAMPLE 176



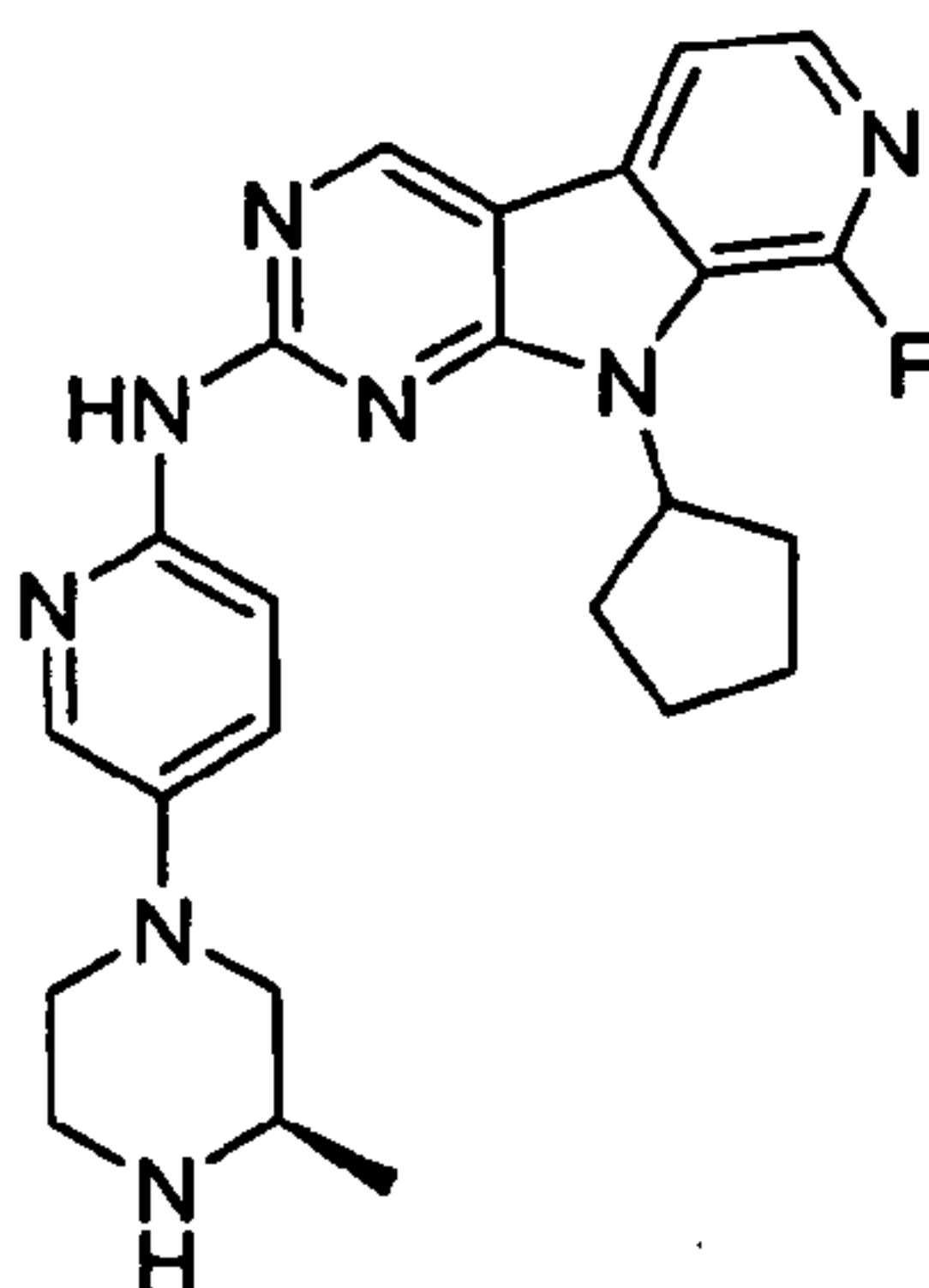
**2-(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)acetamide (260):** Compound **259** (0.077 g, 0.16 mmol) was suspended in DMF (1.5 mL) and 1,1'-carbonyldiimidazole (0.028 g, 0.17 mmol) was added. The reaction was stirred at 70 °C. After 1 h, the suspension was cooled to 0 °C and ammonia gas was sparged therein. The tube was sealed and warmed to 70 °C. After 1 h, the reaction was diluted in water (30 mL) and filtered. Purification by reversed phase HPLC (10-90% acetonitrile in water with 0.1% TFA) provided compound **260** (0.025 g, 26% yield) as a TFA salt. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 1.25 - 1.39 (m, 2 H) 1.70 - 1.84 (m, 4 H) 1.89 (dt, J= 7.27, 3.58 Hz, 1 H) 2.05 (d, J= 7.09 Hz, 4 H) 2.14 (br. s., 2 H) 2.27 (d, J= 8.31 Hz, 2 H) 2.80 (t, J= 10.88 Hz, 2 H) 3.70 (d, J= 12.23 Hz, 2 H) 5.52 (quin, J= 9.05 Hz, 1 H) 6.80 (br. s., 1 H) 7.31 (br. s., 1 H) 7.74 (br. s., 1 H) 7.98 (br. s., 1 H) 8.05 (br. s., 1 H) 8.13 (d, J= 3.91 Hz, 1 H) 8.21 - 8.28 (m, 1 H) 9.51 (s, 1 H) 11.36 (br. s., 1 H) ppm.



**EXAMPLE 177****261**

**9-Cyclopentyl-8-fluoro-N-(5-((2S)-2-methyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Tile compound **261** was prepared using methods described in Example 170 and isolated as the HCl salt. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 0.91 (d, J= 6.36 Hz, 3 H) 1.43 (s, 9 H) 1.67 - 1.81 (m, 2 H) 2.01 (br. s., 2 H) 2.05 - 2.16 (m, 2 H) 2.33 (br. s., 2 H) 2.91 - 3.02 (m, 1 H) 3.63 (d, J= 11.74 Hz, 1 H) 3.75 - 3.96 (m, 2 H) 5.45 (quin, J= 8.99 Hz, 1 H) 7.49 (dd, J=8.93, 2.57 Hz, 1 H) 7.95 - 8.07 (m, 3 H) 8.14 (d, J= 9.05 Hz, 1 H) 9.33 (s, 1 H) 9.92 (s, 1 H) ppm.

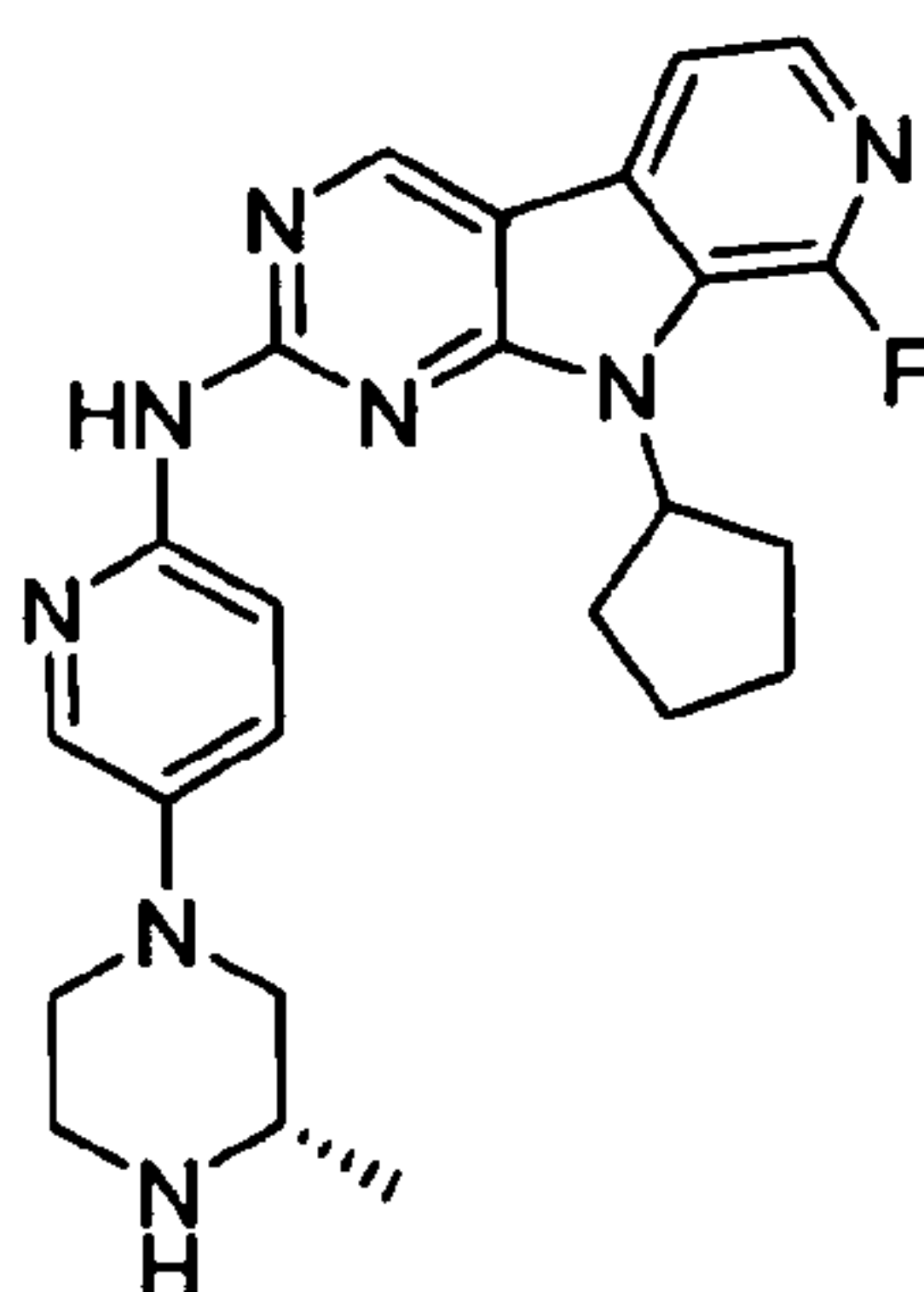
**EXAMPLE 178****262**

**9-Cyclopentyl-8-fluoro-N-(5-((3R)-3-methyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **262** was prepared using methods described in example 170 and isolated as the HCl salt. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 1.35 (d, J= 6.60 Hz, 3 H) 1.62 - 1.86 (m, 2 H) 1.97 - 2.10 (m, 2 H) 2.10 - 2.20 (m, 2 H) 2.21 - 2.34 (m, 2 H) 2.93 (dd, J= 12.47, 11.00 Hz, 1 H) 3.15 (d, J= 6.85 Hz, 2 H) 3.37 - 3.46 (m, 2 H) 3.78 (d, J= 8.31 Hz, 1 H) 3.84 (d, J= 11.98 Hz, 1 H)

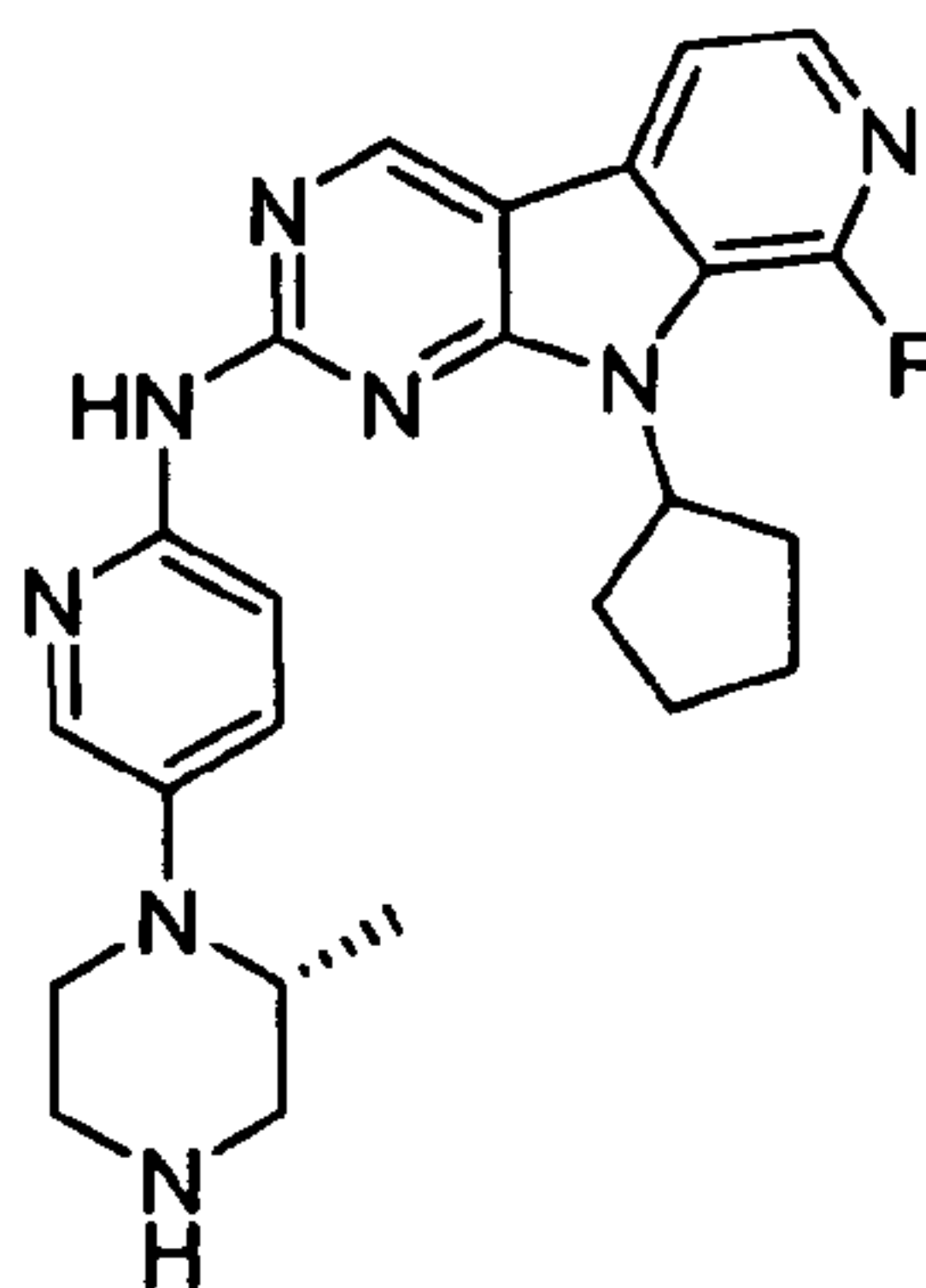


5.53 (quin,  $J = 9.05$  Hz, 1 H) 7.82 (d,  $J = 9.78$  Hz, 1 H) 8.09 (s, 2 H) 8.14 (d,  $J = 3.91$  Hz, 1 H) 8.22 - 8.33 (m, 1 H) 9.43 (br. s., 1 H) 9.54 (s, 1 H) 9.61 (br. s., 1 H) 11.54 (br. s., 1 H) ppm.

**EXAMPLE 179****263**

**9-cyclopentyl-8-fluoro-N-(5-((3S)-3-methyl-1-piperazinyl)-2-pyridinyl)-9H-pyrido-  
[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **263** was prepared using methods described in example 170 and isolated as the HCl salt.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.33 (d,  $J = 6.60$  Hz, 3 H) 1.69 - 1.82 (m, 2 H) 2.04 (t,  $J = 6.72$  Hz, 2 H) 2.14 (d,  $J = 5.87$  Hz, 2 H) 2.21 - 2.33 (m, 2 H) 2.91 (dd,  $J = 12.47, 11.00$  Hz, 1 H) 3.08 - 3.20 (m, 2 H) 3.77 (d,  $J = 9.05$  Hz, 1 H) 3.83 (d,  $J = 11.98$  Hz, 1 H) 5.52 (quin,  $J = 9.05$  Hz, 1 H) 7.81 (d,  $J = 8.80$  Hz, 1 H) 8.00 - 8.10 (m, 2 H) 8.13 (d,  $J = 4.16$  Hz, 1 H) 8.22 - 8.29 (m, 1 H) 9.42 (br. s., 1 H) 9.53 (s, 1 H) 9.57 (d,  $J = 9.29$  Hz, 1 H) 11.50 (br. s., 1 H) ppm.

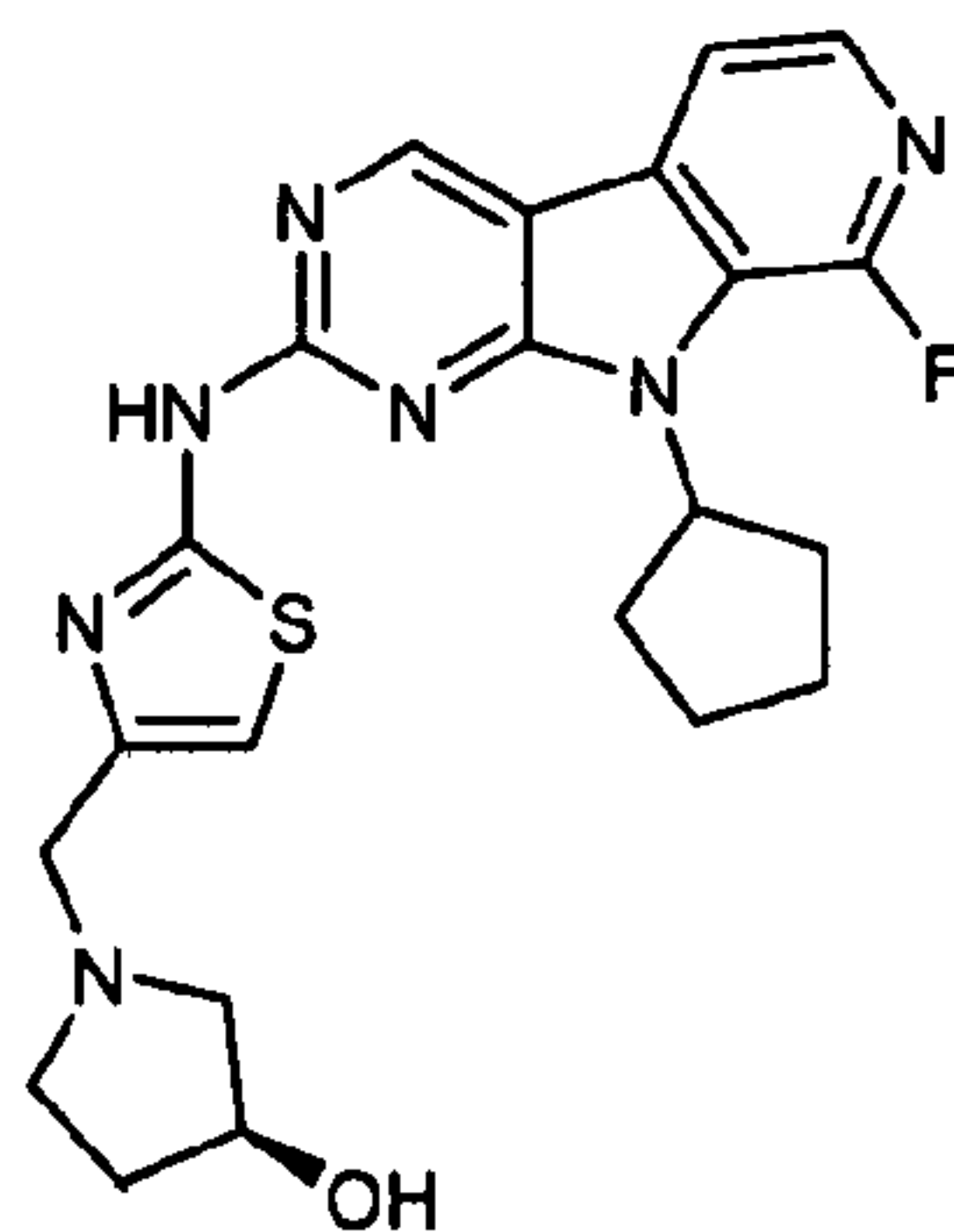
**EXAMPLE 180****264**

**9-Cyclopentyl-8-fluoro-N-(5-((2R)-2-methyl-1-piperazinyl)-2-pyridinyl)-9H-  
pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



Compound **264** was prepared using methods described in example 170 and isolated as the HCl salt.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.15 (d,  $J=6.85$  Hz, 3 H) 1.67 - 1.83 (m, 2 H) 1.95 - 2.08 (m, 2 H) 2.15 (br. s., 2 H) 2.25 (d,  $J=6.60$  Hz, 2 H) 3.06 - 3.17 (m, 1 H) 3.18 - 3.36 (m, 3 H) 3.45 - 3.54 (m, 1 H) 4.06 - 4.20 (m, 1 H) 5.52 (quin,  $J=9.05$  Hz, 1 H) 7.80 (d,  $J=9.29$  Hz, 1 H) 8.01 - 8.12 (m, 2 H) 8.12 - 8.20 (m, 1 H) 8.28 (dd,  $J=4.77, 3.06$  Hz, 1 H) 9.31 (br. s., 1 H) 9.55 (s, 1 H) 9.74 (br. s., 1 H) 11.69 (br. s., 1 H) ppm.

### EXAMPLE 181

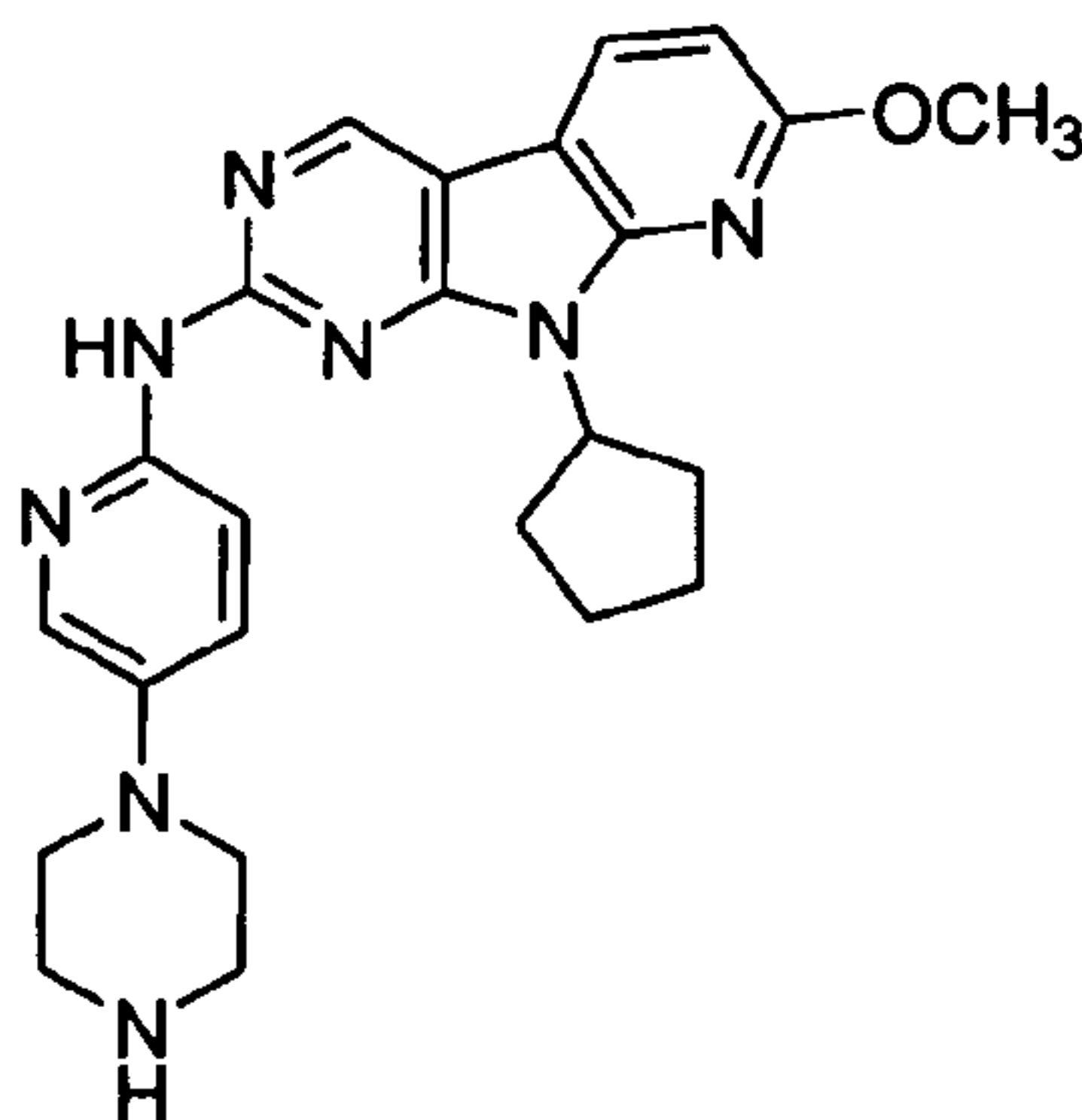


**265**

**(3S)-1-((2-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1,3-thiazol-4-yl)methyl)-3-pyrrolidinol**

Compound **265** was prepared using methods described in example 170.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.48 (2 H, br. s.), 9.30 (1 H, s), 8.08 (1 H, dd,  $J=5.3, 1.8$  Hz), 7.79 (1 H, dd,  $J=5.1, 2.9$  Hz), 6.83 (1 H, s), 5.64 - 5.74 (1 H, m), 4.35 - 4.43 (1 H, m), 3.84 - 3.98 (2 H, m), 3.03 - 3.11 (1 H, m), 2.88 - 2.96 (1 H, m), 2.69 - 2.77 (1 H, m), 2.41 - 2.59 (3 H, m), 2.11 - 2.29 (5 H, m), 1.76 - 1.94 (3 H, m) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 454.1.

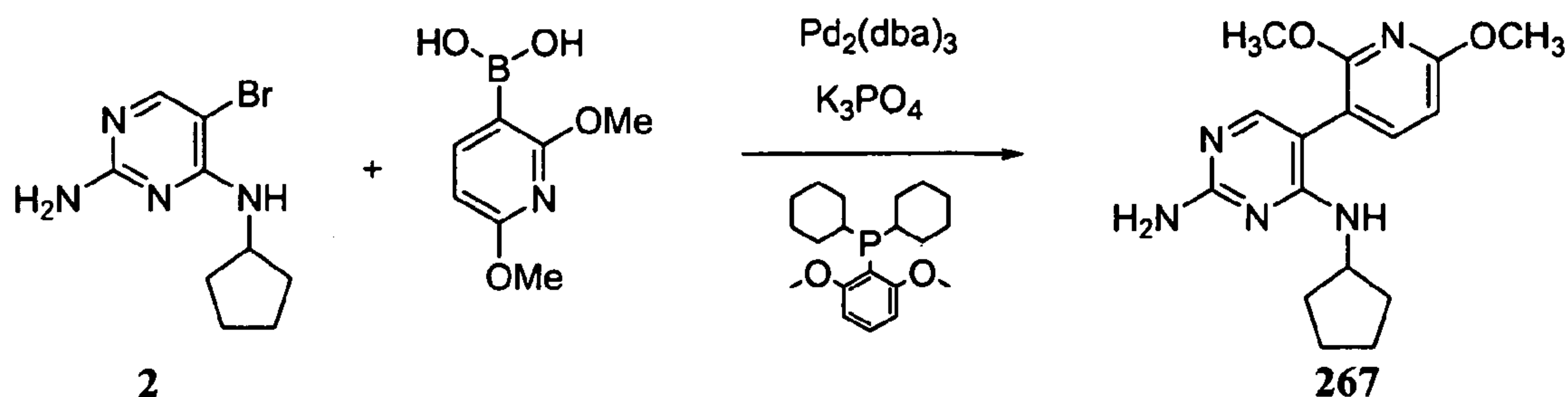
### EXAMPLE 182



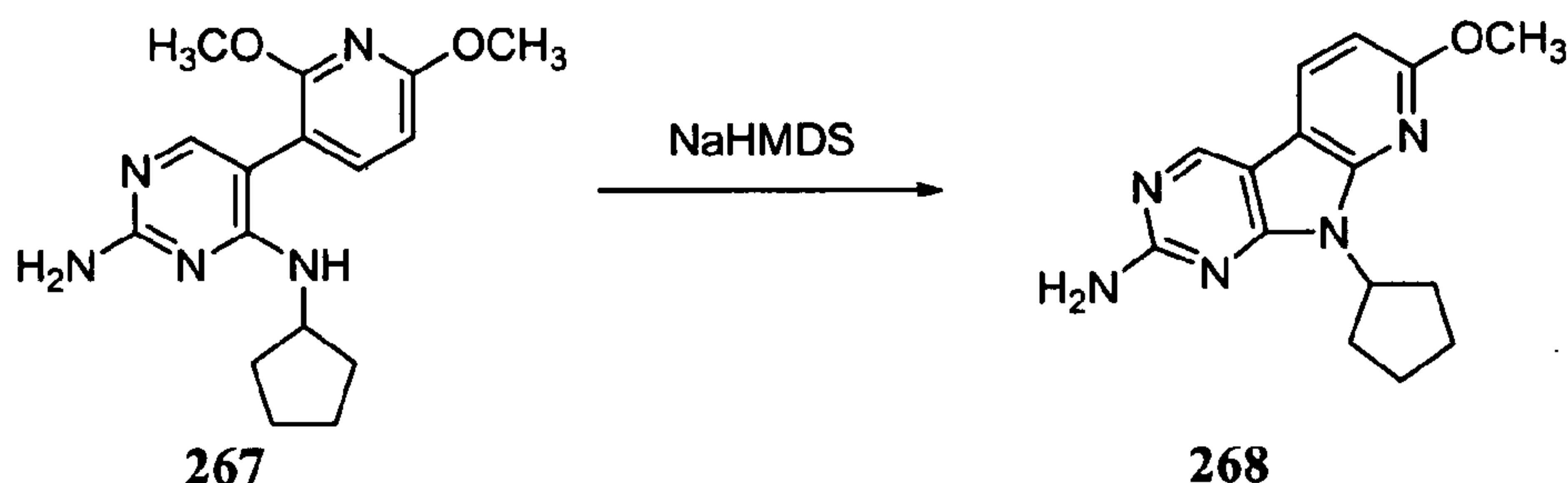
**266**

**9-Cyclopentyl-7-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



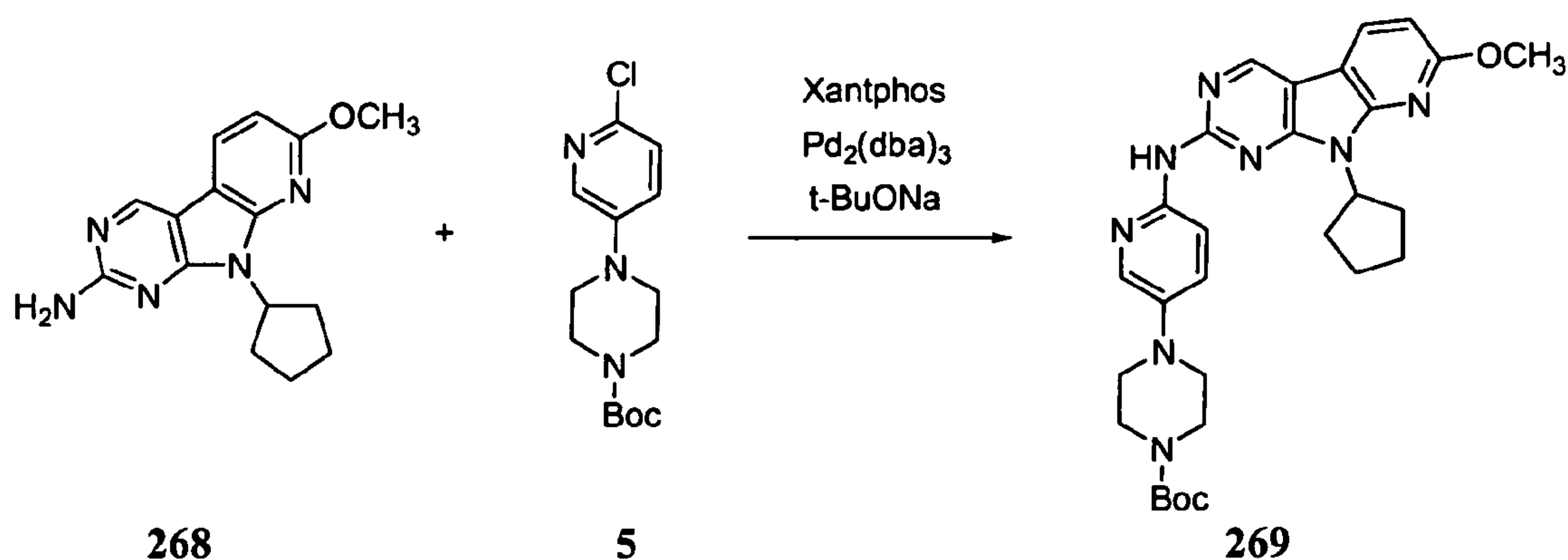


**N4-Cyclopentyl-5-(2,6-dimethoxypyridin-3-yl)pyrimidine-2,4-diamine (267):** Compound **2** (2.00 g, 7.78 mmol), 2,6-dimethoxypyridin-3-ylboronic acid (2.13 g, 11.7 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.214 g, 0.233 mmol), and dicyclohexyl(2,6-dimethoxyphenyl)phosphine (0.156 g, 0.467 mmol), were dissolved in *n*-butanol (2.5 mL). The reaction was purged with argon and heated at 100°C for 19 hours. The resulting solution was added to 80 mL water and extracted with ethyl acetate (2X 150 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give an orange oil. Silica gel chromatography (gradient elution dichloromethane + 2.5% TEA/0-5% methanol) afforded compound **267** as an off-white solid (1.29 g, 53%).

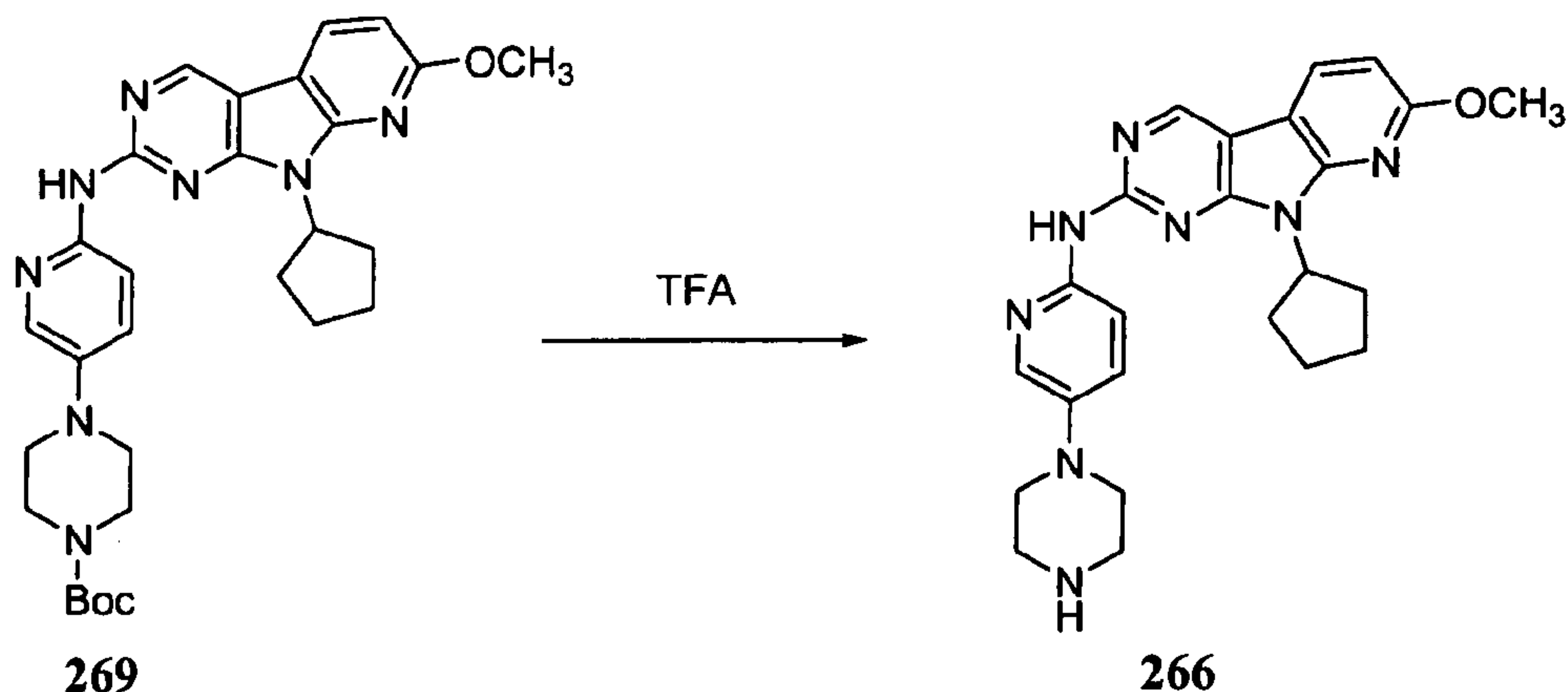


**9-cyclopentyl-7-methoxy-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (268):** A 10 mL reaction vessel was charged with N4-cyclopentyl-5-(2,6-dimethoxypyridin-3-yl)pyrimidine-2,4-diamine (**267**) (50.0 mg, 159 μmol) dissolved in dry pyridine (1 mL) under argon. Sodium bis(trimethylsilyl)amide in THF (1.0M, 0.349 mL, 349 μmol) was added and the reaction heated with microwave energy (300W) for 12 minutes at 150°C. The solvent was removed *in vacuo*. Silica gel chromatography of the residue (gradient elution dichloromethane/0-5% methanol) afforded compound **268** as an off-white solid (28 mg, 62%).





**tert-Butyl 4-(6-((9-cyclopentyl-7-methoxy-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (269):** A 10 mL reaction vessel was charged with compound **268** (100 mg, 353  $\mu$ mol), compound **5** (126 mg, 424  $\mu$ mol), and sodium *t*-butoxide (102 mg, 1059  $\mu$ mol), followed by dioxane (3 mL). The reaction was purged with argon. 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (40.8 mg, 70.6  $\mu$ mol) and tris(dibenzylideneacetone)dipalladium (0) (32.3 mg, 35.3  $\mu$ mol) were added and the reaction was again purged with argon. The reaction was heated with microwave energy (300W) at 120°C for 90 minutes. The resulting solution was diluted with ethyl acetate (75 mL) and added to water (75 mL). The layers were separated and the aqueous phase extracted with ethyl acetate (75 mL) and dichloromethane (75 mL). The combined organics were dried ( $\text{MgSO}_4$ ) and evaporated to give a brown oil. Silica gel chromatography (gradient elution hexanes/50-100% ethyl acetate) afforded a tan solid, which was recrystallized from boiling ethyl acetate to give compound **269** as a white solid (120 mg, 62%)

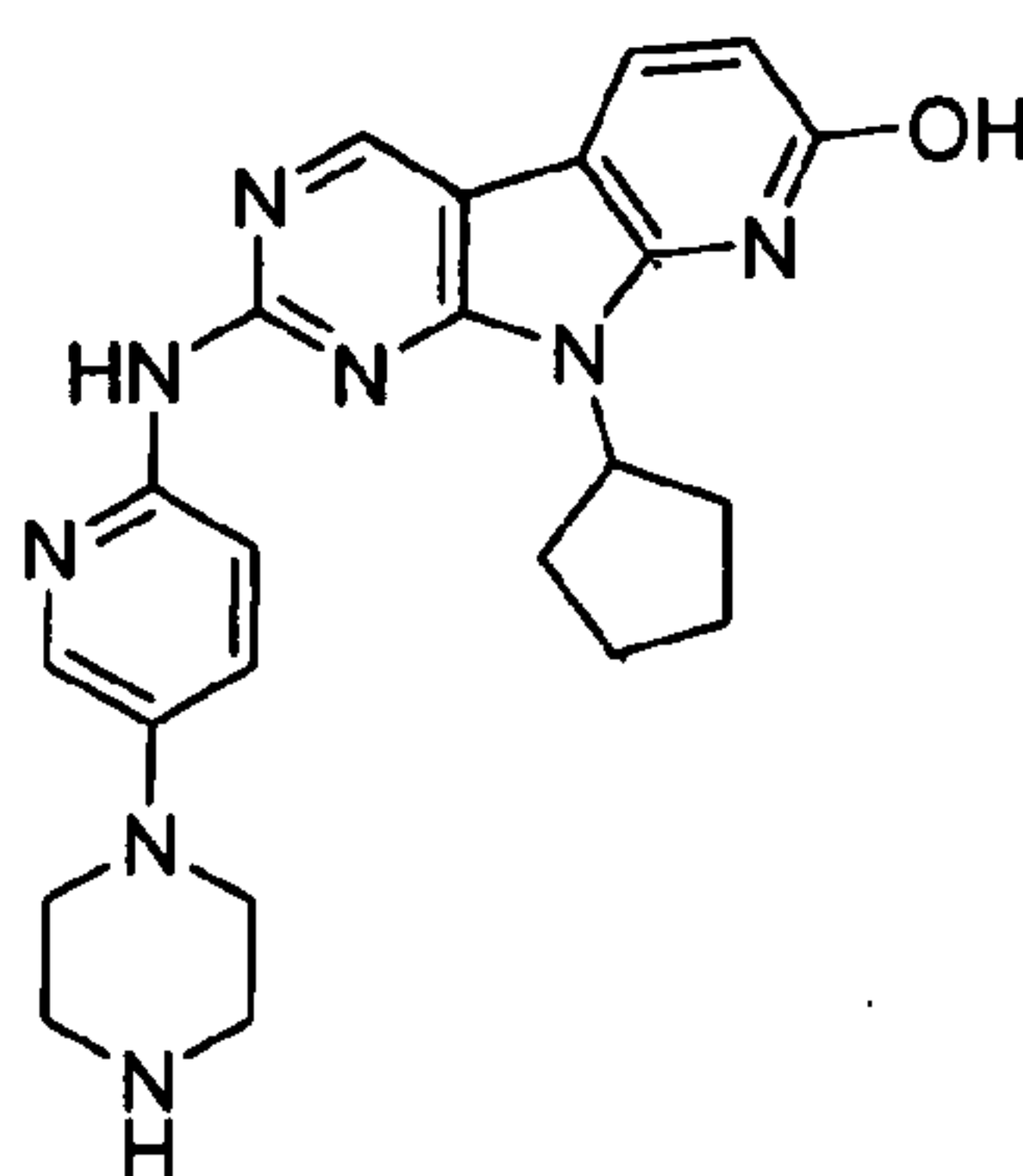


**9-cyclopentyl-7-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (266):** Compound **269** (120 mg, 220  $\mu$ mol) was dissolved in dichloromethane (4 mL). Trifluoroacetic acid (0.400 mL, 2203  $\mu$ mol) was added and the reaction stirred at room temperature for 70 minutes. The reaction was added to aqueous  $\text{K}_2\text{CO}_3$  (10%, 30 mL) and extracted thrice with dichloromethane. The combined organics were dried



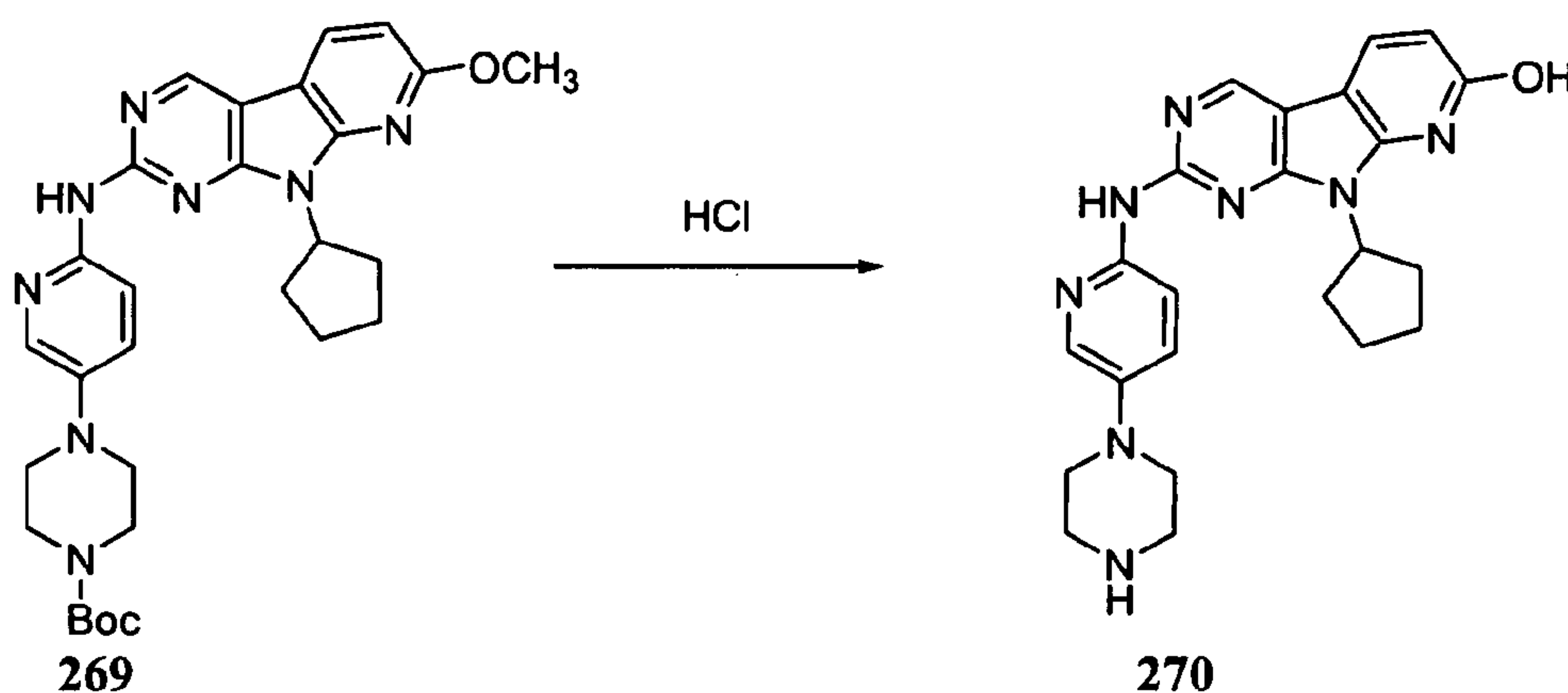
(MgSO<sub>4</sub>) and evaporated to give a pale yellow solid, 82 mg. This residue was dissolved in dioxane (2 mL) and methanol (2 mL) and 1 mL of a saturated solution of HCl in dioxane was added. ethyl acetate (30 mL) followed by diethyl ether (30 mL) were added to precipitate the HCl salt, which was collected and dried *in vacuo* to give compound **266** as a yellow solid (77 mg, 84%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 9.24 - 9.36 (m, 4 H) 9.19 (s, 1 H) 8.52 (s, 1 H) 7.97 (s, 1 H) 7.92 - 7.96 (m, 1 H) 7.44 - 7.54 (m, 1 H) 6.83 (d, *J*=8.56 Hz, 1 H) 5.31 - 5.43 (m, 1 H) 3.94 (s, 3 H) 3.33 - 3.41 (m, 4 H) 3.21 (br. s., 4 H) 1.95 - 2.11 (m, 4 H) 1.70 (none, 2 H) ppm.

### EXAMPLE 183



270

**9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-ol**

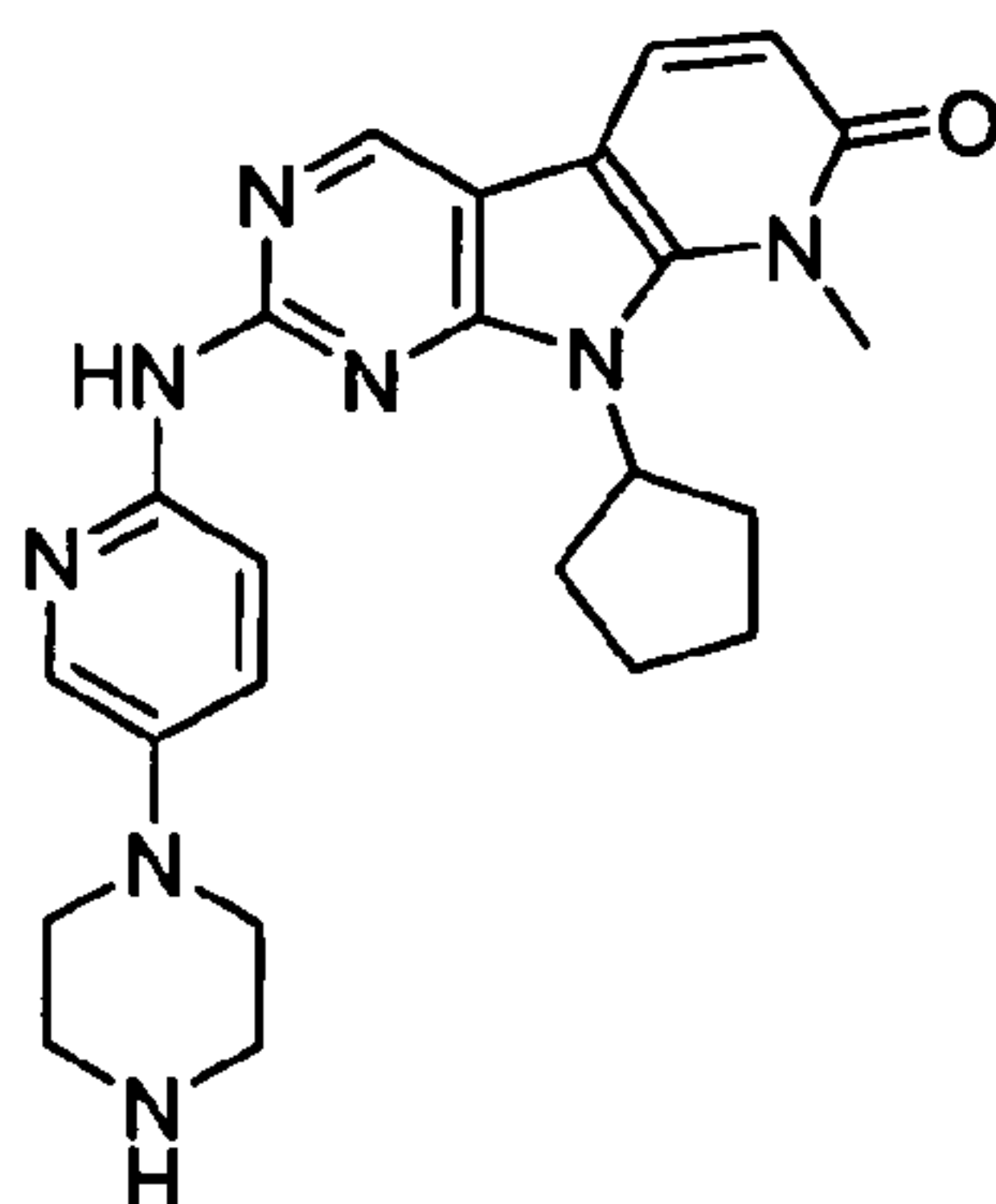


**9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[3',2':4,5]-pyrrolo[2,3-d]pyrimidin-7-ol (270):** A 10 mL reaction tube vessel was charged with compound **269** (56.0 mg, 103 μmol) and concentrated hydrochloric acid (2.00 mL, 103 μmol). The reaction was heated with microwave energy (300W) at 120°C for 1 hour, then an additional 30 minutes at 140°C. The resulting solution was filtered through a 0.45 μm filter and washed with water. The solvent was removed *in vacuo*, and the residue coevaporated with water (10 mL) and then



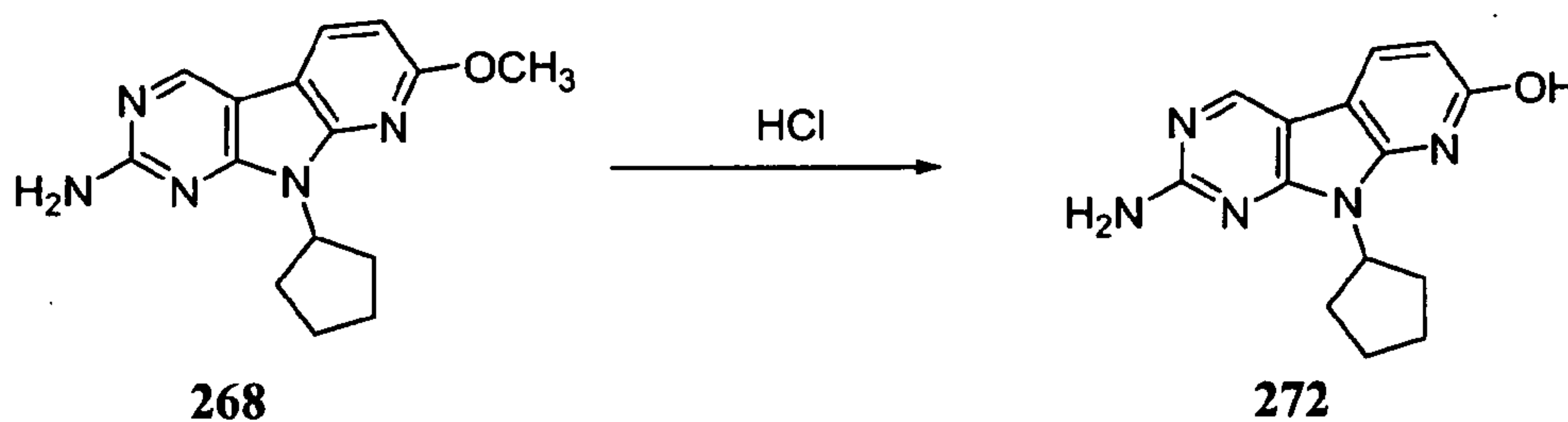
methanol (2X, 10 mL) to give compound **270** as a yellow solid (48 mg). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 11.63 - 11.91 (m, 2 H) 9.40 (br. s., 4 H) 9.19 (s, 1 H) 8.50 (d, *J* = 8.61 Hz, 1 H) 8.04 (d, *J* = 2.74 Hz, 1 H) 7.99 (dd, *J* = 9.39, 2.74 Hz, 1 H) 7.51 (d, *J* = 9.39 Hz, 1 H) 6.69 - 6.78 (m, 1 H) 5.35 (quin, *J* = 8.71 Hz, 1 H) 3.37 - 3.51 (m, 4 H) 3.20 - 3.34 (m, 4 H) 2.06 - 2.18 (m, 2 H) 1.93 - 2.06 (m, 2 H) 1.66 - 1.82 (m, 2 H) ppm.

#### EXAMPLE 184



271

**9-Cyclopentyl-8-methyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one**

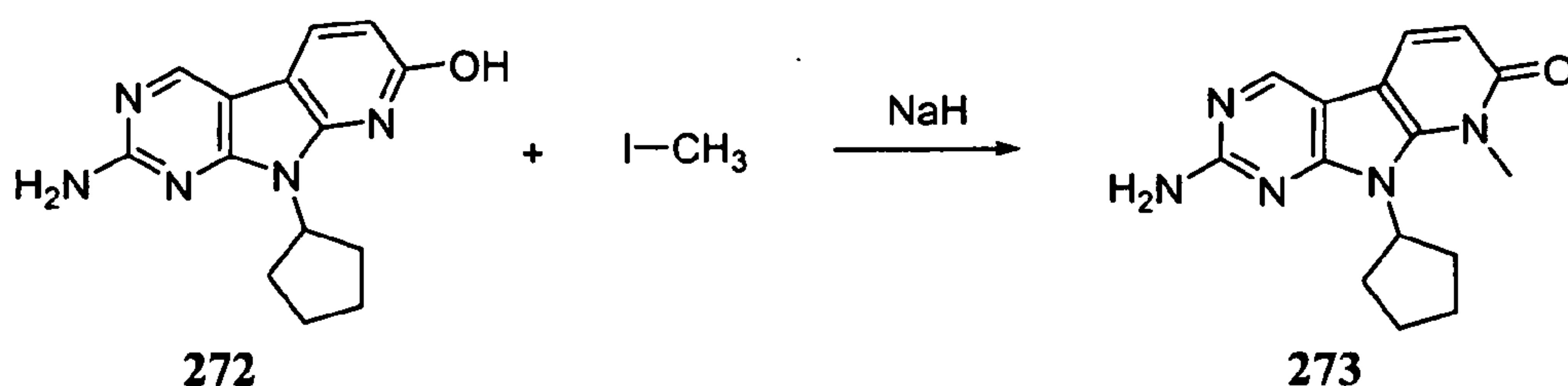


268

272

**2-Amino-9-cyclopentyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-ol (272):**

Compound **268** (150 mg, 529 μmol) was dissolved in conc. hydrochloric acid (2 mL). The reaction was heated with microwave energy (300W) for 40 min. at 140°C. The resulting solution was added to aqueous NaHCO<sub>3</sub> (20 mL, 50% sat.) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give an orange tar. Silica gel chromatography (gradient elution hexanes + 2.5% TEA/0-100% ethyl acetate+2.5% TEA) afforded compound **272** as a tan solid, 120 mg (84%).

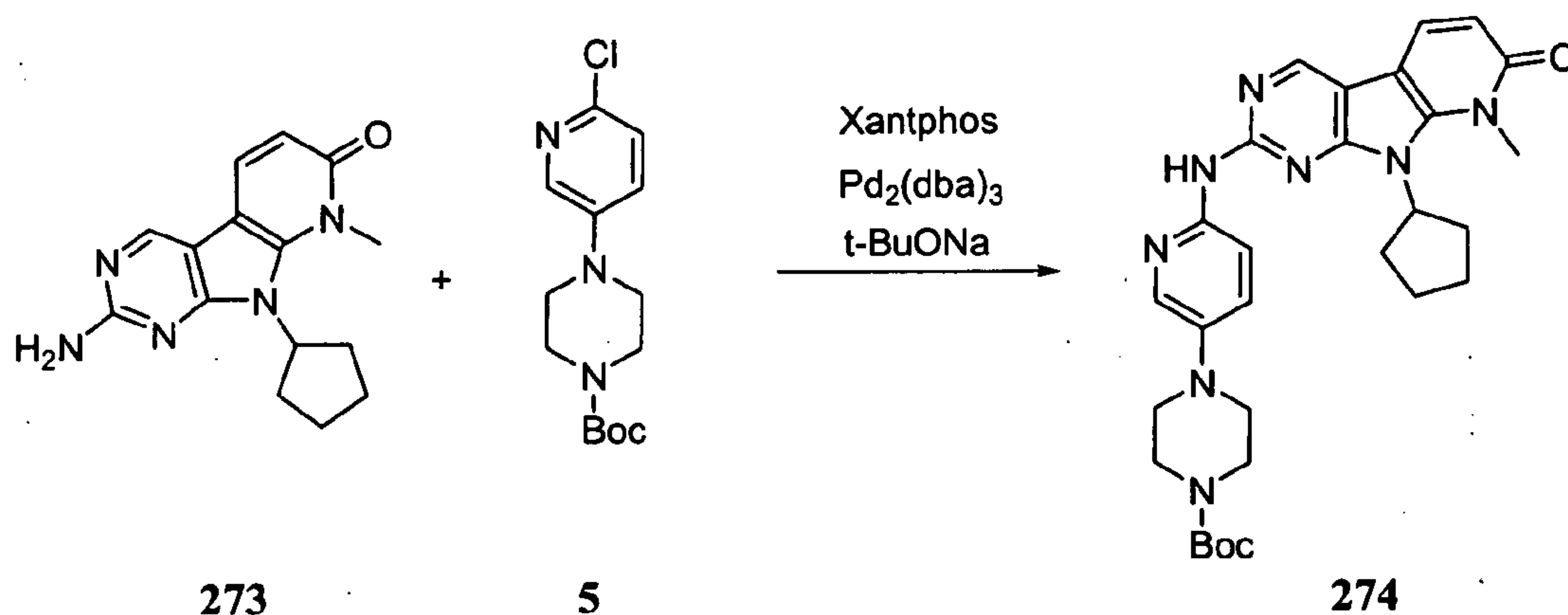


272

273

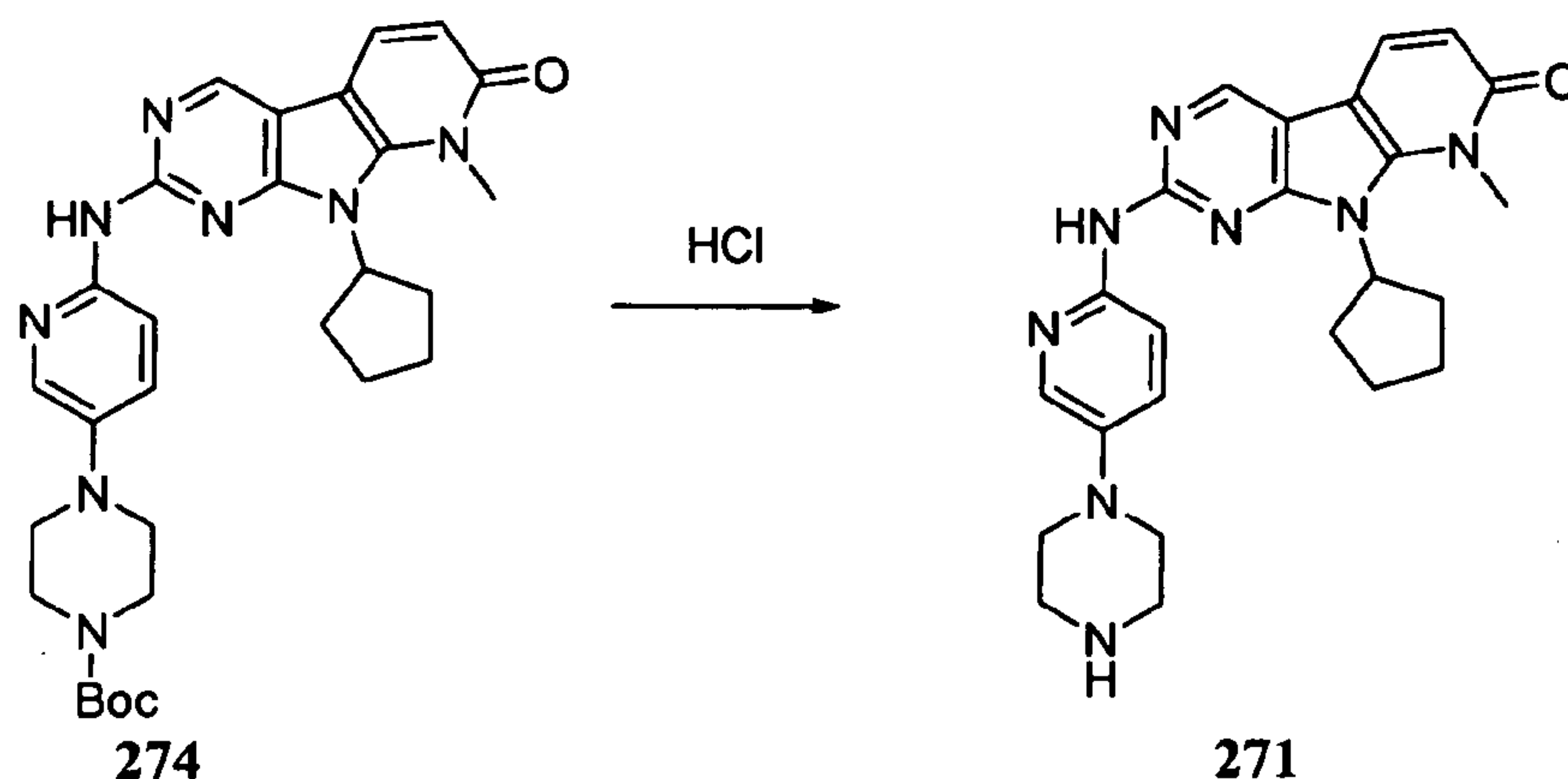


**2-Amino-9-cyclopentyl-8-methyl-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one (273):** Compound **272** (100 mg, 0.37 mmol) was dissolved in dry DMF (1 mL). Sodium hydride, 60% dispersion in oil (16.0 mg, 0.4 mmol) was added and the reaction stirred at 60°C for 20 minutes. Iodomethane (26.5  $\mu$ l, 423  $\mu$ mol) was added and the reaction stirred at 60°C for 2 hr. The solution was allowed to cool and added to water (10 mL) and aqueous  $K_2CO_3$  (saturated, 2 mL), and extracted with ethyl acetate (2X 30 mL), and dichloromethane+10% methanol (2X 30 mL). The combined organics were dried ( $MgSO_4$ ) and evaporated to give an orange solid. Silica gel chromatography (gradient elution hexanes + 2.5% TEA/0-70% ethyl acetate+2.5% TEA) afforded compound **273** as a white solid, 64 mg (61%).



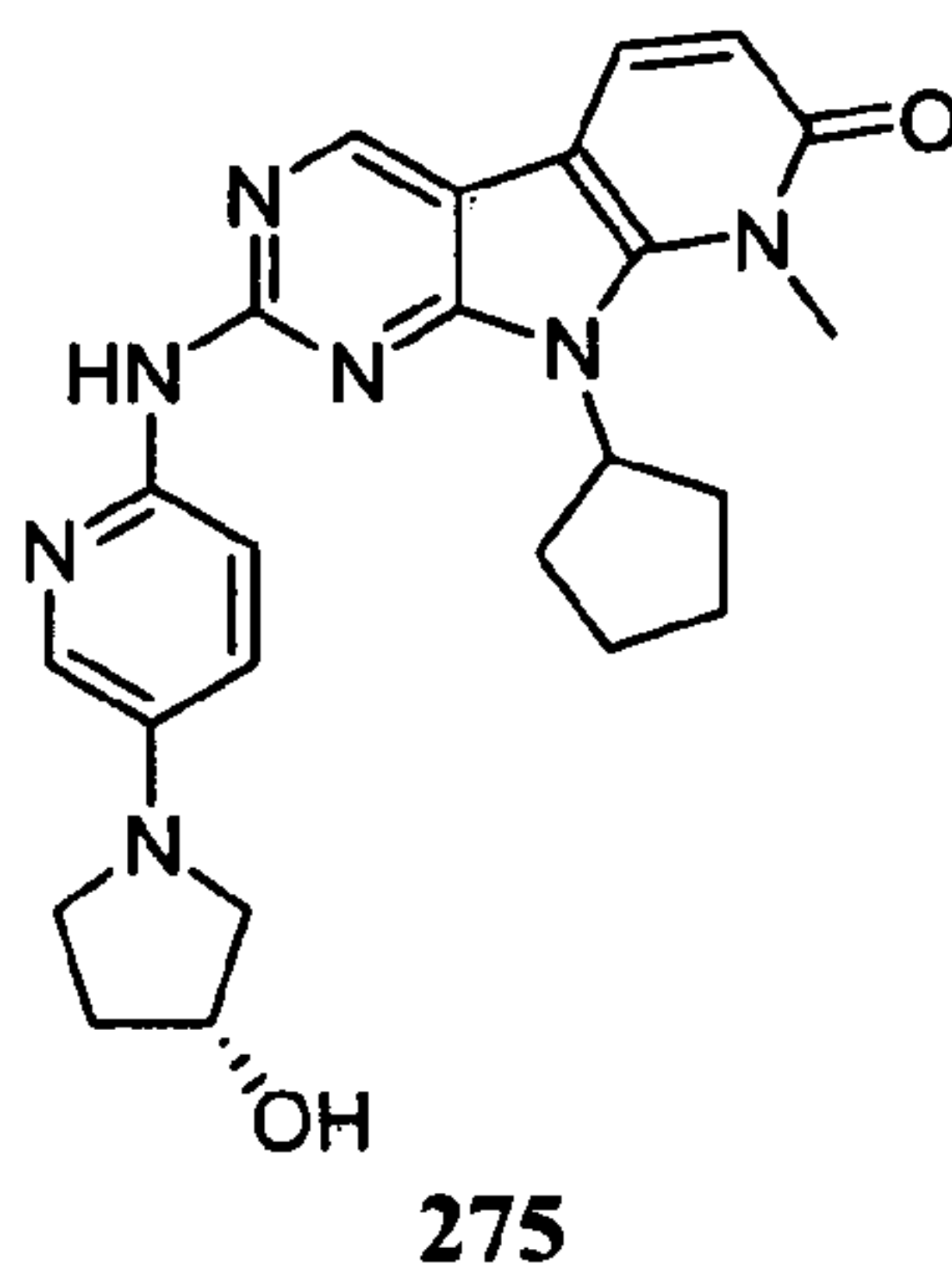
**tert-Butyl 4-(6-((9-cyclopentyl-8-methyl-7-oxo-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (274):** A 10 mL reaction vessel was charged with compound **273** (61.0 mg, 215  $\mu$ mol), compound **5** (70.5 mg, 237  $\mu$ mol), and sodium *t*-butoxide (62.1 mg, 646  $\mu$ mol), followed by dioxane (3 mL). The reaction was purged thoroughly with argon. 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (24.9 mg, 43.1  $\mu$ mol) and tris(dibenzylideneacetone)dipalladium (0) (19.7 mg, 21.5  $\mu$ mol) were added, and the reaction was again purged with argon. The reaction was heated with microwave energy (300W) at 120°C for 90 minutes. The resulting solution was diluted with ethyl acetate (75 mL) and added to water (75 mL). The layers were separated and the aqueous phase extracted with ethyl acetate (75 mL), followed by dichloromethane (75 mL). The combined organics were dried ( $MgSO_4$ ) and evaporated to give the product as a tan solid. Recrystallization from boiling ethyl acetate gave compound **274** as a white solid (74 mg, 63%).





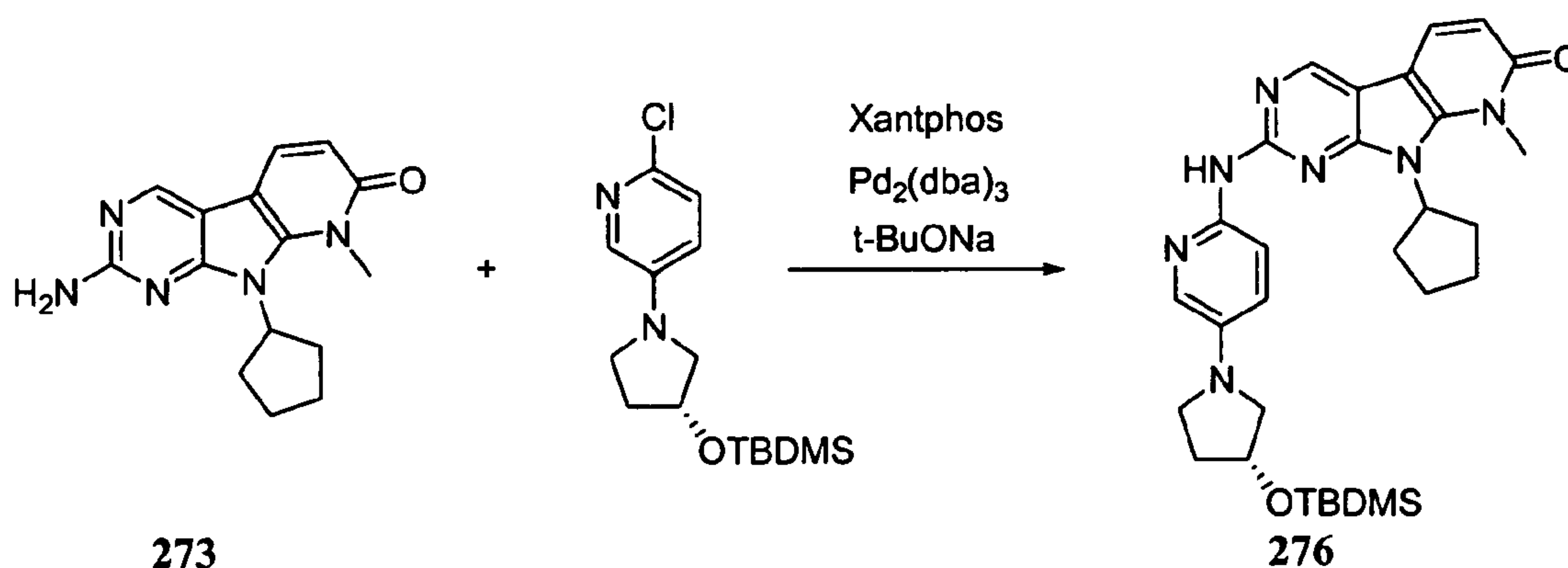
**9-Cyclopentyl-8-methyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one (271):** Compound 274 (51 mg) was dissolved in 2 mL dioxane. Dioxane (1 mL) saturated at room temperature with HCl was added, followed by 1 mL methanol to aid solution. The reaction was stirred at room temperature for 80 min. The solution was then added dropwise to diethyl ether (8 mL) and the resulting precipitate was collected and dried *in vacuo* to give compound 271 as a yellow solid (26 mg, 62%). <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 11.75 (br. s., 1 H) 9.36 (br. s., 2 H) 9.20 (s, 1 H) 8.53 (d, *J* = 8.31 Hz, 1 H) 7.91 - 8.01 (m, 2 H) 7.49 (d, *J* = 9.29 Hz, 1 H) 6.83 (d, *J* = 8.56 Hz, 1 H) 5.37 (quin, *J* = 8.56 Hz, 1 H) 3.35 - 3.43 (m, 5 H) 1.94 - 2.13 (m, 4 H) 1.64 - 1.79 (m, 2 H) ppm.

#### EXAMPLE 185

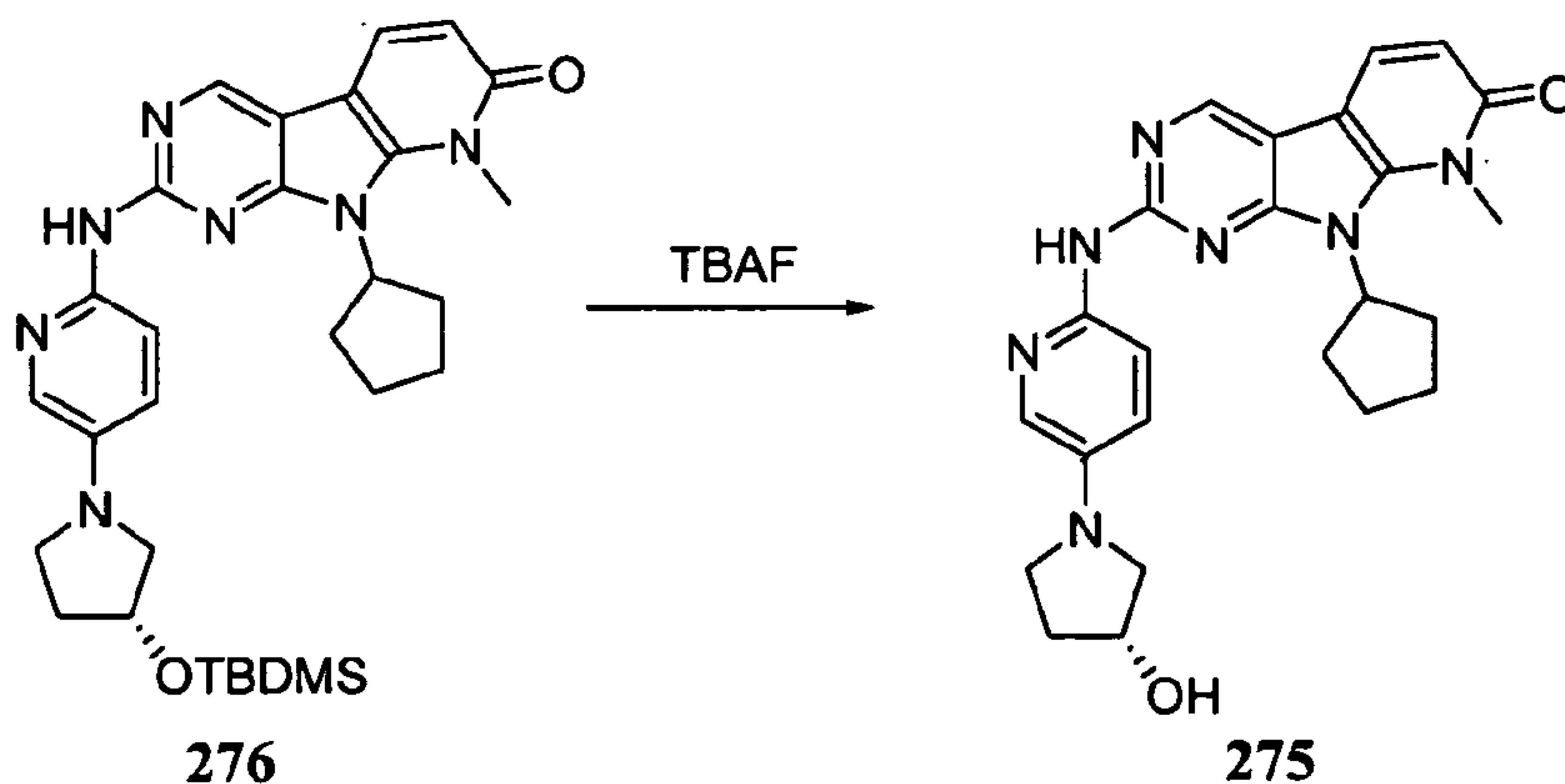


**9-Cyclopentyl-2-((5-((3R)-3-hydroxy-1-pyrrolidinyl)-2-pyridinyl)amino)-8-methyl-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one**





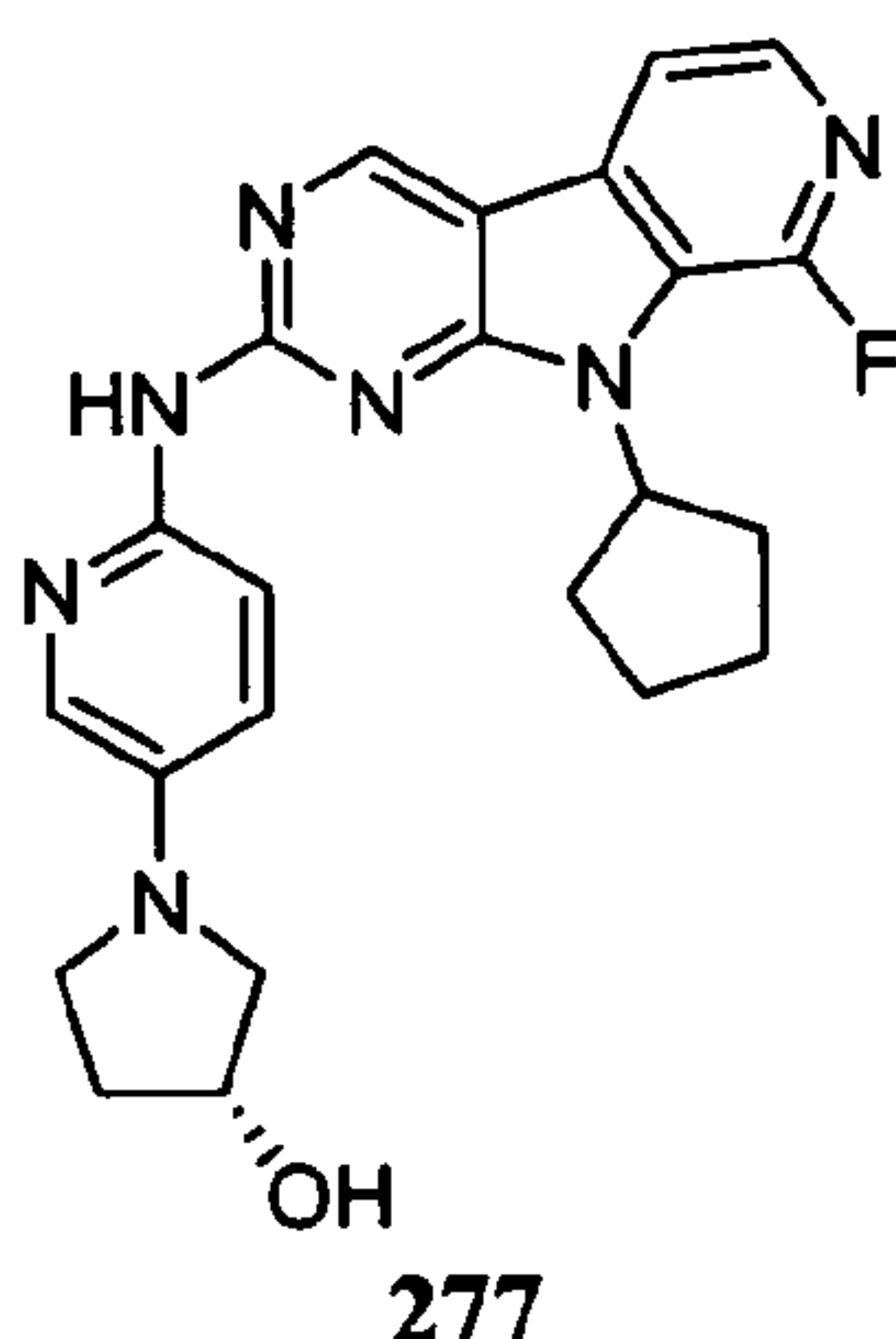
**9-Cyclopentyl-2-((5-((3R)-3-(tert-butyldimethylsilyloxy)pyrrolidin-1-yl)-2-pyridinyl)amino)-8-methyl-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]-pyrimidin-7-one (276):** A 10 mL reaction vessel was charged with compound **273** (55 mg, 193  $\mu$ mol), (R)-5-(3-(*t*-butyldimethylsilyloxy)pyrrolidin-1-yl)-2-chloropyridine (60.3 mg, 193  $\mu$ mol), tris(dibenzylideneacetone)dipalladium (0) (13 mg, 14  $\mu$ mol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (17 mg, 29  $\mu$ mol), and sodium *t*-butoxide (22 mg, 231  $\mu$ mol) in 2 mL dry dioxane. The reaction was purged with argon and heated with microwave energy (300W) for 2 hours at 120°C. The resulting solution was taken up in ethyl acetate (40 mL) and washed with water (30 mL), and brine (30 mL). The organics were dried (MgSO<sub>4</sub>) and evaporated to give a brown oil. Silica gel chromatography (gradient elution hexanes + 2.5% TEA/0-50% ethyl acetate+2.5% TEA) afforded compound **276** as a yellow solid (53 mg, 49%).



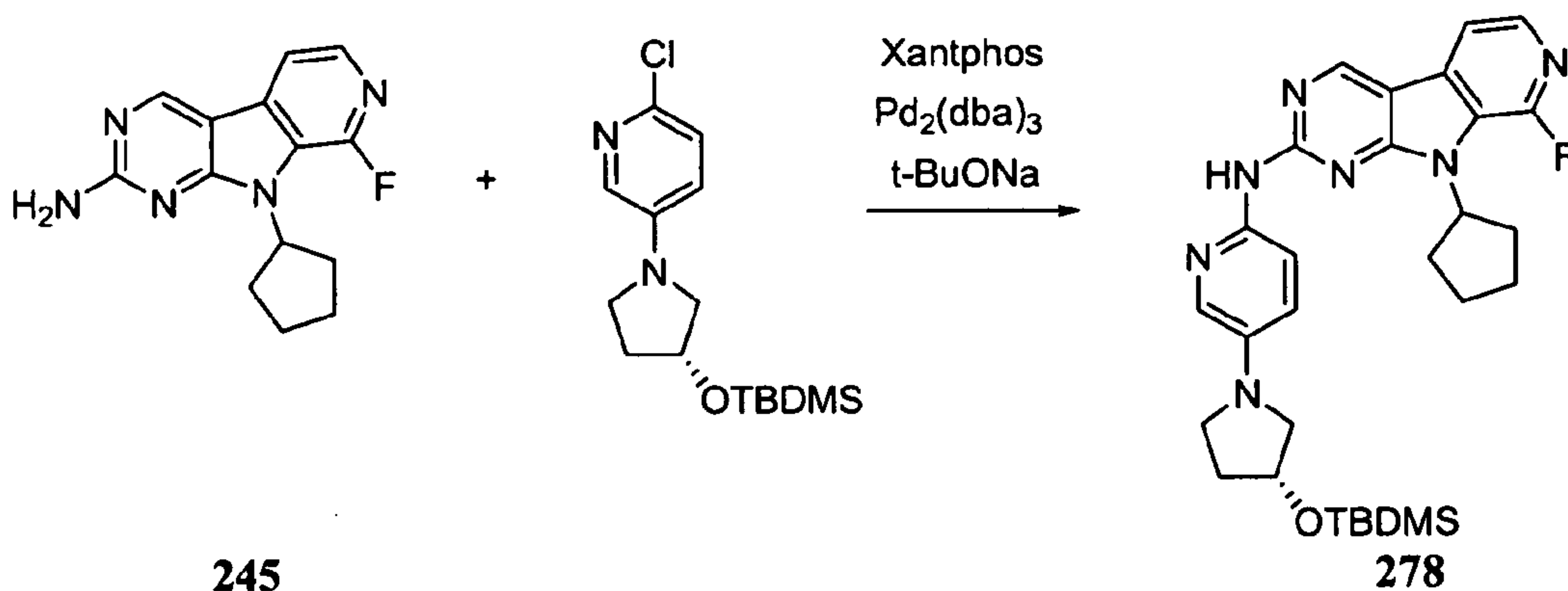
**9-Cyclopentyl-2-((5-((3R)-3-hydroxy-1-pyrrolidinyl)-2-pyridinyl)amino)-8-methyl-8,9-dihydro-7H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-7-one (275):** Compound **276** (53.0 mg, 94.7  $\mu$ mol) was dissolved in THF (2 mL). Tetrabutylammonium fluoride, 1.0M in THF (0.500 mL, 500  $\mu$ mol) was added and the reaction was stirred at room temperature for 4.5 hours. The solvent was evaporated to give an orange oil. Preparative reverse phase HPLC (gradient elution 0.1% TFA in water/10-70% acetonitrile) afforded a yellow solid. This residue



was added to aqueous  $\text{NaHCO}_3$  (saturated, 10 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ( $\text{MgSO}_4$ ) and evaporated to give a yellow solid. This product was taken up in methanol (2 mL) and 1 mL methanol (saturated at room temperature with HCl) was added. 20 mL diethyl ether was added to precipitate the product, which was washed with ether and dried *in vacuo* to give compound **275** as yellow solid (21 mg, 50%).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.21 (s, 2 H) 8.56 (d,  $J$ = 8.56 Hz, 2 H) 7.63 (d,  $J$ = 2.69 Hz, 4 H) 7.44 - 7.57 (m, 2 H) 6.87 (d,  $J$ = 8.56 Hz, 2 H) 5.43 (quin,  $J$ = 8.62 Hz, 1 H) 4.47 (br. s., 1 H) 4.00 (s, 3 H) 3.09 - 3.21 (m, 1 H) 2.00 - 2.22 (m, 5 H) 1.90 - 2.04 (m, 1 H) 1.66 - 1.85 (m, 2 H) ppm.

**EXAMPLE 186a**

**(3R)-1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-pyrrolidinol**

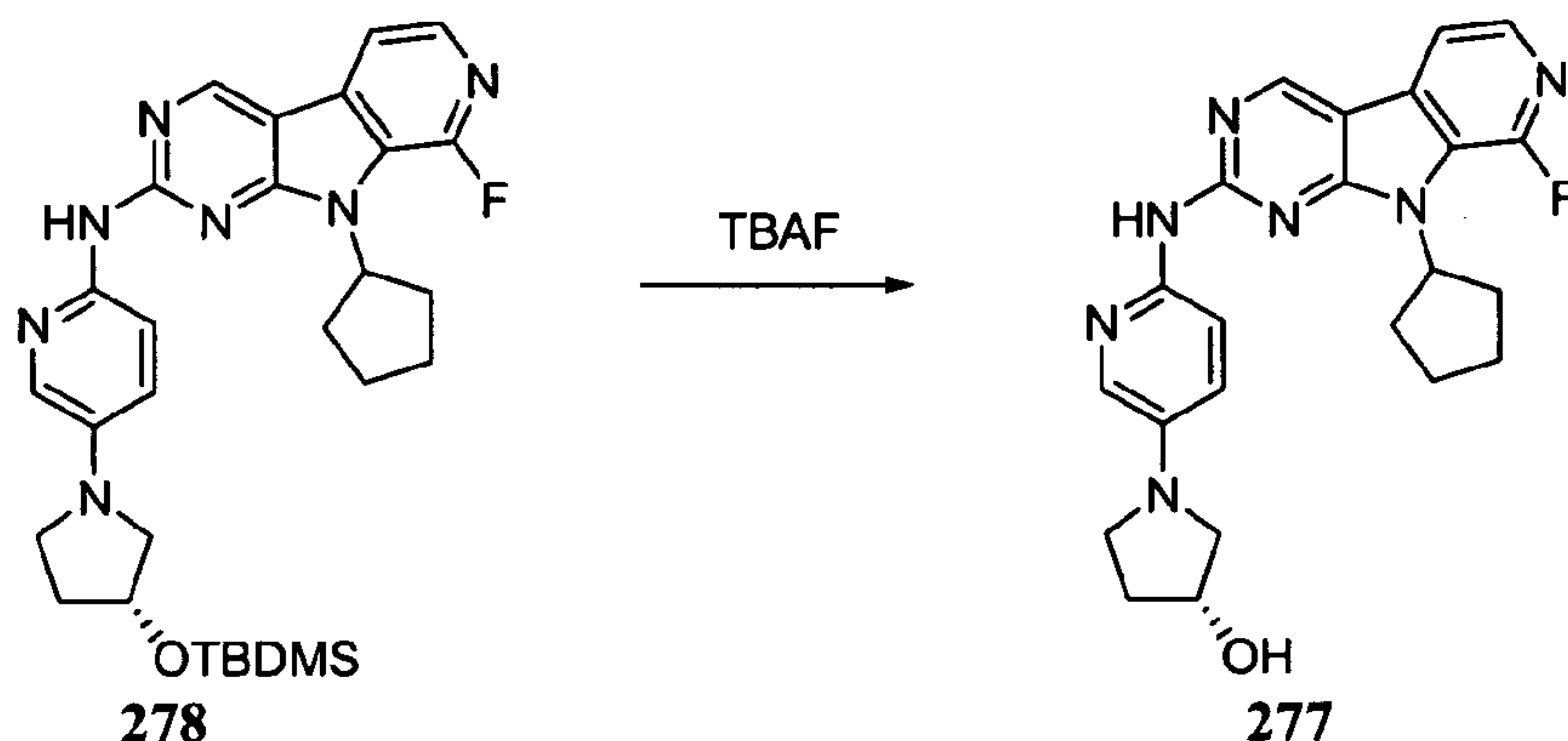


**N-(5-((3R)-3-((tert-butyl(dimethyl)silyl)oxy)-1-pyrrolidinyl)-2-pyridinyl)-9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**(278):** A 10 mL reaction vessel was charged with compound **245** (75.0 mg, 276  $\mu\text{mol}$ ), (R)-5-(3-(*t*-butyldimethylsilyloxy)pyrrolidin-1-yl)-2-chloropyridine (86.5 mg, 276  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (0) (19.0 mg, 20.7  $\mu\text{mol}$ ), 4,5-bis(diphenylphosphino)-

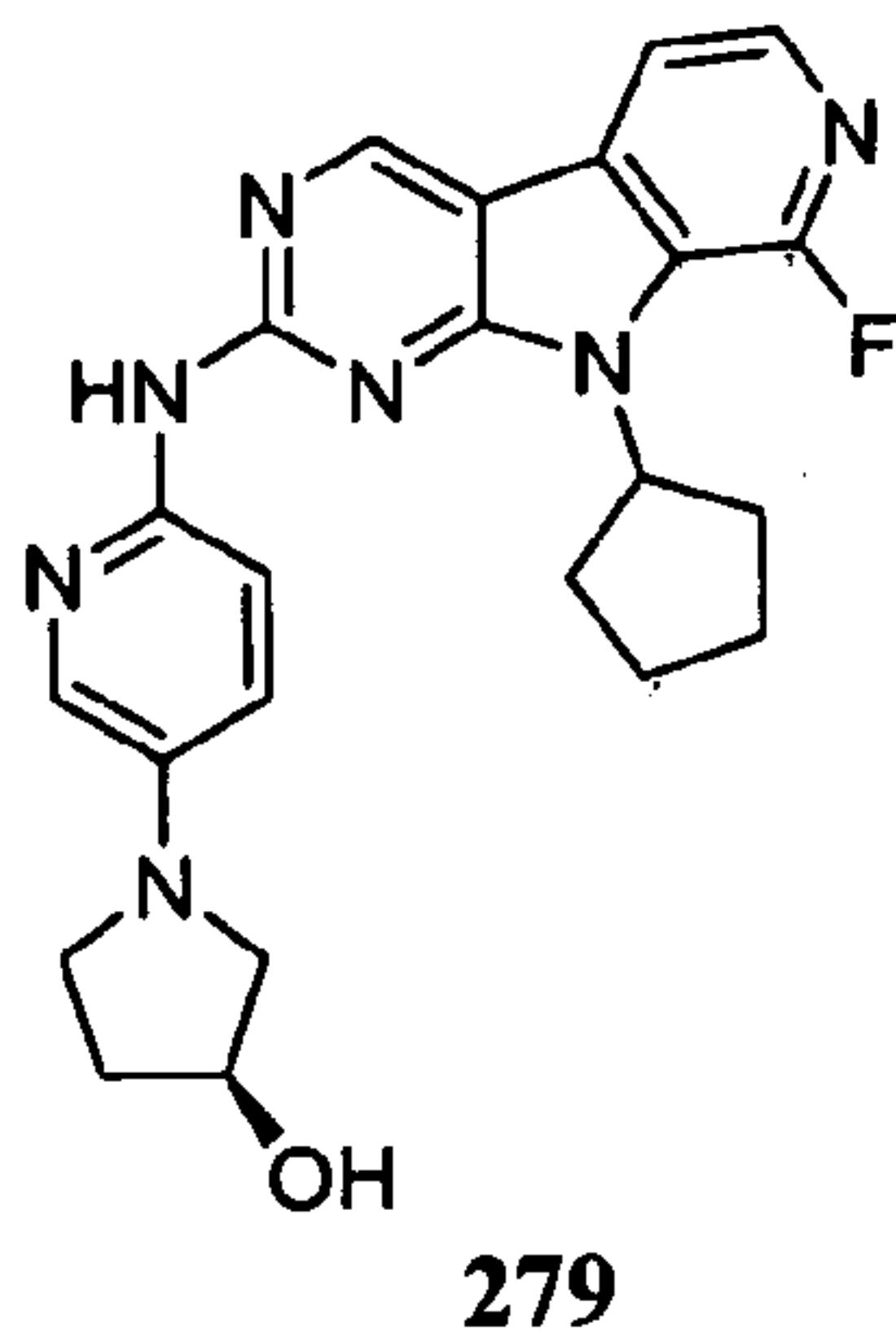


9,9-dimethyl-9H-xanthene (24.0 mg, 41.5  $\mu$ mol), sodium *t*-butoxide (53.1 mg, 553  $\mu$ mol), and dioxane (1.5 mL). The reaction was heated with microwave energy (300W) for 2 hours at 120°C. in the resulting solution was added to ethyl acetate (40 mL) and washed with water (30 mL) followed by brine (30 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated to give an orange oil. Silica gel chromatography (gradient elution 35% ethyl acetate in hexanes) afforded compound **278** as a yellow solid (59 mg, 39%)

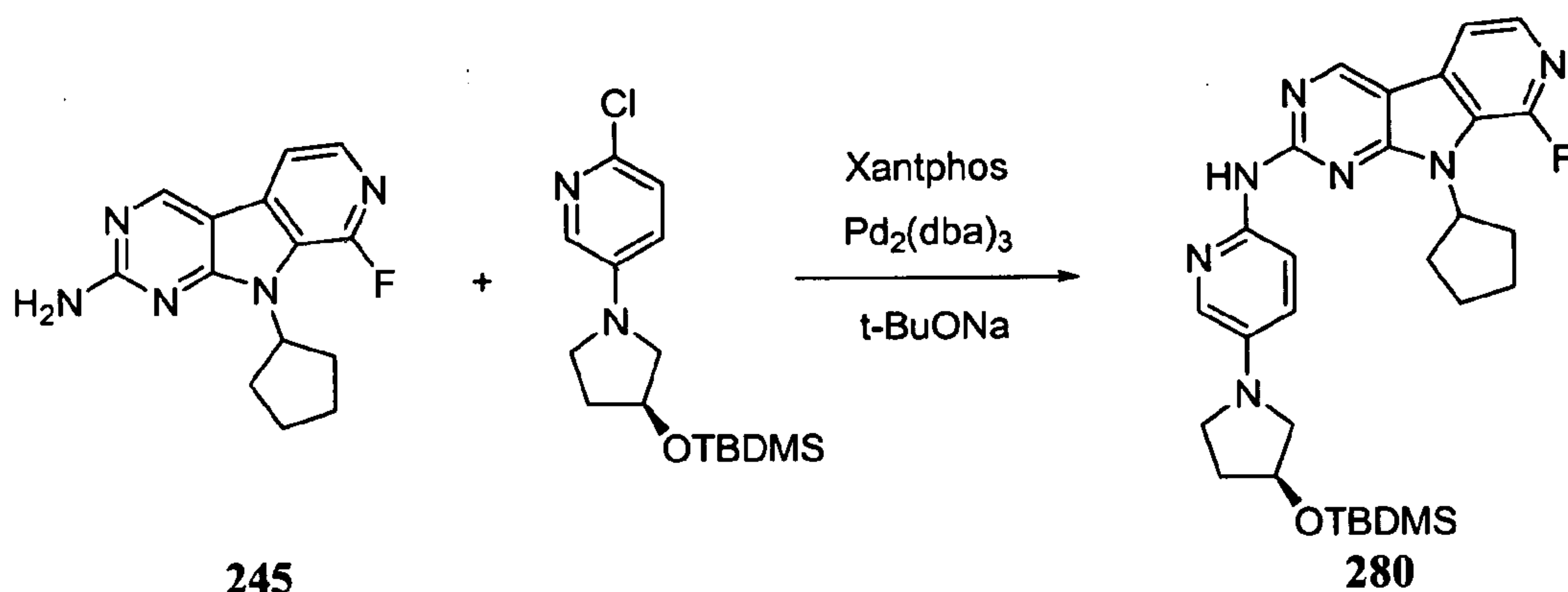


**(3R)-1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-pyrrolidinol (277):** Compound **278** (58 mg, 106  $\mu$ mol) was dissolved in THF (2 mL). Tetrabutylammonium fluoride, 1.0M in THF (0.5 mL, 0.500 mmol) was added and the reaction stirred at room temperature for 4 hours. The solvent was removed to give an orange oil. Silica gel chromatography (gradient elution ethyl acetate+2.5% TEA/0-5% methanol) afforded a yellow solid. This residue was taken up in methanol (2 mL) and HCl in ethanol (1.0M, 0.5 mL) was added. Diethyl ether (20 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **277** as a yellow solid (23 mg, 50%).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.72 (s, 1 H) 9.25 - 9.35 (m, 1 H) 7.94 - 8.11 (m, 4 H) 7.62 - 7.77 (m, 2 H) 7.05 (dd,  $J=8.93, 2.81$  Hz, 1 H) 5.37 - 5.54 (m, 1 H) 4.99 (d,  $J=3.91$  Hz, 1 H) 4.44 (br. s., 1 H) 3.46 (dd,  $J=10.03, 4.89$  Hz, 2 H) 3.05 - 3.16 (m, 1 H) 2.26 - 2.42 (m, 3 H) 1.96 - 2.20 (m, 8 H) 1.85 - 1.96 (m, 2 H) 1.66 - 1.83 (m, 3 H) ppm.

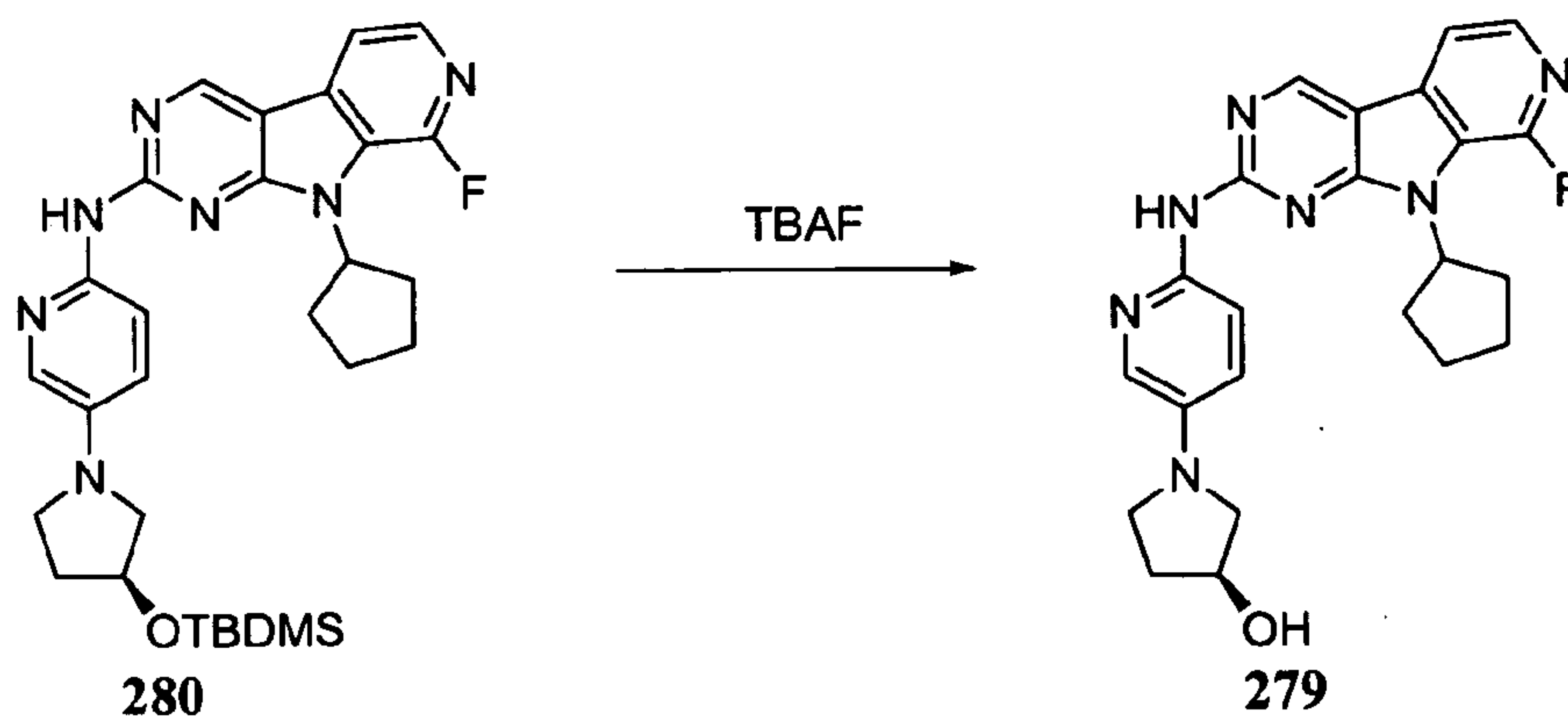


**EXAMPLE 186b**

**(3S)-1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-pyrrolidinol**



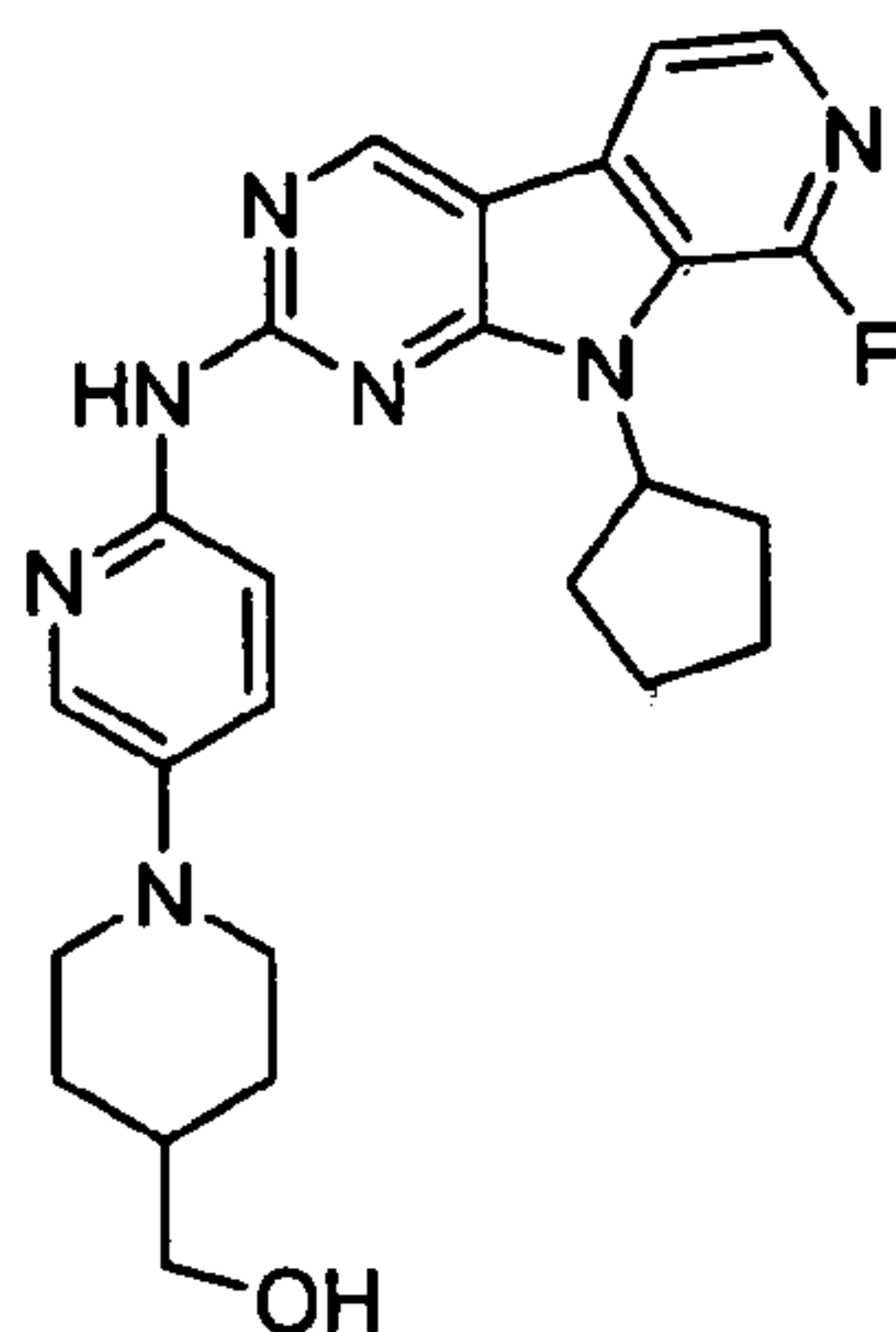
**N-(5-((3S)-3-((tert-butyl(dimethyl)silyl)oxy)-1-pyrrolidinyl)-2-pyridinyl)-9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (280):** Compound 280 was prepared from compound 245 and (S)-5-(3-(tert-butyldimethylsilyloxy)-pyrrolidin-1-yl)-2-chloropyridine using methods described in Example 186a.



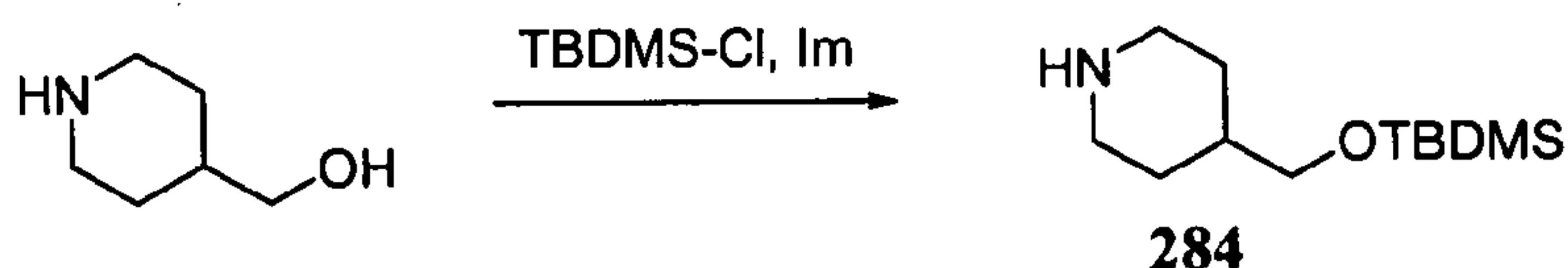
**(3S)-1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-3-pyrrolidinol (279):** Compound 279 was prepared from compound 280 using methods described in Example 186a. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.44 - 9.57



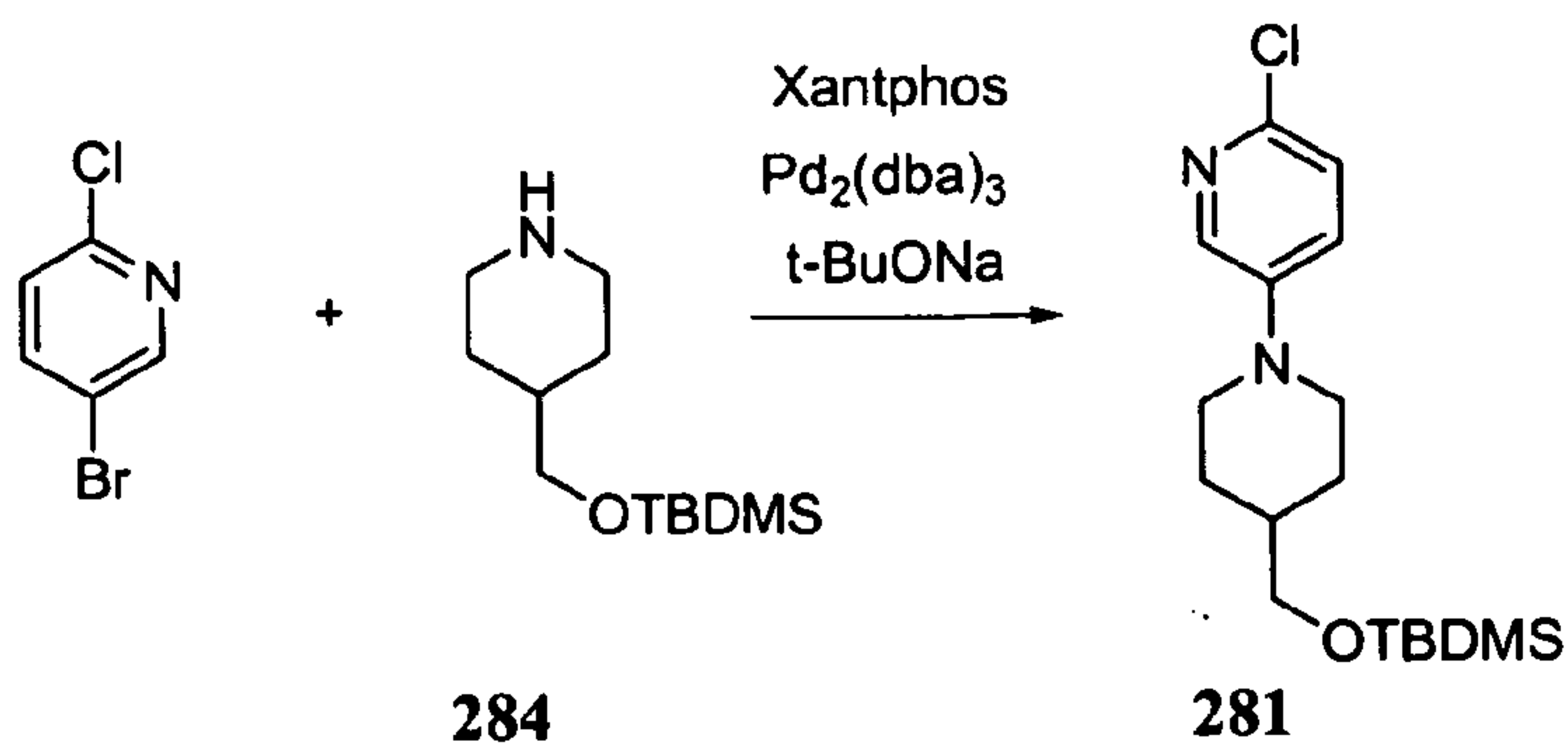
(m, 1 H) 8.22 - 8.33 (m, 1 H) 8.09 - 8.19 (m, 1 H) 7.63 - 7.73 (m, 3 H) 5.45 - 5.59 (m, 1 H) 4.39 - 4.53 (m, 1 H) 3.45 - 3.53 (m, 2 H) 3.39 (none, 3 H) 3.11 - 3.21 (m, 1 H) 3.11 - 3.22 (m, 1 H) 2.20 - 2.34 (m, 2 H) 1.88 - 2.20 (m, 6 H) 1.68 - 1.87 (m, 2 H) ppm

**EXAMPLE 187****283**

**(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)methanol**

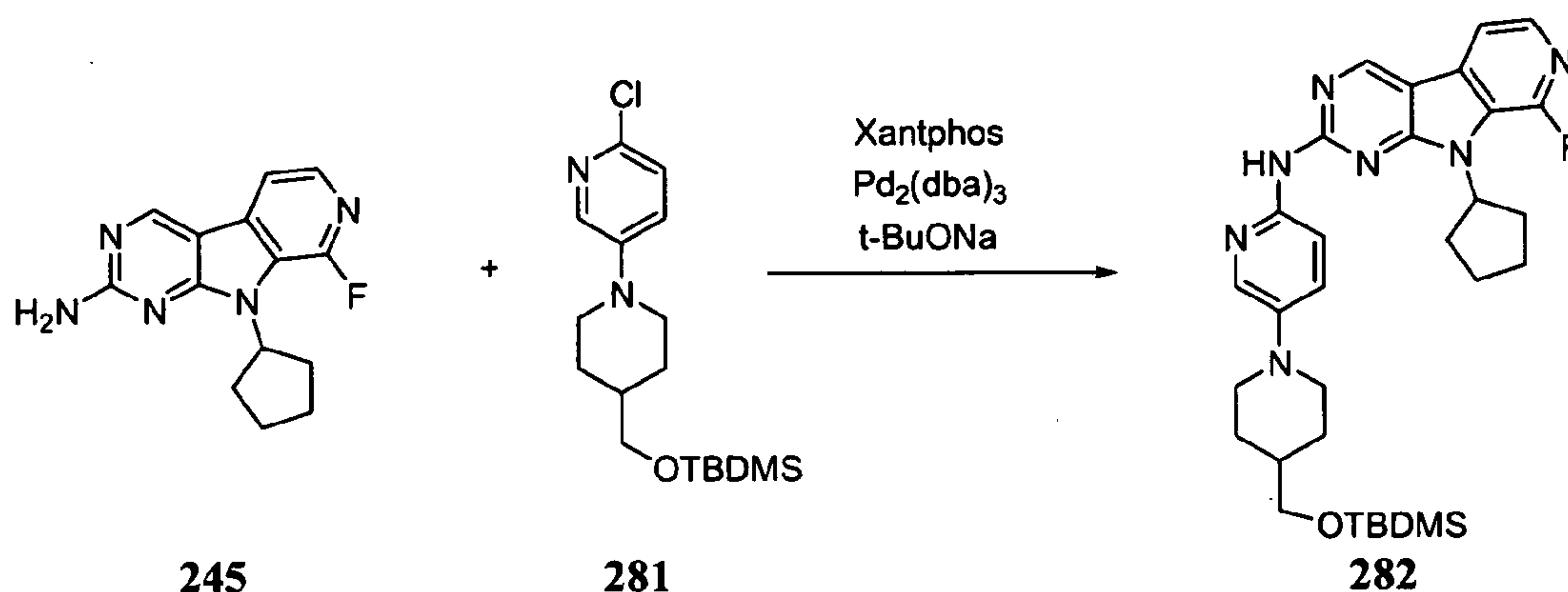
**284**

**4-((*t*-butyldimethylsilyloxy)methyl)piperidine (284):** Piperidin-4-ylmethanol (2.50 g, 21.7 mmol), *t*-butylchlorodimethylsilane (4.13 g, 23.9 mmol), and imidazole (1.48 g, 21.7 mmol) were dissolved in dichloromethane (25 mL) and stirred at room temperature for 18 hours. The reaction was added to aqueous NaHCO<sub>3</sub> (200 mL, 50% saturated) and extracted with dichloromethane (3X 150 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give a yellow oil. Silica gel chromatography (gradient elution dichloromethane+2.5% TEA/0-10% methanol) gave a soft white solid, which was then added to 0.5 M NaOH (100 mL) and extracted with dichloromethane+10% methanol (3X 100 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give compound **284** as a pale yellow oil (4.75 g).

**284****281**



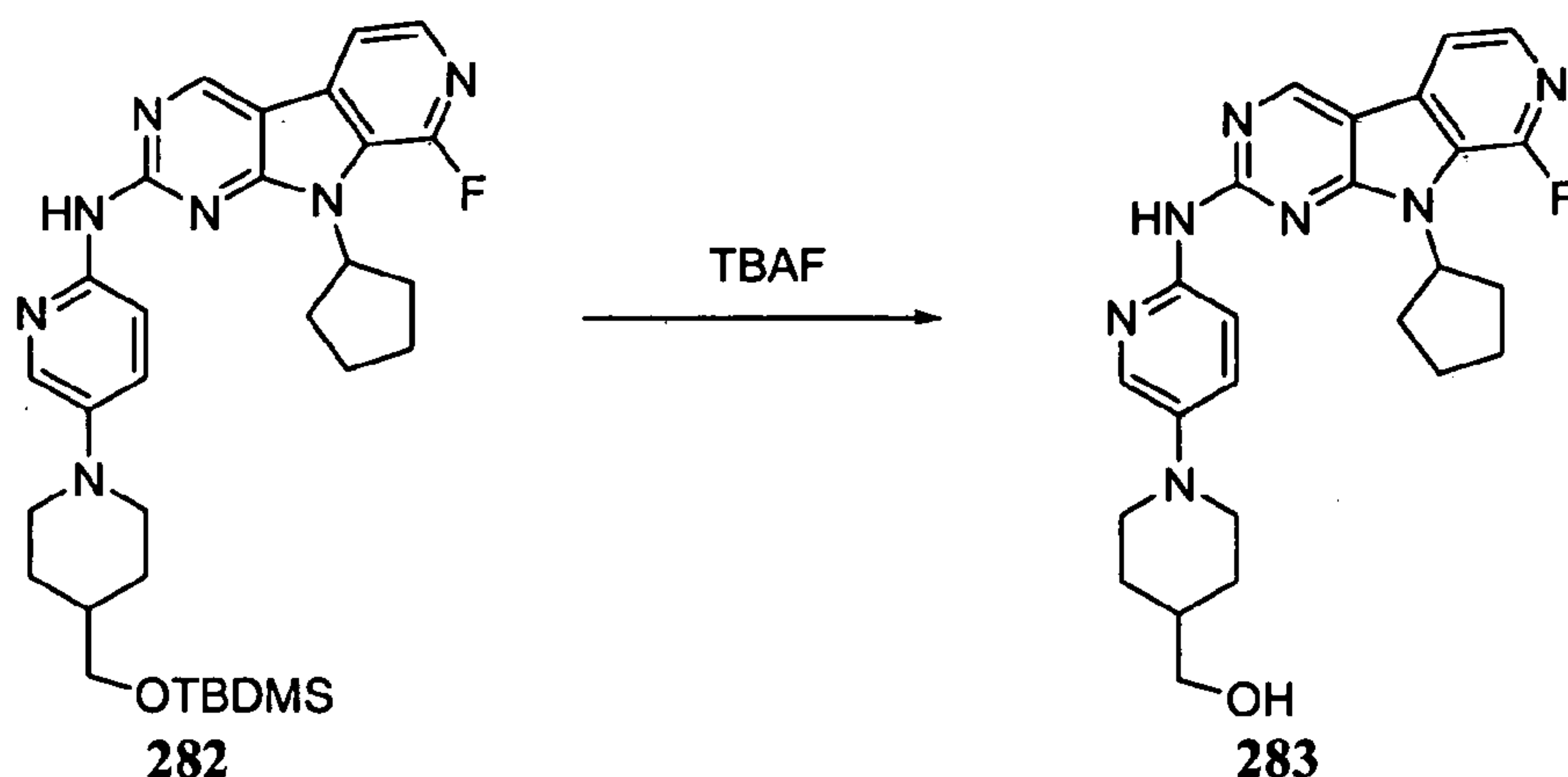
**5-(4-((*t*-butyldimethylsilyloxy)methyl)piperidin-1-yl)-2-chloropyridine (281):** 5-Bromo-2-chloropyridine (1.00 g, 5.20 mmol), 4-((*t*-butyldimethylsilyloxy)-methyl)piperidine (**284**), (1.19 g, 5.20 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.0952 g, 0.104 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.180 g, 0.312 mmol), and sodium *t*-butoxide (0.749 g, 7.79 mmol) were dissolved in 40 mL dioxane under argon. . The reaction was heated at 80°C for 17 hours. The resulting solution was cooled and taken up in ethyl acetate (125 mL) and washed with aqueous K<sub>2</sub>CO<sub>3</sub>, (10%, 100 mL) water (100 mL), and brine (100 mL). The organic phase was dried (MgSO<sub>4</sub>) and evaporated to give an orange oil. Silica gel chromatography (gradient elution hexanes/0-10% ethyl acetate) afforded compound **281** as a white solid (158 mg, 9%).



**N-(5-(4-(((*tert*-Butyl(dimethyl)silyl)oxy)methyl)-1-piperidinyl)-2-pyridinyl)-9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

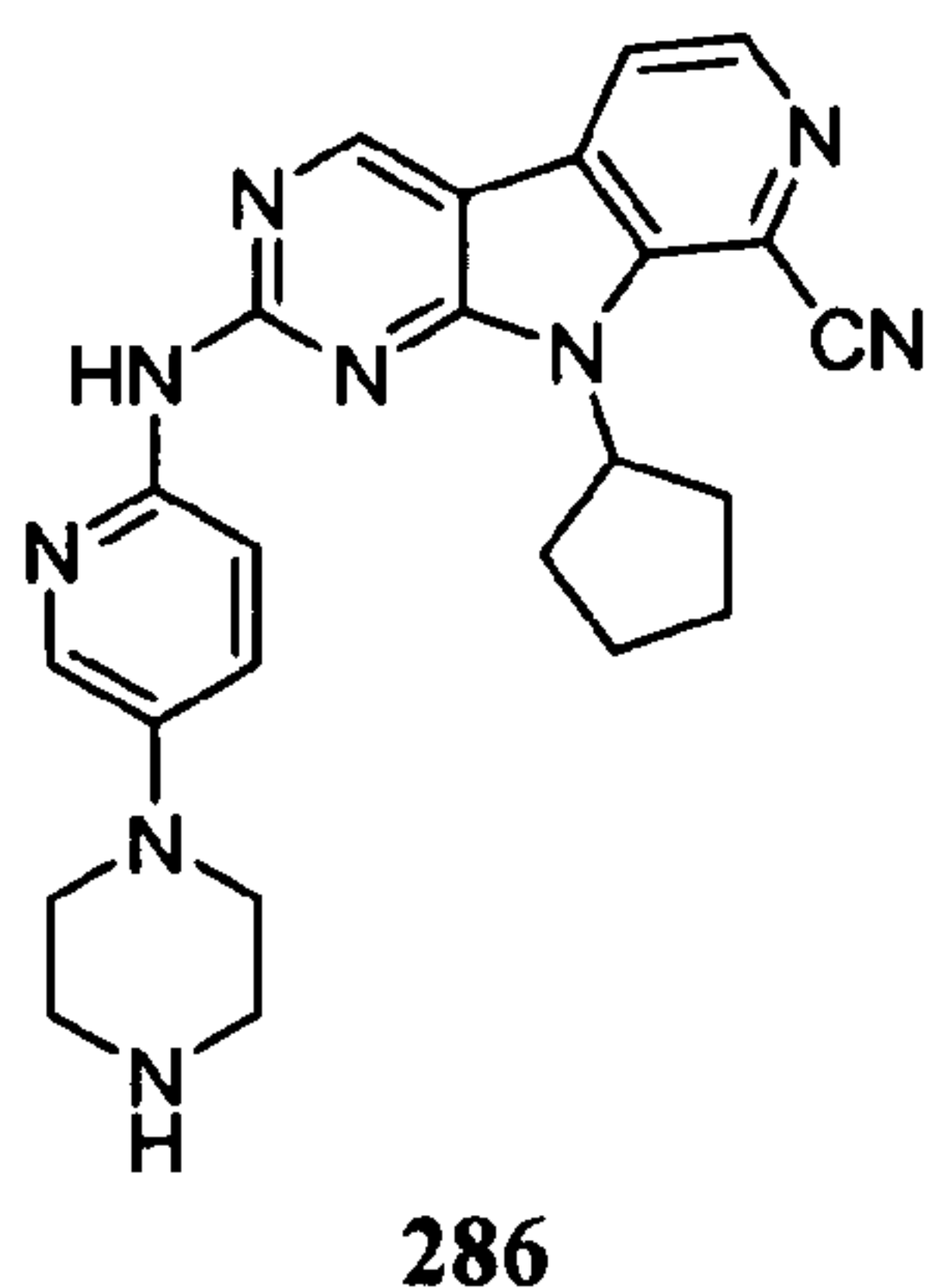
**(282):** A 10 mL reaction vessel was charged with compound **245** (100 mg, 369  $\mu$ mol), compound **281** (126 mg, 369  $\mu$ mol), tris(dibenzylideneacetone)dipalladium (0) (25.3 mg, 27.6  $\mu$ mol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (32.0 mg, 55.3  $\mu$ mol), sodium *t*-butoxide (70.8 mg, 737  $\mu$ mol), and dioxane (1.5 mL). ). The reaction was purged with argon and heated with microwave energy (300W) for 2 hours at 120°C. The resulting solution was added to ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried (MgSO<sub>4</sub>) and evaporated to give an orange oil. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-35% ethyl acetate+2.5% TEA) afforded compound **282** as a yellow solid (121 mg, 57%).





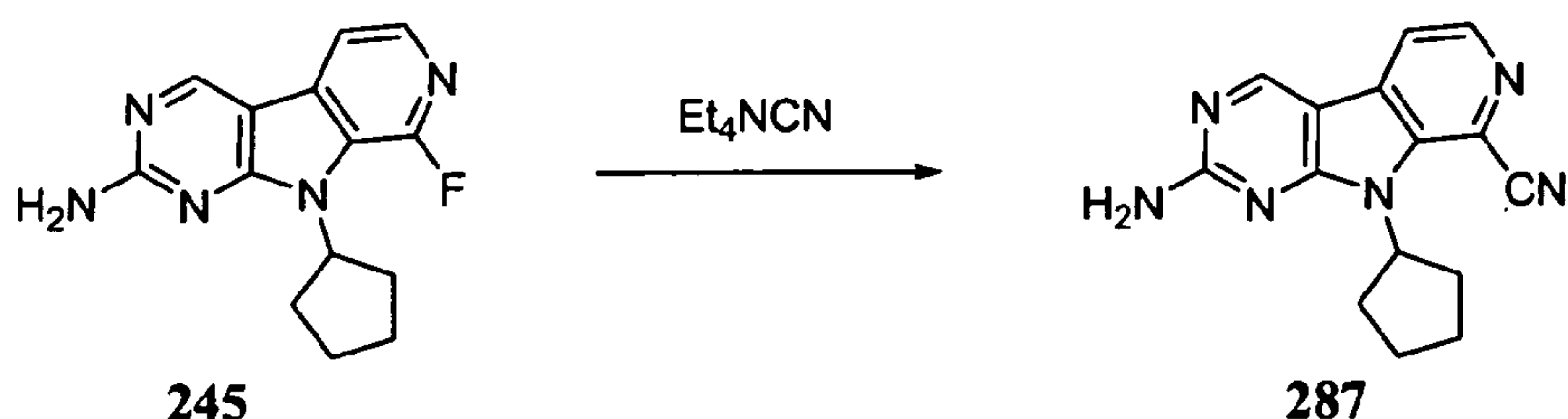
**(1-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)-amino)-3-pyridinyl)-4-piperidinyl)methanol (283):** Compound **282** (118 mg, 205  $\mu$ mol) was dissolved in dry THF (3 mL). Tetrabutylammonium fluoride, 1.0M in THF (0.75 mL, 750  $\mu$ mol) was added and the reaction was stirred at room temperature for 80 minutes. The resulting solution was added to aqueous  $K_2CO_3$  (10%, 30 mL) and extracted with dichloromethane+10% methanol (2X 30 mL). The combined organics were dried ( $MgSO_4$ ) and evaporated to give an orange oil. Silica gel chromatography (gradient elution ethyl acetate+2.5% TEA/0-5% methanol) afforded a yellow solid. This residue was taken up in methanol (1.5 mL) and HCl in ethanol (1.0M, 0.5 mL) was added. Diethyl ether (20 mL) was added to precipitate the product as a yellow solid, which was filtered and dried *in vacuo* to give compound **283** as a yellow solid (26 mg, 27%).  $^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  9.87 (s, 1 H) 9.27 - 9.37 (m, 1 H) 8.11 (d,  $J$ = 9.05 Hz, 1 H) 7.99 - 8.06 (m, 4 H) 7.48 (dd,  $J$ = 9.17, 2.81 Hz, 1 H) 5.46 (quin,  $J$ = 9.11 Hz, 1 H) 4.50 (t,  $J$ = 5.26 Hz, 2 H) 3.70 (d,  $J$ = 11.98 Hz, 2 H) 2.61 - 2.71 (m, 2 H) 2.35 (d,  $J$ = 12.72 Hz, 2 H) 2.10 (br. s., 2 H) 1.95 - 2.06 (m, 2 H) 1.77 (t, 4 H) 1.45 - 1.59 (m, 1 H) 1.28 (qd,  $J$ = 12.23, 3.67 Hz, 2 H) ppm.

#### EXAMPLE 188



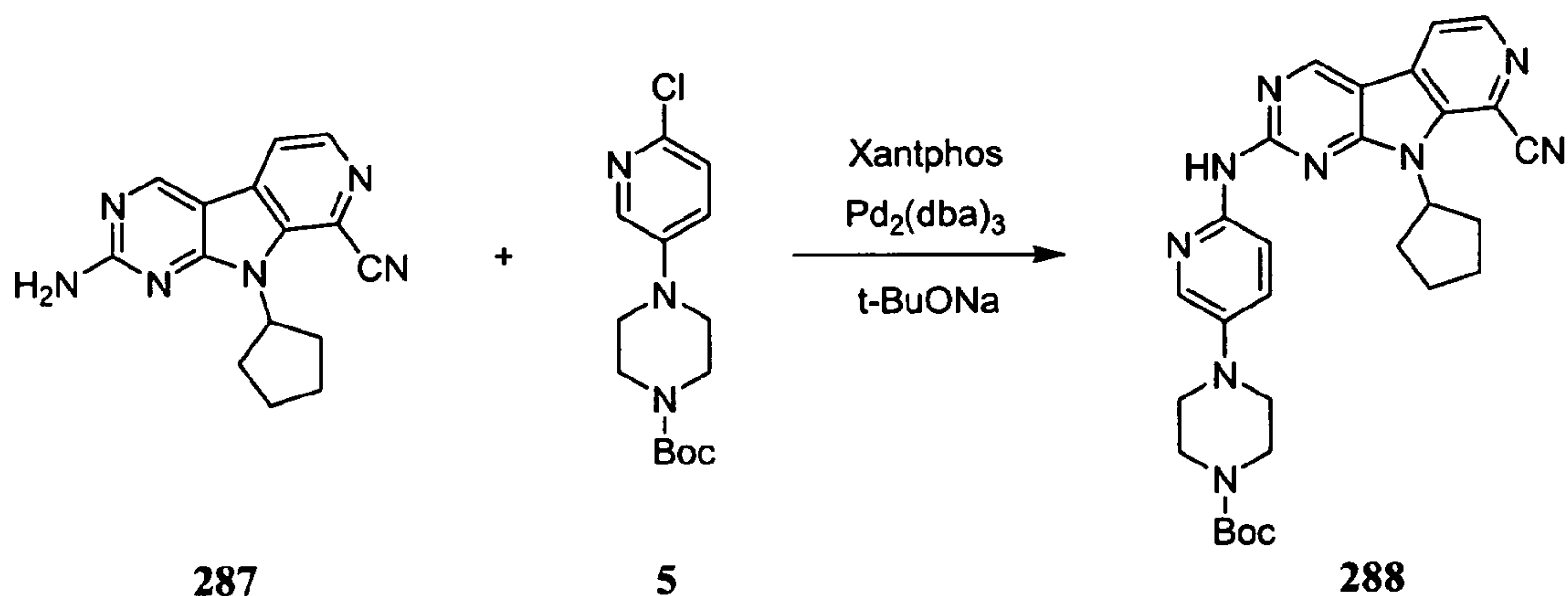
**9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidine-8-carbonitrile**





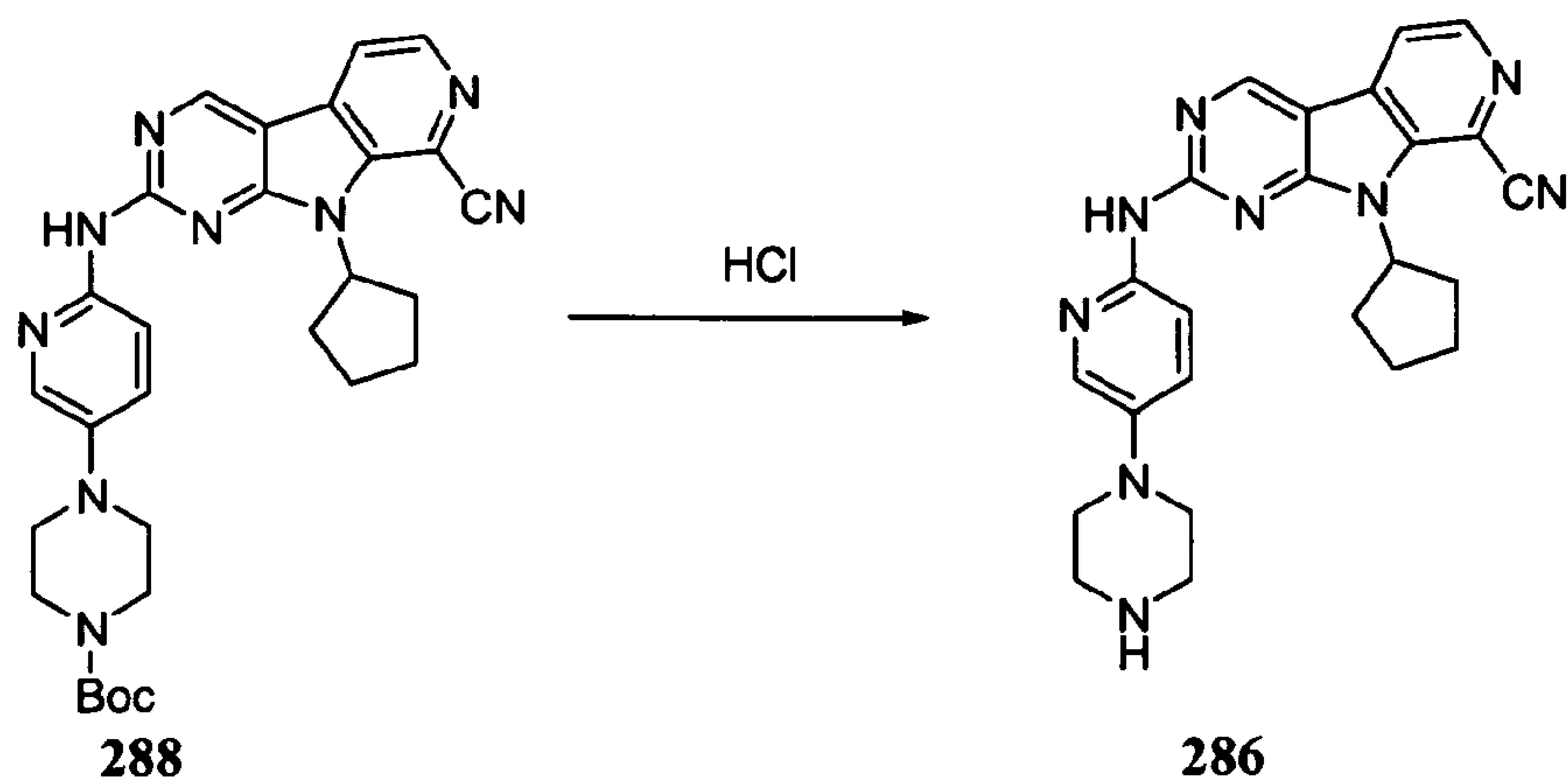
**8-Cyano-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (287):**

Compound **245** (150 mg, 553  $\mu\text{mol}$ ) and tetraethylammonium cyanide (130 mg, 829  $\mu\text{mol}$ ) were dissolved in DMSO (3 mL) and heated at 150°C for 5.5 hours. The reaction was cooled and taken up in ethyl acetate (40 mL). This solution was washed with aqueous  $\text{K}_2\text{CO}_3$  (30 mL), water (30 mL), and brine (30 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated to give an orange solid. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-70% ethyl acetate+2.5% TEA) afforded compound **287** as a tan solid (104 mg, 68%).



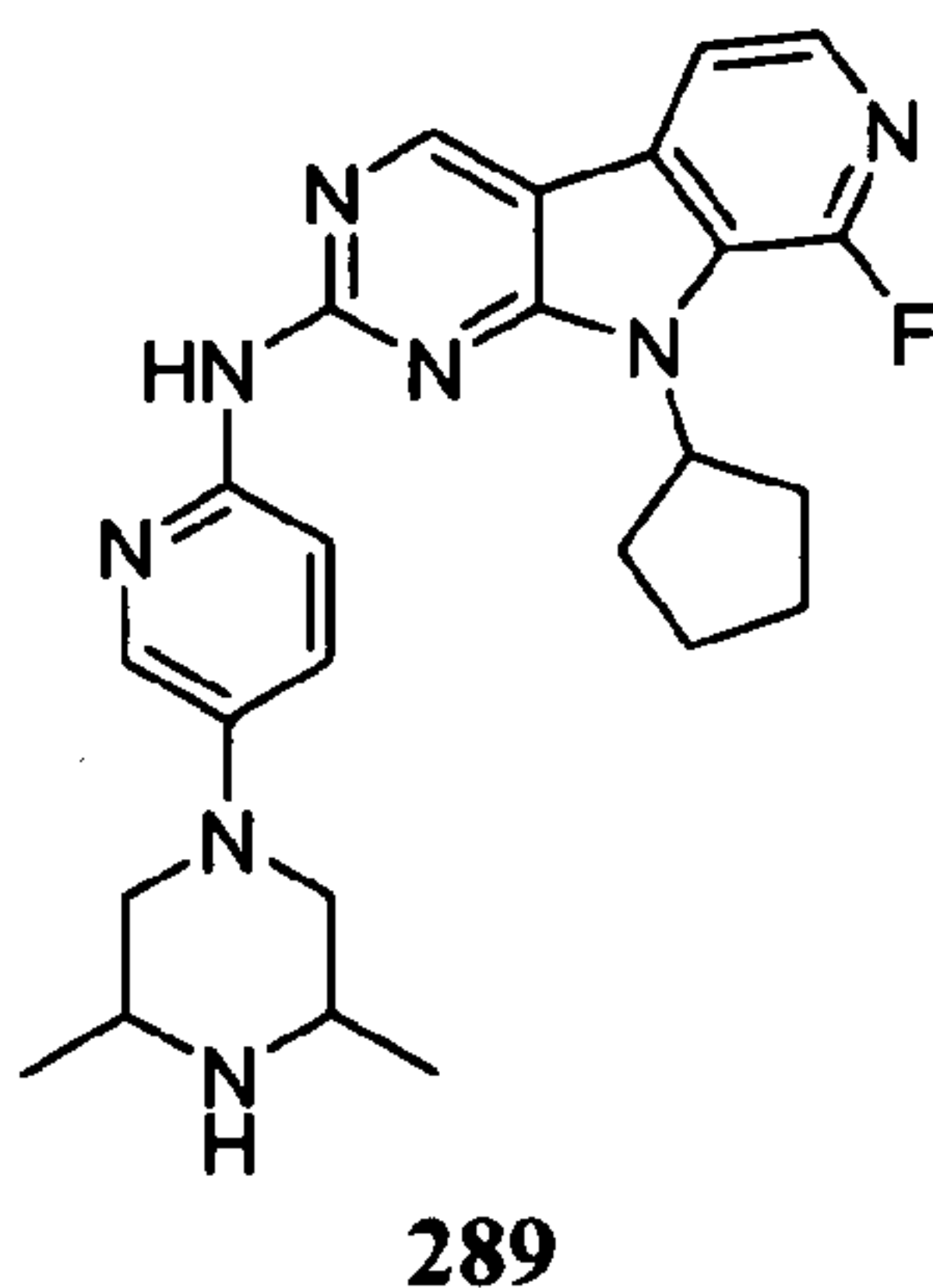
**tert-Butyl 4-(6-((8-cyano-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (288):** A 10 mL reaction vessel was charged with compound **287** (75.0 mg, 269  $\mu\text{mol}$ ), compound **5** (80.2 mg 269  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (0) (19.7 mg, 21.6  $\mu\text{mol}$ ), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (24.9 mg, 43.1  $\mu\text{mol}$ ), sodium *t*-butoxide (51.8 mg, 539  $\mu\text{mol}$ ), and dioxane (2.5 mL). The reaction was purged with argon and heated with microwave energy (300W) for 2 hours at 120°C. The solvent was evaporated *in vacuo*. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA/0-5% methanol) afforded compound **288** as a yellow solid (44 mg, 30%).





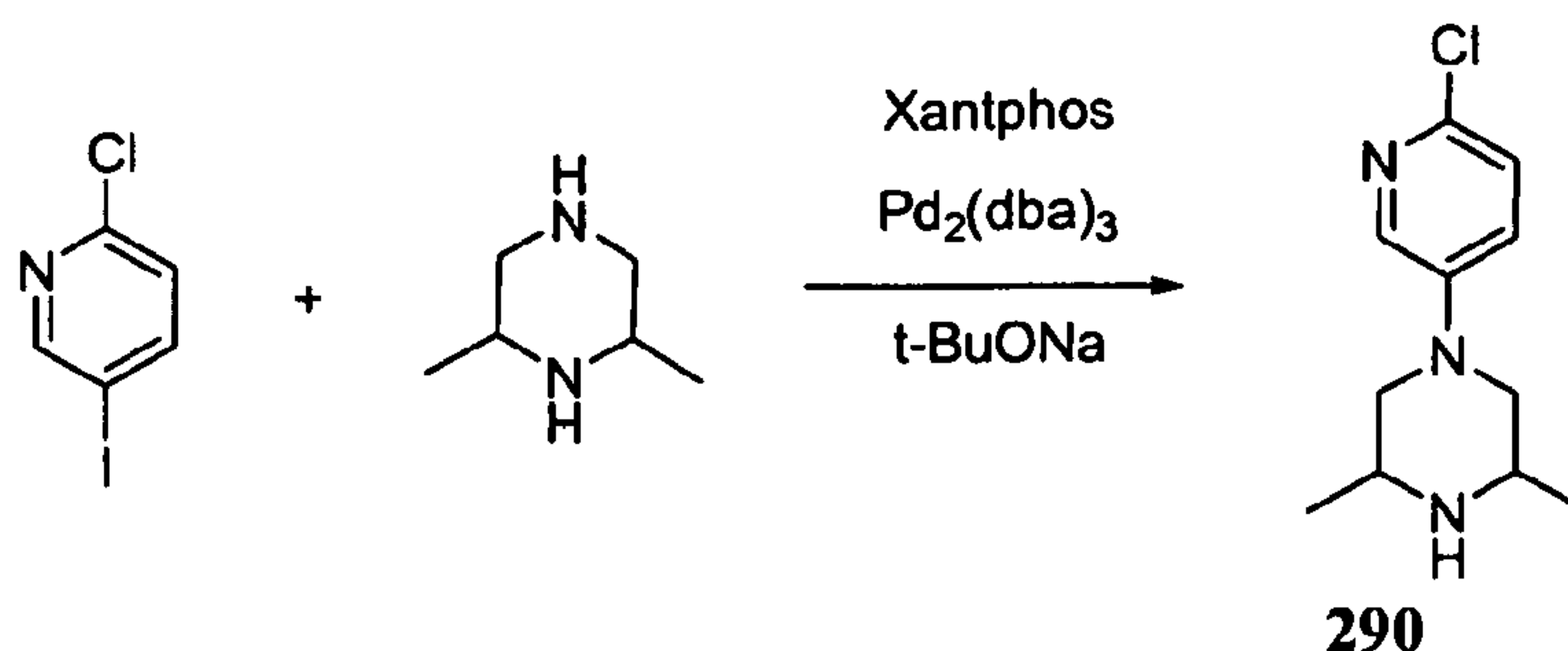
**9-Cyclopentyl-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidine-8-carbonitrile (286):** Compound **288** (44.0 mg, 81.5  $\mu\text{mol}$ ) was suspended in 3 mL methanol. Methanol saturated at room temperature with HCl (1 mL) was added, and the reaction stirred at room temperature for 2.5 hours. The solvents were removed *in vacuo*. The residue was taken up in methanol (10 mL) and stripped again to give compound **286** as a yellow solid (37 mg, 91%).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  1.68 - 1.80 (m, 2 H) 2.01 - 2.20 (m, 4 H) 2.64 (none, 2 H) 3.25 - 3.34 (m, 4 H) 3.34 - 3.44 (m, 5 H) 5.62 - 5.73 (m, 1 H) 7.60 - 7.73 (m, 1 H) 7.98 - 8.07 (m, 1 H) 8.09 - 8.16 (m, 1 H) 8.39 - 8.48 (m, 1 H) 8.58 - 8.65 (m, 1 H) 8.67 - 8.80 (m, 2 H) 9.40 - 9.49 (m, 1 H) 10.32 - 10.51 (m, 1 H) ppm.

### EXAMPLE 189

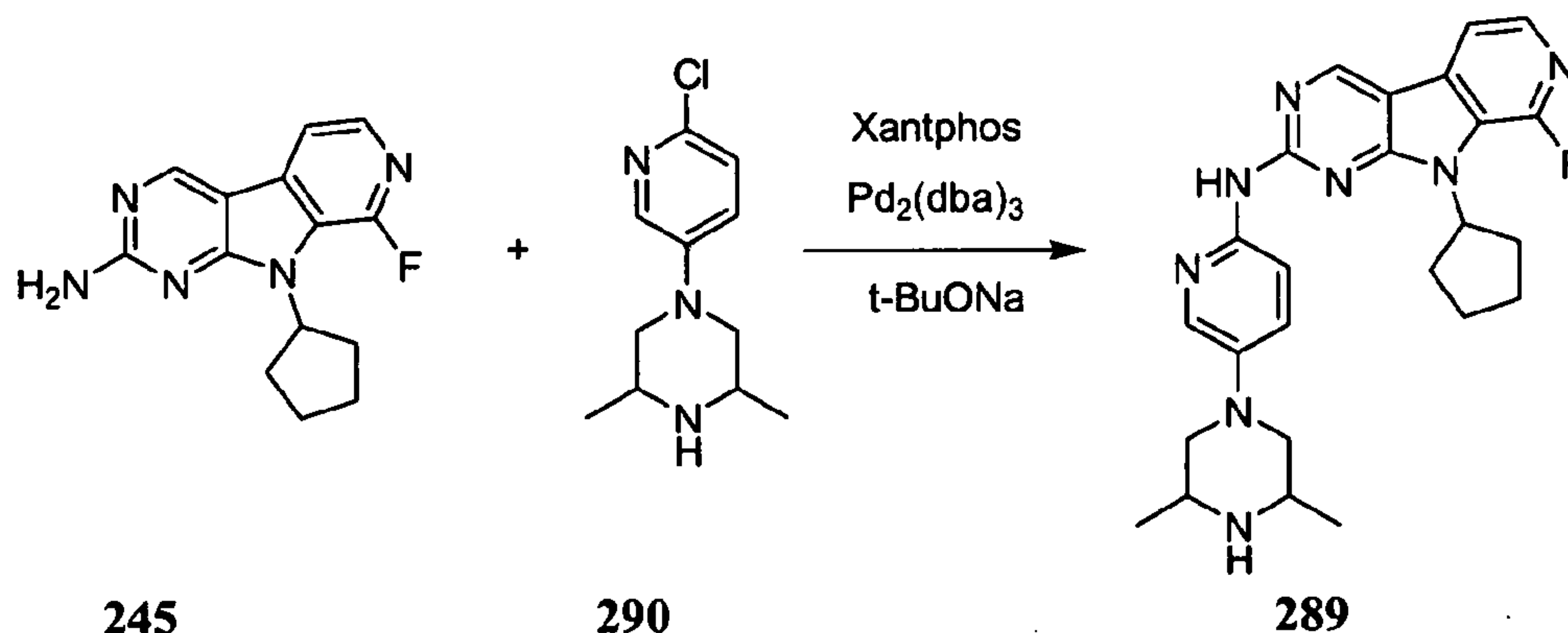


**9-Cyclopentyl-N-(5-(3,5-dimethyl-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**





**1-(6-chloropyridin-3-yl)-3,5-dimethylpiperazine (290):** 2-chloro-5-iodopyridine (1.00 g, 4176  $\mu\text{mol}$ ), 2,6-dimethylpiperidine (477 mg, 4.18 mmol), tris(dibenzylideneacetone)-dipalladium (0) (191 mg, 209  $\mu\text{mol}$ ), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (242 mg, 418  $\mu\text{mol}$ ), and sodium *t*-butoxide (803 mg, 8.35 mmol) were dissolved in 20 mL dioxane. The reaction was purged with argon and heated at 80°C for 4.5 hours. The solvent was removed *in vacuo*. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA/0-5% methanol) afforded compound **290** as an orange solid (545 mg, 58%).

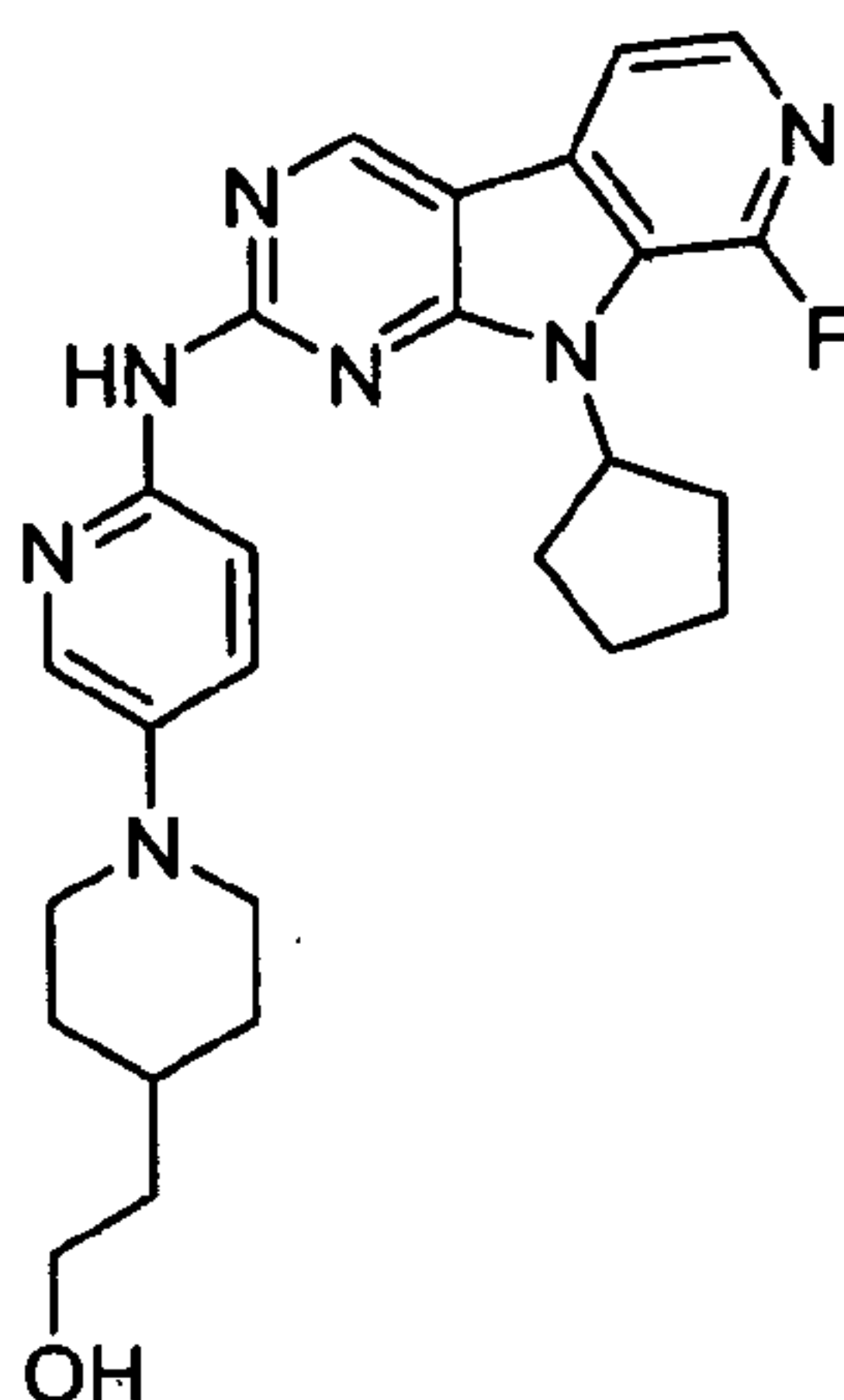


**9-Cyclopentyl-N-(5-(3,5-dimethyl-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrrolo-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (289):** A 10 mL reaction vessel was charged with compound **245** (80.0 mg, 295  $\mu\text{mol}$ ), 1-(6-chloropyridin-3-yl)-3,5-dimethylpiperazine (66.6 mg, 295  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (0) (20.3 mg, 22.1  $\mu\text{mol}$ ), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (25.6 mg, 44.2  $\mu\text{mol}$ ), sodium *t*-butoxide (56.7 mg, 590  $\mu\text{mol}$ ), and dioxane (2.5 mL). The reaction was purged with argon and heated with microwave energy (300W) for 3.5 hours at 120°C. The reaction was taken up in ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated to give an orange oil. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA, 0-8% methanol) afforded a yellow solid. This residue was taken up in 2 mL methanol (2 mL) and 1M ethanolic HCl (1 mL) was added, followed by the addition of diethyl ether (20 mL).



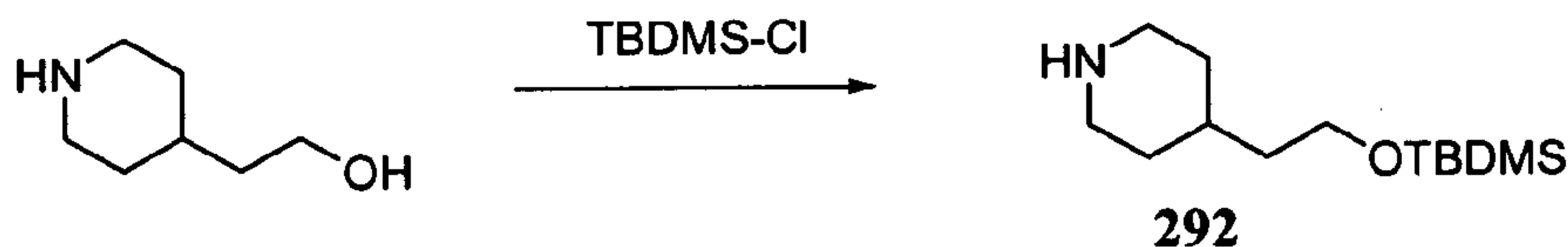
The resulting precipitate was collected and dried *in vacuo* to give compound **289** as a yellow solid (91 mg, 67%)  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.54 - 9.67 (m, 2 H) 9.47 - 9.54 (m, 1 H) 9.05 - 9.23 (m, 1 H) 8.19 - 8.30 (m, 1 H) 8.06 - 8.17 (m, 3 H) 7.94 - 8.04 (m, 1 H) 7.81 - 7.94 (m, 1 H) 5.45 - 5.58 (m, 1 H) 3.81 - 3.94 (m, 2 H) 3.34 - 3.48 (m, 2 H) 2.75 - 2.91 (m, 2 H) 2.23 - 2.35 (m, 2 H) 2.10 - 2.20 (m, 2 H) 2.05 (none, 2 H) 1.68 - 1.86 (m, 2 H) 1.34 (d,  $J=6.60$  Hz, 7 H) ppm.

### EXAMPLE 190



**291**

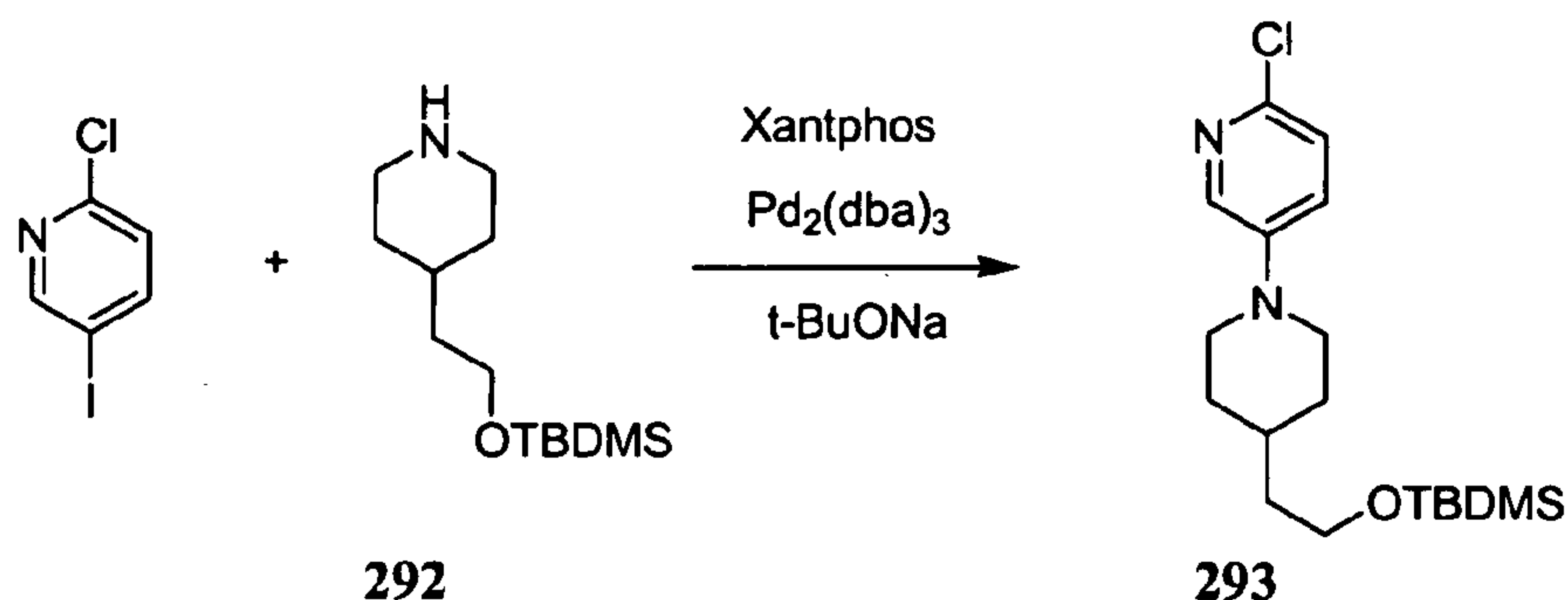
**2-(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrrolo[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)ethanol**



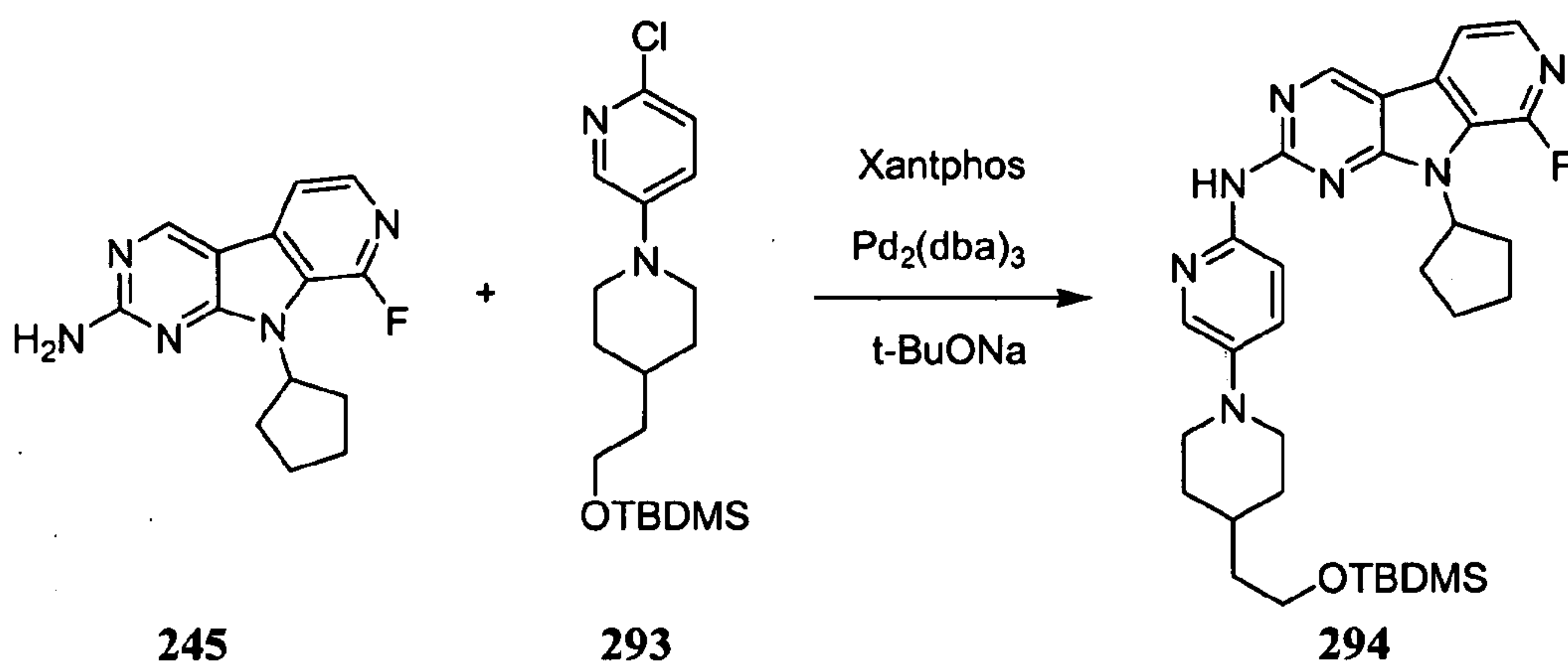
**292**

**4-(2-(*t*-Butyldimethylsilyloxy)ethyl)piperidine (292):** 2-(piperidin-4-yl)ethanol (2.00 g, 15.5 mmol), *t*-butylchlorodimethylsilane (2.57 g, 17.0 mmol), and imidazole (1.05 g, 15.5 mmol) were taken up in dichloromethane (15 mL) and stirred for 22 hours. . This solution was added to aqueous  $\text{K}_2\text{CO}_3$  (80 mL) and extracted with dichloromethane (3X 30 mL). The combined organics were dried ( $\text{MgSO}_4$ ) and evaporated to give a pale yellow oil. Silica gel chromatography (gradient elution dichloromethane+2.5% TEA/0-10% methanol) afforded a white solid. This solid was added to aqueous  $\text{K}_2\text{CO}_3$  (60 mL) and extracted with dichloromethane+10% methanol (3X 30 mL), the organics dried ( $\text{MgSO}_4$ ) and evaporated to give compound **292** as a yellow oil (3.24 g, 86%).



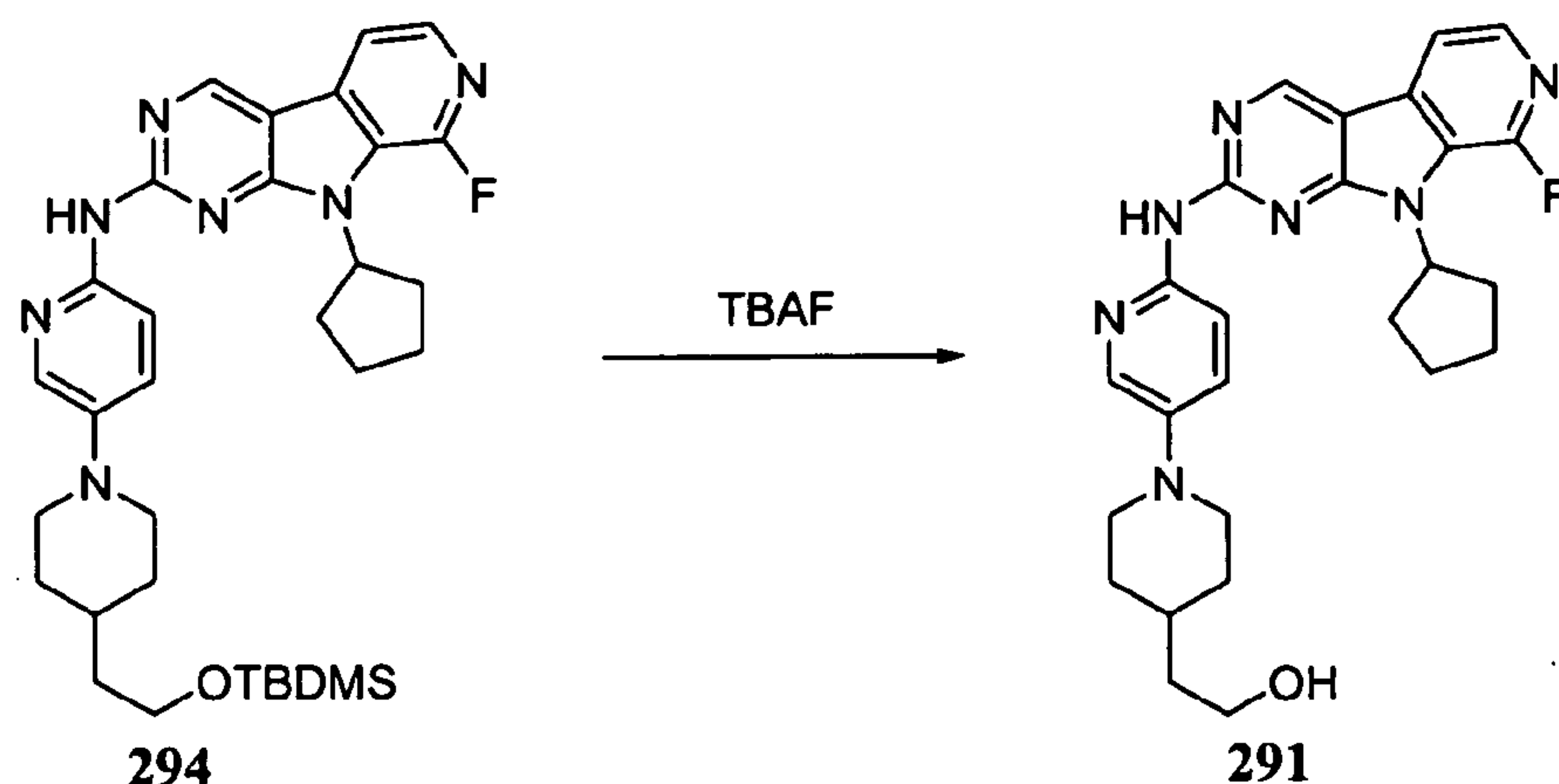


**5-(4-(2-(*t*-Butyldimethylsilyloxy)ethyl)piperidin-1-yl)-2-chloropyridine (293):** 2-chloro-5-iodopyridine (1.00 g, 4.18 mmol), compound **292** (1.02 g, 4.18 mmol), Tris(dibenzylideneacetone)dipalladium (0) (0.191 g, 0.209 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.242 g, 0.418 mmol), and sodium *t*-butoxide (0.803 g, 8.35 mmol) were dissolved in 20 mL dioxane. The reaction was purged with argon and heated at 80°C for 16 hours. The solvent was removed *in vacuo* and silica gel chromatography (gradient elution hexanes/0-10% ethyl acetate) afforded compound **293** as a beige solid (597 mg, 40%).



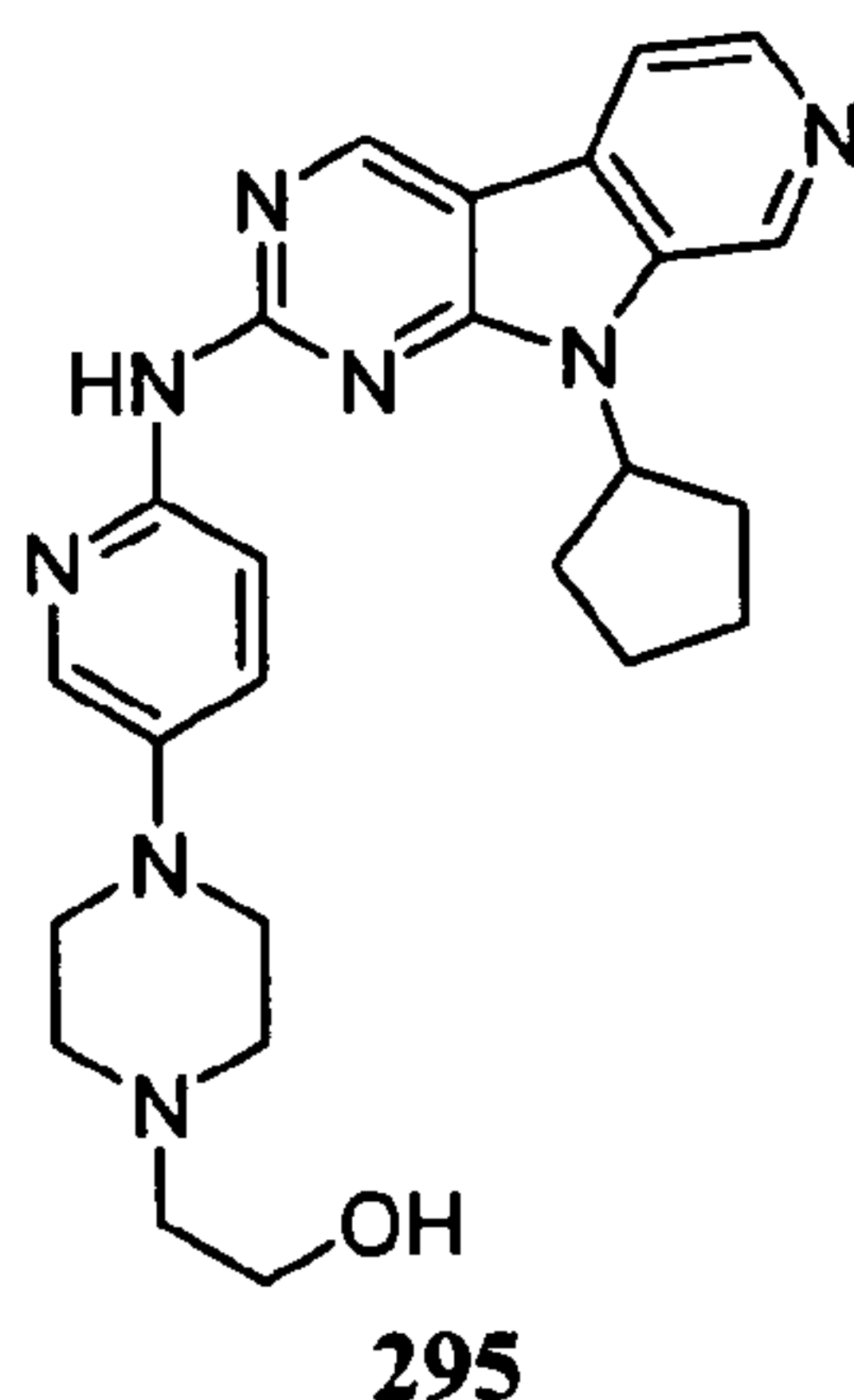
**N-(5-(4-(2-((*tert*-butyl(dimethyl)silyl)oxy)ethyl)-1-piperidinyl)-2-pyridinyl)-9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (294):** A 10 mL microwave reaction tube was charged with compound **245** (80.0 mg, 295  $\mu\text{mol}$ ), 5-(4-(2-(*t*-butyldimethylsilyloxy)ethyl)piperidin-1-yl)-2-chloropyridine (**293**) (105 mg, 295  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (0) (20.3 mg, 22.1  $\mu\text{mol}$ ), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (25.6 mg, 44.2  $\mu\text{mol}$ ), sodium *t*-butoxide (56.7 mg, 590  $\mu\text{mol}$ ), and dioxane (3 mL). The reaction was purged with argon and heated with microwave energy (300W) for 3.5 hours at 120°C. The reaction was taken up in ethyl acetate (40 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated to give an orange oil. Silica gel chromatography (gradient elution hexanes+2.5% TEA/0-100% ethyl acetate+2.5% TEA) afforded compound **294** as a yellow solid (113 mg, 65%).





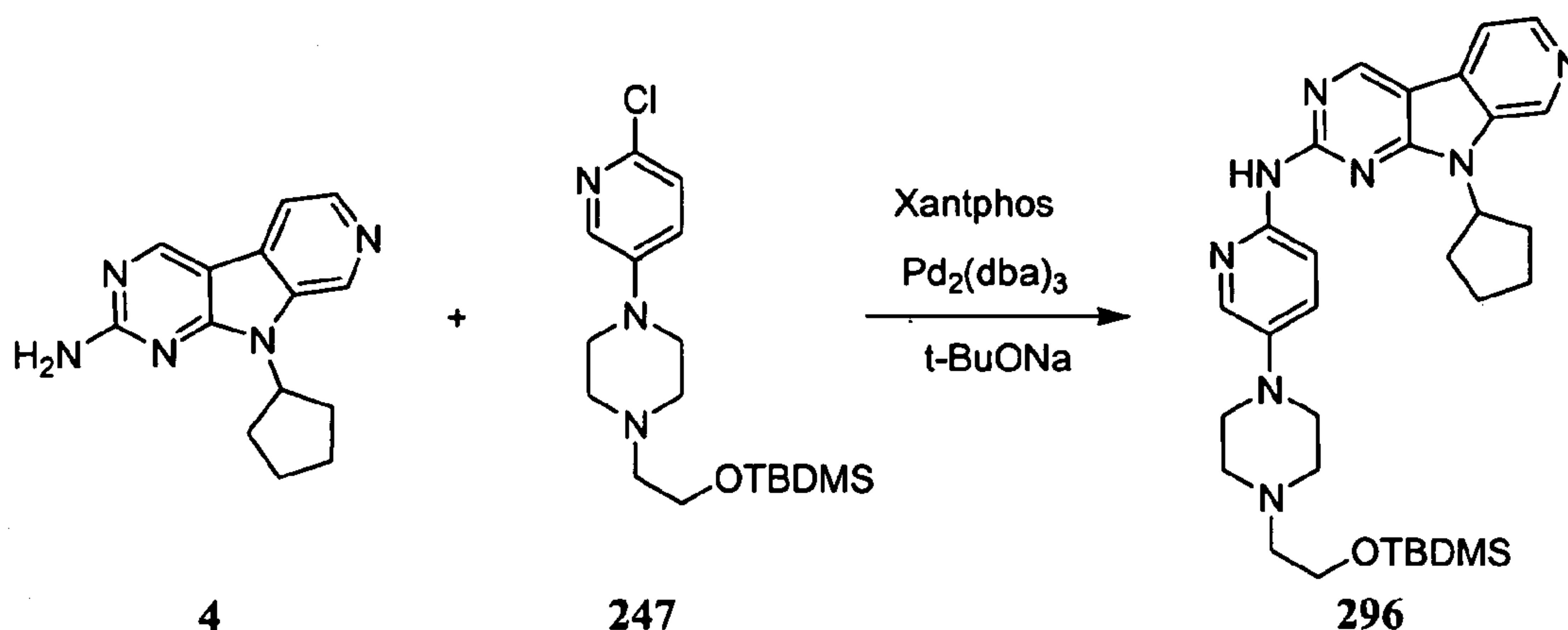
**2-(1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)ethanol (291):** Compound **294** (78 mg, 132  $\mu\text{mol}$ ) was dissolved in dry THF (3 mL). Tetrabutylammonium fluoride, 1.0M in THF (1.00 mL, 1.00 mmol) was added and the reaction stirred at room temperature for 4 hours. The solvent was removed *in vacuo* and silica gel chromatography (gradient elution hexanes+2.5% /0-100% ethyl acetate+2.5% TEA) afforded compound **291** as a beige solid (44 mg, 70%).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.60 - 11.85 (m, 2 H) 9.49 (s, 2 H) 8.19 - 8.24 (m, 2 H) 8.13 - 8.19 (m, 2 H) 8.05 - 8.10 (m, 2 H) 7.96 - 8.04 (m, 2 H) 7.61 - 7.71 (m, 2 H) 5.48 (s, 1 H) 3.64 (d,  $J=11.98$  Hz, 2 H) 3.44 (t,  $J=6.48$  Hz, 2 H) 2.71 - 2.90 (m, 2 H) 2.20 (br. s., 2 H) 2.09 (br. s., 2 H) 2.00 (br. s., 2 H) 1.66 - 1.82 (m, 4 H) 1.52 - 1.66 (m, 1 H) 1.37 (d,  $J=6.60$  Hz, 2 H) 1.28 (none, 2 H) ppm.

#### EXAMPLE 191

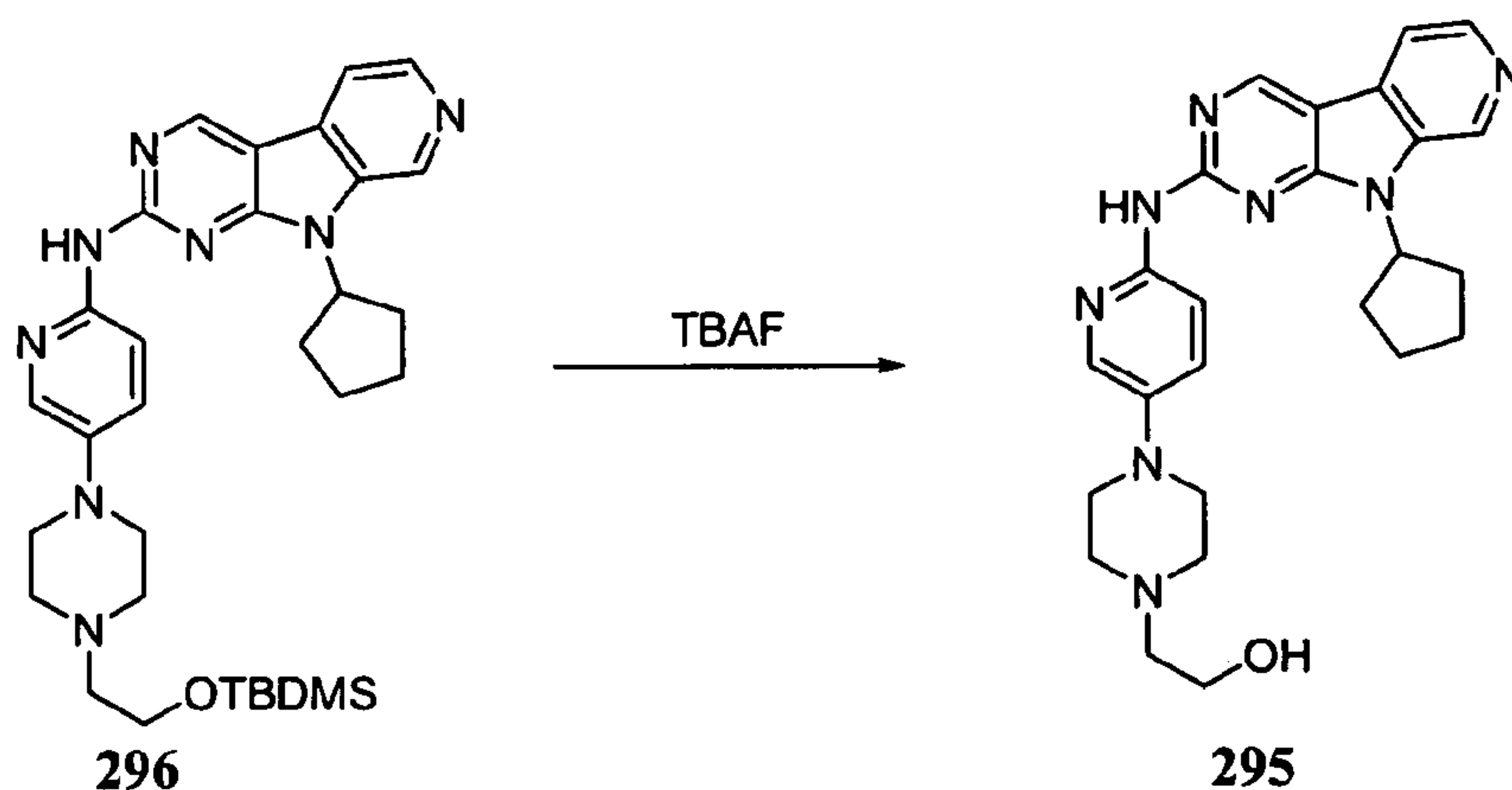


**2-(4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol**





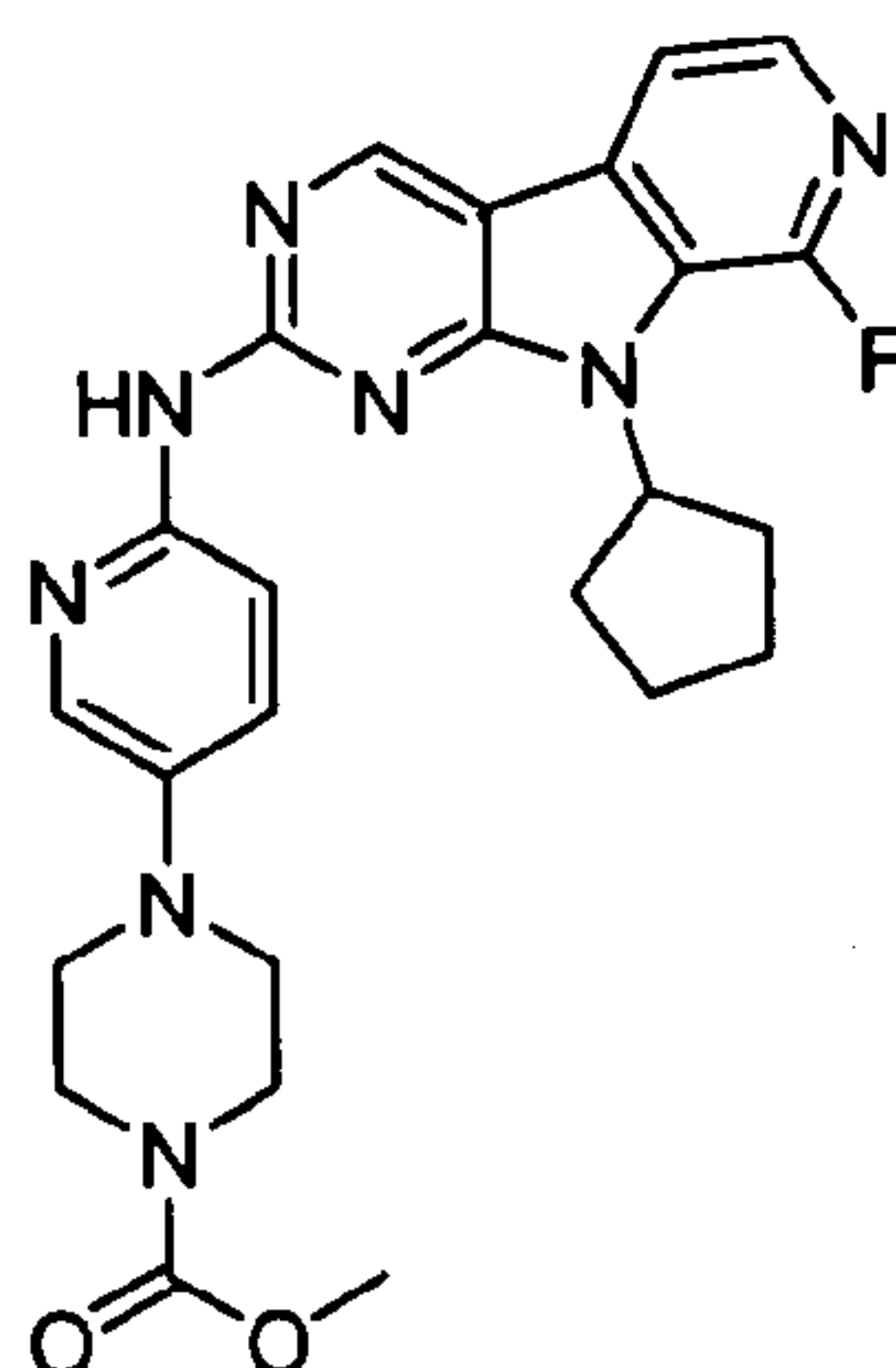
**N-(5-(4-(2-((tert-butyl(dimethyl)silyl)oxy)ethyl)-1-piperazinyl)-2-pyridinyl)-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (296):** A 10 mL reaction vessel was charged with compound **4** (153 mg, 604  $\mu$ mol), compound **247** (215 mg, 604  $\mu$ mol), tris(dibenzylideneacetone)-dipalladium (0) (41.5 mg, 45.3  $\mu$ mol), sodium t-butoxide (69.7 mg, 725  $\mu$ mol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (52.4 mg, 90.6  $\mu$ mol), and dioxane (3 mL). The reaction was purged with argon and heated with microwave energy at 120°C for 3.5 hours. The solvent was removed *in vacuo* and silica gel chromatography (gradient elution hexanes+2.5%/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA/0-5% methanol) afforded compound **296** as a yellow solid (85 mg, 25%).



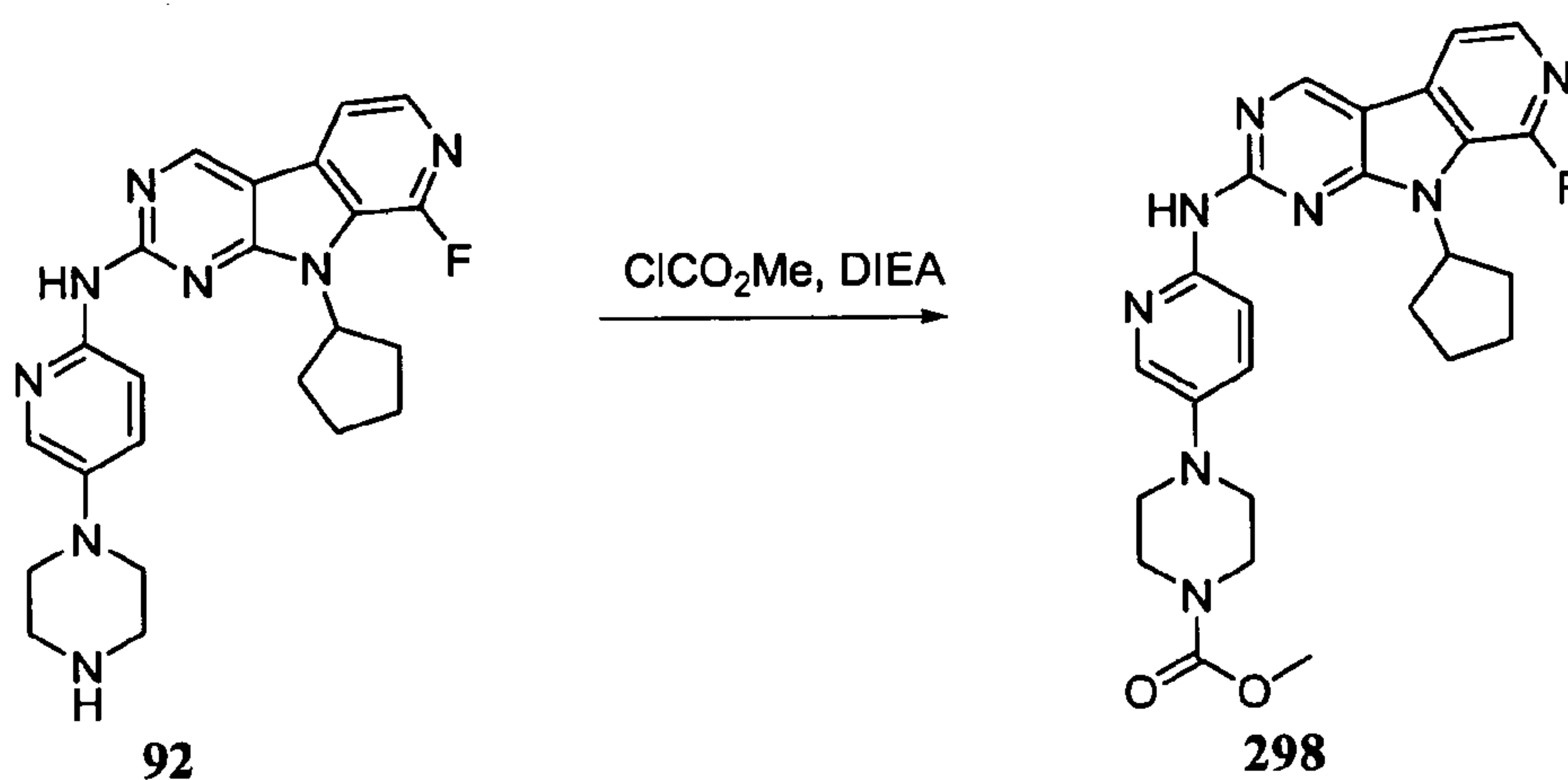
**2-(4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)ethanol (295):** Compound **296** (85.0 mg, 148  $\mu$ mol) was dissolved in dry THF (3 mL). Tetrabutylammonium fluoride, 1.0M in THF (1.00 mL, 1.00mmol) was added and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and silica gel chromatography (gradient elution hexanes+2.5%/0-100% ethyl acetate+2.5% TEA, then ethyl acetate+2.5% TEA/0-5% methanol) afforded a yellow solid. This residue was taken up in methanol (3 mL) and 1M ethanolic HCl (1 mL). Diethyl ether (20 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give



compound **295** as a yellow solid (54 mg, 79%).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.75 - 10.97 (m, 2 H) 9.70 (s, 2 H) 9.47 (s, 1 H) 8.74 (d,  $J=3.67$  Hz, 2 H) 8.16 (d,  $J=2.45$  Hz, 1 H) 7.99 - 8.10 (m, 1 H) 7.84 - 7.99 (m, 1 H) 5.30 - 5.52 (m, 1 H) 3.81 - 3.96 (m, 4 H) 3.62 - 3.72 (m, 2 H) 3.20 - 3.36 (m, 6 H) 2.39 - 2.49 (m, 2 H) 2.02 - 2.20 (m, 4 H) 0.88 (d,  $J=6.85$  Hz, 2 H) ppm.

**EXAMPLE 192****298**

**Methyl 4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate**

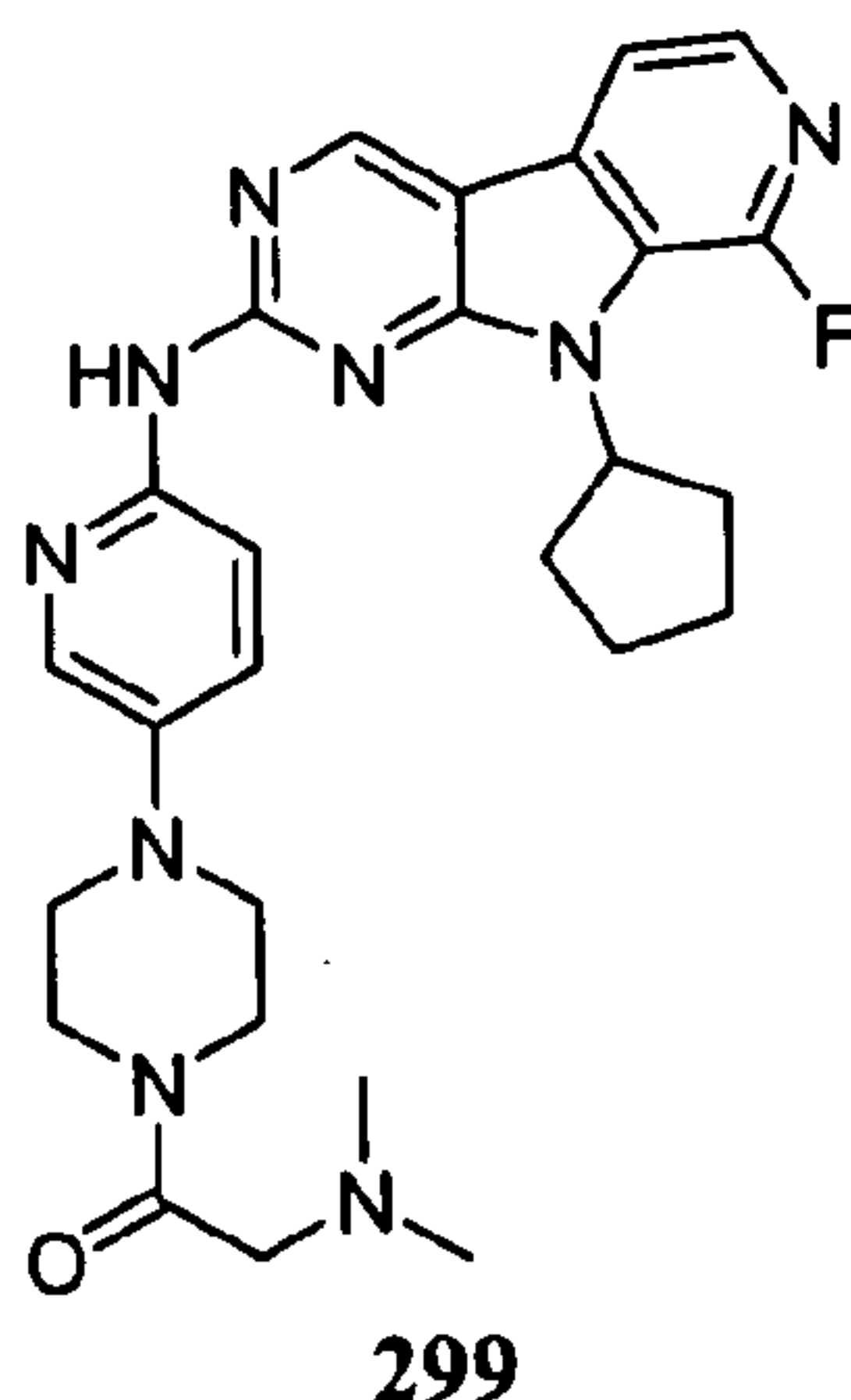
**92****298**

**Methyl 4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (298):** Compound **92** (68.9 mg, 0.159 mmol) was partially dissolved in DMF (2 mL) and DIEA (0.200 mL, 1.15 mmol). Methyl chloroformate (0.0122 mL, 0.159 mmol) was added and the reaction stirred at room temperature 16 for hours. The reaction mixture was diluted with dichloromethane+10% methanol (30 mL) and added to aqueous  $\text{K}_2\text{CO}_3$  (10%, 30 mL). The layers were separated and the aqueous phase extracted with dichloromethane+10% methanol (2X 30 mL). The combined organics were dried ( $\text{MgSO}_4$ ) and evaporated to give a yellow oil. Preparative reverse phase

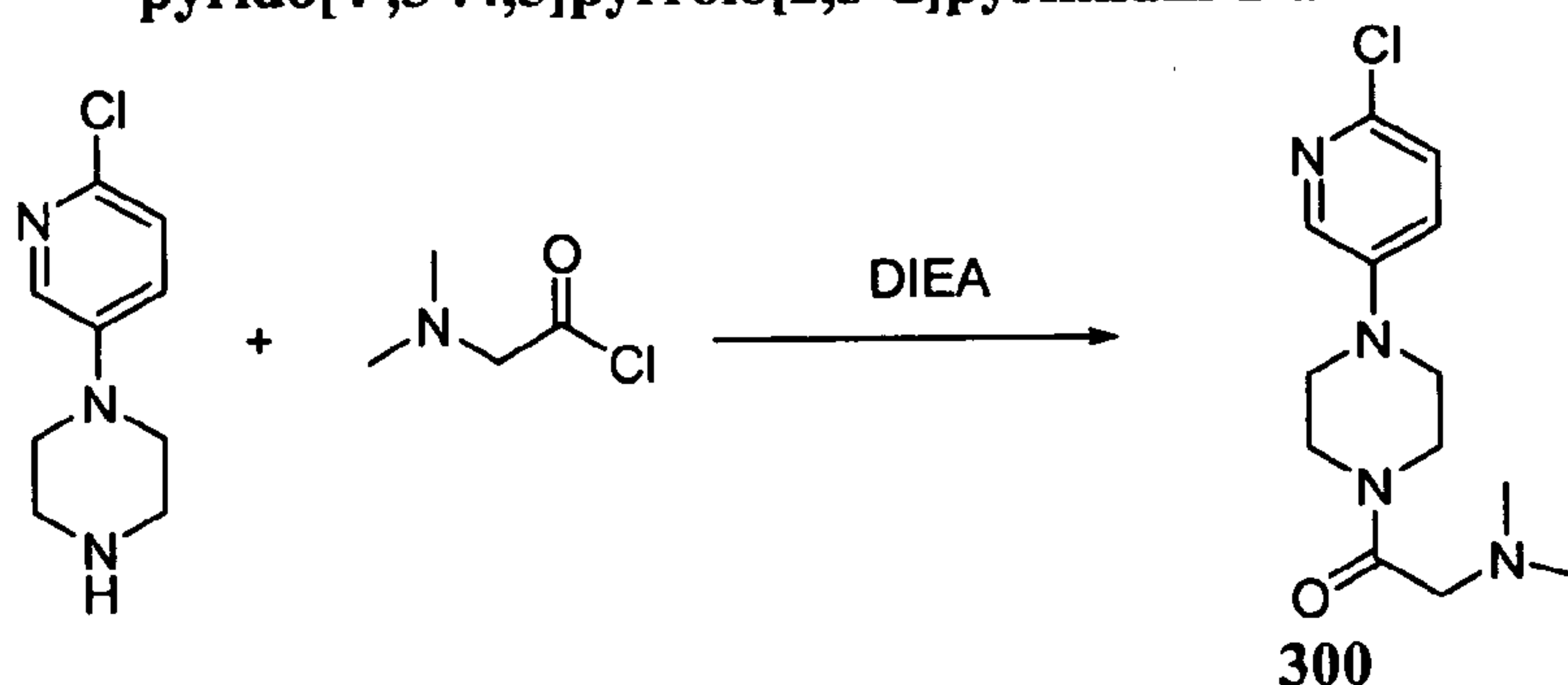


HPLC (gradient elution 0.1% TFA in water/10-70% acetonitrile) afforded a yellow oil. This residue was taken up in aqueous  $K_2CO_3$  and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ( $MgSO_4$ ) and evaporated to give a yellow solid. This was taken up in methanol (2 mL) and 1M HCl in ethanol (0.5 mL) was added. Diethyl ether (10 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **298** as a yellow solid (24 mg, 31%).  $^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  9.54 - 9.66 (m, 1 H) 8.30 - 8.39 (m, 1 H) 8.12 - 8.25 (m, 2 H) 7.98 - 8.09 (m, 1 H) 7.68 - 7.84 (m, 1 H) 5.51 - 5.65 (m, 1 H) 3.71 (s, 4 H) 3.57 - 3.66 (m, 5 H) 3.20 - 3.34 (m, 5 H) 2.25 - 2.40 (m, 2 H) 2.14 - 2.25 (m, 2 H) 2.02 - 2.14 (m, 2 H) 1.83 (none, 2 H) ppm.

### EXAMPLE 193



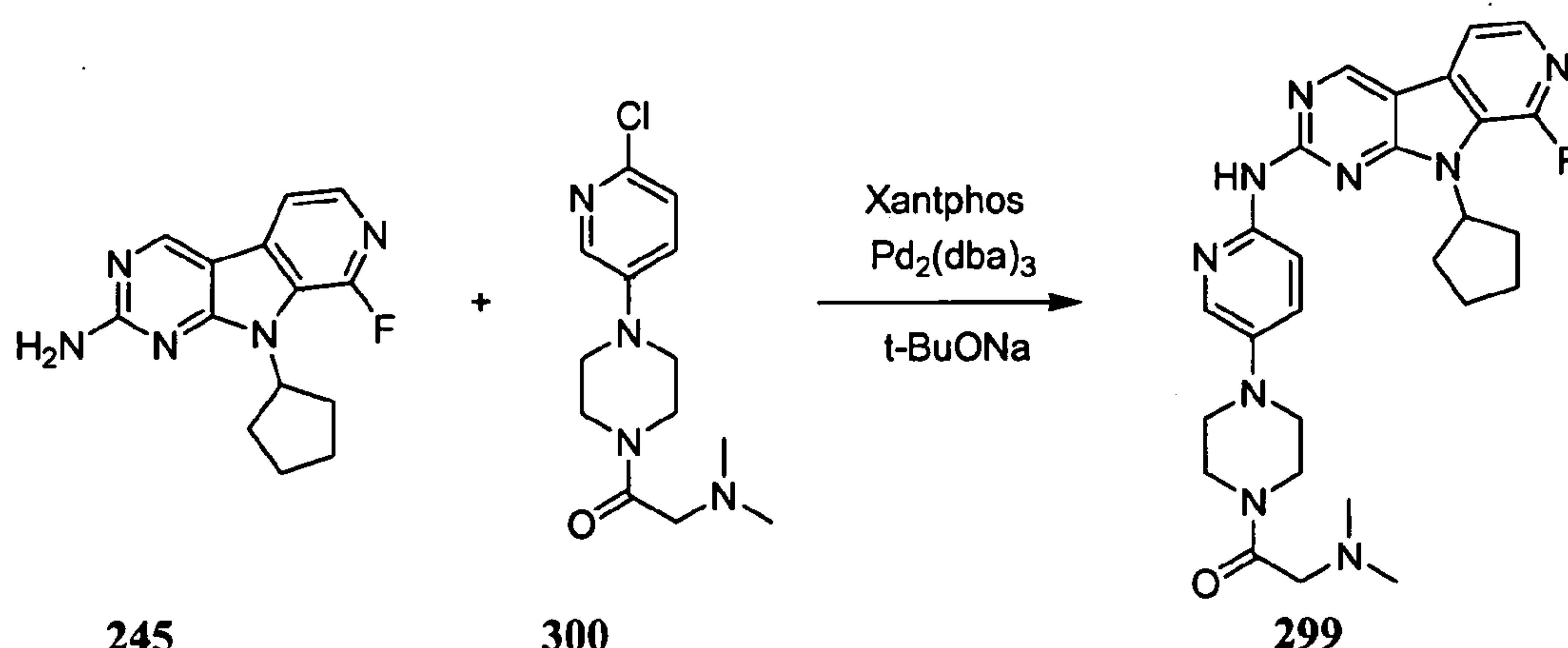
**9-Cyclopentyl-N-(5-(4-((dimethylamino)acetyl)-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



**1-(4-(6-chloropyridin-3-yl)piperazin-1-yl)-2-(dimethylamino)ethanone (300):** 1-(6-chloropyridin-3-yl)piperazine (250 mg, 1265  $\mu$ mol) and dimethylaminoacetyl chloride hydrochloride, 85% (260 mg, 1644  $\mu$ mol) were dissolved in DMF (6 mL) and DIEA (661  $\mu$ L, 3794  $\mu$ mol). The reaction was stirred at room temperature for 4 hours and then 20 hours at 60°C. The resulting solution was taken up in ethyl acetate (80 mL) and washed with aqueous  $K_2CO_3$  (10%, 70 mL), water (70 mL), and brine (70 mL). The organic phase was dried ( $MgSO_4$ ) and evaporated to give a brown oil. Silica gel chromatography (gradient elution

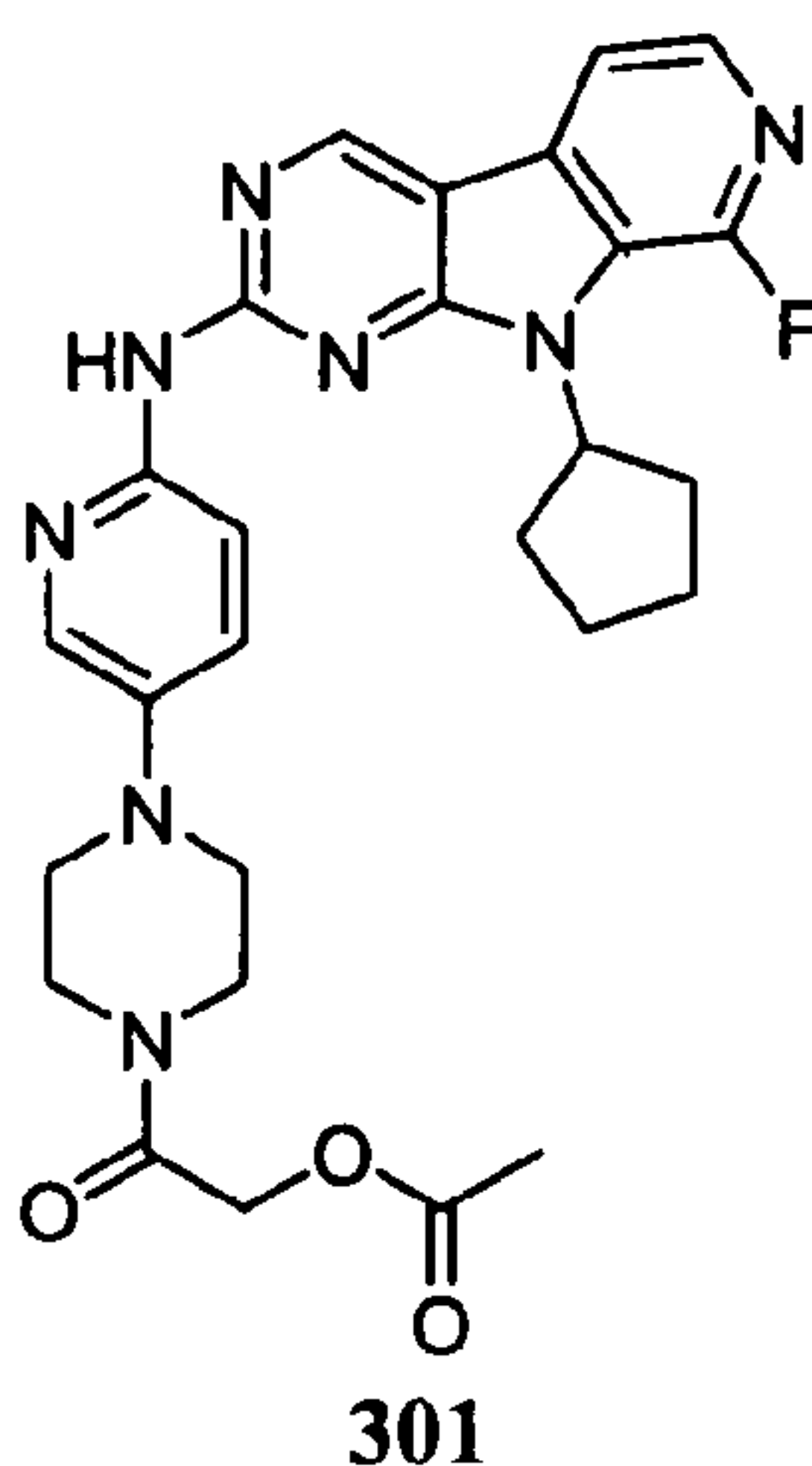


dichloromethane/0-10% 2M NH<sub>3</sub> in methanol) afforded compound **300** as an orange tar (174 mg, 49%).

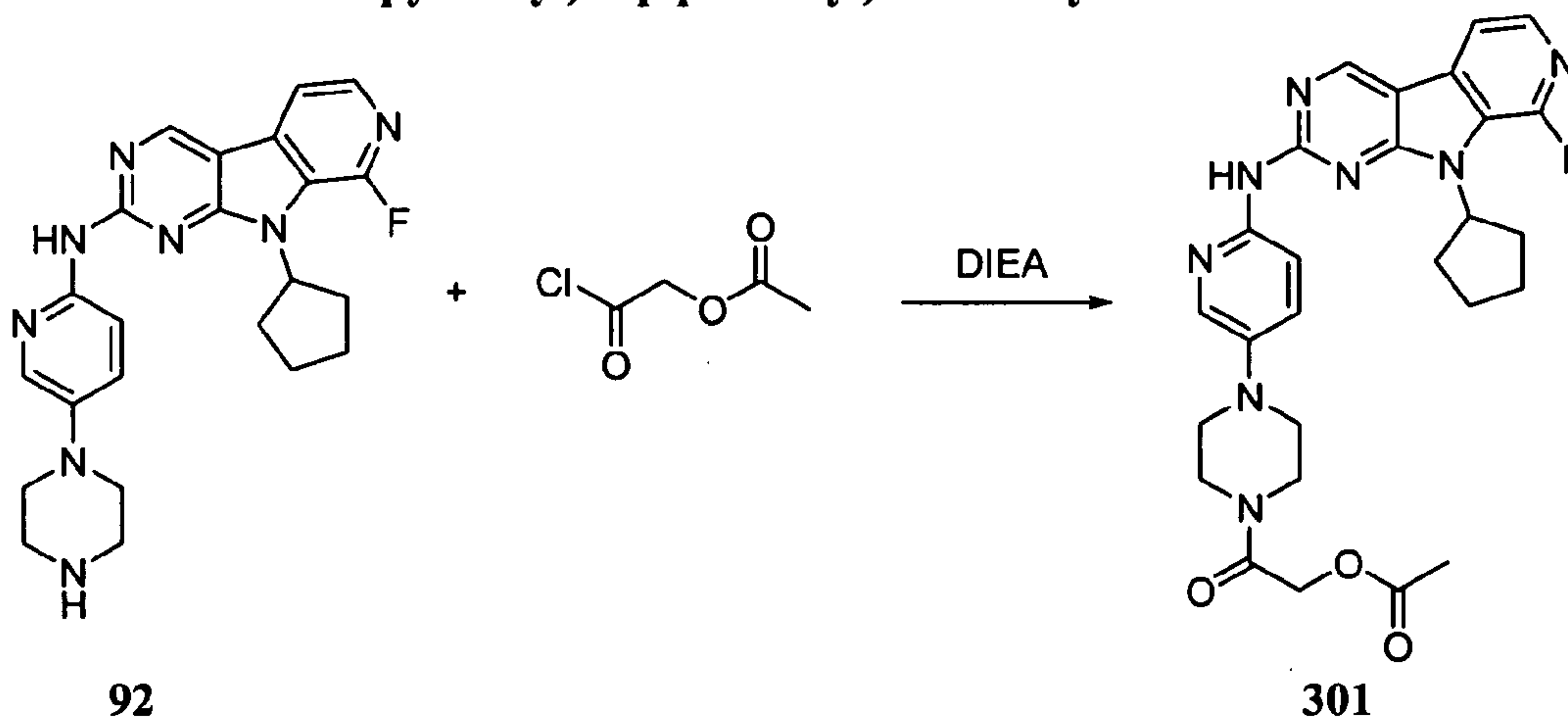


**9-Cyclopentyl-N-(5-(4-((dimethylamino)acetyl)-1-piperazinyl)-2-pyridinyl)-8-fluoro-9H-pyrrolo[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (299):** A 10 mL reaction vessel was charged with compound **245** (100 mg, 369  $\mu\text{mol}$ ), compound **300** (109 mg, 387  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (0) (25.3 mg, 27.6  $\mu\text{mol}$ ), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (32.0 mg, 55.3  $\mu\text{mol}$ ), sodium *t*-butoxide (70.8 mg, 737  $\mu\text{mol}$ ), and dioxane (2.5 mL). The reaction was purged with argon and heated with microwave energy (300W) for 2.5 hours at 120°C. The reaction was added to aqueous K<sub>2</sub>CO<sub>3</sub> (10 %, 30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give an orange oil. Preparative reverse phase HPLC (gradient elution 0.1% TFA in water/10-70% acetonitrile) afforded a yellow oil. This residue was taken up in aqueous K<sub>2</sub>CO<sub>3</sub> (30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give a yellow solid. This was taken up in methanol (2 mL) and 1M HCl in ethanol (0.5 mL) was added. Diethyl ether (10 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **299** as a yellow solid (32 mg, 17%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.43 - 9.61 (m, 1 H) 9.27 - 9.40 (m, 1 H) 8.01 - 8.12 (m, 1 H) 7.91 - 8.01 (m, 1 H) 7.75 - 7.91 (m, 3 H) 7.62 - 7.75 (m, 1 H) 5.27 - 5.42 (m, 1 H) 4.14 - 4.28 (m, 3 H) 3.10 - 3.18 (m, 3 H) 3.06 (none, 3 H) 2.68 (d, *J*=4.65 Hz, 8 H) 2.06 - 2.18 (m, 2 H) 1.93 - 2.06 (m, 2 H) 1.80 - 1.93 (m, 3 H) 1.48 - 1.69 (m, 3 H) ppm.



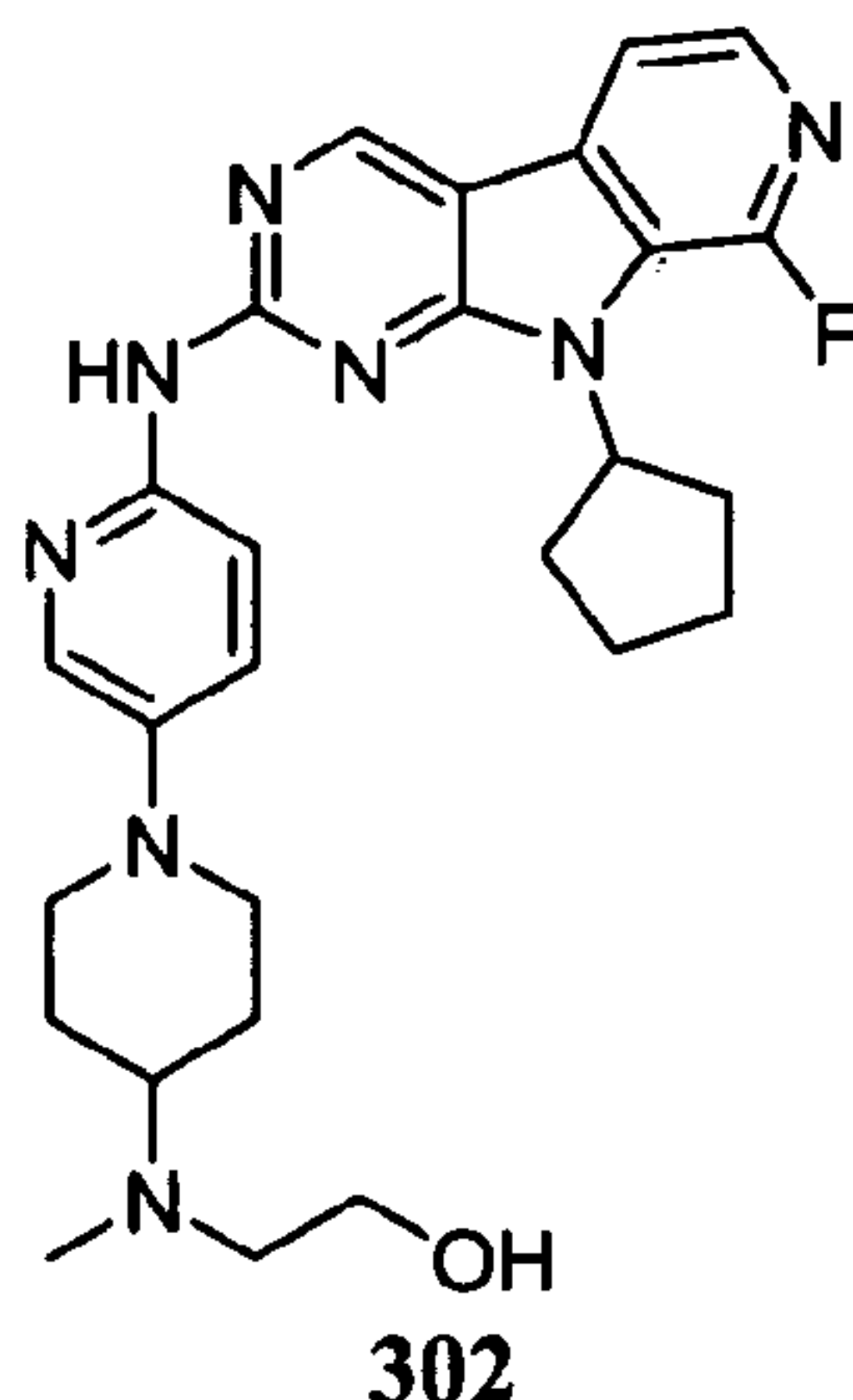
**EXAMPLE 194**

**2-(4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethyl acetate**

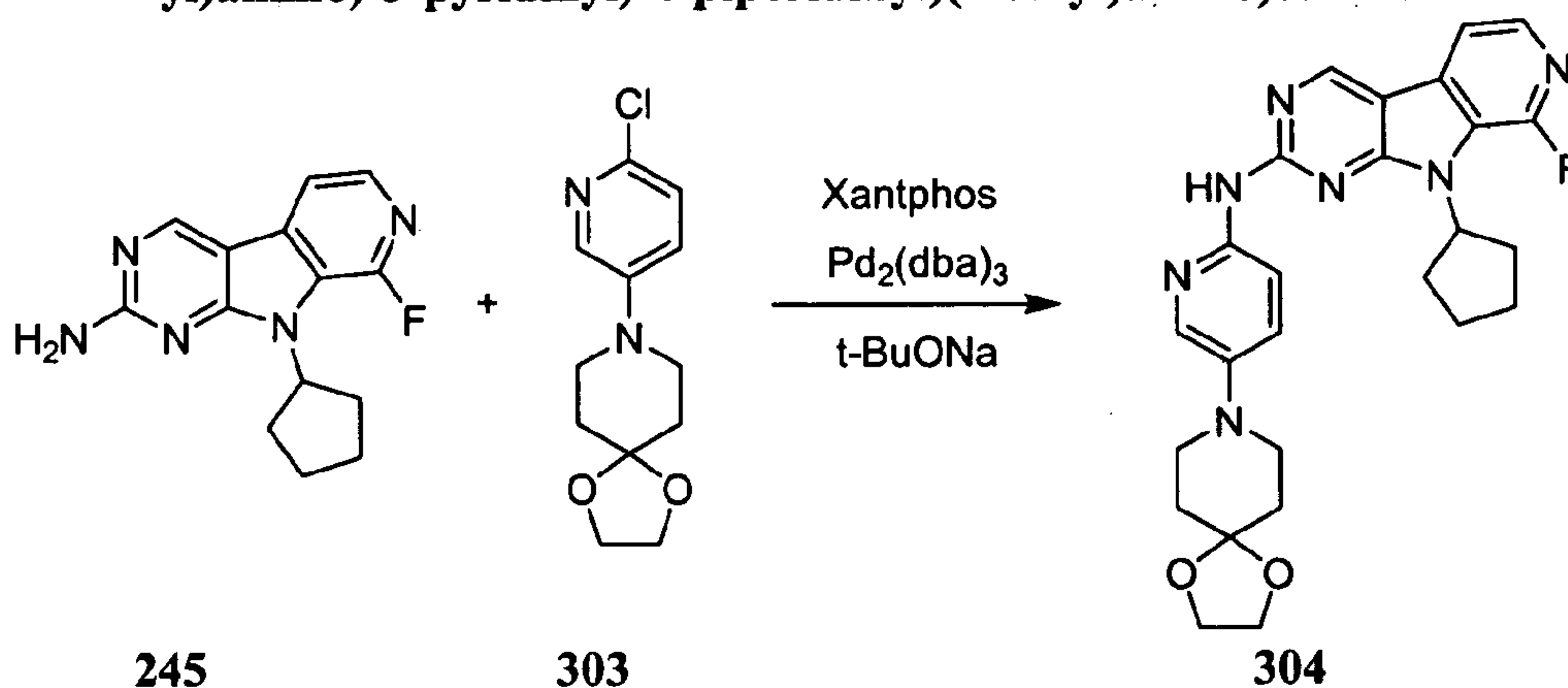


**2-(4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinyl)-2-oxoethyl acetate (301):** Compound **92** (75.0 mg, 173  $\mu\text{mol}$ ) was partially dissolved in DMF (2 mL) and DIEA (0.200 mL, 1148  $\mu\text{mol}$ ). Acetoxyacetyl chloride (0.0196 mL, 182  $\mu\text{mol}$ ) was added and the reaction was stirred at room temperature 16 for hours. The reaction was added to aqueous  $\text{K}_2\text{CO}_3$  (10 %, 30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ( $\text{MgSO}_4$ ) and evaporated to give an orange oil. Preparative reverse phase HPLC (gradient elution 0.1% TFA in water/10-70% acetonitrile) afforded a yellow oil. This residue was taken up in aqueous  $\text{K}_2\text{CO}_3$  (30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ( $\text{MgSO}_4$ ) and evaporated to give a yellow solid. This was taken up in methanol (2 mL) and 1M HCl in ethanol (0.5 mL) was added. Diethyl ether (10 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **301** as a yellow solid (24 mg, 26%). LCMS M+1 found 533.2 calculated 533.2



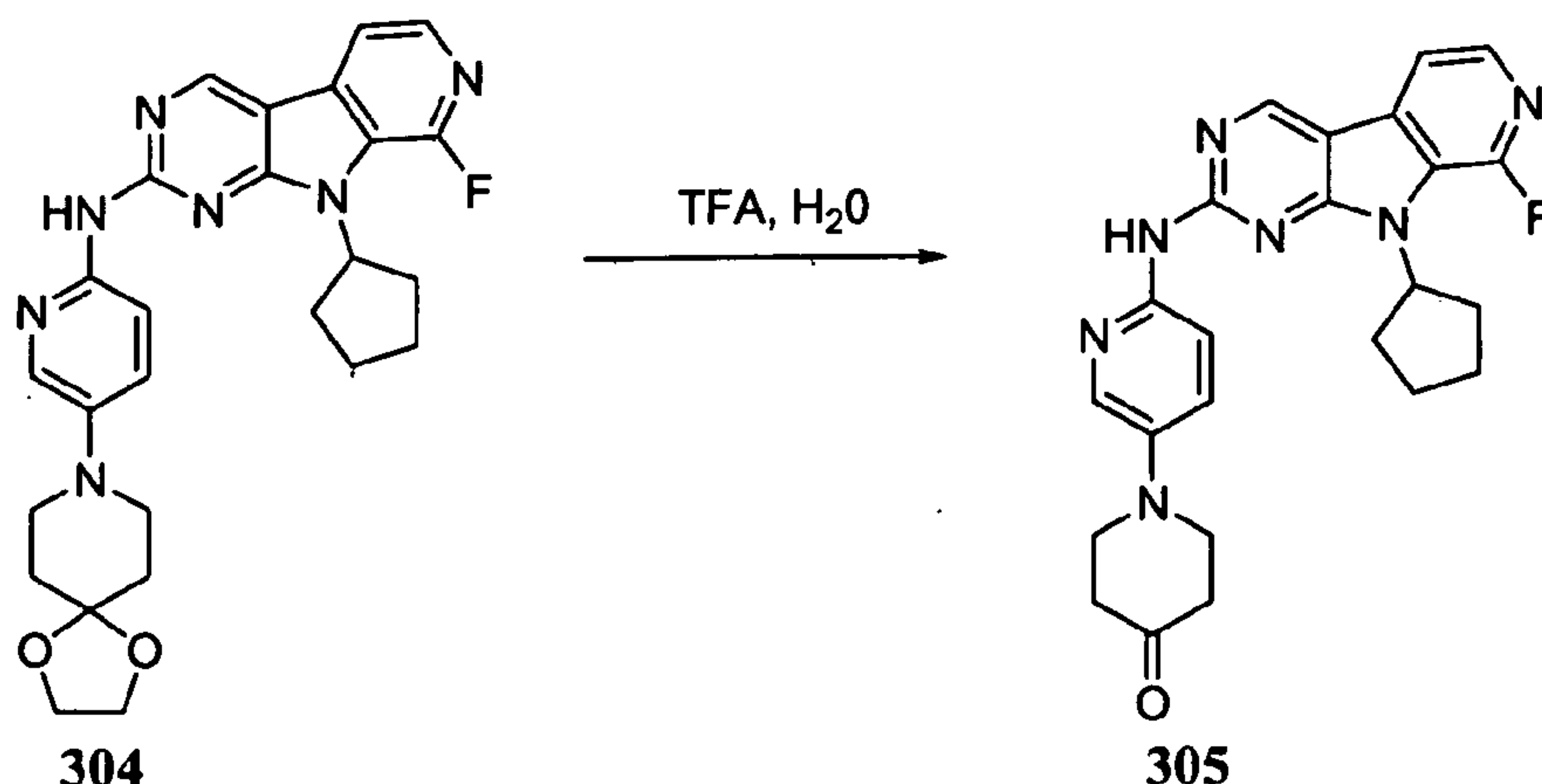
**EXAMPLE 195**

**2-((1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)(methyl)amino)ethanol**

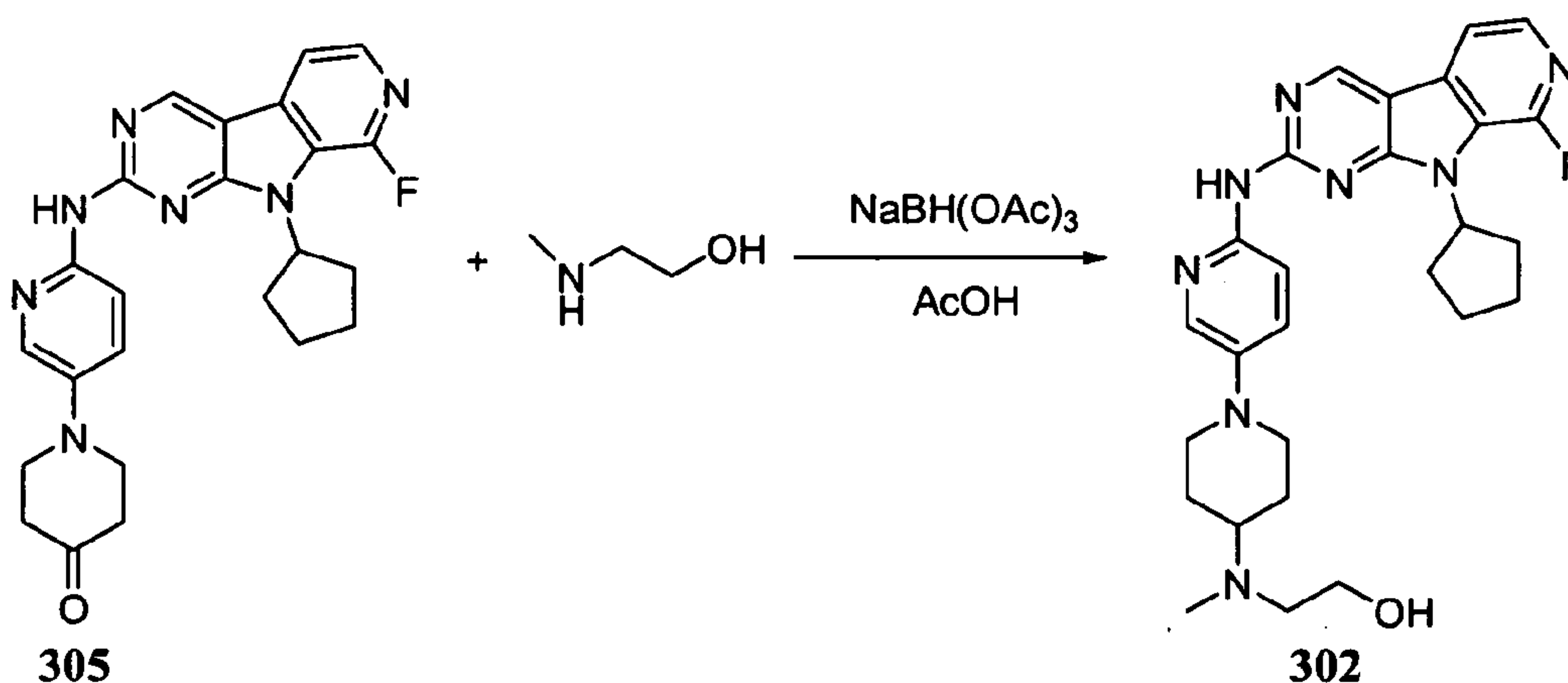


**9-Cyclopentyl-N-(5-(1,4-dioxo-8-azaspiro[45]dec-8-yl)-2-pyridinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (304):** A 35 mL reaction vessel was charged with compound **245** (300 mg, 1.10 mmol), compound **303** (see example 436) [Schön, U. et al. *Tetrahedron Lett.* **2007**, 48, (14), 2519-2525] (310 mg, 1.22 mmol), tris(dibenzylideneacetone)dipalladium (0) (75.9 mg, 82.9  $\mu$ mol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (96.0 mg, 0.166 mmol), sodium *t*-butoxide (213 mg, 2.21 mmol), and dioxane (10 mL). The reaction was purged with argon and heated with microwave energy (300W) for 3 hours at 120°C. The reaction was added to aqueous K<sub>2</sub>CO<sub>3</sub> (10%, 30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give a yellow solid. Silica gel chromatography (gradient elution hexanes+2.5% TEA/50-100% ethyl acetate+2.5% TEA) afforded compound **304** as a yellow solid (228 mg, 42%).





**1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinone (305):** Compound 245 (200 mg, 0.41 mmol) was dissolved in a solution of water (0.150 mL, 8.33 mmol) in trifluoroacetic acid (3.00 mL, 38.9 mmol). The solution was stirred at room temperature for 2 hours and then poured into aqueous  $\text{K}_2\text{CO}_3$  (10%, 30 mL). This was extracted with dichloromethane+10% methanol (3X 30 mL), and the combined organics were dried ( $\text{MgSO}_4$ ) and evaporated to give a yellow solid. Silica gel chromatography (gradient elution hexanes+2.5% TEA/50-100% ethyl acetate+2.5% TEA) afforded compound 305 as a yellow solid (156 mg, 86%).

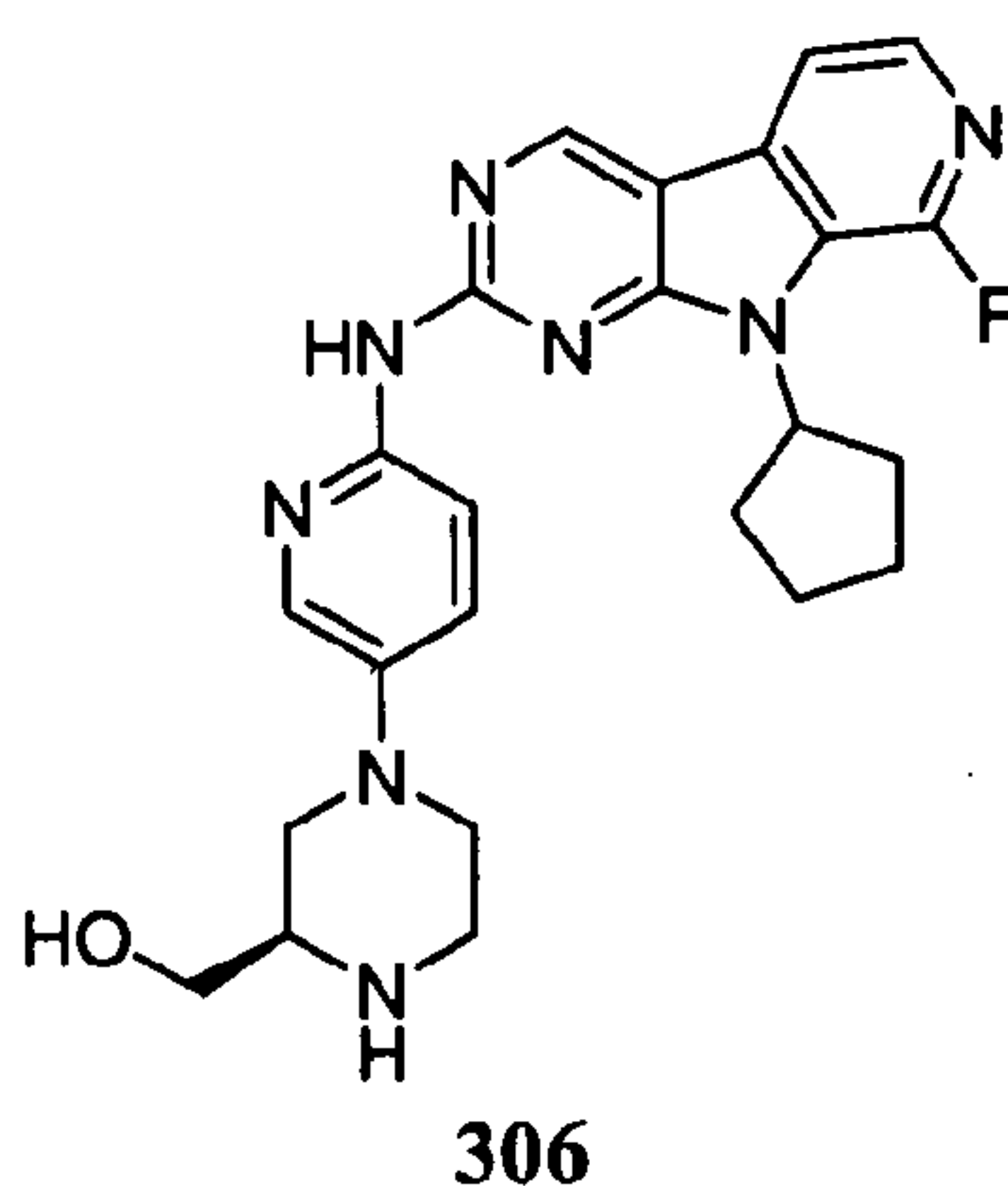


**2-((1-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-4-piperidinyl)(methyl)amino)ethanol (302):** Compound 305 (75.0 mg, 168  $\mu\text{mol}$ ), 2-(methylamino)ethanol (20.2  $\mu\text{L}$ , 253  $\mu\text{mol}$ ), sodium triacetoxyborohydride (53.5 mg, 253  $\mu\text{mol}$ ), and acetic acid (9.64  $\mu\text{L}$ , 168  $\mu\text{mol}$ ) in dichloroethane (2 mL) were stirred at room temperature for 45 hours. The reaction was diluted with dichloromethane+10% methanol (30 mL) and added to aqueous  $\text{K}_2\text{CO}_3$  (10%, 30 mL). The layers were separated and the aqueous phase extracted with dichloromethane +10% methanol (2X 30 mL). The combined organics were dried ( $\text{MgSO}_4$ ) and evaporated to give a yellow oil. Silica gel chromatography (gradient elution ethyl acetate+2.5% TEA/6% 2M  $\text{NH}_3$  in methanol) afforded a yellow solid.

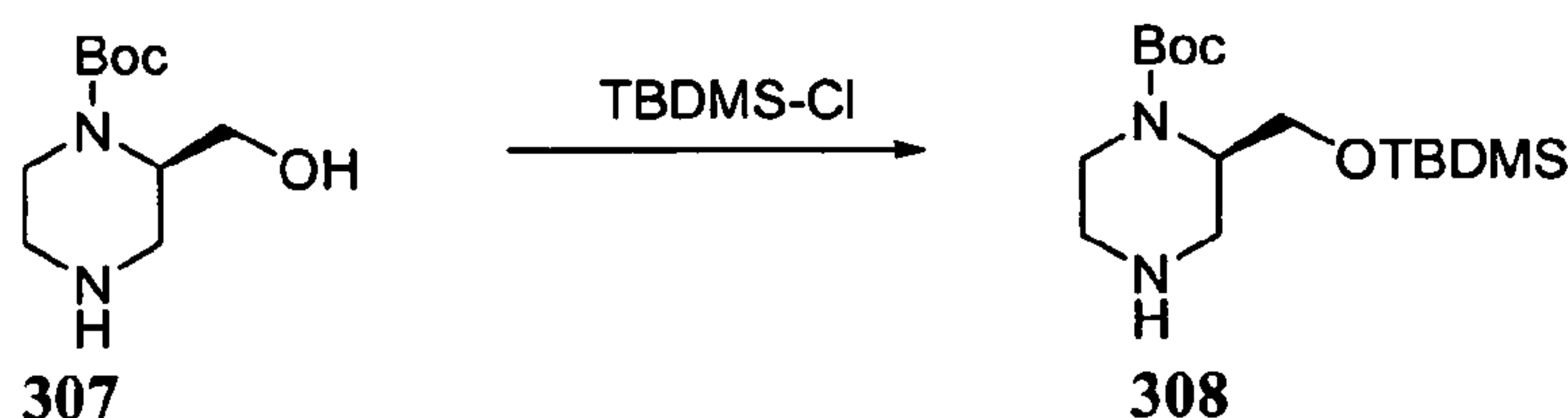


This residue was taken up in methanol (2 mL) and 1M ethanolic HCl (1 mL). Diethyl ether (20 mL) was added to precipitate the product, which was filtered and dried *in vacuo* to give compound **302** as a yellow solid (32 mg, 38%). <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.48 (s, 1 H) 8.16 - 8.25 (m, 1 H) 8.11 (br. s., 1 H) 8.06 (br. s., 1 H) 7.91 - 8.01 (m, 1 H) 7.83 - 7.92 (m, 1 H) 5.42 - 5.59 (m, 1 H) 3.88 (d, *J*=11.74 Hz, 2 H) 3.81 (br. s., 2 H) 3.58 (s, 3 H) 3.48 (d, *J*=2.93 Hz, 3 H) 3.27 - 3.37 (m, 2 H) 3.18 (s, 1 H) 3.06 - 3.15 (m, 1 H) 2.80 - 2.86 (m, 1 H) 2.78 (d, *J*=4.89 Hz, 3 H) 2.25 - 2.35 (m, 1 H) 2.18 - 2.25 (m, 1 H) 2.14 (d, *J*=9.78 Hz, 2 H) 2.04 (br. s., 2 H) 1.77 (br. s., 3 H) ppm.

### EXAMPLE 196



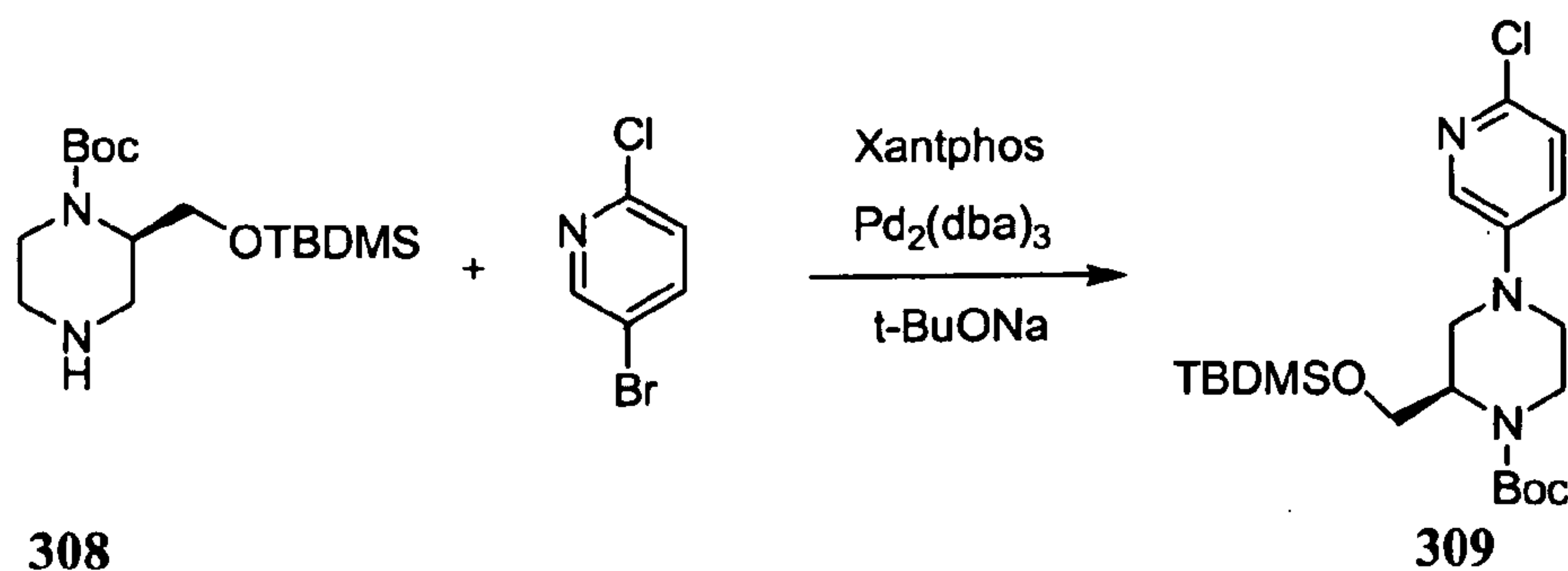
((2*R*)-4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol



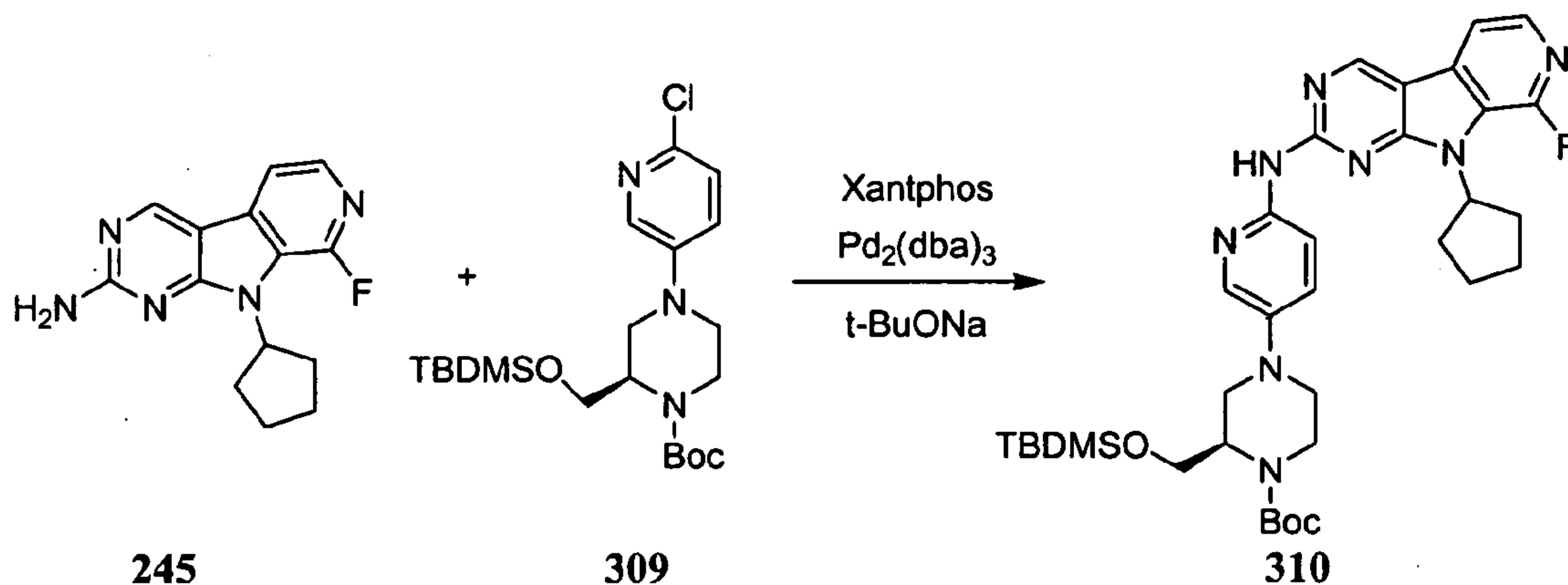
**(R)-*t*-Butyl 2-((*t*-butyldimethylsilyloxy)methyl)piperazine-1-carboxylate (308):**

(*R*)-*t*-Butyl 2-(hydroxymethyl)piperazine-1-carboxylate (1.15 g, 5.32 mmol), *t*-butylchlorodimethylsilane (0.882 g, 5.85 mmol), and imidazole (0.796 g, 11.7 mmol) were stirred in dichloromethane (3 mL) for three days. The solution was added to aqueous K<sub>2</sub>CO<sub>3</sub> (30 mL) and extracted with dichloromethane (3X 30 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give a yellow oil. Silica gel chromatography (gradient elution hexanes/0-50% ethyl acetate) afforded compound **308** as a colorless oil (1.06 g, 60%).





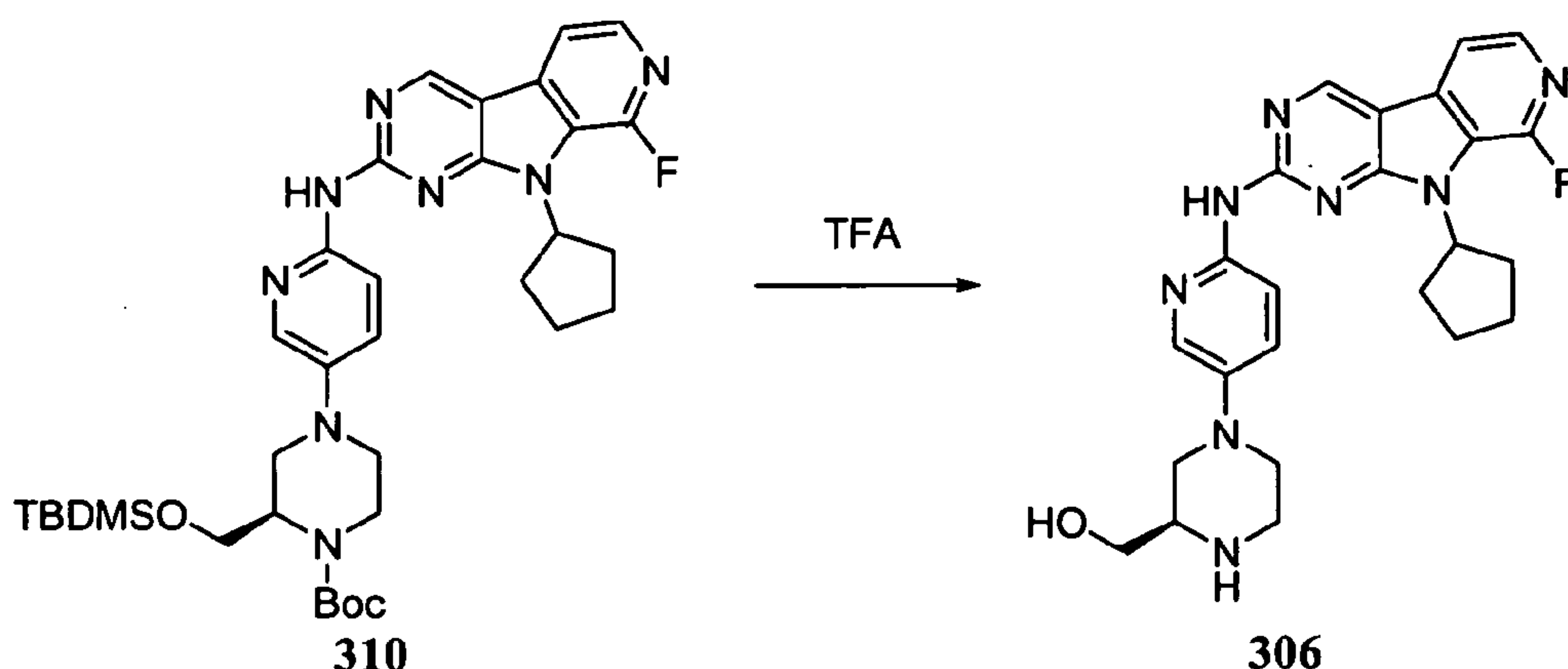
**(R)-*t*-butyl 2-(((*t*-butyldimethylsilyloxy)methyl)-4-(6-chloropyridin-3-yl)piperazine-1-carboxylate (309):** Compound 308 (361 mg, 1091  $\mu$ mol), 5-bromo-2-chloropyridine (200 mg, 1039  $\mu$ mol), Tris(dibenzylideneacetone)dipalladium (0) (71.4 mg, 77.9  $\mu$ mol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (90.2 mg, 156  $\mu$ mol), and sodium *t*-butoxide (200 mg, 2079  $\mu$ mol) were taken up in toluene (5 mL). The reaction was purged with argon and heated at 80°C for 5 hours. The resulting solution was added to aqueous K<sub>2</sub>CO<sub>3</sub> (10%, 30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried (MgSO<sub>4</sub>) and evaporated to give an orange tar. Silica gel chromatography (gradient elution hexanes/0-20% ethyl acetate) afforded compound 309 as a pale yellow oil (219 mg, 48%).



**tert-Butyl (2R)-2-(((tert-butyl(dimethyl)silyl)oxy)methyl)-4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (310):** A 10 mL reaction vessel was charged with compound 245 (83.0 mg, 306  $\mu$ mol), compound 309 (135 mg, 306  $\mu$ mol), tris(dibenzylideneacetone)dipalladium (0) (21.0 mg, 22.9  $\mu$ mol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (26.6 mg, 45.9  $\mu$ mol), sodium *t*-butoxide (58.8 mg, 612  $\mu$ mol), and dioxane (2.5 mL). The reaction was purged with argon and heated with microwave energy (300W) for 2 hours at 120°C. The resulting solution was added to aqueous K<sub>2</sub>CO<sub>3</sub> (30 mL) and extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried (MgSO<sub>4</sub>) and

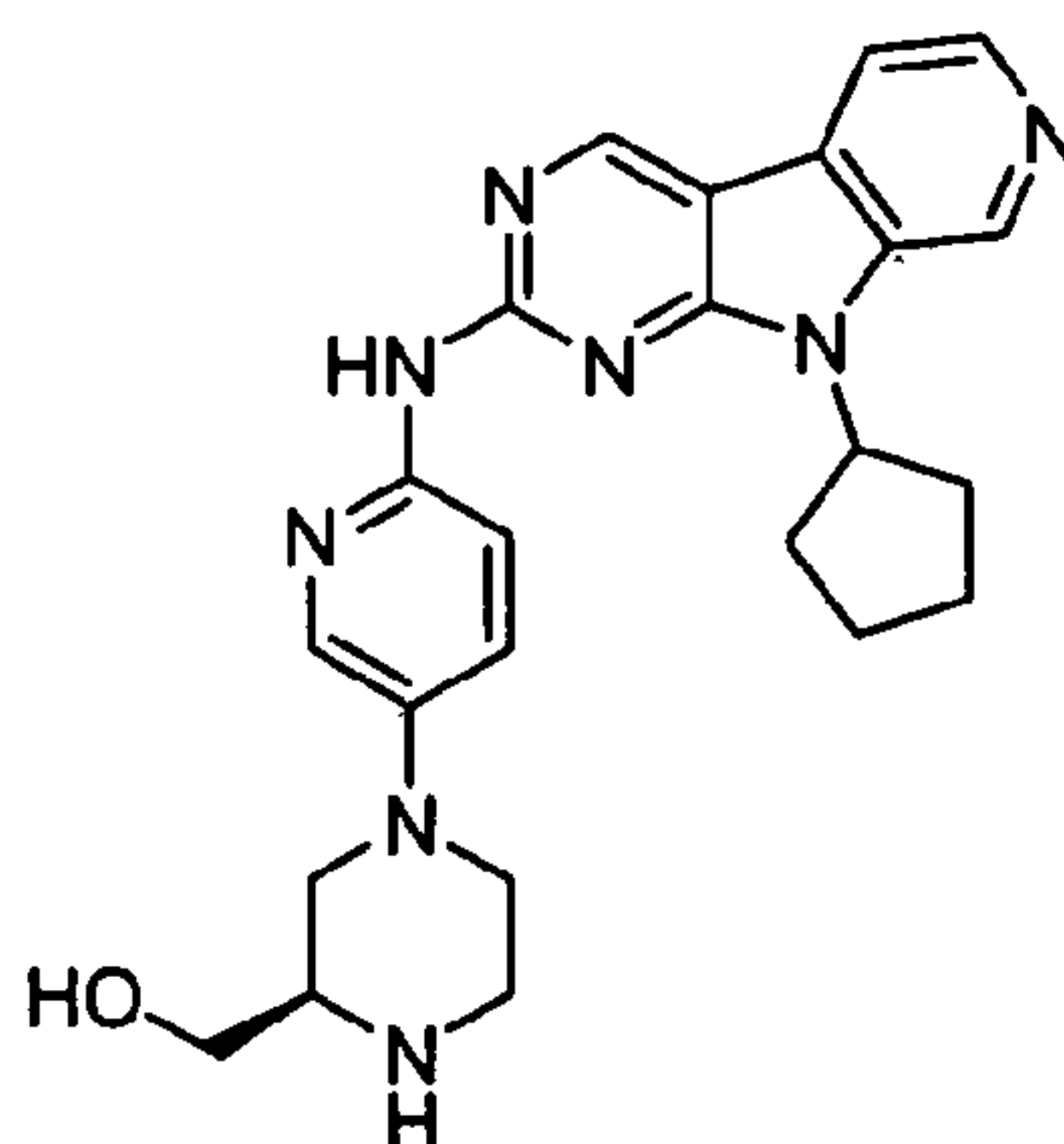


evaporated to give a yellow oil. Silica gel chromatography (gradient elution hexanes/20-100% ethyl acetate) afforded compound **310** as a colorless oil (142 mg, 69%).



**((2R)-4-(6-((9-Cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol (306):** Compound **310** (140 mg, 207  $\mu$ mol) was dissolved in dichloromethane (6 mL). Trifluoroacetic acid (2.00 mL, 2.60 mmol) and 3 drops water were added and the reaction was stirred at room temperature for 3 days. The resulting solution was added dropwise with stirring to aq.  $K_2CO_3$  (10%, 30 mL), which was then extracted with dichloromethane+10% methanol (3X 30 mL). The combined organics were dried ( $MgSO_4$ ) and evaporated to give a yellow oil. Silica gel chromatography (gradient elution ethyl acetate+2.5% TEA/0-100% ethyl acetate+10% 2M  $NH_3$  in methanol) afforded the product as a yellow solid. This residue was taken up in dichloromethane (3 mL) and trifluoroacetic acid (13.3  $\mu$ l, 2.0 equiv.) was added. The solvent was removed *in vacuo* to give compound **306** as a yellow solid (54 mg).  $^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  9.40 (s, 1 H) 9.03 - 9.22 (m, 1 H) 8.65 - 8.82 (m, 1 H) 8.10 (d,  $J=2.93$  Hz, 4 H) 7.64 - 7.78 (m, 1 H) 5.38 - 5.58 (m, 1 H) 3.70 - 3.87 (m, 3 H) 3.61 - 3.69 (m, 1 H) 3.58 (s, 1 H) 3.41 (none, 2 H) 3.15 - 3.29 (m, 1 H) 3.07 - 3.15 (m, 0 H) 2.96 - 3.07 (m, 1 H) 2.83 - 2.94 (m, 1 H) 2.26 - 2.37 (m, 2 H) 2.08 - 2.18 (m, 2 H) 1.97 - 2.08 (m, 2 H) 1.69 - 1.84 (m, 2 H) 1.14 - 1.22 (m, 1 H) ppm.

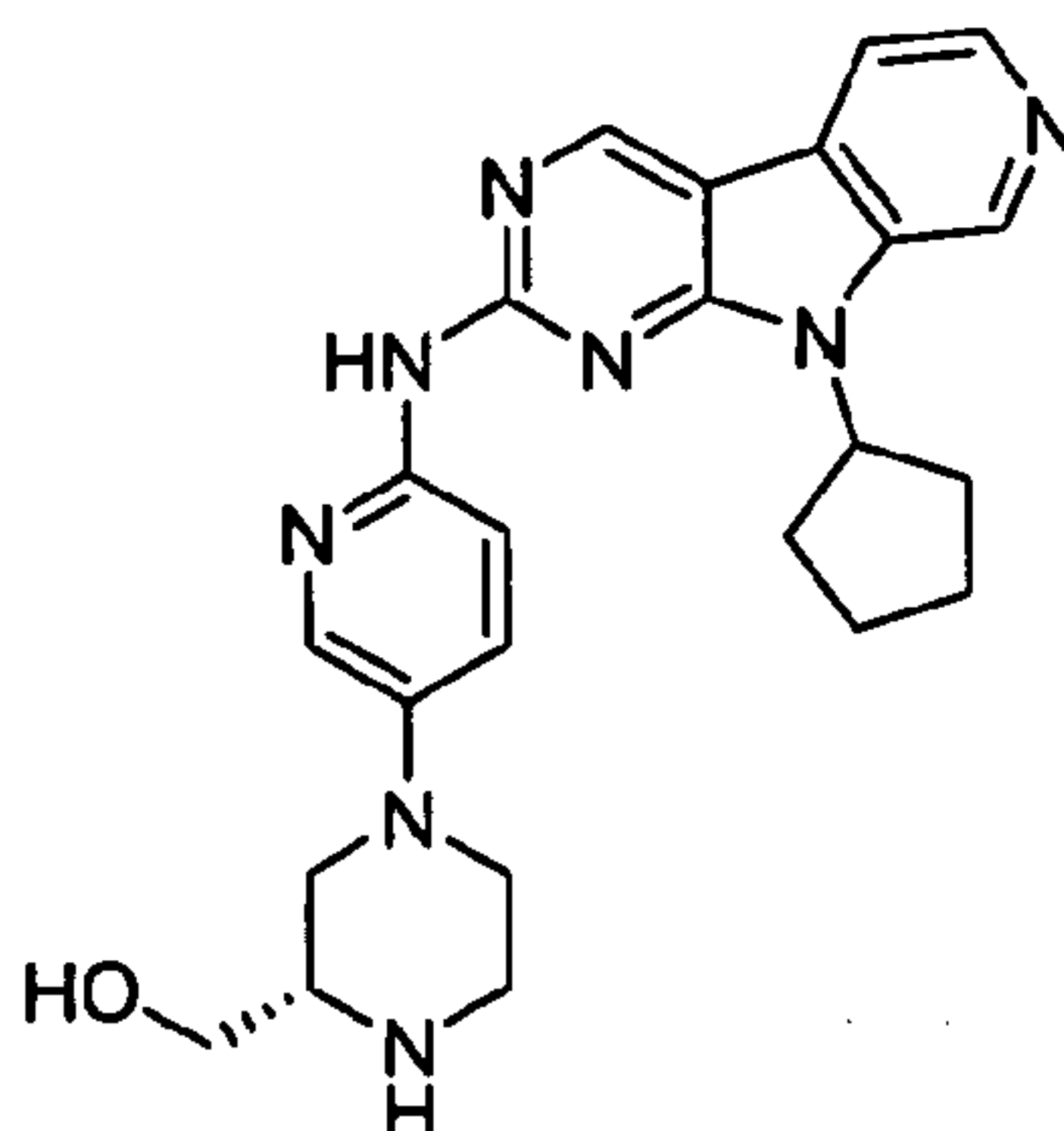


**EXAMPLE 197****311**

**((2R)-4-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol**

Compound **311** was prepared using the methods described in Example 196

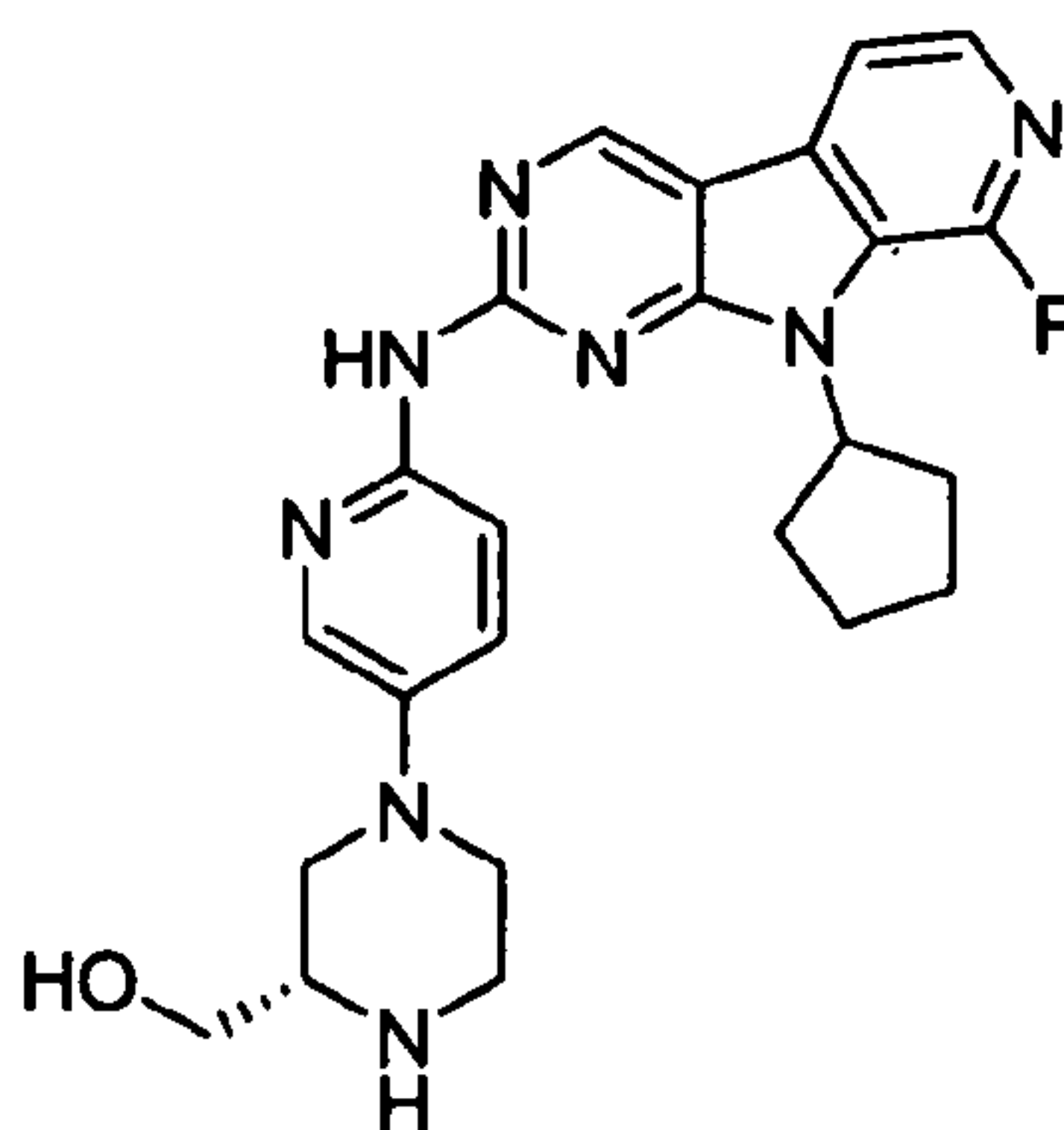
<sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.50 - 9.57 (m, 1 H) 9.26 - 9.34 (m, 1 H) 9.04 - 9.15 (m, 1 H) 8.66 - 8.77 (m, 1 H) 8.60 - 8.66 (m, 1 H) 8.45 - 8.54 (m, 1 H) 8.09 - 8.19 (m, 3 H) 7.57 - 7.67 (m, 1 H) 5.31 - 5.42 (m, 1 H) 3.70 - 3.88 (m, 4 H) 3.60 - 3.70 (m, 1 H) 3.16 - 3.28 (m, 1 H) 2.96 - 3.07 (m, 1 H) 2.84 - 2.94 (m, 2 H) 2.01 - 2.19 (m, 6 H) 1.69 - 1.84 (m, 3 H) 1.10 (none, 1 H) ppm.

**EXAMPLE 198****312**

**((2S)-4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol**

Compound **312** was prepared using the methods described in Example 196. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 9.54 (s, 1 H) 9.32 (s, 1 H) 9.10 - 9.20 (m, 1 H) 8.69 - 8.80 (m, 1 H) 8.65 (d, *J*=6.11 Hz, 1 H) 8.48 - 8.55 (m, 1 H) 8.15 (d, *J*=2.93 Hz, 2 H) 7.59 - 7.67 (m, 1 H) 5.32 - 5.43 (m, 1 H) 3.70 - 3.88 (m, 3 H) 3.60 - 3.69 (m, 1 H) 3.39 (d, 2 H) 3.16 - 3.29 (m, 1 H) 3.07 - 3.16 (m, 1 H) 2.97 - 3.07 (m, 1 H) 2.84 - 2.93 (m, 1 H) 2.38 - 2.48 (m, 2 H) 2.02 - 2.18 (m, 4 H) 1.70 - 1.83 (m, 2 H) 1.19 (s, 1 H) 1.10 (s, 1 H) ppm.

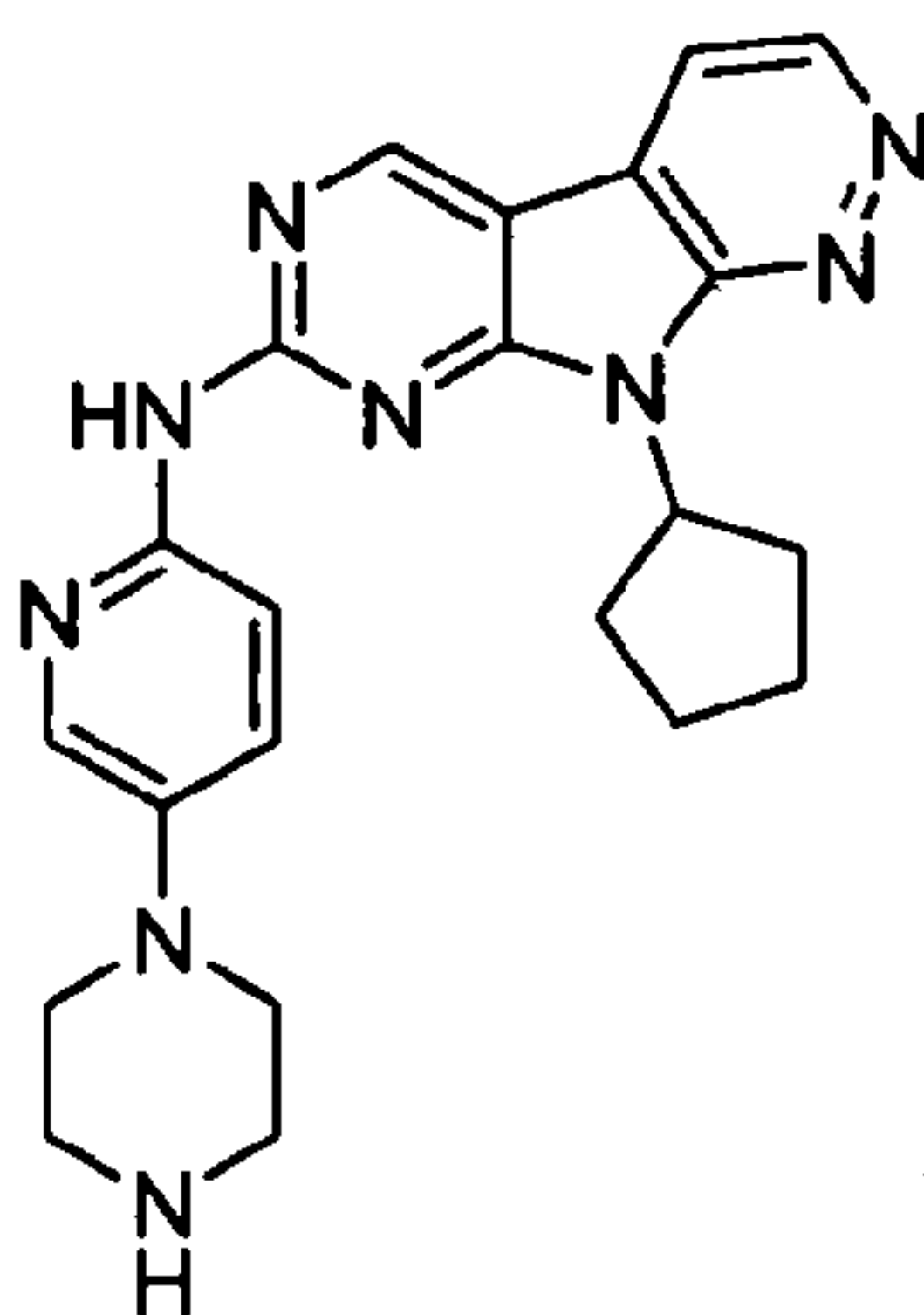


**EXAMPLE 199****313**

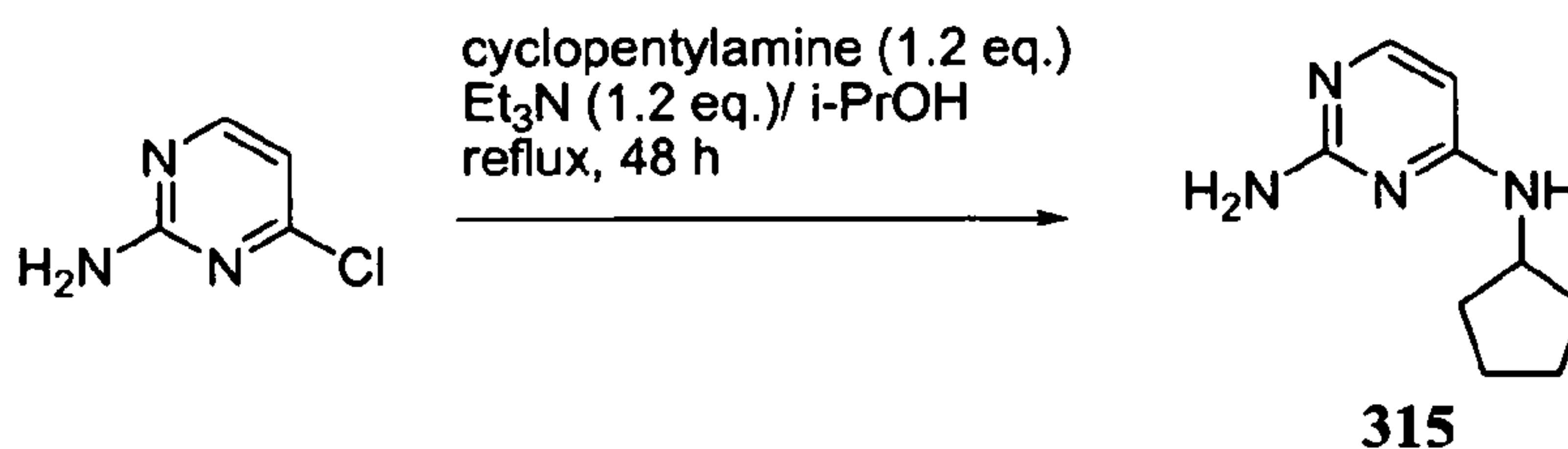
**((2S)-4-(6-((9-cyclopentyl-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)-2-piperazinyl)methanol**

Compound 313 was prepared using the methods described in Example 196.

<sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ 10.39 (none, 1 H) 9.40 (s, 1 H) 9.03 - 9.17 (m, 1 H) 8.60 - 8.80 (m, 1 H) 8.10 (d, *J*=2.45 Hz, 4 H) 7.62 - 7.77 (m, 1 H) 5.41 - 5.55 (m, 1 H) 3.68 - 3.86 (m, 3 H) 3.57 - 3.68 (m, 1 H) 3.35 - 3.42 (m, 2 H) 3.17 - 3.28 (m, 1 H) 2.97 - 3.06 (m, 1 H) 2.84 - 2.93 (m, 1 H) 2.26 - 2.40 (m, 2 H) 2.08 - 2.18 (m, 2 H) 1.97 - 2.08 (m, 2 H) 1.69 - 1.82 (m, 2 H) ppm.

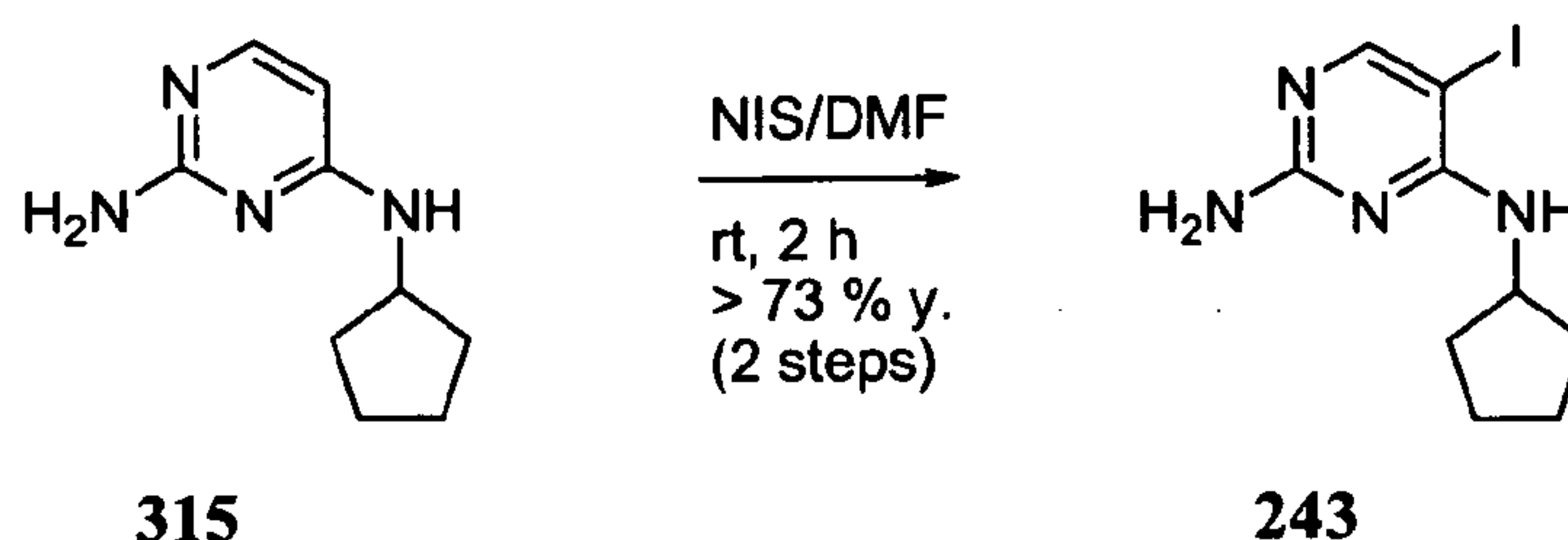
**EXAMPLE 200****314**

**9-Cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine**

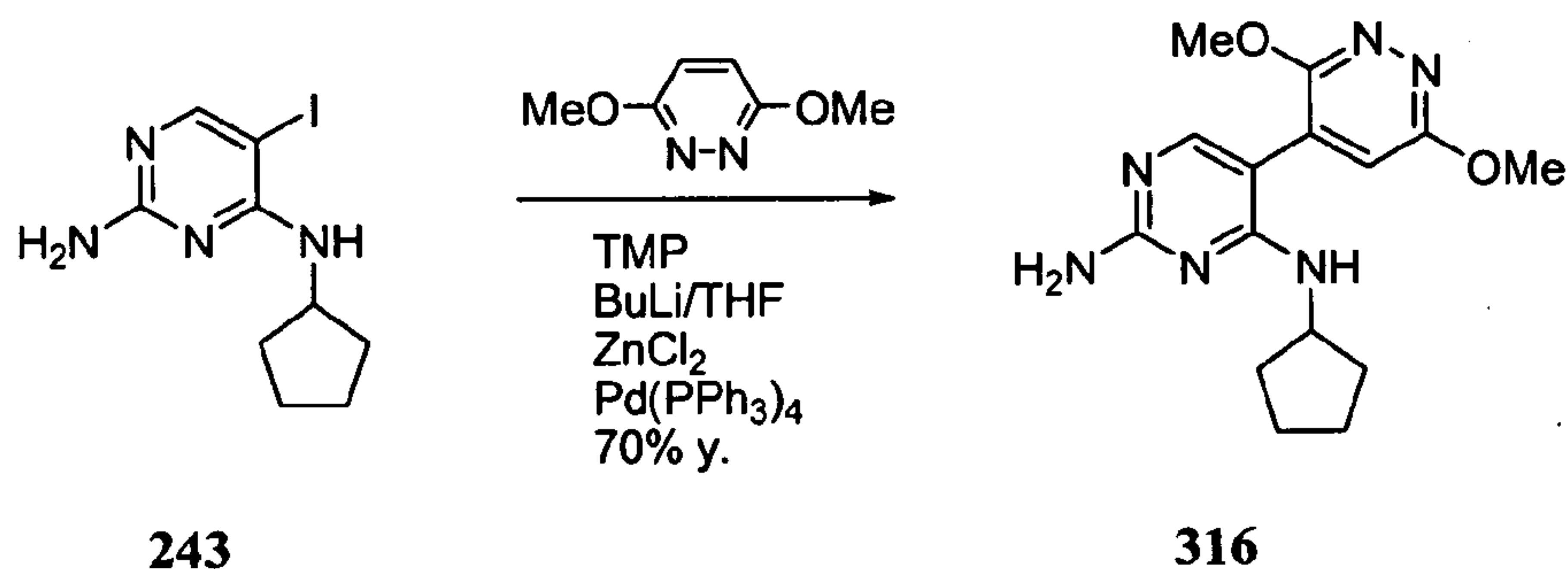
**315**



**N4-Cyclopentyl-2,4-pyrimidinediamine (315):** A mixture of 2-amino-4-chloropyrimidine (22.8 g, 176 mmol), cyclopentylamine (20.9 mL, 211 mmol) and triethylamine (29.4 mL, 211 mmol) in EtOH (200 mL) was heated at reflux (105 °C, oil bath) for 48 h. Upon workup, the volatile was removed *in vacuo*. The residue was poured into ice and saturated Na<sub>2</sub>CO<sub>3</sub> aqueous solution and extracted with ethyl acetate (3 X). The combined organics were washed with saturated Na<sub>2</sub>CO<sub>3</sub> aqueous solution (1 X), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give N4-cyclopentylpyrimidine-2,4-diamine (315) (26.5 g) as a light yellow solid of 92% purity. This batch of material was taken onto the next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 179.1, Calculated 179.1.



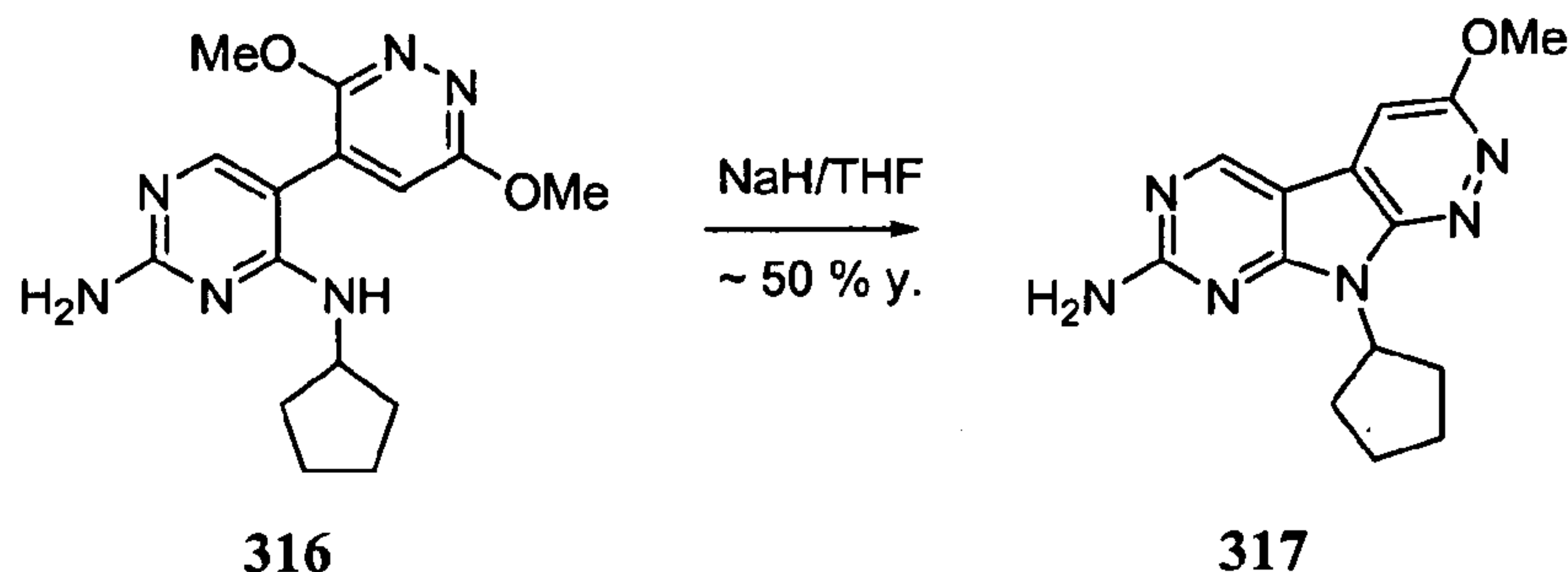
**N4-Cyclopentyl-5-iodo-2,4-pyrimidinediamine (243):** To a stirred solution of compound 315 (25.5 g, 143 mmol) in DMF (120 mL) was added N-iodosuccinimide (32 g, 143 mmol) in two portions at rt. The resulting mixture was stirred at rt for 2 h. Upon workup, the mixture was poured into ice and saturated Na<sub>2</sub>CO<sub>3</sub> aqueous solution with some sodium sulfite and extracted with ethyl acetate (2X). The combined organics were washed with saturated Na<sub>2</sub>CO<sub>3</sub> aqueous solution (3X), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound 243 (39 g, 73% yield in 2 steps). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.89 (1 H, s), 6.18 (2 H, s), 5.63 (1 H, d, J=7.6 Hz), 4.30 (1 H, sxt, J=7.4 Hz), 1.84 - 1.96 (2 H, m), 1.61 - 1.74 (2 H, m), 1.42 - 1.58 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 305.0.



**N4-Cyclopentyl-5-(3,6-dimethoxy-4-pyridazinyl)-2,4-pyrimidinediamine (316):** A solution of butyllithium (2.5M solution in hexanes) (7.5 mL, 19 mmol) was added to cold (acetonitrile-dry ice bath, -34 °C internal), stirred 2,2,6,6-tetramethylpiperidine (3.4 mL, 20 mmol). The resulting mixture was allowed to stand at 0 °C (ice-H<sub>2</sub>O bath) for 30 min. The ice-



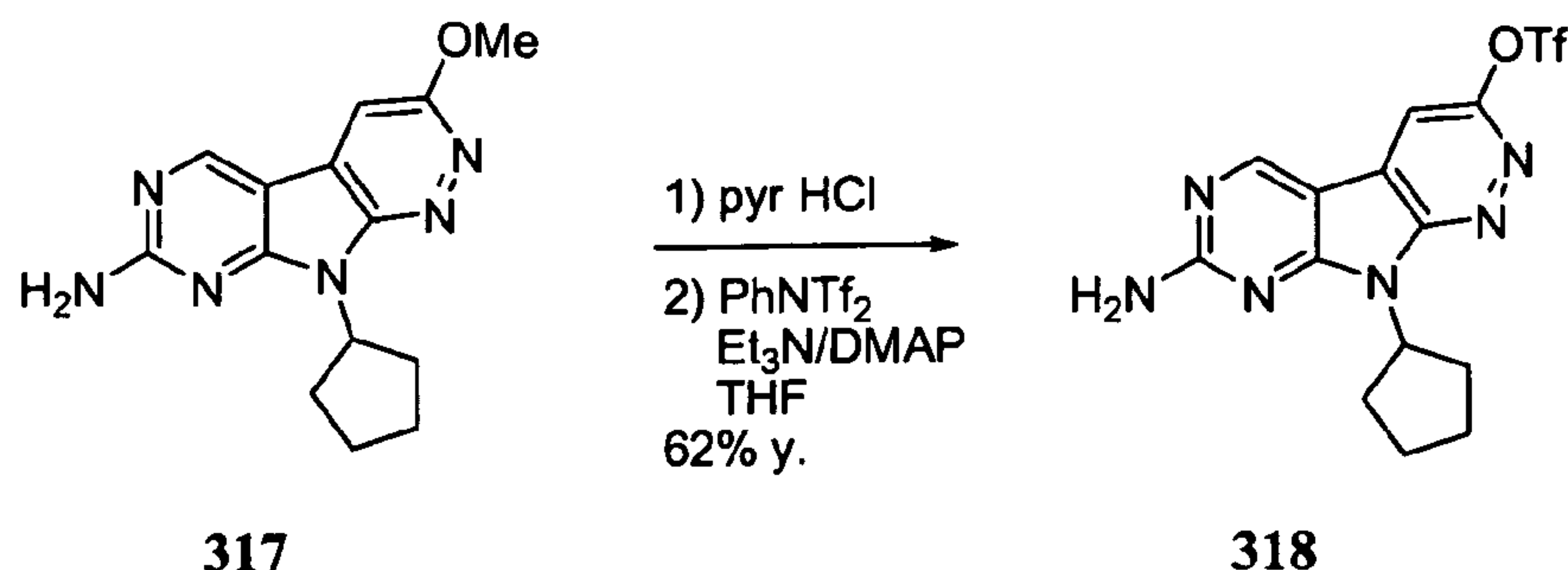
H<sub>2</sub>O was then replaced with dry ice-2-propanol bath and the mixture was cooled to -0 °C. THF (24 mL) was added. A pre-cooled (ice-H<sub>2</sub>O bath) solution of 3,6-dimethoxypyridazine (2.40 g, 17 mmol) in THF (40 mL) was added through a cannula over a period of 30 min. The internal temperature was observed fluctuating between -72 °C and -55 °C. The resulting mixture was stirred at -70 °C for 1.5 h. A solution of zinc(II) chloride (0.5 M in THF) (34 mL, 17 mmol) was added through a syringe over a period of 15 min. The internal temperature fluctuated between -73 °C and -64 °C. The cold bath was removed and the resulting mixture was allowed to warm up to rt (20.5 °C). A solution of compound **243** (1.7 g, 5.7 mmol) and tetrakis(triphenylphosphine)palladium (0.33 g, 0.29 mmol) in THF (20 mL) was added and the resulting mixture was heated at reflux for 18 h. Upon workup, the crude mixture was cooled in an ice-H<sub>2</sub>O before poured into ice and saturated NH<sub>4</sub>Cl aqueous solution and extracted with ethyl acetate (2 X). The combined organics were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/DCM with Et<sub>3</sub>N) to give pure compound **316** (1.2 g, 66% yield) as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.53 (1 H, s), 7.01 (1 H, s), 6.18 - 6.38 (3 H, m), 4.35 - 4.51 (1 H, m, J=7.3, 7.3, 7.3, 7.3, 7.0 Hz), 3.95 (3 H, s), 3.91 (3 H, s), 1.77 - 1.90 (2 H, m), 1.55 - 1.69 (2 H, m), 1.35 - 1.55 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 317.2.



**9-Cyclopentyl-3-methoxy-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (317):**

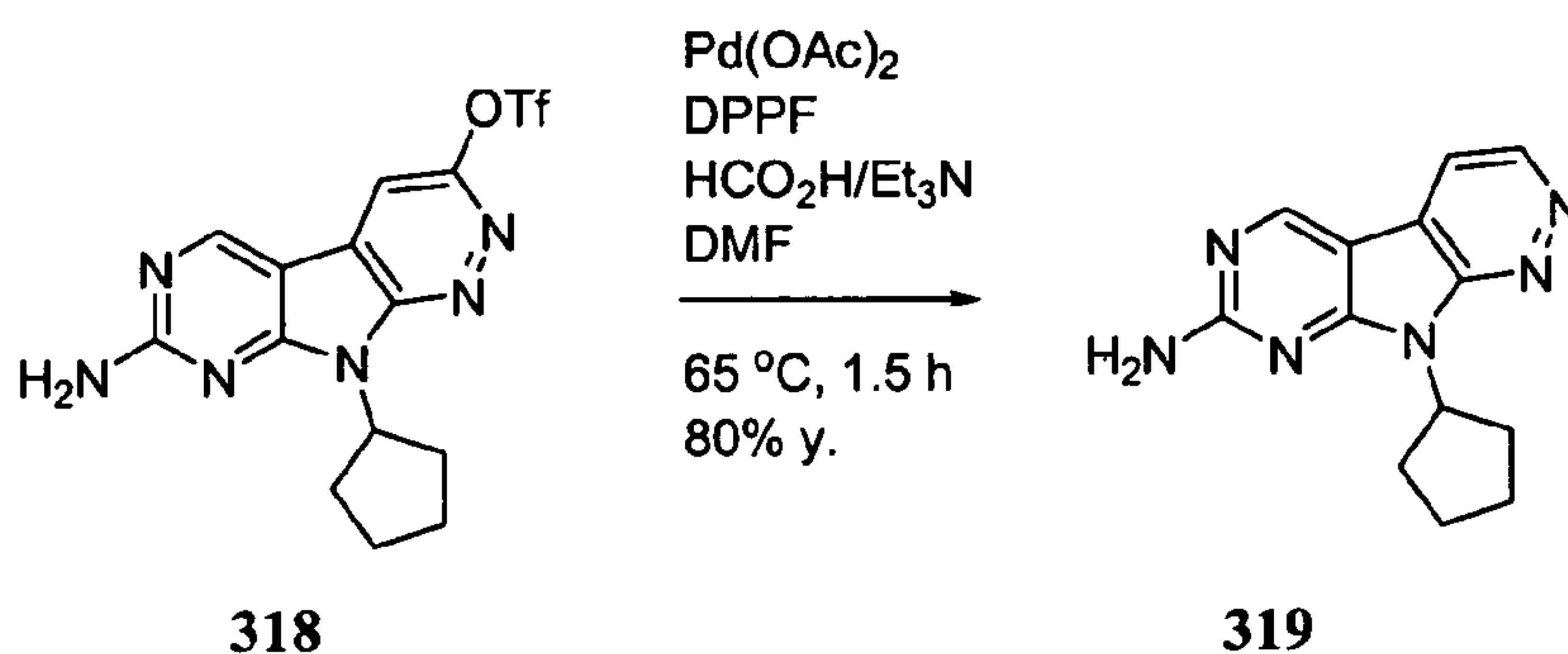
To a 35 mL microwave reaction vessel were placed with compound **316** (200 mg, 0.63 mmol) followed by THF and sodium hydride, (60% in mineral oil, 0.063 g, 1.6 mmol). The resulting mixture was stirred at room temperature for 10 min to allow gas release. Then the vessel was subjected to microwave reaction condition (60 min at 150 °C). The crude mixture was subjected to combi-flash column chromatography (methanol/DCM) to give compound **317** (0.17 g) as a light yellow solid (contaminated with mineral oil). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.97 (1 H, s), 7.57 (1 H, s), 7.28 (2 H, s), 5.28 (1 H, quin, J=8.7 Hz), 4.02 (3 H, s), 2.38 - 2.46 (2 H, m), 1.89 - 2.10 (4 H, m), 1.62 - 1.78 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 285.1.





**7-Amino-9-cyclopentyl-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-3-yl**

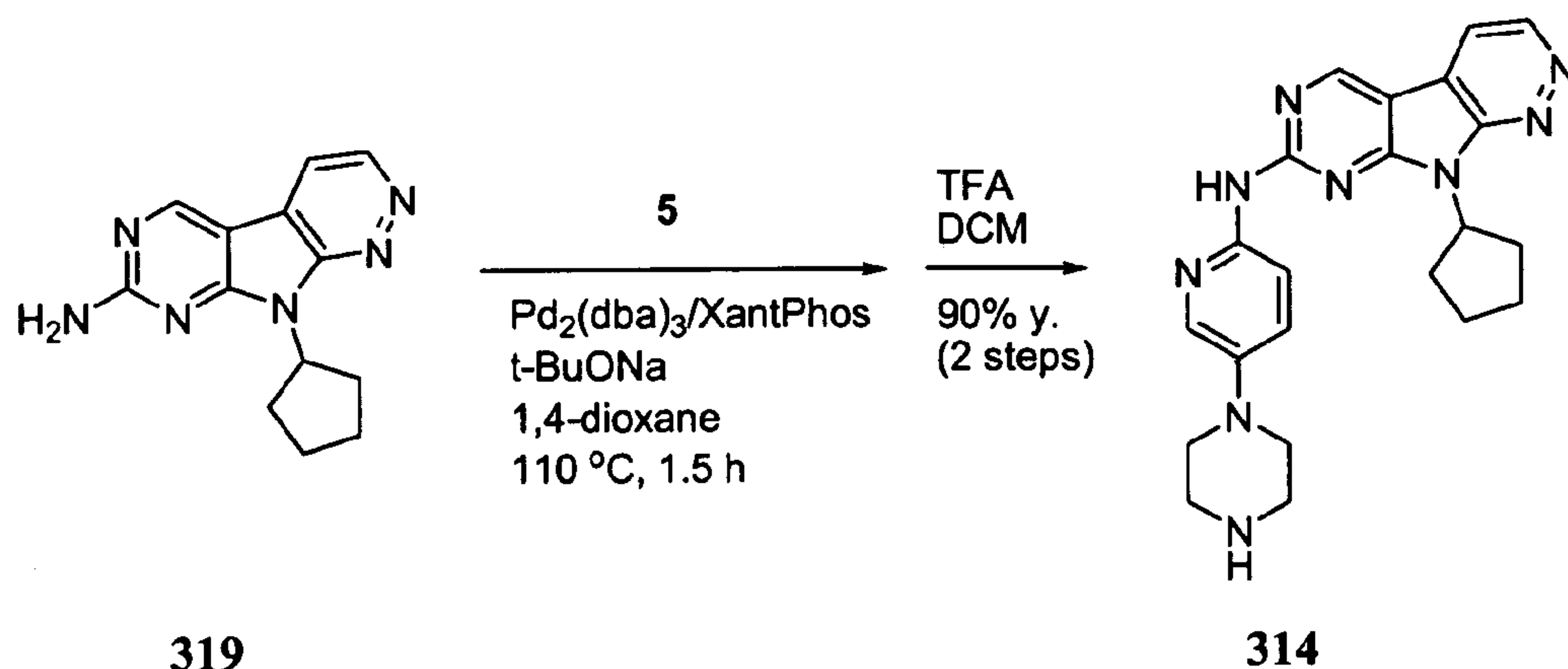
**trifluoromethanesulfonate (318):** A mixture of compound 317 (0.17 g, 0.60 mmol) and pyridine hydrochloride (0.69 g, 6.0 mmol) was heated at 200 °C (oil bath) overnight. After cooling to room temperature, the mixture was dissolved in THF (6 mL). Triethylamine (1.3 mL, 9.0 mmol) (2.0 mL), N,N-dimethylpyridin-4-amine (0.0073 g, 0.060 mmol) (catalytic amount), and N-phenyltrifluoromethanesulfonimide (0.54 g, 1.5 mmol) were added at room temperature. The resulting mixture was sonicated for 10 min and stirred for 2 h. Upon workup, the mixture was subjected to combi-flash column chromatography (ethyl acetate/Hexanes) to give compound 318 (0.15 g, 62% yield) as an off-white solid. LCMS-ESI (POS), M/Z, M+1: Found 403.0.



**9-Cyclopentyl-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (319):** In a 25 mL single-necked round bottom flask were placed compound 318 (94 mg, 234 μmol), palladium diacetate (21 mg, 93 μmol), and 1,1'-bis(diphenylphosphino)ferrocene (130 mg, 234 μmol). The flask was subjected to 3 cycles of evacuation and back-filling with N<sub>2</sub>. DMF (3 mL) was added under N<sub>2</sub> followed by triethylamine (715 μl, 5140 μmol) and formic acid, 98 % (176 μl, 4.67 mmol). The resulting mixture was stirred in an oil bath at 65 °C for 1.5 h. The mixture was poured into ice and saturated NaHCO<sub>3</sub> aqueous solution and extracted with 10% i-PrOH/DCM (2 X). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/DCM with Et<sub>3</sub>N) to give compound 319 (48 mg, 80% yield) as a reddish solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 9.08 (1 H, s), 9.01 (1 H, d, J=5.1 Hz), 8.07 (1 H, d, J=5.1 Hz), 7.28 (2 H, s), 5.42 (1 H,

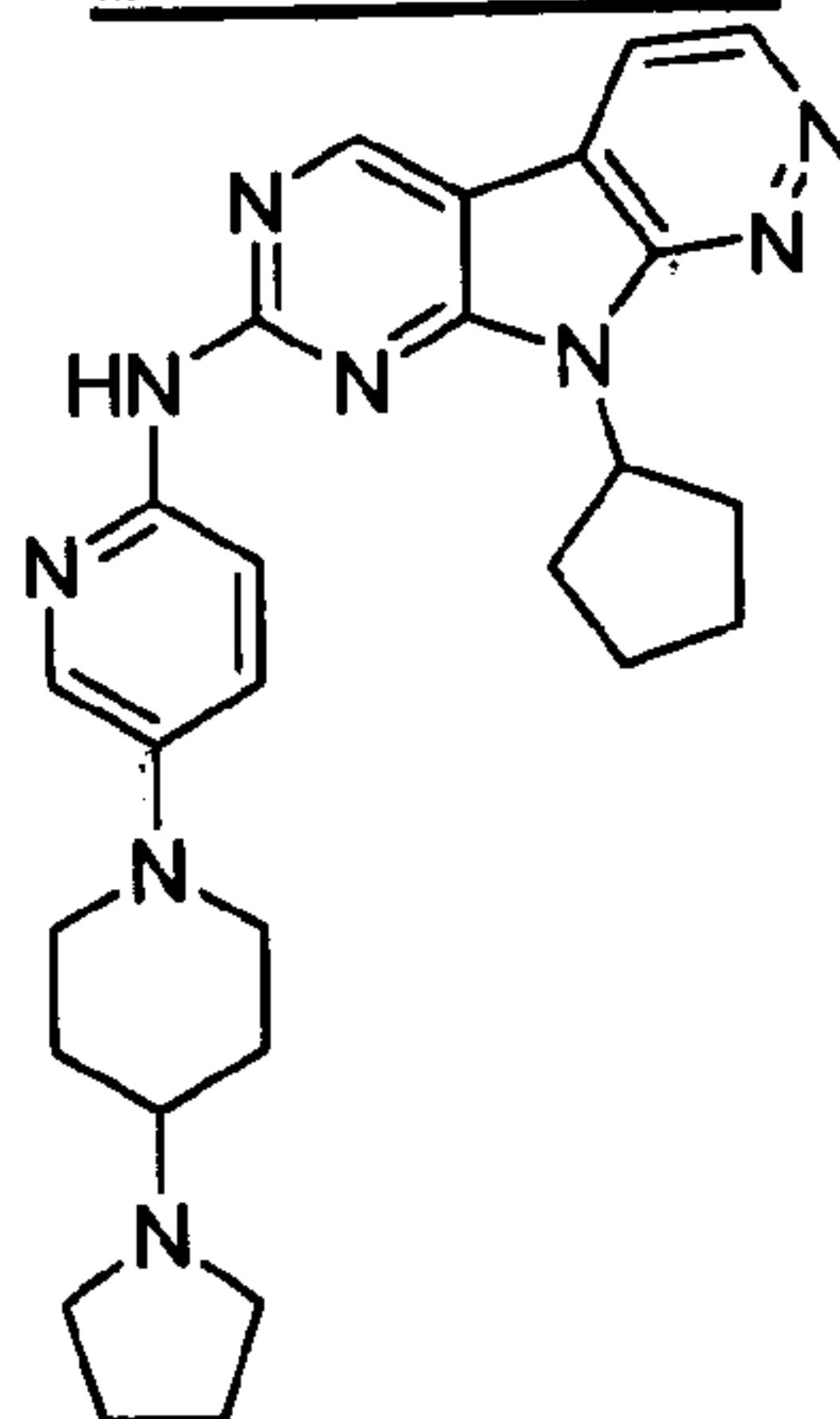


quin,  $J=8.6$  Hz), 2.40 - 2.49 (2 H, m), 1.92 - 2.14 (4 H, m), 1.63 - 1.80 (2 H, m). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 255.1.



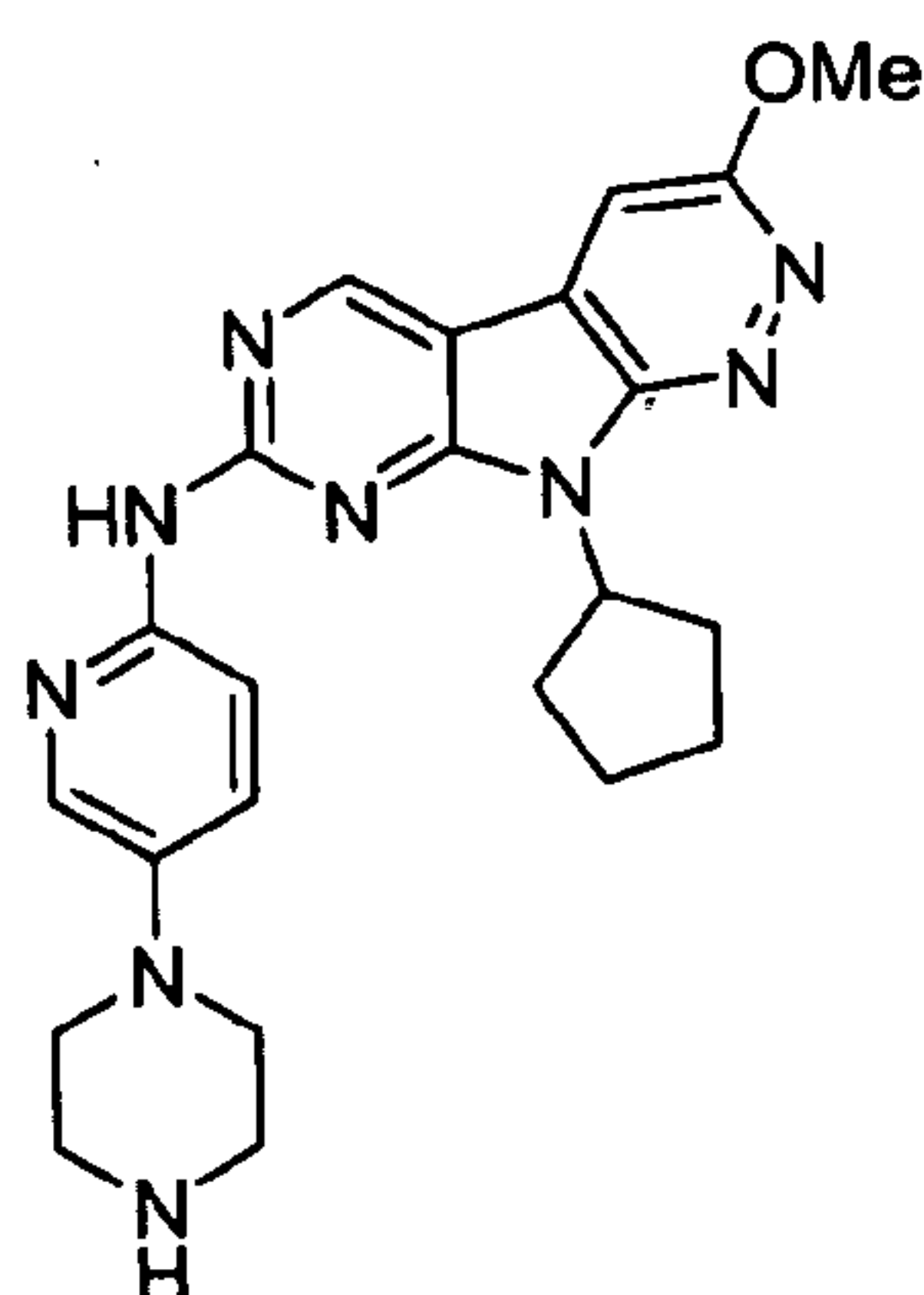
**9-Cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (314):** In a 10 mL microwave reaction vessel were placed compound **5** (42 mg, 142  $\mu$ mol), tris(dibenzylideneacetone)dipalladium (o) (13 mg, 14  $\mu$ mol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (20 mg, 35  $\mu$ mol), and sodium tert-butoxide (41 mg, 425  $\mu$ mol) followed by a solution of compound **319** (36 mg, 142  $\mu$ mol) in 1,4-dioxane (3 mL). The vessel was purged with N<sub>2</sub> for 3 min, then capped and subjected to microwave condition (1.5 h at 110 °C). After the volatiles were removed, the residue was subjected to combi-flash column chromatography (methanol/DCM). A solution of the intermediate in DCM (15 mL) was treated with trifluoroacetic acid (0.70 mL, 9.4 mmol) at room temperature for 1.5 h. After the volatiles were removed, the residue was subjected to preparative reverse phase HPLC (acetonitrile/H<sub>2</sub>O containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **314** (56 mg, bis-TFA salt) as a yellow solid. <sup>1</sup>H NMR (400 MHz, methanol)  $\delta$  ppm 9.47 (1 H, s), 9.23 (1 H, d,  $J=5.5$  Hz), 8.49 (1 H, d,  $J=5.5$  Hz), 7.99 - 8.11 (2 H, m), 7.75 (1 H, d,  $J=9.4$  Hz), 5.68 (1 H, quin,  $J=8.5$  Hz), 3.49 - 3.58 (4 H, m), 3.41 - 3.49 (4 H, m), 2.50 - 2.71 (2 H, m), 2.12 - 2.29 (4 H, m), 1.76 - 1.94 (2 H, m). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 416.2.



**EXAMPLE 201****320**

**9-cyclopentyl-N-(5-(4-(1-pyrrolidinyl)-1-piperidinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine**

Compound **320** was prepared as a TFA salt using chemistry similar to that described in example 200. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 9.46 (1 H, s), 9.22 (1 H, d, J=5.1 Hz), 8.45 (1 H, d, J=5.5 Hz), 8.07 (1 H, dd, J=9.6, 2.9 Hz), 8.00 (1 H, d, J=2.7 Hz), 7.67 (1 H, d, J=9.8 Hz), 5.69 (1 H, qd, J=8.5, 8.2 Hz), 3.92 (2 H, d, J=12.9 Hz), 3.66 - 3.76 (2 H, m), 3.36 - 3.38 (1 H, m), 3.21 (2 H, d, J=11.0 Hz), 2.93 (2 H, td, J=12.5, 2.0 Hz), 2.54 - 2.68 (2 H, m), 2.33 (2 H, d, J=13.3 Hz), 2.13 - 2.27 (6 H, m), 1.96 - 2.10 (2 H, m), 1.79 - 1.95 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 484.2.

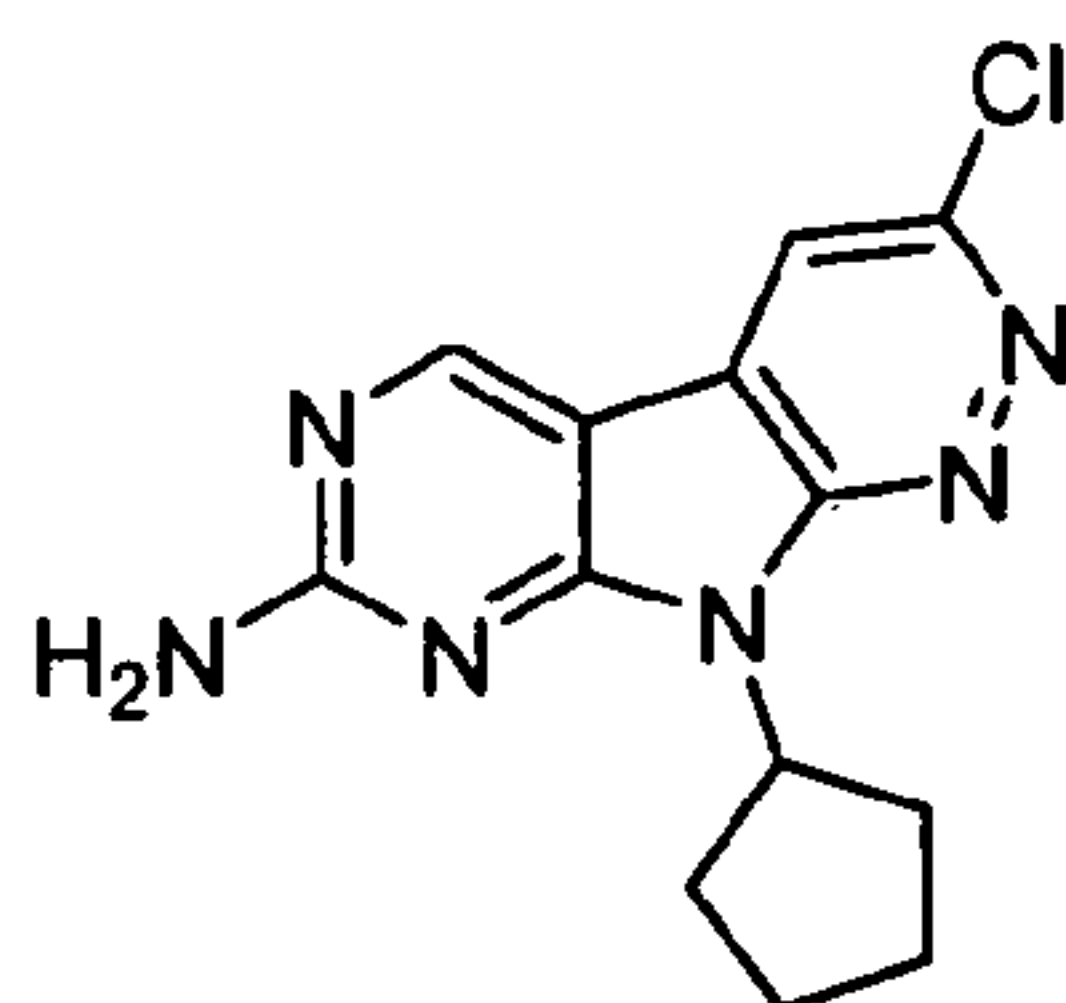
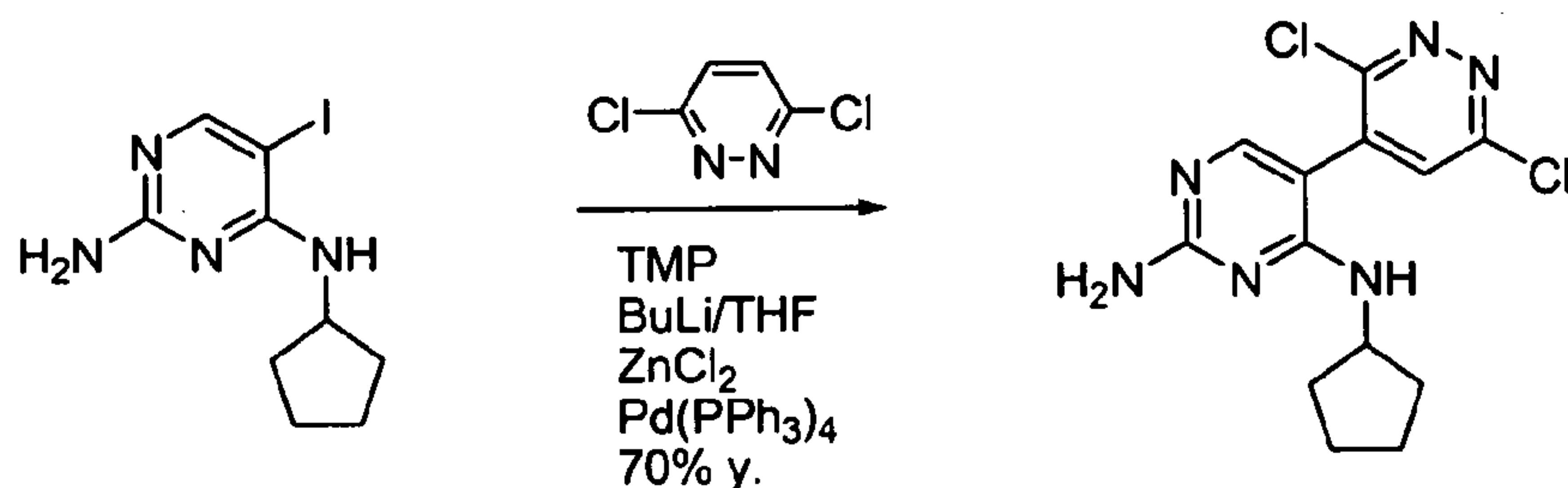
**EXAMPLE 202****321**

**9-cyclopentyl-3-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine**

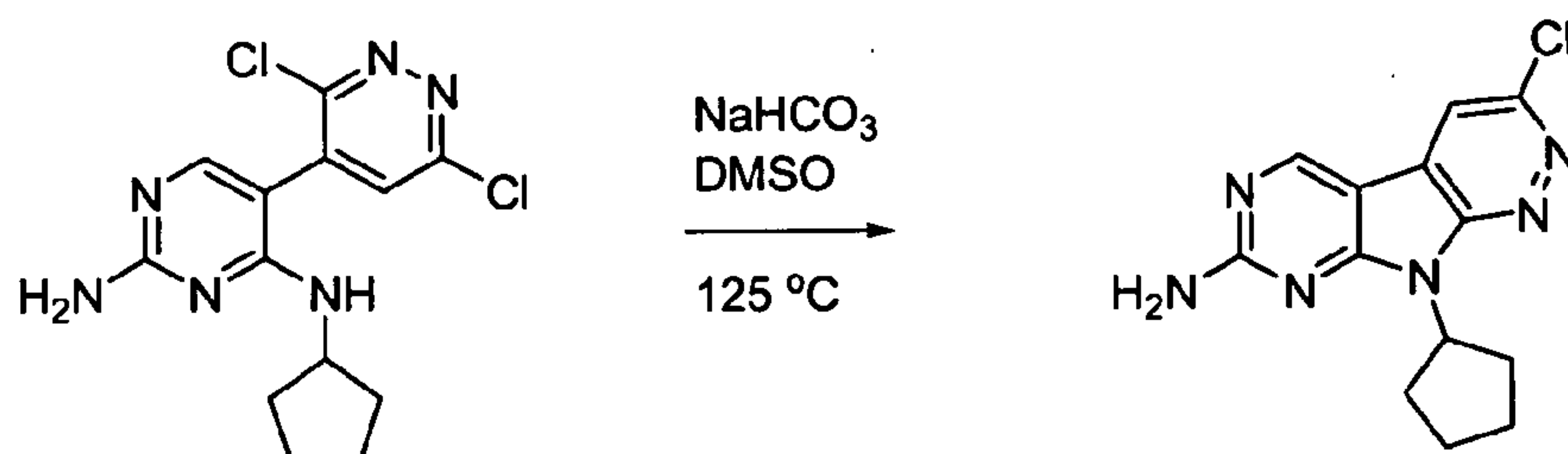
Compound **321** was prepared as a TFA salt from **317** using chemistry similar to that described in example 1. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 9.22 (1 H, s), 8.02 (1 H, d, J=2.7 Hz), 7.95



(1 H, dd, J=9.6, 2.3 Hz), 7.71 (1 H, s), 7.61 - 7.68 (3 H, m), 5.50 (1 H, quin, J=8.6 Hz), 4.15 (3 H, s), 3.45 - 3.54 (4 H, m), 3.37 - 3.45 (4 H, m), 2.48 - 2.66 (2 H, m), 2.04 - 2.22 (4 H, m), 1.73 - 1.89 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 446.0.

**EXAMPLE 203****322****3-chloro-9-cyclopentyl-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine****243****323****N4-Cyclopentyl-5-(3,6-dichloro-4-pyridazinyl)-2,4-pyrimidinediamine (323)**

Compound **323** was prepared from compound **243** and 3,6-dichloropyridazine using chemistry similar to that described in example 200. LCMS-ESI (POS), M/Z, M+1: Found 325.0.

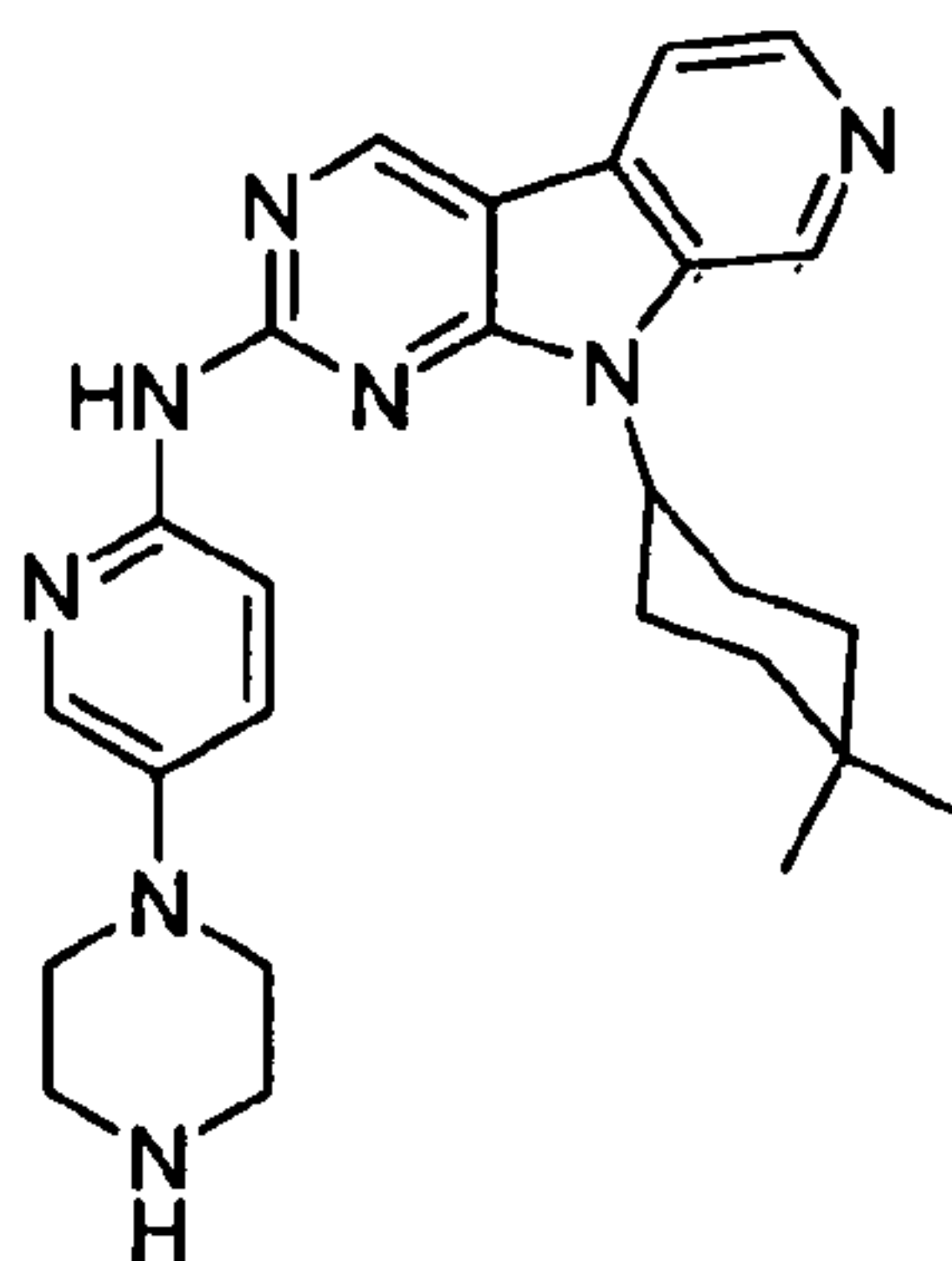
**323****322**

**3-Chloro-9-cyclopentyl-9H-pyrimido[5',4':4,5]pyrrolo[2,3-c]pyridazin-7-amine (322):** A mixture of crude N4-cyclopentyl-5-(3,6-dichloropyridazin-4-yl)pyrimidine-2,4-diamine (**323**) (0.27 g, 0.83 mmol) and sodium bicarbonate (0.065 mL, 1.7 mmol) in DMSO (10 mL) was heated in an oil bath at 110 °C for 11 h. Then the temperature was raised to 125 °C and stirred at this temperature for 200 min at which time LC-MS showed completion. Upon workup, the mixture was poured into ice and saturated NH<sub>4</sub>Cl aqueous solution and extracted with ethyl acetate (3 X). The combined organics were washed with saturated NH<sub>4</sub>Cl aqueous solution (1 X), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was subjected to combi-flash



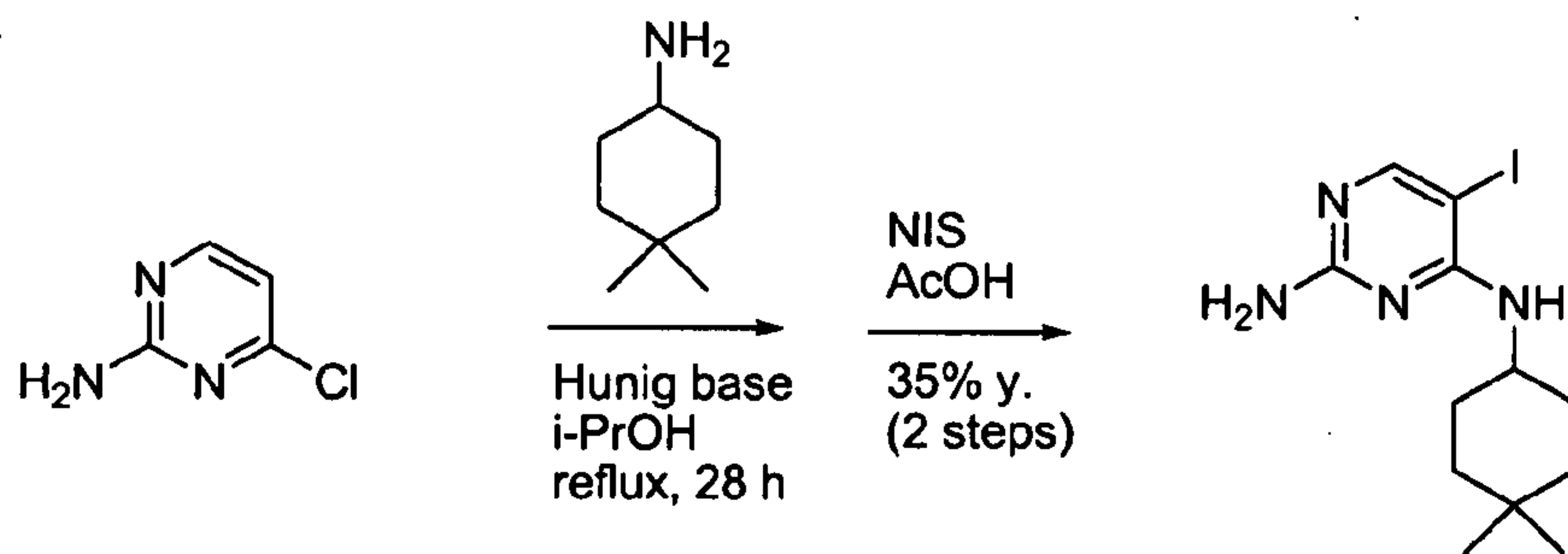
column chromatography (methanol/DCM). The impure product thus obtained was subjected to subjected to preparative reverse phase HPLC (acetonitrile/H<sub>2</sub>O containing 0.1% TFA each). After lyophilization, 15 mg of compound **322** was obtained as a TFA salt as an off-white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 9.06 (1 H, s), 8.21 (1 H, s), 5.50 (1 H, quin, J=8.6 Hz), 2.43 - 2.60 (2 H, m), 1.99 - 2.25 (4 H, m), 1.71 - 1.89 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 289.1.

#### EXAMPLE 204



**324**

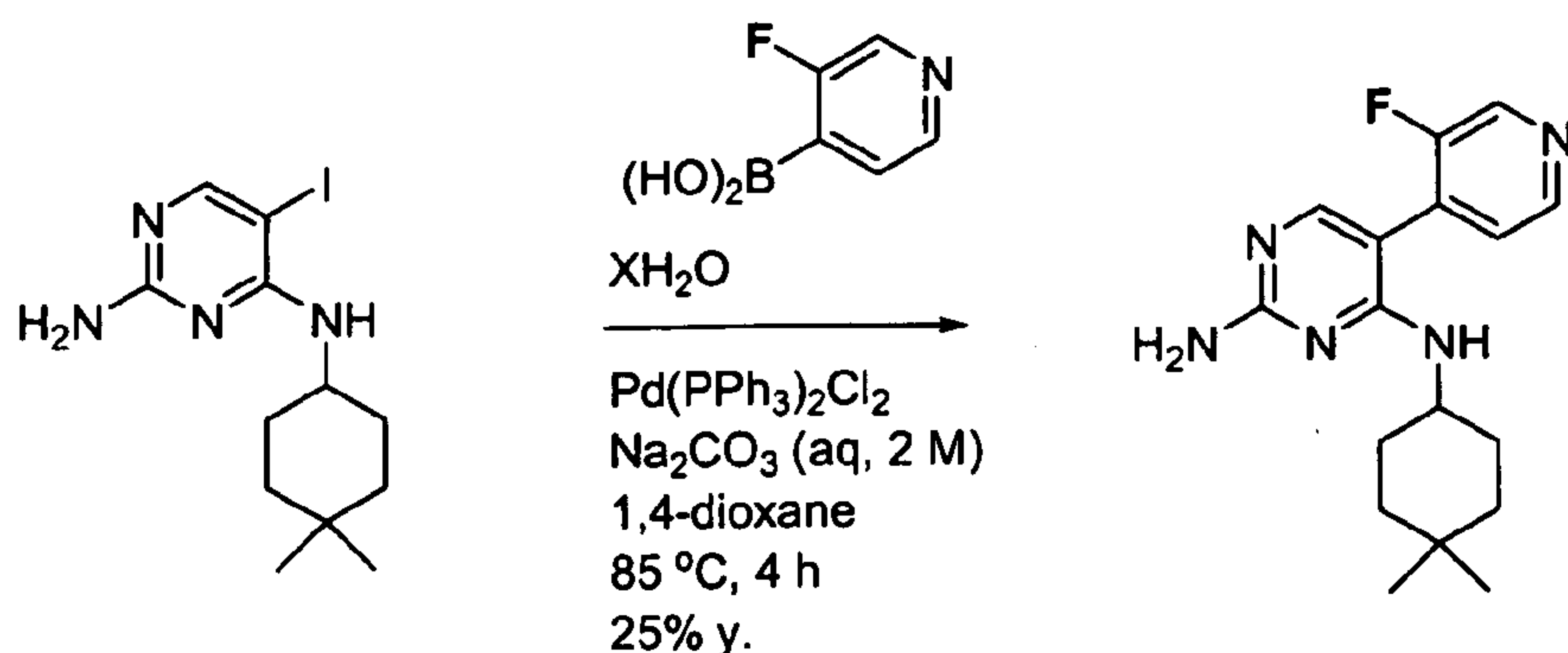
**9-(4,4-dimethylcyclohexyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



**326**

**N4-(4,4-dimethylcyclohexyl)-5-iodo-2,4-pyrimidinediamine (326):** Compound **326** was prepared as an off-white solid using chemistry similar to that described in example 200. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.88 (1 H, s), 6.13 (2 H, s), 5.66 (1 H, d, J=8.6 Hz), 3.78 - 3.95 (1 H, m), 1.49 - 1.66 (4 H, m), 1.30 - 1.41 (2 H, m), 1.15 - 1.28 (2 H, m), 0.94 (3 H, s), 0.91 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 347.0.



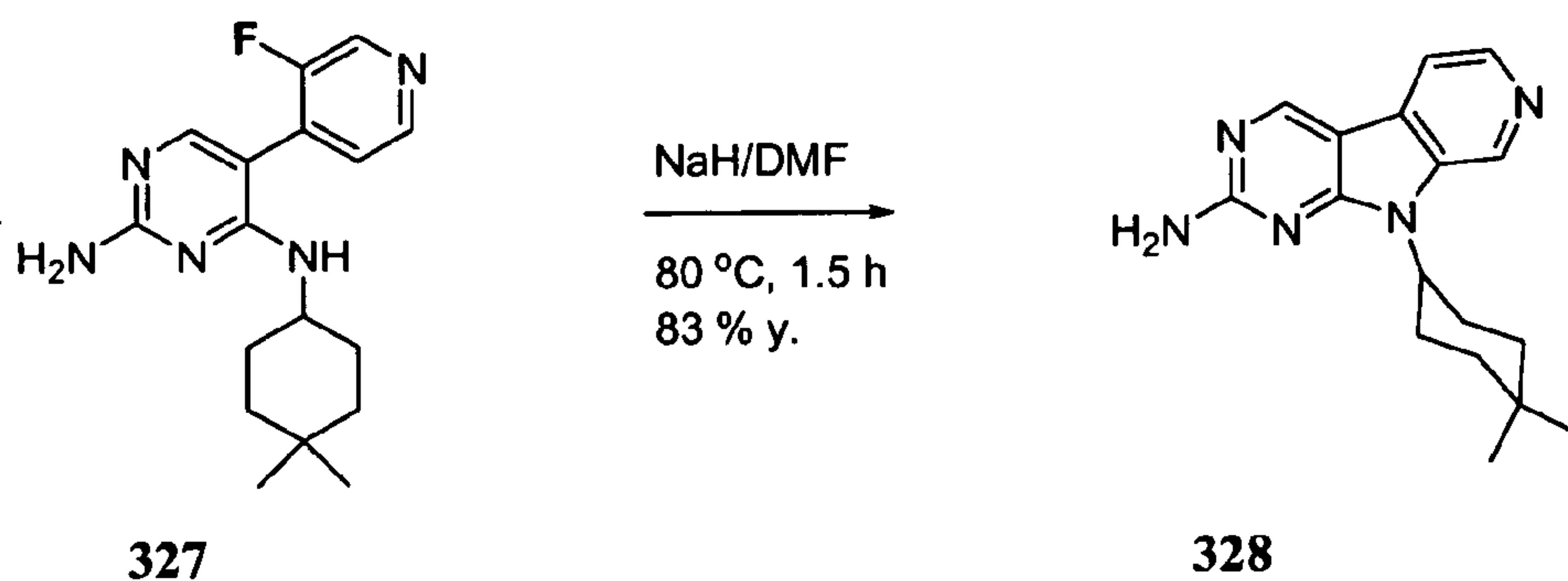


326

327

**N4-(4,4-Dimethylcyclohexyl)-5-(3-fluoro-4-pyridinyl)-2,4-pyrimidinediamine (327):**

To a 50 mL single-necked round bottom flask were placed compound **236** (0.80 g, 2.3 mmol), 3-fluoropyridin-4-ylboronic acid (0.98 g, 6.9 mmol), *trans*-dichlorobis(triphenylphosphine)palladium (III) (0.16 g, 0.23 mmol), 1,4-dioxane (16 mL), and sodium carbonate, 2 N aqueous solution (3.5 mL, 6.9 mmol). The flask was purged with  $\text{N}_2$  for 10 min. The resulting mixture was heated in an oil bath at 80 °C for 50 h. Upon workup, the mixture was poured into saturated  $\text{Na}_2\text{CO}_3$  aqueous solution and extracted with ethyl acetate (2 X). The combined organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **327** (0.18 g, 25% yield) as a light yellow solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 8.56 (1 H, d,  $J=1.7$  Hz), 8.48 (1 H, dd,  $J=4.9, 1.0$  Hz), 7.78 (1 H, s), 7.27 - 7.30 (1 H, m), 4.89 (2 H, s), 4.43 (1 H, d,  $J=7.6$  Hz), 3.88 - 4.01 (1 H, m), 1.79 - 1.88 (2 H, m), 1.26 - 1.43 (6 H, m), 0.94 (3 H, s), 0.91 (3 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 316.1.



327

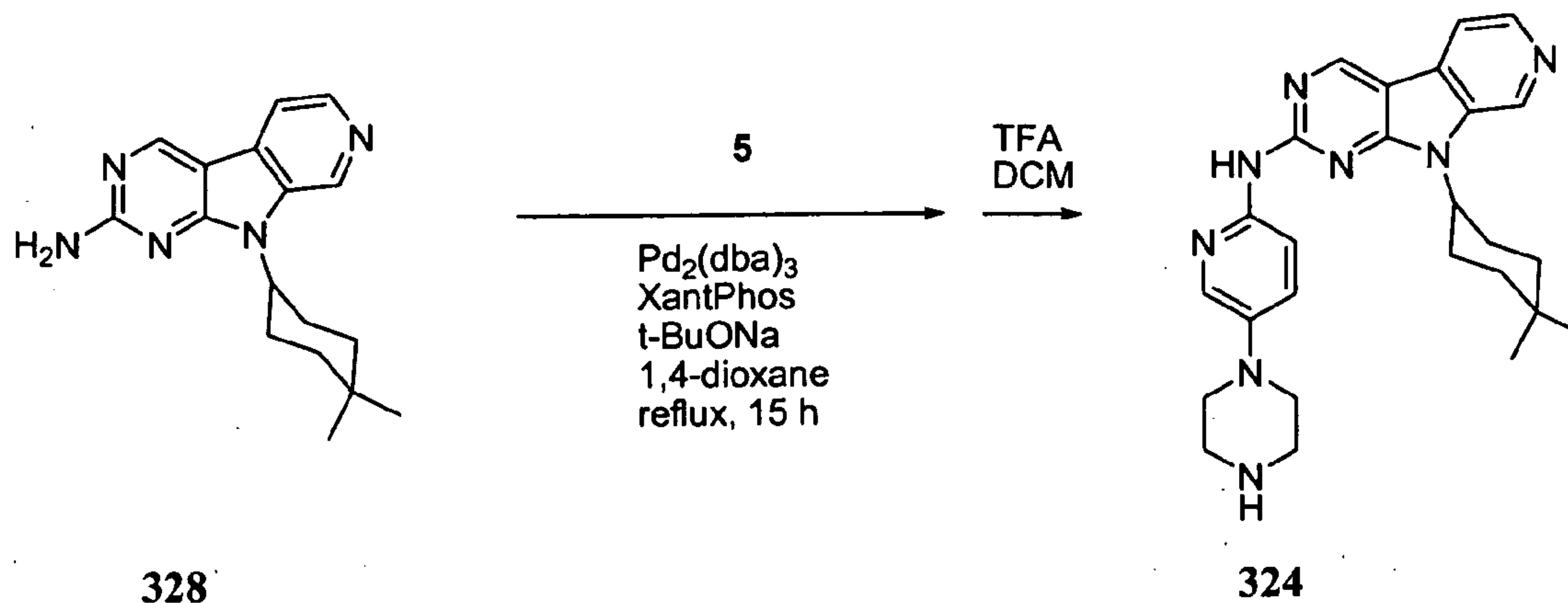
328

9-

**(4,4-Dimethylcyclohexyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (328):** To a stirred solution of compound **327** (0.18 g, 0.57 mmol) in DMF (10 mL) was added sodium hydride, (60% in mineral oil, 0.11 g, 2.3 mmol). The resulting mixture was stirred at 80 °C for 1.5 h. Upon workup, the crude mixture was poured into ice and saturated  $\text{NaHCO}_3$  aqueous solution and extracted with ethyl acetate (2 X) followed by 10% *i*-PrOH/DCM (2 X). The combined organics were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The residue was subjected to combi-flash column chromatography (methanol/DCM with  $\text{Et}_3\text{N}$ ) to give

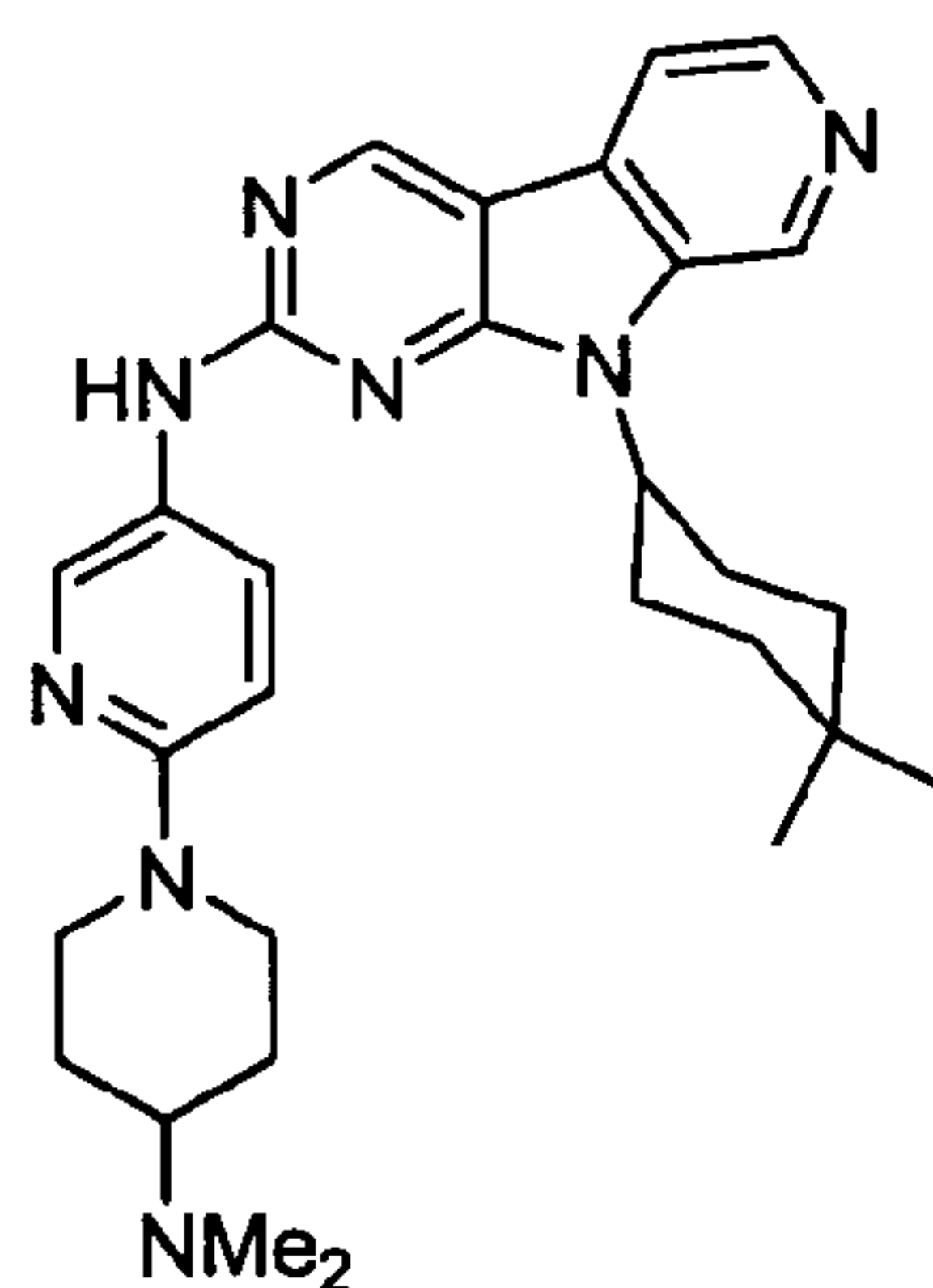


compound **328** (0.14 g, 83% yield) as a light yellow solid.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 9.04 (1 H, s), 8.92 (1 H, s), 8.35 (1 H, d,  $J=4.9$  Hz), 7.92 (1 H, dd,  $J=5.1, 1.0$  Hz), 6.94 (2 H, s), 4.66 - 4.76 (1 H, m,  $J=12.6, 12.6, 4.1, 3.9$  Hz), 2.52 - 2.63 (2 H, m), 1.52 - 1.66 (4 H, m), 1.39 - 1.50 (2 H, m), 1.16 (3 H, s), 1.01 (3 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 296.0.



**9-(4,4-dimethylcyclohexyl)-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (324):** Compound **324** was prepared as a yellow solid (TFA salt) from compound **328** and compound **5** using chemistry similar to that described in example 200.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 10.35 (1 H, s), 9.52 (1 H, s), 9.35 (1 H, s), 8.62 (1 H, d,  $J=5.9$  Hz), 8.49 (1 H, d,  $J=5.9$  Hz), 8.15 (1 H, d,  $J=2.9$  Hz), 8.04 (1 H, d,  $J=9.0$  Hz), 7.51 (1 H, dd,  $J=9.0, 2.9$  Hz), 4.66 - 4.79 (1 H, m), 3.34 - 3.43 (4 H, m), 3.30 (4 H, br. s.), 2.62 - 2.77 (2 H, m), 1.73 (2 H, d,  $J=11.3$  Hz), 1.46 - 1.63 (4 H, m), 1.11 (3 H, s), 1.02 (3 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 457.1.

### EXAMPLE 205



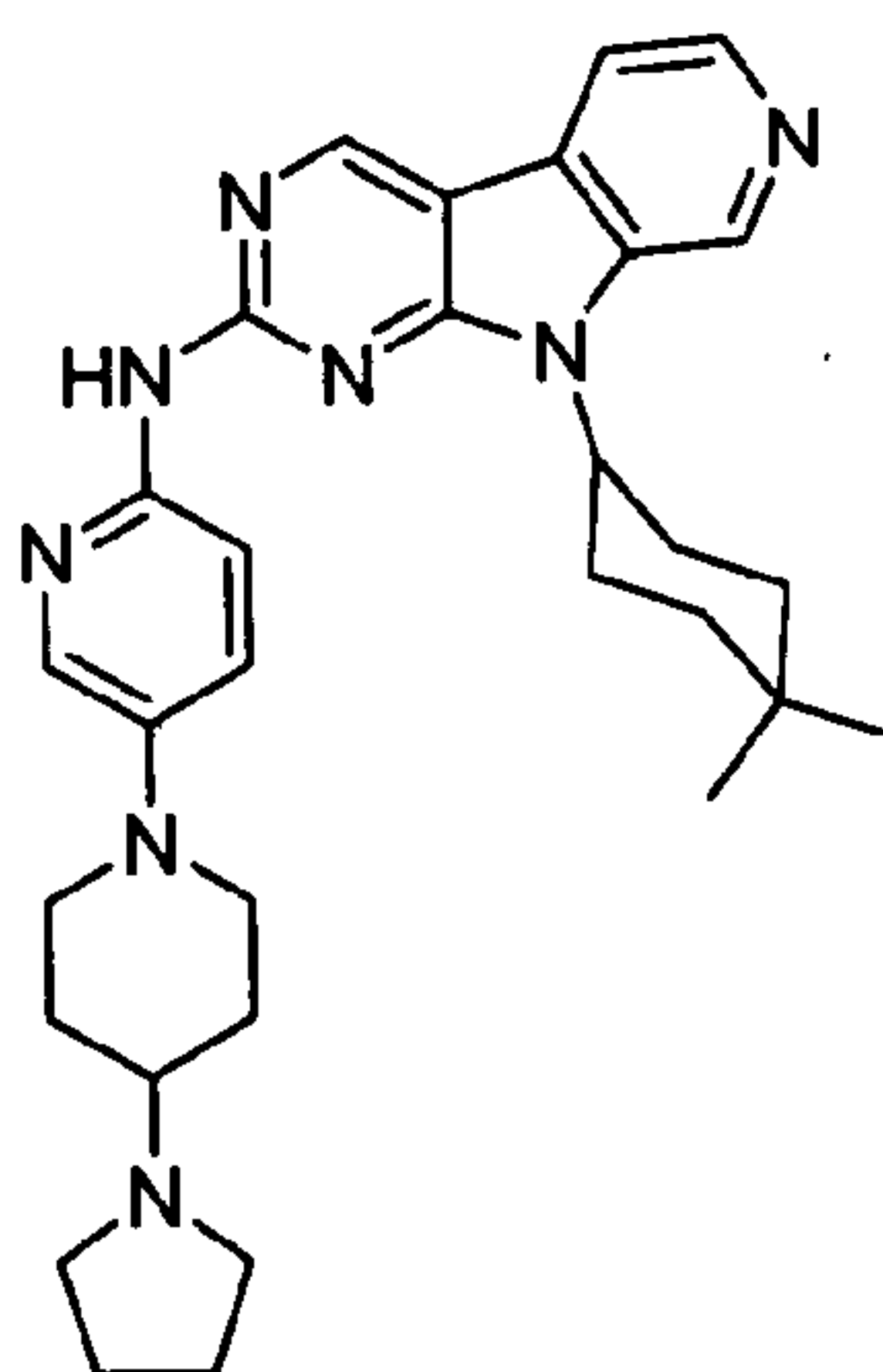
**329**

**N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridinyl)-9-(4,4-dimethylcyclohexyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



Compound **329** was prepared as a yellow solid (TFA salt) from compound **328** and compound **91** using chemistry similar to that described in example 56.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 9.46 - 9.58 (2 H, m), 9.36 (1 H, br. s.), 8.61 (1 H, d,  $J=6.1$  Hz), 8.44 - 8.56 (2 H, m), 7.88 (1 H, dd,  $J=9.0, 2.7$  Hz), 6.95 (1 H, d,  $J=9.3$  Hz), 4.67 (1 H, br. s.), 4.42 (2 H, d,  $J=13.4$  Hz), 3.35 - 3.45 (1 H, m,  $J=12.0, 12.0, 4.0, 4.0, 3.8$  Hz), 2.72 - 2.85 (8 H, m), 2.58 - 2.70 (2 H, m), 2.07 (2 H, d,  $J=10.5$  Hz), 1.69 (2 H, d,  $J=10.5$  Hz), 1.43 - 1.63 (6 H, m), 0.99 (6 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 499.3.

### EXAMPLE 206

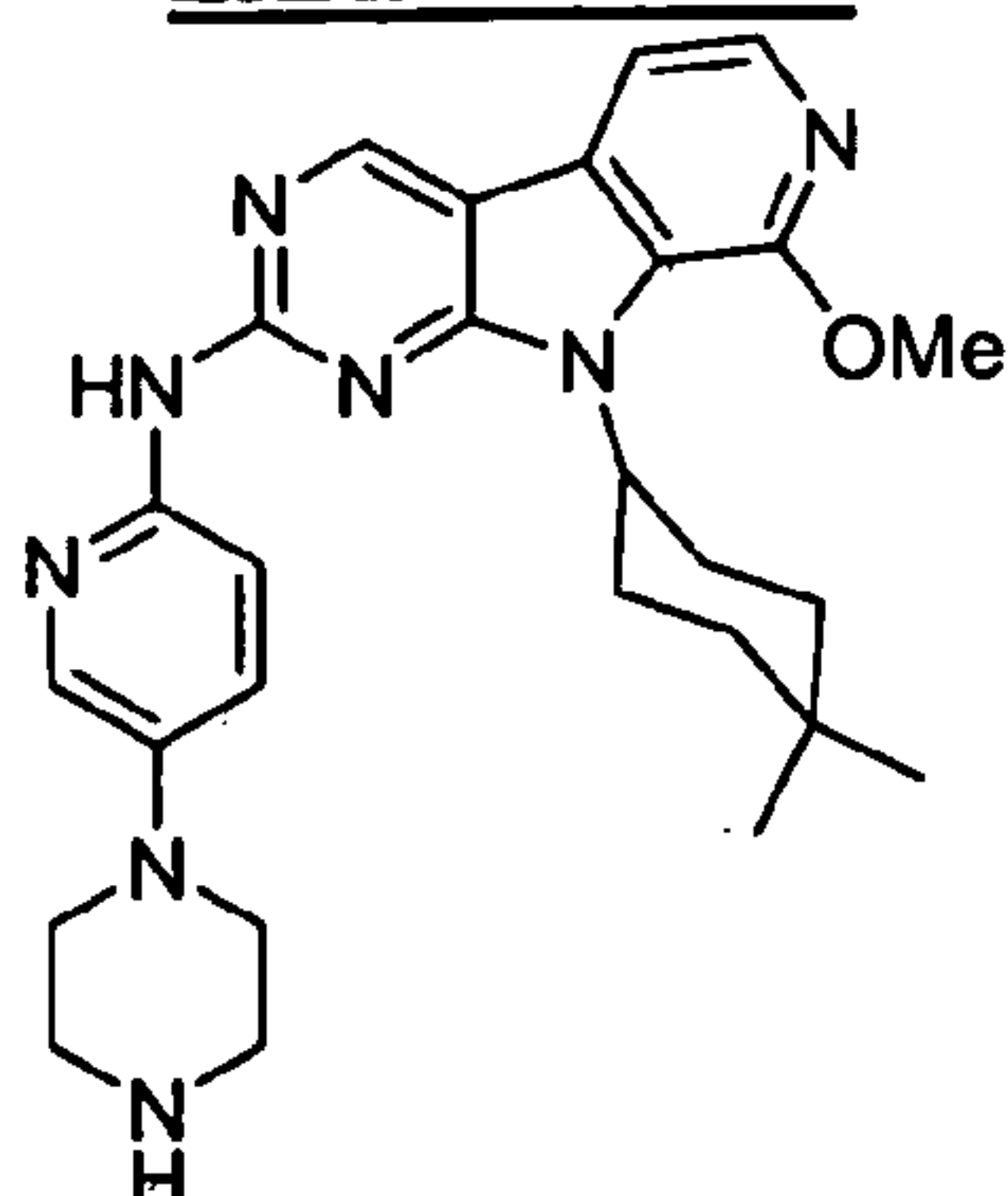


**330**

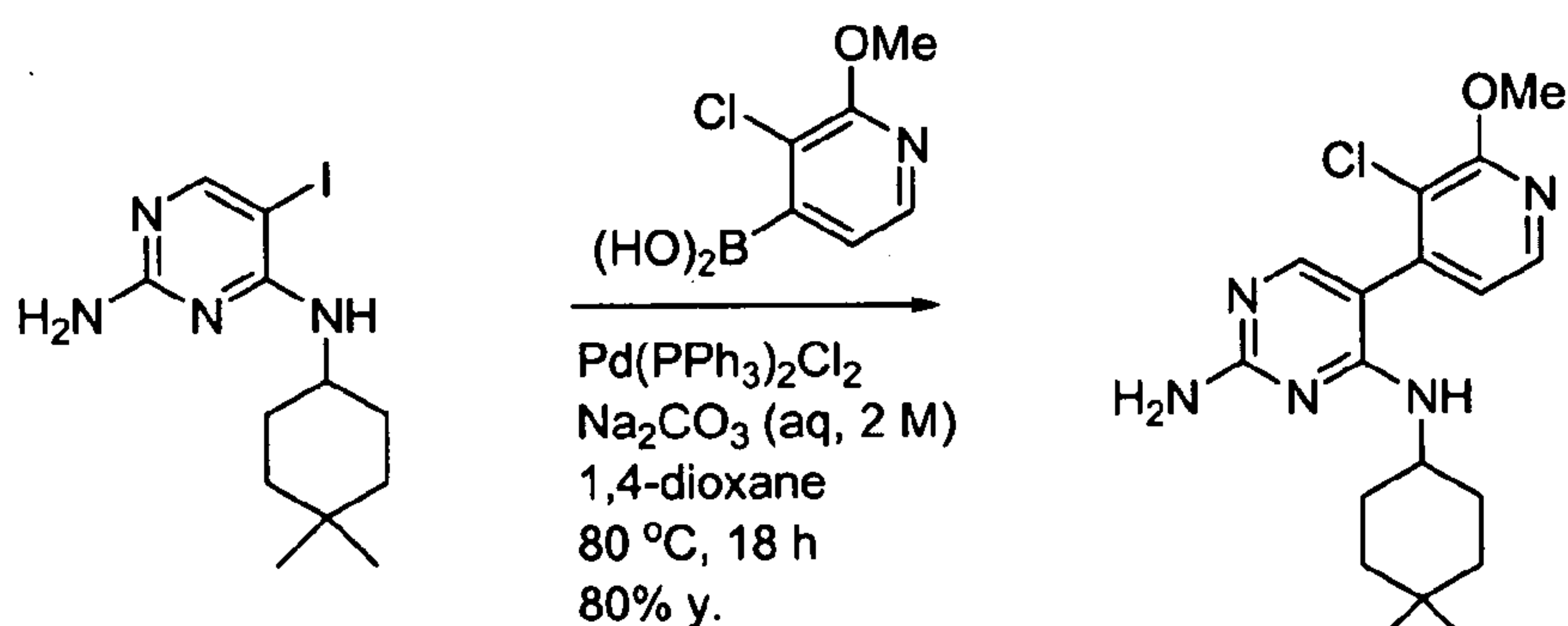
**9-(4,4-dimethylcyclohexyl)-N-(5-(4-(1-pyrrolidinyl)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **330** was prepared as yellow solid (TFA salt) from compound **328** using chemistry similar to that described in example 53.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 9.58 (1 H, s), 9.31 (1 H, s), 8.54 - 8.65 (2 H, m), 8.03 (1 H, d,  $J=2.9$  Hz), 7.99 (1 H, d,  $J=7.3$  Hz), 7.77 (1 H, d,  $J=9.0$  Hz), 4.89 - 5.01 (1 H, m), 3.91 (2 H, d,  $J=12.7$  Hz), 3.71 (2 H, br. s.), 3.34 - 3.42 (1 H, m), 3.15 - 3.26 (2 H, m), 2.87 - 2.99 (2 H, m), 2.72 - 2.88 (2 H, m), 2.33 (2 H, d,  $J=12.0$  Hz), 2.20 (2 H, br. s.), 2.05 (2 H, br. s.), 1.77 - 1.94 (4 H, m), 1.54 - 1.73 (4 H, m), 1.24 (3 H, s), 1.08 (3 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 525.3.



**EXAMPLE 207****331**

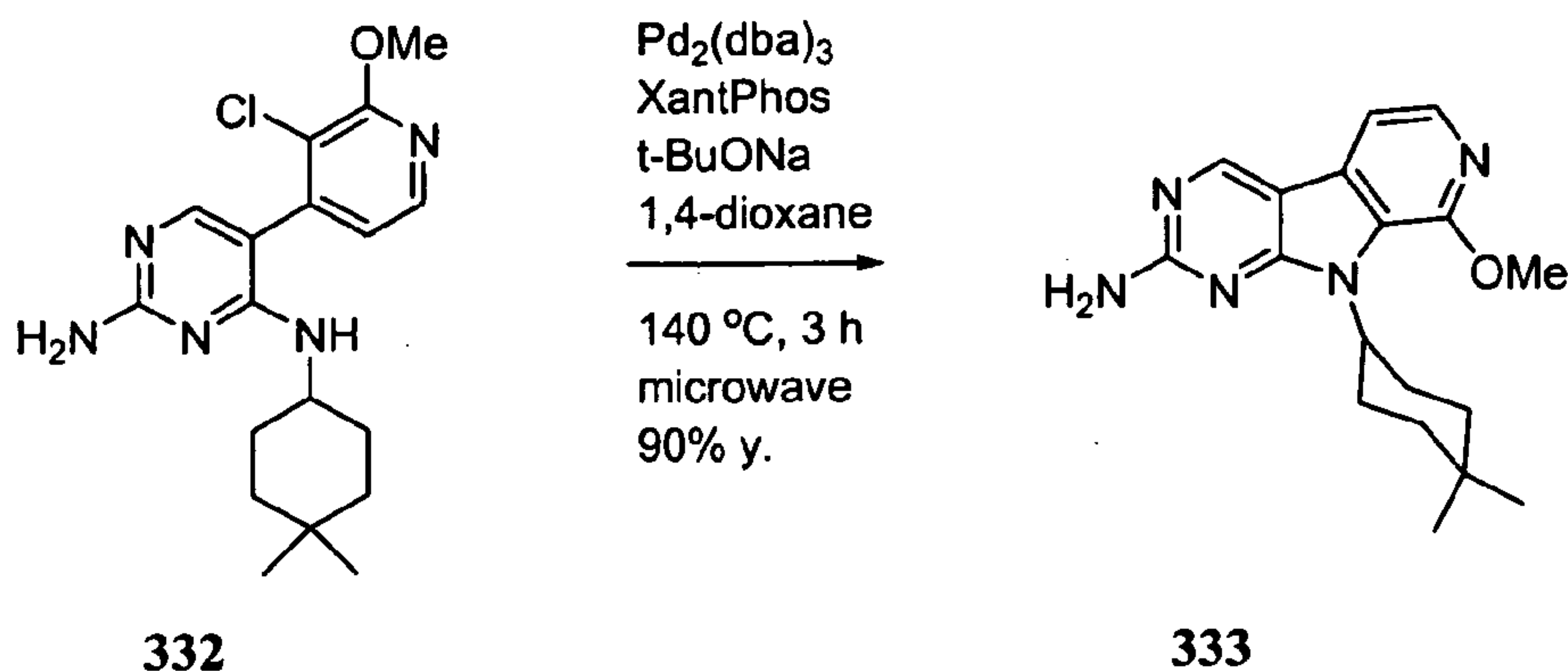
**9-(4,4-dimethylcyclohexyl)-8-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**326****332**

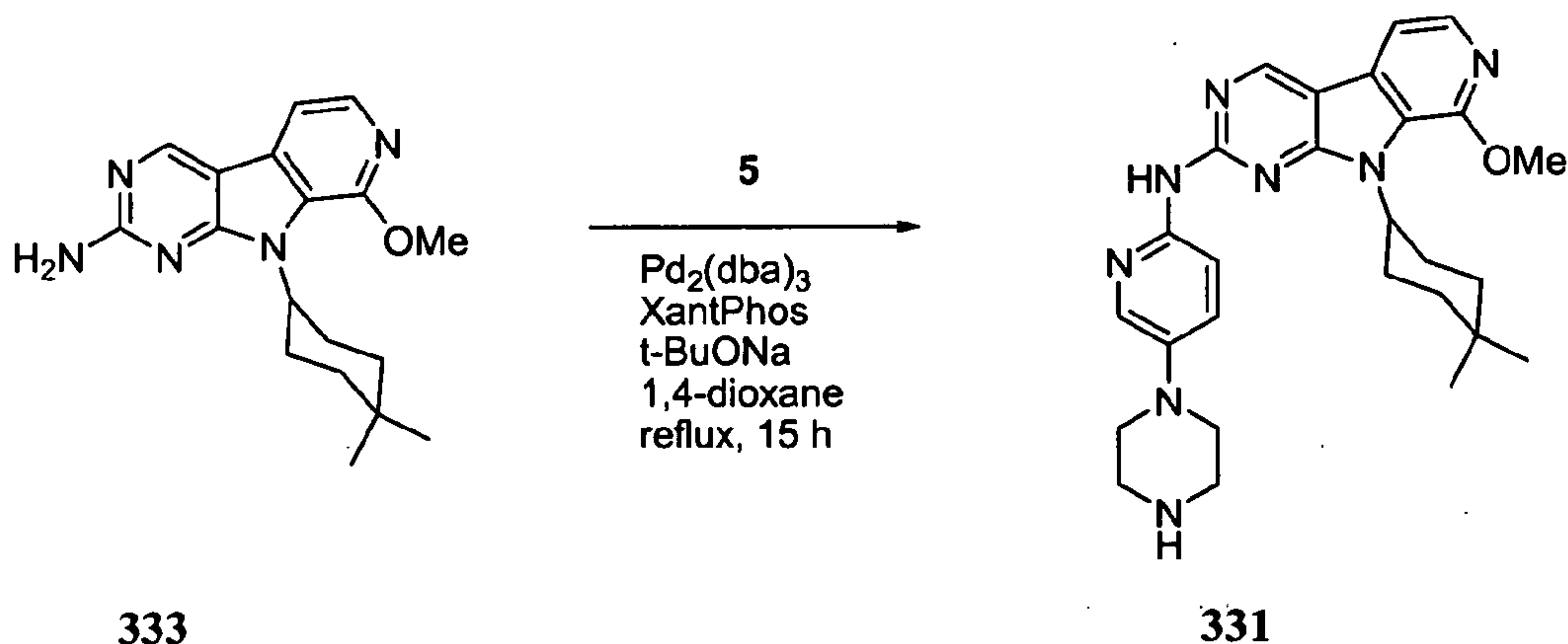
**5-(3-Chloro-2-methoxy-4-pyridinyl)-N4-(4,4-dimethylcyclohexyl)-2,4-pyrimidinediamine**

**(332):** To a 50 mL single-necked round bottom flask were placed compound **326** (0.80 g, 2.3 mmol), 3-chloro-2-methoxypyridin-4-ylboronic acid (1.3 g, 6.9 mmol), and trans-dichlorobis(triphenyl-phosphine)palladium (ii) (0.16 g, 0.23 mmol). The flask was subjected to 3 cycles of evacuation and back-filling with N<sub>2</sub>. 1,4-Dioxane (12 mL) was added followed with sodium carbonate (2 N aqueous solution) (5.8 mL, 12 mmol). The resulting mixture was heated in an oil bath at 80 °C for 18 h. Upon workup, the mixture was poured into ice and saturated NaHCO<sub>3</sub> aqueous solution and extracted with ethyl acetate (3 X). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in *vacuo*. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **332** (0.68 g, 81% yield) as a light yellow solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.09 (1 H, d, J=5.1 Hz), 7.48 (1 H, s), 6.92 (1 H, d, J=5.1 Hz), 6.13 (2 H, s), 5.79 (1 H, d, J=8.3 Hz), 3.91 - 4.02 (4 H, m), 1.26 - 1.63 (6 H, m), 1.13 - 1.25 (2 H, m), 0.88 (6 H, d, J=9.8 Hz). LCMS-ESI (POS), M/Z, M+1: Found 362.0.





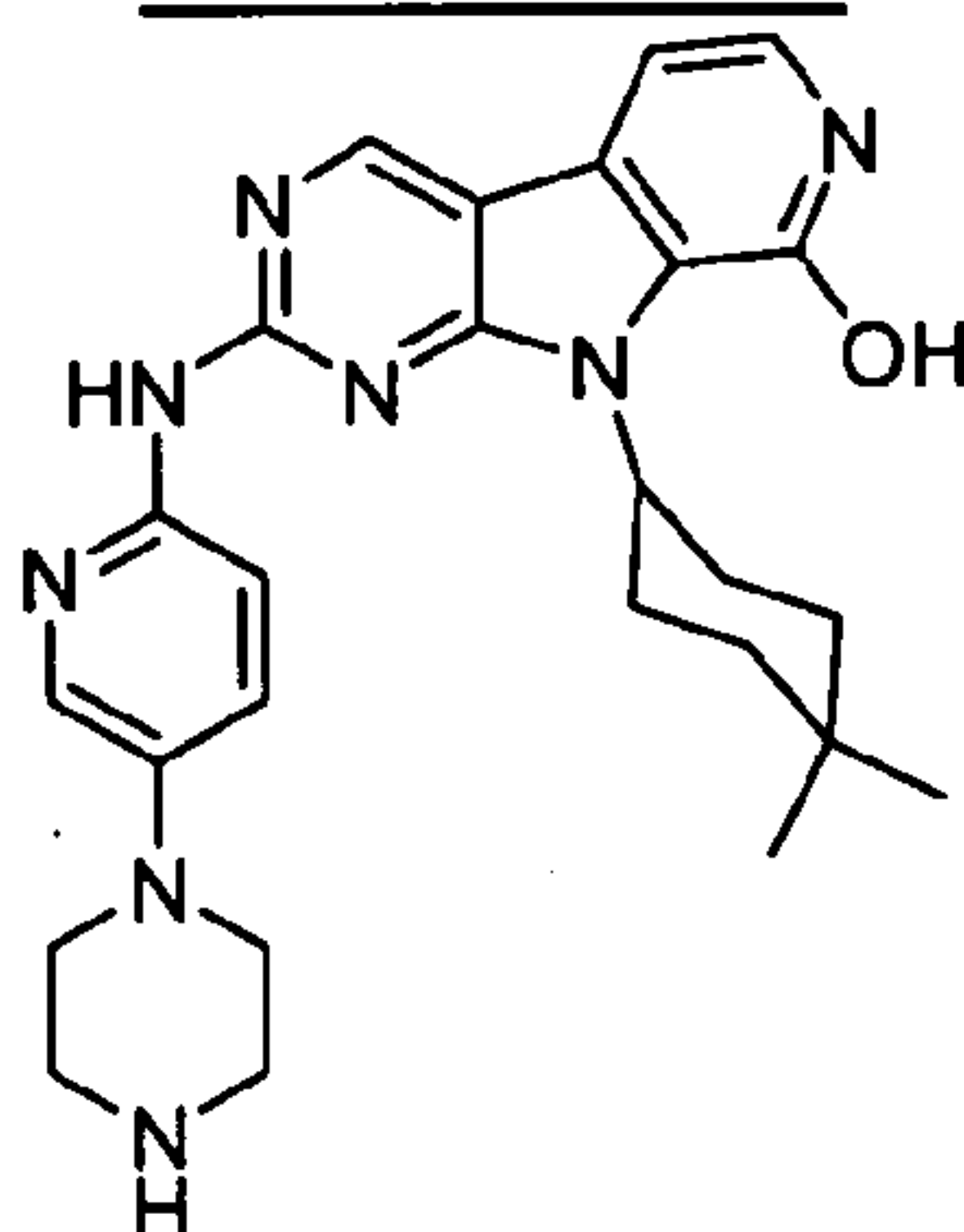
**9-(4,4-Dimethylcyclohexyl)-8-methoxy-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (333):** To a 30 mL microwave reaction vessel were placed compound **332** (0.55 g, 1.5 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.14 g, 0.15 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.22 g, 0.38 mmol), and sodium *tert*-butoxide (0.37 g, 3.8 mmol) followed by 1,4-dioxane (15 mL). The vessel was purged with  $\text{N}_2$  for 5 min, then capped and subjected to microwave condition (3 h at 140 °C). After the volatiles were removed, the crude mixture was taken up in 4% methanol/DCM and subjected to combi-flash column chromatography (1% to 7% methanol in DCM) to give crude compound **333** as an off-white solid (0.65 g).  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 9.01 (1 H, s), 7.92 (1 H, d,  $J=5.1$  Hz), 7.59 (1 H, d,  $J=4.9$  Hz), 6.86 (2 H, br. s.), 4.98 - 5.14 (1 H, m), 4.06 (3 H, s), 1.53 (4 H, br. s.), 1.31 - 1.44 (2 H, m), 1.16 (3 H, s), 1.00 (3 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 326.1.



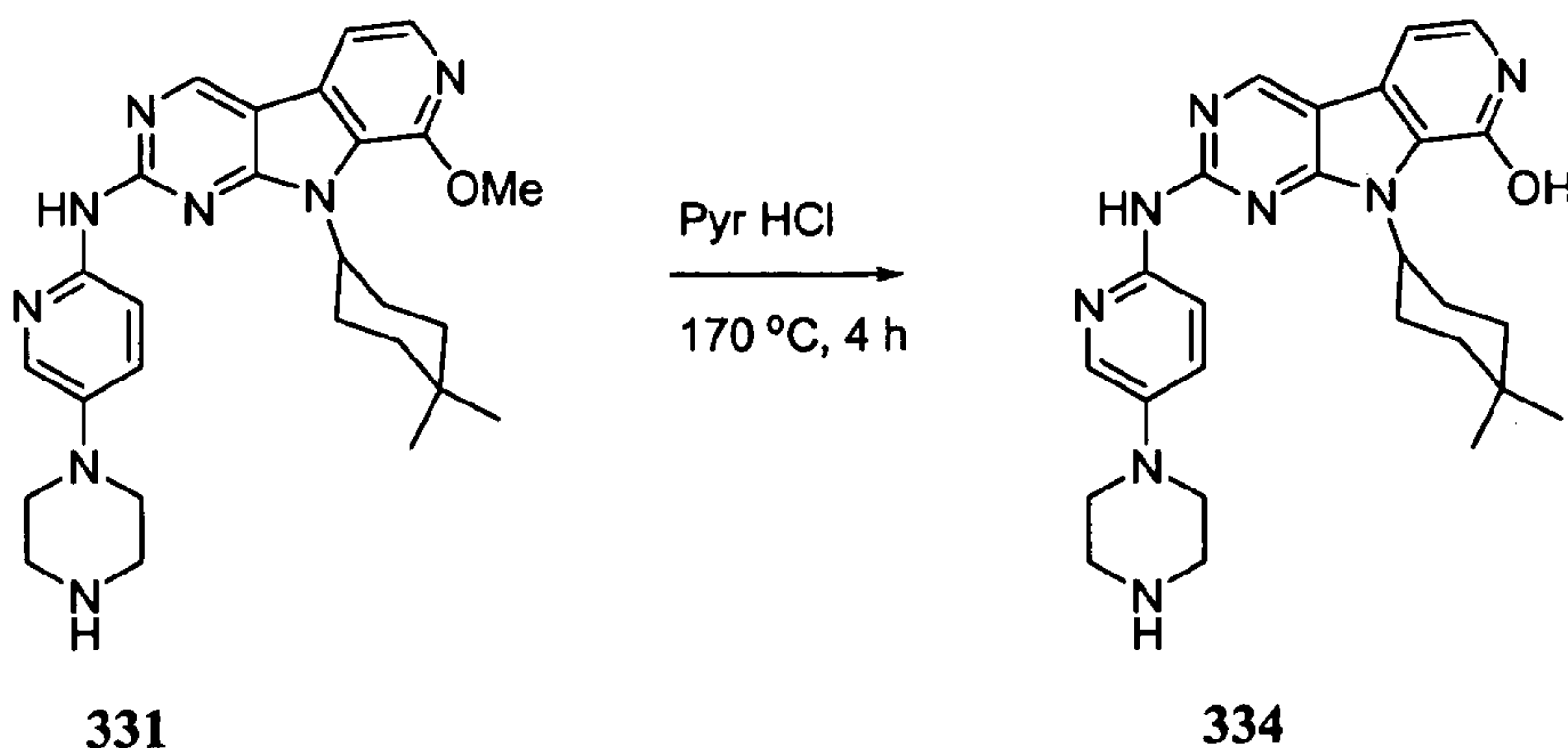
**9-(4,4-Dimethylcyclohexyl)-8-methoxy-N-(5-(1-piperazinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (331):** In a 25 mL round bottom flask were placed compound **333** (130 mg, 399  $\mu\text{mol}$ ), compound **5** (119 mg, 399  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (0) (36.6 mg, 39.9  $\mu\text{mol}$ ), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (57.8 mg, 99.9  $\mu\text{mol}$ ), and sodium *tert*-butoxide (115 mg, 1198  $\mu\text{mol}$ ). The flask was subjected to 3 cycles of evacuation and back-filling with  $\text{N}_2$ . 1,4-Dioxane (5 mL) was added and the resulting mixture was stirred at reflux for 14 h. After the



volatiles were removed, the residue, which contained both Boc protected and deprotected product, was subjected to combi-flash column chromatography (methanol/DCM) followed by reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 60%). Fractions containing the desired product were lyophilized to provided compound **331** (16 mg) as a light yellow solid (TFA salt).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 9.30 (1 H, s), 8.70 (2 H, br. s.), 8.08 (1 H, d,  $J=2.7$  Hz), 7.96 - 8.06 (2 H, m), 7.75 (1 H, br. s.), 5.10 - 5.31 (1 H, m), 4.09 (3 H, s), 3.24 - 3.37 (8 H, m), 1.33 - 1.77 (8 H, m), 1.13 (3 H, br. s.), 1.02 (3 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 487.1.

**EXAMPLE 208****334**

**9-(4,4-dimethylcyclohexyl)-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol**

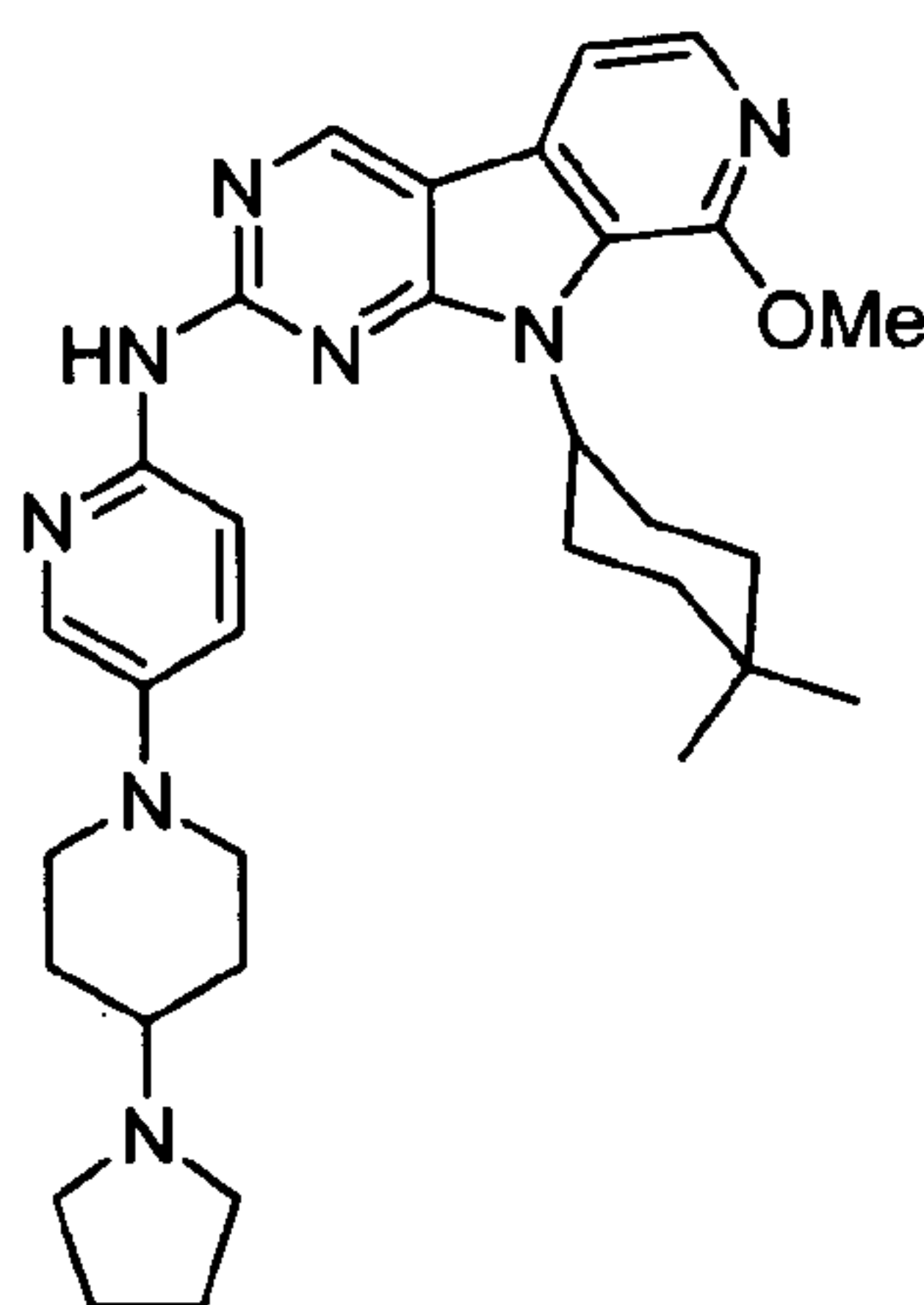
**331****334**

**9-(4,4-dimethylcyclohexyl)-2-((5-(1-piperazinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol (334):** A mixture of compound **331** (90 mg, 153  $\mu\text{mol}$ ) and pyridine hydrochloride (177 mg, 1.53 mmol) was heated at 170  $^{\circ}\text{C}$  (oil bath) for 4 h. After cooling to room temperature, the mixture was subjected to reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 50%). Lyophilization



provided compound **334** (150 mg) as a yellow solid (TFA salt).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  ppm 11.66 (1 H, br. s.), 9.30 (1 H, s), 8.80 (2 H, br. s.), 8.05 (1 H, d,  $J=2.7$  Hz), 7.92 (1 H, d,  $J=8.6$  Hz), 7.75 (1 H, br. s.), 7.28 (1 H, t,  $J=5.7$  Hz), 7.06 (1 H, d,  $J=6.3$  Hz), 3.33 - 3.43 (4 H, m), 3.29 (5 H, d,  $J=1.6$  Hz), 2.71 - 2.94 (2 H, m), 1.47 - 1.70 (4 H, m), 1.31 - 1.45 (2 H, m), 1.16 (3 H, s), 0.99 (3 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 473.2.

### EXAMPLE 209

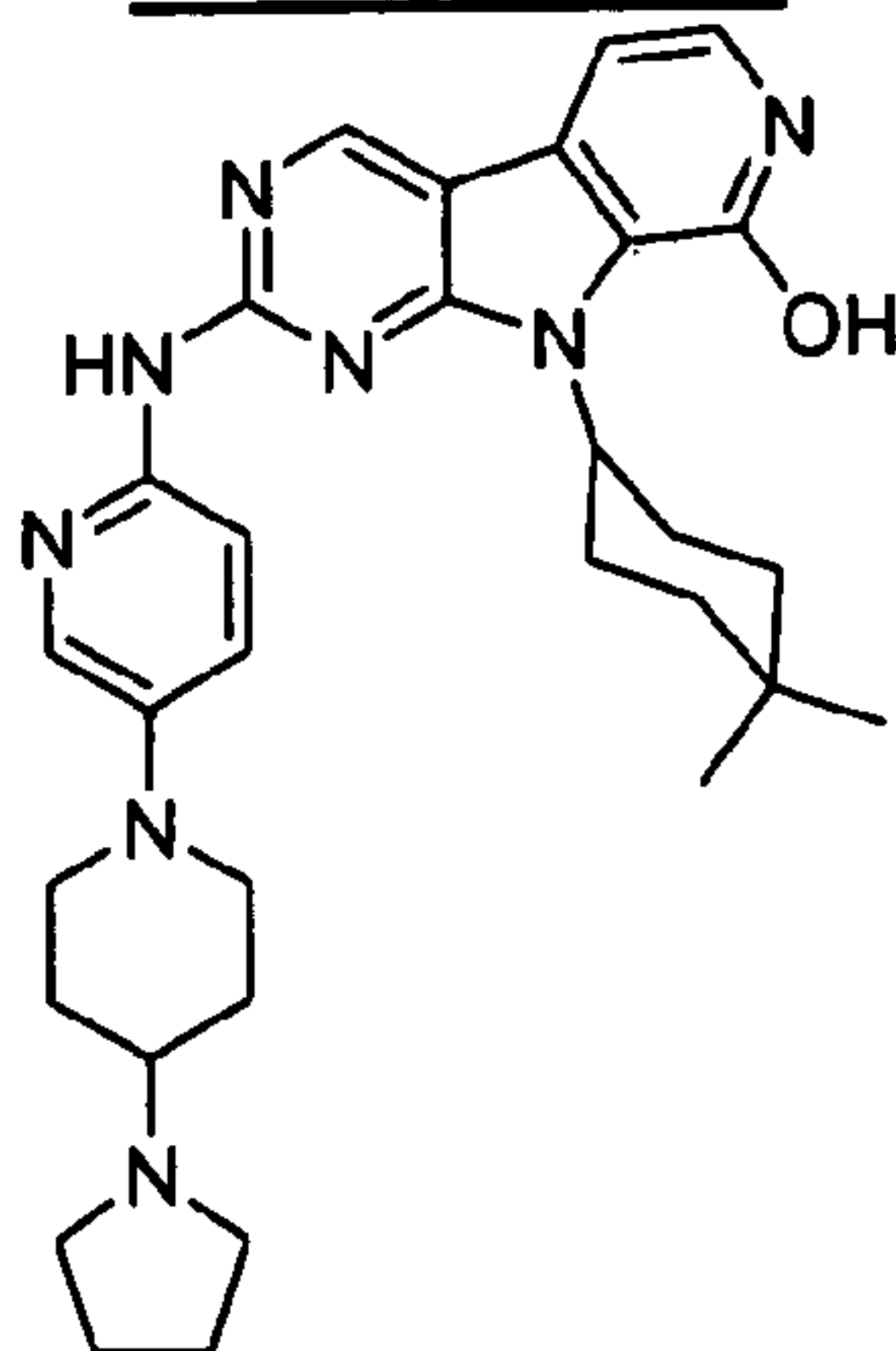


**335**

**9-(4,4-dimethylcyclohexyl)-8-methoxy-N-(5-(4-(1-pyrrolidinyl)-1-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

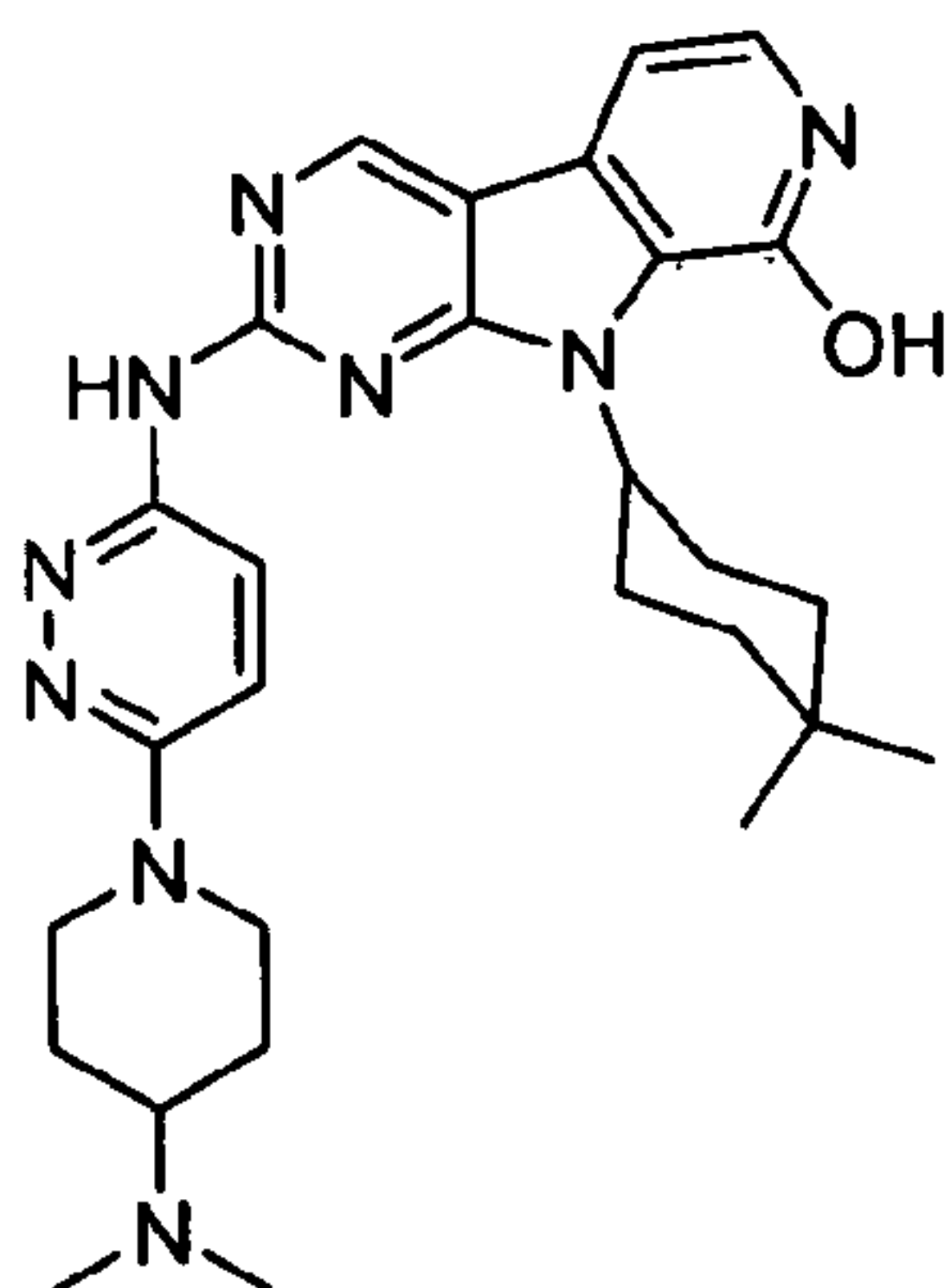
Compound **335** was prepared from compound **333** using chemistry similar to that described in example 56.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 9.33 (1 H, s), 8.02 - 8.16 (2 H, m), 7.96 (1 H, d,  $J=2.7$  Hz), 7.75 (1 H, d,  $J=5.1$  Hz), 7.49 (0 H, br. s.), 5.27 - 5.41 (1 H, m), 4.19 (3 H, s), 3.89 (2 H, d,  $J=12.9$  Hz), 3.71 (2 H, br. s.), 3.35 - 3.42 (1 H, m), 3.15 - 3.26 (2 H, m), 2.91 (2 H, td,  $J=12.5, 2.0$  Hz), 2.33 (2 H, d,  $J=13.3$  Hz), 2.13 - 2.25 (2 H, m), 1.97 - 2.09 (2 H, m), 1.81 - 1.94 (2 H, m), 1.60 - 1.70 (2 H, m), 1.44 - 1.57 (2 H, m), 1.26 (3 H, s), 1.05 (3 H, s). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 555.2.



**EXAMPLE 210****336**

**9-(4,4-dimethylcyclohexyl)-2-((5-(4-(1-pyrrolidinyl)-1-piperidinyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol**

Compound **336** was prepared as a yellow solid (TFA salt) from compound **333** using chemistry similar to that described in example 208. <sup>1</sup>H NMR (400 MHz, *CD*<sub>3</sub>*OD*) δ ppm 9.33 (1 H, s), 8.10 (1 H, dd, J=9.6, 2.9 Hz), 7.93 (1 H, d, J=2.7 Hz), 7.54 (1 H, d, J=9.8 Hz), 7.35 (1 H, d, J=7.0 Hz), 7.15 (1 H, d, J=6.7 Hz), 3.89 (2 H, d, J=12.9 Hz), 3.71 (2 H, br. s.), 3.35 - 3.41 (1 H, m), 3.15 - 3.27 (2 H, m), 2.86 - 3.03 (4 H, m), 2.33 (2 H, d, J=12.5 Hz), 2.20 (2 H, br. s.), 1.96 - 2.11 (2 H, m), 1.81 - 1.95 (2 H, m), 1.56 - 1.76 (4 H, m), 1.42 - 1.55 (2 H, m), 1.26 (3 H, s), 1.03 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 541.3.

**EXAMPLE 211****337**

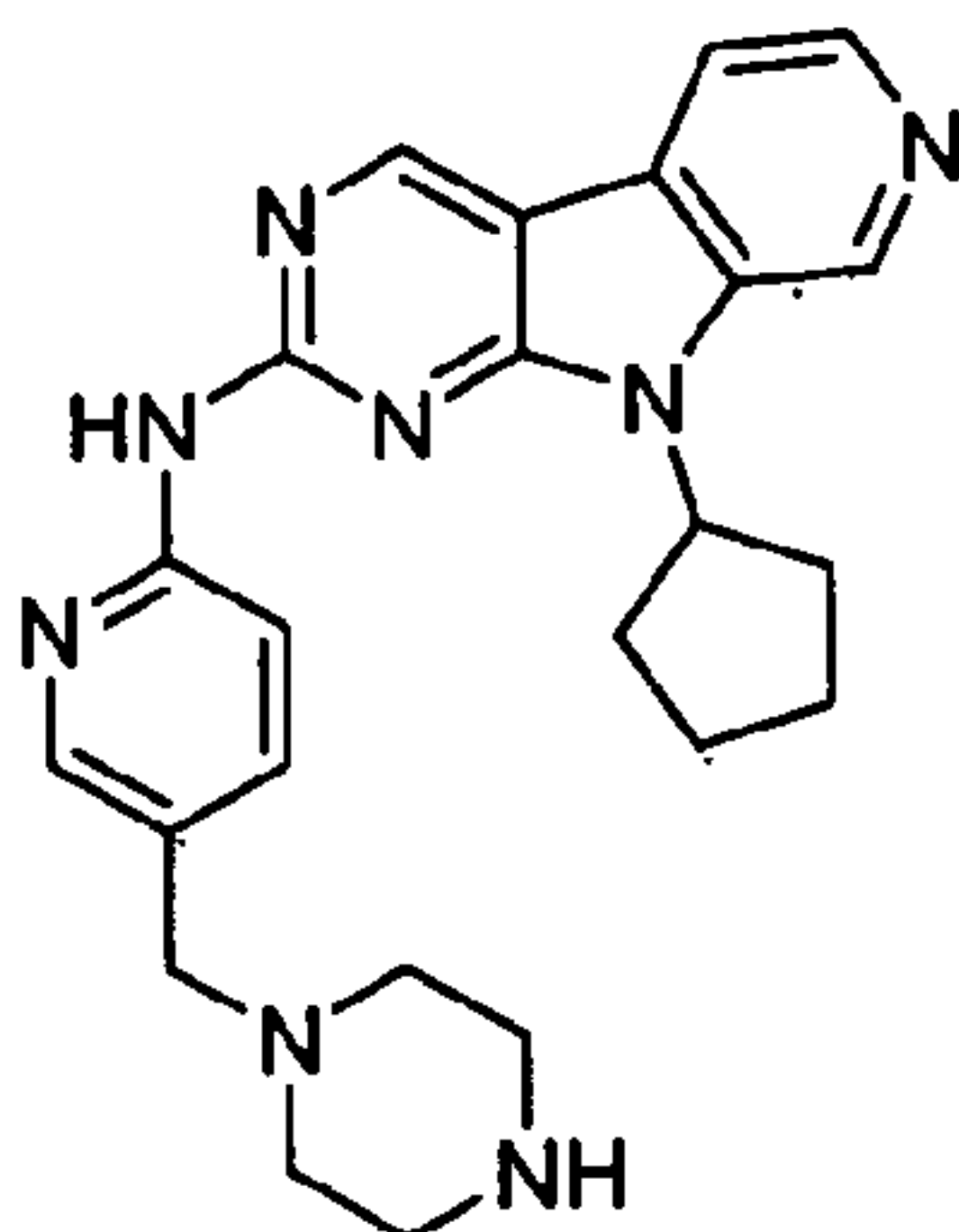
**2-(((6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)amino)-9-(4,4-dimethylcyclohexyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol**

Compound **337** was prepared as a yellow solid (TFA salt) from compound **333** using chemistry similar to that described in example 208. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ ppm 11.63 (1 H, br. s.), 9.49 (1 H, br. s.), 9.29 (1 H, s), 8.06 (1 H, d, J=9.8 Hz), 7.27 (1 H, t, J=5.9 Hz), 7.03 (1



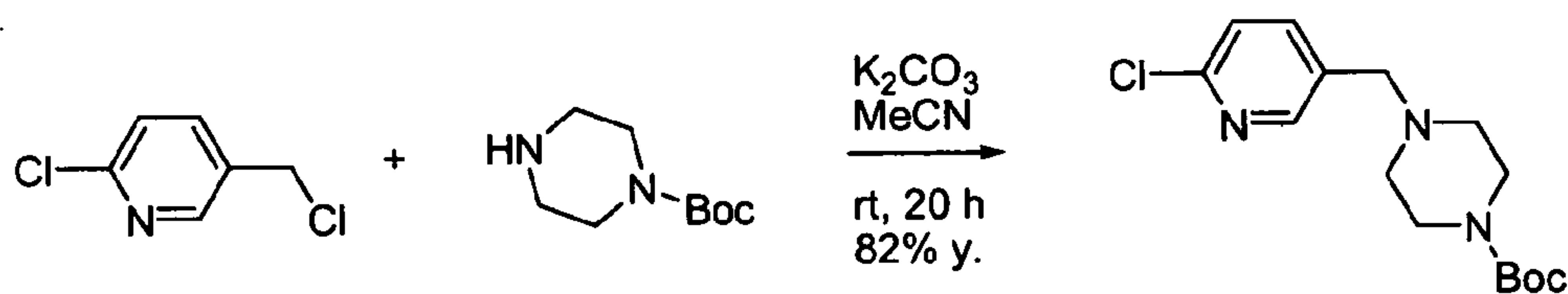
H, d, J=6.1 Hz), 4.42 (2 H, d, J=13.2 Hz), 2.96 (2 H, t, J=12.6 Hz), 2.79 (9 H, d, J=5.1 Hz), 2.03 - 2.16 (2 H, m), 1.48 - 1.71 (6 H, m), 1.29 - 1.42 (2 H, m), 1.10 (3 H, br. s.), 0.98 (3 H, s). LCMS-ESI (POS), M/Z, M+1: Found 516.3.

### EXAMPLE 212



338

**9-cyclopentyl-N-(5-(1-piperazinylmethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



339

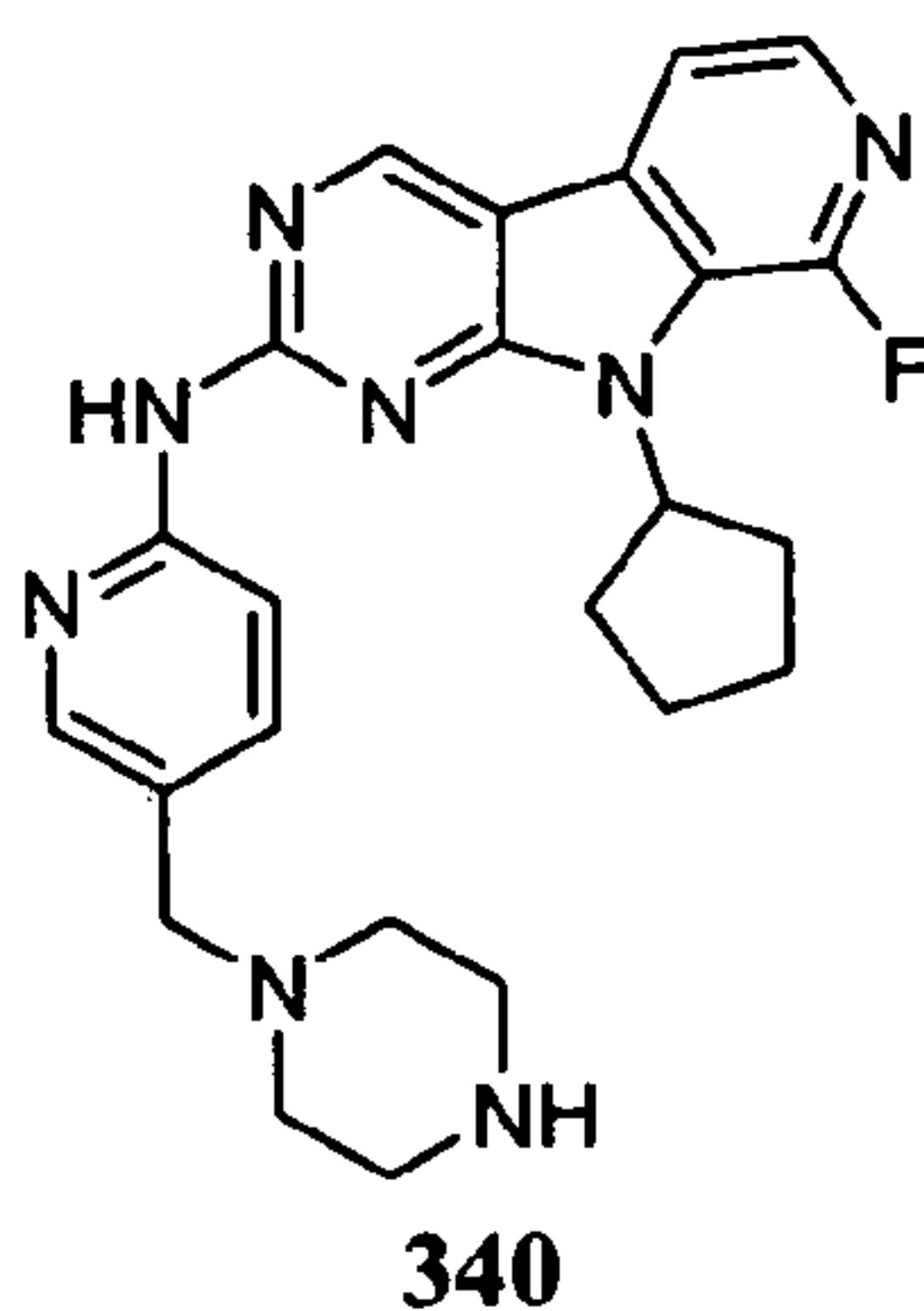
**tert-Butyl 4-((6-chloro-3-pyridinyl)methyl)-1-piperazinecarboxylate (339):** To a stirred suspension of 2-chloro-5-(chloromethyl)pyridine (2.0 g, 12 mmol) in acetonitrile (40 mL) was added potassium carbonate (1.5 mL, 25 mmol) followed by *tert*-butyl 1-piperazinecarboxylate (2.3 g, 12 mmol). The resulting mixture was stirred at room temperature for 20 h. Upon workup, the mixture was poured into ice and 2 N NaOH aqueous solution and extracted with ethyl acetate (2 X). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound 339 (3.17 g, 82% yield) as a thick colorless liquid. <sup>1</sup>H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.32 (1 H, d, J=2.0 Hz), 7.66 (1 H, d, J=7.4 Hz), 7.30 (1 H, d, J=8.2 Hz), 3.50 (2 H, s), 3.37 - 3.47 (4 H, m), 2.38 (4 H, br. s.), 1.46 (9 H, s). LCMS-ESI (POS), M/Z, M+1: Found 312.1.

**9-cyclopentyl-N-(5-(1-piperazinylmethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (338):** Compound 338 was prepared as an off-white solid (TFA salt)



from compound **4** and compound **339** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.68 (1 H, s), 9.35 (1 H, s), 8.68 (2 H, q, J=6.3 Hz), 8.43 (1 H, d, J=1.5 Hz), 8.26 (1 H, dd, J=8.9, 2.1 Hz), 7.88 (1 H, d, J=8.8 Hz), 5.48 (1 H, quin, J=8.7 Hz), 3.78 (2 H, s), 3.27 - 3.30 (4 H, m), 2.83 (4 H, br. s.), 2.48 - 2.59 (2 H, m), 2.15 - 2.31 (4 H, m), 1.83 - 1.97 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 429.2.

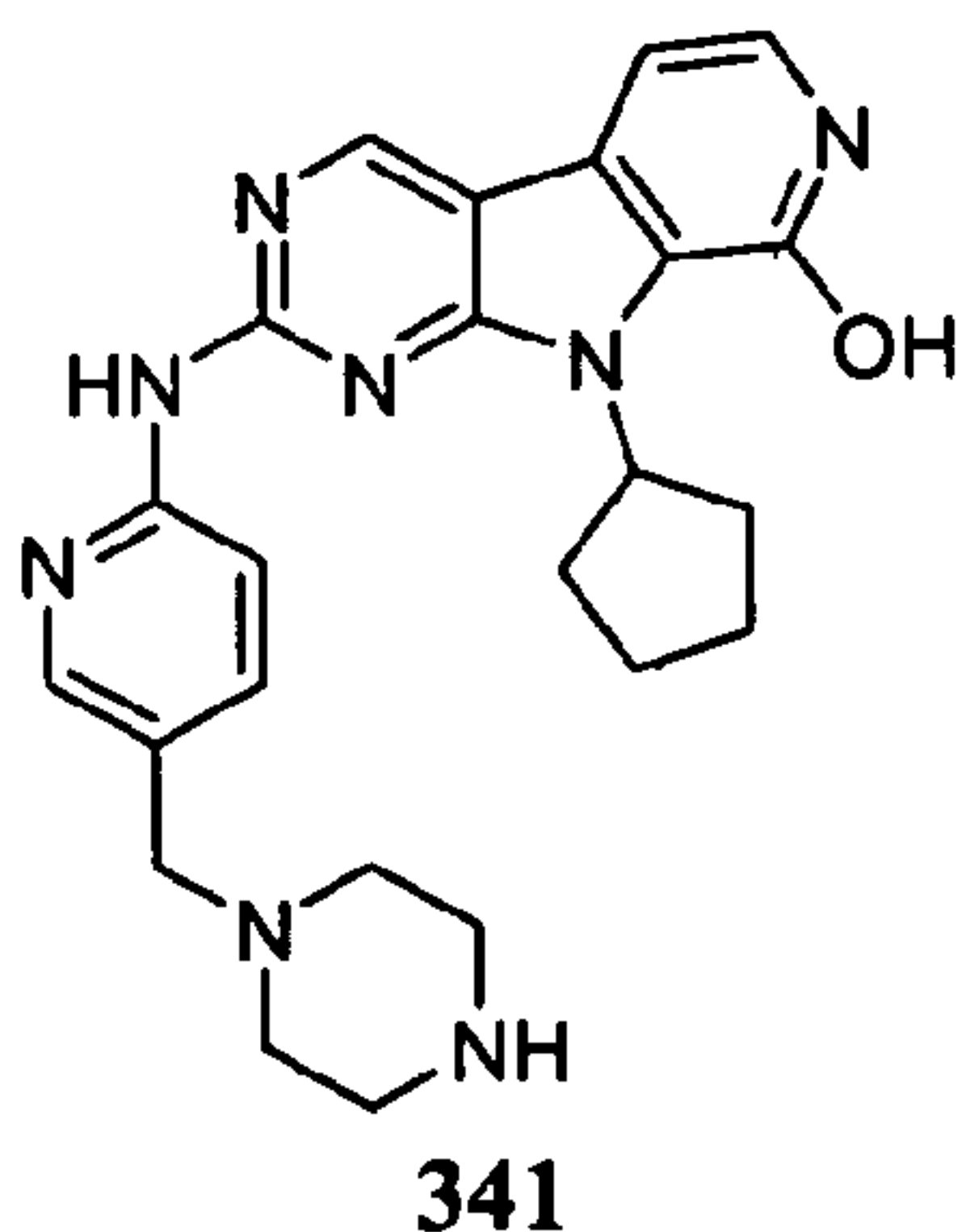
### EXAMPLE 213



**9-cyclopentyl-8-fluoro-N-(5-(1-piperazinylmethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

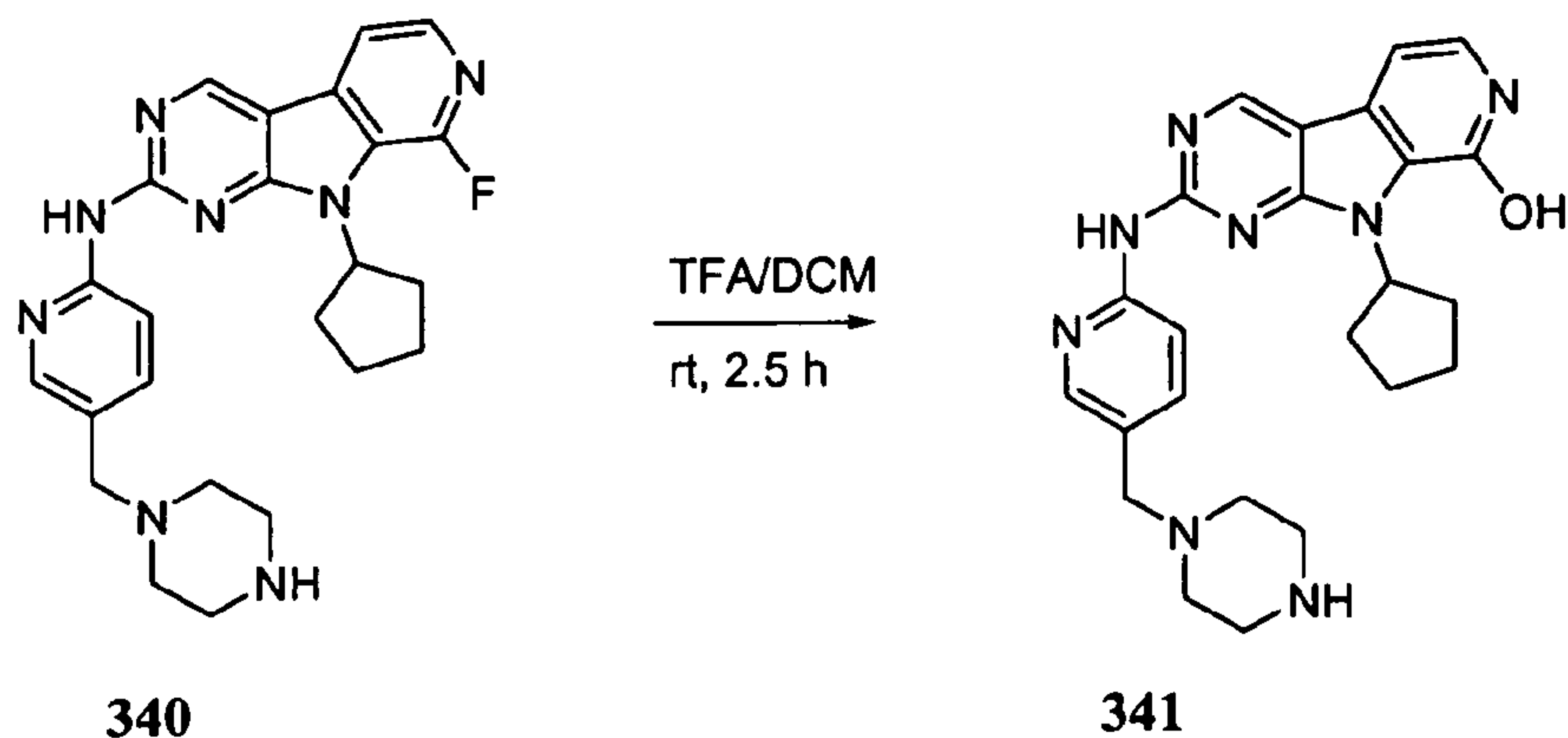
Compound **340** was prepared as an off-white solid (TFA salt) from compound **245** and compound **339** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.49 (1 H, s), 8.40 (1 H, d, J=1.5 Hz), 8.30 (1 H, dd, J=8.9, 2.1 Hz), 8.10 - 8.17 (2 H, m), 7.63 (1 H, d, J=9.0 Hz), 5.66 (1 H, quin, J=9.0 Hz), 3.75 (2 H, s), 3.26 - 3.30 (4 H, m), 2.80 (4 H, br. s.), 2.36 - 2.49 (2 H, m), 2.10 - 2.26 (4 H, m), 1.79 - 1.92 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 447.3.

### EXAMPLE 214



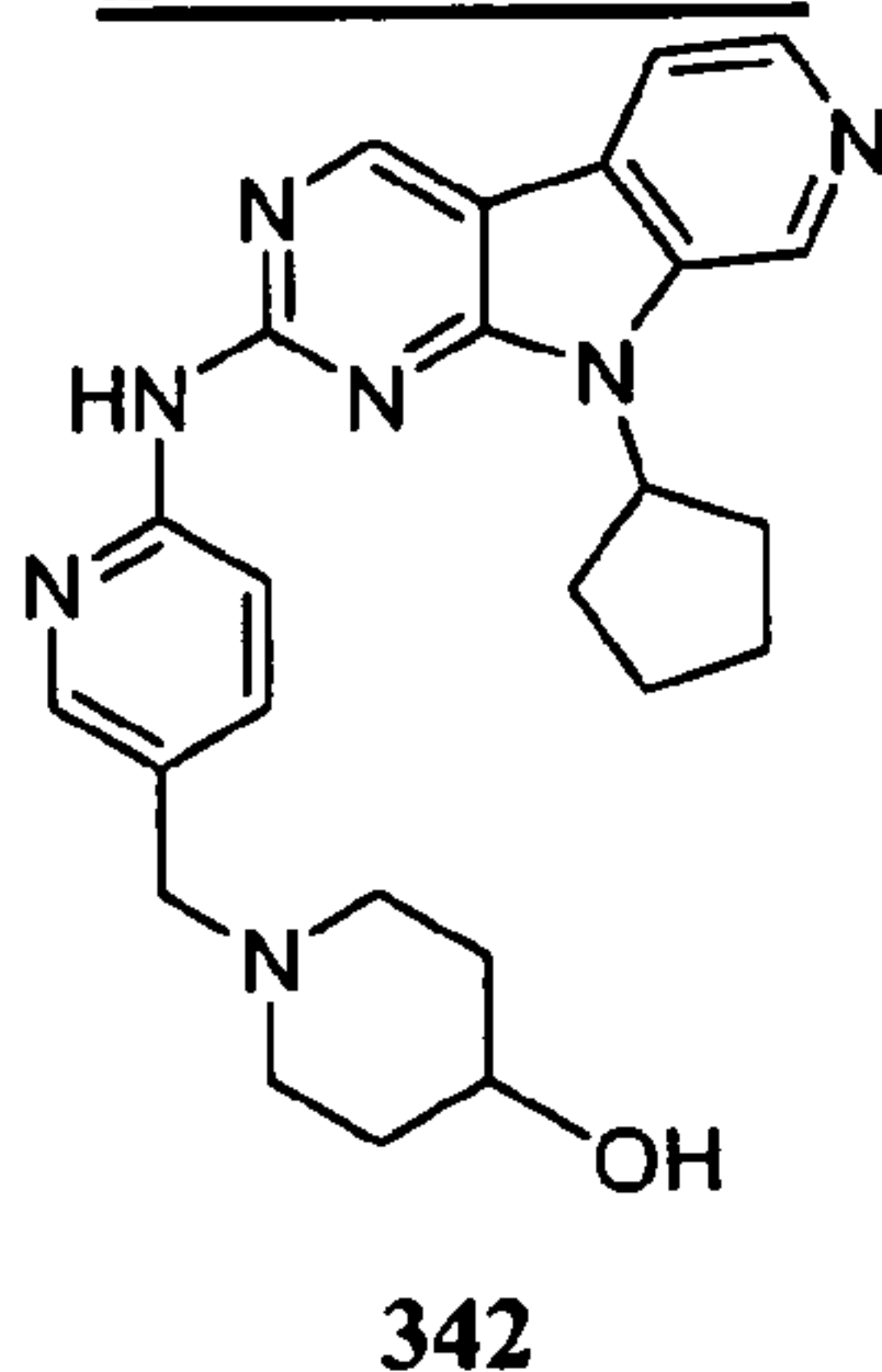
**9-cyclopentyl-2-((5-(1-piperazinylmethyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol**



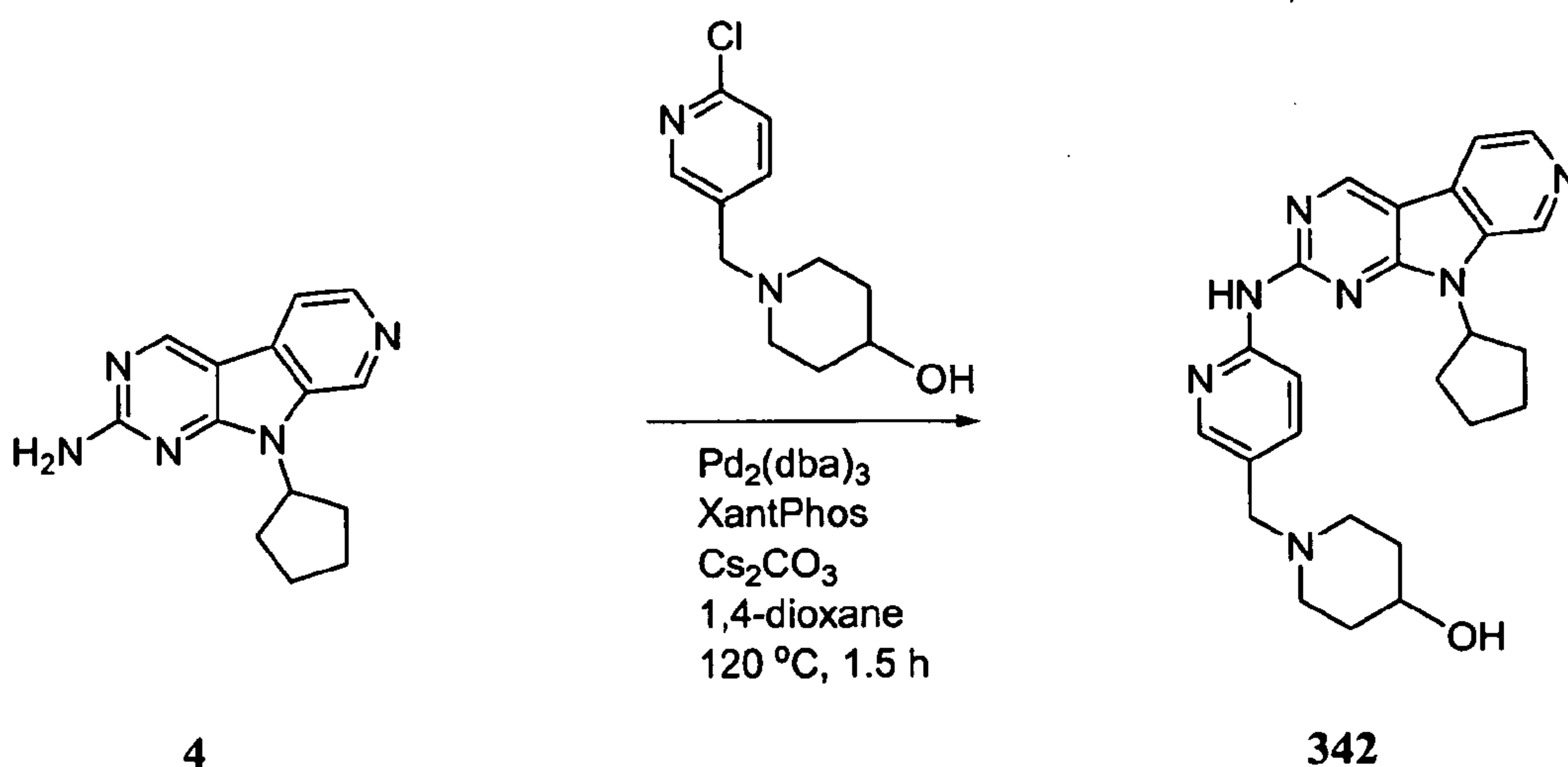


Compound **341** formed as a side product in example 213 and was isolated after reverse phase HPLC as a light yellow solid (TFA salt). LCMS-ESI (POS), M/Z, M+1: Found 445.1.

### EXAMPLE 215



**1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-4-piperidinol**

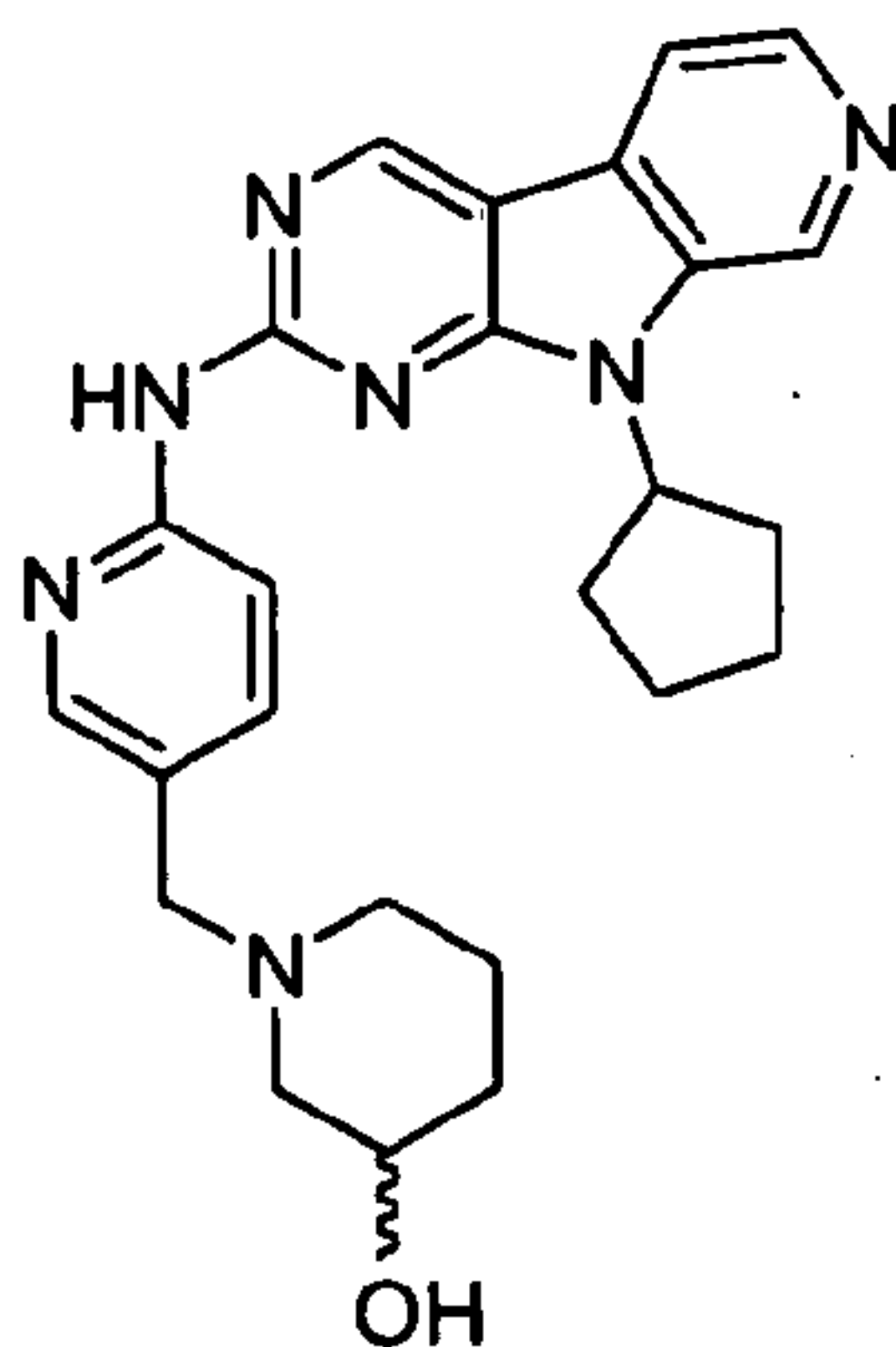


**1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-4-piperidinol (342):** In a 10 mL microwave reaction vessel were placed compound **4** (40 mg, 158  $\mu\text{mol}$ ), 1-(6-chloro-pyridin-3-ylmethyl)piperidin-4-ol (36 mg, 158  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (o) (7.2 mg, 7.9  $\mu\text{mol}$ ), 9,9-dimethyl-4,5-



bis(diphenylphosphino)xanthene (11 mg, 20  $\mu$ mol), and cesium carbonate (25  $\mu$ l, 316  $\mu$ mol) followed by 1,4-dioxane (3 mL). The vessel was purged with N<sub>2</sub> for 5 min, then capped and subjected to microwave condition (1.5 h at 120 °C). After the volatiles were removed, the residue was purified by combi-flash column chromatography followed by reverse phase preparative HPLC (acetonitrile/H<sub>2</sub>O containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **342** (10 mg) as an off-white solid (TFA salt). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 10.00 (1 H, s), 9.32 (1 H, s), 9.03 (1 H, s), 8.46 (1 H, d, J=5.1 Hz), 8.32 (1 H, d, J=8.3 Hz), 8.19 (1 H, d, J=1.7 Hz), 8.04 - 8.10 (1 H, m), 7.72 (1 H, dd, J=8.6, 2.0 Hz), 5.39 (1 H, quin, J=8.8 Hz), 4.54 (1 H, d, J=3.9 Hz), 3.43 (3 H, s), 2.64 - 2.72 (2 H, m), 2.37 - 2.45 (2 H, m), 2.00 - 2.17 (6 H, m), 1.65 - 1.84 (4 H, m), 1.39 (2 H, t, J=9.9 Hz). LCMS-ESI (POS), M/Z, M+1: Found 444.2.

#### EXAMPLE 216

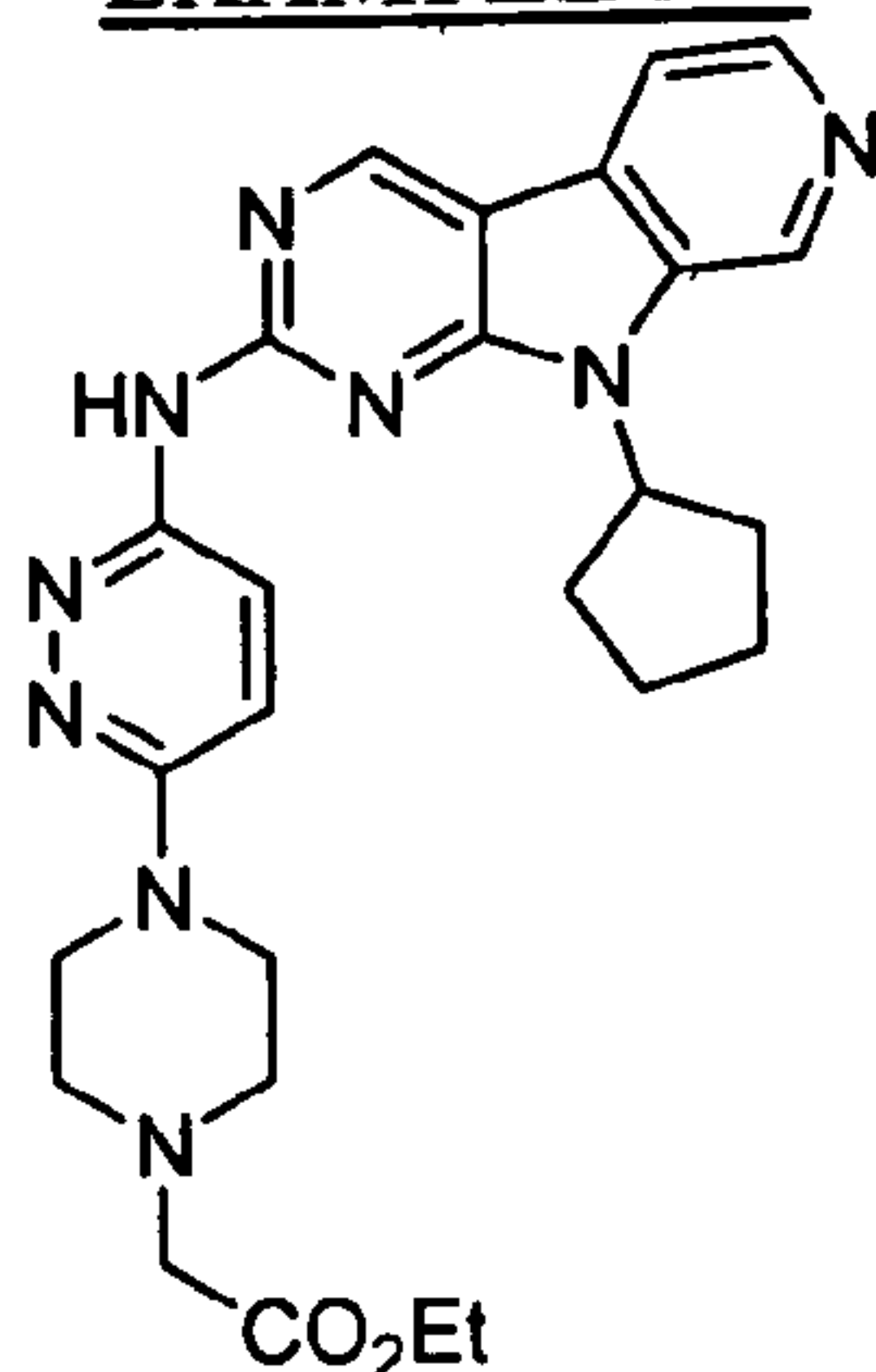


**343**

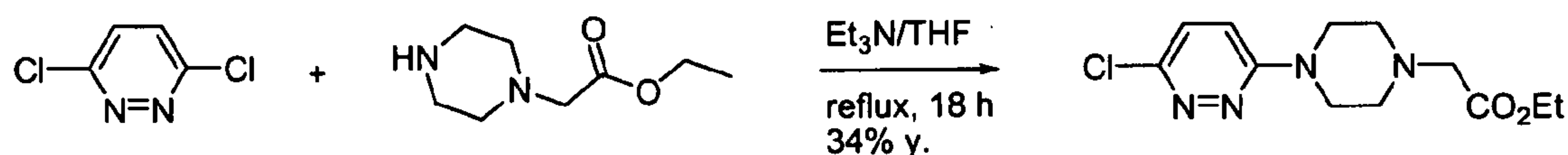
#### 1-(((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-3-piperidinol

Compound **343** was prepared as a light yellow solid (TFA salt) from compound **4** using chemistry similar to that described in example 215. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 9.60 (1 H, s), 9.31 (1 H, s), 8.64 - 8.67 (1 H, m), 8.59 - 8.64 (1 H, m), 8.53 (1 H, d, J=2.0 Hz), 8.41 (1 H, d, J=8.6 Hz), 8.11 (1 H, dd, J=8.8, 2.2 Hz), 5.46 (1 H, quin, J=8.9 Hz), 4.05 - 4.53 (2 H, m), 3.53 (1 H, br. s.), 3.10 (1 H, br. s.), 2.50 - 2.64 (2 H, m), 2.14 - 2.36 (5 H, m), 1.75 - 2.00 (3 H, m). LCMS-ESI (POS), M/Z, M+1: Found 444.2.



**EXAMPLE 217****344**

**ethyl (4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinyl)acetate**

**345**

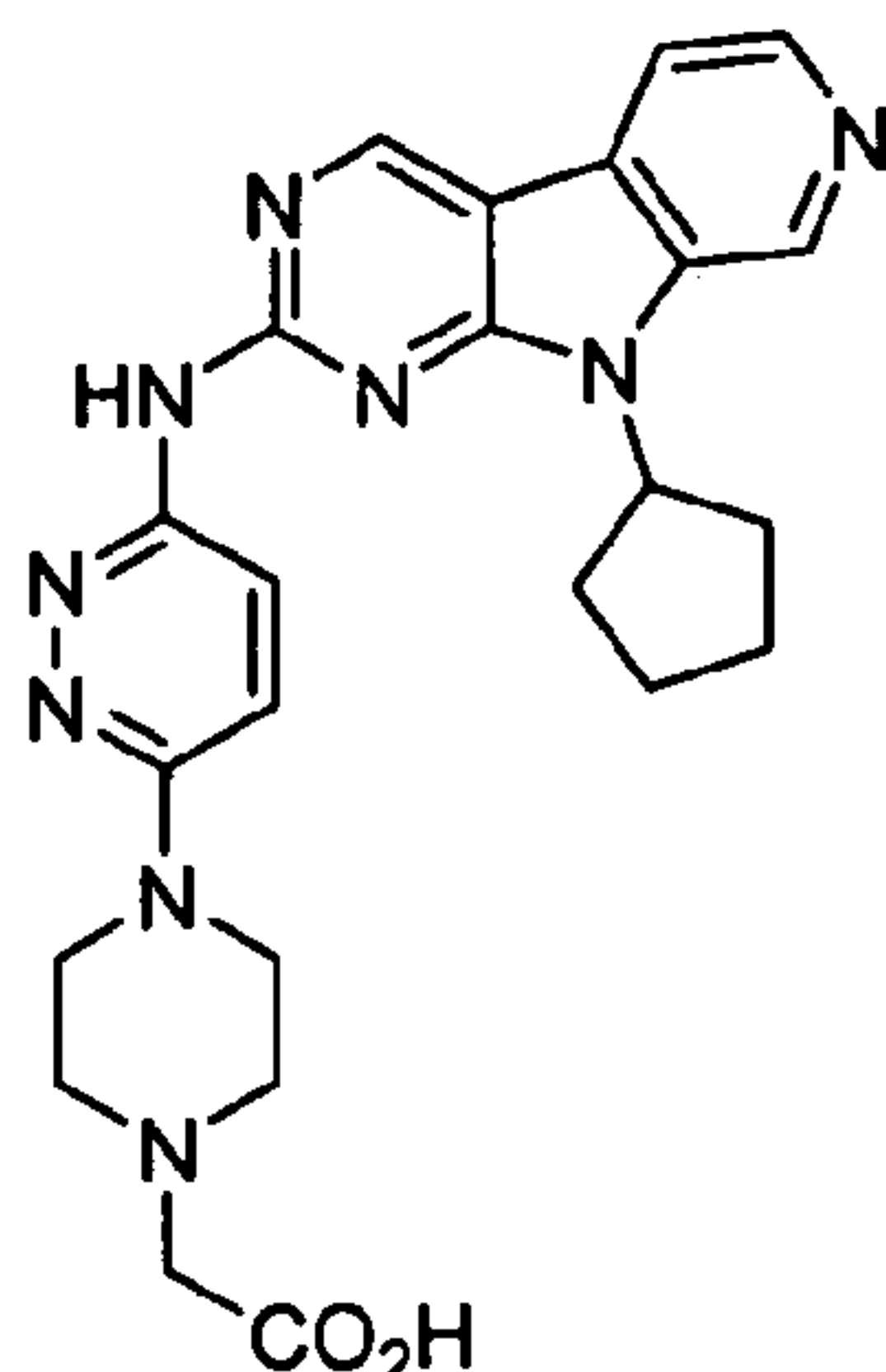
**Ethyl 2-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)acetate (345):** Triethylamine (2.2 mL, 16 mmol) followed by 1-(ethoxycarbonylmethyl)piperazine (2.6 mL, 16 mmol) were added to a stirred suspension of 1-(ethoxycarbonylmethyl)piperazine (2.6 mL, 16 mmol) in THF (40 mL). The resulting mixture was stirred at reflux for 18 h. After cooling, the precipitate was removed by vacuum filtration through a layer of celite. The cake was washed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was subjected to combi-flash column chromatography (methanol/DCM with Et<sub>3</sub>N) to give compound **345** (1.5 g, 34% yield) as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.53 (1 H, d), 7.38 (1 H, d, J=9.4 Hz), 4.09 (2 H, q, J=7.0 Hz), 3.54 - 3.63 (4 H, m), 3.29 (2 H, s), 2.57 - 2.65 (4 H, m), 1.19 (3 H, t, J=7.0 Hz). LCMS-ESI (POS), M/Z, M+1: Found 285.1.

**ethyl (4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinyl)acetate (344):** Compound **344** was prepared as a light yellow solid (TFA salt) from compound **4** and compound **345** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.65 (1 H, s), 9.33 (1 H, s), 8.63 - 8.68 (2 H, m), 8.15 (1 H, d, J=9.8 Hz), 7.94 (1 H, d, J=9.8 Hz), 5.46 (1 H, qt), 4.33 (2 H, q, J=7.1 Hz), 4.11 (2 H, s), 3.98 (4 H, br. s.), 3.46 (4 H, t, J=5.1 Hz), 2.45 - 2.59 (2 H, m), 2.13 - 2.31 (4



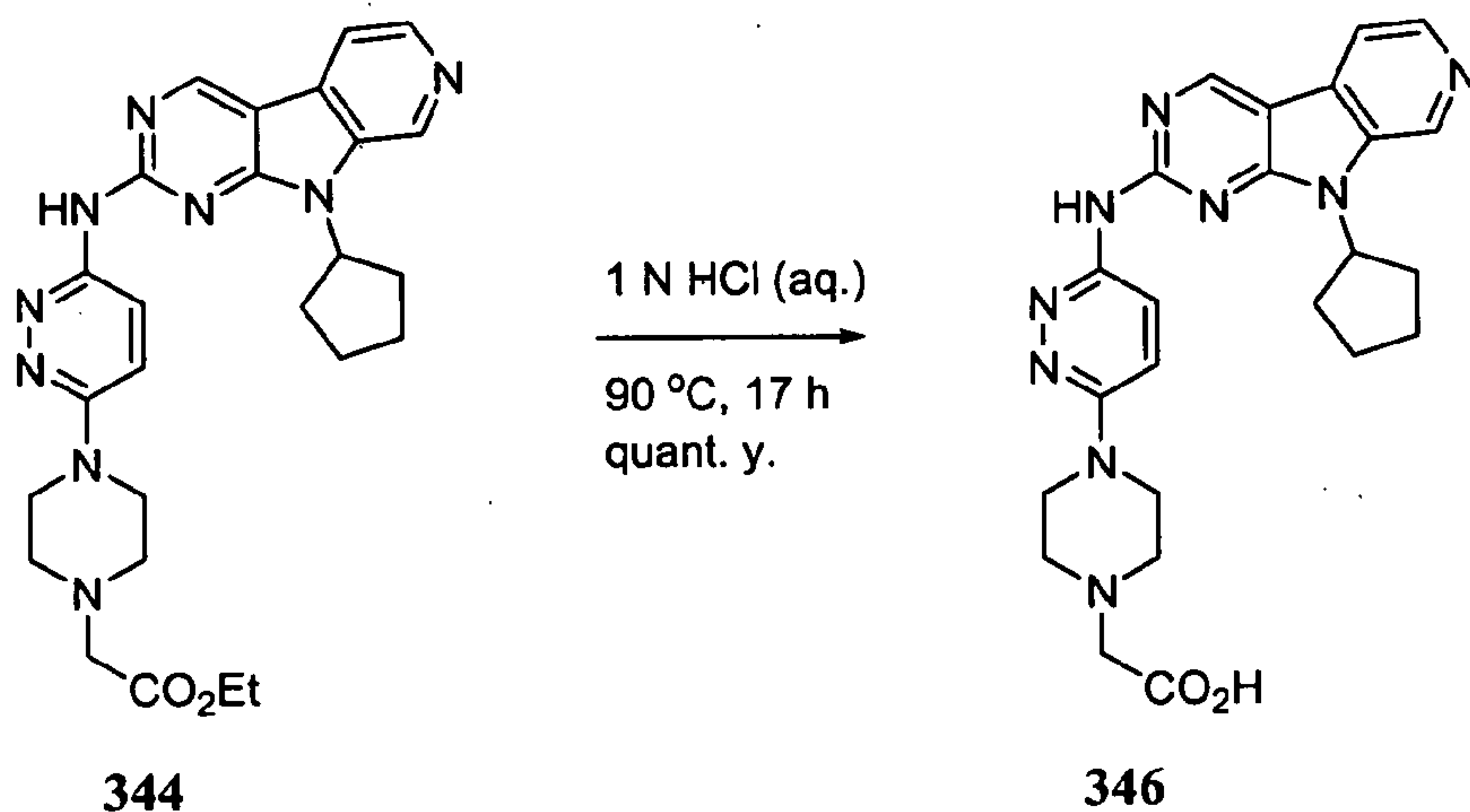
H, m), 1.84 - 1.96 (2 H, m), 1.34 (3 H, t, J=7.2 Hz). LCMS-ESI (POS), M/Z, M+1: Found 502.3.

### EXAMPLE 218



346

**(4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinyl)acetic acid**

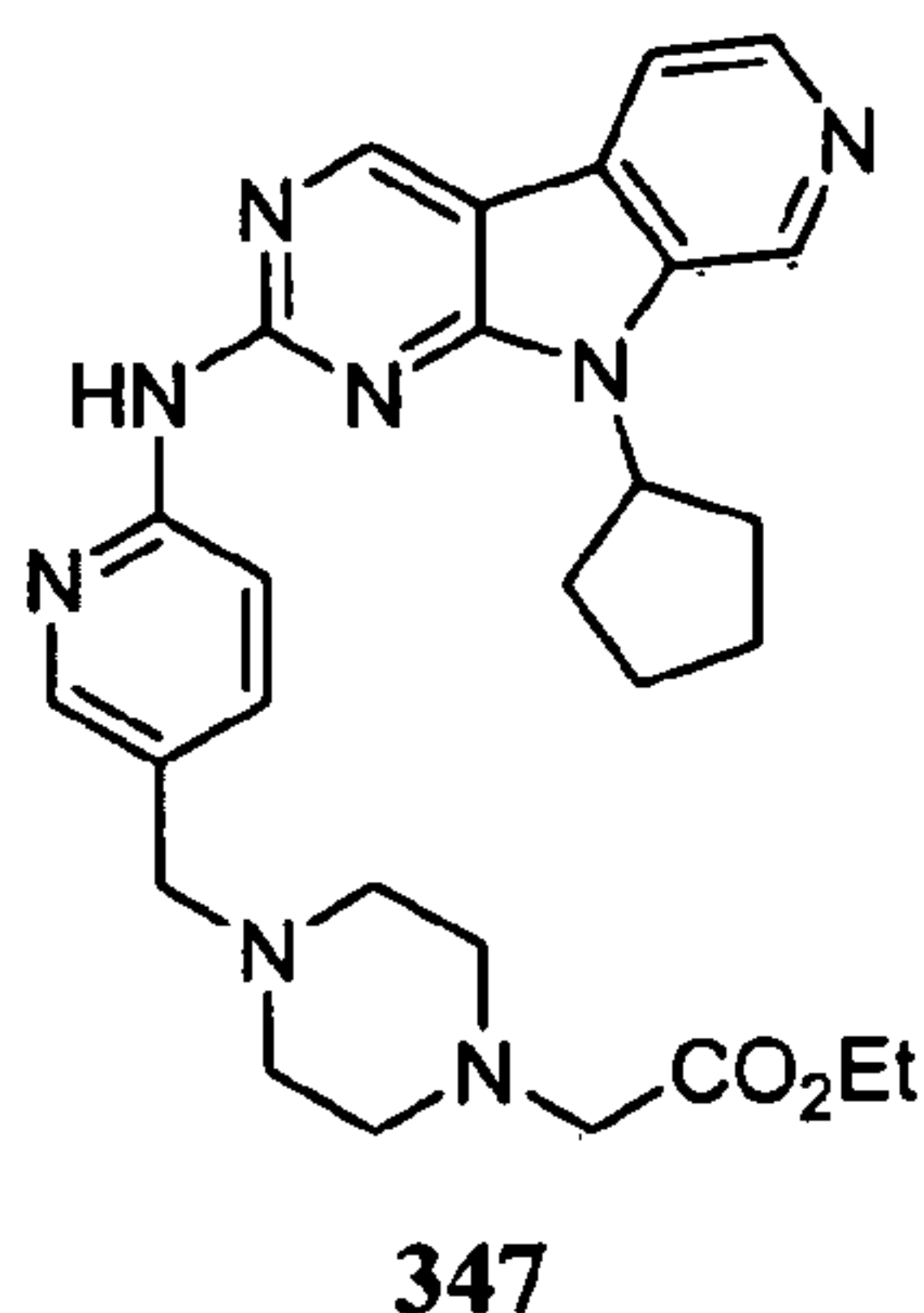


344

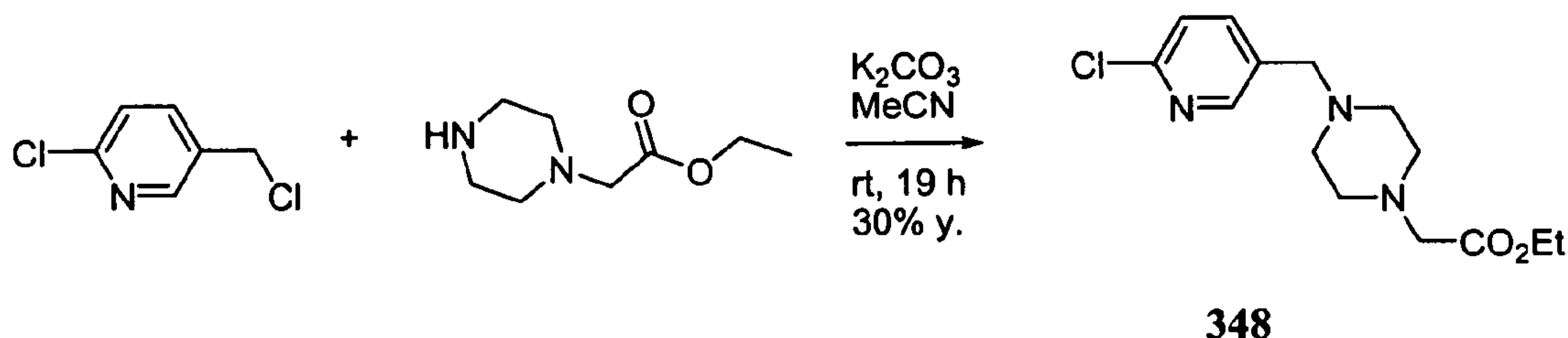
346

**(4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-piperazinyl)acetic acid (346):** A mixture of compound 344 and hydrochloric acid (1 N aqueous solution) (7 mL) was stirred at 90 °C for 17 h. After concentration, the residue was subjected to reverse phase preparative HPLC (acetonitrile/H<sub>2</sub>O containing 0.1% TFA each, 40 min from 10 to 30%). Lyophilization provided compound 346 (50 mg) as a yellow solid (TFA salt). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 10.94 (1 H, br. s.), 9.55 (1 H, s), 9.33 (1 H, s), 8.65 (1 H, d, J=6.1 Hz), 8.53 (1 H, d, J=5.9 Hz), 8.23 (1 H, d, J=9.5 Hz), 7.60 (1 H, d, J=9.8 Hz), 5.34 (1 H, dq, J=8.9, 8.8 Hz), 4.16 (2 H, br. s.), 3.40 (8 H, br. s.), 2.33 - 2.44 (2 H, m), 1.92 - 2.18 (4 H, m), 1.62 - 1.81 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 474.2.



**EXAMPLE 219**

**Ethyl (4-(((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-1-piperazinyl)acetate**

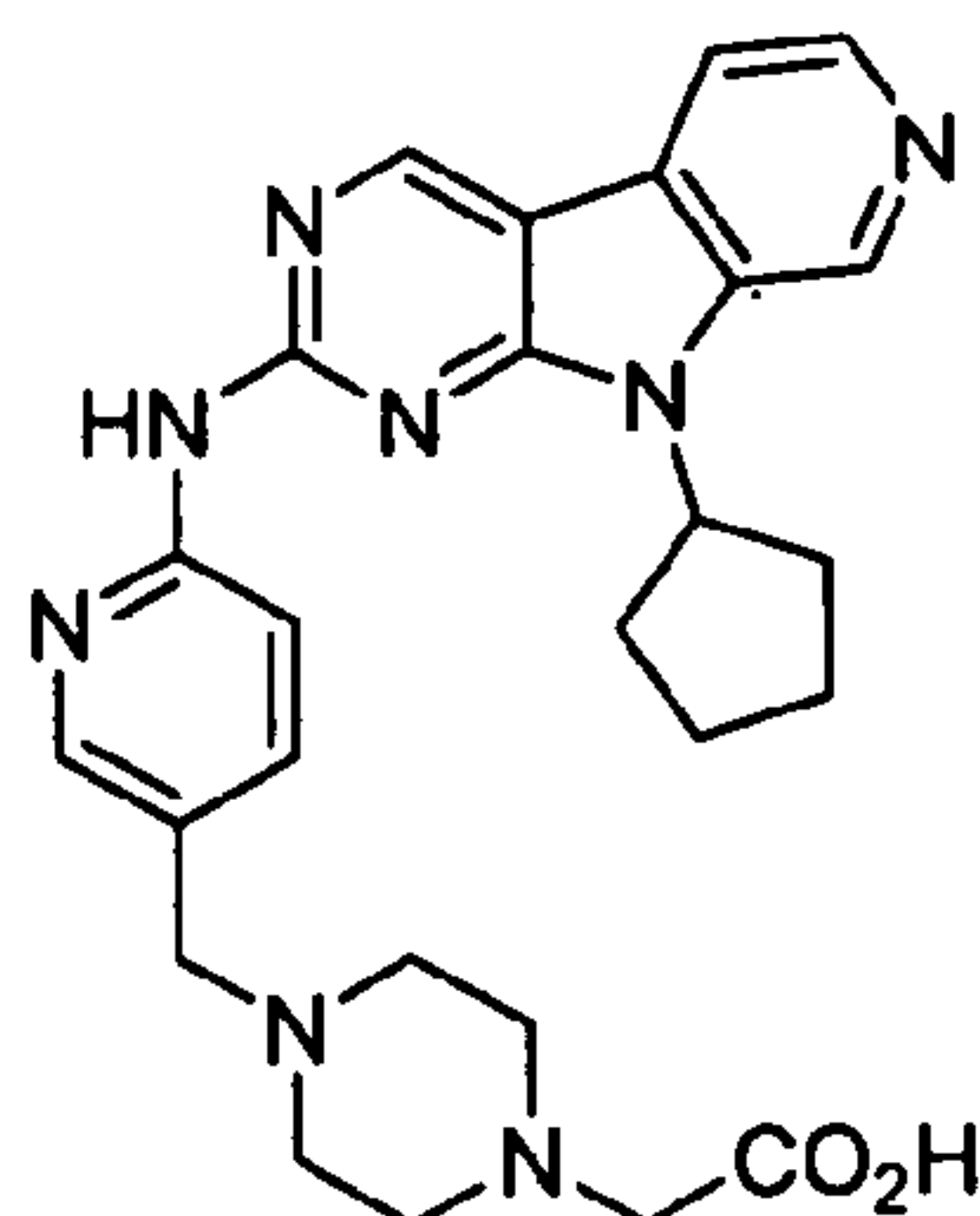


**Ethyl 2-(4-((6-chloropyridin-3-yl)methyl)piperazin-1-yl)acetate (348):** To a stirred suspension of 2-chloro-5-(chloromethyl)pyridine (2.0 g, 12 mmol) in acetonitrile (60 mL) was added potassium carbonate (1.5 mL, 25 mmol) followed by 1-(ethoxycarbonylmethyl)piperazine (2.0 mL, 12 mmol). The resulting mixture was stirred at room temperature for 19 h. The mixture was filtered through celite and the filter cake was washed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was subjected to combi-flash column chromatography (methanol/DCM with Et<sub>3</sub>N) to give compound **348** (1.1 g, 30% yield) as a colorless liquid. <sup>1</sup>H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.31 (1 H, d, J=2.0 Hz), 7.66 (1 H, d, J=6.1 Hz), 7.28 (1 H, d, J=8.1 Hz), 4.18 (2 H, q, J=7.1 Hz), 3.50 (2 H, br. s.), 3.21 (2 H, s), 2.36 - 2.77 (8 H, m), 1.27 (3 H, t, J=7.2 Hz). LCMS-ESI (POS), M/Z, M+1: Found 298.1.

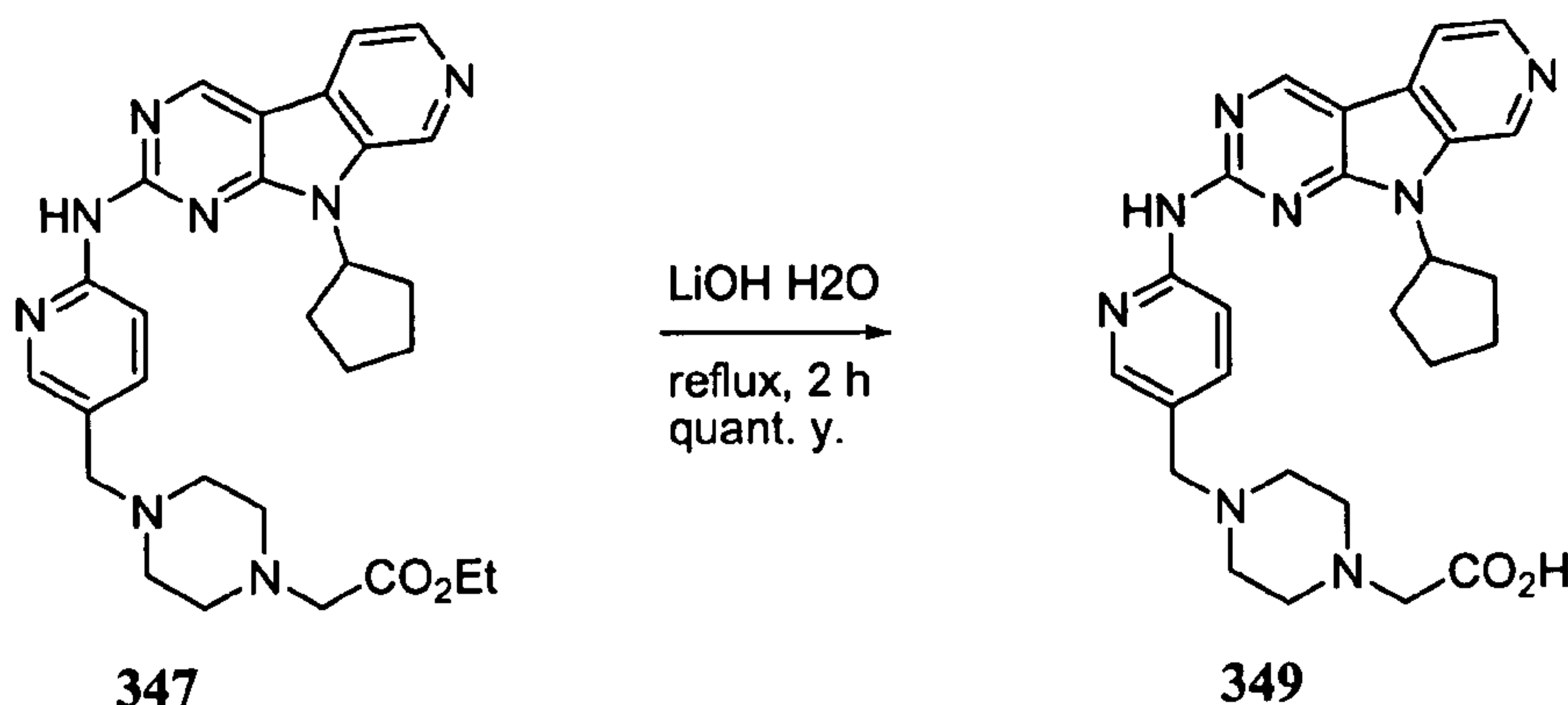
**Ethyl (4-(((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-1-piperazinyl)acetate (347):** Compound **347** was prepared as an off-white solid (TFA salt) from compound **4** and compound **348** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.57 (1 H, s), 9.27 (1 H, s), 8.60 (2 H, s), 8.47 (1 H, d, J=2.0 Hz), 8.32 - 8.43 (1 H, m), 8.07 (1 H, dd, J=8.8, 2.2 Hz), 5.46 (1 H, dq,



J=9.0, 8.9 Hz), 4.12 - 4.28 (4 H, m), 3.65 (2 H, br. s.), 2.96 - 3.21 (8 H, m), 2.48 - 2.61 (2 H, m), 2.15 - 2.31 (4 H, m), 1.85 - 1.99 (2 H, m), 1.28 (3 H, t, J=7.2 Hz). LCMS-ESI (POS), M/Z, M+1: Found 515.2.

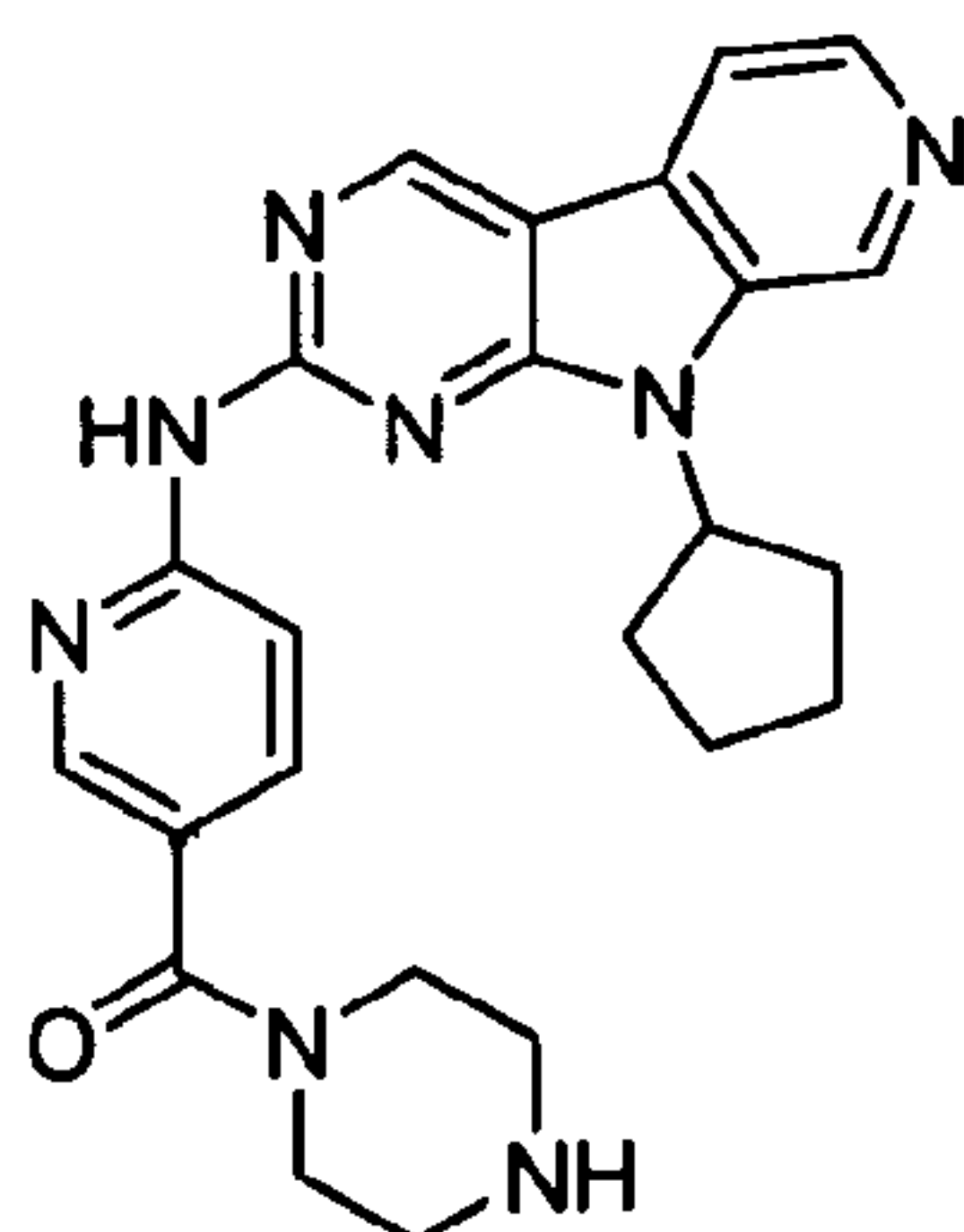
**EXAMPLE 220****349**

**(4-(((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-1-piperazinyl)acetic acid**

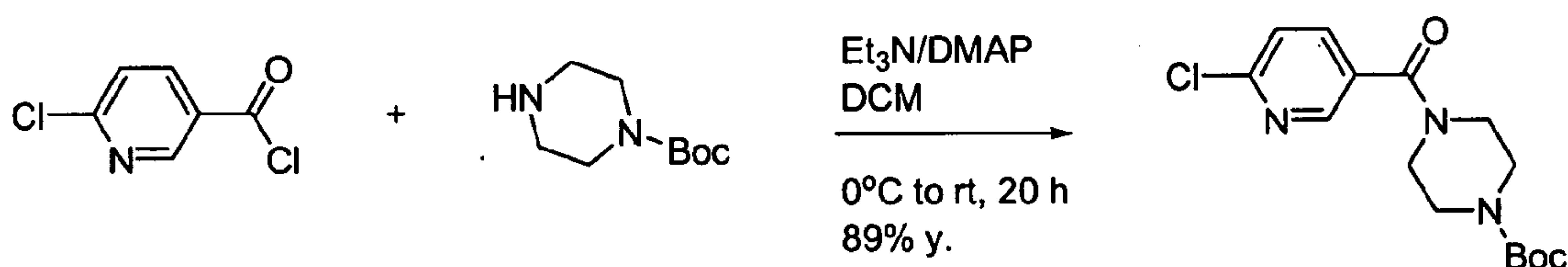
**347****349**

**(4-(((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-1-piperazinyl)acetic acid (349):** A mixture of compound 347 (50 mg, 97  $\mu\text{mol}$ ) and lithium hydroxide, monohydrate (14  $\mu\text{l}$ , 486  $\mu\text{mol}$ ) in methanol (9 mL) and water (3 mL) was heated at reflux for 2 h. After cooling, the crude mixture was subjected to reverse phase preparative HPLC (acetonitrile/H<sub>2</sub>O containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound 349 (40 mg) as a light yellow solid (TFA salt). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 10.84 (1 H, s), 9.62 (1 H, s), 9.38 (1 H, s), 8.68 (1 H, d, J=5.9 Hz), 8.58 (1 H, d, J=6.3 Hz), 8.26 - 8.48 (2 H, m), 7.89 - 8.01 (1 H, m), 5.40 (1 H, quin, J=8.9 Hz), 2.75 - 4.63 (12 H, m), 2.39 - 2.47 (2 H, m), 2.01 - 2.23 (4 H, m), 1.70 - 1.87 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 487.3.



**EXAMPLE 221****350**

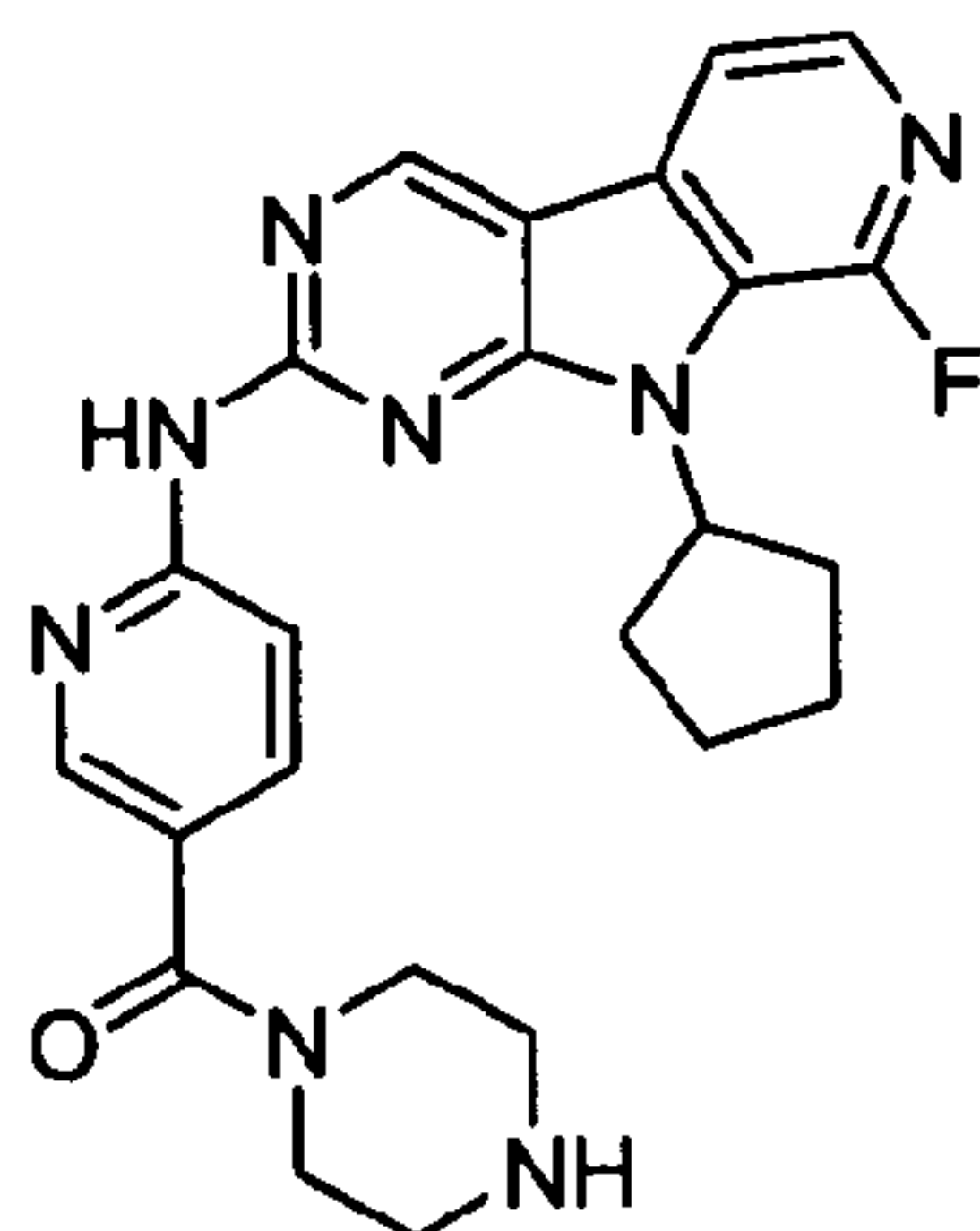
**9-cyclopentyl-N-(5-(1-piperazinylcarbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**351**

**tert-Butyl 4-(2-chloronicotinoyl)piperazine-1-carboxylate (351):** To a stirred ice-cooled solution of tert-butyl 1-piperazinecarboxylate (2.2 g, 12 mmol), triethylamine (3.2 mL, 23 mmol), and 4-dimethylaminopyridine (0.014 g, 0.11 mmol) in DCM (15 mL) was added 6-chloropyridine-3-carbonyl chloride (2.0 g, 11 mmol) in one portion. The resulting mixture was stirred at 0 °C and gradually warmed up to ambient temperature for 20 h. Upon workup, the mixture was subjected to combi-flash column chromatography (methanol/DCM) to give compound **351** (3.3 g, 89% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, *CDCl*<sub>3</sub>) δ ppm 8.46 (1 H, d, J=2.0 Hz), 7.74 (1 H, dd, J=8.2, 2.3 Hz), 7.42 (1 H, dd, J=8.2, 0.8 Hz), 3.20 - 4.02 (8 H, m), 1.48 (9 H, s). LCMS-ESI (POS), M/Z, M+1: Found 326.0.

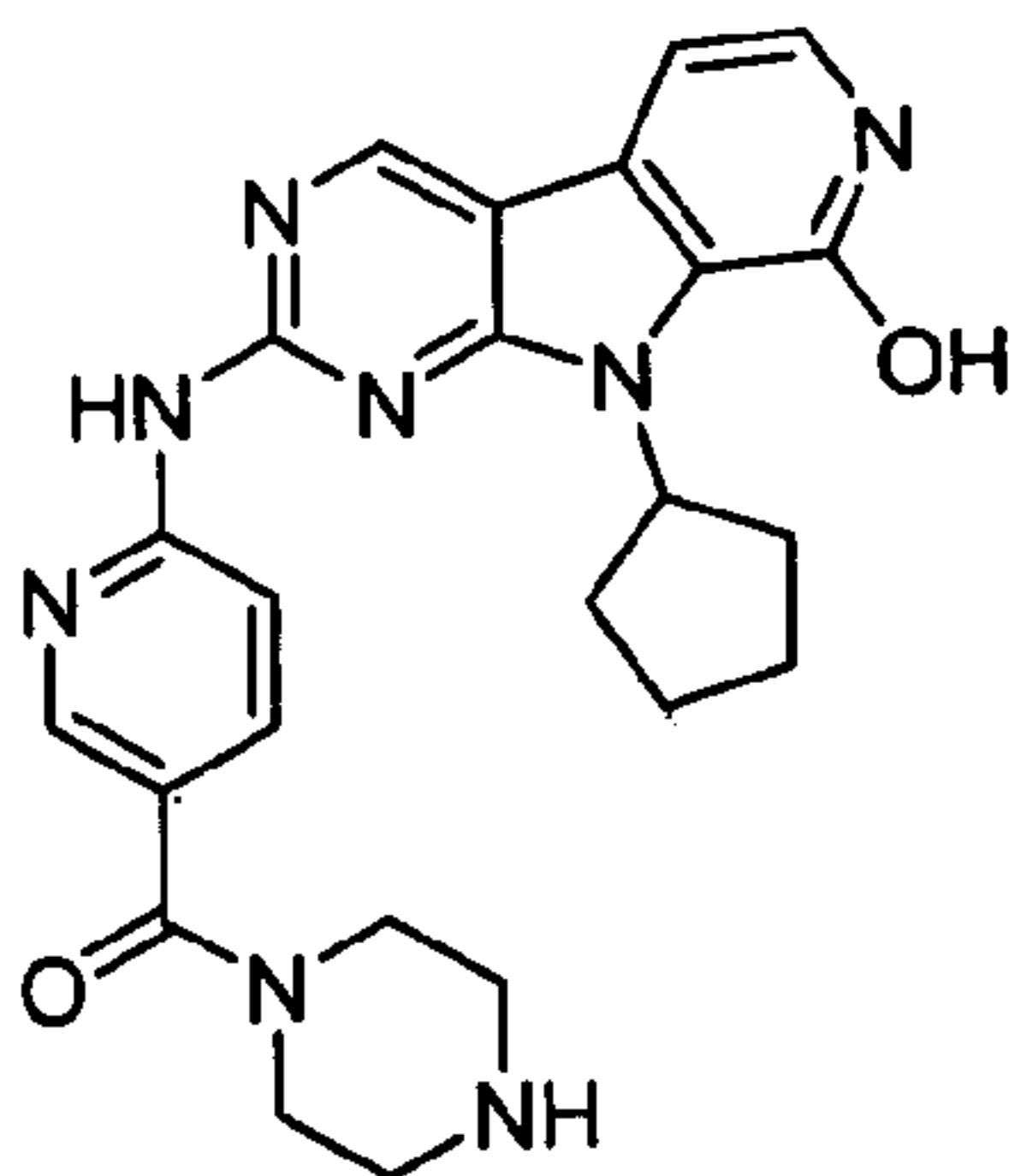
**9-cyclopentyl-N-(5-(1-piperazinylcarbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (350):** Compound **350** was prepared as a light yellow solid (HCl salt) from compound **4** and compound **351** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ ppm 11.06 (1 H, br. s.), 9.70 (1 H, s), 9.47 (1 H, s), 9.39 (2 H, br. s.), 8.67 - 8.75 (2 H, m), 8.51 (1 H, d, J=1.7 Hz), 8.37 (1 H, d, J=8.6 Hz), 8.02 (1 H, dd, J=8.7, 2.3 Hz), 5.43 (1 H, dq, J=8.9, 8.8 Hz), 3.77 (4 H, br. s.), 3.18 (4 H, br. s.), 2.42 - 2.48 (2 H, m), 2.02 - 2.20 (4 H, m), 1.70 - 1.83 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 443.2.



**EXAMPLE 222****352**

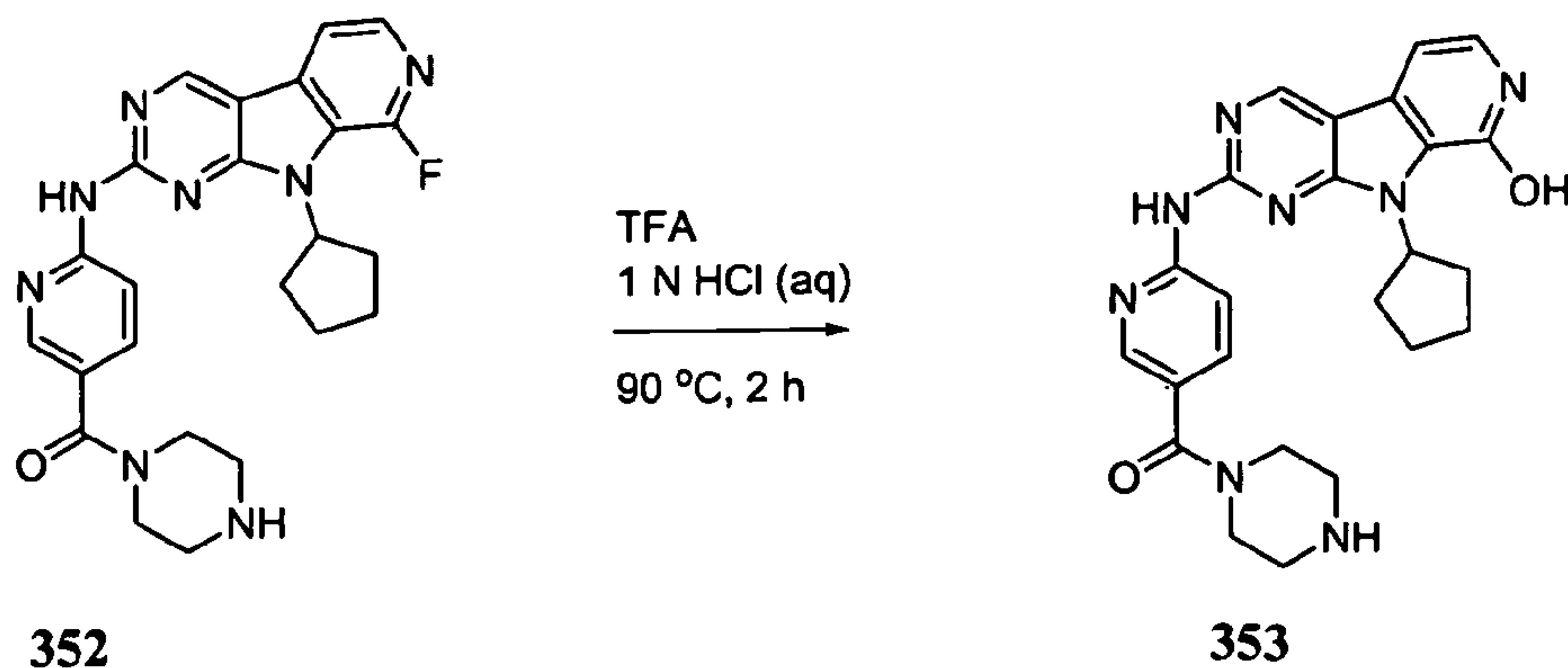
**9-cyclopentyl-8-fluoro-N-(5-(1-piperazinylcarbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **352** was prepared as an off-white solid (TFA salt) from compound **245** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (400 MHz, *DMSO-d*<sub>6</sub>) δ ppm 10.60 (1 H, s), 9.45 (1 H, s), 8.83 (2 H, br. s.), 8.47 (1 H, d, J=1.6 Hz), 8.41 (1 H, d, J=8.6 Hz), 8.12 (1 H, dd, J=5.3, 2.9 Hz), 8.05 - 8.09 (1 H, m), 7.97 (1 H, dd, J=9.0, 2.3 Hz), 5.51 (1 H, quin, J=8.9 Hz), 3.74 (4 H, br. s.), 3.20 (4 H, br. s.), 2.33 - 2.41 (2 H, m), 1.98 - 2.22 (4 H, m), 1.69 - 1.85 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 460.9.

**EXAMPLE 223****353**

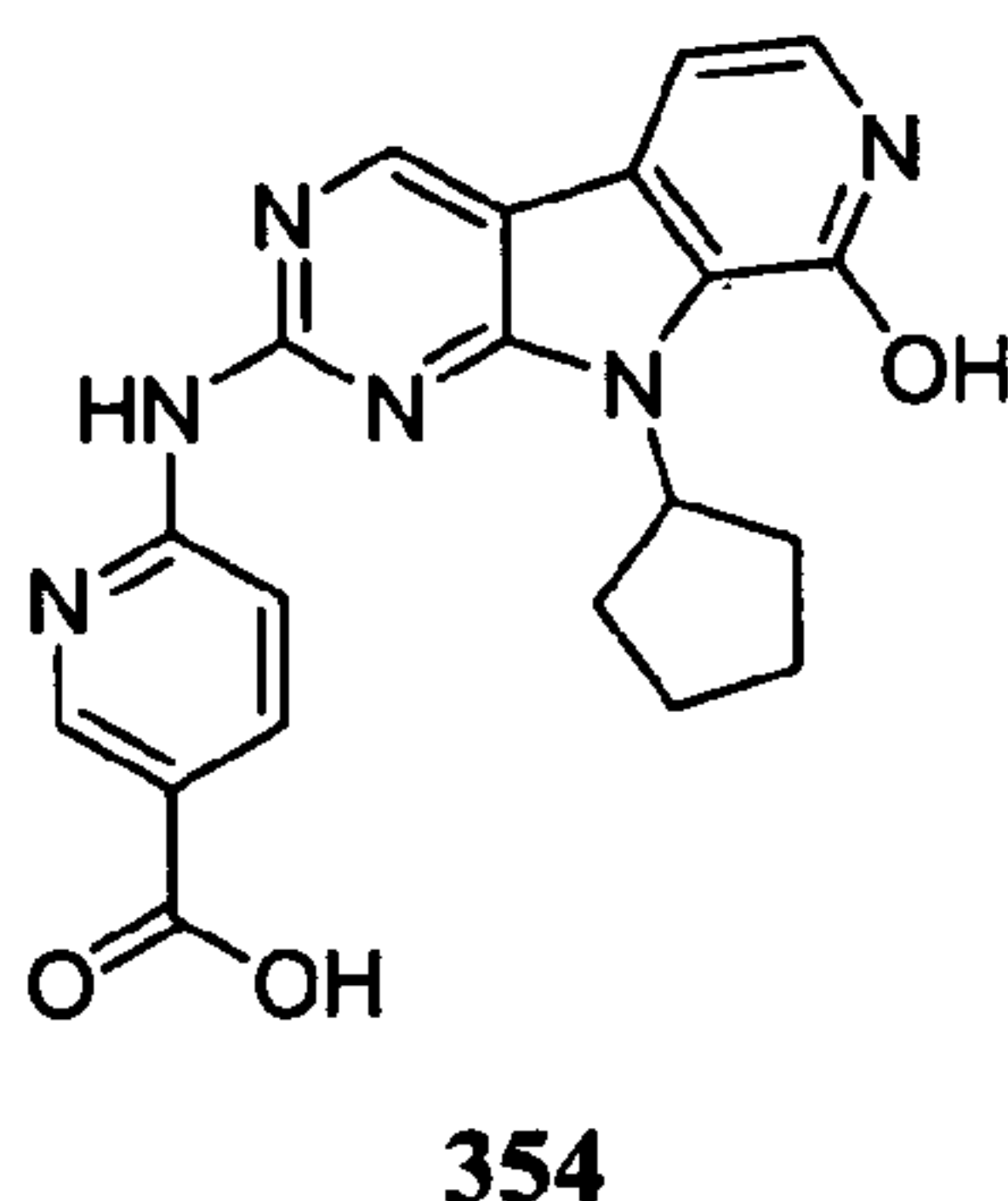
**9-cyclopentyl-2-((5-(1-piperazinylcarbonyl)-2-pyridinyl)amino)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol**





**9-cyclopentyl-2-((5-(1-piperazinylcarbonyl)-2-pyridinyl)amino)-9H-pyrido-[4',3':4,5]pyrrolo[2,3-d]pyrimidin-8-ol (353):** Compound 352 was treated with trifluoroacetic acid (4 mL, 54 mmol) in 1 N hydrochloric acid, aqueous solution (8 mL) for 2 h at 90 °C. After the volatiles were partially removed, the residue was subjected to reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound 353 (8 mg) as a light yellow solid (TFA salt). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 9.30 (1 H, s), 8.54 (1 H, s), 7.95 - 8.20 (2 H, m), 7.34 (1 H, d, J=6.7 Hz), 7.14 (1 H, d, J=6.7 Hz), 6.26 (1 H, dq, J=9.4, 9.1 Hz), 3.93 (4 H, br. s.), 3.33 - 3.38 (4 H, m), 2.53 - 2.70 (2 H, m), 2.04 - 2.28 (4 H, m), 1.68 - 1.91 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 459.2.

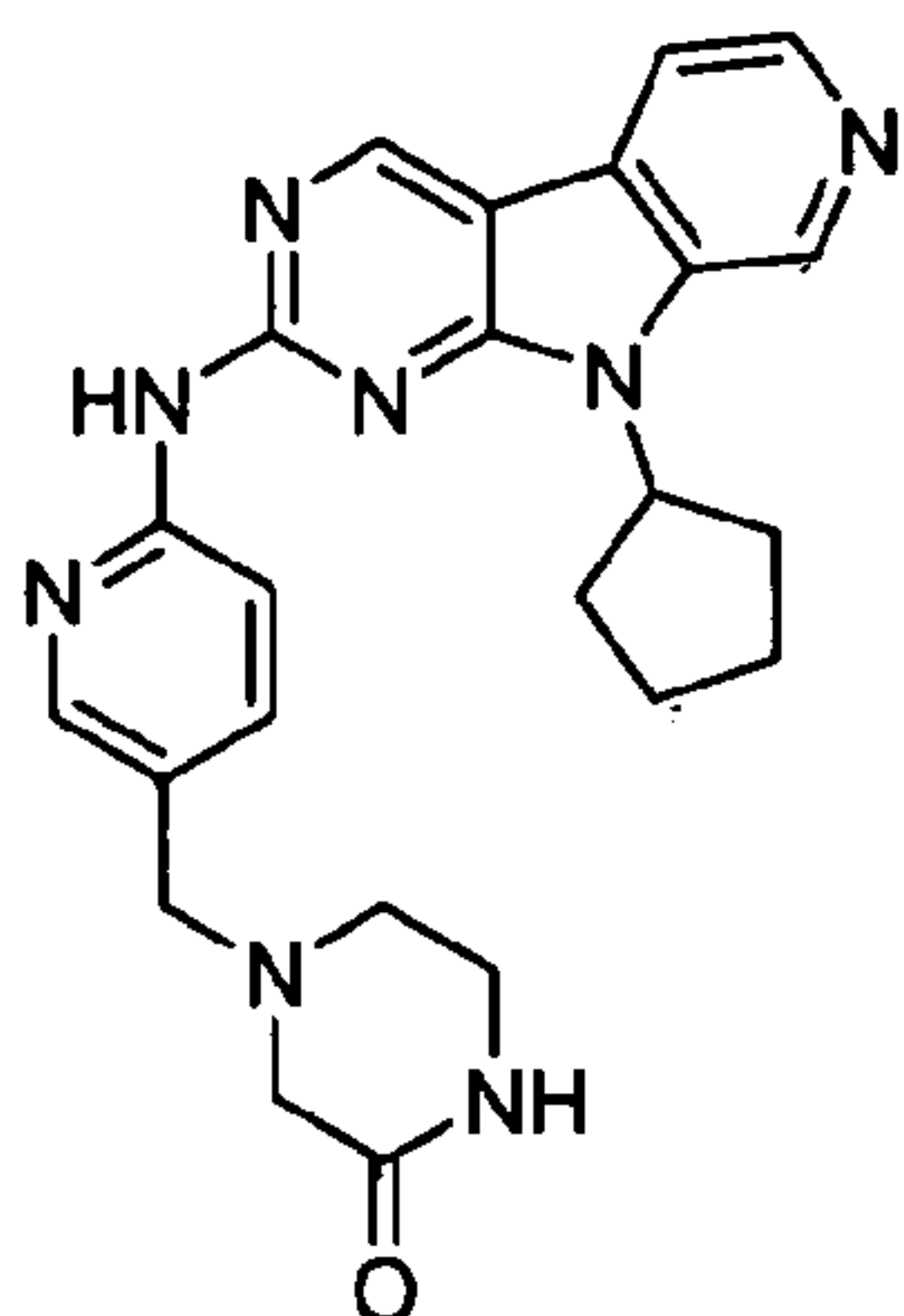
#### EXAMPLE 224



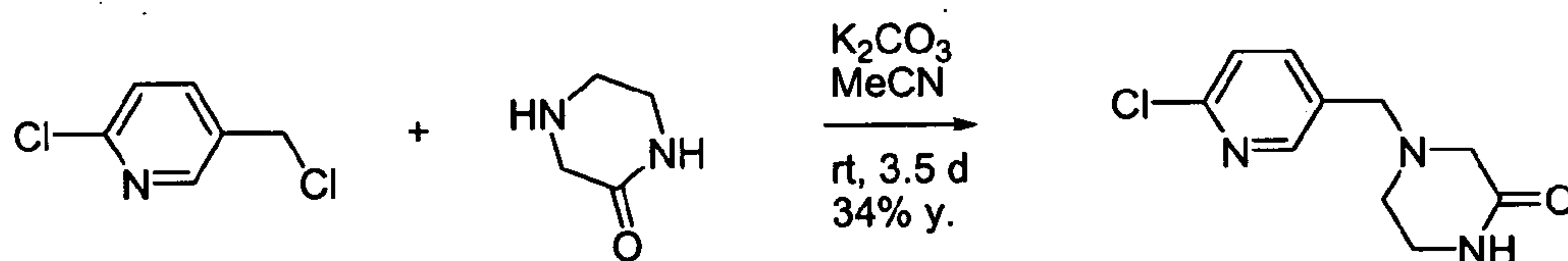
**6-((9-cyclopentyl-8-hydroxy-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinecarboxylic acid**

Compound 354 was obtained in the hydrolysis of compound 352 (example 223) as a light yellow solid (HCl salt). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.42 (1 H, s), 9.04 (1 H, d, J=1.5 Hz), 8.58 (1 H, dd, J=8.9, 2.1 Hz), 7.57 (1 H, d, J=9.0 Hz), 7.40 (1 H, d, J=6.8 Hz), 7.19 (1 H, d, J=6.6 Hz), 6.25 (1 H, dq, J=9.2, 9.0 Hz), 2.52 - 2.65 (2 H, m), 2.07 - 2.25 (4 H, m), 1.73 - 1.87 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 391.1.

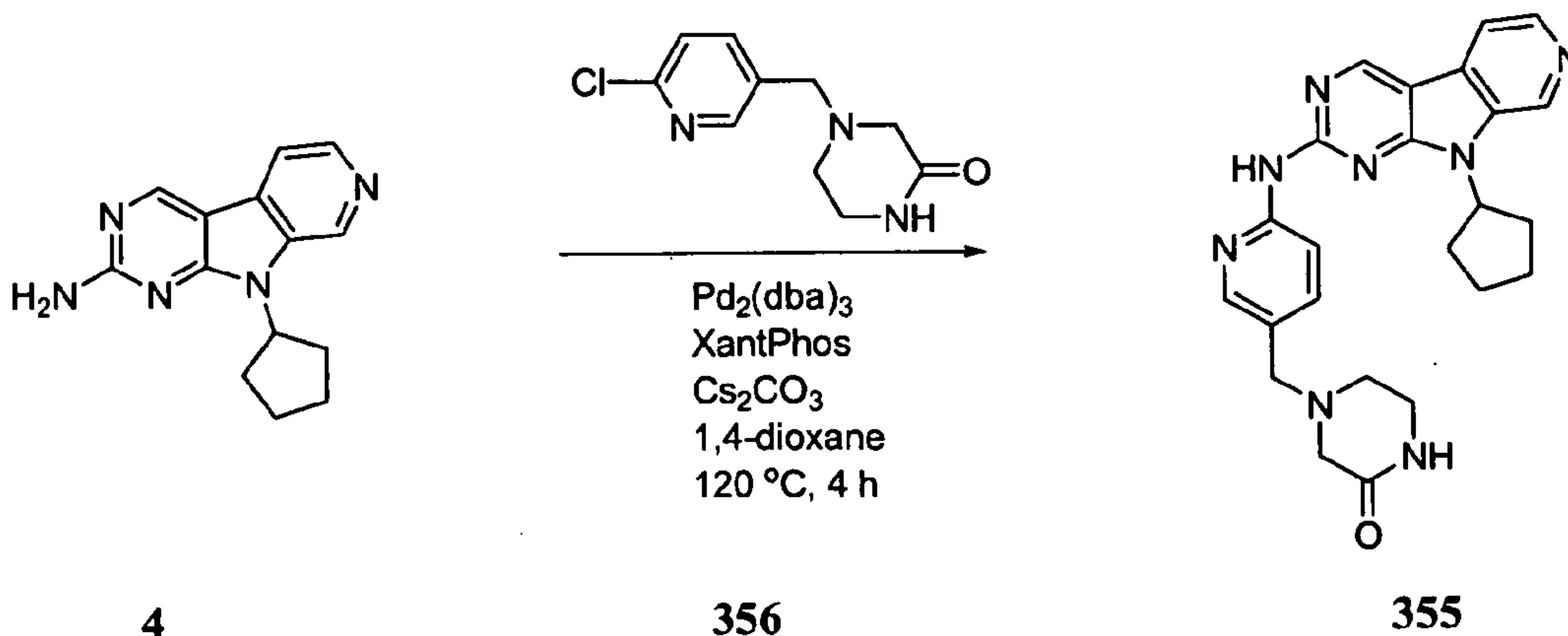


**EXAMPLE 225****355**

**4-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-2-piperazinone**

**356**

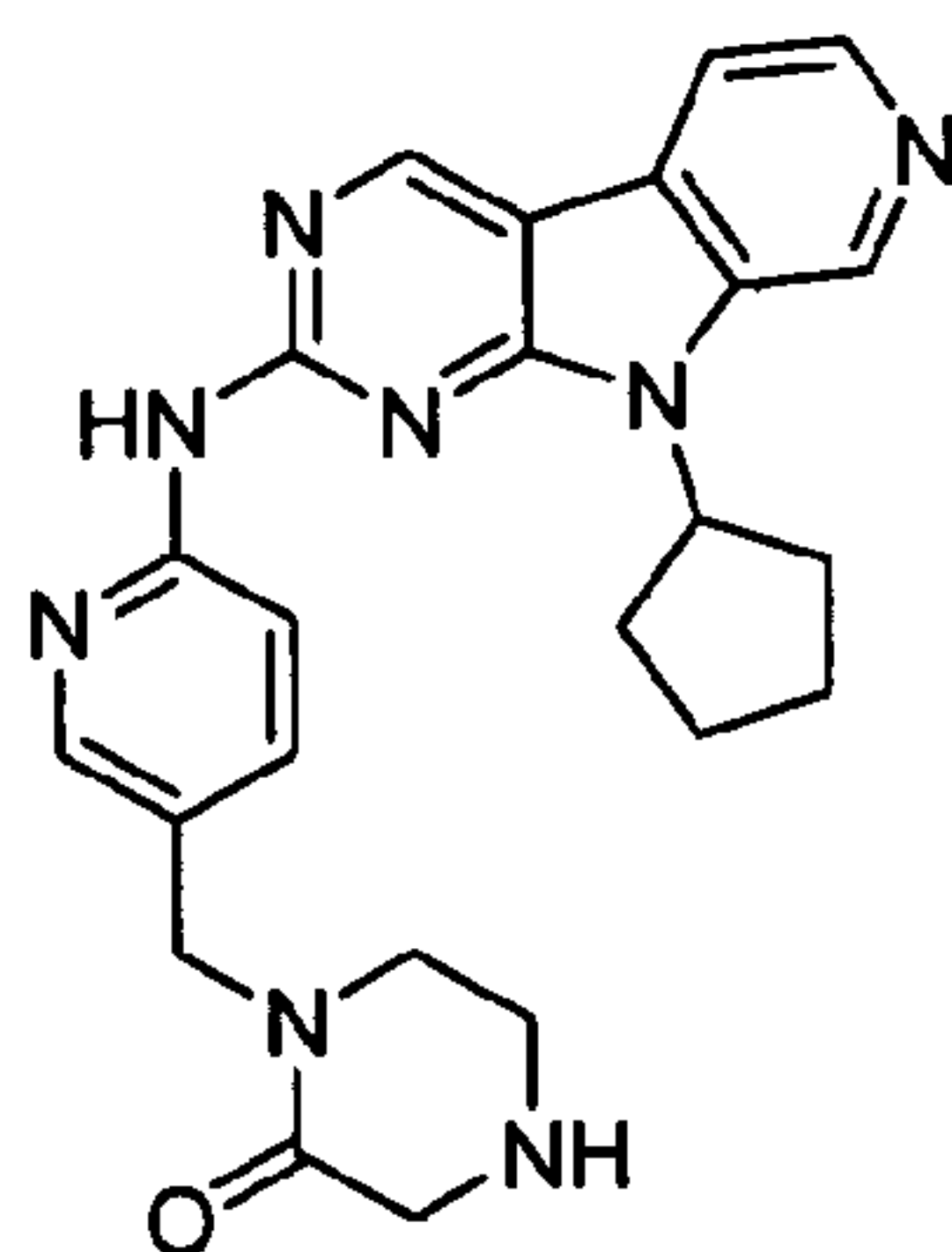
**4-((6-Chloropyridin-3-yl)methyl)piperazin-2-one (356):** A mixture of 2-chloro-5-(chloromethyl)pyridine (1.4 g, 8.4 mmol), piperazinone (0.84 g, 8.4 mmol), and potassium carbonate (1.0 mL, 17 mmol) in a mixed solvent consisting of acetonitrile (40 mL) and THF (20 mL) was stirred at room temperature for 3.5 days. Upon workup, the mixture was filtered through a layer of celite and the cake was washed with ethyl acetate. The filtrate was concentrated in vacuo and the residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **356** (0.65 g, 34% yield) as an off-white solid. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ ppm 8.35 (1 H, d, *J*=2.0 Hz), 7.81 (1 H, dd, *J*=8.1, 2.4 Hz), 7.76 (1 H, br. s.), 7.49 (1 H, d, *J*=8.3 Hz), 3.57 (2 H, s), 3.10 - 3.16 (2 H, m), 2.93 (2 H, s), 2.52 - 2.56 (2 H, m). LCMS-ESI (POS), *M/Z*, *M*+1: Found 226.0.

**4****356****355**



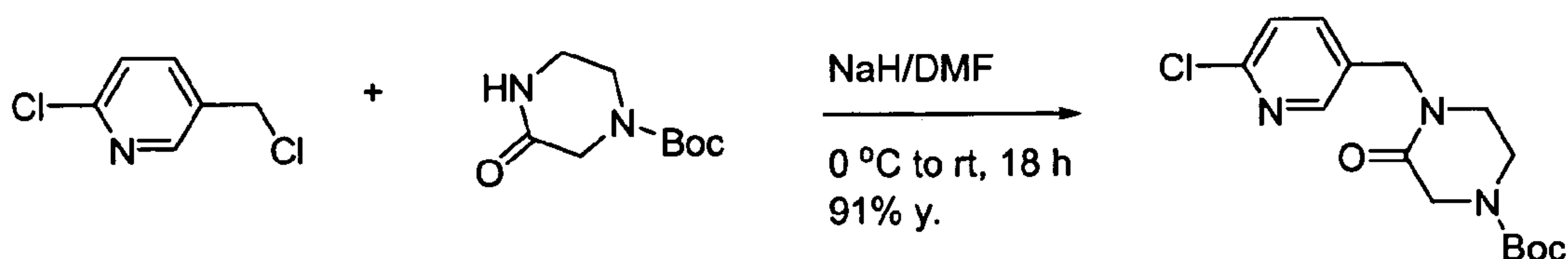
**4-((6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-2-piperazinone (355):** In a 10 mL microwave reaction vessel were placed compound 4 (93 mg, 367  $\mu$ mol), compound 356 (83 mg, 367  $\mu$ mol), tris(dibenzylideneacetone)dipalladium (o) (17 mg, 18  $\mu$ mol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 46  $\mu$ mol), and cesium carbonate (359 mg, 1101  $\mu$ mol) followed by 1,4-dioxane (3 mL). The vessel was purged with N<sub>2</sub> for 5 min, then capped and subjected to microwave irradiation for 4 h at 120 °C. The crude mixture was taken up in 4% methanol/DCM and subjected to combi-flash column chromatography (methanol/DCM) followed by preparative reverse phase HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound 355 (100 mg) as an off-white solid (TFA salt). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 9.67 (1 H, s), 9.34 (1 H, s), 8.69 (1 H, d), 8.66 (1 H, d), 8.48 (1 H, d, J=1.7 Hz), 8.24 (1 H, dd, J=8.8, 2.2 Hz), 8.04 (1 H, d, J=8.6 Hz), 5.48 (1 H, quin, J=8.7 Hz), 4.03 (2 H, s), 3.40 - 3.49 (4 H, m), 3.09 (2 H, t, J=5.3 Hz), 2.48 - 2.60 (2 H, m), 2.14 - 2.32 (4 H, m), 1.85 - 1.98 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 443.2.

#### EXAMPLE 226



357

**1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-2-piperazinone**



358

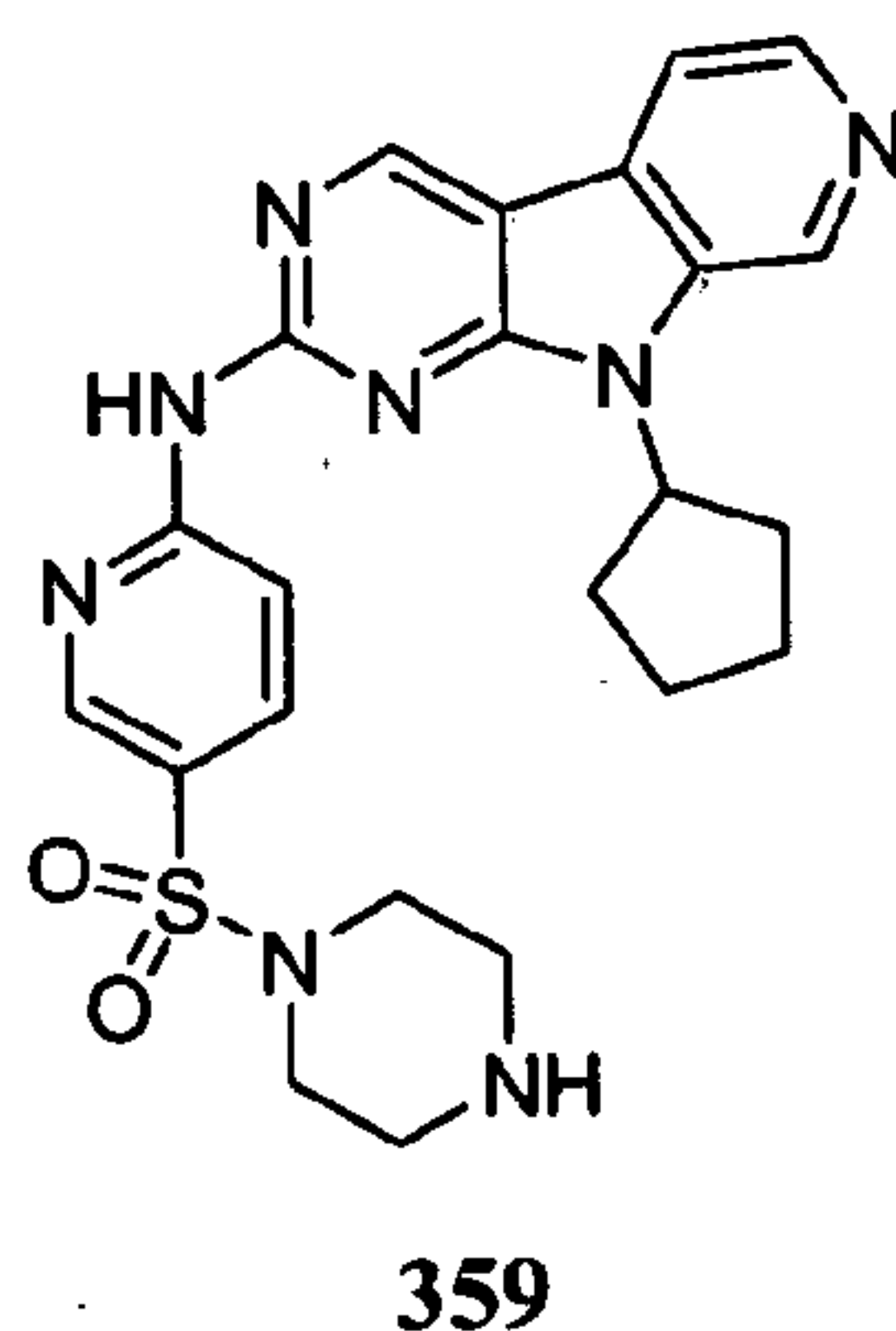
**tert-Butyl 4-((6-chloropyridin-3-yl)methyl)-3-oxopiperazine-1-carboxylate (358):** To a stirred ice-cooled suspension of sodium hydride, (60% dispersion in mineral oil, 0.83 g, 21 mmol) in DMF (15 mL) was added a suspension of *tert*-butyl 3-oxopiperazine-1-carboxylate



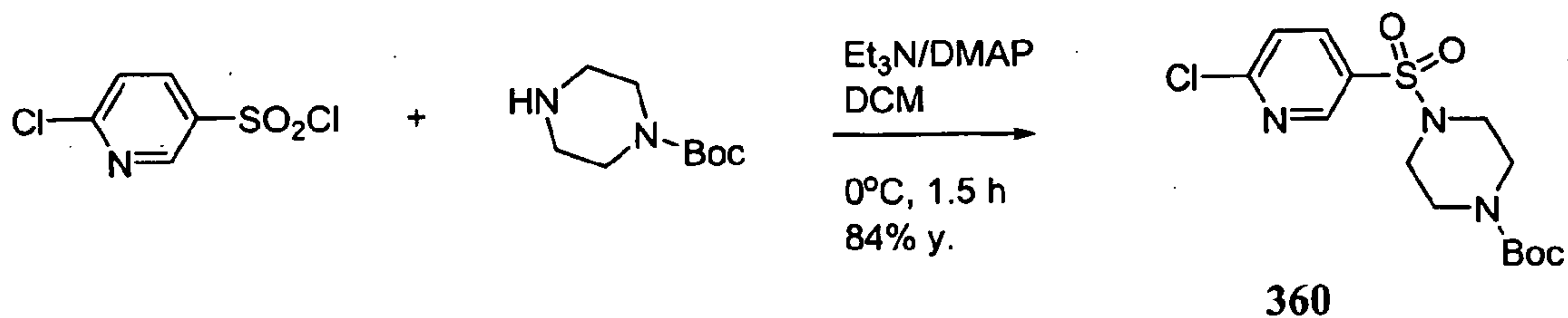
(2.5 g, 12 mmol) in DMF (45 mL) through a syringe. The ice-H<sub>2</sub>O bath was removed and the resulting mixture, which was a suspension, was stirred at ambient temperature for 30 min. Complete dissolution was observed. 2-chloro-5-(chloromethyl)pyridine (2.0 g, 12 mmol) was added in one portion as a solid. The resulting mixture was stirred at ambient temperature for 18 h then poured into ice and saturated NaHCO<sub>3</sub> aqueous solution. It was extracted with ethyl acetate (2 X). The combined organics were washed with saturated NaHCO<sub>3</sub> aqueous solution (3 X), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was subjected to combi-flash column chromatography (methanol/DCM) to give compound **358** (3.65 g, 91% yield) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ ppm 8.31 (1 H, d, J=2.2 Hz), 7.65 (1 H, dd, J=8.3, 2.4 Hz), 7.33 (1 H, d, J=8.1 Hz), 4.59 (2 H, s), 4.15 (2 H, s), 3.62 (2 H, t, J=5.4 Hz), 3.29 (2 H, t, J=5.1 Hz), 1.46 (9 H, s). LCMS-ESI (POS), M/Z, M+1: Found 326.0.

**1-((6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)methyl)-2-piperazinone (357):** Compound **357** was prepared as a off-white solid (TFA salt) from compound **4** and compound **358** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.67 (1 H, s), 9.35 (1 H, s), 8.70 (1 H, d), 8.66 (1 H, d), 8.48 (1 H, d, J=1.7 Hz), 8.20 (1 H, dd, J=8.8, 2.2 Hz), 7.91 (1 H, d, J=8.8 Hz), 5.48 (1 H, quin, J=8.7 Hz), 4.76 (2 H, s), 3.96 (2 H, s), 3.71 (2 H, t, J=5.7 Hz), 3.53 - 3.62 (2 H, m), 2.46 - 2.61 (2 H, m), 2.14 - 2.33 (4 H, m), 1.82 - 1.98 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 442.9.

#### EXAMPLE 227



**9-Cyclopentyl-N-(5-(1-piperazinylsulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



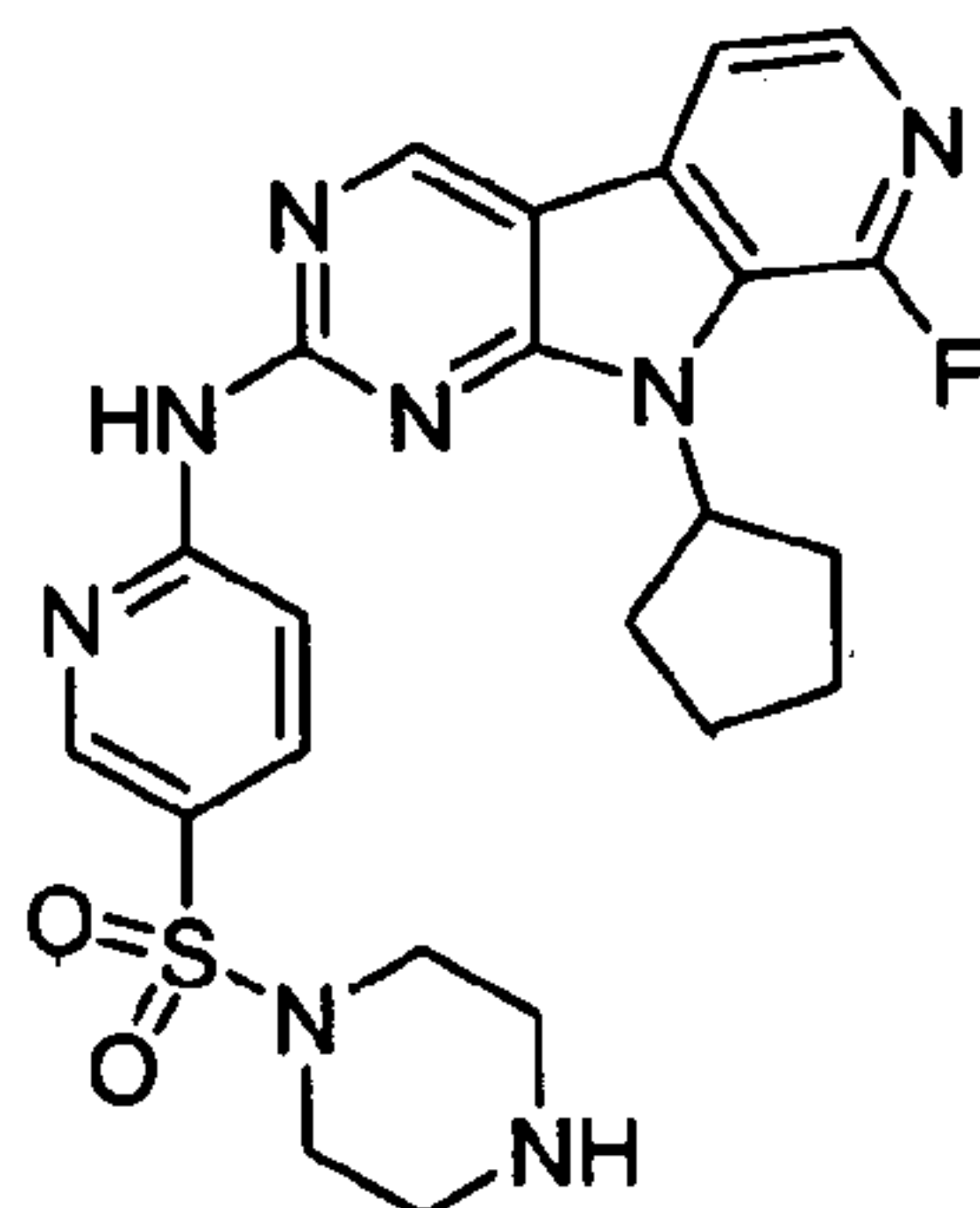


***tert*-Butyl 4-((6-chloro-3-pyridinyl)sulfonyl)-1-piperazinecarboxylate (360):** To a stirred ice-cooled solution of *tert*-butyl 1-piperazinecarboxylate (0.88 g, 4.7 mmol), triethylamine (1.3 mL, 9.4 mmol), and 4-dimethylaminopyridine (0.0058 g, 0.047 mmol) in DCM (10 mL) was added 6-chloropyridine-3-sulfonyl chloride (1.0 g, 4.7 mmol) in one portion. The resulting mixture was stirred at 0 °C and gradually warmed up to ambient temperature for 1.5 h. Upon workup, the mixture was directly subjected to combi-flash column chromatography (methanol/DCM) to give compound **360** (1.44 g, 84% yield) as a white solid.

<sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ ppm 8.75 (1 H, d, J=2.0 Hz), 8.17 (1 H, dd, J=8.4, 2.6 Hz), 7.80 (1 H, d, J=9.0 Hz), 3.40 (4 H, t, J=4.8 Hz), 2.97 (4 H, t, J=5.0 Hz), 1.35 (9 H, s). LCMS-ESI (POS), M/Z, M+1: Found 306 (minus tBu) and 384 (plus Na<sup>+</sup>).

**9-Cyclopentyl-N-(5-(1-piperazinylsulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (359):** Compound **359** was prepared as a white solid (TFA salt) from compound **4** and compound **360** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (500 MHz, *CD*<sub>3</sub>*OD*) δ ppm 9.59 (1 H, s), 9.29 (1 H, s), 8.72 - 8.78 (2 H, m), 8.63 - 8.66 (1 H, m), 8.61 (1 H, d), 8.22 (1 H, dd, J=8.8, 2.4 Hz), 5.51 (1 H, quin, J=8.9 Hz), 3.37 (8 H, s), 2.46 - 2.60 (2 H, m), 2.13 - 2.34 (4 H, m), 1.87 - 2.01 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 478.9.

#### **EXAMPLE 228**

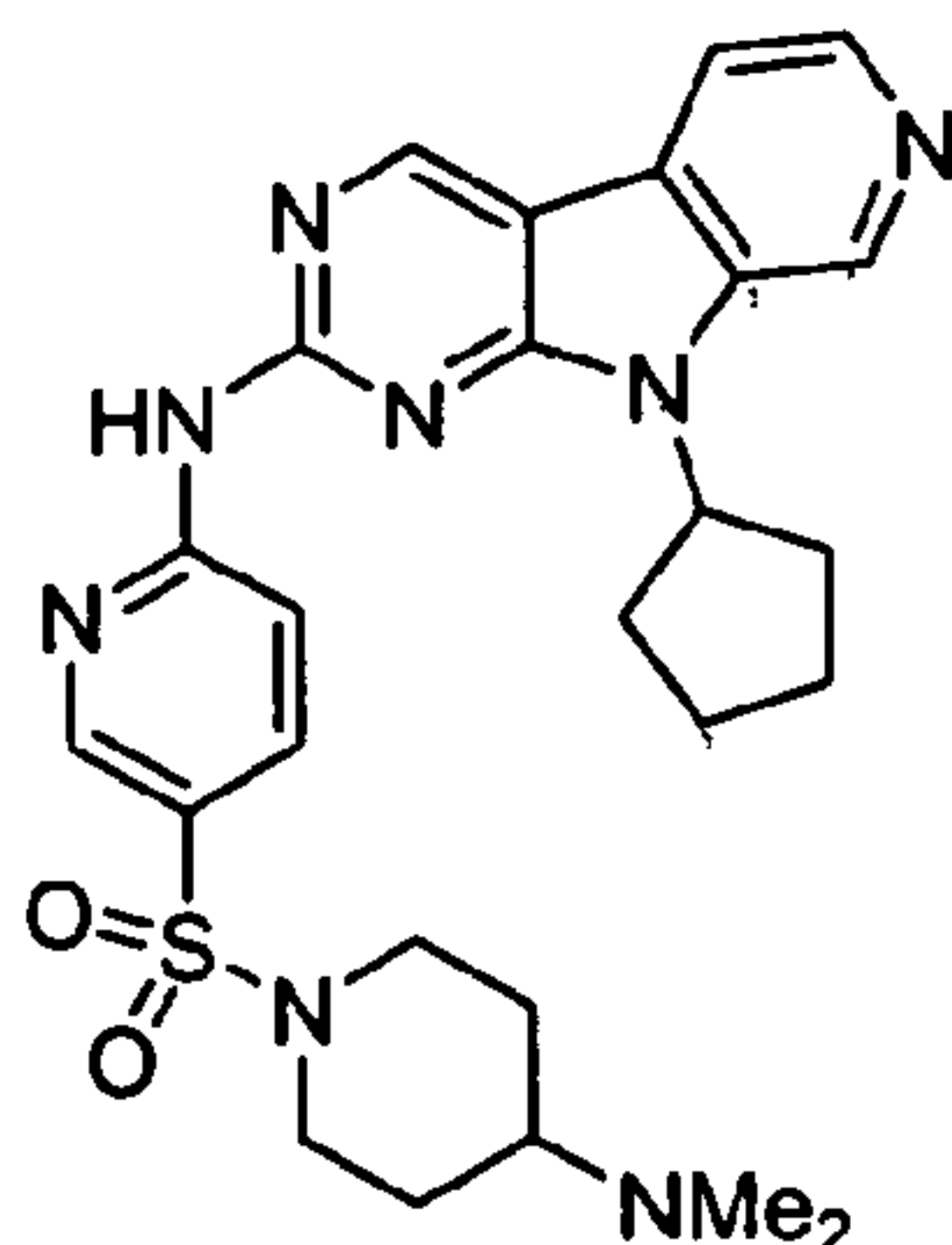


**361**

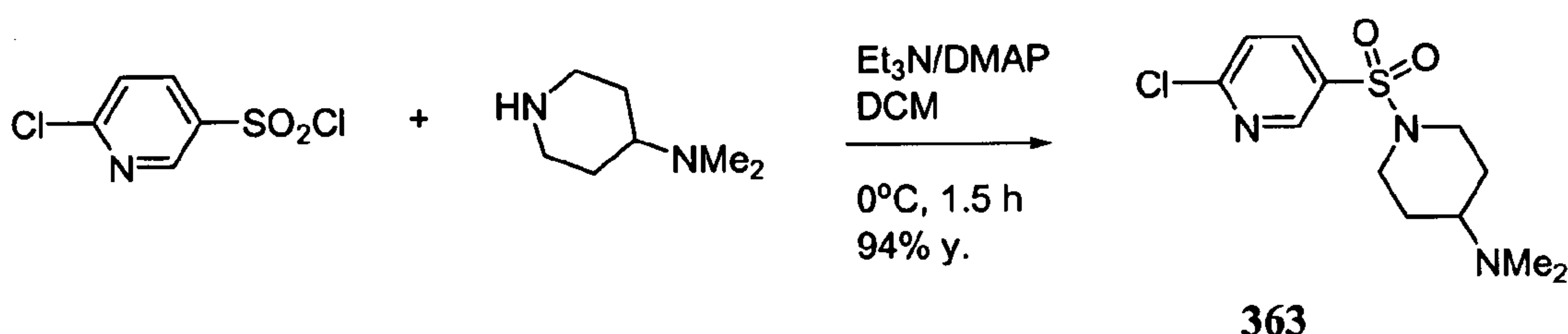
#### **9-cyclopentyl-8-fluoro-N-(5-(1-piperazinylsulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **361** was prepared as a white solid (TFA salt) from compound **245** and compound **360** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (500 MHz, *CD*<sub>3</sub>*OD*) δ ppm 9.37 (1 H, s), 8.73 (1 H, d, J=2.0 Hz), 8.68 (1 H, d, J=8.8 Hz), 8.21 (1 H, dd, J=9.0, 2.4 Hz), 8.01 - 8.08 (2 H, m), 5.67 (1 H, quin, J=9.2 Hz), 3.36 (8 H, s), 2.35 - 2.49 (2 H, m), 2.09 - 2.28 (4 H, m), 1.81 - 1.95 (2 H, m). LCMS-ESI (POS), M/Z, M+1: Found 497.2.



**EXAMPLE 229****362**

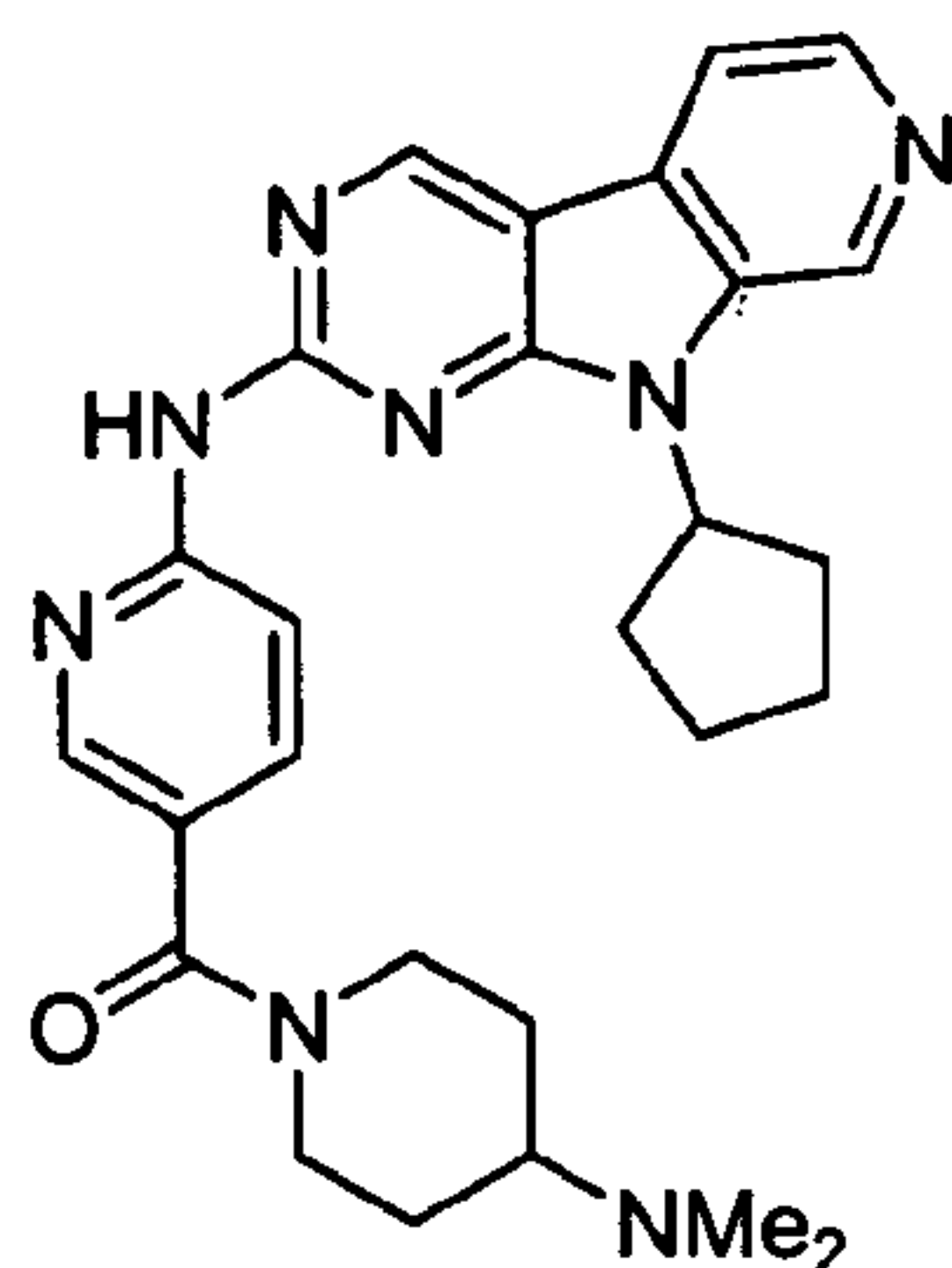
**9-cyclopentyl-N-(5-((4-(dimethylamino)-1-piperidinyl)sulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**363**

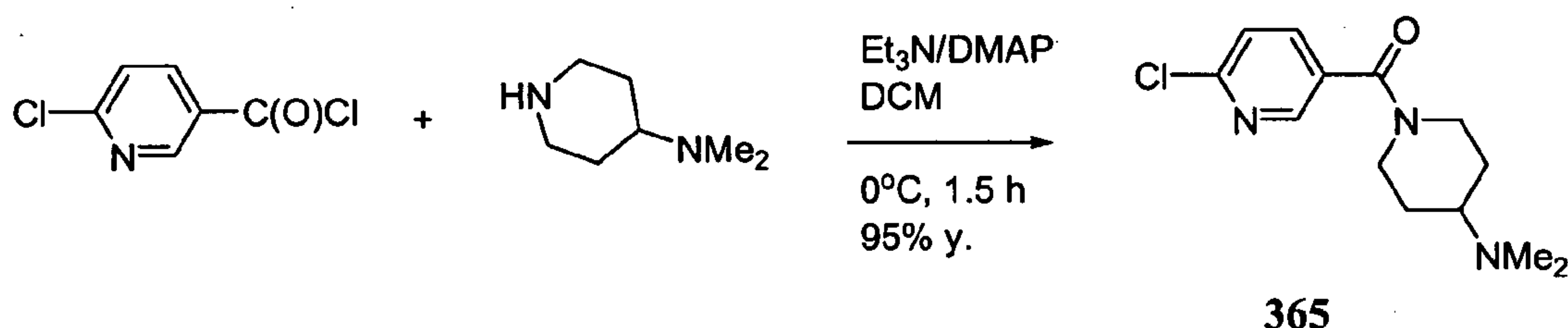
**1-(6-Chloropyridin-3-ylsulfonyl)-N,N-dimethylpiperidin-4-amine (363):** To a stirred ice-cooled solution of 4-(dimethylamino)piperidine (1.2 mL, 9.4 mmol), triethylamine (2.6 mL, 19 mmol), and 4-dimethylaminopyridine (0.012 g, 0.094 mmol) in DCM (18 mL) was added 6-chloropyridine-3-sulfonyl chloride (2.0 g, 9.4 mmol) in one portion. The resulting mixture was stirred at 0 °C for 1.5 h. Upon workup, the mixture was directly subjected to combi-flash column chromatography (methanol/DCM) to give compound **363** (2.7 g, 94% yield) as a white solid. LCMS-ESI (POS), M/Z, M+1: Found 304.0.

**9-cyclopentyl-N-(5-((4-(dimethylamino)-1-piperidinyl)sulfonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (362):** Compound **362** was prepared as an off-white solid (TFA salt) from compound **4** and compound **363** using chemistry similar to that described in example 200. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 9.56 (1 H, s), 9.25 (1 H, s), 8.66 - 8.75 (2 H, m), 8.58 (2 H, s), 8.18 (1 H, dd, J=8.8, 2.5 Hz), 5.50 (1 H, quin, J=8.8 Hz), 4.01 (2 H, d, J=12.5 Hz), 3.22 (1 H, tt, J=12.1, 3.8 Hz), 2.86 (6 H, s), 2.44 - 2.60 (4 H, m), 2.12 - 2.35 (6 H, m), 1.74 - 2.01 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 521.2.



**EXAMPLE 230****364**

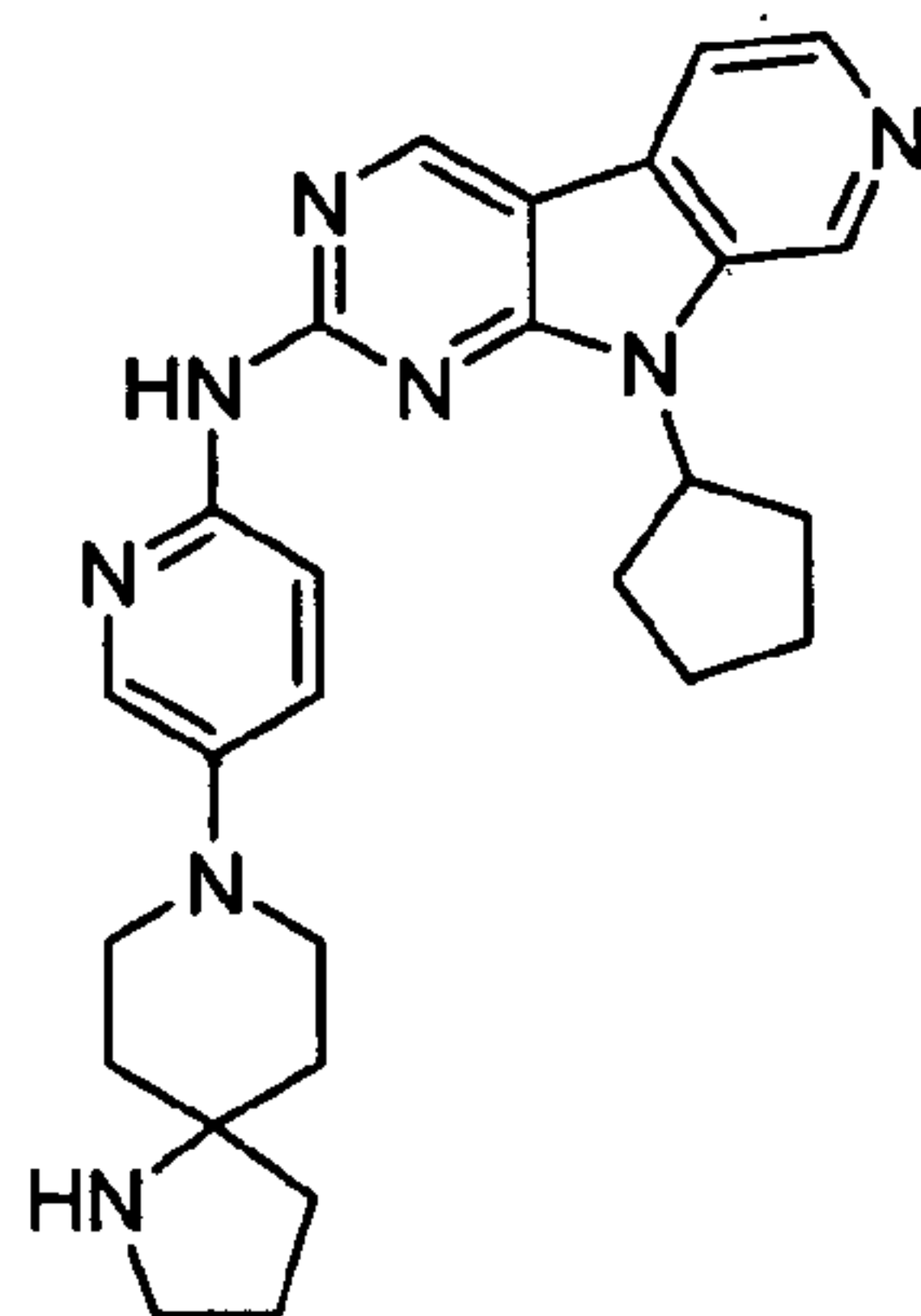
**9-Cyclopentyl-N-(5-((4-(dimethylamino)-1-piperidinyl)carbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**365**

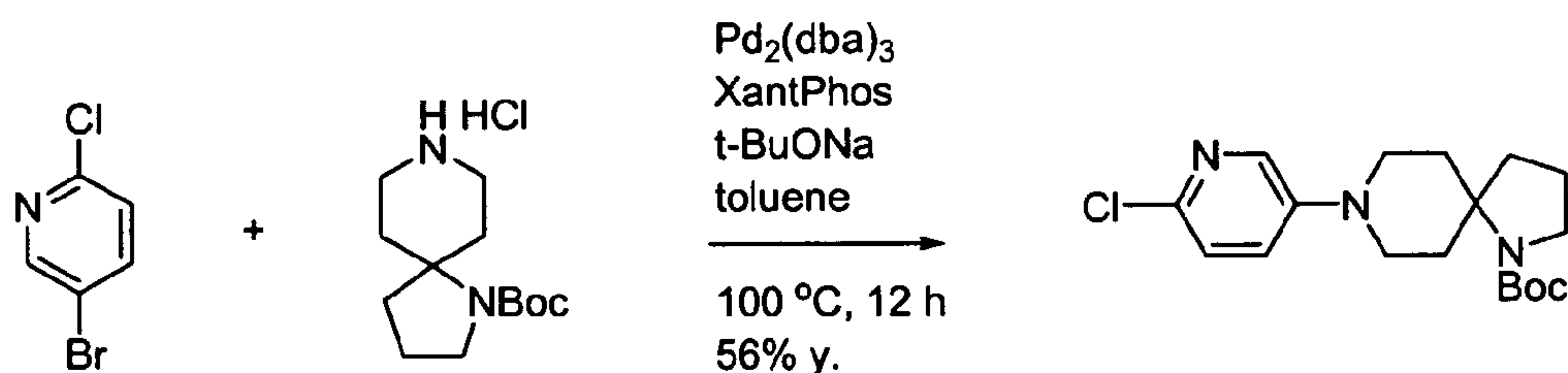
**(6-Chloropyridin-3-yl)(4-(dimethylamino)piperidin-1-yl)methanone (365):** Compound **365** was prepared from 6-chloropyridine-3-carbonyl chloride using chemistry similar to that described in example 226.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 8.47 (1 H, d,  $J=2.3$  Hz), 7.92 (1 H, dd,  $J=8.2, 2.3$  Hz), 7.61 (1 H, d,  $J=8.2$  Hz), 4.35 - 4.60 (1 H, m), 3.57 (1 H, br. s.), 3.09 (1 H, br. s.), 2.81 (2 H, br. s.), 2.39 (6 H, s), 1.67 - 1.98 (2 H, m), 1.48 (2 H, qd,  $J=12.0, 4.3$  Hz). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 268.1.

**9-Cyclopentyl-N-(5-((4-(dimethylamino)-1-piperidinyl)carbonyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (364):** Compound **364** was prepared as a light yellow solid (TFA salt) from compound **4** and compound **365** using chemistry similar to that described in example 200.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 9.57 (1 H, s), 9.27 (1 H, s), 8.56 - 8.64 (2 H, m), 8.51 (1 H, d,  $J=1.7$  Hz), 8.44 (1 H, d,  $J=8.8$  Hz), 8.02 (1 H, dd,  $J=8.7, 2.3$  Hz), 5.47 (1 H, quin,  $J=8.9$  Hz), 3.49 - 3.60 (1 H, m,  $J=12.0, 12.0, 3.8, 3.7$  Hz), 2.91 (6 H, s), 2.48 - 2.61 (2 H, m), 2.02 - 2.34 (6 H, m), 1.85 - 1.98 (2 H, m), 1.70 - 1.85 (2 H, m,  $J=12.3, 12.3, 12.2, 4.4$  Hz). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 485.2.



**EXAMPLE 231****366**

**9-cyclopentyl-N-(5-(1,8-diazaspiro[45]dec-8-yl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**367**

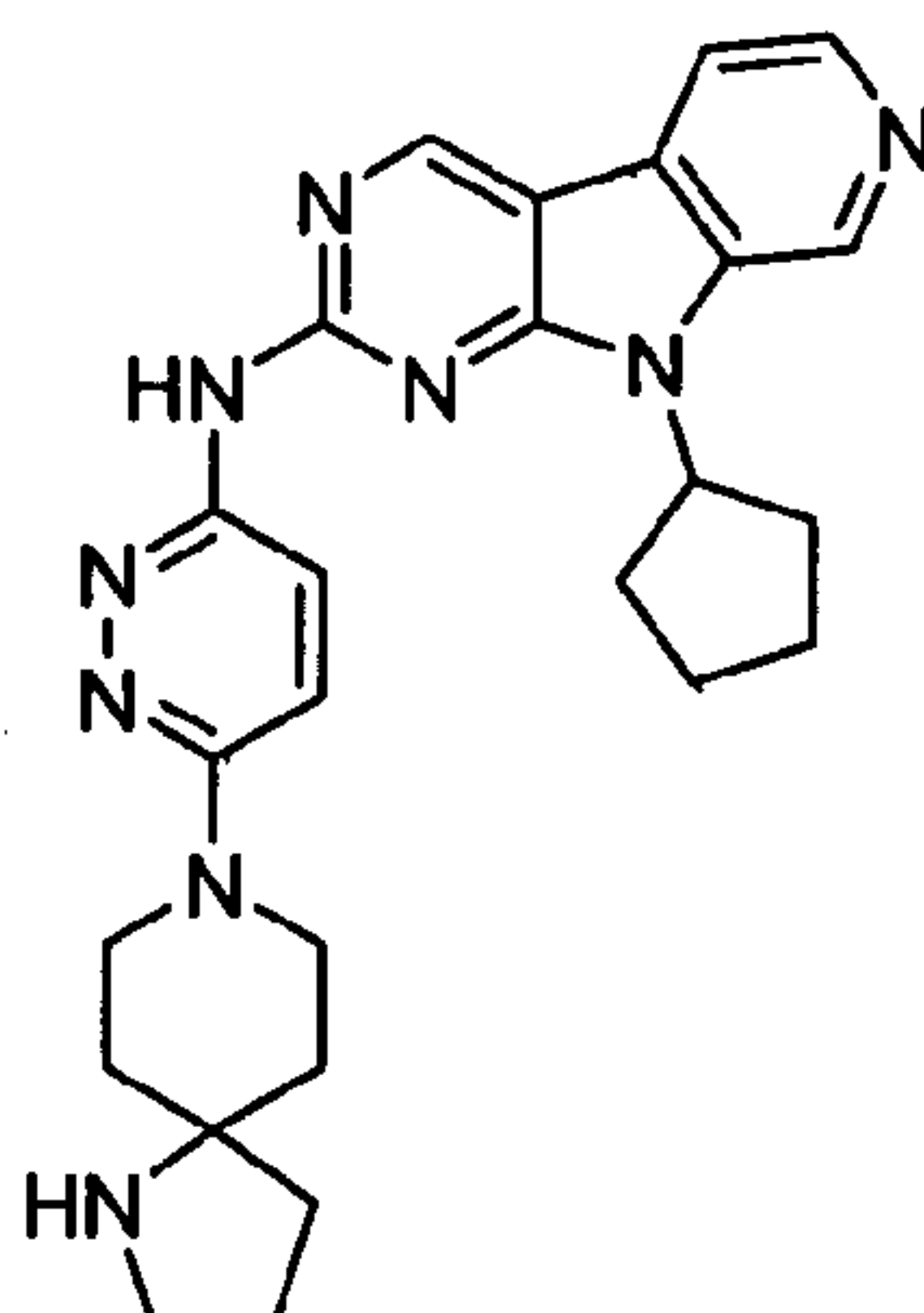
***tert*-Butyl 8-(6-chloro-3-pyridinyl)-1,8-diazaspiro[45]decane-1-carboxylate (367):**

Compound **367** was prepared as an off-white solid using chemistry similar to that described in Example 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.99 (1 H, br. s.), 7.14 (2 H, br. s.), 3.55 - 3.83 (2 H, m), 3.47 (2 H, d,  $J=15.1$  Hz), 2.49 - 3.08 (4 H, m), 1.86 - 2.07 (2 H, m), 1.72 - 1.84 (2 H, m), 1.29 - 1.55 (11 H, m). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 352.1.

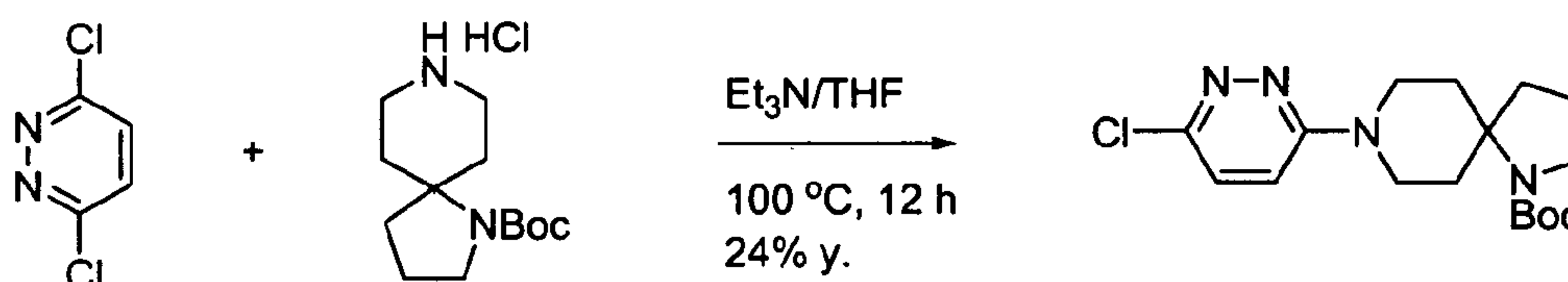
**9-cyclopentyl-N-(5-(1,8-diazaspiro[45]dec-8-yl)-2-pyridinyl)-9H-pyrido-**

**[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (366):** Compound **366** was prepared as a yellow solid (TFA salt) from compound **4** and compound **367** using chemistry similar to that described in example 200.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 9.55 (1 H, s), 9.32 (1 H, s), 8.70 (2 H, br. s.), 8.65 (1 H, d,  $J=6.1$  Hz), 8.54 (1 H, d,  $J=5.9$  Hz), 8.10 (1 H, d,  $J=2.9$  Hz), 8.02 (1 H, d,  $J=8.3$  Hz), 7.65 (1 H, d,  $J=8.3$  Hz), 5.36 (1 H, quin,  $J=8.7$  Hz), 3.57 (2 H, ddd,  $J=12.7, 4.6, 4.4$  Hz), 3.28 (3 H, quin,  $J=6.4$  Hz), 3.06 (2 H, ddd,  $J=12.8, 9.7, 3.2$  Hz), 2.38 - 2.47 (2 H, m), 1.84 - 2.17 (12 H, m), 1.68 - 1.81 (2 H, m). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 469.3.



**EXAMPLE 232****368**

**9-cyclopentyl-N-(6-(1,8-diazaspiro[45]dec-8-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**369**

**tert-Butyl 8-(6-chloro-3-pyridazinyl)-1,8-diazaspiro[45]decane-1-carboxylate (369):**

Compound 369 was prepared using chemistry similar to that described in example 4.

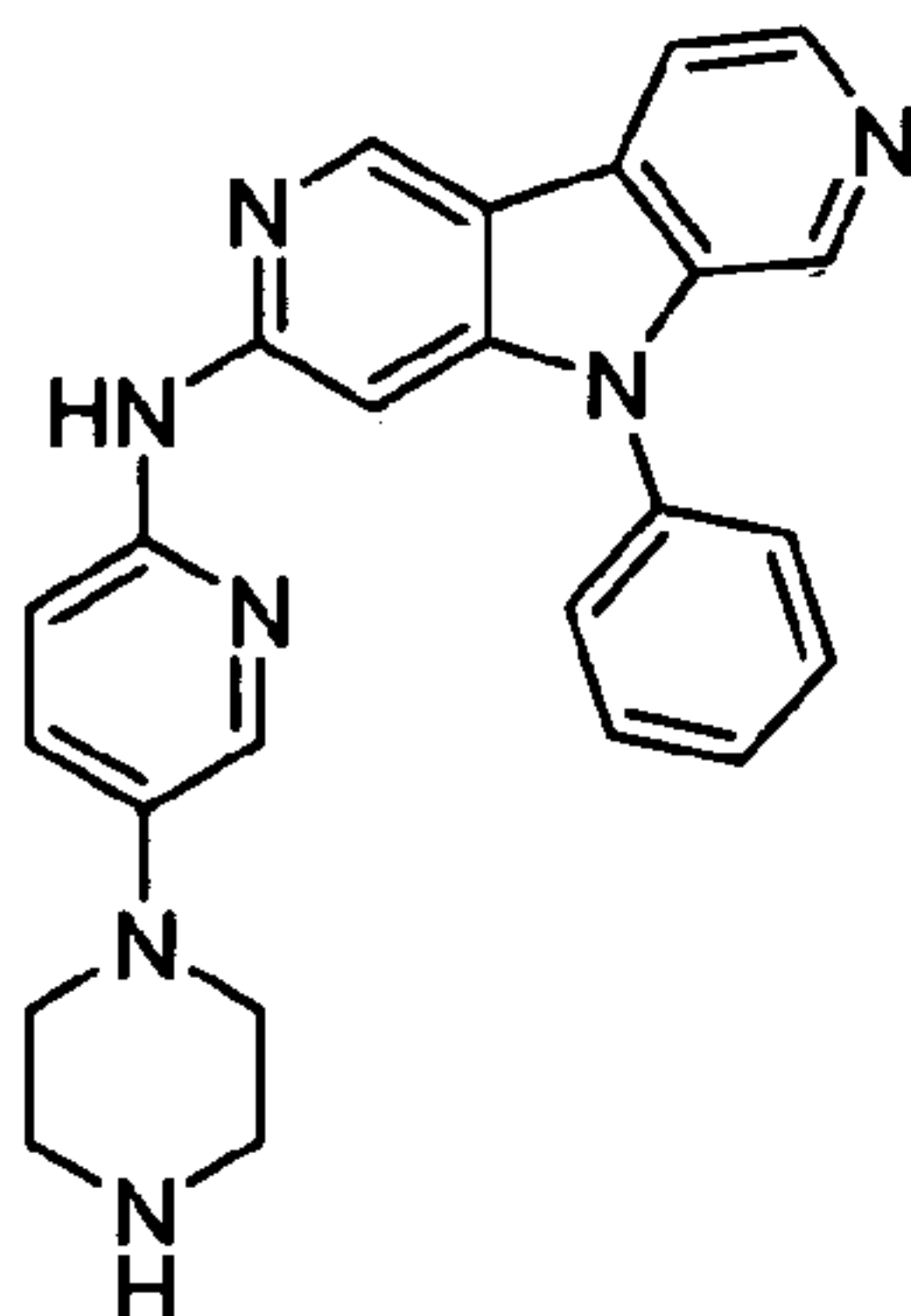
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.24 (1 H, d,  $J=10.0$  Hz), 6.96 (1 H, d,  $J=9.8$  Hz), 4.35 (2 H, d,  $J=12.7$  Hz), 3.39 - 3.55 (2 H, m), 3.03 (2 H, t,  $J=12.8$  Hz), 2.80 - 2.92 (1 H, m), 2.60 (1 H, t,  $J=13.1$  Hz), 1.94 - 2.11 (2 H, m), 1.81 (2 H, quin,  $J=6.8$  Hz), 1.21 - 1.53 (11 H, m).

LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 353.0.

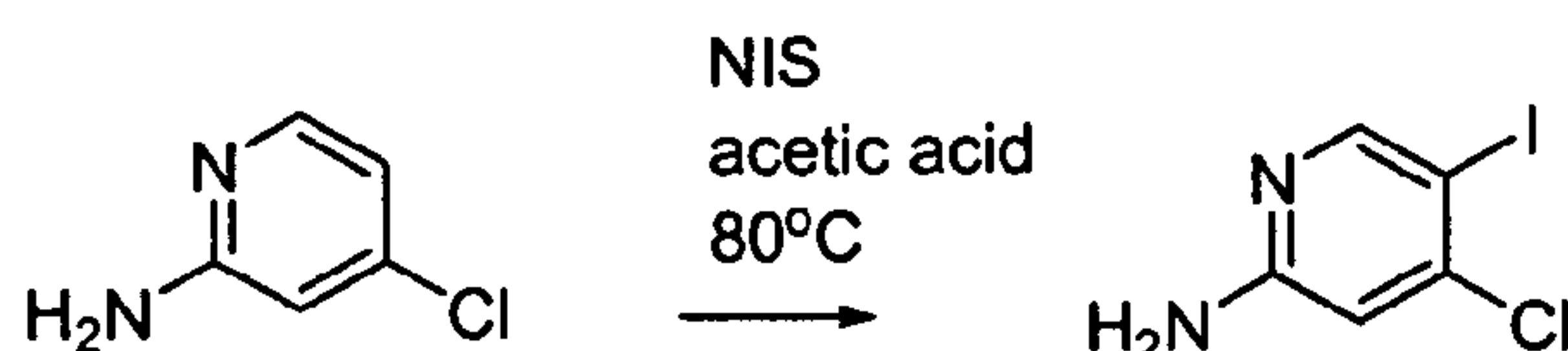
**9-cyclopentyl-N-(6-(1,8-diazaspiro[45]dec-8-yl)-3-pyridazinyl)-9H-pyrido-**

**[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (368):** Compound 368 was prepared as a yellow solid (TFA salt) from compound 4 and compound 369 using chemistry similar to that described in example 200.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 10.98 (1 H, br. s.), 9.55 (1 H, s), 9.31 (1 H, s), 8.68 - 8.76 (1 H, m), 8.65 (1 H, d,  $J=5.9$  Hz), 8.52 (1 H, d,  $J=5.6$  Hz), 8.14 (1 H, d,  $J=9.8$  Hz), 7.66 (1 H, d,  $J=9.3$  Hz), 5.34 (1 H, quin,  $J=8.7$  Hz), 4.04 (1 H, dt,  $J=13.9, 4.4$  Hz), 3.34 - 3.40 (2 H, m), 3.29 (2 H, ddd,  $J=12.5, 6.6, 6.4$  Hz), 2.32 - 2.42 (2 H, m), 1.94 - 2.17 (8 H, m), 1.83 - 1.94 (4 H, m), 1.65 - 1.79 (2 H, m). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 470.2.

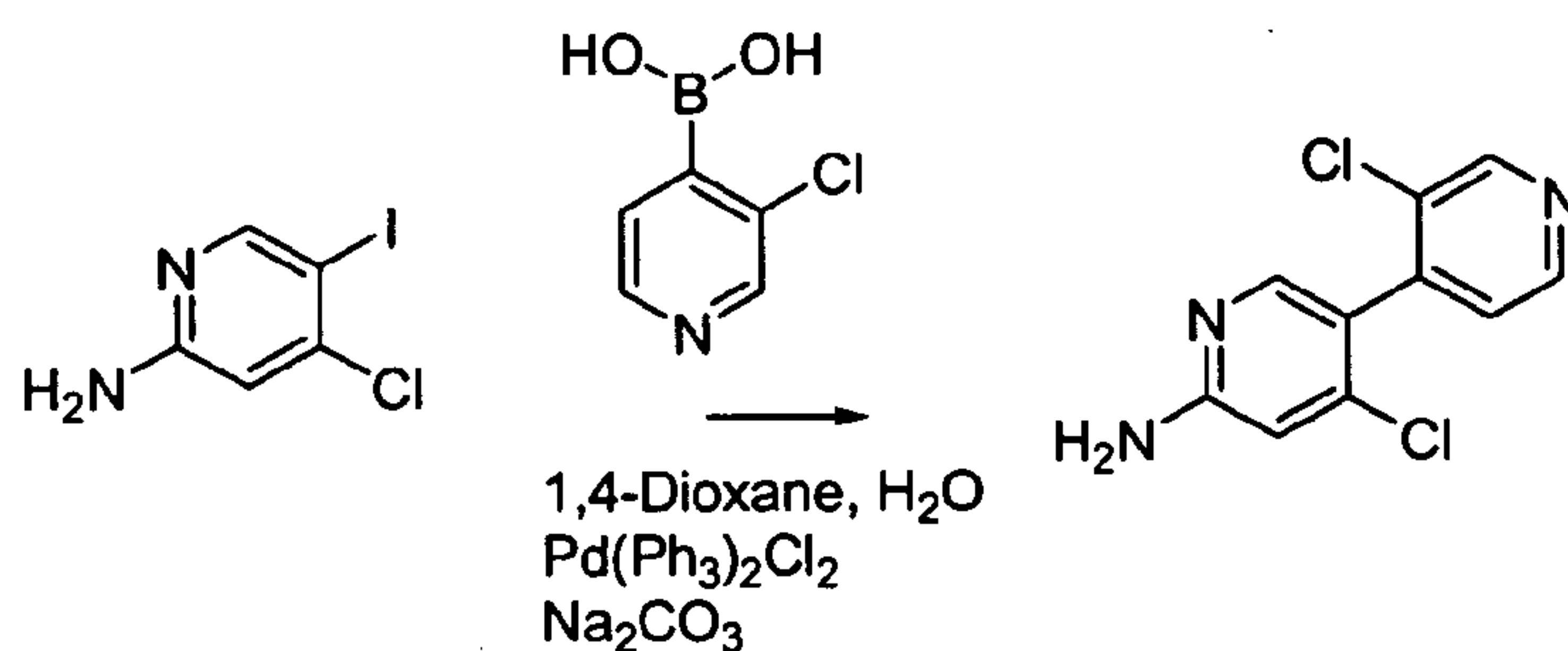


**EXAMPLE 233****370**

**5-phenyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine**

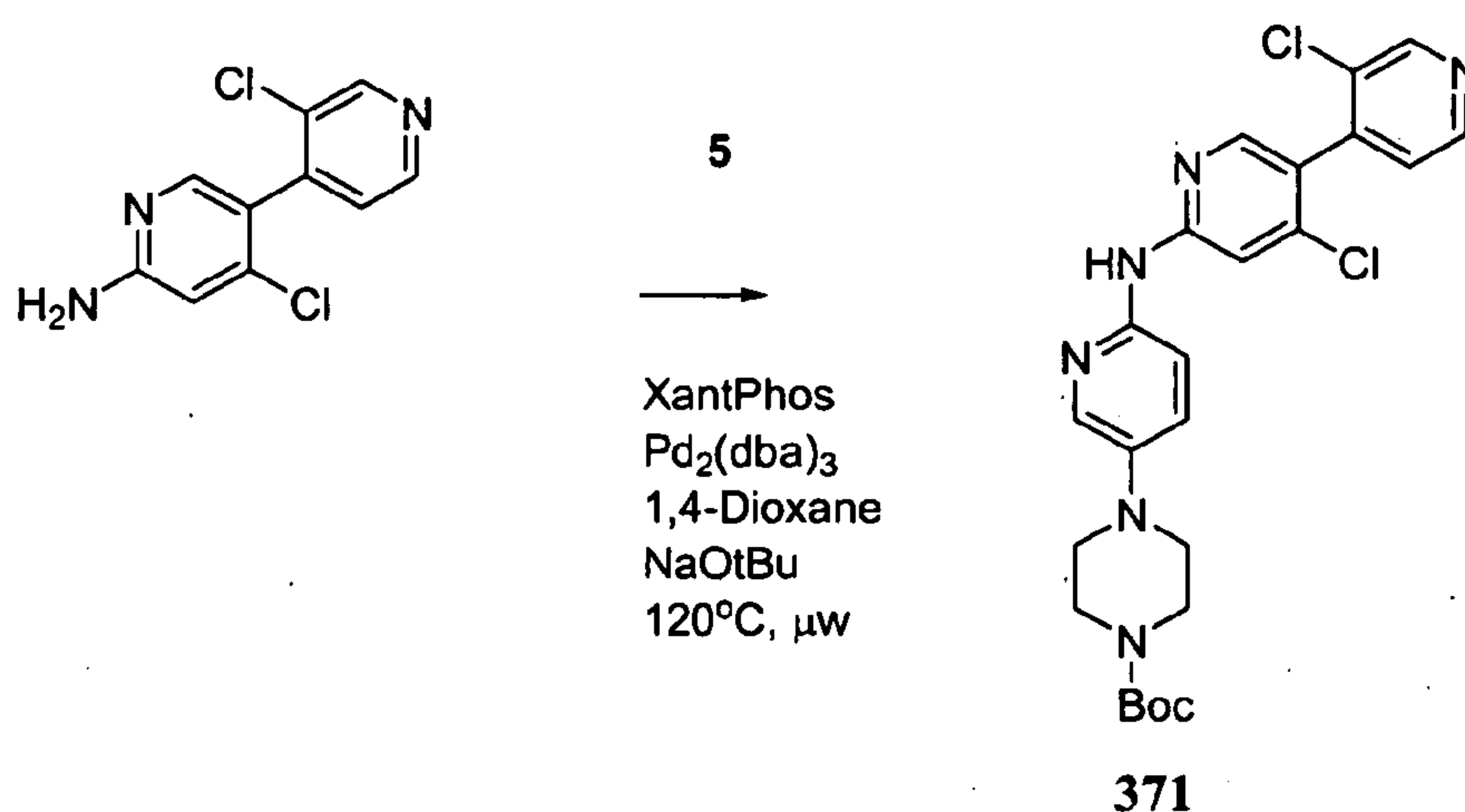


**4-chloro-5-iodopyridin-2-amine.** 4-Chloropyridin-2-amine (0.142 g, 1.10 mmol) and N-iodosuccinimide (0.273 g, 1.22 mmol) were combined in 1.5mL of acetic acid. The solution was sonicated briefly and then heated to 80°C. After 1 hour the solution was cooled to room temperature and then concentrated under vacuum. After adjusting the pH to ~8/9 with aqueous ammonia, a light brown solid was collected by filtration. The solid was purified on a 12g Combiflash column eluting with a gradient of DCM to 5%methanol/0.25%NH<sub>4</sub>OH (~28% in water)/DCM. The fractions containing the product were combined and concentrated under vacuum to give 4-chloro-5-iodopyridin-2-amine (187mg, 67%) as an off-white solid. <sup>1</sup>H NMR (500 MHz, *DMSO-d*<sub>6</sub>) δ ppm 8.20 (1 H, s), 6.69 (1 H, s), 6.40 (2 H, s); LCMS-ESI (POS), M/Z, M+1: Found 254.9.





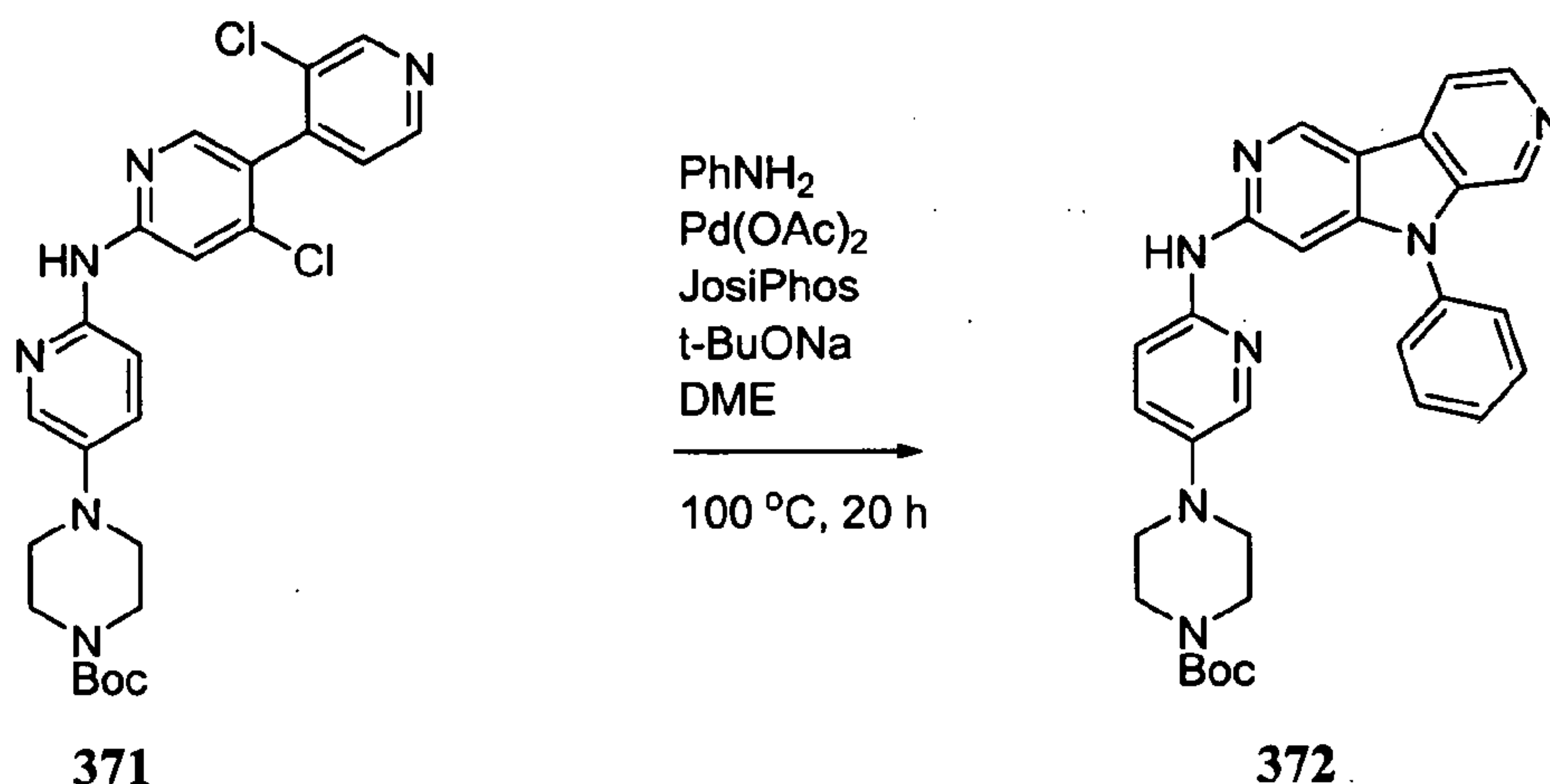
**4-chloro-5-(3-chloropyridin-4-yl)pyridin-2-amine.** 4-Chloro-5-iodopyridin-2-amine (8.100 g, 31.8 mmol), sodium carbonate (5.00g, 47.7 mmol), and 3-chloropyridin-4-ylboronic acid hydrate (11.2g, 63.7mmol) were combined in 100mL of 1,4-Dioxane and 25mL of water. Nitrogen was bubbled through the solution for ~2min before adding trans-dichlorobis(triphenyl-phosphine)palladium (II) (2.05 g, 2.92 mmol). The solution was heated to 60°C overnight. Additional trans-dichlorobis(triphenyl-phosphine)palladium (II) (0.2g, 0.285mmol), 3-chloropyridin-4-ylboronic acid hydrate (4.00g, 22.8mmol), 15mL of water (degassed) and sodium carbonate (1.75g, 16.6mmol) were added. The solution was heated to 100°C for 5 hours. Additional 3-chloropyridin-4-ylboronic acid hydrate (4.00g, 22.8mmol) was added and the reaction continued for 2 h at 100°C. The solution was concentrated under vacuum to 1/5th the volume and extracted between DCM and water. The aqueous layer was extracted with 10%isopropanol/DCM. The combined organics were dried over MgSO<sub>4</sub> and then concentrated under vacuum to give an orange solid. The solid was slurried with DCM and then filtered through a fritted funnel. The solids were washed with additional DCM. The combined filtrate was purified on a 80g Combiflash column (dry loaded), eluting with 2%methanol/0.1%NH<sub>4</sub>OH (~28% in water) /DCM to 8% methanol /0.4% NH<sub>4</sub>OH (~28% in water)/ DCM. The fractions containing the product were concentrated under vacuum to give a yellowish solid. The solids were triturated with DCM to give 4-chloro-5-(3-chloropyridin-4-yl)pyridin-2-amine (3.93g, 51%) as an off white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 8.73 (1 H, s), 8.58 (1 H, d, J=4.9 Hz), 7.87 (1 H, s), 7.44 (1 H, d, J=4.9 Hz), 6.64 (1 H, s), 6.55 (2 H, br. s.); LCMS-ESI (POS), M/Z, M+1: Found 239.9.



**tert-Butyl 4-(6-(4-chloro-5-(3-chloropyridin-4-yl)pyridin-2-ylamino)pyridin-3-yl)piperazine-1-carboxylate (371).** 4-Chloro-5-(3-chloropyridin-4-yl)pyridin-2-amine (0.263

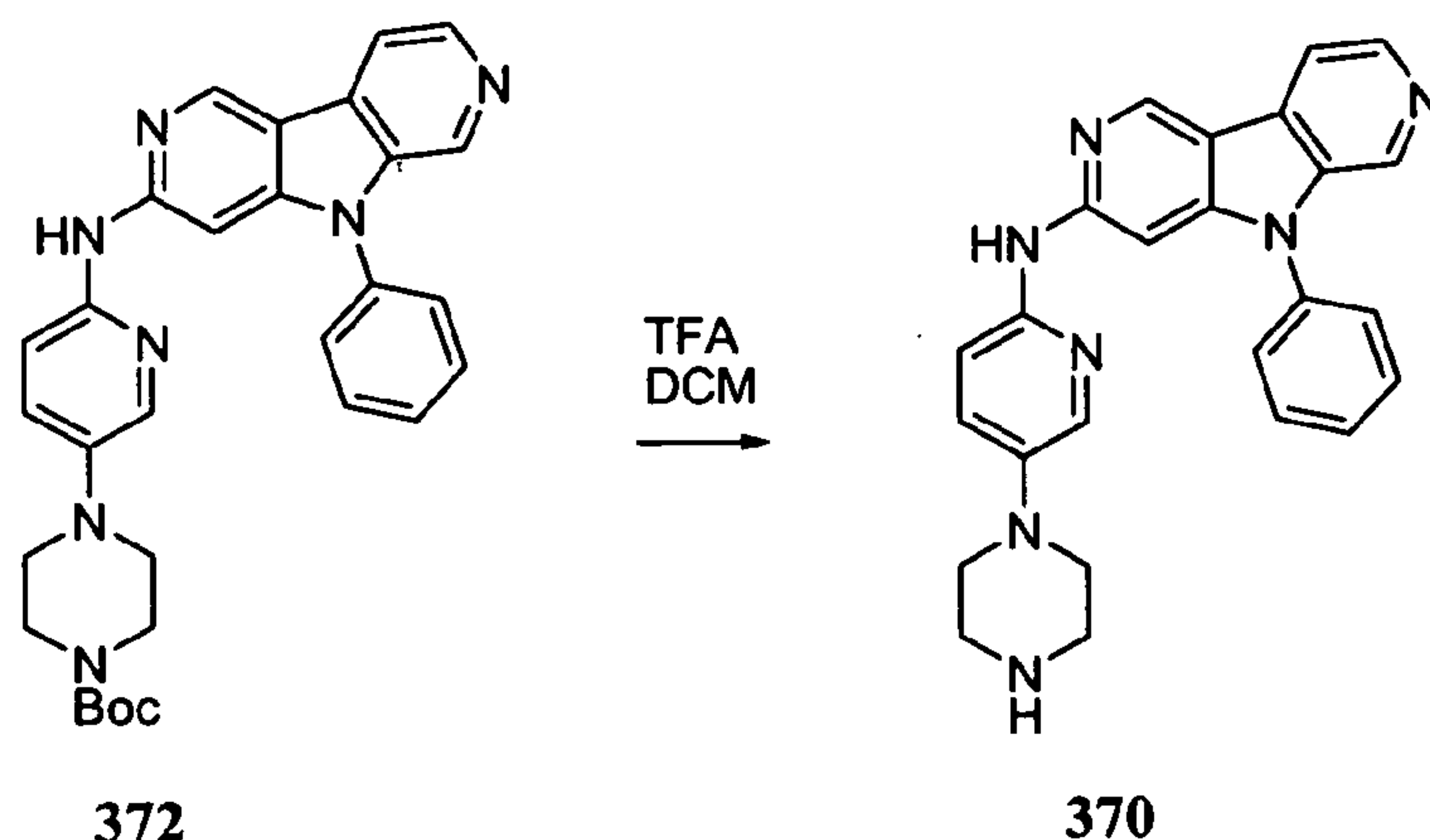


g, 1.10 mmol), sodium 2-methylpropan-2-olate (0.316 g, 3.29 mmol), and compound 5 (0.424 g, 1.42 mmol) were combined in anhydrous 1,4-dioxane (5 mL). Nitrogen was bubbled through the solution for ~1 min before adding 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.0634 g, 0.110 mmol) and  $\text{Pd}_2(\text{dba})_3$  (0.0502 g, 0.0548 mmol). The solution was then heated to 120°C with microwave irradiation for 1 hour. The solution was purified on a 40g CombiFlash column (dry loaded) eluting with a gradient of hexane to ethyl acetate. The fractions containing the product were combined and concentrated under vacuum to give compound 371 (0.492g, 90%) as a yellow solid.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 9.95 (1 H, s), 8.78 (1 H, br. s.), 8.63 (1 H, d,  $J=4.9$  Hz), 8.17 (1 H, s), 8.04 (1 H, s), 8.01 (1 H, d,  $J=2.9$  Hz), 7.55 (1 H, d,  $J=9.0$  Hz), 7.52 (1 H, d,  $J=4.9$  Hz), 7.46 (1 H, dd,  $J=9.0, 2.9$  Hz), 3.41 - 3.54 (4 H, m), 2.99 - 3.10 (4 H, m), 1.42 (9 H, s); LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 501.1.



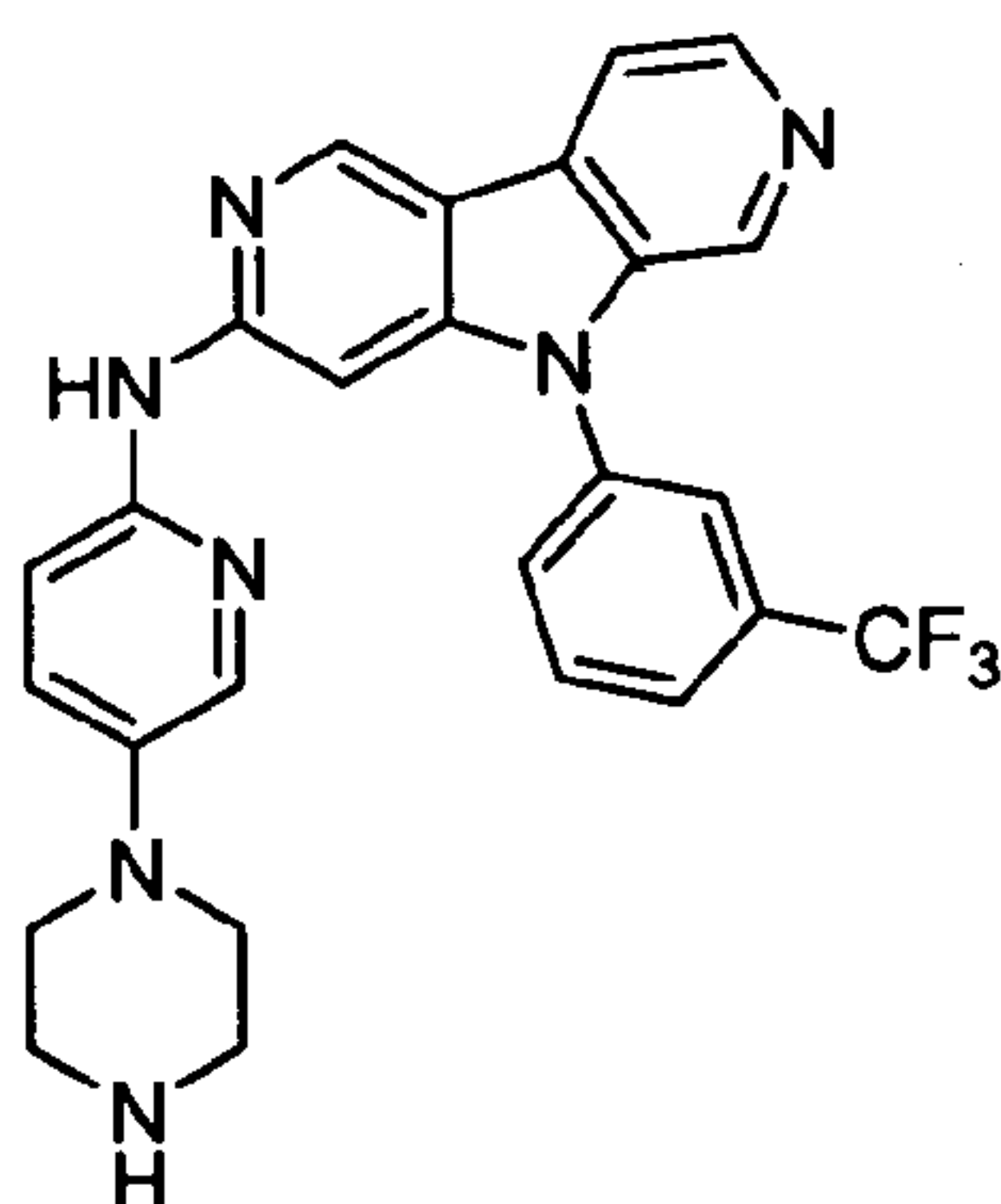
**tert-Butyl 4-(6-((5-phenyl-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (372):** In a 10 mL single-necked round bottom flask were placed *tert*-butyl 4-(6-(4-chloro-5-(3-chloropyridin-4-yl)pyridin-2-ylamino)pyridin-3-yl)piperazine-1-carboxylate (371) (50 mg, 100  $\mu\text{mol}$ ), palladium diacetate (11 mg, 50  $\mu\text{mol}$ ), Josiphos (28 mg, 50  $\mu\text{mol}$ ), and sodium *tert*-butoxide (29 mg, 299  $\mu\text{mol}$ ). The flask was subjected to 3 cycles of evacuation and back-filling with  $\text{N}_2$ . Aniline (36  $\mu\text{l}$ , 399  $\mu\text{mol}$ ) was added under  $\text{N}_2$  followed by 1,2-dimethoxyethane (3 mL). The resulting mixture was stirred at 100 °C for 20 h. After the volatiles were removed, the residue was subjected to combi-flash column chromatography (methanol/DCM). The product containing compound 372 after concentration was used without further purification. LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 522.2.





**5-phenyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine (370):** A solution of crude compound **372** in DCM (8 mL) was treated with trifluoroacetic acid (2.0 mL, 27 mmol) at room temperature for 2 h. After the volatiles were removed, the residue was subjected to reverse phase preparative HPLC (acetonitrile/H<sub>2</sub>O containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **370** (12 mg) as a yellow solid (TFA salt). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.46 (1 H, s), 8.80 (1 H, d, J=0.7 Hz), 8.65 (1 H, d, J=5.6 Hz), 8.53 (1 H, d, J=5.6 Hz), 8.05 (1 H, d, J=2.9 Hz), 7.90 (1 H, dd, J=9.3, 2.9 Hz), 7.77 - 7.83 (2 H, m), 7.68 - 7.76 (3 H, m), 7.24 (1 H, d, J=9.3 Hz), 7.14 (1 H, s), 3.46 - 3.53 (4 H, m), 3.40 - 3.46 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 422.2.

#### EXAMPLE 234



**373**

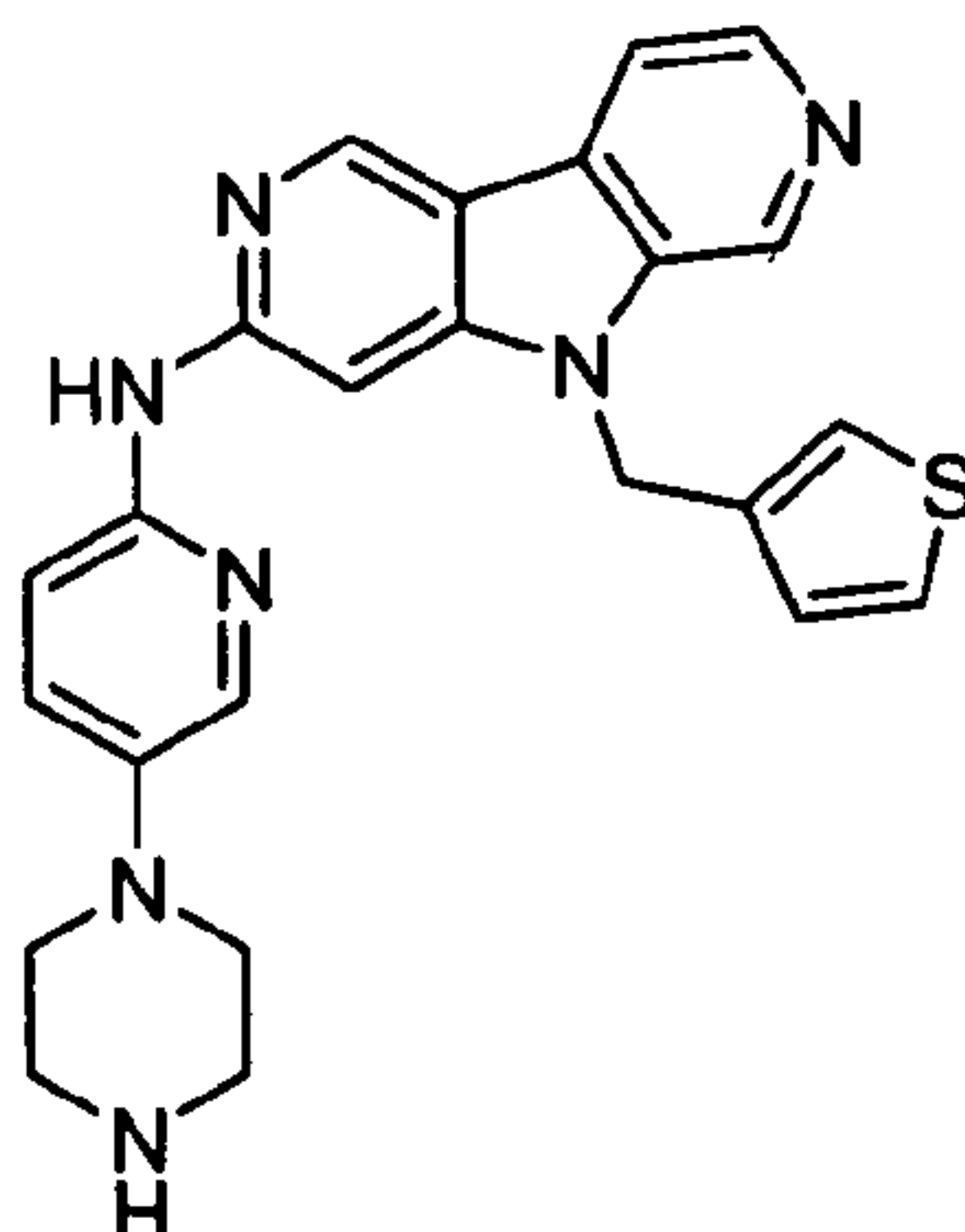
**N-(5-(1-piperazinyl)-2-pyridinyl)-5-(3-(trifluoromethyl)phenyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine**

Compound **373** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.62 (1 H, d, J=1.0 Hz), 9.01 (1 H, s), 8.81 (1 H, d, J=5.4 Hz), 8.74 (1 H, d, J=5.9 Hz), 8.18 (1 H, s), 7.97 - 8.11 (5 H, m),



7.34 (1 H, d, J=9.5 Hz), 7.10 (1 H, s), 3.48 - 3.56 (4 H, m), 3.40 - 3.48 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 490.1.

### **EXAMPLE 235**

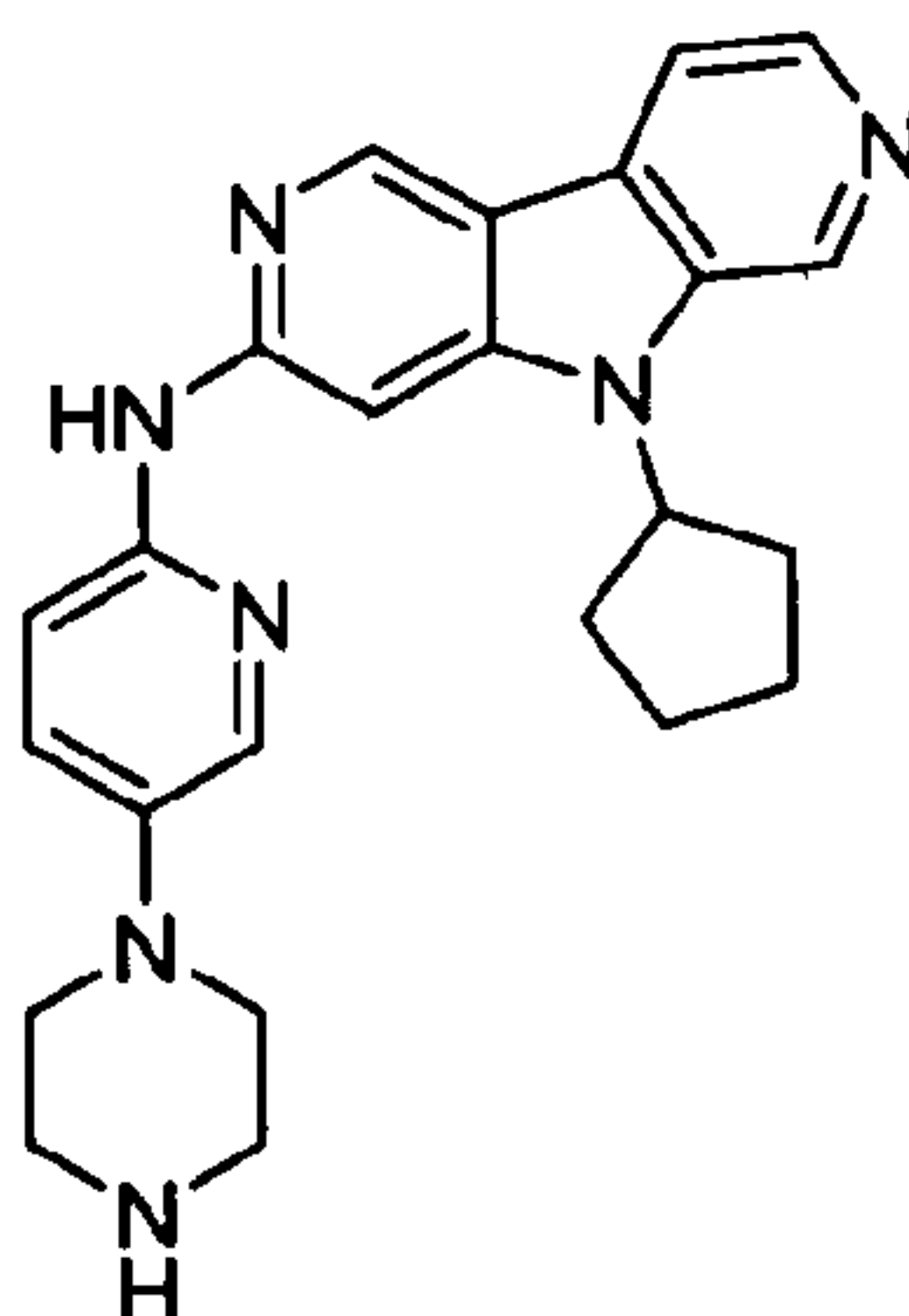


**374**

### **N-(5-(1-piperazinyl)-2-pyridinyl)-5-(3-thiophenylmethyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine**

Compound **374** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.44 (1 H, s), 9.21 (1 H, s), 8.63 (1 H, d, J=5.9 Hz), 8.56 (1 H, d, J=5.6 Hz), 8.05 (1 H, d, J=2.9 Hz), 7.95 (1 H, dd, J=9.5, 2.9 Hz), 7.45 (1 H, dd, J=5.1, 2.9 Hz), 7.40 - 7.43 (1 H, m), 7.37 (1 H, s), 7.30 (1 H, d, J=9.3 Hz), 7.05 (1 H, dd, J=5.1, 1.5 Hz), 5.77 (2 H, s), 3.47 - 3.52 (4 H, m), 3.41 - 3.47 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 441.9.

### **EXAMPLE 236**

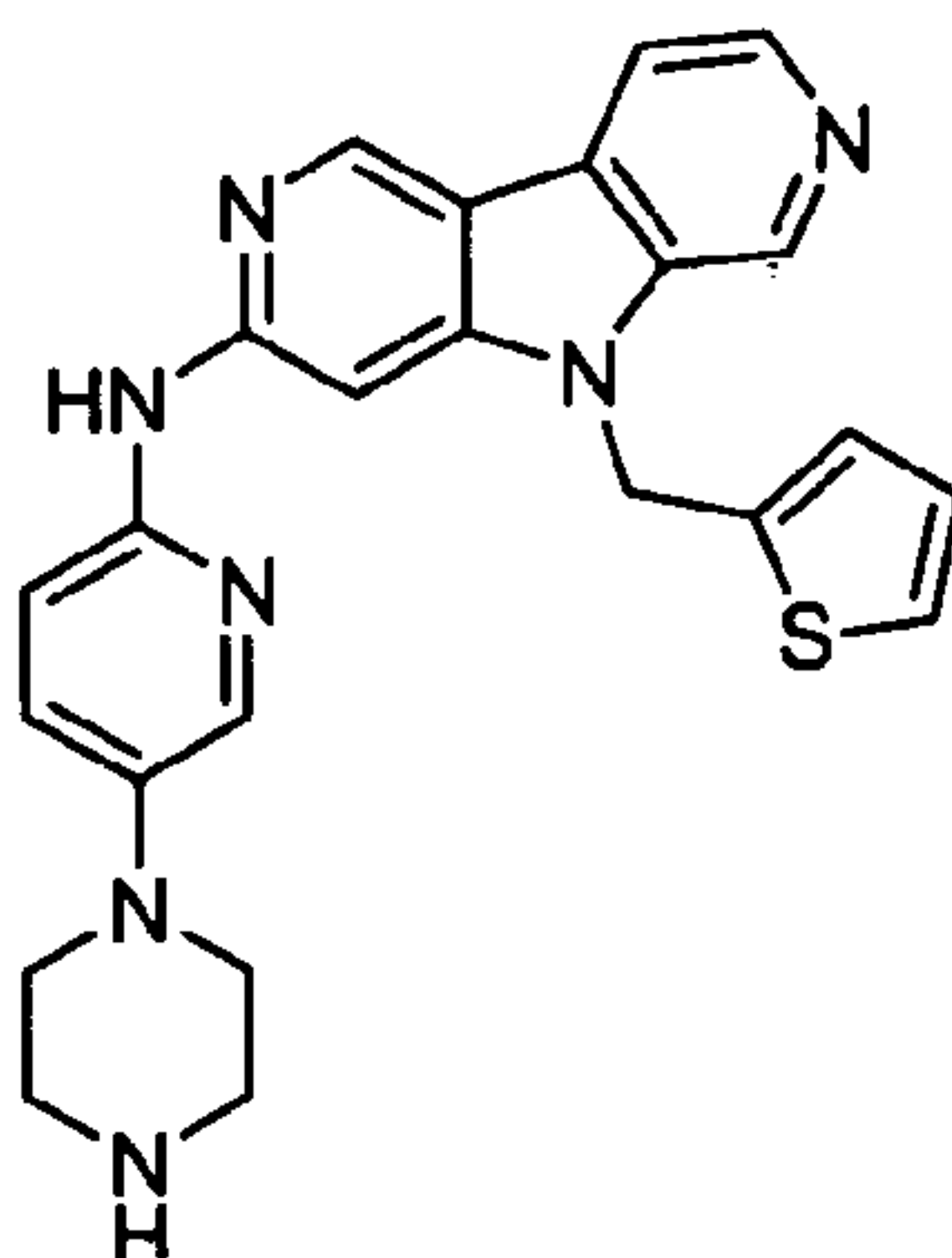


**375**

### **5-cyclopentyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine**

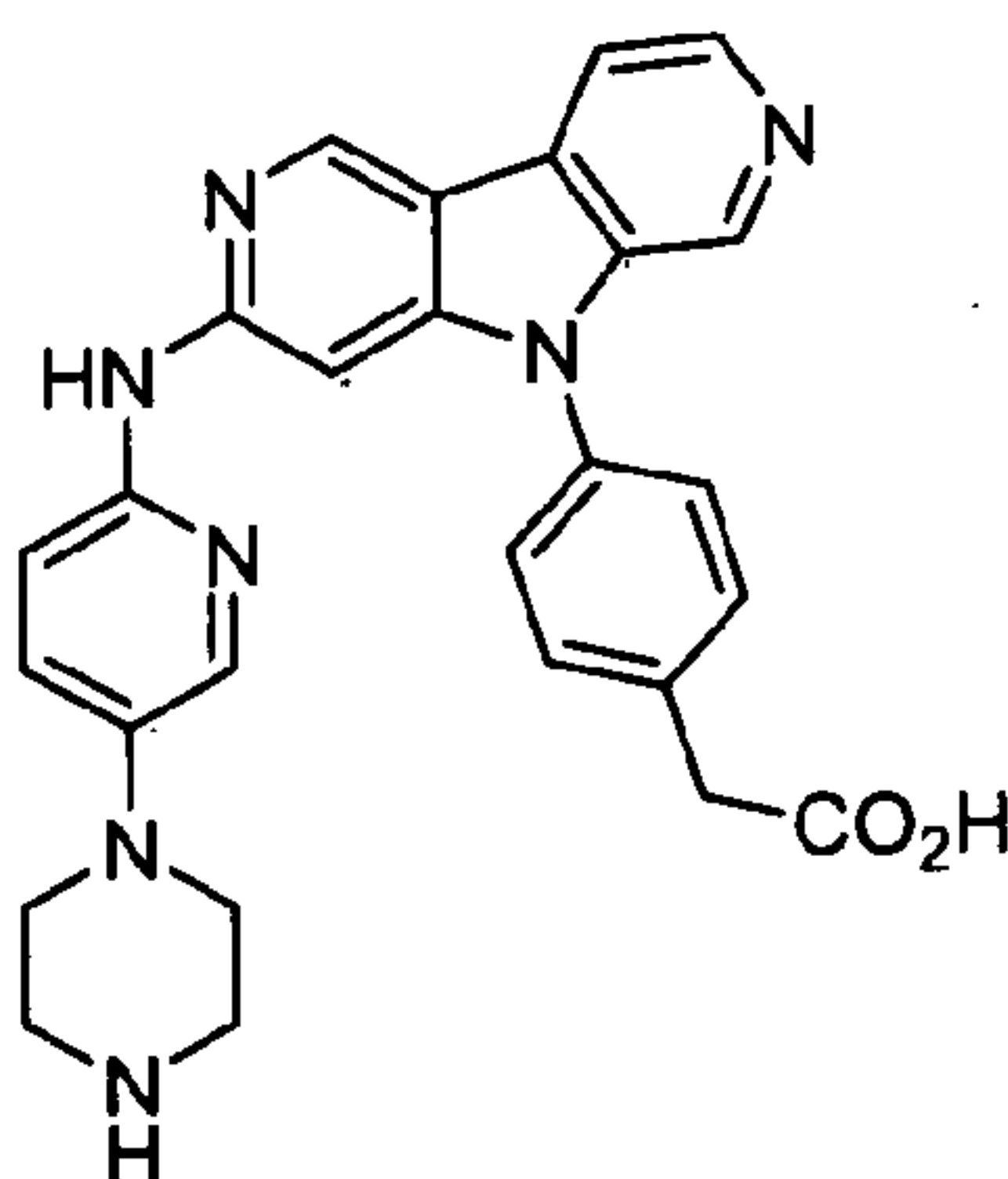
Compound **375** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. LCMS-ESI (POS), M/Z, M+1: Found 414.1.



**EXAMPLE 237****376**

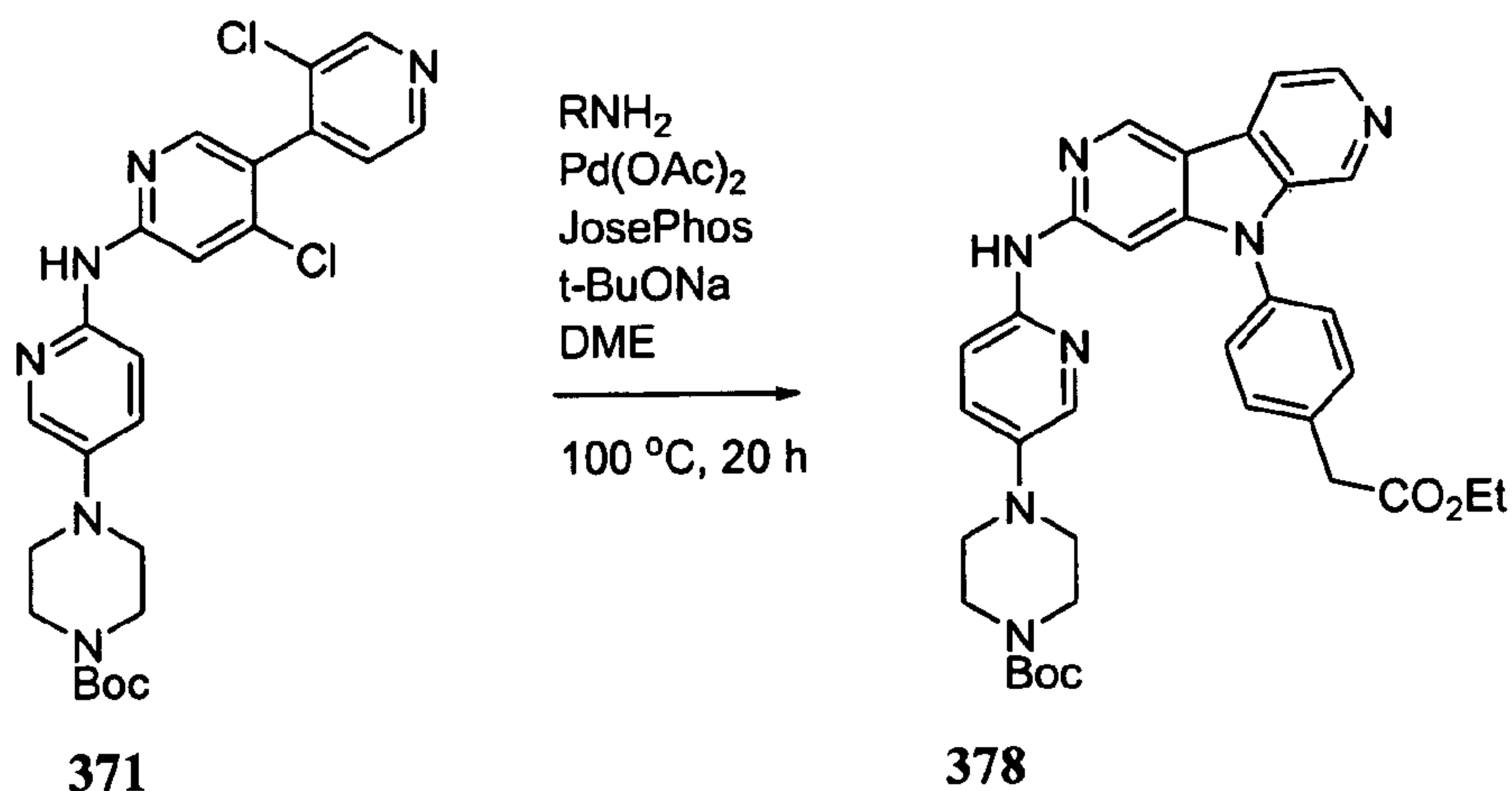
**N-(5-(1-piperazinyl)-2-pyridinyl)-5-(2-thiophenylmethyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine**

Compound **376** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.40 (1 H, d, J=0.7 Hz), 9.25 (1 H, d, J=0.7 Hz), 8.62 (1 H, d, J=5.6 Hz), 8.50 (1 H, d, J=5.6 Hz), 8.06 (1 H, d, J=2.7 Hz), 7.93 (1 H, dd, J=9.3, 2.9 Hz), 7.44 (1 H, s), 7.37 (1 H, dd, J=5.1, 1.2 Hz), 7.31 (1 H, d, J=9.3 Hz), 7.27 (1 H, dd, J=3.7, 1.0 Hz), 7.01 (1 H, dd, J=5.1, 3.4 Hz), 5.96 (2 H, s), 3.47 - 3.53 (4 H, m), 3.42 - 3.47 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 442.1.

**EXAMPLE 238****377**

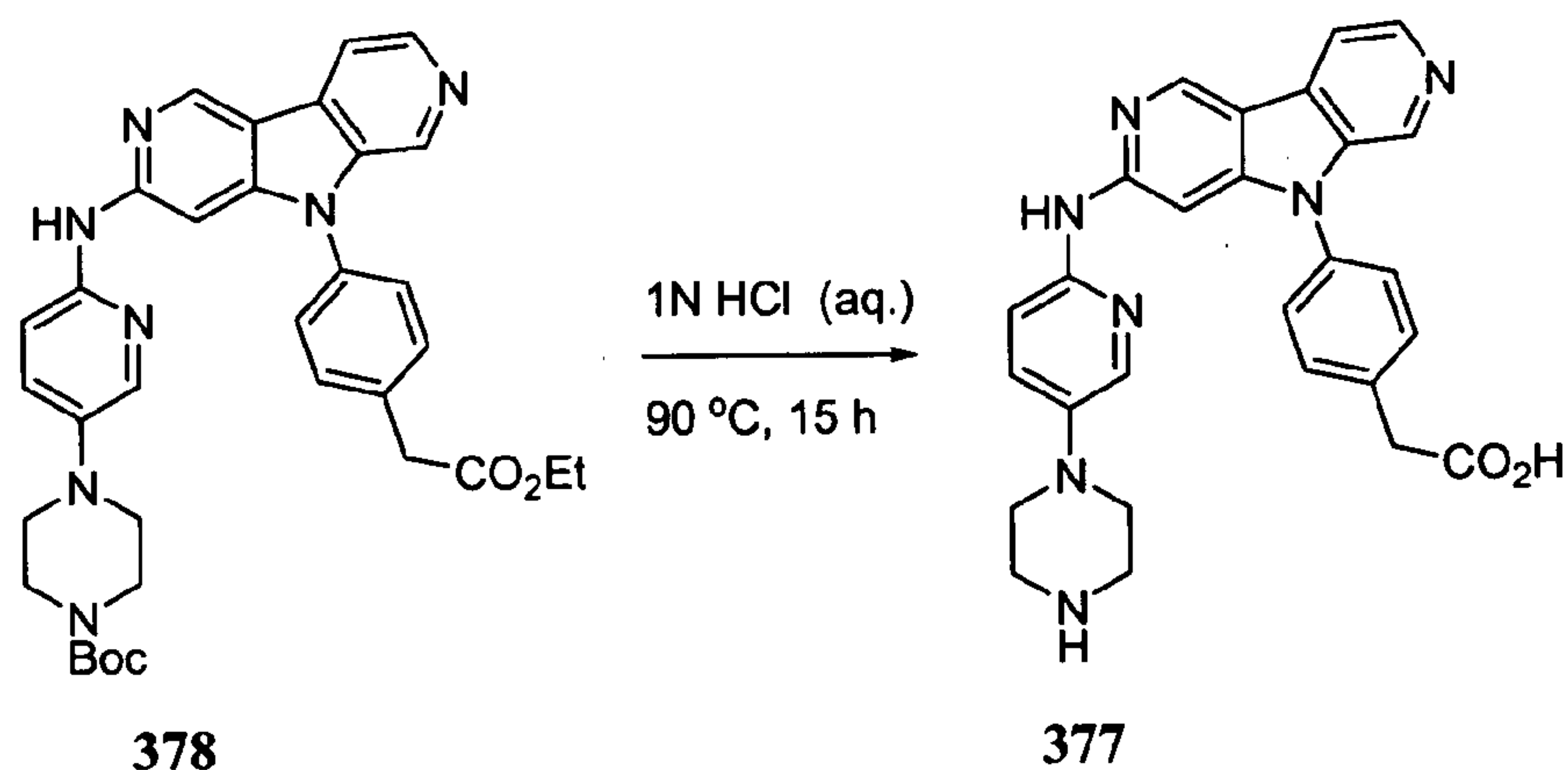
**(4-(3-((5-(1-piperazinyl)-2-pyridinyl)amino)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-5-yl)phenyl)acetic acid**





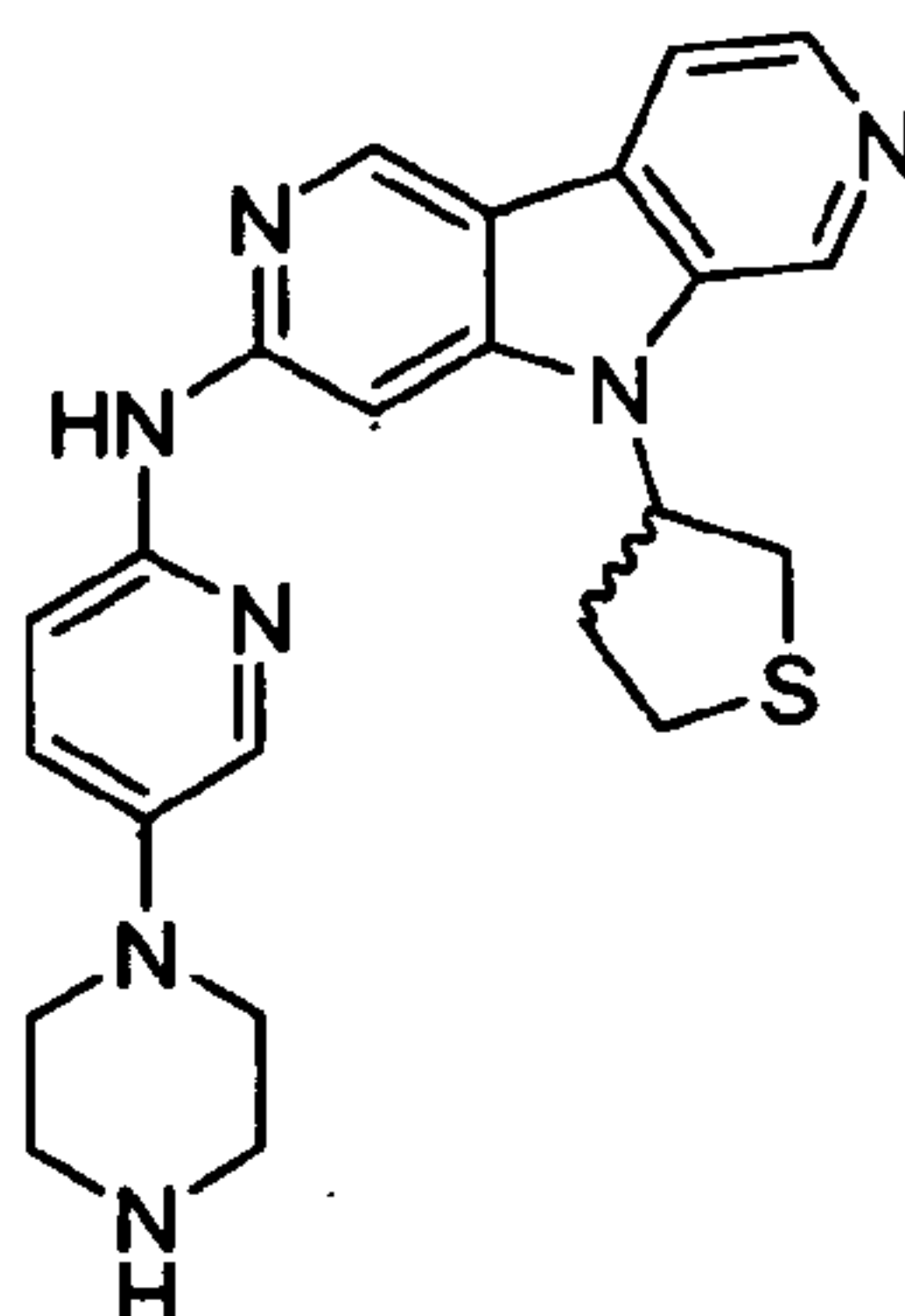
**tert-Butyl 4-(6-((5-(4-(2-ethoxy-2-oxoethyl)phenyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-yl)amino)-3-pyridinyl)-1-piperazinecarboxylate (378)**

Compound **378** was prepared using chemistry similar to that described in example 233. LCMS-ESI (POS), M/Z, M+1: Found 608.3.



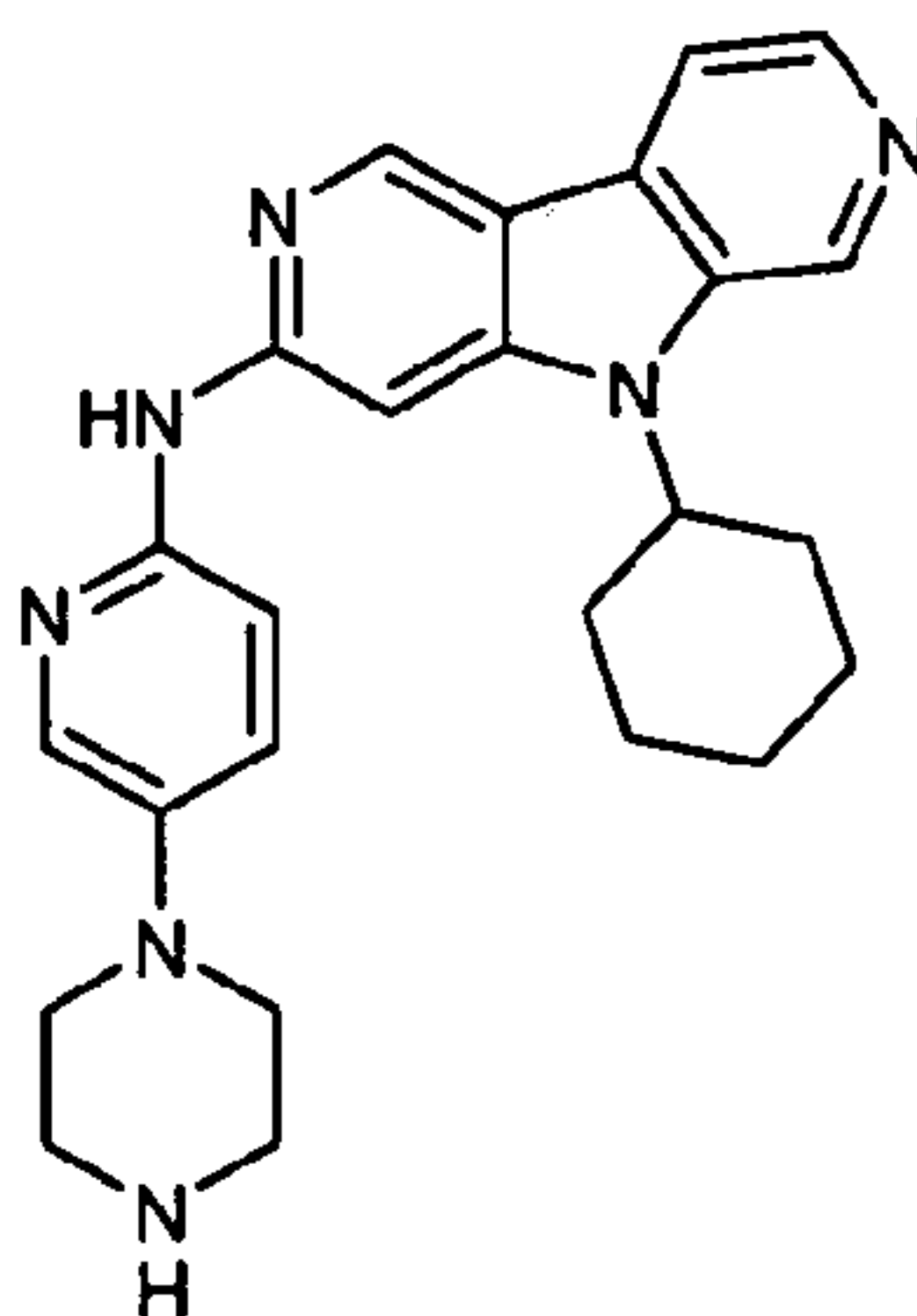
**(4-(3-((5-(1-Piperazinyl)-2-pyridinyl)amino)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-5-yl)phenyl)acetic acid (377):** A mixture of crude compound **378** and 1N hydrochloric acid (aqueous solution) (10 mL, 10.0 mmol) was stirred at 90 °C for 15 h. After concentration, the residue was taken up with 1 N HCl aqueous solution and subjected to reverse phase preparative HPLC (acetonitrile/water containing 0.1% TFA each, 40 min from 10 to 40%). Lyophilization provided compound **377** (6 mg) as a yellow solid (TFA salt). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.48 (1 H, s), 8.85 (1 H, s), 8.66 (1 H, d, J=5.6 Hz), 8.57 (1 H, d, J=5.6 Hz), 8.04 (1 H, d, J=2.7 Hz), 7.93 (1 H, dd, J=9.3, 2.9 Hz), 7.67 - 7.74 (4 H, m), 7.25 (1 H, d, J=9.3 Hz), 7.13 (1 H, s), 3.85 (2 H, s), 3.46 - 3.51 (4 H, m), 3.41 - 3.46 (4 H, m). LCMS-ESI (POS), M/Z, M+1: Found 480.2.



**EXAMPLE 239****379**

**N-(5-(1-piperazinyl)-2-pyridinyl)-5-(tetrahydro-3-thiophenyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine**

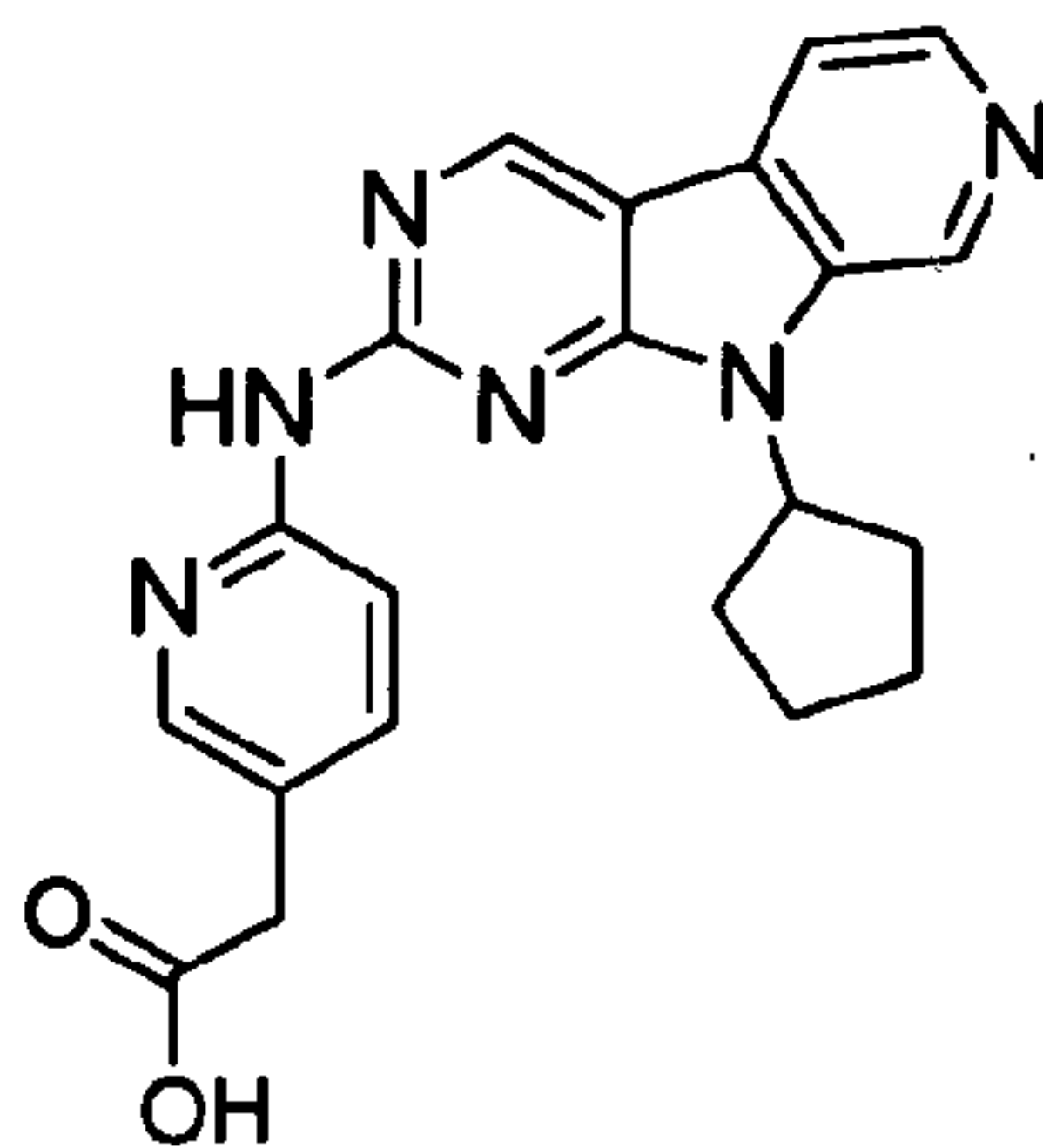
Compound **379** was prepared as a yellow solid (TFA salt) using chemistry similar to that described in example 233.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 9.54 (1 H, s), 9.44 (1 H, s), 8.72 (1 H, d), 8.67 (1 H, d,  $J=5.9$  Hz), 8.08 (1 H, dd,  $J=9.5, 2.9$  Hz), 8.01 (1 H, d,  $J=2.7$  Hz), 7.61 (1 H, s), 7.41 (1 H, d,  $J=9.3$  Hz), 5.64 - 5.74 (1 H, m), 3.48 - 3.56 (6 H, m), 3.42 - 3.47 (4 H, m), 3.12 - 3.20 (2 H, m), 2.59 - 2.81 (2 H, m). LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 432.1.

**EXAMPLE 240****380**

**5-cyclohexyl-N-(5-(1-piperazinyl)-2-pyridinyl)-5H-pyrido[3',4':4,5]pyrrolo[2,3-c]pyridin-3-amine**

Compound **380** was prepared using chemistry similar to that described in example 233.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 9.56 (1 H, s), 9.47 (1 H, s), 8.77 (1 H, d,  $J=6.1$  Hz), 8.65 (1 H, d,  $J=6.1$  Hz), 8.10 (1 H, dd,  $J=9.5, 2.9$  Hz), 8.00 (1 H, d,  $J=2.7$  Hz), 7.54 (1 H, s), 7.42 (1 H, d,  $J=9.5$  Hz), 4.77 - 4.84 (1 H, m), 3.50 - 3.54 (4 H, m), 3.43 - 3.48 (4 H, m), 2.31 - 2.44 (2 H, m), 2.04 - 2.16 (4 H, m), 1.86 - 1.95 (1 H, m), 1.65 - 1.77 (2 H, m), 1.46 - 1.59 (1 H, m); LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 428.2.

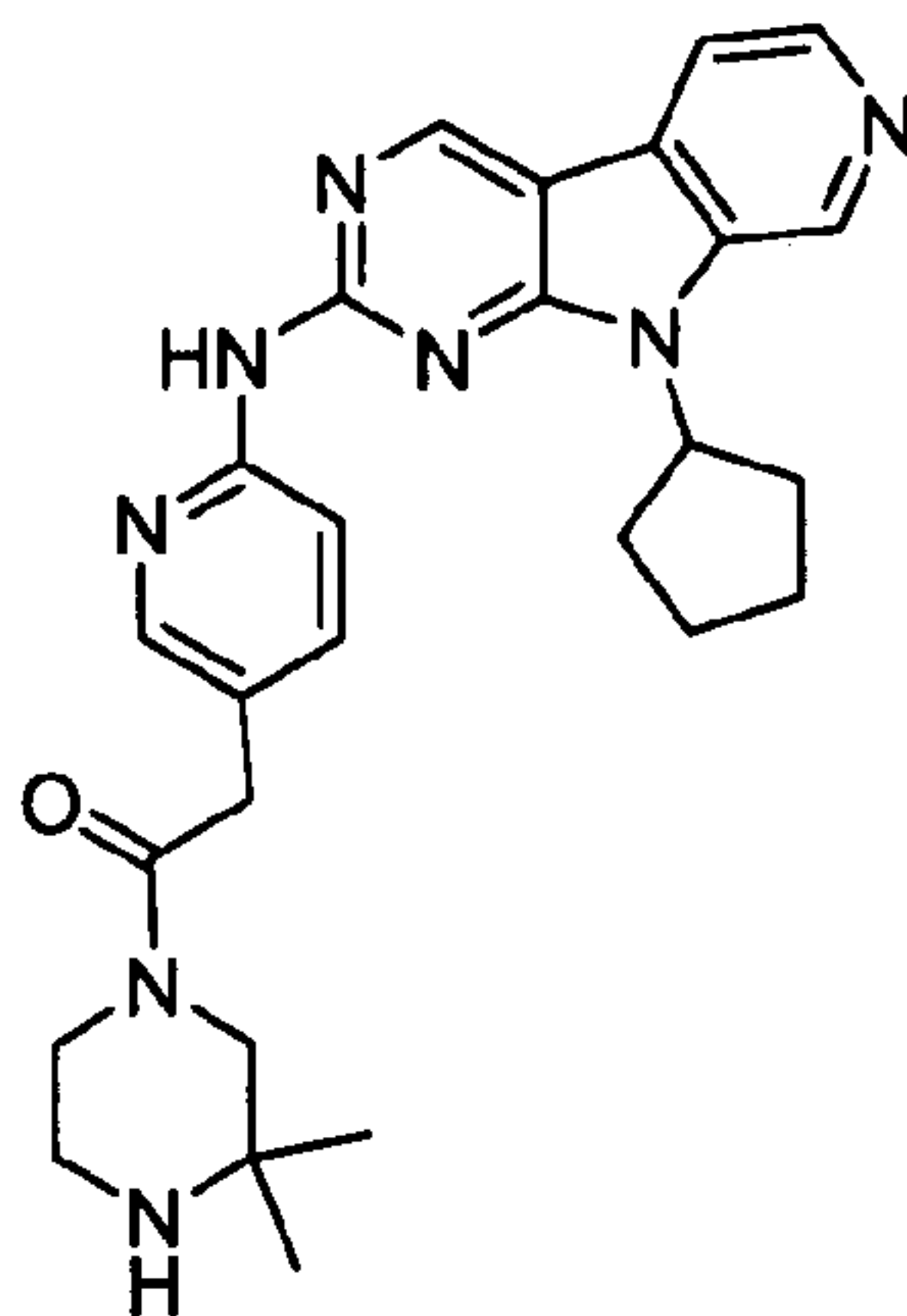


**EXAMPLE 241****381**

**(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)acetic acid**

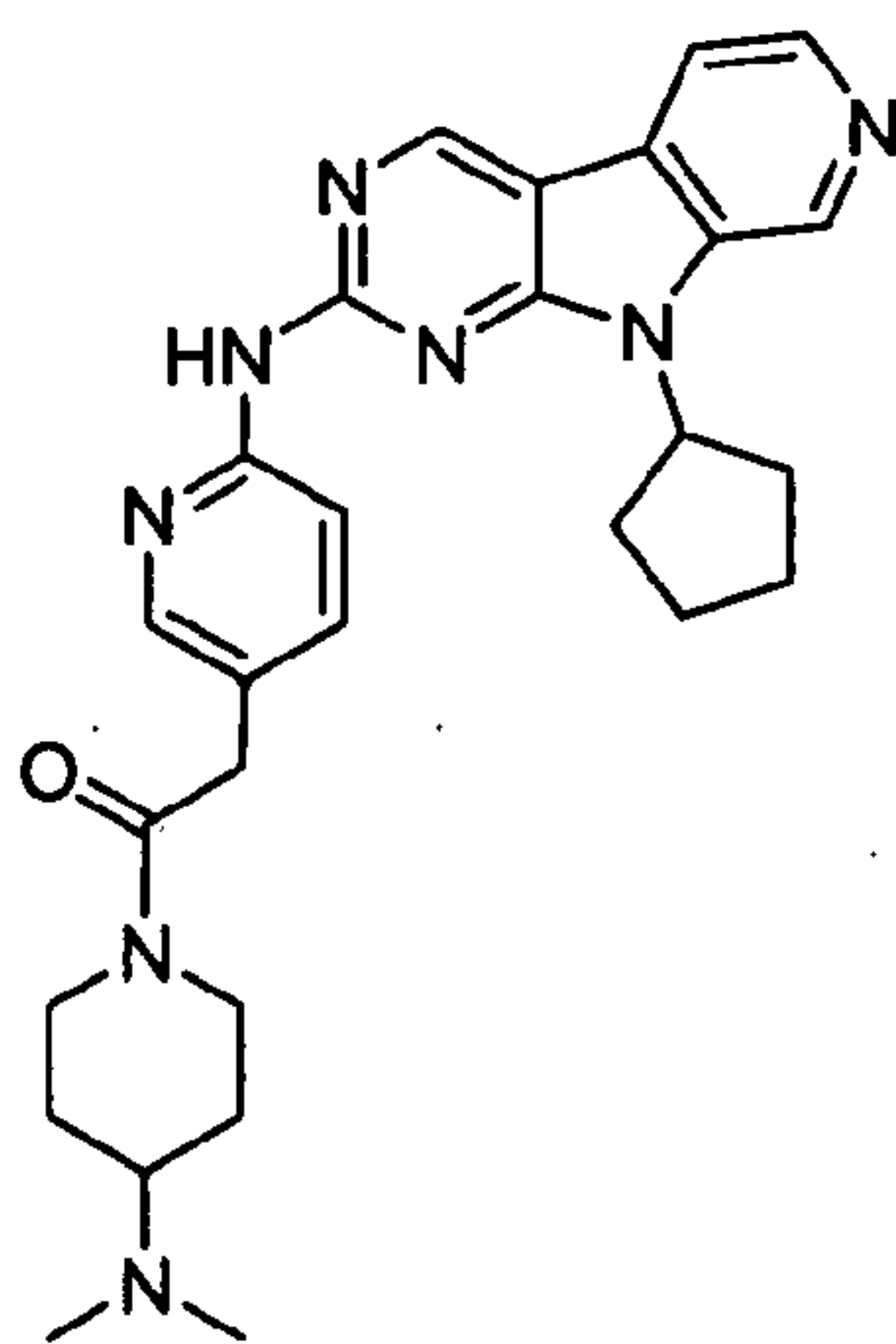
Sodium 2-methylpropan-2-olate (97 mg, 1007  $\mu\text{mol}$ ) was added to a dioxane (3 mL) solution containing methyl 2-(6-chloropyridin-3-yl)acetate (69 mg, 369  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (23 mg, 25  $\mu\text{mol}$ ), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (29 mg, 50  $\mu\text{mol}$ ), and compound 4 (85 mg, 336  $\mu\text{mol}$ ). The resulting mixture was stirred in the microwave at 120 °C for 3 h. The mixture was then purified on silica eluting with a DCM/methanol gradient (0-10%). Desired fractions containing the ester were pooled and concentrated. The ester was then dissolved in a 3 N NaOH / methanol (1:1) solution and stirred for 3 h at 50 °C. Next, the solution was acidified to pH 2 and concentrated to dryness. The resulting residue was then purified by prep HPLC. Desired fractions were pooled and lyophilized to give compound **381** (86 mg, 66% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ , TFA salt)  $\delta$  ppm 1.82 - 2.05 (m, 2 H) 2.11 - 2.38 (m, 4 H) 2.45 - 2.64 (m, 2 H) 3.83 (s, 2 H) 5.50 (qn,  $J=8.61$  Hz, 1 H) 7.84 (d,  $J=8.80$  Hz, 1 H) 8.20 (dd,  $J=9.00, 2.15$  Hz, 1 H) 8.41 (d,  $J=1.57$  Hz, 1 H) 8.56 - 8.73 (m, 2 H) 9.23 - 9.40 (m, 1 H) 9.55 - 9.72 (m, 1 H); LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 389, Calculated 389.



**EXAMPLE 242****382**

**9-cyclopentyl-N-(5-(2-(3,3-dimethyl-1-piperazinyl)-2-oxoethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Triethylamine (4 eq.) was added to a DMF solution containing 2,2-dimethylpiperazine (1.2 eq.), compound **381** (1 eq.), and PyBOP (1.1 eq.). The resulting solution was stirred for 3 h at room temperature. The product was purified via reverse phase HPLC (10-70% acetonitrile/water). Desired fractions were pooled and lyophilized to give compound **382**. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, TFA salt) δ ppm 1.43 (s, 3 H) 1.50 (s, 3 H) 1.93 (d, *J*=6.06 Hz, 2 H) 2.15 - 2.34 (m, 4 H) 2.47 - 2.62 (m, 1 H) 3.43 (dd, *J*=3.33, 1.56 Hz, 1 H) 3.71 (s, 1 H) 3.77 (s, 1 H) 3.83 - 4.00 (m, 2 H) 4.06 (s, 1 H) 5.39 - 5.58 (m, 1 H) 7.94 (br. s., 1 H) 8.09 (dd, *J*=8.71, 2.05 Hz, 1 H) 8.35 (d, *J*=1.76 Hz, 1 H) 8.55 - 8.67 (m, 1 H) 9.29 (s, 1 H) 9.55 - 9.69 (m, 1 H); LCMS-ESI (POS), *M/Z*, *M*+1: Found 577.2, Calculated 577.

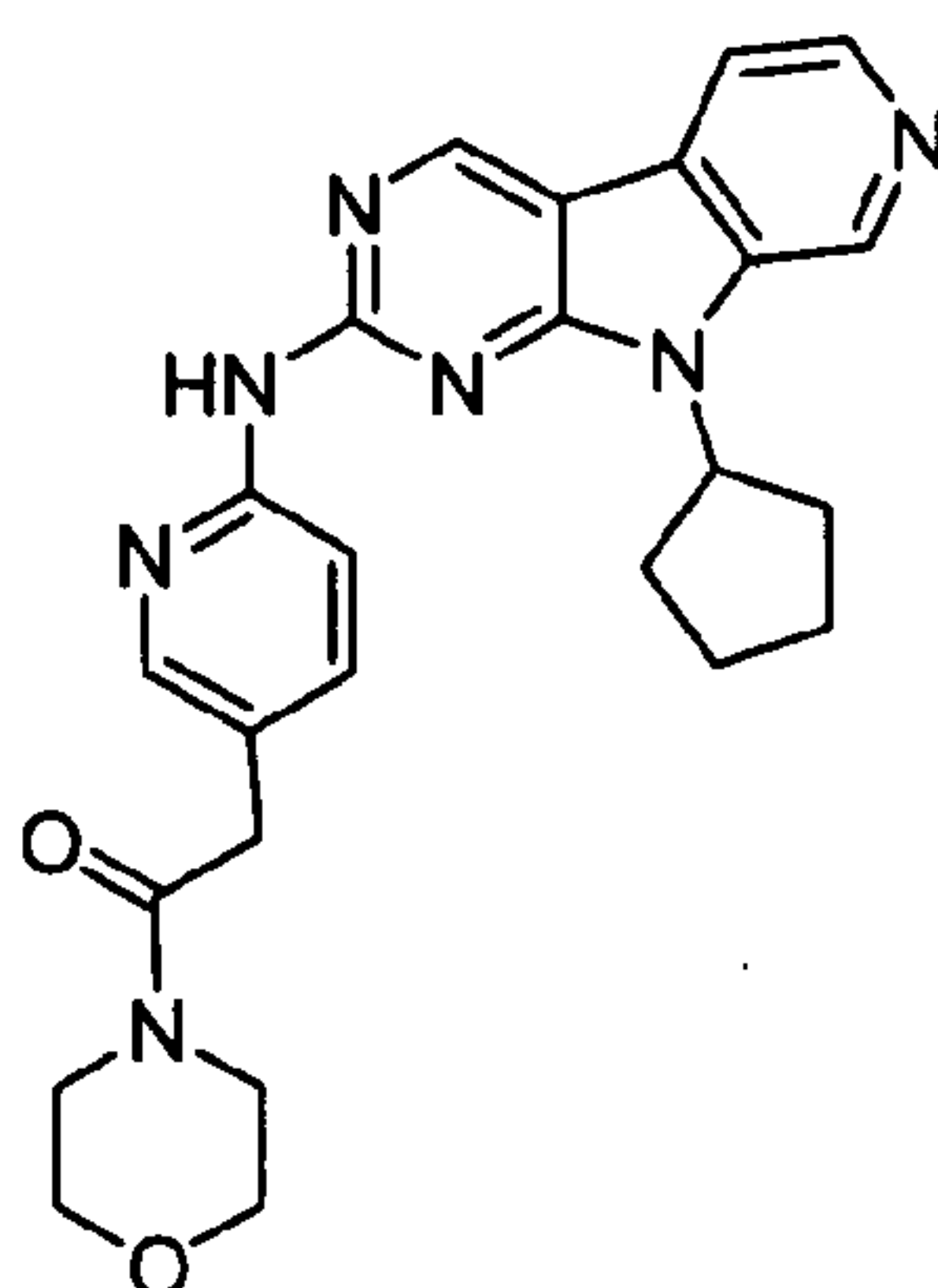
**EXAMPLE 243****383**

**9-cyclopentyl-N-(5-(2-(4-(dimethylamino)-1-piperidinyl)-2-oxoethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



Compound **383** was prepared using chemistry similar to that described in example 242. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, TFA salt) δ ppm 1.65 (dd, *J*=12.35, 4.52 Hz, 1 H) 1.81 (dd, *J*=12.35, 4.28 Hz, 1 H) 1.89 - 2.00 (m, 2 H) 2.11 - 2.35 (m, 6 H) 2.48 - 2.63 (m, 2 H) 2.70 - 2.84 (m, 1 H) 2.93 (s, 6 H) 3.23 - 3.29 (m, 1 H) 3.48 - 3.58 (m, 1 H) 4.01 (s, 2 H) 4.27 - 4.37 (m, 1 H) 4.72 - 4.82 (m, 1 H) 5.50 (qn, *J*=8.80 Hz, 1 H) 7.85 (d, *J*=8.80 Hz, 1 H) 8.14 (dd, *J*=8.80, 1.96 Hz, 1 H) 8.36 (d, *J*=1.71 Hz, 1 H) 8.63 - 8.70 (m, 2 H) 9.34 (s, 1 H) 9.64 - 9.71 (m, 1 H); LCMS-ESI (POS), *M/Z*, *M*+1: Found 499, Calculated 499.

#### EXAMPLE 244

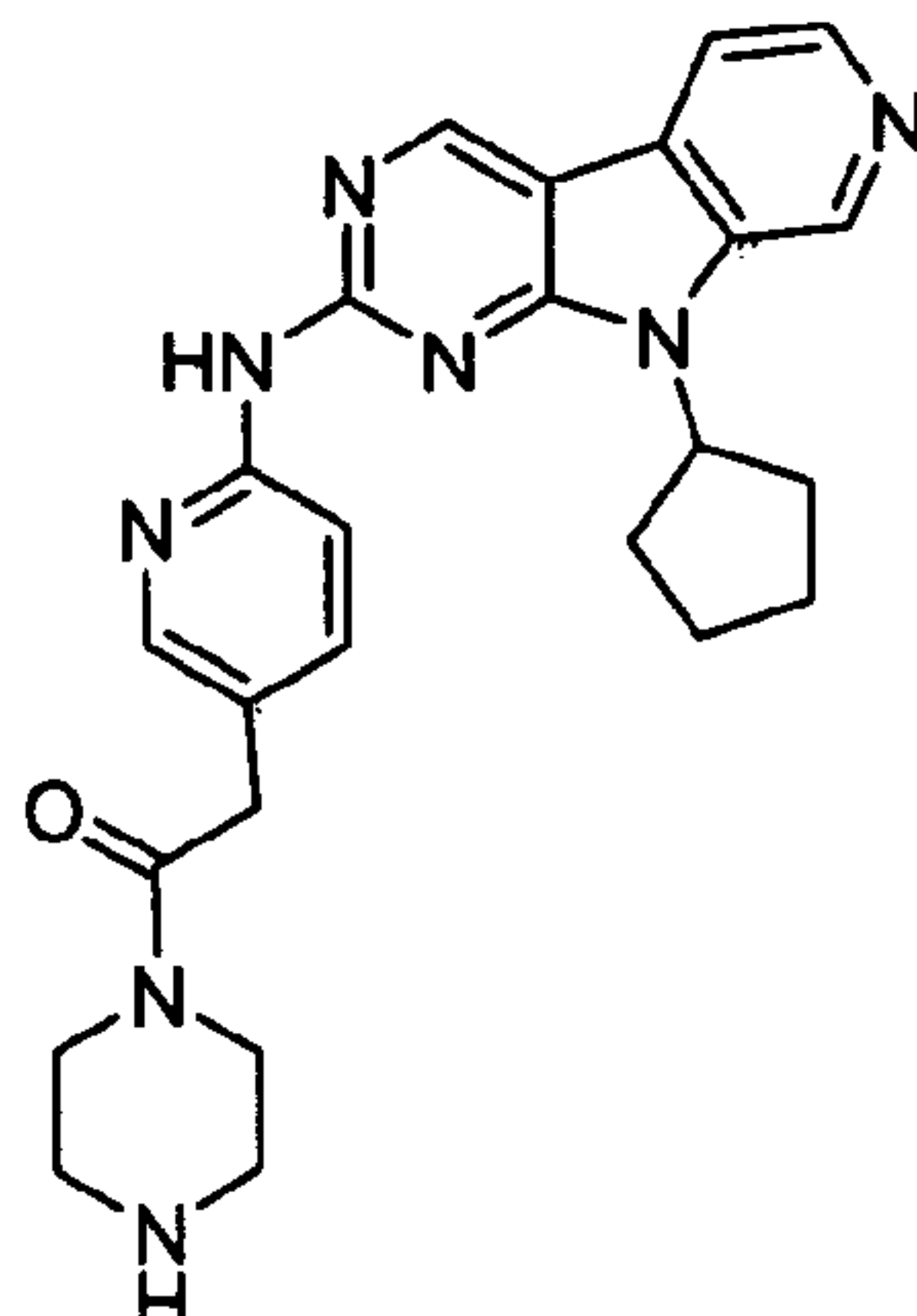


**384**

**9-cyclopentyl-N-(5-(2-(4-morpholinyl)-2-oxoethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

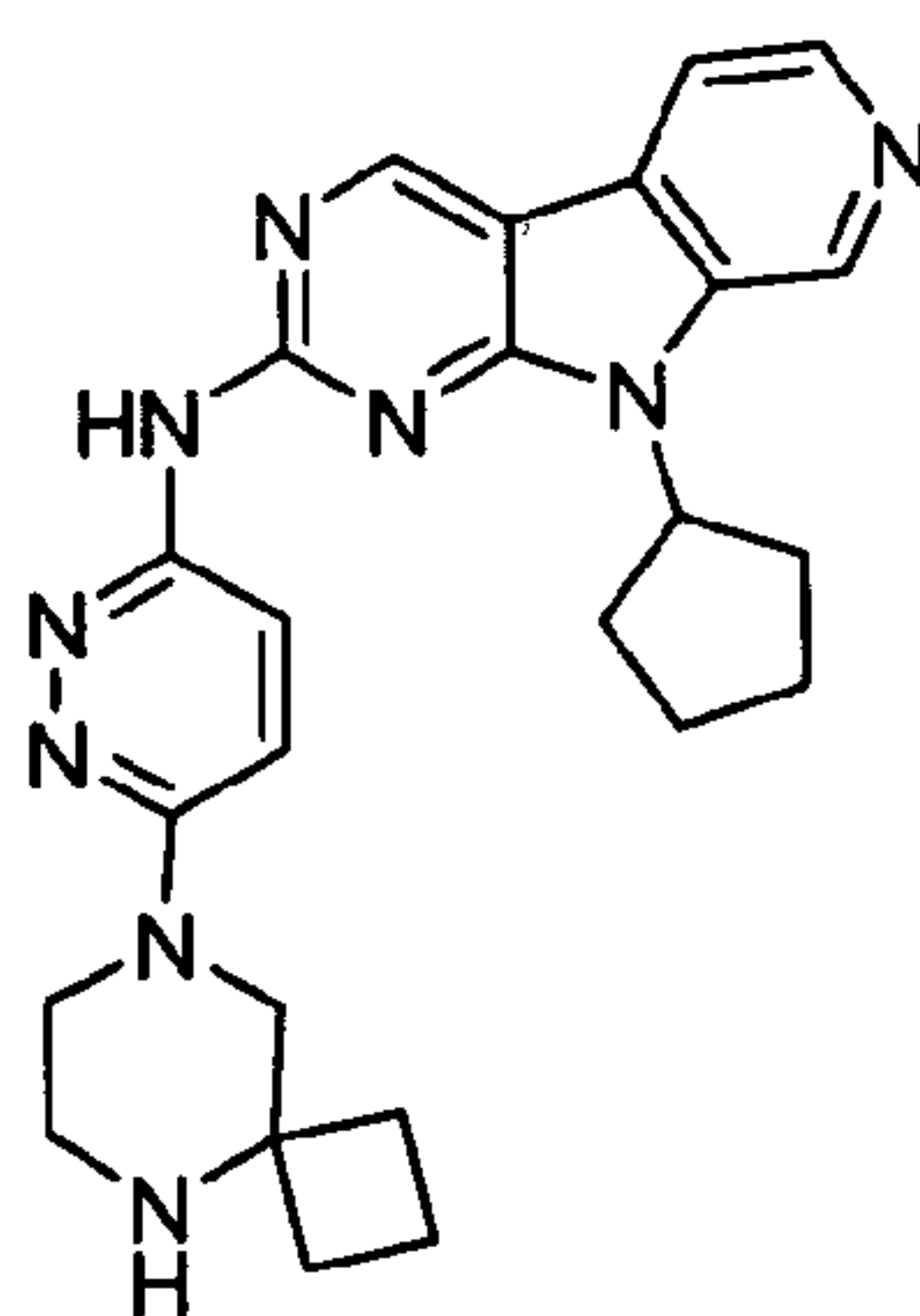
Title compound **384** was prepared using chemistry similar to that described in example 242. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, TFA salt) δ ppm 1.86 - 2.00 (m, 2 H) 2.16 - 2.35 (m, 4 H) 2.47 - 2.63 (m, 2 H) 3.63 - 3.67 (m, 2 H) 3.70 (ddd, *J*=14.37, 4.71, 4.40 Hz, 4 H) 3.74 - 3.78 (m, 2 H) 3.98 (s, 2 H) 5.50 (qn, *J*=8.80 Hz, 1 H) 7.81 (d, *J*=8.80 Hz, 1 H) 8.16 (dd, *J*=8.80, 2.20 Hz, 1 H) 8.36 (d, *J*=1.96 Hz, 1 H) 8.62 - 8.71 (m, 2 H) 9.33 (s, 1 H) 9.62 - 9.71 (m, 1 H); LCMS-ESI (POS), *M/Z*, *M*+1: Found 458, Calculated 458



**EXAMPLE 245****385**

**9-cyclopentyl-N-(5-(2-oxo-2-(1-piperazinyl)ethyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

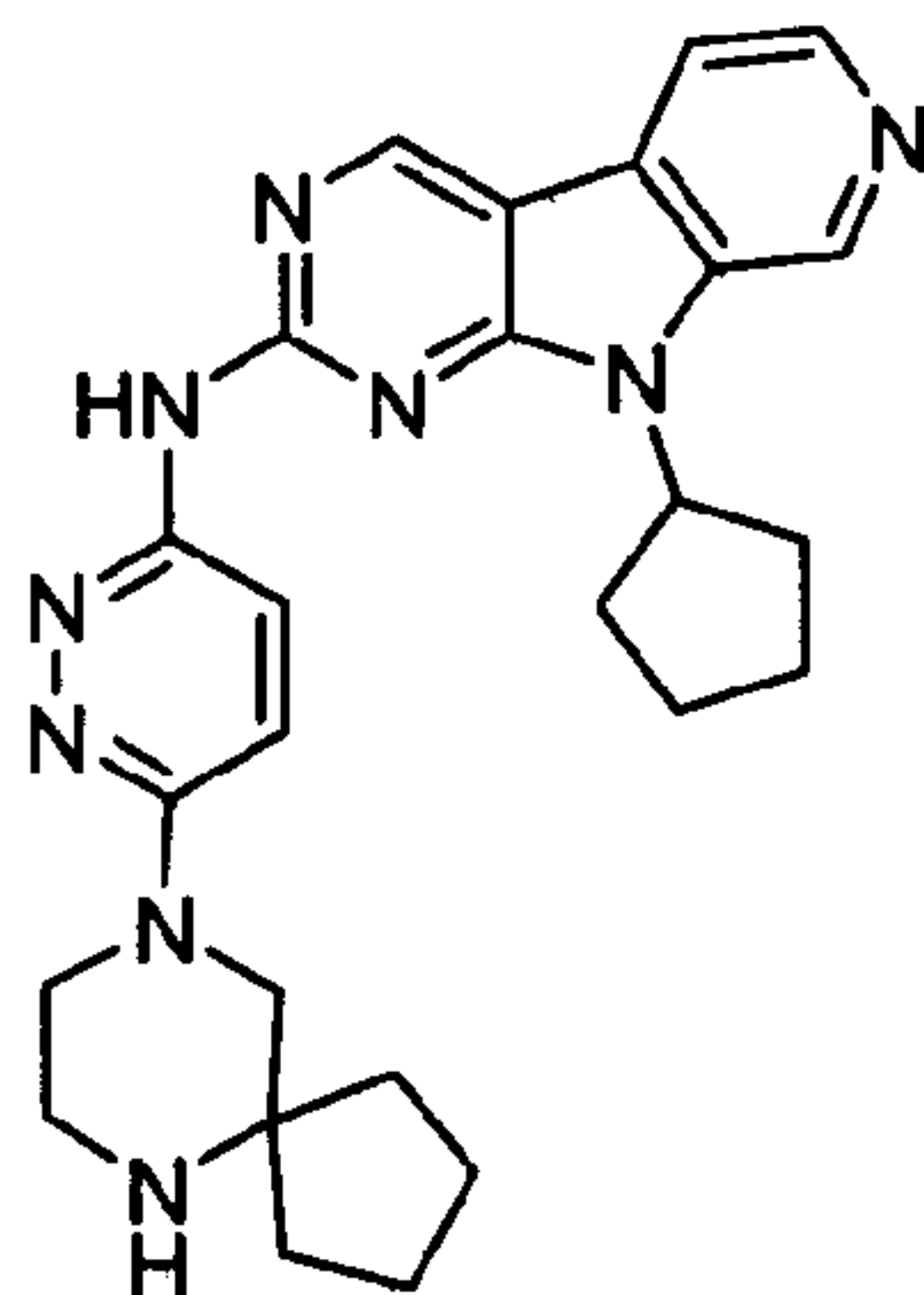
Compound **385** was prepared using chemistry similar to that described in example 242. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, TFA salt) δ ppm 1.94 (ddd, *J*=11.49, 5.62, 5.38 Hz, 2 H) 2.17 - 2.35 (m, 4 H) 2.48 - 2.64 (m, 2 H) 3.30 (ddd, 2 H) 3.36 - 3.40 (m, 2 H) 3.83 - 3.99 (m, 4 H) 4.01 (s, 2 H) 5.50 (qn, *J*=8.80 Hz, 1 H) 7.89 (d, *J*=8.80 Hz, 1 H) 8.11 (dd, *J*=8.80, 1.96 Hz, 1 H) 8.35 (d, *J*=1.71 Hz, 1 H) 8.59 - 8.70 (m, 2 H) 9.30 (s, 1 H) 9.64 (s, 1 H); LCMS-ESI (POS), *M/Z*, *M*+1: Found 457, Calculated 457.

**EXAMPLE 246****386**

**9-cyclopentyl-N-(6-(5,8-diazaspiro[3.5]non-8-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

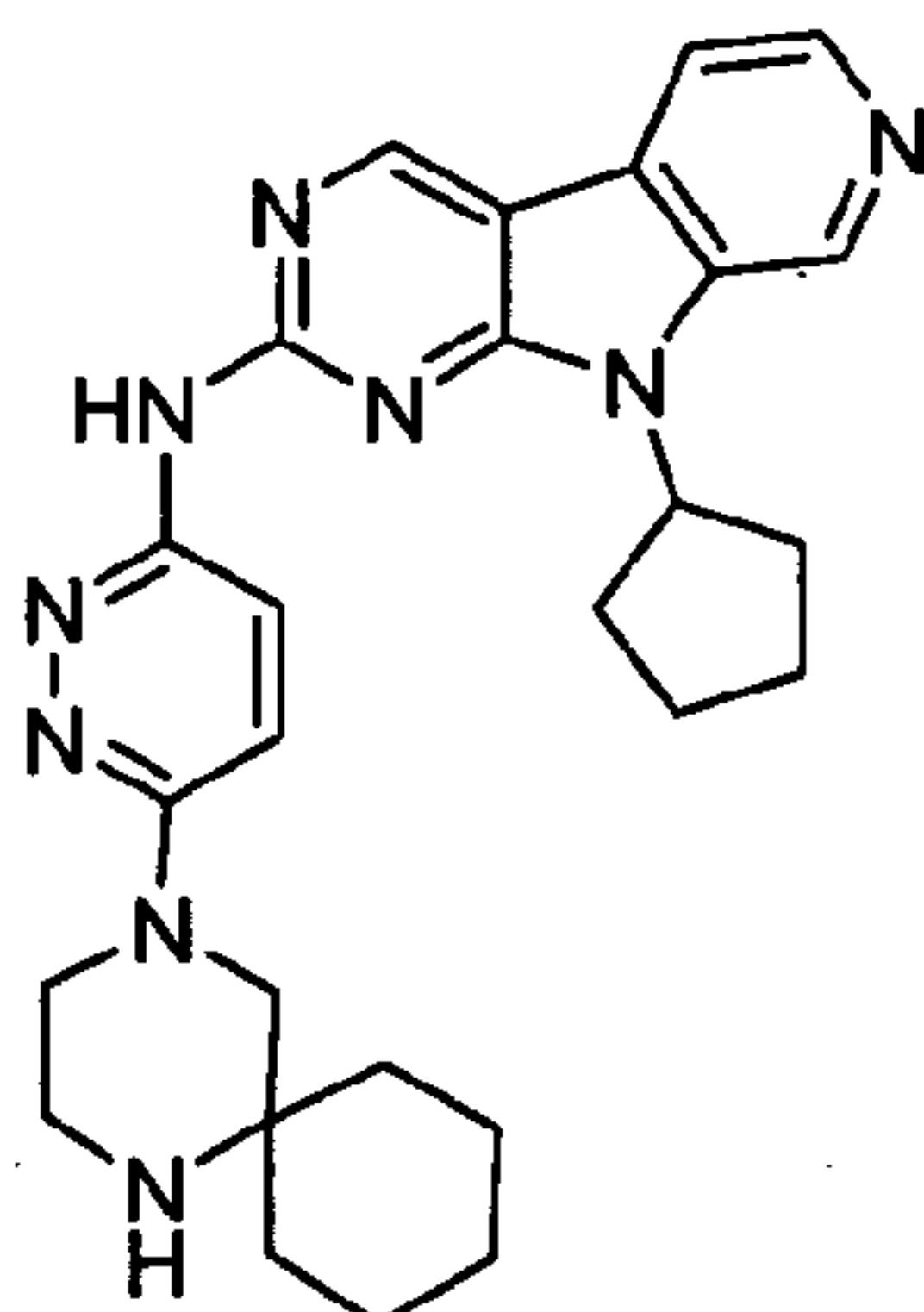
Compound **386** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 1.80 (m, 2 H) 1.93 - 2.22 (m, 6 H) 2.22 - 2.44 (m, 4 H) 3.24 - 3.30 (m, 2 H) 3.69 - 3.82 (m, 2 H) 3.86 (s, 2 H) 5.35 (qn, *J*=8.71 Hz, 1 H) 7.65 (d, *J*=9.78 Hz, 1 H) 8.18 - 8.30 (m, 2 H) 8.41 (d, *J*=5.67 Hz, 1 H) 8.98 (s, 1 H) 9.30 (s, 1 H); LCMS-ESI (POS), *M/Z*, *M*+1: Found 456, Calculated 456.



**EXAMPLE 247****387**

**9-cyclopentyl-N-(6-(6,9-diazaspiro[4.5]dec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

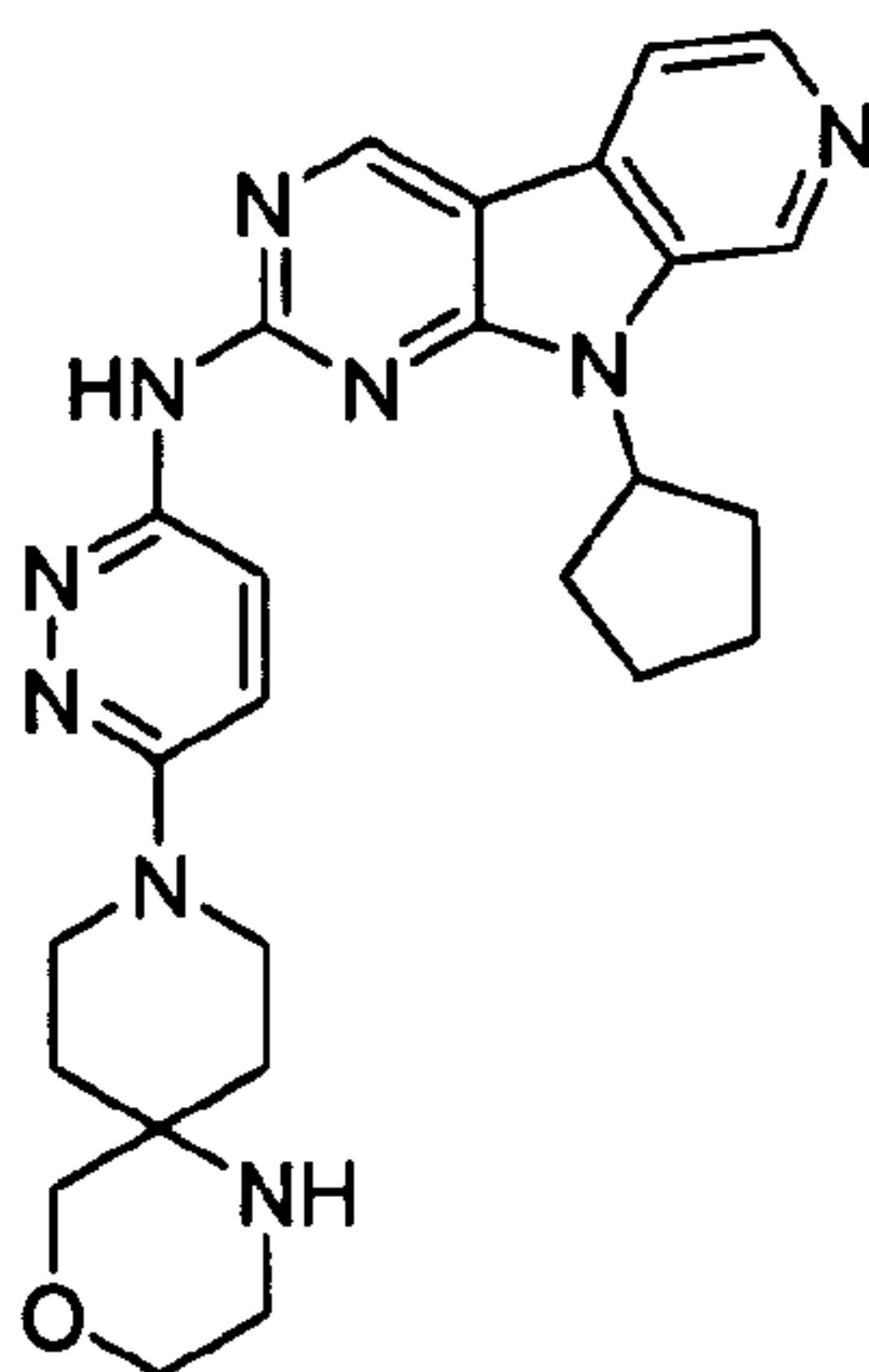
Compound **387** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, TFA salt) δ ppm 1.70 - 1.86 (m, 8 H) 1.88 - 1.99 (m, 2 H) 1.99 - 2.06 (m, 2 H) 2.06 - 2.15 (m, 2 H) 2.26 - 2.40 (m, 2 H) 3.29 - 3.38 (m, 2 H) 3.65 (s, 2 H) 3.73 - 3.84 (m, 2 H) 5.33 (qn, *J*=8.93 Hz, 1 H) 7.48 (d, *J*=10.03 Hz, 1 H) 8.04 (d, *J*=5.38 Hz, 1 H) 8.29 - 8.41 (m, 2 H) 8.85 (s, 1 H) 9.16 (s, 1 H); LCMS-ESI (POS), *M/Z*, *M*+1: Found 470, Calculated 470.

**EXAMPLE 248****388**

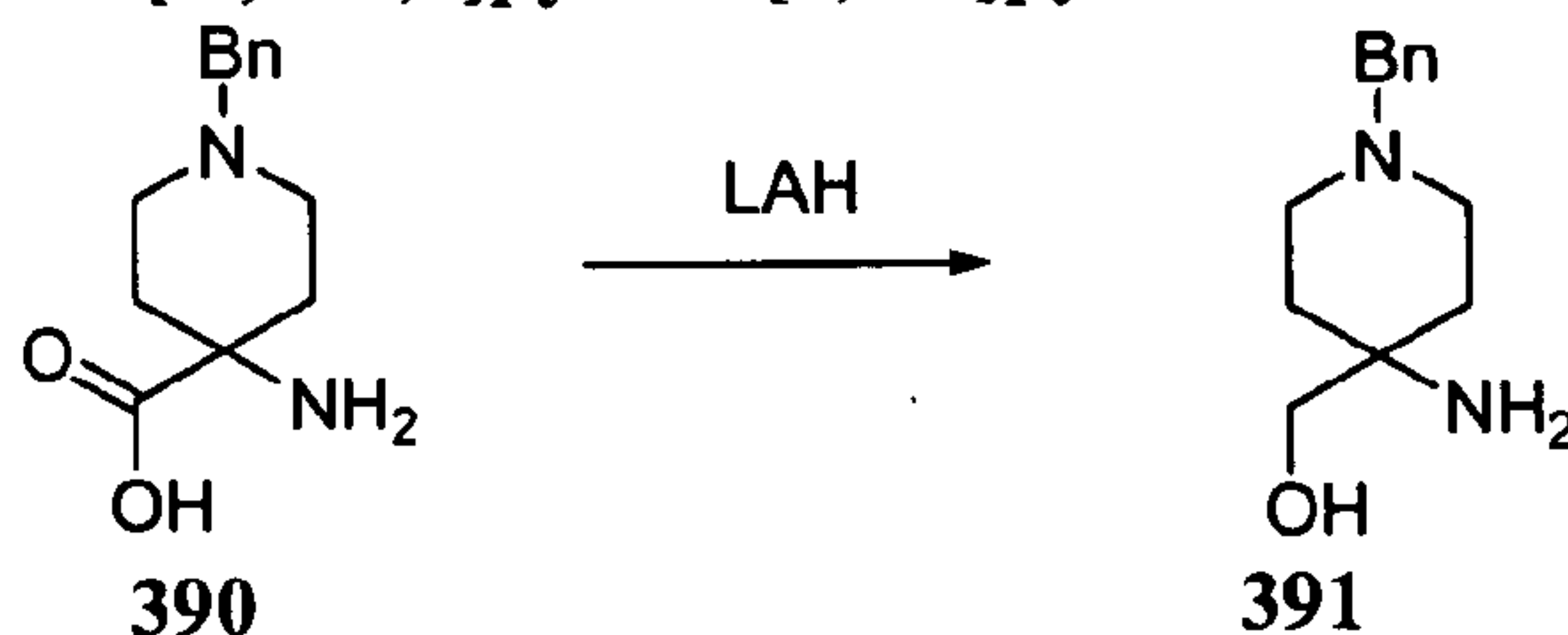
**9-cyclopentyl-N-(6-(1,4-diazaspiro[5.5]undec-4-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **388** was prepared using chemistry similar to that described in example 1. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, TFA salt) δ ppm 1.56 - 1.82 (m, 7 H) 1.82 - 1.97 (m, 2 H) 1.97 - 2.12 (m, 2 H) 2.12 - 2.34 (m, 4 H) 2.42 - 2.61 (m, 2 H) 3.40 - 3.56 (m, 2 H) 3.89 - 4.06 (m, 4 H) 5.47 (qn, *J*=8.80 Hz, 1 H) 7.96 (d, *J*=10.17 Hz, 1 H) 8.12 (d, *J*=9.78 Hz, 1 H) 8.66 (s, 2 H) 9.33 (s, 1 H) 9.66 (s, 1 H); LCMS-ESI (POS), *M/Z*, *M*+1: Found 470, Calculated 470.

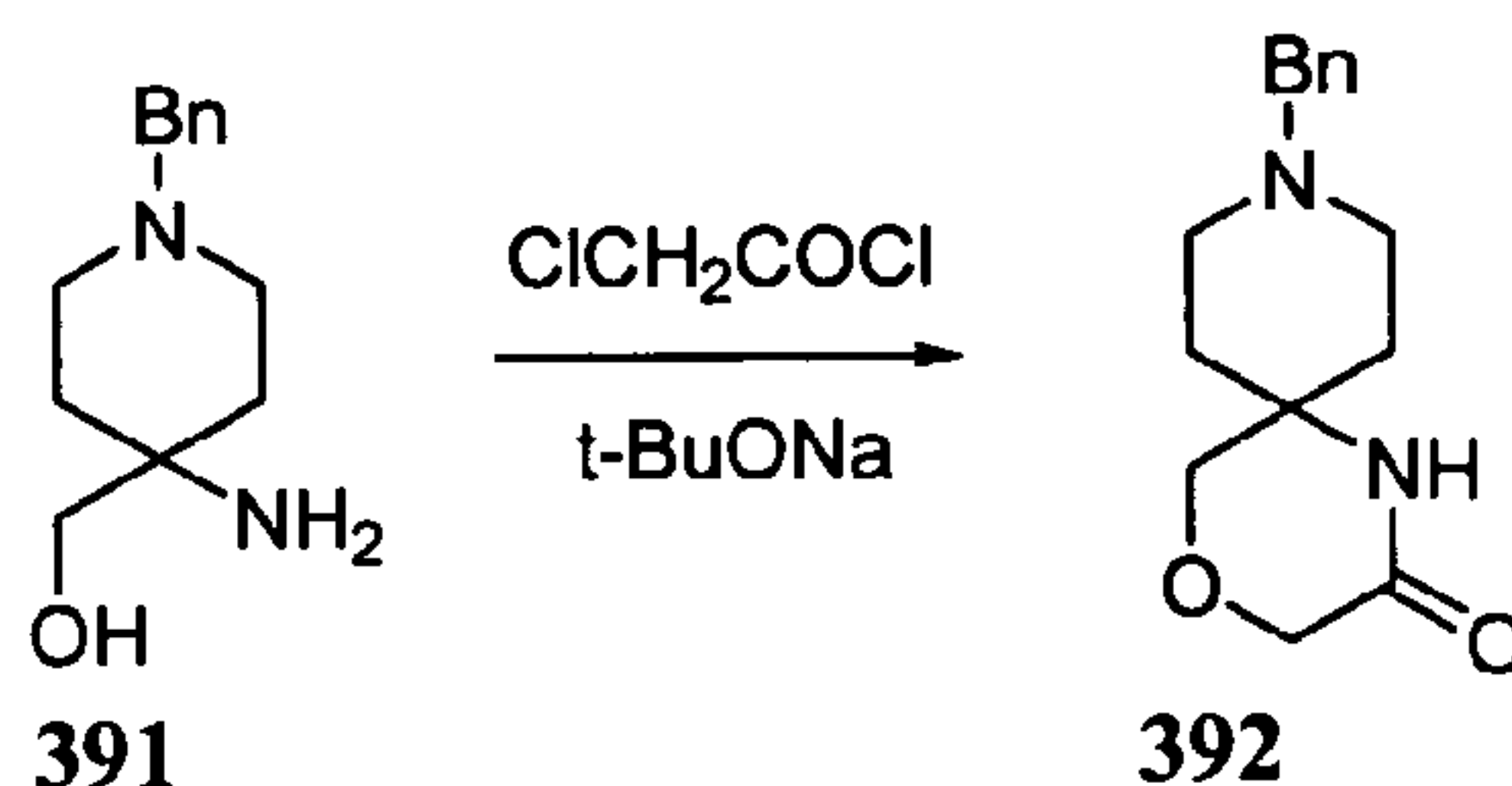


**EXAMPLE 249****389**

**9-cyclopentyl-N-(6-(4-oxa-1,9-diazaspiro[5.5]undec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**390****391**

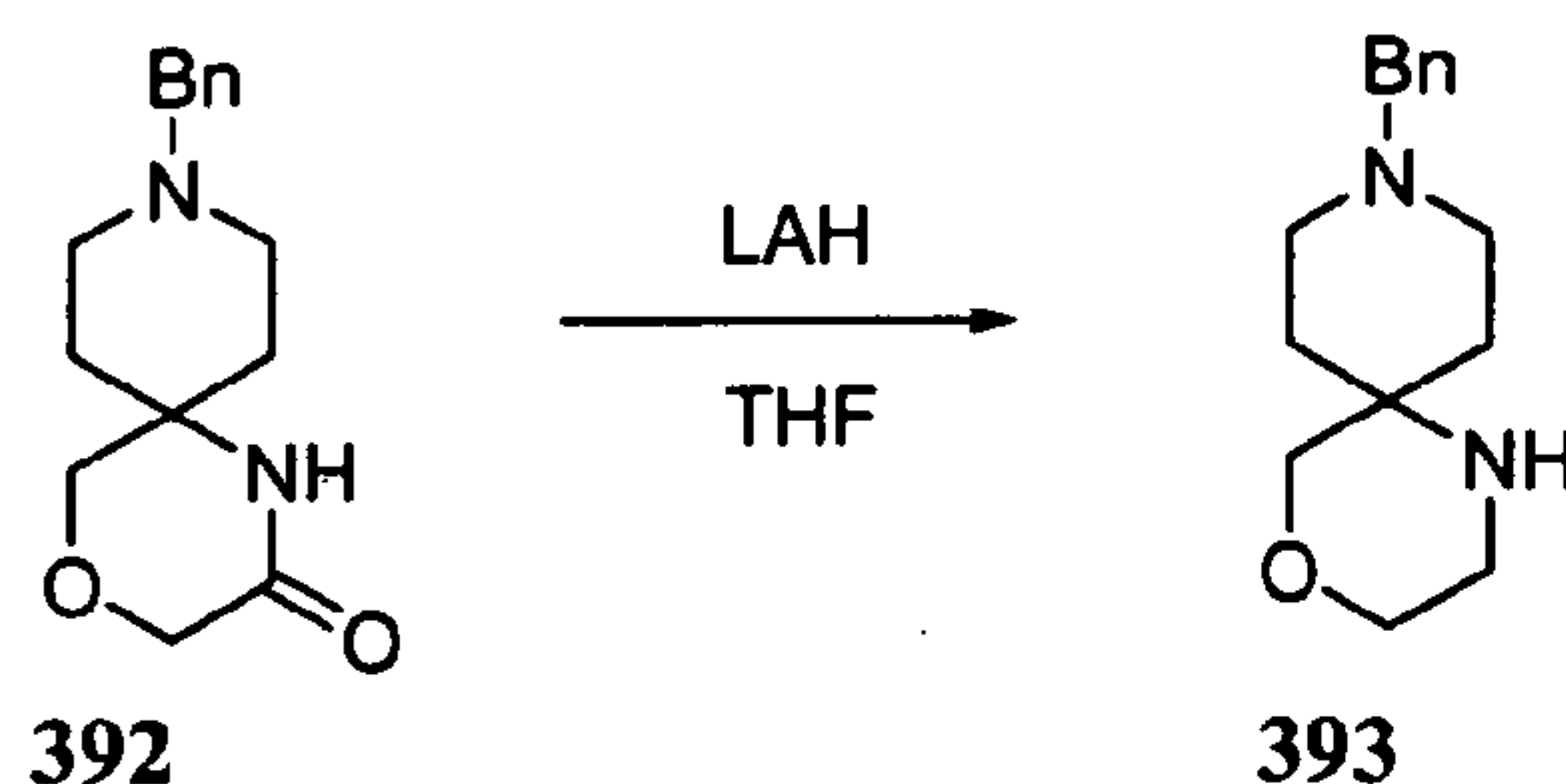
**(4-Amino-1-benzylpiperidin-4-yl)methanol (391):** Lithium aluminum hydride (1.94 g, 51.2 mmol) was added to a THF (100 mL) solution of 4-amino-1-benzylpiperidine-4-carboxylic acid [Albert, J. S. et al. *J. Med. Chem.* **2002**, 45, (18), 3972-3983] (**390**) (3.00 g, 12.8 mmol). The resulting mixture was stirred for 1.5 h at reflux. The reaction was cooled to room temperature and the following additions were made slowly: 2 mL of water followed by 2 mL of 1 N NaOH, and finally 4 mL of water. The mixture was then filtered and concentrated to give compound **391** as a thick clear oil (2.22 g, 79% yield). The material was used in the next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 221, Calculated 221.

**391****392**

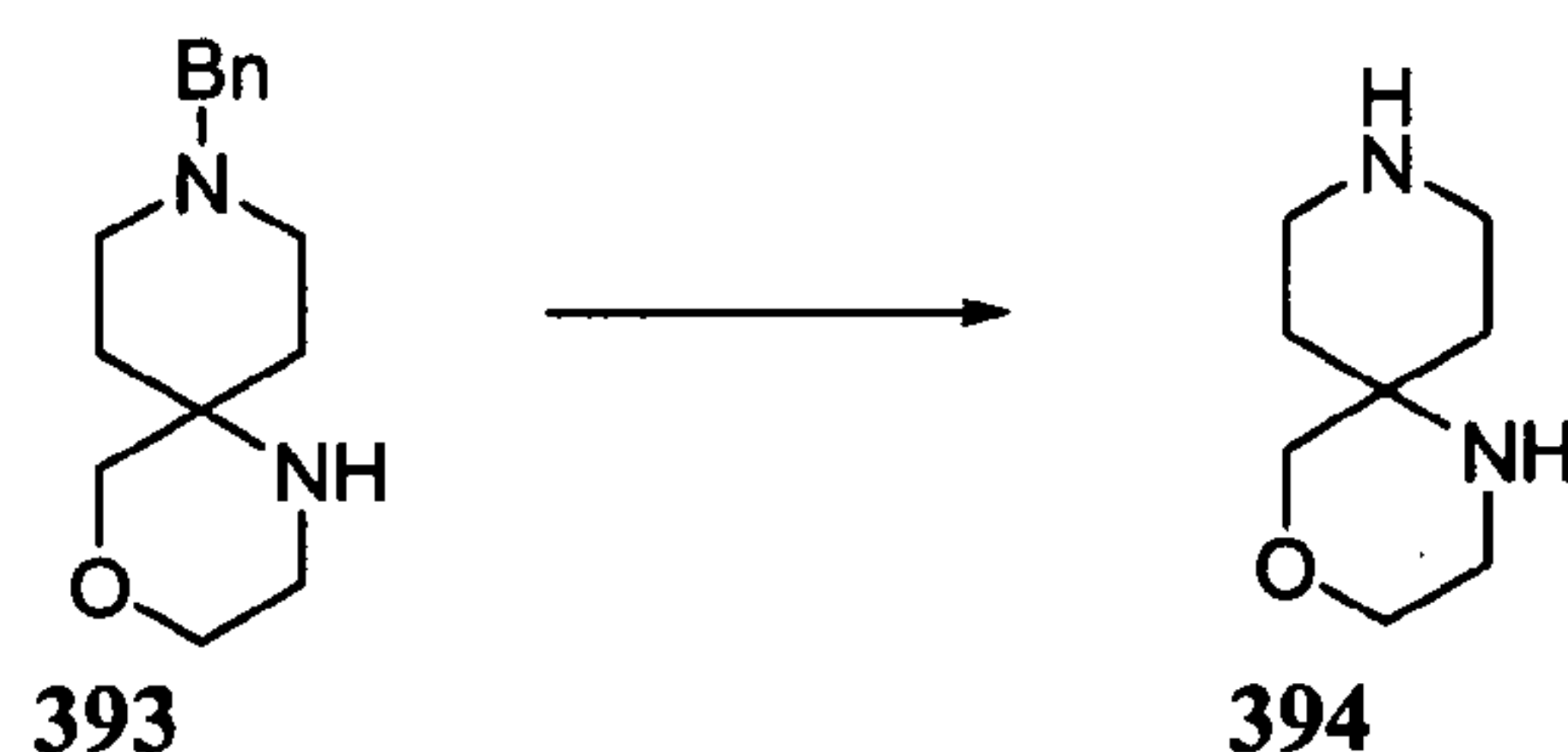
**9-(phenylmethyl)-4-oxa-1,9-diazaspiro[5.5]undecan-2-one (392):** Triethylamine (2 mL 14 mmol) was added to a DCM (50 mL) solution containing chloroacetyl chloride (1 mL, 14 mmol) and compound **391** (3 g, 14 mmol). The resulting mixture was stirred 2h at 23 °C. The solvent was stripped and THF was added followed by potassium tert-butoxide (5 g, 41 mmol). The resulting solution was stirred overnight at room temperature. The reaction was



then concentrated to dryness and the resulting residue was washed with 200 mL of absolute ethanol. The ethanolic solution was then concentrated to give 3.16 g of 9-(phenylmethyl)-4-oxa-1,9-diazaspiro[5.5]undecan-2-one. The material was used in the next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 261, Calculated 261.

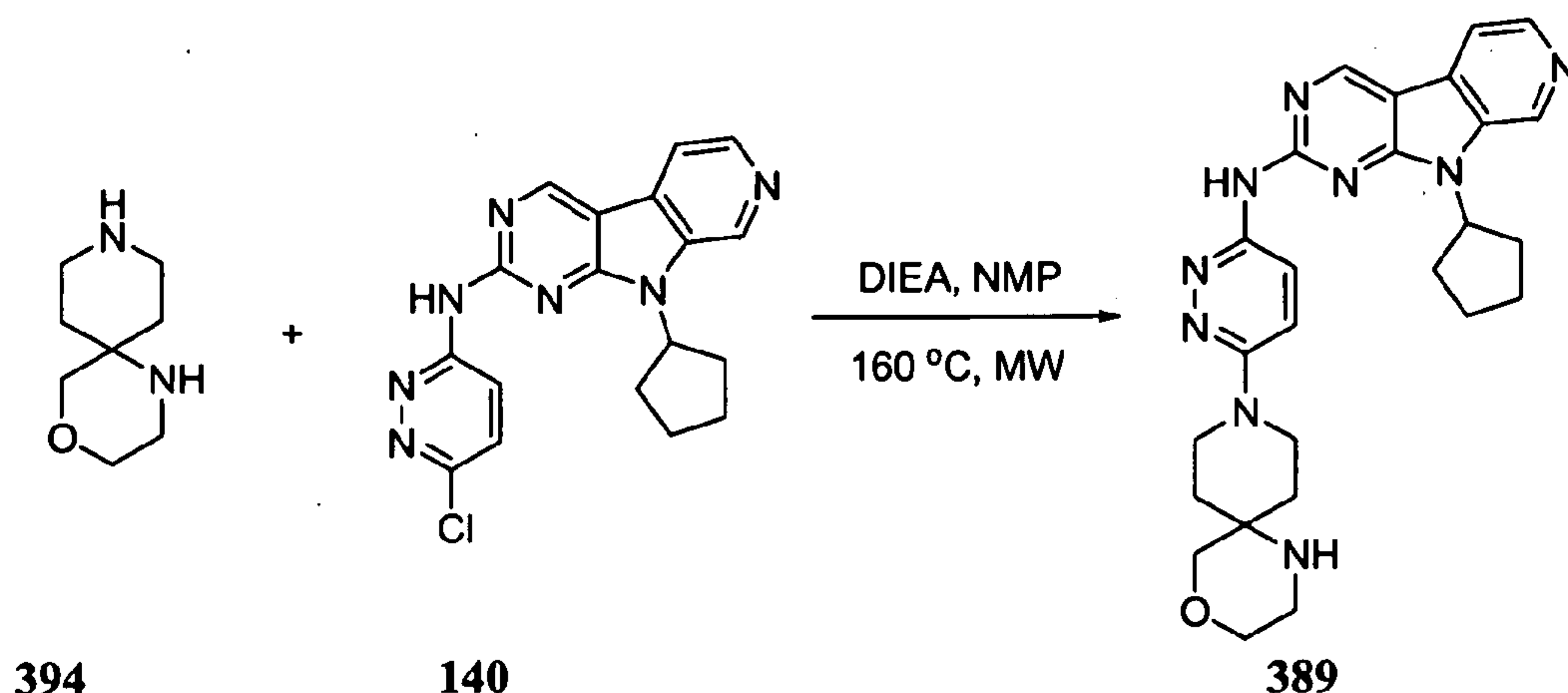


**9-(phenylmethyl)-4-oxa-1,9-diazaspiro[5.5]undecane (393):** LAH (2.00 g, 52.7 mmol) was added to a THF (100 mL) solution containing 9-(phenylmethyl)-4-oxa-1,9-diazaspiro[5.5]undecan-2-one (3.1893 g, 12.3 mmol). The resulting mixture was stirred 1 h at reflux. The reaction was then cooled to room temperature and the following additions were made slowly: 2 mL of water followed by 2 mL of 1 N NaOH, and finally 4 mL of water. The mixture was then filtered and concentrated to give a thick clear oil (2.66g, 88% yield). The material was used in the next step without further purification. LCMS-ESI (POS), M/Z, M+1: Found 247, Calculated 247.



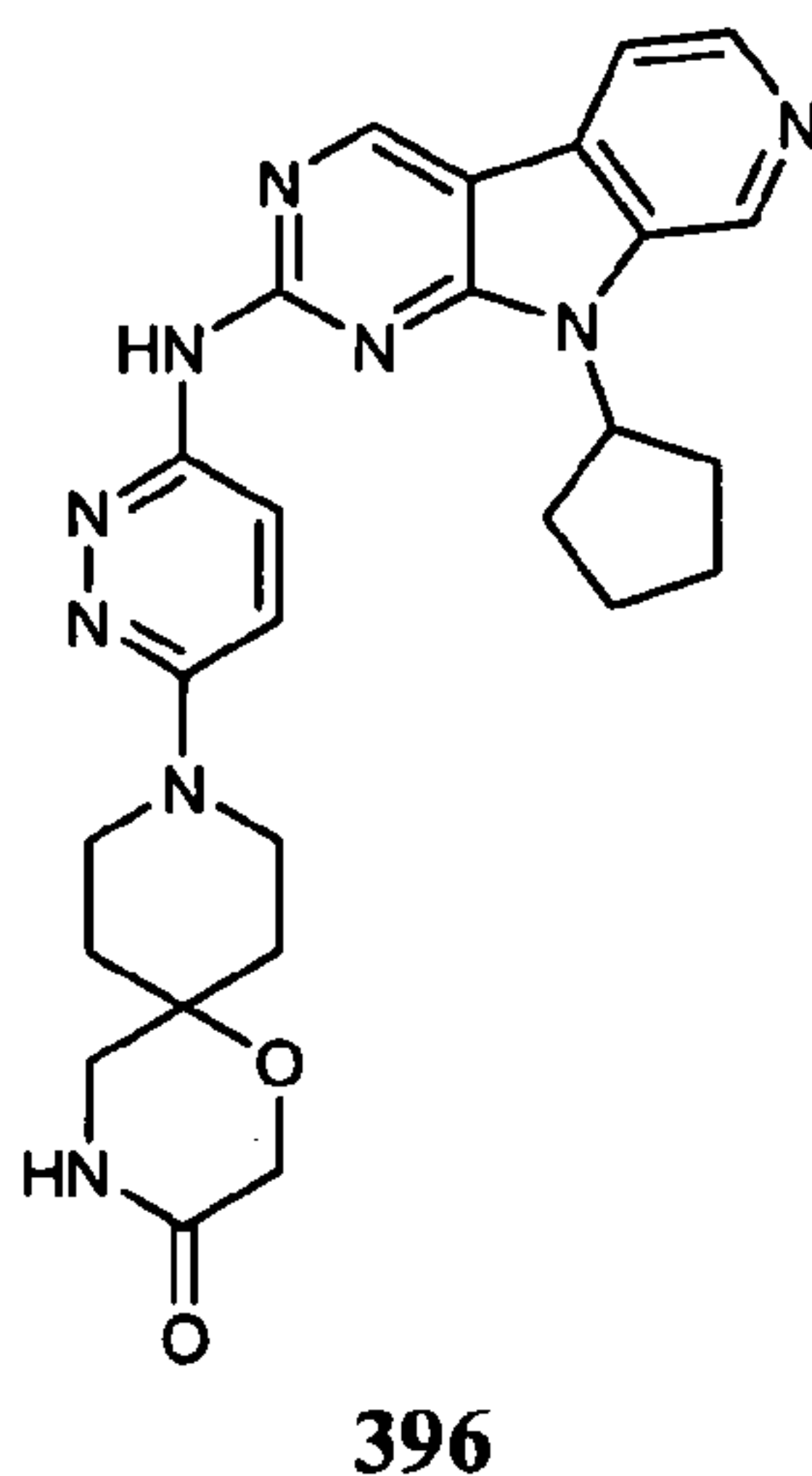
**4-oxa-1,9-diazaspiro[5.5]undecane (395):** Pearlman's Catalyst (28.5 mg, 203  $\mu\text{mol}$ ) was added to an ethanolic (40 mL) solution containing compound 393 (500 mg, 2030  $\mu\text{mol}$ ). The resulting mixture was placed under an atmosphere of hydrogen and stirred overnight at 100 °C (bath temperature). Next, the reaction was cooled to room temperature, filtered, and concentrated to give compound 394 (301 mg, 95% yield). The material was used without further purification. LCMS-ESI (POS), M/Z, M+1: Found 157, Calculated 157.





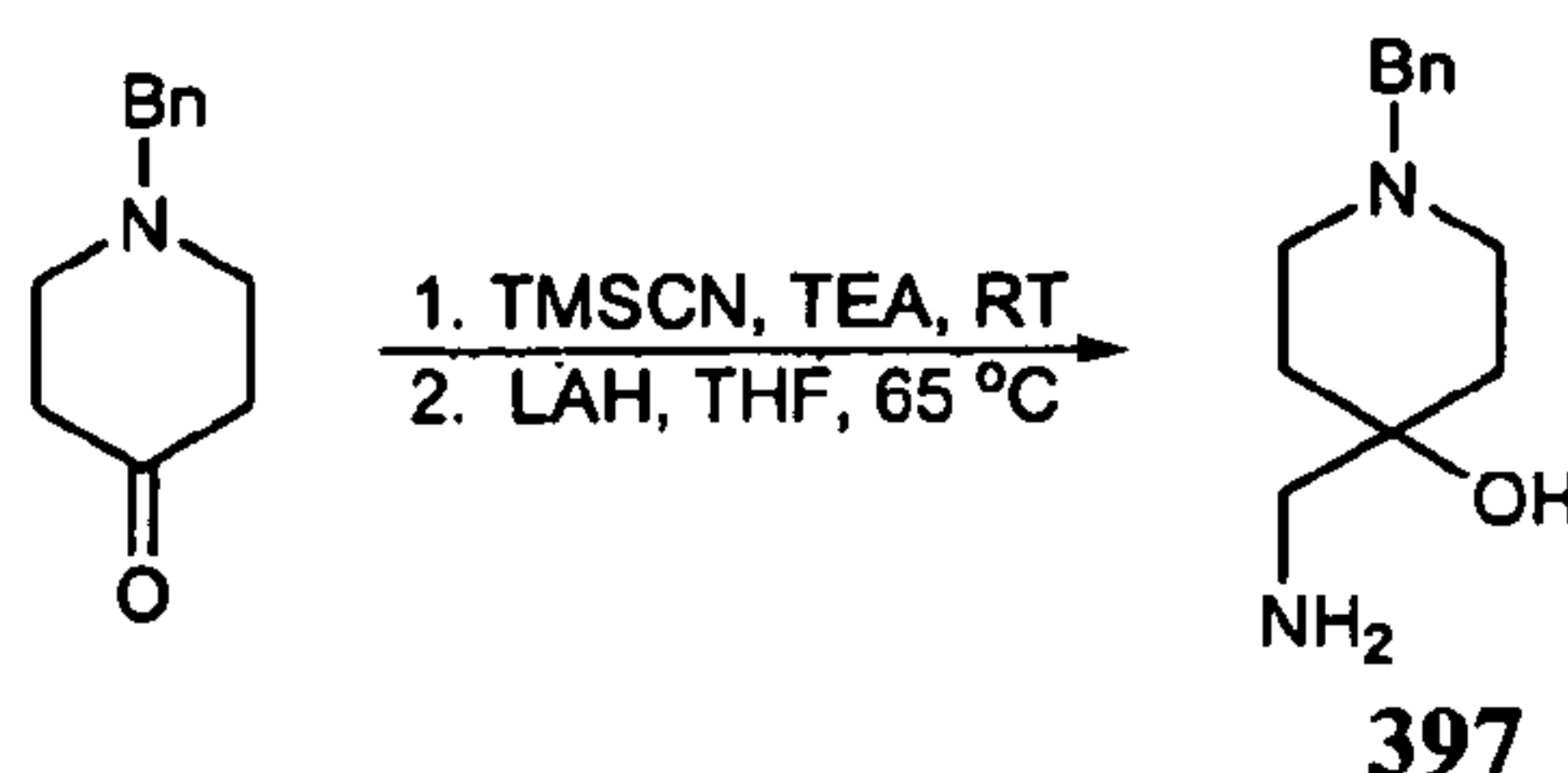
**9-cyclopentyl-N-(6-(4-oxa-1,9-diazaspiro[5.5]undec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (389):** Compound **394** (30 mg, 191  $\mu$ mol) was added to an NMP (4 mL) solution containing compound **140** (70 mg, 191  $\mu$ mol) and N,N-diisopropyl-ethylamine (74 mg, 574  $\mu$ mol). The resulting mixture was heated in a microwave for 12 h at 165 °C. After cooling, the mixture was purified on the reverse phase HPLC (10-50% acetonitrile Method). Desired fractions were pooled and lyophilized to give compound **389** (10 mg, 11% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ , TFA salt)  $\delta$  ppm 1.81 - 2.07 (m, 4 H) 2.10 - 2.38 (m, 6 H) 2.52 (m, 2 H) 3.37 - 3.42 (m, 3 H) 3.42 - 3.54 (m, 2 H) 3.91 - 4.03 (m, 3 H) 4.11 - 4.28 (m, 2 H) 5.49 (qn,  $J=8.80$  Hz, 1 H) 7.97 (d,  $J=9.98$  Hz, 1 H) 8.09 (d,  $J=9.98$  Hz, 1 H) 8.58 - 8.63 (m, 1 H) 8.62 - 8.68 (m, 1 H) 9.30 (s, 1 H) 9.63 (s, 1 H); LCMS-ESI (POS), M/Z, M+1: Found 486, Calculated 486.

#### EXAMPLE 250

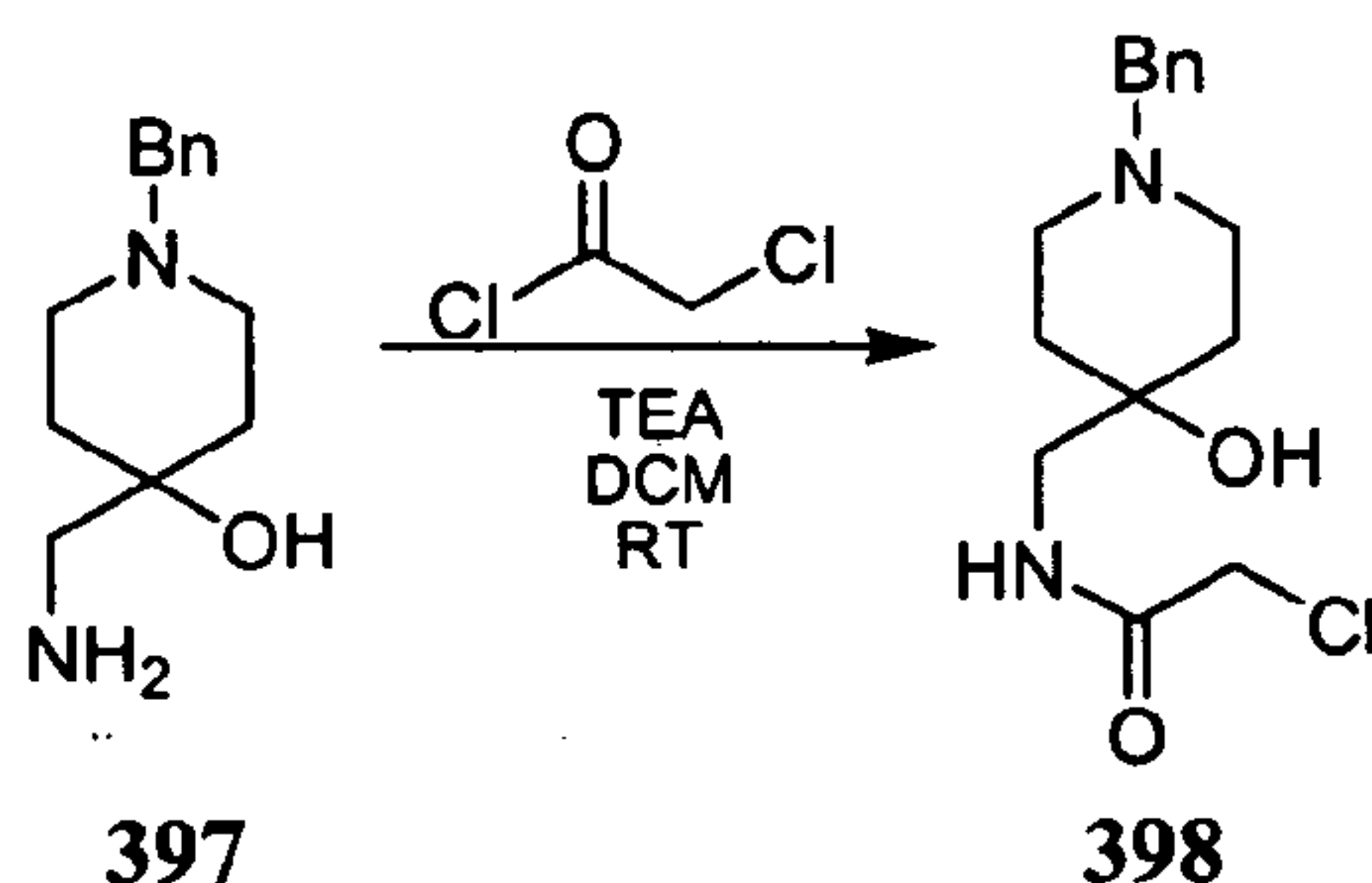


**9-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-oxa-4,9-diazaspiro[5.5]undecan-3-one**



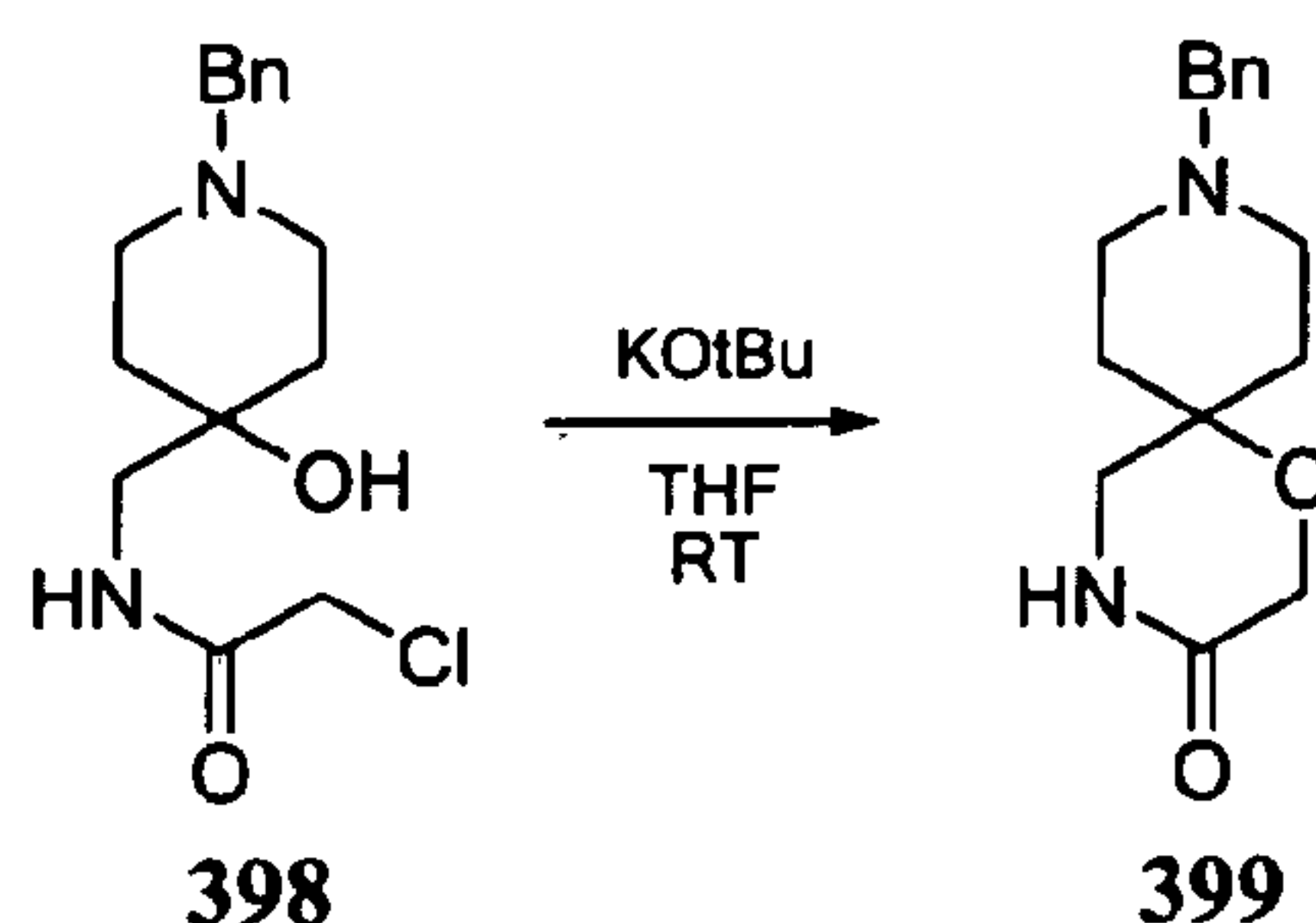


**4-(aminomethyl)-1-benzylpiperidin-4-ol (397):** To a pre-cooled solution (20 °C) of 1-benzyl-4-piperidone (35.0 mL, 196 mmol) and triethylamine (5.5 mL, 40 mmol) was added trimethylsilylcyanide (32.0 mL, 240 mmol), portionwise over 10 minutes. Once the addition was complete, the reaction mixture was stirred at room temperature for 3 hours. This reaction mixture was then cautiously added (10 mL portions over 12 minutes) to a stirring mixture of lithium aluminum hydride (8.5 g, 224 mmol) in tetrahydrofuran (420 mL). Once the addition was complete the reaction mixture was refluxed for 1.5 hours. After cooling to room temperature, the reaction was quenched with water (8.5 mL), followed by 1N NaOH (8.5 mL), and then water (2 x 8.5 mL). The resulting mixture was allowed to stir at room temperature overnight. The solids were filtered off and rinsed with DCM and ethanol. The filtrate was concentrated down to a solid and then purified by flash chromatography (0-20% methanol in DCM with 1% NH<sub>4</sub>OH) to give compound **397** as a yellow solid (39.7 g, 92%). LCMS-ESI (POS), M/Z, M+1: Found 221.2, Calculated 221.2.

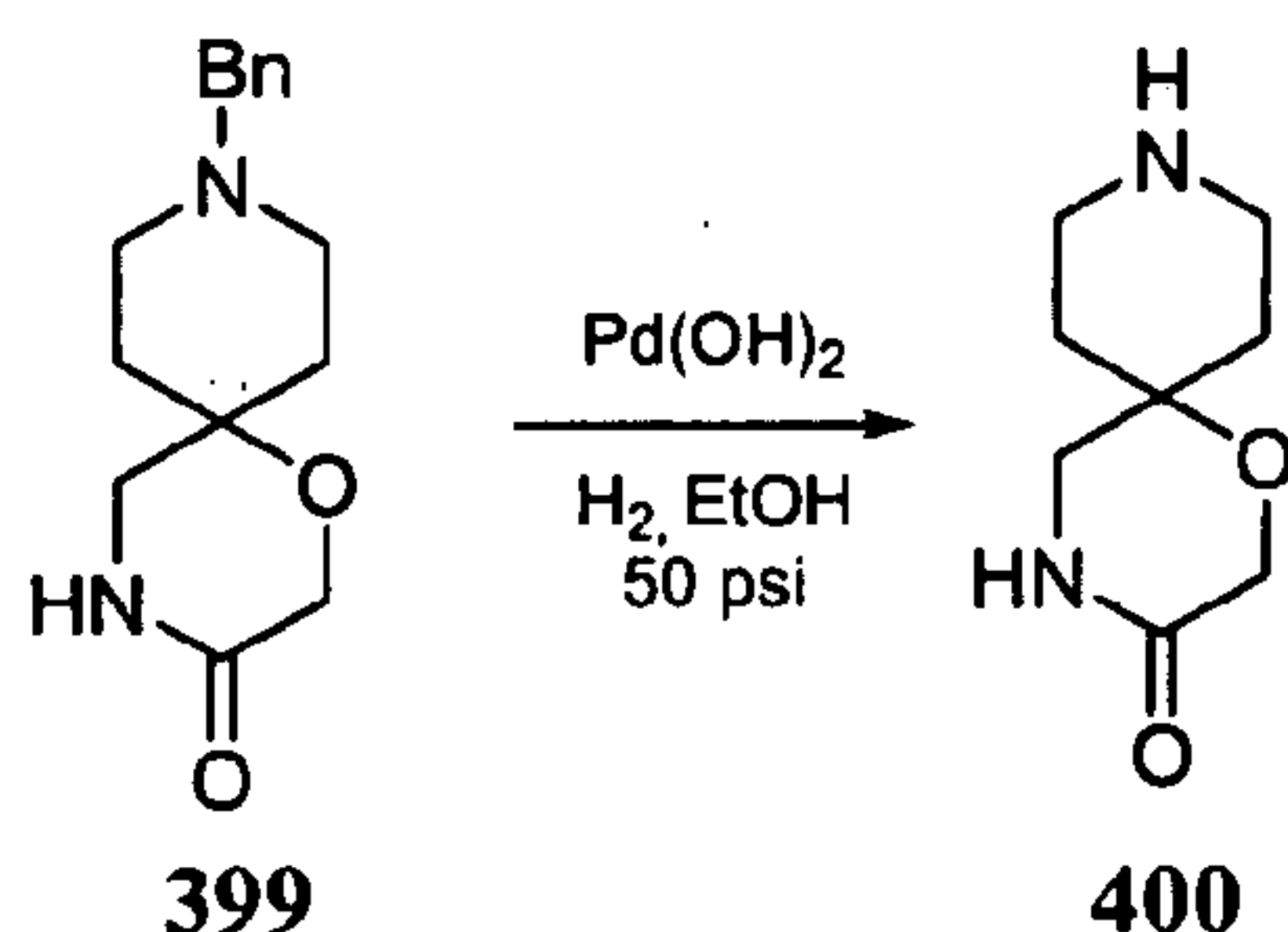


**N-((1-benzyl-4-hydroxypiperidin-4-yl)methyl)-2-chloroacetamide (398):** To a solution of compound **397** (39.7 g, 180 mmol) in dichloromethane (350 mL) was added triethylamine (50.0 mL, 359 mmol), followed by dropwise addition of chloroacetyl chloride (16.5 mL, 207 mmol) over 15 minutes. The resulting solution was stirred at room temperature for 1.25 hours. The crude mixture was diluted with DCM and water, and extracted with DCM twice. The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give compound **398** (41.9 g, 78%). LCMS-ESI (POS), M/Z, M+1: Found 297.1, Calculated 297.1.



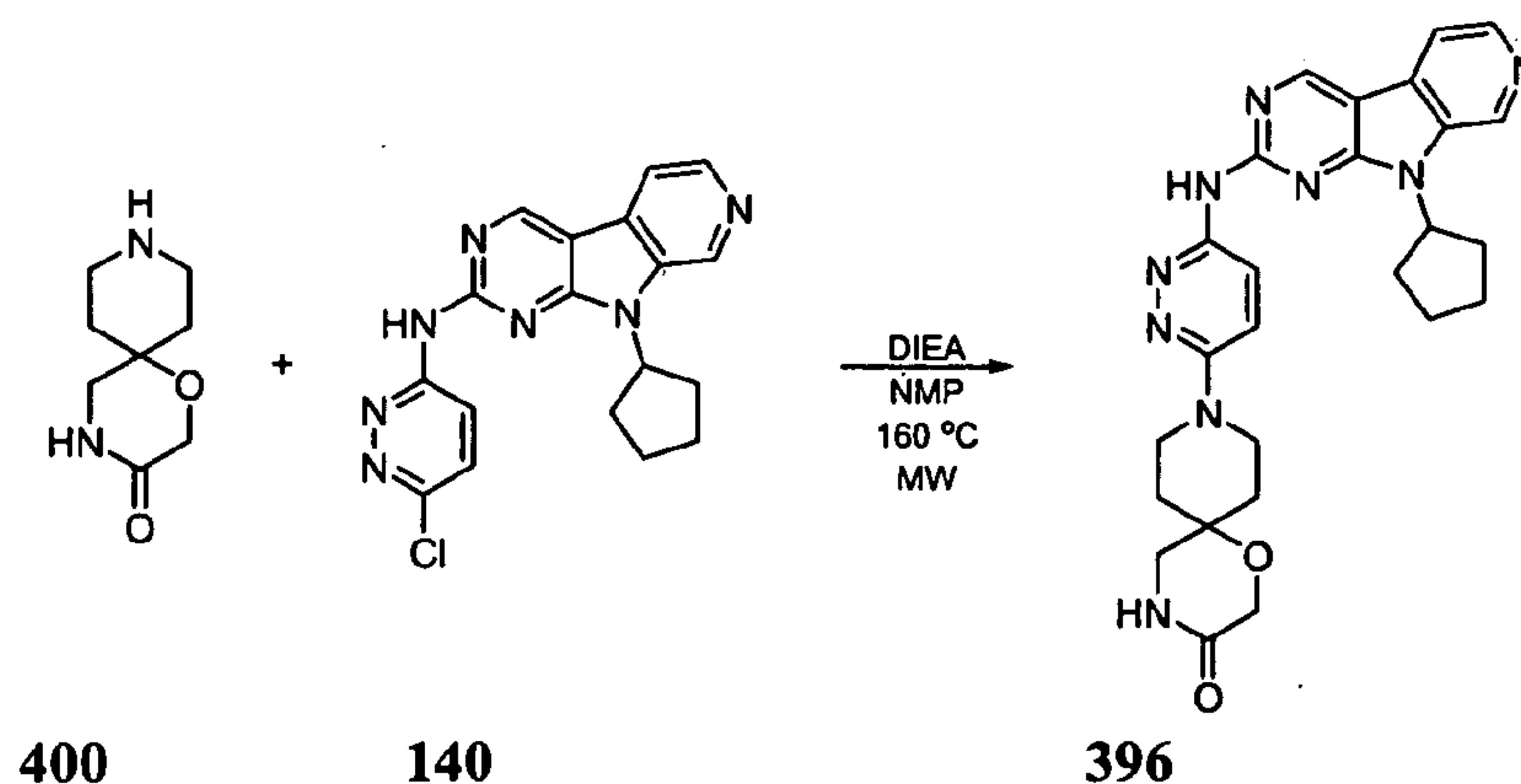


**9-benzyl-1-oxa-4,9-diazaspiro[5.5]undecan-3-one (399):** To a mixture of compound **398** (41.9 g, 141 mmol) in tetrahydrofuran (300 mL) was added potassium tert-butoxide (31.8 g, 283 mmol), portionwise over 40 minutes. After 3.5 hours of stirring at room temperature, the reaction was concentrated in vacuo. The residue was diluted with DCM and water, and then neutralized with 3N HCl. The remaining solids were filtered off and the filtrate was concentrated to an oil. The residue was taken up in hot ethanol (100 mL). After allowing the solution to cool to ~45 °C, the salts were filtered off, and the filtrate was concentrated to a brown solid. The crude material was purified by flash chromatography (0-20% methanol in DCM with 1% NH<sub>4</sub>OH) to give compound **399** as an orange solid (22.8 g, 62%). LCMS-ESI (POS), M/Z, M+1: Found 261.1, Calculated 261.1.



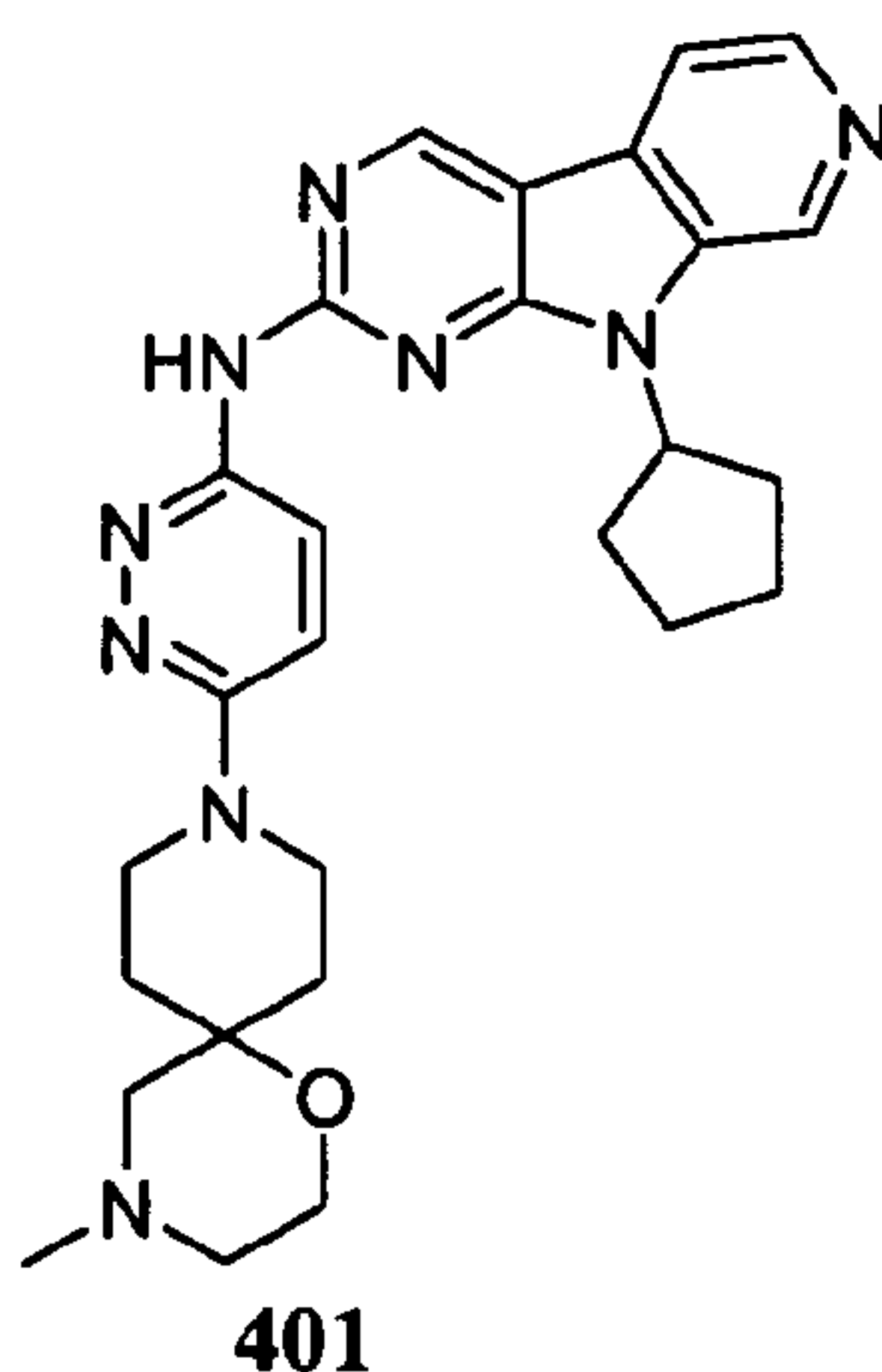
**1-oxa-4,9-diazaspiro[5.5]undecan-3-one (400):** To a solution of compound **399** (316.1 mg, 1214 μmol) in ethanol (15 mL) was added palladium hydroxide, 20 wt % pd (dry basis) on carbon, wet (300 mg, 427 μmol). After hydrogenating the reaction mixture at 50 psi for 6 days, the mixture was filtered thru a plug of celite and concentrated in vacuo to give compound **400** (287.0 mg). LCMS-ESI (POS), M/Z, M+1: Found 171.1, Calculated 171.1.





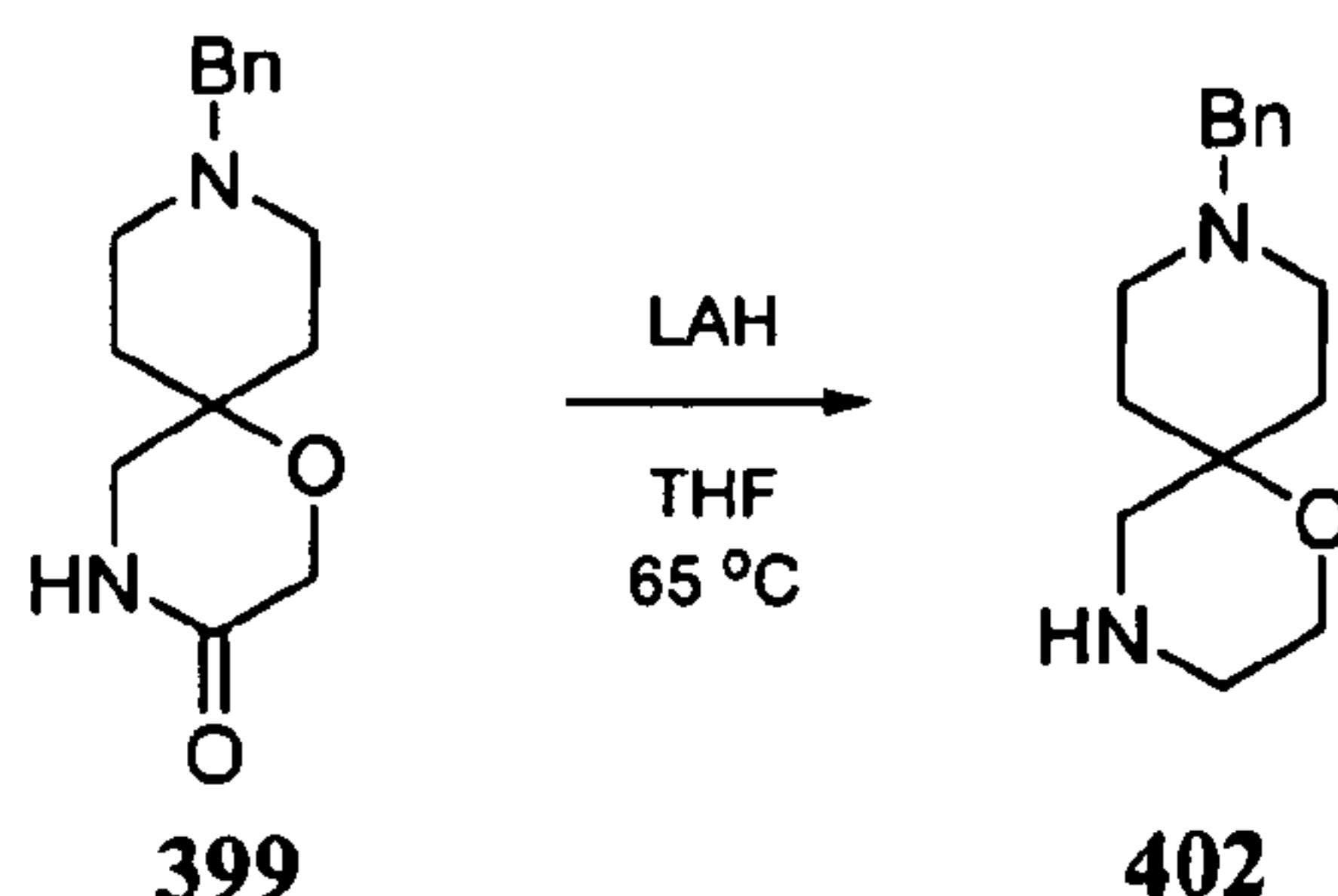
**9-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-1-oxa-4,9-diazaspiro[5.5]undecan-3-one (396):** To a mixture of compound 400 (110.0 mg, 646  $\mu$ mol) and compound 140 (40.0 mg, 109  $\mu$ mol) in N-methylpyrrolidinone (1.50 mL) was added N,N-diisopropylethylamine (DIEA) (0.100 mL, 575  $\mu$ mol). The resulting mixture was heated at 160  $^{\circ}$ C under microwave irradiation for 6 h. The crude material was purified by reverse phase HPLC (acetonitrile/H<sub>2</sub>O containing 0.1% TFA each, 25 min from 10 to 40%). The isolated material was further purified by prep-TLC (10% methanol in DCM with 1% NH<sub>4</sub>OH) to give compound 396 as a yellow solid (2.5 mg, 5%). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  9.21 (s, 1 H) 8.91 (s, 1 H) 8.37 - 8.46 (m, 2 H) 8.08 (d,  $J$ =5.38 Hz, 1 H) 7.46 (d,  $J$ =10.03 Hz, 1 H) 5.43 (quin, 1 H) 4.21 (s, 2 H) 4.06 (ddd,  $J$ =13.27, 3.48, 3.30 Hz, 2 H) 3.37 - 3.42 (m, 4 H) 2.44 (dd,  $J$ =12.96, 8.31 Hz, 2 H) 2.08 - 2.24 (m, 4 H) 2.03 (d,  $J$ =13.45 Hz, 2 H) 1.84 - 1.93 (m, 2 H) 1.74 - 1.83 (m, 2 H) ppm; LCMS-ESI (POS), M/Z, M+1: Found 500.2, Calculated 500.2.

#### EXAMPLE 251

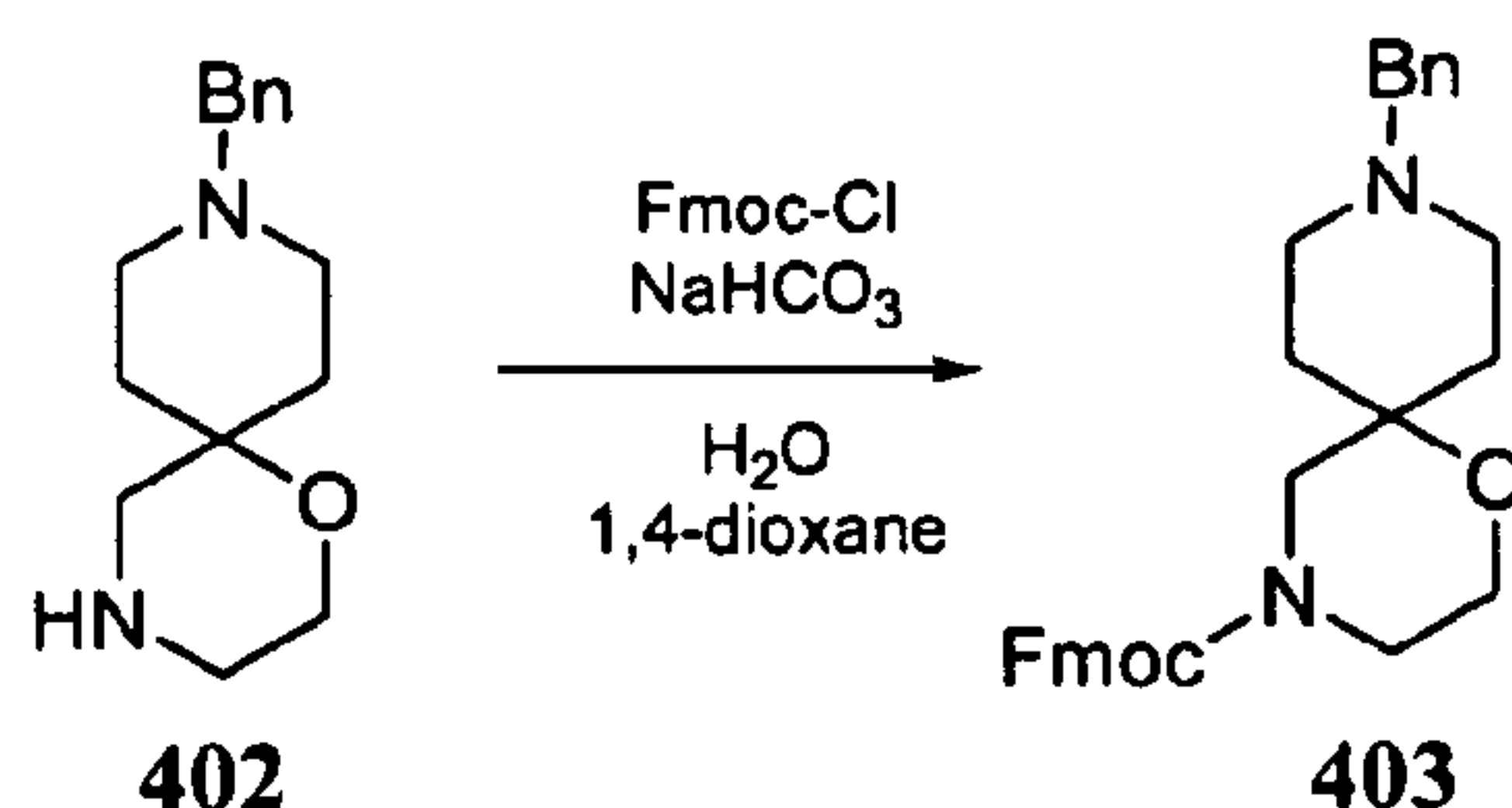


**9-cyclopentyl-N-(6-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

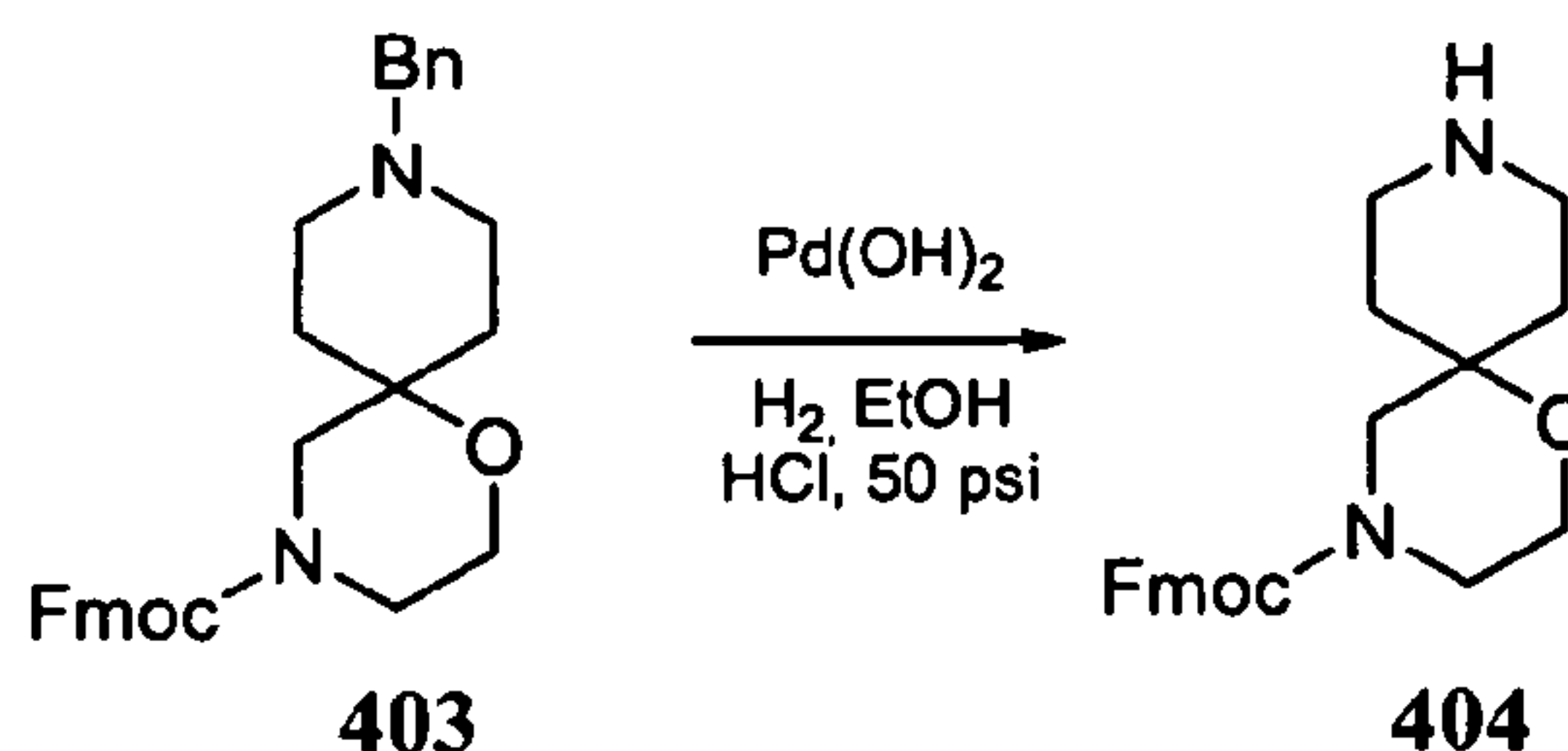




**9-benzyl-1-oxa-4,9-diazaspiro[5.5]undecane (402):** To a stirring mixture of lithium aluminum hydride (2.22 g, 58.5 mmol) in tetrahydrofuran (70 mL) was added compound **399** (3.60 g, 13.8 mmol), portionwise over three minutes. After 1.25 hours of reflux the reaction was cooled to room temperature and quenched with water (2.22 mL), then 1N NaOH (2.22 mL), then water (2 x 2.22 mL). The remaining solids were filtered off, and the filtrate was concentrated to give compound **402** (2.81 g, 82%). LCMS-ESI (POS), M/Z, M+1: Found 247.1, Calculated 247.2.



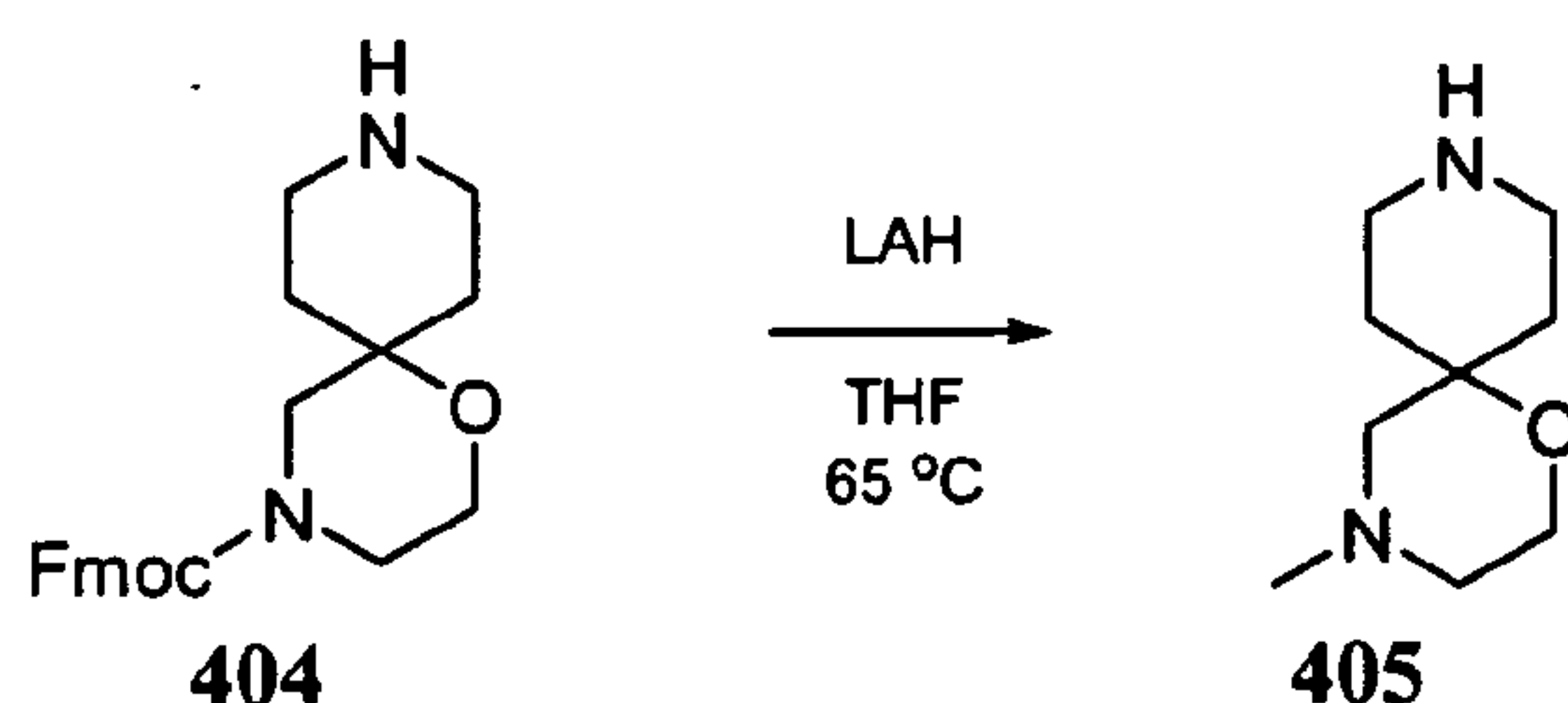
**9H-fluoren-9-ylmethyl-9-(phenylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (403):** To a solution of compound **402** (2.81 g, 11.4 mmol) in 1,4-dioxane (53 mL) was added 10% sodium bicarbonate in water (21.5 mL) followed by 9-fluorenylmethyl chloroformate (2.96 g, 11.4 mmol). The resulting mixture was stirred at room temperature for four hours, and then neutralized with 3N HCl. The solution was concentrated to a solid and then purified by flash chromatography (0-10% methanol in DCM with 1% NH<sub>4</sub>OH) to give compound **403** as a white solid (1.2 g, 22.5%). LCMS-ESI (POS), M/Z, M+1: Found 469.1, Calculated 469.2.



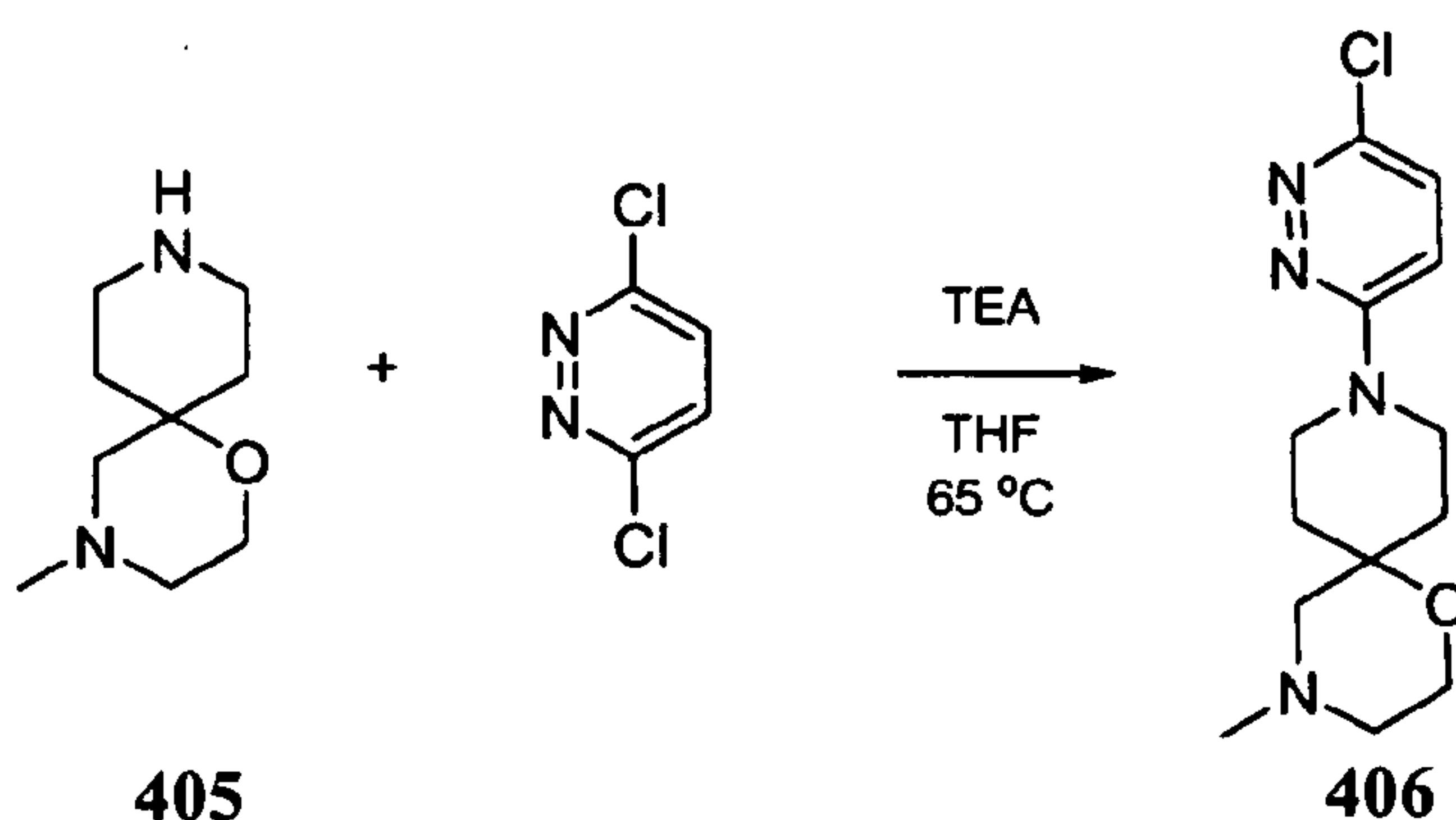
**9H-fluoren-9-ylmethyl-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate(404):** To a solution of compound **403** (1.43 g, 3.05 mmol) in ethanol (27 mL) was added palladium



hydroxide, 20 wt % pd (dry basis) on carbon, wet (1.51 g, 2.15 mmol), followed by hydrochloric acid (0.10 mL). The sealed glass tube was then evacuated and purged with hydrogen three times. The sealed tube was then charged with hydrogen (50 psi), and allowed to stir at room temperature for three days. HPLC showed ~85% conversion to the desired product. After filtering the mixture through a plug of celite, the filtrate was concentrated to a solid and purified by flash chromatography (0-20% methanol in DCM with 1% NH<sub>4</sub>OH) to give compound **404** (709 mg, 61%) as a white solid. LCMS-ESI (POS), M/Z, M+1: Found 379.1, Calculated 379.2.

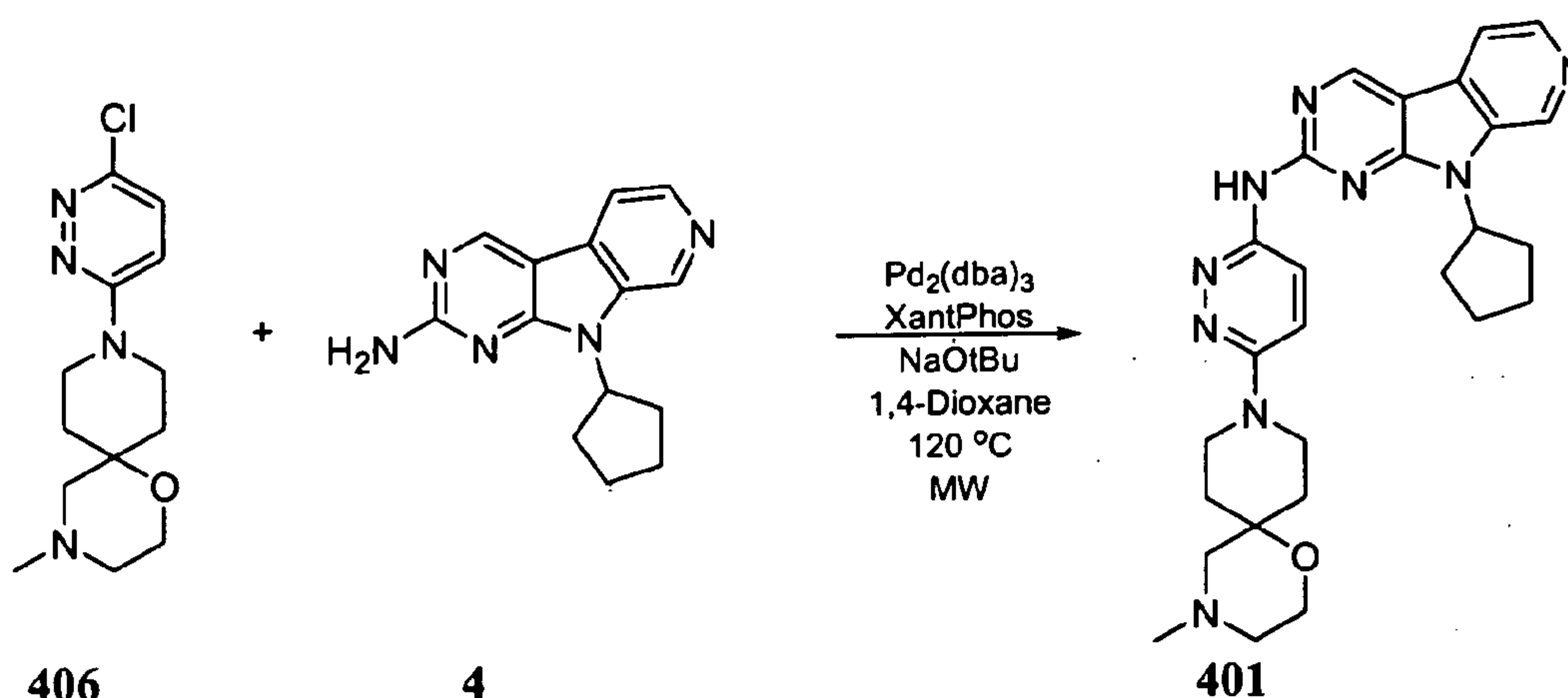


**4-methyl-1-oxa-4,9-diazaspiro[5.5]undecane (405):** To a mixture of compound **404** (586.4 mg, 1.545 mmol) in tetrahydrofuran (20 mL) was added lithium aluminum hydride (240.5 mg, 6.34 mmol). After 1.5 hours at reflux the reaction was cooled to room temperature and quenched with water (240.5  $\mu$ L), followed by 1N NaOH (240.5  $\mu$ L), and then water (2 x 240.5  $\mu$ L). The remaining solids were filtered off, and the filtrate was concentrated to give compound **405** (406 mg), as a sticky white solid. LCMS-ESI (POS), M/Z, M+1: Found 171.1, Calculated 171.1.



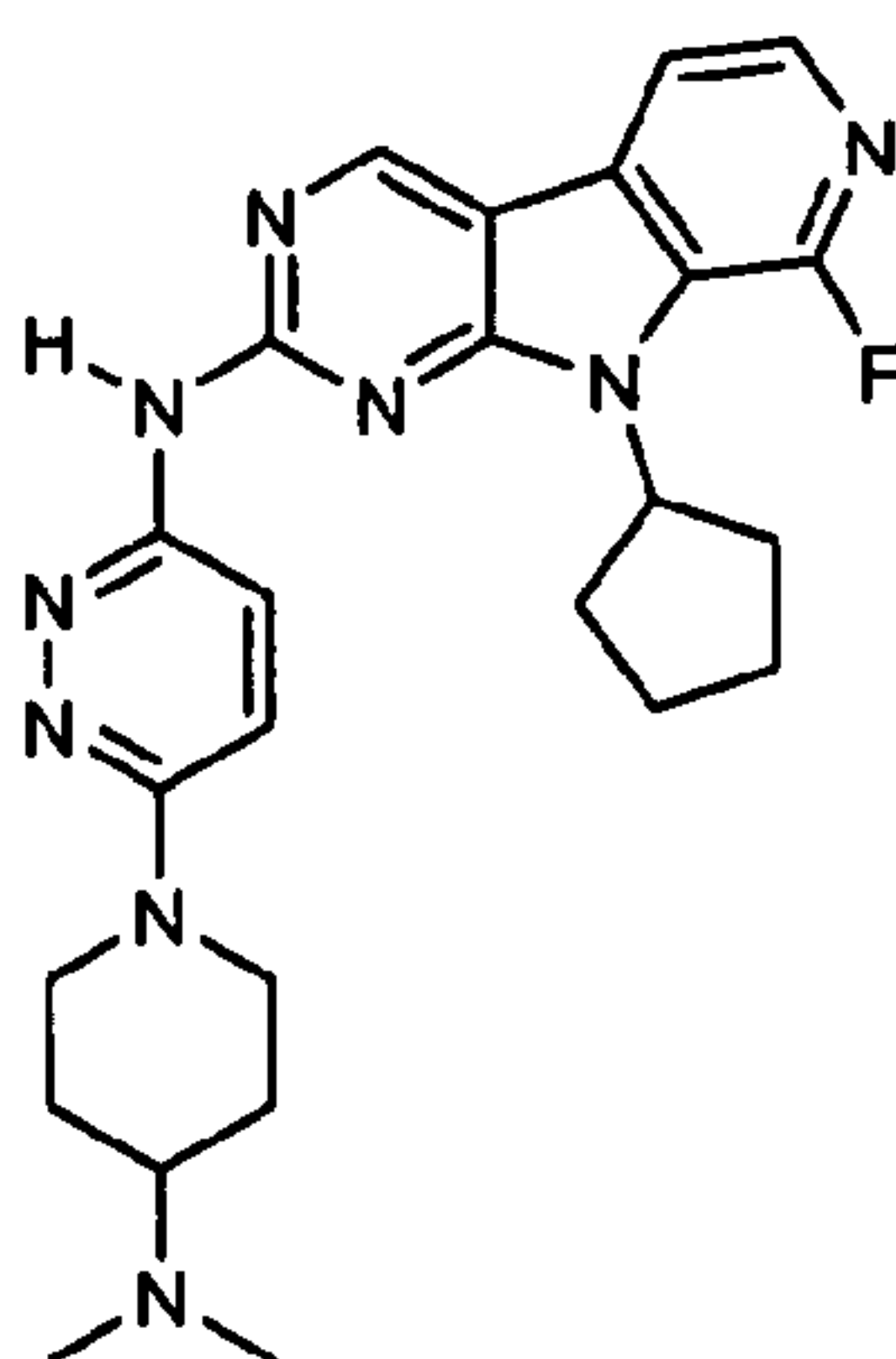
**9-(6-chloro-3-pyridazinyl)-4-methyl-1-oxa-4,9-diazaspiro[5.5]undecane (406):** To a solution of compound **405** (406.0 mg, 2.39 mmol) in tetrahydrofuran (17 mL) was added 3,6-dichloropyridazine (361.7 mg, 2.43 mmol), followed by triethylamine (0.680 mL, 4.89 mmol). The resulting solution was stirred at reflux for 38 hours. The reaction mixture was then concentrated and the residue was purified by reverse phase HPLC (acetonitrile/H<sub>2</sub>O containing 0.1% TFA each, 25 min from 10 to 40%) to give compound **406** as a sticky yellow solid (303 mg, 45%). LCMS-ESI (POS), M/Z, M+1: Found 283.1, Calculated 283.1.





**9-cyclopentyl-N-(6-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undec-9-yl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (401):** To a solution of compound 4 (53.2 mg, 0.210 mmol) in 1,4-dioxane (3 mL) were added compound 406 (61.3 mg, 0.22 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (32.0 mg, 55.3  $\mu\text{mol}$ ), tris(dibenzylideneacetone)dipalladium (o) (30.9 mg, 33.7  $\mu\text{mol}$ ), and sodium *tert*-butoxide (103.9 mg, 1.08 mmol). After purging with argon for 3 minutes, the reaction mixture was heated at 120 °C under microwave irradiation for 1.5 h. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC (acetonitrile/ $\text{H}_2\text{O}$  containing 0.1% TFA each, 25 min from 10 to 30%) to give compound 401 as a TFA salt (26.7 mg, 15%).  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.67 (s, 1 H) 9.35 (s, 1 H) 8.67 (br. s., 2 H) 7.99 - 8.14 (m, 2 H) 5.48 (quin, 1 H) 4.09 - 4.21 (m, 2 H) 3.94 - 4.07 (m, 2 H) 3.34 - 3.63 (m, 2 H) 2.93 (s, 3 H) 2.42 - 2.62 (m, 4 H) 2.11 - 2.33 (m, 6 H) 1.59 - 1.99 (m, 6 H) ppm; LCMS-ESI (POS),  $M/Z$ ,  $M+1$ : Found 500.4, Calculated 500.3.

#### EXAMPLE 252



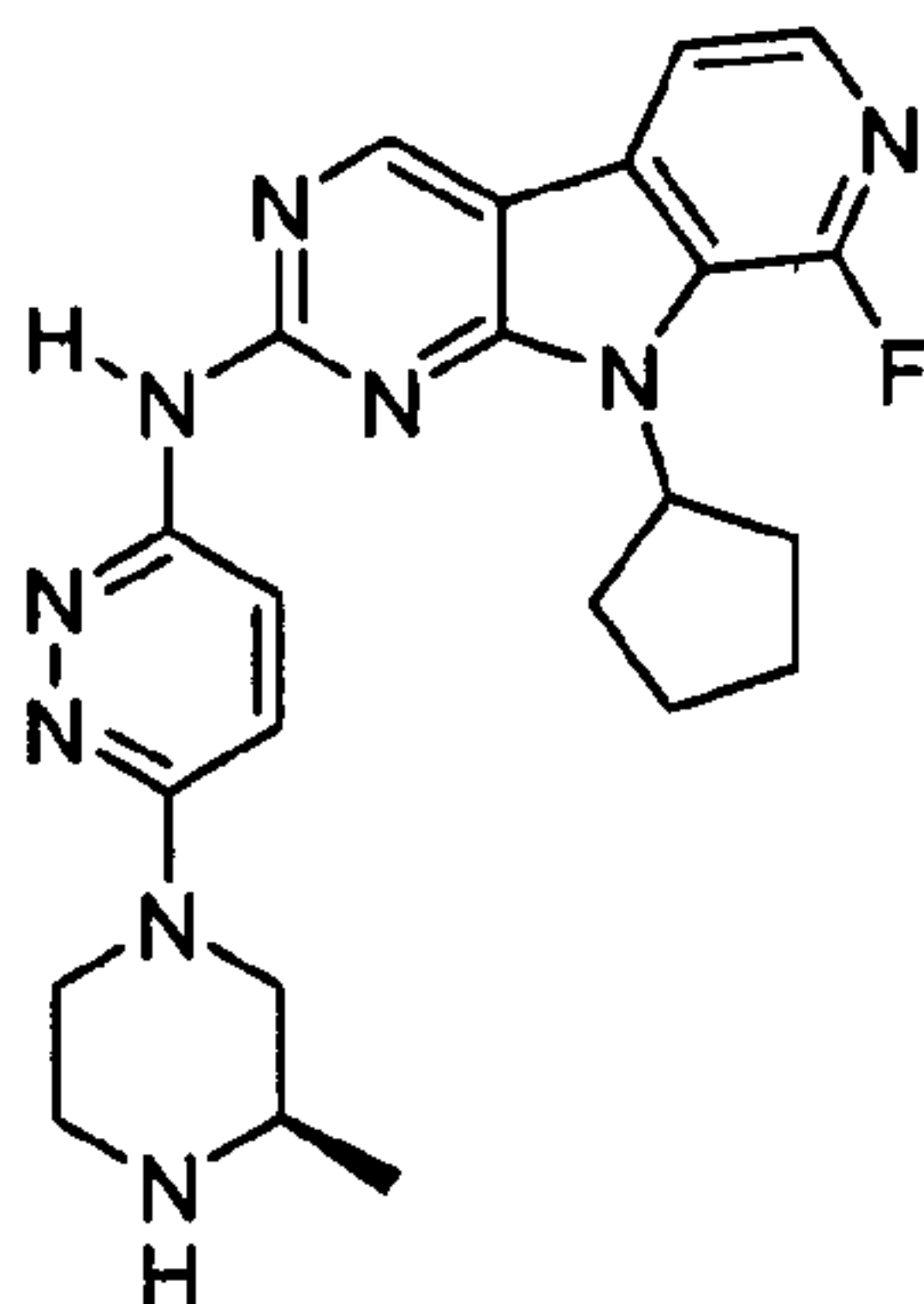
407

**9-Cyclopentyl-N-(6-(4-(dimethylamino)-1-piperidinyl)-3-pyridazinyl)-8-fluoro-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



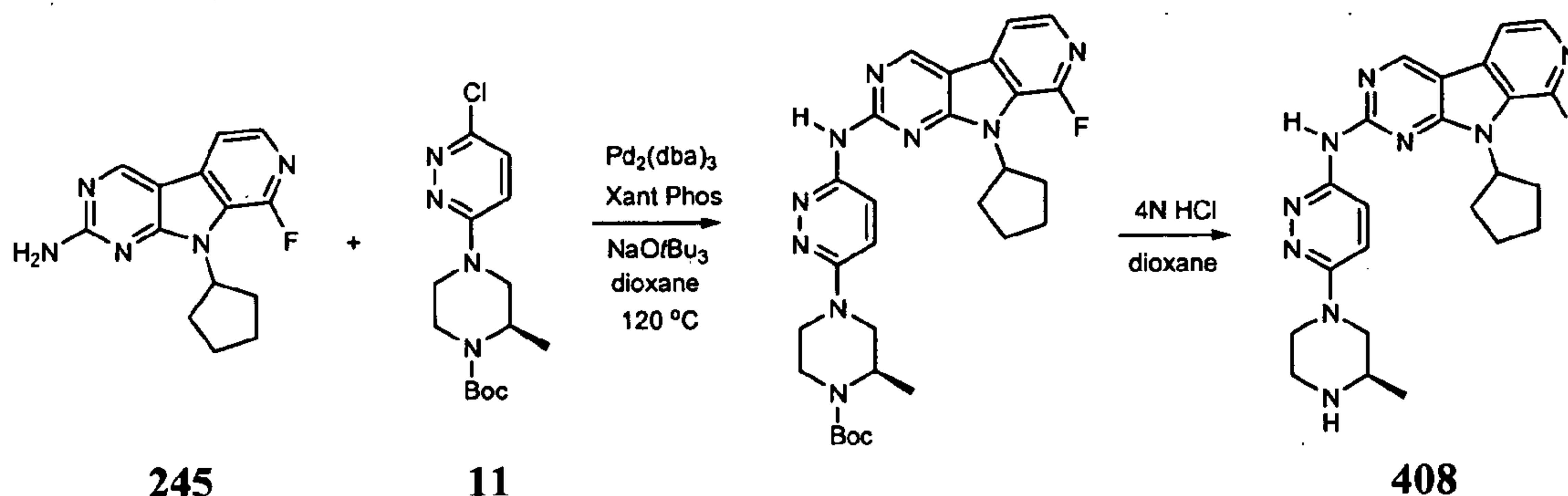
Compound **407** was prepared from compound **245** using chemistry similar to that described in example 4. The yield is 45%. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.47 (1 H, s), 8.11 (2 H, s), 8.08 (1 H, d, *J*=10.0 Hz) 7.88 (1 H, d, *J*=10.0 Hz), 5.65 (1 H, t, *J*=9.0 Hz), 4.54 - 4.58 (2 H, m), 3.60 (1 H, m), 3.17 (2 H, ddd, *J*=14.5, 12.5, 1.8 Hz), 2.44 (2 H, m), 2.10 - 2.33 (6 H, m), 1.71 - 1.95 (4 H, m); LCMS-ESI (POS), *M/Z*, *M*+1: Found 476.2, Calculated 476.3

### EXAMPLE 253



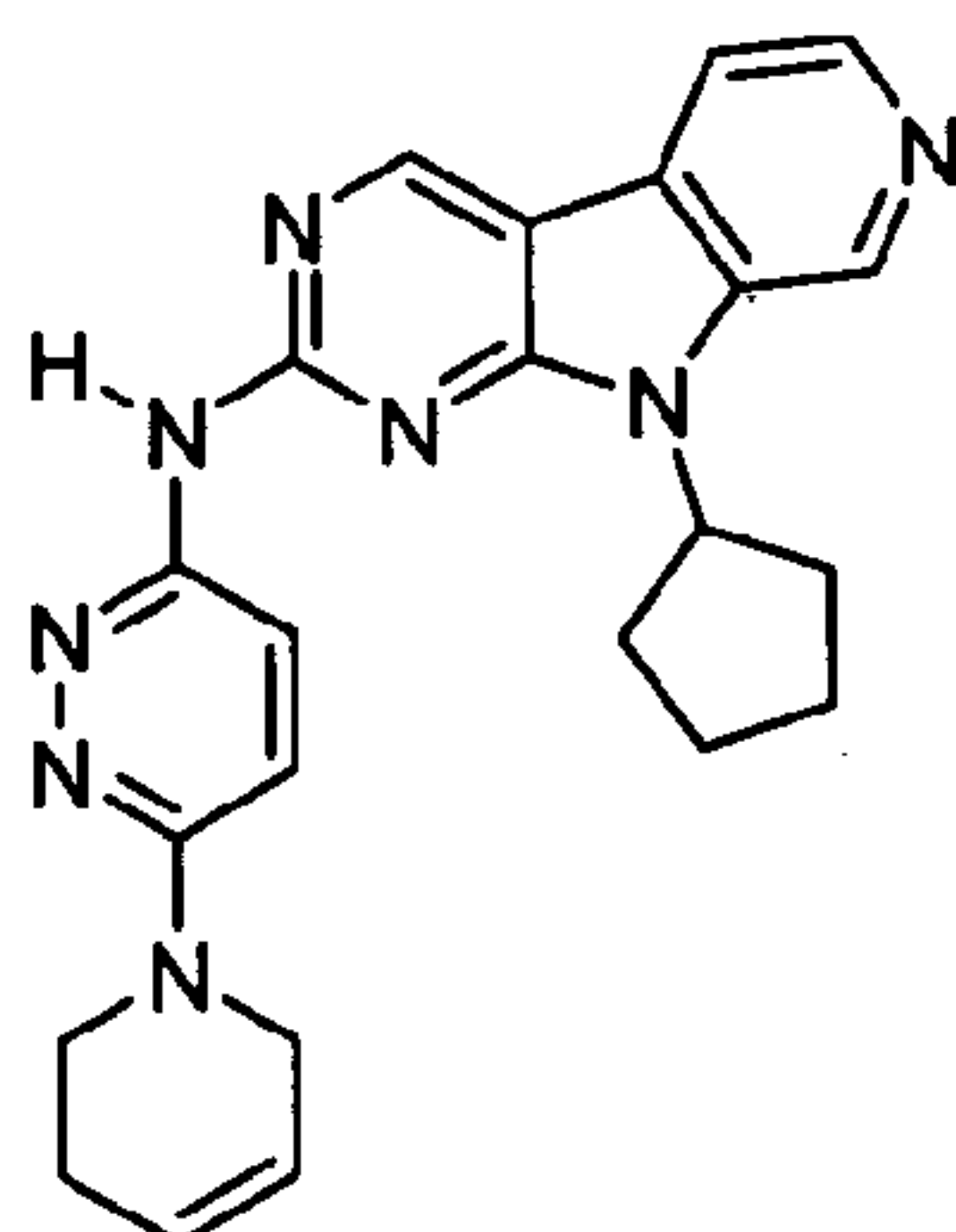
**408**

**9-Cyclopentyl-8-fluoro-N-(6-((3R)-3-methyl-1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

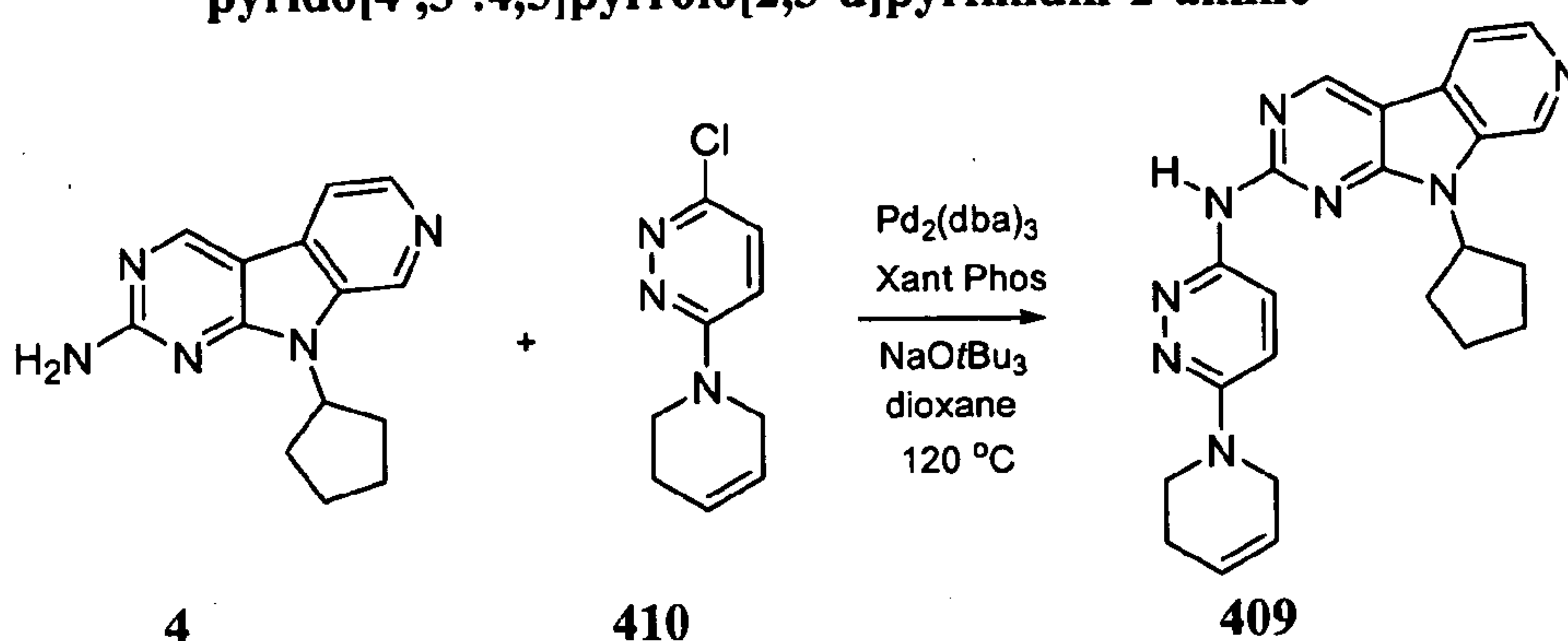


**9-Cyclopentyl-8-fluoro-N-(6-((3R)-3-methyl-1-piperazinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (408):** Compound **408** was prepared from compound **245** and compound **11** using chemistry similar to that described in example 4. The two step yield is 12%. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.48 (1 H, s), 8.10 - 8.14 (2 H, m), 8.00 (1 H, d, *J*=10 Hz), 8.05 (1 H, d, *J*=10 Hz), 5.66 (1 H, t, *J*=9.0 Hz), 4.43 - 4.49 (2 H, m), 3.52 - 3.62 (2 H, m), 3.29 - 3.48 (2 H, m), 3.20 (1 H, dd, *J*=14.4, 10.8 Hz), 2.45 (2 H, ddd, *J*=9.2, 7.0, 4.5 Hz), 2.13 - 2.27 (4 H, m), 1.87-1.88 (2 H, m), 1.46 (3 H, d, *J*=6.6 Hz); LCMS-ESI (POS), *M/Z*, *M*+1: Found 448.1, Calculated 448.2



**EXAMPLE 254****409**

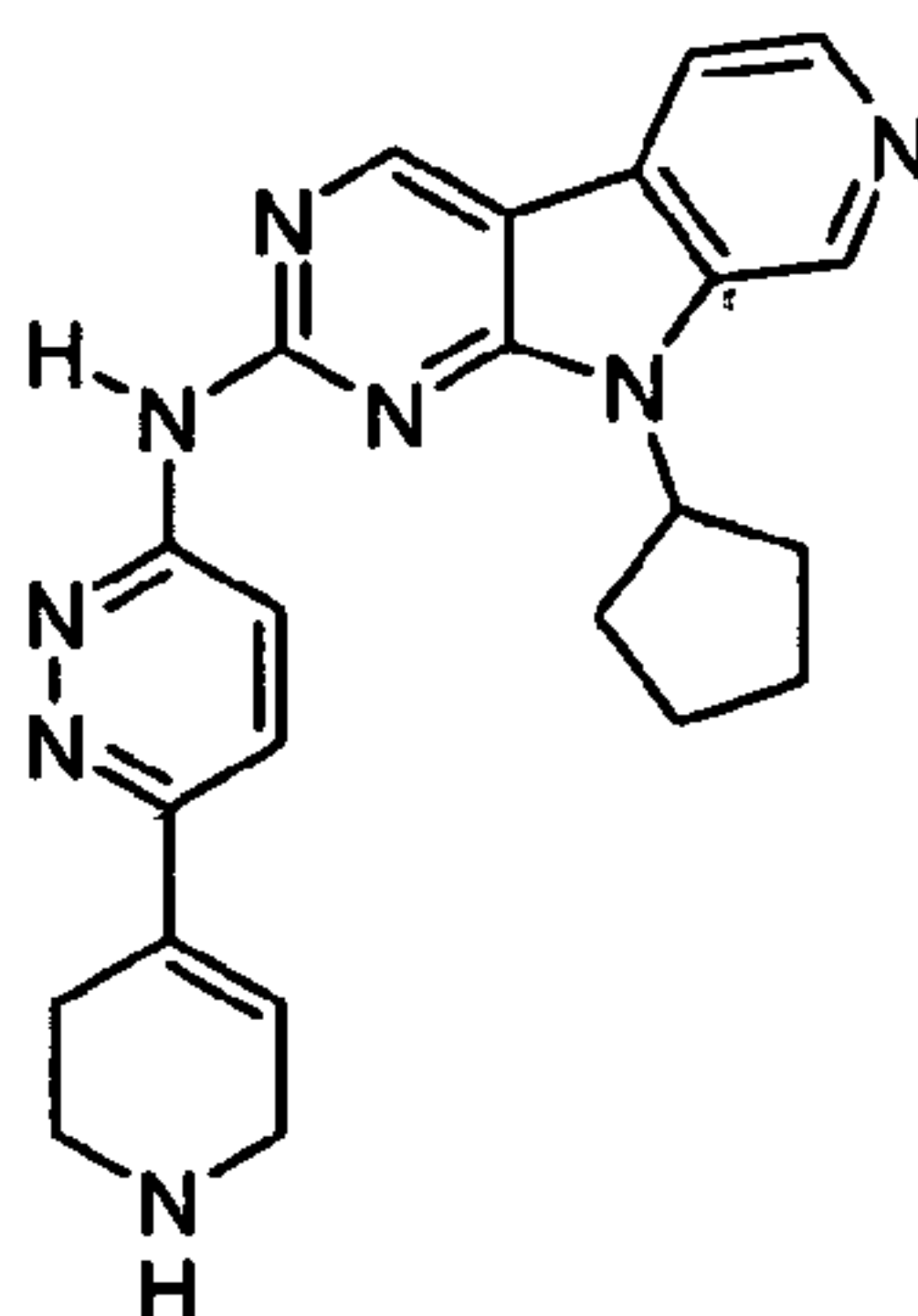
**9-Cyclopentyl-N-(6-(3,6-dihydro-1(2H)-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**4****410****409**

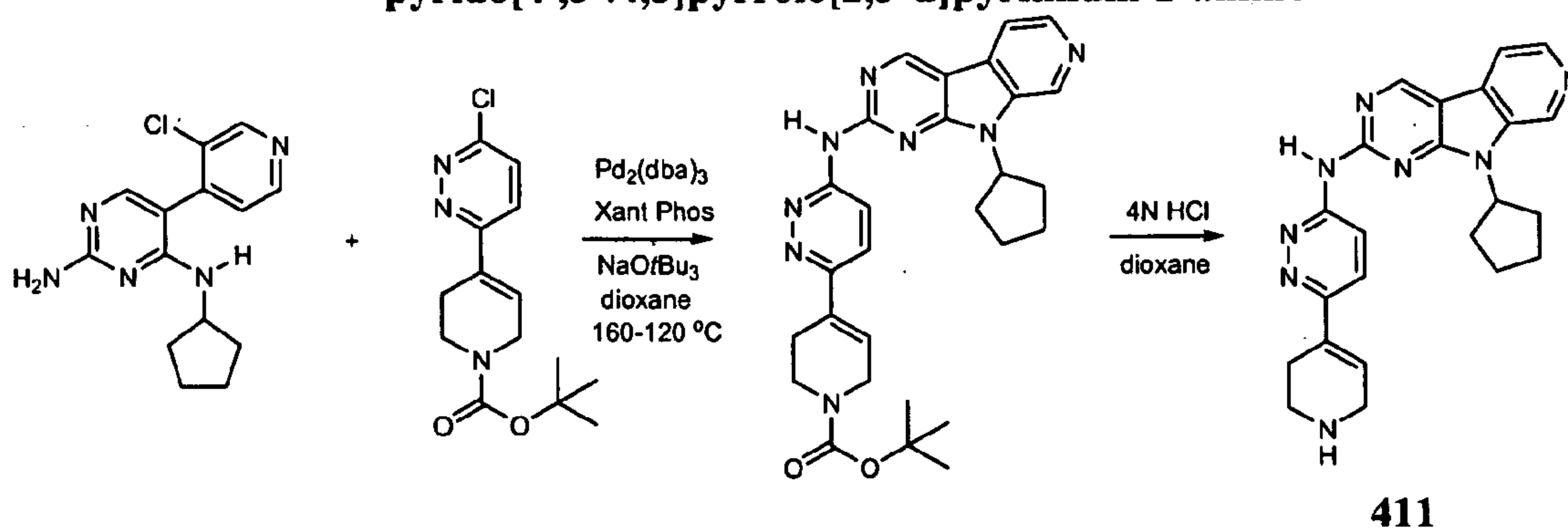
**3-Chloro-6-(3,6-dihydro-1(2H)-pyridinyl)pyridazine (410)** was prepared using chemistry similar to that described for compound 11. The yield is 86%. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 7.44 (1 H, d, J=9.5 Hz), 7.29 (1 H, d, J=9.5 Hz), 5.96 (1 H, m, J=10.1, 4.1, 4.1, 2.3, 2.1 Hz), 5.85 (1 H, m, J=10.1, 3.3, 3.3, 2.0, 1.7 Hz), 4.05 (2 H, dq, J=2.9, 2.8 Hz), 3.80 (2 H, t, J=5.6 Hz), 2.30 (2 H, d, J=2.7 Hz); LCMS-ESI (POS), M/Z, M+1: Found 196.0, Calculated 196.1.

**9-Cyclopentyl-N-(6-(3,6-dihydro-1(2H)-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (409):** Compound 409 was prepared from compound 4 and compound 410 using chemistry similar to that described in example 1. The yield is 20%. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.68 (1 H, d, J=1.5 Hz), 9.36 (1 H, s), 9.36 (1 H, d, J=0.5 Hz), 8.69 (3 H, t, J=2.2 Hz), 8.60 - 8.72 (1 H, m), 8.22 (1 H, d, J=10.5 Hz), 8.08 (1 H, dd, J=10.0, 1.0 Hz), 6.02 - 6.09 (1 H, m, J=8.1, 4.1, 4.1, 2.0 Hz), 5.89 (1 H, dddd, J=8.4, 3.4, 3.3, 1.5 Hz), 5.50 (2 H, t, J=8.8 Hz), 4.17 (3 H, qd, J=2.7, 2.6 Hz), 3.87 (3 H, t, J=5.7 Hz), 2.47 - 2.60 (3 H, m), 2.37 - 2.43 (2 H, m, J=6.1, 6.1, 3.5, 2.2 Hz), 2.15 - 2.35 (7 H, m), 1.87 - 1.99 (3 H, m); LCMS-ESI (POS), M/Z, M+1: Found 413.2, Calculated 413.2.

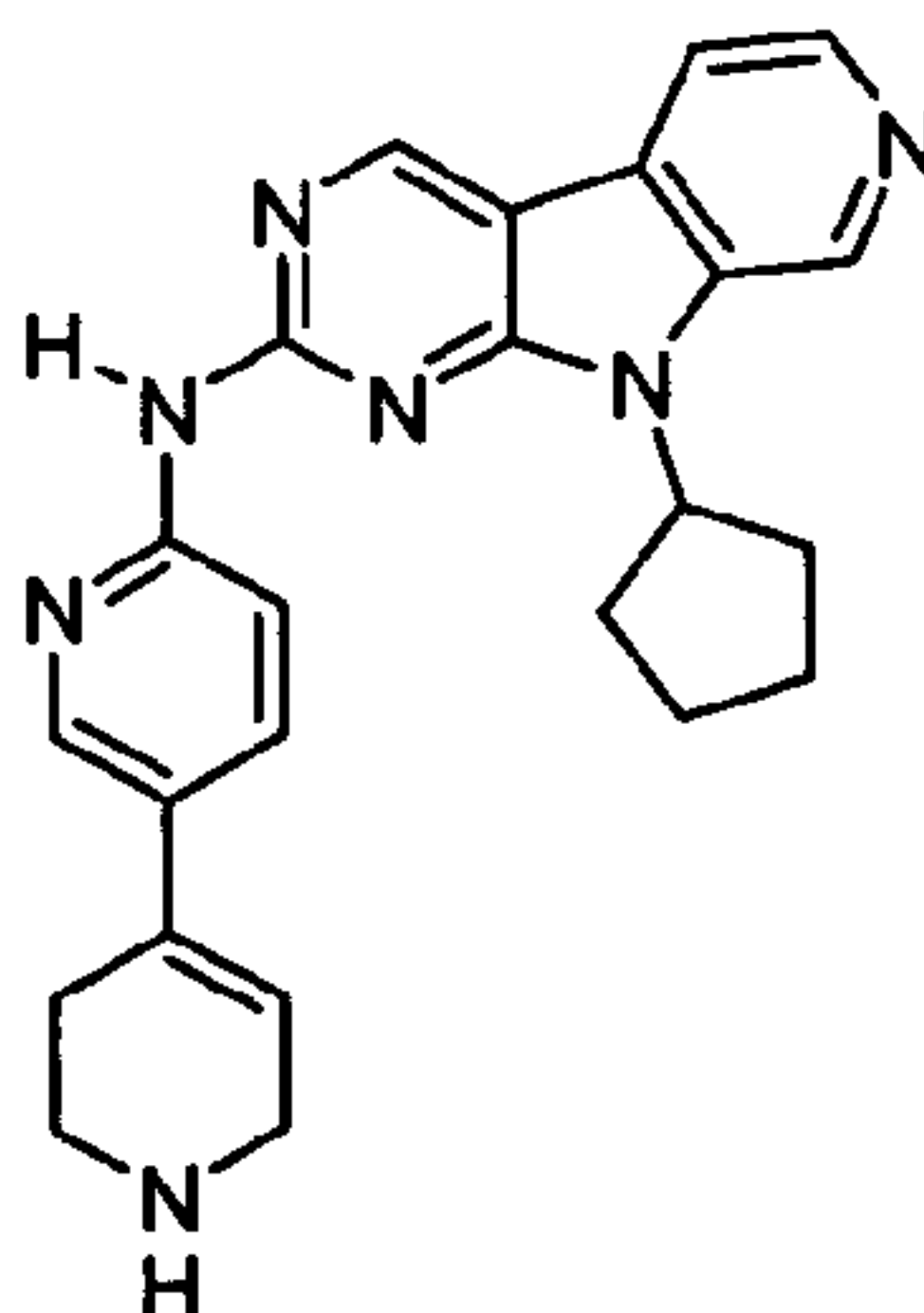


**EXAMPLE 255****411**

**9-Cyclopentyl-N-(6-(1,2,3,6-tetrahydro-4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

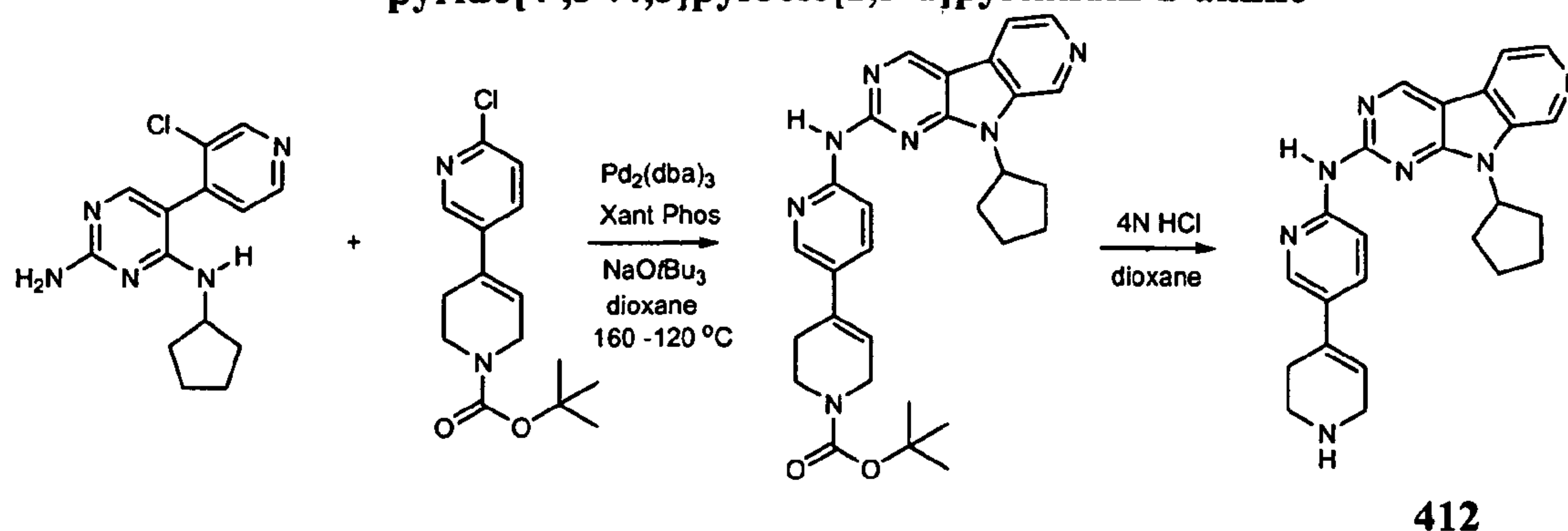
**411**

**9-Cyclopentyl-N-(6-(1,2,3,6-tetrahydro-4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (411):** Compound 411 was prepared using chemistry similar to that described in example 20. The two step yield is 29%. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.62 (1 H, s), 9.30 (1 H, s), 8.61 - 8.73 (3 H, m), 8.15 (1 H, d, *J*=9.5 Hz), 6.77 (1 H, tt, *J*=3.5, 1.7 Hz), 5.50 (1 H, t, *J*=8.8 Hz), 4.01 (1 H, q, *J*=2.8 Hz), 3.07 - 3.12 (1 H, m, *J*=6.2, 4.1, 2.0, 2.0 Hz), 2.49 - 2.60 (2 H, m), 2.13 - 2.33 (4 H, m), 1.93 (1 H, dt, *J*=8.8, 2.3 Hz), 1.88 - 1.98 (1 H, m); LCMS-ESI (POS), *M/Z*, *M*+1: Found 413.2, Calculated 413.2.

**EXAMPLE 256****412**

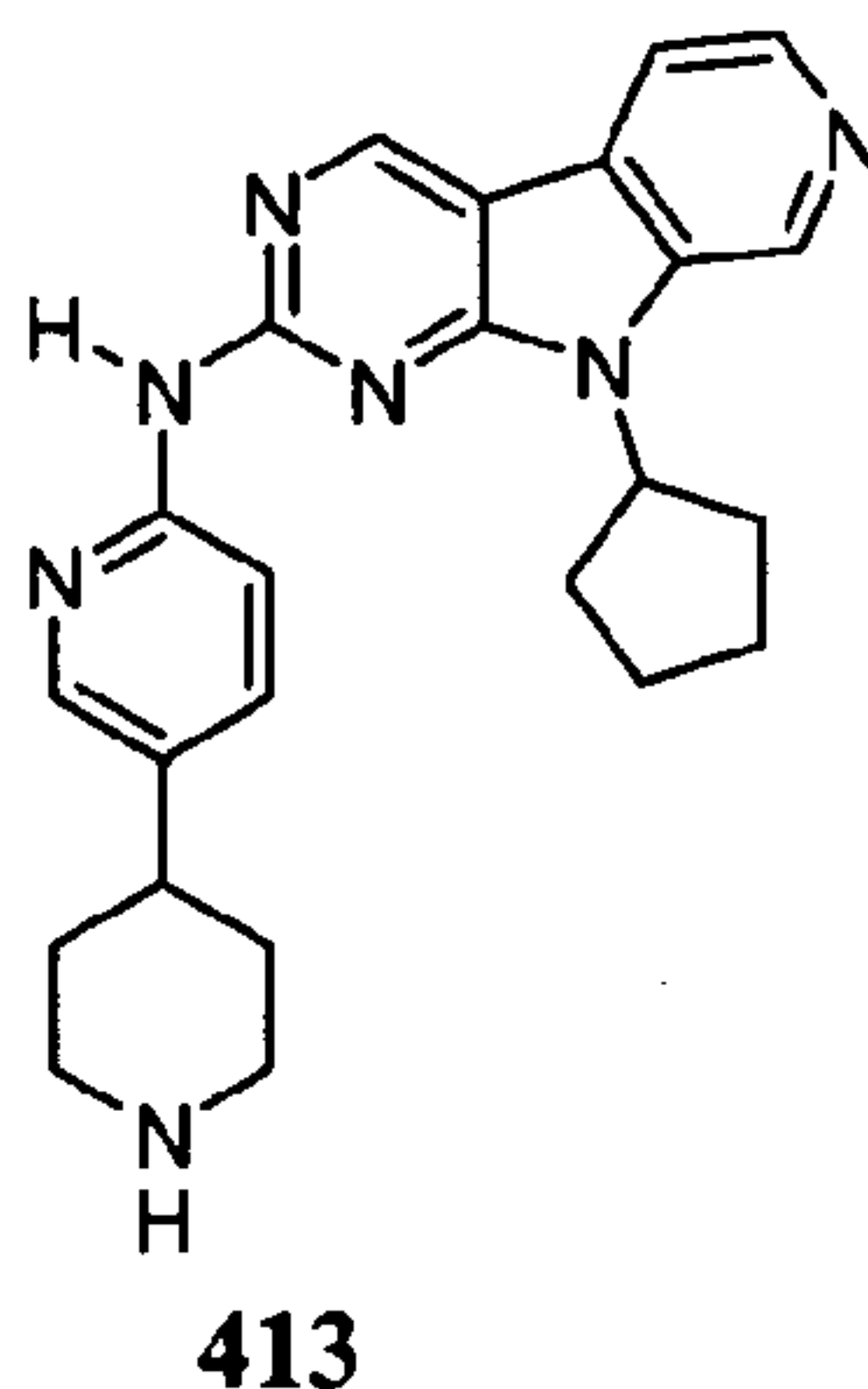


**9-Cyclopentyl-N-(1',2',3',6'-tetrahydro-3,4'-bipyridin-6-yl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



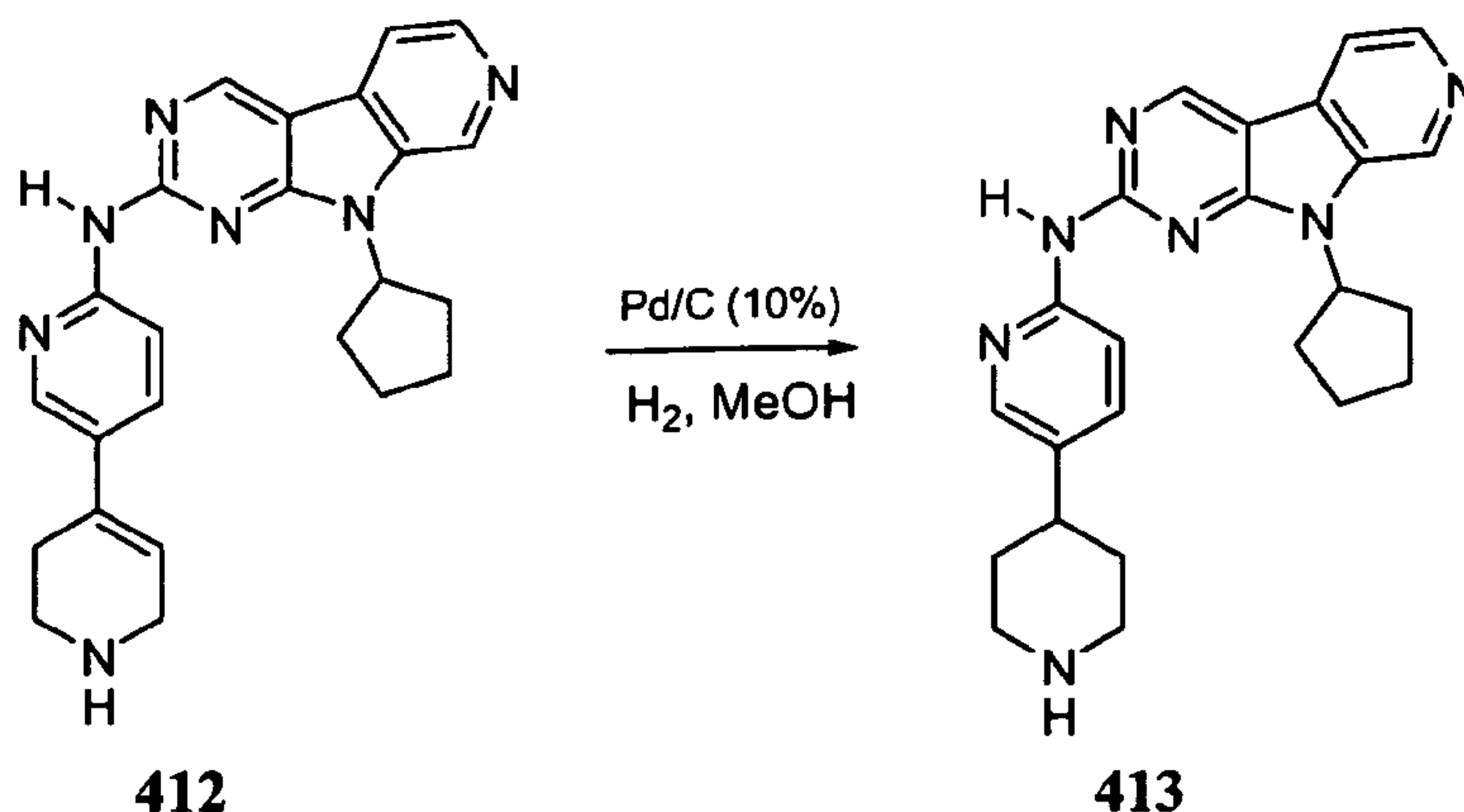
**9-Cyclopentyl-N-(1',2',3',6'-tetrahydro-3,4'-bipyridin-6-yl)-9H-pyrido[4',3':4,5]-pyrrolo[2,3-d]pyrimidin-2-amine (412):** Compound 412 was prepared using chemistry similar to that described in example 20. The two step yield is 70%. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.90 (1 H, s), 9.50 (1 H, s), 8.92 (1 H, d, *J*=6.1 Hz), 8.75 - 8.83 (1 H, m), 8.57 - 8.65 (2 H, m), 7.73 - 7.78 (1 H, m), 6.52 (1 H, tt, *J*=3.5, 1.7 Hz), 5.54 (1 H, quin, *J*=8.7 Hz), 3.96 - 4.01 (2 H, m), 3.68 (6 H, s), 3.58 (2 H, t, *J*=6.1 Hz), 2.88 - 2.95 (2 H, m, *J*=6.3, 6.3, 2.2, 2.1, 2.1 Hz), 2.57 (2 H, dq, *J*=12.8, 8.5 Hz), 2.21 - 2.37 (4 H, m), 1.89 - 2.00 (2 H, m); LCMS-ESI (POS), *M/Z*, *M*+1: Found 412.1, Calculated 412.2.

**EXAMPLE 257**



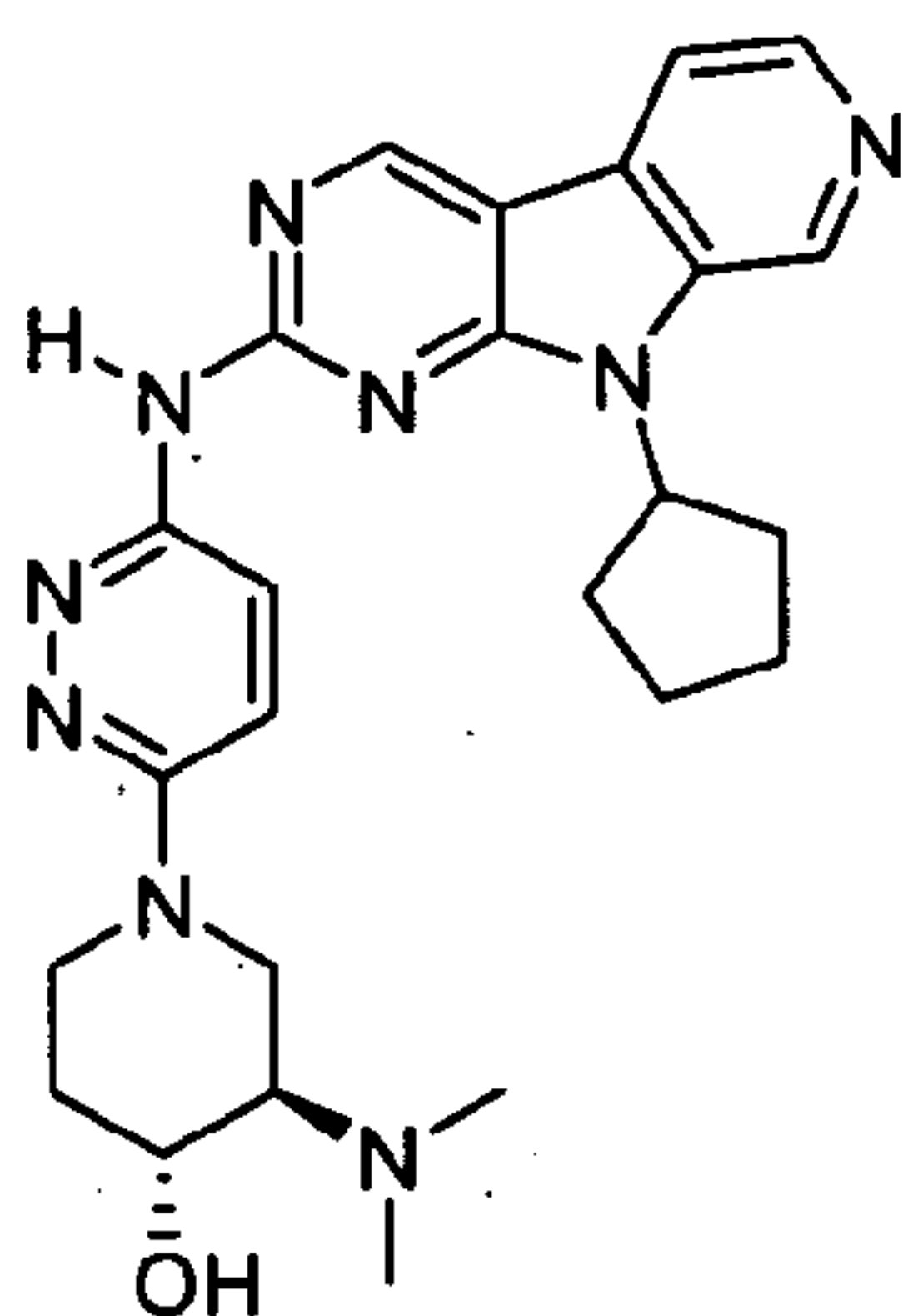
**9-cyclopentyl-N-(5-(4-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



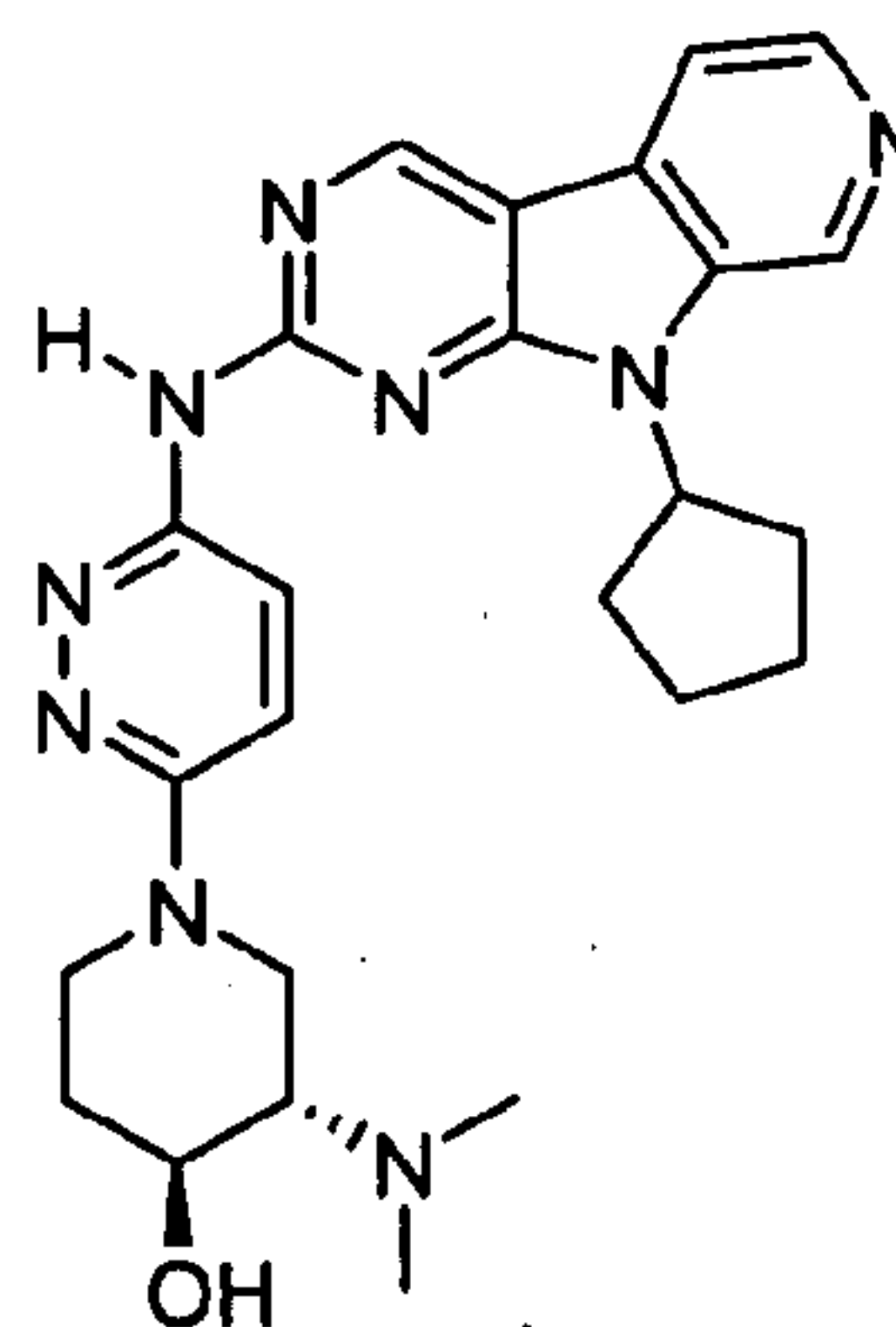


**9-Cyclopentyl-N-(5-(4-piperidinyl)-2-pyridinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (413):** To a solution of compound **412** (90mg, 0.22 mmol) in methanol (5mL) was added Pd/C (10% wt, dry basis) (50mg). The reaction was stirred at room temperature with H<sub>2</sub> balloon for 3 hours. Insolubles were removed by filtration. The filtrate was purified using prep-HPLC to give compound **413** as a yellow solid (30mg, 33%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 10.98 (1 H, br. s.), 9.64 (1 H, s), 9.42 (1 H, s), 8.83 (1 H, dd, *J*=3.5, 1.1 Hz), 8.71 (1 H, d, *J*=6.1 Hz), 8.55 - 8.68 (2 H, m), 8.30 (1 H, d, *J*=2.7 Hz), 8.17 (1 H, d, *J*=8.6 Hz), 7.85 (1 H, dd, *J*=8.8, 2.4 Hz), 5.41 (1 H, dq, *J*=8.9, 8.8 Hz), 3.43 (2 H, dd, *J*=10.4, 2.3 Hz), 2.96 (3 H, tt, *J*=12.1, 3.7 Hz), 2.42 (2 H, m), 2.00-2.08 (4H, m), 1.68 - 1.92 (2 H, m); LCMS-ESI (POS), *M/Z*, *M*+1: Found 414.2, Calculated 414.2.

### EXAMPLE 258



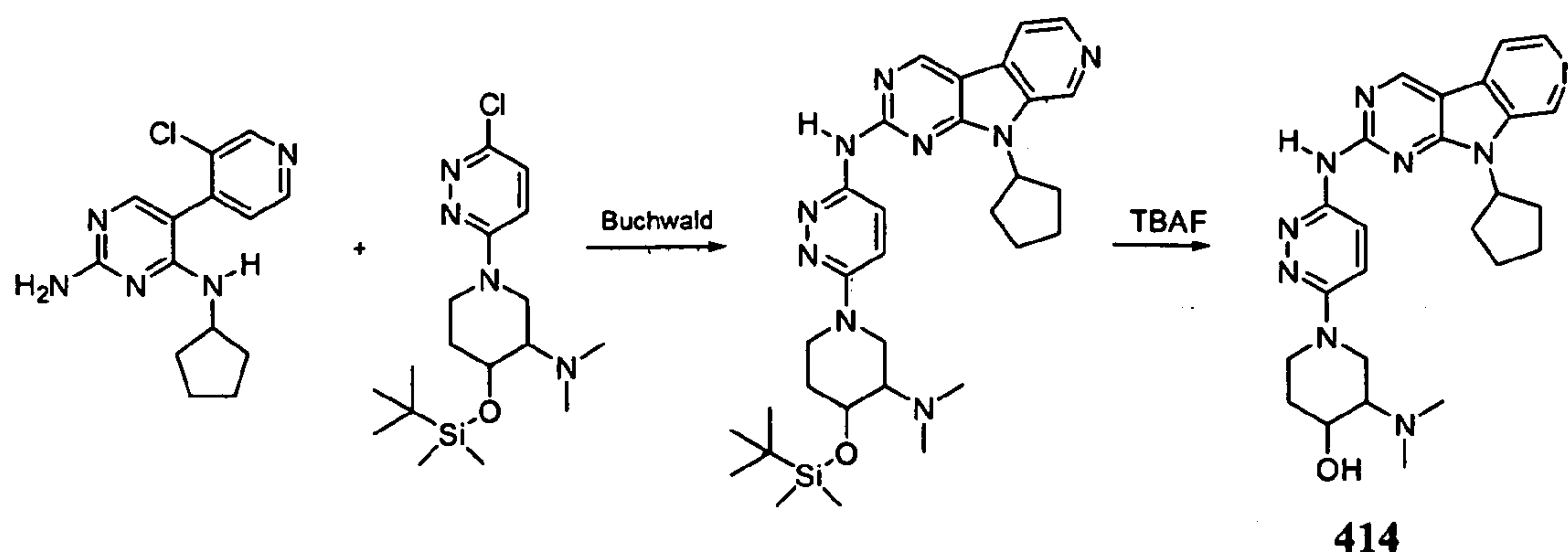
**414A** (chirality arbitrarily assigned)



**414B**

**1-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-3-(dimethylamino)-4-piperidinol**





**(3R\*,4R\*)-1-(6-((9-Cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridazinyl)-3-(dimethylamino)-4-piperidinol (414):** Compound 414 was prepared using chemistry similar to that described in example 20. The crude coupling product (50mg, 0.085mmol) was treated with 5 mL of 1M TBAF (in THF) at room temperature for 3 hours. After removal of solvent, the residue was dissolved in DMSO and purified by prep-HPLC to give the racemic alcohol 414 (33mg, 82%). This compound was dissolved in 2 mL of MeOH and to this solution was added 4 drops of 4 N HCl in dioxane. The solution was concentrated to give a yellow solid as an HCl salt.

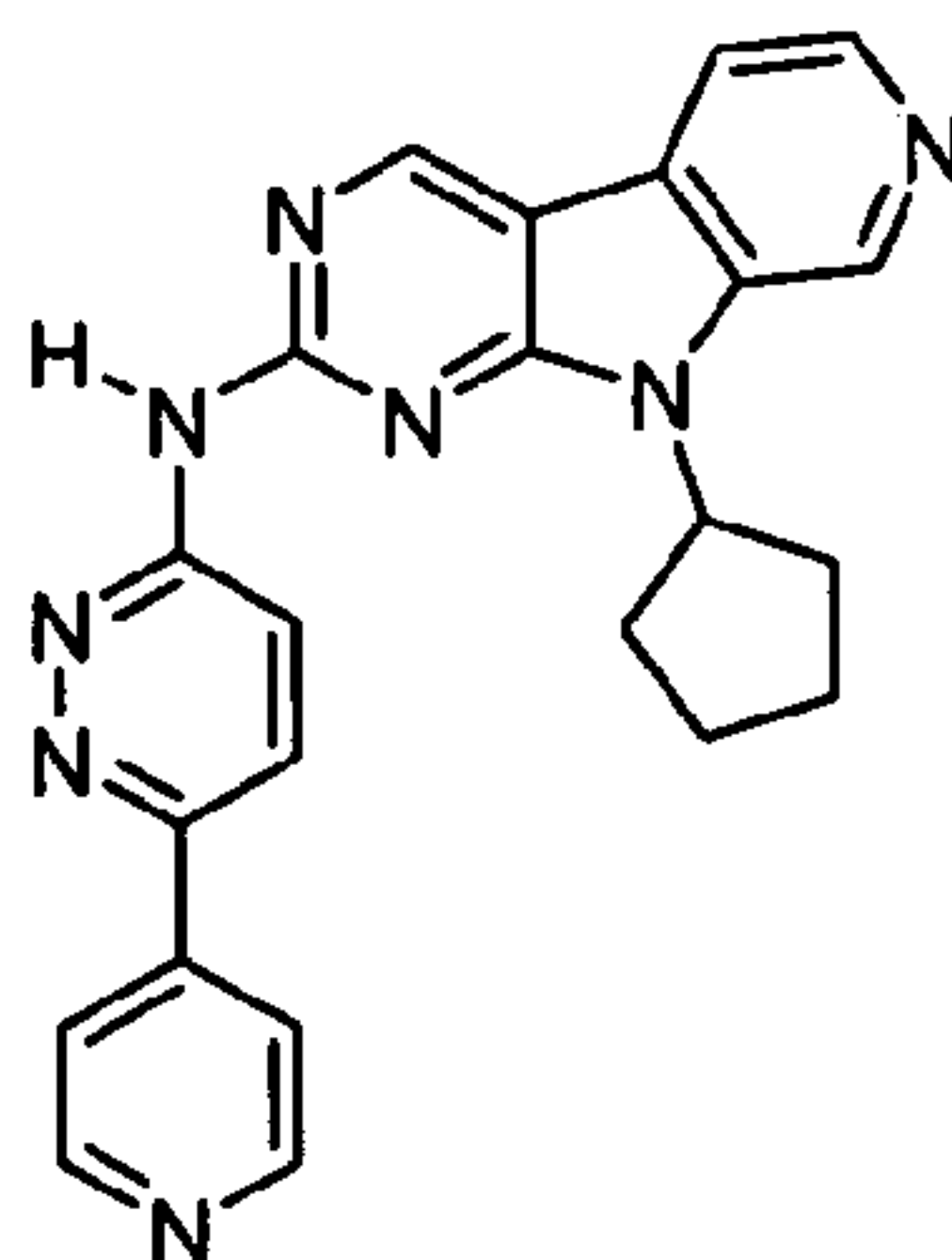
<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.77 (1 H, s), 9.44 (1 H, s), 8.78 (1 H, d, *J*=6.1 Hz), 8.72 (1 H, d, *J*=6.1 Hz), 8.14 (1 H, m), 8.05 (1 H, m, *J*=10.0 Hz), 5.50 (1 H, quin, *J*=8.7 Hz), 4.80 (1 H, m), 4.33 (1 H, m), 4.15 (1 H, ddd, *J*=10.3, 8.0, 4.9 Hz), 3.26 (1 H, m), 2.66 (2 H, m), 2.15 - 2.34 (4 H, m), 1.85 - 1.98 (2 H, m), 1.61 - 1.80 (1 H, m); LCMS-ESI (POS), *M/Z*, *M*+1: Found 474.2, Calculated 474.3.

The two enantiomers were resolved by SFC (Resolution conditions: 250x30 mm AS-H SFC column with 50g/min methanol (0.2% DEA)+ 75g/min CO<sub>2</sub> on Thar 350 SFC. Outlet pressure = 140 bar; Temp. = 24 C; Wavelength = 264 nm. Multiple 0.5 mL injections of 22 mg/8 mL sample in methanol solution (2.75mg/mL). Cycle time = 5.0 min; run time = 6.0 min) to give yellow solids. Compound 414A has a retention time 4.13 minute and compound 414B has a retention time 4.43 minute. NMR as the free base (each enantiomer). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ ppm 9.09 (1 H, s), 8.77 (1 H, s), 8.23 - 8.33 (2 H, m), 7.94 (1 H, d, *J*=5.1 Hz), 7.28 (1 H, d, *J*=10.0 Hz), 5.29 (2 H, t, *J*=8.8 Hz), 4.27 (1 H, ddd, *J*=13.1, 4.2, 2.1 Hz), 4.07 (1 H, dd, *J*=11.2, 2.4 Hz), 3.77 (1 H, td, *J*=9.9, 4.6 Hz), 2.82 - 2.94 (2 H, m), 2.38 (6 H, s), 2.30 (2 M, m), 1.94 - 2.13 (6 H, m), 1.77 (2 H, dt, *J*=12.0, 6.8 Hz), 1.51 (1 H, ddd, *J*=10.4, 2.2, 2.1 Hz); LCMS-ESI (POS), *M/Z*, *M*+1: Found 474.2, Calculated 474.3; each ee 99%.



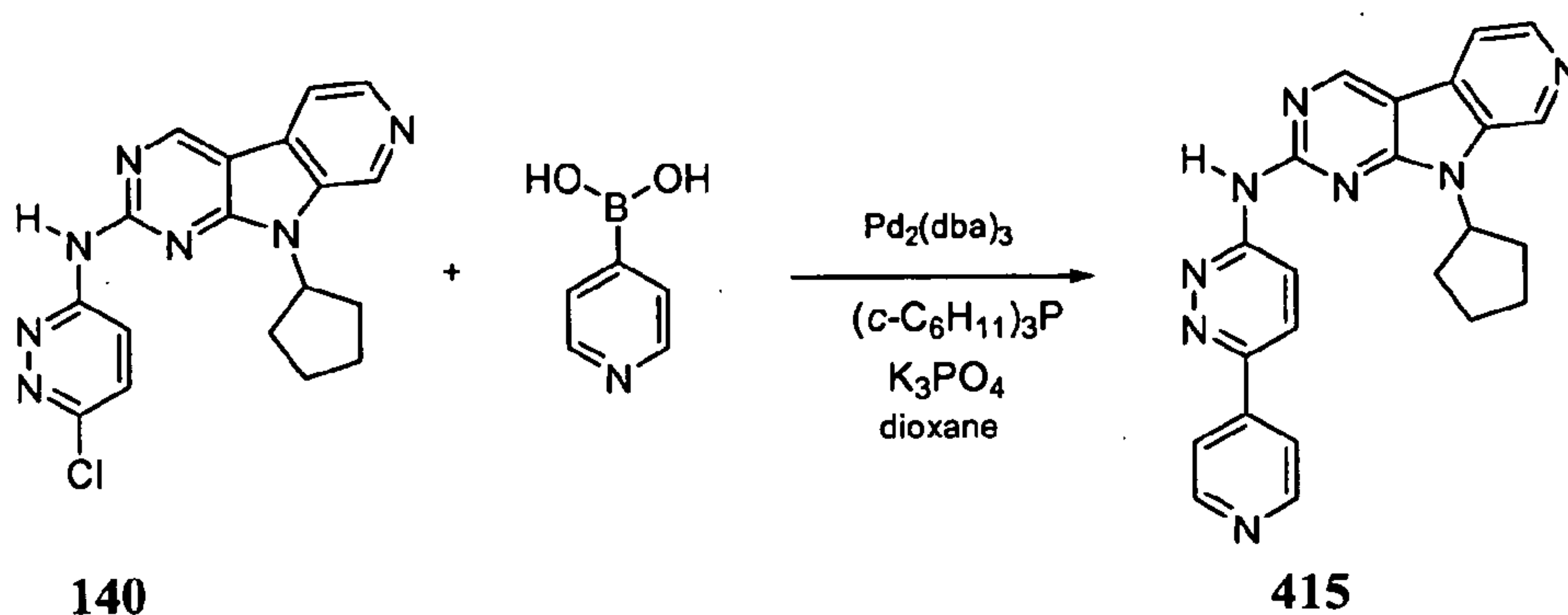
For convenience, they are arbitrarily assigned the structures as drawn, with absolute configuration remaining uncertain. Biological data reported in table 9 for compound **414A** as example 258A and for compound **414B** as example 258B.

### EXAMPLE 259



**415**

**9-cyclopentyl-N-(6-(4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



**140**

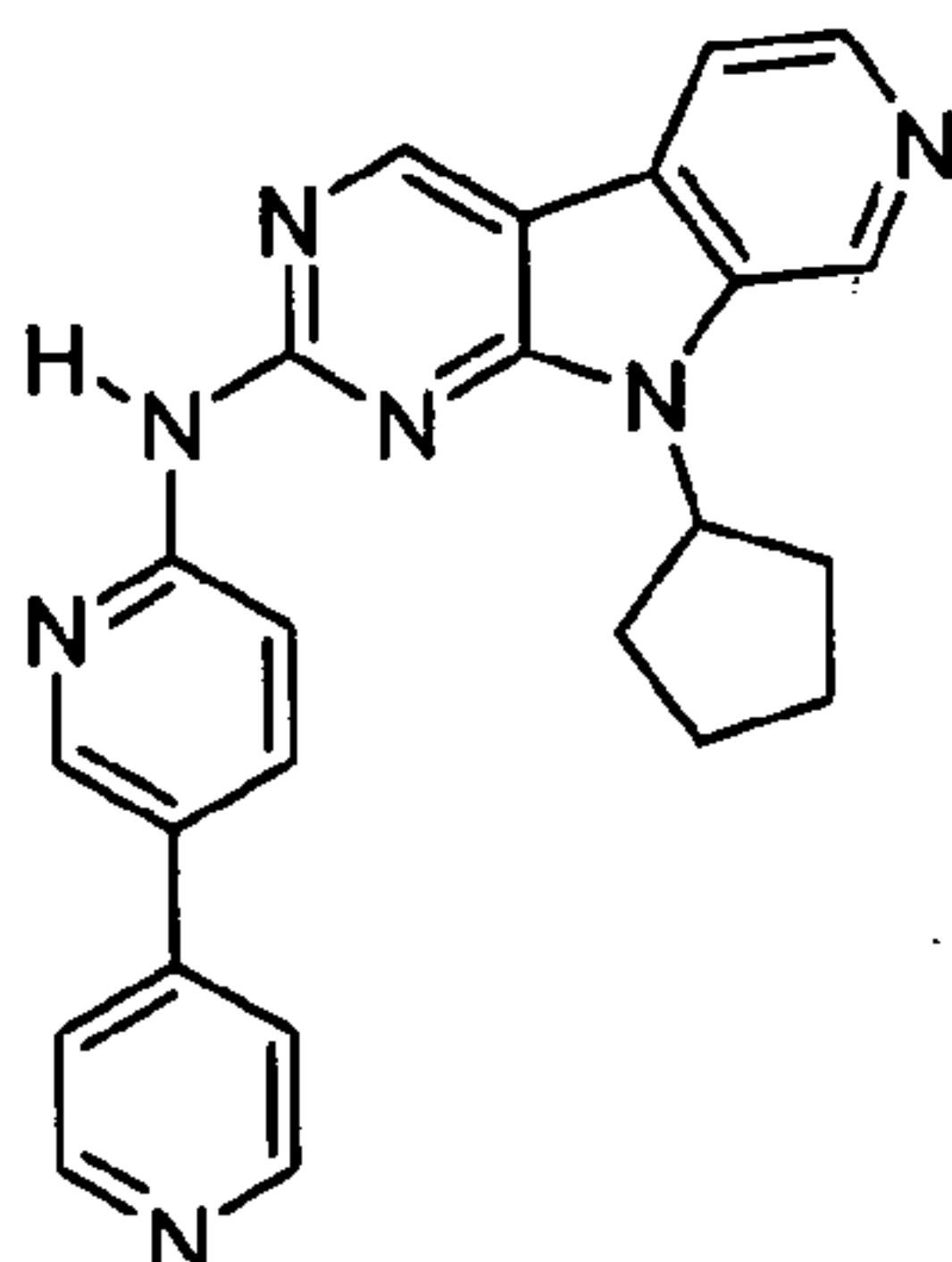
**415**

**9-cyclopentyl-N-(6-(4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (415):** To a solution of compound **140** (199mg, 544  $\mu$ mol) in dioxane (3mL) were added pyridin-4-ylboronic acid (66.9 mg, 544  $\mu$ mol),  $\text{Pd}_2(\text{dba})_3$  (24.9 mg, 27.2  $\mu$ mol), tricyclohexylphosphine (15.3 mg, 54.4  $\mu$ mol), and potassium phosphate (231 mg, 1.09 mmol) (in 1mL of water). The reaction mixture was purged with  $\text{N}_2$  for 20 minutes and the reaction was heated at 100 °C for 18 hours. DCM was added to the reaction and the mixture was washed with water and brine. The organic layer was dried with sodium sulfate. The product was purified using Combiflash (DCM/methanol) followed by trituration with ethyl acetate to give compound **415** as a yellow solid (63mg, 28%).  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  ppm 9.25 (1 H, s), 8.97 - 9.05 (2 H, m), 8.92 (1 H, s), 8.79 (2 H, d,  $J=6.1$  Hz), 8.57 (1 H, d,  $J=5.1$  Hz), 8.00 - 8.08 (3 H, m), 7.96 (1 H, dd,  $J=5.1, 1.2$  Hz), 5.48 (1 H, quin,  $J=8.9$  Hz),



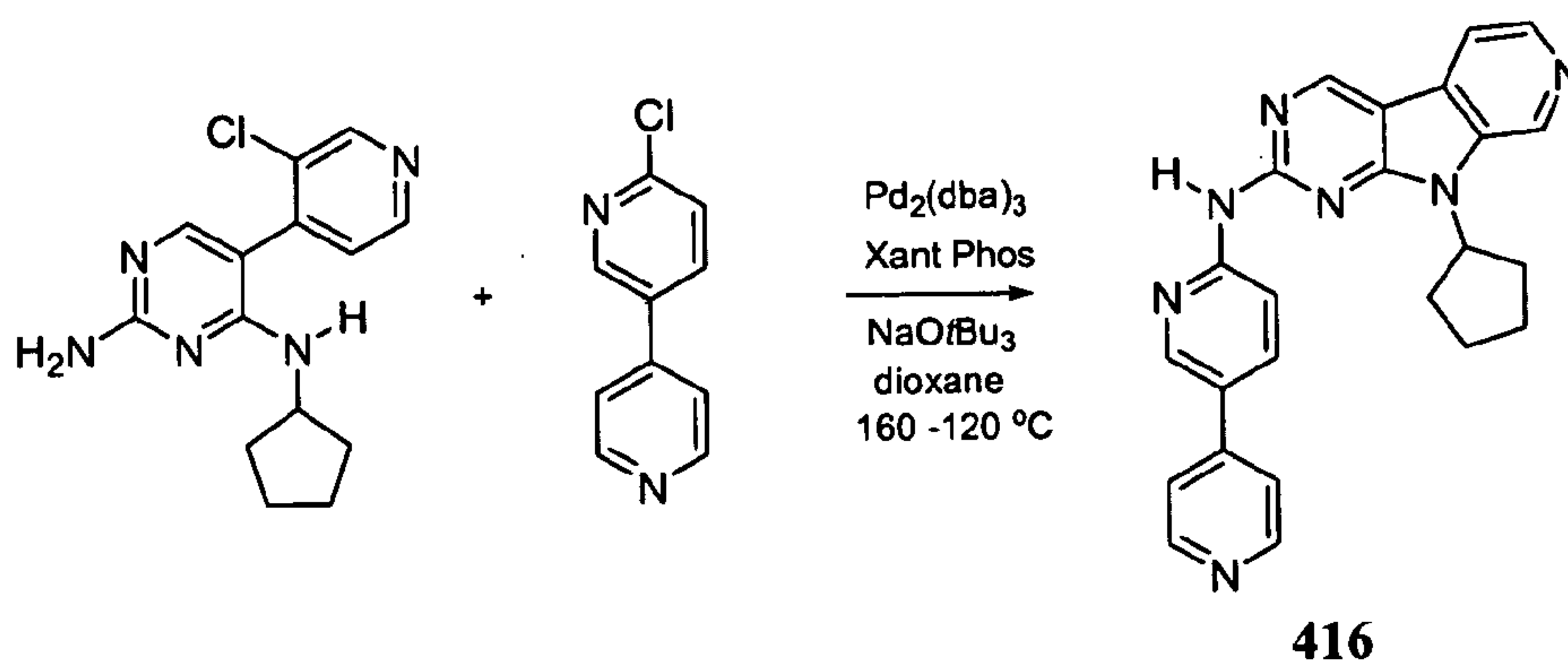
2.48(2 H, m), 2.20-2.28 (4 H, m), 1.95 (2 H, dddd,  $J=8.2, 4.5, 4.3, 4.2$  Hz), 1.63 (2 H, br. s.); LCMS-ESI (POS), M/Z, M+1: Found 409.1, Calculated 409.2.

### EXAMPLE 260



**416**

**N-3,4'-bipyridin-6-yl-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**



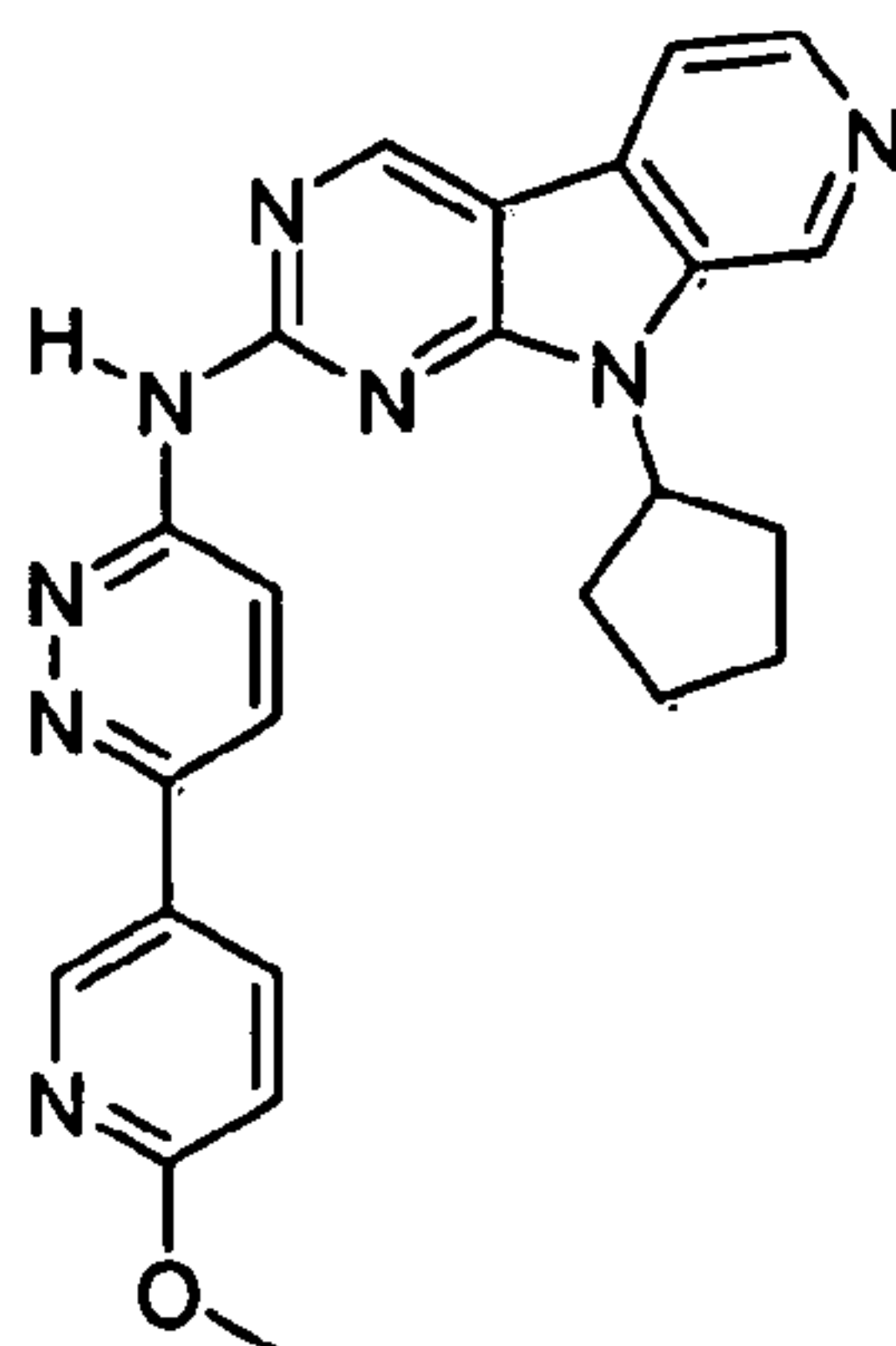
**416**

**N-3,4'-bipyridin-6-yl-9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

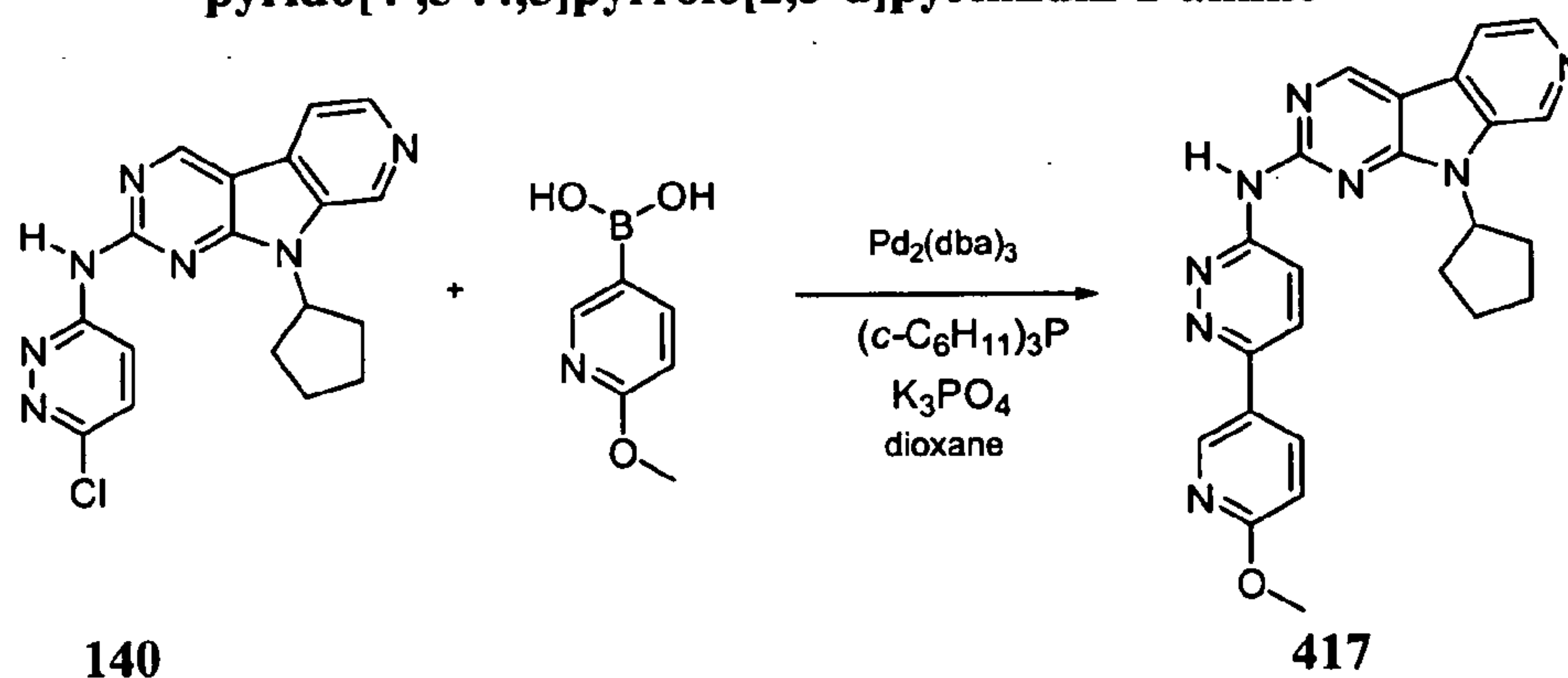
**(416):** Compound **416** was prepared using chemistry similar to that described in example 20.

The yield is 65%.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  ppm 9.23 (1 H, s), 8.99 (1 H, d,  $J=1.2$  Hz), 8.65 - 8.81 (4 H, m), 8.54 (1 H, d,  $J=5.1$  Hz), 8.12 (1 H, dd,  $J=8.7, 2.6$  Hz), 7.94 (1 H, dd,  $J=5.1, 1.2$  Hz), 7.54 - 7.63 (2 H, m), 5.48 (1 H, quin,  $J=9.0$  Hz), 2.46 - 2.57 (2 H, m), 2.13 - 2.31 (4 H, m), 1.89 - 2.00 (2 H, m,  $J=11.4, 7.8, 7.7, 7.7, 3.8$  Hz), 1.63 (1 H, br. s.); LCMS-ESI (POS), M/Z, M+1: Found 408.2, Calculated 408.2.



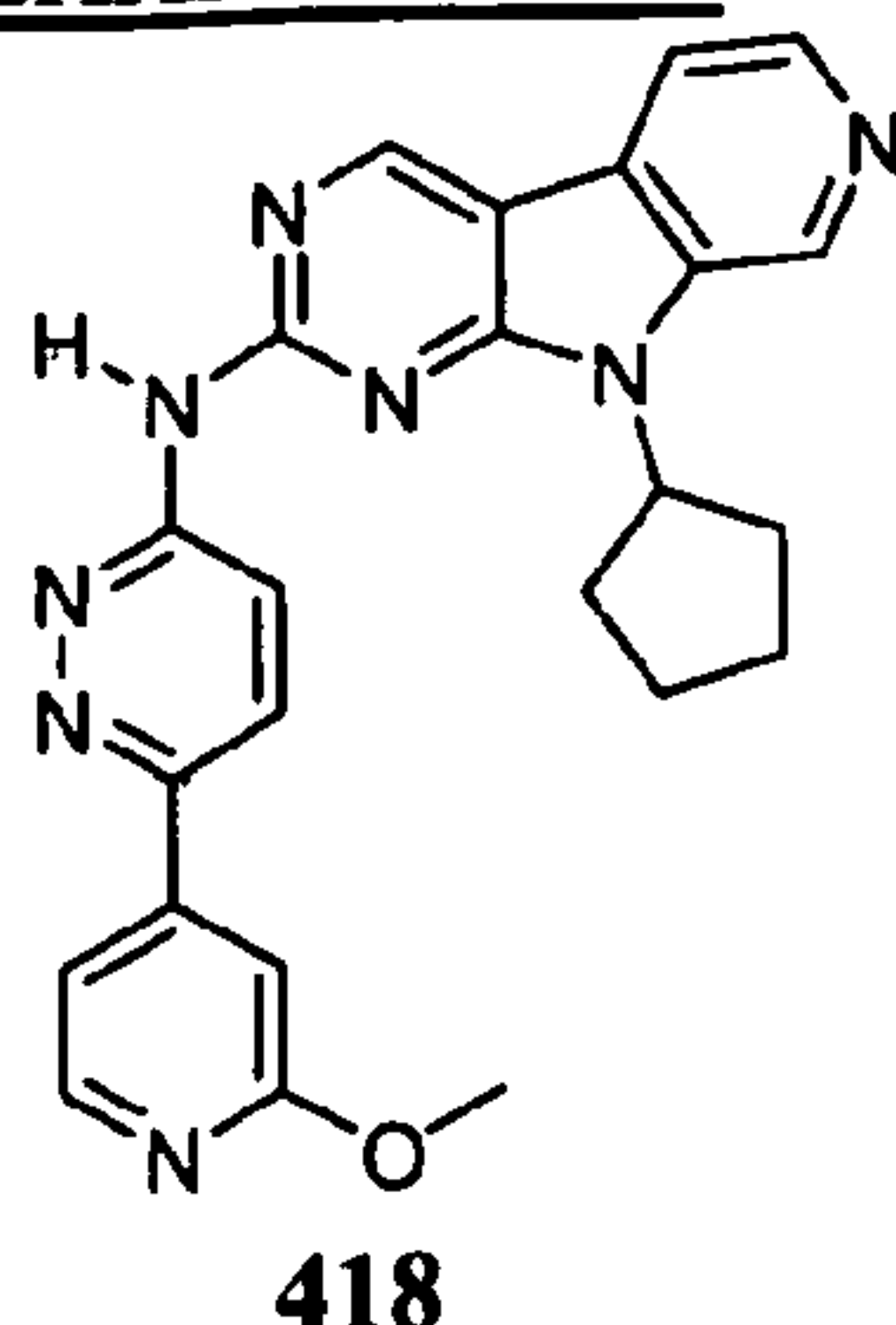
**EXAMPLE 261****417**

**9-Cyclopentyl-N-(6-(6-methoxy-3-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

**140****417**

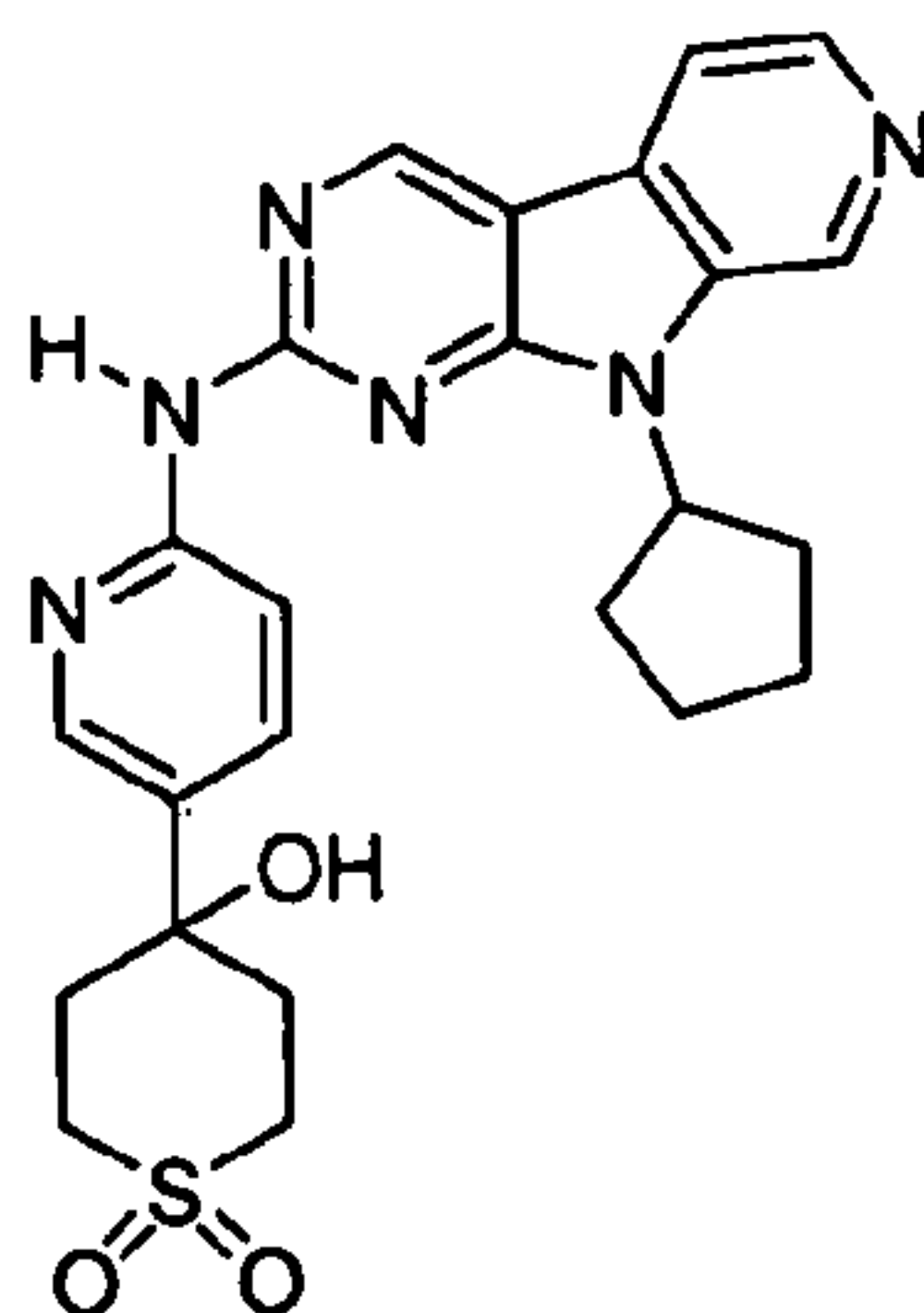
**9-Cyclopentyl-N-(6-(6-methoxy-3-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine (417):** Compound 417 was prepared using chemistry similar to that described in example 259. The yield is 26%. <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ ppm 9.31 (1 H, d, *J*=1.7 Hz), 8.99 (1 H, d, *J*=0.7 Hz), 8.92 (1 H, d, *J*=9.3 Hz), 8.85 (1 H, d, *J*=2.4 Hz), 8.56 (1 H, d, *J*=5.6 Hz), 8.40 (1 H, dd, *J*=8.7, 2.6 Hz), 8.10 - 8.15 (1 H, m), 7.97 (1 H, d, *J*=9.5 Hz), 6.94 (1 H, d, *J*=8.6 Hz), 5.45 (1 H, qd, *J*=9.0, 8.8 Hz), 4.05 (3 H, s), 2.43 - 2.52 (2 H, m), 2.16 - 2.33 (4 H, m), 1.91 - 2.00 (2 H, m); LCMS-ESI (POS), *M/Z*, *M*+1: Found 439.0, Calculated 439.2.



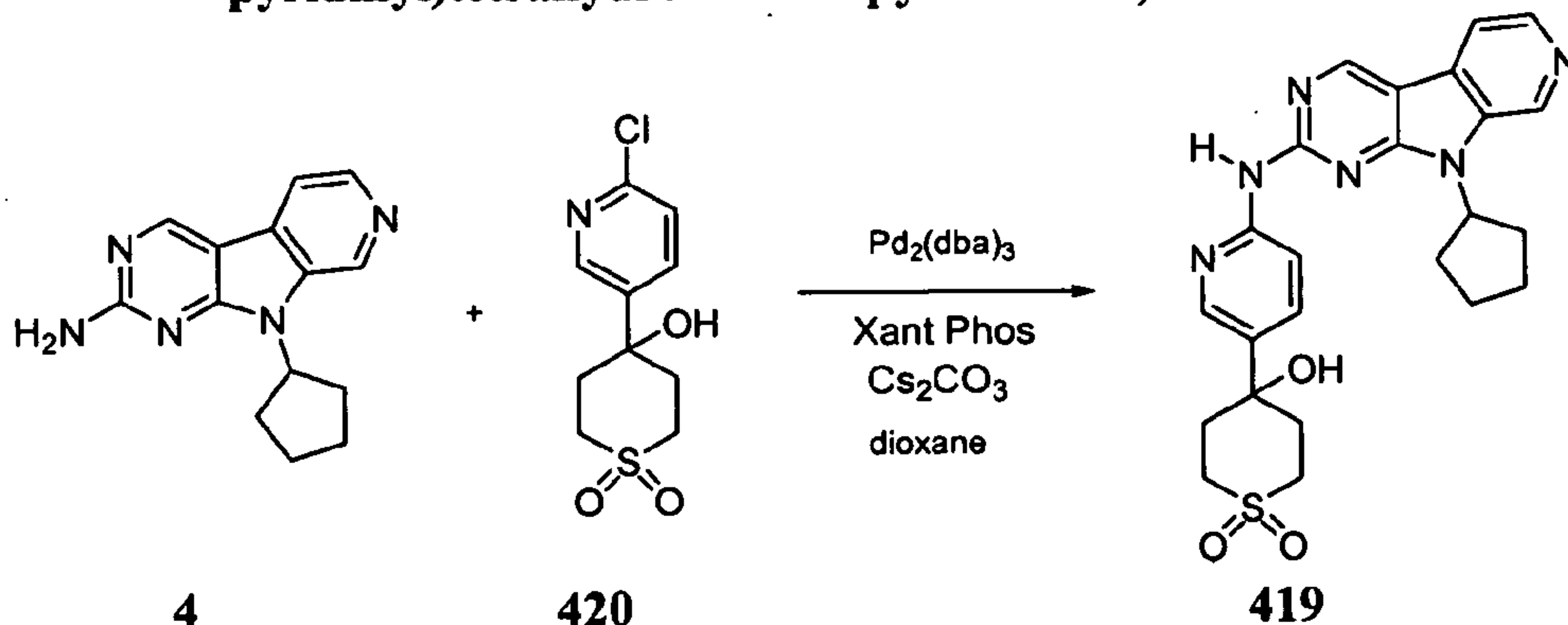
**EXAMPLE 262**

**9-Cyclopentyl-N-(6-(2-methoxy-4-pyridinyl)-3-pyridazinyl)-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-amine**

Compound **418** was prepared using chemistry similar to that described in example 259. The yield is 52%. <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ ppm 9.23 (1 H, s), 8.97 - 9.02 (2 H, m), 8.75 (1 H, s), 8.56 (1 H, d, *J*=5.1 Hz), 8.34 (1 H, d, *J*=5.4 Hz), 7.96 - 8.03 (2 H, m), 7.65 (1 H, dd, *J*=5.4, 1.7 Hz), 7.44 (1 H, dd, *J*=1.5, 0.7 Hz), 5.47 (1 H, quin, *J*=9.0 Hz), 5.36 (25 H, d, *J*=1.2 Hz), 2.44 - 2.53 (2 H, m, *J*=13.0, 9.0, 8.7, 8.7 Hz), 2.16 - 2.31 (4 H, m), 1.90 - 1.99 (2 H, m, *J*=8.2, 4.5, 4.2, 4.2 Hz), 1.59 (1 H, d, *J*=8.1 Hz); LCMS-ESI (POS), *M/Z*, *M*+1: Found 439.1, Calculated 439.2.

**EXAMPLE 263**

**4-(6-((9-cyclopentyl-9H-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-pyridinyl)tetrahydro-2H-thiopyran-4-ol 1,1-dioxide**





# **DEMANDES OU BREVETS VOLUMINEUX**

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS  
COMPREND PLUS D'UN TOME.**

**CECI EST LE TOME \_\_1\_\_ DE \_\_2\_\_**

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

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# **JUMBO APPLICATIONS / PATENTS**

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE  
THAN ONE VOLUME.**

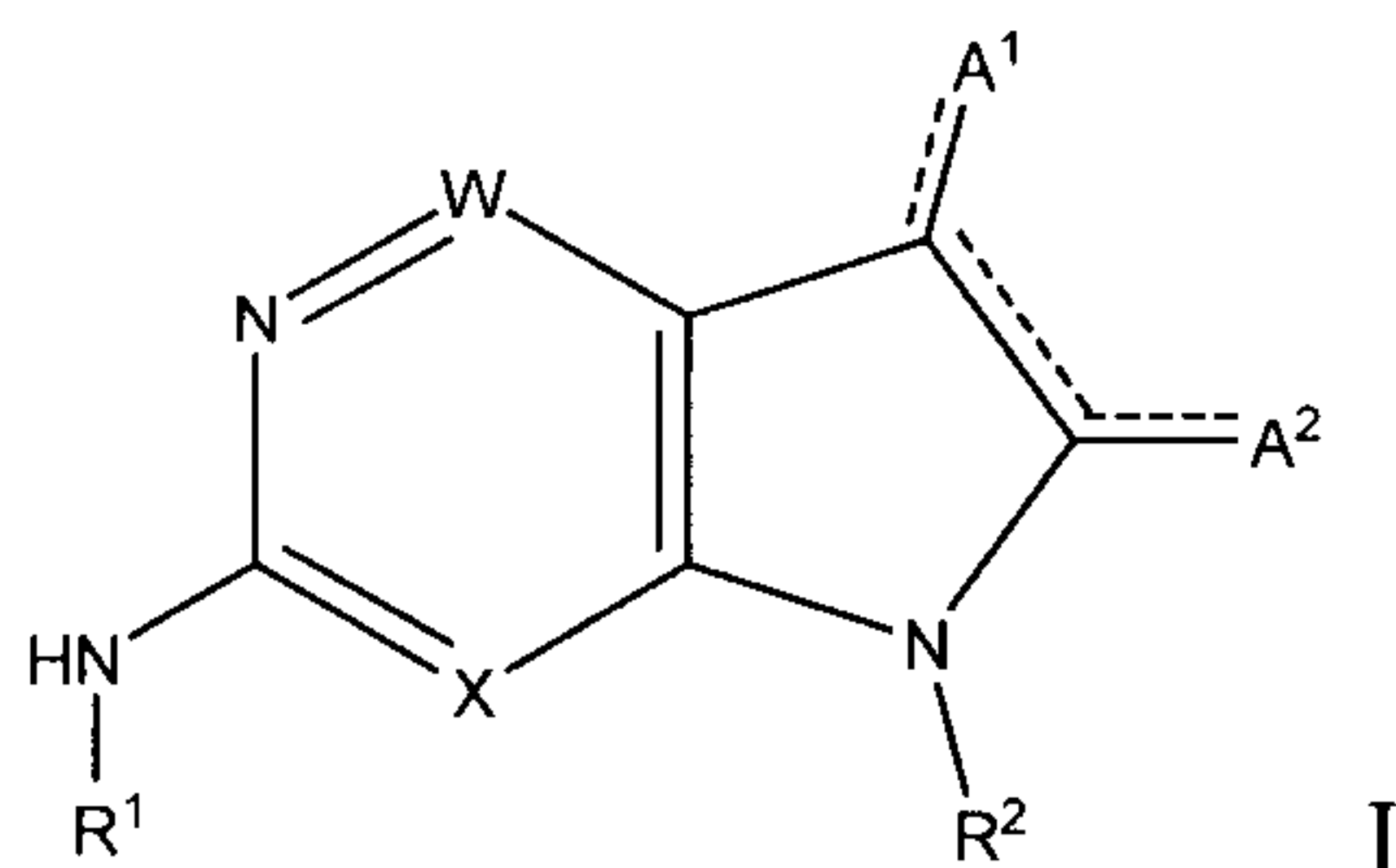
**THIS IS VOLUME \_\_1\_\_ OF \_\_2\_\_**

NOTE: For additional volumes please contact the Canadian Patent Office.



**What is Claimed is:**

1. A compound of Formula I



or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, wherein

W is CH and X is CH or N;

A<sup>1</sup> and A<sup>2</sup> together with ring carbon atoms to which they are attached combine to form benzene, pyridine, pyridone, pyrimidine, pyridazine, or isothiazole any of which may be optionally substituted with one R<sup>x</sup> substituent selected from the group consisting of -F, -Cl, -CN, -OCH<sub>3</sub>, -OH, and -CH<sub>3</sub>;

R<sup>1</sup> is -Y-(methylene)<sub>m</sub>-R<sup>a</sup>;

Y is phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiazolyl, or thiadiazolyl any of which may be optionally substituted with one -CH<sub>3</sub>;

R<sup>a</sup> is piperazinyl, piperidinyl, pyrrolidinyl, 1,4-diazepanyl, dioxothiomorpholinyl, morpholinyl, azabicyclo[3.2.1]octyl, tetrahydropyridinyl, pyridinyl, dioxotetrahydrothiopyranyl, dioxodihydrothiopyranyl, azabicyclo[3.1.0]hexyl, piperazinonyl, 1,8-diazaspiro[4.5]decyl, 5,8-diazaspiro[3.5]nonyl, 6,9-diazaspiro[4.5]decyl, 1,4-diazaspiro[5.5]undecyl, 4-oxa-1,9-diazaspiro[5.5]undecyl, 1-oxa-4,9-diazaspiro[6.6]undecanonyl, 1-oxa-4,9-diazaspiro[5.5]undecyl, -N(H)(CH<sub>3</sub>), -N(H)(CH<sub>2</sub>CH<sub>3</sub>), -N(H)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -N(H)(C(H)(CH<sub>3</sub>)<sub>2</sub>), -N(H)(pyrrolidine), -N(H)(dioxotetrahydrothiophene), -N(H)(piperidine), -N(CH<sub>3</sub>)(piperidine), -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), or -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -SO<sub>2</sub>-piperazinyl, -SO<sub>2</sub>-piperidinyl, -O piperidinyl, -C(=O)-piperazinyl, -C(=O)-piperidinyl, -C(=O)-



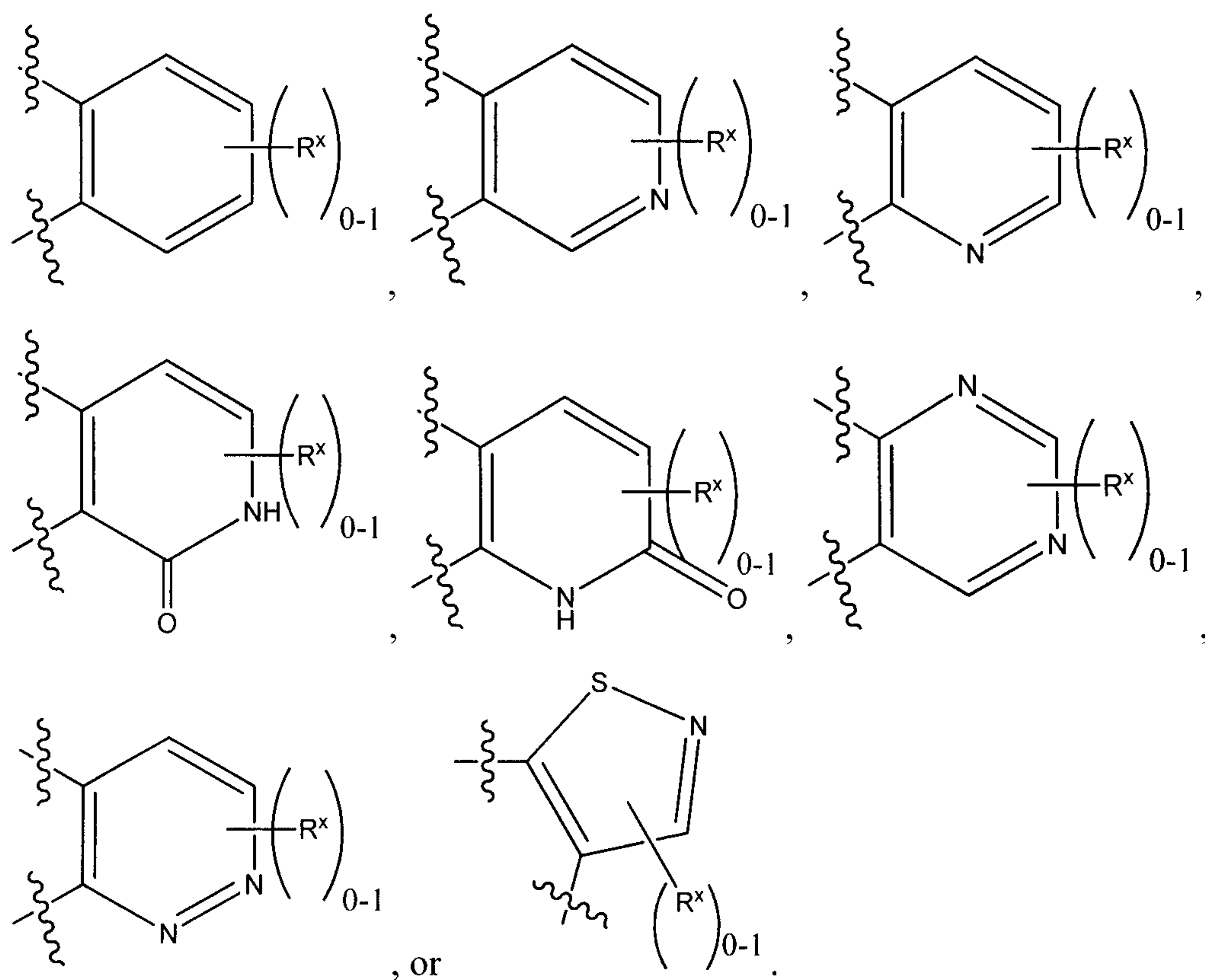
morpholinyl,  $-\text{CO}_2\text{H}$ , or  $-\text{CO}_2\text{CH}_2\text{CH}_3$ , any of which may be optionally independently substituted with one or two  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}(\text{CH}_3)_2$ ,  $-\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{CN}$ ,  $-\text{CH}_2\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$ ,  $-\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $-\text{CN}$ ,  $-\text{F}$ ,  $-\text{CF}_3$ ,  $-\text{C}(=\text{O})\text{OCH}_3$ ,  $-\text{C}(=\text{O})\text{OH}$ ,  $-\text{C}(=\text{O})\text{CH}_3$ ,  $-\text{C}(=\text{O})\text{CH}_2\text{OH}$ ,  $-\text{C}(=\text{O})\text{CH}_2\text{OC}(=\text{O})\text{CH}_3$ ,  $-\text{C}(=\text{O})\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{NH}_2$ ,  $-\text{CH}_2\text{C}(=\text{O})\text{OCH}_3$ ,  $-\text{CH}_2\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{C}(=\text{O})\text{OH}$ ,  $-\text{CH}_2\text{C}(=\text{O})\text{NH}_2$ ,  $-\text{NH}_2$ ,  $-\text{N}(\text{H})\text{CH}_3$ ,  $-\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{N}(\text{CH}_3)_2$ ,  $-\text{N}(\text{CH}_2\text{CH}_3)_2$ ,  $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$ ,  $-\text{N}(\text{H})\text{C}(\text{H})(\text{CH}_3)\text{CH}_2\text{OH}$ ,  $-\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{OH}$ ,  $-\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ ,  $-\text{N}(\text{H})\text{CH}_2\text{CH}(\text{CH}_3)(\text{OH})$ ,  $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{NH}(\text{CH}_3)$ ,  $-\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{NH}(\text{CH}_3)$ ,  $-\text{N}(\text{H})\text{CH}(\text{CH}_2\text{OH})_2$ ,  $-\text{N}(\text{H})\text{CH}_2\text{C}(\text{H})(\text{OH})\text{CH}_2\text{OH}$ ,  $-\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$ ,  $-\text{N}(\text{H})\text{CH}_2\text{CF}_3$ ,  $-\text{N}(\text{H})\text{cyclopropyl}$ ,  $-\text{N}(\text{H})\text{cyclobutyl}$ ,  $-\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{N}(\text{H})\text{CH}(\text{CH}_3)_2$ ,  $-\text{N}(\text{CH}_3)\text{CH}_2\text{C}(=\text{O})\text{OH}$ ,  $-\text{N}(\text{H})\text{CH}_2\text{C}(=\text{O})\text{OCH}_3$ ,  $-\text{N}(\text{H})\text{CH}_2\text{C}(=\text{O})\text{OH}$ ,  $-\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$ , cyclopropyl, pyrrolidinyl, hydroxypyrrolidinyl, piperidinyl, hydroxypiperidinyl, morpholinyl, azetidiny, or hydroxyazetidiny;

$\text{R}^2$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}(\text{CH}_3)_2$ ,  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}_2\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ , indanyl, phenyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, tetrahydropyranyl, tetrahydrothiopyranyl, dioxotetrahydrothiopyranyl, tetrahydrothiophenyl, pyrrolidinyl, tetrahydrofuranlyl,  $-\text{CH}_2(\text{cyclopropyl})$ ,  $-\text{CH}_2(\text{cyclohexyl})$ ,  $-\text{C}(\text{H})(\text{CH}_3)(\text{cyclohexyl})$ , or  $-\text{CH}_2(\text{thiophenyl})$ , any of which may be optionally independently substituted with one or two substituents selected from the group consisting of  $-\text{F}$ ,  $-\text{CH}_3$ ,  $-\text{CF}_3$ ,  $-\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{CH}_2\text{OH}$ , and  $-\text{CH}_2\text{CO}_2\text{H}$ ; and

$m$  is independently 0 or 1.

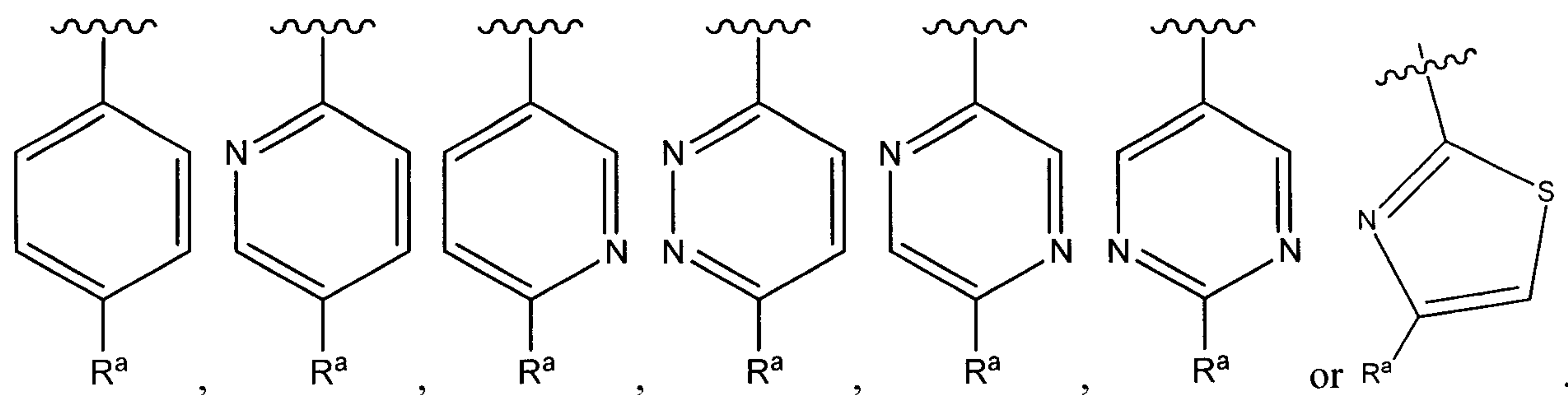


2. The compound of claim 1 wherein  $A^1$  and  $A^2$  together with the ring atoms to which they are attached combine to form



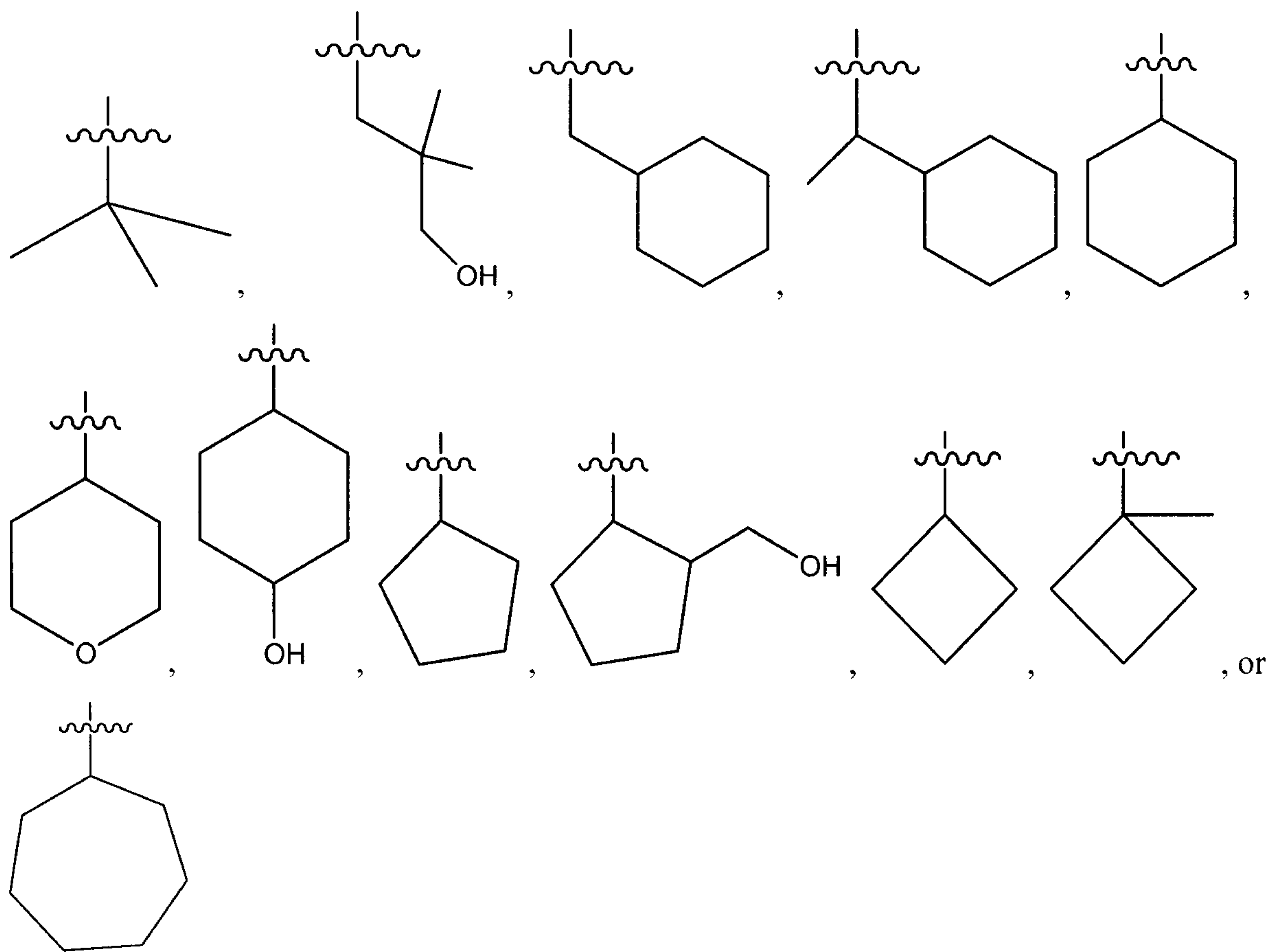
3. The compound of claim 1 wherein Y is phenyl, pyridinyl, pyrimidinyl or thiazolyl.

4. The compound of claim 1 wherein  $R^1$  is

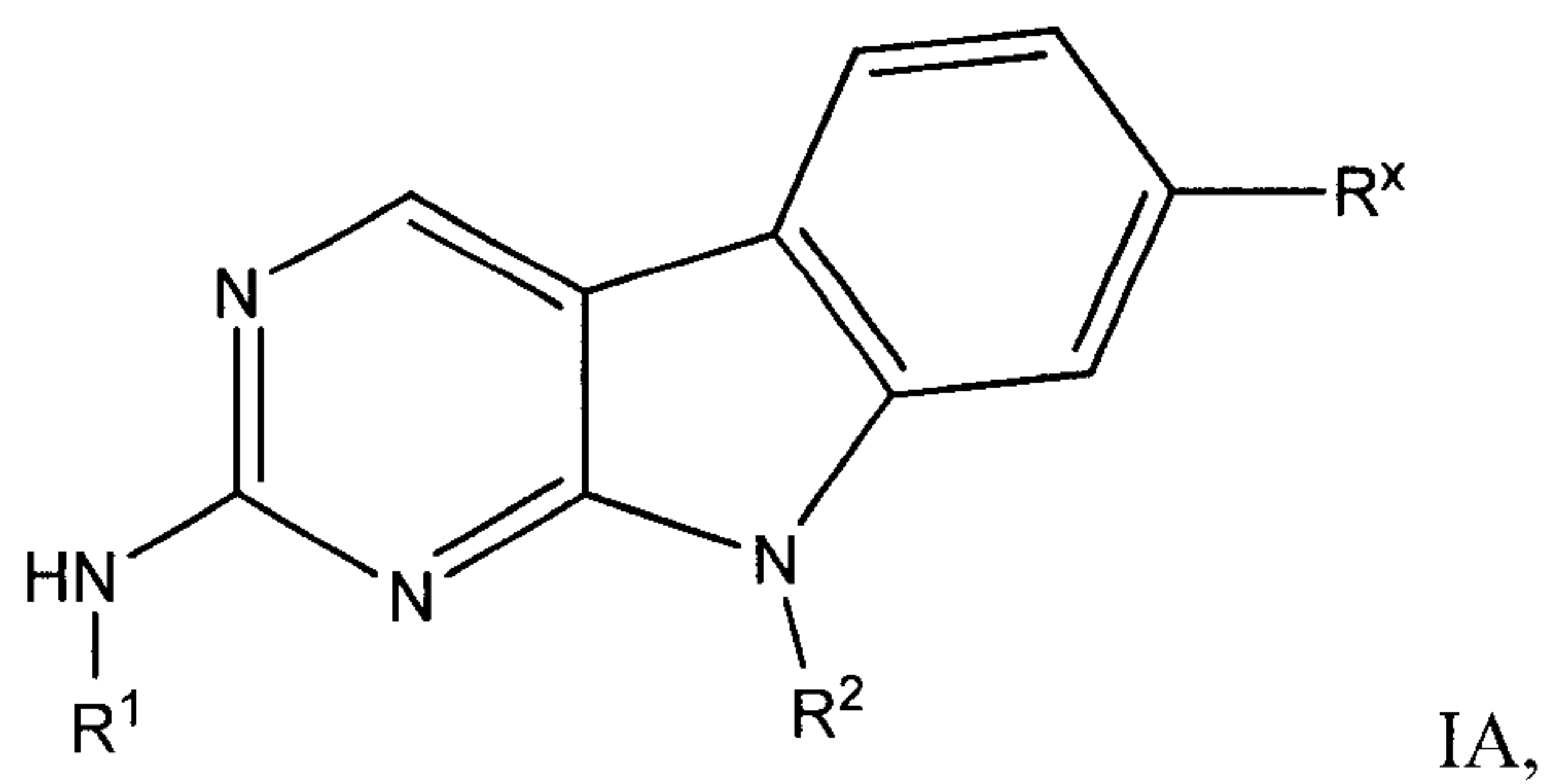




5. The compound of claim 4 wherein  $R^2$  is



6. The compound of claim 1 having the following formula IA

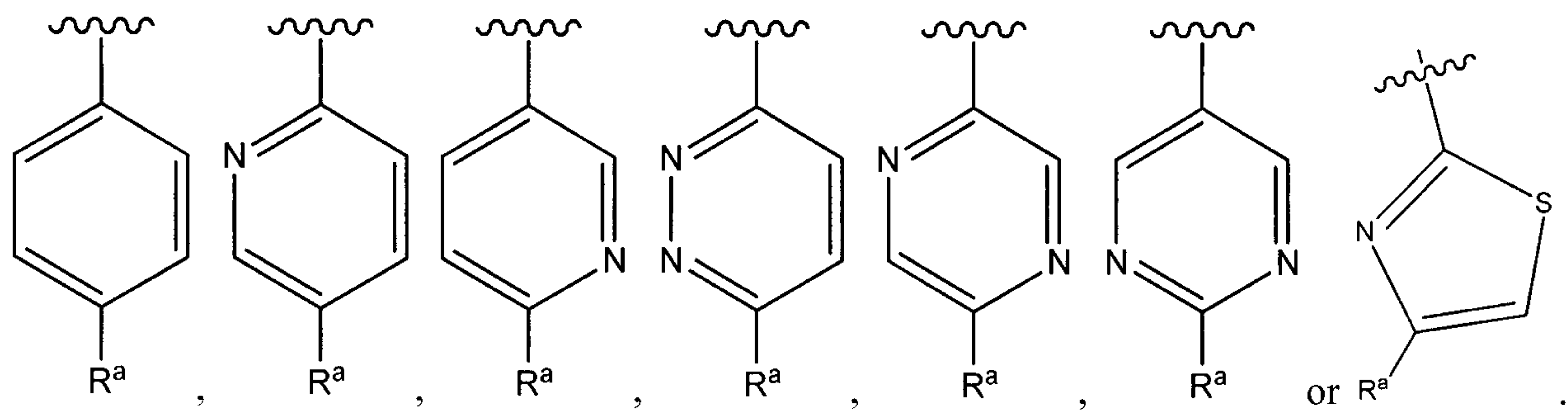


wherein  $R^1$ ,  $R^2$  and  $R^x$  are as defined in claim 1.

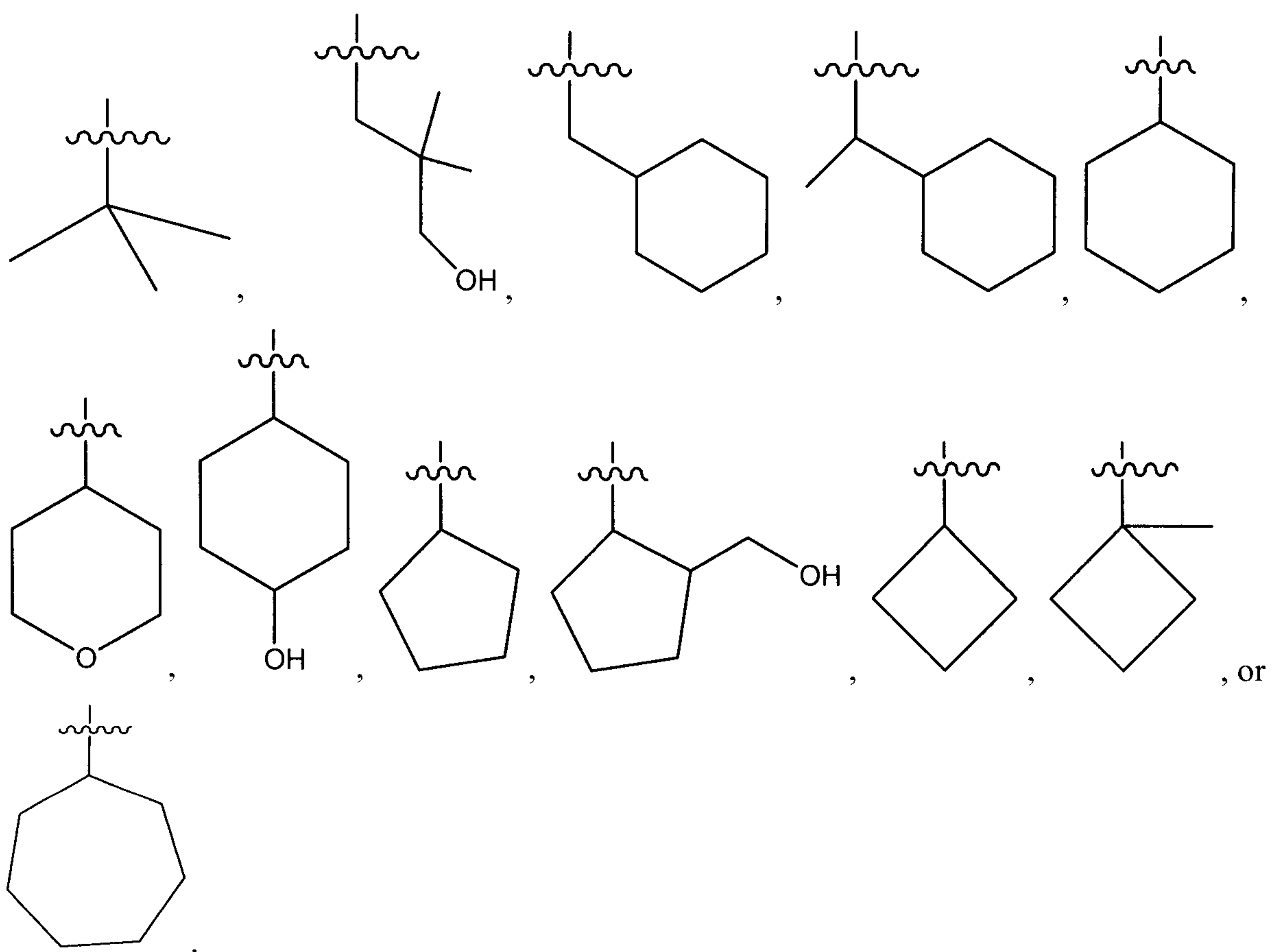
7. The compound of claim 6 wherein Y is phenyl, pyridinyl, pyrimidinyl or thiazolyl.



8. The compound of claim 6 wherein  $R^1$  is

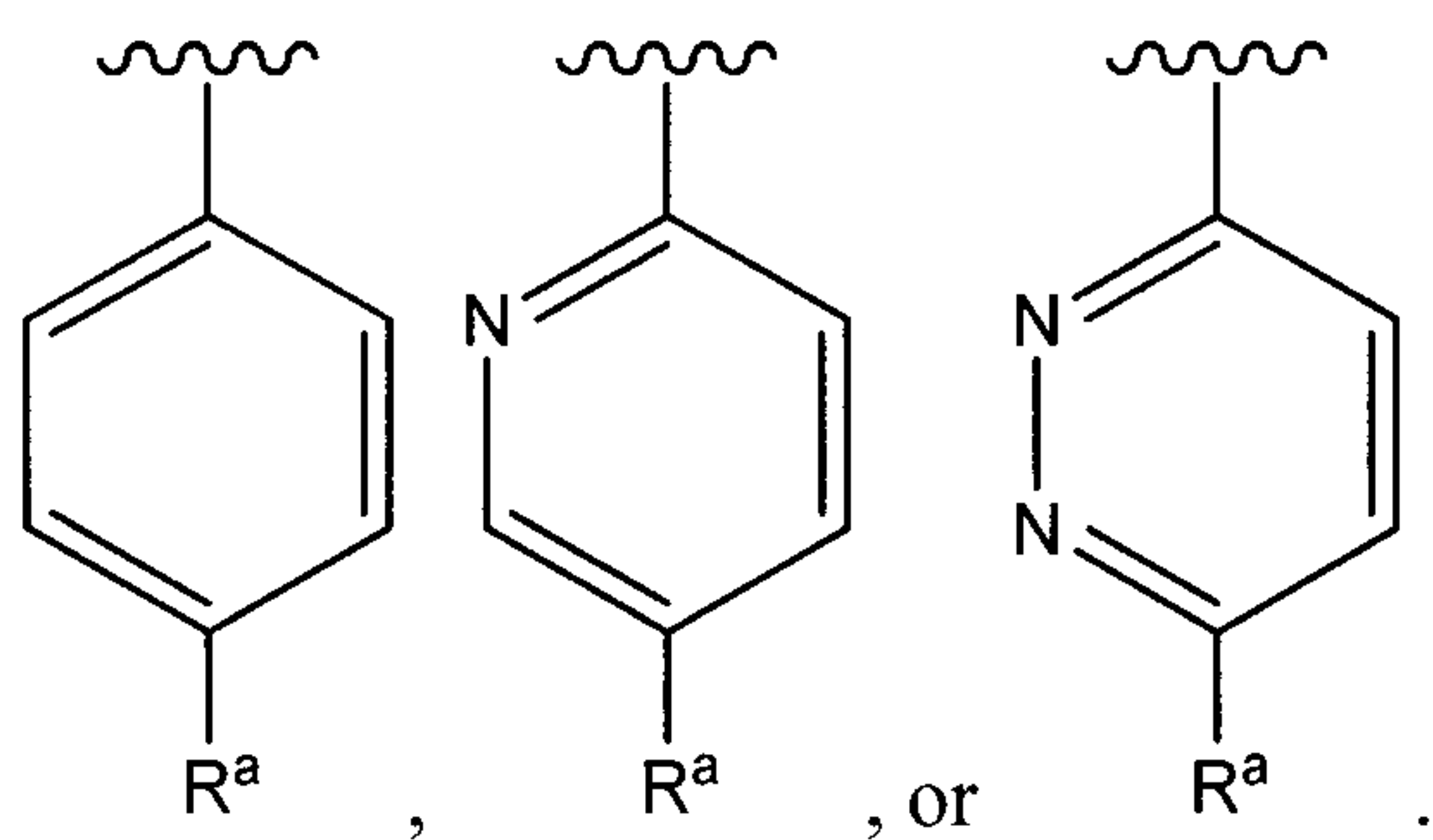


9. A compound of claim 8 wherein  $R^2$  is

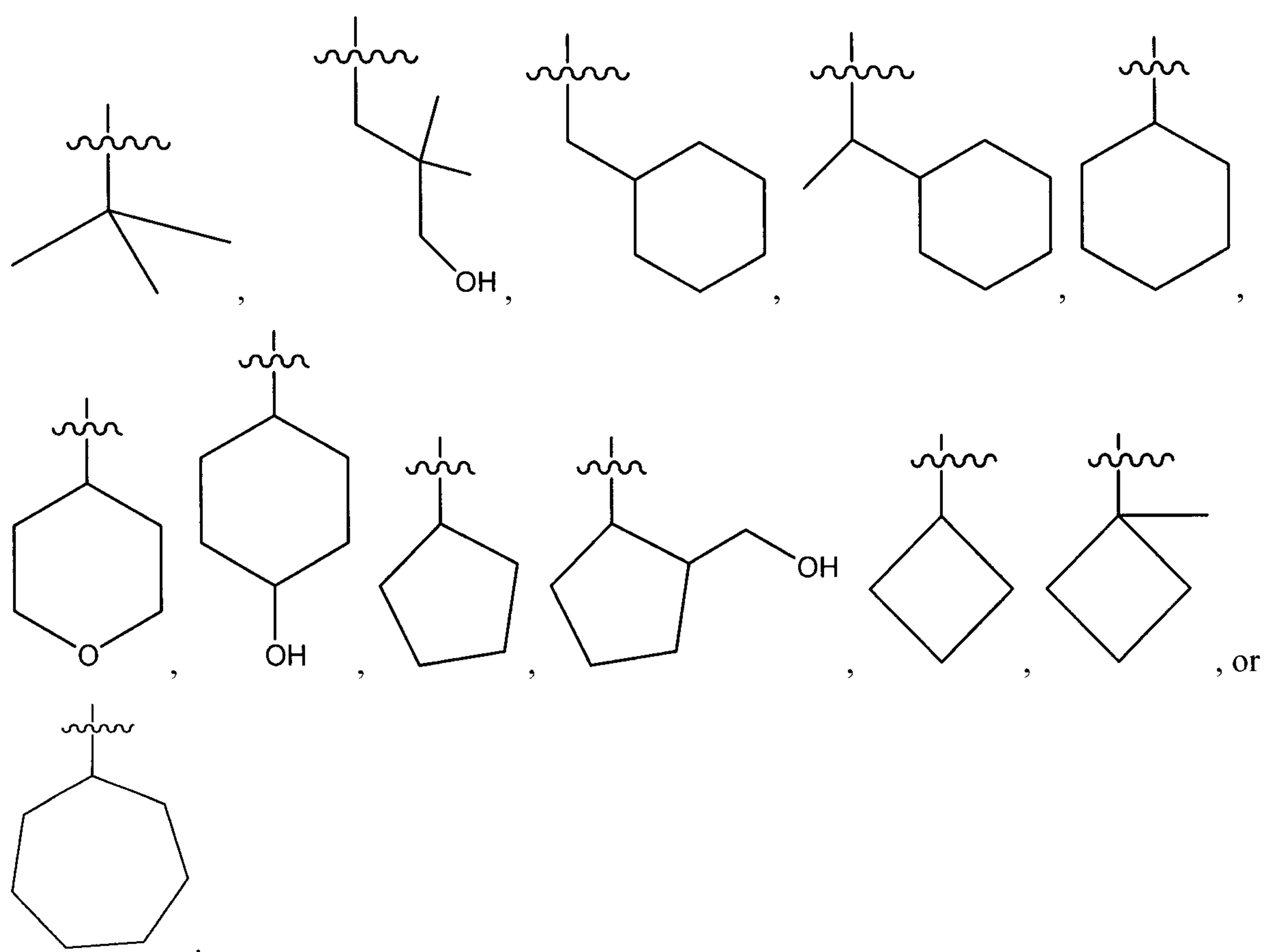




10. The compound of claim 8 wherein  $R^1$  is

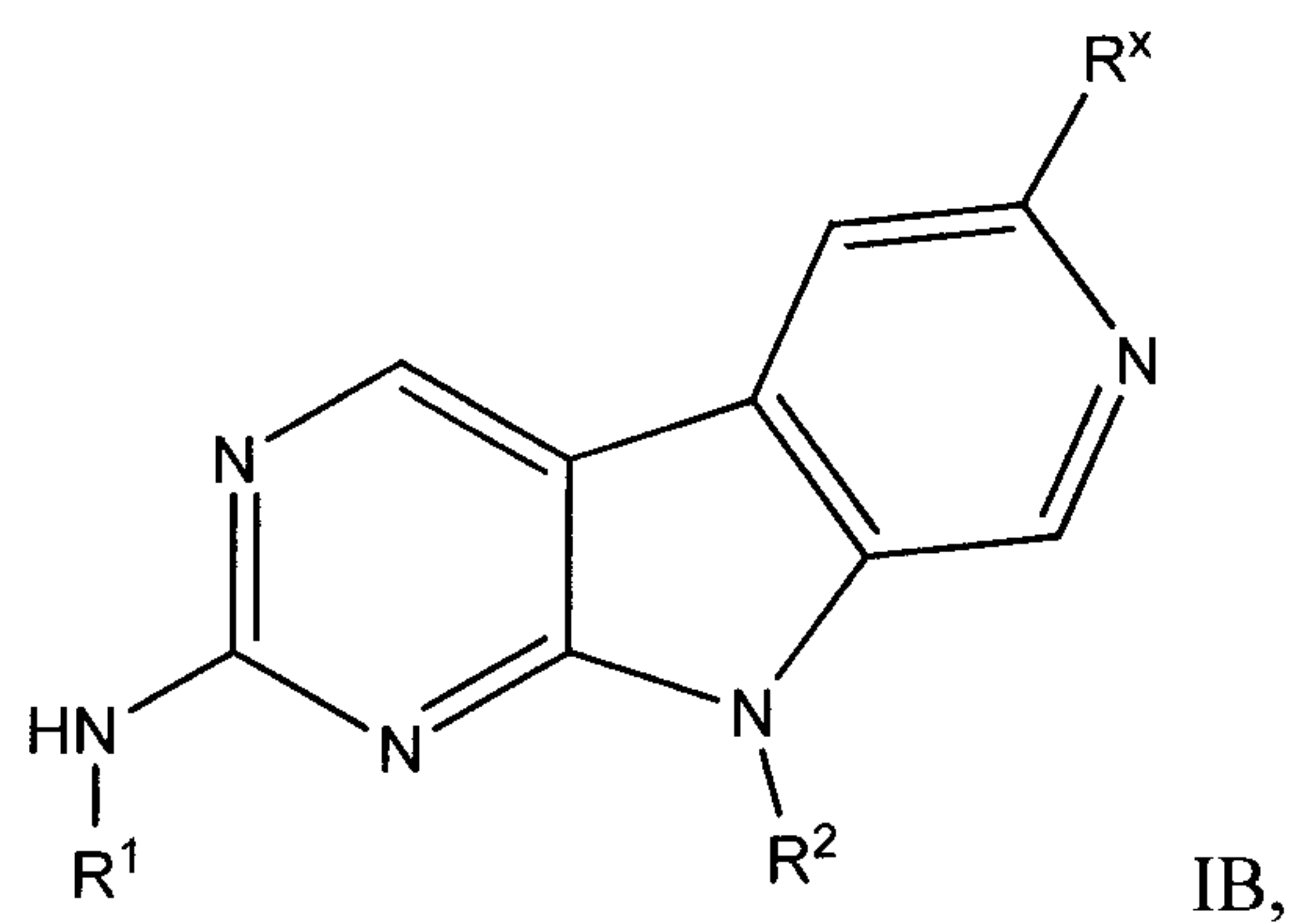


11. The compound of claim 10 wherein  $R^2$  is





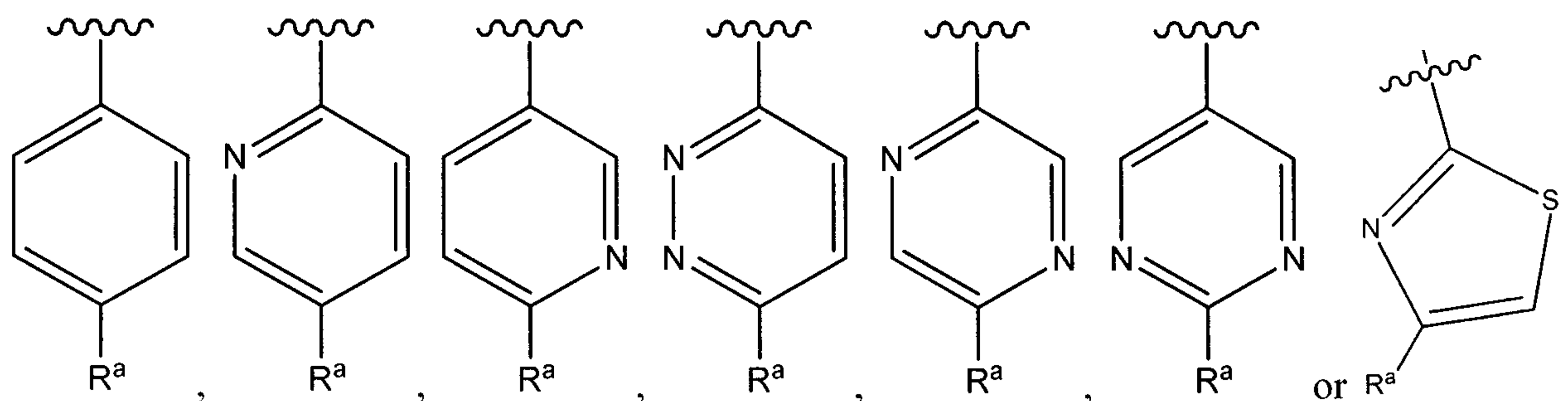
12. The compound of claim 1 having the following formula IB



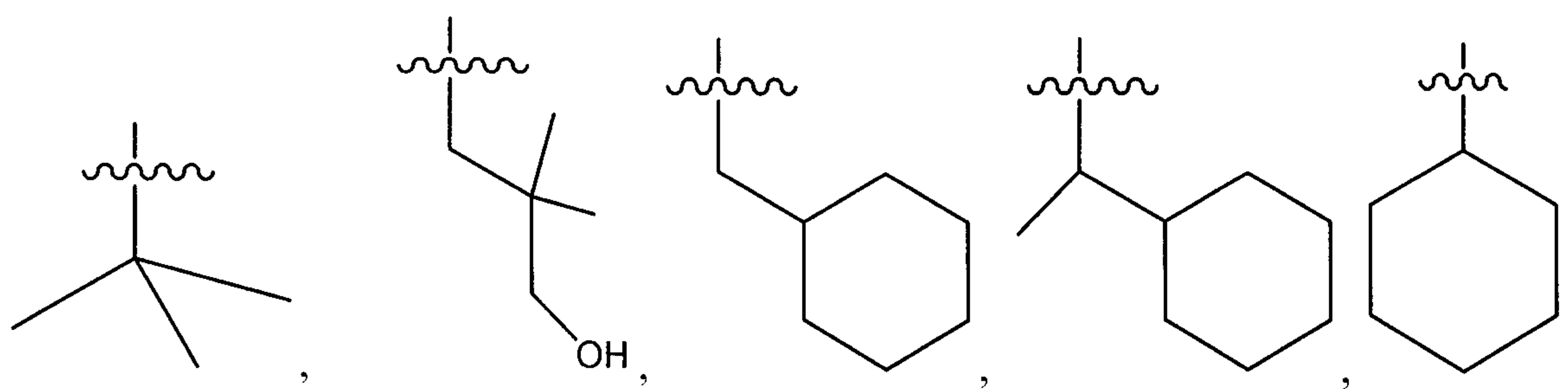
wherein  $R^1$ ,  $R^2$  and  $R^x$  are as defined in claim 1.

13. The compound of claim 12 wherein Y is phenyl, pyridinyl, pyrimidinyl or thiazolyl.

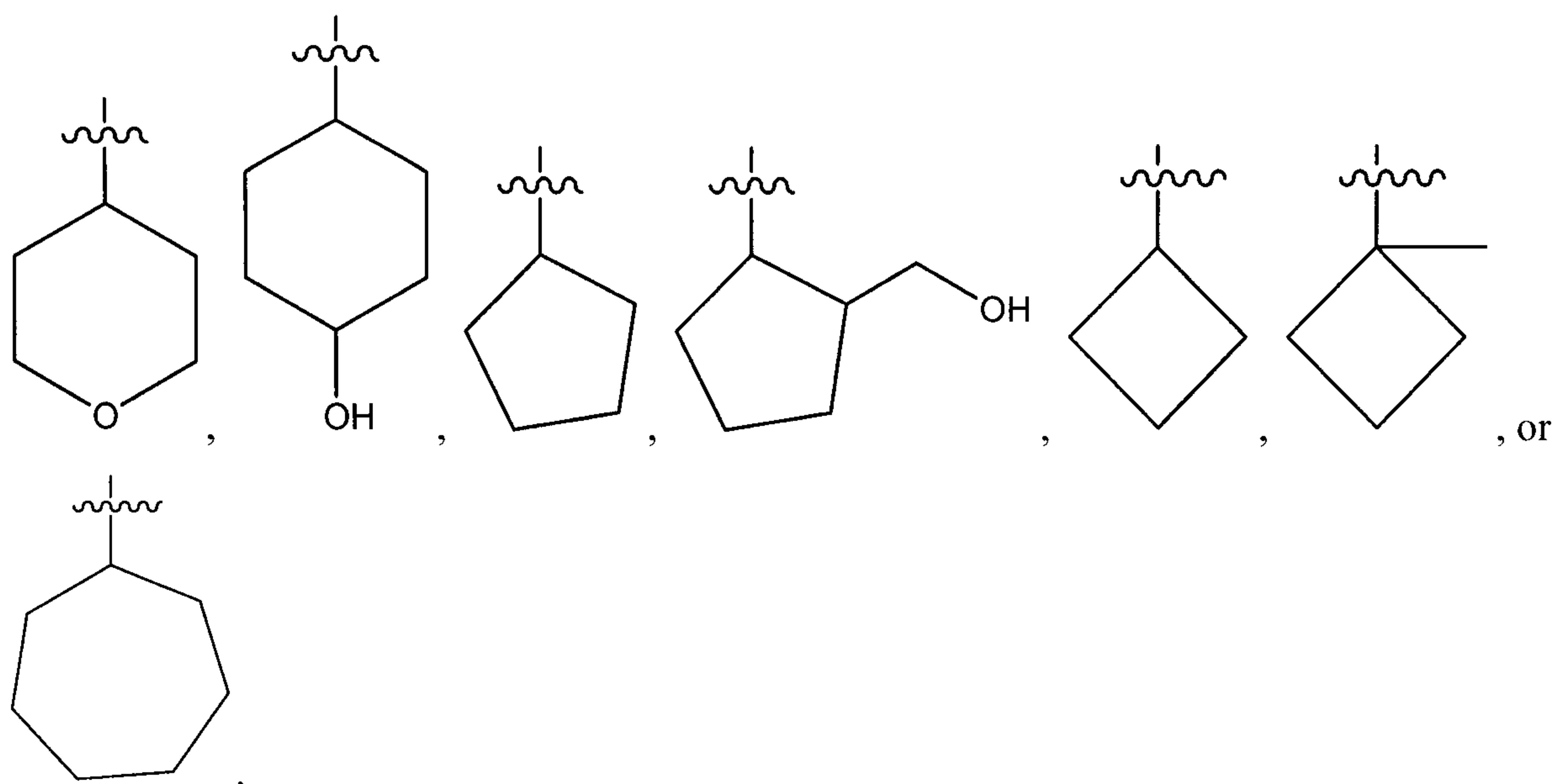
14. The compound of claim 12 wherein  $R^1$  is



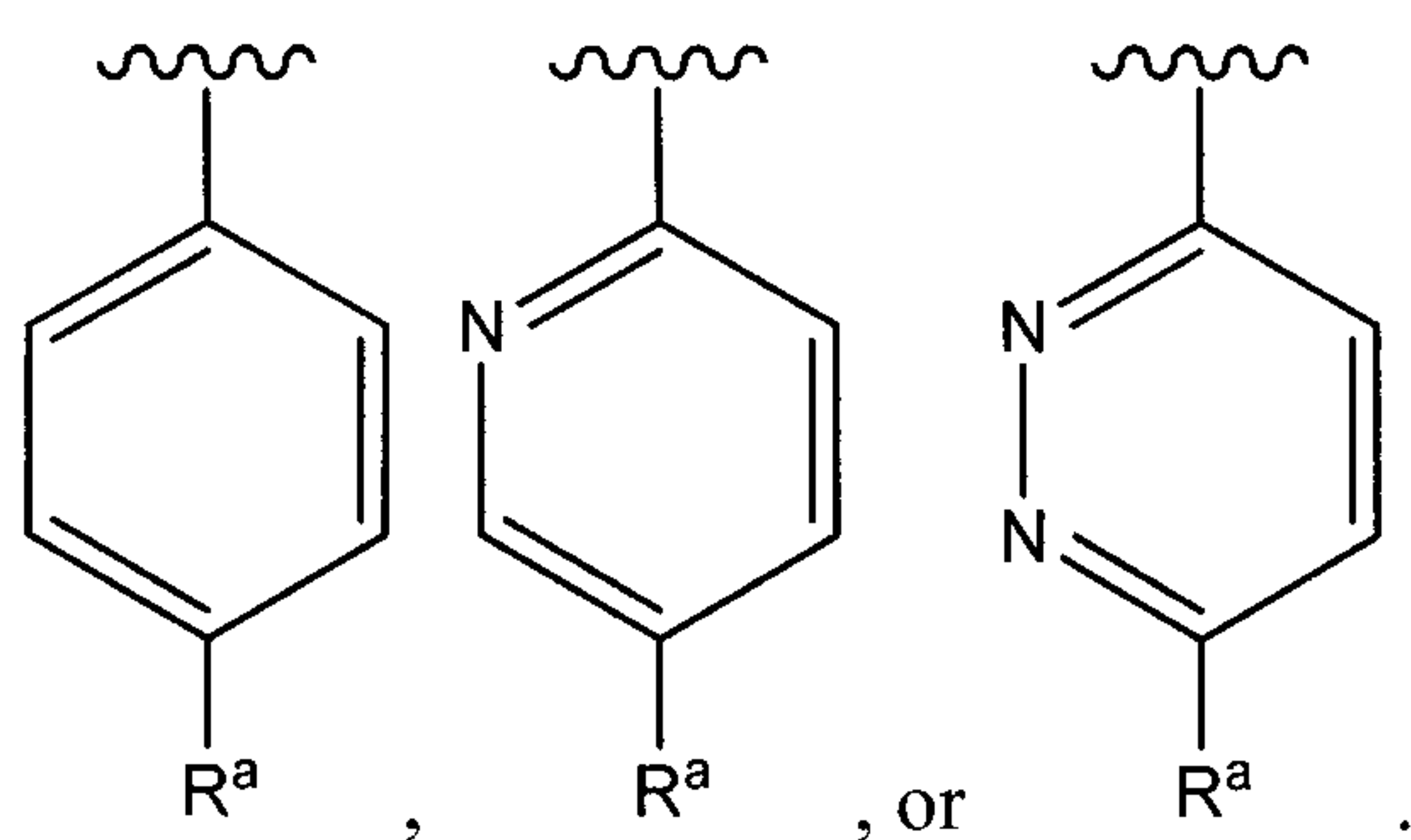
15. The compound of claim 14 wherein  $R^2$  is



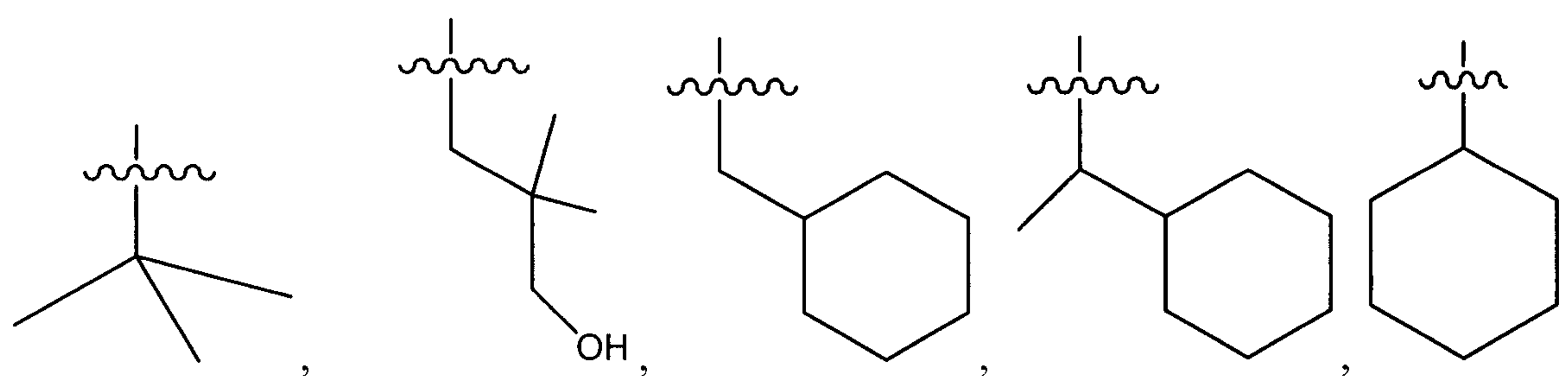




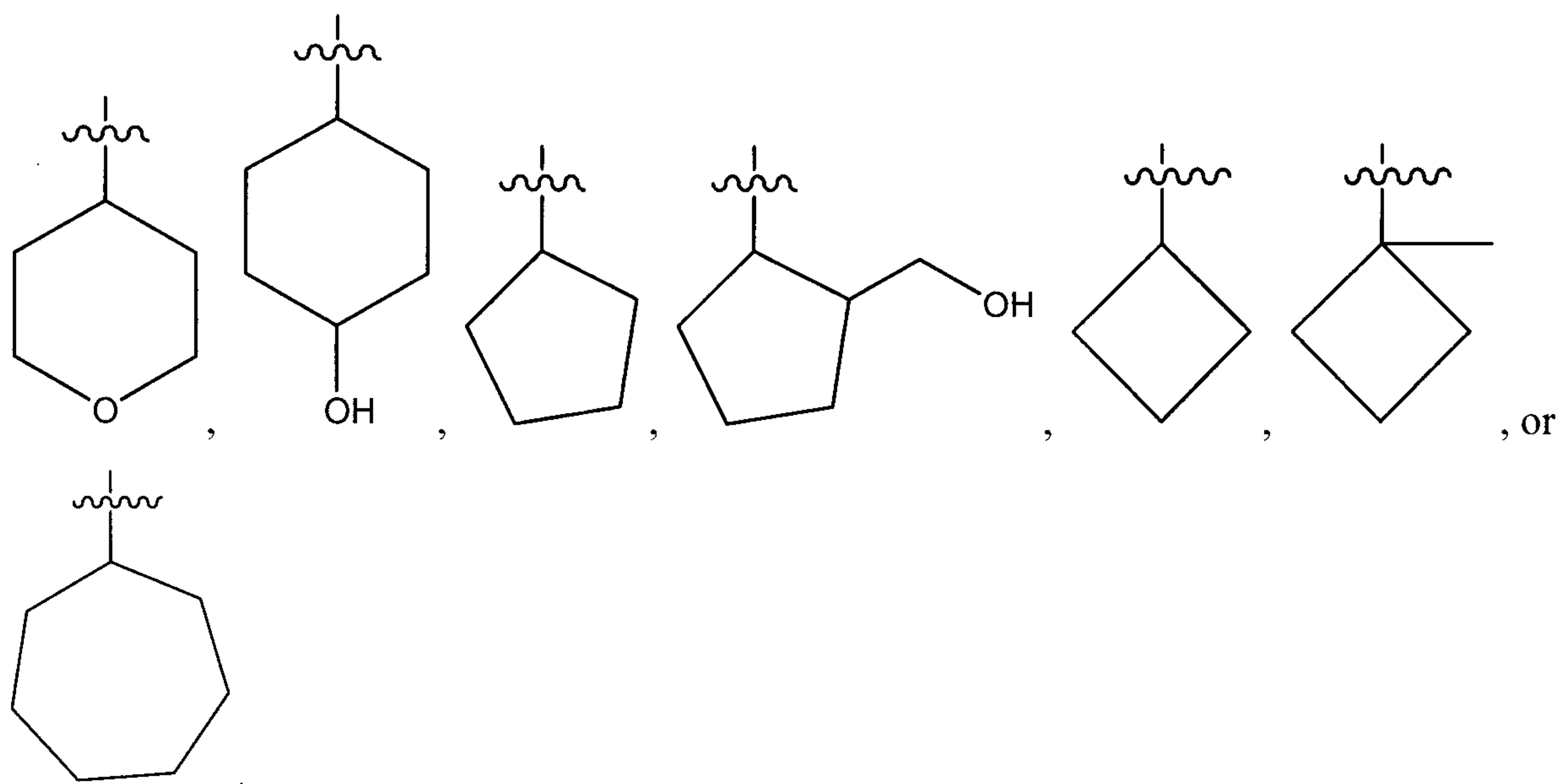
16. The compound of claim 14 wherein  $R^1$  is



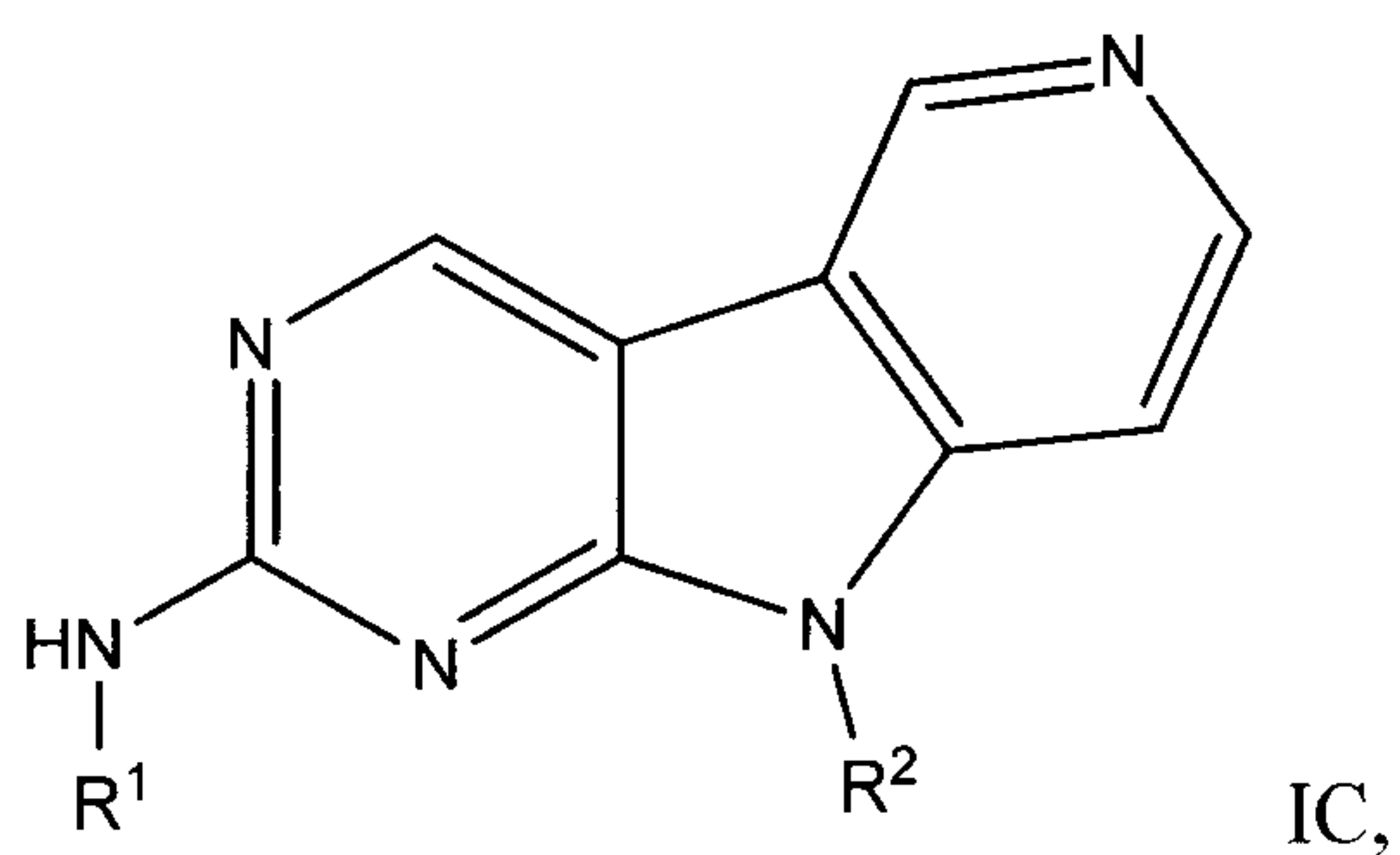
17. The compound of claim 16 wherein  $R^2$  is







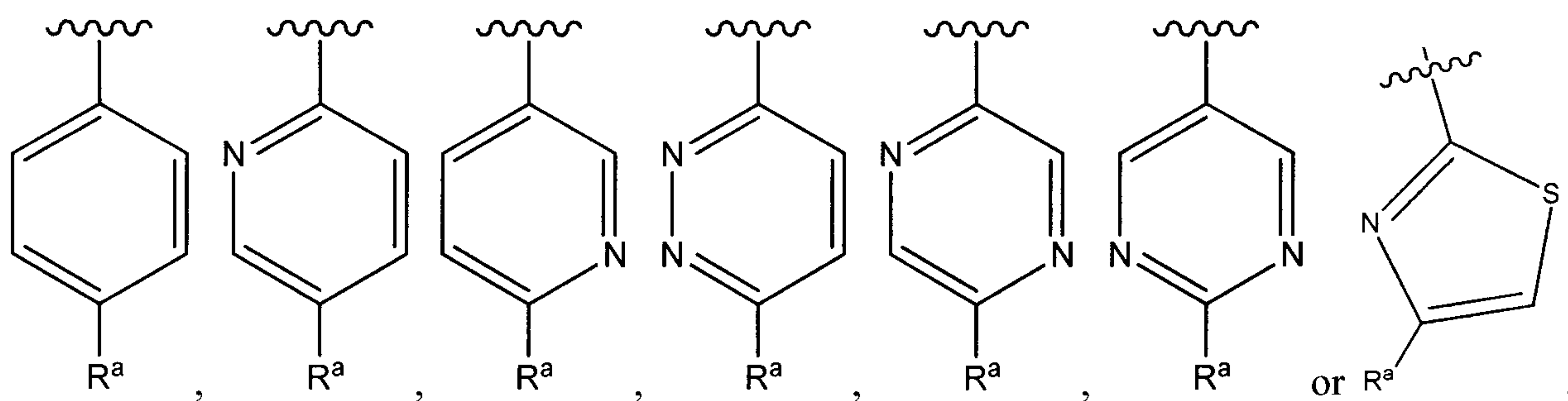
18. The compound of claim 1 having the following formula IC



wherein  $R^1$  and  $R^2$  are as defined in claim 1.

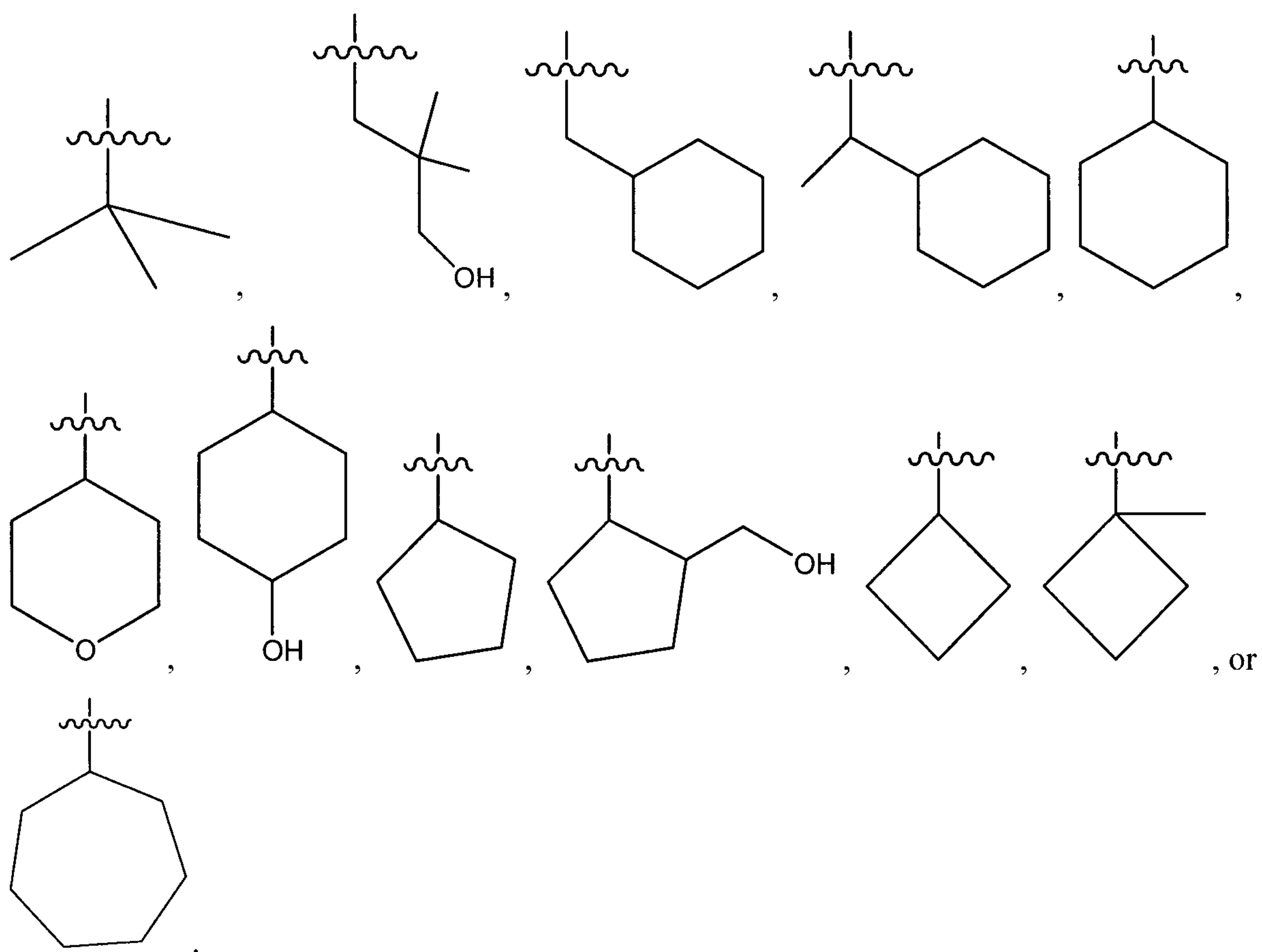
19. The compound of claim 18 wherein Y is phenyl, pyridinyl, pyrimidinyl or thiazolyl.

20. The compound of claim 18 wherein  $R^1$  is

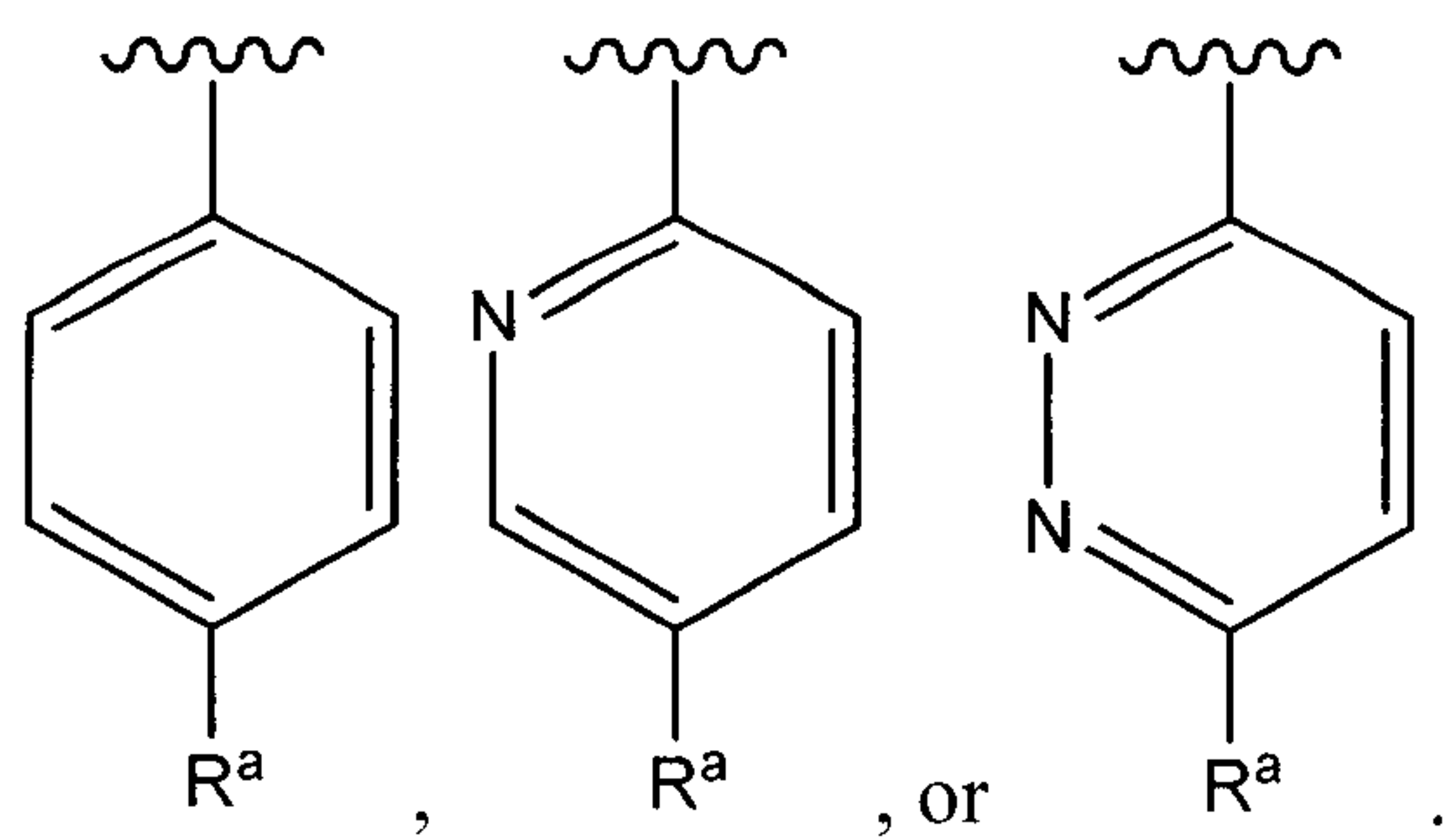




21. The compound of claim 20 wherein  $R^2$  is

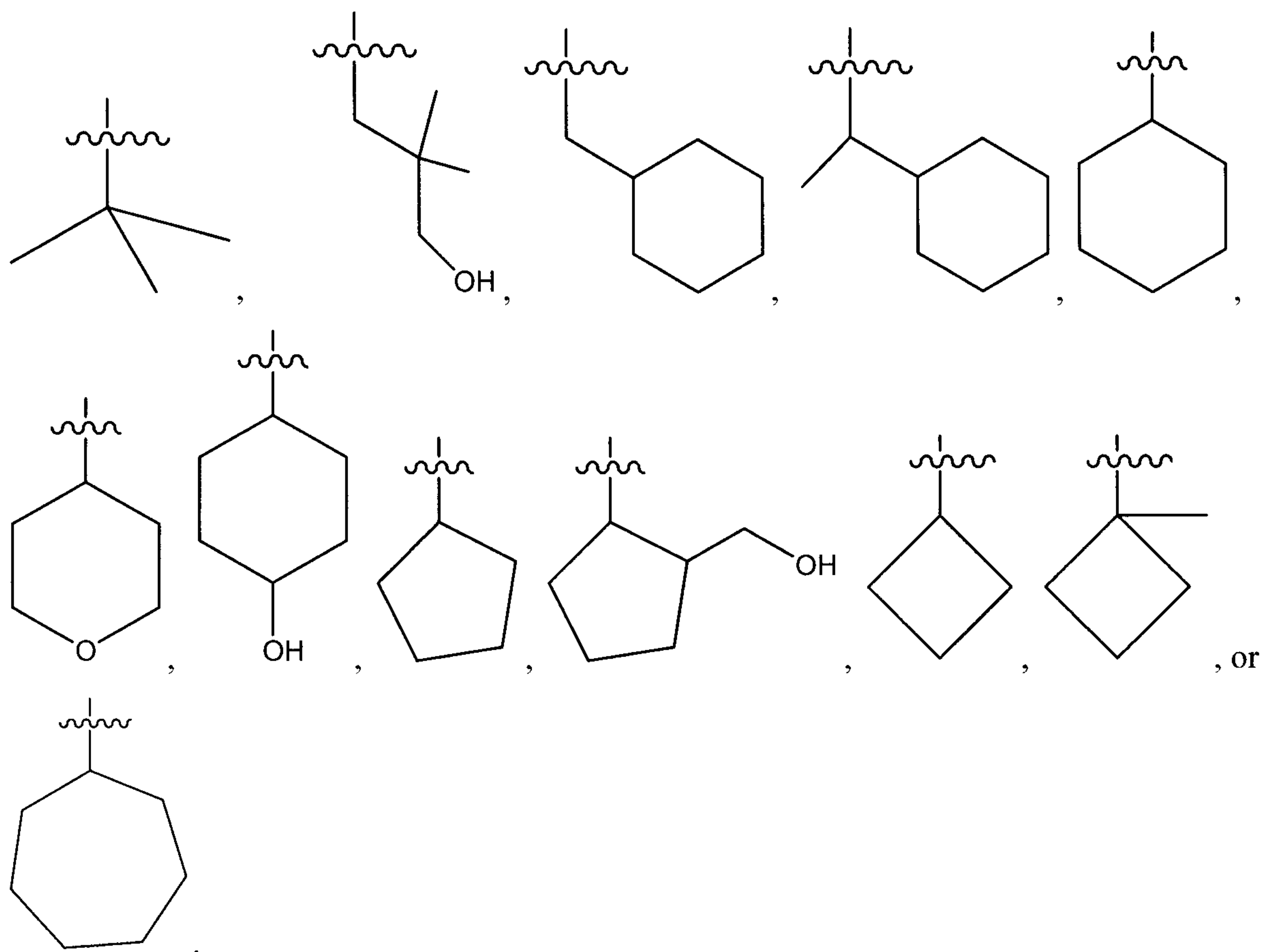


22. The compound of claim 20 wherein  $R^1$  is

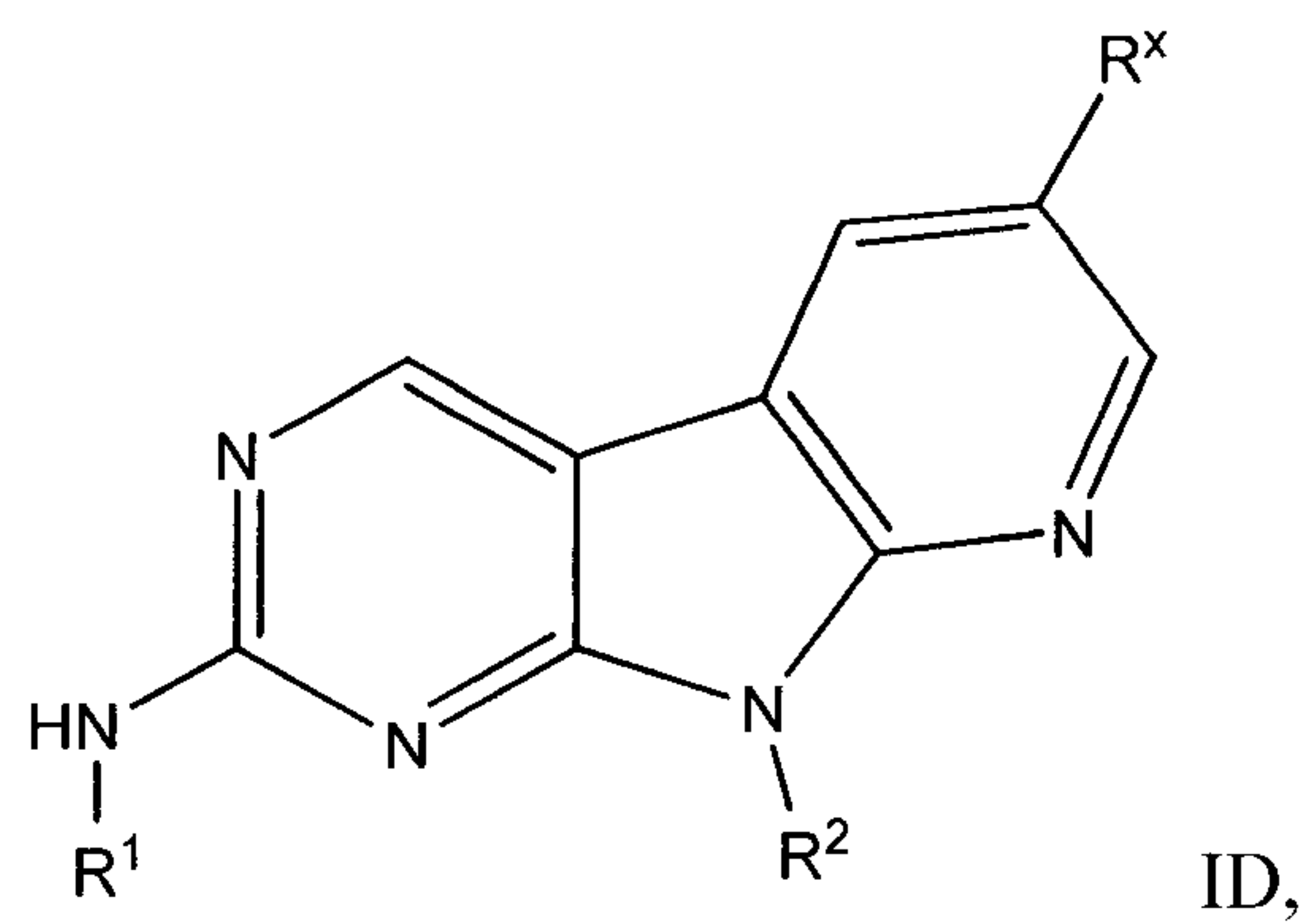




23. The compound of claim 22 wherein R<sup>2</sup> is



24. The compound of claim 1 having the following formula ID

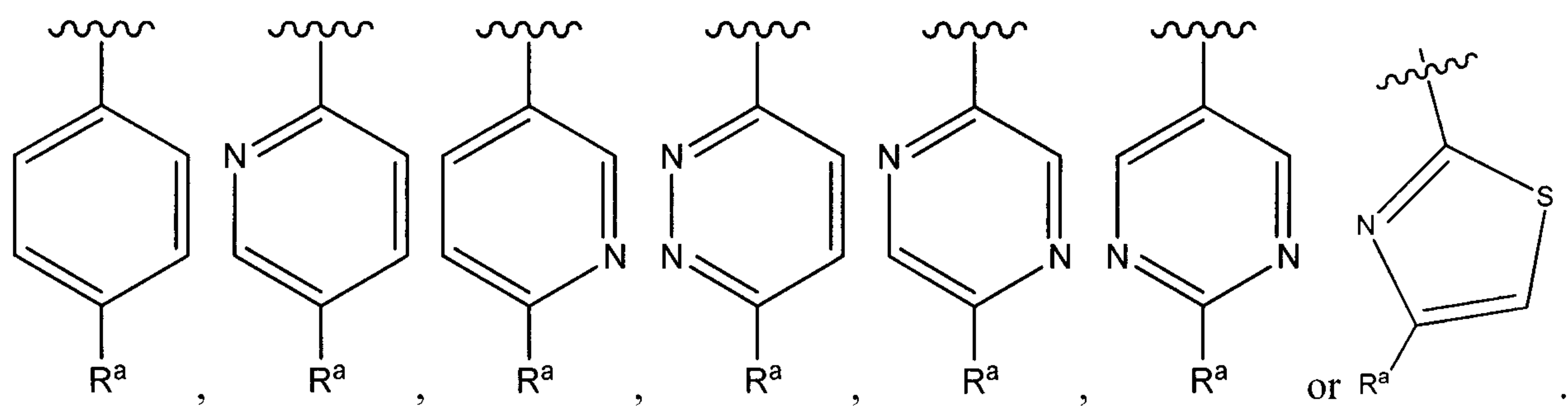


wherein  $R^1$ ,  $R^2$  and  $R^x$  are as defined in claim 1.

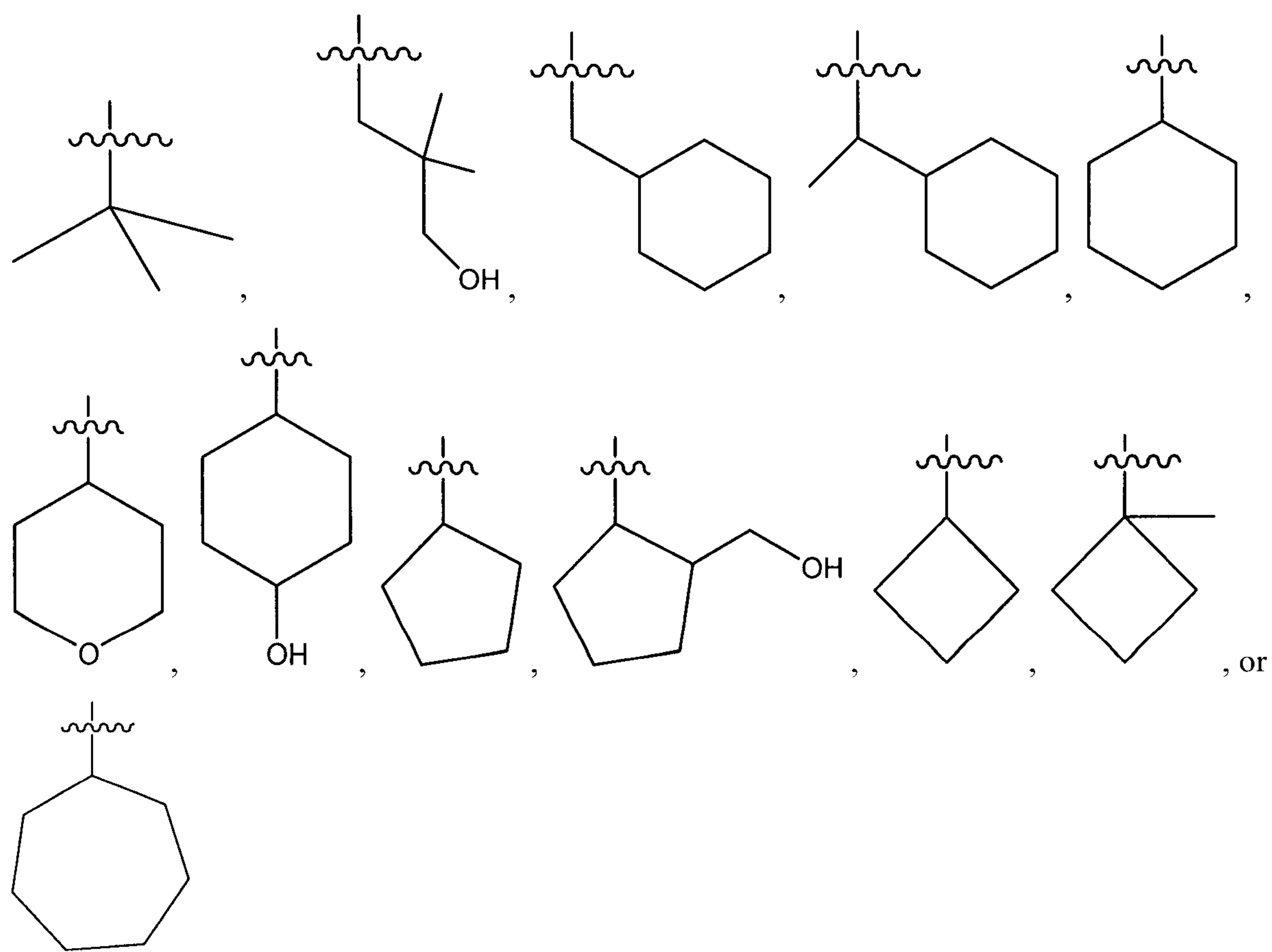


25. The compound of claim 24 wherein Y is phenyl, pyridinyl, pyrimidinyl or thiazolyl.

26. The compound of claim 24 wherein  $R^1$  is

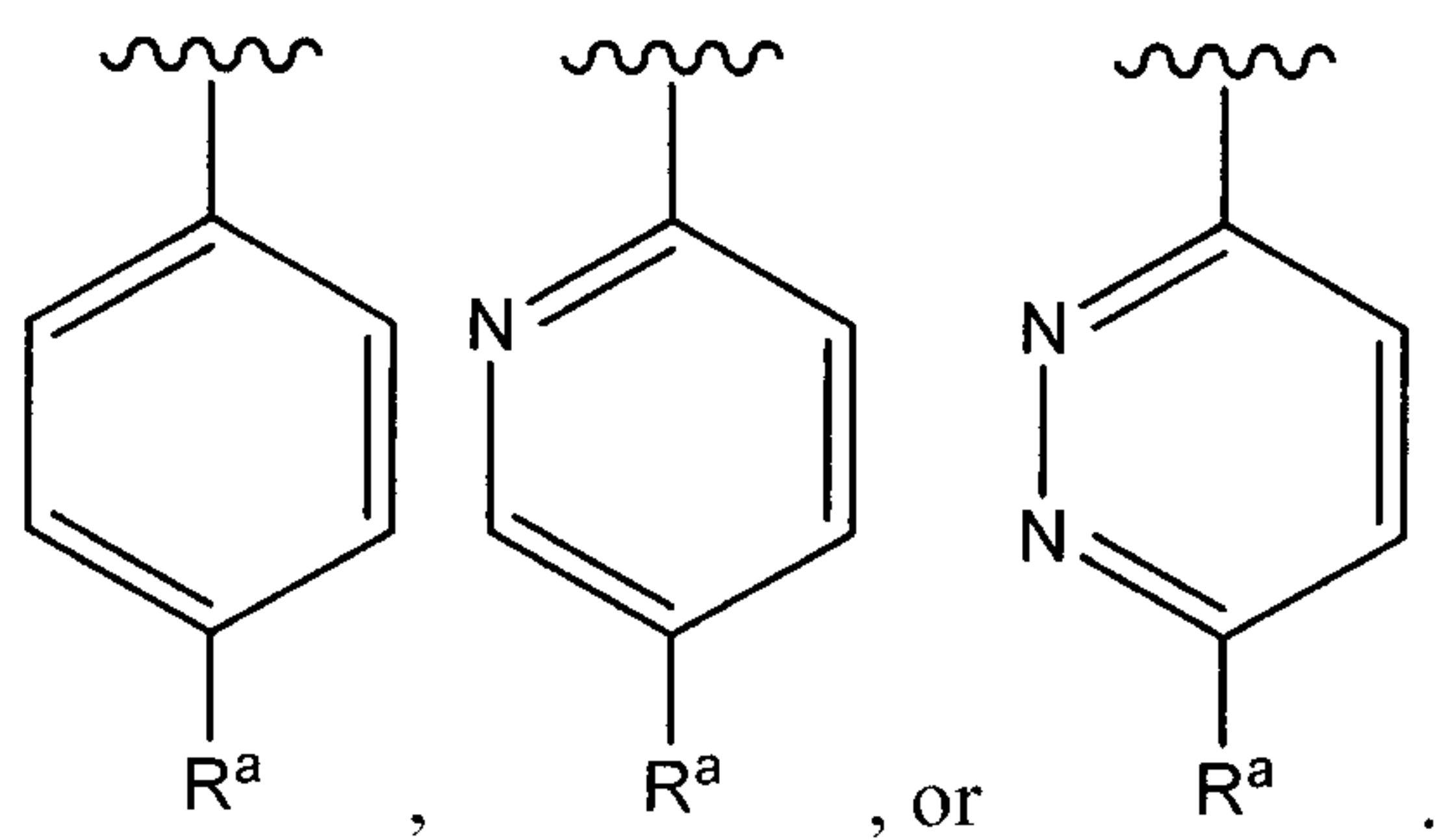


27. The compound of claim 26 wherein  $R^2$  is

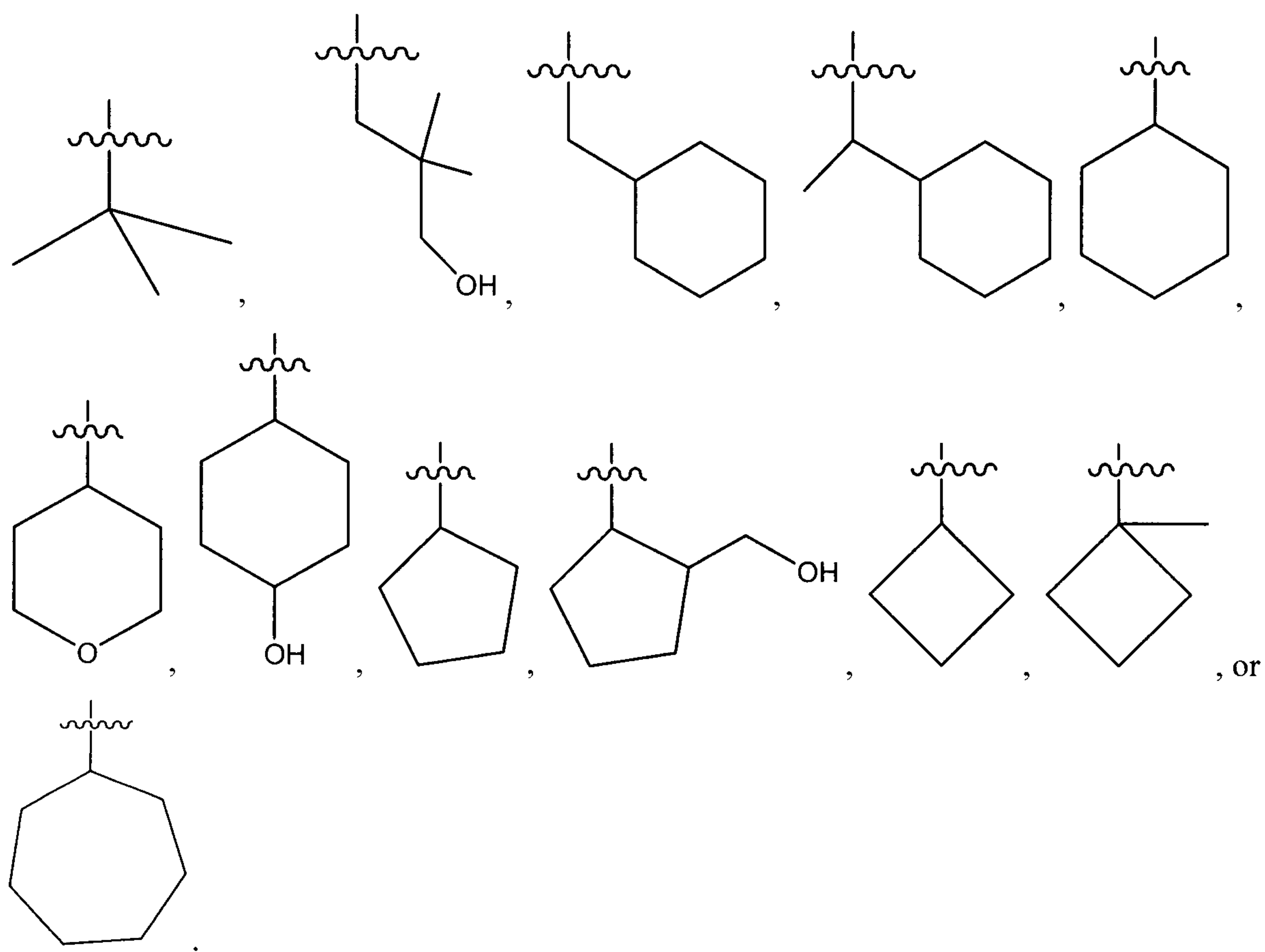




28. The compound of claim 26 wherein  $R^1$  is

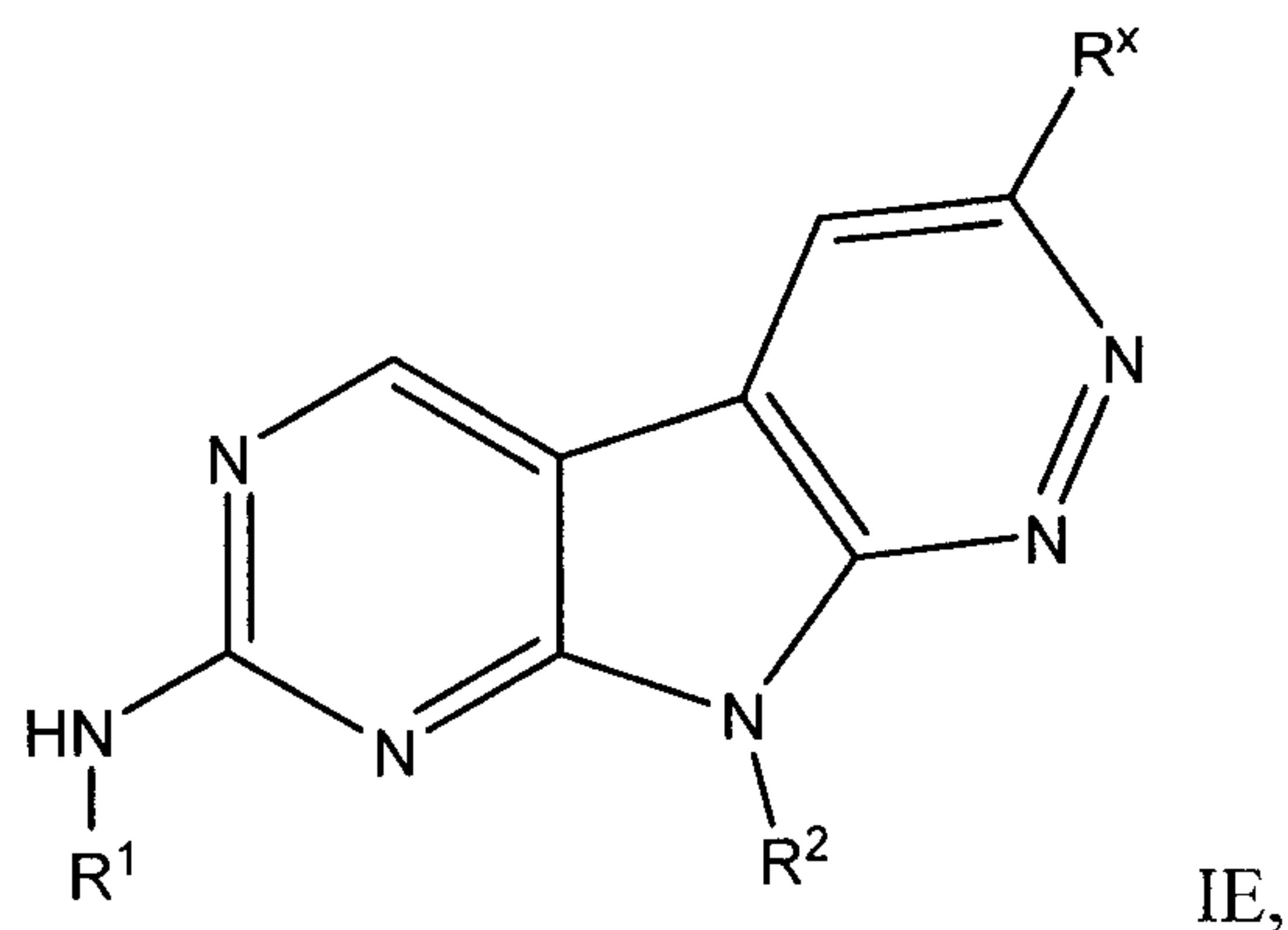


29. The compound of claim 28 wherein  $R^2$  is





30. The compound of claim 1 having the following formula IE



wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>x</sup> are as defined in claim 1.

31. A pharmaceutical composition comprising the compound defined in any one of claims 1-30 together with a pharmaceutically acceptable vehicle adjuvant or diluent.

32. A use of an effective amount of the compound defined in any one of claims 1-30, for treating cancer in a subject.

33. A use of an effective amount of the compound defined in any one of claims 1-30, for the preparation of a medicament for treating cancer in a subject.

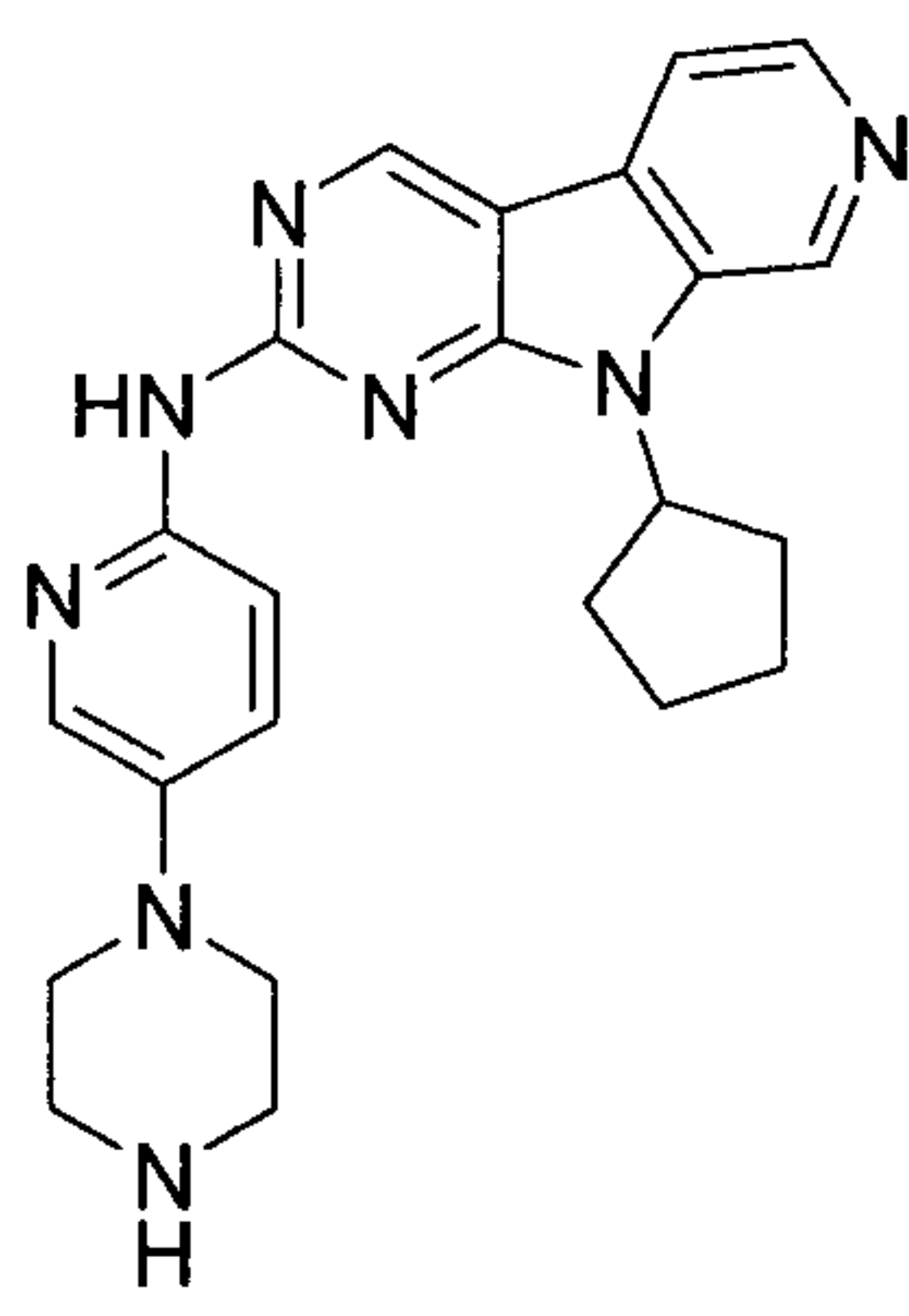
34. A use of an effective amount of the compound defined in any one of claims 1-30, and at least one compound selected from the group consisting of an antibiotic-type agent, an alkylating agent, an antimetabolite agent, a hormonal agent, an immunological agent, an interferon-type agent and a miscellaneous agent, for treating cancer in a subject.

35. A use of an effective amount of the compound defined in any one of claims 1-30, and at least one compound selected from the group consisting of an antibiotic-type agent, an alkylating agent, an antimetabolite agent, a hormonal agent, an immunological agent, an interferon-type agent and a miscellaneous agent, for the preparation of a medicament for treating cancer in a subject.

36. A use of an effective amount of the compound defined in any one of claims 1-30, for reducing tumor size in a subject.



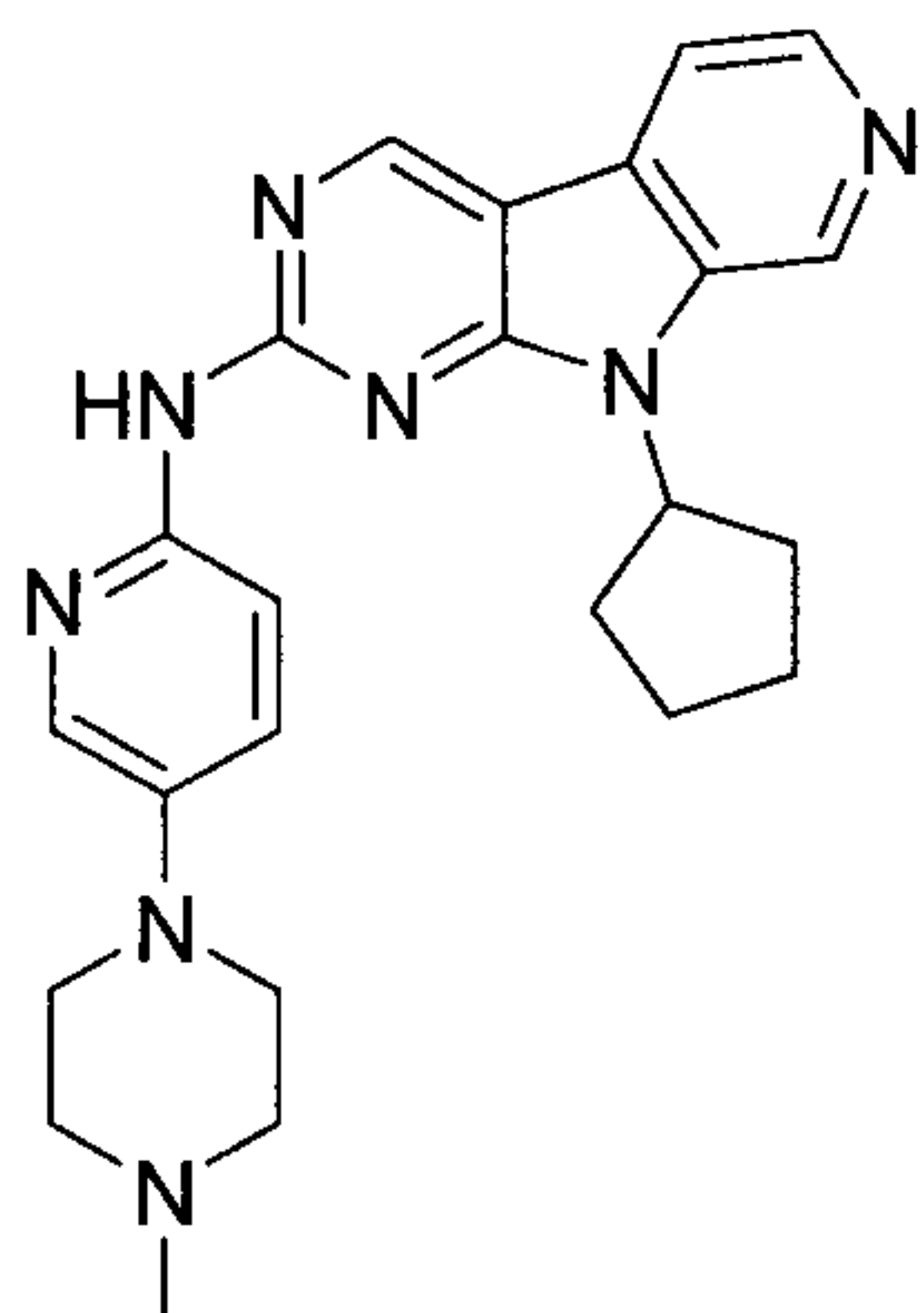
37. A use of an effective amount of the compound defined in any one of claims 1-30, for the preparation of a medicament for reducing tumor size in a subject.
38. A use of an effective amount of the compound defined in any one of claims 1-30, for treating cdk4 or cdk6 mediated disorders in a subject.
39. A use of an effective amount of the compound defined in any one of claims 1-30, for the preparation of a medicament for treating cdk4 or cdk6 mediated disorders in a subject.
40. A use of an effective amount of the compound defined in any one of claims 1-30, for reducing metastasis in a tumor in a subject.
41. A use of an effective amount of the compound defined in any one of claims 1-30, for the preparation of a medicament for reducing metastasis in a tumor in a subject.
42. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

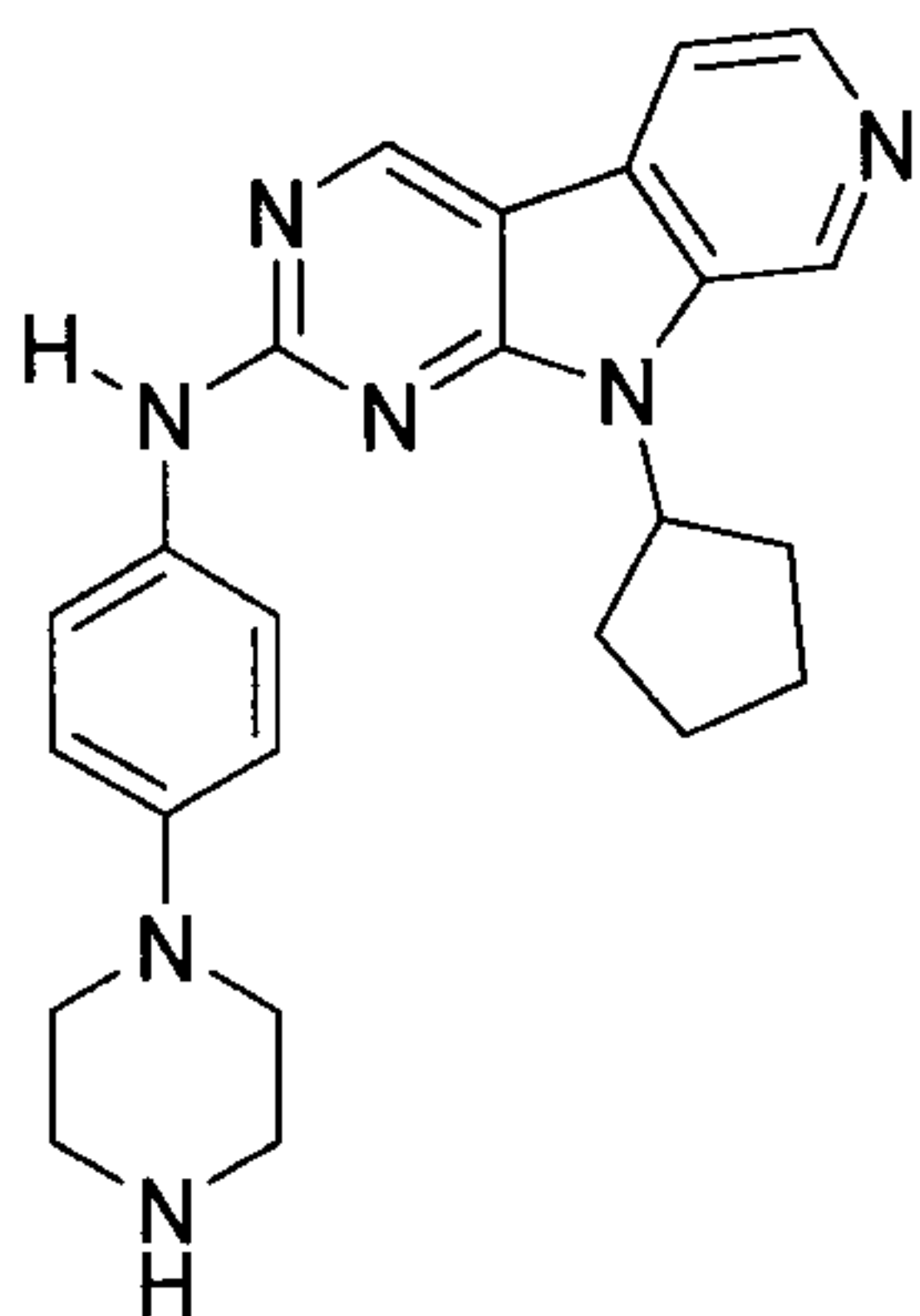


43. The compound of claim 1, wherein the compound is



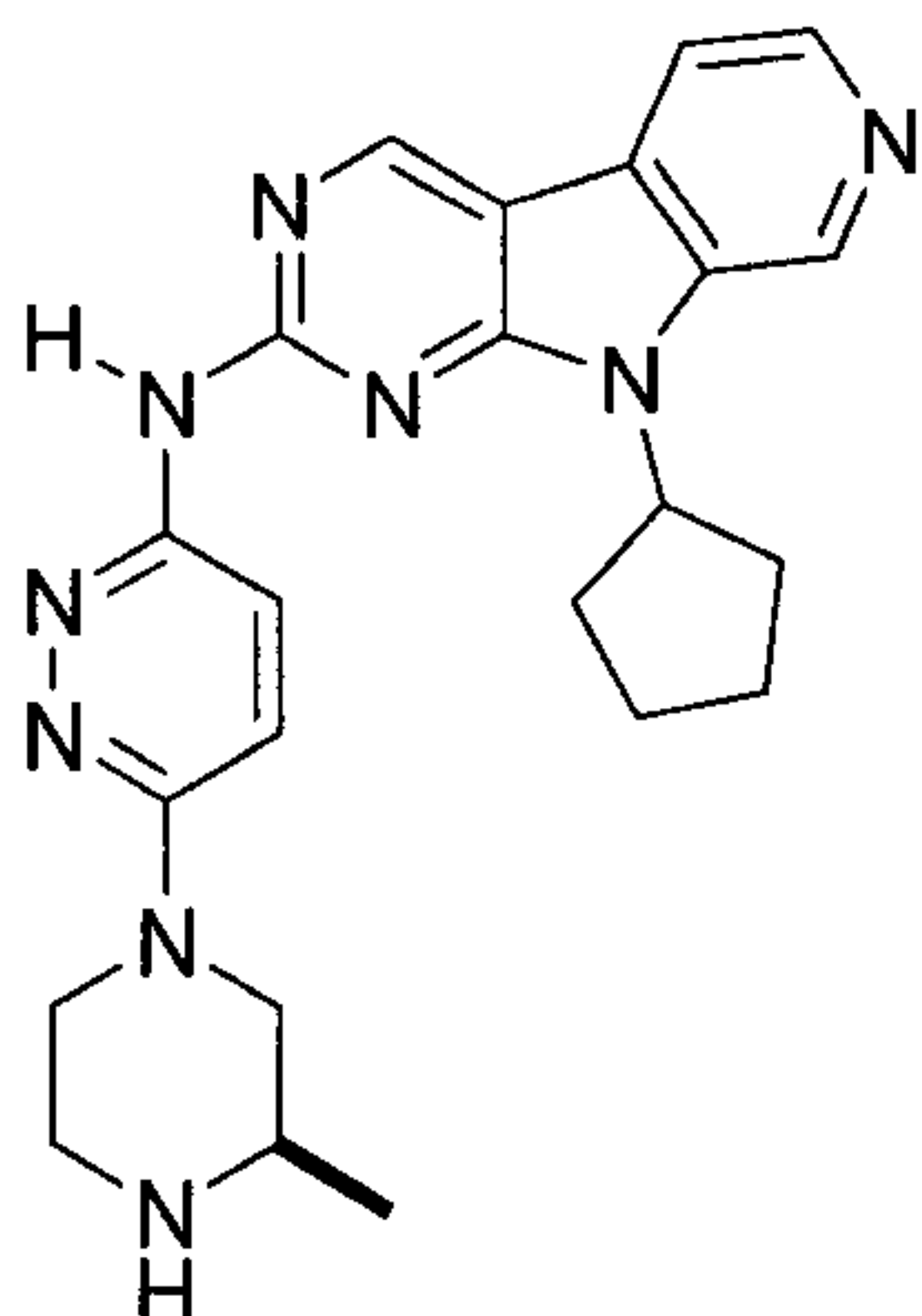
or a pharmaceutically acceptable salt thereof.

44. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

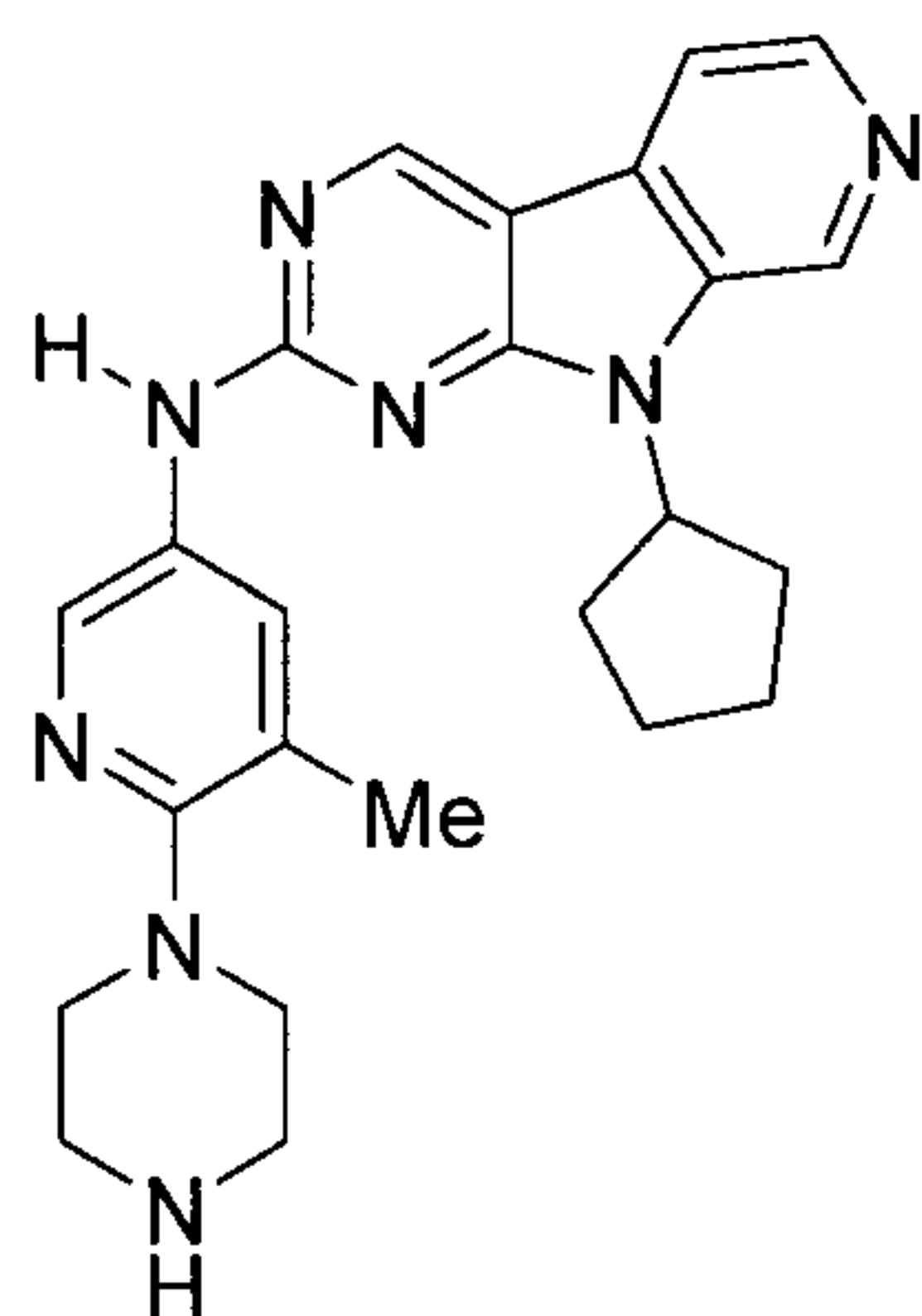
45. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

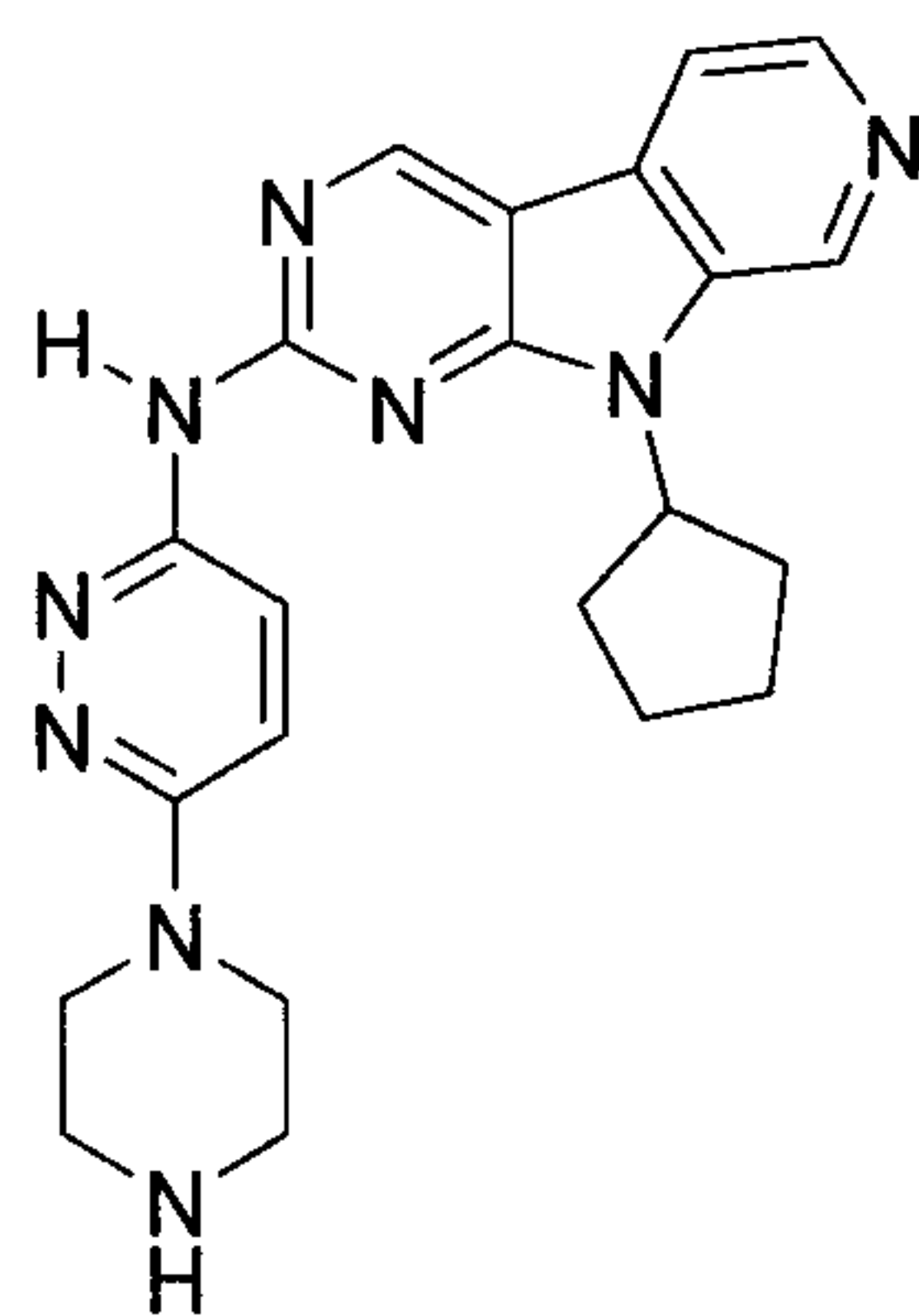


46. The compound of claim 1, wherein the compound is



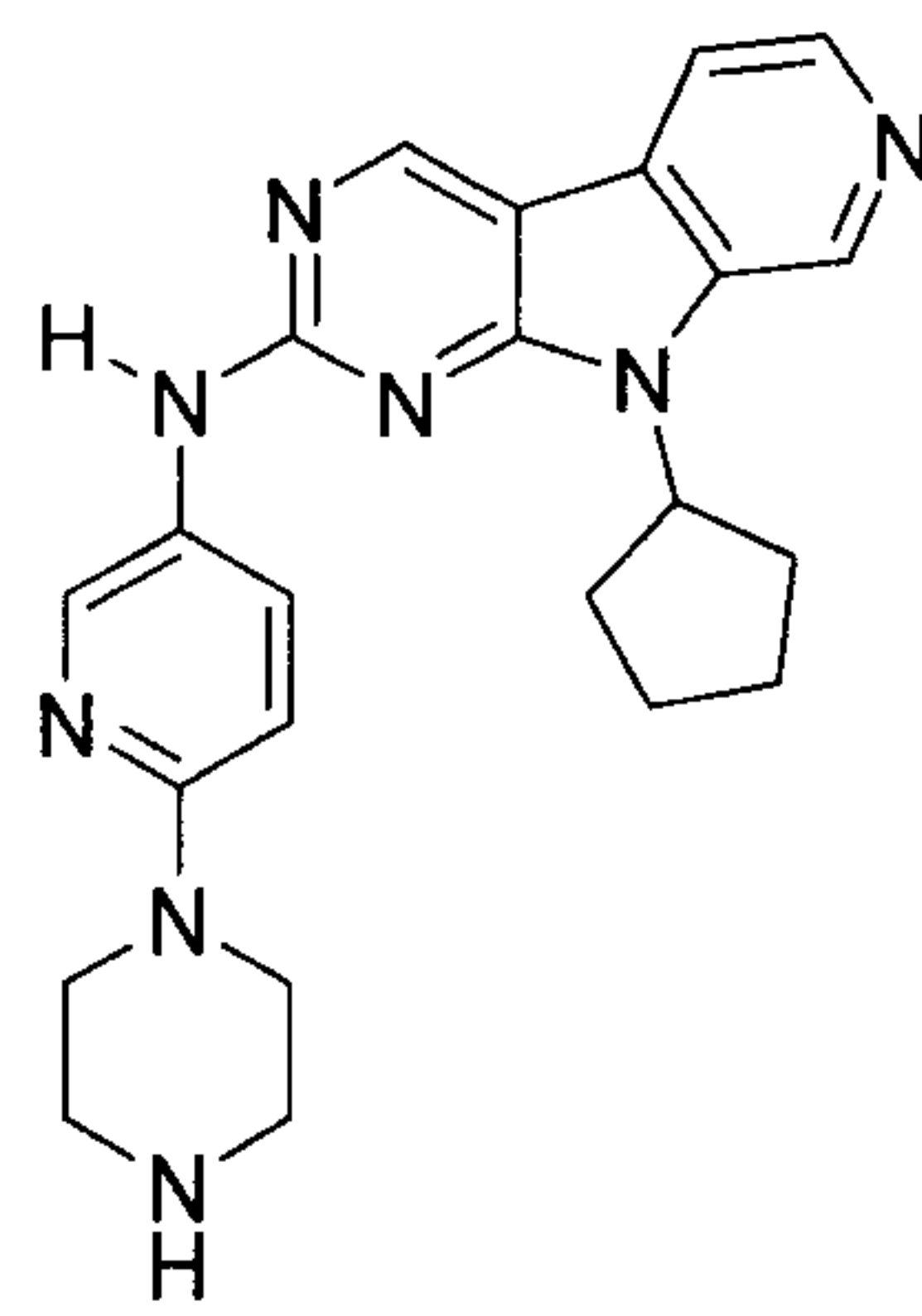
or a pharmaceutically acceptable salt thereof.

47. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

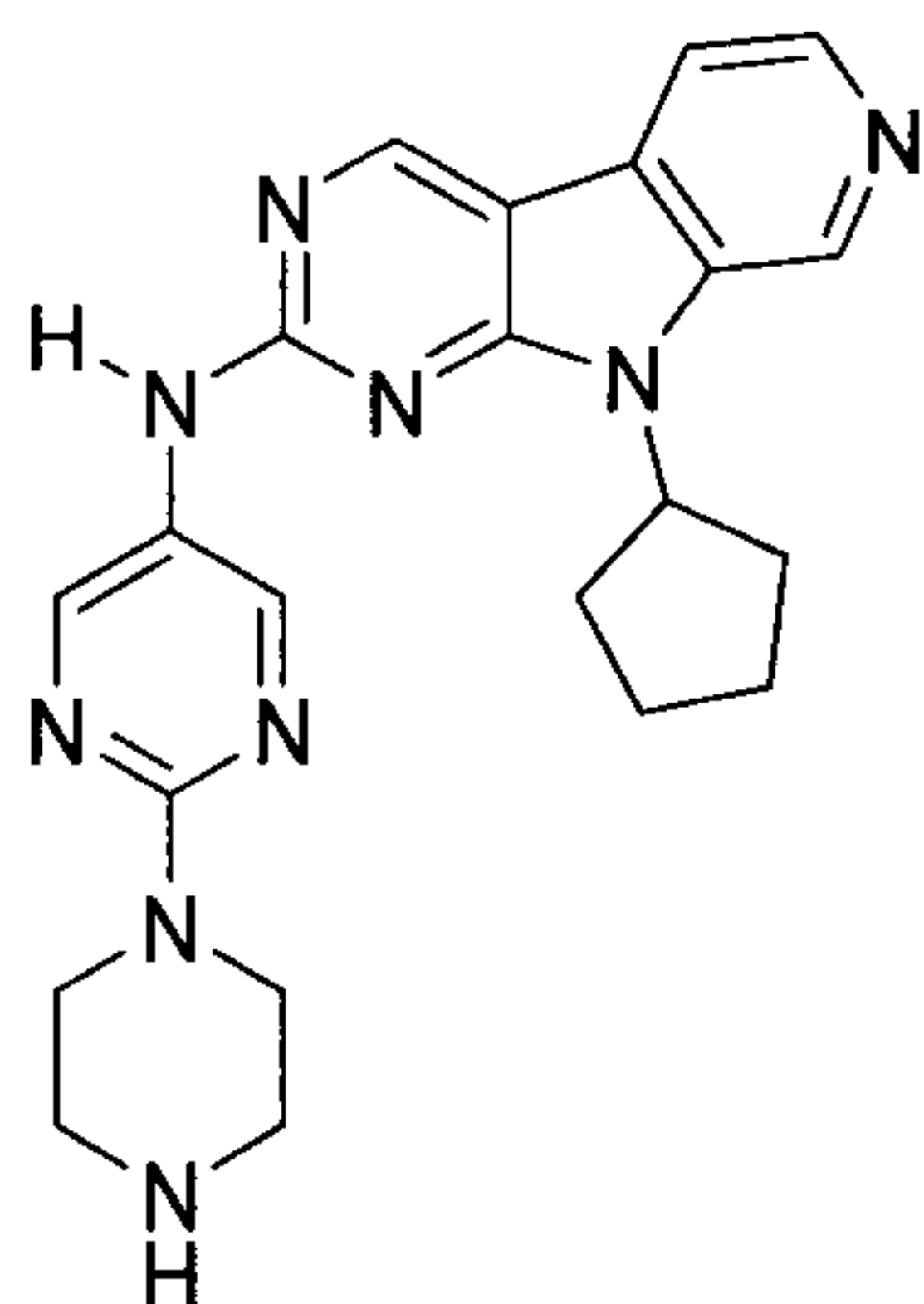
48. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

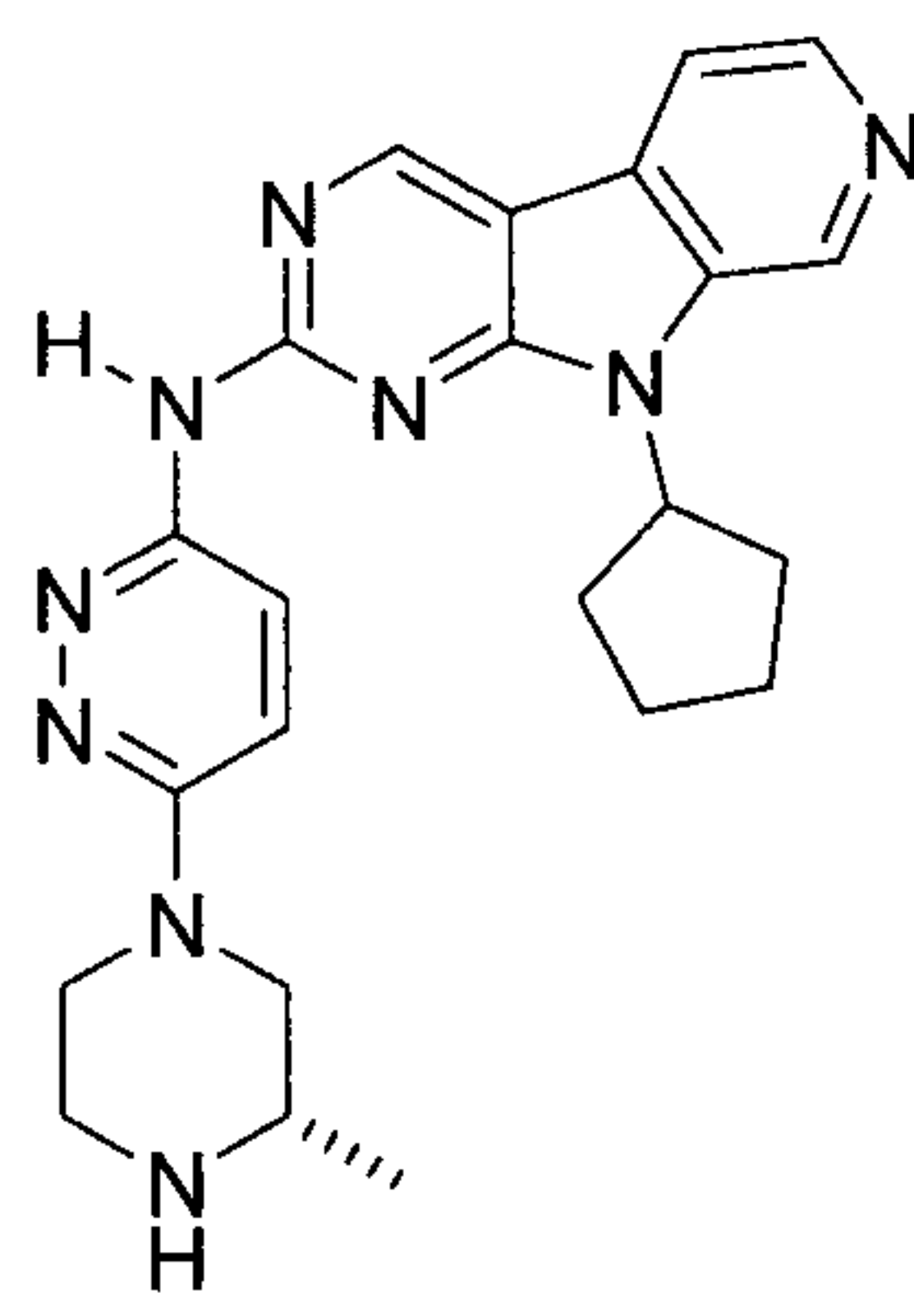


49. The compound of claim 1, wherein the compound is



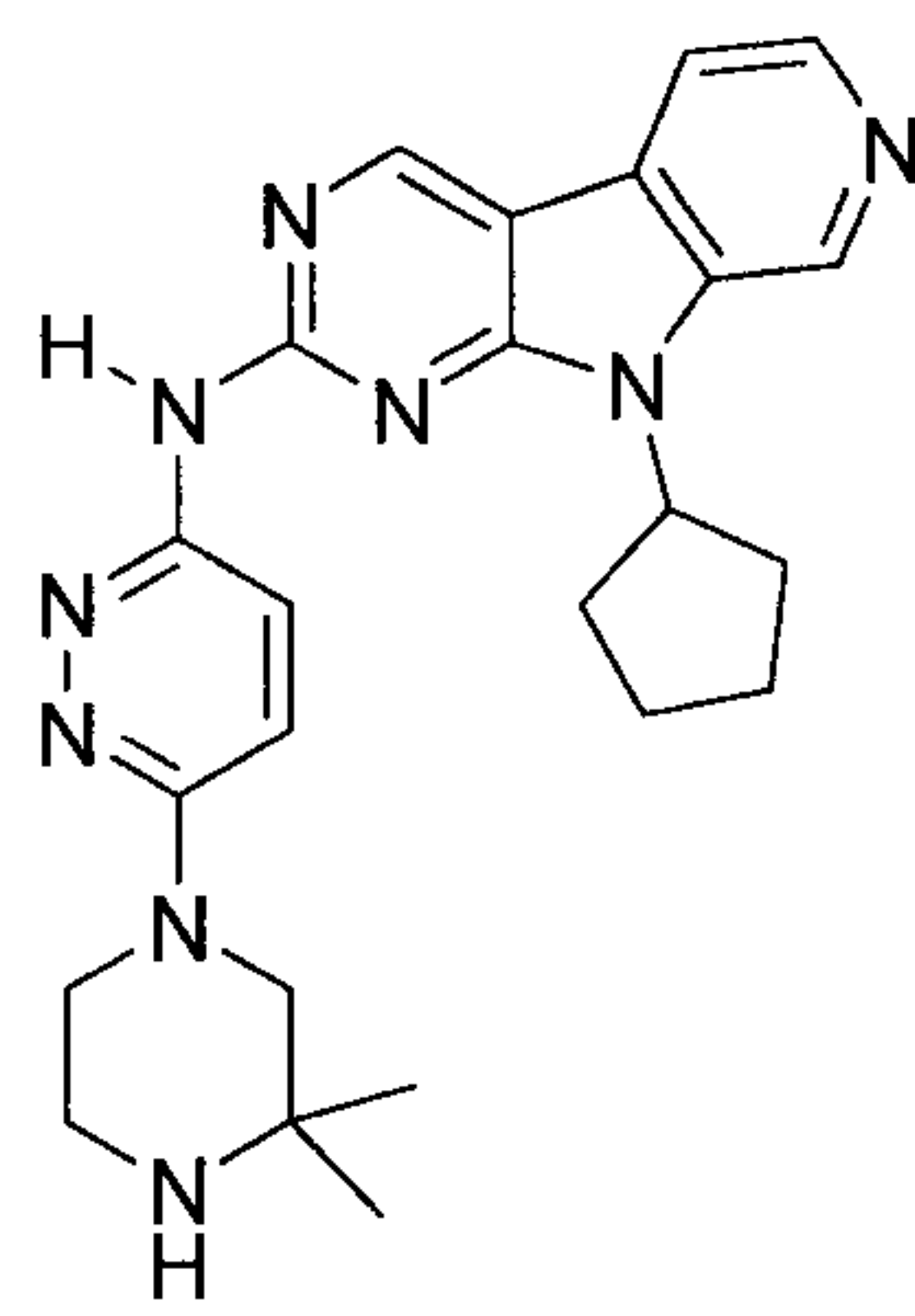
or a pharmaceutically acceptable salt thereof.

50. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

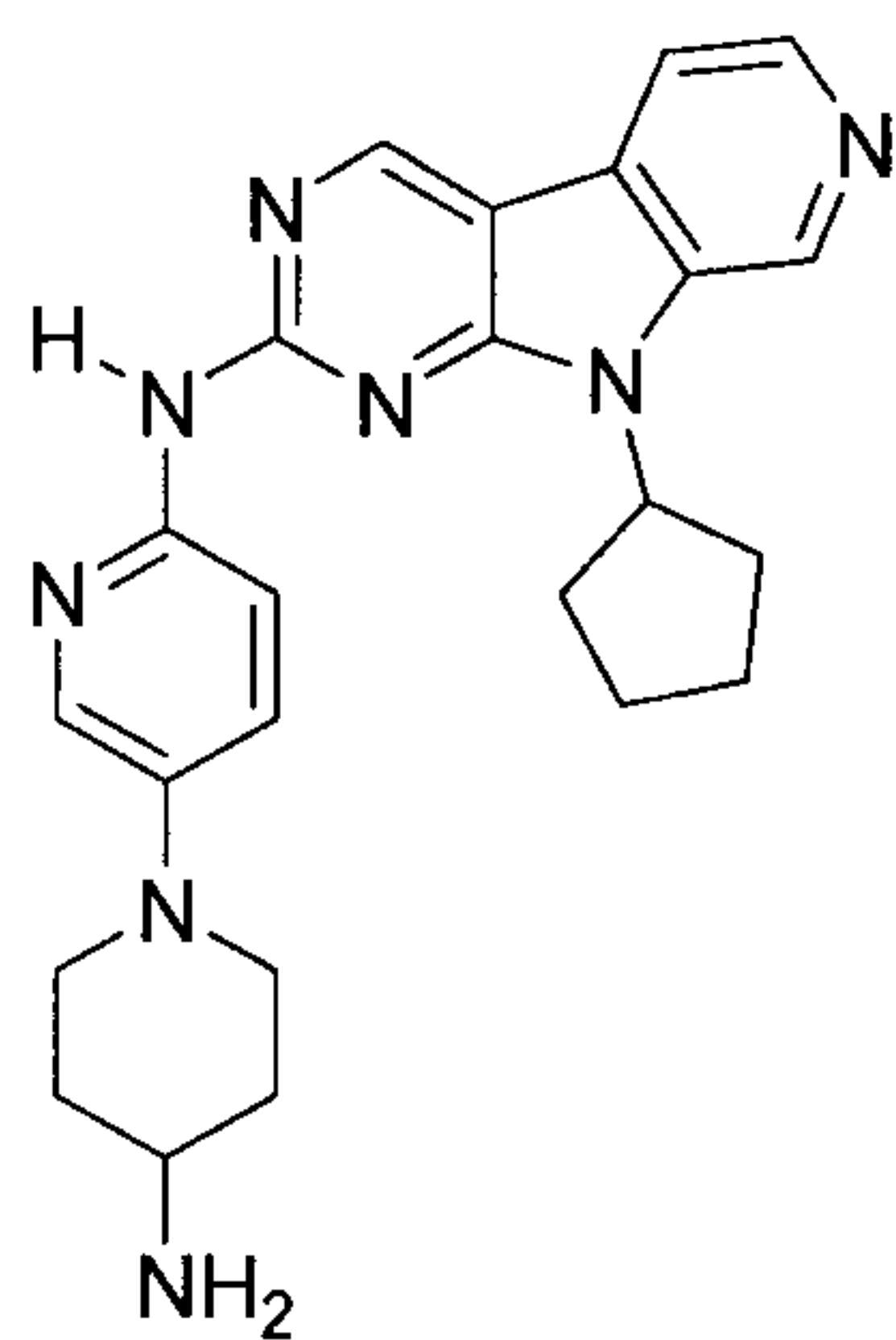
51. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

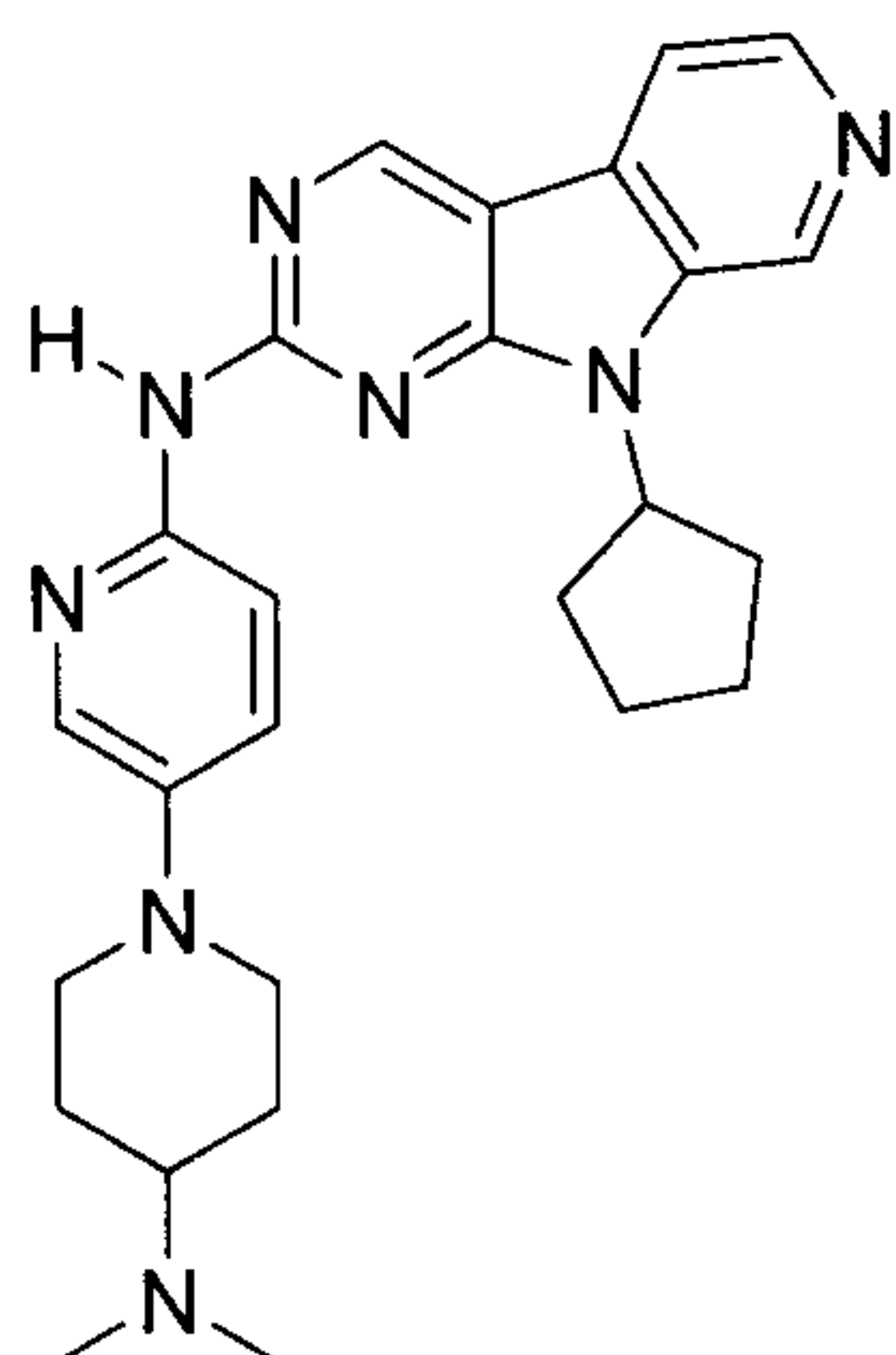


52. The compound of claim 1, wherein the compound is



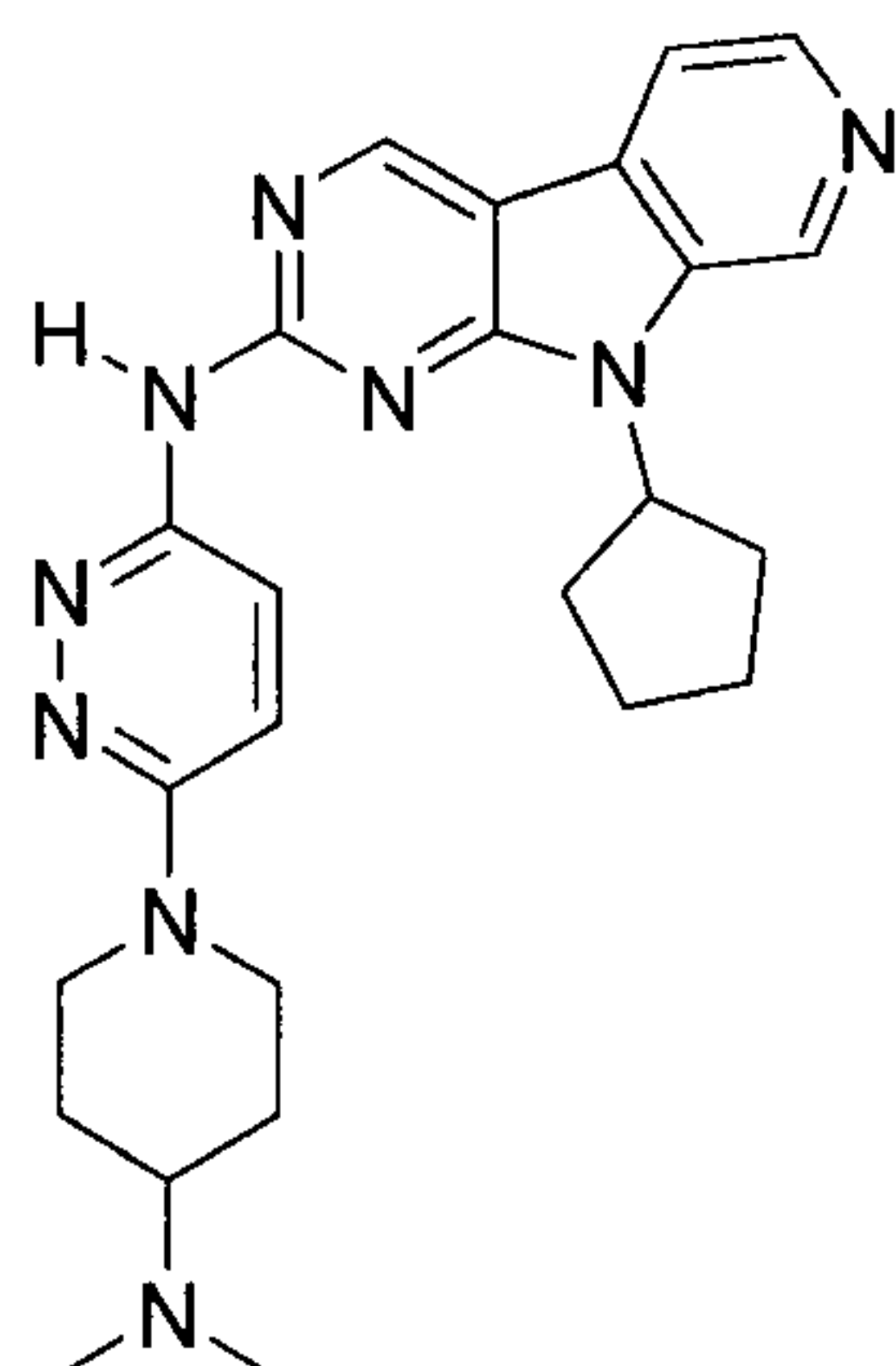
or a pharmaceutically acceptable salt thereof.

53. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

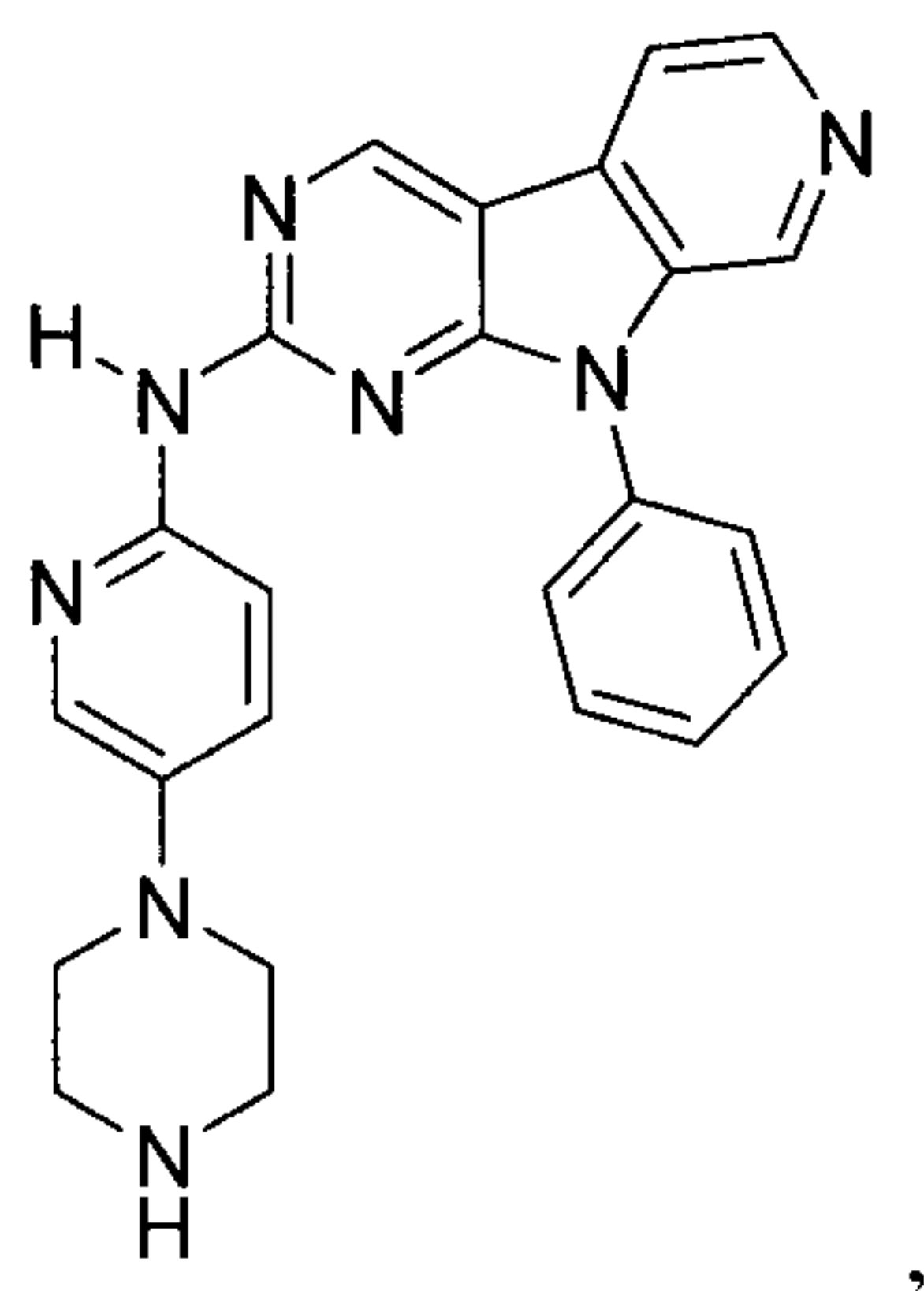
54. The compound of claim 1, wherein the compound is





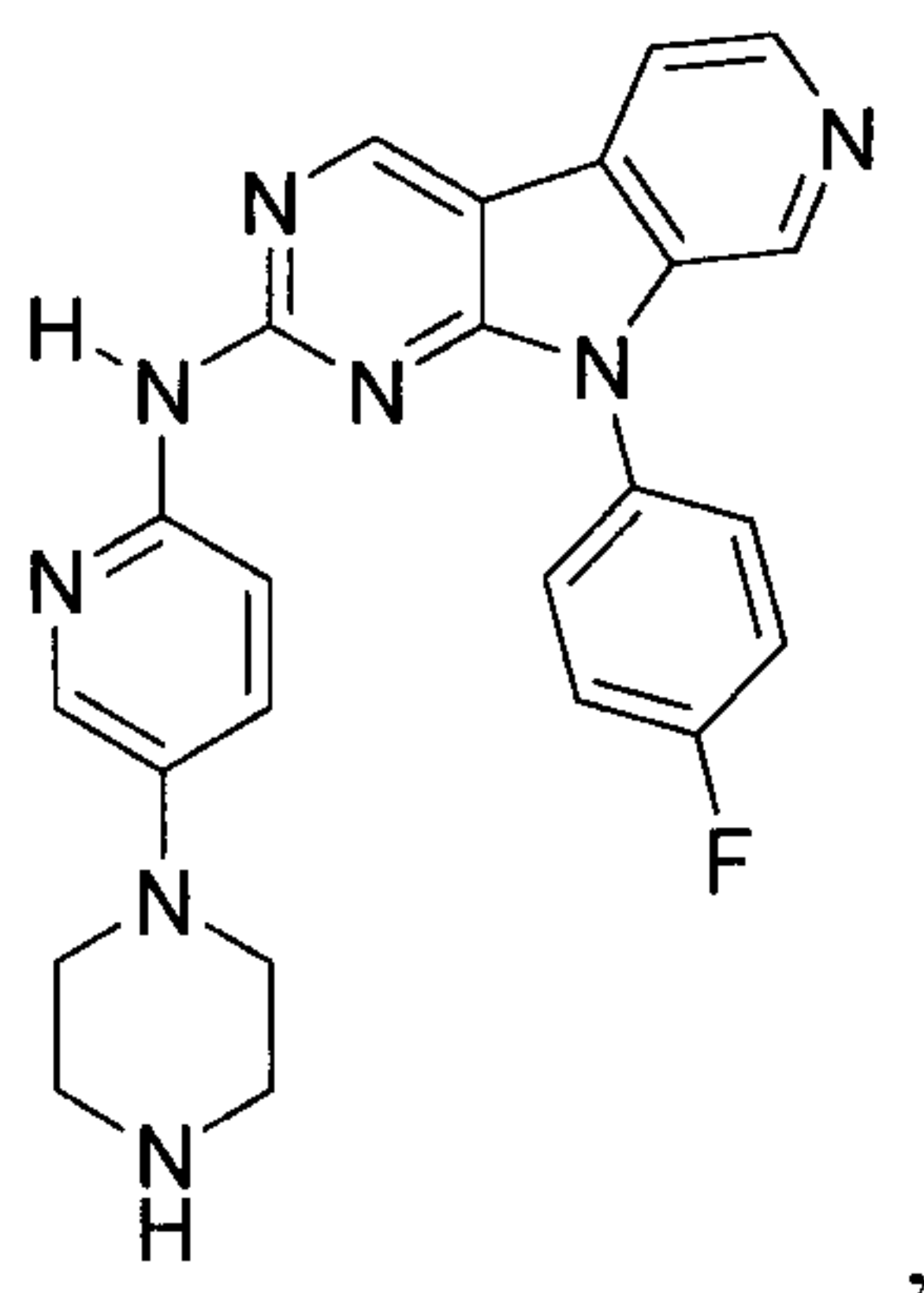
or a pharmaceutically acceptable salt thereof.

55. The compound of claim 1, wherein the compound is



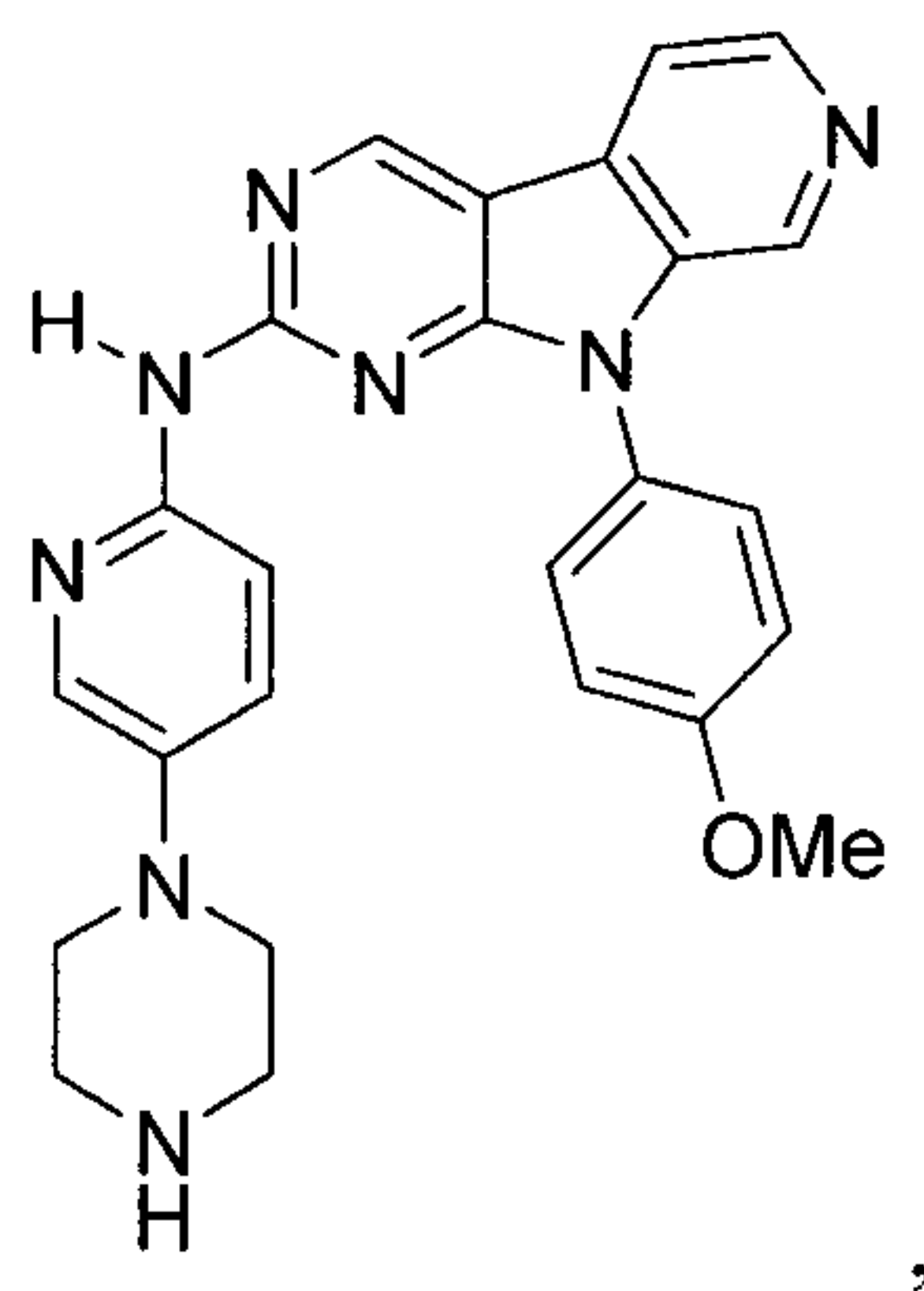
or a pharmaceutically acceptable salt thereof.

56. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

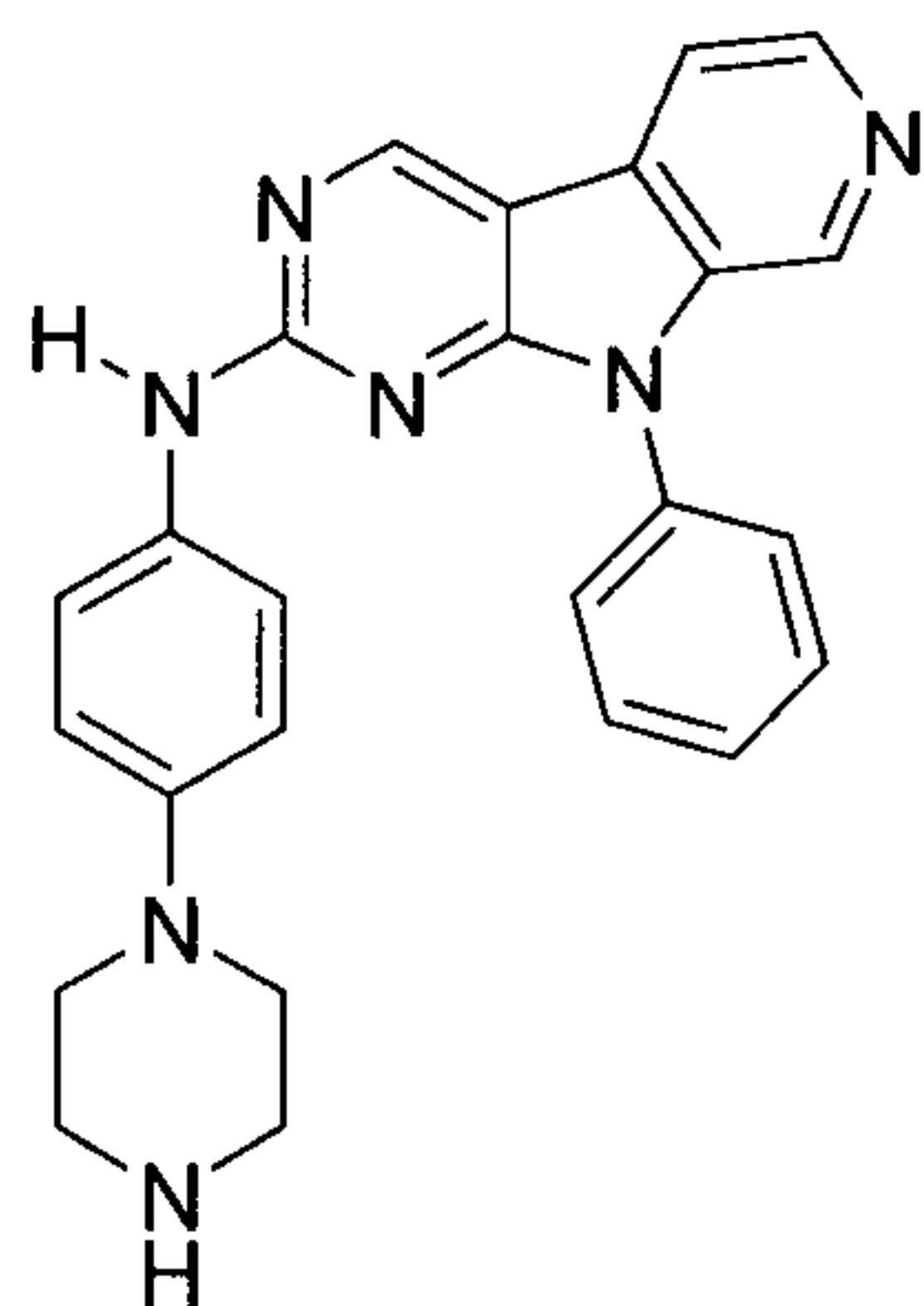
57. The compound of claim 1, wherein the compound is





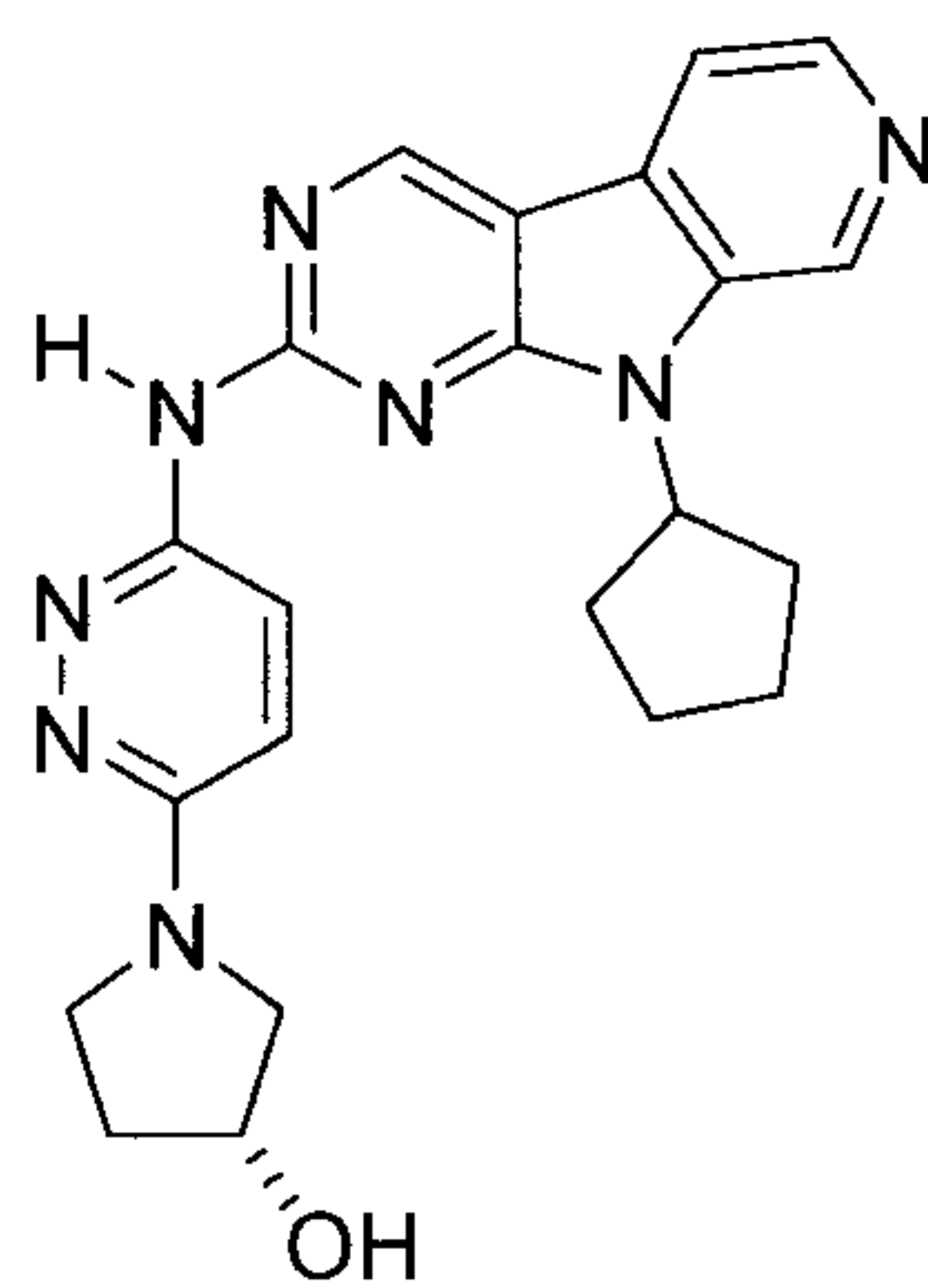
or a pharmaceutically acceptable salt thereof.

58. The compound of claim 1, wherein the compound is



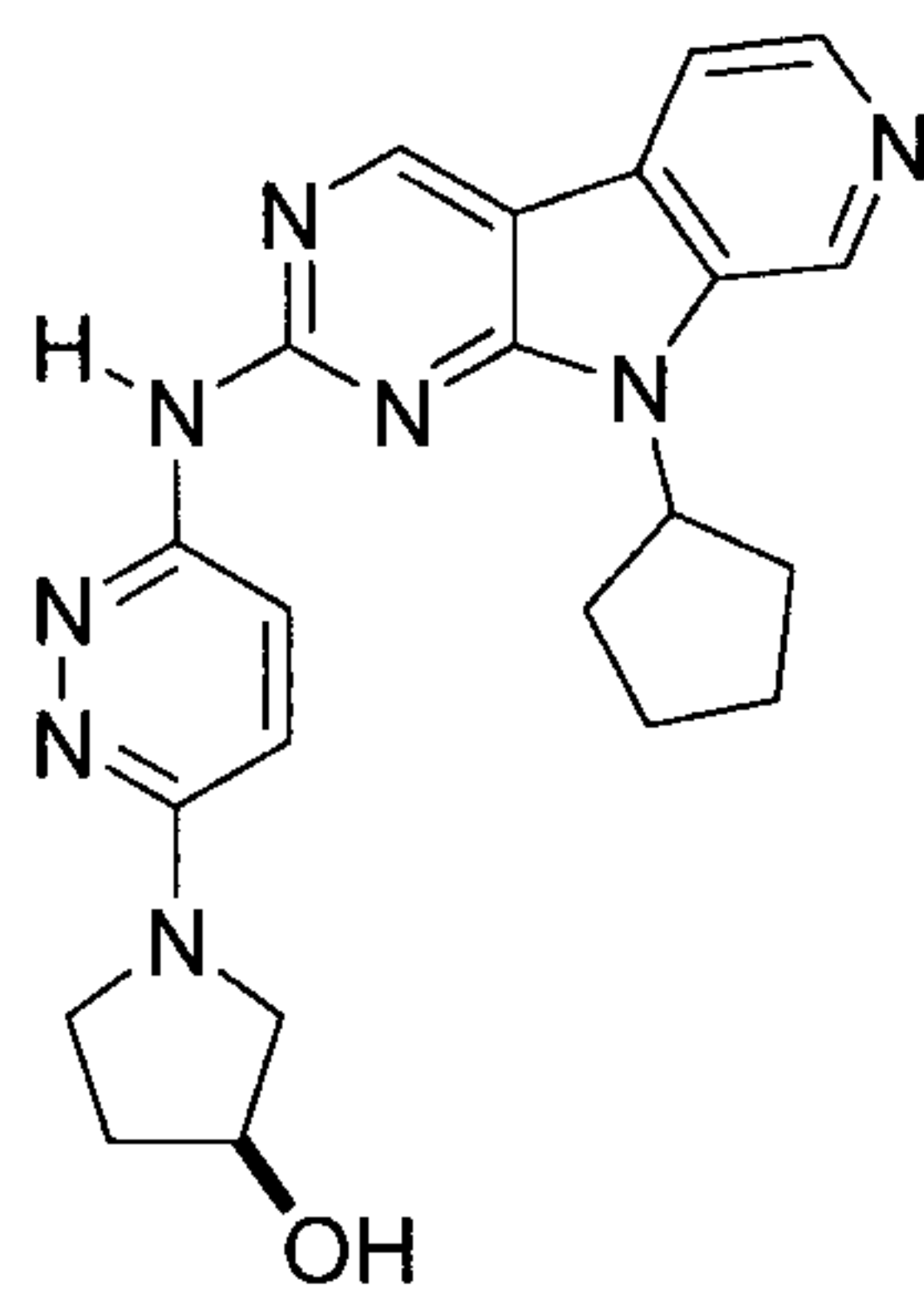
or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

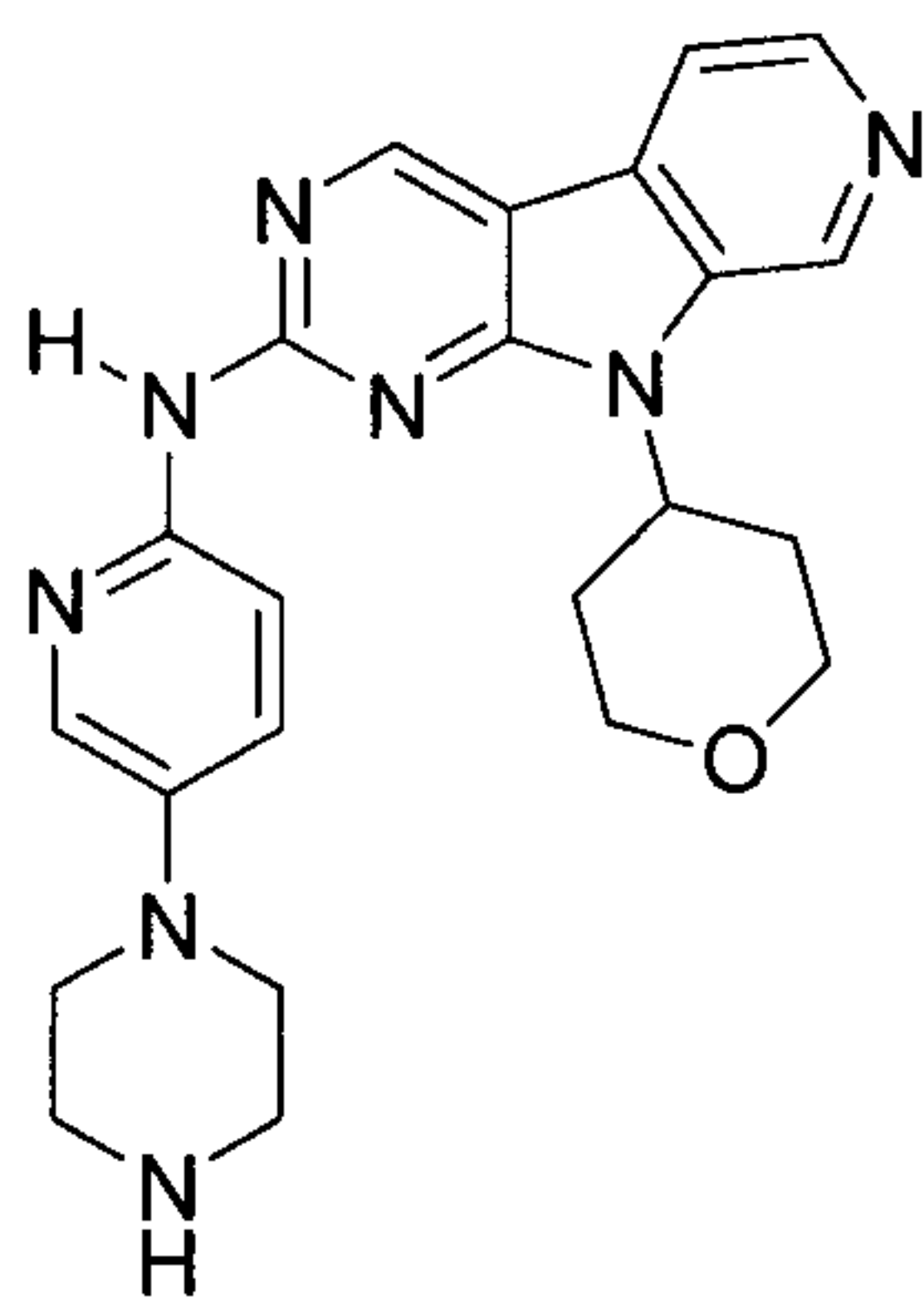
60. The compound of claim 1, wherein the compound is





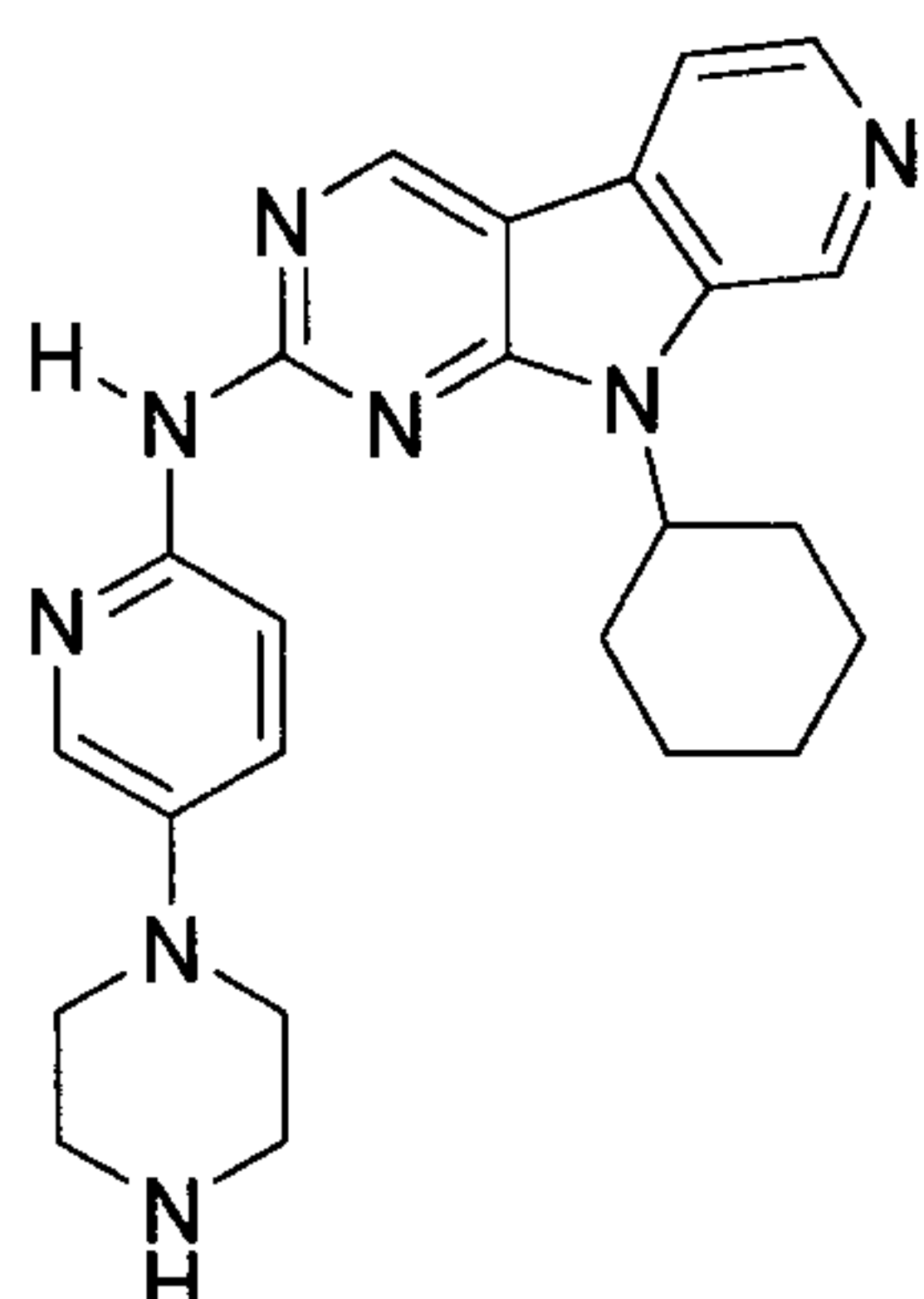
or a pharmaceutically acceptable salt thereof.

61. The compound of claim 1, wherein the compound is



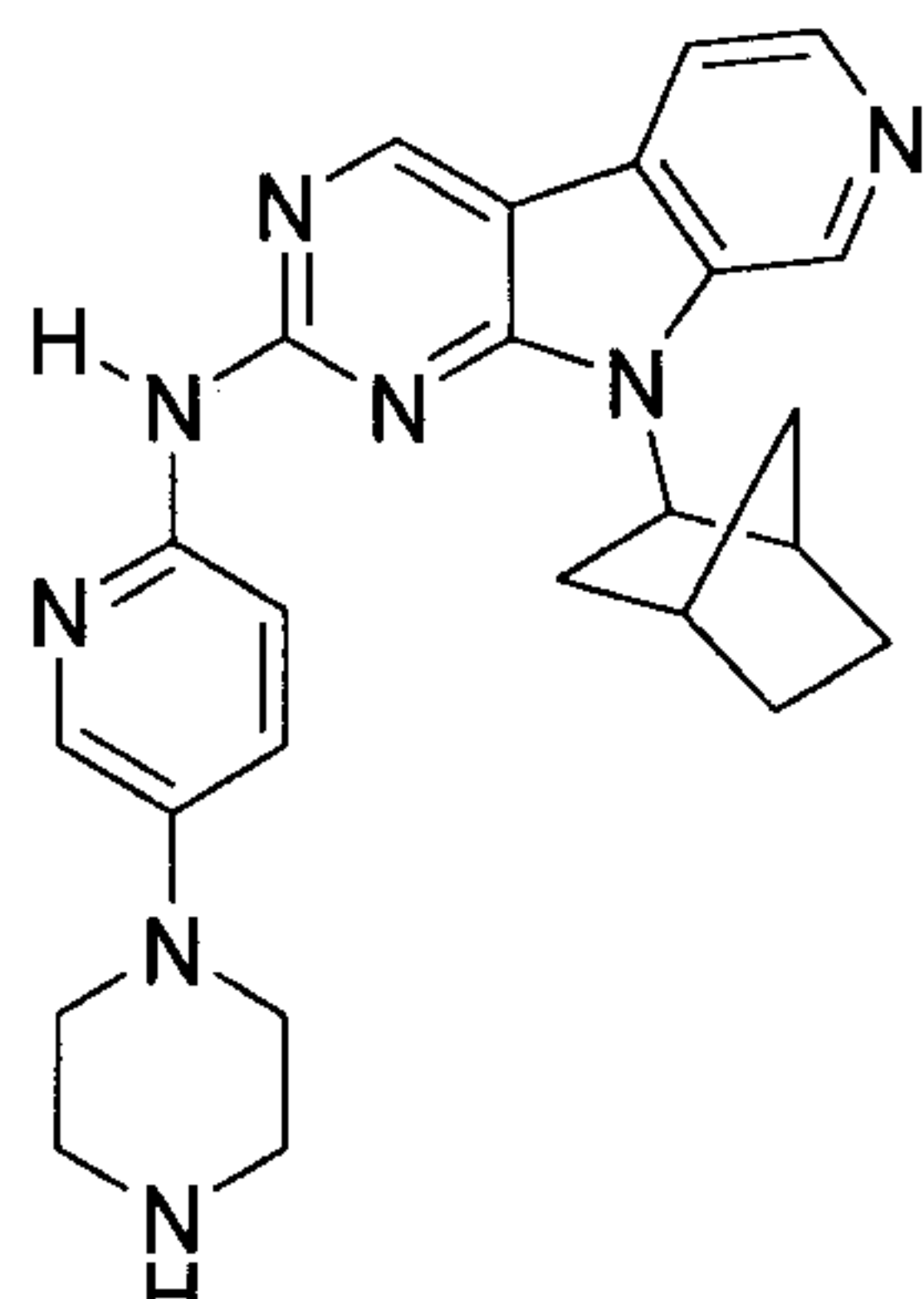
or a pharmaceutically acceptable salt thereof.

62. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

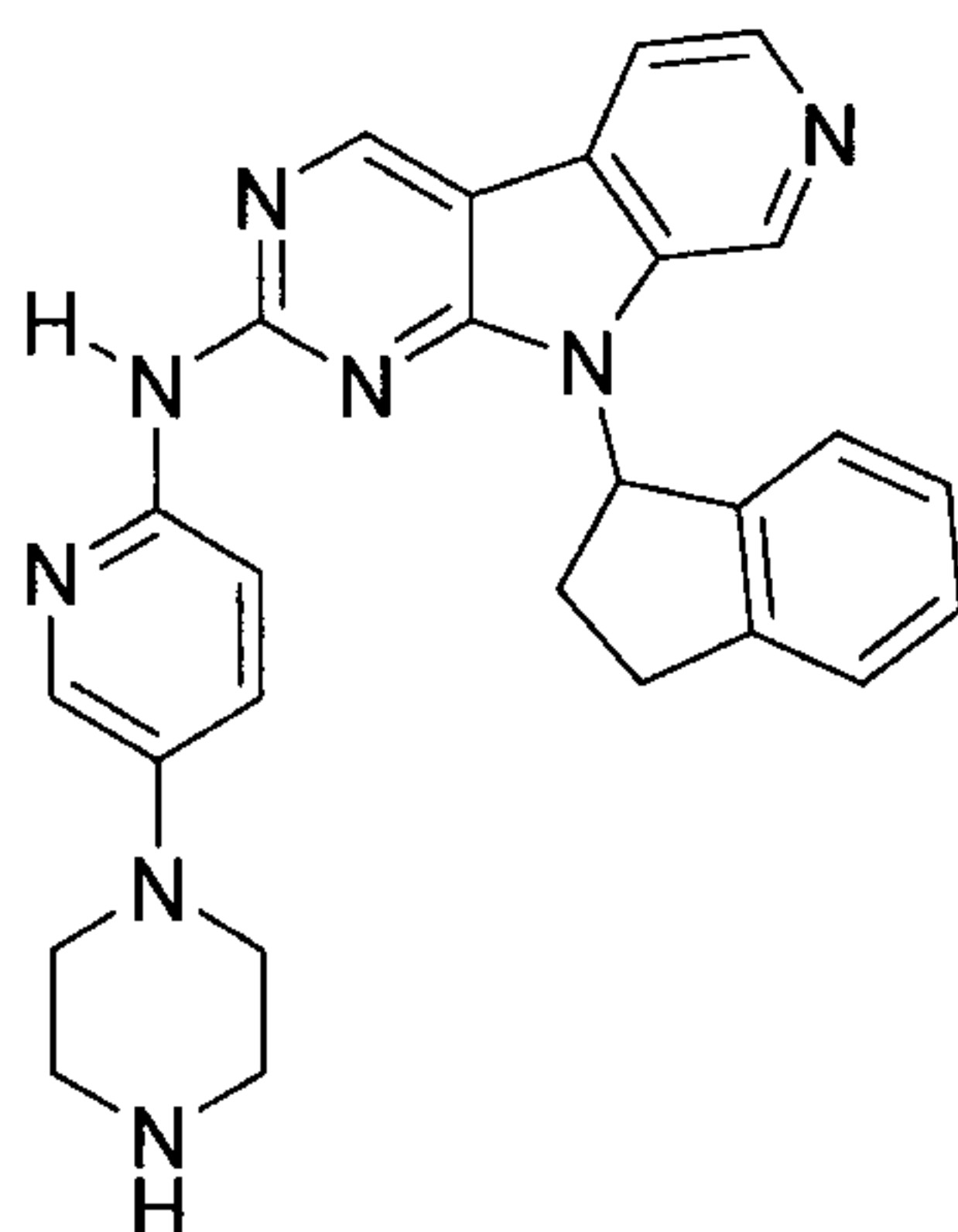
63. The compound of claim 1, wherein the compound is





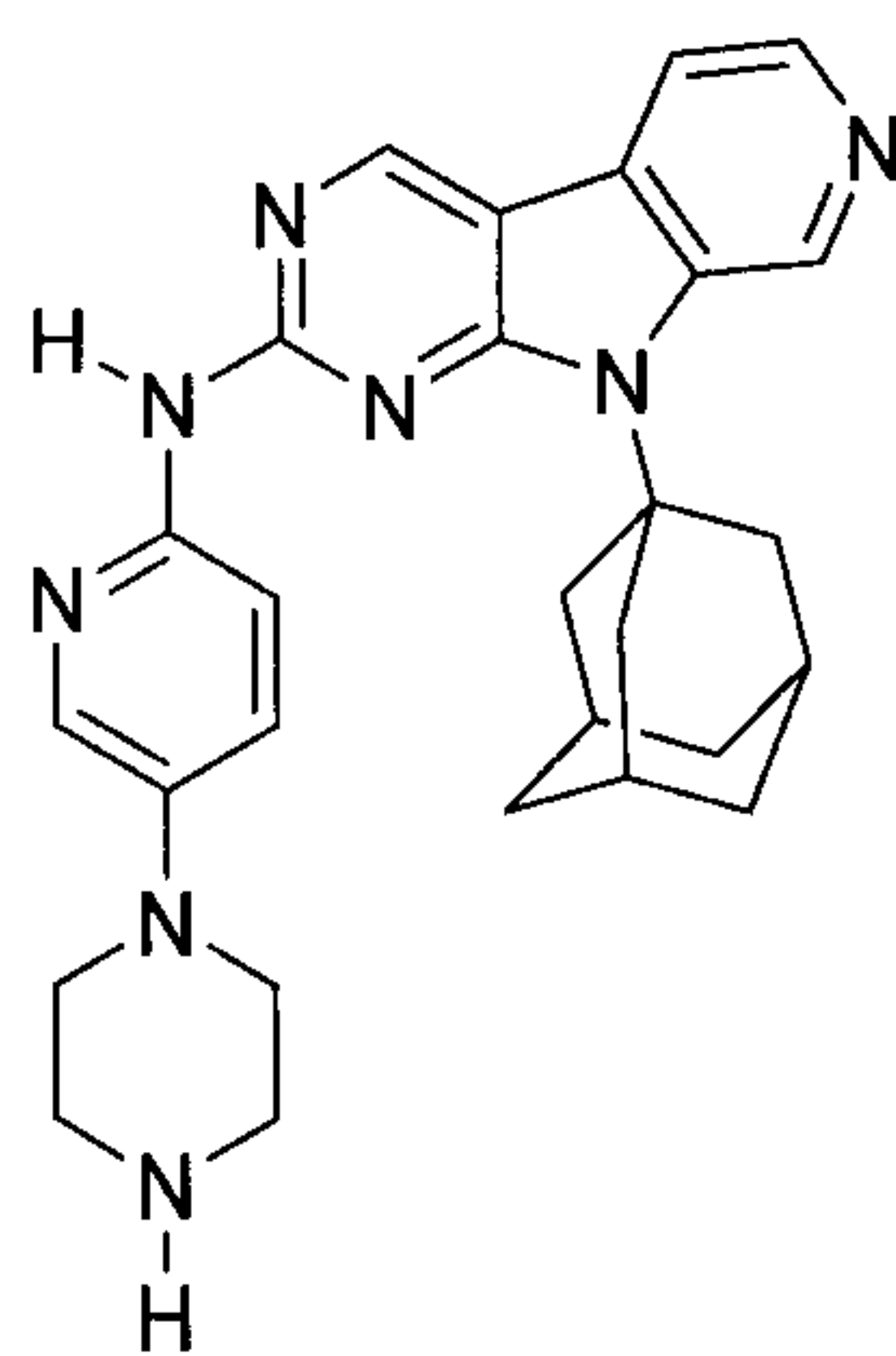
or a pharmaceutically acceptable salt thereof.

64. The compound of claim 1, wherein the compound is



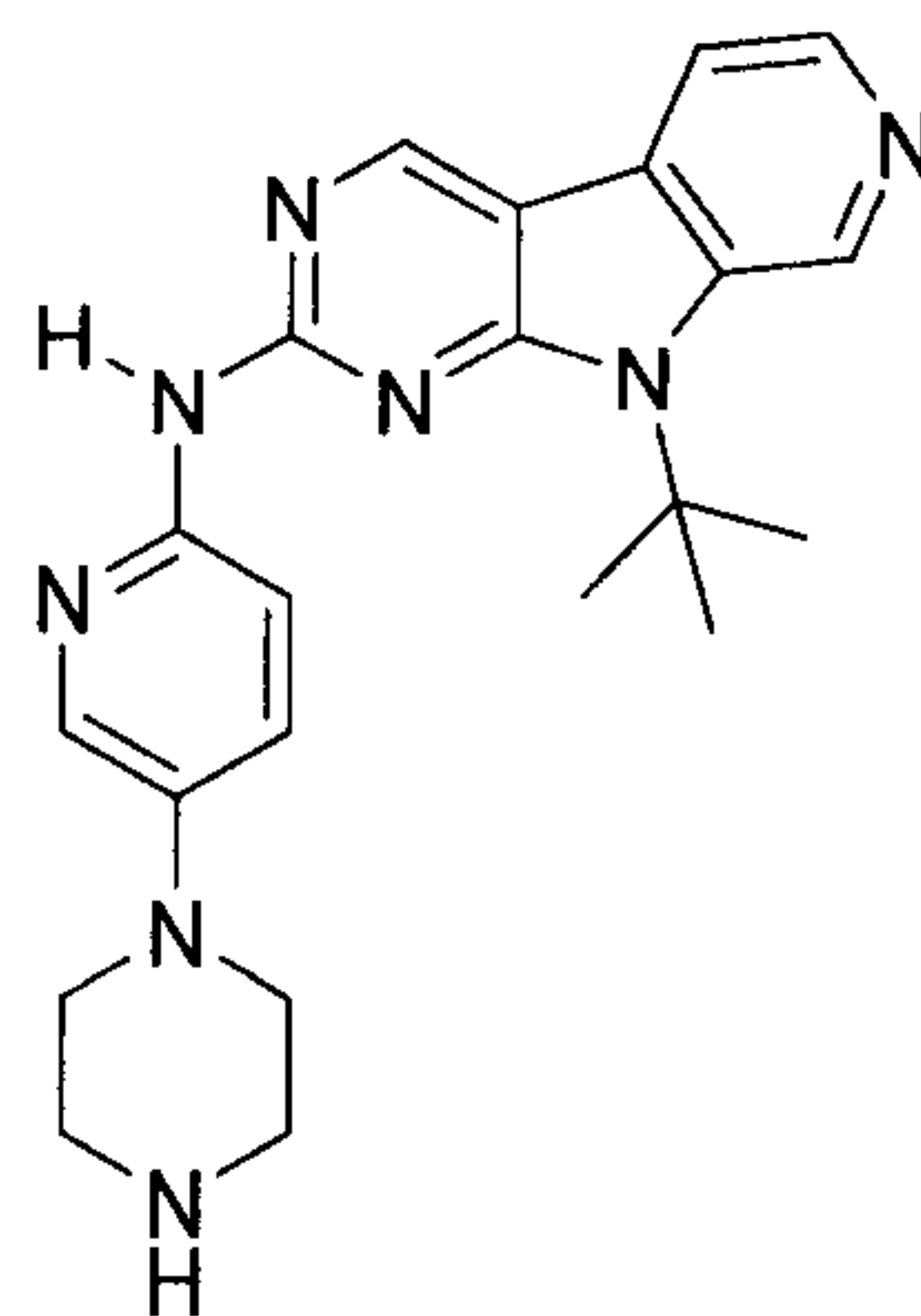
or a pharmaceutically acceptable salt thereof.

65. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

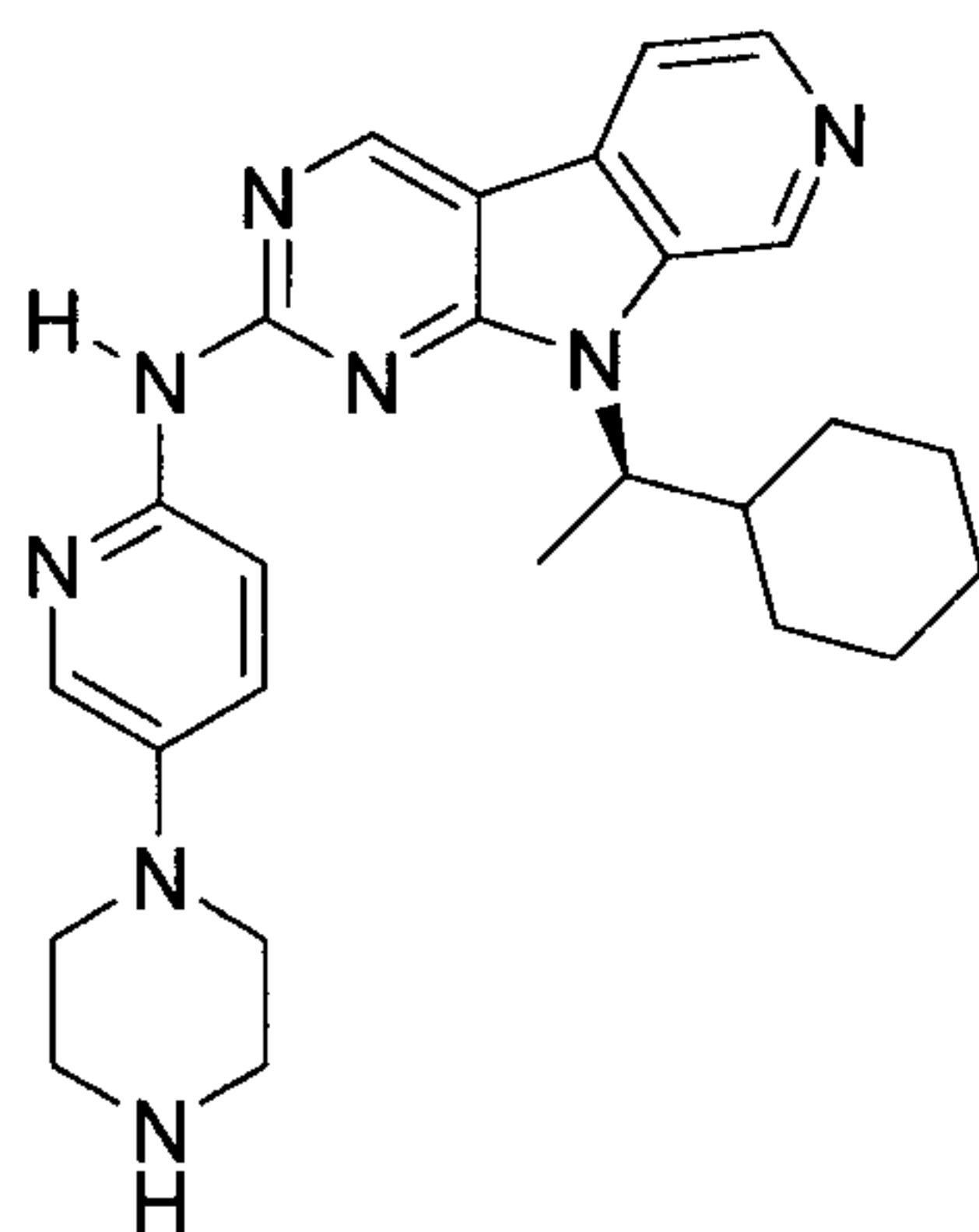
66. The compound of claim 1, wherein the compound is





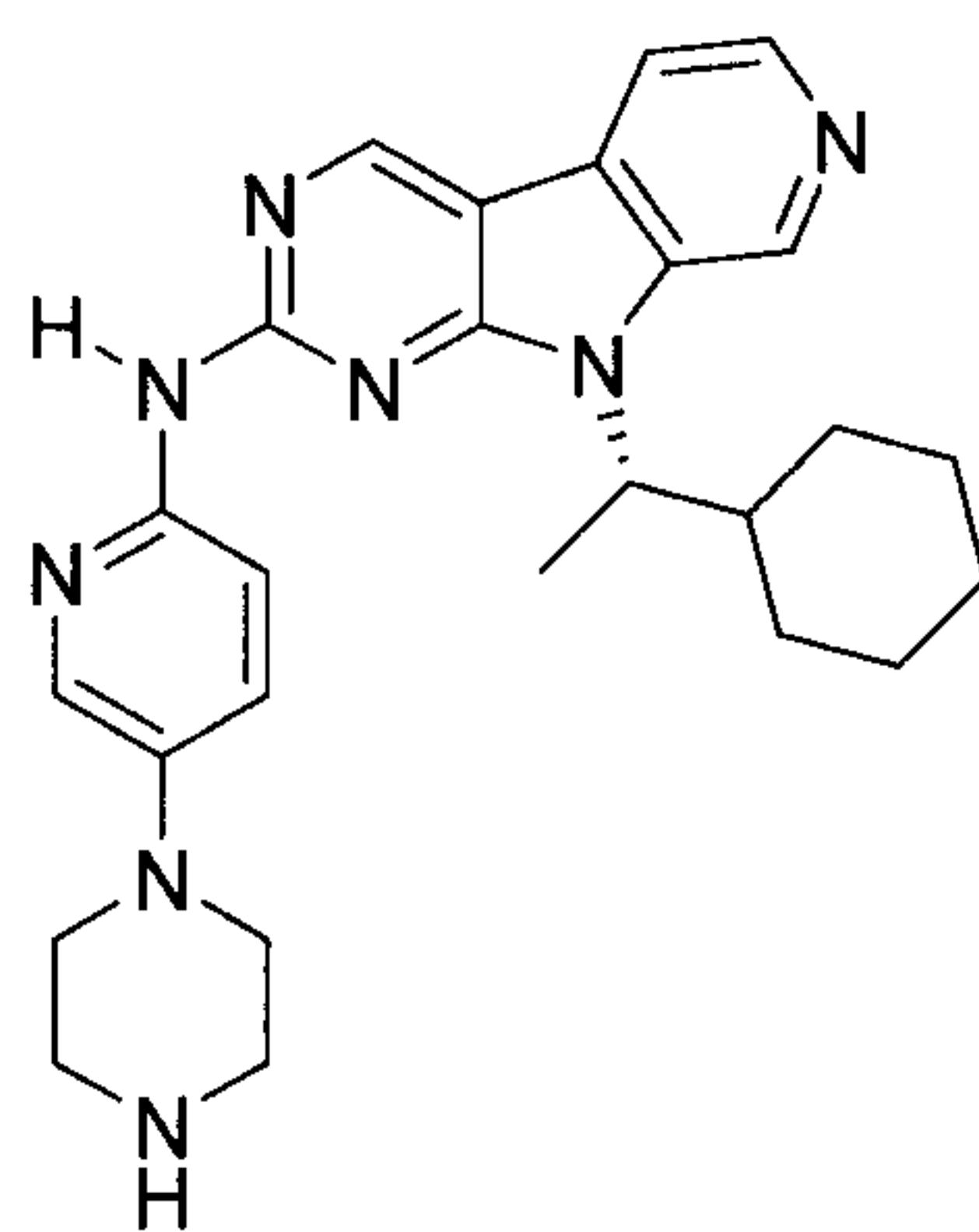
or a pharmaceutically acceptable salt thereof.

67. The compound of claim 1, wherein the compound is



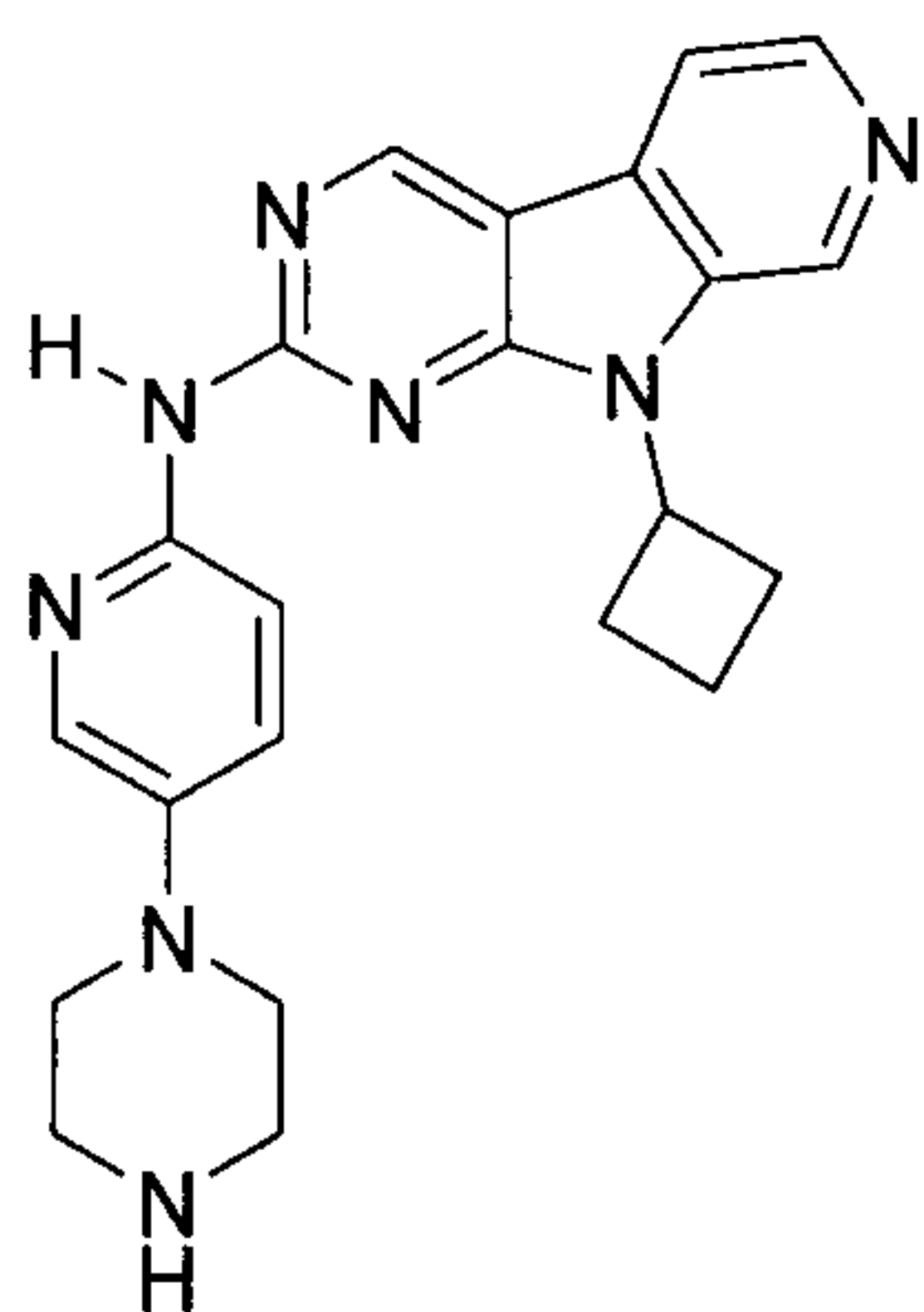
or a pharmaceutically acceptable salt thereof.

68. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

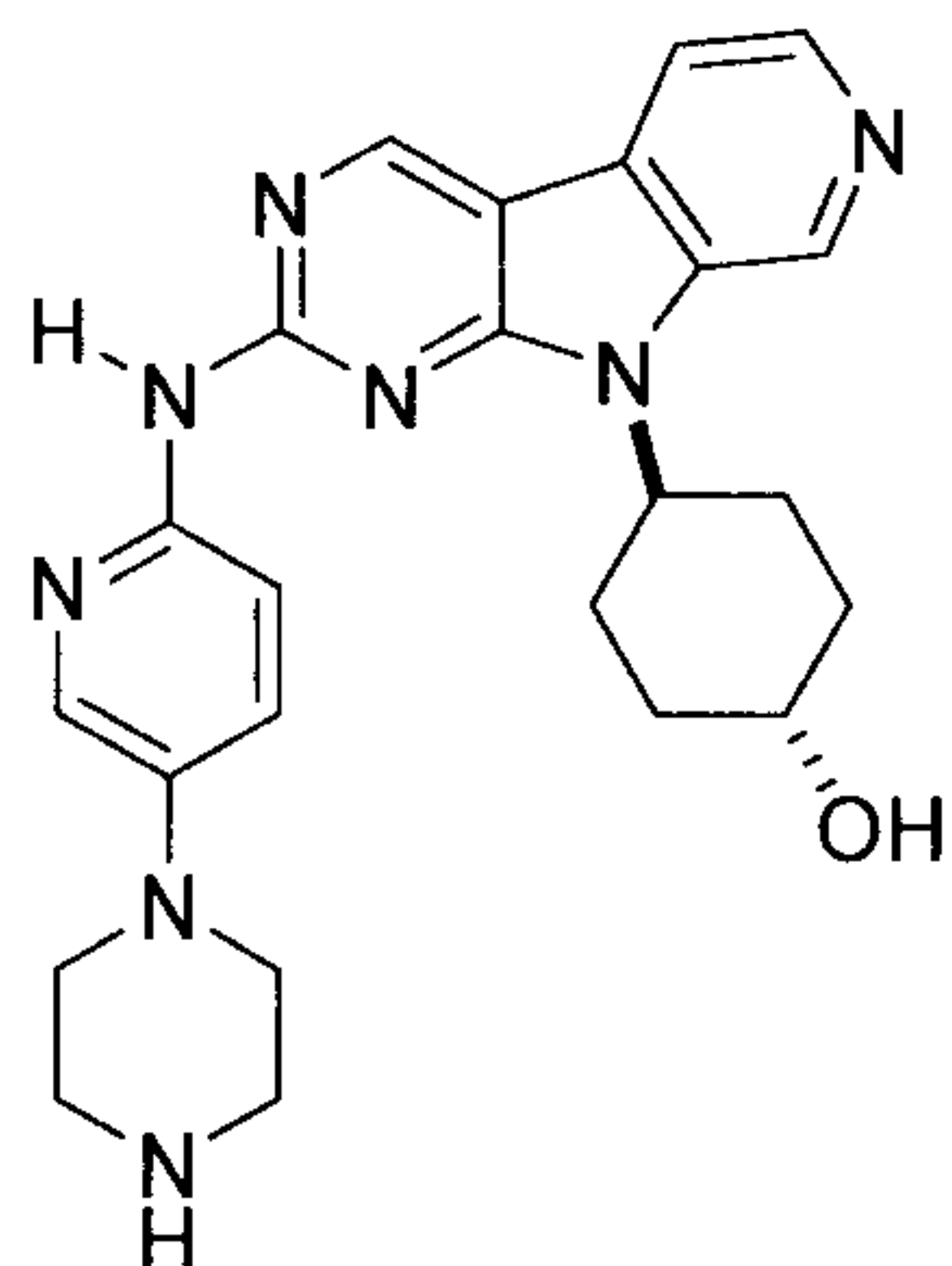
69. The compound of claim 1, wherein the compound is





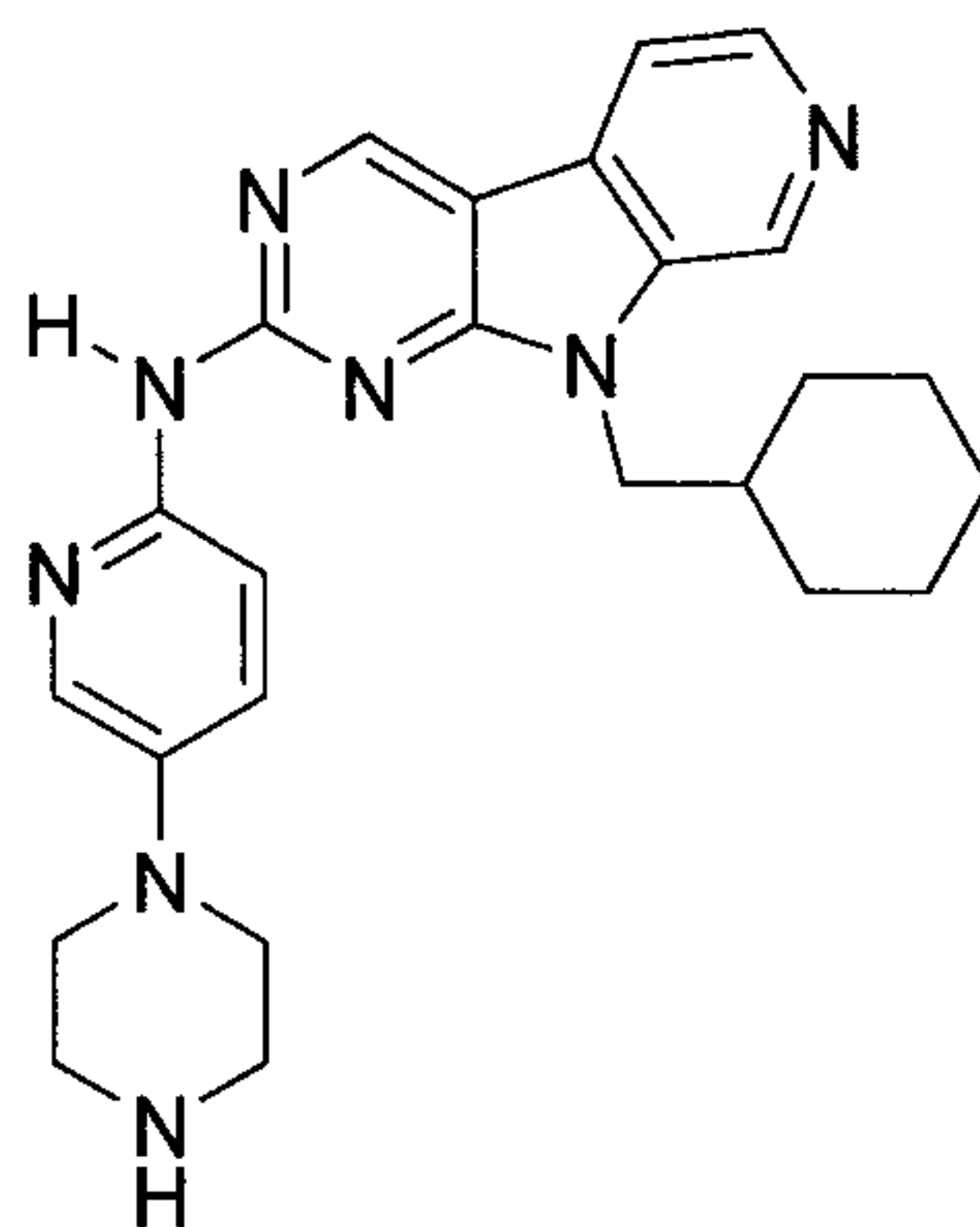
or a pharmaceutically acceptable salt thereof.

70. The compound of claim 1, wherein the compound is



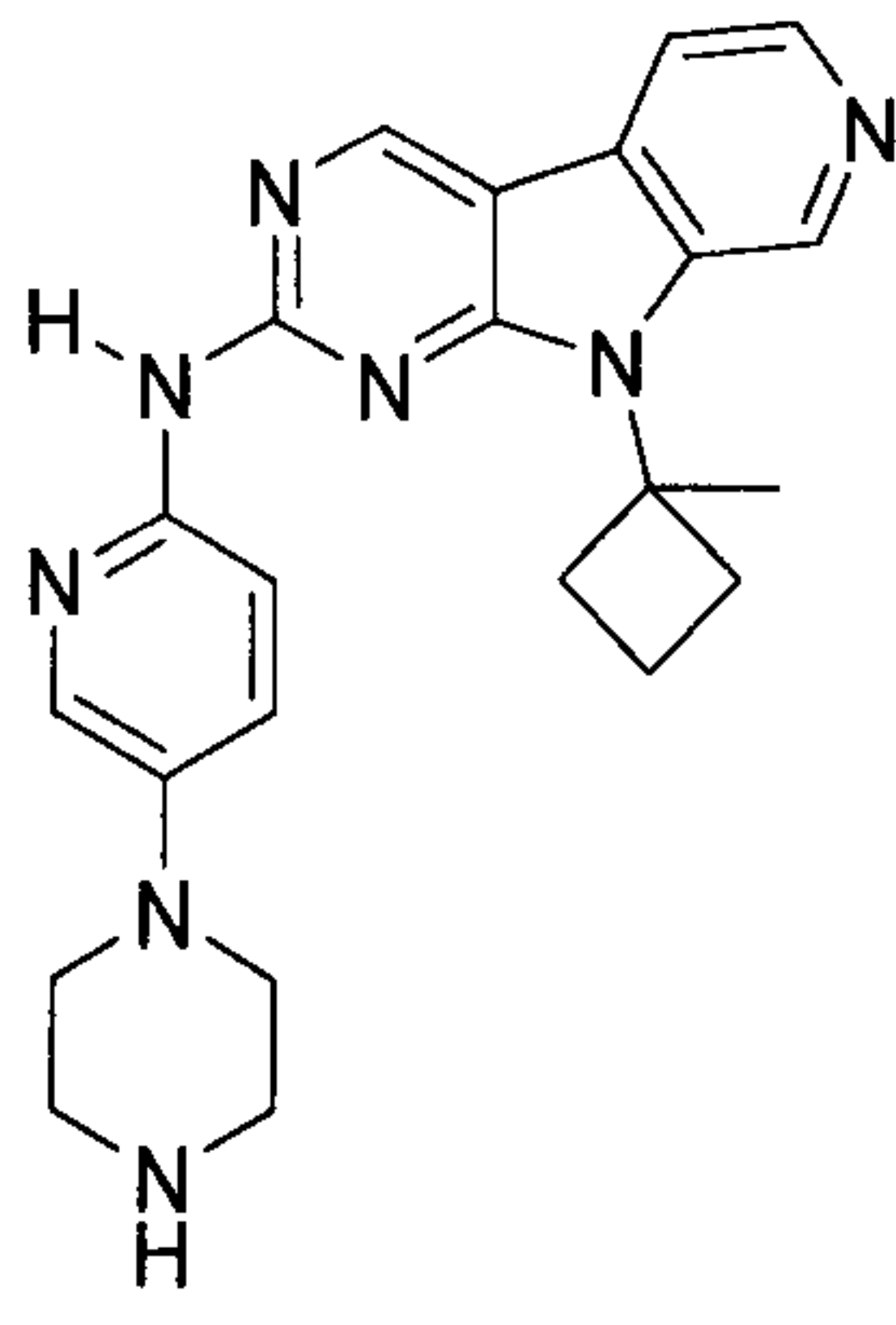
or a pharmaceutically acceptable salt thereof.

71. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

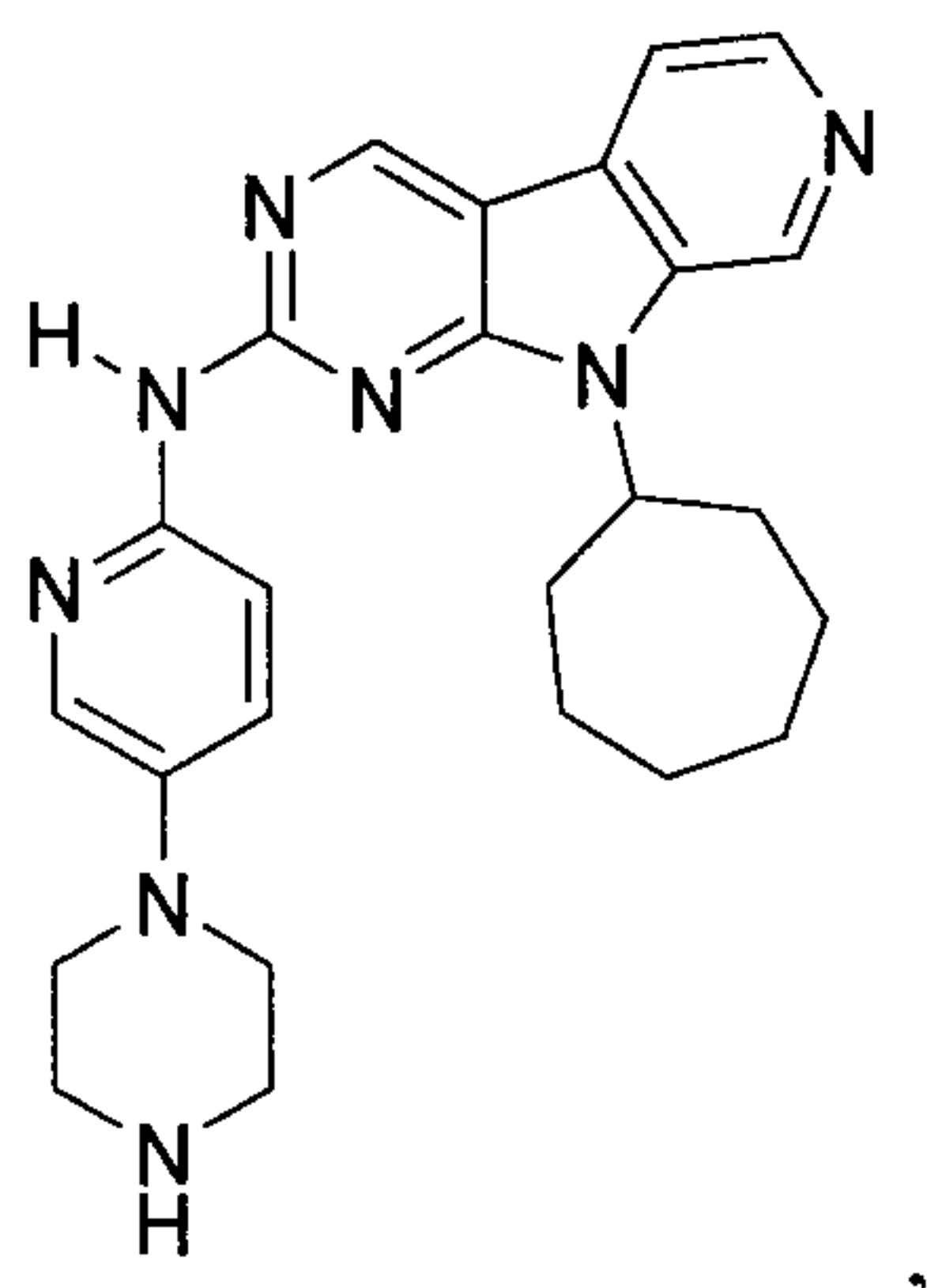
72. The compound of claim 1, wherein the compound is





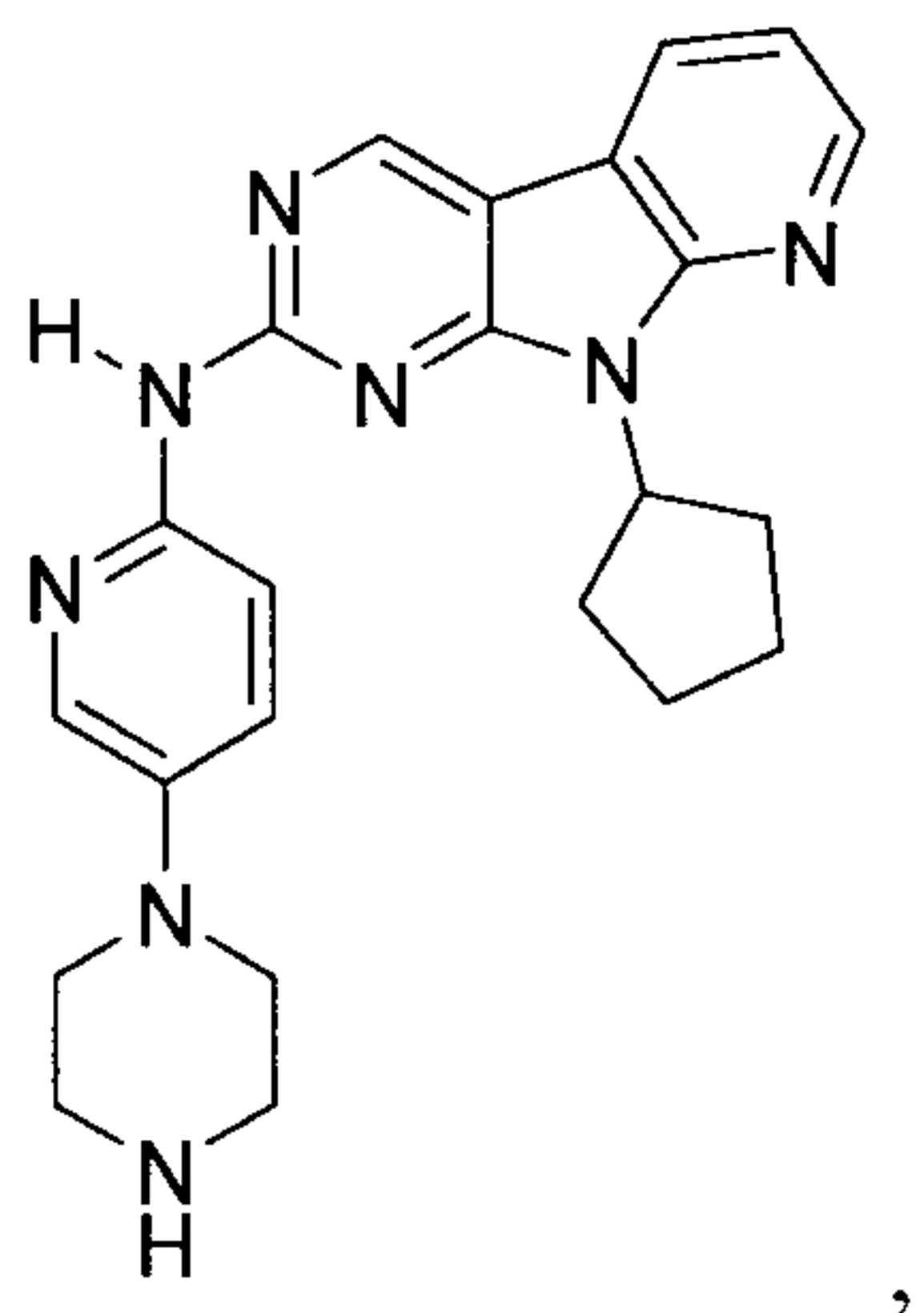
or a pharmaceutically acceptable salt thereof.

73. The compound of claim 1, wherein the compound is



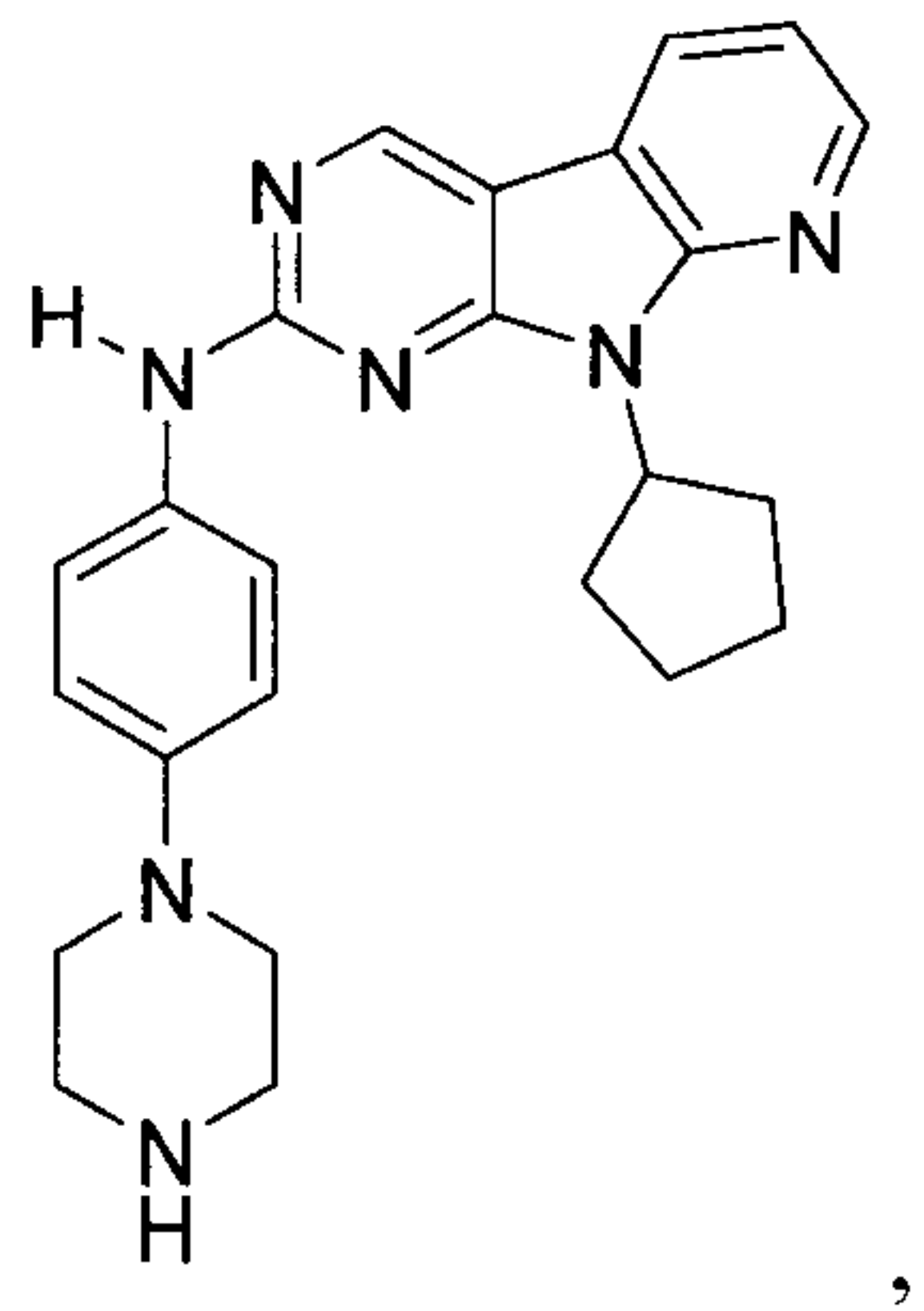
or a pharmaceutically acceptable salt thereof.

74. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

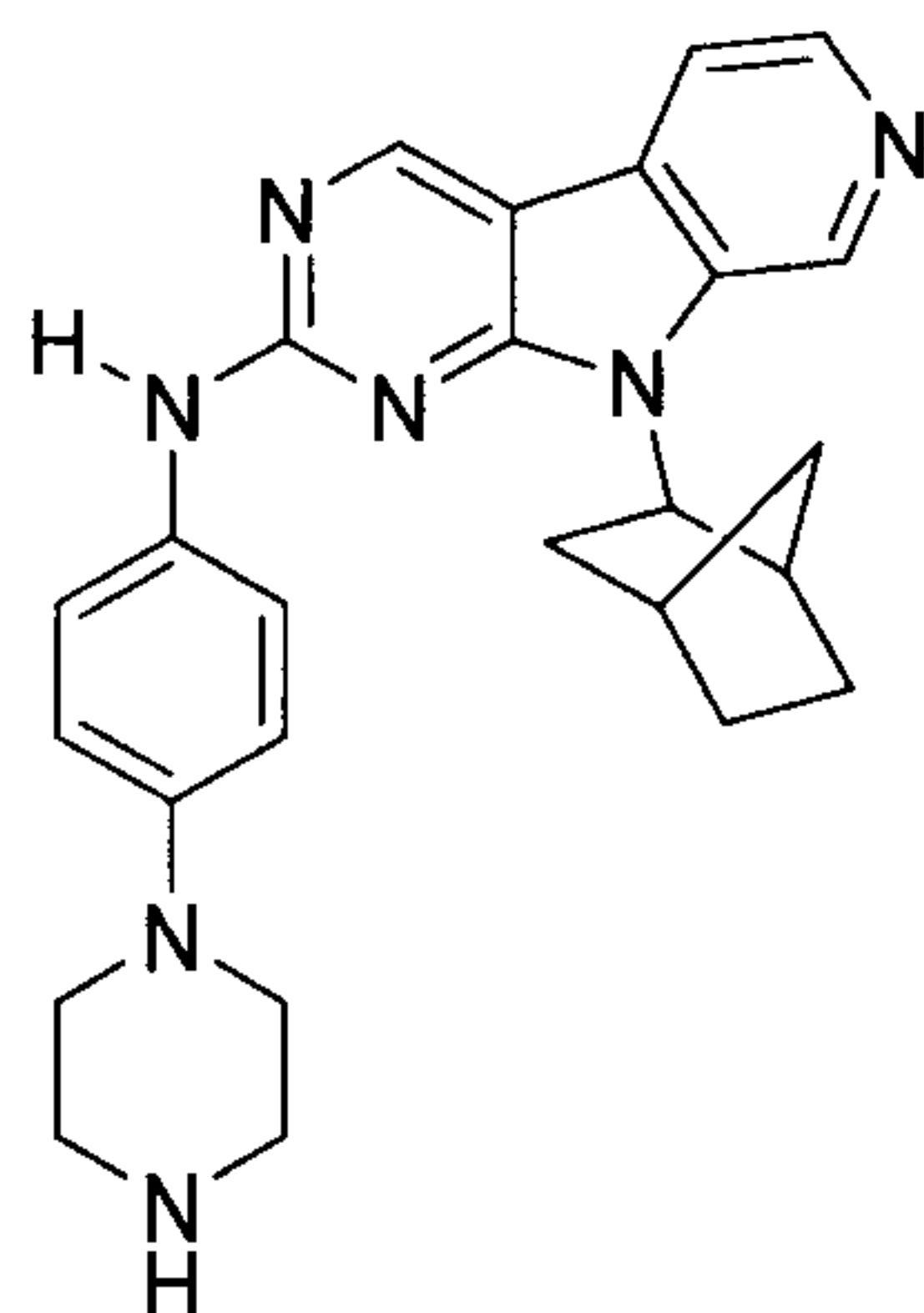
75. The compound of claim 1, wherein the compound is





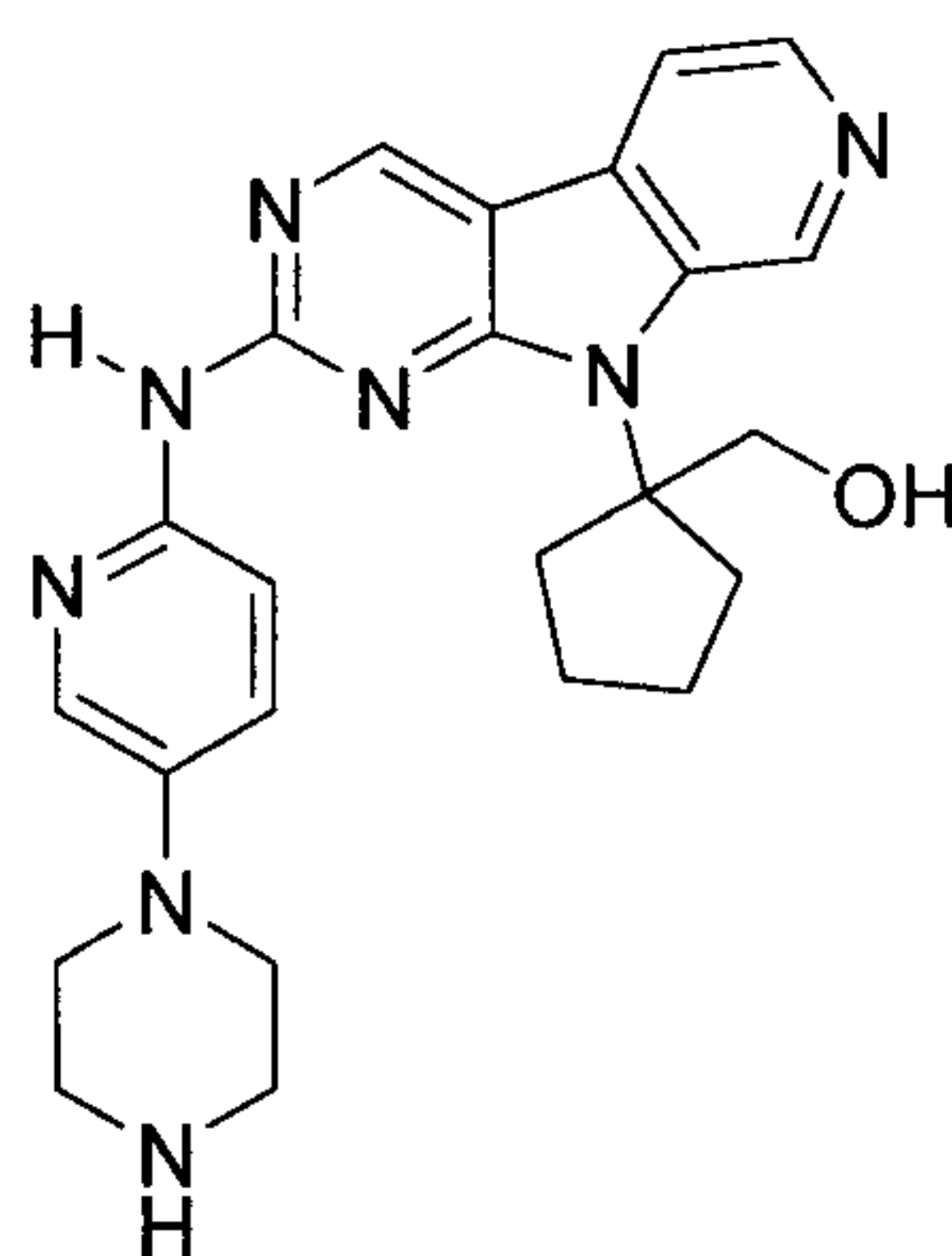
or a pharmaceutically acceptable salt thereof.

76. The compound of claim 1, wherein the compound is



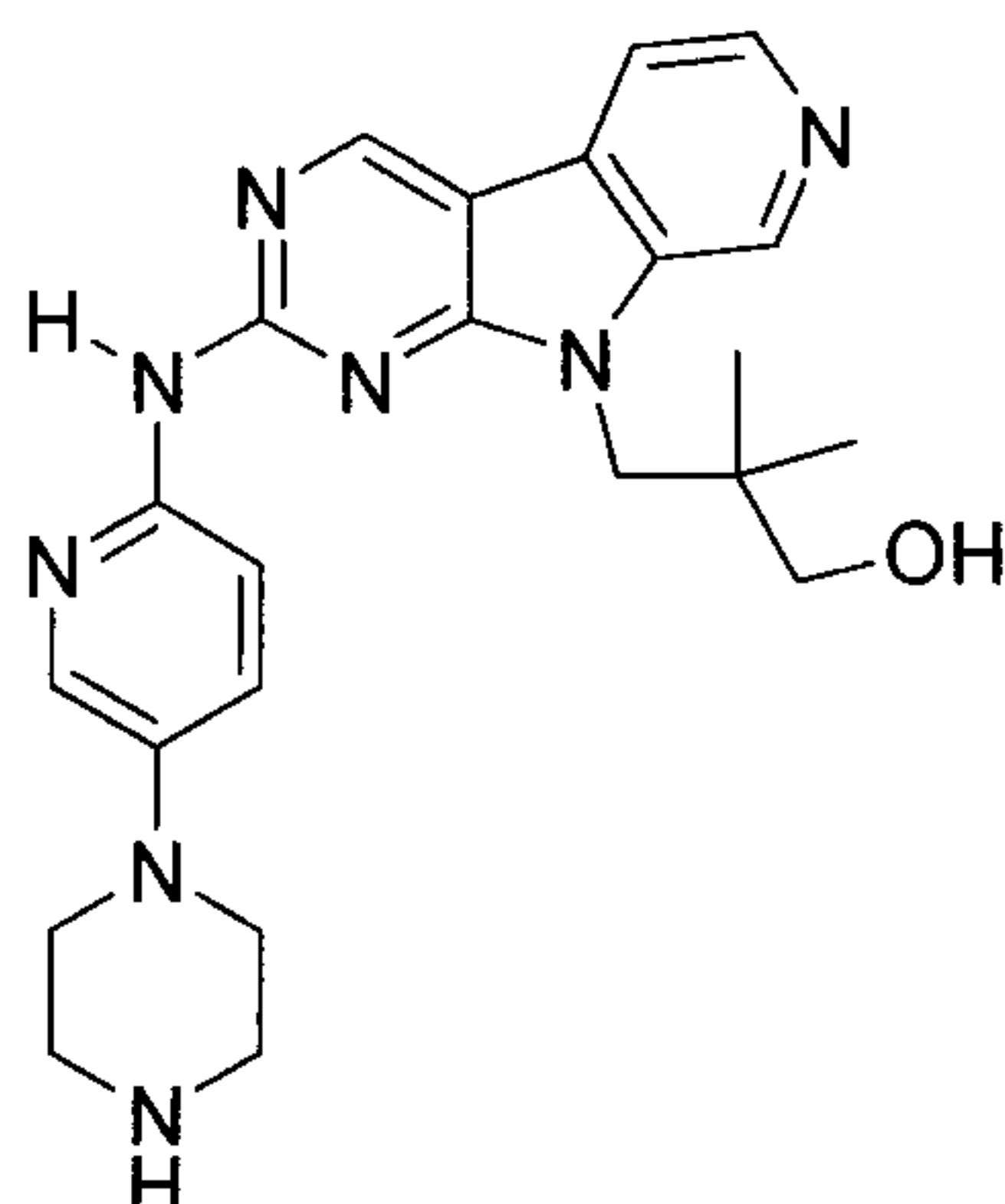
or a pharmaceutically acceptable salt thereof.

77. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

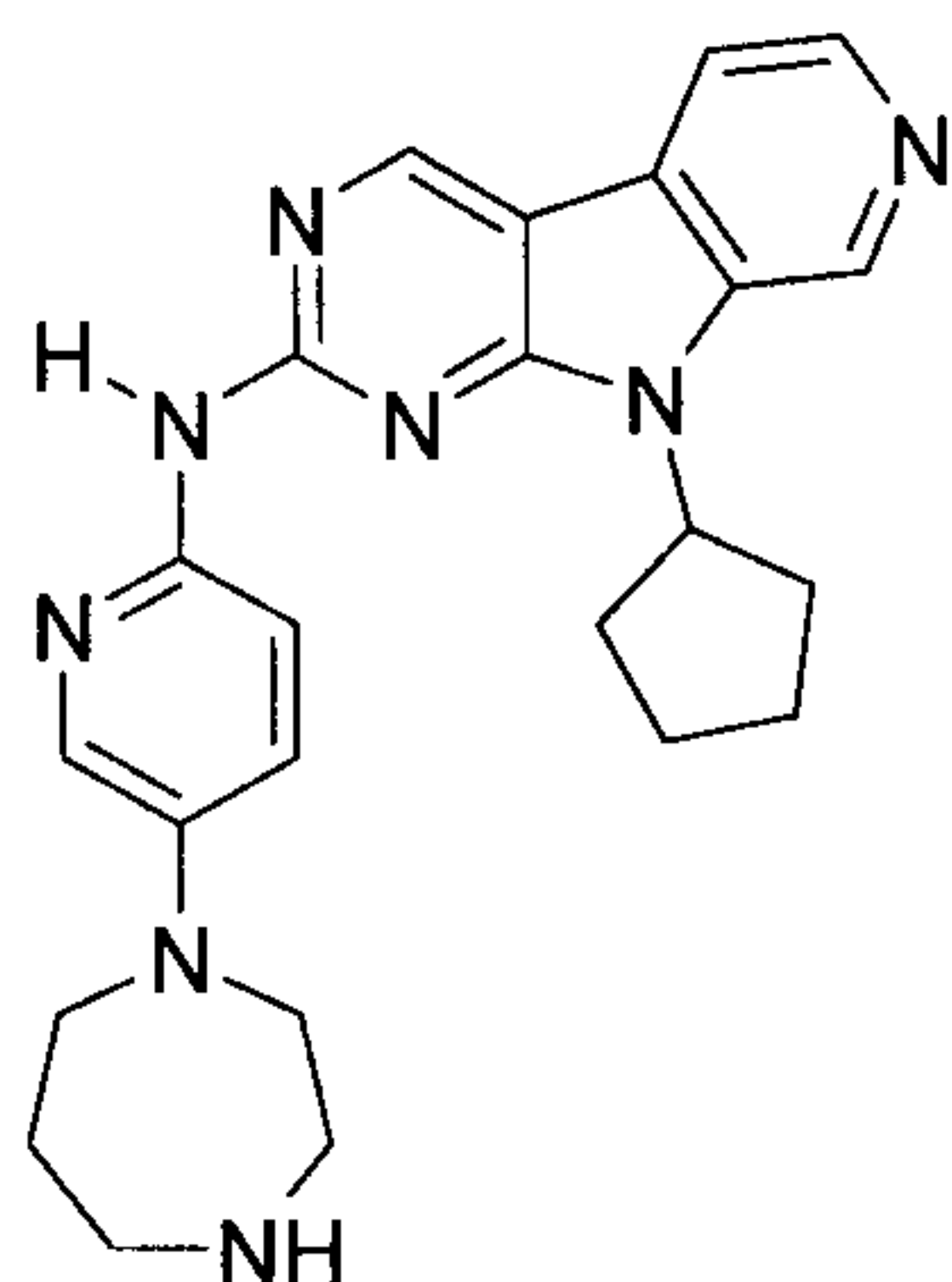
78. The compound of claim 1, wherein the compound is





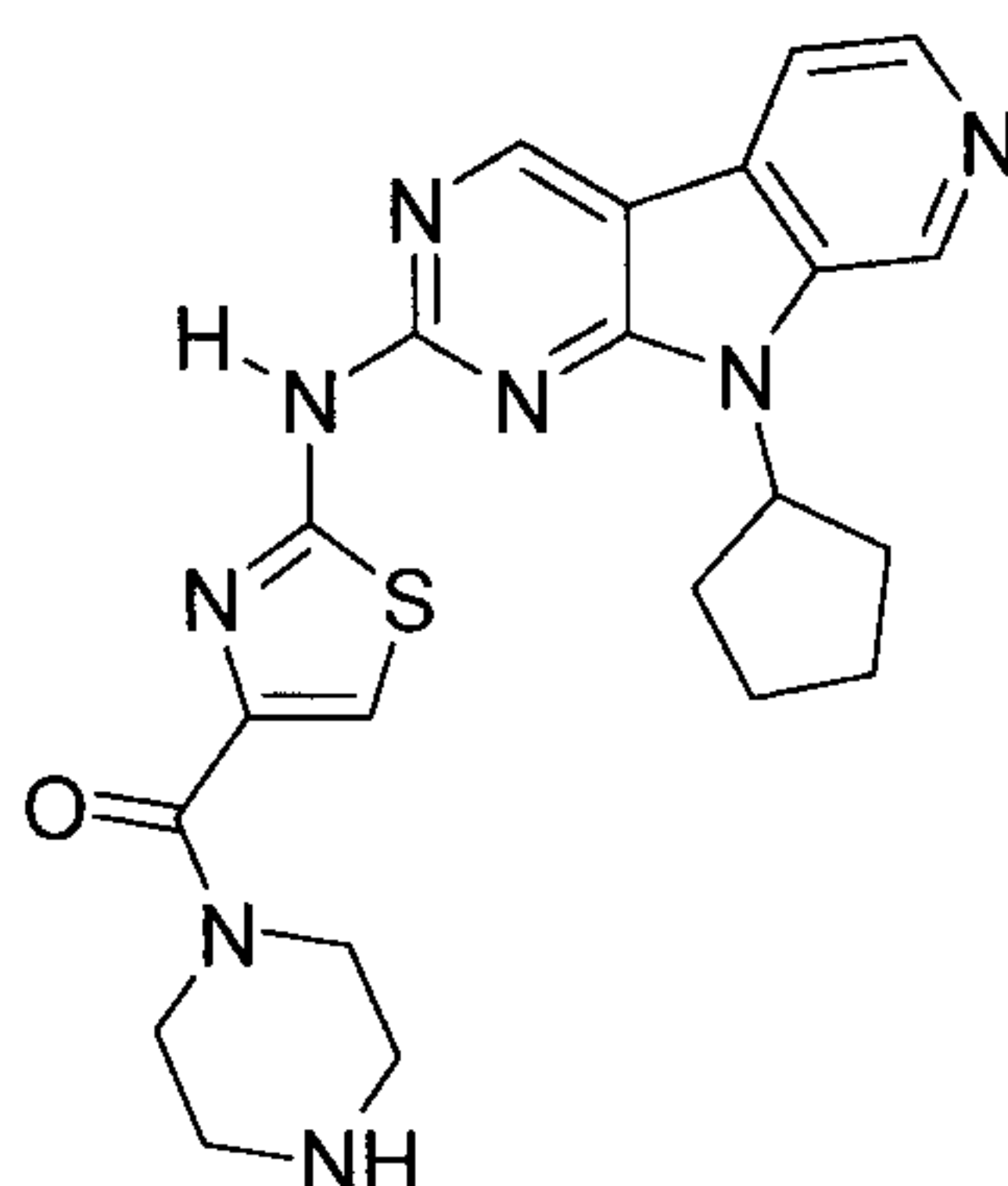
or a pharmaceutically acceptable salt thereof.

79. The compound of claim 1, wherein the compound is



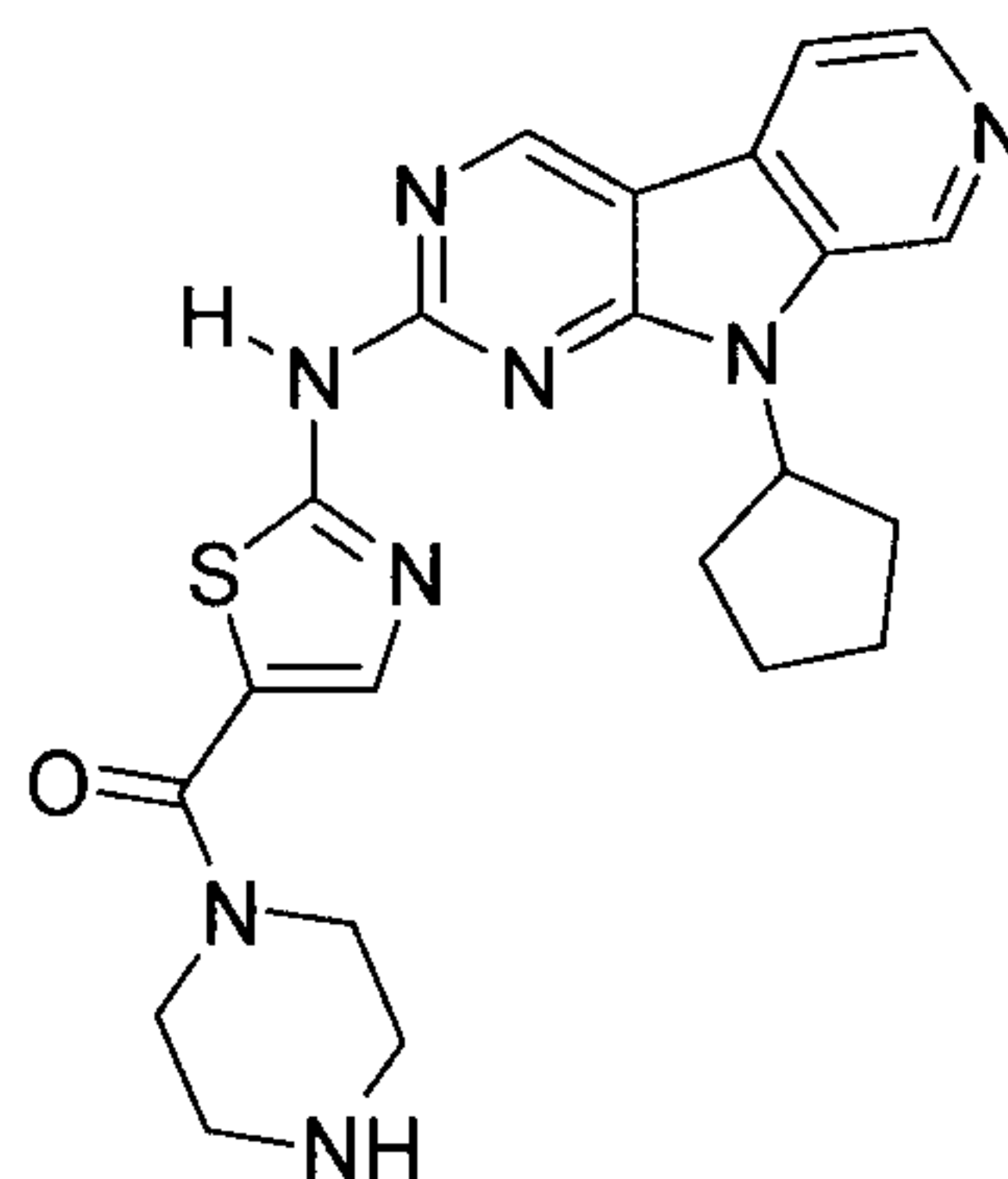
or a pharmaceutically acceptable salt thereof.

80. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

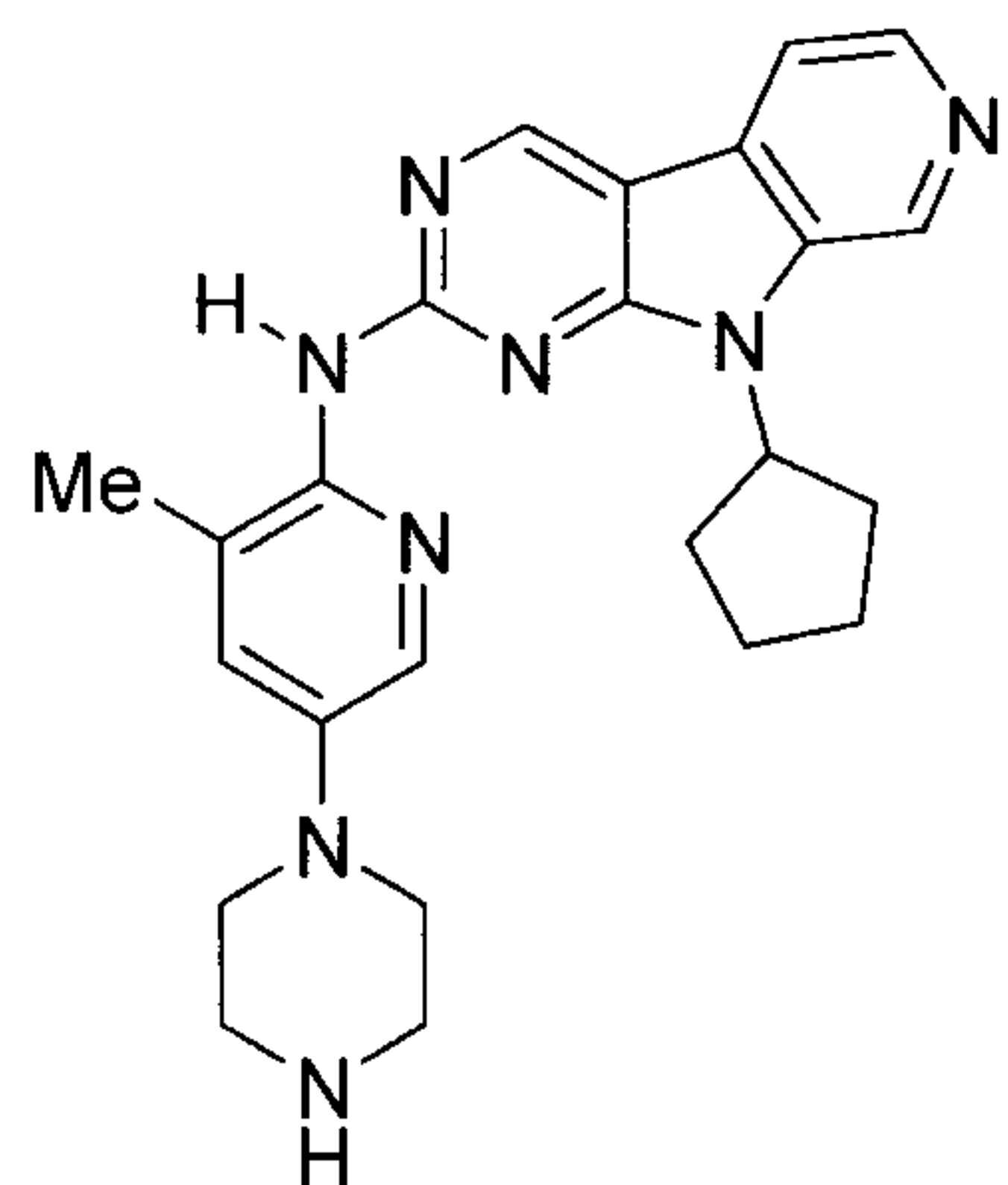
81. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

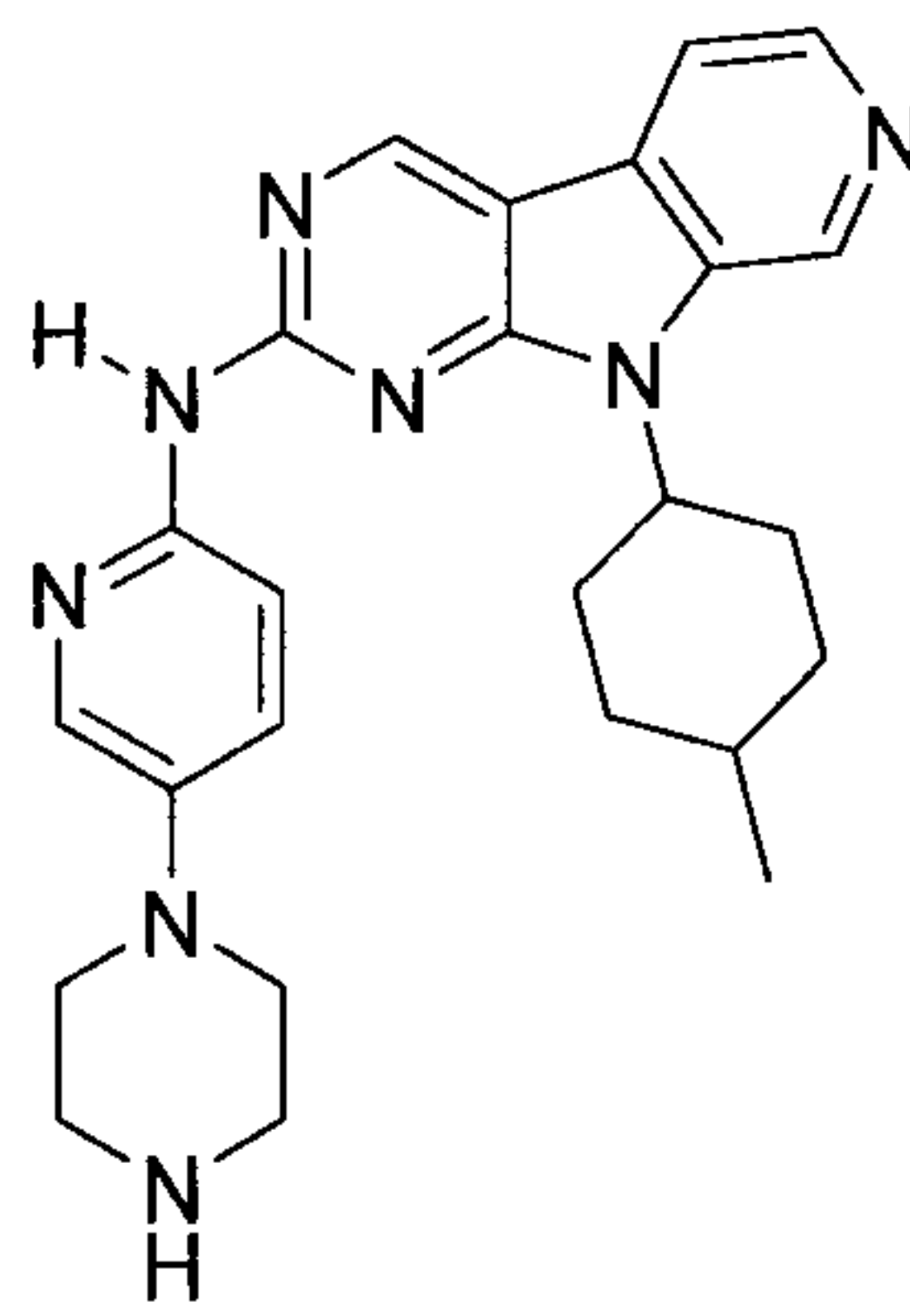


82. The compound of claim 1, wherein the compound is



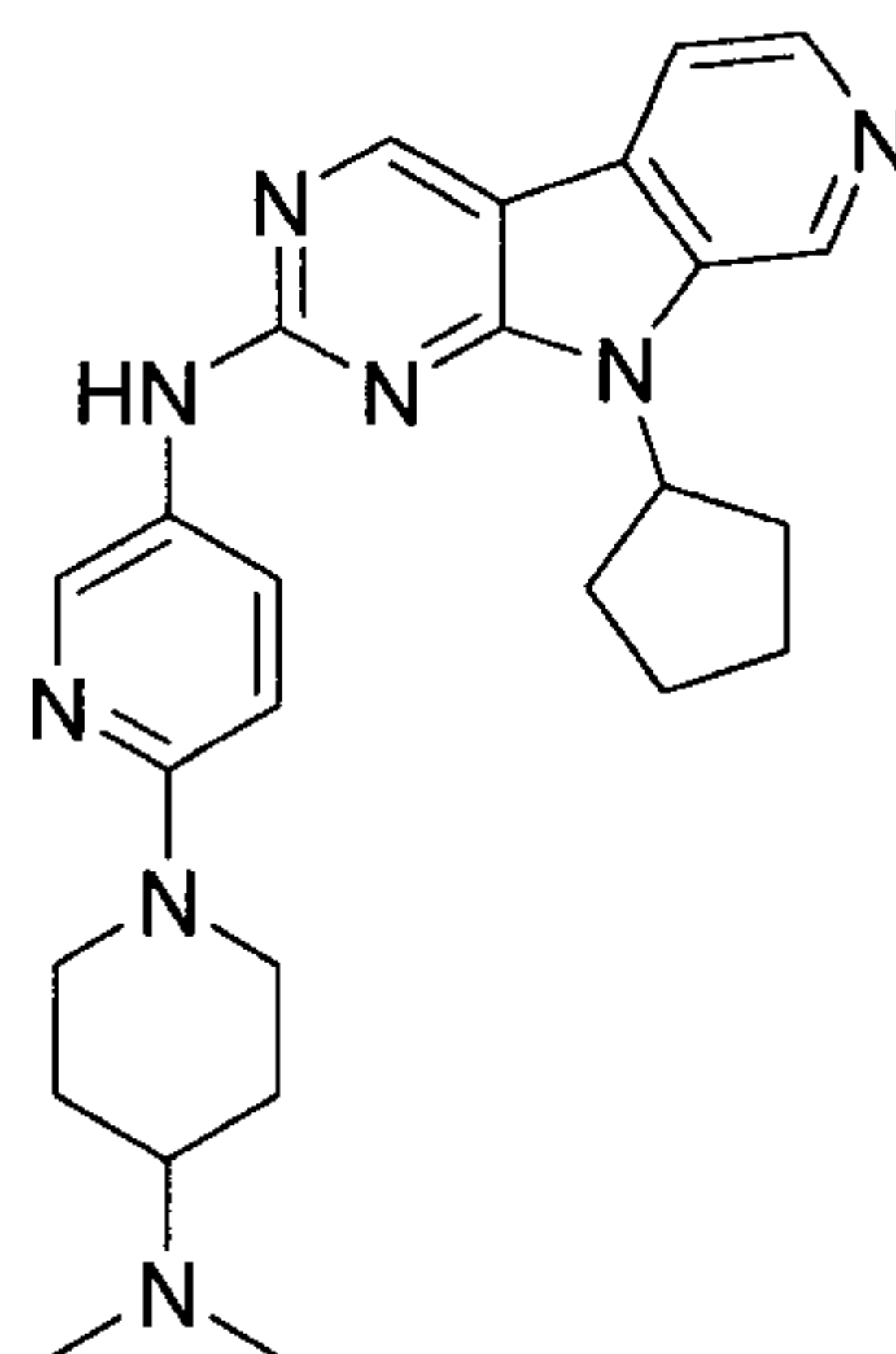
or a pharmaceutically acceptable salt thereof.

83. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

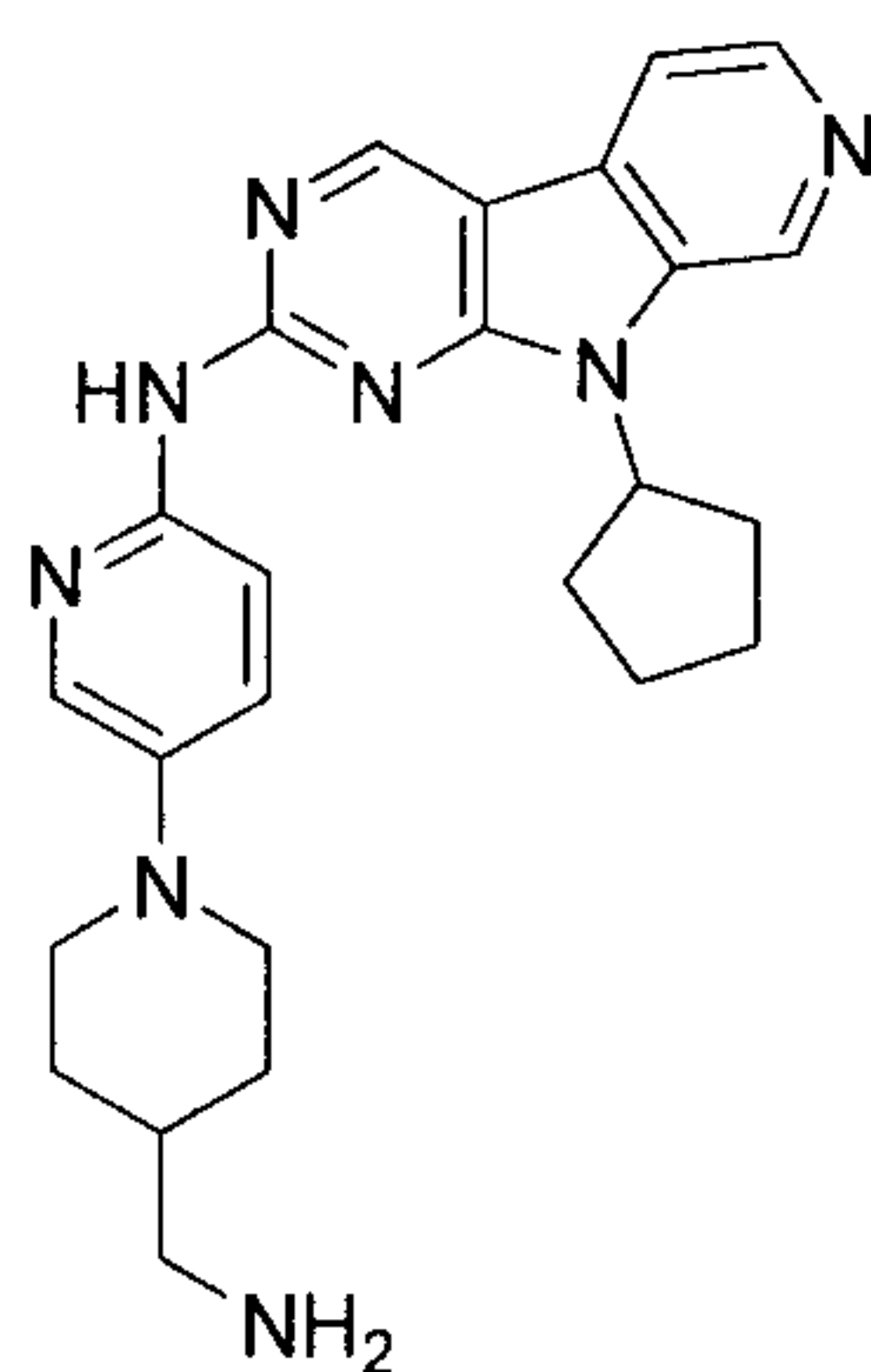
84. The compound of claim 1, wherein the compound is





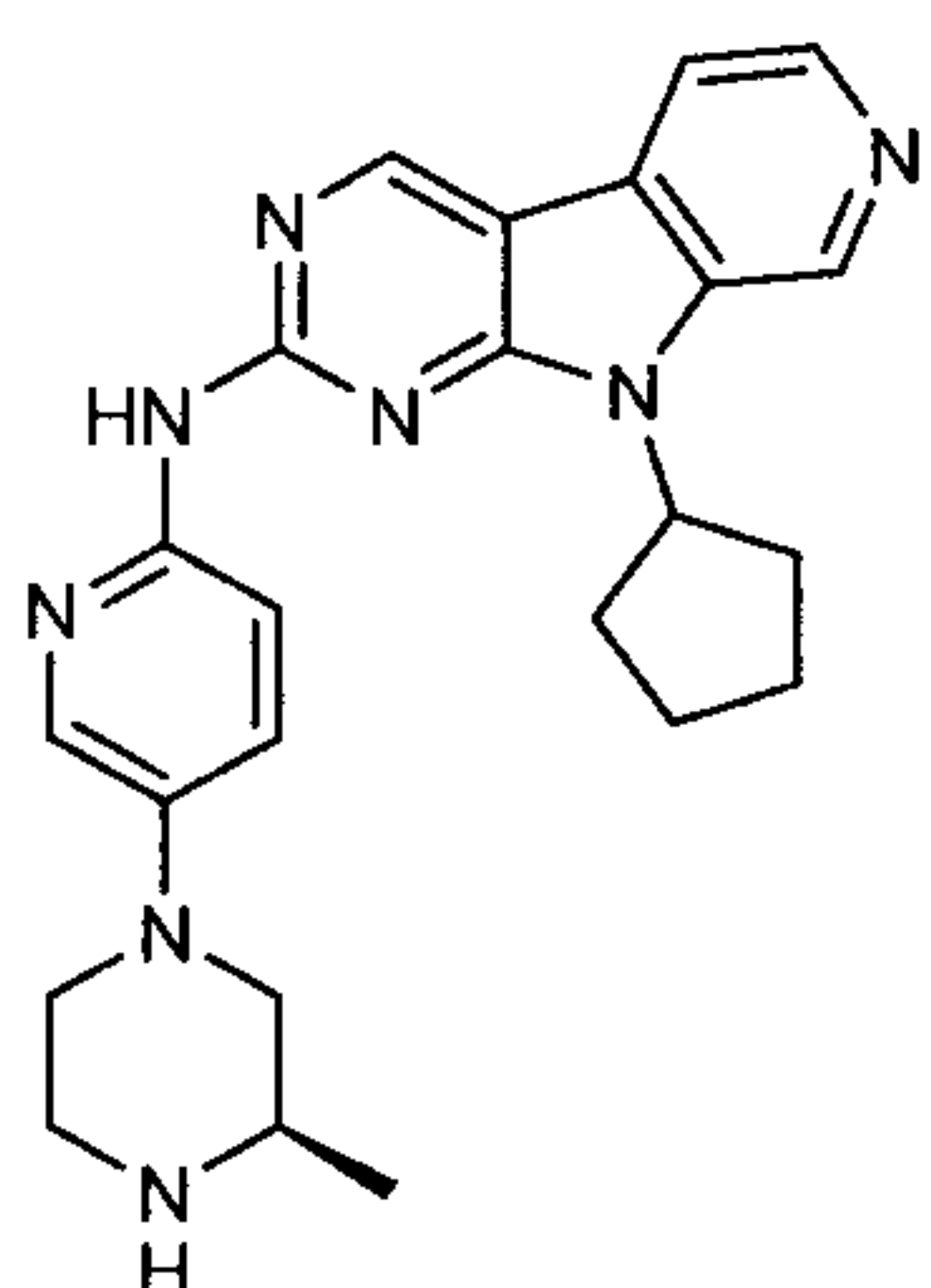
or a pharmaceutically acceptable salt thereof.

85. The compound of claim 1, wherein the compound is



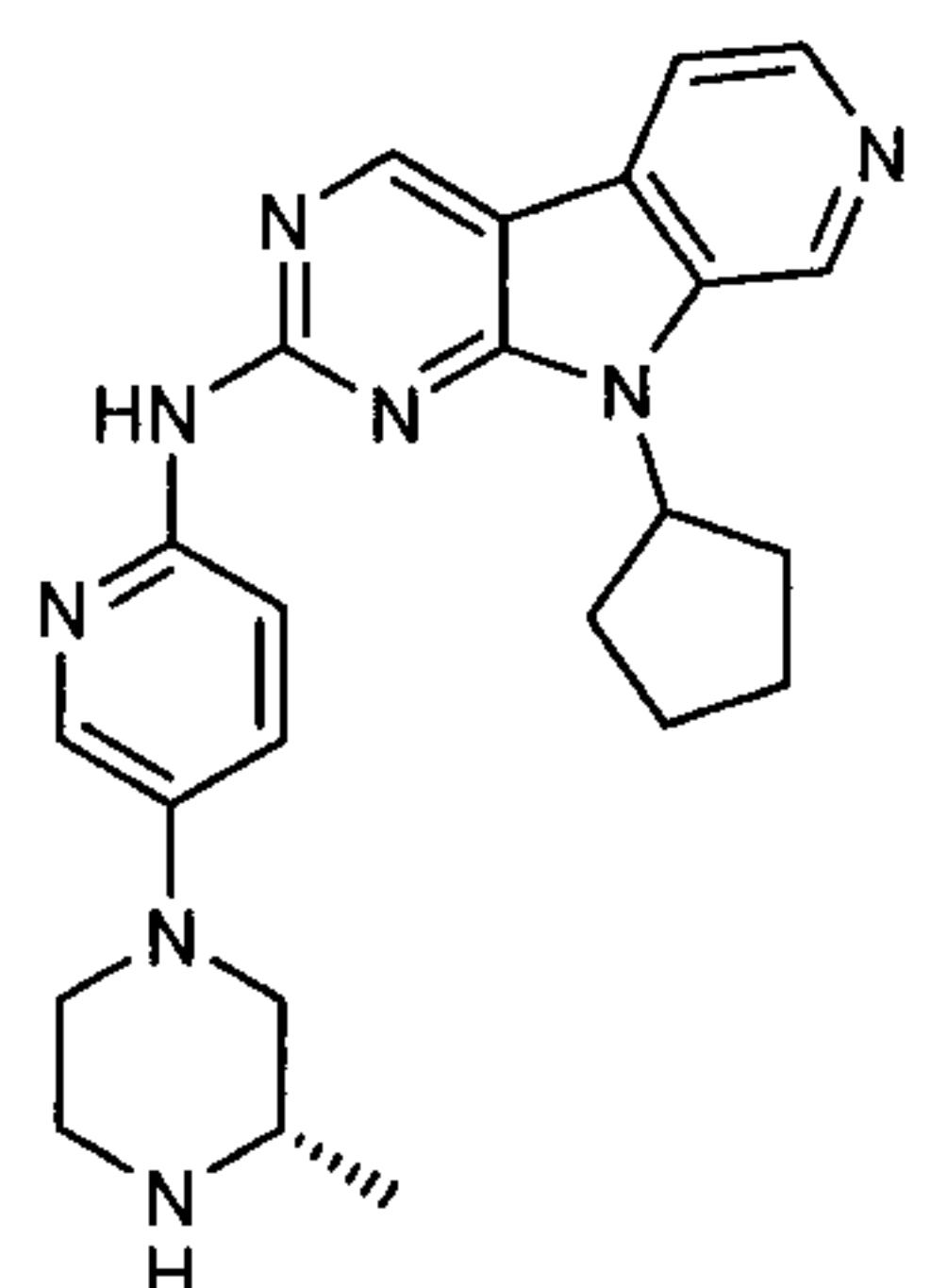
or a pharmaceutically acceptable salt thereof.

86. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

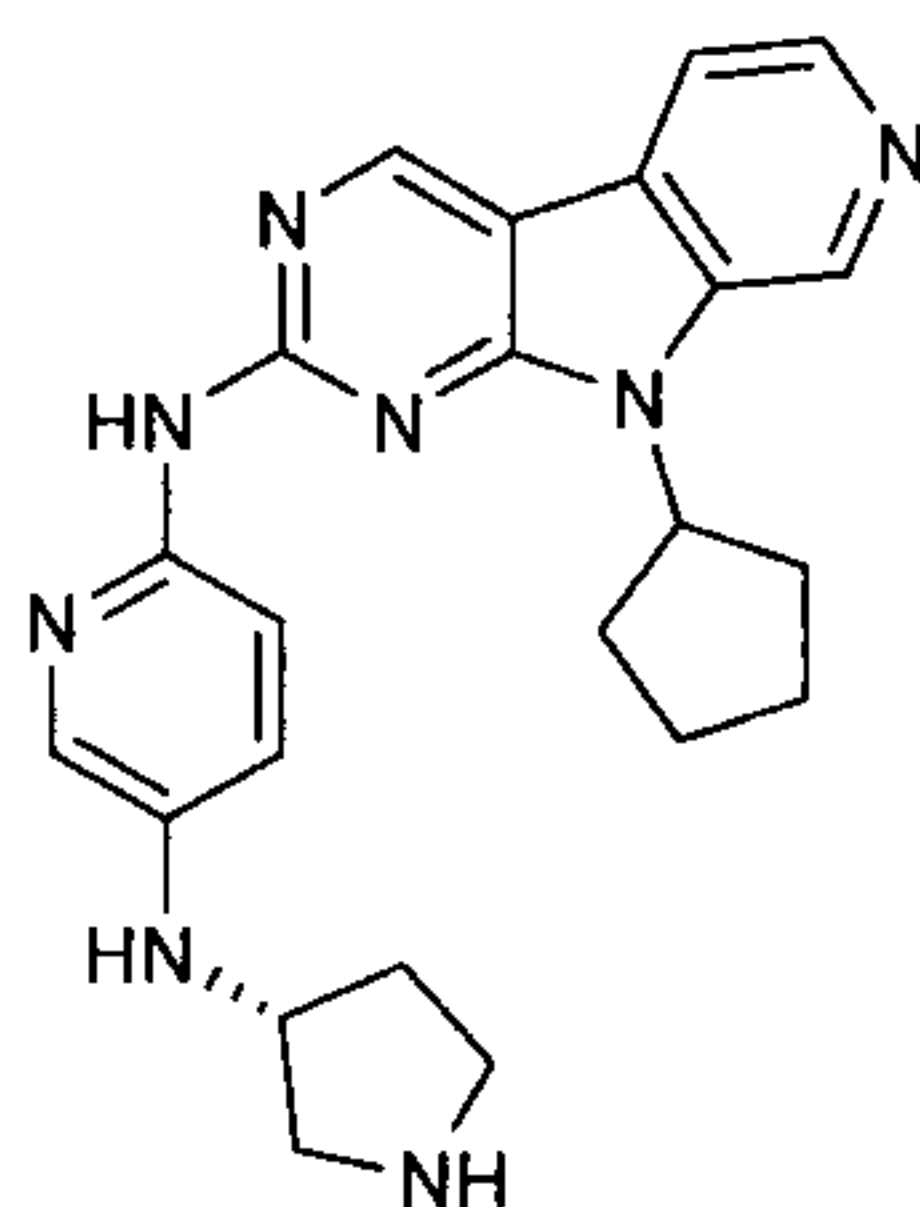
87. The compound of claim 1, wherein the compound is





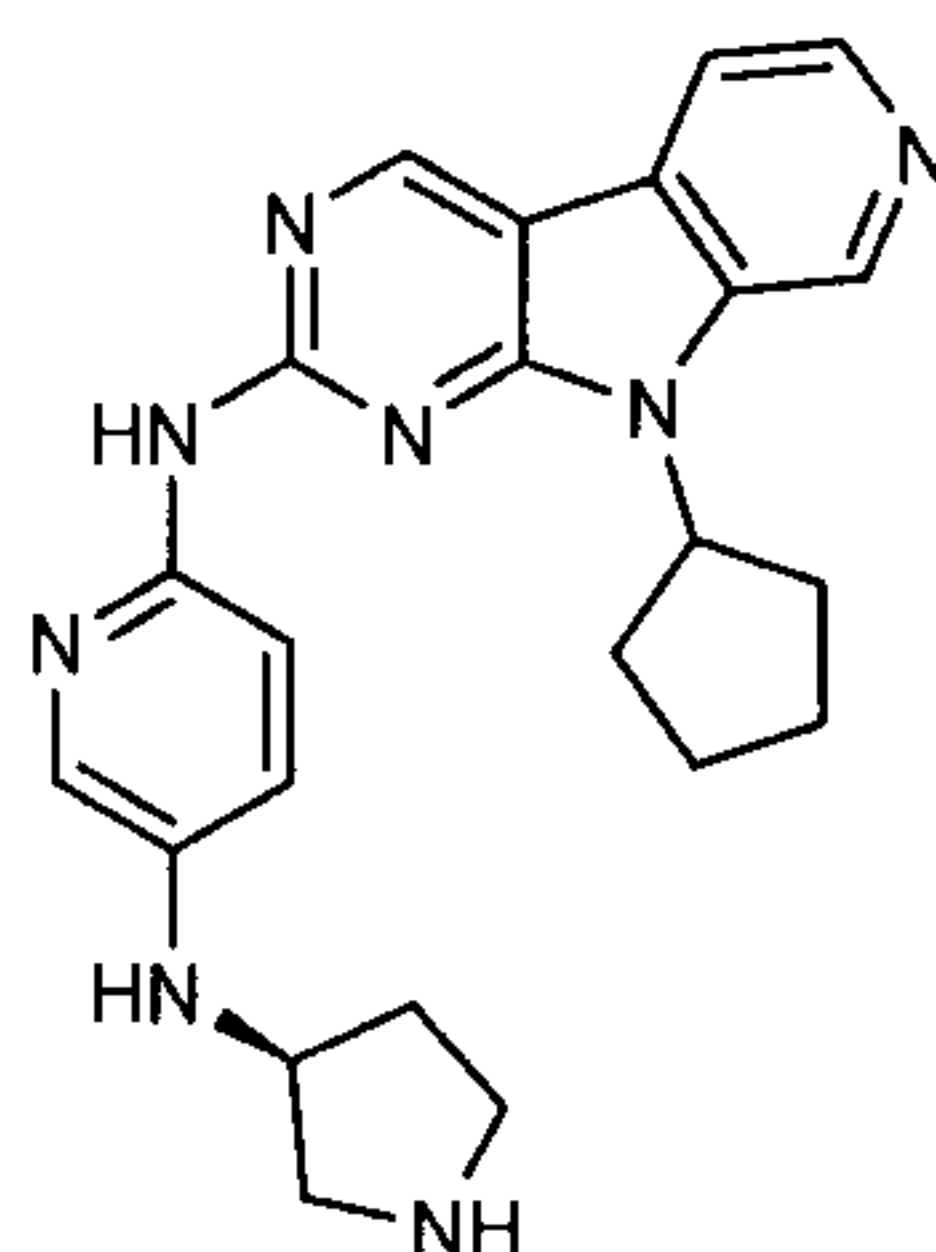
or a pharmaceutically acceptable salt thereof.

88. The compound of claim 1, wherein the compound is



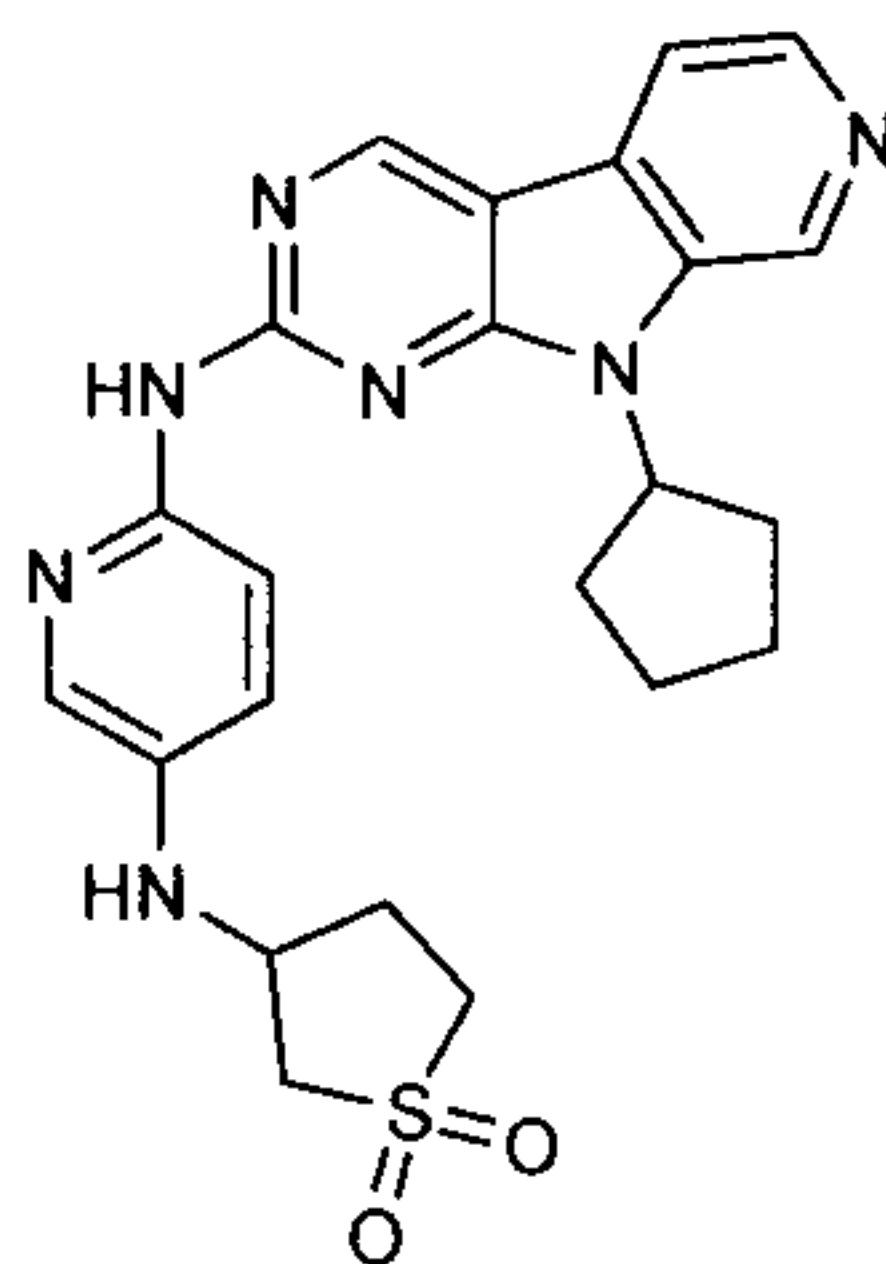
or a pharmaceutically acceptable salt thereof.

89. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

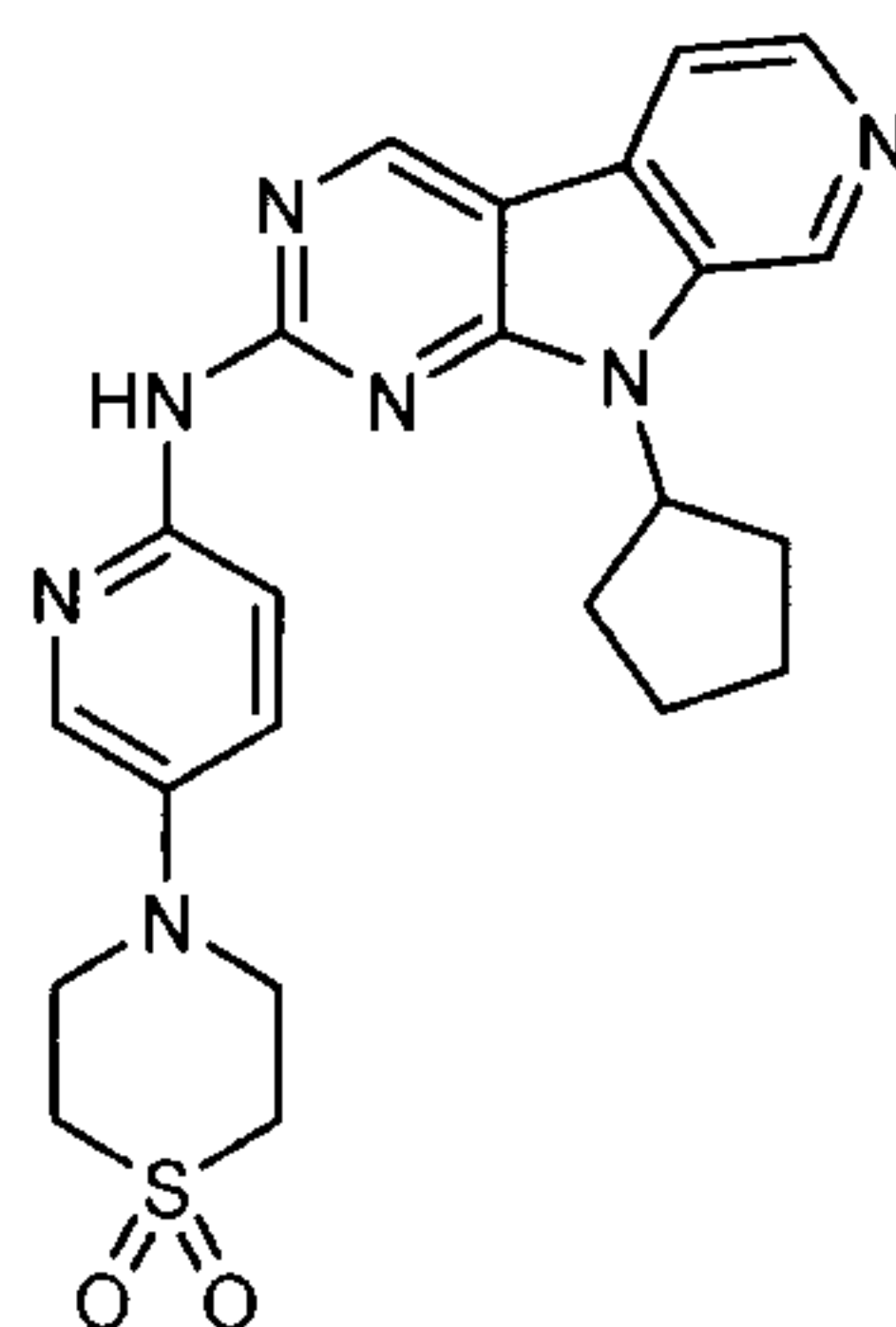
90. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

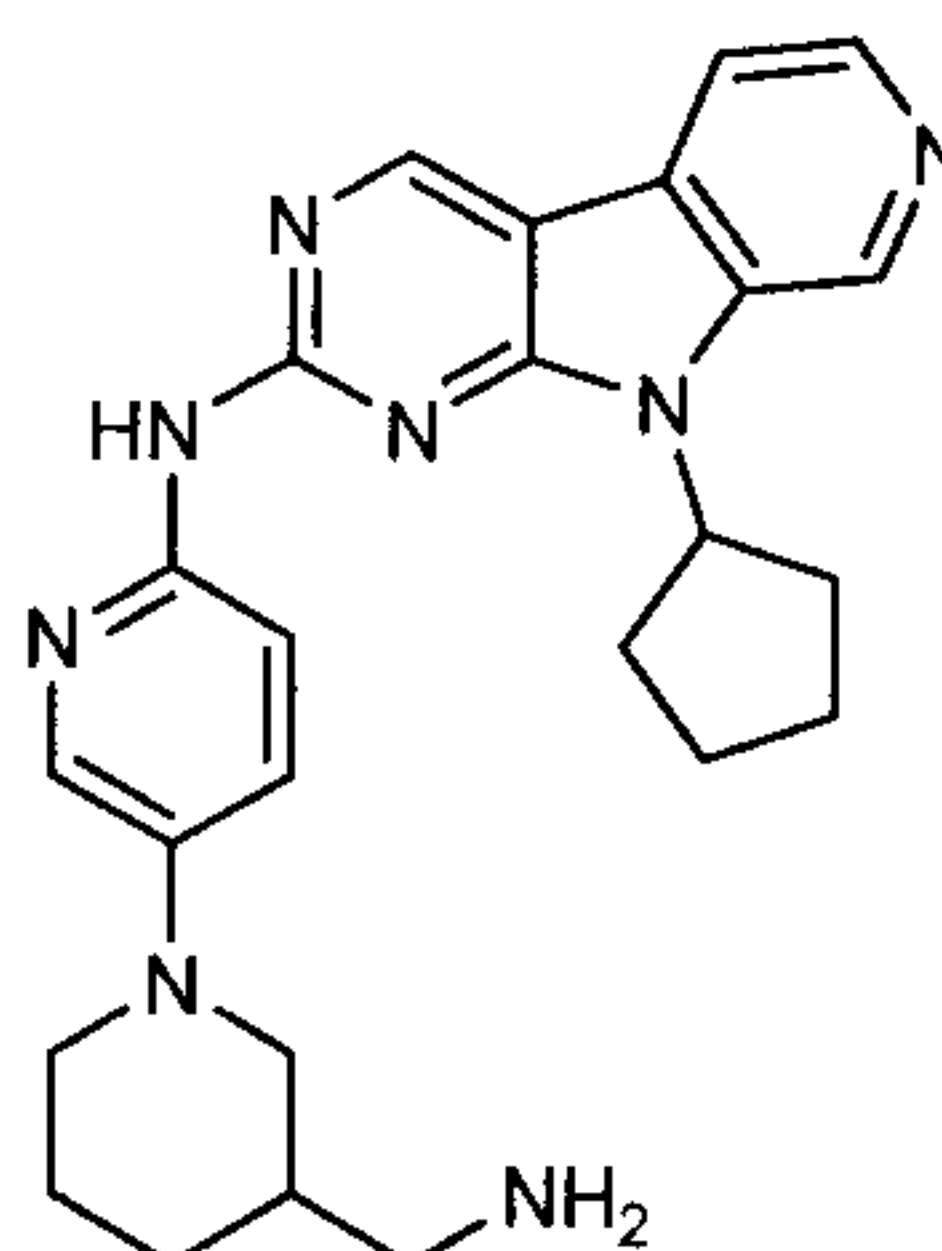


91. The compound of claim 1, wherein the compound is



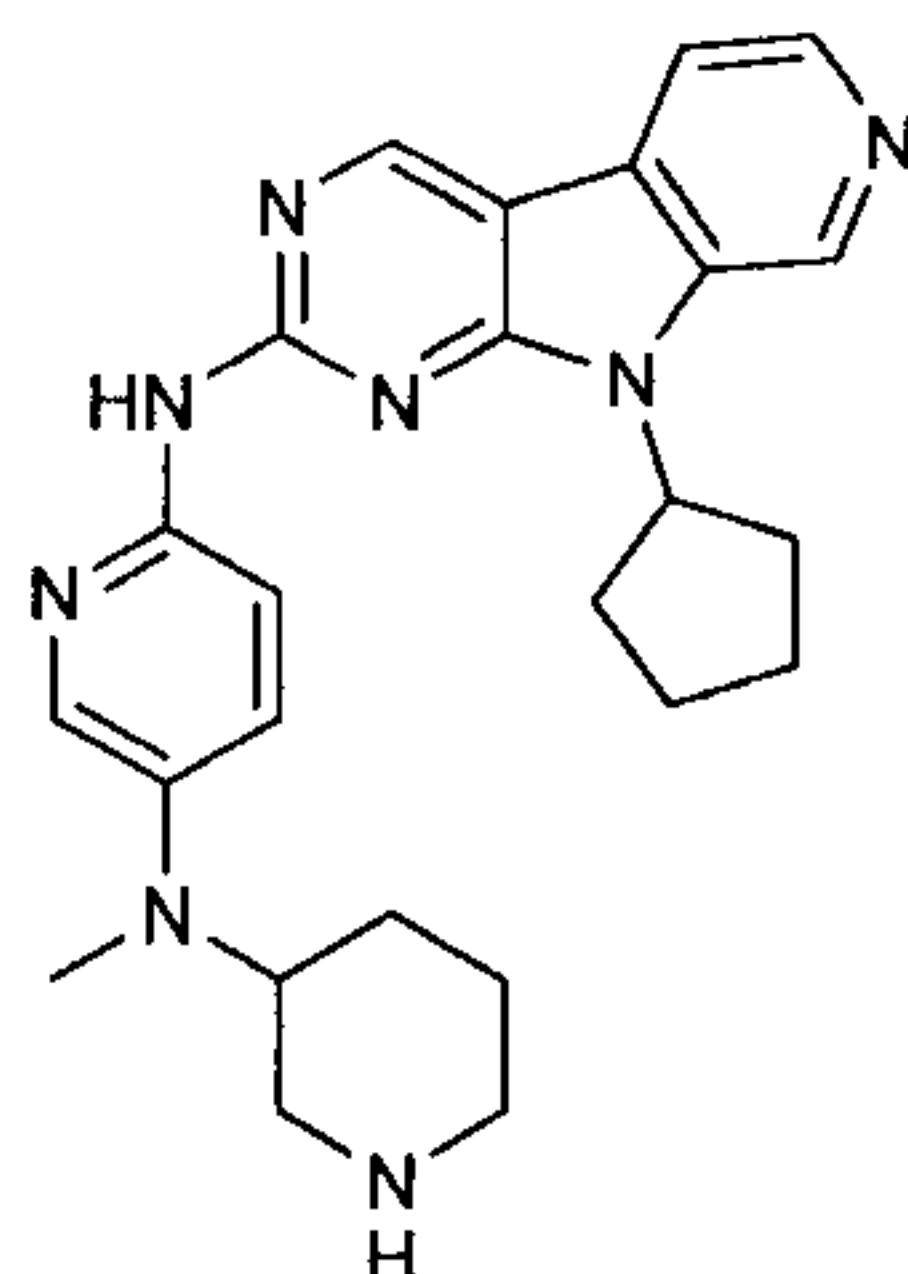
or a pharmaceutically acceptable salt thereof.

92. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

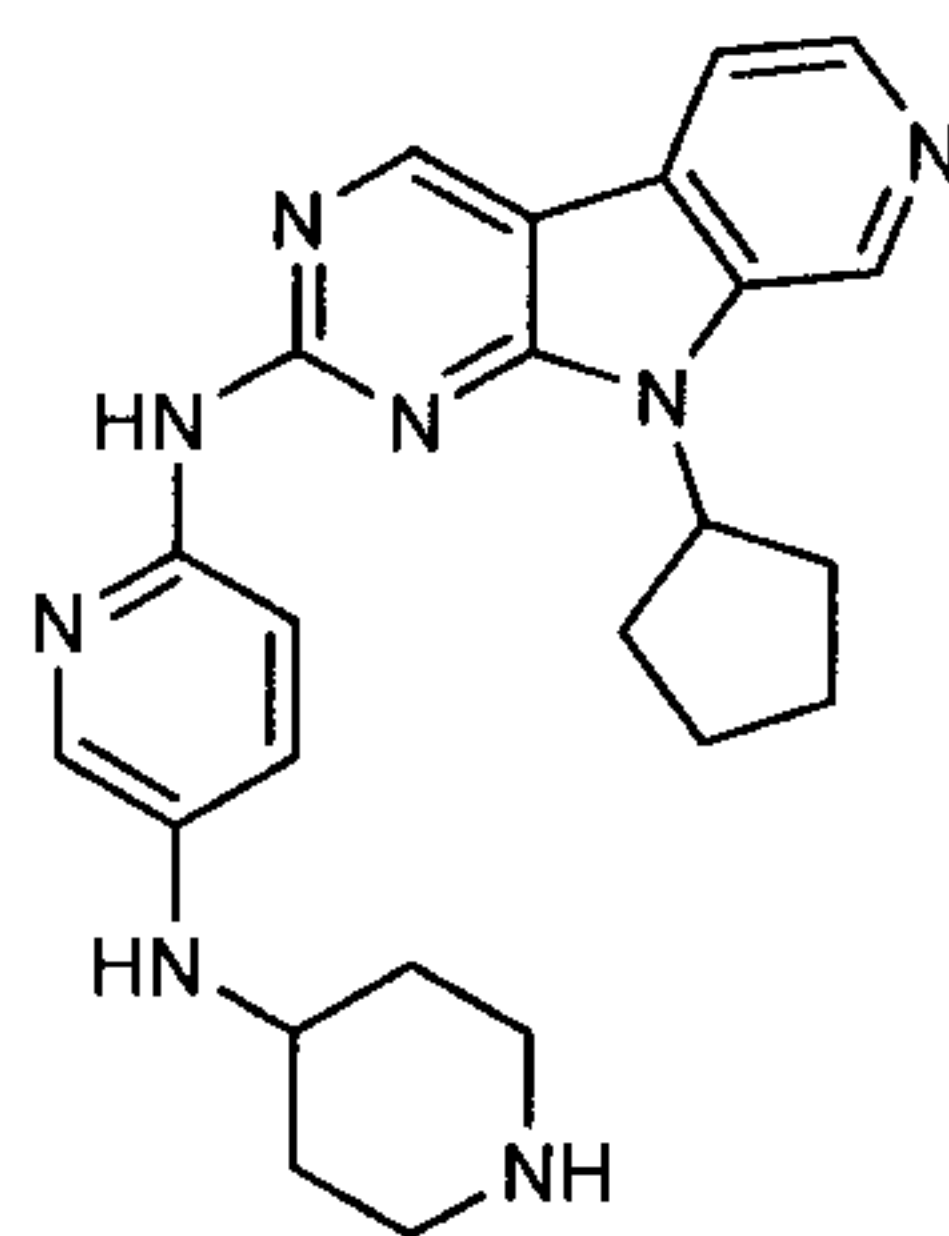
93. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

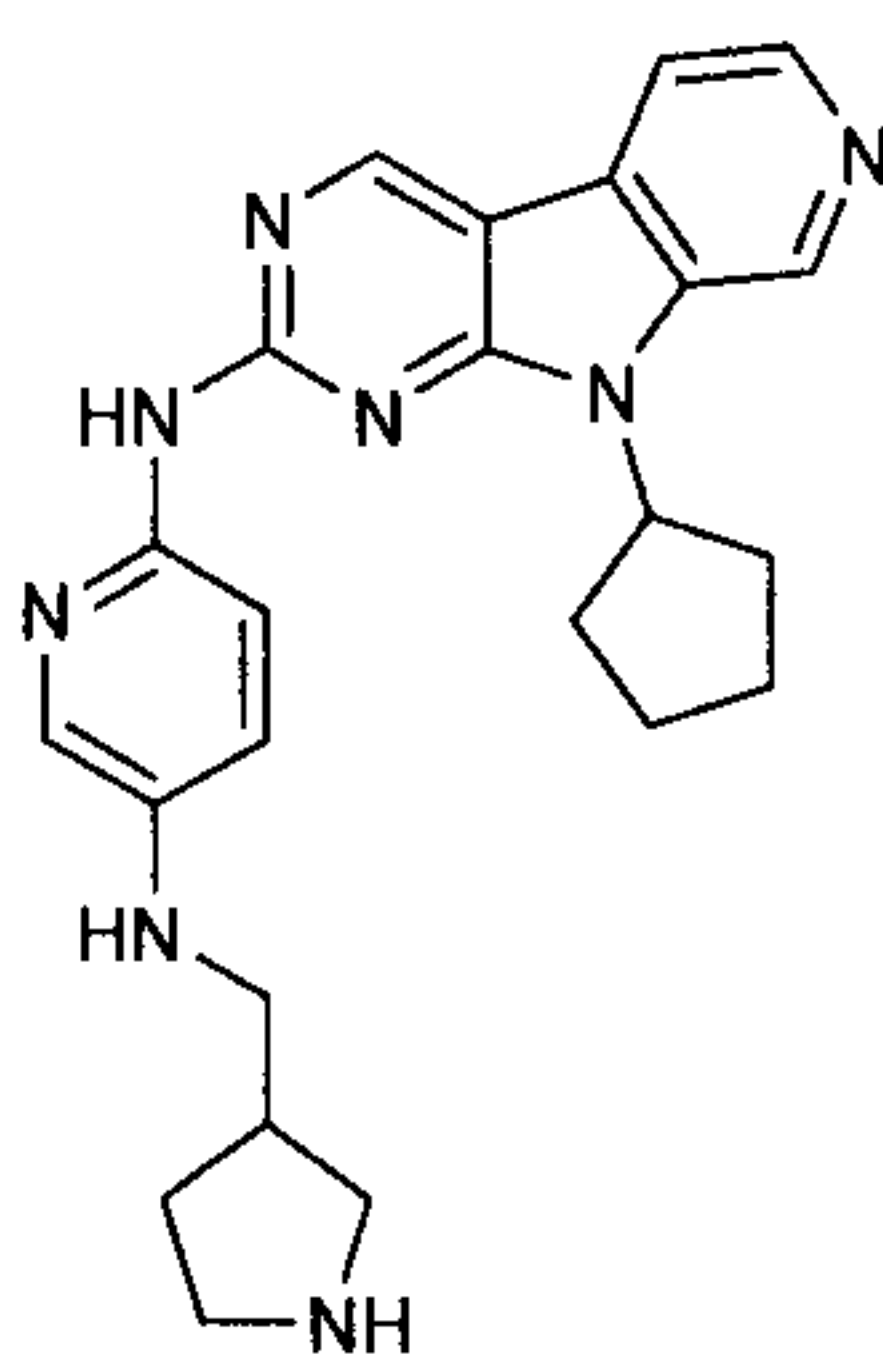


94. The compound of claim 1, wherein the compound is



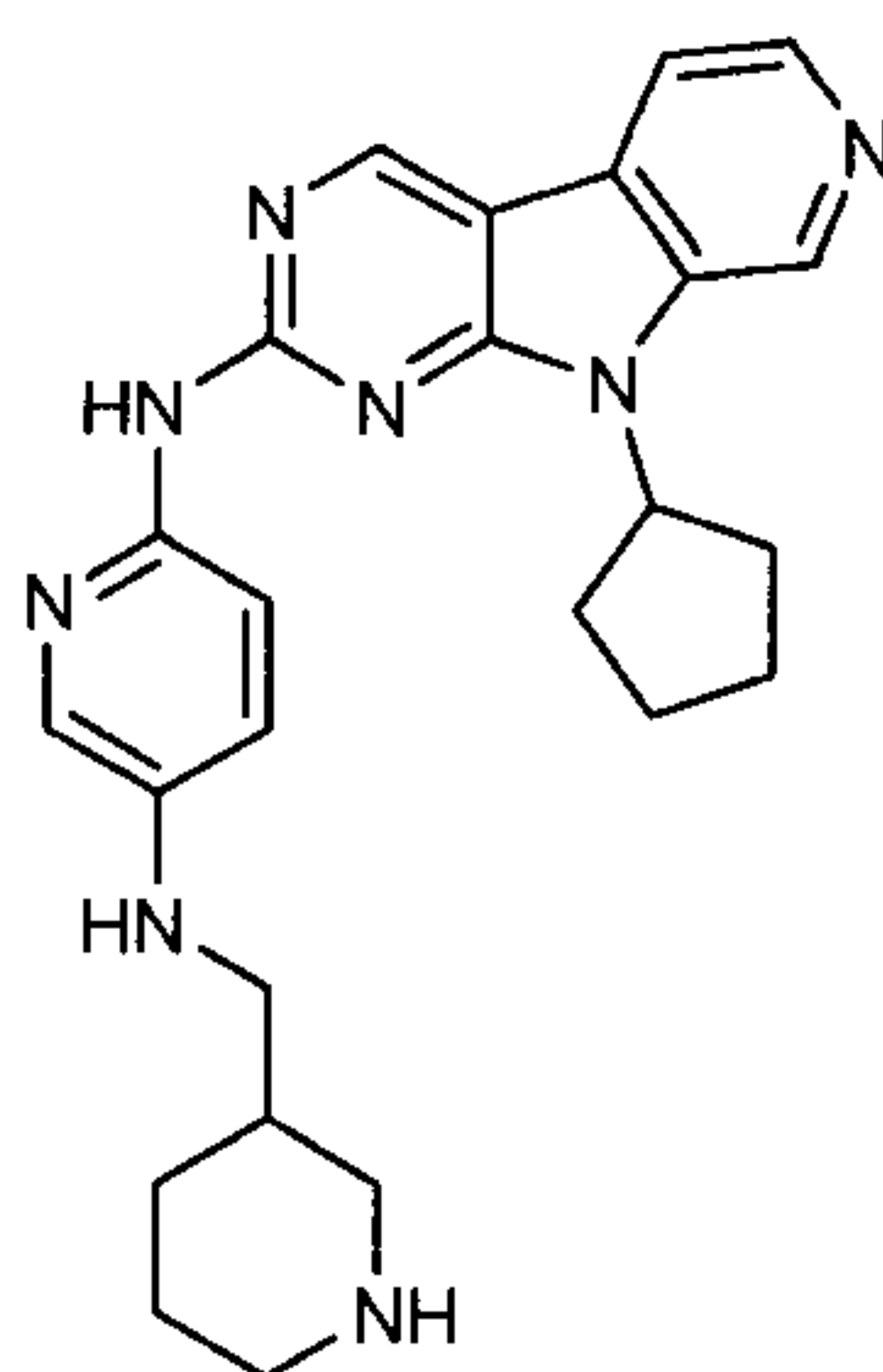
or a pharmaceutically acceptable salt thereof.

95. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

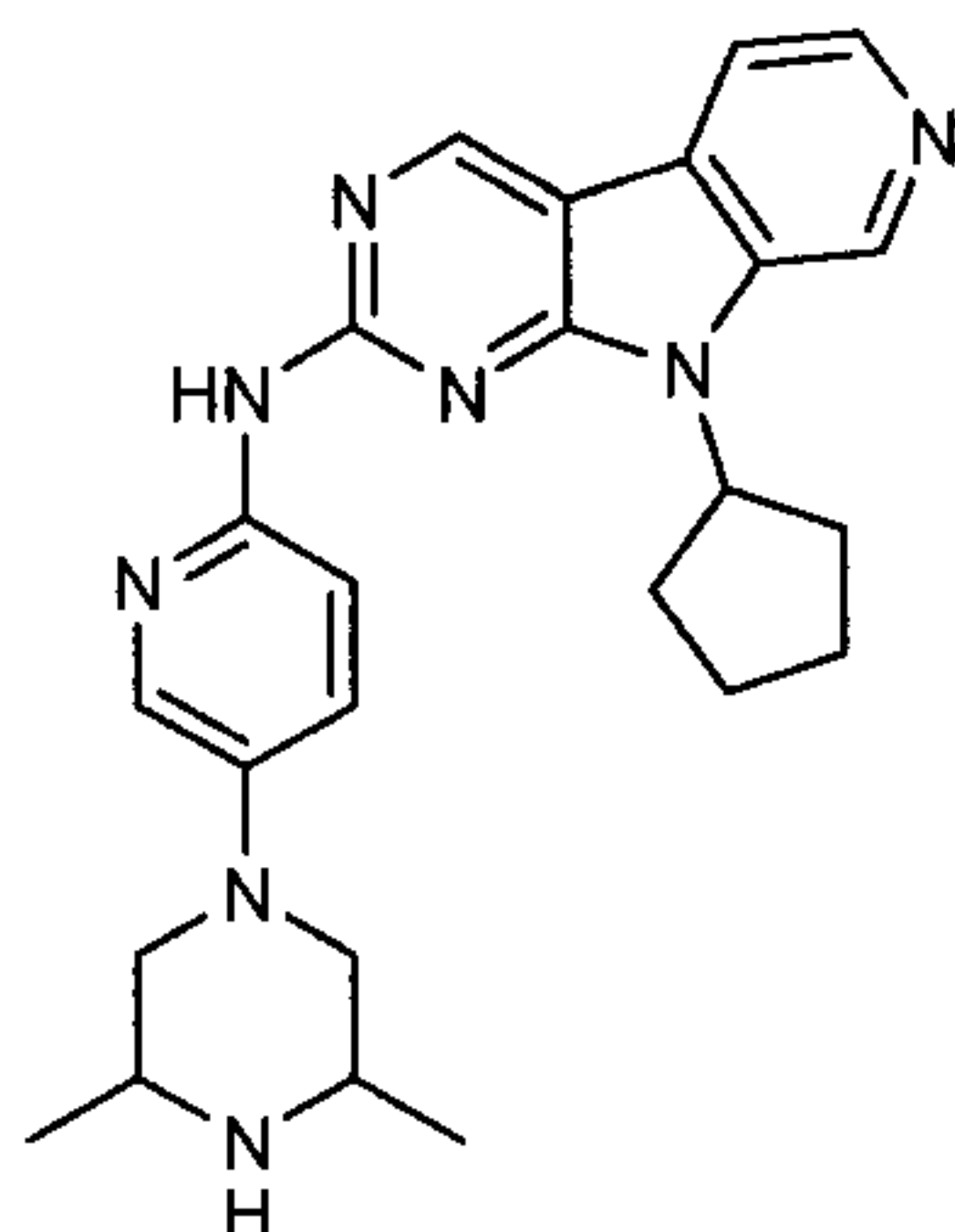
96. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

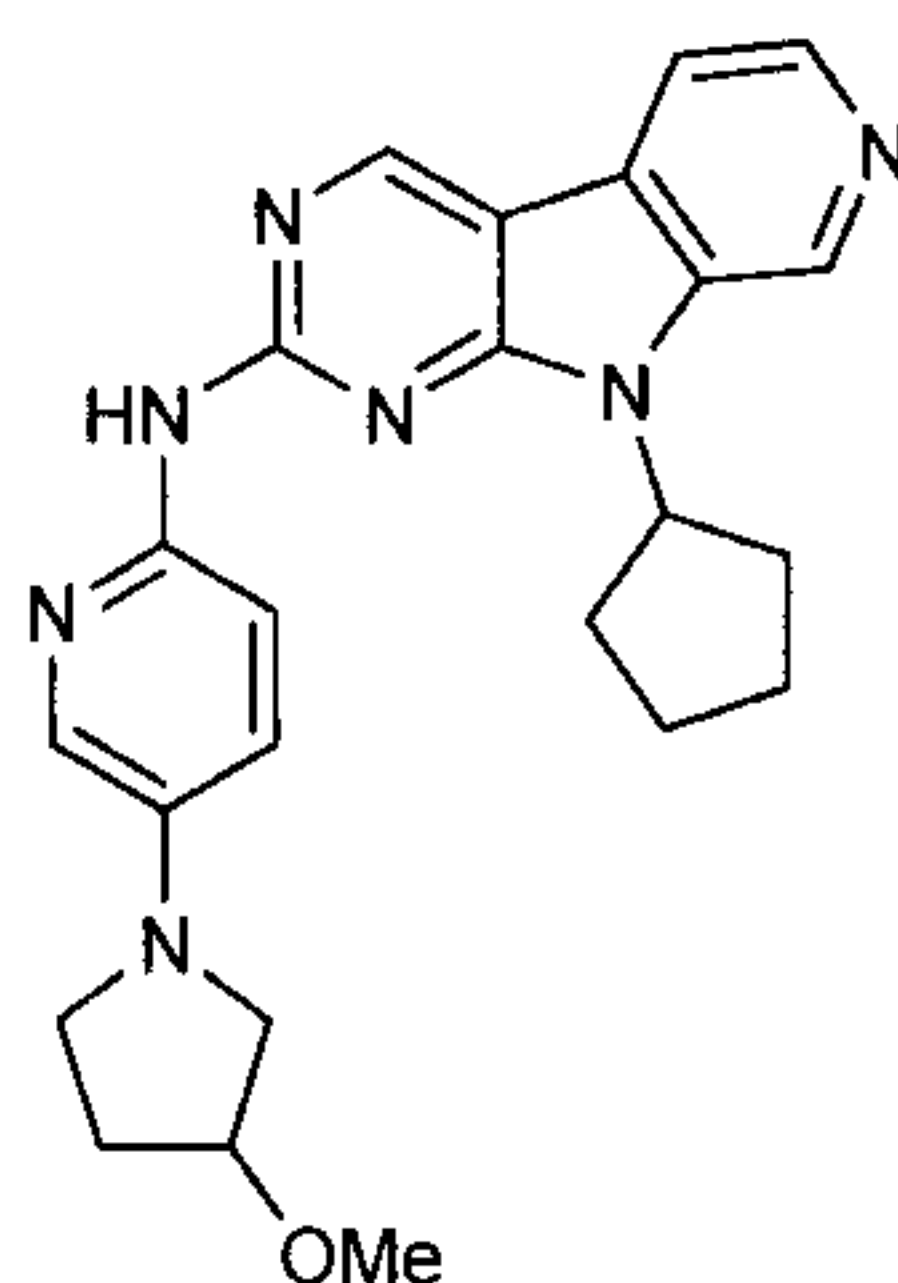


97. The compound of claim 1, wherein the compound is



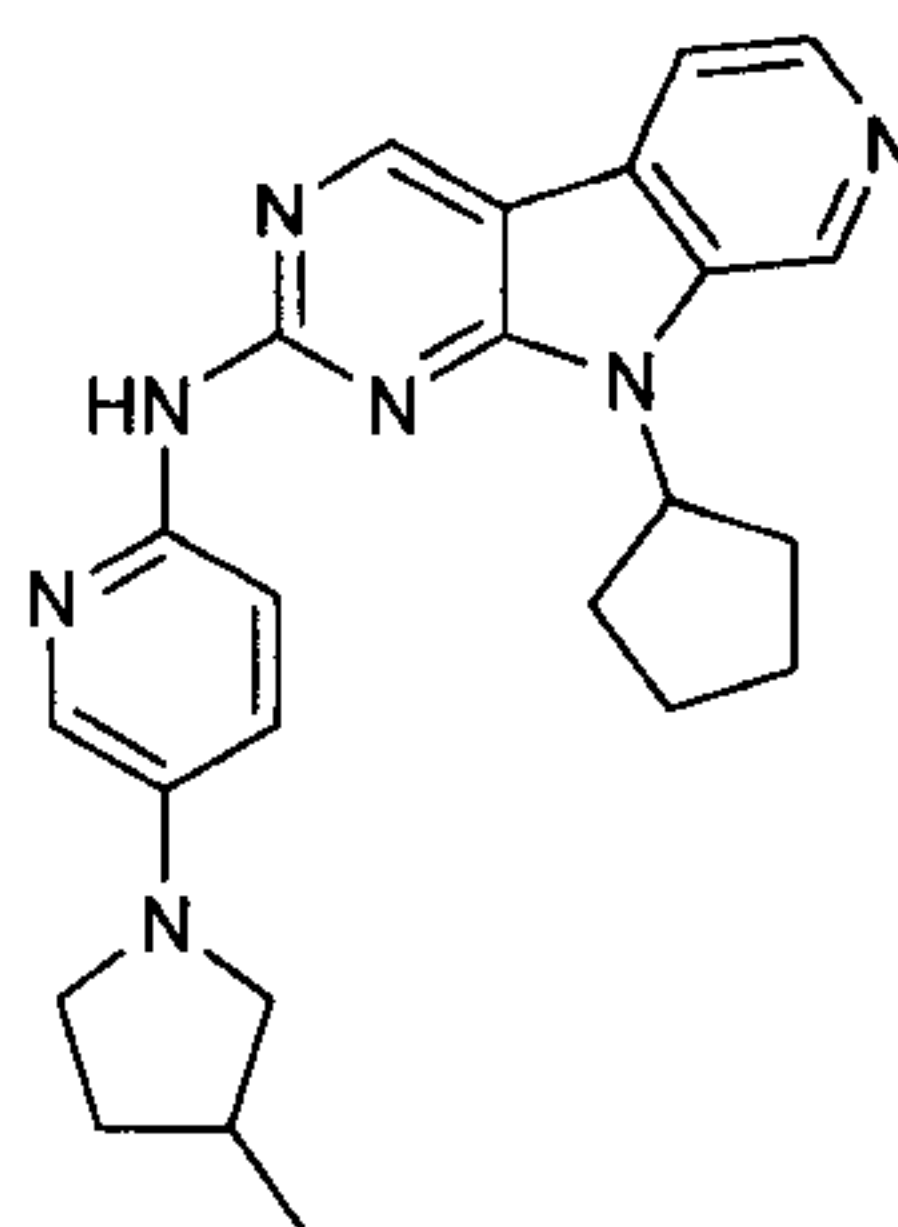
or a pharmaceutically acceptable salt thereof.

98. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

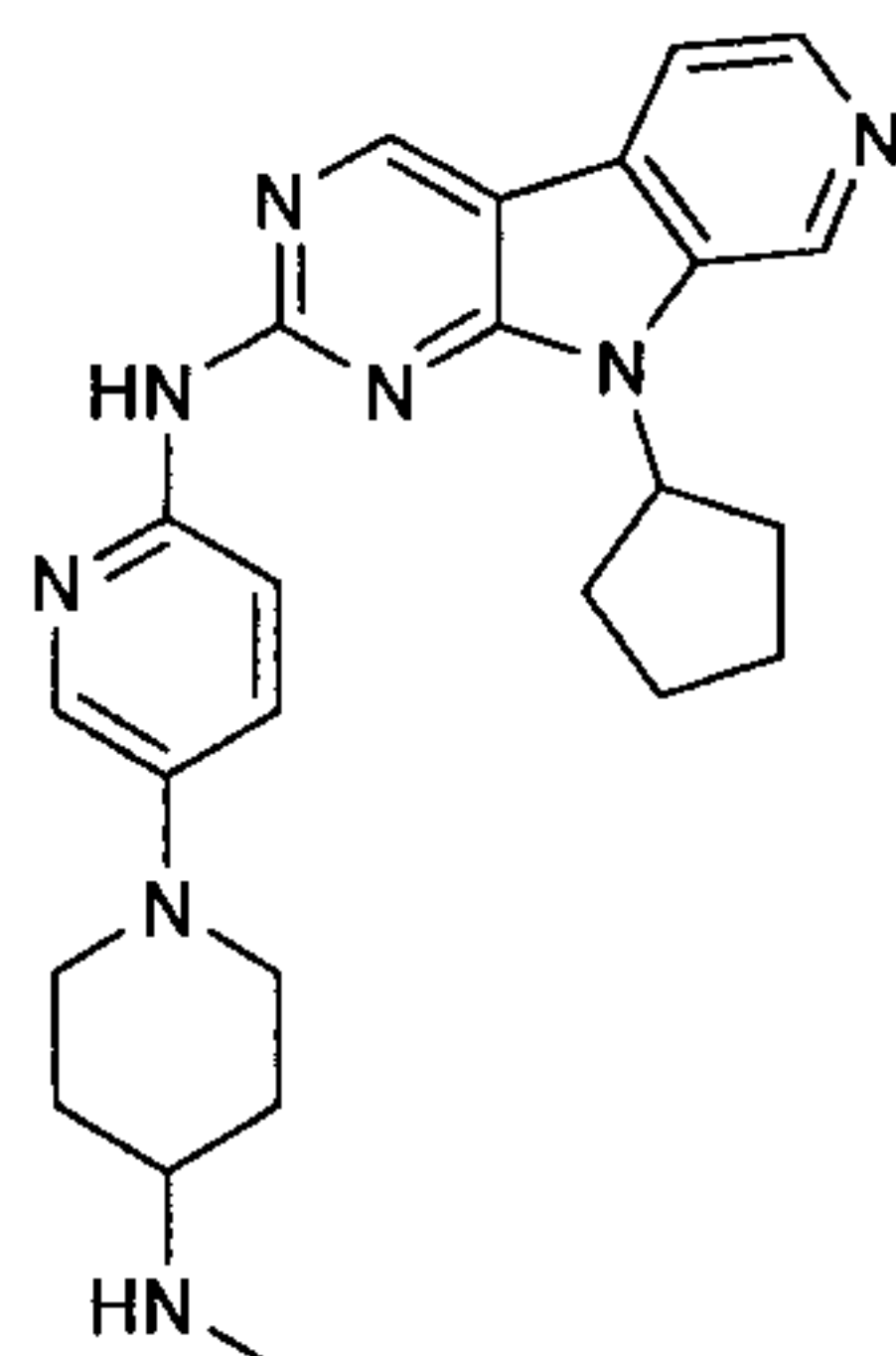
99. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

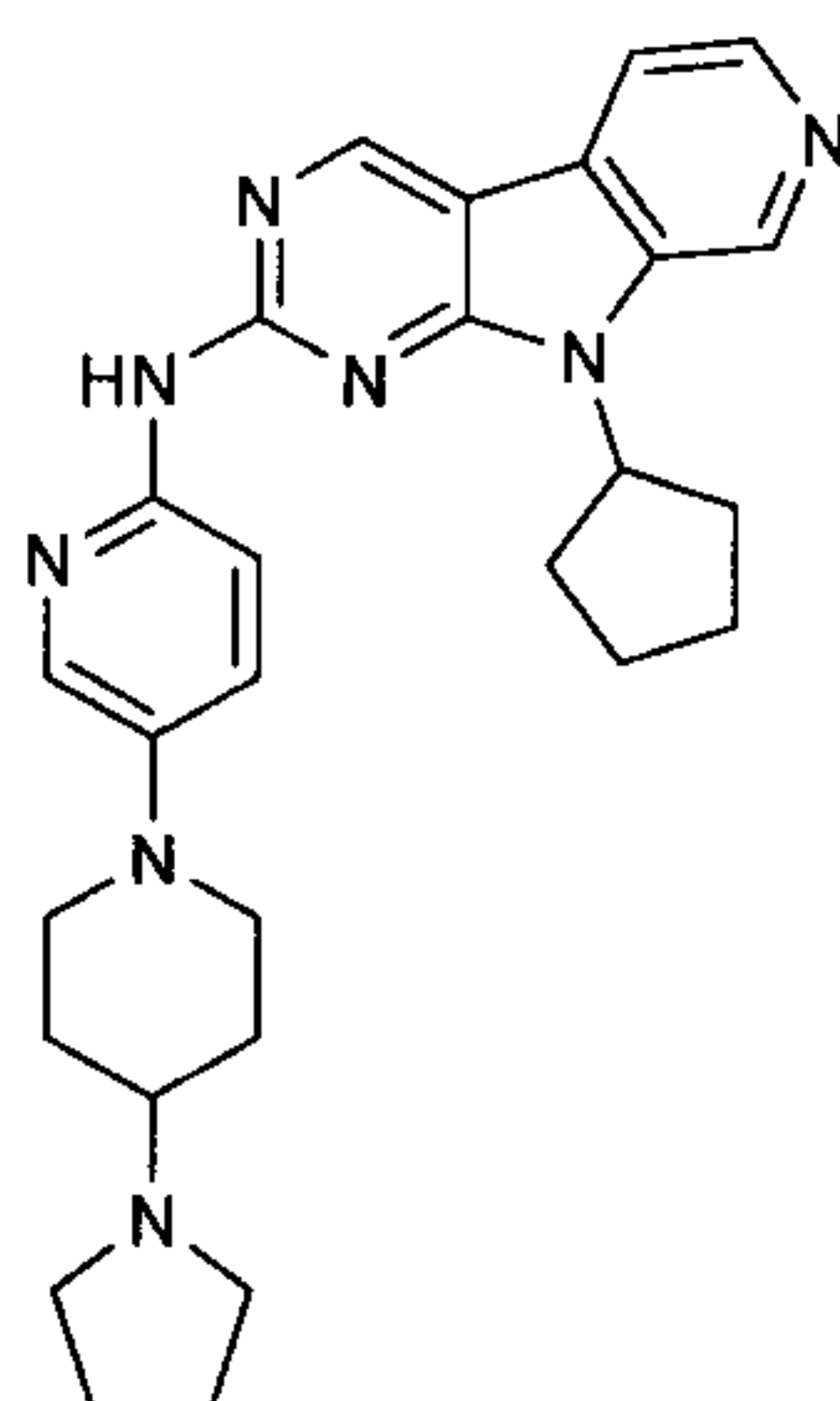


100. The compound of claim 1, wherein the compound is



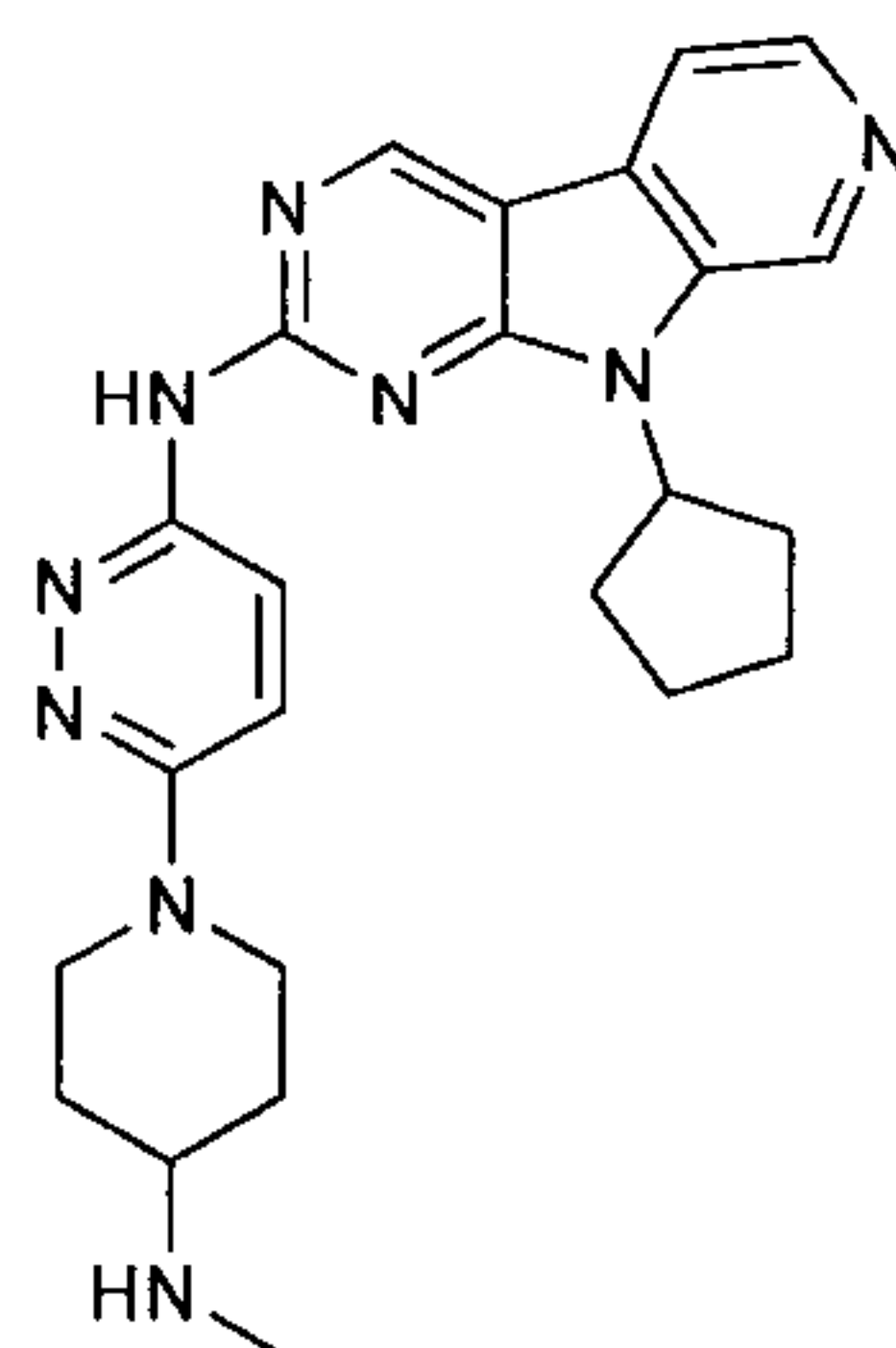
or a pharmaceutically acceptable salt thereof.

101. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

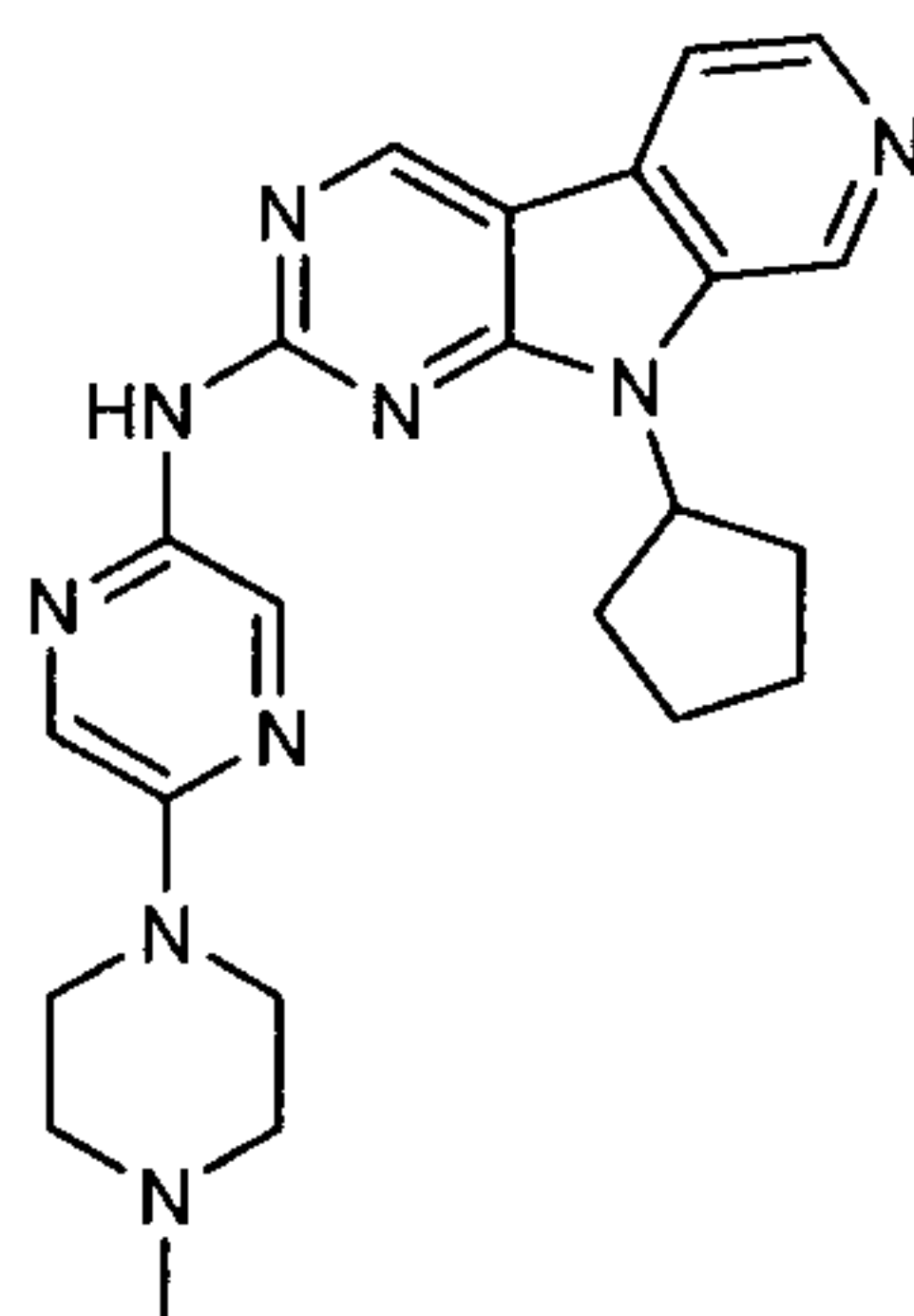
102. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

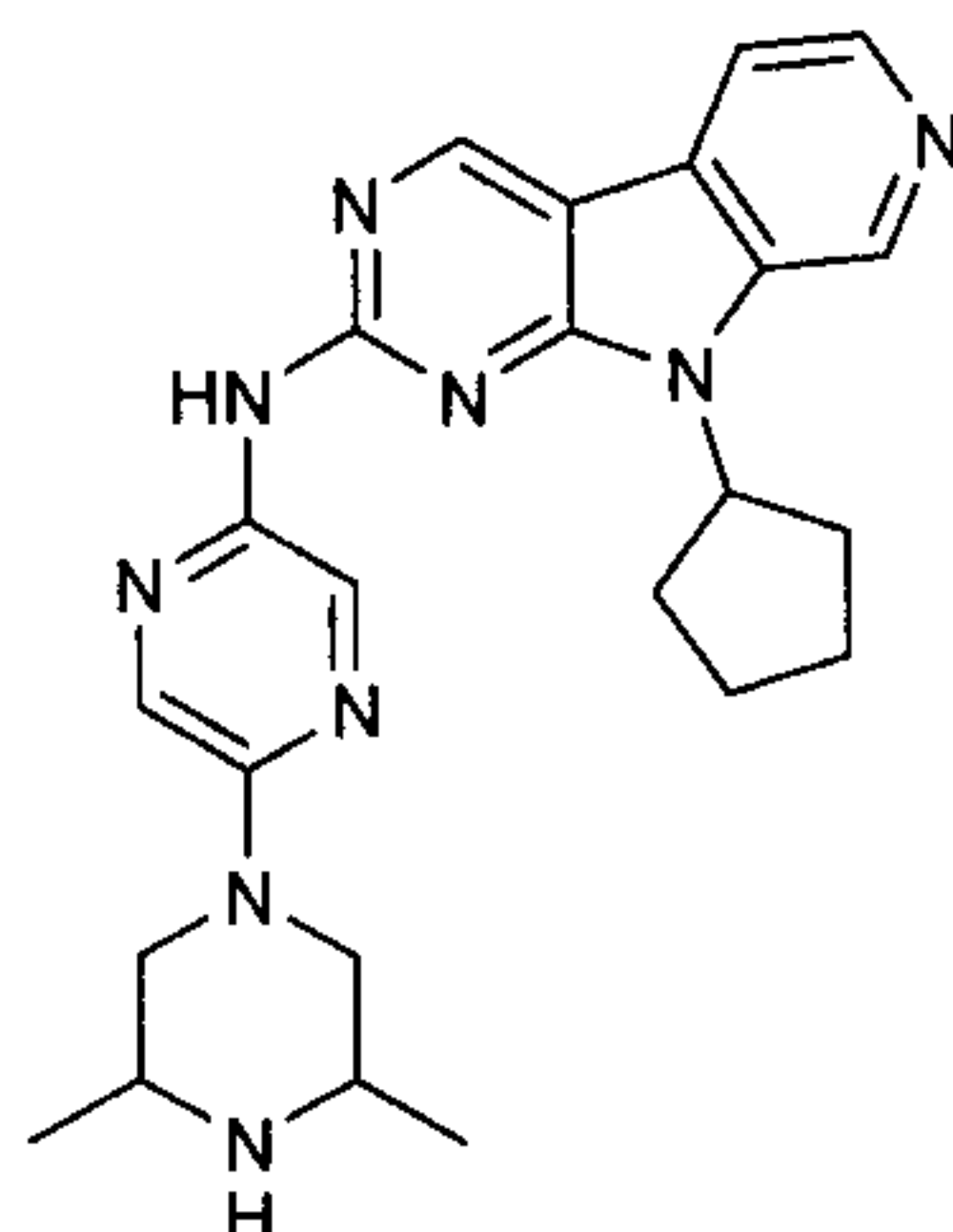


103. The compound of claim 1, wherein the compound is



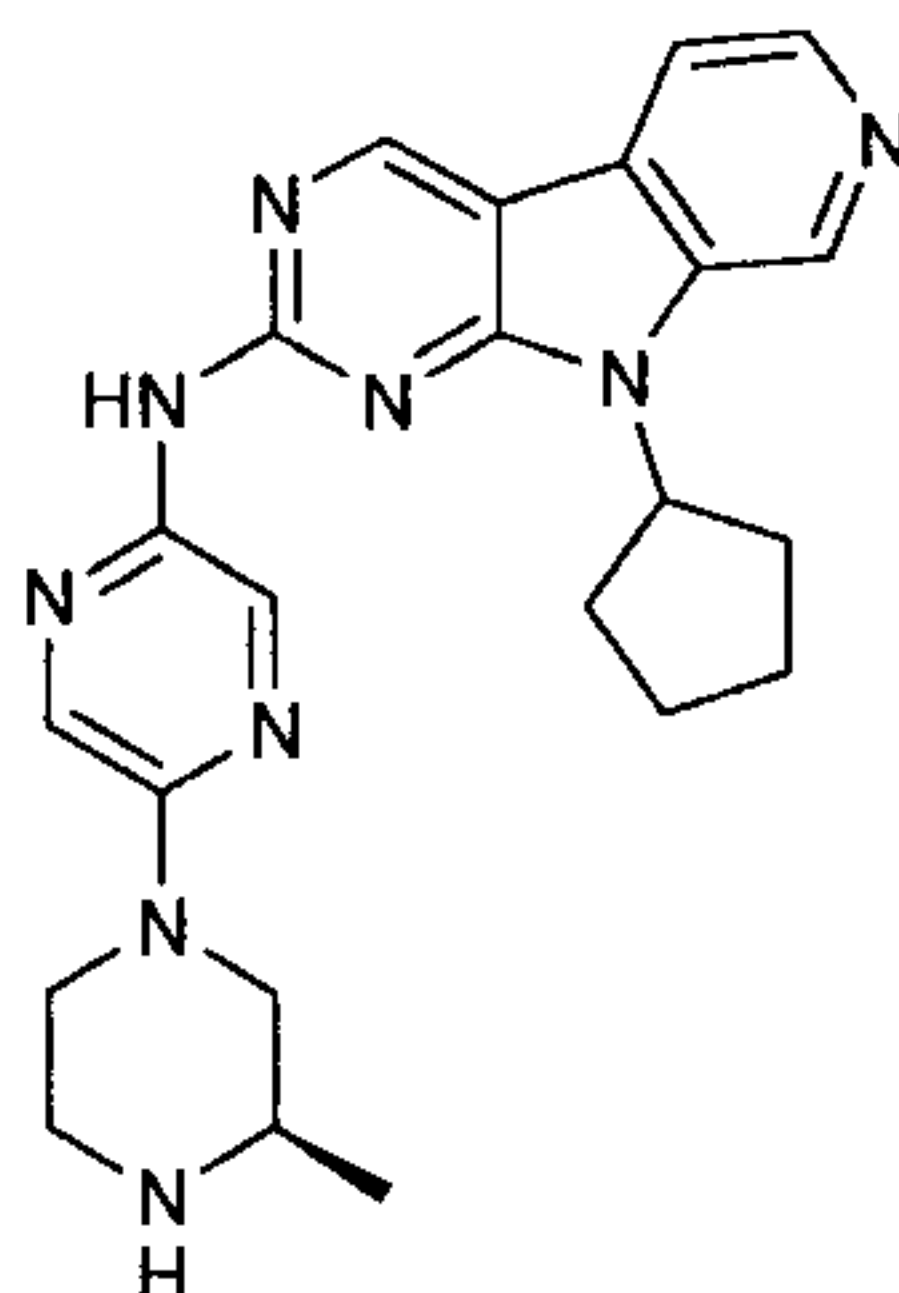
or a pharmaceutically acceptable salt thereof.

104. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

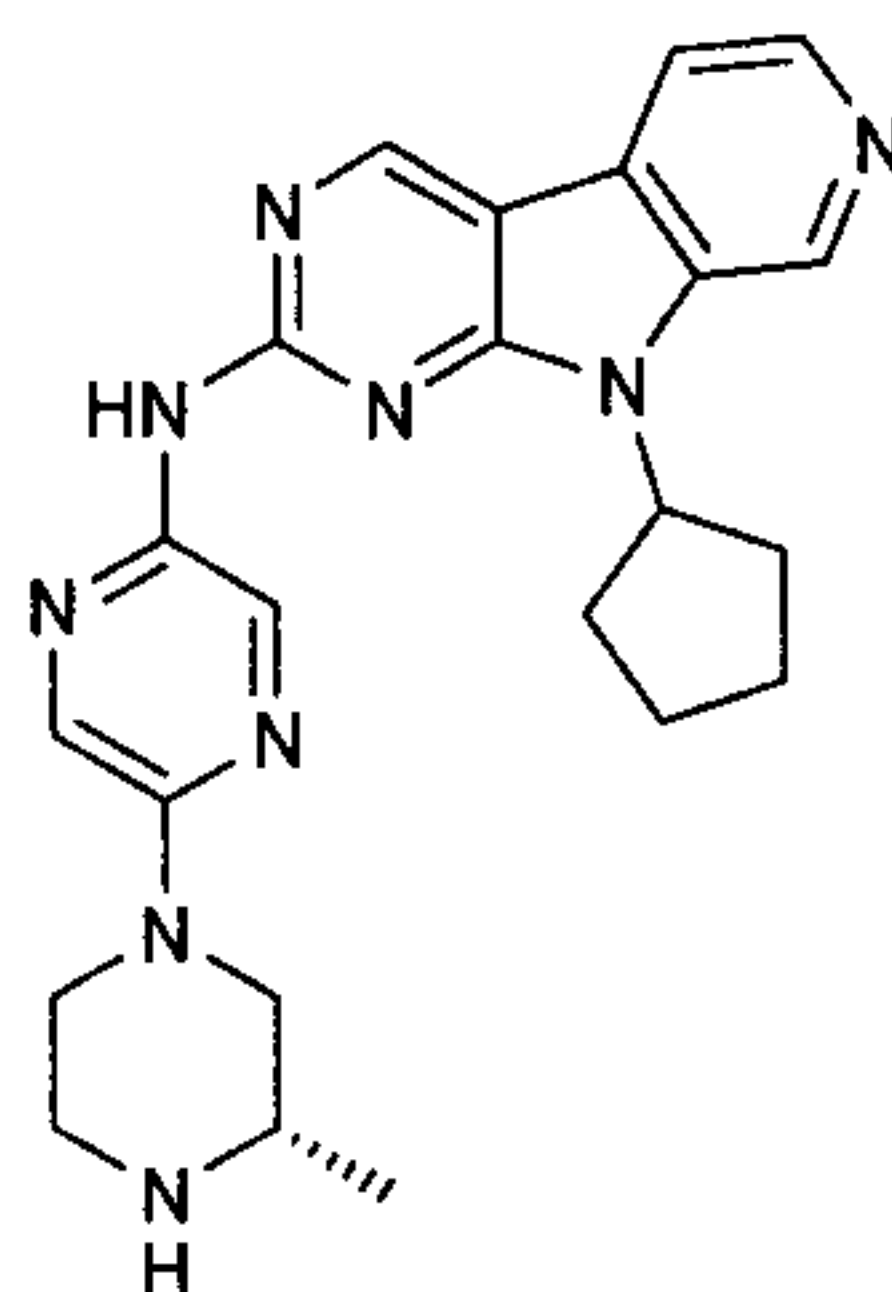
105. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

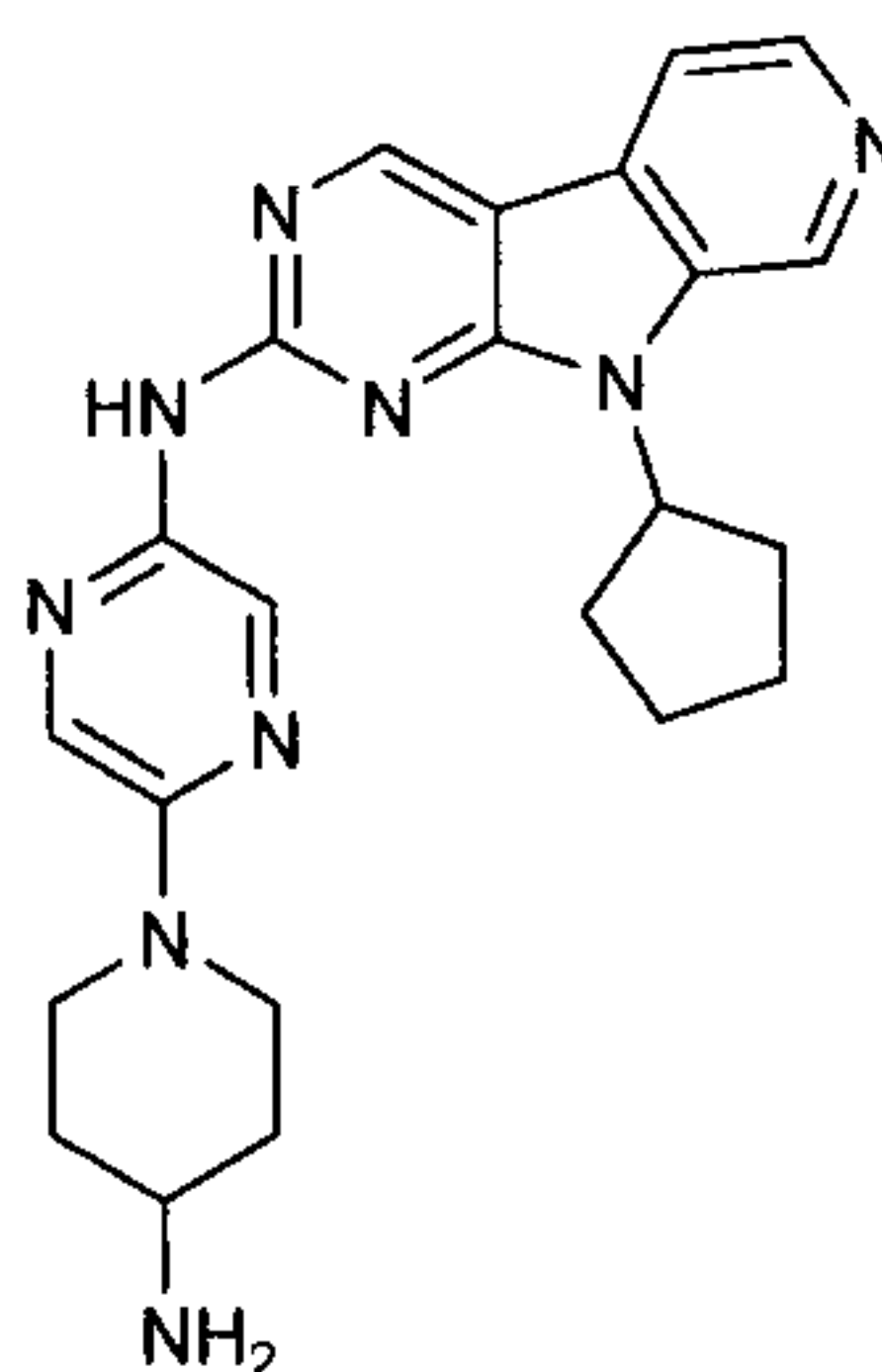


106. The compound of claim 1, wherein the compound is



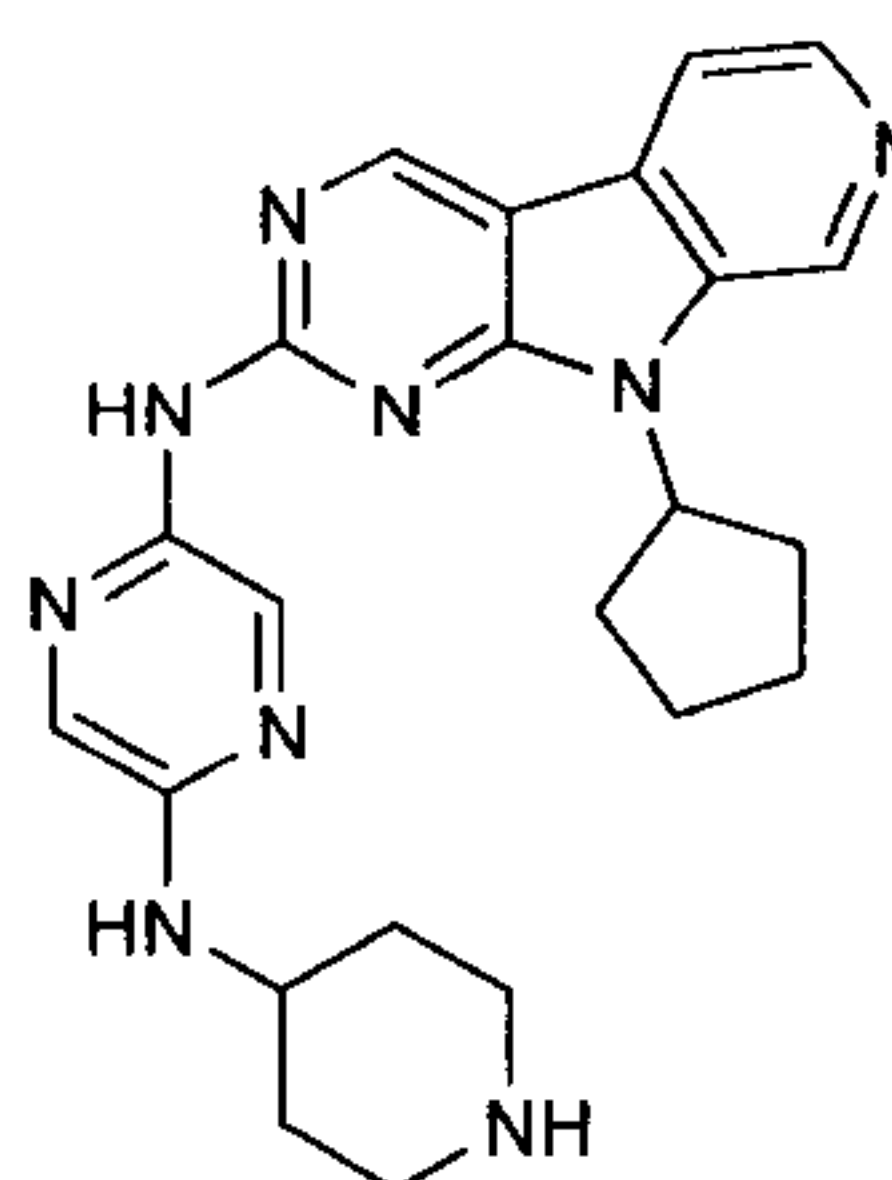
or a pharmaceutically acceptable salt thereof.

107. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

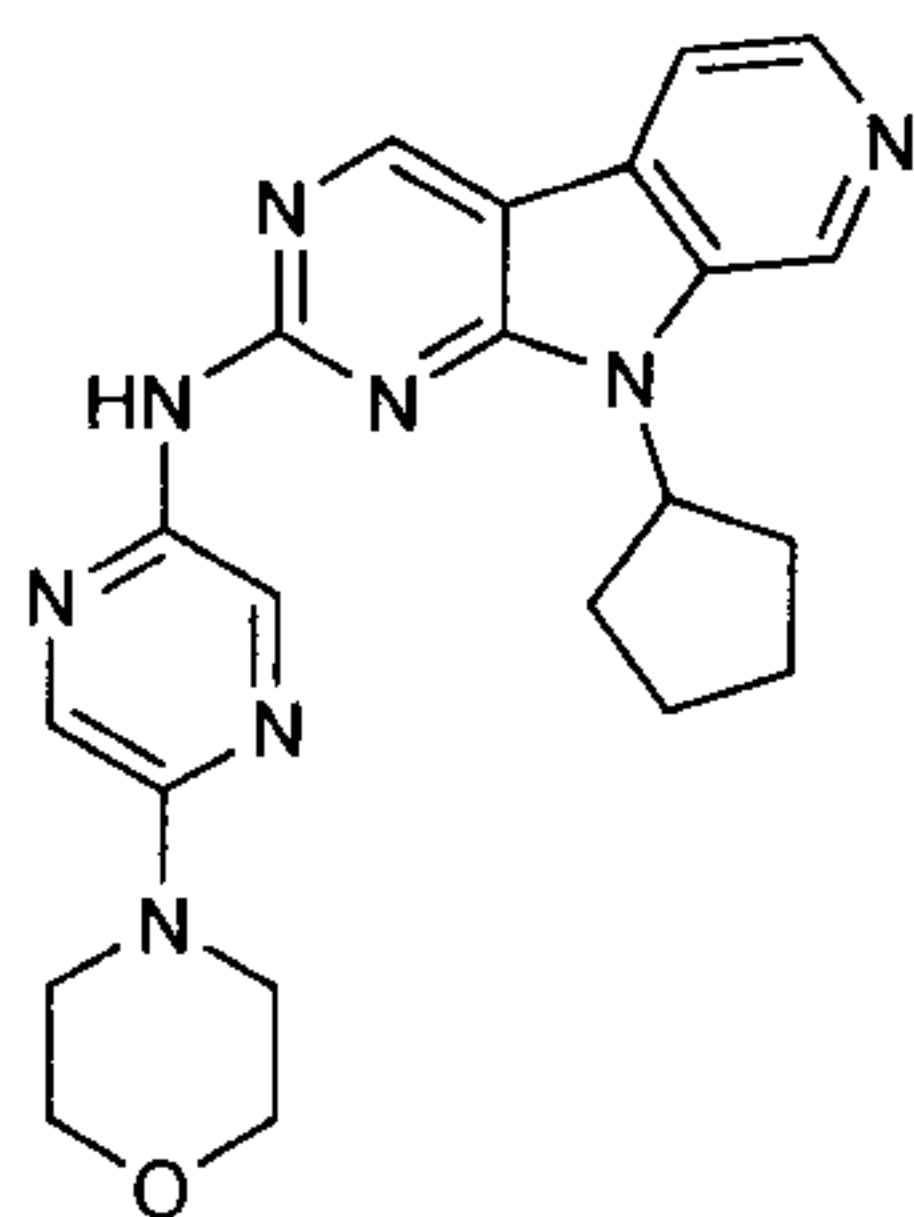
108. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

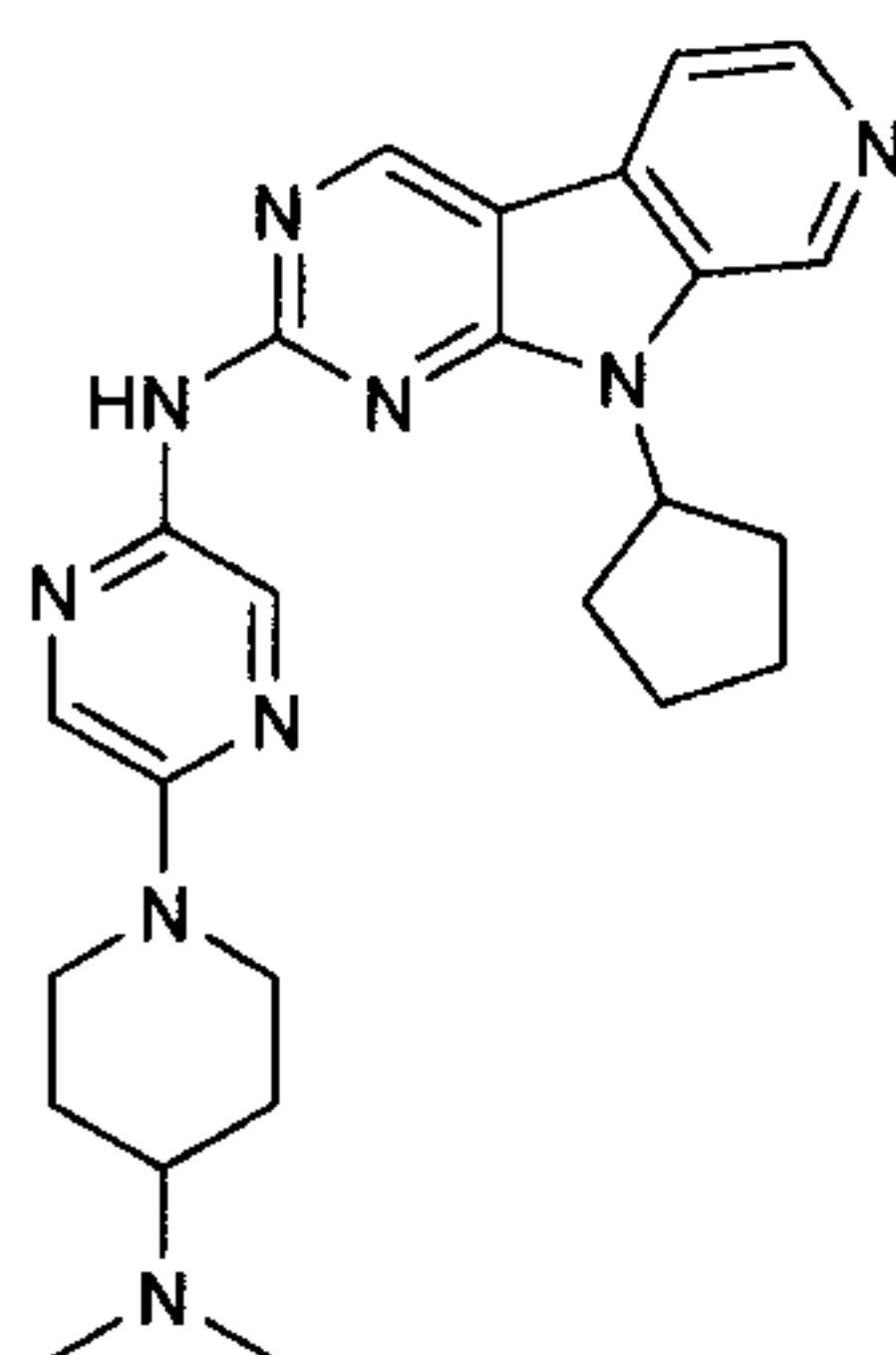


109. The compound of claim 1, wherein the compound is



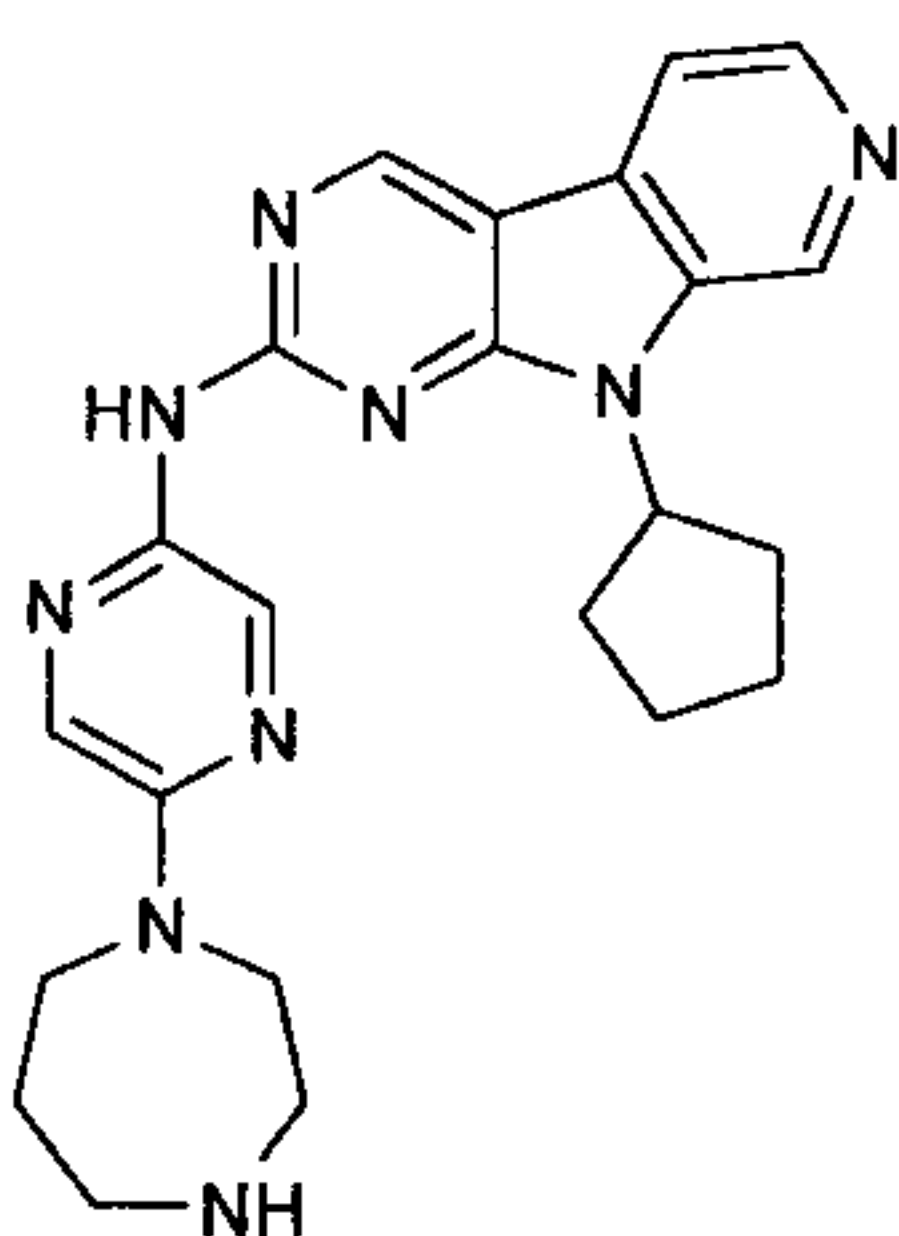
or a pharmaceutically acceptable salt thereof.

110. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

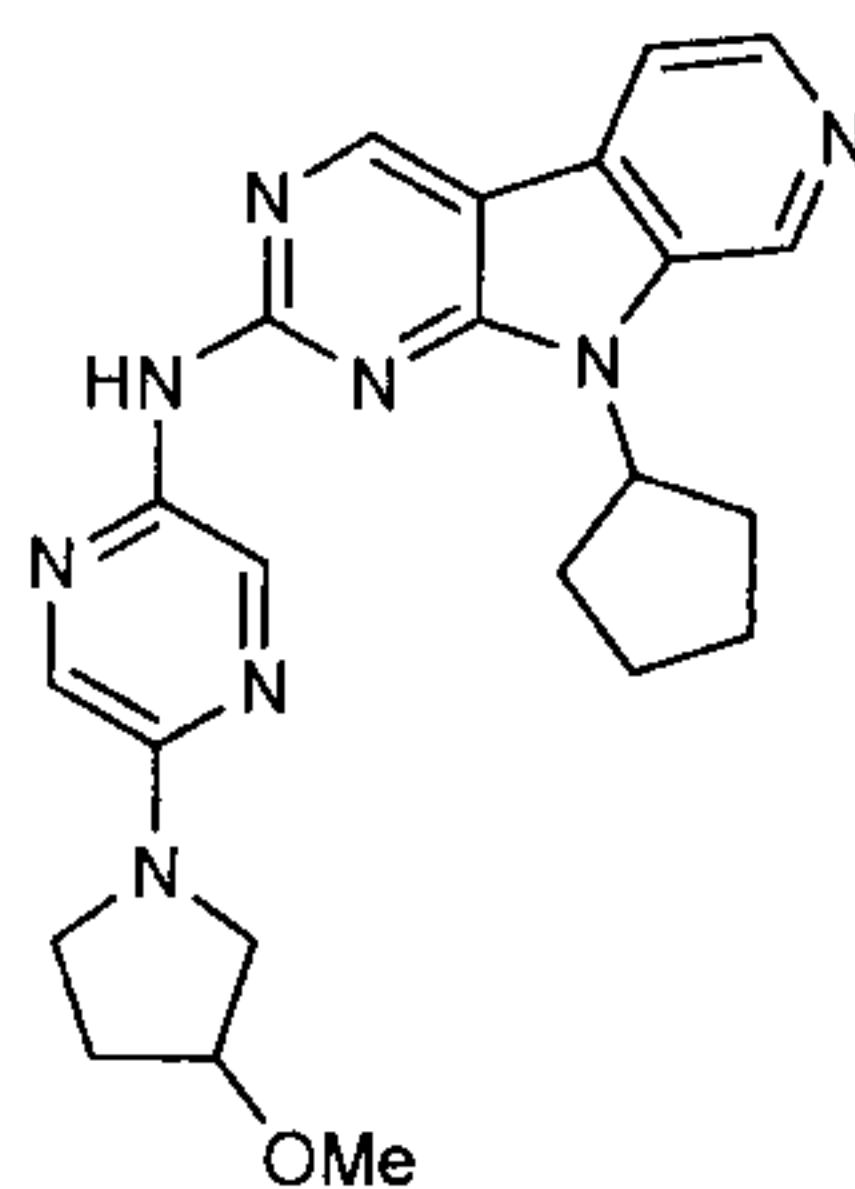
111. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

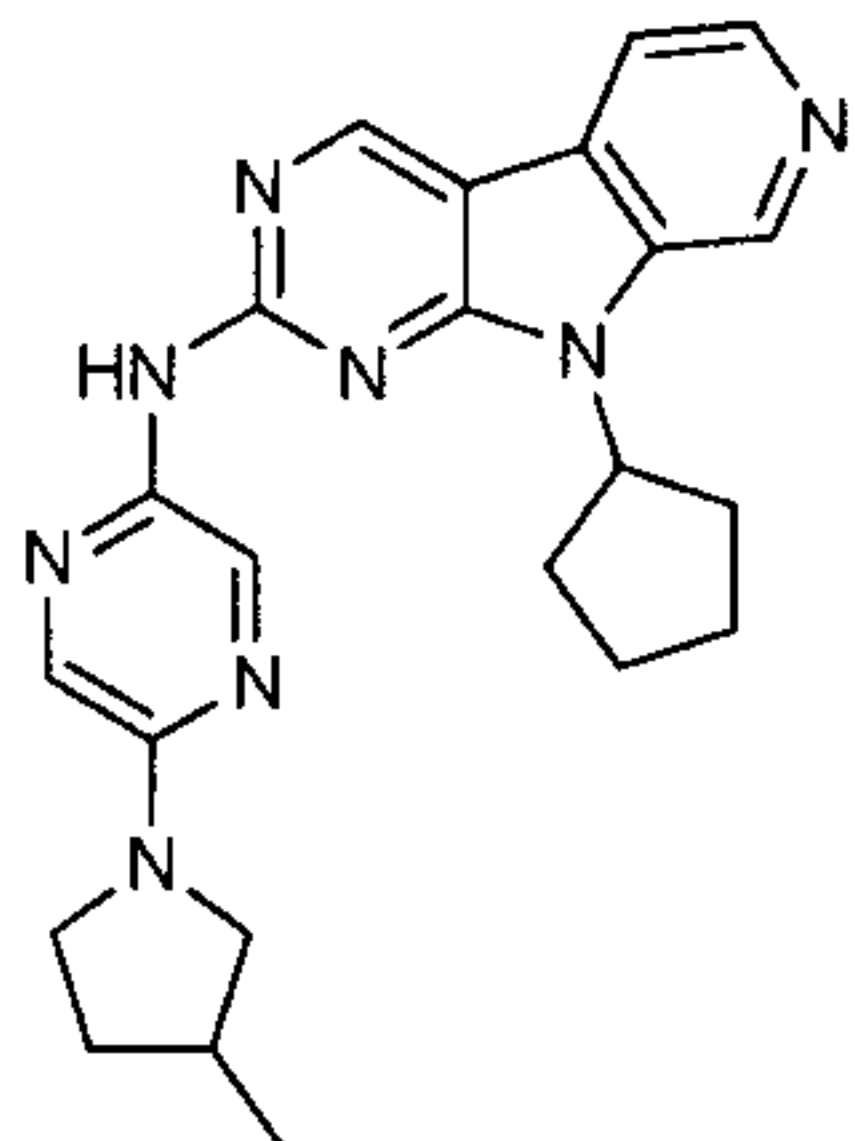


112. The compound of claim 1, wherein the compound is



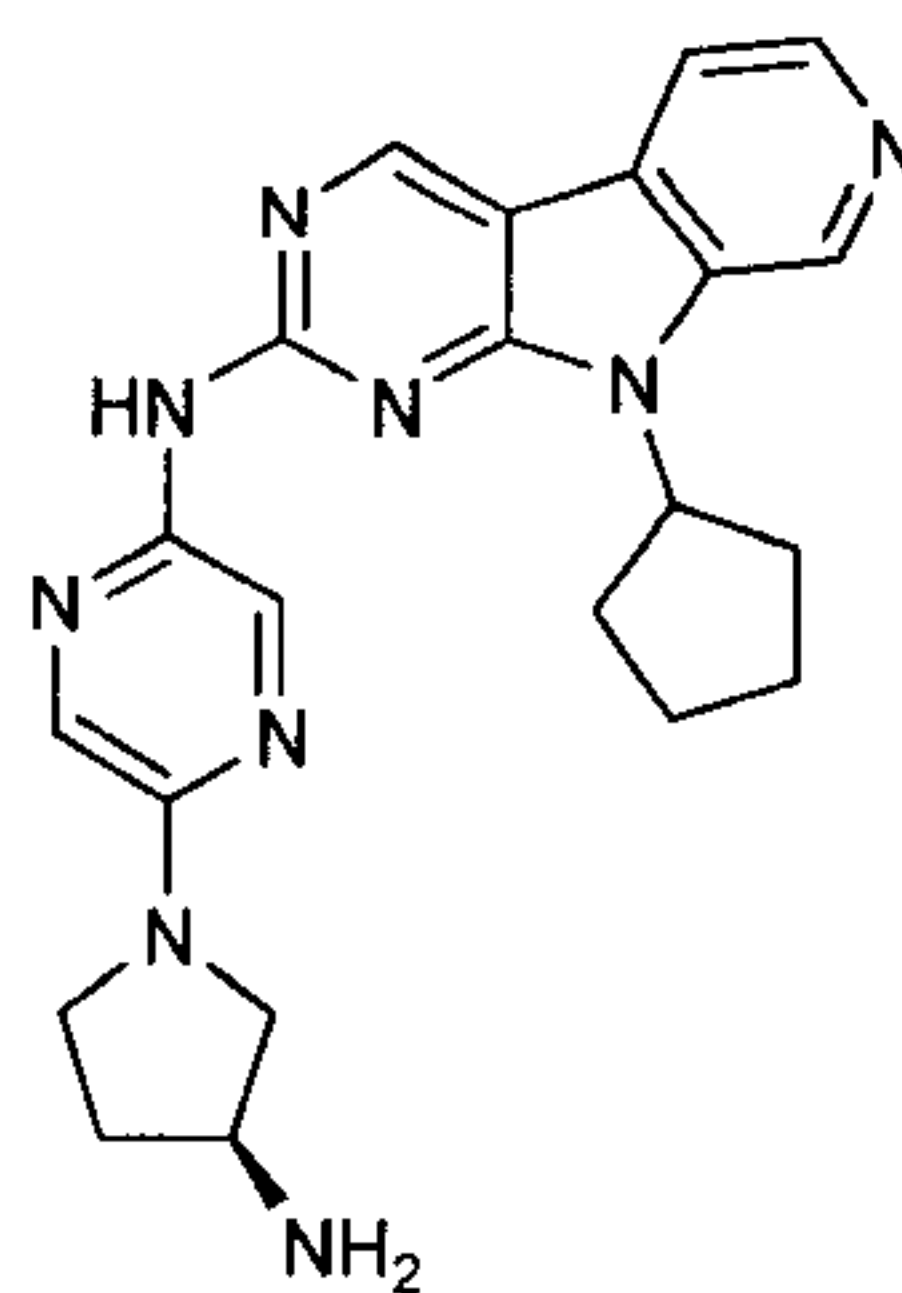
or a pharmaceutically acceptable salt thereof.

113. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

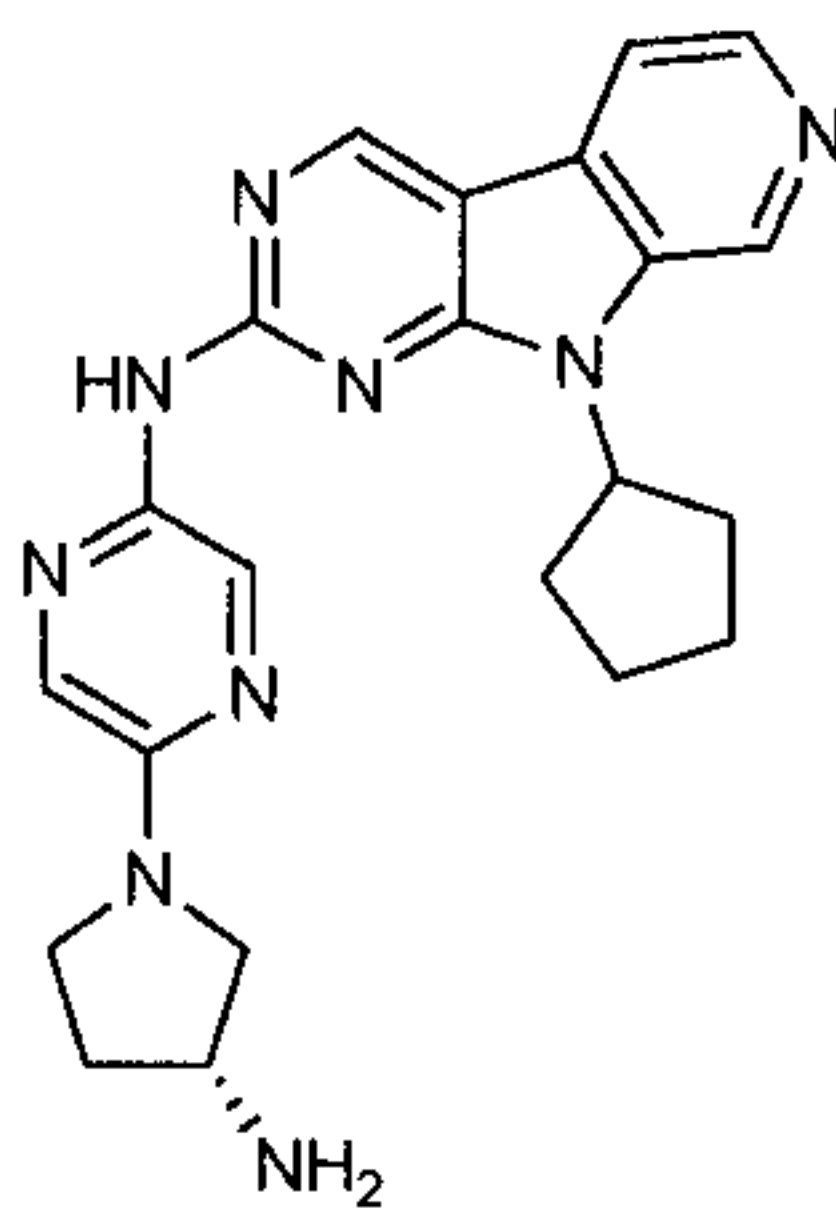
114. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

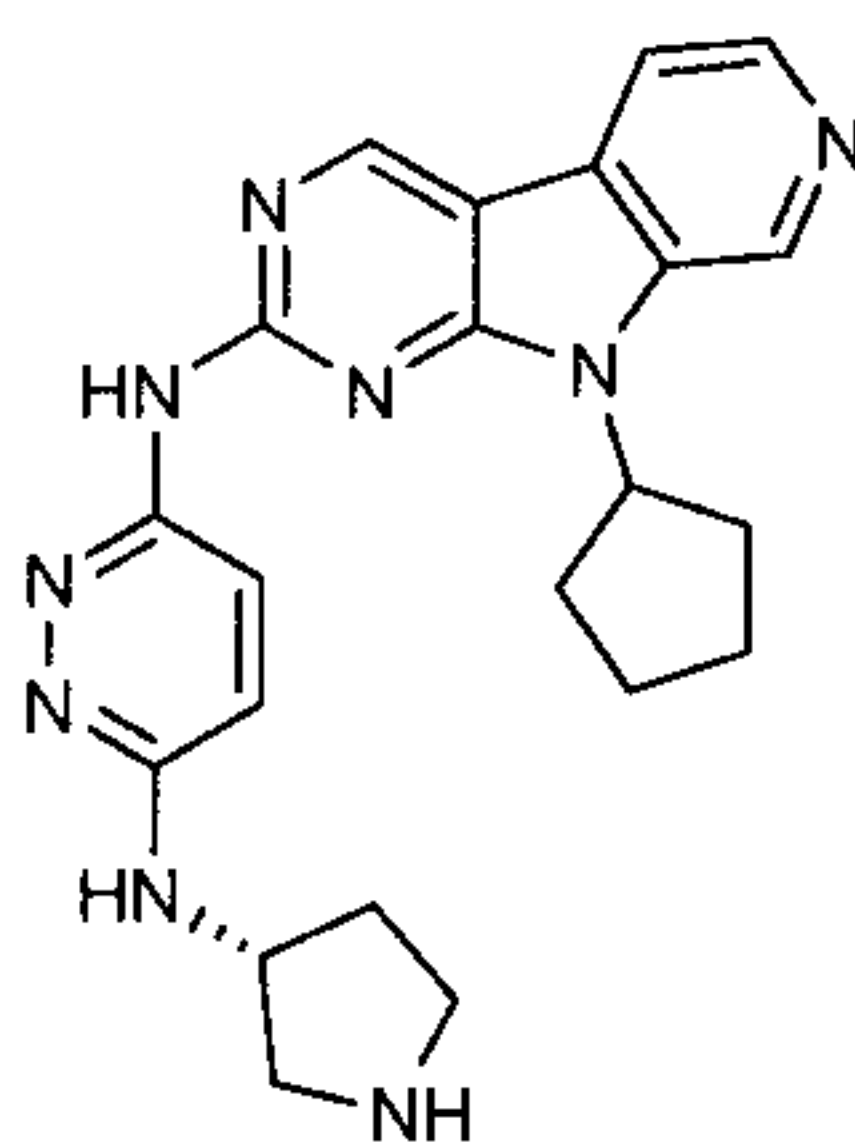


115. The compound of claim 1, wherein the compound is



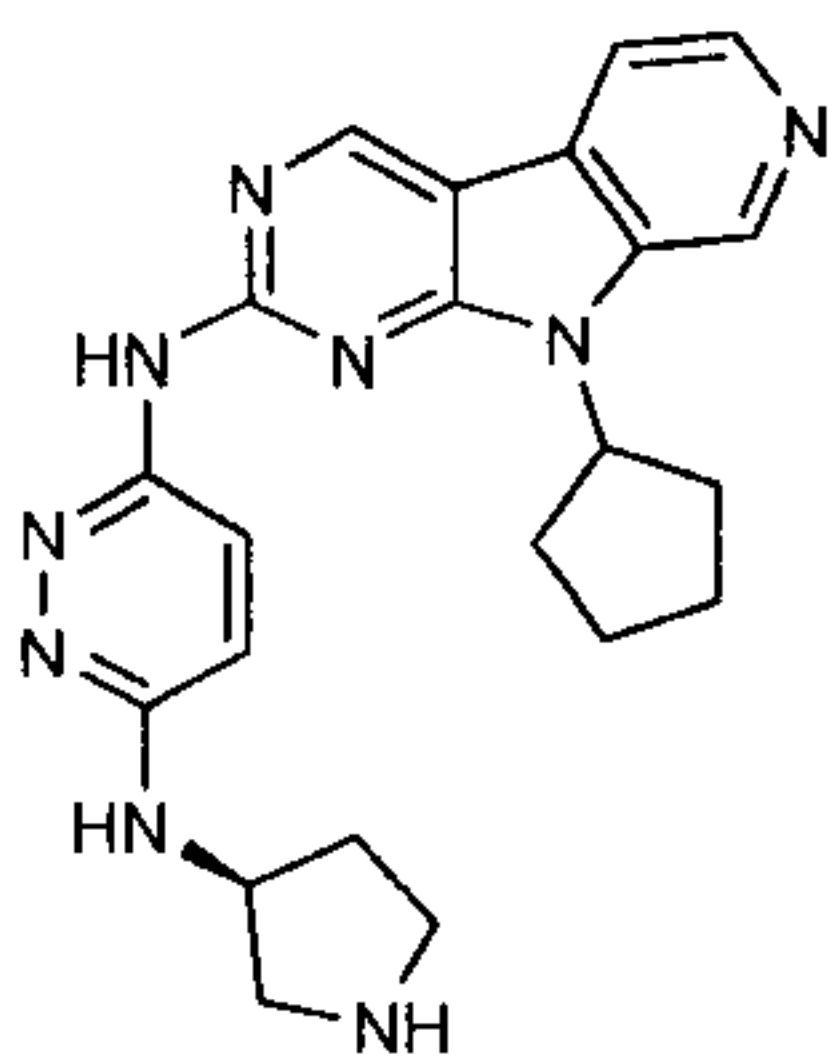
or a pharmaceutically acceptable salt thereof.

116. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

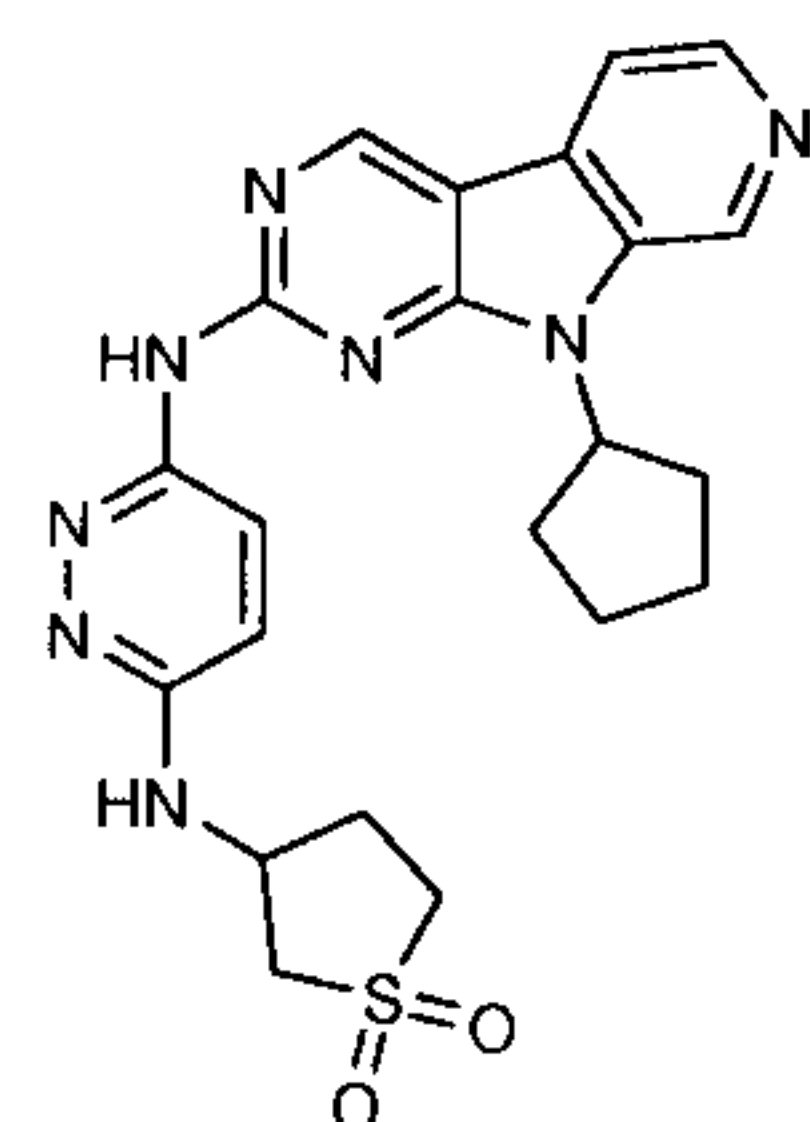
117. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

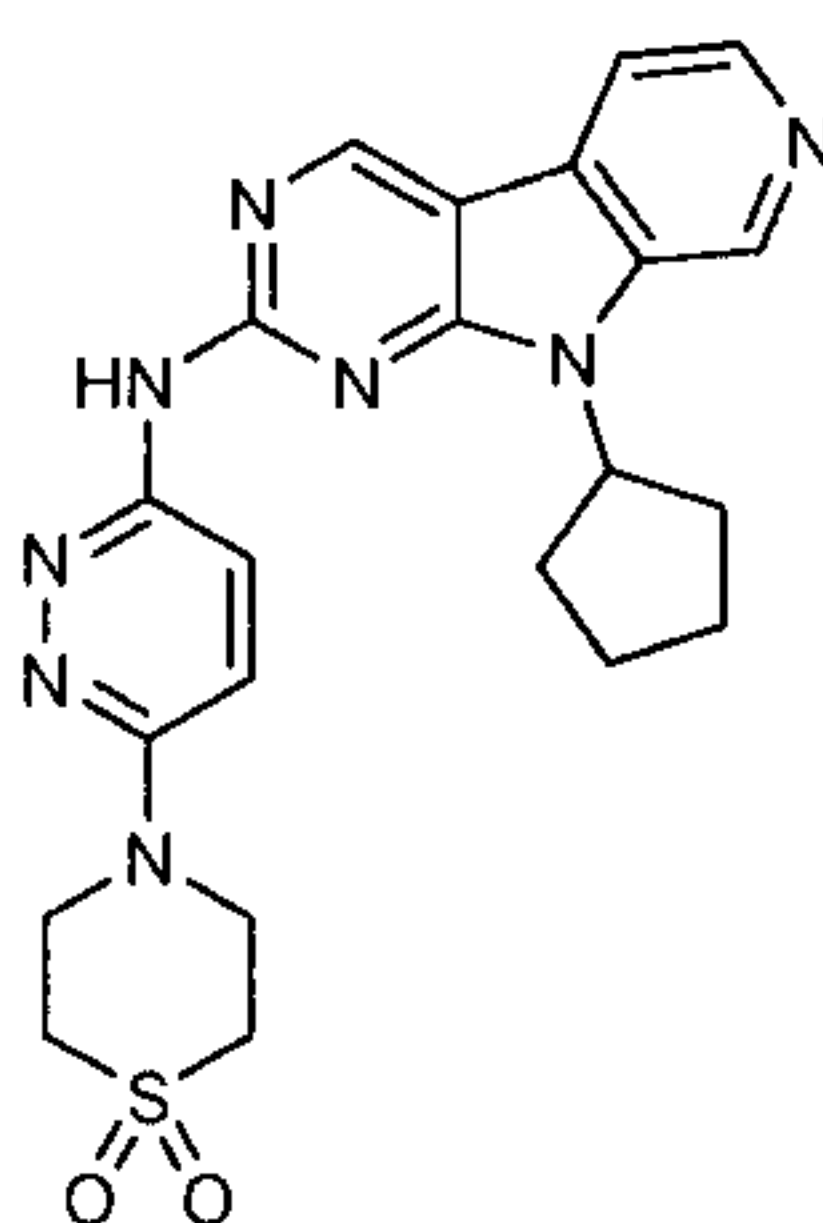


118. The compound of claim 1, wherein the compound is



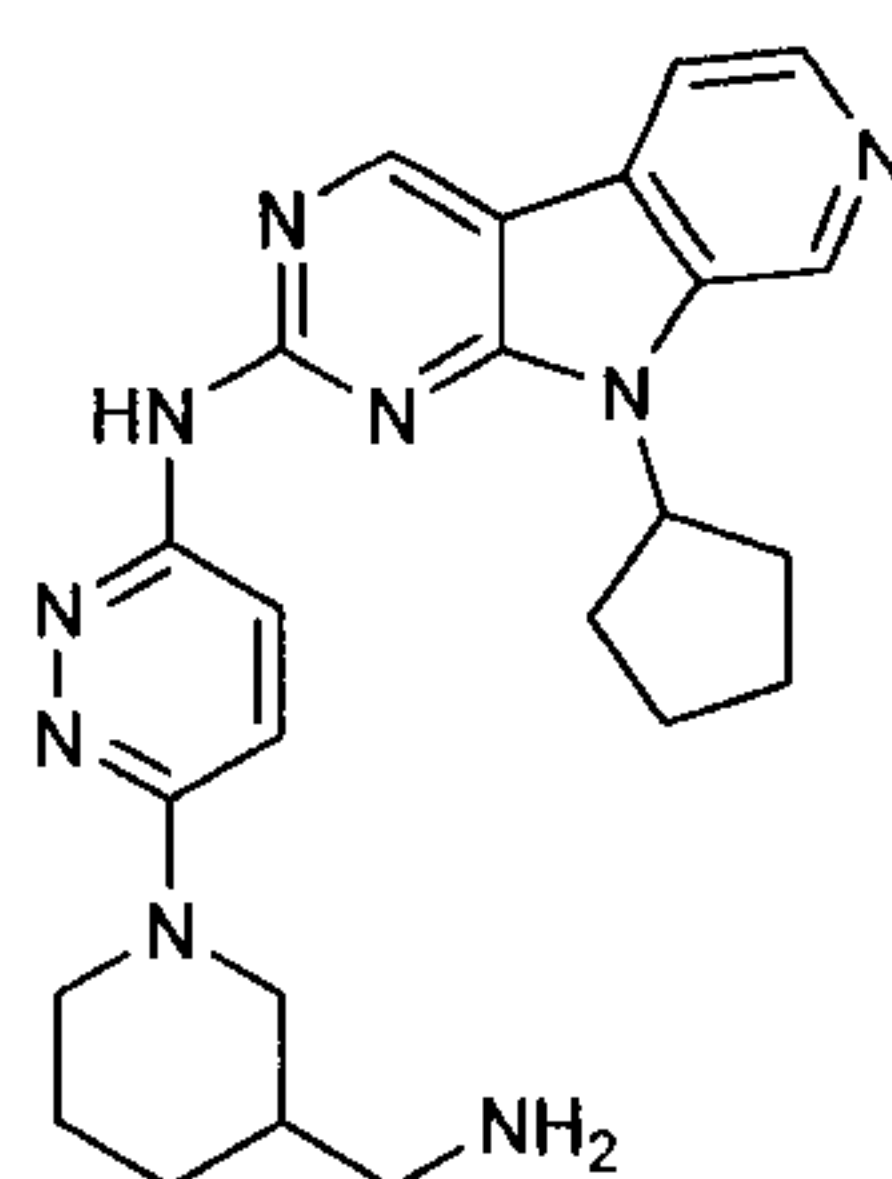
or a pharmaceutically acceptable salt thereof.

119. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

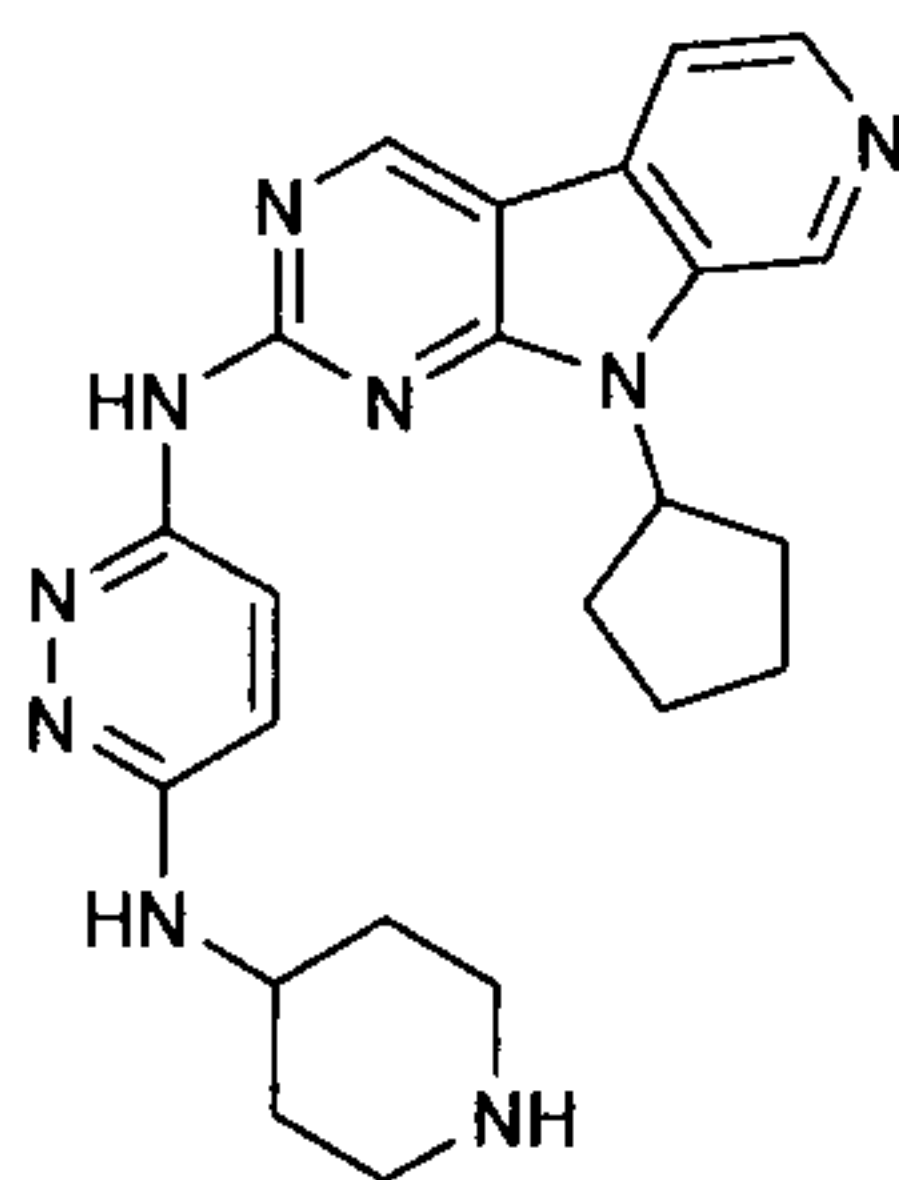
120. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

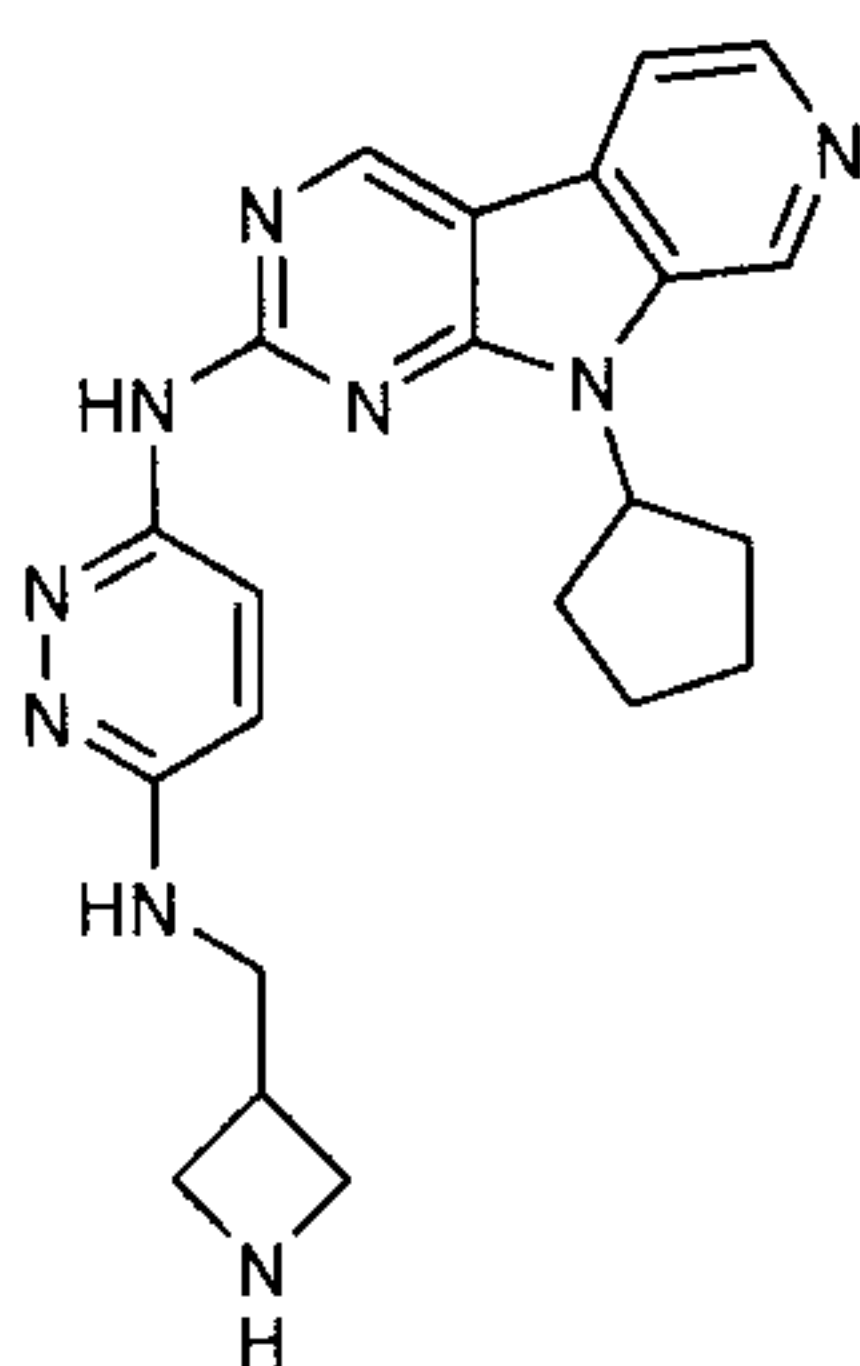


121. The compound of claim 1, wherein the compound is



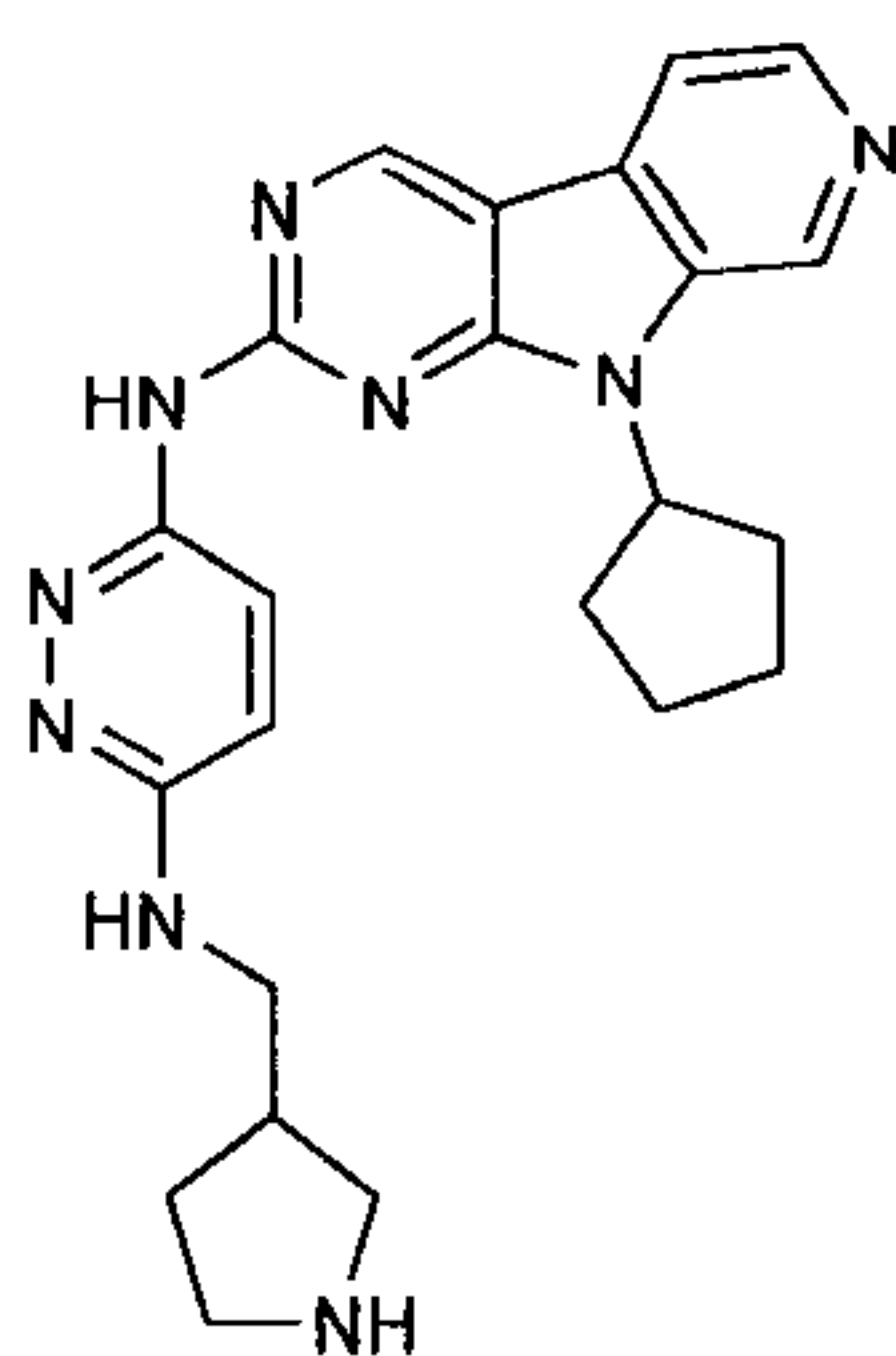
or a pharmaceutically acceptable salt thereof.

122. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

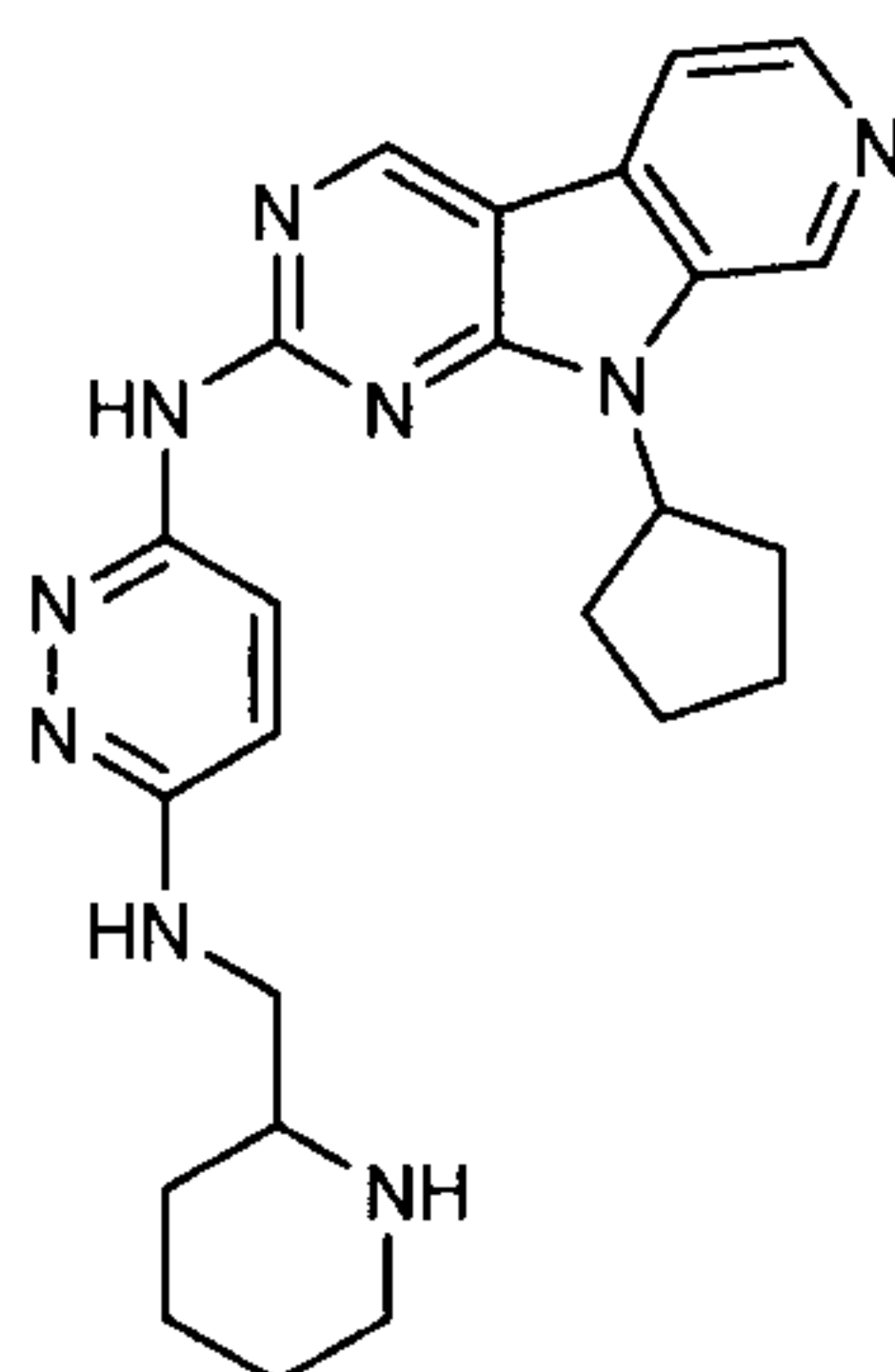
123. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

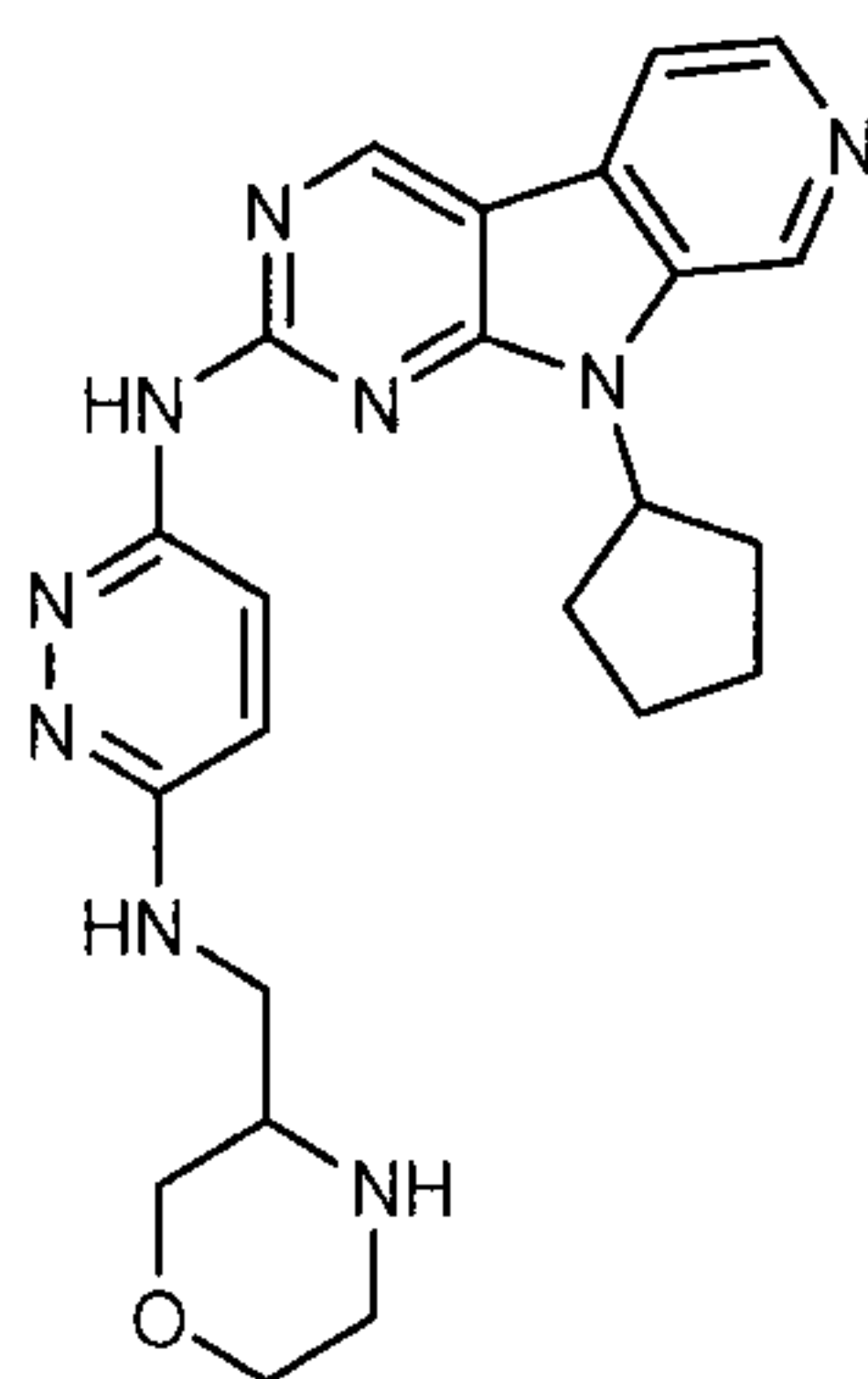


124. The compound of claim 1, wherein the compound is



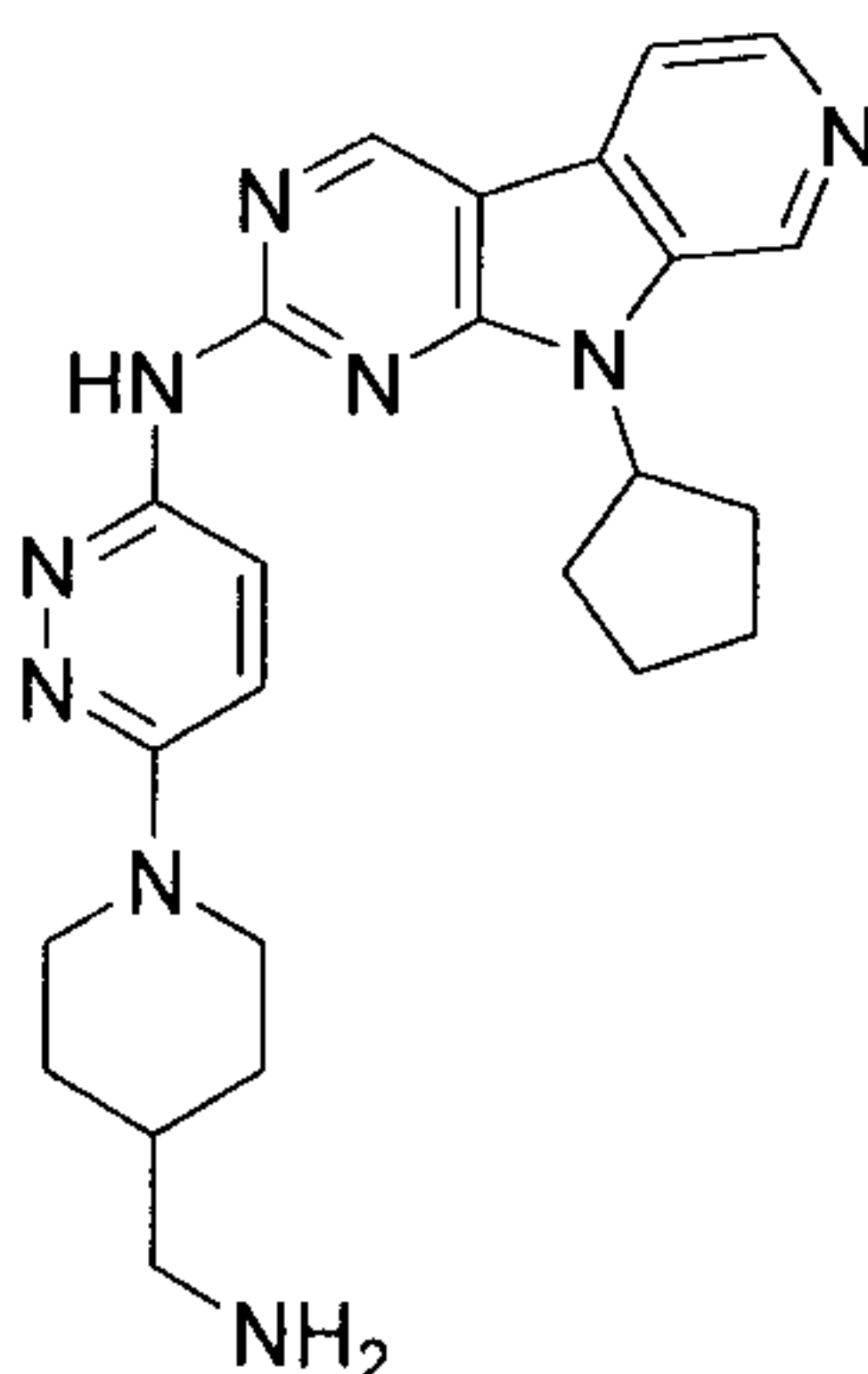
or a pharmaceutically acceptable salt thereof.

125. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

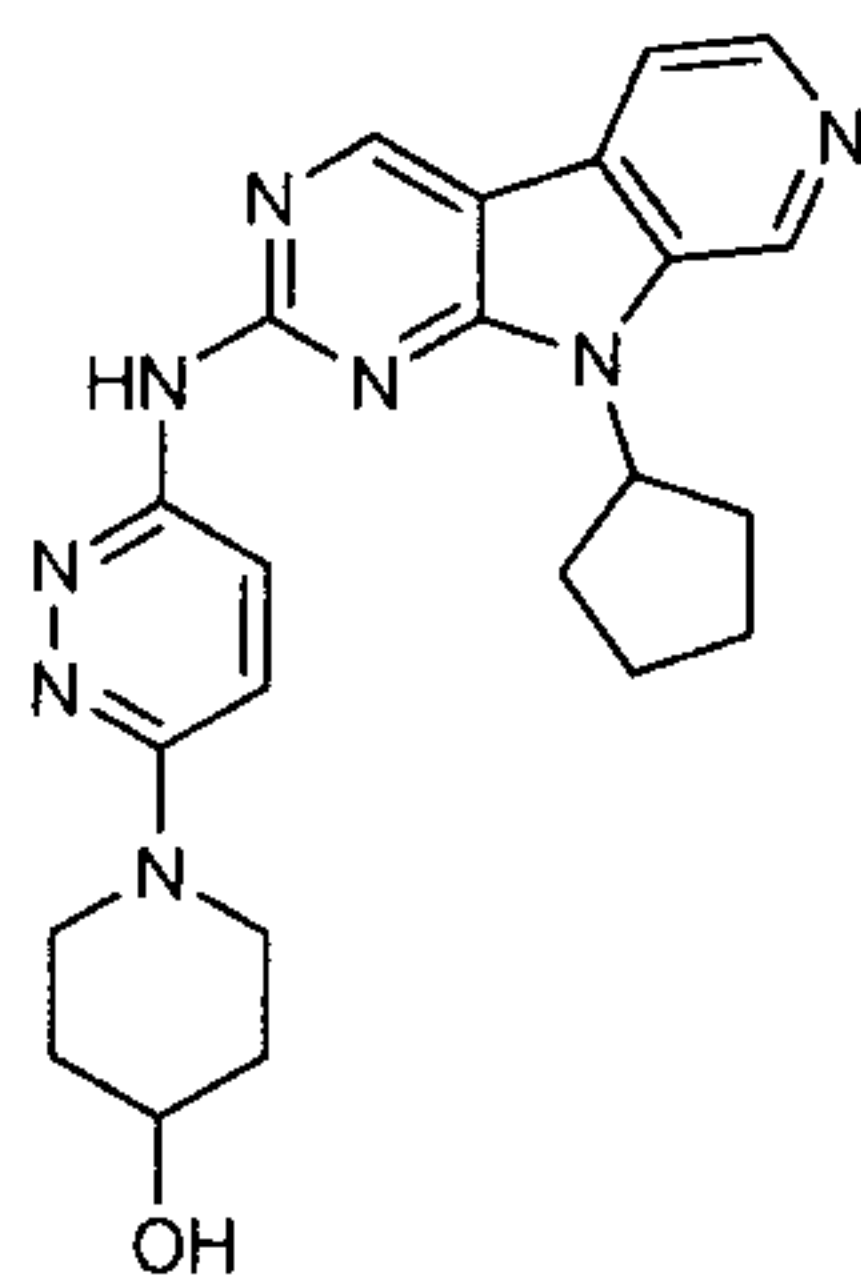
126. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

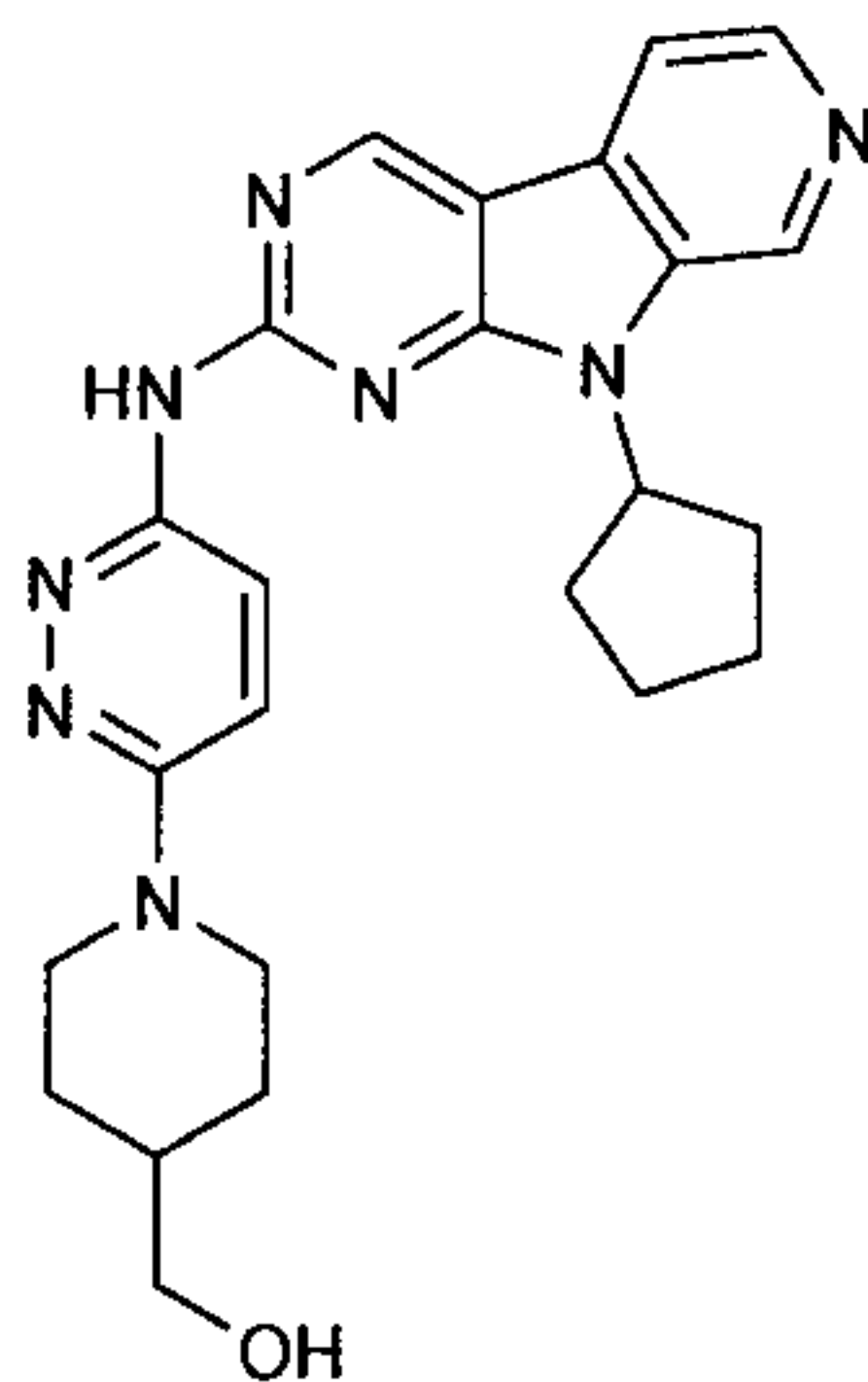


127. The compound of claim 1, wherein the compound is



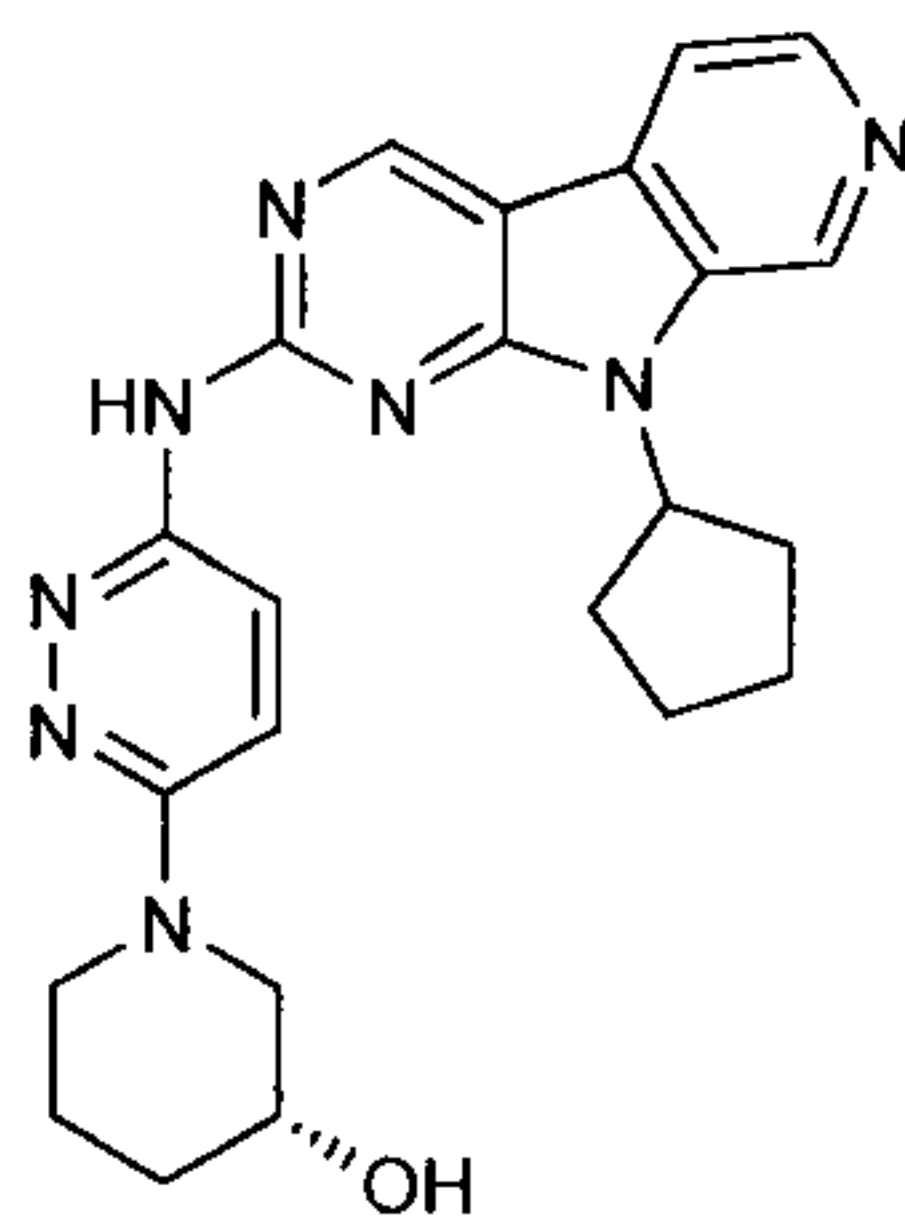
or a pharmaceutically acceptable salt thereof.

128. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

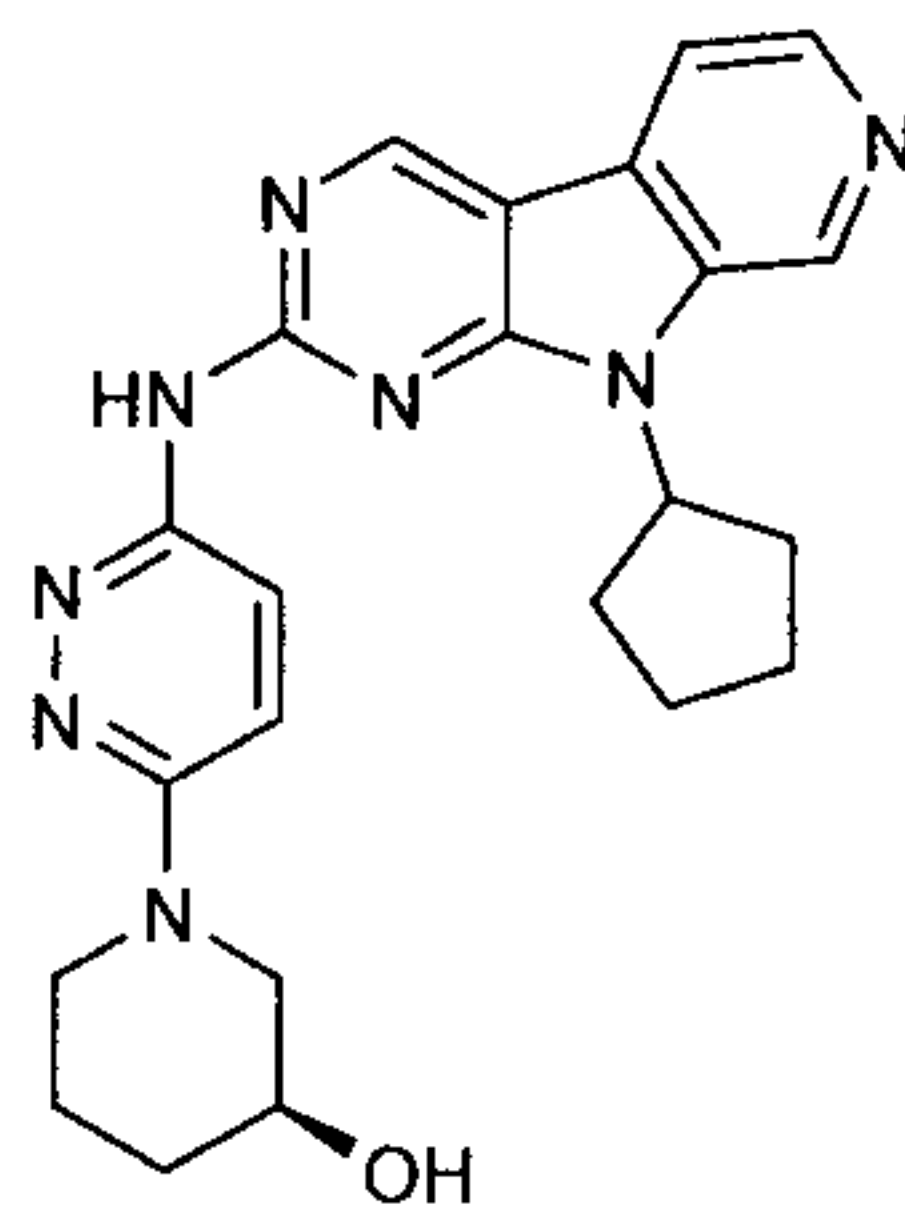
129. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.



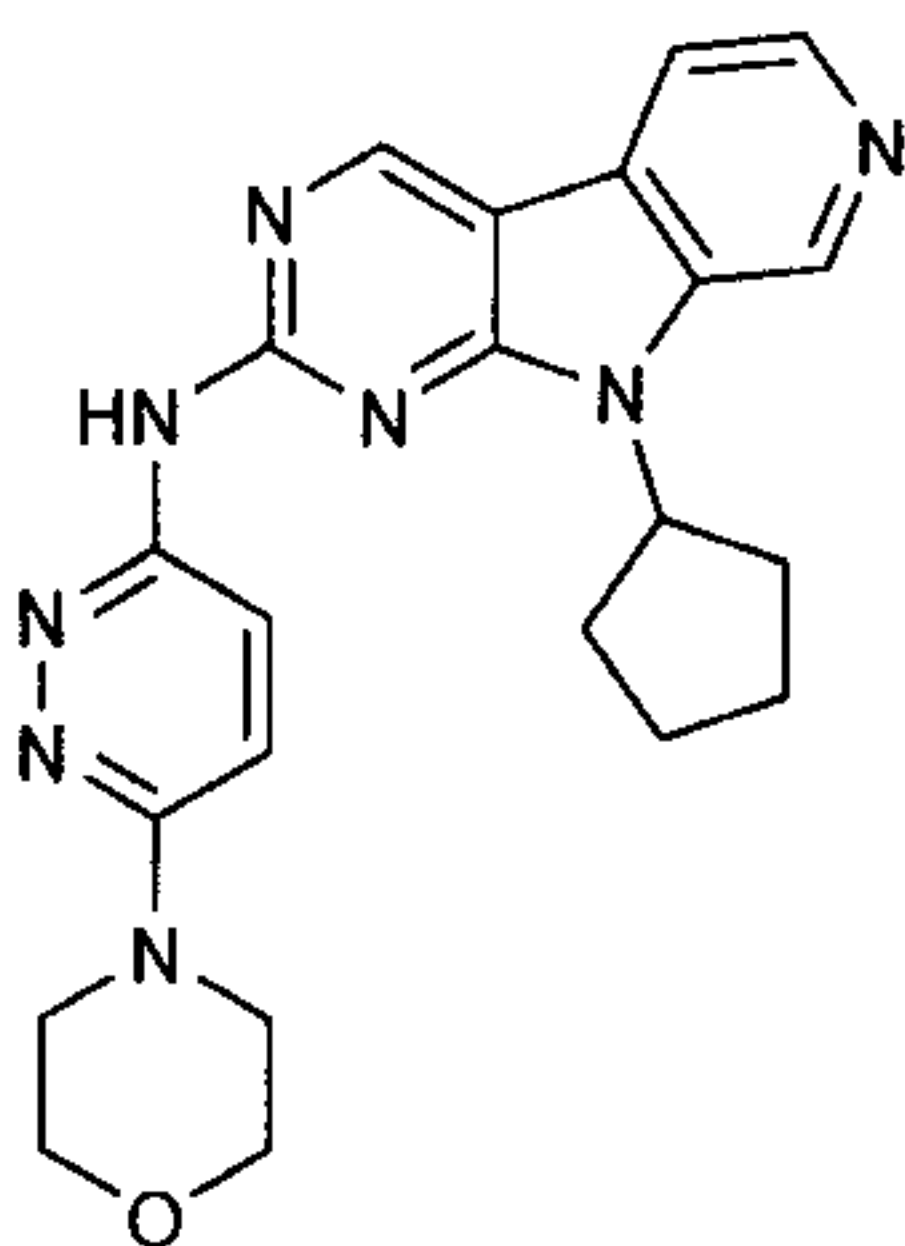
130. The compound of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

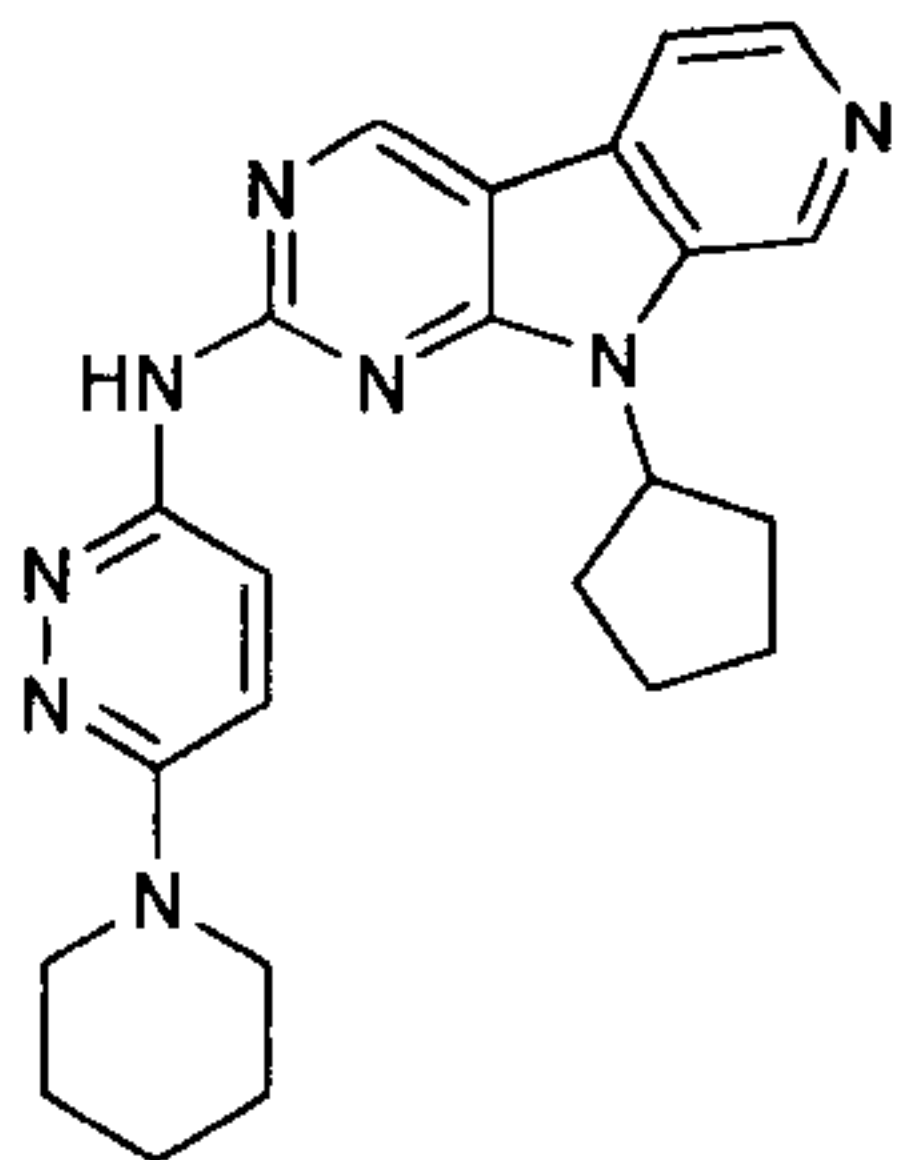
131. The compound of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

132. The compound of claim 1, wherein the compound is

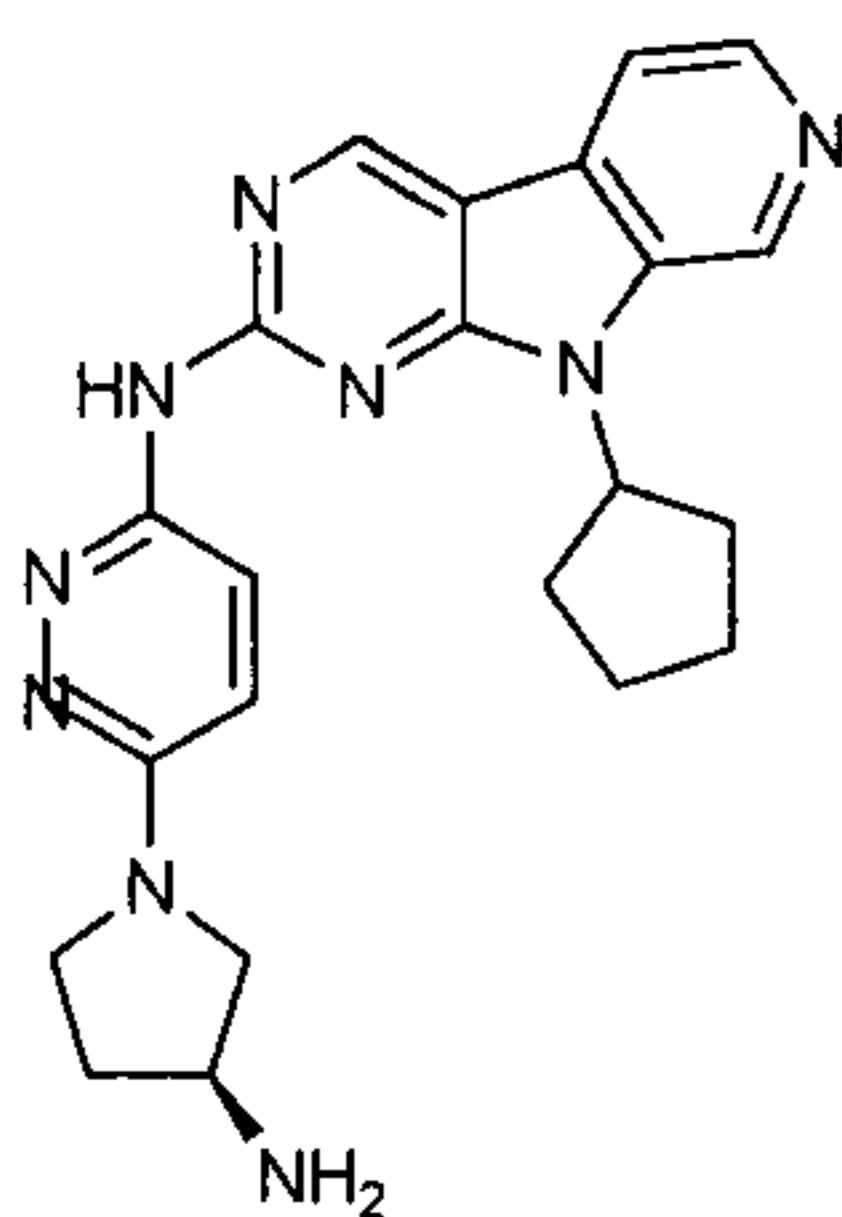


,

or a pharmaceutically acceptable salt thereof.

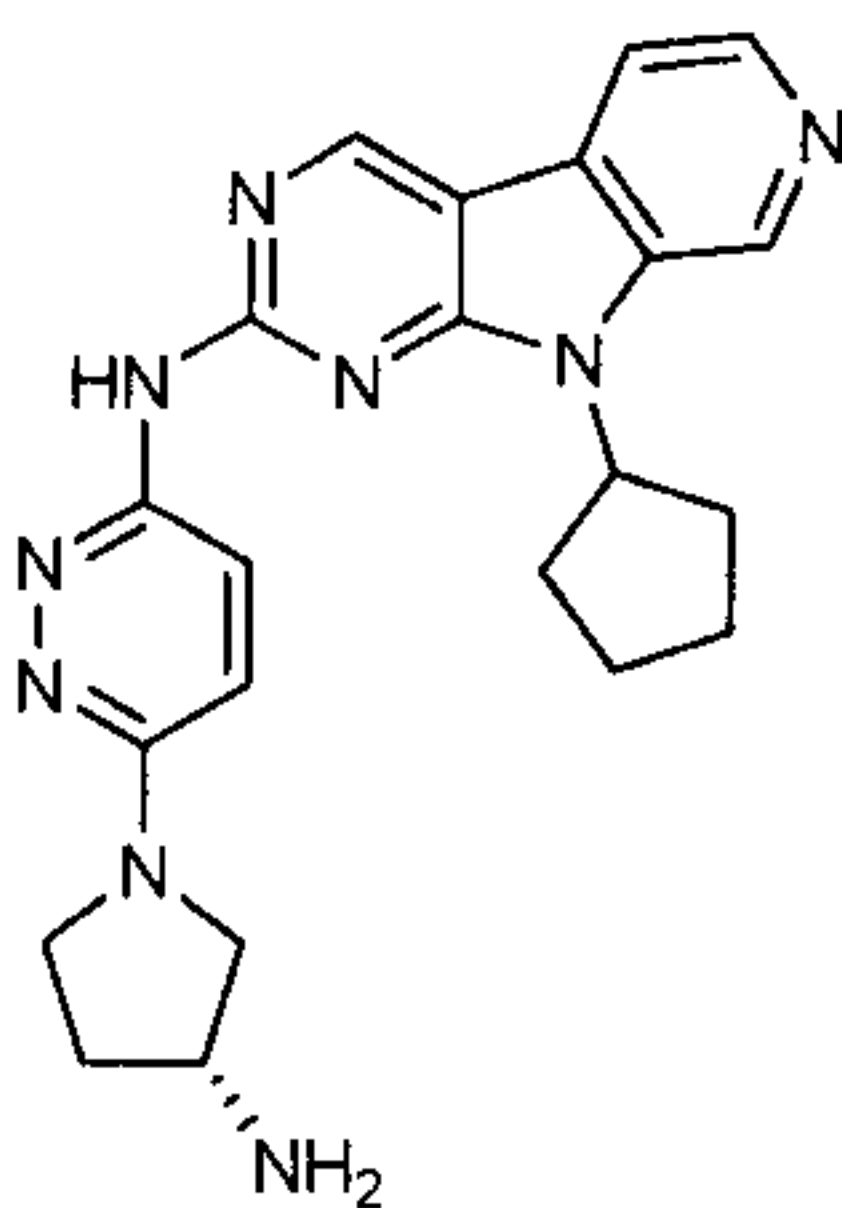


133. The compound of claim 1, wherein the compound is



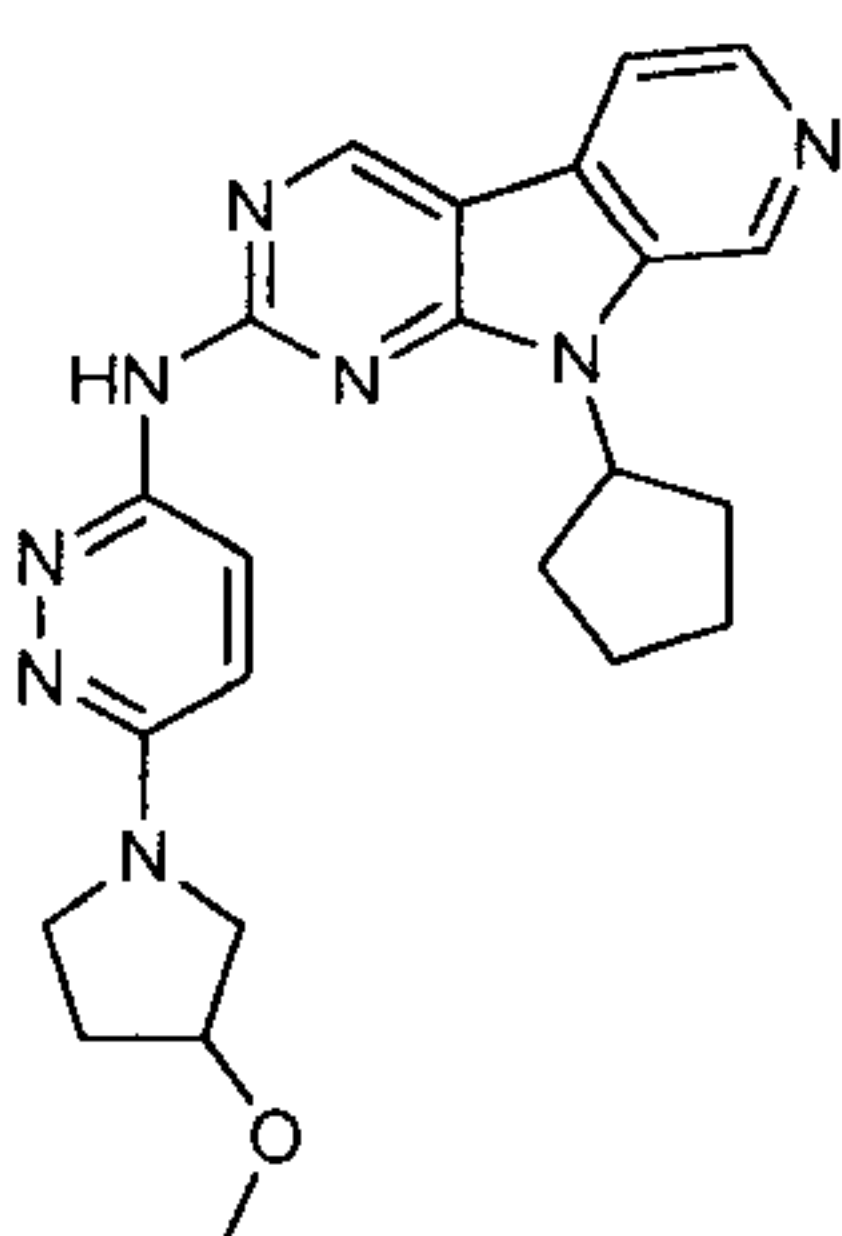
or a pharmaceutically acceptable salt thereof.

134. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

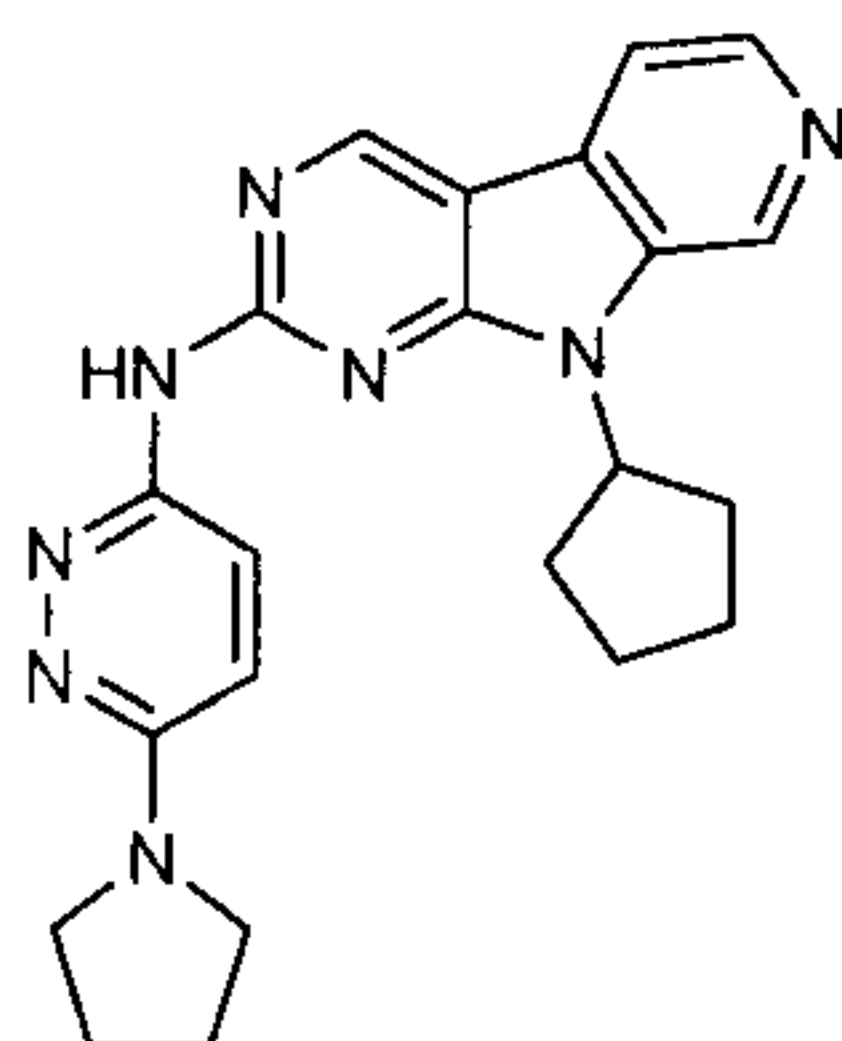
135. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

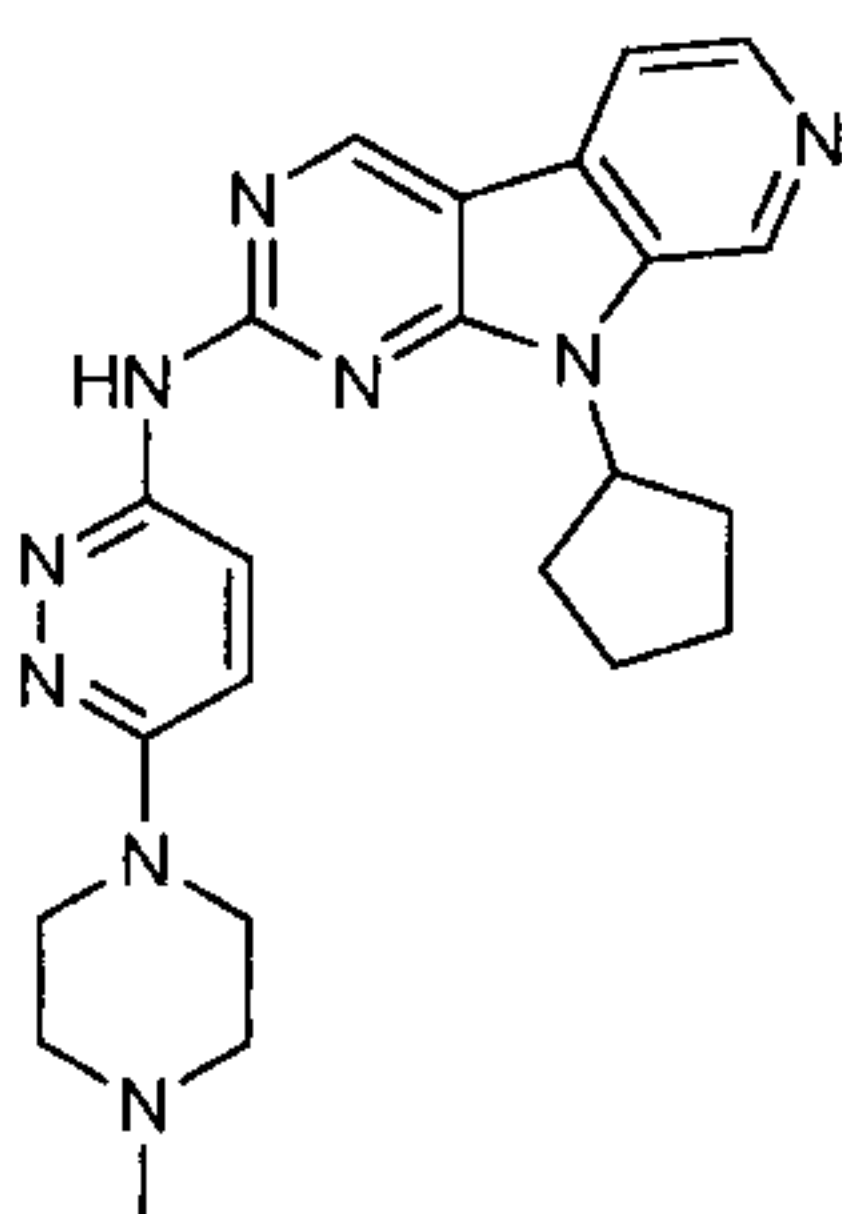


136. The compound of claim 1, wherein the compound is



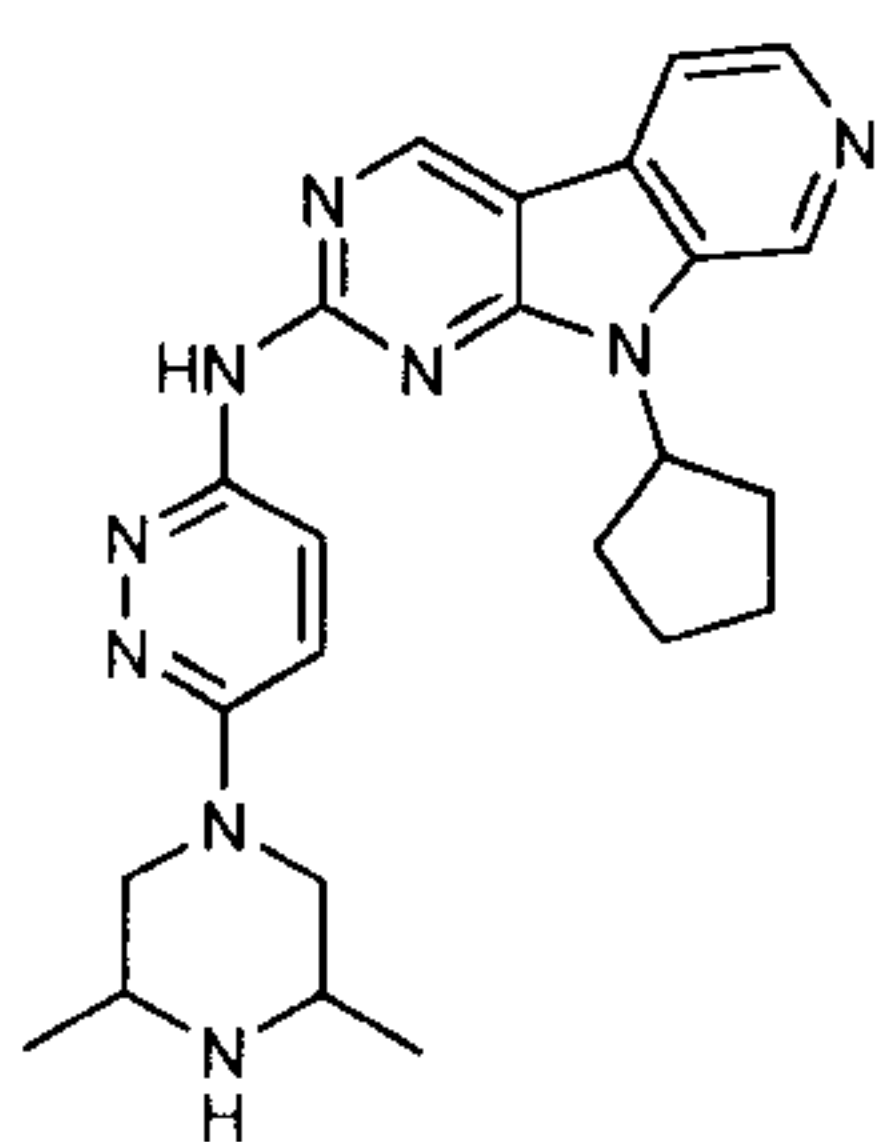
or a pharmaceutically acceptable salt thereof.

137. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

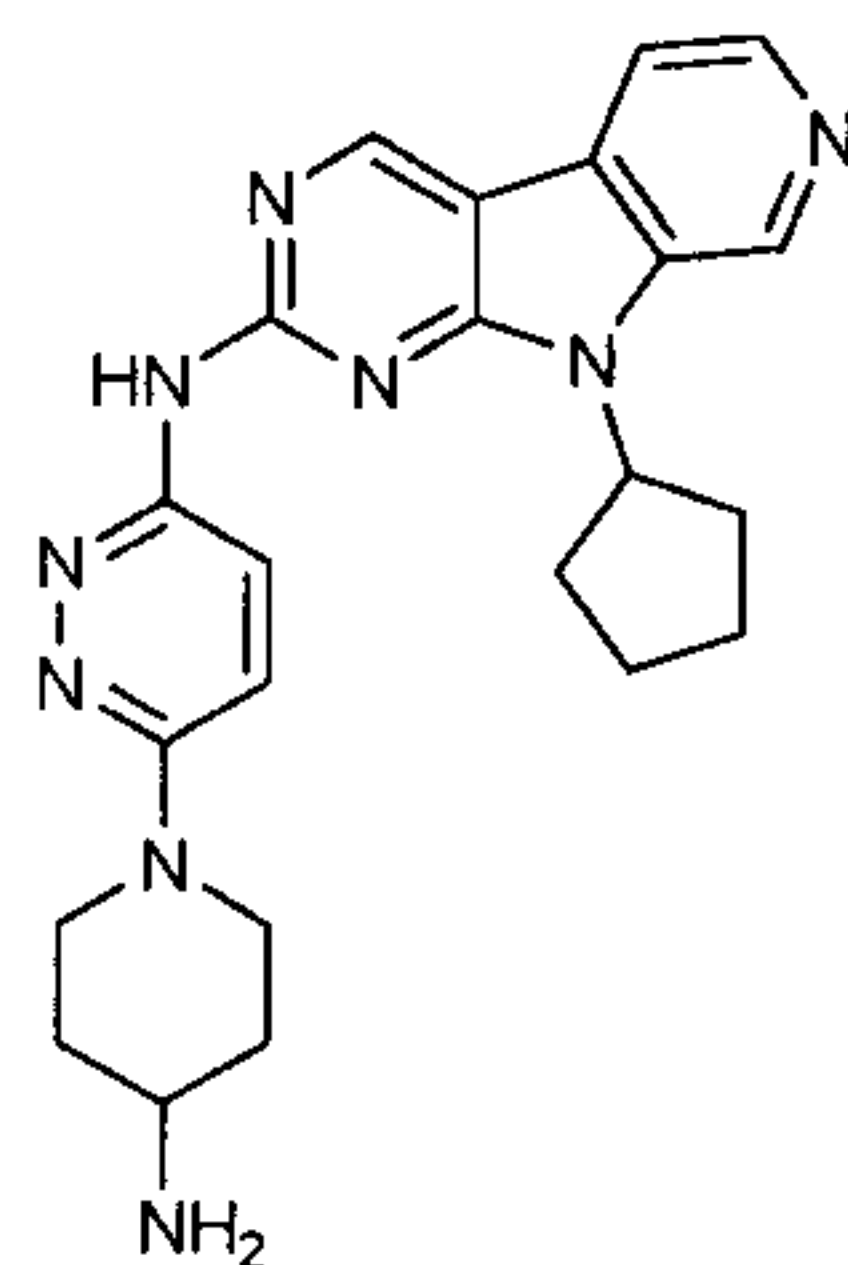
138. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

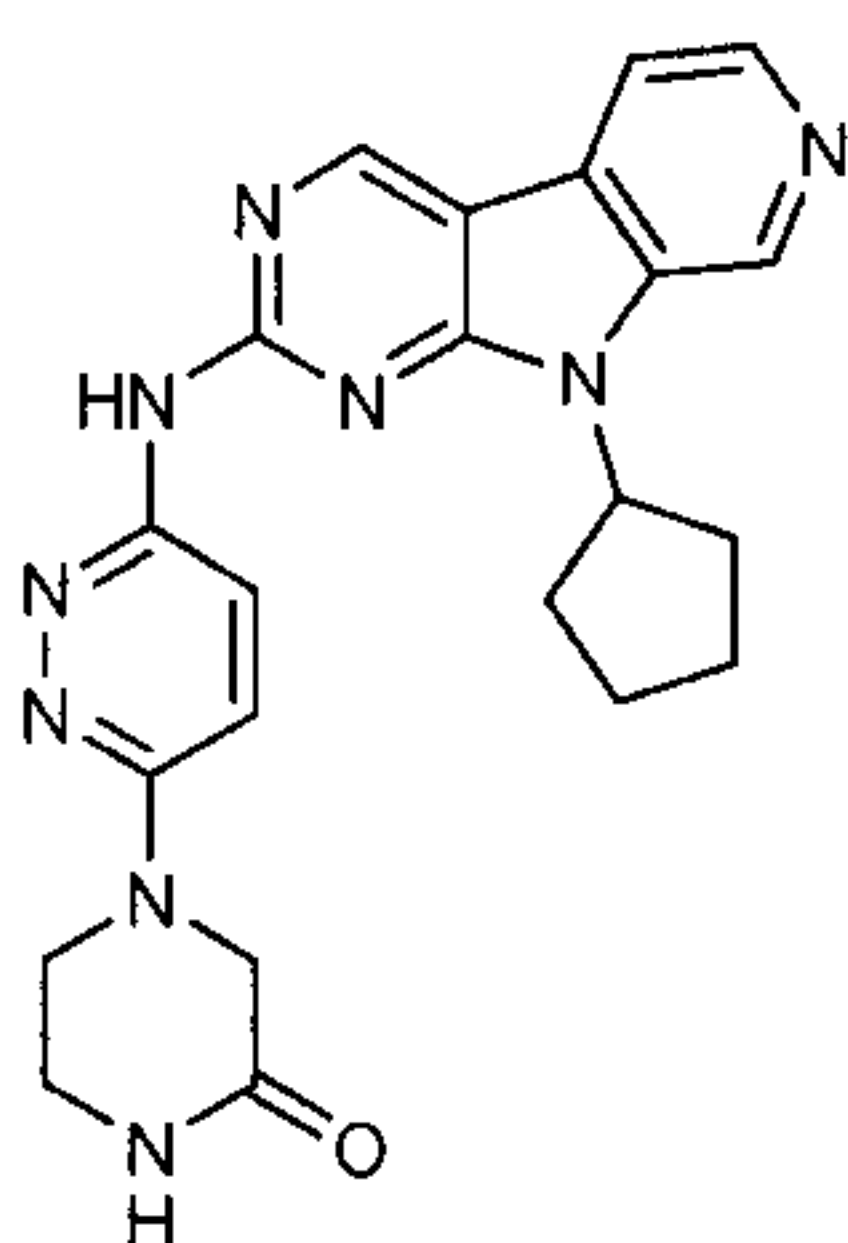


139. The compound of claim 1, wherein the compound is



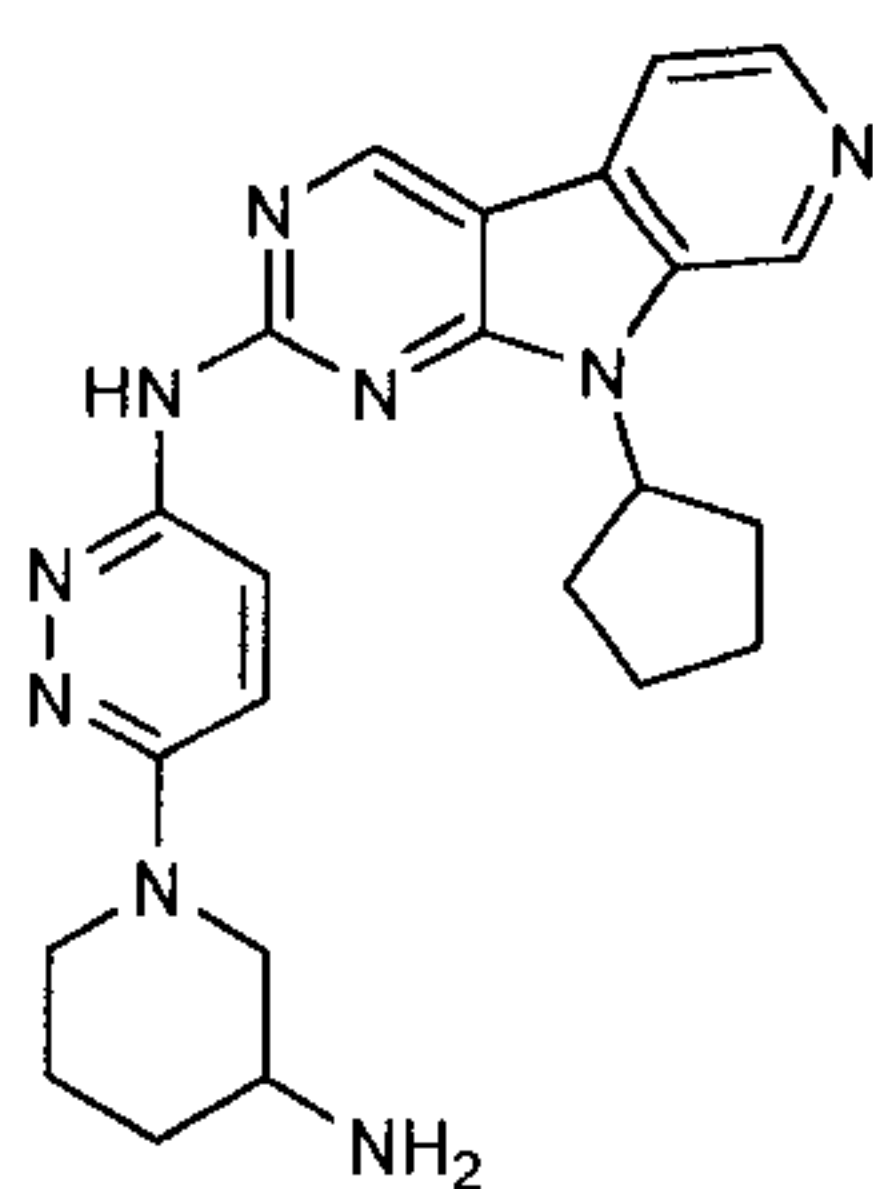
or a pharmaceutically acceptable salt thereof.

140. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

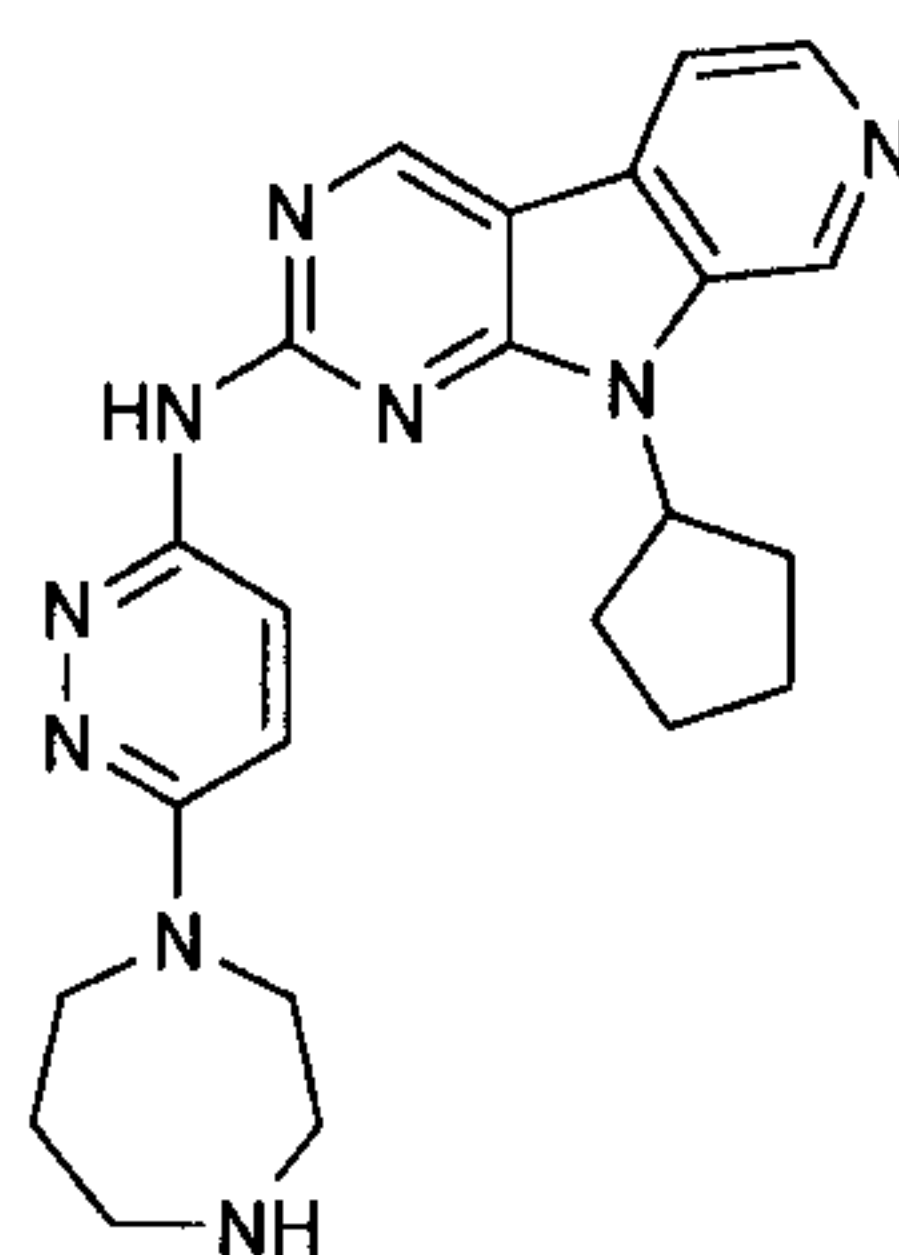
141. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

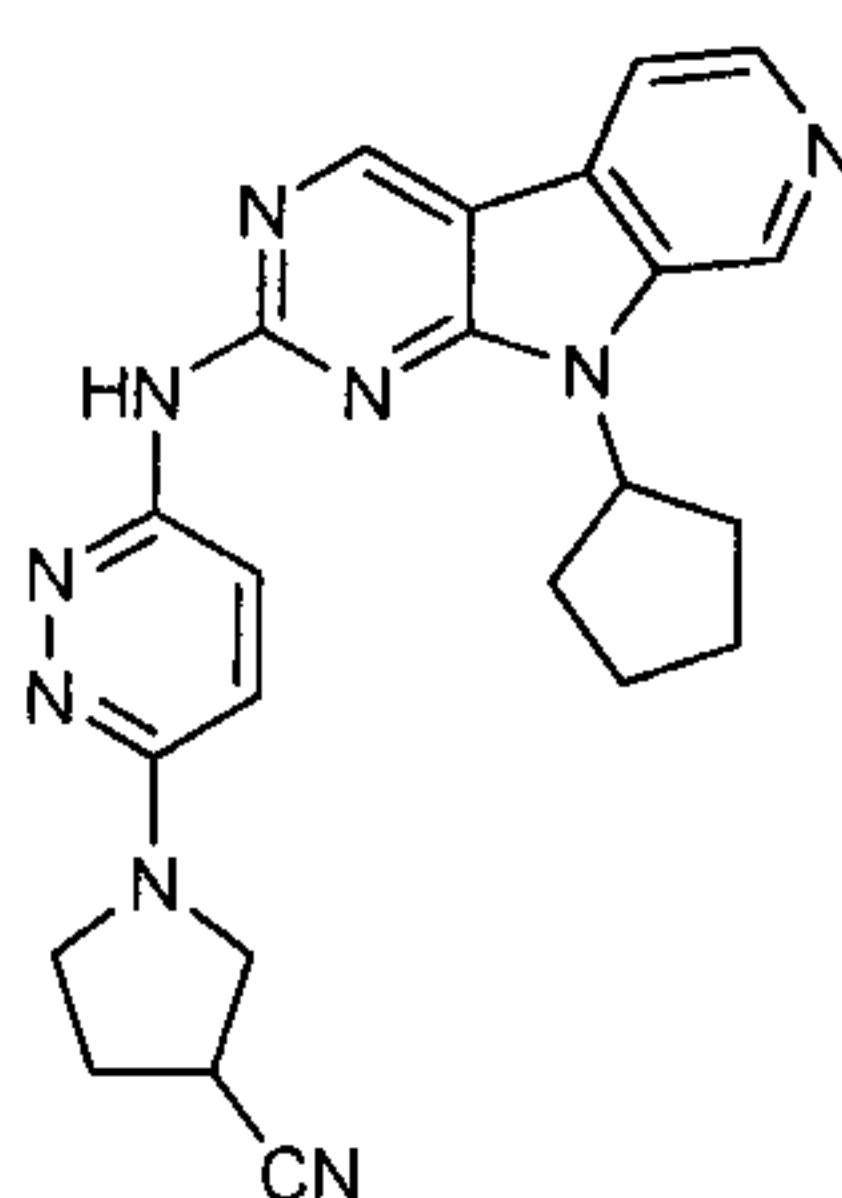


142. The compound of claim 1, wherein the compound is



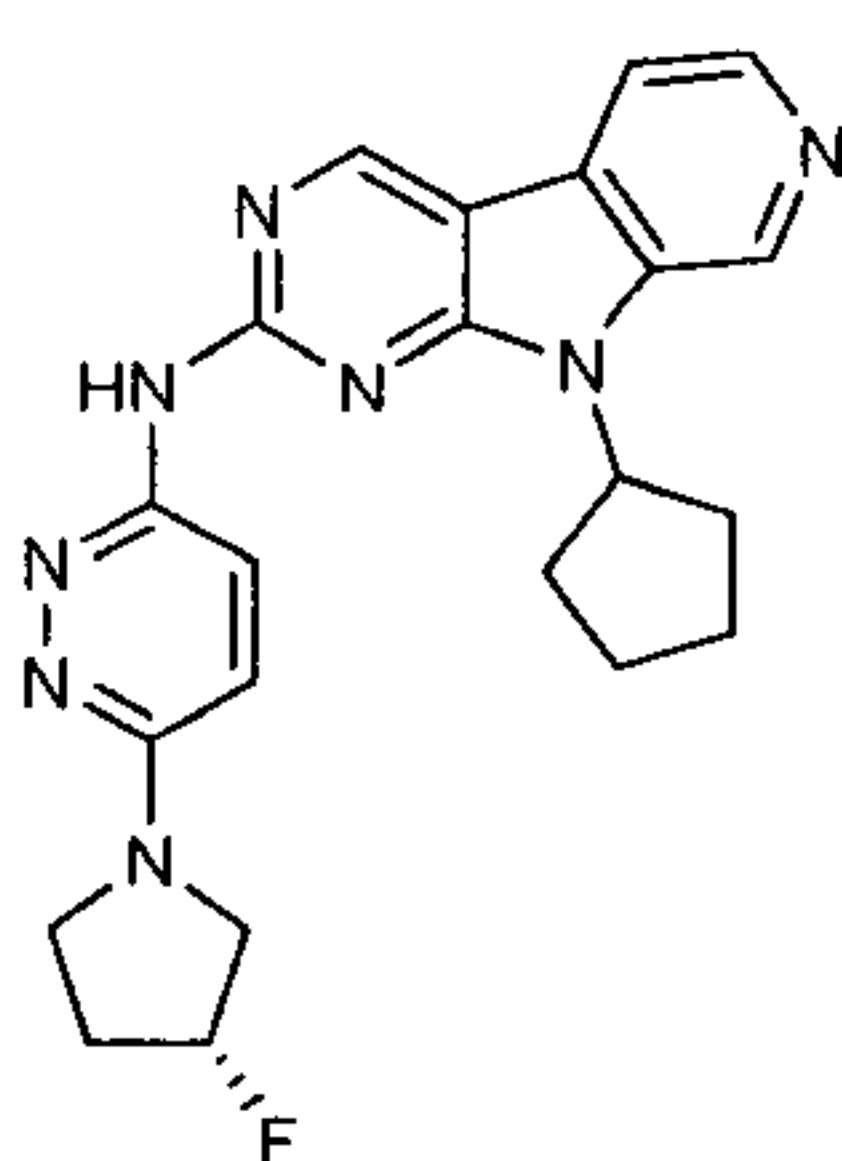
or a pharmaceutically acceptable salt thereof.

143. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

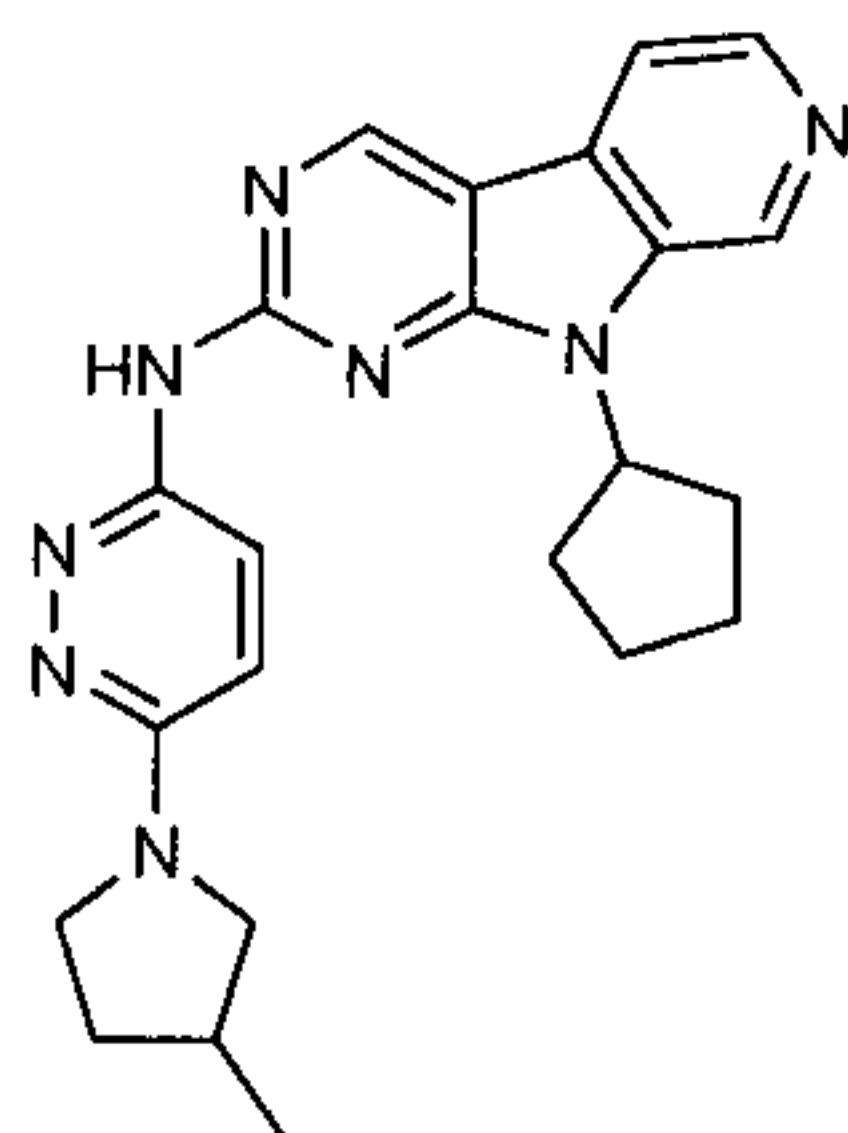
144. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.



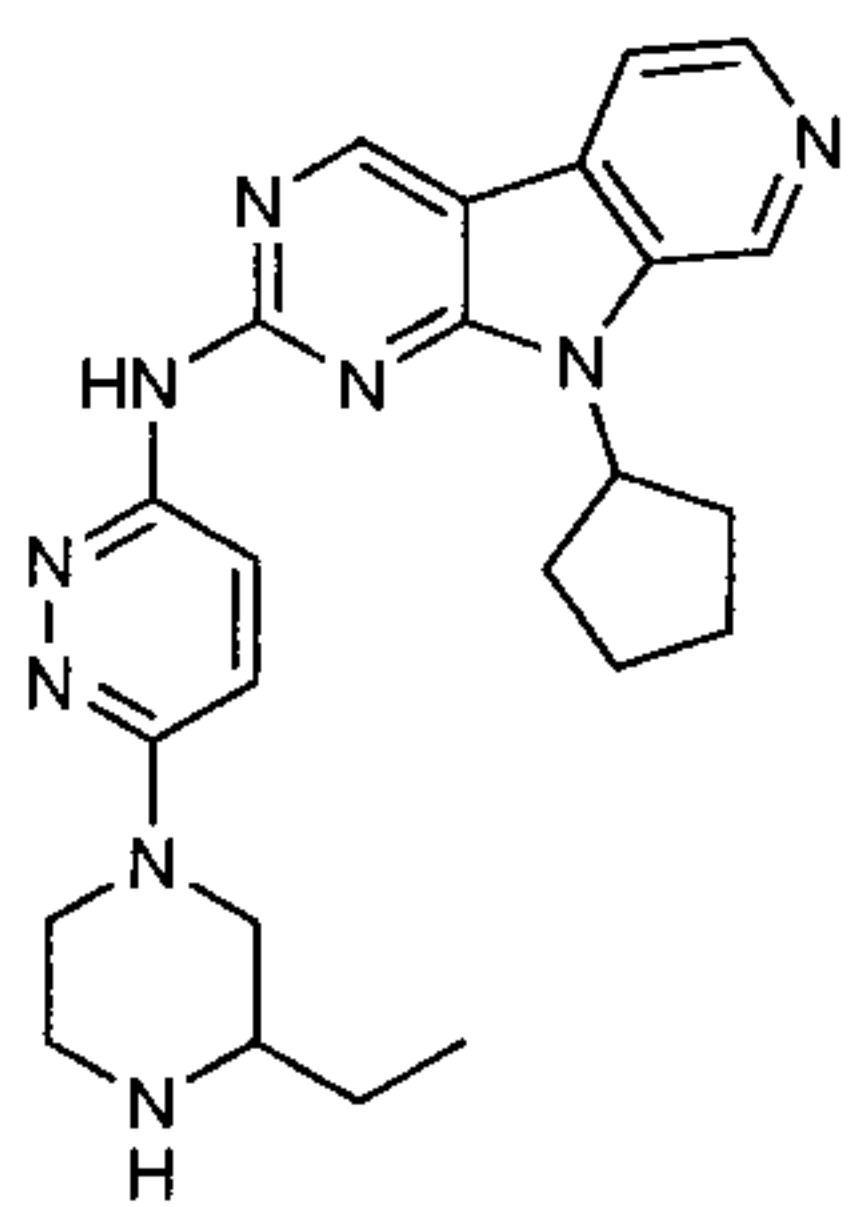
145. The compound of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

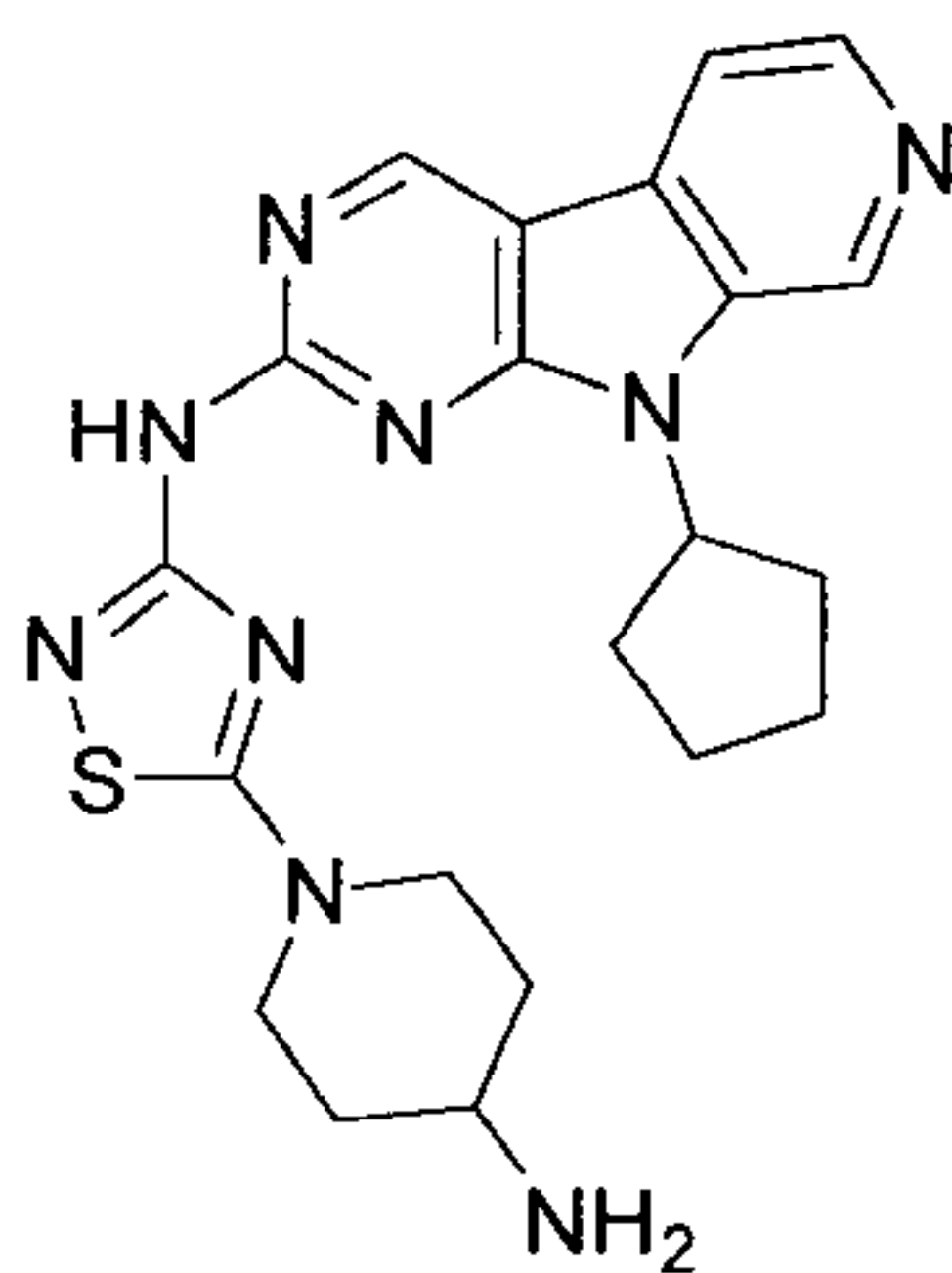
146. The compound of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

147. The compound of claim 1, wherein the compound is

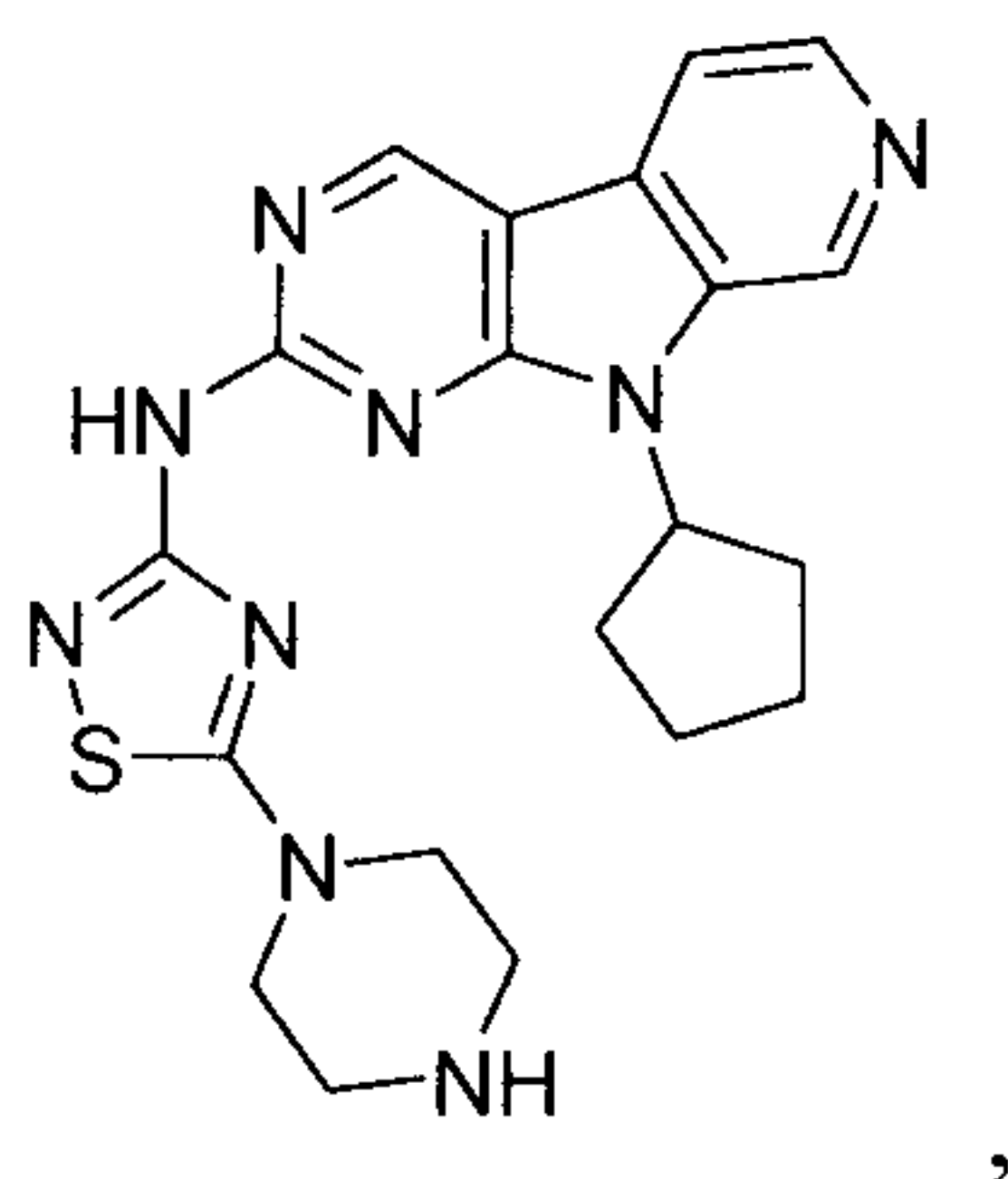


,

or a pharmaceutically acceptable salt thereof.

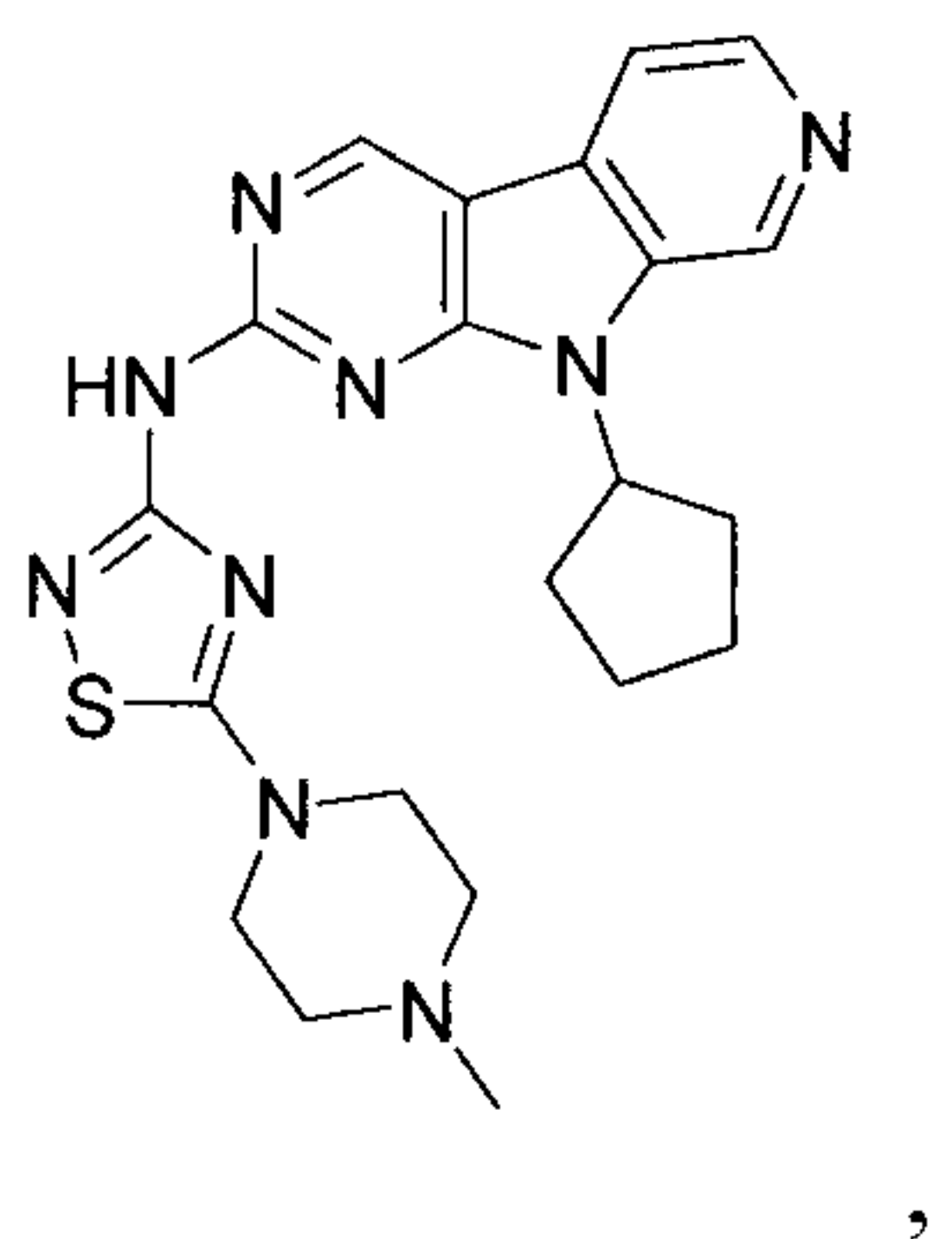


148. The compound of claim 1, wherein the compound is



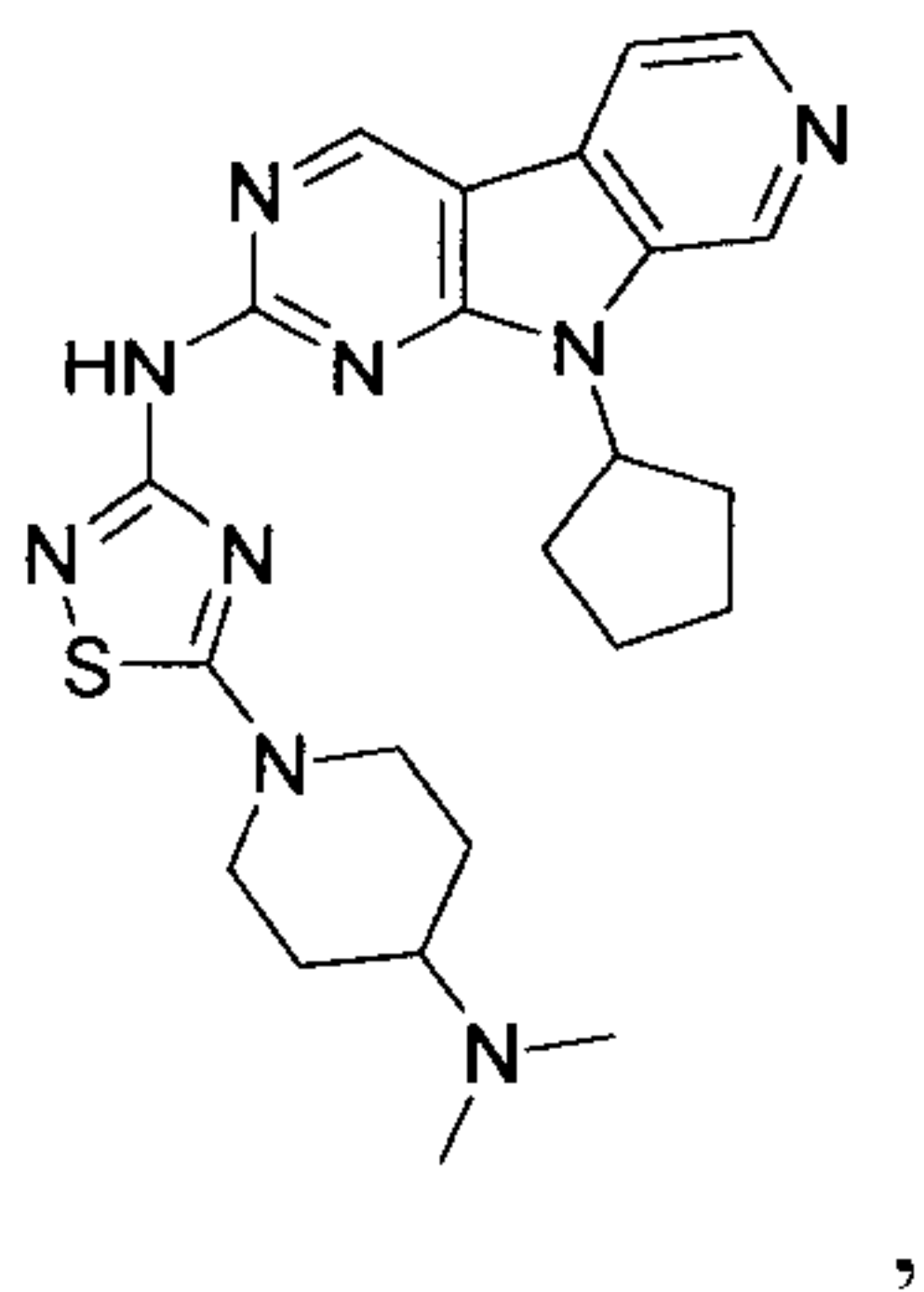
or a pharmaceutically acceptable salt thereof.

149. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

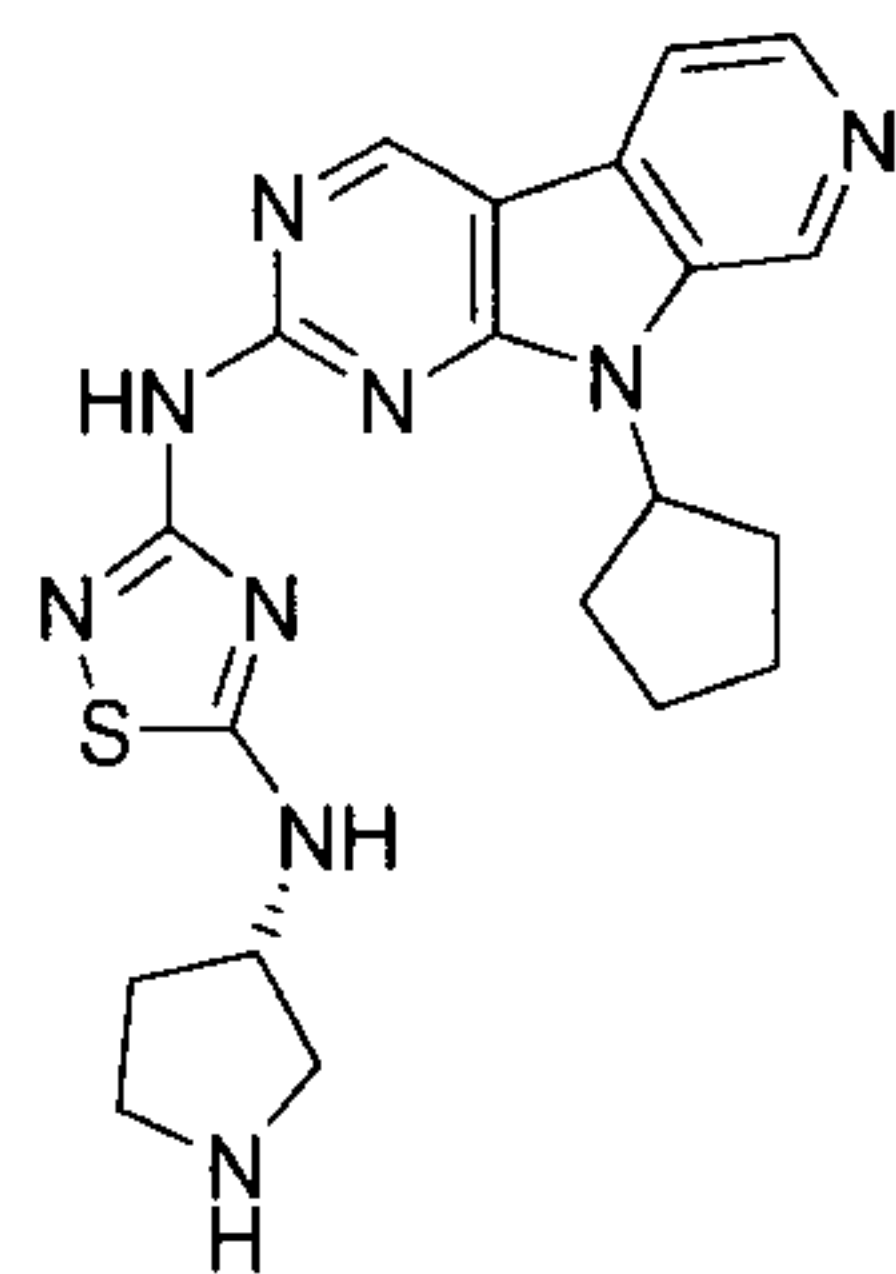
150. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

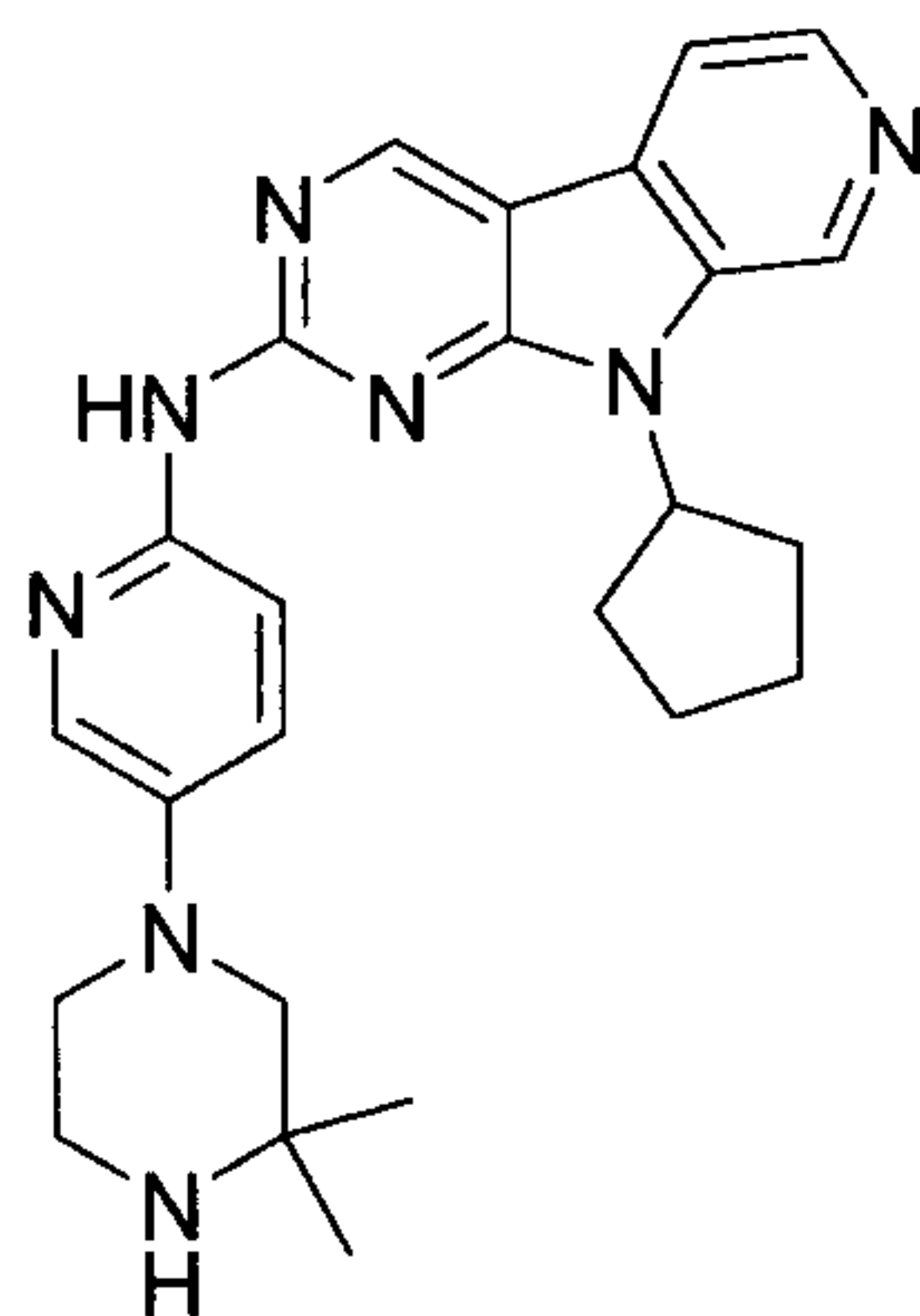


151. The compound of claim 1, wherein the compound is



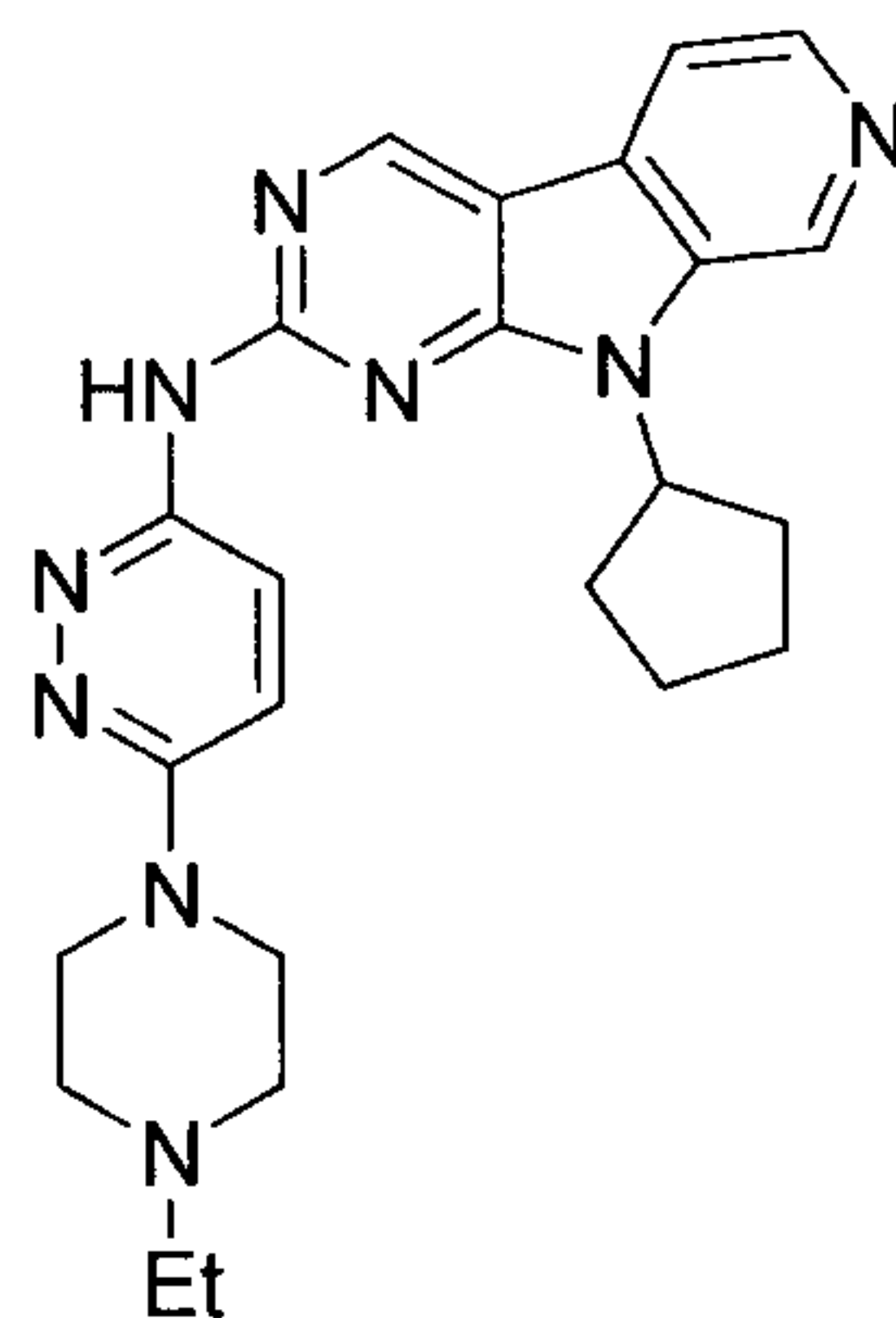
or a pharmaceutically acceptable salt thereof.

152. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

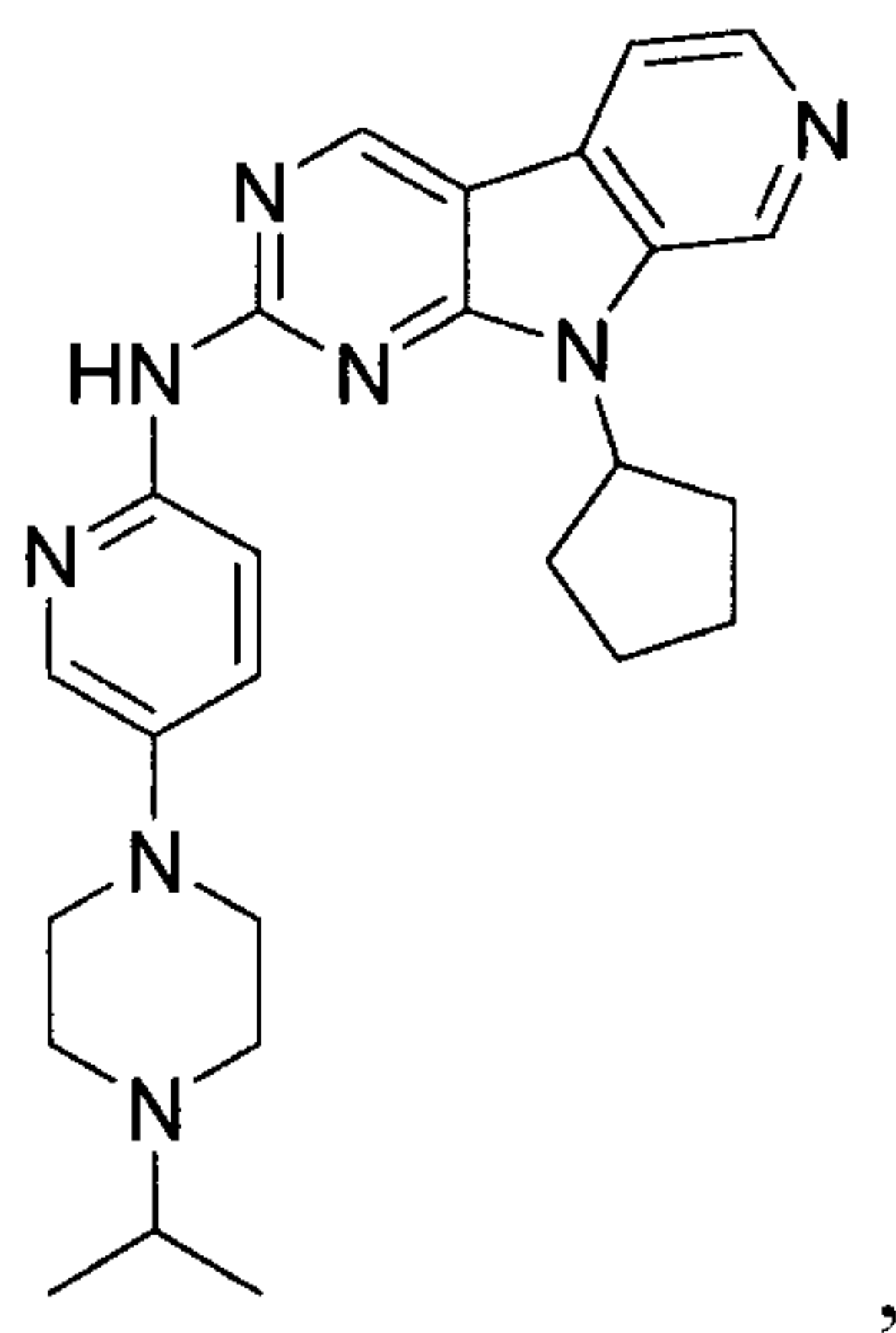
153. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

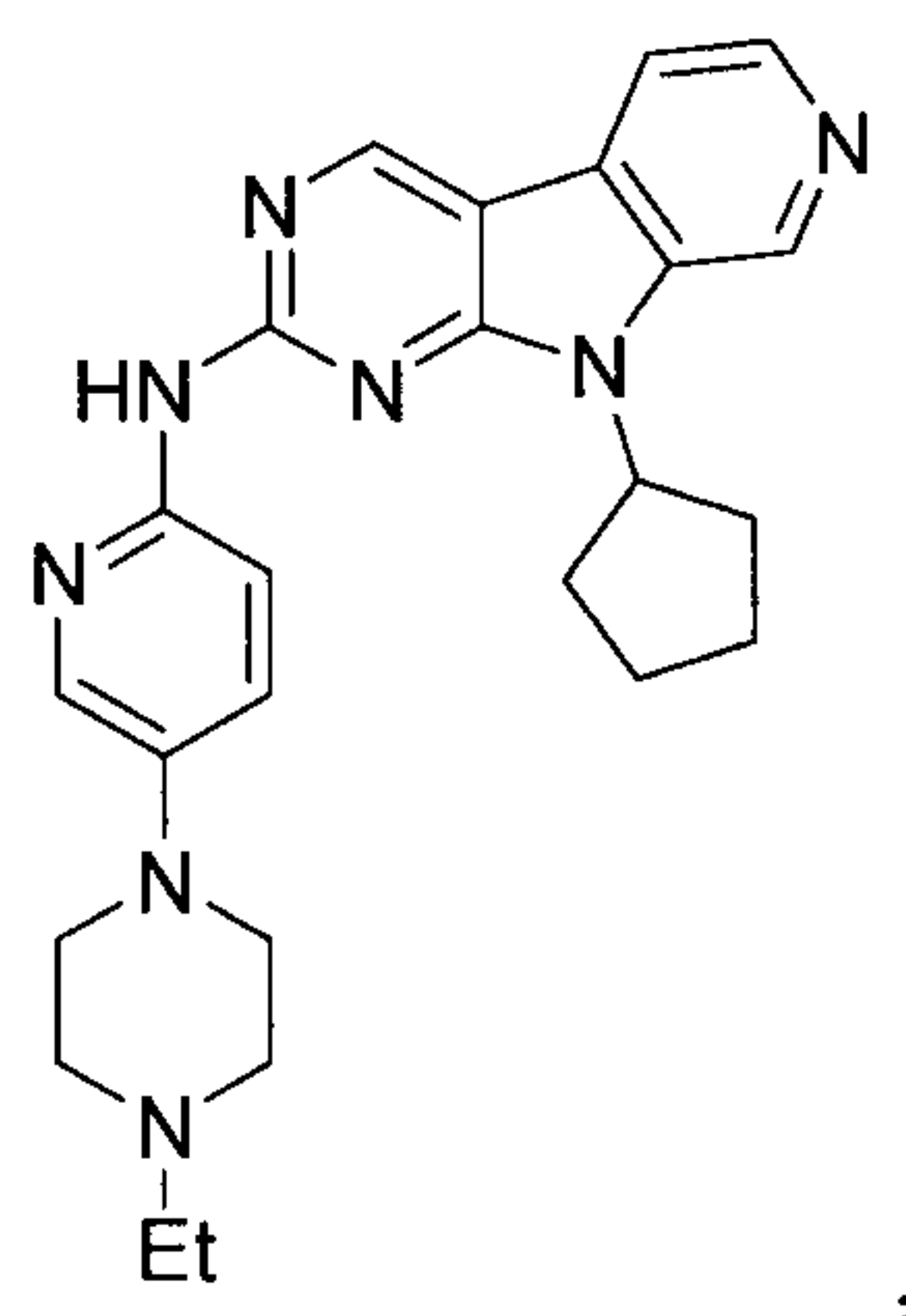


154. The compound of claim 1, wherein the compound is



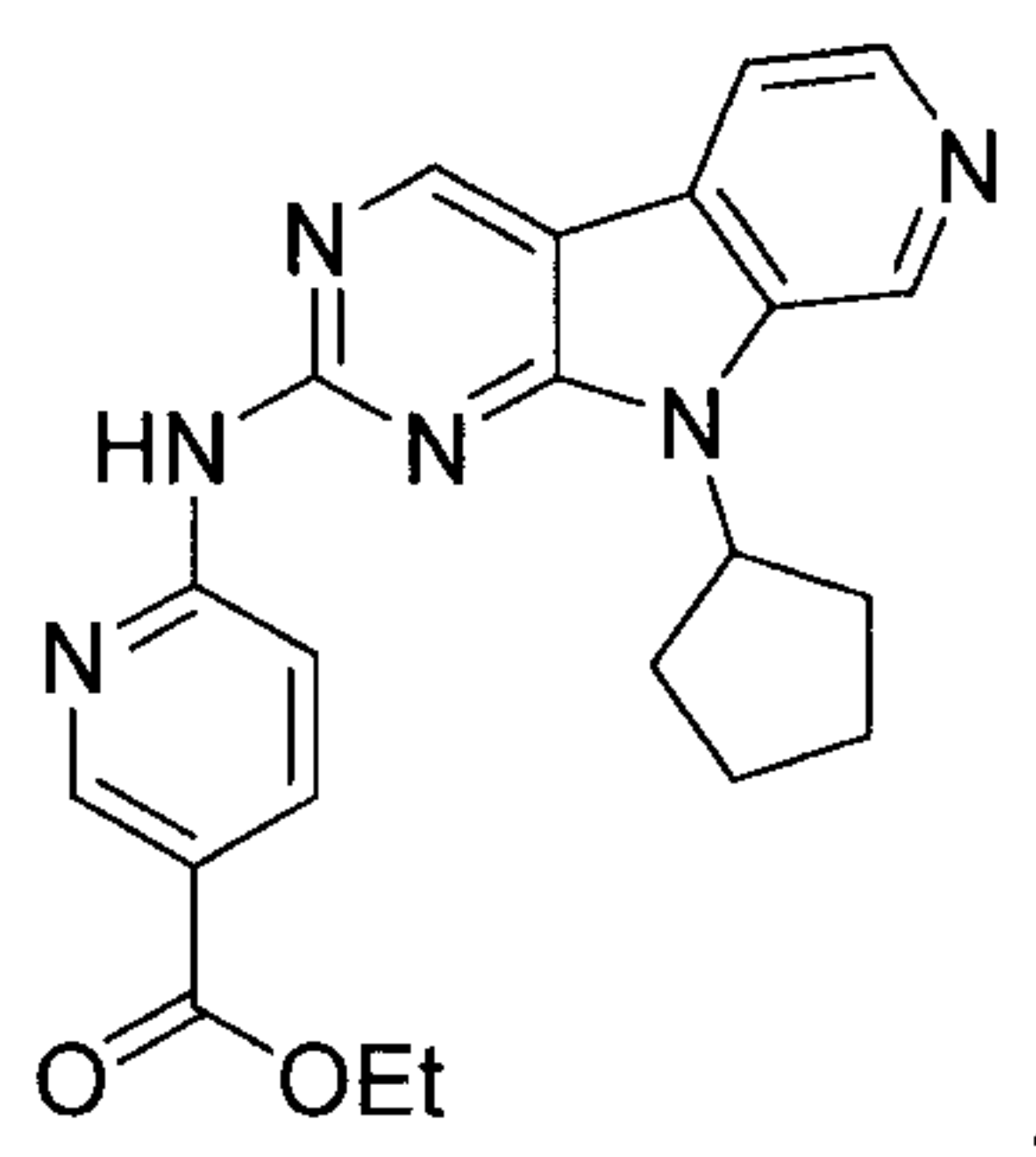
or a pharmaceutically acceptable salt thereof.

155. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

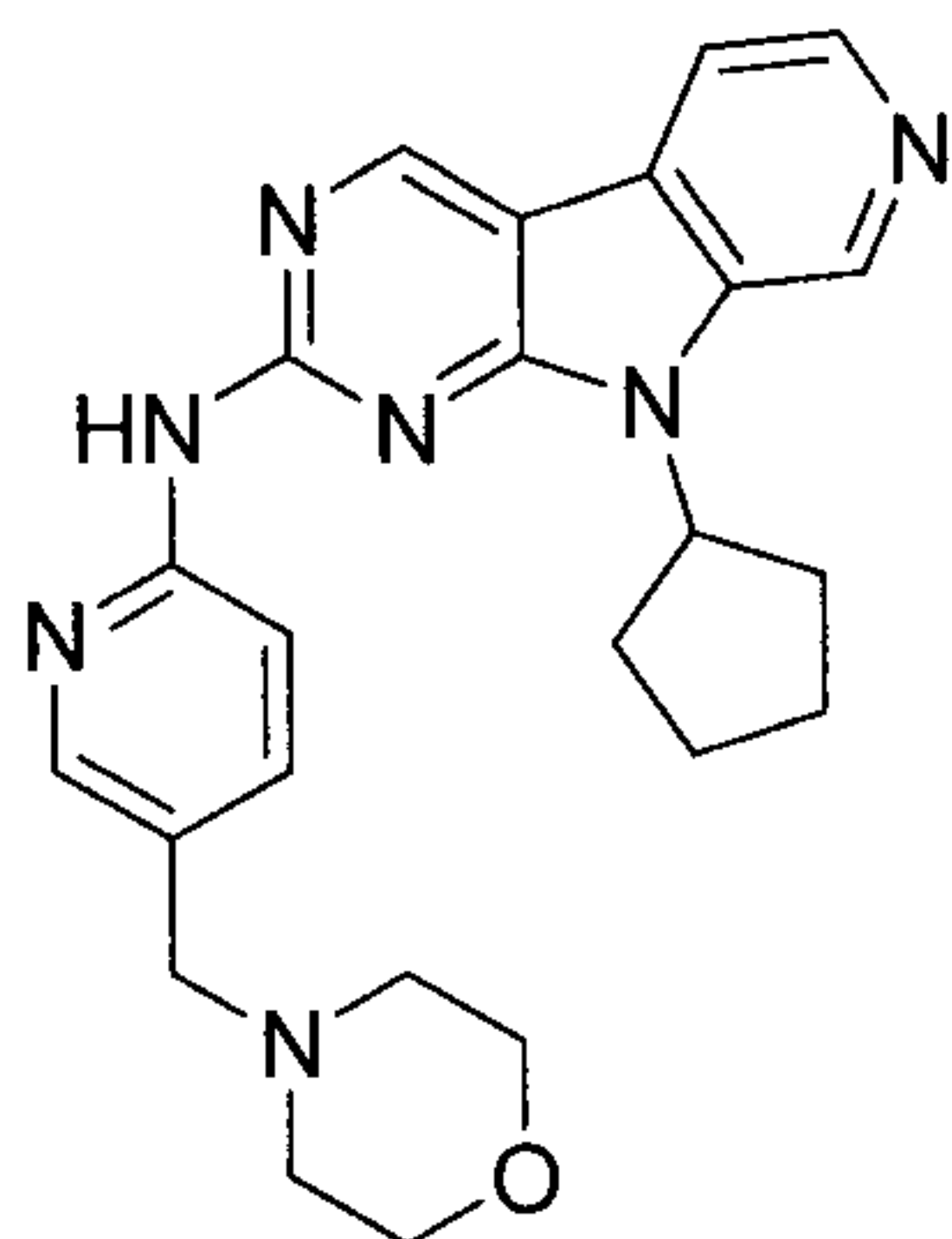
156. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

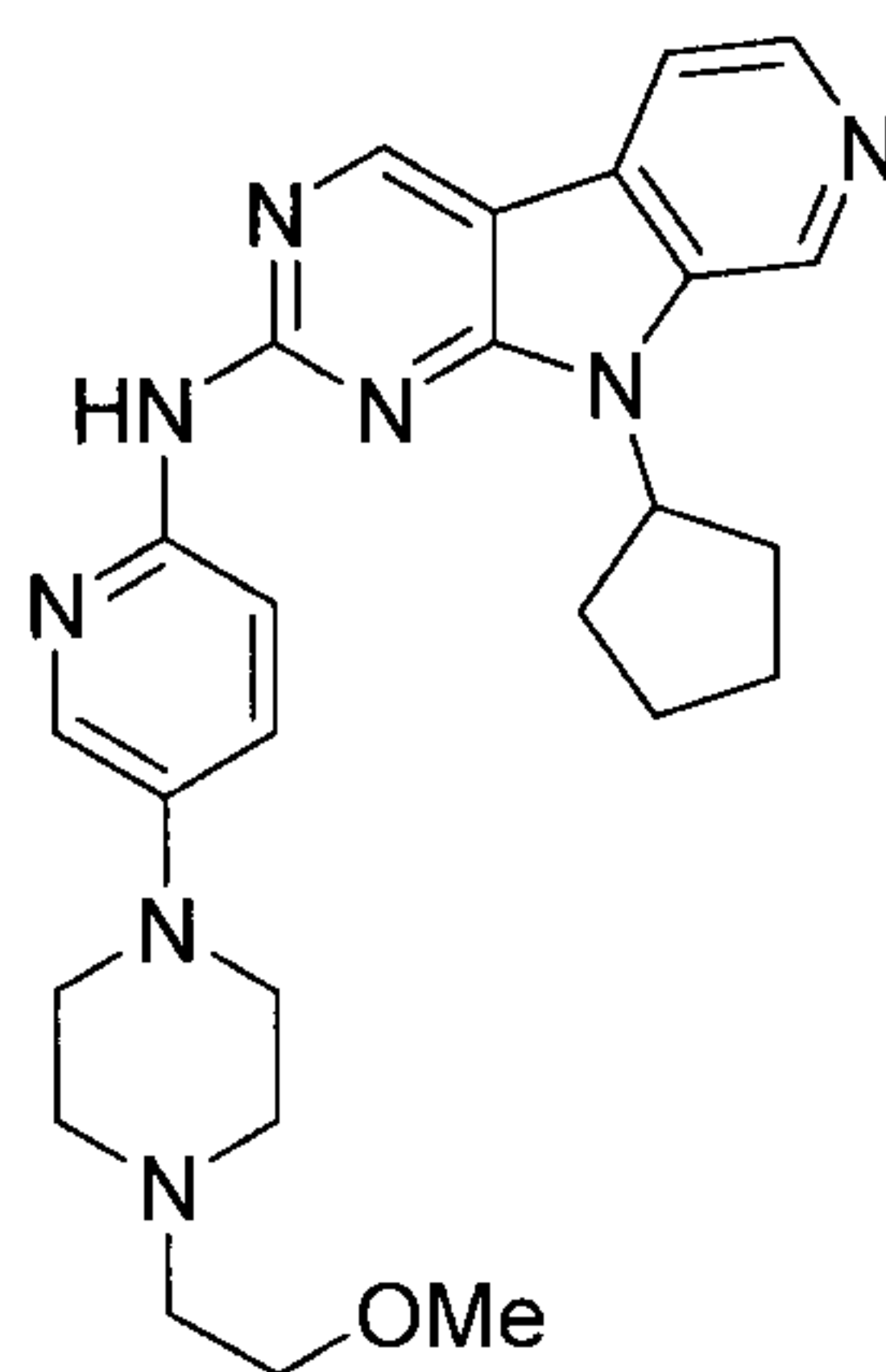


157. The compound of claim 1, wherein the compound is



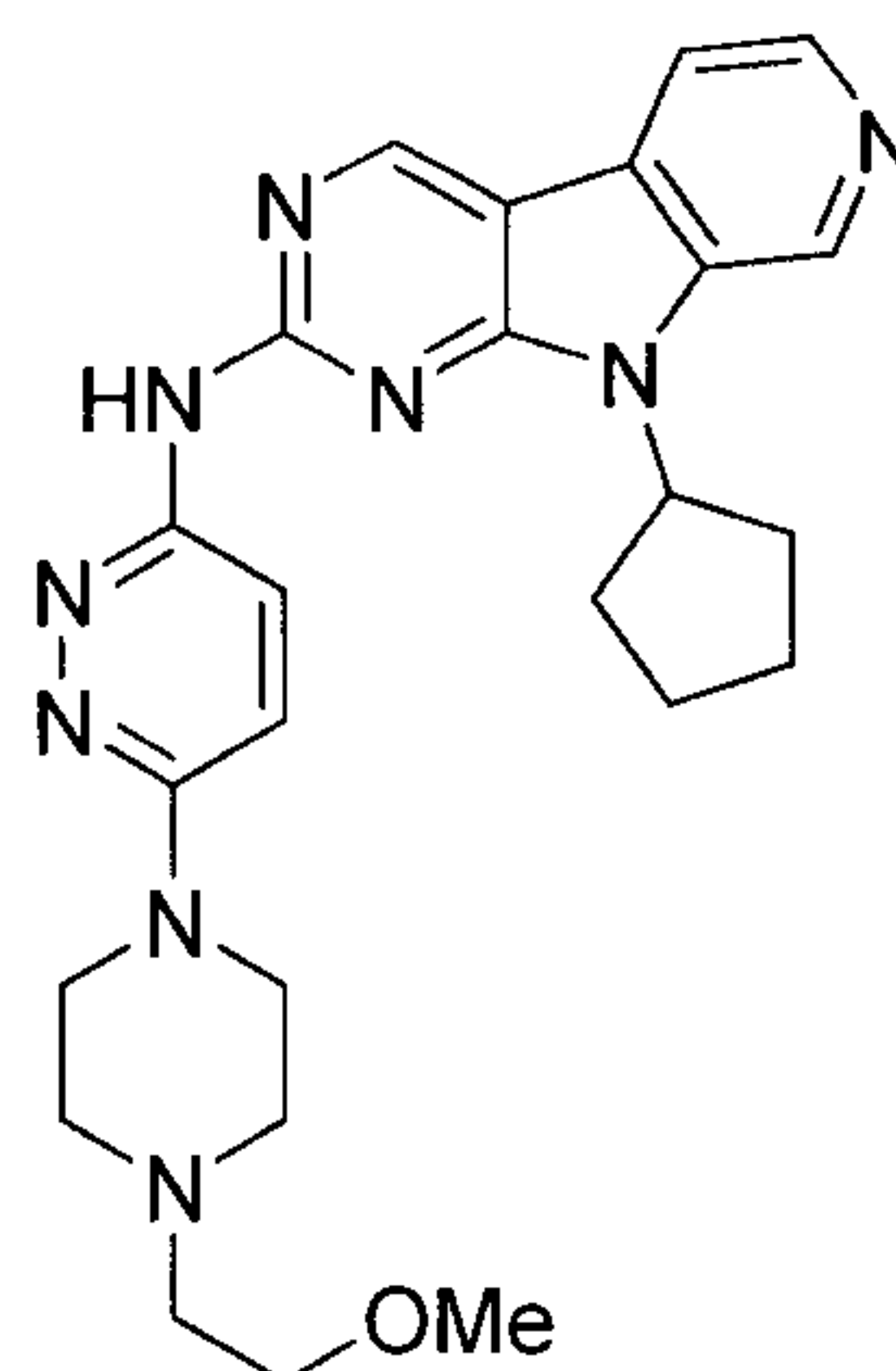
or a pharmaceutically acceptable salt thereof.

158. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

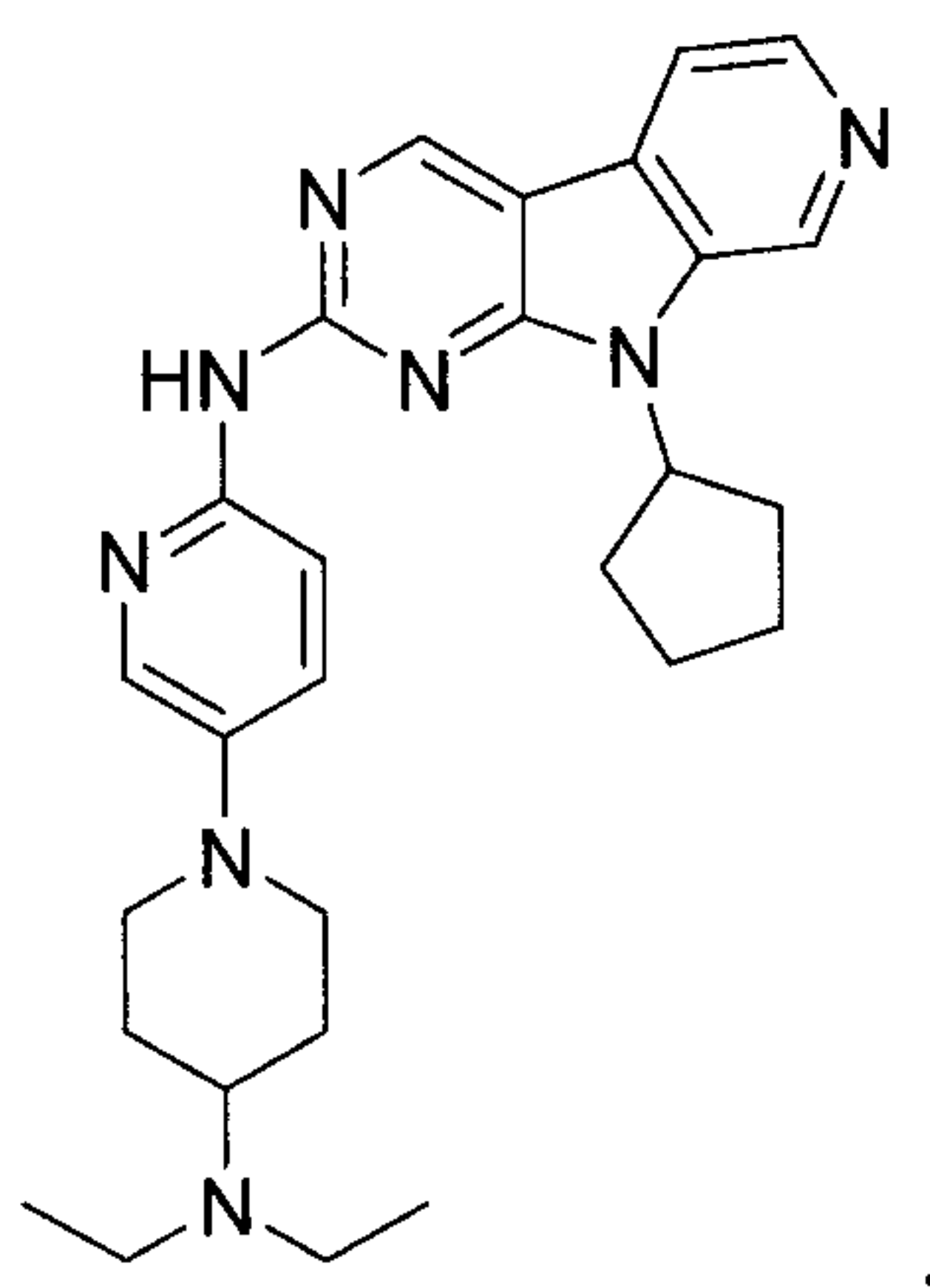
159. The compound of claim 1, wherein the compound is





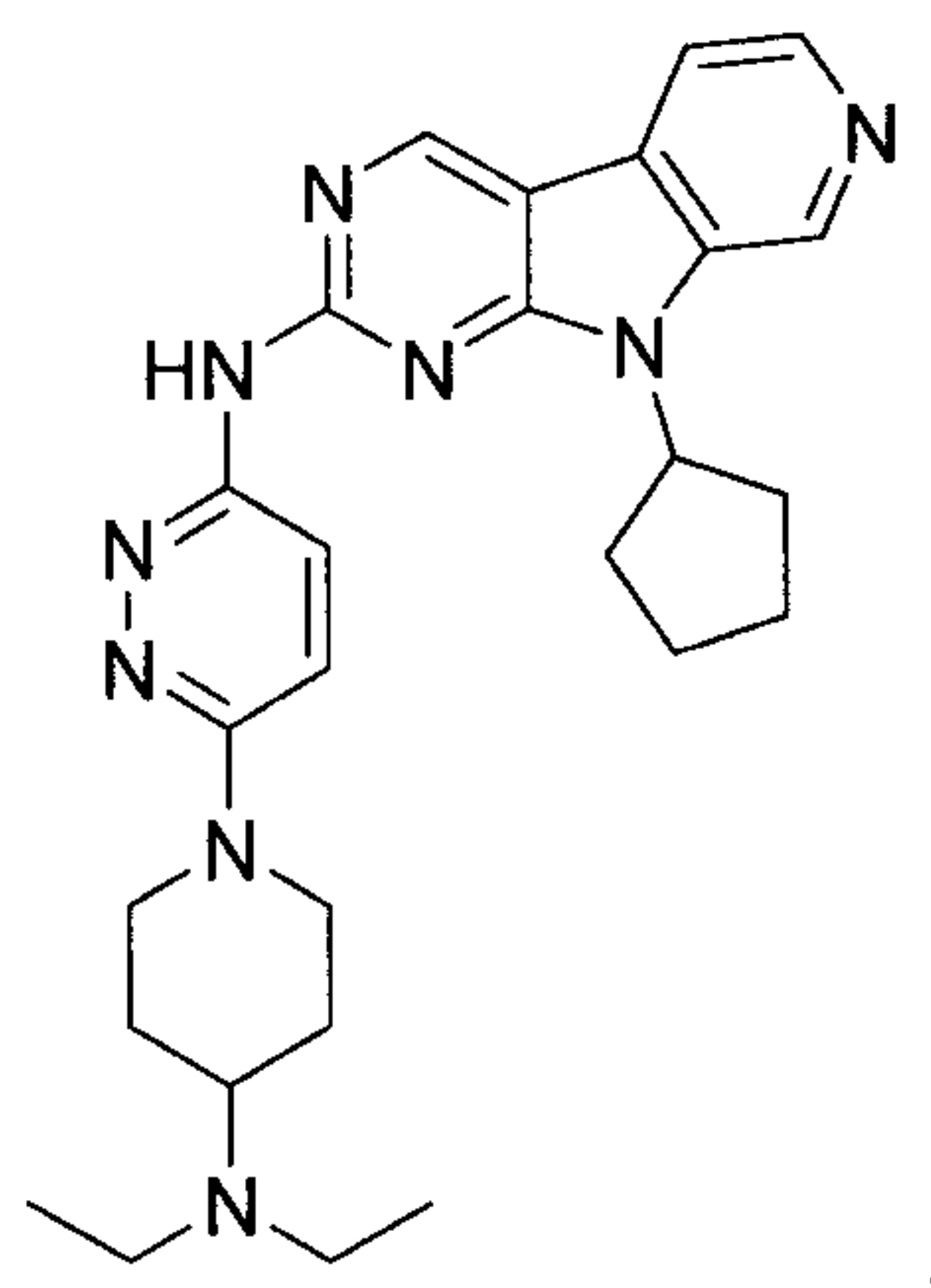
or a pharmaceutically acceptable salt thereof.

160. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

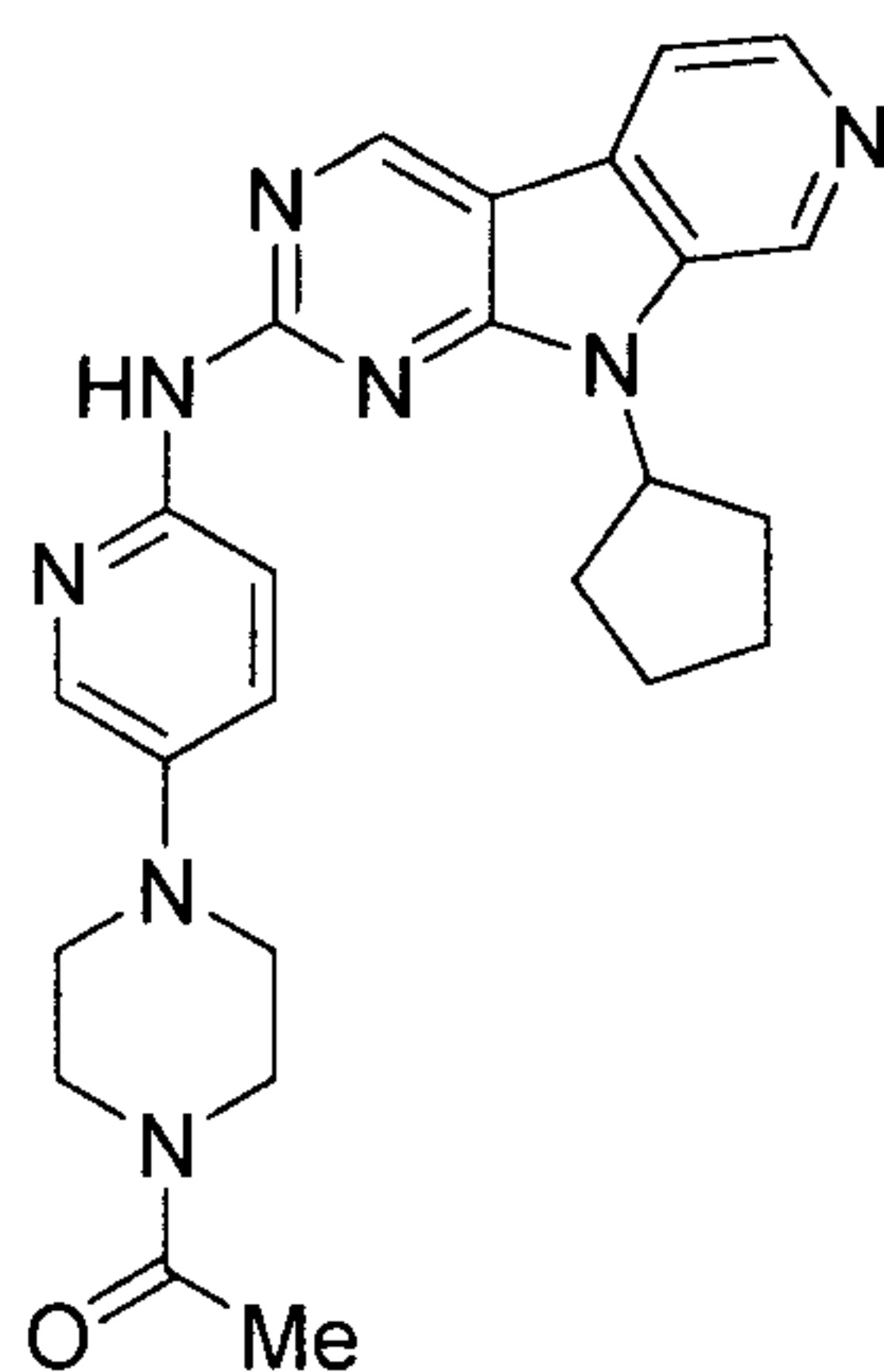
161. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

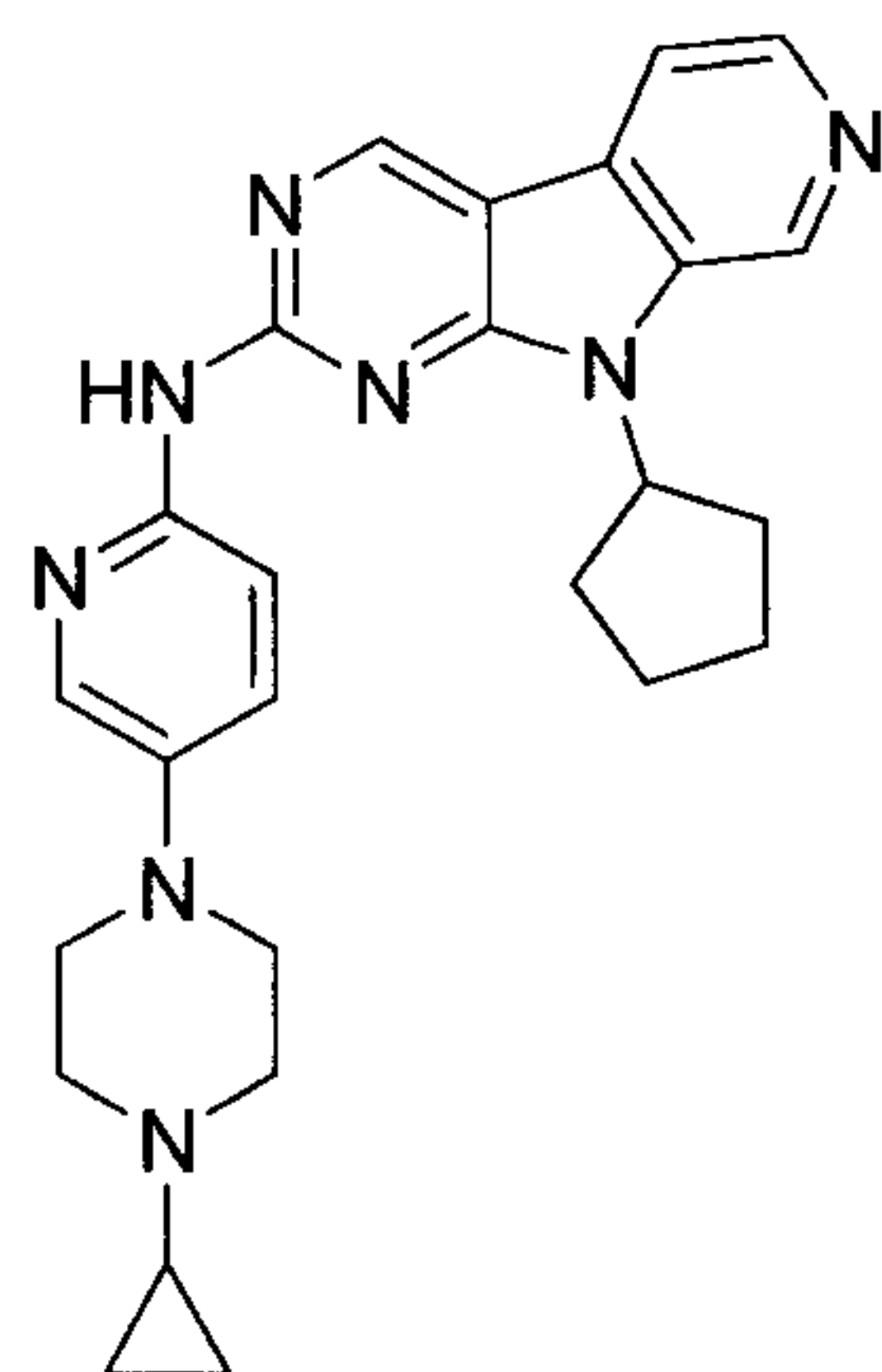


162. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

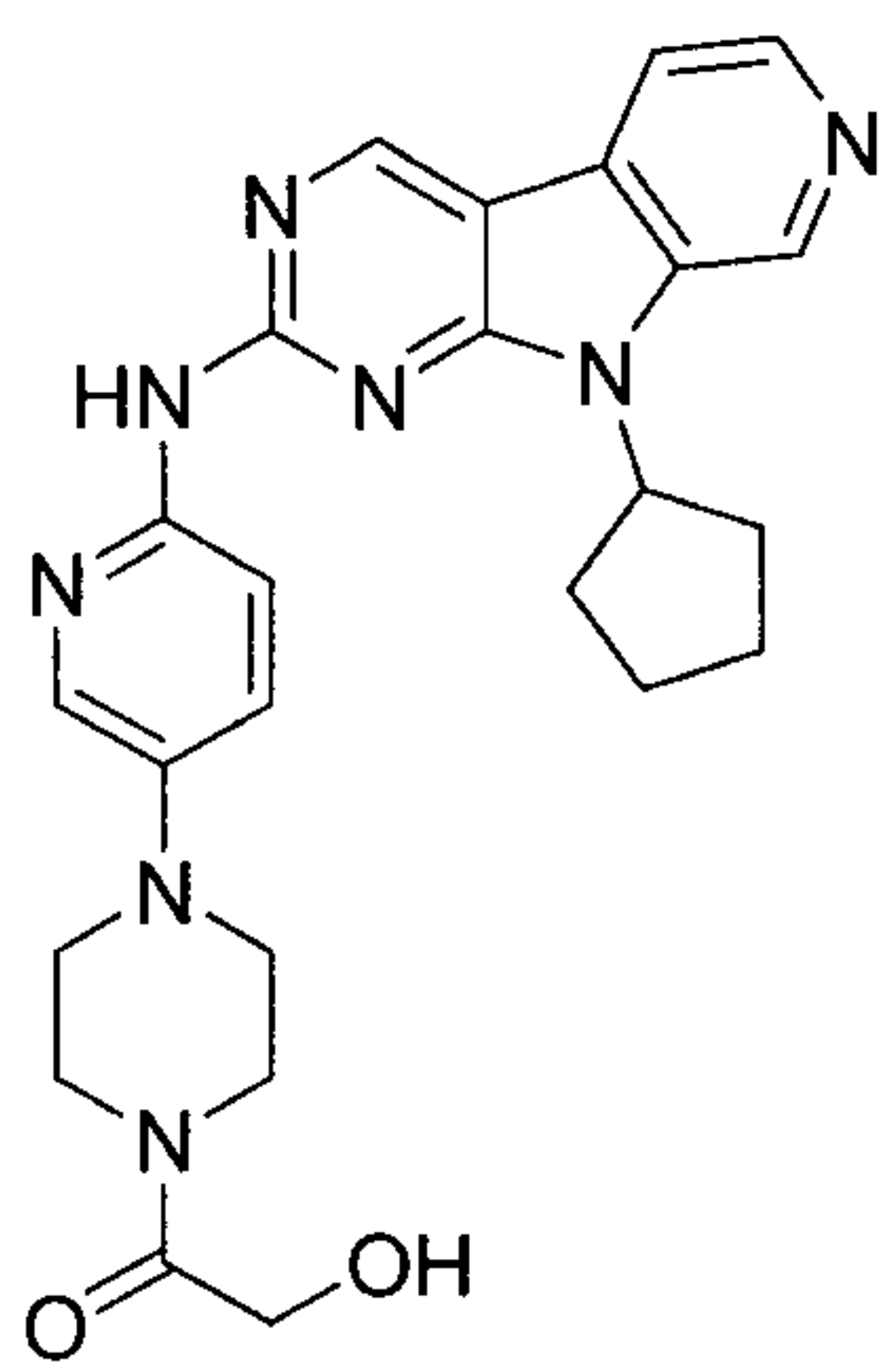
163. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

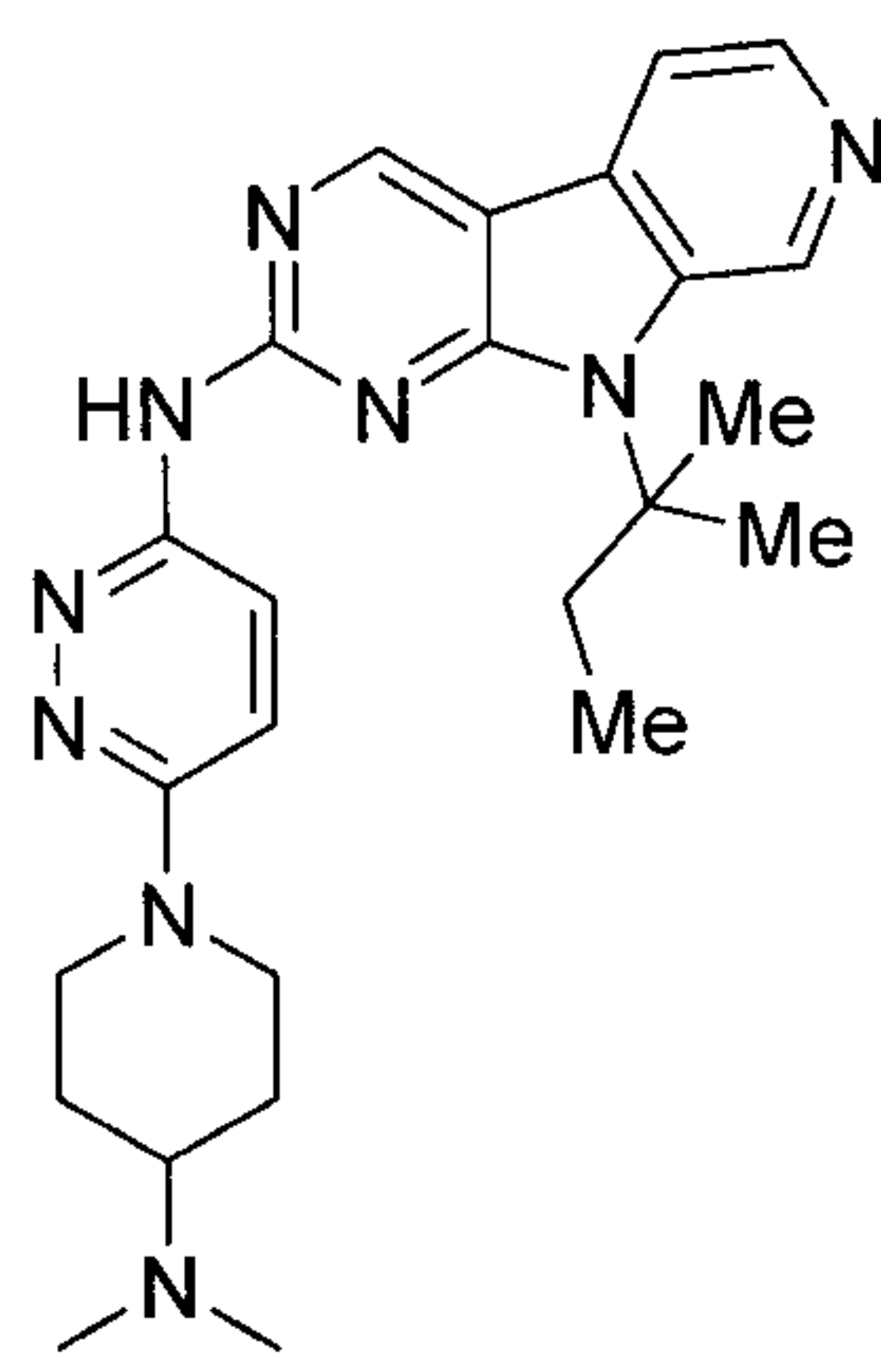


164. The compound of claim 1, wherein the compound is



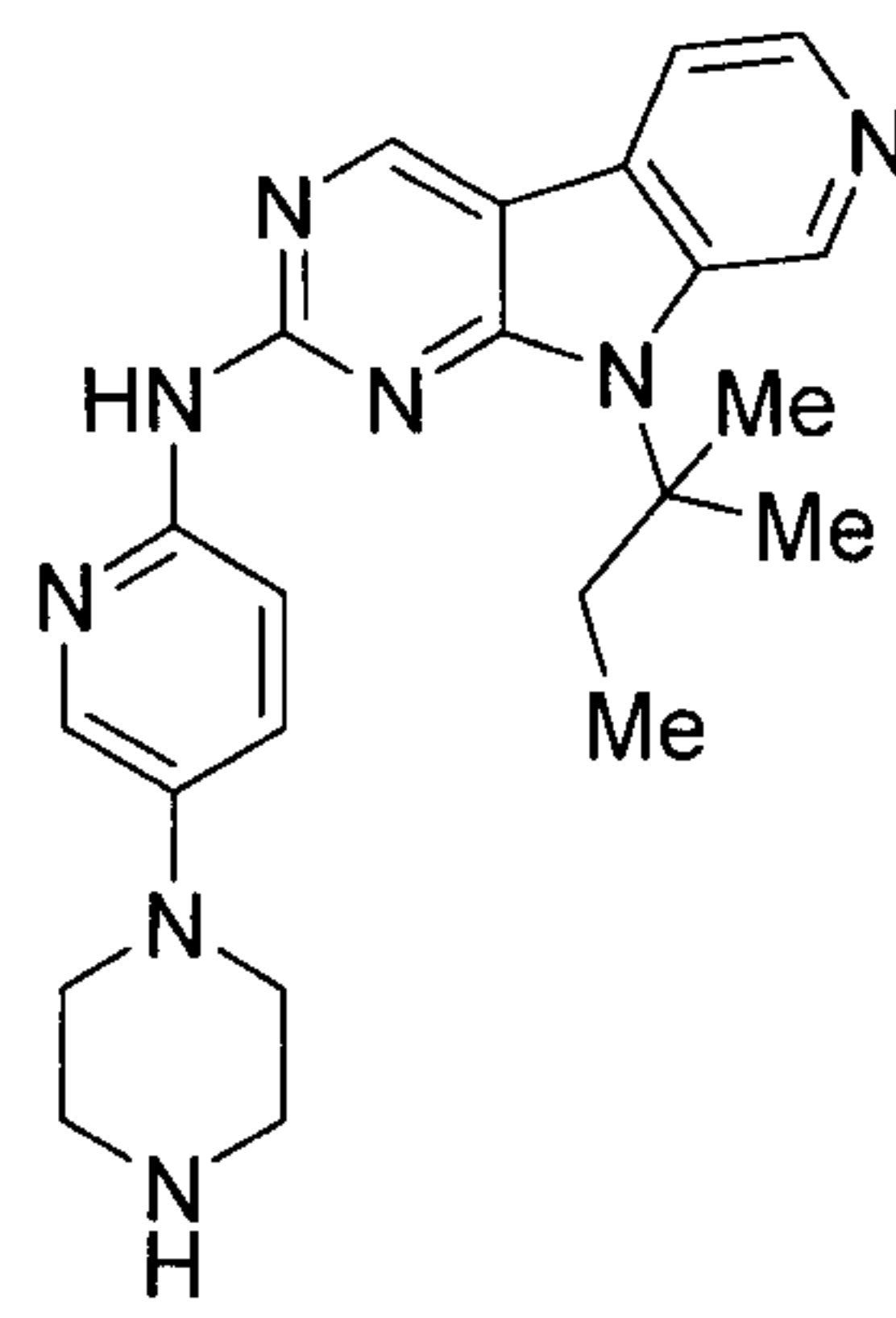
or a pharmaceutically acceptable salt thereof.

165. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

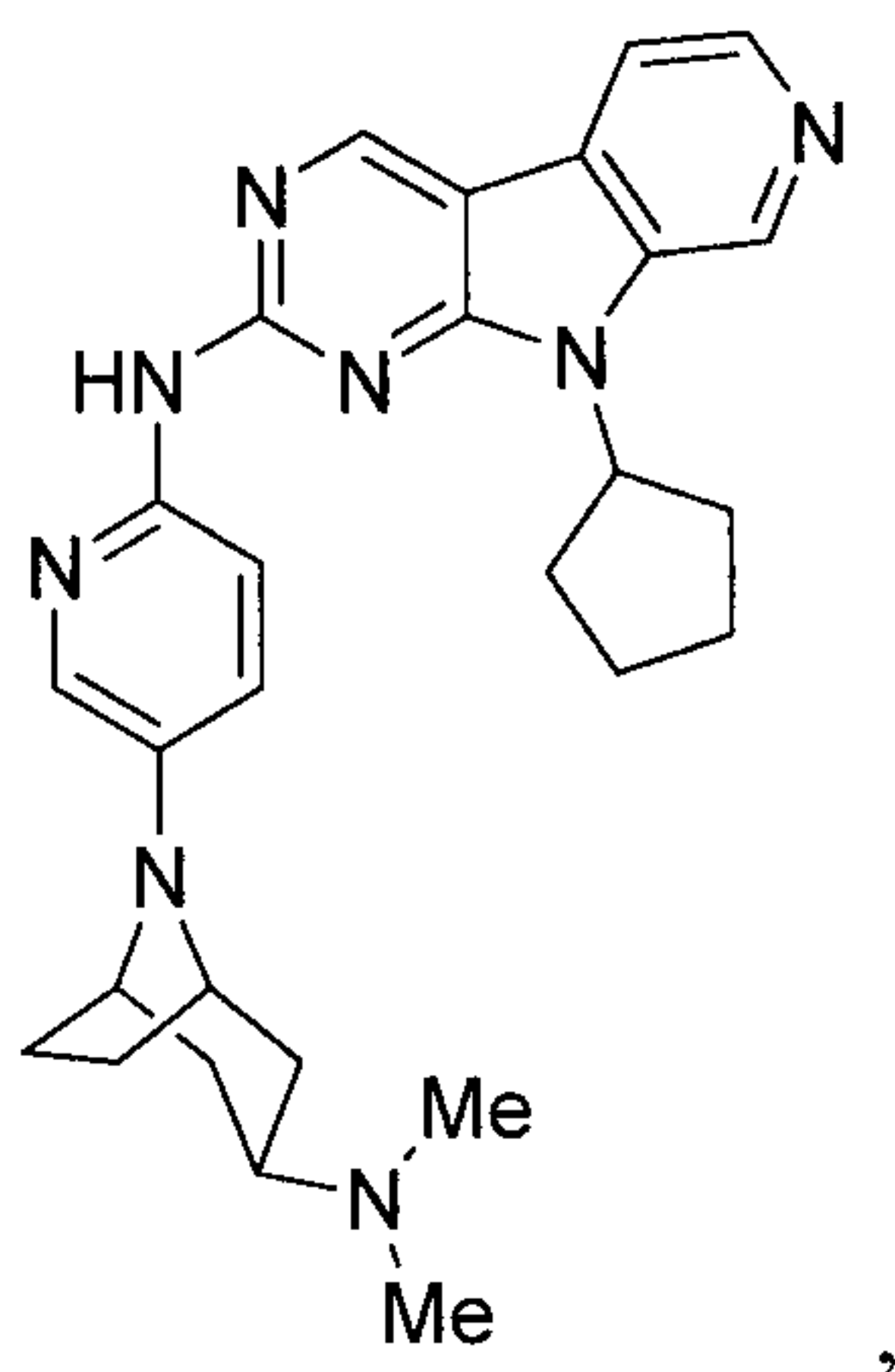
166. The compound of claim 1, wherein the compound is





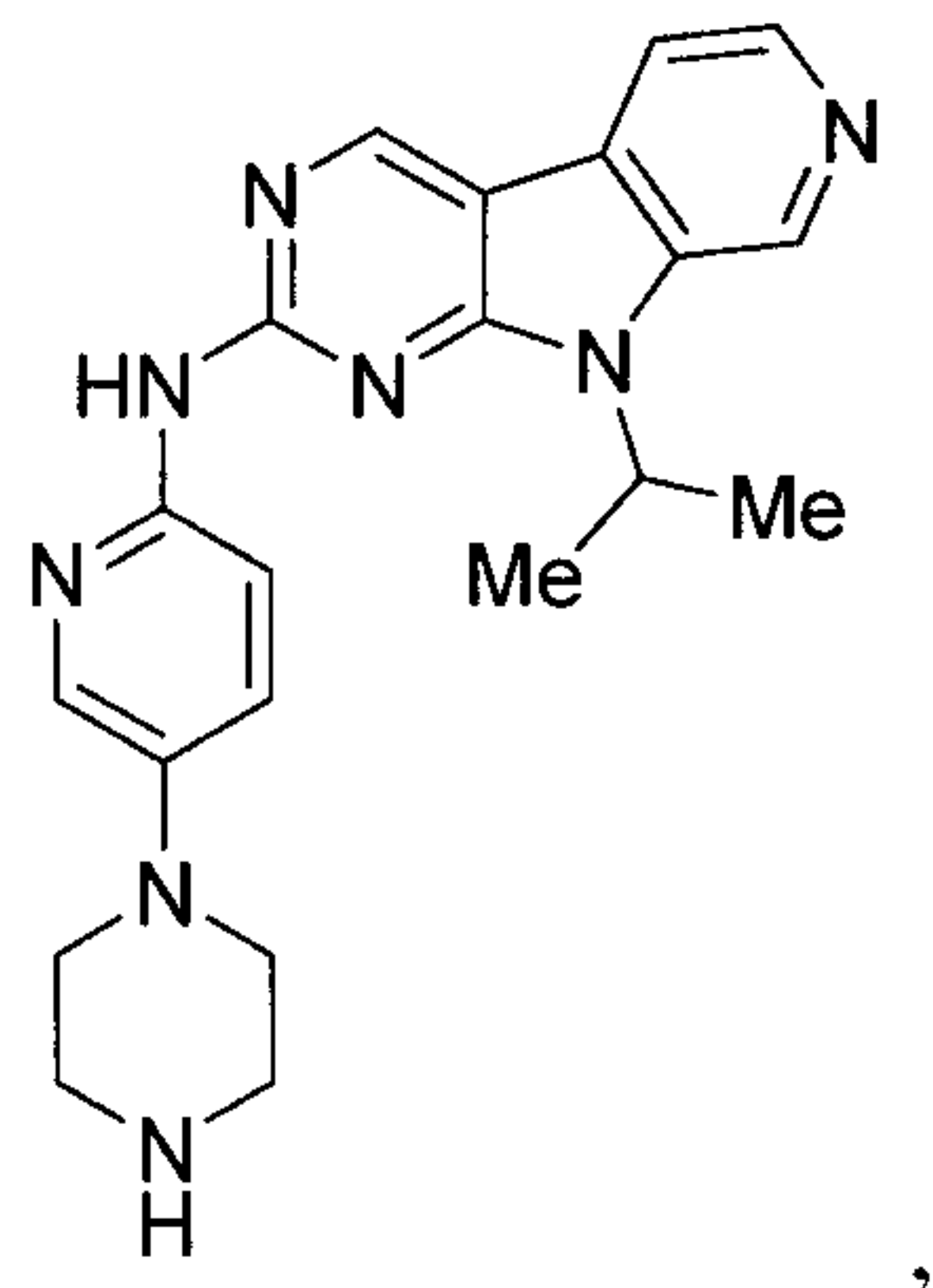
or a pharmaceutically acceptable salt thereof.

167. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

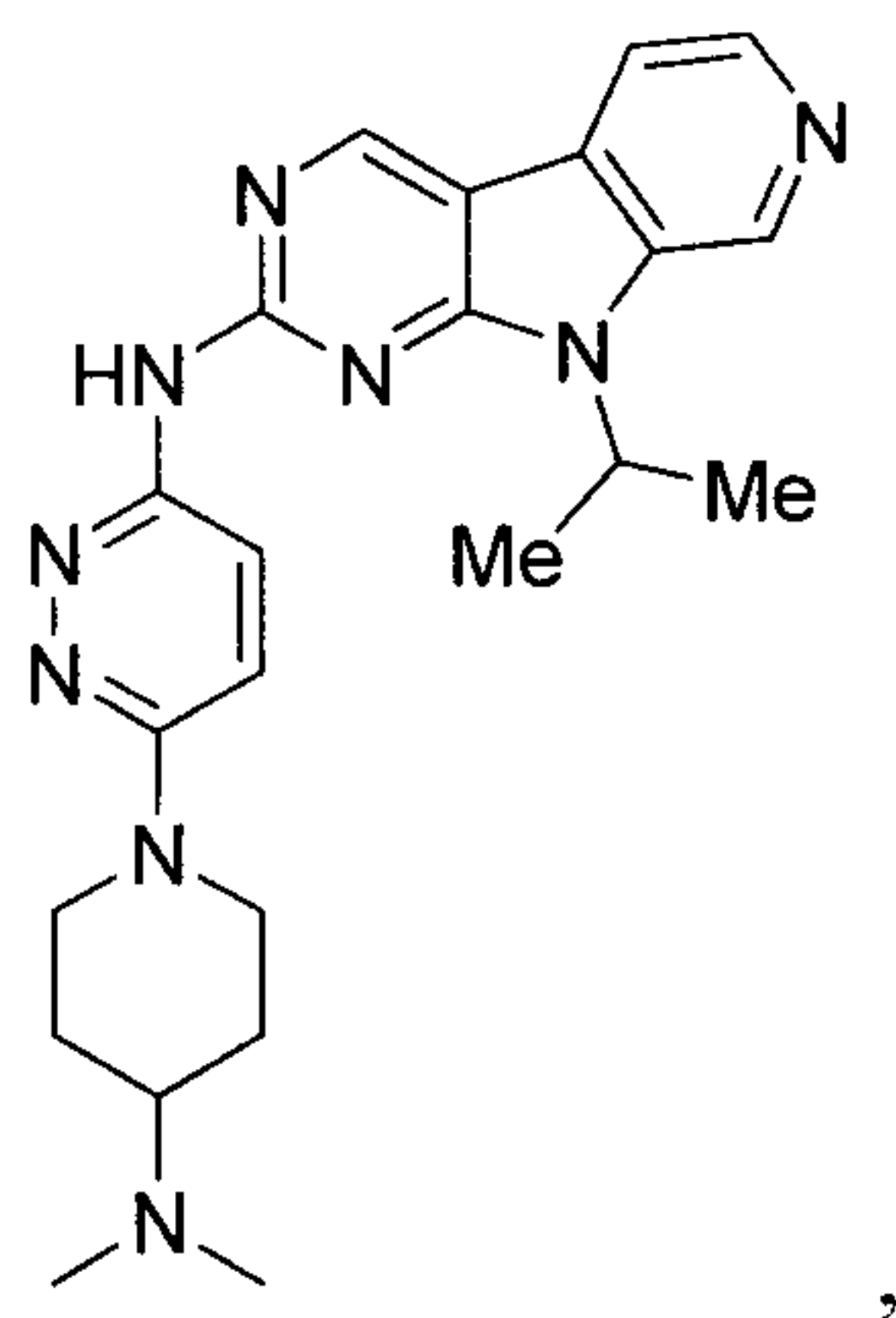
168. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

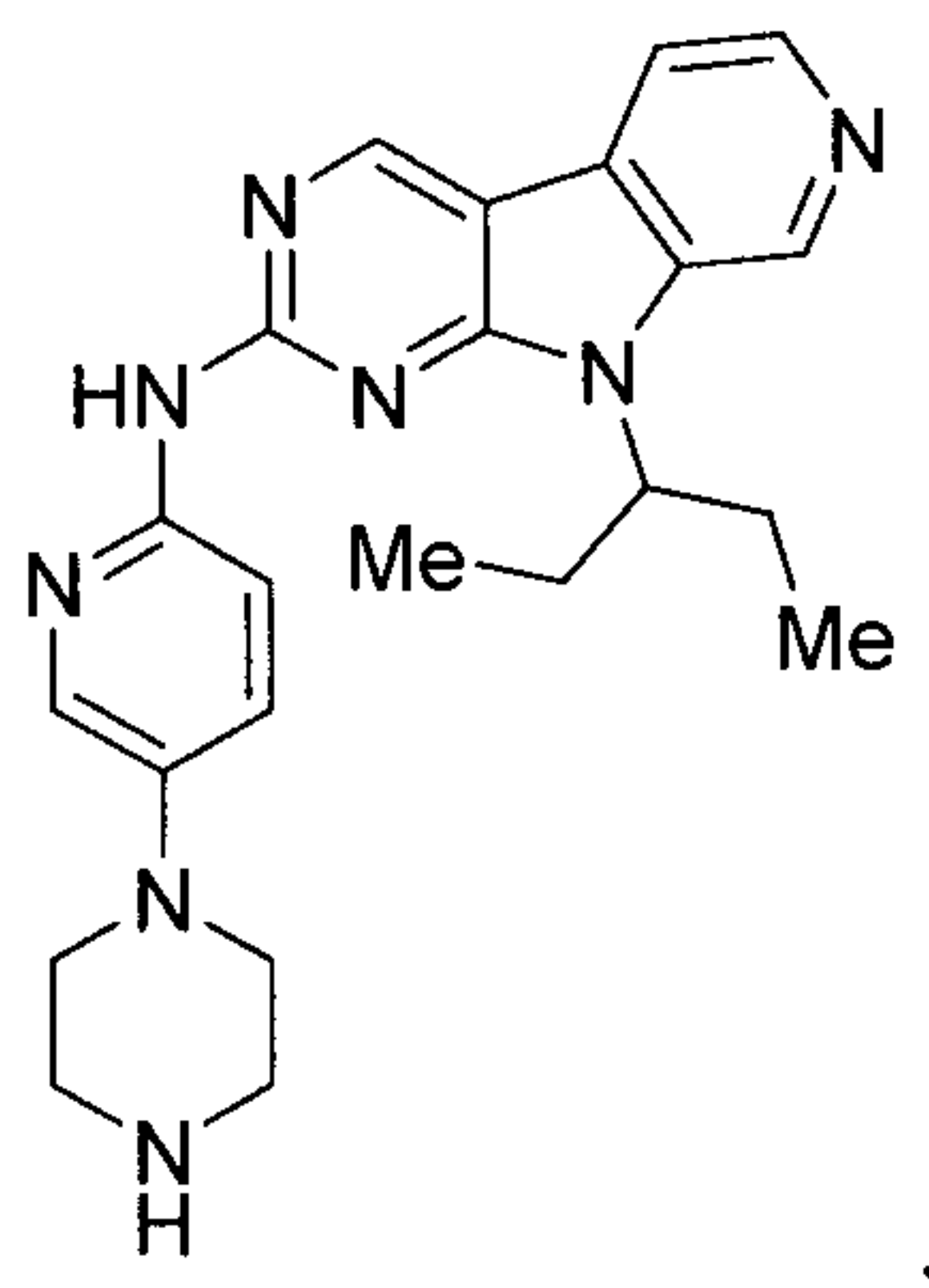


169. The compound of claim 1, wherein the compound is



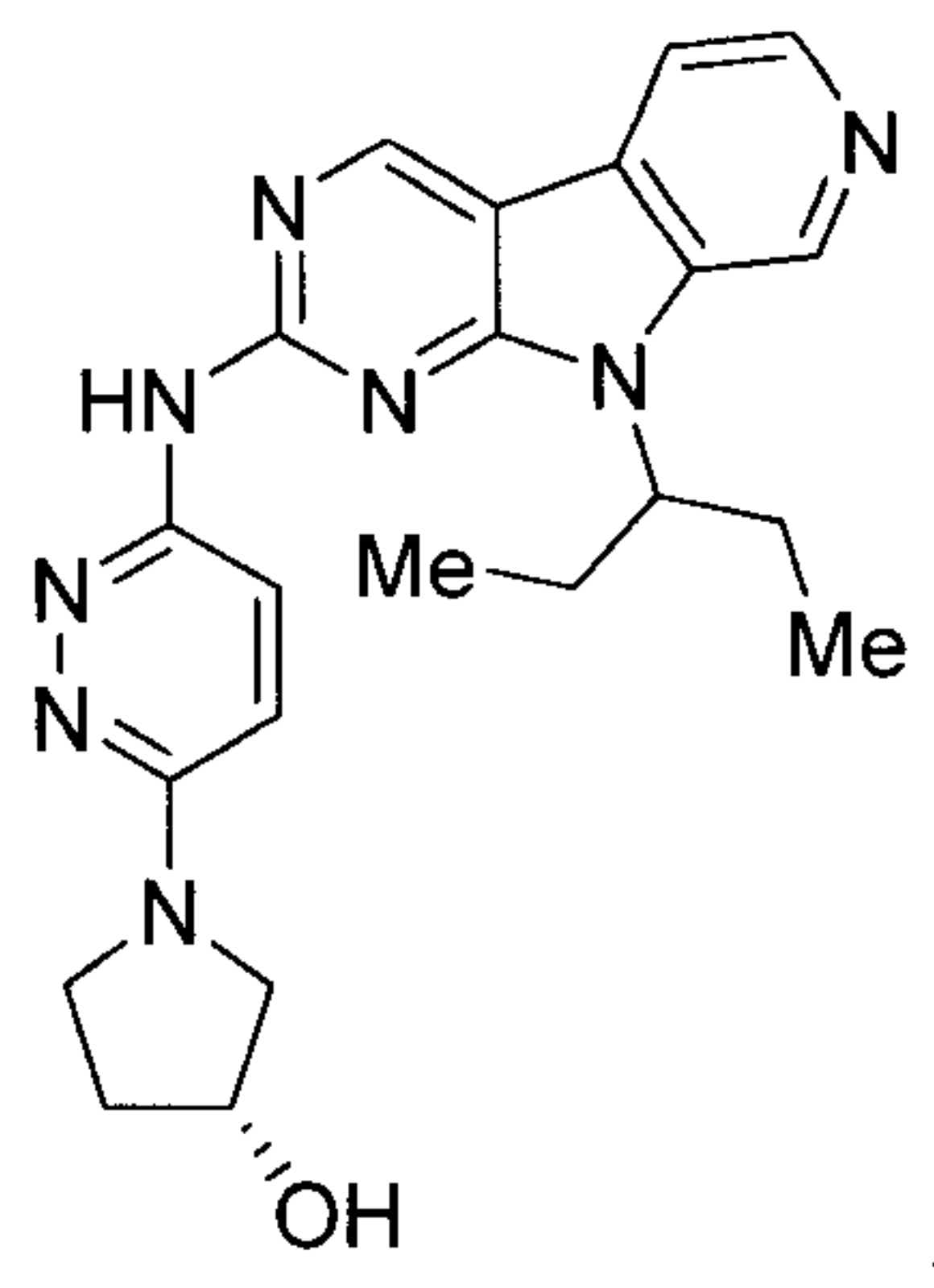
or a pharmaceutically acceptable salt thereof.

170. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

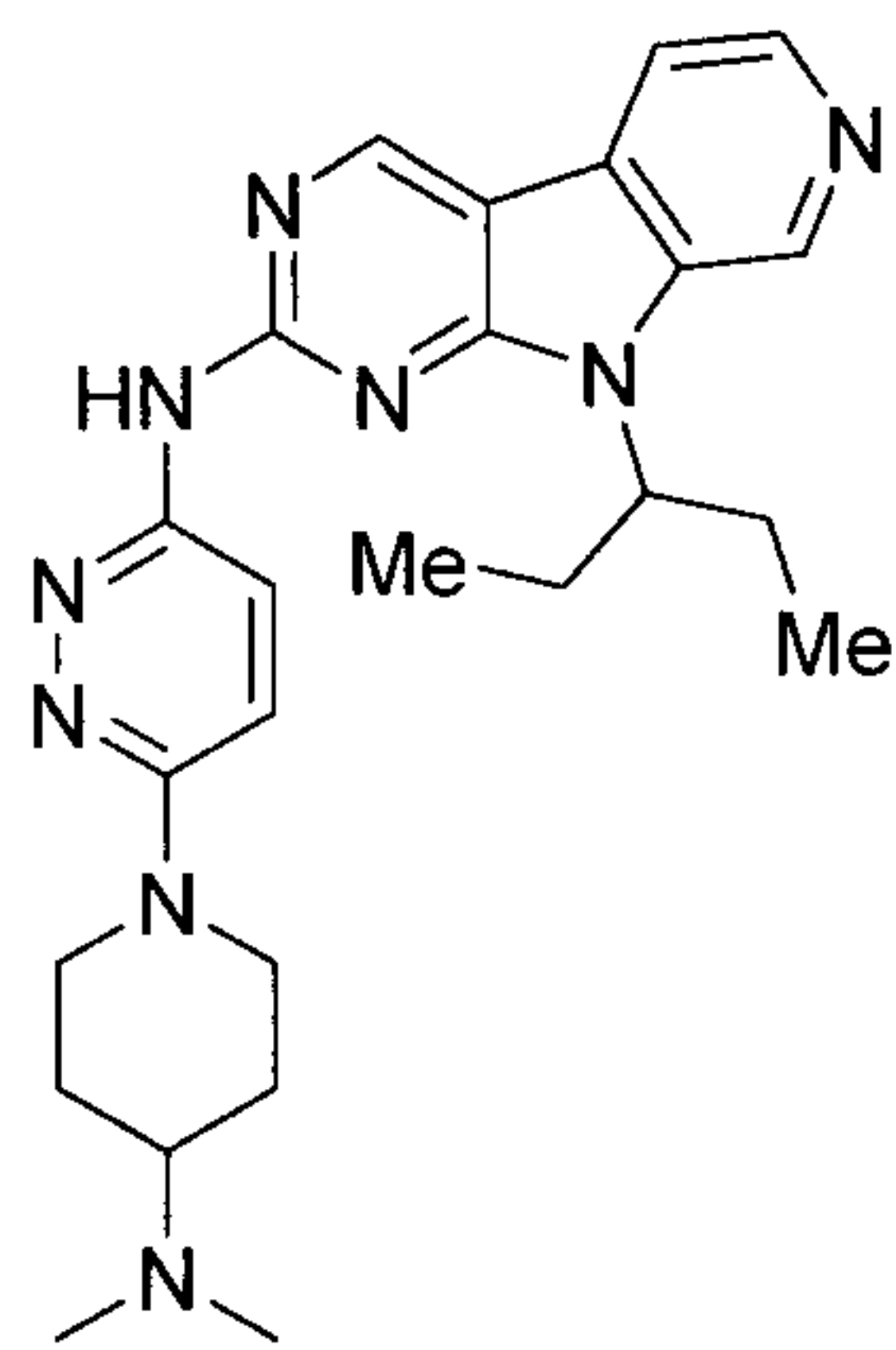
171. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

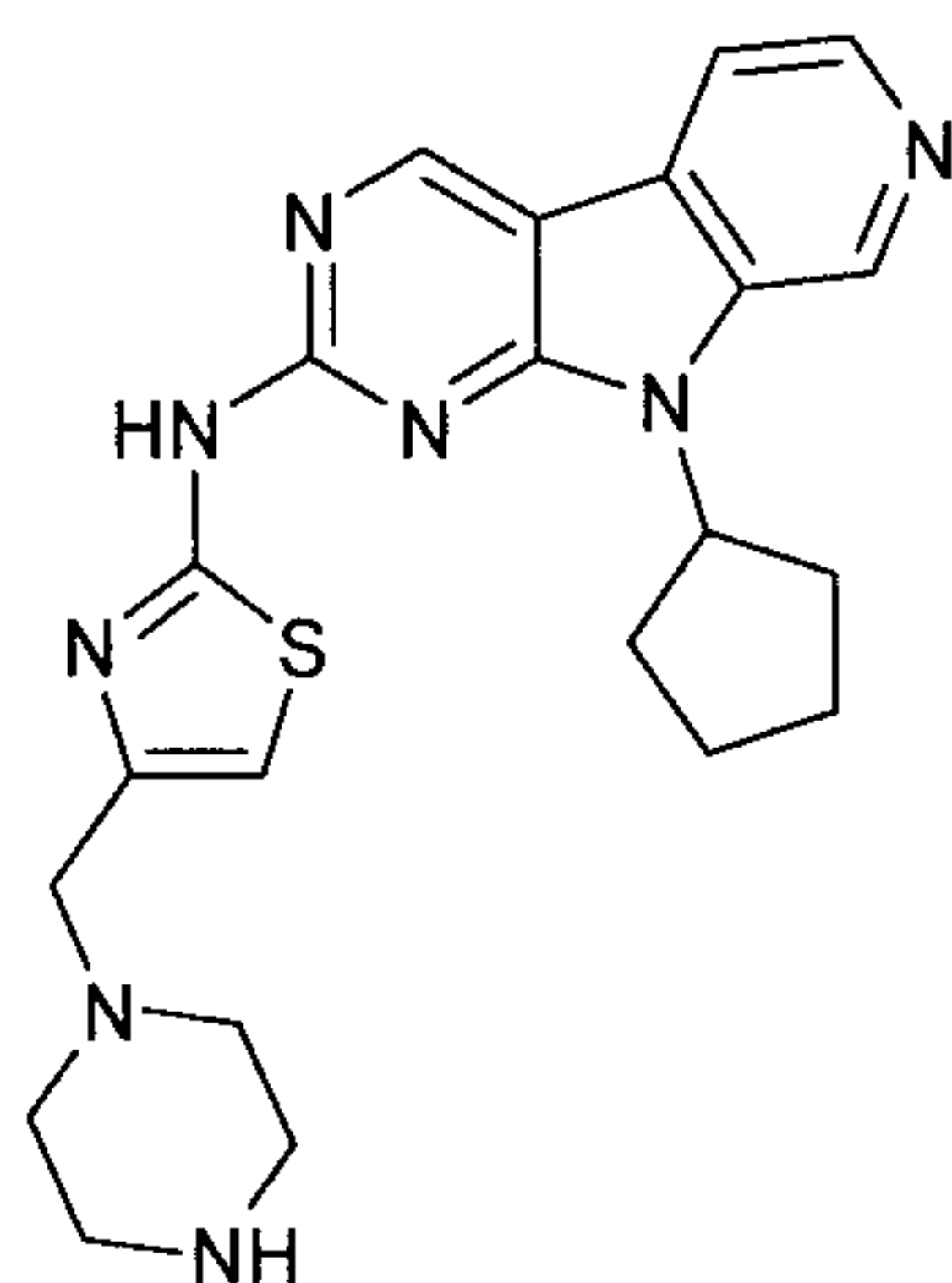


172. The compound of claim 1, wherein the compound is



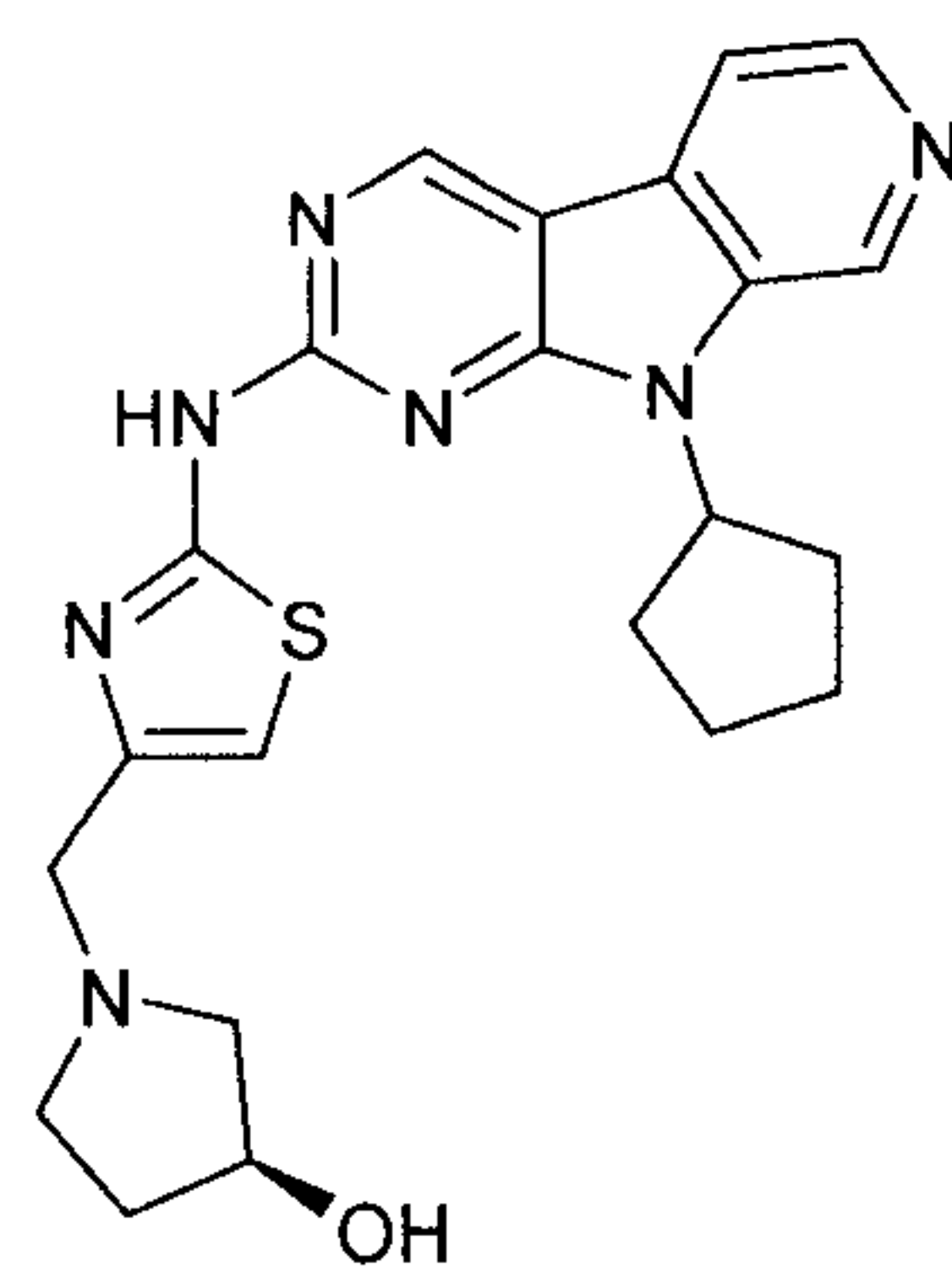
or a pharmaceutically acceptable salt thereof.

173. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

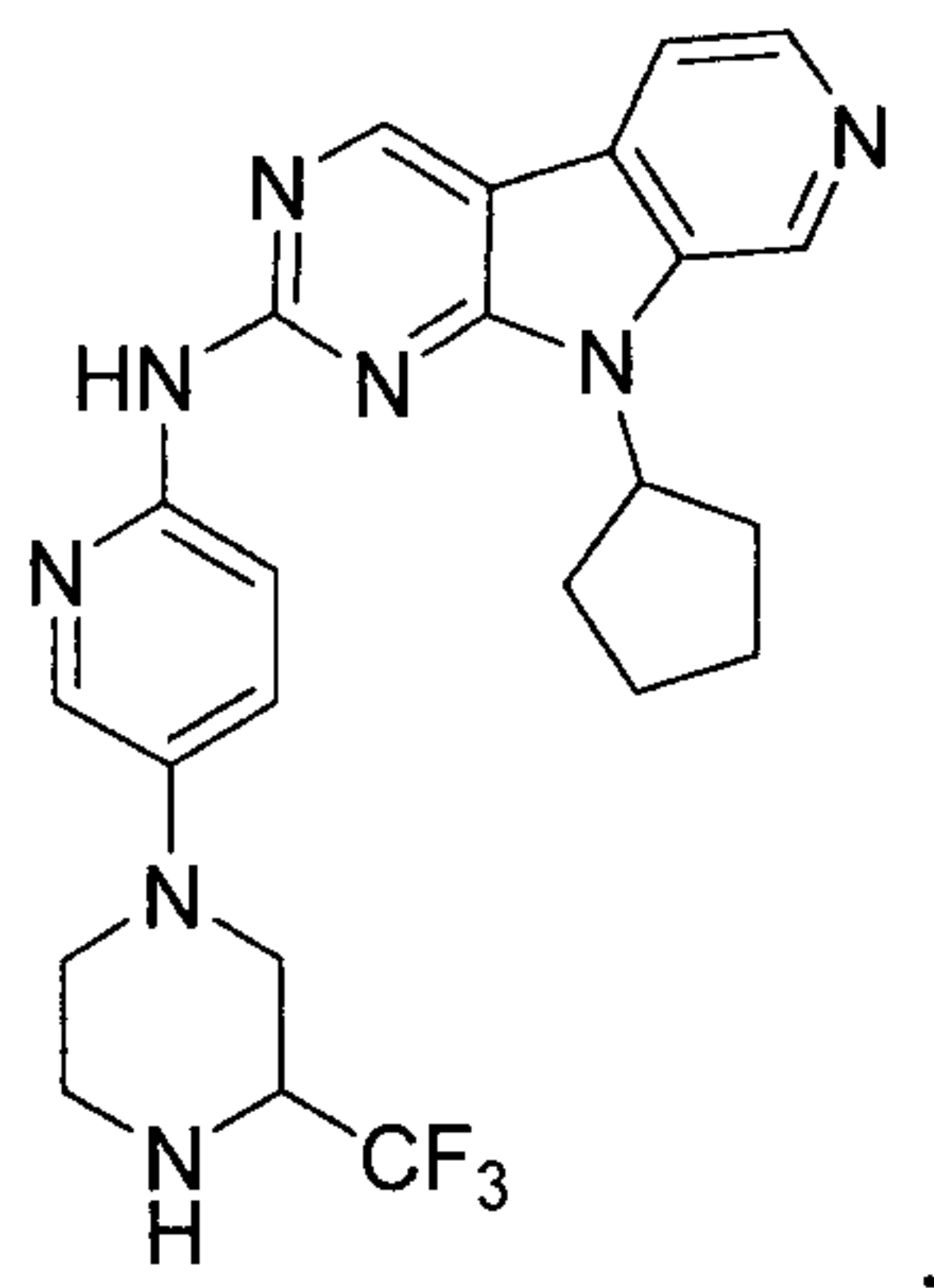
174. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

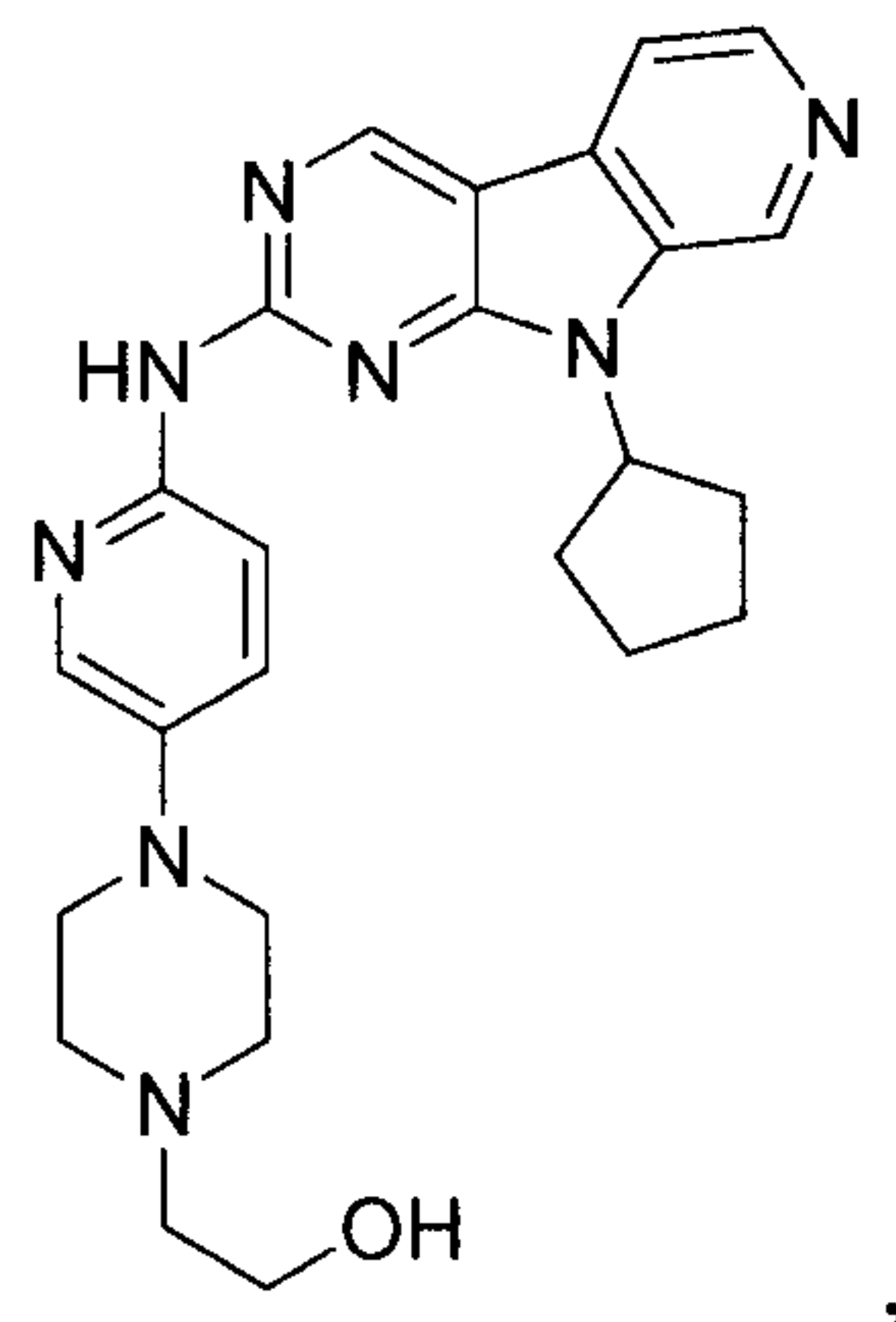


175. The compound of claim 1, wherein the compound is



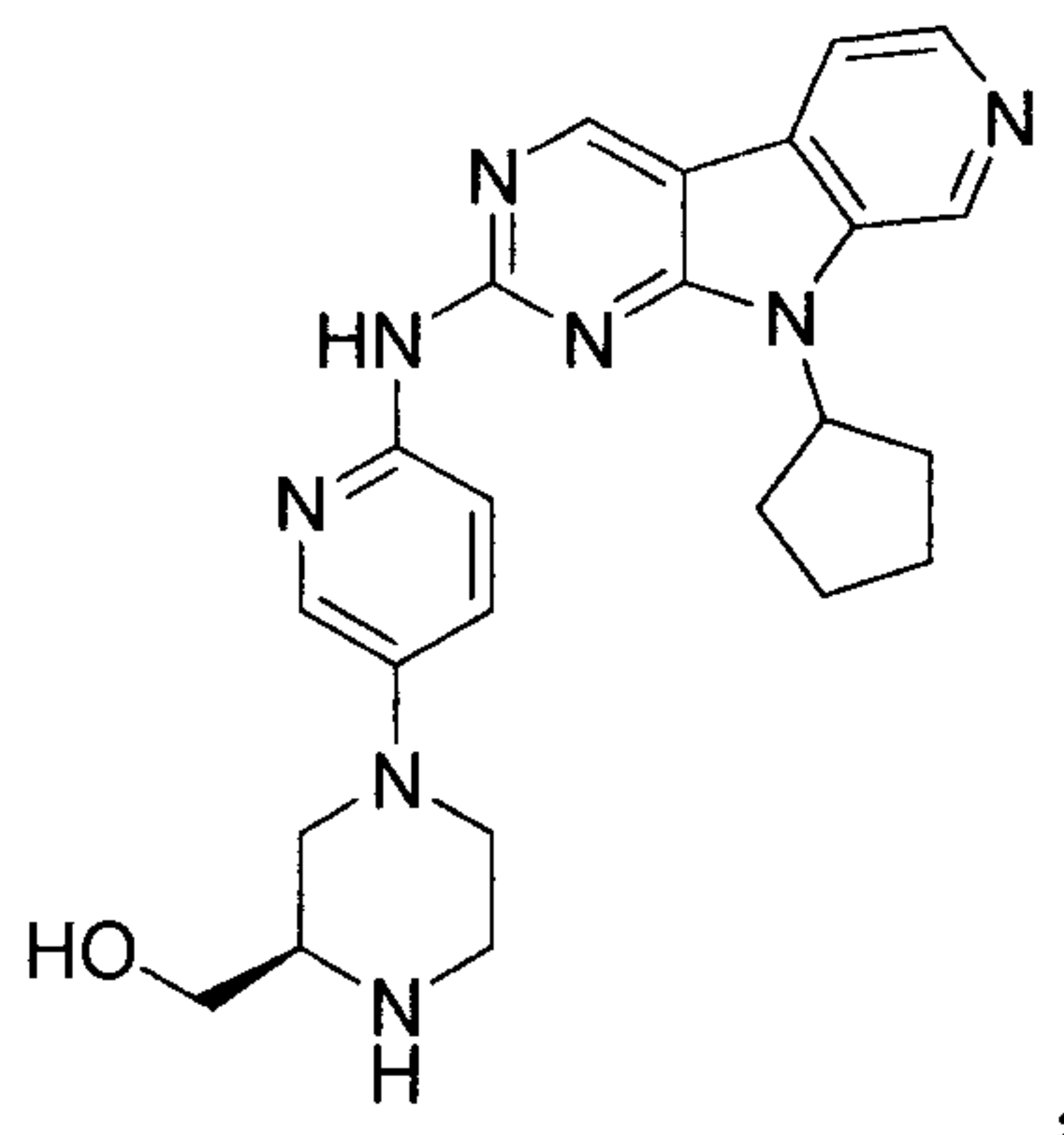
or a pharmaceutically acceptable salt thereof.

176. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

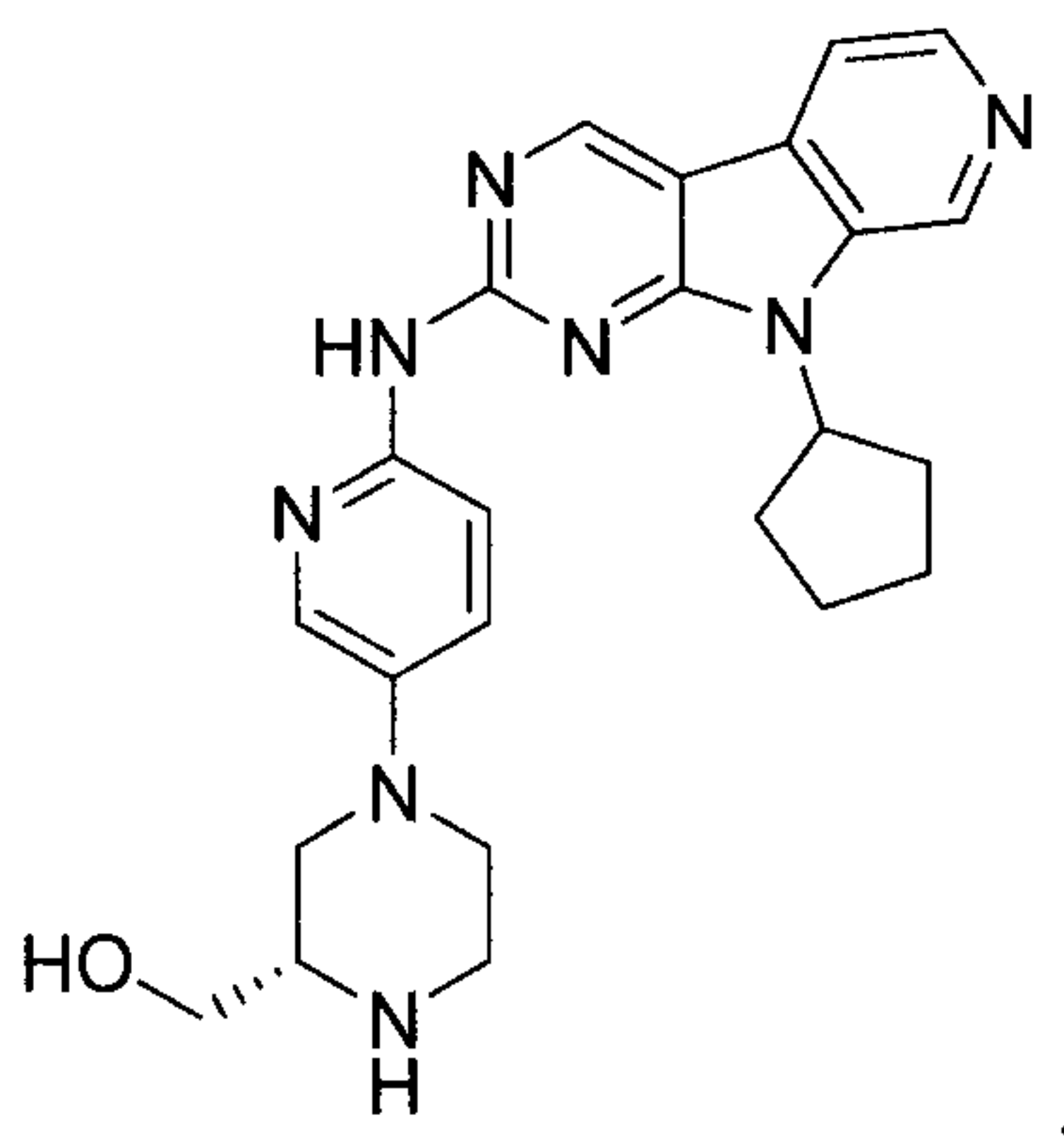
177. The compound of claim 1, wherein the compound is





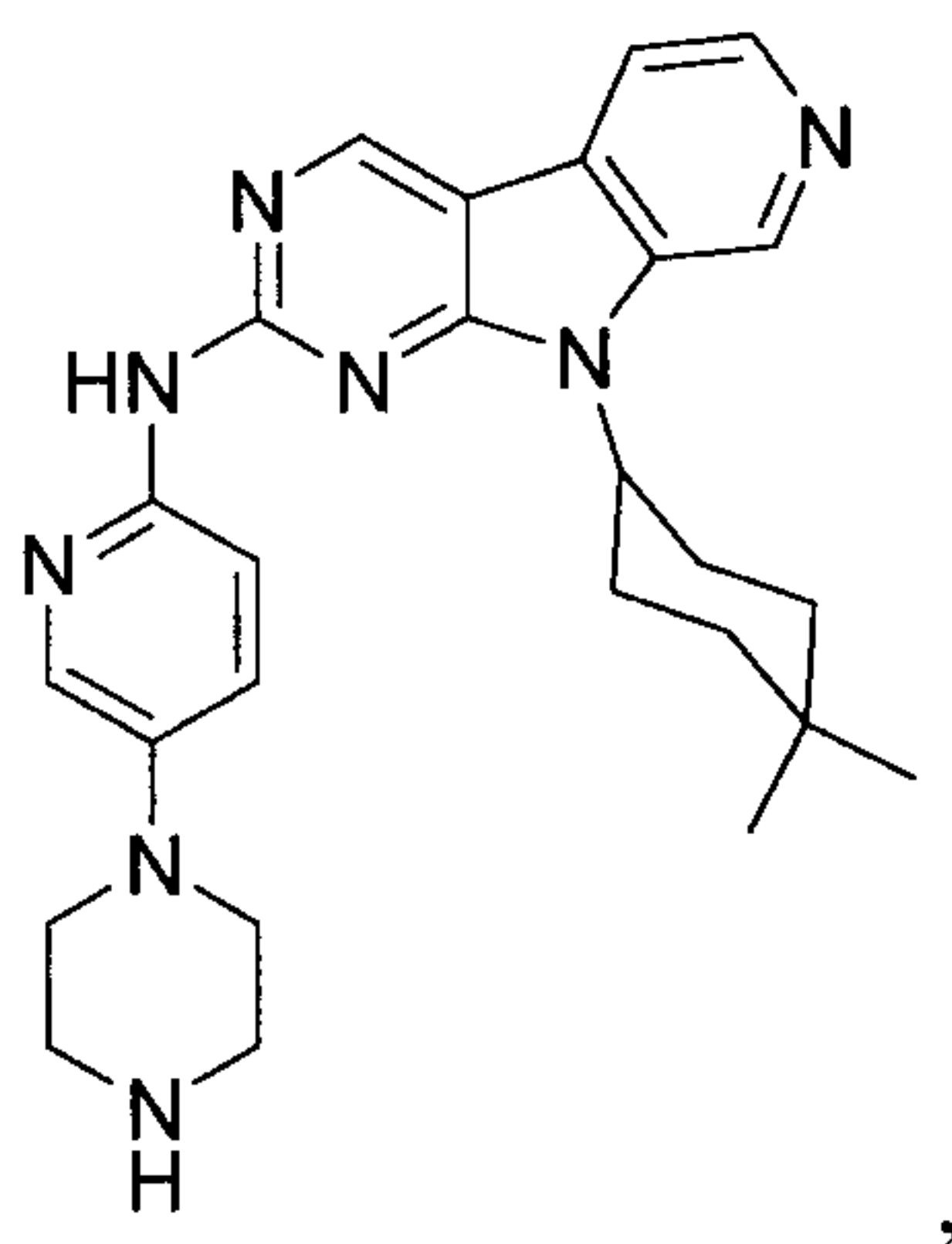
or a pharmaceutically acceptable salt thereof.

178. The compound of claim 1, wherein the compound is



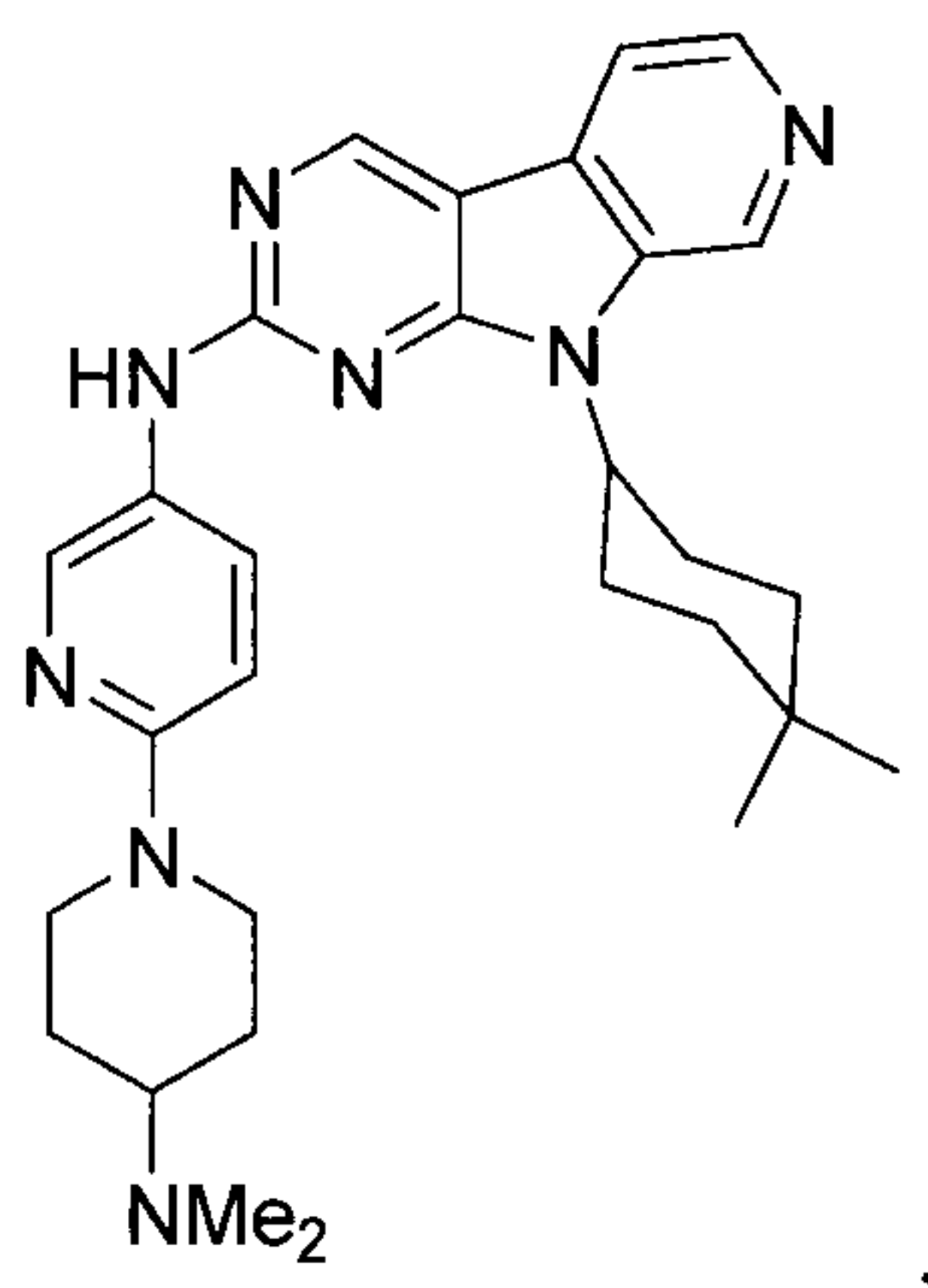
or a pharmaceutically acceptable salt thereof.

179. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

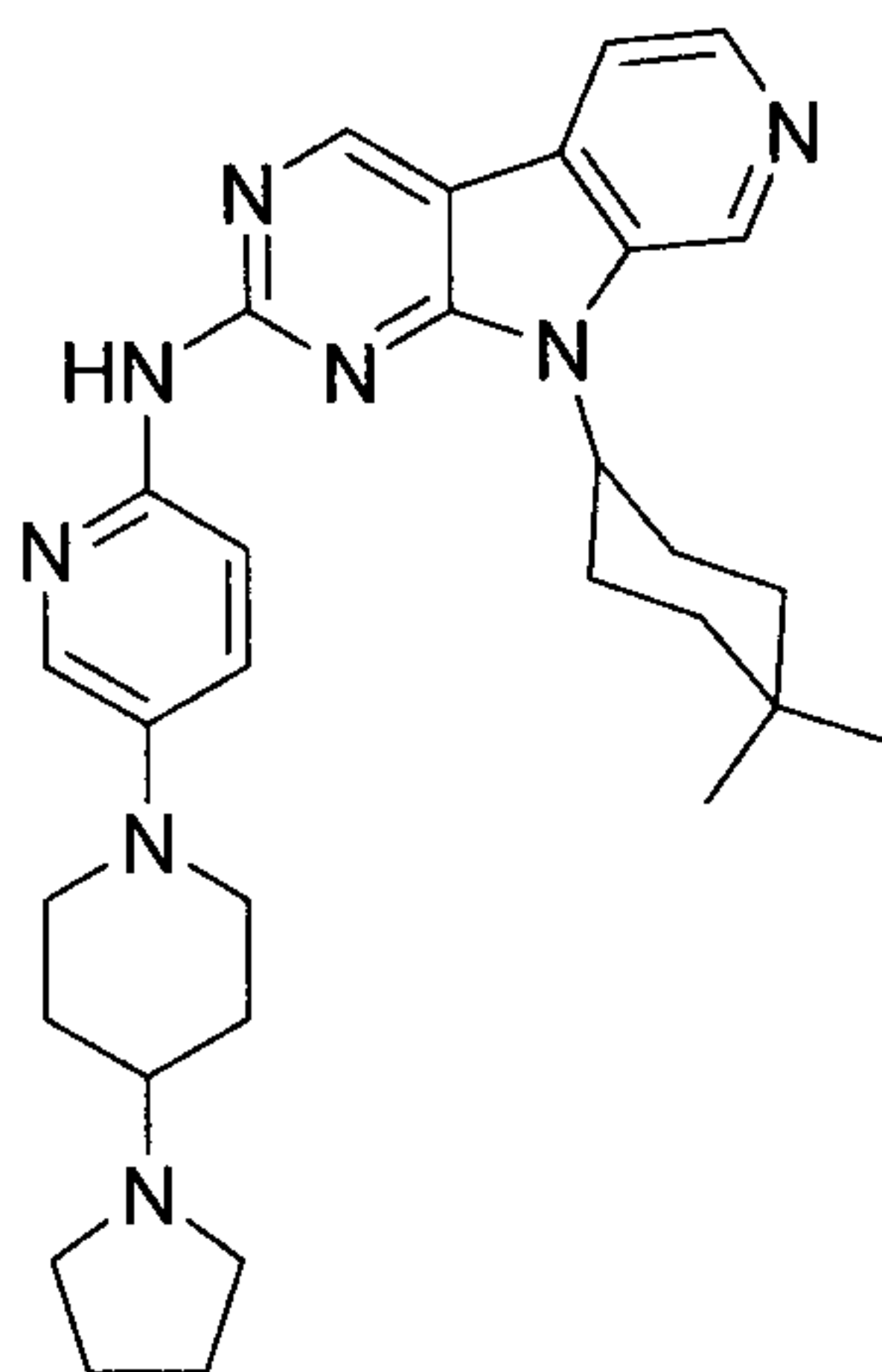
180. The compound of claim 1, wherein the compound is





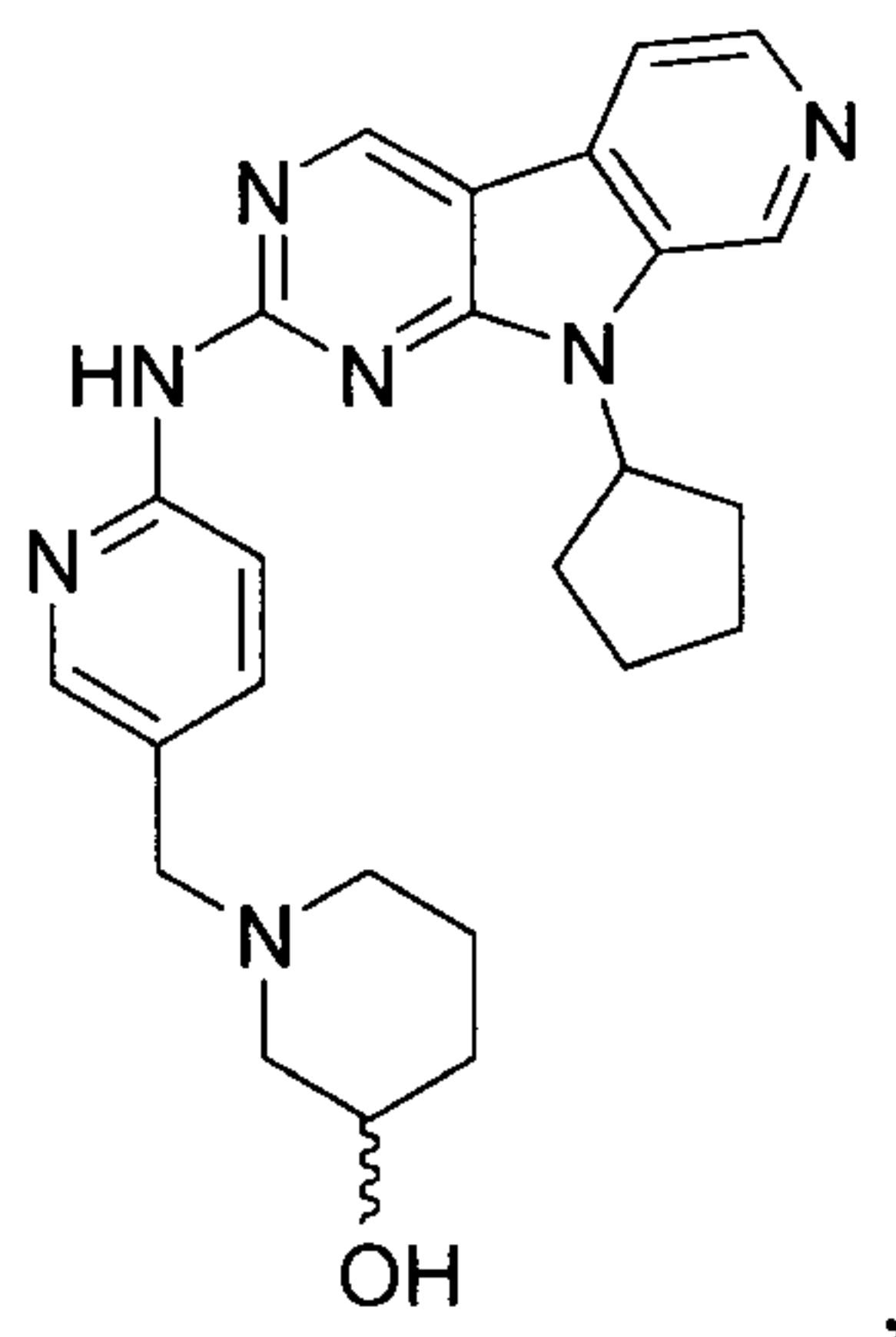
or a pharmaceutically acceptable salt thereof.

181. The compound of claim 1, wherein the compound is



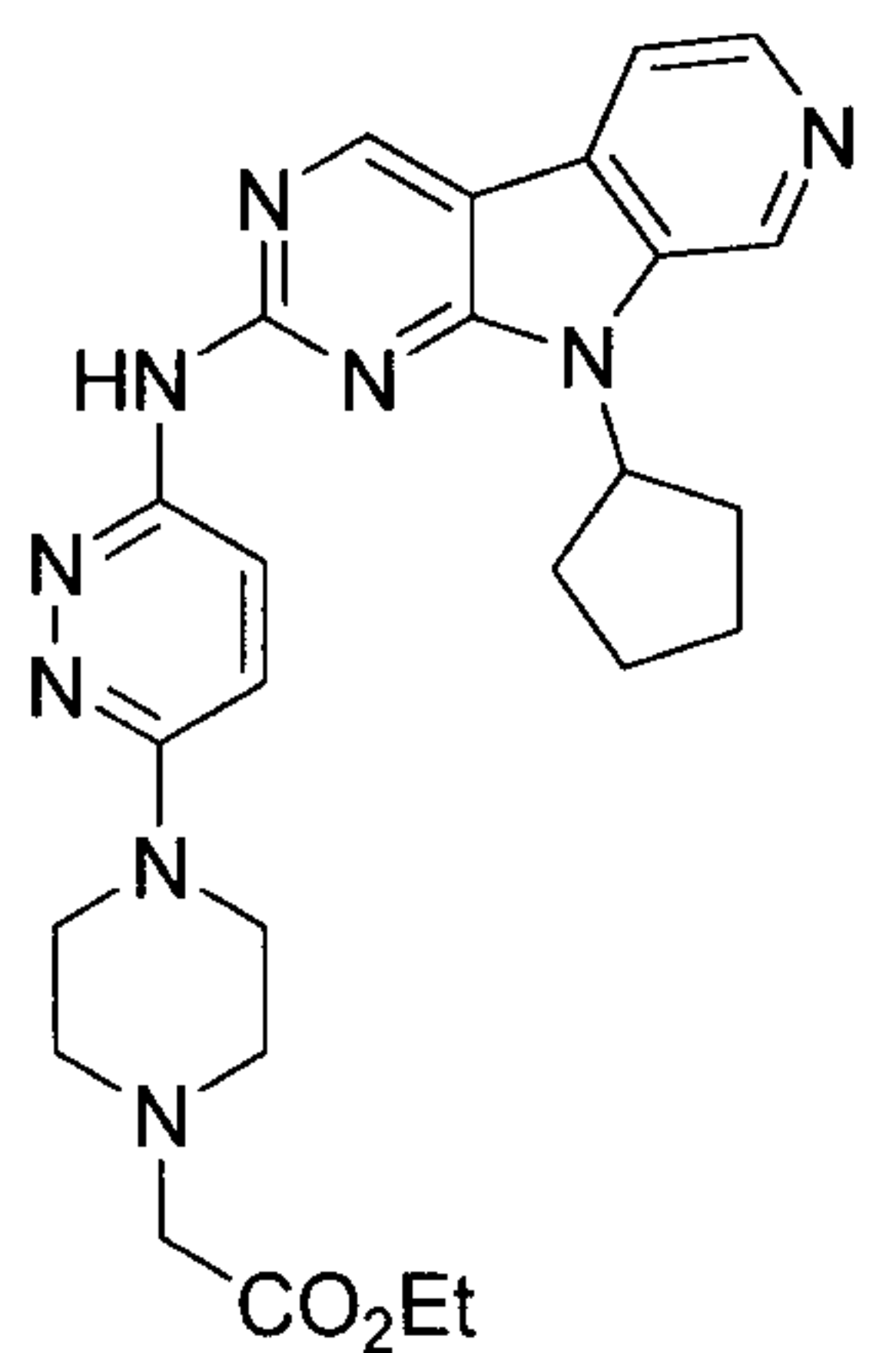


183. The compound of claim 1, wherein the compound is



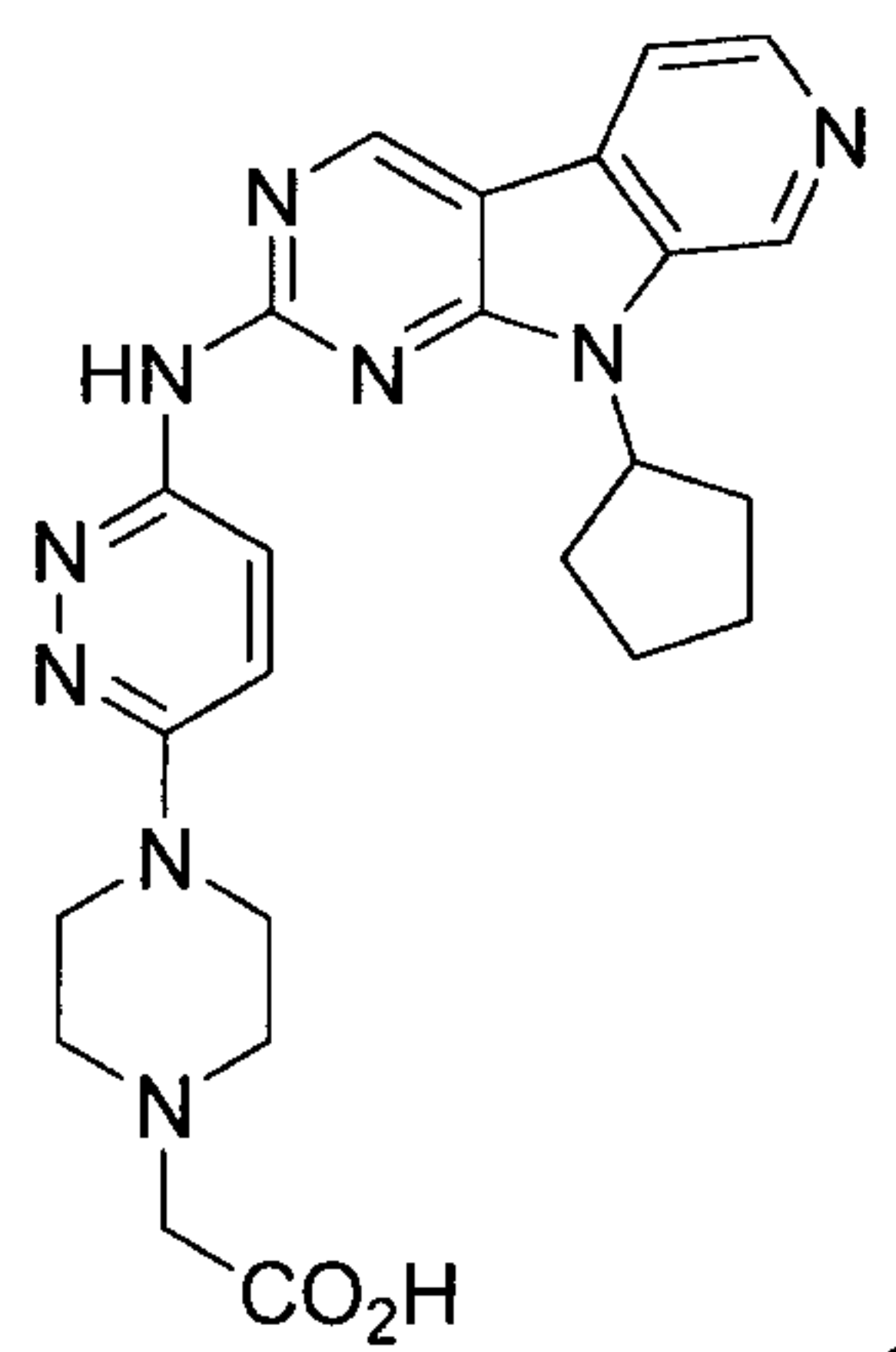
or a pharmaceutically acceptable salt thereof.

184. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

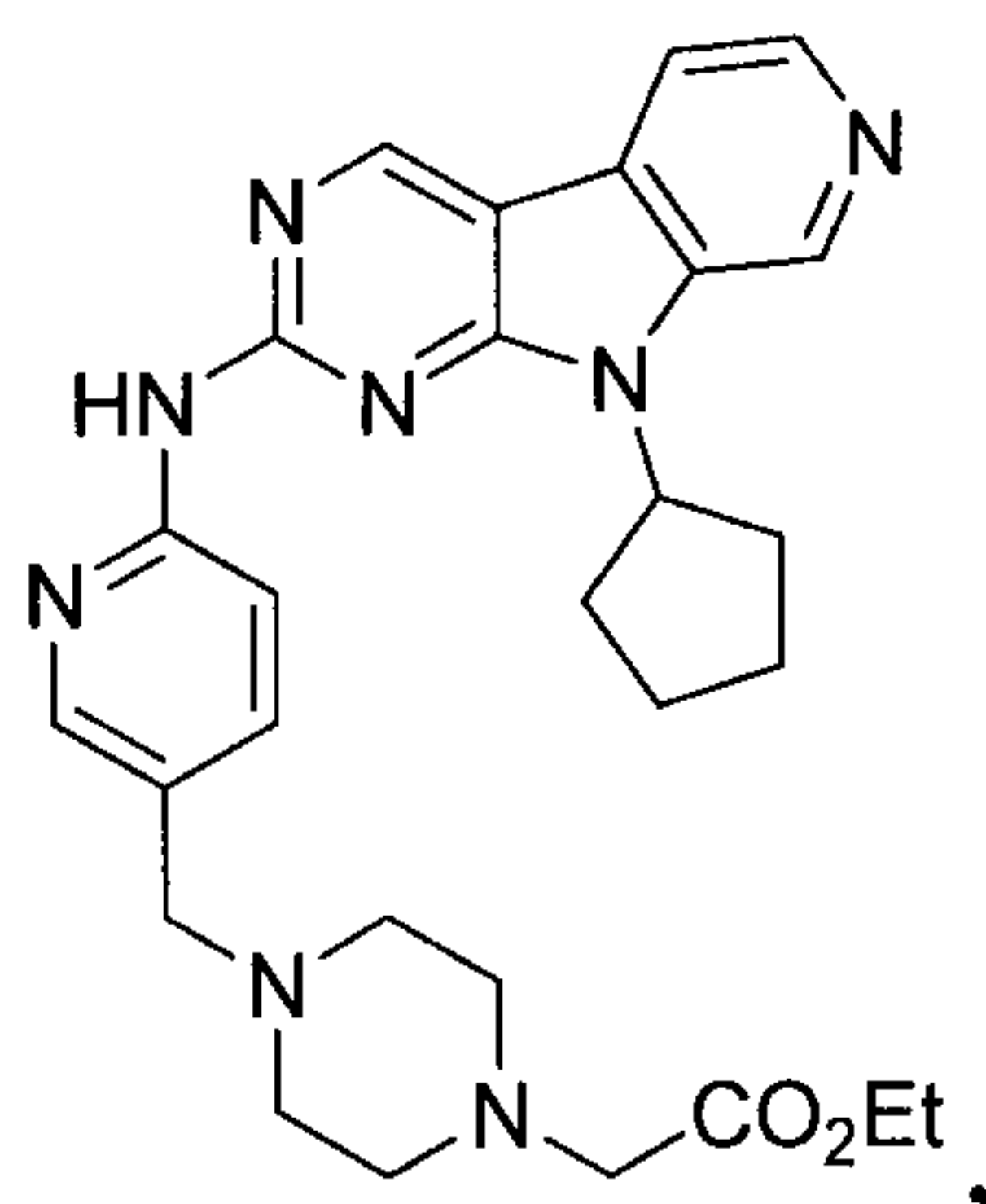
185. The compound of claim 1, wherein the compound is





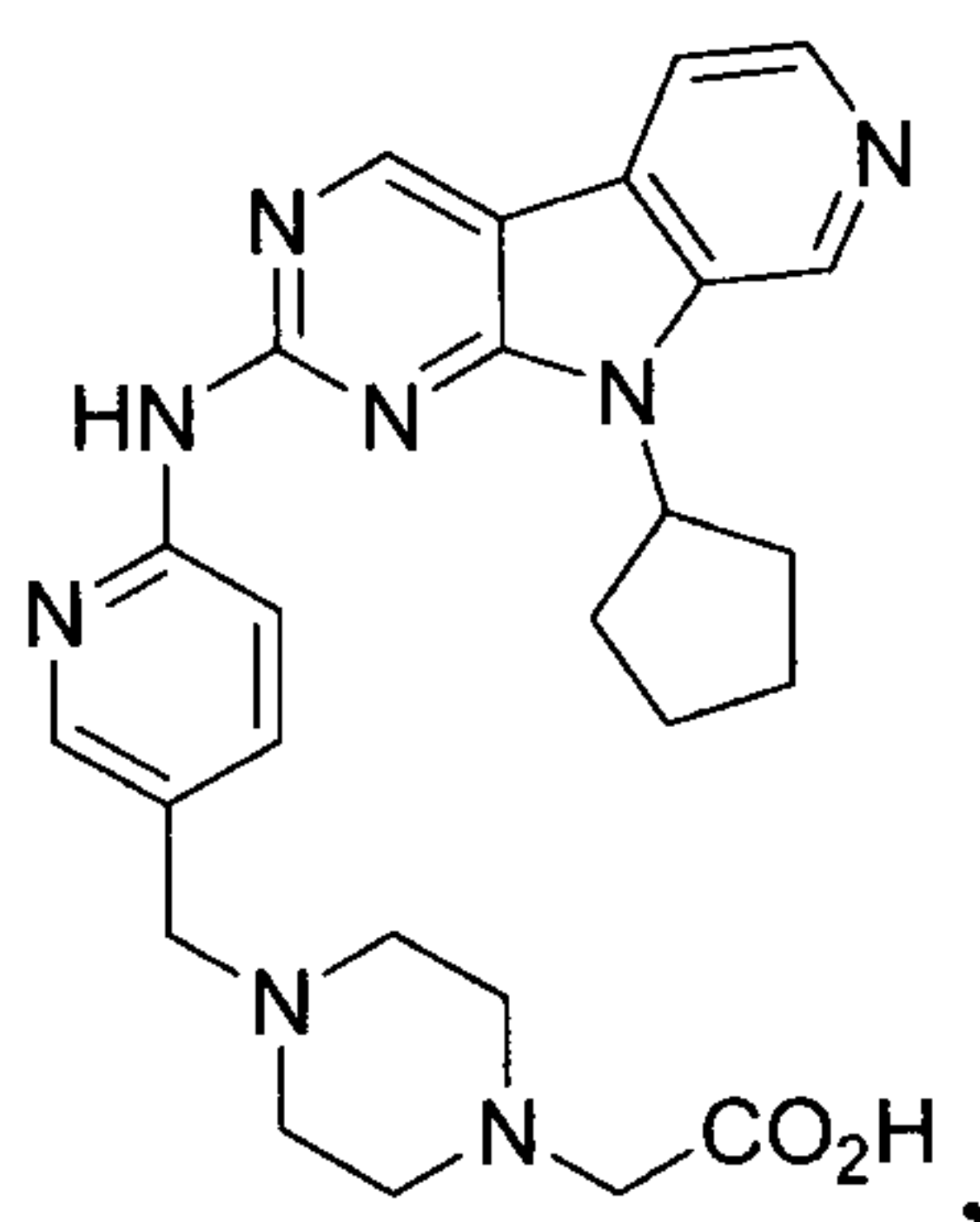
or a pharmaceutically acceptable salt thereof.

186. The compound of claim 1, wherein the compound is



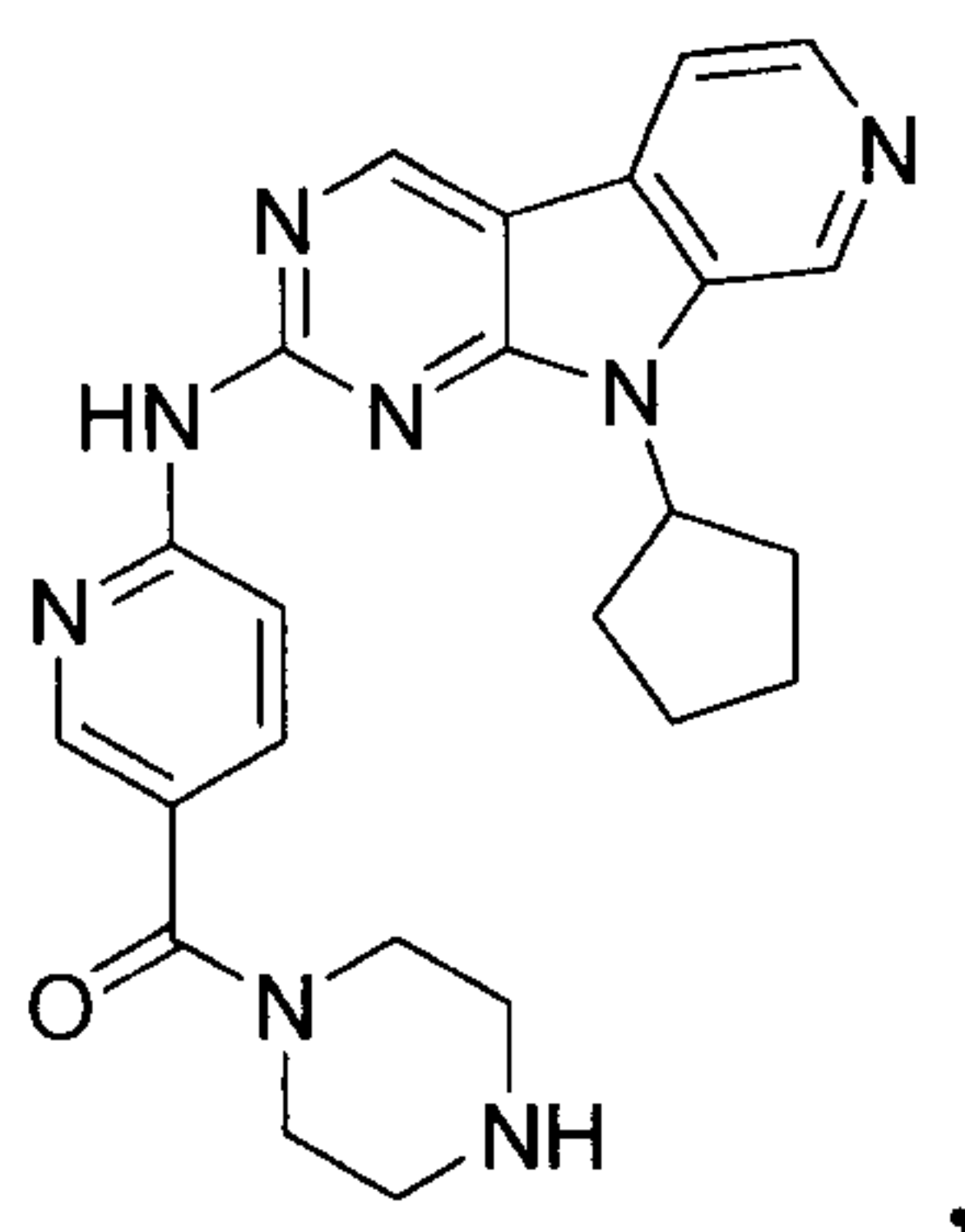
or a pharmaceutically acceptable salt thereof.

187. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

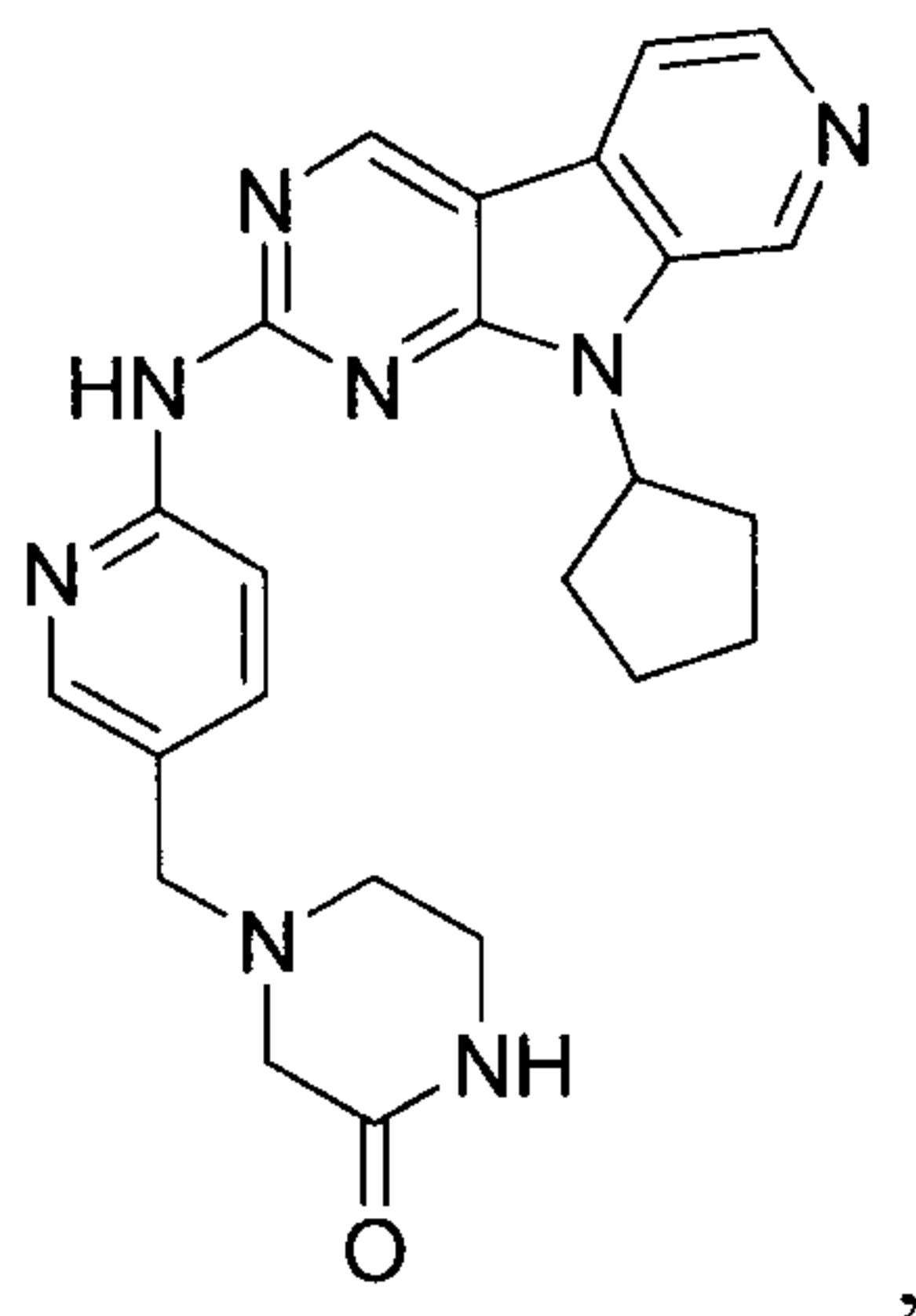
188. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

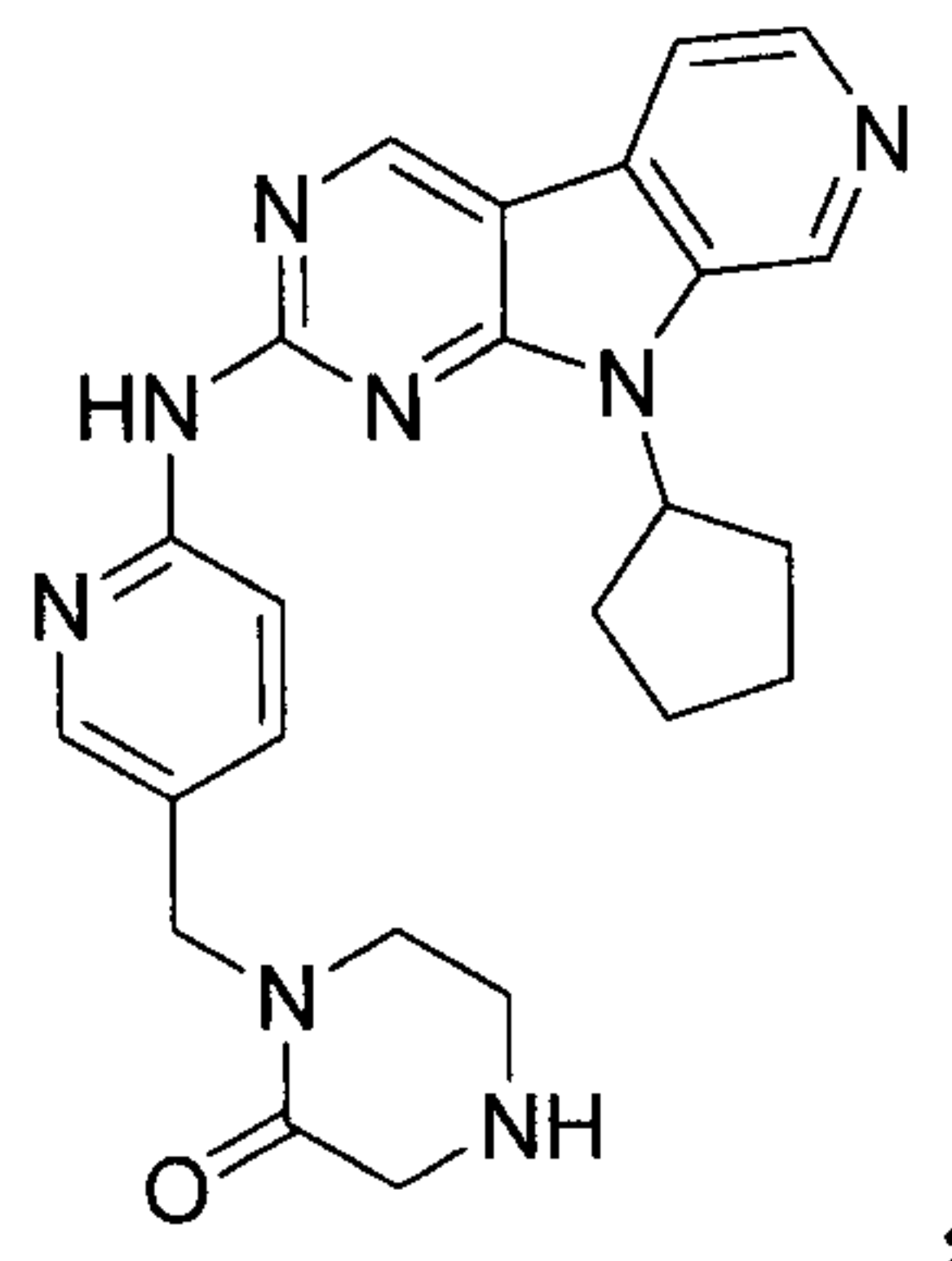


189. The compound of claim 1, wherein the compound is



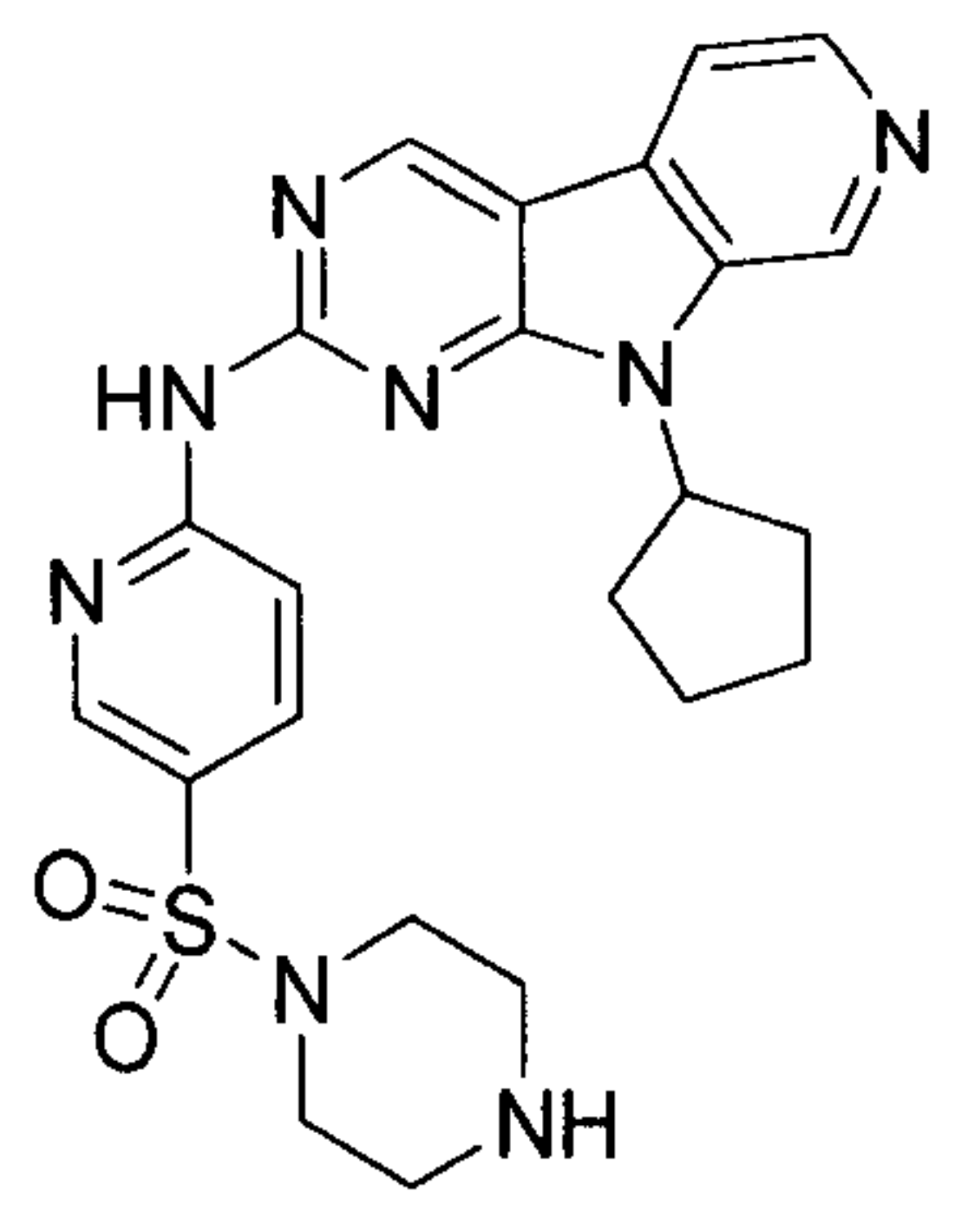
or a pharmaceutically acceptable salt thereof.

190. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

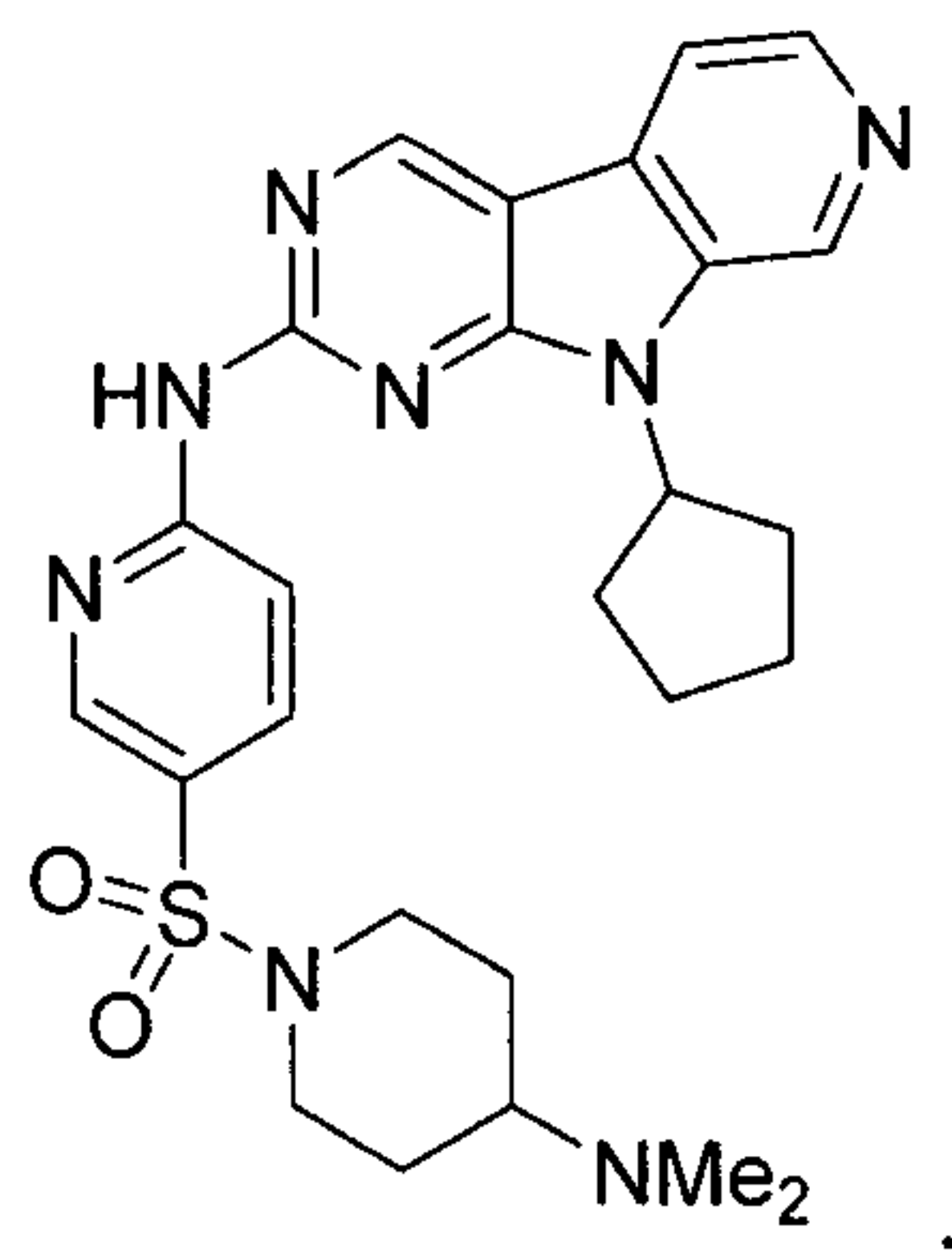
191. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

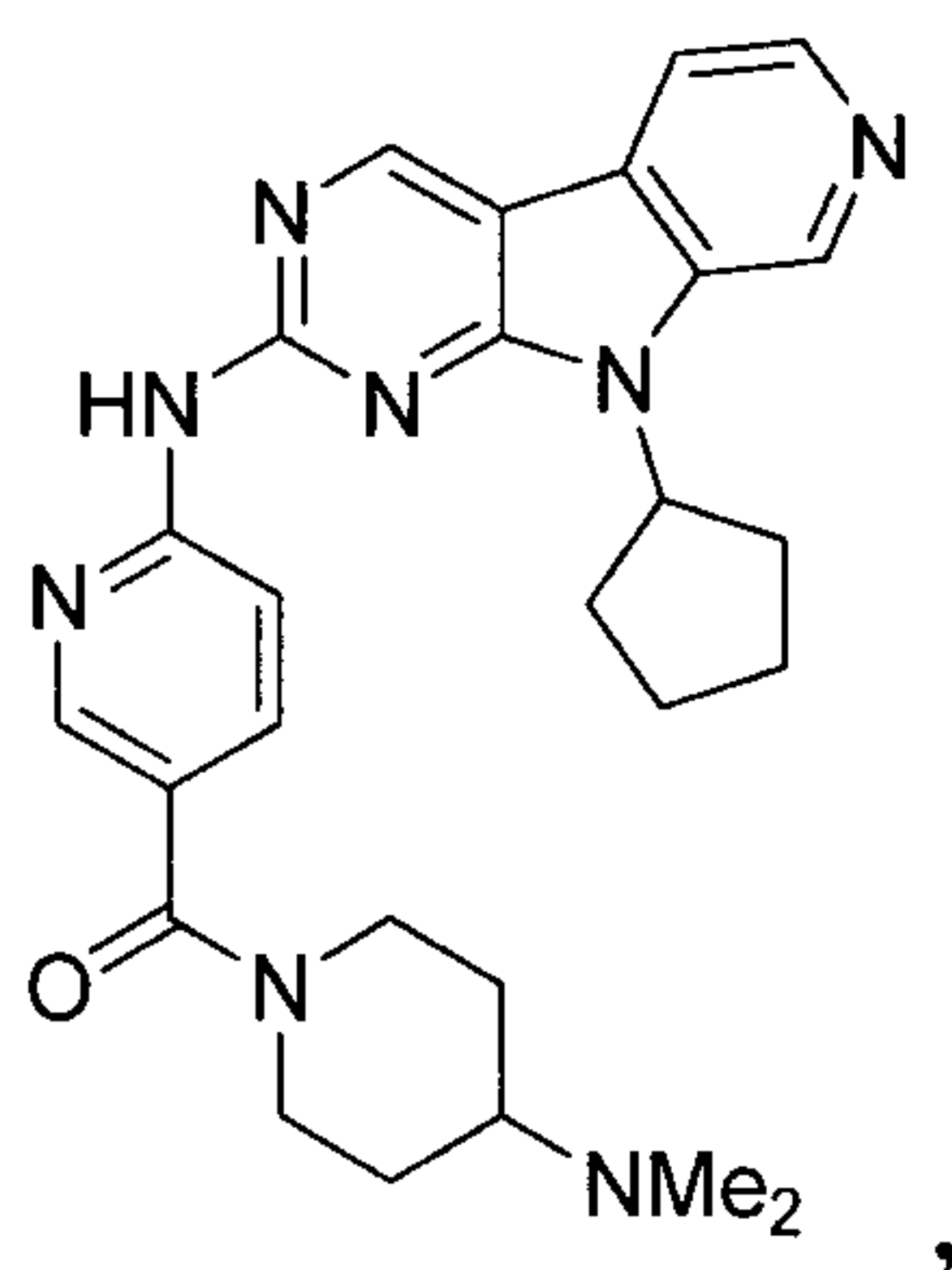


192. The compound of claim 1, wherein the compound is



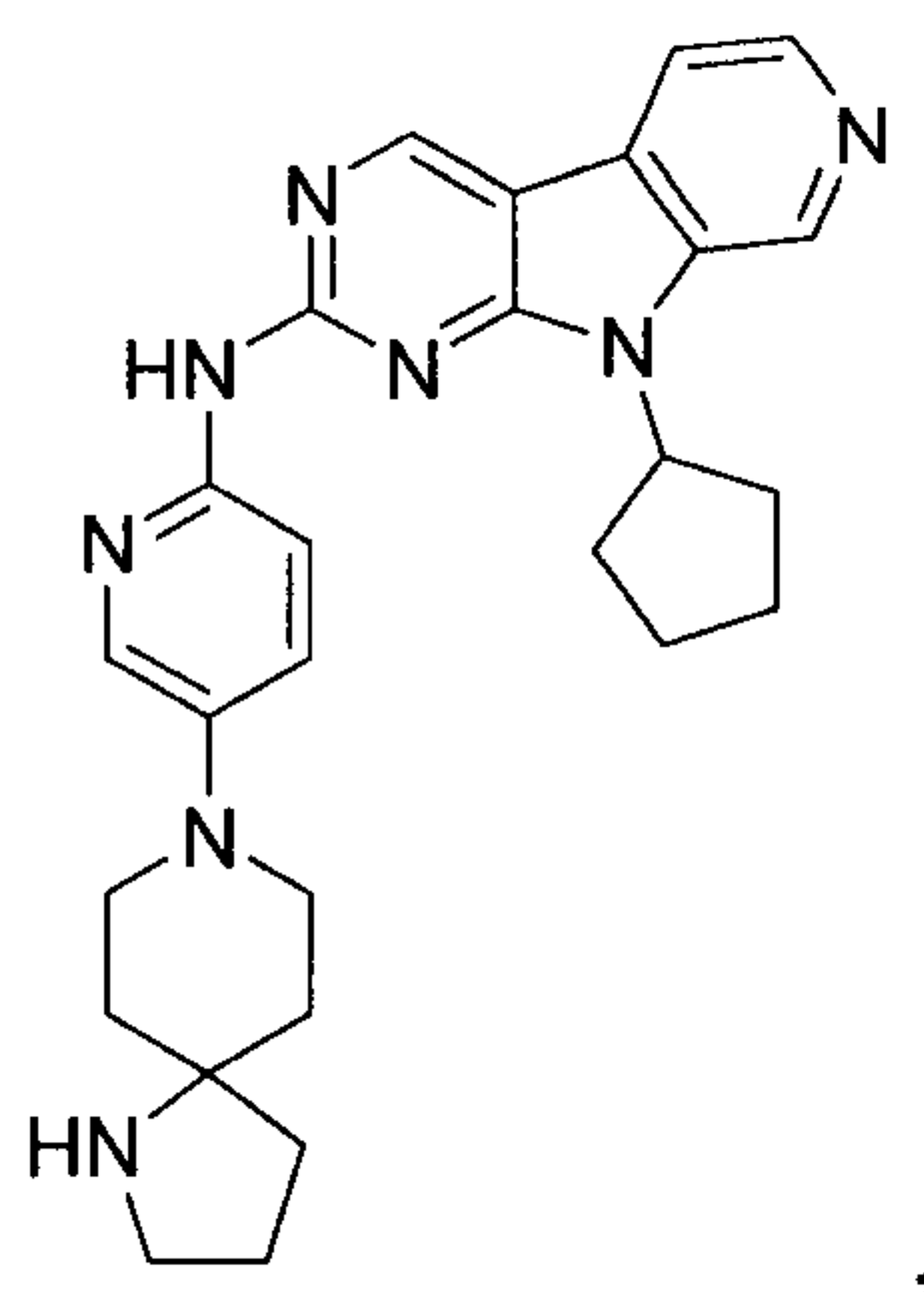
or a pharmaceutically acceptable salt thereof.

193. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

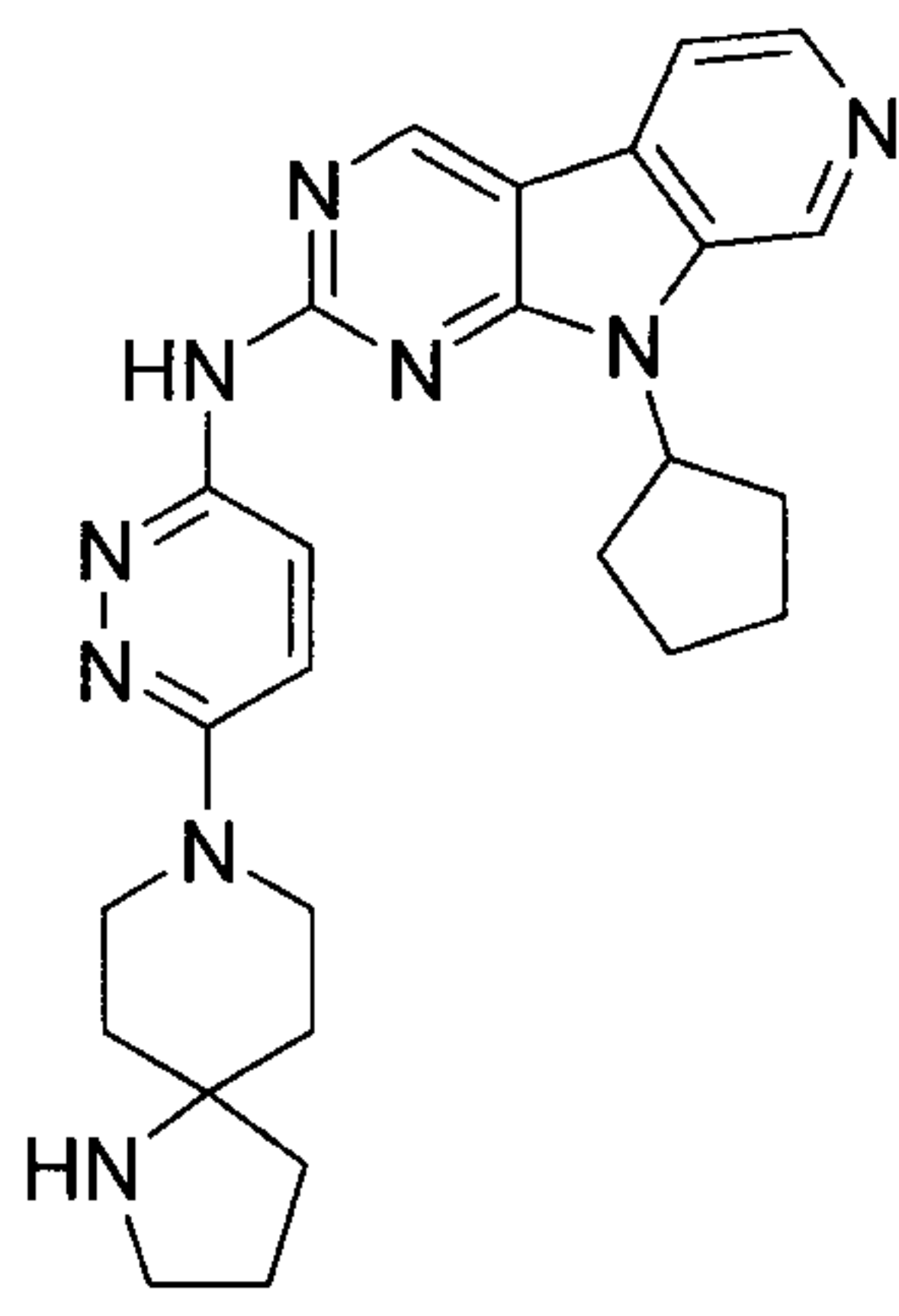
194. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

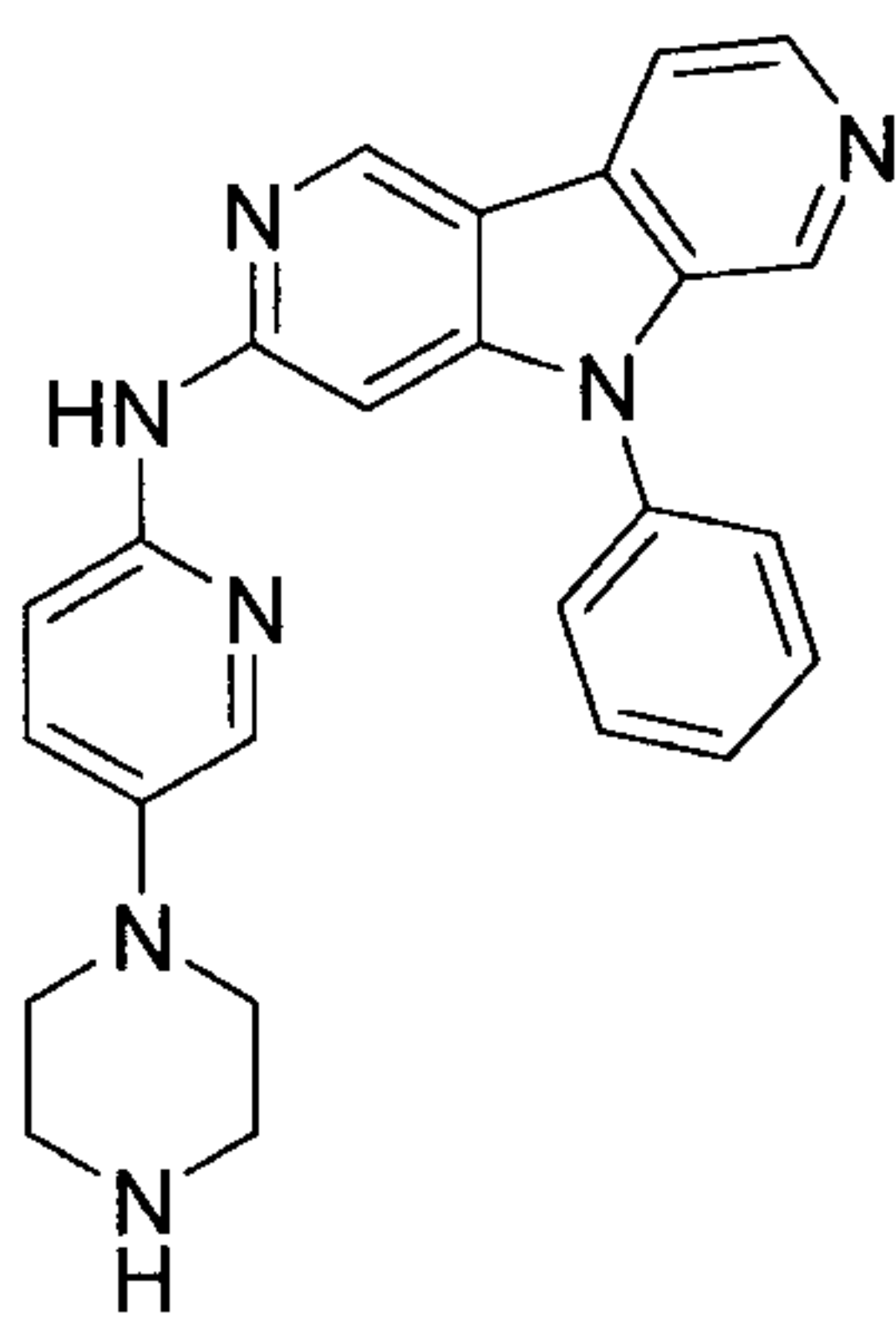


195. The compound of claim 1, wherein the compound is



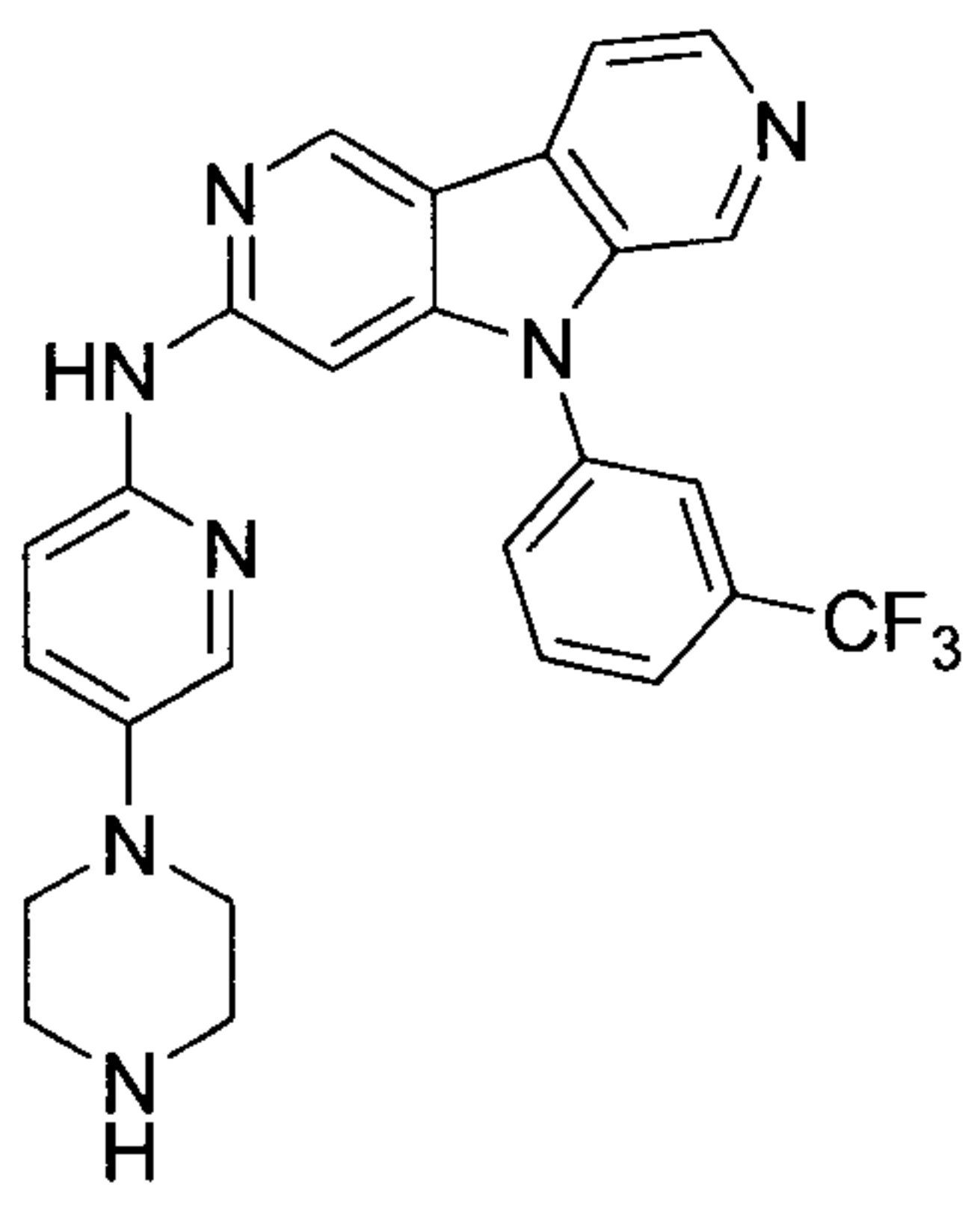
or a pharmaceutically acceptable salt thereof.

196. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

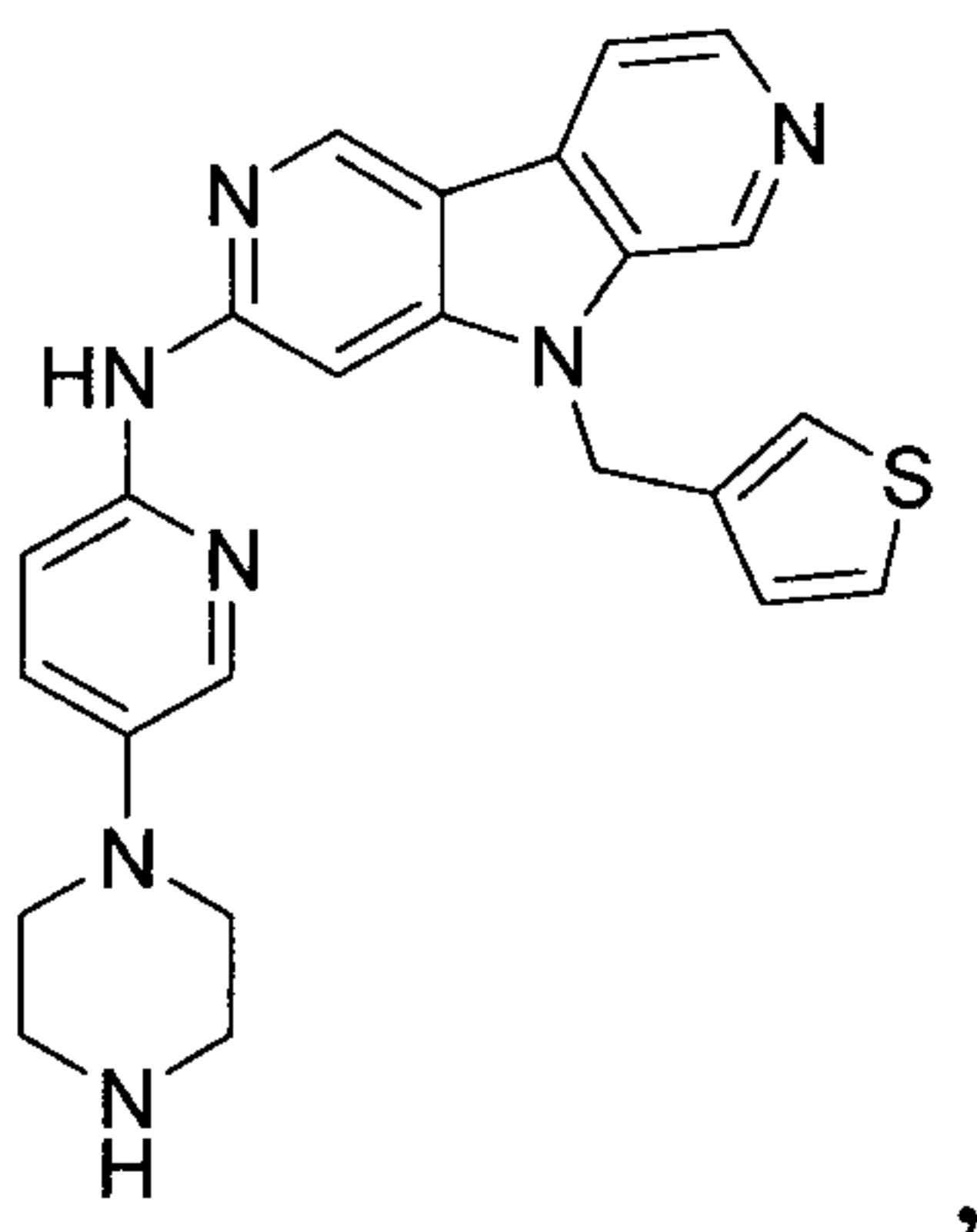
197. The compound of claim 1, wherein the compound is





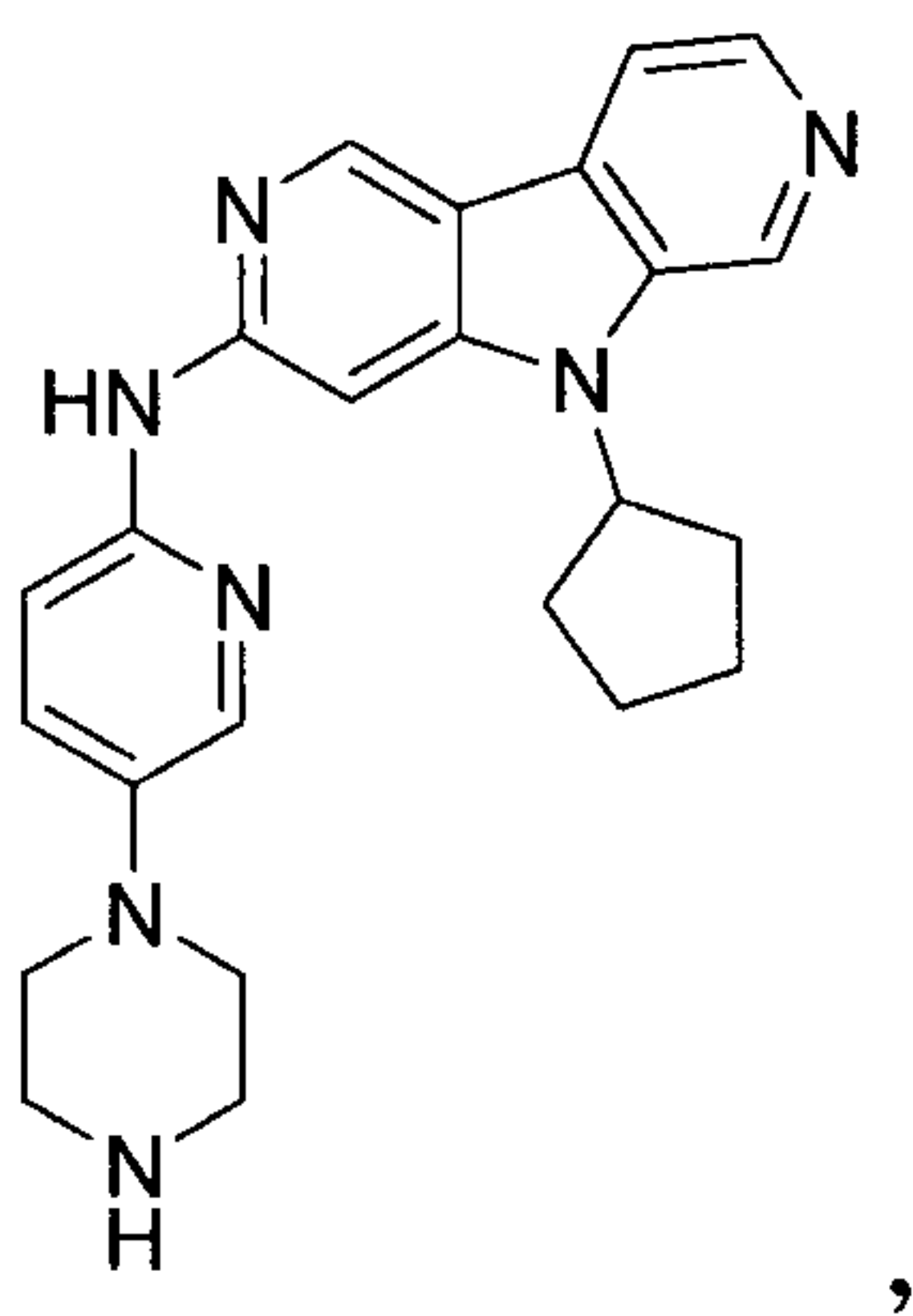
or a pharmaceutically acceptable salt thereof.

198. The compound of claim 1, wherein the compound is



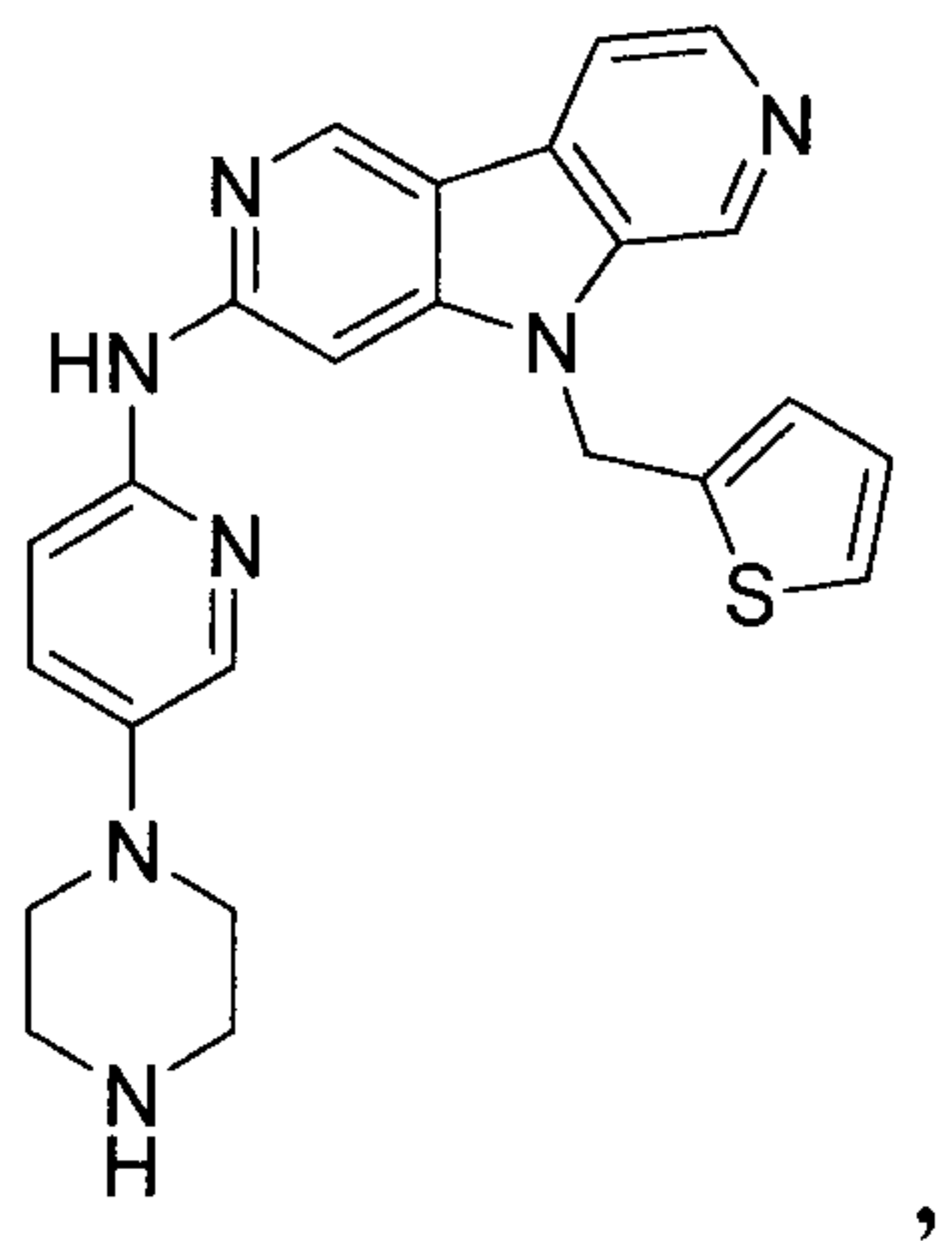
or a pharmaceutically acceptable salt thereof.

199. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

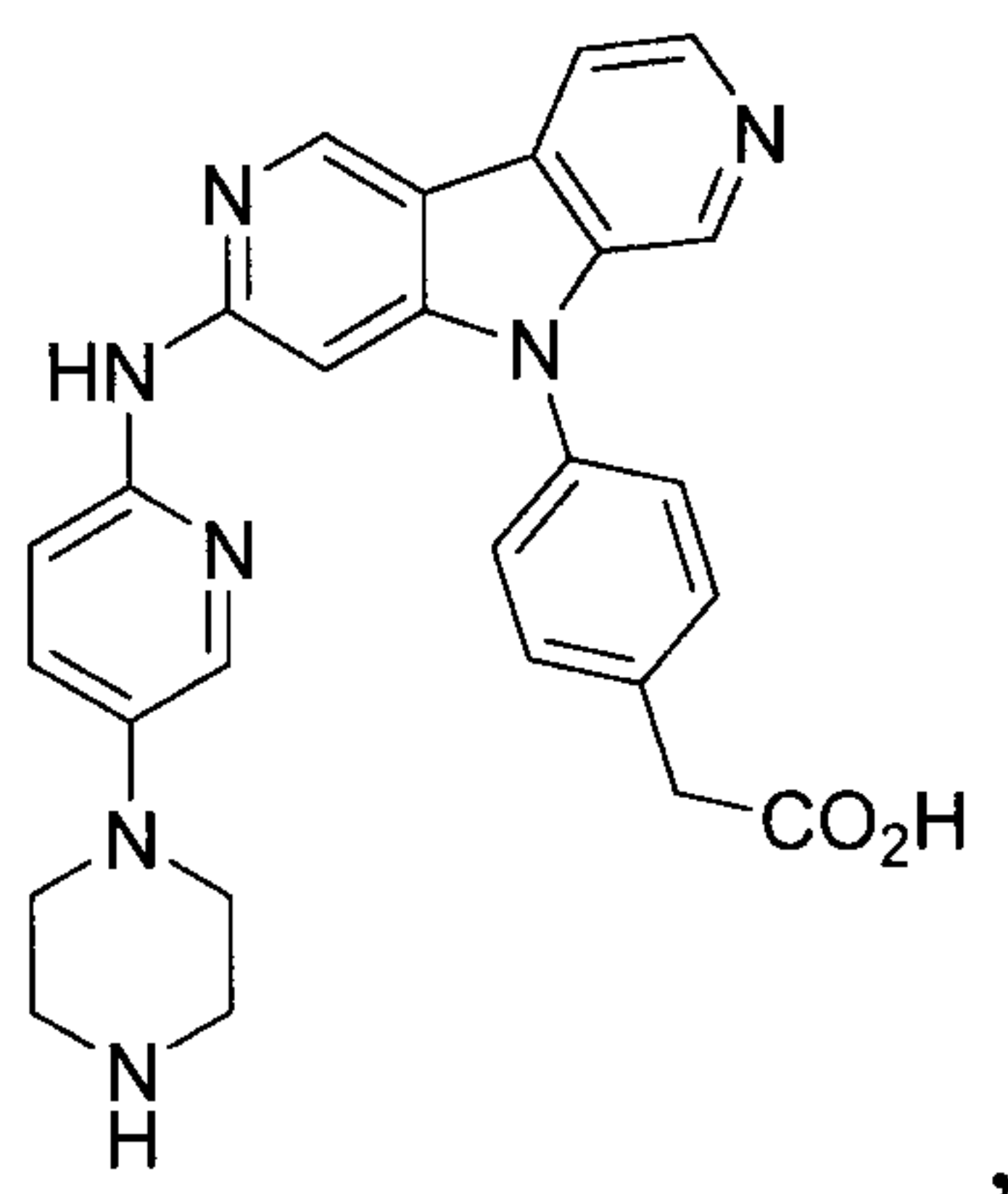
200. The compound of claim 1, wherein the compound is





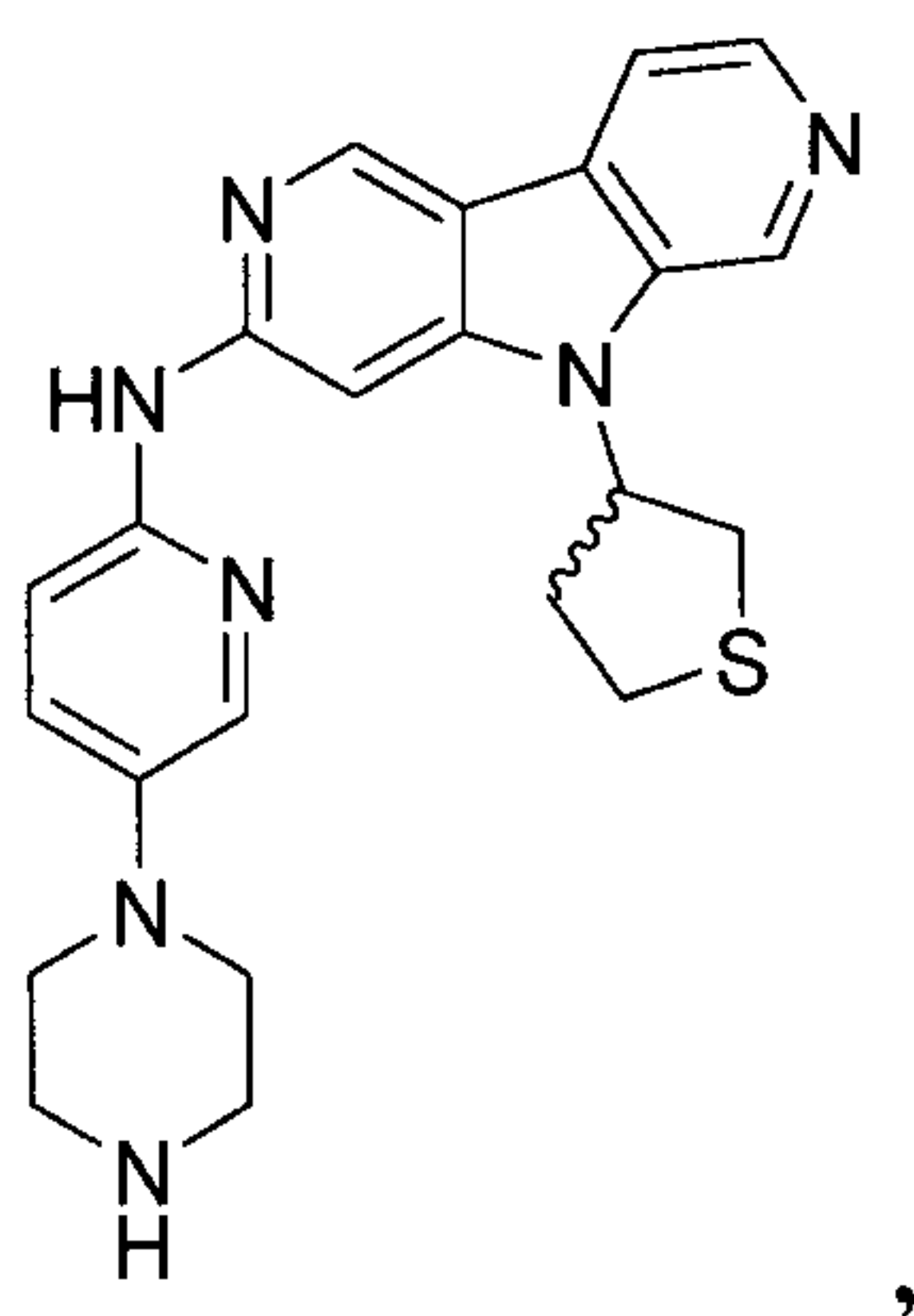
or a pharmaceutically acceptable salt thereof.

201. The compound of claim 1, wherein the compound is



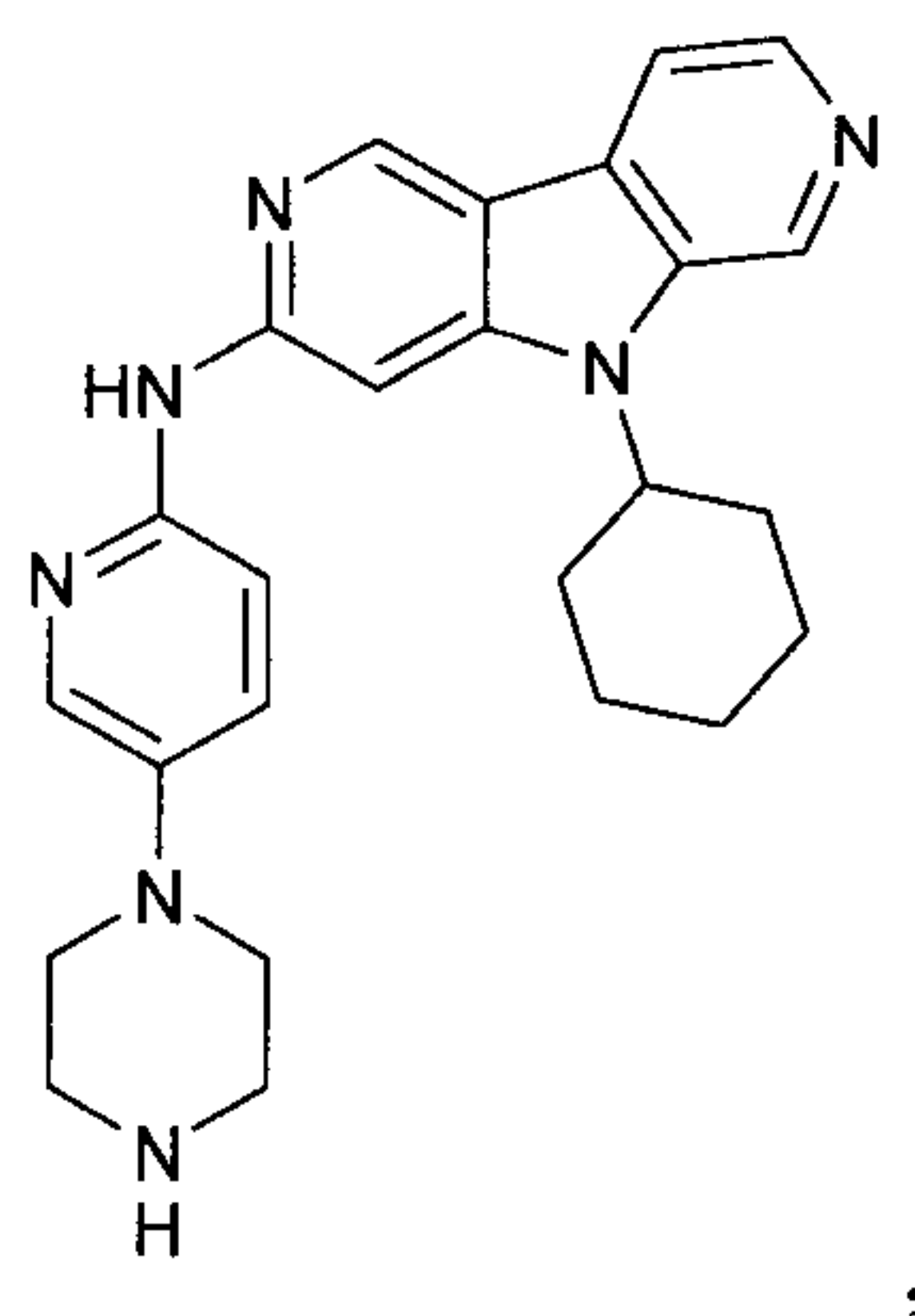
or a pharmaceutically acceptable salt thereof.

202. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

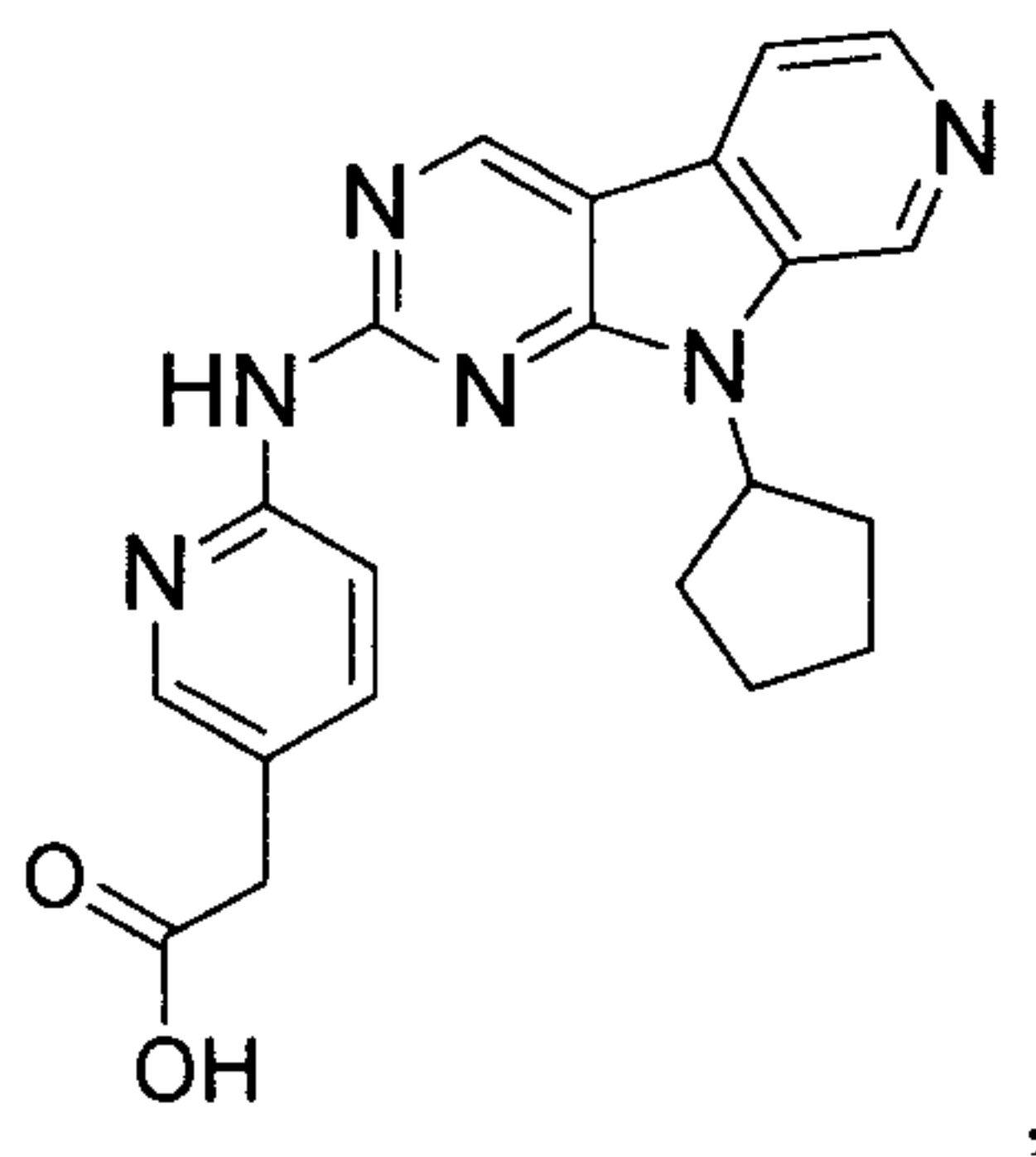
203. The compound of claim 1, wherein the compound is





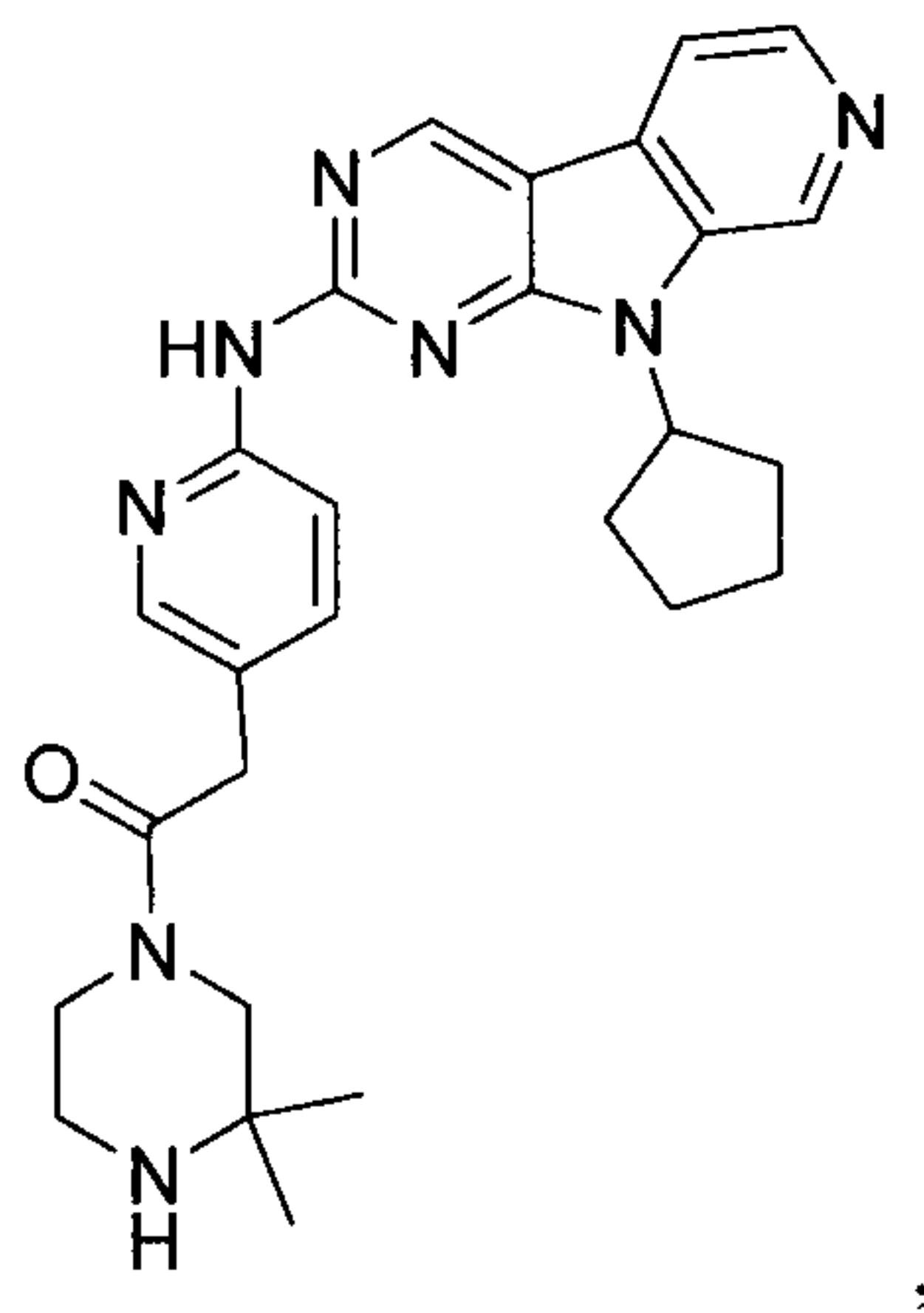
or a pharmaceutically acceptable salt thereof.

204. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

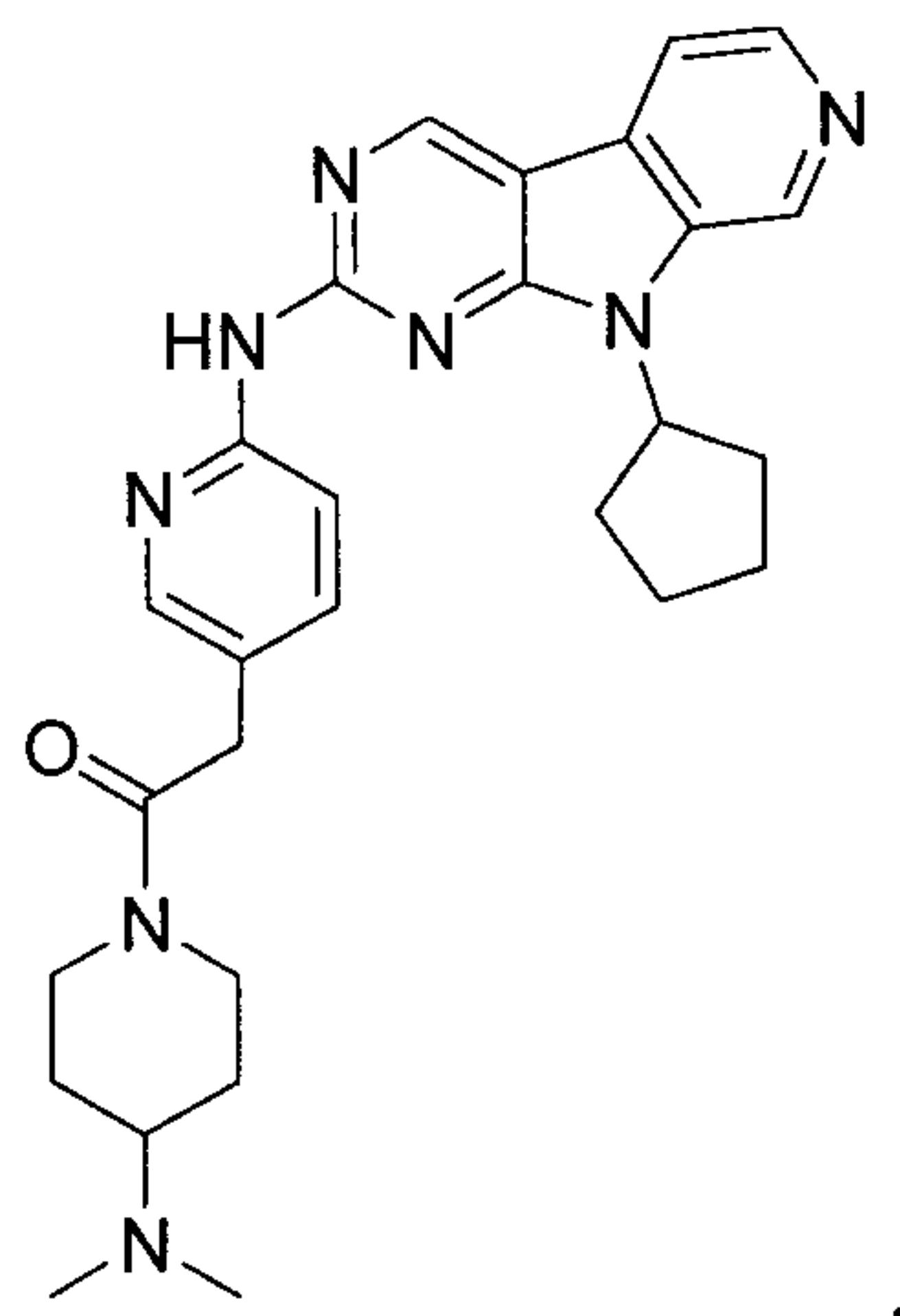
205. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

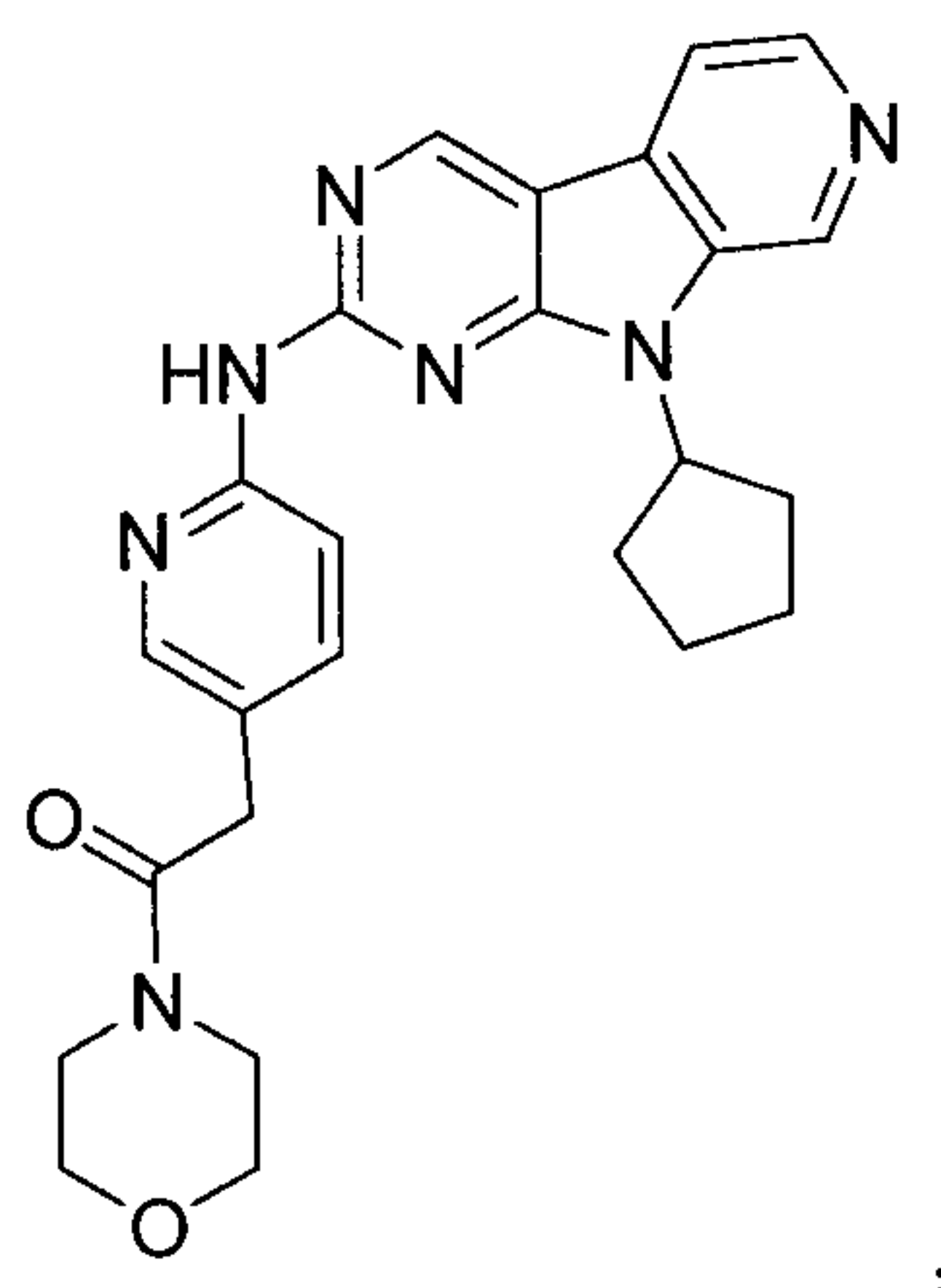


206. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

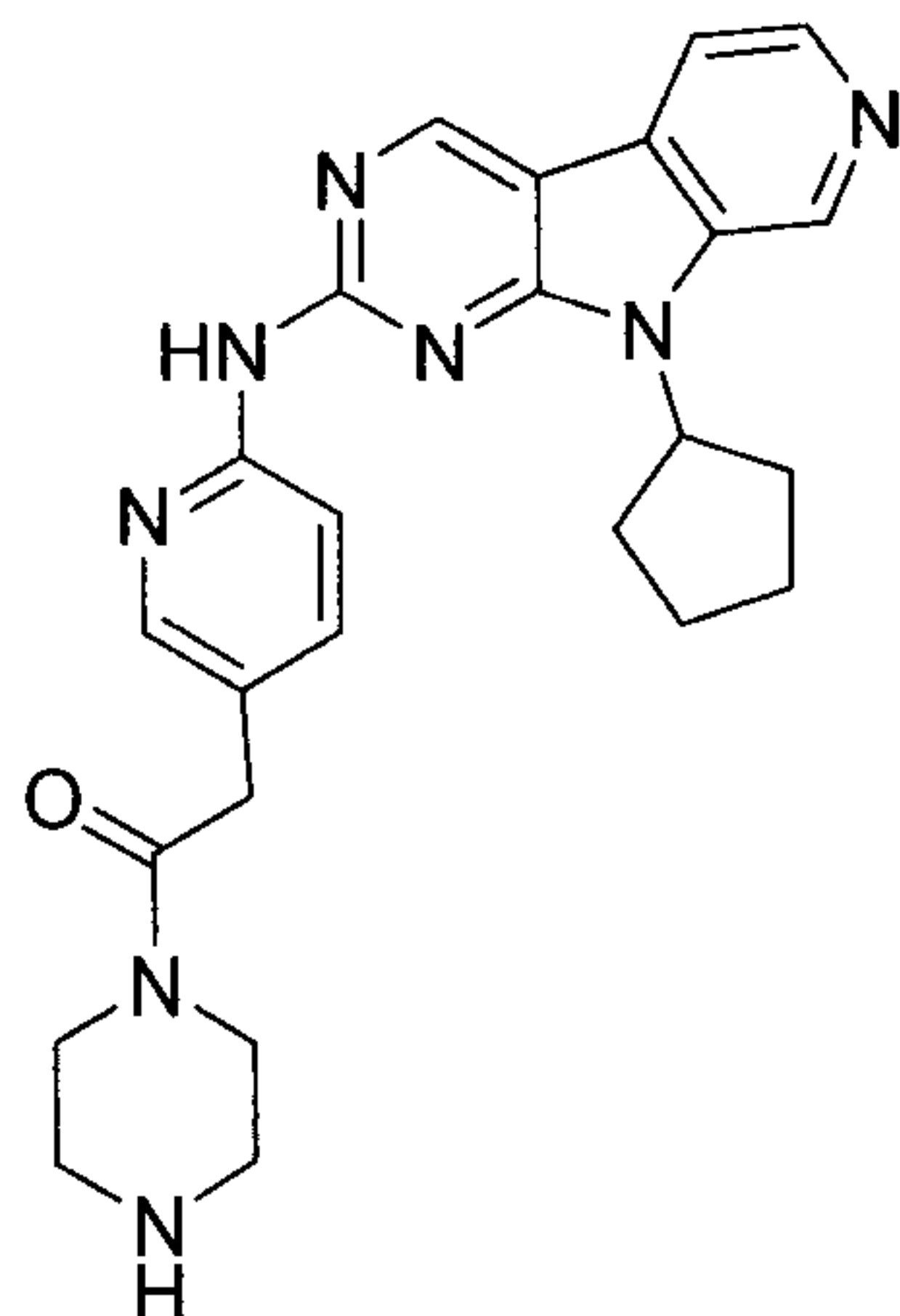
207. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

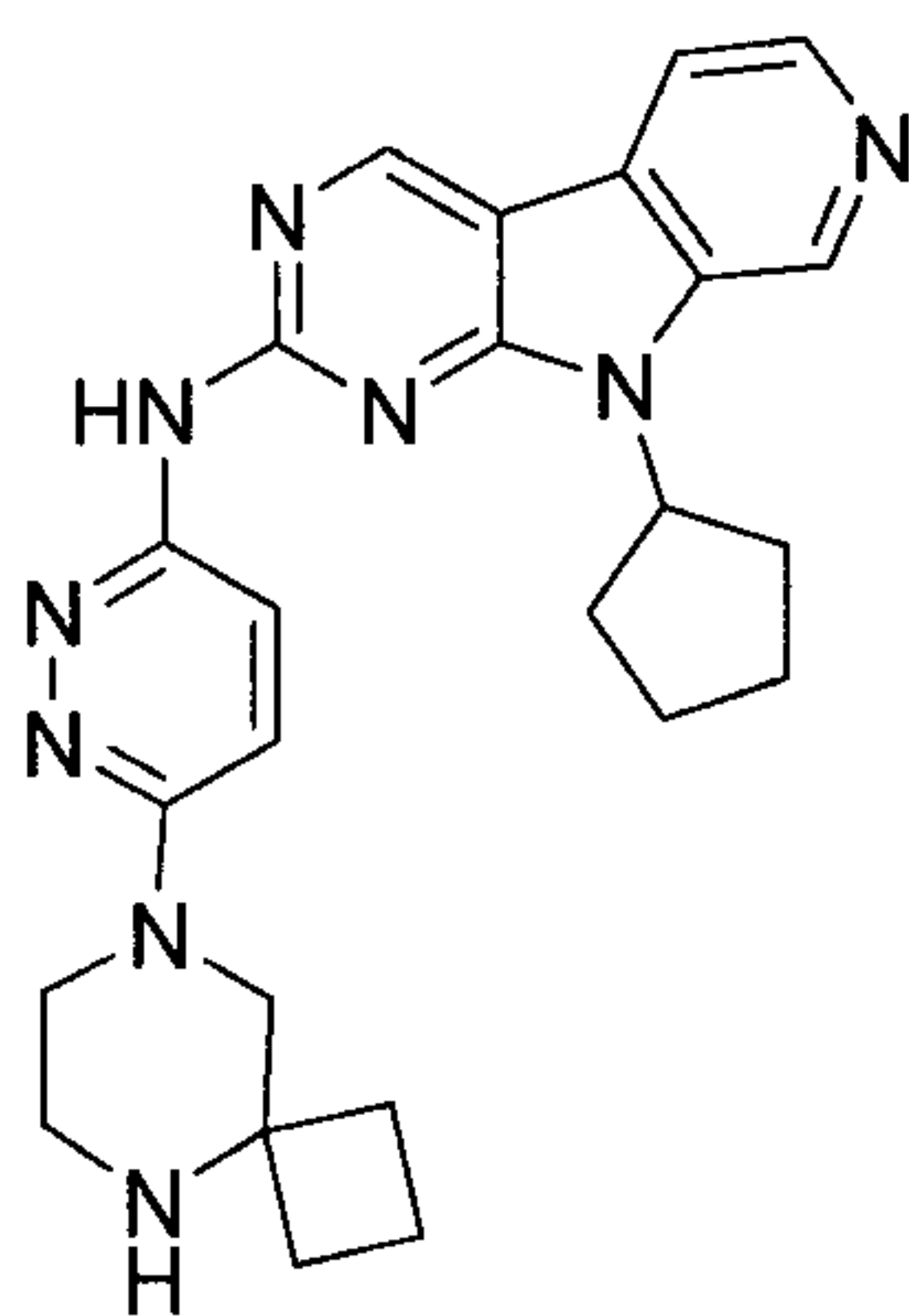


208. The compound of claim 1, wherein the compound is



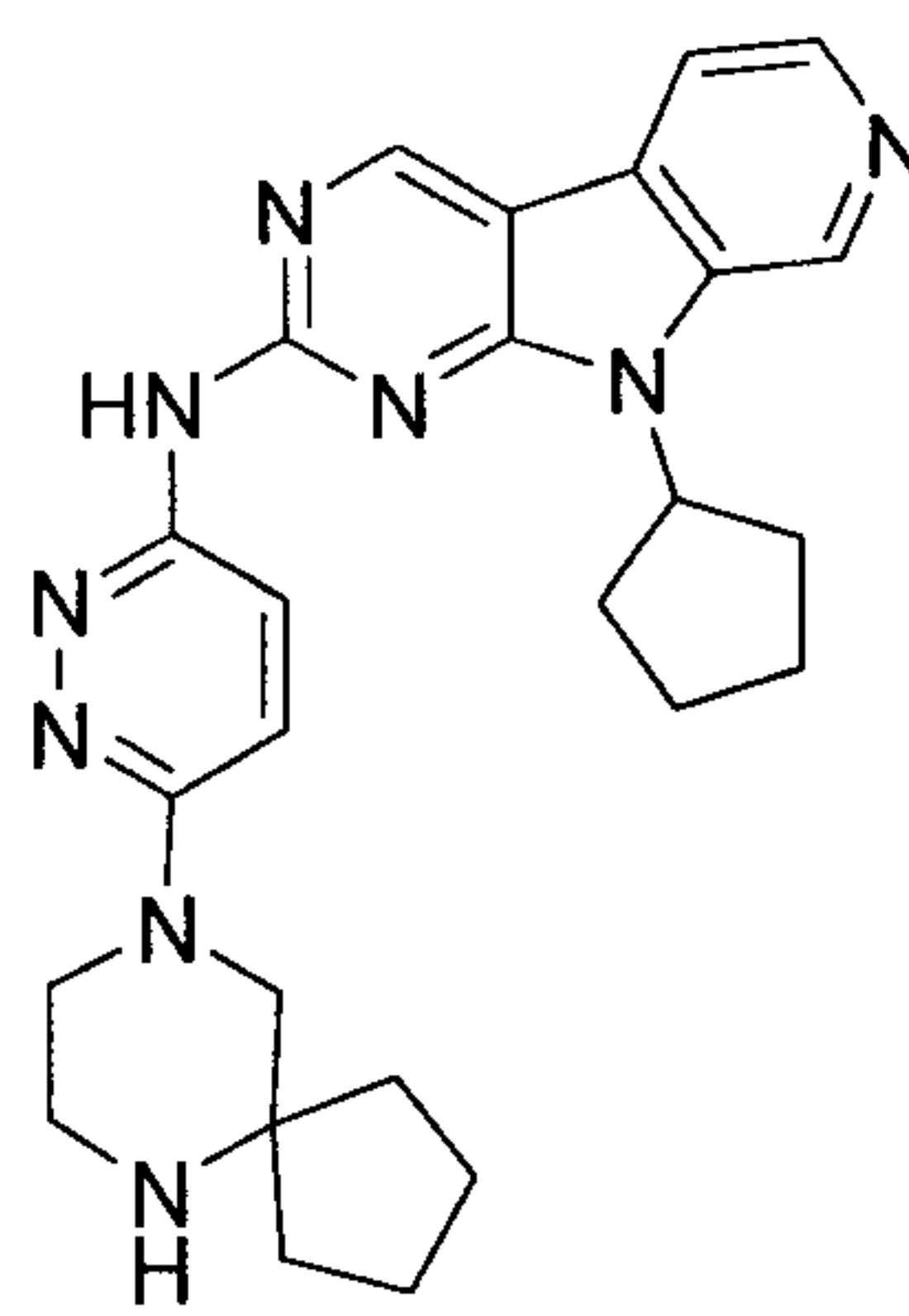
or a pharmaceutically acceptable salt thereof.

209. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

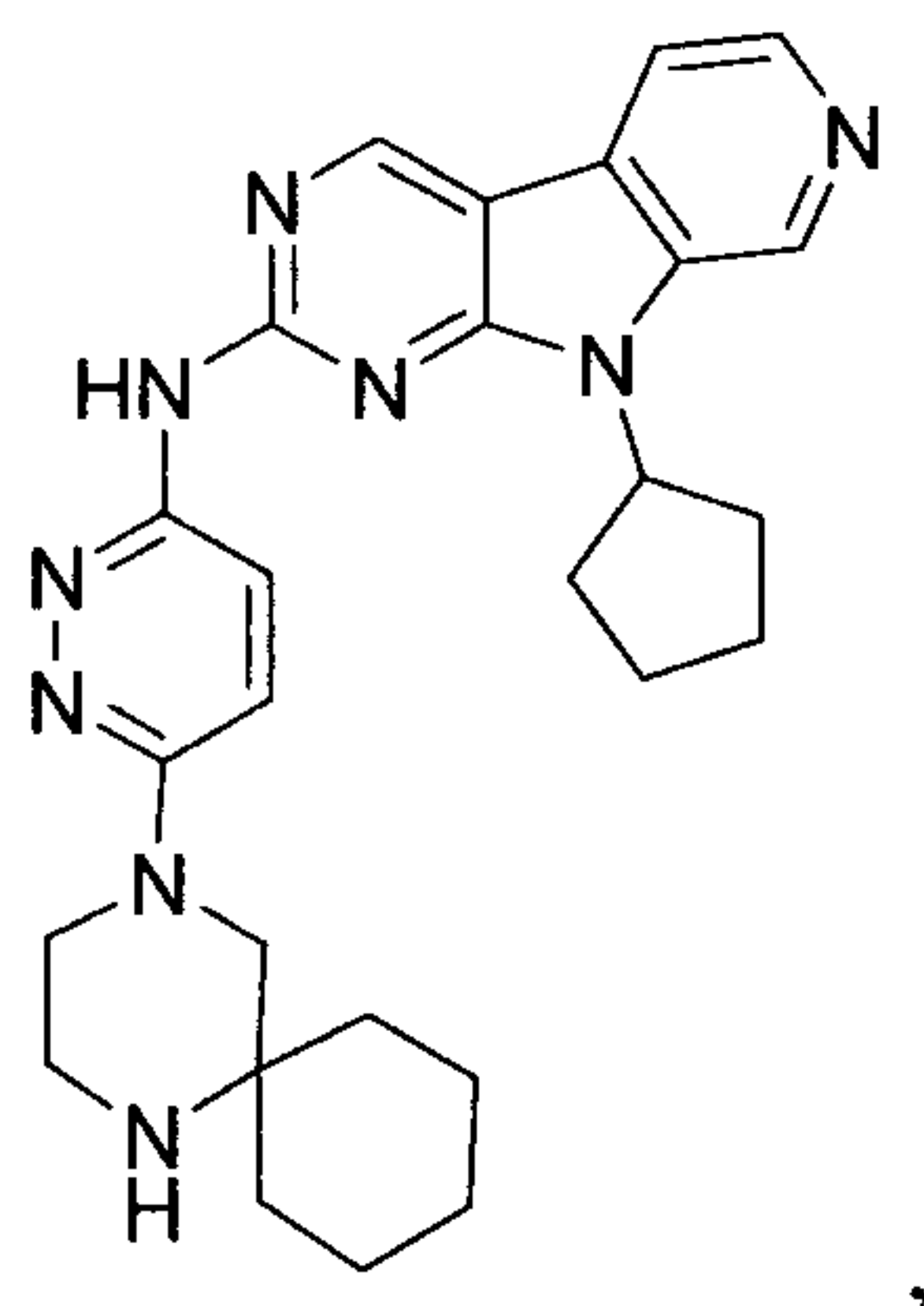
210. The compound of claim 1, wherein the compound is





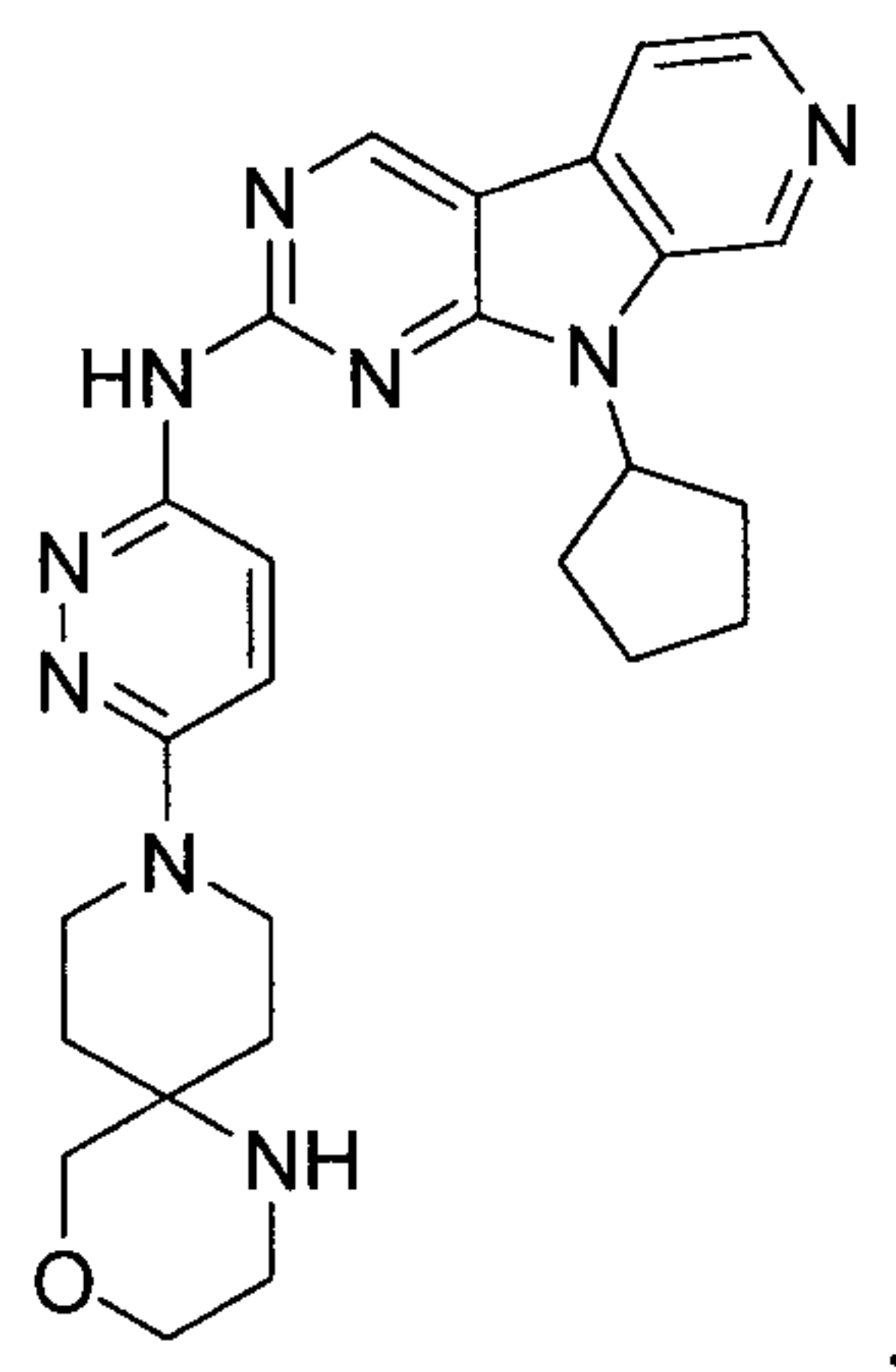
or a pharmaceutically acceptable salt thereof.

211. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

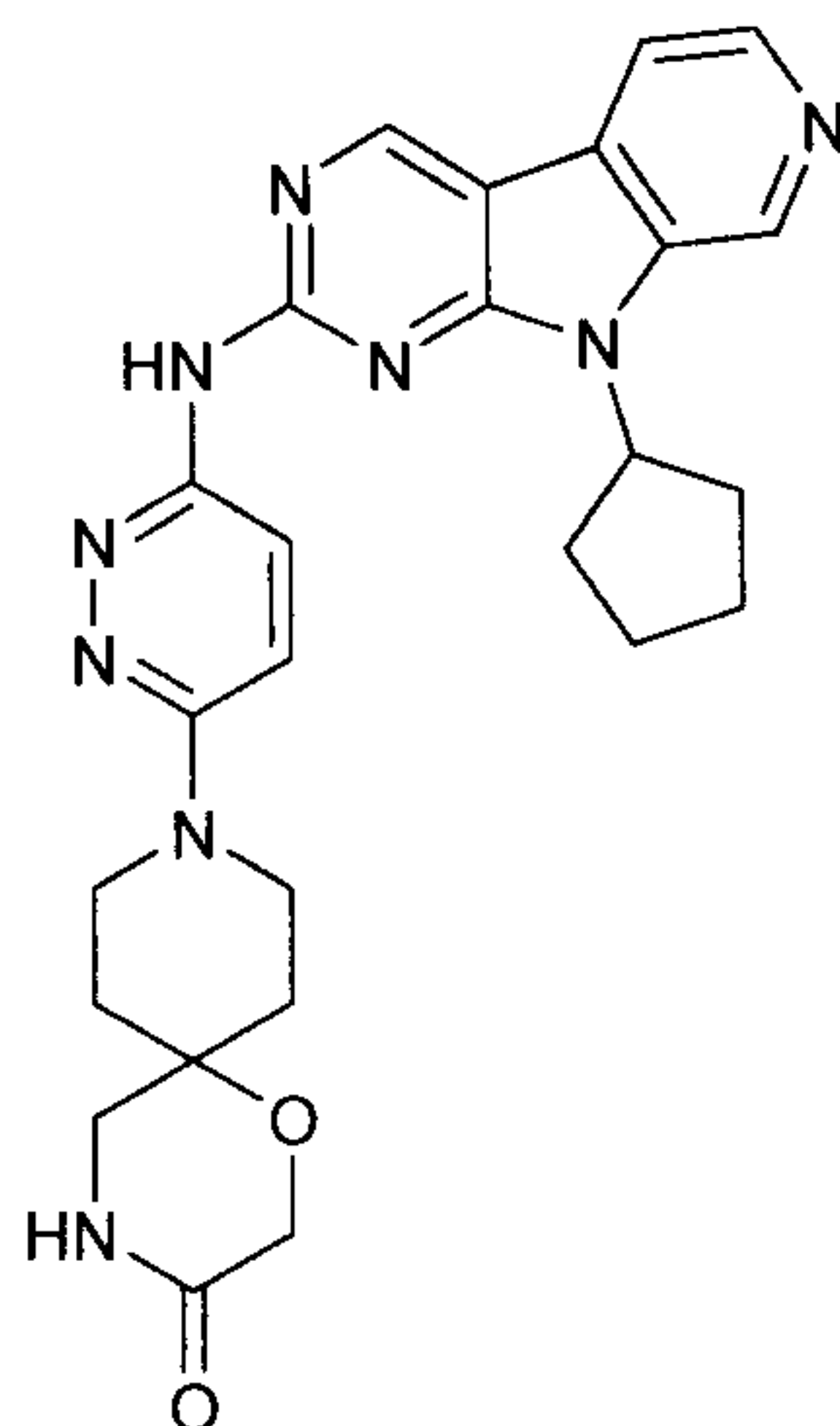
212. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

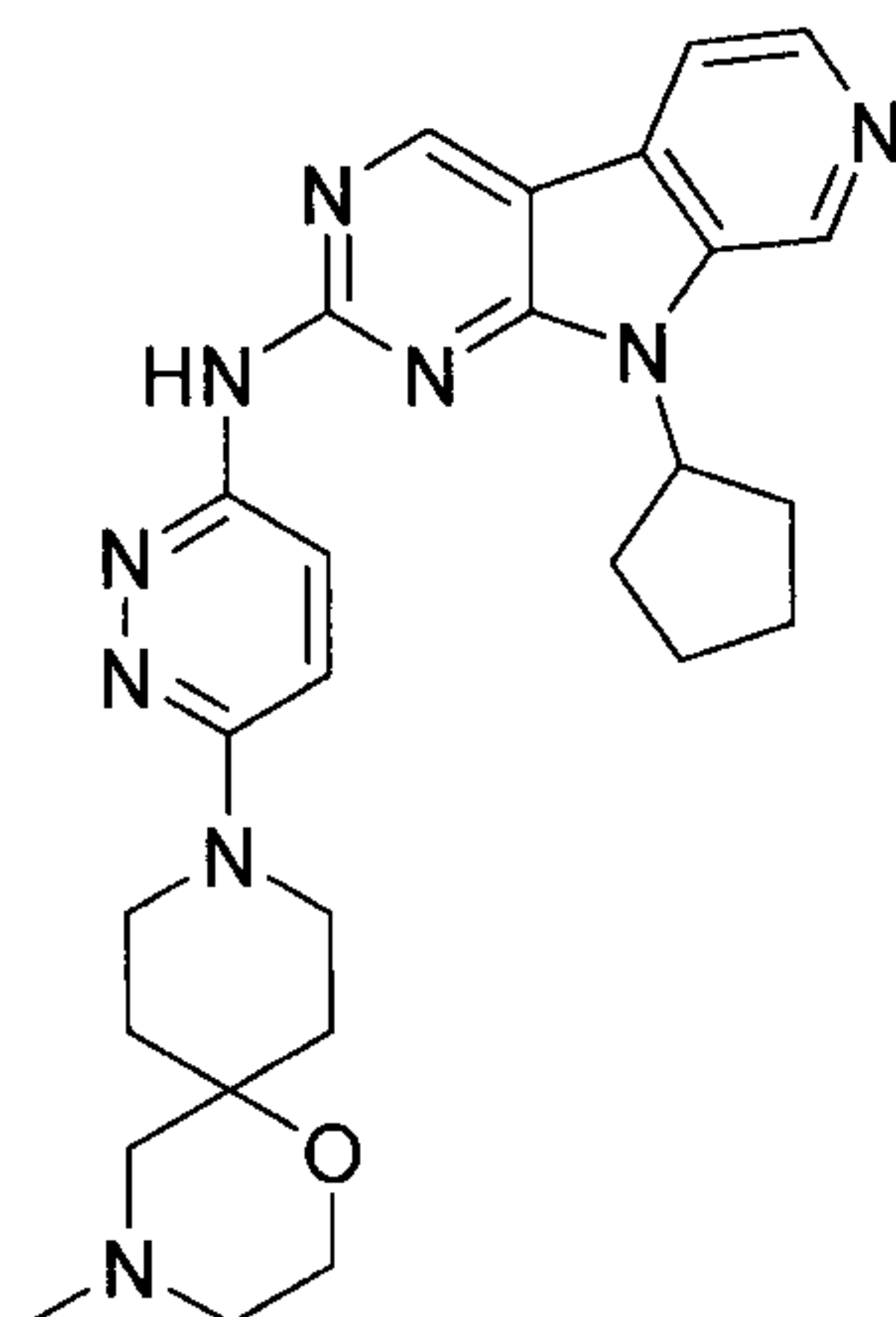


213. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

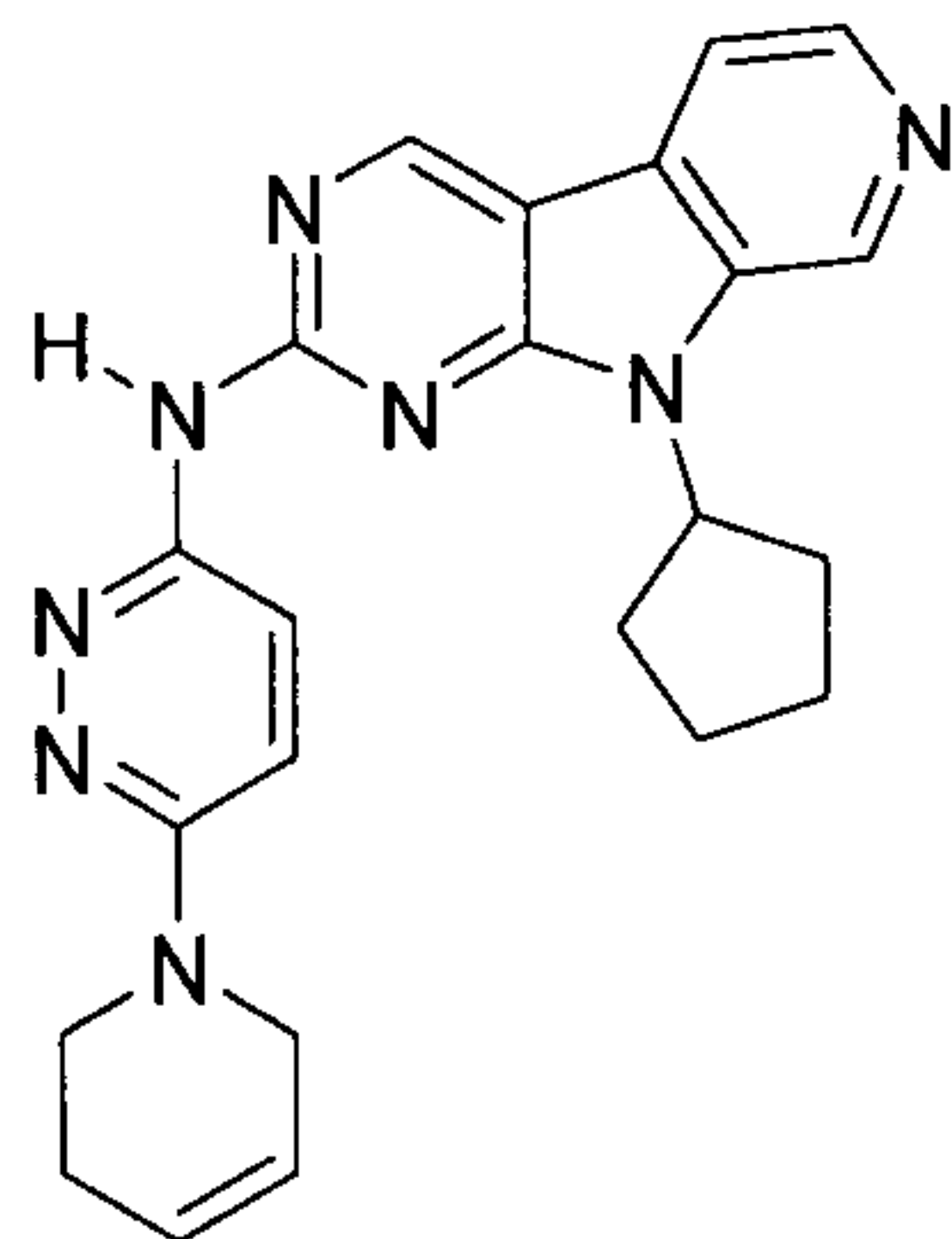
214. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.



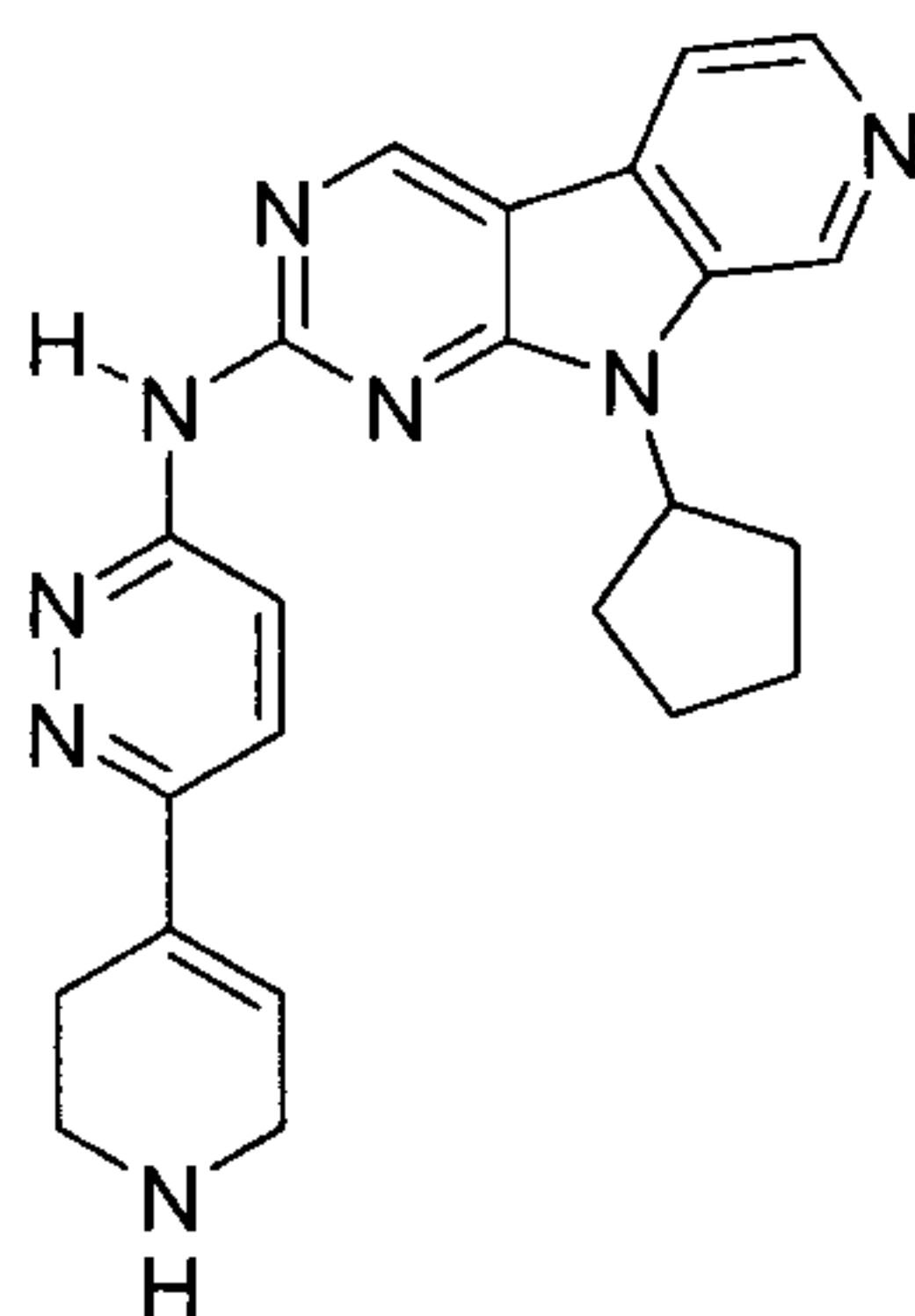
215. The compound of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

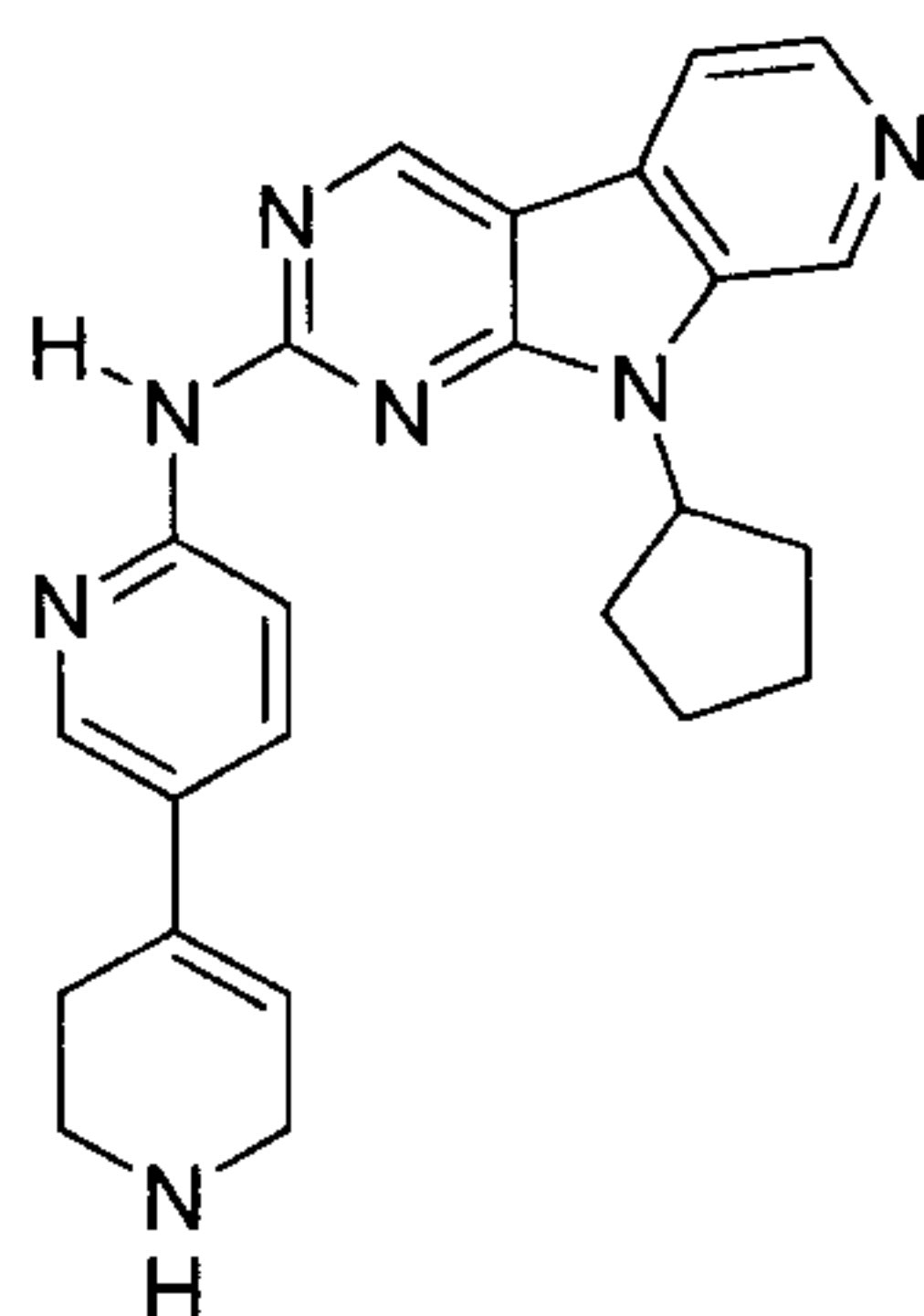
216. The compound of claim 1, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

217. The compound of claim 1, wherein the compound is

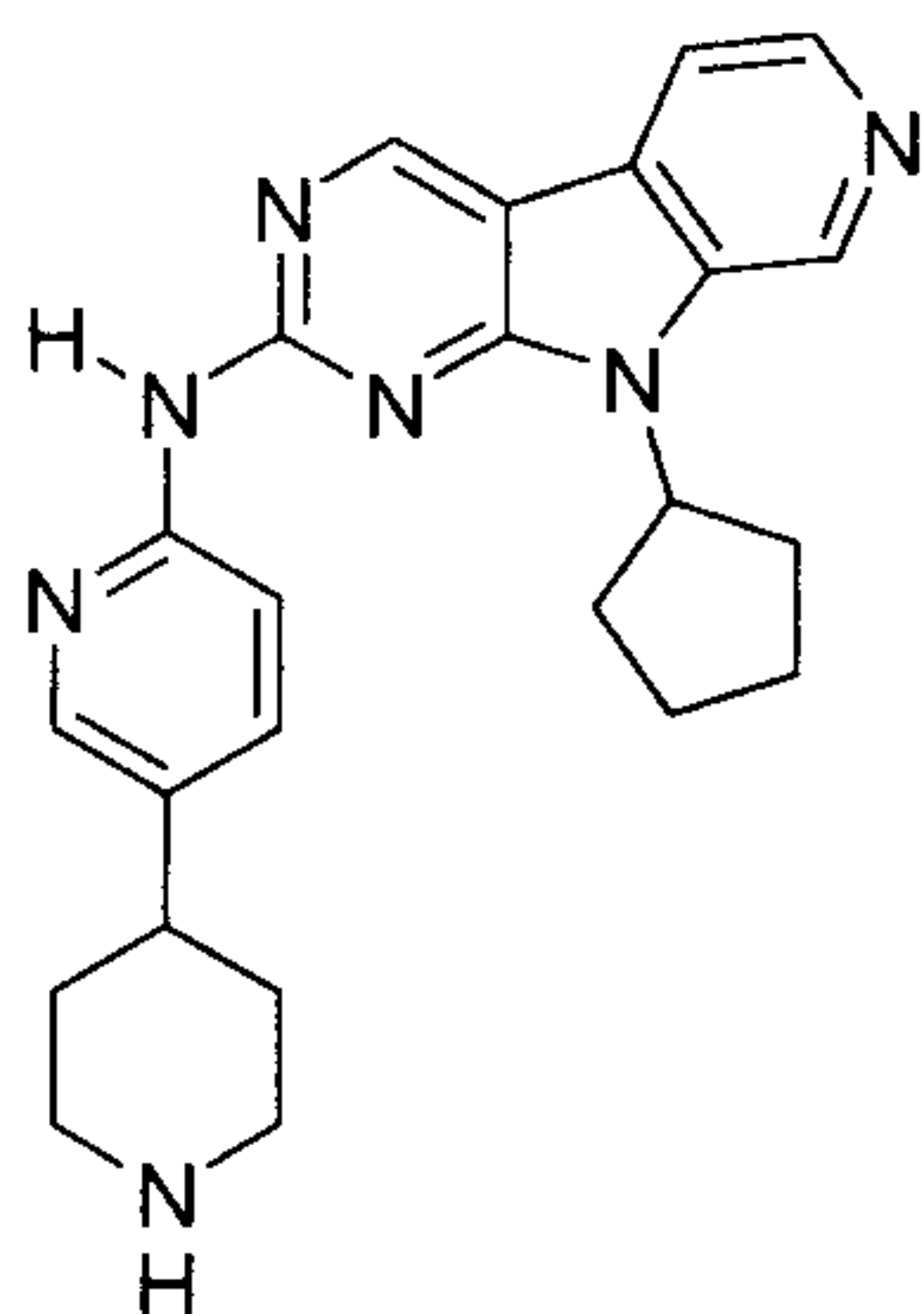


,

or a pharmaceutically acceptable salt thereof.

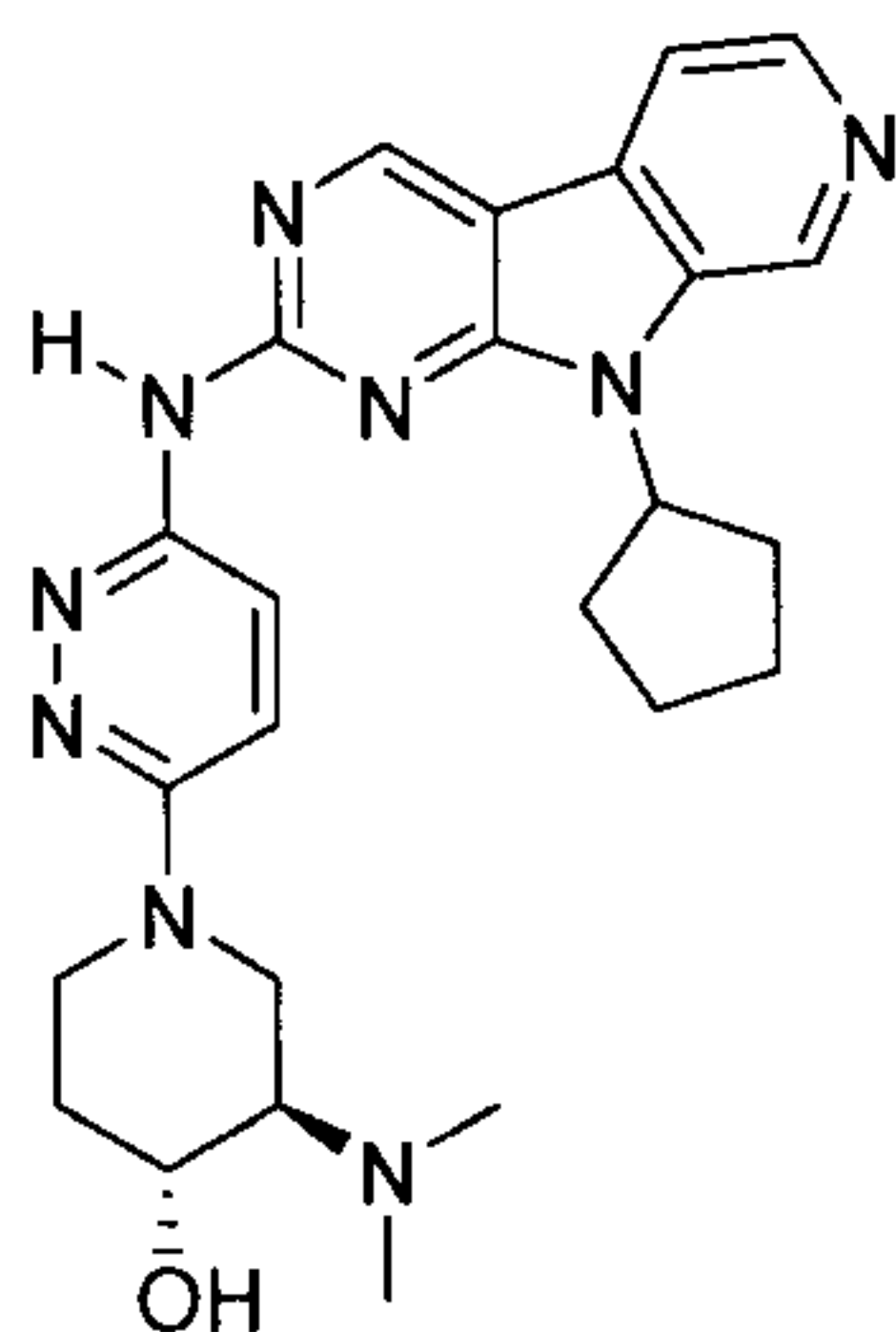


218. The compound of claim 1, wherein the compound is



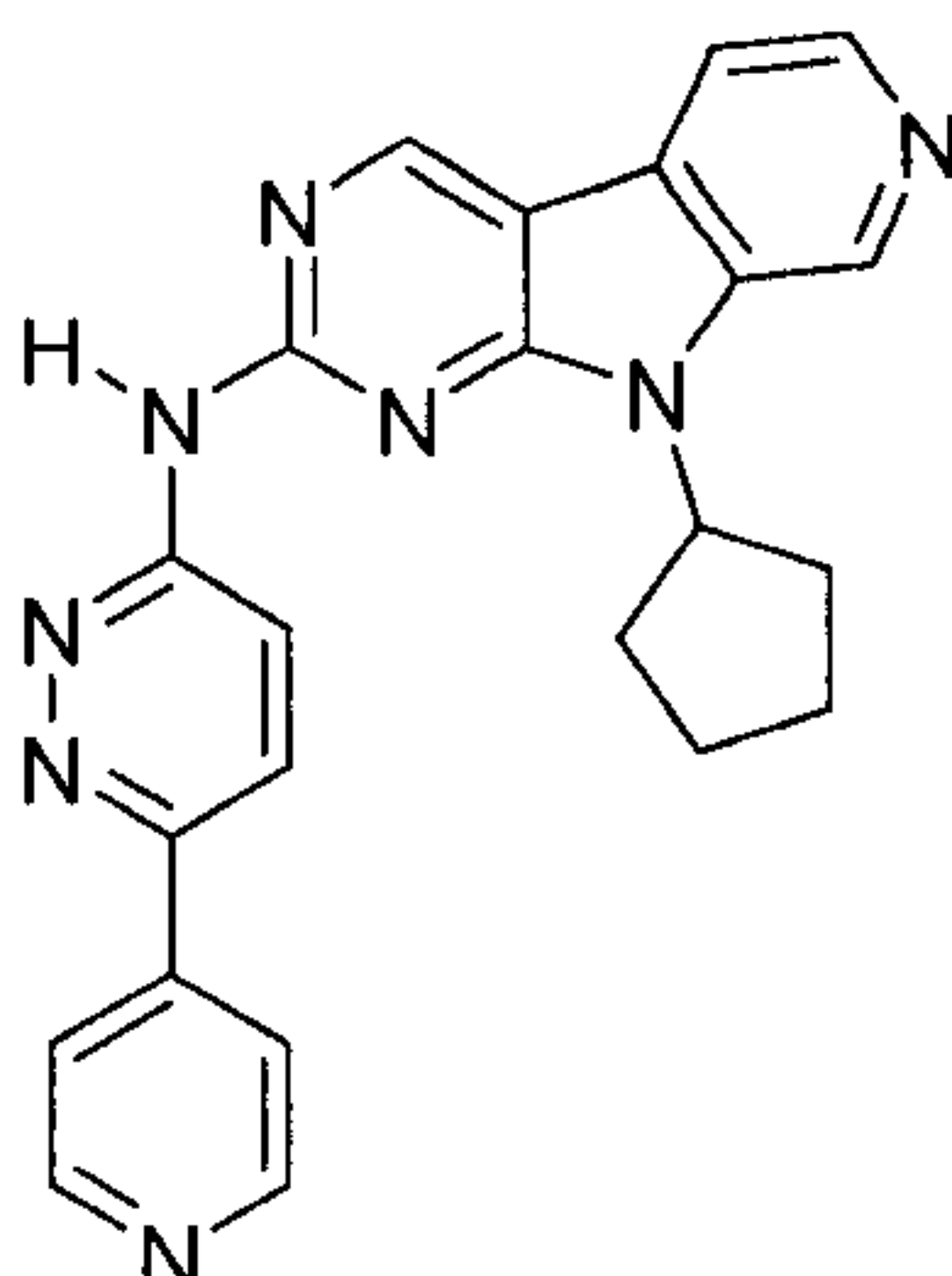
or a pharmaceutically acceptable salt thereof.

219. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

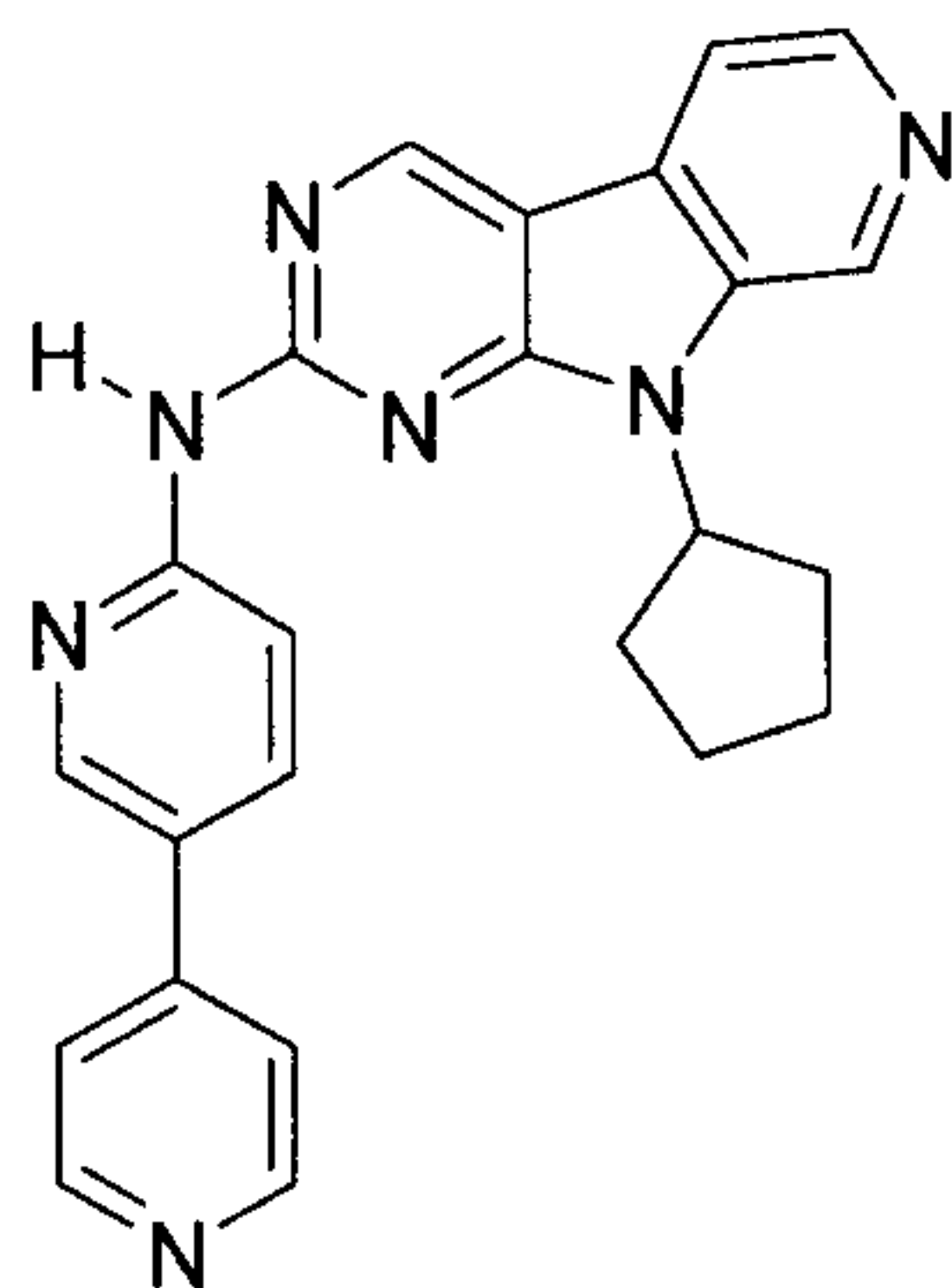
220. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

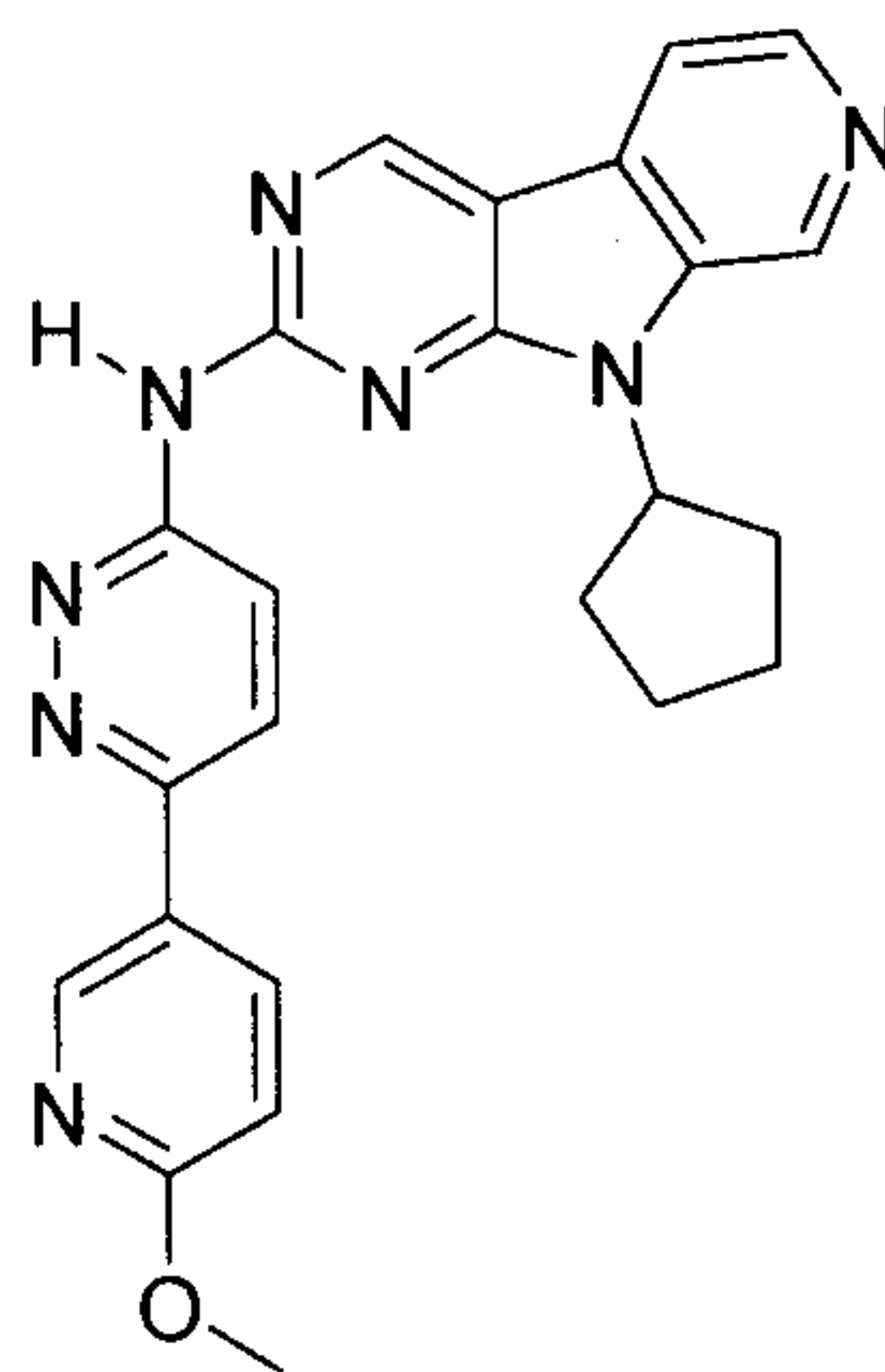


221. The compound of claim 1, wherein the compound is



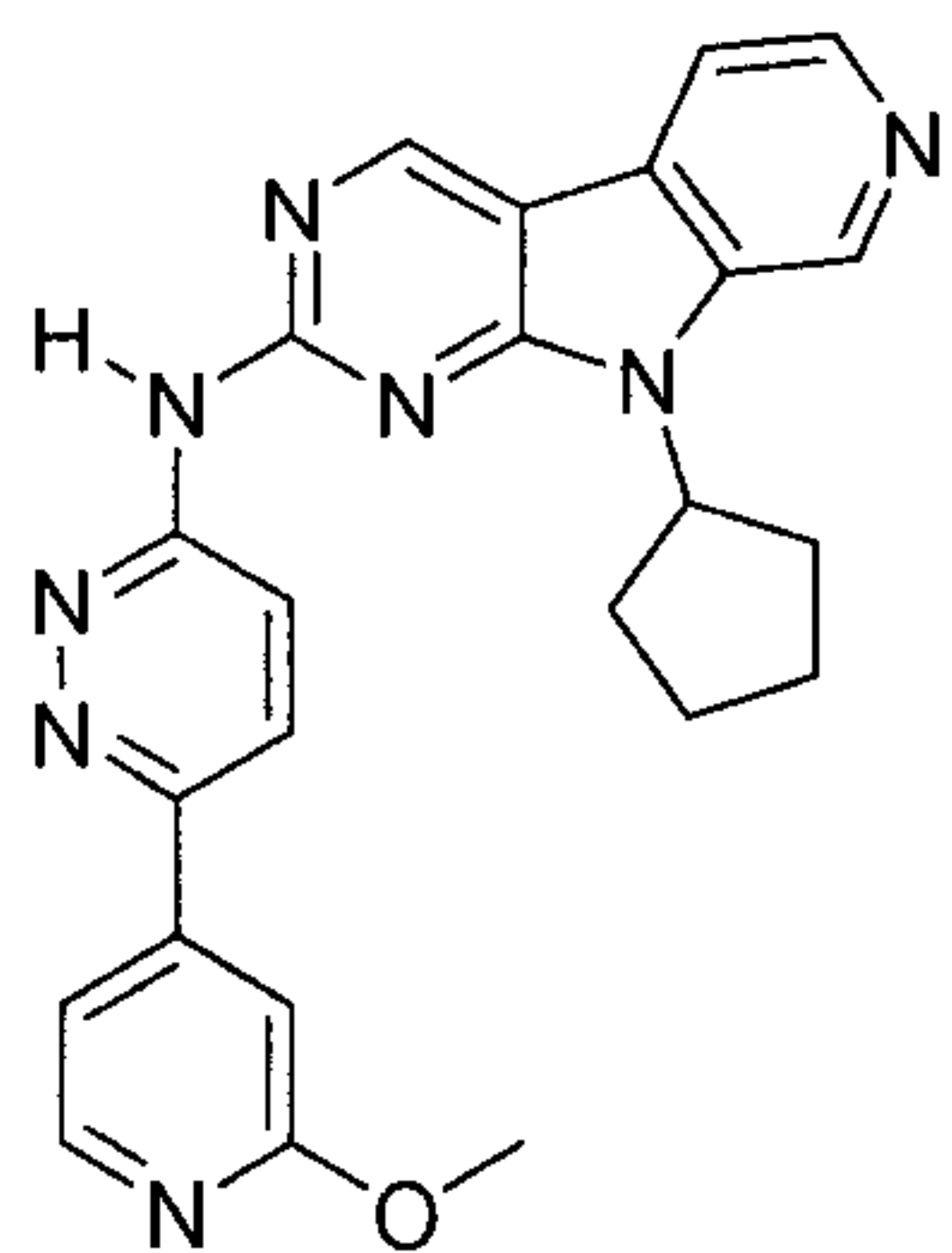
or a pharmaceutically acceptable salt thereof.

222. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

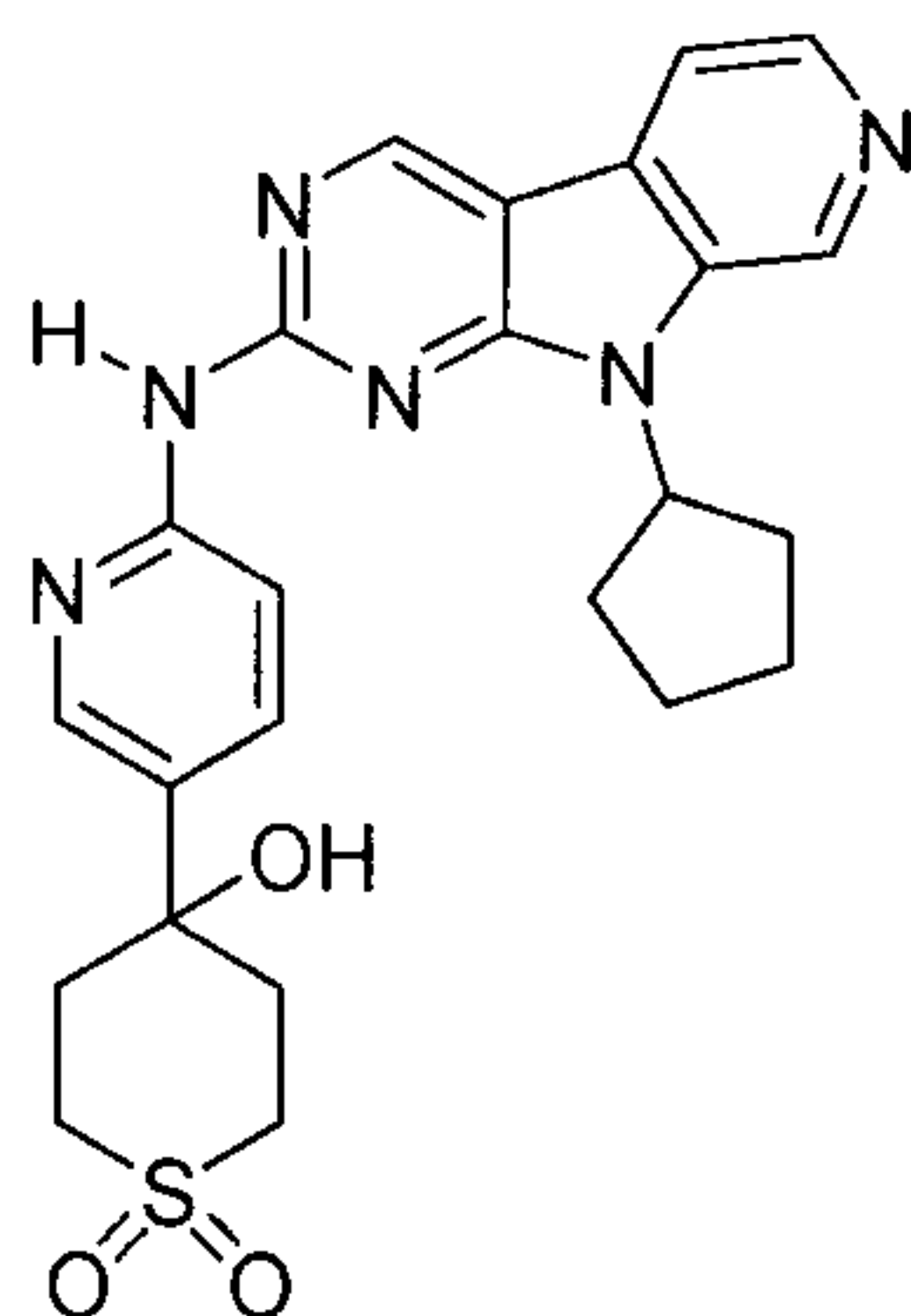
223. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

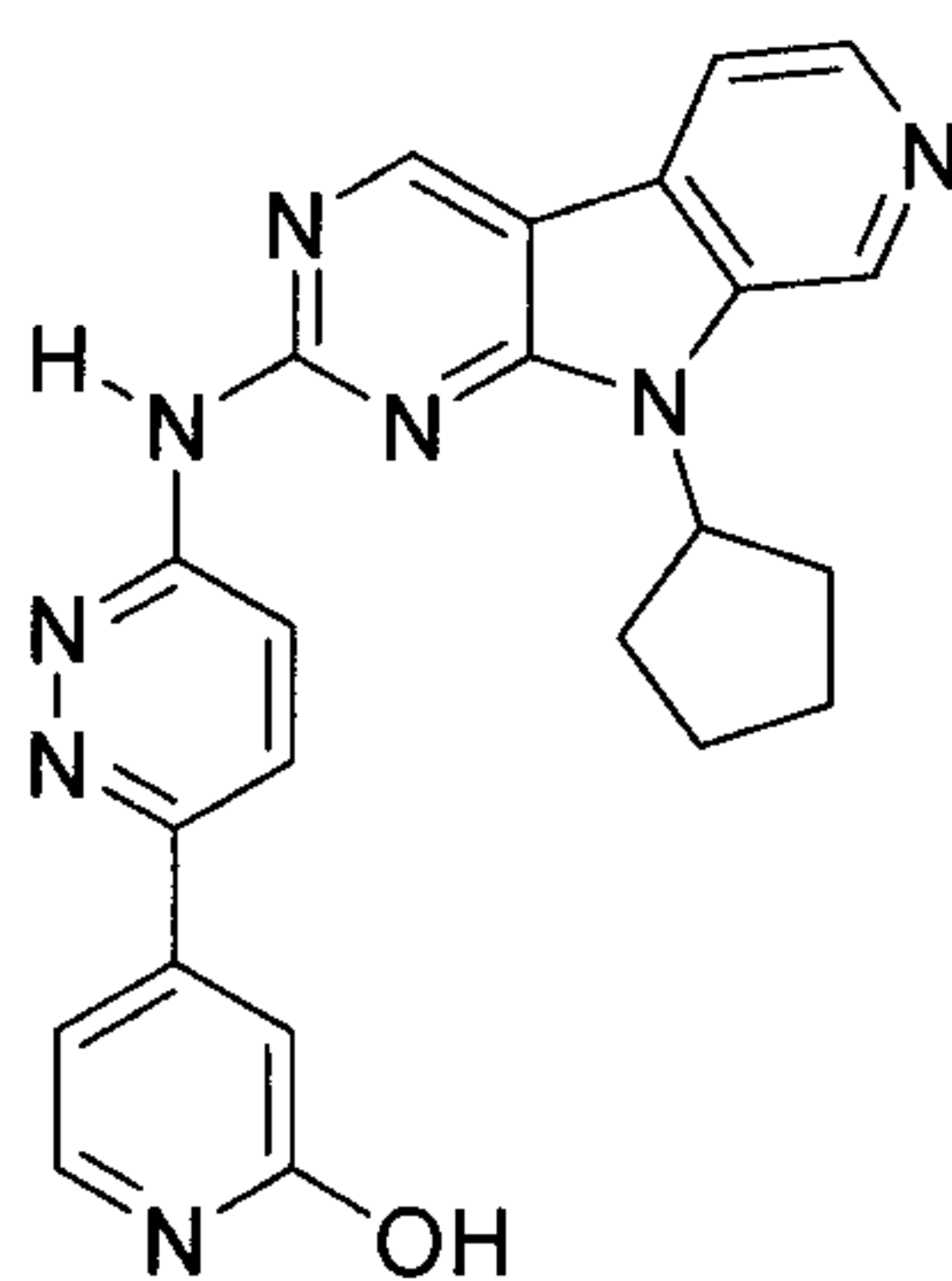


224. The compound of claim 1, wherein the compound is



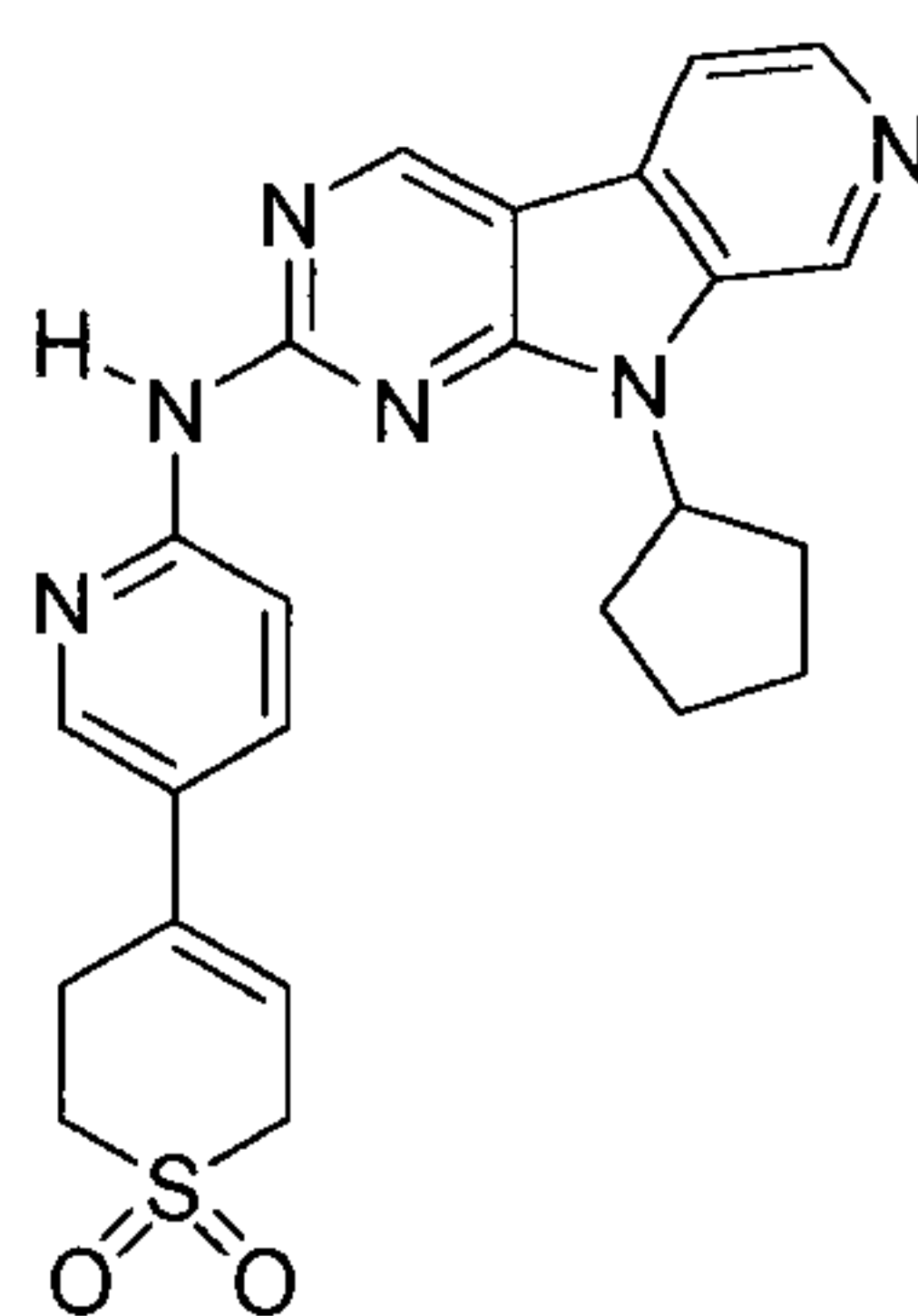
or a pharmaceutically acceptable salt thereof.

225. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

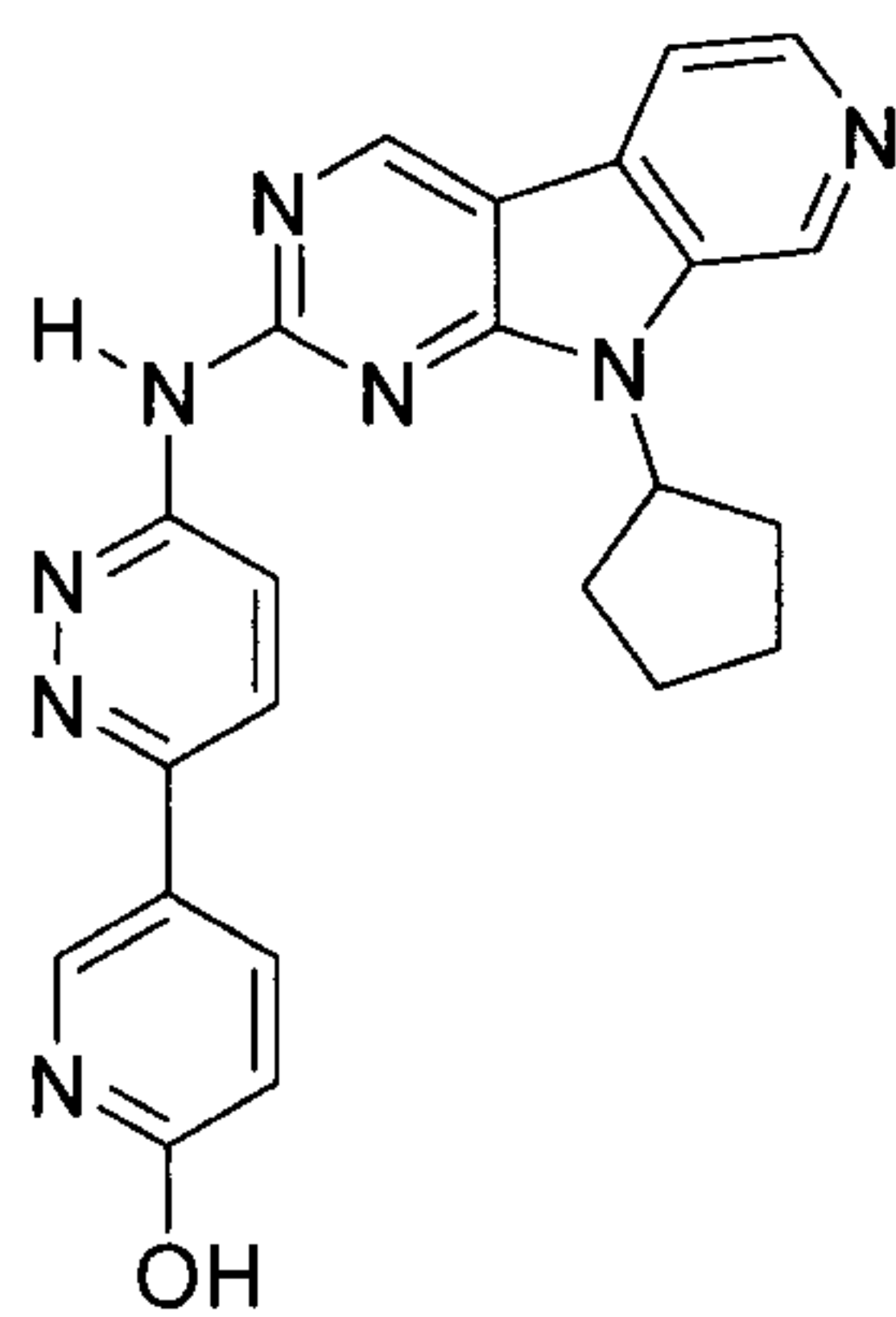
226. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

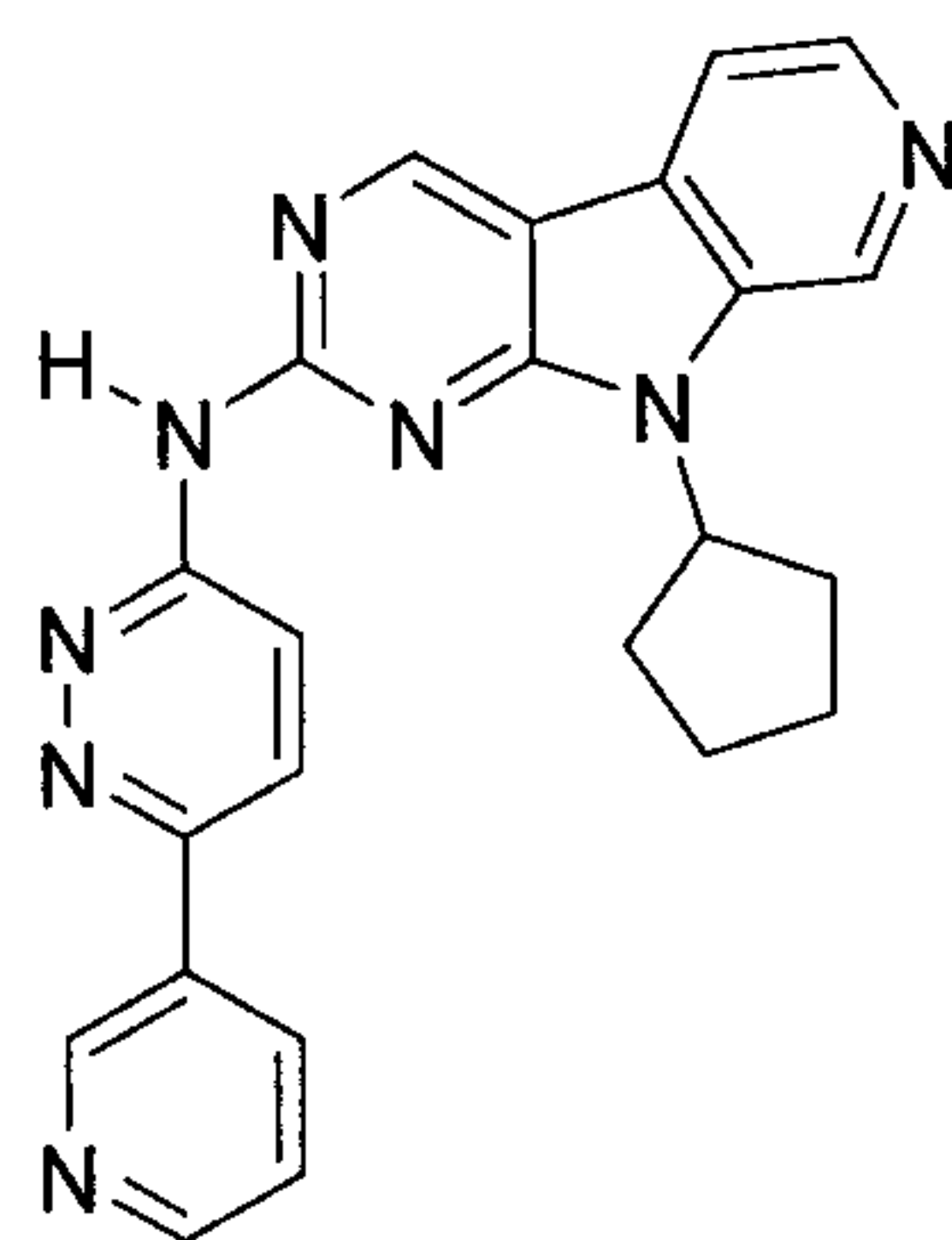


227. The compound of claim 1, wherein the compound is



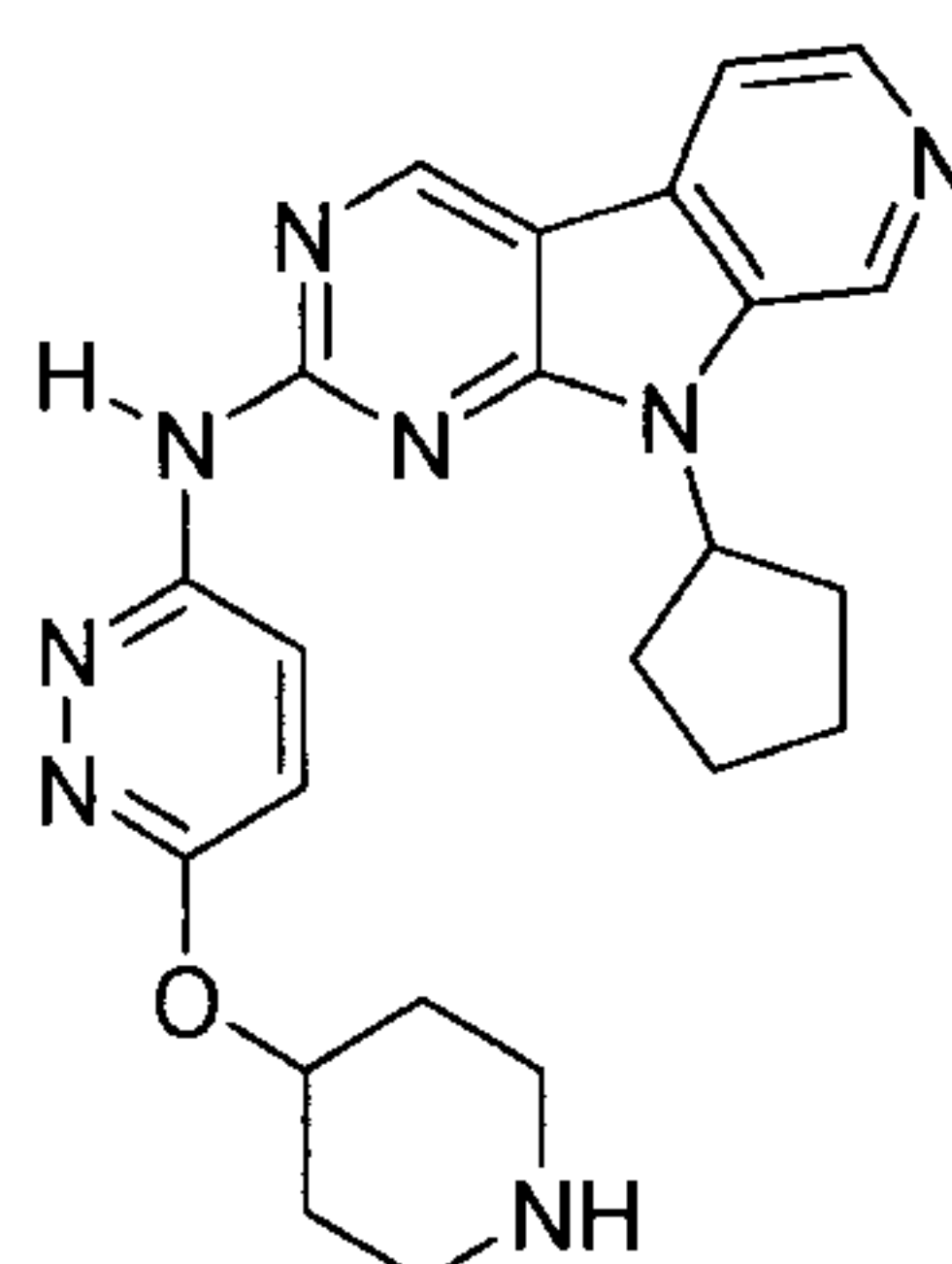
or a pharmaceutically acceptable salt thereof.

228. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

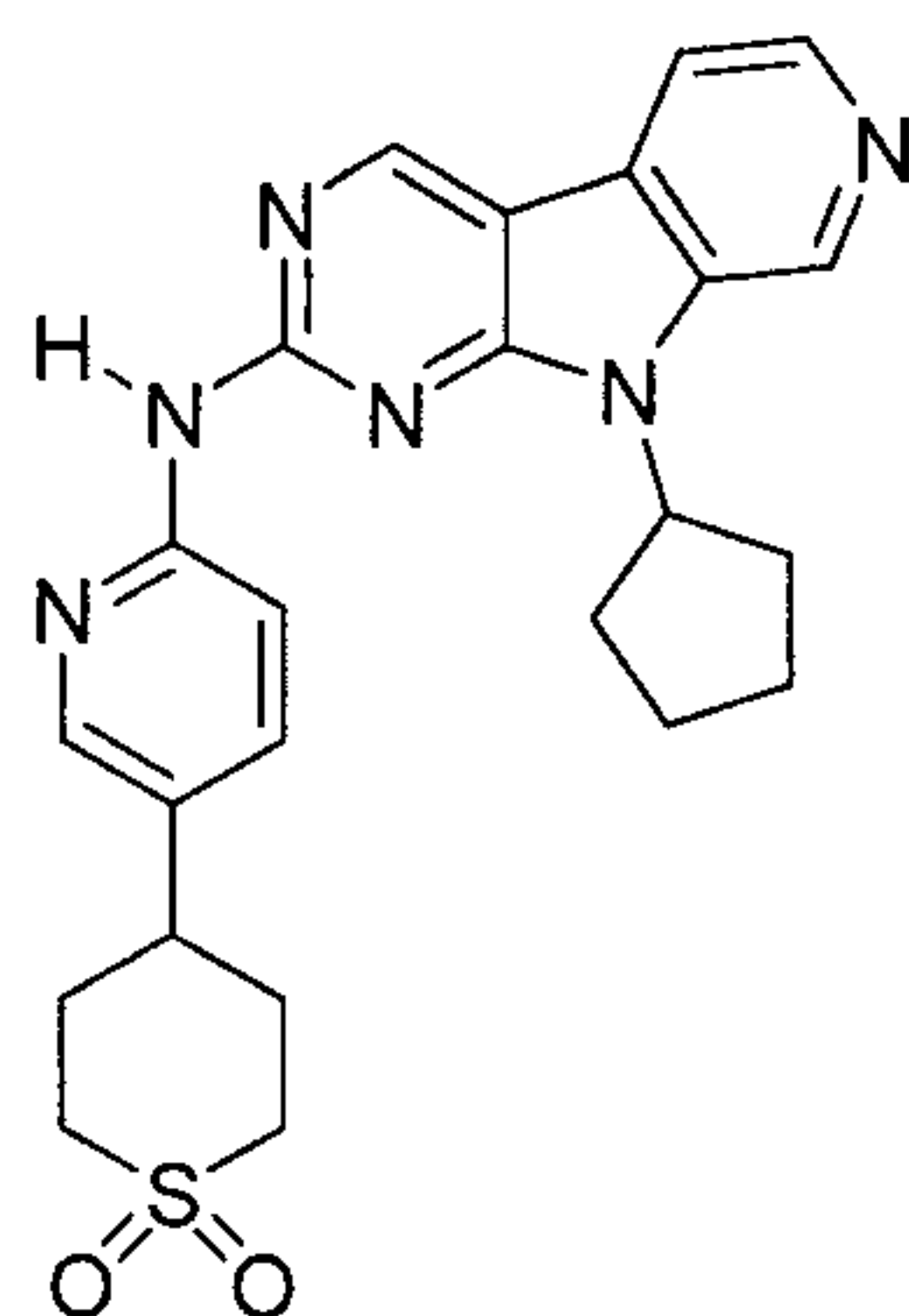
229. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

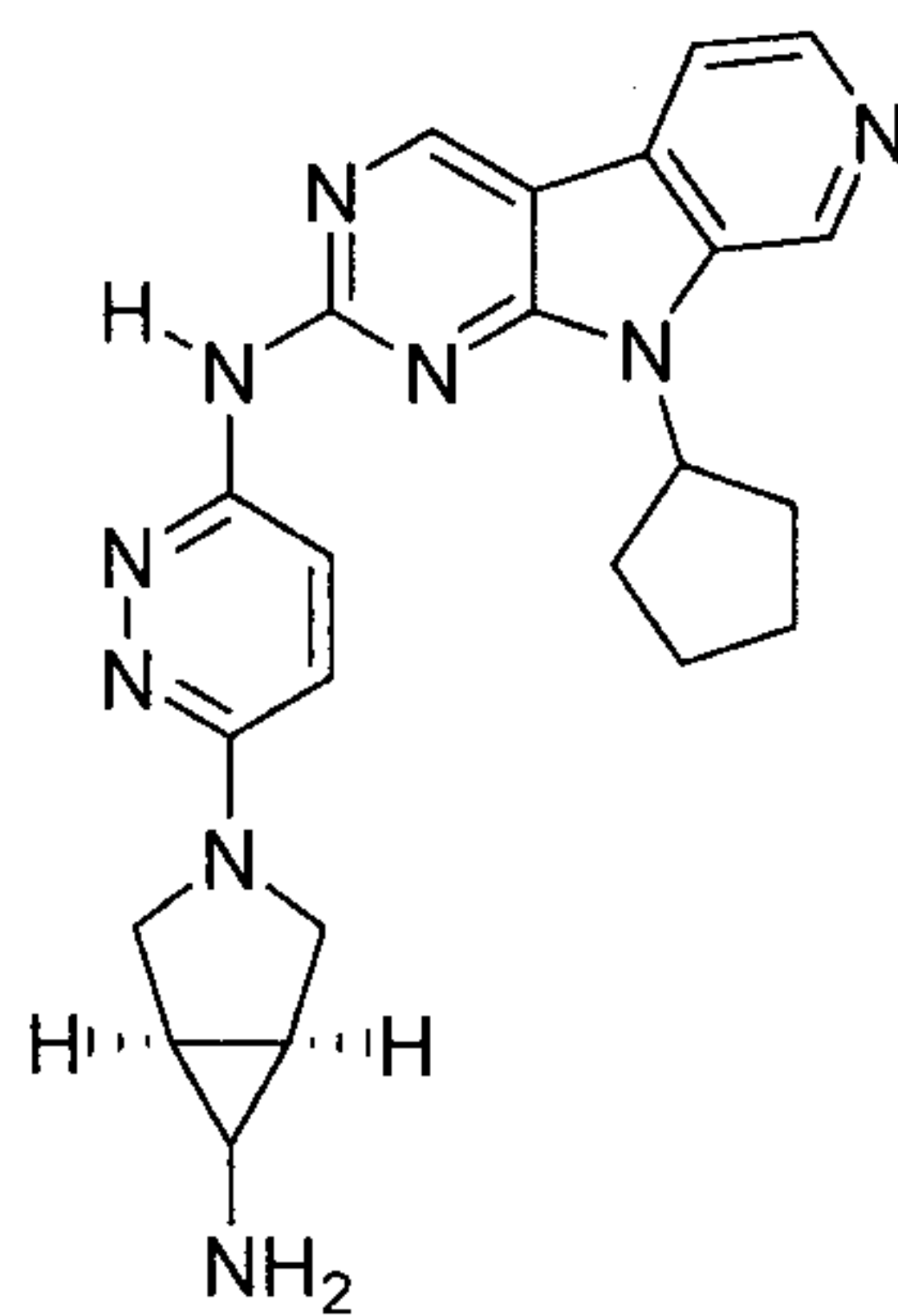


230. The compound of claim 1, wherein the compound is



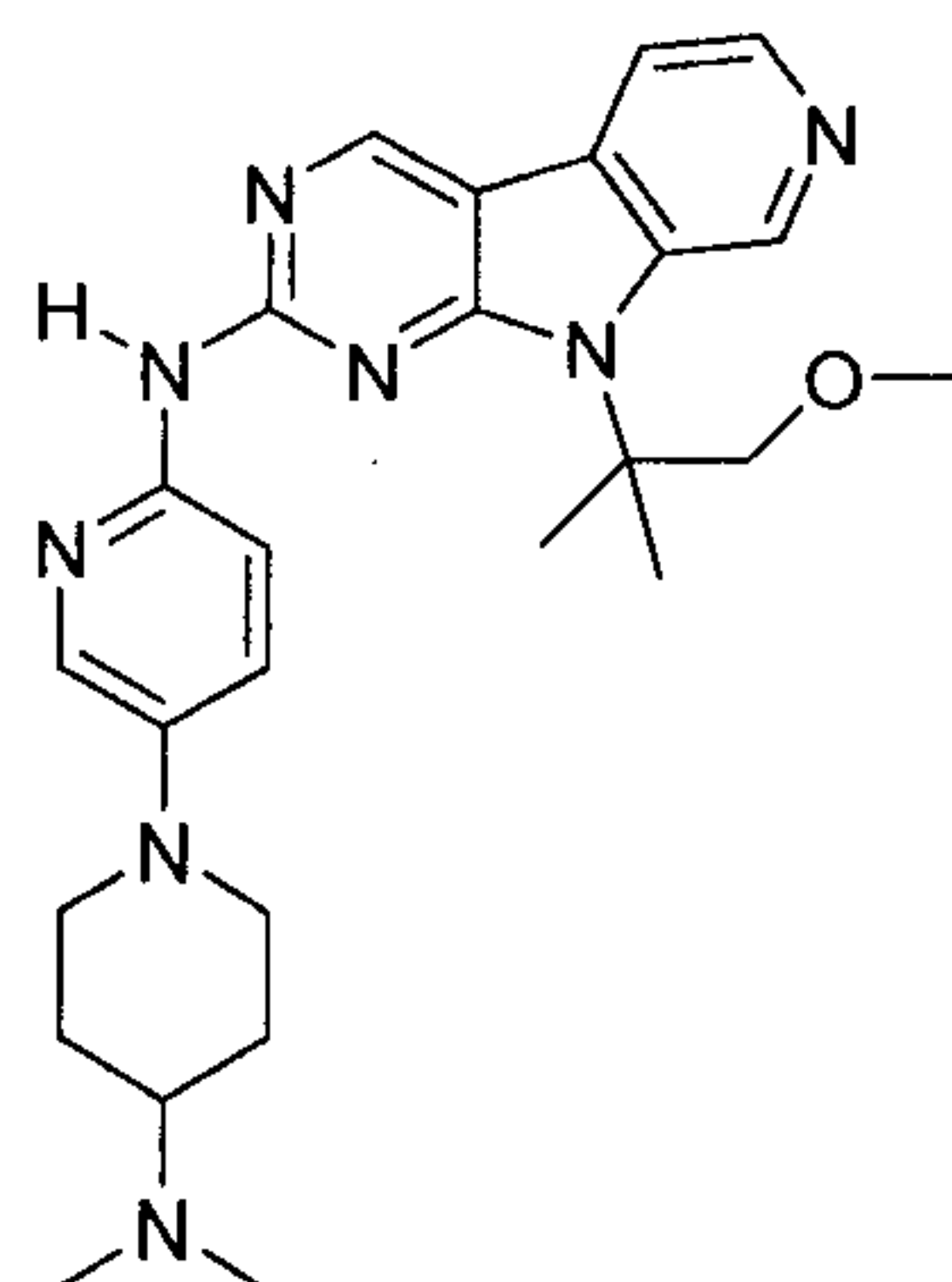
or a pharmaceutically acceptable salt thereof.

231. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

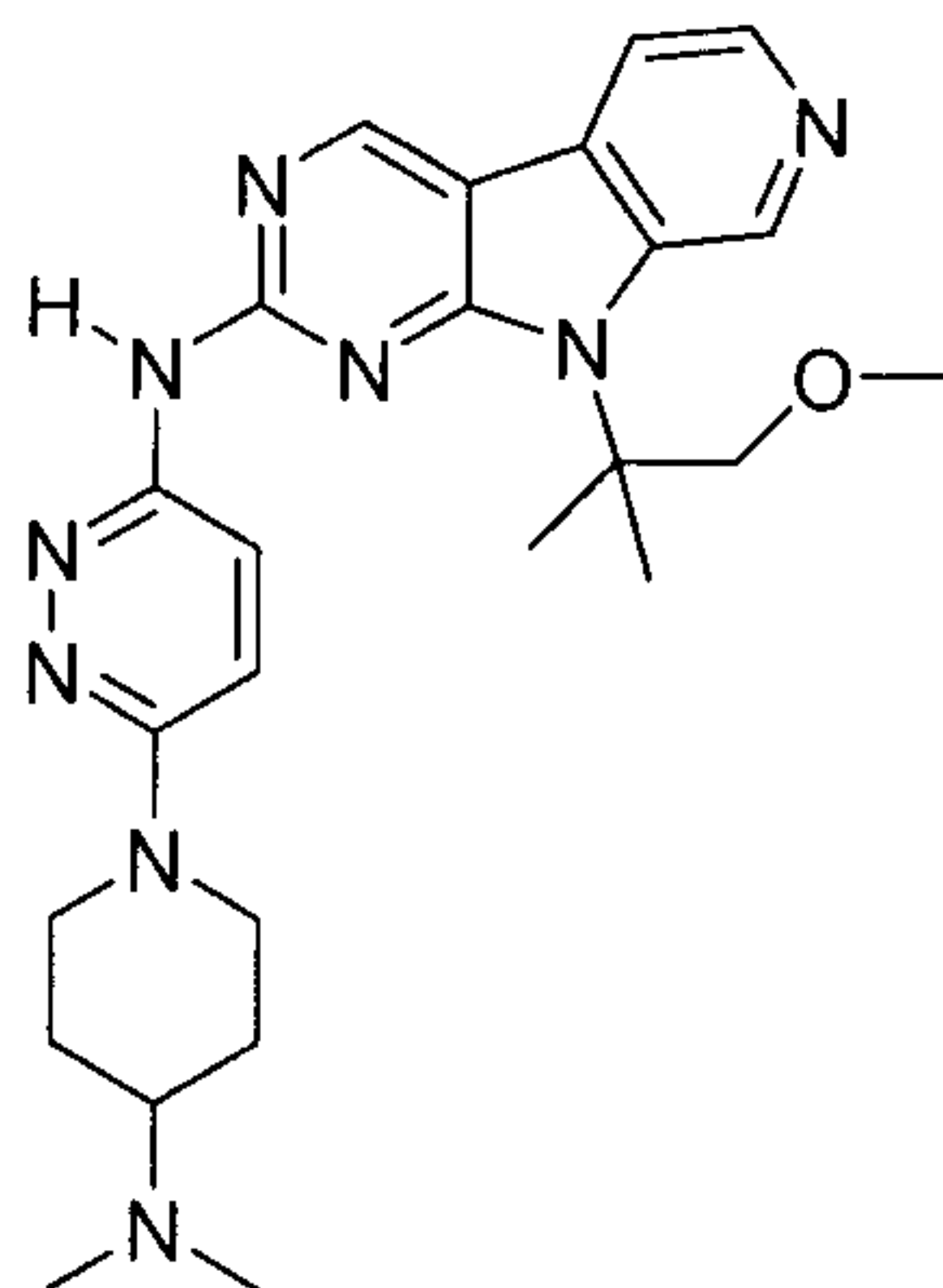
232. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

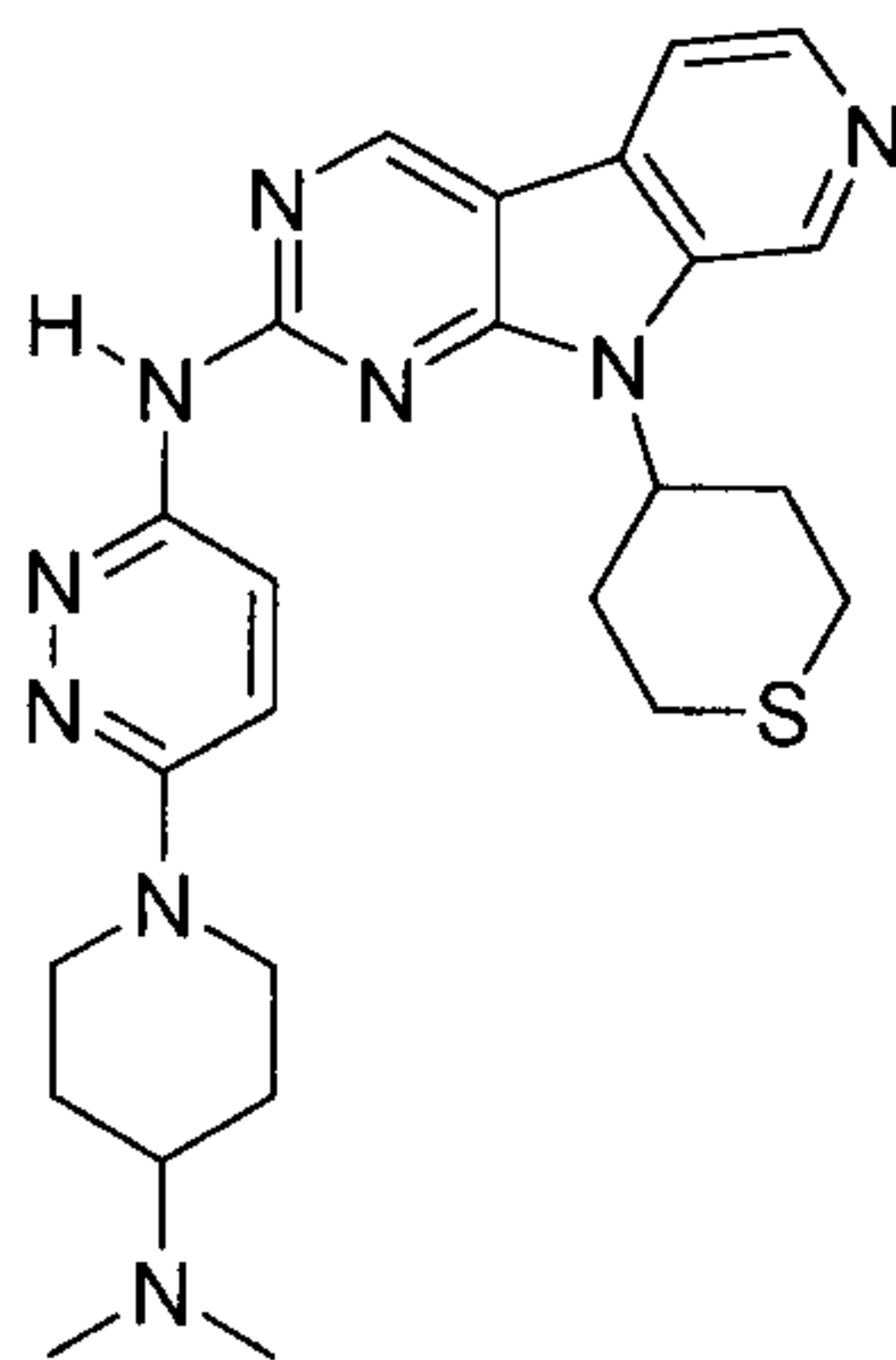


233. The compound of claim 1, wherein the compound is



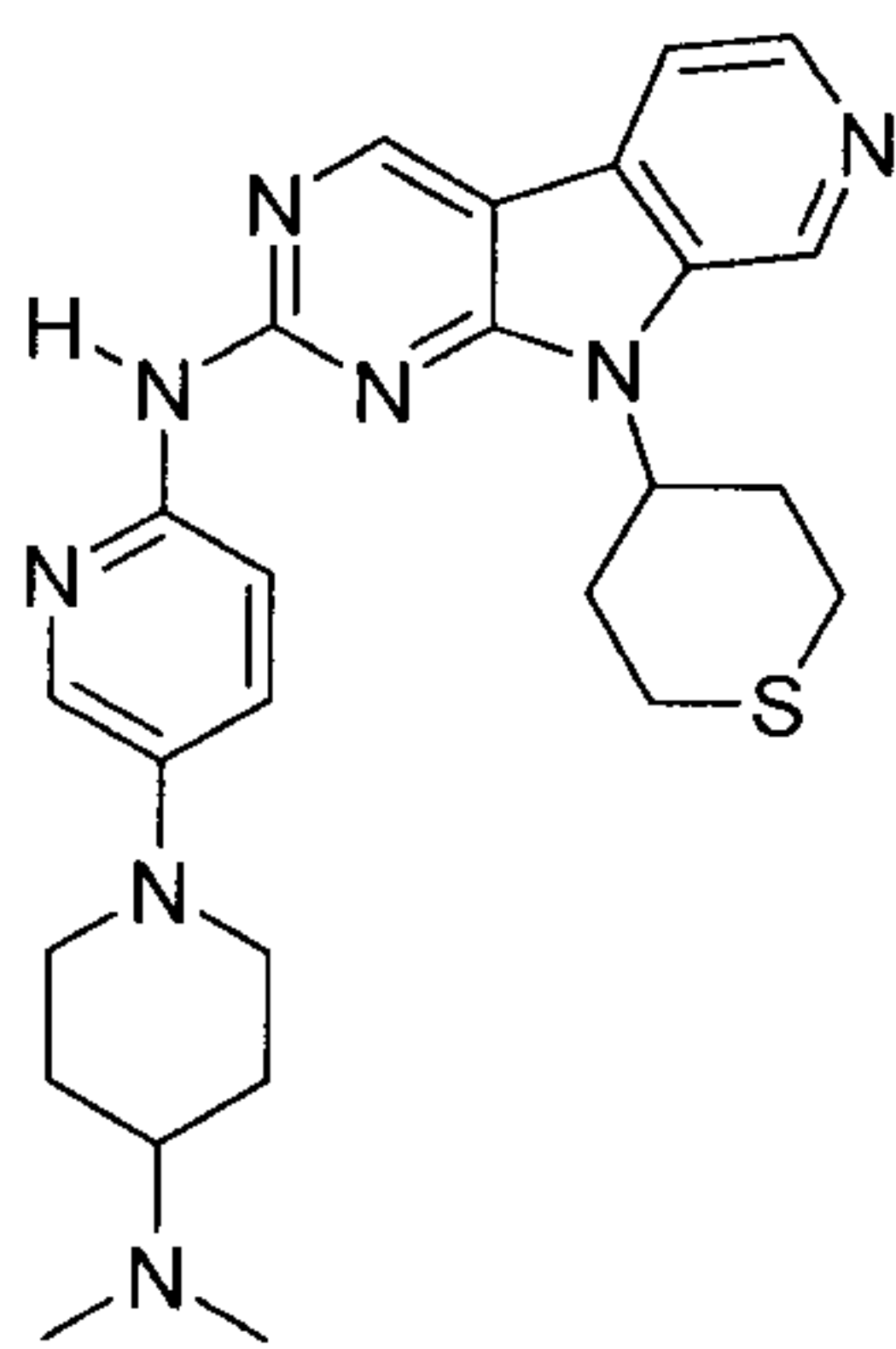
or a pharmaceutically acceptable salt thereof.

234. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

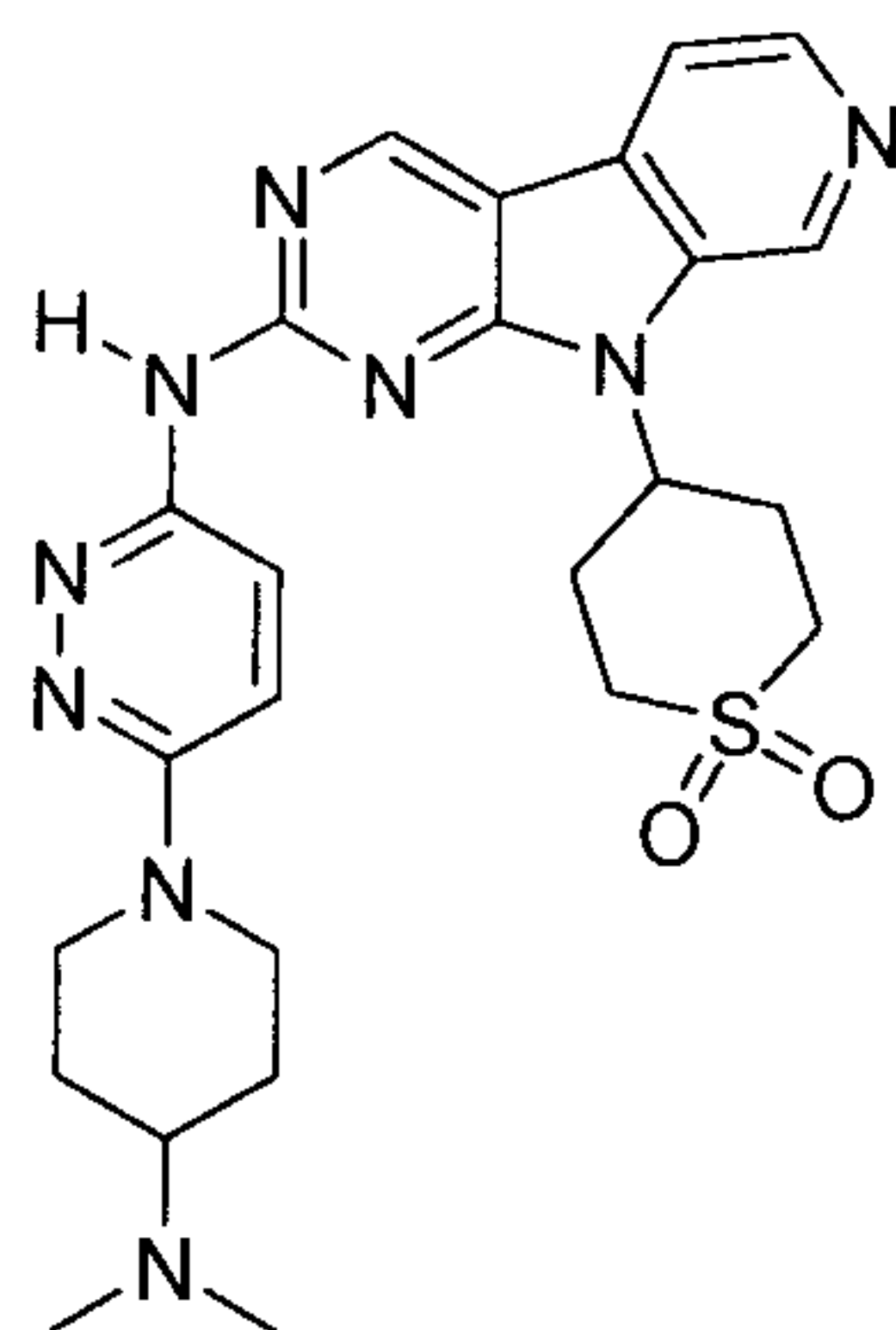
235. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

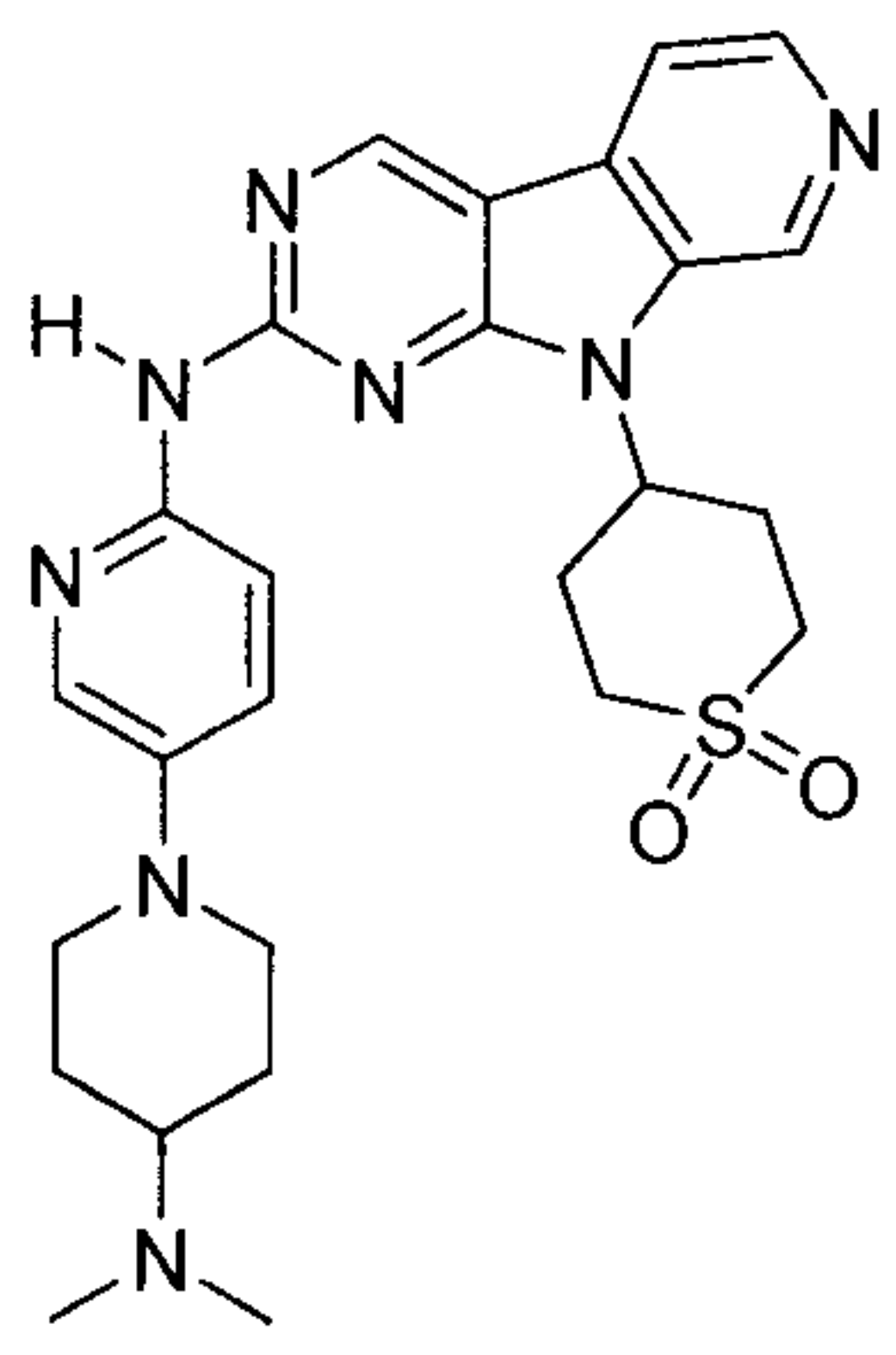


236. The compound of claim 1, wherein the compound is



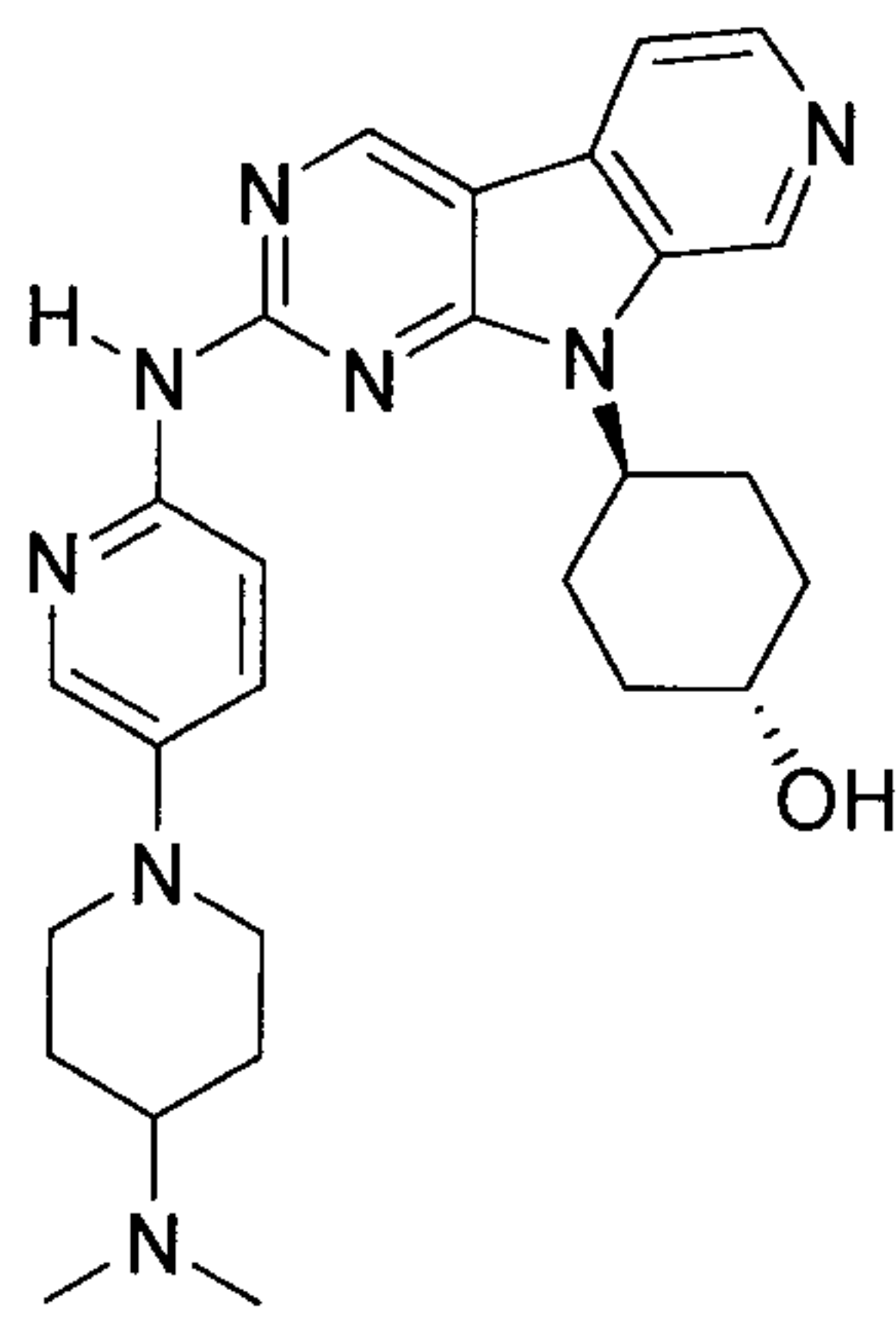
or a pharmaceutically acceptable salt thereof.

237. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

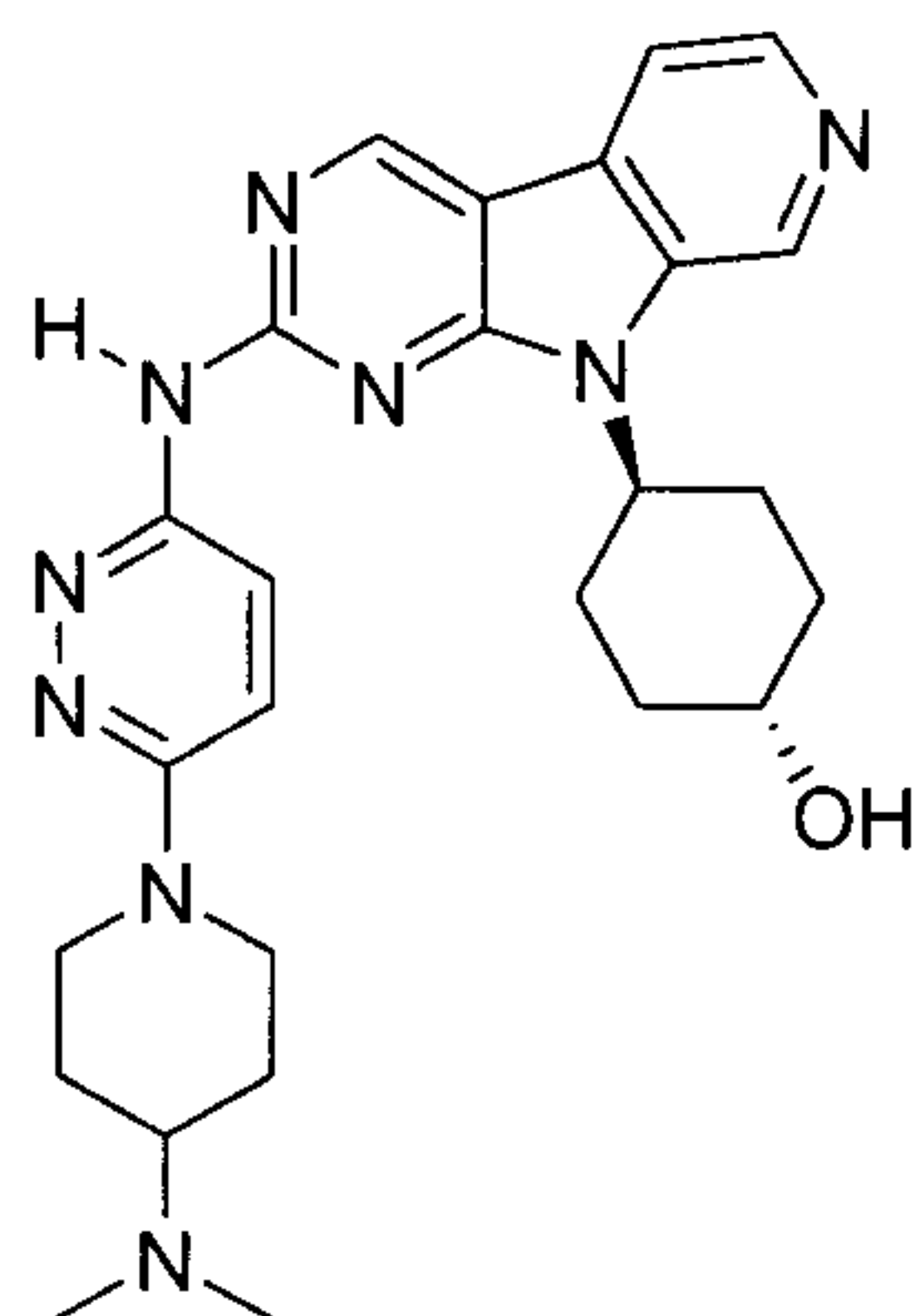
238. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

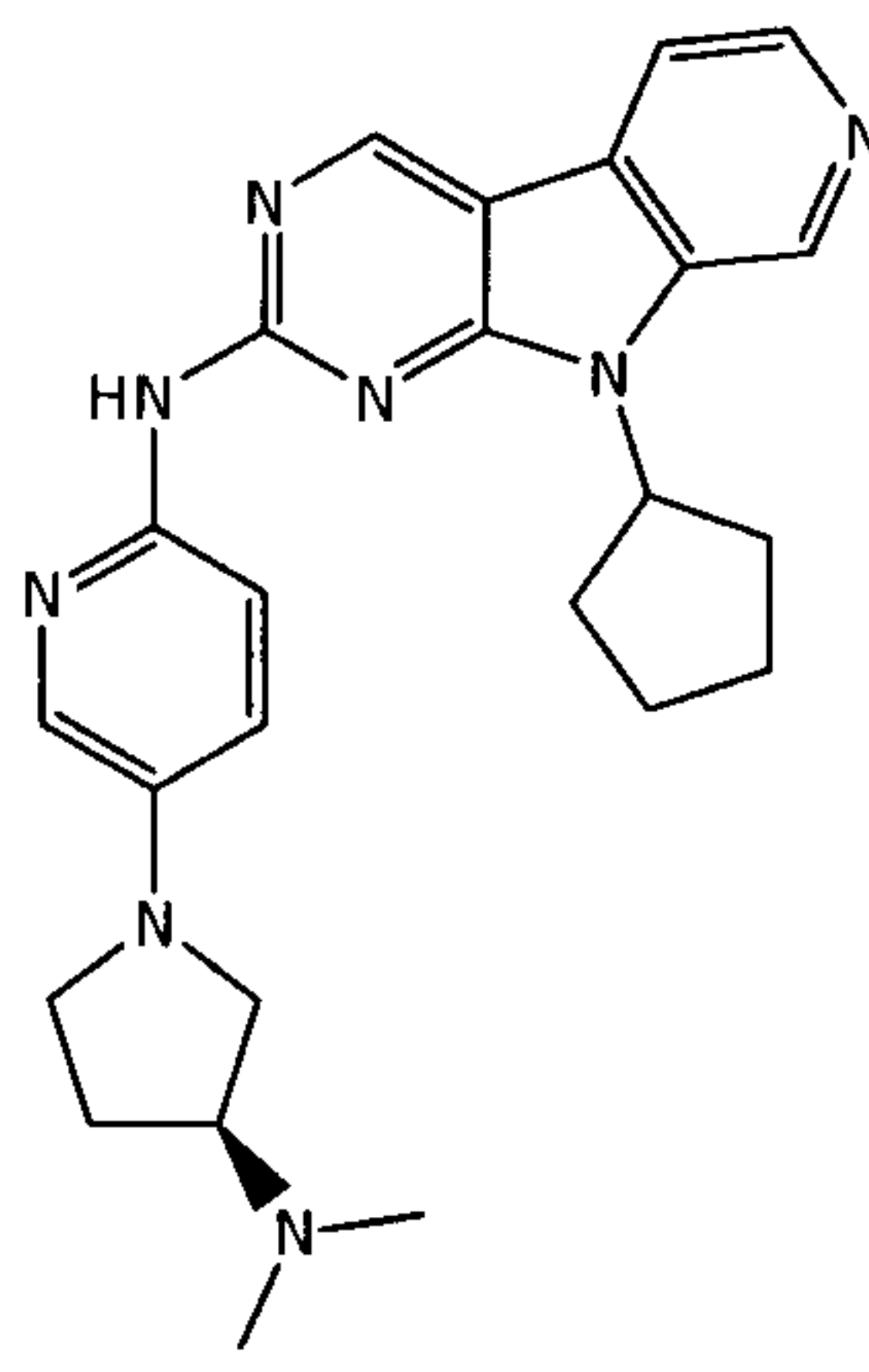


239. The compound of claim 1, wherein the compound is



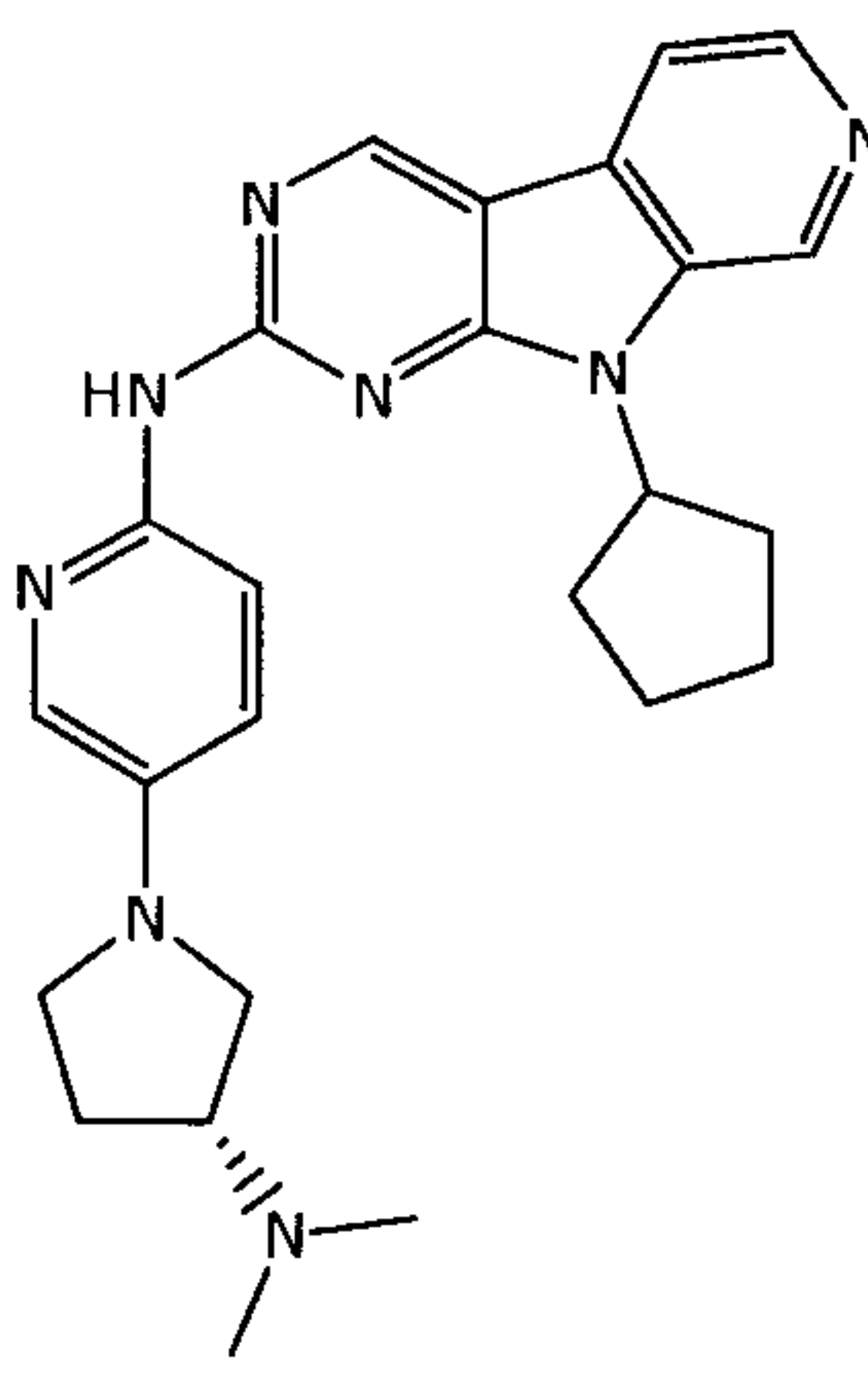
or a pharmaceutically acceptable salt thereof.

240. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

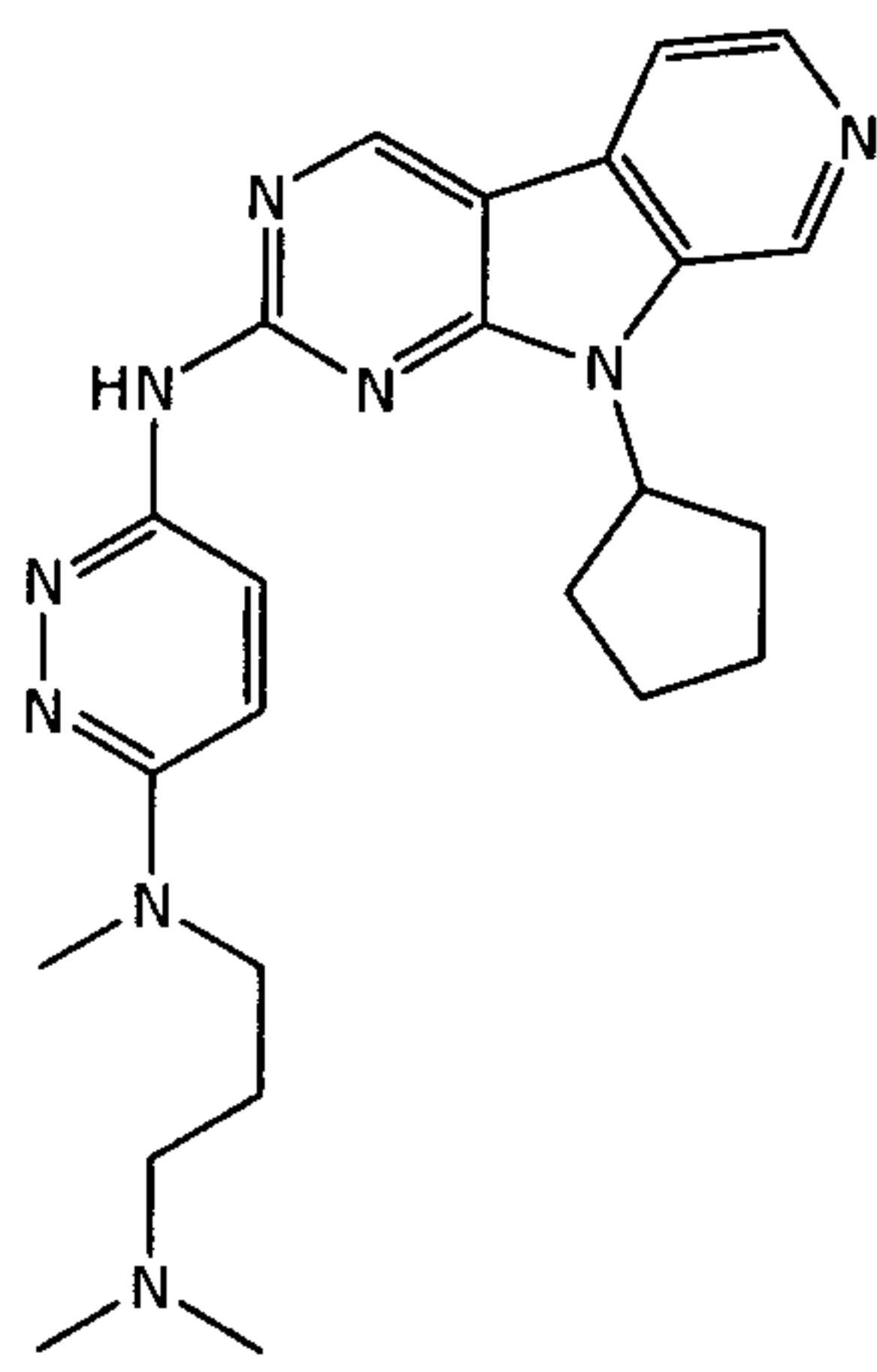
241. The compound of claim 1, wherein the compound is





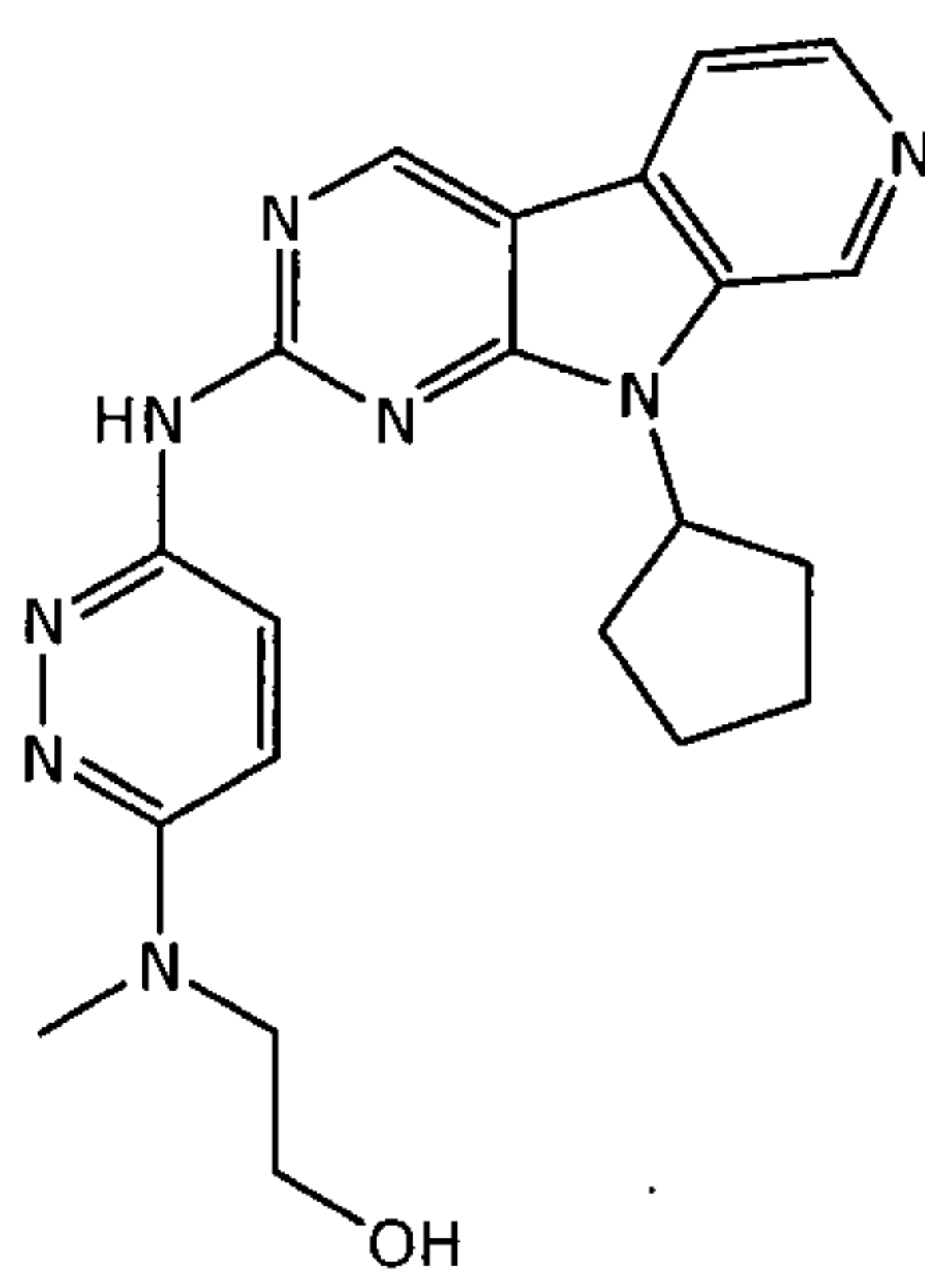
or a pharmaceutically acceptable salt thereof.

242. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

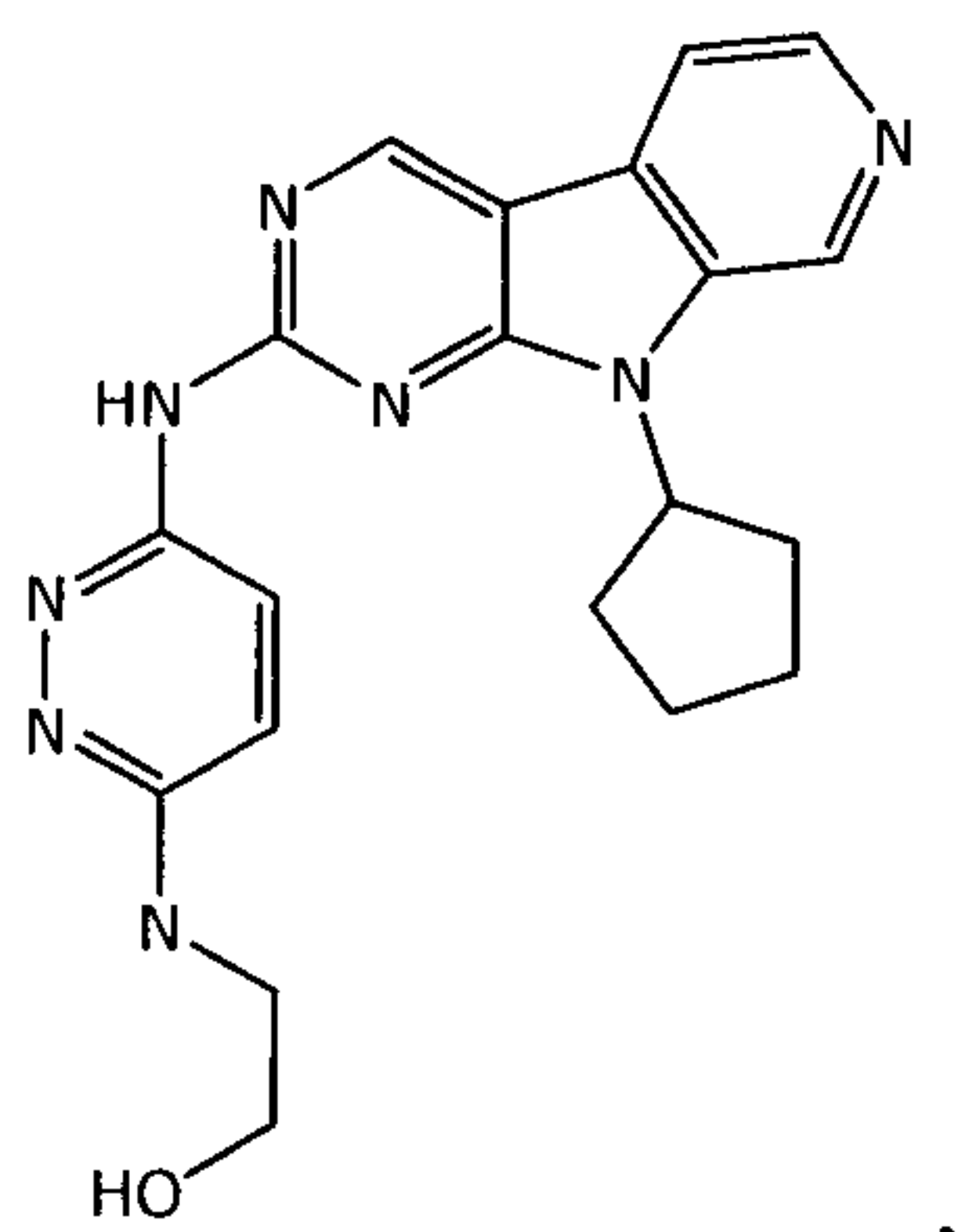
243. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

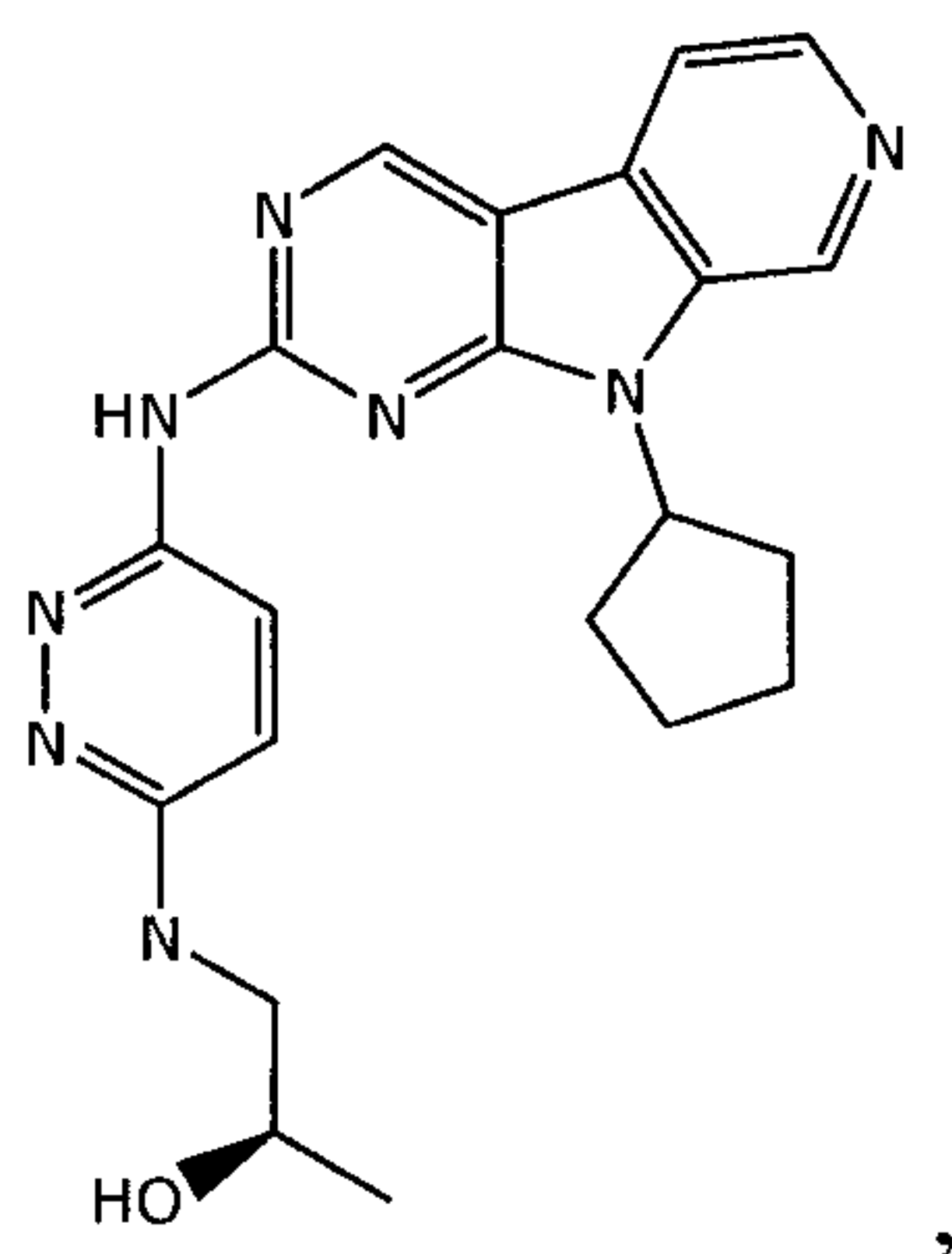


244. The compound of claim 1, wherein the compound is



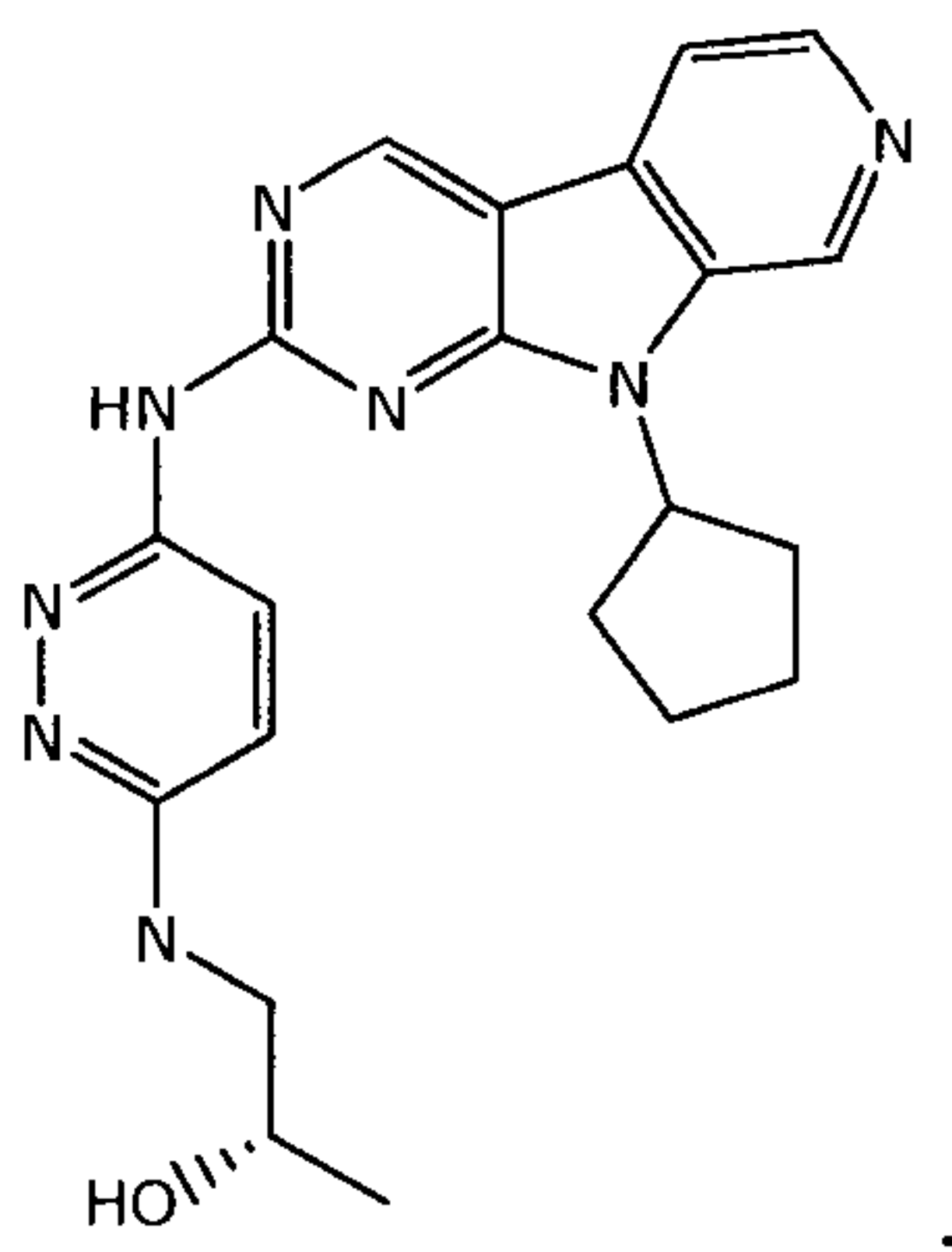
or a pharmaceutically acceptable salt thereof.

245. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

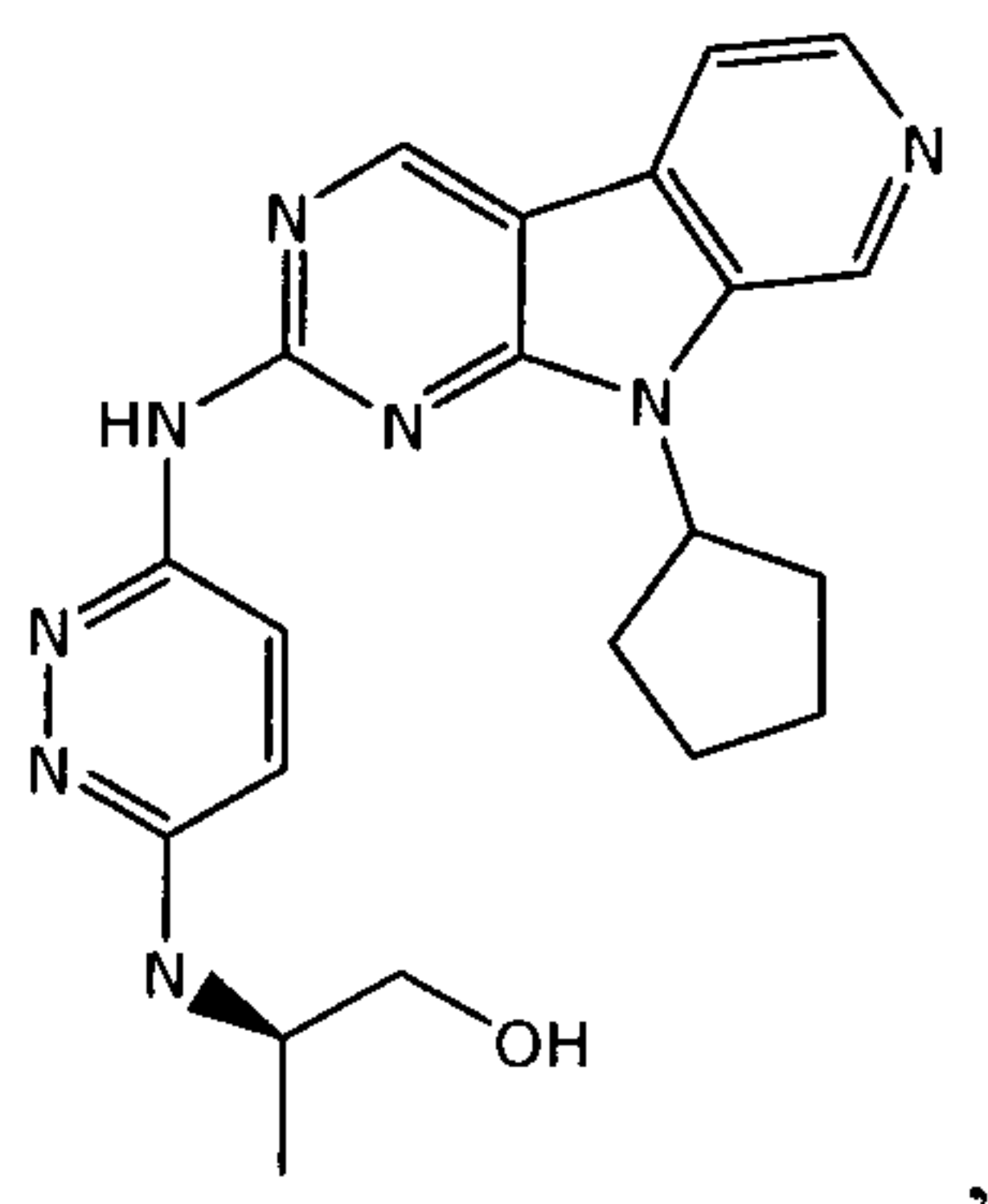
246. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

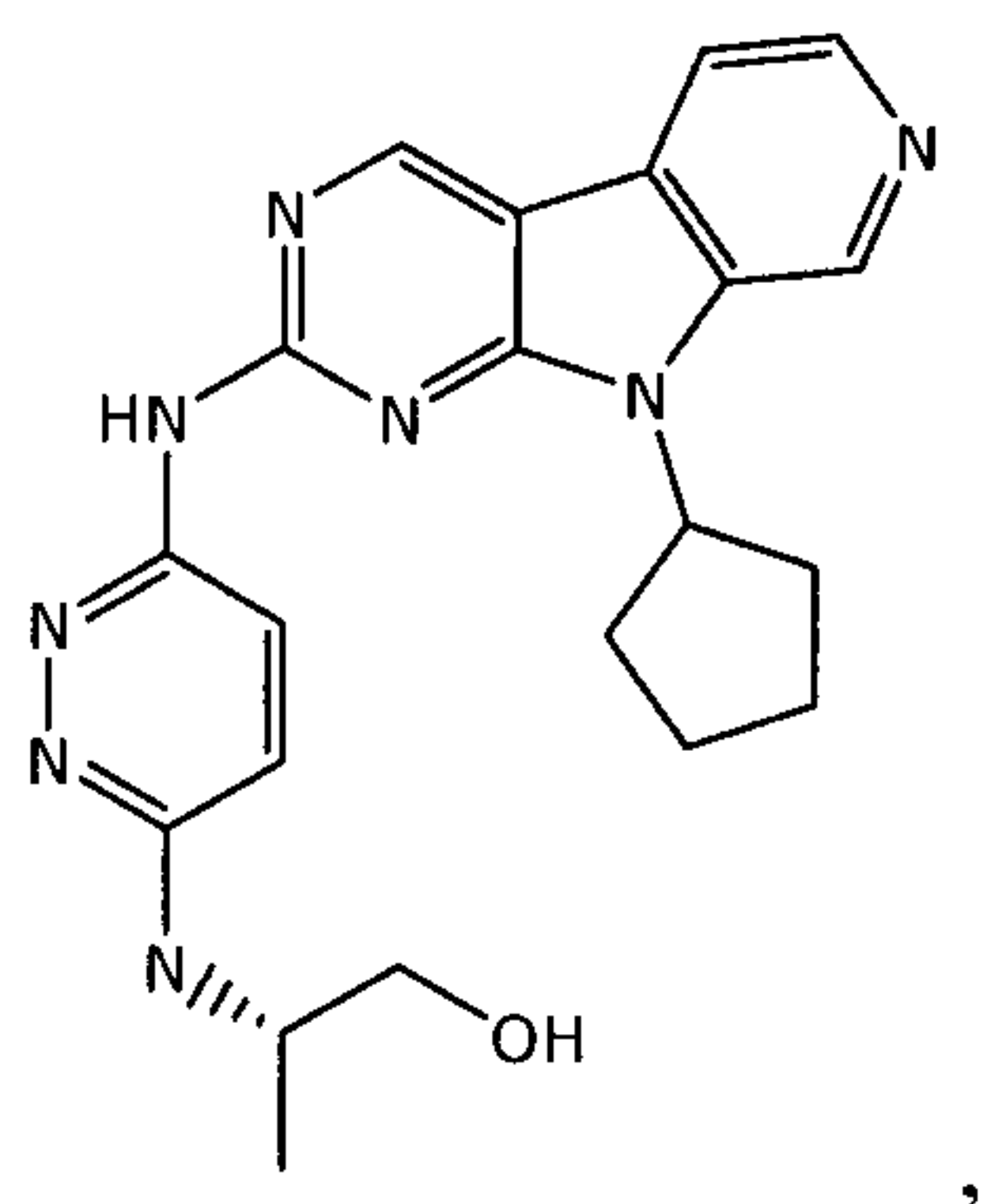


247. The compound of claim 1, wherein the compound is



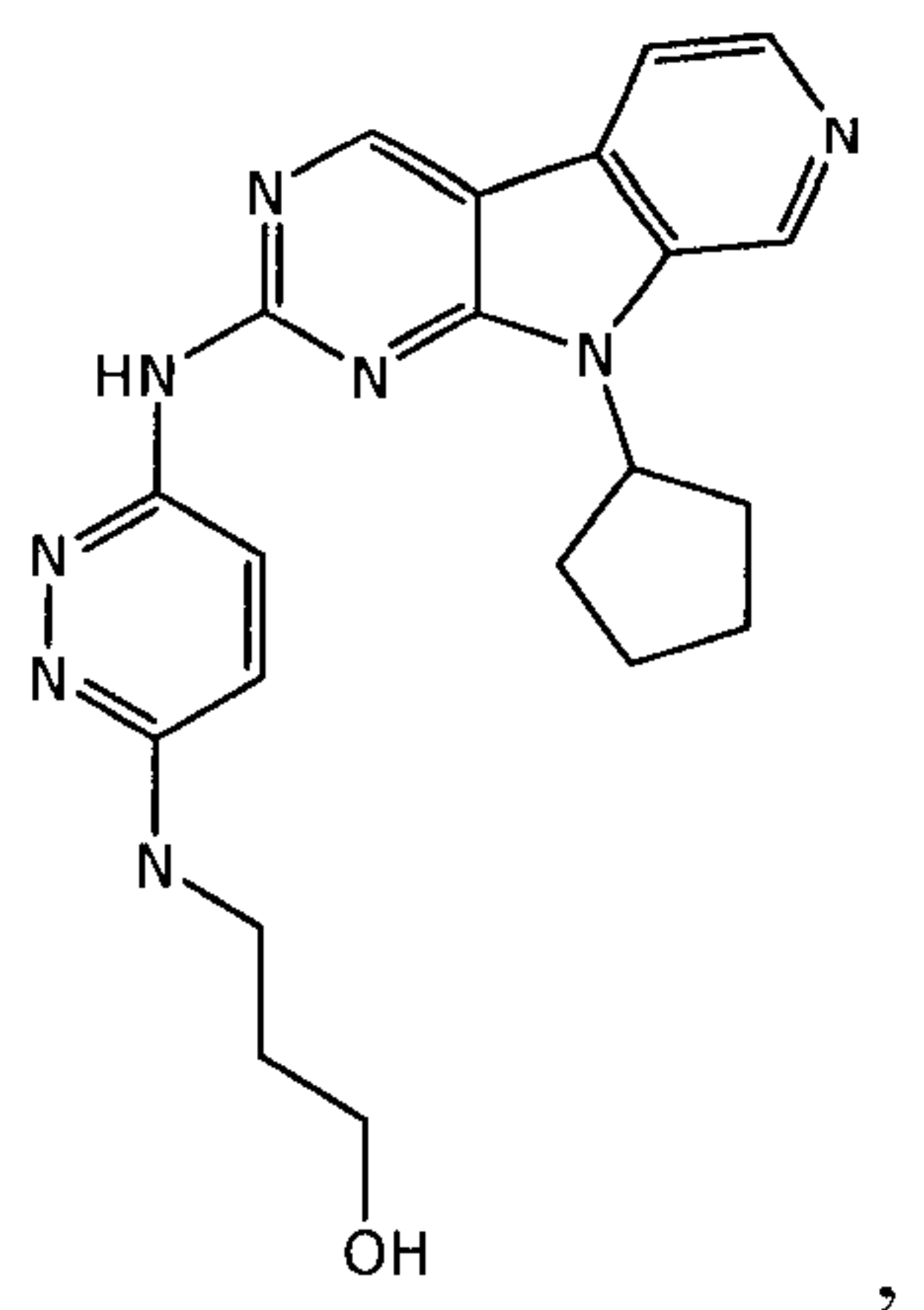
or a pharmaceutically acceptable salt thereof.

248. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

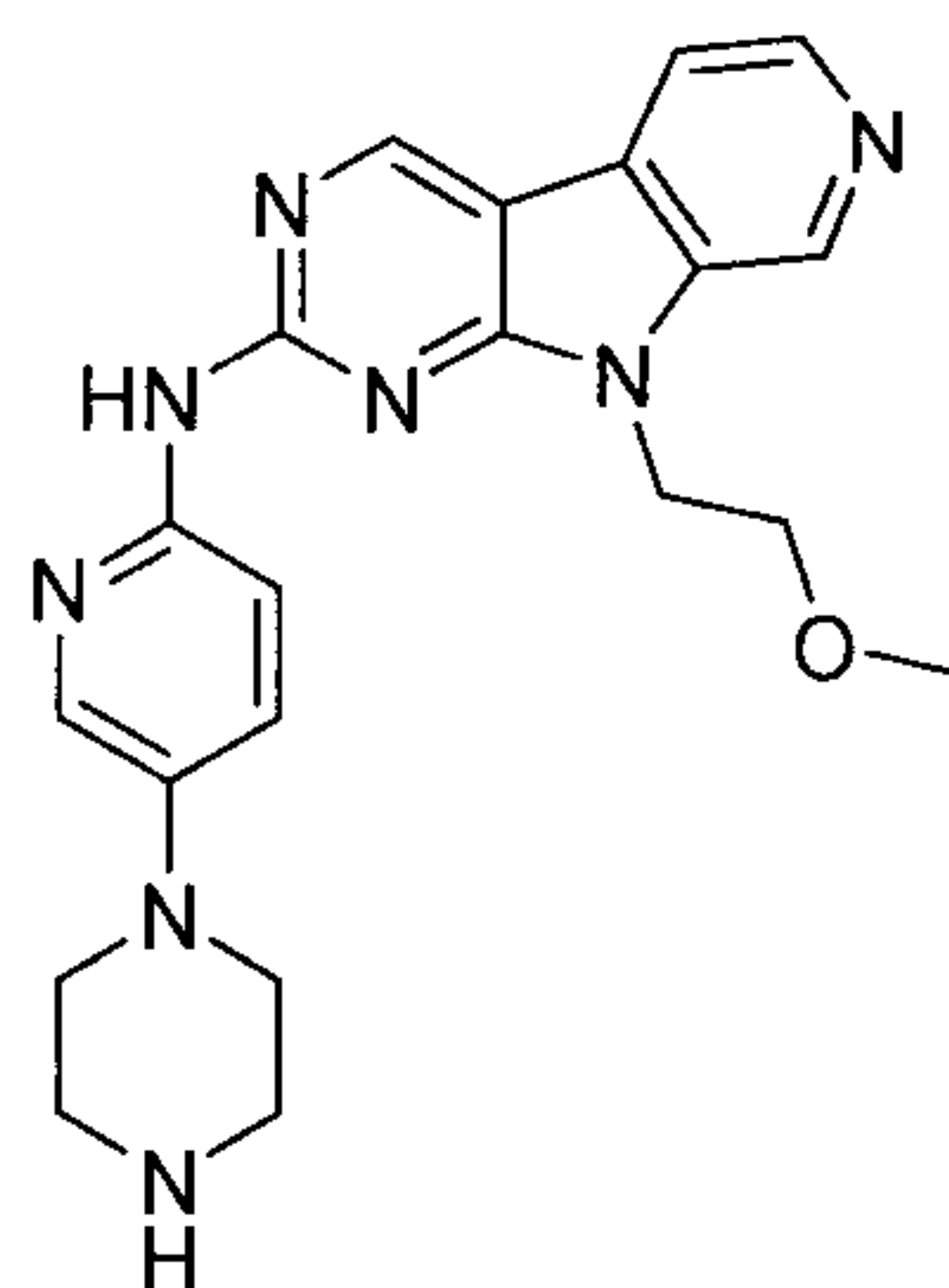
249. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

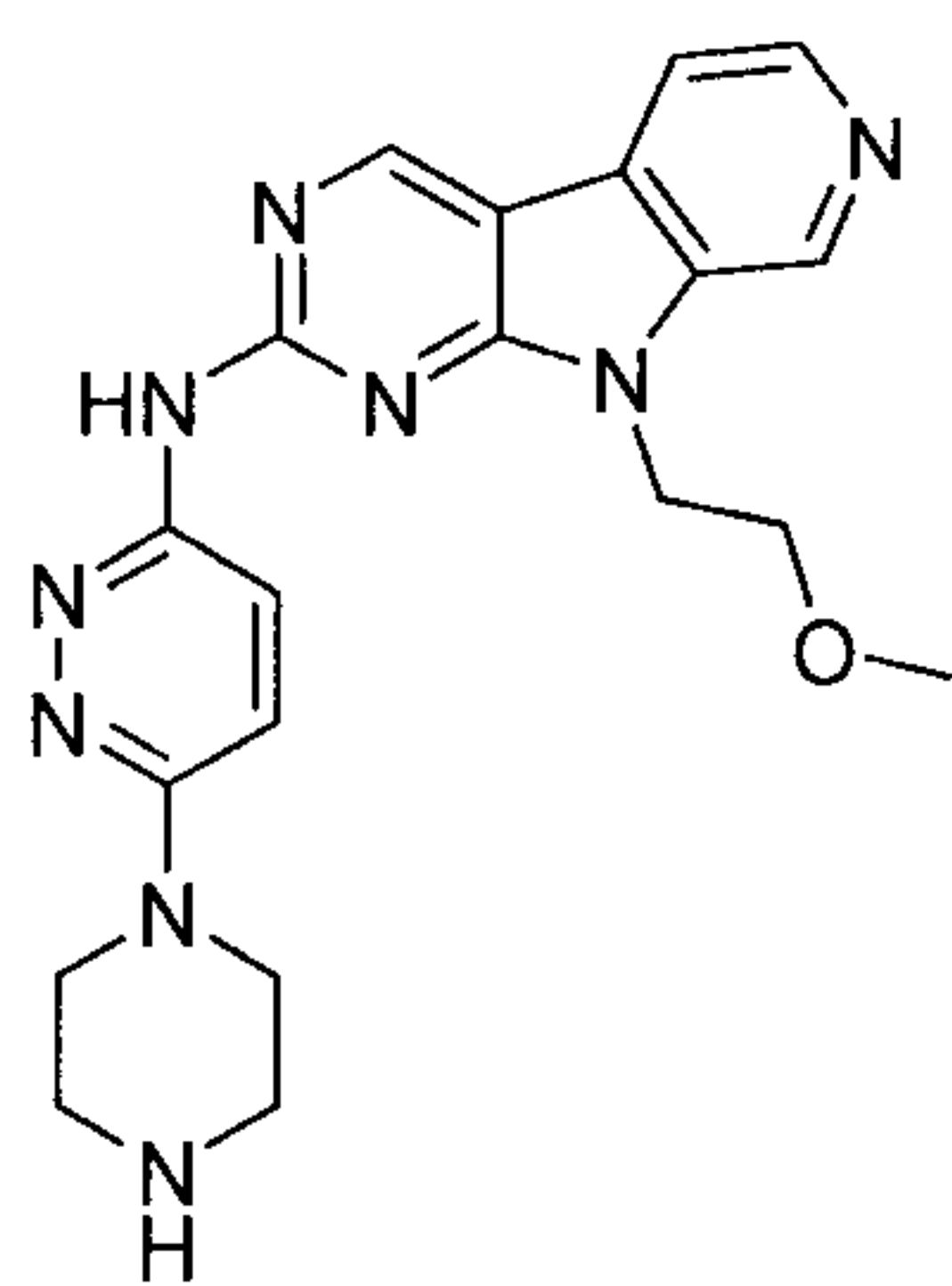


250. The compound of claim 1, wherein the compound is



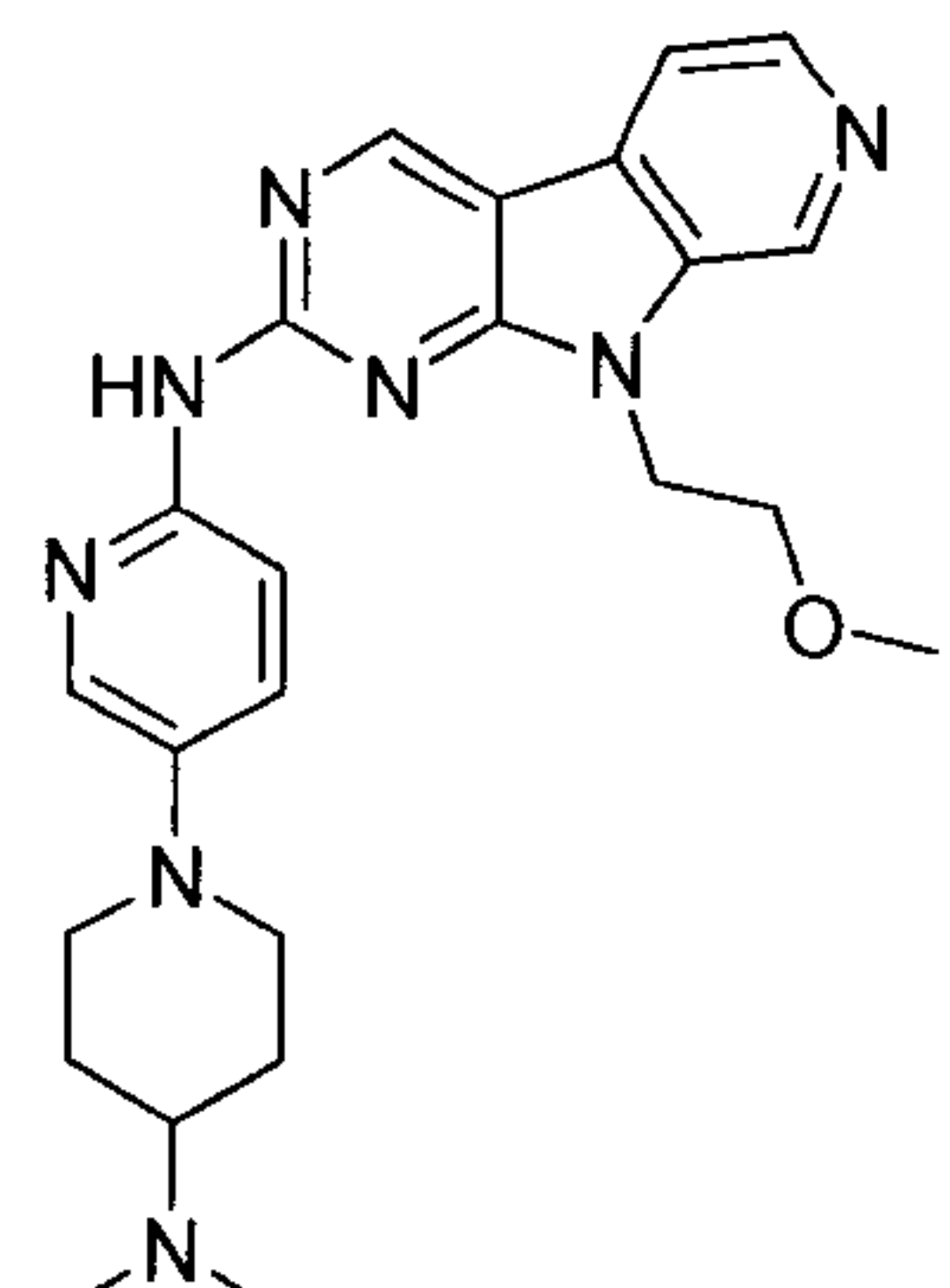
or a pharmaceutically acceptable salt thereof.

251. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

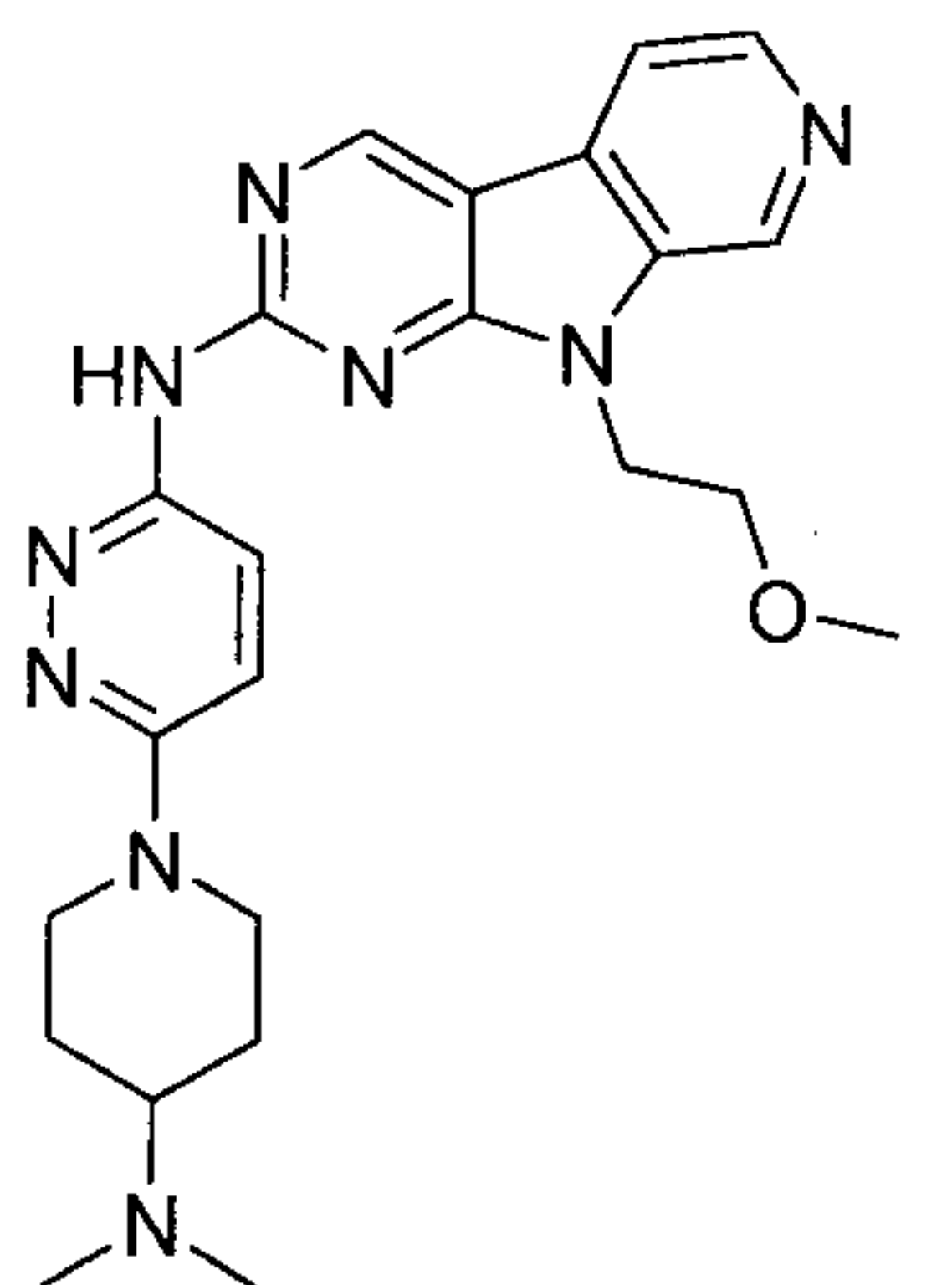
252. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

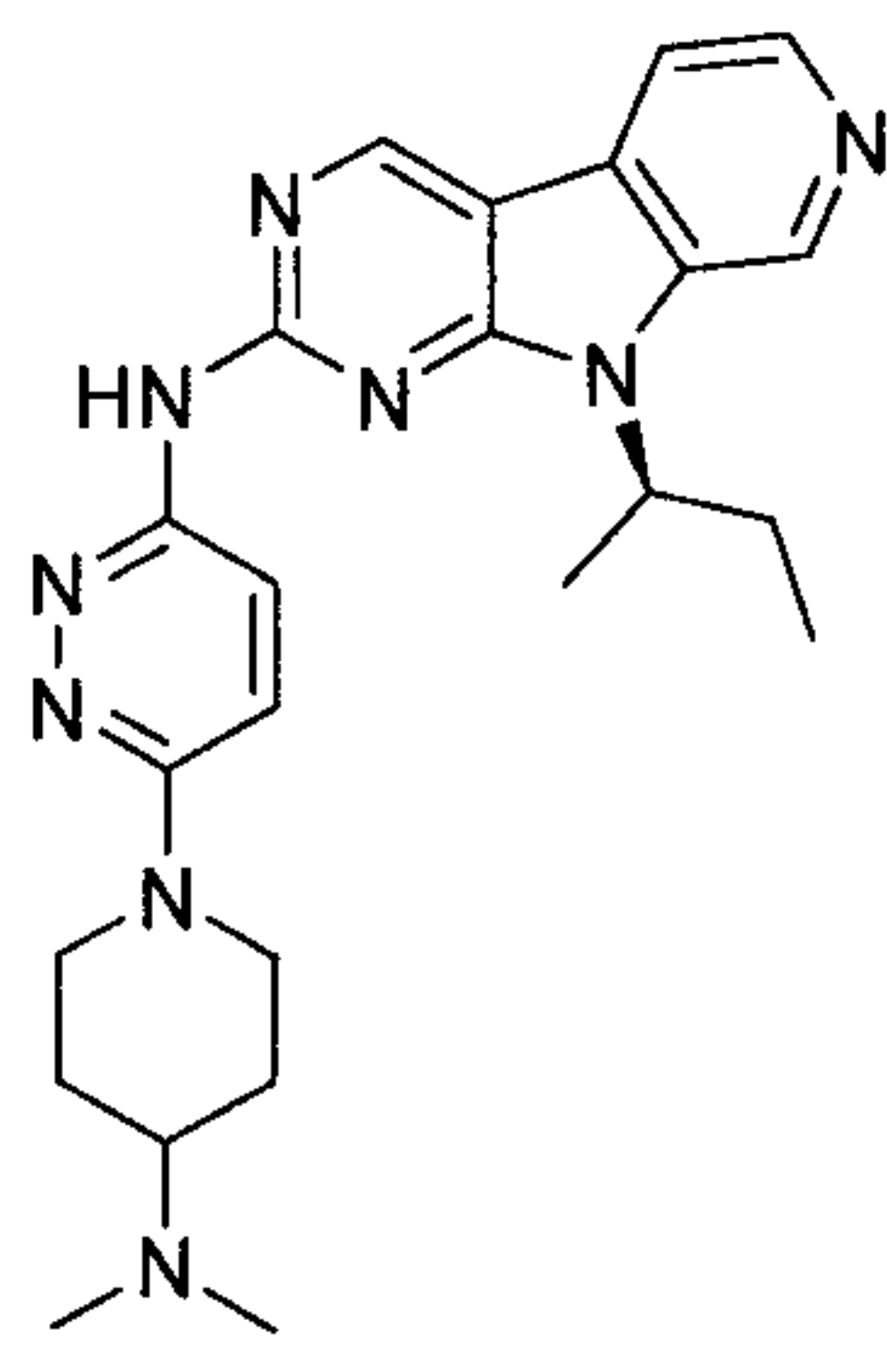


253. The compound of claim 1, wherein the compound is



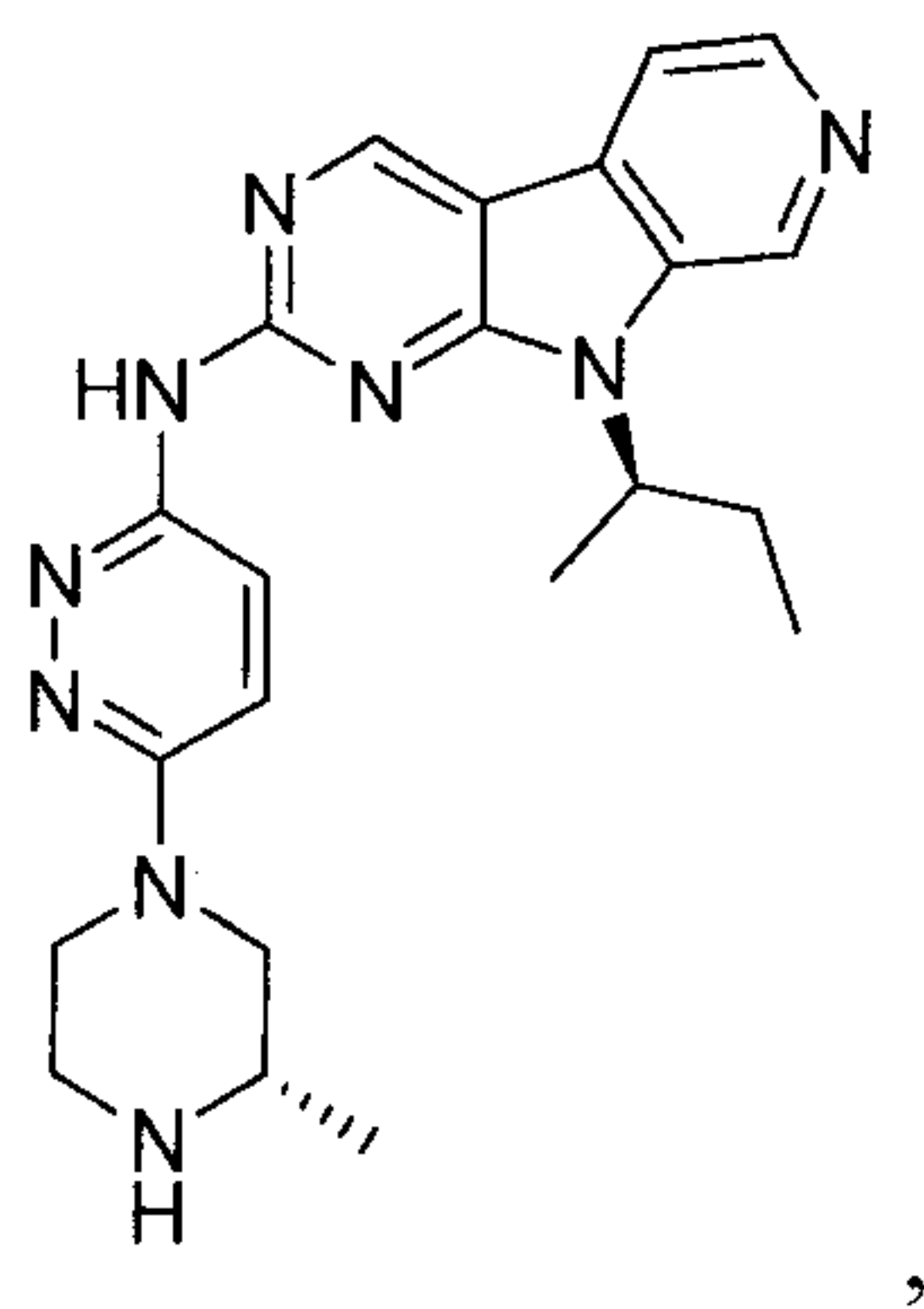
or a pharmaceutically acceptable salt thereof.

254. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

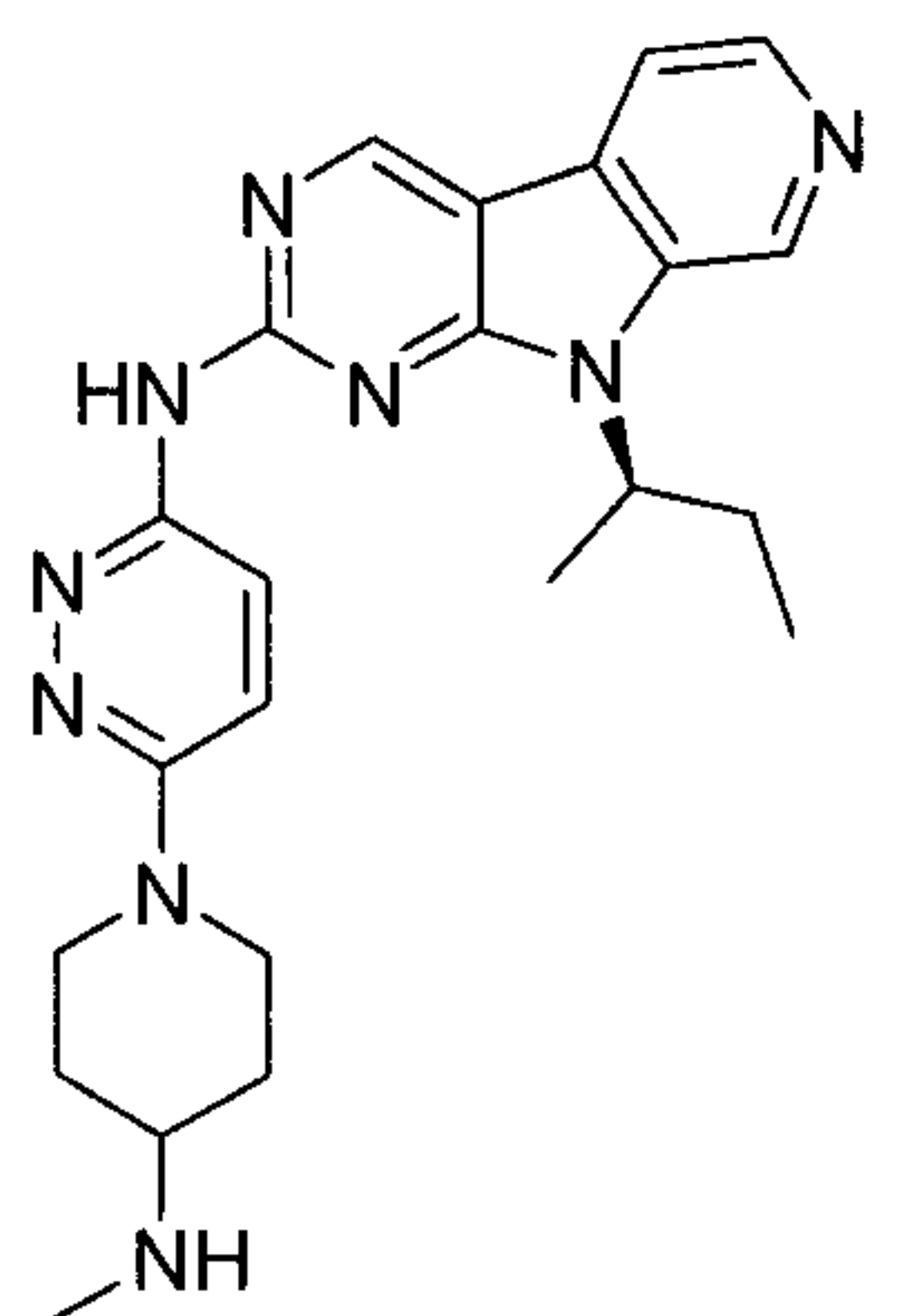
255. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

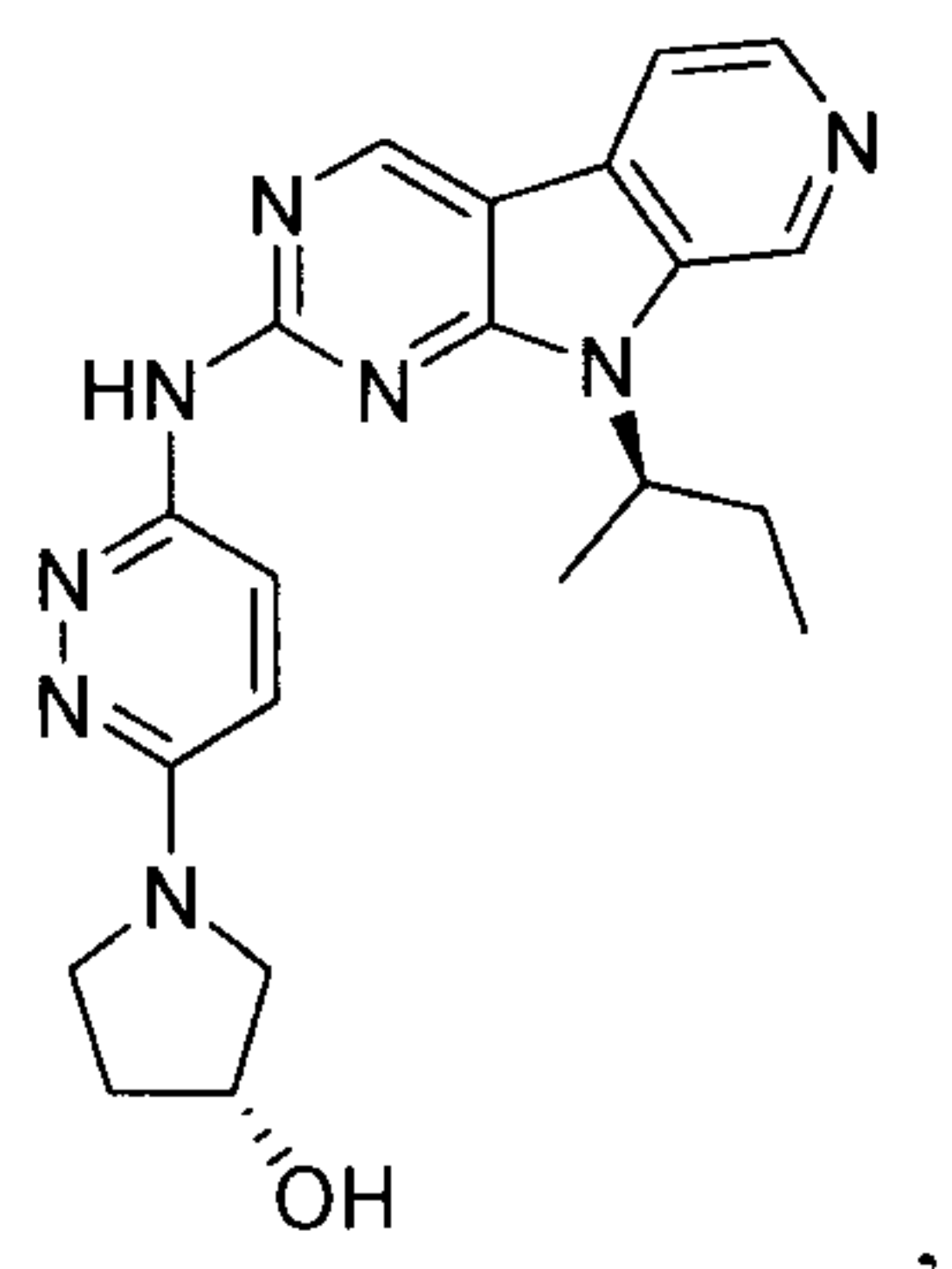


256. The compound of claim 1, wherein the compound is



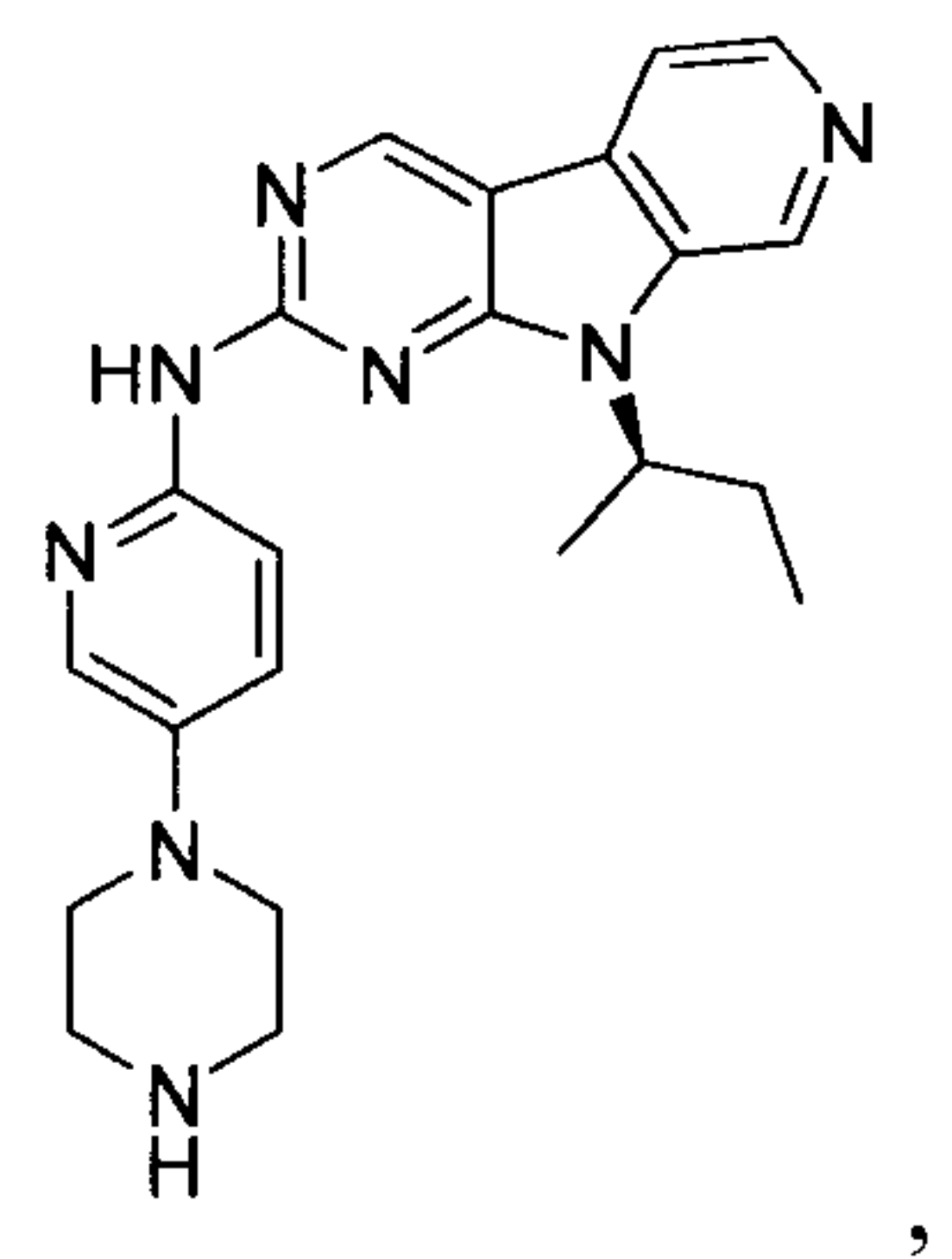
or a pharmaceutically acceptable salt thereof.

257. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

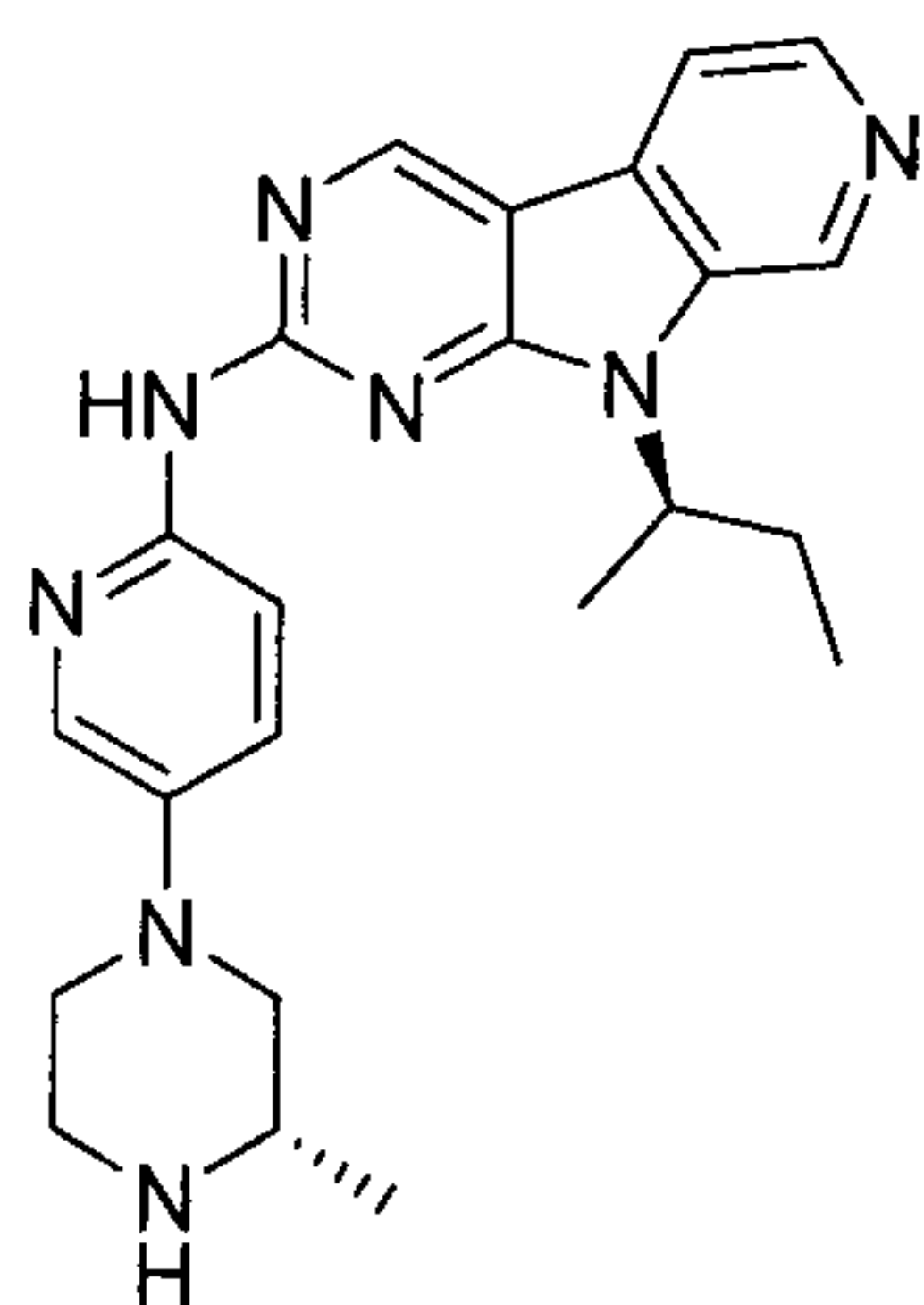
258. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

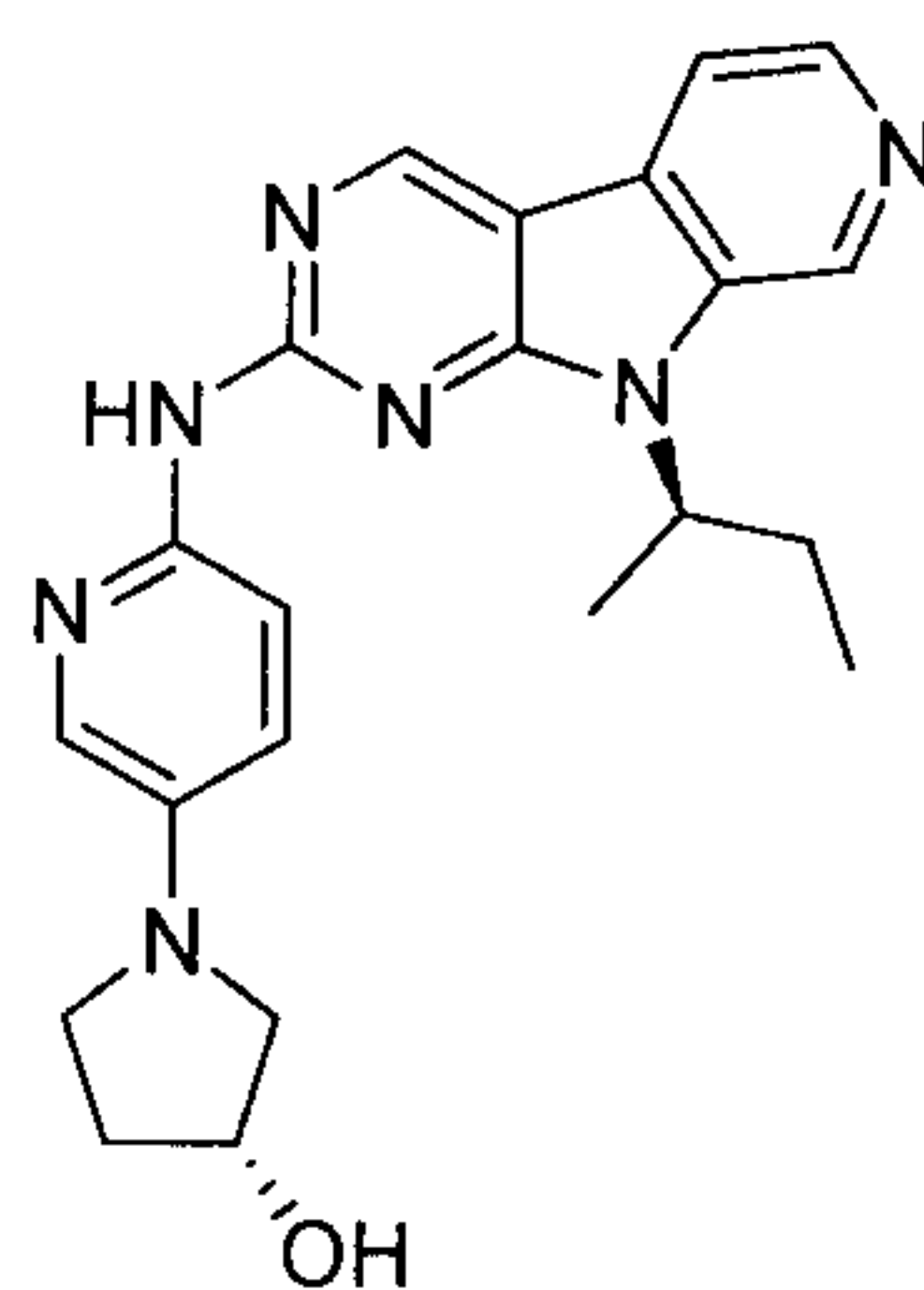


259. The compound of claim 1, wherein the compound is



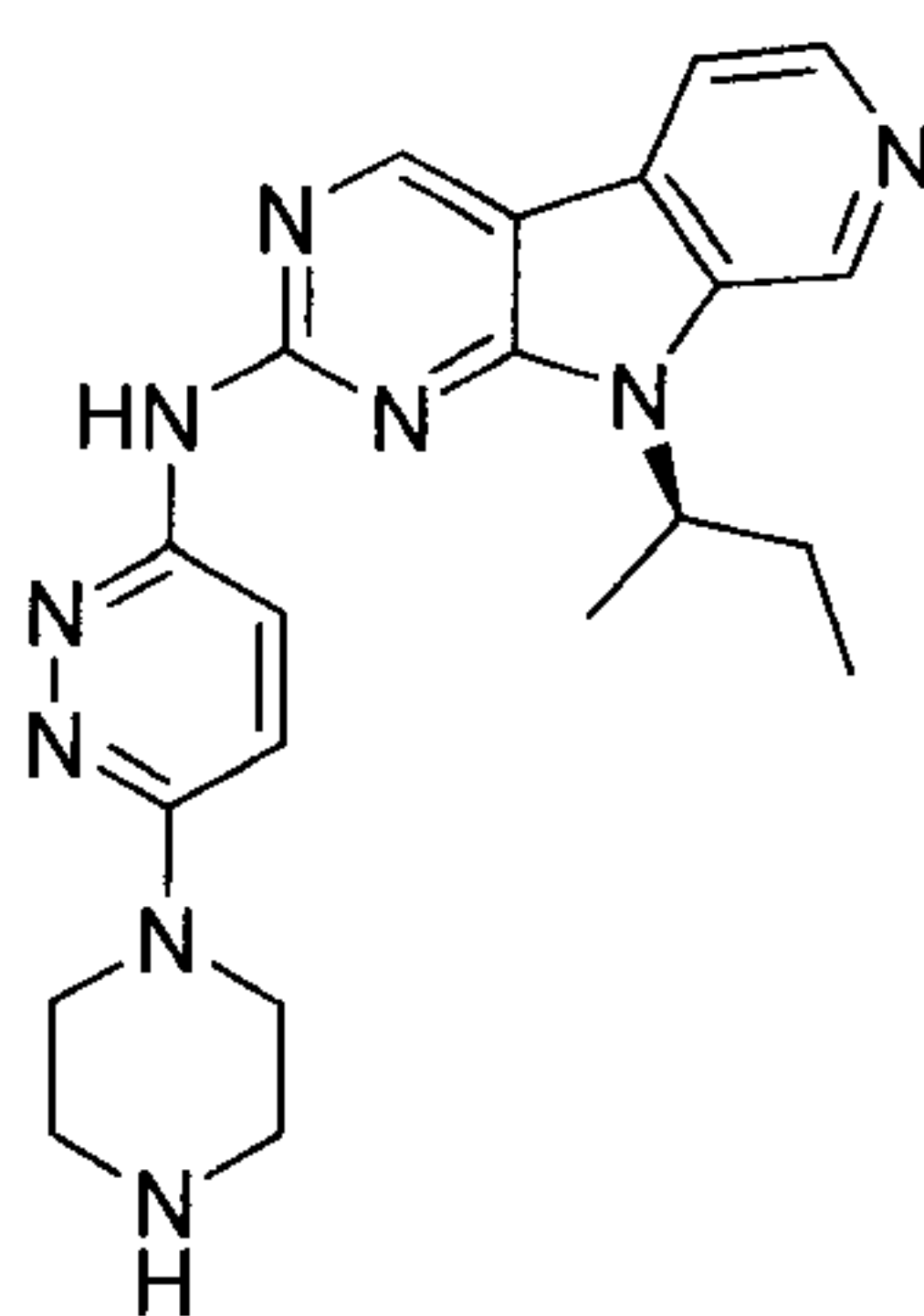
or a pharmaceutically acceptable salt thereof.

260. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

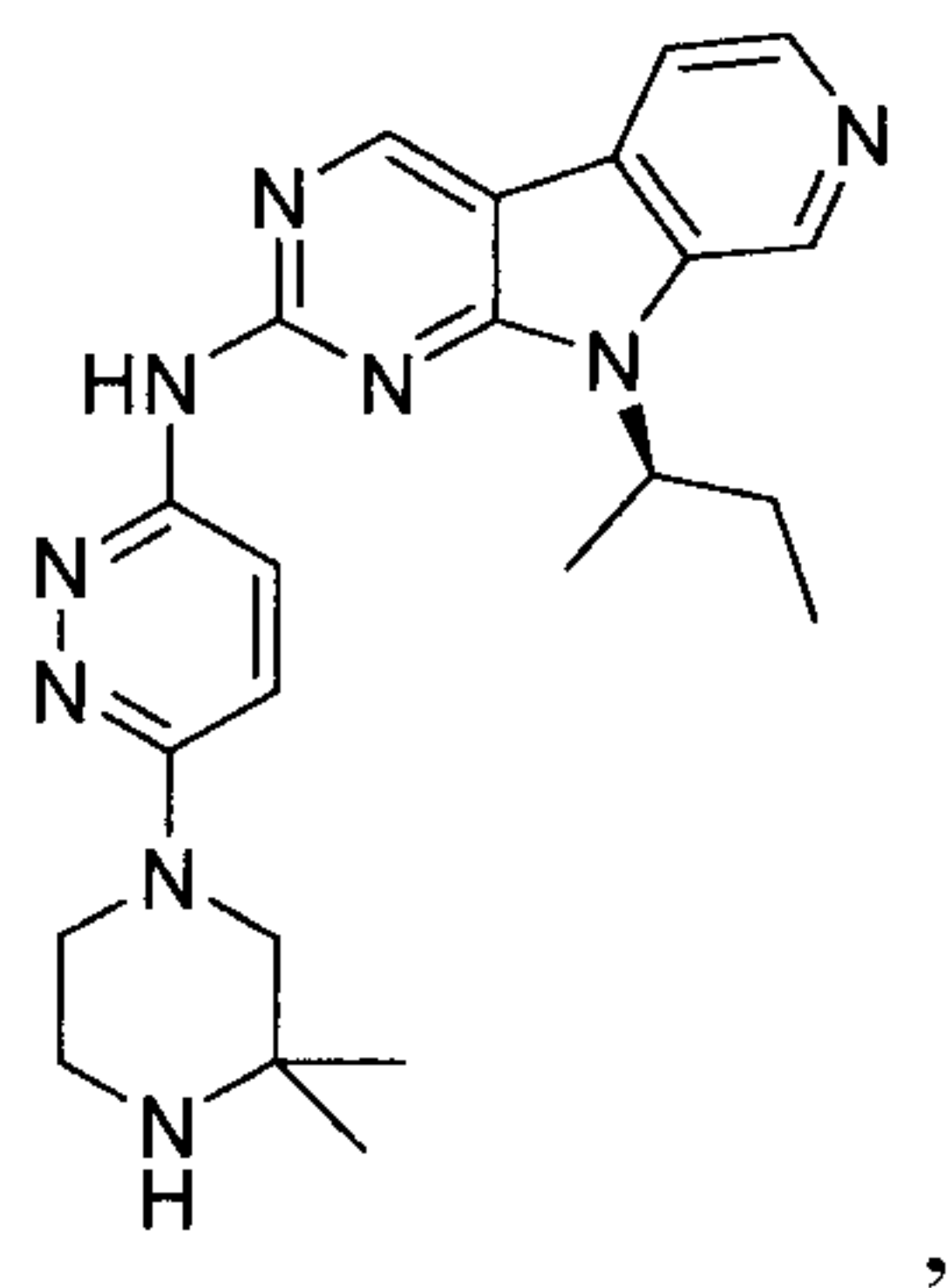
261. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

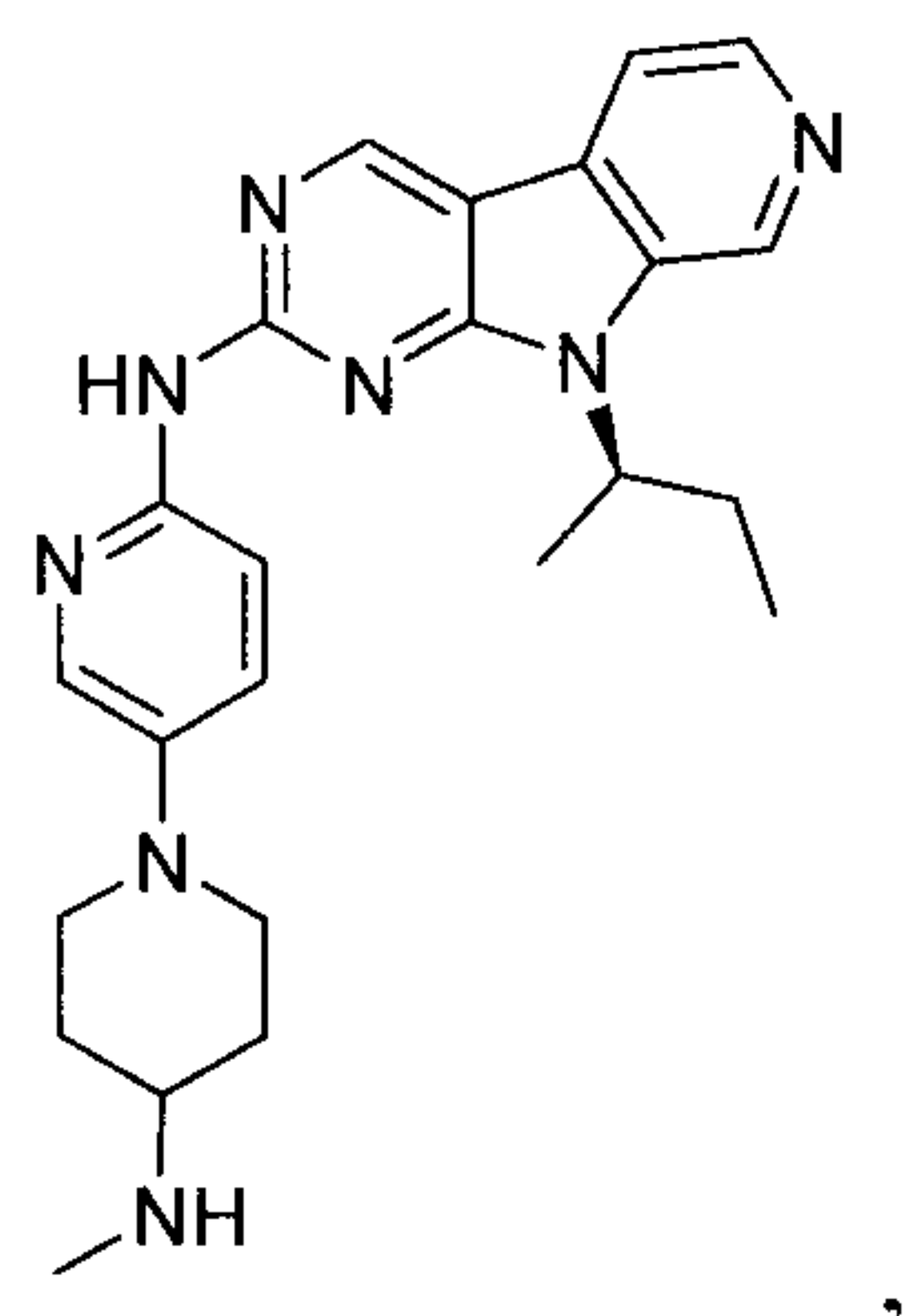


262. The compound of claim 1, wherein the compound is



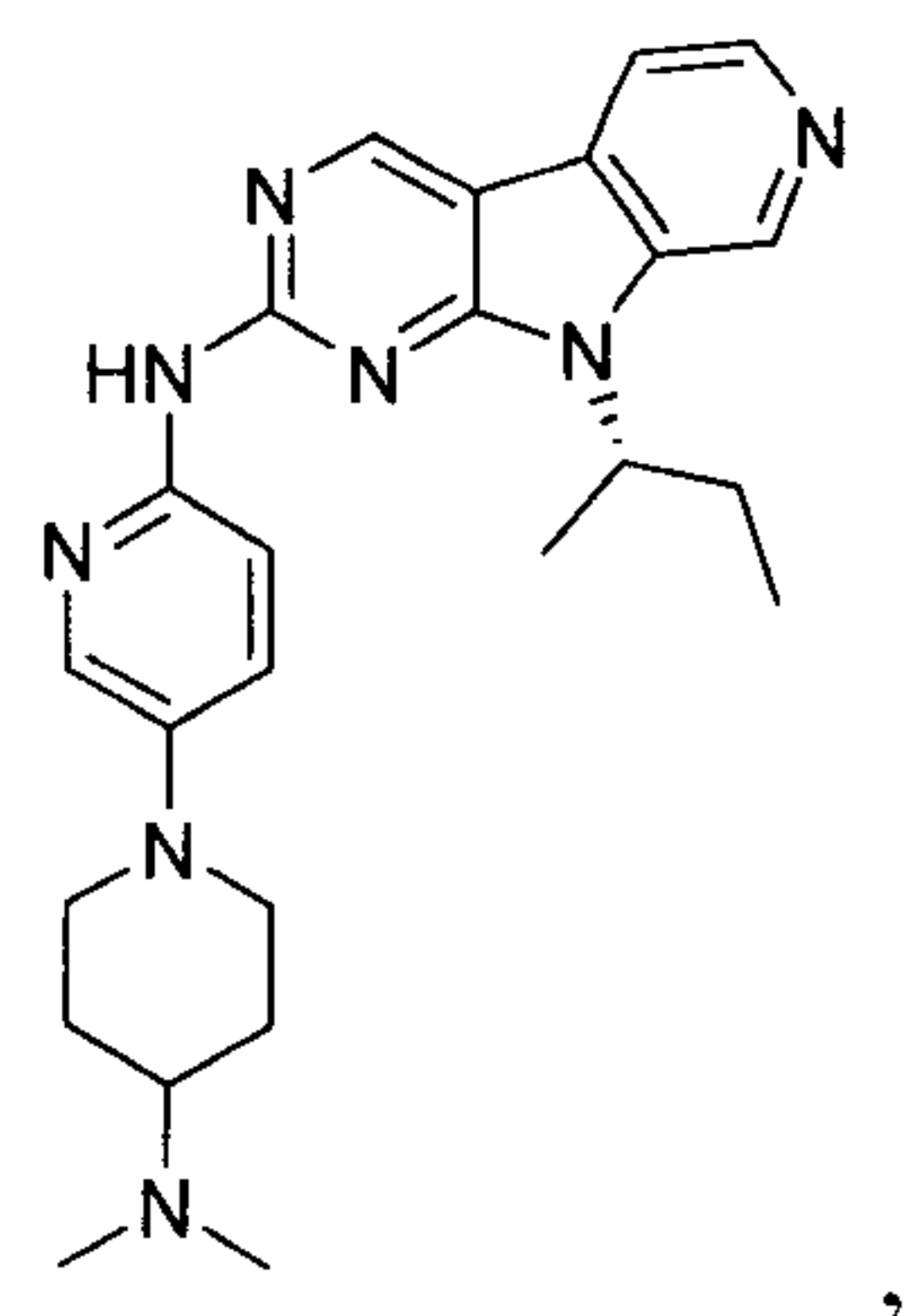
or a pharmaceutically acceptable salt thereof.

263. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

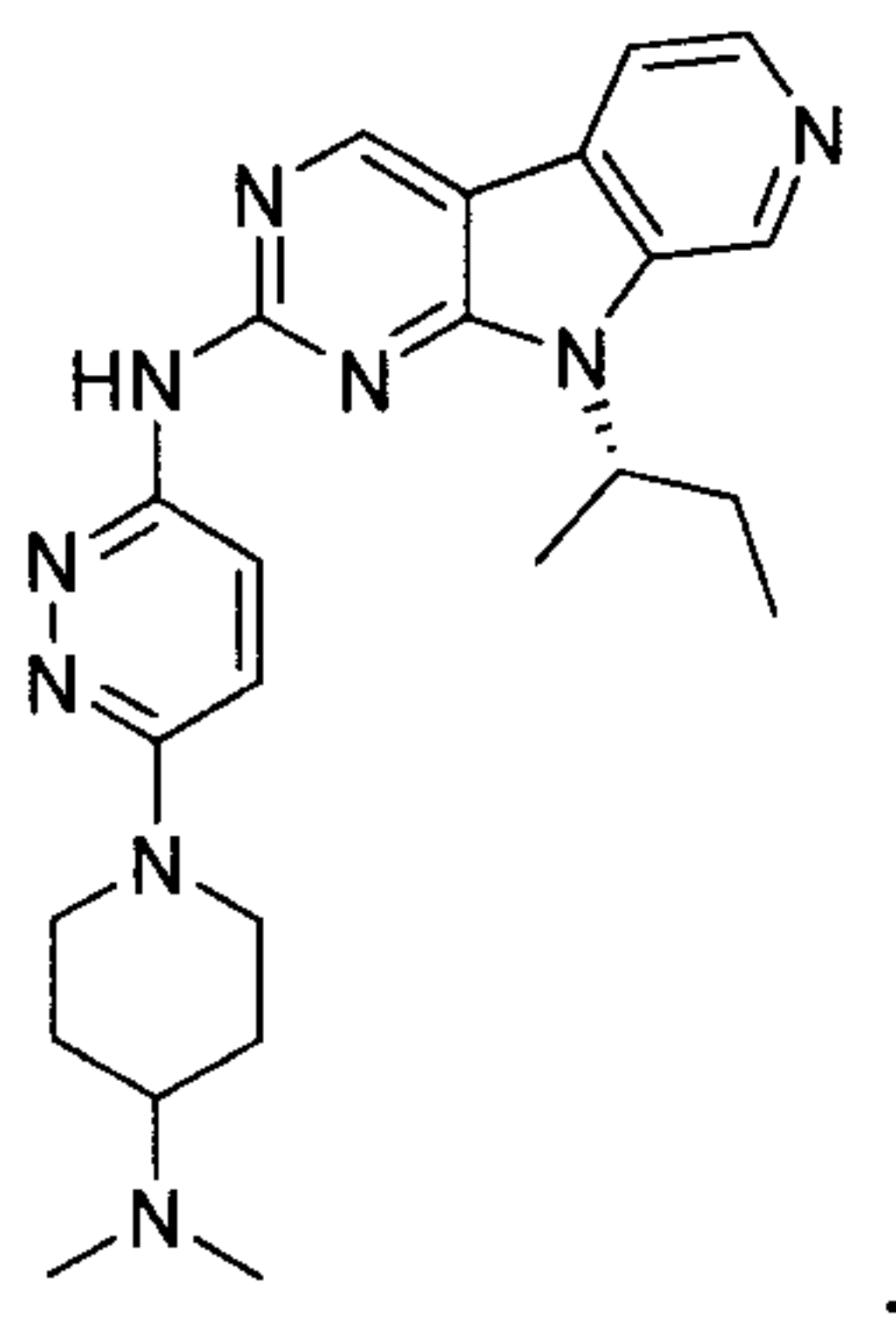
264. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

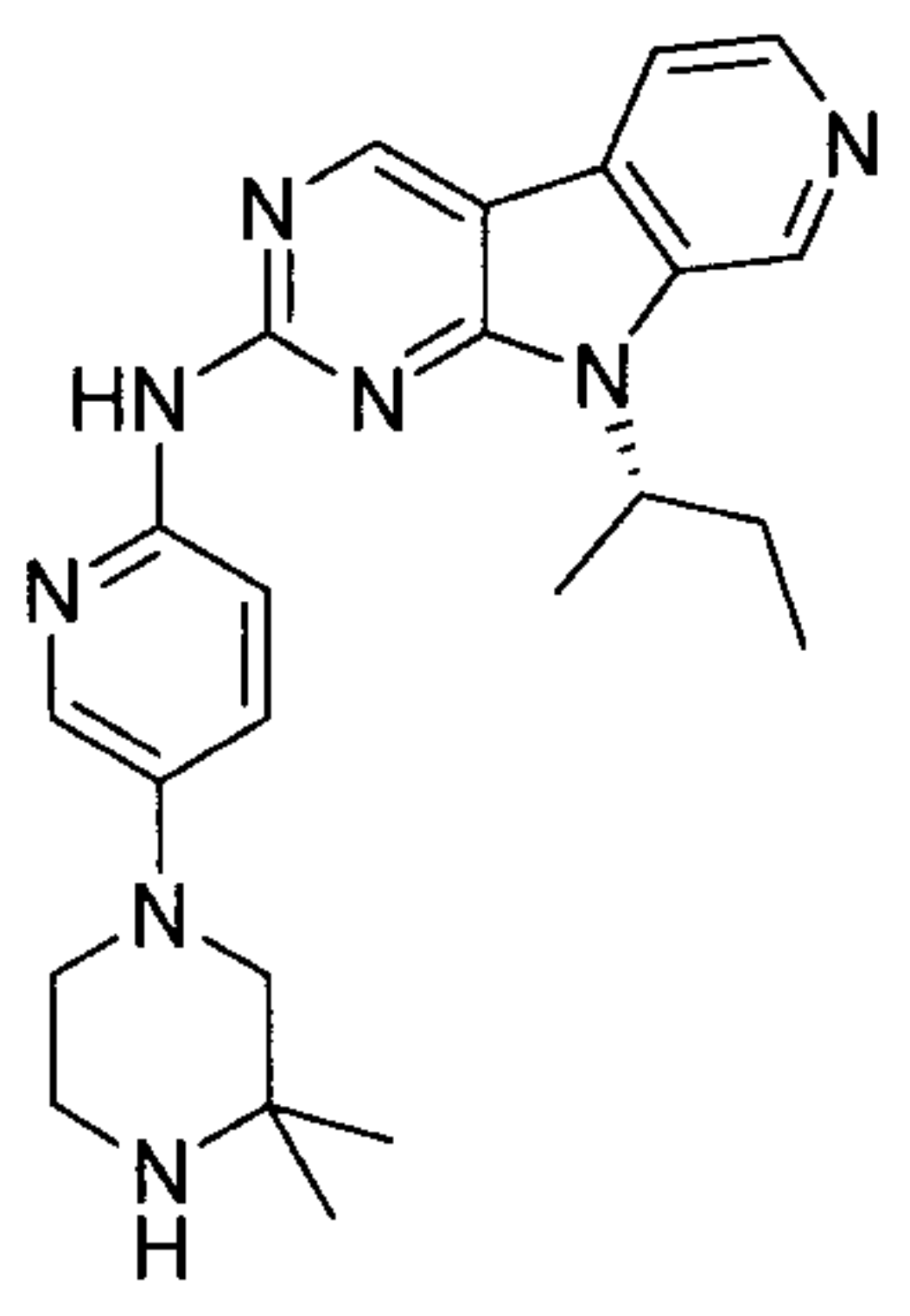


265. The compound of claim 1, wherein the compound is



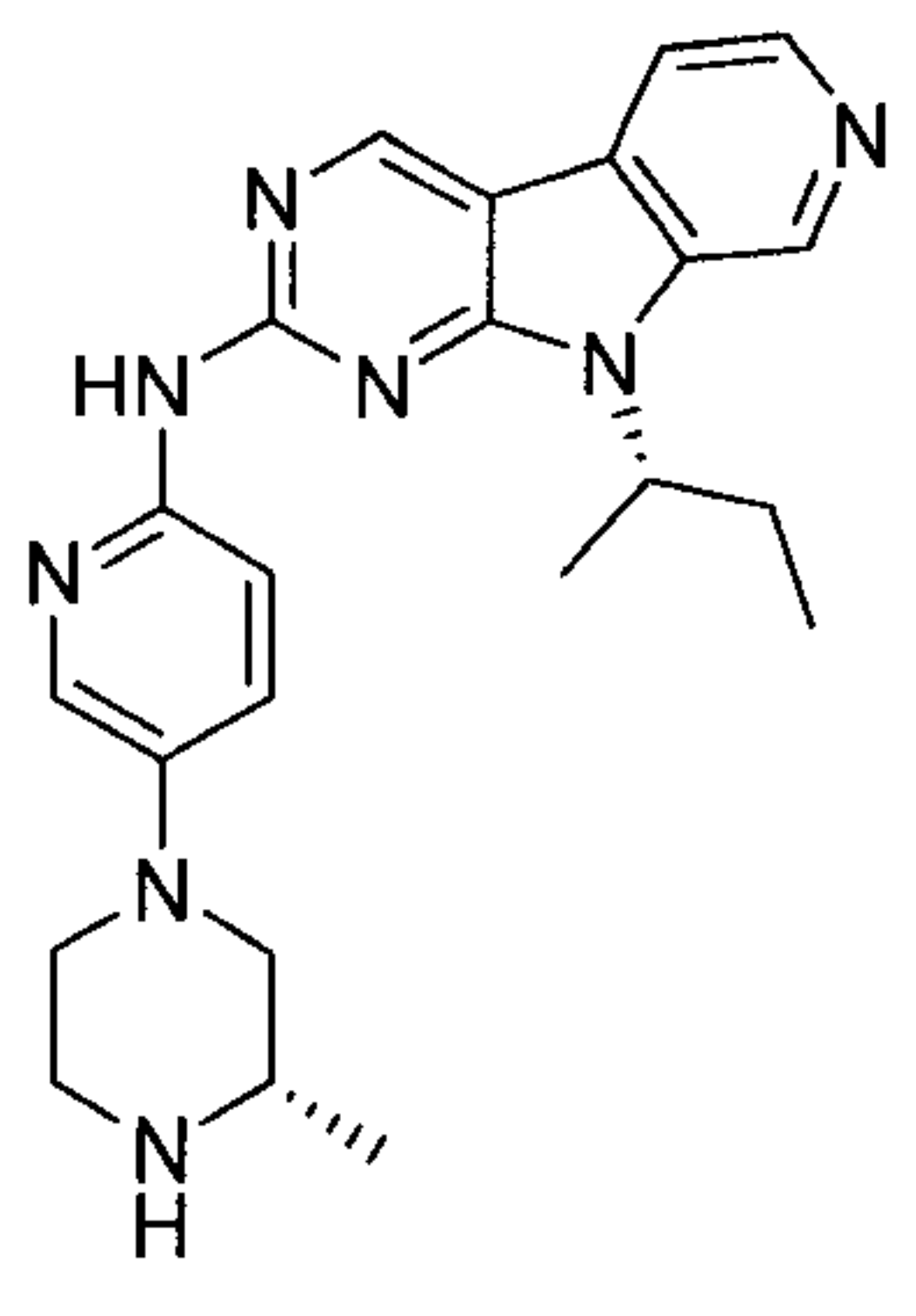
or a pharmaceutically acceptable salt thereof.

266. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

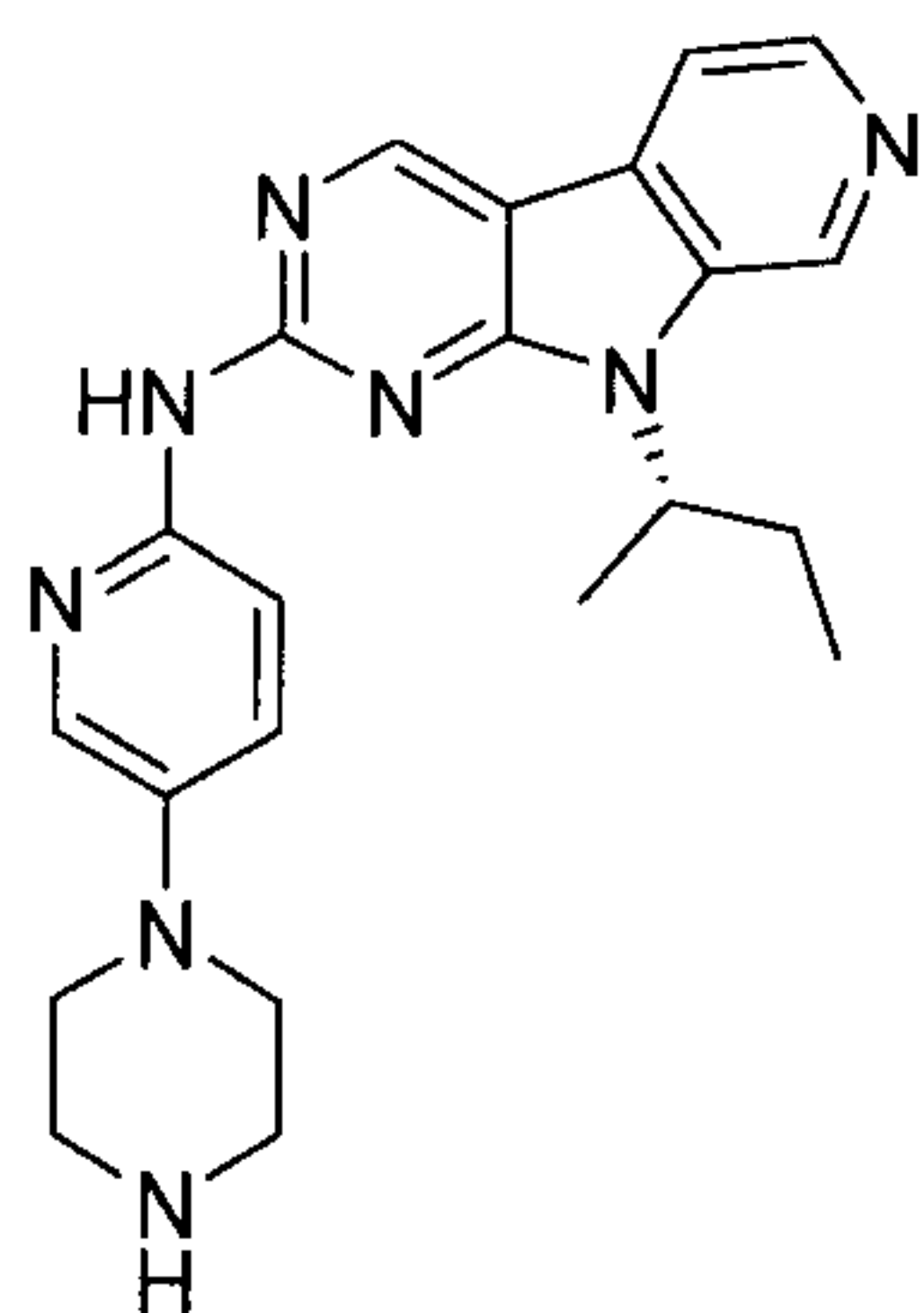
267. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

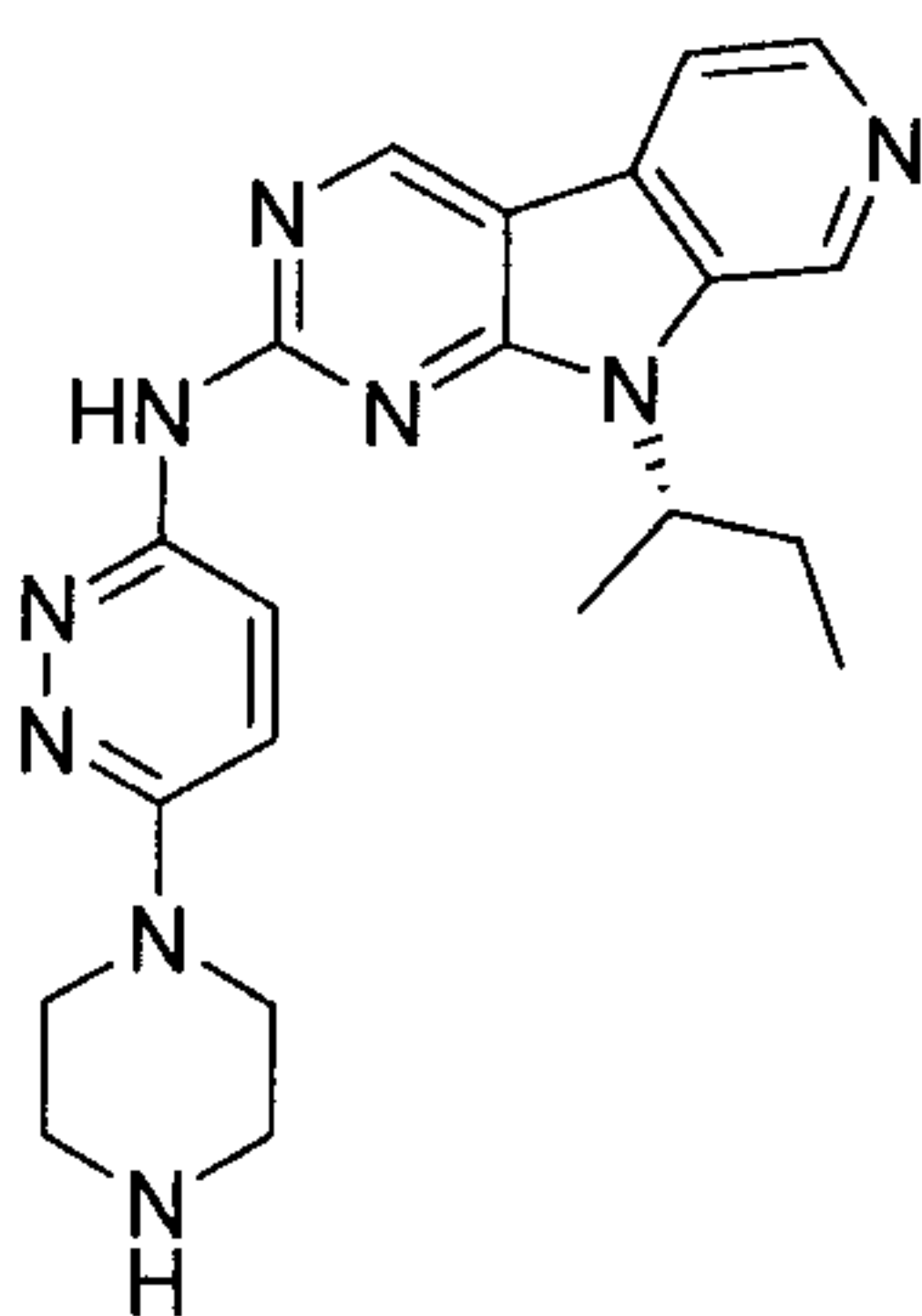


268. The compound of claim 1, wherein the compound is



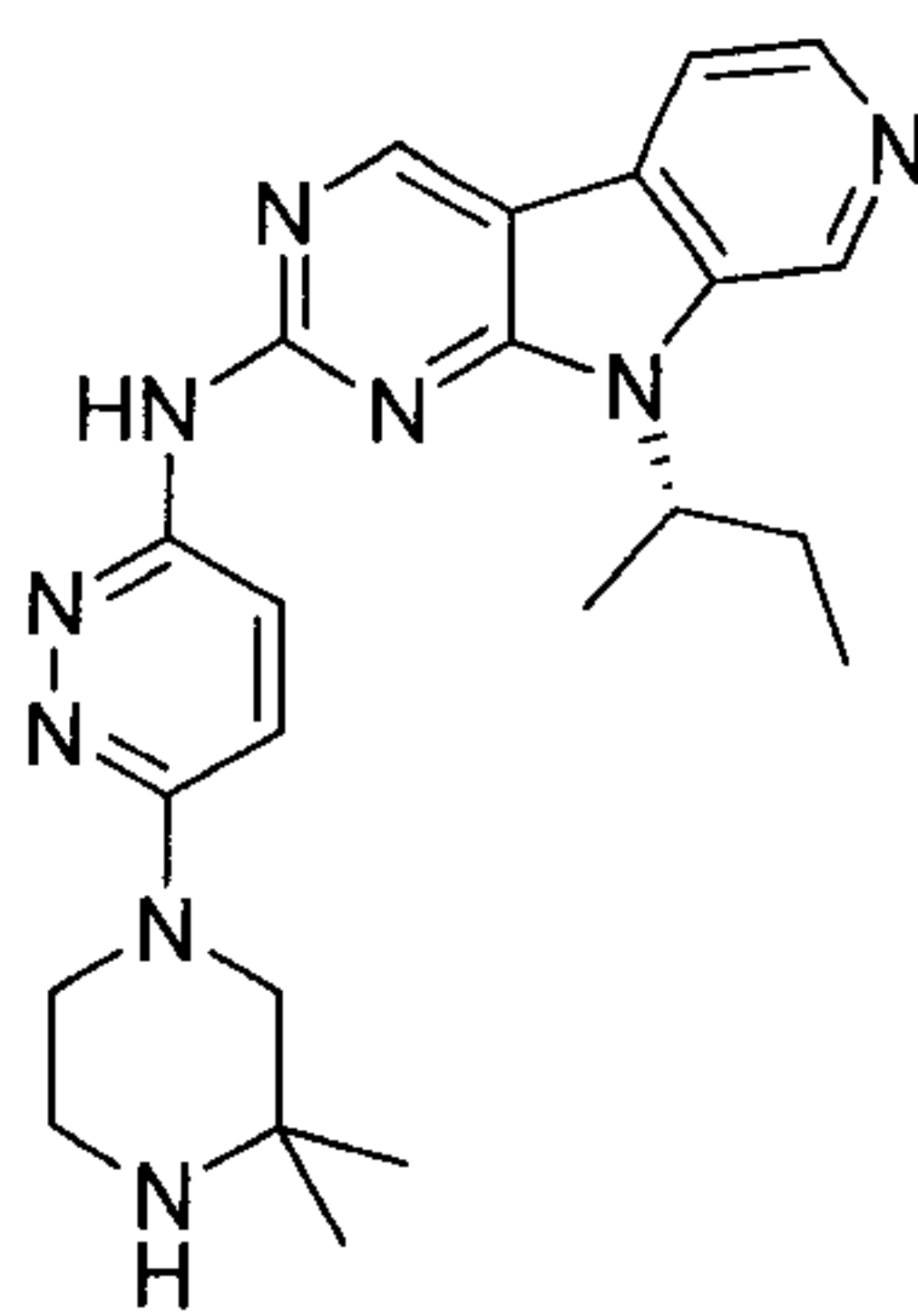
or a pharmaceutically acceptable salt thereof.

269. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

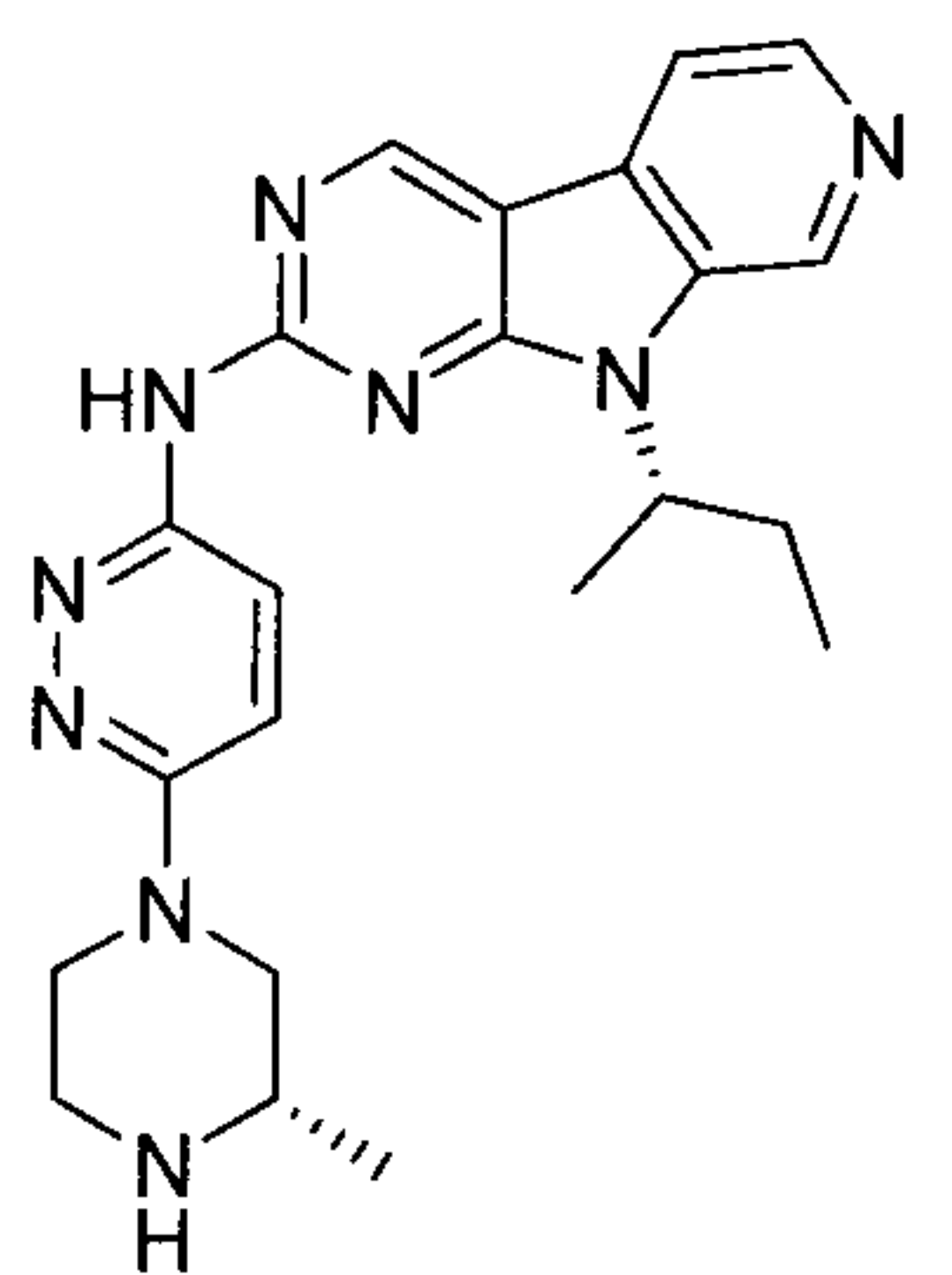
270. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

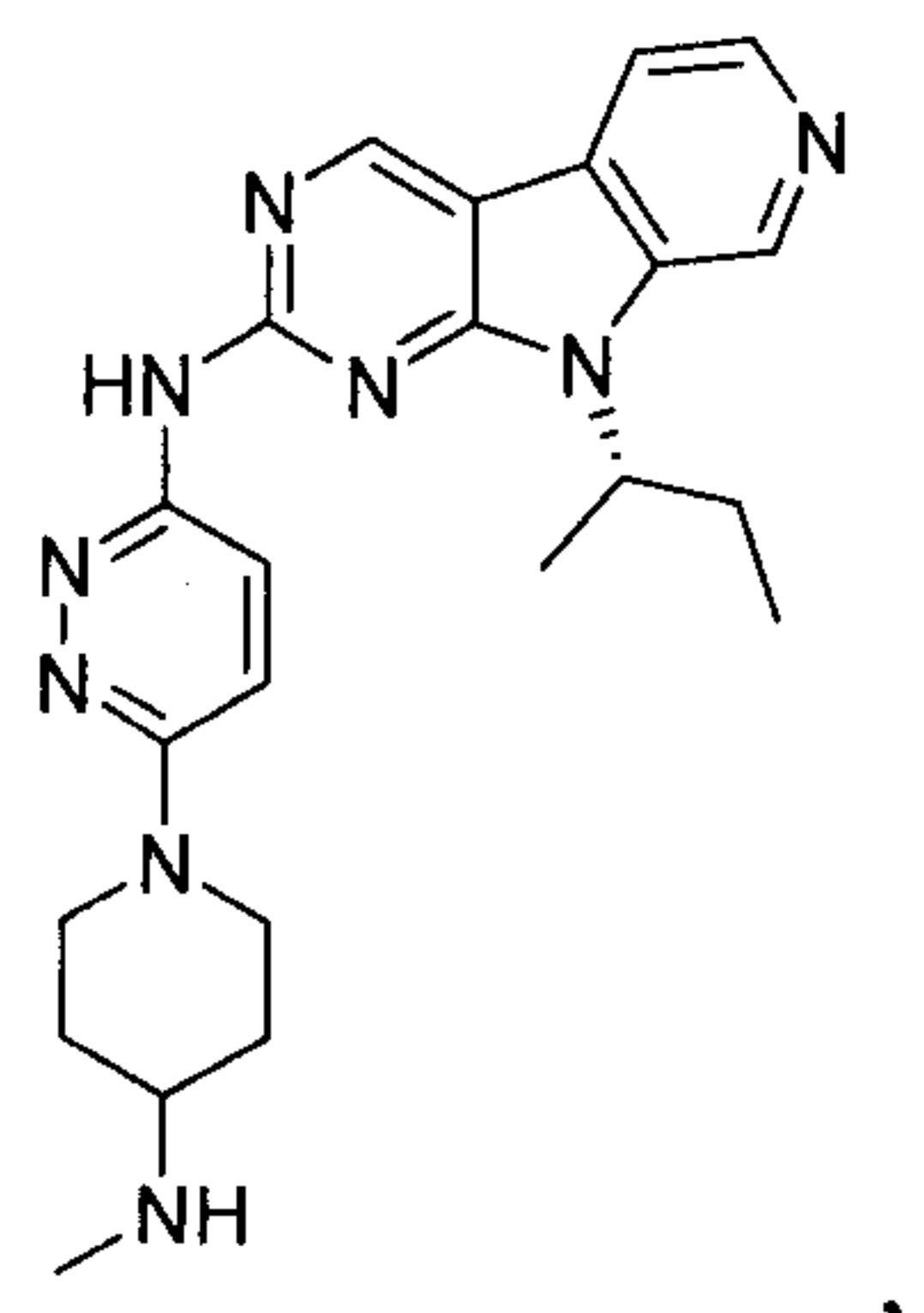


271. The compound of claim 1, wherein the compound is



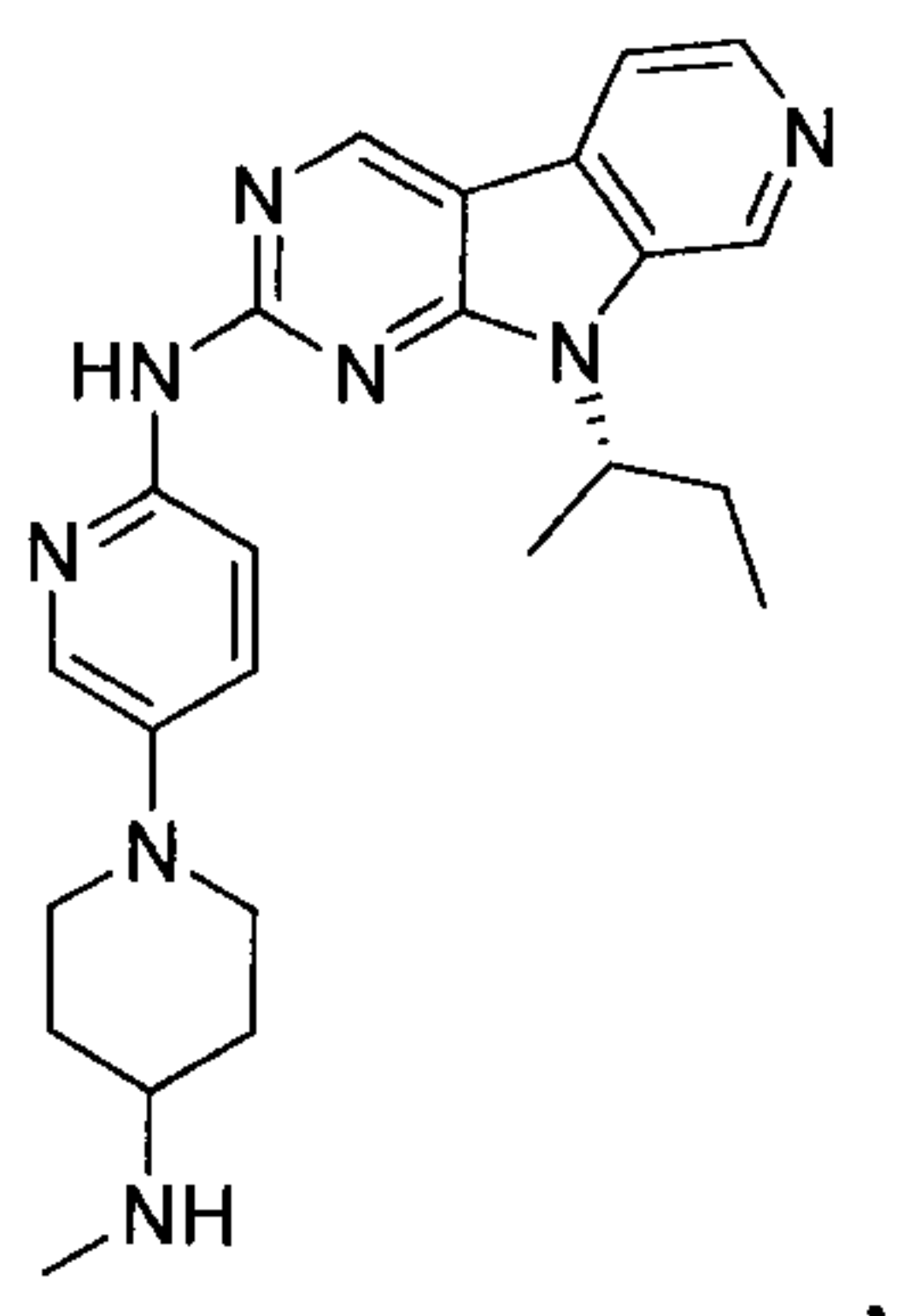
or a pharmaceutically acceptable salt thereof.

272. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

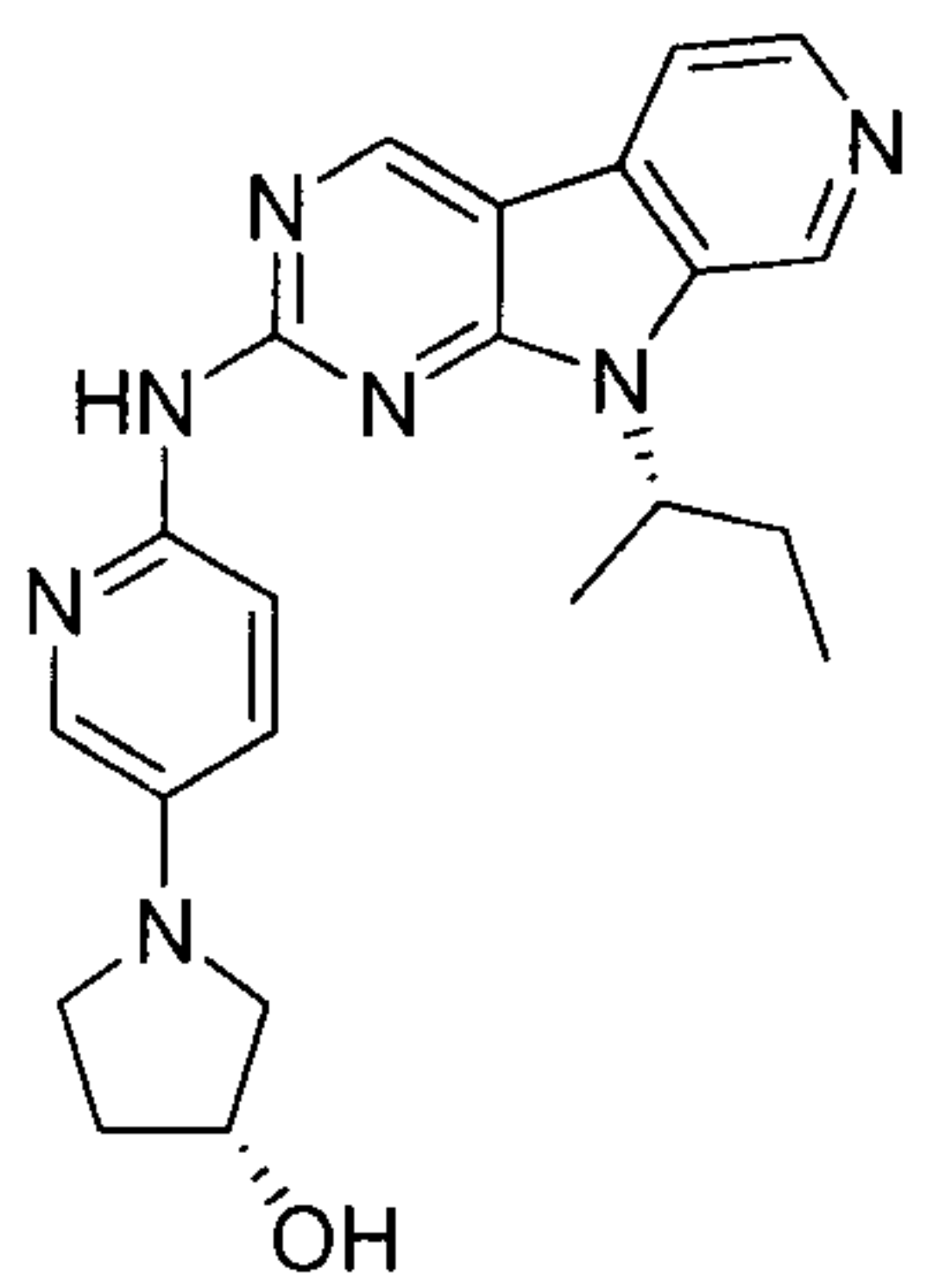
273. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

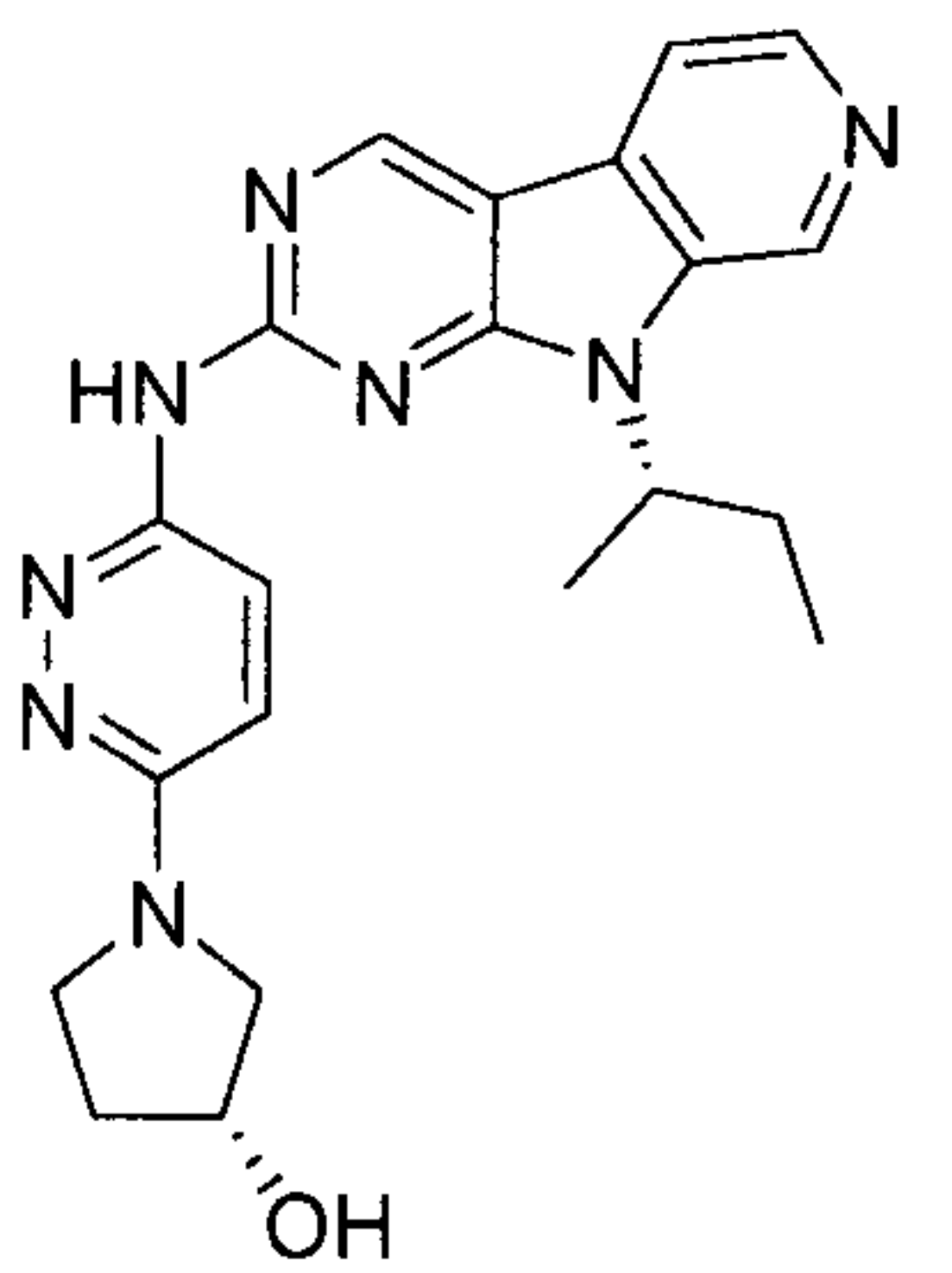


274. The compound of claim 1, wherein the compound is



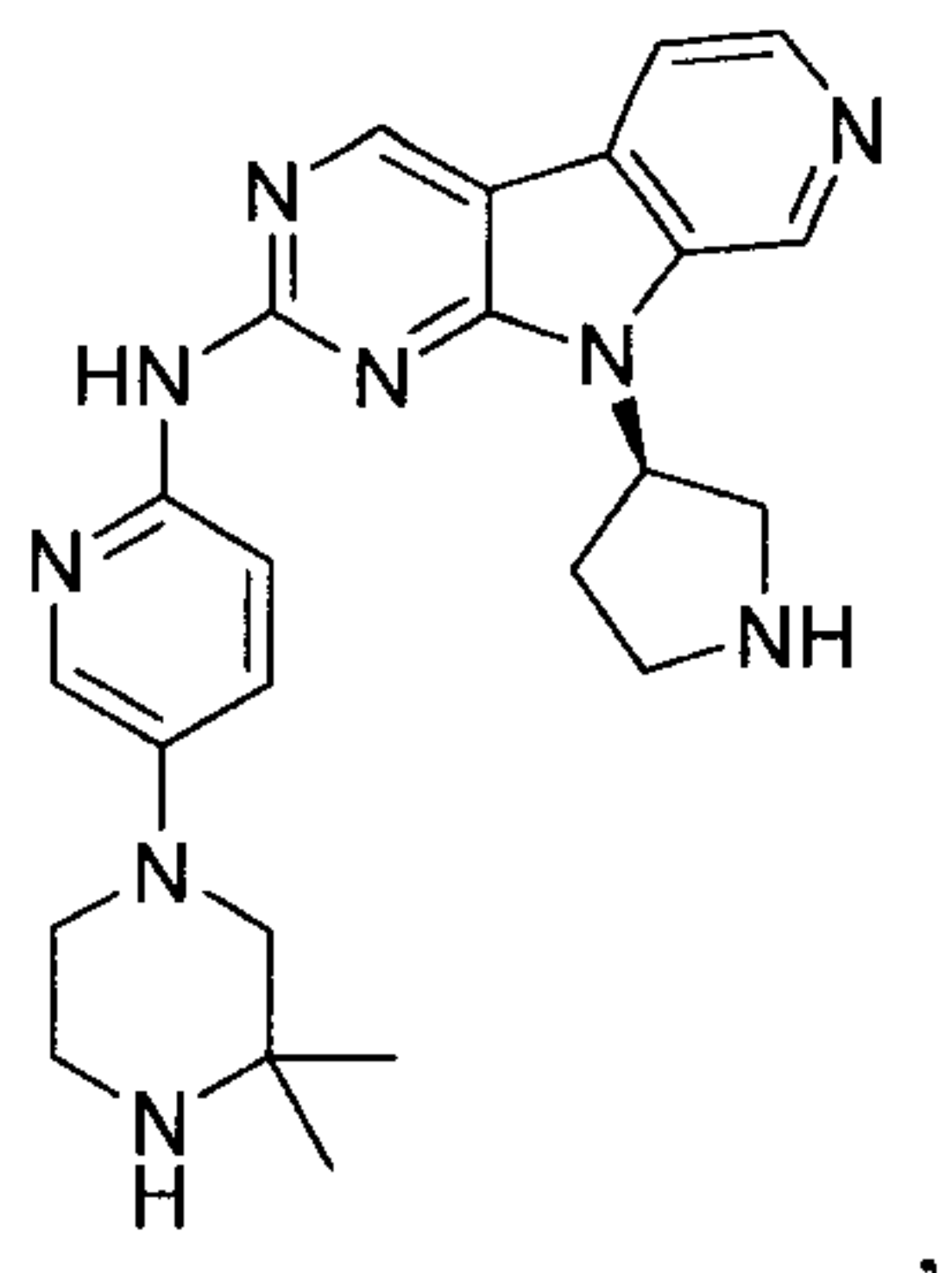
or a pharmaceutically acceptable salt thereof.

275. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

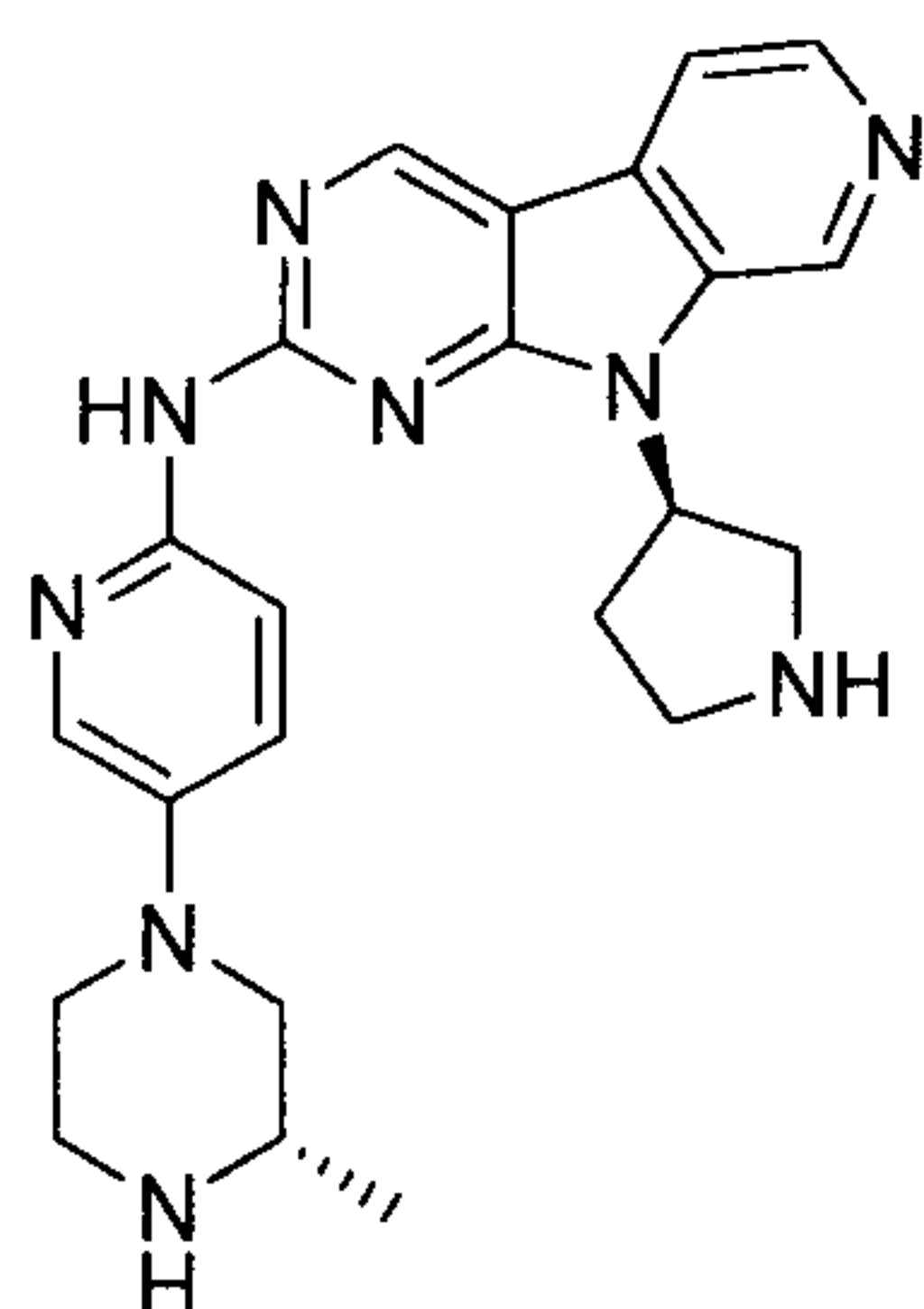
276. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

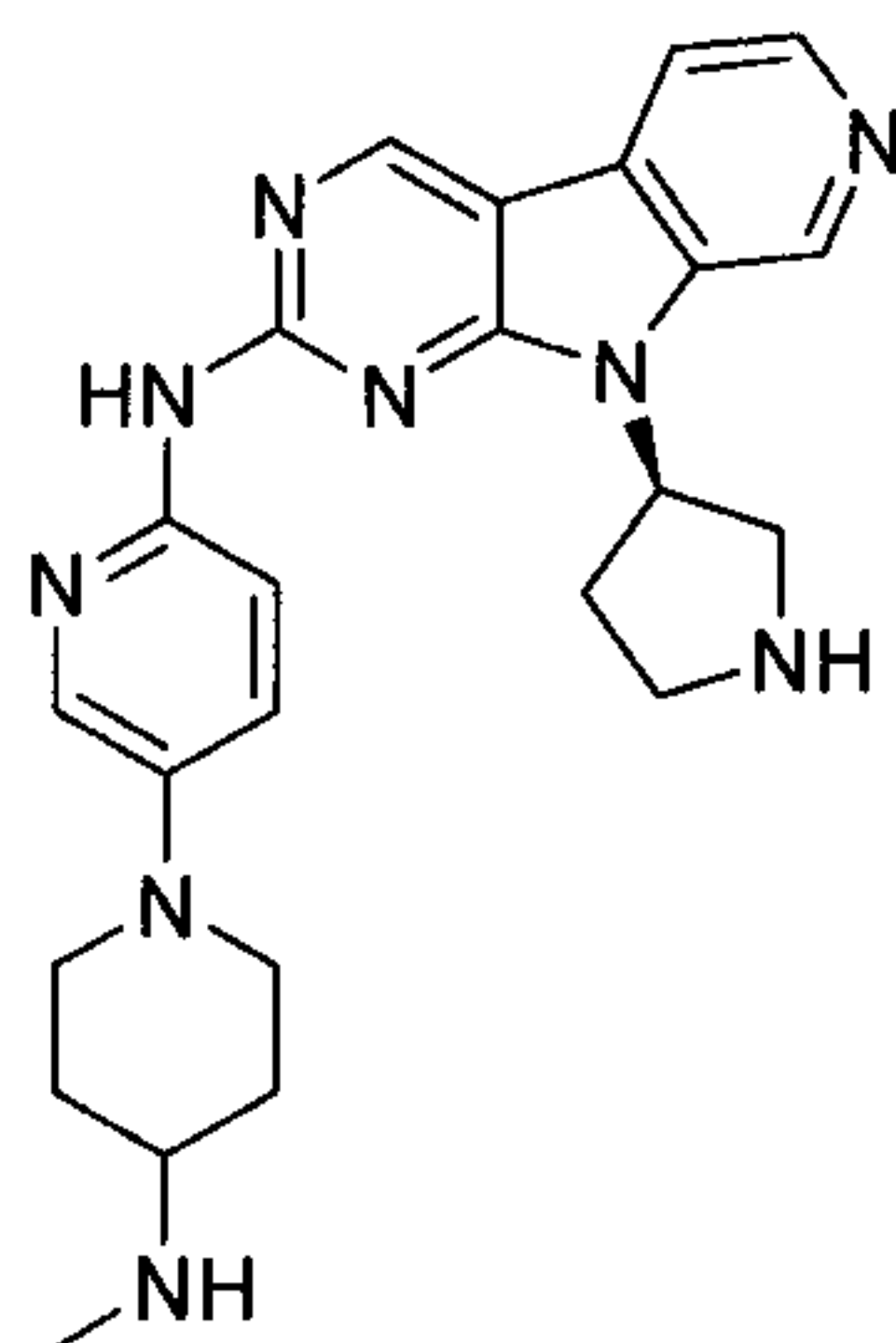


277. The compound of claim 1, wherein the compound is



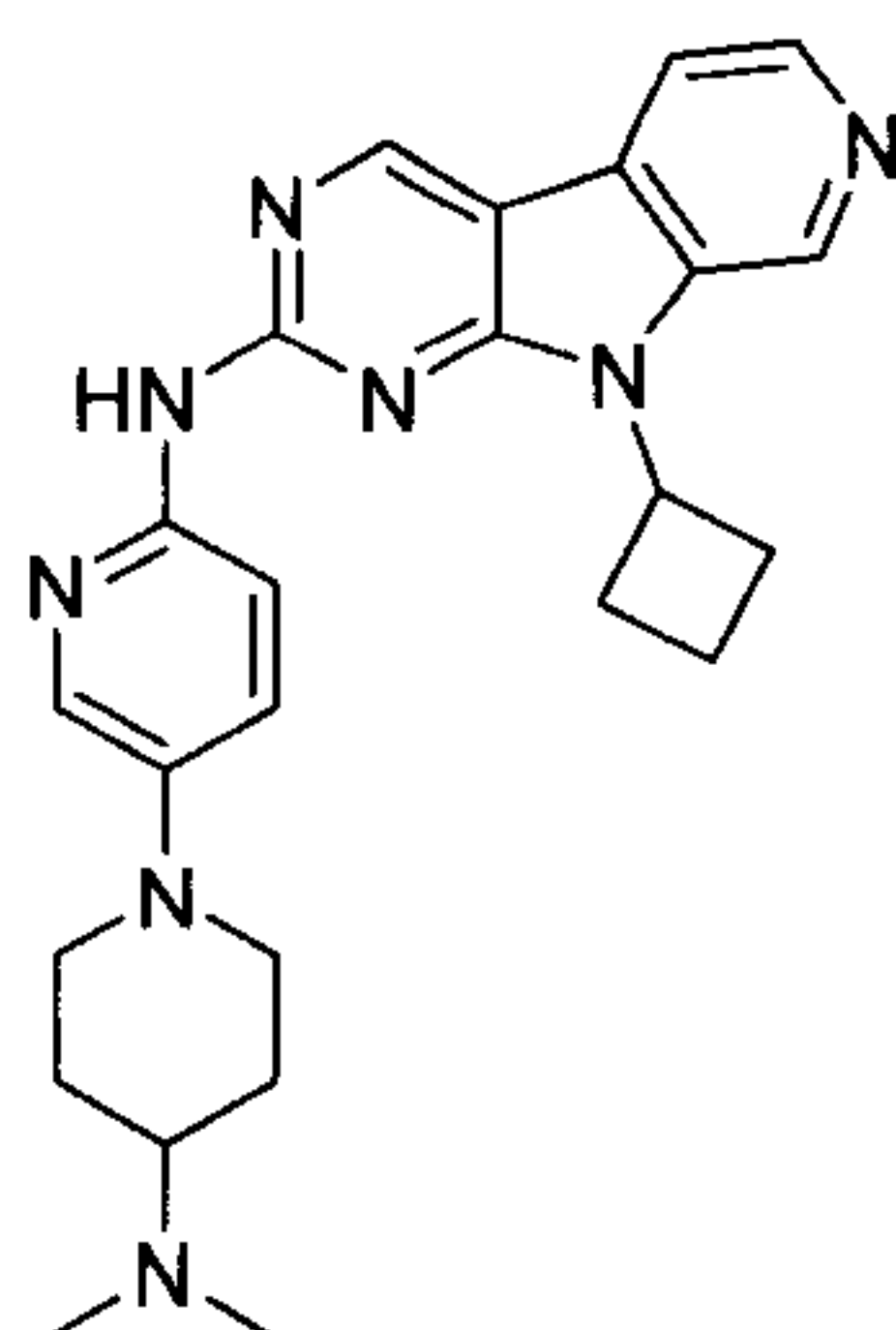
or a pharmaceutically acceptable salt thereof.

278. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

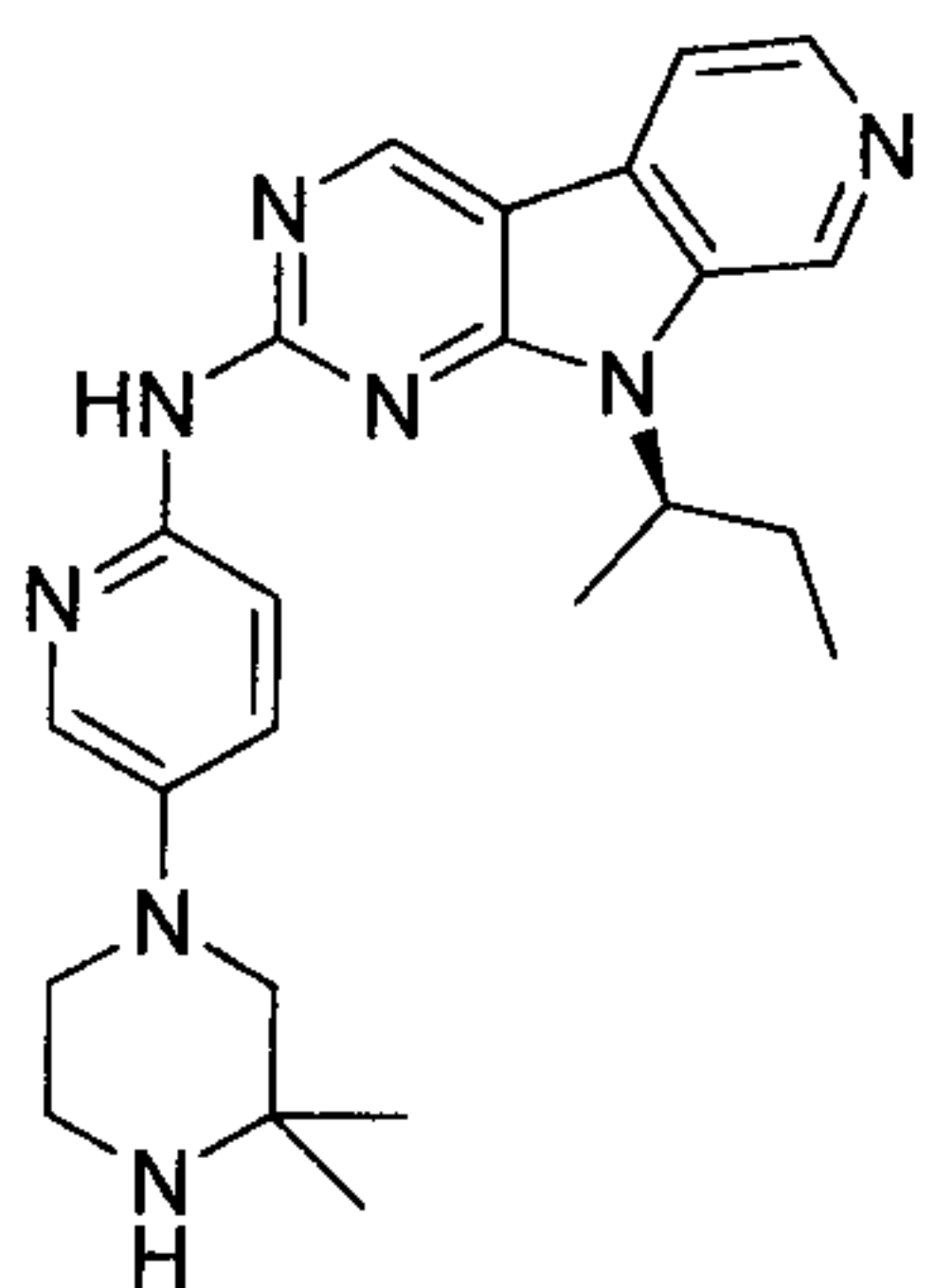
279. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

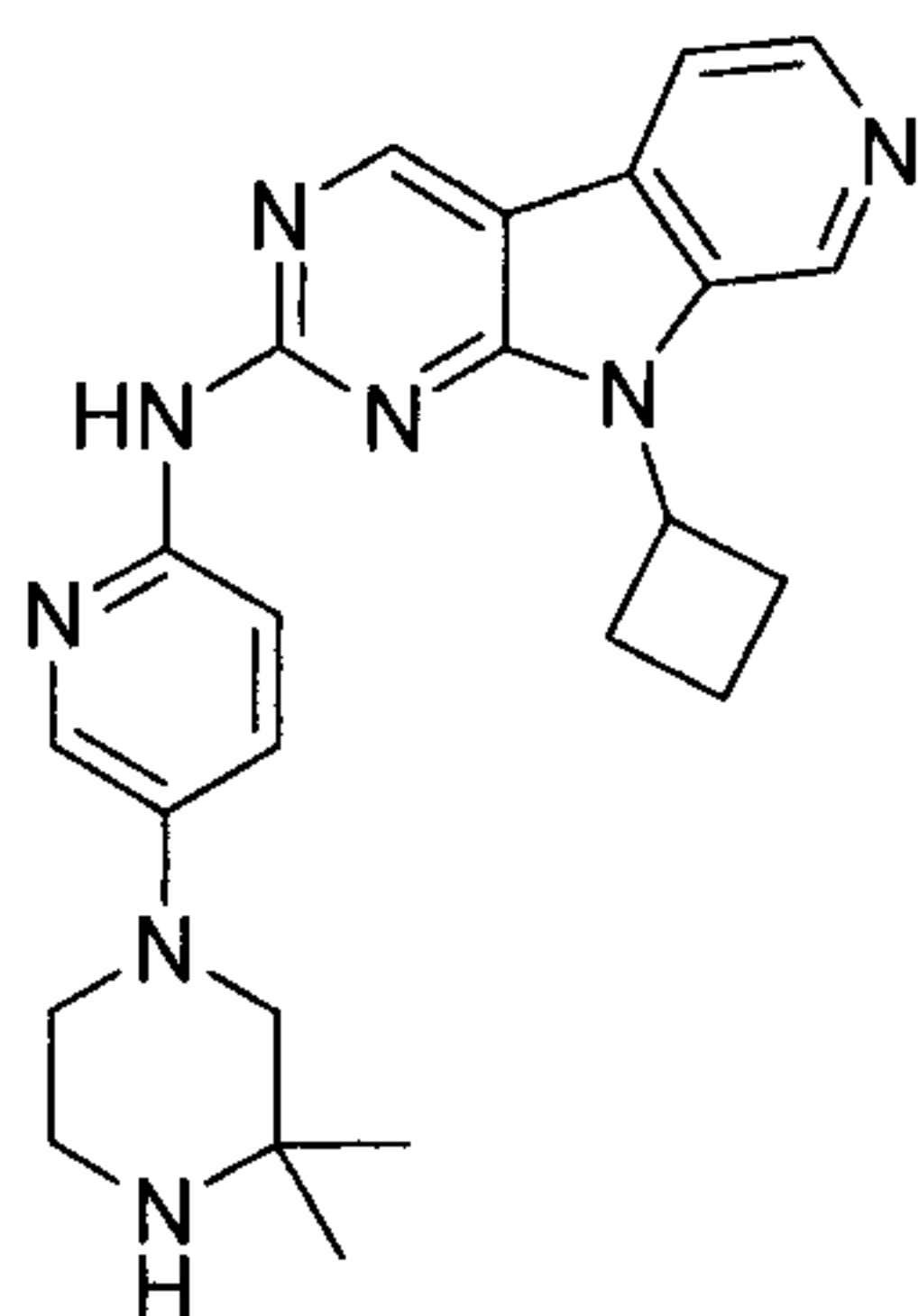


280. The compound of claim 1, wherein the compound is



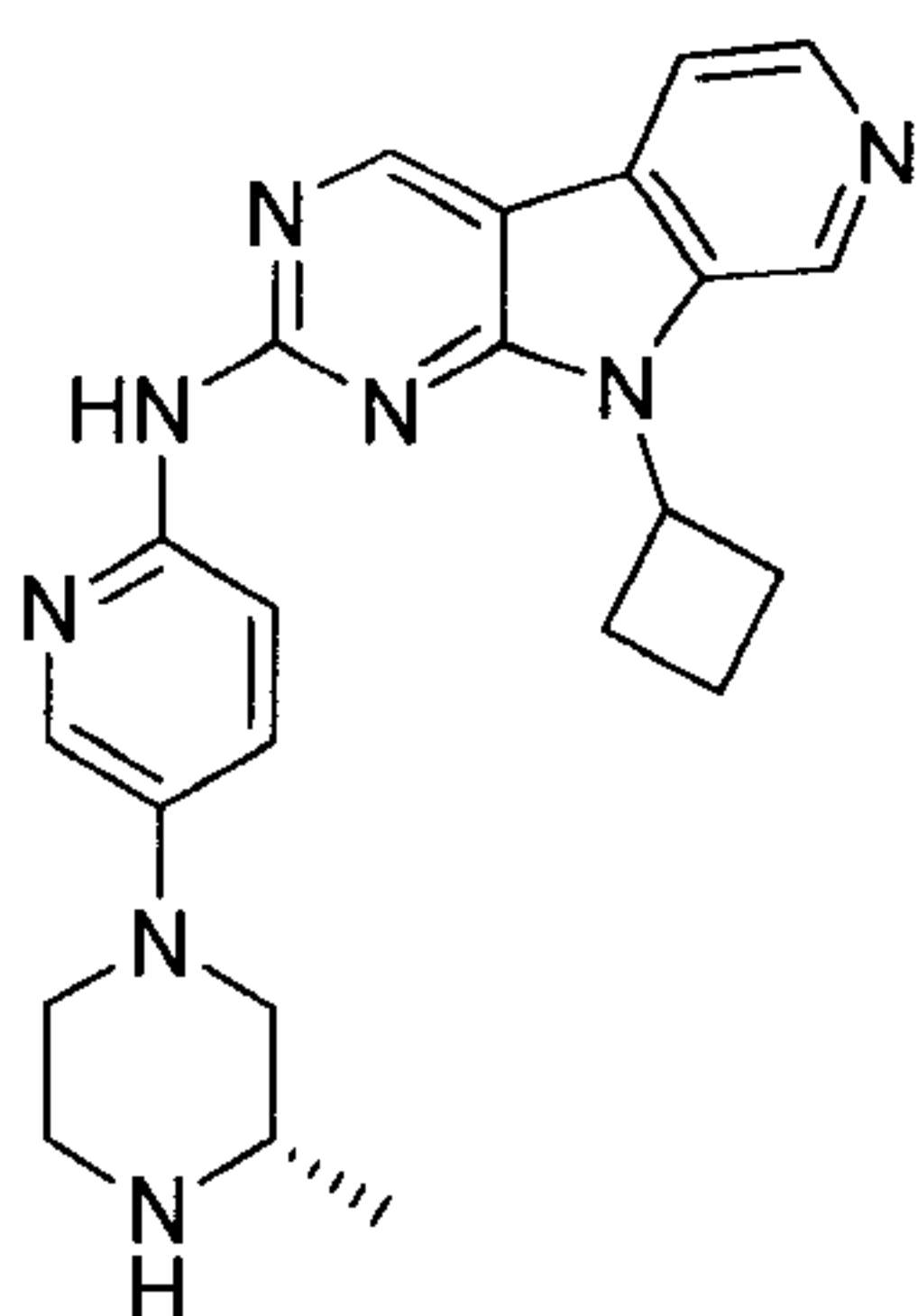
or a pharmaceutically acceptable salt thereof.

281. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

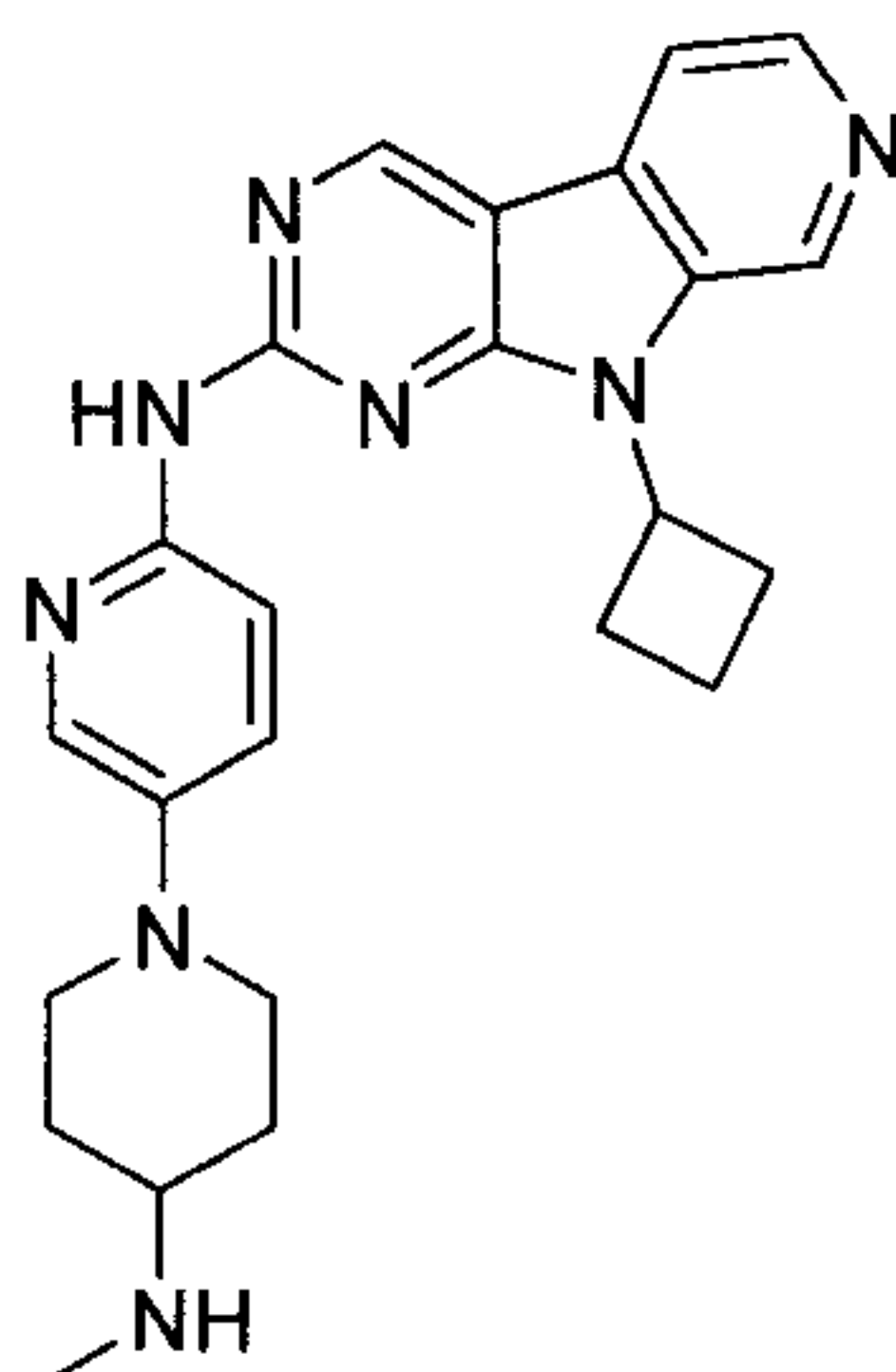
282. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

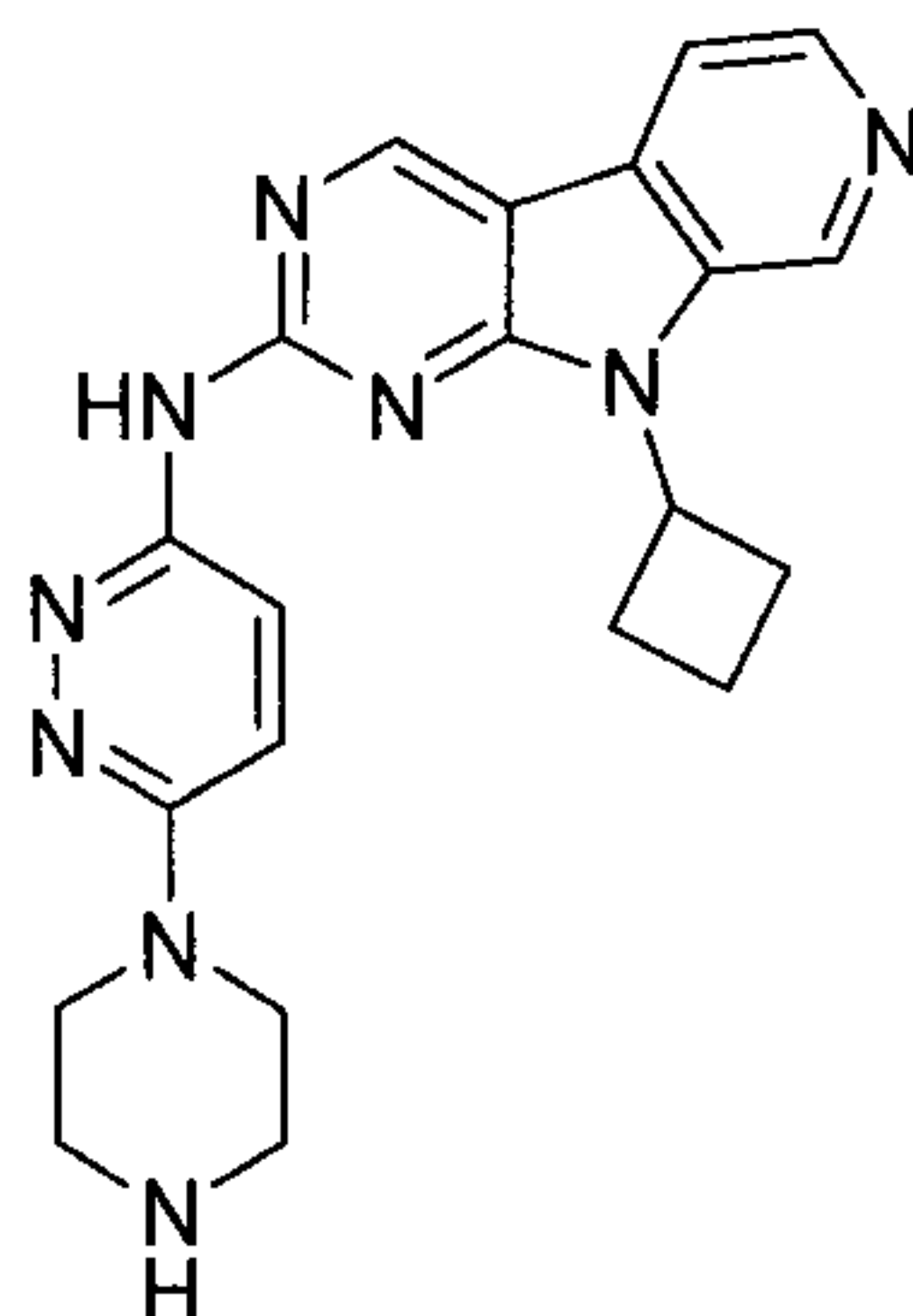


283. The compound of claim 1, wherein the compound is



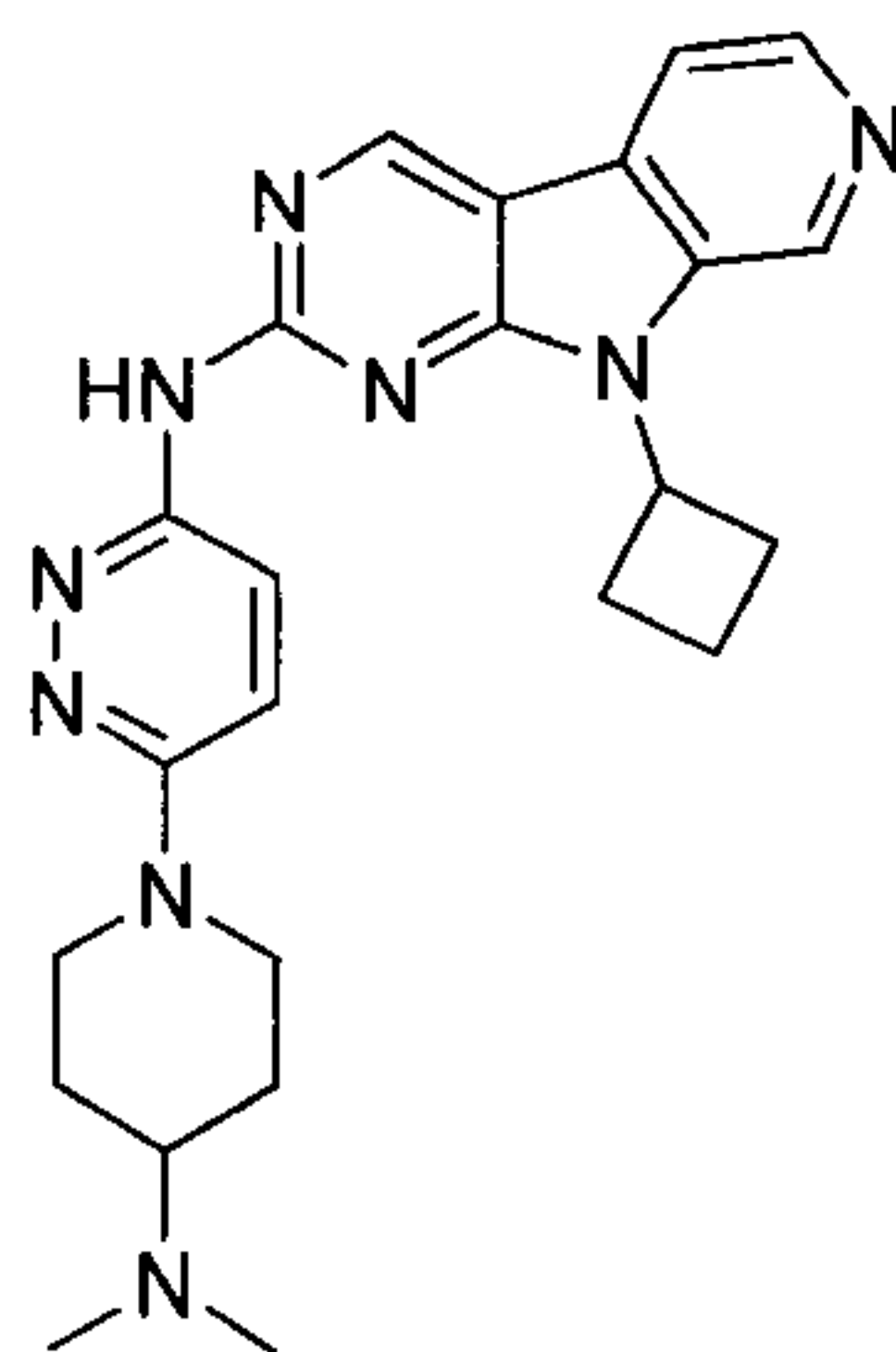
or a pharmaceutically acceptable salt thereof.

284. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

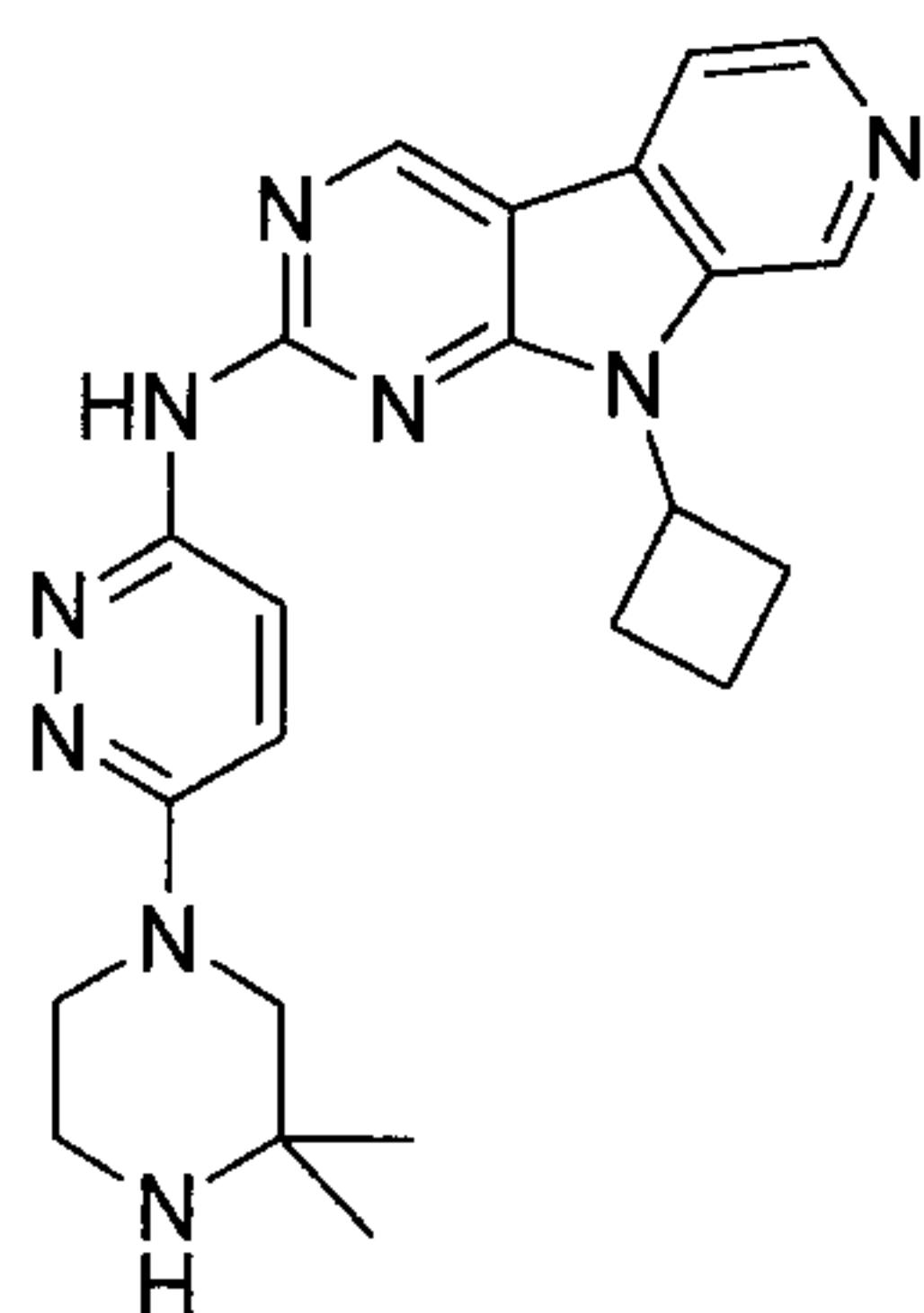
285. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

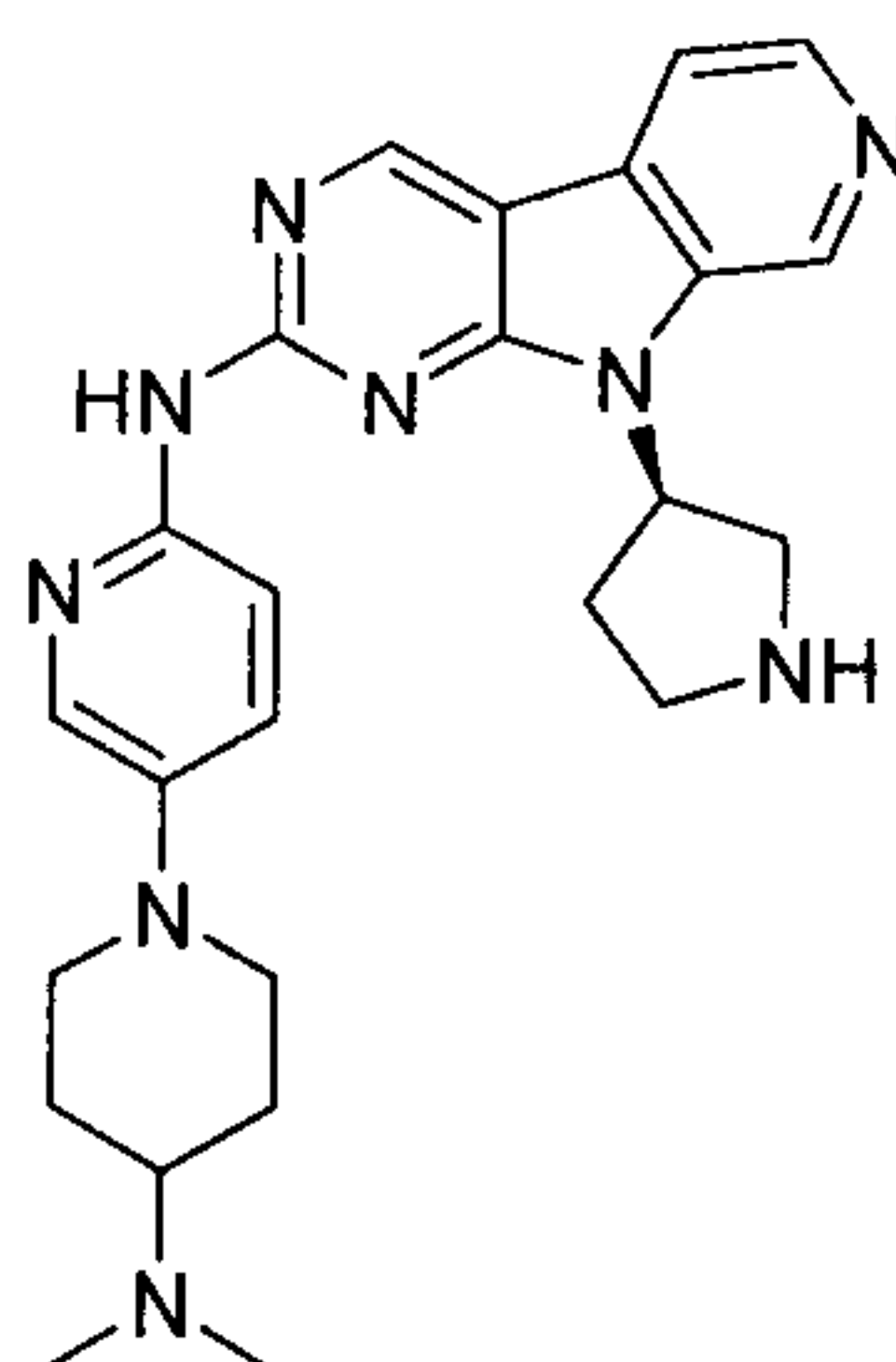


286. The compound of claim 1, wherein the compound is



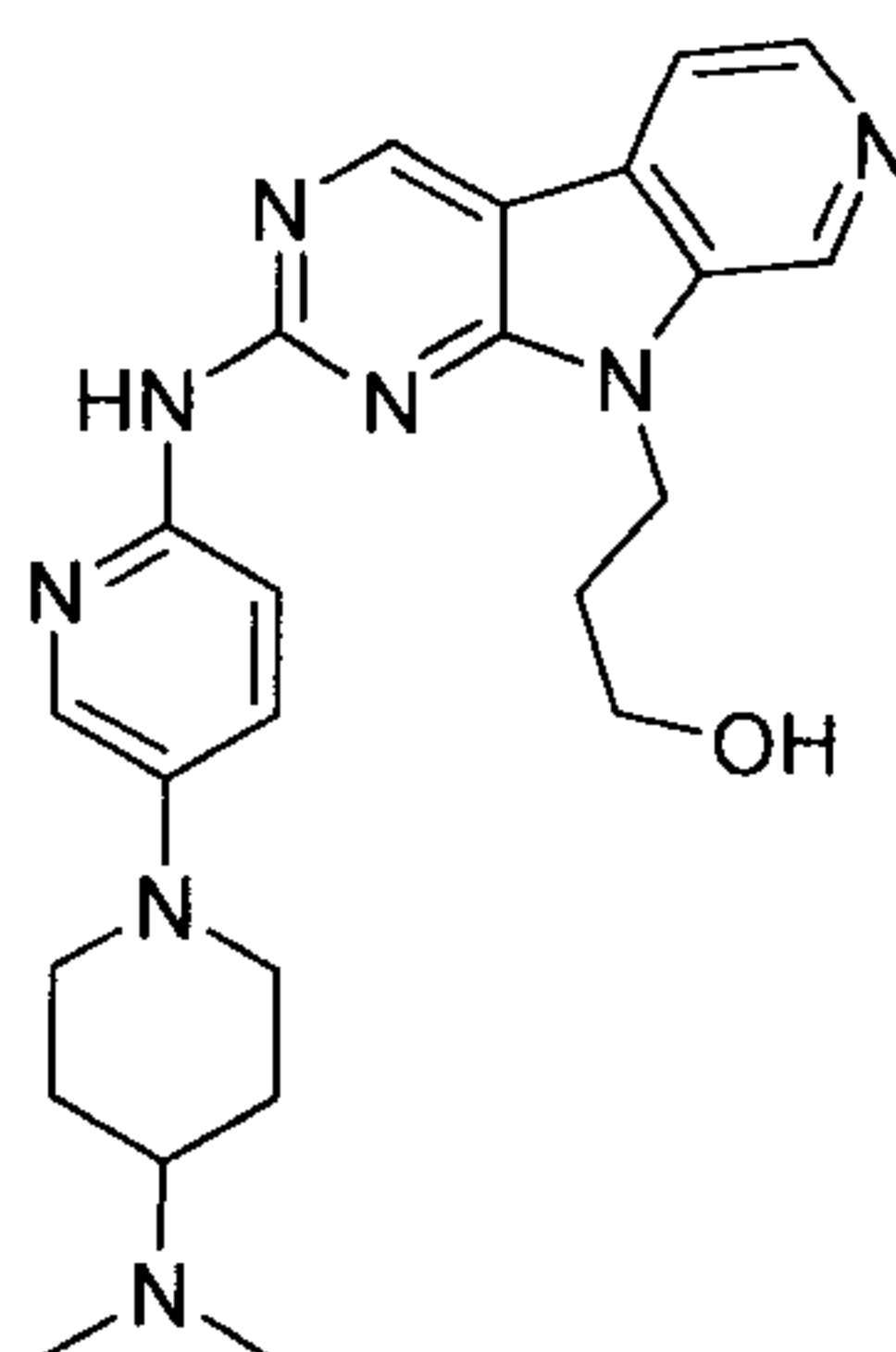
or a pharmaceutically acceptable salt thereof.

287. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

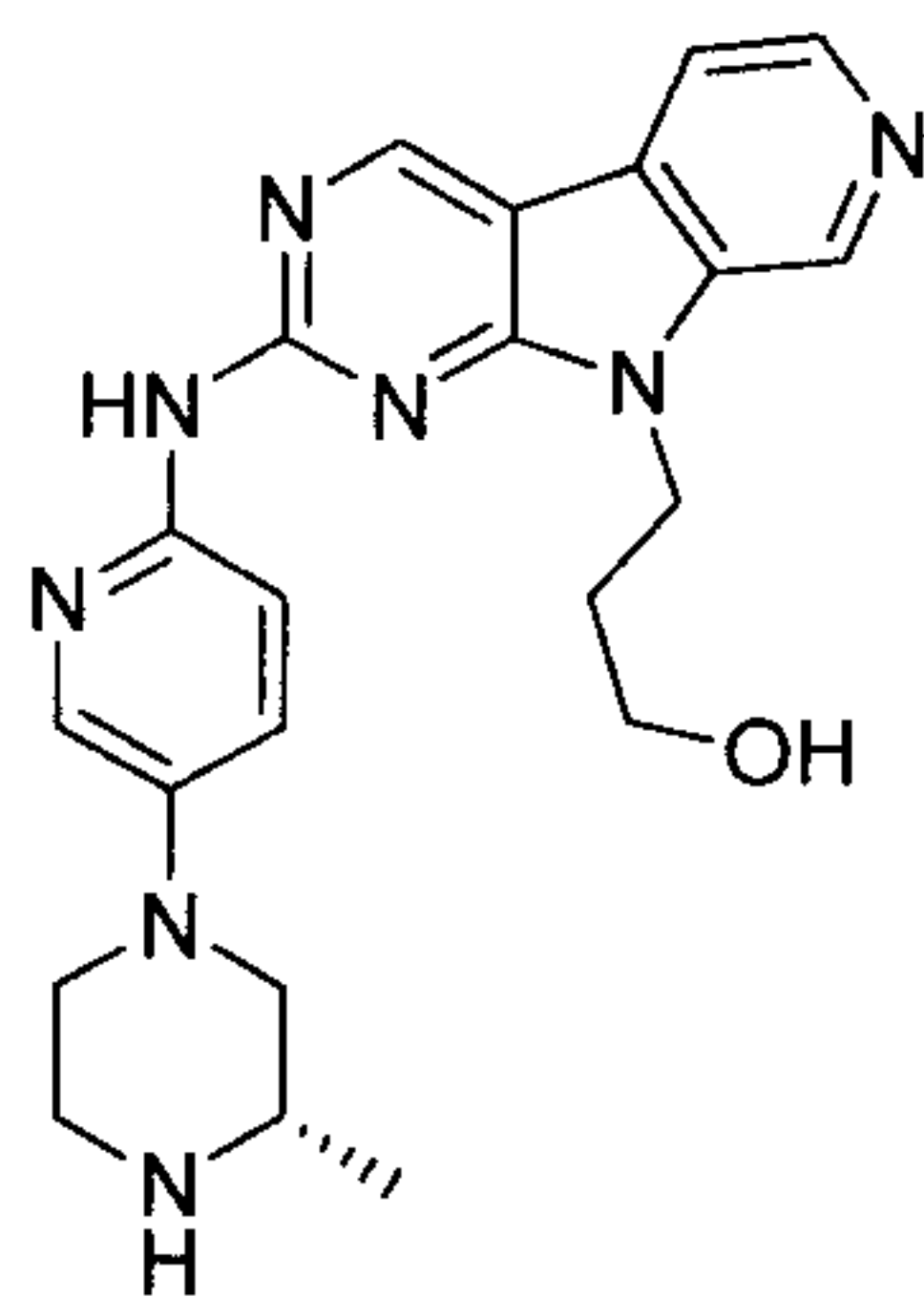
288. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

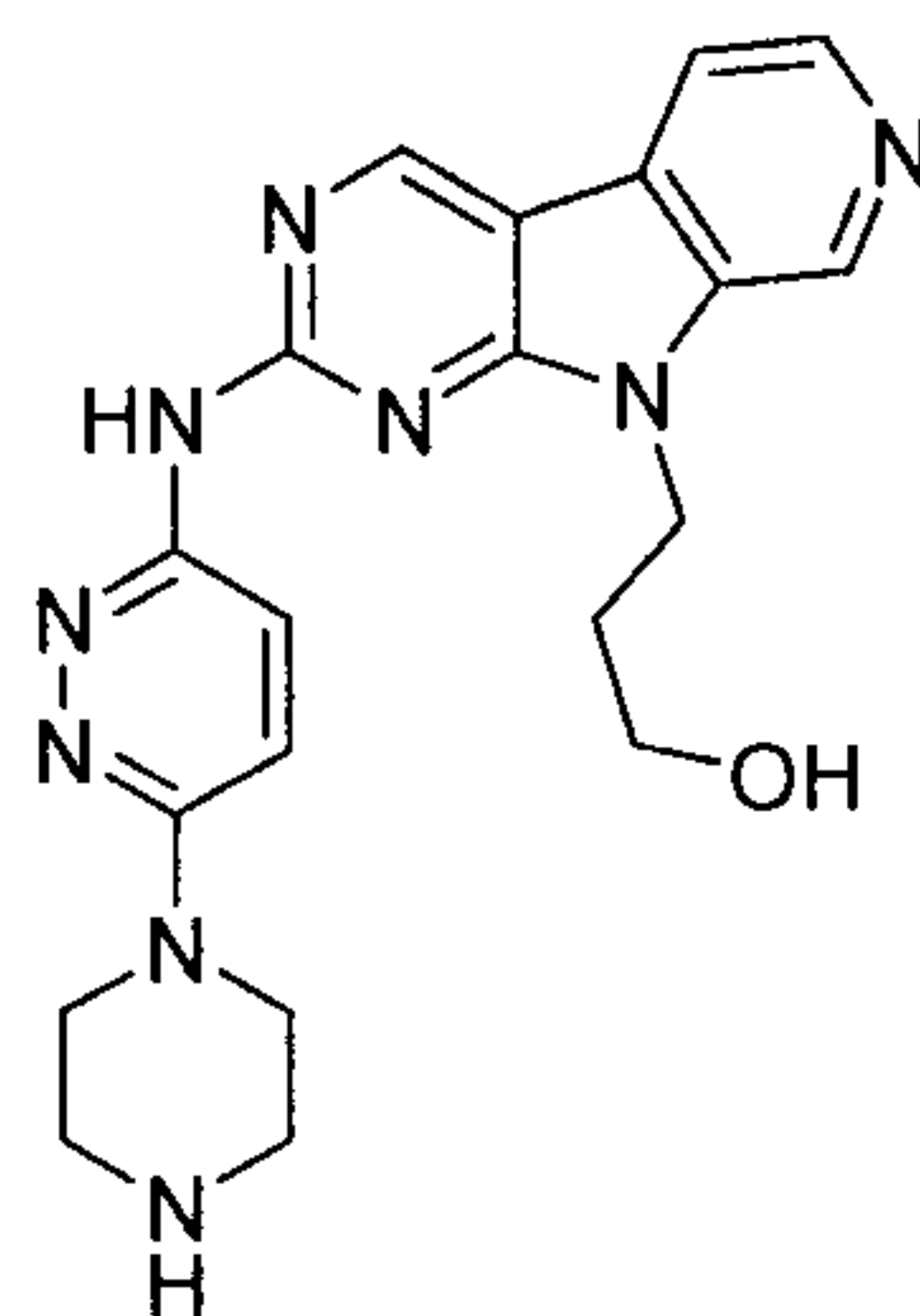


289. The compound of claim 1, wherein the compound is



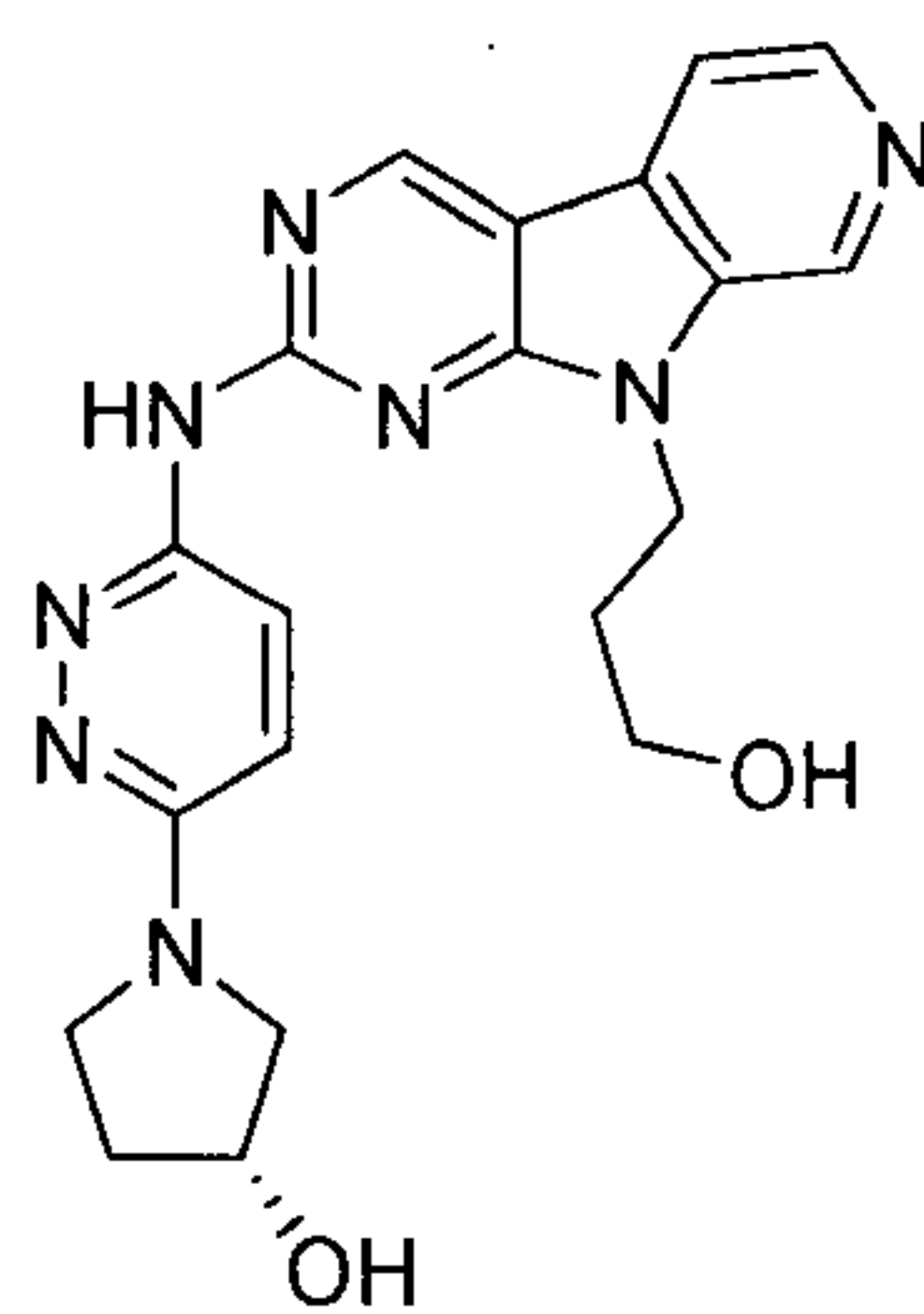
or a pharmaceutically acceptable salt thereof.

290. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

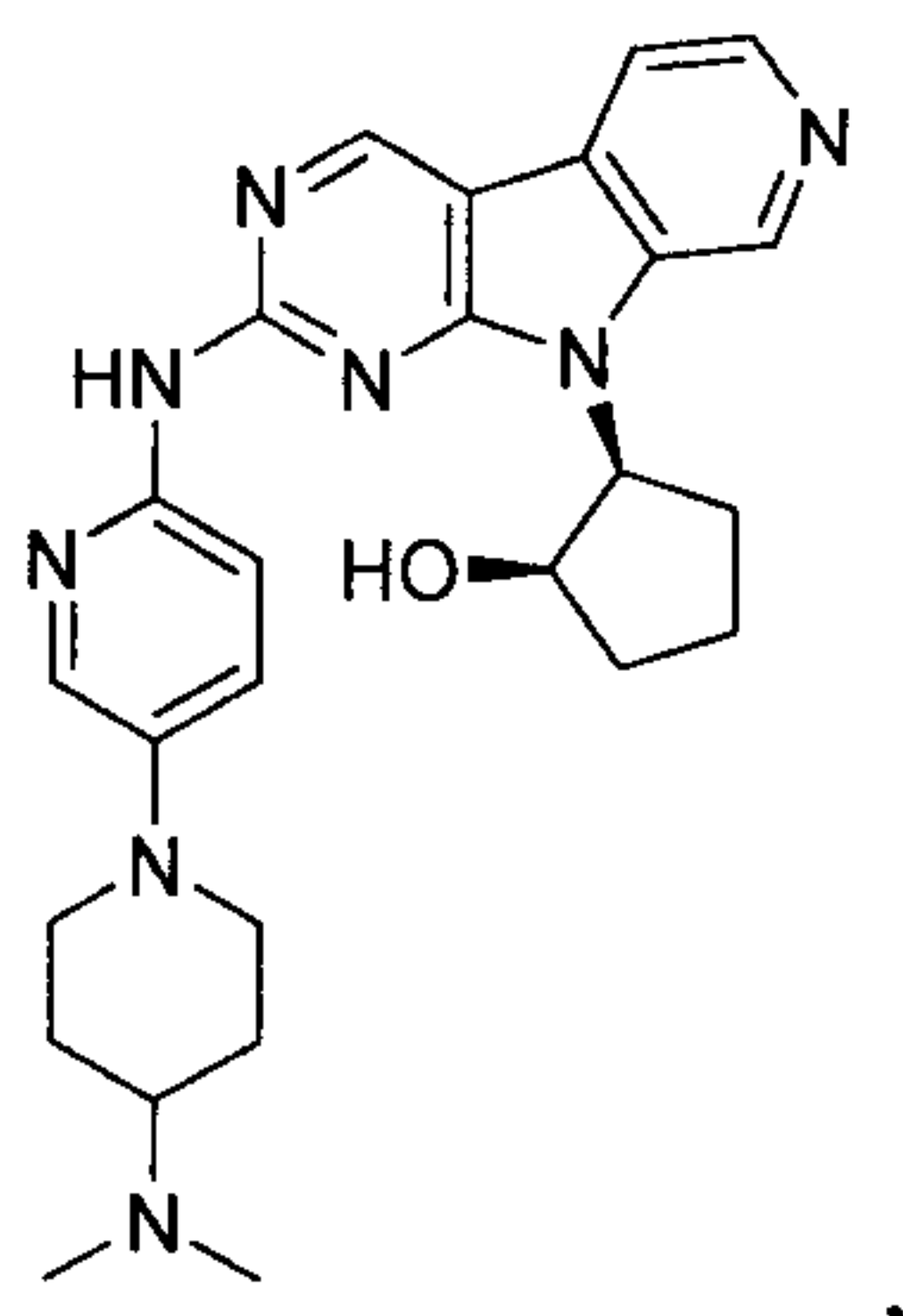
291. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

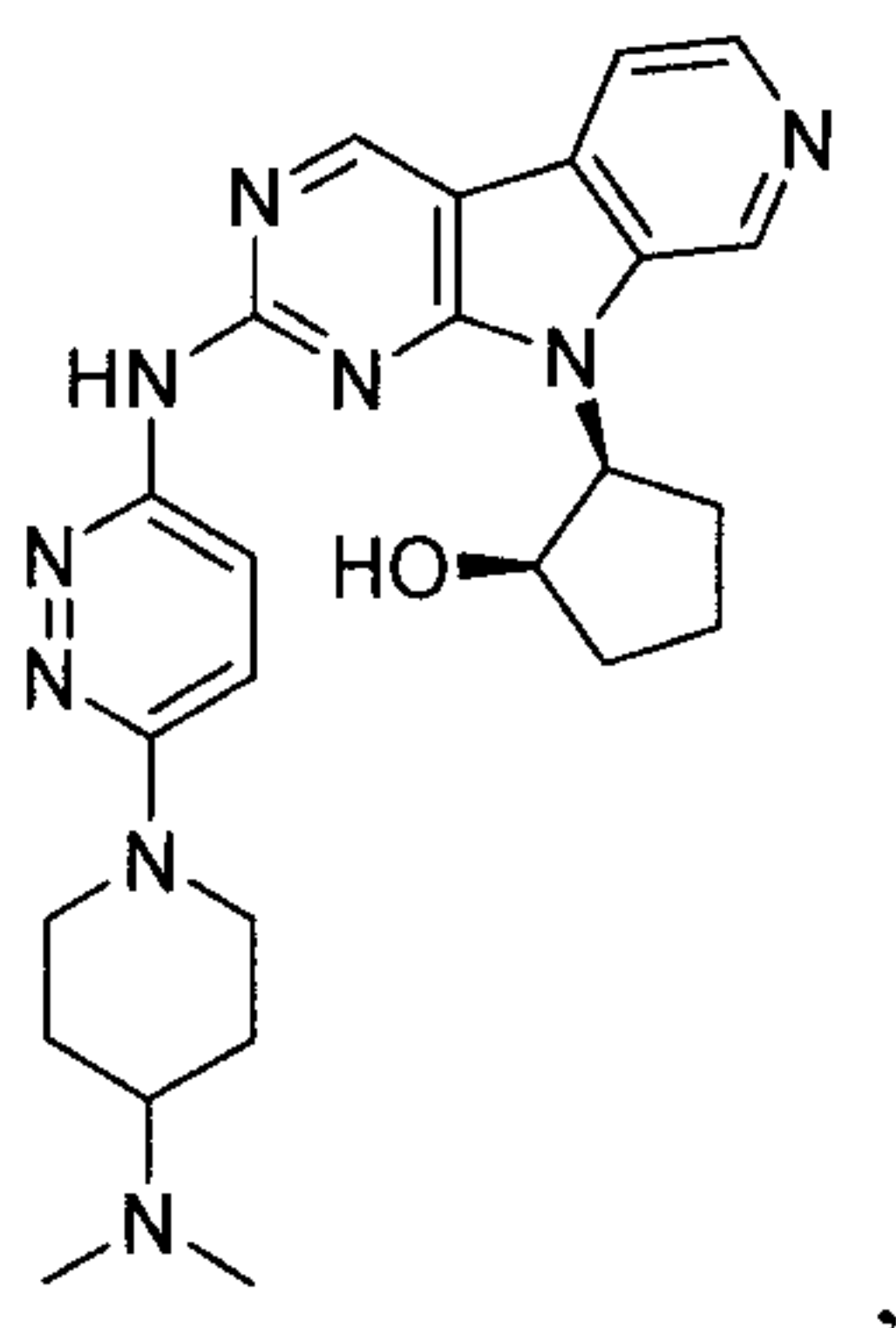


292. The compound of claim 1, wherein the compound is



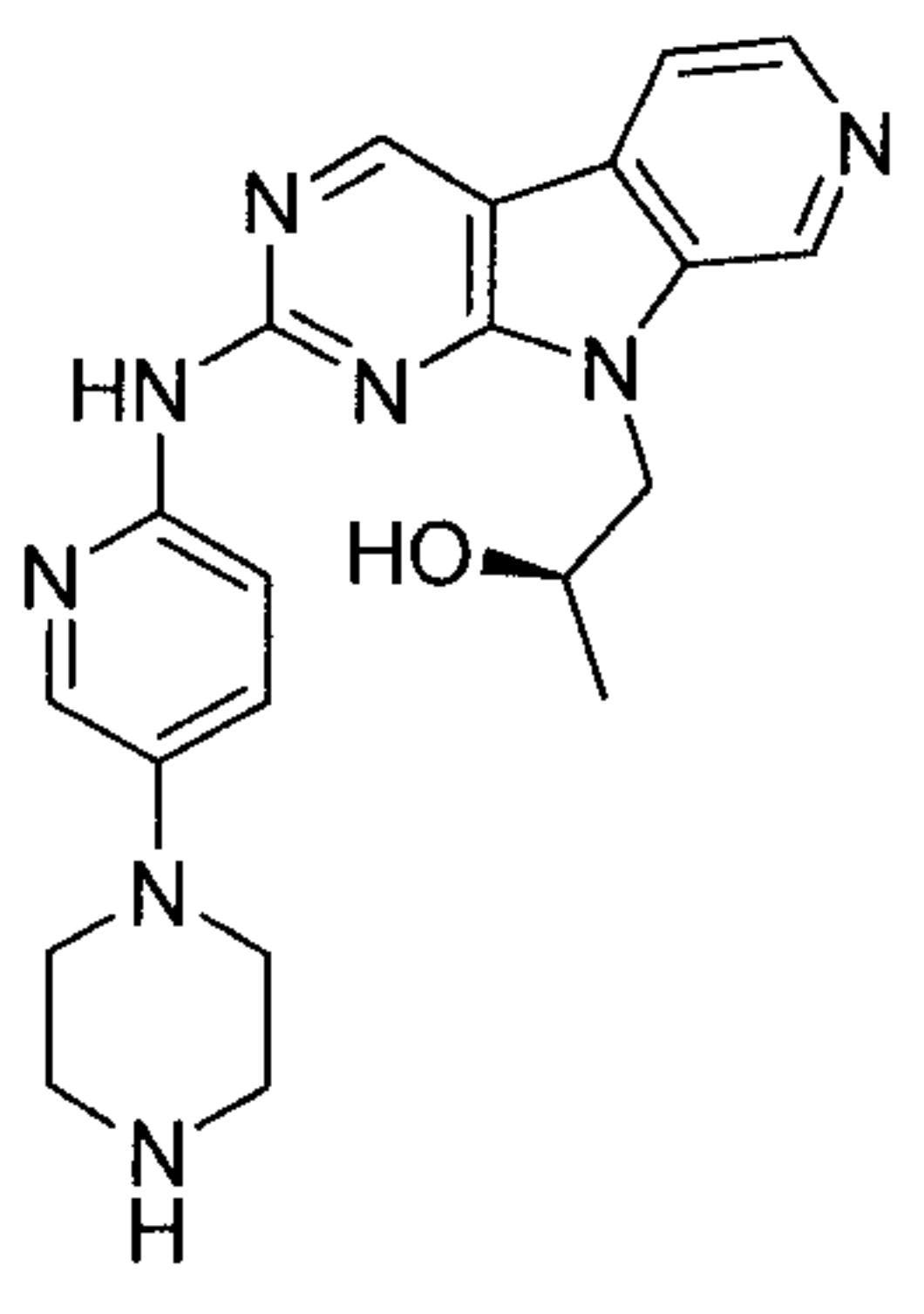
or a pharmaceutically acceptable salt thereof.

293. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

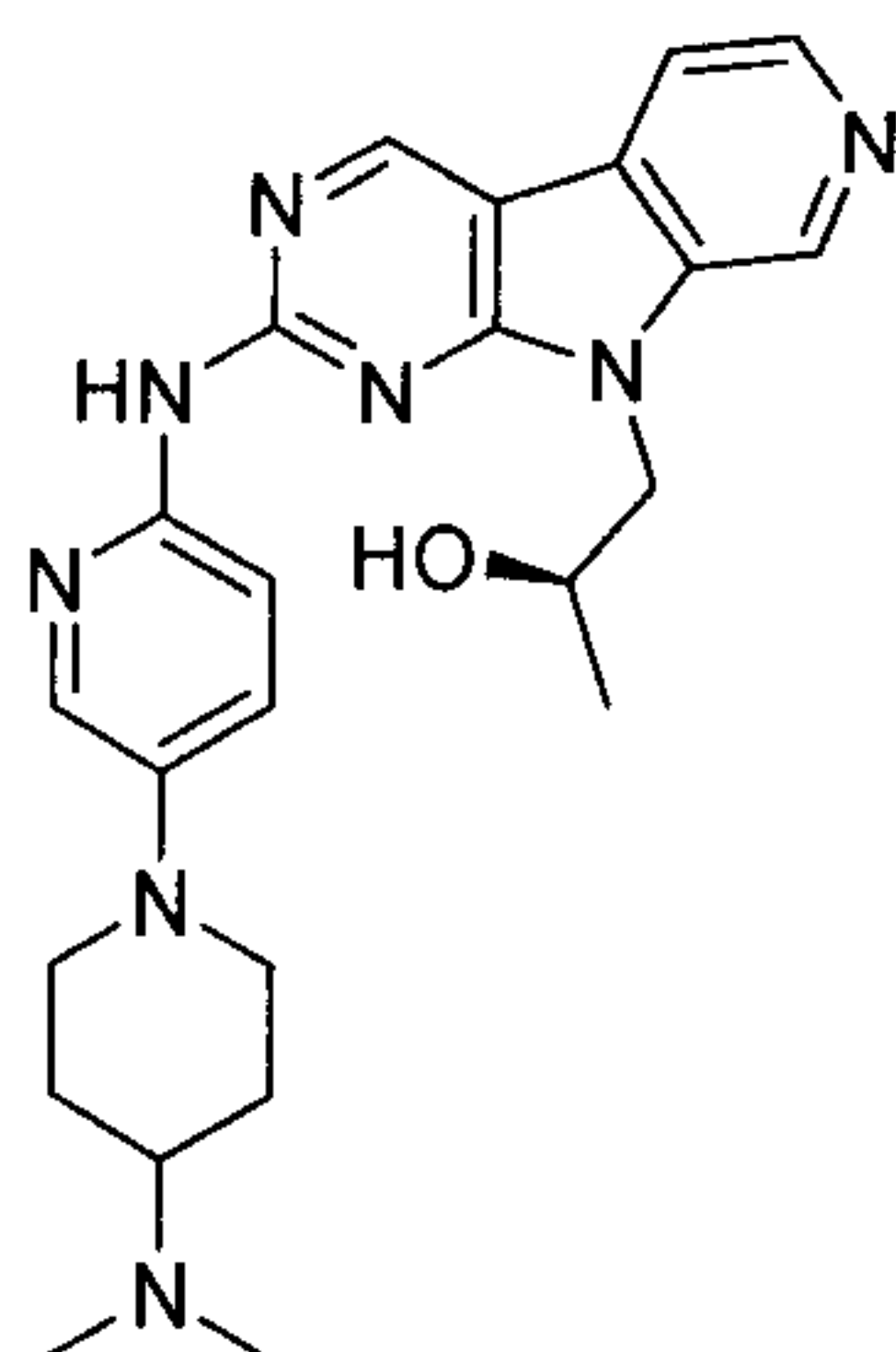
294. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

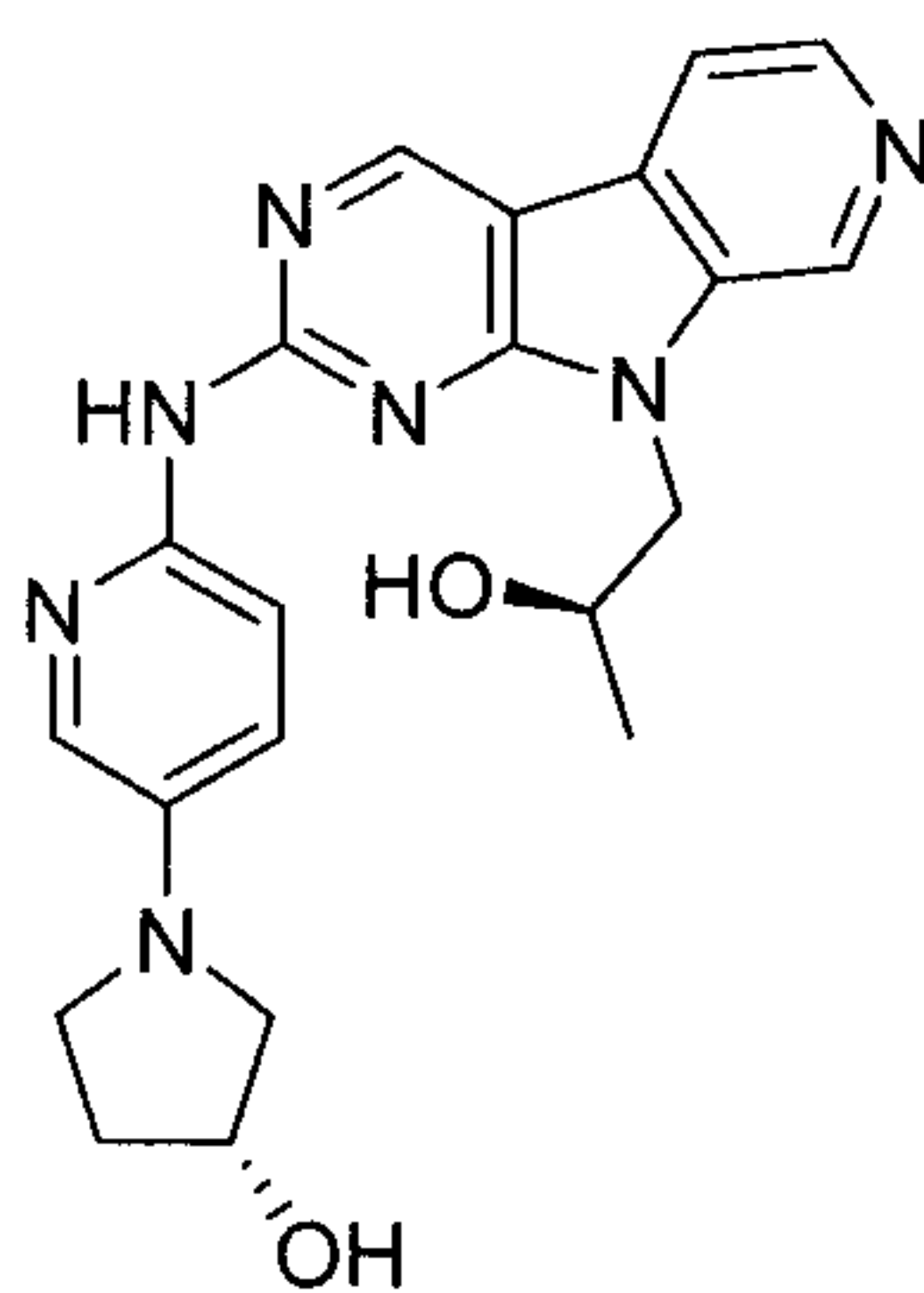


295. The compound of claim 1, wherein the compound is



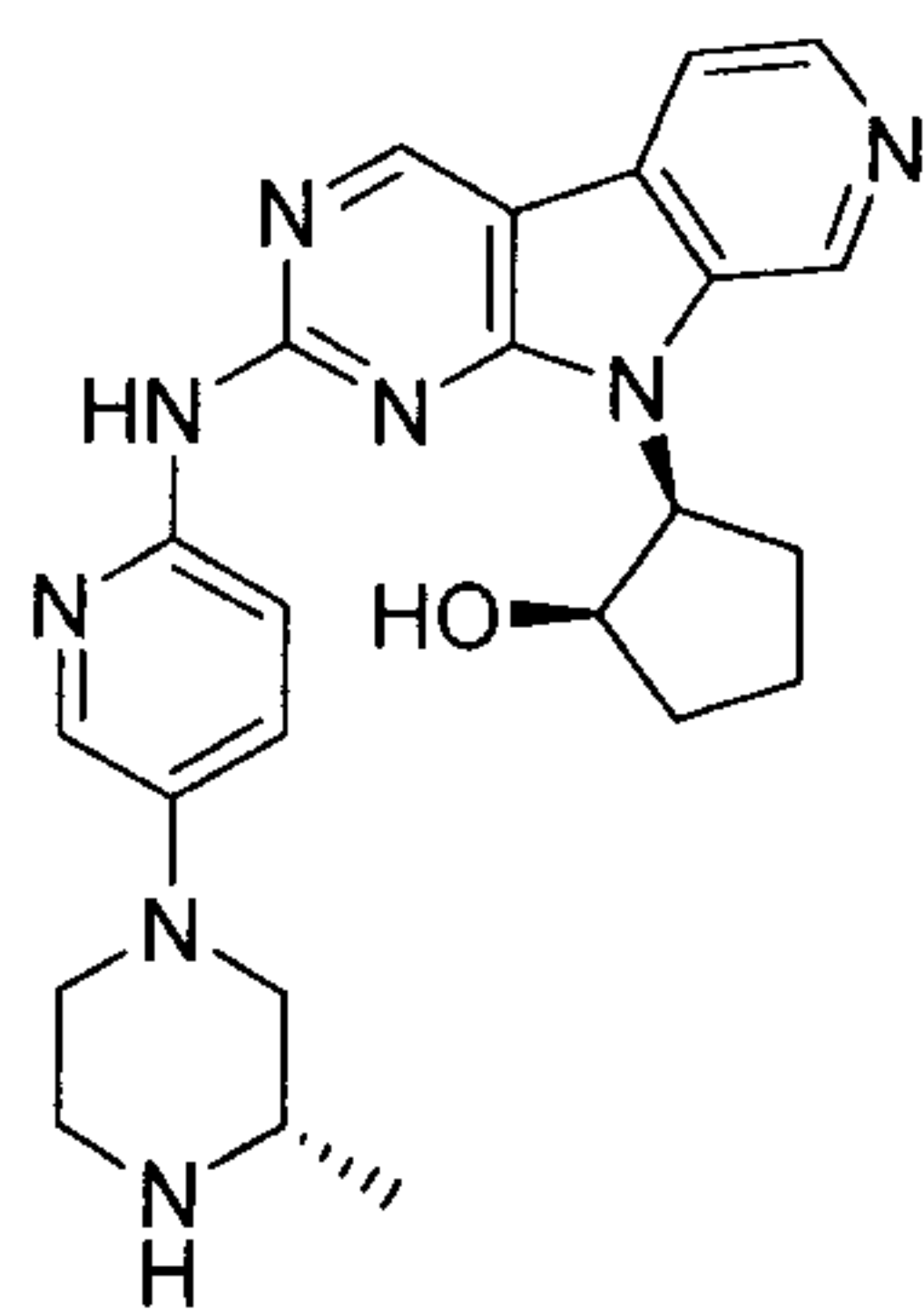
or a pharmaceutically acceptable salt thereof.

296. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

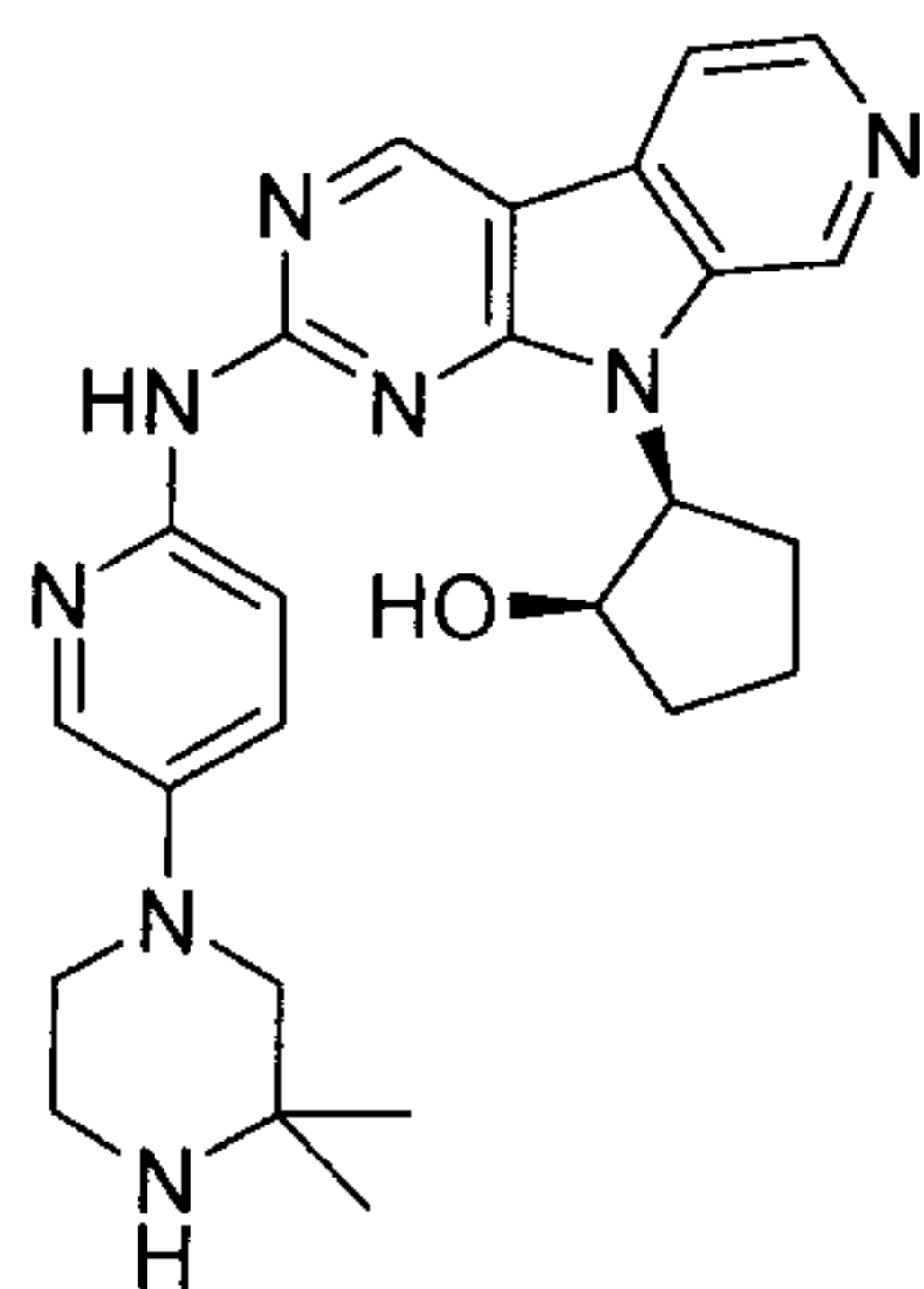
297. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

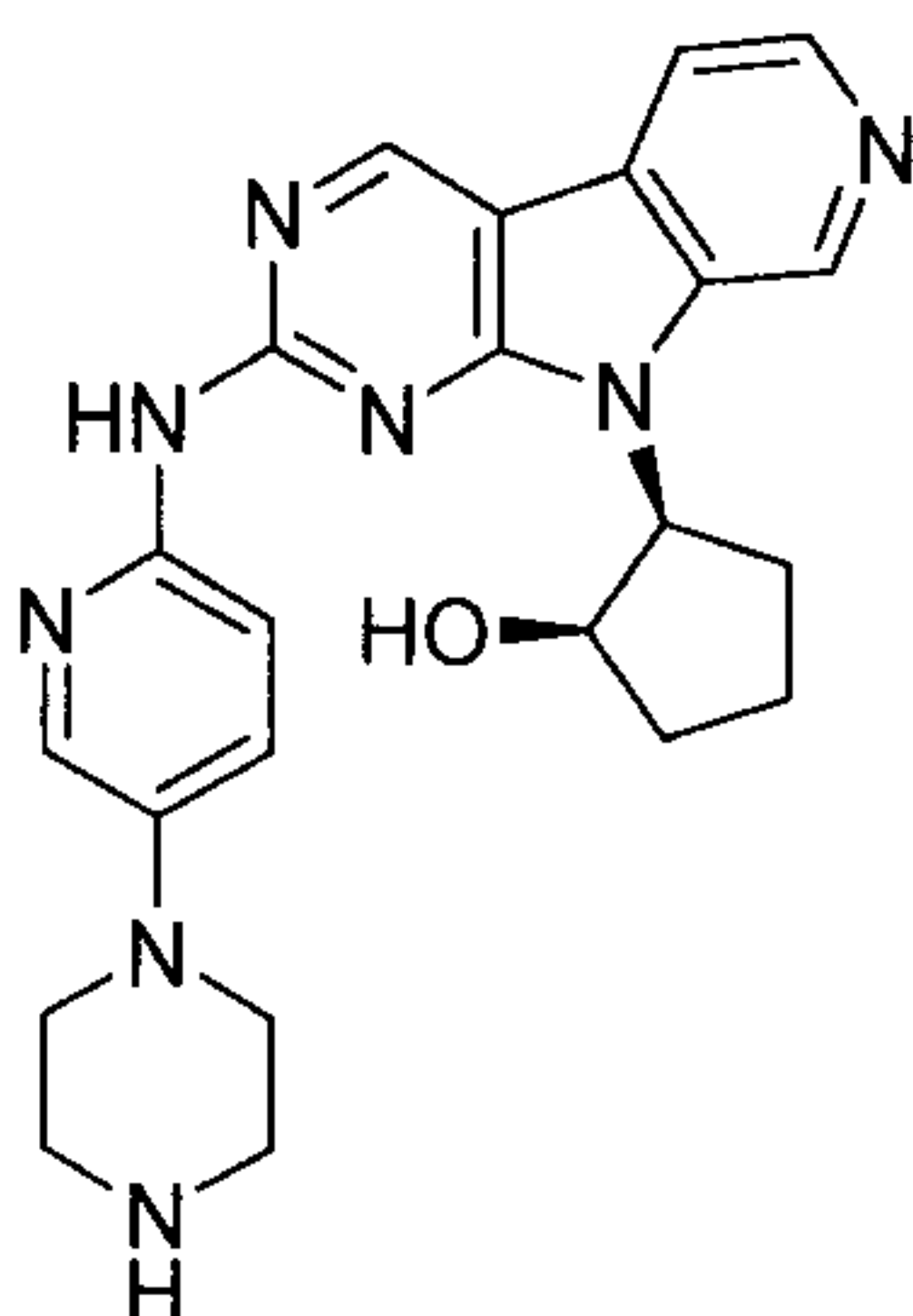


298. The compound of claim 1, wherein the compound is



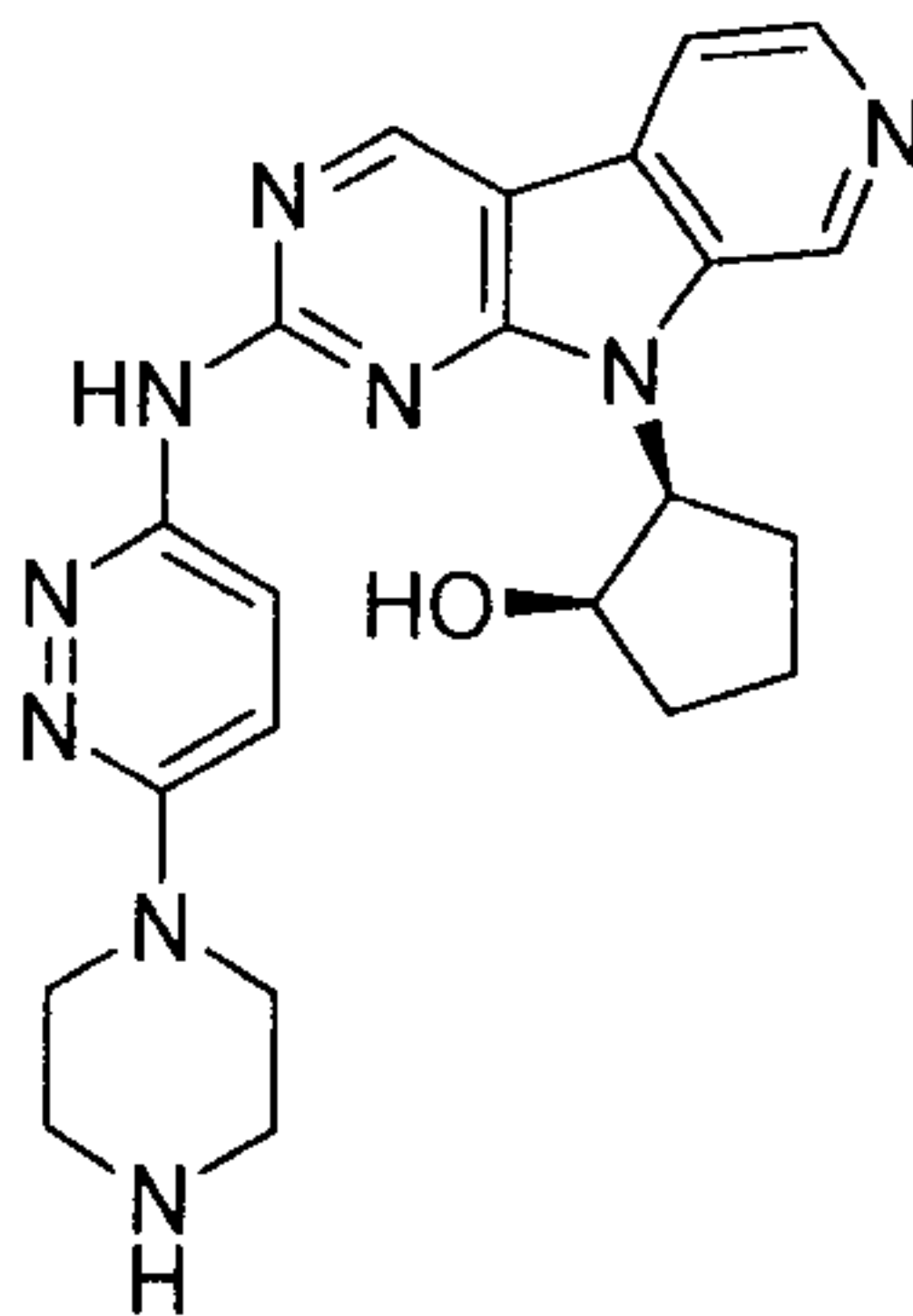
or a pharmaceutically acceptable salt thereof.

299. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

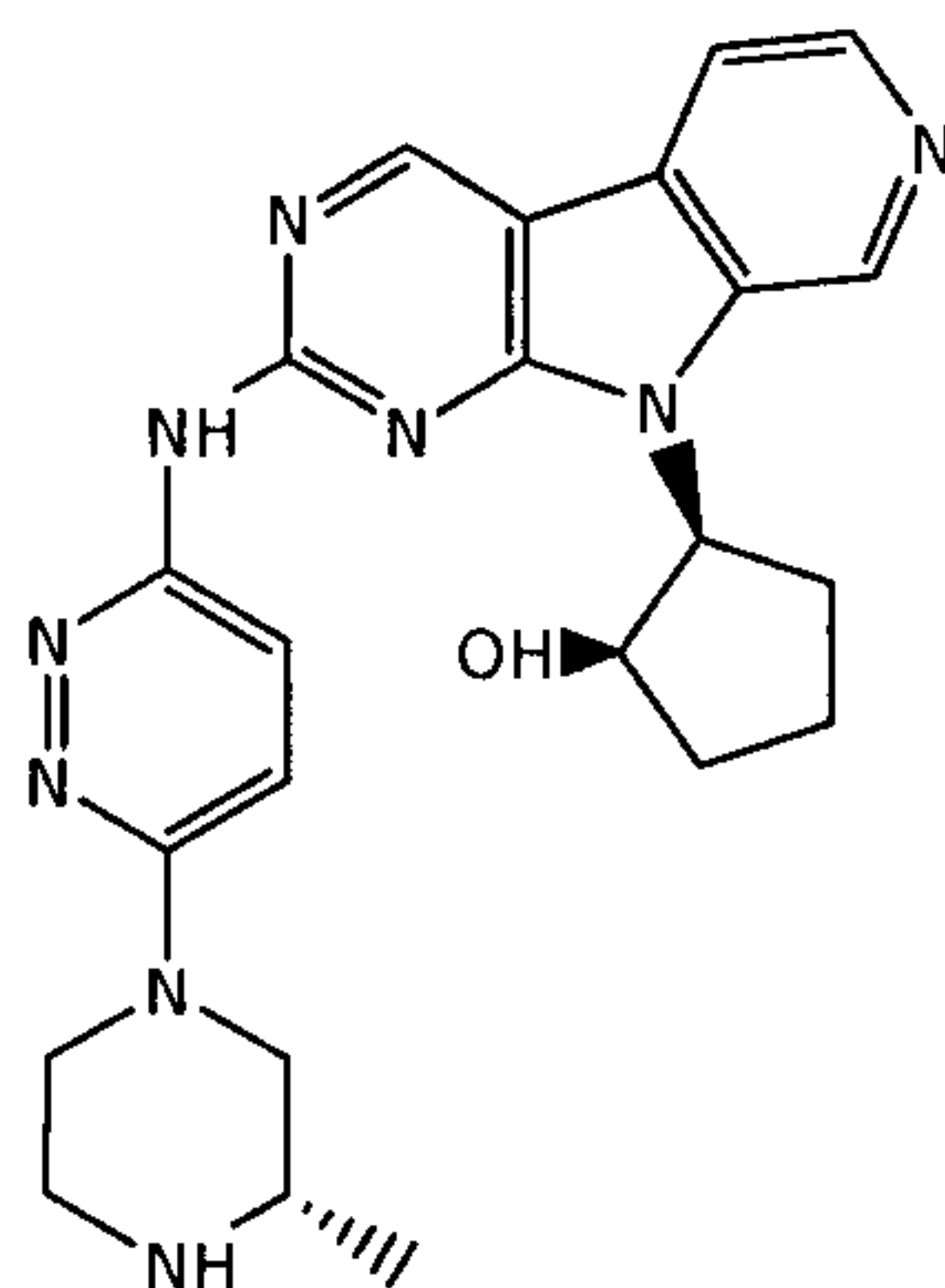
300. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

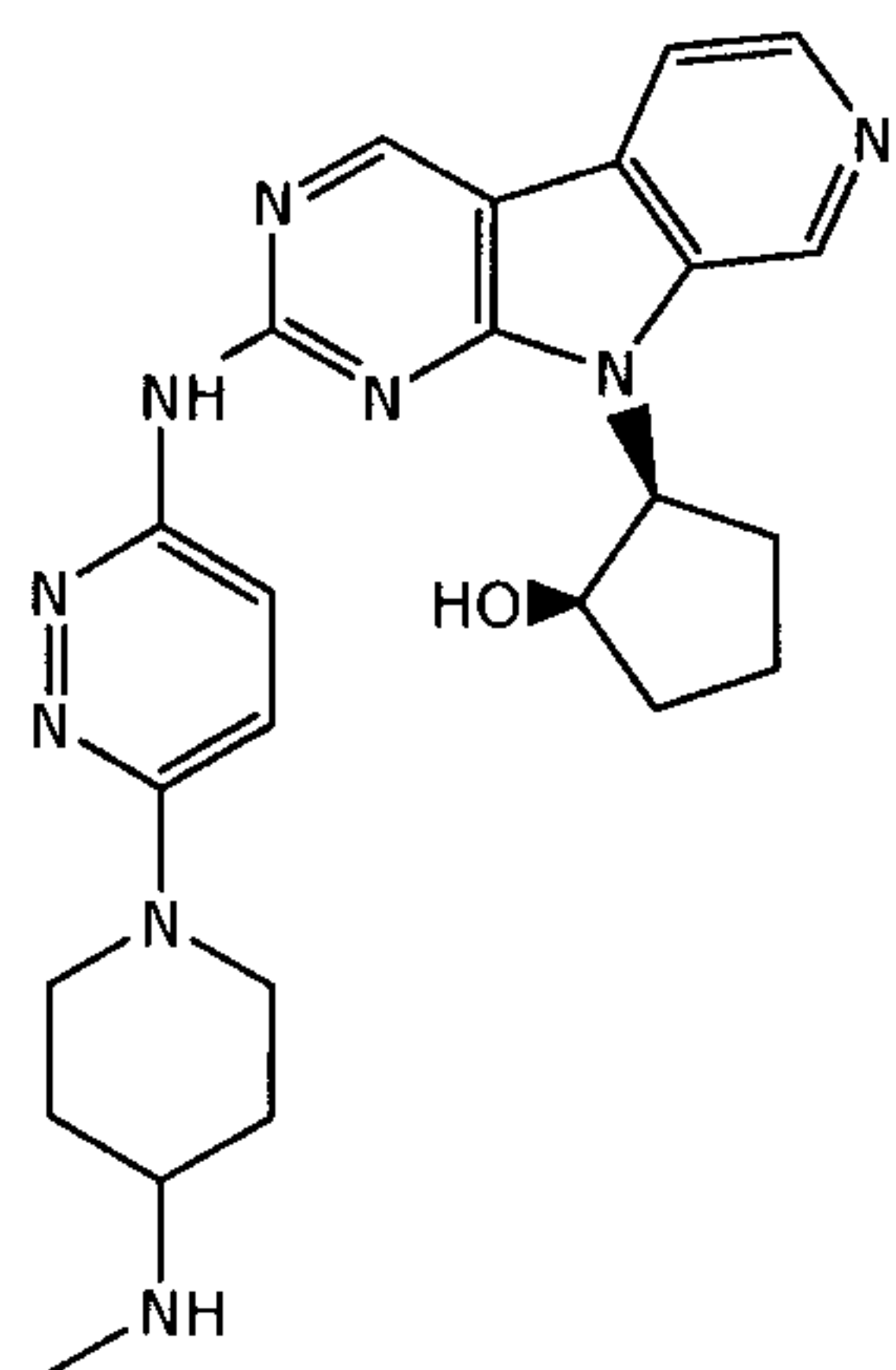


301. The compound of claim 1, wherein the compound is



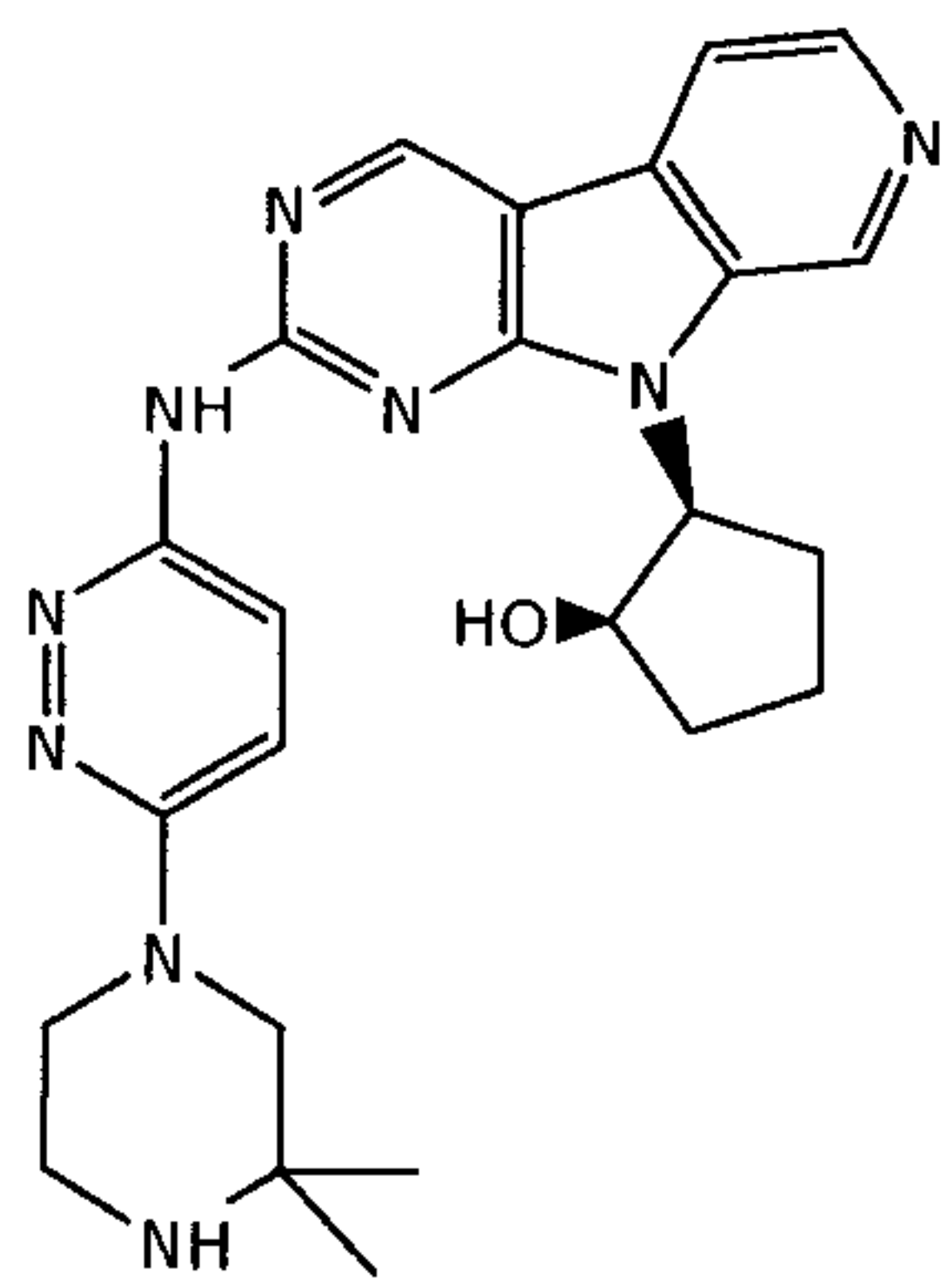
or a pharmaceutically acceptable salt thereof.

302. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

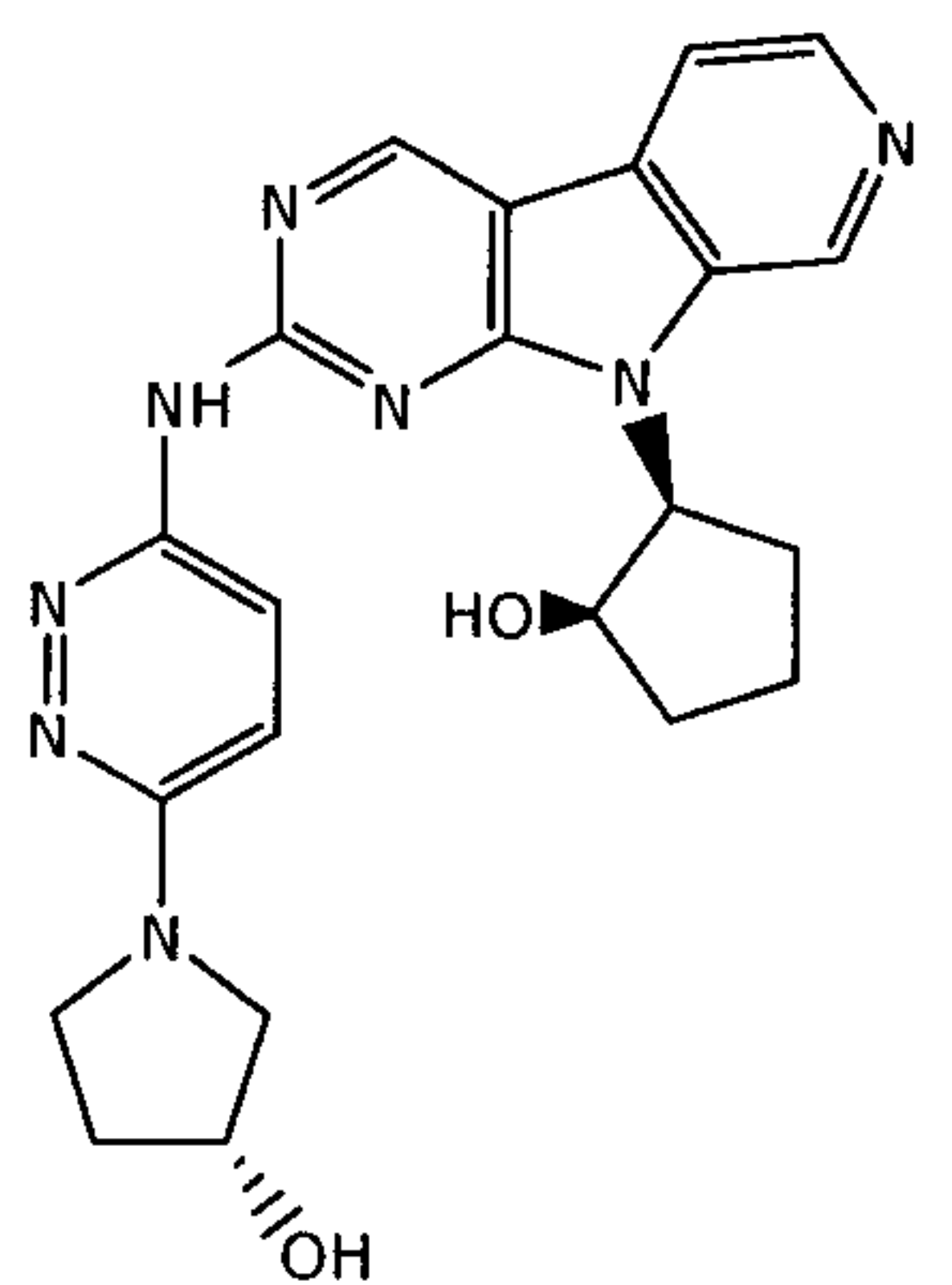
303. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

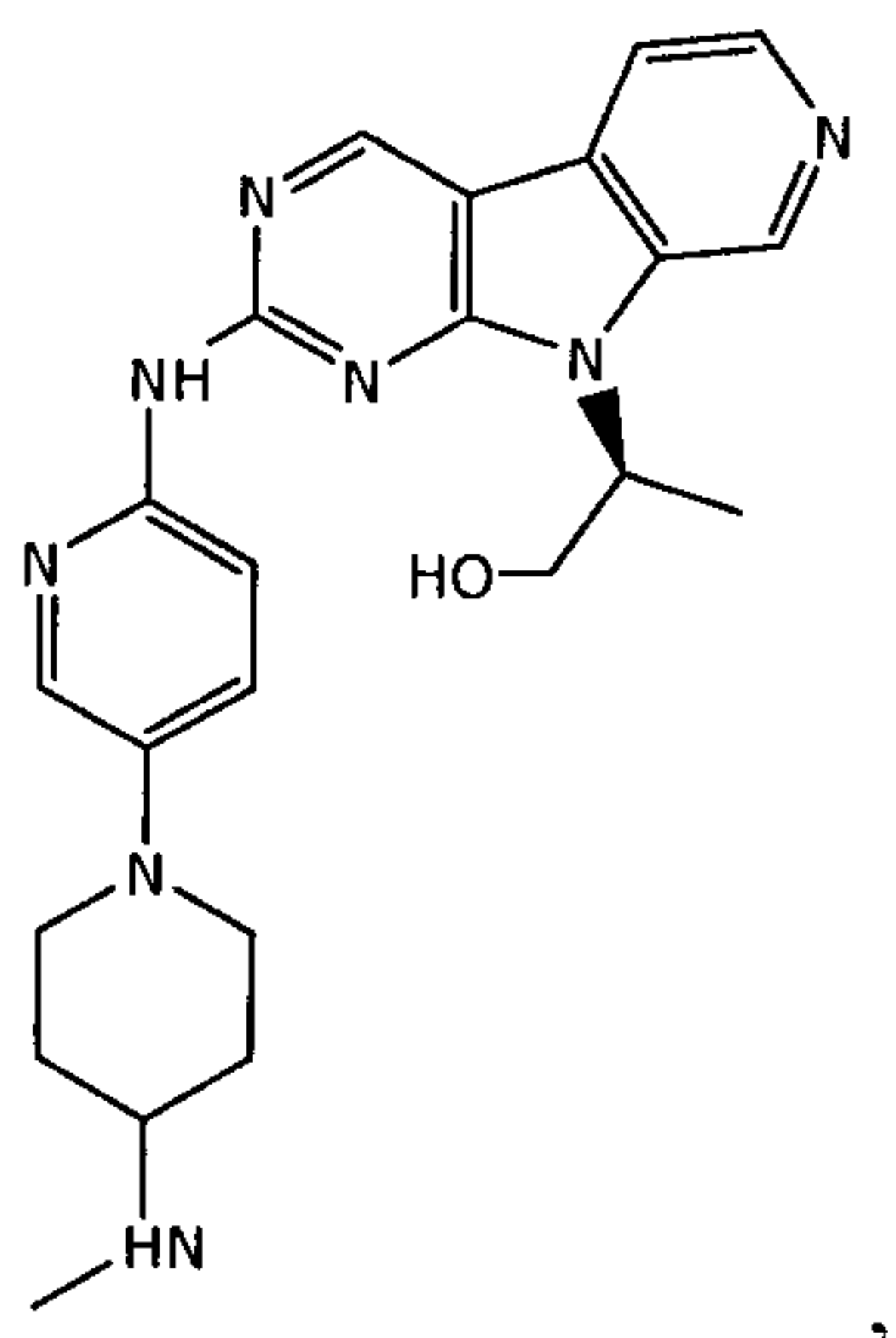


304. The compound of claim 1, wherein the compound is



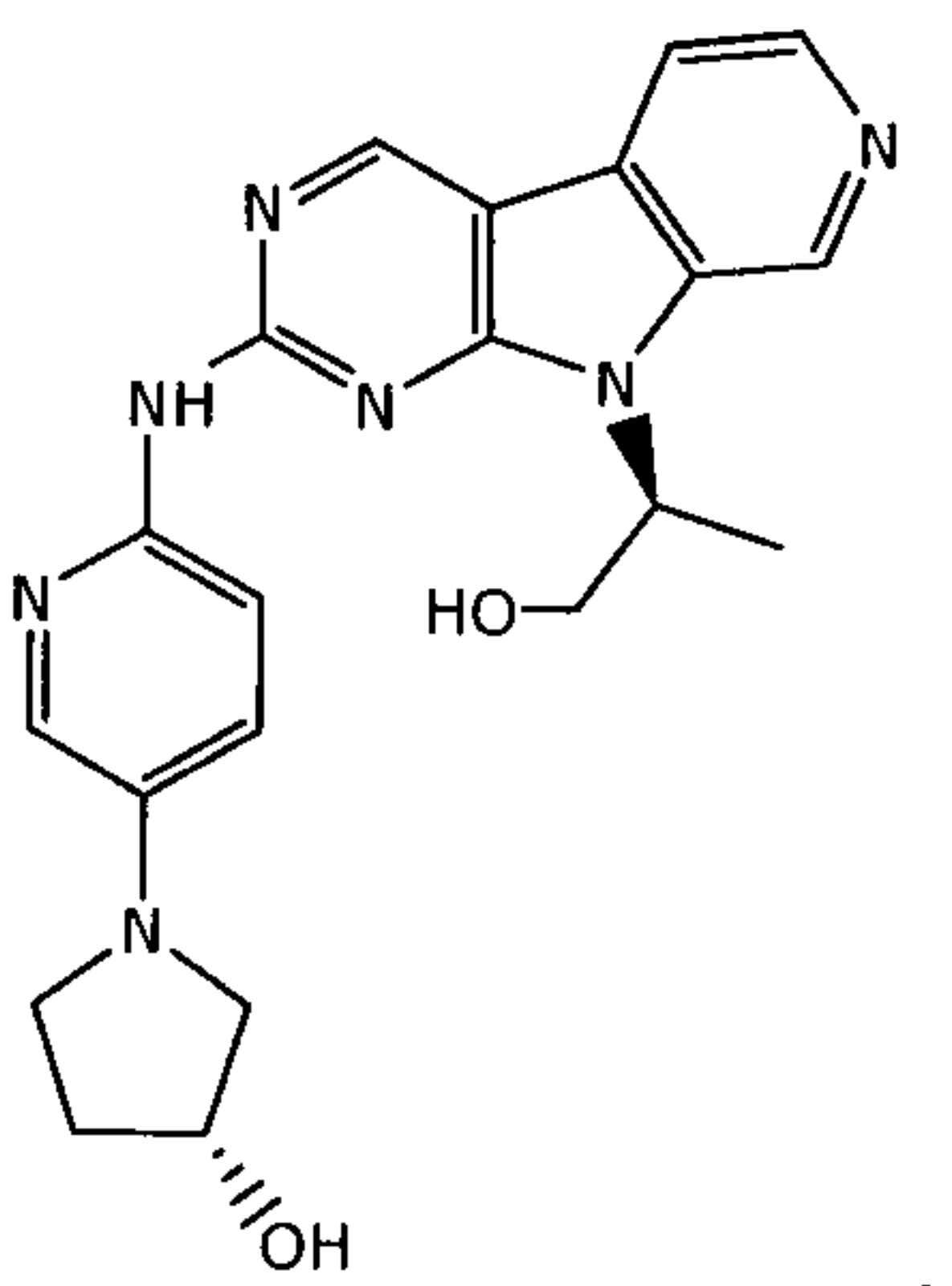
or a pharmaceutically acceptable salt thereof.

305. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

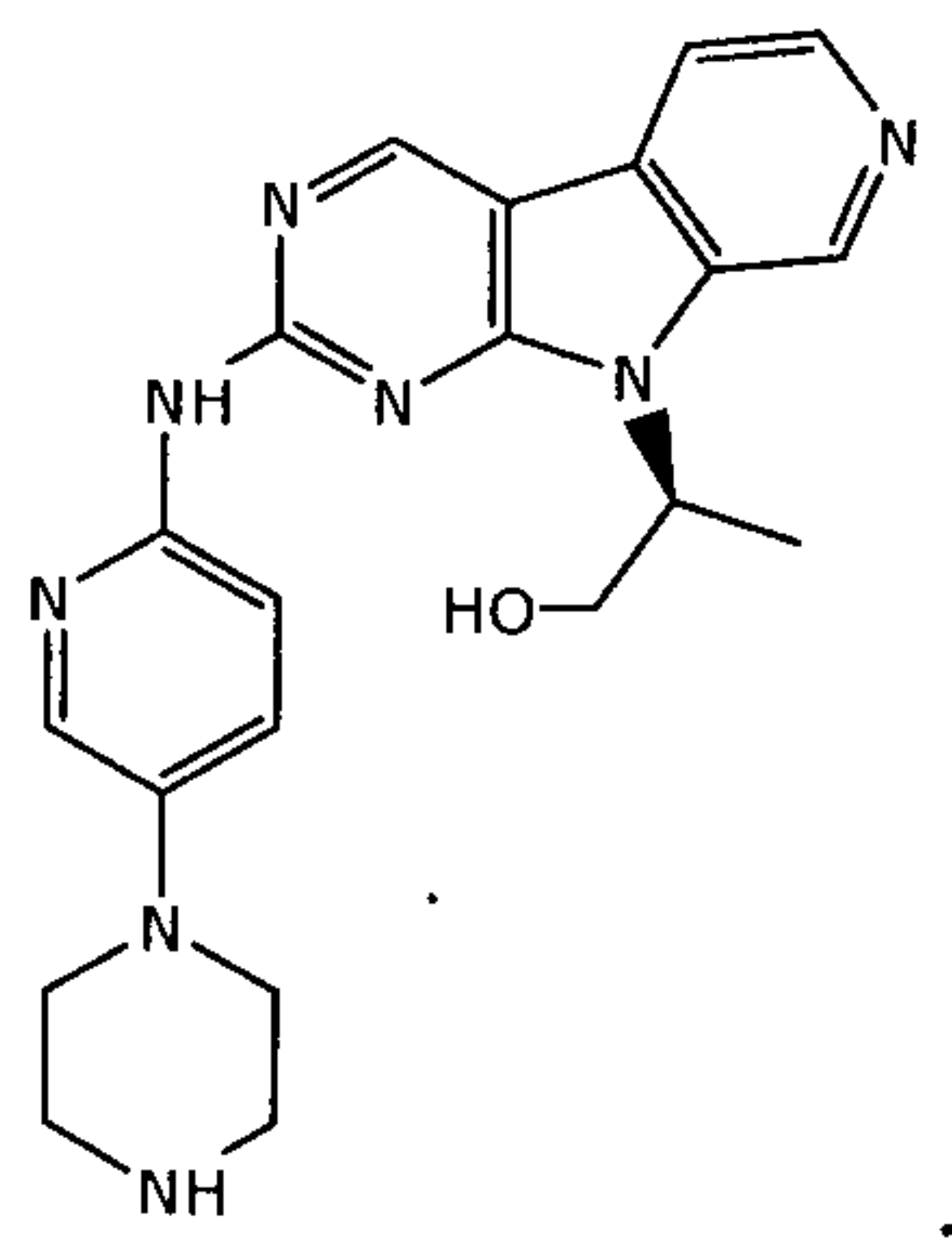
306. The compound of claim 1, wherein the compound is





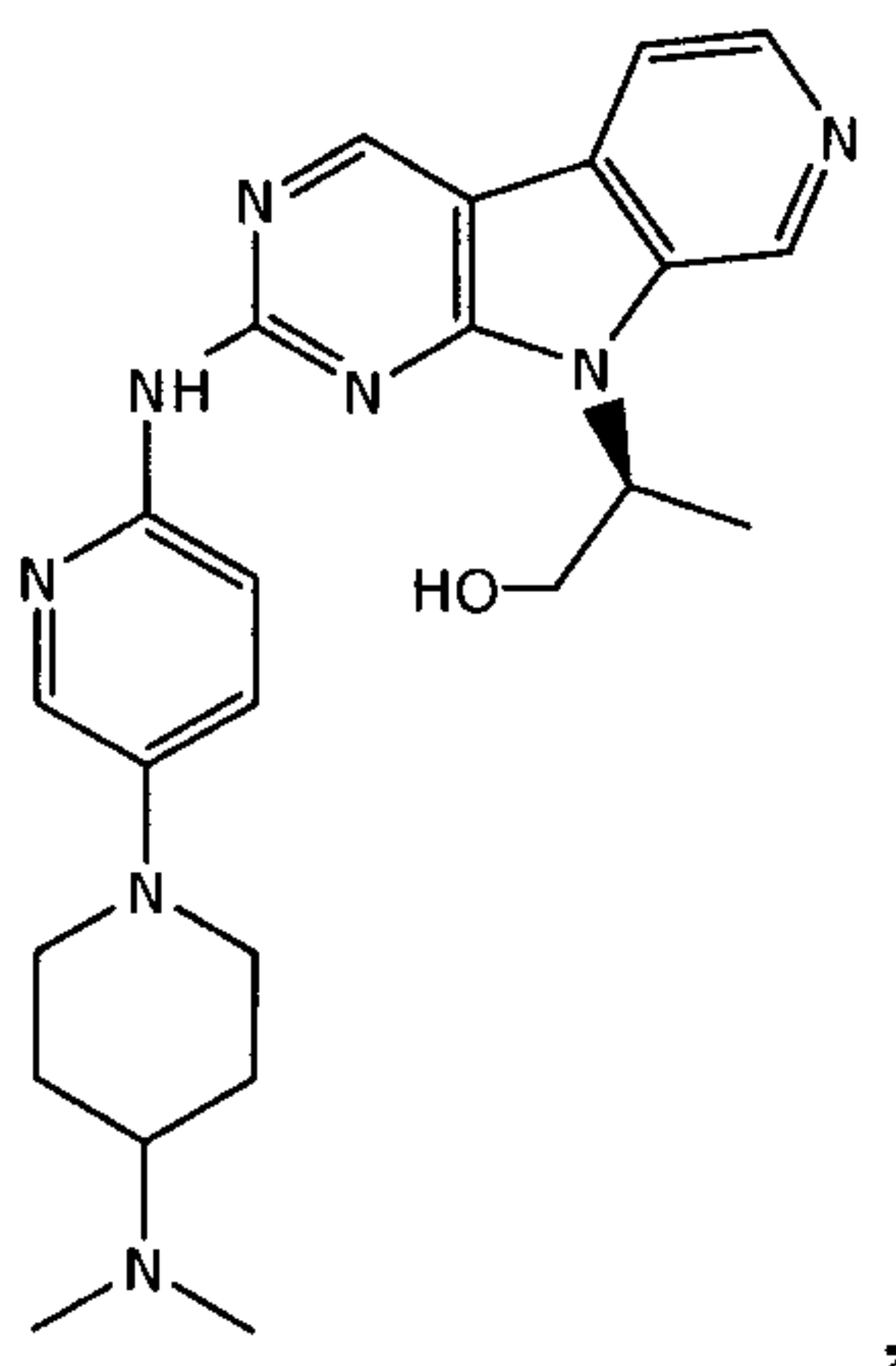
or a pharmaceutically acceptable salt thereof.

307. The compound of claim 1, wherein the compound is



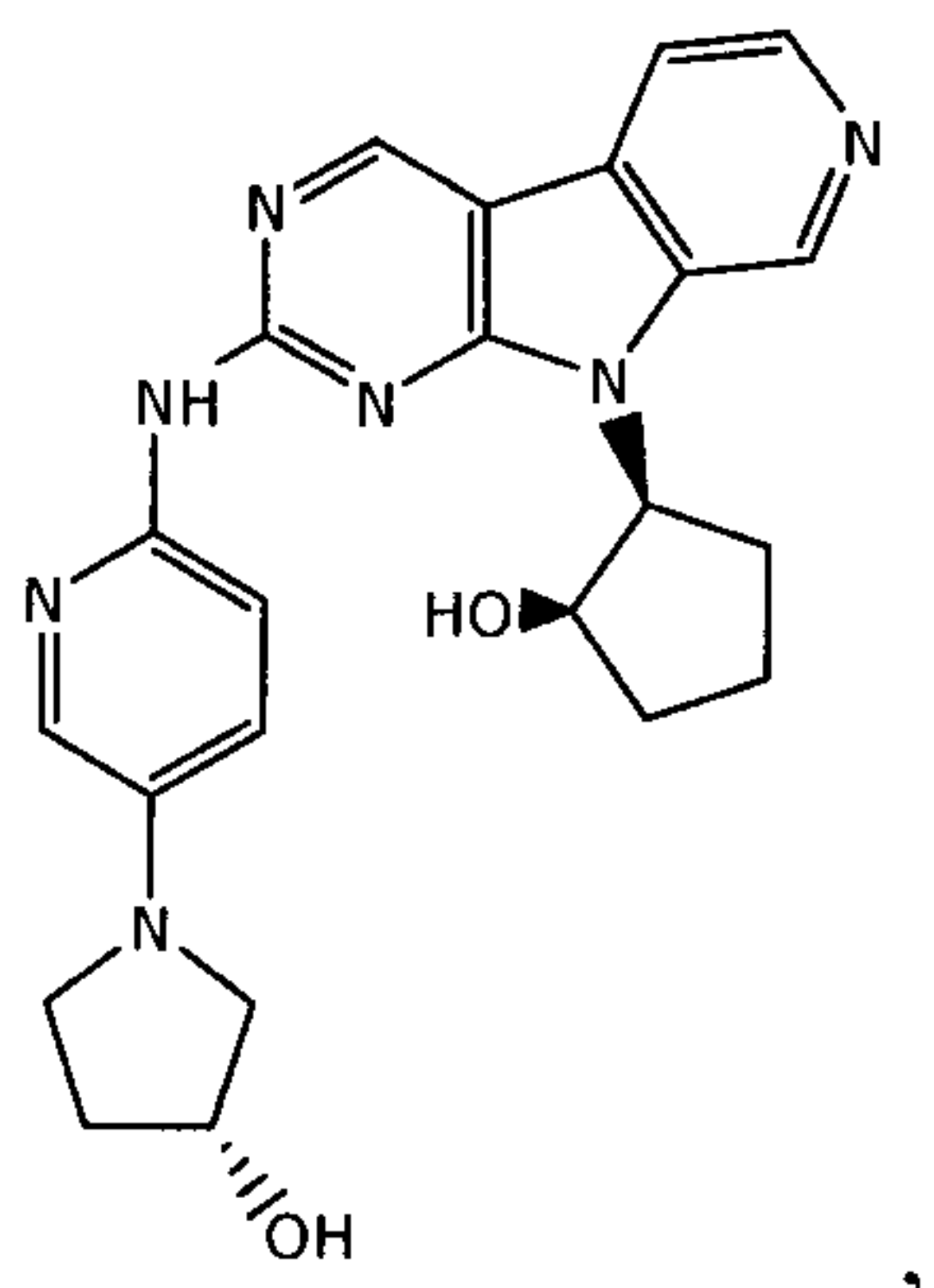
or a pharmaceutically acceptable salt thereof.

308. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

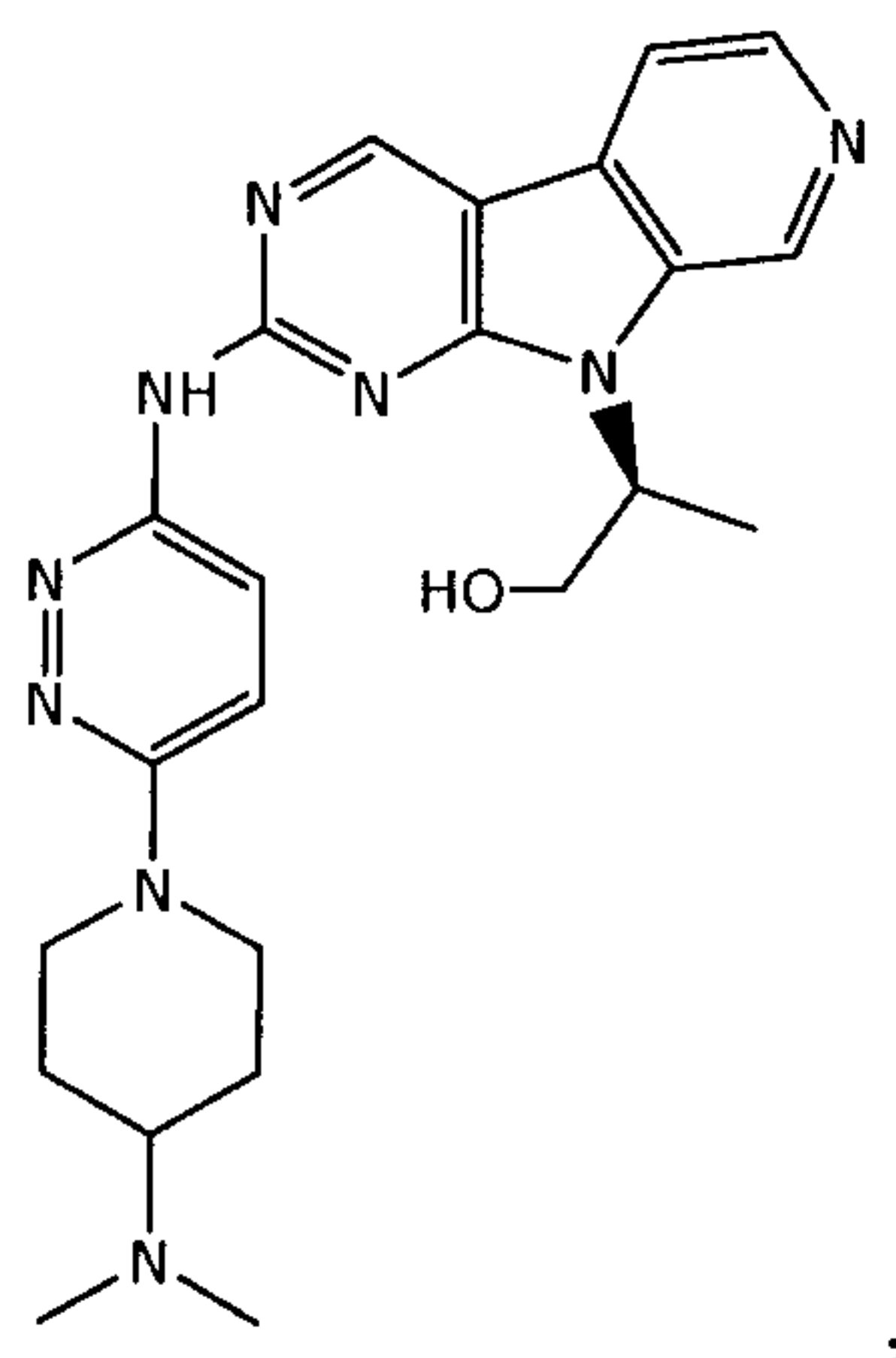
309. The compound of claim 1, wherein the compound is





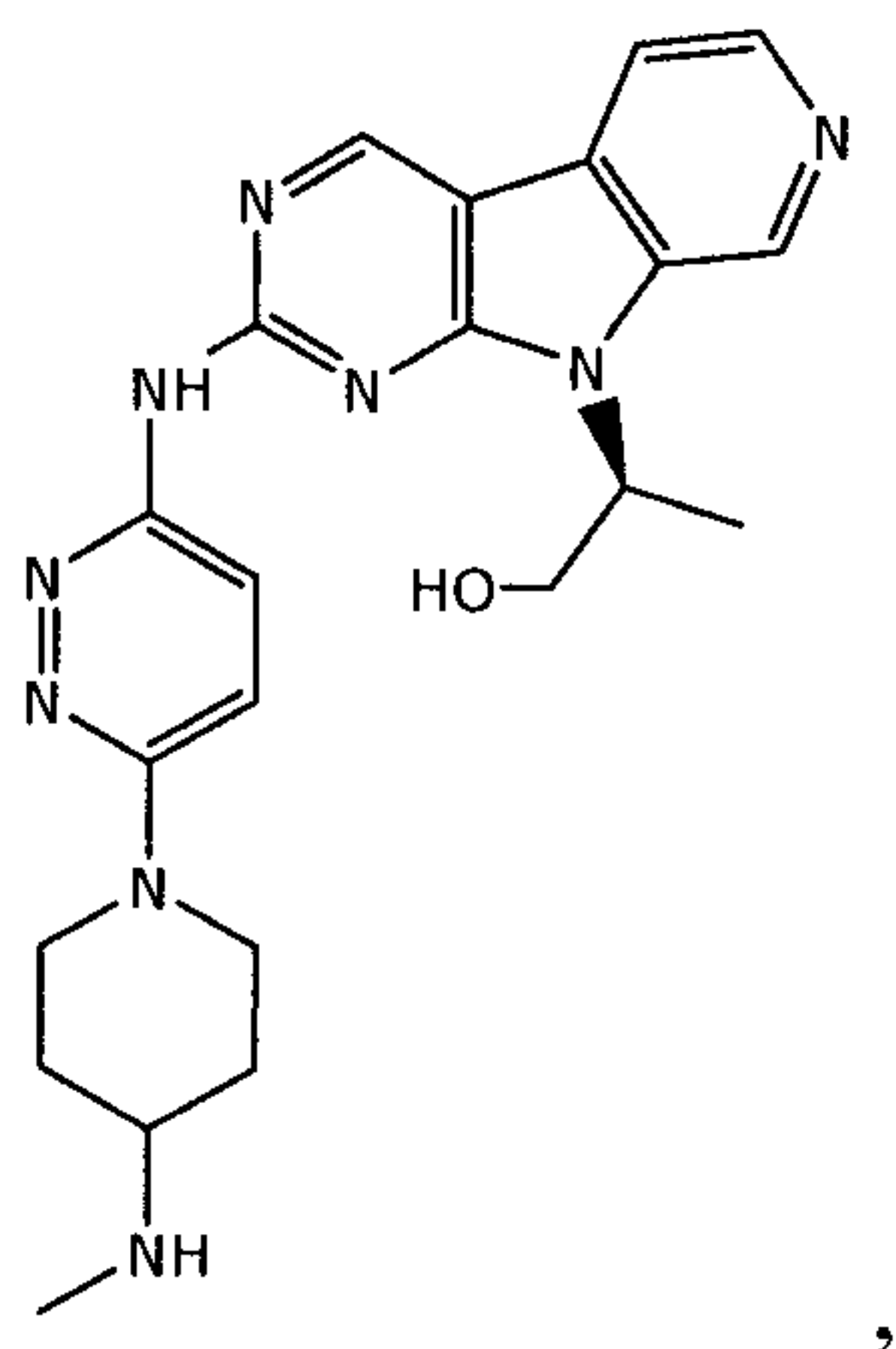
or a pharmaceutically acceptable salt thereof.

310. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

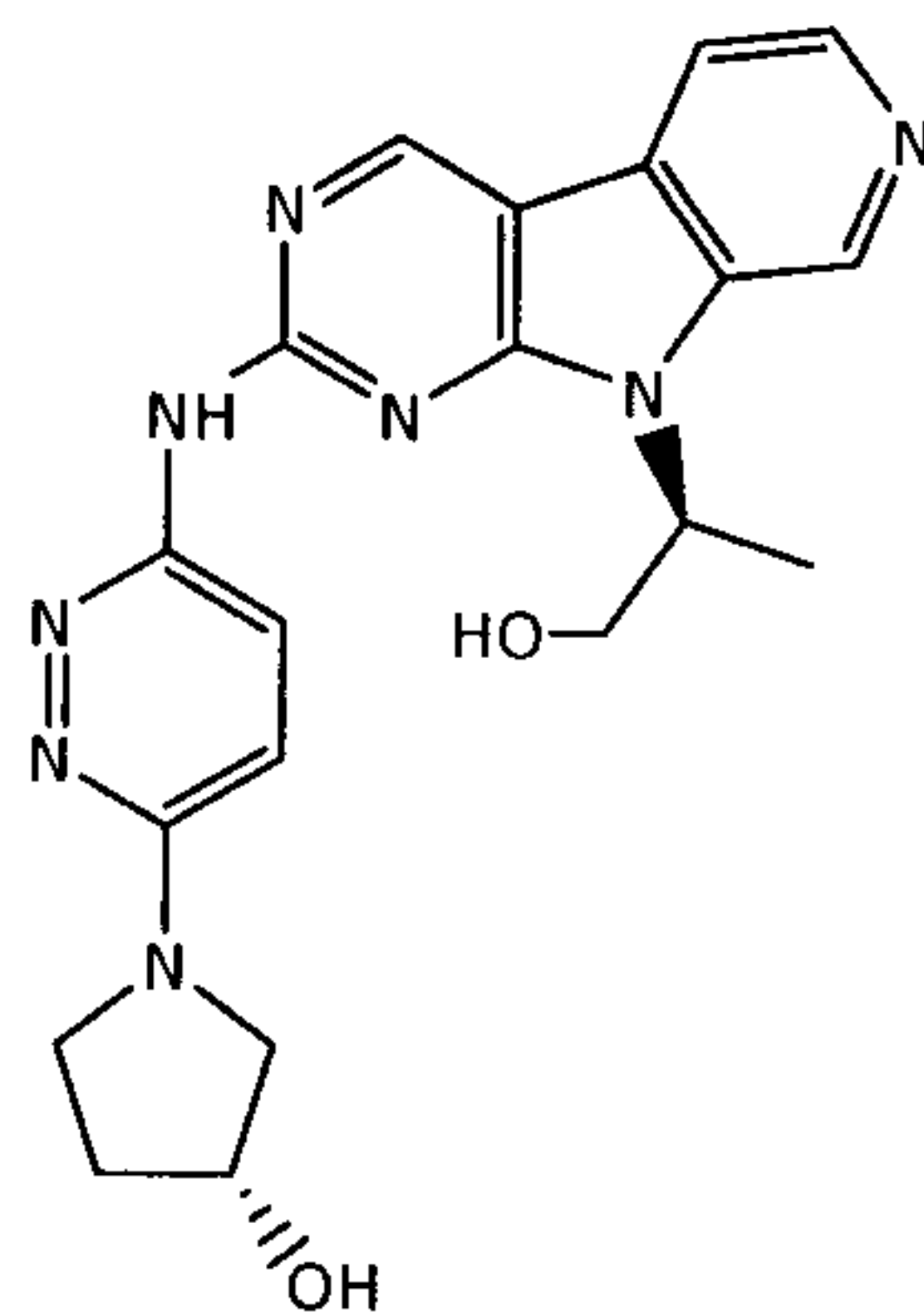
311. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

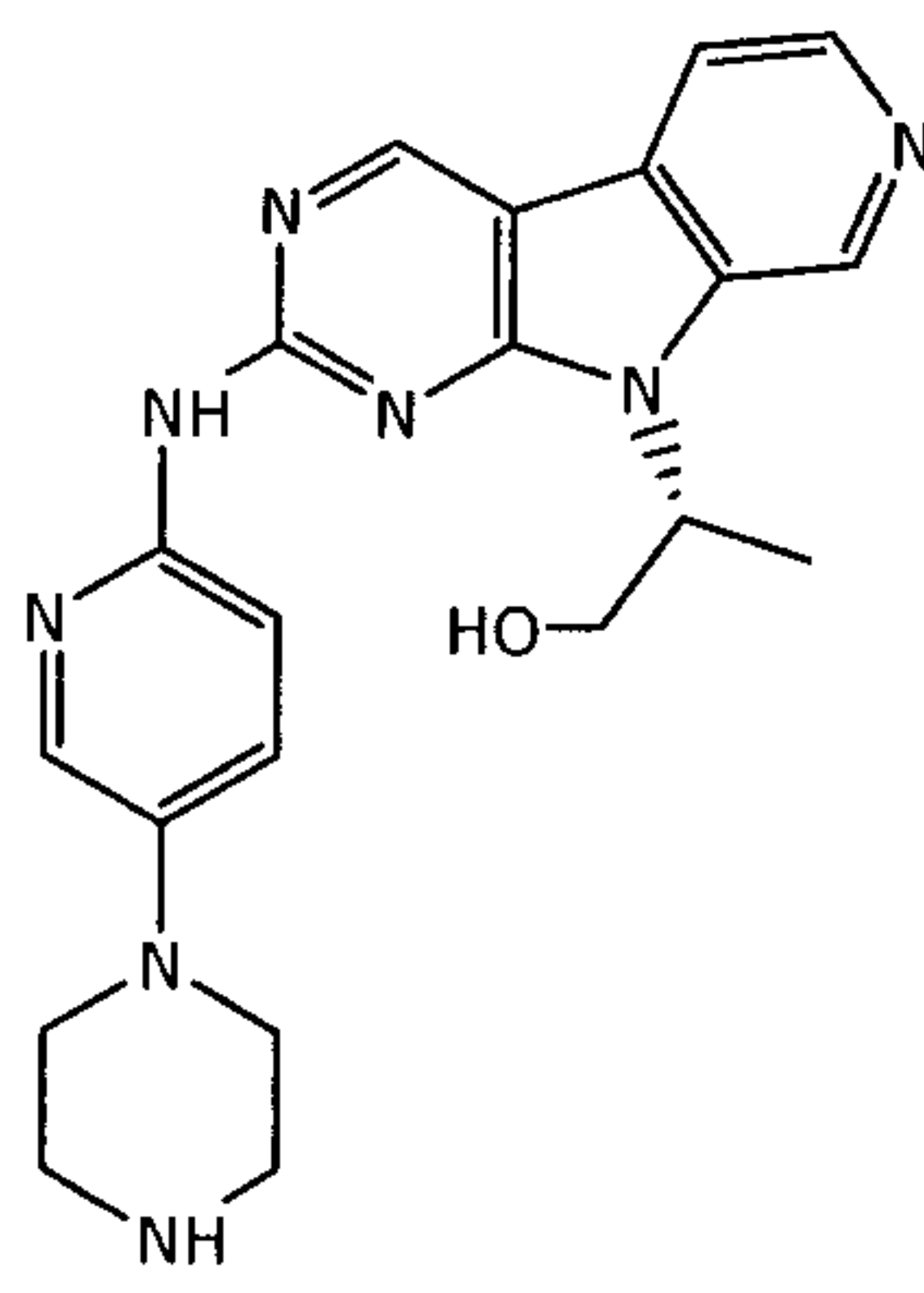


312. The compound of claim 1, wherein the compound is



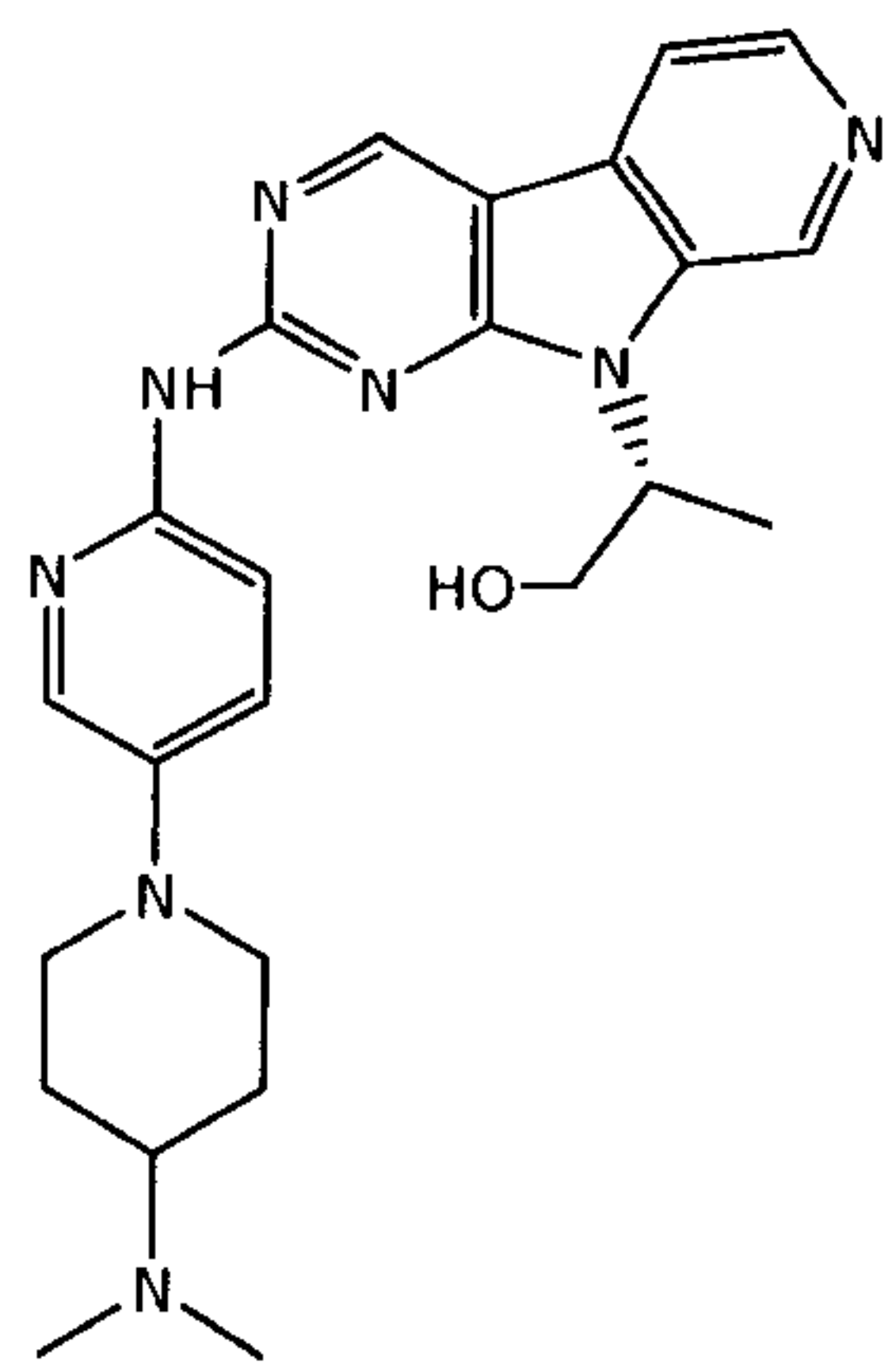
or a pharmaceutically acceptable salt thereof.

313. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

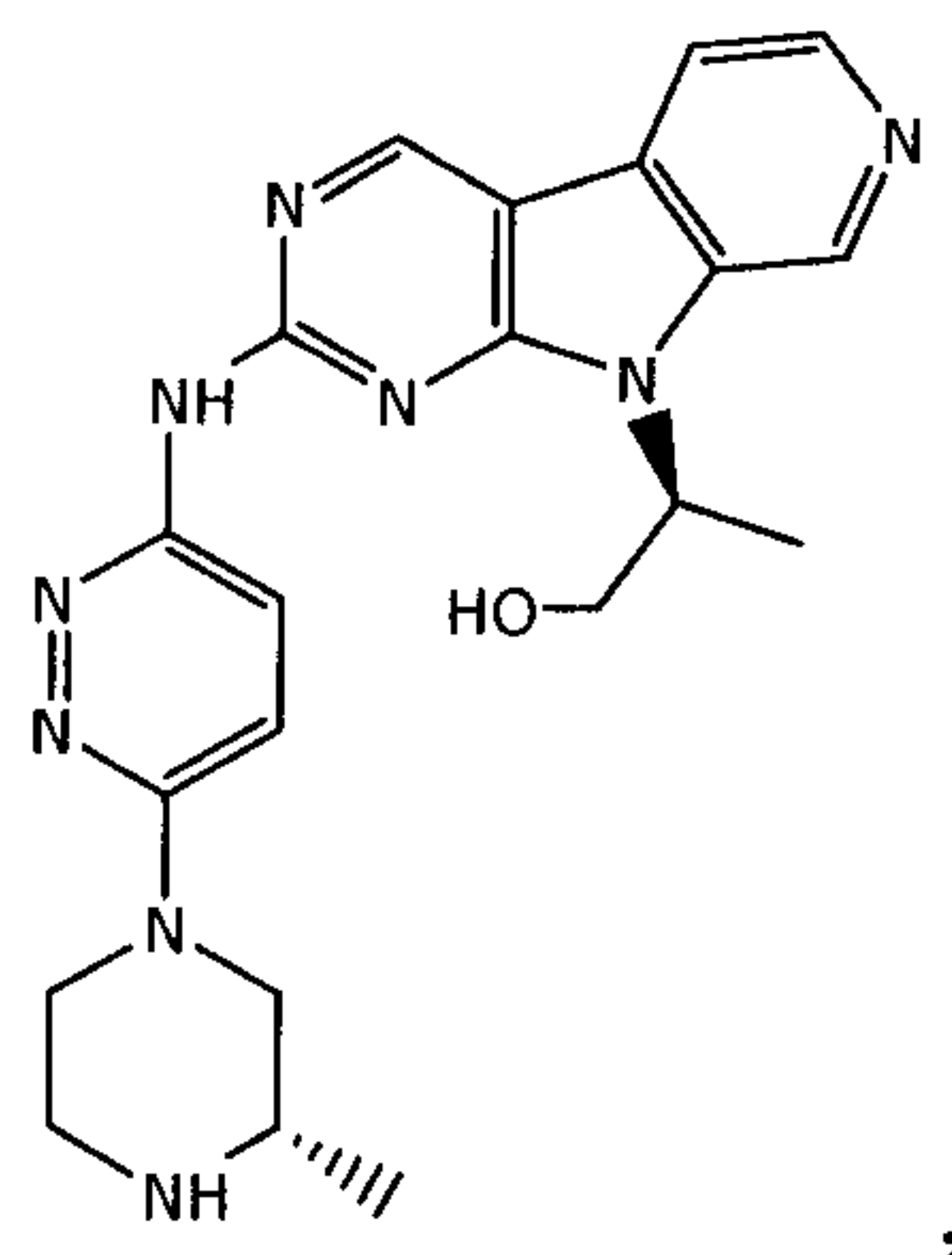
314. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

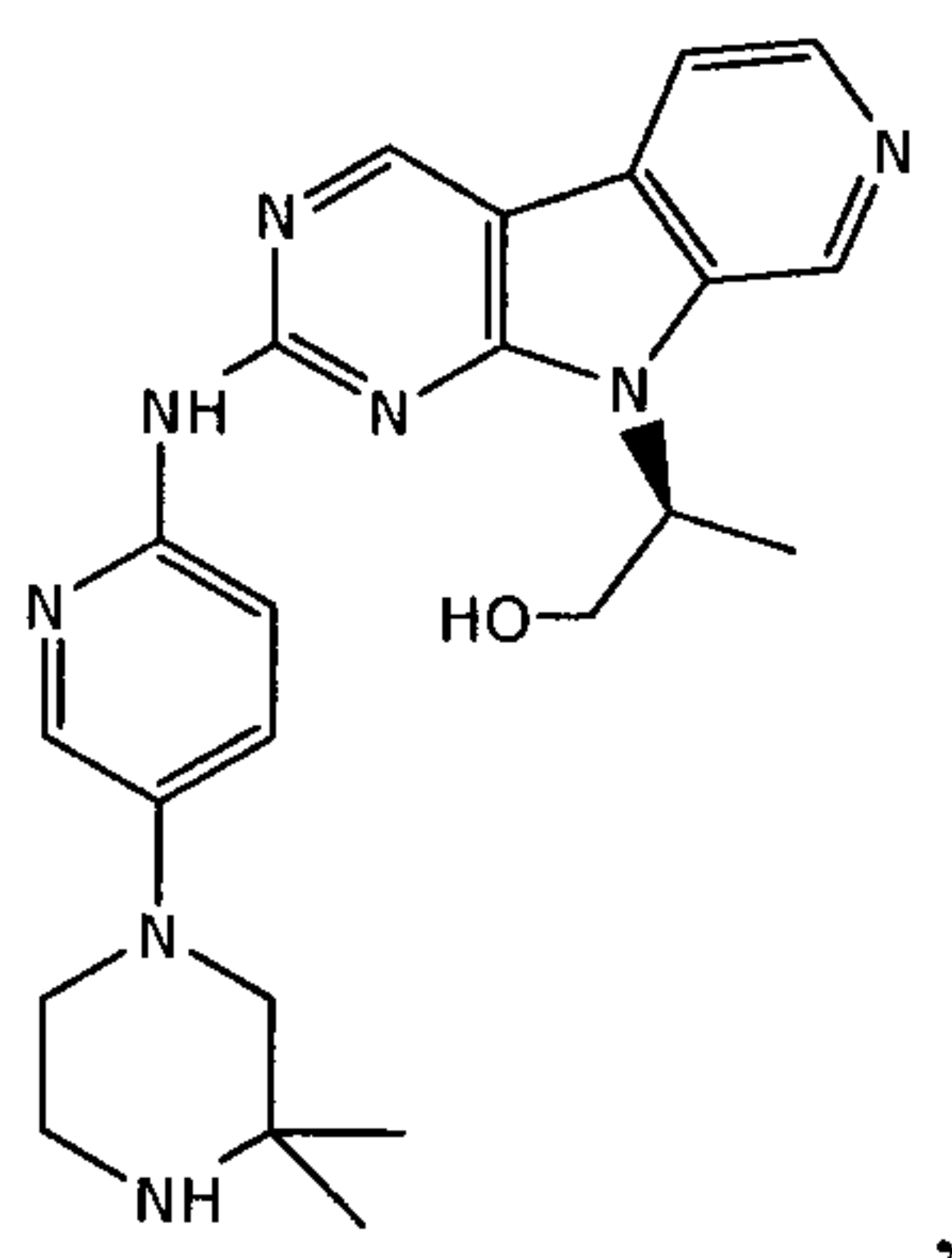


315. The compound of claim 1, wherein the compound is



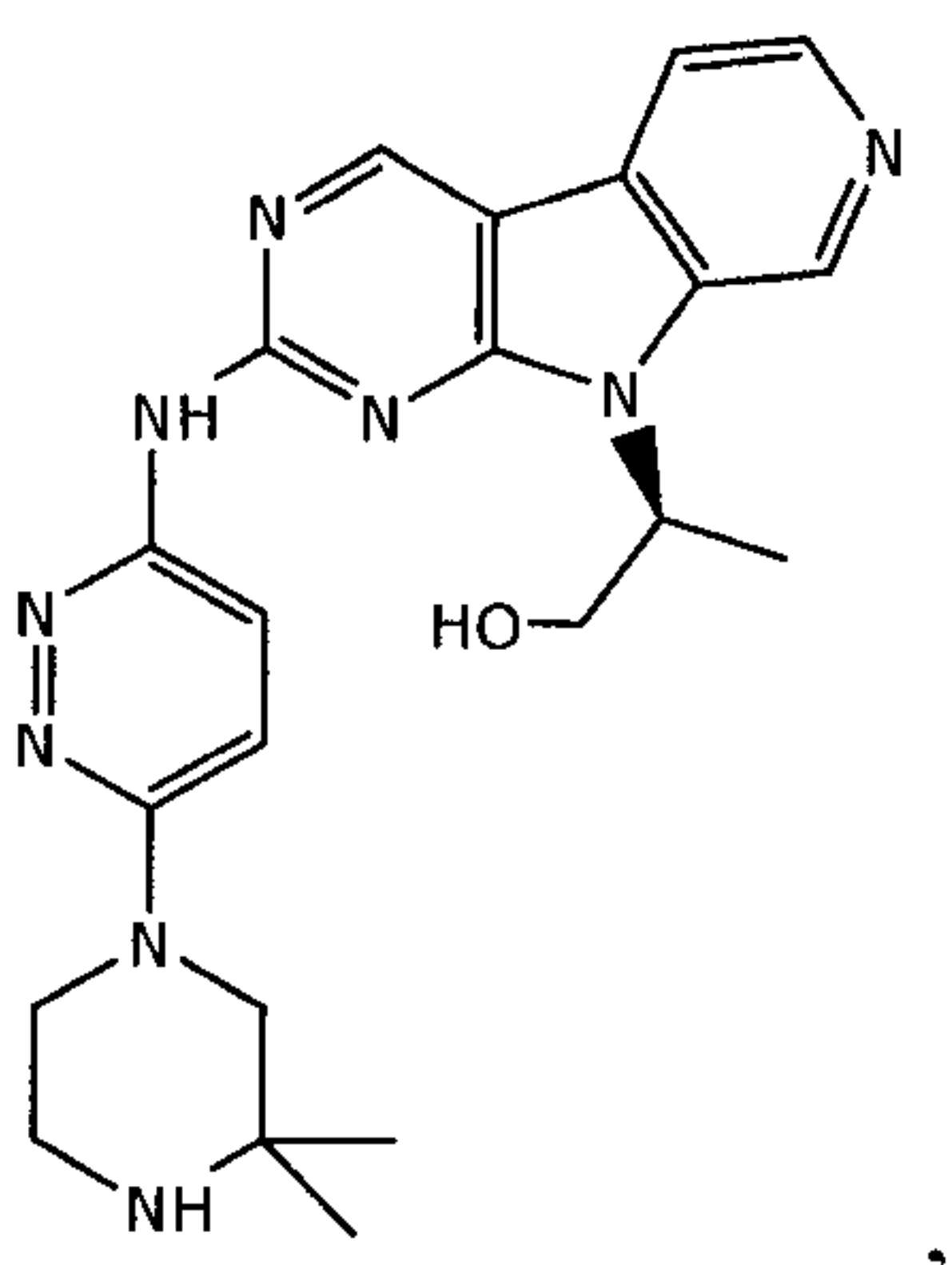
or a pharmaceutically acceptable salt thereof.

316. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

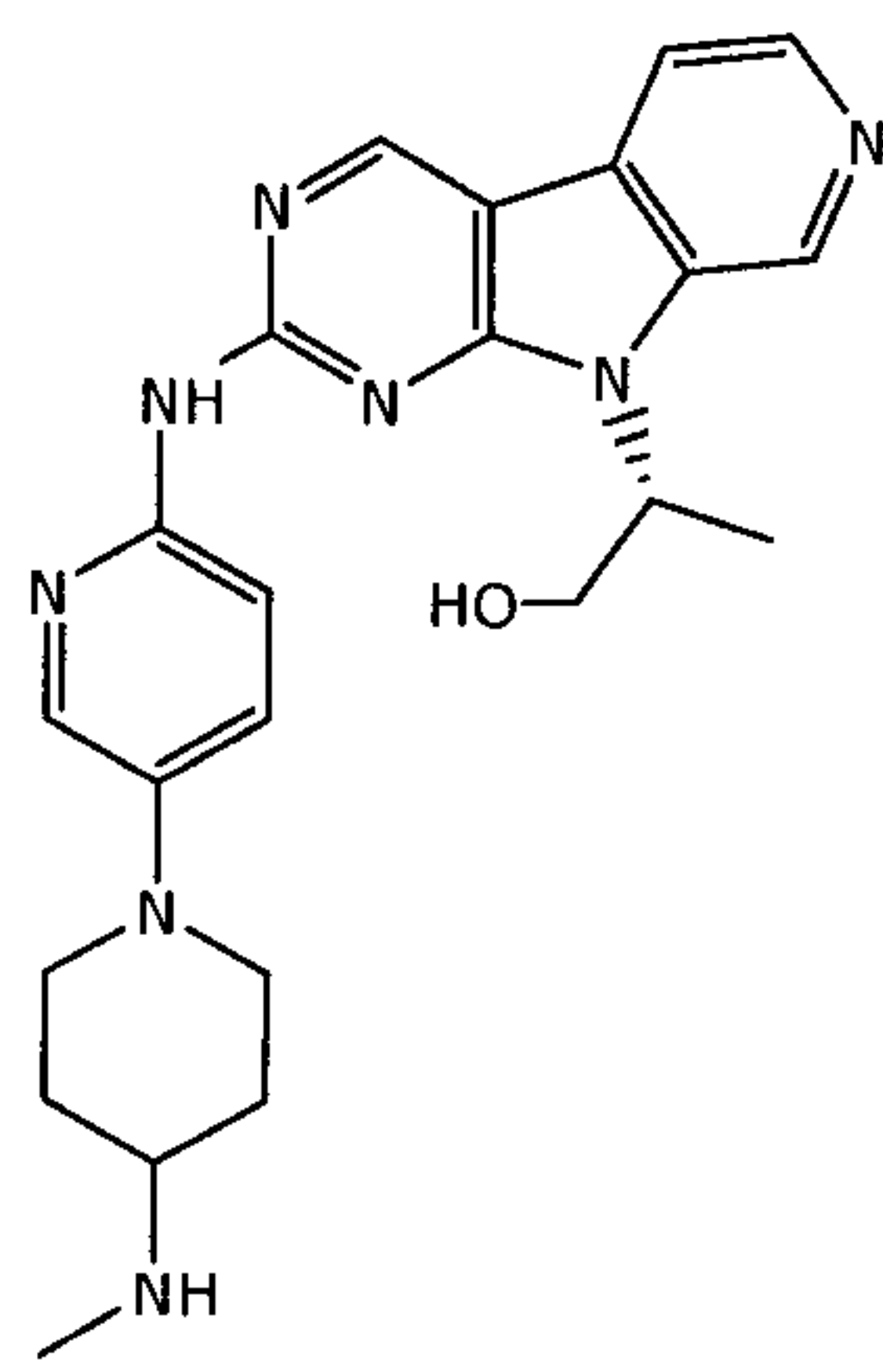
317. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

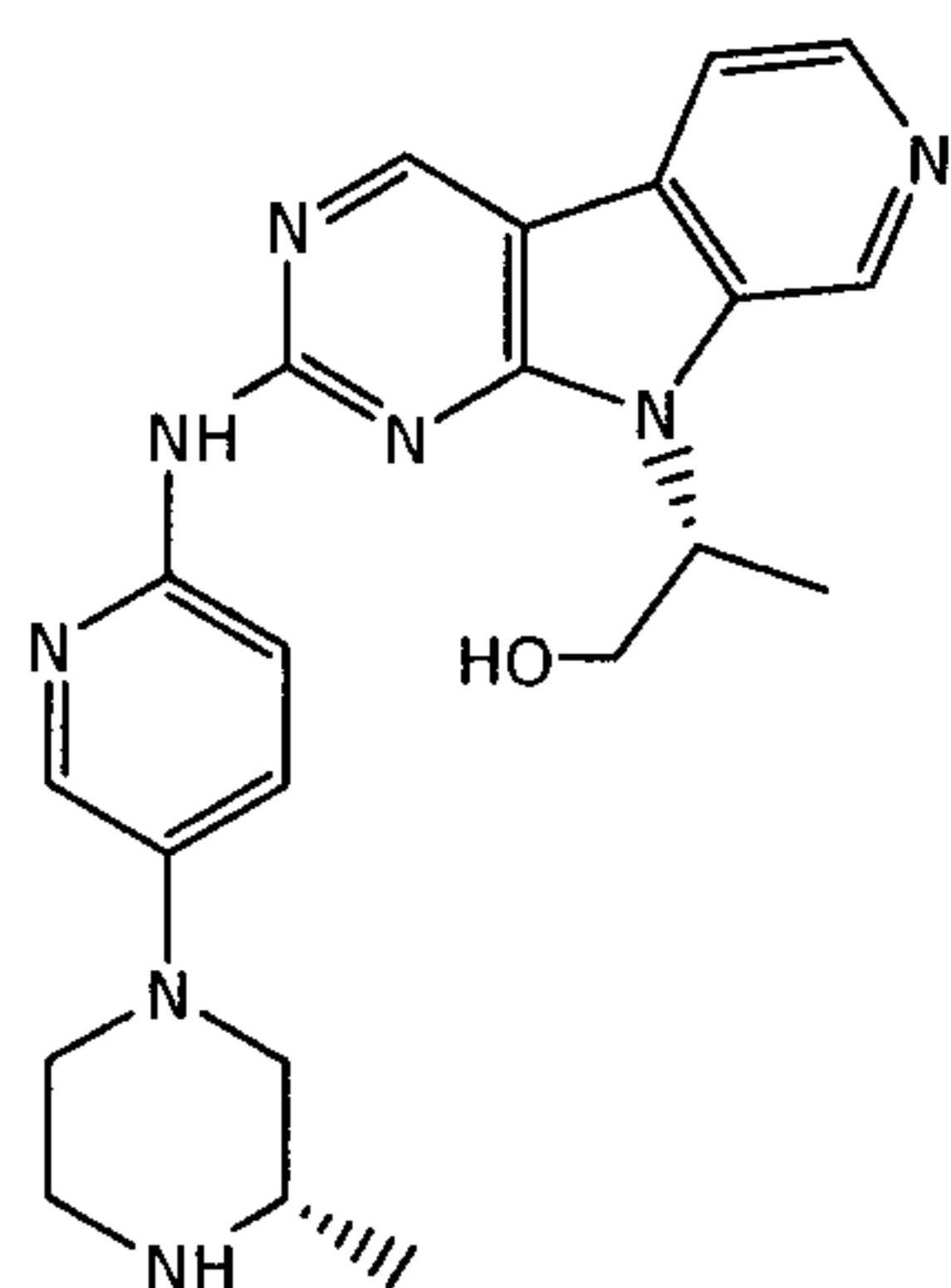


318. The compound of claim 1, wherein the compound is



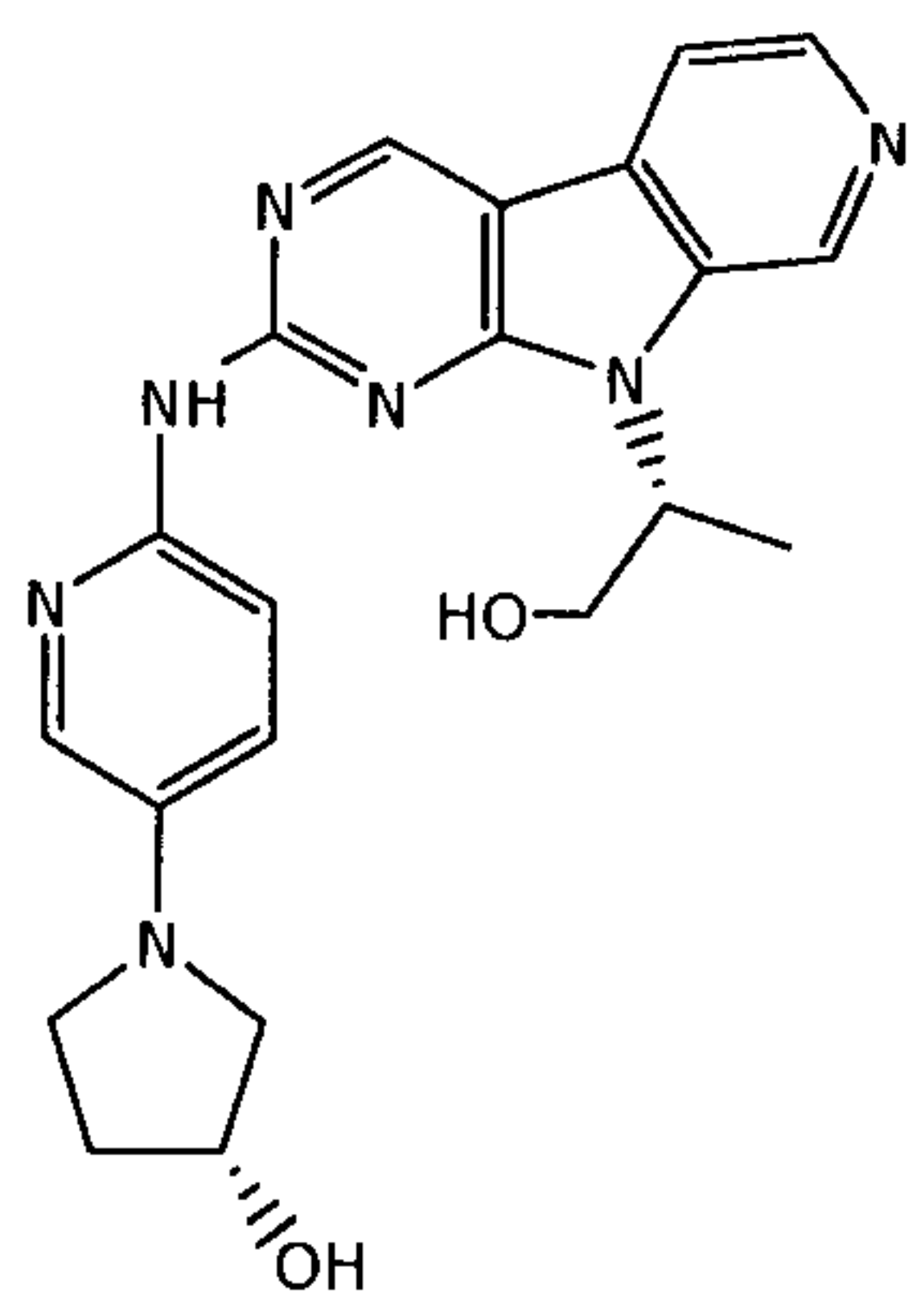
or a pharmaceutically acceptable salt thereof.

319. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

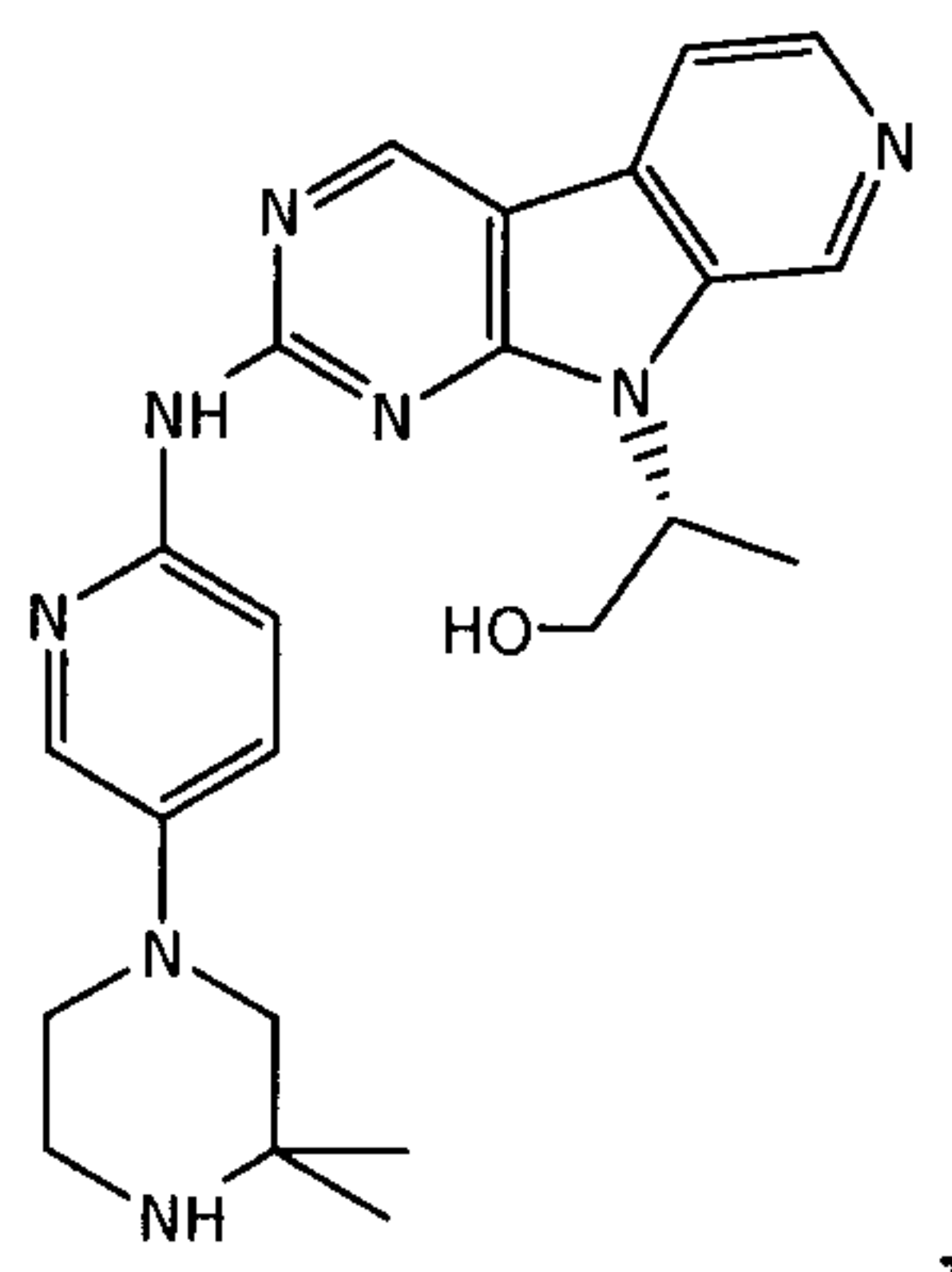
320. The compound of claim 1, wherein the compound is





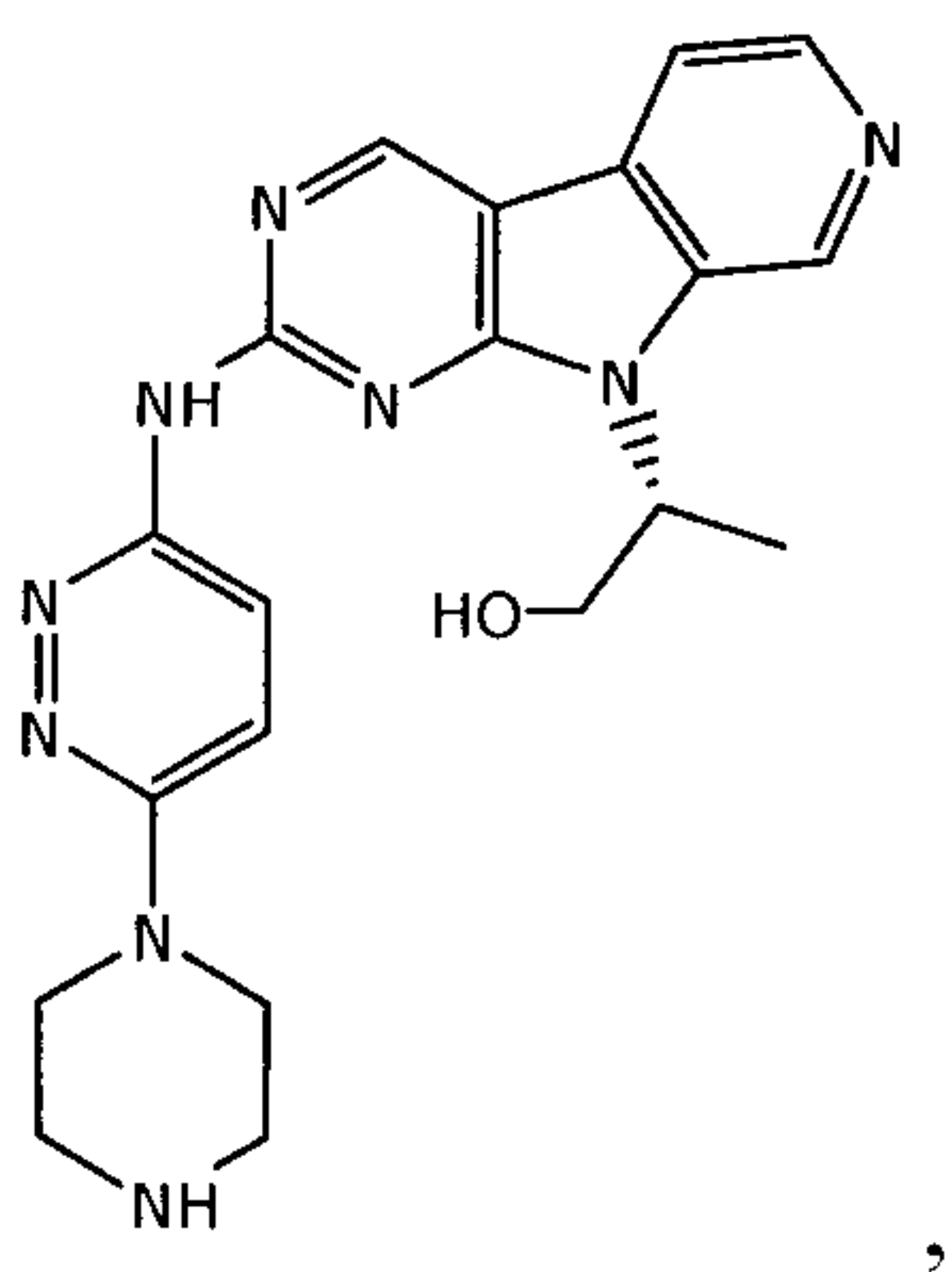
or a pharmaceutically acceptable salt thereof.

321. The compound of claim 1, wherein the compound is



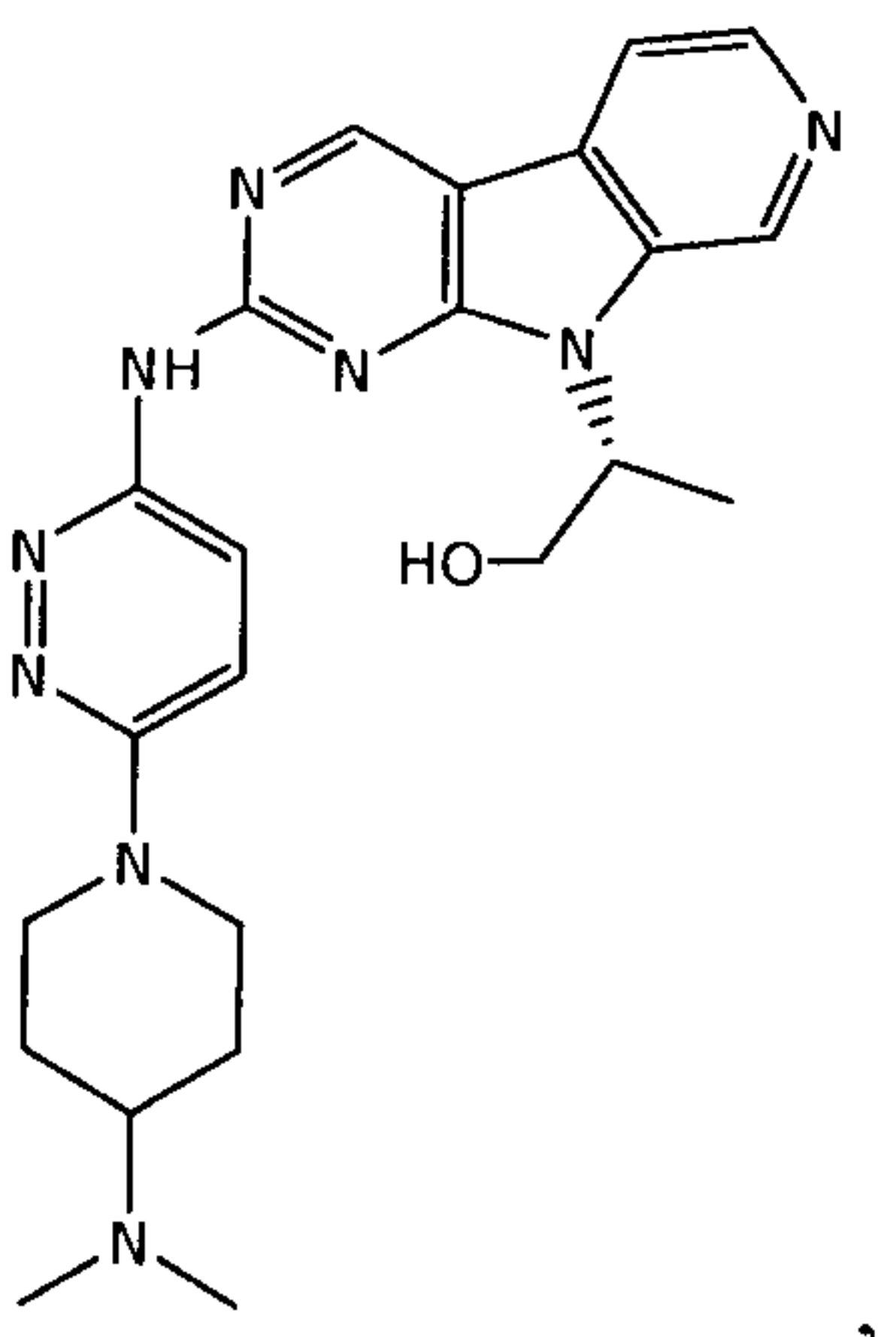
or a pharmaceutically acceptable salt thereof.

322. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

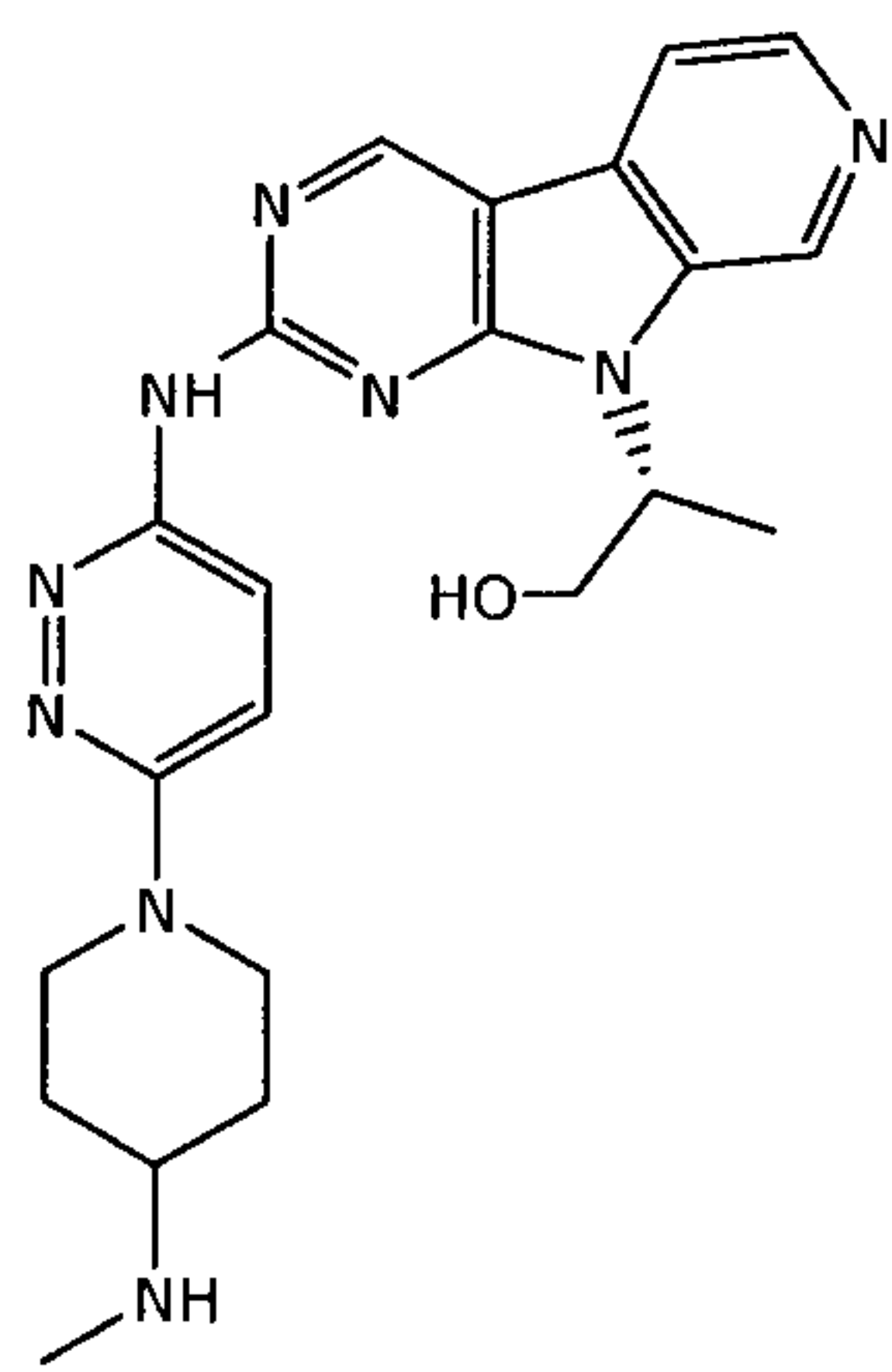
323. The compound of claim 1, wherein the compound is





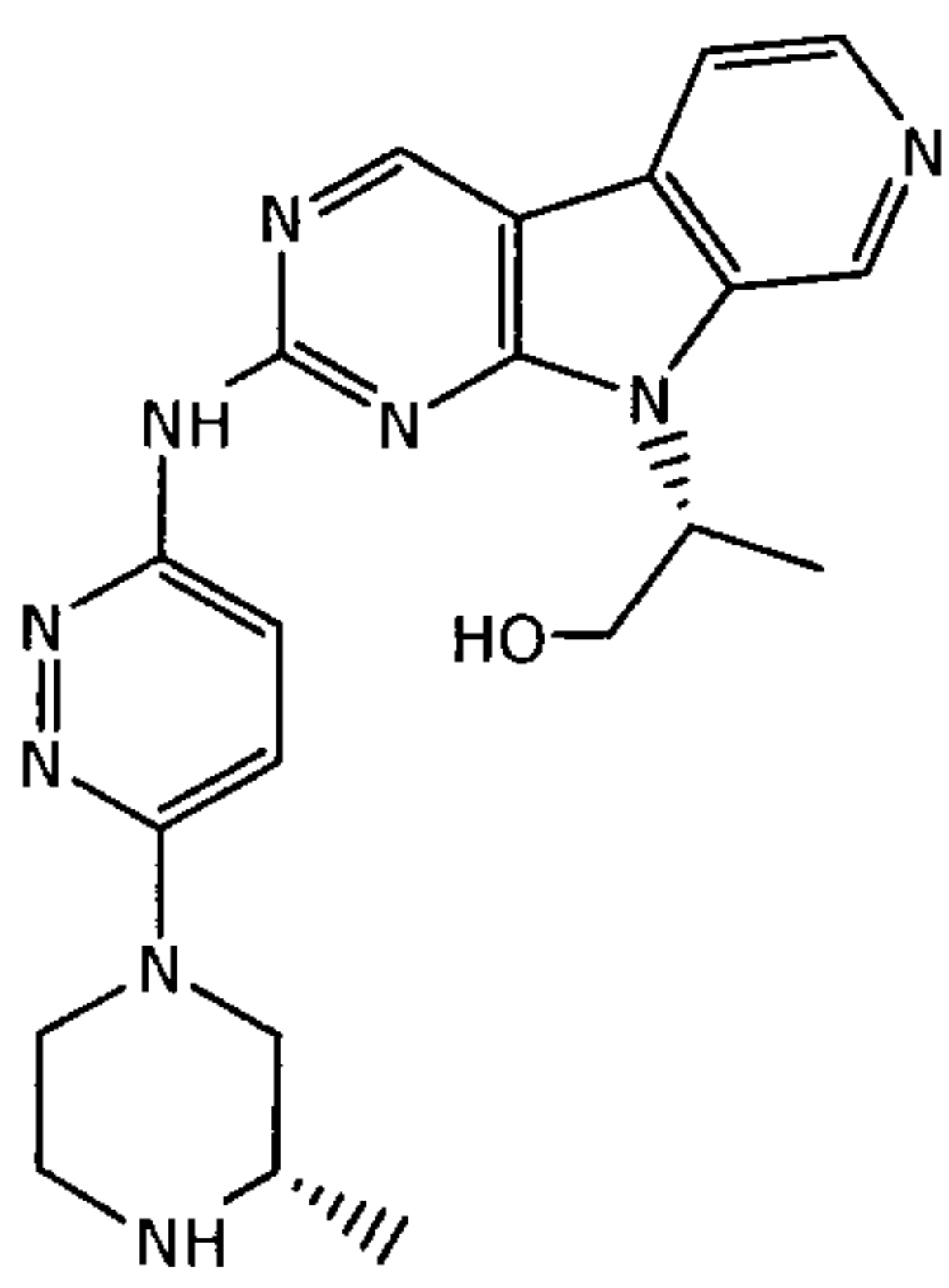
or a pharmaceutically acceptable salt thereof.

324. The compound of claim 1, wherein the compound is



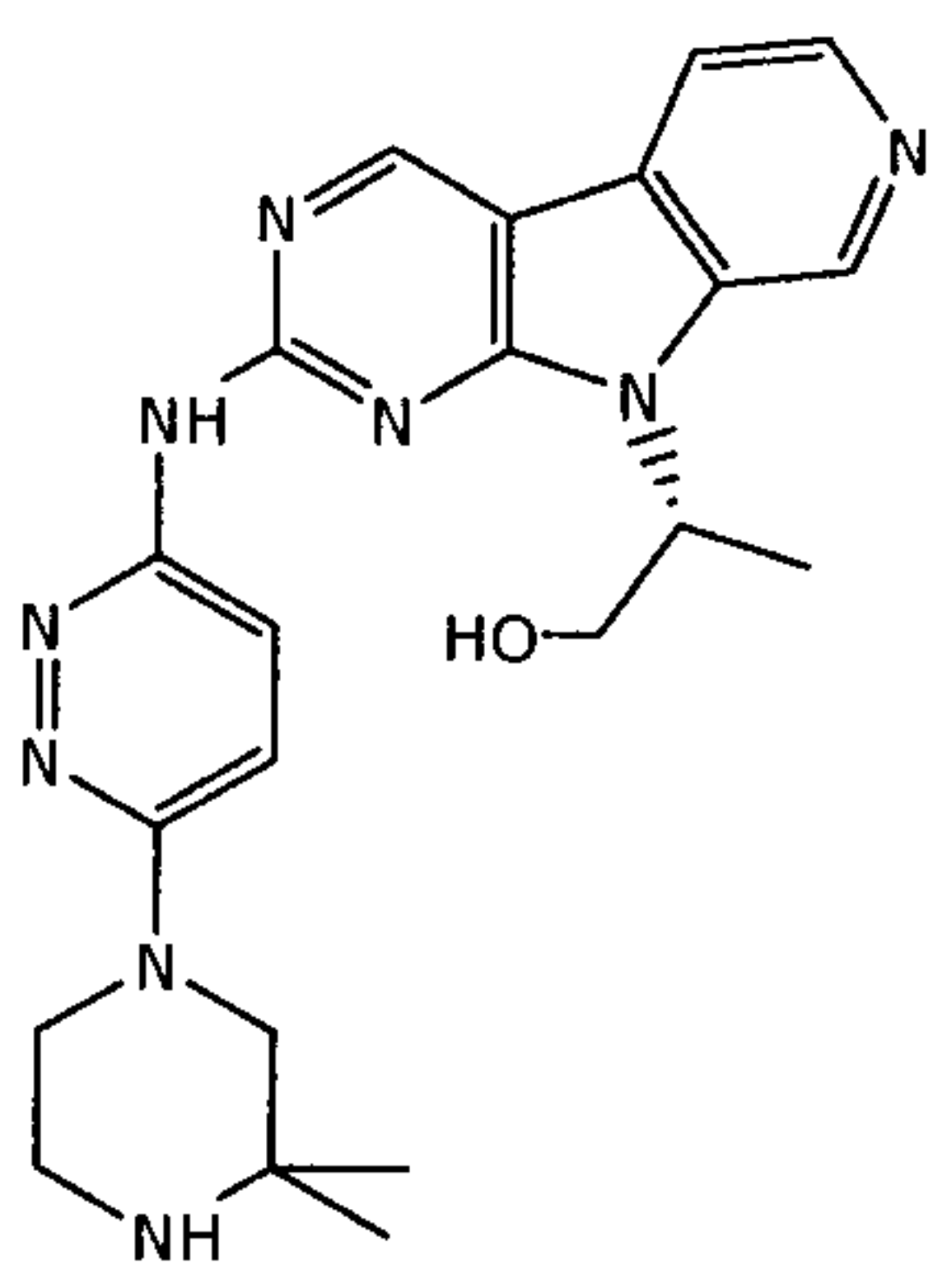
or a pharmaceutically acceptable salt thereof.

325. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

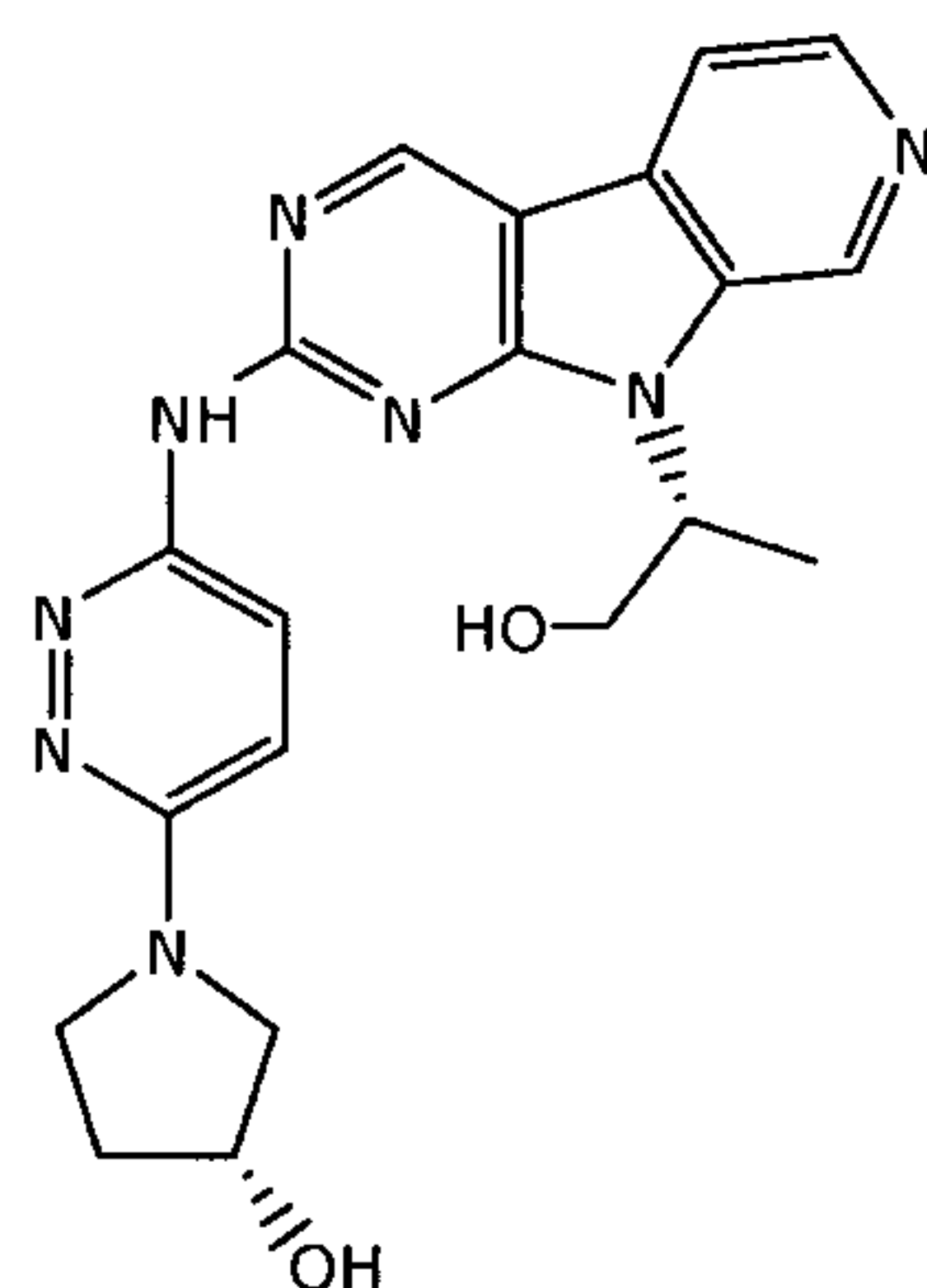
326. The compound of claim 1, wherein the compound is





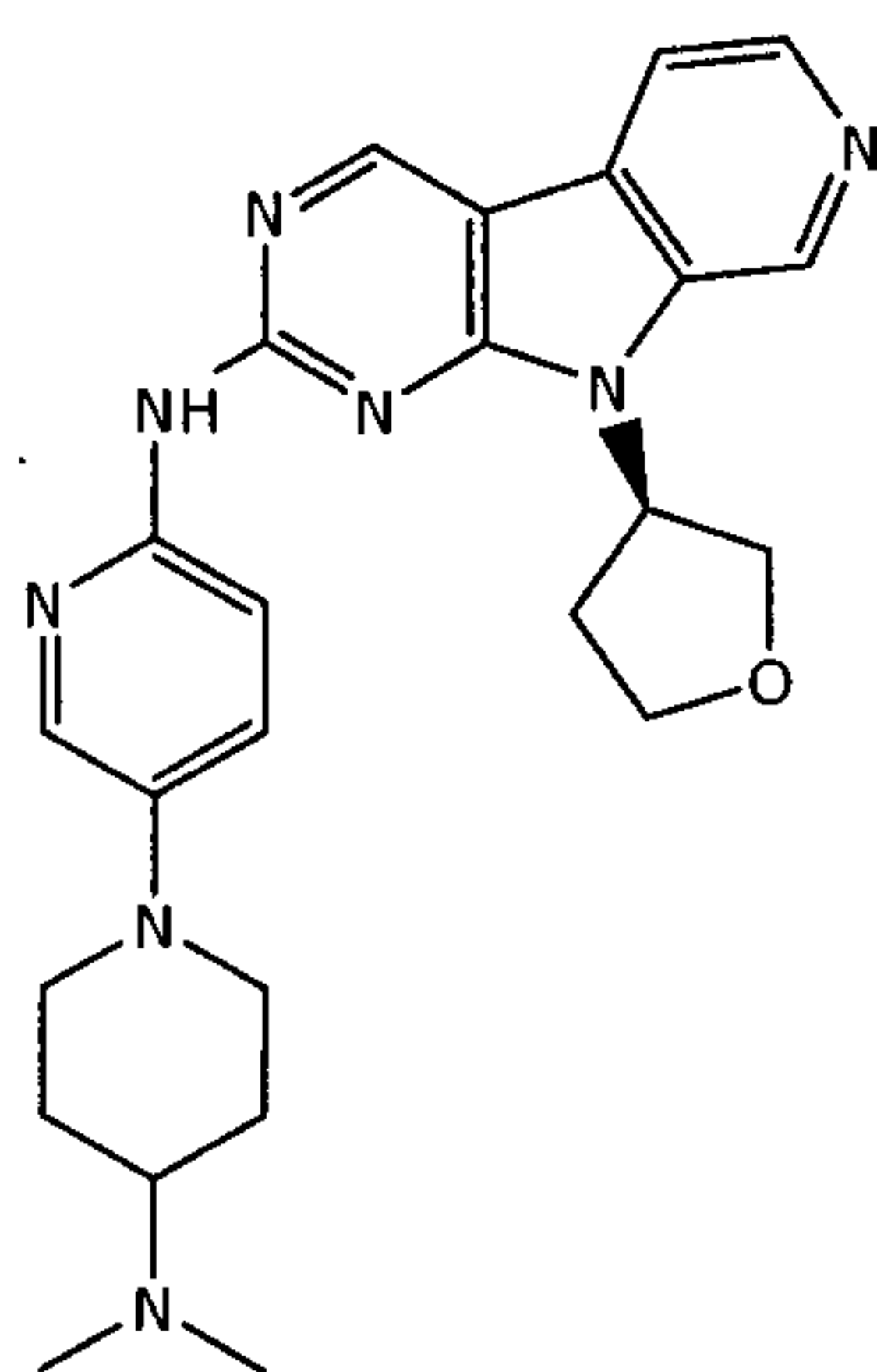
or a pharmaceutically acceptable salt thereof.

327. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

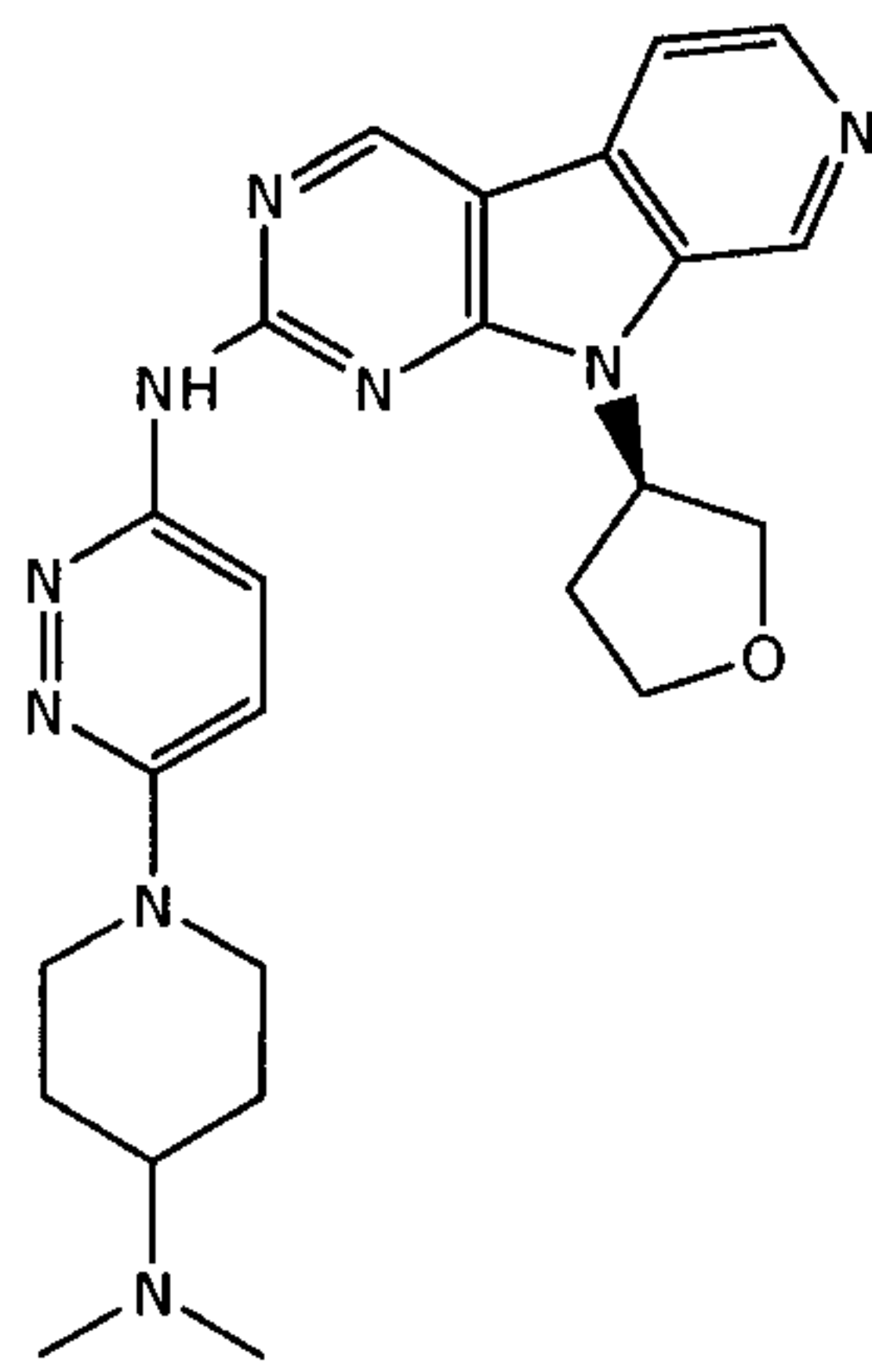
328. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

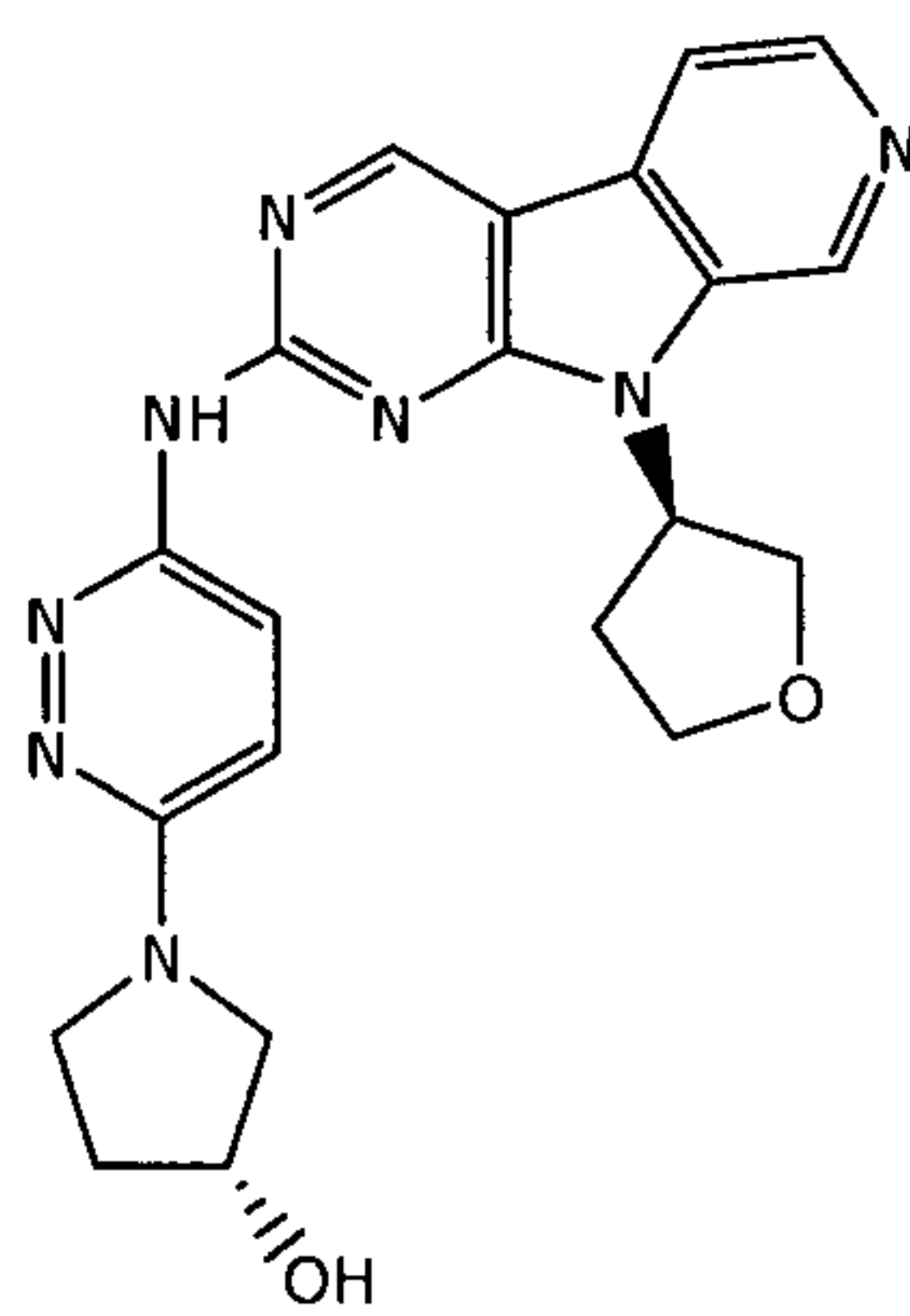


329. The compound of claim 1, wherein the compound is



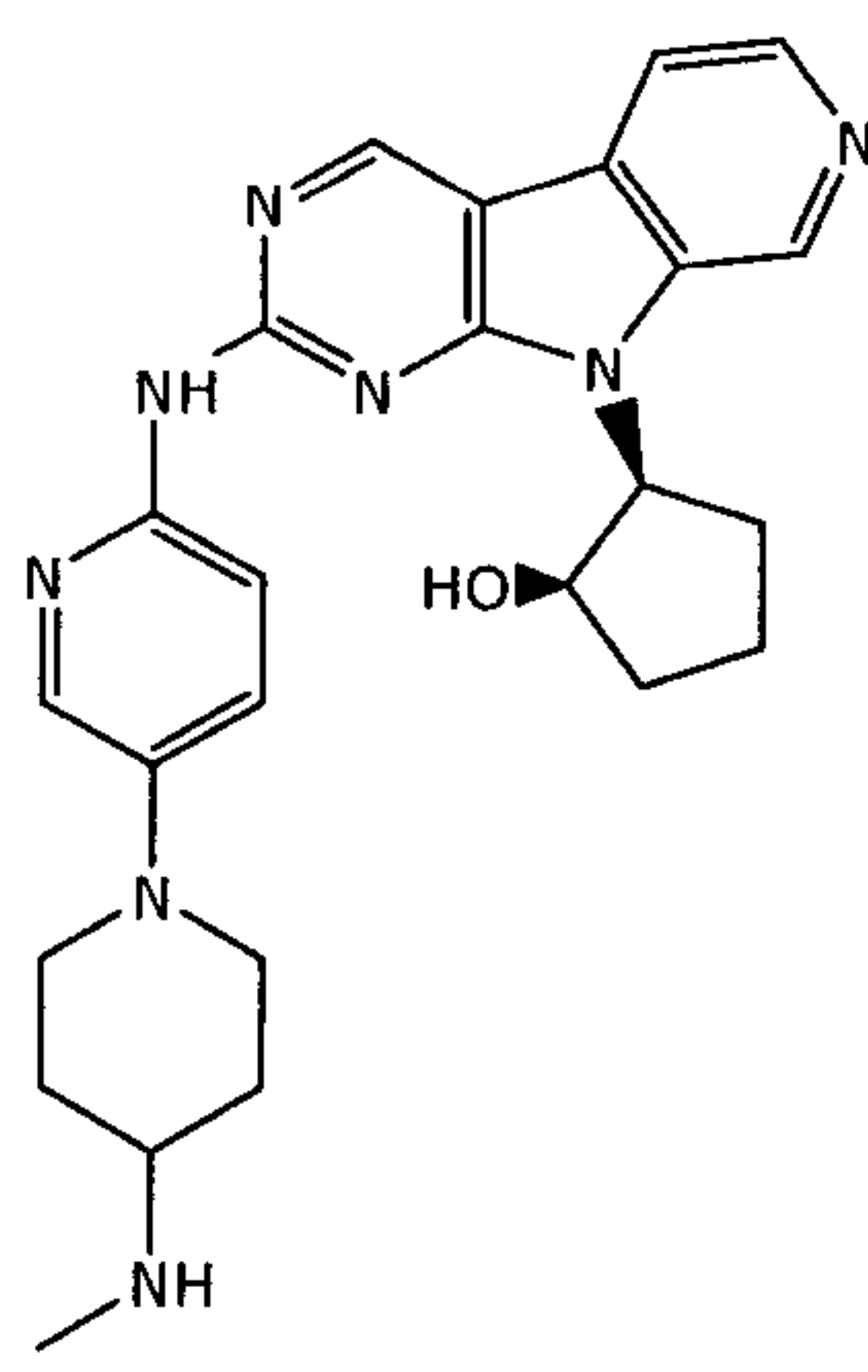
or a pharmaceutically acceptable salt thereof.

330. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

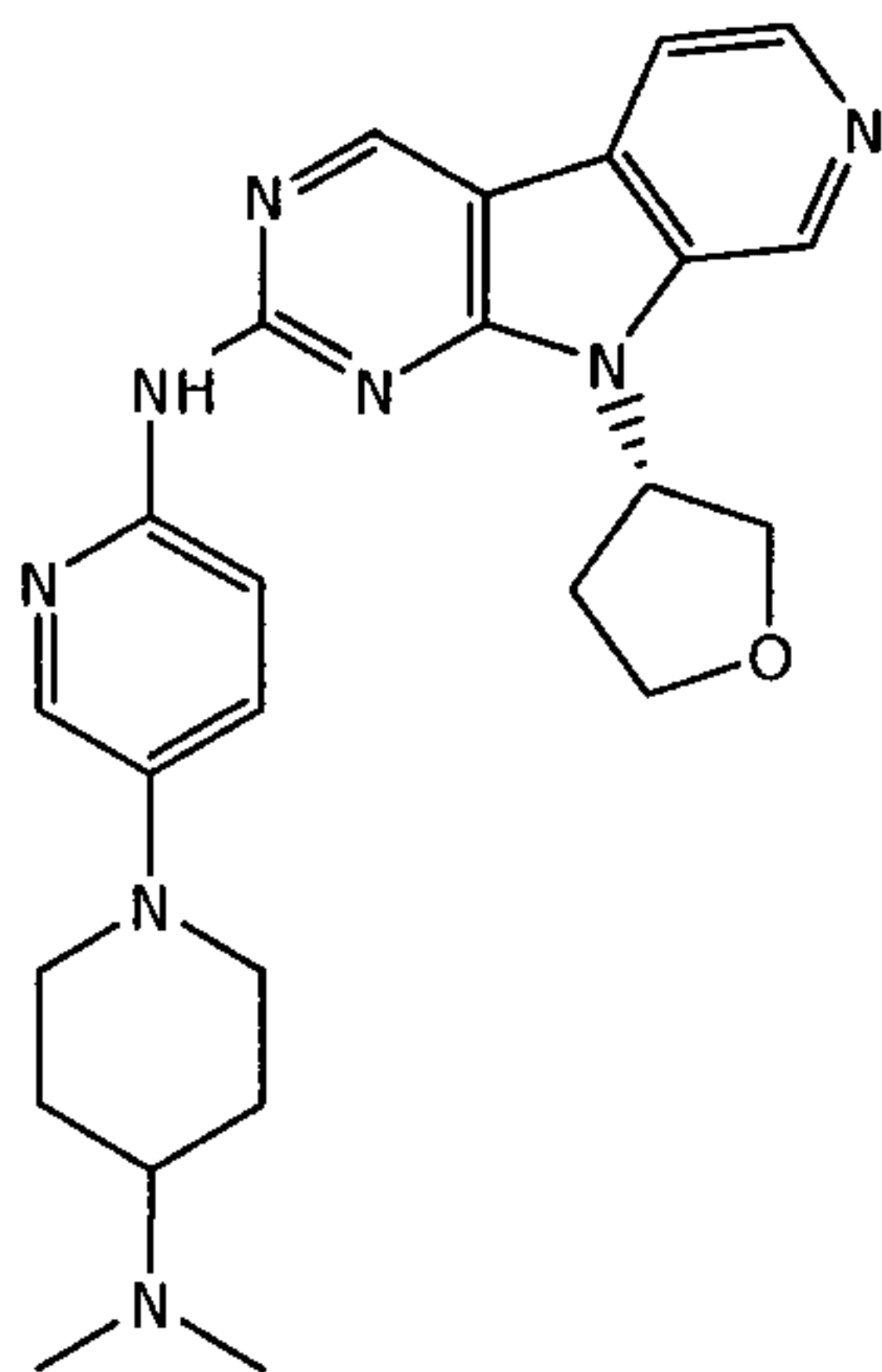
331. The compound of claim 1, wherein the compound is





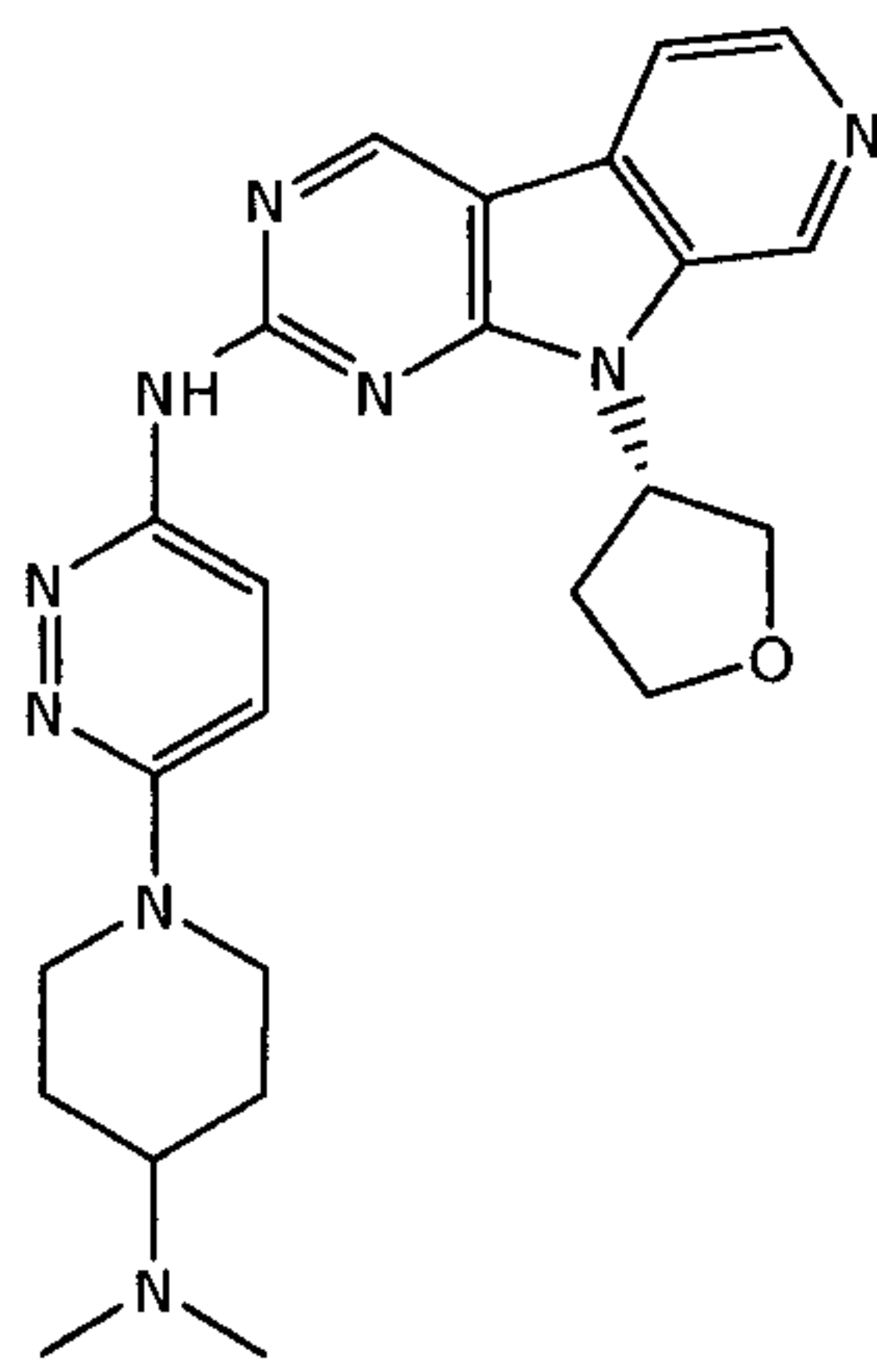
or a pharmaceutically acceptable salt thereof.

332. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

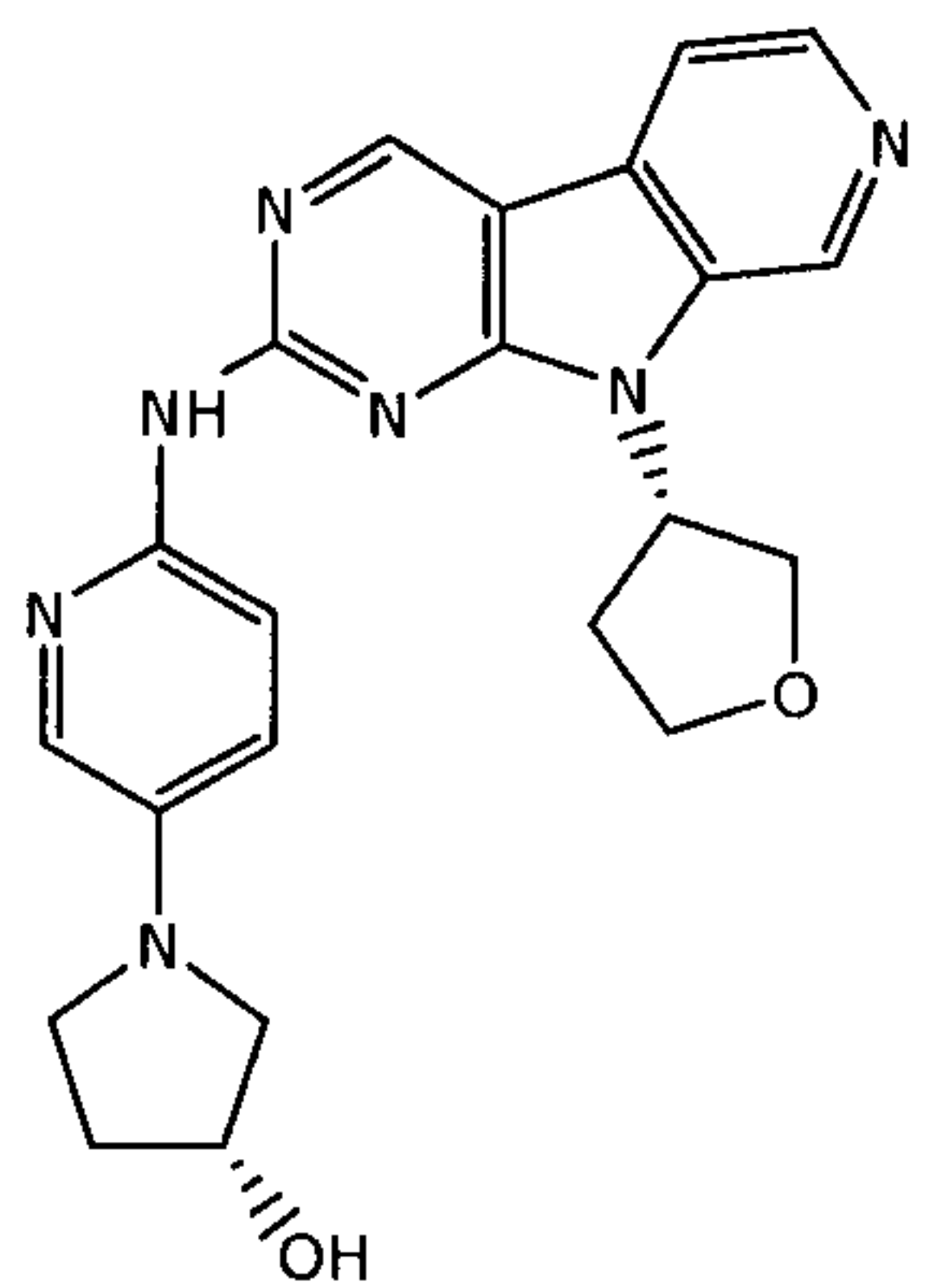
333. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

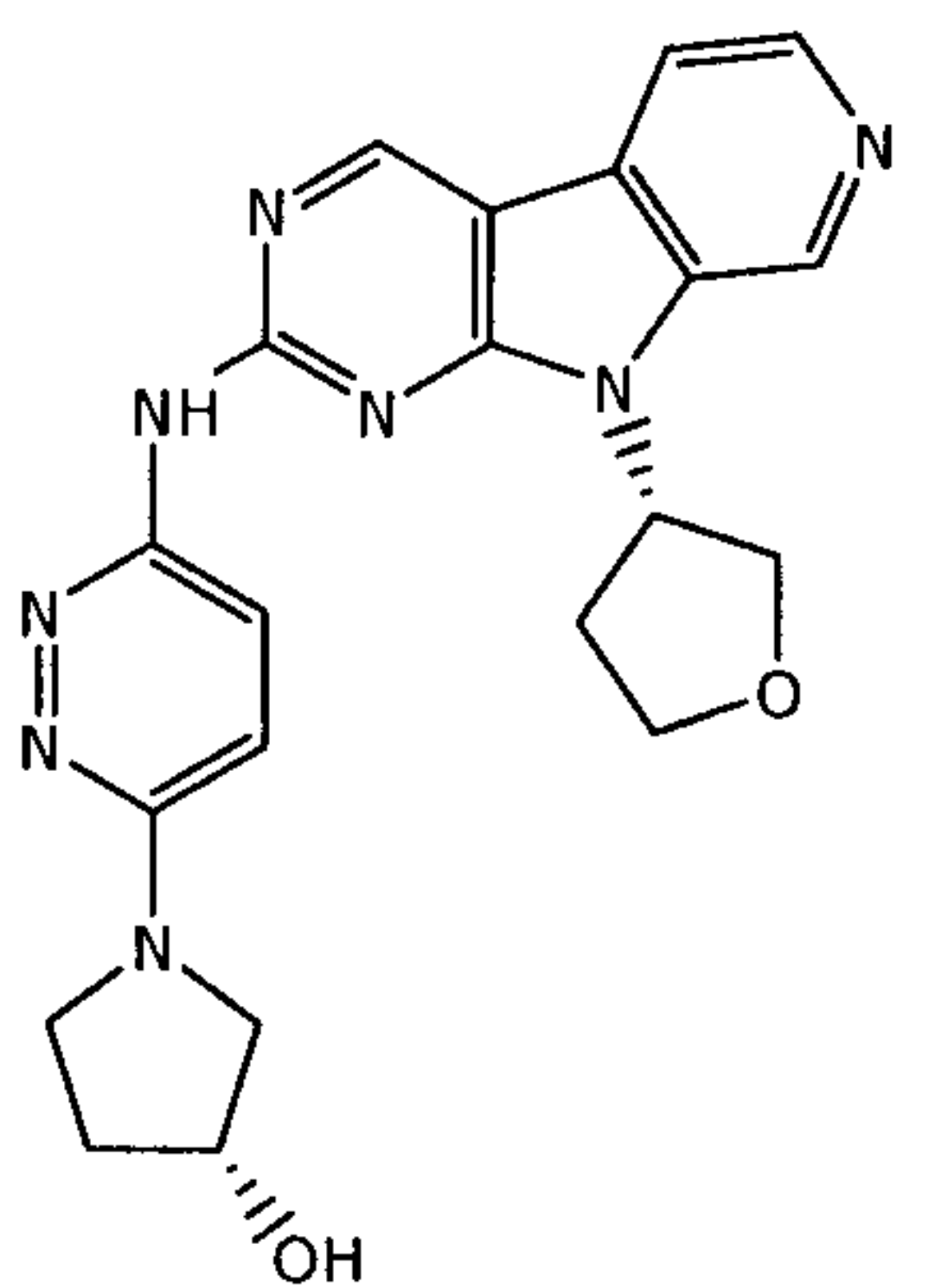


334. The compound of claim 1, wherein the compound is



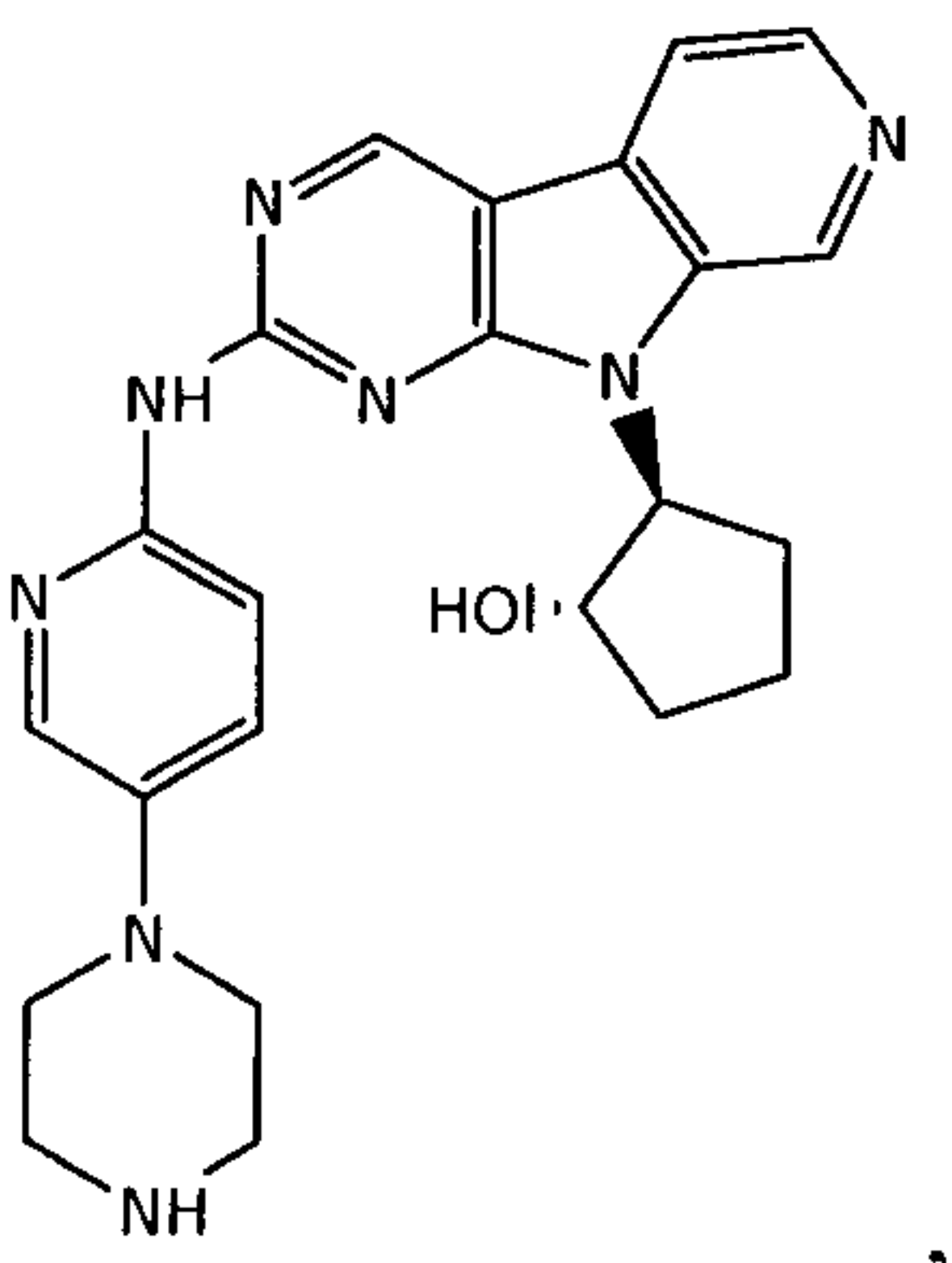
or a pharmaceutically acceptable salt thereof.

335. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

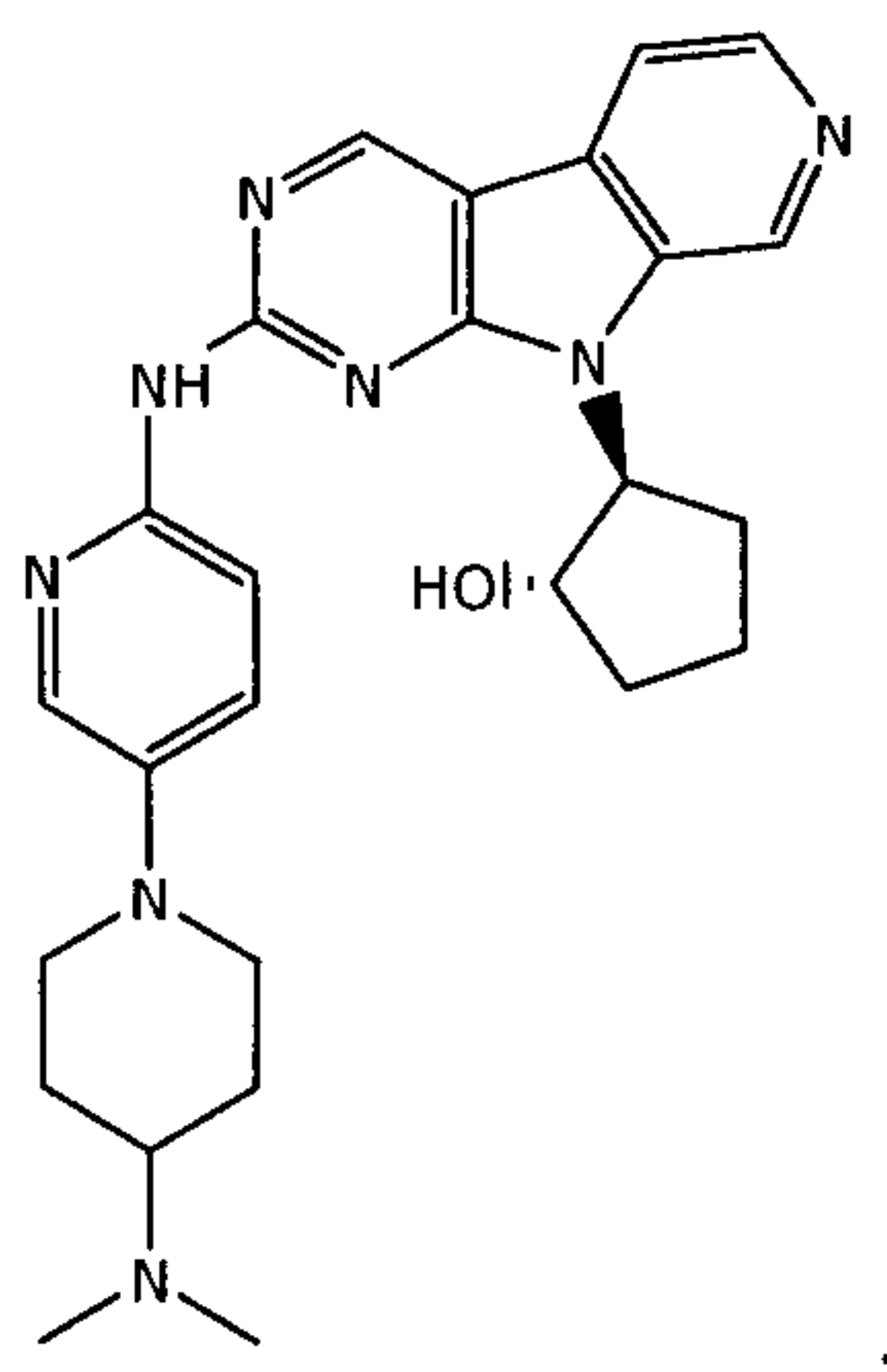
336. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

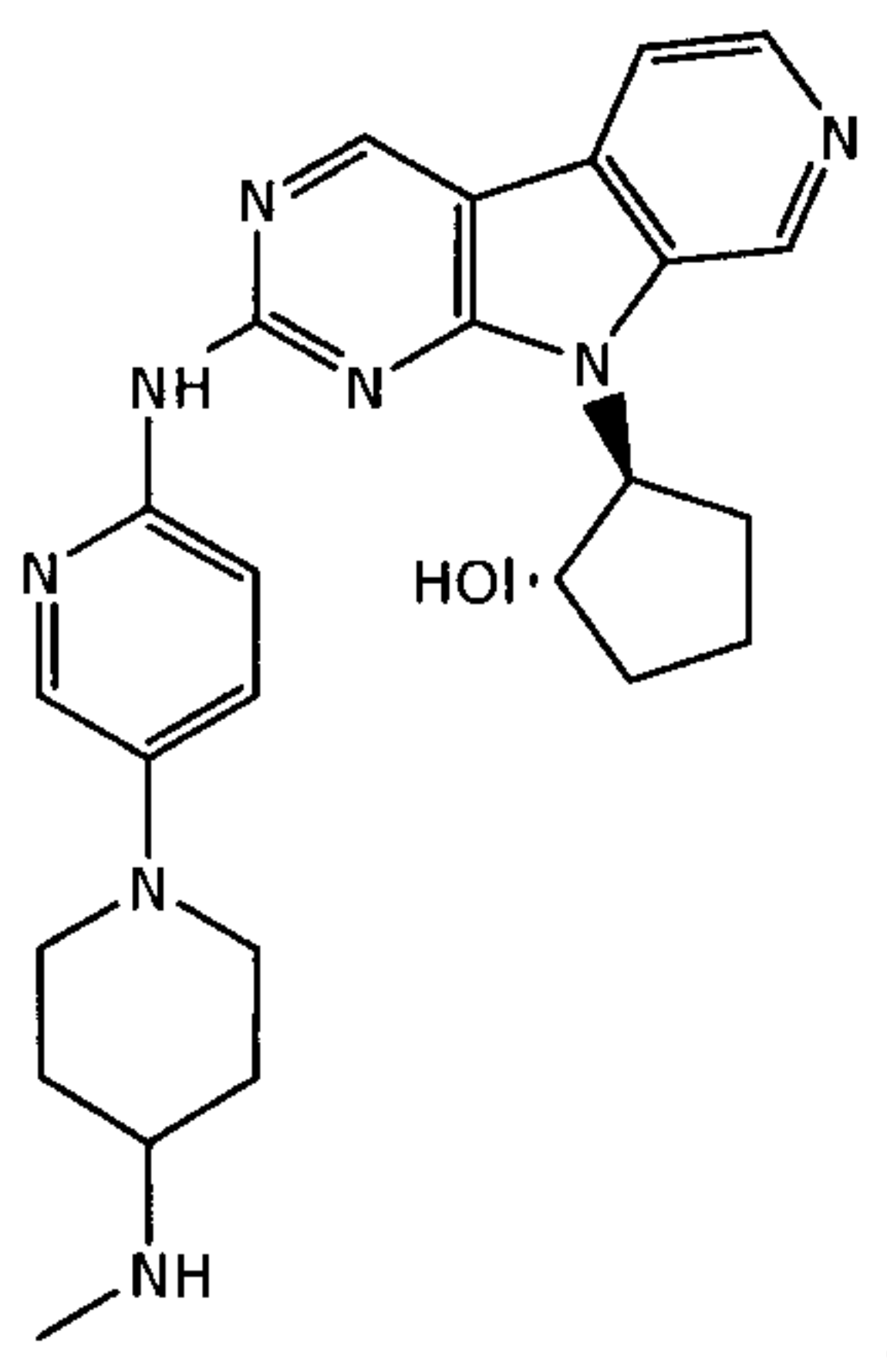


337. The compound of claim 1, wherein the compound is



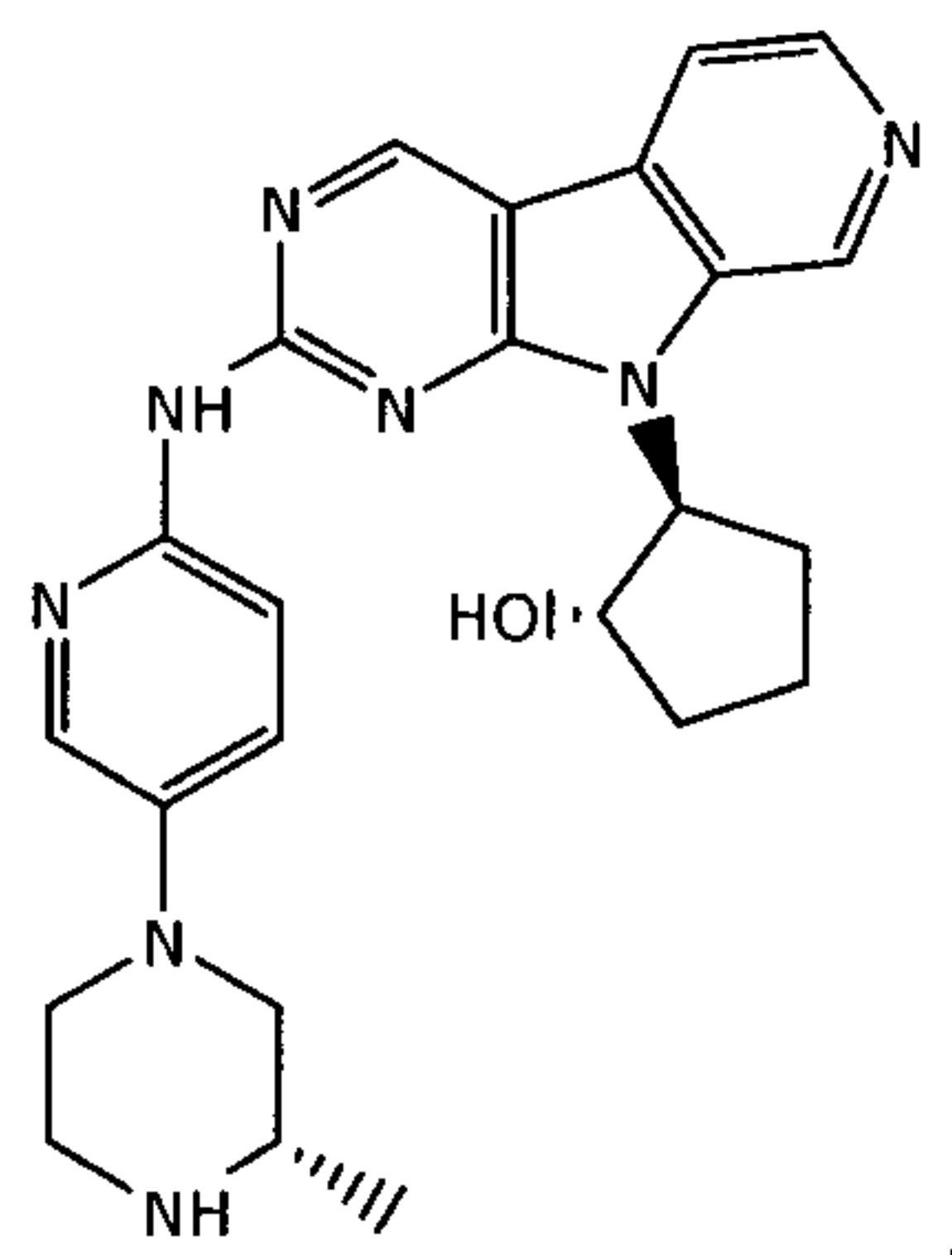
or a pharmaceutically acceptable salt thereof.

338. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

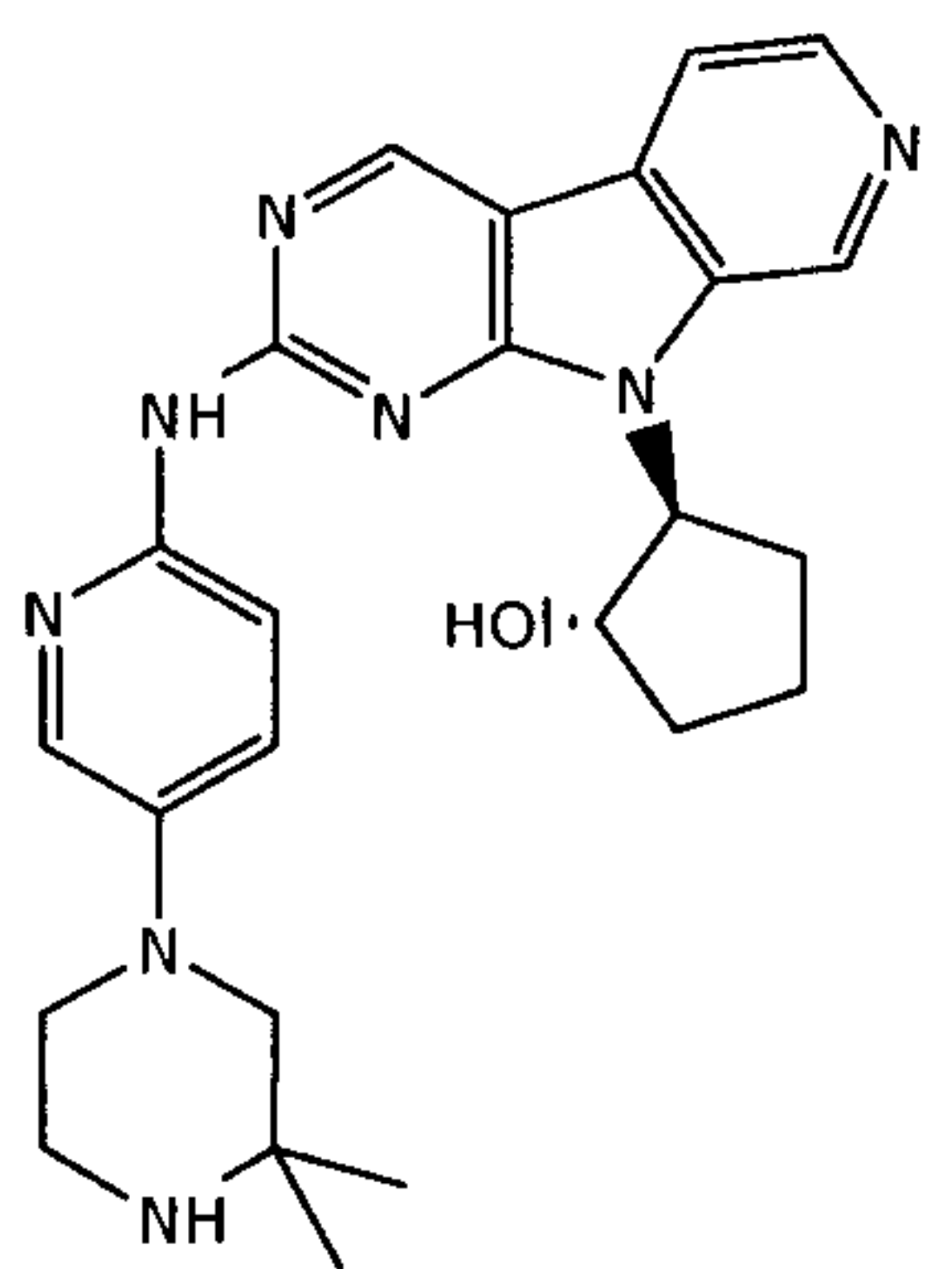
339. The compound of claim 1, wherein the compound is





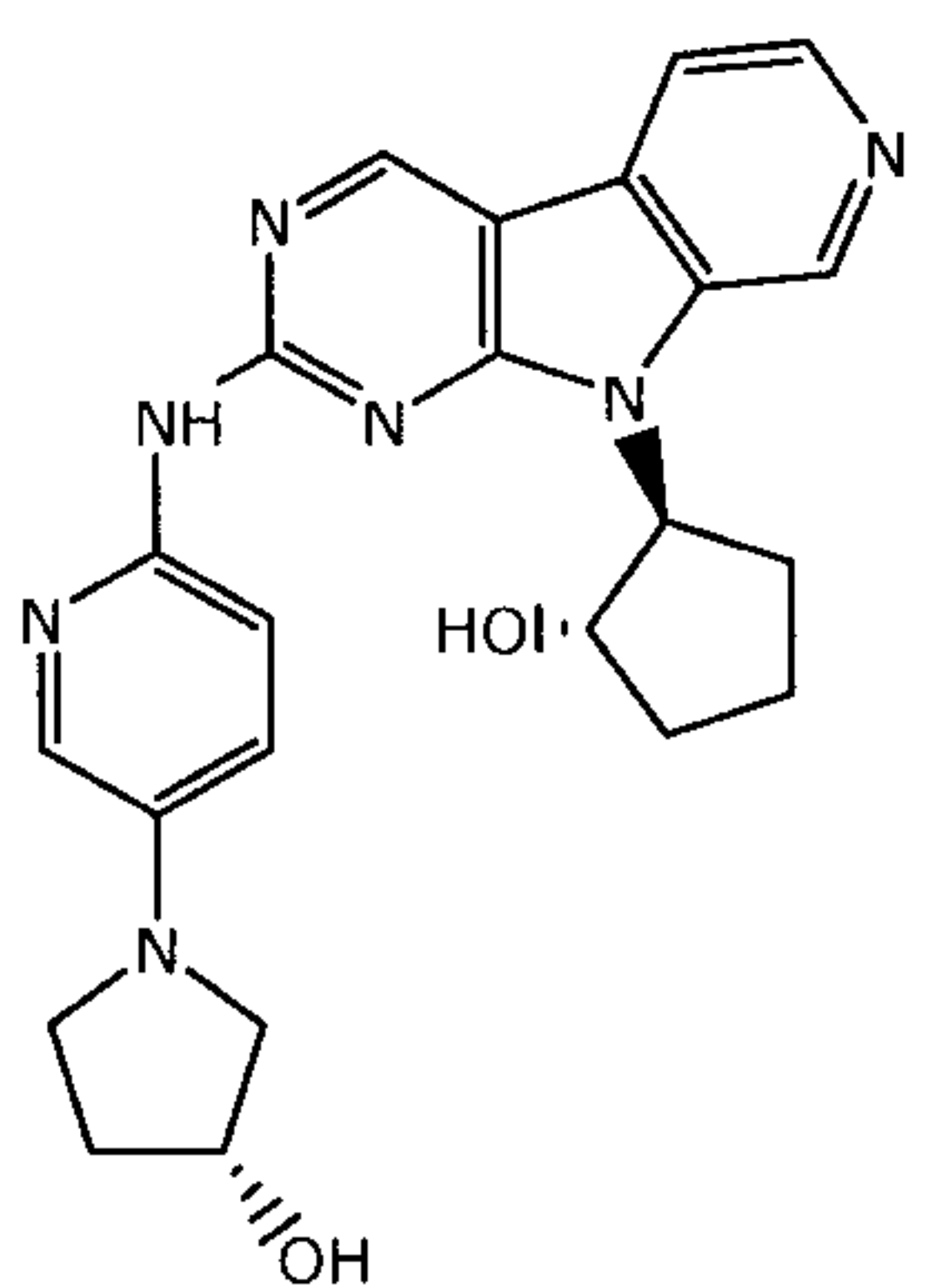
or a pharmaceutically acceptable salt thereof.

340. The compound of claim 1, wherein the compound is



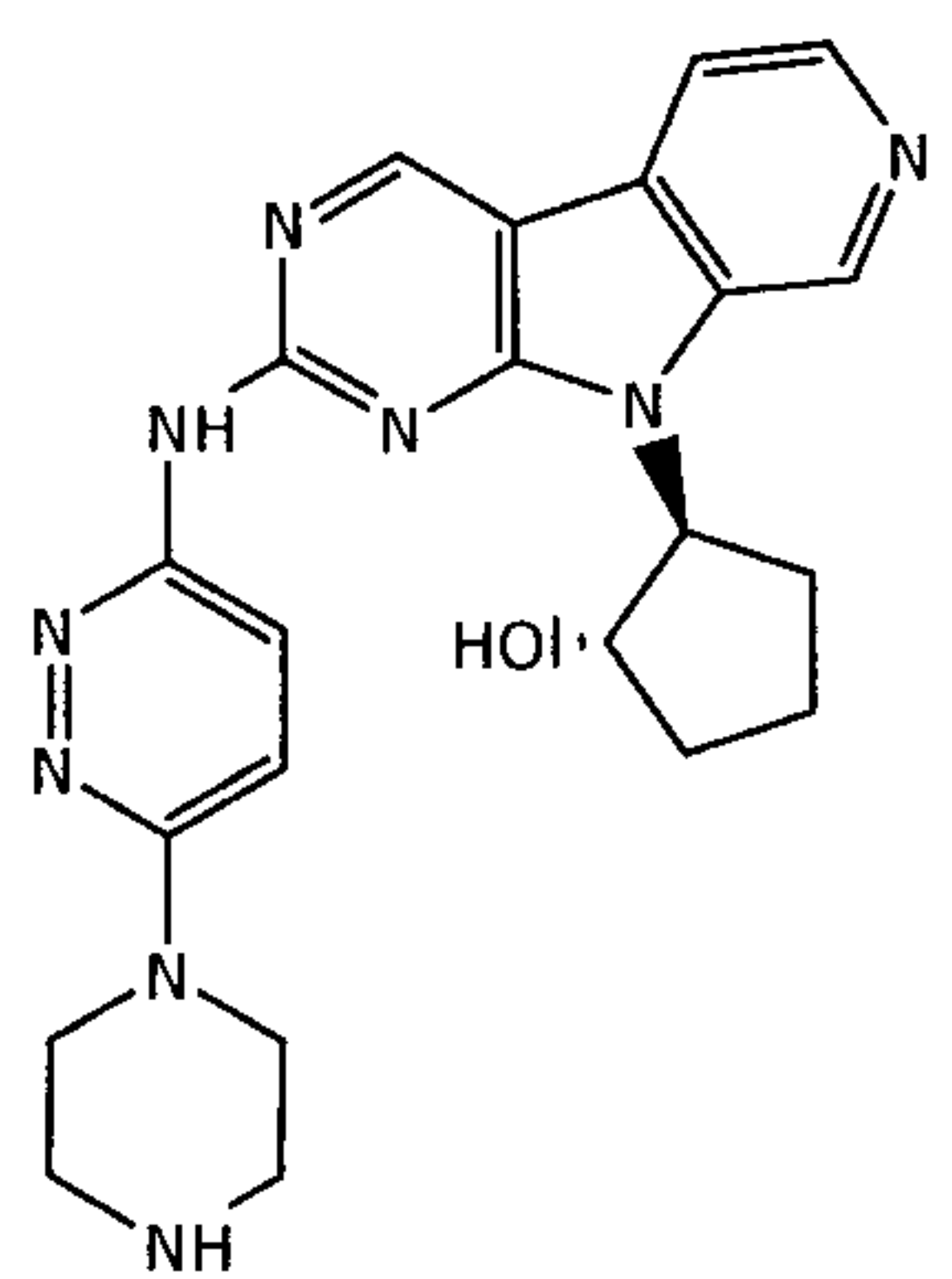
or a pharmaceutically acceptable salt thereof.

341. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

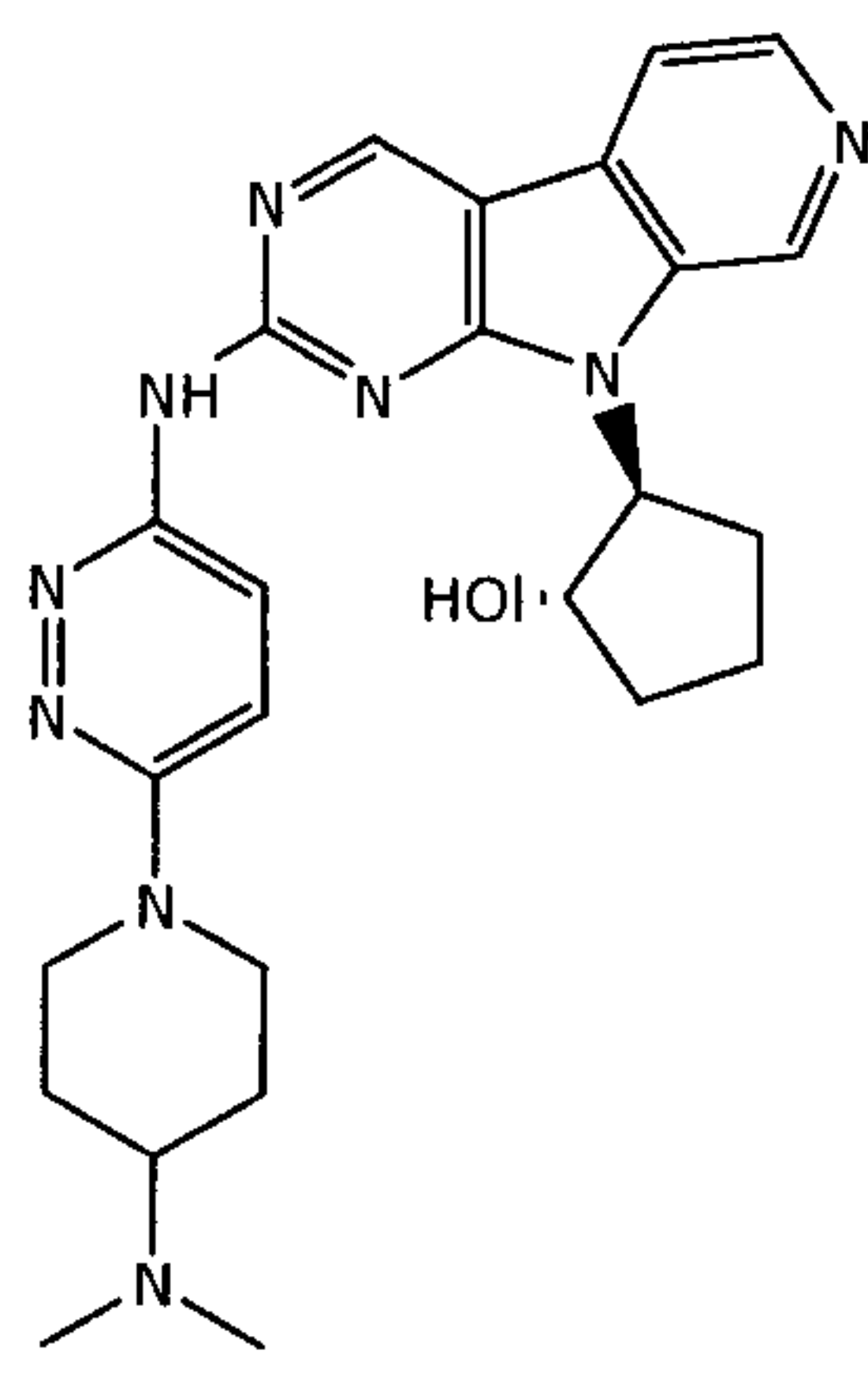
342. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

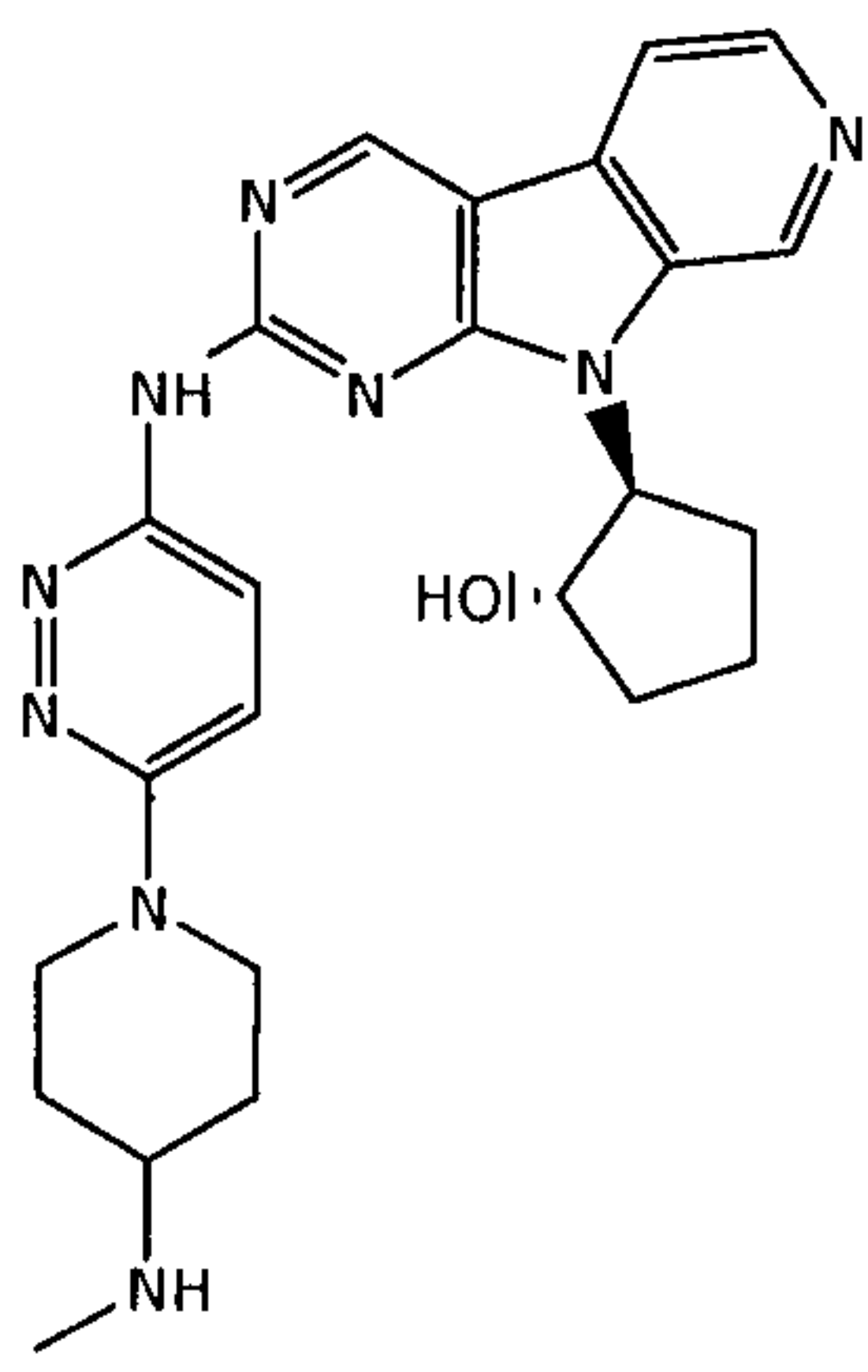


343. The compound of claim 1, wherein the compound is



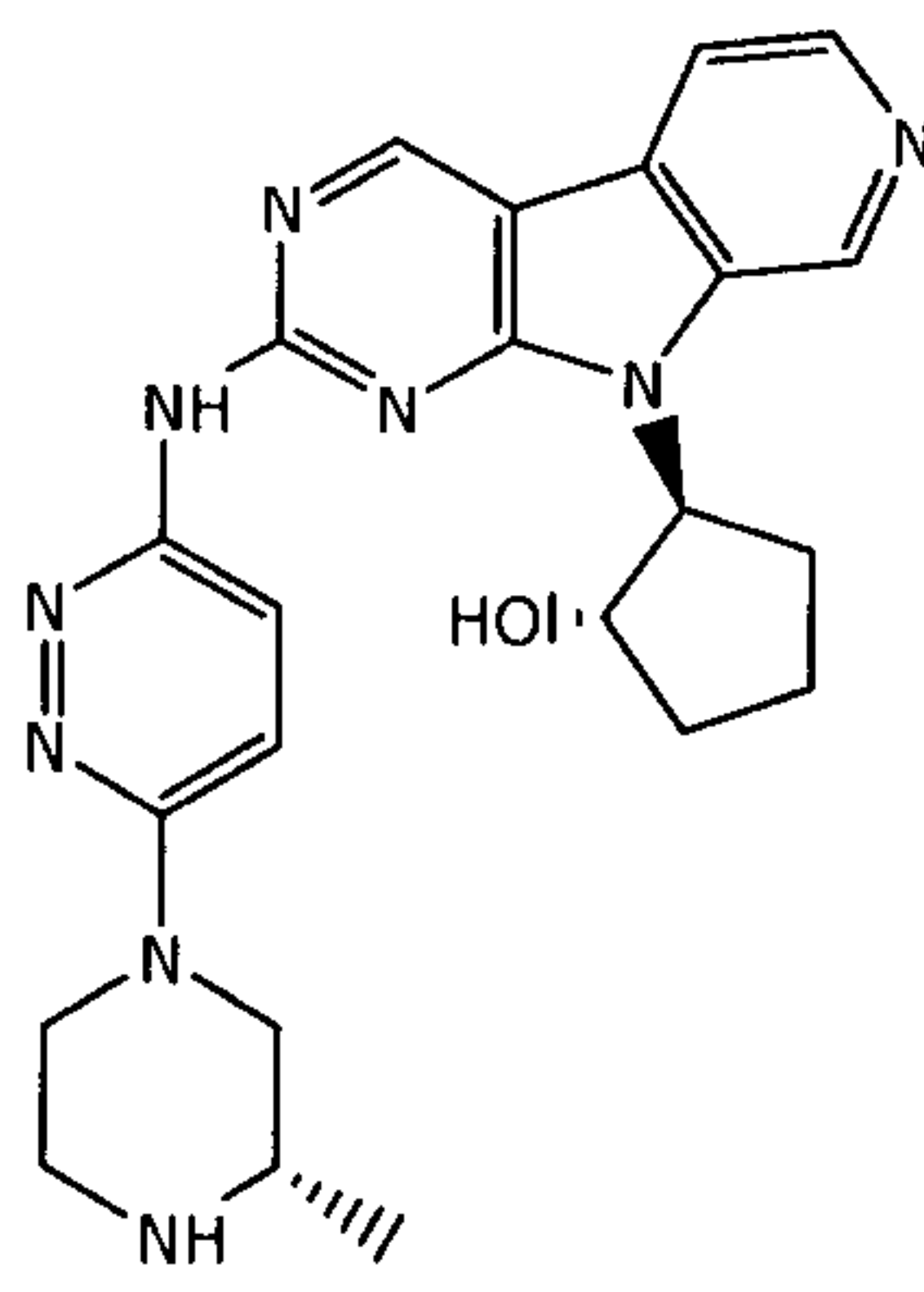
or a pharmaceutically acceptable salt thereof.

344. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

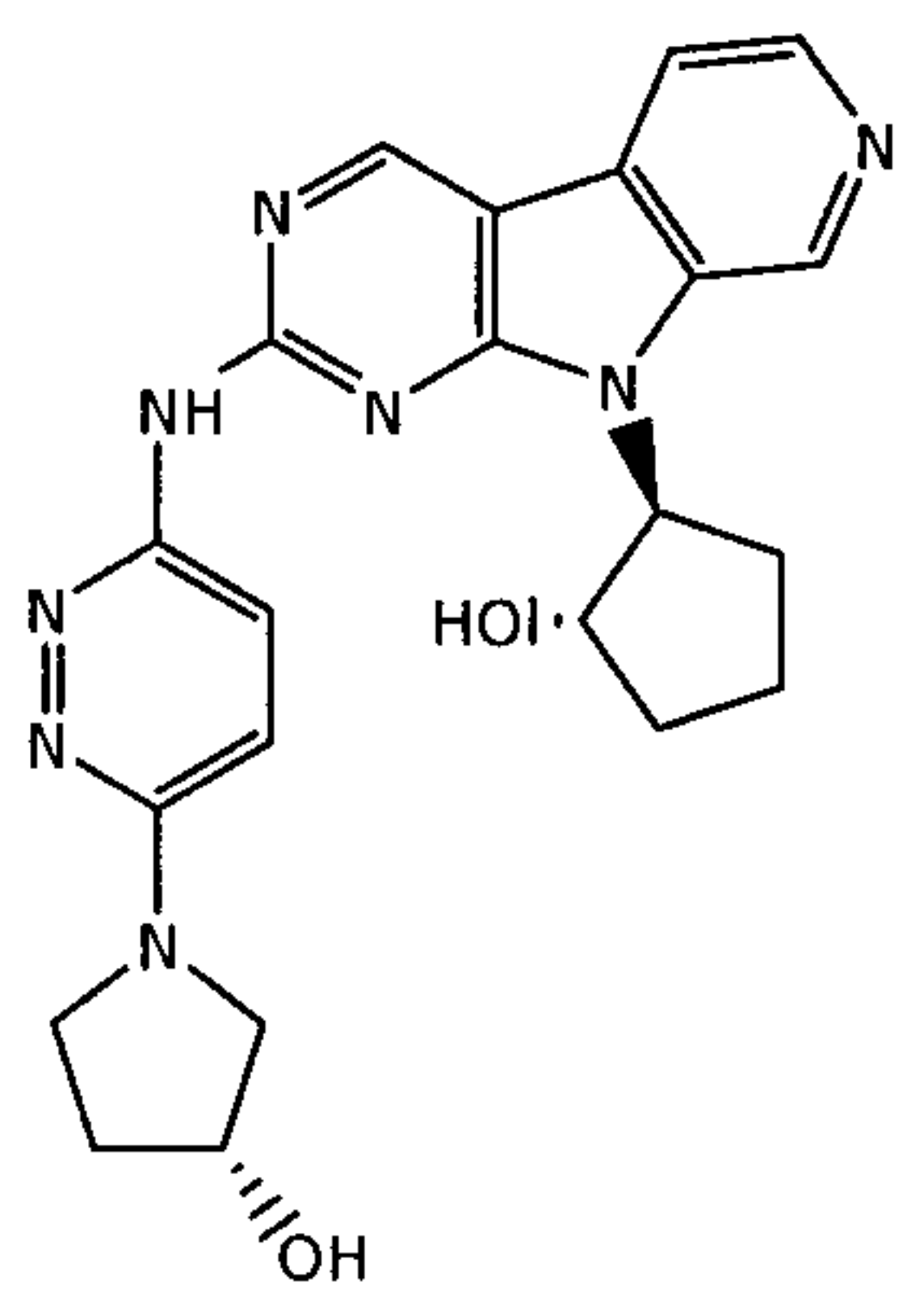
345. The compound of claim 1, wherein the compound is





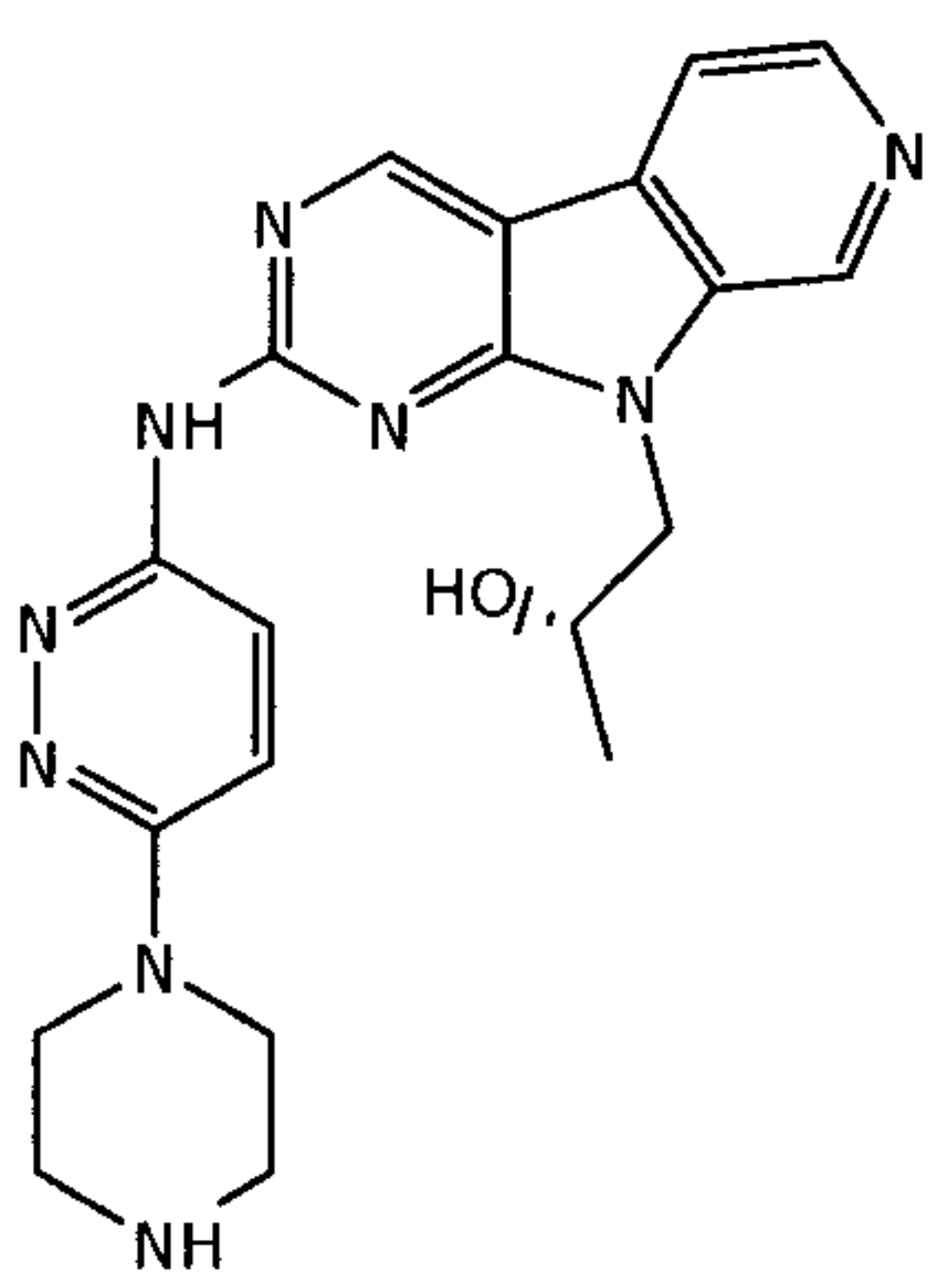
or a pharmaceutically acceptable salt thereof.

346. The compound of claim 1, wherein the compound is



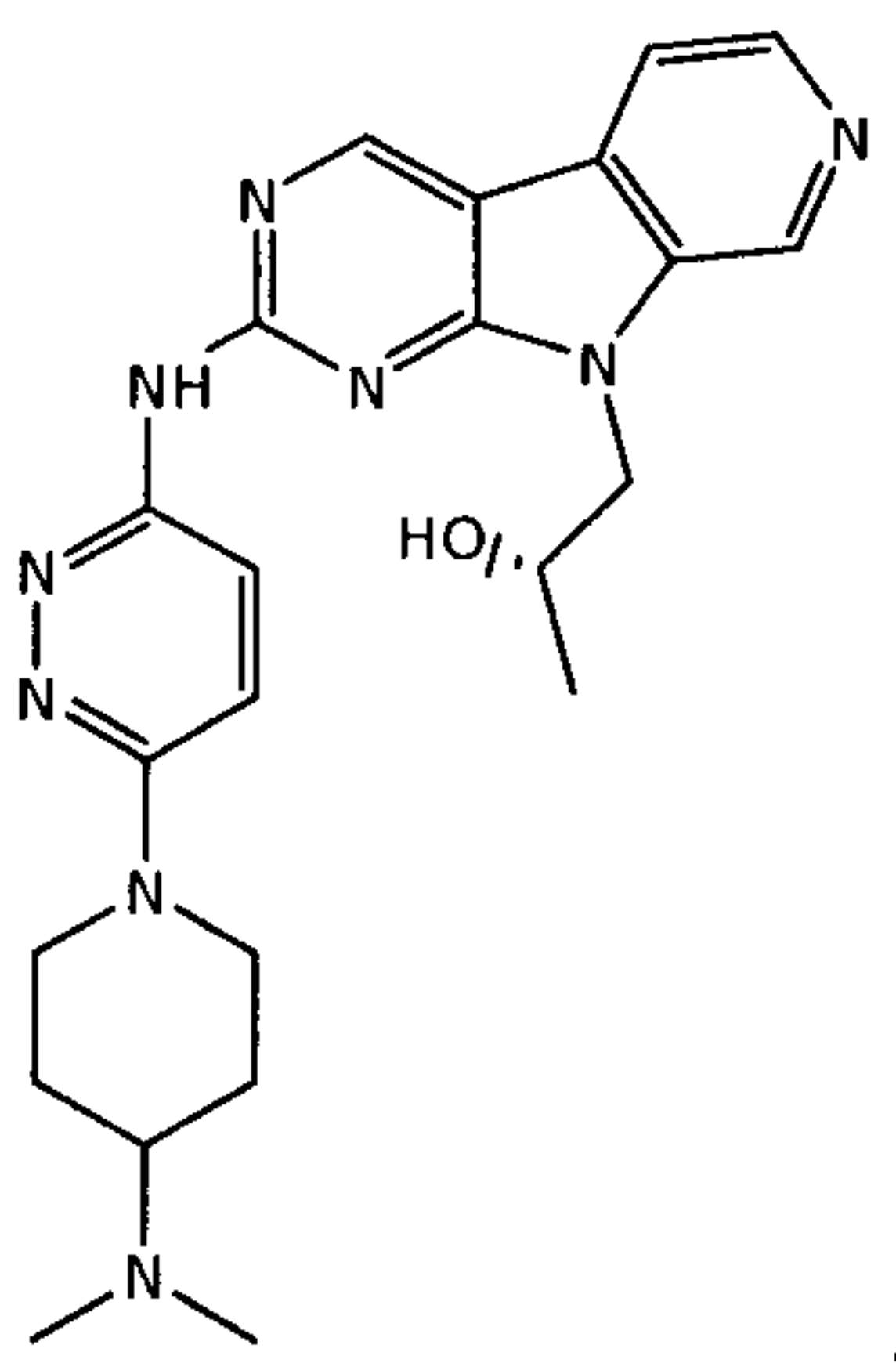
or a pharmaceutically acceptable salt thereof.

347. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

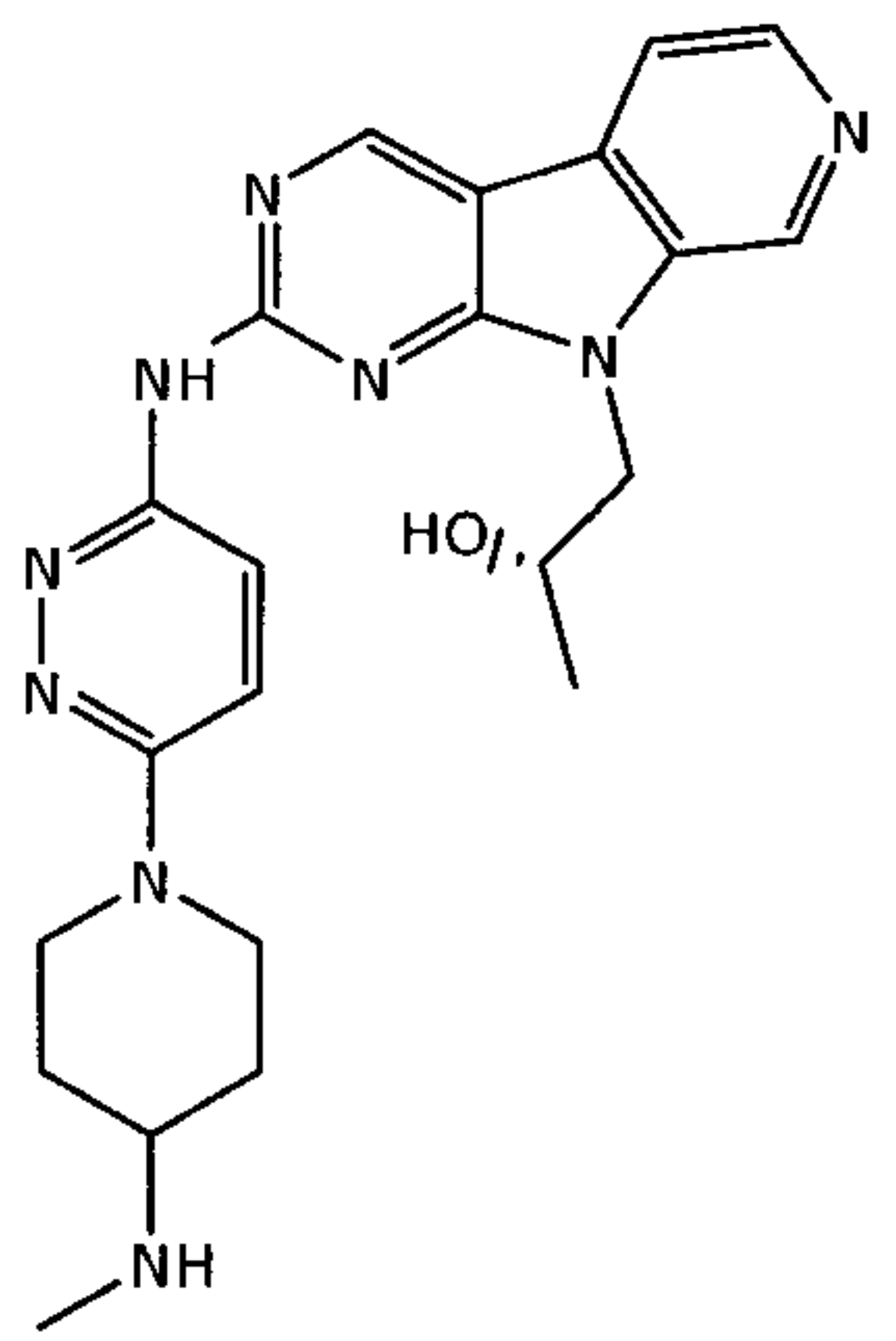
348. The compound of claim 1, wherein the compound is





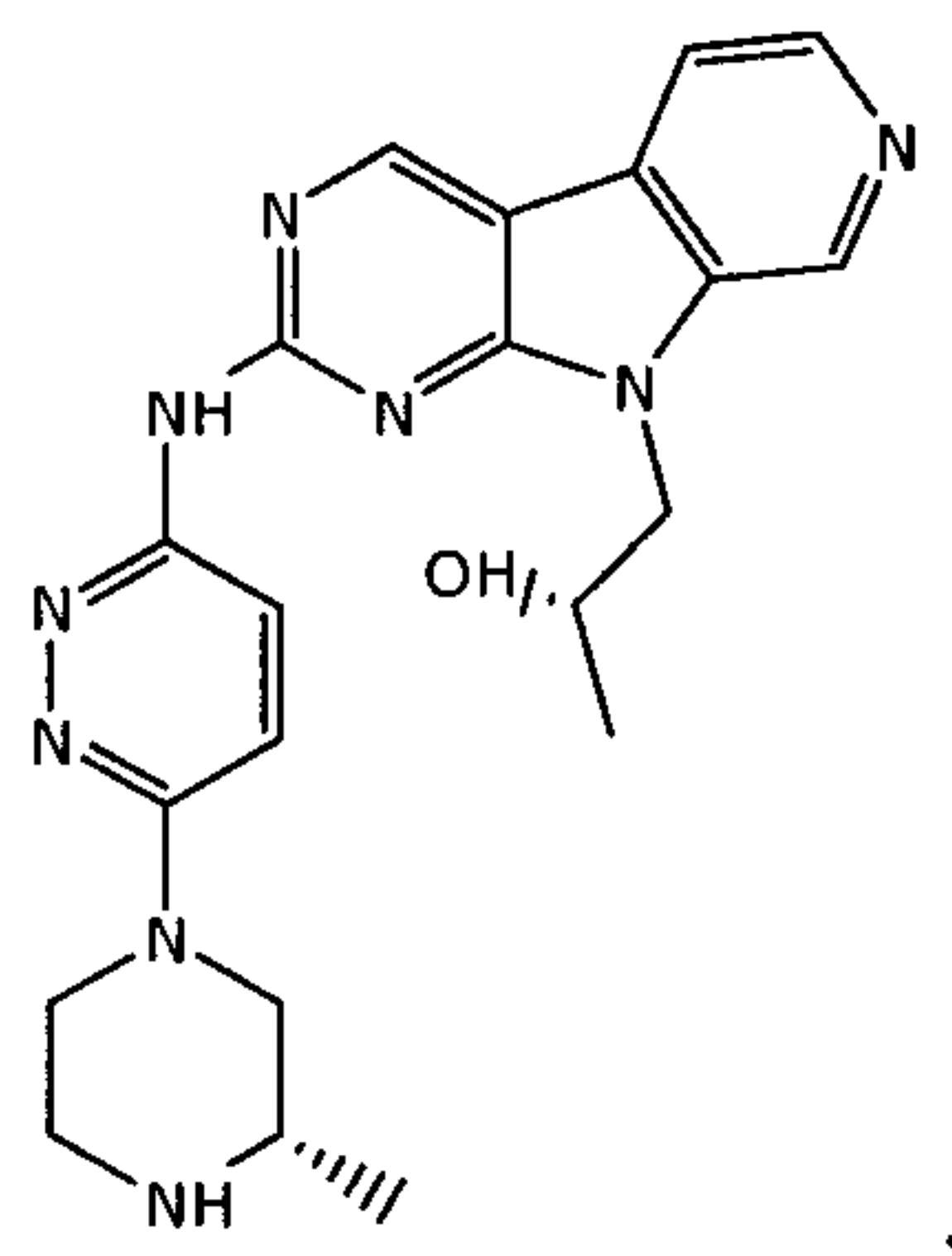
or a pharmaceutically acceptable salt thereof.

349. The compound of claim 1, wherein the compound is



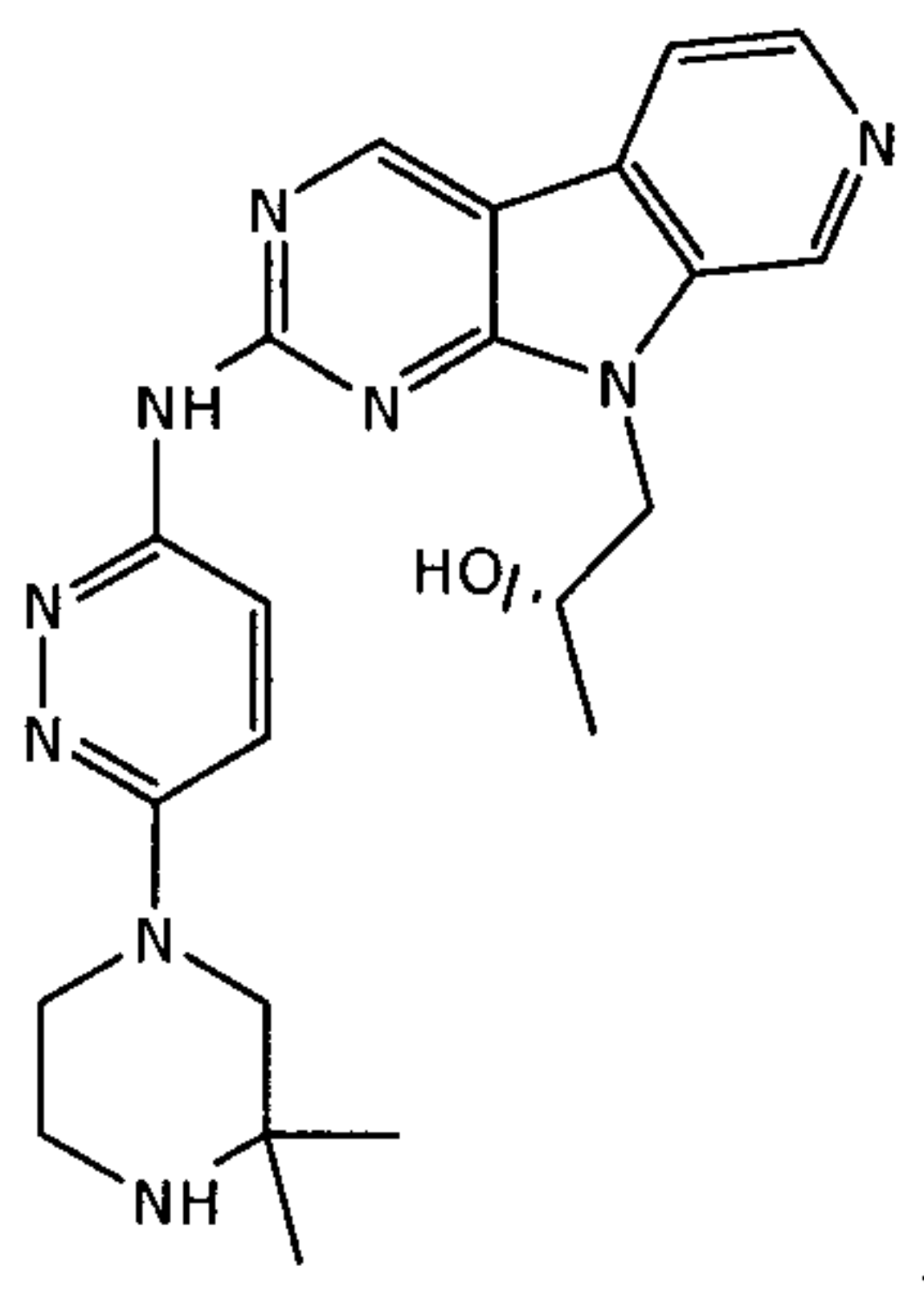
or a pharmaceutically acceptable salt thereof.

350. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

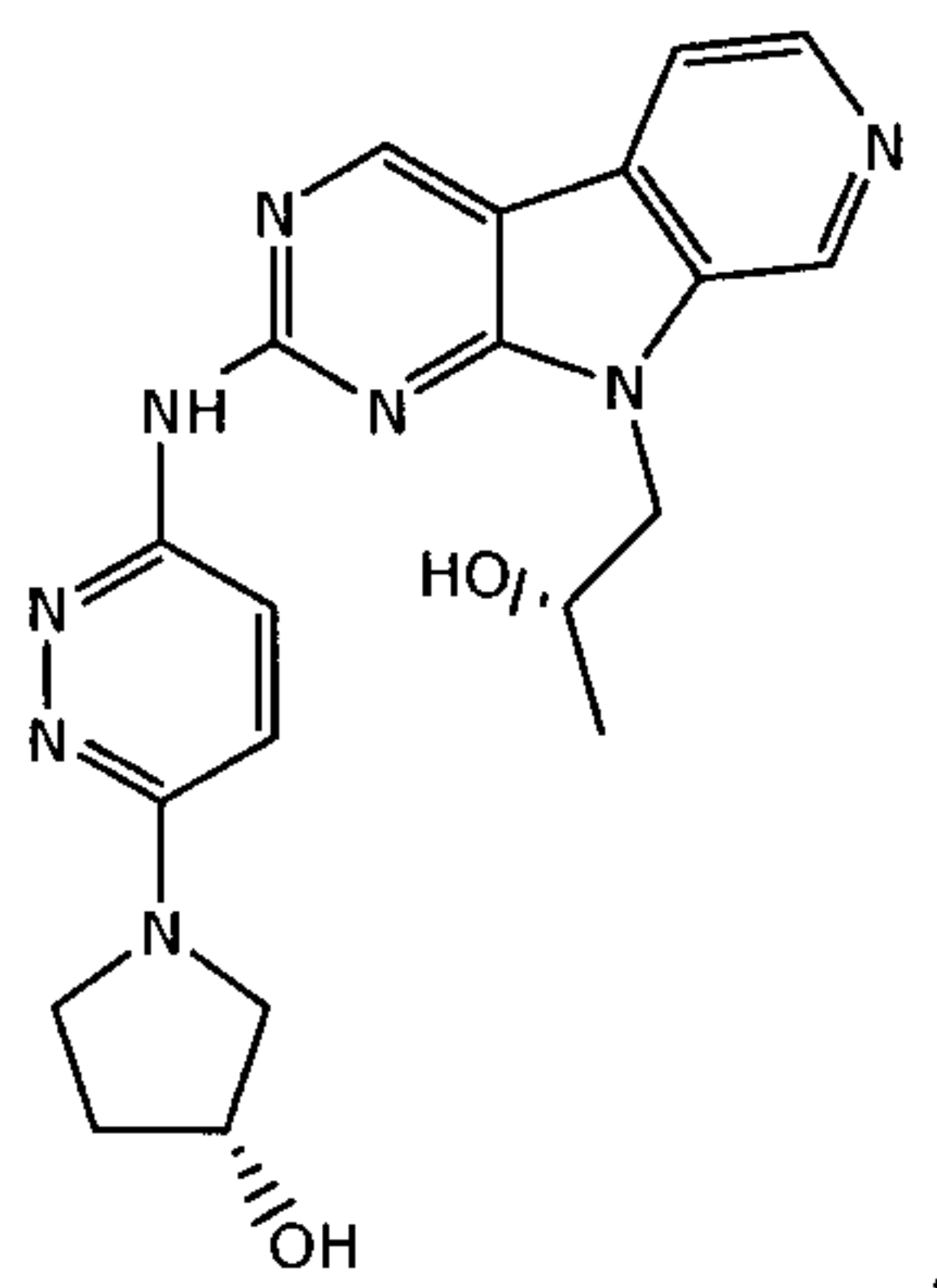
351. The compound of claim 1, wherein the compound is





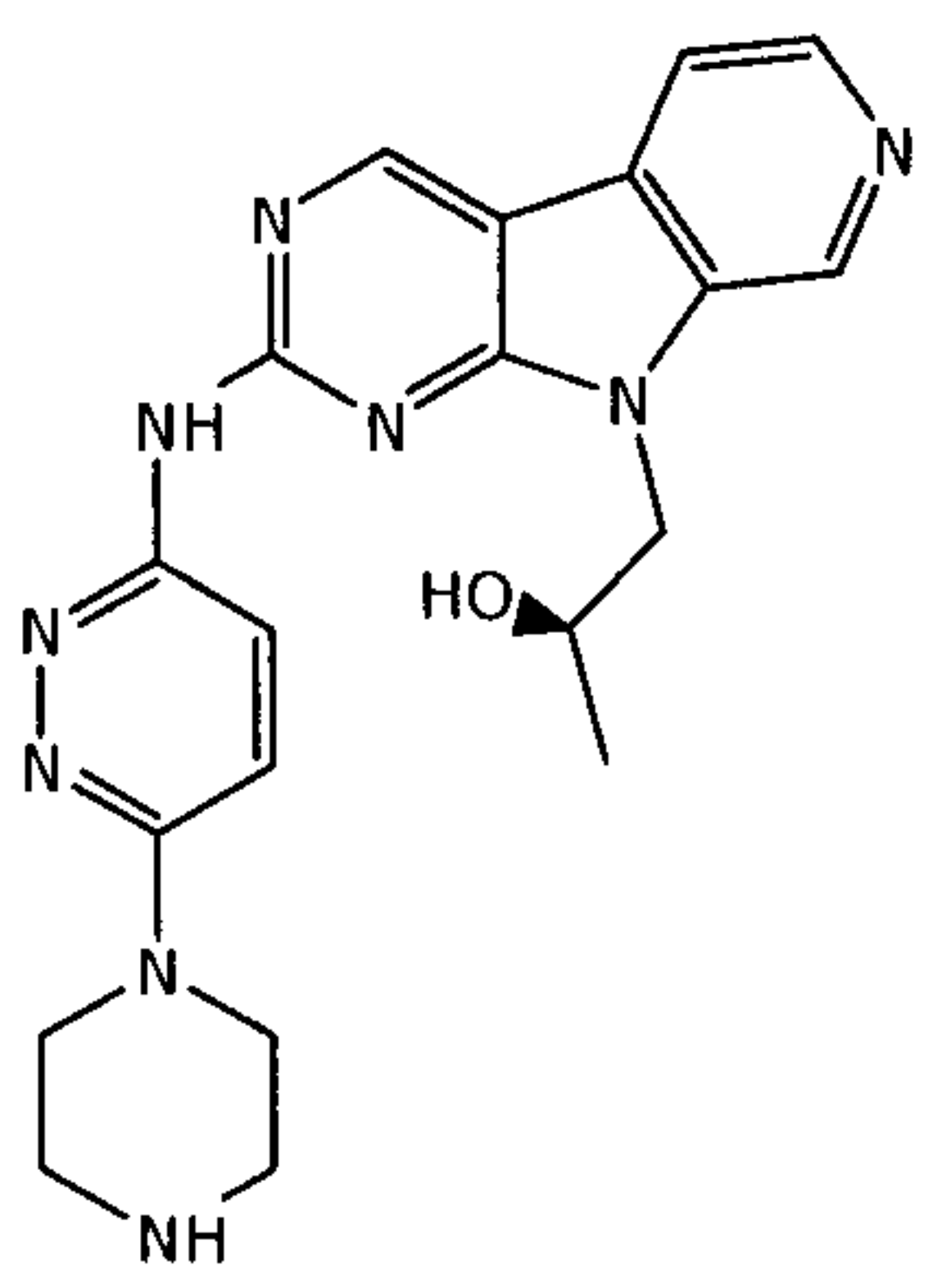
or a pharmaceutically acceptable salt thereof.

352. The compound of claim 1, wherein the compound is



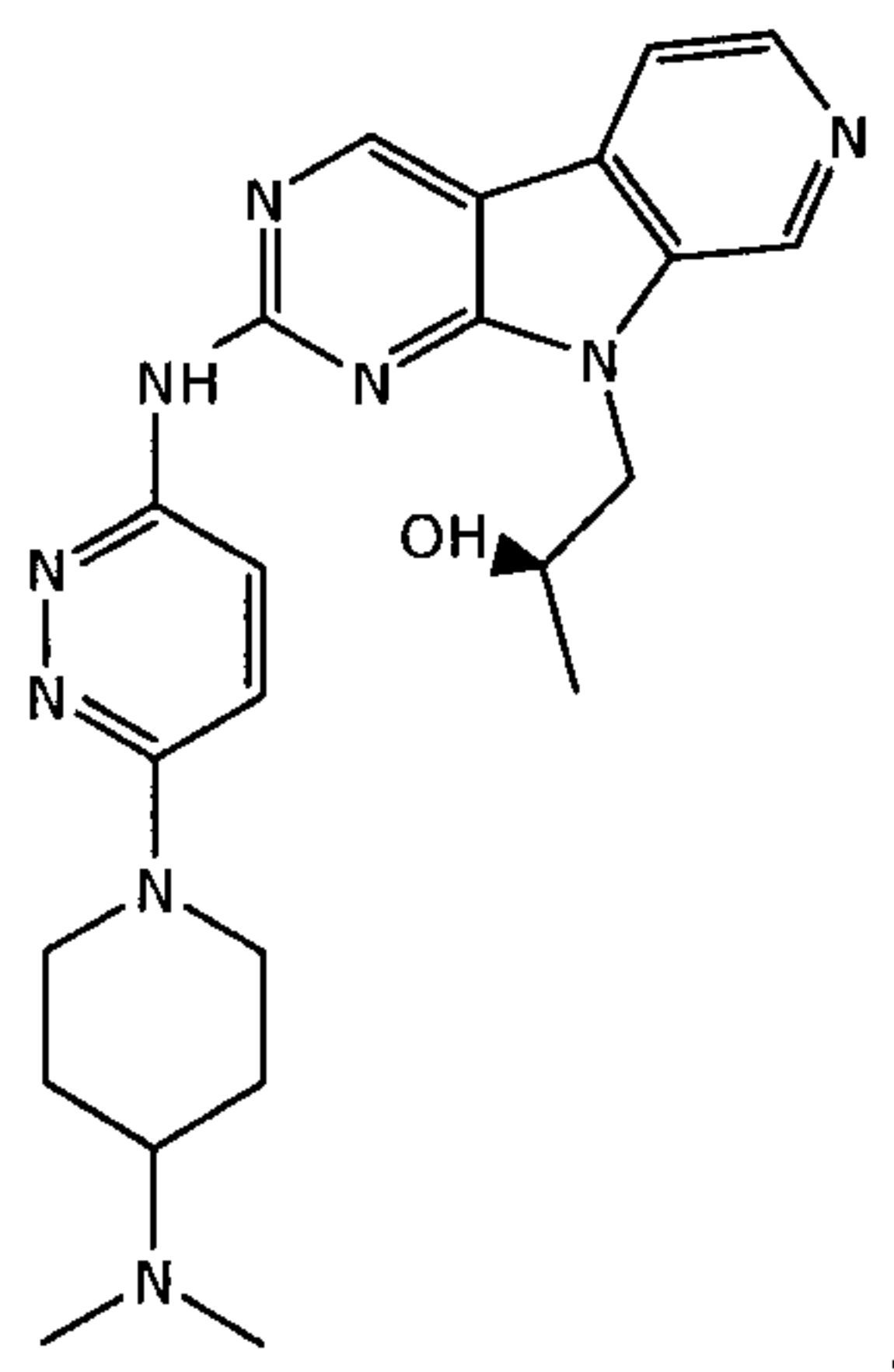
or a pharmaceutically acceptable salt thereof.

353. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

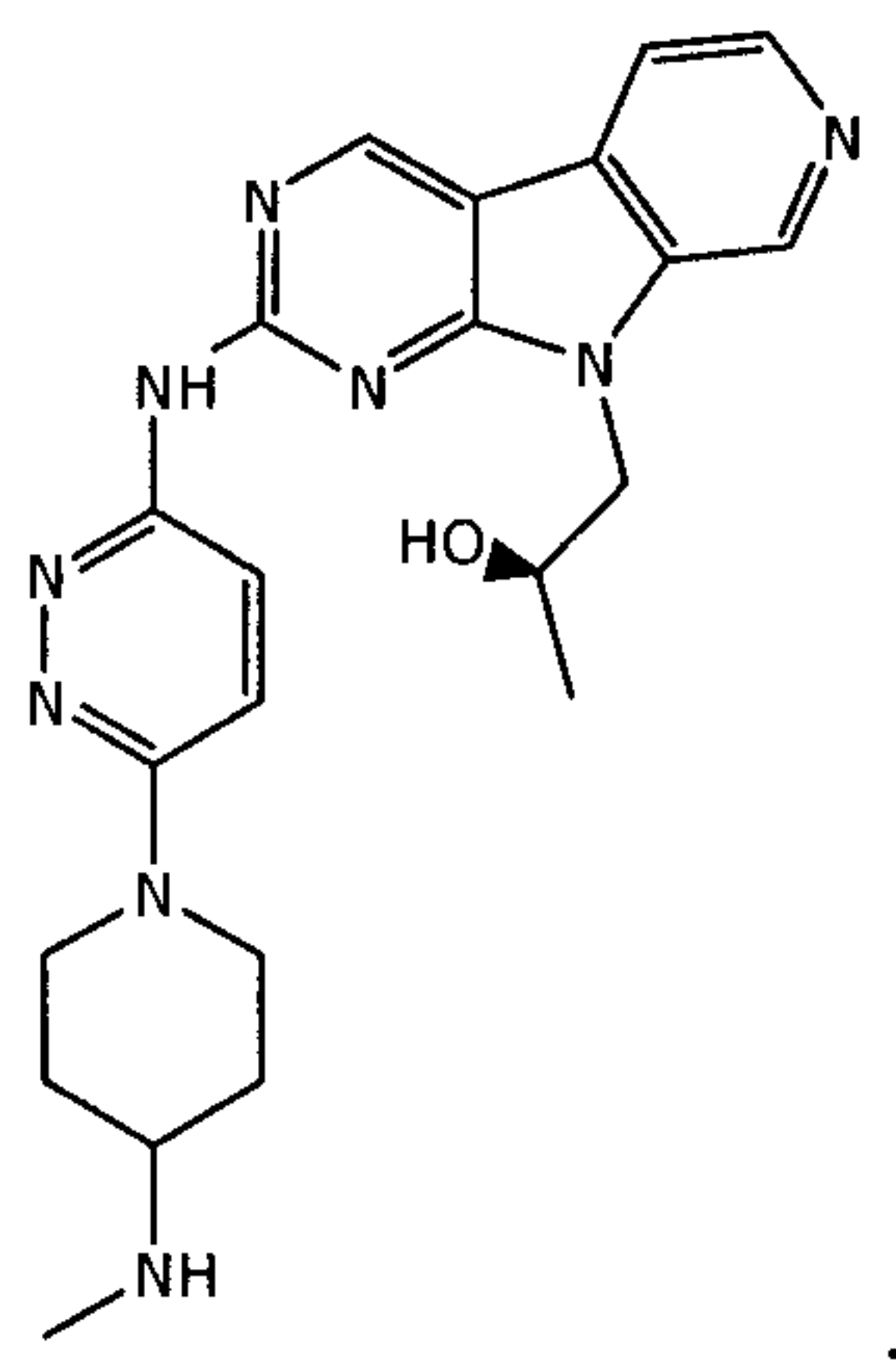
354. The compound of claim 1, wherein the compound is





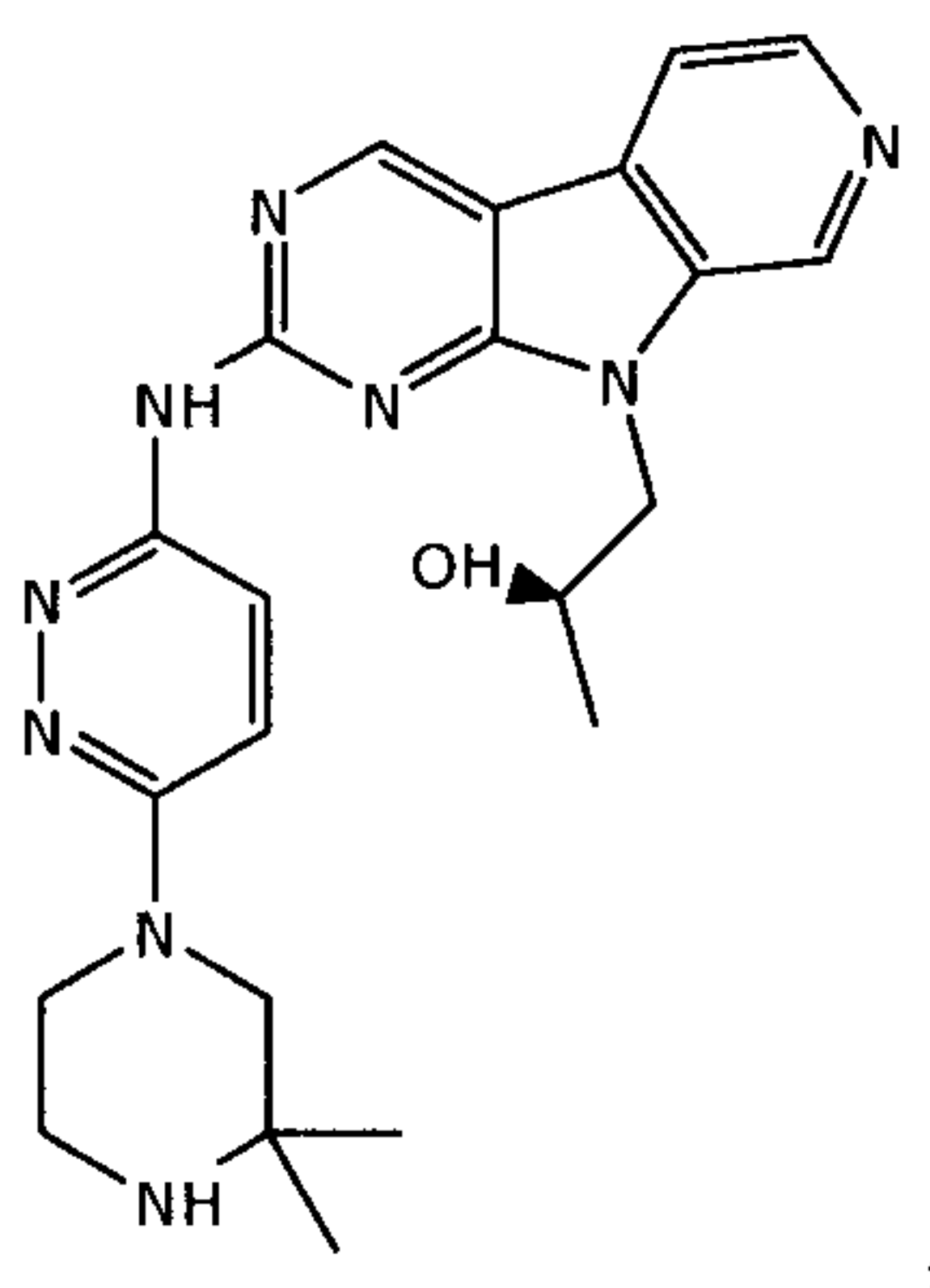
or a pharmaceutically acceptable salt thereof.

355. The compound of claim 1, wherein the compound is



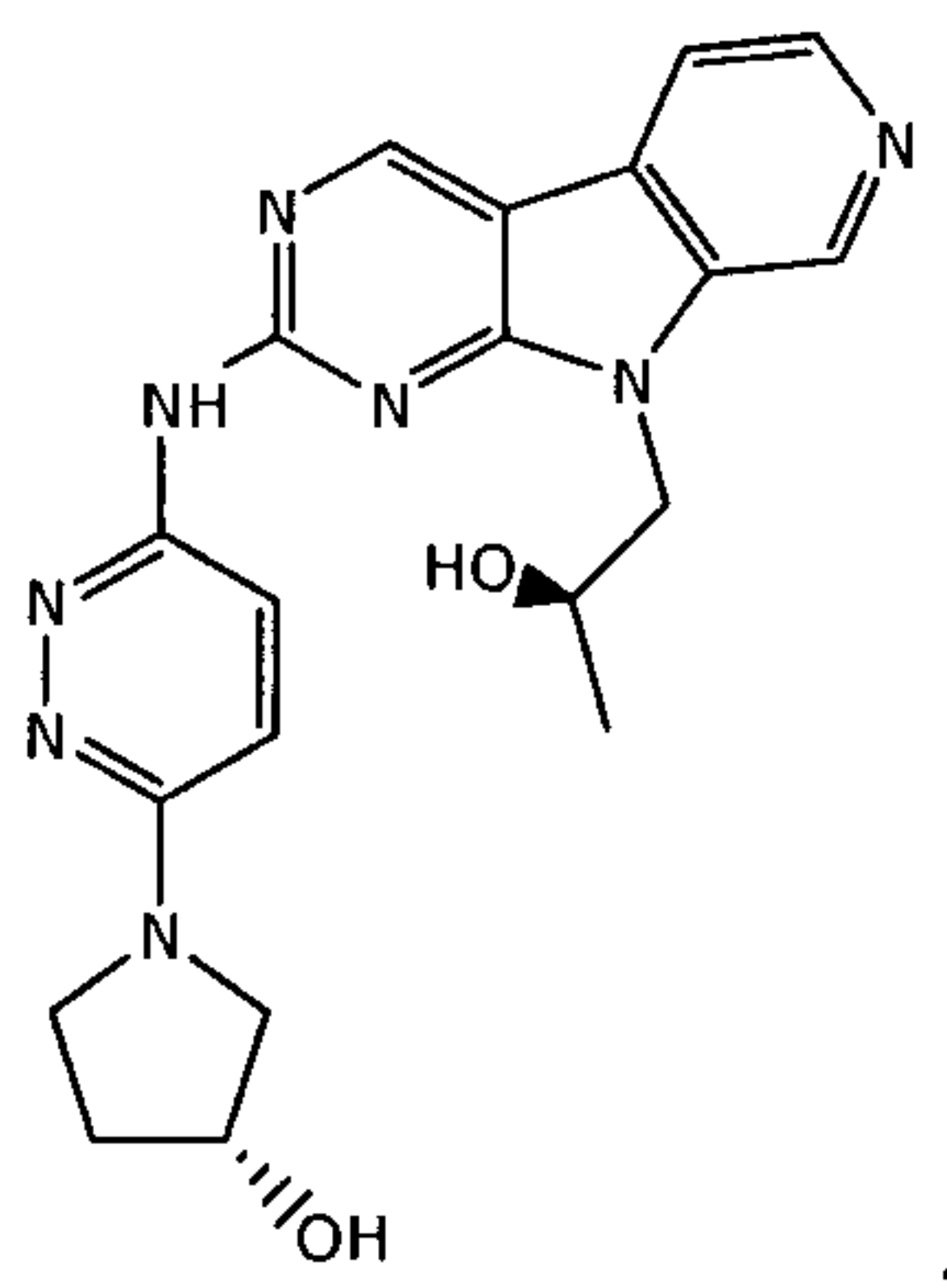
or a pharmaceutically acceptable salt thereof.

356. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

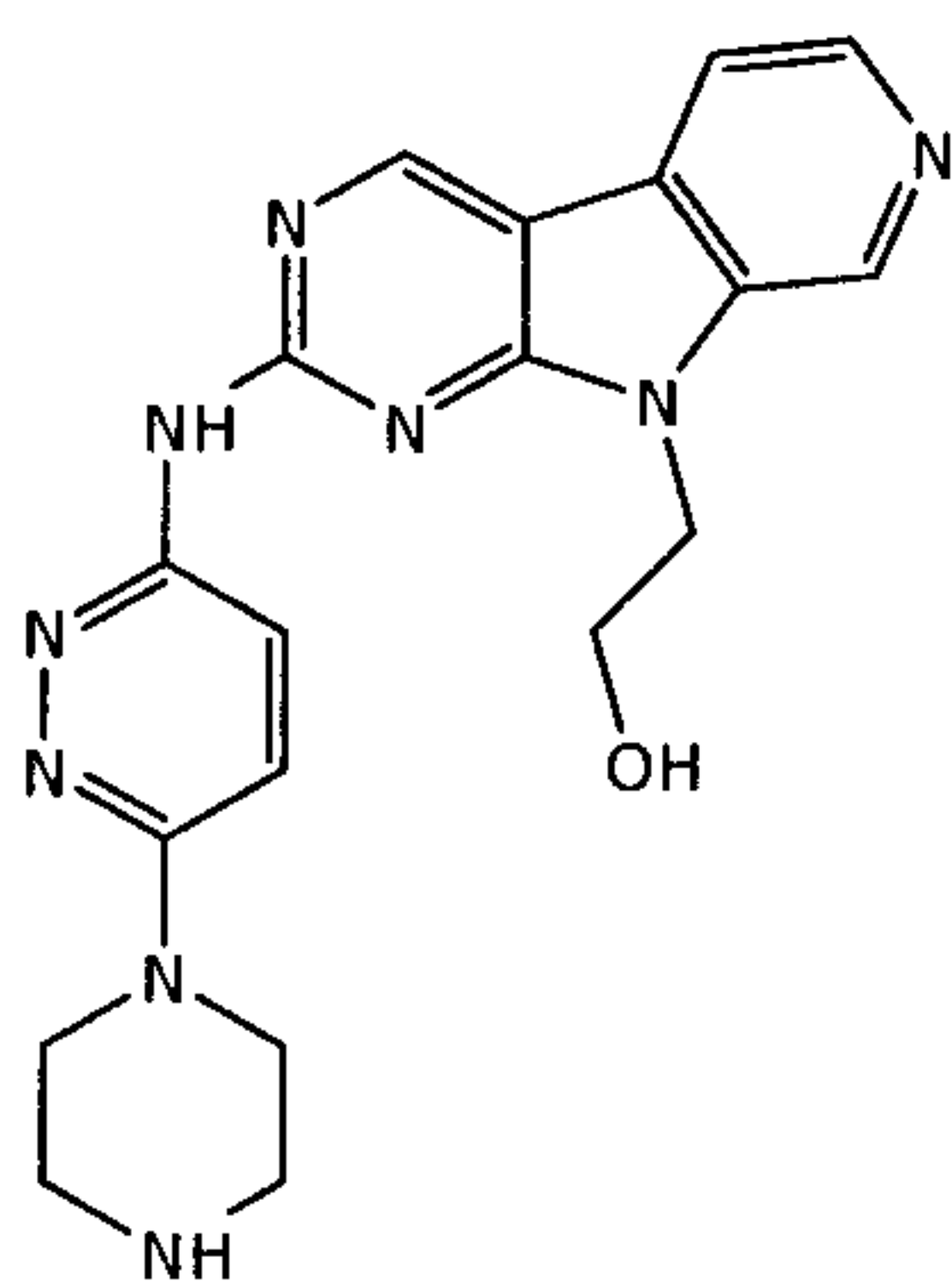
357. The compound of claim 1, wherein the compound is





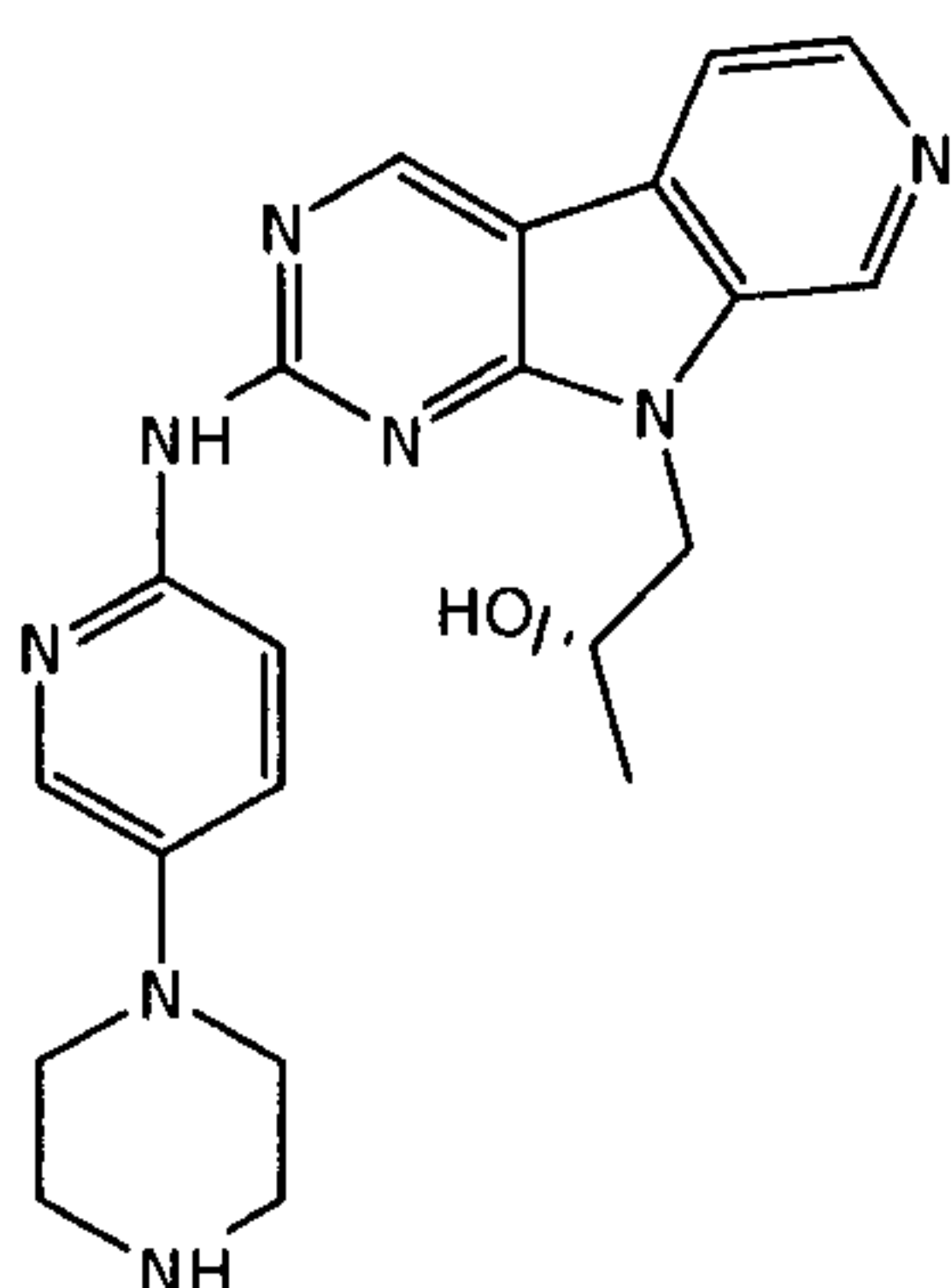
or a pharmaceutically acceptable salt thereof.

358. The compound of claim 1, wherein the compound is



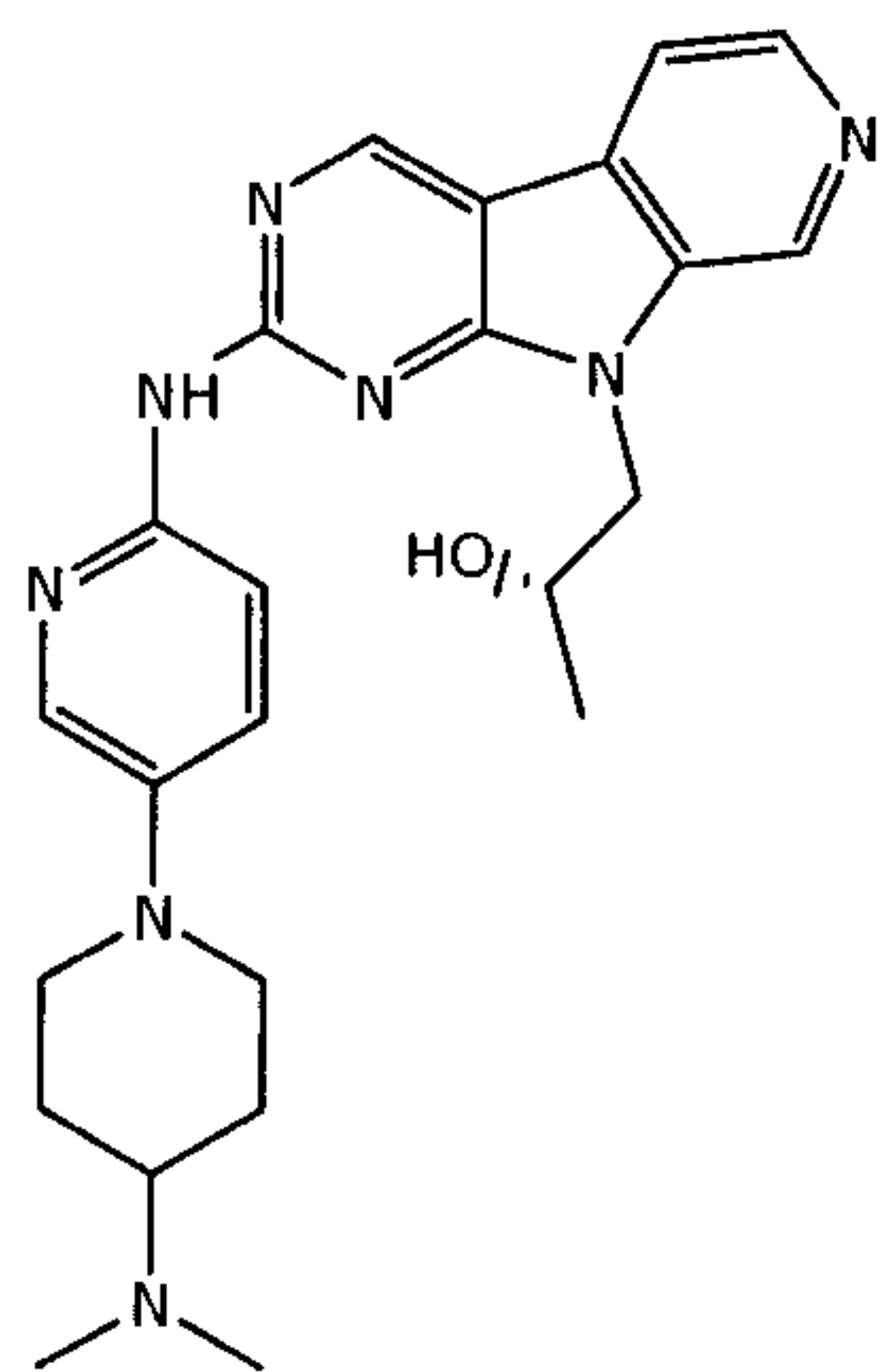
or a pharmaceutically acceptable salt thereof.

359. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

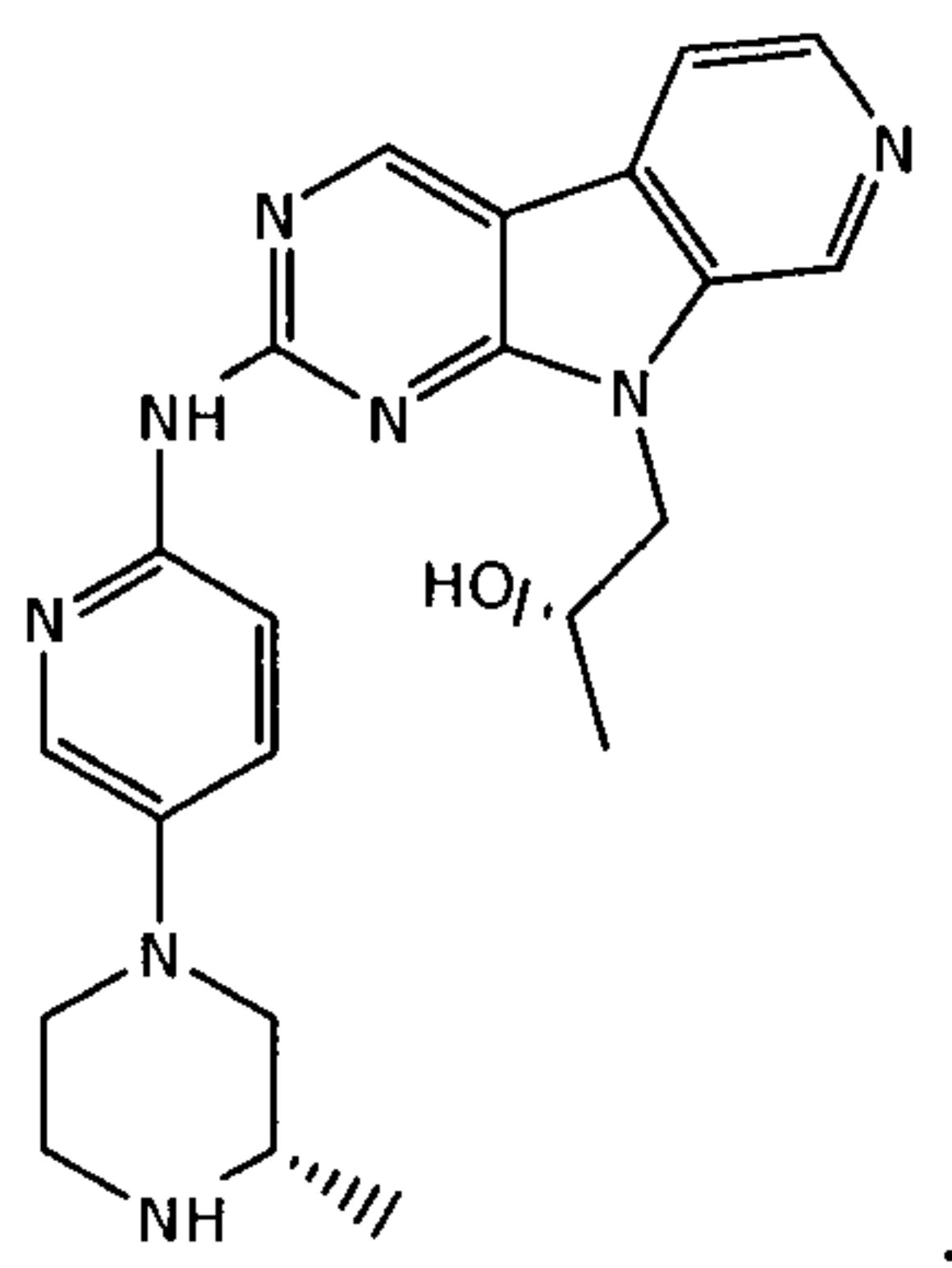
360. The compound of claim 1, wherein the compound is





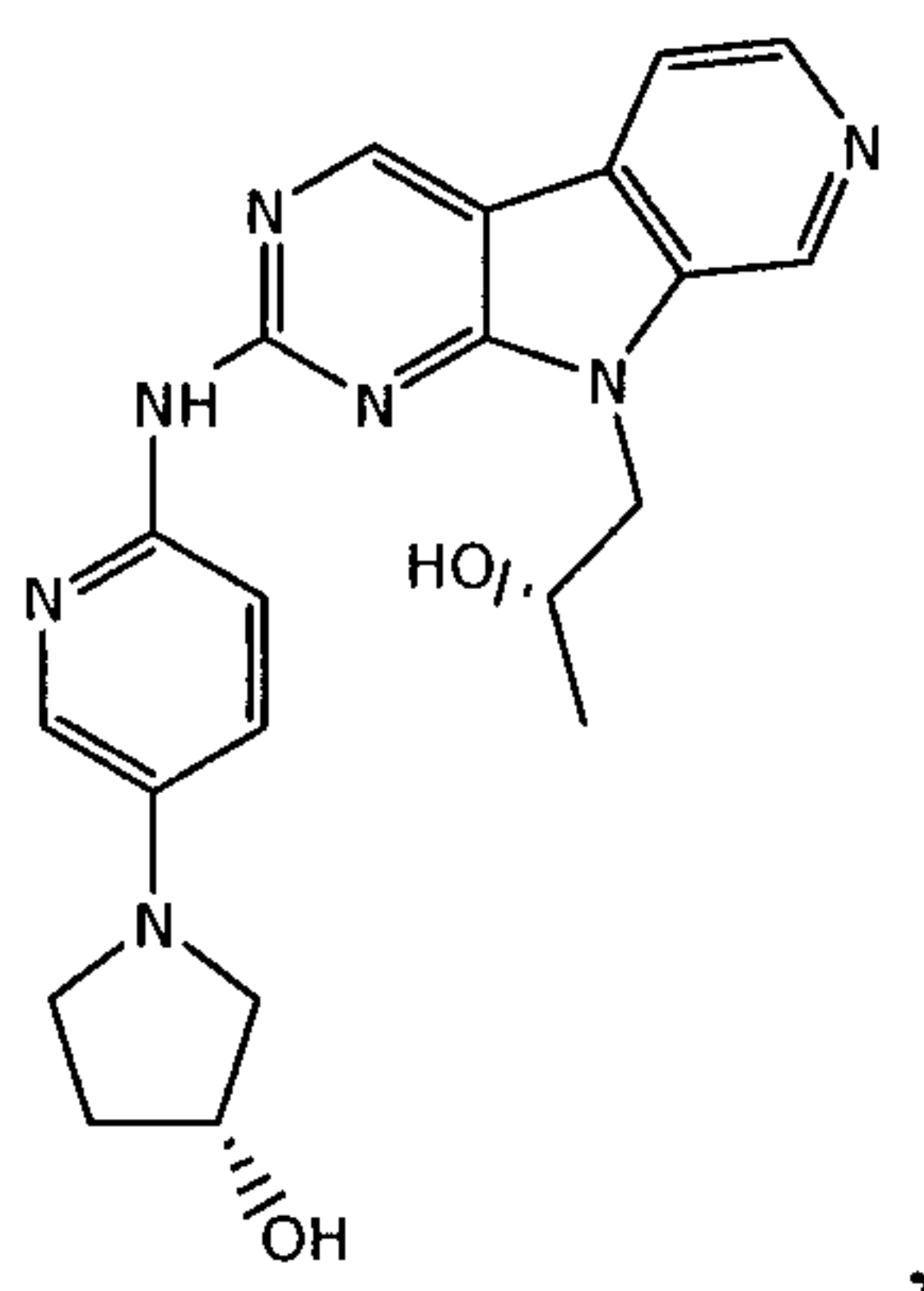
or a pharmaceutically acceptable salt thereof.

361. The compound of claim 1, wherein the compound is



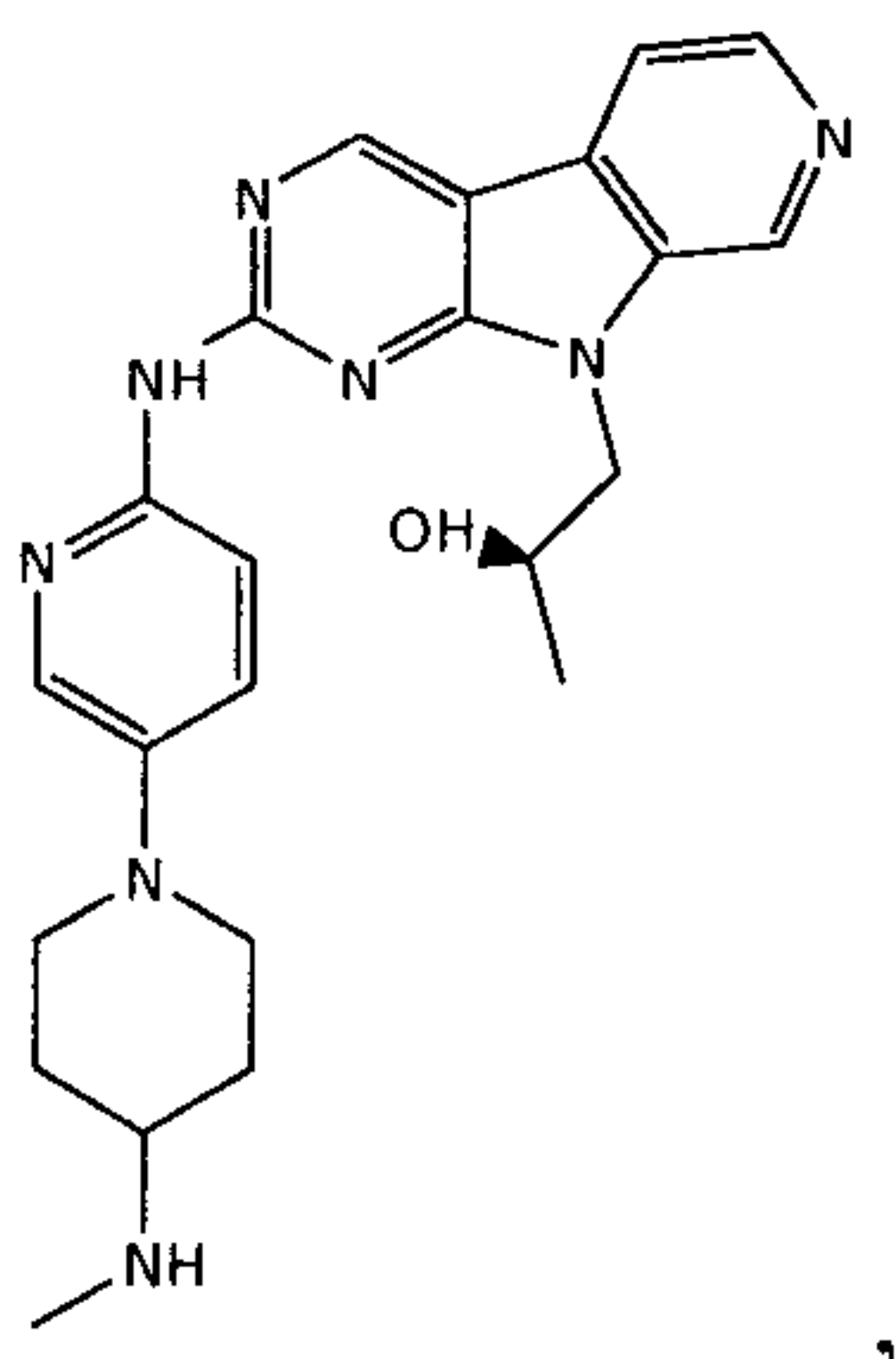
or a pharmaceutically acceptable salt thereof.

362. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

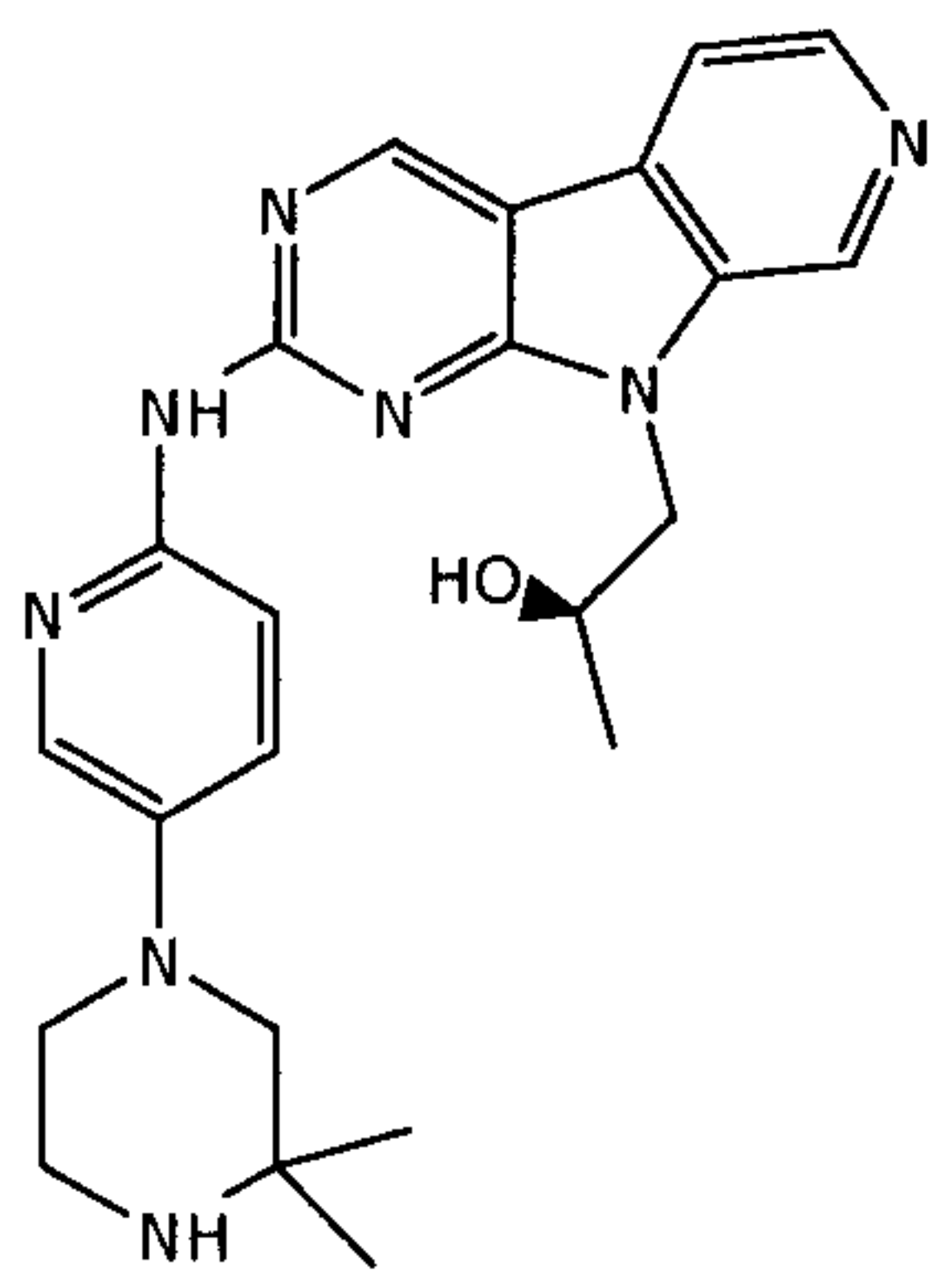
363. The compound of claim 1, wherein the compound is





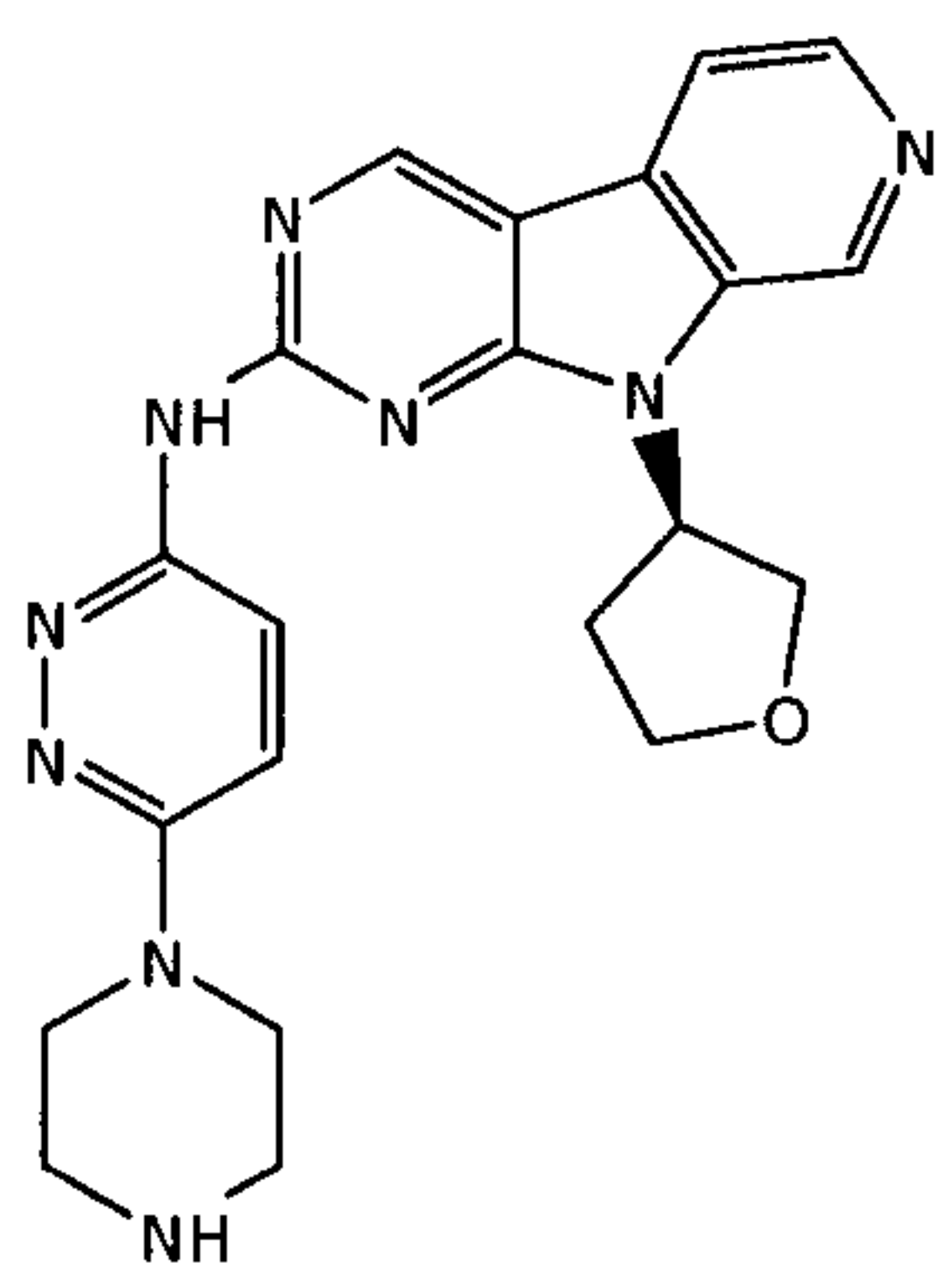
or a pharmaceutically acceptable salt thereof.

364. The compound of claim 1, wherein the compound is



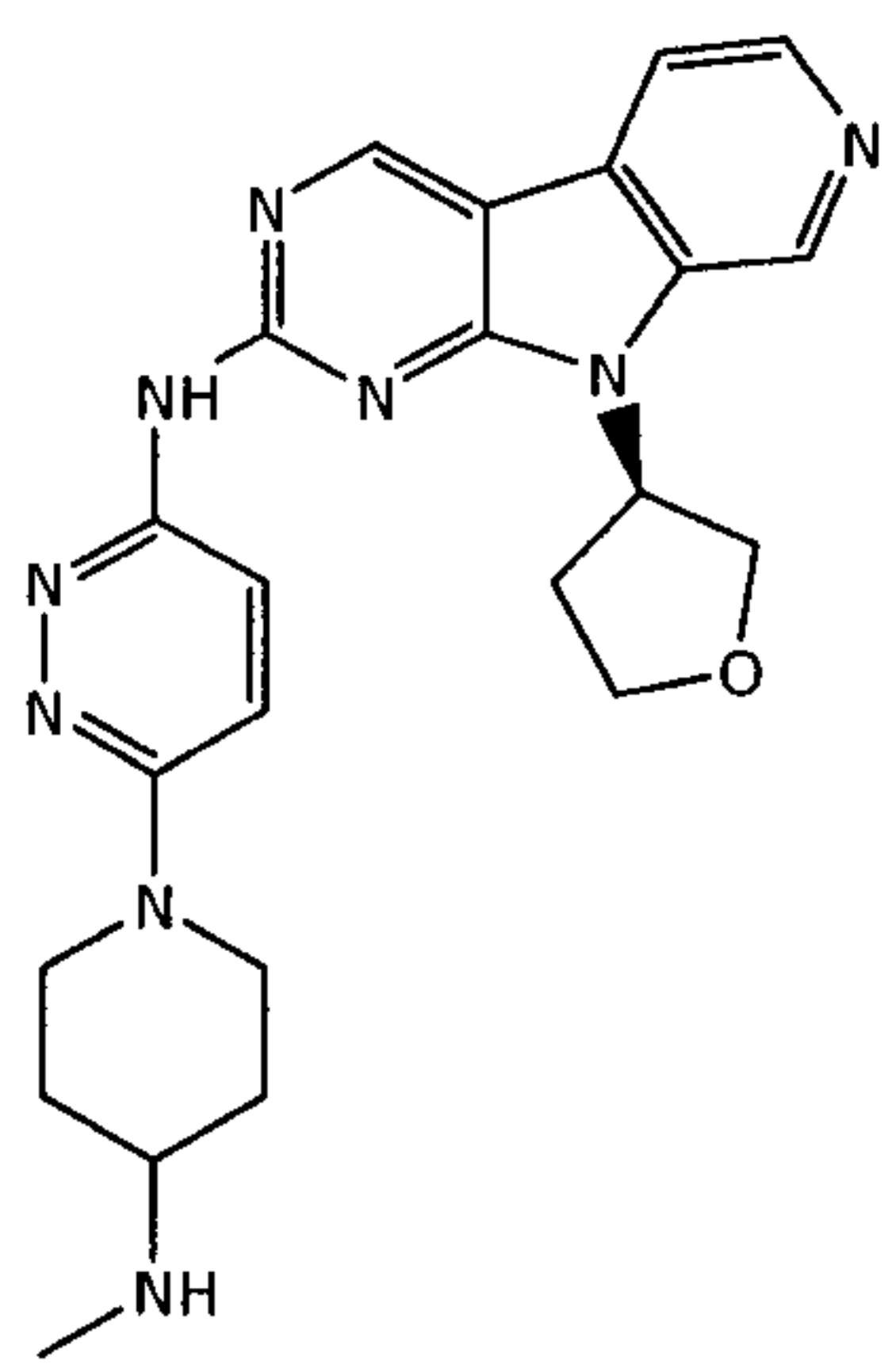
or a pharmaceutically acceptable salt thereof.

365. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

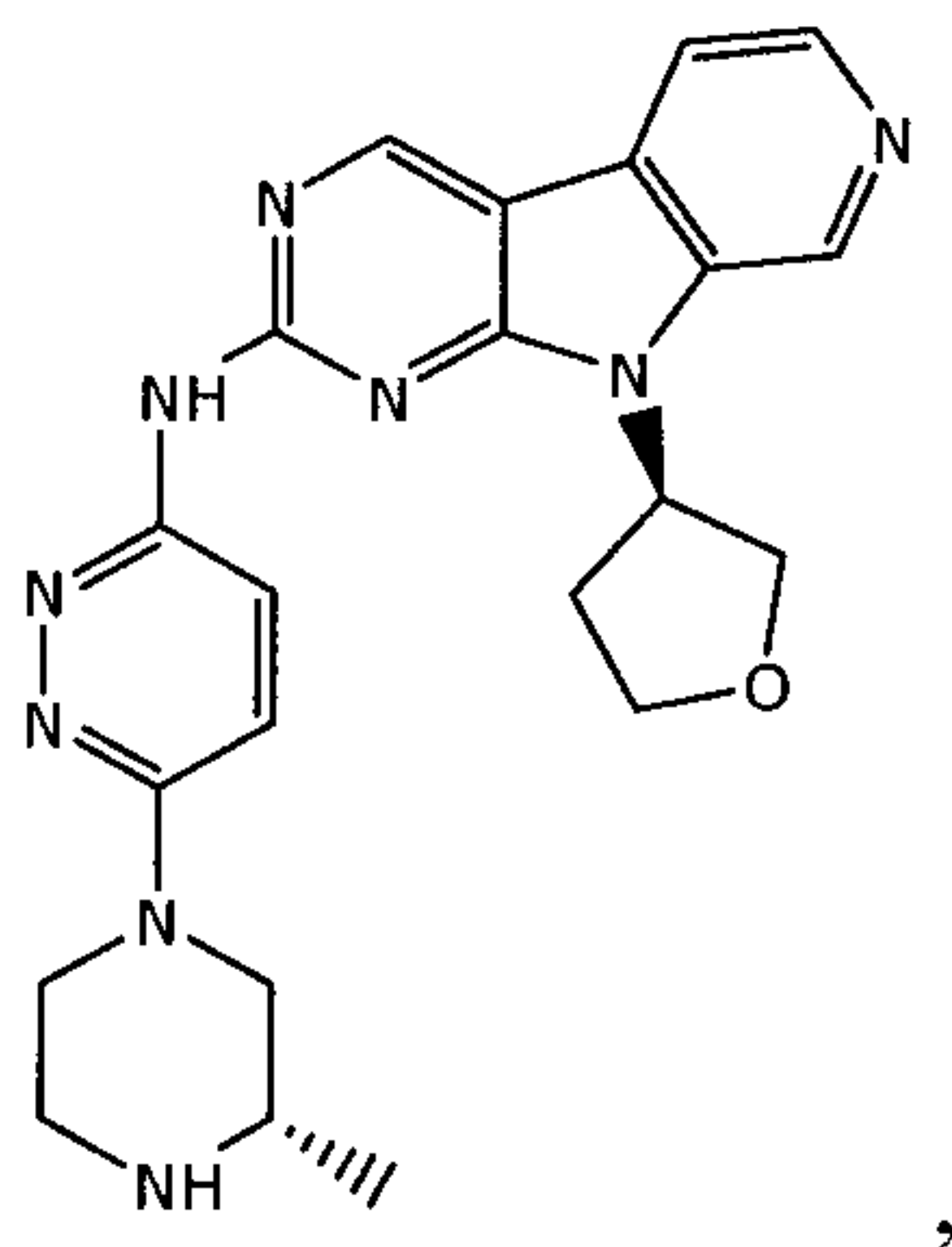
366. The compound of claim 1, wherein the compound is





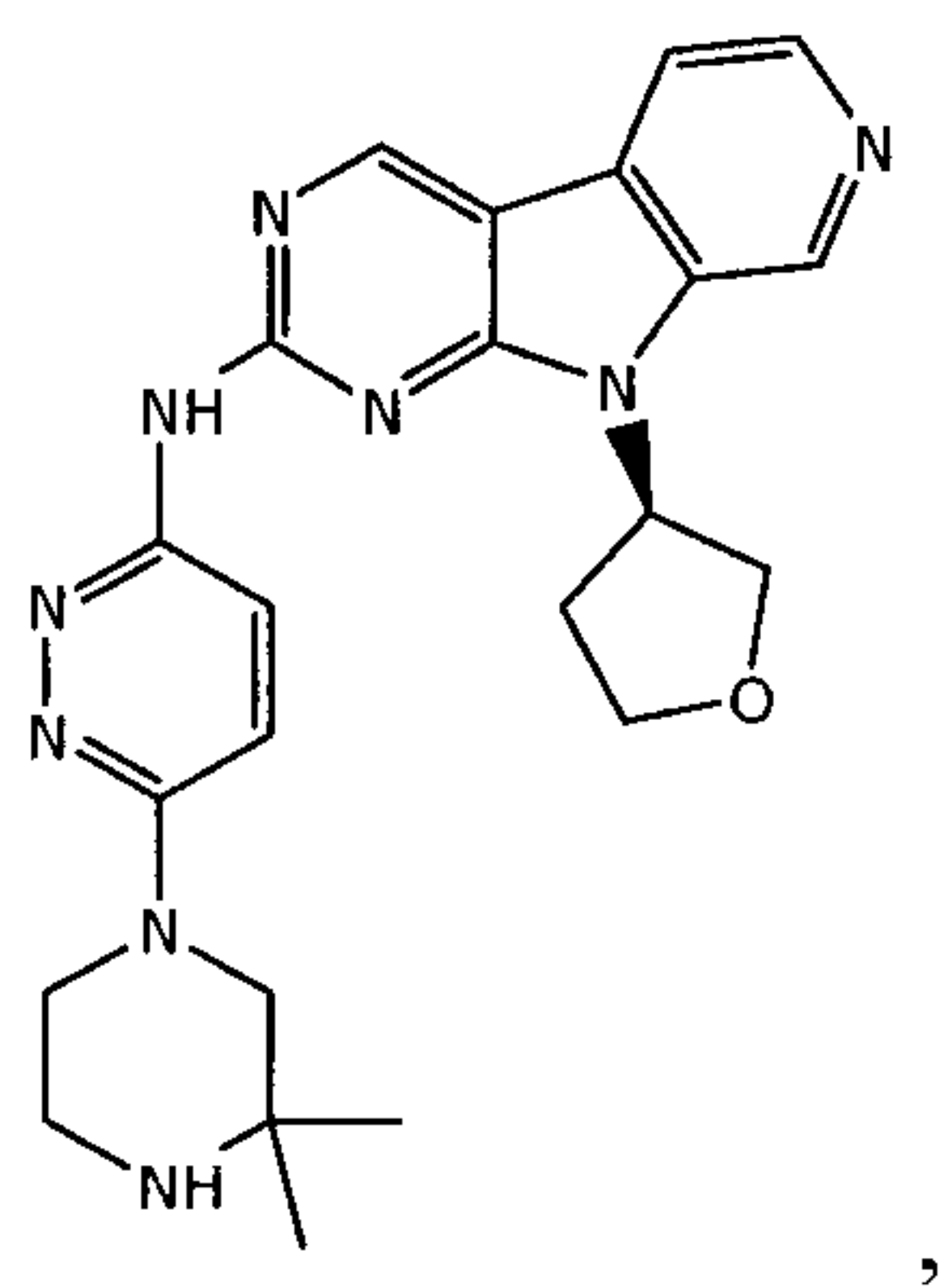
or a pharmaceutically acceptable salt thereof.

367. The compound of claim 1, wherein the compound is



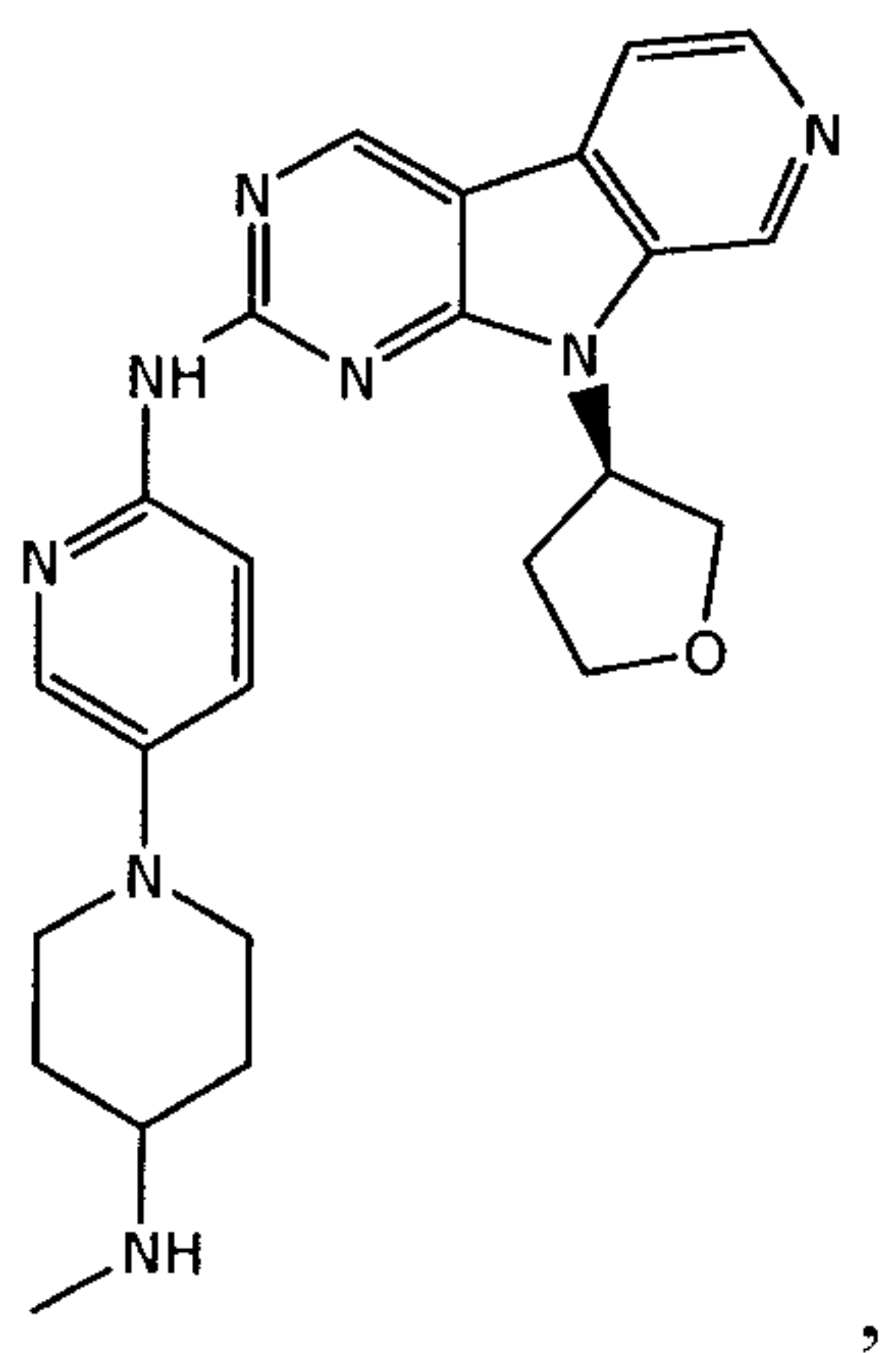
or a pharmaceutically acceptable salt thereof.

368. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

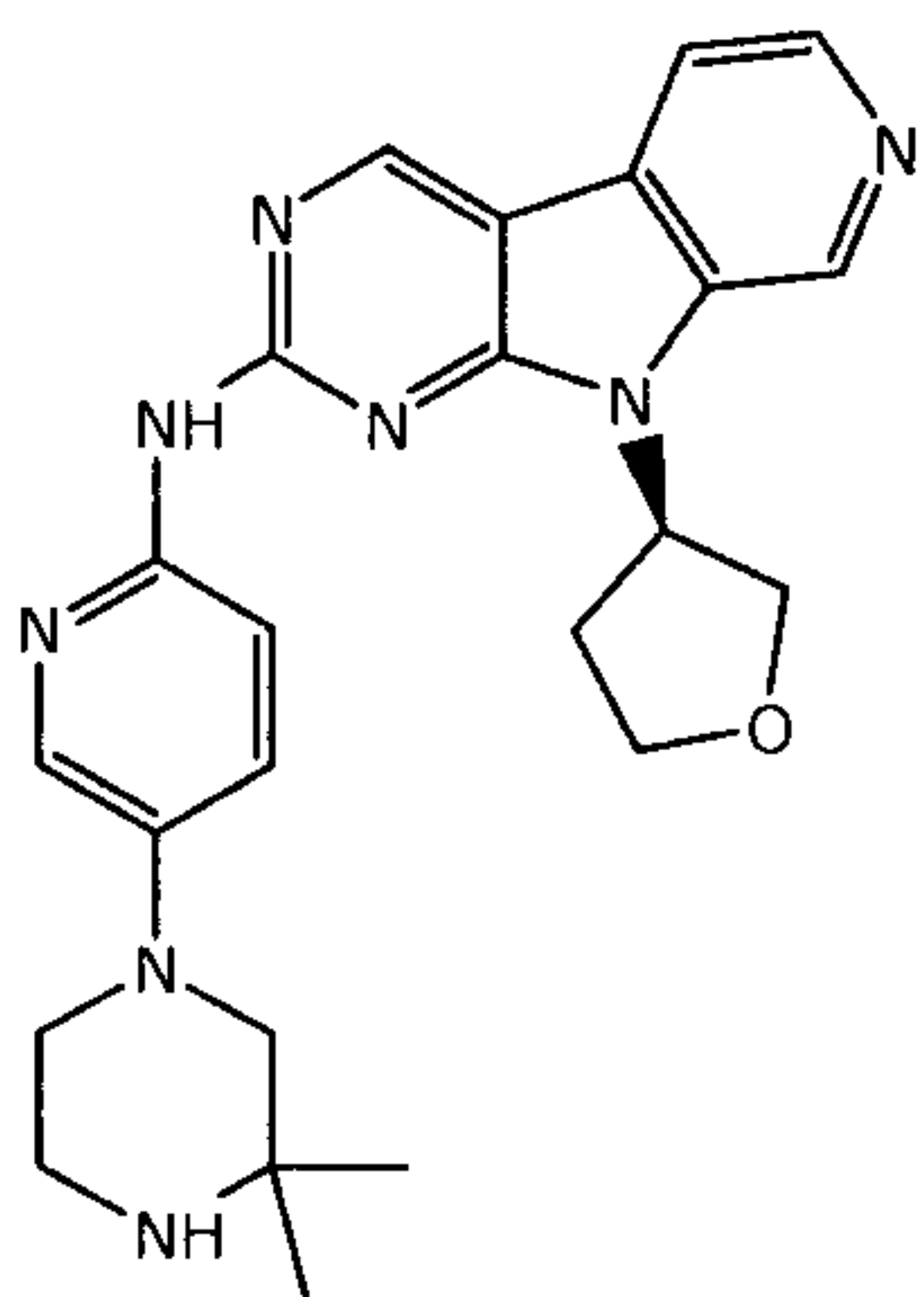
369. The compound of claim 1, wherein the compound is





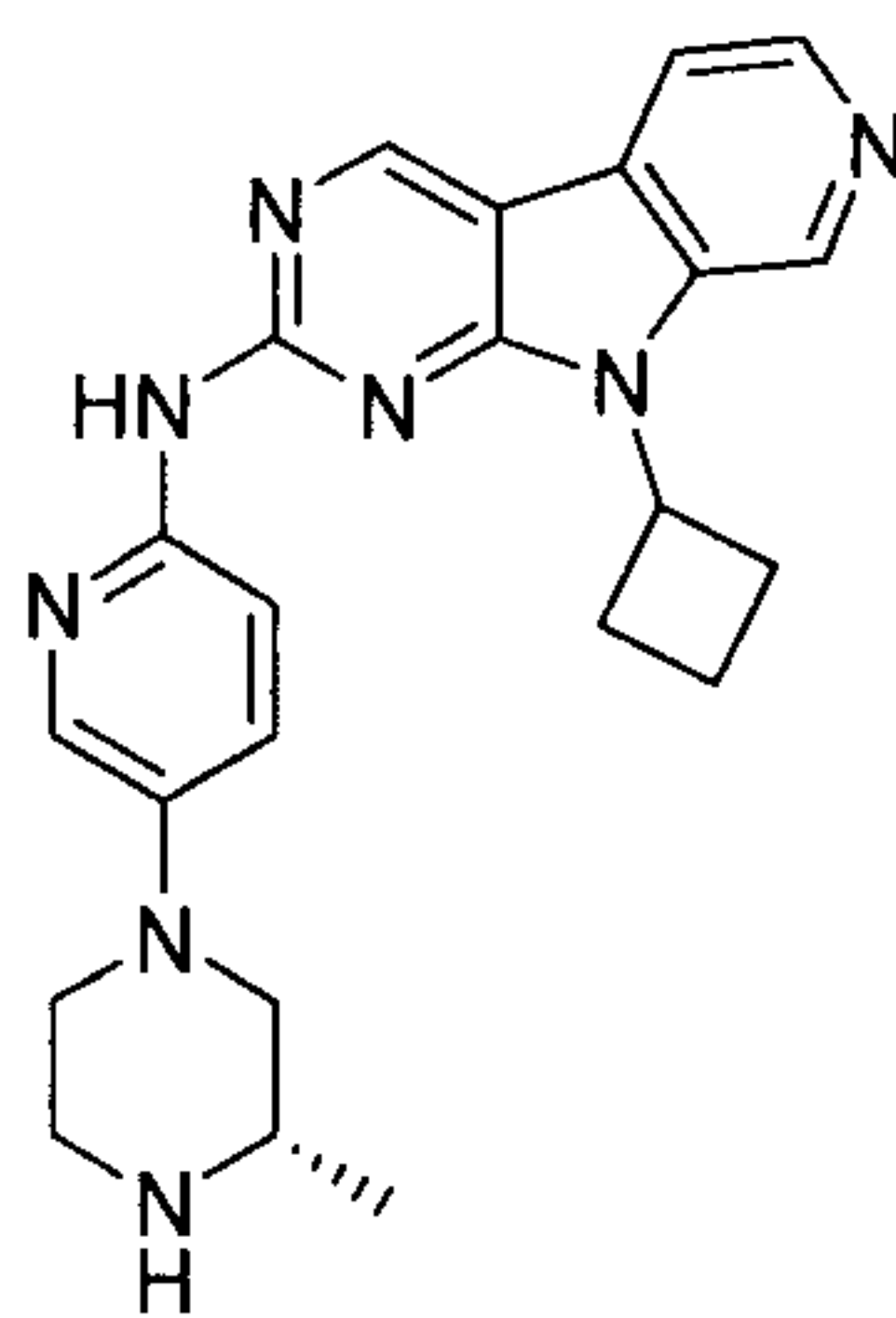
or a pharmaceutically acceptable salt thereof.

370. The compound of claim 1, wherein the compound is



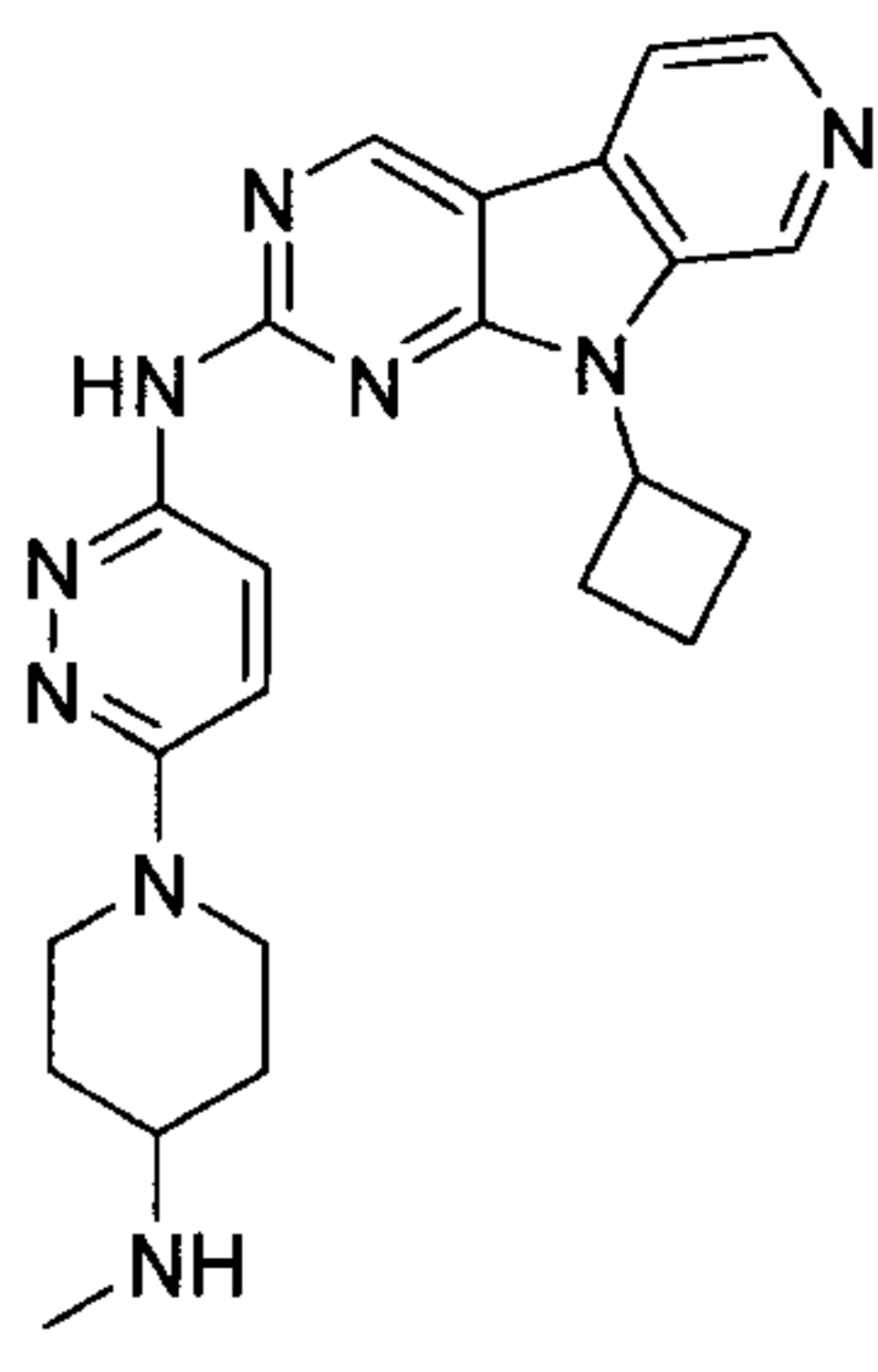
or a pharmaceutically acceptable salt thereof.

371. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

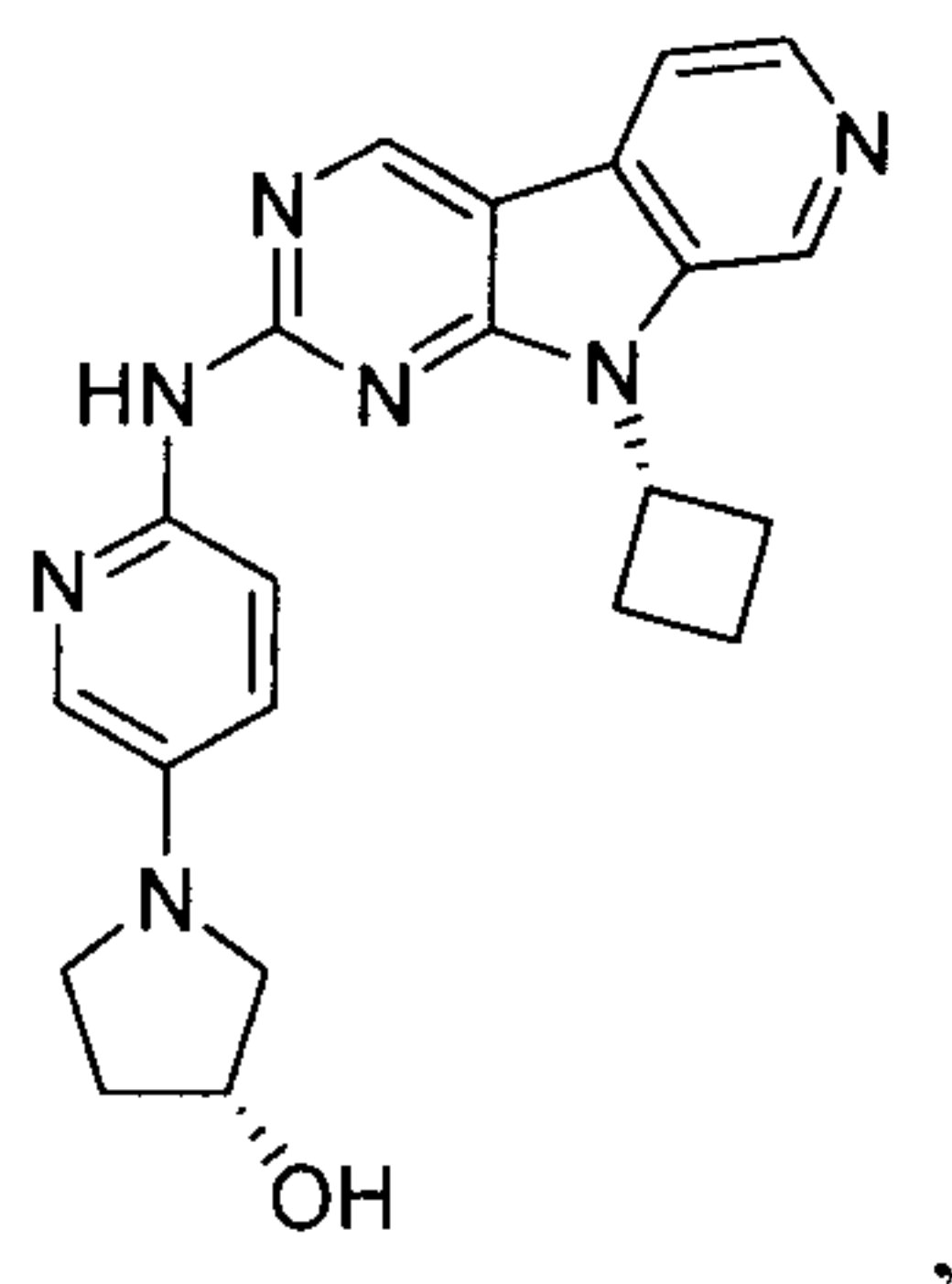
372. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

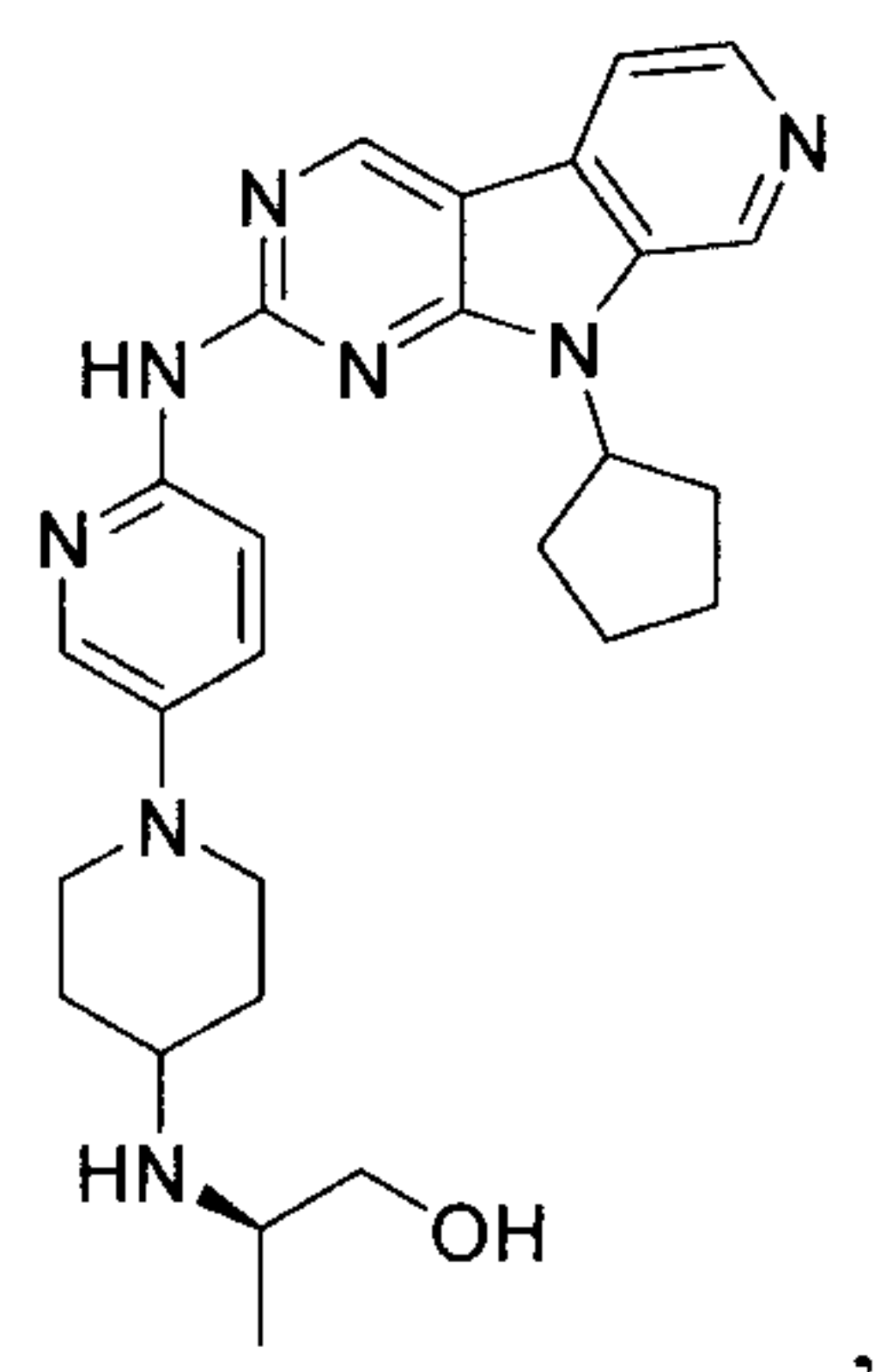


373. The compound of claim 1, wherein the compound is



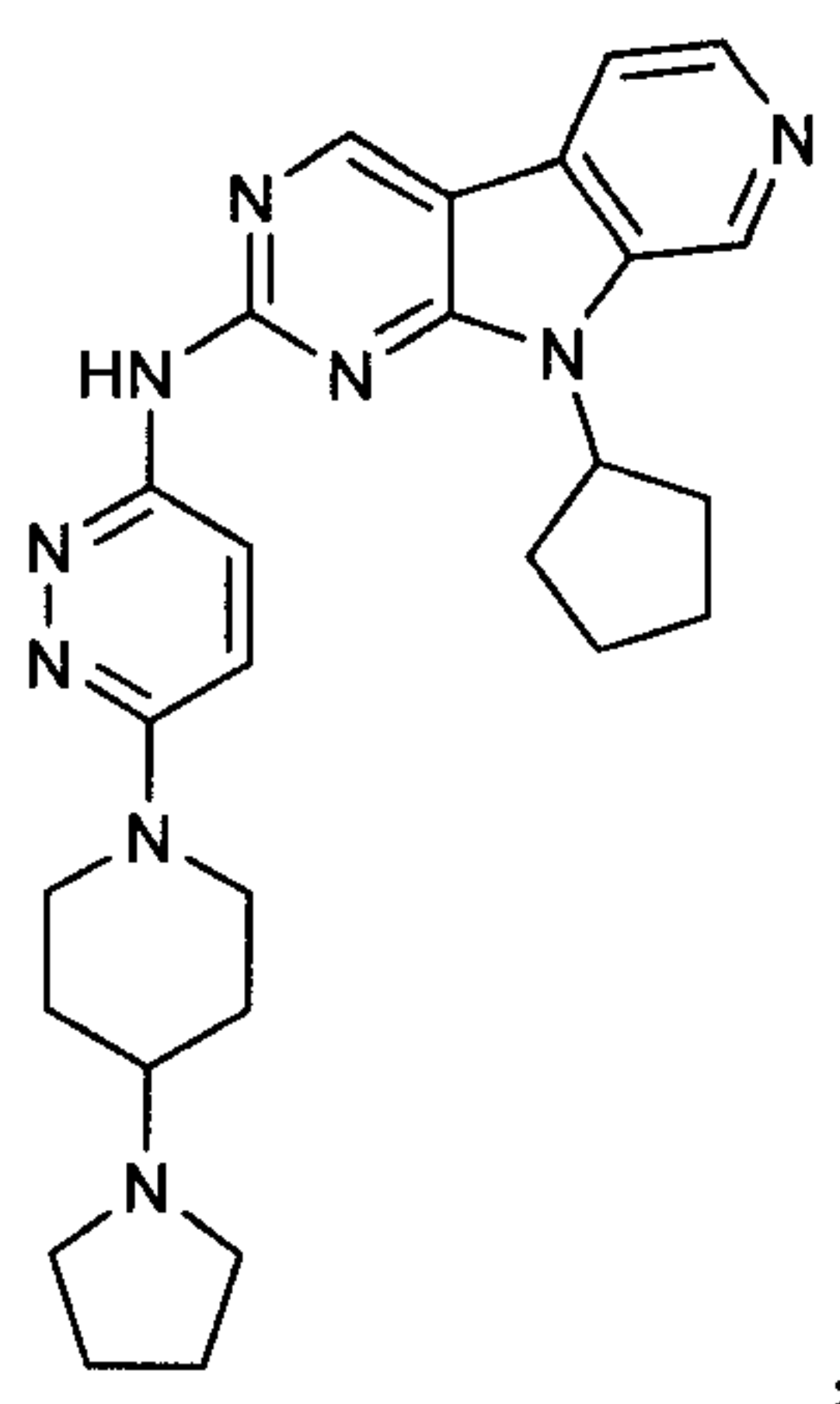
or a pharmaceutically acceptable salt thereof.

374. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

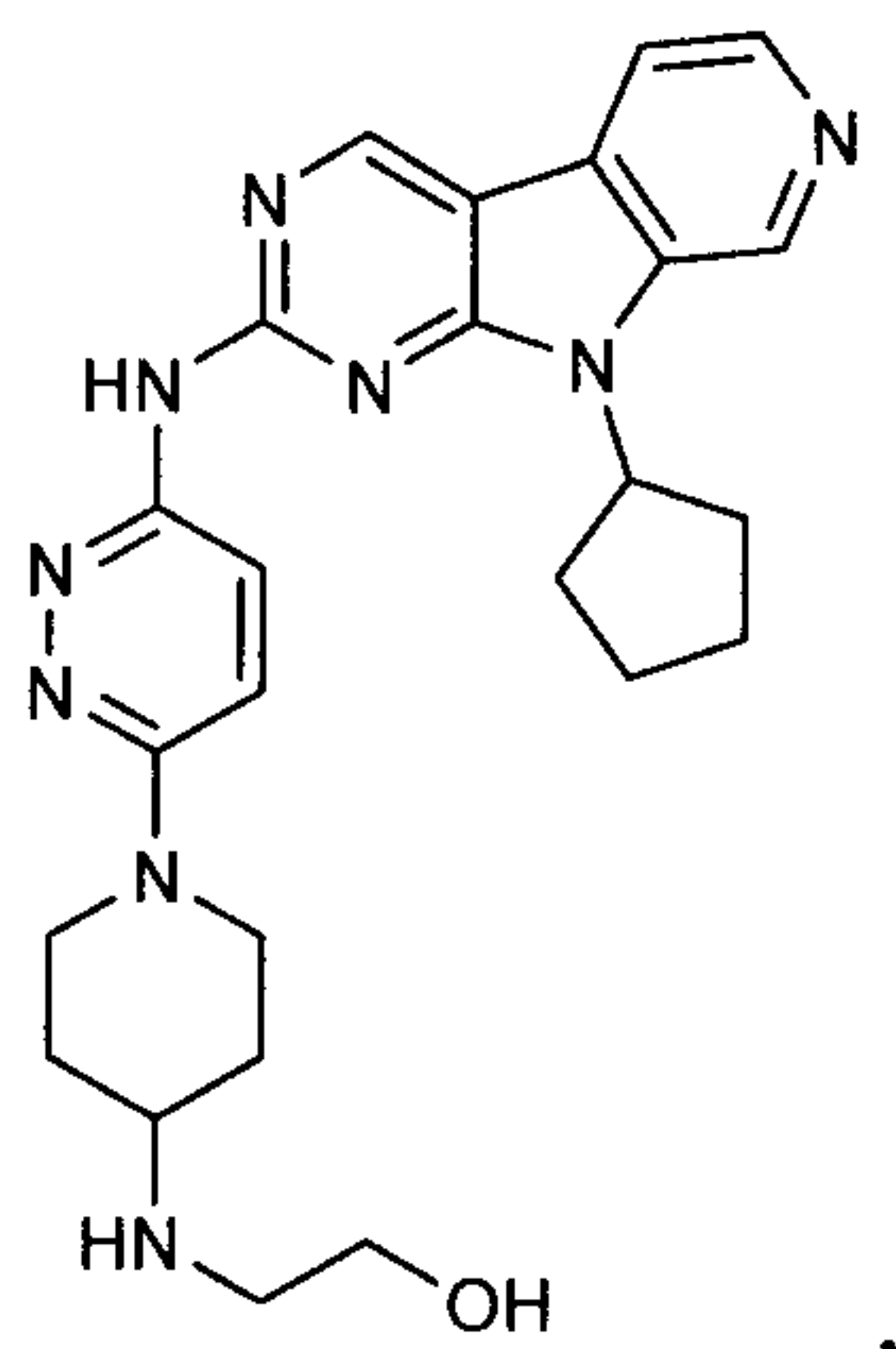
375. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

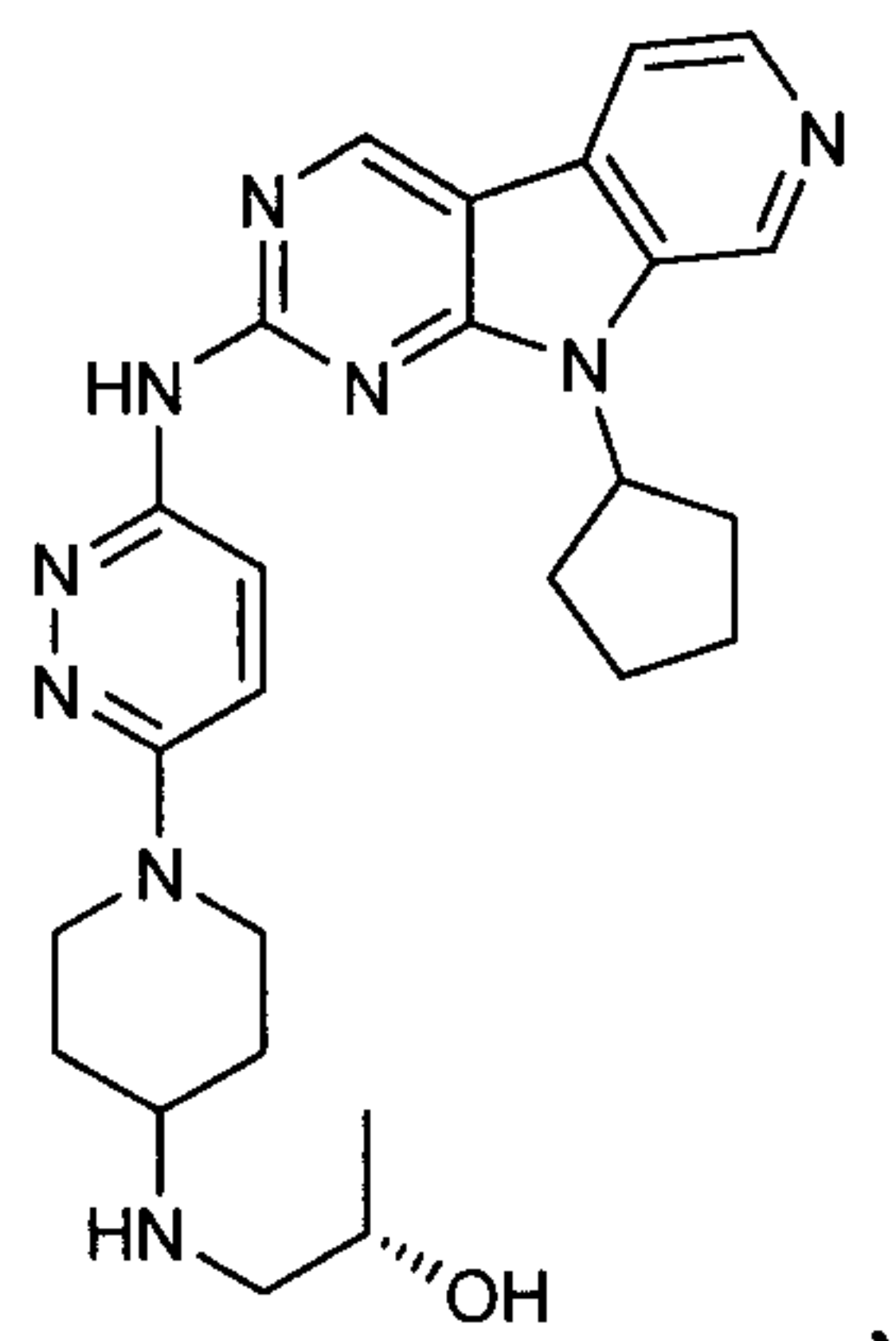


376. The compound of claim 1, wherein the compound is



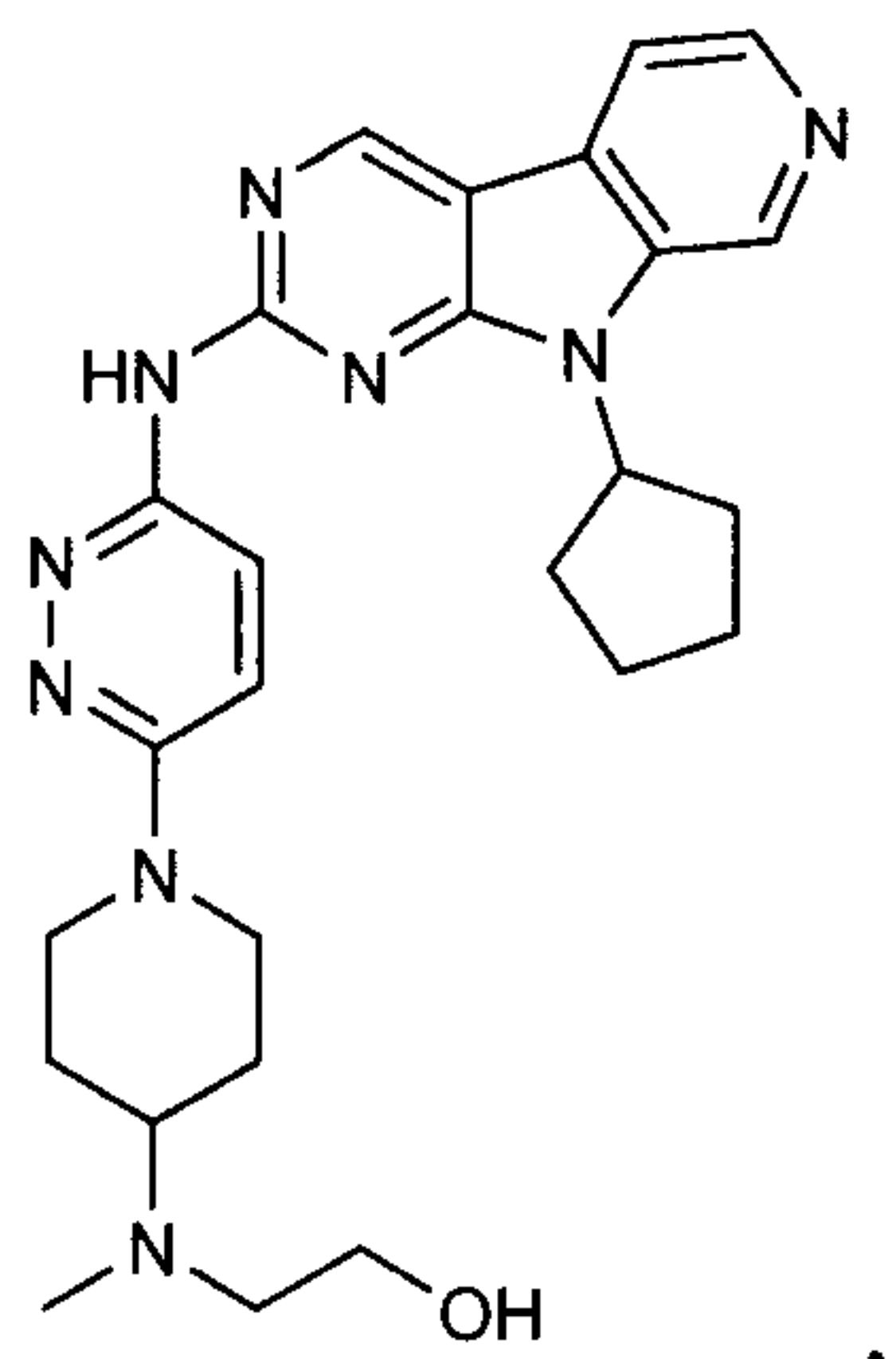
or a pharmaceutically acceptable salt thereof.

377. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

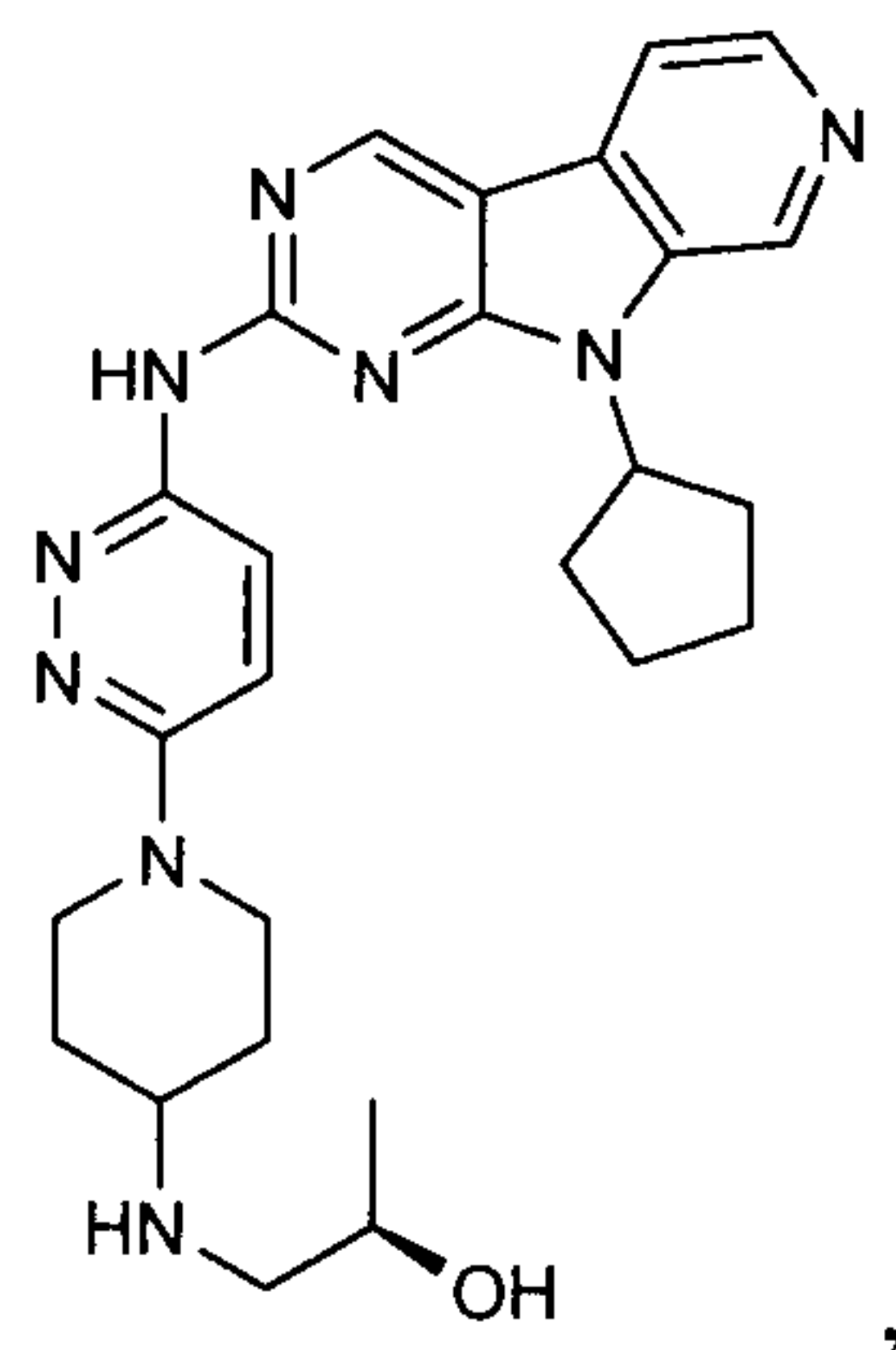
378. The compound of claim 1, wherein the compound is





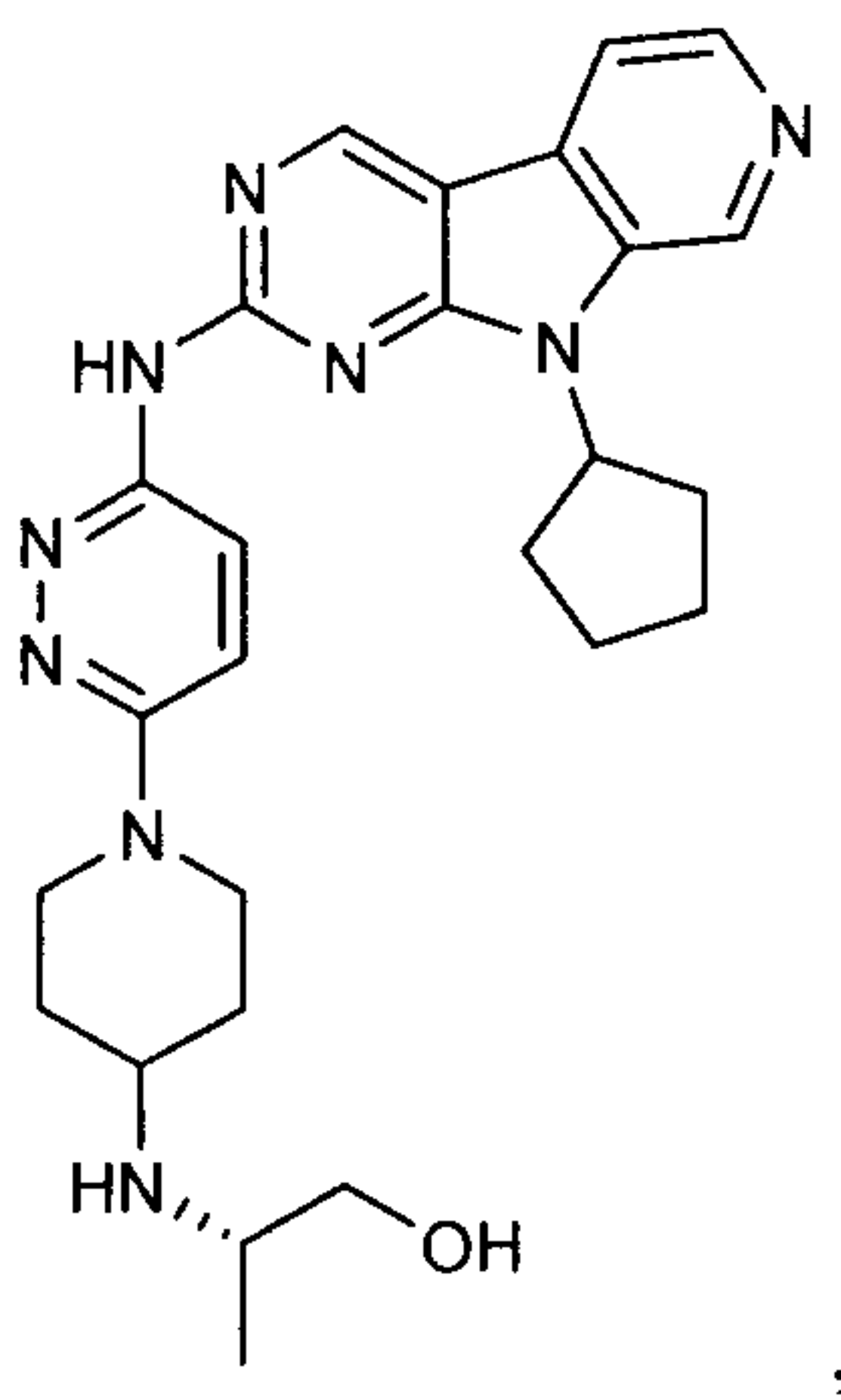
or a pharmaceutically acceptable salt thereof.

379. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

380. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

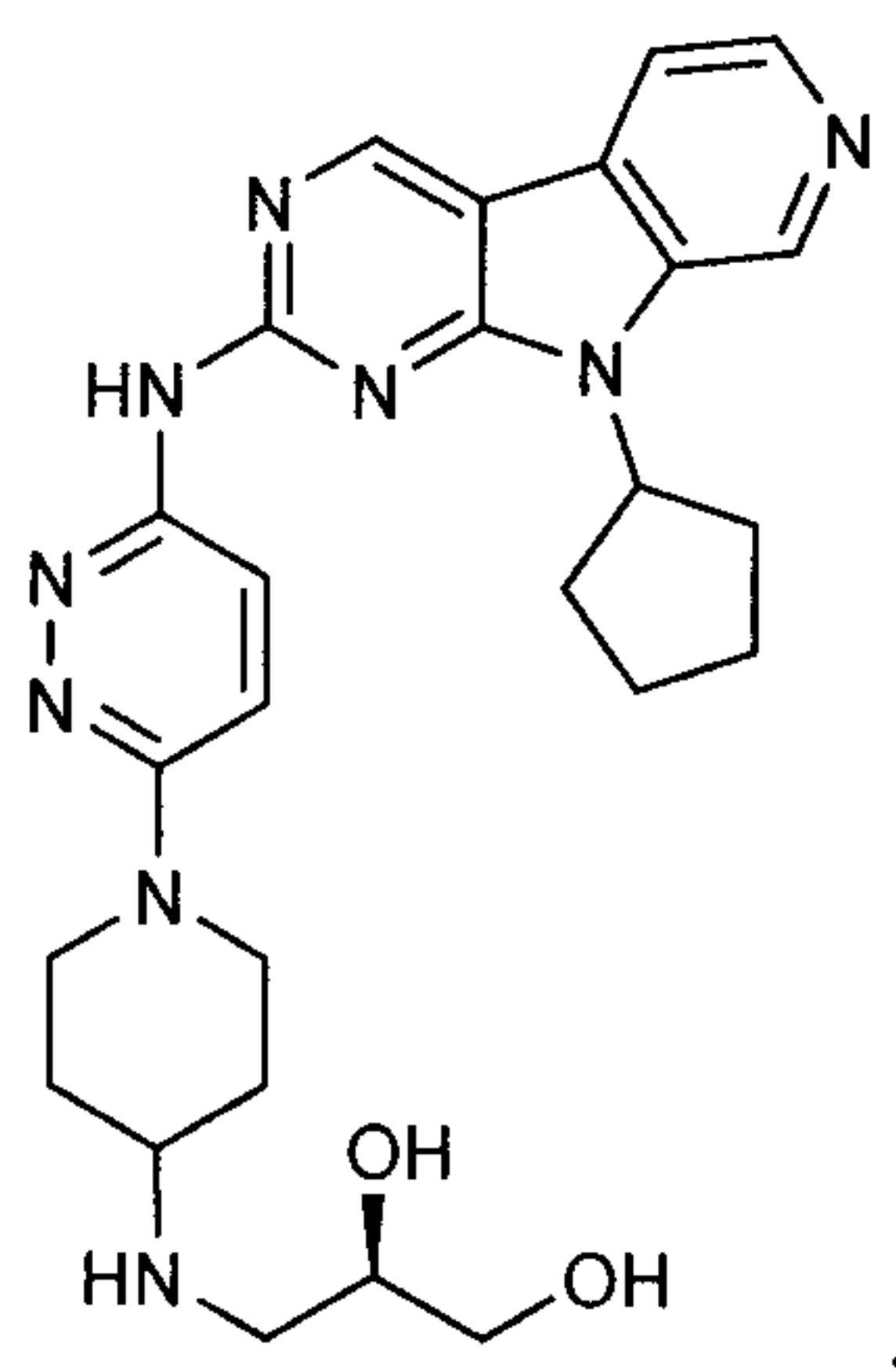






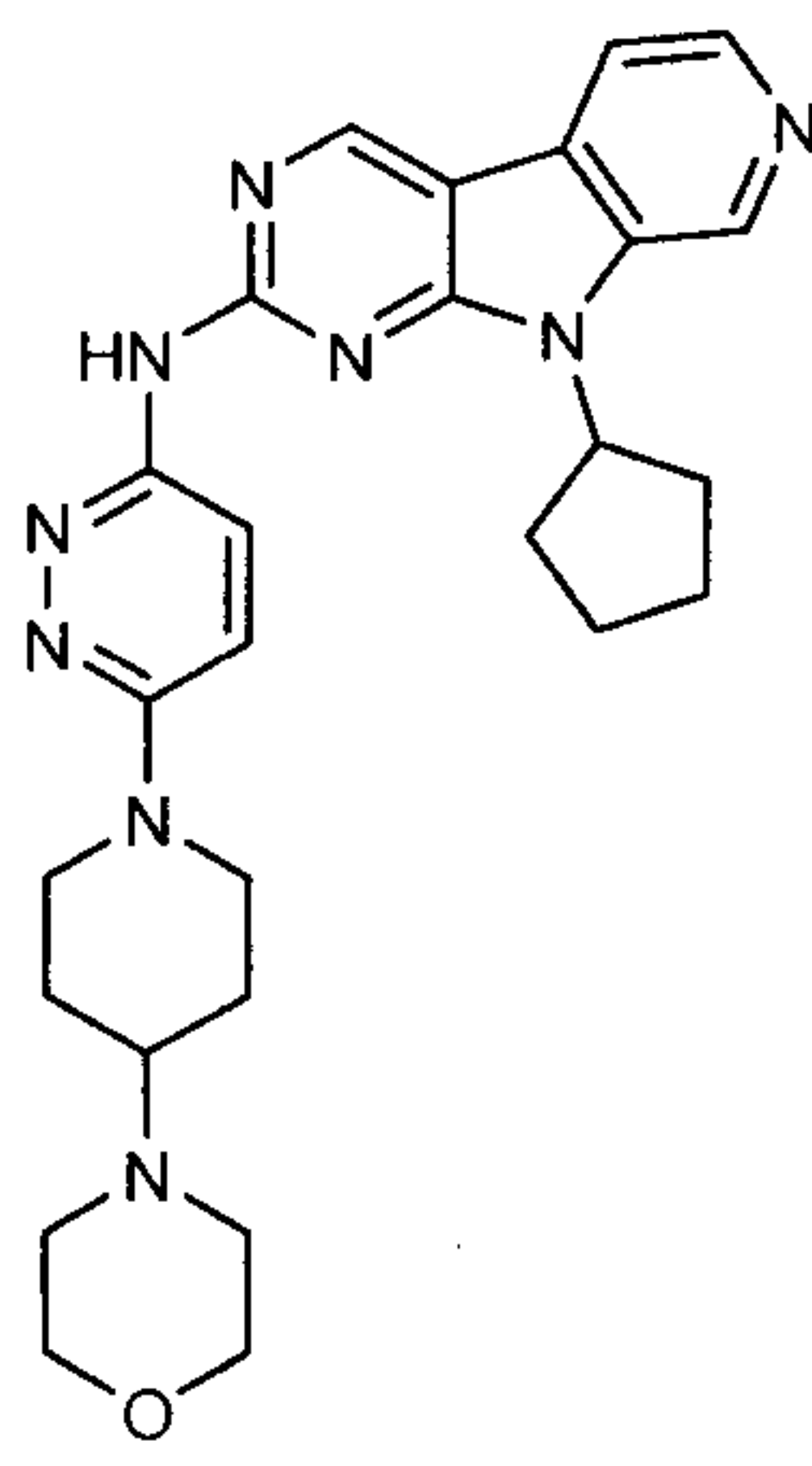
or a pharmaceutically acceptable salt thereof.

384. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

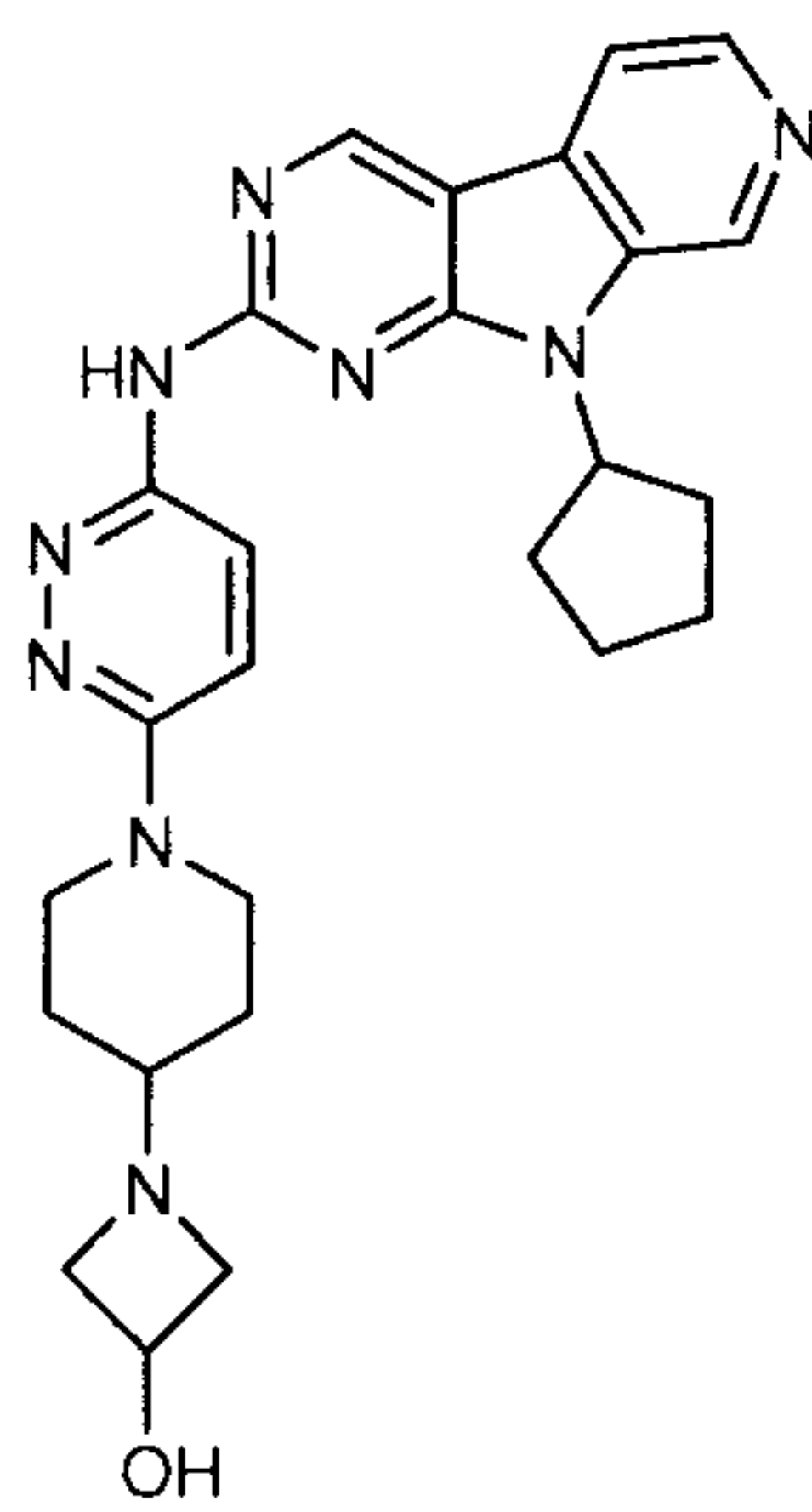
385. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

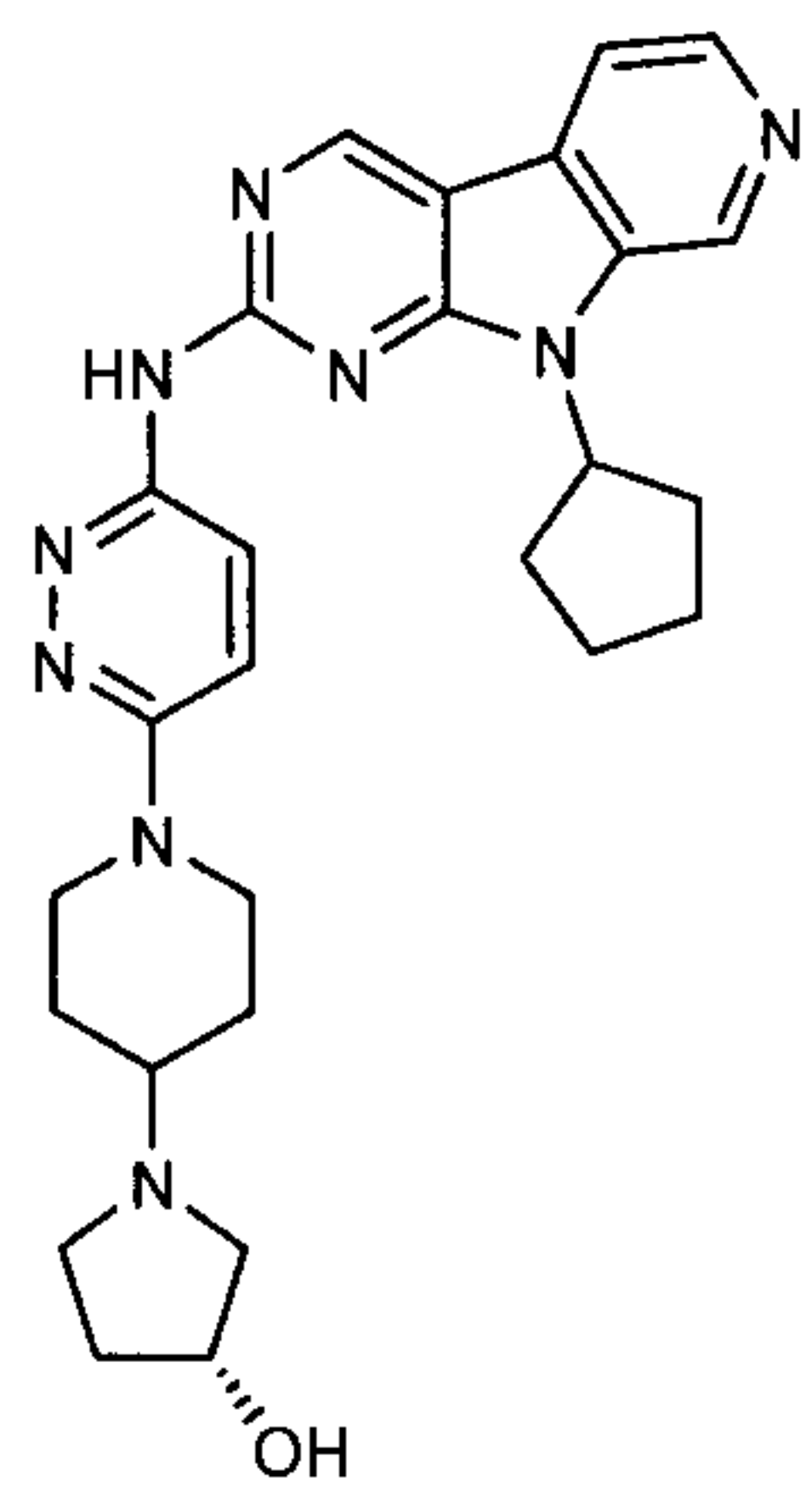


386. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

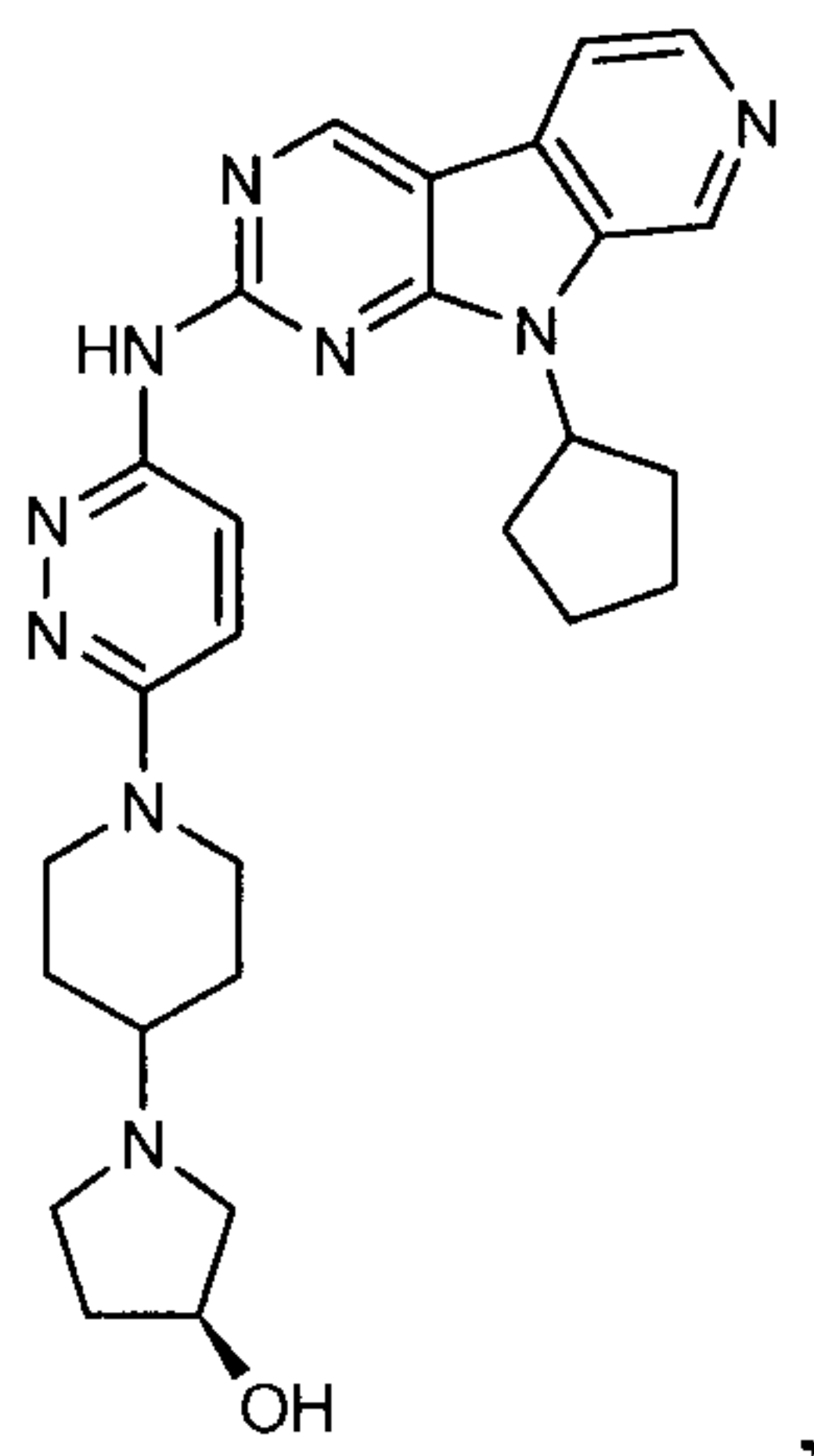
387. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

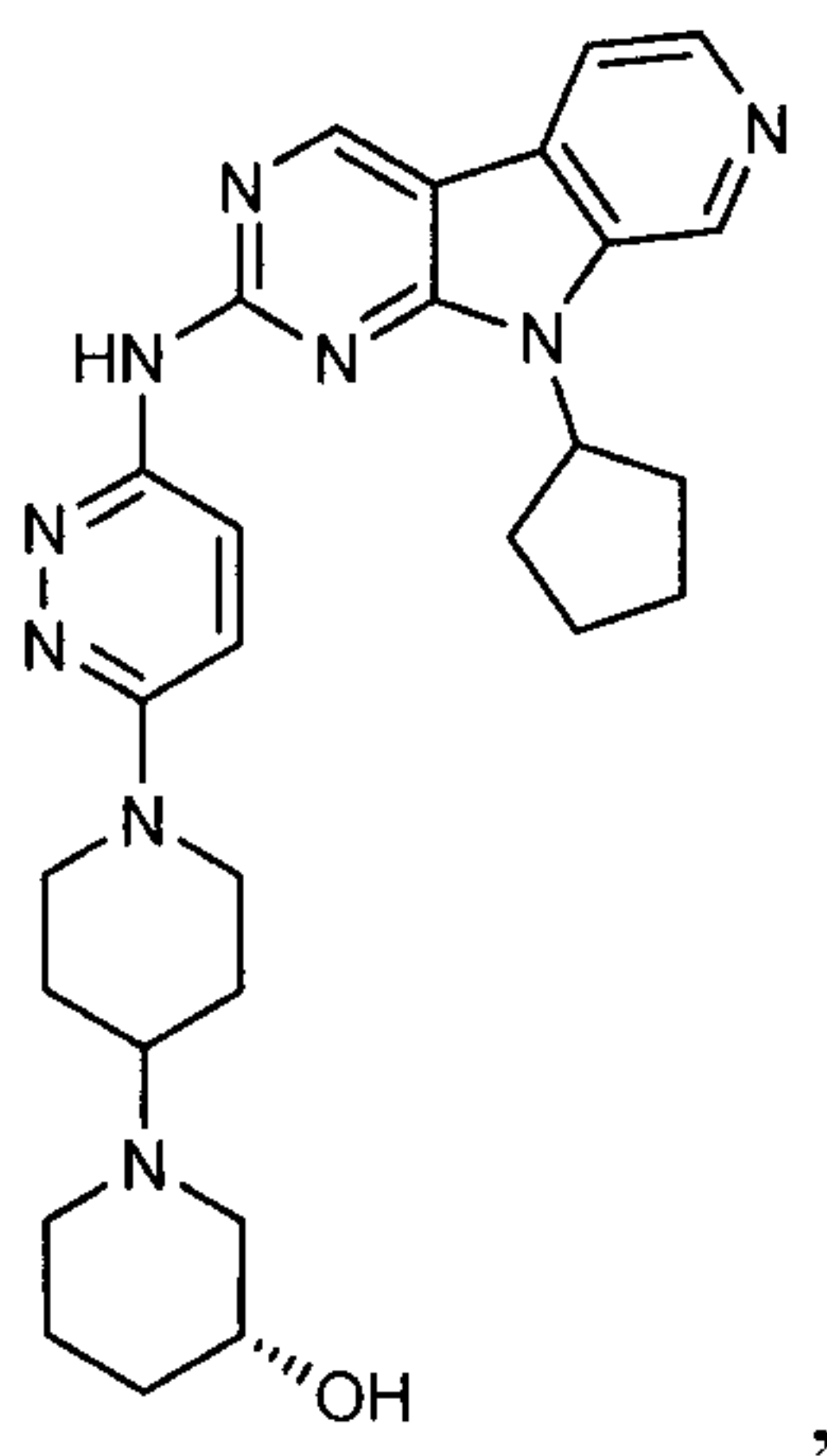


388. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

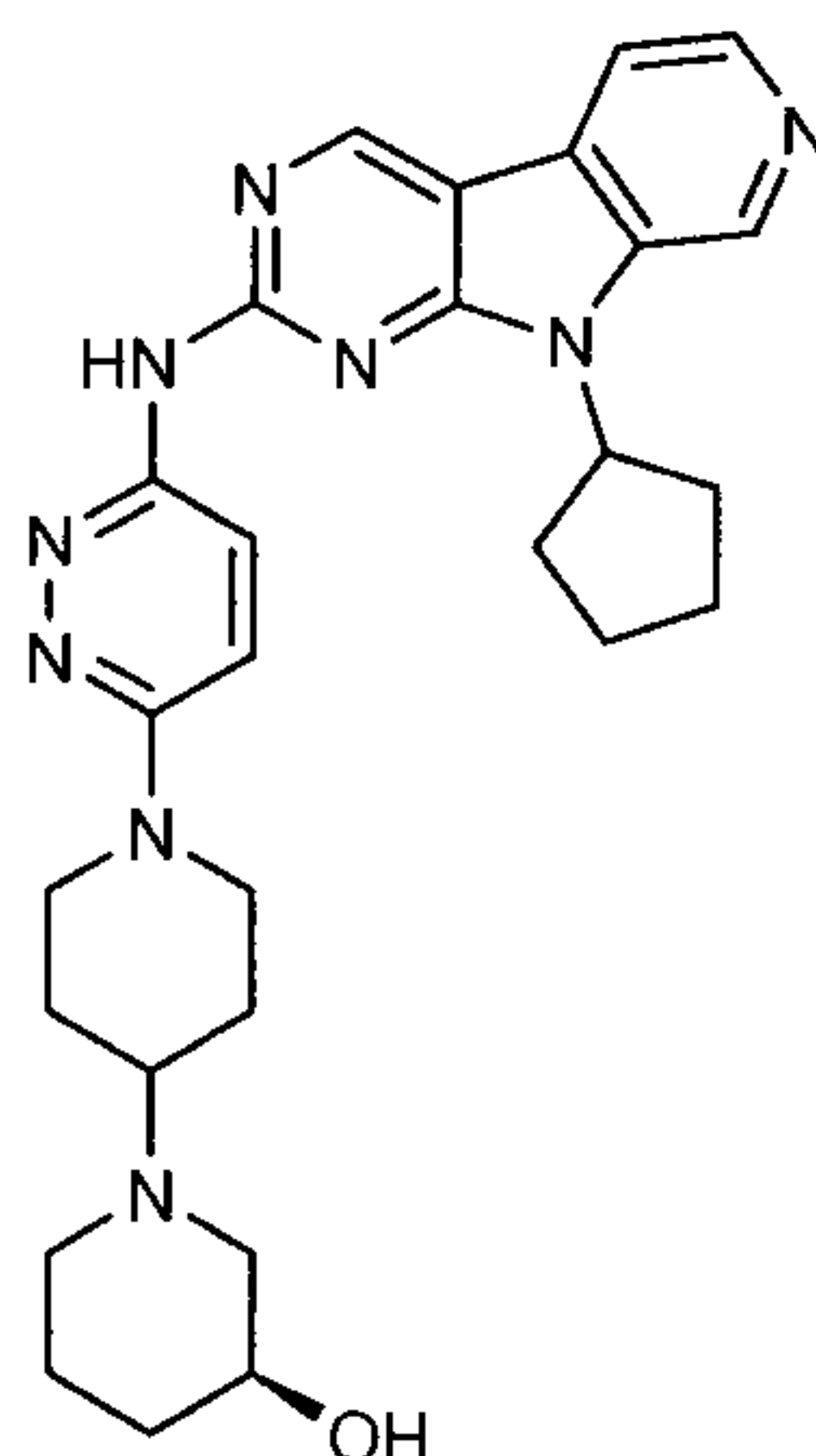
389. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

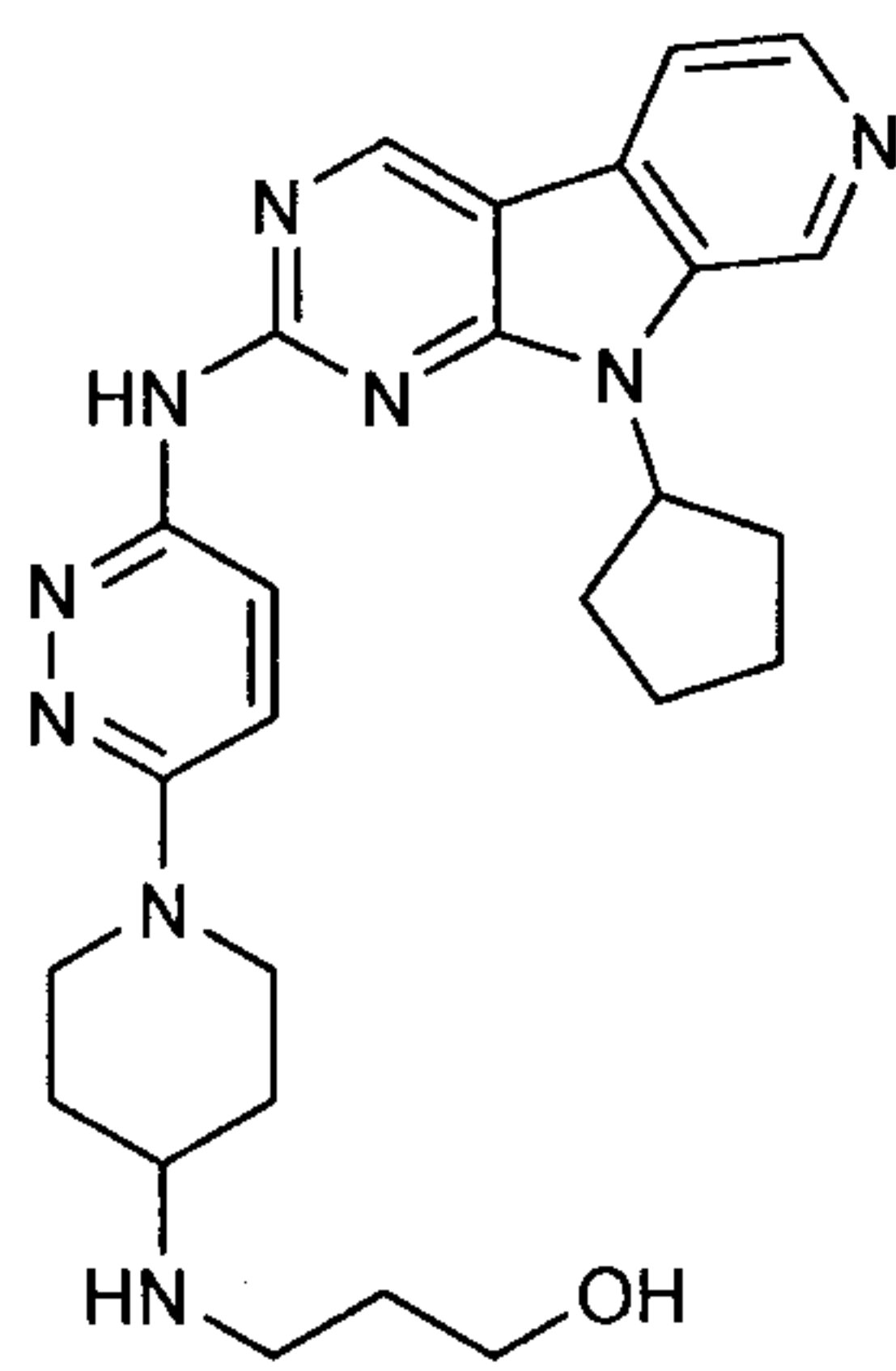


390. The compound of claim 1, wherein the compound is



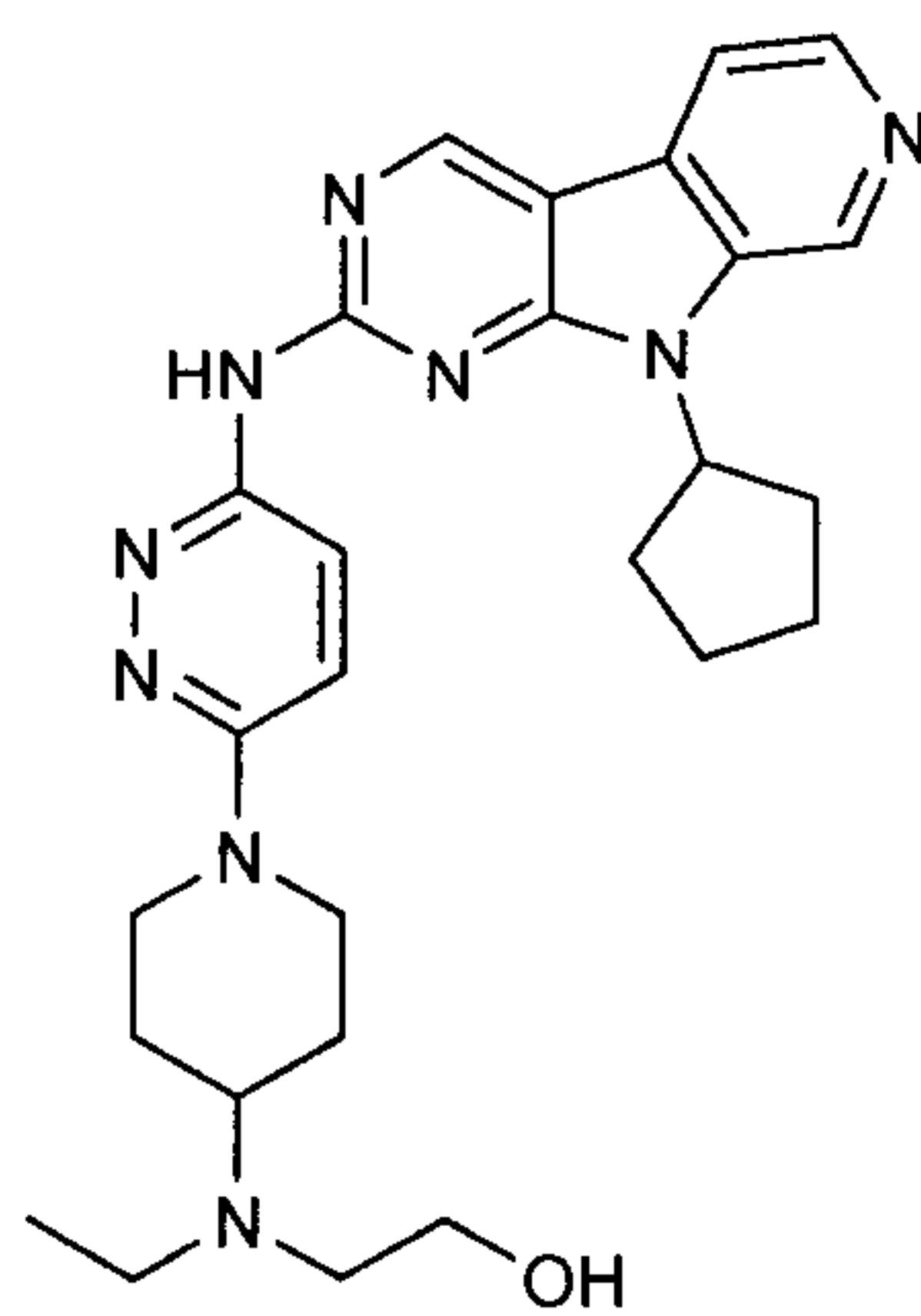
or a pharmaceutically acceptable salt thereof.

391. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

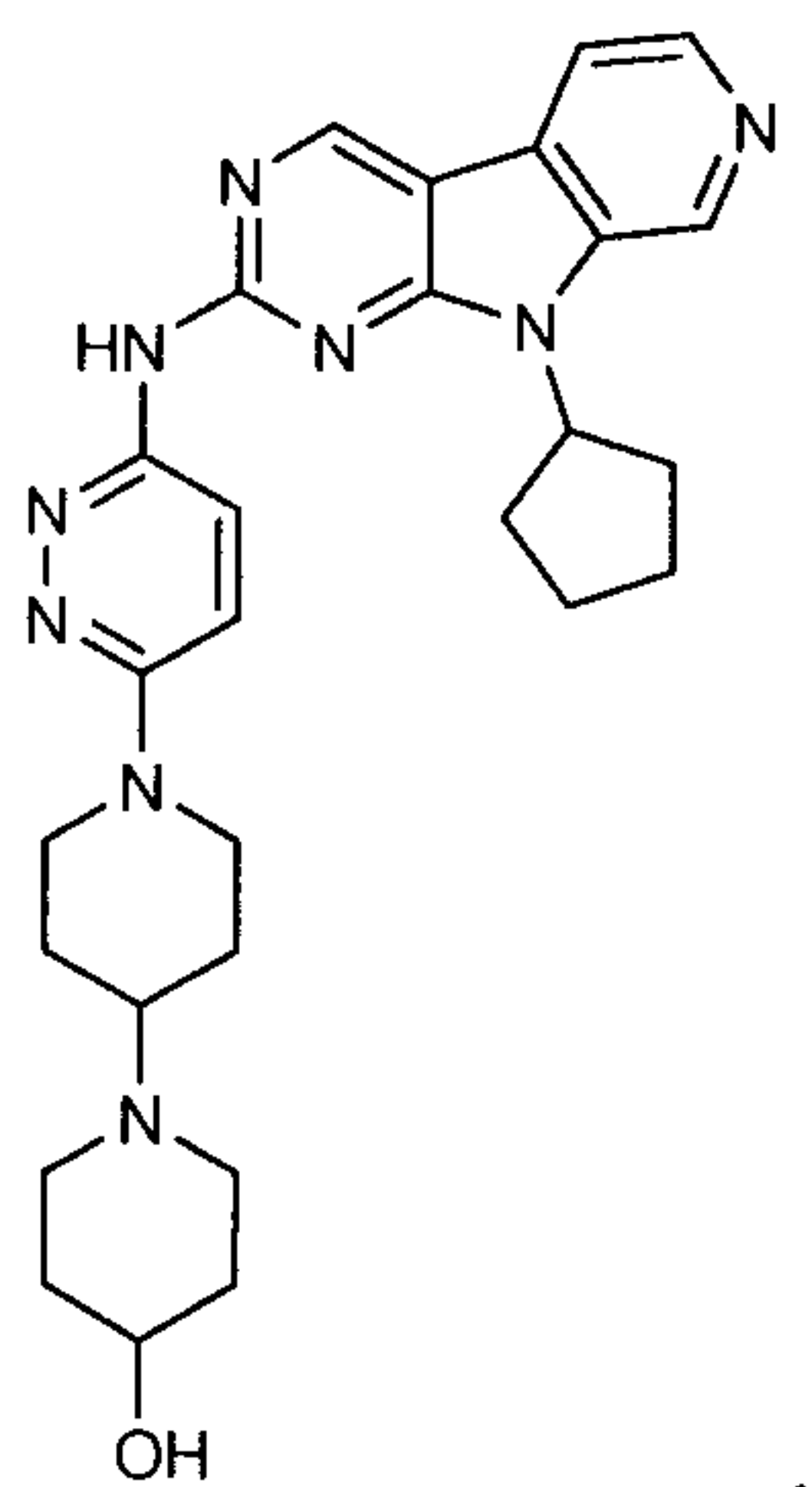
392. The compound of claim 1, wherein the compound is





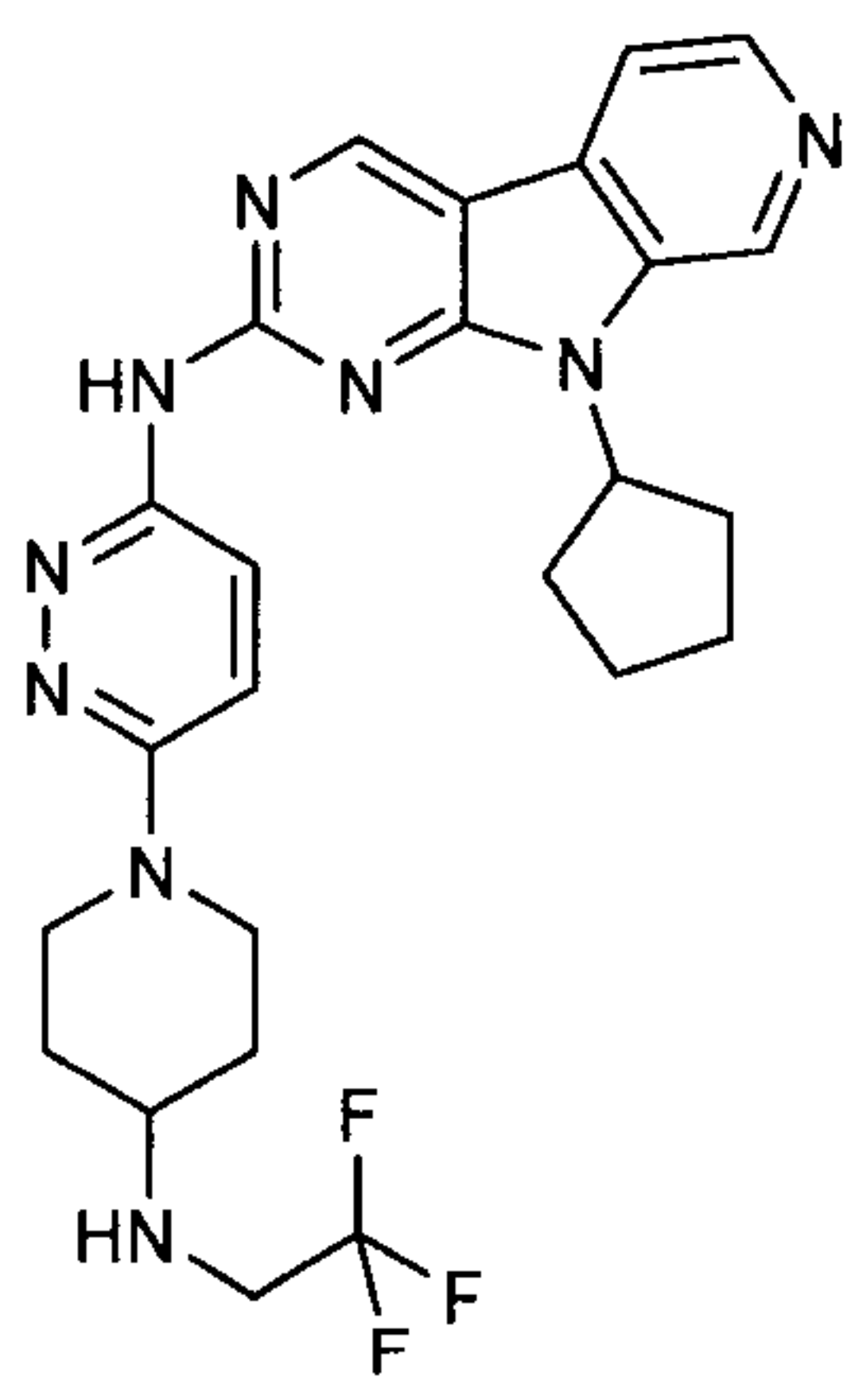
or a pharmaceutically acceptable salt thereof.

393. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

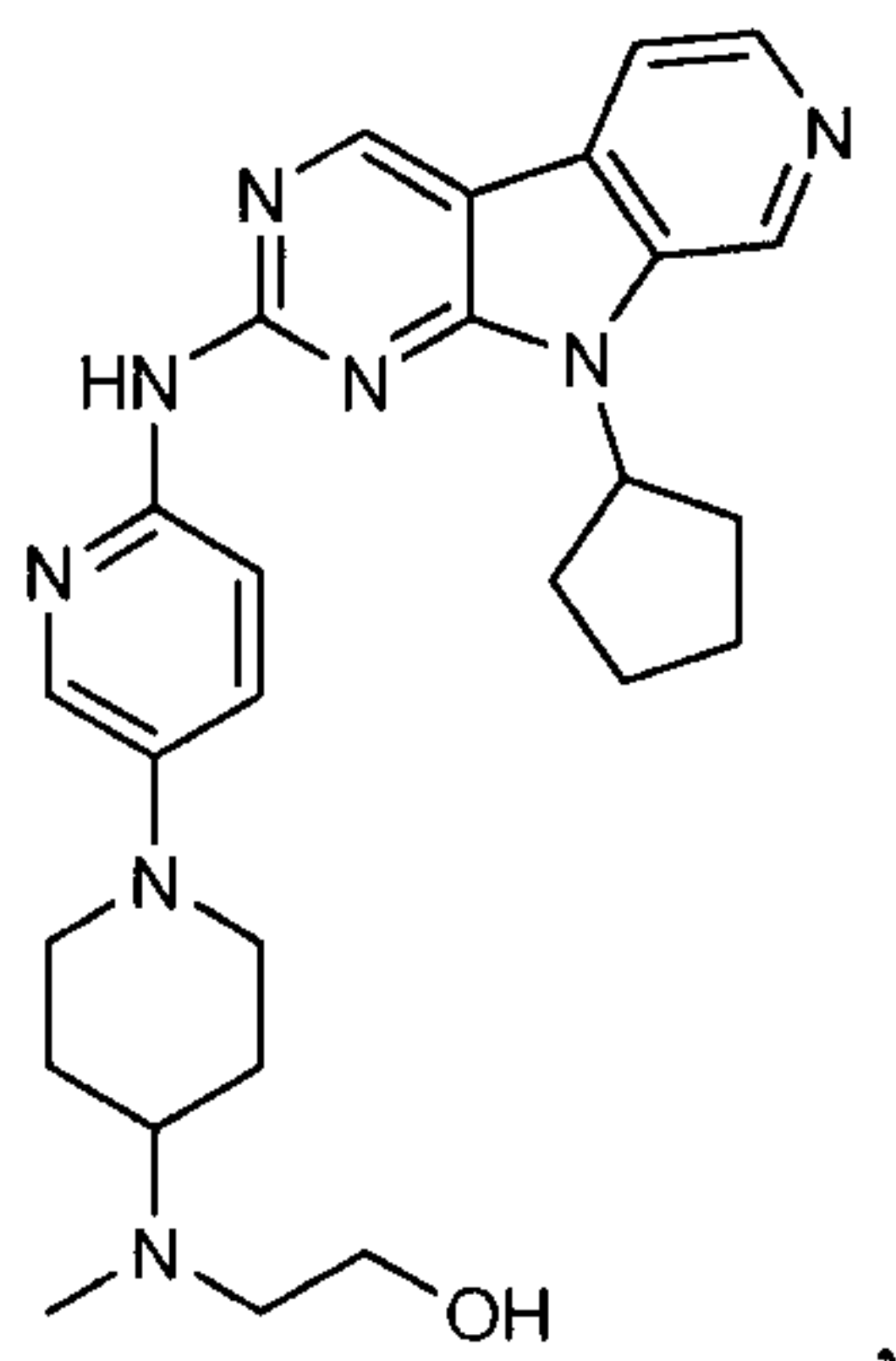
394. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

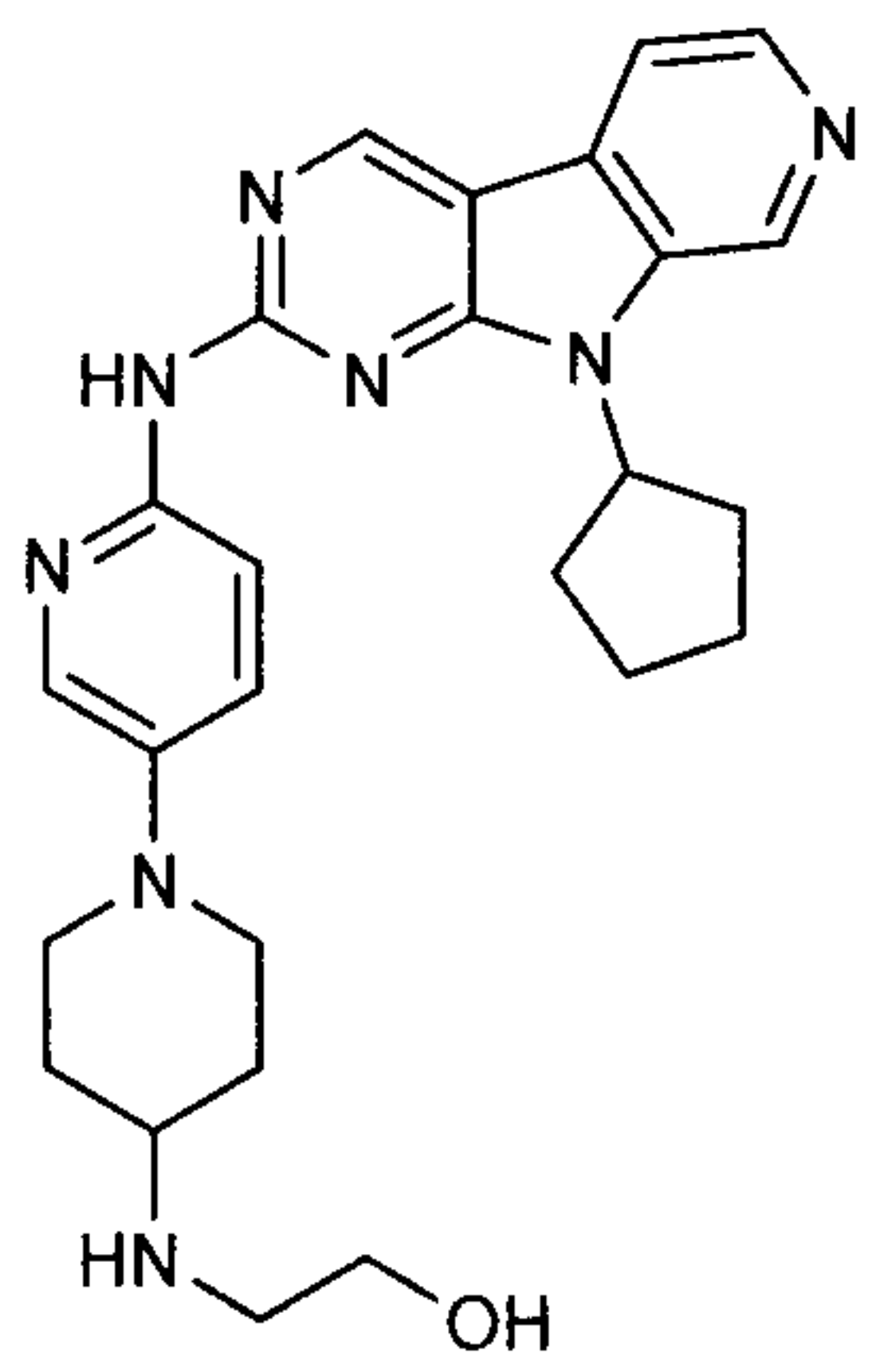


395. The compound of claim 1, wherein the compound is



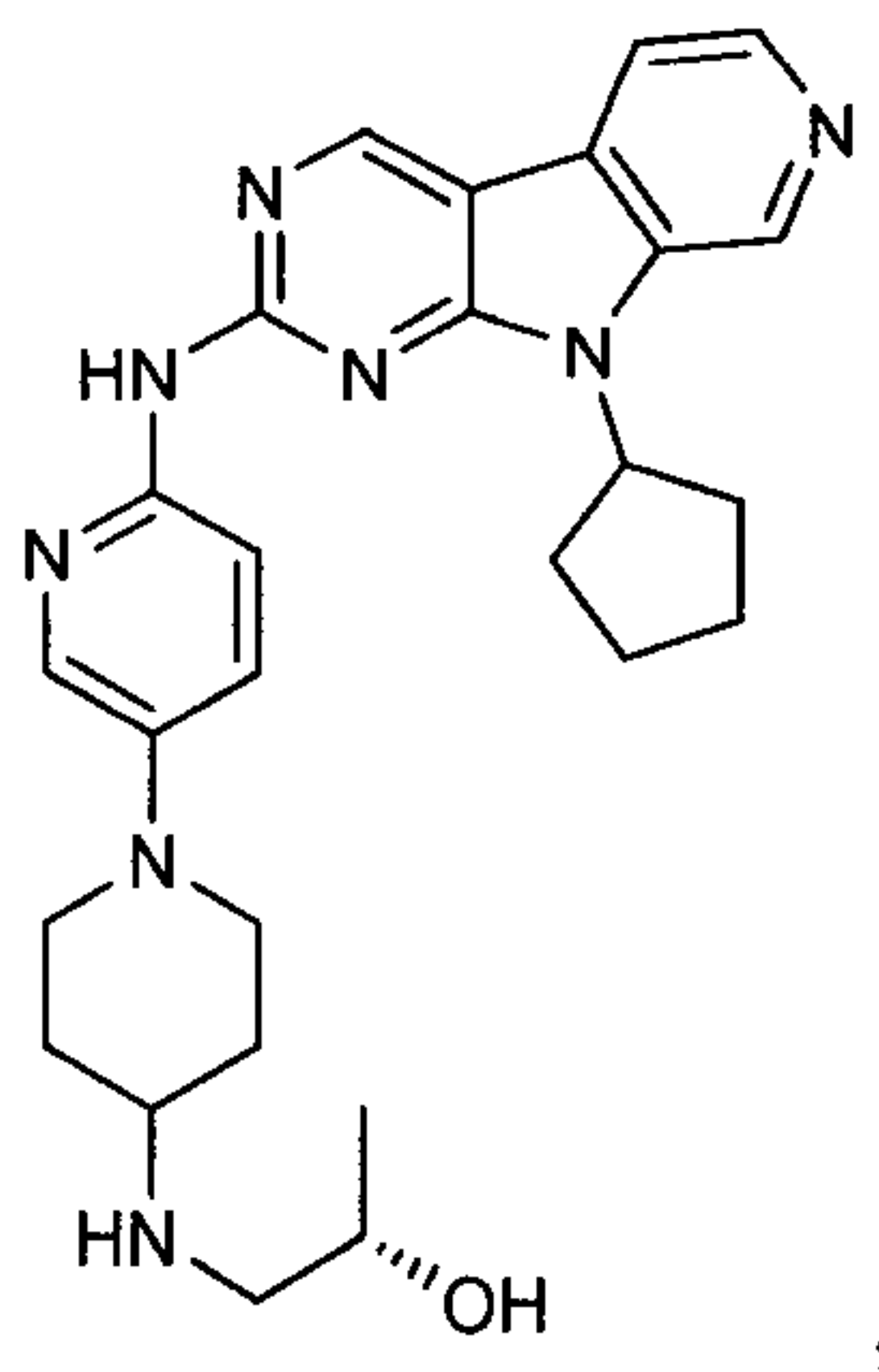
or a pharmaceutically acceptable salt thereof.

396. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

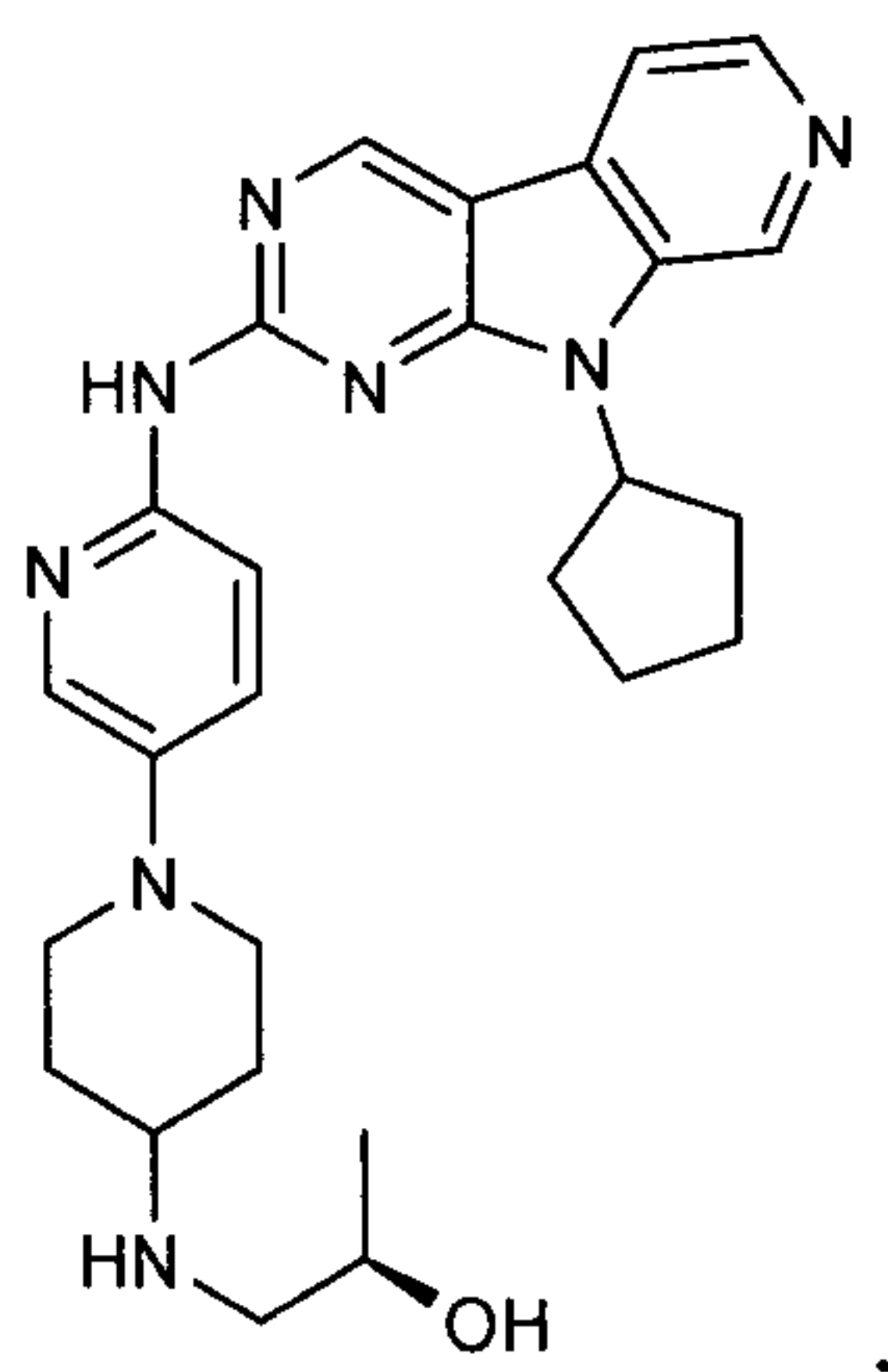
397. The compound of claim 1, wherein the compound is





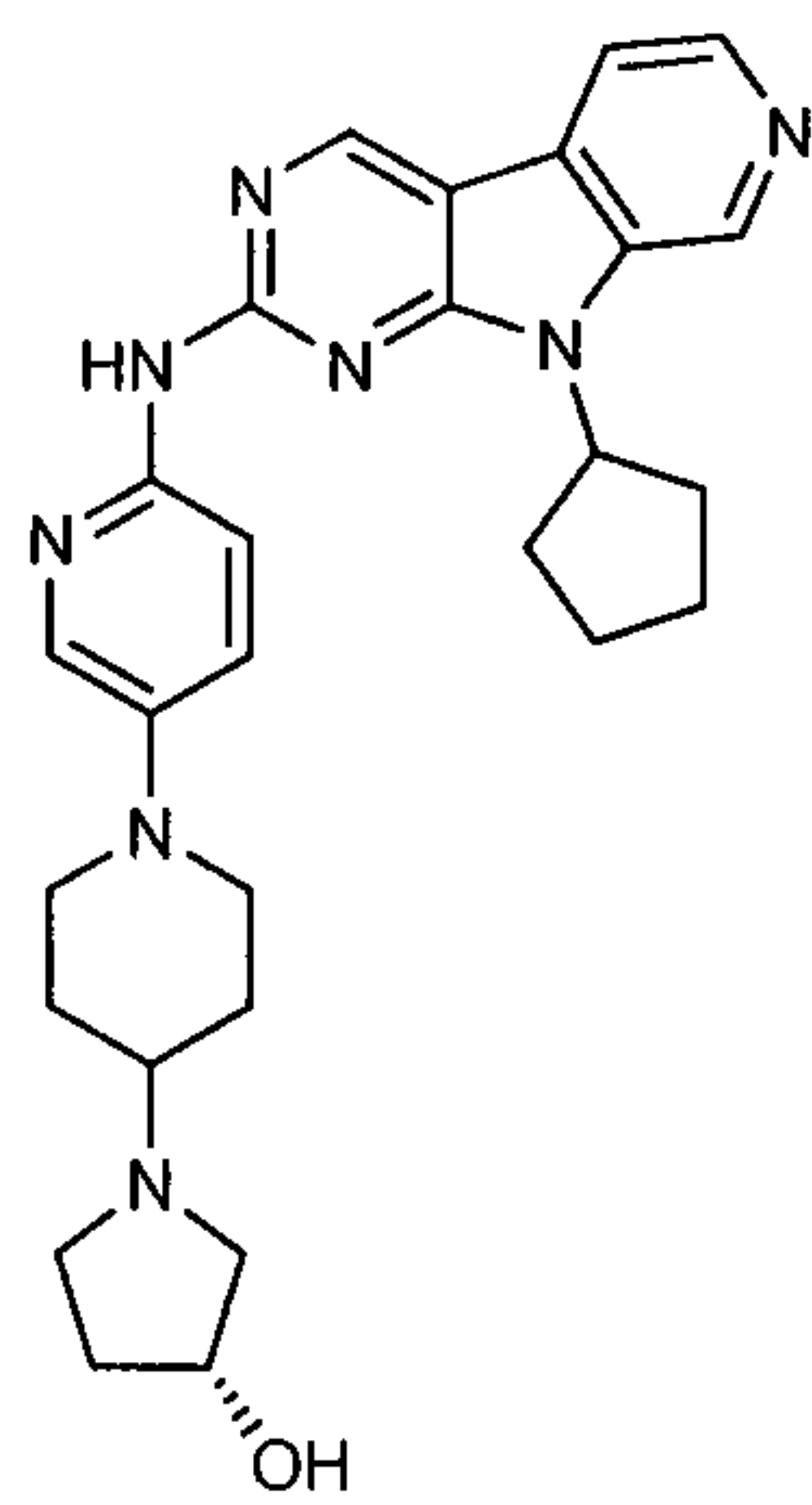
or a pharmaceutically acceptable salt thereof.

398. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

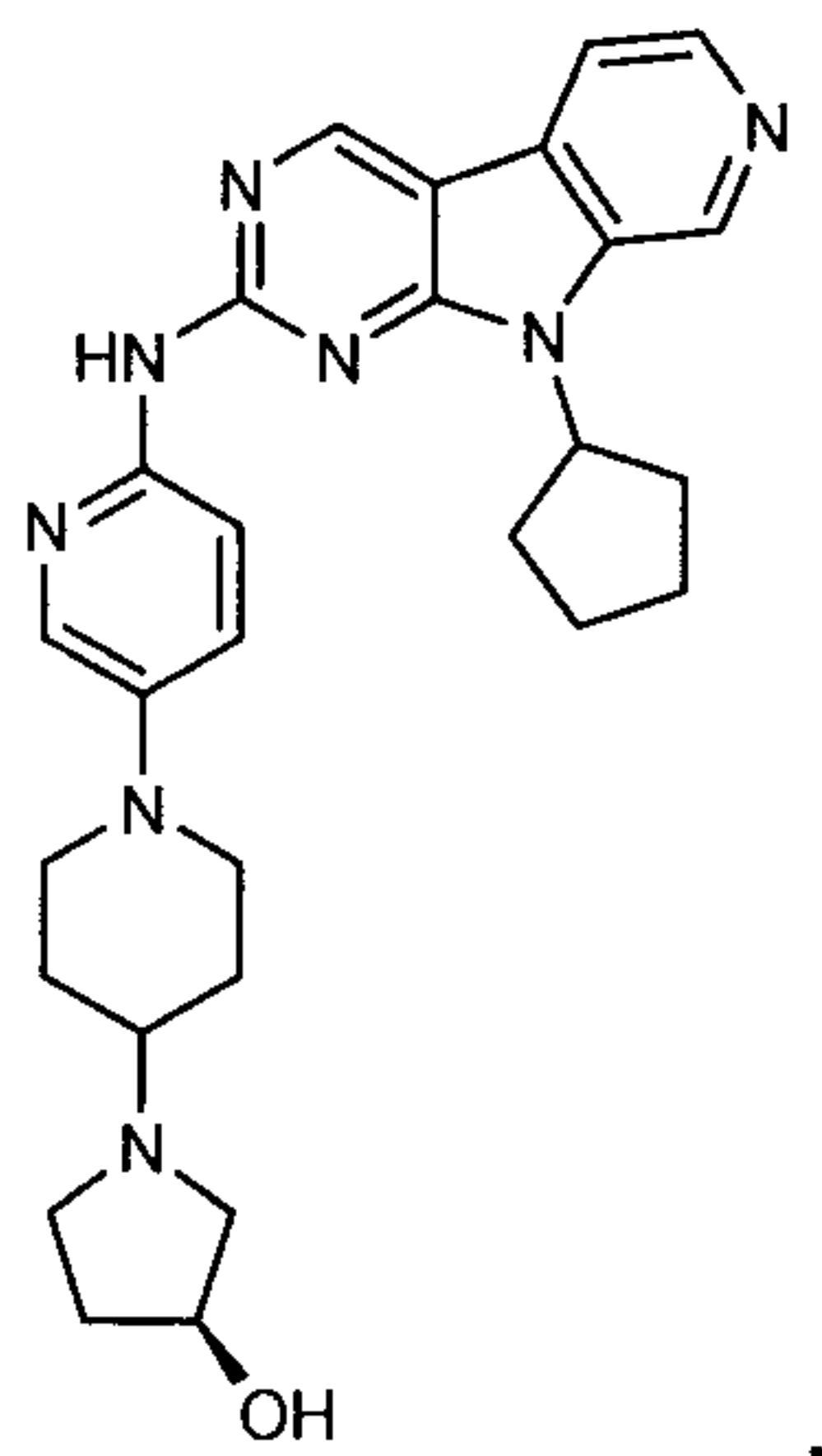
399. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

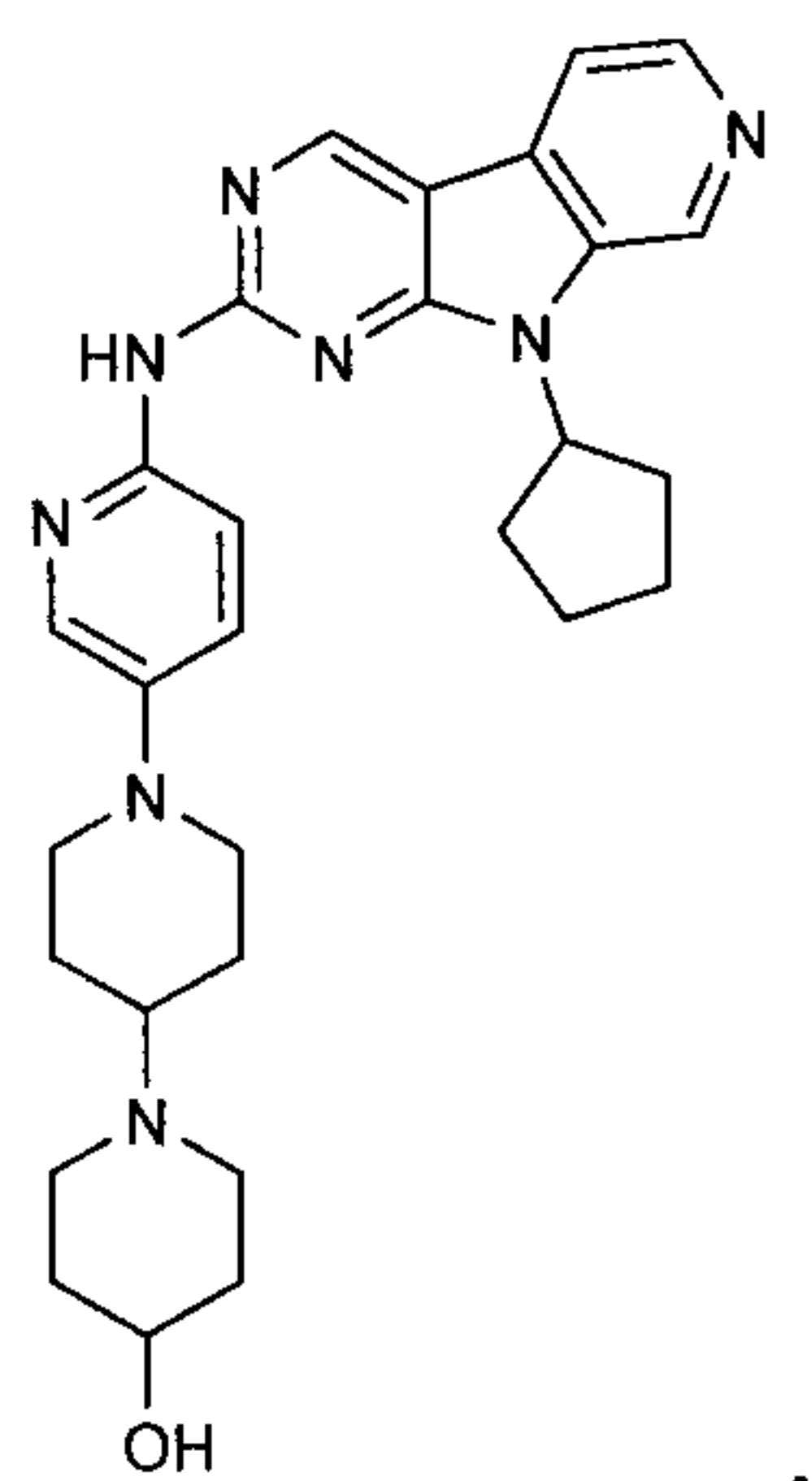


400. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

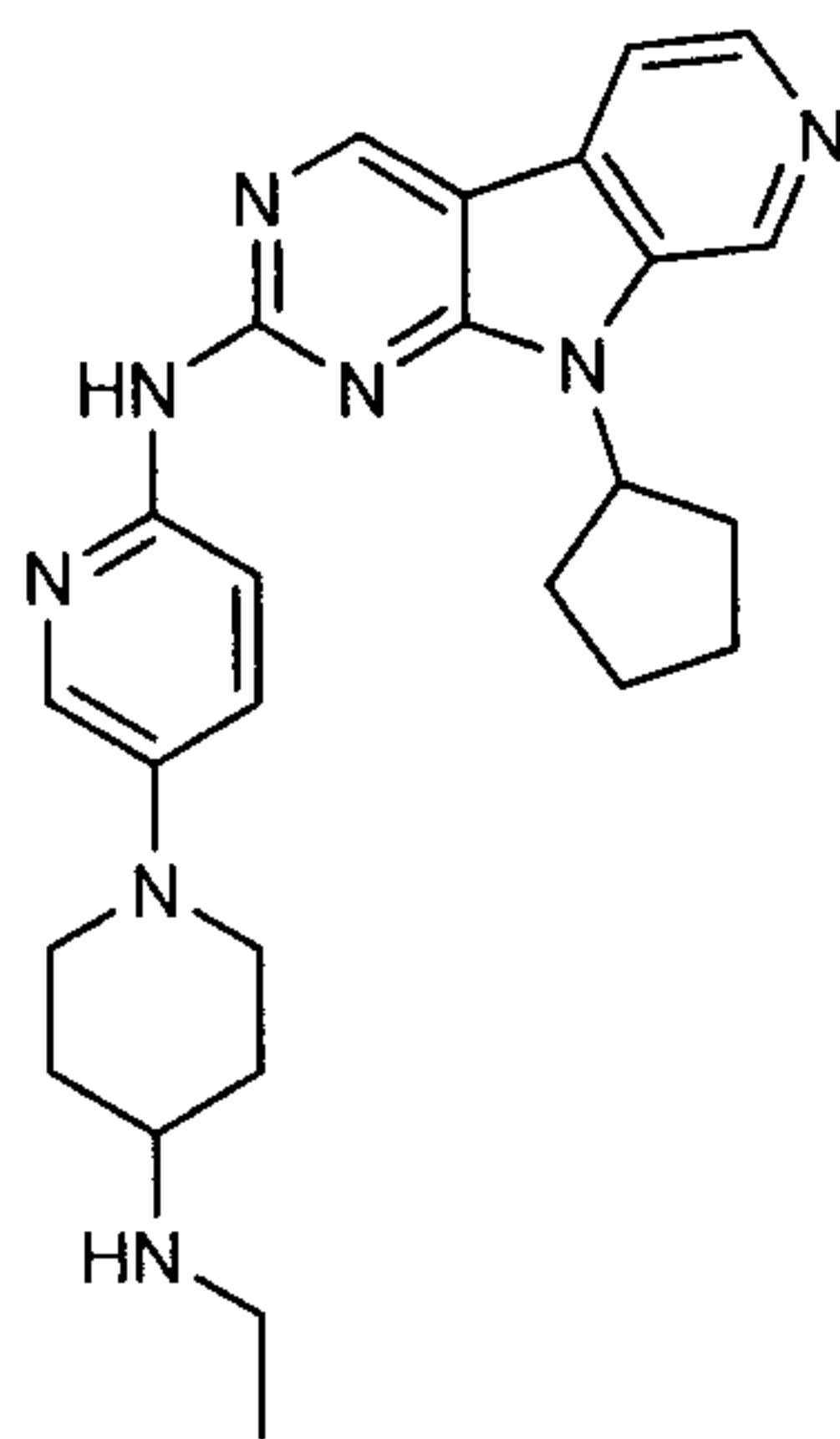
401. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

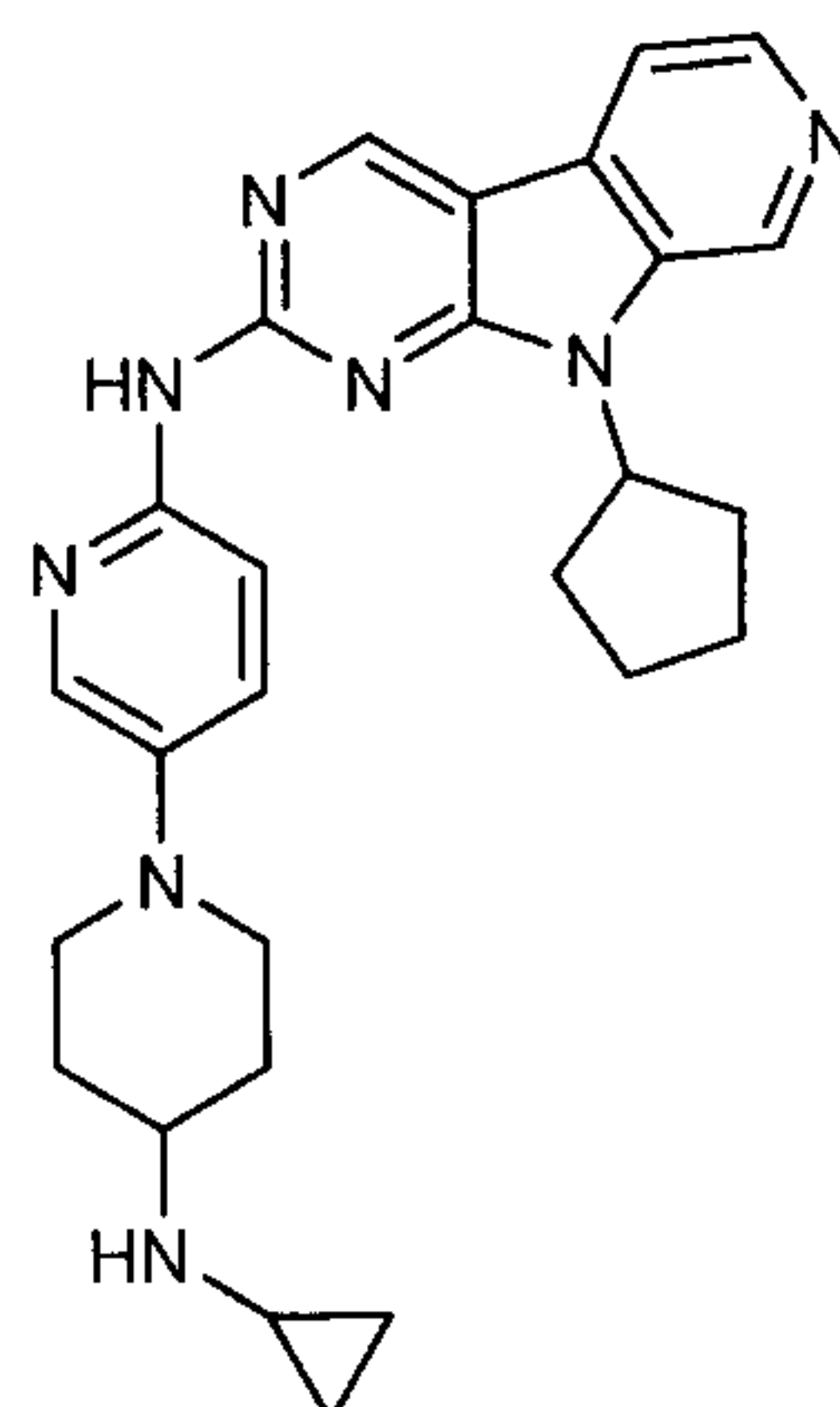


402. The compound of claim 1, wherein the compound is



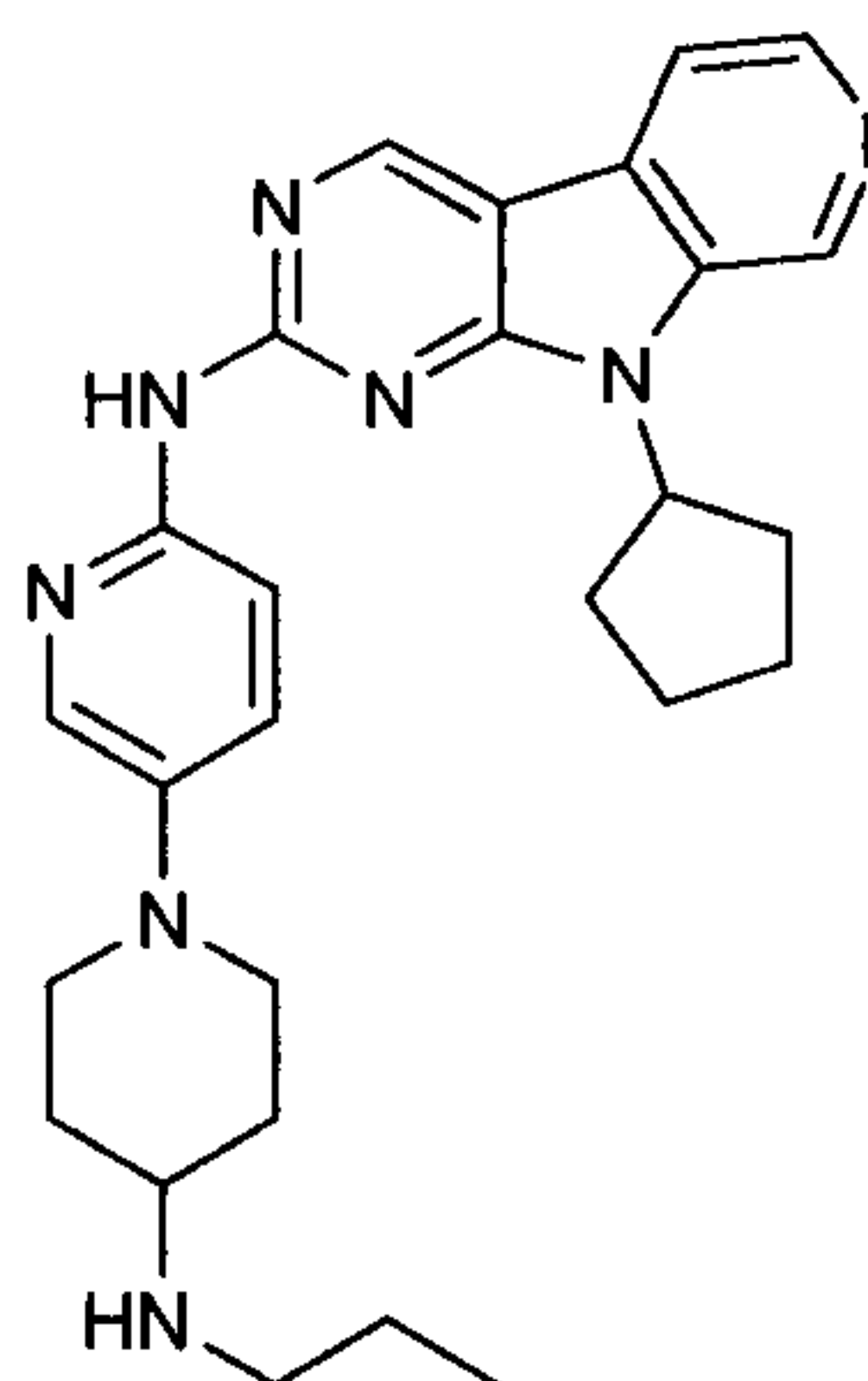
or a pharmaceutically acceptable salt thereof.

403. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

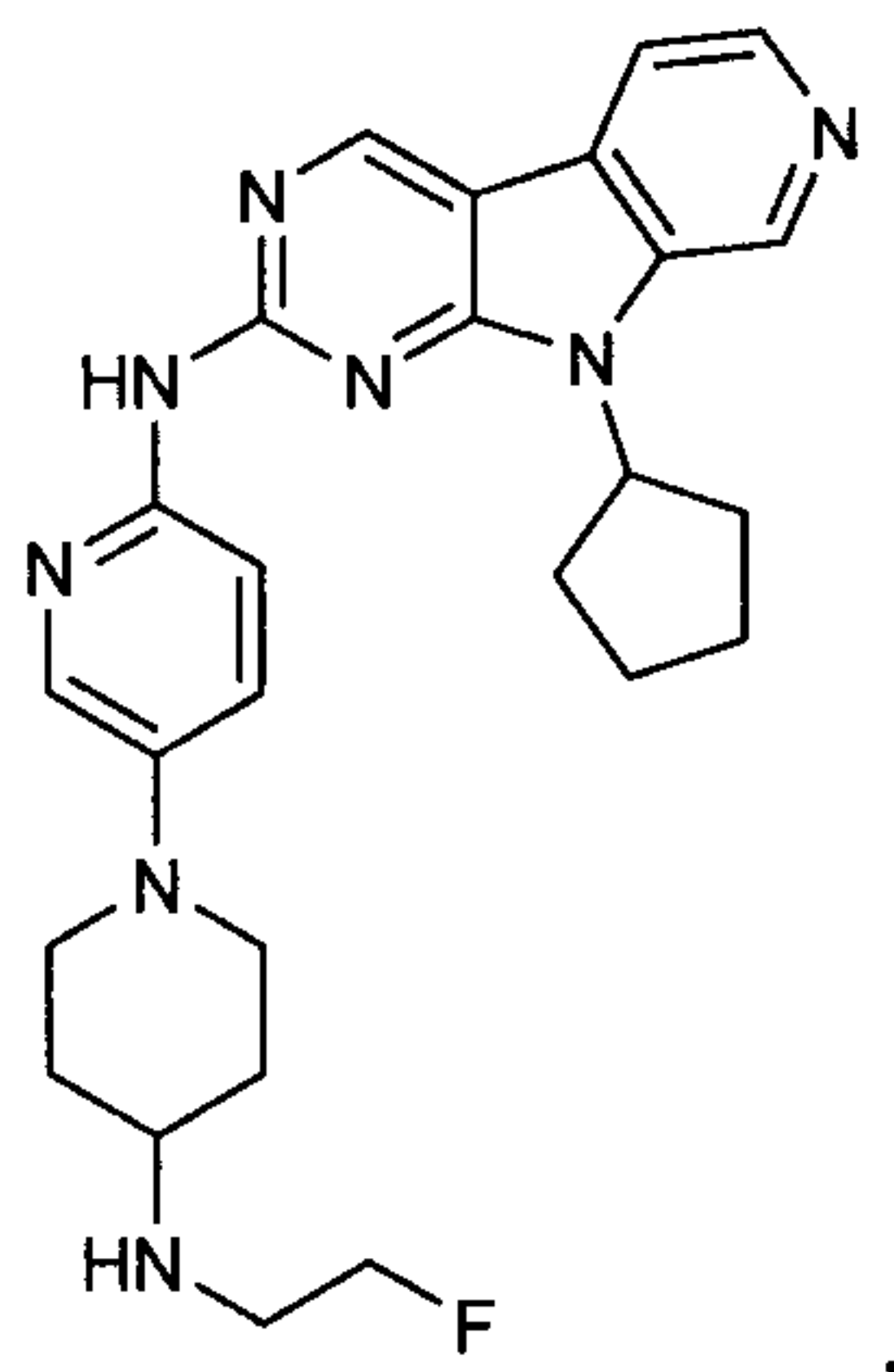
404. The compound of claim 1, wherein the compound is





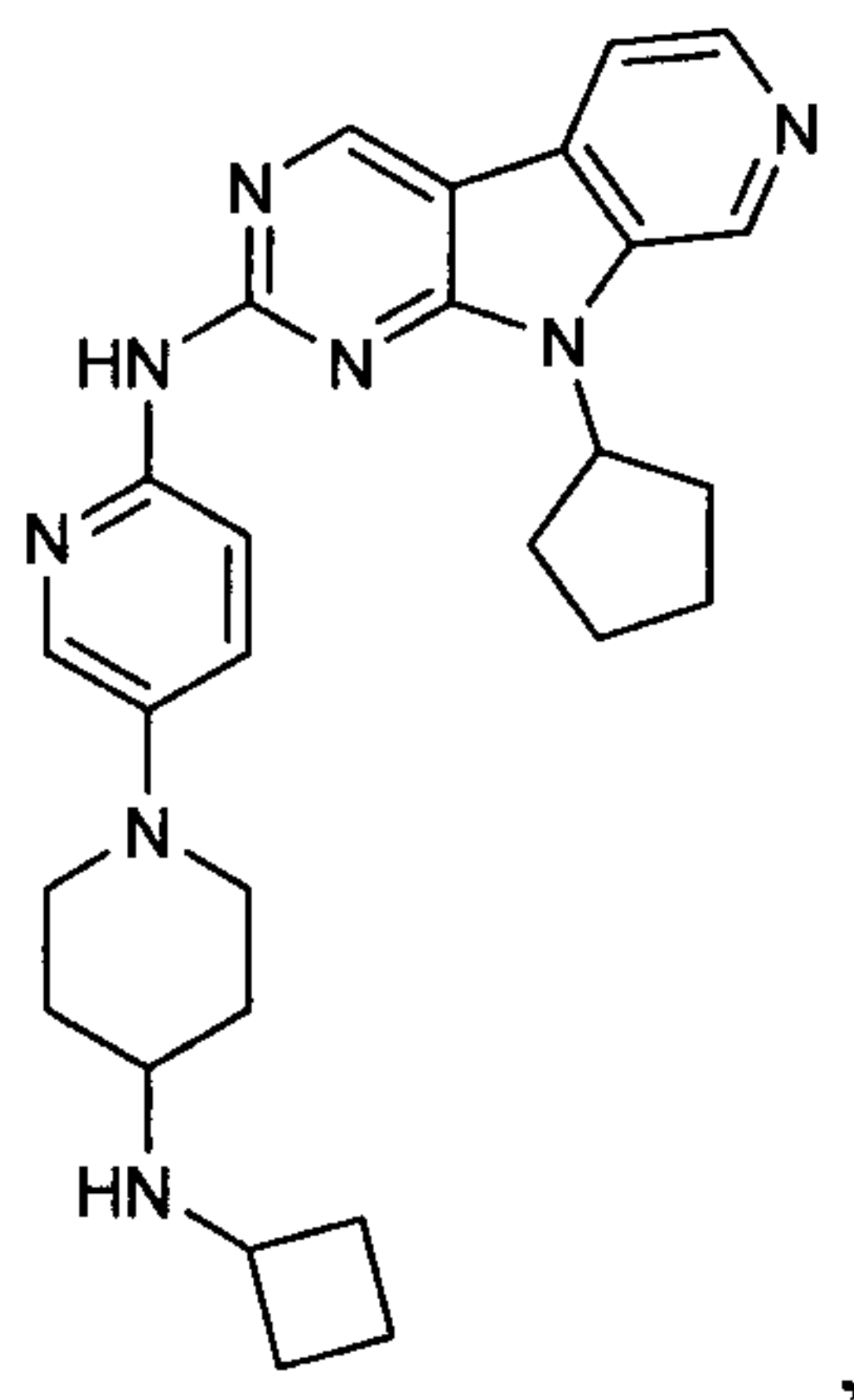
or a pharmaceutically acceptable salt thereof.

405. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

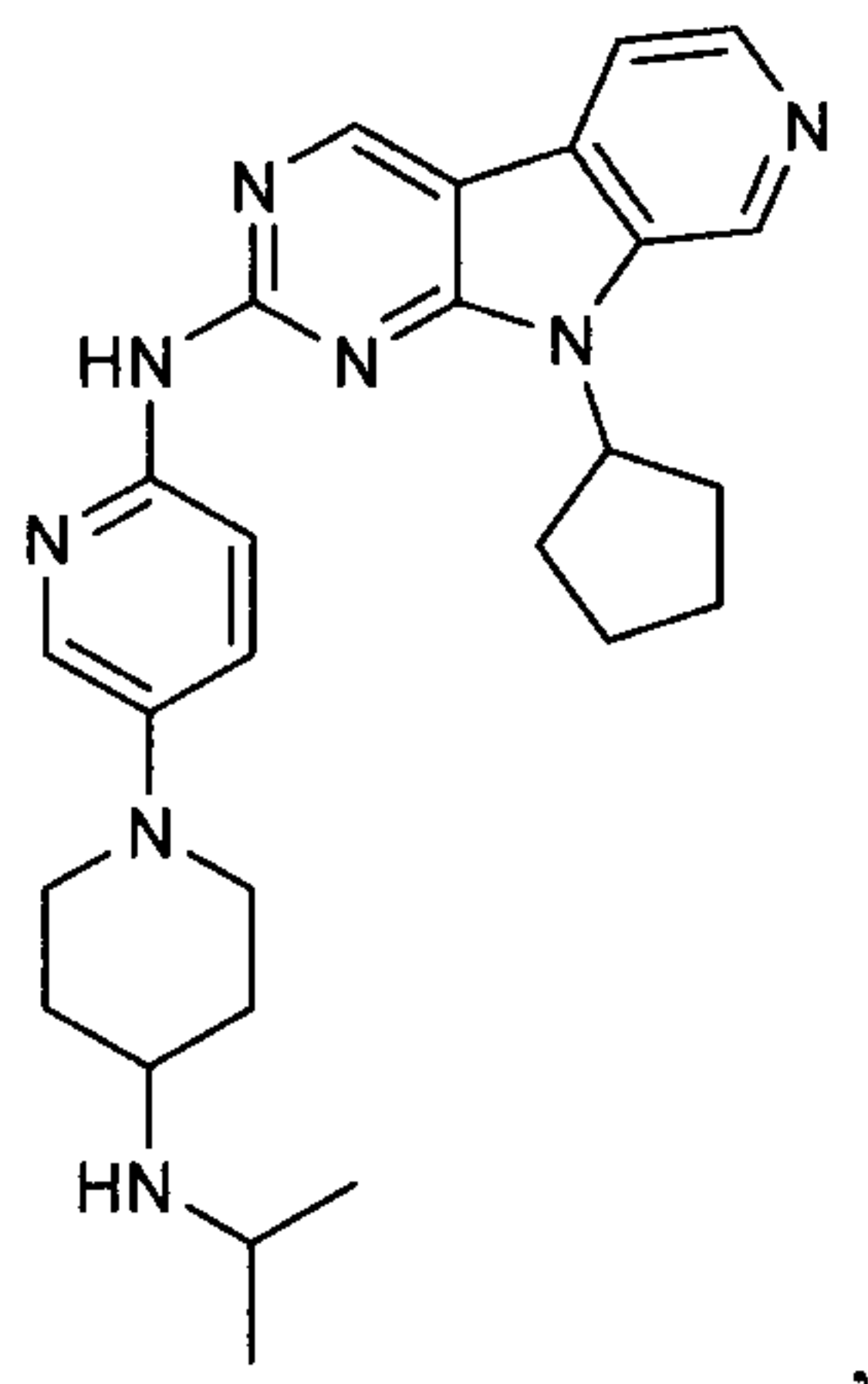
406. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

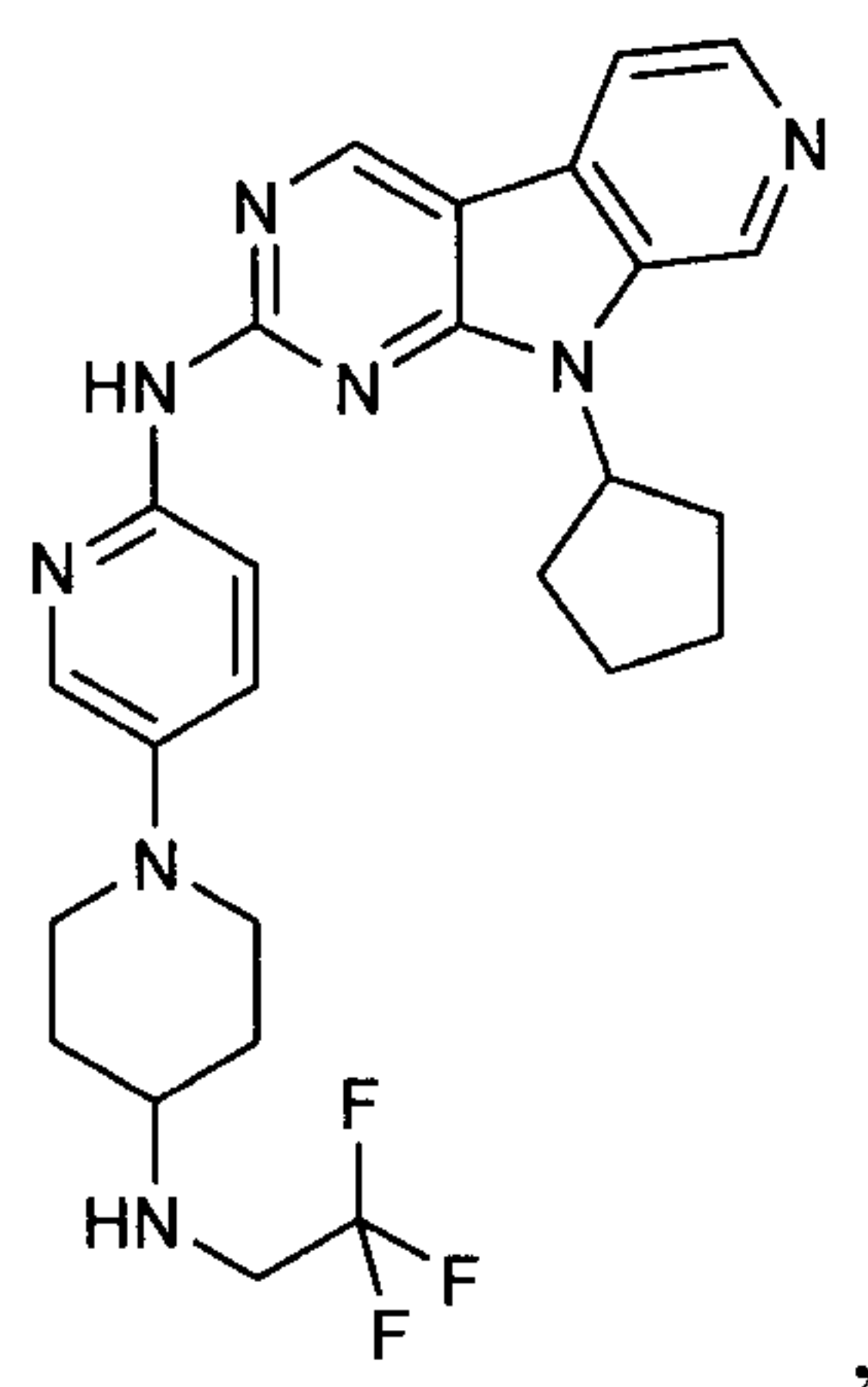


407. The compound of claim 1, wherein the compound is



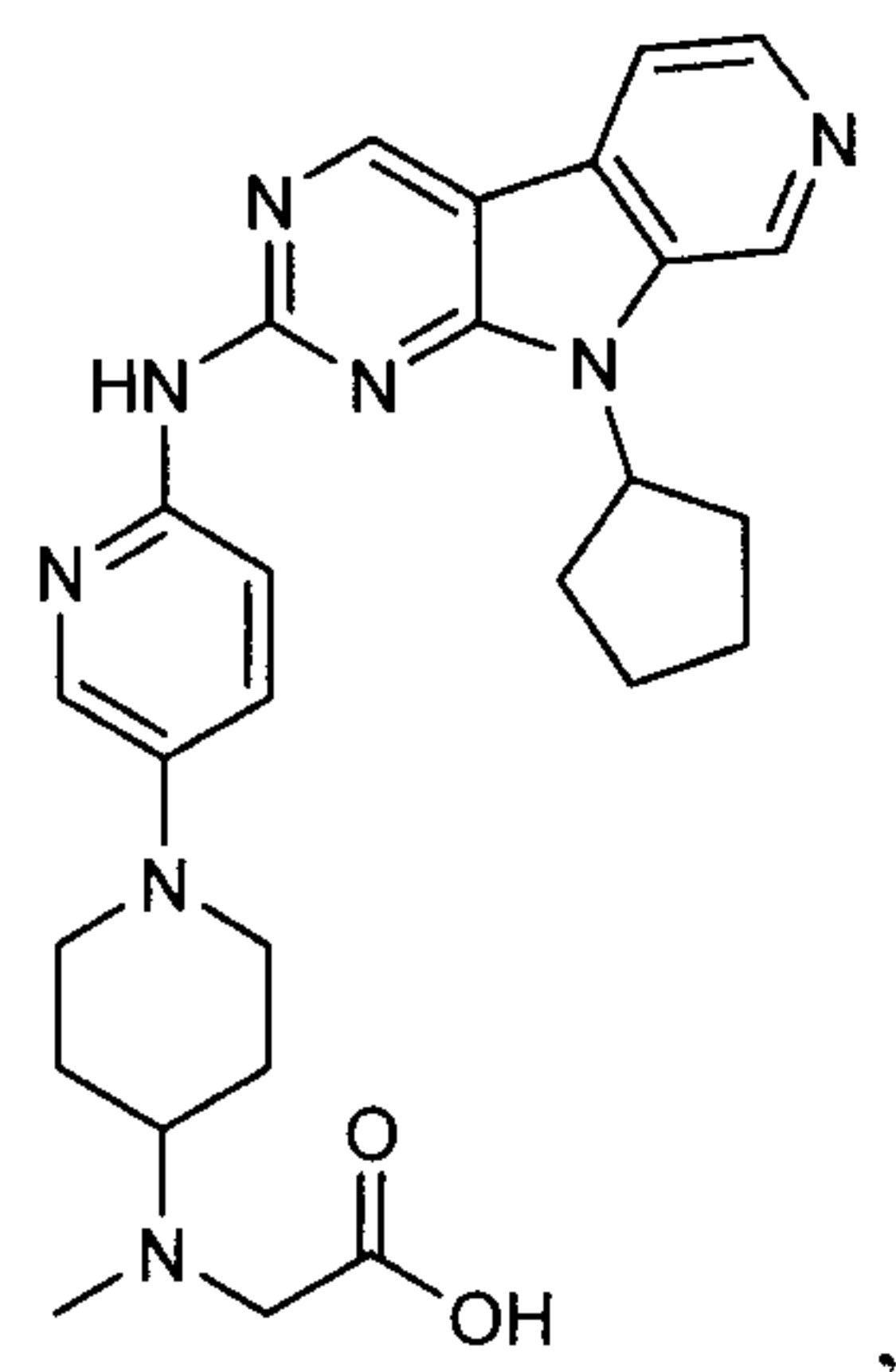
or a pharmaceutically acceptable salt thereof.

408. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

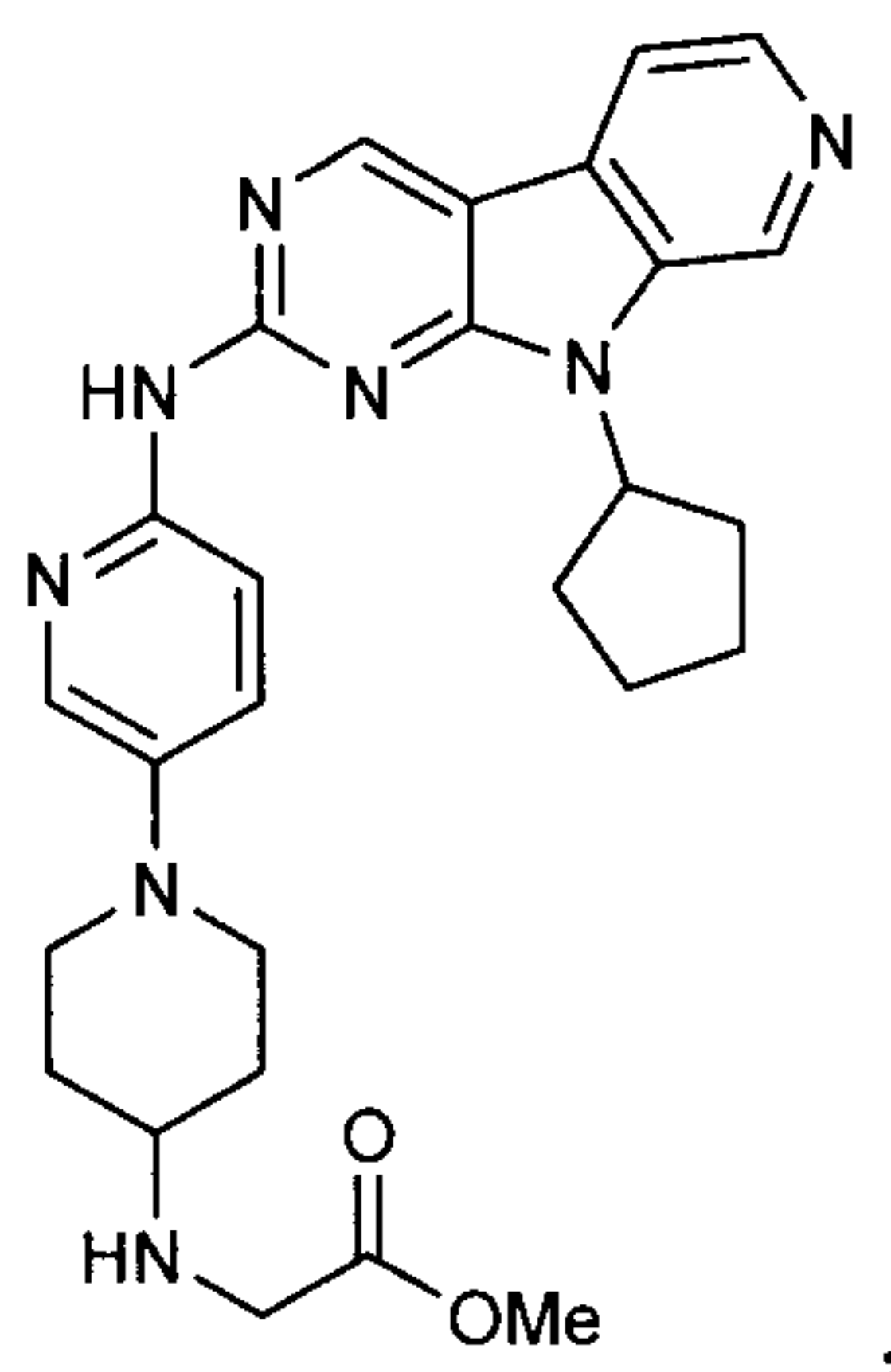
409. The compound of claim 1, wherein the compound is





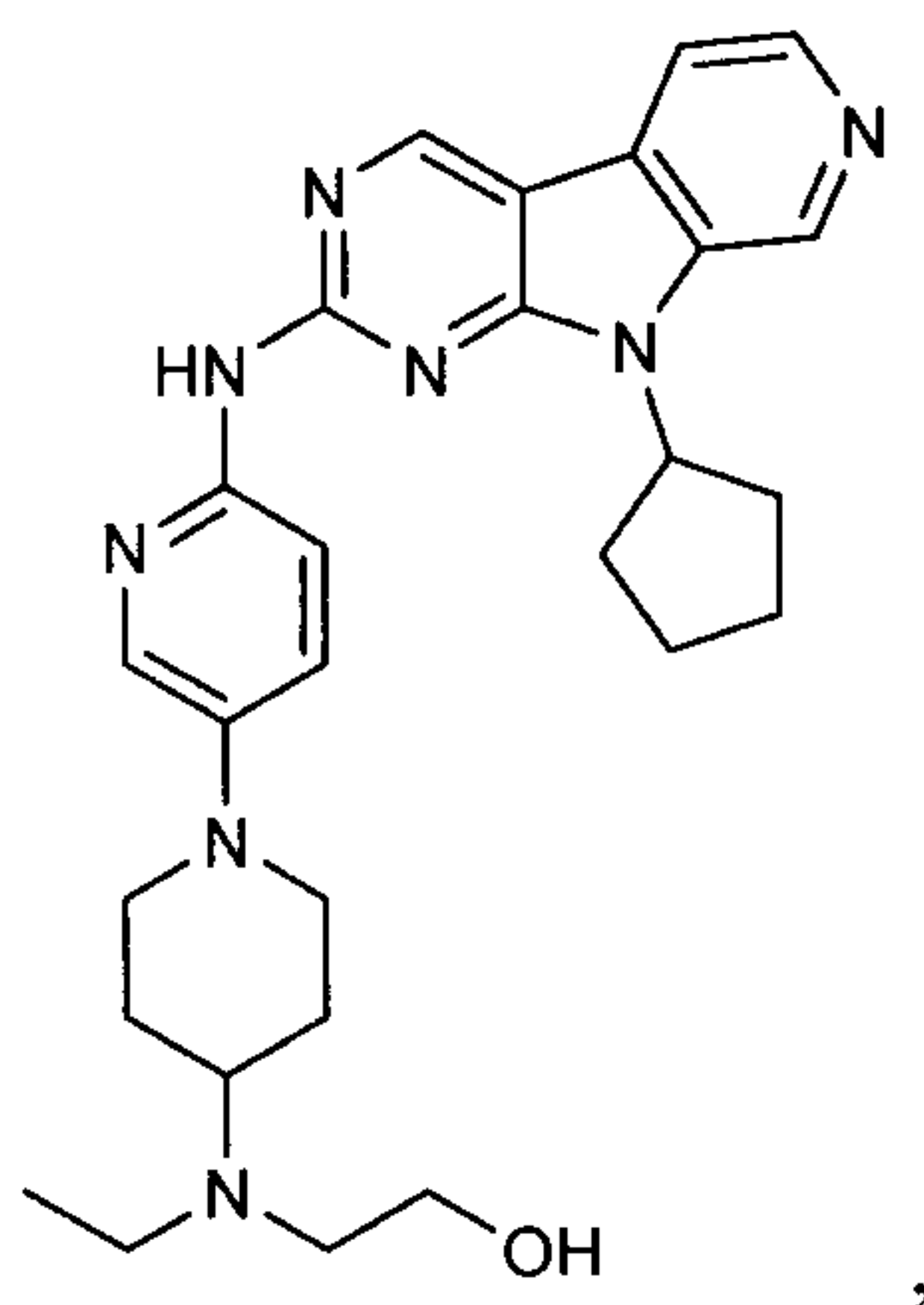
or a pharmaceutically acceptable salt thereof.

410. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

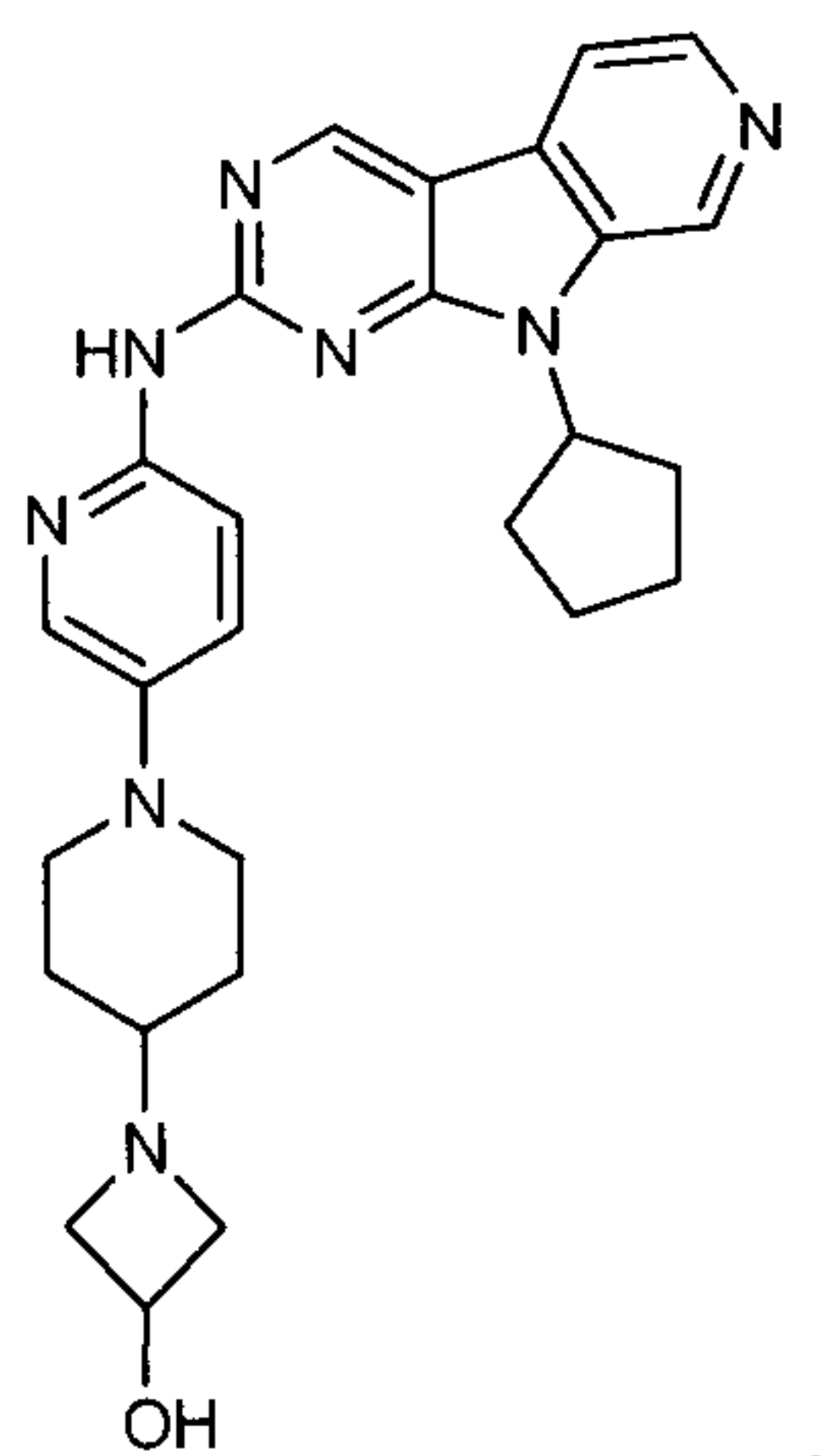
411. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

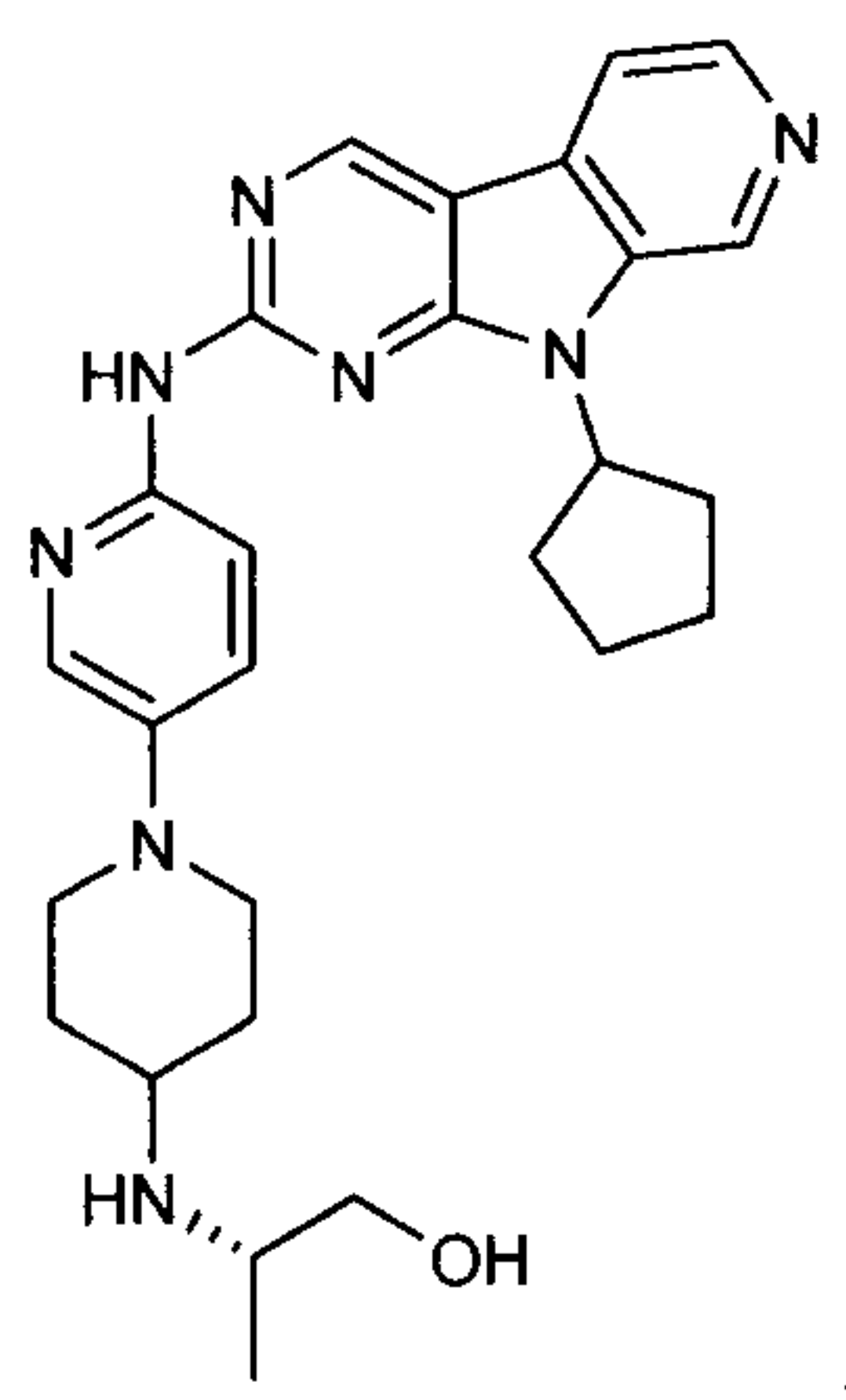


412. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

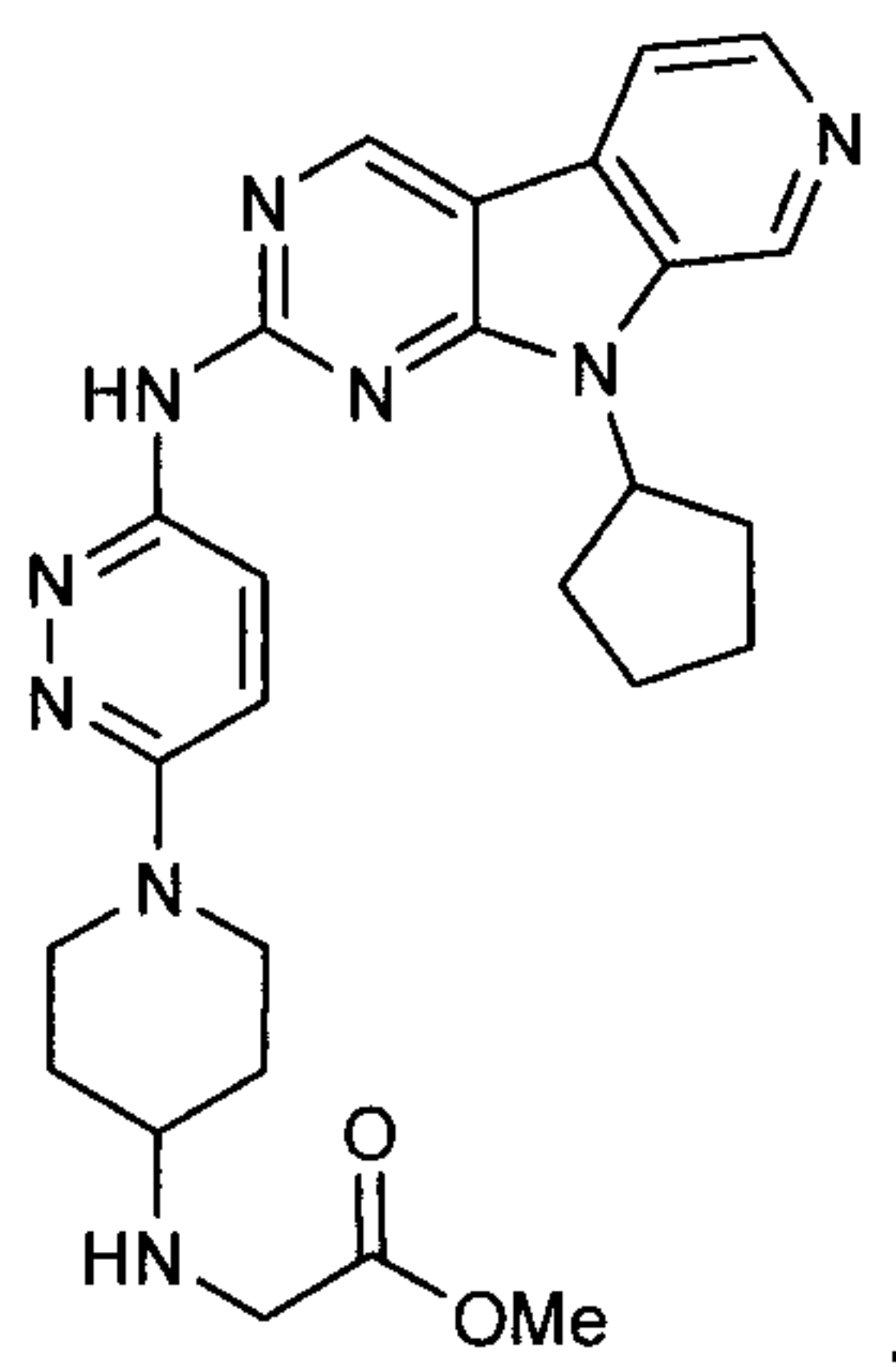
413. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

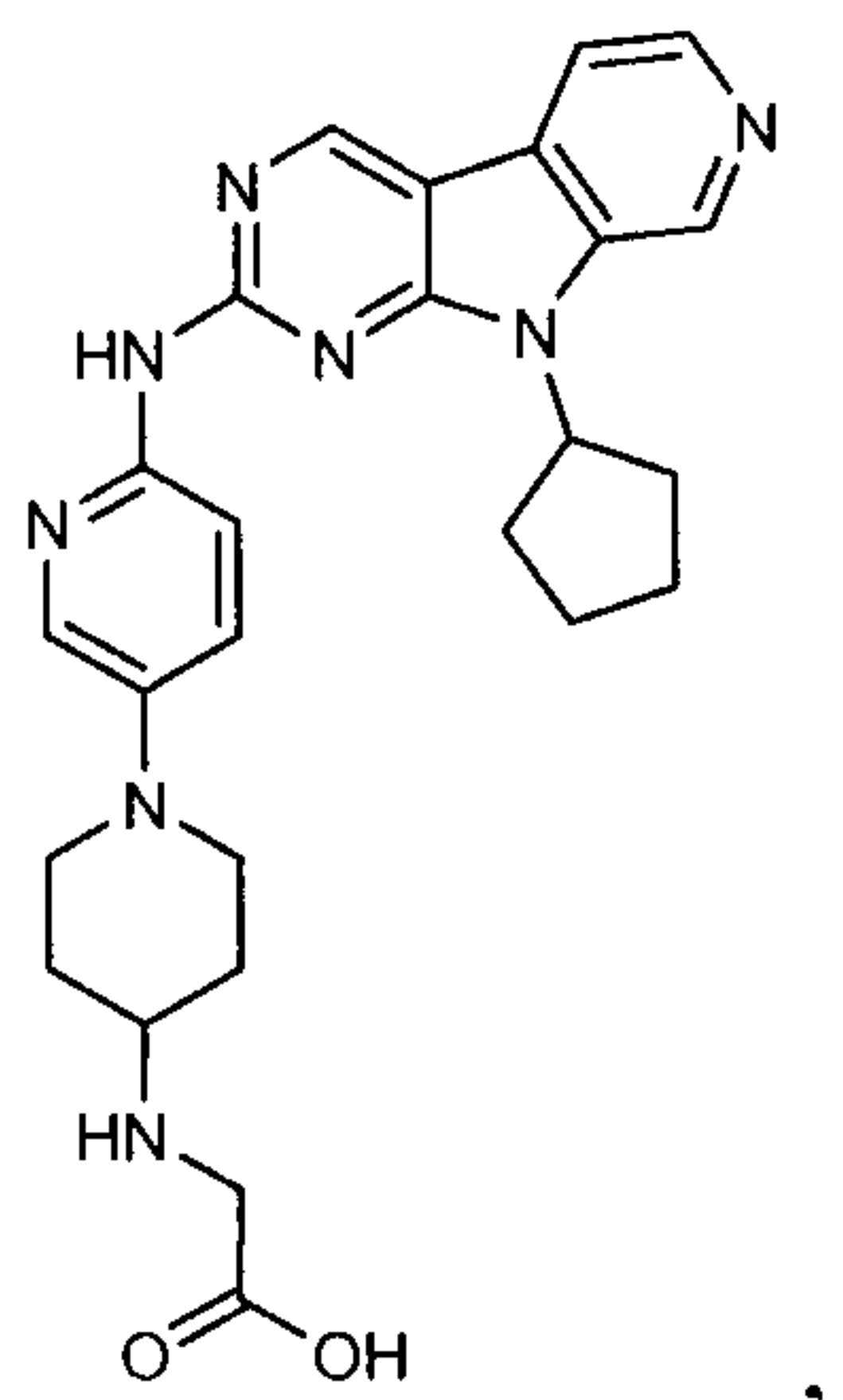


414. The compound of claim 1, wherein the compound is



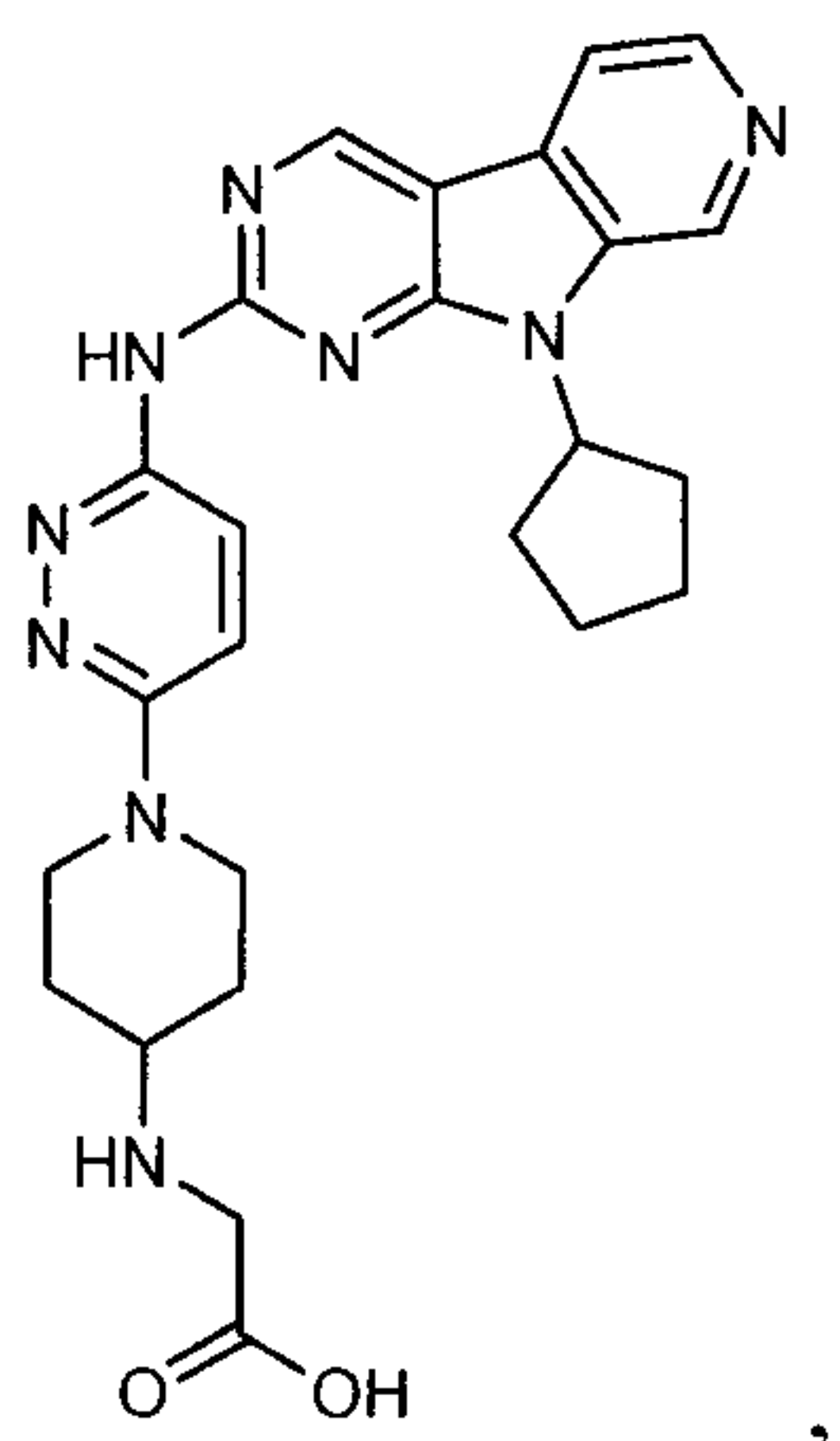
or a pharmaceutically acceptable salt thereof.

415. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

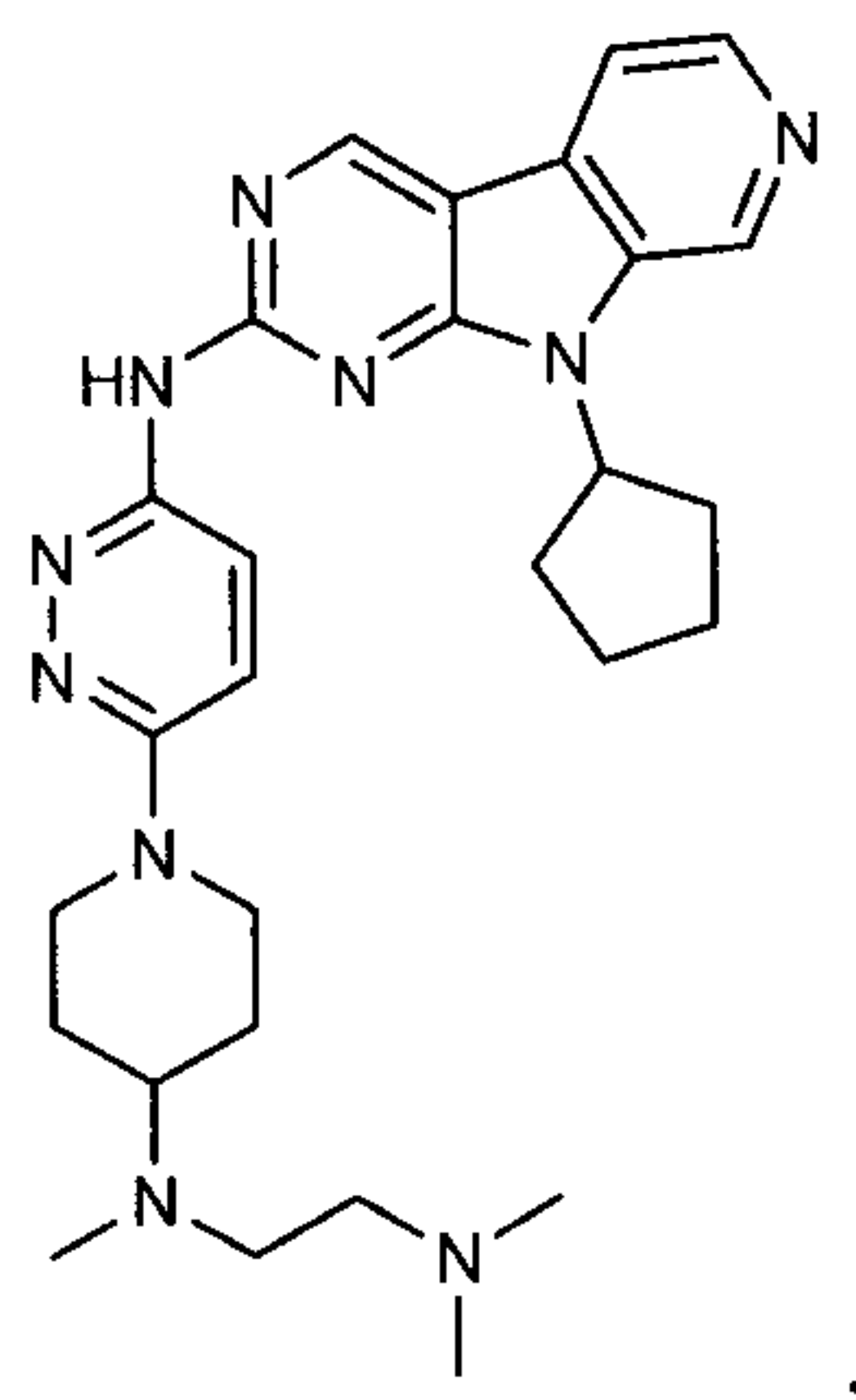
416. The compound of claim 1, wherein the compound is





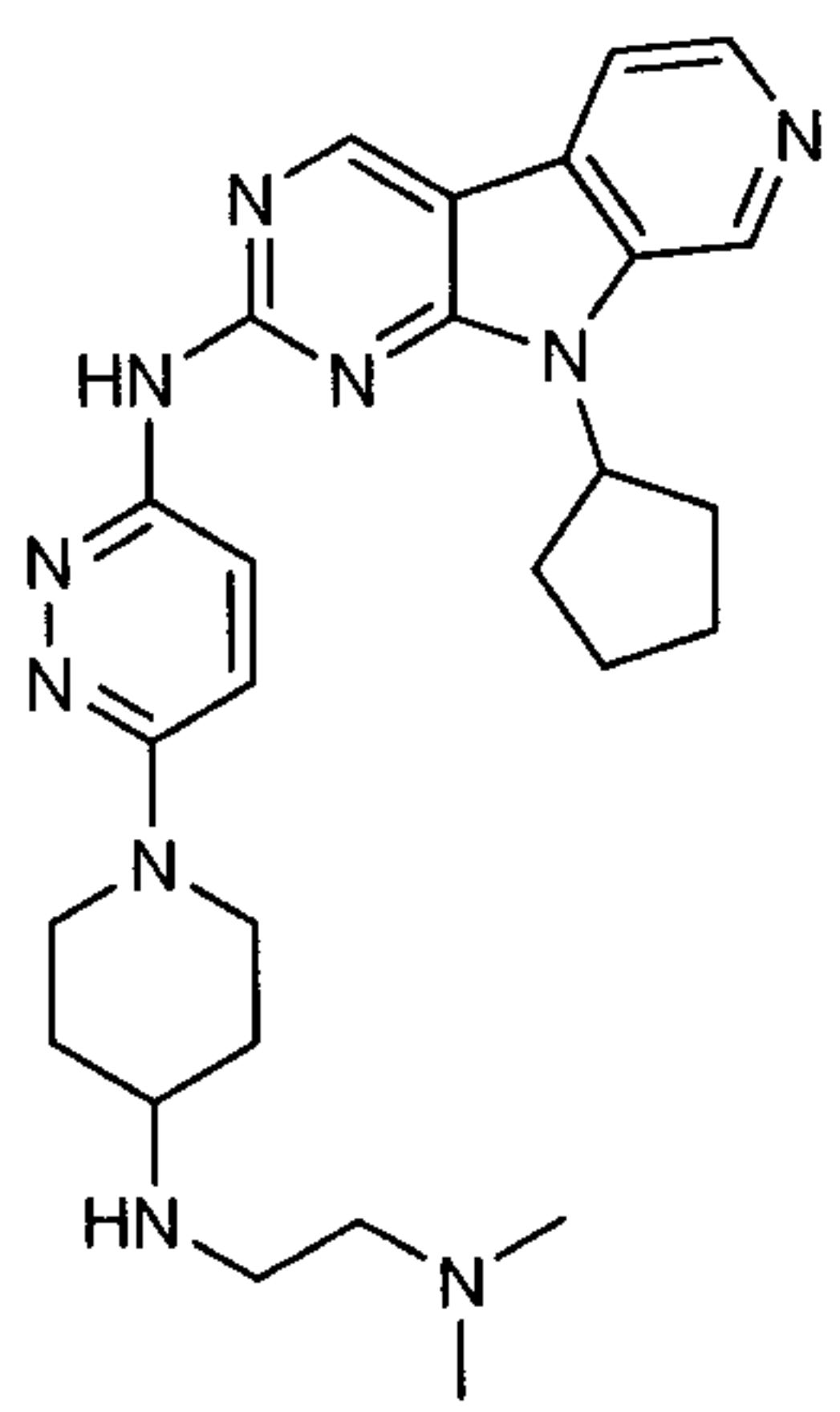
or a pharmaceutically acceptable salt thereof.

417. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

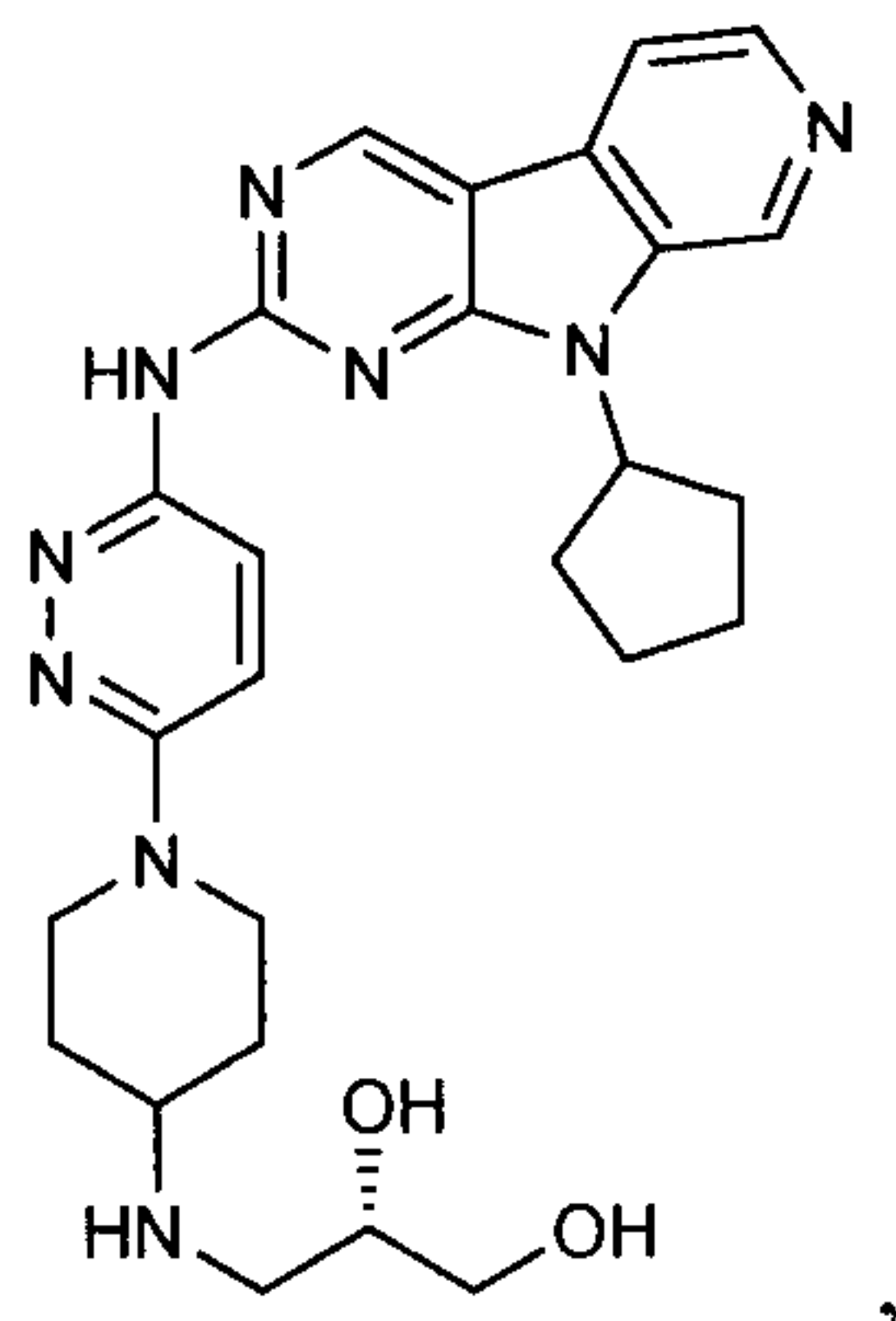
418. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

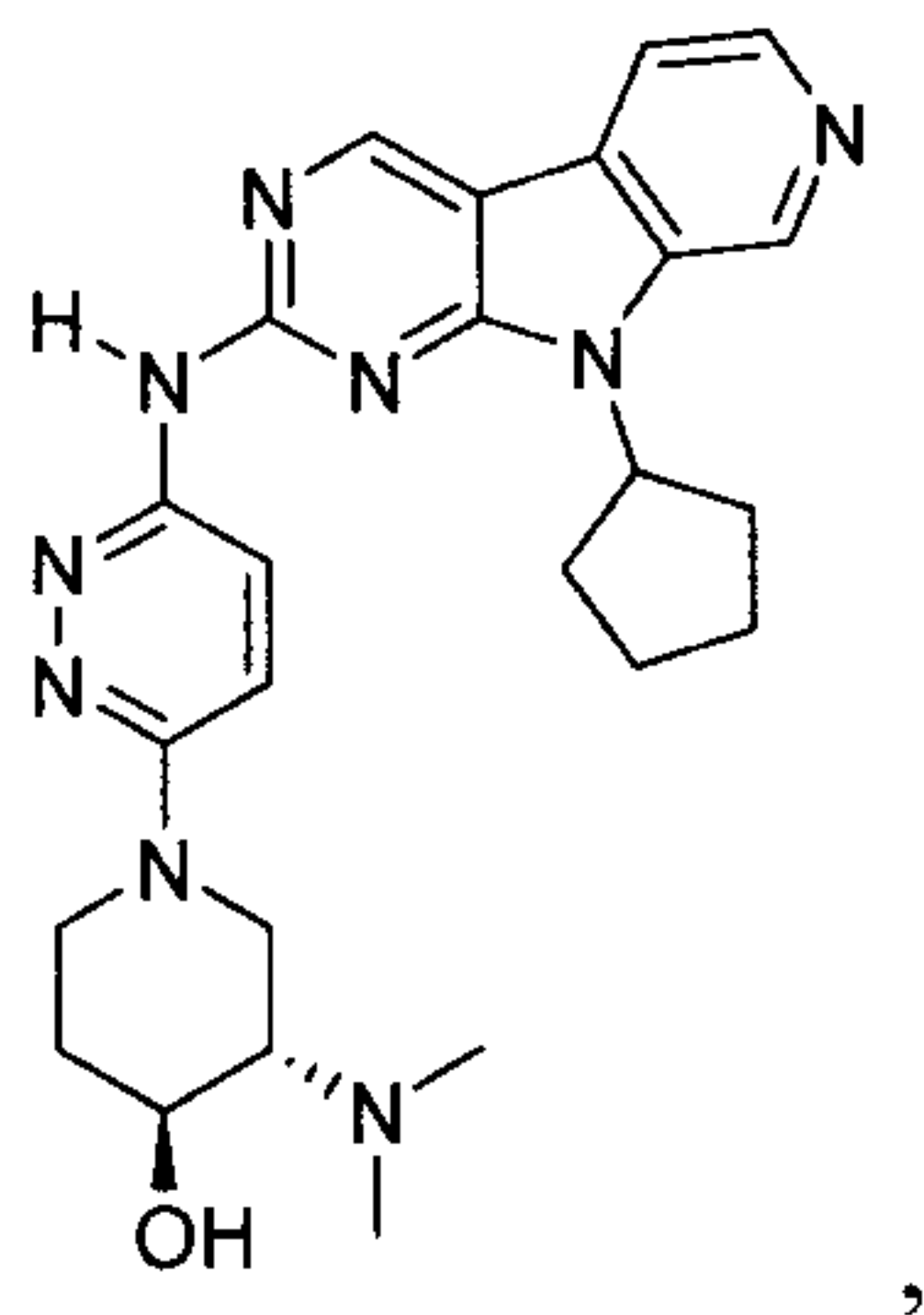


419. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

420. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

421. A pharmaceutical composition comprising the compound defined in any one of claims 42-420 together with a pharmaceutically acceptable vehicle adjuvant or diluent.

422. A use of an effective amount of the compound defined in any one of claims 42-420, for treating cancer in a subject.

423. A use of an effective amount of the compound defined in any one of claims 42-420, for the preparation of a medicament for treating cancer in a subject.

424. A use of an effective amount of the compound defined in any one of claims 42-420, and at least one compound selected from the group consisting of an antibiotic-type agent, an



alkylating agent, an antimetabolite agent, a hormonal agent, an immunological agent, an interferon-type agent and a miscellaneous agent, for treating cancer in a subject.

425. A use of an effective amount of the compound defined in any one of claims 42-420, and at least one compound selected from the group consisting of an antibiotic-type agent, an alkylating agent, an antimetabolite agent, a hormonal agent, an immunological agent, an interferon-type agent and a miscellaneous agent, for the preparation of a medicament for treating cancer in a subject.

426. A use of an effective amount of the compound defined in any one of claims 42-420, for reducing tumor size in a subject.

427. A use of an effective amount of the compound defined in any one of claims 42-420, for the preparation of a medicament for reducing tumor size in a subject.

428. A use of an effective amount of the compound defined in any one of claims 42-420, for treating cdk4 or cdk6 mediated disorders in a subject.

429. A use of an effective amount of the compound defined in any one of claims 42-420, for the preparation of a medicament for treating cdk4 or cdk6 mediated disorders in a subject.

430. A use of an effective amount of the compound defined in any one of claims 42-420, for reducing metastasis in a tumor in a subject.

431. A use of an effective amount of the compound defined in any one of claims 42-420, for the preparation of a medicament for reducing metastasis in a tumor in a subject.